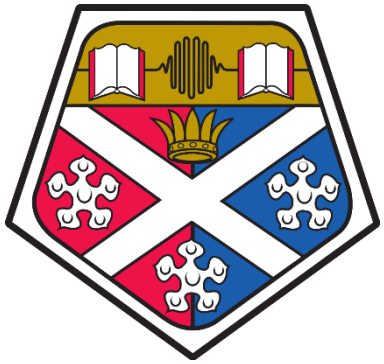
University of Strathclyde

Department of Pure and Applied Chemistry



Metal-free functionalisation of alkenes

A thesis submitted to the University of Strathclyde in part fulfilment of regulations for the degree of Doctor of Philosophy in Chemistry.

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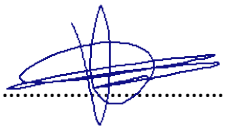
Supervised by Professor Nicholas Tomkinson

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 ...13/06/2017...

Abstract

This thesis describes two novel metal-free transformations, a method to selectively synthesise *anti*-diols from readily available alkene starting materials and an oxidative heterocyclisation of homoallylic nucleophiles for the synthesis of biologically significant hetereocycles.

Chapter 1 describes a metal-free methodology for the preparation of *anti*-diols from alkenes. A selection of *trans*-stilbene and styrene derivatives were synthesised and reacted under optimal reaction conditions to give *anti*-diols in good to excellent yields and selectivities. Substituted indene and naphthalene starting materials were also prepared providing significantly better *syn*:*anti* diastereoselectivities.

Chapter 2 demonstrates a novel oxidative heterocyclisation under metal-free conditions for the preparation of oxygenated heterocycles, a class of compounds with potential biological applications. For this reason, Citalopram, an antidepressant, was synthesised using this approach. This transformation provided access to γ-lactone, tetrahydrofuran and *iso*benzofuranone scaffolds in high levels of diastereoselectivity.

Chapter 3 represents a new methodology for the intramolecular aminohydroxylation of alkenes from protected homoallylic amines in the presence of a malonoyl peroxide. This transformation was also applied to *N*-protected cinnamylhydroxylamines for the generation of *iso*xazolidines.

Chapter 4 describes the experimental procedures and analytical data generated for all the compounds synthesised.

Chapters 5 and 6 contain the appendix and bibliography sections of the thesis.

Acknowledgements

First of all, I would like to thank Prof. Nick Tomkinson, my academic supervisor, for giving me the chance to pursue my PhD within his research group. It has been a pleasure to work for you, thanks for all you support, advice and all the chemistry that you taught me. Thanks to you now I am in love with chemistry and for this reason I want to keep doing research with a PostDoc. Also, a big thanks to your family, they have been super nice with me, and I really appreciate that. I honestly only have words of gratitude.

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I would like to use the next sentences to dedicate this thesis to my mum. Unfortunately she is not here to see everything I have done, but I am pretty sure she is proud of me and drives me to the right decisions from the very top of the sky. Love you.

Table of Contents

Abbreviations

Å	Angstrom
Ac	Acetyl
AIBN	Azobisisobutyronitrile
AQN	Anthraquinone
APCI	Atmospheric pressure chemical ionisation
appt	Apparent triplet
Asp	Aspartic acid
aq	Aqueous
Ar	Aryl
atm	atmospheres
ATR	Attenuated total reflectance
bs	Broad singlet
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Br	Broad
Bu	Butyl
BV	Baeyer-Villiger
Bz	Benzoyl
cat	Catalytic
CAN	Ceric ammonium nitrate
Cbz	Carbobenzyloxy
CHMO	Cyclohexanone monooxygenases
CI	Chemical ionisation
COSY	Correlation spectroscopy
Conv	Conversion
CSA	Camphorsulfonic acid
Cy	Cyclohexane

d	Doublet
DCE	1,2-Dichloroethane
dd	Doublet of doublets
ddd	Doublet doublet of doublets
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DET	Diethyl tartrate
DIBAL	Diisobutylaluminium hydride
dt	Doublet of triplets
dq	Doublet of quartets
$(DHQD)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
DEAD	Diethyl azodicarboxylate
decomp	Decomposed
DMAP	*N*,*N*-Dimethyl-4-aminopyridine
DMF	Dimethylformamide
DMM	Dimethoxymethane
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
dq	Doublet of quartets
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	Ethylenediaminetetraacetic acid
ee	Enantiomeric excess
EI	Electron ionisation
equiv	Equivalent/s
er	Enantiomeric ratio
ESI	Electrospray ionisation
Et	Ethyl
g	Gram

GABOB	γ-amino-β-hydroxybutyric acid
GC	Gas chromatography
h	Hour/s
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
Hz	Hertz
IBX	2-Iodoxybenzoic acid
IPA	Isopropanol
IR	Infrared
J	Joule
J	Coupling constant
L	Ligand
LA	Lewis acid
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
Lit	Literature
LRMS	Low resolution mass spectrometry
Luperox	*tert*-Butyl peroxide
m	Meta
m	Multiplet
M	Molar
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
Mes	Mesityl

mg	Milligram/s
MHz	Megahertz
min	Minute/s
mL	Millilitre/s
mmol	Millimole/s
m.p.	Melting point
MS	Mass spectrometry
MS (in schemes)	Molecular sieves
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
NMM	*N*-Methylmorpholine
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear Magnetic resonance
NOE	Nuclear Overhauser effect
Ns	Nosyl
Nu	Nucleophile
o	*ortho*
o/n	overnight
Ox	Oxidation
p	*para*
pent	Pentet
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Pg	Protecting Group
Ph	Phenyl
Phth	Phthlyl
PIDA	(Diacetoxyiodo)benzene

PIFA	[Bis(trifluoroacetoxy)iodo]benzene
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
^{i}Pr	Isopropyl
PTSA	*p*-Toluenesulfonic acid
pyr	Pyridine
q	Quartet
R_f	Retention factor
rt	Room temperature
s	Singlet
S_N1	Nucleophilic substitution unimolecular
S_N2	Nucleophilic substitution bimolecular
T	Temperature
t (in schemes)	Time
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBAB	Tetra-*n*-butylammonium bromide
TBDPS	*tert*-Butyldiphenylsilane
TBME	Methyl *tert*-butyl ether
TBS	*tert*-Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
Tf	Trifluoromethyl sulfonyl
TFA	Trifluoroacetic acid
TFE	Tetrafluoroethylene
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl

Tol	Tolyl
TPAP	Tetrapropylammonium perruthenate
Ts	Toluenesulfonyl/Tosyl
TS	Transition state
Tyr	Tyrosine
UHP	Urea hydrogen peroxide
z	Charge

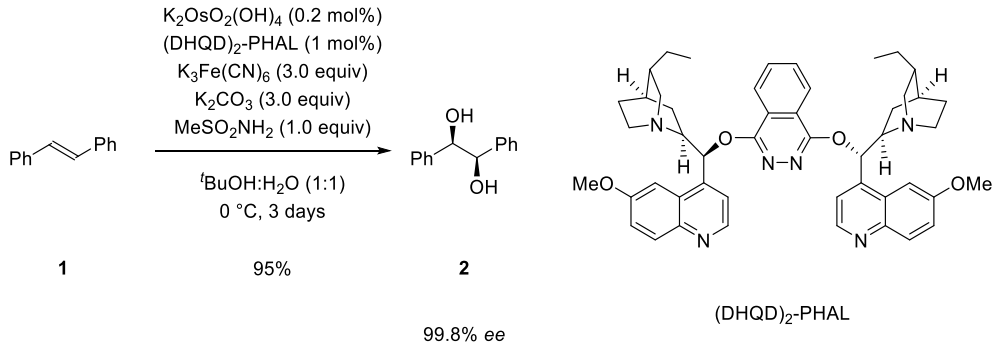
Chapter 1: *anti*-Dihydroxylation of Alkenes with Malonoyl Peroxides

1 Introduction to the Dihydroxylation of Alkenes

Alkene dihydroxylation is one of the most important reactions in synthetic chemistry.[1] The 1,2-diol moiety is present in many natural and pharmaceutical products, making the direct dihydroxylation reaction a valuable synthetic tool.

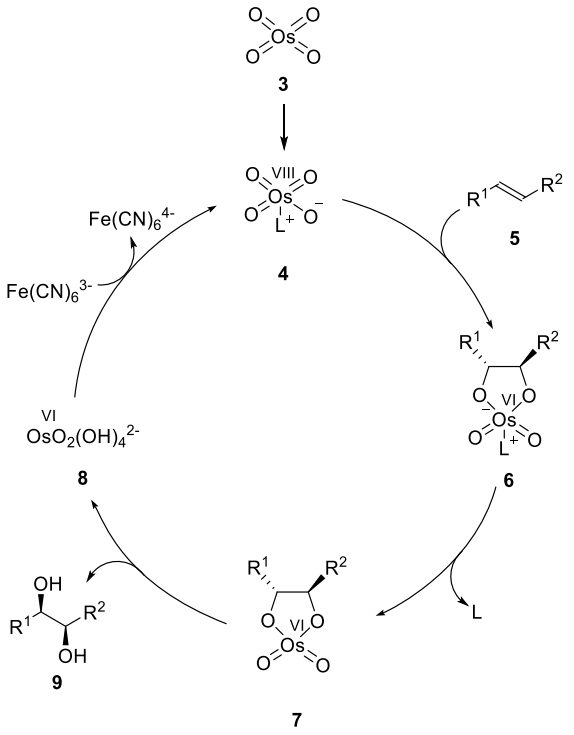
syn-Vicinal diols are traditionally prepared by metal-catalysed dioxygenation of alkenes. The choice method for this transformation is the Sharpless dihydroxylation using OsO_4 as a catalyst.[2] The high yields, excellent enantiomeric control and broad substrate scope make this the "gold standard" method for the *syn*-dioxygenation of alkenes.

For this reaction a source of osmium is used with the $(DHQD)_2$-PHAL chiral ligand and a stoichiometric amount of potassium ferrocyanide as the oxidant to give diol **2** in 95% yield for *trans*-stilbene and a 99.8% *ee* (Scheme **1**). Given the success of this transformation, commercially available AD-mix α and AD-mix β can be purchased as pre-packaged mixtures of $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3 together with the appropriate chiral ligand $(DHQ)_2$-PHAL or $(DHQD)_2$-PHAL.



Scheme 1. Asymmetric Sharpless *syn*-dihydroxylation.

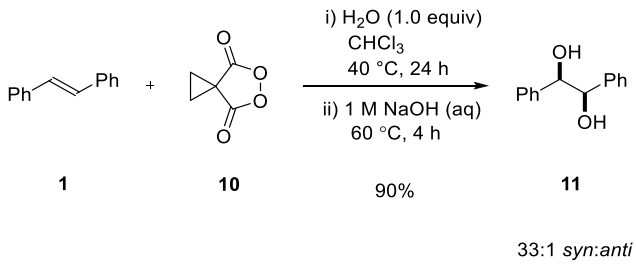
Mechanistically, the Sharpless asymmetric dihydroxylation starts with the generation of the OsO_4–ligand complex **4** (Scheme **2**). The subsequent [3+2] cycloaddition with alkene **5** gives the cyclic osmium intermediate **7** after loss of a molecule of ligand L. Once the oxidised product is released from the osmium centre through hydrolysis, the Os^{VI} **8** is re-oxidised to Os^{VIII} **4** by the iron salt.



Scheme 2. Sharpless dihydroxylation catalytic cycle.

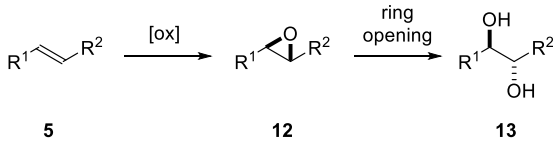
The high cost, toxicity and low natural abundance of osmium, coupled with the large amounts of inorganic waste generated during the reaction (to oxidise 1 kg of *trans*-stilbene **1** generates 10 kg of inorganic waste), are serious drawbacks to this reaction. Efforts are continuously being made in this field to develop alternative metal-catalysed[3-12] or metal-free[13] alternatives.

An example of a metal-free methodology for the dioxygenation of alkenes which has been developed in the Tomkinson group[13] involves treating *trans*-stilbene **1** with malonoyl peroxide **10** and one equivalent of H_2O in $CHCl_3$ to give the diol **11** after hydrolysis in a 90% yield and an excellent *syn*:*anti* ratio of 33:1 (Scheme **3**).



Scheme 3. Metal-free *syn*-dihydroxylation.

The complementary *anti*-vicinal diols are commonly prepared through a two-step synthetic procedure.The first step would be the epoxidation of alkene **5** using either peroxy acids, or the Sharpless,[14] Jacobsen[15] or Shi[16] epoxidations, followed by a ring-opening reaction providing access to the desired *anti*-diol **13** (Scheme **4**).



Scheme 4. General two-step synthetic procedure for the generation of *anti*-diols.

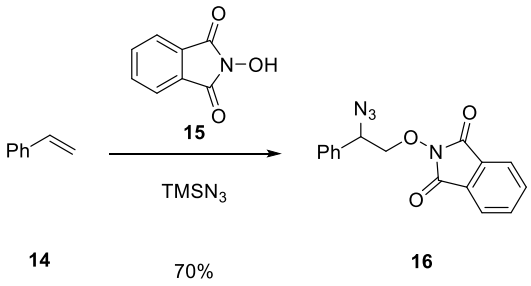
A number of alternative processes have also been developed to perform this overall net transformation. Within this introduction, selected methods for the *anti*-dioxygenation of alkenes will be discussed.

1.1 Previous Methodologies for the *anti*-Dioxygenation of Alkenes

1.1.1 Metal-based methodologies

1.1.1.1 Copper

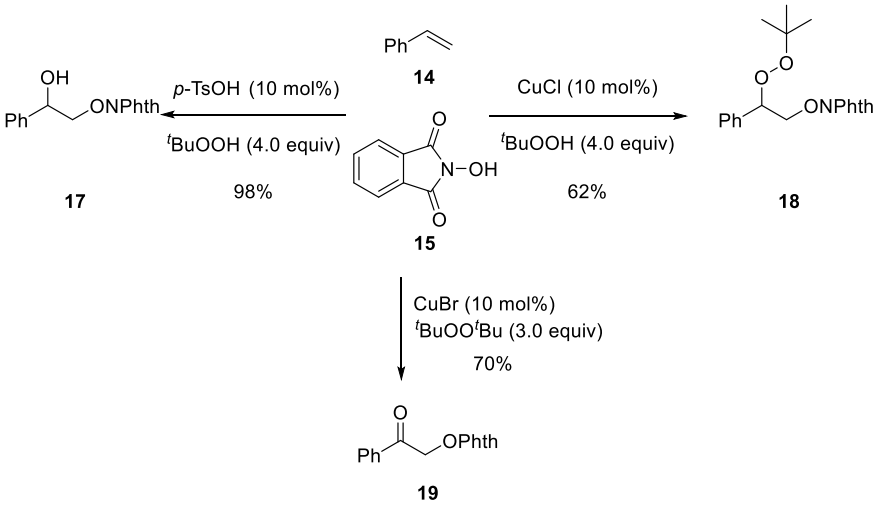
The use of copper in the dioxygenation reaction has been widely explored over the past years and significant progress has been achieved within the Liang group in China. They previously reported a metal-free hydroxyamination of alkenes using *N*-hydroxyphthalimide **15** and $TMSN_3$ through a proposed radical mechanism (Scheme **5**).[17]



Scheme 5. Metal-free hydroxyamination of alkenes with *N*-hydroxyphthalimide **15** and $TMSN_3$.

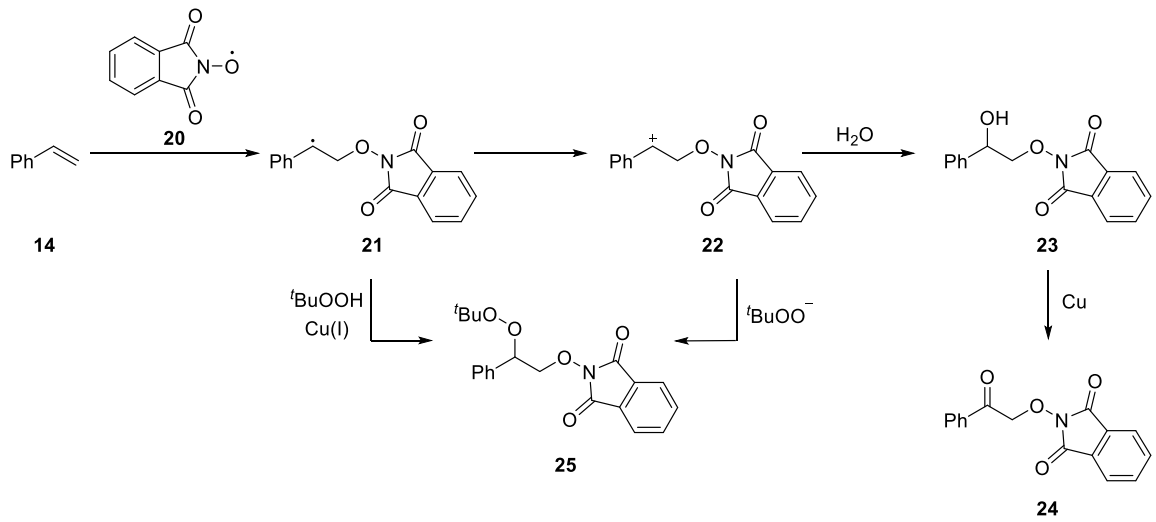
Following this they postulated that if oxygen radicals were used instead of azide radicals, dioxygenation of alkenes should be possible.[18] Ketones, peroxides and alcohol can be obtained in this transformation depending on the reaction conditions (Scheme **6**). The reaction of styrene **14**

with *N*-hydroxyphthalimide **15** and *tert*-butylhydroperoxide in the presence of catalytic CuCl, results in the formation of peroxides **18**. If catalytic *p*-TsOH is used then alcohols **17** are generated. Finally, ketones **19** are generated using *tert*-butyl peroxide and catalytic CuBr. Overall, they have developed a simple method that proceeds under mild conditions and offers the potential to deliver three different functional groups by switching reagents.



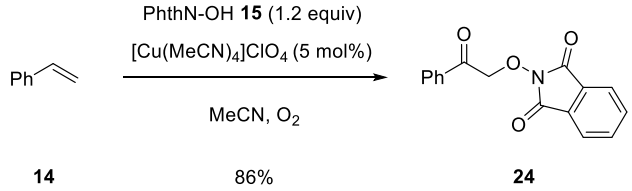
Scheme 6. Metal-based dioxygenation of alkenes.

A plausible mechanism was proposed to account for these observations (Scheme **7**).[18] *N*-hydroxyphthalimide **15** is converted into the radical species **20** which reacts with styrene **14** to give the more stable benzyl radical **21**. In the presence of peroxide, radical **21** can be oxidised to cation **22**, which in aqueous conditions will rapidly be attacked by H_2O to produce **23** and further oxidation with Cu would give ketone **24**. Reaction of radical **21** with a peroxyl radical or reaction of cation **22** with a peroxide anion would deliver peroxide **25**.



Scheme 7. Proposed mechanism.

Under similar reaction conditions, the Woerpel group also developed a dioxygenation reaction using molecular O_2 as an alternative oxygen source (Scheme **8**).[19] Treatment of styrene **14** and *N*-hydroxyphthalimide **15** with a catalytic amount of a copper catalyst in the presence of O_2 led to the *α*-oxygenated ketone **24** in a 86% yield. A variety of styrenes were successfully dioxygenated as well as cyclic alkenes, indenes and enynes, although for enynes higher catalyst loadings were required.

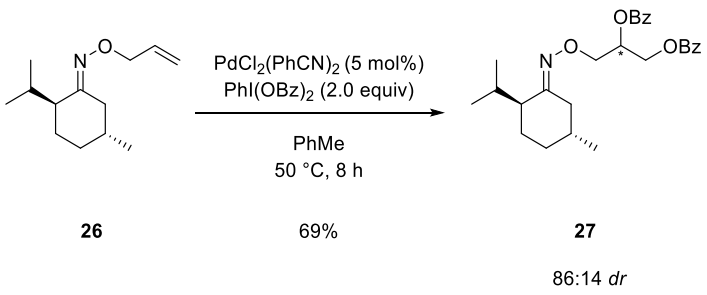


Scheme 8. Cu-catalysed dioxygenation.

1.1.1.2 Palladium

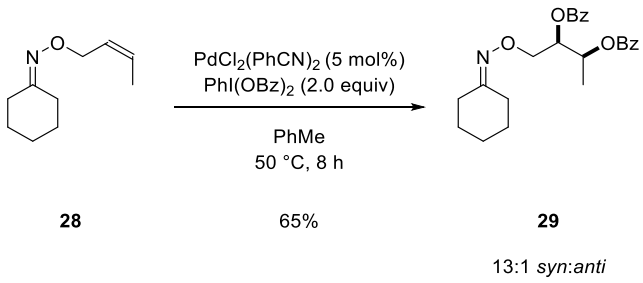
In 2012, Sanford *et al.* developed an asymmetric dioxygenation of alkenes catalysed by palladium.[20] These reactions are mechanistically different compared to the osmium dioxygenation systems. While the osmium-catalysed process proceeds through a concerted [3+2] cycloaddition mechanism to achieve *syn*-dioxygenation, palladium systems operate in discrete steps, adding the two functional groups in a step-wise manner. Palladium has been used in numerous alkene transformations, including dioxygenation,[21] hydroxyamination,[22] diamination,[23] aminohalogenation[24] and aryl halogenation.[25]

Chiral oxime ethers were chosen by the Sanford group as they are effective directing ligands, especially for C–H activation,[26] and they are easily synthesised (Scheme **9**). Chiral alkene **26** reacted with catalytic Pd^{II} in the presence of an hypervalent iodine reagent providing access to dibenzoylated product **27** in 69% yield.



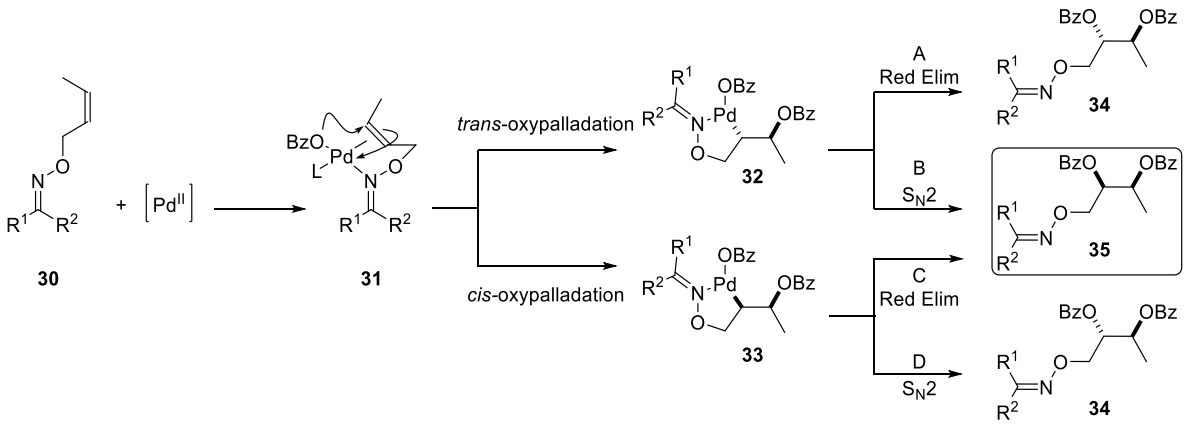
Scheme 9. Pd-catalysed dioxygenation.

Mechanistically, there is not unequivocal evidence to rationalise the stereochemical outcome of this reaction (Scheme **11**). However the use of the 1,2-disubstituted oxime ether **28** allowed them to suggest a mechanistic pathway for this transformation since the reaction outcome for oxime ether **28** provided *syn*-dibenzoylated product **29** with good levels of diastereoselectivity (Scheme **10**).



Scheme 10. Diastereoselectivity with 1,2-disubstituted alkene.

Oxime ether **30** contains a *Z*-alkene that coordinates with the palladium catalyst. Subsequent oxypalladation can occur either *via cis*-oxypalladation **32** or *trans*-oxypalladation **33**. The new C–O bond can then be formed either by reductive elimination of **33** or *via* S_N2 reaction of **32** to give *syn*-dibenzoylated product **35**.

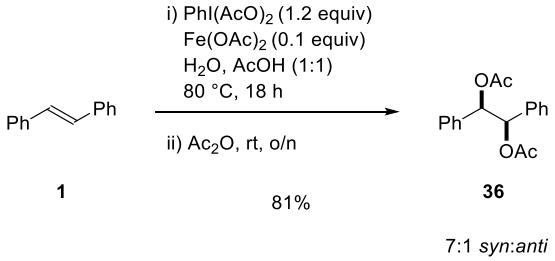


Scheme 11. Proposed mechanism for dibenzoylation of oxime ether **30** with Pd^{II}.

1.1.1.3 Iron

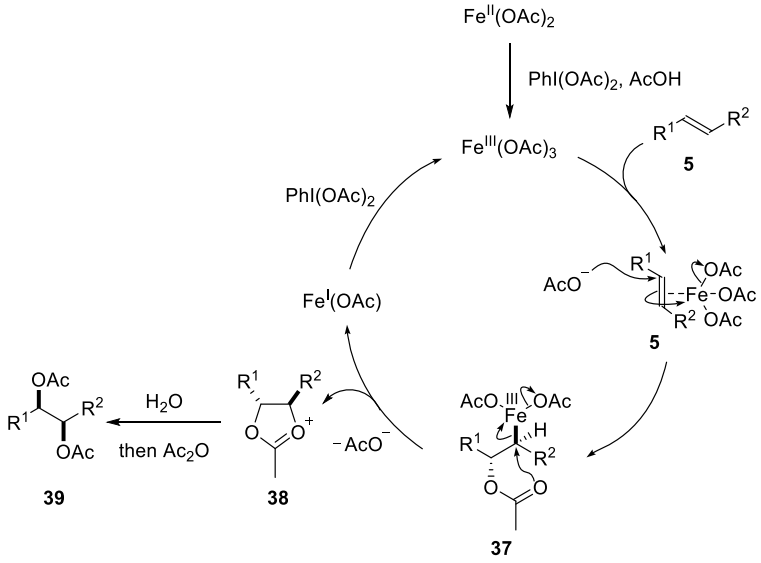
Since iron is benign and biocompatible, chemistry with this metal as a catalyst has been increasingly investigated in recent years.[27] A recent paper by Sreedhar *et al.* describes an iron-catalysed diacetoxylation of alkenes with $PhI(OAc)_2$ (PIDA) as oxidant.[28] Reaction of *trans*-stilbene **1** with the catalytic $Fe(OAc)_2$ and a stoichiometric amount of PIDA provides the

desired diacetoxylated product **36** in high yield and good diastereoselectivity (*syn*:*anti* 7:1) (Scheme **12**).



Scheme 12. Fe-catalysed dioxygenation.

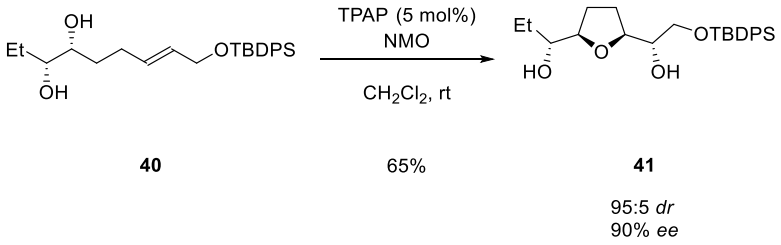
Mechanistically, it was suggested an *in situ* oxidation of Fe^{II} with $PhI(OAc)_2$ and AcOH occurred to give $Fe^{III}(OAc)_3$ (Scheme **13**). This active catalytic species then coordinates to the alkene **5** followed by a *trans*-addition to give intermediate **37**. Rapid dioxonium **38** formation from intermediate **37** followed by acetoxylation or hydrolysis provided the desired *syn-bis*-acetate **39**.



Scheme 13. Proposed mechanism for Fe-catalysed dioxygenation.

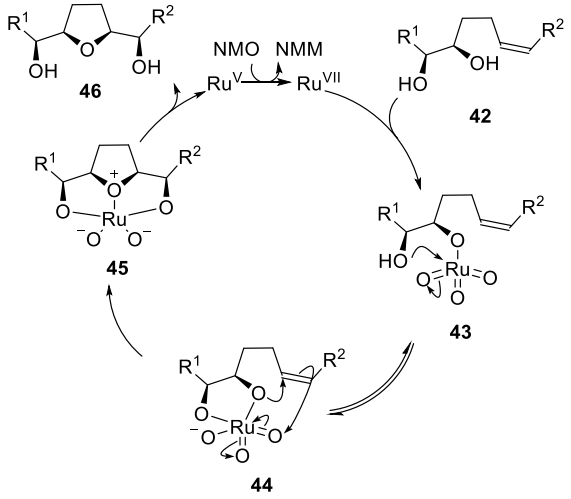
1.1.1.4 Ruthenium

Chiral tetrahydrofuran rings represent an important motif in biologically active molecules. For this reason, the efficient synthesis of enantiopure tetrahydrofuran rings is still an important challenge in organic chemistry. In 2010 Stark *et al.* reported a stereocontrolled oxidative cyclisation of hydroxyalkenes to afford tetrahydrofuran structures with catalytic amounts of ruthenium (Scheme **14**).[29]



Scheme 14. Oxidative cyclisation with Ru^{VII}.

They believe that the catalytic species Ru^{VII} reacts with diol **42** to give intermediate **43** which is in equilibrium with the cyclic Ru^{VII} diester **44** (Scheme **15**). Intermediate **44** can undergo a [3+2] cycloaddition with the alkene in an analogous manner to OsO_4 to give the ruthenium ester **45** (Scheme **2**). Finally, tetrahydrofuran adduct **46** is released after hydrolysis and Ru^{V} is reoxidised to the active catalyst Ru^{VII} by NMO. Overall this method represents an efficient process for the *syn*-dioxygenation of alkenes, however it is a highly substrate-specific processs.

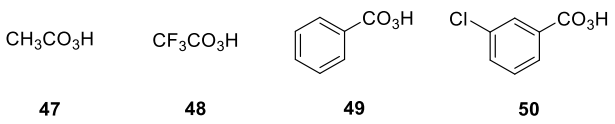


Scheme 15. Mechanism for Ru-catalysed oxidative cyclisation.

1.1.2 *Via* epoxidation and ring opening

1.1.2.1 Epoxidation with peroxyacids

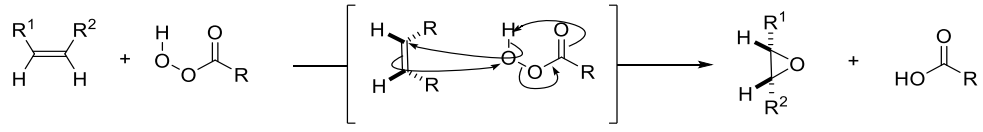
Alkene epoxidation with peroxyacids is also an efficient process. The peroxycarboxylic acids most commonly used are: peracetic acid **47**, pertrifluoroacetic acid **48**, perbenzoic acid **49** and *m*-chloroperbenzoic acid (*m*-CPBA) **50** (Scheme **16**).



47 **48** **49** **50**

Scheme 16. Peroxyacids frequently used in alkene epoxidation.

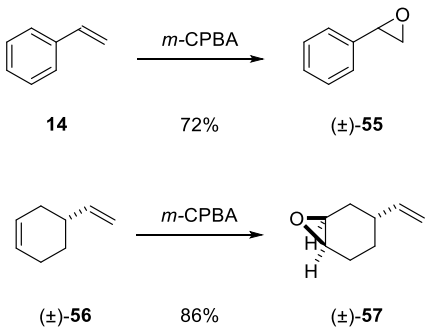
The reaction proceeds *via* a concerted mechanism with the epoxide being formed in a single step on reaction between alkene **51** and peroxyacid **52** (Scheme **17**). Electron-withdrawing substituents on the alkene slow down the reaction whereas electron-donating substituents in the peracid enhance the reaction.



51 **52** **51** **52** **53** **54**

Scheme 17. Mechanism of the epoxidation of an alkene with a peroxyacid.

The reaction is highly regio- and chemoselective, reacting preferentially with electron-rich alkenes. The reaction frequently proceeds with good diastereoselectivity on substrates that contain a pre-existing stereogenic centre due to the approach of the peroxide from the least hindered face of the alkene (Scheme **18**).



14 72% (±)-**55**

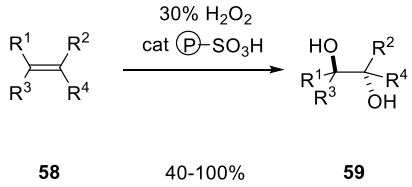
(±)-**56** 86% (±)-**57**

Scheme 18. Examples of epoxidation with *m*-chloroperbenzoic acid.

1.1.2.2 Epoxidation with hydrogen peroxide

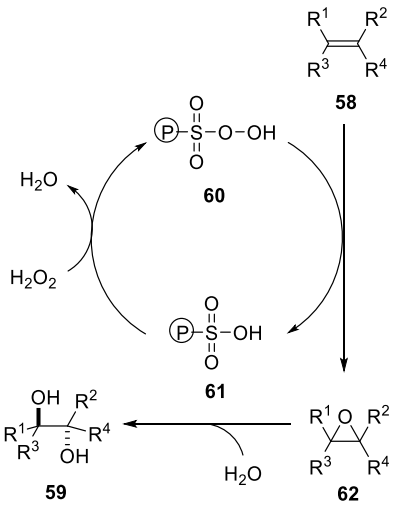
The use of hydrogen peroxide for epoxide formation represents a significant improvement over peracids due to the increased atom efficiency, theoretically producing H_2O as the sole co-product. Hydrogen peroxide can be a clean oxidant only if it is used in a controlled manner and without organic solvents or other toxic compounds. Tanaka[30] and co-workers developed a catalytic

dihydroxylation of alkenes using hydrogen peroxide without the need for an organic solvent and in a metal-free environment (Scheme **19**).



Scheme 19. Alkene dioxygenation using H_2O_2.

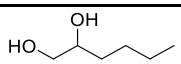
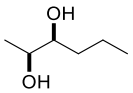
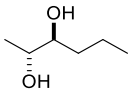
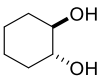
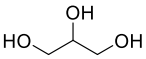
They reported the synthesis of 1,2-diols **59** from alkene **58** using 30% aqueous H_2O_2 catalysed by a resin-supported sulfonic acid, thus obtaining diol **59** in good to excellent yields (40–100%). The method allows recycling of the catalyst as shown in the proposed catalytic cycle (Scheme **20**).



Scheme 20. Proposed catalytic cycle for the formation of *anti*-diol **59**.

Some examples of the range of substrates examined are given in Table **1**. They reported that the reactivity of internal alkenes was higher than that of terminal alkenes. Dihydroxylation of *cis*- (Table **1**, Entry 2) and *trans*-2-hexene (Table **1**, Entry 3) afforded the corresponding diols stereospecifically. Whilst the reaction of selected functionalised alkenes was described, the functional group tolerance of the transformation was not well explored.

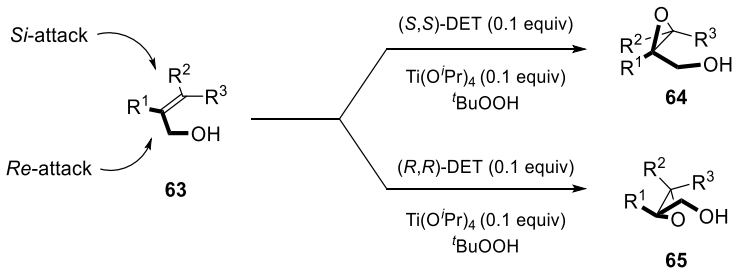
Table 1. Substrate scope.

Entry	Product	Yield[a]/%
1		40
2		67
3		85
4		98
5		93

[a]Isolated yield after chromatographic purification.

1.1.2.3 Sharpless Epoxidation

In 1980, Sharpless discovered a new metal-catalysed asymmetric epoxidation reaction, which was far more selective than previous processes.[14] The reaction proceeds in one step using (*S*,*S*)- or (*R*,*R*)-diethyl tartrate (DET), catalytic titanium tetraisopropoxide and *tert*-butyl hydroperoxide as the stoichiometric oxidant, which are all commercially available at an acceptable cost (Scheme **21**).



Scheme 21. Sharpless Asymmetric epoxidation of allylic alcohols.

This enantioselective reaction is used for the preparation of 1,3-epoxy alcohols **64** or **65** from allylic alcohol **63** (Scheme **21**). The stereochemistry of the resultant epoxide is induced by the chiral ligand DET. Figure **1** shows the proposed transition state of this reaction, DET (red) imparts chirality on the epoxidised product while, *tert*-butyl hydroperoxide (blue) is used as the oxidant.

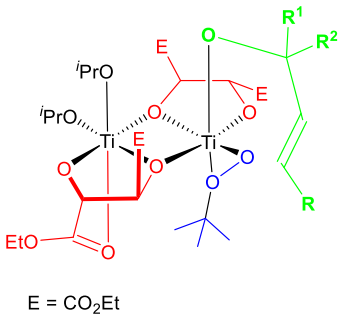
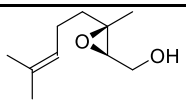
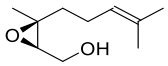
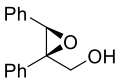
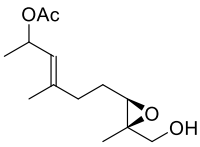


Figure 1. Transition state Asymmetric Sharpless Epoxidation.

Several allylic alcohol substrates were examined and some are summarised in Table **2**.[14] Sharpless was co-awarded the Nobel Prize in Chemistry in 2001, in part for this powerful reaction, which facilitates the synthesis of natural and pharmaceutical products.[31]

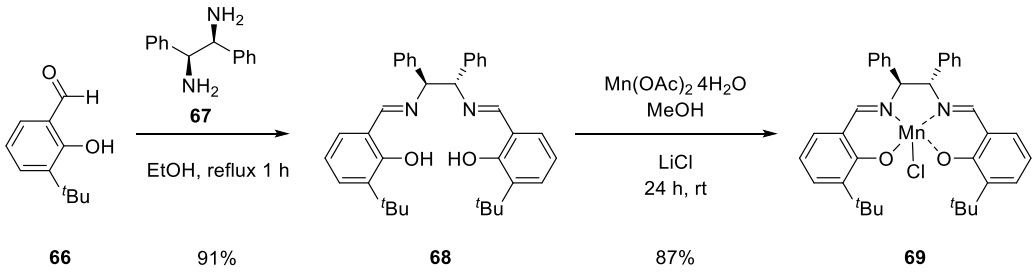
Table 2. Substrate scope.

Entry	Product	Yield[a]/%	*ee*[b]/%
1		77	95
2		79	94
3		87	>95
4		70	>95

[a]Isolated yield after chromatographic purification.[b]*ee* ratios were determined by ^{1}H NMR spectroscopy.

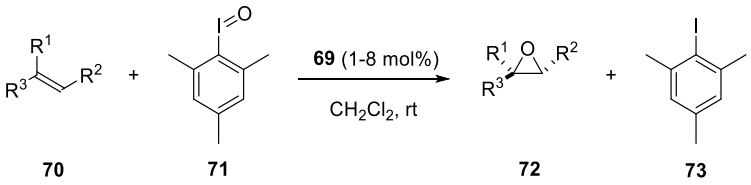
1.1.2.4 Jacobsen Epoxidation[15]

In 1991, Jacobsen and co-workers developed a highly enantioselective epoxidation of simple alkenes with chiral salen-based **69** prepared in a two-step procedure from the readily available (*R*,*R*)- or (*S*,*S*)-1,2-diamino-1,2-diphenylethane **67** and the appropriate salicylaldehyde **66** (Scheme **22**).[32]



Scheme 22. Chiral salen **69** synthesis.

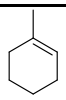
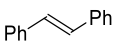
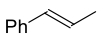
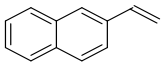
The reaction is performed under aerobic conditions using iodosylmesitylene **71** as the oxidant with 1-8% catalyst **69** loadings (Scheme **23**).



Scheme 23. Asymmetric epoxidation with chiral Mn-salen complexes.

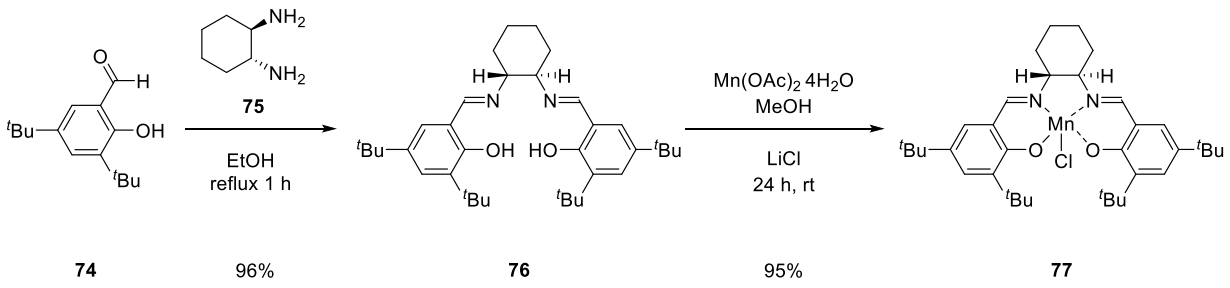
The product epoxides are formed in moderate *ee* with a wide range of tolerated substrates; including mono-, di- and tri-substituted alkenes (Table **3**).

Table 3. Substrate scope.

Entry	Substrate	Yield[a]/%	*ee*[b]/%
1		50	59
2		63	33
3		93	20
4		75	57
5		72	67

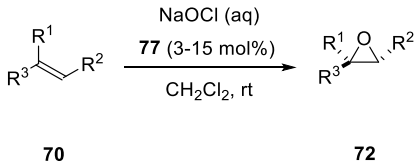
[a]Isolated yield after chromatographic purification. [b]*ee* was determined by ^{1}H NMR spectroscopy.

A year later, they improved the selectivity of the reaction by introducing a second set of *tert*-butyl groups in the *para*-position to the aromatic ring, and a 1,2-diaminocyclohexyl backbone. The catalyst **77** is prepared in a similar two-step procedure from the readily available di-*tert*-butylsalicylaldehyde **74** and 1,2-diaminocyclohexane **75** (Scheme **24**).



Scheme 24. Chiral salen complex **77**.

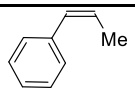
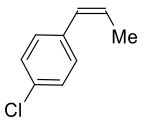
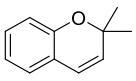
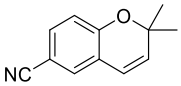
The reaction was carried out under aerobic conditions with bleach (NaOCl) as the oxidant with 3-15% catalyst **77** loading (Scheme **25**).



Scheme 25. Asymmetric epoxidation with chiral salen complexes.

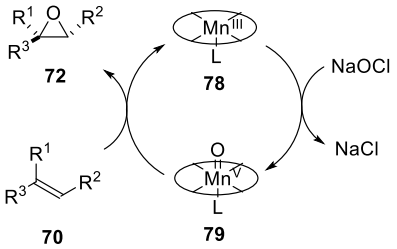
As shown in Table **4**, using catalyst **77**, the product epoxides were synthesised in excellent enantioselectivities (92–97% *ee*) from a variety of *cis*-disubstituted alkenes, providing a significant improvement on the enantioselectivities obtained using catalyst **69** (20–67% *ee*).

Table 4. Substrate scope.

Entry	Substrate	Yield[a]/%	*ee*[b]/%
1		84	92
2		67	92
3		72	98
4		96	97

[a]Isolated yield after chromatographic purification.[b]*ee* was determined by ^{1}H NMR spectroscopy or GC.

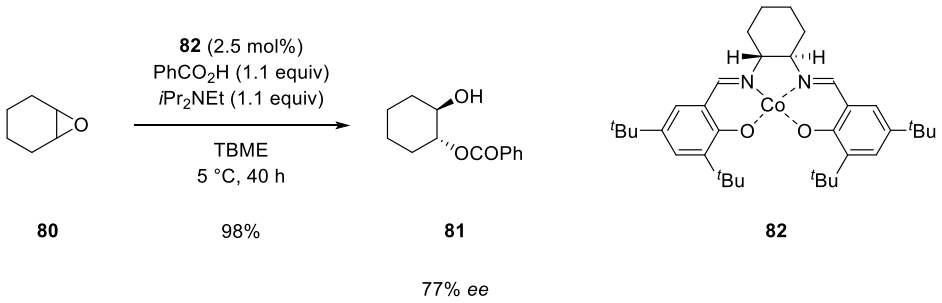
Both reactions are proposed to follow the same mechanism; the difference being the oxidant. A simplified catalytic cycle is shown in Scheme **26** where the reaction proceeds through a Mn^{V}-oxo-complex **79**.[15,32] Mn^{III} catalytic species **78** is oxidised by bleach to produce a molecule of NaCl and oxidised Mn^{V} species **79**, which is able to transfer the oxygen to the alkene **70**.



Scheme 26. Catalytic cycle for epoxide formation using Manganese.

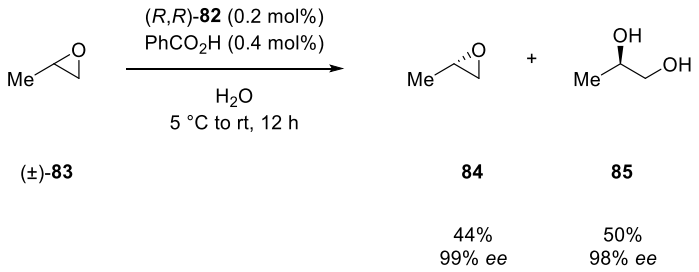
Whilst the transformation was effective for a number of substrate classes, low selectivities were observed using terminal alkenes as substrate. Alternative ligands for the selective epoxidation of terminal alkenes were not explored at that time. In an attempt to gain access to enantiopure terminal epoxides, Jacobsen developed a hydrolytic kinetic resolution (HKR) of racemic terminal alkenes using a chiral (salen)Co(II) catalyst **82** under acidic conditions.[33]

Previous work had shown that complex **82** can ring-open *meso*-epoxides such as **80** under acidic conditions in excellent yield (98%) with good enantioselectivity (77% *ee*) (Scheme **27**).[34]



Scheme 27. Ring-opening of *meso*-epoxides with **82**.

Application of this methodology to racemic terminal epoxide **83** provided evidence of a selective ring-opening procedure. Reaction of racemic epoxide **83** with chiral catalyst **82** under acidic conditions provided excellent results. Unreacted chiral epoxide **84** was isolated along with diol **85** in high *ee*'s of 99% and 98%, respectively (Scheme **28**). Switching to the other enantiomer of chiral catalyst **82**, allowed isolation of the opposite enantiomer of epoxide **84**.

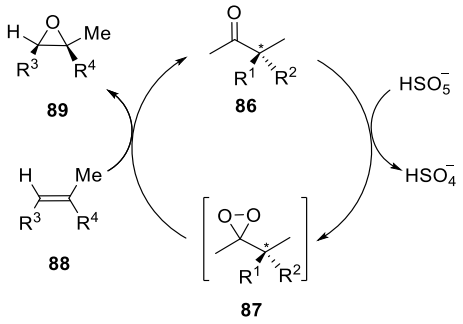


Scheme 28. Selective ring-opening of terminal epoxide **83**.

1.1.2.5 Epoxidations with dioxirane

The first asymmetric epoxidation of alkenes with *in situ* generated dioxirane was reported by Curci and co-workers in 1984.[35] They developed a new alkene epoxidation process using potassium peroxomonosulfate (oxone®) in the presence of chiral ketones.

Kinetic and ^{18}O-labelling experiments suggested that the epoxidation reaction proceeded *via* dioxirane intermediate **87**. Ketone **86** is oxidised by stoichiometric amounts of oxone® giving dioxirane intermediate **87** (Scheme **29**). Ketone **86** is then regenerated by selective epoxidation of alkene **88**. The overall process discovered by Curci provided an excellent opportunity for further reaction development.

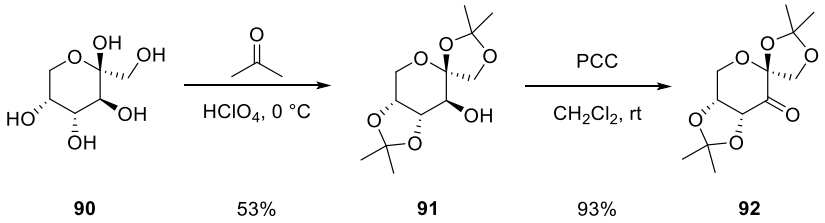


Scheme 29. Proposed mechanism for epoxide **89** formation through a dioxirane intermediate **87**.

1.1.2.5.1 Shi Epoxidation of *trans*-Alkenes

Inspired by Curci's work, Shi[16] developed an improved asymmetric variant of this reaction with a chiral ketone as the catalyst. A carbohydrate proved to be a good catalyst scaffold due to the fact that (a) they are chiral, inducing asymmetry in the reaction; (b) they are readily available and (c) they contain a high degree of oxygen substitution α to oxygen, activating the ketone through the inductive effect and (d) they have rigid conformations minimising epimerisation of stereogenic

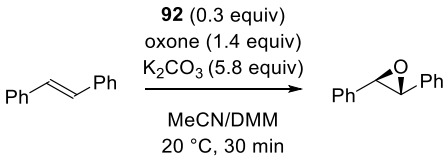
centres. With these factors in mind, they discovered ketone **92**, which was easily prepared from *D*-fructose **90**. Double diol protection of *D*-fructose **90** with acetone followed by PCC oxidation of the free hydroxyl group provided ketone **92** in a two-step procedure and in a 49% overall yield (Scheme **30**).[16]



90 53% **91** 93% **92**

Scheme 30. Synthesis of ketone **92**.

Asymmetric epoxidation using ketone **92** was attempted using *trans*-stilbene **1** as the test substrate. Although the epoxide **93** was formed in excellent enantiomeric excess (98% *ee*), further optimisation was carried out including pH, solvent and temperature. The optimal pH was found to be 10.5, which can be easily achieved by adding K_2CO_3 to the reaction mixture. Additional studies showed that a mixture of MeCN/DMM (1:2) at 20 °C provided the optimal solvents system for the epoxidation reaction (Scheme **31**).



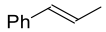
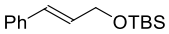
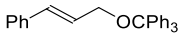
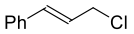
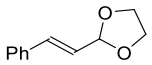
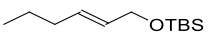
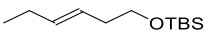
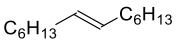
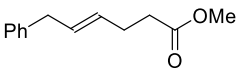
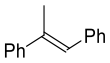
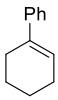
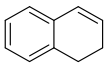
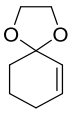
1 85% **93**

98% *ee*

Scheme 31. Shi epoxidation of *trans*-stilbene.

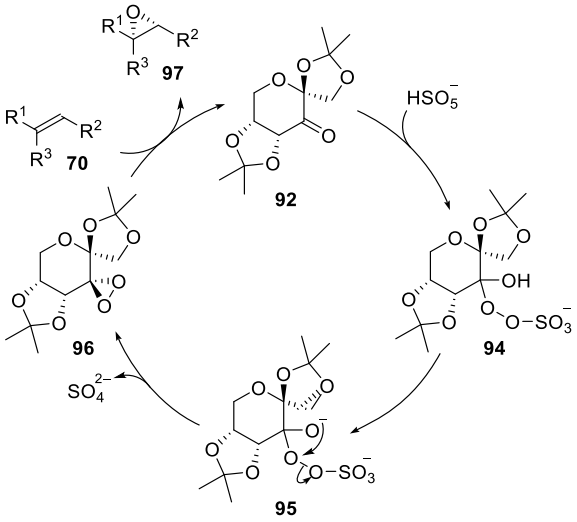
Using these conditions, a substrate scope was examined and the best results with *trans*-di-substituted and tri-substituted alkenes are shown in Table **5**. However, the reaction was not effective with *cis*-alkenes (Table **5**, Entries 12–13) and terminal alkenes (Table **5**, Entries 14–15) where moderate yields (43–95%) and/or *ee* (12–61%) were obtained.

Table 5. Substrate scope.

Entry	Substrate	Yield[a]/%	*ee*[b]/%
1		93	92
2		71	95
3		55	94
4		49	96
5		41	93
6		80	93
7		84	87
8		70	91
9		68	92
10		89	96
11		69	91
12		92	12
13		43	61
14		90	24
15		95	19

[a]Isolated yield after chromatographic purification.[b]*ee* was determined by HPLC, ^{1}H NMR spectroscopy or GC.

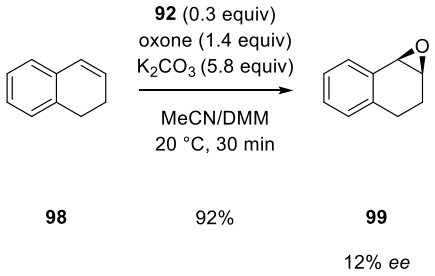
Based on these results, Shi proposed a plausible catalytic cycle for the formation of epoxides (Scheme **32**).[16] Ketone **92** reacts with oxone to give intermediate **94**. Deprotonation of the hydroxyl group provided alkoxide **95** which undergoes ring closure to form dioxirane **96**, with the loss of SO_4^{2-}. Dioxirane intermediate **96** is formed which is able to oxidise alkene **70**, to give epoxide **97**, releasing ketone **92** back into the catalytic cycle.



Scheme 32. Proposed catalytic cycle for the epoxidation reaction with ketone **92.**

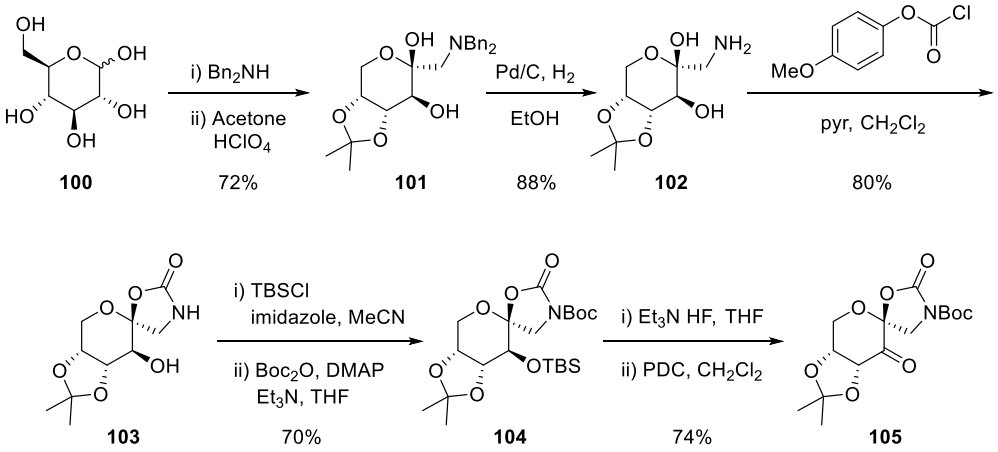
1.1.2.5.2 Shi Epoxidation of *cis*-Alkenes

Shi and co-workers further investigated the reasons behind the disappointing enantioselectivity observed with *cis*-alkene **98** in the epoxidation process (Scheme **33**) in the hope of finding a solution.



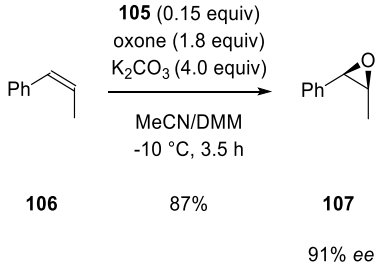
Scheme 33. Shi Epoxidation with ketone **92** with low *ee*.

Ketone **105** proved to be the key for the epoxidation of *cis*-alkenes.[36] Ketone **105** was synthesised through a nine-step procedure with a 26% overall yield (Scheme **34**). Synthesis of ketone **105** commenced by Amadori rearrangement[37] of carbohydrate **100** followed by diol protection to give intermediate **101**. Benzyl removal with Pd/C under a H_2 atmosphere followed by carbamate formation afforded cyclised product **103**. Then, alcohol TBS-protection and amine Boc-protection gave protected amine alcohol **104**. Finally, ketone **105** was isolated by TBS deprotection with HF followed by PDC oxidation.



Scheme 34. Synthesis of ketone **105**.

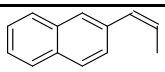
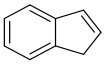
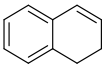
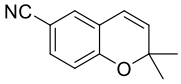
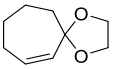
cis-β-Methylstyrene **106** was reacted with ketone **105** in the presence of oxone giving the epoxidised product **107** in 87% yield and 91% *ee* (Scheme **35**). This result highlighted the substrate specificity of this epoxidation as *trans-β*-methylstyrene did not undergo epoxidation under the same conditions.



Scheme 35. *cis-β*-Methylstyrene epoxidation.

High *ee* values were obtained for a number of cyclic and acyclic *cis*-alkenes using this catalyst; a selection of which are shown in Table **6**.[36]

Table 6. Substrate scope.

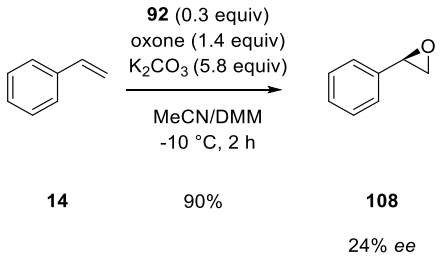
Entry	Substrate	Yield[a]/%	*ee*[b]/%
1		91	92
2		88	83
3		88	84
4		61	91
5		88	94

[a]Isolated yield after chromatographic purification.[b]*ee* was determined by HPLC or GC.

1.1.2.5.3 Shi Epoxidation of terminal alkenes

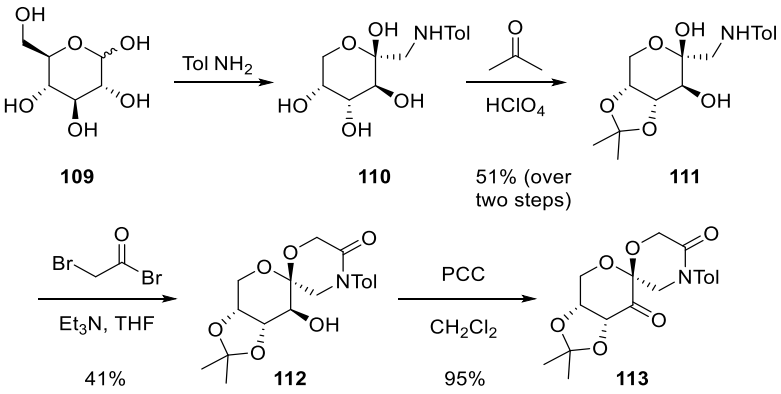
Despite the promising results for the enantioselective epoxidation of *trans*-alkenes and *cis*-alkenes with different chiral ketones, terminal alkenes still posed a considerable challenge. In 2008 Shi and co-workers successfully developed an epoxidation methodology for terminal alkenes.[38]

Epoxidation of terminal alkenes using ketone **92** was examined and resulted in poor levels of enantioselectivity (20–50% *ee*) despite the transformation giving the product in 90% isolated yield (Scheme **36**).



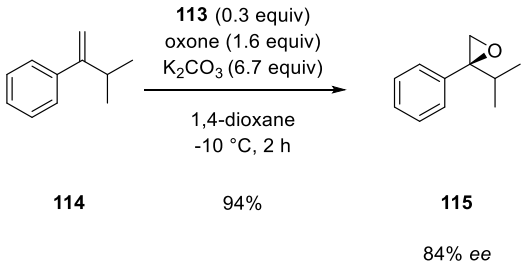
Scheme 36. Shi Epoxidation with ketone **92** with low *ee*.

Shi searched for a new catalyst that would favour epoxidation of terminal alkenes and ketone **113** was synthesised in four steps from *D*-glucose **109** in a 20% overall yield (Scheme **37**). Amadori rearrangement[37] of carbohydrate **109** followed by diol protection provided compound **111**. Lactam formation and PCC oxidation of the alcohol afforded desired product **113**.



Scheme 37. Synthesis of ketone **113**.

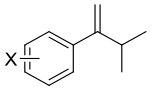
Initially, *α*-isopropylstyrene **114** was studied and, after optimisation, epoxide **115** was formed in an excellent 94% yield and 84% *ee* (Scheme **38**).



Scheme 38. Epoxidation of *α*-isopropylstyrene **114**.

Furthermore, other 1,1-disubstituted alkenes underwent epoxidation with good enantioselectivity (62–88% *ee*) (Table **7**). These results suggested that substrates with bulky alkyl groups in the *α*-position of the alkene gave high enantioselectivities in the reaction when compared to substrates which lacked bulky *α*-substituents. Substitution of the aryl group was also tolerated (74–88% *ee*) as shown in Table **7** entries 7–12.

Table 7. Substrate scope.

Entry	Substrate	Yield[a]/%	*ee*[b]/%
			
1	R = Me	60	62
2	R = Et	71	78
3	R = *n*-Pr	90	75
4	R = *i*-Bu	54	74
5	R = Cy	62	77
			
6	X = H	71	84
7	X = *p*-^{i}Pr	51	82
8	X = *p*-OMe	94	84
9	X = *p*-F	78	74
10	X = *p*-Br	68	78
11	X = *m*-F	74	81
12	X = *o*-F	72	88

[a]Isolated yield after chromatographic purification.[b]*ee* was determined by HPLC or GC.

Ultimately, Shi and co-workers developed procedures for the selective epoxidation of *trans*, *cis* and terminal alkenes, using different chiral ketones in each case (Figure **2**). The epoxide products can then be opened with oxygen nucleophiles resulting in the overall *anti*-dioxygenation of alkenes. Whilst providing a series of efficient methods a key limitation is the fact that only one enantiomer of the starting sugar is commercially available at a reasonable cost to make the process financially viable.

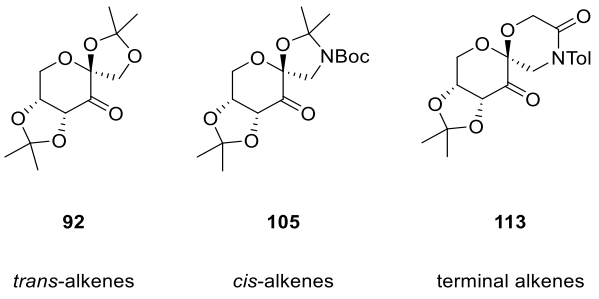


Figure 2. Shi chiral ketones for epoxidation of alkenes.

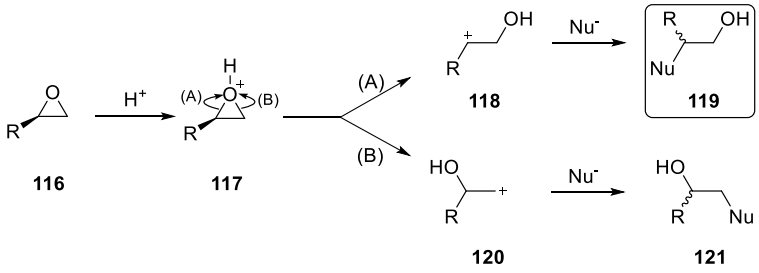
1.1.2.6 Ring opening of epoxides

The ring-opening of epoxides with a nucleophile provides access to a variety of *anti*-products.[39] The ring-opening reaction can proceed either by an S_N1 process, to give *syn*:*anti* mixtures, or through an S_N2 mechanism to give the product as a single stereoisomer. The mechanism of the ring-opening is highly dependent on the reaction conditions, the nature of the epoxide and the nucleophile.

1.1.2.6.1 Epoxide opening *via* S_N1 process

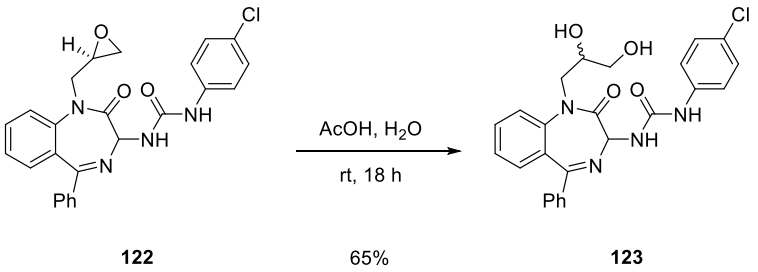
If the reaction proceeds under acidic conditions S_N1 is generally the dominant mechanism due to the fact that a protonated epoxide is more electrophilic and creates a better leaving group. In this case, weak nucleophiles are required such as H_2O or ROH.

For non-symmetrical epoxides, two different scenarios are possible (Scheme **39**). When epoxide **116** is protonated the epoxide can open to give a secondary carbocation **118** (path A) or to give a primary carbocation **120** (path B). Secondary carbocations are more stable than primary carbocations, therefore, the major product alcohol **119** is expected. Due to the fact that a planar carbocation **118** is formed and this can rotate about the σ-bond, an erosion of stereochemical integrity is expected.



Scheme 39. Mechanistic pathways for the ring-opening of epoxides *via* S_N1 reaction.

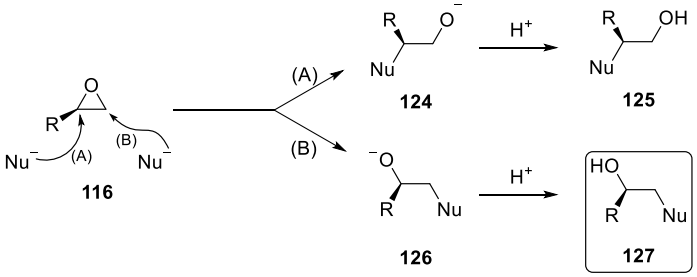
An example of an epoxide ring-opening under acidic conditions is shown in Scheme **40**.[40] This transformation was involved in the preparation of 1,4-benzodiazepine scaffolds **123**. Thus, treatment of the terminal epoxide of functionalised benzodiazepine **122** under acidic conditions provided 1,2-diol **123** as a mixture of diasteromers.



Scheme 40. Ring-opening epoxide under acidic conditions.

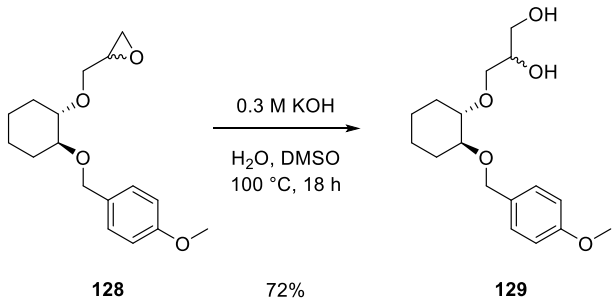
1.1.2.6.2 Epoxide opening v*ia* S_N2 process

If the reaction proceeds under basic conditions using strong nucleophiles such as RMgX, RLi, HO^-, S_N2 is the dominant mechanism observed. In this case, an alkoxide is the leaving group which is converted to an alcohol on acidic work-up. Similar to S_N1 conditions, non-symmetrical epoxides lead to two different possible products (Scheme **41**). A strong nucleophile can react through the most substituted carbon to give **124** (path A) or through the less substituted carbon to give **126** (path B). In this case, steric effects dominate and therefore the nucleophilic attack preferentially occurs at the less substituted carbon (path B).



Scheme 41. Mechanistic pathway for the ring-opening of epoxides *via* S_N2 reaction.

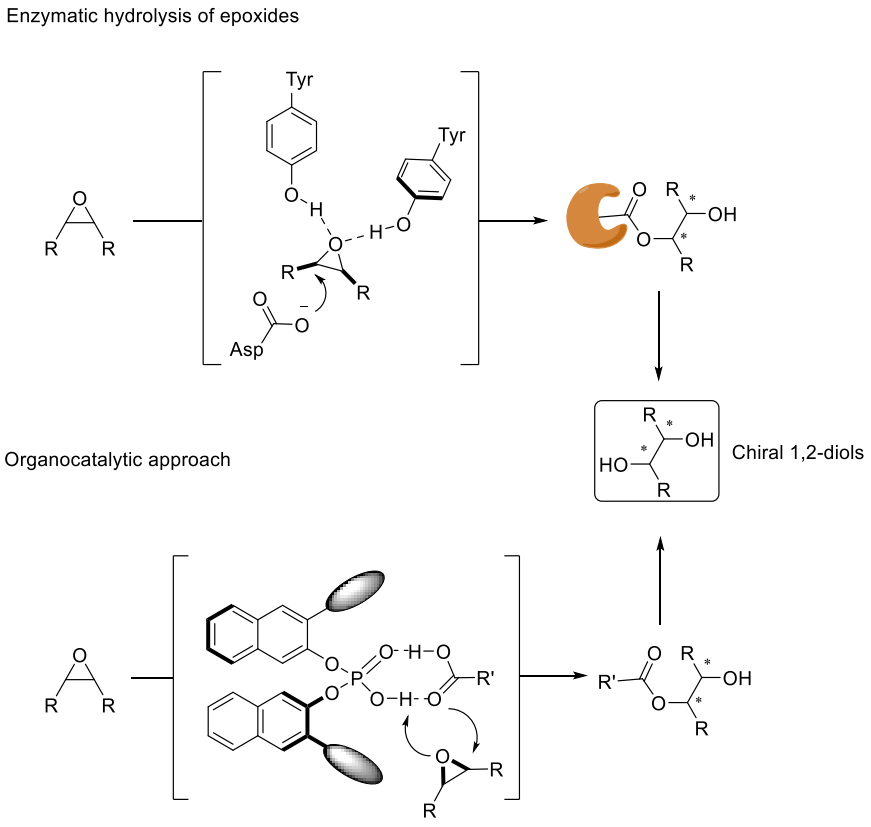
For example, Gilbert *et al.* reported a ring-opening of epoxide **128** under basic conditions (0.3 M KOH) for the synthesis **129** (Scheme **42**).[41] Thus, heating a 0.3 M solution of KOH with terminal epoxide **128** in DMSO provided the corresponding 1,2-diol product **129** in a good 72% yield as a racemic mixture.



Scheme 42. Example of S_N2 ring-opening epoxide.

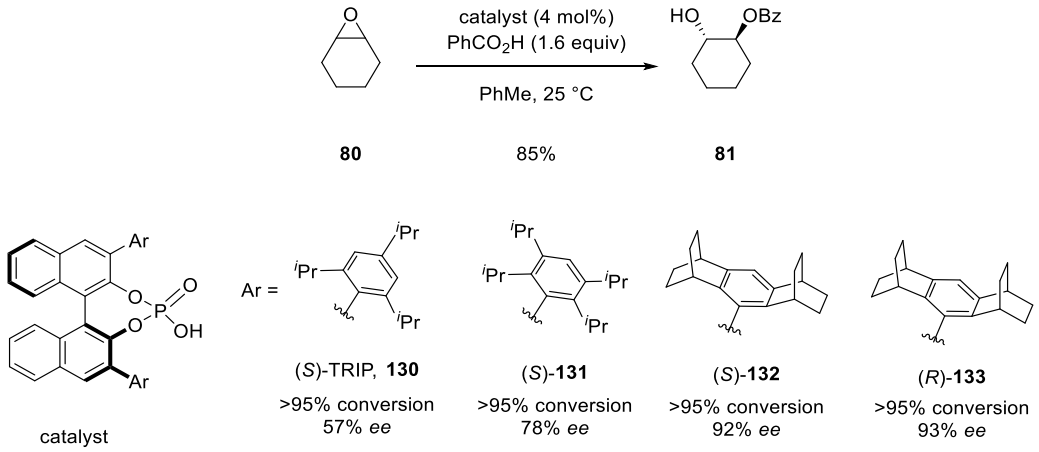
1.1.2.6.3 Organocatalytic asymmetric hydrolysis of epoxides

In a recent report, List described the hydrolytic ring opening of epoxides using a chiral phosphoric acid catalyst.[42] This methodology drew inspiration from an enzymatic process which involves a carboxylate nucleophile ring-opening (Scheme **43**).[43]



Scheme 43. Enzymatic and organocatalytic hydrolysis of epoxides.

List reported the first asymmetric hydrolytic ring-opening of epoxides under metal-free conditions.[42] For this, they focused on the ring-opening of cyclohexene oxide **80** with benzoic acid, using BINOL-derived phosphoric acids **130**–**133** as the catalysts (Scheme **44**).

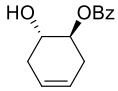
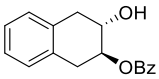
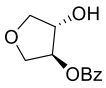
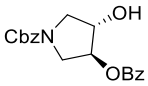
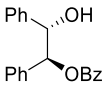


Scheme 44. Epoxide ring-opening with benzoate using phosphoric acids.

The reaction catalysed by (*S*)-TRIP **130** gave the desired product **81** (>95% conversion, 57% *ee*). With (*S*)-**131** the *ee* of the product was enhanced (>95% conversion, 78% *ee*). With the more bulky catalysts, (*S*)-**132** or (*R*)-**133**, the transformation proved to be even more selective (>95% conversion, 92–93% *ee*) (Scheme **44**).

With the optimised conditions, several *meso*-epoxides were examined, including cyclic (Table **8**, Entries 1–5) and acyclic (Table **8**, Entries 6–7) epoxides. It was found that heteroatoms were well tolerated (Table **8**, Entries 4–5). Unfortunately, this reaction was only examined with *meso*-epoxides. The related kinetic resolution of non-symmetrical epoxides has not been described using this system.

Table 8. Substrate scope.

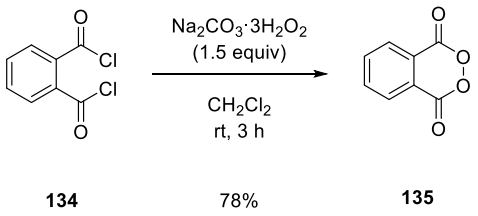
Entry	Product	Temperature/°C	Yield[a]/%	*ee*[b]/%
1		-5	86	87
2		-5	73	89
3		10	83	90
4		25	83	88
5		25	85	82

[a]Isolated yield after chromatographic purification.[b]*ee* determined by HPLC.

1.1.3 Metal-free methodologies

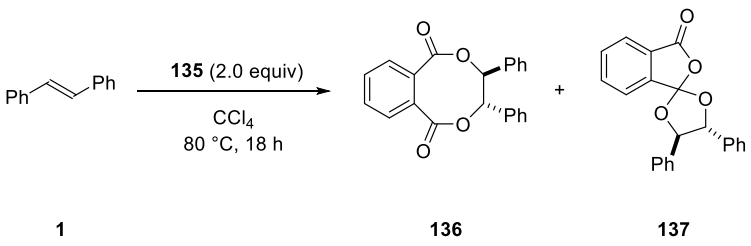
1.1.3.1 *Via* Peroxides

The use of peroxides in the dihydroxylation of alkenes provides a cleaner methodology when compared to metal-based precedents discussed before. For example, the use of phthaloyl peroxide **135** was studied in the early 1950s by Greene.[44] Phthaloyl peroxide **135** can be synthesised in one step from commercially available phthaloyl chloride **134** with sodium percarbonate added in one portion (Scheme **45**).[45] Phthaloyl peroxide **135** is highly shock sensitive and particulary dangerous. Therefore, it should only be used with special safety procedures by experienced chemists'.



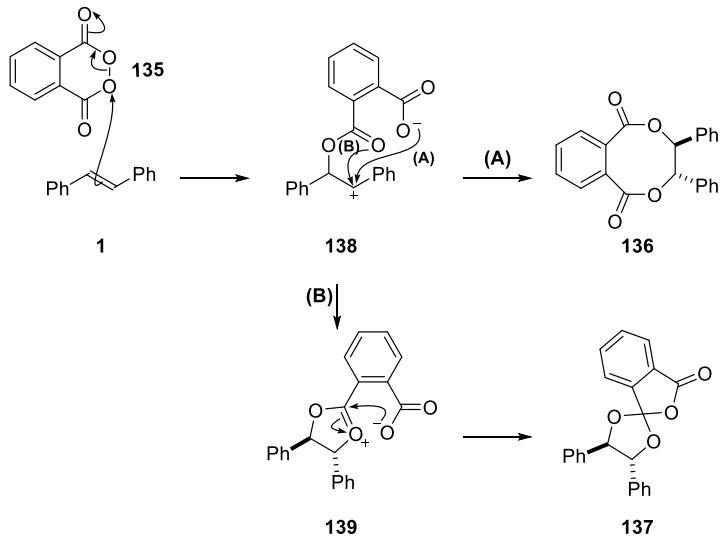
Scheme 45. Synthesis of phthaloyl peroxide **135**.

Greene developed a metal-free dioxygenation of alkenes using phthaloyl peroxide **135** which provided access to the eight-membered ring diester **136** and spirocyclic compound **137** (Scheme **46**). However, he did not extend this methodology further due to the extreme sensitivity of **135**.[44]



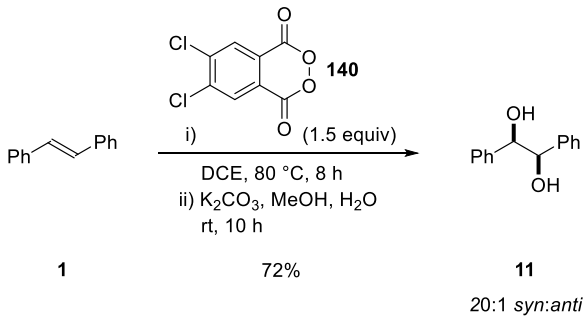
Scheme 46. Dioxygenation of alkenes with phthaloyl peroxide **135**.

Mechanistically, phthaloyl peroxide **135** is ring-opened through the labile O–O bond, to form a zwitterionic species **138** (Scheme **47**). At this stage, two pathways are possible. Route **A** allows the formation of an eight-membered ring **136**. But if route **B** occurs, dioxonium intermediate **139** is formed followed by ring-closure through the carboxylate to give stable spiroisobenzofuran compound **137**.



Scheme 47. Mechanistic pathway.

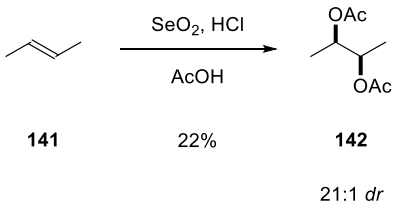
More recently, Siegel further extended this methodology using substituted phthaloyl peroxide **140** to provide access to *syn*-diol **11** with high levels of diastereoselectivity.[45] For example, treatment of *trans*-stilbene **1** with 1.5 equiv of phthaloyl peroxide **140** provided *syn*-diol **11** after basic hydrolysis in a *syn*:*anti* diastereoselectivity of 20:1 (Scheme **48**). The intermediates of this transformation were isolated and proved to be analogous to those that Greene reported, the eight-membered ring and the spirocyclic compound. Although the good results were obtained with phthaloyl peroxide **140**, the shock sensitive nature of **140** precluded any further studies.



Scheme 48. Siegel's dihydroxylation of alkenes with phthaloyl peroxide **140**.

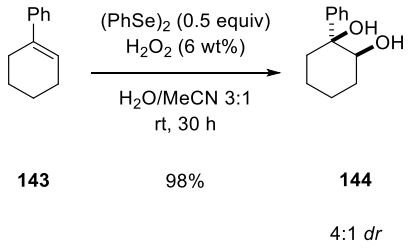
1.1.3.2 *Via* Selenium reagents

SeO_2 is used in organic chemistry as an oxidant as it can be reduced to Se(0) which precipitates and can be easily removed by filtration.[46] In the late 60s, Tsutsumi *et al.* reported a *syn*-dihydroxylation of alkenes using commercially available SeO_2 (Scheme **49**).[46] Treatment of alkene **141** with SeO_2 under acidic conditions provided the desired dioxygenated product **142**. Although the yields of this transformation were low (22%), the diastereoselectivities of the acetoxylated product **142** were high (*syn*:*anti* 21:1).



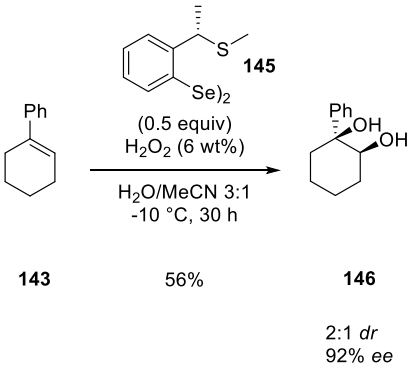
Scheme 49. Diacetoxylation of alkenes with SeO_2.

In 2008, Tiecco *et al.* developed a metal-free dihydroxylation of alkenes using diphenyl diselenide, $(PhSe)_2$, catalysis.[47] Organoselenium compounds are easily oxidised and this can promote the oxidation of organic molecules such as alkenes through catalysis. Treatment of alkene **143**, in the presence of catalytic amounts of $(PhSe)_2$, with H_2O_2 to oxidise the organoselenium compound, provided dihydroxylated product **144** in high yield (98%) and good diastereoselectivity (*syn*:*anti* 4:1) (Scheme **50**).



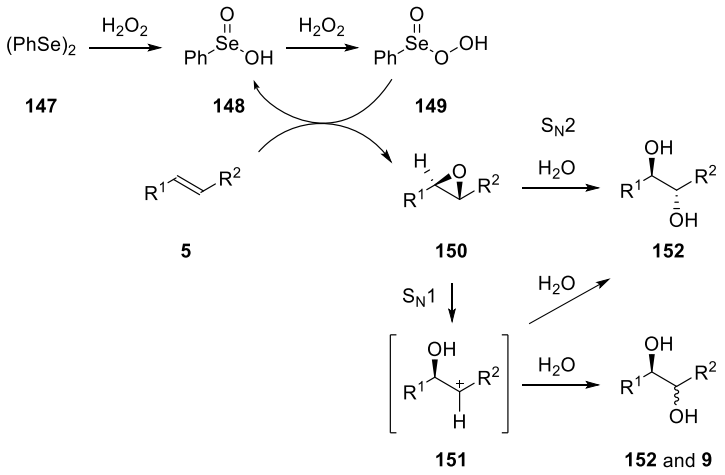
Scheme 50. Dihydroxylation of alkenes with SeO_2.

The reaction has the potential to be used with chiral organoselenium compounds providing enantiomerically enriched 1,2-diols. In the same paper, Tiecco *et al.* also reported a catalytic asymmetric dihydroxylation of alkenes using chiral diselenide **145** (Scheme **51**). Treatment of alkene **143** with chiral organoselenide **145** provided the desired 1,2-diol **146**. Although diastereoselectivity was low (*dr* 2:1) the enantioselectivity achieved was excellent (92% *ee*) under the reaction conditions employed. Despite the excellent results using this methodology for the preparation of enantiomerically pure 1,2-diols, the scope for this transformation did not explore the functional group tolerance.



Scheme 51. Asymmetric dihydroxylation of alkenes with chiral organoselenide **145**.

Mechanistically, diphenyl diselenide **147** is oxidised to perseleninic acid **149** (Scheme **52**). Then, alkene **5** is epoxidised by **150** providing **148** back to the catalytic cycle. At this stage, chiral organoselenium compounds could favour one of the faces of the alkene. Epoxide **150** can then be ring-opened by a molecule of H_2O to give *anti*-diol **152** through an S_N2 reaction. But, if epoxide **150** is ring-opened *via* S_N1 reaction, carbocation intermediate **151** would be formed giving *syn*-diol and *anti*-diol mixtures (**9** and **152**).

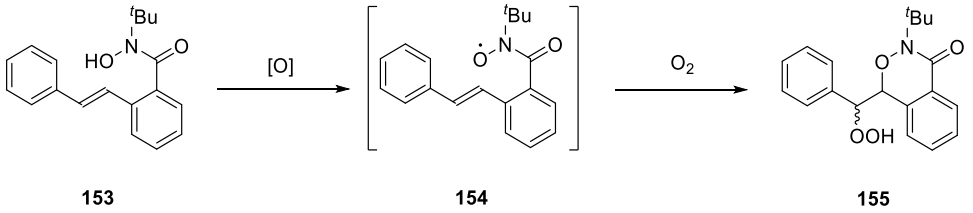


Scheme 52. Mechanistic pathway.

1.1.3.3 *Via* Hydroxamic acids

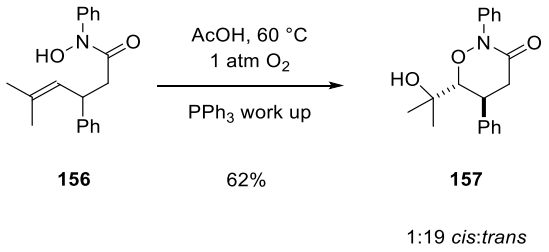
Most methods for the dihydroxylation of alkenes use transition-metal catalysts; however, Alexanian and co-workers have developed a metal-free approach using oxygen, a cleaner oxidant.[48] Alexanian based his work on the earlier studies of Perkins.[49]

Perkins observed an amidoxyl-radical cyclisation followed by oxygenation (Scheme **53**). Hydroxamic acid **153** underwent spontaneous oxidation and intramolecular cyclisation, followed by an oxygenation to give **155** as a mixture of diasteromers.



Scheme 53. Perkins spontaneous radical cyclisation.

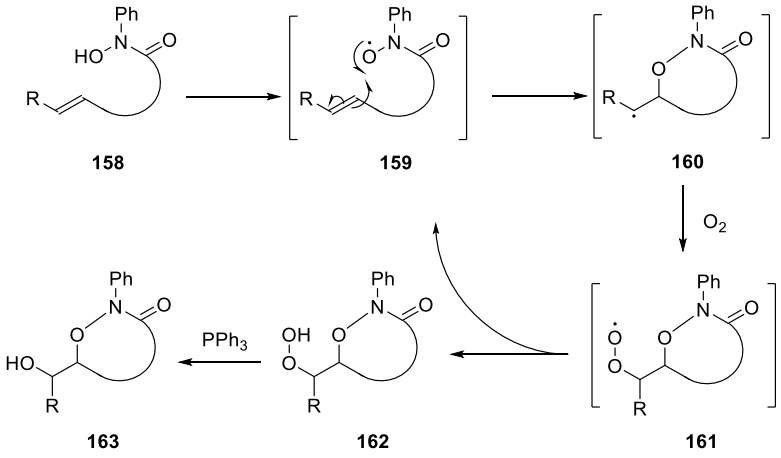
Given the previous results, Alexanian suggested that an alkene cyclisation with a tethered amidoxyl radical, formed *in situ* from *N*-aryl hydroxamic acid **156** in the presence of oxygen, could the desired cyclised product **157** (Scheme **54**).[48]



Scheme 54. Example of Alexanian's *anti*-dioxygenation reaction with hydroxamic acid **156**.

The reaction was performed on a range of substrates and it was found that the process tolerated a wide variety of alkenes including di-substituted substrates (62–88% yield), further substitution on the alkene moiety (62–79% yield), a conjugated alkene (63% yield) and an α-diallyl hydroxamic acid (75% yield).

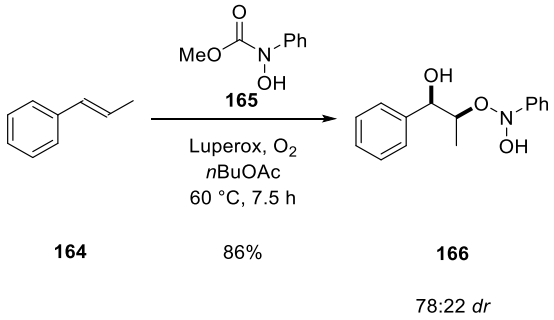
The proposed mechanism is shown in Scheme **55**, and is similar to that proposed by Perkins. The first step is the formation of the amidoxyl radical species **159**, which is followed by cyclisation, leading to another radical species **160**. This intermediate reacts with oxygen to form an alkylhydroperoxy radical **161**, which abstracts a hydrogen atom from the starting material to generate the alkylhydroperoxide **162**. The deoxygenated product **163** is formed by reduction of the product with PPh_3 or Me_2S. The 1,2-diol product can be obtained from a one pot reaction in which zinc reduces the N–O bond.



Scheme 55. Proposed mechanism for the intramolecular reaction.

Alexanian developed an intermolecular version for the *anti*-dioxygenation of alkenes using *N*-hydroxy *N*-phenyl carbamate **165** which avoids the need to synthesise the tethered hydroxamic acid **156** for the intramolecular cyclisation (Scheme **56**). High yields were obtained when terminal alkenes were tested (78–89%). In addition, with disubstituted alkenes the desired product was

obtained in good yield and moderate *syn*:*anti* selectivity (1:4.5). The corresponding diol can be obtained by N–O bond reduction of **166** with Zn metal (Scheme **56**).[50]



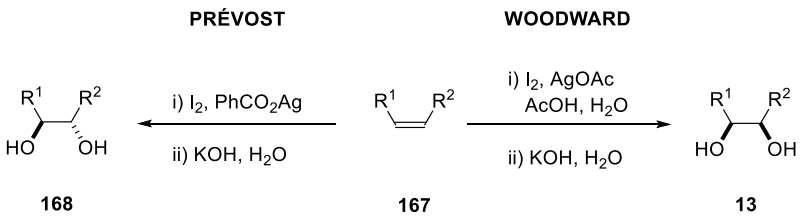
Scheme 56. Intermolecular *anti*-dioxygenation reaction with hydroxamic acids.

1.1.3.4 *Via* hypervalent iodine

The use of hypervalent iodine reagents has experienced rapid development in the past two decades.[51,52] This growing interest in iodine compounds is mainly due to the mild reaction conditions and the high selectivity observed in many reactions combined with the low toxicity and commercial availability of iodine species. Organic iodine^{III} and iodine^{V} are commonly used in organic chemistry as reagents for a number of selective oxidative transformations.

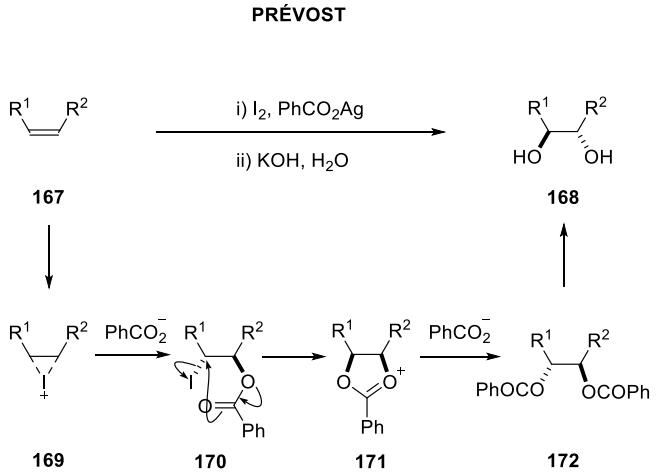
1.1.3.4.1 Prévost and Woodward reactions

The Prévost reaction allows the synthesis of *anti*-diols from alkenes by the addition of iodine followed by nucleophilic displacement with benzoate under anhydrous conditions in the presence of a silver salt.[53] By contrast, the Woodward reaction allows the synthesis of *syn*-diols from alkenes through a nucleophilic displacement of iodine with acetate in the presence of H_2O.[54] Hydrolysis of both intermediate diesters provides the corresponding diol **168** or **13** (Scheme **57**).

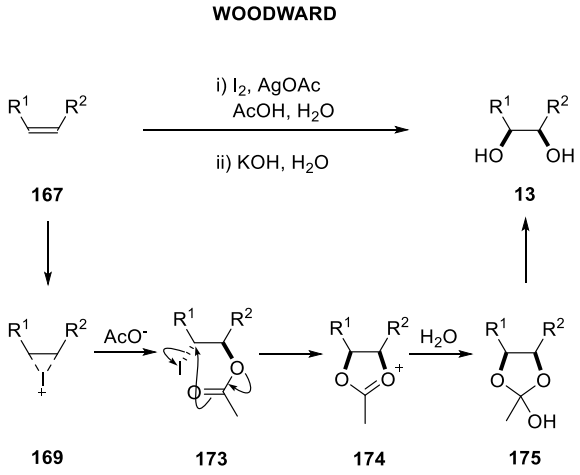


Scheme 57. Prévost and Woodward dihydroxylations.

Mechanistically, both reactions proceed through similar pathways (Scheme **58** and Scheme 59). In both cases, the initial addition of iodine to the alkene **167** leads to a cyclic iodonium ion **169**. The next step is ring opening with a nucleophile. In the Prévost reaction, the nucleophile is a benzoate anion to give **170**, whereas in the Woodward reaction an acetate anion is the nucleophile to give **173**. The oxygen of the carbonyl group then ring closes to give dioxonium species **171** or **174**. The regiochemistry of the ring opening of the common dioxonium species **171** or **174** results in divergence of the mechanisms and hence differing reaction products. With the Prévost reaction a second molecule of benzoate anion ring opens the dioxonium **171** to give the diester **172** with inversion of configuration, whereas in the Woodward variant H_2O hydrolyses the dioxonium intermediate **174** giving **175**. Finally, hydrolysis of both intermediates provides the diol **168** or **13**.



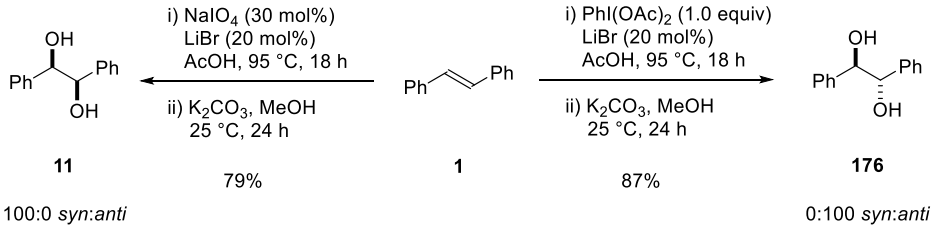
Scheme 58. Prévost mechanism for the dormation of *anti*-diols.



Scheme 59. Woodward mechanism for the formation of *syn*-diols.

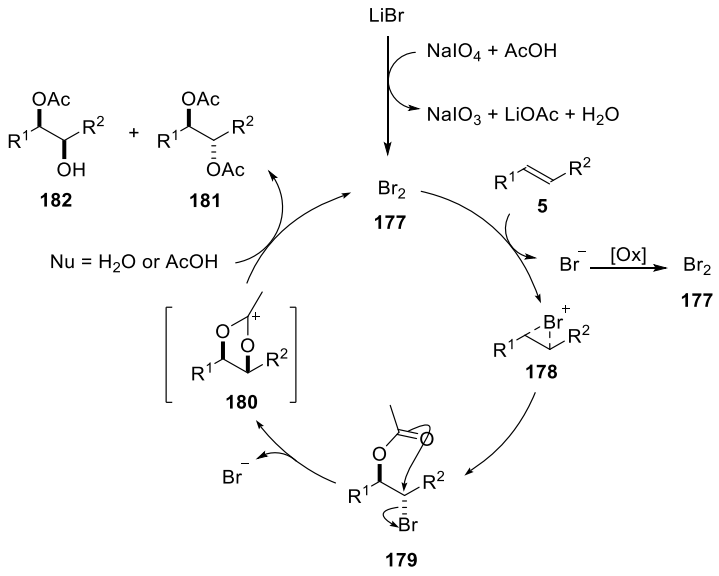
1.1.3.4.2 Prévost and Woodward variants

Sudalai[55] and co-workers developed a Prévost-Woodward variant which is highlighted for the simplicity, environmental friendliness and the readily accessible reagents used. They developed a practical and metal-free procedure for the dihydroxylation of alkenes catalysed by LiBr using commercially available $NaIO_4$ or $PhI(OAc)_2$ as the oxidant in AcOH to produce selectively the *syn*- **11** or the *anti*-diol **176**, respectively (Scheme **60**).



Scheme 60. Catalytic approach to the Prévost-Woodward dihydroxylation of alkenes.

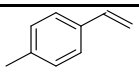
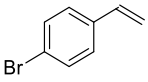
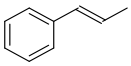
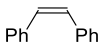
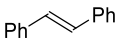
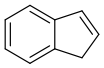
Mechanistically, they proposed an *in situ* oxidation of bromide to bromine **177** by $NaIO_4$ and AcOH. Bromine **177** then reacts with alkene **5** leading to cyclic bromonium ion **178** (Scheme **61**). AcOH can then ring open the cyclic bromonium ion **178** to get the *trans*-bromoacetate **179**. Dioxonium ion **180** is then formed and undergoes hydrolysis with H_2O to give the *syn*-hydroxy acetate **182**. Reaction with AcOH gives the *anti*-*bis*-acetate **181**. Both **181** and **182** are hydrolysed under basic conditions to give the corresponding diols.



Scheme 61. Proposed catalytic cycle for dihydroxylation.

Several alkenes were examined in this transformation: aliphatic, substituted styrene derivatives, allylic, disubstituted alkenes, *α,β*-unsaturated alkenes, with both electron-donating and electron-withdrawing groups each of which underwent *syn*-dihydroxylation with excellent yields and selectivity (Table **9**).

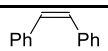
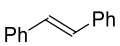
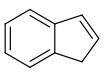
Table 9. Substrate scope.

Entry	Substrate	Yield[a]/%	dr[b]/*syn*:*anti*
1		89	-
2		90	-
3		84	88:12
4		87	99:1
5		79	100:0
6		87	98:2
7		85	-
8		83	92:8
9		86	-
10		86	90:10

[a]Isolated yield after chromatographic purification.[b]Diastereomeric ratios were determined by GC.

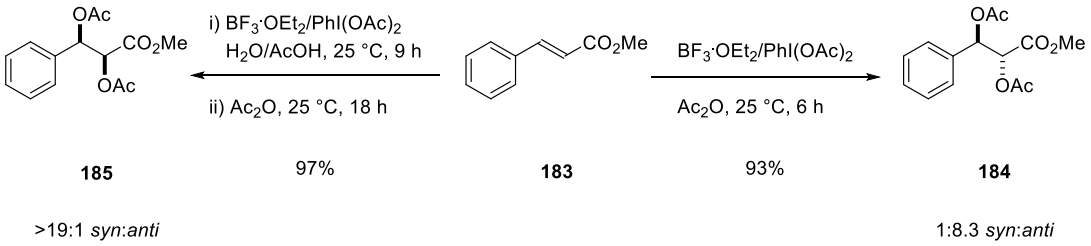
For the *anti*-dihydroxylation version (Scheme **60**), the reaction requires anhydrous conditions, and the catalytic $NaIO_4$ is replaced by $PhI(OAc)_2$ as the oxidant (Table **10**).

Table 10. Substrate scope.

Entry	Substrate	Yield[a]/%	dr[b]/*syn*:*anti*
1		84	0:100
2		87	0:100
3		79	0:100

[a]Isolated yield after chromatographic purification.[b]Diastereomeric ratios were determined by GC.

Li[56] and co-workers were working in the same field, and after extensive investigations they developed an efficient method for the diastereoselective diacetoxylation of alkenes mediated by $BF_3{\cdot}OEt_2$/PIDA inspired by the Prévost-Woodward reaction (Scheme **62**). This work avoids the need of the high temperatures used in Sudalai's procedure.



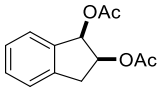
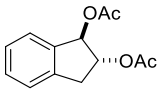
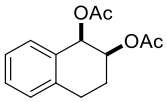
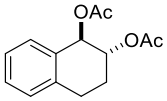
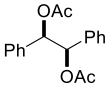
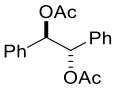
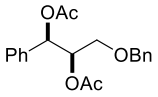
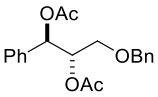
185 97% **183** 93% **184**

>19:1 *syn*:*anti* 1:8.3 *syn*:*anti*

Scheme 62. Selective dihydroxylation developed by Li.

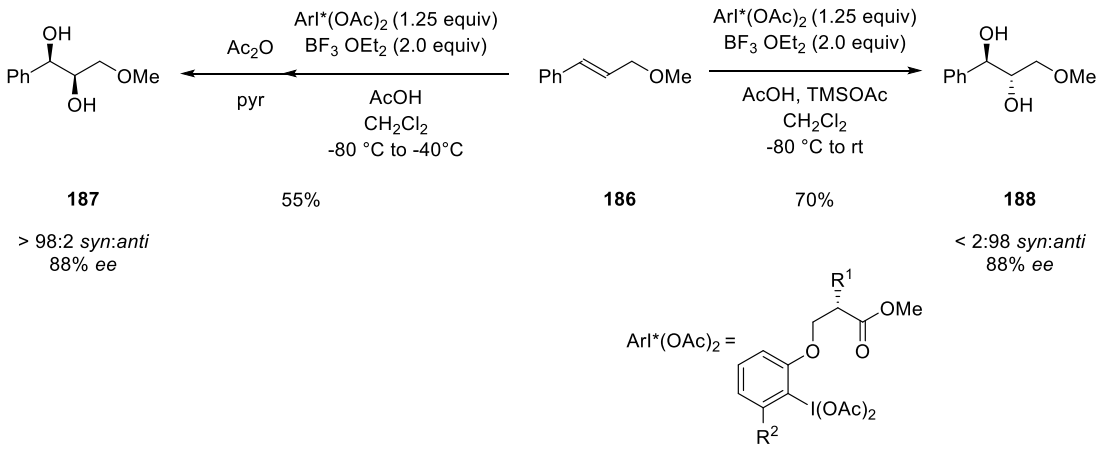
For example, indene reacted with catalytic amounts of $BF_3{\cdot}OEt_2$ and stoichiometric $PhI(OAc)_2$ in AcOH to give the *syn*-dioxygenated product in an excellent yield (93%) and selectivity (>19:1 *syn*:*anti*) (Table **11**, Entry 1). After optimisation, several types of alkenes were examined. A variety of terminal alkenes, styrene derivates bearing electron-donating or electron-withdrawing groups along with allyl benzyl ether can be oxidised smoothly to produce the diacetate products in high to moderate yields (Table **11**).

Table 11. Substrate scope.

Entry	Product	Yield[a]/%	dr[b]/*syn*:*anti*
1		93	>19:1
2		91	>1:19
3		80	9.1:1
4		90	1:17
5		76	12.5:1
6		72	1:1.4
7		70	>99:1
8		67	1:12.5

[a]Isolated yield. [b]Diastereomeric ratios were determined by ^{1}H NMR spectroscopy.

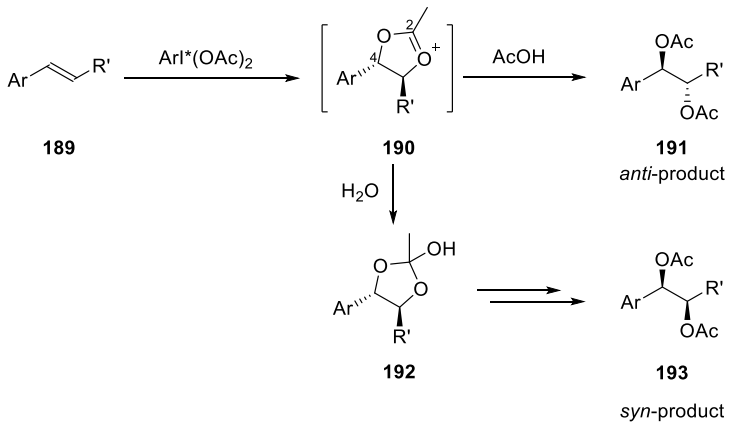
Fujita[57] and co-workers developed an enantioselective Prévost-Woodward reaction using a chiral hypervalent iodine(III) reagent (Scheme **63**). A complementary reaction was developed for the synthesis of both *syn*- **187** and *anti*-diol **188** through the use of TMSOAc.



Scheme 63. Metal-free enantioselective dihydroxylation of alkenes.

Reaction of alkene **186** with chiral hypervalent iodine in the presence of $BF_3{\cdot}OEt_2$, TMSOAc and AcOH at -80 °C afforded the *anti*-diol **188** in high levels of diastereo- and enantioselectivity (Scheme **63**). By contrast, without TMSOAc present, the *syn*- product **187** was isolated with excellent results after a subsequent acylation step.

The enantioselectivity of the reaction can be explained by considering the dioxonium species **190** similar to the intermediate proposed for the Prévost-Woodward reactions (Scheme **64**). Once dioxonium intermediate **190** is formed addition of H_2O at the 2-position results in formation of the *syn*-product **193**. In contrast, the *anti*-product **191** is formed *via* S_N2 ring opening of dioxonium intermediate **190** with AcOH or acetate. The configuration obtained for the *anti*-product indicates that the S_N2 reaction occurs at the benzylic position where a developing positive charge can be stabilised.

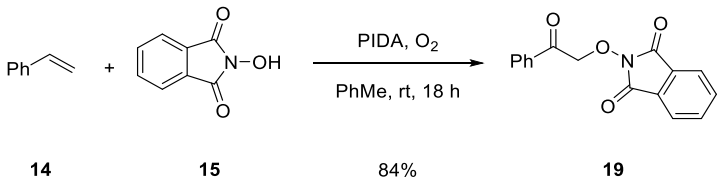


Scheme 64. Enantioselective Prévost-Woodward variant.

1.1.3.4.3 Alternative methodologies using I(III) and I(V)

Oxygen, one of the most abundant chemical elements in the earth's crust, would be a desirable reagent in organic reactions. In previous sections several metal-based and metal-free dioxygenation reactions have been described. Metal-free systems would be ideal as they should not have any of the associated toxicity issues. Since incorporation of oxygen atoms into alkenes represents an important transformation in order to synthesise biological active molecules, studies in this field are still on-going.

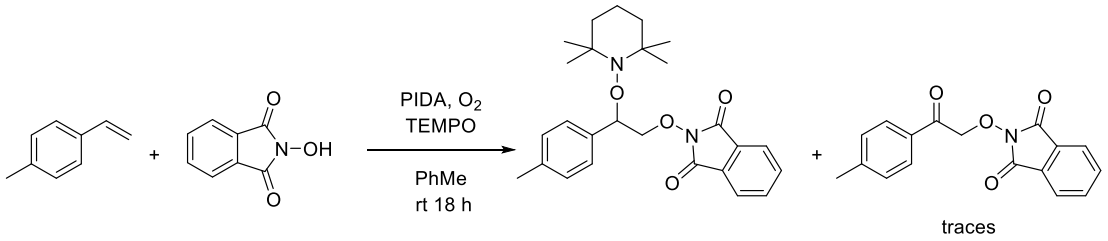
The use of phenyliodonium diacetate (PIDA) has been widely studied as an alternative to transition-metal containing systems. Recently, Adimurthy *et al.* developed a method for the synthesis of *α*-oxygenated ketones **19** from alkenes, such as **14**, using *N*-hydroxyphthalimide **15** with PIDA and molecular oxygen (Scheme **65**).[58]



14 **15** 84% **19**

Scheme 65. Metal-free synthesis of α-oxygenated ketones.

In order to understand the mechanism for this transformation, experiments using TEMPO under the optimised conditions were studied (Scheme **66**). These experiments supplied clear evidence that a radical mechanism was occurring in the reaction, as compound **195** was isolated in a 87% yield.

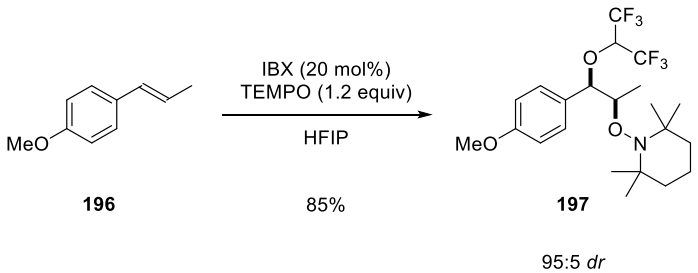


194 **15** 87% **195** **19**

Scheme 66. Mechanistic insights with TEMPO.

The use of TEMPO in organic chemistry has been thoroughly investigated as it is a stable radical trap.[59] Reactions such as the stereoselective aminooxygenation[60] and oxyarylation[61] have been applied using this chemistry; however dioxygenation had remained unsuccessful until last year.

Donohoe developed a protocol to effect the dioxygenation of alkenes using TEMPO with high levels of diastereoselectivily (Scheme **67**).[62] Reaction of alkene **196** with a catalytic amount of IBX and stoichiometric TEMPO in HFIP as the solvent provided the dioxygenated product **197** in good yield (85%) and excellent diastereomeric ratio 95:5.

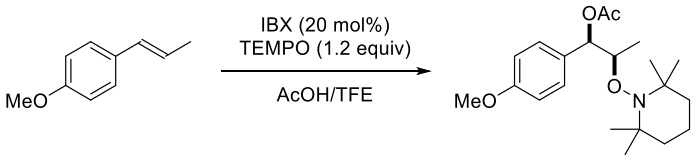


196 85% **197**

95:5 *dr*

Scheme 67. Using TEMPO in a dioxygenation reaction.

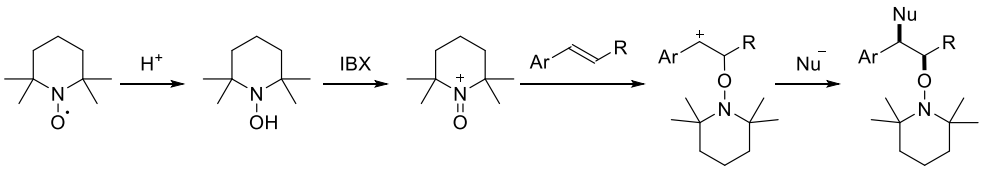
If the solvent is switched to a mixture of AcOH in TFE, an acetate group is incorporated into the final dioxygenated product **198** (Scheme **68**). In a similar fashion alkene **196** was treated with a catalytic amount of IBX and stoichiometric TEMPO using AcOH/TFE as the solvent providing the dioxygenated product **198** with incorporation of the acetate group at the benzylic position. Other carboxylic acids can also be used in order to introduce a variety of alcohol protecting groups at the benzylic position. The *syn*-disposition of the two new C–O bonds was confirmed by X-ray crystallography.



196 93% **198**

Scheme 68. Using TEMPO in a dioxygenation reaction with AcOH/TFE solvent.

Mechanistically, they proposed the generation of hydroxylamine **200** by proton abstraction of TEMPO (Scheme **69**) followed by IBX oxidation to give oxoamonium cation **201**. Benzylic carbocation **202** can then be formed which is trapped by a nucleophile affording **203**.



199 **200** **201** **202** **203**

Scheme 69. Mechanistic pathway.

This methodology provided access to *syn*-dioxygenated products from electron-rich alkenes with high levels of diastereoselectivity. Switching the solvent of the reaction afforded different protected benzylic alcohols.

1.2 Conclusions

In summary, several dioxygenation procedures have been described. The metal-based methods are valuable due to their high yields and excellent diastereoselectivities. However, due to the high toxicity and low natural abundance of many of the metals used, metal-free systems are highly desirable.

Although generation of *anti*-diols *via* epoxidation and ring opening involves a two-step procedure, the excellent results in terms of yield and enantiomeric excess, makes this a good strategy for the preparation of *anti*-diols. The Sharpless epoxidation gives high levels of enantioselectivity induced by DET, although allyl alcohols are required as starting material. Excellent results were obtained for the Jacobsen epoxidation, even terminal alkenes, in which kinetic resolution provided enantiopure epoxides. Shi asymmetric epoxidation requires different ketone catalysts to be synthesised (3–8 steps) depending on the nature of the alkene starting material (*cis*, *trans* or terminal).

Hydrogen peroxide or peroxy acids provide a safe and clean method for the synthesis of epoxides. A recent study by List provides another outstanding method to obtain *anti*-diols using chiral phosphoric acids as organocatalysts. However, this reaction only works for *meso*-epoxides. The use of phthaloyl peroxide provided access to dioxygenated alkenes, although the use of this peroxide is not widely explored due to the explosive nature of this compound.

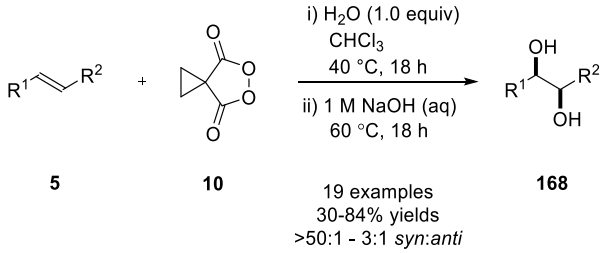
Selenium compounds, either selenium oxide or diphenyl diselenide, have been studied for the preparation of 1,2-diol moieties. However, application of this methodology is starting material restricted. The use of chiral diaryl diselenide compounds provides a strong metal-free method for the enantiomeric synthesis of this scaffold.

The use of hydroxamic acids as a source of dioxygenation of alkenes has two main advantages: no toxic metals are required and molecular oxygen is used as the sole oxidant. The scope of this methodology provided high yields of dioxygenated products although the use of Zn metal was required for the reduction of the N–O bond present in the product.

Due to the strong electrophilic nature of hypervalent iodine reagents they can be potentially attacked by a nucleophile. The excellent results obtained with these reagents provided a new strategy for the synthesis of 1,2-dioxygenated motifs without the need to use metals in the reaction.

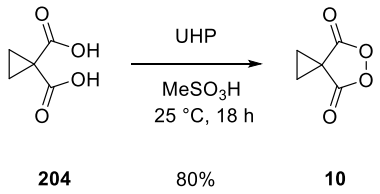
2 Previous Work by The Group

Additional work in the dihydroxylation field was carried out by Jones and Tomkinson.[63] They developed a successful procedure for the synthesis of *syn*-diols using malonoyl peroxides in a metal-free system with excellent diastereomeric ratios and yields (Scheme **70**).



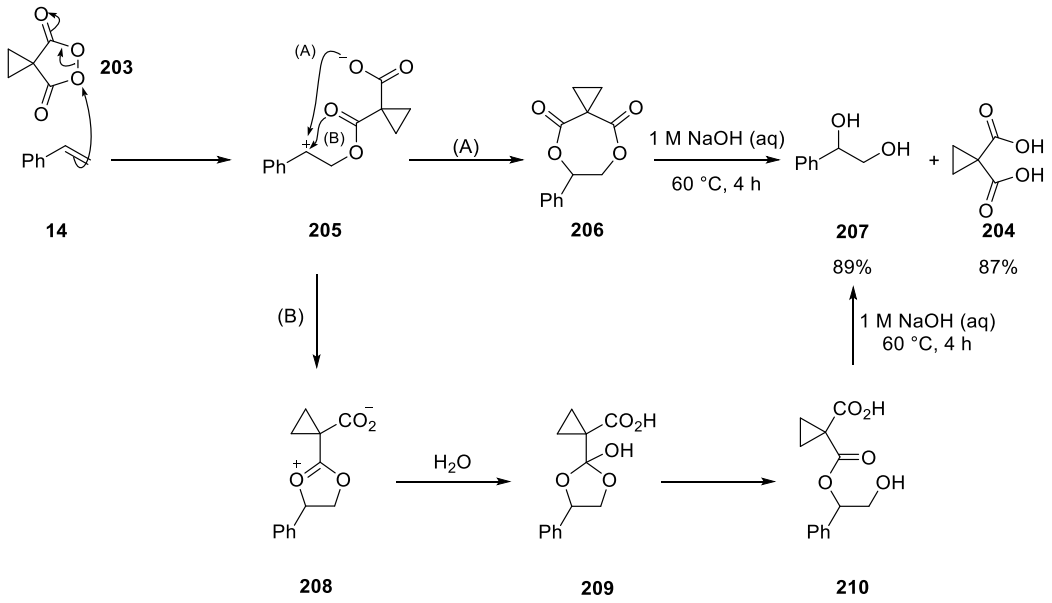
Scheme 70. *Syn*-dihydroxylation in metal-free conditions.

Malonoyl peroxide **10** can be easily prepared in one-step from the commercially available diacid **204** (Scheme **71**). Reaction of commercially available diacid **204** in the presence of UHP in methanesulfonic acid provided malonoyl peroxide **10** in good yield. The reaction is simple and proceeds under mild conditions.



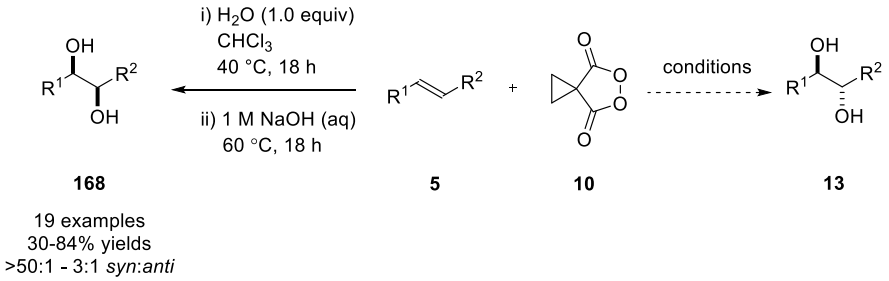
Scheme 71. Synthesis of malonoyl peroxide **10**.

Mechanistically, for the dioxygenation process they proposed a potential dioxonium intermediate **208** analogous to the Prévost-Woodward reaction (Scheme **72**). Treatment of styrene **14** with malonoyl peroxide **10** allowed the formation of zwitterionic species **205**. Then, two alternatives are possible. Route **A** follows the formation of a seven-membered ring **206** which, after hydrolysis, gives *syn*-diol **207**. Through route **B**, dioxonium intermediate **208** is formed and in the presence of a molecule of H_2O, an unstable hemihydrate **209** which breaks down to give the corresponding ester alcohol **210**. After hydrolysis, ester alcohol **210** leads to the diol **207**. Cyclopropane-1,1-dicarboxylic acid **204** can be recovered (87%) after hydrolysis.



Scheme 72. Proposed mechanism for the *syn*-dihydroxylation with malonoyl peroxide **10**.

With this in mind, and based on the reactivity of malonoyl peroxides, the possibility of developing a complementary *anti*-dihydroxylation was considered. According to the Prévost reaction, it is well documented that avoiding the presence of H_2O and using AcOH as the nucleophile within the reaction could lead to the *anti*-diol product **13** (Scheme **73**). Based upon this proposal, the project of this Ph.D started with the aim to develop a metal-free *anti*-dihydroxylation procedure.

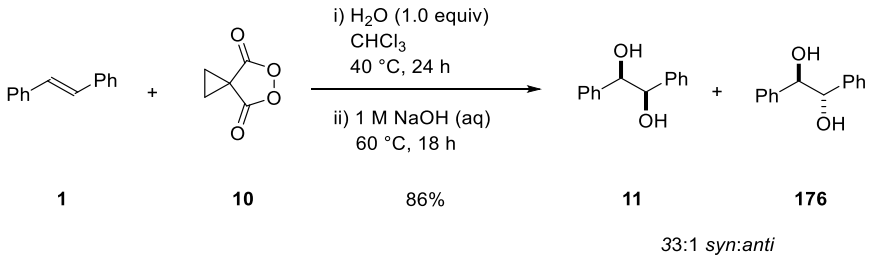


Scheme 73. Aim of the project: develop a complementary *anti*-dihydroxylation with malonoyl peroxide **10**.

3 Results and Discussion

3.1 Metal-free *syn*-Dihydroxylation reaction

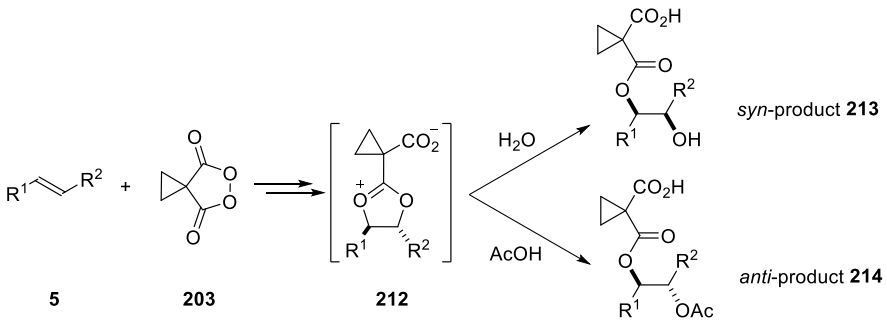
To confirm the reactivity of peroxide **10** as a reagent for the dioxygenation of alkenes, a literature reaction was repeated (Scheme **74**).[13] This reaction was developed by Jones in 2010.



Scheme 74. Metal-free *syn*-dihydroxylation.

trans-Stilbene **1** was treated with 1.2 equivalents of malonoyl peroxide **10** in the presence of H_2O (1.0 equiv) using $CHCl_3$ as the solvent (Scheme **74**). The mixture was stirred at 40 °C for 24 h. The crude reaction mixture was then hydrolysed using 1 M NaOH at 60 °C for 4 h to afford diol **11** in a 86% yield and a ratio *syn*:*anti* of 33:1, as determined by ^{1}H NMR spectroscopy of the crude reaction mixture. These results were identical to the literature precedent, showing that this reaction is robust and repeatable.

Once the *syn*-dihydroxylation was confirmed with similar results to literature precedent, a complementary *anti*-dihydroxylation of alkenes was investigated. Our initial hypothesis is outlined in Scheme **75**. The potential origin of the *anti*-diol **214** comes from the interception of the dioxonium intermediate **212** with AcOH, giving rise to the desired *anti*-product **214**. Whereas, the *syn*-product **213** could be formed by fortuitous H_2O present in the AcOH reagent.



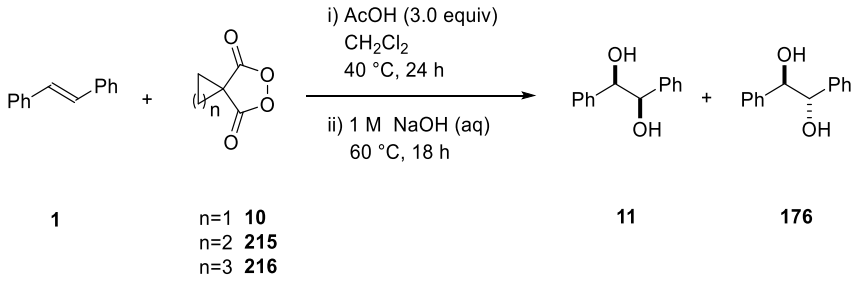
Scheme 75. *Syn*- and *anti*-dihydroxylation intermediates **213** and **214**.

3.2 *anti*-Dihydroxylation reaction

3.2.1 First set of optimisation conditions

3.2.1.1 Optimisation of the Malonoyl Peroxide

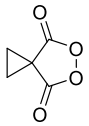
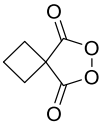
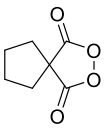
In the development of the *syn*-dihydroxylation procedure, it was found that the diastereomeric ratio could be altered through altering the peroxide structure[13,63] with larger spirocyclic ring sizes leading to reduced levels of stereoselectivity. We therefore examined the effect of **10**, **215** and **216** in the *anti*-dihydroxylation reaction of *trans*-stilbene **1** (Scheme **76**).



Scheme 76. *anti*-Dihydroxylation with alternative malonoyl peroxides.

trans-Stilbene **1** was chosen for optimisation. Cyclopropyl, cyclobutyl or cyclopentyl containing malonoyl peroxides **10**, **215** and **216** were examined, in the presence of 3.0 equiv of bench AcOH in CH_2Cl_2 at 40 °C for 24 h. Hydrolysis of the intermediate was carried out to give the 1,2-diol **11** and **176** (Scheme **76**). The *syn*:*anti* ratio of the products was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. The amount of 1,2-diol was not quantified.

Table 12. Results using alternative peroxides.

Entry	Peroxide		*syn*:*anti*[a]
1		**10**	1:7
2		**215**	1:8
3[b]		**216**	1:6

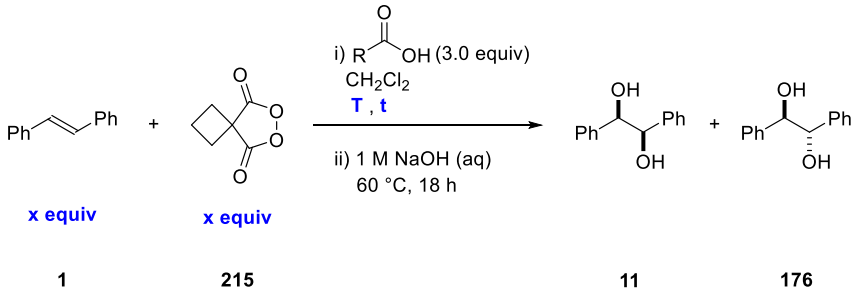
[a]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b]Using 3.0 equivalents of malonoyl peroxide **216**.

Two principal conclusions were drawn from these experiments. First, increasing the ring size resulted in an increase in the stereoselectivity of the process, with the cyclobutyl containing malonoyl peroxide **215** (Table **12**, Entry 2) showing increased amounts of the *anti*-diol **176** in the crude reaction mixture when compared to cyclopropyl containing malonoyl peroxide **10** (Table **12**, Entry 1). In addition, it was also observed that increasing the ring size decreased the apparent rate of reaction with 3.0 equivalents of the cyclopentyl containing malonoyl peroxide **216** (Table **12**, Entry 3) being necessary in order to push the reaction to completion inside 24 h. Based upon these results cyclobutyl containing malonoyl peroxide **215** was chosen for further optimisation studies.

3.2.1.2 Optimisation of variables

Following these results, a number of key variables were selected for further investigation. These included the number of peroxide equivalents, the number of alkene equivalents, temperature and time. The results from these investigations are contained in Table **13** with alkene **1** as the starting material since it is a cheap and commercially available chemical.

Table 13. Reaction optimisation.



Entry	1 (equiv)	10 (equiv)	Time/h	Temp/°C	R	Conv[a]/%	*syn*:*anti*[a]
1	1.0	1.5	24	40	Me	72	1:8
2	1.0	1.5	48	40	Me	56	1:7
3	1.0	1.5	24	50	Me	64	1:8
4	1.0	2.0	24	40	Me	82	1:10
5	1.0	2.5	24	40	Me	90	1:6
6	2.0	1.0	24	40	Me	-	1:6
7	1.0	2.0	24	40	Ph	73	1:9
8	1.0	2.0	24	40	*p*-MeO-Ph	65	1:9
9	1.0	2.0	24	40	*p*-NO_2-Ph	77	1:8

[a]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

When *trans*-stilbene **1** was treated with 1.5 equivalents of malonoyl peroxide **215** at 40 °C for 24 h (Table **13**, Entry 1), the reaction was found to proceed in 72% conversion and with a *syn*:*anti* selectivity of 1:8, as determined by ^{1}H NMR spectroscopy of the crude reaction mixture. When the same reaction was run for 48 h (Table **13**, Entry 2) the conversion was found to decrease (56%). This drop in conversion is believed to be due to product decomposition. At this stage however, we were more concerned with the stereoselectivity of the reaction and elected to continue the screening process with this reaction set up. Increasing the temperature to 50 °C (Table **13**, Entry 3) showed no improvement in the stereoselectivity (1:8 *syn*:*anti*).

When *trans*-stilbene **1** was treated with 2.0 equivalent of cyclobutyl-containing malonoyl peroxide **215** (Table **13**, Entry 4) the conversion increased (82%) and, more importantly, the stereoselectivity was enhanced to 1:10 *syn*:*anti*. Encouraged by the results obtained using 2.0 equivalents of malonoyl peroxide **215**, 2.5 equivalents were used (Table **13**, Entry 5), resulting in a higher conversion of 90% but the *syn*:*anti* ratio dropped to 1:6. Finally, using an excess of the alkene (2.0 equiv) (Table **13**, Entry 6) did not lead to any further improvement (1:6 *syn*:*anti*).

The next parameter to be investigated was the effect of the acid source. To this end, three different benzoic acids were examined (Table **13**, Entries 7–9). For benzoic acid the conversion reached 73% conversion after 24 h with a 1:9 *syn*:*anti* ratio. When 4-methoxybenzoic acid was used, the ratio was not improved (1:9 *syn*:*anti*) and the conversion dropped to 65%. 4-Nitrobenzoic acid did not give any enhancement to the reaction profile either. Therefore, AcOH was chosen as the most suitable acid for further investigation due to atom economy.

After an extensive optimisation of the *anti*-dihydroxylation reaction with malonoyl peroxide **215**, a conclusion was extracted: malonoyl peroxide **215** was not optimal for this transformation. Fluctuations in the conversion rates and capricious results when the reactions were repeated under the same reaction conditions provide evidence that malonoyl peroxide **215** was not the appropiate oxidant for this transformation. Therefore, the use of cyclobutyl containing malonoyl peroxide **215** was abandoned for this reaction. Instead, cyclopropyl containing malonoyl peroxide **10** was used in the next set of optimisations with AcOH as the acid source.

3.2.2 Second set of optimisation conditions

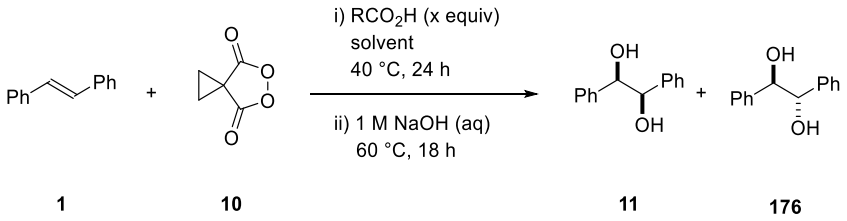
The alkene used for the optimisation was *trans*-stilbene **1** since it is a cheap and commercially available chemical. The first reaction involved treatment of *trans*-stilbene **1** with malonoyl peroxide **10** under standard *syn*-dihydroxylation conditions in the presence of AcOH instead of H_2O (Table **14**, Entry 1) achieving an *anti*:*syn* ratio of 1:2. This was an encouraging result and provided a strong indication the reaction outcome could be altered through modification

of the reaction medium. Next, $CHCl_3$ was replaced by AcOH as the reaction solvent (Table **14**, Entry 1, *anti*:*syn* 2:1) yielding the *anti*-diol **176** as the major product and through pre-drying the solvent, the selectivity improved (Table **14**, Entry 3, *anti*:*syn* 4:1).

Examination of different solvents showed that less polar solvents improved the stereochemical outcome (Table **14**, Entries 4–6) and CH_2Cl_2 was chosen as the best solvent under the optimised conditions. Increasing the number of equivalents (2.0 equiv) of AcOH showed an improvement in the diastereoselectivity to an *anti*:*syn* ratio of 7:1 (Table **14**, Entry 7). Increasing the amount of AcOH further did not provide any enhancement to the reaction outcome (Table **14**, Entries 8–9). Addition of acetic anhydride to the reaction mixture was examined, and no significant change in the selectivity was observed (Table **14**, Entry 10, *anti*:*syn* 6:1).

The number of equivalents of malonoyl peroxide **10** was also studied. It was found that 1.5 equiv of **10** were optimal with an excellent yield and good selectivity (Table **14**, Entry 11, *anti*:*syn* 7:1, 92%). Introduction of different carboxylic acids made no significant difference in the selectivity of the reaction (Table **14**, Entries 14–15). Therefore, based on this screening, Entry 11 was chosen as the optimal reaction conditions.

Table 14. *anti*-Dihydroxylation reaction optimisation.[a]



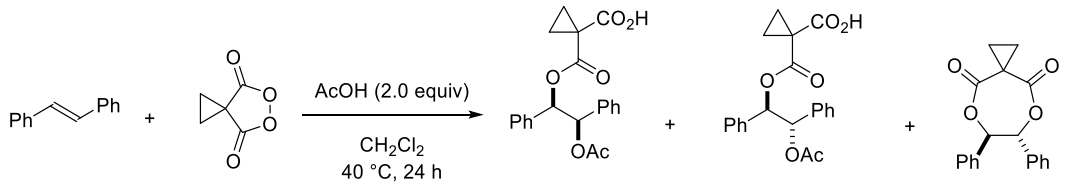
1 **10** **11** **176**

Entry	Solvent	R	RCO_2H (equiv)	10 (equiv)	Yield (%)[b]	*syn*:*anti*[c]
1	$CHCl_3$	Me	1.0	1.2	78	2:1
2	AcOH	Me	35	1.2	66	1:2
3[d]	AcOH	Me	35	1.2	43	1:4
4	CH_2Cl_2	Me	1.0	1.2	78	1:6
5	PhMe	Me	1.0	1.2	72	1:4
6	THF	Me	1.0	1.2	43	1:1
7	CH_2Cl_2	Me	2.0	1.2	72	1:7
8	CH_2Cl_2	Me	3.0	1.2	77	1:5
9	CH_2Cl_2	Me	5.0	1.2	75	1:5
10[e]	CH_2Cl_2	Me	2.0	1.2	77	1:6
11	**CH_2Cl_2**	**Me**	**2.0**	**1.5**	**92**	**1:7**
12	CH_2Cl_2	Me	3.0	1.5	95	1:6
13	CH_2Cl_2	Me	2.0	2.0	91	1:6
14	CH_2Cl_2	Ph	2.0	1.5	75	1:6
15	CH_2Cl_2	4-$MeOC_6H_4$	2.0	1.5	68	1:6

[a]All reactions were performed in duplicate with *trans*-stilbene (1.0 mmol) at 0.5 M concentration. [b]Isolated yield after column chromatography. [c]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d]Bench AcOH was used for entries 1 and 2. In entries 3−15, the acid was dried over 3 Å molecular sieves prior to use. [e]0.7 equiv Ac_2O added.

3.2.3 *anti*-Dihydroxylation reaction intermediates

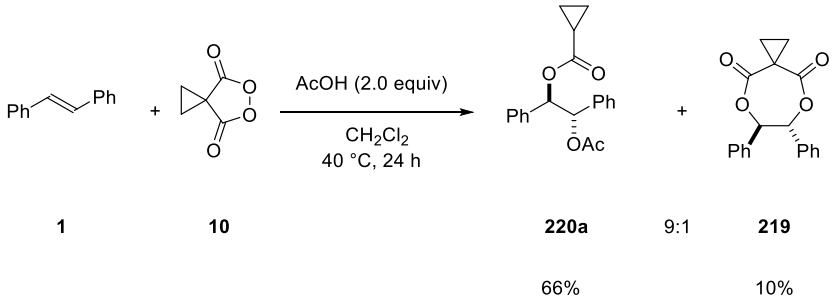
With the optimal conditions developed, we were interested in determining the reaction intermediates with a view to further improving the results. For this, reaction of *trans*-stilbene **1** with malonoyl peroxide **10** in the presence of AcOH in CH_2Cl_2 at 40 °C for 24 h afforded a mixture of three possible compounds. It was believed that intermediates shown in Scheme **77**, carboxylic acids, *syn*-**217** and *anti*-**218**, along with the seven-membered ring diester **219** were accessible under the reaction conditions used.



1 **10** **217** **218** **219**

Scheme 77. *anti*-Dihydroxylation intermediates according to the *syn*-dihydroxylation.

We believed two of the proposed intermediates **217** and **218**, containing a carboxylic acid, should be easily separated from the seven-membered ring diester **219** with a basic workup. However, this was unsuccessful, suggesting that the reaction intermediate did not contain a free carboxylic acid. Silica gel flash chromatography was required for the separation of the products. After purification, the major product proved to be **220a** (66%), the decarboxylated version of **218**, and the minor product was the seven-membered ring diester **219** (10%) (Scheme **78**). Therefore, the *anti*-dihydroxylation occurs with decarboxylation in a 9:1 ratio with seven-membered ring formation (**220a**:**219**) as determined by ^{1}H NMR spectroscopy of the crude reaction mixture. Purity of *anti-bis*-ester **220a** was confirmed by GC-MS to be 1:35 (*syn*:*anti*) *anti-bis*-ester **220a** (Figure 3).



Scheme 78. *anti*-Dihydroxylation intermediates, **220a** and **219**.

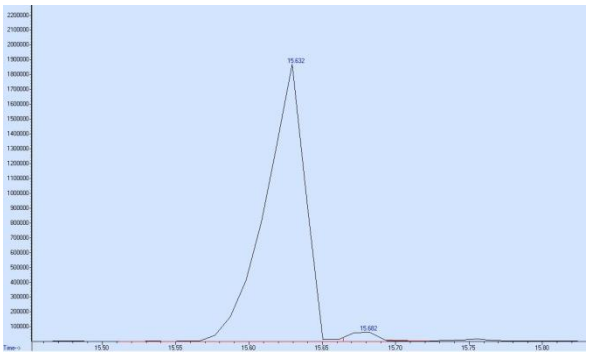
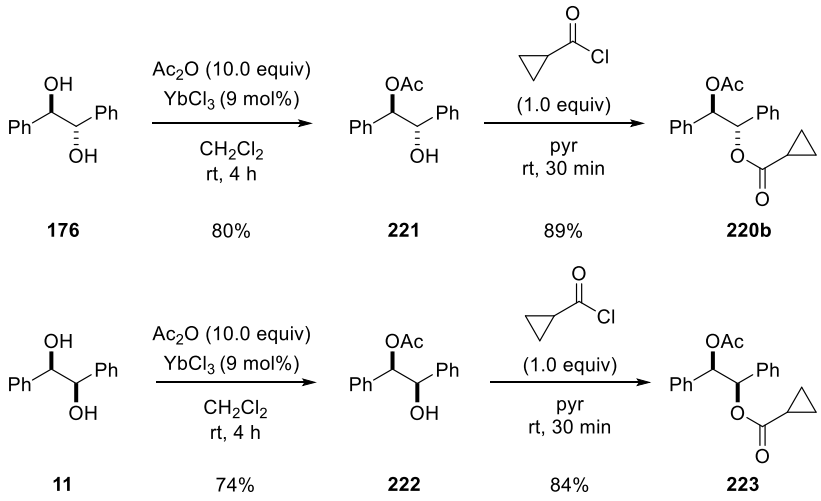


Figure 3. GC-MS of *anti-bis*-ester **220a** after purification.

It is worth noting, in the *anti*-dihydroxylation procedure the reaction proceeds with decarboxylation of malonoyl peroxide **10**, which does not happen in the *syn*-dihydroxylation protocol. We believed this is due to the nucleophilicity of H_2O compared to AcOH. AcOH is much less nucleophilic than H_2O and the attack on dioxonium intermediate **212** (Scheme **75**) will therefore be much slower, allowing time for decarboxylation of **212** to give *anti-bis*-ester **220a**.

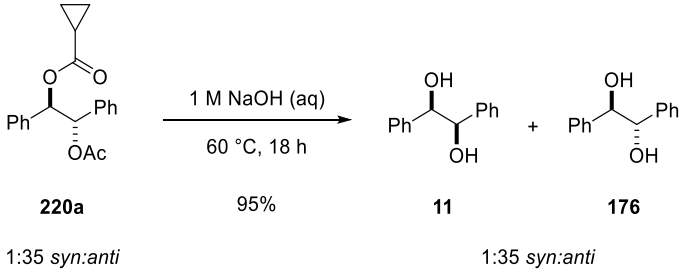
Samples of *anti-bis*-ester **220a** and *syn-bis*-diester **223** were independently synthesised[64] (Scheme **79**) in order to unequivocally assign the product obtained in our *anti*-dihydroxylation.

Thus, monoacetylation reaction of commercially available *syn*-diol **11** and *anti*-diol **176** followed by ester formation of the second alcohol with cyclopropanecarbonyl chloride provided the corresponding *syn*- and *anti*-*bis*-esters **223** and **220b**.[64] Comparing both *bis*-esters, **223** and **220b**, with the product isolated from the *anti*-dihydroxylation intermediate step **220a**, it was confirmed that *anti*-*bis*-ester **220a** was the product obtained.



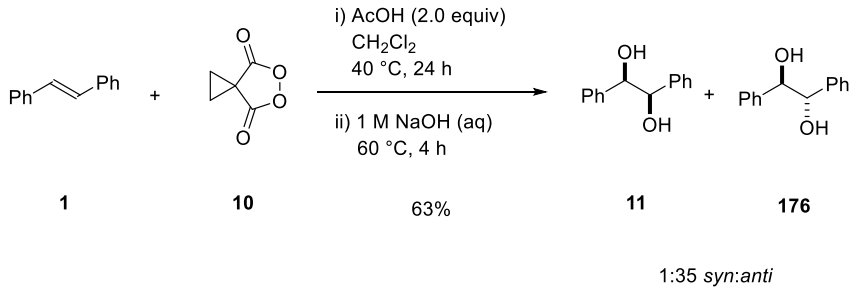
Scheme 79. Independent synthesis of potential intermediates.

Once the intermediates **220a** and **219** from the *anti*-dihydroxylation reaction had been identified and the relative stereochemistry determined through independent synthesis, *anti*-*bis*-ester **220a** was then hydrolysed under standard reaction conditions (1 M NaOH, 60 °C, 18 h) (Scheme **80**).



Scheme 80. Hydrolysis of *anti*-*bis*-ester **220a**.

Hydrolysis of *anti*-*bis*-ester **220a** (1:35 *syn*:*anti*) was carried out without compromise of the levels of diastereoselectivity delivering the *anti*-diol **176** (95%; 1:35 *syn*:*anti*). This level of selectivity was comparable to the *syn*-dihydroxylation reaction.[63] Thus, an *anti*-dihydroxylation had been successfully developed using a two-step procedure under metal-free conditions with an overall yield of 63% and an excellent 1:35 *syn*:*anti* selectivity (Scheme **81**).

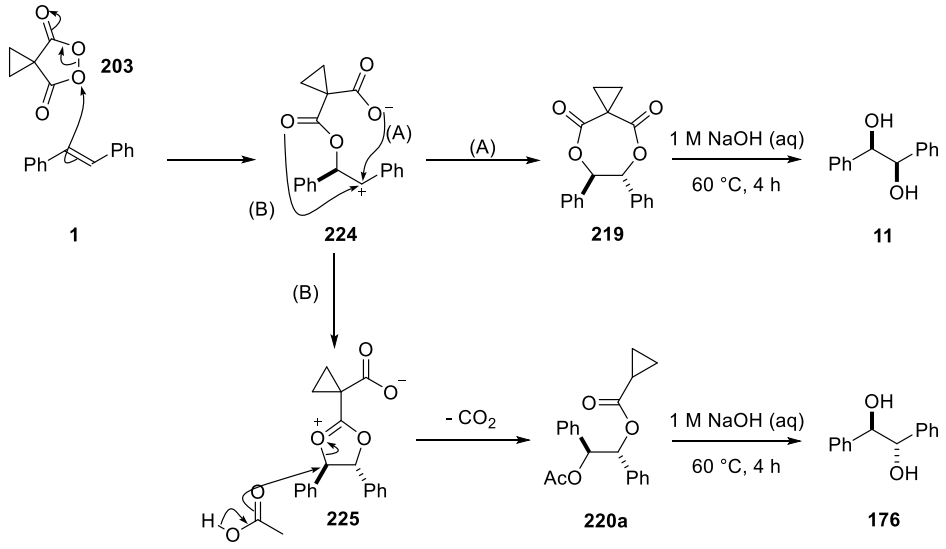


Scheme 81. Optimal *anti*-dihydroxylation reaction conditions.

3.2.4 Proposed mechanism

Having fully characterised the reaction intermediates, a mechanism for the transformation was proposed. Mechanistically, a pathway that involves the formation of a dioxonium intermediate **225** analogous to the Prévost-Woodward reaction was proposed (Scheme **82**). Treatment of *trans*-stilbene **1** with malonoyl peroxide **10** allowed the formation of zwitterionic species **224**. At this stage, two pathways are possible. Route **A** allows the formation of the seven-membered ring intermediate **219** which, after hydrolysis, affords the *syn*-diol **11**. Reaction of **224** *via* route **B** results in dioxonium intermediate **225**. In the presence of a molecule of AcOH dioxonium **225** ring-opens to give the corresponding *anti-bis*-ester **220a** after decarboxylation which, after hydrolysis, affords the corresponding *anti*-diol **176**.

It is not clear at this stage whether the decarboxylation step occurs before or after the addition of AcOH. It is known in the *syn*-dihydroxylation process that decarboxylation of the product does not occur (Scheme **72**). In the *syn*-dihydroxylation the nucleophile is H_2O. As H_2O is significantly more nucleophilic than AcOH it can be expected that the lifetime of dioxonium intermediate **225** is longer in the *anti*-dihydroxylation process giving time for the decarboxylation process to occur. Therefore, we speculate that decarboxylation occurs prior to AcOH addition.



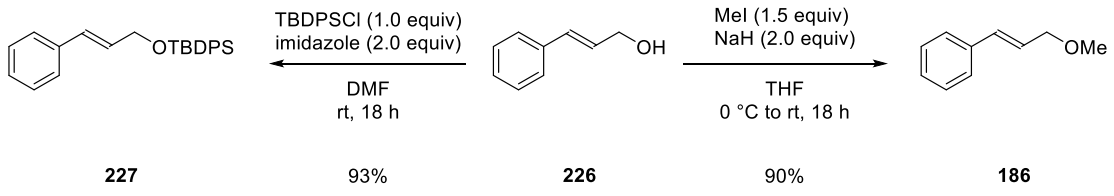
Scheme 82. Proposed mechanism.

3.2.5 Substrate Scope and Limitations

3.2.5.1 Synthesis of the starting materials

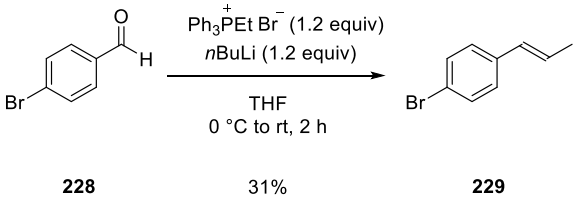
After optimising this metal-free *anti*-dihydroxylation reaction using *trans*-stilbene **1** as a starting material, the next step was to extend the scope of the reaction to different types of alkene starting materials. This work was carried out in collaboration with a co-worker, S. Davidson.

Alkenes **227** and **186** were readily synthesised in high yields by alcohol protection of commercially available cinnamyl alcohol **226** (Scheme **83**).



Scheme 83. Preparation of oxygenated alkenes **186** and **227**.

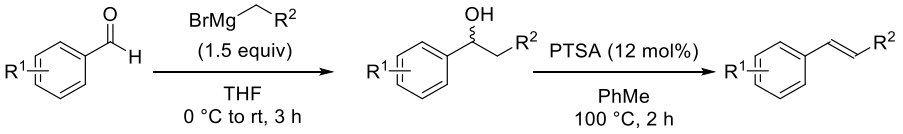
A Wittig reaction was applied to synthesise alkene **229** (31%) using commercially available *p*-bromobenzaldehyde **228** and the corresponding commercially available triphenylphosphonium salt (Scheme **84**).[65]



228 31% **229**

Scheme 84. Synthesis of alkene **229**.

Grignard reactions were used for the synthesis of alkenes **235**, **236** and **237**. Racemic mixtures of alcohols **232**, **233** and **234** were obtained from Grignard addition to the aryl aldehydes **230** and **231**. Desired alkenes were isolated after dehydration with PTSA (Scheme **85**).



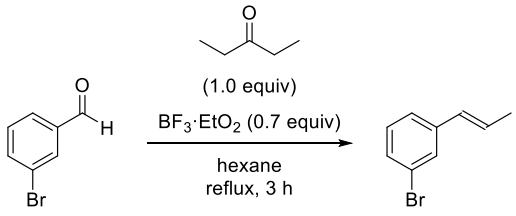
230 R^1 = Mes
231 R^1 = H

232 R^1 = Mes R^2 = Me 61%
233 R^1 = H R^2 = Cy 92%
234 R^1 = NO_2 R^2 = Me

235 R^1 = Mes R^2 = Me 59%
236 R^1 = H R^2 = Cy 81%
237 R^1 = NO_2 R^2 = Me 78%

Scheme 85. Grignard addition followed by dehydration.

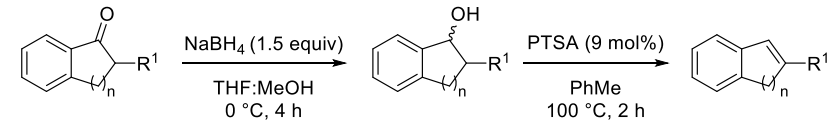
An aldol Grob reaction was carried out for the synthesis of *m*-bromostyrene **239**.[66] Thus, reaction of 3-bromobenzaldehyde **238** in the presence of $BF_3{\cdot}OEt_2$ and 1.0 equiv of 3-pentanone provided the corresponding alkene **239** in a high 92% yield (Scheme **86**).



238 92% **239**

Scheme 86. Aldol Grob reaction.

In a similar way, substituted indenes **248**–**250** and substituted dihydronaphthalene **251** were synthesised by reduction of ketones **240**–**243** with $NaBH_4$ followed by dehydration of the racemic mixture of alcohols **244**–**247** with PTSA (Scheme **87**). Yields are presented for the two-step procedures.



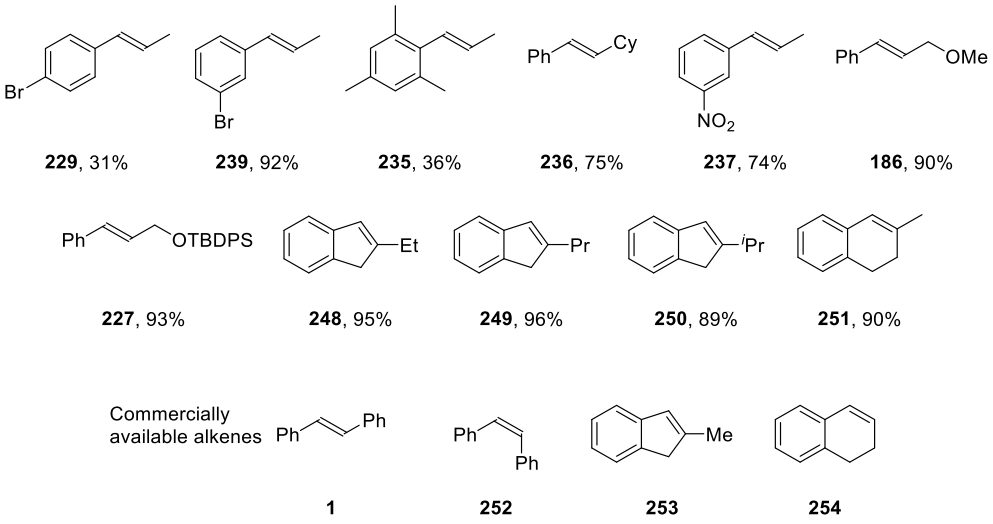
240 n = 1 R^1 = Et
241 n = 1 R^1 = Pr
242 n = 1 R^1 = ^{i}Pr
243 n = 2 R^1 = Me

244 n = 1 R^1 = Et
245 n = 1 R^1 = Pr
246 n = 1 R^1 = ^{i}Pr
247 n = 2 R^1 = Me

248 n = 1 R^1 = Et 95%
249 n = 1 R^1 = Pr 96%
250 n = 1 R^1 = ^{i}Pr 89%
251 n = 2 R^1 = Me 90%

Scheme 87. $NaBH_4$ reduction followed by dehydration.

To summarise, Figure **4** shows the substrates prepared for the *anti*-dihydroxylation of alkenes along with the commercially available substrates examined.



229, 31% **239**, 92% **235**, 36% **236**, 75% **237**, 74% **186**, 90%

227, 93% **248**, 95% **249**, 96% **250**, 89% **251**, 90%

1 **252** **253** **254**

Figure 4. Substrate scope for the *anti*-dihydroxylation of alkenes.

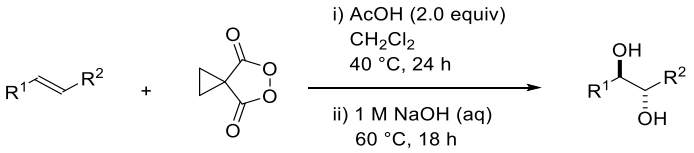
3.2.5.2 Substrate Scope

The reaction worked well for *trans*-stilbene (Table **15**, Entry 1) giving the desired *anti*-diol **176** in good yield and acceptable ratios (92%; 1:7 *syn*:*anti*). Low selectivities were observed when *cis*-stilbene **252** was used as the substrate (Table **15**, Entry 2). This result suggests the use of the *syn*-dihydroxylation procedure of *trans*-stilbene **1** in order to prepare diol **11**. It is belived that the lack of selectivity for *cis*-stilbene **252** is due to a rapid σ-bond rotation of the zwitterionic intermediate **224** (Scheme **82**, page **57**).

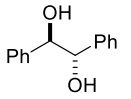
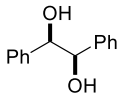
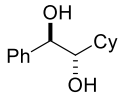
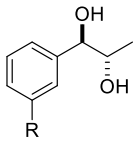
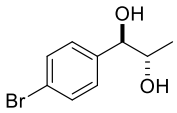
The reaction also proceeded well for a number of styrene derivatives (Table **15**, Entries 3–7). When a cyclohexane ring was incorporated into the alkene starting material the reaction was efficient (77%), although low levels of diastereoselectivity were obtained (*syn*:*anti* 1:4) (Table **15**, Entry 3). Different substituents on the aromatic ring were also introduced (Table **15**, Entries 4–6).

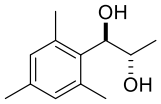
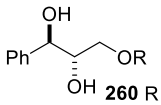
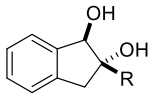
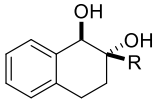
m-Bromomethylstyrene was examined and the corresponding *anti*-diol **256** was isolated with low levels of selectivity (*syn*:*anti* 1:3) (Table **15**, Entry 4). Introduction of a more electron-withdrawing group, *m*-nitromethylstyrene **237**, slowed down the reaction giving a poor yield (35%) and low selectivity (*syn*:*anti* 1:2) (Table **15**, Entry 4). This provided a limitation of this methodology. Acceptable results were obtained when mesityl alkene **235** was examined under the optimised *anti*-dihydroxylation reaction conditions giving the *anti*-diol **259** in excellent yield (90%) and good diastereoselectivity (*syn*:*anti* 1:5) (Table **15**, Entry 6). Cinnamyl alcohol with a methyl ether **186** or silyl ether **227** provided similar results of low levels of diastereoselectivity (*syn*:*anti* 1:2) (Table **15**, Entry 7).

Table 15. Substrate Scope.



5 **10** **176**

Entry	Product		Yield[a] (%)	*syn*:*anti*[b]
1		**176**	92	1:7
2		**11**	79	3:4
3		**255**	77	1:4
4		**256** R = Br	76	1:3
		257 R = NO_2	35	1:2
5		**258**	79	1:4

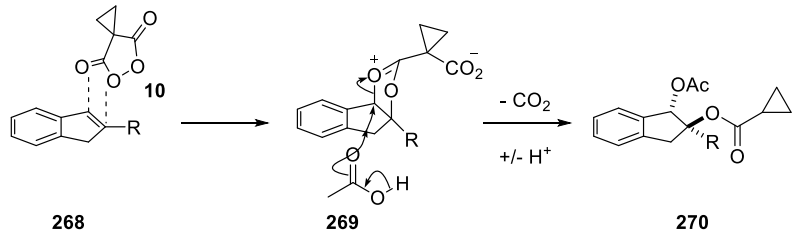
Entry	Product		Yield[a] (%)	*syn*:*anti*[b]
6		**259**	90	1:5
7		**260** R = Me	63	1:2
		261 R = TBDPS	52	1:2
8		**262** R = Me	80	1:8
		263 R = Et	79	1:8
		264 R = Pr	70	1:13
		265 R = ^{i}Pr	83	1:10
9		**266** R = H	80	1:3
		267 R = Me	75	1:13

[a]Isolated yield. [b] Diastereoselectivity determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

An interesting result was obtained with substituted indenes and dihydronaphthalenes as starting materials. 2-Methylindene **253** (Table **15**, Entry 8) reacted under the optimal conditions

and interestingly a single regioisomer of the *anti-bis*-ester was obtained. The regiochemistry of the addition of the AcOH was determined by 2D NMR spectroscopy, occurring at the benzylic position. This will be discussed in further detail below. The corresponding *anti*-diol **262** was isolated after hydrolysis in good selectivity (*syn*:*anti* 1:8) (Table **15**, Entry 8). When 2-ethylindene **248** was used the corresponding *anti*-diol **263** was also obtained with the same results (*syn*:*anti* 1:8) (Table **15**, Entry 8). Increasing the chain length to propyl and *iso*propyl the *anti*-diols were obtained with excellent results up to *syn*:*anti* 1:13 (Table **15**, Entry 8). This trend holds true with dihydronaphthalenes, no substitution on the second position (Table **15**, Entry 9) gives poor selectivity, whereas when a methyl group was incorporated on the second position (Table **15**, Entry 9) the diastereoselectivity increased up to *syn*:*anti* 1:13.

An explanation of the results obtained with indene derivatives **248–251** is shown in Scheme **88**. The approach of the malonoyl peroxide **10** occurs such as to minimise the steric interaction of the cyclopropyl group with the R group for the formation of dioxonium intermediate **269**. Then the sterics play an important role and the addition of the AcOH occurs only at the benzylic position, as it is the less sterically encumbered carbon. The electronics are also a key factor for this transformation, since the benzylic position is the more electrophilic centre. The formation of the minor *syn*-diol comes exclusively from the formation of the seven-membered ring intermediate.



Scheme 88. Reaction pathway to explain regioselectivity.

Electron poor alkenes did not prove very reactive, limiting the wider use of this methodology. The requirement for this *anti*-dihydroxylation reaction to be successful is to have an alkene attached to an aromatic group, which we believe stabilises the developing positive charge of the zwitterionic species **225** (Scheme **82**, page **57**).

3.3 Conclusions

With the intent to develop a metal-free *anti*-dihydroxylation of alkenes, a series of three different malonoyl peroxides **10**, **215** and **216** were synthesised (Figure **5**) and were reacted with several alkenes containing different functionalities (Figure **6**).

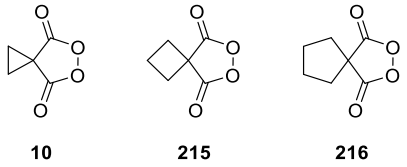


Figure 5. Malonoyl peroxides synthesised.

The non-commercially available alkenes that were reacted with malonoyl peroxide **10** were prepared using different strategies, either by ketone reduction to an alcohol, using $NaBH_4$, followed by dehydration, or by Grignard addition followed by dehydration or by Wittig reaction of an aldehyde with the appropriate triphenylphosphonium salt (Figure **6**).

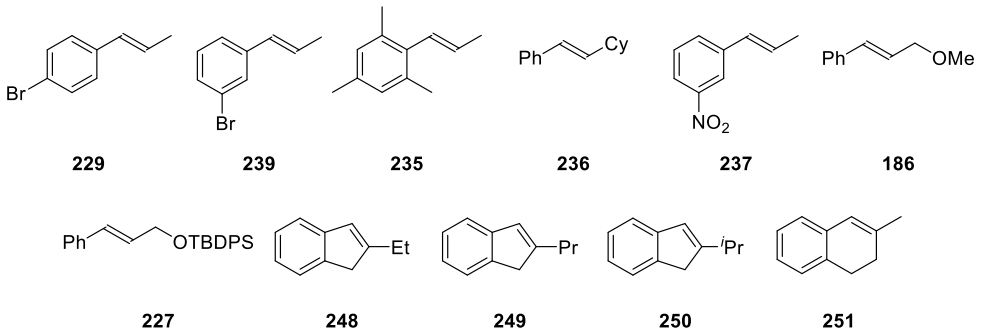
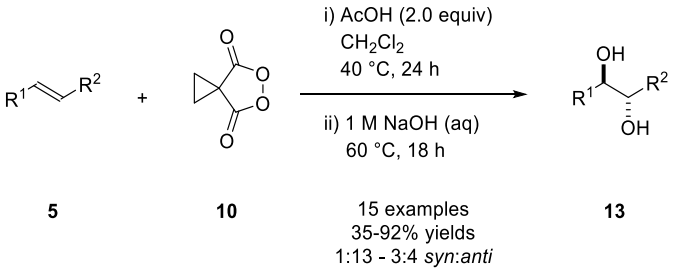


Figure 6. Alkenes synthesised.

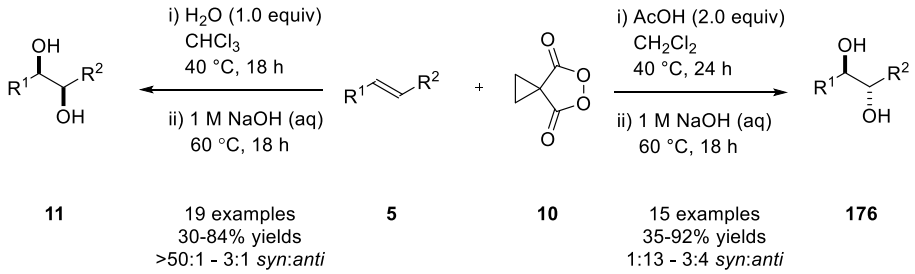
After an extensive optimisation of the reaction with *trans*-stilbene as the starting material, optimal conditions for this methodology where developed which are shown in Scheme **89**.



Scheme 89. General scheme for the *anti*-dihydroxylation of alkenes.

Reaction of alkene **5** with 1.5 equivalents of malonoyl peroxide **10** and 2.0 equivalents of AcOH using CH_2Cl_2 as the solvent provided the desired *anti*-diol **176** after alkaline hydrolysis. The methodology has been applied to 15 examples, including stilbene, styrene, indene and naphthalene derivatives, in poor to excellent yields (35–92%) and selectivities (*syn*:*anti* 1:13–3:4) (Scheme 89).[67]

We have therefore developed a complementary dihydroxylation of alkenes under metal-free conditions to give access to either *syn*- or *anti*-diols simply by switching the nature of the reaction solvent (Scheme **90**).



Scheme 90. Selective *syn*- and *anti*-dihydroxylation of alkenes with malonoyl peroxide **10**.

Chapter 2: Alkene Dioxygenation with Malonoyl Peroxides: Synthesis of γ-Lactones, Isobenzofuranones and Tetrahydrofurans

1 Introduction to the Dioxygenation of Alkenes

Saturated oxygen heterocycles are a common scaffold in natural and pharmaceutical products, and the synthetic community has expanded considerable efforts to prepare this class of molecule.[68] The richest sources of polyketide macrolides are marine organisms.[69] A large number of these structures have been isolated from sponges, algae and dinoflagellates. However, the very small quantities of compound which are isolated from natural sources limit biological studies, and therefore, biological activity or mechanism of action cannot always be determined.

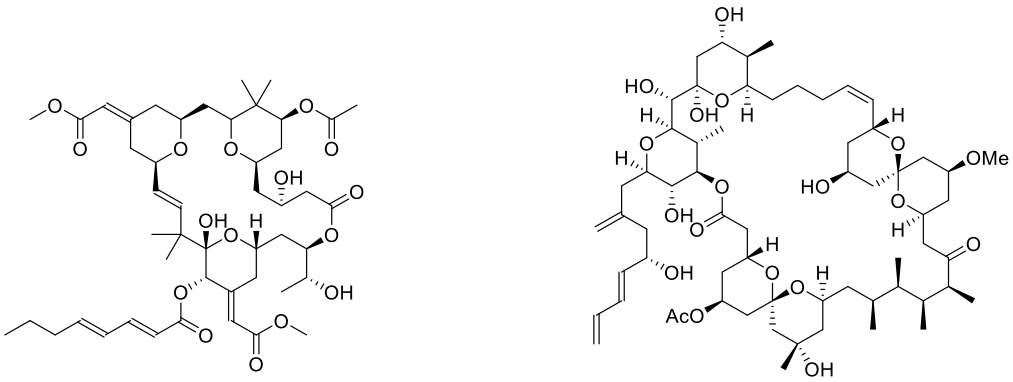


Figure 7. Examples of macrolides in nature.

Bryostatin 1, **271**, was first isolated in 1960 by George Pettit from *Bugula neritina* and to date there are 20 different bryostatin analogues which have been identified (Figure **7**).[70] These molecules are potent modulators of protein kinase C, and they are under investigation as potential anti-cancer and anti-HIV agents. Neurological effects have also been studied for bryostatin as a potential treatment for Alzheimer's disease. Owing to the complexity of the molecule, few total syntheses have been reported in the literature. The shortest synthesis reported to date is a 36-step effort, developed by Krische in 2011.[71] Within its core structure Bryostatin 1, **271**, contains three saturated oxygen heterocycles.

Another example of a molecule containing saturated oxygen heterocycles is spongistatin **272**, a 42-membered macrolide that was first synthesised by Evans in 1997.[72] These macrolides have exceptional antitumor activities against many cell types.[73]

Bryostatin 1, **271**, and spongistatin **272** are only two examples of the many oxygenated molecules with biological activity present in nature.[68] Many methodologies have been applied to the synthesis of oxygenated heterocycles, with potential extrapolation to the synthesis of biologically relevant saturated heterocycles. And the development of iodocyclisations,[74] many variants can be used to prepare other types of heterocycle.[75] Nitrogen heterocycles are also an attractive synthetic target

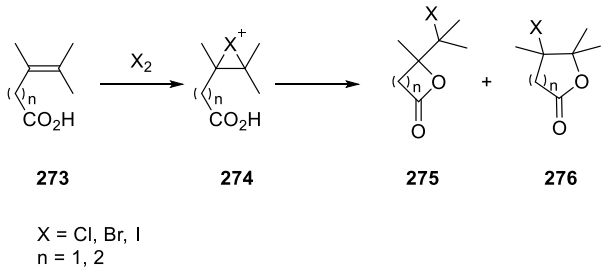
which can be synthesised by alkene activation and intramolecular ring closure with either an amide or an amine. However, amides are not the best choice for these cyclisations as regiochemistry issues such as O-attack *vs* N-attack frequently arise.[76]

Precedent in the literature usually constructs five-membered oxygenated heterocycles by intramolecular cyclisations of homoallylic carboxylic acids or homoallylic alcohols.[75] Often, the precursors for these cyclisations must be activated and trapped intramolecularly with a nucleophile.[77,78] Within this introduction, selected methods for the use of unactivated of alkenes in the formation of saturated oxygen heterocycles will be discussed.

1.1 Methods for Intramolecular Cyclisation of Unactivated Alkenes

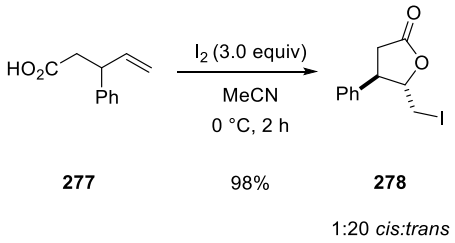
1.1.1 Halocyclisations

Heterocycle synthesis has emerged as a key reaction in organic chemistry, and the activation of alkenes **273** followed by intramolecular cyclisation has been thoroughly investigated.[79] The use of iodine or bromine as alkene activators through iodonium or bromonium ion **274** formation has received significant attention.[80] Scheme **91** shows how X_2 (X = Cl, Br, I) can activate alkene **273** resulting in a cationic three-membered ring intermediate **274** which can be ring opened by an intramolecular attack of a pendant carboxylic acid. Through this addition, two possible regioisomers **275** or **276** can form depending on the regiochemistry of the ring-closure step.



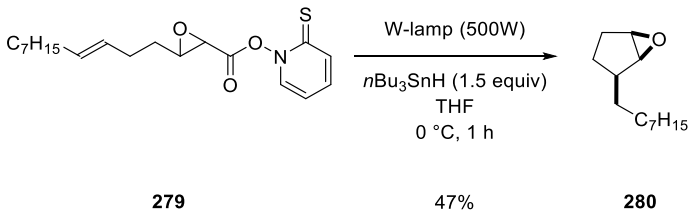
Scheme 91. General scheme for iodolactonisation with X_2.

In 1978 Myerson and co-workers showed how γ-lactones **278** could be isolated over δ-lactones, despite both the formal 5-*exo* cyclisation and 6-*endo* cyclisation being favoured. The authors suggested that the presence of a stereogenic carbon on the starting material **277** provides high levels of diastereoselectivity in favour of the *trans*-product **278** over the *cis*-product as determined by ^{13}C NMR analysis (Scheme **92**).[81]



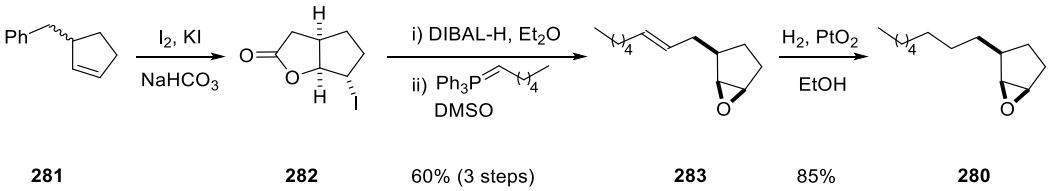
Scheme 92. Iodolactonisation with I_2.

Wang *et al.* developed a C–C bond formation reaction with oxiranyl radicals.[82] Epoxide **280** was synthesised by visible-light photolysis of starting material **279** through oxiranyl formation (Scheme **93**).



Scheme 93. Synthesis of epoxide **280**.

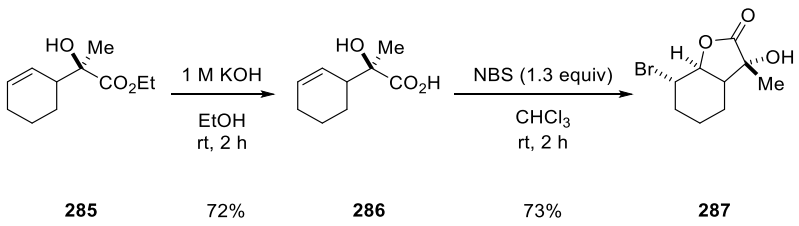
In order to confirm the assigned stereochemistry of epoxide **280**, an independent synthesis of **280** was carried out. Thus, iodolactone **282** was synthesised using carboxylic acid **281** as the starting material which was subjected to iodocyclisation with I_2 and KI to give fused ring **282** (Scheme **94**). DIBAL-H reduction followed by Wittig reaction provided epoxide **283**. Hydrogenation of alkene **283** provided the desired product **280** which, in comparison with the compound prepared above, confirmed the stereochemistry obtained during the photolysis process shown in Scheme **93**.



Scheme 94. Independent synthesis of epoxide **280**.

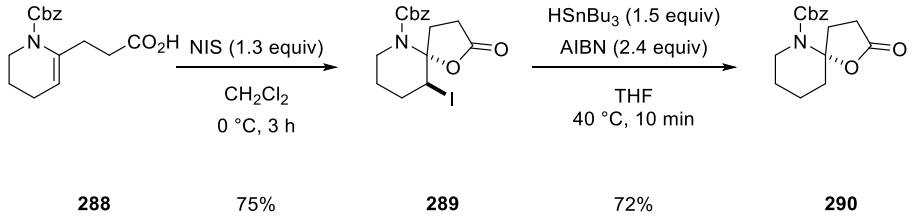
In another example, determination of the relative stereochemistry of **287** came from a bromolactonisation of the saturated carboxylic acid **286** after hydrolysis of ester **285** (Scheme **95**).[83] Since *N*-bromosuccinimide (NBS) is a source of Br^+, alkenes can be activated towards nucleophilic

addition of a pendant carboxylic acid. The structure of the diastereomerically pure bromolactone **287** was confirmed by X-ray crystallography.



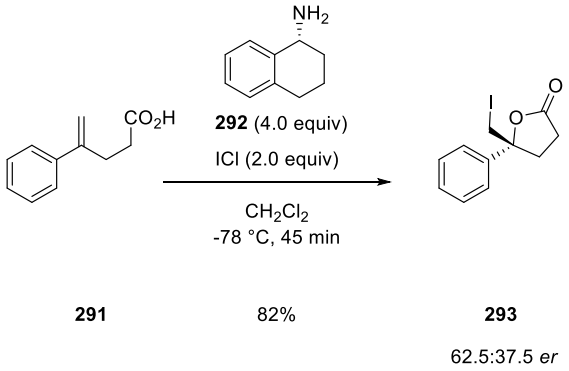
Scheme 95. Bromolactonisation with NBS.

Iodosuccinimide (NIS) is another common method for introducing iodine across alkenes (Scheme **96**). The intramolecular cyclisation of unsaturated carboxylic acid **288** was successfully achieved by using NIS under very mild conditions. However, iodolactone **289** proved very unstable and reduction of **289** was carried out with tri-*n*-butyltin hydride and AIBN to give the reduced product **290**.[84]



Scheme 96. Iodolactonisation with NIS.

Wirth *et al.* examined a reagent-controlled reaction of homoallylic carboxylic acids, such as **291** in the presence of ICl and chiral amine **292** (Scheme **97**).[85] γ-Lactones, **293**, were isolated from carboxylic acid **291** in good yields, although low levels of enantioselectivity were obtained (*er* 62.5:37.5). Several chiral amines and different sources of I^+ were examined in order to optimise the reaction, however, they showed little change in the enantioselectivity observed within this reaction.



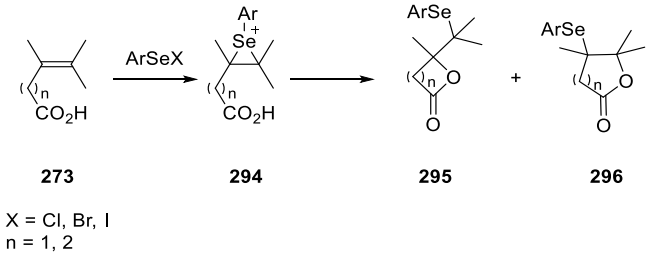
Scheme 97. Substrate controled iodolactonisation.

Although the enantioselectivities of this protocol were not high, the use of this methodology proved to tolerate several functional groups on the aromatic ring, both electron-withdrawing and electron-donating groups being accepted within the substrates. The use of commercially available reagents, chiral amines and ICl, makes this lactonisation a straightforward and particularly useful reaction.

1.1.2 Selenocyclisations

Alkenes can also be activated with arylselenium halides. Campos and Petragnani reported this type of chemistry in 1960.[86] Two years later, they also reported alternative tellurium compounds that were capable of carrying out this transformation.[87]

Scheme **98** shows how ArSeX can activate alkene **273** to form a selenium containing three-membered ring **294**, which can be opened by intramolecular attack of a pendant nucleophile.[88] Two regioisomers, **295** and **296**, can be formed from this transformation,.



Scheme 98. General scheme for selenolactonisation with ArSeX.

Phenylselenofunctionalisation is a common procedure used to activate alkenes that has been widely explored for the preparation of a variety of five- and six-membered rings.[88] Regiochemistry can be controlled by choosing the appropiate reagents, in order to obtain the desired kinetic or the thermodynamic product.

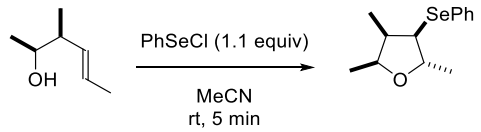
1.1.2.1 Selenofunctionalisation with unsaturated alcohols

Tetrahydrofuran and tetrahydropyran heterocycles can be prepared by cycloselenofunctionalisation of unsaturated alcohols. Normally, cyclisations are favoured or disfavoured according to Baldwin's rules;[77] the more versatile cyclisation is the favourable 5-*exo-trig* process, however the 5-*endo-trig*, a commonly disfavoured process, can also be employed in selenocyclisations.

1.1.2.1.1 5-*endo-Trig*

According to Baldwins rules, cyclisation can happen when the participating orbitals are correctly oriented and overlap between the nucleophile and the electrophile can occur. For these reasons there are a series of cyclisations that theoretically cannot happen based on the lack of orbital overlap, however they can be carried out successfully if the appropriate considerations are adopted.

An example of a formal 5-*endo*-trig cyclisation using PhSeCl and alkene alcohol **297** is shown in Scheme **99**. Reaction of alkenol **297** with 1.1 equiv of PhSeCl provided the *trans*-selenoether product **298** selectively in 87% yield.[89] NOE experiments provided confirmation of the relative stereochemistry of ether product **298**.



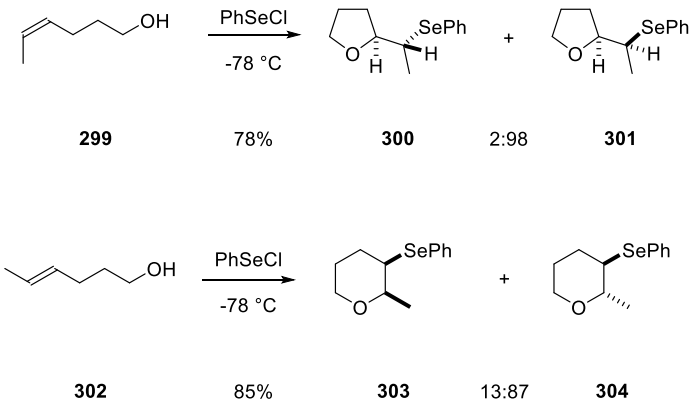
297 87% **298**

Scheme 99. 5-*endo-Trig* selenolactonisation with PhSeCl.

1.1.2.1.2 5-*exo*-*Trig*

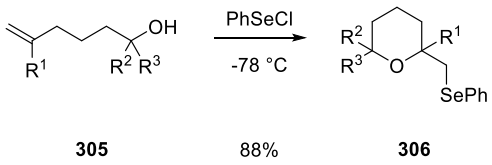
5-*exo*-*Trig* is by far the most versatile route to synthesise tetrahydrofurans since it is favoured according to Baldwin's rules. However, regioselectivity issues can occur when performing a 5-*exo*-*trig* cyclisation, due to the potential of a competitive favoured 6-*endo*-*trig* cyclisation. Selected examples are shown in Scheme **100** and Scheme **101**.

For Δ^4 alkenols the regiochemistry is directed by the alkene substituents. *cis*-Alkenol **299** was treated with PhSeCl to give tetrahydrofuran **301** selectively. By contrast, *trans*-alkenol **302** when treated under the same reaction conditions provided the tetrahydropyran **304** instead (Scheme **100**).



Scheme 100. Selenocyclisation with Δ^4 alkenols.

For Δ^5 alkenols, the 6-*exo*-*trig* cyclisation was only possible for the synthesis of tetrahydropyrans **306** (Scheme **101**).[88]



Scheme 101. Selenocyclisation with Δ^5 alkenols.

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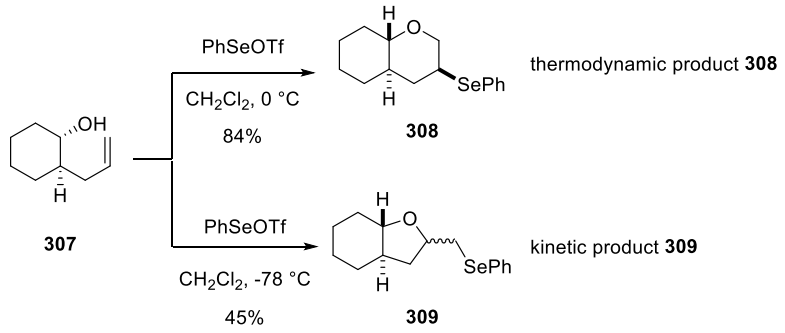
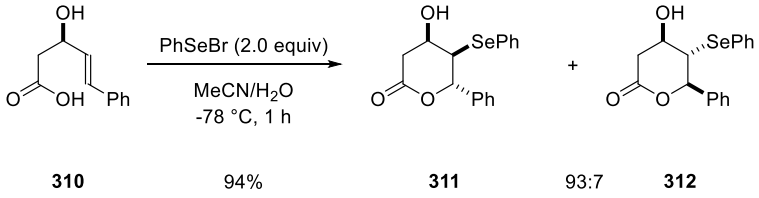
Phenylselenyl triflate reagents are also used in selenocyclysations to produce the desired oxygenated heterocycles. The regiochemistry of the reaction can be controlled by the temperature of the reaction in order to obtain the thermodynamic product **308** (PhSeOTf at 0 °C) or the kinetic (PhSeOTf at -78 °C) product **309** (Scheme **102**).[88]



Scheme 102. Thermodynamic and kinetic selenocyclisation products.

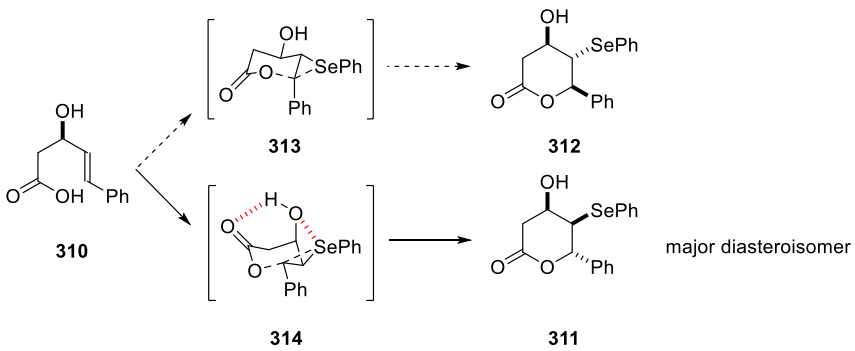
1.1.2.2 Selenofunctionalisation with unsaturated carboxylic acids

Lactones with different ring sizes can also be prepared by cycloselenofunctionalisation of saturated carboxylic acids. In 2002, Noto *et al.* developed a stereocontrolled synthesis of γ-lactones and δ-lactones through selenolactonisation.[90] They used the *β*-hydroxy acid **310** for their studies providing the δ-lactone **311** as the major diastereoisomer (93:7, **311**:**312**) (Scheme **103**).



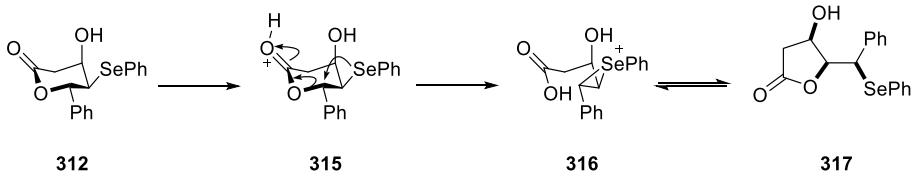
Scheme 103. Diastereoselective selenocyclisation.

The major diastereoisomer occurs *via* transition state **314** which is stabilised through an intramolecular H-bond and a Se–O interaction (Scheme **104**). None of these interactions are present in transition state **313**, making this a higher energy transition state, therefore, the axial position of the hydroxyl group in the final product **311** is preferred.



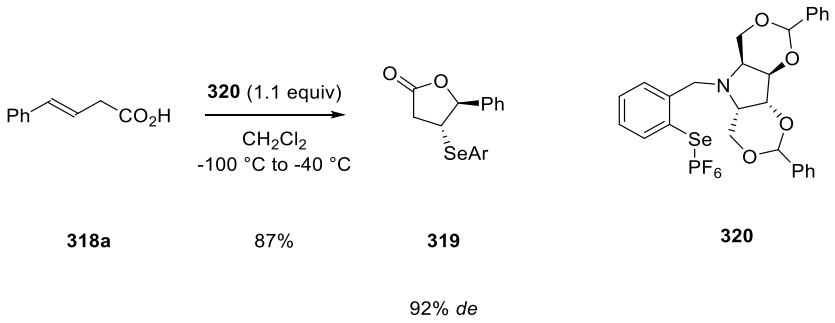
Scheme 104. Transition state postulated for selenocyclisation.

Interestingly, the δ-lactone **312** can also be converted into the γ-lactone **317** under acidic conditions (Scheme **105**). Treatment of the δ-lactone **312** with silica gel in CH_2Cl_2 resulted in protonation of **315**. Subsequent, intramolecular selenium attack on the *α*-position of the lactone provided open-chain selenium ion **316**. Intermediate **316** can then cyclise to give the thermodynamically more stable γ-lactone **317** by 5-*exo* cyclisation.



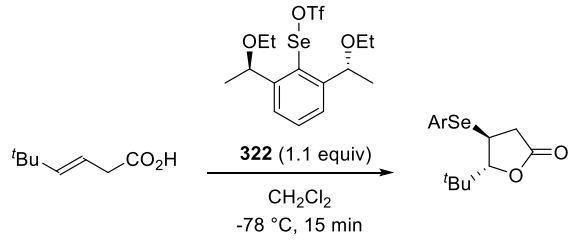
Scheme 105. Treatment of a δ-lactone under acidic conditions.

Chiral selenium reagents have also been examined to induce asymmetry into the process. For example, Fujita *et al.* published an asymmetric intramolecular selenolactonisation and selenoetherification using the chiral arylselenidehexafluorophosphate **320**.[91] Treatment of homoallylic carboxylic acid **318a** with the chiral selenium reagent **320** gave the γ-lactone **319** in excellent yield and high diastereoselectivity under their optimised reaction conditions (Scheme **106**).



Scheme 106. Selenolactonisation with chiral organoselenium reagent **320**.

At the same time, in Canada, Malefant *et al.* developed an asymmetric process using a C_2-symmetric organoselenium reagent **322** (Scheme **107**).[92] Carboxylic acid **321** was treated with chiral selenium reagent **322** for the preparation of heterocycle **323**.

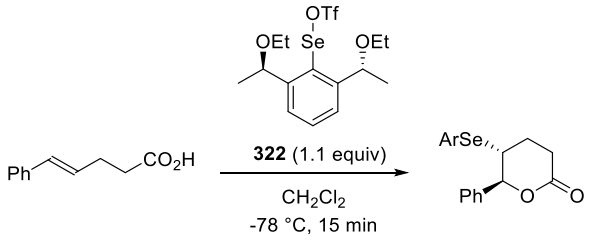


321 72% **323**

20:1 *dr*

Scheme 107. 5-*exo* Cyclisation with chiral organoselenium reagent **322**.

These cyclisations occurred with excellent facial selectivity, providing the best results with the 6-*endo*-cyclisations, up to 40:1 selectively when using alkene **324** as a substrate (Scheme **108**). Although 6-*endo* cyclised product **325** was isolated, further exposure of **325** under acidic conditions gave the thermodynamic 5-*exo* cyclised product.



324 65% **325**

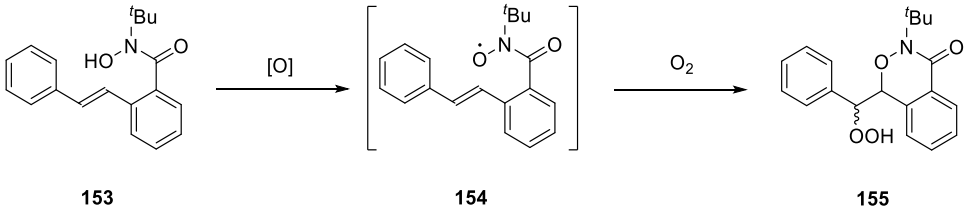
40:1 *dr*

Scheme 108. 6-*endo* Cyclisation with chiral organoselenium reagent **322**.

1.1.3 *Via* hydroxamic acids

Most methods for the dihydroxylation of alkenes use transition-metal catalysts; however, Alexanian and co-workers have recently developed a metal-free approach using oxygen, a cleaner oxidant.[48] Alexanian based his work on the earlier studies of Perkins.[49]

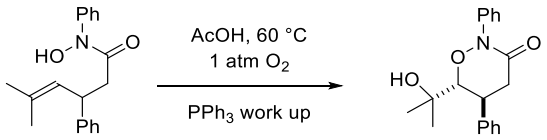
Perkins observed an amidoxyl-radical cyclisation followed by oxygenation (Scheme **109**). Hydroxamic acid **153** underwent spontaneous oxidation and intramolecular cyclisation, followed by an oxygenation to give **155** as a mixture of diasteromers.



153 **154** **155**

Scheme 109. Perkins spontaneous radical cyclisation.

Given the previous results, Alexanian suggested that an alkene cyclisation with a tethered amidoxyl radical, formed *in situ* from *N*-aryl hydroxamic acid **156** in the presence of oxygen, could afford the desired product (Scheme **110**).[48]



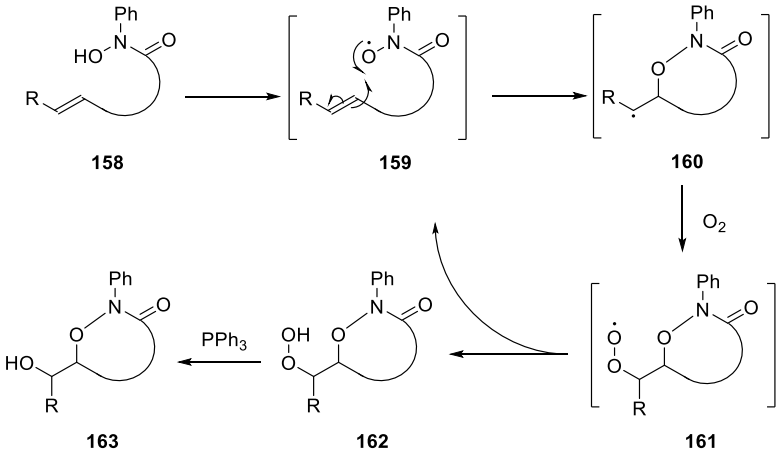
156 62% **157**

1:19 *cis*:*trans*

Scheme 110. Example of Alexanian's *anti*-dioxygenation reaction with hydroxamic acid **156**.

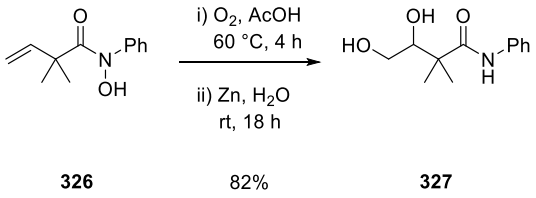
The reaction was performed on a range of substrates and it was found that the process tolerated a wide variety of alkenes including disubstituted substrates (62–88% yield), further substitution on the alkene moiety (62–79% yield), a conjugated alkene (63% yield) and an α-diallyl hydroxamic acid (75% yield).

The proposed mechanism is shown in Scheme **111**, and is similar to that proposed by Perkins. The first step is the formation of the amidoxyl radical species **159**, which is followed by cyclisation, leading to another radical species **160**. This intermediate reacts with oxygen to form an alkylhydroperoxy radical **161**, which abstracts a hydrogen atom from the starting material to generate the alkylhydroperoxide **162**. The deoxygenated product **163** is formed by reduction of the product with PPh_3 or Me_2S.



Scheme 111. Proposed mechanism for the intramolecular reaction.

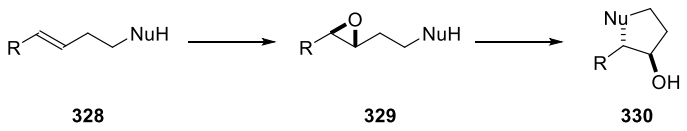
Moreover, this methodology provides an alternative reaction for the preparation of 1,2-diol moieties (Scheme **112**). These products can be obtained from a one-pot reaction of hydroxamic acid **326** in the presence of Zn in H_2O, which resulted in the reduction of the N–O bond, giving the corresponding 1,2-diol **327**.



Scheme 112. One pot reaction for the preparation of 1,2-diols.

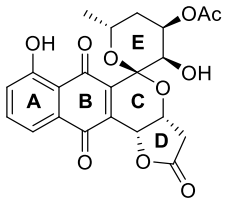
1.1.4 Intramolecular ring-opening of epoxides

Asymmetric epoxide formation was discussed in *Chapter 1*. Taking advantage of this, having a stereochemically pure epoxide **329** starting material with a pendant nucleophile, can selectively lead to cyclised product **330** (Scheme **113**). Usually, these transformations require a two-step synthesis, and functional groups are frequently an issue.



Scheme 113. General two-step synthetic procedure for the generation of cyclised products **330**.

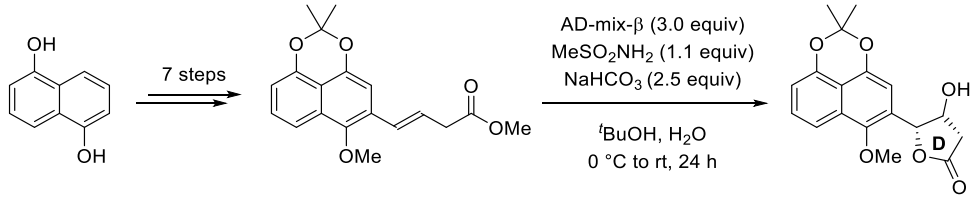
An asymmetric Sharpless dihydroxylation followed by cyclisation strategy has been applied in the enantioselective total synthesis of griseusins, which are potent antibiotic, antifungal and anticancer compounds (Figure **8**).[93] Griseusins are pyranonaphthoquinone metabolites with five rings, one of which is a spirocyclic ring (E ring).



331

Figure 8. Griseusin A structure **331**.

The starting material for the formation of ring D was successfully synthesised from commercially available 1,5-dihydronaphthalene **332** in 23% yield over seven steps (Scheme **114**). With alkene ester **333** in hand, asymmetric dihydroxylation was carried out to provide enantiomerically pure 1,2-diol. Then, intramolecular cyclisation of the benzylic alcohol on the ester group provided enantiomerically enriched ring D after a loss of a molecule of MeOH.

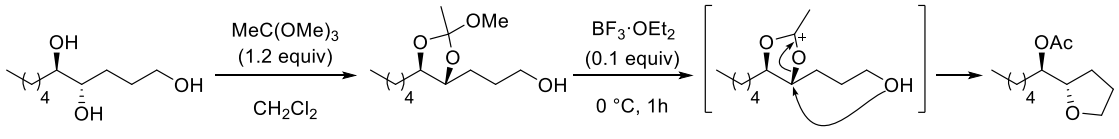


332 23% **333** 84% **334**

97% *ee*

Scheme 114. Asymmetric Sharpless dihydroxylation followed by intramolecular cyclisation.

In a similar way, in 2005, Borhan *et al.* developed a one-pot selective cyclisation of 1,2,*n*-triols for the preparation of tetrahydrofurans and tetrahydropyrans, using a five-membered ring ortho-ester intermediate **336** (Scheme **115**).[94]



335 **336** **337** **338**

99%

Scheme 115. One-pot cyclisation of 1,2,*n*-triols.

1,2,5-Triol **335** was protected with trimethyl orthoacetate to give **336** (Scheme **115**). This overall transformation depends exclusively on the formation of the five-membered ring ortho-ester **336**. Once ortho-ester **336** was formed, different Lewis acids were examined, with the optimum results occurring with $BF_3 \cdot OEt_2$. The Lewis acid rapidly eliminated a methoxy group, leading to a very reactive acetoxonium intermediate **337**, which was trapped intramolecularly by the pendant alcohol, providing cyclised product **338** in a high 99% yield.

1.2 Conclusions

It is clear that the interest to develop stereocontrolled syntheses of saturated oxygen heterocycles with activated alkenes has increased over the past decades, one of the reasons being the easy access to the compounds and precursors. In general, the cyclisations described provide access to a *trans*-orientation of the oxygen substituents since they are derived from the ring-opening of iodonium or selenarium ions.

The regiochemistry of the ring-opening process is normally dictated by electronic effects and influenced by sterics. Different regioisomers can be obtained from electrophilic alkene activation followed by ring-opening with a nucleophile. Reaction conditions can also play an important role in the outcome, where by 5-*exo* cyclisation, is normally obtained under kinetic control, whereas 6-*endo* cyclisation occurs under thermodynamic conditions. For this reason, these cyclisations are a good strategy to use in the synthesis of a variety of heterocyclic ring structures.

Halocyclisations have been used for the construction of important scaffolds, since iodine reagents have shown low-toxicity and high reactivity. These tranformations have proved to be useful synthetic methods for the introduction of an oxygen and a halogen across a double bond, while using readily available starting materials such as I_2, NBS, NIS and KI.

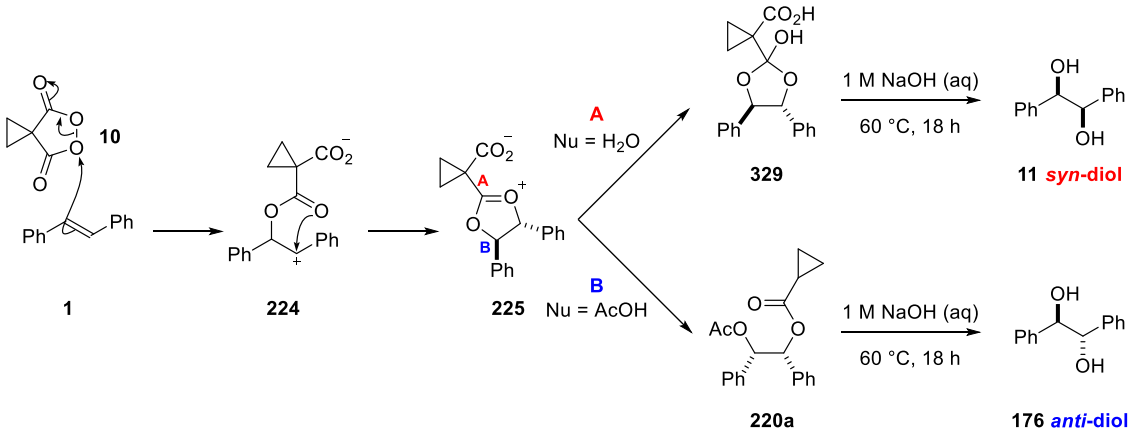
Selenocyclisations have the drawback that the reagents frequently need to be prepared, adding an additional step to the synthesis of the desired heterocycle, although some of them are commercially available. A valuable fact using organoselenium reagents is that the reactions occur using catalytic amounts instead of steochiometric. Also, they allow further manipulation of the cyclised products, providing selenium-free compounds, the selenium being removed under very mild conditions.

Another strategy to prepare heterocyclic scaffolds is by the intramolecular nucleophilic attack of an enantiomerically pure 1,2-diol to a β-methyl ester. The enantiopure 1,2-diol moiety can be prepared by Sharpless asymmetric Dihydroxylation, and therefore the corresponding intramolecular nucleophilic attack would give access to enantiopure cyclised products.

2 Previous Work

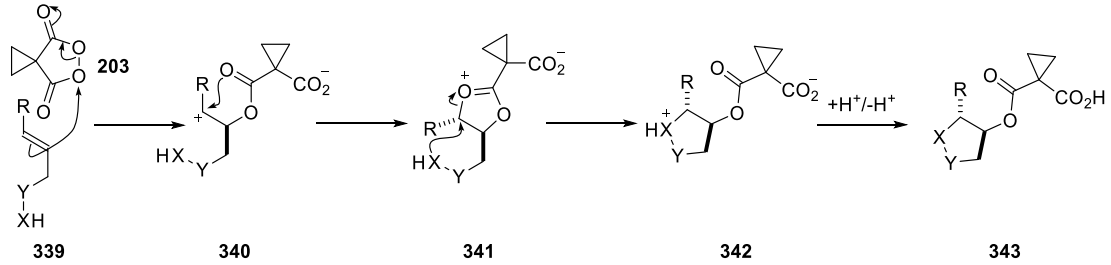
After successfully developing an effective and selective *anti*-dihydroxylation of alkenes under metal-free conditions,[67] we focussed our attention to the potent oxidative power of our malonoyl peroxide **10**.

Scheme **116** shows how malonoyl peroxide **10** can be used for the synthesis of both *syn*[13,95] and *anti*-diols[67] through the same dioxonium intermediate **225**.



Scheme 116. Alkene dioxygenation with malonoyl peroxide **10**.

The reactivity of dioxonium intermediate **225** was further expanded. Intramolecular cyclisation was subsequently investigated, since the synthesis of potential biologically active heterocycles under metal-free conditions could prove useful for the organic chemistry community.



Scheme 117. Proposed mechanistic pathway for the synthesis of heterocycles.

The idea for this project was to react a series of homoallylic nucleophiles **339** with malonoyl peroxide **10** to form the dioxonium intermediate **341** in a similar manner to the *syn*- and *anti*-dihydroxylation of alkenes (Scheme **117**). In the presence of a pendant nucleophile, this can ring close to form a heterocycle *via* an S_N2 process through opening of the dioxonium intermediate **341** to form the corresponding heterocycle **343** after proton transfer.

3 Results and Discussion

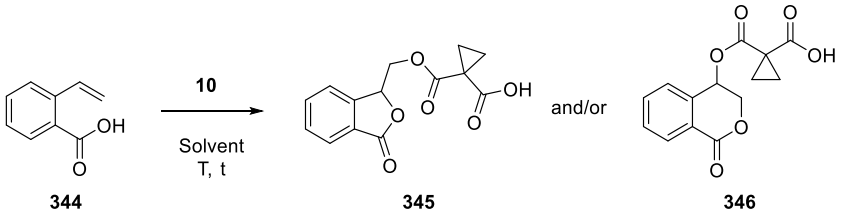
3.1 Synthesis of *Iso*benzofuranones

3.1.1 Optimisation

Initial studies were performed on the commercially available 2-vinylbenzoic acid **344** and are outlined in Table **16**. Reaction of 2-vinylbenzoic acid **344** with malonoyl peroxide **10** under standard *anti*-dihydroxylation conditions (40 °C, 24 h in CH_2Cl_2) indicated the formation of cyclised products, **345** and/or **346**, according to ^{1}H NMR spectroscopy of crude reaction mixture (Table **16**, Entry 1). This was an encouraging result and provided a strong indication that malonoyl peroxide **10** could be used to perform an oxidative heterocyclisation. Variation of temperature, time and the number of equivalents of **10** were investigated, but these did not improve conversion of starting material **344** (Table **16**, Entries 2–5). In addition, examination of different solvents and additives did not lead to an increased conversion (Table **16**, Entries 6–10).

Previous investigations into the use of malonoyl peroxide **10** in the *syn*-dihydroxylation of alkenes showed clear evidence that the use of a fluorinated alcohol as the solvent could significantly accelerate the reaction rate.[96-98] The reaction was therefore carried out in HFIP at 40 °C resulting in a 91% conversion (Table **16**, Entry 11). Full conversion was achieved by warming the reaction up to 50 °C for 24 h (Table **16**, Entry 12), providing a standard set of conditions for this reaction (1.5 equiv of malonoyl peroxide **10** at 50 °C, 24 h in HFIP).

Table 16. Intramolecular cyclisation optimisation



344 **345** **346**

Entry	Solvent	Additive	10 (equiv)	Temp/°C	Time/h	Conv[a] /%
1	CH_2Cl_2	-	1.5	40	24	30
2	CH_2Cl_2	-	1.5	50	24	47
3	CH_2Cl_2	-	1.5	40	48	44
4	CH_2Cl_2	-	1.5	40	120	72
5	CH_2Cl_2	-	3.0	40	24	45
6	CH_2Cl_2	*p*-Nitrophenol (1.0 equiv)	1.5	40	24	43
7	CF_3CH_2OH	-	1.5	40	24	60
8	PhMe	CF_3CH_2OH (1.0 equiv)	1.5	40	24	33
9	PhMe	$(CF_3)_3COH$ (1.0 equiv)	1.5	40	24	37
10	IPA	-	1.5	50	24	-
11	HFIP	-	1.5	40	24	91
12	**HFIP**	**-**	**1.5**	**50**	**24**	**99**

[a]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures.

3.1.2 Confirmation of the formal 5-*exo* cyclisation product

With the optimal conditions in hand, the product obtained was thoroughly investigated in order to identify whether, an overall formal 5-*exo* cyclisation **345**, or an overall formal 6-*endo* cyclisation **346**, had occurred. In order to fully characterise the product formed, 2D NMR experiments were carried out. However, these experiments did not give a clear indication as to the identity of the isolated product. Fortunately, crystallisation of the product from EtOAc gave a sample which could be analysed by X-ray crystallography (Figure **9**).

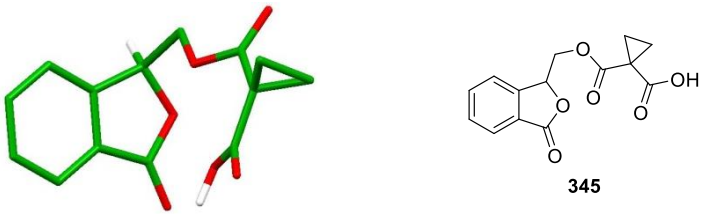
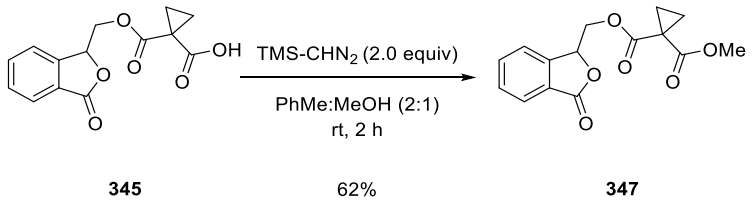


Figure 9. Crystal structure of oxidative heterocyclisation product **345**.

The structure shown by the X-ray analysis is that of an overall formal 5-*exo* cyclisation product **345** (Figure **9**). The reaction was repeated to obtain a yield for this transformation and *iso*benzofuranone **345** was isolated in a good yield of 76% under the optimised conditions.

Treatment of the crude reaction product with TMS-CHN_2 in PhMe and MeOH at rt for 2 h gave the methyl ester **347** which was isolated in a 62% yield (Scheme **118**).

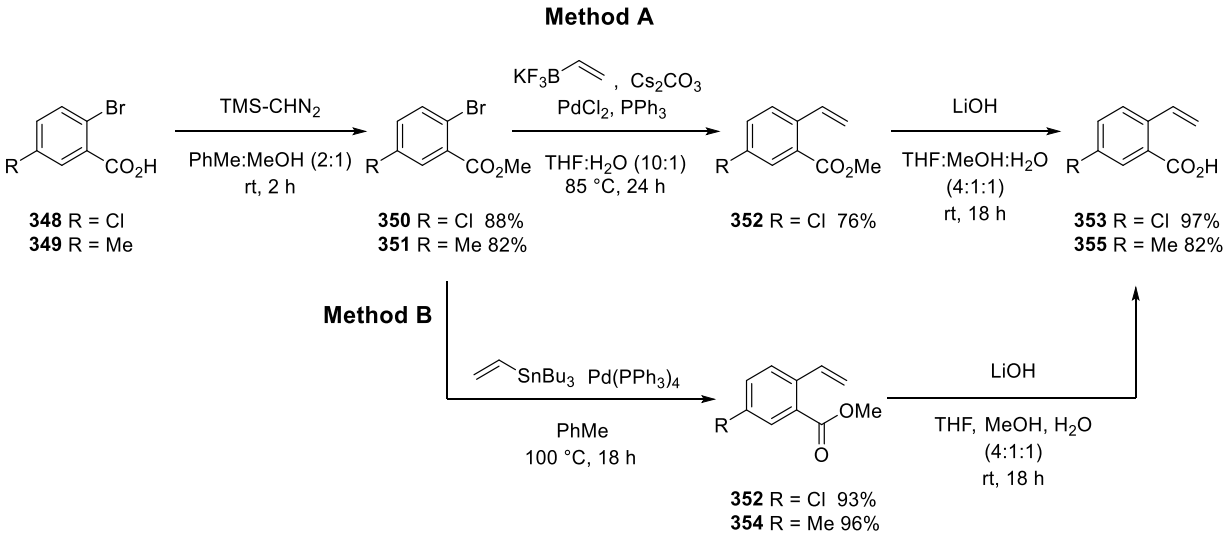


Scheme 118. Methyl ester formation.

3.1.3 Reaction profile

3.1.3.1 Synthesis of starting materials

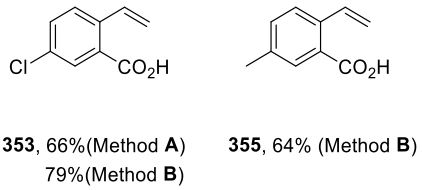
After developing optimised conditions, the next step was to investigate the scope of the transformation. Substituted 2-vinyl benzoic acids were prepared by a three-step route (Scheme **119**).[99]



Scheme 119. General scheme for the synthesis of 2-vinyl benzoic acids.

Commercially available 2-bromo-substituted benzoic acids **348** and **349** were transformed into the corresponding methyl ester **350** and **351** using TMS-CHN_2. A modified Suzuki reaction was performed for the introduction of a vinyl group using potassium vinyltrifluoroborate, to give **352** (76%). Finally, hydrolysis of the methyl ester **352** with aqueous LiOH gave substituted vinyl benzoic acid **353**. Alternatively, due to reproducibility issues of the Suzuki reaction, an analogous Stille reaction was employed for the introduction of the vinyl group using a vinyltributyltin reagent to prepare both **352** and **354**.[100] Hydrolysis of **354** gave the corresponding carboxylic acid **355** (82%).

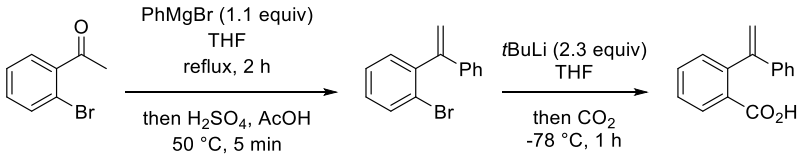
Figure **10** shows each of the 2-vinyl benzoic acids synthesised, either *via* Method **A** (Suzuki reaction) or Method **B** (Stille reaction), the yields presented are for the three steps.



353, 66%(Method **A**) 79%(Method **B**) **355**, 64% (Method **B**)

Figure 10. Substituted 2-vinyl benzoic acids synthesised.

Benzoic acid **358** was synthesised by a two-step procedure starting with commercially available 2-bromoacetophenone **356** (Scheme **120**).[101] Grignard reaction of **356** with a commercially available solution of phenylmagnesium bromide in THF provided a tertiary alcohol which was dehydrated under the acidic reaction conditions affording phenylvinylbenzene **357** (52%) (Scheme 120). Crude **357** was then treated with *t*BuLi followed by CO_2 addition to give the corresponding the benzoic acid **358** after acidic work-up in an overall 33% yield.



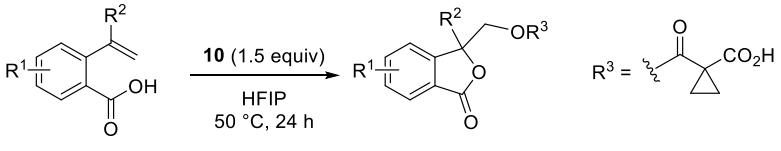
356 52% **357** 64% **358**

Scheme 120. Synthesis of benzoic acid **358**.

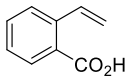
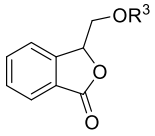
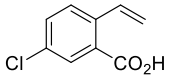
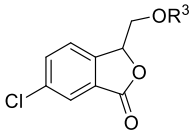
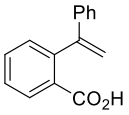
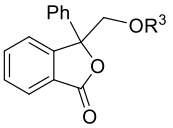
3.1.3.2 Substrate Scope

With the substituted vinyl benzoic acids synthesised and the optimal conditions developed (HFIP at 50 °C for 24 h, Table **16**), oxidative heterocyclisations with malonoyl peroxide **10** were examined (Table **17**).

Table 17. Substrate Scope.



359 **360**

Entry	Alkene	Product	Yield[a] (%)
1	 **344**	 **345**	76%
2	 **353**	 **362**	68%
3	 **358**	 **363**	71%

[a]Isolated yield.

Table **17** shows the substrate scope of the successfully isolated *iso*benzofuranones. Electron-donating substituents on the aromatic ring, such as 4-Me **355** gave complex crude reaction mixtures. This was attributed to the formation of both 5-*exo* cyclisation and 6-*endo* cyclisation products. Purification by silica gel flash column chromatography of these products proved to be challenging and was not successfully achieved. When the reaction was carried out with 5-chloro-2-vinyl benzoic acid **353** the reaction proceed well under the optimised conditions and isolation of the 5-*exo* cyclised **362** product after purification was successfully achieved in a 68% yield.

Substitution on the vinyl group with a phenyl (**358**) was also examined (Table **17**, Entry 3). The desired *iso*benzofuranone product **363** from the overall 5-*exo* cyclisation was isolated in a 71% yield after purification.

Due to the difficulties encountered during the application of this oxidative heterocyclisation on different substrates, resulting in mixtures of cyclised products in most of them, the scope was not further expanded. Purification of the crude reaction mixtures were a challenge, getting mixtures of cyclised products with other unsolved impurities. Therefore, we decided to explore this oxidative heterocyclisation using homoallylic carboxylic acids, where the potential for competing cyclisations modes was removed.

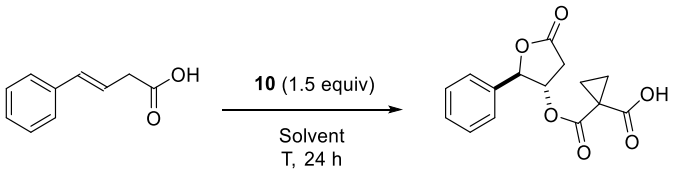
3.2 Synthesis of γ-Lactones

3.2.1 Optimisation

Studies began with commercially available *trans*-styrylacetic acid **318a**. An optimisation of this reaction was carried out in order to find optimal conditions for this transformation (Table **18**).

Reaction of *trans*-styrylacetic acid **318a** under standard *anti*-dihydroxylation conditions (1.5 equiv of malonoyl peroxide **10**, at 40 °C, 24 h in CH_2Cl_2) showed formation of the of cyclised γ-lactone **364a** in a *cis*:*trans* diastereoselectivity of 1:6 (Table **18**, Entry 1), as determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

Table 18. Intramolecular cyclisation optimisation[a]



318a **364a**

Entry	Solvent	Additive	Temp/°C	Conv[b]/%	*cis*:*trans*[b]
1	CH_2Cl_2	-	40	88	1:6
2	CH_2Cl_2	HFIP (1.0 equiv)	40	98	1:3
3	CH_2Cl_2	HFIP (2.0 equiv)	40	97	1:3
4	CH_2Cl_2	HFIP (1.0 equiv)	25	57	1:3
5	CH_2Cl_2	HFIP (2.0 equiv)	25	61	1:3
6	CH_2Cl_2	HFIP (1.0 equiv)	50	100	1:3
7[c]	HFIP	-	50	100	1:13
8	**HFIP**	**-**	**25**	**100**	**1:19**
9	EtOH	-	25	-	-
10	IPA	-	25	-	-

[a]All reactions performed in duplicate with *trans*-styrylacetic acid **318a** (1.0 mmol) at 0.5 M concentration. [b]Determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [c]Solvent dried over 3 Å molecular sieves for 24 h prior to use.

The use of CH_2Cl_2 with HFIP as an additive was investigated. Different equivalents of HFIP (1.0–2.0 equiv) and various reaction temperatures (25, 40 and 50 °C) were examined giving higher conversions but a descreased *cis*:*trans* diastereoselectivity (Table **18**, Entries 2–6). When dry HFIP was used as the reaction solvent, improved results were obtained with the *cis*:*trans* diastereoselectivity reaching 1:13 (Table **18**, Entry 7). Further improvement was observed with commercial unpurified HFIP, in which the reaction proceeded at rt with an improved *cis*:*trans* diastereoselectivity of 1:19 (Table **18**, Entry 8). Non-fluorinated alcoholic solvents were also

examined without success (Table **18**, Entries 9 and 10). These gave complex crude reaction mixtures, potentially due to reaction of the alcoholic solvent with malonoyl peroxide **10**, suggesting that a less nucleophilic fluorinated alcohol is required for this transformation.[102] HFIP is thought to act as a hydrogen bond donor to malonoyl peroxide **10**, increasing the reactivity through polarisation.

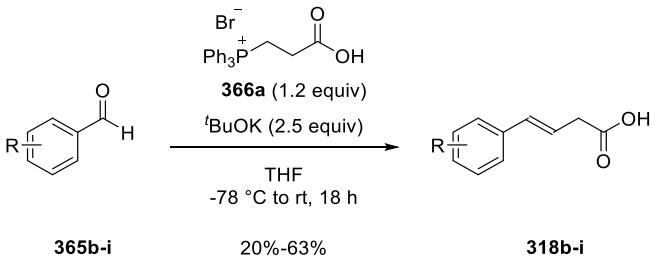
Based upon this screening, Entry 8 was adopted as the standard set of conditions for this transformation (1.5 equiv of malonoyl peroxide **10**, at 25 °C, 24 h in HFIP).

3.2.2 Substrate Scope and Limitations

Having successfully optimised the reaction for the synthesis of γ-lactones using *trans*-styrylacetic acid **318a** as a starting material, the new methodology was applied to alternative homoallylic carboxylic acid starting materials.

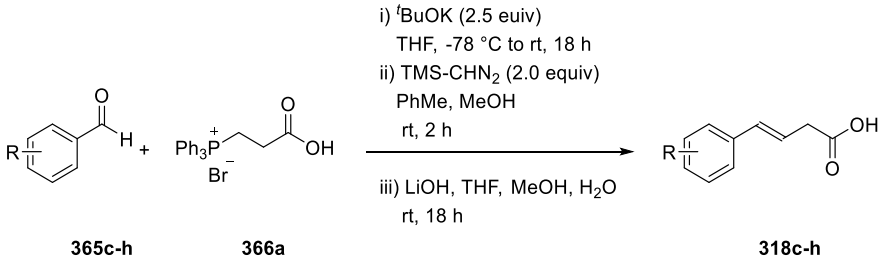
3.2.2.1 Synthesis of starting materials

A family of homoallylic carboxylic acids **318b-i** were synthesised *via* Wittig reaction of aldehydes **365b-i** and the corresponding carboxylic acid triphenylphosphonium bromide salt **366a** (Scheme **121**).[103]



Scheme 121. General scheme for synthesis of homoallylic carboxylic acids **318b-i.**

For homoallylic carboxylic acids **318c-h**, the Wittig reaction gave *cis*/*trans* mixtures which could not be purified. For this reason, transformation of the carboxylic acid **318c-h** into the methyl ester with TMS-CHN_2 allowed separation and purification of the *cis*/*trans* products. Hydrolysis of pure *trans*-alkene ester yielded the desired carboxylic acid **318c-h** as a single diastereoisomer (Scheme **122**).



Scheme 122. Three-step synthesis for isolation of *trans*-carboxylic acids **318c-h**.

Figure **11** shows the homoallylic carboxylic acids synthesised for use in this work with the corresponding isolated yields.

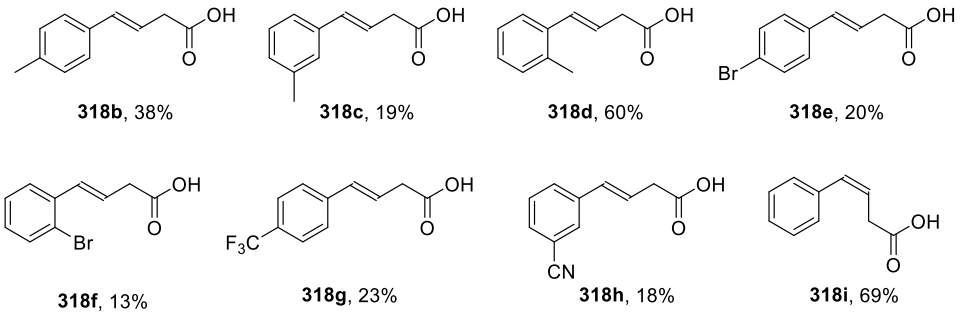
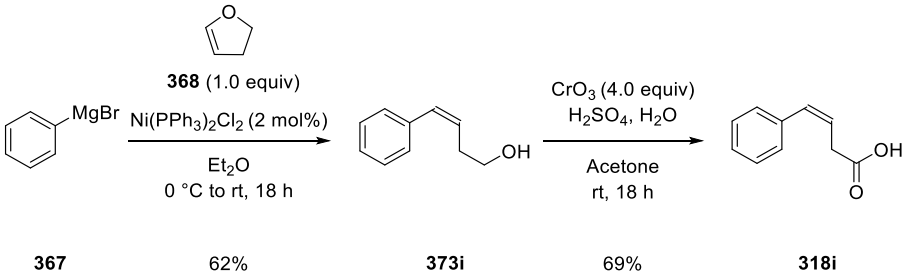


Figure 11. Substrate scope alkenes.

cis-Carboxylic acid staring material **318i** was synthesised in a two-step synthesis (Scheme 123). First, reaction of phenylmagnesium bromide **367** with 2,3-dihydrofuran **368** using a Ni catalyst provided (*Z*)-4-phenylbut-3-en-1-ol **373i** in good yield (62%).[104] The corresponding carboxylic acid **318i** was isolated after Jones oxidation in a 69% yield.

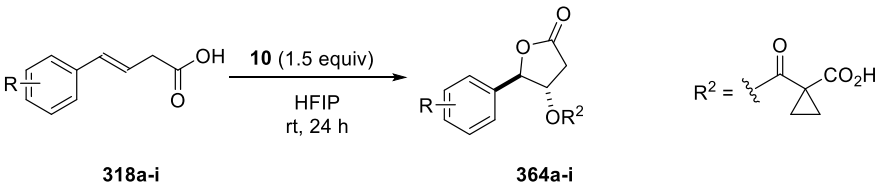


Scheme 123. Synthesis of carboxylic acid **318i**.

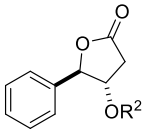
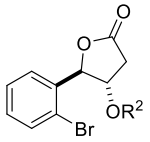
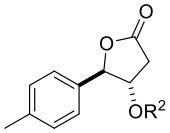
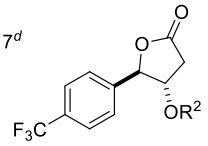
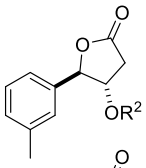
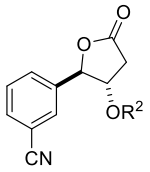
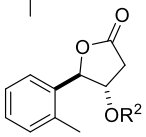
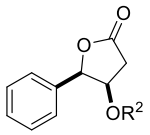
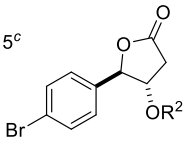
3.2.2.2 Substrate Scope

Having successfully synthesised the desired starting materials, the cyclisation of these substrates with malonoyl peroxide **10** was examined under the optimal conditions previously developed (1.5 equiv of malonoyl peroxide **10** in HFIP at 25 °C for 24 h).

Table 19. Substrate Scope.



318a-i **364a-i**

Entry	Product	Yield[a] (%)	*cis*:*trans*[b]	Entry	Product	Yield[a] (%)	*cis*:*trans*[b]
1	 **364a**	69	1:19	6[c]	 **364f**	67	1:8
2	 **364b**	70	1:10	7[d]	 **364g**	59	1:5
3	 **364c**	53	1:18	8[d]	 **364h**	61	1:2
4	 **364d**	51	1:10	9	 **364i**	58	5:1
5[c]	 **364e**	67	1:13				

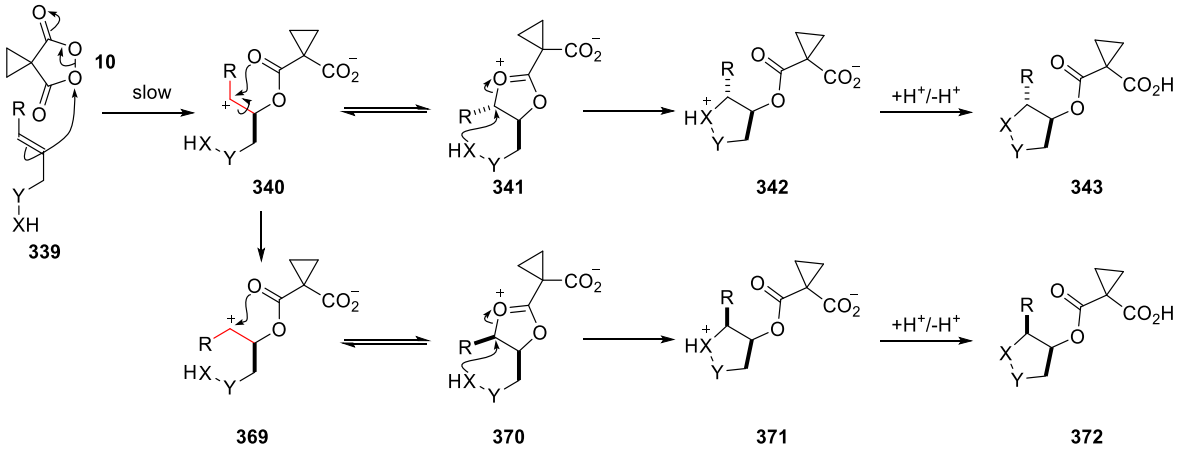
[a]Isolated yield. [b]Diastereoselectivity determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [c]Reaction conducted at 50 °C. [d]Reaction conducted at 50 °C for 72 h.

The γ-lactone synthesised from the optimisation table was isolated in a 69% yield and an excellent *cis*:*trans* diastereoselectivity of 1:19 (Table **19**, Entry 1). The reaction worked well for methyl-substituted aromatic rings in the *para*-, *meta*- and *ortho*-position, giving acceptable yields and selectivities (Table **19**, Entries 2–4, 51–70%). Bromo-substituents on the aromatic ring were also tolerated, although higher temperatures (50 °C) were needed for full conversion, giving the desired γ-lactone in good yields (67%) and *cis*:*trans* diastereoselectivity (1:8–1:13) (Table **19**, Entries 5–6).

Electron-withdrawing groups on the aromatic ring led to a lowered reactivity of the alkene and thus higher temperatures and longer reaction times were required to achieve full conversion. In addition, lower diastereoselectivities were obtained through introduction of a *p*-trifluoromethyl (1:5) and *m*-nitrile (1:2) group (Table **19**, Entries 7–8).

Altering the stereochemistry of the starting alkene provided access to the opposite diastereoisomer of the product. Thus, using (*Z*)-4-phenylbut-3-enoic acid **318i** resulted in the *cis*-γ-lactone **364i** in a moderate *cis*:*trans* selectivity of 5:1 (Table **19**, Entry 9).

A potential mechanism for this transformation is shown in Scheme **124**. With deactivated alkenes, slower nucleophilic attack of alkene **339** on the malonoyl peroxide **10** occurred. This explains the higher temperatures required for these substrates. In the intermediate **340** the open chain benzylic carbocation can freely rotate about the highlighted bond. This rotation leads to erosion of stereochemical integrity in the product. Attack of the carbonyl group in **369** on the carbocation forms dioxonium intermediate **370**. Subsequent nucleophilic attack followed by proton transfer would lead to the observed diastereomeric mixture of products **372** and **343**.



Scheme 124. Proposed mechanistic pathway giving rise to diastereomeric mixtures.

3.2.3 Confirmation of the relative stereochemistry

Determination of the *cis*:*trans* diatereomeric ratios of the γ-lactones synthesised in this metal-free oxidative heterocyclisation was provided by ^{1}H NMR spectroscopy on the crude reaction mixtures. Vicinal proton-proton coupling, $^{3}J_{HH}$, is described by the Karplus equation.[105] This equation describes an approximate relationship between the vicinal coupling constant and the dihedral angle between protons.

For the γ-lactones synthesised, two chiral centres are generated in the reaction and therefore the relative stereochemistry has to be determined. In this case, only relative stereochemistry can be reported. Figure **12** shows the ^{1}H NMR of the crude reaction mixture of cyclised products, *cis*-**364i** and *trans*-product **364a**. Comparison of both gave evidence of the relative stereochemistry of each cyclised product. The top ^{1}H NMR spectrum is from the cyclisation of (*Z*)-4-phenylbut-3-enoic acid **318i** showing a coupling constant of H^1 with H^2 of 4.4 Hz.

By contrast, the bottom ^{1}H NMR spectrum is from the cyclisation of (*E*)-4-phenylbut-3-enoic acid **318a** showing a broad single peak showing no clear coupling between H^1 and H^2. In five-membered rings the vicinal proton-proton coupling constant is higher for *cis*-stereoisomers. Therefore, by comparison of both coupling constants, cyclisation of (*Z*)-4-phenylbut-3-enoic acid **318i** provided access to the *cis*-stereoisomer **364i**, and (*E*)-4-phenylbut-3-enoic acid **318a** afforded *trans*-stereoisomer **364a**.

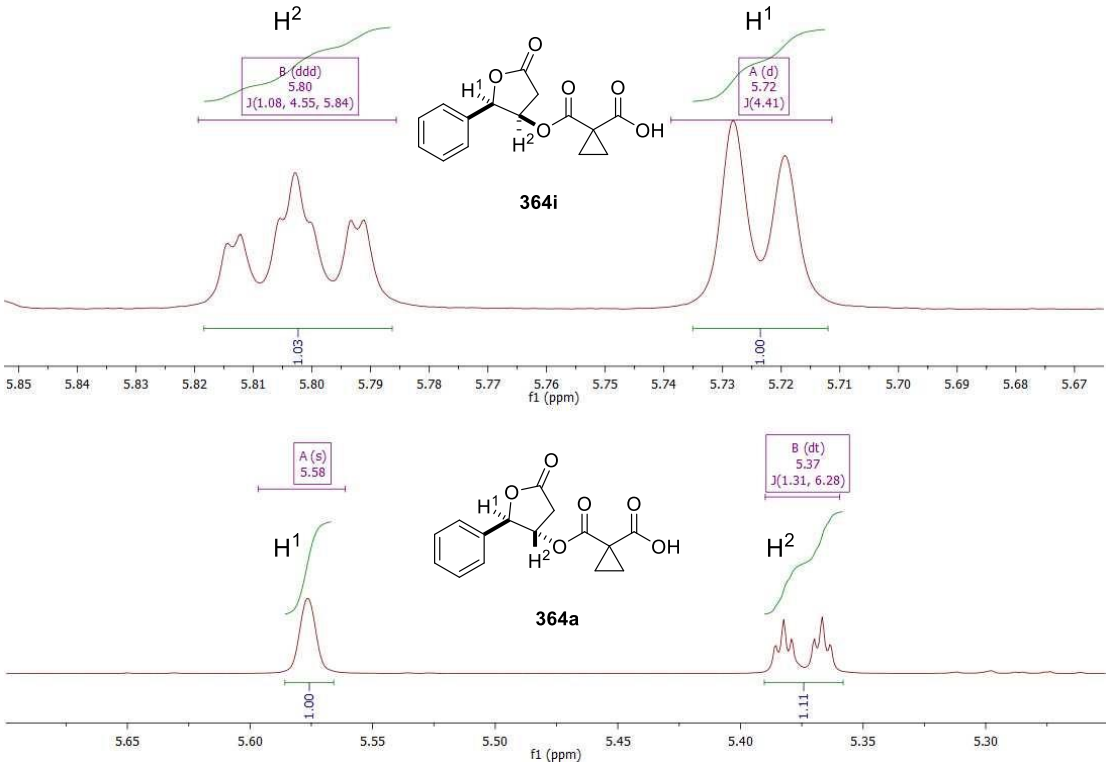


Figure 12. Top: ^{1}H NMR spectrum of the crude reaction mixture of (*Z*)-4-phenylbut-3-enoic acid **318i** starting material. Bottom: ^{1}H NMR spectrum of the crude reaction mixture of (*E*)-4-phenylbut-3-enoic acid **318a** starting material.

Further confirmation was sought in order to fully confirm the *trans*-relationship of the two protons attached to the stereogenic centres generated. For this, crystals of γ-lactone **364e** were grown from EtOAc. These crystals were analysed and Figure **13** shows the solved crystal structure. The relative stereochemistry matched predictions previously made from the ^{1}H NMR spectrum, and a

trans-relationship between the two protons on the chiral centres generated was observed. Although the picture shows defined stereocentres, the crystal itself is a racemic mixture.

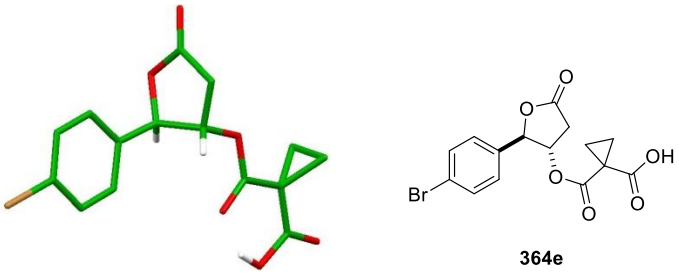


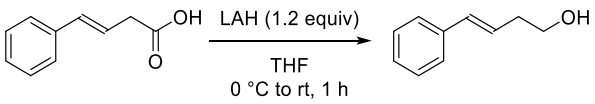
Figure 13. Crystal structure of **364e**.

3.3 Synthesis of Tetrahydrofurans

Having developed a metal-free oxidative heterocyclisation of homoallylic carboxylic acids and 2-vinyl benzoic acids for the synthesis of γ-lactones and *iso*benzofuranones respectively, the next step was to further extend this methodology. Generation of different types of oxygenated heterocycles was investigated and cyclisation of homoallylic alcohols for the synthesis of tetrahydrofuran motifs was next studied.

3.3.1 Optimisation

trans-4-Phenylbut-3-en-1-ol **373a** was chosen for optimising the reaction, and was synthesised by lithium aluminium hydride reduction of *trans*-styrylacetic acid **318a** (Scheme **125**).[106]

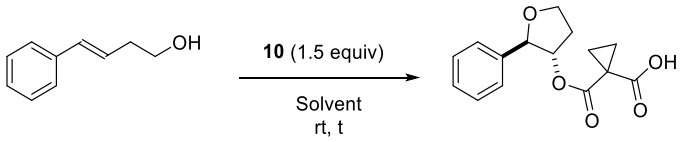


318a 78% **373a**

Scheme 125. Synthesis of *trans*-4-phenylbut-3-en-1-ol **373a**.

Data relevant to the development of the cyclisation is shown in Table **20**. Following the precedent set by the studies using carboxylic acids, the use of HFIP was initially examined. Dry HFIP afforded the desired cyclic ether after 6 h with a good *cis*:*trans* selectivity of 1:11 (Table **20**, Entry 2). Performing the reaction in commercial HFIP gave the *trans*-product **374a** after only 3 h at rt (Table 20, Entry 3; *cis*:*trans* 1:18).

Table 20. Optimisation[a]



373a **374a**

Entry	Solvent	Additive	Time/h	Conv[b]/%	*cis*:*trans*[b]
1[c]	HFIP	-	4	87	1:12
2[c]	HFIP	-	6	100	1:11
3	**HFIP**	**-**	**3**	**100**	**1:18**
4	MeOH	-	3	19	1:1
5	EtOH	-	3	56	1:5
6	IPA	-	3	41	n.d.
7	EtOH	HFIP (1.0 equiv)	3	61	1:4
8	EtOH	HFIP (2.0 equiv)	3	61	1:4

[a]All reactions performed in duplicate with *trans*-4-phenylbut-3-en-1-ol (1.0 mmol) at 0.5 M concentration. [b]Determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [c]Solvent dried over 3 Å molecular sieves for 24 h prior to use.

Similar to the previous studies using carboxylic acids, the use of the non-fluorinated alcohols methanol (Table **20**, Entry 4), ethanol (Table **20**, Entry 5) and isopropanol (Table **20**, Entry 6), gave complex mixtures with low conversions. Use of 1.0 or 2.0 equiv of HFIP (Table **20**, Entries 7–8) with ethanol had no notable influence on the reaction outcome.

Based upon this screening we adopted a standard set of conditions for the reaction of alkenes containing a pendant alcohol functionality with 1.5 equiv of peroxide **10** at rt for 3 h in HFIP as the reaction solvent (Table **20**, Entry 3).

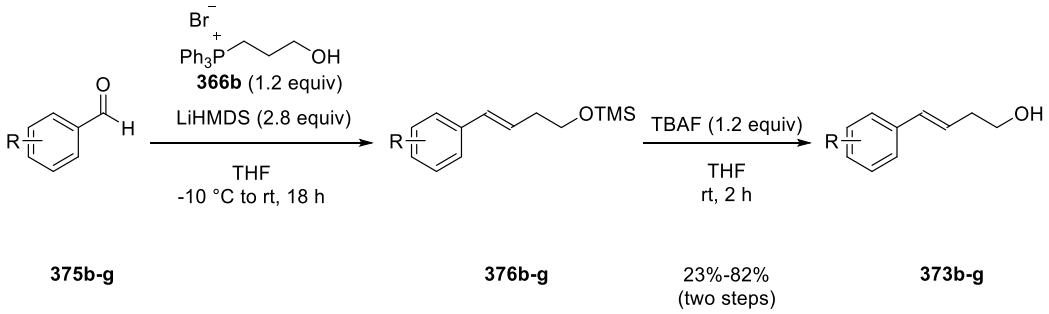
3.3.2 Substrate Scope and Limitations

Having optimised the oxidative heterocyclisation with homoallylic alcohols for the generation of tetrahydrofuran rings, the substrate scope was investigated.

3.3.2.1 Synthesis of starting materials

Similar to the homoallylic carboxylic acid **318b-h** synthesis, a family of homoallylic alcohols **373b-g** were synthesised by Wittig reaction. The reaction of aldehydes **375b-g** and the alcohol containing triphenylphosphonium bromide salt **366b** in the presence of a base provided protected TMS-homoallylic alcohols **376b-g** (Scheme **126**).[107] An additional TBAF deprotection step was

required, due to mixtures of deprotected and protected alcohols after the Wittig reaction. Treatment of the crude reaction mixtures with 1.2 equiv of TBAF gave the target compounds **376b-g** in 23–82% yield over two steps. A different base could be used in order to avoid the additional TBAF deprotection, however this was not intended and LiHMDS was used for all the Wittig reactions.



Scheme 126. General scheme for synthesis of homoallylic alcohols **373b-g.**

Figure **14** shows the alkenes with pendant alcohols **373b-g** synthesised by a Wittig strategy for determining the scope of this oxidative heterocyclisation for the preparation of tetrahydrofurans. Yields presented are after column chromatography purification.

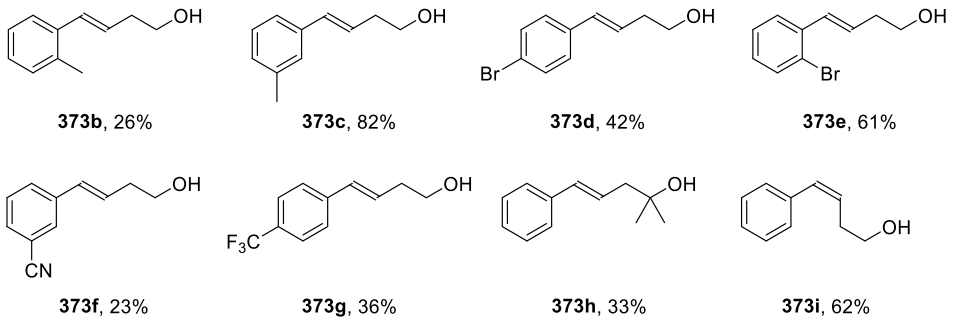
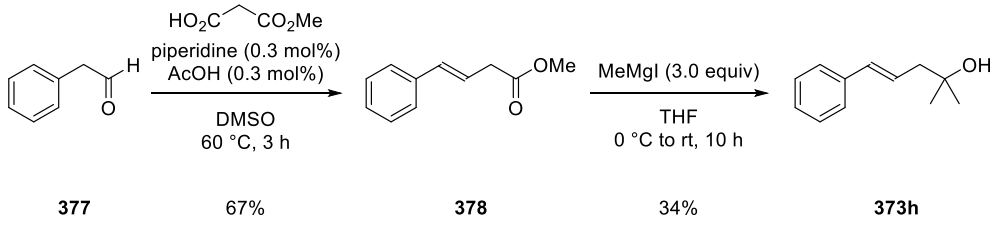


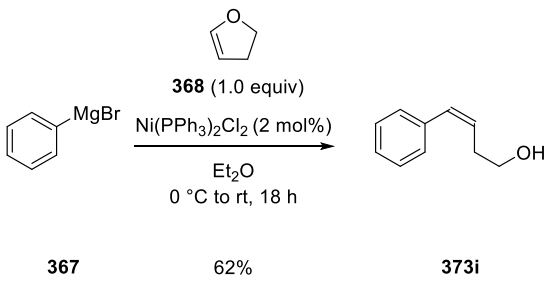
Figure 14. Substrate scope homoallylic alcohols.

In addition, homoallylic alcohol **373h** was prepared by a two-step procedure (Scheme **127**). Knoevenagel condensation of phenylactetaldehyde **377** with monomethyl malonate followed by a double Grignard addition with methylmagnesium iodide gave alcohol **373h**.[108]



Scheme 127. Synthesis of homoallylic alcohol **373h**.

Synthesis of (*Z*)-4-phenylbut-3-en-1-ol **373i** was carried out by treatment of phenylmagnesium bromide **367** with 2,3-dihydrofuran **368** using a Ni(II) catalyst (Scheme **128**).[104]



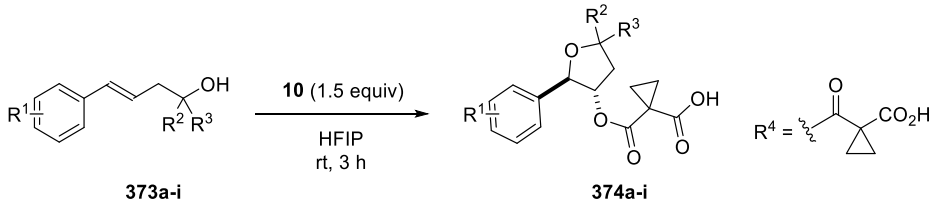
Scheme 128. Synthesis of (*Z*)-4 phenylbut-3-en-1-ol **373i**.

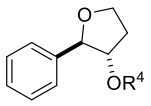
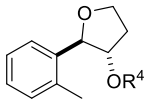
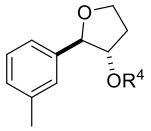
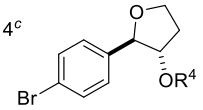
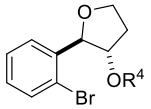
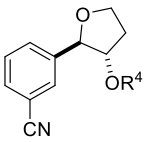
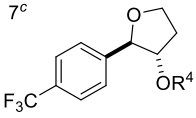
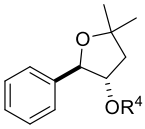
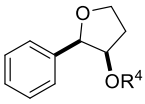
3.3.2.2 Substrate scope

Having synthesised the homoallylic alcohol starting materials, they were examined in this new methodology. The previously developed optimal conditions were used and cyclic ethers were isolated.

Cyclic ether **374a** was isolated in an 80% yield and an excellent *cis*:*trans* diastereoselectivity of 1:18 (Table **21**, Entry 1). Introduction of an electron-donating group on the aromatic group in the *para*-, *meta*- and *ortho*-positions provided tetrahydrofuran rings in good yields (44–78%) and selectivities (1:5–1:16) (Table **21**, Entries 2–5). In the case of *para*- and *meta*-bromine substitution, higher temperatures (50 °C) were needed for full conversion. Electron-withdrawing groups were also introduced on the aromatic ring and excellent results were obtained (Table **21**, Entries 6–7) with *cis*:*trans* diastereoselectivities of up to 1:27. Introduction of dimethyl substitution adjacent to the alcohol nucleophile proved efficatious giving the desired oxygenated heterocycle **374h** in an 82% yield and a *cis*:*trans* diastereoselectivity of 1:16 (Table **21**, Entry 8). (*Z*)-4-Phenylbut-3-en-1-ol **373i** was also examined and the *cis*-diastereoisomer **374i** was isolated as the major product in a 67% yield and a *cis*:*trans* selectivity of 5:1 (Table **21**, Entry 9).

Table 21. Substrate Scope.



Entry	Product		Yield[a] (%)	*cis*:*trans*[b]
1		**374a**	80	1:18
2		**374b**	56	1:13
3		**374c**	44	1:16
4[c]		**374d**	67	1:15
5[c]		**374e**	78	1:5
6[c]		**374f**	80	1:27
7[c]		**374g**	59	1:21
8		**374h**	82	1:16
9		**374i**	67	5:1

[a]Isolated yield. [b]Diastereoselectivity determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [c]Reaction conducted at 50 °C.

3.3.3 Confirmation of the relative stereochemistry

As carried out with the γ-lactone series for the determination of the relative stereochemistry of the products, ^{1}H NMR spectra of the crude reaction mixture of cyclic ethers **374a** and **374i** was undertaken.

Figure **15** shows the ^{1}H NMR of the crude reaction mixture of cyclised products, *cis*-**374i** and *trans*-product **374a**. Comparison of both gave evidence of the relative stereochemistry of each cyclised product. The top ^{1}H NMR spectrum is from the cyclisation of (*Z*)-4-phenylbut-3-en-1-ol **373i** showing a coupling constant of H^1 with H^2 of 4.2 Hz. By contrast, the bottom ^{1}H NMR spectrum resulting from cyclisation of (*E*)-4-phenylbut-3-en-1-ol **373a** showed a coupling constant of H^1 with H^2 of 1.6 Hz. In five-membered rings the vicinal proton-proton coupling constant is higher for

cis-stereoisomers. Therefore, by comparison both coupling constants, cyclisation of (*Z*)-4-phenylbut-3-en-1-ol **373i** provided access to *cis*-stereoisomer **374i**, and (*E*)-4-phenylbut-3-en-1-ol **373a** afforded *trans*-stereoisomer **374a**.

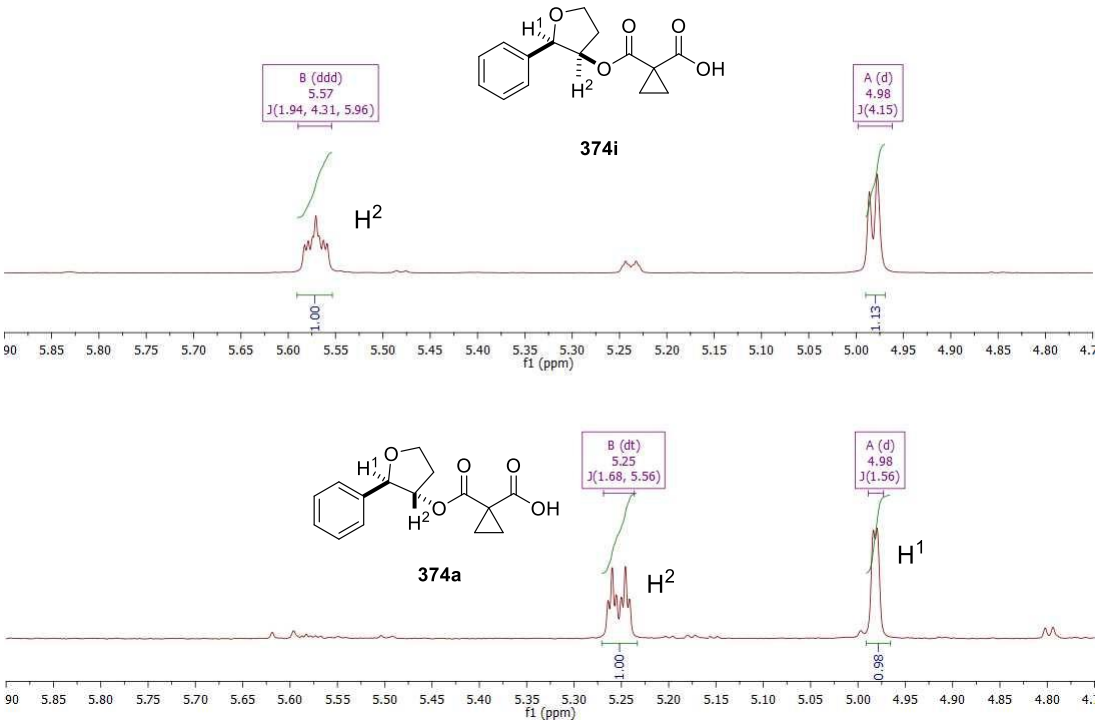


Figure 15. Top: ^{1}H NMR spectrum of the crude reaction mixture of (*Z*)-4-phenylbut-3-en-1-ol **373i** starting material. Bottom: ^{1}H NMR spectrum of the crude reaction mixture of (*E*)-4-phenylbut-3-en-1-ol **373a** starting material.

Additional evidence was found when a single crystal of pure cyclic ether **374h** was grown. The solved X-ray structure is shown in Figure **16**, confirming the predictions previously made, clearly showing the *trans*-relationship of the two protons attached to the chiral centres generated.

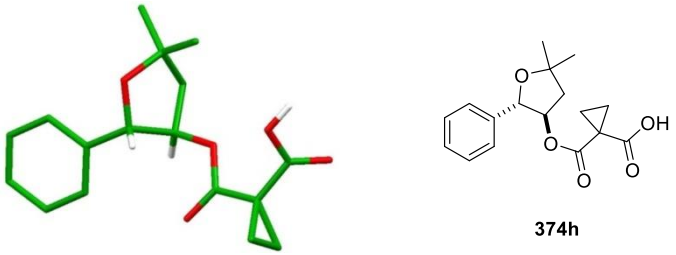
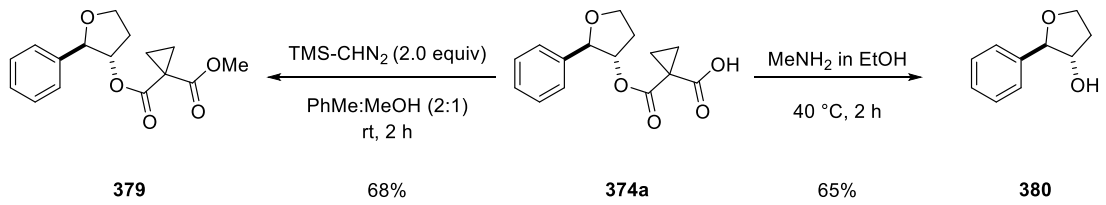


Figure 16. Crystal structure of **374h**.

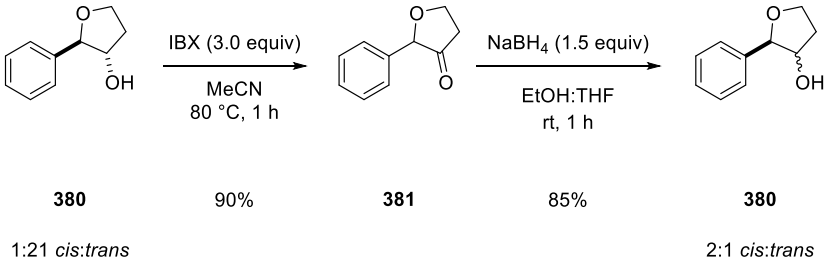
3.3.4 Further chemistry with cyclic ether 379

In order to ease purification and allow further functionalisation of the product, cyclic ether **374a** was converted into the corresponding alcohol **380** by ethanolic aminolysis. Cyclic ether **374a** was treated with a solution of methylamine in ethanol and heated to 40 °C for 2 h. After this time, alcohol **380** was isolated in 65% yield (Scheme **129**). The relative stereochemistry of the stereogenic centres was not affected under these conditions. The presence of the carboxylic acid in **374a** was further confirmed by methyl ester formation to give **379** (68%).



Scheme 129. Further chemistry with **374a**.

Confirmation of the *cis*:*trans* benzylic peaks in the ^{1}H NMR spectrum was further studied (Scheme **130**). Oxidation of alcohol **380** with IBX followed by a selective reduction of ketone **381** with $NaBH_4$ gave a *cis*:*trans* diastereomeric mixture (2:1) of the corresponding alcohol **380** (Figure 17). By comparing the benzylic peaks of the *cis*- and *trans*-product after the $NaBH_4$ reduction, it was possible to reinforce the selectivity found in the oxidative heterocyclisation.



Scheme 130. Confirmation of diastereomeric ratio of cyclic ether alcohol **380**.

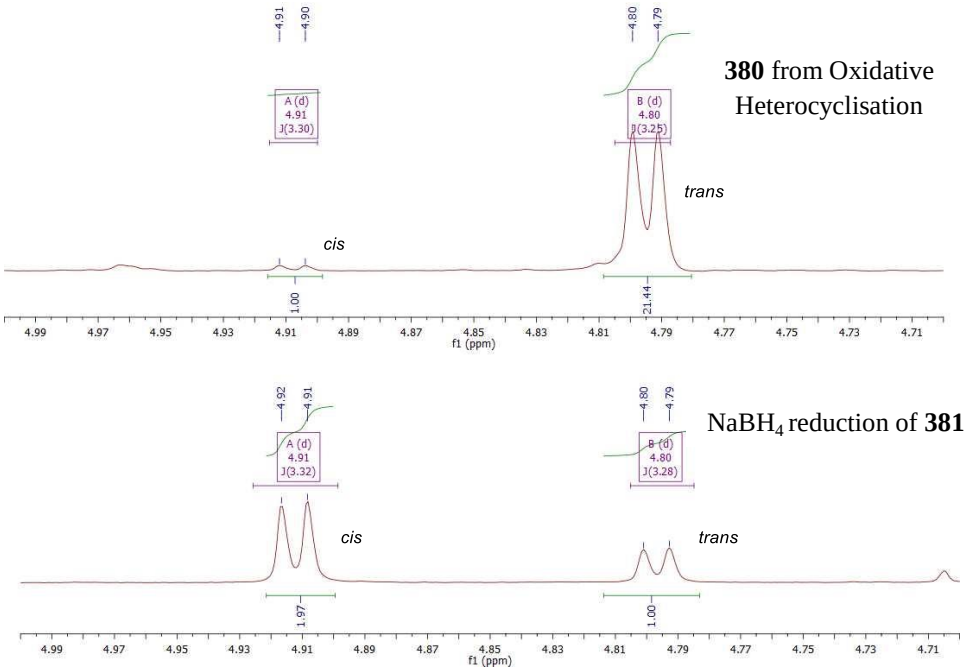
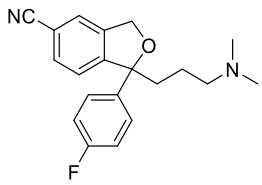


Figure 17. Top: ^{1}H NMR spectrum of cyclic ether **380** after hydrolysis. Bottom: ^{1}H NMR spectrum of cyclic ether **380** after $NaBH_4$ reduction of **381**.

3.4 Synthesis of Citalopram

A novel oxidative transformation with malonoyl peroxide **10** had been developed for the synthesis of *iso*benzofuranones, γ-lactones and cyclic ethers. This unique methodology was applied in the synthesis of Citalopram **382** (Figure **18**). Citalopram **382** was selected as the target due to the presence of an *iso*benzofuran motif in the core of the active molecule.



382

Figure 18. Active pharmaceutical ingredient of Citalopram **382**.

Citalopram **382** is a drug used for the treatment of depression and in 1998 it was approved by the U.S. Food and Drug Administration for this indication.[109] Although it is used as an antidepressant, in some countries it can also be prescribed for panic disorders or for the treatment obsessive-compulsive disorders. It is one of the most effective antidepressants after mirtazapine,[110] venlafaxine[111] and sertraline.[112]

Due to the presence of a single chiral centre, Citalopram exists as two optical isomers (Figure 19). While Citalopram is sold as a racemic mixture, only the *S*-enantiomer is active.

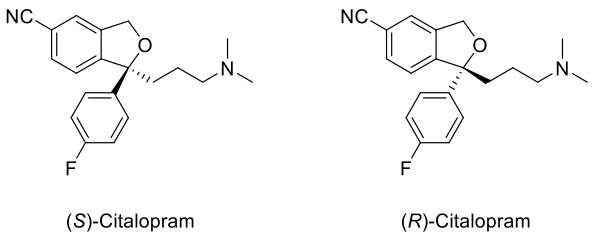
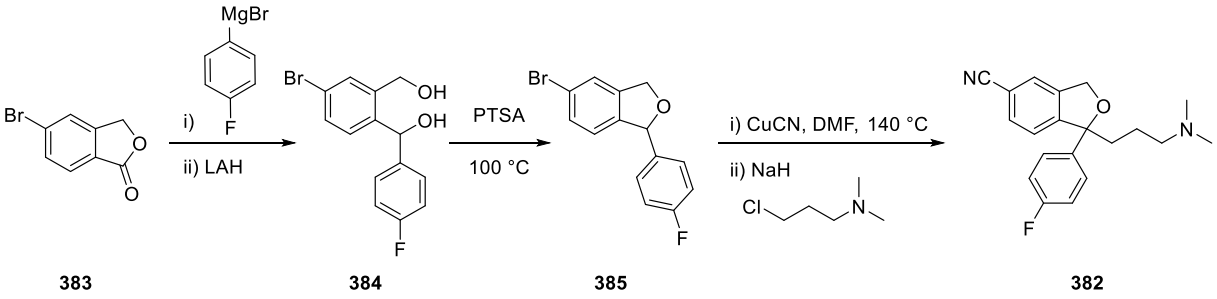


Figure 19. Citalopram enantiomers.

3.4.1 First synthesis of Citalopram

The first reported synthesis of Citalopram **382** was in 1979 by Blancafort *et al.*[113,114] (Scheme 131). This synthesis involved the reaction of 5-bromophthalide **383** with 4-fluorophenylmagnesium bromide to give a ketone which was reduced with lithium aluminium hydride to give diol **384**. Acid-catalysed intramolecular cyclisation then generated the *iso*benzofuran ring **385**. Introduction of the nitrile functionality using CuCN by S_NAr followed by reaction with 3-(dimethylamino)propyl chloride in the presence of a NaH as a base gave racemic Citalopram **382** as the final product over five steps.

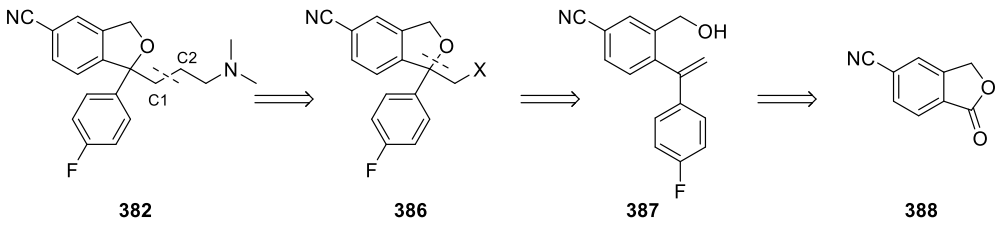


Scheme 131. First reported synthesis of Citalopram **382**.

Subsequently, alternative methodologies have been developed where the majority involved Grignard addition either into 5-bromophthalide **383** or to 5-cyanophthalide **388**.[115,116]

3.4.2 Transition metal-free synthesis of Citalopram

The novel oxidative heterocyclisation with malonoyl peroxide **10** previously described was applied to the synthesis of Citalopram **382**. Disconnection of the molecule is shown in Scheme **132**.



Scheme 132. Citalopram retrosynthesis.

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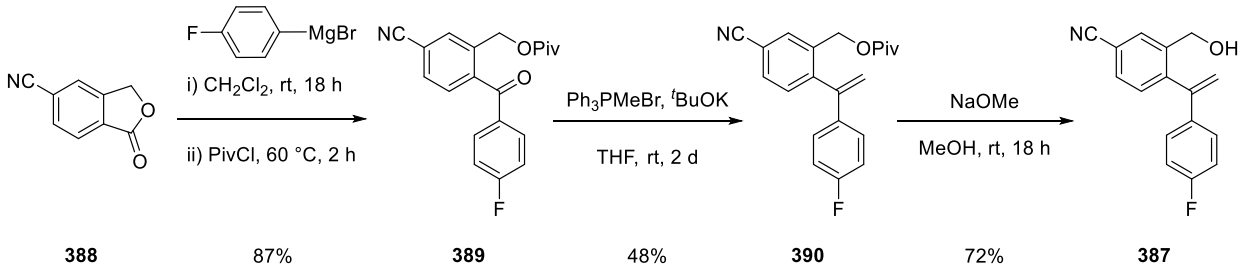
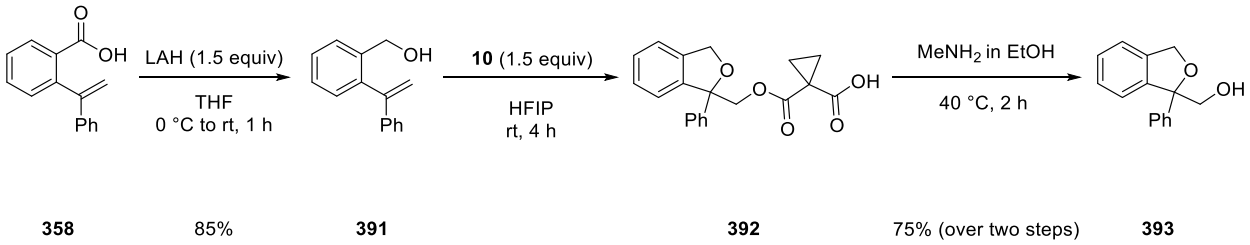
With the use of our novel heterocyclisation as the key step, the first disconnection would be through the sp^3-sp^3 C–C bond. Next, disconnection of the *iso*benzofuran ring was made, and therefore alkene alcohol **387** had to be synthesised.

Synthesis of alkene alcohol **387** was reported by France[117] in 2013, providing access to gram quantities of material in only three steps (Scheme **133**). Treatment of 5-cyanophthalide **388** with 4-fluorophenylmagnesium bromide followed by alcohol protection with pivaloyl chloride provided ketone **389** in 87% yield. Wittig reaction with methyltriphenylphosphonium bromide provided alkene **390** in a 48% yield. Alcohol **387** was isolated after methanolysis of **390** with sodium methoxide in methanol. Synthesis of **387** was accomplished in a three-step procedure with a 30% overall yield (Scheme **133**).



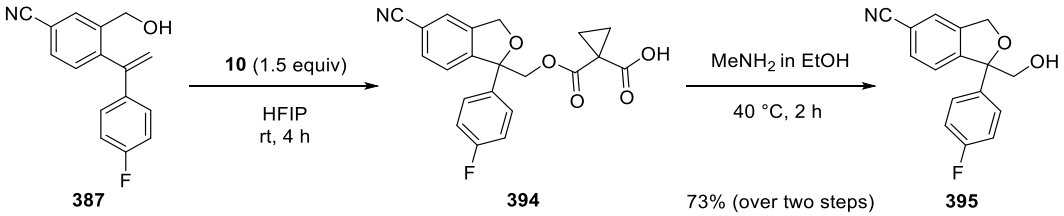
Scheme 133. Synthesis of **387**.

Before running the cylisation reaction of alkene alcohol **387** with malonoyl peroxide **10**, the oxidative heterocyclisation was applied to a similar substrate as a test reaction to confirm it could be used for **387**. Reaction of alkene **391**, prepared by reduction of benzoic acid **358**, with malonoyl peroxide **10** provide cyclised product **392**, which after ethanolysis, gave alcohol **393** in a 75% isolated yield (Scheme **134**).



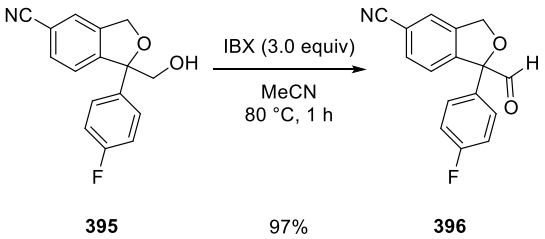
Scheme 134. Reaction of malonoyl peroxide **10** with test substrate **391**.

Successful results from the previous reaction, drove us to examine the novel oxidative heterocyclisation with malonoyl peroxide **10** using substrate **387** (Scheme **135**). Optimal reaction conditions were applied, although longer reaction times were needed due to the nitrile and fluoride electron-withdrawing groups on the aromatic rings. The reaction proceeded well in HFIP at rt for 15 h providing carboxylic acid **394**, which was characterised and used in the next step without further purification. Aminolysis led to alcohol **395** in a 73% yield over two steps.



Scheme 135. Application of oxidative heterocyclisation with malonoyl peroxide **10**.

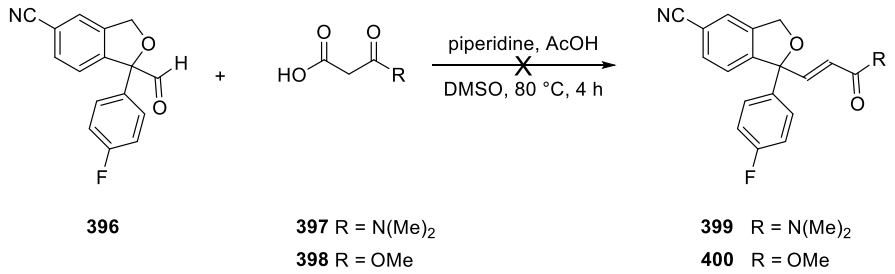
At this stage, functionalisation of **395** proved challenging due to the hindered nature of the primary alcohol, for this reason, oxidation of alcohol **395** with IBX was carried out to give aldehyde **396** in a 97% yield (Scheme **136**).



Scheme 136. IBX oxidation.

Although aldehyde **396** proved a reactive species compared to alcohol **395**, aldehyde **396** also proved difficult to functionalise. A modified Knoevenagel reaction was examined using

N,*N*-dimethyl-3-oxo-*β*-alanine **397** with aldehyde **396** (Scheme **137**) to form an *α*,*β*-unsaturated amide **399**. However, only starting material was recovered after work-up. Also, a Doebner-Knoevenagel reaction was examined with monomethyl malonate **398**, however, this transformation did not offer any improvement in the reaction outcome.

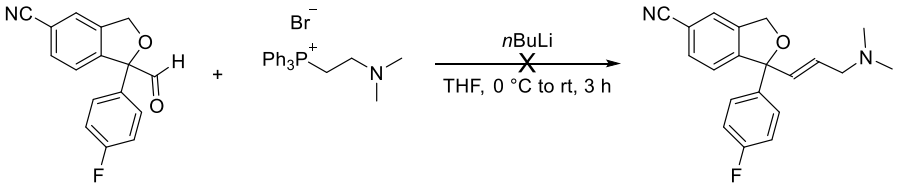


396 **397** R = $N(Me)_2$ **399** R = $N(Me)_2$

398 R = OMe **400** R = OMe

Scheme 137. Intended Knoevenagel reaction.

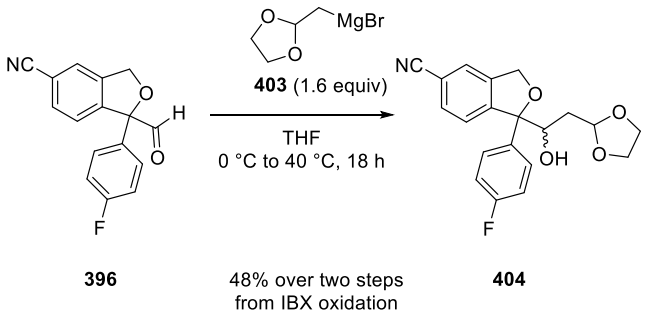
In another attempt to functionalise aldehyde **396** a Wittig reaction was carried out. Using commercially available 2-dimethylaminoethyltriphenylphosphonium bromide **401** with *n*BuLi to form the ylide, followed by addition of aldehyde **396** did not provide *α*,*β*-unsaturated amine **402** (Scheme 138). Although aldehyde **396** was fully consumed, ^{1}H NMR of the crude reaction mixture showed a complex mixture from which we were unable to identify any of the desired reaction product **402**.



396 **401** **402**

Scheme 138. Attempted Wittig reaction.

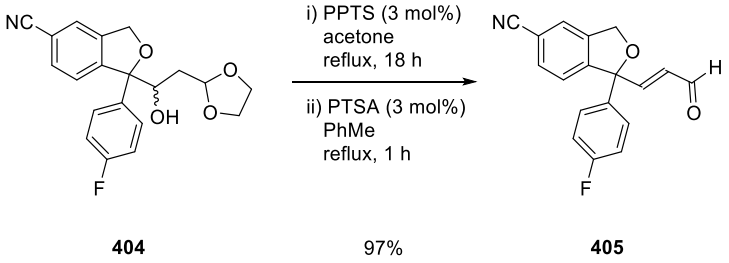
Due to the failure of both the Wittig and Knoevenagel reactions, Grignard addition to aldehyde **396** was next examined, despite the fact this increased the number of steps required in the synthesis (Scheme **139**).



Scheme 139. Grignard addition.

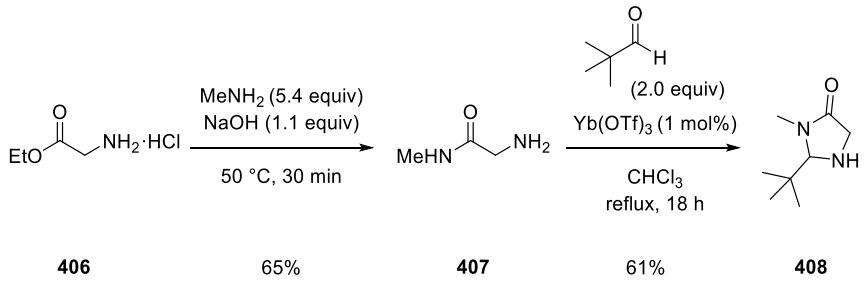
Pleasingly, the reaction proceeded well by treating crude aldehyde **396** with commercially available (1,3-dioxolan-2-ylmethyl)magnesium bromide **403** to give the alcohol **404** as a 1:1 mixture of diastereoisomers in a 48% yield over two steps (Scheme **139**). Separation of both diastereoisomers for characterisation was attempted but proved challenging. However, this stereocentre was removed in the next step, and so separation of the isomers was not necessary.

Following the effective Grignard addition, hydrolysis of the acetal was successfully achieved for the formation of aldehyde **405** using catalytic amount (3 mol%) of pyridinium *p*-toluenesulfonate (PPTS) which was followed by dehydration with *p*-toluenesulfonic acid (PTSA) to give *α*,*β*-unsaturated aldehyde **405** (Scheme **140**). Increasing the catalytic amount of PPTS (30 mol%) allowed both reactions to be carried out in one-pot, giving **405** in a 68% yield.



Scheme 140. Hydrolysis elimination reaction.

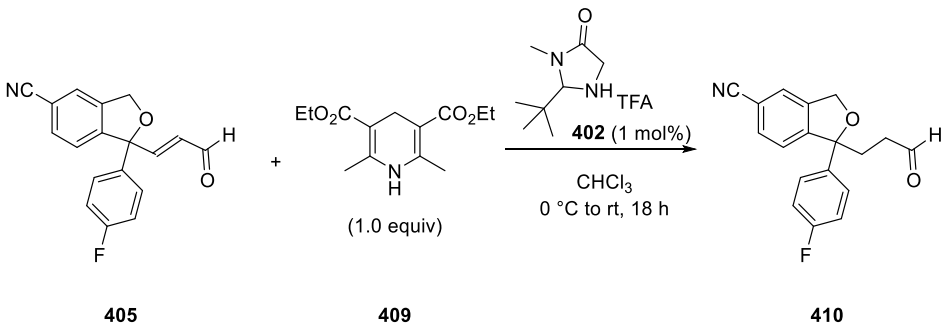
With the synthesis of Citalopram almost complete, the next step was the reduction of *α*,*β*-unsaturated aldehyde **405**. Literature research provided an example where an *α*,*β*-unsaturated aldehyde was reduced asymmetrically using a chiral imidazolidinone catalyst in the presence of the Hantzsch ester **409** as the hydride source.[118] Since the alkene reduction did not provide potential stereocentres, the imidazolidinone catalyst was not synthesised in a stereocontrolled manner. Synthesis of the racemic imidazolidinone catalyst was reported by Tomkinson in 2011 (Scheme 141).[119]



Scheme 141. Synthesis of the imidazolidinone catalyst **408.**

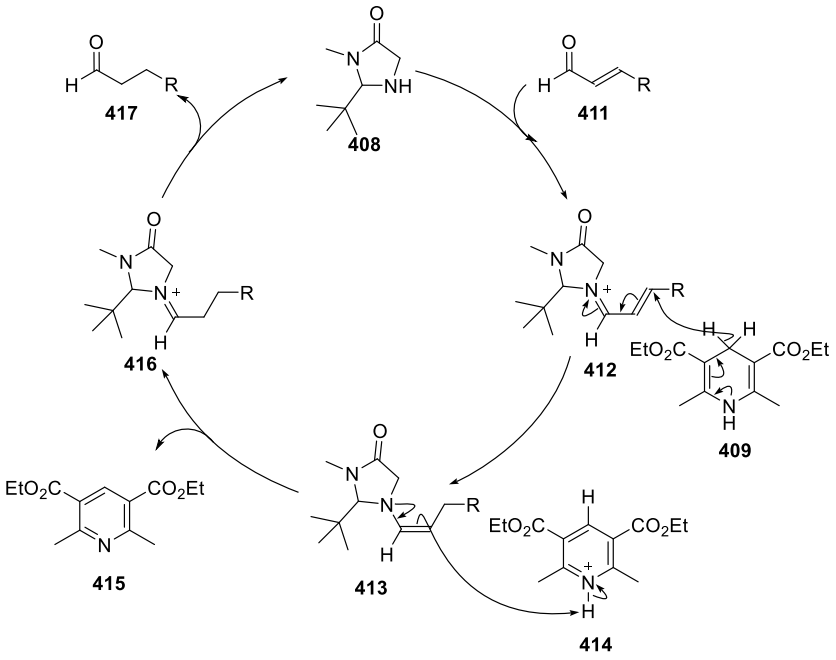
Glycine ethyl ester hydrochloride **406** was reacted in an ethanolic solution of methylamine with a stoichiometric amount of sodium hydroxide to give amino amide **407**. Then, amino amide **407** was refluxed with pivaldehyde and a catalytic amount of ytterbium(III) trifluoromethanesulfonate to afford imidazolidinone catalyst **408** in a 40% overall yield after two steps (Scheme **141**). With the imidazolidinone catalyst **408** available, the organocatalytic conjugate reduction of the *α,β*-unsaturated aldehyde **405** was examined.

Reaction of *α,β*-unsaturated aldehyde **405** with a stoichiometric amount of Hantzsch ester **409**, a catalytic amount of imidazolidinone catalyst **402** and TFA efficiently reduced the alkene functionality giving aldehyde **410**, which was used in the next step without further purification (Scheme **142**).



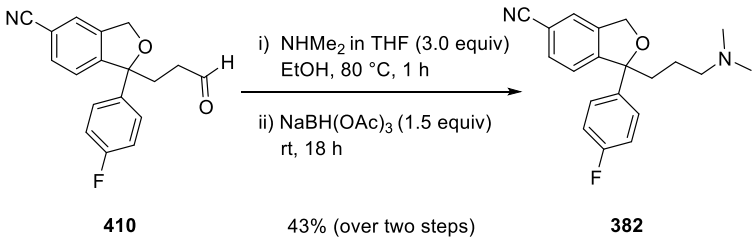
Scheme 142. Organocatalytic conjugate reduction.

Mechanistically, the reaction proceeds as shown in Scheme **143**. Condensation of imidazolidinone catalyst **402** with the *α,β*-unsaturated aldehyde **405** provided iminium ion intermediate **412** (Scheme **143**). Then, Hantzsch ester **409** reacts in a conjugate manner with iminium ion intermediate **412** to give enamine **413** and pyridinium salt **414**. This pyridinium salt **414** protonates enamine **413** to give iminium **416** and pyridine **415**. Then, hydrolysis of **416** releases the imidazolidinone catalyst **408** back into the catalytic cycle and gives the corresponding saturated aldehyde product **417**.



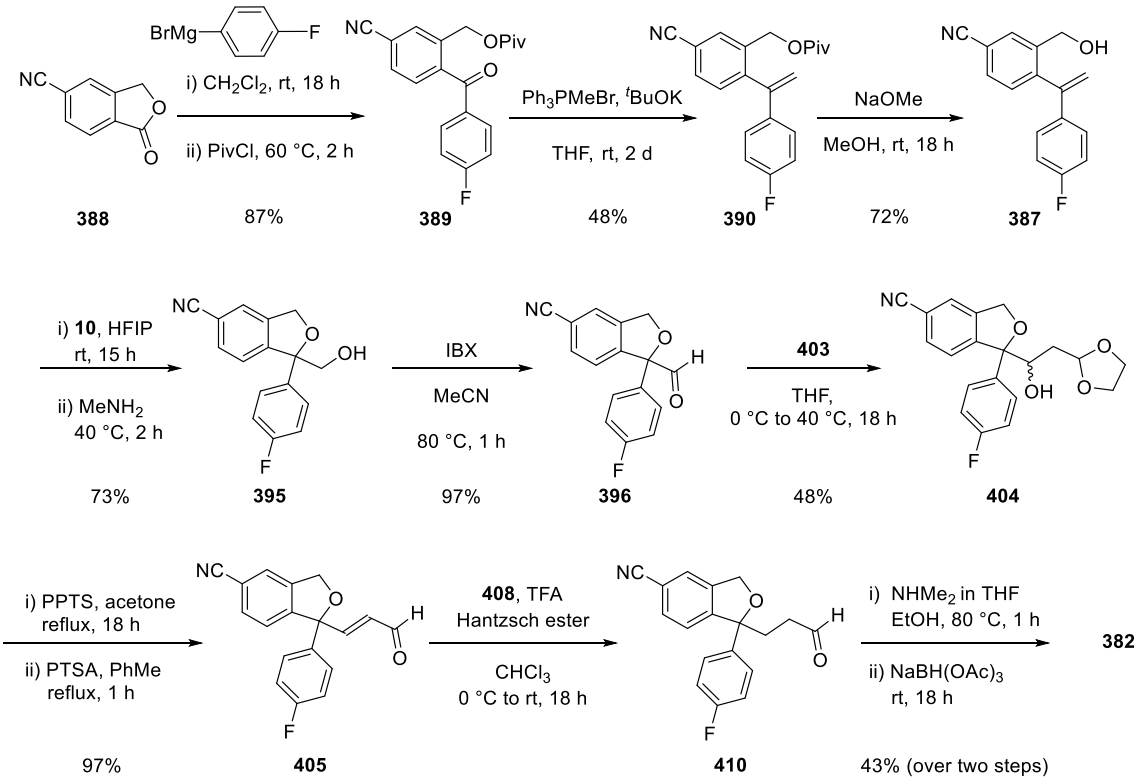
Scheme 143. Organocatalytic conjugate reduction mechanism.

The final reductive amination step was carried out by reaction of aldehyde **410** with dimethylamine followed by addition of sodium triacetoxyborohydride (Scheme **144**). Final product, Citalopram was isolated with a 43% yield after two steps, the organocatalytic conjugate reduction and the reductive amination.



Scheme 144. Reductive amination reaction.

To summarise, Citalopram has been prepared in a transition-metal free synthesis applying the novel oxidative heterocyclisation of alkene alcohol **387** with malonoyl peroxide **10** as one of the key steps for the generation of the *iso*benzofuran ring. Citalopram **382** has been synthesised in a total of 11 steps (10 steps if hydrolysis of the acetal and elimination of H_2O take place in one-pot) and an overall yield of 4.4% (Scheme **145**).

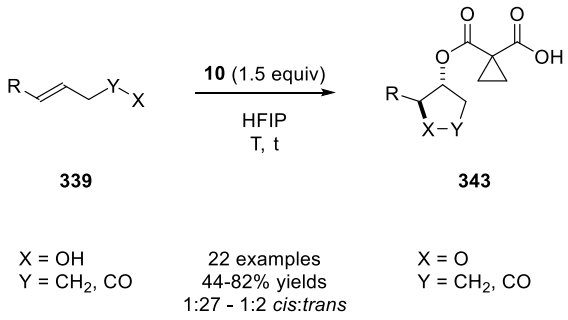


Scheme 145. Synthesis of Citalopram **382**.

3.5 Conclusions

A series of different homoallylic carboxylic acids were synthesised, typically by Wittig reaction of an aromatic aldehyde and a triphenylphosphonium bromide salt. In a similar fashion, homoallylic alcohols were prepared by Wittig reaction of an aromatic aldehyde with the appropriate triphenylphosphonium bromide salt. Substituted 2-vinyl benzoic acids were generally synthesised in a three step synthesis, involving a Suzuki or Stille coupling.

Three families of different starting materials **339** have been prepared with the purpose of developing a novel oxidative heterocyclisation. Pleasingly, a metal-free cyclisation has been described, using the starting materials prepared, for the synthesis of *iso*benzofuranones, γ-lactones and cyclic ethers (Scheme **146**).



Scheme 146. Oxidative heterocyclisation general scheme.

Furthermore, high levels of retention of stereochemistry of the starting material were obtained, despite the fact that the reaction proceeds *via* an open chain benzylic carbocation intermediate. Structure verification of the relative stereochemistry of the products was provided by X-ray analysis of representative examples.

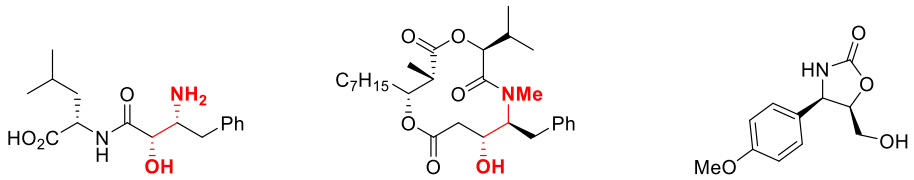
Application of this metal-free methodology in the synthesis of Citalopram, an antidepressant, has also been achieved. Citalopram was synthesised over 11 steps with a 4.4% overall yield through a transition metal-free synthesis.[120]

Chapter 3: Alkene Aminohydroxylation with Malonoyl Peroxides: Synthesis of Pyrrolidines

1 Introduction

Introduction of an amine functional group into an organic molecule can be achieved by a number of methods, including reductive amination of aldehydes or ketones, the Gabriel synthesis or reduction of nitriles, amides and nitro-compounds. Vicinal functionalisation of alkenes is one of the most studied transformations in organic chemistry[121-123] due to its utility in the synthesis of biologically active molecules. However, introduction of 1,2-amino alcohols directly onto alkenes has received less attention and methodologies for this transformation are still the focus of active research.

The 1,2-amino alcohol moiety is present in a large variety of biologically active molecules.[124] For example, Bestatin **418**, a *syn*-α-hydroxy-β-amino acid (Figure **20**) is widely used as an aminopeptidase inhibitor exhibiting antitumor activity.[125] Hapalosin **419** (Figure **20**), a 12-membered cyclic compound with an *anti*-β-hydroxy-γ-amino functional group in its structure, has been shown to have multidrug resistance-reversing activity.[126,127]



Bestatin, 418 **Hapalosin, 419** **Cytoxazone, 420**

Figure 20. Structures containing 1,2-aminoxygenated moieties.

Another potent chemotherapeutic compound is Cytoxazone **420**. This oxazolidinone heterocycle was synthesised by Sudalai and co-workers in 2006 using a Rh-catalysed diastereoselective amination as one of the key steps.[128] It is therefore not surprising that methods to synthesise 1,2-amino alcohol moieties have attracted the attention of many research groups around the world.

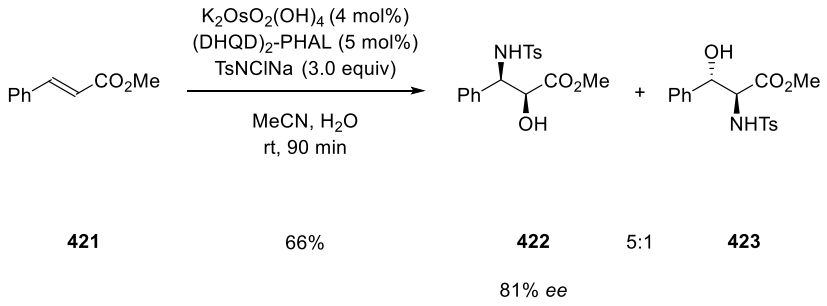
2 Methods for the Aminohydroxylation of Alkenes

2.1 Transition metal-based methods

2.1.1 Osmium

The most powerful reaction for the enantioselective generation of vicinal amino alcohols was first reported by Sharpless *et al.* in 1996.[129] This work was published after the discovery of the asymmetric *syn*-dihydroxylation of alkenes,[2] using osmium catalysis.

The Sharpless asymmetric aminohydroxylation of alkenes uses $K_2OsO_2(OH)_4$ and $(DHQD)_2$-PHAL, a chiral ligand which directs the enantioselectivity of the reaction. Stoichiometric amounts of the nitrogen source, chloramine-T, are required which undertakes a dual role: i) as a reagent and ii) as a reoxidant. Reaction of alkene **421** with catalytic amounts of Os^{VIII} and chiral ligand in the presence of a nitrogen source provided *syn*-aminohydroxylated product **422** in good yield (66%) with good levels of enantioselectivity (81% *ee*) (Scheme **147**).



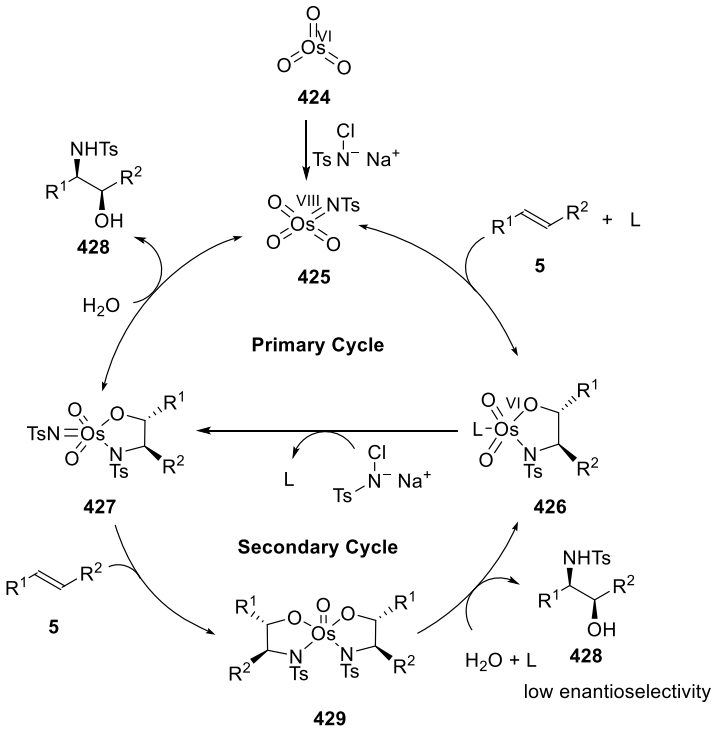
Scheme 147. Enantioselective aminohydroxylation of alkenes.

Mechanistically, it has been established that the reaction proceeds through two linked catalytic cycles (Scheme **148**).

The primary cycle starts with the oxidation of Os^{VI} **424** to Os^{VIII} **425** with chloramine-T to give an imidotrioxoosmium(VIII) **425** species. Addition of a chiral ligand and alkene **5** generates azaglycolate intermediate **426** through a [3+2] cycloaddition, reducing Os^{VIII} back to Os^{VI}. At this stage, the absolute stereochemistry has been established due to the coordination of the chiral ligand to the osmium metal centre. Reoxidation of **426** with chloramine-T gives species **427**, which after hydrolysis leads to aminohydroxylated product **428** with high levels of enantioselectivity.

In the competing secondary cycle, intermediate **427** can also be intercepted by a second molecule of alkene **5**. This generates bis(azaglycolate) osmium species **429** in a ligand-free [3+2] cycloaddition. Low levels of enantioselectivity in the product are obtained after hydrolysis of **429**

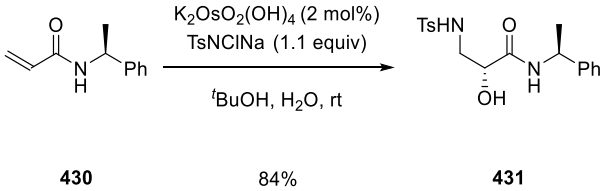
from the secondary cycle, due to the absence of a chiral ligand in bis(azaglycolate)osmium intermediate **429**.



Scheme 148. Catalytic cycle for the aminohydroxylation of alkenes.

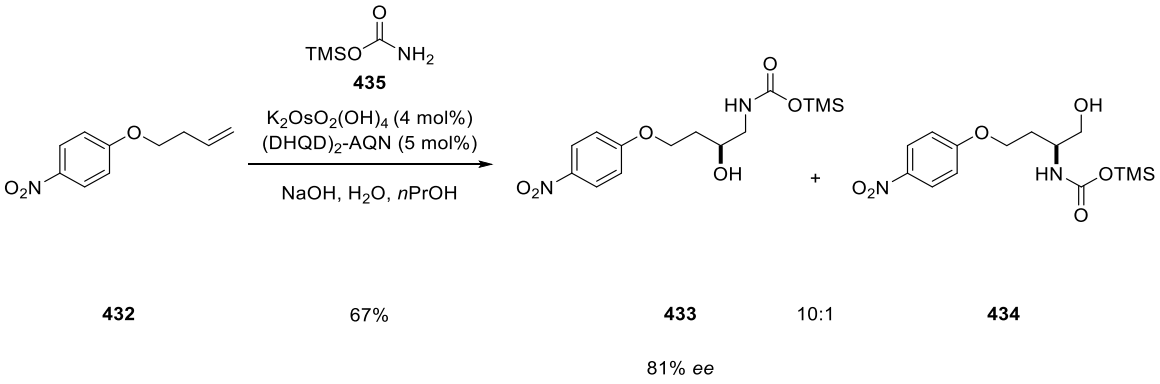
The mechanism and regiochemistry of the [3+2] cycloaddition were supported by computational studies undertaken by Strassner in 2010.[130] With the aim of further enhancing the outcome of this reaction, different nitrogen sources have been introduced as well as a number of different chiral ligands.

Muñiz *et al.* developed the first asymmetric aminohydroxylation of acrylamides without the need for a chiral ligand.[131] Reaction of chiral acrylamide **430** under Sharpless aminohydroxylation conditions provided aminohydroxylated product **431** as a single regioisomer and diastereoisomer (Scheme **149**). However, the methodology was not applicable to internal alkenes due to low levels of regio- and diastereoselectivity.



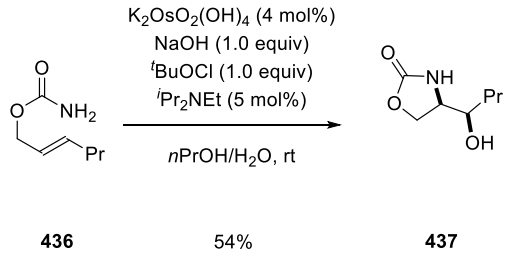
Scheme 149. Muñiz Sharpless aminohydroxylation variant.

In 2005, McLeod *et al.* developed a substrate-controlled synthesis of potential *γ*-amino-*β*-hydroxybutyric **433** acid (GABOB) structures (Scheme **150**). This methodology uses homoallylic ether **432** as starting material and trimethylsilyl carbamate **435** as the nitrogen source, giving the desired regioisomer **433** in a 10:1 ratio **433**:**434** and a 81% *ee*.[132]



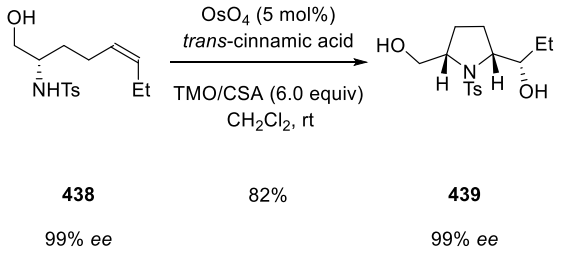
Scheme 150. McLeod Sharpless aminohydroxylation variant.

Efforts were made by Donohoe *et al*. in this field using tethered nitrogen starting materials due to the highly substrate-dependent procedures reported.[133] Achiral allylic carbamates **436**, prepared in a two-step procedure, were subjected to standard Sharpless aminohydroxylation conditions to synthesise hydroxyl oxazolidinones **437** (Scheme **151**). Although low yields were obtained (54%), the regiochemistry was fully controlled. Addition of chiral ligands did not yield products which were enantioenriched. The reaction was further expanded through use of chiral allylic carbamates, resulting in high levels of *syn*-diastereoselectivity.[134]



Scheme 151. Regioselective aminohydroxylation of allylic carbamates.

Following a reported procedure for the preparation of tetrahydrofuran rings through an oxidative cyclisation with osmium tetroxide,[135] stereoselective synthesis of pyrrolidines using this methodology was carried out by Donohoe *et al.* (Scheme **152**).[136] Enantiopure homoallylic amino alcohol **438** was treated under Sharpless aminohydroxylation reaction conditions to give *cis*-pyrrolidine **439** as a single diastereoisomer.

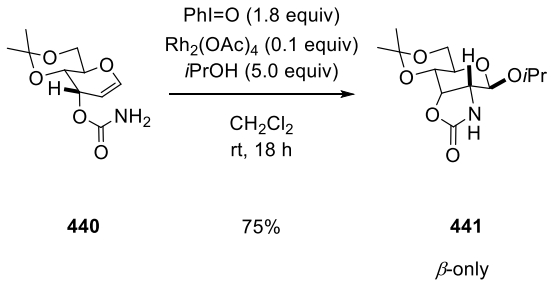


Scheme 152. Application to the synthesis of pyrrolidines.

The excellent yields and enantioselectivities using osmium catalysis for the aminohydroxylation of alkenes has provided a reliable methodology. However, the lack of diversity within the starting materials restricts the procedure, and alternatives are required.

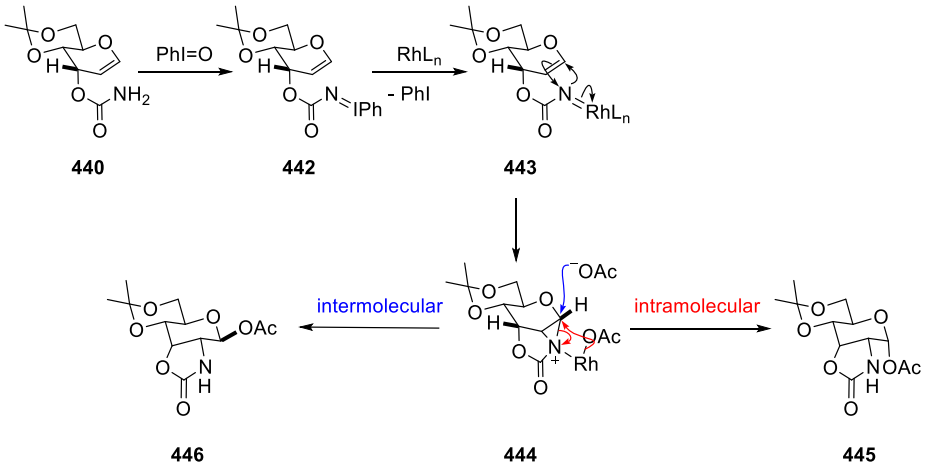
2.1.2 Rhodium

The use of rhodium catalysts in the synthesis of 1,2-amino alcohols has also been examined, which proceeds *via* a different mechanism to the osmium catalysed procress described above. Rojas developed a Rh-catalysed amidoglycosylation with alcohols.[137] Thus, treatment of carbamate **440** with an excess of iodosobenzene in the presence of an external alcohol and a catalytic amount of Rh^{II} provided aminooxygenated cyclised product **441** in good yield where only the β-glycosylation anomer **441** was observed (Scheme **153**).



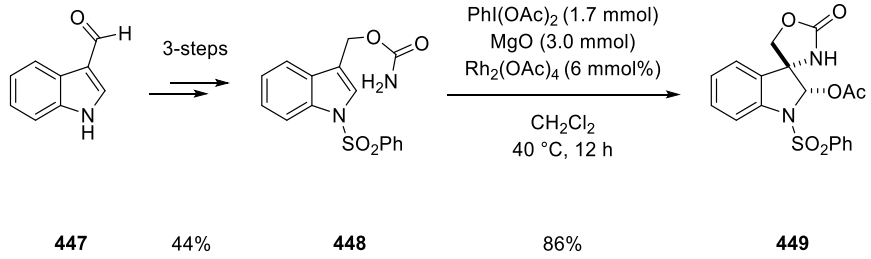
Scheme 153. Metal-based amidoglycosylation

Rojas proposed a plausible mechanism for this metal-catalysed reaction (Scheme **154**). Iminoiodinane **442** is formed followed by loss of iodobenzene to generate metalanitrene **443**. Aziridinium ring **444** is then formed leading to two possible routes and two possible diastereoisomers. The *cis*-product **445** can be formed if nucleophilic attack occurs intramolecularly. By contrast, the *trans*-product **446** can be formed by the addition of an external nucleophile to aziridinium ion **444**.



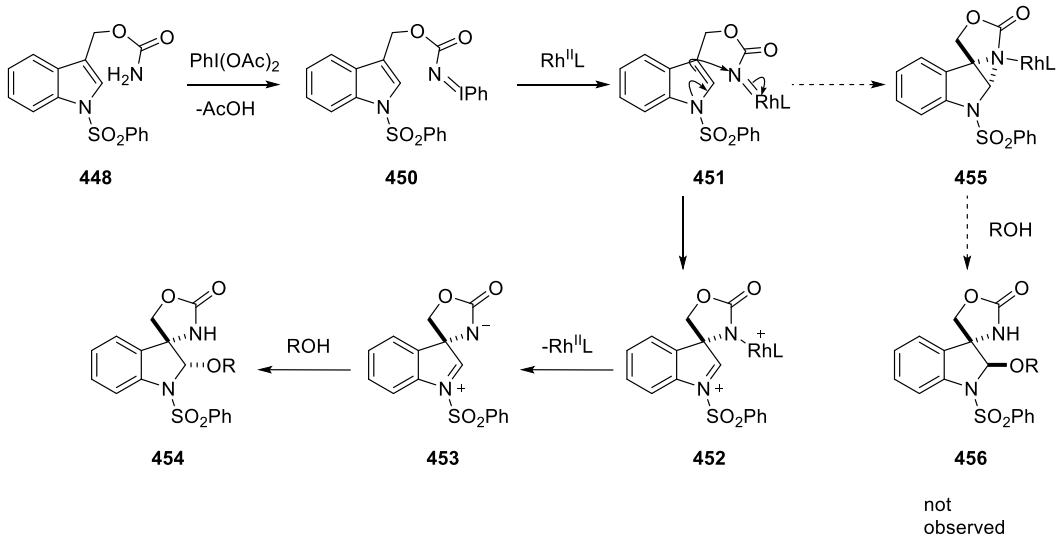
Scheme 154. Rojas plausible mechanism.

Inspired by Du Bois,[138] Stengel *et al.* developed an intramolecular cyclisation of allylic carbamates to give indole structures (Scheme **155**).[139] Allylic carbamate indoles **448** were synthesised in a three-step procedure from commercially available indole-3-carboxyaldehyde **447** in an overall 44% yield.



Scheme 155. Intramolecular cyclisation with Rh-catalysis.

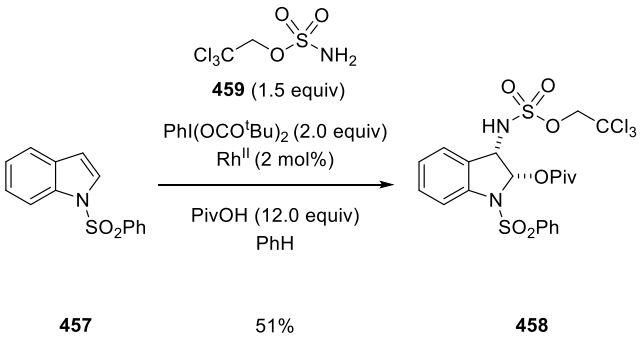
Under the Du Bois reaction conditions, treatment of carbamate indole **448** with stoichiometric amounts of PIDA and MgO in the presence of a Rh^{II} catalyst provided oxazolidinone **449** as a single diastereoisomer in high yield (Scheme **155**). Mechanistically, it was postulated that aziridinium intermediate **455** would be formed followed by S_N2 ring opening with the corresponding nucleophile, according to Rojas' precedent (Scheme **156**).[137] However, the expected aziridine product **455** was not observed. Instead, spirocyclisation of intermediate **452** followed by stereoselective addition of acetic acid took place to give aminoacylated product **454**. X-ray analysis confirmed the structure of **454**, providing evidence that an alternative mechanism was operative.



Scheme 156. Proposed reaction mechanism.

Good yields and high diastereosectivities of the aminohydroxylated products were obtained when the methodology was expanded to other carbamate indole starting materials. However, reaction of 2-substituted indole carbamates gave diastereomeric mixtures of the final product.

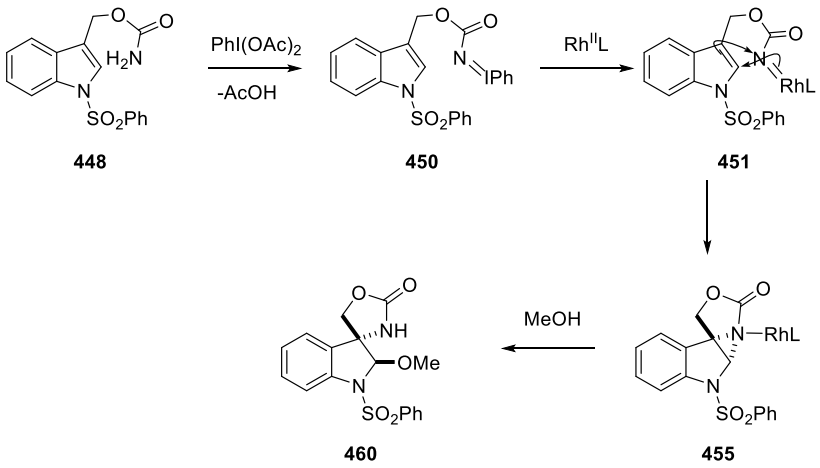
Nine years later, Dauban *et al.* developed an intermolecular aminohydroxylation of phenylsulfonylindoles **457** with total regio- and diastereocontrol in the presence of PivOH as the nucleophile.[140] Consistent with Stengel's work, *cis*-aminohydroxylated products **458** were isolated (Scheme **157**).



Scheme 157. Catalytic aminohydroxylation of indoles.

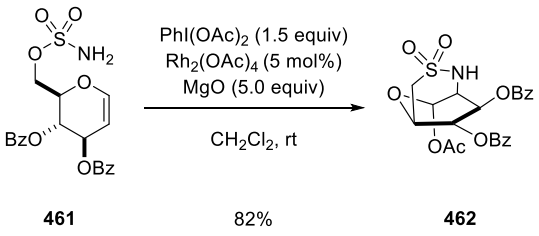
The same group extended the reaction scope to encompass other oxygen nucleophiles, and the use of MeOH provided *trans*-aminohydroxylated product **460**. For this transformation, they proposed aziridinium intermediate **455** formation, followed by an S_N2 ring opening to give **460** (Scheme **158**). Compared to the PivOH example (Scheme **157**), MeOH is a less hindered nucleophile and therefore it

can ring-open aziridinium ions through an S_N2 reaction, whereas PivOH attacks intermediate **453** rapidly from the least-hindered face. These experiments, suggest the identity of the product depends exclusively on the nature of the nucleophile.



Scheme 158. Intermolecular aminohydroxylation with MeOH.

Liu *et al.* applied the aminohydroxylation reaction to the synthesis of sugar derivatives with tethered sulfonamides.[141] This methodology provided access to 1,2-aminoglycosides **462** with a wide variety of oxygen nucleophiles, including carboxylic acids. Reaction of sulfonamide **461** under Du Bois' reaction conditions selectively generated *trans*-1,2-aminoglycoside **462** in high yield (Scheme 159). The *trans*-product provided evidence that the reaction mechanism likely occurred through aziridinium formation followed by ring-opening *via* an S_N2 process.

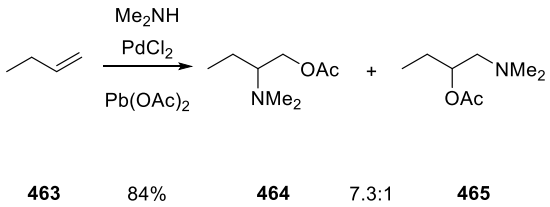


Scheme 159. Rh-catalysed reaction for sulfonamide substrates.

The use of Rh catalysis for the aminohydroxylation has provided an alternative to the osmium catalysis. Overall, the yields obtained were high, however, the lack of enantioselective methods and the restriction of using specific substrates makes this methodology limited.

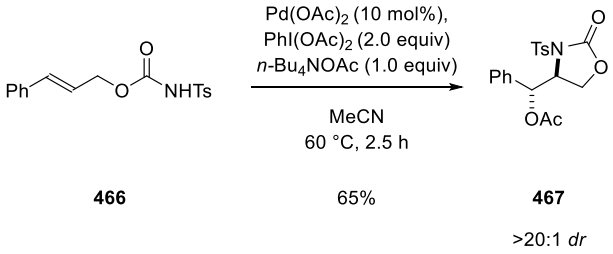
2.1.3 Palladium

The first palladium-mediated aminohydroxylation reaction was reported in 1975 by Bäckvall using stoichiometric amounts of palladium on both terminal and internal alkenes.[142] Reaction of terminal alkene **463** with $PdCl_2$ in the presence of methylamine provided a regioisomeric mixture of *β*-amino alkyl palladium(II) (not isolated). The Pd–C bond was then oxidised with lead(II) to provide aminoacetate products **464** and **465** in a 7.3:1 ratio (Scheme **160**). However, further optimisation of this reaction was not carried out due to the use of stoichiometric amounts of palladium and poor functional group tolerance.



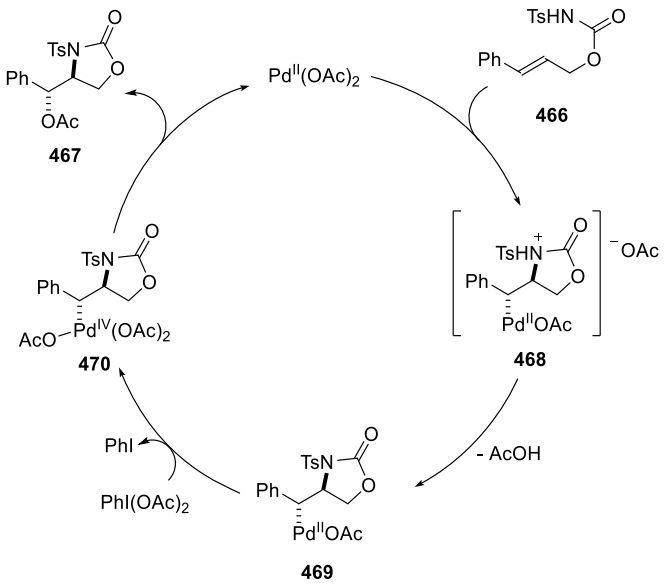
Scheme 160. Bäckvall Pd-catalysed aminoacetoxylation.

Sorensen *et al.* made important progress in palladium-mediated aminoacetoxylation by using an iodine(III) reagent as the oxidant, circumventing the need for toxic lead reagents.[143] Reaction of homoallylic *N*-tosylated carbamate **466** with catalytic amounts of $Pd(OAc)_2$ with an excess of the iodine(III) reagent afforded oxazolidinone **467** with high levels of diastereoselectivity (*syn*:*anti* >20:1) (Scheme **161**).



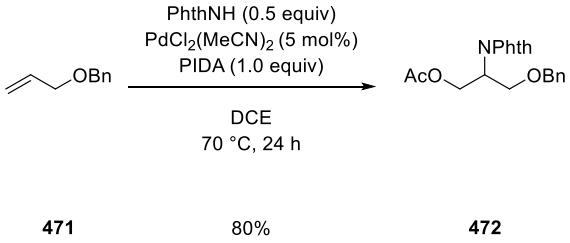
Scheme 161. Pd-mediated cyclisation of *N*-tosyl carbamates.

The mechanism of this transformation was studied and is shown in Scheme **162**. t*rans*-Aminopalladation takes place with homoallylic *N*-tosylated carbamate **466** to give protonated intermediate **468**. After deprotonation, $PhI(OAc)_2$ oxidises Pd^{II} to Pd^{IV} and reductive elimination liberates aminoacetoxylated product **467** releasing Pd^{II} back into the catalytic cycle.



Scheme 162. Proposed catalytic cycle.

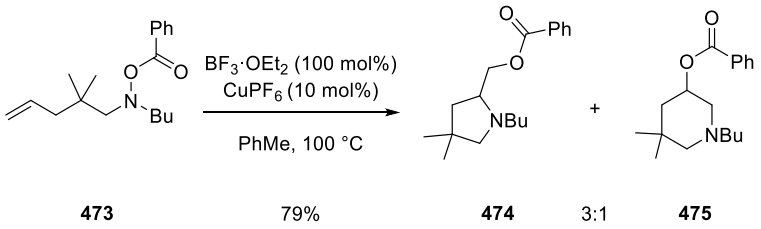
A similar catalytic cycle has been proposed by Stahl *et al.* during development of one of the first intermolecular aminoacetoxylations of alkenes with Pd^{II}.[144] Reaction of alkene **471** with catalytic amounts of Pd^{II} with phthalimide as the nitrogen nucleophile and a stoichiometric amount of PIDA delivered aminoacetoxylated product **472** in high yield and with complete control of the regiochemistry (Scheme **163**). However, this reaction proved to be ineffective when internal alkenes were employed as substrates.



Scheme 163. Aminoacetylation with Pd^{II} and phthalimide.

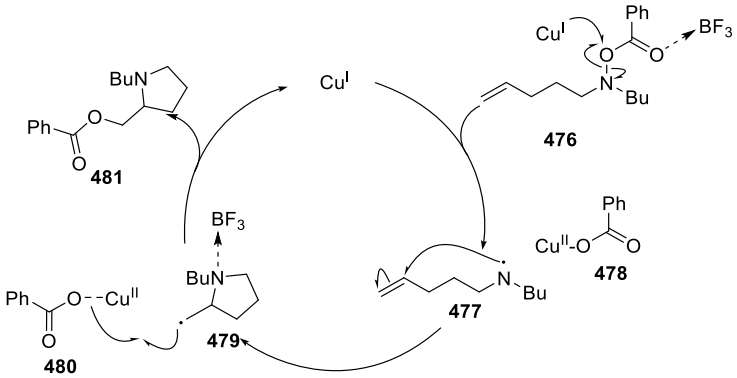
2.1.4 Copper

The aminohydroxylation reaction has also been studied with Cu-catalysts. In 2002 Göttlich *et al.* published a cyclisation of unsaturated *N*-benzoyloxyamines *via* a postulated radical mechanism to prepare cyclic aminoalcohols.[145] Reaction of *N*-benzoyloxyamine **473** in the presence of a Lewis acid and a Cu^{I} catalyst provided a mixture of regioisomers **474** and **475** in a 3:1 ratio (Scheme **164**).



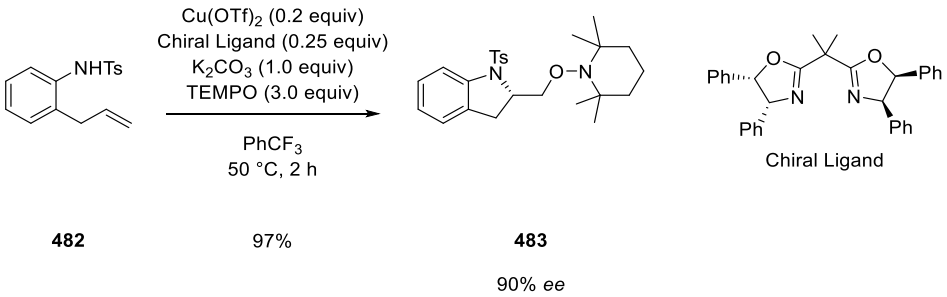
Scheme 164. Cu-catalysed cyclisation.

A radical mechanism was proposed for this transformation (Scheme **165**). First, the N–O bond is reduced by Cu^{I} giving radical species **477**. Then, 5-*exo*-trig cyclisation occurs to deliver pyrrolidine radical **479** which further reacts with copper species **480** reducing it back to Cu^{I} and giving final product **481**.



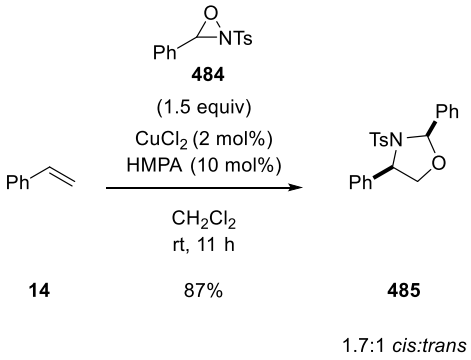
Scheme 165. Proposed radical mechanism.

The first enantioselective intramolecular aminoxygenation reaction using a Cu-catalyst was developed by Chemler *et al.* in 2008[146] after the publication of a catalytic enantioselective carboamination of alkenes with stoichiometric amounts of MnO_2.[147] The reaction was shown to work under similar conditions using catalytic amounts of $Cu(OTf)_2$ and stoichiometric amounts of TEMPO on allylic aniline **482** (Scheme **166**).



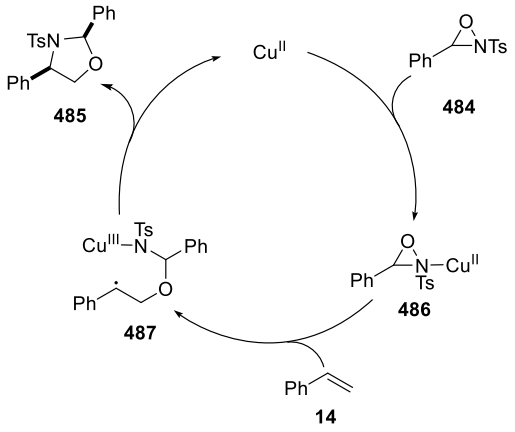
Scheme 166. Enantioselective aminooxygenation reaction with Cu-catalyst.

The serendipitous discovery of an intermolecular aminohydroxylation of alkenes was developed by Yoon *et al*. in 2007.[148] The use of *N*-sulfonyl oxaziridines for the epoxidation of alkenes resulted in an accidental synthesis of oxazolidines. Reaction of styrene **14** with *N*-sulfonyl oxaziridine **484** in the presence of a Cu^{II}-catalyst and HMPA provided oxazolidine **485** in high yield with full control of the regiochemistry, bearing the amino group at the benzylic position (Scheme **167**).



Scheme 167. Intermolecular aminohydroxylation of alkenes with Cu^{II}.

Mechanistically, the Cu^{II}-catalyst likely coordinates with oxaziridine **484** to give metallo-oxaziridine intermediate **486** (Scheme **168**). Reaction of intermediate **486** with styrene gives the most stable radical **487**. Intramolecular cyclisation affords oxyaminated product **485** and regenerates the catalytic Cu^{II} species.

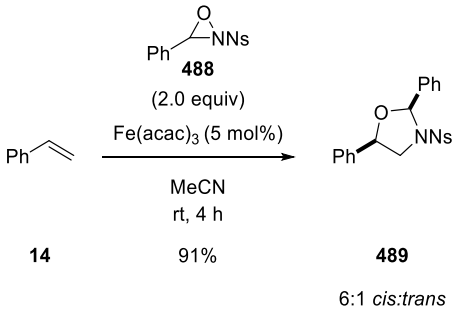


Scheme 168. Mechanistic pathway for Cu^{II} aminohydroxylation.

2.1.5 Iron

In 2010 Yoon *et al.* reported an Fe^{III}-catalysed aminohydroxylation reaction for the synthesis of oxaziridines.[149] The opposite regioselectivity was obtained when compared to the Cu^{II}-catalysed aminohydroxylation reaction described above by the same group (Scheme **167**).[148] Reaction of styrene

14 with *N*-sulfonyl oxaziridine **488** in the presence of an Fe^{III}-catalyst afforded cyclised product **489** in high yield and with full control of the regiochemistry, incorporating the oxygen at the benzylic position (Scheme **169**).



Scheme 169. Intermolecular aminohydroxylation of alkenes with Fe^{III}.

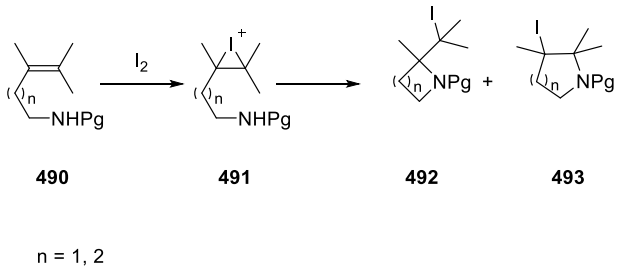
After two years, the same group developed an asymmetric version of the Fe^{III}-catalysed aminohydroxylation of alkenes using chiral ligands to achieve enantioselectivities up to 95% *ee* as a single regioisomer.[150] However, mechanistic insights have not been reported to date.

2.2 Metal-free methodologies

As previously described, metal-based methodologies for the aminohydroxylation of alkenes have been widely used in organic chemistry. However, there are serious drawbacks for metal-based reactions such as the toxic, air-sensitive and expensive nature of the reagents. Furthermore, removal of traces of metals present in final products can pose a problem, especially at an industrial scale. For these reasons, metal-free methodologies for the aminohydroxylation of alkenes are required.

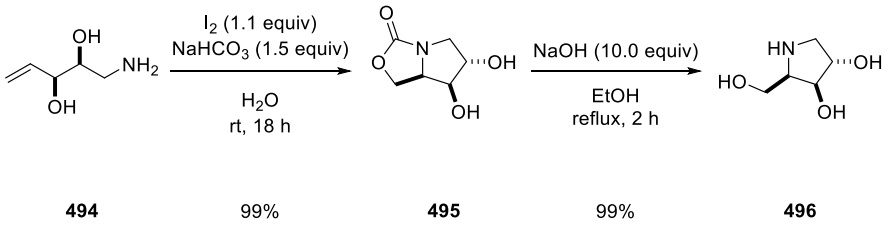
2.2.1 Iodine(0)

Iodocyclisation reactions with nitrogen nucleophiles are used for the formation of vicinal amino iodine moieties. For this, activation of alkene **490** with iodine(0) allows formation of iodonium species **491**, then nitrogen nucleophilic attack provides access to 1,2-amino iodide structures **492** and/or **493** (Scheme **171**). Further manipulations of 1,2-amino iodide species can provide aminohydroxylated prodcuts.



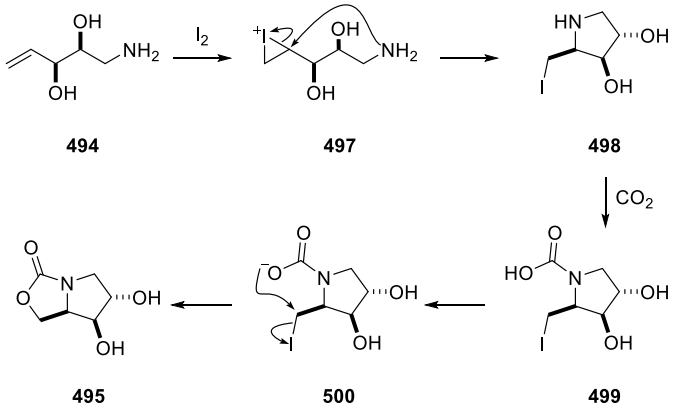
Scheme 170. General scheme for iodocyclisation with I_2.

Stoker *et al.* developed a one-pot halocyclisation with stoichiometric amounts of I_2, followed by carbonylation to synthesise hydroxypyrrolidine **496** (Scheme **171**).[151] Quantitative amounts of pyrrolidine **496** were obtained when unactivated alkene **494** was treated with I_2 in the presence of $NaHCO_3$. Alkaline hydrolysis of **495** afforded the corresponding aminohydroxylated product **496**.



Scheme 171. Iodolactamisation with iodine(0).

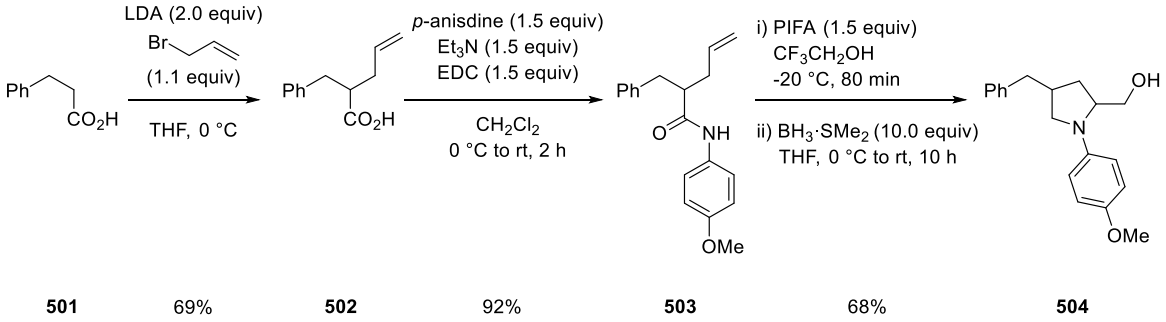
Mechanistically, unsaturated amine **494** was activated with I_2 giving iodonium intermediate **497** (Scheme **172**). Ring-opening of intermediate **497** with the amino group in a 5-*exo*-tet cyclisation occurred to give haloamine product **498**. Cyclic carbamate **495** was then isolated after reacting the haloamine product **498** with CO_2, generated *in situ* from $NaHCO_3$.



Scheme 172. Mechanistic pathway.

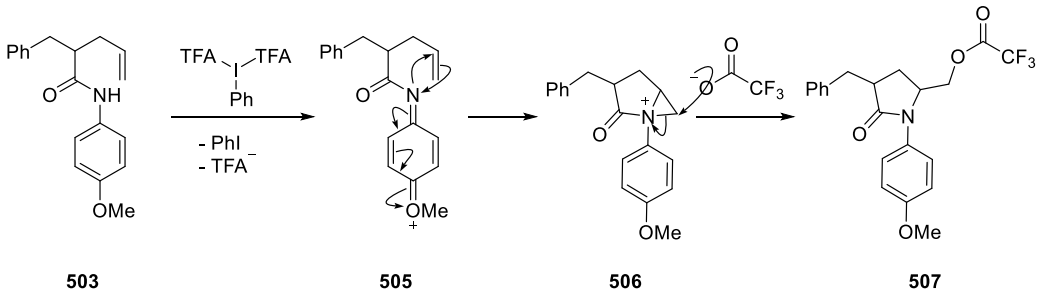
2.2.2 Iodine(III)

San Martin *et al.* were one of the initial groups working with hypervalent iodine. In 2004 they reported an intramolecular amidohydroxylation of alkenes using iodine(III) in a fluorinated alcoholic solvent with full control of regiochemistry (Scheme **173**).[152] Substituted amide **503**, synthesised in a two-step procedure from commercially available hydrocinnamic acid **501**, was treated with PIFA followed by amide reduction with BH_3 to give aminohydroxylated compound **504**.



Scheme 173. Intramolecular cyclisation with PIFA.

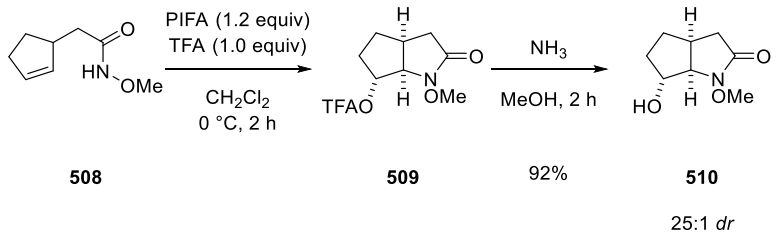
Mechanistically, they proposed an oxidation of amide **503** with PIFA to generate *N*-acylnitrenium species **505** (Scheme **174**). Then, intramolecular cyclisation occurs affording aziridinium intermediate **506**. Trifluoroacetic acid anion attack provided aminoacetylated product **507**. This methodology is restricted to terminal alkenes with the amide installed at the *β*-position and it is also limited to have a *N*-*p*-methoxyphenyl group to enable formation of the aziridinium ion **506**.



Scheme 174. Proposed mechanism.

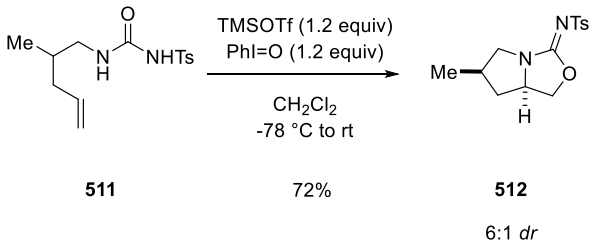
A related intramolecular oxyamidation was developed in 2010 by Wardrop *et al.*[153] under similar reaction conditions. They developed a diastereoselective reaction expanding the amide scope, and avoiding the use of a *N*-*p*-methoxyphenyl protecting group. Reaction of *O*-methyl hydroxamic acid **508** with stoichiometric amounts of PIFA and TFA gave fused ring **509** (Scheme **175**). Quenching with ammonia to remove the TFA group afforded hydroxyaminated product **510**. The

authors suggested a similar reaction mechanism to that of San Martin's for this transformation. An aziridine species was proposed as the key intermediate, due to the observed *trans*-diastereoselectivity of the reaction.



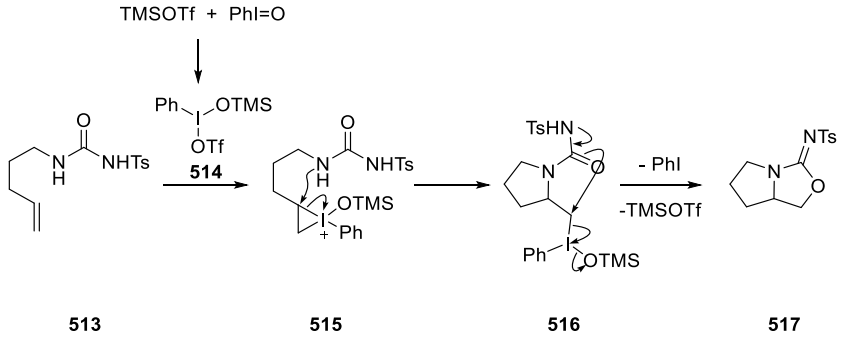
Scheme 175. Oxidative cyclisation with PIFA.

Michael *et al.* further extended the scope of the cyclisations of unactivated alkenes with iodine(III) using urea derivatives as the starting material.[154] Oxidative heterocyclisation of urea **511** in the presence of an activator (TMSOTf) and an iodonium(III) reagent provided fused ring **512** in high yield and with moderate diastereoselectivity (Scheme **176**).



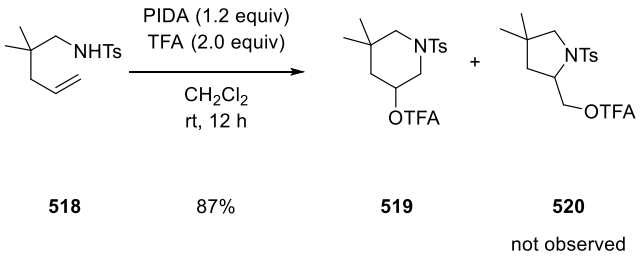
Scheme 176. Oxidative heterocyclisation of urea **512**.

Mechanistically, they proposed an ionic mechanism in which the first step involves alkene **513** activation with the active iodonium(III) **514** reagent, generated from PhI=O and TMSOTf, to give iodonium intermediate **515** (Scheme **177**). Ring-opening of iodonium intermediate **515** by nucleophilic attack of the more reactive nitrogen of the urea scaffold **515** afforded intermediate **516** in which a second cyclisation through the oxygen atom provided the desired product **517**.



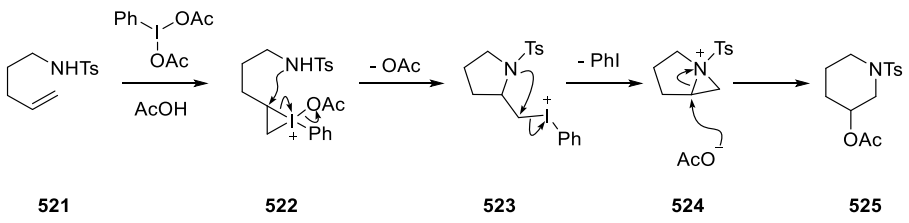
Scheme 177. Proposed mechanistic pathway.

More recently, the same group reported the cyclisation of *N*-tosylated amines **518** with PIDA.[155] This methodology provided access to piperidine **519** scaffolds in an unusual *endo* cyclisation (Scheme **178**).



Scheme 178. Unusual *endo* cyclisation.

The authors previously developed a cyclisation of unactivated alkenes with iodine(III), reporting a mechanistic pathway for the formation of the *exo*cyclic product. However, the regiochemical outcome of the formation of piperidine scaffolds suggests that the mechanism does not proceed by a simple iodonium intermediate followed by a ring opening to give the kinetic *exo*cyclised product. Alternatively, alkene **521** is activated and ring-opened giving the kinetic aminoiodinated product **523** (Scheme **179**). Then, instead of iodine displacement with an external nucleophile, the sulfonamide displaces iodobenzene intramolecularly and aziridinium **524** is formed. Intermolecular nucleophilic attack on the tertiary carbon provided the observed formal *endo* cyclised product **525**.



Scheme 179. Proposed mechanistic pathway.

2.3 Conclusions

A series of metal-based methodologies for the aminohydroxylation of alkenes have been described. In general, these methods provide aminohydroxylated products in high yields and good to excellent diastereoselectivities, but they frequently have regioselectivity issues.

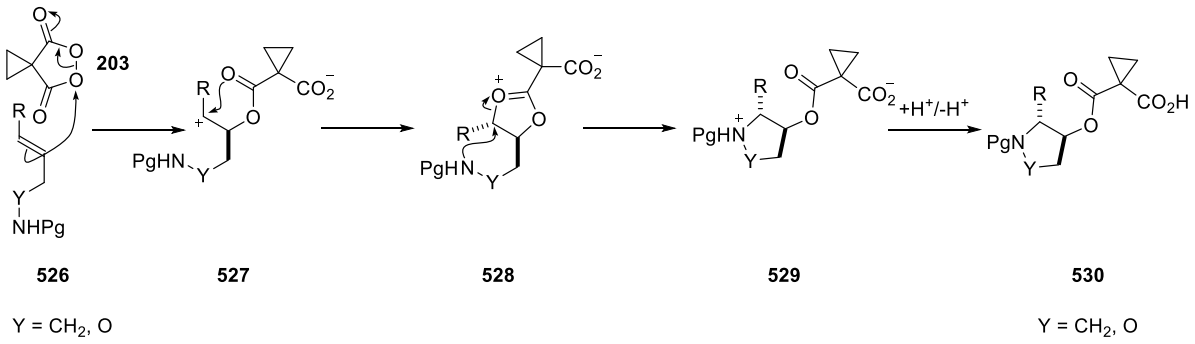
The asymmetric Sharpless aminohydroxylation using osmium has been the benchmark reaction to which many methodologies are compared. Despite the utility of the reaction, the use of toxic and expensive metals makes some of these transformations a challenge and alternative reactions are required. Moreover, the removal of metals in final products is not easily achievable.

Metal-free procedures have been reported. These include the use of iodine(0) and iodine(III) reagents, offering to the organic community a wide variety of methodologies for this transformation. However, in most cases, specific starting materials are required for the reaction to be successful.

3 Previous Work

Having successfully developed an effective and selective heterocyclisation of homoallylic carboxylic acids and homoallylic alcohols under metal-free conditions (*Chapter 2*) we next investigated the use of this versatile methodology for the synthesis of other heterocyclic scaffolds. Based on our proposed mechanism, the process was applied to nitrogen-based nucleophiles.

The aim of this project was to react a series of protected homoallylic amines nucleophiles **529** with malonoyl peroxide **10** to form dioxonium intermediate **528** (Scheme **180**). In the presence of a pendant nitrogen nucleophile, this could cyclise to form heterocycles *via* an S_N2 process, opening dioxonium intermediate **528** and forming the desired nitrogen heterocycle **530** after proton transfer.



Scheme 180. Proposed mechanistic pathway.

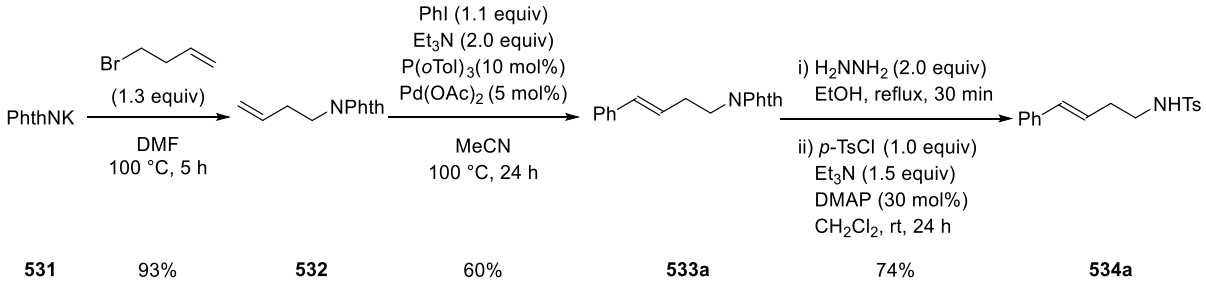
4 Results and Discussion

4.1 Synthesis of Pyrrolidines

4.1.1 Optimisation

Studies began with the synthesis of sulfonamide **534a**. Preparation of sulfonamide **534a** was carried out *via* a four-step synthesis with a 41% overall yield using Gabriel's procedure for the introduction of the nitrogen atom (Scheme **181**).[156]

The synthesis commenced by reaction of commercially available potassium phthalimide **531** *via* an S_N2 process with commercial 4-bromobut-1-ene to give phthalimide **532** in 93% yield, which was used in the next step without further purification. Heck reaction of **532** with iodobenzene in the presence of a Pd^{II} catalytic species provided phthalimide **533a** which was fully characterised after purification by silica gel flash chromatography. Finally, hydrazine mediated deprotection of the phthalimide by formation of insoluble 2,3-dihydrophthalazine-1-4-dione, followed by *N*-tosyl protection gave the desired homoallylic *N*-tosylated amine **534a** (74%).



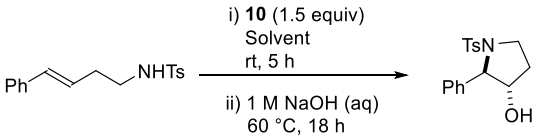
Scheme 181. Synthesis of homoallylic amine **534a**.

Having gained access to gram quantities of homoallylic *N*-tosylated amine **534a**, the reaction with malonoyl peroxide **10** was examined (Table **22**).

Using the standard reaction conditions developed for the analogous cyclisations of oxygen-based nucleophiles described in *Chapter 2*, HFIP was used with a reaction time of 5 h. Pyrrolidine **535a** was isolated using commercial HFIP as the solvent in 69% yield and in an acceptable *cis*:*trans* diastereoselectivity of 1:9 (Table **22**, Entry 1). The use of dry solvents improved selectivities in both the *anti*-dihydroxylation of alkenes and the oxygen-based heterocyclisation.This was also the case with this transformation whereby further improvement came when pre-dried HFIP was used, increasing the *cis*:*trans* diastereoselectivity up to 1:13 (Table **22**, Entry 2). At present we have little insight into the reason why the presence of H_2O in the reaction mixture affects the diastereoselectivity of the final product for these oxidative heterocyclisations. The use of the

chlorinated solvents $CHCl_3$ and CH_2Cl_2 provided low conversions to the pyrrolidine **535a** (Table 22, Entries 3–4) and no reaction was observed when either methanol or EtOAc was chosen as the reaction solvent (Table **22**, Entries 5–6).

Table 22. Optimisation.[a]



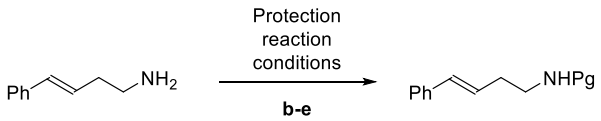
534a **535a**

Entry	Solvent	Conv[b]/ %	Yield[c]/ %	*cis*:*trans*[b]
1	HFIP	100	69	1:9
2[d]	HFIP	100	71	1:13
3	CH_2Cl_2	16	-	-
4	$CHCl_3$	8	-	-
5[e]	MeOH	-	-	-
6[e]	EtOAc	-	-	-

[a]All reactions performed in duplicate with (*E*)-4-methyl-*N*-(4-phenylbut-3-en-1-yl)benzenesulfonamide at 0.5 M concentration for 5 h. [b]Determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [c]Yields quoted are isolated yields of major isomer. [d]Solvent dried over 3 Å molecular sieves for 24 h prior to use. [e]Starting material recovered.

Based upon these results we adopted a standard set of conditions for the reaction of alkenes containing pendant *N*-tosylated amine functionality with 1.5 equiv of peroxide **10** at rt for 5 h in HFIP as the reaction solvent (Table **22**, Entry 6).

Having developed a set of optimal reaction conditions for the cyclisation of homoallylic *N*-tosylated amines **534a**, the influence of the *N*-protecting group on the reaction was further investigated. For this **534b-e** were prepared using the appropriate electrophile in combination of the corresponding base for the introduction of Ns, Boc, Cbz and Ac groups (Scheme **182**).



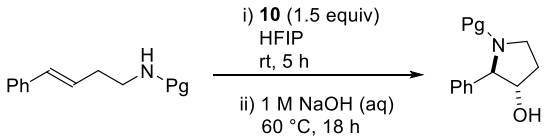
536 **534b-e**

534b: NsCl, Et_3N, 0 °C to rt, 18 h, 98%.
534c: Boc_2O, K_2CO_3, 40 °C, 18 h, 83%.
534d: $BnCO_2Cl$, $NaHCO_3$, rt, 18 h, 85%.
534e: AcCl, Et_3N, 0 °C to rt, 18 h, 72%.

Scheme 182. *N*-protecting groups.

Table **23** shows the use of different nitrogen protecting groups for the heterocyclisation with malonoyl peroxide **10**. The use of a more electron-withdrawing *N*-nosyl group resulted in a much slower reaction (27% conversion) and no *cis*:*trans* diastereoselectivity (1:1) (Table **23**, Entry 2). Using carbamate protecting groups, such as Boc, Cbz or Ac, complex reaction mixtures were obtained which proved impossible to characterise due to the challenges encountered during purification of the crude reaction mixtures (Table **23**, Entries 3–5). Based on these results, *p*-toluenesulfonamide was chosen as the optimal *N*-protecting group for this transformation.

Table 23. Optimisation the *N*-protecting group.[a]

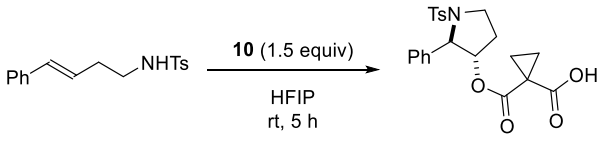


536 **537**

Entry	Pg	Conv[b]/%	Yield[c]/%	*cis*:*trans*[b]
1	Ts	100	71	1:13
2	Ns	27	-	1:1
3	Boc	100	-	-
4	Cbz	100	-	-
5	Ac	100	-	-

[a]All reactions performed in duplicate with (*E*)-4-methyl-*N*-(4-phenylbut-3-en-1 yl)benzenesulfonamide at 0.5 M concentration for 5 h. [b]Determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [c]Yields quoted are isolated yields of major isomer.

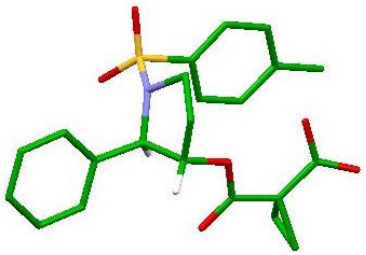
A crystal of **538** was grown by co-worker, S. Davidson, to provide evidence of the structure and the relative stereochemistry of the product. Oxidative heterocyclisation of sulfonamide **534a** with malonoyl peroxide **10** gave carboxylic acid **538** in 79% yield (Scheme **183**).

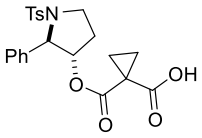


534a 79% **538**

Scheme 183. Oxidative heterocyclisation reaction intermediate.

The X-ray structure of **538** confirms the *trans*-relationship of the two protons attached to the stereogenic centres of the pyrrolidine product (Figure **21**).





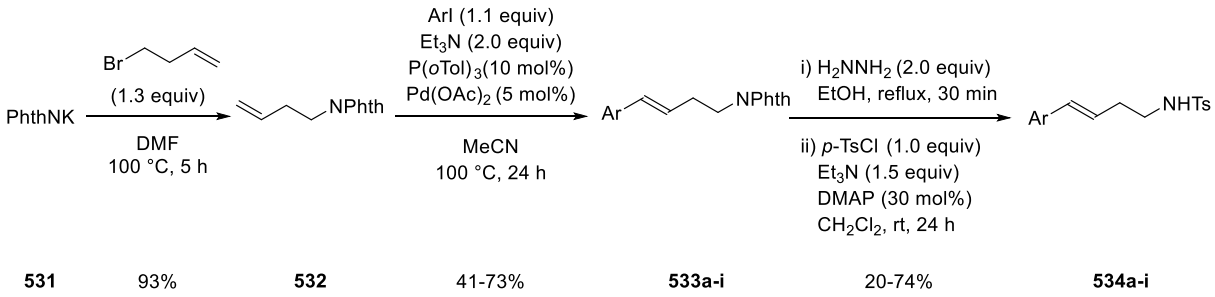
538

Figure 21. Crystal structure of pyrrolidine **538**.

4.1.2 Substrate Scope and Limitations

4.1.2.1 Synthesis of starting materials

With the purpose of further expanding this methodology, a series of alternative substrates were generated for the synthesis of further pyrrolidines.



Scheme 184. Synthesis of homoallylic *N*-tosylated amines.

A variety of homoallylic *N*-tosylated amines were prepared using the same strategy developed for the synthesis of **534a** (Scheme **184**). S_N2 reaction of potassium phthalimide **531** with 1-bromo-but-3-ene (1.3 equiv), then Heck coupling with an aryl iodide followed by hydrazine mediated deprotection and *N*-tosylation provided a variety of different substrates **534a-i** with a series of functional groups on the aromatic ring (Figure **22**). The yields presented are for the four-step synthesis, the final *N*-tosylation proving the most challenging step. Although 1.0 equiv of *p*-TsCl was used, the yields dropped due to the formation of the double *N*-tosyl protected amine.

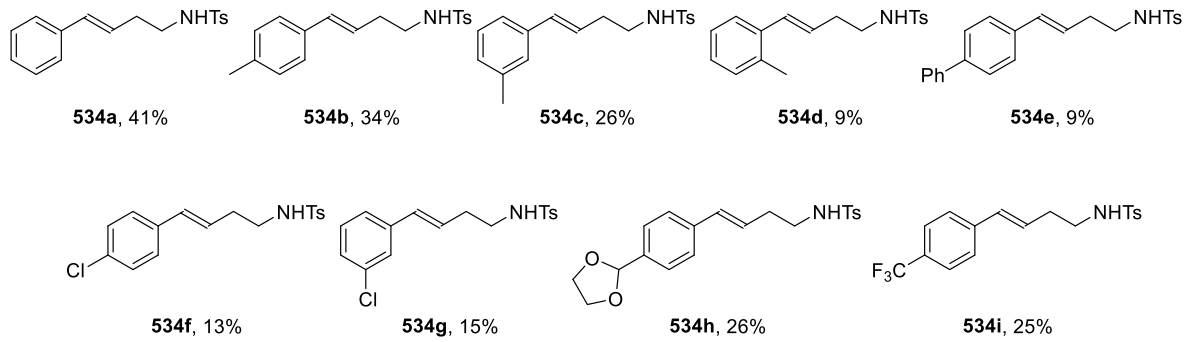
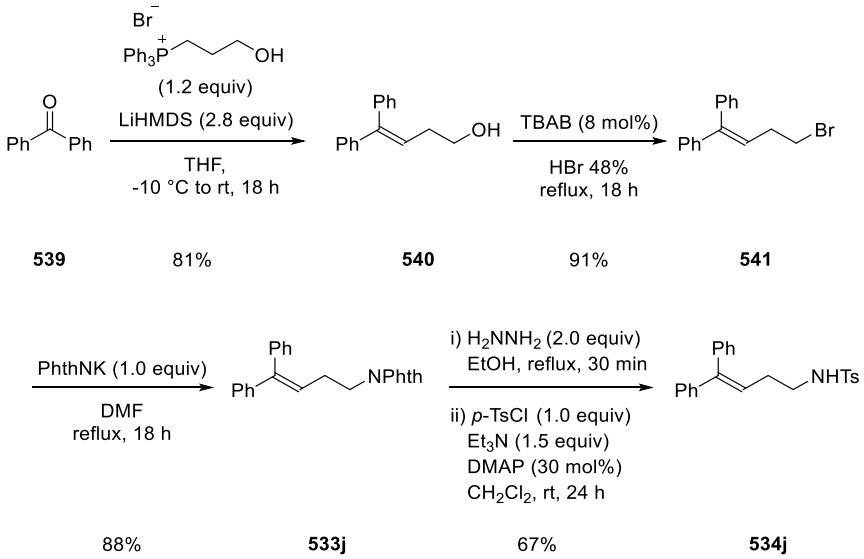


Figure 22. Substrate scope.

Tri-substituted alkene **534j** was also synthesised through a different strategy. A five-step synthesis was carried out in a 43% overall yield (Scheme **185**). Thus, benzophenone **539** was subjected to a Wittig reaction to give alkene **540**. Bromination of the primary alcohol provided compound **541** in which subsequent S_N2 displacement with potassium phthalimide afforded **533j**. Hydrazine mediated deprotection followed by *N*-tosylation provided tri-substituted substrate **534j**.



Scheme 185. Synthesis of tri-substituted alkene **534j**.

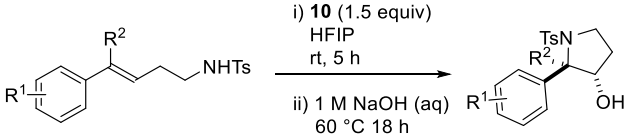
4.1.2.2 Substrate Scope

The scope of this transformation was investigated using the homoallylic *N*-tosylated amines described above, under the reaction conditions developed for the preparation of pyrrolidine **538**.

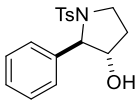
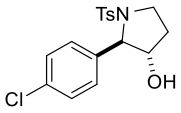
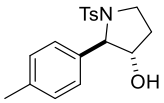
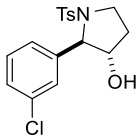
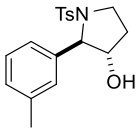
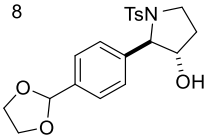
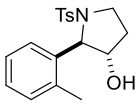
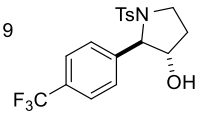
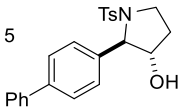
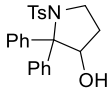
Pyrrolidine **535a** was isolated in 71% yield and an excellent *cis*:*trans* diastereoselectivity of 1:13 (Table **24**, Entry 1). This methodology proved to work when methyl substituents were introduced

on the aromatic group at the *para*-, *meta*- and *ortho*-positions in good yields (66–72%) with moderate selectivities (*cis*:*trans* 1:4–1:7) (Table **24**, Entries 2–4). *para*-Phenyl substitution was also examined, giving aminohydroxylated product **535e** in a good 72% yield and good *cis*:*trans* diastereoselectivity of 1:9 (Table **24**, Entry 5). Furthermore, *para*- and *meta*-chlorine substitution on the aromatic ring also afforded the desired pyrrolidine after hydrolysis, however, lower yields (52–67%) were obtained (Table **24**, Entries 6–7). Introduction of a protected aldehyde at the *para*-position of the aromatic ring proved to be tolerated, although lower yields were obtained due to acetal hydrolysis, confirmed by detection of an aldehyde peak at 9.97 ppm in the ^{1}H NMR of the crude reaction mixture (Table **24**, Entry 8).

Table 24. Substrate scope.



534a-j **535a-j**

Entry	Product	Yield[a] (%)	*cis*:*trans*[b]	Entry	Product	Yield[a] (%)	*cis*:*trans*[b]
1		**535a** 71	1:13	6		**535f** 67	1:9
2		**535b** 66	1:7	7		**535g** 52	1:6
3		**535c** 71	1:4	8		**535h** 55	1:9
4		**535d** 72	1:4	9		**535i** 19	-
5		**535e** 72	1:9	10		**535j** 82	-

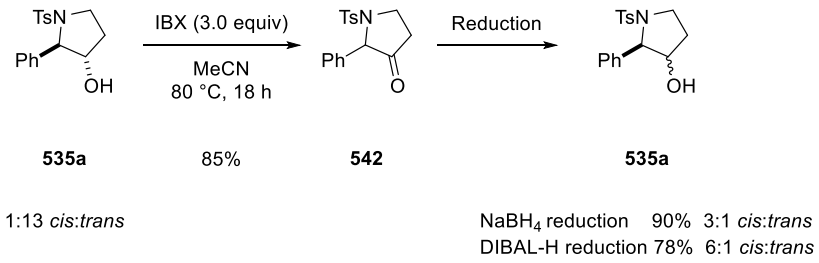
[a]Yields quoted are isolated yields of major isomer. [b]Diastereoselectivity determined by ^{1}H NMR spectroscopy on the crude reaction mixture.

Unfortunately, the reaction was less successful when a trifluoromethyl group was introduced at the *para*-position of the aromatic ring. Substrate **534i** was reacted under the optimal conditions, however, higher temperatures (50 °C) were required for full conversion of the starting material. Pyrrolidine **535i** was isolated in a low 19% yield. Frustratingly, the *cis*:*trans* diastereoselectivity was not determined for this transformation due to overlapping peaks in the ^{1}H NMR spectrum (Table **24**, Entry 9). The major product of the reaction was found to be the dihydroxylated product of the alkene in a 65% yield, which was confirmed by ^{1}H NMR, ^{13}C NMR and by LCMS. The dihydroxylated product is thought to be formed due to the low reactivity of alkene **534i** and the rapid interception of the dioxonium intermediate **528** with H_2O (Scheme **180**, page **128**).

Tri-substituted alkene **534j** was also examined and the corresponding pyrrolidine **535j** was isolated in high yield (82%) (Table **24**, Entry 10).

4.1.3 Further chemistry with pyrrolidine 535a

With the intention to prepare an unnatural amino acid **545**, further functionalisation of the pyrrolidine product **535a** was investigated. First, IBX oxidation of alcohol **535a** was carried out monitoring the reaction by TLC and ketone **542** was isolated in high yield (85%) (Scheme **186**). ^{1}H NMR confirmed the oxidation of alcohol **535a** due to the disappearance of the C*H*OH signal and through ^{13}C NMR by the appearance of the carbonyl signal at 213.1 ppm. Ketone **542** was subjected to reduction conditions using $NaBH_4$ to give a diastereomeric mixture (*cis*:*trans* 3:1) of the pyrrolidine alcohol **535a**



Scheme 186. IBX oxidation of pyrrolidine **535a**.

By comparing the benzylic peaks of the *cis*- and *trans*-product after the $NaBH_4$ reduction, it was able to reinforce the selectivity found in the oxidative heterocyclisation. Using a more hindered and reactive reducing agent, DIBAL-H, the *cis*:*trans* diastereoselectivity increased to 6:1. Worth note, chemical shifts were a bit different for the DIBAL-H reduction due to the experiment was run in GlaxoSmithKline in Stevenage and the other two in University of Strathclyde in Glasgow.

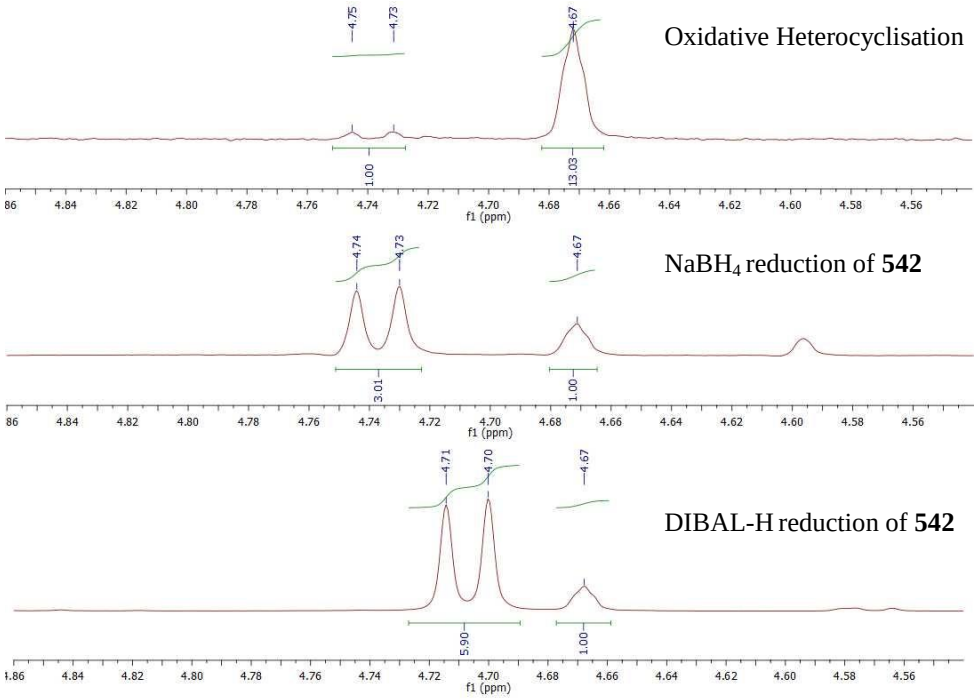
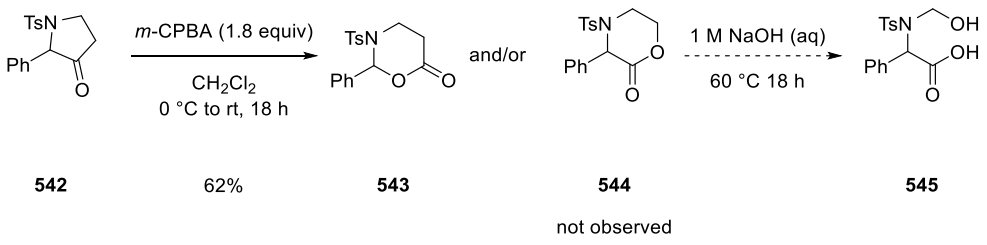


Figure 23. Top: ^{1}H NMR spectrum of pyrrolidine **535a** after hydrolysis. Middle: ^{1}H NMR spectrum of reduction of **535a** with $NaBH_4$. Bottom: ^{1}H NMR spectrum of reduction of **535a** with DIBAL-H.

Non-symmetrical ketone **542** was then subjected to Baeyer-Villiger (BV) oxidation with *m*-CPBA. Two potential regioisomers **543** and/or **544** can be obtained from this reaction, since BV oxidation depends on the migratory ability of the substituents attached to the ketone (Scheme **187**). Regioisomer **544** would be desirable, since further hydrolysis of lactone **544** would lead to an unnatural amino acid derivative **545** within this transformation. Oxazinanone **543** was exclusively formed in moderate yield (62%). The structure of oxazinanone **543** was confirmed by ^{1}H NMR spectroscopy, the chemical shift of the benzylic proton further shifted by being attached to an oxygen provided enough evidence that **543** was obtained instead of **544**. ^{13}C NMR also provided evidence that **543** was formed due to the peak at 87.0 ppm, from the benzylic carbon attached to the oxygen and nitrogen.

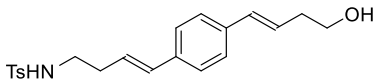


Scheme 187. Baeyer-Villiger oxidation.

Therefore, the preparation of unnatural amino acid **545** was abandoned due to the failure to generate **544**.

4.1.4 Competition substrate 546

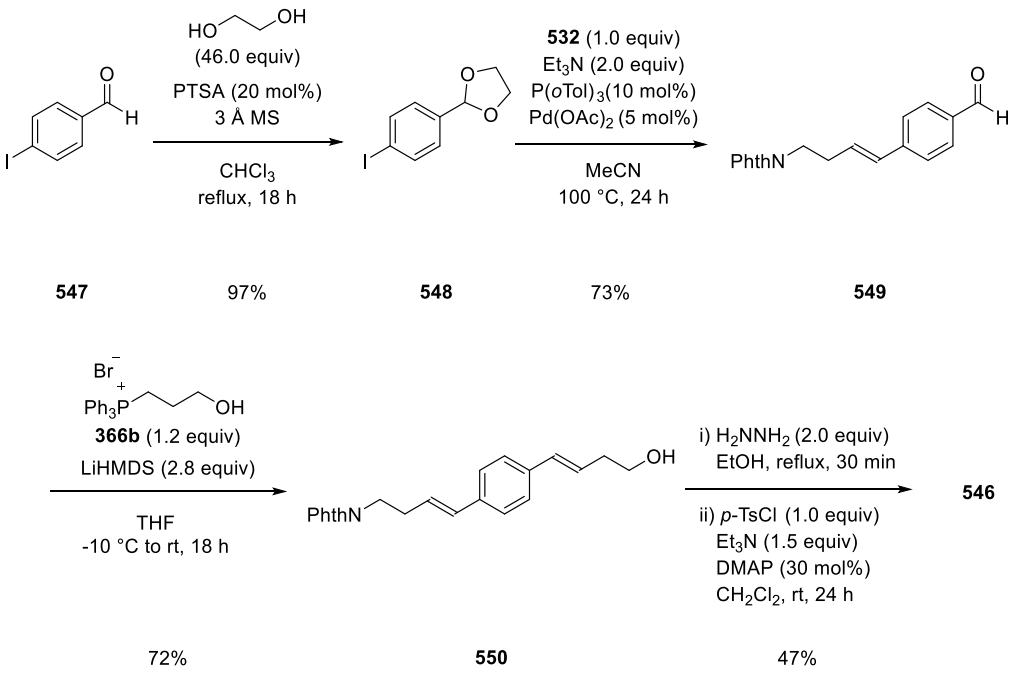
The synthesis of cyclic ethers was developed through an oxidative heterocyclisation of homoallylic alcohols with malonoyl peroxide **10**, described in *Chapter 2*. Following the methodology described previously, the synthesis of pyrrolidines was explored and successfully achieved. For this reason, a competitive heterocyclisation reaction was envisaged through a substrate containing both homoallylic alcohol and homoallylic *N*-tosylated amine, with the aim to investigate which heterocycle would be formed more readily. Thus, substrate **546** was targeted (Figure **24**).



546

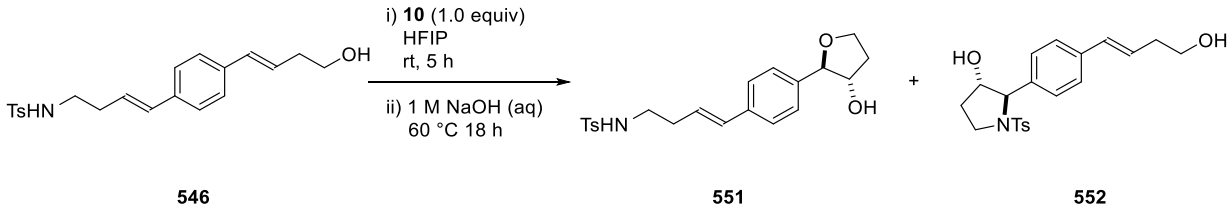
Figure 24. Substrate for competitive cyclisation.

Synthesis of **546** commenced by acetal protection of commercially available *p*-iodobenzaldehyde **547** to give **548** in a high 97% yield by displacement of H_2O, using activated 3 Å molecular sieves in the presence of ethylene glycol and PTSA (Scheme **188**).[157] Heck reaction of **548** under standard reaction conditions with alkene **532** provided coupled compound **549** in a good 73% yield after purification by silica gel flash chromatography.[158] Under the Heck reaction conditions followed by acidic work-up, the acetal was hydrolysed to the corresponding aldehyde **549**, which was confirmed by the 9.96 ppm peak in the ^{1}H NMR spectra of the product. Aldehyde **549** was subjected to Wittig reaction with triphenylphosphonium salt **366b** and an excess of LiHMDS to give *bis*-alkene **550**.[107] Finally, hydrazine deprotection followed by *N*-tosylation provided final product **546** over six steps and a 19% overall yield.



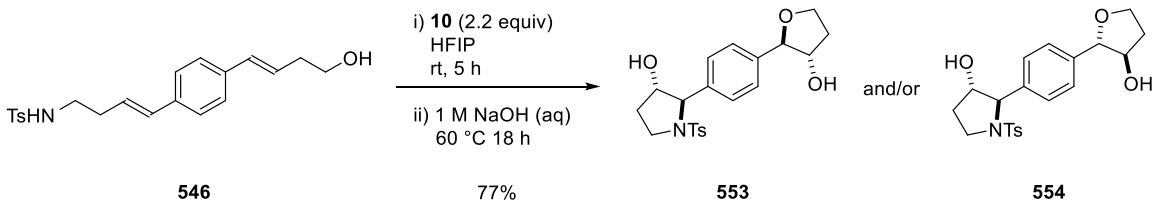
Scheme 188. Synthesis of **546**.

With *bis*-alkene **546** in hand, oxidative heterocyclisation with malonoyl peroxide **10** was investigated (Scheme **189**). An initial reaction of **546** with 1.0 equiv of malonoyl peroxide **10** provided a 1:1 mixture of **551** and **552** which was confirmed by LCMS, without isolation an separation of the products. This experiment suggested that malonoyl peroxide **10** does not react selectively with **546**, and it is the alkene group that drives reactivity. According to previous experiments, the relative stereochemistry of the products **551** and **552** can be assigned a *trans*-disposition, however no evidence was obtained to support this proposal.



Scheme 189. Oxidative heterocyclisation of **546** with malonoyl peroxide **10** (1.0 equiv).

Due to the lack of alkene selectivity with malonoyl peroxide **10**, excess malonoyl peroxide **10** was added in order to form two heterocycles (Scheme **190**). Thus, reaction of **546** with 2.2 equiv of malonoyl peroxide **10** provided cyclisation of both the homoallylic alcohol and homoallylic *N*-tosylated amine.



546 77% **553** **554**

Scheme 190. Oxidative heterocyclisation of **546** with malonoyl peroxide **10** (2.2 equiv).

Examination of the ^{1}H NMR spectrum of the crude reaction mixture showed a clear indication the cyclisation was succesful with the disappearance of all the vinyl signals and characteristical peaks at 4.74 ppm and 4.64 ppm due to the benzylic protons of the tetrahydrofuran and pyrrolidine rings, repectively (Figure **25**). LCMS data was also consistent with the double cyclisation taking place an unresolved broad peak at 3.9 min (Figure **26**) having the expected mass of 404.1 $[M+H]^{+}$ and a HRMS of 404.1527.

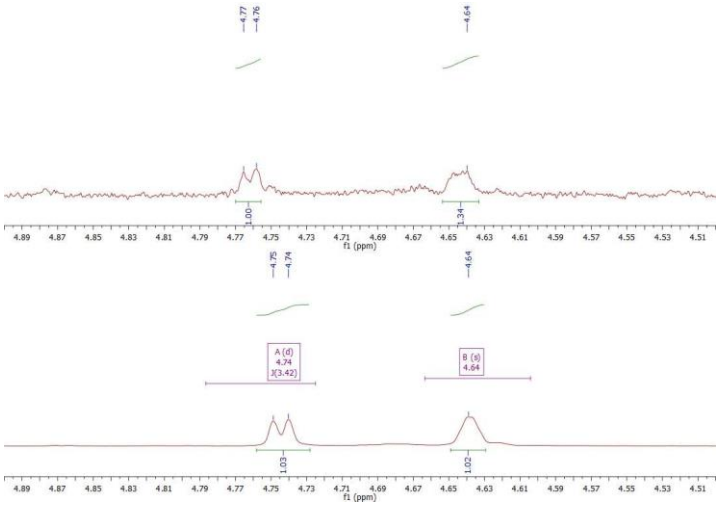


Figure 25. Top: Expanded area of the ^{1}H NMR spectrum of crude reaction mixture. Bottom: Expanded area of the ^{1}H NMR spectrum of purified sample.

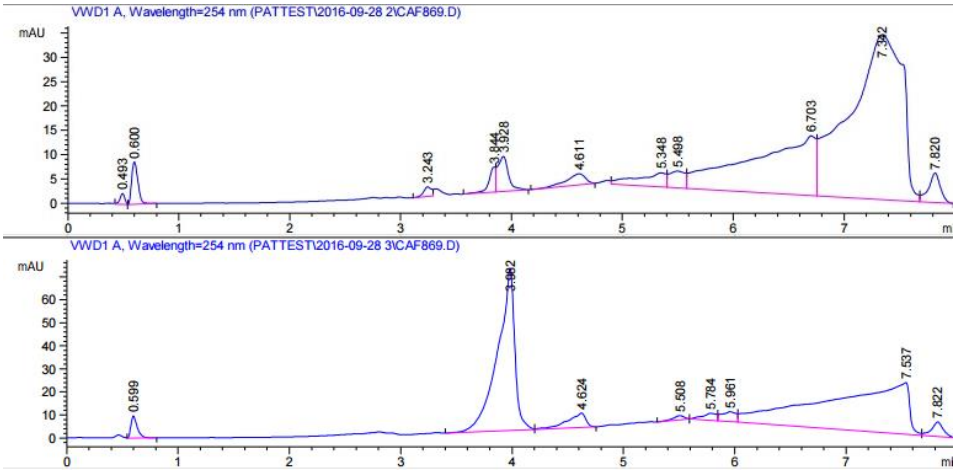
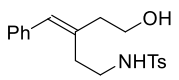


Figure 26. Top: UV active LCMS of crude reaction mixture. Bottom: UV active LCMS of crude reaction mixture of purified sample.

A single spot was isolated by column chromatography which showed the same ^{1}H NMR spectrum between 4.5–5.0 ppm and the same profile by LCMS at 3.9 min (Figure **25** and Figure **26**). From this data we conclude that the expected double cyclisation had taken place, however, no conclusive evidence if the isomer **553** or **554** (or a mixture of both) was obtained during this experiment. Despite the considerable effort made in preparing probe molecule **546** we elected to reassess our strategy to compare the relative reactivities of NHTs and hydroxyl nucleophiles in our intramolecular cyclisations.

4.1.5 Competition substrate 555

With the purpose of obtaining more information about the reactivity of activated alkenes with pendant nucleophiles in the presence of malonoyl peroxide **10**, tri-substituted alkene **555** was designed (Figure **27**). However, extensive synthetic efforts were not successful in the timeless of this work, and are described herein.

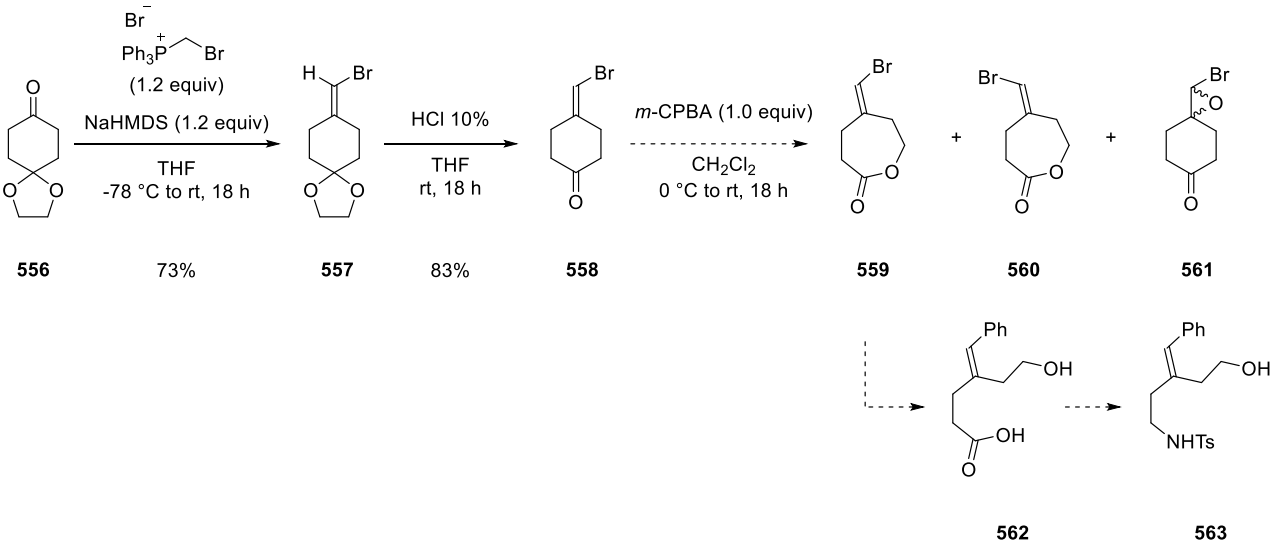


555

Figure 27. Substrate **555**.

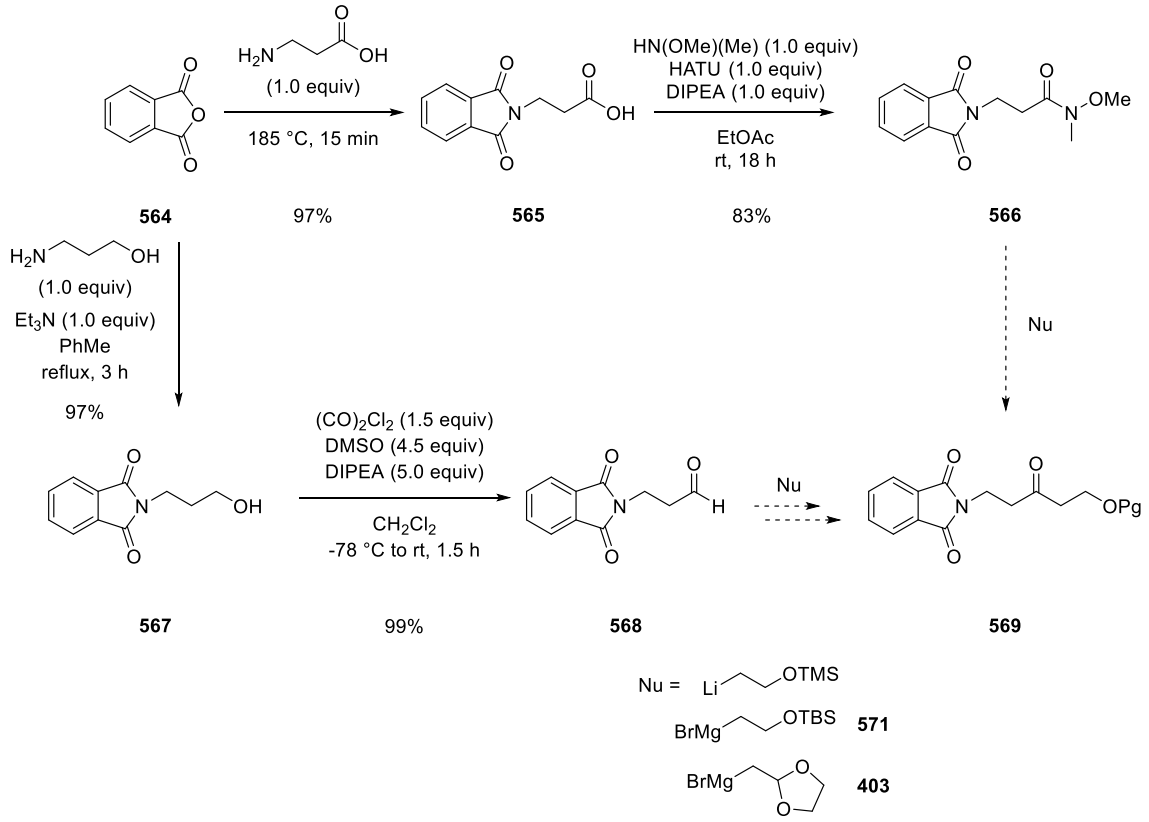
Three different strategies were examined to prepare substrate **555**. Inspiration from Reetz's previous work provided the first strategy for the synthesis of **555** (Scheme **191**).[159] This involved a Wittig reaction between commercially available 1,4-cyclohexanedione monoethylene ketal **556** and

(bromomethyl)triphenylphosphonium bromide followed by acetal removal under acidic conditions to give ketone **558**. Next, oxidation of ketone **558** through a BV reaction was investigated, however, it was not possible to use Reetz's catalyst, a wild-type cyclohexanone monooxygenases (CHMO), due to lack of availability, and instead, *m*-CPBA was used giving a 1:1 mixture of BV products **559** and **560** along with epoxide **561**. This strategy was abandoned due to the challenges in separation of the complex mixture after BV reaction.



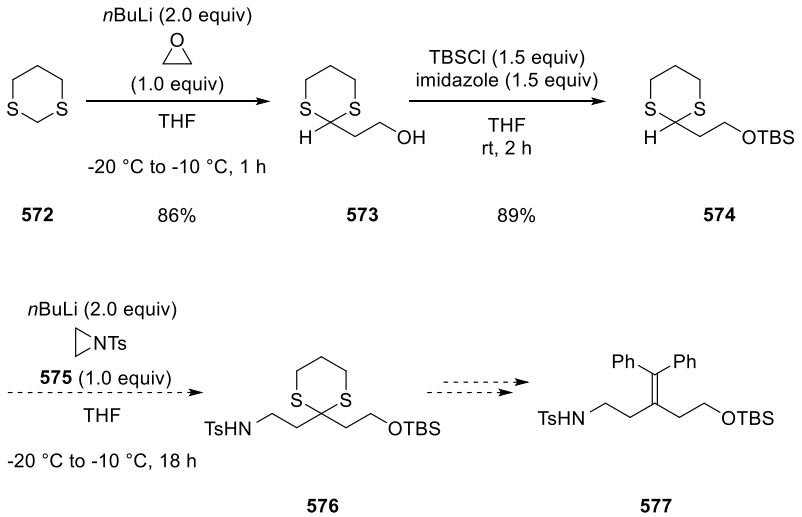
Scheme 191. Strategy 1.

A second strategy commenced by condensing *β*-alanine with phthalic anhydride **564** to give phthalimide **565** in a 97% yield (Scheme **192**). The corresponding carboxylic acid **565** was converted into the Weinreb amide **566** and reacted with a variety of different nucleophiles. However, the desired product **569** was not obtained with any of the nucleophiles, **570**, **571** and **403**, employed yielding either starting material or degraded product. Phthalimide **568**, with a pendant aldehyde was also synthesised. Phthalic anhydride **564** was reacted with 3-amino-1-propanol by removing H_2O using a Dean-Stark apparatus to give phthalimide **567** in a 97% yield. Swern oxidation of **567** gave aldehyde **568** in quantitative yield. Aldehyde **568** was reacted with nucleophiles, **570**, **571** and **403**, without success under a variety of reaction conditions. All these reactions failed, and it is thought to be due to a competing reaction with the reactive phthalimide core.



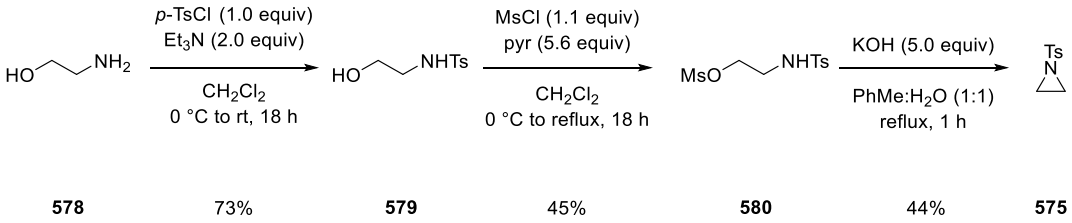
Scheme 192. Strategy 2.

With these strategies proving challenging for the synthesis of substrate **555**, our attention turned to dithiane chemistry with the aim to synthesise **577**. Dithianes can be used as umpolung equivalents of aldehydes/ketones. For this reason, 1,3-dithiane **572** was deprotonated with *n*BuLi in the presence of ethylene oxide to give alcohol **573** in a 86% yield (Scheme **193**).



Scheme 193. Strategy 3.

Alcohol **573** was then protected with TBSCl in the presence of imidazole to give **574** in 89% yield. Protected alcohol **574** was then deprotonated with *n*BuLi in the presence of tosylated aziridine **575** which had been, prepared in three steps from commercially available ethanolamine **575** in a 14% overall yield (Scheme **194**).[160]



Scheme 194. Synthesis of aziridine **575**.

Although the reaction of protected alcohol **574** with aziridine **575** proceeded with full conversion of the starting material, the isolated product was not unequivocally characterised. Collected data, ^{1}H NMR, ^{13}C NMR, COSY, HSQC, HMBC, deptq and LCMS, were not enough to provide convincing unequivocal evidence of the generation of dithiane **576**.

This strategy has been abandoned due to lack of time, however, alternative reactions are ongoing by a co-worker, S. Lucas.

4.2 Synthesis of *Iso*xazolidines

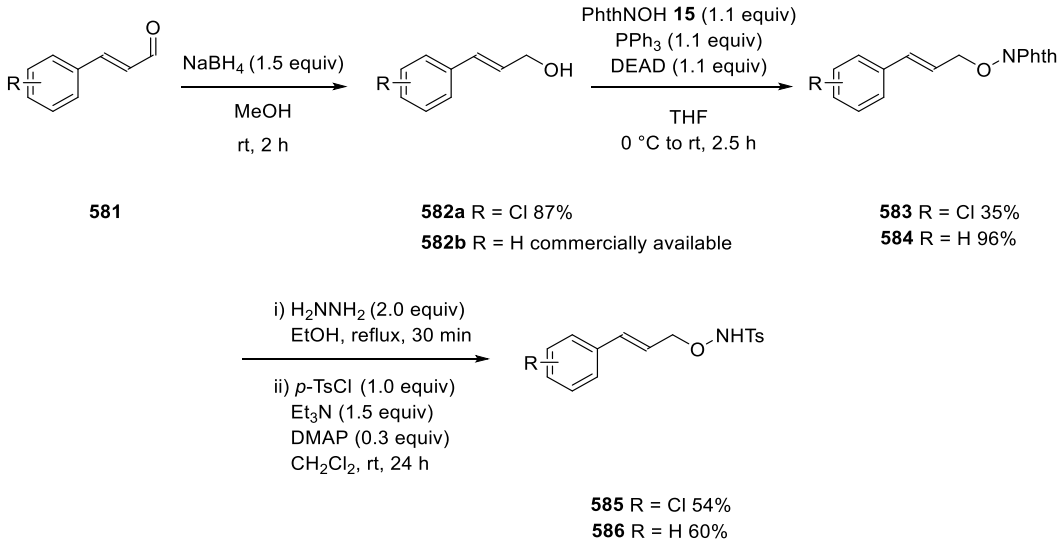
With the ambition to further expand this oxidative heterocyclisation with nitrogen-based nucleophiles, a family of different nitrogen containing heterocycles was investigated. Thus, a number of *N*-tosylated *O*-cinnamylhydroxylamines were synthesised with the intention of preparing *iso*xazolidines.

4.2.1 Synthesis of starting materials

N-tosylated *O*-cinnamylhydroxylamine **586** was synthesised in a three-step process with a 58% overall yield or in a four-step procedure if the cinnamyl alcohol **582a** was not commercially available (Scheme **195**). In that case, cinnamyl alcohol **582a** was isolated by treatment of **581** with $NaBH_4$.

With cinnamyl alcohol **582a** in hand, synthesis of **585** was continued by treatment of **582a** under standard Mitsunobu reaction conditions with commercial *N*-hydroxyphthalimide **15** and a

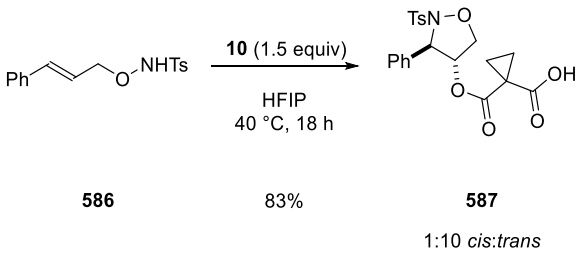
stoichiometric amount of DEAD in the presence of PPh_3. This allowed the formation of a new C–O bond. The yield varied depending upon the reactivity of the cinnamyl alcohol substrate. Following a similar strategy for the generation of homoallylic *N*-tosyl amines **534a-i**, hydrazine deprotection followed by *N*-tosylation provided the desired product **585** and **586** in good yields (54–60% over two steps).



Scheme 195. Synthesis of *N*-tosylated *O*-cinnamylhydroxylamine **585** and **586**.

4.2.2 Oxidative heterocyclisation

Having successfully synthesised *N*-tosylated *O*-cinnamylhydroxylamine **586**, the oxidative heterocyclisation was examined. Reaction of benzenesulfonamide **586** under the optimal reaction conditions previously developed for the preparation of pyrrolidines (HFIP, rt, 5 h), *iso*xazolidine **587** was confirmed by both ^{1}H NMR spectroscopy and LCMS, however the reaction was not complete after this time. The reaction was then monitored by ^{1}H NMR spectroscopy reaching full conversion at rt after 39 h. In an attempt to reduce reaction times, the temperature was increased to 40 °C, providing *iso*xazolidine **587** after 18 h in good yield (83%) and good *cis*:*trans* diastereoselectivity of 1:10 (Scheme **196**).



Scheme 196. Oxidative heterocyclisation for the synthesis of *iso*xazolidines.

Confirmation of the structure and relative stereochemistry of *iso*xazolidine **587** came from X-ray analysis. The solved X-ray structure for **587** confirms the *trans*-relationship of the two protons attached to the newly formed stereogenic centres (Figure **28**).

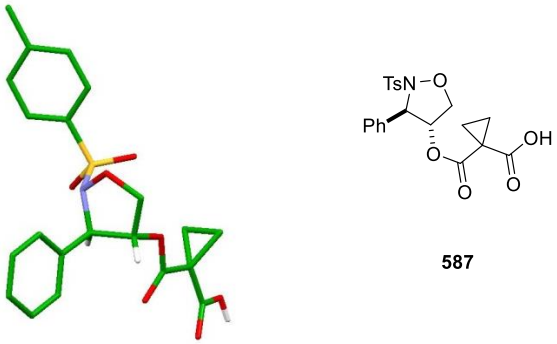
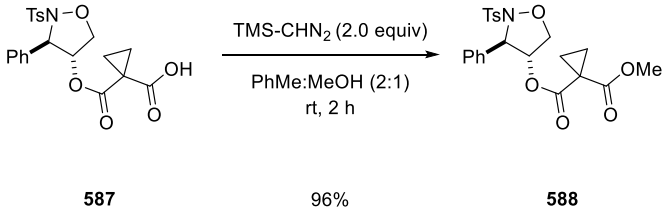


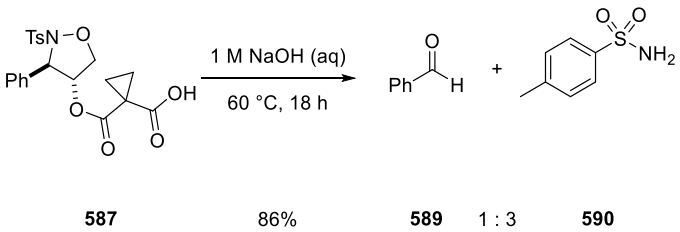
Figure 28. Crystal structure of *iso*xazolidines **587**.

To ease manipulation of the cyclised product, methyl ester formation from of the carboxylic acid **587** was carried out with TMS-CHN_2 in methanol and toluene to give ester **588** in high yield without compromising the stereochemical integrity of the heterocycle (Scheme **197**).



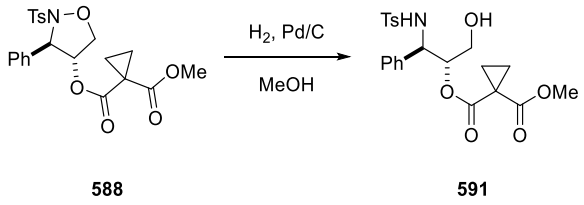
Scheme 197. Methyl ester formation.

Further chemistry was attempted with *iso*xazolidine **587** which would provide more useful scaffolds. Hydrolysis of ester **587** to give the corresponding alcohol would be desirable (Scheme **198**). Unfortunately, alkaline hydrolysis of *iso*xazolidine **587** at rt yielded benzaldehyde **589** and *p*-toluenesulfonamide **590** in a 1:3 ratio, repectively, which were confirmed by GC/MS and ^{1}H NMR spectroscopy.



Scheme 198. Alkaline hydrolisis of *iso*xozolidine **587**.

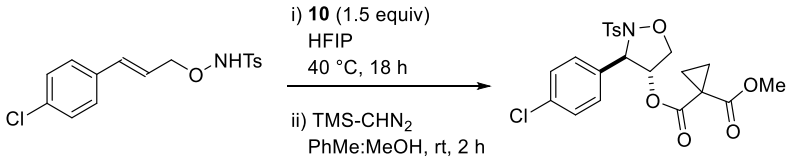
Reduction of the N–O bond was also attempted using an H_2 CUBE with a Pd/C cartridge with the aim of synthesising ring-opened compound **591** (Scheme **199**). The reaction was followed by LCMS, and although *iso*xazolidine **588** was fully consumed, the desired product **591** was not isolated, which is thought to be due to the high polarity of this product.



588 **591**

Scheme 199. Hydrogenation reaction of *iso*xazolidine **588**.

The cyclisation methodology was also applied to substrate **586** providing *iso*xazolidine **592** in 85% yield over two steps with good levels of diastereoselectivity, *cis*:*trans* 1:7 (Scheme **200**).



586 85% **592**

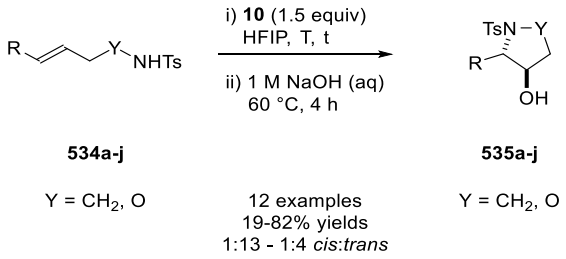
1:7 *cis*:*trans*

Scheme 200. Application of oxidative heterocyclisation to substrate **586**.

4.3 Conclusions

A family of homoallylic *N*-tosylated amines **534a-j** were synthesised to prepare pyrrolidine scaffolds **535a-j** by oxidative heterocyclisation. A four-step synthesis from potassium phthalimide **531** was carried out for the preparation of **534a-j** substrates. This involved a Heck reaction, hydrazine mediated deprotection and *N*-tosylation. Thus, different functionalities were introduced on the aromatic ring of the nine amines prepared.

Having optimised the reaction with *N*-tosylated amine **534a**, pyrrolidines **535a-j** were isolated using malonoyl peroxide **10** as the oxidant (Scheme **201**). Subsequent hydrolysis of the corresponding carboxylic acid intermediate (confirmed by X-ray analysis) provided the desired aminohydroxylated cyclic product with good to high levels of *cis*:*trans* diastereoselectivity (up to *cis*:*trans* 1:13). This methodology has also been successfully applied to the analogous synthesis of *iso*xazolidine **585** and **586**, affording the corresponding cyclised products with good selectivities.



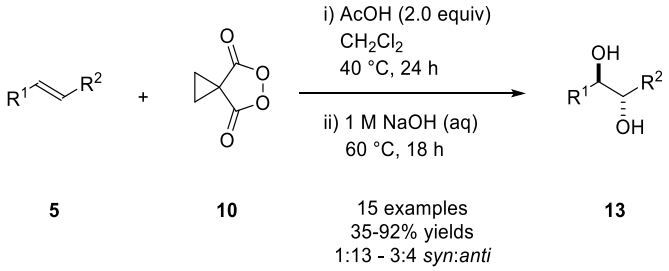
Scheme 201. Oxidative heterocyclisation general scheme.

Combination of a homoallylic protected amine with a homoallylic alcohol in the same substrate has been examined using a *bis*-alkene **546**. It was found that using 1.0 equivalent of malonoyl peroxide **10** did not provide selective oxidative heterocyclisation of either alkene. Therefore, excess of oxidant (2.2 equiv of **10**) was used and the double cyclised product as a diastereomeric mixture of **553** and **554**, was isolated. The relative stereochemistry of the product(s) was not determined.

Overall, this transformation provided access to aminooxygenated heterocycles from readily available starting materials. One of the most attractive points of this transformation is the metal-free reaction conditons. The use of malonoyl peroxide **10** to promote oxidative heterocyclisations provides a clean methodology without the need to use expensive oxidant reagents or toxic metals, maintaining or even enhancing the diastereoselectivity of the products when compared to the literature precedent.

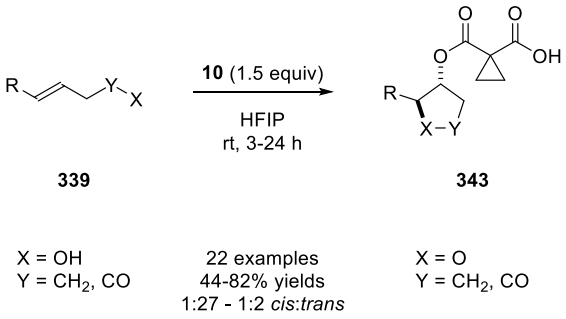
4.4 Future Work

Within this thesis two different methodologies were developed for the functionalisation of alkenes. First, alkene *anti*-dihydroxylation under metal-free conditions using **10** as the oxidant was successfully achieved for the selective preparation of *anti*-diols over 15 examples, including stilbene, styrene, indene and naphthalene derivatives (Scheme **202**).



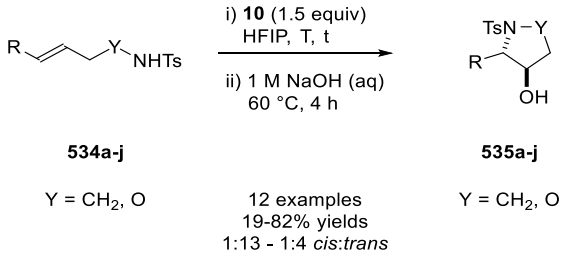
Scheme 202. *anti*-Dihydroxylation reaction with malonoyl peroxide **10**.

After this, an oxidative intramolecular heterocyclisation procedure was developed for the synthesis of oxygenated heterocycles, isobenzofuranones, γ-lactones and tetrahydrofuran ring scaffolds (Scheme **203**). This transformation was shown to work over 22 examples, and the synthetic utility of the methodology was shown through the synthesis of Citalopram, an antidepressant.



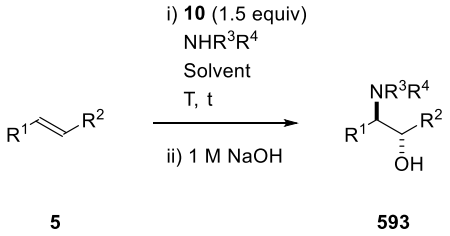
Scheme 203. Intramolecular heterocyclisation for the synthesis of oxygenated heterocyles.

Further expansion of this methodology was carried out for the synthesis of *α*-hydroxypyrrolidines (Scheme **204**). The reaction conditions were well tolerated over 12 examples affording the desired *trans*-pyrrolidines **343**.



Scheme 204. Intramolecular heterocyclisation for the synthesis of nitrogen containing heterocyles.

The possibility to further expand this transformation into an intermolecular reaction would represent a significant extension to this methodology. Thus, reaction of alkene **5** using malonoyl peroxide **10** as the oxidant in the presence of an appropriate nitrogen nucleophile would provide the first intermolecular example of aminohydroxylated product **593** under metal-free conditions using malonoyl peroxide **10** as the stoichiometric oxidant (Scheme **205**). Current work within the group is focused on achieving this goal.



Scheme 205. Intermolecular aminohydroxylation of alkenes.

Chapter 4: Experimental

1 General Techniques

All temperatures are expressed in °C.

Commercially available solvents and reagents were used without further purification or drying and all reactions performed under an air atmosphere unless otherwise stated. Dry solvents were obtained by standard operating procedure for Innovative Technology Solvent Purification System. All glassware used for air/moisture sensitive reactions was previously dried in the oven at 150 °C for 5–16 h.

NMR spectra were recorded using a Bruker DPX400, DPX500, AV400 or AVIII600 (with cyroprobe) referenced to tetramethylsilane. Chemical shifts are reported in parts per million (ppm) and coupling constants (J) in Hz. The following abbreviations are used for multiplicities: s = singlet; d = doublet; t = triplet; m = multiplet; dd = doublet of doublets; ddd = doublet doublet of doublets. If not specifically stated, the NMR experiments were run at 20 °C.

IR spectra were recorded from solid samples 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.

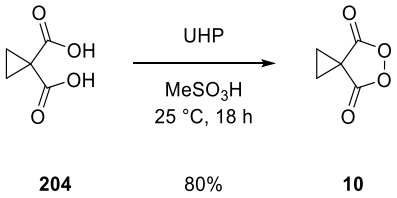
Column chromatography was carried out using 200–400 mesh silica gel using an eluent system stated in each experimental section.

Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF254 that were visualised under UV light (at 254 nm).

LC–MS samples were carried out using Agilent technologies using a gradient of 5–95% acetonitrile/ H_2O. GC-MS was performed using an Agilent 7890A GC system, equipped with a 30 m DB5MS column connected to a 5975C inert XL CI MSD with Triple-Axis Detector. High-resolution mass spectra were obtained courtesy of the EPSRC Mass Spectrometry Service at University of Wales, Swansea, U.K. using the ionisation methods specified.

Caution: Peroxides are particularly dangerous. These procedures should be carried out by knowledgeable laboratory workers. DSC data for malonoyl peroxide **10** is given in Tomkinson *et al*., *J. Am. Chem. Soc.* **2010**, *132*, 14409 (page S89, Supporting Information) and shows an onset temperature of 114.5 °C.

2 Synthesis of Malonoyl Peroxide 10



204 80% **10**

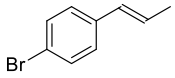
Methane sulfonic acid (30 mL) was placed in a round bottom flask equipped with a large magnetic stirrer bar and immersed in a bath of H_2O at 22 °C. Urea hydrogen peroxide (9.82 g, 104 mmol) was added in a single portion and stirred for 30 seconds. Cyclopropane-1,1-dicarboxylic acid **204** (5 g, 38.5 mmol) was added in a single portion and the reaction stirred vigorously for 18 h. The reaction mixture was poured into a mixture of ice (80 g) and EtOAc (100 mL) and the layers separated. The aqueous layer was extracted with EtOAc (2 × 100 mL) and the combined organics were washed with $NaHCO_3$ (2 × 50 ml), brine (20 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the desired peroxide **10** (3.9 g, 30.5 mmol, 80%) as a white solid without further purification.

m.p. 90 °C; IR (thin film)/cm^{-1}: 1827, 1798, 1358; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.11 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 23.6, 19.8.

3 Experimental Chapter 1

3.1 Synthesis of starting materials

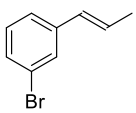
4-Bromo-*β*-methylstyrene 229[65]



In a 3-neck flask, dried and flushed with nitrogen gas, was added ethyltriphenylphosphonium chloride (5.8 g, 18.0 mmol) and anhydrous THF (60 mL). The system was fitted with a reflux condenser under an inert nitrogen atmosphere. The suspension was cooled to 0 °C and *n*BuLi (7.1 mL, 18.0 mmol) was added dropwise. The mixture was stirred for 30 min at 0 °C to give a white solution. After this time, 4-bromobenzaldehyde **228** (3.0 g, 16.0 mmol) in anhydrous THF (5 mL) was added dropwise. The mixture was allowed to warm slowly to rt before being stirred under reflux for 2 h to produce a pale yellow solution. The mixture was allowed to cool to rt and THF was removed under reduced pressure. H_2O (30 mL) was added and the organic phase was extracted from the aqueous layer with EtOAc (3 × 30 mL). The organic phases were combined, filtered and dried over $MgSO_4$ before being concentrated under reduced pressure to give a yellow oil. The crude reaction mixture was passed through a small plug of silica, eluting with petroleum ether to give colourless oil. To isomerise the small amount of the *cis* alkene, a single crystal of I_2 was added with petroleum ether (10 mL) and the solution was left near a window in bright sunlight for 24 h. After this time, the solution was passed again through a small plug of silica with petroleum ether (40–60 °C). The solvent was removed under reduced pressure to give the *title* compound **229** (1.0 g, 5.0 mmol, 31%) as a white solid.

m.p. 174–178 °C [Lit[7] 182–183 °C]; IR (ATR)/cm^{-1}: 3026, 2926, 1492; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.34 (d, *J* = 15.8 Hz, 1H), 6.23 (dq, *J* = 15.8, 6.4 Hz, 1H), 1.87 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4, 131.0, 129.4, 126.8, 126.1, 119.8, 18.0; LRMS (GC-CI) *m/z* 197.0 $[M^{79}Br+H]^+$.

(*E*)-1-Bromo-3-(prop-1-en-1-yl)benzene 239[66]

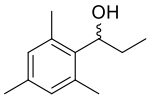


Boron trifluoride diethyl etherate (0.7 mL, 5.7 mmol) was added *via* syringe to a mixture of 3-bromobenzaldehyde **238** (1.0 mL, 8.6 mmol) and 3-pentanone (0.9 mL, 8.6 mmol) in hexane (20 mL). The reaction mixture was stirred at reflux for 3 h and then quenched with H_2O (10 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL), washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation to obtain the desired product as a yellow

oil. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 9:1) gave the *title* compound **239** (1.0 g, 5.1 mmol, 92%) as a yellow oil and a single isomer.

IR (ATR)/cm^{-1}: 3026, 2926, 2364, 2340, 1492; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.47 (m, 1H), 7.32–7.29 (m, 1H), 7.24–7.22 (m, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 6.32 (d, *J* = 15.7 Hz, 1H), 6.24 (dq, *J* = 15.7, 6.1 Hz, 1H), 1.89 (dd, *J* = 6.1, 1.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.2, 130.1, 129.8, 129.7, 128.9, 127.5, 124.6, 122.8, 18.6; LRMS (GC-CI) *m/z* 197.0 [M^{79}Br+H]$^{+}$.

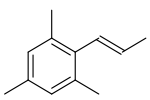
1-Mesitylpropan-1-ol 232[161]



In a 3-necked flask, dried and flushed with nitrogen gas, was added magnesium turnings (1.4 g, 59.2 mmol) and anhydrous THF (25 mL). The system was fitted with a reflux condenser. Bromoethane (3.8 mL, 49.2 mmol) was slowly added and the mixture was heated to reflux for 30 min. After this time, the black solution was allowed to cool to rt. Mesitaldehyde **230** (4.9 mL, 32.8 mmol) in dry THF (35 mL) was added dropwise at 0 °C. The mixture was stirred at rt for 3 h to give a white-grey solution. After this time, the solution was carefully quenched by the dropwise addition of H_2O (2 mL). The solvent was removed under reduced pressure and a solution of EDTA (30 g, 0.1 mmol) in H_2O (100 mL) with EtOAc (75 mL) was added and the resulting mixture was stirred at rt for 1 h. The phases were separated and the aqueous phase was further extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation affording the *title* compound **232** (3.6 g, 20.0 mmol, 61%) as a yellow oil, which was used in the next step without further purification. A sample was purified by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 9:1) for characterisation purposes.

IR (ATR)/cm^{-1}: 3385, 2972, 2927, 2870; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 2H), 5.06 (dd, *J* = 8.4, 6.2 Hz, 1H), 2.40 (s, 6H), 2.25 (s, 3H), 2.03–1.96 (m, 1H), 1.87–1.77 (m, 1H), 0.98 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9, 136.5, 136.2, 130.3, 73.1, 28.9, 20.8, 11.2; LRMS (GC-CI) *m/z* 161.1 [M-OH]$^{+}$.

1,3,5-Trimethyl-2-((*E*)-prop-1-enyl)benzene 235[65]

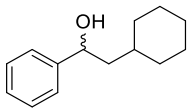


1-Mesitylpropan-1-ol **232** (3.6 g, 20.2 mmol) and *p*-TsOH monohydrate (0.5 g, 2.4 mmol) were added to a round bottom flask with benzene (30 mL) as the solvent. The system was fitted with a Dean-Stark

condenser and the mixture was heated to reflux for 2 h. The dark red solution was cooled to rt and quenched with Et_3N (five drops). H_2O (30 mL) was added and the phases were separated. The aqueous layer was further extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation to give a crude product which was purified by silica gel flash column chromatography (petroleum ether (40–60 °C)) to give the *title* compound **235** (1.9 g, 11.9 mmol, 59%) as a colourless oil and a single isomer.

IR (ATR)/cm^{-1}: 3012, 2916, 2854, 1480, 1375; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 2H), 6.32 (d, *J* = 16.0 Hz, 1H), 5.67 (dq, *J* = 16.0, 6.5 Hz, 1H), 2.27 (s, 9H), 1.91 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0, 135.7, 134.9, 130.1, 128.5. 128.4, 21.0, 20.9, 18.9; LRMS (ESI) *m/z* 160.1 $[M]^+$.

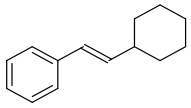
2-Cyclohexyl-1-phenylethanol 233[65]



In a 3-necked flask, dried and flushed with nitrogen gas, were added magnesium turnings (0.8 g, 32.9 mmol) and anhydrous THF (15 mL). The system was fitted with a reflux condenser. (Bromomethyl)cyclohexane (3.9 mL, 28.2 mmol) was slowly added and the mixture was heated to reflux for 30 min. After this time, the solution was allowed to cool to rt, before benzaldehyde **231** (1.90 mL, 18.8 mmol) in dry THF (20 mL) was added dropwise at 0 °C. The mixture was stirred at rt for 5 h to give a black-grey solution. After this time, the solution was carefully quenched by the dropwise addition of H_2O (2 mL). The solvent was removed under reduced pressure and a solution of EDTA (30.0 g, 0.1 mmol) in H_2O (100 mL) with EtOAc (75 mL) was added. The resulting mixture was stirred at rt for 1 h. The layers were separated and the aqueous phase was further extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation affording the *title* compound **233** as a yellow oil (3.6 g, 17.4 mmol, 92%), which was used in the next step without further purification. A sample was purified by silica gel flash column chromatography (petroleum ether (40–60 °C):Et_2O 8:2) for analytical purposes.

m.p. 55–57 °C [Lit[162] 54–56 °C]; IR (ATR)/cm^{-1}: 3250, 2950, 2925, 2861, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.25 (m, 5H), 4.78 (dd, *J* = 8.5, 5.2 Hz, 1H), 1.88–1.62 (m, 6H), 1.55–1.37 (m, 2H), 1.27–1.16 (m, 3H), 1.02–0.83 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5, 128.6, 127.6, 126.0, 72.3, 47.2, 34.4, 34.1, 33.1, 26.7, 26.4, 26.3; LRMS (GC-CI) *m/z* 187.1 $[M\text{-}OH]^+$.

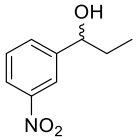
(*E*)-(2-Cyclohexylvinyl)benzene 236[65]



2-Cyclohexyl-1-phenylethanol **233** (3.6 g, 17.4 mmol) and *p*-TsOH monohydrate (0.4 g, 2.3 mmol) were added to a round bottom flask with benzene (60 mL) as the solvent. The system was fitted with a Dean-Stark condenser, and the mixture was heated to reflux for 2.5 h. The dark red solution was cooled to rt and quenched with Et_3N (five drops). H_2O (30 mL) was added and the phases were separated. The aqueous layer was further extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation to give a pale yellow oil. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C)) gave the *title* compound **236** (2.6 g, 14.1 mmol, 81%) as a colourless oil.

IR (ATR)/cm^{-1}: 3012, 2920, 2854, 2848, 1446; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.34 (m, 2H), 7.31–7.25 (m, 2H), 7.21–7.17 (m, 1H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.18 (dd, *J* = 16.0, 6.9 Hz, 1H), 2.18–2.12 (m, 1H), 1.83–1.67 (m, 5H), 1.35–1.15 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 137.0, 128.6, 127.4, 126.9, 126.1, 41.3, 33.1, 26.3, 26.2; LRMS (GC-CI) *m/z* 186.2 $[M]^+$.

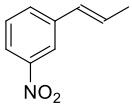
1-(3-Nitrophenyl)propan-1-ol 234[7]



In a 3-necked flask dried and flushed with nitrogen gas, 3-nitropropiophenone (2.0 g, 11.2 mmol) was added, dissolved in ethanol (10 mL) and cooled to 0 °C using an ice bath. $NaBH_4$ (0.5 g, 12.3 mmol) was added and the reaction mixture was stirred for 2 h at 0 °C. After this time, 1 M HCl solution (10 mL) was added to quench the reaction. H_2O (30 mL) was added and then the aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation to give the *title* compound **234** (2.0 g, 10.8 mmol, 95%) as a yellow oil without further purification.

IR (ATR)/cm^{-1}: 3543, 3365, 2974, 2931, 2878, 1525, 1348; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (appt, *J* = 1.8 Hz, 1H), 8.03 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.45 (appt, *J* = 7.9 Hz, 1H), 4.67 (appt, *J* = 6.4 Hz, 1H), 3.00 (bs, 1H), 1.80–1.69 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2, 146.8, 132.2, 129.3, 122.3, 120.9, 74.5, 32.0, 9.8; LRMS (GC-CI) *m/z* 182.1 $[M+H]^+$.

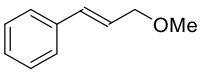
(*E*)-1-Nitro-3-(prop-1-en-1-yl)benzene 237[163]



1-(3-Nitrophenyl)propan-1-ol **234** (1.7 g, 9.4 mmol) and *p*-TsOH monohydrate (0.2 g, 1.2 mmol) were added to a round-bottom flask with toluene (30 mL) as the solvent. The system was fitted with a Dean-Stark condenser and the mixture was heated to reflux for 24 h. The dark red solution was cooled to rt and quenched with Et_3N (five drops). H_2O (10 mL) was added and the phases were separated. The aqueous layer was further extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation to give a pale yellow oil. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C)) gave the *title* compound **237** (1.2 g, 7.3 mmol, 78%) as a brown oil.

IR (ATR)/cm^{-1}: 3088, 3028, 2852, 2950, 2358, 2341, 1526, 1348; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (appt, *J* = 1.9 Hz, 1H), 8.02 (ddd, *J* = 8.1, 2.1, 1.0 Hz, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.44 (appt, *J* = 7.9 Hz, 1H), 6.46 (d, *J* = 16.2 Hz, 1H), 6.39 (m, 1H), 1.93 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7, 139.8, 131.8, 129.4, 129.1, 121.4, 120.5, 18.6; LRMS (CI) *m/z* 164.3 $[M+H]^+$.

(*E*)-(3-Methoxyprop-1-en-1-yl)benzene 186[65]

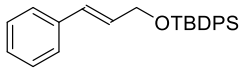


Cinnamyl alcohol **226** (1.9 mL, 14.9 mmol) was stirred in anhydrous THF (15 mL) under an inert nitrogen atmosphere. The solution was cooled to 0 °C and sodium hydride (60% dispersion in mineral oil, 1.2 g, 29.9 mmol) was added portionwise over 10 min. The reaction was stirred at 0 °C for 1 h before methyl iodide (1.4 mL, 22.4 mmol), in anhydrous THF (5 mL), was added dropwise. The reaction mixture was allowed to warm slowly to rt and stirred for a further 18 h. After this time, the reaction was quenched by cooling to 0 °C and adding H_2O (30 mL) dropwise. Et_2O (20 mL) was added and the phases were separated. The aqueous layer was further extracted with Et_2O (3 × 20 mL). The organic layers were combined, washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation to give a yellow oil. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C): Et_2O 9:1) gave the *title* compound **186** (2.0 g, 13.3 mmol, 90%) as a yellow oil.

IR (ATR)/cm^{-1}: 3059, 3026, 2981, 2924, 2819; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.39 (m, 2H), 7.35–7.31 (m, 2H), 7.27–7.23 (m, 1H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.30 (dt, *J* = 15.9, 6.0 Hz, 1H), 4.11

(dd, *J* = 6.0, 1.4 Hz, 2H), 3.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9, 132.6, 128.7, 127.8, 126.6, 126.1, 73.2, 58.1; LRMS (ES + APCI) *m/z* 148.0 $[M]^+$.

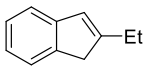
tert-Butyl(cinnamyloxy)diphenylsilane 227[164]



Cinnamyl alcohol **226** (1.0 mL, 7.5 mmol) was stirred in anhydrous DMF (10 mL) under an inert nitrogen atmosphere at rt. Imidazole (1.0 g, 15.0 mmol) was added followed by TBDPSCl (2.0 mL, 7.5 mmol). The reaction mixture was stirred at rt for 18 h. After this time, the mixture was diluted with ether (10 mL) and washed with 1 M HCl (3 × 20 mL) and brine (3 × 20 mL). The organic layers were combined and dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation to give a yellow oil. Purification by silica gel flash column chromatography (CH_2Cl_2) gave the *title* compound **227** (2.5 g, 6.7 mmol, 93%) as a colourless oil.

IR (ATR)/cm^{-1}: 3130, 2987, 2951, 2856, 1681, 1111; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.74 (m, 4H), 7.48–7.31 (m, 10H), 7.27–7.23 (m, 1H), 6.67 (dt, *J* = 15.8, 1.6 Hz, 1H), 6.31 (dt, *J* = 15.8, 4.9 Hz, 1H), 4.41 (dd, *J* = 4.9, 1.6 Hz, 2H), 1.13 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 135.7, 133.9, 129.8, 129.7, 128.9, 128.7, 127.8, 127.4, 126.6, 64.7, 27.0, 19.5; LRMS (GC-CI) *m/z* 371.1 $[M-H]^+$.

2-Ethyl-1*H*-inden 248



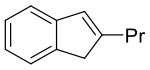
In a 3-necked flask, dried and flushed with nitrogen gas, 2-ethyl-1-indanone (1.0 g, 6.2 mmol) was added, dissolved in THF:MeOH (30:15 mL) and cooled to 0 °C using an ice bath. $NaBH_4$ (0.4 g, 9.4 mmol) was added and the reaction mixture was stirred for 4 h at rt. After this time, 1 M HCl solution (10 mL) was added to quench the reaction. H_2O (30 mL) was added and was extracted with EtOAc (3 × 50 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation to give the *title* compound as a yellow oil which was used in the next step without further purification.

Crude 2-ethyl-2,3-dihydro-1*H*-inden-1-ol **244** and *p*-TsOH monohydrate (0.1 g, 0.6 mmol) were added to a round-bottom flask with benzene (20 mL) as the solvent. The system was fitted with a Dean-Stark condenser and the mixture was heated to reflux for 2 h. The dark red solution was cooled to rt and quenched with Et_3N (five drops). H_2O (10 mL) was added and the phases were separated. The aqueous layer was further extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary

evaporation to give a pale yellow oil. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C)) gave the *title* compound **248** (0.9 g, 5.9 mmol, 95%) as a brown oil.

IR (ATR)/cm^{-1}: 3040, 3015, 2961, 2932, 2876, 2841; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.22 (appt, *J* = 7.4 Hz, 1H), 7.10 (appt, *J* = 7.3 Hz, 1H), 6.51 (s, 1H), 3.32 (s, 2H), 2.52 (q, *J* = 7.5 Hz, 2H), 1.23 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7, 145.9, 143.3, 126.4, 125.3, 123.7, 123.5, 120.0, 41.1, 24.5, 13.5; LRMS (GC-CI) *m/z* 144.1 $[M]^+$.

2-Propyl-1*H*-inden 249

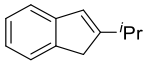


In a 3-necked flask dried and flushed with nitrogen gas, 2-propyl-1-indanone (1.0 g, 5.7 mmol) was added, dissolved in THF:MeOH (28:14 mL) and cooled to 0 °C using an ice bath. $NaBH_4$ (0.3 g, 8.6 mmol) was added and the reaction mixture was stirred for 4 h at rt. After this time, 1 M HCl solution (10 mL) was added to quench the reaction. H_2O (30 mL) was added and extracted with EtOAc (3 × 50 mL). The organic phases were combined, washed with brine (30 mL) and dried over $MgSO_4$. The solvent was removed by rotary evaporation to give the *title* compound as a yellow oil which was used in the next step without further purification.

Crude 2-propyl-2,3-dihydro-1*H*-inden-1-ol **245** and *p*-TsOH monohydrate (0.1 mg, 0.5 mmol) were added to a round-bottom flask with benzene (20 mL) as the solvent. The system was fitted with a Dean-Stark condenser and the mixture was heated to reflux for 2 h. The dark red solution was cooled to rt and quenched with Et_3N (five drops). H_2O (10 mL) was added and the phases were separated. The aqueous layer was further extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation to give a pale yellow oil. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C)) gave the *title* compound **249** (0.8 g, 5.1 mmol, 96%) as a brown oil.

IR (ATR)/cm^{-1}: 3020, 2970, 2912, 2830; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.3 Hz, 1H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.22 (appt, *J* = 7.4 Hz, 1H), 7.10 (appt, *J* = 7.3 Hz, 1H), 6.51 (s, 1H), 3.31 (s, 2H), 2.47 (t, *J* = 7.5 Hz, 2H), 1.69–1.60 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7, 144.5, 144.6, 127.6, 126.0, 124.5, 123.9, 119.0, 37.7, 30.0, 21.0, 14.1 ; LRMS (CI) *m/z* 158.1 $[M]^+$.

2-Isopropyl-1*H*-inden 250

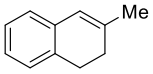


In a 3-necked flask dried and flushed with nitrogen gas, 2-isopropyl-1-indanone (500 mg, 2.9 mmol) was added, dissolved in THF:MeOH (15:7 mL) and cooled to 0 °C using an ice bath. $NaBH_4$ (162 mg, 4.3 mmol) was added and the reaction mixture was stirred for 2 h at rt. After this time, 1 M HCl solution (10 mL) was added to quench the reaction. H_2O (30 mL) was added and extracted with EtOAc (3 × 50 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation to give the *title* compound as a yellow oil which was used in the next step without further purification.

Crude 2-isopropyl-2,3-dihydro-1*H*-inden-1-ol **246** and *p*-TsOH monohydrate (51 mg, 0.3 mmol) were added to a round-bottom flask with benzene (10 mL) as the solvent. The system was fitted with a Dean-Stark condenser. The mixture was heated to reflux for 2 h. The dark red solution was cooled to rt and quenched with Et_3N (five drops). H_2O (10 mL) was added and the phases were separated. The aqueous layer was further extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation to give a pale yellow oil. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C)) gave the *title* compound **250** (450 mg, 2.8 mmol, 89%) as a brown oil.

IR (ATR)/cm^{-1}: 2950, 2940, 2866; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 7.3, 0.7 Hz, 1H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.10 (td, *J* = 7.3, 1.3 Hz, 1H), 6.51 (bs, 1H), 3.35 (bs, 2H), 2.78–2.73 (m, 1H), 1.22 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1, 140.2, 133.1, 131.3, 128.9, 128.4, 127.1, 126.0, 46.1, 18.7, 11.1; LRMS (GC-CI) *m/z* 158.1 $[M]^+$.

3-Methyl-1,2-dihydronaphthalene 251



In a 3-necked flask dried and flushed with nitrogen gas, 2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (1.0 g, 6.2 mmol) was added, dissolved in EtOH (20 mL) and cooled to 0 °C using an ice bath. $NaBH_4$ (0.7 g, 18.7 mmol) was added and the reaction mixture was stirred for 2 h at rt. After this time, 1 M HCl solution (10 mL) was added to quench the reaction. H_2O (30 mL) was added and extracted with EtOAc (3 × 50 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation to give the *title* compound as a yellow oil which was used in the next step without further purification.

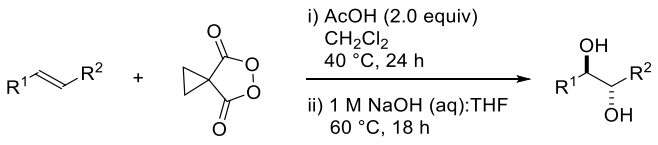
Crude 2-methyl-1,2,3,4-tetrehydronaphthalen-1-ol **247** and *p*-TsOH monohydrate (0.1 g, 0.6 mmol) were added to a round-bottom flask with benzene (10 mL) as the solvent. The system was fitted with a Dean-Stark condenser and the mixture was heated to reflux for 18 h. The dark red solution was cooled to rt and quenched with Et_3N (five drops). H_2O (10 mL) was added and the phases were separated. The aqueous layer was further extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation to give a pale yellow oil. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C)) gave the *title* compound **251** (0.8 g, 5.6 mmol, 90%) as a yellow oil.

IR (ATR)/cm^{-1}: 3445, 3012, 2981, 2922, 2880, 2826; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.04 (m, 3H), 6.96 (d, *J* = 7.3 Hz, 1H), 6.22 (s, 1H), 2.82 (t, *J* = 8.2 Hz, 2H), 2.24 (t, *J* = 8.2 Hz, 2H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3, 135.2, 134.2, 127.3, 126.5, 126.1, 125.2, 122.9, 29.0, 28.2, 23.6; LRMS (GC-CI) *m/z* 144.1 $[M]^+$.

3.2 Standard procedure for drying AcOH

Commercially available molecular sieves (3 Å) were placed into a round bottom flask and heated with a mantle set to 120 °C under vacuum (4.1 mbar) for 2 h. The molecular sieves were allowed to cool down over a 30 min period, after which time the activated molecular sieves (20% w/v) were placed into a commercial bottle of AcOH ≥ 99.99% (25 mL). Storage over 3 Å molecular sieves for >48 h provided AcOH of a consistent quality for the experiments performed in these studies.

3.3 General Procedure 1: *anti*-Dihydroxylation of alkenes



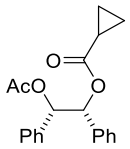
5 **10** **13**

A CH_2Cl_2 solution (0.5 M) of malonoyl peroxide **10** (1.5 equiv), 3 Å molecular sieves and dry AcOH (2.0 equiv) was allowed to stand at rt for 2 h under inert atmosphere. After this time, the dried solution was transferred to a new flask containing the appropriated alkene, then sealed with a Teflon cap and placed under an argon atmosphere. The mixture was stirred at 40 °C for 24 h. The solvent was removed by rotary evaporation to give a crude product, which was directly treated with 1 M NaOH:THF (1:1 (0.1 M)). The resulting solution was stirred at 60 °C for 18 h, allowed to cool to rt and the organic phase was extracted with EtOAc (× 3). The combined organics were washed with

brine, dried over $MgSO_4$ and filtered. Removal of the solvent under reduced pressure gave the crude diol product. If necessary, the product was purified by flash column chromatography on silica gel to afford the *target* compound.

3.4 Isolation of reaction intermediates

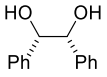
(±)-(1*R*,2*S*)-2-Acetoxy-1,2-diphenylethyl cyclopropanecarboxylate 220a



Reaction of *trans*-stilbene **1** (500 mg, 2.8 mmol), malonoyl peroxide **10** (530 mg, 4.1 mmol) and AcOH (320 µL, 5.5 mmol) in CH_2Cl_2 (5.5 mL) according to the General Procedure **1** for 24 h at 40 °C. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):Et_2O 8:2) gave the *title* compound **220a** (580 mg, 1.8 mmol, 65%) as a white solid.

m.p. 110–113 °C; IR (ATR)/cm^{-1}: 3067, 2988, 2970, 1736, 1732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.26 (m, 6H), 7.21–7.18 (m, 4H), 6.10 (d, *J* = 5.8 Hz, 1H), 6.07 (d, *J* = 5.8 Hz, 1H), 2.01 (s, 3H), 1.60 (tt, *J* = 8.0, 4.7 Hz, 1H), 0.95–0.77 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 169.8, 136.4, 136.2, 128.5, 128.4, 128.20, 128.16, 127.8, 127.6, 76.8, 76.4, 21.1, 13.2, 8.7, 8.5; LRMS (GC-CI) m/z 265.1 $[M\text{-}OAc]^+$; HRMS (EI) calculated for $C_{20}H_{20}O_4$ $[M+NH_4]^+$ 342.1700, found 342.1699.

***meso*-Hydrobenzoin 176. Hydrolysis of intermediate 220a.**

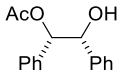


(±)-(1*R*,2*S*)-2-Acetoxy-1,2-diphenylethyl cyclopropanecarboxylate **220a** (50 mg, 0.2 mmol) was hydrolysed using 1 M NaOH:THF (1:1 (2 mL)). The mixture was stirred at 60 °C for 18 h. After this time, the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and filtered. Removal of the solvent under reduced pressure gave the desired diol **176** (29 mg, 0.1 mmol, 89%) as a white solid without further purification.

m.p. 128–131 °C, Lit[165] [133 °C]; IR (ATR)/cm^{-1}: 3300, 3156, 2980, 2845; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.29 (m, 6H), 7.27–7.23 (m, 4H), 4.85 (s, 2H), 2.15 (bs, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9, 128.4, 128.3, 127.2, 78.3; LRMS (GC-CI) m/z 197.1 $[M\text{-}OH]^+$.

3.5 Preparation of potential intermediates

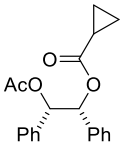
(±)-(1*S*,2*R*)-2-Hydroxy-1,2-diphenyl[64] 221



Acetic anhydride (2.2 mL, 23.3 mmol) was added to a stirred solution of *meso*-hydrobenzoin **176** (500 mg, 2.3 mmol) and $YbCl_3$ (12 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (5.8 mL) under a nitrogen atmosphere. After 4 h the reaction mixture was poured into a saturated solution of sodium bicarbonate and stirred rapidly for 30 min before the organics were separated, dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation and purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 7:3) gave the *title* compound **221** (480 mg, 1.8 mmol, 80%) as a white solid.

m.p. 86–88 °C, Lit[166] [88–89 °C]; IR (ATR)/cm^{-1}: 3449, 3064, 3032, 2928, 1724; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.28 (m, 6H), 7.27–7.24 (m, 4H), 5.91 (d, *J* = 6.0 Hz, 1H), 5.00 (dd, *J* = 6.0, 3.8 Hz, 1H), 2.01 (s, 3H), 1.26 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 139.7, 136.5, 128.6, 128.4, 128.3, 128.2, 127.9, 127.1, 79.0, 76.5, 21.2; LRMS (GC-CI) m/z 197.0 $[M\text{-}OAc]^+$; HRMS (EI) calculated for $C_{16}H_{16}O_3$ $[M+Na]^+$ 279.0992, found 279.0993.

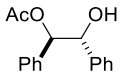
(±)-(1*R*,2*S*)-2-Acetoxy-1,2-diphenylethyl cyclopropanecarboxylate 220b



(1*S*,2*R*)-2-Hydroxy-1,2-diphenyl **221** (50 mg, 0.2 mmol) was stirred with pyridine (0.5 mL) and then cyclobutanecarbonyl chloride (18 µL, 0.2 mmol) was added. After 30 min the reaction was stopped and the solvent was removed by rotary evaporation. Crude material was dissolved in EtOAc (10 mL) and washed with H_2O (10 mL), 2 M HCl (10 mL) and brine (10 mL). The organics were dried over $MgSO_4$, filtered and removed in vacuum to give the desired product **220b** (55 mg, 0.2 mmol, 89%) as a white solid without further purification.

m.p. 110–112 °C; IR (ATR)/cm^{-1}: 3066, 3034, 2960, 1733; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.27 (m, 6H), 7.21–7.18 (m, 4H), 6.09 (d, *J* = 5.8 Hz, 1H), 6.07 (d, *J* = 5.8 Hz, 1H), 2.01 (s, 3H), 1.63–1.56 (m, 1H), 0.95–0.77 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 169.8, 136.3, 136.1, 128.5, 128.4, 128.19, 128.15, 127.8, 127.6, 76.8, 76.3, 21.1, 13.2, 8.7, 8.6; LRMS (CGC-I) m/z 265.0 $[M\text{-}OAc]^+$; HRMS (EI) calculated for $C_{20}H_{20}O_4$ $[M+NH_4]^+$ 342.1700, found 342.1699.

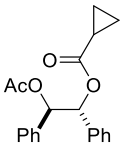
(±)-(1*R*,2*R*)-2-Hydroxy-1,2-diphenyl[64] 222



Acetic anhydride (2.2 mL, 23.3 mmol) was added to a stirred solution of (*R*,*R*)-hydrobenzoin **11** (500 mg, 2.3 mmol) and $YbCl_3$ (12 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (5.8 mL) under a nitrogen atmosphere. After 2 h the reaction mixture was poured into a saturated solution of sodium bicarbonate and stirred rapidly for 30 min. The organics were separated, dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation and purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 7:3) to give the *title* compound **222** (440 mg, 1.7 mmol, 74%) as a white solid.

m.p. 98–100 °C, Lit[167] [88 °C]; IR (ATR)/cm^{-1}: 3447, 3088, 3064, 2926, 1738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.21 (m, 6H), 7.15–7.11 (m, 4H), 5.86 (d, *J* = 7.4 Hz, 1H), 4.93 (dd, *J* = 7.4, 3.5 Hz, 1H), 2.52 (d, *J* = 3.5 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 139.2. 137.0, 128.34, 128.29, 128.2, 127.4, 127.2, 80.2, 77.3, 21.3 (1 C missing); LRMS (GC-CI) m/z 197.0 $[M\text{-}OAc]^+$; HRMS (EI) calculated for $C_{16}H_{16}O_3$ $[M+NH_4]^+$ 274.1438, found 274.1443.

(±)-(1*R*,2*R*)-2-Acetoxy-1,2-diphenylethyl cyclopropanecarboxylate 223

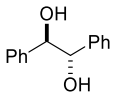


(1*R*,2*R*)-2-Hydroxy-1,2-diphenyl **222** (50 mg, 0.2 mmol) was stirred with pyridine (0.5 mL) and then cyclobutanecarbonyl chloride (18 µL, 0.2 mmol) was added. After 30 min the solvent was removed by rotary evaporation. Crude material was dissolved in EtOAc (10 mL) and washed with H_2O (10 mL), 2 M HCl (10 mL) and brine (10 mL). The organics were dried over $MgSO_4$, filtered and removed in vacuum to give the desired product **223** (52 mg, 0.2 mmol, 84%) as a white solid without further purification.

m.p. 72–74 °C; IR (ATR)/cm^{-1}: 3066, 3034, 2965, 1737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.20 (m, 6H), 7.16–7.13 (m, 4H), 6.08 (s, 2H), 2.09 (s, 3H), 1.72–1.65 (m, 1H), 1.04–0.82 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 170.0, 136.3, 136.2, 128.5, 128.4, 128.3, 127.7, 127.6, 77.3, 76.9, 21.2, 13.2, 8.7, 8.6 (1 C missing); LRMS (GC-CI) m/z 265.0 $[M\text{-}OAc]^+$.

3.6 Analytical data for diols

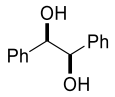
meso-Hydrobenzoin 176



Reaction of *trans*-stilbene (180 mg, 1.0 mmol), malonoyl peroxide **10** (192 mg, 1.5 mmol) and AcOH (115 µL, 2.0 mmol) according to the General Procedure **1** for 24 h at 40 ºC, followed by hydrolysis in 1 M NaOH:THF (20 mL, 1:1) gave crude diol **176** (1:7 *syn*:*anti*) (198 mg, 0.9 mmol, 92%) as a white solid without further purification.

m.p. 128-131 °C, Lit[165] [133 °C]; IR (thin film)/cm^{-1}: 3300, 3156, 2980, 2845; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.29 (m, 6H), 7.27–7.23 (m, 4H), 4.84 (s, 2H), 2.15 (bs, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9, 128.3, 128.2, 127.2, 78.2; LRMS (GC-CI) m/z 197.1 $[M\text{-}OH]^+$.

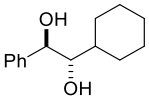
(±)-Hydrobenzoin 11



Reaction of *cis*-stilbene (180 mg, 1.0 mmol), malonyl peroxide **10** (192 mg, 1.5 mmol) and AcOH (115 µL, 2.0 mmol) according to the General Procedure **1** for 24 h at 40 °C, followed by hydrolysis in 1 M NaOH:THF (20 mL, 1:1) gave crude diol (3:4 *syn*:*anti*). Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 1:1) to give the *title* compound **11** (169 mg, 0.79 mmol, 79%) as a white solid.

m.p. 108–110 °C, Lit[96] [104–105 °C]; IR (thin film)/cm^{-1}: 3500, 3390, 2898, 1454, 1197, 1038; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (m, 8H), 7.15–7.13 (m, 2H), 4.73 (s, 2H), 2.79 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0, 128.3, 127.2, 127.1, 79.2; LRMS (GC-CI) m/z 197.0 $[M\text{-}OH]^+$; HRMS (NSI) calculated for $C_{14}H_{14}O_2$ $[M+Na]^+$ 237.0886, found 237.0883.

(±)-(1*R*,2*S*)-1-Phenyl-2-cyclohexylethane-1,2-diol 255

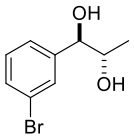


Reaction of (*E*)-2-(cyclohexylvinyl)benzene **236** (186 mg, 1.0 mmol), malonoyl peroxide **10** (192 mg, 1.5 mmol) and AcOH (115 µL, 2.0 mmol) according to the General Procedure **1** for 24 h at 40 ºC, followed by hydrolysis in 1 M NaOH:THF (20 mL, 1:1) gave crude diol (1:4 *syn*:*anti*). Purification by

silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 8:2) to give the *title* compound **255** (171 mg, 0.8 mmol, 77%) as a white solid.

m.p. 92–96 °C; IR (thin film)/cm^{-1}: 3570, 3050, 2976, 2870; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.31 (m, 5H), 4.68–4.66 (m, 1H), 3.56–3.54 (m, 1H), 2.70 (d, *J* = 3.8 Hz, 1H), 1.92 (d, *J* = 3.8 Hz, 1H), 1.72–1.64 (m, 5H), 1.17–1.06 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 128.6, 128.2, 127.4, 79.1, 74.8, 39.2, 30.1, 27.5, 26.5, 26.2, 26.0; LRMS (GC-CI) m/z 203.1 $[M\text{-}OH]^+$; HRMS (EI) calculated for $C_{14}H_{20}O_2$ $[M+NH_4]+$ 238.1802.

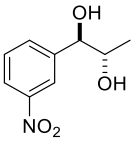
(±)-(1*R*,2*S*)-1-(2-Bromophenyl)propane-1,2-diol 256



Reaction of (*E*)-1-bromo-3-(prop-1-en-1-yl)benzene **239** (197 mg, 1.0 mmol), malonyl peroxide **10** (192 mg, 1.5 mmol) and AcOH (115 µL, 2.0 mmol) according to the General Procedure **1** for 24 h at 40 °C, followed by hydrolysis in 1 M NaOH:THF (20 mL, 1:1) gave crude diol (1:3 *syn*:*anti*). The crude material was then purified by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 2:1) to give the *title* compound **256** (176 mg, 0.8 mmol, 76%) as a pale yellow solid.

m.p. 90–92 °C; IR (thin film)/cm^{-1}: 3261, 2924, 1416, 1001; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.51 (m, 1H), 7.46–7.41 (m, 1H), 7.30–7.26 (m, 1H), 7.23 (appt, *J* = 7.7 Hz, 1H), 4.68 (d, *J* = 4.0 Hz, 1H), 4.06–3.98 (m, 1H), 2.47 (s, 1H), 1.92 (s, 1H), 1.07 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 131.0, 130.0, 129.8, 125.4, 122.7, 71.3, 17.3; LRMS (GC-CI) m/z 212.9 $[M\text{-}OH]^+$; HRMS (NSI) calculated for $C_9H_{11}{}^{79}BrO_2$ $[M+Na]^+$ 252.9835, found 252.9838.

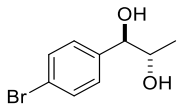
(±)-(1*R*,2*S*)-1-(3-Nitrophenyl)propane-1,2-diol 257



Reaction of (*E*)-1-nitro-3-(prop-1-en-1-yl)benzene **237** (163 mg, 1.0 mmol), malonoyl peroxide **10** (192 mg, 1.5 mmol) and AcOH (115 µL, 2.0 mmol) according to the General Procedure **1** for 24 h at 40 °C, followed by hydrolysis in 1 M NaOH:THF (20 mL, 1:1) gave crude diol (1:2 *syn*:*anti*). Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 6:4) to give the *title* compound **257** (70 mg, 0.4 mmol, 35%) as a colourless oil.

IR (thin film)/cm^{-1}: 3390, 3379, 2976, 2926, 2877, 2713, 1526, 1348; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21–8.20 (m, 1H), 8.12–8.09 (m, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.51 (td, *J* = 7.6, 3.1 Hz, 1H), 4.81 (d, *J* = 3.6 Hz, 1H), 4.08–4.05 (m, 1H), 3.24 (bs, 1H), 2.55 (bs, 1H), 1.02 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4, 142.7, 132.9, 129.3, 122.8, 121.8, 76.4, 71.1, 17.1; LRMS (GC-CI) m/z 152.1 $[M\text{-EtO}]^+$; HRMS (EI) calculated for $C_9H_{11}O_4N$ $[M+NH_4]^+$ 215.1026, found 215.1024.

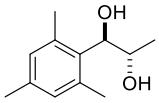
(±)-(1*R*,2*S*)-1-(4-Bromophenyl)propane-1,2-diol 258



Reaction of (*E*)-1-bromo-4-(prop-1-en-1-yl)benzene **229** (197 mg, 1.0 mmol), malonyl peroxide **10** (192 mg, 1.5 mmol) and AcOH (115 µL, 2.0 mmol) according to the General Procedure **1** for 24 h at 40 °C, followed by hydrolysis in 1 M NaOH:THF (20 mL, 1:1) gave crude diol (1:4 *syn*:*anti*). Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 2:1) to give the *title* compound **258** as a pale yellow solid (183 mg, 0.8 mmol, 79%).

m.p. 68–70 °C; IR (thin film)/cm^{-1}: 3403, 3233, 2980, 2893, 1401, 1012; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dt, *J* = 8.4, 2.4 Hz 2H), 7.23 (dt, *J* = 8.3, 2.2 Hz, 2H), 4.66 (d, *J* = 4.1 Hz, 1H), 3.99 (qd, *J* = 6.4, 4.2 Hz, 1H), 2.53 (bs, 1H), 1.97 (bs, 1H), 1.04 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 131.6, 128.5, 121.8, 76.9, 71.2, 17.2; LRMS (GC-CI) m/z 212.9 $[M\text{-OH}]^+$; HRMS (NSI) calculated for $C_9H_{11}{}^{79}BrO_2$ $[M+Na]^+$ 252.9835, found 252.9838.

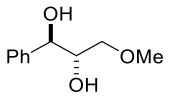
(±)-(1*R*,2*S*)-1-(2,4,6-Trimethylphenyl)propane-1,2-diol 259



Reaction of (*E*)-1,3,5-trimethyl-2-(prop-1-en-1-yl)benzene **235** (160 mg, 1.0 mmol), malonoyl peroxide **10** (192 mg, 1.5 mmol) and AcOH (115 µL, 2.0 mmol) according to the General Procedure **1** for 24 h at 40 ºC, followed by hydrolysis in 1 M NaOH:THF (20 mL, 1:1) gave crude diol **259** (1:5 *syn*:*anti*) (175 mg, 0.9 mmol, 90%) as a white solid without further purification.

m.p. 75–79 °C; IR (thin film)/cm^{-1}: 3350, 3277, 2974, 2926; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 2H), 4.88 (d, *J* = 8.1 Hz, 1H), 4.16-4.13 (m, 1H), 2.41 (s, 6H), 2.25 (s, 3H), 1.37 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6, 137.5, 133.5, 130.6, 76.3, 70.0, 21.1, 20.9, 20.0; LRMS (GC-CI) m/z 177.1 $[M\text{-OH}]^+$; HRMS (EI) calculated for $C_{12}H_{22}O_2N_1$ $[M+NH_4]^+$ 212.1645, found 212.1643.

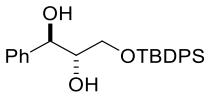
(±)-(1*R*,2*S*)-3-Methoxy-1-phenylpropane-1,2-diol 260



Reaction of (*E*)-(3-methoxyprop-1-en-1-yl)benzene **186** (148 mg, 1.0 mmol), malonoyl peroxide **10** (192 mg, 1.5 mmol) and AcOH (115 µL, 2.0 mmol) according to the General Procedure **1** for 24 h at 40 ºC followed by hydrolysis in 1 M NaOH:THF (20 mL, 1:1) gave crude diol (1:2 *syn*:*anti*). Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):Et_2O 8:2) afforded the *title* compound **260** (115 mg, 0.6 mmol, 63%) as a colourless oil.

IR (thin film)/cm^{-1}: 3406, 3136, 2933, 2877; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.28 (m, 5H), 4.86–4.84 (m, 1H), 3.96–3.92 (m, 1H), 3.45 (dd, *J* = 9.7, 6.3 Hz, 1H), 3.36 (dd, *J* = 6.3, 3.2 Hz, 1H), 3.34 (s, 3H), 3.21 (bs, 1H), 2.80 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.5, 128.5, 127.8, 126.3, 75.4, 73.4, 73.1, 59.2; LRMS (GC-CI) m/z 165.1 $[M\text{-}OH]^+$; HRMS (EI) calculated for $C_{10}H_{14}O_3$ $[M+NH_4]^+$ 200.1281, found 200.1277.

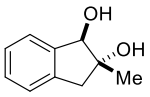
(±)-(1*R*,2*S*)-3-((*tert*-Butyldiphenylsilyl)oxy)-1-phenylpropane-1,2-diol 261



Reaction of *tert*-butyl(cinnamyloxy)diphenylsilane **227** (372 mg, 1.0 mmol), malonoyl peroxide **10** (192 mg, 1.5 mmol) and AcOH (115 µL, 2.0 mmol) according to the General Procedure **1** for 24 h at 40 ºC, followed by hydrolysis in 1 M NaOH:THF (20 mL, 1:1) gave crude diol (1:2 *syn*:*anti*). Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 8:2) afforded the *title* compound **261** (210 mg, 0.5 mmol, 52%) as a colourless oil.

IR (thin film)/cm^{-1}: 3437, 2958, 2883, 2859; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.62 (m, 5H), 7.45-7.31 (m, 10H), 4.88 (d, *J* = 5.2 Hz, 1H) , 3.91–3.87 (m, 1H), 3.79 (dd, *J* = 10.5, 5.6 Hz, 1H), 3.70 (dd, *J* = 10.5, 4.2 Hz, 1H), 3.14 (bs, 1H), 2.72 (bs, 1H), 1.10 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.5, 135.7, 135.6, 130.1, 128.5, 128.0, 126.8, 126.4, 75.7, 74.4, 65.0, 27.0, 19.3; LRMS (GC-CI) m/z 239.1 $[M\text{-}TBDPS]^+$; HRMS (EI) calculated for $C_{25}H_{30}O_3Si_1$ $[M+NH_4]^+$ 424.2302, found 424,2301.

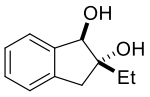
(±)-(1*R*,2*R*)-2,3-Dihydro-1*H*-indene-2-methyl-1,2-diol 262



Reaction of 2-methyl-1-*H*-indene **253** (100 µL, 0.8 mmol), malonoyl peroxide **10** (145 mg, 1.1 mmol) and AcOH (85 µL, 1.5 mmol) according to the General Procedure **1** for 24 h at 40 ºC, followed by hydrolysis in 1 M NaOH:THF (20 mL, 1:1) gave crude diol **262** (1:8 *syn*:*anti*) (98 mg, 0.6 mmol, 80%) as a white solid without further purification.

m.p. 114–116 °C; IR (thin film)/cm^{-1}: 3357, 2932, 2973, 2848; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.37 (m, 1H), 7.27–7.24 (m, 2H), 7.23–7.19 (m, 1H), 4.92 (s, 1H), 3.06 (d, *J* = 15.8 Hz, 1H), 2.97 (d, *J* = 15.8 Hz, 1H), 1.92 (s, 2H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 140.4, 128.8, 127.3, 125.4, 124.7, 83.4, 83.0, 45.1, 21.8; LRMS (GC-CI) m/z 147.0 $[M\text{-}OH]^+$; HRMS (EI) calculated for $C_{10}H_{12}O_2$ $[M+NH_4]^+$ 182.1176, found 182.1172.

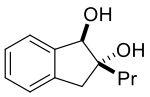
(±)-(1*R*,2*R*)-2,3-Dihydro-1*H*-indene-2-ethyl-1,2-diol 263



Reaction of 2-ethyl-1-*H*-indene **248** (158 mg, 1.0 mmol), malonoyl peroxide **10** (192 mg, 1.5 mmol) and AcOH (115 µL, 2.0 mmol) according to the General Procedure **1** for 24 h at 40 ºC, followed by hydrolysis in 1 M NaOH:THF (20 mL, 1:1) gave crude diol (1:8 *syn*:*anti*). Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):Et_2O 2:8) afforded the *title* compound **263** (140 mg, 0.8 mmol, 79%) as a white solid.

m.p. 83–85 °C; IR (thin film)/cm^{-1}: 3372, 2965, 2939, 2880; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42–7.41 (m, 1H), 7.29–7.23 (m, 3H), 4.82 (s, 1H), 3.15 (d, *J* = 16.3 Hz, 1H), 2.85 (d, *J* = 16.3 Hz, 1H), 1.89–1.83 (m, 1H), 1.78–1.72 (m, 2H), 1.70 (bs, 1H), 1.06 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) 143.2, 141.3, 129.1, 127.3, 125.7, 125.4, 84.4, 82.6, 43.0, 27.3, 8.1; LRMS (GC-CI) m/z 161.1 $[M\text{-}OH]^+$; HRMS (EI) calculated for $C_{11}H_{14}O_2Na$ $[M+Na]^+$ 201.0886, found 201.0886.

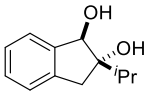
(±)-(1*R*,2*R*)-2,3-Dihydro-1*H*-indene-2-propyl-1,2-diol 264



Reaction of 2-propyl-1-*H*-indene **249** (158 mg, 1.0 mmol), malonoyl peroxide **10** (192 mg, 1.5 mmol) and AcOH (115 µL, 2.0 mmol) according to the General Procedure **1** for 24 h at 40 ºC, followed by hydrolysis in 1 M NaOH:THF (20 mL, 1:1) gave crude diol (1:13 *syn*:*anti*). Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):Et_2O 2:8) afforded the *title* compound **264** (134 mg, 0.7 mmol, 70%) as a white solid.

m.p. 104–106 °C; IR (thin film)/cm^{-1}: 3385, 2958, 2932, 2870; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42–7.41 (m, 1H), 7.29–7.23 (m, 3H), 4.80 (d, *J* = 5.9 Hz, 1H), 3.14 (d, *J* = 16.1 Hz, 1H), 2.84 (d, *J* = 16.1 Hz, 1H), 1.81–1.68 (m, 3H), 1.67 (bs, 1H), 1.61–1.54 (m, 1H), 1.53–1.45 (m, 1H), 1.00 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.2, 141.3, 129.1, 127.3, 125.7, 125.4, 84.2, 82.8, 43.4, 37.0, 17.2, 14.9; LRMS (GC-CI) m/z 175.1 $[M\text{-}OH]^+$; HRMS (EI) calculated for $C_{12}H_{16}O_2$ $[M+Na]^+$ 215.1043 found 215.1040.

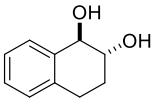
(±)-(1*R*,2*S*)-2,3-Dihydro-1*H*-indene-2-ethyl-1,2-diol 265



Reaction of 2-isopropyl-1-*H*-indene **250** (50 mg, 1.0 mmol), malonoyl peroxide **10** (61 mg, 1.5 mmol) and AcOH (36 µL, 2.0 mmol) according to the General Procedure **1** for 24 h at 40 ºC, followed by hydrolysis in 1 M NaOH:THF (20 mL, 1:1) gave crude diol (1:13 *syn*:*anti*). Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 7:3) afforded the *title* compound **265** (49 mg, 0.3 mmol, 83%) as a yellow solid.

m.p. 68–70 °C; IR (thin film)/cm^{-1}: 3417, 2963. 2913, 2874; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.2 Hz, 1H), 7.28–7.20 (m, 3H), 4.66 (s, 1H), 3.08 (d, *J* = 16.4 Hz, 1H), 2.80 (d, *J* = 16.4 Hz, 1H), 2.23–2.18 (m, 1H), 1.58 (bs, 1H), 1.36 (bs, 1H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.7, 142.5, 129.3, 127.3, 126.0, 85.6, 81.4, 43.5, 31.2, 17.04, 16.96 (1 carbon missing); LRMS (GC-CI) m/z 175.1 $[M\text{-}OH]^+$; HRMS (EI) calculated for $C_{12}H_{16}O_2$ $[M+Na]^+$ 215.1043, found 215.1044.

(±)-(1*R*,2*R*)-1,2,3,4-Tetrahydronaphthalene-1,2-diol 266

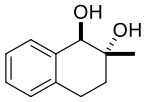


Reaction of 1,2-dihydronaphthalene **254** (130 µL, 1.0 mmol), malonoyl peroxide **10** (192 mg, 1.5 mmol) and AcOH (115 µL, 2.0 mmol) according to the General Procedure **1** for 24 h at 40 ºC, followed by hydrolysis in 1 M NaOH:THF (20 mL, 1:1) gave crude diol (1:3 *syn*:*anti*). Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 1:1) afforded the *title* compound **266** (132 mg, 0.8 mmol, 80%) as a white solid.

m.p. 107–109 °C Lit[168] [115–115.5 °C]; IR (thin film)/cm^{-1}: 3363, 2928, 2893, 2868; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.54 (m, 1H), 7.25–7.19 (m, 2H), 7.11–7.09 (m, 1H), 4.58 (appt, *J* = 7.2 Hz, 1H), 3.86–3.80 (m, 1H), 2.97–2.91 (m, 2H), 2.30 (d, *J* = 3.4 Hz, 1H), 2.21–2.12 (m, 2H), 1.92–1.82 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2, 135.8, 128.4, 127.7, 127.1, 126.6,

75.3, 73.7, 28.8, 27.8; LRMS (GC-CI) m/z 147.1 $[M\text{-}OH]^+$; HRMS (EI) calculated for $C_{10}H_{12}O_2$ $[M+Na]^+$ 187.0730, found 187.0727.

(±)-(1*R*,2*R*)-2-Methyl-1,2,3,4-tetrahydronaphthalene-1,2-diol 267



Reaction of 3-methyl-1,2-dihydronaphthalene **251** (144 mg, 1.0 mmol), malonoyl peroxide **10** (192 mg, 1.5 mmol) and AcOH (115 µL, 2.0 mmol) according to the General Procedure **1** for 24 h at 40 ºC, followed by hydrolysis in 1 M NaOH:THF (20 mL, 1:1) gave crude diol (1:13 *syn*:*anti*). Purification by silica gel flash columnchromatography (petroleum ether (40–60 °C):EtOAc 1:1) afforded the *title* compound **267** (174 mg, 0.8 mmol, 75%) as a white solid.

m.p. 74–76 °C; IR (thin film)/cm^{-1}: 3387, 2971, 2932, 2850; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.48 (m, 1H), 7.25–7.19 (m, 2H), 7.15–7.10 (m, 1H), 4.54 (d, *J* = 5.4 Hz, 1H), 2.99–2.83 (m, 2H), 2.14 (appd, *J* = 5.4 Hz, 1H), 2.04–1.97 (m, 1H), 1.93–1.88 (m, 1H), 1.87 (s, 1H), 1.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 135.2, 128.7, 127.8, 127.7, 126.6, 76.5, 72.3, 33.2, 26.9, 21.7; LRMS (GC-CI) m/z 201.0 $[M+Na]^+$; HRMS (EI) calculated for $C_{11}H_{14}O_2Na$ $[M+Na]^+$ 201.0886.

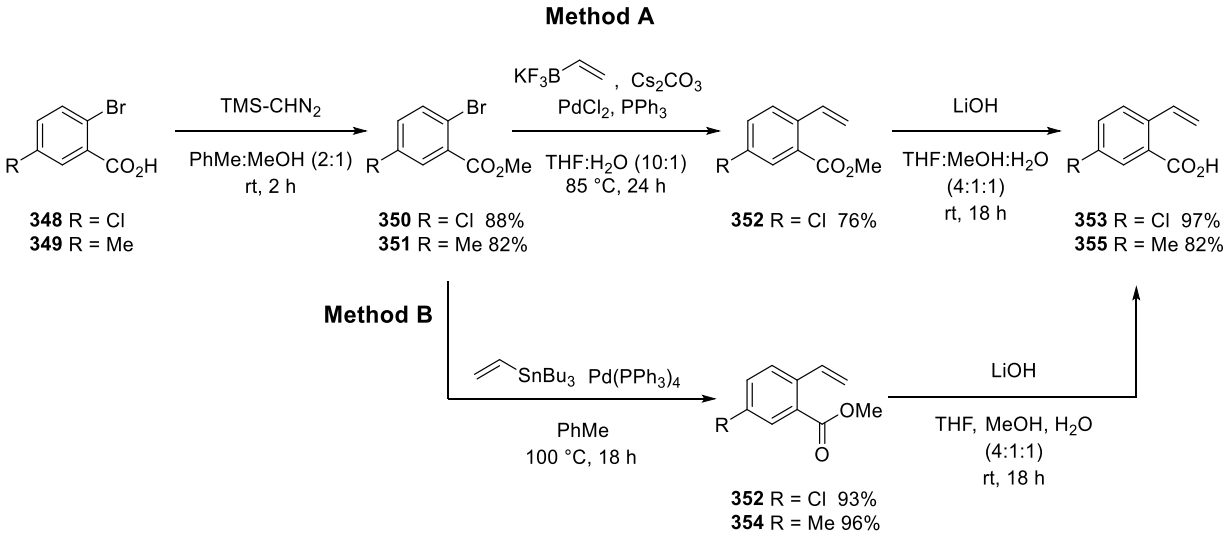
4 Experimental Chapter 2

4.1 Standard procedure for drying HFIP

Commercially available molecular sieves (3 Å) were placed into a round bottom flask and heated with a mantle set to 120 °C under vacuum (4.1 mbar) for 2 h. The molecular sieves were allowed to cool down over 30 min after which time the activated molecular sieves (20% w/v) were placed into a commercial bottle of HFIP (100 mL). Storage over 3 Å molecular sieves for >48 h provided HFIP of a consistent quality for the experiments performed in these studies.

4.2 Synthesis of carboxylic acid starting materials

4.2.1 Synthesis of Vinyl Benzoic Acids



General Procedure 2. Methyl ester formation. Benzoic acid **348–349** (1.0 equiv) was dissolved in PhMe (0.4 M) and MeOH (1 M). Then a solution of TMS-CHN_2 (2 M in Et_2O, 1.3 equiv) was added dropwise. The mixture was stirred at rt for 2 h before the solvents being concentrated *in vacuo*. Purification by silica gel flash column chromatography afforded methyl ester **350–351.**

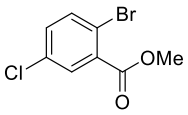
General Procedure 3. Vinyl coupling, Method A.[99] A dry three-neck flask was charged with methyl ester **350** (1.0 equiv), potassium vinyltrifluoroborate (1.0 equiv), Cs_2CO_3 (3.0 equiv), $PdCl_2$ (1 mol%), PPh_3 (5 mol%). The reactants were then dissolved in THF (0.3 M) and degassed H_2O (2.6 M). The resulting mixture was stirred at 85 °C for 40 h. Then the mixture was allowed to cool to rt, diluted with CH_2Cl_2 (5 mL) and H_2O (3 mL) and filtered through Celite®. The organics were separated, dried

over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography afforded methyl vinylbenzoate **352**.

General Procedure 4. Vinyl coupling, Method B.[100] A dry three-neck flask was charged with methyl ester **350** or **351** (1.0 equiv), vinyltributyltin reagent (1.1 equiv) and $Pd(PPh_3)_4$ (5 mol%) and dissolved with PhMe (0.12 M). The mixture was stirred at 100 °C for 18 h. The mixture was allowed to cool to rt and filtered through Celite®. The organics were washed with brine (× 2), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography afforded methyl vinylbenzoate **352** or **354**.

General Procedure 5. Hydrolysis.[99] Methyl vinylbenzoate **352** or **354** (1.0 equiv) was dissolved in a mixture of THF:H_2O:MeOH (0.2 M, 4:1:1) before the addition of LiOH (2.7 equiv). The resulting mixture was stirred at rt for 18 h. The solvent was evaporated and the residue was dissolved in H_2O:CH_2Cl_2 (10 mL, 1:1). The layers were separated and the aqueous phase was acidified with HCl 1 M to pH = 1. Et_2O (30 mL) was added and the layers were separated. The aqueous layer was further extracted with Et_2O (× 2). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure afforded vinyl benzoic acid **353** or **355**.

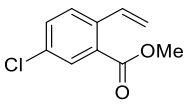
Methyl 2-bromo-chlorobenzoate 350



2-Bromo-5-chlorobenzoic acid **348** (540 mg, 2.3 mmol) was dissolved in PhMe (6.0 mL) and MeOH (2.5 mL). A solution of TMS-CHN_2 (2 M in Et_2O, 1.5 mL, 3.0 mmol) was added dropwise according to General Procedure **2** to give methyl 2-bromo-5-chlorobenzoate **350** (506 mg, 2.0 mmol, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 2.6 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.31 (d, *J* = 8.6, 2.6 Hz, 1H), 3.94 (s, 3H).

Methyl 5-chloro-2-vinylbenzoate 352



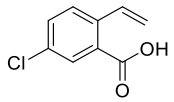
Vinyl coupling, Method A. Methyl 2-bromo-5-chlorobenzoate **350** (165 mg, 0.9 mmol), potassium vinyltrifluoroborate (121 mg, 0.9 mmol), Cs_2CO_3 (840 mg, 2.6 mmol), $PdCl_2$ (3 mg, 0.02 mmol), PPh_3 (14 mg, 0.1 mmol) and dissolved with THF (3.0 mL) and degassed H_2O (0.3 mL) according to General Procedure **3** to give methyl 5-chloro-2-vinylbenzoate **352** (128 mg, 0.7 mmol, 76%).

Vinyl coupling, Method B. Methyl 2-bromo-5-chlorobenzoate **350** (441 mg, 1.8 mmol), vinyltributyltin (570 μL, 2.0 mmol) and $Pd(PPh_3)_4$ (104 mg, 0.1 mmol) were dissolved with PhMe

(15 mL) according to General Procedure **4** to give methyl 5-chloro-2-vinylbenzoate **352** (300 mg, 1.6 mmol, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 2.3 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.46–7.38 (m, 2H), 5.64 (dd, *J* = 17.4, 1.1 Hz, 1H), 5.38 (dd, *J* = 11.0, 1.1 Hz, 1H), 3.91 (s, 3H).

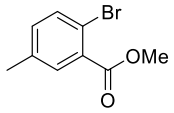
5-Chloro-2-vinylbenzoic acid 353



To a solution of methyl 5-chloro-2-vinylbenzoate **352** (128 mg, 0.7 mmol) in a mixture of THF:H_2O:MeOH (3 mL, 4:1:1) was added LiOH (41 mg, 1.7 mmol) according to General Procedure **5** to give 5-chloro-2-vinylbenzoic acid **353** (115 mg, 0.6 mmol, 97%) as a white solid.

m.p. 97–99 °C; IR (thin film)/cm^{-1}: 3078, 2982, 1697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 2.2 Hz, 1H), 7.57–7.47 (m, 3H), 5.67 (dd, *J* = 17.4, 1.0 Hz, 1H), 5.41 (dd, *J* = 11.0, 1.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 139.2, 135.0, 134.0, 133.6, 133.3, 131.1, 129.1, 117.7; LRMS (ES + APCI) *m/z* 181.1 $[M-H]^-$.

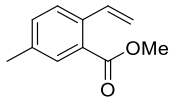
Methyl 2-bromo-5-methylbenzoate 351



2-Bromo-5-methylbenzoic acid **349** (500 mg, 2.3 mmol) was dissolved in PhMe (6.0 mL) and MeOH (2.5 mL). Then a solution of TMS-CHN_2 (2 M in Et_2O, 1.5 mL, 3.0 mmol) was added dropwise according to General Procedure **2** to give methyl 2-bromo-5-methylbenzoate **351** (430 mg, 1.9 mmol, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 1.9 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.15–7.12 (m, 1H), 3.92 (s, 3H), 2.33 (s, 3H).

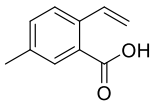
Methyl 5-methyl-2-vinylbenzoate 354



Vinyl coupling, Method B. Methyl 2-bromo-5-methylbenzoate **351** (403 mg, 1.8 mmol), vinyltributyltin (570 μL, 2.0 mmol) and $Pd(PPh_3)_4$ (104 mg, 0.1 mmol) were dissolved with PhMe (15 mL) according to General Procedure **4** to give methyl 5-methyl-2-vinylbenzoate **354** (301 mg, 1.7 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.41 (dd, *J* = 17.5, 11.0 Hz, 1H), 7.30–7.28 (m, 1H), 5.61 (d, *J* = 17.5, 1.4 Hz, 1H), 5.30 (d, *J* = 11.0, 1.4 Hz, 1H), 3.90 (s, 3H), 2.37 (s, 3H).

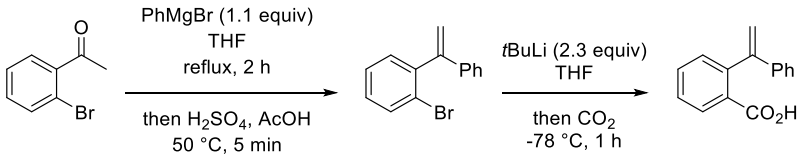
5-Methyl-2-vinylbenzoic acid 355



To a solution of methyl 5-methyl-2-vinylbenzoate **354** (300 mg, 1.7 mmol) in a mixture of THF:H_2O:MeOH (6.3 mL, 4:1:1) was added LiOH (108 mg, 4.5 mmol) according to General Procedure **5** to give 5-methyl-2-vinylbenzoic acid **355** (226 mg, 1.4 mmol, 82%) as a white solid.

m.p. 145 °C decomp; IR (thin film)/cm^{-1}: 3092, 2941, 2903, 1700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (bs, 1H), 7.56 (dd, *J* = 17.4, 10.9 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.36 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.64 (dd, *J* = 17.4, 1.2 Hz, 1H), 5.34 (dd, *J* = 11.0, 1.2 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 138.0, 137.6, 136.0, 134.1, 131.8, 127.6, 127.2, 116.1, 21.1; LRMS (ES + APCI) *m/z* 163.1 $[M+H]^+$.

4.2.1.1 Synthesis of (2-(1-Phenylvinyl)benzoic acid 358[101]



356 52% **357** 64% **358**

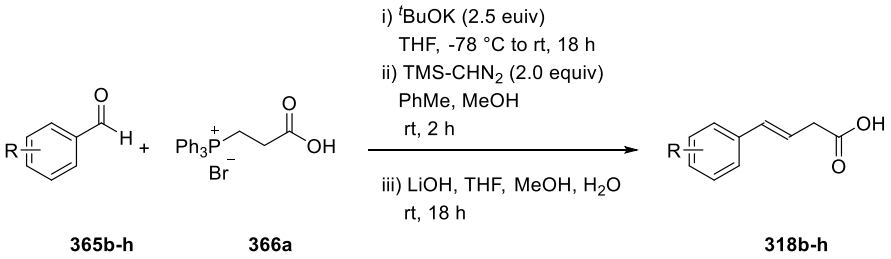
2'-Bromacetophenone **356** (2.0 mL, 14.8 mmol) was added dropwise to a stirred solution of phenylmagnesium bromide (1 M in THF, 16.3 mL, 16.3 mmol). The mixture was stirred at reflux for 2 h, then cooled to rt and quenched with a saturated solution of NH_4Cl (15 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL), and the combined extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude carbinol was dissolved in a solution of H_2SO_4 in AcOH (4 mL, 20% *v*/*v*) and heated at 50 °C for 5 min. The mixture was then poured into Et_2O:H_2O (100 mL, 1:1) and the aqueous was extracted with Et_2O (3 × 100 mL). The organics were washed with a saturated solution of $NaHCO_3$ (3 × 100 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C)) to afford 1-bromo-2-(1-phenylvinyl)benzene **357** (2.0 g, 7.7 mmol, 52%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.37–7.26 (m, 7H), 7.21 (ddd, *J* = 8.0, 6.8, 2.4 Hz, 1H), 5.84 (d, *J* = 1.0 Hz, 1H), 5.27 (d, *J* = 1.0 Hz, 1H).

To a cooled (-78 °C) solution of 1-bromo-2-(1-phenylvinyl)benzene **357** (1.50 g, 5.8 mmol) in Et_2O (11 mL) was added *t*BuLi (1.7 M in pentane, 7.80 mL, 13.3 mmol) dropwise. The resulting mixture turned yellow and after 50 min CO_2 gas was bubbled through the reaction for 10 min. The resulting solution was allowed to warm to rt and was stirred for 30 min before being quenched with a saturated solution of $NaHCO_3$ (50 mL). The aqueous layer was washed with Et_2O (3 × 20 mL), and the aqueous was acidified with 1 M HCl to pH = 1 (50 mL). The aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organics were dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude material was re-crystallised from hexane to afford the *title* compound **358** (0.83 g, 3.7 mmol, 64%) as a white solid.

m.p. 134–136 °C, Lit[169] [130–131 °C]; IR (thin film)/cm^{-1}: 3064, 3032, 2880, 1697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 1.1, 7.8 Hz, 1H), 7.56 (td, *J* = 1.4, 7.5 Hz, 1H), 7.43 (td, *J* = 1.3, 7.6 Hz, 1H), 7.37 (dd, *J* = 1.1, 7.6 Hz, 1H), 7.24–7.20 (m, 5H), 5.67 (s, 1H), 5.22 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 149.7, 143.8, 141.0, 132.6, 131.7, 130.8, 129.6, 128.2, 127.8, 127.6, 126.9, 114.5; LRMS (ES + APCI) *m/z* 225.1 $[M+H]^+$.

4.2.2 General Procedure 6: Synthesis of arylbut-3-enoic acids 318b-h[170]

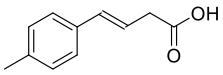


To a solution of (2-carboxyethyl)triphenylphosphonium bromide **366a** (1.2 equiv) in anhydrous THF (0.5 M) was added aryl aldehyde **365b-h** (1.0 equiv). The mixture was cooled to -78 °C before the addition of ^{t}BuOK (2.5 equiv) in anhydrous THF (1.0 M) over 2 h. The resulting mixture was stirred at rt for a further 18 h after which time the solvent was evaporated and the residue was re-dissolved in H_2O:CH_2Cl_2 (1:1). The layers were separated and the aqueous layer was acidified with 1 M HCl to pH = 1. Et_2O was added and the layers were separated. The aqueous layer was further extracted with Et_2O (× 2). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography afforded arylbut-3-enoic acids **318b-h**.

It was not possible to purify some arylbut-3-enoic acids and *cis*/*trans* mixtures were obtained. In order to get pure isomers, carboxylic acids were converted to the corresponding methyl ester:[171]

The mixture of *cis*/*trans* arylbut-3-enoic acids **318b-h** (1.0 equiv) was dissolved in PhMe (0.2 M) and MeOH (0.5 M). Then a solution of TMS-CHN_2 in Et_2O (2.0 equiv) was added dropwise. The mixture was stirred at rt for 2 h before the solvents were evaporated under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):Et_2O) mixtures afforded *trans*-isomer ester. Pure *trans*-arylbut-3-enoic acids were obtained after hydrolysis in THF:H_2O:MeOH (4:1:1) with LiOH (3.0 equiv). The mixture was stirred at rt for 18 h after which time the solvent was evaporated and the residue was re-dissolved in H_2O:CH_2Cl_2 (1:1). The layers were separated and the aqueous layer was acidified with 1 M HCl to pH = 1. The solution was diluted with Et_2O and the layers were separated. The aqueous layer was further extracted with Et_2O (× 2). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* affording pure carboxylic acids **318b-h**.

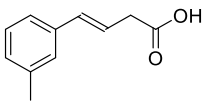
(*E*)-4-(*p*-Tolyl)but-3-enoic acid 318b[172]



Reaction of 4-methylbenzaldeyde (1.0 g, 8.3 mmol), (2-carboxyethyl)triphenylphosphonium bromide **366a** (4.1 g, 10.0 mmol) and ^{t}BuOK (2.3 g, 20.8 mmol) in THF (30 mL) according to General Procedure **6** afforded crude acid as a *cis*/*trans* mixture (1:8). Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 3:7) afforded the *title* compound **318b** (0.6 g, 3.1 mmol, 38%) as a white solid.

m.p. 106–108 °C, Lit[172] [113–114 °C]; IR (thin film)/cm^{-1}: 3013, 2927, 1711; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.9 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.23 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.29 (dd, *J* = 7.1, 1.4 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.7, 137.6, 134.0, 129.4, 128.7, 126.4, 120.0, 38.2, 21.3; LRMS (ES + APCI) *m/z* 177.0 $[M+H]^+$.

(*E*)-4-(*m*-Tolyl)but-3-enoic acid 318c[170]

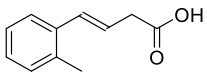


Reaction of 3-methylbenzaldehyde (1.0 mL, 8.3 mmol), (2-carboxyethyl)triphenylphosphonium bromide **366a** (4.1 g, 10.0 mmol) and ^{t}BuOK (2.3 g, 20.8 mmol) in THF (40 mL) according to General Procedure **6** afforded crude acid as a *cis*/*trans* mixture (1:10). The crude material was dissolved in PhMe (20 mL) and MeOH (8 mL) before the addition of TMS-CHN_2 (2 M in Et_2O,

4.0 mL, 8.0 mmol). Purification by silica gel flash column chromatography (CH_2Cl_2:MeOH 96:4) afforded pure *trans* compound as a colourless oil (0.4 g, 1.7 mmol, 20% over two steps). The *trans* isomer was dissolved in a mixture of THF:H_2O:MeOH (6 mL, 4:1:1) and hydrolysed with LiOH (0.1 g, 4.4 mmol) to afford the *title* compound **318c** (0.4 g, 1.6 mmol, 97%) as a white solid.

m.p. 32–34 °C; IR (thin film)/cm^{-1}: 3027, 2921, 2862, 1709; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22–7.16 (m, 3H), 7.06–7.05 (m, 1H), 6.49 (d, *J* = 15.9 Hz, 1H), 6.27 (dt, *J* = 15.9, 7.1 Hz, 1H), 3.30 (dd, *J* = 7.1, 1.3 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 138.3, 136.7, 134.2, 128.6, 128.6, 127.2, 123.7, 120.7, 38.2, 21.5; LRMS (ES + APCI) *m/z* 177.0 $[M+H]^+$.

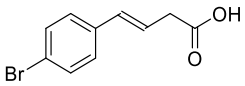
(*E*)-4-(*o*-Tolyl)but-3-enoic acid 318d[170]



Reaction of 2-methylbenzaldehyde (1.0 g, 8.3 mmol), (2-carboxyethyl)triphenylphosphonium bromide **366a** (4.1 g, 10.0 mmol) and ^{t}BuOK (2.3 g, 20.8 mmol) in THF (40 mL) according to General Procedure **6** afforded crude acid as a *cis*/*trans* mixture (1:2). The crude material was dissolved in PhMe (30 mL) and MeOH (12 mL) before the addition of TMS-CHN_2 (2 M in Et_2O, 6.2 mL, 12.4 mmol). Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):Et_2O 96:4) afforded pure *trans* compound as a colourless oil (1.0 g, 5.3 mmol, 63% over two steps). The *trans* isomer was dissolved in a mixture of THF:H_2O:MeOH (12 mL, 4:1:1) and hydrolysed with LiOH (0.2 g, 8.4 mmol) to afford the *title* compound **318d** (0.9 g, 5.1 mmol, 96%) as a white solid.

m.p. 49–50 °C, Lit[173] [53–55 °C]; IR (thin film)/cm^{-1}: 3023, 2954, 2912, 1707; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.43 (m, 1H), 7.19–7.12 (m, 3H), 6.73 (d, *J* = 15.7 Hz, 1H), 6.17 (dt, *J* = 15.7, 7.1 Hz, 1H), 3.33 (dd, *J* = 7.1, 1.5 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.1, 135.9, 135.4, 132.1, 130.4, 127.8, 126.3, 125.9, 122.3, 38.4, 19.9; LRMS (ES + APCI) *m/z* 177.0 $[M+H]^+$.

(*E*)-4-(4-Bromophenyl)but-3-enoic acid 318e[170]

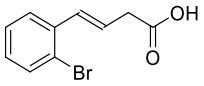


Reaction of 4-bromobenzaldeyde (2.0 g, 10.8 mmol), (2-carboxyethyl)triphenylphosphonium bromide **366a** (5.4 g, 12.9 mmol) and ^{t}BuOK (3.0 g, 27.0 mmol) in THF (40 mL) according to General Procedure **6** afforded crude acid as a *cis*/*trans* mixture (1:13). The crude material was dissolved in PhMe (15 mL) and MeOH (6 mL) before the addition of TMS-CHN_2 (2 M in Et_2O, 3.0 mL, 6.0 mmol). Purification by silica gel flash column chromatography (CH_2Cl_2:MeOH 96:4) afforded pure *trans* compound as a colourless oil (0.6 g, 2.1 mmol, 20% over two steps). The pure *trans* isomer

was dissolved in a mixture of THF:H_2O:MeOH (8 mL, 4:1:1) and hydrolysed with LiOH (0.2 g, 5.7 mmol) afforded the *title* compound **318e** (0.5 g, 2.1 mmol, 99%) as a yellow solid.

m.p. 112–114 °C, Lit[174] [110 °C]; IR (thin film)/cm^{-1}: 3024, 2931, 1701; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.28 (dt, *J* = 15.9, 7.1 Hz, 1H), 3.29 (dd, *J* = 7.1, 1.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 135.7, 133.0, 131.8, 128.0, 121.8, 121.7, 37.9; LRMS (ES + APCI) *m/z* 240.9 $[M+H]^+$.

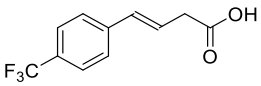
(*E*)-4-(2-Bromophenyl)but-3-enoic acid 318f[170]



Reaction of 2-bromobenzaldeyde (1.3 mL, 10.8 mmol), (2-carboxyethyl)triphenylphosphonium bromide **366a** (5.4 g, 12.9 mmol) and ^{t}BuOK (3.0 g, 27.0 mmol) in THF (50 mL) according to General Procedure **6** afforded crude acid as a *cis*/*trans* mixture (1:2). The crude material was dissolved in PhMe (21 mL) and MeOH (9 mL) before the addition of TMS-CHN_2 (2 M in Et_2O, 4.0 mL, 8.3 mmol). Purification by silica gel flash column chromatography (CH_2Cl_2:MeOH 96:4) afforded pure *trans* compound as a colourless oil (0.4 g, 1.4 mmol, 13% over two steps). The *trans* isomer was dissolved in a mixture of THF:H_2O:MeOH (5.0 mL, 4:1:1) and hydrolysed with LiOH (0.1 g, 3.7 mmol) afforded the *title* compound **318f** (0.3 g, 1.4 mmol, 99%) as a white solid.

m.p. 90–91 °C; IR (thin film)/cm^{-1}: 3064, 2927, 2857, 1707; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.28–7.25 (m, 2H), 7.10 (td, *J* = 8.0, 1.5 Hz, 1H), 6.87 (d, *J* = 15.8 Hz, 1H), 6.25 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.36 (dd, *J* = 7.1, 1.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 133.1, 132.9, 129.2, 127.7, 127.3, 124.0, 123.6, 122.1, 38.0; LRMS (ES + APCI) *m/z* 240.9 $[M+H]^+$.

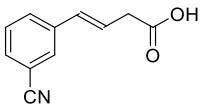
(*E*)-4-(4-(Trifluoromethyl)phenyl)but-3-enoic acid 318g[170]



Reaction of 4-(trifluoromethyl)benzaldeyde (1.6 mL, 11.5 mmol), (2-carboxyethyl)triphenylphosphonium bromide **366a** (5.7 g, 13.8 mmol) and ^{t}BuOK (3.2 g, 28.7 mmol) in THF (60 mL) according to General Procedure **6** afforded crude acid as a *cis*/*trans* mixture (1:13). The crude material was dissolved in PhMe (21 mL) and MeOH (9 mL) before the addition of TMS-CHN_2 (2 M in Et_2O, 4.4 mL, 8.7 mmol). Purification by silica gel flash column chromatography (CH_2Cl_2:MeOH 96:4) afforded pure *trans* compound as a colourless oil (0.7 g, 2.9 mmol, 25% over two steps). The *trans* isomer was dissolved in a mixture of THF:H_2O:MeOH (11 mL, 4:1:1) and hydrolysed with LiOH (0.19 g, 7.6 mmol) afforded the *title* compound **318g** (0.6 g, 2.6 mmol, 92%) as an orange oil.

IR (thin film)/cm^{-1}: 3138, 2950, 1697, 1401; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.39 (dt, *J* = 15.9, 7.0 Hz, 1H), 3.34 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.2, 140.2, 132.9, 129.9, 129.6, 126.6, 125.8–125.7 (m), 123.7, 38.0; LRMS (ES + APCI) *m/z* 231.1 $[M+H]^+$.

(*E*)-4-(3-Cyanophenyl)but-3-enoic acid 318h[172]

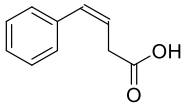


Reaction of 3-formylbenzonitrile (1.0 g, 7.6 mmol), (2-carboxyethyl)triphenylphosphonium bromide **366a** (3.8 g, 9.2 mmol) and ^{t}BuOK (2.1 g, 19.0 mmol) in THF (40 mL) according to General Procedure **6** affording crude acid as a *cis*/*trans* mixture (1:7). The crude material was dissolved in PhMe (14 mL) and MeOH (6 mL) before the addition of TMS-CHN_2 (2 M in Et_2O, 2.7 mL, 5.5 mmol). Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 7:3) afforded pure *trans* compound as a colourless oil (0.3 g, 1.5 mmol, 20% over two steps). The *trans* isomer was dissolved in a mixture of THF:H_2O:MeOH (6.0 mL, 4:1:1) and hydrolysed with LiOH (0.1 g, 4.0 mmol) afforded the *title* compound **318h** (0.3 g, 1.4 mmol, 91%) as a white solid.

m.p. 76–78 °C, Lit[172] [81–83 °C]; IR (thin film)/cm^{-1}: 2930, 2850, 2358, 1707; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.36 (dt, *J* = 16.0, 7.0 Hz, 1H), 3.34 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 138.0, 132.0, 131.2, 130.6, 130.0, 129.6, 124.0, 118.8, 113.0, 37.9; LRMS (ES + APCI) *m/z* 188.0 $[M+H]^+$.

4.2.3 Synthesis of other acid starting materials

(*Z*)-4-Phenylbut-3-enoic acid 318i[175]

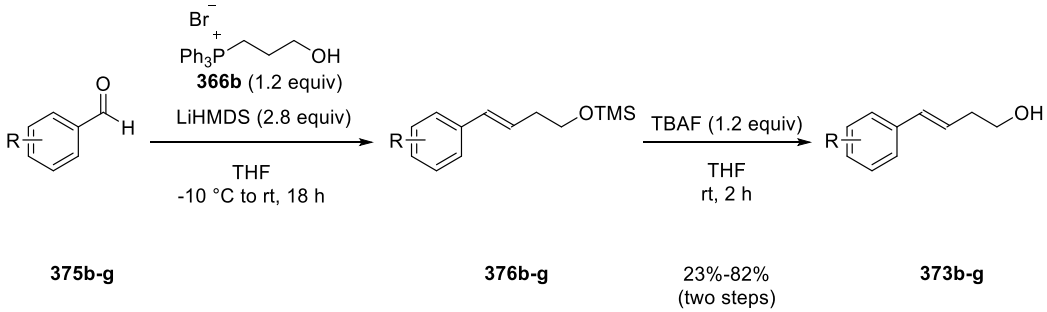


Jones reagent was prepared from CrO_3 (3.1 g, 31.6 mmol), H_2SO_4 (6.0 mL, 1.4 M) and H_2O (13.0 mL, 0.6 M). The mixture was stirred for 10 min before being added dropwise to a solution of (*Z*)-4-phenylbut-3-en-1-ol **373i** (1.2 g, 7.9 mmol) in acetone (200 mL). The mixture was stirred at rt for 18 h before quenching it with H_2O (100 mL), the organics were extracted from the aqueous with EtOAc (3 × 100 mL), dried over $MgSO_4$ and filterated before removing the solvent *in vacuo*. Purification by silica gel flash column chromatography (CH_2Cl_2:MeOH 98:2) afforded the *title* compound **318i** (0.9 g, 5.4 mmol, 69%) as a colourless oil.

IR (thin film)/cm^{-1}: 3076, 3034, 2926, 1701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.35 (m, 2H), 7.29–7.26 (m, 3H), 6.69 (d, *J* = 11.5 Hz, 1H), 5.89 (dt, *J* = 11.5, 7.4 Hz, 1H), 3.41 (dd, *J* = 7.4, 1.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.1, 136.5, 132.8, 128.8, 128.5, 127.4, 122.5, 33.9; LRMS (ES + APCI) *m/z* 180.1 $[M+NH_4]^+$.

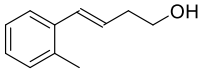
4.3 Synthesis of alcohol starting materials

4.3.1 General Procedure 7. Synthesis of arylbut-3-en-1-ol 373b-g[107]



To a three-neck round-bottom flask, dried and flushed with argon gas, was added (3-hydroxypropyl)triphenylphosphonium bromide **366b** (1.2 equiv) in anhydrous THF (0.5 M). The suspension was cooled to -10 °C using a NaCl/ice bath. A 1 M solution of LiHMDS (2.8 equiv) was added dropwise. The mixture was stirred at -10 °C for 1 h. After this time, the aryl aldehyde **375b-g** (1.0 equiv) was added dropwise and the resulting mixture was stirred at -10 °C for 2 h. The mixture was allowed to warm to rt and stirred for further 15 h. A saturated aqueous solution of NH_4Cl was added. The organic layer was extracted from the aqueous with Et_2O (× 2), dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was dissolved in THF (0.1 M) and TBAF·$3H_2O$ (1.2 equiv) was added. The mixture was stirred at rt for 2 h before being washed with H_2O and extracted with Et_2O (× 2). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by silica gel flash column chromatography with petroleum ether (40–60 °C):EtOAc mixtures afforded the *target* arylbut-3-en-1-ol **373b-g**.

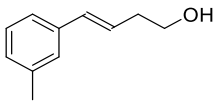
(*E*)-4-(*o*-Tolyl)but-3-en-1-ol 373b[107]



Reaction of 2-methylbenzaldehyde (1.0 g, 8.3 mmol), (3-hydroxypropyl)triphenylphosphonium bromide **366b** (4.0 g, 10.0 mmol) and LiHMDS (21.0 mL, 21.0 mmol) in THF (22 mL) according to General Procedure **7** afforded crude *cis*/*trans* mixtures (1:8) along with the protected TMS-alcohol. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):Et_2O 1:1) afforded the *title* compound **373b** (0.4 g, 2.2 mmol, 26%) as a colourless oil.

IR (thin film)/cm^{-1}: 3353, 2940, 2885; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.42 (m, 1H), 7.17–7.13 (m, 3H), 6.71 (d, *J* = 15.7 Hz, 1H), 6.08 (dt, *J* = 15.7, 7.2 Hz, 1H), 3.78–3.76 (m, 2H), 2.54–2.50 (m, 2H), 2.34 (s, 3H), 1.47 (bs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.5, 135.2, 130.9, 130.4, 127.8, 127.4, 126.2, 125.6, 62.2, 36.9, 20.0; LRMS (ES + APCI) *m/z* 163.1 $[M+H]^+$.

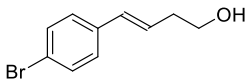
(*E*)-4-(*m*-Tolyl)but-3-en-1-ol 373c[107]



Reaction of 3-methylbenzaldehyde (2.0 g, 15.0 mmol), (3-hydroxypropyl)triphenylphosphonium bromide **366b** (7.2 g, 18.0 mmol) and LiHMDS (42.0 mL, 42.0 mmol) in THF (65 mL) according to General Procedure **7** afforded crude *cis*/*trans* mixtures (1:33) along with the protected TMS-alcohol. The crude material was dissolved in THF (150 mL) before the addition of TBAF·3H_2O (2.3 g, 9.0 mmol). Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 7:3) afforded the *title* compound **373c** (2.0 g, 12.3 mmol, 82% over two steps) as a colourless oil.

IR (thin film)/cm^{-1}: 3348, 3024, 2927, 2875; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.15 (m, 3H), 7.05–7.03 (m, 1H), 6.48 (d, *J* = 15.8 Hz, 1H), 6.19 (dt, *J* = 15.8, 7.2 Hz, 1H), 3.80–3.74 (m, 2H), 2.51–2.46 (m, 2H), 2.34 (s, 3H), 1.46 (bs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 137.3, 133.0, 128.6, 128.2, 126.9, 126.2, 123.4, 61.2, 36.5, 21.5; LRMS (ES + APCI) *m/z* 163.1 $[M+H]^+$.

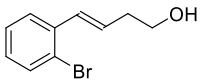
(*E*)-4-(4-Bromophenyl)but-3-en-1-ol 373d[107]



Reaction of 4-bromobenzaldehyde (1.0 g, 5.4 mmol), (3-hydroxypropyl)triphenylphosphonium bromide **366b** (2.6 g, 6.5 mmol) and LiHMDS (15.1 mL, 15.1 mmol) in THF (15 mL) according to General Procedure **7** afforded crude *cis*/*trans* mixtures (1:11) along with the protected TMS-alcohol. The crude material was dissolved in THF (55 mL) before the addition of TBAF·3H_2O (0.9 g, 3.2 mmol). Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 7:3) afforded the *title* compound **373d** (0.5 g, 2.2 mmol, 42% over two steps) as a colourless oil.

IR (thin film)/cm^{-1}: 3371, 2977, 2930; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.44 (d, *J* = 15.9 Hz, 1H), 6.21 (dt, *J* = 15.9, 7.1 Hz, 1H), 3.79–3.75 (m, 2H), 2.51–2.46 (m, 2H), 1.38 (t, *J* = 5.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.3, 131.6, 131.4, 127.7, 127.5, 120.9, 61.9, 36.3; LRMS (ES + APCI) *m/z* 227.0 $[M+H]^+$.

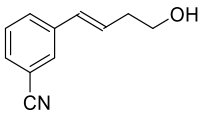
(*E*)-4-(2-Bromophenyl)but-3-en-1-ol 373e[107]



Reaction of 2-bromobenzaldehyde (0.8 g, 4.2 mmol), (3-hydroxypropyl)triphenylphosphonium bromide **366b** (2.0 g, 5.0 mmol) and LiHMDS (11.6 mL, 11.6 mmol) in THF (11 mL) according to General Procedure **7** afforded crude *cis*/*trans* mixtures (1:4) along with the protected TMS-alcohol. The crude material was dissolved in THF (83 mL) before the addition of TBAF·3H$_2$O (1.3 g, 5.0 mmol). Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):Et$_2$O 7:3) afforded the *title* compound **373e** (0.6 g, 2.6 mmol, 61%) as a colourless oil.

IR (thin film)/cm^{-1}: 3318, 3058, 2930, 2878; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.53 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.50 (d, *J* = 7.8, 1.6 Hz, 1H), 7.27–7.23 (m, 1H), 7.10–7.06 (m, 1H), 6.83 (d, *J* = 15.8 Hz, 1H), 6.17 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.80–3.77 (m, 2H), 2.56–2.51 (m, 2H), 1.55 (bs, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 137.3, 133.0, 131.7, 129.8, 128.7, 127.6, 127.1, 123.4, 62.1, 36.6; LRMS (ES + APCI) *m/z* 226.9 [M+H]$^+$.

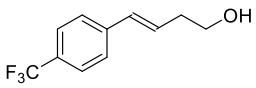
(*E*)-3-(4-Hydroxybut-1-en-1-yl)benzonitrile 373f[107]



Reaction of 3-formylbenzonitrile (1.0 g, 7.6 mmol), (3-hydroxypropyl)triphenylphosphonium bromide **366b** (3.7 g, 9.2 mmol) and LiHMDS (21.4 mL, 21.4 mmol) in THF (30 mL) according to General Procedure **7** afforded crude *cis*/*trans* mixtures (1:8) along with the protected TMS-alcohol. The crude material was dissolved in THF (140 mL) before the addition of TBAF·3H$_2$O (2.4 g, 9.2 mmol). Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):Et$_2$O 8:2) afforded the *title* compound **373f** (0.3 g, 1.8 mmol, 23% over two steps) as a colourless oil.

IR (thin film)/cm^{-1}: 3413, 3013, 2930, 2885, 2233; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.60 (s, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 6.45 (d, *J* = 15.9 Hz, 1H), 6.30 (dt, *J* = 15.9, 7.0 Hz, 1H), 3.78–3.76 (m, 2H), 2.52–2.48 (m, 2H), 1.81 (bs, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 138.7, 130.6, 130.4, 129.8, 129.7, 129.5, 119.0, 112.9, 62.0, 36.4; LRMS (ES + APCI) *m/z* 174.1 [M+H]$^+$.

(*E*)-4-(4-(Trifluoromethyl)phenyl)but-3-en-1-ol 373g[107]

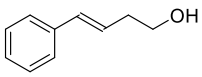


Reaction of 4-(trifluoromethyl)benzaldehyde (1.0 g, 5.7 mmol), (3- hydroxypropyl) triphenylphosphonium bromide **366b** (2.8 g, 6.9 mmol) and LiHMDS (16.0 mL, 16.0 mmol) in THF (15 mL) according to General Procedure **7** afforded crude *cis*/*trans* mixtures (1:8) along with the protected TMS-alcohol. The crude material was dissolved in THF (115 mL) before the addition of TBAF·3H_2O (0.4 g, 6.9 mmol). Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 7:3) afforded the *title* compound **373g** (0.5 g, 2.1 mmol, 36% over two steps) as a white solid.

m.p. 49–50 °C; IR (thin film)/cm^{-1}: 3348, 3013, 2945, 2885, 1324; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 6.53 (d, *J* = 15.9 Hz, 1H), 6.33 (dt, *J* = 15.9, 7.1 Hz, 1H), 3.80–3.78 (m, 2H), 2.54–2.50 (m, 2H), 1.53 (bs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.9, 131.6, 129.6, 129.2 ($J_{C\text{-}F}$ = 32.4 Hz), 126.4, 125.6 ($J_{C\text{-}F}$ = 3.8 Hz), 124.4 ($J_{C\text{-}F}$ = 271.6 Hz), 62.0, 36.5; LRMS (ES + APCI) *m/z* 217.1 $[M+H]^+$.

4.3.2 Synthesis of other alcohol starting materials

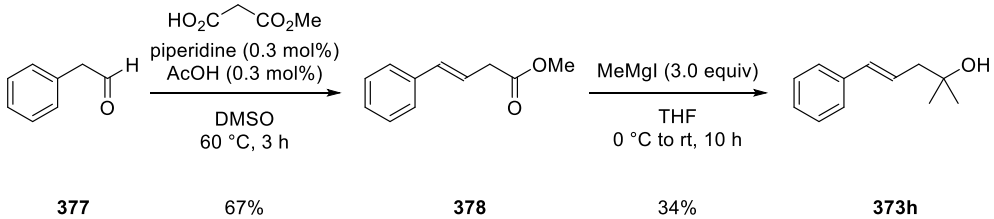
(*E*)-4-Phenylbut-3-en-1-ol 373a[176]



To a cooled solution (0 °C) of *trans*-styrylacetic acid **318a** (500 mg, 3.1 mmol) in THF (2.5 mL) was added a solution of $LiAlH_4$ (140 mg, 3.7 mmol) in THF (3.7 mL) dropwise. The mixture was stirred at 0 °C for 20 min and at rt for a further 40 min. The reaction was quenched with H_2O (0.2 mL) followed by a 1 M solution of NaOH (0.5 mL). The mixture was filtered through Celite®, and the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 6:4) afforded the *title* compound **373a** (360 mg, 2.4 mmol, 78%) as a colourless oil.

IR (thin film)/cm^{-1}: 3376, 3027, 2935, 2880; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.36 (m, 2H), 7.33–7.29 (m, 2H), 7.24–7.20 (m, 1H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.21 (dt, *J* = 15.9, 7.2 Hz, 1H), 3.79–3.74 (m, 2H), 2.52–2.47 (m, 2H), 1.51 (bs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 133.0, 128.7, 127.4, 126.5, 126.2, 62.2, 36.6; LRMS (ES + APCI) *m/z* 149.1 $[M+H]^+$.

(*E*)-2-Methyl-5-phenylpent-4-en-2-ol 373h[108]



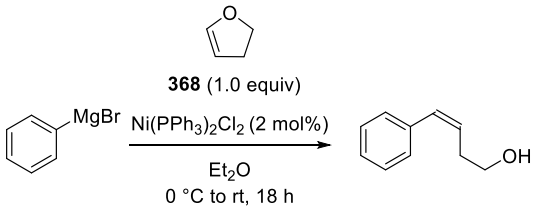
To a solution of monomethyl malonate (7.8 mL, 75.0 mmol) in DMSO was added a solution of piperidine (67 μL, 0.1 mmol) and AcOH (39 μL, 0.1 mmol) in DMSO (2 mL). The mixture was heated to 60 °C and phenylacetaldehyde **377** (4.0 mL, 34.0 mmol) was added dropwise over 90 min. The mixture was stirred for a further 90 min at 60 °C before cooling the mixture to rt. H_2O (75 mL) was added and the organics were extracted from the aqueous with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 8:2) afforded compound **378** (4.0 g, 22.7 mmol, 67%) as a colourless oil.

IR (thin film)/cm^{-1}: 3027, 2954, 1737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.37 (m, 2H), 7.33–7.29 (m, 2H), 7.26–7.22 (m, 1H), 6.50 (d, *J* = 15.9 Hz, 1H), 6.30 (dt, *J* = 15.9, 7.1 Hz, 1H), 3.72 (s, 3H), 2.26 (dd, *J* = 7.1, 1.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 137.0, 133.6, 128.7, 127.7, 126.4, 121.8, 52.1, 38.4; LRMS (ES + APCI) *m/z* 176.9 $[M+H]^+$.

To a cooled (0 °C) solution of (*E*)-methyl 4-phenylbut-3-enoate **378** (2.0 g, 11.3 mmol) in anhydrous THF (20 mL) was added a solution of MeMgI (3 M in THF, 11.0 mL, 33.0 mmol). The cooling bath was removed and the mixture was allowed to warm at rt and stirred for 10 h. Then saturated aqueous NH_4Cl (10 mL) was added to quench the reaction, the layers were separated and extracted with EtOAc (3 × 20 mL). The organics were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 7:3) afforded the *title* compound **373h** (0.7 g, 3.8 mmol, 34%) as a colourless oil.

IR (thin film)/cm^{-1}: 3399, 3032, 2972, 2927; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.36 (m, 2H), 7.33–7.29 (m, 2H), 7.24–7.20 (m, 1H), 6.47 (d, *J* = 15.8 Hz, 1H), 6.33–6.26 (m, 1H), 2.39 (dd, *J* = 7.5, 1.0 Hz, 2H), 1.52 (bs, 1H), 1.28 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 133.9, 128.7, 127.4, 126.3, 125.9, 71.1, 47.5, 29.4; LRMS (ES + APCI) *m/z* 159.1 $[M-OH]^+$.

(*Z*)-4-Phenylbut-3-en-1-ol 373i[177]



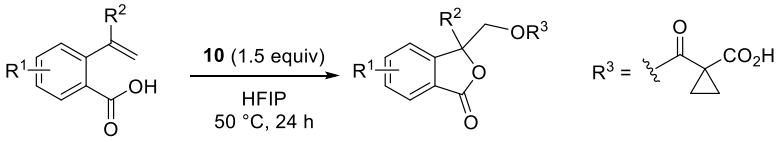
To a cooled (0 °C) solution of phenylmagnesium bromide **367** (3 M in Et_2O, 8.0 mL, 24.0 mmol) was slowly added bis(triphenylphosphine)nickel dichloride (0.3 g, 0.5 mmol). Then dihydrofuran **368** (1.8 mL, 24.0 mmol) was added at 0 °C and the mixture was stirred at rt for 18 h. The resulting mixture was poured into a saturated solution of NH_4Cl (50 mL). The organics were extracted from the

aqueous with Et_2O (3 × 50 mL), dried over $MgSO_4$, filtered and solvent was removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 6:4) afforded the *title* compound **373i** (2.2 g, 14.8 mmol, 62%) as a colourless oil.

IR (thin film)/cm^{-1}: 3321, 3018, 2935, 2880; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.30 (m, 4H), 7.25–7.21 (m, 1H), 6.59 (d, *J* = 11.7 Hz, 1H), 5.70 (dt, *J* = 11.7, 7.4, 1H), 3.78–3.73 (m, 2H), 2.65–2.60 (m, 2H), 1.38 (t, *J* = 5.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 131.8, 128.9, 128.4, 127.0, 62.7, 32.1 (1 carbon missing); LRMS (ES + APCI) *m/z* 149.1 $[M+H]^+$.

4.4 Oxidative Heterocyclisation with Malonoyl Peroxide 10

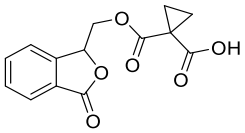
4.4.1 General Procedure 8: Cyclisations for the synthesis of *Iso*benzofuranones



359 **360**

Malonoyl peroxide **10** (1.5 equiv) was added to a solution of alkene **359** in HFIP (0.5 M). The mixture was stirred at 50 °C for 24 h. The solvent was removed under reduced pressure affording *iso*benzofuranone **360**. Purification by silica gel flash column chromatography with EtOAc:AcOH mixtures afforded the *target* compound **360**.

(±)-1-(((3-oxo-1,3-Dihydroisobenzofuran-1-yl)methoxy)carbonyl)cycloporpane-1-carboxylic acid 345

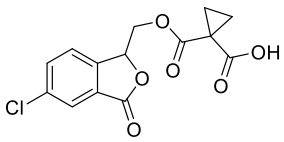


Reaction of 2-vinylbenzoic acid **344** (148 mg, 1.0 mmol) and malonoyl peroxide **10** (192 mg, 1.5 mmol) in HFIP (2.0 mL) according to General Procedure **8** afforded *iso*benzofuranone **345**. Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **345** (191 mg, 0.8 mmol, 76%) as a white solid.

m.p. 136–138 °C; IR (thin film)/cm^{-1}: 3096, 2958, 1768, 1730, 1692; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.6 Hz, 1H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 5.68 (dd, *J* = 5.0, 2.4 Hz, 1H), 4.70 (dd, *J* = 12.2, 2.6 Hz, 1H), 4.52 (dd, *J* = 12.2, 5.5 Hz, 1H), 1.84–1.80 (m, 1H), 1.74–1.65 (m, 2H), 1.34–1.30 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2,

170.2, 169.5, 144.9, 134.7, 130.5, 126.5, 126.3, 122.2, 77.9, 65.6, 25.3, 22.5; LRMS (ES + APCI) *m/z* 277.0 $[M+H]^+$; HRMS calculated for $C_{14}H_{11}O_6$ $[M-H]^-$ 275.0563, found 275.0561.

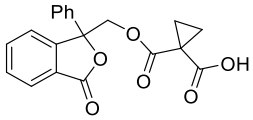
(±)-1-(((5-Chloro-3-oxo-1,3-dihydroisobenzofuran-1-yl)methoxy)carbonyl)cycloporpane-1-carboxylic acid 362



Reaction of 5-chloro-2-vinylbenzoic acid **353** (60 mg, 0.3 mmol) and malonoyl peroxide **10** (63 mg, 0.5 mmol) in HFIP (1.0 mL) according to General Procedure **8** afforded *iso*benzofuranone **362**. Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **362** (69 mg, 0.2 mmol, 68%) as a colourless oil.

IR (thin film)/cm^{-1}: 3164, 3092, 2984, 2928, 1757, 1734, 1688; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.71 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.45 (t, *J* = 8.1 Hz, 1H), 5.66 (dd, *J* = 5.3, 2.7 Hz, 1H), 4.69 (dd, *J* = 12.3, 2.7 Hz, 1H), 4.48 (dd, *J* = 12.3, 5.6 Hz, 1H), 1.86–1.75 (m, 2H), 1.70–1.66 (m, 1H), 1.42–1.38 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.7, 170.3, 168.1, 143.1, 136.9, 135.0, 128.4, 126.2, 123.6, 77.9, 65.3, 25.5, 22.3, 22.2; LRMS (ES + APCI) *m/z* 311.0 $[M+H]^+$; HRMS calculated for $C_{14}H_{11}{}^{35}ClO_6$ $[M-H]^-$ 309.0171, found 309.0162.

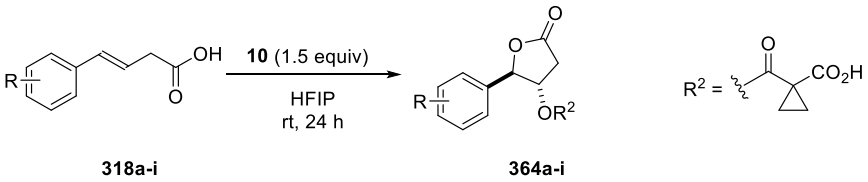
(±)-1-(((3-oxo-1-Phenyl-1,3-dihydroisobenzofuran-1-yl)methoxy)carbonyl)cycloporpane-1-carboxylic acid 363



Reaction of 2-(1-phenylvinyl)benzoic acid **358** (224 mg, 1.0 mmol) and malonoyl peroxide **10** (192 mg, 1.5 mmol) in HFIP (2.0 mL) according to General Procedure **8** afforded *iso*benzofuranone **363**. Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **363** (250 mg, 0.7 mmol, 71%) as a colourless oil.

IR (thin film)/cm^{-1}: 3491, 3096, 2920, 1759, 1740, 1692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.95 (m, 1H), 7.77–7.73 (m, 1H), 7.64–7.60 (m, 2H), 7.54–7.52 (m, 2H), 7.45–7.39 (m, 3H), 4.86 (d, *J* = 11.9 Hz, 1H), 4.81 (d, *J* = 11.9 Hz, 1H), 1.71–1.66 (m, 1H), 1.60–1.55 (m, 1H), 1.43–1.38 (m, 1H), 1.02–0.92 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 170.0, 169.0, 148.3, 135.8, 134.8, 130.5, 129.6, 129.3, 126.3 126.2, 125.4, 122.8, 87.4, 68.4, 25.1, 22.4, 22.3; LRMS (ES + APCI) *m/z* 353.0 $[M+H]^+$; HRMS calculated for $C_{20}H_{16}O_6$ $[M-H]^-$ 351.0874, found 351.0868.

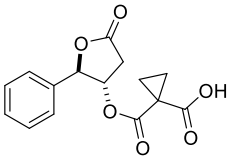
4.4.2 General Procedure 9: Cyclisation for the synthesis of γ-Lactones



318a-i 364a-i

Malonoyl peroxide **10** (1.5 equiv) was added to a solution of alkene **318a-i** in HFIP (0.5 M). The mixture was stirred at rt for 24 h. The solvent was removed under reduced pressure affording γ-lactone **364a-i**. Purification by silica gel flash column chromatography with EtOAc:AcOH mixtures afforded the *target* compound.

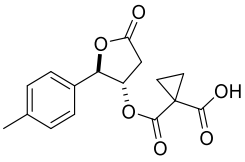
(±)-1-((((2*R*,3*S*)-5-oxo-2-Phenyltetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 364a



Reaction of (*E*)-4-phenylbut-3-enoic acid **318a** (100 mg, 0.6 mmol) and malonoyl peroxide **10** (118 mg, 0.9 mmol) in HFIP (1.2 mL) according to General Procedure **9** afforded lactone **364a** (1:19 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **364a** (123 mg, 0.4 mmol, 69%) as a colourless oil.

IR (thin film)/cm^{-1}: 3034, 1790, 1759, 1688; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.44–7.41 (m, 2H), 7.39–7.36 (m, 3H), 5.57 (bs, 1H), 5.36 (bd, *J* = 6.3 Hz, 1H), 2.93 (dd, *J* = 18.5, 6.3 Hz, 1H), 2.59 (d, *J* = 18.5 Hz, 1H), 1.89–1.84 (m, 2H), 1.80–1.74 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 173.6, 170.4, 135.3, 129.4, 129.3, 124.9, 84.9, 78.1, 32.8, 25.9, 22.34, 22.31; LRMS (ES + APCI) *m/z* 291.0 $[M+H]^+$; HRMS calculated for $C_{15}H_{14}O_6$ $[M-H]^-$ 289.0718, found 289.0710.

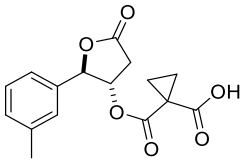
(±)-1-((((2*R*,3*S*)-5-oxo-2-(*p*-Tolyl)tetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 364b



Reaction of (*E*)-4-(*p*-tolyl)but-3-enoic acid **318b** (100 mg, 0.6 mmol) and malonoyl peroxide **10** (109 mg, 0.9 mmol) in HFIP (1.1 mL) according to General Procedure **9** afforded lactone **364b** (1:10 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **364b** (121 mg, 0.4 mmol, 70%) as a colourless oil.

IR (thin film)/cm^{-1}: 3173, 2952, 1790, 1760, 1693; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (s, 4H), 5.53 (bs, 1H), 5.36 (bd, *J* = 6.3 Hz, 1H), 2.94 (dd, *J* = 18.5, 6.3 Hz, 1H), 2.56 (d, *J* = 18.5 Hz, 1H), 2.38 (s, 3H), 1.99–1.94 (m, 2H), 1.87–1.80 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 172.8, 169.0, 138.8, 131.6, 129.4, 124.2, 84.2, 77.7, 32.1, 24.9, 22.33, 22.25, 20.7; LRMS (ES + APCI) *m/z* 305.0 $[M+H]^+$; HRMS calculated for $C_{16}H_{16}O_6$ $[M-H]^-$ 303.0874, found 303.0873.

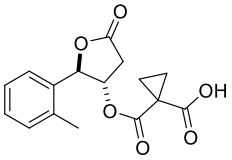
(±)-1-((((2*R*,3*S*)-5-oxo-2-(*m*-Tolyl)tetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 364c



Reaction of (*E*)-4-(*m*-tolyl)but-3-enoic acid **318c** (50 mg, 0.3 mmol) and malonoyl peroxide **10** (55 mg, 0.4 mmol) in HFIP (0.6 mL) according to General Procedure **9** afforded lactone **364c** (1:18 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **364c** (45 mg, 0.2 mmol, 53%) as a colourless oil.

IR (thin film)/cm^{-1}: 3120, 2964, 1791, 1755, 1695; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.16 (bs, 2H), 5.53 (bs, 1H), 5.38 (bd, *J* = 6.2 Hz, 1H), 2.94 (dd, *J* = 18.6, 6.2 Hz, 1H), 2.58 (d, *J* = 18.6 Hz, 1H), 2.39 (s, 3H), 1.97–1.94 (m, 2H), 1.87–1.80 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9, 173.7, 171.0, 139.3, 135.3, 130.0, 129.2, 125.4, 121.9, 84.9, 78.1, 32.9, 26.1, 21.9, 21.9, 21.6; LRMS (ES + APCI) *m/z* 305.0 $[M+H]^+$; HRMS calculated for $C_{16}H_{16}O_6$ $[M-H]^-$ 303.0874, found 303.0871.

(±)-1-((((2*R*,3*S*)-5-oxo-2-(*o*-Tolyl)tetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 364d

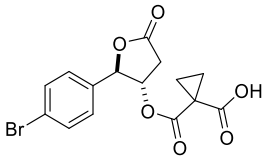


Reaction of (*E*)-4-(*o*-tolyl)but-3-enoic acid **318d** (100 mg, 0.6 mmol) and malonoyl peroxide **10** (109 mg, 0.9 mmol) in HFIP (1.1 mL) according to General Procedure **9** afforded lactone **364d** (1:10 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **364d** (87 mg, 0.3 mmol, 51%) as a colourless oil.

IR (thin film)/cm^{-1}: 3120, 2935, 1790, 1763, 1690; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2H), 7.26–7.25 (m, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 5.68 (bs, 1H), 5.41 (dt, *J* = 6.1 Hz, 1H), 3.03 (dd, *J* = 18.6, 6.1 Hz, 1H), 2.56 (dd, *J* = 18.6 Hz, 1H), 2.36 (s, 3H), 1.97-1.92 (m, 2H), 1.82–1.81

(m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 173.7, 170.8, 134.9, 133.2, 131.5, 129.3, 126.9, 124.1, 82.7, 76.4, 33.8, 26.0, 21.9, 19.1 (1 carbon missing); LRMS (ES + APCI) *m/z* 305.0 $[M+H]^+$; HRMS calculated for $C_{16}H_{16}O_6$ $[M-H]^-$ 303.0874, found 303.0873.

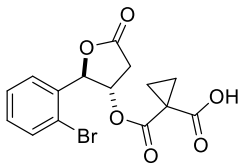
(±)-1-((((2*R*,3*S*)-2-(4-Bromophenyl)-5-oxotetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 364e



Reaction of (*E*)-4-(4-bromophenyl)but-3-enoic acid **318e** (100 mg, 0.4 mmol) and malonoyl peroxide **10** (80 mg, 0.6 mmol) in HFIP (0.8 mL) according to General Procedure **9** at 50 °C for 24 h afforded lactone **364e** (1:13 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **364e** (101 mg, 0.3 mmol, 67%) as a colourless solid.

m.p. 160 °C decomp.; IR (thin film)/cm^{-1}: 3132, 2960, 2820, 1794, 1757, 1698; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.36 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 5.52 (bs, 1H), 5.30 (bd, *J* = 6.5 Hz, 1H), 2.90 (dd, *J* = 18.6, 6.5 Hz, 1H), 2.62 (d, *J* = 18.6 Hz, 1H), 1.86–1.81 (m, 2H), 1.76–1.71 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 173.2, 170.2, 134.4, 132.6, 126.6, 123.5, 84.3 77.8, 32.6, 25.9, 22.4 (1 carbon missing); LRMS (ES + APCI) *m/z* 368.9 $[M+H]^+$; HRMS calculated for $C_{15}H_{13}{}^{79}BrO_6$ $[M-H]^-$ 366.9823, found 366.9820.

(±)-1-((((2*R*,3*S*)-2-(2-Bromophenyl)-5-oxotetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 364f

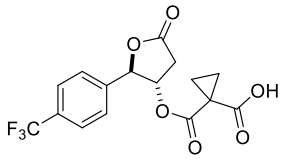


Reaction of (*E*)-4-(2-bromophenyl)but-3-enoic acid **318f** (100 mg, 0.4 mmol) and malonoyl peroxide **10** (80 mg, 0.6 mmol) in HFIP (0.8 mL) according to General Procedure **9** at 50 °C for 24 h afforded lactone **364f** (1:8 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **364f** (101 mg, 0.3 mmol, 67%) as a white solid.

m.p. 148 °C decomp.; IR (thin film)/cm^{-1}: 3064, 2954, 1795, 1757, 1688; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.31–7.27 (m, 2H), 5.77 (bs, 1H), 5.46 (bd, *J* = 6.4 Hz, 1H), 2.97 (dd, *J* = 18.9, 6.4 Hz, 1H), 2.59 (dd, *J* = 18.9, 1.1 Hz, 1H), 1.97–1.95 (m, 2H), 1.91–1.87 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 173.8, 171.2, 134.6,

133.7, 130.9, 128.3, 126.2, 83.8, 76.1, 33.9, 26.1, 21.9, 21.5; LRMS (ES + APCI) *m/z* 368.9 $[M+H]^+$; HRMS calculated for $C_{15}H_{13}{}^{79}BrO_6$ $[M-H]^-$ 366.9823, found 366.9807.

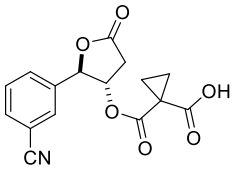
(±)-1-((((2*R*,3*S*)-5-oxo-2-(4-(Trifluoromethyl)phenyl)tetrahydrofuran-3 yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 364g



Reaction of (*E*)-4-(4-trifluoromethylphenyl)but-3-enoic acid **318g** (50 mg, 0.2 mmol) and malonoyl peroxide **10** (42 mg, 0.3 mmol) in HFIP (0.5 mL) according to General Procedure **9** at 50 °C for 72 h afforded lactone **364g** (1:5 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **364g** (46 mg, 0.1 mmol, 59%) as a colourless oil.

IR (thin film)/cm^{-1}: 3147, 2950, 1795, 1750, 1690; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 5.62 (bs, 1H), 5.36 (bd, *J* = 6.3 Hz, 1H), 2.90 (dd, *J* = 18.6, 6.4 Hz, 1H), 2.63 (d, *J* = 18.4 Hz, 1H), 1.95–1.90 (m, 2H), 1.81–1.77 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2, 173.1, 170.6, 139.4, 131.8 (J_{C-F} = 32.9 Hz), 126.4 (m), 125.4, 84.1, 77.7, 32.5, 26.1, 22.1 (1 carbon missing); LRMS (ES + APCI) *m/z* 358.9 $[M+H]^+$; HRMS calculated for $C_{16}H_{13}F_3O_6$ $[M-H]^-$ 357.0591, found 357.0591.

(±)-1-((((2*R*,2*S*)-2-(3-Cyanophenyl)-5-oxotetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 364h

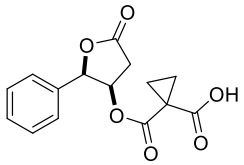


Reaction of (*E*)-4-(3-cyanophenyl)but-3-enoic acid **318h** (50 mg, 0.3 mmol) and malonoyl peroxide **10** (51 mg, 0.4 mmol) in HFIP (0.5 mL) according to General Procedure **9** at 50 °C for 72 h afforded lactone **364h** (1:2 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **364h** (52 mg, 0.2 mmol, 61%) as a colourless oil.

IR (thin film)/cm^{-1}: 3114, 2958, 2926, 2852, 2231, 1790, 1755, 1720; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.69–7.66 (m, 2H), 7.60–7.58 (m, 1H), 5.59 (bs, 1H), 5.33 (bd, *J* = 6.5 Hz, 1H), 2.92 (dd, *J* = 18.7, 6.5 Hz, 1H), 2.67 (dd, *J* = 18.7, 1.3 Hz, 1H), 1.94–1.88 (m, 2H), 1.82–1.76 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 172.4, 170.8, 137.3, 132.9, 130.3, 129.3, 128.6, 118.1, 113.8,

83.6, 77.5, 32.5, 26.2, 21.8 (1 carbon missing); LRMS (ES + APCI) *m/z* 316.0 $[M+H]^+$; HRMS calculated for $C_{16}H_{13}NO_6$ $[M-H]^-$ 314.0670, found 314.0670.

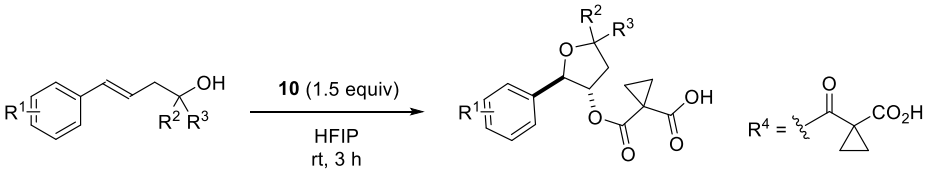
(±)-1-((((2*R*,3*R*)-5-oxo-2-Phenyltetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 364i



Reaction of (*Z*)-4-phenylbut-3-enoic acid **318i** (158 mg, 1.0 mmol) and malonoyl peroxide **10** (187 mg, 1.5 mmol) in HFIP (2.0 mL) according to General Procedure **9** afforded lactone **364i** (5:1 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **364i** (163 mg, 0.6 mmol, 58%) as a colourless oil.

IR (thin film)/cm^{-1}: 3124, 3029, 2937, 1789, 1753, 1686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.38 (m, 3H), 7.30–7.27 (m, 2H), 5.80 (ddd, *J* = 6.1, 4.4, 1.2 Hz, 1H), 5.72 (d, *J* = 4.4 Hz, 1H), 3.12 (dd, *J* = 18.4, 6.1 Hz, 1H), 2.76 (dd, *J* = 18.4, 1.2 Hz, 1H), 1.73–1.67 (m, 1H), 1.49–1.41 (m, 2H), 0.79–0.72 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 173.0, 169.8, 132.7, 129.4, 128.9, 125.7, 82.9, 73.2, 36.2, 25.2, 22.6, 22.1; LRMS (ES + APCI) *m/z* 291.0 $[M+H]^+$; HRMS calculated for $C_{15}H_{14}O_6$ $[M+H]^+$ 291.0863, found 291.0865.

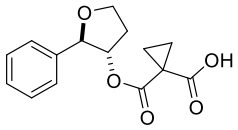
4.4.3 General Procedure 10. Cyclisation for the synthesis of Tetrahydrofurans



373a-i **374a-i**

Malonoyl peroxide **10** (1.5 equiv) was added to a solution of alkene **373a-i** in HFIP (0.5 M). The mixture was stirred at rt for 3 h. The solvent was removed under reduced pressure. Purification by silica gel flash column chromatography with EtOAc:AcOH mixtures afforded the *target* compound **374a-i**.

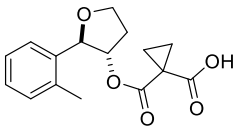
(±)-1-((((2*R*,3*S*)-2-Phenyltetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 374a



Reaction of (*E*)-4-phenylbut-3-en-1-ol **373a** (50 mg, 0.3 mmol) and malonoyl peroxide **10** (65 mg, 0.5 mmol) in HFIP (0.7 mL) according to General Procedure **10** afforded ether **374a** (1:18 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **374a** (75 mg, 0.3 mmol, 80%) as a colourless oil.

IR (thin film)/cm^{-1}: 3080, 2987, 2950, 2883, 1727, 1673; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.34 (m, 4H), 7.32–7.28 (m, 1H), 5.24 (dt, *J* = 5.4, 1.3 Hz, 1H), 4.98 (d, *J* = 1.3 Hz, 1H), 4.29 (td, *J* = 8.6, 2.4 Hz, 1H), 4.03 (ddd, *J* = 6.3, 8.6, 10.4 Hz, 1H), 2.29–2.23 (m, 1H), 2.01–1.95 (m, 1H), 1.93–1.88 (m, 2H), 1.84–1.78 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 170.5, 139.4, 128.8, 128.2, 125.5, 85.1, 83.4, 67.7, 30.9, 25.5, 22.48, 22.45; LRMS (ES + APCI) *m/z* 277.0 $[M+H]^+$; HRMS calculated for $C_{15}H_{16}O_5$ $[M-H]^-$ 275.0925, found 275.0926.

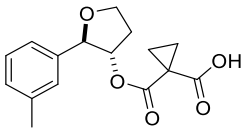
(±)-1-((((2*R*,3*S*)-2-(*o*-Tolyl)tetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 374b



Reaction of (*E*)-4-(*o*-tolyl)but-3-en-1-ol **373b** (50 mg, 0.3 mmol) and malonoyl peroxide **10** (59 mg, 0.5 mmol) in HFIP (0.6 mL) according to General Procedure **10** afforded ether **374b** (1:13 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **374b** (50 mg, 0.2 mmol, 56%) as a colourless oil.

IR (thin film)/cm^{-1}: 3062, 3019, 2982, 2885, 1727, 1673; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.29 (m, 1H), 7.22–7.20 (m, 2H), 7.17–7.16 (m, 1H), 5.27 (d, *J* = 5.1 Hz, 1H), 5.11 (bs, 1H), 4.36 (td, *J* = 8.5, 1.4 Hz, 1H), 4.01 (ddd, *J* = 10.8, 8.6, 6.0 Hz, 1H), 2.32 (s, 3H), 2.30–2.26 (m, 1H), 2.00–1.96 (m, 1H), 1.94–1.92 (m, 2H), 1.85–1.79 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3, 170.5, 137.5, 134.7, 130.7, 128.1, 126.4, 125.3, 82.6, 82.1, 67.7, 31.6, 25.5, 22.4, 19.3 (1 carbon missing); LRMS (ES + APCI) *m/z* 291.0 $[M+H]^+$; HRMS calculated for $C_{16}H_{18}O_5$ $[M-H]^-$ 289.1081, found 289.1077.

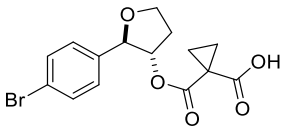
(±)-1-((((2*R*,3*S*)-2-(*m*-Tolyl)tetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 374c



Reaction of (*E*)-4-(*m*-tolyl)but-3-en-1-ol **373c** (50 mg, 0.3 mmol) and malonoyl peroxide **10** (59 mg, 0.5 mmol) in HFIP (0.6 mL) according to General Procedure **10** afforded ether **374c** (1:16 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **374c** (40 mg, 0.1 mmol, 44%) as a colourless oil.

IR (thin film)/cm^{-1}: 3080, 3049, 2967, 2878, 1760, 1731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.5 Hz, 1H), 7.15–7.10 (m, 3H), 5.25–5.23 (m, 1H), 4.95 (bs, 1H), 4.29 (td, *J* = 8.6, 2.4 Hz, 1H), 4.02 (ddd, *J* = 6.3, 8.5, 10.2 Hz, 1H), 2.36 (s, 3H), 2.30–2.20 (m, 1H), 2.01-1.96 (m, 1H), 1.93–1.88 (m, 2H), 1.85–1.79 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 170.5, 139.3, 138.5, 128.9, 128.7, 126.1, 122.6, 85.1, 83.4, 67.7, 31.0, 25.5, 22.5, 22.4, 21.6; LRMS (ES + APCI) *m/z* 291.0 $[M+H]^+$; HRMS calculated for $C_{16}H_{18}O_5$ $[M-H]^-$ 289.1080, found 289.1078.

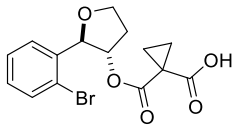
(±)-1-((((2*R*,3*S*)-2-(4-Bromophenyl)tetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 374d



Reaction of (*E*)-4-(4-bromophenyl)but-3-en-1-ol **373d** (50 mg, 0.2 mmol) and malonoyl peroxide **10** (42 mg, 0.5 mmol) in HFIP (0.5 mL) according to General Procedure **10** afforded ether **374d** (1:15 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **374d** (52 mg, 0.2 mmol, 67%) as a colourless oil.

IR (thin film)/cm^{-1}: 3110, 2986, 2950, 2885, 1760, 1731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 5.18 (d, *J* = 5.5 Hz, 1H), 4.98 (bs, 1H), 4.28 (td, *J* = 8.6, 2.3 Hz, 1H), 4.08 (ddd, *J* = 6.2, 8.6, 10.4 Hz, 1H), 2.24–2.15 (m, 1H), 2.02–1.97 (m, 1H), 1.93–1.89 (m, 2H), 1.83–1.76 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 170.5, 138.4, 131.9, 127.3, 122.1, 84.7, 83.2, 67.8, 30.8, 25.6, 22.5 (1 carbon missing); LRMS (ES + APCI) *m/z* 354.9 $[M+H]^+$; HRMS calculated for $C_{15}H_{15}{}^{79}BrO_5$ $[M-H]^-$ 353.0030, found 353.0026.

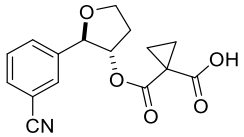
(±)-1-((((2*R*,3*S*)-2-(2-Bromophenyl)tetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 374e



Reaction of (*E*)-4-(2-bromophenyl)but-3-en-1-ol **373e** (55 mg, 0.2 mmol) and malonoyl peroxide **10** (47 mg, 0.4 mmol) in HFIP (0.5 mL) according to General Procedure **10** afforded ether **374e** (1:5 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **374e** (66 mg, 0.2 mmol, 78%) as a colourless oil.

IR (thin film)/cm^{-1}: 3064, 3054, 2928, 2885, 1762, 1701; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.41 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.18 (td, *J* = 7.7, 1.6 Hz, 1H), 5.33 (bd, *J* = 5.3 Hz, 1H), 5.21 (bs, 1H), 4.38 (td, *J* = 8.5, 1.7 Hz, 1H), 4.01 (ddd, *J* = 11.2, 8.6, 5.8 Hz, 1H), 2.24–2.16 (m, 1H), 2.04–2.00 (m, 1H), 1.95–1.90 (m, 3H), 1.85–1.82 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3, 170.5, 138.6, 133.0, 129.8, 127.9, 127.3, 121.7, 84.1, 82.2, 68.1, 31.8, 25.4, 22.9 22.3; LRMS (ES + APCI) *m/z* 355.0 $[M+H]^+$; HRMS calculated for $C_{15}H_{15}{}^{79}BrO_5$ $[M-H]^-$ 353.0030, found 353.0026.

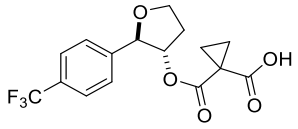
(±)-1-((((2*R*,3*S*)-2-(3-Cyanophenyl)tetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 374f



Reaction of (*E*)-3-(4-hydroxybut-1-en-1-yl)benzonitrile **373f** (50 mg, 0.3 mmol) and malonoyl peroxide **10** (55 mg, 0.4 mmol) in HFIP (0.6 mL) according to General Procedure **10** at 50 °C for 20 h afforded ether **374f** (1:27 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **374f** (70 mg, 0.2 mmol, 80%) as a colourless oil.

IR (thin film)/cm^{-1}: 3123, 2990, 2894, 2358, 1762, 1675; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.70 (m, 1H), 7.66–7.63 (m, 1H), 7.62–7.60 (m, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 5.20 (dt, *J* = 1.4, 5.4 Hz, 1H), 4.99 (bs, 1H), 4.33 (td, *J* = 8.6, 2.3 Hz, 1H), 4.06 (ddd, *J* = 10.6, 8.7, 6.1 Hz, 1H), 2.23–2.14 (m, 1H), 2.07–2.01 (m, 1H), 1.97–1.92 (m, 2H), 1.86–1.79 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 170.2, 141.1, 131.8, 130.1, 129.6, 129.2, 118.7, 113.0, 84.4, 83.2, 68.1, 30.8, 25.6, 22.6, 22.5; LRMS (ES + APCI) *m/z* 302.0 $[M+H]^+$; HRMS calculated for $C_{16}H_{15}NO_5$ $[M-H]^-$ 300.0877, found 300.0872.

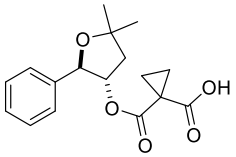
(±)-1-((((2*R*,3*S*)-2-(4-(Trifluoromethyl)phenyl)tetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 374g



Reaction of (*E*)-4-(4-(trifluoromethyl)phenyl)but-3-en-1-ol **373g** (60 mg, 0.3 mmol) and malonoyl peroxide **10** (53 mg, 0.4 mmol) in HFIP (0.6 mL) according to General Procedure **10** at 50 °C for 20 h afforded ether **374g** (1:21 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **374g** (57 mg, 0.2 mmol, 59%) as a colourless oil.

IR (thin film)/cm^{-1}: 3118, 3028, 2954, 2922, 1762, 1731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 5.23 (dt, *J* = 5.5, 1.5 Hz, 1H), 5.03 (bs, 1H), 4.32 (td, *J* = 8.6, 2.3 Hz, 1H), 4.06 (ddd, *J* = 6.2, 8.6, 10.5 Hz, 1H), 2.25–2.15 (m, 1H), 2.05–1.99 (m, 1H), 1.97–1.92 (m, 2H), 1.86–1.79 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 170.3, 143.4, 130.5 ($J_{C\text{-}F}$ = 32.6 Hz), 125.9, 125.8 ($J_{C\text{-}F}$ = 3.6 Hz), 84.7, 83.3, 68.0, 30.8, 25.5, 22.54, 22.51 (1 carbon missing); LRMS (ES + APCI) *m/z* 345.0 $[M+H]^+$; HRMS calculated for $C_{16}H_{15}F_3O_5$ $[M-H]^-$ 343.0799, found 343.0789.

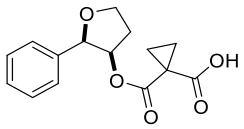
(±)-1-((((2*R*,3*S*)-5-5-Dimethyl-2-phenyltetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 374h



Reaction of (*E*)-2-methyl-5-phenylpent-4-en-2-ol **373h** (50 mg, 0.3 mmol) and malonoyl peroxide **10** (54 mg, 0.4 mmol) in HFIP (0.6 mL) according to General Procedure **10** afforded ether **374h** (1:16 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **374h** (70 mg, 0.2 mmol, 82%) as a white solid.

m.p. 93–95 °C; IR (thin film)/cm^{-1}: 3095, 2968, 2898, 1760, 1679; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.36 (m, 4H), 7.33–7.28 (m, 1H), 5.20–5.17 (m, 1H), 4.96 (d, *J* = 4.1 Hz, 1H), 2.27 (dd, *J* = 13.9, 7.1 Hz, 1H), 1.95–1.87 (m, 3H), 1.84–1.78 (m, 2H), 1.48 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 170.4, 139.7, 128.8, 128.3, 125.9, 84.4, 84.2, 82.0, 43.9, 29.6, 28.2, 25.3, 22.6, 22.3; LRMS (ES + APCI) *m/z* 305.0 $[M+H]^+$; HRMS calculated for $C_{17}H_{20}O_5$ $[M-H]^-$ 303.1238, found 303.1232.

(±)-1-((((2*R*,3*R*)-2-Phenyltetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 374i

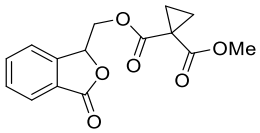


Reaction of (*Z*)-4-phenylbut-3-en-1-ol **373i** (100 mg, 0.7 mmol) and malonoyl peroxide **10** (129 mg, 1.0 mmol) in HFIP (1.3 mL) according to General Procedure **10** afforded ether **374i** (5:1 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **374i** (123 mg, 0.5 mmol, 67%) as a colourless oil.

IR (thin film)/cm^{-1}: 3105, 3060, 2984, 2878, 1759, 1673; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.33 (m, 3H), 7.30–7.27 (m, 2H), 5.57 (ddd, *J* = 6.0, 4.3, 1.9 Hz, 1H), 4.98 (d, *J* = 4.3 Hz, 1H), 4.21–4.16 (m, 1H), 4.03–3.99 (m, 1H), 2.52–2.45 (m, 1H), 2.14–2.08 (m, 1H), 1.68 (ddd, *J* = 9.6, 8.6, 3.4 Hz, 1H), 1.50 (ddd, *J* = 9.6, 8.6, 3.4 Hz, 1H), 1.39 (ddd, *J* = 9.6, 8.6, 3.4Hz, 1H), 0.72 (ddd, *J* = 9.6, 8.6, 3.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 170.5, 136.2, 128.4, 128.1, 126.3, 83.0, 77.7, 66.7, 33.4, 25.0, 22.4, 21.8; LRMS (ES + APCI) *m/z* 277.0 $[M+H]^+$; HRMS calculated for $C_{15}H_{16}O_5$ $[M-H]^-$ 275.0927, found 275.0926.

4.5 Further chemistry with cyclised products

(±)-1-Methyl 1-((3-oxo-1,3-dihydroisobenzofuran-1-yl)methoxy) cycloporpane-1,1-carboxylate 347

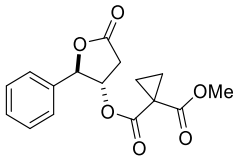


Crude (±)-1-(((3-oxo-1,3-dihydroisobenzofuran-1-yl)methoxy)carbonyl)cycloporpane-1-carboxylic acid **345** (0.1 mmol) was dissolved in PhMe (0.7 mL) and MeOH (0.3 mL) before the addition of TMS-CHN_2 (2 M in Et_2O, 0.1 mL, 0.2 mmol). The mixture was stirred at rt for 2 h before the solvents were removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 7:3) afforded *title* compound **347** (26 mg, 0.1 mmol, 62% over two steps) as a colourless oil.

IR (thin film)/cm^{-1}: 2951, 2963, 1768, 1736, 1727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.7 Hz, 1H), 7.71 (td, *J* = 7.5, 1.1 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.7, 0.8 Hz, 1H), 5.67–5.65 (m, 1H), 4.60 (dd, *J* = 12.1, 3.7 Hz, 1H), 4.53 (dd, *J* = 12.1, 5.1 Hz, 1H), 3.65 (s, 3H), 1.42–1.25

(m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 169.8, 169.3, 145.9, 134.4, 130.0, 126.7, 126.0, 122.5, 78.4, 64.7, 52.8, 27.8, 17.3; LRMS (ES + APCI) *m/z* 291.0 $[M+H]^+$.

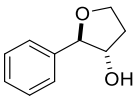
(±)-1-Methyl 1-((2*R*,3*S*)-5-oxo-2-phenyltetrahydrofuran-3-yl)cyclopropane-1,1-dicarboxylate 361



Crude (±)-1-((((2*R*,3*S*)-5-oxo-2-phenyltetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid **364a** (0.6 mmol) was dissolved in PhMe (3.0 mL) and MeOH (1.2 mL) before the addition of TMS-CHN_2 (2 M in Et_2O, 0.6 mL, 1.2 mmol). The mixture was stirred at rt for 2 h before the solvents were removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 7:3) afforded *title* compound **361** (136 mg, 0.5 mmol, 74% over two steps) as a colourless oil.

IR (thin film)/cm^{-1}: 2950, 2921, 1780, 1740, 1732; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.35 (m, 5H), 5.60 (bs, 1H), 5.33 (dt, *J* = 6.3, 1.3 Hz, 1H), 3.77 (s, 3H), 2.90 (dd, *J* = 18.4, 6.4 Hz, 1H), 2.61 (dd, *J* = 18.4, 1.4 Hz, 1H), 1.59–1.51 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 169.7, 169.5, 136.0, 129.2, 129.0, 125.0, 85.1, 77.1, 52.9, 33.0, 28.1, 17.3; LRMS (ES + APCI) *m/z* 305.0 $[M+H]^+$.

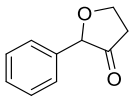
(±)-(2*R*,3*S*)-2-Phenyltetrahydrofuran-3-ol 380



Crude (±)-1-((((2*R*,3*S*)-2-phenyltetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid **374a** (1.0 mmol) was dissolved in 33% $MeNH_2$ in EtOH (10 mL, 80.0 mmol). The resulting mixture was stirred at 40 °C for 4 h before the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 6:4) afforded the *title* compound **380** (105 mg, 0.6 mmol, 64% over two steps) as a yellow oil.

IR (ATR)/cm^{-1}: 3486, 2950, 2917, 2872; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.33 (m, 4H), 7.31–7.27 (m, 1H), 4.79 (d, *J* = 3.4 Hz, 1H), 4.30 (bs, 1H), 4.22 (td, *J* = 8.5, 3.9 Hz, 1H), 4.14 (td, *J* = 8.7, 7.0 Hz, 1H), 2.19 (dtd, *J* = 13.1, 8.7, 6.0 Hz, 1H), 1.96 (ddt, *J* = 13.1, 7.1, 3.6 Hz, 1H), 1.87 (bs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.9, 128.6, 127.7, 125.6, 87.7, 79.0, 67.3, 34.3; LRMS (ES + APCI) *m/z* 165.1 $[M+H]^+$.

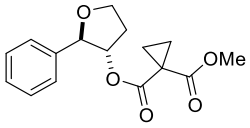
2-Phenyldihydrofuran-3(*2H*)-one 381



(2*R*,3*S*)-2-Phenyltetrahydrofuran-3-ol **380** (0.2 g, 1.4 mmol) was dissolved in degassed MeCN (6.9 mL). IBX (1.2 g, 4.1 mmol) was added and the mixture was stirred at 80 °C for 18 h after which time the mixture was filtered through Celite® and the solvent removed under reduced pressure affording **381** (200 mg, 1.2 mmol, 90%) as a colourless oil without further purification.

IR (ATR)/cm^{-1}: 2922, 2903, 2842, 1759; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.29 (m, 5H), 7.79 (d, *J* = 3.4 Hz, 1H), 4.75 (bs, 1H), 4.50 (dt, *J* = 9.3, 6.7 Hz, 1H), 4.29 (dt, *J* = 9.3, 8.0 Hz, 1H), 2.65–2.62 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.1, 135.7, 128.7, 128.3, 126.1, 81.0, 64.9, 36.7; LRMS (GC-CI) *m/z* 162.1 $[M]^+$.

(±)-1-Methyl ((2*R*,3*S*)-2-phenyltetrahydrofuran-3-yl)cyclopropane-1,1-dicarboxylilate 379

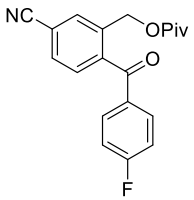


Crude (±)-1-((((2*R*,3*S*)-2-phenyltetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid **374a** (1.0 mmol) was dissolved in PhMe (4.5mL) and MeOH (1.8 mL) before the addition of TMS-CHN_2 (2 M in Et_2O, 1.0 mL, 2.0 mmol). The mixture was stirred at rt for 2 h before the solvents were removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 6:4) afforded *title* compound **379** (198 mg, 0.7 mmol, 68% over two steps) as a colourless oil.

IR (thin film)/cm^{-1}: 2987, 2950, 2894, 1736, 1679; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.33 (m, 4H), 7.29–7.25 (m, 1H), 5.19 (dt, *J* = 5.6, 1.7 Hz, 1H), 5.02 (d, *J* = 1.2 Hz, 1H), 4.29 (td, *J* = 8.4, 2.3 Hz, 1H), 4.15–4.05 (m, 1H), 3.77 (s, 3H), 2.25–2.15 (m, 1H), 2.04–1.99 (m, 1H), 1.54–1.48 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.5, 140.2, 128.6, 127.8, 125.6, 85.3, 82.1, 67.9, 52.7, 31.2, 28.3, 17.0, 16.9; LRMS (ES + APCI) *m/z* 291.0 $[M+H]^+$.

4.6 Synthesis of Citalopram 382

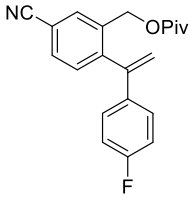
5-Cyano-2-(4-fluorobenzoyl)benzyl pivalate 389[117]



To a cooled (0 °C) solution of 5-cyanophthalide **388** (2.0 g, 12.6 mmol) in CH_2Cl_2 (20 mL) was added a solution of 4-fluorophenylmagnesium bromide (1 M in THF, 14.0 mL, 14.0 mmol). The resulting mixture was then allowed to warm to rt and was stirred for 18 h. Pivaloyl chloride (1.5 mL, 12.5 mmol) was added and the mixture was heated at 60 °C and stirred for 2 h. The reaction mixture was poured into a cold solution of NH_4Cl (50 mL) and extracted with Et_2O (3 × 50 mL). The organics were washed with brine (100 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 8:2) afforded the *title* compound **389** as (3.7 g, 10.9 mmol, 87%) as a pale yellow oil.

IR (ATR)/cm^{-1}: 2971, 2932, 2870, 2233, 1729, 1667; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84–7.81 (m, 2H), 7.80 (d, J = 0.8 Hz, 1H), 7.70 (dd, J = 7.8, 1.5 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.18–7.15 (m, 2H), 5.17 (s, 2H), 1.08 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.1, 177.9, 168.5 ($J_{C\text{-}F}$ = 257.4 Hz), 141.7, 137.5, 133.1 ($J_{C\text{-}F}$ = 9.7 Hz), 132.7 ($J_{C\text{-}F}$ = 3.2 Hz), 132.5, 131.3, 129.2, 117.9, 116.2 ($J_{C\text{-}F}$ = 22.1 Hz), 114.7, 63.0, 38.9, 27.1; LRMS (ES + APCI) *m/z* 340.0 $[M+H]^+$.

5-Cyano-2-(1-(4-fluorophenyl)vinyl)benzyl pivalate 390[117]

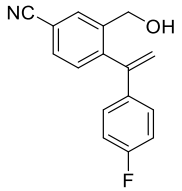


To a suspension of methyl triphenylphosphonium bromide (7.6 g, 21.3 mmol) in anhydrous THF (20 mL) was added a solution of ^{t}BuOK (2.4 g, 21.3 mmol) in anhydrous THF (20 mL) giving a bright yellow suspension. After 15 min, a solution of 5-cyano-2-(4-fluorobenzoyl)benzyl pivalate **389** (3.8 g, 11.2 mmol) in anhydrous THF (20 mL) was added. The resulting green suspension was stirred at rt for 2 days. The reaction mixture was quenched with H_2O (100 mL) and extracted with Et_2O (3 × 100 mL). The organics were washed with brine (100 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography

(petroleum ether (40–60 °C):EtOAc 8:2) afforded the *title* compound **390** (1.8 g, 5.3 mmol, 48%) as a pale yellow oil.

IR (ATR)/cm^{-1}: 2971, 2932, 2906, 2870, 2231, 1729; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 0.9 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.20–7.17 (m, 2H), 7.02–6.98 (m, 2H), 5.82 (s, 1H), 5.23 (s, 1H), 4.88 (s, 2H), 1.18 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 163.0 ($J_{C\text{-}F}$ = 248.9 Hz), 145.6, 145.5, 136.4, 135.4, 131.7 ($J_{C\text{-}F}$ = 10.9 Hz), 131.1, 128.5, 128.4, 118.7, 116.9, 115.9 ($J_{C\text{-}F}$ = 21.5 Hz), 112.2, 63.0, 39.0, 27.3; LRMS (ES + APCI) *m/z* 355.1 $[M+NH_4]^+$.

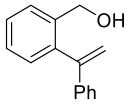
4-(1-(4-Fluorophenyl(vinyl)3-hydroxymethyl)benzonitrile 387[117]



To a solution of 5-cyano-2-(1-(4-fluorophenyl)vinyl)benzyl pivalate **390** (1.80 g, 5.3 mmol) in MeOH (9 mL) was added NaOMe (0.12 mg, 2.1 mmol). The mixture was stirred at rt for 18 h before evaporation of the solvent. The residue was re-dissolved in Et_2O (60 mL) and saturated solution of NH_4Cl (60 mL) was added. The layers were separated and the aqueous was further extracted with Et_2O (3 × 100 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 8:2) afforded the *title* compound **387** (0.97 mg, 3.8 mmol, 72%) as a pale yellow oil.

IR (ATR)/cm^{-1}: 3426, 3088, 2928, 2850, 2231; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.20–7.17 (m, 2H), 7.02–6.98 (m, 2H), 5.79 (s, 1H), 5.23 (s, 1H), 4.46 (s, 2H), 1.77 (bs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9 ($J_{C\text{-}F}$ = 248.8 Hz), 145.9, 144.6, 140.5, 135.49, 135.46 131.1 ($J_{C\text{-}F}$ = 3.0 Hz), 130.8, 128.3 ($J_{C\text{-}F}$ = 8.1 Hz), 118.9, 116.6, 115.8 ($J_{C\text{-}F}$ = 21.6 Hz), 112.1, 62.0; LRMS (ES + APCI) *m/z* 254.0 $[M+H]^+$.

(2-(1-Phenylvinyl)phenyl)methanol 391

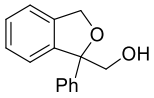


To a cooled solution (0 °C) of (2-(1-phenylvinyl)benzoic acid **358** (1.0 g, 4.5 mmol) in THF (9.0 mL) was added a solution of $LiAlH_4$ (0.2 g, 5.4 mmol) in THF (5.4 mL) dropwise. The mixture was stirred at 0 °C for 20 min and at rt for a further 40 min. The reaction was quenched with H_2O (0.5 mL) followed by a 1 M solution of NaOH (1.0 mL). The mixture was filtered through Celite®, and the

solvent was removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 6:4) afforded the *title* compound **391** (0.8 g, 3.8 mmol, 85%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.49 (m, 1H), 7.41–7.37 (m, 2H), 7.36–7.27 (m, 7H), 5.80 (d, *J* = 1.3 Hz, 1H), 5.26 (d, *J* = 1.3 Hz, 1H), 4.44 (bs, 2H); LRMS (ES + APCI) *m/z* 211.0 $[M+H]^+$.

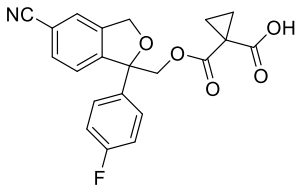
(1-Phenyl-1,3-diydroisobenzofuran-1-yl)methanol 393



Reaction of (2-(1-phenylvinyl)phenyl)methanol **391** (173 mg, 0.8 mmol) and malonoyl peroxide **10** (158 mg, 1.2 mmol) in HFIP (3.6 mL) according to General Procedure **10** at rt for 4 h to give crude carboxylic acid which was used in the next step without further purification. Crude carboxylic acid **392** (1.2 mmol) was dissolved in 33% $MeNH_2$ in EtOH (8.0 mL, 65.6 mmol). The mixture was stirred at 40 °C for 2 h before the solvent was removed under reduced pressure.Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 6:4) afforded the *title* compound **393** (139 mg, 0.6 mmol, 75% over two steps) as a colourless oil.

IR (ATR)/cm^{-1}: 3348, 3250, 3043, 2948, 2881; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.51 (m, 2H), 7.45–7.40 (m, 1H), 7.37–7.28 (m, 5H), 7.25–7.23 (m, 1H), 5.24 (d, *J* = 12.3 Hz, 1H), 5.19 (d, *J* = 12.3 Hz, 1H), 4.08 (s, 2H), 2.07 (bs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9, 141.3, 139.9, 128.6, 128.2, 127.7, 125.7, 122.4, 121.4, 92.1, 72.3, 68.6 (1 carbon missing); LRMS (GC-CI) *m/z* 195.1 $[M\text{-}MeOH]^+$.

(±)-1-(((5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)methoxy)carbonyl)cyclopropane-1-carboxylic acid 394

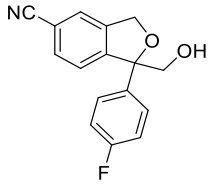


Reaction of 4-(1-(4-fluorophenyl(vinyl)3-hydroxymethyl)benzonitrile **387** (450 mg, 1.8 mmol) and malonoyl peroxide **10** (341 mg, 2.7 mmol) in HFIP (3.6 mL) according to General Procedure **10** for at rt 15 h gave crude carboxylic acid **394**. The crude material was used in the next step without further purification.

IR (ATR)/cm^{-1}: 3450, 3112, 2971, 2932, 2872, 2231, 1753, 1731; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.9 Hz, 1H), 7.59 (s, 1H), 7.44–7.42 (m, 3H), 7.10–7.06 (m, 2H), 5.22 (d, *J* = 13.0 Hz, 1H),

5.18 (d, *J* = 13.0 Hz, 1H), 4.70 (d, *J* = 11.9 Hz, 1H), 4.64 (d, *J* = 11.9 Hz, 1H), 1.75–1.65 (m, 2H), 1.41–1.37 (m, 1H), 1.23–1.19 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3, 170.5, 162.9 ($J_{C\text{-}F}$ = 248.7 Hz), 145.1, 141.0, 134.9 ($J_{C\text{-}F}$ = 3.2 Hz), 132.3, 127.3 ($J_{C\text{-}F}$ = 8.2 Hz), 125.6, 123.2, 118.2, 116.1 ($J_{C\text{-}F}$ = 21.7 Hz), 113.1, 89.6, 71.8, 69.3, 23.8, 22.4, 22.3; LRMS (ES + APCI) *m/z* 382.0 $[M+H]^+$; HRMS calculated for $C_{21}H_{16}FNO_5$ $[M-H]^-$ 380.0940, found 380.0933.

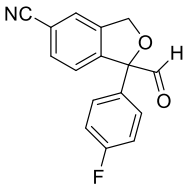
(±)-1-(4-Fluorophenyl)-1-(hydroxymethyl)-1,3-dihydroisobenzofuran-5-carbonitrile 395



Crude 1-(((5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)methoxy)carbonyl)cyclopropane-1-carboxylic acid **394** (1.8 mmol) was dissolved in 33% $MeNH_2$ in EtOH (18 mL, 142.4 mmol). The mixture was stirred at 40 °C for 2 h before the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 6:4) afforded the *title* compound **395** (350 mg, 1.3 mmol, 73% over two steps) as a pale yellow oil.

IR (ATR)/cm^{-1}: 3365, 3125, 2917, 2865, 2229; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.64 (m, 1H), 7.55 (s, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.46–7.41 (m, 2H), 7.07–7.02 (m, 2H), 5.25 (d, *J* = 12.9 Hz, 1H), 5.17 (d, *J* = 12.9 Hz, 1H), 4.05 (d, *J* = 6.7 Hz, 2H), 1.97 (t, *J* = 6.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6 ($J_{C\text{-}F}$ = 247.7 Hz), 146.6, 141.2, 136.2 ($J_{C\text{-}F}$ = 2.5 Hz), 132.1, 127.5 ($J_{C\text{-}F}$ = 8.0 Hz), 125.4, 123.4, 118.6, 115.7 ($J_{C\text{-}F}$ = 21.6 Hz), 112.4, 91.9, 71.7, 68.2; LRMS (ES + APCI) *m/z* 270.0 $[M+H]^+$; HRMS calculated for $C_{16}H_{12}FNO_2$ $[M+Na]^+$ 292.0744, found 292.0743.

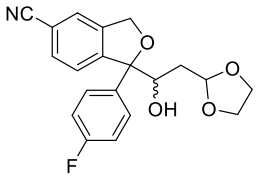
(±)-1-(4-Fluorophenyl)-1-formyl-1,3-dihydroisobenzofuran-5-carbonitrile 396



1-(4-Fluorophenyl)-1-(hydroxymethyl)-1,3-dihydroisobenzofuran-5-carbonitrile **395** (135 mg, 0.5 mmol) was dissolved in degassed MeCN (2.5 mL). IBX (421 mg, 1.5 mmol) was added and the mixture was stirred at 80 °C for 1 h after which time the mixture was filtered through Celite® and the solvent removed under reduced pressure affording **396** (129 mg, 0.48 mmol, 97%) as a colourless oil without further purification.

IR (ATR)/cm^{-1}: 3073, 2958, 2928, 2859, 2231, 1725; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.67–7.63 (m, 2H), 7.57 (s, 1H), 7.51–7.48 (m, 2H), 7.11–7.07 (m, 2H), 5.37 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.5, 163.1 ($J_{C\text{-}F}$ = 248.8 Hz), 142.9, 140.6, 132.0 ($J_{C\text{-}F}$ = 3.2 Hz), 127.7 ($J_{C\text{-}F}$ = 8.2 Hz), 125.4, 124.6, 118.4, 116.2 ($J_{C\text{-}F}$ = 21.8 Hz), 113.3, 94.1, 77.4, 72.7; LRMS (ES + APCI) *m/z* 268.0 $[M+H]^+$; HRMS calculated for $C_{16}H_{10}FNO_2$ $[M+H]^+$ 268.0768, found 268.0771.

(±)-1-(2-(1,3-Dioxalan-2-yl)-1-hydroxyethyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile 404



To a solution of 1-(4-fluorophenyl)-1-formyl-1,3-dihydroisobenzofuran-5-carbonitrile **396** (135 mg, 0.5 mmol) in anhydrous THF (2.5 mL) was added a solution of (1,3-dioxolan-2-ylmethyl)magnesium bromide **403** (0.5 M in THF, 1.5 mL, 0.8 mmol) dropwise at 0 °C. The resulting mixture was allowed to warm to rt then heated to 40 °C for 18 h. A saturated solution of NH_4Cl (5 mL) was added to quench the reaction, and the organics were extracted from the aqueous with EtOAc (3 × 10 mL). The combined organics were washed with brine (50 mL) dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 6:4) afforded the *title* compound **404** as a 1:1 mixture of diastereoisomers (86 mg, 0.2 mmol, 48% over two steps) as a colourless oil.

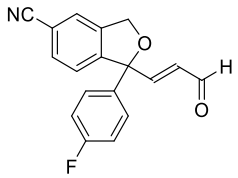
Further purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 6:4) allowed separation of each diastereoisomer for characterisation.

Diastereoisomer 1: ^{1}H NMR (500 MHz, $CDCl_3$) 7.78 (d, *J* = 8.0 Hz, 1H), 7.65–7.60 (m, 3H), 7.49 (s, 1H), 7.03 (t, *J* = 8.8 Hz, 2H), 5.26–5.13 (m, 2H), 5.02 (dd, *J* = 4.5, 4.0 Hz, 1H), 4.41–4.39 (m, 1H), 3.99–3.92 (m, 2H), 3.88–3.80 (m, 2H), 3.19 (d, *J* = 2.6 Hz, 1H), 1.95–1.91 (m, 1H), 1.67–1.61 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.5 ($J_{C\text{-}F}$ = 246.9 Hz), 148.1, 140.5, 136.0 ($J_{C\text{-}F}$ = 3.1 Hz), 131.9, 128.1 ($J_{C\text{-}F}$ = 8.0 Hz), 125.1, 124.7, 118.8, 115.2 ($J_{C\text{-}F}$ = 21.2 Hz), 112.2, 103.6, 91.5, 77.4, 73.5, 71.7, 68.3, 65.2, 64.9, 35.1 (extra carbon).

Diastereoisomer 2: ^{1}H NMR (500 MHz, $CDCl_3$) 7.70 (d, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.51–7.48 (m, 3H), 7.03 (t, *J* = 8.7 Hz, 2H), 5.24 (d, *J* = 12.7 Hz, 1H), 5.12 (d, *J* = 12.7 Hz, 1H), 5.04 (t, *J* = 4.2 Hz, 1H), 4.53 (ddd, *J* = 10.3, 3.0, 1.5 Hz, 1H), 4.01–3.92 (m, 2H), 3.89–3.81 (m, 2H), 3.09 (d, *J* = 3.3 Hz, 1H), 1.88 (ddd, *J* = 14.6, 3.8, 1.5 Hz, 1H), 1.72 (ddd, *J* = 14.7, 10.3, 4.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4 ($J_{C\text{-}F}$ = 247.3 Hz), 147.1, 141.2, 137.2 ($J_{C\text{-}F}$ = 2.8 Hz), 131.8,

127.7 (J_{C-F} = 8.1 Hz), 125.1, 124.1, 118.5, 115.6 (J_{C-F} = 21.3 Hz), 112.2, 103.5, 92.6, 77.4, 73.4, 72.1, 65.2, 64.9, 34.8 (extra carbon).

(±)-(*E*)-1-(4-Fluorophenyl)-1-(3-oxoprop-1-en-1-yl)-1,3-dihydroisobenzofuran-5-carbonitrile 405



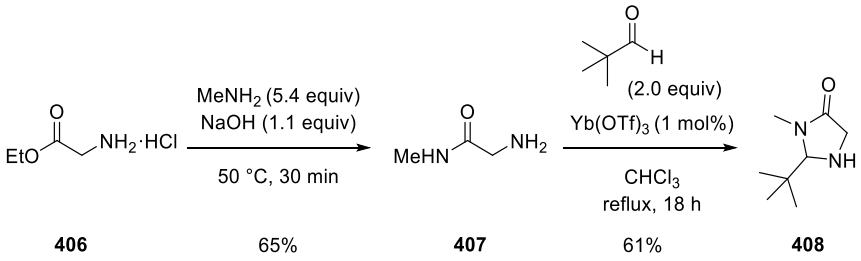
To a solution of 1-(2-(1,3-dioxalan-2-yl)-1-hydroxyethyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile **404** (110 mg, 0.3 mmol) in acetone (3 mL) was added H_2O (1.0 mL) and PPTS (3 mg, 0.02 mmol). The mixture was heated at 50 °C for 18 h after which time the solvent was removed under reduced pressure and the crude product was re-dissolved in EtOAc (10 mL). The organics were washed with saturated solution of $NaHCO_3$ (2 × 10 mL), brine (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude was dissolved in PhMe (1.0 mL). *p*-TsOH (12 mg, 0.1 mmol) was added and the mixture was heated at reflux using a Dean-Stark condenser for 1 h. The dark red solution was cooled to rt and was quenched with Et_3N (five drops). H_2O (10 mL) was added and the phases were separated. The aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 6:4) afforded the *title* compound **405** (88 mg, 0.3 mmol, 97% over two steps) as a brown oil.

IR (ATR)/cm^{-1}: 2931, 2857, 2361, 2339, 2237, 1691; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, *J* = 7.6 Hz, 1H), 7.68–7.65 (m, 1H), 7.61 (s, 1H), 7.35–7.31 (m, 3H), 7.11 (d, *J* = 15.0 Hz, 1H), 7.09–7.05 (m, 2H), 6.34 (dd, *J* = 15.6 Hz, 7.6 Hz, 1H), 5.26 (d, *J* = 13.0 Hz, 1H), 5.19 (d, *J* = 13.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.8, 162.9 (J_{C-F} = 249.1 Hz), 154.8, 146.2, 140.5, 136.3 (J_{C-F} = 3.2 Hz), 132.3, 131.2, 128.3 (J_{C-F} = 8.4 Hz), 125.8, 123.9, 118.3, 115.9 (J_{C-F} = 21.6 Hz), 113.0, 90.2, 71.6; LRMS (ES + APCI) *m/z* 338.0 $[M+HCOO^-]^-$; HRMS calculated for $C_{18}H_{12}FNO_2$ $[M+H]^+$ 294.0925, found 294.0938.

Alternatively one-pot procedure for hydrolysis and dehydration reaction. To a solution of 1-(2-(1,3-dioxalan-2-yl)-1-hydroxyethyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile **404** (150 mg, 0.40 mmol) in acetone (4 mL) was added H_2O (1.0 mL) and PPTS (23 mg, 0.12 mmol). The mixture was heated at 50 °C for 18 h after which time the solvent was removed under reduced pressure and the crude product was re-dissolved in EtOAc (10 mL). The organics were washed with saturated solution of $NaHCO_3$ (2 × 10 mL), brine (20 mL), dried over $MgSO_4$ and filtered.

Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 6:4) afforded the *title* compound **405** (80 mg, 0.27 mmol, 68%) as a brown oil.

Synthesis of imidazolidinone 408

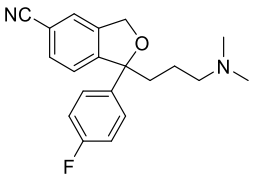


Glycine ethyl ester hydrochloride **406** (5.2 g, 37.5 mmol) was dissolved in an ethanolic solution of $MeNH_2$ (25 mL, 201.0 mmol). The mixture was stirred for 30 min at 50 °C, before the addition of NaOH (1.6 g, 40.4 mmol). The mixture was stirred for additional 30 min before evaporation of the solvent. The organics were extracted from the aqueous with EtOAc (3 × 50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure affording **407** (2.1 g, 24.3 mmol, 65%) as yellow oil without further purification.

Amino amide **407** (88 mg, 1.0 mmol) was dissolved in $CHCl_3$ (2 mL) before the addition of pivaldehyde (220 μL, 2.0 mmol) and ytterbium trifluoromethanesulfonate (6 mg, 0.01 mmol). The mixture was stirred at reflux for 8 h. The mixture was then cooled to rt before the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 6:4) afforded the *title* compound **408** (95 mg, 0.6 mmol, 61%) as a yellow oil.

IR (ATR)/cm^{-1}: 2931, 2830, 1654; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.11 (bd, J = 1.4 Hz, 1H), 3.51–3.37 (m, 1H), 2.94 (s, 3H), 2.43 (bs, 1H), 0.95 (bs, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 85.2, 49.3, 37.7, 31.2, 25.7; LRMS (ES + APCI) *m/z* 157.1 $[M+H]^+$.

(±)-1-(3-Dimethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile[117] **382**



To a solution of (*E*)-1-(4-fluorophenyl)-1-(3-oxoprop-1-en-1-yl)-1,3-dihydroisobenzofuran-5-carbonitrile **405** (56 mg, 0.2 mmol) in $CHCl_3$ (1.0 mL) was added 2-(*tert*-butyl)-3-methylimidazolidin-4-one[178] **402** (6 mg, 0.02 mmol) in TFA (3 μL) at 0 °C followed

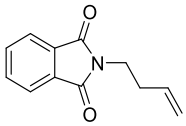
by the addition of diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate **409** (Hantzsch ester) (52 mg, 0.2 mmol). The reaction was warmed to rt and stirred for 18 h. Et_2O (3 mL) was added and the solution was passed through a small plug of silica before evaporating the solvent under reduced pressure. The crude material was then used in the next step without further purification. Crude 1-(4-fluorophenyl)-1-(3-oxopropyl)-1,3-dihydroisobenzofuran-5-carbonitrile **410** (0.2 mmol) was dissolved in EtOH (2.0 mL) and a solution of Me_2NH (2 M in THF, 285 μL, 0.6 mmol) was added. The resulting mixture was heated at 80 °C for 1 h and was cooled to rt before the addition of $NaBH(OAc)_3$ (52 mg, 0.3 mmol). Stirring was continued at rt for 18 h. The reaction was quenched with 1 M HCl (1.0 mL) then separated between Et_2O (5 mL) and saturated $NaHCO_3$ solution (5 mL). The organics were extracted from the aqueous with Et_2O (3 × 10 mL), washed with brine (10 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography (CH_2Cl_2:MeOH:NH_3 95:4:1) afforded the *title* compound **382** (28 mg, 0.1 mmol, 43% over 2 steps) as a colourless oil.

IR (ATR)/cm^{-1}: 2953, 2872, 2781, 2360, 2231; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.8 Hz, 1H), 7.50 (s, 1H), 7.43–7.40 (m, 2H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.00 (t, *J* = 8.6 Hz, 1H), 5.19 (d, *J* = 12.9 Hz, 1H), 5.14 (d, *J* = 12.9 Hz, 1H), 2.27–2.16 (m, 4H), 2.14 (s, 6H), 1.51–1.43 (m, 1H), 1.37–1.30 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2 ($J_{C\text{-}F}$ = 246.2 Hz), 149.7, 140.5, 139.7 ($J_{C\text{-}F}$ = 3.2 Hz), 132.0, 126.9 ($J_{C\text{-}F}$ = 8.1 Hz), 125.3, 122.9, 118.8, 115.5 ($J_{C\text{-}F}$ = 21.2 Hz), 111.7, 91.3, 71.4, 59.6, 45.5, 39.1, 22.3; LRMS (ES + APCI) *m/z* 325.1 $[M+H]^+$.

5 Experimental Chapter 3

5.1 Synthesis of starting materials

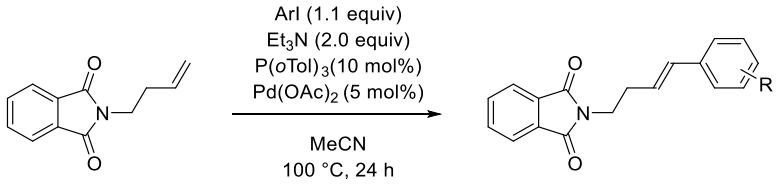
2-(But-3-en-1-yl)isoindoline-1,3-dione 532[179]



A dry three-neck flask was charged with potassium phthalimide **531** (3.6 g, 19.2 mmol) in DMF (12 mL). 4-Bromobut-1-ene (1.5 mL, 14.8 mmol) was added and the mixture was stirred at reflux for 5 h. The mixture was allowed to cool 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 **532** (2.8 g, 13.8 mmol, 93%) as a brown solid without further purification.

m.p. 49–51 °C, Lit[180] [50–52 °C]; IR (thin film)/cm^{-1}: 3075, 2974, 2939, 1772, 1705; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.82 (m, 2H), 7.71–7.69 (m, 2H), 5.79 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.06 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.01 (d, *J* = 10.2 Hz, 1H), 3.76 (t, *J* = 7.1 Hz, 2H), 2.47–2.42 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 134.6, 134.0, 132.3, 123.3, 117.7, 37.5, 33.0; LRMS (ES + APCI) *m/z* 202.1 $[M+H]^+$.

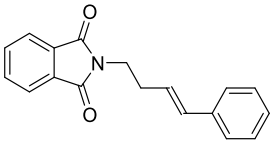
5.1.1 Synthesis of Aryl Phthalimides. General Procedure 11: Heck Coupling[158]



532 **533a-i**

A dry three-neck flask fitted with a condenser was charged with aryl iodide (1.1 equiv) and Et_3N (2.0 equiv) in MeCN (0.05 M). 2-(But-3-en-1-yl)isoindoline-1,3-dione **532** (1.0 equiv) was added followed by P(*o*-tol)$_3$ (10 mol%) and $Pd(OAc)_2$ (5 mol%). The mixture was stirred at reflux upon completion followed by TLC. The solution was allowed to cool to rt, passed through a plug of Celite® and the solvent was concentrated *in vacuo*. The crude residue was re-dissolved in EtOAc (100 mL) and washed with 2 M HCl (× 2), H_2O (× 2), dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. Purification by silica gel flash column chromatography with hexane:EtOAc mixtures afforded the *target* compounds **533a-i**.

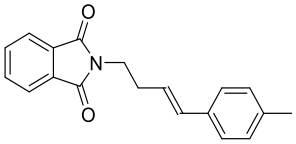
(*E*)-2-(4-Phenylbut-3-en-1-yl)isoindoline-1,3-dione 533a



Phenyl iodide (1.7 mL, 14.76 mmol) and Et_3N (3.7 mL, 26.8 mmol) were dissolved in MeCN (270 mL) followed by addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione **532** (2.7 g, 13.4 mmol), P(*o*-tol)$_3$ (407 mg, 1.3 mmol) and $Pd(OAc)_2$ (150 mg, 0.7 mmol) according to General Procedure **11** the mixture was heated at reflux for 16 h. Purification by silica gel flash column chromatography (hexane:EtOAc 9:1) afforded the *title* compound **533a** (2.2 g, 7.9 mmol, 60%) as a white solid.

m.p. 138–139 °C, Lit[181] [133.5–135.5 °C]; IR (thin film)/cm^{-1}: 3054, 3025, 2935, 1695; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.82 (m, 2H), 7.70–7.69 (m, 2H), 7.30–7.27 (m, 4H), 7.20–7.18 (m, 1H), 6.43 (d, *J* = 15.8 Hz, 1H), 6.18 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.85 (t, *J* = 7.1 Hz, 2H), 2.63–2.59 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 146.7, 137.4, 134.1, 132.8, 132.2, 128.6, 127.4, 126.3, 123.4, 37.7, 32.4; LRMS (ES + APCI) *m/z* 278.0 $[M+H]^+$.

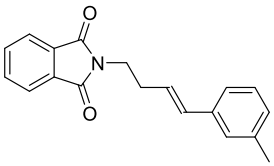
(*E*)-2-(4-*p*-Tolyl)but-3-en-1-yl)isoindoline-1,3-dione 533b



4-Iodotoluene (600 mg, 2.7 mmol) and Et_3N (700 μL, 5.0 mmol) were dissolved in MeCN (50 mL) followed by addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione **532** (500 mg, 2.5 mmol), P(*o*-tol)$_3$ (75 mg, 0.3 mmol) and $Pd(OAc)_2$ (28 mg, 0.1 mmol) according to General Procedure **11**, the mixture was heated at reflux for 24 h. Purification by silica gel flash column chromatography (hexane:EtOAc 9:1) afforded the *title* compound **533b** (432 mg, 1.5 mmol, 60%) as a white solid.

m.p. 121–122 °C, IR (thin film)/cm^{-1}: 3023, 2922, 2854, 1708; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.81 (m, 2H), 7.71-7.68 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.12 (dt, *J* = 15.9, 7.2 Hz, 1H), 3.83 (t, *J* = 7.2 Hz, 2H), 2.62–2.57 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 137.1, 134.6, 134.0, 132.6, 132.3, 129.3, 126.2, 125.2, 123.4, 37.8, 32.4, 21.3; LRMS (ES + APCI) *m/z* 292.0 $[M+H]^+$.

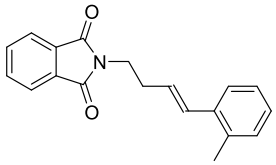
(*E*)-2-(4-*m*-Tolyl)but-3-en-1-yl)isoindoline-1,3-dione 533c



3-Iodotoluene (350 μL, 2.7 mmol) and Et_3N (700 μL, 5.0 mmol) were dissolved in MeCN (50 mL) followed by addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione **532** (500 mg, 2.5 mmol), P(*o*-tol)$_3$ (75 mg, 0.3 mmol) and $Pd(OAc)_2$ (28 mg, 0.1 mmol) according to General Procedure **11**, the mixture was heated at reflux for 20 h. Purification by silica gel flash column chromatography (hexane:EtOAc 9:1) afforded the *title* compound **533c** (528 mg, 1.8 mmol, 73%) as a colourless oil.

IR (thin film)/cm^{-1}: 3055, 2940, 2857, 1712; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.82 (m, 2H), 7.70–7.68 (m, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.11 (s, 1H), 7.11–7.09 (m, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.40 (d, *J* = 15.8 Hz, 1H), 6.16 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.84 (t, *J* = 7.1 Hz, 2H), 2.63–2.58 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 138.1, 137.3, 134.0, 132.8, 132.3, 128.5, 128.2, 127.0, 126.0, 123.43, 123.37, 37.8, 32.4, 21.5; LRMS (ES + APCI) *m/z* 292.0 [M+H]$^+$.

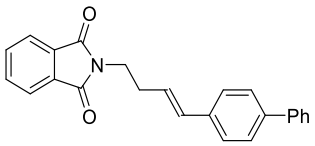
(*E*)-2-(4-*o*-Tolyl)but-3-en-1-yl)isoindoline-1,3-dione 533d



2-Iodotoluene (350 μL, 2.7 mmol) and Et_3N (700 μL, 5.0 mmol) were dissolved in MeCN (50 mL) followed by addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione **532** (500 mg, 2.5 mmol), P(*o*-tol)$_3$ (75 mg, 0.3 mmol) and $Pd(OAc)_2$ (28 mg, 0.1 mmol) according to General Procedure **11** the mixture was heated at reflux for 16 h. Purification by silica gel flash column chromatography (hexane:EtOAc 9:1) afforded the *title* compound **533d** (300 mg, 1.0 mmol, 42%) as a white solid.

m.p. 132–134 °C; IR (thin film)/cm^{-1}: 3056, 3017, 2939, 2855, 1706; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.83 (m, 2H), 7.71–7.69 (m, 2H), 7.35 (d, *J* = 6.9 Hz, 1H), 7.14–7.06 (m, 3H), 6.59 (d, *J* = 15.6 Hz, 1H), 6.12 (dt, *J* = 15.6, 7.5 Hz, 1H), 3.86 (t, *J* = 7.0 Hz, 2H), 2.66–2.61 (m, 2H), 2.20 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) 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* 292.0 [M+H]$^+$.

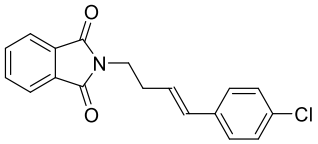
(*E*)-2-(4-([1,1'-Biphenyl]-4-yl)but-3-en-1-yl)isoindoline-1,3-dione 533e



4-Iodo-1,1'-biphenyl (1.7 g, 6.1 mmol) and Et_3N (1.5 mL, 11.0 mmol) were dissolved in MeCN (110 mL) followed by addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione **532** (1.1 g, 5.5 mmol), P(*o*-tol)$_3$ (168 mg, 0.6 mmol) and $Pd(OAc)_2$ (62 mg, 0.3 mmol) according to General Procedure **11**, the mixture was heated at reflux for 72 h. Purification by silica gel flash column chromatography (hexane:EtOAc 8:2) afforded the *title* compound **533e** (0.8 g, 2.3 mmol, 41%) as a white solid.

m.p. 198 °C (decomp); IR (thin film)/cm^{-1}: 2987, 2935, 2879, 1720; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.82 (m, 2H), 7.72–7.67 (m, 2H), 7.59–7.56 (m, 2H), 7.53–7.50 (m, 2H), 7.44–7.40 (m, 2H), 7.38–7.36 (m, 2H), 7.35–7.30 (m, 1H), 6.47 (d, *J* = 15.8 Hz, 1H), 6.22 (d, *J* = 15.8, 7.1 Hz, 1H), 3.87 (d, *J* = 7.1 Hz, 2H), 2.67–2.61 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 140.9, 140.2, 136.5, 134.1, 132.31, 132.26, 128.9, 127.3, 127.1, 126.7, 126.5, 123.4, 37.7, 32.5 (1 carbon missing); LRMS (ES + APCI) *m/z* 371.1 $[M+NH_4]^+$; HRMS calculated for $C_{24}H_{19}NO_2$ $[M+H]^+$ 354.1489, found 354.1491.

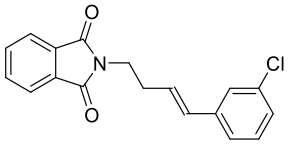
(*E*)-2-(4-(4-Chlorophenyl)but-3-en-1-yl)isoindoline-1,3-dione 533f



1-Chloro-4-iodobenzene (1.3 g, 5.5 mmol) and Et_3N (1.4 mL, 10.0 mmol) were dissolved in MeCN (100 mL) followed by addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione **532** (1.0 g, 4.97 mmol), P(*o*-tol)$_3$ (151 mg, 0.5 mmol) and $Pd(OAc)_2$ (56 mg, 0.3 mmol) according to General Procedure **11**, the mixture was heated undater reflux for 42 h. Purification by silica gel flash column chromatography (hexane:EtOAc 9:1) afforded the *title* compound **533f** (1.1 g, 3.4 mmol, 68%) as a white solid.

m.p. 130–131 °C, Lit[182] [130.5–132.0 °C]; IR (thin film)/cm^{-1}: 3058, 3025, 3002, 2939, 1699; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.82 (m, 2H), 7.71–7.69 (m, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.37 (d, *J* = 15.8 Hz, 1H), 6.15 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.84 (t, *J* = 7.1 Hz, 2H), 2.62–2.58 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 135.9, 134.1, 133.0, 132.2, 131.5, 128.8, 127.5, 127.1, 123.4, 37.6, 32.4; LRMS (ES + APCI) *m/z* 328.9 $[M+H]^+$.

(*E*)-2-(4-(3-Chlorophenyl)but-3-en-1-yl)isoindoline-1,3-dione 533g

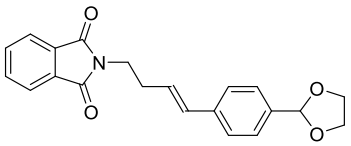


1-Chloro-3-iodobenzene (2.0 g, 8.4 mmol) and Et_3N (2.1 mL, 15.2 mmol) were dissolved in MeCN (150 mL) followed by addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione **532** (1.53 g, 7.6 mmol), P(*o*-tol)$_3$ (232 mg, 0.8 mmol) and $Pd(OAc)_2$ (86 mg, 0.4 mmol) according to General Procedure **11**, the mixture was heated at reflux for 48 h. Purification by silica gel flash column chromatography (hexane:EtOAc 9:1) afforded the *title* compound **532g** (1.8 g, 5.8 mmol, 76%) as a brown solid.

m.p. 106–108 °C; IR (thin film)/cm^{-1}: 3056, 3025, 2935, 2854, 1708; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.81 (m, 2H), 7.72–7.68 (m, 2H), 7.26 (s, 1H), 7.21–7.14 (m, 3H), 6.36 (d, *J* = 15.8 Hz, 1H), 6.19 (dt, *J* = 15.7, 7.1 Hz, 1H), 3.84 (t, *J* = 7.1 Hz, 2H), 2.63–2.59 (m, 2H); ^{13}C NMR

(126 MHz, $CDCl_3$) δ 168.5, 139.2, 134.6, 134.1, 132.1, 131.5, 129.8, 128.0, 127.3, 126.3, 124.5, 123.4, 123.4, 37.6, 32.2; LRMS (ES + APCI) *m/z* 329.0 $[M+H]^+$.

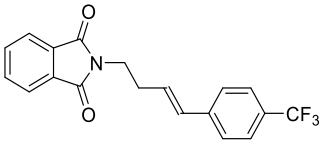
(*E*)-2-(4-(4-(1,3-Dioxalan-2-yl)phenyl)but-3-en-1-yl)isoindoline-1,3-dione 533h



2-(4-Iodophenyl)-1,-dioxalane (3.0 g, 10.9 mmol) and Et_3N (2.8 mL, 19.7 mmol) were dissolved in MeCN (200 mL) followed by addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione **532** (2.0 g, 9.9 mmol), P(*o*-tol)$_3$ (301 mg, 1.0 mmol) and $Pd(OAc)_2$ (111 mg, 0.5 mmol) according to General Procedure **11**, the mixture was heated at reflux for 72 h. Purification by silica gel flash column chromatography (hexane:EtOAc 9:1) afforded the *title* compound **533h** (1.6 g, 4.6 mmol, 46%) as a white solid.

m.p. 120–121 °C; IR (thin film)/cm^{-1}: 3026, 2945, 2883, 1706; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.80 (m, 2H), 7.71–7.67 (m, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.42 (d, *J* = 15.8 Hz, 1H), 6.19 (d, *J* = 15.8, 7.1 Hz, 1H), 5.78 (s, 1H), 4.12–4.10 (m, 2H), 4.04–4.00 (m, 2H), 3.85 (d, *J* = 7.1 Hz, 2H), 2.63–2.59 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 138.4, 136.9, 134.1, 132.4, 132.2, 127.0, 126.8, 126.3, 123.4, 103.7, 65.4, 37.7, 32.4; LRMS (ES + APCI) *m/z* 350.0 $[M+H]^+$; HRMS calculated for $C_{21}H_{19}NO_4$ $[M+H]^+$ 350.1387, found 350.1387.

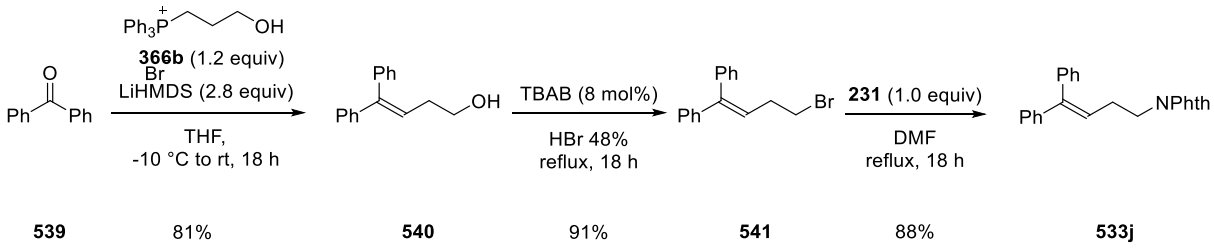
(*E*)-2-(4-(4-Trifluoromethylphenyl)but-3-en-1-yl)isoindoline-1,3-dione 533i



1-Iodo-4-(trifluoromethyl)benzene (803 µL, 5.5 mmol) and Et_3N (1.4 mL, 9.9 mmol) were dissolved in MeCN (100 mL) followed by addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione **532** (1.0 g, 5.0 mmol), P(*o*-tol)$_3$ (151 mg, 0.5 mmol) and $Pd(OAc)_2$ (56 mg, 0.3 mmol) according to General Procedure **11**, the mixture was heated at reflux for 18 h. Purification by silica gel flash column chromatography (hexane:EtOAc 9:1) afforded the *title* compound **533i** (1.2 g, 3.5 mmol, 70%) as a white solid.

m.p. 150 °C decomp; IR (thin film)/cm^{-1}: 2997, 2866, 1699; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.82 (m, 2H), 7.713–7.69 (m, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 6.45 (d, *J* = 15.8 Hz, 1H), 6.31–6.25 (m, 1H), 3.87 (t, *J* = 7.0 Hz, 2H), 2.66–2.62 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 140.8, 134.2, 134.1, 132.2, 131.5, 129.3, 127.7 (J_{C-F} = 348.5 Hz), 126.4, 125.6 (J_{C-F} = 3.75 Hz), 123.4, 37.5, 32.4; LRMS (ES + APCI) *m/z* 346.0 $[M+H]^+$.

5.1.2 Synthesis of 2-(4,4-diphenylbut-3-en-1-yl)isoindoline-1,3-dione 533j



To a three-neck round-bottom flask dried and flushed with argon was added (3-hydroxypropyl)triphenylphosphonium bromide **366b** (2.6 g, 6.6 mmol) in anhydrous THF (12 mL). The resulting suspension was cooled to -10 °C using a NaCl/ice bath. A 1 M solution of LiHMDS (15 mL) was added dropwise and the mixture was stirred at -10 °C for 1 h. Benzophenone **539** (1.0 g, 5.5 mmol) was then added dropwise and stirred at -10 °C for 2 h. The mixture was allowed to warm to rt and stirred for a further 18 h. A saturated aqueous solution of NH_4Cl (50 mL) was then added. The organic layer was extracted with Et_2O (2 × 100 mL), dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 6:4) afforded 4,4-diphenylbut-3-en-1-ol **540** (1.0 g, 4.5 mmol, 81%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.36 (m, 2H), 7.34–7.26 (m, 2H), 7.25–7.19 (m, 6H), 6.12 (t, *J* = 7.5 Hz, 1H), 3.73 (t, *J* = 6.5 Hz, 2H), 2.44–2.38 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5, 142.5, 141.1, 140.0, 130.0, 128.4, 128.3, 127.4, 127.3, 125.4, 62.8, 33.5.

To a solution of 4,4-diphenylbut-3-en-1-ol **540** (300 mg, 1.3 mmol) in a 48% solution of HBr (1.6 mL) was added TBAB (17 mg, 0.1 mmol). The mixture was stirred at reflux for 18 h. The mixture was then allowed to cool to rt and diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The organic layer was extracted with CH_2Cl_2 (2 × 20 mL), washed with $NaHCO_3$ (50 mL), brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to afford (4-bromobut-1-ene-1,1diyl)dibenzene **541** (350 mg, 1.2 mmol, 91%) as a yellow oil.

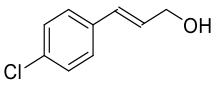
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.27 (m, 5H), 7.25–7.22 (m, 3H), 7.19–7.17 (m, 2H), 6.09 (t, *J* = 7.3 Hz, 1H), 3.43 (t, *J* = 7.0 Hz, 2H), 2.71–2.66 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 137.9, 128.4, 127.2, 125.9, 124.6, 32.44, 32.42.

A dry three-neck flask was charged with potassium phthalimide **531** (360 mg, 1.9 mmol) in anhydrous DMF (10 mL). (4-bromobut-1-ene-1,1diyl)dibenzene **541** (558 mg, 1.9 mmol) was added and mixture was stirrer at reflux for 18 h. The mixture was allowed to cool to rt, poured into ice and extracted with CH_2Cl_2 (3 × 50 mL). The organics were washed with 0.2 M KOH (50 mL), H_2O (50 mL), dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 9:1) afforded the *title* compound **533j** (600 mg, 1.7 mmol, 88%) as a white solid.

m.p. 120–121 °C; IR (thin film)/cm^{-1}: 2967, 2921, 2908, 2872, 1718, 1701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.78 (m, 2H), 7.71–7.66 (m, 2H), 7.27–7.18 (m, 8H), 7.02–6.99 (m, 2H), 6.07 (t, *J* = 7.6 Hz, 1H), 3.81–3.78 (m, 2H), 2.57–2.52 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 144.5, 142.5, 139.6, 134.0, 132.3, 129.8, 128.3, 128.2, 127.5, 127.2, 125.2, 123.3, 37.8, 29.0 (missing 1 carbon); LRMS (ES + APCI) *m/z* 354.0 $[M+H]^+$.

5.1.3 Synthesis of *N*-tosylated *O*-cinnamylhydroxylamine starting materials

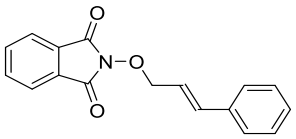
(*E*)-3-(4-Chlorophenyl)prop-2-en-1-ol 582a[183]



To a cooled (0 °C) solution of 4-chlorocinnamaldehyde **581** (500 mg, 3.0 mmol) in MeOH (8.6 mL) was added $NaBH_4$ (131 mg, 3.5 mmol) and the resulting mixture was stirred at rt for 30 min. After this time, the mixture was quenched with H_2O (30 mL) and diluted with CH_2Cl_2 (10 mL). The organics were extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic were washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation to give the *title* compound **582a** (441 mg, 2.6 mmol, 87%) as a white solid which was used in the next step without further purification.

m.p. 52–53 °C, Lit[184] [54–56 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.30 (m, 2H), 7.29–7.27 (m, 2H), 6.58 (dt, *J* = 15.9, 1.5 Hz, 1H), 6.34 (dt, *J* = 15.9, 5.6 Hz, 1H), 4.33 (d, *J* = 5.6 Hz, 2H), 1.49 (bs, 1H).

2-(Cinnamyloxy)isoindoline-1,3-dione 584

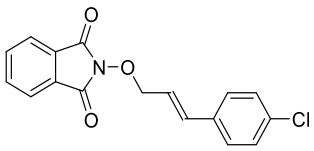


A dry three-neck flask was charged with cinnamyl alcohol **582b** (2.2 g, 16.0 mmol), triphenylphosphine (4.6 g, 17.6 mmol) and *N*-hydroxyphthalimide **15** (2.9 g, 17.6 mmol) in anhydrous THF (64 mL). The solution was cooled to 0 °C and diethyl azadicarboxylate (2.2 M in PhMe, 8.0 mL, 17.6 mmol) was added dropwise. The mixture was warmed to rt and stirred for 2.5 h. The solvent was removed by rotary evaporation before purification by silica gel flash column chromatography (hexane:EtOAc 8:2) to afford the *title* compound **584** (4.3 g, 15.4 mmol, 96%) as a white solid.

m.p. 148–150 °C, Lit[185] [116-118 °C]; IR (thin film)/cm^{-1}: 3058, 3028, 2948, 1790; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82–7.80 (m, 2H), 7.74–7.71 (m, 2H), 7.38–7.37 (m, 2H), 7.32–7.29 (m, 2H),

7.27–7.24 (m, 1H), 6.67 (d, *J* = 15.9 Hz, 1H), 6.47 (dt, *J* = 15.9, 7.1 Hz, 1H), 4.87 (dd, *J* = 7.1, 0.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.0, 137.7, 136.0, 134.6, 129.0, 128.8, 128.6, 127.1, 123.7, 122.2, 78.8; LRMS (ES + APCI) *m/z* 297.0 $[M+NH_4]^+$.

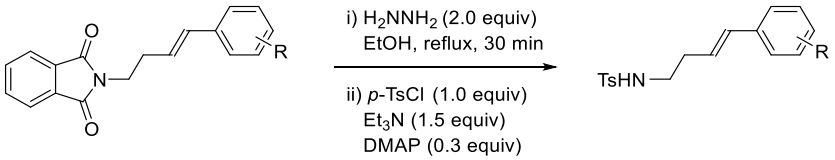
(*E*)-2-((3-(4-Chlorophenyl)allyl)oxy)isoindoline-1,3-dione 583



A dry three-neck flask was charged with (*E*)-3-(4-chlorophenyl)prop-2-en-1-ol **582a** (300 mg, 1.8 mmol), triphenylphosphine (513 mg, 2.0 mmol) and *N*-hydroxyphthalimide **15** (320 mg, 2.0 mmol) in anhydrous THF (7.0 mL). The solution was cooled to 0 °C and diethyl azadicarboxylate (2.2 M in PhMe, 0.9 mL, 1.96 mmol) was added dropwise. The mixture was warmed to rt and stirred for 2.5 h. The solvent was removed by rotary evaporation before purification by silica gel flash column chromatography (hexane:EtOAc 8:2) to afford *title* compound **583** (200 mg, 0.6 mmol, 35%) as a white solid.

m.p. 138–140 °C; IR (thin film)/cm^{-1}: 3050, 2948, 1788, 1742; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.81 (m, 2H), 7.74–7.72 (m, 2H), 7.32–7.27 (m, 4H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.44 (dt, *J* = 15.9, 7.0 Hz, 1H), 4.85 (dd, *J* = 7.0, 1.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.8, 136.1, 134.5, 134.3, 134.2, 128.87, 128.85, 128.1, 123.6, 122.8, 78.5; LRMS (ES + APCI) *m/z* 314.0 $[M+H]^+$; HRMS calculated for $C_{17}H_{12}{}^{35}ClNO_3$ $[M+H]^+$ 314.0578, found 314.0583.

5.1.4 General Procedure 12: Hydrazine and Tosylation[186]

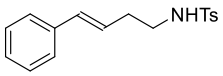


533a-i **534a-i**

To a solution of the corresponding (*E*)-2-(4-arylbut-3-en-1-yl)isoindoline-1,3-dione **533a-i** (1.0 equiv) in EtOH (0.26 M) was added hydrazine monohydrate (2.0 equiv). 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 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 (0.30 M) under argon atmosphere and Et_3N (1.5 equiv) was added. The mixture

was cooled to 0 °C, and *p*-toluenesulfonyl chloride (1.0 equiv) and DMAP (0.3 equiv) 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 of the crude material by silica gel flash column chromatography with hexane:EtOAc mixtures afforded the *N*-tosylated compound **534a-i**.

(*E*)-4-Methyl-*N*-(4-phenylbut-3-en-1-yl)benzenesulfonamide 534a

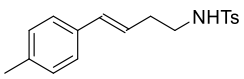


To a solution of (*E*)-2-(4-phenylbut-3-en-1-yl)isoindoline-1,3-dione **533a** (2.2 g, 7.4 mmol) in EtOH (32 mL) was added hydrazine monohydrate (771 μL, 15.8 mmol) according to General Procedure **12** to give (*E*)-4-phenylbut-3-en-1-amine.

To a solution of (*E*)-4-phenylbut-3-en-1-amine (1.2 g, 7.9 mmol) in CH_2Cl_2 (65 mL) was added Et_3N (2.3 mL, 16.2 mmol) followed by *p*-TsCl (1.8 g, 9.8 mmol) and DMAP (0.6 g, 4.9 mmol) according to General Procedure **12**. Purification by silica gel flash column chromatography (hexane:EtOAc 9:1) afforded the *title* compound **534a** (1.8 g, 6.0 mmol, 74%) as a white solid.

m.p. 52–54 °C; IR (thin film)/cm^{-1}: 3272, 3058, 3023, 2922; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.31–7.27 (m, 6H), 7.24–7.21 (m, 1H), 6.36 (d, *J* = 15.9 Hz, 1H), 5.98 (dt, *J* = 15.9, 7.1 Hz, 1H), 4.43 (bs, 1H), 3.13–3.09 (m, 2H), 2.43 (s, 3H), 2.39–2.35 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 137.2, 136.9, 133.5, 129.9, 128.7, 127.7, 127.3, 126.3, 125.6, 42.7, 33.2, 21.7; LRMS (ES + APCI) *m/z* 319.1 $[M\ ]^+$.

(*E*)-4-Methyl-*N*-(4-(*p*-tolyl)but-3-en-1-yl)benzenesulfonamide 534b



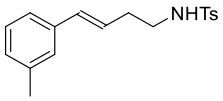
To a solution of (*E*)-2-(4-(*p*-tolyl)but-3-en-1-yl)isoindoline-1,3-dione **533b** (430 mg, 1.5 mmol) in EtOH (6.0 mL) was added hydrazine monohydrate (143 μL, 3.0 mmol) according to General Procedure **12** to give (*E*)-4-(*p*-tolylbut)-3-en-1-amine.

To a solution of (*E*)-4-(*p*-tolylbut)-3-en-1-amine (165 mg, 1.0 mmol) in CH_2Cl_2 (4.0 mL) was added Et_3N (210 μL, 1.5 mmol) followed by *p*-TsCl (190 mg, 1.2 mmol) and DMAP (37 mg, 0.3 mmol) according to General Procedure **12**. Purification by silica gel flash column chromatography (hexane:EtOAc 8:2) afforded the *title* compound **534b** (192 mg, 0.6 mmol, 61%) as a white solid.

m.p. 82–84 °C; IR (thin film)/cm^{-1}: 3276, 3047, 3017, 2939; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.32 (d, *J* = 15.8 Hz, 1H), 5.97 (dt, *J* = 15.8, 7.1 Hz, 1H), 4.37 (t, *J* = 5.4 Hz, 1H), 3.12–3.08 (m, 2H), 2.43

(s, 3H), 2.37–2.34 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 137.5, 137.2, 134.1, 133.4, 129.9, 129.4, 127.3, 126.2, 124.5, 42.7, 33.1, 21.7, 21.3; LRMS (ES + APCI) *m/z* 316.0 $[M+H]^+$.

(*E*)-4-Methyl-*N*-(4-(*m*-tolyl)but-3-en-1-yl)benzenesulfonamide 534c

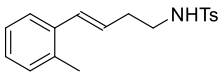


To a solution of (*E*)-2-(4-(*m*-tolyl)but-3-en-1-yl)isoindoline-1,3-dione **533c** (340 mg, 1.2 mmol) in EtOH (4.5 mL) was added hydrazine monohydrate (113 μL, 2.3 mmol) according to General Procedure **12** to give (*E*)-4-(*m*-tolylbut)-3-en-1-amine.

To a solution of (*E*)-4-(*m*-tolylbut)-3-en-1-amine (189 mg, 1.2 mmol) in CH_2Cl_2 (4.0 mL) was added Et_3N (245 μL, 1.8 mmol) followed by *p*-TsCl (223 mg, 1.2 mmol) and DMAP (43 mg, 0.4 mmol) according to General Procedure **12**. Purification by silica gel flash column chromatography (hexane:EtOAc 8:2) afforded the *title* compound **534c** (145 mg, 0.5 mmol, 39%) as a colourless oil.

IR (thin film)/cm^{-1}: 3277, 3023, 2919, 2861; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.10 (s, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.33 (d, *J* = 15.8 Hz, 1H), 5.97 (dt, *J* = 15.8, 7.0 Hz, 1H), 4.66 (t, *J* = 5.8 Hz, 1H), 3.11–3.07 (m, 2H), 2.42 (s, 3H), 2.38–2.33 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.5, 138.2, 137.1, 136.9, 133.4, 129.8, 128.6, 128.4, 127.3, 127.0, 125.5, 123.4, 42.7, 33.1, 21.6, 21.5; LRMS (ES + APCI) *m/z* 316.0 $[M+H]^+$.

(*E*)-4-Methyl-*N*-(4-(*o*-tolyl)but-3-en-1-yl)benzenesulfonamide 534d



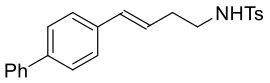
To a solution of (*E*)-2-(4-(*o*-tolyl)but-3-en-1-yl)isoindoline-1,3-dione **533d** (275 mg, 0.9 mmol) in EtOH (3.6 mL) was added hydrazine monohydrate (92 μL, 1.9 mmol) according to General Procedure **12** to give (*E*)-4-(*o*-tolylbut)-3-en-1-amine.

To a solution of (*E*)-4-(*o*-tolylbut)-3-en-1-amine (151 mg, 0.9 mmol) in CH_2Cl_2 (4.0 mL) was added Et_3N (200 μL, 1.4 mmol) followed by *p*-TsCl (179 mg, 0.9 mmol) and DMAP (35 mg, 0.3 mmol) according to General Procedure **12**. Purification by silica gel flash column chromatography (hexane:EtOAc 8:2) afforded the *title* compound **534d** (64 mg, 0.2 mmol, 22%) as a colourless oil.

IR (thin film)/cm^{-1}: 3272, 3021, 2922, 2865; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.1 Hz, 2H), 7.32–7.31 (m, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.15-7.11 (m, 3H), 6.58 (d, *J* = 15.7 Hz, 1H), 5.86 (dt, *J* = 15.7, 7.1 Hz, 1H), 4.65 (bs, 1H), 3.11 (t, *J* = 6.7 Hz, 2H), 2.42 (s, 3H), 2.42–2.37 (m, 2H),

2.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 137.2, 136.1, 135.2, 131.2, 130.4, 129.8, 127.5, 127.4, 127.0, 126.2, 125.6, 42.8, 33.4, 21.6, 19.9; LRMS (ES + APCI) *m/z* 316.0 $[M+H]^+$.

(*E*)-2-(4-([1,1'-Biphenyl]-4-yl)but-3-en-1-yl)-4-methylbenzenesulfonamide 534e

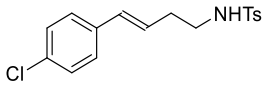


To a solution of (*E*)-2-(4-([1,1'-biphenyl]-4-yl)but-3-en-1-yl)isoindoline-1,3-dione **533e** (300 mg, 0.9 mmol) in EtOH (3.5 mL) was added hydrazine monohydrate (82 μL, 1.7 mmol) according to General Procedure **12** to give (*E*)-4-([1,1'-biphenyl]-4-yl)but-3-en-1-amine.

To a solution of (*E*)-4-([1,1'-biphenyl]-4-yl)but-3-en-1-amine (189 mg, 0.9 mmol) in CH_2Cl_2 (3.0 mL) was added Et_3N (177 μL, 1.3 mmol) followed by *p*-TsCl (162 mg, 0.9 mmol) and DMAP (31 mg, 0.3 mmol) according to General Procedure **12**. Purification by silica gel flash column chromatography (hexane:EtOAc 9:1) afforded the *title* compound **534e** (75 mg, 0.2 mmol, 23%) as a white solid.

m.p. 126–128 °C; IR (thin film)/cm^{-1}: 3276, 3051, 3025, 2922, 2865; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 7.3 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.03 (dt, *J* = 15.9, 7.1 Hz, 1H), 4.59 (t, *J* = 6.0 Hz, 1H), 3.14–3.10 (m, 2H), 2.42 (s, 3H), 2.41–2.37 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 140.8, 140.4, 137.1, 136.0, 132.9, 129.9, 128.9, 127.5, 127.4, 127.3, 127.0, 126.7, 125.8, 42.7, 33.2, 21.7; LRMS (ES + APCI) *m/z* 378.0 $[M+NH_4]^+$; HRMS calculated for $C_{23}H_{23}NO_2S$ $[M+H]^+$ 378.1522, found 378.1522.

(*E*)-*N*-(4-(4-Chlorophenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide 534f



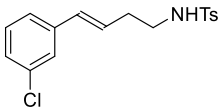
To a solution of (*E*)-2-(4-(4-chlorophenyl)but-3-en-1-yl)isoindoline-1,3-dione **533f** (444 mg, 1.4 mmol) in EtOH (5.5 mL) was added hydrazine monohydrate (138 μL, 2.8 mmol) according to General Procedure **12** to give (*E*)-4-(4-chlorophenyl)but-3-en-1-amine.

To a solution of (*E*)-4-(4-chlorophenyl)but-3-en-1-amine (150 mg, 0.8 mmol) in CH_2Cl_2 (3.0 mL) was added Et_3N (172 μL, 1.2 mmol) followed by *p*-TsCl (157 mg, 0.8 mmol) and DMAP (30 mg, 0.3 mmol) according to General Procedure **12**. Purification by silica gel flash column chromatography (hexane:EtOAc 8:2) afforded the *title* compound **534f** (57 mg, 0.2 mmol, 20%) as a white solid.

m.p. 90–92 °C; IR (thin film)/cm^{-1}: 3360, 3250, 2947, 2826; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.30 (d, *J* = 15.9 Hz, 1H), 5.96 (dt, *J* = 15.9, 7.0 Hz, 1H), 4.78 (t, *J* = 5.9 Hz, 1H), 3.10–3.07 (m, 2H), 2.41

(s, 3H), 2.37–2.33 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 137.1, 135.5, 133.1, 132.0, 129.9, 128.8, 127.5, 127.2, 126.6, 42.6, 33.1, 21.6; LRMS (ES + APCI) *m/z* 336.0 $[M+H]^+$.

(*E*)-*N*-(4-(3-Chlorophenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide 534g

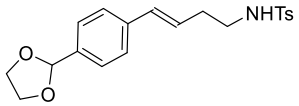


To a solution of (*E*)-2-(4-(3-chlorophenyl)but-3-en-1-yl)isoindoline-1,3-dione **533g** (1.8 g, 5.8 mmol) in EtOH (22 mL) was added hydrazine monohydrate (560 μL, 11.5 mmol) according to General Procedure **12** to give (*E*)-4-(3-chlorophenyl)but-3-en-1-amine.

To a solution of (*E*)-4-(3-chlorophenyl)but-3-en-1-amine (1.1 g, 5.8 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (1.2 μL, 8.7 mmol) followed by *p*-TsCl (1.1 g, 5.8 mmol) and DMAP (0.2 g, 1.7 mmol) according to General Procedure **12**. Purification by silica gel flash column chromatography (hexane:EtOAc 8:2) afforded the *title* compound **534g** (0.4 g, 1.2 mmol, 21%) as a colourless oil.

IR (thin film)/cm^{-1}: 3272, 3060, 3025, 2921, 2870; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.24 (m, 1H), 7.21–7.17 (m, 2H), 7.13 (d, *J* = 7.1 Hz, 1H), 6.29 (d, *J* = 15.9 Hz, 1H), 5.99 (dt, *J* = 15.9, 7.0 Hz, 1H), 4.68 (bs, 1H), 3.12–3.08 (m, 2H), 2.42 (s, 3H), 2.39–2.35 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 138.8, 137.1, 134.6, 131.9, 129.9, 127.5, 127.4, 127.3, 126.1, 124.6, 42.6, 33.1, 21.7 (1 carbon missing); LRMS (ES + APCI) *m/z* 352.9 $[M+NH_4]^+$; HRMS calculated for $C_{17}H_{18}{}^{35}ClNO_2S$ $[M+H]^+$ 336.0820, found 336.0823.

(*E*)-*N*-(4-(4-(1,3-Dioxalan-2-yl)phenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide 534h



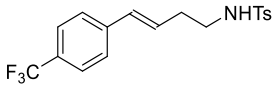
To a solution of (*E*)-2-(4-(4-(1,3-dioxalan-2-yl)phenyl)but-3-en-1-yl)isoindoline-1,3-dione **533h** (400 mg, 1.1 mmol) in EtOH (4.5 mL) was added hydrazine monohydrate (111 μL, 2.3 mmol) according to General Procedure **12** to give (*E*)-(4-(4-(1,3-dioxalan-2-yl)phenyl)but-3-en-1-yl)-1-amine.

To a solution of (*E*)-(4-(4-(1,3-dioxalan-2-yl)phenyl)but-3-en-1-yl)-1-amine (250 mg, 1.1 mmol) in CH_2Cl_2 (4.0 mL) was added Et_3N (240 μL, 1.7 mmol) followed by *p*-TsCl (217 mg, 1.1 mmol) and DMAP (42 mg, 0.3 mmol) according to General Procedure **12**. Purification by silica gel flash column chromatography (hexane:EtOAc 6:4) afforded the *title* compound **534h** (260 mg, 0.7 mmol, 61%) as a colourless oil.

IR (thin film)/cm^{-1}: 3264, 3026, 2948, 2883; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.30–7.27 (m, 4H), 6.36 (d, *J* = 15.9 Hz, 1H), 5.99 (dt, *J* = 15.8, 7.1 Hz, 1H),

5.79 (s, 1H), 4.43 (t, *J* = 5.8 Hz, 1H), 4.15–4.11 (m, 2H), 4.05–4.01 (m, 2H), 3.13–3.08 (m, 2H), 2.42 (s, 3H), 2.39–2.34 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0, 137.2, 136.6, 136.5, 132.3, 129.2, 126.6, 126.2, 125.7, 125.6, 103.0, 64.8, 42.0, 32.5, 21.0; LRMS (ES + APCI) *m/z* 374.0 $[M+H]^+$; HRMS calculated for $C_{20}H_{23}NO_4S$ $[M+H]^+$ 374.1421, found 374.1420.

(*E*)-4-Methyl-*N*-(4-(4-trifluoromethyl)phenyl)but-3-en-1-yl)benzenesulfonamide 534i

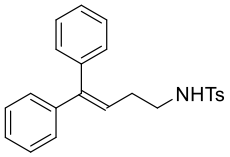


To a solution of (*E*)-2-(4-(4-trifluoromethylphenyl)but-3-en-1-yl)isoindoline-1,3-dione **533i** (1.0 g, 2.9 mmol) in EtOH (11 mL) was added hydrazine monohydrate (280 μL, 5.8 mmol) according to General Procedure **12** to give (*E*)-4-(4-(trifluoro)phenyl)but-3-en-1-amine.

To a solution of (*E*)-4-(4-(trifluoro)phenyl)but-3-en-1-amine (623 mg, 3.0 mmol) in CH_2Cl_2 (9.6 mL) was added Et_3N (604 μL, 4.3 mmol) followed by *p*-TsCl (551 mg, 2.9 mmol) and DMAP (106 mg, 0.9 mmol) according to General Procedure **12**. Purification by silica gel flash column chromatography (hexane:EtOAc 8:2) afforded the *title* compound **534i** (409 mg, 1.1 mmol, 38%) as a white solid.

m.p. 121–122 °C; IR (thin film)/cm^{-1}: 3330, 3244, 2991, 2875; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.11 (m, 1H), 4.39 (t, *J* = 5.9 Hz, 1H), 3.15–3.11 (m, 2H), 2.42 (s, 3H), 2.42–2.39 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7, 140.4, 137.1, 132.0, 129.9, 129.4 (d, $J_{C\text{-}F}$ = 33.1 Hz), 128.7, 127.3, 126.4, 125.6 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.3 (d, $J_{C\text{-}F}$ = 272.0 Hz); LRMS (ES + APCI) *m/z* 370.0 $[M+H]^+$.

***N*-(4,4-Diphenylbut-3-en-1-yl)-4-methylbenzenesulfonamide 534j**



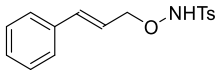
To a solution of 2-(4,4-Diphenylbut-3-en-1-yl)isoindoline-1,3-dione **533j** (280 mg, 0.8 mmol) in EtOH (3.0 mL) was added hydrazine monohydrate (77 μL, 1.6 mmol) according to General Procedure **12** to give 4,4-diphenylbut-3-en-1-amine.

To a solution of 4,4-diphenylbut-3-en-1-amine (176 mg, 0.8 mmol) in CH_2Cl_2 (2.6 mL) was added Et_3N (165 μL, 1.2 mmol) followed by *p*-TsCl (166 mg, 0.9 mmol) and DMAP (29 mg, 0.2 mmol) according to General Procedure **12**. Purification by silica gel flash column chromatography (hexane:EtOAc 8:2) afforded the *title* compound **534j** (200 mg, 0.5 mmol, 67%) as a colourless oil.

IR (thin film)/cm^{-1}: 3281, 3053, 3023, 2922; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.38–7.29 (m, 3H), 7.27–7.22 (m, 5H), 7.20–7.15 (m, 2H), 7.12–7.10 (m, 2H), 5.97 (t, *J* = 7.4 Hz,

1H), 4.76 (bs, 1H), 3.07–3.02 (m, 2H), 2.41 (s, 3H), 2.30–2.24 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 143.4, 142.1, 139.6, 137.0, 129.8, 128.4, 128.2, 127.35, 127.31, 127.2, 124.7, 43.1, 29.9, 21.6; LRMS (ES + APCI) *m/z* 378.1 $[M+H]^+$; HRMS calculated for $C_{23}H_{23}NO_2S$ $[M+H]^+$ 378.1522, found 378.1521.

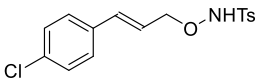
_N_-(Cinnamyloxy)-4-methylbenzenesulfonamide 586



To a solution of crude 2-(cinnamyloxy)isoindoline-1,3-dione **584** (16.1 mmol) in anhydrous CH_2Cl_2 (65 mL) was added Et_3N (2.7 mL, 19.3 mmol) followed by *p*-TsCl (3.4 g, 17.7 mmol). The resulting mixture was stirred at rt for 15 h. H_2O (50 mL) was then added and the organics were extracted from the aqueous with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. Purification by silica gel flash column chromatography (hexane:EtOAc 8:2) to afford the *title* compound **586** (2.9 g, 9.6 mmol, 60%) as a white solid.

m.p. 109–110 °C, Lit[187] [103 °C]; IR (thin film)/cm^{-1}: 3220, 3058, 3026, 2924, 2870; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.38–7.25 (m, 7H), 6.91 (bs, 1H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.22 (dt, *J* = 15.9, 6.8 Hz, 1H), 4.61 (dd, *J* = 6.8, 1.1 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.1, 136.3, 136.0, 133.8, 129.9, 128.77, 128.75, 128.4, 126.9, 122.9, 78.1, 21.8; LRMS (ES + APCI) *m/z* 321.0 $[M+NH_4]^+$.

(*E*)-*N*-((3-(4-Chlorophenyl)allyl)oxy)-4-methylbenzenesulfonamide 585

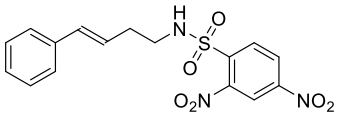


To a solution of crude (*E*)-2-((3-(4-chlorophenyl)allyl)oxy)isoindoline-1,3-dione **583** (0.6 mmol) in anhydrous CH_2Cl_2 (2.2 mL) was added Et_3N (120 µL, 0.8 mmol) and *p*-TsCl (107 mg, 0.6 mmol). The resulting mixture was stirred at rt for 15 h. H_2O (50 mL) was then added and the organics were extracted from the aqueous with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. Purification by silica gel flash column chromatography (hexane:EtOAc 8:2) to afford the *title* compound **585** (102 mg, 0.3 mmol, 54%) as a white solid.

m.p. 116–118 °C; IR (thin film)/cm^{-1}: 3216, 3064, 2922, 2852; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.26 (s, 4H), 7.07 (bs, 1H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.20 (dt, *J* = 15.9, 6.7 Hz, 1H), 4.59 (bd, *J* = 6.7 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.1, 134.8, 134.5, 134.0, 133.7, 129.9, 128.9, 128.7, 128.0, 123.7, 77.8, 21.8; LRMS (ES + APCI) *m/z* 355.0 $[M+NH_4]^+$; HRMS calculated for $C_{16}H_{16}{}^{35}ClNO_3S$ $[M+H]^+$ 338.0612, found 338.0616.

5.1.5 Synthesis of alternative homallylic *N*-protected amines

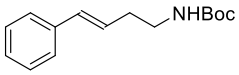
(*E*)-2,4-Dinitro-*N*-(4-phenylbut-3-en-1-yl)benzenesulfonamide 534b



To a cooled (0 °C) solution of (*E*)-4-phenylbut-3-en-1-amine (200 mg, 1.4 mmol) in CH_2Cl_2 (14 mL) was added Et_3N (284 μL, 2.0 mmol) followed by addition of 2,4-dinitrobenzenesulfonyl chloride (471 mg, 1.8 mmol). The resultant mixture was then stirred at rt for 18 h, before quenching with a saturated solution of NH_4Cl (20 mL). The organic layer was extracted with CH_2Cl_2 (3 × 50 mL), washed with brine (100 mL), dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. Purification by silica gel flash column chromatography (hexane:EtOAc 8:2) afforded the *title* compound **534b** (502 mg, 1.3 mmol, 98%) as a yellow solid.

m.p. 130–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.36–8.34 (m, 1H), 8.27–8.24 (m, 1H), 7.24–7.17 (m, 3H), 7.11–7.08 (m, 2H), 6.29 (d, *J* = 15.8 Hz, 1H), 5.83 (dt, *J* = 15.8, 7.3 Hz, 1H), 5.41 (bt, *J* = 5.6 Hz, 1H), 3.46–3.42 (m, 2H), 2.46–2.41 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.4, 140.0, 136.3, 134.0, 132.1, 128.8, 128.3, 127.2, 126.0, 125.2, 120.9, 44.1, 33.6 (missing 1 carbon); LRMS (ES + APCI) *m/z* 378.1 $[M+H]^+$.

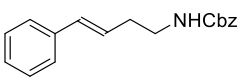
***tert*-Butyl (*E*)-(4-phenylbut-3-en-1-yl)carbamate 534c**



To a solution of (*E*)-4-phenylbut-3-en-1-amine (316 mg, 2.1 mmol) in CH_2Cl_2 (4 mL) was added K_2CO_3 (591 mg, 4.3 mmol) followed by addition of di-*tert*-butyl dicarbonate (468 mg, 2.1 mmol). The resultant mixture was then stirred at 40 °C for 18 h, before the addition of H_2O (20 mL) and the stirring was extended for an extra hour. Layer were separated and the organic layer was washed with brine (30 mL), dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. Purification by silica gel flash column chromatography (hexane:EtOAc 9:1) afforded the *title* compound **534c** (441 mg, 1.8 mmol, 83%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.21 (d, *J* = 7.2 Hz, 1H), 6.45 (d, *J* = 15.8 Hz, 1H), 6.15 (dt, *J* = 15.8, 7.1 Hz, 1H), 4.59 (bs, 1H), 3.28–3.23 (m, 2H), 2.42–2.38 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 137.4, 132.4, 128.7, 127.4, 127.2, 126.2, 40.2, 33.7, 28.6 (missing 1 carbon); LRMS (ES + APCI) *m/z* 248.1 $[M+H]^+$.

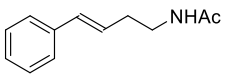
Benzyl (*E*)-(4-phenylbut-3-en-1-yl)carbamate 534d



To a solution of (*E*)-4-phenylbut-3-en-1-amine (308 mg, 2.1 mmol) in H_2O (10 mL) and acetone (21 mL) was added $NaHCO_3$ (200 mg, 2.4 mmol) followed by addition of benzyl chloroformate (335 μL, 2.4 mmol). The resultant mixture was then stirred at rt for 18 h, before evaporation of the solvent and the precipitate was filtered affording the *title* compound **534d** (498 mg, 1.8 mmol, 85%) as a white solid.

m.p. 90–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–8.7.28 (m, 9H), 7.24–7.20 (m, 1H), 6.45 (d, *J* = 15.9 Hz, 1H), 6.14 (dt, *J* = 15.9, 7.3 Hz, 1H), 5.10 (s, 2H), 4.83 (bs, 1H), 3.38–3.34 (m, 2H), 2.46–2.41 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 145.7, 143.0, 137.2, 136.7, 132.7, 128.69, 128.65, 128.2, 127.5, 126.8, 126.2, 66.8, 40.7, 33.6; LRMS (ES + APCI) *m/z* 282.1 $[M+H]^+$.

(*E*)-(4-phenylbut-3-en-1-yl)acetamide 534e

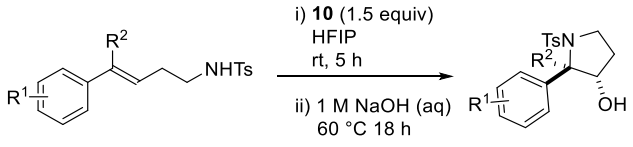


To a cooled (0 °C) solution of (*E*)-4-phenylbut-3-en-1-amine (200 mg, 1.4 mmol) in CH_2Cl_2 (6 mL) was added Et_3N (206 μL, 2.0 mmol) followed by addition of acetyl chloride (97 μL, 1.4 mmol). The resultant mixture was then stirred at rt for 18 h, before washing with a 1 M HCl solution (20 mL) followed by 1 M NaOH solution (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation affording the *title* compound **534e** (190 mg, 1.0 mmol, 72%) as a yellow semi-solid.

^{1}H NMR (400 MHz, $CDCl_3$) 7.36–7.28 (m, 5H), 7.24–7.20 (m, 1H), 6.45 (d, *J* = 15.8 Hz, 1H), 6.14 (dt, *J* = 15.8, 7.1 Hz, 1H), 5.62 (bs, 1H), 3.42–3.37 (m, 2H), 2.45–2.39 (m, 2H), 1.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 137.2, 132.5, 128.7, 127.5, 127.0, 126.2, 39.1, 33.2, 23.5; LRMS (ES + APCI) *m/z* 190.1 $[M+H]^+$.

5.2 Oxidative heterocyclisation with Malonoyl Peroxide 10

5.2.1 General Procedure 13: Cyclisations for the synthesis of Pyrrolidines

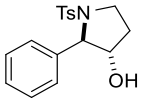


534a-j **535a-j**

Malonoyl peroxide **10** (1.5 equiv) was added to a solution of alkene **534a-j** (1.0 equiv) in HFIP (0.5 M). The mixture was 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 (1:1 (0.1 M)). The solution was stirred at

60 °C for 18 h, allowed to cool to rt and the aqueous phase was extracted with EtOAc (× 3). The combined organics were washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded the crude pyrrolidine product. Purification by silica gel flash column chromatography eluting with hexane:EtOAc mixtures afforded the *target* compound **535a-j**.

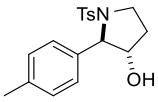
(±)-(2*R*,3*S*)-2-Phenyl-1-tosylpyrrolidin-3-ol 535a



Reaction of (*E*)-4-methyl-*N*-(4-phenylbut-3-en-1-yl)benzenesulfonamide **534a** (25 mg, 0.08 mmol) and malonoyl peroxide **10** (16 mg, 0.12 mmol) in HFIP (0.2 mL) according to General Procedure **13** followed by hydrolysis in 1 M NaOH:THF (0.8 mL, 1:1) gave the crude alcohol (1:13 *cis*:*trans*). Purification by silica gel flash column chromatography (hexane:EtOAc 4:6) gave the *title* compound **535a** (18 mg, 0.06 mmol, 71%) as a white solid.

m.p. 148–149 °C, Lit[188] [155–156 °C]; IR (thin film)/cm^{-1}: 3474, 3065, 3034, 2929, 2892; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 2H), 7.34–7.33 (m, 4H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.28–7.26 (m, 1H), 4.66 (bs, 1H), 4.18 (bs, 1H), 3.73 (td, *J* = 9.4, 2.1 Hz, 1H), 3.53 (td, *J* = 9.9, 7.0 Hz, 1H), 2.43 (s, 3H), 2.07–2.00 (m, 1H), 1.77–1.73 (m, 1H), 1.37–1.38 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7, 139.9, 134.7, 129.7, 128.7, 128.9, 127.7, 126.3, 79.1, 72.0, 46.8, 31.5, 21.7; LRMS (ES + APCI) *m/z* 318.0 $[M+H]^+$.

(±)-(2*R*,3*S*)-2-(*p*-Tolyl)-1-tosylpyrrolidin-3-ol 535b

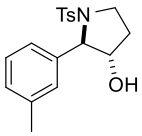


Reaction of (*E*)-4-methyl-*N*-(4-(*p*-tolyl)but-3-en-1-yl)benzenesulfonamide **534b** (100 mg, 0.32 mmol) and malonoyl peroxide **10** (61 mg, 0.48 mmol) in HFIP (0.7 mL) according to General Procedure **13** followed by hydrolysis in 1 M NaOH:THF (3.2 mL, 1:1) gave the crude alcohol (1:7 *cis*:*trans*). Purification by silica gel flash column chromatography (hexane:EtOAc 4:6) gave the *title* compound **535b** (69 mg, 0.21 mmol, 66%) as a white solid.

m.p. 135–136 °C; IR (thin film)/cm^{-1}: 3401, 3029, 2960, 2899; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 4.62 (bs, 1H), 4.13 (bs, 1H), 3.70 (ddd, *J* = 9.3, 8.6, 2.4 Hz, 1H), 3.50 (td, *J* = 9.9, 6.9 Hz, 1H), 2.42 (s, 3H), 2.33 (s, 3H), 2.07–1.97 (m, 1H), 1.75–1.69 (m, 1H), 1.54 (bs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 137.3, 137.1, 134.7, 129.7, 129.3, 127.9, 126.2, 79.0, 71.8,

46.8, 31.5, 21.7, 21.2; LRMS (ES + APCI) *m/z* 332.0 $[M+H]^+$; HRMS calculated for $C_{18}H_{21}NO_3S$ $[M+H]^+$ 332.1315, found 332.1316.

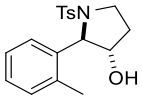
(±)-(2*R*,3*S*)-2-(*m*-Tolyl)-1-tosylpyrrolidin-3-ol 535c



Reaction of (*E*)-4-methyl-*N*-(4-(*m*-tolyl)but-3-en-1-yl)benzenesulfonamide **534c** (50 mg, 0.16 mmol) and malonoyl peroxide **10** (30 mg, 0.24 mmol) in HFIP (0.3 mL) according to General Procedure **13** followed by hydrolysis in 1 M NaOH:THF (1.9 mL, 1:1) gave the crude alcohol (1:6 *cis*:*trans*). Purification by silica gel flash column chromatography (hexane:EtOAc 4:6) gave the *title* compound **535c** (37 mg, 0.11 mmol, 71%) as a white solid.

m.p. 102–104 °C; IR (thin film)/cm^{-1}: 3525, 3489, 3478. 3462, 3447, 2950, 2921; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.12–7.10 (m, 2H), 7.06 (d, *J* = 7.4 Hz, 2H), 4.63 (bs, 1H), 4.14 (bs, 1H), 3.71 (ddd, *J* = 9.4, 8.5, 2.4 Hz, 1H), 3.53 (td, *J* = 9.9, 6.9 Hz, 1H), 2.42 (s, 3H), 2.32 (s, 3H), 2.07–1.98 (m, 1H), 1.76–1.70 (m, 1H), 1.55 (bd, *J* = 2.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 139.9, 138.3, 134.8, 129.7, 128.6, 128.4, 127.8, 127.0, 123.4, 79.0, 72.0, 46.9, 31.5, 21.7, 21.6; LRMS (ES + APCI) *m/z* 332.0 $[M+H]^+$; HRMS calculated for $C_{18}H_{21}NO_3S$ $[M+H]^+$ 332.1315, found 332.1316.

(±)-(2*R*,3*S*)-2-(*o*-Tolyl)-1-tosylpyrrolidin-3-ol 535d

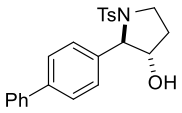


Reaction of (*E*)-4-methyl-*N*-(4-(*o*-tolyl)but-3-en-1-yl)benzenesulfonamide **534d** (100 mg, 0.32 mmol) and malonoyl peroxide **10** (61 mg, 0.48 mmol) in HFIP (0.6 mL) according to General Procedure **13** followed by hydrolysis in 1 M NaOH:THF (3.2 mL, 1:1) gave the crude alcohol (1:4 *cis*:*trans*). Purification by silica gel flash column chromatography (hexane:EtOAc 4:6) gave the *title* compound **535d** (76 mg, 0.23 mmol, 72%) as a white solid.

m.p. 173–175 °C; IR (thin film)/cm^{-1}: 3504, 3064, 2948, 2922, 2854; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.36–7.34 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.20–7.12 (m, 3H), 4.85 (bs, 1H), 4.06 (bs, 1H), 3.76 (td, *J* = 8.9, 1.6 Hz, 1H), 3.54 (ddd, *J* = 11.0, 9.3, 6.7 Hz, 1H), 2.42 (s, 3H), 2.38 (s, 3H), 2.10–2.01 (m, 1H), 1.79–1.74 (m, 1H), 1.59 (bs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.6, 138.2, 134.8, 134.5, 134.4, 130.5, 129.7, 127.8, 127.5, 126.4, 126.2,

123.8, 77.6, 69.7, 46.9, 31.5, 21.7, 19.6; LRMS (ES + APCI) *m/z* 332.0 $[M+H]^+$; HRMS calculated for $C_{18}H_{21}NO_3S$ $[M+H]^+$ 332.1315, found 332.1317.

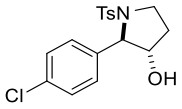
(±)-(2*R*,3*S*)-2-([1,1'-Biphenyl]-4-yl)-1-tosylpyrrolidin-3-ol 535e



Reaction of (*E*)-2-(4-([1,1'-biphenyl]-4-yl)but-3-en-1-yl)-4-methylbenzenesulfonamide **534e** (40 mg, 0.11 mmol) and malonoyl peroxide **10** (20 mg, 0.16 mmol) in HFIP (0.2 mL) according to General Procedure **13** followed by hydrolysis in 1 M NaOH:THF (1.0 mL, 1:1) gave the crude alcohol (1:9 *cis*:*trans*). Purification by silica gel flash column chromatography (hexane:EtOAc 4:6) gave the *title* compound **535e** (30 mg, 0.08 mmol, 72%) as a white solid.

m.p. 190–192 °C, decomp.; IR (thin film)/cm^{-1}: 3450, 3010, 2947, 2920; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.1 Hz, 2H), 7.50–7.47 (m, 4H), 7.45–7.40 (m, 4H), 7.29–7.23 (m, 3H), 4.70 (bs, 1H), 4.22 (bs, 1H), 3.77–3.73 (m, 1H), 3.55 (dt, *J* = 16.8, 8.5 Hz, 1H), 2.43 (s, 3H), 2.11–2.05 (m, 1H), 1.79–1.75 (m, 1H), 1.50 (bs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7, 140.9, 140.7, 139.0, 134.7, 129.7, 128.9, 127.9, 127.5, 127.3, 126.8, 79.1, 71.8, 46.9, 31.6, 21.7 (missing 1 carbon); LRMS (ES + APCI) *m/z* 394.0 $[M+H]^+$; HRMS calculated for $C_{23}H_{23}NO_3S$ $[M+H]^+$ 394.1471, found 394.1472.

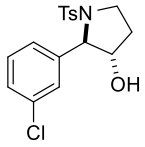
(±)-(2*R*,3*S*)-2-(4-Chlorophenyl)-1-tosylpyrrolidin-3-ol 535f



Reaction of (*E*)-*N*-(4-(4-chlorophenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide **534f** (100 mg, 0.30 mmol) and malonoyl peroxide **10** (57 mg, 0.45 mmol) in HFIP (0.6 mL) according to General Procedure **13** followed by hydrolysis in 1 M NaOH:THF (2.6 mL, 1:1) gave the crude alcohol (1:9 *cis*:*trans*). Purification by silica gel flash column chromatography (hexane:EtOAc 4:6) gave the *title* compound **535f** (69 mg, 0.20 mmol, 67%) as a white solid.

m.p. 169–171 °C; IR (thin film)/cm^{-1}: 3558, 3499, 2937, 2889; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.7 Hz, 2H), 7.31–7.26 (m, 6H), 4.60 (bs, 1H), 4.11 (bs, 1H), 3.72–3.69 (m, 1H), 3.52–3.47 (m, 1H), 2.42 (s, 3H), 2.02–1.95 (m, 1H), 1.75–1.72 (m, 1H), 1.58 (bs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.8, 138.6, 134.4, 129.8, 128.8, 128.9, 127.9, 127.7, 78.9, 71.4, 46.9, 31.5, 21.7; LRMS (ES + APCI) *m/z* 351.9 $[M]^+$; HRMS calculated for $C_{17}H_{18}{}^{35}ClNO_3S$ $[M+H]^+$ 352.0769, found 352.0772.

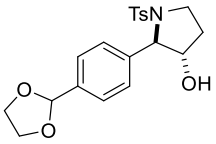
(±)-(2*R*,3*S*)-2-(3-Chlorophenyl)-1-tosylpyrrolidin-3-ol 535g



Reaction of (*E*)-*N*-(4-(3-chlorophenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide **534g** (60 mg, 0.18 mmol) and malonoyl peroxide **10** (34 mg, 0.27 mmol) in HFIP (0.4 mL) according to General Procedure **13** followed by hydrolysis in 1 M NaOH:THF (0.4 mL, 1:1) gave the crude alcohol (1:6 *cis*:*trans*). Purification by silica gel flash column chromatography (hexane:EtOAc 4:6) gave the *title* compound **535g** (33 mg, 0.09 mmol, 52%) as a white solid.

m.p. 96–98 °C; IR (thin film)/cm^{-1}: 3489, 3062, 2952, 2922, 2954; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.27 (s, 1H), 7.25–7.21 (m, 3H), 4.63 (bs, 1H), 4.12 (bs, 1H), 3.70 (td, *J* = 9.3, 2.3 Hz, 1H), 3.52 (td, *J* = 9.9, 6.9 Hz, 1H), 2.42 (s, 3H), 2.06–1.96 (m, 1H), 1.77–1.73 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.9, 142.2, 134.6, 134.5, 130.0, 129.8, 127.8, 126.5, 124.6, 78.9, 71.4, 46.9, 31.6, 21.7 (missing 1 carbon); LRMS (ES + APCI) *m/z* 351.9 $[M]^+$; HRMS calculated for $C_{17}H_{18}{}^{35}ClNO_3S$ $[M+H]^+$ 352.0769, found 352.0770.

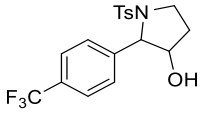
(±)-(2*R*,3*S*)-2-(4-(1,3-Dioxalan-2-yl)phenyl)-1-tosylpyrrolidin-3-ol 535h



Reaction of (*E*)-*N*-(4-(4-(1,3-dioxalan-2-yl)phenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide **534h** (200 mg, 0.54 mmol) and malonoyl peroxide **10** (103 mg, 0.80 mmol) in HFIP (1.1 mL) according to General Procedure **13** followed by hydrolysis in 1 M NaOH:THF (5.3 mL, 1:1) gave the crude alcohol (1:9 *cis*:*trans*). Purification by silica gel flash column chromatography (hexane:EtOAc 1:1) gave the *title* compound **535h** (115 mg, 0.30 mmol, 55%) as a white solid.

m.p. 146–148 °C; IR (thin film)/cm^{-1}: 3517, 3054, 2922, 2887, 2852, 1702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 5.79 (s, 1H), 4.66 (bs, 1H), 4.13–4.07 (m, 3H), 4.05–4.00 (m, 2H), 3.71–3.66 (m, 1H), 3.51 (dt, *J* = 9.9, 6.9 Hz, 1H), 2.41 (s, 3H), 2.01–1.92 (m, 1H), 1.73–1.75 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 141.1, 137.4, 134.7, 129.7, 127.9, 126.8, 126.4, 103.6, 78.9, 71.8, 65.4, 46.9, 31.4, 21.7; LRMS (ES + APCI) *m/z* 390.0 $[M+H]^+$; HRMS calculated for $C_{20}H_{23}NO_5S$ $[M+H]^+$ 390.1370, found 390.1370.

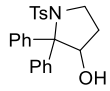
(±)-(2*R*,3*S*)-1-Tosyl-2-(4-(trifluoromethyl)phenyl)pyrrolidine-3-ol 535i



Reaction of (*E*)-4-methyl-*N*-(4-(4-trifluoromethyl)phenyl)but-3-en-1-yl)benzenesulfonamide **534i** (50 mg, 0.1 mmol) and malonoyl peroxide **10** (35 mg, 0.3 mmol) in HFIP (0.6 mL) according to General Procedure **13** followed by hydrolysis in 1 M NaOH:THF (2.6 mL, 1:1) gave the crude alcohol. Purification by silica gel flash column chromatography (hexane:EtOAc 4:6) gave the *title* compound **535i** (10 mg, 0.03 mmol, 19%) as a white solid.

m.p. 119–120 °C; IR (thin film)/cm^{-1}: 3541, 2996, 2888; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.69 (bs, 1H), 4.15 (bs, 1H), 3.74–3.70 (m, 1H), 3.55–3.50 (m, 1H), 2.42 (s, 3H), 2.01–1.95 (m, 1H), 1.78–1.74 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.1, 144.0, 134.3, 130.0 ($J_{C\text{-}F}$ = 13.8 Hz), 129.8, 127.9, 126.8, 125.7 ($J_{C\text{-}F}$ = 3.6 Hz), 124.2 ($J_{C\text{-}F}$ = 272.0 Hz), 78.9, 71.5, 47.0, 31.6, 21.7; LRMS (ES + APCI) *m/z* 386.0 $[M+H]^+$.

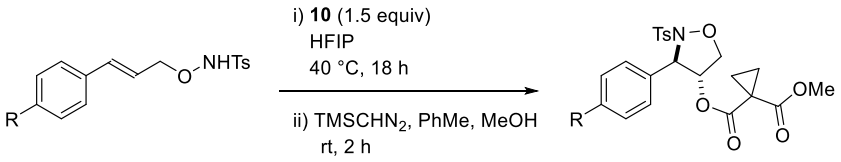
(±)-2,2-Diphenyl-1-tosylpyrrolidin-3-ol 535j



Reaction of *N*-(4,4-diphenylbut-3-en-1-yl)-4-methylbenzenesulfonamide **534j** (80 mg, 0.21 mmol) and malonoyl peroxide **10** (41 mg, 0.32 mmol) in HFIP (0.4 mL) according to General Procedure **13** followed by hydrolysis in 1 M NaOH:THF (2.1 mL, 1:1) gave the crude alcohol. Purification by silica gel flash column chromatography (hexane:EtOAc 6:4) gave the *title* compound **535j** (68 mg, 0.17 mmol, 82%) as a white solid.

m.p. 153–154 °C; IR (thin film)/cm^{-1}: 3502, 3054, 2980, 2954; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.47 (m, 2H), 7.43–7.34 (m, 3H), 7.30–7.25 (m, 3H), 7.20–7.17 (m, 2H), 6.96 (d, *J* = 8.1 Hz, 2H), 6.86–6.83 (m, 2H), 4.79 (dd, *J* = 7.9, 6.0 Hz, 1H), 4.04 (ddd, *J* = 9.4, 8.4, 3.9 Hz, 1H), 3.62 (ddd, *J* = 9.4, 8.4, 7.2 Hz, 1H), 2.33 (s, 3H), 2.17–2.10 (m, 1H), 1.77–1.67 (m, 1H), 1.43 (bs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3, 139.0, 138.5, 138.2, 130.8, 130.0, 128.9, 127.93, 127.89, 127.7, 126.6, 79.2, 77.1, 46.4, 30.6, 21.5 (1 carbon missing); LRMS (ES + APCI) *m/z* 394.0 $[M+H]^+$; HRMS calculated for $C_{23}H_{23}NO_3S$ $[M+H]^+$ 394.1471, found 394.1471.

5.2.2 General Procedure 14: Cyclisation for the synthesise of *iso*xazolidinones

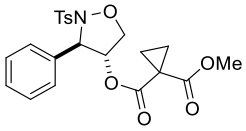


585 R = Cl
586 R = H

592 R = Cl
588 R = H

Malonoyl peroxide **10** (1.5 equiv) was added to a solution of alkene **585** or **586** (1.0 equiv) in HFIP (0.5 M). The mixture was stirred at 40 °C for 18 h before removal of the solvent by rotary evaporation. The residue was re-dissolved in PhMe (0.2 M) and MeOH (0.5 M) and a solution of TMS-CHN_2 in Et_2O (2.0 equiv) was added dropwise. The resulting mixture was stirred at rt for 2 h before the solvents were evaporated under reduced pressure. Purification of the crude material by silica gel flash column chromatography with petroleum ether (40–60 °C): Et_2O mixtures afforded the *target* compounds.

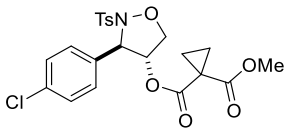
(±)-1-Methyl 1-((3*R*,4*S*)-3-phenyl-2-tosylisoxazolidin-4-yl) cyclopropane-1,1-dicarboxylate 588



To a solution of *N*-(cinnamyloxy)-4-methylbenzenesulfonamide **586** (185 mg, 0.43 mmol) in HFIP (0.9 mL) was added malonoyl peroxide **10** (82 mg, 0.65 mmol) according to General Procedure **14** to give crude isoxazolidine (1:10 *cis*:*trans*) which was dissolved in PhMe (2.2 mL) and MeOH (0.9 mL) before the addition of TMS-CHN_2 (2 M in Et_2O, 0.43 mL, 0.86 mmol) according to General Procedure **14**. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 6:4) afforded the *title* compound **588** (154 mg, 0.35 mmol, 80% over two steps) as a colourless oil.

IR (thin film)/cm^{-1}: 3028, 3062, 2954, 1727; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 7.3 Hz, 2H), 7.38–7.35 (m, 4H), 7.31 (t, *J* = 7.3 Hz, 1H), 5.52 (ddd, *J* = 6.0, 4.1, 1.7 Hz, 1H), 5.56 (bs, 1H), 4.38 (dd, *J* = 9.3, 6.2 Hz, 1H), 4.34 (dd, *J* = 9.3, 4.1 Hz, 1H), 3.80 (s, 3H), 2.46 (s, 3H), 1.67–1.51 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 169.4, 145.2, 137.3, 133.9, 129.8, 129.2, 129.0, 128.3, 126.6, 83.8, 74.4, 67.0, 53.0, 27.9, 21.9, 17.6, 17.5; LRMS (ES + APCI) *m/z* 463.0 $[M+NH_4]^+$; HRMS calculated for $C_{22}H_{23}NO_7S$ $[M+H]^+$ 446.1268, found 446.1266.

(±)-1-((3*R*,4*S*)-3-(4-Chlorophenyl)-2-tosylisoxazolidin-4-yl) 1-methylcyclopropane-1,1-dicarboxylate 592

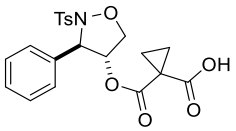


To a solution of (*E*)-*N*-((3-(4-chlorophenyl)allyl)oxy)-4-methylbenzenesulfonamide **585** (66 mg, 0.20 mmol) in HFIP (0.4 mL) was added malonoyl peroxide **10** (38 mg, 0.29 mmol) according to General Procedure **14** to give crude isoxazolidine (1:7 *cis*:*trans*) which was dissolved in PhMe (1.0 mL) and MeOH (0.4 mL) before the addition of TMS-CHN_2 (2 M in Et_2O, 0.2 mL, 0.40 mmol) ording to General Procedure **14**. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 6:4) afforded the *title* compound **592** (80 mg, 0.17 mmol, 85% over 2 steps) as a white solid.

m.p. 110–112 °C; IR (thin film)/cm^{-1}: 3040, 2930, 2904, 1719, 1697; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 5.46 (td, *J* = 5.2, 1.6 Hz, 1H), 5.41 (bs, 1H), 4.35 (d, *J* = 5.2 Hz, 2H), 3.79 (s, 3H), 2.46 (s, 3H), 1.66–1.52 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 169.5, 145.3, 135.8, 134.3, 133.6, 129.9, 129.2, 129.1, 128.0, 83.7, 74.2, 66.5, 53.0, 27.9, 21.9, 17.6, 17.5; LRMS (ES + APCI) *m/z* 497.0 $[M+NH_4]^+$; HRMS calculated for $C_{22}H_{22}{}^{35}ClNO_7S$ $[M+H]^+$ 480.0884, found 480.0879.

5.2.2.1 Reaction Intermediate Isolation

(±)-1-((((3*R*,4*S*)-3-Phenyl-2-tosylisoxazolidin-4-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 587



To a solution of *N*-(cinnamyloxy)-4-methylbenzenesulfonamide **586** (151 mg, 0.50 mmol) in HFIP (1.0 mL) was added malonoyl peroxide **10** (96 mg, 0.75 mmol) according to General Procedure **14** (without the TMS-CHN_2 methyl ester formation) to give crude *iso*xazolidine (1:10 *cis*:*trans*). Purification by silica gel flash column chromatography (EtOAc then EtOAc:AcOH 0.5%) afforded the *title* compound **587** (178 mg, 0.41 mmol, 83%) as a white solid for characterisation and X-ray analysis purposes.

m.p. 137–139 °C; IR (thin film)/cm^{-1}: 3550, 2930, 2852,1716, 1660; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.19 (bs, 1H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.44–7.34 (m, 7H), 5.61 (ddd, *J* = 6.0, 3.1, 0.7 Hz, 1H),

5.54 (bs, 1H), 4.44 (dd, *J* = 9.6, 3.1 Hz, 1H), 4.39 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.47 (s, 3H), 2.18–2.14 (m, 1H), 2.06–2.03 (m, 1H), 1.99–1.93 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 170.0, 145.5, 136.3, 133.7, 129.9, 129.2, 129.1, 128.7, 126.5, 84.9, 74.6, 66.9, 25.6, 23.5, 23.2, 21.9; LRMS (ES + APCI) *m/z* 432.0 $[M+H]^+$; HRMS calculated for $C_{21}H_{21}NO_7S$ $[M-H]^-$ 430.0966, found 430.0954.

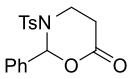
5.3 Further chemistry with Pyrrolidine 535a

(±)-2-Phenyl-1-tosylpyrrolidin-3-one 542

(2*R*,3*S*)-2-phenyl-1-tosylpyrrolidin-3-ol **535a** (100 mg, 0.32 mmol) was dissolved in degassed MeCN (1.6 mL). IBX (265 mg, 0.95 mmol) was added and the mixture was stirred at 80 °C for 18 h. The mixture was filtered through Celite® and the solvent removed under reduced pressure. Purification by silica gel flash column chromatography (hexane:EtOAc 4:6) afforded the *title* compound **542** (84 mg, 0.27 mmol, 85%) as a colourless oil.

m.p. 124–126 °C, Lit[189] [140–141 °C]; IR (thin film)/cm^{-1}: 2950, 2924, 2855, 1753; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.32–7.27 (m, 7H), 4.59 (s, 1H), 3.94 (ddd, *J* = 10.8, 8.9, 5.6 Hz, 1H), 3.72 (ddd, *J* = 10.8, 8.5, 7.6 Hz, 1H), 2.63–2.56 (m, 1H), 2.49–2.43 (m, 1H), 2.43 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.3, 144.4, 135.6, 133.9, 130.0, 128.8, 128.4, 127.8, 127.0, 67.3, 44.2, 35.9, 21.7; LRMS (ES + APCI) *m/z* 316.1 $[M+H]^+$.

(±)-2-Phenyl-3-tosyl-1.3-oxazinan-6-one 543



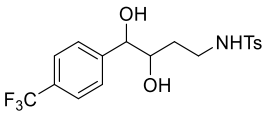
2-Phenyl-1-tosylpyrrolidin-3-one **542** (68 mg, 0.2 mmol) was dissolved in CH_2Cl_2 (0.6 mL). *m*-CPBA (67 mg, 0.4 mmol) was added at 0 °C and the reaction was stirred for 18 h. The mixture was washed with Na_2SO_4 (3 × 10 mL) followed by $NaHCO_3$ (3 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was revoved under reduced pressure. Purification by silica gel flash column chromatography (hexane:EtOAc 7:3) afforded the *title* compound **543** (45 mg, 0.1 mmol, 62%) as a colourless oil.

IR (thin film)/cm^{-1}: 2930, 2914, 2897, 2861; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.47–7.37 (m, 7H), 7.20 (bs, 1H), 3.81–3.74 (m, 1H), 3.41 (ddd, *J* = 14.4, 8.4, 7.4 Hz, 1H), 2.46

(s, 3H), 2.26–2.21 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 145.3, 136.6, 136.0, 130.6, 129.5, 129.4, 127.8, 126.0, 87.0, 37.6, 28.3, 21.8; LRMS (ES + APCI) *m/z* 332.1 $[M+H]^+$.

5.4 Undesired product from oxidative hetereocyclisation

(±)-*N*-(3,4-Dihydroxy-4-(4-trifluoromethyl)phenyl)butyl)-4-methylbenzenesulfonamide 594

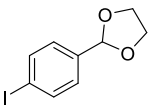


Reaction of (*E*)-4-methyl-*N*-(4-(4-trifluoromethyl)phenyl)but-3-en-1-yl)benzenesulfonamide **534i** (50 mg, 0.14 mmol) and malonoyl peroxide **10** (35 mg, 0.27 mmol) in HFIP (0.3 mL) according to General Procedure **13** followed by hydrolysis in 1 M NaOH:THF (2.1 mL, 1:1). Purification by silica gel flash column chromatography (hexane:EtOAc 4:6) gave undesired *title* compound **594** (34 mg, 0.08 mmol, 62%) as a white solid.

m.p. 140–142 °C; IR (thin film)/cm^{-1}: 3342, 3103, 2974, 2878; ^{1}H NMR (400 MHz, CD_3CN) δ 7.67–7.63 (m, 4H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 5.52 (t, *J* = 5.9 Hz, 1H), 4.45 (t, *J* = 4.8 Hz, 1H), 3.68 (d, *J* = 4.6 Hz, 1H), 3.64–3.58 (m, 1H), 3.13 (d, *J* = 5.3 Hz, 1H), 2.93–2.88 (m, 2H), 2.41 (s, 3H), 1.45–1.40 (m, 2H); ^{13}C NMR (101 MHz, CD_3CN) δ 147.8, 144.4, 138.4, 130.6, 129.7 ($J_{C\text{-}F}$ = 31.8 Hz), 128.4, 127.8, 125.8 ($J_{C\text{-}F}$ = 3.3 Hz), 125.5 ($J_{C\text{-}F}$ = 271.3 Hz), 76.8, 73.8, 41.2, 33.3, 21.4; LRMS (ES + APCI) *m/z* 404.0 $[M+H]^+$.

5.5 Synthesis of compound 546

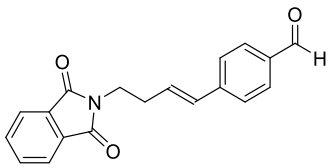
2-(4-Iodophenyl)-1,3-dioxolane 548[157]



4-Iodobenzaldehyde **547** (1.0 g, 4.3 mmol) in 3 Å molecular sieves was dissolved in $CHCl_3$ (30 mL) before the addition of *p*-TsOH (0.2 g, 0.9 mmol) followed by ethylene glycol (10 mL, 179.7 mmol). The resulting mixture was heated to 80 °C for 16 h. After allowing to cool to rt the mixture was washed with H_2O (50 mL) and $NaHCO_3$ (50 mL). The organics were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* affording the *title* compound **548** (1.1 g, 4.0 mmol, 93%) as a white solid without further purification.

m.p. 47–49 °C, Lit[157] [48–50 °C]; IR (thin film)/cm^{-1}: 2990, 2880; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 5.76 (s, 1H), 4.12–4.01 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6, 128.5, 103.3, 65.5; LRMS (ES + APCI) *m/z* 277.1 $[M+H]^+$.

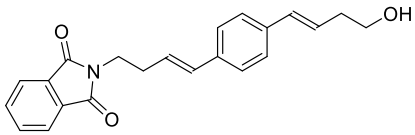
(*E*)-4-(4-(1,3-Dioxoisoindolin-2-yl)but-1-en-1-yl)benzaldehyde 549



2-(4-Iodophenyl)-1,3-dioxolane **548** (3.6 g, 13.1 mmol) and Et_3N (3.3 mL, 23.9 mmol) were dissolved in MeCN (220 mL) followed by addition of 2-(but-3-en-1-yl)isoindoline-1,3-dione **532** (2.4 g, 11.9 mmol), tri-*o*-tolylphosphine (363 mg, 1.2 mmol) and $Pd(OAc)_2$ (134 mg, 0.6 mmol) according to General Procedure **11** the mixture was heated at reflux for 16 h. Purification by silica gel flash column chromatography (hexane:EtOAc 9:1) afforded the *title* compound **549** (1.0 g, 3.3 mmol, 28%) as a white solid.

m.p. 144–145 °C; IR (thin film)/cm^{-1}: 2816, 2723, 1703, 1682; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.86–7.83 (m, 2H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.72–7.70 (m, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.37 (dt, *J* = 16.0, 7.1 Hz, 1H), 3.89 (t, *J* = 7.1 Hz, 2H), 2.70–2.64 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.8, 168.5, 143.4, 135.4, 134.1, 132.2, 131.8, 130.4, 130.2, 126.8, 123.4, 37.4, 32.5; LRMS (ES + APCI) *m/z* 306.2 $[M+H]^+$; HRMS calculated for $C_{19}H_{15}NO_3$ $[M+H]^+$ 306.1126, found 306.1125.

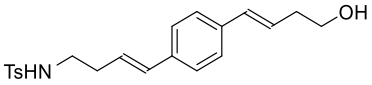
2-((*E*)-4-(4-((*E*)-4-Hydroxybut-1-en-1-yl)phenyl)but-3-en-1-yl)isoindoline-1,3-dione 550



To a three-neck round-bottom flask, dried and flushed with argon, was added (3-hydroxypropyl)triphenylphosphonium bromide **366b** (1.30 g, 3.34 mmol) in anhydrous THF (7.4 mL). The suspension was cooled to -10 °C using a NaCl/ice bath. A 1 M solution of LiHMDS (7.8 mL, 7.8 mmol) was added dropwise. The mixture was stirred at -10 °C for 1 h. After this time, (*E*)-4-(4-(1,3-dioxoisoindolin-2-yl)but-1-en-1-yl)benzaldehyde **549** (0.9 g, 2.8 mmol) in anhydrous THF (2.1 mL) was added dropwise and stirred -10 °C for 2 h according to General Procedure **7**. The mixture was allowed to cool to rt and stirred for a further 15 h. A saturated aqueous solution of NH_4Cl was then added. The organic layer was extracted with Et_2O (2 × 100 mL), dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by silica gel flash column chromatography (hexane:EtOAc 7:3) afforded the *title* compound **550** (0.3 g, 0.6 mmol, 20%) as a white solid.

IR (thin film)/cm^{-1}: 3560, 2925, 2855, 1720, 1669; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.79 (m, 2H), 7.70–7.65 (m, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.39 (d, *J* = 15.9 Hz, 2H), 6.22–6.11 (m, 2H), 3.83 (t, *J* = 7.1 Hz, 2H), 3.69 (t, *J* = 6.8 Hz, 2H), 2.63–2.57 (m, 2H), 2.46–2.40 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 136.8, 136.1, 134.0, 132.4, 132.2, 131.5, 126.9, 126.4, 126.3, 125.9, 123.3, 62.5, 37.7, 36.7, 32.4; LRMS (ES + APCI) *m/z* 348.0 $[M+H]^+$; HRMS calculated for $C_{22}H_{21}NO_3$ $[M+H]^+$ 348.1598, found 348.1594.

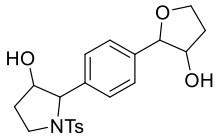
_N_-((_E_)-4-(4-((_E_)-4-Hydroxybut-1-en-1-yl)phenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide 546



To a solution of 2-((*E*)-4-(4-((*E*)-4-hydroxybut-1-en-1-yl)phenyl)but-3-en-1-yl)isoindoline-1,3-dione **550** (200 mg, 0.6 mmol) in EtOH (2.2 mL) was added hydrazine monohydrate (56 µL, 1.2 mmol). The mixture was stirred at rt for 10 min and at reflux for 30 min. The solution was allowed to cool to rt a 1 M solution of NaOH was added (50 mL). Ethanol was evaporated before extracting the organics from the aqueous with EtOAc (3 × 50 mL). The combined oganics were washed with brine (100 mL), dried over $MgSO_4$, filtered and 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 (1.5 mL) under an atmosphere of argon and Et_3N (96 µL, 0.69 mmol) was added. The mixture was cooled to 0 °C, *p*-TsCl (88 mg, 0.5 mmol) and DMAP (17 mg, 0.1 mmol) were added and the resulting mixture was stirred at rt for 24 h. The solution was then diluted with CH_2Cl_2 (50 mL), washed with 2 M HCl (100 mL) and brine (100 mL). The combined organics were dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. Purification by silica gel flash column chromatography (hexane:EtOAc 1:1) afforded the *title* compound **546** (80 mg, 0.2 mmol, 37%) as a white solid.

m.p. 110–112 °C; IR (thin film)/cm^{-1}: 3287, 3255, 3209, 2960, 2919, 2872, 2855, 1723, 1714; ^{1}H NMR (400 MHz, $CDCl_3$) 7.74 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 4H), 7.21 (d, *J* = 8.3 Hz, 2H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.32 (d, *J* = 15.9 Hz, 1H), 6.20 (dt, *J* = 15.9, 7.1 Hz, 1H), 5.96 (dt, *J* = 15.9, 7.1 Hz, 1H), 4.61 (t, *J* = 6.0 Hz, 1H), 3.76 (t, *J* = 6.3 Hz, 2H), 3.12–3.07 (m, 2H), 2.51–2.45 (m, 2H), 2.42 (s, 3H), 2.38–2.3 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 137.1, 136.6, 135.9, 133.0, 132.5, 129.9, 127.3, 126.50, 126.45, 126.4, 125.4, 62.2, 42.7, 36.6, 33.2, 21.7; LRMS (ES + APCI) *m/z* 389.1 $[M+NH_4]^+$; HRMS calculated for $C_{21}H_{25}NO_3S$ $[M+H]^+$ 372.1628, found 372.1630.

2-(4-(3-Hydroxytetrahydrofuran-2-yl)phenyl)-1-tosylpyrrolidin-3-ol 553 or **554**



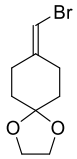
Reaction of *N*-((*E*)-4-(4-((*E*)-4-Hydroxybut-1-en-1-yl)phenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide **546** (30 mg, 0.08 mmol) and malonoyl peroxide **10** (23 mg, 0.18 mmol) in HFIP (0.2 mL) according to General Procedure **13** followed by hydrolysis in 1 M NaOH:THF (0.8 mL, 1:1) gave the crude alcohol. Purification by silica gel flash column chromatography (hexane:EtOAc 6:4) afforded the *title* compound **553** or **554** (25 mg, 0.06 mmol, 77%) as a colourless oil.

IR (thin film)/cm^{-1}: 3456, 2922, 2885, 2854; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.36–7.30 (m, 6H), 4.75 (d, *J* = 3.5 Hz, 1H), 4.64 (bs, 1H), 4.27 (dt, *J* = 6.5, 3.4 Hz, 1H), 4.23–4.10 (m, 3H), 3.75–3.69 (m, 1H), 3.54–3.48 (m, 1H), 2.43 (s, 3H), 2.24–2.14 (m, 1H), 2.06–1.92 (m, 3H), 1.76–1.71 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7, 140.3, 139.4, 138.8, 129.7, 127.9, 126.4, 125.9, 87.4, 79.0, 71.8, 67.3, 46.9, 34.4, 31.5, 29.9, 21.7; LRMS (ES + APCI) *m/z* 404.1 $[M+H]^+$; HRMS calculated for $C_{21}H_{25}NO_5S$ $[M+H]^+$ 404.1532, found 404.1527.

5.6 Synthesis of compound 555

5.6.1 Strategy 1

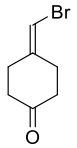
8-(Bromoethylene)-1,4-dioxaspiro[4.5]decane 557



To a cooled (-78 °C) solution of (bromomethyl)triphenylphosphonium bromide (7.4 g, 17.0 mmol) in anhydrous THF (40 mL) was dropwise added NaHMDS (1 M in THF, 17.0 mL, 17.0 mmol). After stirring for 1 h, a solution of 1,4-cyclohexanedione monoethylene acetal **556** (2.2 g, 14.2 mmol) in THF (10 mL) was added. The resulting mixture was allowed to warm at rt and stirred for 18 h. Petroleum ether (100 mL) was added and the suspension was filtered through Celite® and the solvent was removed under reduced pressure. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 9:1) afforded the *title* compound **557** as (2.4 g, 10.3 mmol, 73%) a colourless oil.

IR (thin film)/cm^{-1}: 2982, 2877, 2812; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92–5.91 (m, 1H), 3.99–3.95 (m, 4H), 2.51–2.47 (m, 2H), 2.36–2.32 (m, 2H), 1.72–1.67 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 108.5, 99.1, 64.6, 35.5, 34.5, 32.2, 28.0.

4-(Bromomethylene)cyclohexane-1-one 558

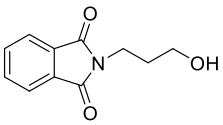


To a solution of 8-(bromoethylene)-1,4-dioxaspiro[4.5]decane **557** (400 mg, 1.72 mmol) in THF (19 mL) was added HCl 10% (9.4 mL). The mixture was stirred at rt for 18 h. Then, EtOAc:H_2O (1:1, 50 mL) was added and the layers were separated. The organics were further extracted from the aqueous with EtOAc (3 × 50 mL), dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. Purification by silica gel flash column chromatography (hexane:EtOAc 1:1) afforded the *title* compound **558** (269 mg, 1.42 mmol, 83%) as a colourless oil.

IR (thin film)/cm^{-1}: 2993, 2841, 1755; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14–6.13 (m, 1H), 2.70–2.66 (m, 2H), 2.60–2.56 (m, 2H), 2.47 (t, *J* = 7.1 Hz, 2H), 2.41 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.2, 140.0, 101.9, 40.3, 39.4, 32.3, 28.7.

5.6.2 Strategy 2

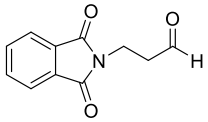
2-(3-Hydroxypropyl)isoindoline-1,3-dione 567



To a solution of 3-aminopropan-1-ol (2.0 mL, 26.6 mmol) in PhMe (40 mL) was added Et_3N (3.7 mL, 26.6 mmol) followed by phthalic anhydride **564** (4.0 g, 26.6 mmol). The reaction was stirred for 3 h at 125 °C while removing H_2O with a Dean-Stark apparatus. The mixture was allowed to cool to rt and the solvent was evaporated affording the *title* compound **567** (5.3 g, 25.9 mmol, 97%) as a white solid without further purification.

m.p. 76–78 °C, Lit[190] [73–75 °C]; IR (thin film)/cm^{-1}: 3521, 2941, 2839; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.83 (m, 2H), 7.75–7.70 (m, 2H), 3.86 (t, *J* = 5.8 Hz, 2H), 3.62 (t, *J* = 5.8 Hz, 2H), 1.91–1.85 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 134.2, 132.1, 123.5, 59.2, 34.4, 31.4; LRMS (ES + APCI) *m/z* 206.0 $[M+H]^+$.

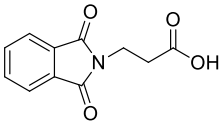
3-(1,3-Dioxoisoindolin-2-yl)propanal 568



To a cooled (-78 °C) solution of oxalyl chloride (2.0 mL, 21.9 mmol) in anhydrous CH_2Cl_2 (12.1 mL) was added dry DMSO (4.7 mL, 65.7 mmol) dropwsie. The mixture was stirred for 30 min before the addition of 2-(3-hydroxypropyl)isoindoline-1,3-dione **567** (3.0 g, 14.6 mmol) in anhydrous CH_2Cl_2 (5.5 mL). The mixture was further stirred for 30 min followed by addition of DIPEA (12.7 mL, 73.0 mmol) and stirring was continued for 30 min. Then, the mixture was warmed to rt and a solution of NaH_2PO_4 (2.6 g, 21.9 mmol) in H_2O (5 mL) was added. The organic layer was extracted from the aqueous with CH_2Cl_2 (3 × 50 mL), washed with 1 M HCl (100 mL) and dried over $MgSO_4$. The solvent was removed by rotary evaporation to give the *title* compound **568** (2.9 g, 14.3 mmol, 99%) as a white solid without further purification.

m.p. 116–117 °C, Lit[191] [116–118 °C]; IR (thin film)/cm^{-1}: 2941, 2839 1720; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (t, *J* = 1.3 Hz, 1H), 7.86–7.84 (m, 2H), 7.73–7.71 (m, 2H), 4.04 (t, *J* = 7.0 Hz, 2H), 2.88 (td, *J* = 7.0, 1.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.6, 168.1, 134.3, 132.1, 123.5, 42.5, 31.8; LRMS (ES + APCI) *m/z* 204.0 $[M+H]^+$.

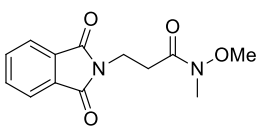
3-(1,3-Dioxoisoindolin-2-yl)propanoic acid 565



Phthalic anhydride **564** (2.0 g, 13.5 mmol) was mixed with 3-aminopropanoic acid (1.2 g, 13.5 mmol) and the mixture was warmed to 185 °C. The solids began to melt until obtain a completely homogeneous solution. The stirring was continued for 15 min at the same temperature. The mixture was allowed to cool to rt and the product solidify affording pure 3-(1,3-dioxoisoindolin-2-yl)propanoic acid **565** (2.9 g, 13.2 mmol, 97%) as a white solid without any further purification.

m.p. 169–170 °C, Lit[192] [161–163 °C]; IR (thin film)/cm^{-1}: 3023, 2972, 2874, 1702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.83 (m, 2H), 7.74–7.70 (m, 2H), 4.00 (t, *J* = 7.3 Hz, 2H), 2.79 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 168.1, 134.2, 132.2, 123.6, 33.7, 32.6; LRMS (ES + APCI) *m/z* 219.9 $[M+H]^+$.

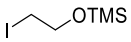
3-(1,3-Dioxoisoindolin-2-yl)-*N*-methoxy-*N*-methylpropanamide 566



To a solution of 3-(1,3-dioxoisoindolin-2-yl)propanoic acid **565** (2.96 g, 13.50 mmol) and HATU (5.13 g, 13.50 mmol) in EtOAc (135 ml) was added *N*-ethyl-*N*-isopropylpropan-2-amine (2.3 ml, 13.50 mmol). The mixture was stirred for 5 min followed by the addition of *N*,*O*-dimethylhydroxylamine (0.83 g, 13.50 mmol). The resulting mixture was stirred at rt for 18 h. Upon completion H_2O (100 mL) was added the layers were separated. The organics were further extracted from the aqueous layer, washed with brine (200 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. Purification by silica gel flash column chromatography (hexane:EtOAc 2:8) afforded the *title* compound **566** (269 mg, 1.42 mmol, 83%) as a colourless oil.

m.p. 73–75 °C; IR (thin film)/cm^{-1}: 2951, 2914, 1712, 1645; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.83 (m, 2H), 7.71–7.69 (m, 2H), 4.02 (t, *J* = 7.3 Hz, 1H), 3.67 (s, 3H), 3.16 (s, 3H), 2.85 (bt, *J* = 6.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.83, 168.3, 134.1, 132.3, 123.4, 61.4, 34.0, 32.3, 30.9; LRMS (ES + APCI) *m/z* 263.0 $[M+H]^+$; HRMS calculated for $C_{13}H_{14}N_2O_4$ $[M+H]^+$ 263.1026, found 263.1025.

(2-Iodoethoxy)trimethylsilane 570

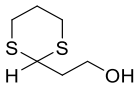


Chlorotrimethylsilane (3.3 mL, 26.0 mmol) was added to a solution of 2-iodoethan-1-ol (2.0 mL, 25.6 mmol) and Et_3N (3.7 mL, 26.5 mmol) in THF (20 mL) at 0°. The resulting mixture was stirred for 30 min at 0 °C and for further 6 h at rt. Removal of the solvent under reduced pressure afforded pure (2-iodoethoxy)trimethylsilane **570** (5.2 g, 21.3 mmol, 83%) as a colourless oil without further purification

IR (thin film)/cm^{-1}: 2955, 2899, 2847, 1250, 1075, 836; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (t, *J* = 6.9 Hz, 2H), 3.20 (t, *J* = 6.9 Hz, 2H), 0.14 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 64.0, 6.7, 0.2; LRMS (GC-CI) m/z 228.9 $[M-CH_3]^+$.

5.6.3 Strategy 3

2-(1,3-Dithian-2-yl)ethan-1-ol 573

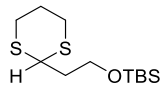


To a solution of 1,3-dithiane **572** (1.4 g, 12.0 mmol) in anhydrous THF (60 mL) was added *n*BuLi (9.6 mL, 24.0 mmol) dropwise at rt. The resulting mixture was stirred for 15 min before cooling the mixture at -20 °C for the addition of ethylene oxide (0.5 mL, 12.0 mmol) in anhydrous THF (15 mL). The mixture was stirred for 45 min at -10 °C before quenching it with NH_4Cl (50 mL). Then, layers

were separated and the aqueous phase was further extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation to afford the *title* compound **573** (1.7 g, 10.3 mmol, 86%) as a yellow oil without further purification.

IR (thin film)/cm^{-1}: 2974, 2866, 2843; ^1H NMR (400 MHz, $CDCl_3$) δ 4.24 (t, *J* = 7.1 Hz, 1H), 3.83 (t, *J* = 5.9 Hz, 2H), 2.93–2.81 (m, 4H), 2.16–2.08 (m, 1H), 2.05–2.00 (m, 2H), 1.95–1.83 (m, 1H), 1.69 (bs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 59.9, 44.5, 38.1, 30.4, 30.1, 26.0; LRMS (ES + APCI) *m/z* 165.0 $[M+H]^+$.

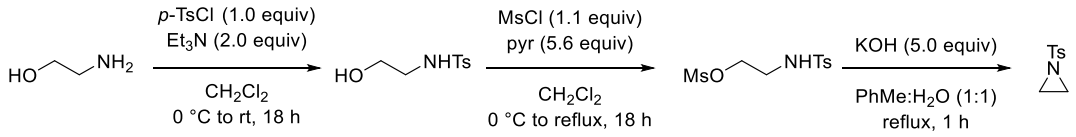
(2-(1,3-Dithian-2-yl)ethoxy)(*tert*-butyl)dimethylsilane 574



To a solution of 2-(1,3-dithian-2-yl)ethan-1-ol **573** (1.0 g, 6.1 mmol) in THF (6 mL) was added imidazole (0.8 g, 12.2 mmol) followed by TBSCl (1.4 g, 9.1 mmol). The resulting mixture was stirred at rt for 2 h. H_2O (10 mL) was added and the organics were extracted from the aqueous layer with Et_2O (3 × 50 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. Purification by silica gel flash column chromatography (hexane:EtOAc 95:5) afforded the *title* compound **574** (1.5 g, 5.4 mmol, 89%) as a colourless oil.

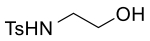
IR (thin film)/cm^{-1}: 2853, 2830; ^1H NMR (400 MHz, $CDCl_3$) δ 4.18 (t, *J* = 7.1 Hz, 1H), 3.77 (t, *J* = 6.4 Hz, 2H), 2.90–2.81 (m, 4H), 2.14–2.06 (m, 1H), 1.98–1.9 (m, 2H), 1.93–1.83 (m, 1H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 59.6, 44.0, 38.6, 30.3, 26.2, 26.1, 25.9, 18.5, 5.2; LRMS (ES + APCI) *m/z* 279.0 $[M+H]^+$.

Synthesis of 1-Tosylaziridine 575[184]



578 73% **579** 45% **580** 44% **575**

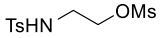
_N_-(2-Hydroxyethyl)-4-methylbenzenesulfonamide 579[184]



To a a cooled (0 °C) solution of ethanolamine **578** (2.0 mL, 33.1 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (4.9 mL, 66.2 mmol) followed by *p*-TsCl (6.3 g, 33.1 mmol). The resulting mixture was stirred at rt for 18 h. The mixture was then washed with $NaHCO_3$ (20 mL). The organics were dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. Purification by silica gel flash column chromatography (petroleum ether (40–60 °C):EtOAc 1:1) afforded the *title* compound **579** (5.2 g, 24.2 mmol, 73%) as a white solid.

m.p. 52–54 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 5.39 (bs, 1H), 3.70–3.66 (m, 2H), 3.10–3.05 (m, 2H), 2.56 (bs, 1H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8, 136.8, 129.9, 127.3, 61.4, 45.3, 21.6; LRMS (ES + APCI) *m/z* 232.9 $[M+NH_4]^+$.

2-((4-Methylphenyl)sulfonamido)ethyl methanesulfonate 580[184]



To a cooled (0 °C) solution of pyridine (11 mL) in CH_2Cl_2 (30 mL) was added MsCl (2.0 mL, 25.8 mmol). The resulting mixture was stirred at 0 °C for 20 min. *N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide **579** (5.2 g, 24.2 mmol) was added in CH_2Cl_2 (30 mL) and the resulting mixture was then stirred at rt for 20 min followed by reflux for 18 h. The mixture was allowed to cool to rt and was washed with 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 (petroleum ether (40–60 °C):EtOAc 1:1) afforded the *title* compound **580** (3.2 g, 10.9 mmol, 45%) as a white solid.

m.p. 73–74 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 4.94 (bs, 1H), 3.27 (t, *J* = 5.1 Hz, 2H), 3.33–3.29 (m, 2H), 3.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1, 138.8, 130.1, 127.2, 68.4, 42.5, 37.7, 21.7; LRMS (ES + APCI) *m/z* 311.0 $[M+NH_4]^+$.

1-Tosylaziridine 575[150]

To a solution of 2-((4-methylphenyl)sulfonamido)ethyl 4-methylbenzenesulfonate **580** (1.0 g, 3.4 mmol) in PhMe (6.0 mL) was added KOH (0.9 g, 17.0 mmol) in H_2O (5 mL). The resulting biphasic mixture was heated at 90 °C for 1 h. The layers were separated and the aqueous was further extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with brine (100 mL), dried

over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation affording the *title* compound **575** (0.3 g, 1.5 mmol, 44%) as a yellow solid without further purification.

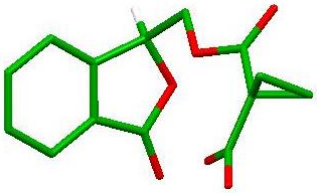
m.p. 55–56 °C, Lit[193] [52–54 °C]; ^{1}H NMR (500 MHz, DMSO) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 2.41 (s, 3H), 2.34 (s, 4H); ^{13}C NMR (101 MHz, DMSO) δ 144.6, 134.3, 129.9, 127.7, 27.1, 21.0; LRMS (ES + APCI) *m/z* 198.0 $[M+H]^+$.

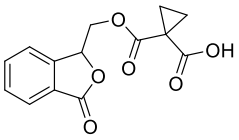
Appendix

1 X-Ray Crystallographic Data

X-Ray data for (±)-1-(((3-oxo-1,3-Dihydroisobenzofuran-1-yl)methoxy)carbonyl)cycloporpane-1-carboxylic acid 345

CCDC 1452327





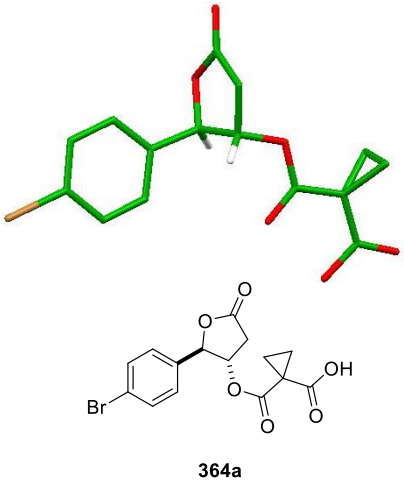
345

Table **25**. Crystal data and structure refinement for **345**.

Identification code	tom_caf369	
Empirical formula	$C_{14}H_{12}O_6$	
Formula weight	276.24	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.9639(7) Å	α= 92.174(7)°.
	b = 8.2187(7) Å	β= 109.731(7)°.
	c = 9.6010(7) Å	γ = 92.209(7)°.
Volume	590.21(8) $Å^3$	
Z	2	
Density (calculated)	1.554 Mg/m^3	
Absorption coefficient	0.123 mm^{-1}	
F(000)	288	
Crystal size	0.30 x 0.30 x 0.12 mm^3	
Theta range for data collection	3.26 to 29.01°.	
Index ranges	-10<=h<=10, -11<=k<=11, -13<=l<=12	
Reflections collected	9615	
Independent reflections	2915 [R(int) = 0.0315]	
Completeness to theta = 27.00°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.95182	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2915 / 0 / 185	
Goodness-of-fit on F^2	1.029	
Final R indices [I>2sigma(I)]	R1 = 0.0375, wR2 = 0.0851	
R indices (all data)	R1 = 0.0475, wR2 = 0.0923	
Largest diff. peak and hole	0.323 and -0.228 $e.Å^{-3}$	

X-Ray data for (±)-1-((((2*R*,3*S*)-2-(4-Bromophenyl)-5-oxotetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 364a

CCDC 1452326



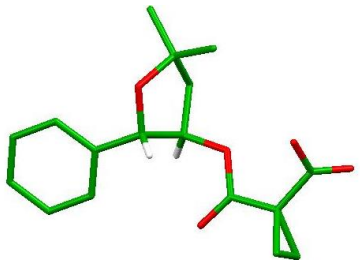
364a

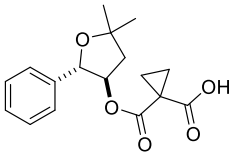
Table **26**. Crystal data and structure refinement for **364a**.

Identification code	tom_caf_564	
Empirical formula	$C_{15}H_{13}BrO_6$	
Formula weight	369.16	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 2_1/c	
Unit cell dimensions	a = 14.5589(5) Å	α= 90°.
	b = 5.3450(2) Å	β= 98.725(4)°.
	c = 18.6931(8) Å	γ = 90°.
Volume	1437.81(10) Å^3	
Z	4	
Density (calculated)	1.705 Mg/m^3	
Absorption coefficient	2.886 mm^{-1}	
F(000)	744	
Crystal size	0.4 x 0.35 x 0.08 mm^3	
Theta range for data collection	2.795 to 28.989°.	
Index ranges	-19<=h<=19, -7<=k<=6, -24<=l<=24	
Reflections collected	12579	
Independent reflections	3605 [R(int) = 0.0374]	
Completeness to theta = 27.000°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.54610	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3605 / 0 / 203	
Goodness-of-fit on F^2	1.058	
Final R indices [I>2sigma(I)]	R1 = 0.0336, wR2 = 0.0685	
R indices (all data)	R1 = 0.0466, wR2 = 0.0736	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.449 and -0.482 e.Å^{-3}	

X-Ray data for (±)-1-((((2*R*,3*S*)-5-5-Dimethyl-2-phenyltetrahydrofuran-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 374h

CCDC 1452328



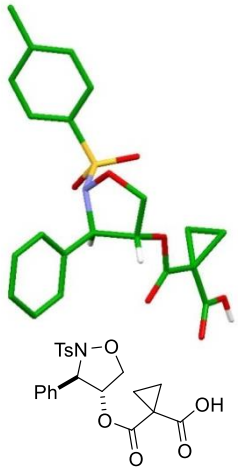


374h

Table **27**. Crystal data and structure refinement for **374h**.

Identification code	tom_caf104	
Empirical formula	$C_{17}H_{20}O_5$	
Formula weight	304.33	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 10.6142(6) Å	α= 90°.
	b = 6.9676(3) Å	β= 97.064(5)°.
	c = 21.0046(11) Å	γ = 90°.
Volume	1541.61(14) $Å^3$	
Z	4	
Density (calculated)	1.311 Mg/m^3	
Absorption coefficient	0.096 mm^{-1}	
F(000)	648	
Crystal size	0.5 x 0.12 x 0.02 mm^3	
Theta range for data collection	3.08 to 27.50°.	
Index ranges	-13<=h<=13, -8<=k<=8, -27<=l<=24	
Reflections collected	10198	
Independent reflections	3397 [R(int) = 0.0336]	
Completeness to theta = 26.00°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.96976	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3397 / 0 / 205	
Goodness-of-fit on F^2	1.024	
Final R indices [I>2sigma(I)]	R1 = 0.0435, wR2 = 0.0880	
R indices (all data)	R1 = 0.0691, wR2 = 0.0990	
Largest diff. peak and hole	0.307 and -0.235 $e.Å^{-3}$	

X-Ray data for 1-((((3*R*,4*S*)-3-Phenyl-2-tosylisoxazolidin-4-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 587



587

Table **28**. Crystal data and structure refinement for **587**.

Identification code	ferrer_caf652	
Empirical formula	C21 H21 N O7 S	
Formula weight	431.45	
Temperature	123(2) K	
Wavelength	1.54180 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 16.6619(6) Å	α= 90°.
	b = 10.7864(3) Å	β= 101.846(3)°.
	c = 11.6368(3) Å	γ = 90°.
Volume	2046.85(11) $Å^3$	
Z	4	
Density (calculated)	1.400 Mg/m^3	
Absorption coefficient	1.793 mm^{-1}	
F(000)	904	
Crystal size	0.18 x 0.14 x 0.04 mm^3	
Theta range for data collection	4.92 to 73.18°.	
Index ranges	-20<=h<=20, -12<=k<=13, -14<=l<=14	
Reflections collected	18649	
Independent reflections	4075 [R(int) = 0.0344]	
Completeness to theta = 70.00°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.74640	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4075 / 0 / 276	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0456, wR2 = 0.1218	
R indices (all data)	R1 = 0.0534, wR2 = 0.1296	
Largest diff. peak and hole	0.412 and -0.250 $e.Å^{-3}$	

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