The Development of Organic Peroxide Mediated Oxidations

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I. Declaration

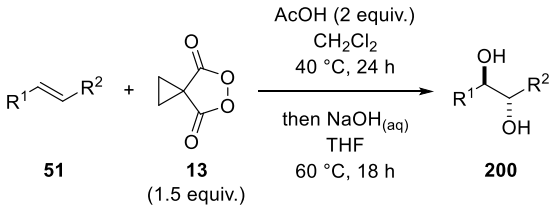
This thesis is the result of the author's original research. It has been composed by the author and has not previously been submitted for examination which has led to the award of a degree.

Signed: Date:

II. Abstract

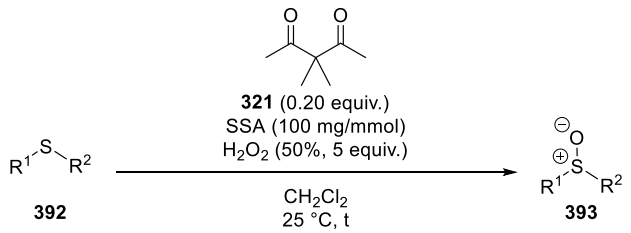
This thesis describes the development of two novel metal-free oxidations processes: a method to selective synthesis *anti*-diols directly from commercially available alkene starting materials and an organocatalytic sulfoxidation procedure using diketones as catalysts.

Chapter 1 describes a novel metal-free method for the one-pot *anti*-dihydroxylation of alkenes to form diols using malonoyl peroxide **13**. The reaction conditions were optimised and the scope of the optimal conditions were examined with a variety of stilbene, styrene and indene derivatives to give the corresponding anti-diols in good to excellent yields and selectivities. Following this, a variety of mechanistic investigations were undertaken, revealing key intermediates and allowing the proposal of a mechanism.



Scheme 1-1. Optimised conditions of *anti*-dihydroxylation discussed in *Chapter 1*.

Chapter 2 demonstrates the development of an organocatalytic sulfoxidation using diketone catalysts. Following a significant optimisation process, the scope of sulfoxidation, showing a wide tolerance of functional groups, was explored. Mechanistic investigation was also undertaken, exploring the intermediates isolated from the procedure and an exploration of the reactivity using tool compounds. The stoichiometric process was also investigated to generate kinetics and a postulated transition state.



Scheme 1-2. Optimised conditions of organocatalytic sulfoxidation discussed in *Chapter 2*.

Chapter 3 contains the experimental procedures and analytical data generated for all the compounds synthesised within this thesis.

III. Acknowledgements

First and foremost I would like to give special thanks to my supervisor Professor Nicholas Tomkinson for allowing me the opportunity to come and study a PhD under his stewardship. It has been an absolute pleasure to work with Nick throughout the almost 5 years that I have been a member of his group. He has constantly nurtured my love for chemistry, helped me to grow significantly as a chemist and always showed a keen interest in me as a person. I couldn't have asked for a better, more supportive mentor for my PhD.

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Thanks to all the staff at Strathclyde uni, particularly Craig, Pat, Lindsey, the Johns, Billy and Paul. Your banter, expertise and help were always welcome and appreciated.

Finally, to my friends and family, I couldn't have done this without you. To Mum and Dad, thank you for every advantage that you have given me in life. I am really proud to have made it this far and I owe you both for that. I love you both. To Kizzy, you have been my rock throughout my PhD, you've kept me sane when I couldn't do it myself anymore, you've kept me laughing and smiling throughout and you've always supported me. Thank you, here's to our future, I love you. And to my friends, particularly Steve, Helen, Jem, Greg, Rob, MJ and James thank you for the laughs, beers, video games, music and banter and here's to many more. It's been awesome.

IV. Contents

V. Abbreviations

°C	- degrees celcius
Å	- Angstrom
A Alk 1	- monomolecular acid catalysed hydrolysis *via* alkyl bond
Ac	- acetate
AD-mix	- asymmetric dihydroxylation mixture
AIBN	- azobisisobutyronitrile
APCI	- atmospheric pressure chemical ionisation
aq.	- aqueous
Ar	- aryl
ASAP	- atmospheric sample analysis probe
atm.	- atmosphere
ATR	- attenuated total reflection
BHT	- butylated hydroxytoluene
BINOL	- 1,1'-bi-2-naphthol
Boc	- *tert*-butyl carbamate
Bn	- benzyl
cal	- calories
CI	- chemical ionisation
CSA	- camphor sulfonic acid
dba	- dibenzylideneacetone
DCC	- 1,1`-dicyclohexylcarbodiimide
DCE	- 1,2-dichloroethane
DET	- diethyl tartrate
DFT	- density functional theory
$(DHQD)_2$-PHAL	- phthalazine adduct with dihydroquinidine
$(DHQ)_2$-PHAL	- phthalazine adduct with dihydroquinine
DIPEA	- diisopropylethylamine
DLP	- dilauryl peroxide
DMAP	- 4-dimethylaminopyridine
DMDO	- dimethyldioxirane
DME	- 1,2-dimethyoxyethane
DMF	- dimethylformamide
DMM	- dimethyoxymethane
DMSO	- dimethylsulfoxide
dppf	- 1,1`-bis(diphenylphosphino)ferrocene
dr	- diastereomeric ratio
ee	- enantiomeric excesss
EDTA	- ethylene diamine tetraacetic acid
EI	- electron impact
ESI	- electrospray ionisation
Et	- ethyl
equiv.	- equivalents
EWG	- electron withdrawing group
GCMS	- gas chromatography mass spectrometry
g	- grams
h	- hours
halo	- halogen

HATU	- 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HFIP	- hexafluoroisopropanol
HMBC	- heteronuclear multiple-bond correlation spectroscopy
HPLC	- high pressure liquid chromatography
HRMS	- high resolution mass spectrometry
Hz	- Hertz
*i*Pr	- *iso*-propyl
IR	- infrared
LCMS	- liquid chromatography mass spectrometry
LD_{50}	- median lethal dose
LRMS	- low resolution mass spectrometry
M	- molar
*m*CPBA	- *meta*-chloroperbenzoic acid
Me	- methyl
min	- minutes
mol	- moles
MP	- melting point
Ms	- methanesulfonyl
*n*Bu	- *n*-butyl
N_2	- nitrogen gas
NMR	- nuclear magnetic resonance
*n*Pr	- *n*-propyl
NSI	- nanospray ionisation
Nu	- nucleophile
Nu[O]	- oxidised nucleophile
O_2	- oxygen gas
*o*tol	- *ortho*-tolyl
PCC	- pyridinium chlorochromate
pH	- potential of hydrogen
Ph	- phenyl
PIDA	- phenyl iodide diacetate
Piv	- pivalate
ppb	- parts per billion
ppm	- parts per million
PTFE	- polytetrafluoroethylene
PTSA	- *para*-toluenesulfonic acid
py	- pyridine
R	- organic functional group
rt	- room temperature
SET	- single electron transfer
S_N2	- bimolecular nucleophilic substitution
Spiro	- spirocyclic
SSA	- silica sulfuric acid
SPS	- solvent purification system
t	- time
T	- temperature
TBAI	- tetrabutylammonium iodide
TBHP	- *tert*-butyl hydroperoxide
*t*Bu	- *tert*-butyl
TEMPO	- (2,2,6,6-tetramethylpiperidin-1-yl)oxyl

Tf	- trifluoromethylsulfonyl
TFE	- 2,2,2-trifluoroethanol
THF	- tetrahyrofuran
TLC	- thin layer chromatography
Torr	- millimetre of mercury
TMS	- trimethyl silyl
Ts	- tosyl
UHP	- urea-hydrogen peroxide adduct
UV	- ultraviolet
wt	- weight
w/v	- weight for volume
w/w	- weight for weight

Chapter 1: *Anti*-Dihydroxylation of Alkenes

Chapter 1. *Anti*-Dihydroxylation of Alkenes

1.1 Introduction

The vicinal diol moiety is found in many natural products and drug candidates and can also serve as a highly versatile synthetic handle.[1] Although several methods exist for the formation of this functional group, the most commonly used route to obtain vicinal diols **2** is *via* the dihydroxylation of an alkene **1** (**Figure 1-1**).[2]

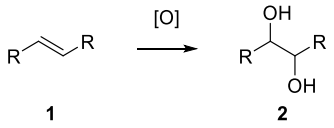
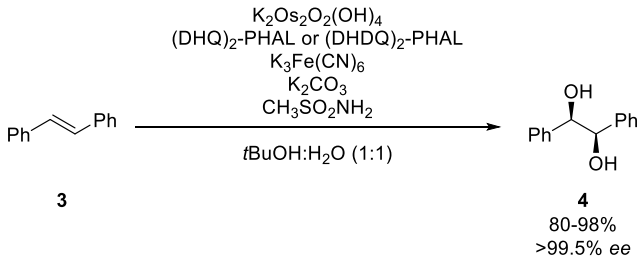


Figure 1-1. The dihydroxylation reaction.

Alkene dihydroxylation is an important component of the synthetic chemist's toolkit because alkenes are ubiquitous in organic molecules. A significant research investment has been dedicated to alkene dihydroxylation since the first example was discovered over 80 years ago.[3] A number of procedures exist to perform this transformation and the gold-standard is undoubtedly the Sharpless asymmetric dihydroxylation reaction.[4] First reported in 1980,[5] the Sharpless reaction was built upon the OsO_4 catalysed Upjohn dihydroxylation.[6] By adding the chiral quinine ligands $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL, Sharpless and co-workers were able to prepare vicinal diols **3** in high yields and excellent enantioselectivity (**Scheme 1-1**).[7]



Scheme 1-1. The Sharpless asymmetric dihydroxylation of trans-stilbene **3**.[7]

The popularity of this reaction has led to the complicated reaction mixtures being sold by chemical suppliers, such as Sigma-Aldrich, as AD-mix-α and AD-mix-β. This has greatly simplified the reaction set-up.

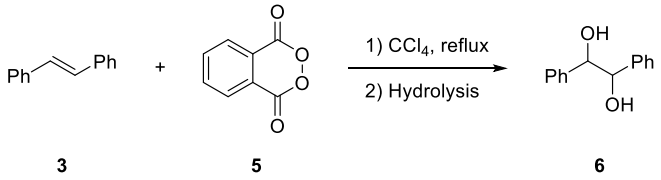
The Sharpless method is currently without equal and used widely,[8] but is not without its drawbacks. The reaction produces large quantities of inorganic waste (roughly 10 kg for every kg of *trans*-stilbene reacted) which, when coupled with the high toxicity of OsO_4 ($LD_{50(mouse)}$ = 162 mg/kg, workplace exposure limit = 0.6 ppb); the low abundance of osmium in the Earth's crust (15 ppb);[9] and its cost (£119 for 250 mg from Sigma-Aldrich as of 18/07/2017), make the reaction ill-suited to scale-up and limits industrial application. The Sharpless method is also limited to the production of *syn*-diol products and does not currently have a modification allowing the production of the corresponding *anti*-diols. A significant level of investigation and research has been dedicated to creating alternatives which address some of the drawbacks associated with this important reaction.

1.1.1 Metal-Free Dihydroxylation

To overcome the difficulties associated with using osmium as a catalyst for the dihydroxylation of alkenes many groups have sought to use other transition metals, such as ruthenium, manganese and iron, for the dihydroxylation procedure and these are summarised in a recent review by Donohoe and co-workers.[1]

As an alternative to metal-catalysed dihydroxylation, metal-free methods have been developed and received significant attention from the scientific community. Several prevalent, metal-free methods for the *syn*-dihydroxylation of alkenes exist, such as: the Woodward reaction using hypervalent iodine and carboxylate salts;[2] the reaction of selenium dioxide with 1,3-dienes;[10] and various radical based methods using hydroxylamines.[11]

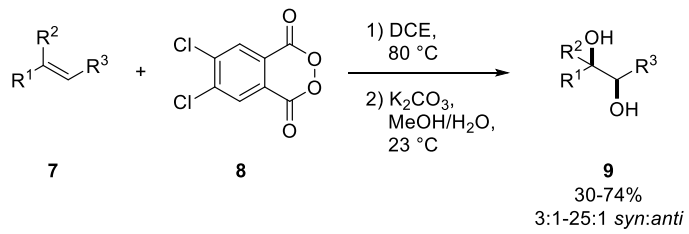
Organic peroxides have also been shown to have great utility in the *syn*-dihydroxylation of alkenes. First reported over 60 years ago,[12] organic peroxides received little attention for this procedure until recent years. Originally, phthaloyl peroxide **5** was shown by Greene to react with *trans*-stilbene **3** in refluxing carbon tetrachloride to produce two oxygenated products, which upon hydrolysis gave the corresponding *syn*-diol **6** (**Scheme 1-2**).[12-13]



3 **5** **6**

Scheme 1-2. Greene's dihydroxylation of *trans*-stilbene **3** with phthaloyl peroxide **5**.[13a]

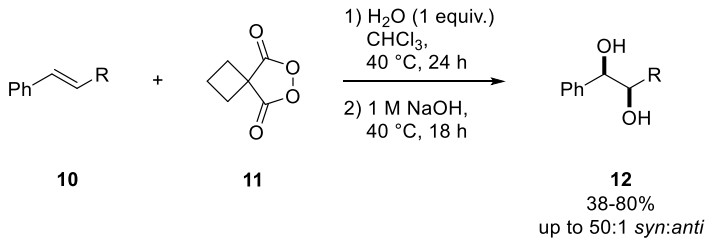
Despite the pioneering work by Greene, the shock sensitive nature of phthaloyl peroxide **5** has limited its use as a dihydroxylation reagent.[12] Siegel and co-workers sought to address this by developing a variety of analogues of peroxide **5** in an attempt to both optimise the reaction and find a safer alternative.[14] This was mainly achieved through an alternative synthesis strategy for the peroxides which limited the production of sensitive by-products and improved peroxide purification. Structurally, the addition of chlorine atoms to the aromatic ring of the phthaloyl peroxide slightly improved its reactivity (65%, 20:1 *dr* with **5** *vs.* 72%, 20:1 *dr* with 3,4-dichlorophthaloyl peroxide **8**) although no comment was made as to whether this improved the safety of the reagent. Using peroxide **8**, Siegel and co-workers achieved good diastereoselectivities and yields (3:1–25:1 *syn*:*anti*, 30–74%) for their optimised procedure (**Scheme 1-3**).



7 **8** **9**

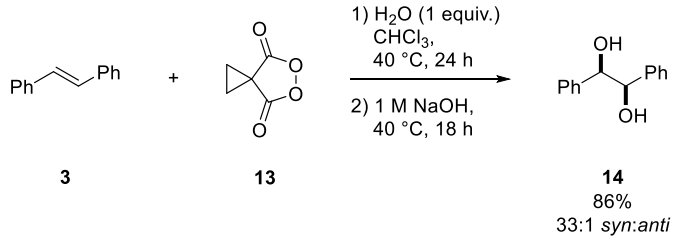
Scheme 1-3. Siegel's dihydroxylation conditions using peroxide **8**.[14]

Malonoyl peroxides have recently been developed as a safer alternative to phthaloyl peroxides. Spirocyclic malonoyl peroxide **11**, easily prepared from cyclobutane-1,1-dicarboxylic acid, has been used within the Tomkinson group to oxidise styrene and stilbene derivatives **10** in good yields (38–80%) with diastereoselectivities up to 50:1 *syn*:*anti* (**Scheme 1-4**).[15]



Scheme 1-4. *Syn*-dihydroxylation with spirocyclic malonoyl peroxide **11**.[15]

Evidence of increased thermal and shock stability, coupled with their ability to react under milder conditions (40 °C as opposed to 80 °C) showed malonoyl peroxide reagents to be an improvement upon phthaloyl peroxides.[15] The malonoyl system was further improved upon with the development of spirocyclic malonoyl peroxide **13**, which proved to be a more efficient oxidant for the *syn*-dihydroxylation procedure. Peroxide **13** reacted with *trans*-stilbene **3** to produce diol **14** in an 86% yield and 33:1 diastereoselectivity, as opposed to the 80% yield and 28:1 diastereoselectivity observed with peroxide **11** (**Scheme 1-5**).[16]

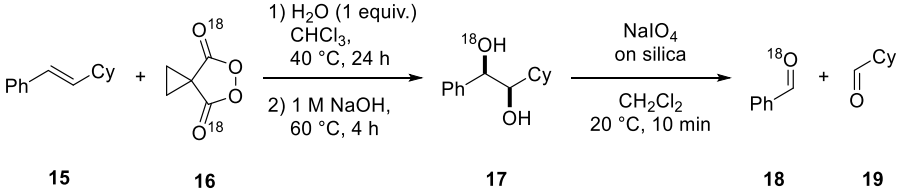


Scheme 1-5. *Syn*-dihydroxylation with spirocyclic malonoyl peroxide **13**.[16]

This work was backed up with a relative rate study, which showed that increased strain within the peroxide ring (noted by an increase in OC—C—CO bond angle in the crystal structure and not a lengthening of the O—O bond) increased the rate of the dihydroxylation reaction.

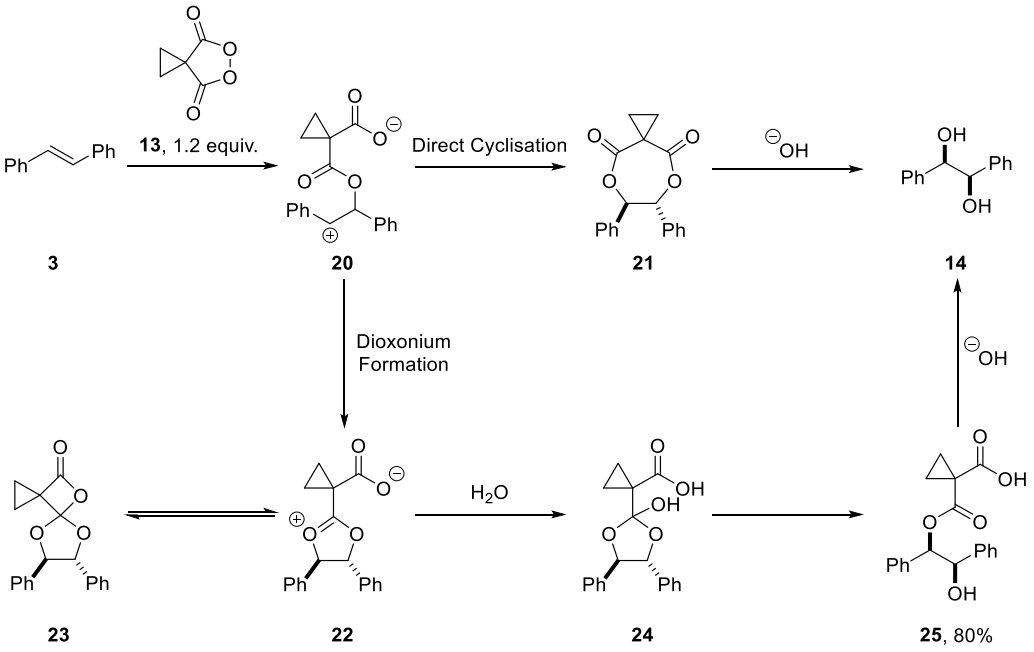
Following this, the group carried out several mechanistic studies to probe the transformation. Hammett analysis, reaction with a Newcomb radical clock and computational work all suggested that the reaction proceeded through an ionic mechanism, rather than a radical or single electron transfer (SET) process. This work was supported using ^{18}O labelled peroxide **16** which showed the incorporation of only one ^{18}O atom in product **17**. This was shown unequivocally *via* oxidative cleavage of

17 into aldehydes **18** and **19** with analysis by mass spectrometry revealing only **18** to contain an ^{18}O label (**Scheme 1-6**).[17]



Scheme 1-6. ^{18}O labelled peroxide **16** has been shown to incorporate only one ^{18}O atom into the product.[17]

Using this data, a mechanism for the reaction of malonoyl peroxides **13** and alkenes **3** was proposed (**Scheme 1-7**).



Scheme 1-7. Proposed reaction sequence for the *syn*-dihydroxylation of alkenes.[17]

It was proposed that nucleophilic attack of alkene **3** on peroxide **13**, cleaving the weak O—O bond, leads to zwitterion **20**. At this point, charge recombination through direct cyclisation leads to 7-membered ring **21** (which had been isolated as a single diastereoisomer in a 14% yield for *trans*-stilbene **3**). Alternatively, cyclisation through the nearby oxygen lone pair on the ester leads to dioxonium **22**. Computational studies suggested the existence of spirocyclic compound **23** which was calculated to be 5.8 kcal mol^{-1} lower in energy than **22**. Dioxonium **22** could also react with the water present in the reaction to form orthoester **24** which would collapse to form ester **25** (which was isolated in an 80% yield for *trans*-stilbene **3**). Spirocyclic compound **23**

was not observed during the groups studies, although indirect evidence suggested its existence. They postulate that **23** was in equilibrium with dioxonium **22** and that its ability to further react prevented the isolation of **23**. Finally, hydrolysis of both **21** and **25** would provide *syn*-diol **14**.

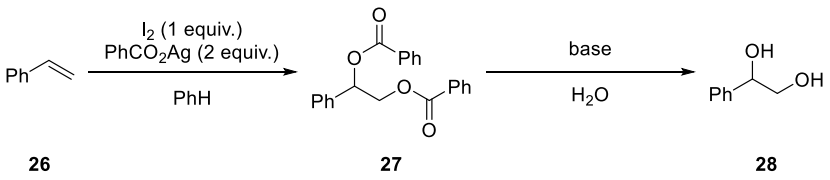
An extensive review of alternative metal-free *syn*-dihydroxylations has been published by the group and covers methods which are outwith the scope of this review.[18]

1.1.2 *Anti*-Dihydroxylation

Whilst many methods for the one-pot *syn*-dihydroxylation have become prevalent in recent years, direct *anti*-dihydroxylation methods have received far less attention. Despite this, one-pot *anti*-dihydroxylation methods have been reported. More commonly, *anti*-diols and their equivalents are accessed *via* epoxidation and subsequent ring opening in a two-step procedure.

1.1.2.1 The Prévost Reaction

The Prévost reaction is arguably the most well-known and studied of the direct *anti*-dioxygenation methods. In a series of reports published between 1933 and 1937,[3,19] Prévost showed that a 2:1 mixture of silver benzoate and iodine (which he postulated formed a chemical of the formula ($(C_6H_5CO_2)_2AgI$) in dry benzene would react with styrene **26** to form diester **27** which would give diol **28** upon basic hydrolysis.



Scheme 1-8. The Prévost reaction of styrene **26**.[3,19]

The mechanism of the Prévost reaction has been the subject of much study. While investigating the effect of neighbouring groups on substitution reactions, Winstein and Buckles postulated the existence of halonium **30** and dioxonium **32** ions in the reaction of 1,2-dihalides **29** and α-haloacetates **31** with silver acetate to explain the apparent retention of stereochemistry (**Figure 1-2**).[20]

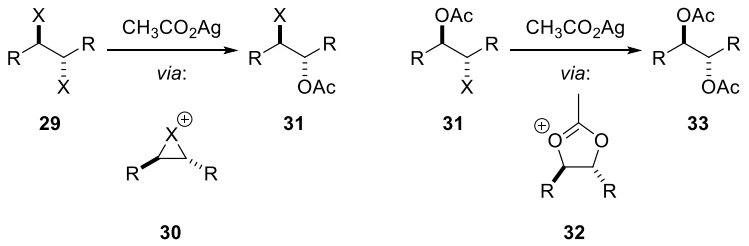


Figure 1-2. Winstein and Buckles postulated halonium **30** and dioxonium **32** intermediates.[20]

A follow up study revealed that dioxonium formation in the presence of wet acetic acid lead to *syn*-α-hydroxyester **34** (**Figure 1-3**).[21]

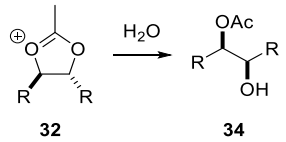
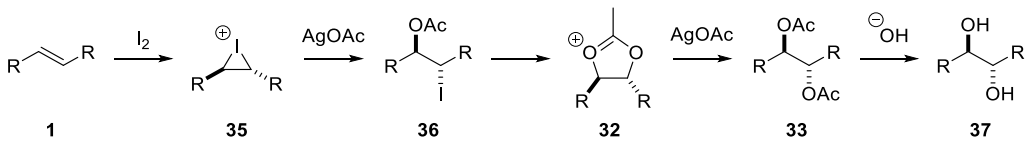


Figure 1-3. Dioxonium ions **32** were shown to collapse into *syn*-α-hydroxyesters **34** in the presence of water.[21]

This was later confirmed in a study by Wiberg and Saegebarth who used ^{18}O-labelling to give further evidence for the existence of dioxonium intermediates in the Prévost reaction.[22] The "wet" Prévost reaction would continue to be developed, eventually dubbed the Woodward reaction, becoming a staple of research towards metal-free *syn*-dihydroxylation.[23] Until recently, the Woodward-Prévost reaction has been the only general method for the production of both *syn*- and *anti*-diols from the corresponding alkene.

Around a decade after the initial work of Winstein and Buckles, Wilson was able to publish a mechanism for the Prévost reaction that was consistent with their findings (**Scheme 1-9**).[24]

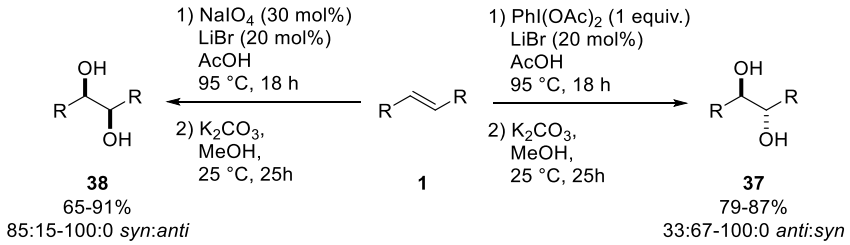


Scheme 1-9. Wilson's mechanism for the Prévost reaction.[24]

Wilson proposed that alkene **1** nucleophilically attacks a molecule of iodine, leading to iodonium ion **35**. Iodonium **35** is then nucleophilically attacked by the silver acetate forming *anti*-α-iodoester **36**. A subsequent ring closing to dioxonium **32** and ring

opening by another molecule of silver acetate gives the dioxygenated product **33** with a retention of the *anti* configuration. **33** can be hydrolysed to give *anti*-diol **37** as required.

The Woodward-Prévost dihydroxylation is a versatile reaction, however, it is not without its drawbacks. The use of expensive silver carboxylate salts (which had so far only been circumvented by the use of highly toxic thallium salts[23b]) and stoichiometric molecular iodine resulted in a significant level of organic and inorganic waste. In an attempt to address these concerns, Sudalai reported a modification of the Woodward-Prévost conditions, using catalytic lithium bromide (**Scheme 1-10**).[2]



Scheme 1-10. LiBr catalysed Woodward-Prévost reaction developed by Sudalai.[2]

Sudalai had previously reported on the oxidising potential of mixtures of lithium bromide and $NaIO_4$ with both alkenes and alkanes.[25] Using those observations, Sudalai was able to develop a *syn*-dihydroxylation procedure that gave high yields (65–91%) and good diastereoselectivity (85:15–100:0, *syn*:*anti*). The *syn* procedure arose as a result of water produced during the $NaIO_4$ mediated oxidation of LiBr. In order to circumvent this and produce *anti*-diols from the procedure, Sudalai employed the use of (diacetoxyiodo)benzene as the stoichiometric oxidant. Using this method, Sudalai was able to produce 5 *anti*-diols from the corresponding alkenes in good yields (79–87%) and varying diastereoselectivity (33:67–100:0, *anti*:*syn*). Using their previous studies and cyclic voltammetry, Sudalai proposed a catalytic cycle for the transformation (**Figure 1-4**).

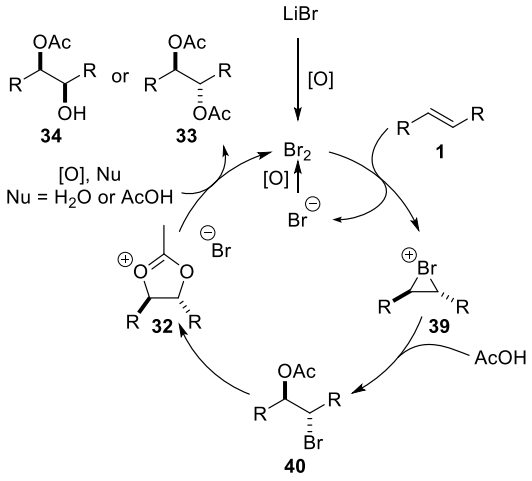
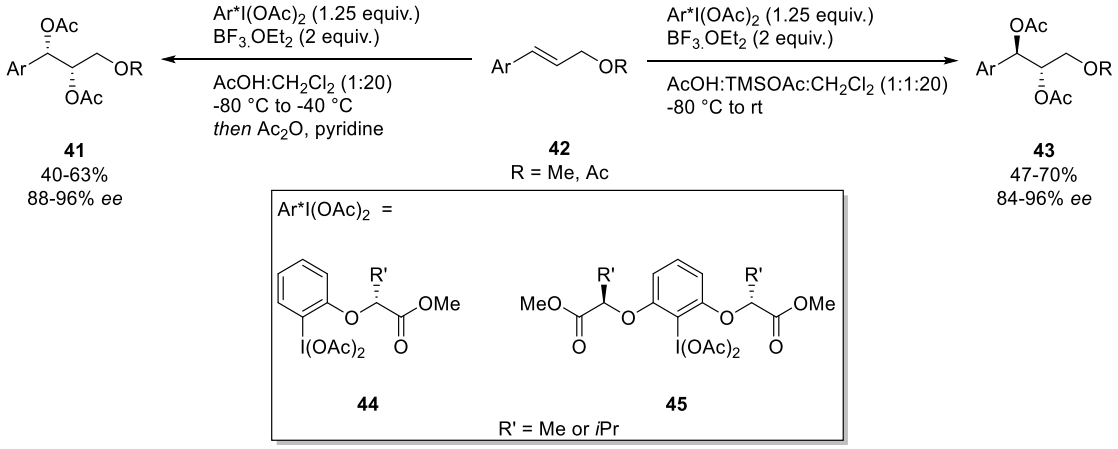


Figure 1-4. The catalytic cycle for Sudalai's modification of the Woodward-Prévost reaction.[2]

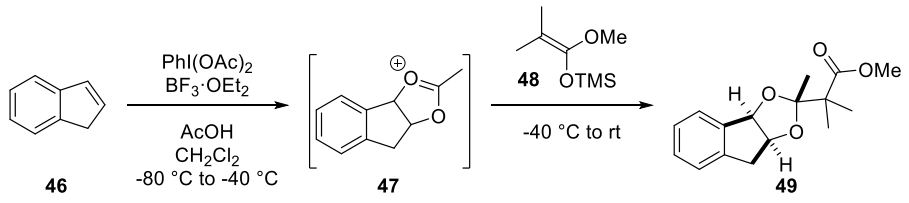
Bromine was generated by *in situ* oxidation of lithium bromide with $NaIO_4$/$PhI(OAc)_2$. Bromine then reacts with alkene **1** to produce bromonium ion **39** which undergoes ring opening to afford α-bromoester **40**. Intramolecular elimination of bromide furnishes dioxonium ion **32** which reacts with water to produce *syn*-hydroxyester **34,** or acetic acid to produce *anti*-diester **33**. Interestingly, Sudalai attributed the reduction of diastereoselectivity to an S_N2 procedure on intermediate **40**. However, this failed to explain why reduced diastereoselectivity was only observed for two substrates, cyclohexene (77:23 *anti*:*syn*) and β-methylstyrene (33:67 *anti*:*syn*).

Several groups had developed alternate routes to chiral diols using α-haloesters in a Prévost-type reaction.[26] Building on this methodology, Fujita and co-workers used chiral hypervalent iodine reagents **44** and **45** to perform the first enantioselective variant of the Prévost-Woodward reaction (**Scheme 1-11**).[27]



Scheme 1-11. Fujita's enantioselective Prévost reaction.[27]

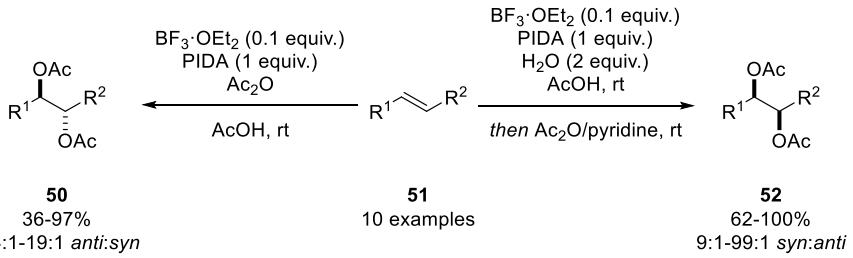
Fujita subjected a limited scope of four cinnamyl alcohol derivatives **42** to *anti*-dihydroxylation, obtaining the *anti*-diacetates **43** exclusively in all but one example (the *p*-tolyl substrate was suggested to have undergone an S_N1 ring opening of the dioxonium intermediate as opposed to an S_N2, explaining the 88:12 *anti*:*syn* ratio) in moderate yields (47–70%) and high enantioselectivity (84–96%). Similar results were observed in a complementary *syn*-dihydroxylation procedure which required an extra esterification step to afford the *syn*-diacetate products **41**. Fujita also used the same conditions to dioxygenate a variety of styrene derivatives, affording *S*-diacetates from the *syn* procedure and *R*-diacetates from the *anti*-procedure. Interestingly, Fujita gave strong evidence for the presence of dioxonium intermediate **47** in the reaction by trapping it with ketene silyl acetal **48** to afford product **49** in 52% yield (**Scheme 1-12**).



Scheme 1-12. Trapping of dioxonium **47** with ketene silyl acetal **48** was demonstrated by Fujita.[27]

Despite the various successes, Fujita's variation of the Prévost reaction had significant limitations. An extremely limited substrate scope, very low temperatures, a complicated mixture of reagents and use of super-stoichiometric $BF_3{\cdot}OEt_2$ and hypervalent iodine reagent detract from the applicability. Shortly after Fujita's publication, Li and co-workers published a similar report that was able to address a

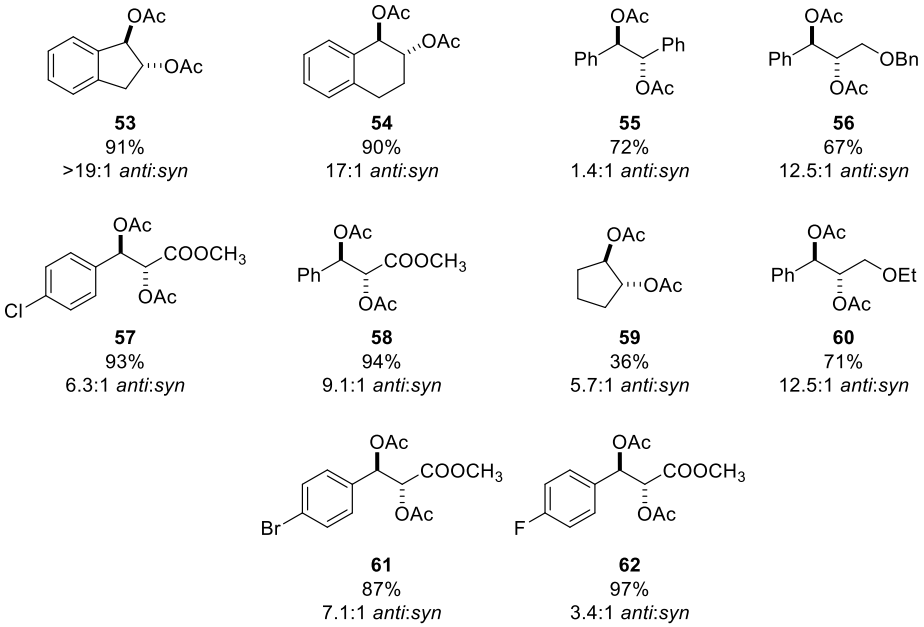
number of the limitations of Fujita's procedure in a diastereoselective manner (**Scheme 1-13**).[28]



Scheme 1-13. Li's $BF_3{\cdot}OEt_2$ catalysed Prévost reaction.[28]

Using catalytic $BF_3{\cdot}OEt_2$ (10 mol%) as a Lewis acid and (diacetoxyiodo)benzene (PIDA) as the oxidant, Li was able to develop a robust protocol for both *syn*- and *anti*-dioxygenation of alkenes. A wide scope of alkenes were subjected to both the *syn*- and *anti*- procedures. Generally, yields and diastereoselectivities were much higher for the *syn*-procedure than the *anti*-procedure but both proved to be successful. A summary of the results from the *anti*-procedure are given below in **Table 1-1**.

Table 1-1. Substrate scope of Li's $BF_3{\cdot}OEt_2$ catalysed Prévost reaction.[28]



Anti-diacetates **50** were obtained in generally high yields and with good diastereoselectivity. Both indene and 1,2-dihydronapthalene reacted to give their *anti*-diacetates (**53** and **54** respectively) in yields (91% and 90%) and diastereoselectivities (>19:1 and 17:1) that closely matched those of their

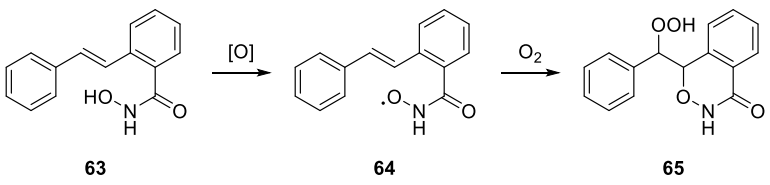
syn- counterparts. Cinnamyl alcohols and chalcone derivatives also performed well in the reaction, however, *trans*-stilbene and cyclopentene did not, giving a low diastereoselectivity (1:4.1, 5.7:1) and yield (72%, 36%) of products **55** and **59** respectively. Unfortunately, no reason for these poor results was given in the report.

Although Li's variation of the Prévost reaction was operationally more useful than Fujita's procedure (occurring at room temperature and using a substoichiometric amount of Lewis Acid), it lacked Fujita's enantioselectivity. Whilst this likely could be addressed by the use of Fujita's chiral hypervalent iodine reagents, Fujita's procedure also gave diacetates in a generally higher diastereoselectivity. Objectively, both procedures suffer from a limited scope that mostly requires the use of styryl derivatives and a low atom economy for the procedure.

In conclusion, the Prévost reaction was developed 80 years ago as the first example of alkene dioxygenation. Although it has since been surpassed by metal-catalysed reactions, the Prévost reaction remains an area of high interest. Significant developments have overcome early challenges, such as the need for expensive silver carboxylate salts, and have allowed for enantioselective and catalytic transformations. The Prévost reaction is also the first example of a dioxygenation that can completely reverse the diastereoselectivity of the reaction through a simple reagent switch.

1.1.2.2 Hydroxamic Acids

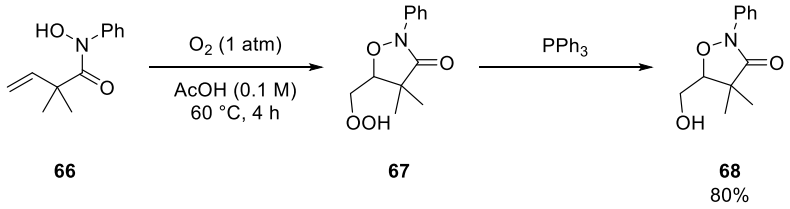
Whilst attempting to investigate the rate of various reactions of hydroxamic acid radicals, Perkins noted that the stilbene derived hydroxamic acid **63**, which was expected to give rise to radical **64** upon one-electron oxidation, underwent a rapid and quantitative cyclisation to give dioxygenated product **65** as a 1:1 mixture of diastereoisomers (**Scheme 1-14**).[29]



Scheme 1-14. Radical dioxygenation observed by Perkins.[29]

A number of years later, Alexanian picked up on the observations of Perkins and set out to develop a general method for alkene dioxygenation using tethered hydroxamic

acids. Following a reductive work-up with triphenylphosphine, Alexanian was able to produce differentiated diol product **68** from hydroxamic acid **66** in an 80% yield (**Scheme 1-15**).[30]

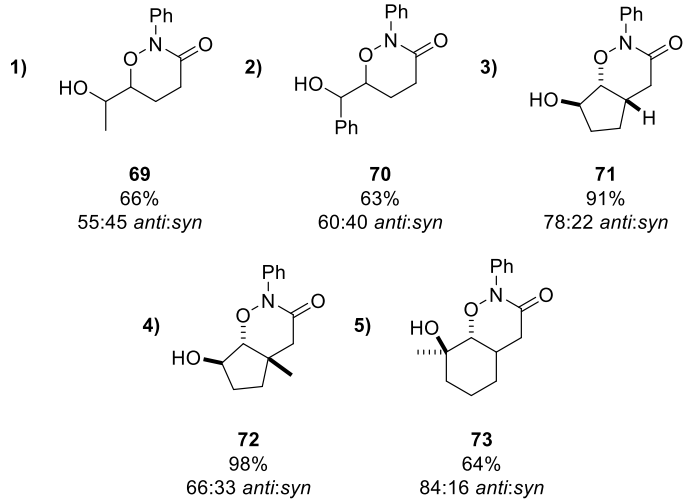


66 **67** **68** 80%

Scheme 1-15. Alexanian's radical dioxygenation using tethered hydroxamic acids **66** and oxygen.[30]

Upon investigating the scope and diasterecontrol of the reaction, Alexanian found that selected substrates proceeded with moderate diastereoselectivity and a preference for *trans*-alkene difunctionalisation, making this an *anti*-dioxygenation procedure (**Table 1-2**).

Table 1-2. Alexanian's study of diastereocontrol in the hydroxamic acid dioxygenation reaction.[30]



69 66% 55:45 *anti*:*syn*

70 63% 60:40 *anti*:*syn*

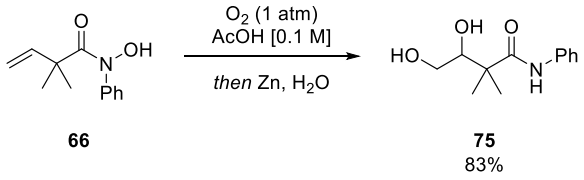
71 91% 78:22 *anti*:*syn*

72 98% 66:33 *anti*:*syn*

73 64% 84:16 *anti*:*syn*

Despite generally high to excellent yields (63–98%) only a limited number of substrates were examined in order to determine their diastereoselectivity. Cyclic alkenes (**Examples 3-5**, **Table 1-2**) showed a moderate preference for *anti*-dioxygenation (66:33–84:16 *anti*:*syn*) although this was less apparent in acyclic examples (**Examples 1-2**, **Table 1-2**) which showed only a slight preference for *anti*-dioxygenation (55:45–60:40 *anti*:*syn*). It is likely that the increased diastereoselectivity observed in the cyclic substrates was associated with the cyclic nature of the substrates, however, this was not discussed within the paper.

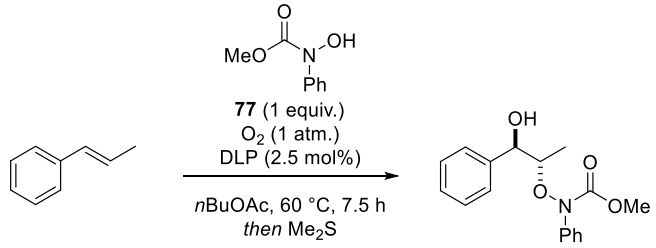
In an attempt to streamline the synthesis of diols, Alexanian developed a one-pot procedure for their synthesis. Following oxidation of the alkene, addition of Zn metal prior to work-up reduced both the peroxide and N—O bond, giving diol **75** in an overall yield of 83% (**Scheme 1-16**).[30]



66 **75** 83%

Scheme 1-16. Alexanian used a reductive Zn metal work up to produce diols **75** in a one-pot procedure.[30]

Whilst the procedure was a novel contribution to the field, the potential of this reaction was held back by its requirement for the substrates to bear the reacting groups. In order to address this challenge, Alexanian set out to develop an intermolecular variant of the reaction, using *N*-hydroxy-*N*-phenylcarbamate **77** to achieve his goals (**Scheme 1-17**).[31]



76 (1.2 equiv.) **78** 86% 78:22 *anti*:*syn*

Scheme 1-17. Intermolecular variation of Alexanian's radical alkene dioxygenation.[31]

Alexanian had previously discovered that the addition of dilauryl peroxide (DLP) could be used to accelerate the reaction rate with sluggish substrates, presumably by increasing the rate of initiation of the reaction.[30] As such, DLP was added to the reaction in order to overcome extended reaction times (up to 3 days). Using this methodology, Alexanian was able to dioxygenate a significant and varied substrate scope (22 examples) in moderate to high yields (48–93%). All substrates showed exceptionally high degrees of regiocontrol, with only one product quoted for every reaction. The radical of *N*-hydroxy-*N*-phenylcarbamate **77** would react with an alkene in order to form a stabilised radical which would then be trapped by triplet state

molecular oxygen. In spite of the successes of his previous work, Alexanian only showed two examples which examined the diastereoselectivity in the reaction. The first, β-methylstyrene **76** (**Scheme 1-17**) showed a moderate *anti*-selectivity (78:22 *anti*:*syn*) which was consistent with his previous observations in the intramolecular reaction.[30] The second substrate, norbornene **79** (**Figure 1-5**), gave a much lower level of diastereocontrol (1.2:1 *syn*:*anti*).

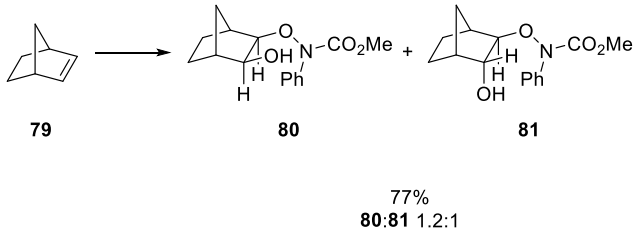


Figure 1-5. Norbornene showed a slight preference for syn-dioxygenation.[31]

Despite being discussed in little detail within the paper itself, it could be argued that the origin of diastereoselectivity within this reaction is explained by sterics. In the β-methylstyrene **76** example, the carbamate group could have been sterically encumbering enough to force a preference for *anti* addition across the alkene. In the norbornene **79** example, the shape of the substrate may have limited the ability of the carbamate to dictate the diastereoselectivity of the reaction.

Alexanian has subsequently developed the conditions of this reaction in order to perform alkene oxyamination,[32] alkene hydration,[33] tandem C—O and C—C bond forming reactions,[34] and the ketooxygenation of alkenes,[35] providing a useful portfolio of bond forming processes.

In conclusion, the recent application of hydroxamic acids in a radical alkene dioxygenation reaction has provided synthetic chemists with another powerful tool for synthesis. Despite being a less explored area of synthetic chemistry, Alexanian's reports hint at a wider applicability for the reaction than that of the Woodward-Prévost reaction. Nonetheless, both Alexanian's reaction and the Woodward- Prévost reaction are useful methods of direct alkene dioxygenation.

1.1.3 *Anti*-diols by Epoxidation.

Even with a number of efforts to develop the direct synthesis of *anti*-diols **83** from the corresponding alkene **1**, the most widely used and traditional method of *anti*-diol **83**

preparation is to form the corresponding epoxide **82** followed by S_N2 hydrolysis (**Figure 1-6**).[36]

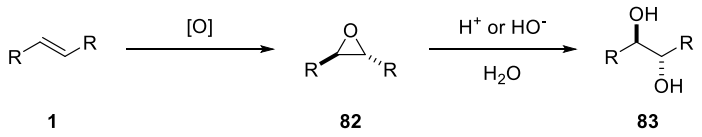


Figure 1-6. Anti-vicinal-diols **83** are traditionally prepared from the alkene **1** by the corresponding epoxide **82**.[36]

Typically, the epoxides of electron-rich, nucleophilic alkenes are prepared by the use of peroxyacids such as *meta*-chloroperbenzoic acid (*m*CPBA) **84**. Peroxyacids feature a weak O—O bond which is attacked by the electron-rich π-bond of the alkene. The result is a diastereoselective transformation in which the stereochemistry of alkene **1** is reflected in the stereochemistry of the epoxide **82**. Epoxide formation by peroxyacids is a concerted process which involves a 3,5-spirocyclic transition state **84** and liberates the corresponding carboxylic acid **85** as a co-product (**Figure 1-7**).

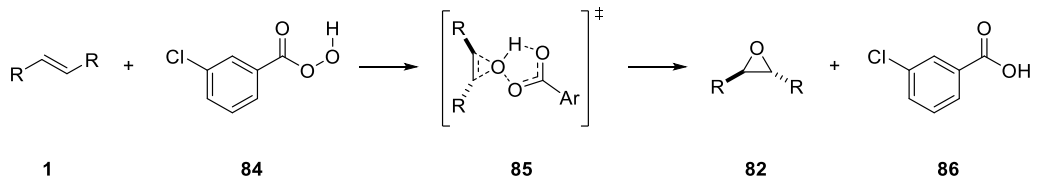


Figure 1-7. Epoxidation by *m*CPBA is common practice in organic chemistry.[36]

Usually, these reactions are carried out in solvents in which the carboxylic acid co-product **86** is precipitated. As well as simplifying product isolation, this prevents the product epoxide **82** being degraded under the reaction. Because of this, dimethyldioxirane (DMDO) has been prepared as an alternative to peracids.[37] DMDO **88** is a highly reactive organic peroxide species formed from the reaction of acetone and a complex mixture of potassium salts known by its commercial name Oxone®. Oxone®, which reacts as potassium peroxymonosulfate, is usually used to generate DMDO at low concentrations *in situ* as the reagent is believed to be unstable. Much like peroxyacids, DMDO **88** is subject to nucleophilic attack by electron-rich alkenes **1**, going through a concerted transition state **89** to yield epoxide **82** as product and regenerating acetone **87** as the only co-product (**Figure 1-8**).

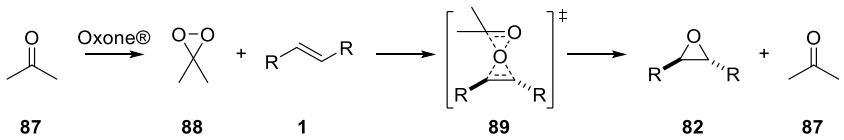


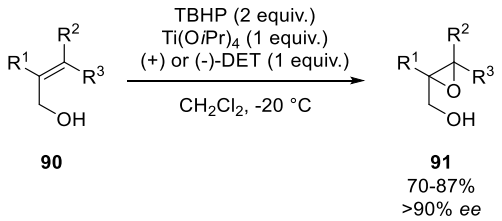
Figure 1-8. Alkene epoxidation with DMDO **88**.[37]

Electron-poor alkenes can also undergo oxidation *via* a nucleophilic epoxidation.[36] This method uses hydrogen peroxide under basic reaction conditions. Unlike peracids and DMDO, this is a stepwise procedure and can lead to loss of the stereochemical information of the double bond.

Whilst DMDO and peracids can provide epoxides stereoselectively, resulting in the *anti*-diol upon hydrolysis, the real strength of using an epoxidation strategy for the synthesis of *anti*-diols is found in the various methods by which epoxides can be prepared enantioselectively. The three key reactions of this class are the Jacobsen-Katsuki epoxidation, the Shi epoxidation and the Sharpless Asymmetric Epoxidation.

1.1.3.1 Sharpless Asymmetric Epoxidation

Alongside his pioneering work on the dihydroxylation of alkenes, Sharpless developed the first asymmetric epoxidation methodology.[38] Using the commercially available reagents titanium tetraisopropoxide, diethyl tartrate (DET) and *tert*-butyl hydroperoxide (TBHP) the group were able to oxidise a variety of allylic alcohols **90** to the corresponding epoxides **91** in excellent yield and enantioselectivity (**Scheme 1-18**).



Scheme 1-18. The first example of asymmetric alkene epoxidation by Sharpless.[38]

Despite being exclusively applicable to allylic alcohols, Sharpless was able to show a reasonable scope for the reaction over just 7 substrates. The reaction was shown to be tolerant of a variety of functionality, including other alkenes and esters as well as aromatic and alkyl functionality. The reaction was also highly tolerant of substitution

around the alkene, provided it was part of the allylic alcohol. Upon inspection of the substrate scope with both enantiomers of DET, it was discovered that both enantiomers of epoxide could be prepared from the same alkene simply by switching the enantiomer of DET used in the reaction. Based on the results, Sharpless was able to provide a simple mnemonic for predicting which face of the alkene oxygen will add to, depending on the enantiomer of DET used (**Figure 1-9**).

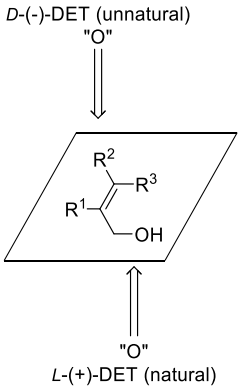


Figure 1-9. The mnemonic provided by Sharpless to show the correlation between DET enantiomer and facial selectivity.[38]

Within the report, Sharpless stated that stoichiometric Ti(O*i*Pr)$_4$ and DET were not required in all cases and that some alkenes could be epoxidised with similar yields and enantioselectivity with as little as 10% loading of metal and ligand. Over time, Sharpless showed that stoichiometric quantities of these reagents were indeed unnecessary, using only 50 mol% in the synthesis of (2*S*,3*S*)-3-propyloxiranemethanol.[39] Seeing the obvious benefits to waste and purification, Sharpless sought to refine the method so as to make it catalytic in both Ti(O*i*Pr)$_4$ and DET.[40] Sharpless found that the addition of either 3 or 4 Å molecular sieves resulted in reactions which had previously stalled at 50–60% conversion and achieved low enantioselectivity (39–80% *ee*) being able to reach full conversion in the presence of catalytic Ti(O*i*Pr)$_4$ (5–10 mol%) and DET (6–13 mol%) (**Scheme 1-10**).

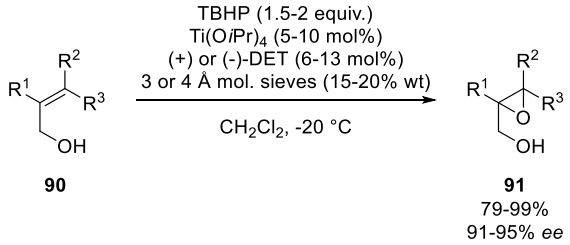


Figure 1-10. Catalytic version of the Sharpless asymmetric epoxidation.[40]

Only two substrates were examined over the course of this work, however, Sharpless stated that he expected this catalytic system would perform as well as in the stoichiometric procedure. Over the course of the work, Sharpless identified that water was responsible for the reduction in reactivity and enantioselectivity, thus explaining the addition of molecular sieves to the reaction.

In order to understand the mechanism of the process, a great deal of time has been spent investigating the catalyst structure.[41] In his previous reports, Sharpless reported a premixing of DET and Ti(O*i*Pr)$_4$ prior to the addition of TBHP and allylic alcohol substrate.[38,40] Using these conditions Sharpless was able to obtain crystallographic information that allowed him to propose **94** as his active catalyst species (**Figure 1-11**).[41a] Unfortunately, rapid dissociation and ligand exchange occurs at Ti and an exact structure has yet to be published.[41b] Combining this structural work with extensive kinetic studies,[42] Sharpless was able to update a previously proposed mechanism[43] to support these discoveries (**Figure 1-11**).

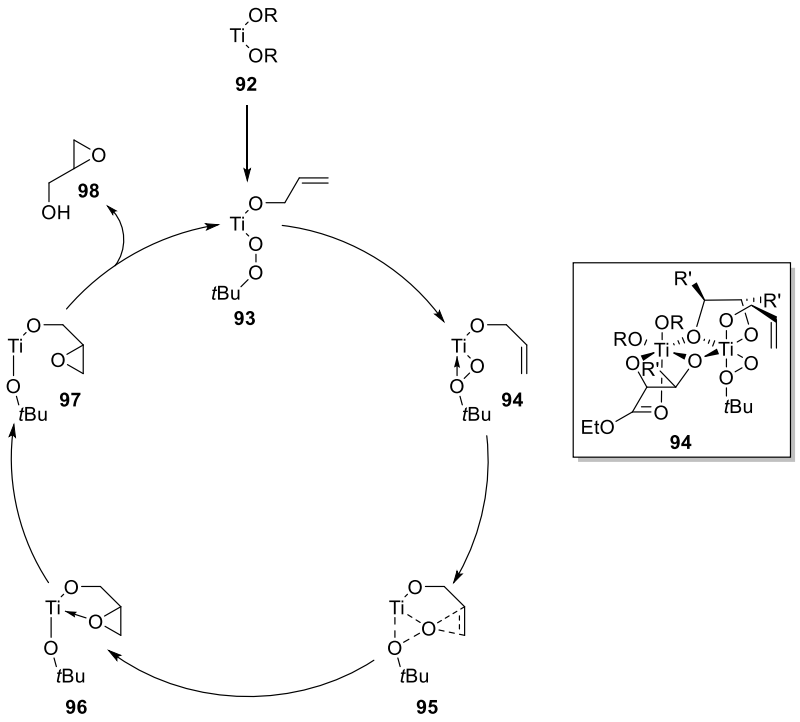


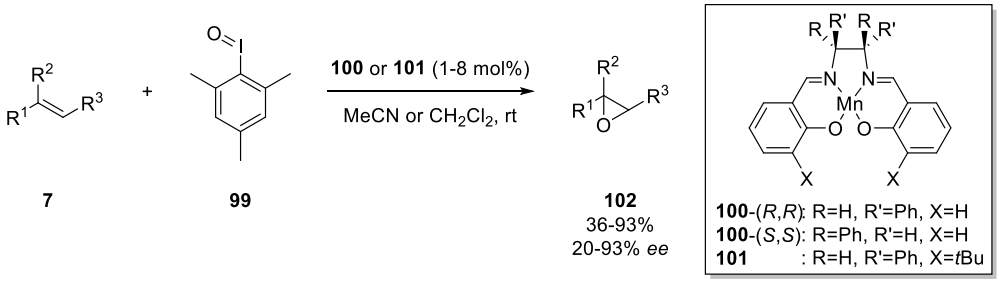
Figure 1-11. The proposed catalytic cycle and active species of the Sharpless asymmetric epoxidation.[42]

The proposal was that following formation of the Ti-tartrate structure, ligand exchange occurs with TBHP and substrate to form **93**. The second oxygen of TBHP begins to bond datively to the Ti and active species **94** is formed. Following oxygen transfer, newly formed epoxide **98** then dissociates to allow the catalytic cycle to propagate. Although much of this is guesswork, it can be stated that: 1) the active catalyst likely exists as a dimer in solution; 2) both the allylic alcohol and the TBHP bind to the titanium and react while bound to it; 3) the allylic alcohol and the TBHP must be bound through axial coordination sites in order to account for the enantiofacial selectivity observed in the product.

In conclusion, Sharpless provided a highly useful reaction that caused interest in non-enzyme controlled enantioselective chemistry to soar. Whilst restricted solely to allylic alcohols, the reaction consistently produces high yields and excellent enantioselectivities. This has made the Sharpless asymmetric epoxidation a staple of the organic chemist's toolkit. Although full mechanistic elucidation remains a challenge due to the oxophillic nature of titanium, a useful mnemonic allows the chemist to predict the stereochemical outcome of the reaction based on the enantiomer of DET used.

1.1.3.2 Jacobsen-Katsuki Epoxidation

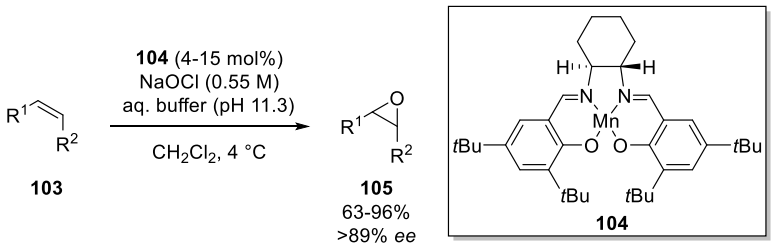
In a follow up to his previous work with oxochromium(V) species,[44] Kochi discovered that cationic manganese-salen complexes were effective catalysts for the epoxidation of alkenes using iodosobenzene **99** as the terminal oxidant.[45] These results were observed by the groups of Jacobsen and Katsuki, both of whom set out to create their own asymmetric variants of the reaction by modifying the pro-chiral salen ligands. In his initial work, Jacobsen discovered that chiral manganese-salen complexes **100** and **101** could be synthesised in high overall yields (68–74%) from readily available chiral pool reagents.[46] These complexes were then tested on nine alkenes bearing a variety of different substitutions (**Scheme 1-19**).



Scheme 1-19. Jacobsen's initial asymmetric epoxidation conditions.[46]

Jacobsen's conditions produced varied yields (36–93%) and varied enantioselectivity (20–93% *ee*) to the substrates examined. However, closer inspection reveals some obvious traits. The reaction performs well when the substrates were mono- or *cis*-di-substituted alkenes. *Gem*-di- and *trans*-di-substituted alkenes were both epoxidised with much lower selectivity and yield than their counterparts. It should be noted that at the time, these enantioselectivities were a vast improvement on existing procedures in the literature.

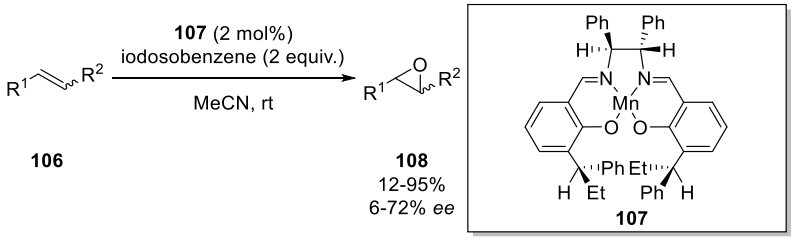
Jacobsen continued to develop these catalysts showing that a diaminocyclohexane derivative of his original complex **104** was a better alternative, using aqueous sodium hypochlorite as the stoichiometric oxidant. Jacobsen was able to oxidise a small number of *cis*-alkenes in good yields (63–84%) and excellent enantioselectivity (>89% *ee*) (**Scheme 1-20**).[47]



Scheme 1-20. Jacobsen's improved conditions for *cis*-alkene epoxidation.[47]

Although limited in scope, Jacobsen's updated conditions were a significant improvement upon his earlier work. Combined with the use of a more benign terminal oxidant (Jacobsen was able to use household bleach for this procedure, as opposed to the hypervalent iodine reagents used previously). Jacobsen's procedure is a valuable complementary technique to other asymmetric epoxidation routes.

Concurrent to the initial observations of Jacobsen,[46] Katsuki developed an alternative manganese catalyst.[48] Instead of focusing on alterations to the ethylenediamine backbone of the salen ligands, Katsuki chose to focus on building chiral steric bulk around the salicylaldehyde portion of the ligand, leading to catalysts such as **107** (**Scheme 1-21**).

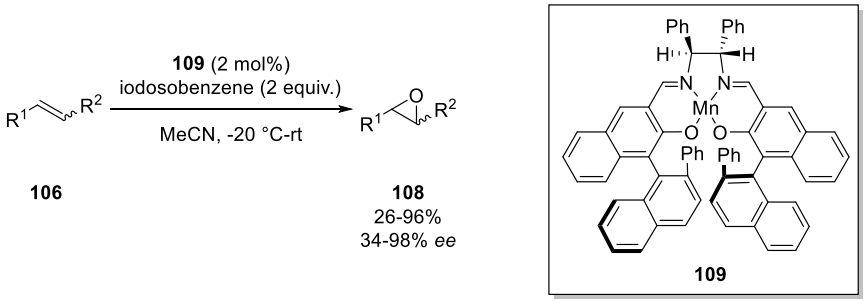


Scheme 1-21. Katsuki's initial catalyst design.[48a]

Much like the early work of Jacobsen,[46] Katsuki's catalysts demonstrated varied yields (12–95%) and enantioselectivities (6–72%) over only 4 substrates. While harder to fully examine due to the substrate limitations, it is obvious to the reader that, much like Jacobsen, Katsuki's reaction favours *cis*-alkenes, such as dihydronapthalene (65% yield, 72% *ee*) and *cis*-β-methylstyrene (12% yield, 68% *ee*) as opposed to the *trans*-alkene substrates examined.

Katsuki continued to develop his catalysts further, choosing to focus his efforts on the exploration of chirality around the phenyl ring of his salen ligands. Ultimately, he

would arrive at a BINOL derived-salen ligand for his second-generation catalyst **109** (**Scheme 1-22**).[49]



Scheme 1-22. Katsuki's asymmetric epoxidation using his second-generation catalyst **109**.[49]

With one exception (*cis*-β-methylstyrene, 26% yield, 34% *ee*), Katsuki showed a slightly larger scope of *cis*-alkenes for epoxidation with reasonable yields (41–96%) and enantioselectivites (70–98% *ee*) which were shown to be an improvement upon existing conditions. In line with changes made by Jacobsen,[47] subsequent work by Katsuki would show a revision to the epoxidation conditions to allow the use of bleach (NaClO) as a terminal oxidant.[50] This allowed Katsuki to expand the substrate scope of epoxidation to include tri-substituted alkenes (26–91% yield, 83–>99% *ee*)[50] and dienes (37–82% yield, 77–94% *ee*)[51] as substrates in varied yields but generally high enantioselectivities.

Much like Jacbosen, Katsuki's epoxidation conditions are relatively ineffective outside of *cis*-di- and tri-substituted alkenes. That being said, these reactions both provided the first insight into the asymmetric epoxidation of unfunctionalised alkenes, a great step forward from the work carried out by Sharpless. Mechanistically, the Jacobsen-Katsuki epoxidation has been the subject of much debate (**Figure 1-13**).[52]

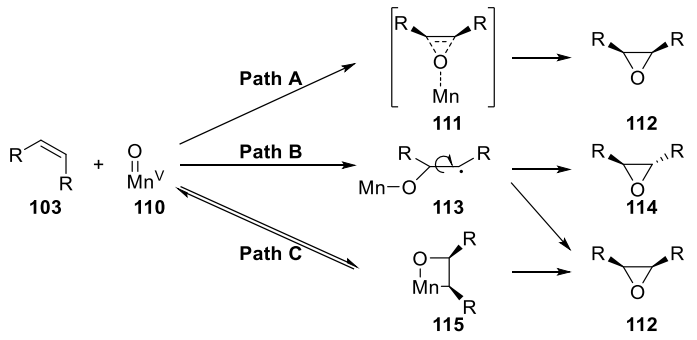


Figure 1-12. Potential mechanism of the Jacobsen-Katsuki epoxidation.[52]

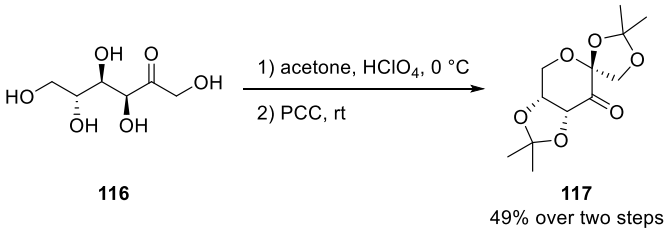
It is widely believed that an oxo-Mn(V) salen complex **110**, obtained *via in situ* oxidation of the cationic Mn(III) salen complexes used by both Jacobsen and Katsuki, is the catalytically active species in the reaction despite limited evidence for their existence in solution under the reaction conditions. Although a mechanism involving the direct transfer of oxygen from Mn **110** to alkene **103** is believed to account for the reaction (**Path A**, **Figure 1-13**), a free radical pathway has been postulated to explain examples under which *trans*-epoxides **114** are obtained from *cis*-alkenes **103** (**Path B**, **Figure 1-13**). A mechanism involving the reversible formation of a manganaoxetane **115** has also been debated (**Path C**, **Figure 1-13**).

The Jacobsen-Katsuki epoxidation reaction is a versatile method for the production of enantioenriched epoxides from the corresponding *cis*-alkene. The reaction has garnered much attention from the synthetic community, however, an exact mechanism has yet to be published and as such the development of an enantioselective procedure for *trans*-alkenes remains elusive.

1.1.3.3 Shi Epoxidation

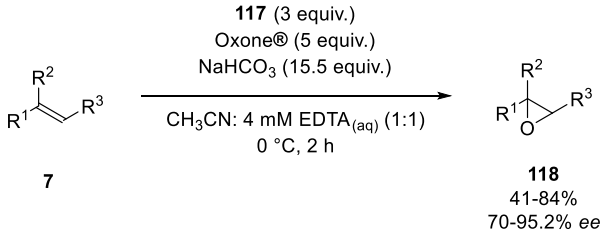
The epoxidation of alkenes by dioxiranes such as DMDO, formed *in situ* from the reaction of ketones and Oxone, has already been discussed (**Pages 17**–**18**). Curci was the first to take this methodology and attempt to develop an asymmetric variant using a camphor-derived ketone.[53] The reaction proceeded in high yields (60–92%), however, the products were isolated with low enantioselectivities (<13% *ee*). Although mostly stoichiometric in ketone (only three reactions featured sub-stoichiometric loadings of ketone), this reaction served as a proof of concept that transition metal free enantioselective epoxidation was possible. This work was marginally improved by Yang (achieving 87% *ee* for a single substrate, with the remaining 6 substrates falling

between 5–50% *ee*).[54] Following this, Shi chose to examine naturally occurring fructose as a chiral-scaffold for this reaction. The group readily prepared reagent **117** from fructose **116** in two steps with a 49% overall yield (**Scheme 1-23**).[55]



Scheme 1-23 The formation of Shi's 1st generation catalyst **117** from fructose **116**.[55]

Using an excess of reagent **117** (3 equiv.) and Oxone (5 equiv.) in a buffered basic solution, Shi was able to epoxidise a significant number (15 examples) of *trans*-di- and tri-substituted alkenes **7** to the corresponding epoxide **118** in generally high yields (41–81%) with high to excellent enantioselectivity (70–95.2% *ee*) (**Scheme 1-24**).



Scheme 1-24. Shi's first generation asymmetric epoxidation reaction.[55]

Despite the large number of substrates examined by Shi, most of the examples were limited to alkenes containing only aryl or alkyl substitution. Several ethers and alcohols were also examined, however, suggesting that this methodology might also tolerate functionality. Based on the stereochemistry of the resulting products, Shi was able to propose a mechanistic rationale to explain the observed stereoselectivity (**Figure 1-14**).

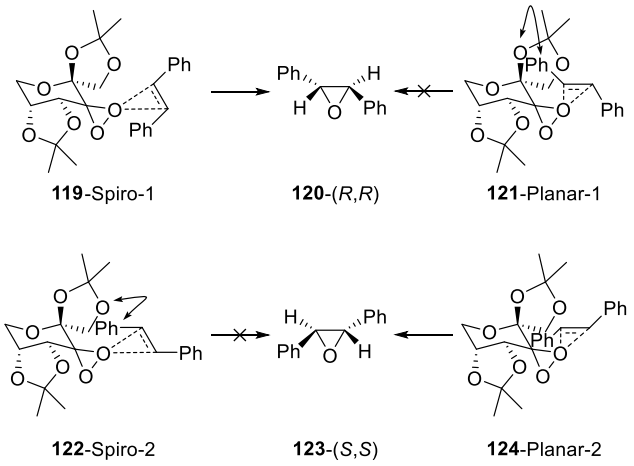


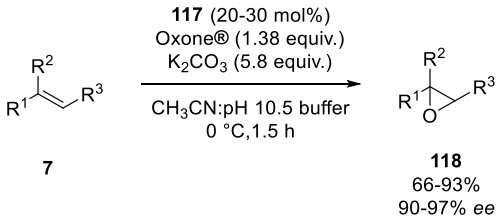
Figure 1-13. Postulated transition states in the Shi epoxidation.[55]

Shi postulated two transition states for the reaction, one involving a spirocyclic (**119**-Spiro) approach of the reactive species and the other favouring a planar (**124**-Planar) alignment of the two species. As the alkene can only approach from the top face of the ring, the adjacent acetyl group controls the resulting stereochemistry of the reaction. If the two species were approaching each other with a planar alignment, it would be expected that the reaction would proceed through transition state **124**–Planar-2, giving rise to **123**-(*S*,*S*) as the product. In contrast, if the reaction proceeded with a spirocyclic alignment of reactants, transition state **119**-Spiro-1 would be expected, giving rise to **120**-(*R*,*R*) as the product. As **120**-(*R*,*R*) was the observed product, Shi proposed that the reaction went through a spirocyclic transition state. This would later be supported by computational work carried out by Houk and concerted spirocyclic transition states are now generally accepted for epoxidations by dioxiranes.[56]

Despite being able to epoxidise a new class of alkenes, Shi's reaction suffered major drawbacks from the super-stoichiometric loadings of all the reagents. It is likely that 3 equivalents of ketone were required in order to maintain enantioselectivity as Shi believed that the ketone decomposed over the course of the reaction. This was made apparent when a test reaction revealed that longer reaction times lead to higher yields using the model substrate, but with a decreased enantioselectivity.

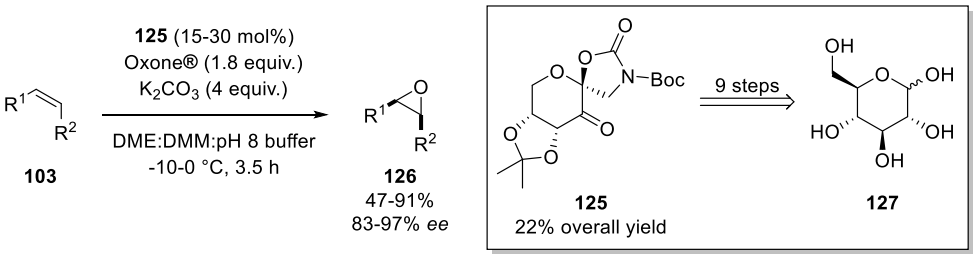
Upon investigation of the literature, it became apparent to Shi that strict pH control was important for the reaction.[57] The rapid decomposition of Oxone[58] as well as a background uncatalysed epoxidation by Oxone had been shown to occur at high pH.[59]

As a result, Shi had been conducting epoxidations in the pH range 7–8. At this pH, the fructose catalyst **117** was found to undergo decomposition *via* a Bayer-Villiger oxidation process. After optimisation of the reaction pH, Shi was able to develop new conditions at pH 10.5 which allowed a substoichiometric loading of catalyst (**Scheme 1-25**).



Scheme 1-25. Shi's optimised catalytic epoxidation reaction.[57]

With these improved conditions, Shi was able to epoxidise a similar scope of mostly aryl and alkyl substituted *trans*-di- and tri-substituted alkenes in good yield (66–93%) and excellent enantioselectivity (90–97% *ee*). Shi would later disclose that the epoxidation of *cis*-alkenes was a challenge for this system, with *cis*-β-methylstyrene being epoxidised in only 34% *ee*.[60] Shi found that catalyst **125**, prepared in 9 steps from glucose **127**, was highly effective in the epoxidation of *cis*-alkenes (**Scheme 1-26**).

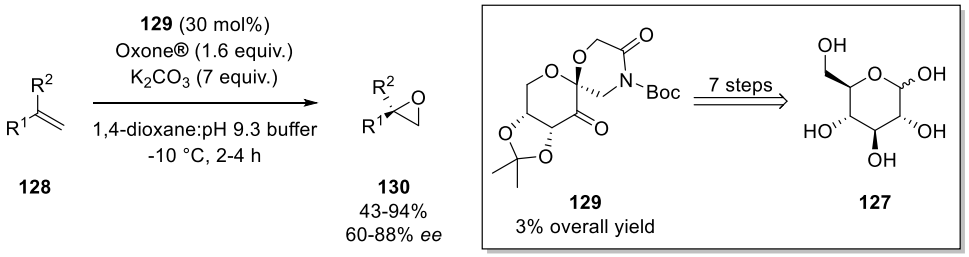


Scheme 1-26. Shi's second generation catalyst **125**.[60]

Shi exposed a reasonable scope (11 examples) of *cis*-alkenes to these modified conditions, generating epoxides **126** in moderate to good yields (47–91%) and excellent enantioselectivities (83–97% *ee*). It should be noted that in order to obtain the highest enantioselectivities, substrates were required to have conjugation through to another π-system (*i.e.* R^1 = aryl or alkynyl in **103/126**) as *cis*-1-cyclohexyl-1-propene was epoxidised in a 67% *ee* (no yield was given for the transformation). A

small number of *trans*-di- and tri-substituted alkenes (4 examples) were also exposed to the reaction conditions, although they did not generally perform as well.[57]

Shi continued to focus on developing catalysts to probe the relationship between catalyst structure and substrate enantioselectivity.[61] 1,1-Disubstituted alkenes **128** proved to be a problem for his current scaffolds, obtaining low enantioselectivity under the conditions examined (30–58% *ee* with catalyst **117**). This led to the development of catalyst **129** (synthesised from glucose **127** in 7 steps) which was shown to be useful in the oxidation of these challenging substrates (**Scheme 1-27**).



Scheme 1-27. Shi's third generation of catalyst **129**.[61]

Shi applied the new conditions and catalyst **129** to a wide scope of substrates (22 examples). Although maintaining similar yields to those experienced in previous variations of the reaction (43–94%), enantioselectivities failed to reach the same levels previously reported but were still high nonetheless (60–88% *ee*). Interestingly, most examples were restricted to styryl derivaties (R^1 = aryl) and enantioselectivities increased in line with steric demand around the α-position of R^2. This, in combination with the observed stereoselectivities of the products, caused Shi to propose a planar transition state **131** for the reaction, in contrast to those observed for his previous catalysts (**Figure 1-15**).

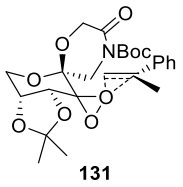


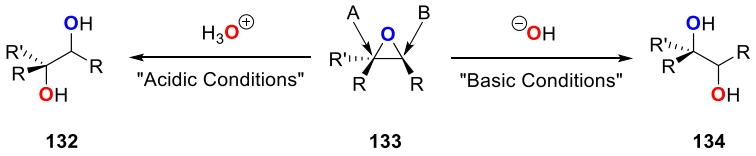
Figure 1-14. Proposed planar transition state **131** for Shi's third generation catalyst **129**.[61]

In conclusion, the Shi epoxidation was the first transition metal free catalytic process for the asymmetric synthesis of epoxides from alkenes. Using catalysts readily

prepared from naturally occurring fructose **116** and glucose **127** and Oxone® as the terminal oxidant, Shi was able to show applicability to a wide range of alkene substitution patterns. Although the scope is much broader than that of the Jacobsen-Katsuki and Sharpless methods, the need for *cis*-di- and 1,1-di-substituted alkenes to be styryl in nature to obtain high enantioselectivities could make the other methods the more useful choice.

1.1.3.4 Epoxide Opening Reaction

In order to furnish vicinal diols from epoxides, the epoxide must be opened with an oxygen based nucleophile, usually in the form of water, a carboxylate or an alcohol. Nucleophilic substitution of an epoxide occurs *via* an S_N2 mechanism, meaning that the process is stereospecific and will always produce *anti*-diol products. However, care must be taken over the choice of conditions used as epoxides contain two electrophilic centres. Different conditions often lead to products with different regiochemistry (**Scheme 1-28**).[36]



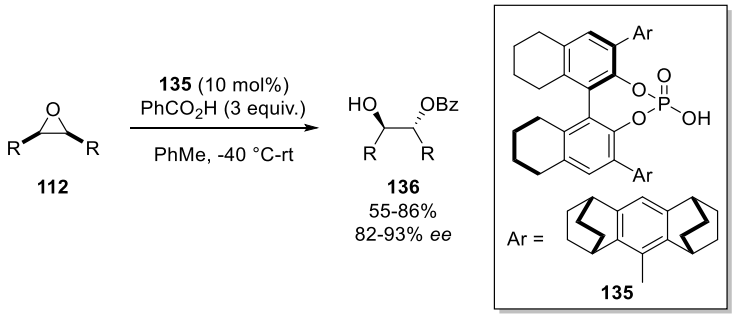
Scheme 1-28. Epoxide **133** ring opening gives different regioisomers under basic and acidic conditions.[36]

Under acidic conditions, the epoxide **133** becomes protonated causing a lengthening of the C—O bonds. The most significant lengthening occurs between the oxygen and the carbon with the most stable developing carbocation (**carbon A** in **Scheme 1-28**). Water (or another nucleophile) is then able to open the epoxide at this centre, giving rise to diol **132**. Under basic conditions, the approaching nucleophile (hydroxide in this case) opens the epoxide from the least sterically hindered carbon (**carbon B** in **Scheme 1-28**) leading to diol **134** after work-up. The regiochemical implications of these processes can have a profound effect on the product stereochemistry as these products are enantiomers of one another.

Unfortunately, these reactions rarely give products as described above. Often, the differences in steric environment and/or electronics at each carbon are not significant enough to exclusively lead to an individual regioisomeric product. Some effort has been dedicated to this synthetic challenge: Jacobsen was able to perform the kinetic

resolution of terminal epoxides using a cobalt derivative of his salen catalyst;[62] Shibasaki was able to enantioselectively ring open *meso*-epoxides with phenol nucleophiles and a BINOL derived heterobimetallic catalyst;[63] and Schneider was also able to enantioselectively ring open *meso*-epoxides to alcohols and amines with a scandium triflate/chiral bipyridine catalyst system.[64]

In an elegant study, List recently employed the use of chiral, BINOL-derived phosphoric acids **135** in the first reported metal-free desymmetrisation of *meso*-epoxides **112** (**Scheme 1-29**).[65]



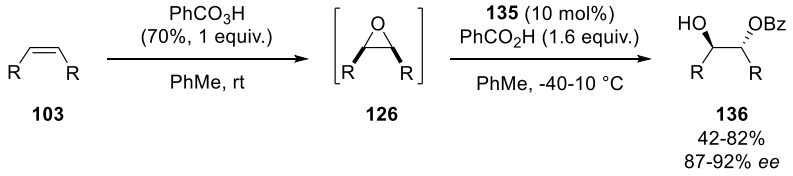
Scheme 1-29. Phosphoric acid **135** catalysed desymmetrisation of *meso*-epoxides **112** by List.[65]

The BINOL-derived phosphoric acids developed by List were designed to mimic naturally occurring epoxide hydrolases, fulfilling a dual role as activator of the carboxylate nucleophile and chiral environment for the subsequent ring-opening. Using these conditions, List examined a wide variety of *meso*-epoxides **112** (12 examples) including cyclic and acyclic examples. Generally, substrates were converted in good yield (55–86%) and gave products with high enantioselectivities (82–93% *ee*) which were unaffected by the presence of other heteroatoms within the substrate (a dihydropyrrole and dihydrofuran derivative gave the dioxygenated products in 88% and 90% *ee* respectively).

Despite the drawbacks, epoxide formation and subsequent ring-opening is widely exploited and remains the preferred method of vicinal *anti*-diol synthesis. Whilst developments by the likes of Jacobsen and List add feasibility and generality to this route, the controlled enantioselective ring opening of epoxides appears limited to *meso*- and terminal epoxides by current synthetic strategies, suggesting the need for direct *anti*-dihydroxylation procedures which could potentially have increased utility.

1.1.3.5 One-pot Methods *via* Epoxide Formation

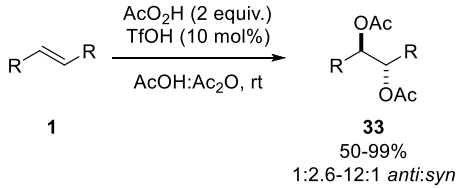
In recent years, a number of groups have sought to facilitate the overall *anti*-dihydroxylation procedure by developing a one-pot epoxidation/ring-opening procedure. List followed on from his asymmetric desymmetrisation of *meso*-epoxides by applying the conditions in a one-pot context.[65] After performing an epoxidation of symmetrical *cis*-alkenes **103** with perbenzoic acid, List added the phosphoric acid catalyst **135** along with extra benzoic acid to afford dioxygenated products **136** (**Scheme 1-30**).



Scheme 1-30. A one-pot epoxidation/ring-opening procedure developed by List.[65]

The dioxygenated products produced by this methodology were obtained in good yield (42–82%) and high enantioselectivities (87–92% *ee*) which were in agreement with his previously examined scope. In one example, List went on to show that commonly used *m*CPBA could be used in the reaction. In this case, cyclohexene underwent the reaction with slightly diminished yield and enantioselectivity (71% yield and 87% *ee* compared to 80% yield and 92% *ee* using peroxybenzoic acid) however, the reaction did not require that more benzoic acid be added in the second step, as the *meta*-chlorobenzoic acid co-product from the oxidation was able to perform the ring opening.

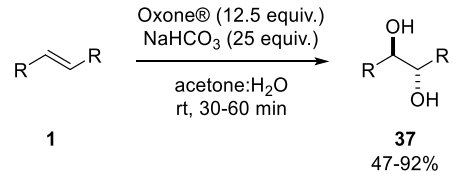
During an attempt to develop a catalytic variant of the Woodward-Prévost reaction by generating (diacetoxyiodo)benzene *in situ*, Gade discovered that triflic acid could be used to catalyse a one-pot *anti*-dihydroxylation of alkenes with peracetic acid *via* the corresponding epoxide (**Scheme 1-31**).[66]



Scheme 1-31. One-pot anti-dihydroxylation developed by Gade.[66]

A scope of mostly terminal aryl and alkyl substituted alkenes were examined under these conditions. Generally, yields for this procedure were high (50–99%) and lower yields could be improved through the use of *m*CPBA as the oxidant as opposed to peracetic acid (the yield for styrene improved from 50% to 94% under these conditions). Only a limited number of substrates (4 examples) were given to explore the diastereoselectivity. Cyclohexene produced the corresponding *anti*-diacetate in good diastereoselectivity (12:1 *anti*:*syn*). The same however, cannot be said for the other substrates. Dihydronaphthalene showed no evidence of diastereoselectivity and both *trans*- and *cis*-stilbene were reported to give their corresponding *syn*-diacetates, in defiance of the proposed mechanism of the reaction, albeit with low diastereoselectivity (2.6:1 and 1.8:1 *syn*:*anti* respectively). Although not discussed at length within the paper, this could be due to the reaction conditions allowing repeated substitution of the acetate groups, leading to a compromise in selectivity. If this were the case, the high diastereoselectivity observed for cyclohexene could potentially be due to the *trans*-product being the lowest in energy.

Oxone has also been used successfully in *anti*-dihydroxylation reactions. Vankar reported that the addition of Oxone and $NaHCO_3$ to alkenes in acetone generated diols (**Scheme 1-32**).[67]

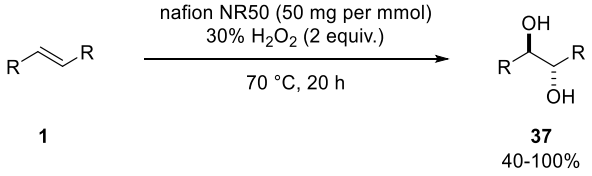


Scheme 1-32. Vankar developed an Oxone mediated dihydroxylation reaction.[67]

A small scope was oxidised in good yields (47–92%) except when *cis*-stilbene was the substrate (which gave the corresponding epoxide as product). Most substrates were enol ethers used in the formation of sugar like products and as such gave little insight

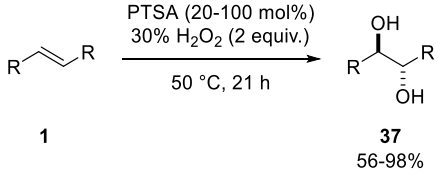
into the diastereoselectivity of the reaction, although, cyclohexene was apparently converted into the corresponding *anti*-diol as a single diastereomer. Although no mechanistic rational was given in the paper, the conditions (along with the *cis*-stilbene and cyclohexene results) suggest epoxide formation and subsequent ring-opening under the reaction conditions. Oxone may have been solely responsible for the epoxidation itself or may have reacted with acetone to form DMDO *in situ*.

Around the same time, Sato proposed a set of conditions that would form a polymer supported Oxone analogue from a polymer supported sulfonic acid (nafion NR50) and 30% aqueous hydrogen peroxide, free from the use of organic solvents (**Scheme 1-33**).[68]



Scheme 1-33. Polymer supported sulfonic acid catalysed anti-dihydroxylation by Sato.[68]

A large number of substrates (12 examples) were examined under the reaction conditions, forming diol products in generally high yields (40–100%). Although all of the substrates for which the diastereoselectivity of the reaction could be deteremined were shown to give the *anti*-diol product selectively, the scope was limited in that only alkyl substituted alkenes were examined, giving no indication of functional group tolerance for the reaction. In an attempt to address the cost of the process (nafion is expensive) and high temperature requirement of this reaction, Afonso subsequently reported the use of *para*-toluenesulfonic acid (PTSA) as a catalyst for this procedure (**Scheme 1-34**).[69]



Scheme 1-34. PTSA catalysed anti-dihydroxylation.[69]

Using this procedure, diols were obtained in good yield (56–98%). Again, the procedure was shown to give *anti*-diols exclusively but substrates were mostly alkyl

or aryl in nature. Afonso, however, went on to explore functional group tolerance under the reaction conditions later in the report. This data showed that a variety of typically acid labile functional groups, such as amides, carbamates, acetyls and silanes were stable to the reaction conditions, suggesting a much broader scope for these conditions as opposed to those proposed by Sato.

In summary, several groups have reported methods which make it possible for the organic chemist to bypass epoxide isolation and directly obtain *anti*-diols. Despite the obvious advantages of these procedures, limited or unproven scope and scrambling of stereochemistry under the reaction conditions provides a need for alternative procedures.

1.1.4 Conclusions

A number of procedures for the formation of *anti*-diol products from alkene starting materials have been described. Generally, one of two routes may be adopted: 1) synthesis of the corresponding epoxide and subsequent ring-opening or; 2) direct alkene dihydroxylation.

Epoxidation can be achieved by a number of methods such as the use of peracids or dioxiranes including the Shi epoxidation or by metal catalysed procedures including the Jacobsen-Katsuki and the Sharpless epoxidations. Each of these methods have their advantages, such as the asymmetric formation of the products. All these methods share a common drawback however, in that epoxide ring-opening can lead to a regioisomeric mixture of products, compromising the stereochemical integrity of the transformation.

Direct methods for the formation of *anti*-diols from alkenes are far less explored than the corresponding methods for epoxidation and *syn*-dihydroxylation. By far the most developed method for the *anti*-dihydroxylation of alkenes is the Woodward-Prévost reaction, although other procedures do exist. These methods succeed in that they allow the one-pot formation of dioxygenated products from alkenes through simple procedures, although the diastereoselectivity of these processes are generally not as high as those from epoxidation and asymmetric methods have not been extensively explored.

1.2 Aims and Objectives

The scope and mechanism of alkene *syn*-dihydroxylation by malonoyl peroxides has been well explored and is well understood within the group.[15-16,18,70] Of particular importance to the mechanism of the procedure is the proposed dioxonium intermediate **22**, formed upon reaction of alkene **3** and peroxide **13** (**Figure 1-16**).

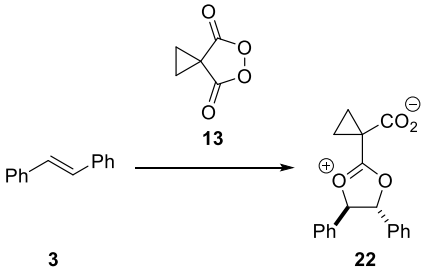


Figure 1-15. Formation of dioxonium **22** by malonoyl peroxide **13**.[17]

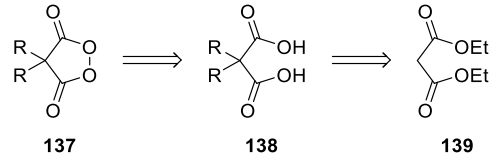
Dioxonium **22** is similar in structure to those proposed in the Woodward-Prévost reaction.[20] It was proposed that it would be possible to intercept the dioxonium intermediate **22** of the malonoyl peroxide procedure in order to synthesise *anti*-diol products with only a simple reagent switch.

We set out to discover if a complementary *anti*-dihydroxylation procedure to our existing *syn*-dihydroxylation procedure could be developed.

1.3 Results and Discussion

1.3.1 Peroxide Formation

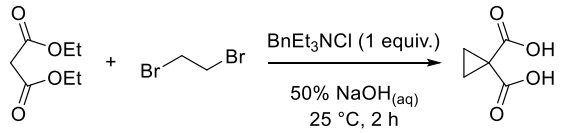
Malonoyl peroxide reagents **137** are not commercially available and must be synthesised prior to use (**Scheme 1-35**).



137 **138** **139**

Scheme 1-35. Retrosynthetic analysis of malonoyl peroxides **137**.

Fortunately, malonoyl peroxides **137** are readily synthesised from the corresponding malonic acids **138**. For the most part these acids are commercially available, however, in the case of 1,1-cyclopropane dicarboxylic acid **141** and 1,1-cyclohexane dicarboxylic acid **144**, it is more cost effective to synthesise directly from diethyl malonate **139** (**Scheme 1-36**).

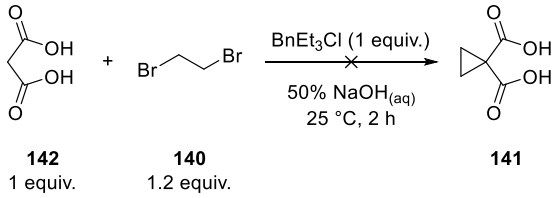


139 1 equiv. **140** 1.2 equiv. **141** 67%

Scheme 1-36. Synthesis of malonic acid **141**.

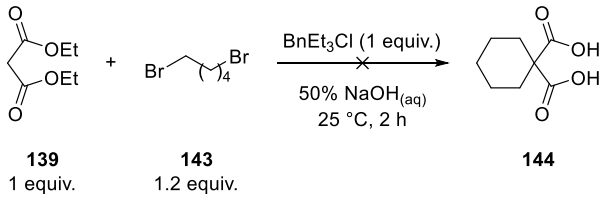
Following the procedure developed by Danishefsky,[71] a premixed solution of 1,2-dibromoethane **140** and diethyl malonate **139** were added to a suspension of $BnEt_3NCl$ in 50% (*w*/*w*) $NaOH_{(aq)}$ and the multiphasic solution was stirred for 2 hours. During the reaction, $BnEt_3NCl$ acts as a phase transfer catalyst for the hydroxide, allowing the deprotonation of diethyl malonate **139** and its subsequent reaction with dibromoethane **140**. Saponification occurs following alkylation, giving malonic acid **141** in a 67% yield after acidic work-up.

Alkylation was shown to occur prior to saponification by a co-worker Michael Rawling, who subjected malonic acid **142** to the reaction conditions. None of the desired product **141** was observed under these conditions, suggesting that alkylation occurs prior to saponification (**Scheme 1-37**).[72]



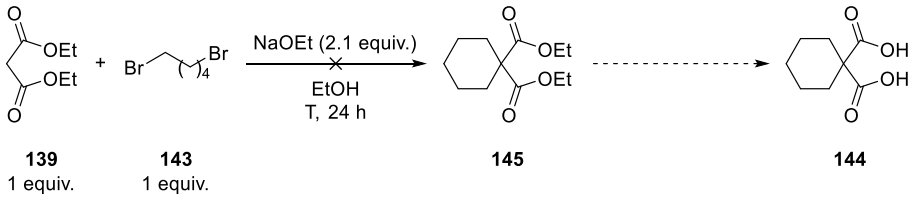
Scheme 1-37. Formation of alkylated malonic acid **141** fails under Danishefsky's conditions when malonic acid **142** is the starting material.[72]

Danishefsky's procedure also fails for the synthesis of 1,1-cyclohexane dicarboxylic acid **144** (**Scheme 1-38**).



Scheme 1-38. Danishefsky's procedure failed in the synthesis of malonic acid **144**.

During the reaction, the organic reagents proceeded to clump together within the reaction vessel, preventing stirring of the mixture. It is likely that the increased lipophilicity of 1,5-dibromopentane **143** when compared to 1,2-dibromoethane **140** may have prevented mixing of the organic reagents within the aqueous medium. Unfortunately, no product was recovered from this experiment. Instead, a stepwise approach to the synthesis of malonic acid **144** was undertaken (**Scheme 1-39**).



Scheme 1-39. Attempted synthesis of malonic acid **144** by a two-step process.

Diethyl malonate **139** and 1,5-dibromopentane **143** were reacted with NaOEt under a variety of conditions, ranging from room temperature to 50 °C and using bottled NaOEt and NaOEt made freshly from ethanol and sodium. ^{1}H NMR spectroscopy suggested product formation under these conditions, however, the reaction consistently produced an impurity which could not be separated by distillation. The peroxide corresponding to malonic acid **147** was synthesised from an existing sample

of **144** within the group and found to be ineffective in the *anti*-dihydroxylation procedure. In the interest of time, the synthesis of **144** was abandoned to focus on the development of the *anti*-dihydroxylation process with other malonoyl peroxides.

Malonoyl peroxides **137** were then synthesised directly from the corresponding malonic acids **138** (**Table 1-3**). Synthesis of malonoyl peroxide **146** was carried out by Carla-Alamillo Ferrer.[73]

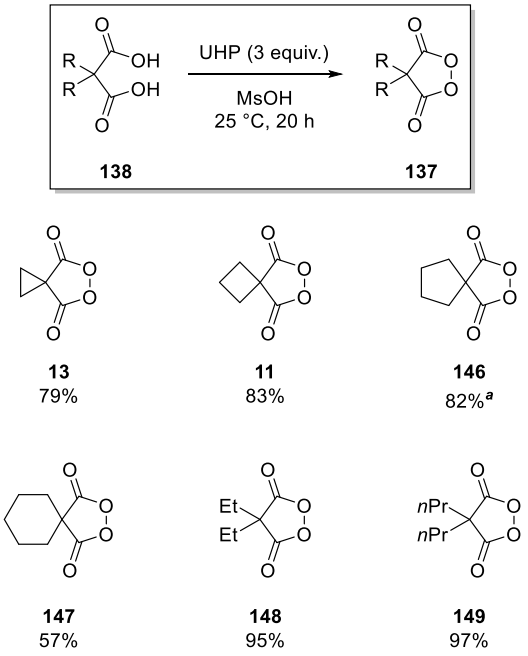


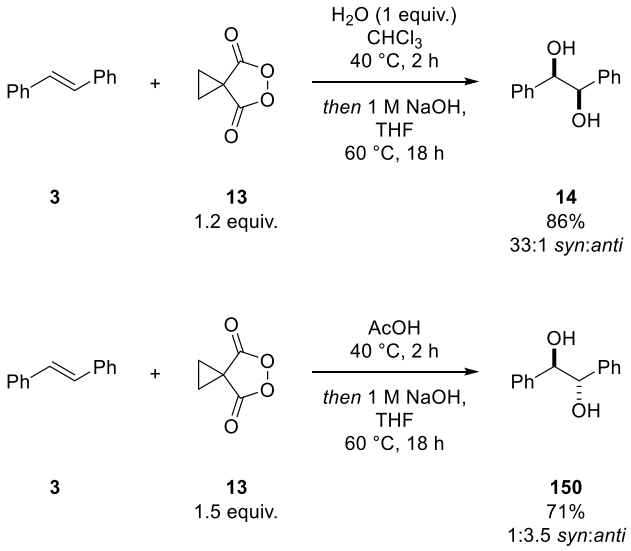
Table 1-3. Peroxide formation results. [a]Compound synthesised by Carla-Alamillo Ferrer.

Malonic acids **138** were treated with urea-hydrogen peroxide adduct (UHP), an anhydrous source of H_2O_2, in MsOH at room temperature overnight. Following a basic work-up (to remove unreacted starting material), malonoyl peroxides **137** were obtained in good yields (57–97%) with a high level of consistency (**13** and **11** were obtained with 65–79% and 67–83% yield respectively over multiple attempts). It should be stressed that care must be taken when storing and handling malonoyl peroxides **137**. Although no incident has occurred within the group, organic peroxides are known to be shock sensitive.[12] DSC calculations on peroxide **13** have shown it to have an onset temperature of 114.5 °C.[74] As such, the use of Kevlar gloves, parafilm wrapped or plastic containers and Teflon-coated, plastic or bone spatulas while handling and storing these materials is a requirement. Reactions should also be conducted behind appropriate blast shielding.

In conclusion, five known malonoyl peroxides were synthesised for use in the development and application of a novel *anti*-dihydroxylation procedure. With a robust route to their synthesis in place, work on the *anti*-dihydroxylation reaction began.

1.3.2 Mechanistic Rationale

Work previously carried out by Rawling had shown that a simple solvent switch, in tandem with vigorous drying of solvents and reagents could cause a 36-fold switch in selectivity for dihydroxylation (**Scheme 1-40**).[72]



Scheme 1-40. Comparison between reported *syn*-dihydroxylation[16] and initial *anti*-dihydroxylation conditions.[72]

The reaction of *trans*-stilbene **3** with 1.2 equivalents of malonoyl peroxide **13** in the presence of 1 equivalent of water in $CHCl_3$ has been shown to produce the corresponding *syn*-diol **14** after hydrolysis in good yield (86%) and diastereoselectivity (33:1 *syn*:*anti*).[16] When the reaction is performed in AcOH a preference is shown for the *anti*-diol **150** (3.5:1 *anti*:*syn*) after hydrolysis.[72] It was our hypothesis that the divergence in diastereoselectivity of the reaction arose as a result of different reaction paths at dioxonium intermediate **22** (**Figure 1-16**).

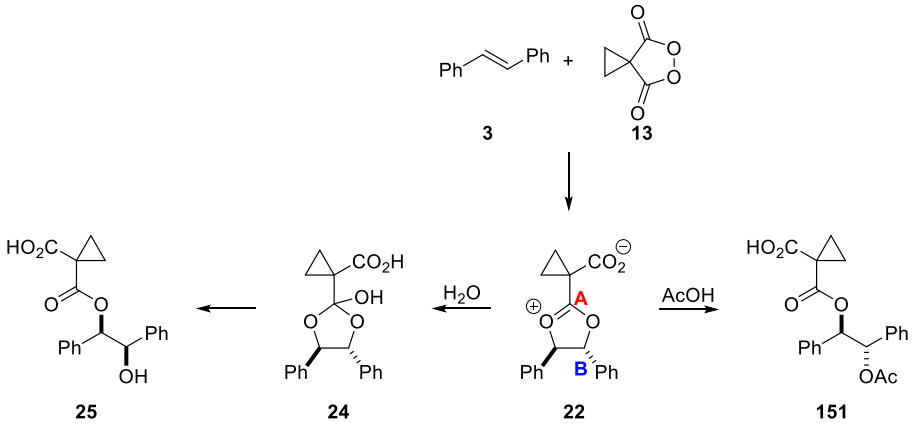


Figure 1-16. The proposed origin of diastereoselectivity reversal.

It had been shown that reaction of peroxide **13** and alkene **3** led to the formation of dioxonium **22**. In the *syn*-dihydroxylation reaction, water approaches the dioxonium **22** at **carbon A** and intermediate **24** subsequently collapses to form *syn*-ester **25**.[17] In line with the observations made by various groups studying the Prévost methodology,[2,27-28] we believed that AcOH would ring open the dioxonium at **carbon B** *via* an S_N2 substitution. This would give an inversion of stereochemistry at that centre and lead to *anti*-diester **151**. Due to the different sites of attack for both nucleophiles, it was imperative that water be sequestered from the reaction to prevent the formation of **25**, which would lower the diastereoselectivity of the process. Molecular sieves (3 Å), activated under vacuum (<1 Torr) at elevated temperatures (~270 °C) for 2 hours, were previously found to be the most convenient and effective method of drying bench acetic acid for the reaction.[72] Other methods of drying and sieve activation were investigated, however, none were found to improve the diastereoselectivity of the reaction beyond that of the conditions described above.

For our early studies on the reaction, a focus on the diastereomeric outcome of the reaction was chosen for optimisation. This was easily identified by ^{1}H NMR spectroscopy for *trans*-stilbene *syn* and *anti*-diol products **14** and **150**. (**Figure 1-17**).

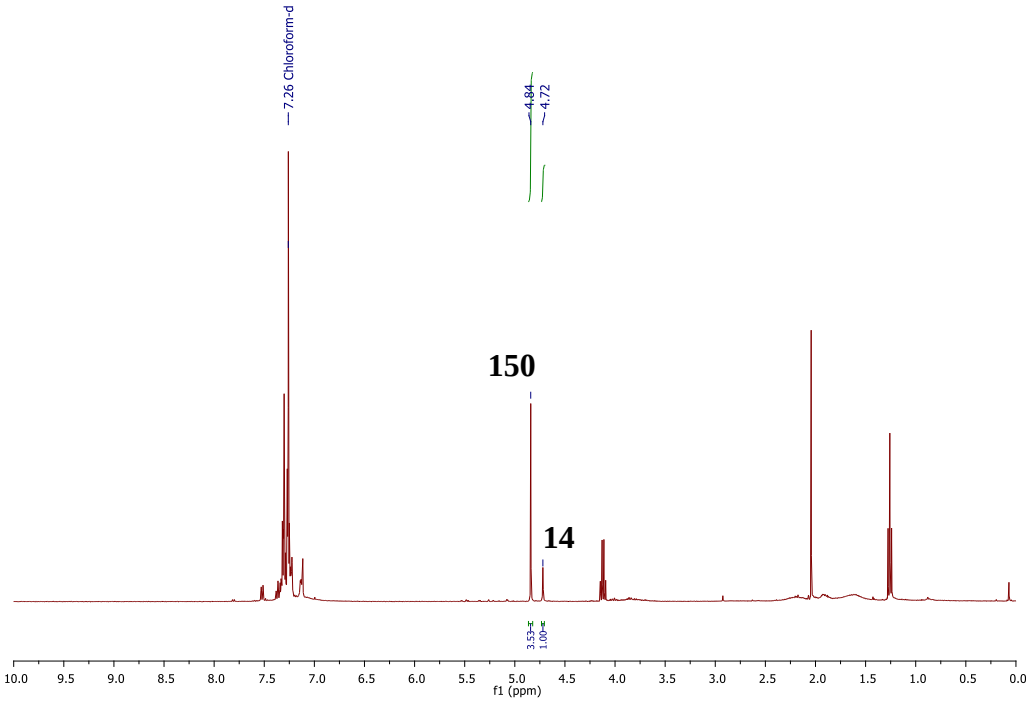


Figure 1-17. ^{1}H NMR spectrum of crude material after hydrolysis showing a 3.5:1 selectivity for *anti*-diol **150** (4.84 ppm) over *syn*-diol **14** (4.72 ppm).

In conclusion, it was believed that a complementary *anti*-dihydroxylation procedure could be developed using AcOH as a secondary nucleophile based on existing knowledge of the *syn*-procedure and its similarities to the Prévost-Woodward reaction. Exclusion of water from the reaction was found to be important for diastereocontrol. Drying the reagents and solvents with activated molecular sieves (3 Å) had previously been shown to be the best method.

1.3.3 Early Reaction Optimisation

For our early studies on the *anti*-dihydroxylation reaction, it was determined that solvent optimisation might give us the greatest improvement in diastereoselectivity. Acetic acid is an extremely hygroscopic solvent and despite optimised drying methods it was suggested that removing all of the water from the reaction might not be possible. Peroxide structure and acetic acid equivalents were also deemed to be important to the reaction. As well as examining the reaction diastereoselectivity, ^{1}H NMR spectroscopy was also used to give an idea of the reactions relative conversion by comparison of remaining stilbene **3** with observed diol product **150** (**Table 1-4**).

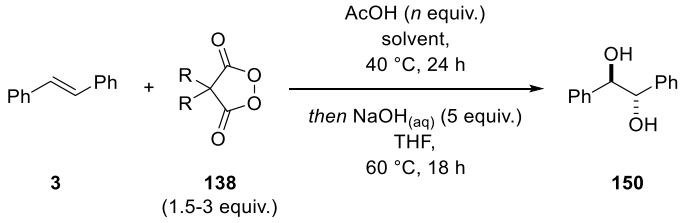


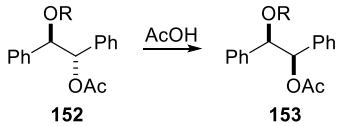
Table 1-4. Early reaction optimisation conditions.

Entry	R	Solvent	AcOH equiv.	Conversion (%)[a]	*dr* (*anti*:*syn*)[a]
1[b]	-$(CH_2)_2$- **13**	AcOH	35	81%	3.5:1
2[b]	-$(CH_2)_2$- **13**	CH_2Cl_2	3	94%	6:1
3[b]	-$(CH_2)_2$- **13**	MeCN	3	68%	1:1
4[b]	-$(CH_2)_2$- **13**	EtOAc	3	53%	1:5
5[b]	-$(CH_2)_2$- **13**	$CHCl_3$	3	55%	1:1
6[b]	-$(CH_2)_2$- **13**	1,4-Dioxane	3	56%	1:5
7[b]	-$(CH_2)_2$- **13**	1,2-Dichloroethane	3	76%	2.5:1
8[b]	-$(CH_2)_2$- **13**	Toluene	3	100%	1:1
9[b]	-$(CH_2)_2$- **13**	CH_2Cl_2	1	82%	6:1
10[b]	-$(CH_2)_2$- **13**	CH_2Cl_2	5	100%	5:1
11[c]	-$(CH_2)_3$- **11**	CH_2Cl_2	3	70%	7.4:1
12[d,e]	-$(CH_2)_5$- **145**	CH_2Cl_2	3	6%	1:1
13[d,e]	Et **148**	CH_2Cl_2	3	9%	1:13
14[d,e]	*n*Pr **149**	CH_2Cl_2	3	26%	12:1

[a]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture after hydrolysis. [b]1.5 equiv. of peroxide used. [c]2 equiv. of peroxide used. [d]3 equiv. of peroxide used. [e]Hydrolysed with KO*t*Bu (12 equiv.) and water (3 equiv.) at 25 °C in THF for 24 hours.

Anti-dihydroxylation reactions were carried out in telfon sealed vials under nitrogen. As malonoyl peroxides had been observed to be mildly hygroscopic, peroxide, AcOH (stored over activated molecular sieves for a minimum of 24 hour prior to use) and solvent (obtained from the SPS or purchased as anhydrous) were further dried over activated molecular sieves, under nitrogen, for 2 hours. This solution was then added to *trans*-stilbene **3** to initiate the reaction. All reactions were carried out at 0.5 M with respect to *trans*-stilbene **3**. CH_2Cl_2 (**Entry 2**) showed the greatest improvement in diastereoselectivity of all the solvents examined (6:1 *anti*:*syn*). Other than AcOH and CH_2Cl_2, 1,2-dichloroethane (**Entry 7**, 2.5:1 *dr*) was the only other solvent to show a preference for *anti*-diol formation. The other solvents examined either displayed a poor conversion, poor diastereoselectivity or both. These could potentially be explained by poor exclusion of water from the reaction, although there may be other explanations, such as peroxide decomposition. CH_2Cl_2 was selected as the best solvent for the reaction.

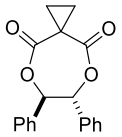
The effect of changing the equivalents of AcOH were then investigated. Reducing the equivalents of AcOH to one (**Entry 9**) had no effect on the diatereoselectivity of the reaction, however, the reaction did not reach completion. Interestingly, upon increasing the equivalents to 5 (**Entry 10**), the diastereoselectivity of the reaction was actually reduced (5:1 *anti*:*syn*). Again, this could possibly be explained by an inability to exclude all of the water from the reaction but could be a result of the excess AcOH undergoing a subsequent S_N2 reaction with the product, leading to racemisation and a decrease in the diastereoselectivity (**Figure 1-18**).



152 **153**

Figure 1-18. An S_N2 reaction with AcOH on **152** may have been responsible for the reduction of diastereoselectivity.

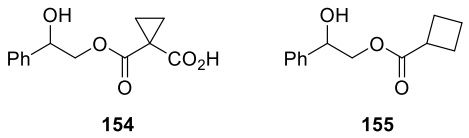
Three equivalents of AcOH was adopted in subsequent transformations and the effects of peroxide structure on the reaction were investigated. It was proposed that the main source of *syn*-diol within the reaction using peroxide **13** was the formation of *syn*-7-membered ring **21** (**Figure 1-19**).



21

Figure 1-19. *syn*-7-membered ring **21** was proposed to be the main source of *syn*-diol in the *anti*-dihydroxylation.

It was our proposal that the peroxide structure would have the biggest effect on the rate of formation of **21** and, subsequently, the diastereoselectivity of the reaction. This belief was reinforced by previous work on the *syn*-dihydroxylation within the group which had showed that intermediates **154** formed from peroxide **13** retained the carboxylate group formed after opening of the peroxide by the alkene.[17] Intermediates **155** from peroxide **11**, however, underwent a decarboxylation following peroxide opening (**Figure 1-20**).[15]



154 **155**

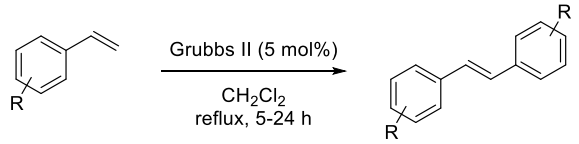
Figure 1-20. **154** and **155** were isolated during mechanistic studies of the *syn*-dihydroxylation with peroxides **154** and **155**.

To our delight, increasing the ring size on the back bone of the peroxide, going from **13** to **11**, did indeed have the desired effect. The diastereoselectivity of the reaction was increased (6:1 to 7.4:1 *anti*:*syn*, **Table 1-4 Entries 2** and **11**) although an increased loading of peroxide (2 equiv.) was required to attain reasonable levels of conversion (70%). Unfortunately, larger cyclic malonoyl peroxide **147** and the acyclic peroxides **148** and **149** (**Entries 12**, **13** and **14**) were not efficient within the transformation. **147** and **148** featured low conversion (6% and 9% respectively) and no *anti*-selectivity (1:1 and 1:13 *anti*:*syn* respectively) despite further increasing the peroxide loadings (3 equiv.). **149** was more encouraging, although the conversion was still poor (26%) the diastereoselectivity of the reaction was significantly improved (12:1 *anti*:*syn*). Reactions using peroxides **147**, **148** and **149** also required different hydrolysis conditions in order to facilitate diol formation from the reaction intermediates. Peroxide **11** was therefore selected as the optimal at this stage due to the increase in diastereoselectivity of the reaction when compared to peroxide **13**.

In conclusion, performing the reaction in CH_2Cl_2 with 3 equivalents of AcOH and 2 equivalents of peroxide **11** were found to be the optimal conditions. At this stage it was believed that more information could be gained by investigating the reaction in more detail. As such, we began to simultaneously explore both the scope and the mechanism of the reaction.

1.3.4 Peroxide 11 Substrate Scope

We sought to examine the reaction conditions against several other stilbene derivatives in order to further investigate the reactions potential. Prior to their reaction, stilbene derivatives **159**–**161** were required to be synthesised (**Scheme 1-41**).

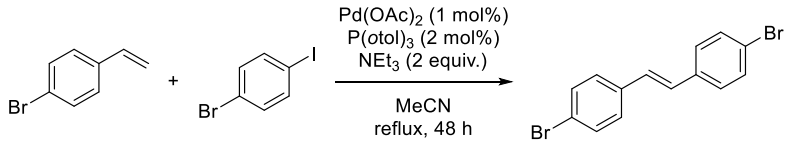


156 R = 4-Me
157 R = 2-Me
158 R = 4-Br

159 R = 4-Me 88%
160 R = 2-Me 60%
161 R = 4-Br 22%

Scheme 1-41. Grubbs homometathesis was used to synthesise stilbene derivatives **159**–**161**.[75]

Stilbene derivatives **159**–**161** were synthesised by Grubbs homometathesis reaction, using Grubbs second generation catalyst, adapted from a procedure by Mata.[75] Tolylstilbenes **159** and **160** were obtained in high yields (88% and 60% respectively) following purification. The reaction proved to be low yielding for 4-bromostyrene **158** (22%) failing to produce usable quantities of stilbene derivative **161**. As such, an alternative procedure previously used by Rawling was adapted for its synthesis (**Scheme 1-42**).[72]



158
1 equiv.

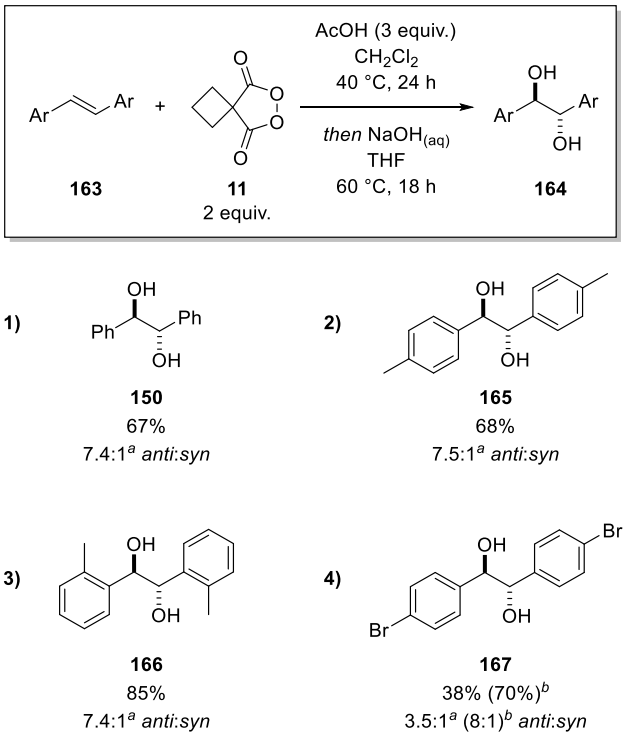
162
1.01 equiv.

161
73%

Scheme 1-42. Heck cross coupling was the prefered route to stilbene derivative **161**.[72]

The Heck cross coupling of 4-bromostyrene **158** and 4-bromoiodobenzene **162** was the preferred method of synthesis for stilbene derivative **161**, which was isolated in a 73% yield after purification. Using peroxide **11**, stilbene derivatives **3**–**161** were subjected to the optimised *anti*-dihydroxylation conditions and the results are summarised below in **Table 1-5**.

Table 1-5. Substrate scope of anti-dihydroxylation with peroxide **11**.



[a]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b]Reaction carried out with 4 equiv. of peroxide **11**, 6 equiv. of AcOH and at a concentration of 0.25 M.

Trans-stilbene **3** (**Table 1-5**, **Entry 1**) was transformed into its corresponding *anti*-diol **150** in a reasonable yield (67%) and an excellent diastereoselectivity (7.4:1), a 40-fold change in selectivity for *anti*-diol **150** from the *syn* procedure.[17] As expected, tolylstilbenes **159** and **160** produced similar results to stilbene **3**. *Anti*-diols **165** and **166** were formed in reasonable yield (68% and 85% respectively) and excellent diastereoselectivity (7.5:1 and 7.4:1 *anti*:*syn* respectively). Somewhat disappointingly, dibromostilbene **161** proved to be a challenging substrate, with the corresponding *anti*-diol **167** being formed in low yield (38%) and reasonable diastereoselectivity (3.5:1 *anti*:*syn*). Whilst it could be argued that this was a result of the less nucleophilic alkene being less reactive under the reaction conditions (only a 50% relative conversion of starting material into product was observed by ^{1}H NMR spectroscopy), it was observed that dibromostilbene **161** appeared to have poor solubility under the reaction conditions. As such, the reaction of dibromostilbene **161** was run at half the concentration (0.25 M) and with twice the loading of peroxide **11** and AcOH (4 and 6 equiv. respectively). This resulted in *anti*-diol **167** being formed in high yield (70%) and with excellent diastereoselectivity (8:1 *anti*:*syn*). It should be noted that under the

conditions examined none of the reactions appeared to reach completition (the corresponding stilbenes could still be observed in the ^{1}H NMR spectra of the crude reaction mixtures).

In conclusion, the peroxide **11** mediated *anti*-dihydroxylation reaction of stilbene substrates was found to produce *anti*-diols with excellent diastereoselectivity (up to 8:1 *anti*:*syn*) and reasonable yield (up to 85%). However, under these conditions, none of the reactions reached competition and starting material was always observed within the ^{1}H NMR spectra of the crude reaction mixtures.

1.3.5 Peroxide 11 Mechanistic Investigation

Concurrent to the investigation of the reaction scope of *anti*-dihydroxylation with peroxide **11** we were interested in investigating the mechanism of the reaction. Based on our knowledge of the *syn*-dihydroxylation mechanism that had previously been investigated, we proposed a mechanism for the transformation (**Figure 1-21**).

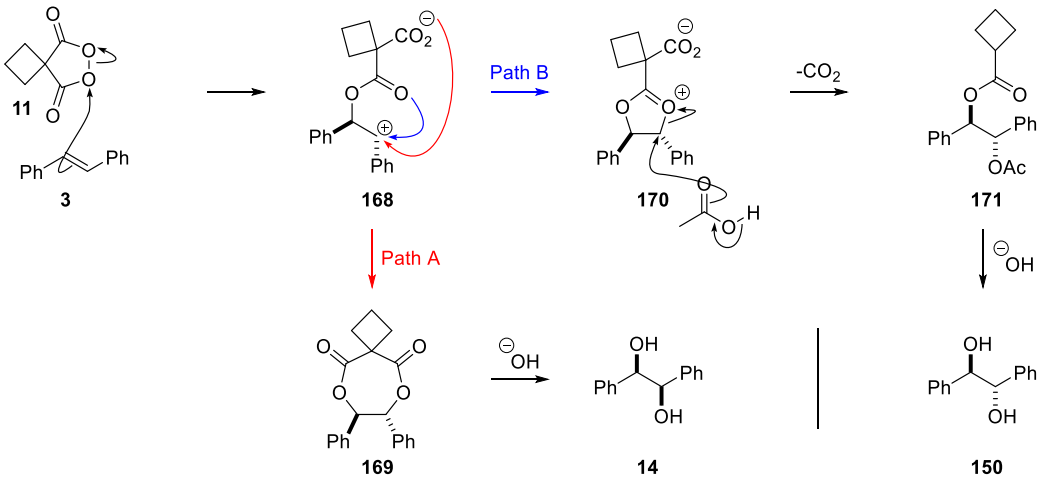
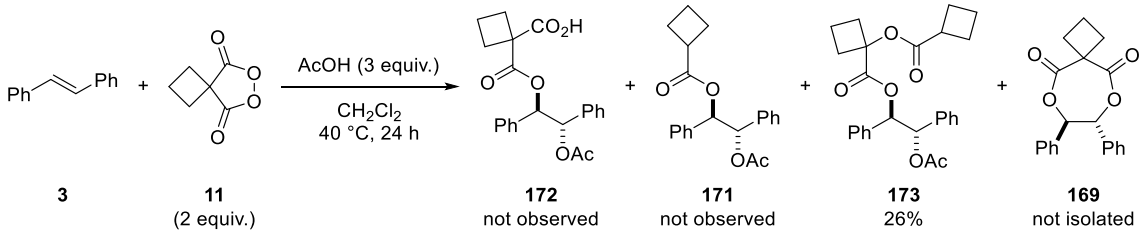


Figure 1-21. Proposed mechanism of *anti*-dihydroxylation with peroxide **11**.

In the *syn*-dihydroxylation it was proposed that peroxide **11** was attacked by alkene **3** leading to zwitterion **168**. At this point, two possible paths exist: 1) direct charge combination leading to the formation of 7-membered ring **169** (Path A) or; 2) ring closing *via* a lone pair on the adjacent carbonyl, leading to dioxonium **170** (Path B). It is proposed that at this stage the mechanism differs to that reported for the *syn*-dihydroxylation. Without a molecule of water present, dioxonium **170** is opened *via* an S_N2 mechanism to give *anti*-diester **171**, akin to the opening of dioxonium ions by AcOH in the Prévost mechanism.[2] It was believed that decarboxylation will occur

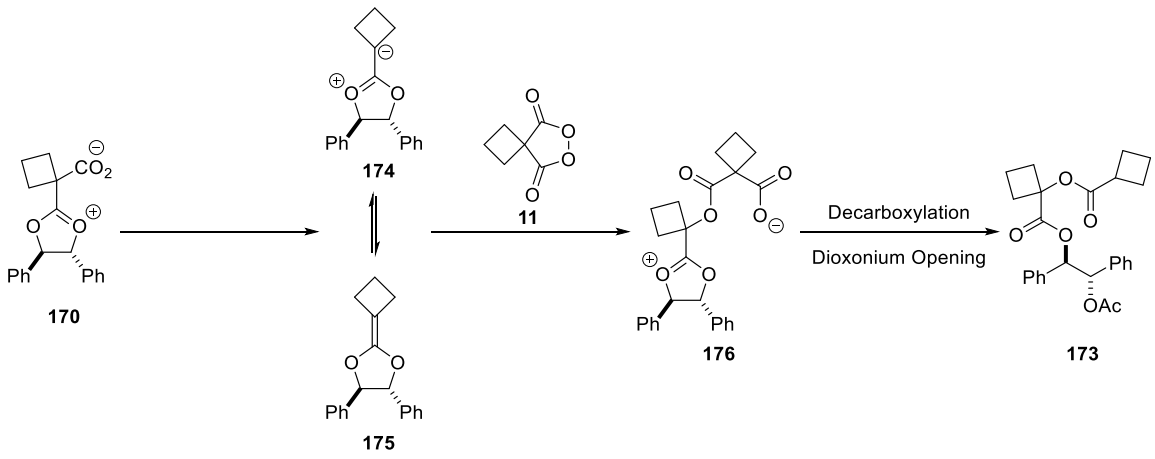
for intermediates formed from peroxide **11**, as was the case for its use in the *syn*-dihydroxylation.[15] Based on the observed formation of 7-membered ring **169**, it is possible that this occurs after the formation of dioxonium **170** however, computational work carried out for the *syn*-dihydroxylation suggests that formation of **169** and **170** are governed by two discrete transition states which are dictated by the approach of the alkene and the peroxide prior to reaction.[17] Hydrolysis of 7-membered ring **169** would lead to *syn*-diol **12** whereas hydrolysis of diester **170** would lead to *anti*-diol **150**.

As a first attempt to understand the mechanism of the reaction, an experiment was conducted in order to evaluate the structure of the intermediates of the reaction prior to hydrolysis (**Scheme 1-43**).



Scheme 1-43. Isolation of anti-dihydroxylation intermediates using peroxide **11**.

In agreement with the hypothesis, carboxylated intermediate **172** was not observed in the ^{1}H NMR spectra of the crude reaction mixture and was not isolated from the reaction. However, no evidence for the presence of decarboxylated intermediate **171** was identified either. 7-membered ring **169** was identified in the ^{1}H NMR spectra of the crude reaction mixture, however, it was unable to be separated from unidentified impurities within the reaction. Curiously, intermediate **173** was isolated from the crude reaction mixture in a 26% yield.



Scheme 1-44. Potential mechanism for the formation of intermediate **173**.

Scheme 1-44 proposes a mechanism for the formation of intermediate **173**. Based on the structure, it is believed that dioxonium **174** must react with another molecule of peroxide **11** and that this must occur after decarboxylation but prior to ring opening by AcOH. As for the exact structure of the dioxonium after decarboxylation, it could potentially exist as either zwitterion **174** or as ketene acetal **175**. Similar examples of both structures are reported within the literature. Dioxonium ions, such as **174**, have long been reported in conjunction with the Prévost reaction[2,20] and zwitterionic dioxonium species were reported to exist previously within the group.[17] Ketene acetals, such as **175**, are also prevalent within the literature. A search of closely related structures suggests that zwitterion **174** may be more likely to exist[76] due to the high strain in ketene acetal **175**. Regardless both **174** and **175** are nucleophilic at carbon and would react with another molecule of **11** to form **176**. Subsequent decarboxylation and dioxonium ring opening as shown previously would then lead to intermediate **173**.

In conclusion, the mechanistic investigation of the *anti*-dihydroxylation reaction with peroxide **11** revealed the reaction to be more complicated than first anticipated. Due to the complicated nature of the mechanism for peroxide **11** as well as the reactions apparent inability to reach completion it was proposed that the reaction optimisation should be revisited.

1.3.6 Reaction Optimisation

For the second round of reaction optimisation, a more methodical approach was adopted. Peroxide **13** was chosen as the oxidant for the reaction as we believed that it would be less mechanistically complicated than peroxide **11**. This time, a set of

experiments was planned and it was decided that optimisation should focus on reaction yield, along with the diastereoselectivity of the transformation (**Table 1-6**).

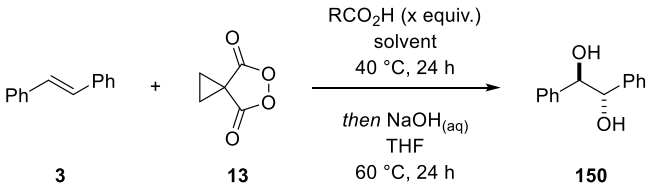


Table 1-6. Optimisation of anti-dihydroxylation.

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

[a]All reactions performed in duplicate at 0.5 M concentration. [b]Isolated yield after column chromatography. [c]Determined by ^1H NMR spectroscopy of the crude reaction mixture. [d]Bench acetic acid used in entries 1 and 2. In entries 3-15, acetic acid was dried for a minimum of 24 h over activated mol. sieves (3 Å). [e]Ac_2O added at 0.7 equiv.

Using the conditions of the *syn*-dihydroxylation as a basis for optimisation, *trans*-stilbene **3** and peroxide **13** (1.2 equiv.) were reacted in $CHCl_3$ with the equivalent of water in the reaction replaced with bench AcOH (**Table 1-6**, **Entry 1**). Following basic hydrolysis, the reaction still showed a preference for the *syn*-dihydroxylation (78% yield, 1:2 *anti*:*syn*), however, this result was far from the 33:1 reported in the presence of water. Performing the reaction in bench AcOH as solvent (**Entry 2**) increased the diastereoselectivity, now in favour of the *anti*-diol **150** (66%, 2:1 *anti*:*syn*). Drying the reaction with molecular sieves (3 Å) further increased the diastereoselectivity, albeit at the cost of the yield of the procedure (43%, 4:1 *anti*:*syn*, **Entry 3**). On investigating the solvent choice for the reaction, it was discovered that

apolar, hydrophobic solvents were best for the reaction. CH_2Cl_2 (**Entry 4**) provided the best result in terms of both yield and diastereoselectivity (78%, 6:1 *anti*:*syn*) with toluene (**Entry 5**) providing a slightly lower diastereoselectivity (72%, 4:1 *anti*:*syn*) and THF being generally unsuitable for the reaction (43%, 1:1 *anti*:*syn*). Investigating the equivalents of AcOH within the reaction (**Entries 7–9**) showed that an increase to 2 equiv. (**Entry 7**) was optimal, providing the *anti*-diol **150** in excellent diastereoselectivity (72%, 7:1 *anti*:*syn*). As with the work on peroxide **11**, higher concentrations of AcOH (**Entries 8** and **9**) proved detrimental to the reaction, either due to increased difficulty supressing water from the reaction or possible S_N2 inversion of the acetate group on the ester intermediates. The addition of Ac_2O to the reaction (**Entry 10**, in attempt to sequester any water that had not already been removed by the mol. sieves) had no overall effect on the reaction. Varying the peroxide **13** equiv. (**Entries 11-13**) revealed 1.5 equiv. as the optimal conditions for the reaction (**Entry 11**, 92%, 7:1 *anti*:*syn*). Finally, it was revealed that the reaction could tolerate alternative carboxylic acids as the secondary nucleophile, although the use of benzoic acid (**Entry 14**, 75%, 6:1 *anti*:*syn*) and 4-methoxybenzoic acid (**Entry 15**, 68%, 6:1 *anti*:*syn*) only lead to a reduced overall yield.

1.3.6.1 Karl Fischer Titrations

During the course of the reaction optimisations, a loss of diastereoselectivity was noted. Two conditions were changed at the same time when the loss of diastereoselectivity was noticed, a new bottle of *trans*-stilbene was used and butyl rubber caps were being used in place of Teflon coated caps. ^{1}H NMR spectroscopy of the reaction intermediates prior to hydrolysis suggested products resulting from the presence of water. In order to determine the origin of the water in the reaction, a variety of solutions were tested for water content by Karl-Fischer titration (**Table 1-7**).

Table 1-7. Karl-Fischer titration of various CH_2Cl_2 solutions.

Entry	Conditions	Results
1	SPS CH_2Cl_2	2.13 ppm
2	SPS CH_2Cl_2 over sieves for 2 h (Teflon cap)	21.8 ppm
3	SPS CH_2Cl_2 over sieves for 2 h (butyl rubber cap)	293.3 ppm
4	SPS CH_2Cl_2 + 1 mmol stilbene (Teflon cap)	170.27 ppm
5	SPS CH_2Cl_2 + AcOH + peroxide **13** (Teflon Cap)	n/a[a]

[a]Solution reacted with Karl-Fischer solution and reading was not possible.

From the results it was clear to see that the butyl caps were the source of water egress into the reaction (293 ppm, **Entry 3**). This likely occurred as a result of the CH_2Cl_2 permeating the butyl caps. Returning to Teflon coated vial caps saw a reaffirmation of the diastereoselectivity of the reaction.

In conclusion, a new set of conditions based around the use of the more reactive peroxide **13** was found to be optimal. Carrying out the reaction in CH_2Cl_2 with 2 equiv. of AcOH and 1.5 equiv. of peroxide **13** was found to produce *anti*-hydrobenzoin **150** in an excellent yield and diastereoselectivity (92%, 7:1 *anti*:*syn*). The reaction was carried out in microwave vials sealed with Teflon caps, which were shown to be essential to the reaction. With greater confidence in having found the best possible conditions for the reaction, it was decided to move on and examine the scope of the transformation.

1.3.7 Reaction Scope

1.3.7.1 Synthesis of Alkenes

Having found the optimal conditions for the *anti*-dihydroxylation reaction of *trans*-stilbene **3**, a set of alkenes were proposed in order to test the scope of the reaction (**Figure 1-22**).

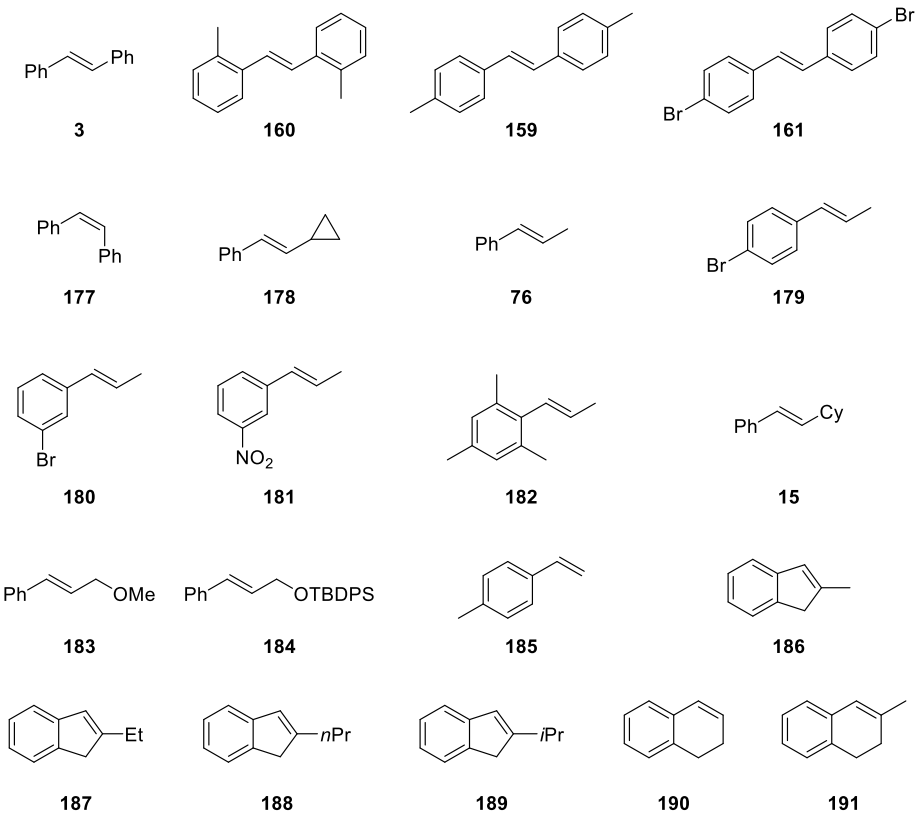
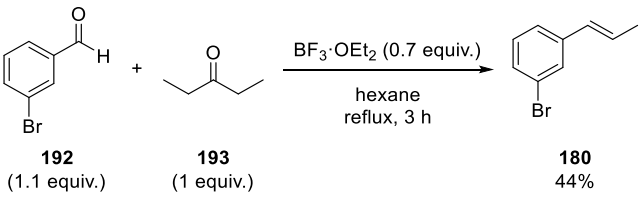


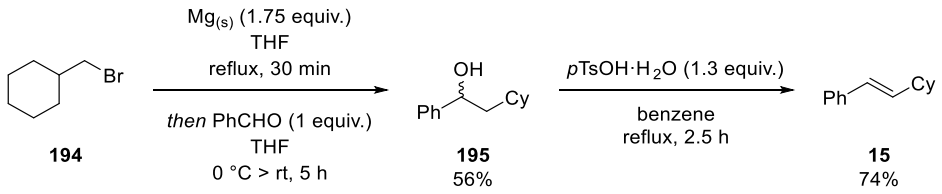
Figure 1-22. Planned alkene substrates.

A number of these substrates were not commerically available and therefore were required to be synthesised prior to use in the reaction. Stilbene derivatives **159**–**161** were synthesised as previously described (**Page 45–46**). 3-Bromo-β-methylstyrene **180** was conveniently synthesised in one step from the benzaldehyde **192** by an Aldol-Grob reaction (**Scheme 1-45**).[77]



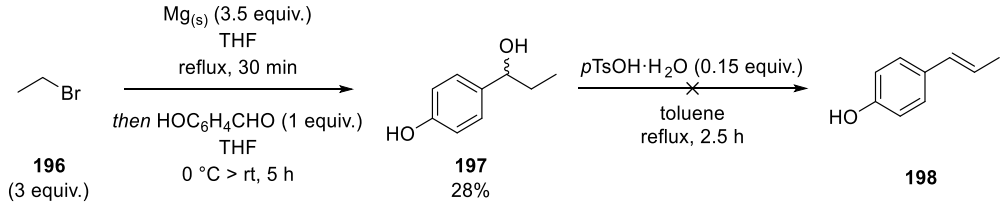
Scheme 1-45. Synthesis of alkene **180** by aldol-Grob reaction.[77]

Bromostyrene derivative **180** was isolated in a 44% yield following purification, exclusively as the *E*-isomer. Alkene **15** was synthesised *via* a two-step procedure (**Scheme 1-46**).



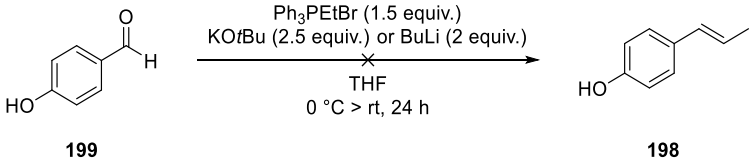
Scheme 1-46. Synthesis of alkene **15**.

First, the Grignard of bromomethylcyclohexane **194** was formed and reacted with benzaldehyde to form alcohol **195** in a 56% yield. This alcohol was then dehydrated in a Dean-Stark apparatus in the presence of *p*TsOH in benzene to afford alkene **15** in a 74% yield (an overall yield of 41%), exclusively as the *E*-isomer. Using this methodology, 3-nitrostyrene and trimethylstyrene derivatives **181** and **182** were synthesised by Carla Alamillo-Ferrer.[73] An attempt was also made to synthesise the 4-hydroxystyrene derivative **198** using this methodology (**Scheme 1-47**).



Scheme 1-47. Attempted synthesis of alkene **198** by Grignard addition.

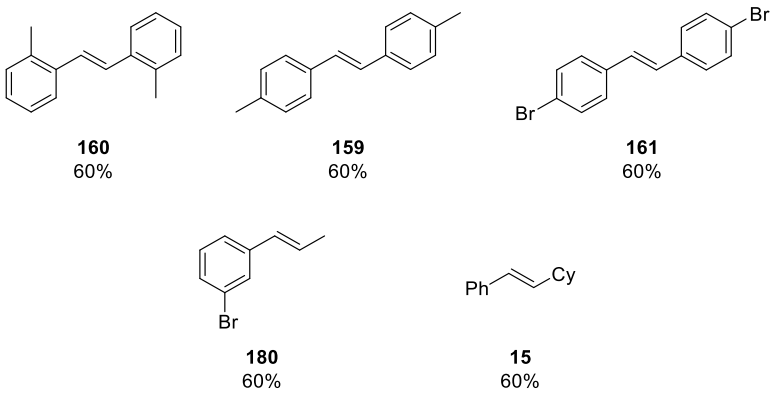
Ethylmagnesium bromide was formed and reacted with 4-hydroxybenzaldehyde to form alcohol **197** in a yield of 28%. This material was then subject to Dean-Stark conditions which unfortunately yielded none of the desired product. A Wittig reaction was selected to be the best alternative route to alkene **198** (**Scheme 1-48**).



Scheme 1-48. Attempted synthesis of alkene **198** by Wittig reaction.

Unfortunately, the Wittig reaction using KO*t*Bu as the base provided no observable product. This was likely due to the acidic phenol proton on aldehyde **199** reacting with either the base or the deprotonated phosphonium reagent. In an attempt to circumvent this difficulty, BuLi was chosen as the base as it was believed that this would allow

for the deprotonation of both the phenol **199** and the phosphonium salt. While product was observed in this case, it was obtained as a 1:1 mixture of the *E* and *Z* isomers of the alkene, which were inseparable by chromatography. As such, the synthesis of alkene **198** was abandoned in order for focus to be applied to the reaction scope.



160 60%
159 60%
161 60%
180 60%
15 60%

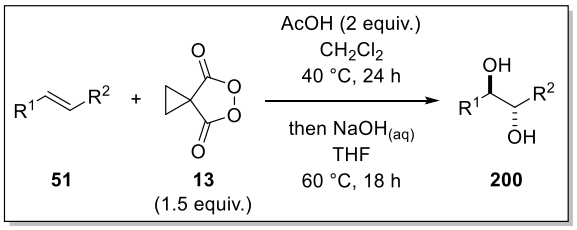
Scheme 1-49. Alkenes synthesised as substrates for the *anti*-dihydroxylation reaction.

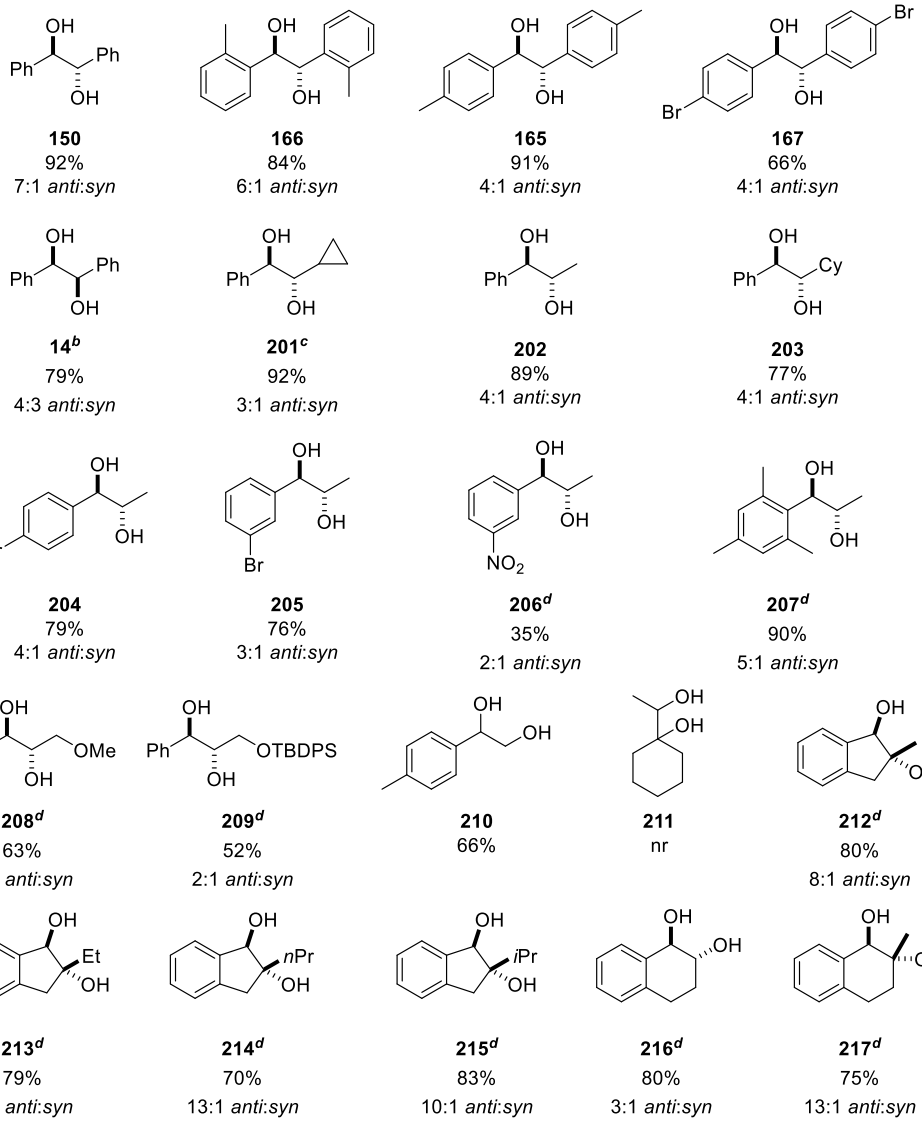
In summary, five additional alkenes (**Figure 1-49**) were successfully synthesised as substrates for the optimised *anti*-dihydroxylation reaction using a variety of different methodologies.

1.3.7.2 Substrate Scope

A scope of 22 alkenes was subjected to *anti*-dihydroxylation under the established optimal conditions. These results are summarised in **Table 1-8**.

Table 1-8. Anti-dihydroxylation substrate scope.





[a]Yields quoted are isolated yields. All reactions run in duplicate, yields are quoted as an average of two experiments. Diastereoselectivity deteremined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b]Reaction used *cis*-stilbene as starting material. [c]Starting material alkene was a 3:1 mixture of *E*:*Z* isomers. [d]Substrates examined by Carla Alamillo-Ferrer.[73]

Trans-stilbene and its derivatives were well tolerated in the reaction, producing the corresponding *anti*-diols **150** and **159-161** in high yield and modest diastereoselectivity (66–92%, 4:1–7:1 *anti*:*syn*). *Cis*-stilbene resulted in the

corresponding diol **14** in a good yield but poor diastereoselectivity (79%, 4:3 *anti*:*syn*). It is believed that this loss in diastereoselectivity occurs as a result of σ-bond rotation prior to dioxonium formation in order to relieve steric strain, rather than the effect of any extraneous water on the reaction (**Figure 1-23**).

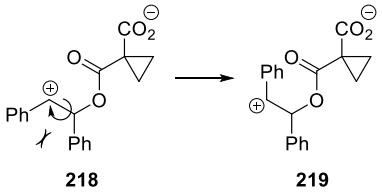


Figure 1-23. Rotation of zwitterion prior to dioxonium formation.

This was further evidenced by a relative lack of peaks in the ~5 ppm region of the ^{1}H NMR spectra of the crude material prior to hydrolysis, which would suggest products formed by the presence of water (**Figure 1-24**).

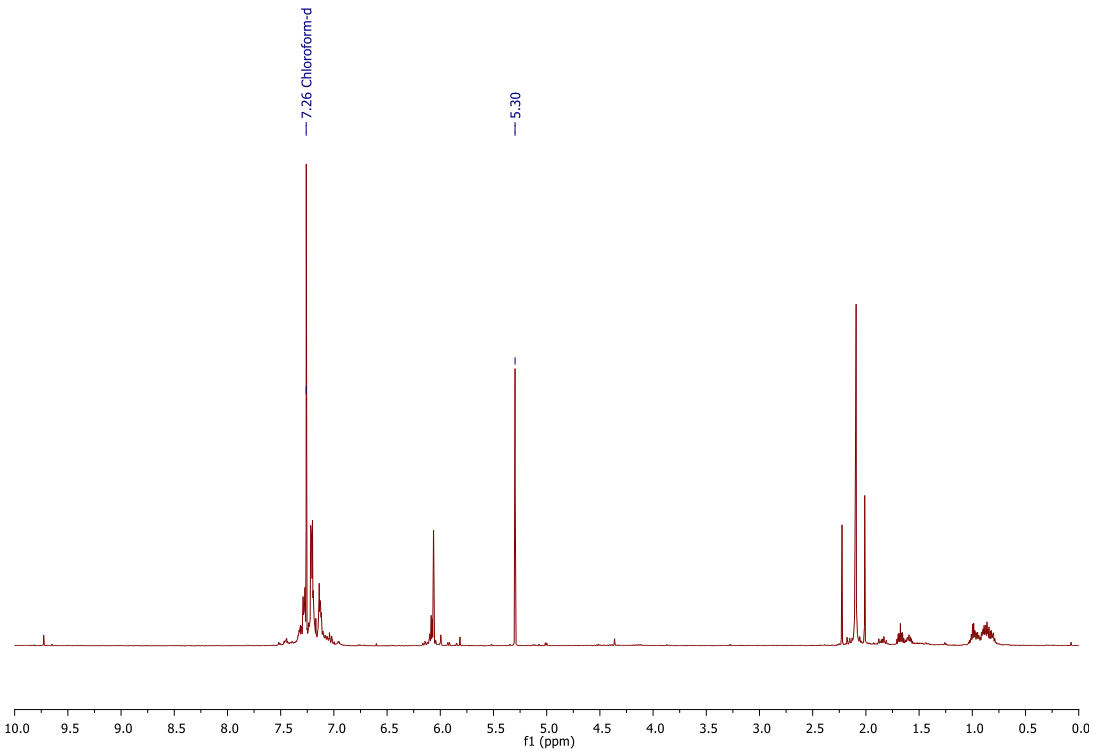
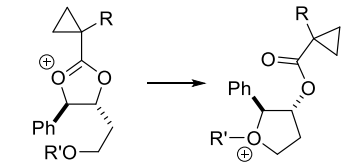


Figure 1-24. ^{1}H NMR spectra of crude material prior to hydrolysis for *cis*-stilbene **177**.

The preferred route to diol **14** would therefore be *via* the *syn*-dihydroxylation of *trans*-stilbene **3** rather than the *anti*-dihydroxylation of *cis*-stilbene **177**.

β-Cyclopropylstyrene was converted into its *anti*-diol **201** in excellent yield and with a retention of the double bond integrity (92%, 3:1 *anti*:*syn* from a 3:1 *E*:*Z* alkene). Further β-alkylstyrene examples were converted into their respective *anti*-diols **202**–**206** in generally high yields with reasonable diastereoselectivity (76–90%, 3:1–5:1 *anti*:*syn*). The one exception to this was the 3-nitro derivative for which the corresponding *anti*-diol **206** was obtained in low yield and diastereoselectivity (35%, 2:1 *anti*:*syn*). It is believed that this is a result of the reduced nucleophilicity of alkene **181** which only reached low levels of conversion due to the strongly electron withdrawing nature of the nitro group.

The *anti*-diols of cinnamyl alcohol derivatives **208** and **209** were prepared by Carla Alamillo-Ferrer[73] in modest yield and low diastereoselectivity (52–63%, 2:1 *anti*:*syn*). It could be argued that the generally lower observed diastereoselectivities for these substrates may have been as a result of oxonium ion **221** formation competing with dioxonium **220** (**Figure 1-25**).



220
R = H or CO_2H

221
R = H or CO_2H

Figure 1-25. Potential explaination of stereochemical erosion for substrates **208** and **209**.

Ring opening of oxonium **221** by AcOH would lead to an intermediate which would produce *syn*-diol as opposed to *anti*-diol **208**/**209** upon hydrolysis. Although this is purely conjecture, the reaction of cinnamyl alcohol (R` = H) with peroxide **11** was recently reported to form tetrahydrofurans by a similar mechanism.[78] However, were this the case, it would be expected that the diastereoselectivities of **208** and **209** would vary due to the large steric differences in the R` groups.

The reaction of 4-methylstyrene produced the corresponding diol **210** in modest yield (66%). As this was a lower yield of diol **210** than in the *syn*-dihydroxylation reaction (90%)[16] it is believed that the *syn*-dihydroxyation methodology would be the preferred synthesis of diol **210**. Unfortunately, the limitations of the methodology were shown

in the reaction of a cyclohexilidene which produced a messy mixture of compounds, from which diol **211** could not be isolated.

A variety of indene and dihydronaphthalene derivatives **212–217** were investigated by Carla Alamillo-Ferrer[73] in good yield and excellent diastereoselectivity (70–83%, 3:1–13:1 *anti*:*syn*). Interestingly, it was revealed that increasing the steric bulk in position 2 of the indene led to increased levels of diastereoselectivity. It is believed that this example supports computational work previously carried out on the *syn*-dihydroxylation, which suggest that formation of dioxonium **222** arises from an *endo* **223** interaction of peroxide **13** and alkene **186-191** whereas 7-membered ring **224** arises from the *exo* **225** interaction (**Figure 1-26**).[70]

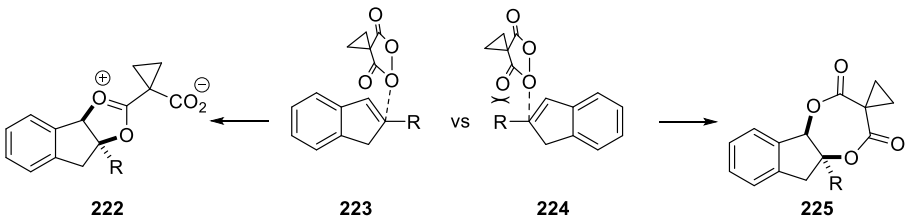


Figure 1-26. *Endo* **223** vs. *exo* **224** transition state comparison.

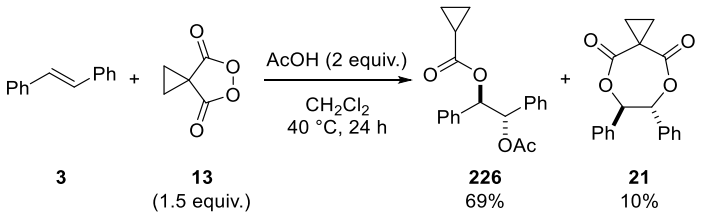
Although the calculations were carried out for *trans*-stilbene **3** under the *syn*-dihydroxylation conditions, it is proposed that the same findings can be applied to the indene derivatives under the *anti*-dihydroxylation conditions. As dioxonium **222** is believed to be the source of *anti*-diol whereas 7-membered ring **225** is proposed to be the source of *syn*-diol (and therefore reduction of reaction diastereoselectivity, discussed on **Pages 44–45**), the relationship between these two transition states is important to the reaction diastereoselectivity. As this size of R is increased, the *endo* transition state **223** will be favoured over the *exo* **224** due to steric interactions, which is reflected in the diastereoselectivity of the products.

In summary, the optimal *anti*-dihydroxylation conditions were tested on 22 alkene substrates. Stilbene, styrene, indene and dihydronaphthalene derivatives were converted into their respective diols in generally high yields and generally reasonable to excellent diastereoselectivity (35–92%, 4:3–13:1 *anti*:*syn*). Unfortunately aliphatic alkenes were not shown to be tolerated by the reaction, however, this was already a known limitation for the malonoyl peroxide reagents.

1.3.8 Mechanistic Investigations

1.3.8.1 Reaction Intermediates of *Trans*-Stilbene 3

In an effort to gain an understanding of the reaction mechanism, it was determined that the first step should involve the isolation of the reaction intermediates prior to hydrolysis (**Scheme 1-50**).



Scheme 1-50. Synthesis of reaction intermediates.

The reaction between *trans*-stilbene **3** and peroxide **13** in the presence of 2 equiv. of AcOH yielded two intermediates, diester **226** and 7-membered ring **21** in a 69% and 10% yield respectively. The identity of these compounds was independently confirmed by synthesis of **226**, **21** and the *syn*-diastereomer of **226** by Carla Alamillo-Ferrer.[73] The mechanism of formation of 7-membered ring **21** is previously reported and is believed to arise from a direct coupling of charges following nucleophilic ring opening of peroxide **13** (**Figure 1-27**).[17]

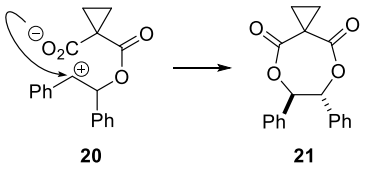


Figure 1-27. Formation of 7-membered ring **21**.[17]

It is believed that diester **226** originates from a ring opening of dioxonium **22** by AcOH. The intermediate must then undergo a decarboxylation to form diester **226** (**Figure 1-28**).

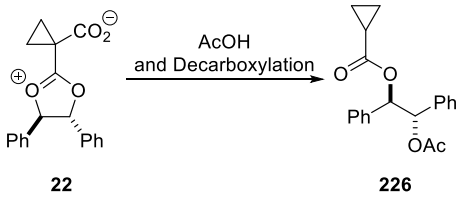
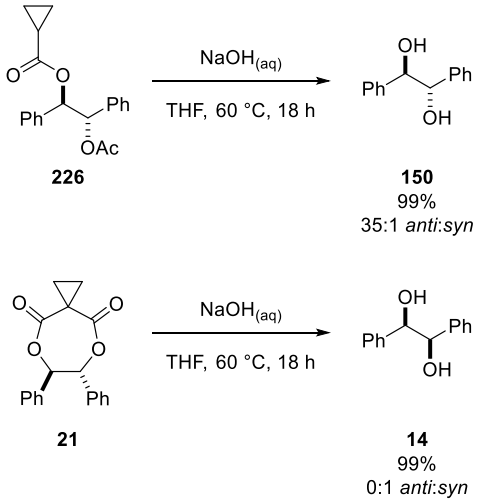


Figure 1-28. Formation of diester **226**.

The exact order of decarboxylation and dioxonium ring opening cannot be identified with the available data, however, it is believed that dioxonium ring opening follows decarboxylation. This is due to the differing nucleophilicities of AcOH and water. Water is much more nucleophilic than acetic acid and therefore the rate of dioxonium **22** collapse is faster than decarboxylation for the *syn*-dihydroxylation process and therefore it does not occur. In the *anti*-dihydroxylation, ring opening of dioxonium **22** is slower than decarboxylation due to the reduced nucleophilicity of AcOH.

1.3.8.2 Hydrolysis of *Trans*-Stilbene Intermediates

Interestingly, the isolated ratio of diester **226** and 7-membered ring **21** was roughly 7:1 (69%:10%). As this closely mirrored the diastereomeric ratio of the reaction (7:1) it was believed that both of these intermediates would hydrolyse to give the *anti*- and *syn*-diols **150** and **14** respectively (**Scheme 1-51**).



Scheme 1-51. Hydrolysis of reaction intermediates.

The hydrolysis of 7-membered ring **21** was already reported by Michael Rawling to produce pure *syn*-diol **14** in a 99% yield.[72] Hydrolysis of diester **226** obtained *via* the *anti*-dihydroxylation yielded *anti*-diol **150** (35:1 *anti*:*syn*) in a 99% yield.

Examination of diester **226** by GCMS revealed two peaks (retention time 15.632 and 15.682 minutes respectively) in a ratio of 35:1 (**Figure 1-29**).

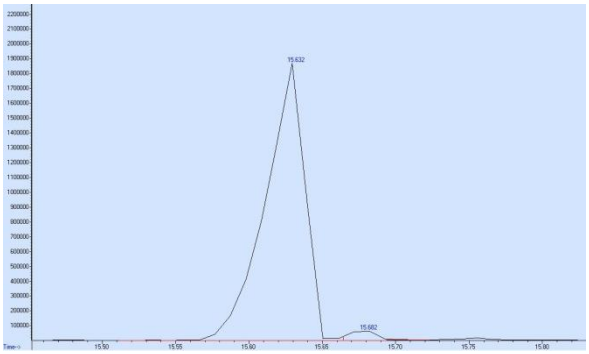


Figure 1-29. GCMS trace of diester **226**, showing two peaks.

These peaks were believed to correspond to the *anti*- and *syn*-diastereomers of diester **226** respectively, revealing a highly diastereoselective process. Theoretically, isolation of intermediates at this stage could give access to products of much higher diastereoselectivity if required, with a slight reduction in yield.

As hypothesised, diester **226** and 7-membered ring **21** appear to be the intermediate sources of *anti*- and *syn*-diol **150** and **14** repectively. Having isolated the intermediates in the reaction with *trans*-stilbene **3** and identified their structure, we were interested in determining the regioselectivity of dioxonium opening for non-symmetrical alkenes.

1.3.8.3 Regioselectivity of Dioxonium Opening.

It was postulated that, for a non-symmetrical alkene such as *p*-tolylstyrene **185**, two possible regioisomeric sites of dioxonium **227** ring opening existed (**Figure 1-30**).

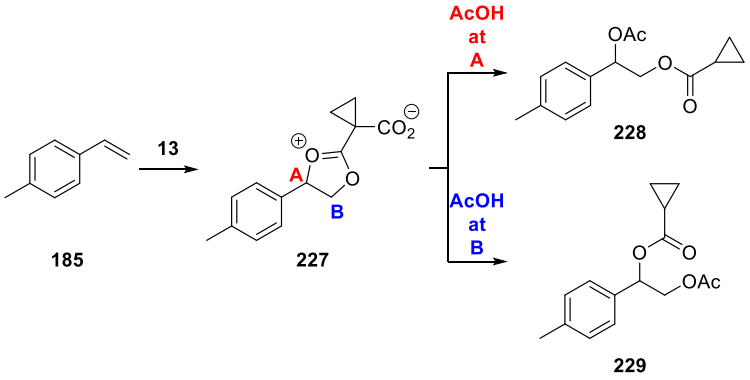


Figure 1-30. Two potential regioisomeric intermediates **228** and **229** exist for non-symmetrical alkenes.

AcOH could potentially open dioxonium **227** at either **carbon A** or **carbon B**, leading to diester **228** and **229** respectively. This could be useful, as selectivity could lead to the synthesis of differentially protected hydroxyl groups. To determine any selectivity within the reaction, the independent synthesis of **228** and **229** was proposed (**Figure 1-31**).

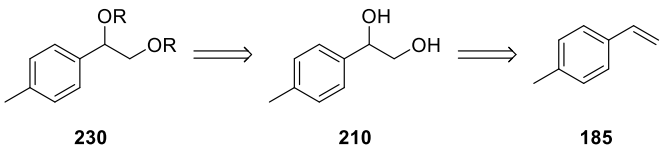
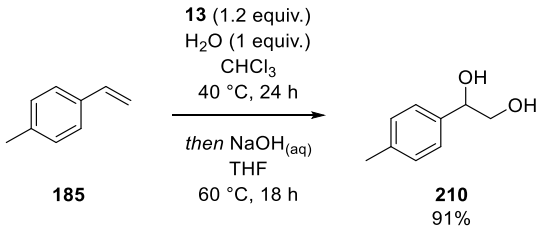


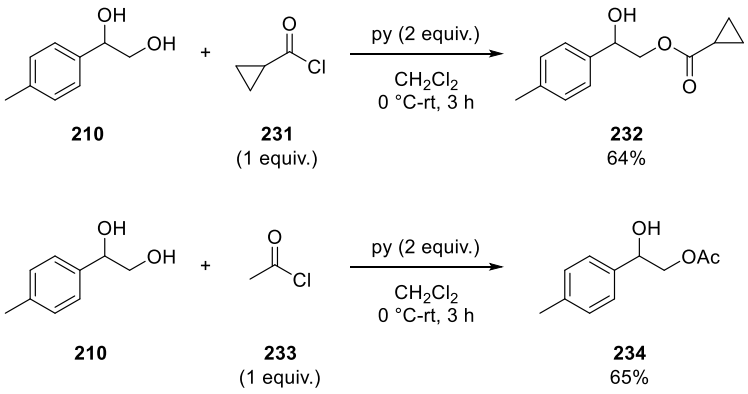
Figure 1-31. Proposed synthesis of diesters **228** and **229**.

Synthesis of diesters **228** and **229** could be achieved by sequential esterification of the primary and then the secondary alcohol from diol **210**. Diol **210** could be synthesised by dihydroxylation of styrene **185** (**Scheme 1-52**).



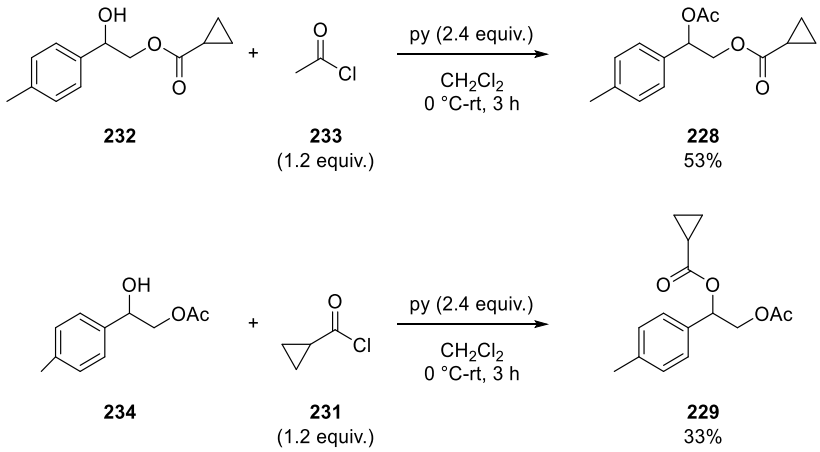
Scheme 1-52. Synthesis of diol **210**.

The synthesis of diol **210** was achieved by malonoyl peroxide mediated *syn*-dihydroxylation of styrene **185** in 91% yield. Diol **210** was then split into two pots. One portion was treated with an equivalent of acid chloride **231** and the other with an equivalent of AcCl **233**, both in the presence of pyridine (**Scheme 1-53**).



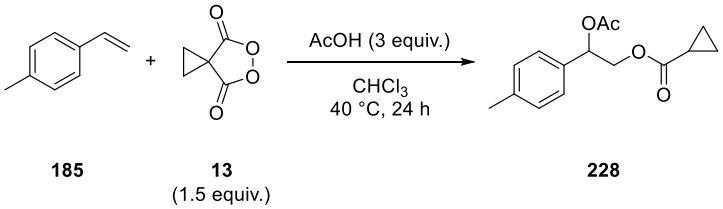
Scheme 1-53. Synthesis of esters **232** and **234**.

Esters **232** and **234** were isolated in 64% and 65% yield using strict equivalent control to prevent diesterification. Diesters **228** and **229** were then synthesised from esters **232** and **234** (**Scheme 1-54**).



Scheme 1-54. Synthesis of diesters **228** and **229**.

Diesters **228** and **229** were synthesised in 53% and 33% yield respectively. With these authentic samples available, the *anti*-dihydroxylation of styrene **185** was carried out under the standard conditions (**Scheme 1-55**).



Scheme 1-55. Analysis of AcOH regiochemistry.

The crude reaction mixture was analysed by HMBC NMR spectroscopy and compared to the HMBC NMR spectra of the pure materials **228** and **229** (**Figure 1-32**).

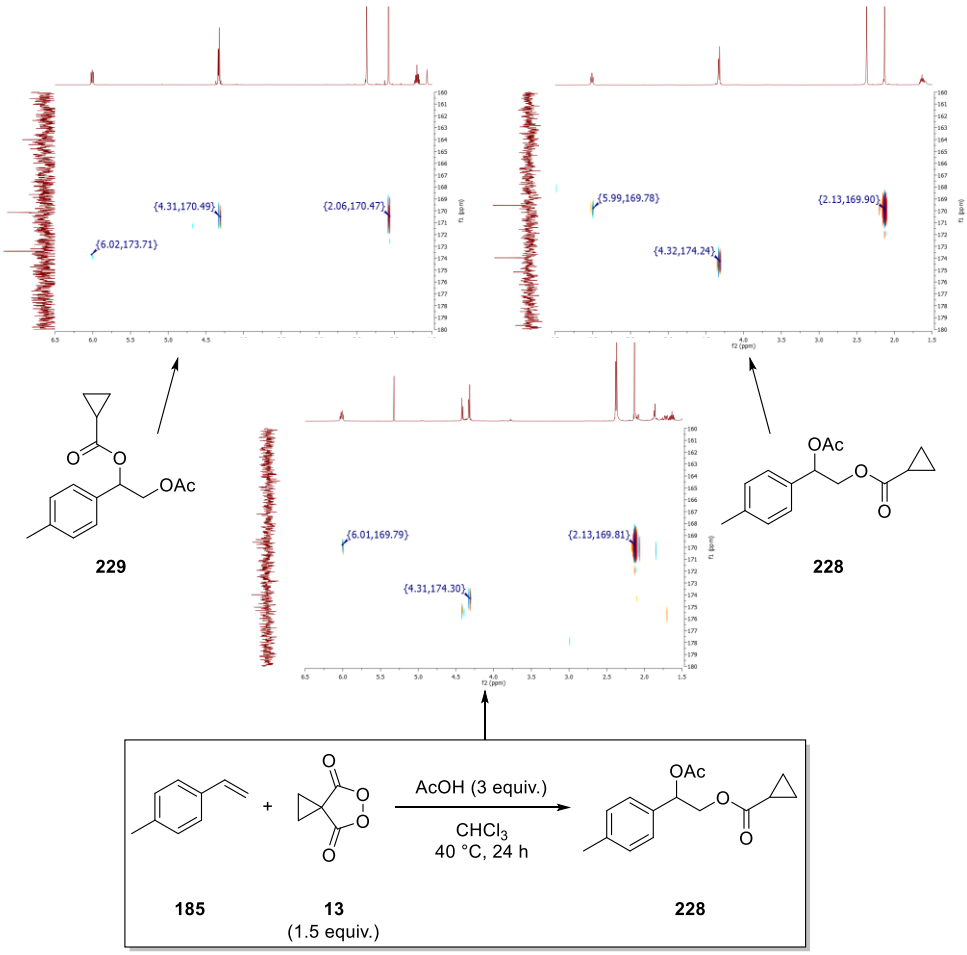


Figure 1-32. Comparison of HMBC spectra for **228**, **229** and the crude reaction mixture from the *anti*-dihydroxylation of styrene **185** showing the key correlations.

The HMBC NMR spectra of the three samples are shown above in **Figure 1-32**. For diester **229** the key correlations between the acetate protons (2.06 ppm) and the terminal protons (4.31 ppm) with the acetate carbonyl (170.5 ppm) can be obeserved. In diester **228** key correlations were observed between the acetate protons (2.13 ppm) and the benzylic proton (5.99 ppm) with the acetate carbonyl (169.8 ppm). All of these

correlations are as expected given the structures. In the spectra of the crude reaction mixture, correlations are observed between the acetate protons (2.13 ppm) and the benzylic protons (6.01 ppm) with the acetate carbonyl (169.8 ppm). Given the correlations observed and their similarity to independently synthesised diester **228** it is proposed that diester **228** is the only regioisomer formed in the reaction, at least by detection on an NMR scale. This intermediate occurs as a result of acetic acid ring opening dioxonium **227** at the benzylic carbon, likely due to the electron withdrawing nature of the aromatic ring making it the more electrophilic centre (**Figure 1-33**).

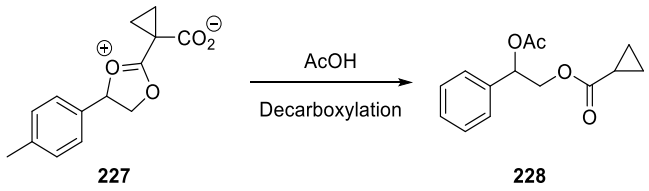
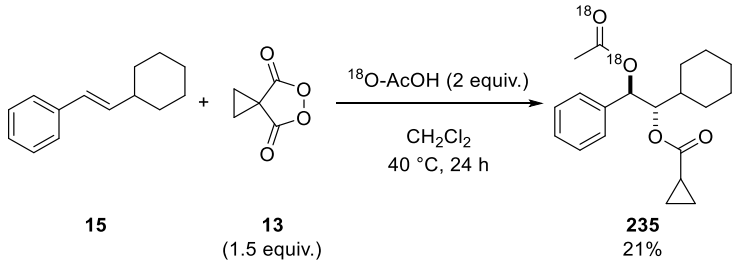


Figure 1-33. Evidence suggests dioxonium **227** ring opening occurs at the benzylic position leading to diester **228**.

In order to provide further evidence for the hypothesis, it was determined that an experiment could be conducted with ^{18}O labelled acetic acid.

1.3.9 ^{18}O-Labelling Experiments

^{18}O-Labelled acetic acid was purchased and used in the *anti*-dihydroxylation of non-symmetrical alkene **15** (**Scheme 1-56**).



Scheme 1-56. *Anti*-dihydroxylation with ^{18}O-labelled AcOH.

Diester **235** was isolated from the reaction in a low 21% yield. The low yield is likely explained by the small scale of the reaction. Initially, the regioselectivity of the ester functional groups were arbitrarily assigned based on comparison with previous experiments. This regioselectivity was supported by HMBC NMR spectra of diester **235** (**Figure 1-34**).

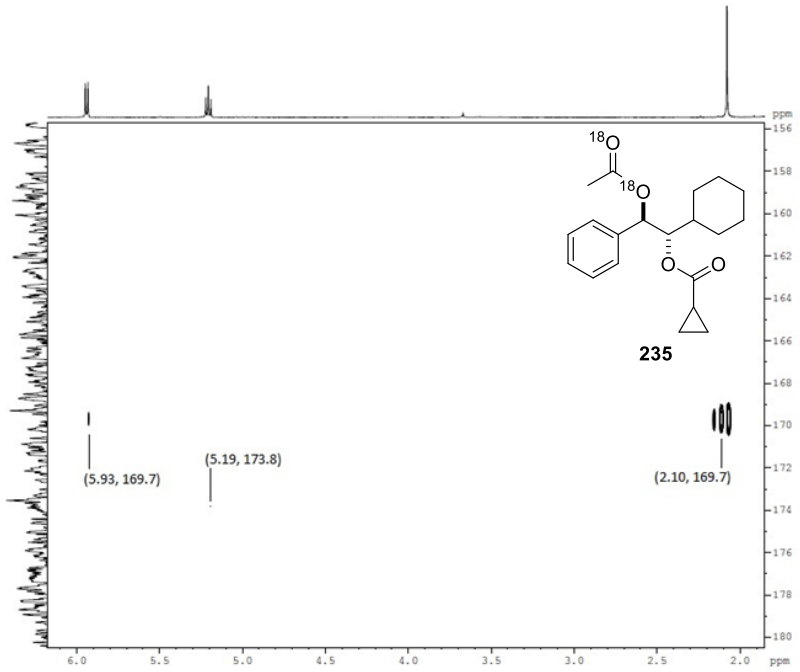


Figure 1-34. HMBC NMR spectra of diester **235**, zoomed in to show the key interactions.

Correlations can be observed between the acetate protons (2.10 ppm) and the benzylic proton (5.93 ppm) with the acetate carbonyl (169.7 ppm) supporting the predicted regiochemistry of diester **235** This conclusion was confirmed by single crystal X-ray of an unlabelled sample of diester **235** (**Figure 1-35**).

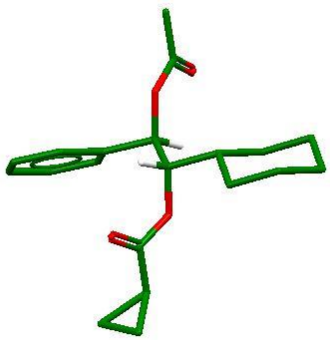
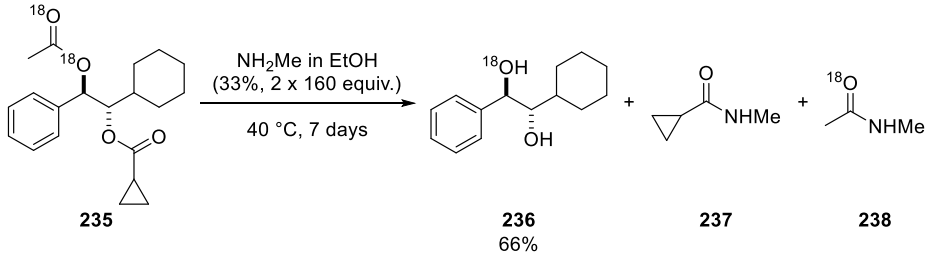


Figure 1-35. X-ray crystal structure of an unlabelled sample of diester **235**.

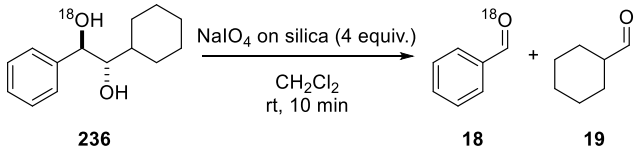
As well as confirming the hypothesis of AcOH opening the dioxonium at the benzylic position, the crystal structure also clearly shows the *anti*-relationship of the two ester

groups. To further support this conclusion, diester **235** was subjected to aminolysis conditions (**Scheme 1-57**).



Scheme 1-57. Aminolysis of diester **235**.

The aminolysis of diester **235** produced ^{18}O-labelled diol **236** in a 66% yield after an extended reaction time (7 days). GCMS of the crude reaction mixture also revealed amides **237** and **238**, with a single ^{18}O label incorporated in amide **238**. Diol **236** was then subjected to oxidative cleavage by $NaIO_4$ on silica (**Scheme 1-58**).



Scheme 1-58. Oxidative cleavage of diol **236**.

Oxidative cleavage of diol **236** resulted in aldehydes **18** and **19**, with the ^{18}O label exclusively and entirely incorporated in benzaldehyde **18**. This confirmed both the hypothesis that *anti*-diol **236** is formed exclusively from the ring opening of the dioxonium by AcOH and that the regioselectivity of the dioxonium ring opening is controlled by the electronics of the dioxonium.

1.3.10 Proposed Mechanism of *Anti*-Dihydroxylation

Having thoroughly examined the conditions of the reaction and developed a thorough understanding of both the *syn*- and *anti*-dihydroxylation reactions, the proposed mechanism for the reaction is shown below in **Figure 1-36**.

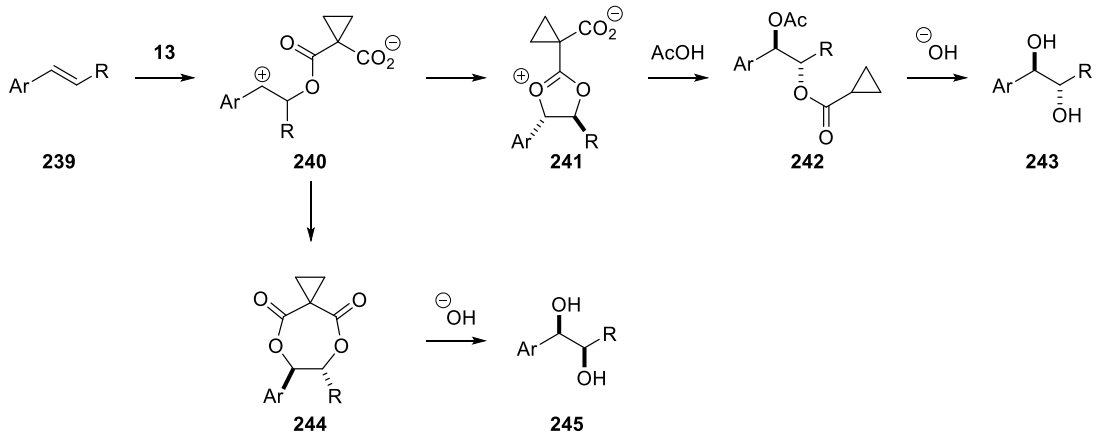
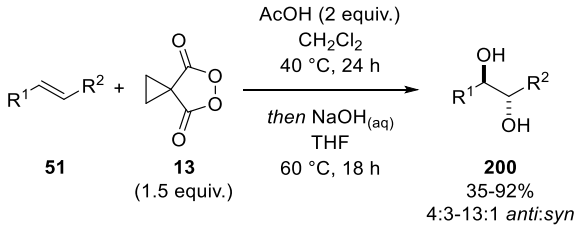


Figure 1-36. Proposed reaction mechanism of anti-dihydroxylation.

The initial reaction of peroxide **13** and alkene **239** forms zwitterion **240**. Direct charge combination gives 7-membered ring **244** which leads to the unwanted *syn*-diol **245** upon hydrolysis. Alternatively, formation of dioxonium **240** occurs *via* cyclisation of the oxygen lone pair of the ester. Dioxonium ion **241** is then opened by AcOH regioselectively, at the most electronically favourable carbon (the benzylic position), forming diester **242**. Hydrolysis of diester **242** gives *anti*-diol **243**. The ratio of dioxonium **242** formation to 7-membered ring **244** is controlled by the substrate alkene **239** and is reflected by the reaction diastereoselectivity.

1.4 Conclusions and Future Work

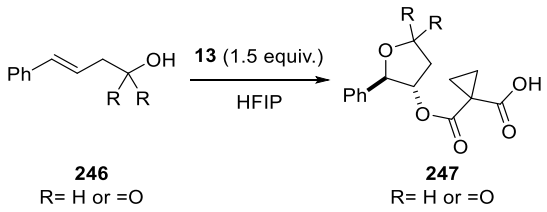
In summary, a novel one-pot *anti*-dihydroxylation reaction has been developed using malonoyl peroxides **13** in a manner complementary to an existing *syn*-dihydroxylation procedure. This process was optimised using *trans*-stilbene **3** as the model substrate. The optimal conditions were found to be 1.5 equiv. of peroxide **13** and 2 equiv. of AcOH in CH_2Cl_2 as the solvent. Using these optimal conditions a scope of 21 alkenes **51** were successfully converted into their *anti*-diols **200** in generally high yields (35–92%) and good to excellent diastereoselectivities (4:3–13:1 *anti*:*syn*) (**Scheme 1-59**).



Scheme 1-59. Optimised *anti*-dihydroxylation procedure.

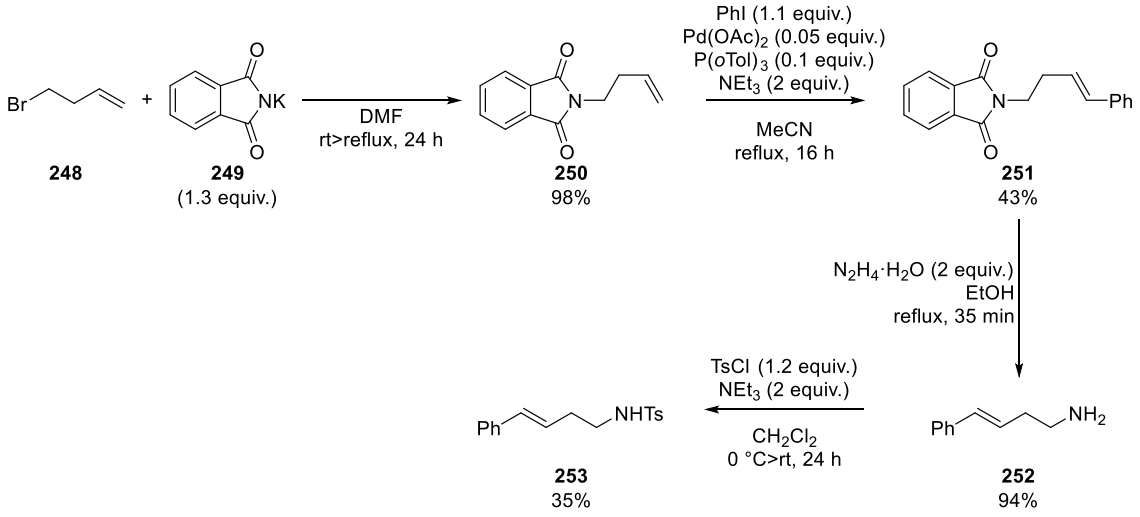
Mechanistic studies were undertaken which showed the origin of the oxygen atoms in the resultant diols, the structure of the intermediates prior to hydrolysis and the regioselectivity of dioxonium ring opening. These results were subsequently published.[74]

The scope and applicability of malonoyl peroxide mediated dihydroxylations has seen significant growth since the conclusion of this project. An intramolecular variant of the *anti*-dihydroxylation reaction has been developed that allows for the synthesis of tetrahydrofurans and lactones (**Scheme 1-60**).[78]



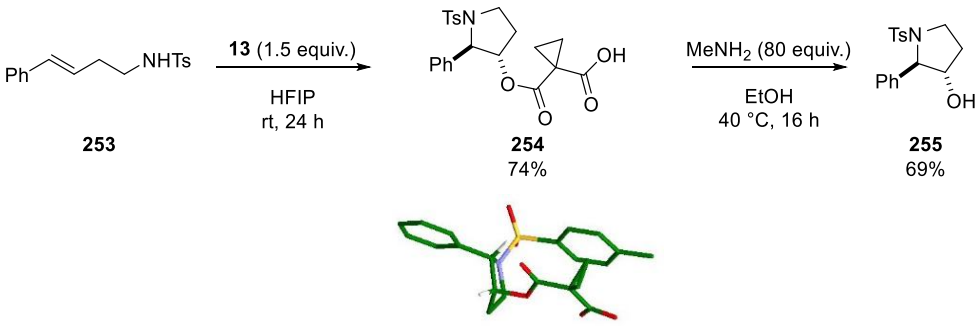
Scheme 1-60. Oxidative cyclisation with malonoyl peroxide **13**.[78]

Using this reaction as a template, we were also interested to see if we could develop an intramolecular oxyamination reaction derived from this methodology. To that end, alkene **253** was synthesised in this project to test this idea (**Scheme 1-61**).



Scheme 1-61. Synthesis of alkene **253**.

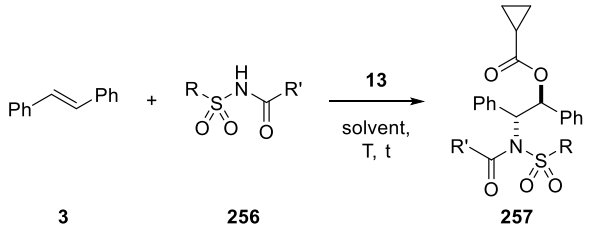
Alkylation of potassium phthalimide **249** with alkene **248** gave alkene **250** in a 98% yield, greater than the yield observed by Xiaoxu (78%).[79] Heck cross-coupling of alkene **250** with phenyl iodide yielded styrene **251** in a 43% yield was adapted from existing Heck conditions within the lab.[72] Subsequent phthalimide deprotection with hydrazine in refluxing ethanol gave amide **252** in 94% yield. Malonoyl peroxides have been known to react destructively with amines and as such, amine **252** was protected with tosyl chloride to give sulfonamide **253** in a 35% yield (13.8% overall yield). Sulfonamide **253** was then treated with peroxide **13** in HFIP (**Scheme 1-62**).



Scheme 1-62. Synthesis of and crystal structure of pyrrolidine **254**.

Pleasingly, sulfonamide **253** reacted with peroxide **13** to form pyrrolidine **254** which was isolated in a 74% yield. The structure of **254** was confirmed by single crystal X-ray. This was the first example of oxyamination shown with malonoyl peroxides. This methodology has subsequently been optimised and expanded by Carla Alamillo-Ferrer and is currently awaiting publication.

Currently, work within the group is focused on the development of an organocatalytic variant of the dihydroxylation reaction (detailed in **Chapter 2**) and an intermolecular oxyamination using sulfonimides **256** as secondary nucleophiles (**Scheme 1-63**).



Scheme 1-63. Intermolecular oxyamination with malonoyl peroxide **13** is a current focus of research within the group.

Chapter 2: *Organocatalytic Sulfoxidation*

Chapter 2. Organocatalytic Sulfoxidation

2.1 Introduction

Catalysis is a core concept of chemistry describing the decrease in activation energy of a reaction caused by the addition of a substance which can be recovered upon completition. Traditionally, catalysis has been carried out by metals, either heterogeneous such as the iron salts used in the Haber process[80] or homogeneous palladium derivatives in cross-coupling processes such as the Suzuki-Miyaura reaction.[81]

Organocatalysis specifically refers to "the acceleration of chemical reactions with a substoichiometric amount of organic compound" and was a term coined by MacMillan in 2000.[82] Following this definition, the number of publications containing the concept of "Organocatalysis" has grown exponentially (**Figure 2-1**).

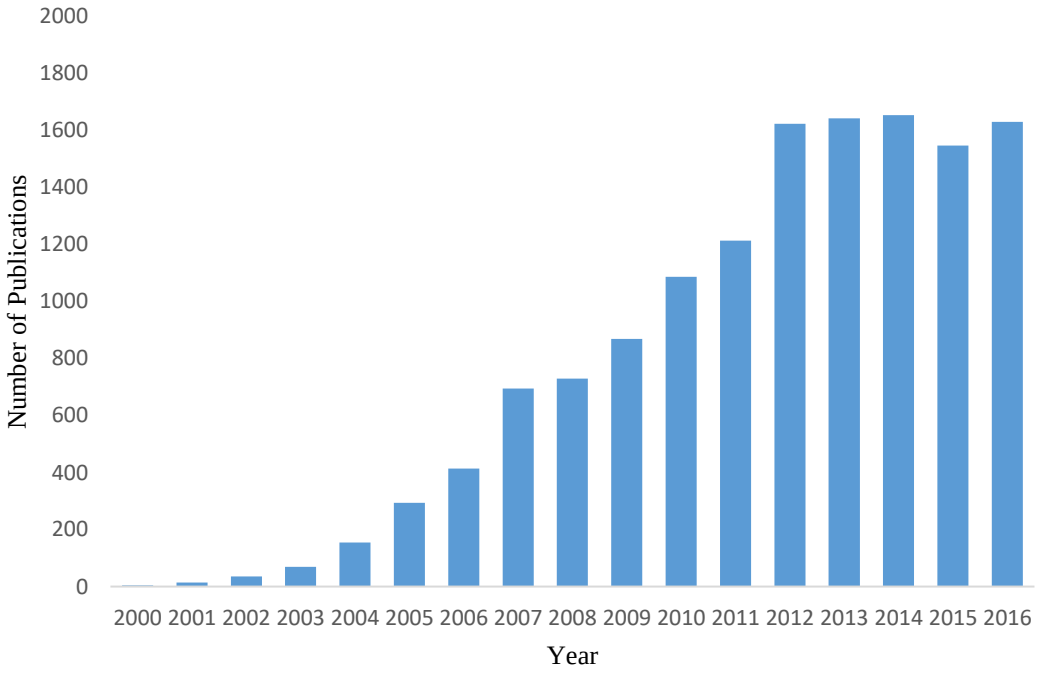


Figure 2-1. Growth of publications containing the concept "Organocatalysis" (Scifinder September 2017)

Despite this, focus on the development of oxidation reactions using organocatalytic methodologies has been limited. Perhaps the most well-known example of organocatalytic oxidation is the Shi epoxidation, which uses fructose derived reagents

(such as **117**) for the epoxidation of alkenes **7** with Oxone® as the stoichiometric oxidant (**Figure 2-2**).[55]

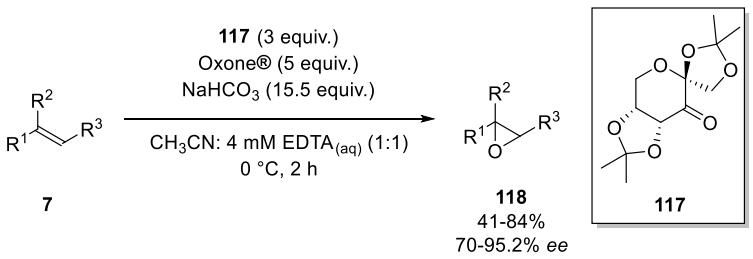


Figure 2-2. The Shi epoxidation.[55]

Details of the work carried out by Shi and co-workers can be found described on **Pages 25–30**. The Shi epoxidation is not the only reported procedure to make use of ketones as catalyst for oxidation reactions.

2.1.1 Ketone Derived Catalysts – Perhydrates

α-Hydroxy hydroperoxides, more commonly known as perhydrates **259**, are a versatile class of organic peroxides. These compounds are generally formed from aldehydes or ketones by the addition of hydrogen peroxide, although they may also be prepared by the photolysis of alcohols and the ozonolysis of alkenes in the presence of water (**Figure 2-3**).[83]

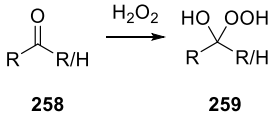
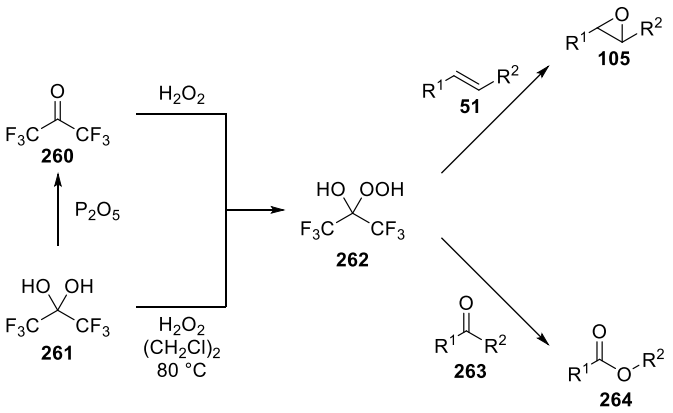


Figure 2-3. Perhydrates **259** can be formed from aldehydes and ketones.[83]

Isolated examples of perhydrates, however, are limited. Often, perhydrates return to the corresponding ketone and hydrogen peroxide upon standing.[84] Of exception to this statement however, is the perhydrate of hexafluoroacetone **262**. Perhydrate **262** has received notable attention within the literature due to its high oxidation potential, equal in ability to that of peracids as demonstrated by its utility in the epoxidation of alkenes[85] and the Baeyer-Villager oxidation of ketones.[86] The synthesis of **262** can be achieved from hexafluoroacetone **260**, however, as **260** itself requires liberation from the commercially available hydrate **261** by distillation over P_2O_5 and is a gas at room

temperature, the preferred route of synthesis is directly from the hydrate **261** (**Scheme 2-1**).[83]



Scheme 2-1. Preparation and reactions of perhydrate **262**.[83,85-86]

These reactions of perhydrate **262** liberate hydrate **261** as a co-product and as a result, the catalytic implications of perhydrate **262** were quickly noted.[85] It was suggested that a simple catalytic cycle should be obtainable whereby hexafluoroacetone **260** would react with hydrogen peroxide to form perhydrate **262** that on reaction with a nucleophile (*i.e.* an alkene) would lead to the oxidised nucleophile (*i.e.* an epoxide) as a product and hydrate **261**. Hydrate **261** should then react with another molecule of hydrogen peroxide under its own acidity (pKa = 6.76) to reform perhydrate **262** and a molecule of water (**Figure 2-4**).[83]

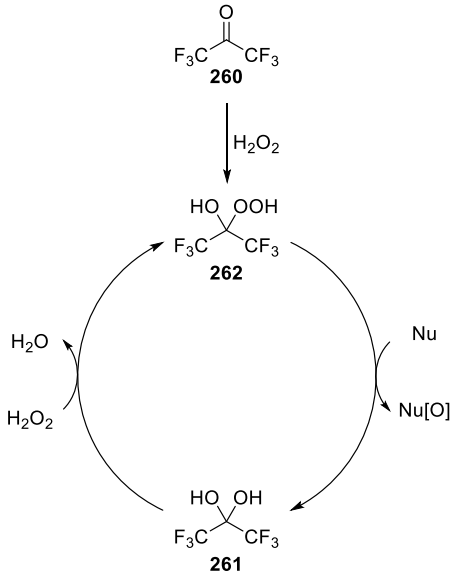
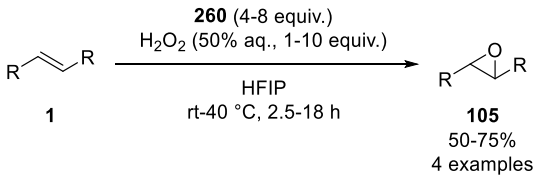


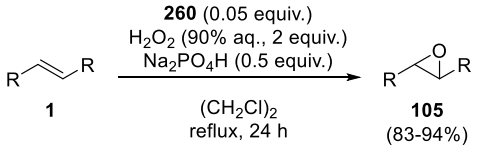
Figure 2-4. Proposed catalytic cycle for perhydrate **262**.[83]

In 1973, a patent by Kim revealed that this was indeed possible.[87] Kim demonstrated that a small variety of mostly alkyl substituted alkenes could be converted to the corresponding epoxide in reasonable yield using this methodology (**Scheme 2-2**).



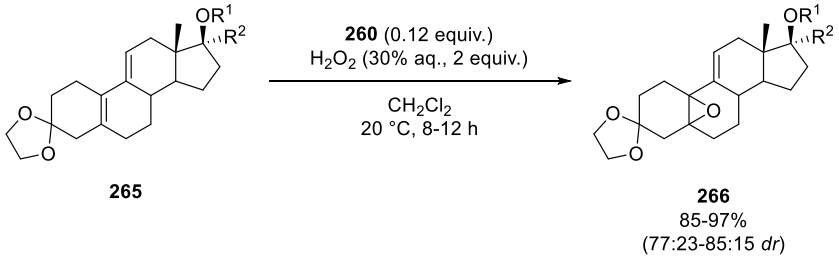
Scheme 2-2. Epoxidation with hexafluoroacetone **260** reported by Kim.[87]

Although Kim demonstrated that this was indeed possible, superstoichiometric loadings of both "catalyst" **260** and hydrogen peroxide make this process open to improvement. However, Kim provided a proof of concept that perhydrate **262** could indeed by formed *in situ*. Biloski and co-workers were able to use this information in order to report a truly catalytic process using hexafluoroacetone **260** (**Scheme 2-3**).[88]



Scheme 2-3. Catalytic procedure developed by Biloski and co-workers.[88]

Using only 5 mol% of **260**, Bilowski was able to epoxidise three substrates in a very high yield (83–94%). The process was buffered with disodium hydrogen phosphate to prevent ring opening of the epoxides formed under the acidic conditions created by hydrate **261**. In spite of the limited examples provided, the buffering of the reaction and the high observed yields suggest that the procedure should be generally applicable, at least in the case of alkyl substituted alkenes. Building upon this procedure, Hanson and co-workers adopted the catalytic procedure in order to epoxidise a variety of steroid derivatives (**Scheme 2-4**).[89]

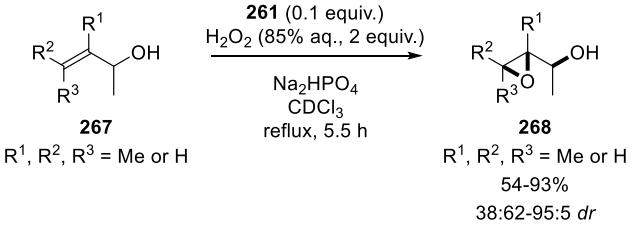


Scheme 2-4. Catalytic procedure demonstrated by Hanson and co-workers.[89]

Hanson and co-workers successfully converted five substrates **265** to their corresponding epoxide **266** in high yield (85–97%) and with reasonable selectivity for the α-face of the alkene (77:23–85:15 *dr*). Interestingly, the process also appeared to be completely regioselective for the more substituted 5,10-epoxide. A major advantage of this procedure was the use of 30% aqueous hydrogen peroxide, which is both safer to handle and less prone to degredation upon storage than hydrogen peroxide of higher concentrations, as used by Kim and Bilowski.

Despite this process being catalytic with regards to hexafluoroacetone **260**, the reaction was not without drawbacks. Hexafluoroacetone **260** is known to be highly toxic and exists as a gas at room temperature. Direct use of the hydrate **261** was therefore a preferred option, as it is a liquid at room temperature. Along with investigating the ability of hydrate **261** as a catalyst, Adam and co-workers also sought to investigate

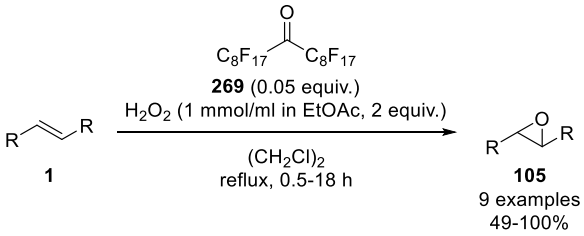
the diastereoselectivity of the perhydrate in greater detail, by reacting it with a variety of allylic alcohols **267** (**Scheme 2-5**).[90]



Scheme 2-5. Epoxidation of alkenes with hydrate **261** as catalyst.[90]

Adam and co-workers were able to show the epoxidation of seven allylic alcohols **267** in moderate to high yield (54–93%). Generally speaking, Adam found that the epoxidation reaction had a preference for the *syn*-product of the reaction (62:38 *dr*), which was enhanced by the presence of 1,3-allylic strain (91:9–95:5 *dr*). The only exception to this, were two substrates in which 1,2-allylic strain was present, which exhibited a preference for the *anti*-product (38:62–39:61 *dr*). These results were found to be in-line with those of both *m*CPBA and DMDO when compared to the literature results for those oxidants, suggesting the involvement of hydrogen bonding between the substrate and perhydrate **262** within the transition state.[91]

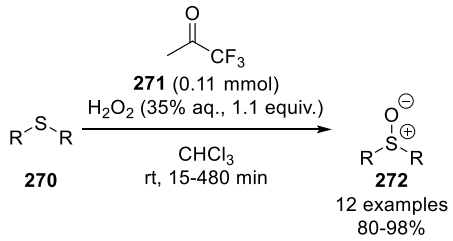
Although the use of hexafluoroacetone **260** as its hydrate **261** was an improvement in terms of handling when compared to existing procedures, it still required the set-up of complicated apparatus such as cryogenic condensers to ensure that no catalyst was lost during the procedure. In an attempt to circumvent the need for such apparatus, van Vilet and co-workers developed an analogous procedure using perfluoroheptadecan-9-one **269** as a catalyst. In an initial test of catalyst **269** van Vilet found that it was 4 times more efficient than hexafluoroacetone **260** as a catalyst in the oxidation of cyclooctene (initial reaction rate of 10 h^{-1} with **269** instead of 2.4 h^{-1} with **260**). van Vilet and co-workers then began to investigate the substrate scope of this catalytic procedure (**Scheme 2-6**).[92]



Scheme 2-6. Catalytic oxidation with perfluoroheptadecan-9-one **269** as catalyst.[92]

Using perfluoroheptadecan-9-one **269** as catalyst, van Vilet and co-workers were able to epoxidise a variety of alkyl substituted alkenes **1** in mostly high yields (49–100%). The main advantage of this process, when compared to that developed by Adam, was the catalyst was easily recoverable by crystallisation at 0 °C of the crude reaction mixture and subsequent filtration resulting in an 80% recovery.

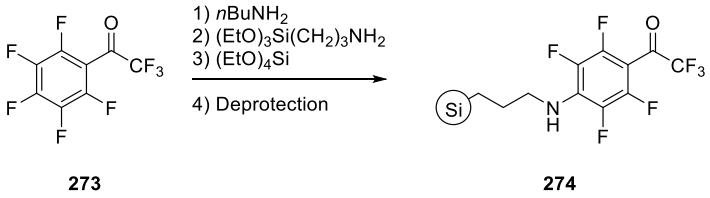
Beyond alkene oxidation, only limited examples of catalytic oxidation of heteroatoms with perhydrate catalysts exist despite extensive examination of the stoichiometric process.[84] Lupatteti and co-workers reported a chemoselective, catalytic sulfoxidation procedure using 1,1,1-trifluoroacetone **271** as catalyst (**Scheme 2-7**).[93]



Scheme 2-7. Catalytic sulfoxidation reported by Lupatteti and co-workers.[93]

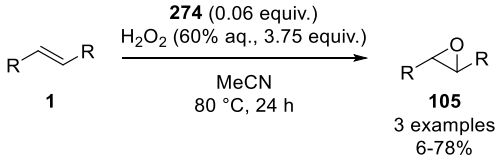
Lupatteti and co-workers were successfully able to obtain twelve examples of sulfoxidation using this catalytic process which proceeded in high yield (80–98%), proposing that the active species in the reaction was the perhydrate of ketone **271**. Despite having developed what appears to be a highly chemoselective process, it is entirely possible that the observed chemoselectivity in this reaction is due to stoichiometric control of the hydrogen peroxide. Perhydrates have previously been reported to form the corresponding sulfone when used in excess.[94]

Neimann and Neumann developed a silicate modified with perfluoroketone pendants for use in a perhydrate type catalytic cycle. The heterogeneous catalyst **274** was prepared from perfluoroacetylacetone **273** in 5 steps (**Scheme 2-8**).[95]



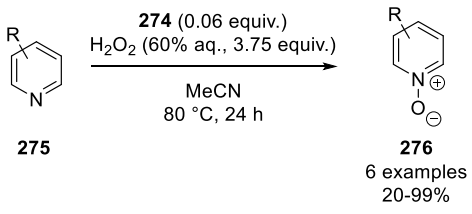
Scheme 2-8. Synthesis of heterogeneous silicate catalyst **274**.[95]

Neimann and Neumann then exemplified the ability of **274** in the epoxidation of alkenes (**Scheme 2-9**).



Scheme 2-9. Catalytic oxidation of alkenes with **274**.[95]

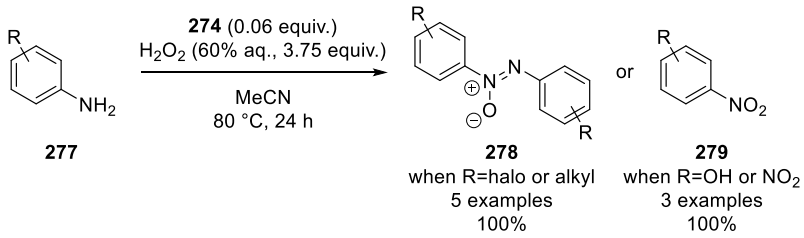
Unfortunately, **274** appeared to be a poor catalyst for the selective oxidation of alkenes **1**. Although three epoxides **105** were successfully obtained from cyclooctene (78%), oct-2-ene (16%) and oct-1-ene (6%), the yields were generally poor. The use of more nucleophilic alkenes **1** such as cyclohexene resulted in degradation of epoxide products **105** under the reaction conditions, with diols and ketones formed as a result of aqueous cleavage or pinacol rearrangement of the epoxide products. Although not mentioned in the paper, this could potentially be prevented *via* buffering of the reaction conditions as reported by Adam in the catalytic epoxidation of allylic alcohols.[90] The catalytic system was shown to be much more successful in the oxidation of pyridines **275** (**Scheme 2-10**).



Scheme 2-10. The catalytic oxidation of pyridines **275** with **274**.

Pyridine *N*-oxides **276** were obtained from the reaction as the sole products in generally high yields (83–99%) with only 8-hydroxylquinoline (20%) and 2,6-dichloropyridine (0%) as exceptions, presumably due to sterics and electronics

respectively. Despite this high yielding reaction seemingly proving a success, the results should be taken with caution, as only a limited scope of pyridine, quinoline and methyl substituted pyridines were reported, suggesting the functional group tolerance of the reaction may be limited. Finally, the reaction of **274** with anilines **277** lead to some surprising results (**Scheme 2-11**).



Scheme 2-11. The catalytic oxidation of anilines **277** with **274**.

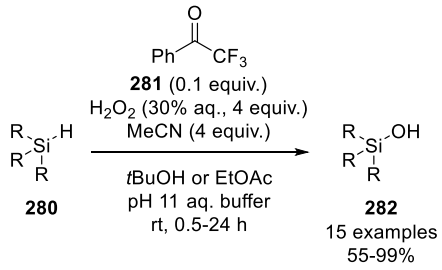
Aniline, alkyl-substituted anilines and halo-substitiuted anilines all formed the dimeric azoxy compounds **278** as product in quantitative yields. When anilines bearing nitro or hydroxy groups were treated under the reaction conditions, nitro compounds **279** were the sole products isolated in quantitative yields for all examples except those bearing *ortho* nitro groups, which were unreactive. Despite the correlation in these results, no conclusions about the origin of the selectivity between products **278** and **279** was determined within the confines of the report.

In conclusion, perhydrates, such as those formed from the reaction of hexafluoroacetone **260** and hydrogen peroxide, have been known in the literature for more than 30 years as effective and potent organic oxidising reagents. Unfortunately, despite the obvious potential for the development of catalytic processes using these reagents, limited work has been undertaken to develop the reagents. This is likely due to the reactivity of perhydrates, which appear to react indiscriminately with a wide range of functionalities.[83] Development is also hindered by the volatility and toxicity of the favoured catalyst hexafluoroacetone **260**, which is a gas at room temperature and therefore requires sealed reaction systems and the use of cryogenic condensers.

2.1.2 Ketone Derived Catalysts – 2,2,2-Trifluoroacetophenone 281

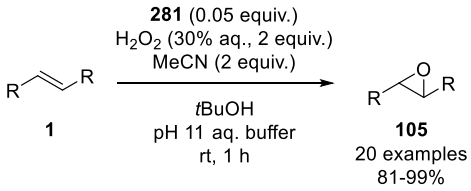
In 2013, the Kokotos group sought to develop a novel organocatalytic process for the oxidation of silanes **280** to silanols **282** claiming that with the exception of Shi,[60] "investigators researching organocatalysis [had] not been so actively involved in

oxidation reactions". To that end, the group discovered 2,2,2-trifluoroacetophenone **281** as an effective catalyst for the oxidation of silanes **280** with hydrogen peroxide as the stoichiometric oxidant (**Scheme 2-12**).[96]



Scheme 2-12. Catalytic oxidation of silanes **280** with **281**.[96]

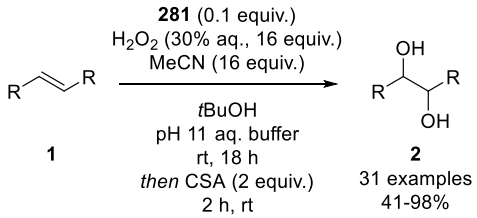
Kokotos and co-workers described 15 examples of silane **280** oxidations with their catalytic systems in high yields (55–99%). Within their scope, Kokotos was able to oxidise silanes selectively in the presence of aryl alkynes (87%), alkyl alkynes (94%), alkenes (92%), thiophene (92%) and TMS moieties (55%) suggesting a highly selective and mild procedure under the optimised conditions. Although the general solvent for the reaction was *t*BuOH, EtOAc was used in some of the examples noted potentially to prevent oxidation of some of the vulnerable functionalities. Following the success of this methodology, Kokotos and co-workers were able to develop a catalytic method for alkene epoxidation using **281** (**Scheme 2-13**).[97]



Scheme 2-13. Catalytic epoxidation of alkenes **1** with **281**.[97]

Using slightly altered conditions from their previous work, Kokotos and co-workers were able to successfully oxidise 20 alkenes **1** to the corresponding epoxides **105** in very high yields (81–99%). The reaction was shown to be highly tolerant of cyclic alkenes (98–99%), styrene (98%) and its alkyl and halogen substituted analogues (91–99%), *trans*-alkenes (98%), 1,1-disubstituted alkenes (97%) and tri-substituted alkenes (98–99%). Less reactive alkenes, such as 1-decene (97%) were also compatible with the reaction, although required longer reaction times and more H_2O_2 and MeCN. Challenging electron deficient alkenes such as methyl vinyl ketone (98%) were also

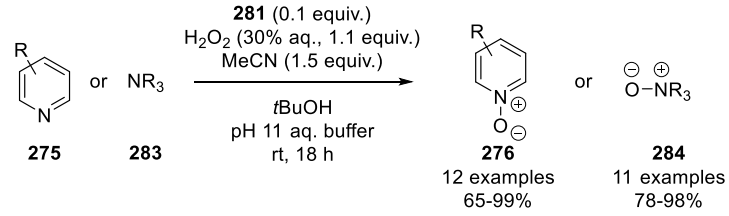
successfully reacted under the standard conditions. Unfortunately, only limited functionality was explored, however, a primary (81%) and secondary alcohol (98%) both proceeded through the reaction with no reported oxidation of the hydroxy group. Recently, Kokotos has further developed this procedure, coupling it with acid catalysed ring opening of the epoxide to generate a one-pot dihydroxylation procedure (**Scheme 2-14**).[98]



Scheme 2-14. One-pot dihydroxylation of alkenes with catalytic **281**.[98]

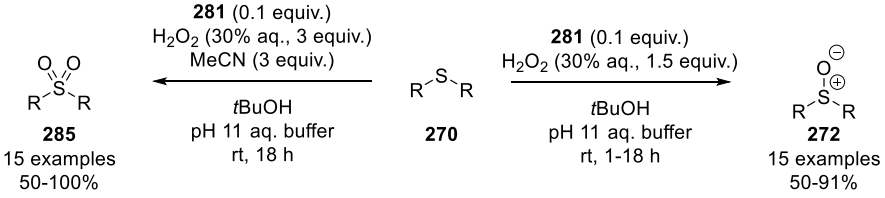
Using CSA as the reagent to promote epoxide ring opening, Kokotos was able to dihydroxylate a vast scope of alkenes comprised of aryl substituted homoallylic alcohols (67–95%), alkyl substituted homoallylic alcohols (50–91%) and styrenes (41–98%). Despite the scope, which revealed the reaction to be tolerant of amides, sulfonamides and benzylic alcohols, the major drawback of the reaction was the lack of observed diastereoselectivity. Most substrates examined were reported as a 1:1 mixture of diastereomers. This process has been further developed to include the intramolecular ring opening of epoxides by amines,[99] giving pyrrolidines or indolines, and alcohols, giving dihydrobenzofurans.[100]

Kokotos and co-workers have also successfully employed this catalytic system in the oxidation of a variety of heteroatoms. In 2014, Kokotos successfully examined the oxidation of pyridines **275** and tertiary amines **283** to their corresponding *N*-oxides **276** and **284** (**Scheme 2-15**). [101]



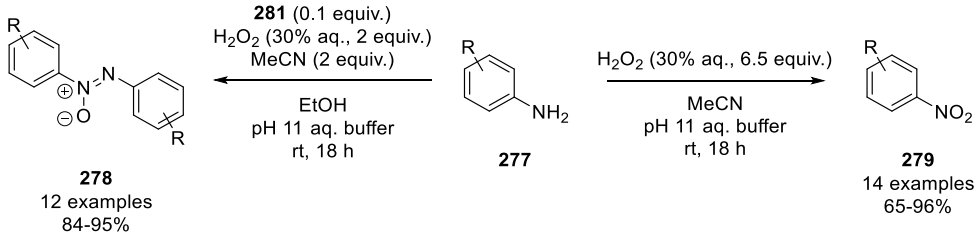
Scheme 2-15. Catalytic oxidation of pyridines **275** and tertiary amine **283** with **281**.

N-Oxides **276** and **284** were formed in generally high yields (65–99% and 78–98% respectively), even for sterically challenging substrates such as 2,6-lutidene (65%). Despite a large substrate scope showing high levels of generality in the oxidation of both pyridines **275** and tertiary amines **284**, no electron deficient pyridines were subject to the reaction conditions, suggesting a potential limitation to the process. The group have also reported a sulfoxidation procedure (**Scheme 2-16**).[102]



Scheme 2-16. Catalytic sulfoxidation using **281**.[102]

Sulfoxides **272** were obtained in modest to high yields (50–91%) using the catalyst **281**. Interestingly, unlike the rest of the transformations using **281**, MeCN was not required in order to perform the oxidation. By increasing the loading of hydrogen peroxide from 1.5 equiv. to 3 equiv. Kokotos was also able to isolate the sulfone **285** in generally excellent yields (50–100%). Finally, using a modified version of this catalyst system, Kokotos was able to oxidise anilines **277** to dimeric azoxy compounds **278**. He also showed that the corresponding nitro-arenes **279** could be obtained in the absence of catalyst **281** (**Scheme 2-17**).[103]



Scheme 2-17. Synthesis of dimeric azoxy compounds **278** and nitro-arenes **279** by Kokotos.[103]

Using the catalytic system, dimeric azoxy compounds **278** were synthesised in high yield (84–95%). Similarly, nitro-arenes **279** were also prepared in high yield (65–96%). Interestingly, the variety of substrates explored in both reactions was quite different. Whilst the formation of nitro-arenes **279** appeared to be highly tolerant of a variety of substrates with a variety of electron donating and electron withdrawing substrates in all positions around the arene. In the formation of the dimeric azoxy compounds **278**, substitution seemed limited to inductively and mesomerically electron donating groups (*i.e.* ethers, halogens and alkyl groups) in the *para* position suggesting that the procedure might be limited sterically and electronically.

Mechanistically, the structure of the catalyst would suggest that the active form of the catalyst may be a perhydrate as seen previously on **Pages 76–83**. However, Kokotos and co-workers have spent a considerable effort into the investigation of the reaction mechanism. Initially, studies carried out by Kokotos revealed that MeCN was pivotal to the reaction, with only 1% formation of silanol observed in the absence of MeCN in his first report.[96] This evidence was supported by ^{19}F NMR which revealed that the mixing of hydrogen peroxide, **281** and MeCN resulted in the formation of something that was neither the ketone, hydrate or perhydrate. Reaction in the presence of BHT, AIBN and TEMPO all allowed the reaction to proceed as normal, suggesting an ionic procedure. Armed with the knowledge that MeCN and hydrogen peroxide could form intermediate **287**,[104] Kokotos and co-workers were able to propose a catalytic cycle for the process (**Figure 2-5**).

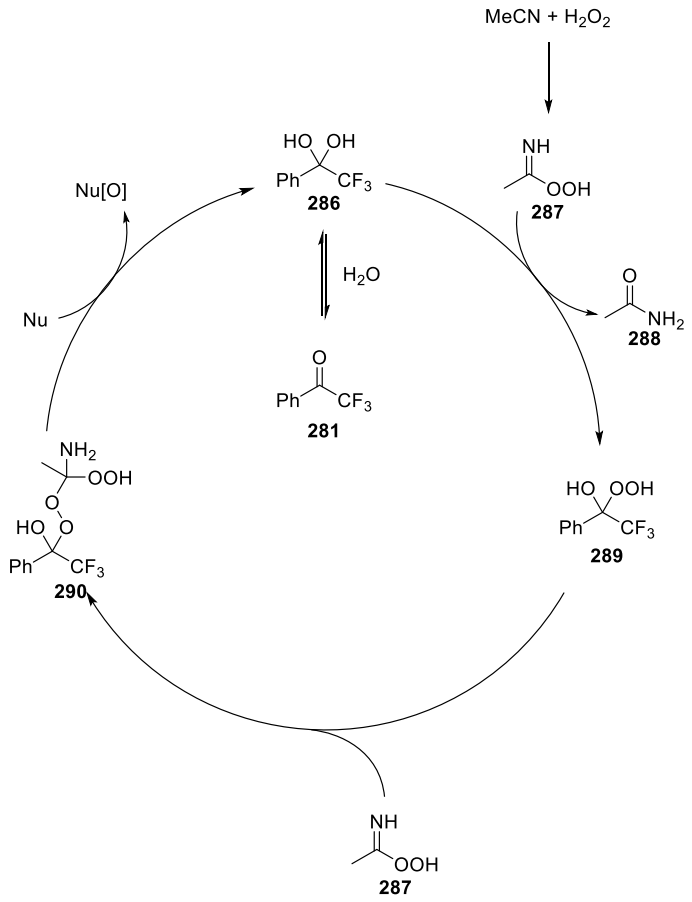


Figure 2-5. Proposed catalytic cycle for 2,2,2-trifluoroacetophenone **281** oxidations.[103]

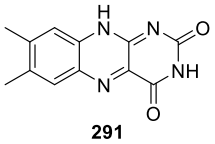
Under the buffered basic reaction conditions 2,2,2-trifluoroacetophenone **281** was converted to its hydrate **286** and MeCN was converted to the Payne intermediate **287**.[104] Reaction of the Payne intermediate **287** and hydrate **286** was suggested to form perhydrate **289** which then reacted with another molecule of Payne intermediate **287** to form the active species **290**. The existence of **290** was proposed based on extensive HRMS work which showed a mass corresponding to its existence.[103] **290** was then proposed to be responsible for the oxidation of all the nucleophiles examined. It was suggested that **290** could potentially decompose to the corresponding dioxolane, however, this suggestion was dismissed as the catalytic cycle was unable to replicate the oxidation of adamantane and aryl iodides, both of which dioxolanes have been shown to accomplish.

In conclusion, 2,2,2-trifluoroacetophenone **281** has been been developed into a successful organocatalyst for the oxidation of silanes, alkenes, pyridines, tertiary amines, sulfides and anilines using cheap and green reagents. This mechanistically discreet catalytic procedure differentiates itself from the reaction of perhydrates by

allowing the selective oxidation of certain functionalities in the presence of other oxidisable groups by being tunable.

2.1.3 Flavin Chemistry

Increasingly, new developments within organic chemistry imitate processes found within nature. Flavins are enzyme cofactors found in nature which are vital for a number of processes, including the oxidative degradation of chemicals such as sulfides, amines and aldehydes.[105] Key to the activity of flavin is the heterocyclic core, 7,8-dimethylisoalloxazine **291** (**Figure 2-6**).



291

Figure 2-6. 7,8-Dimethylisoalloxazine **291** is the core of flavin.

In 1989, Murahashi and co-workers were the first group to report a fully synthetic catalytic oxidation procedure using a flavin derived catalyst **293** (**Scheme 2-7**).[106]

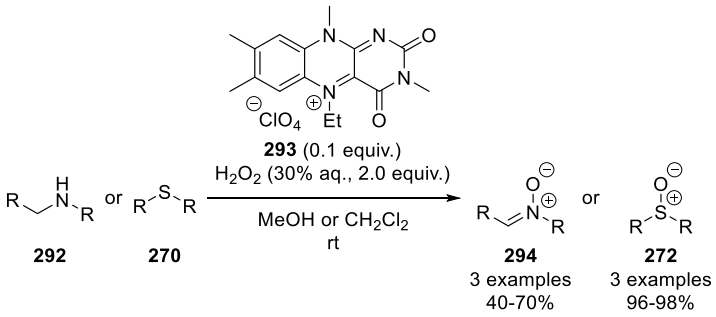


Figure 2-7. The first reported synthetic flavin catalysed oxidation.[106]

Murahashi was able to demonstrate the potential of **293** by oxidising a limited scope of secondary amines **292** to the corresponding nitrone **294** in moderate yields (40–70%) and three sulfides **270** into their corresponding sulfoxides **272** in excellent yields (96–98%). It should be noted that the observed sulfoxidation was not a chemoselective process as extended reaction times did allow for the formation of the corresponding sulfone, albeit at a significantly slower rate. Murahashi postulated a catalytic cycle for the reaction involving the addition of hydrogen peroxide at position 4a on **293** (**Figure 2-8**).

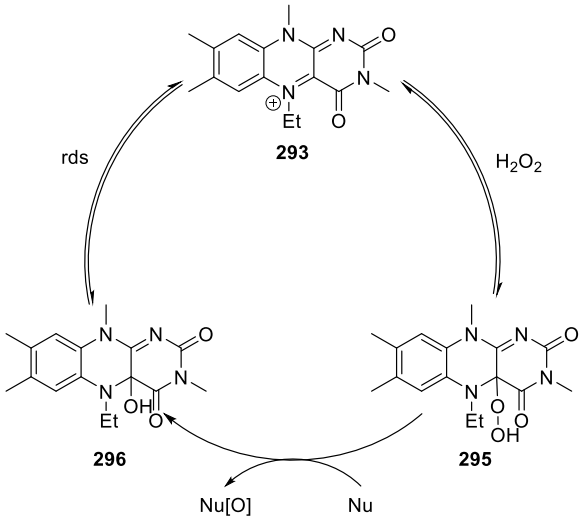
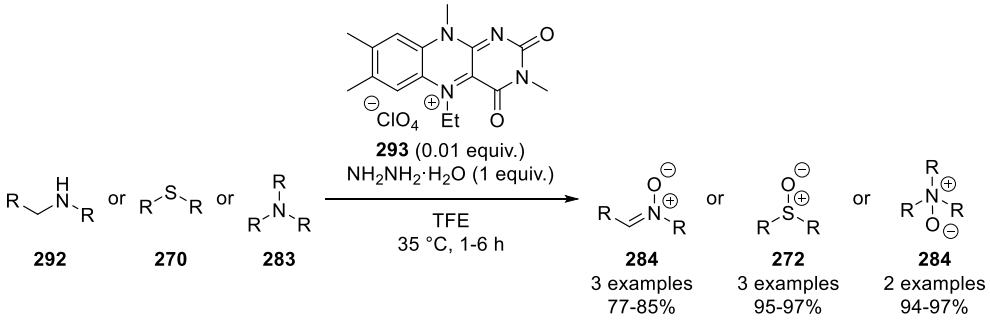


Figure 2-8. Catalytic cycle of flavin **293** catalysed oxidation.

Cation **293** reacts reversibly with hydrogen peroxide to form the active species **295**. Peroxide **295** is then able to react with a nucleophile, forming hydroxy compound **296** as a biproduct. Loss of water then regenerates cation **293**. Murahashi performed extensive mechanistic work monitoring the kinetics of each individual step of the process which revealed the loss of water to be the rate determining step of the overall process. More recently, Murahashi has developed a modification of this procedure which involves the use of aerobic oxidation conditions (**Scheme 2-16**).[107]

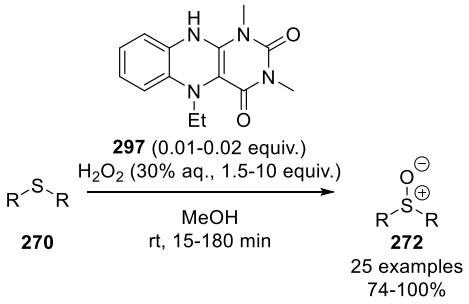


Scheme 2-18. Aerobic catalysis with flavin derivative **293**.[107]

Using only 1 mol% of catalyst **293**, trifluoroethanol as solvent and 1 equiv. of hydrazine hydrate as both the stoichiometric reductant for the catalyst and the proton source for the reaction, Murahashi was able to oxidise a variety of substrates. Sulfides **270** were easily converted to the corresponding sulfoxide **272** with no evidence of over oxidation in excellent yields (95–97%). Similarly, tertiary amines **283** were converted into their oxides **284** in excellent yields (94–97%). Finally, secondary amines **292** were

successfully converted to the nitrones **294** in high yields (77–85%). Of particular note were the oxidation of dithiane, which produced the monooxygenated product exclusively (97%) and a secondary amine bearing a pendant sulfoxide functionality, which was oxidised to the nitrone with no apparent oxidation of the sulfoxide functionality (77%).

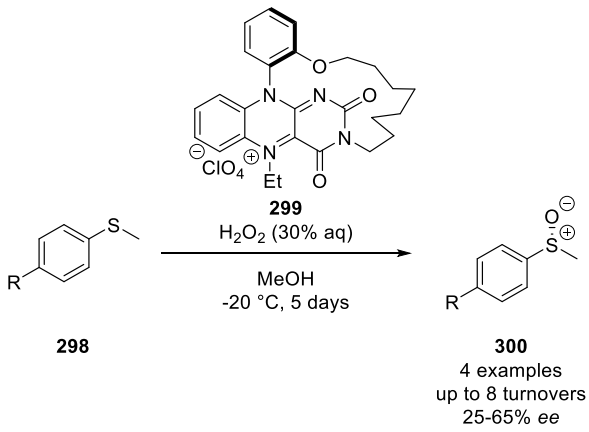
The scope of the procedure was greatly increased by Bäckvall and co-workers, who employed the reduced version of **293** as a catalyst for the process (**Scheme 2-19**).[108]



Scheme 2-19. Catalytic procedure by Bäckvall using flavin derivative **297**.[108]

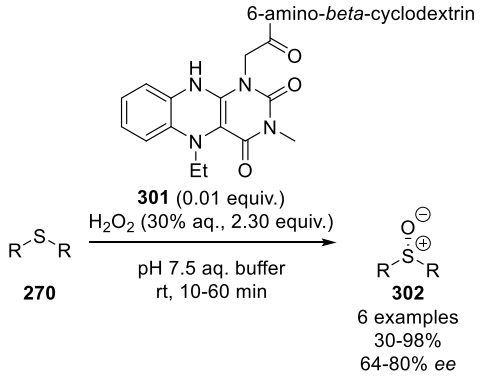
Bäckvall was successfully able to oxidise a significant scope of 25 sulfides **270** across two publications to the corresponding sulfoxides **272** in excellent yield (74–100%). In the first paper,[108a] Bäckvall showed a chemoselective process in the presence of a range of vulnerable functionalities, including an aniline (100%), a carboxylic acid (100%) and a vinyl ester (99%). In the second paper,[108b] Bäckvall expanded upon that chemoselectivity by exclusively examining allylic and vinylic sulfides. The mild nature of the procedure was further exemplified within these substrates by the presence of primary alcohols, aldehydes, tertiary amines and alkynes, which all proceeded through the reaction with no evidence of oxidation. Unsurprisingly, vinylic sulfides required higher loadings of both catalyst and hydrogen peroxide due to their reduced nucleophilicity, which led to reduced overall yield (74–80%) when compared to the other substrates, presumably due to over oxidation. Interestingly, the difference between Bäckvall's catalyst **297** and Murahashi's catalyst **293** prompted Bäckvall to investigate the structure-activity relationship of the catalysts. Bäckvall found that *N*,*N*,*N*-1,3,5-trisubstituted flavin derivatives such as **297** were significantly more reactive than *N*,*N*,*N*-3,5,10-trisubstituted catalysts such as **293**. The reactivity of the catalysts could be improved by the addition of electron donating groups in the 7 and 8 postitions, however, this also facilitated the oxidative degradation of the catalysts.[108a]

An enantioselective variant of the procedure was reported by Shinkai in 1988 using a flavin derivative with planar chirality **299** (**Scheme 2-20**).



Scheme 2-20. First enantioselective sulfoxidation catalysed by flavin derivative **299**.

Four examples of *para*-substituted aryl methyl sulfides **298** were successfully oxidised to the enantioenriched sulfoxides **300** with the (*R*)-(+) configuration in low to moderate enantioselectivity (25-65% *ee*). With the exception of the *para*-cyano substrate, which unsurprisingly performed poorly under the reaction conditions due to its reduced nucleophilicity, all substrates were oxidised with between 2 and 8 turnovers of catalyst **299** (i.e. a catalyst loading of 0.12–0.5 equiv.). Some 30 years later, Mojr and co-workers made the first subsequent novel contribution to this field with catalyst **301** (**Scheme 2-21**).[109]

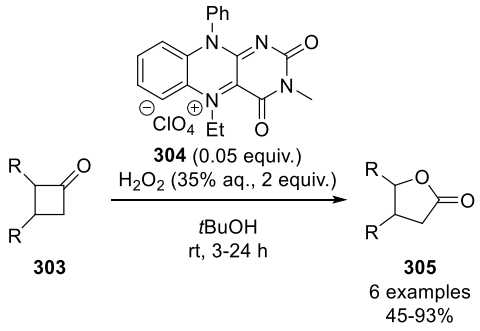


Scheme 2-21. Enatioselective oxidation of sulfides with catalyst **301**.[109]

Using a flavin catalyst conjugated to β-cyclodextrin **301** in very low loading (1 mol%), Mojr and co-workers were able to prepare six enantioenriched sulfoxides **302** in generally high yield (30–98%) and moderate to high enantioselectivity (64–80% *ee*).

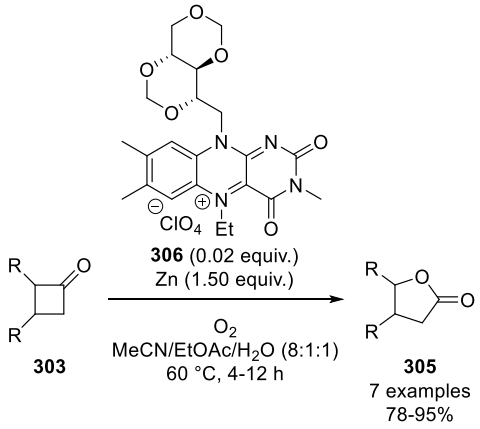
Mojr and co-workers reported that their catalyst was “distinguished from other organocatalysts by fast, near-quantitative conversions and high enantioselectivities” although gave no examples to support their claim.

As well as performing electrophilic oxidations, flavin derived compounds can perform nucleophilic oxidations such as the Baeyer-Villiger oxidation.[110] Mazzini and co-workers developed the first flavin derivative catalysed Baeyer-Villiger oxidation reaction (**Scheme 2-22**).[111]



Scheme 2-22. Catalytic Baeyer-Villiger oxidation with flavin derivative **304**.

Mazzini and co-workers oxidised five substituted cyclobutanones **303** into their corresponding lactones **305** in high yields (83–93%). Mazzini commented within the discussion that, despite the effectiveness of this procedure with cyclobutanone substrates, the catalytic system was ineffective against cyclohexanones, cyclopentanones and linear ketones. Despite this, α-methoxycyclohexanone was converted into its corresponding lactone in a moderate yield (45%). Regardless of a limited scope comprised of activated ketones, Mazzini provided a proof of concept for the reaction. More recently, Imada and co-workers reported an aerobic variant of this procedure (**Scheme 2-23**).[112]



Scheme 2-23. Aerobic catalytic Baeyer-Villiger oxidation with flavin derivative **306**.[112]

Flavin derivative **306** was synthesised readily from vitamin B2 in 4 steps. Catalyst **306** was then employed in the oxidation of an almost identical substrate scope to that explored by Mazzini with oxygen as the oxidant and zinc as a reductant to regenerate the catalyst. Seven cyclobutanones **303** were oxidised to their corresponding lactones **305** in high yield (78–95%). Unfortunately, the aerobic procedure appeared to lose regioselectivity, with 2-substituted cyclobutanones producing an almost 1:1 mixture of the potential regioisomeric products. However, in an effort to show the utility of this process, Imada and co-workers subjected an alkene and a sulfide to the reaction conditions, resulting in high levels of recovery of the alkene (97%) and sulfide (88%) with no observed epoxide and only small quantities of sulfoxide (3%) suggesting a highly chemoselective process.

In conclusion, the development of biomimetic synthetic flavin catalysts for the purpose of organocatalytic oxidation reactions has provided a variety of successful protocols for the formation of sulfoxides, nitrones, pyridine and tertiary amine *N*-oxides, and lactones. Extremely low catalyst loadings, the use of "green" solvents and highly efficient terminal oxidants (hydrogen peroxide and molecular oxygen) make many of these reactions highly desirable. The development of flavin chemistry is held back, however, by the difficult and often laborious synthesis of many of these reagents, which hinder catalyst development.

2.1.4 Conclusions

Within the ever-expanding field of organocatalysis, organocatalytic oxidation reactions have received less attention than other organocatalytic processes. Although

protocols such as the dioxiraine mediated Shi epoxidation are well known, a desire for novel protocols using efficient terminal oxidants such as hydrogen peroxide has been expressed.

Early investigations into organocatalytic oxidations appeared to focus on the formation of perhydrates from α-haloketones. Following the development of a wealth of stoichiometric procedures using perhydrates, considerable investment was spent on the development of catalytic procedures using these compounds. Unfortunately, interest in these compounds has waned in recent years, presumably due to the highly reactive and apparently promiscuous nature of these perhydrate compounds.

Currently, two methods using hydrogen peroxide as the terminal oxidant are prevalent: 1) the 2,2,2-trifluoroacetophenone **281** and acetonitrile system developed within the Kokotos lab and 2) the biomimetic flavin catalysts. Both processes appear highly tuneable, as demonstrated by the highly chemoselective procedures reported. Currently, the development of flavin catalysis seems limited by the considerable effort required to synthesise the catalysts.

2.2 Aims and Objectives

Within the malonoyl peroxide mediated dihydroxylation it was proposed that two major challenges still existed for the reaction, in order to bring it to the gold standard achieved by other dihydroxylation reactions: 1) asymmetry and 2) catalysis. Attempts to introduce asymmetry have been met with very limited success,[72] however, catalysis had not yet been examined.

Catalysis was seen as a challenge for the malonoyl peroxide mediated dihydroxylation due to incompatibilities between the conditions required for formation of the malonoyl peroxide **13** and the conditions required to liberate diol **14** from the intermediate ester **25** (**Figure 2-9**).

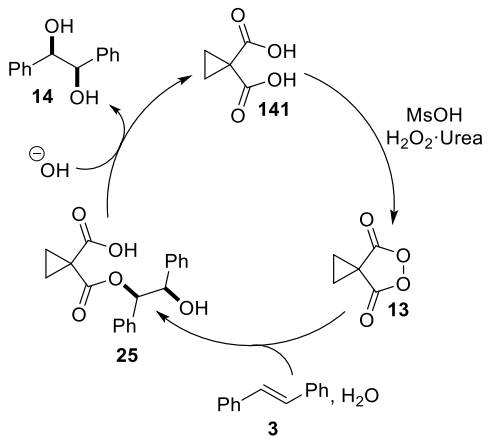


Figure 2-9. The malonoyl peroxide **13** mediated syn-dihydroxylation imagined as a catalytic cycle.

In the peroxide formation reaction, it is believed that MsOH plays two vital roles. First and foremost, MsOH acts as an acid catalyst, allowing substitution of the groups at the acyl carbon of malonic acid **141**. Secondly, MsOH plays a role as a dehydrating agent, assisting with the removal of water from the reaction promoting the formation of peroxide **13**. Both of these roles are incompatible with the subsequent steps of the reaction procedure. The reaction of alkene **3** and peroxide **13** requires an equivalent of water to form ester **25**. The hydrolysis of ester **25** to liberate diol **14** and malonic acid **141** is routinely carried out under basic aqueous conditions. Theoretically, the entire process could be carried out under acidic conditions, however, an acidic ester hydroloysis could potentially pose a difficulty if it meant the hydrolysis would proceed *via* an A Alk 1 mechanism (**Figure 2-10**).

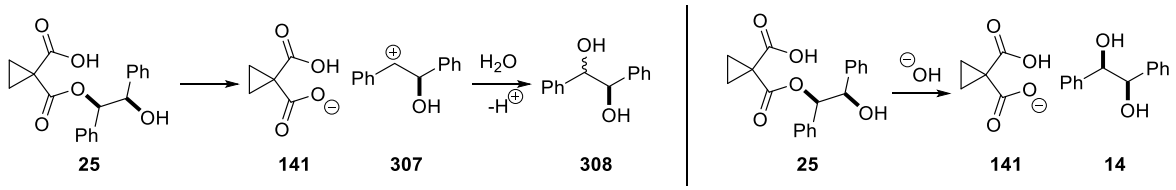


Figure 2-10. Comparison of A Alk 1 and B Ac 2 hydrolysis mechanisms of ester **25**.

Under acidic conditions, hydrolysis of ester **25** could lead to carbocation **307** which would lose diastereochemical integrity upon formation of diol **308**.

Alternatively, it was proposed that a 1,3-dicarbonyl species **309** could, under mildly acidic or Lewis acidic conditions, form a reactive organoperoxide species **311** which could undergo reaction with a nucleophile (**Figure 2-11**).

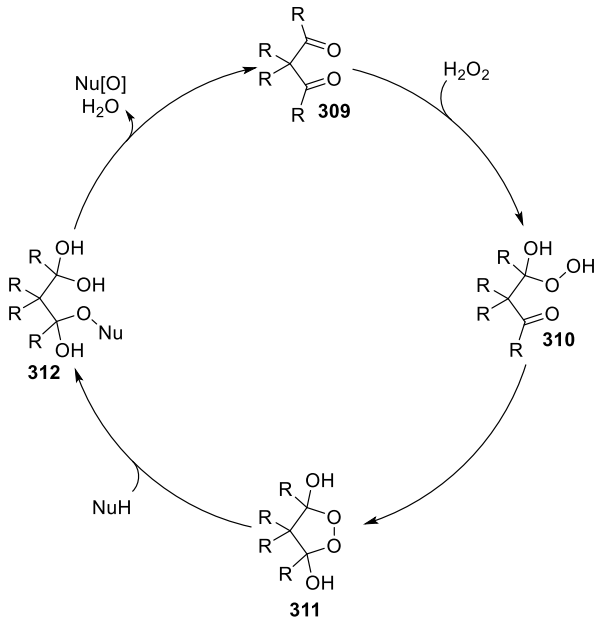
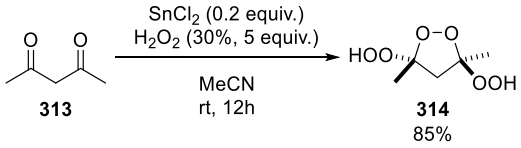


Figure 2-11. Proposed catalytic cycle based on a 1,3-diketone **309**.

Theoretically, a 1,3-diketone **309** could react with hydrogen peroxide under Lewis acidic or protic conditions to form a peroxyhemiacetal **310** which could then cyclise to form dioxolane **311**. Dioxolane **311** could then be made to react with a nucleophile, forming intermediate **312** which could then collapse back to diketone **312** *via* acetal chemistry and the loss of water and Nu[O].

With this in mind, a search of literature surrounding compounds related to dioxolane **311** revealed peroxide **314**, formed under Lewis acidic conditions from acetylacetone **313** and hydrogen peroxide (**Scheme 2-24**).[113]

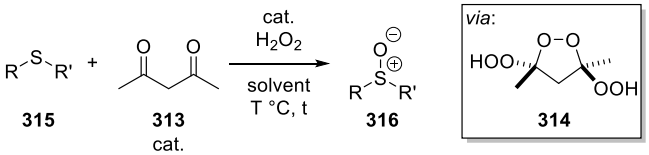


Scheme 2-24. Synthesis of peroxide **314** reported by Azarifar.[113c]

Azarifar and co-workers have used dioxolane **314** for a variety of processes, including: the epoxidation of α,β-unsaturated ketones;[113b] the chemoselective oxidation of sulfides to the corresponding sulfoxide;[113c] the regioselective bromination and iodination of aromatic substrates;[113e] the selective oxidation of secondary alcohols to ketones;[113h] the synthesis of azoxy dimers from primary aromatic amines;[113i] and the direct conversion of benzylhalides, benzylamines, benzylalcohols and aryl aldehydes into nitriles with NH_4Br.[113k]

Given the mild conditions of its synthesis and its apparent versatility as a reagent, it was suggested that peroxide **314** would be a good starting point for the development of a novel catalytic methodology.

The aim of this project was to develop methodology for the catalytic oxidation of sulfides, gain a mechanistic understanding of the process and use that understanding to grow the procedure towards becoming a novel, catalytic dihydroxylation procedure (**Scheme 2-25**).

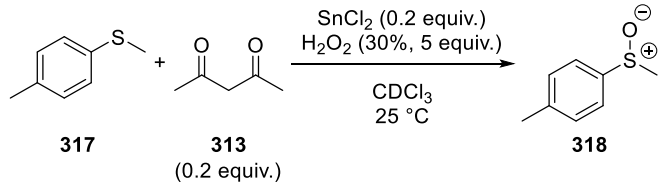


Scheme 2-25. This project aimed to produce a novel catalytic oxidation procedure.

2.3 Results and Discussion

2.3.1 Initial Results

Initially, an arbitrary set of conditions, loosely based on the work carried out by Azarifar[113c] were proposed for the reaction. Aqueous hydrogen peroxide (30%, 5 equiv.) was added to a solution of sulfide **317**, acetylacetone **313** (20 mol%) and tin(II) chloride (20 mol%) in $CDCl_3$. The relative conversion of sulfide **317** into sulfoxide **318** was monitored by ^1H NMR spectroscopy (**Figure 2-12**).



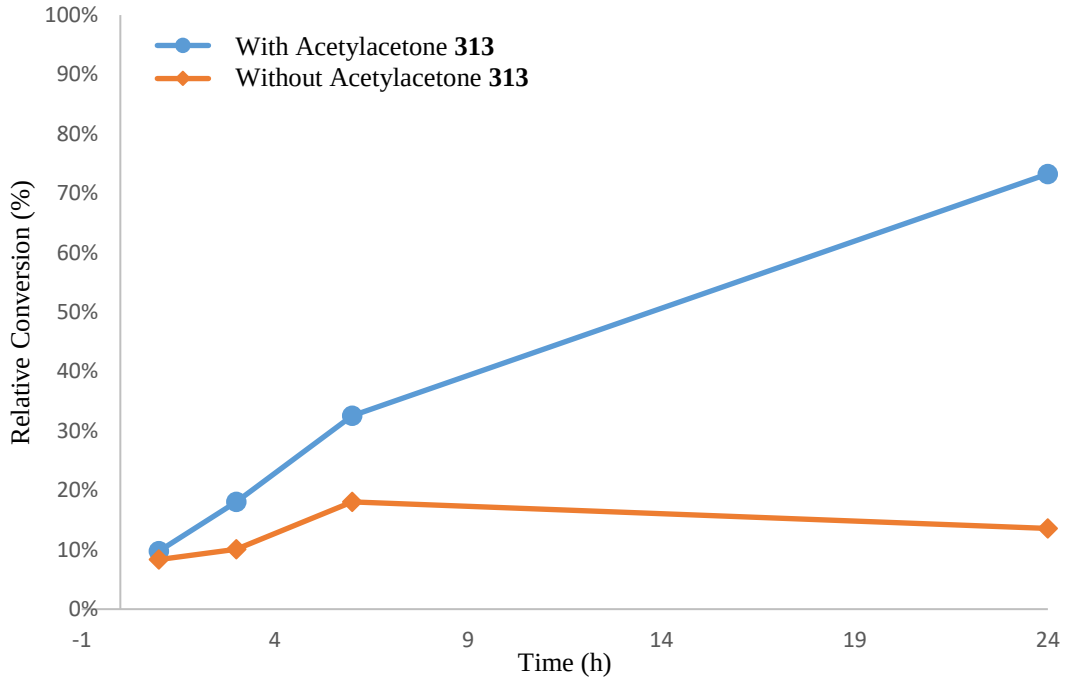


Figure 2-12. Comparison of reaction with and without acetylacetone **313**.

Pleasingly, the difference in levels of conversion observed in the presence and absence of acetylacetone **313** suggested that the reaction was indeed catalytic in acetylacetone **313** as hoped. As optimising the reaction would require the exploration of a variety of different conditions it was deemed that ^1H NMR spectroscopy would be an inefficient way to monitor the reactions. HPLC was therefore proposed as an effective technique

to monitor the reaction. Standard solutions of both sulfide **317** and sulfoxide **318** were made and analysed using HPLC to generate calibration graphs (**Figure 2-13**).

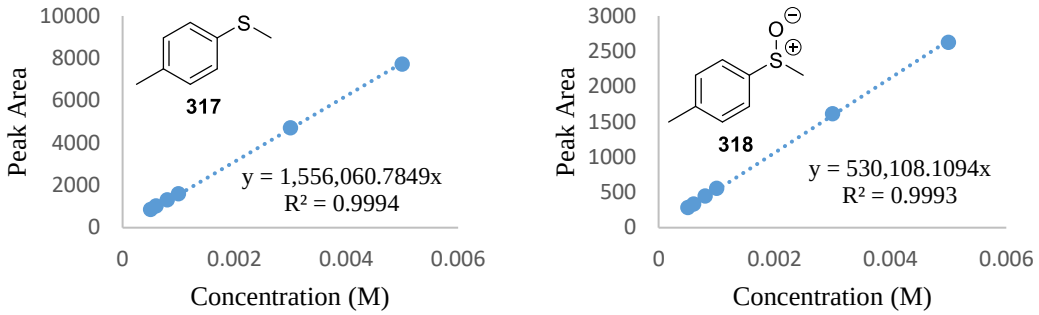
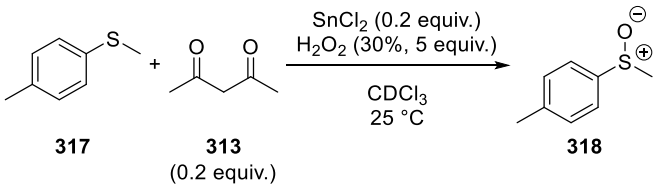


Figure 2-13. HPLC calibration plots of sulfide **317** and sulfoxide **318**.

To ensure consistency with between the results observed by HPLC and ^{1}H NMR spectroscopy, the initial experiment was repeated and the data from the two systems compared (**Figure 2-14**).



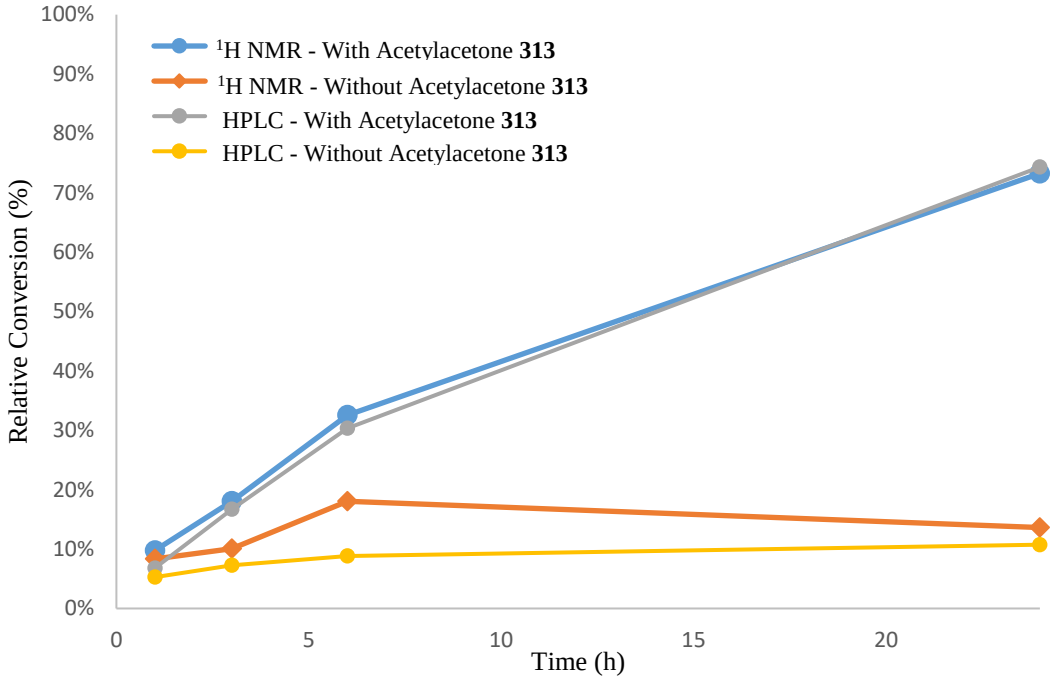


Figure 2-14. Comparison of HPLC and ^{1}H NMR spectroscopy for reaction monitoring.

Pleasingly, the HPLC results appeared to agree almost exactly with the ^{1}H NMR results and as such, HPLC was adopted as the preferred reaction monitoring technique for the optimisation of the reaction.

2.3.2 Optimisation of Reaction Conditions: $SnCl_2$ Method

With a robust method for monitoring the reaction progress we began to investigate the variables within the reaction, beginning with the reaction solvent.

2.3.2.1 Solvents

The catalytic sulfoxidation reaction was performed with six different solvents of various properties and the results are displayed below in **Figure 2-15**.

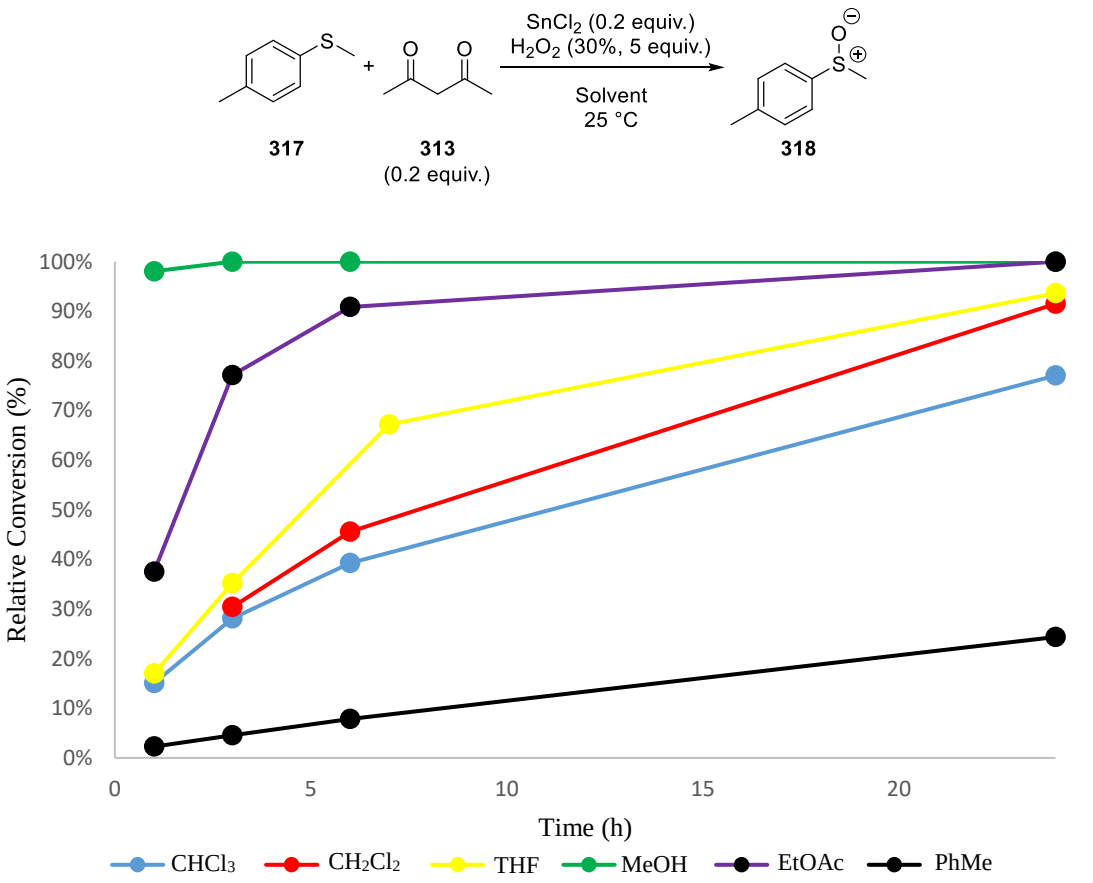


Figure 2-15. Solvent screen with ketone **313**.

Unsurprisingly, conducting the reaction in CH_2Cl_2 (92%) provided a similar level of conversion after 24 hours as the reaction in $CHCl_3$ (77%). Using PhMe (24%) as a solvent resulted in a much slower conversion of sulfide **317** into sulfoxide **318**. When THF (94%), EtOAc (100%) and MeOH (100%) were used as the reaction solvent sulfide **317** was converted into sulfoxide **318** much more rapidly. In order to confirm which of these results were due to the catalytic process and not the direct reaction between sulfide **317** and hydrogen peroxide, the reactions were repeated in the absence of acetylacetone **313** (**Figure 2-16**).

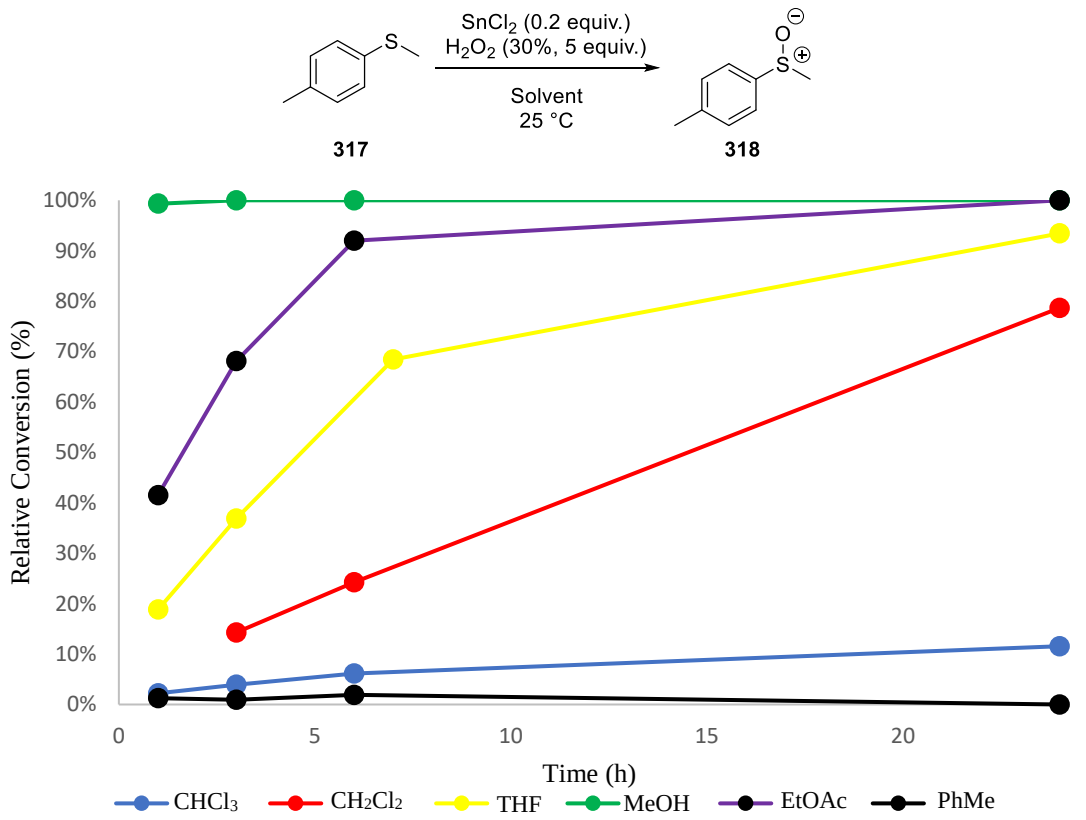


Figure 2-16. Solvent screen in the absence of ketone **313**.

The results in the absence of ketone **313** reavealed that the background sulfoxidation by hydrogen peroxide was significant and the observed rate increase in MeOH (100%), EtOAc (100%) and THF (93%) were not a direct result of the catalytic process. Of the examined solvents, only $CHCl_3$ (12%), CH_2Cl_2 (79%) and PhMe (0%) showed any evidence of a catalytic process involving acetylacetone **313**. $CHCl_3$ was clearly the optimal solvent for the reaction as it showed the greatest difference between the activity of the catalytic process and the suppression of the background oxidation. As a result, $CHCl_3$ was carried forward as the solvent for the reaction.

2.3.2.2 H_2O_2 Equiv.

With the optimal solvent of $CHCl_3$ discovered, hydrogen peroxide equivalents were examined (**Figure 2-17**).

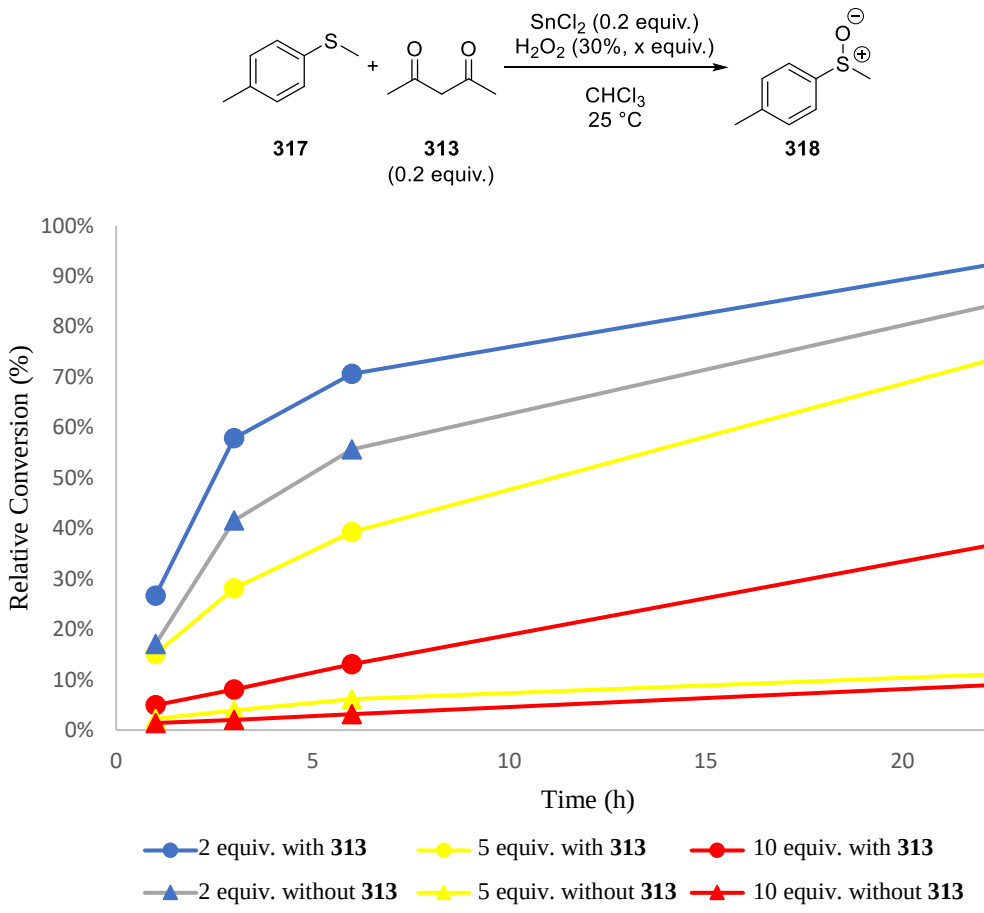


Figure 2-17. Optmisation of H_2O_2 equivalents.

Interestingly, both the catalytic process and the background reaction appeared to have an inverse dependence on the concentration of hydrogen peroxide. As the stoichiometry was decreased from 5 equiv. to 2 equiv. of hydrogen peroxide, both the rate of the background process and the catalytic process became higher, resulting in the two processes becoming almost indistinguishable. Increasing the equivalents of hydrogen peroxide from 5 equiv. to 10 equiv. resulted in the suppression of the catalytic process to a significant degree, roughly halving the rate of relative conversion. Equivalents of 50% hydrogen peroxide were also investigated, however, under these conditions there appeared to be no difference between the rate of the catalysed and background processes and as such, 30% H_2O_2 was preferred. Urea hydrogen peroxide adduct was also examined under the reaction conditions, however, no reaction was observed. It is believed that this was due to poor solubility of urea hydrogen peroxide in the reaction medium.

Based on these results it is proposed that the effect of changing the equivalents of hydrogen peroxide may be more complex and due to the biphasic nature of the reaction. Potentially, the biphase could be important in separating the hydrogen peroxide from sulfide **317**, with acetylacetone **313** acting as a phase transfer reagent for peroxide from the aqueous layer to the organic layer. Unfortunately, we were unable to devise an experiment to probe this hypothesis and 5 equivalents of 30% aqueous hydrogen peroxide were carried forward as optimal.

2.3.2.3 $SnCl_2$ Equiv.

The optimisation of the Lewis acid co-catalyst within the reaction was then examined. A variety of alternative known Lewis acids such as $Yb(OTf)_3$, $AlCl_3$, I_2 and $MgCl_2$ were used within the reaction (20 mol%), however, none of them and any effect within the reaction. Similarly, a variety of related tin(II) Lewis acids such as SnF_2 and $SnCl_2 \cdot H_2O$ were also used within the reaction and showed exactly the same reaction profile as $SnCl_2$. The only remaining variable surrounding the Lewis acid were the equivalents of $SnCl_2$ used within the process (**Figure 2-18**).

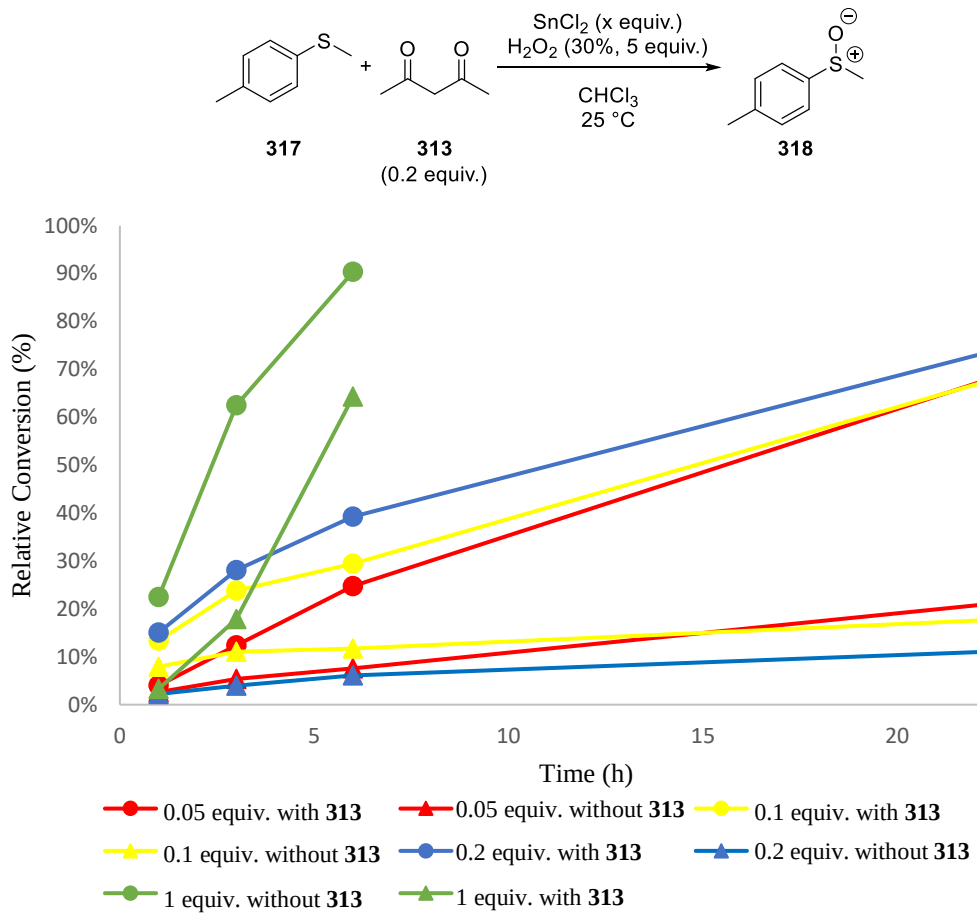


Figure 2-18. Optimisation of $SnCl_2$ equivalents.

The experiments showed little change in reaction profile when decreasing the equivalents of $SnCl_2$ within the reaction. Despite a small decrease in the rate of relative conversion of sulfide **317** in the catalytic process (77% to 72% going from 0.2 equiv. to 0.05 equiv. after 24 hours) and a small increase on the background procedure (12% to 22% going from 0.2 equiv. to 0.05 equiv. after 24 hours), we believe that these results are within experimental error. More noticeably, increasing the equivalents of $SnCl_2$ to 1 equiv. had a profound effect on the rate of both the catalytic process (90% after only 6 hours) and the background (64% after only 6 hours), increasing the rate of relative conversion for both processes. As a result, 0.2 equiv. of $SnCl_2$ was maintained as optimal for the process.

2.3.2.4 Acetylacetone 313 Equiv.

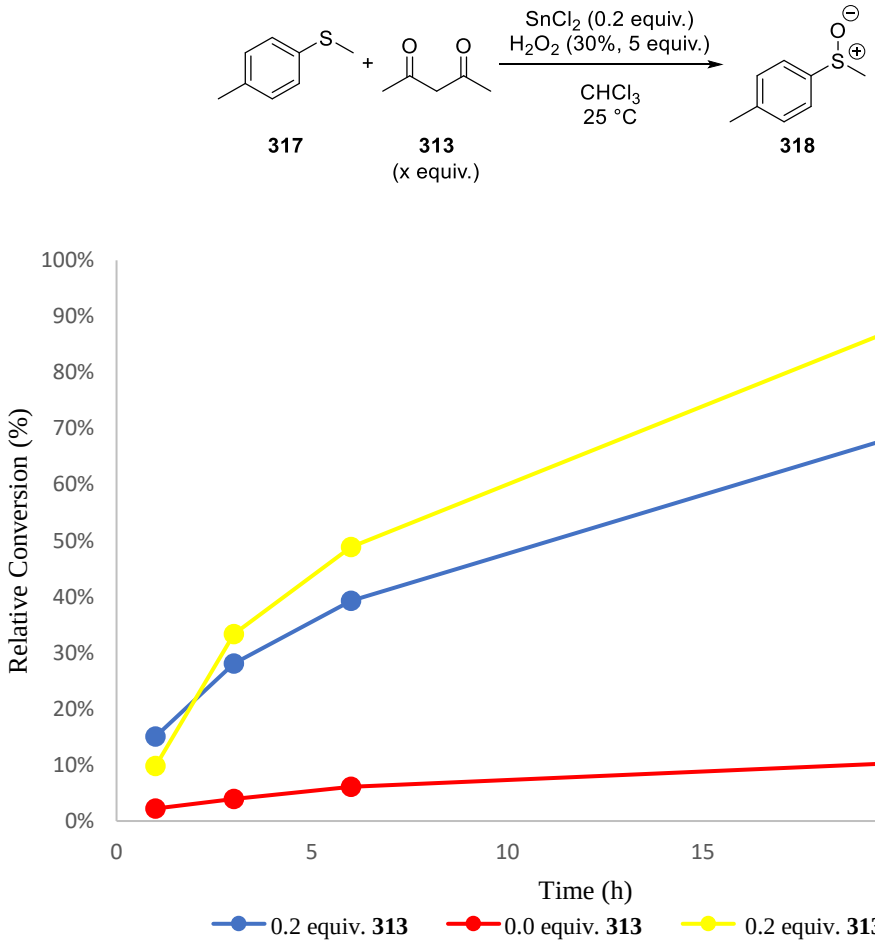
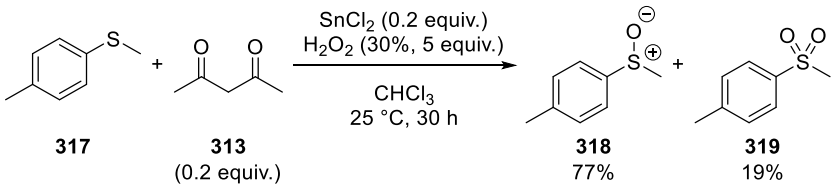


Figure 2-19. Optimisation of acetylacetone **313** equivalents.

Upon investigating the equiv. of acetylacetone **313** within the reaction it was discovered that increasing to a full equivalent of acetylacetone **313** had a negligible effect on the reaction profile, barely increasing it over the rate with 0.2 equiv (48% after 6 hours as opposed to 39%). It is believed therefore that the rate at which the active species of formed from acetylacetone **313** cannot be increased by increasing the amount of acetylacetone **313** and hence, the rate of the reaction cannot be increased by increasing **313** concentration. As a result, 0.2 equiv. of acetylacetone **313** selected as optimal for the reaction.

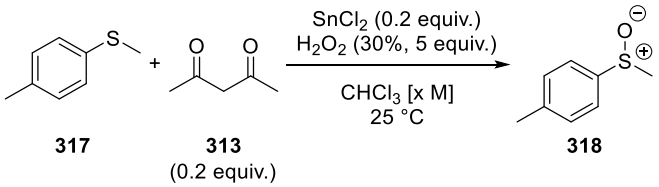
2.3.2.5 Reaction Concentration

Despite the various steps of optimisation on the reaction, nothing had improved the rate of the reaction. The reaction was run to completion on a 1 mmol scale and the products isolated (**Scheme 2-26**).



Scheme 2-26. Isolation of products under current conditions.

Unfortunately, the reaction produced a significant quantity of the overoxidised product sulfone **319**, despite a reasonably high yield of sulfoxide **318**. As such, further optimisation of the reaction conditions was deemed necessary. Until this point, the effect of changing the reaction concentration in $CHCl_3$ had been unexplored. Therefore, the reaction was run at a variety of different concentrations and the results are summarised in **Figure 2-20**.



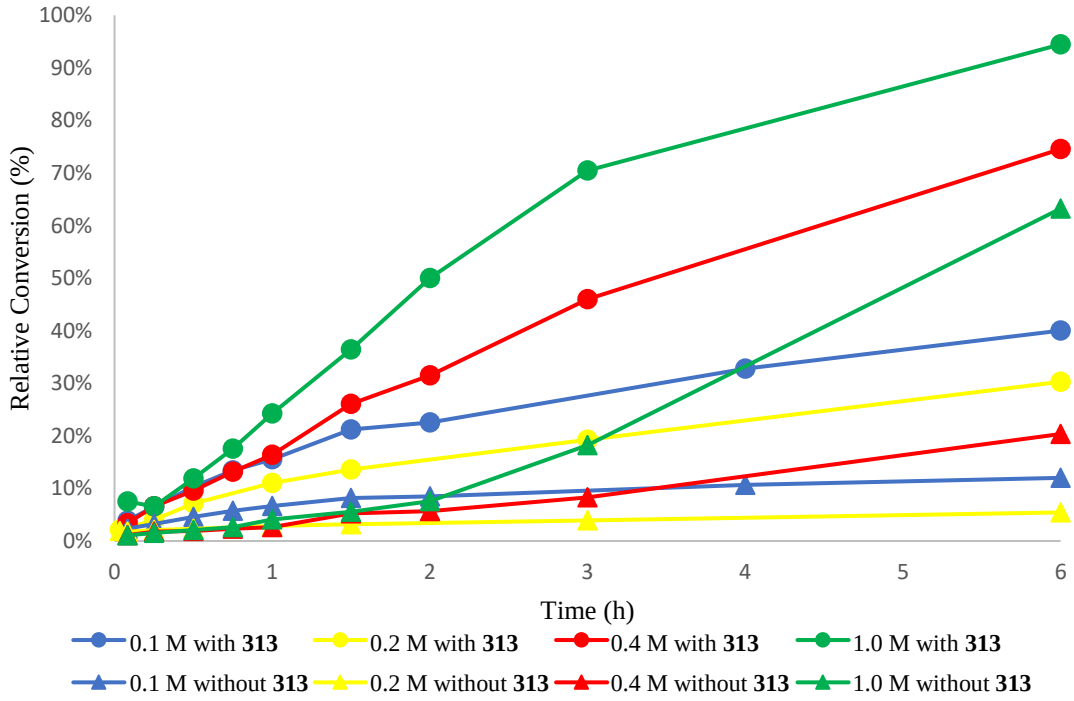


Figure 2-20. Optimisation of reaction concentration in $CHCl_3$.

Increasing the concentration from 0.2 M to 0.4 M appeared to have a significant effect on the rate of the reaction, more than doubling the rate of relative conversion of the

catalytic process (30% to 75%) whilst only marginally increasing the rate of the background oxidation (5% to 20%). Further increasing the concentration to 1.0 M continued to improve the rate of the catalysed process (94%), however, it also had a significant effect on the background, more than tripling it (63%). As a result, 0.4 M was selected as the optimal concentration for the reaction.

2.3.2.6 Other Ketones

The final variable that required investigation was the structure of the ketone used within the reaction. It was suggested that 3,3-dimethylacetylacetone **321** might improve the rate of reaction for two reasons: 1) in our proposal, a species such as dioxolane **320** was believed to be responsible for the oxidation process and the addition of the gem-dimethyl group should improve the rate of formation of active species due to the Thorpe-Ingold effect (**Figure 2-21**).[114]

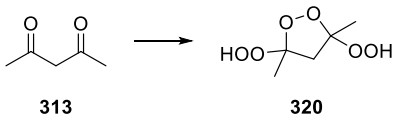


Figure 2-21. The rate of formation of proposed active species **320** should be effected by the Thorpe-Ingold effect.

2) it was proposed that enolisation of acetylacetone **313** would prevent the formation of active species **320** and therefore reduce the rate of the reaction. Acetylacetone **313** was shown to exist in a 3:1 ratio of enol:keto form by ^{1}H NMR spectroscopy under the reaction conditions. As the gem-dimethyl group would prevent enol formation it was suggested that **321** should increase the rate of reaction. As a result, the reaction was run with 0.2 equiv. of 3,3-dimethylacetylacetone **321** (**Figure 2-22**).

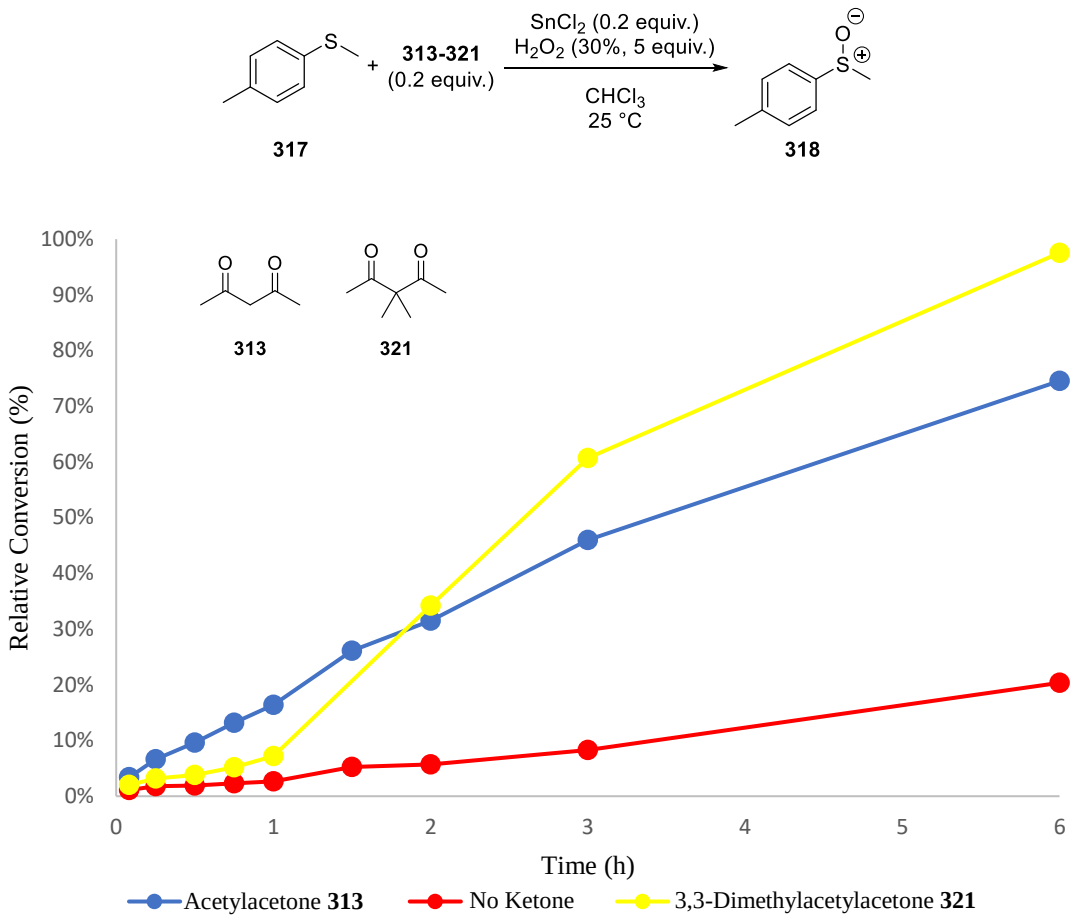
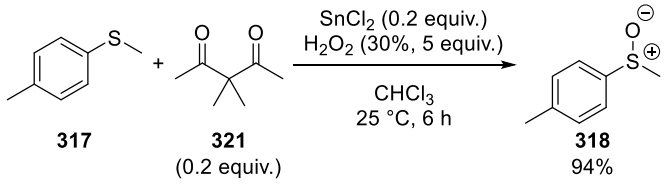


Figure 2-22. Optimisation of ketone structure.

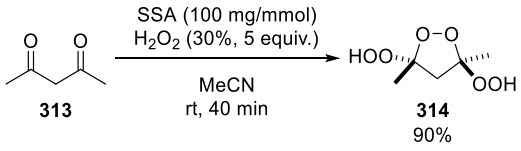
Pleasingly, the reaction was now shown to reach full conversion within 6 hours using 3,3-dimethylacetylacetone **321** as opposed to acetylacetone **313** (74%, 6 h). These conditions were now believed to be optimal for this process and the isolation of sulfoxide **318** was conducted (**Scheme 2-28**).



Scheme 2-27. Isolation of sulfoxide **318** using optimal conditions.

Using the optimal conditions, sulfoxide **318** was prepared in an excellent isolated yield of 94% after 6 hours. This result is further discussed within the substrate scope found on **Pages 134-138**.

Despite believing we had found the optimal procedure for this catalytic sufoxidation we had become interested a report where Azarifar had been able to use silica-supported sulfuric acid (SSA) as a catalyst for the formation of dioxolane **314** (**Scheme 2-29**).[113g]



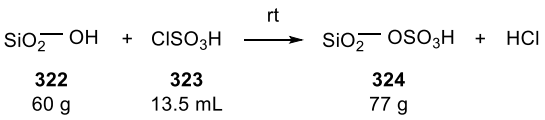
Scheme 2-28. Synthesis of dioxolane **314** with SSA reported by Azarifar.[113g]

As a result, we were interested in determining if SSA could potentially be used as a catalyst for the catalytic sulfoxidation process instead of $SnCl_2$ as we believed it was a less toxic and more environmentally benign reagent. Concurrent to the examination of the substrate scope using the $SnCl_2$ method, the reaction using SSA was also investigated.

2.3.3 Optimisation of Reaction Conditions: SSA Method

2.3.3.1 Synthesis of SSA

SSA **324** is a reagent that was initially reported by Zolfigol, synthesised from silica **322** and chlorosulfonic acid **323**.[115] SSA has been used as a recyclable heterogeneous catalyst that allows for the addition of a quantifiable amount of proton to a reaction. We were able to synthesise SSA from chlorosulfonic acid **323** and silica using the Zolfigol process (**Scheme 2-30**).[116]



Scheme 2-29. Synthesis of SSA.[116]

Treatment of silica **322** (60 g) with chlorosulfonic acid **323** (13.5 mL) resulted in the synthesis of SSA **324** (77 g). Over the course of the reaction, HCl gas was evolved and was quenched by bubbling the gas through a solution of NaOH. The SSA was then titrated against NaOH, revealing it to have an acid concentration of 5.6 mmol H^+ per gram.

2.3.3.2 Mass of SSA

We chose to begin our investigation of SSA as a catalyst for the reaction by investigating the loading of SSA (**Figure 2-23**).

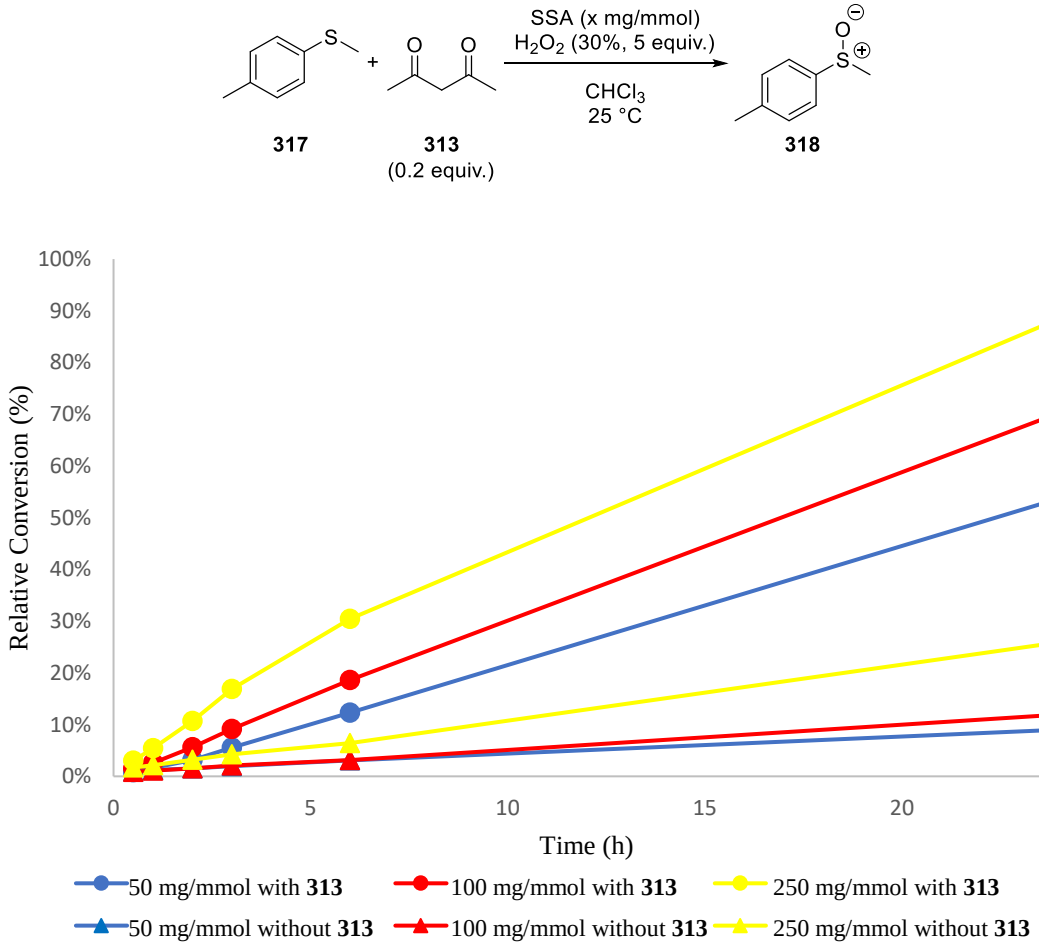


Figure 2-23. Optimisation of SSA equivalence.

Pleasingly, SSA was found to be an active co-catalyst for the catalytic sulfoxidation reaction. As the loading of SSA was increased the rate of both the catalysed process and the uncatalysed background process was found to increase. We believed that a loading of 100 mg/mmol struck the best balance between the rate of the catalysed process and the background process and as a result this was carried forward.

Because the nature of the Bronsted acid co-catalyst SSA was different to that of the Lewis acid $SnCl_2$, it was felt that it would be prudent to re-examine all of the optimised conditions, including solvents, equivalents, peroxide source and concentration.

2.3.3.3 Solvent

In order to determine the best solvent for the reaction using SSA, 9 different solvents were examined with the new co-catalyst (**Figure 2-24**).

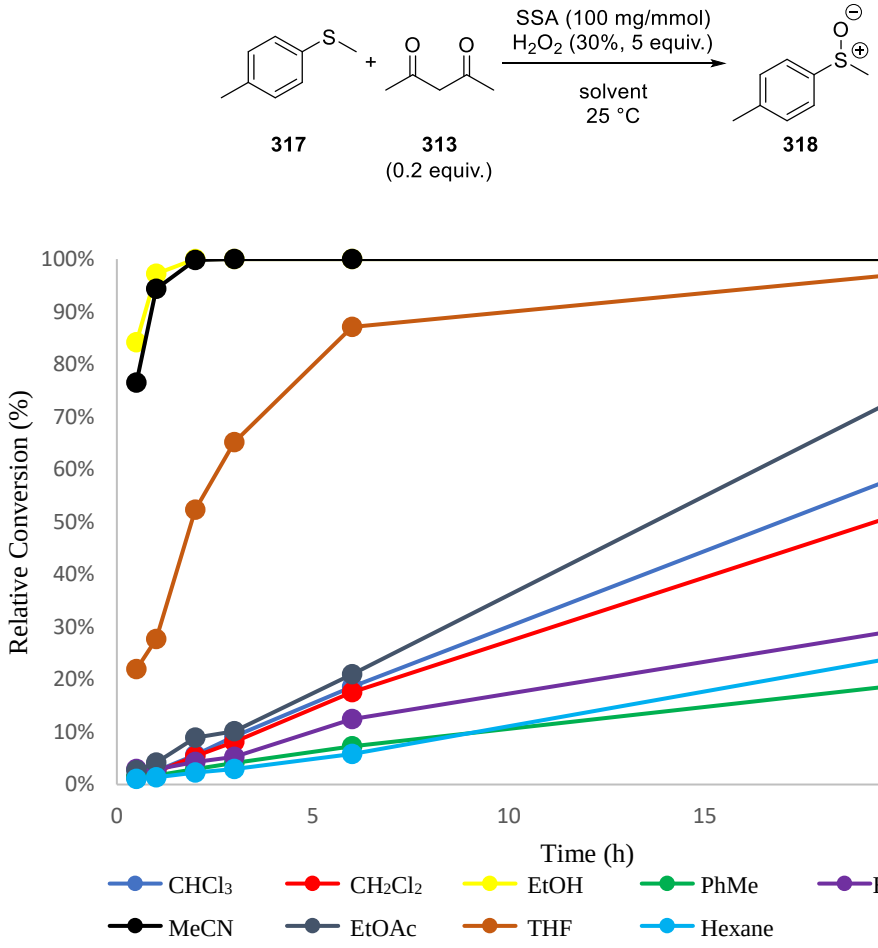


Figure 2-24. Optimisation of solvents

In a similar set of results to those observed with $SnCl_2$ as a catalyst (**Figure 2-15**, **Page 102**), miscible solvents such as MeCN and EtOH were found to be the solvents which promoted formation of sulfoxide **318** to the greatest degree. $CHCl_3$, CH_2Cl_2 and EtOAc all provided comparable results while Et_2O, hexane and PhMe all gave relatively poor conversion to sulfoxide **318**. As before, the reactions were also conducted in the absence of acetylacetone **313** in order to determine the level of uncatalysed background oxidation (**Figure 2-25**).

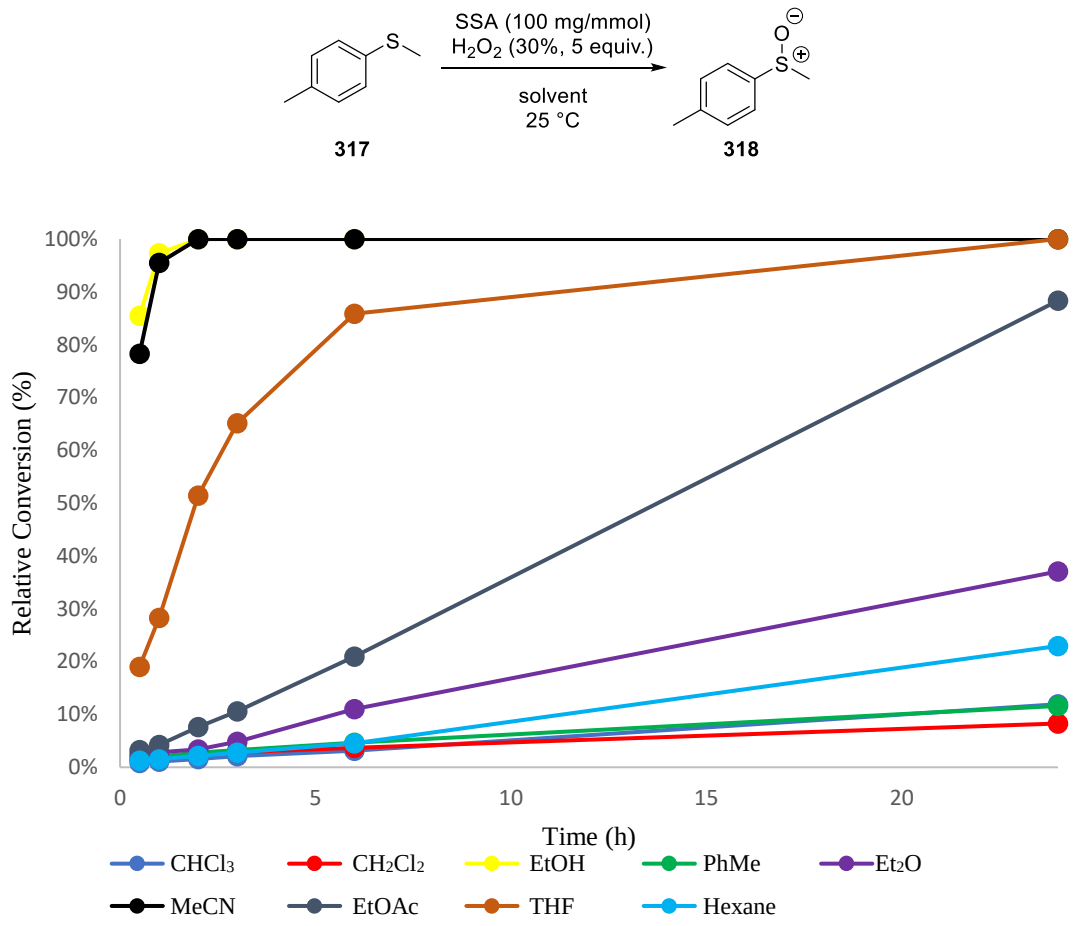


Figure 2-25. Solvent screen in the absence of ketone **313**.

Miscible and ethereal solvents (MeCN, EtOH, THF, EtOAc and Et_2O) were shown to be producing sulfoxide **318** as the result of an uncatalysed background oxidation. $CHCl_3$ and CH_2Cl_2 were shown to produce similar results both in the presence and absence of acetylacetone **313** suggesting that both could be used interchangeably. For the sake of consistency and due to its slightly better window of operation than CH_2Cl_2, $CHCl_3$ was maintained as the optimal solvent for the reaction.

2.3.3.4 Concentration

Reaction concentration had been shown to be an important factor in optimising the conditions for the $SnCl_2$ method. As a result, we were interested to examine it in the context of the SSA catalysed reaction (**Figure 2-26**).

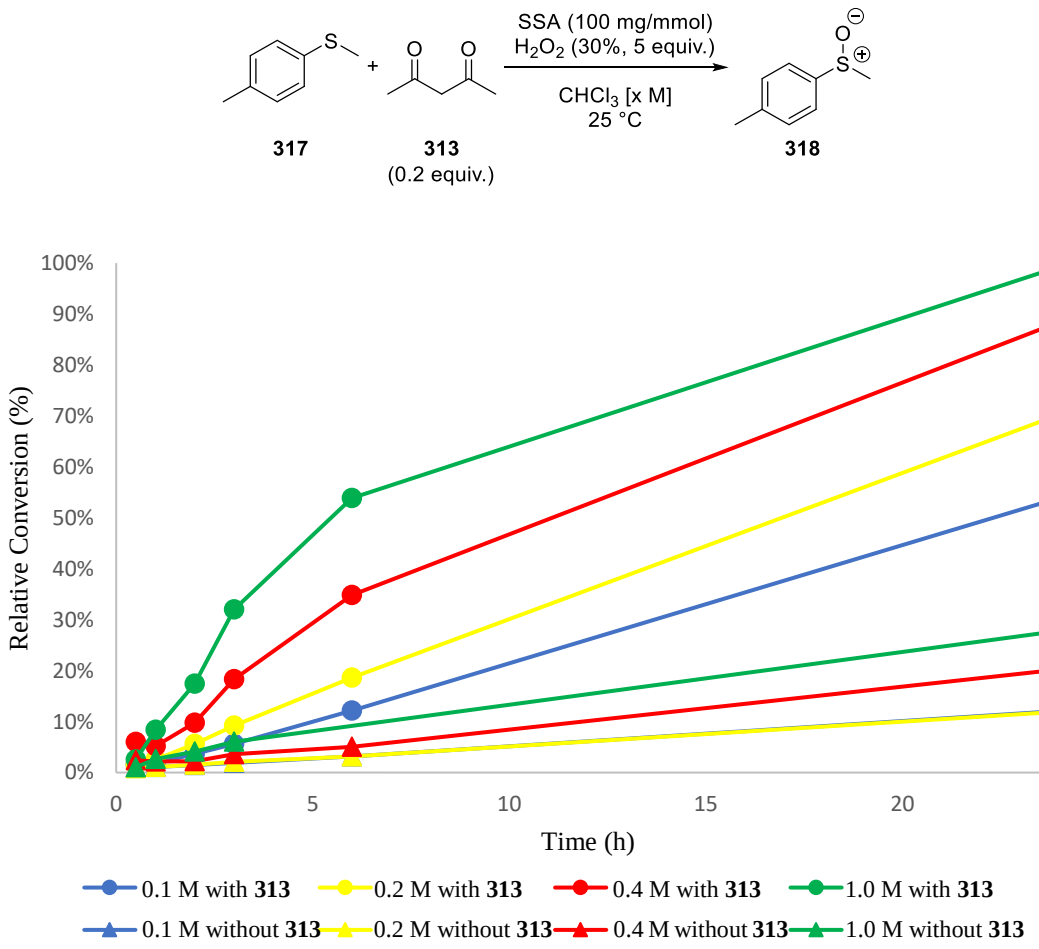


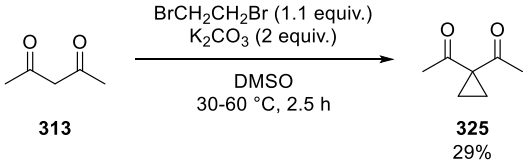
Figure 2-26. Optimisation of reaction concentration in $CHCl_3$

The rate of the reaction was found to increase for both the catalysed reaction (53% to 100% going from 0.1 M to 1.0 M at 24 h) and the background oxidation (12% to 28% going from 0.1 M to 1.0 M at 24 h) with increased concentration. 0.4 M (88% catalysed, 20% uncatalysed) was suggested to be the optimal concentration as it struck the greatest balance between rate of the catalysed process and suppression of the background reaction as well as giving consistent results.

2.3.3.5 Synthesis of Ketones

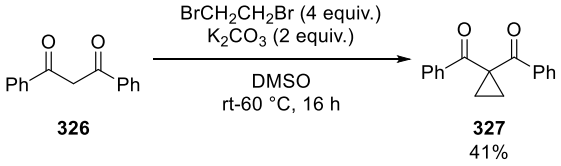
Within the optimisation of the SSA method we were interested to gain a much greater insight into the reactivity of the ketone within the reaction. As a result, a variety of different ketones were examined. Whilst the vast majority of these compounds were commercially available, several required synthesis prior to reaction. Ketones **325**–**357** were proposed in order to examine the effects of substitution on the backbone of the ketone as well as investigating the effect of changing the methyl groups to something

more sterically encumbered. Known ketone **325** was synthesised *via* the cyclopropanation of acetylacetone **313** (**Scheme 2-31**).[117]



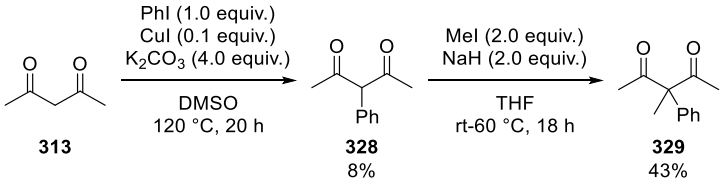
Scheme 2-30. Synthesis of ketone **325**.[117]

Ketone **325** was prepared in a low yield of 29% yield after alkylation with dibromoethane (61% published yield). The low yield was a result of complications within purification, resulting from an azeotroping mixture of byproducts during distillation. A similar set of conditions were employed in the synthesis of known ketone **327** (**Scheme 2-32**).[118]



Scheme 2-31. Synthesis of ketone **327**.[118]

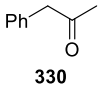
Ketone **327** was prepared in a 41% yield following purification (60% published yield). Phenyl substituted ketone **329** proved to be a challenging target to access. A variety of methods involving the synthesis of **329** from the corresponding malonate *via* the Weinreb amide proved unsuccessful. Ultimately, an Ullman coupling was performed to install the phenyl moiety on acetylacetone **313**, with ketone **329** being finally prepared *via* alkylation (**Scheme 2-33**).



Scheme 2-32. Synthesis of ketone **329**.

Ketone **329** was obtained in an overall yield of 3.4%. This low yield was the result of an exceptionally low yield from the Ullman coupling. The vast majority of the crude

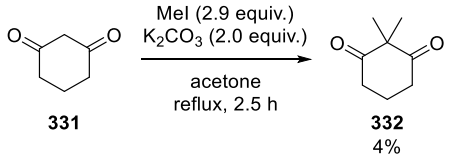
reaction mixture from this transformation appeared to be phenylacetone **330**, suggesting that the majority of the material underwent a de-acetylation over the course of the reaction (**Figure 2-27**).



330

Figure 2-27. Phenylacetone **330** was the major product of the Ullman coupling used to synthesise **328**.

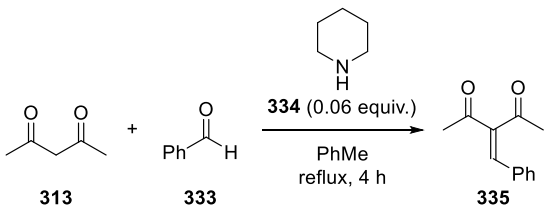
Ketone **332** was prepared *via* alkylation of cyclohexa-1,3-dione **331** with methyl iodide (**Scheme 2-34**).[119]



331 **332** 4%

Scheme 2-33. Synthesis of ketone **332**.[119]

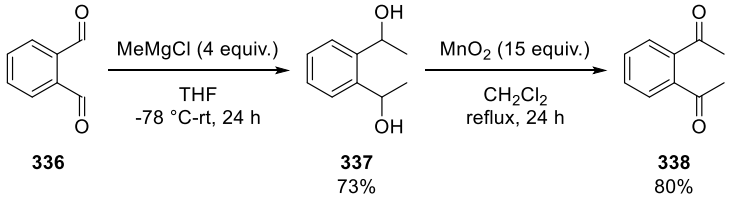
Dimethyl ketone **332** was synthesised in an 4% yield following purification. No explaination was available to explain the discrepancy when compared to the literature yield (51%). Ketone **335** and **338** were proposed to examine the effect of increasing the strain by changing the hybridisation of the methylene carbon on the backbone of the proposed active species. Access to **335** was achieved by Knoevenagel condensation of benzaldehyde **333** on acetylacetone with piperidine **334** as catalyst (**Scheme 2-35**).



313 **333** (1 equiv.) **335** 38%

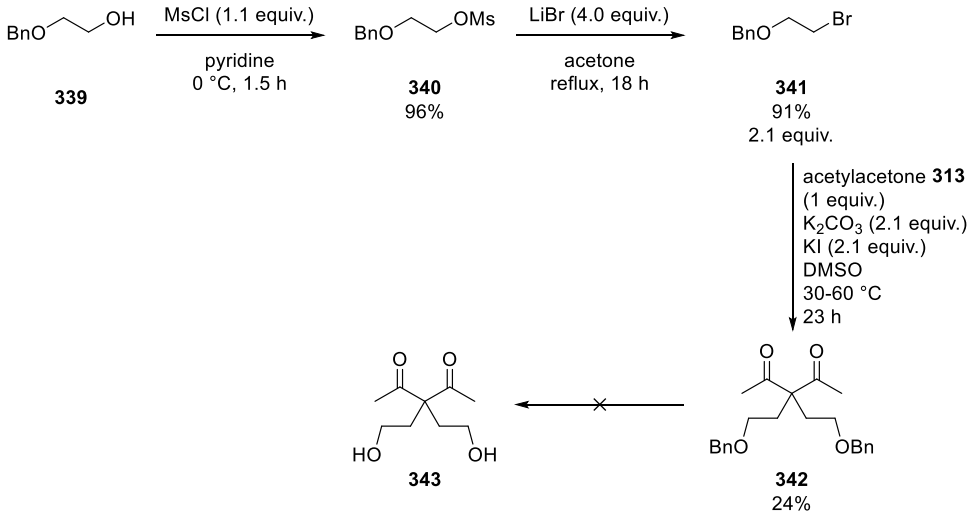
Scheme 2-34. Synthesis of ketone **335**.

The Knoevenagel condensation produced ketone **335** in a 38% yield. Ketone **338** was prepared by nucleophilic addition of methyl magnesium chloride to aldehyde **336** and subsequent oxidation of the resulting alcohol **337** with MnO_2 adapted from a process by (**Scheme 2-36**).[120]



Scheme 2-35. Synthesis of ketone **338**.[120]

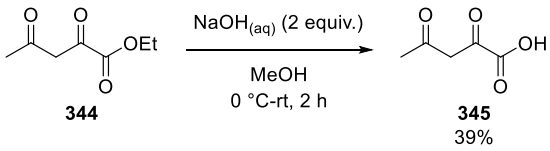
Ketone **338** was successfully isolated in a total yield of 58% over two steps, comparable to the published yield (49%). A variety of ketones featuring groups that would increase the aqueous solubility were prepared in the belief that this could increase the rate of active species formation. Dihydroxy ketone **343** was targeted, starting from alcohol **339** (**Scheme 2-37**).



Scheme 2-36. Synthetic route to ketone **343**.

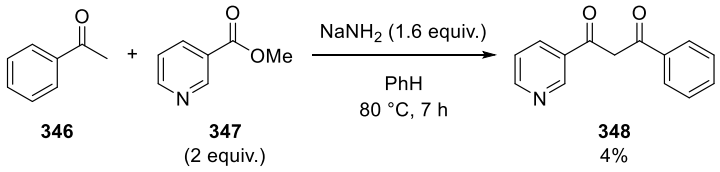
Alcohol **339** was mesylated with MsCl in a 96% yield. Attempts to alkylate acetylacetone **313** with **340** resulted only in the product of oxygen alkylation. As a result, a Finkelstein reaction was used to prepare bromide **341** in a 91% yield which was used to alkylate acetylacetone to form **342** in a 24% yield. Unfortunately, attempts to remove the benzyl protecting groups by hydrogenation were unsuccessful. Despite this, ketone **342** was retained for examination as a potential catalyst.

As well as ester **344**, acid **345** was deemed to be a ketone for investigation. Acid **345** was prepared *via* hydrolysis of ester **344** with NaOH (**Scheme 2-38**).



Scheme 2-37. Synthesis of ketone **345**.

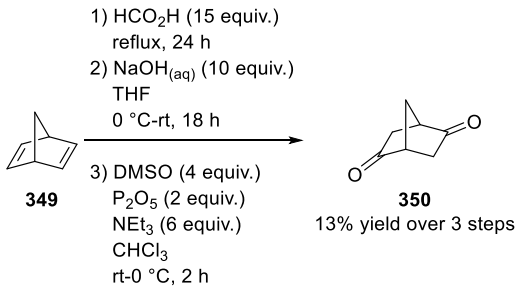
Acid **345** was synthesised in a 39% yield. Ketone **348** was proposed to become protonated under the reaction conditions, increasing its aqueous solubility and potentially increasing the rate of formation of the active species. Ketone **348** was synthesised by reaction of acetophenone **346** and methyl nicotinate **347** (**Scheme 2-39**).[121]



Scheme 2-38. Synthesis of ketone **348**.[121]

Ketone **348** was produced in a 4% yield. The low yield was attributed to degradation of the base $NaNH_2$, as the bottle appeared to be old. Fortunately, the reaction produced a sufficient quantity of ketone **348** to carry out the investigation.

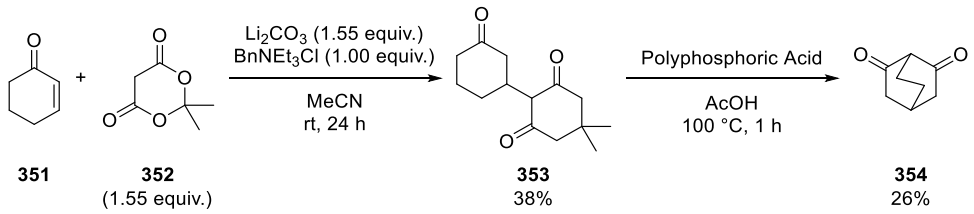
Finally, we were interested in examining ketones with the potential to participate in an enantioselective procedure. As a result, racemic ketones **350**–**357** were prepared to test if chiral ketones could function as catalyst. Ketone **350** was synthesised from norbornadiene **349** (**Scheme 2-40**).[122]



Scheme 2-39. Synthesis of ketone **350**.[122]

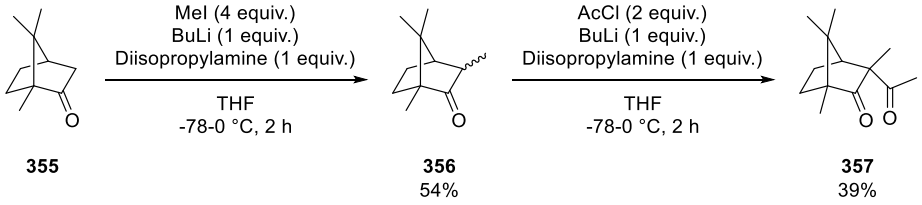
Trans-formylation of norbornadiene **349**, followed by hydrolysis of the resulting diester and oxidation of the alcohol resulted in a 13% yield of diketone **350** over 3

steps. Bicyclic ketone **354** was synthesised in a two-step procedure from cyclohexenone **351** and Meldrum's acid **352** (**Scheme 2-41**).[123]



Scheme 2-40. Synthesis of ketone **354**.[123]

Michael addition of Meldrum's acid **352** to cyclohexenone **351** resulted in intermediate **353** in a yield of 38%. Acid catalysed cyclisation of intermediate **353** resulted in the synthesis of bicyclic ketone **354** in a yield of 26%. Finally, camphor derived ketone **357** was synthesised *via* methylation and subsequent acylation of (+)-camphor **355** (**Scheme 2-42**).



Scheme 2-41. Synthesis of ketone **357**.

Methylation of camphor **355** resulted in intermediate **356** as a 3:1 mixture of diastereomers. Interestingly, the subsequent acylation of intermediate **356** resulted in a 39% yield of ketone **357**, which was isolated as a single diastereoisomer.

In conclusion, twelve ketones were synthesised, which, along with a variety of commercially available ketones, were proposed to be able to examine the tolerance of different functionalities within the diketone catalyst.

2.3.3.6 Optimisation of Ketones

2.3.3.6.1 Exploration of Central Methylene

As observed within the optimisation of the $SnCl_2$ method, changing the central methylene of acetylacetone **313** into a *gem*-dimethyl group resulted in a significant increase in the relative rate of the reaction. We were therefore interested in exploring

the effect of adding methyl groups to the central methylene carbon of both acetylacetone **313** and cyclohexa-1,3-dione **331** (**Figure 2-28**).

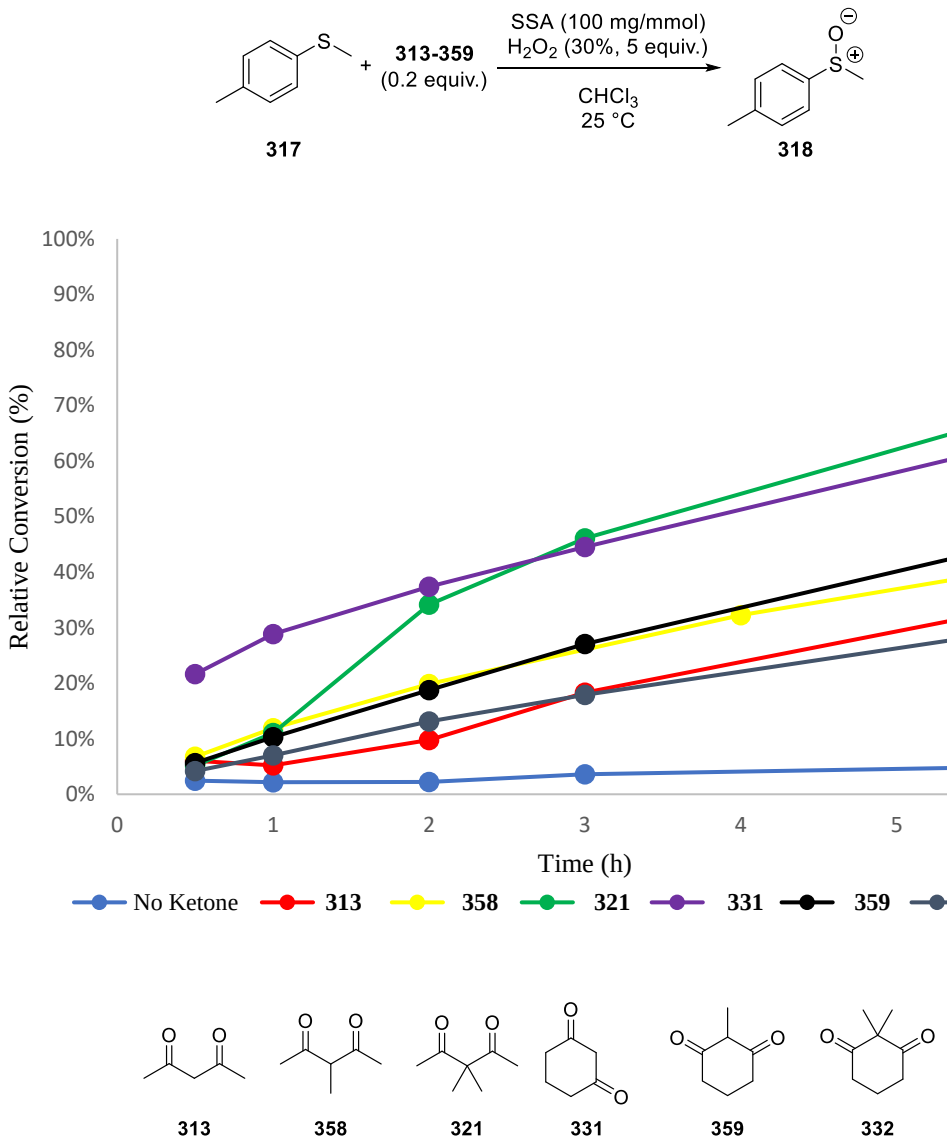


Figure 2-28. The effect of adding methyl groups to the central methylene of both acetylacetone **313** and cyclohexa-1,3-dione **331**.

Cyclohexa-1,3-dione **331** appeared significantly more reactive within the SSA catalysed process than acetylacetone **313**. Interestingly, the addition of methyl groups to both of these structures had the opposite effect between acetylacetone **313** and cyclohexa-1,3-dione **331**. The addition of methyl groups to acetylacetone **313** had the effect of increasing the rate of relative conversion of the reaction, with 3,3-dimethylacetylacetone **321** proving to be the most active of the six ketones examined, whereas the opposite appeared to be true for cyclohexa-1,3-dione **331**. It is believed that these results support the hypothesis of a cyclic active species. The

addition of methyl groups to acetylacetone **313** would increase the rate of formation of a cyclic species due to the impact of the Thorpe-Ingold effect. Similarly, the addition of methyl groups to cyclohexa-1,3-dione **331** would reduce the rate of formation of a cyclic species due to increased steric encumbrance. However, these assumptions are made based on the idea that the rate determining step of the reaction between the active species and the sulfide, with a dependence on the concentration of the active species. As we have been yet unable to show this, these statements may be incorrect. As 3,3-dimethylacetylacetone **321** was shown to provide the greatest improvement in rate to the reaction, it was examined in further transformations.

Having explored the effect of methyl substitution on the ketone backbone, we were interested to examine the effect of a variety of EWG on the reaction. It was proposed that ketones with EWGs might be more susceptible to nucleophilic attack by peroxide, thus increasing the rate of the reaction by increasing the rate of active species formation (**Figure 2-29**).

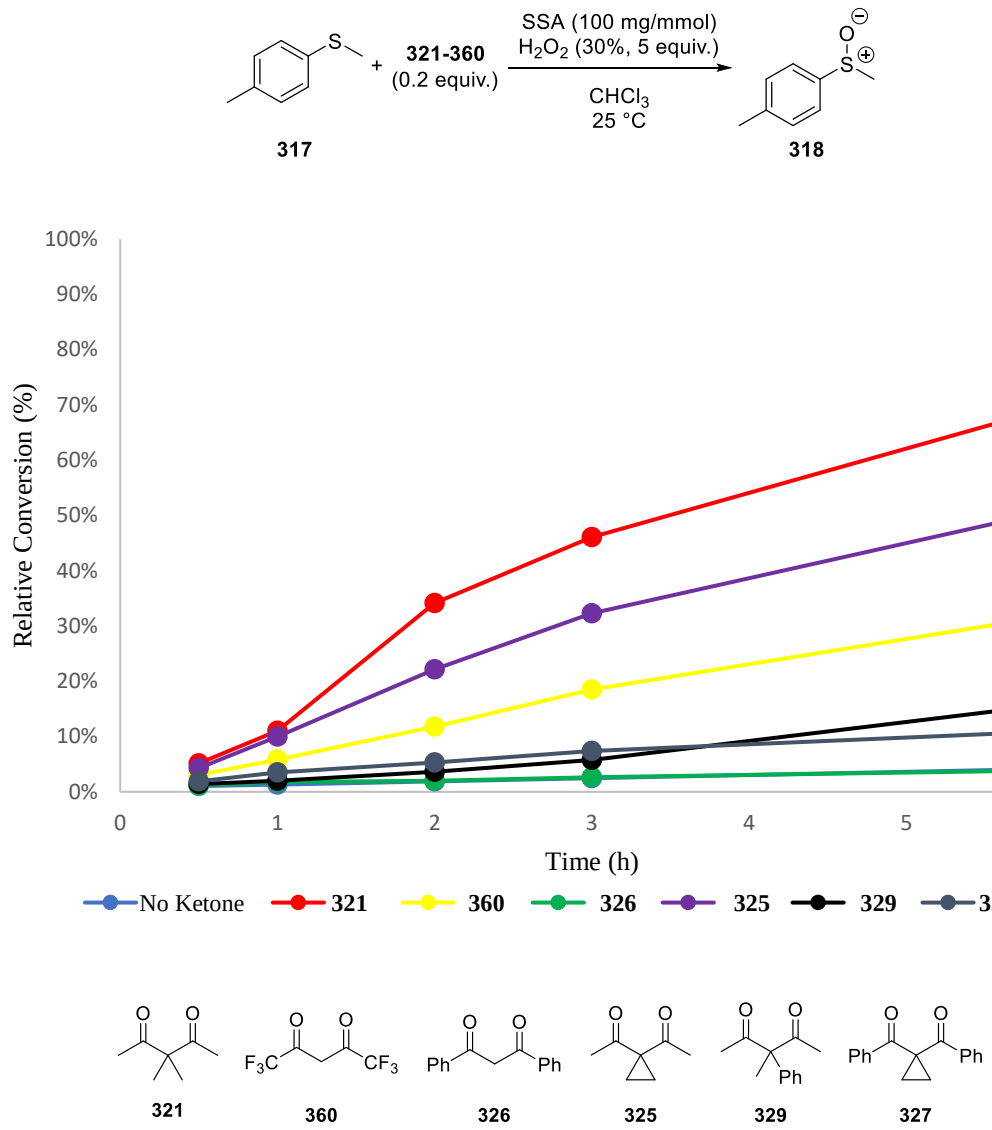


Figure 2-29. The effect of EWGs on the rate of the reaction.

Of the ketones examined, all ketones bearing phenyl groups proved highly ineffective within the reaction, with **326**, **327** and **329** barely increasing the rate of reaction over the rate of the background oxidation, suggesting that these ketones were not catalytically active. Bistrifluoromethyl ketone **360** also proved significantly less effective in the reaction than 3,3-dimethylacetylacetone **321**. The ^{1}H NMR of **360** revealed that it was entirely in its enol form in $CDCl_3$ and, as stated on **Page 109**, it is proposed that the enol form reduces the rate of formation of the active species. Finally, cyclopropanated ketone **325** was shown to be an effective catalyst for the reaction, although not to the same extent as 3,3-dimethylacetylacetone **321**.

It was postulated that investigating the effect of varying the backbone length and substituents on the ketone might have a positive effect on the reaction (**Figure 2-30**).

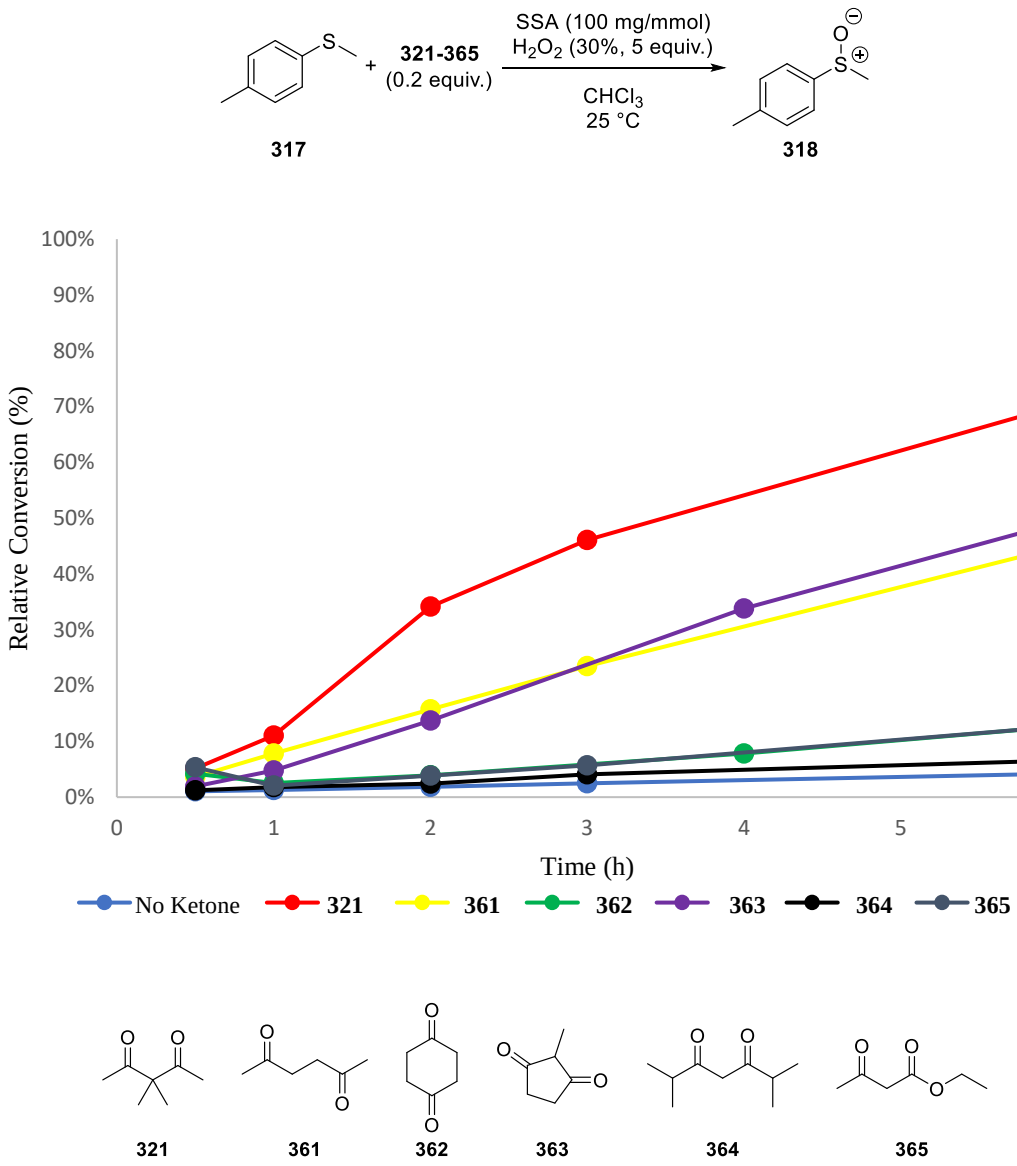


Figure 2-30. The effect of ketones **321**-**365** on the reaction rate.

Interestingly, increasing the backbone length with ketone **361** gave a minor improvement to the rate of the reaction over acetylacetone **313**, however, it was nowhere near the levels achieved by 3,3-dimethylacetylacetone **321**. Constraining the 1,4-diketone to a ring through the use of **362** completely removed its catalytic ability. Reducing the ring size from 6 membered ring **359** to 5 membered ring **363** had a neligable effect on the rate of the reaction. Isoproyl ketone **364** and ester **365** were both ineffective at catalysing the reaction.

Proposing a cyclic intermediate as the reactive catalytic species, we believed that adding some sp^2 character to the structures may make the resulting active species more reactive by increasing the strain within the ring (**Figure 2-31**).

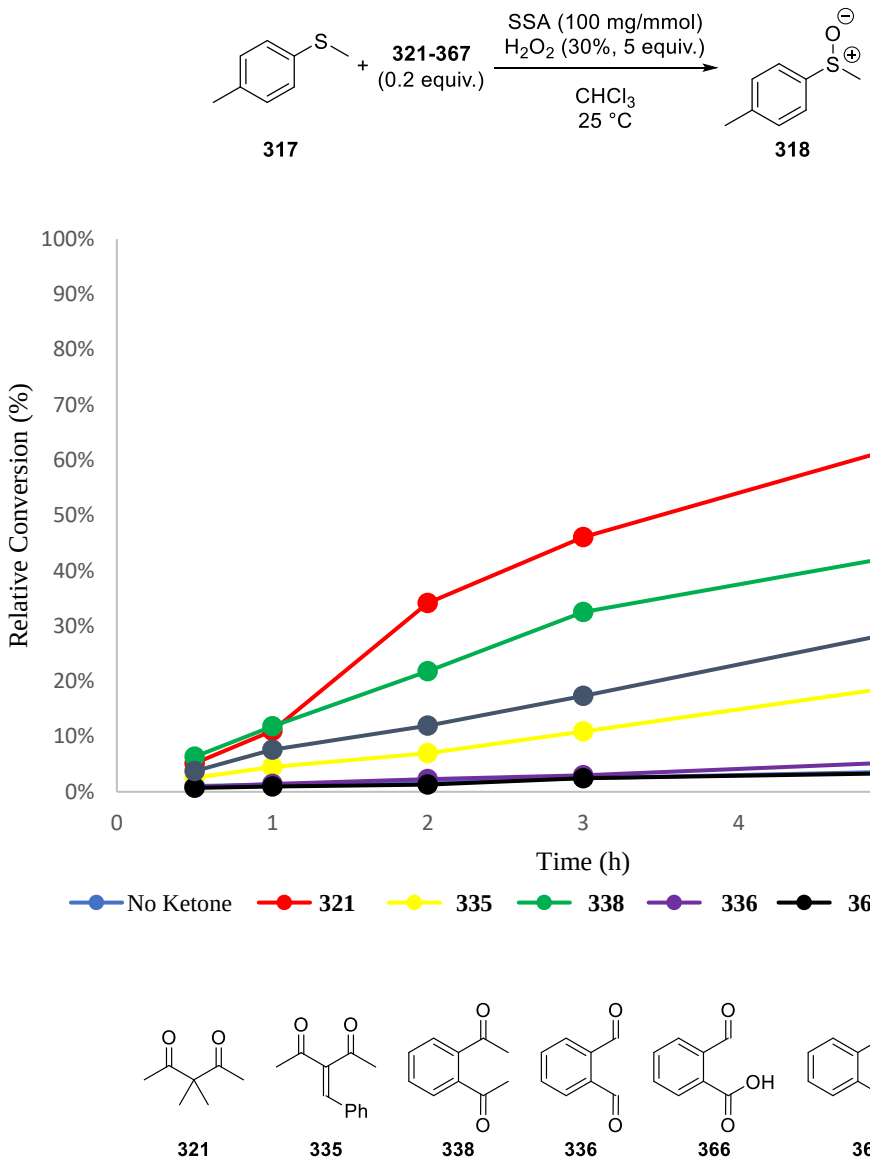


Figure 2-31. The effect of introducing sp2 character on the backbone of the catalyst.

Unfortunately, the addition of sp^2 character to the catalyst had a general trend of reducing the reactivity of the catalyst. Interestingly, aldehydes **336** and **367** were completely ineffective within the reaction, potentially due to oxidation of the aldehydes under the reaction conditions (**Figure 2-32**).

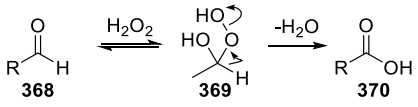


Figure 2-32. Oxidation of aldehydes under the reaction conditions might explain their lack of reactivity.

Next, ketones **321**–**373** were examined under the reaction conditions (**Figure 2-33**).

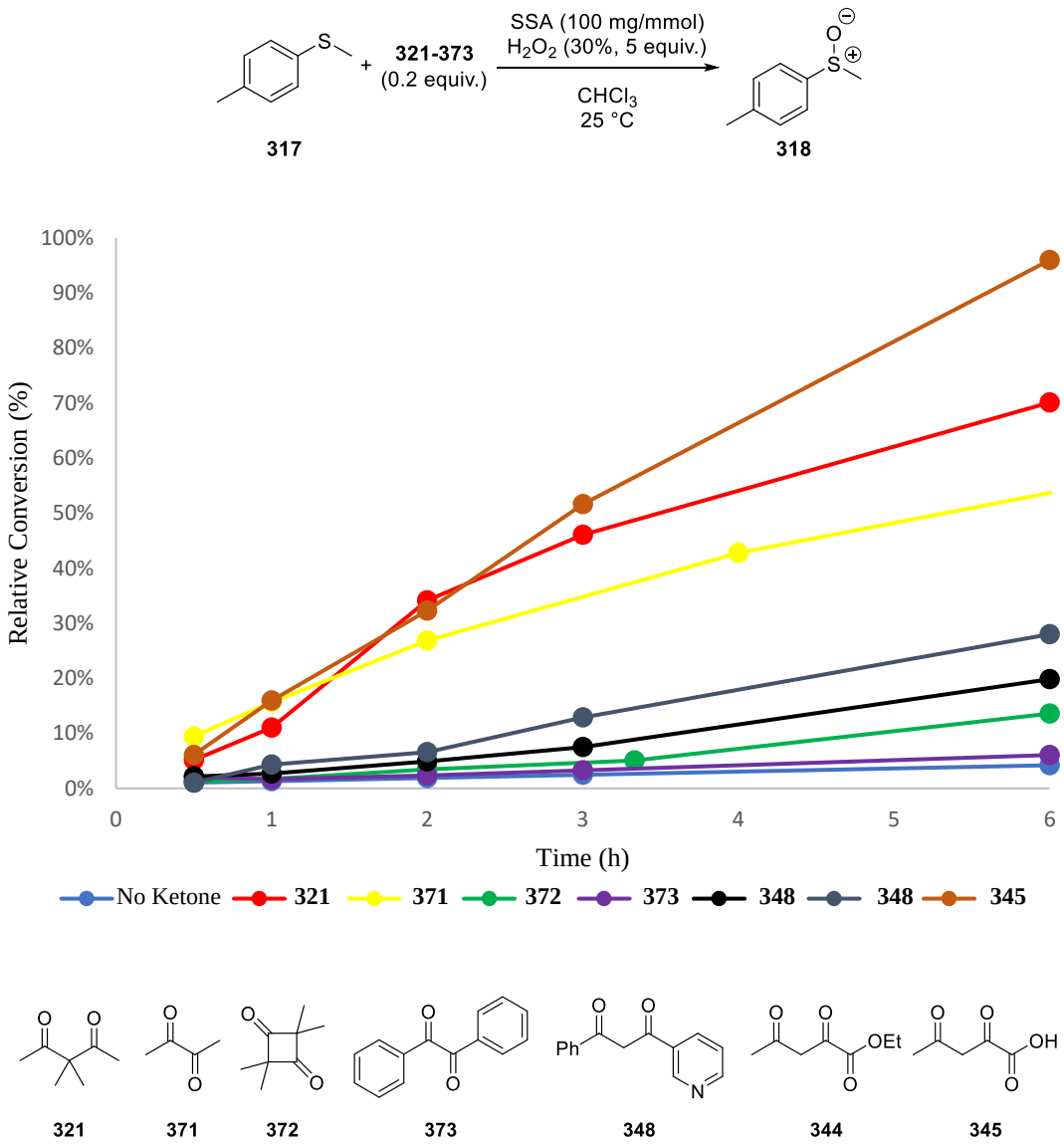


Figure 2-33. The effect of ketones **321-373** on the reaction rate.

Interestingly, butadione **371** showed a high level of activity. As this substrate would be unable to form a cyclic active species it is unknown what caused this ketone to show such high levels of activity. Ketones **372** and **373** were shown to barely improve the rate of reaction over the background process. Ketone **348**, which was proposed to become protonated under the reaction conditions, hopefully improving its aqueous solubility and therefore the rate of formation of the active species, also had only a small catalytic effect on the reaction. Carboxylic acid **345** showed a reasonable increase in rate over 3,3-dimethylacetylacetone **321**. It is proposed, however, that this may be the result of a different mechanism to that of 3,3-dimethylacetylacetone **321** as the ester **345** was significantly less efficient and as such, **345** was discounted.

We were interested to examine the ability of chiral ketones within the reaction, as it was postulated that enantiopure ketones may allow access to an enantioselective procedure. As such, a variety of racemic ketones were subjected to the reaction conditions (**Figure 2-34**).

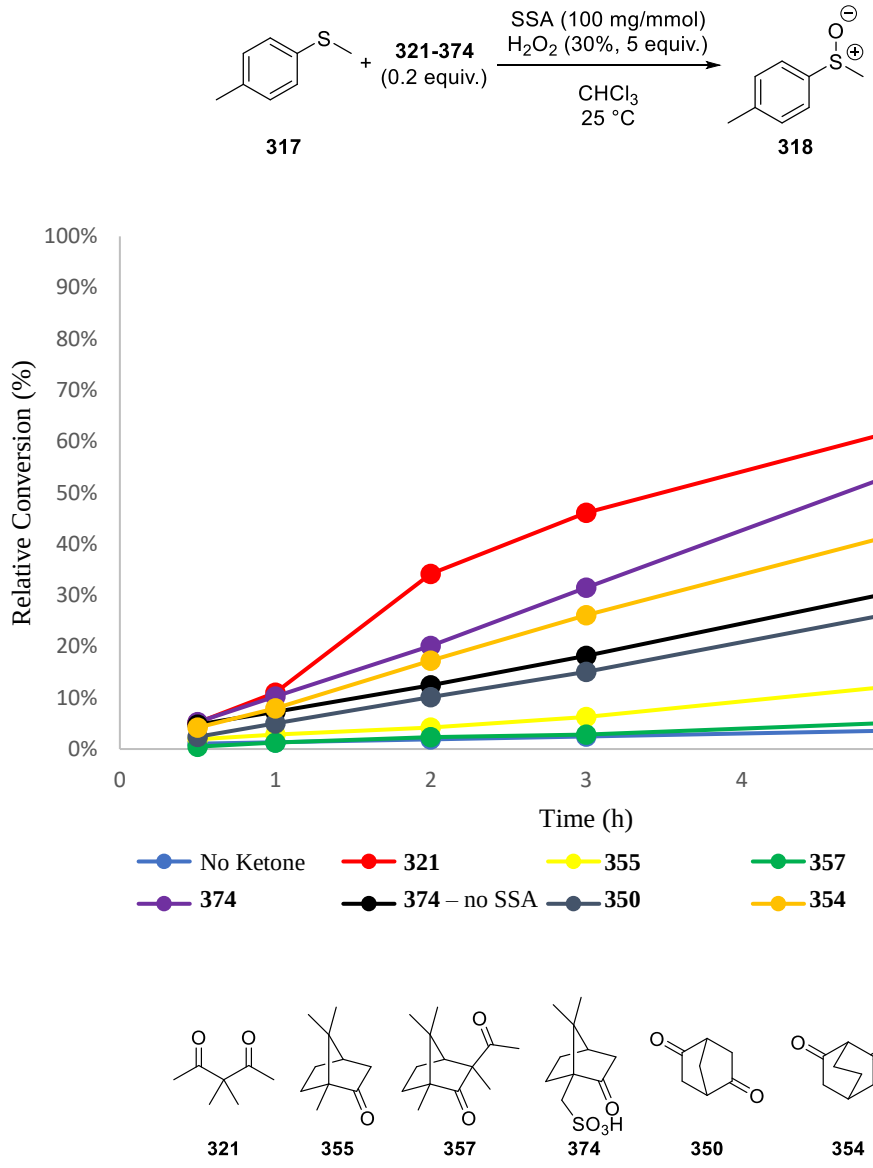


Figure 2-34. Examining the use of chiral ketones on the reaction.

Unfortunately, none of the ketones displayed the same level of activity of 3,3-dimethylacetylacetone **321** with the exception of camphor-sulfonic acid (CSA) **374**. However, a blank reaction conducted in the absence of SSA suggested that the vast majority of the activity of observed with CSA **374** may have been the result of its acidity.

In order to show that the catalytic activity of the ketones within the reaction was not due to the formation of a *gem*-peroxide structure or some form of hydrogen bonding adduct with hydrogen peroxide, a variety of negative controls were run under the reaction conditions (**Figure 2-35**).

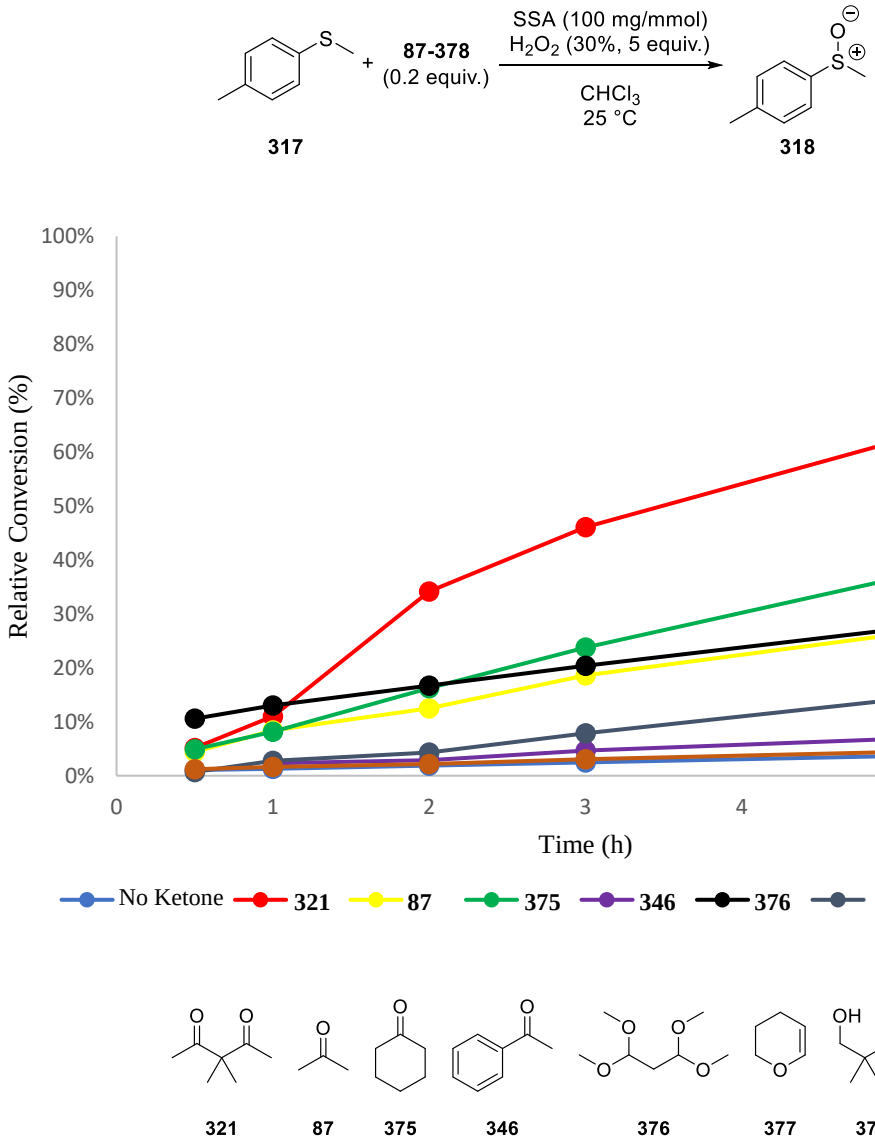


Figure 2-35. Negative control compounds.

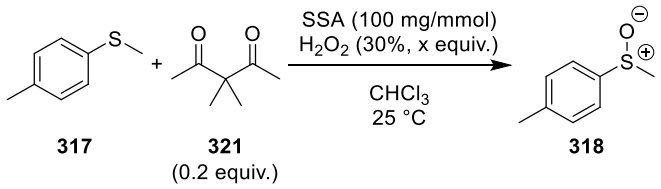
Acetone **87**, cyclohexanone **375** and acetophenone **346** all catalysed the reaction at a significantly reduced rate than 3,3-dimethylacetylacetone **321**, suggesting that the activity observed with 3,3-dimethylacetylacetone **321** was not the result of the formation of *gem*-peroxides. Malonaldehyde bis dimethylacetyl **376** and dihydropyran **377** were also, highly ineffective under the reaction conditions. Neopentyl glycol **378** was used under the reaction conditions to show that the catalytic activity of

3,3-dimethylacetylacetone **321** was not the result of the formation of a hydrogen bonding adduct. As **378** showed no catalytic effect on the reaction, we are confident that this is not the case.

Having thoroughly examined the structure of the ketone on the rate of the reaction, it was revealed that 3,3-dimethylacetylacetone **321** was indeed optimal for the reaction.

2.3.3.7 30% H_2O_2 Equiv.

After extensively examining the structure of the ketone on the rate of the catalytic process and determining that **321** was optimal, the equiv. of hydrogen peroxide used within the reaction was next investigated (**Figure 2-36**).



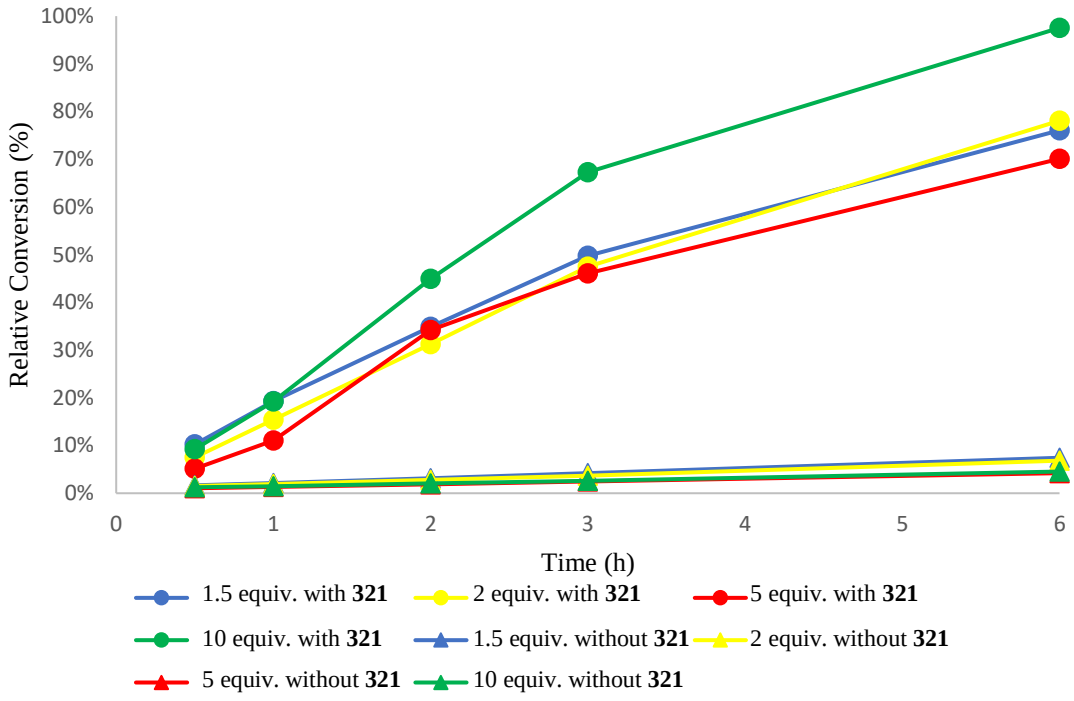


Figure 2-36. The effect of 30% hydrogen peroxide equivalents on the reaction.

Interestingly, changing the equiv. of hydrogen peroxide used within the reaction had a completely different effect on the SSA reaction than the $SnCl_2$ catalysed process (**Page 103-105**). This time, changing the equiv. of hydrogen peroxide within the SSA

reaction had an almost negligible effect on both the catalysed process and the background process, although higher loadings did appear to slightly increase the rate of the catalysed process.

2.3.3.8 50% H_2O_2 Equiv.

With the interesting results observed when using 30% hydrogen peroxide in the SSA method, we also wanted to examine the effect of 50% hydrogen peroxide on the reaction (**Figure 2-37**).

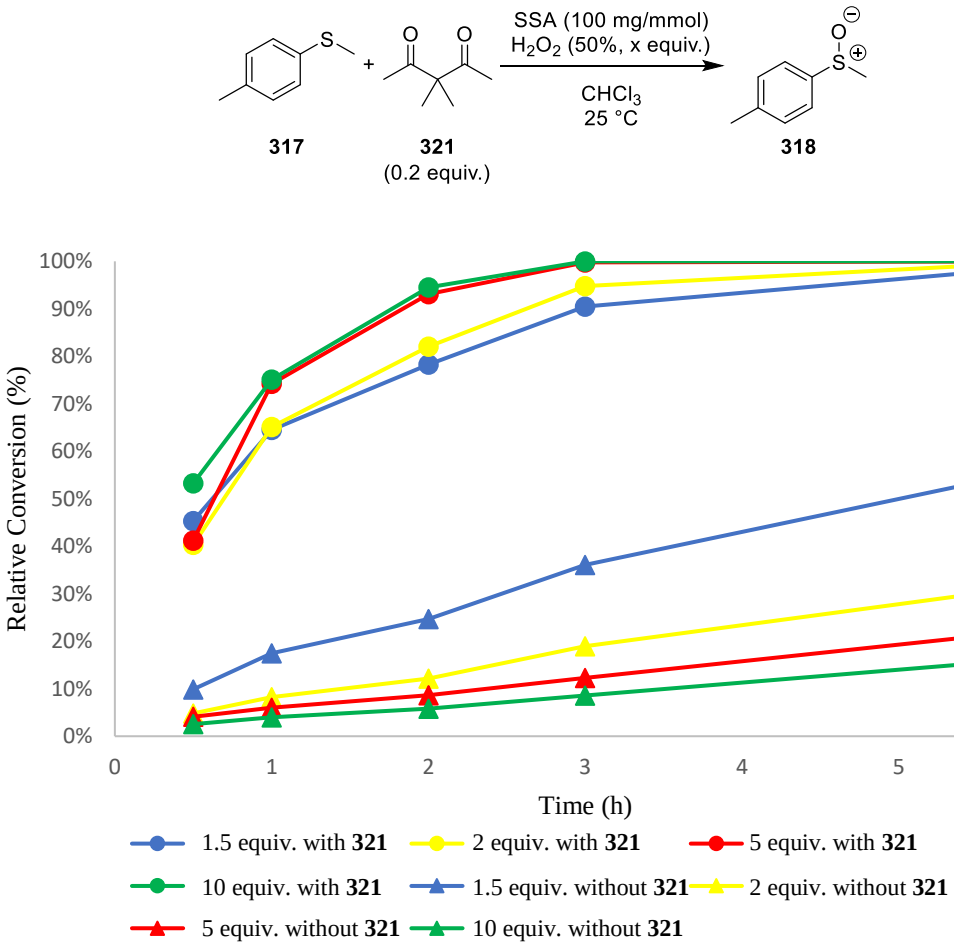


Figure 2-37. The effect of 50% hydrogen peroxide equivalents on the reaction.

The use of 50% hydrogen peroxide within the SSA conditions showed a marked improvement over the use of 30% hydrogen peroxide. Using 5 equivalents of 50% hydrogen peroxide allowed the reaction to reach full completion within 3 hours, also a marked improvement on the optimal $SnCl_2$ conditions (100%, 6 hours). Similar to the 30% H_2O_2 results with SSA, increasing the number of equivalents of hydrogen peroxide allowed only a minor improvement in the relative rate of formation of

sulfoxide **318**. However, increasing the number of equivalents did have an effect in suppressing the background oxidation process. 5 equiv. of 50% hydrogen peroxide was believed to be optimal, striking the best balance between efficiency, the rate of the catalysed process and the rate of the background oxidation.

2.3.3.9 Ketone 321 Equiv.

Finally, the effect of varying the equivalents of ketone **321** on the reaction were investigated (**Figure 2-38**).

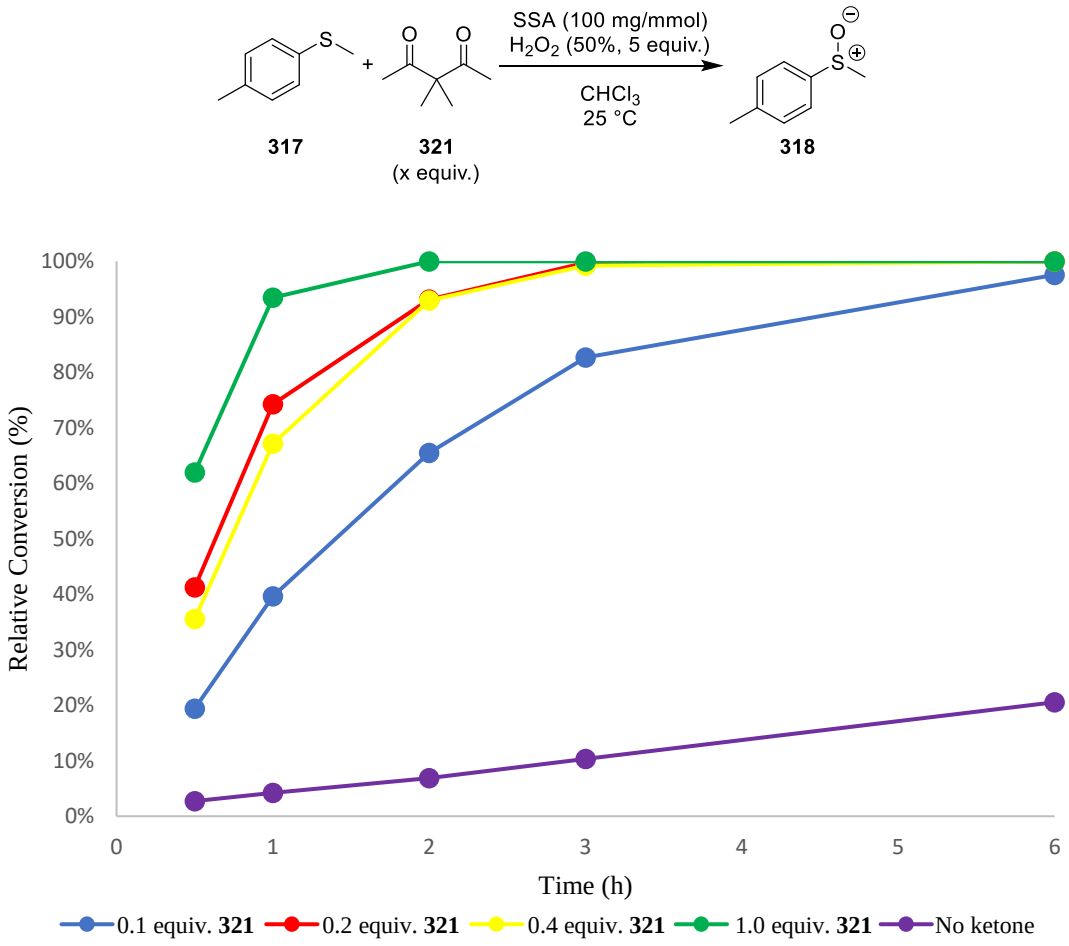


Figure 2-38. The effect of varying ketone **321** equiv.

Increasing the equivalents of ketone **321** from 0.2 equiv. to 0.4 equiv. produced no improvement in the reaction outcome. Further increasing to 1.0 equivalent did provide an improvement but the use of 0.2 equiv. was preferred as it was more economical. Reducing to 0.1 equiv. of ketone **321** had a noticeably detrimental impact on the reaction and as such 0.2 equiv. was taken forward as optimal.

In conclusion, two sets of optimal conditions were developed for the catalytic sulfoxidation procedure, one based around the use of $SnCl_2$ as the co-catalyst and one based around the use of SSA. The SSA conditions, which use 5 equiv. of 50% hydrogen peroxide are preferred for the process as the sulfoxide **318** was isolated more efficiently (in less than 3 hours) and the catalyst is less toxic and more environmentally benign than tin(II) compounds.

2.3.4 Reaction Scope and Limitations

With optimal conditions available, the project focus shifted to examining the scope and limitations of both the $SnCl_2$ and SSA catalysed sulfoxidation methods.

2.3.4.1 Substrate Synthesis

Although the vast majority of substrates were commercially available, several required synthesis (**Figure 2-39**).

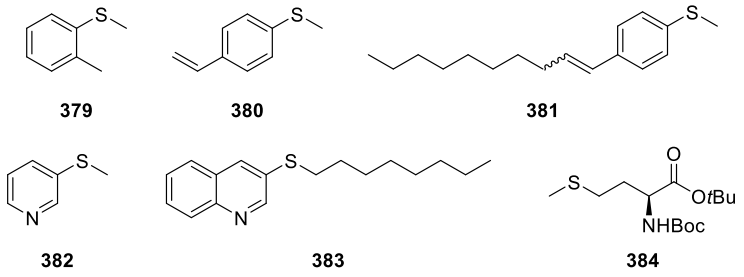
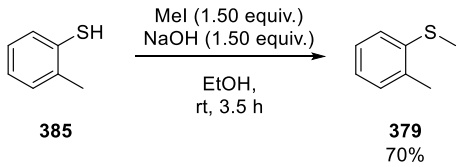


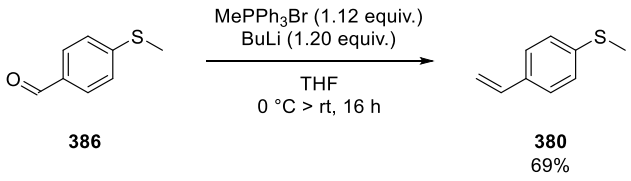
Figure 2-39. Substrates requiring synthesis.

The synthesis of *ortho*-tolyl sulfide **379** was easily achieved *via* alkylation of the corresponding thiol **385** with methyl iodide in 70% yield (**Scheme 2-43**).



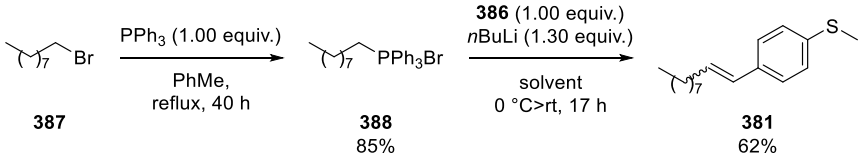
Scheme 2-42. Synthesis of sulfide **379**.

Sulfide **380** was produced *via* Wittig reaction between aldehyde **386** and methyltriphenylphosphonium bromide under basic reaction conditions in a 69% yield (**Scheme 2-44**).



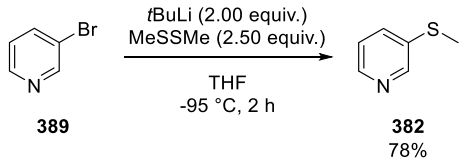
Scheme 2-43. Synthesis of sulfide **380**.

Sulfide **381** was prepared in a similar manner to **380**. First, phosphonium salt **388** was synthesised by S_N2 displacement of nonanebromide **387** with triphenylphosphine in an 85% yield. A Wittig reaction was then performed with aldehyde **386** and phosphonium salt **387** to give the corresponding alkene product as a 1:1 mixture of *E*- and *Z*-diastereomers. Small amounts of both diasterioisomers were separated by column chromatography for identification purposes but the majority of the material was carried on as a 1:1 mixture.



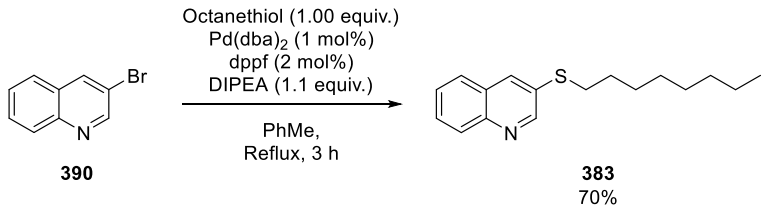
Scheme 2-44. Synthesis of sulfide **381**.

The synthesis of pyridyl derivative **382** was achieved *via* a lithium-halogen exchange and trapping the anion with dimethyldisulfide (**Scheme 2-46**).



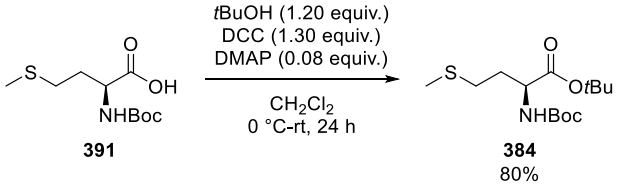
Scheme 2-45. Synthesis of sulfide **382**.

Pyridyl derivative **382** was isolated in a 78% yield following purification. Quinoline derivative **383** was prepared *via* a novel cross-coupling method developed by Okauchi (**Scheme 2-47**).[124]



Scheme 2-46. Synthesis of sulfide **383**.[124]

Quinoline derivative **383** was prepared in a 70% yield. Finally, the synthesis of bis-protected methionine **384** was achieved by esterification of the Boc protected amino acid **391** (**Scheme 2-48**).[125]



Scheme 2-47. Synthesis of bis-protected methionine **384**.[125]

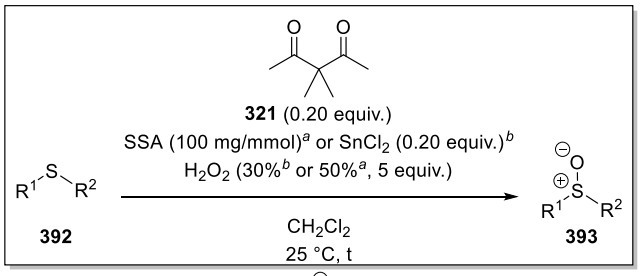
Bis-protected methionine **384** was obtained in an 80% yield using a DCC coupling method.

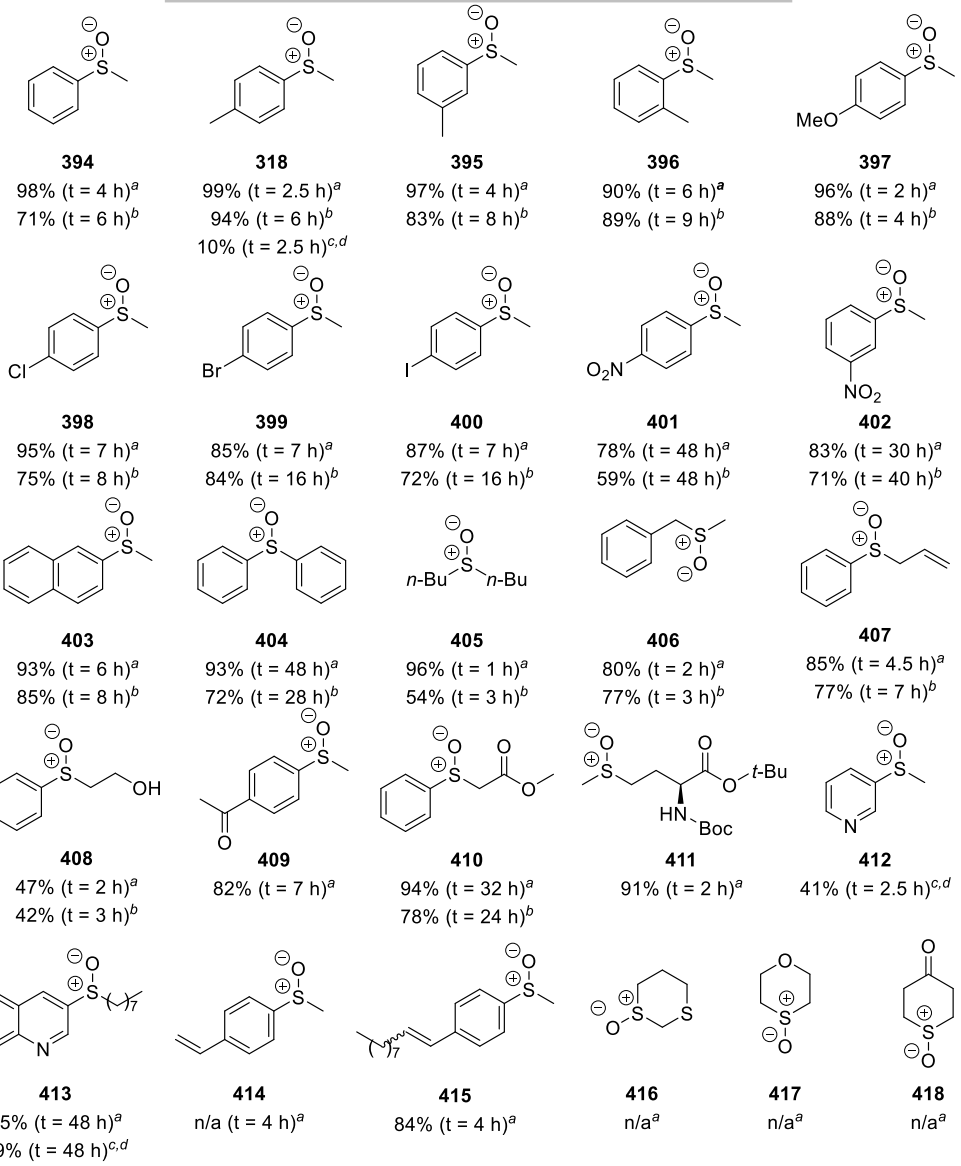
In conclusion, six substrates (**379**–**384**) were successfully prepared in generally high yields (62–80%) using a variety of different techniques for use in the examination of the catalytic sulfoxidation reaction we had developed.

2.3.4.2 Substrate Scope

With optimal conditions available a substrate scope of 26 sulfides was undertaken to test the scope and limitations of the reaction. Several substrates were subjected to the $SnCl_2$ conditions as well as the SSA conditions. A few select substrates were also tested in the absence of ketone to determine if their oxidation was the result of the catalytic process or a background oxidation by the hydrogen peroxide (**Table 2-1**).

Table 2-1. Catalytic sulfoxidation substrate scope and limitations.





394	**318**	**395**	**396**	**397**
98% (t = 4 h)[a]	99% (t = 2.5 h)[a]	97% (t = 4 h)[a]	90% (t = 6 h)[a]	96% (t = 2 h)[a]
71% (t = 6 h)[b]	94% (t = 6 h)[b]	83% (t = 8 h)[b]	89% (t = 9 h)[b]	88% (t = 4 h)[b]
	10% (t = 2.5 h)[c,d]			

398	**399**	**400**	**401**	**402**
95% (t = 7 h)[a]	85% (t = 7 h)[a]	87% (t = 7 h)[a]	78% (t = 48 h)[a]	83% (t = 30 h)[a]
75% (t = 8 h)[b]	84% (t = 16 h)[b]	72% (t = 16 h)[b]	59% (t = 48 h)[b]	71% (t = 40 h)[b]

403	**404**	**405**	**406**	**407**
93% (t = 6 h)[a]	93% (t = 48 h)[a]	96% (t = 1 h)[a]	80% (t = 2 h)[a]	85% (t = 4.5 h)[a]
85% (t = 8 h)[b]	72% (t = 28 h)[b]	54% (t = 3 h)[b]	77% (t = 3 h)[b]	77% (t = 7 h)[b]

408	**409**	**410**	**411**	**412**
47% (t = 2 h)[a]	82% (t = 7 h)[a]	94% (t = 32 h)[a]	91% (t = 2 h)[a]	41% (t = 2.5 h)[c,d]
42% (t = 3 h)[b]		78% (t = 24 h)[b]		

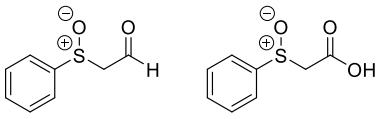
413	**414**	**415**	**416**	**417**	**418**
75% (t = 48 h)[a]	n/a (t = 4 h)[a]	84% (t = 4 h)[a]	n/a[a]	n/a[a]	n/a[a]
79% (t = 48 h)[c,d]					

[a]Using the SSA/50% H_2O_2 method. [b]Using the $SnCl_2$/30% H_2O_2 method. [c]Using the SSA/50% H_2O_2 method in the absence of diketone **321**. [d]Result of a single experiment. All other experiments are an average of two experiments.

Using the SSA method, phenyl and tolyl derivatives **318**–**396** were prepared in very high yields (90–99%). Interestingly, the reactions required a longer reaction time as the steric encumberance around sulfur was increased (2.5 hours for **318**, 6 hours for

396). Electron rich sulfoxide **397** was also isolated in excellent yield (96%). Substrates bearing electron withdrawing groups such as halides (**398**–**400**, 85–95%) and nitro-groups (**401**–**402**, 78–83%) were similarly well tolerated by the reaction. These substrates showed another trend, revealing that the electronics of the substrate had an effect on the overall rate of the reaction. Electron poor substrates required much longer (7 hours for **398**, 48 hours for **401**) to reach completion than electron rich substrates (2 hours for **397**). More sterically demanding substrates, such as 2-naphthyl **403** and diphenyl **404** sulfoxides were also produced in high yields (both 93%) suggesting that highly sterically demanding substrates were tolerated by the reaction, even though extended reaction times were required (up to 48 h). The reaction was also highly tolerant of alkyl sulfides, as demonstrated by the high yielding synthesis of di-*n*-butyl sulfoxide **405** and benzyl methyl sulfoxide **406** (96% and 80%).

In an attempt to discover any limitations of the reaction, a variety of substrates containing oxidisable and acid labile functionalities were subjected to the transformation. Sulfoxides containing an alkene **407** and styrene **415** were synthesised in high yield (85% and 84%) with no evidence of alkene oxidation. Synthesis of sulfoxide **414** was also performed and although the sulfoxide appeared to have been readily prepared problems arose during purification and the substrate was abandoned due to time constraints. Although the sulfoxide of primary alcohol **408** was produced in a low yield (47%), it is believed that this was not due to oxidation of the alcohol moiety, as none of corresponding aldehyde **419** or carboxylic acid **420** were observed during the work-up and purification of **408** and this was simply reflective of the water solubility of the product (**Figure 2-40**).



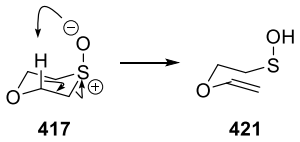
419 **420**

Figure 2-40. **419** and **420** were not observed during the work-up and purification of **408**.

Similarly, sulfoxide **409** was prepared in a high yield (82%) with no evidence of Bayer-Villiger oxidation of the ketone. Ester **410** was isolated in high yield (94%) with no observed degradation of the ester functionality. Impressively, sulfoxide **411** was produced in high yield (91%) despite containing two acid labile protecting groups, suggesting the SSA within the reaction was mild. Quinoline derivative **413** was

synthesised using the catalytic conditions in high yield (75%) however, an earlier investigation of pyridyl substrate **412** had shown that its oxidation occurred in the absence of ketone (41%) and unfortunately it was found that this also applied for this substrate (79% yield in the absence of ketone) as such, we believe that the oxidation of pyridyl derivatives cannot yet be achieved *via* this method. This is likely due to the protonation of the basic nitrogen occurring under the reaction conditions, allowing the substrate to transition into the aqueous phase and become oxidised under the acidic and oxidative aqueous conditions.

Another limitation of the reaction that became apparent during the investigation was found using substrates **416**–**418**. These low molecular weight sulfoxides were either not observed during the reaction or were inseparable from complicated reaction mixtures. It is believed that this is due to the biphasic nature of the reaction mixture. Sulfoxides **416**–**418** are highly hydrophilic meaning that they are likely to partition into the aqueous phase of the reaction mixture where they may be vulnerable to over oxidation. Sulfoxide **417** in particular may also be vulnerable to sulfoxide elimination generating the highly reactive sulfenic acid **421** which could decompose to a variety of additional products (**Scheme 2-49**).



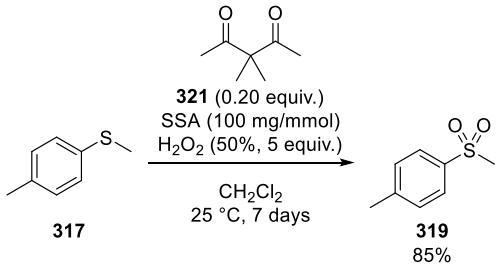
417 **421**

Scheme 2-48. Potential sulfoxide elimation of substrate **417**.

Using the $SnCl_2$ method, similar trends were observed for most of the substrates examined. Products were obtained in generally high yields (42–94%) which were slightly lower on average than those obtained with the SSA method. Most substrates also required slightly longer reaction times than with the SSA method to reach completion. This may be due to the use of 30% H_2O_2 as opposed to 50% H_2O_2.

In order to quantify the extent of background oxidation in the absence of ketone catalyst, substrate **318** was subjected to the reaction conditions in the absence of ketone. Under these conditions, only a 10% yield of sulfoxide **318** was isolated, with the remaining material accounted for by unreacted starting material.

Finally, we were interested to see if the method could be applied to the synthesis of sulfones. As such, sulfide **317** was subjected to the reaction conditions for an extended period of time (**Scheme 2-50**).



Scheme 2-49. Synthesis of sulfone **319** under catalytic conditions.

Sulfone **319** was prepared under the catalytic conditions in an 85% yield after 7 days from sulfide **317**. Despite showing that the oxidation of sulfide **317** into sulfoxide **318** is accelerated by the presence of ketone **321**, it is believed that the transformation of sulfoxide **318** into sulfone **319** was the result of an uncatalyzed background process. It should be noted that no significant over oxidation to the corresponding sulfones was observed for the products isolated under the standard reaction conditions and time scales.

In conclusion, 21 substrates were successfully oxidised to the corresponding sulfoxide using the SSA method. Several sulfides were also transformed successfully into the sulfoxide using the $SnCl_2$ method, although the results were generally higher yielding and faster using the SSA method. The method was generally quite tolerant of sterically and electronically varied substrates, as well as a large variety of oxidisable and acid-labile functional groups. However, sulfides which contained highly hydrophilic sulfoxides or basic groups were generally not well tolerated, possibly due to the biphasic nature of the reaction.

2.3.5 Mechanistic Insight

2.3.5.1 Structure of Active Species

Having developed optimised conditions for the reaction and investigated its scope and limitations, we were interested in gaining a mechanistic understanding of the process. Based on the reported stoichiometric procedure[113c] we believed that the reaction

initially involved the formation of organic peroxide **422** from the reaction of ketone **321** and hydrogen peroxide which would serve as the reactive species (**Figure 2-41**).

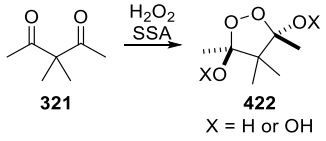
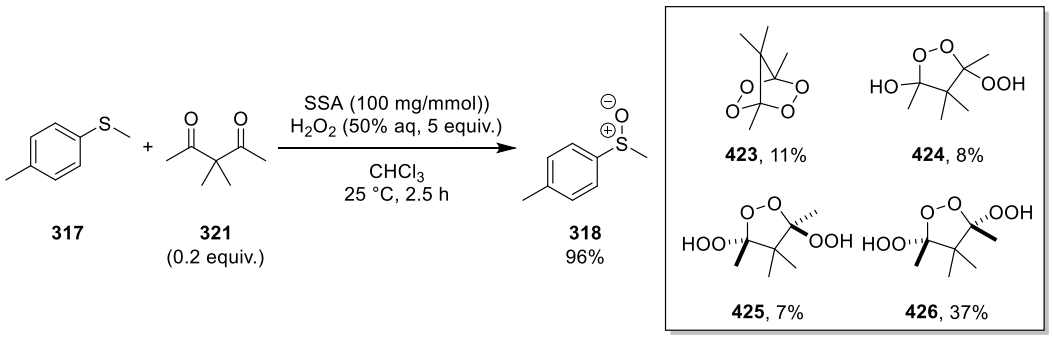


Figure 2-41. Organic peroxide **422** was proposed to be the reactive species.

In order to test our hypothesis, the standard reaction using sulfide **317** was scaled up to 10 mmol in order to allow for the isolation of products derived from ketone **321** (**Scheme 2-51**).



Scheme 2-50. Isolation of reaction intermediates derived from ketone **321**.

Interestingly, the reaction proceeded with a comparable yield on a 10 mmol scale to the yield observed on a 1 mmol scale, producing sulfoxide **318** in a 96% yield. At the end of the reaction, ketone **321** was not observed, however, four peroxide species **423**–**426** related to ketone **321** were isolated in a total yield of 63%. The common 1,2-dioxolane motif observed in these peroxide structures supported our hypothesis that an organic peroxide was the active species within our catalytic system.

Unfortunately, peroxides **423**–**426** proved to be unstable following isolation, quickly decomposing in a matter of hours. It is believed that this may have been the result of a pinacol rearrangement, as previously noted by Payne (**Figure 2-42**).[126]

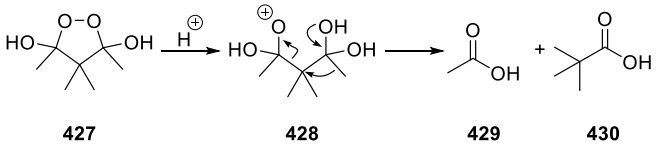
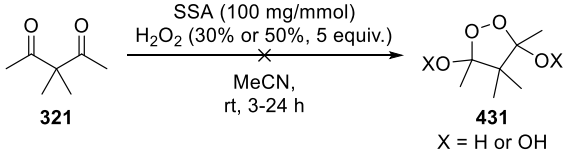


Figure 2-42. Pinacol rearrangement decomposition of peroxide **427**.[126]

Although no quantitative evidence was obtained for this, peaks at δ 2.10 and 1.23, believed to correspond to AcOH **429** and pivalic acid **430**, could be observed in the ^{1}H NMR spectra. When coupled with the odour of acetic acid arising from the vessel we believe this pinacol rearrangement is the cause of decomposition. Similarly, the independent synthesis of peroxides related to ketone **321** failed to produced stable products, with **424** being observed but never isolated (**Scheme 2-52**).



Scheme 2-51. Independent synthesis of peroxides related to **431** was unsuccessful.

Within his report on the oxidative rearrangement of diketones, Payne noted that rearrangement did not occur with acetylacetone **313**.[126] As such, we set out to use peroxide compounds derived from acetylacetone **313** to further delineate the mechanism.

2.3.5.2 Synthesis of Tool Compounds

Initially, we were interested in the reactivity of both the *endo*- and *exo*-cyclic peroxides observed within the reaction mixture. Based on the structures observed, peroxides **320**–**433** were proposed as tool compounds to study the mechanism of the reaction (**Figure 2-43**).

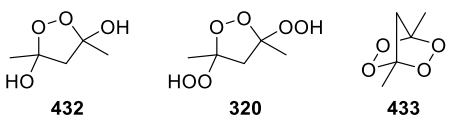
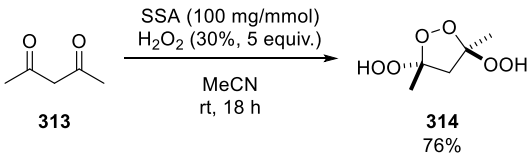


Figure 2-43. Target tool compounds for mechanism study.

The synthesis of peroxide **320** was achieved using the SSA method outlined by Azarifar.[113g]



313 **314** 76%

Scheme 2-52. Synthesis of peroxide **314**.[113g]

Acetylacetone **313** was treated with hydrogen peroxide and SSA, furnishing peroxide **314** in a 76% yield. Azarifar showed suggested a *trans* relationship of the hydroperoxide groups of peroxide **320** (i.e. **314**).[113g] This was determined by the ^{1}H NMR spectra of **320** which showed that it contained only two proton environments. These environments corresponded to 6 methyl protons and 2 methylene protons suggesting a *trans*-relationship of the hydroperoxide groups. We have confirmed this by a single crystal X-ray structure of peroxide **314** which clearly showed the *trans*-relationship of the peroxide groups (**Figure 2-44**).

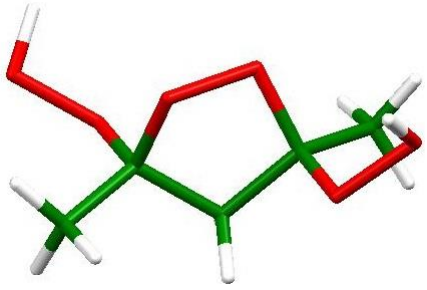
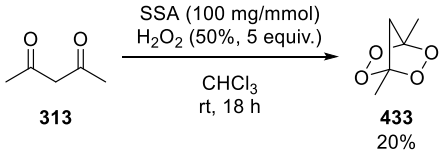


Figure 2-44. Single crystal X-ray structure of peroxide **314**.

In attempting to synthesise peroxide **314** trace amounts of impurity were often encountered. We believed this to be the known tetraoxane **433**. Based on this observation and the isolation of teroxane **423** from the reaction mixture we proposed that treating ketone **313** under the catalytic sulfoxidation conditions could potentially yield tetraoxane **433** (**Scheme 2-54**).



Scheme 2-53. Synthesis of peroxide **433**.

Tetraoxane **433** was synthesised in a 20% yield, with the vast majority of the remaining material being accounted for by peroxide **314**. The structure of tetraoxane **433** was also confirmed by single crystal X-ray structure (**Figure 2-45**).

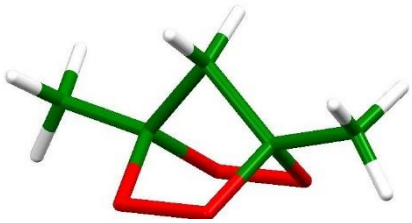
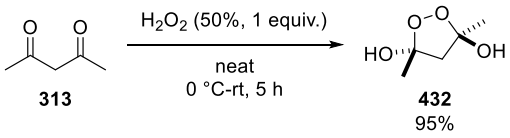


Figure 2-45. X-ray crystal structure of tetraoxane **433**.

Finally, the synthesis of peroxide **432** was achieved *via* a procedure developed by Milas and co-workers (**Scheme 2-55**).[127]



Scheme 2-54. Synthesis of peroxide **432**.[127]

The neat mixing of acetylacetone **313** and a single equivalent of hydrogen peroxide provided dioxolane **432** in a 95% yield. Similarly to peroxide **314**, the ^{1}H NMR spectra of dioxolane **432** suggested that the hydroxyl groups had a *trans* relationship. This was confirmed by single crystal X-ray structure (**Figure 2-46**).

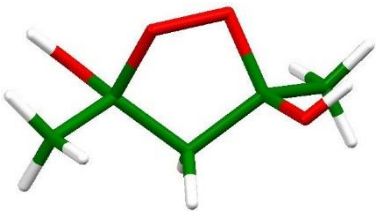
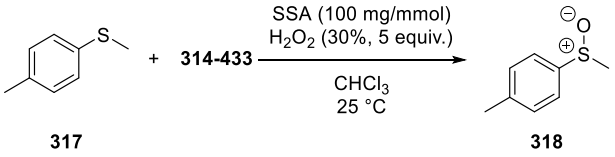


Figure 2-46. X-ray crystal structure of peroxide **432**.

In conclusion, peroxides **314**, **432** and **433** were successfully synthesised, with single crystal X-ray structures confirming both their structures and the *trans* relationship of the hydroxyl/hydroperoxyl groups.

2.3.5.3 Investigating Tool Compounds 314, 432 and 433

In order to test the hypothesis that any of tool compounds **314**, **432** and **433** were involved within the catalytic cycle of the reaction, it was proposed that the standard sulfoxidation reaction be run with 0.2 equivalents of each of the tool compounds in place of ketone **313**. These reactions were monitored by HPLC and the results are summarised below (**Figure 2-47**).



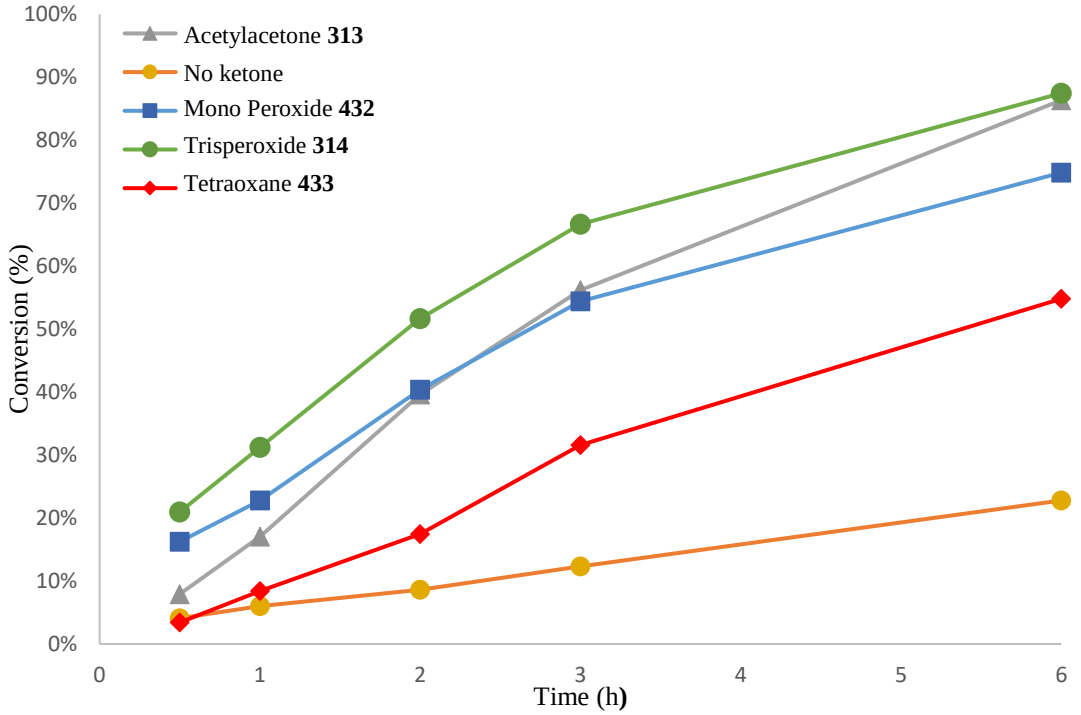
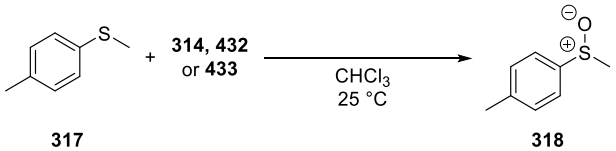


Figure 2-47. Reaction conversion rates when using tool compounds **314**, **432** and **433** and acetylacetone **313** as catalysts.

From the results it is clear to see that both trisperoxide **314** and monoperoxide **432** allow the reaction to progress with a similar rate to that of acetylacetone **313**. When compared to the uncatalysed background process, it can be seen that these structures all have a catalytic effect on the reaction and that these structures are therefore catalytically competent and could therefore be involved in the mechanism of the reaction. Interestingly, tetraoxane **433** also appears to be catalytically competent, although to a lesser degree than the other structures given the noticeably reduced rate of conversion of sulfide **317** into sulfoxide **318**. These results suggested that the rate of reaction of the *endo*- and *exo*-cyclic peroxide moieties may be different. As such, an experiment was devised to test the relative rates of reaction of the tool compounds under sub-stoichiometric conditions. 0.2 equivalents of tool compounds **314**, **432** and **433** were reacted with sulfide **318** in $CHCl_3$ and the reaction was monitored by HPLC (**Figure 2-48**).



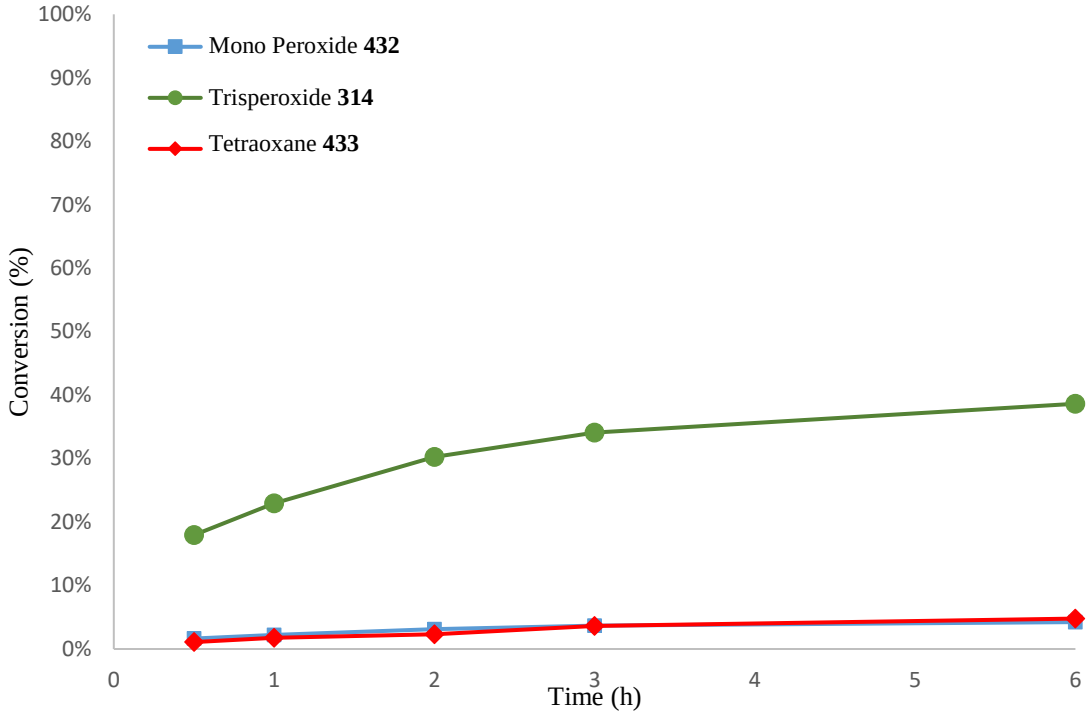
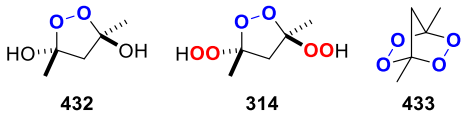


Figure 2-48. Sulfoxidation reaction rates under sub-stoichiometric conditions with tool compounds **314**, **432** and **433**.

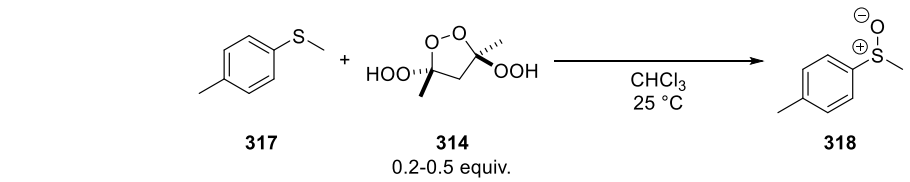
Interestingly, of the three tool compounds tested, only trisperoxide **314** appeared to provide any notable level of conversion of sulfide **317** into sulfoxide **318**. This evidence strongly suggested that only the *exo*-cyclic peroxide moieties could be responsible for the oxidation of sulfide **317** as both monoperoxide **432** and tetraoxane **433** contain only *endo*-cyclic peroxide moieties (**Figure 2-49**).



432 **314** **433**

Figure 2-49. Tool compounds **314-433** with *endo*-cyclic (**blue**) and *exo*-cyclic (**red**) peroxide moieties highlighted.

This result was further evidenced by the level of conversion achieved by trisperoxide **314**. 0.2 equivalents of trisperoxide **314** roughly allowed a 40% conversion of sulfide **317** into sulfoxide **318** showing that two equiv. of oxygen atom were transferred from this reagent. To confirm this observation, trisperoxide **314** was then reacted at two further stoichiometries, using 0.33 and 0.5 equivalents (**Figure 2-50**).



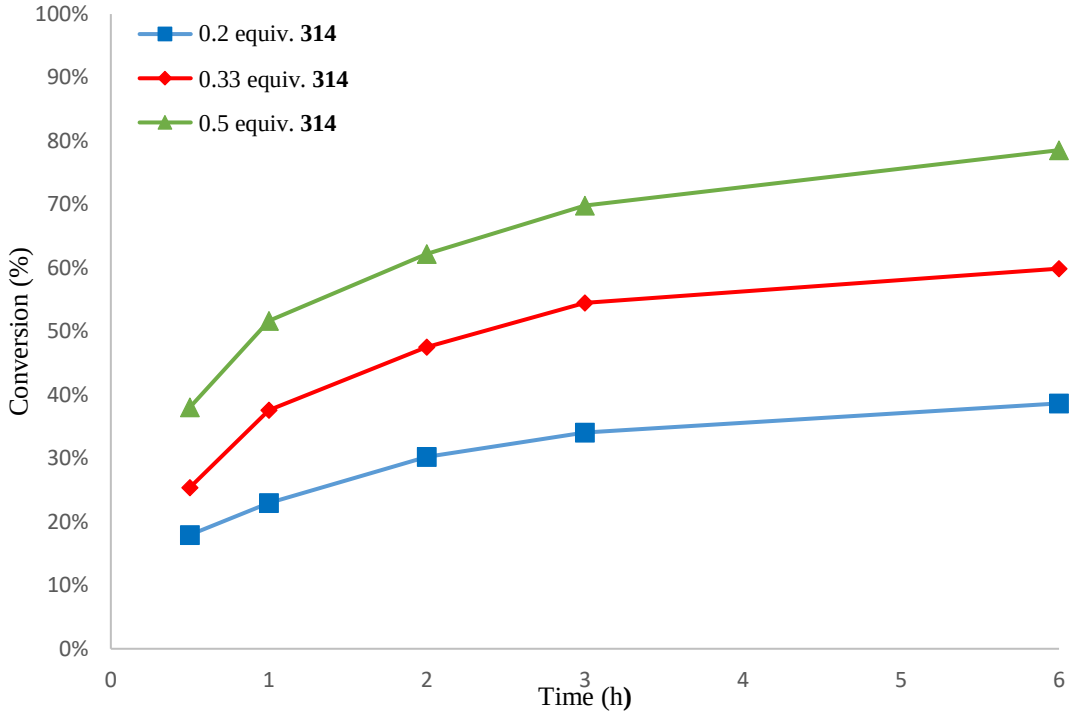


Figure 2-50. Sulfoxidation rates of different sub-stoichiometries of trisperoxide **314**.

A similar trend was experienced at increased stoichiometries. Only two equivalents of oxygen were transferred from trisperoxide **314** to sulfide **317** suggesting that the *exo*-peroxides were solely responsible for the oxidation (**Figure 2-51**).

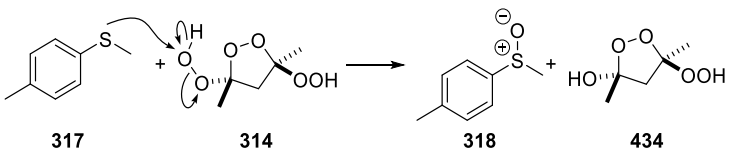
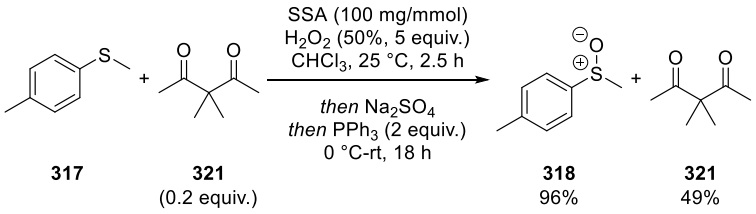


Figure 2-51. Proposed mechanism of stoichiometric oxidation.

This was further backed up by a TLC of the crude reaction mixtures, which suggested the presence of monoperoxide **432** at the end of the reaction. Unfortunately, attempts to recover monoperoxide **432** from the reaction were unsuccessful due to its high water solubility and further evidence for its presence using mass spectrometry techniques could not be achieved due to the reactive nature of the peroxide bonds.

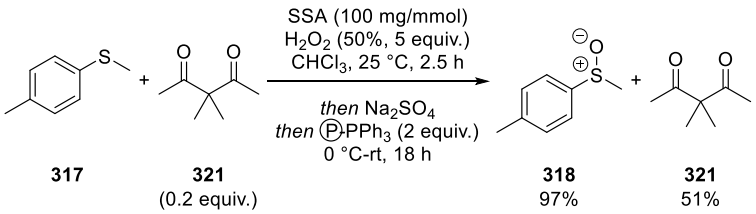
2.3.5.4 Catalyst Recovery

With it being proposed that the reaction was catalytic in ketone **321** we believed that it should be possible to recover the material after completion of the reaction. However, ketone **321** was not observed during the intermediate isolation (**Page 139**). It is likely that this was the result of the excess hydrogen peroxide used in the reaction, leading to the formation of peroxide species. In order to recover ketone **321** it was suggested that the reaction mixture be treated with PPh_3 to reduce any peroxides formed to regenerate ketone **321** (**Scheme 2-56**).



Scheme 2-55. Recovery of ketone **321** using PPh_3.

Upon completion of the oxidation reaction, Na_2SO_4 was added to the reaction mixture to dry the reaction mixture before filtration. After cooling to 0 °C, PPh_3 was then added to the mixture and it was stirred for 18 hours. This resulted in a 49% recovery of ketone **321** after purification. Although this reaction showed that ketone **321** was recoverable at the end of the reaction it was believed that the yield may have been reduced due to difficulties in separating it from triphenylphosphine oxide. To overcome this challenge, polymer supported PPh_3 was employed for the process which allowed the reductant to be removed by filtration prior to isolation (**Scheme 2-57**).



Scheme 2-56. Recovery of ketone **321** using polymer supported PPh_3.

Although the use of polymer supported PPh_3 drastically improved the ease of isolation of both ketone **321** and sulfoxide **318** this did not increase the recovered yield of ketone **321** (51%).

Several factors may account for the low recovery of ketone **321** at the end of the reaction. An independent aqueous work-up on an isolated sample of ketone **321** revealed that 30% of the material was lost to the aqueous phase despite repeated extraction with CH_2Cl_2. Similarly, material was lost on the rotary evaporator when a sample was left for an extended period of time (30 minutes, 10 Torr, 40 °C). PPh_3 may have encouraged decomposition of peroxides formed from ketone **321**. This belief was enforced by an ^1H NMR study of the reaction of tool compound **314** with half an equivalent of PPh_3 showed that it did not produce monoperoxide **432** as expected (**Figure 2-52**).

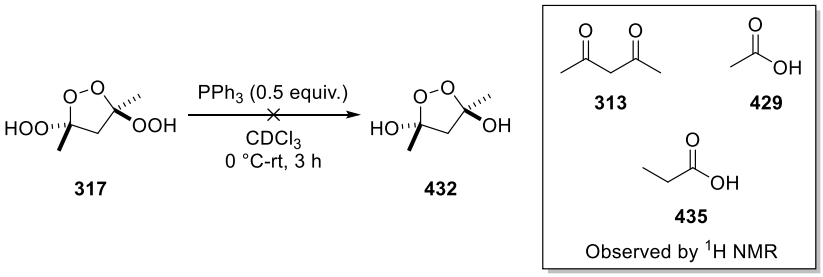


Figure 2-52. Reaction of tool compound **317** with PPh_3.

Interestingly, instead of reacting with tool compound **317** to produce monoperoxide **432,** PPh_3 seemed to react indiscriminately with **317**, leading to acetylacetone **313**, acetic acid **429** and propanoic acid **435** being observed in the ^1H NMR spectra of the crude reaction mixture. It is believed that the origin of the carboxylic acids can be traced to a similar pinacol rearrangement as earlier described (**Page 140**).[126] With all these considerations taken into account, it was proposed that a 51% recovery of ketone **321** was in fact, reasonable.

2.3.5.5 Involvement of Carboxylic Acids

Intermediates formed from ketone **321**, such as monoperoxide **436**, have been shown to undergo a pinacol rearrangement to form carboxylic acids such as **429** and **430** (**Figure 2-53**).[126]

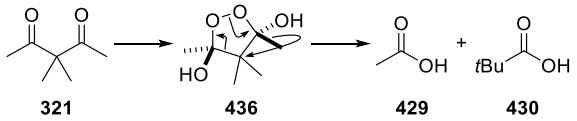


Figure 2-53. Proposed formation of carbxylic acids **429** and **430**.[126]

There was therefore the possibility that the active species within the reaction may actually be related to carboxylic acids **429** and **430**. In order to examine the catalytic ability of carboxylic acids **429** and **430** the catalytic sulfoxidation reaction was performed with these reagents in place of ketone **321** and monitored by HPLC (**Figure 2-54**).

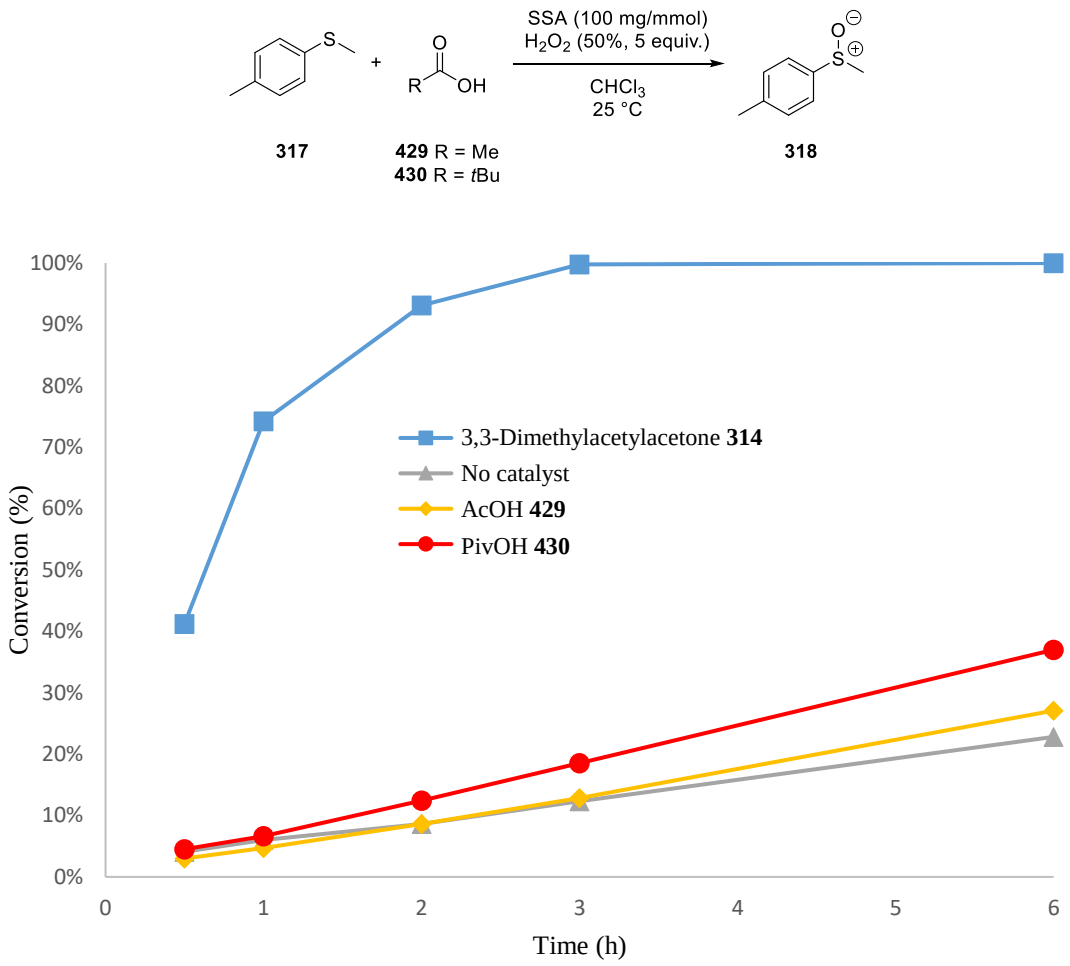
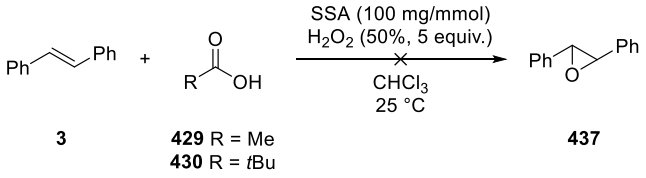


Figure 2-54. Catalytic activity of acetic **429** and pivalic acid **430**.

As clearly shown by the results, both AcOH **429** and PivOH **430** had little to no impact on the rate of the reaction over the background, uncatalysed process and it is therefore proposed that they play no role in catalytic cycle. It is believed that any observed increase in rate is a result of an increase in the concentration of H^+ available in the reaction rather than through the formation of a peracid species. This belief is backed up by two results: 1) within the substrate scope of the reaction (**Page 134-138**) several ester compounds were examined and shown to be high yielding with no clear degredation of the ester moieties; and 2) the reaction of both AcOH **429** and PivOH **430** with alkene **3** under the catalytic sulfoxidation conditions resulted in no change in the starting material (**Scheme 2-58**).



Scheme 2-57. Reaction of alkene **3** with AcOH **429** and PivOH **430** under catalytic sulfoxidation conditions.

Were a peracid formed under the reaction conditions, epoxide **437** would have been observed.

2.3.5.6 Proposed Catalytic Cycle

Based on the results observed when investigating tool compounds **314**, **432** and **433** a catalytic cycle is proposed below (**Figure 2-55**).

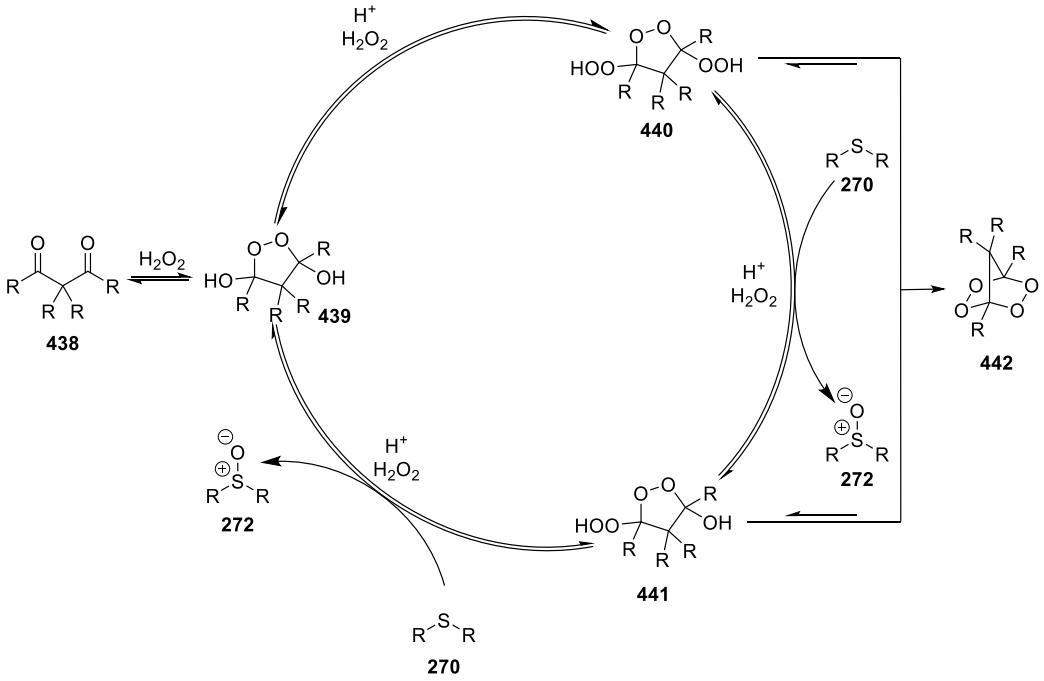


Figure 2-55. Proposed catalytic cycle of the catalytic sulfoxidation reaction.

It is believed that the process begins with ketone **438** reacting with an equivalent of hydrogen peroxide to form monoperoxide **439**. Acid catalysed acetal chemistry then allows the hydroxyl groups of monoperoxide **439** to exchange with hydrogen peroxide in solution to form trisperoxide **440**. **440** then reacts with sulfide **270** through one of the *exo*-cyclic peroxide moieties, forming sulfoxide **272** and diperoxide **441**. **441** can then either react with another molecule of sulfide **270** to complete the catalytic cycle or with a molecule of hydrogen peroxide to return to trisperoxide **440**. Diperoxide **441**

may also be accessed directly from monoperoxide **439** by the action of a single molecule of hydrogen peroxide. Tetraoxane **442** is believed to be formed from the cyclisation of one of the *exo*-cyclic peroxide groups on the second acetal carbon (**Figure 2-56**).

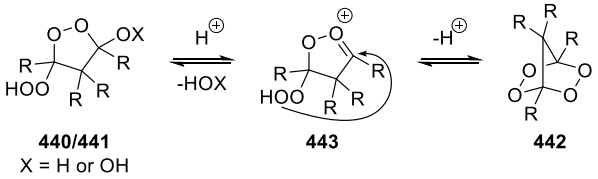


Figure 2-56. Mechanism of formation of tetraoxane **442**.

It is proposed that tetraoxane **442** exists as an inactive form of peroxide. This is due to the lower observed rate of reaction when using tetraoxane **433** as the catalyst, which suggests that tetraoxane **433** forms an active species of the catalyst much more slowly than the other examined tool compounds.

In conclusion, the use of tool compounds **314**, **432** and **433** has allowed the elucidation of a potential mechanistic pathway for the reaction. A catalytic cycle has been proposed, the catalyst has been shown to be partially recoverable and the involvement of any potential products of catalyst degradation within the process have been shown not to occur.

2.3.6 Investigation of the Stoichiometric Reaction

2.3.6.1 Determining the Order of the Reaction

Until this point, all of the mechanistic investigations on the reaction had centred on the catalytic process. Several of the results had pointed to the rate limiting step of the reaction being the oxidation of the sulfide into the sulfoxide (**Figure 2-57**).

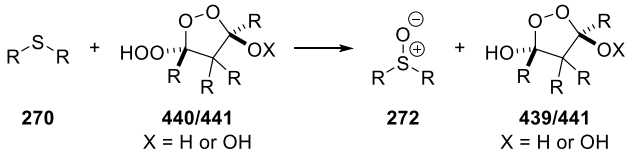
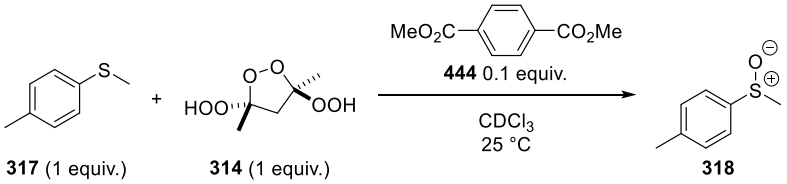


Figure 2-57. The reaction of sulfide **270** and peroxide **440/441** is proposed to be the rate limiting step of the reaction.

For example, the substrate scope (**Page 134-138**) showed a clear reaction rate dependence on the nucleophilicity of sulfide **270**. As such, it was suggested that investigation of the stoichiometric procedure may provide insight into the reaction as a whole. With that in mind, tool compound **314** was used in a study of the reaction kinetics (**Figure 2-58**).



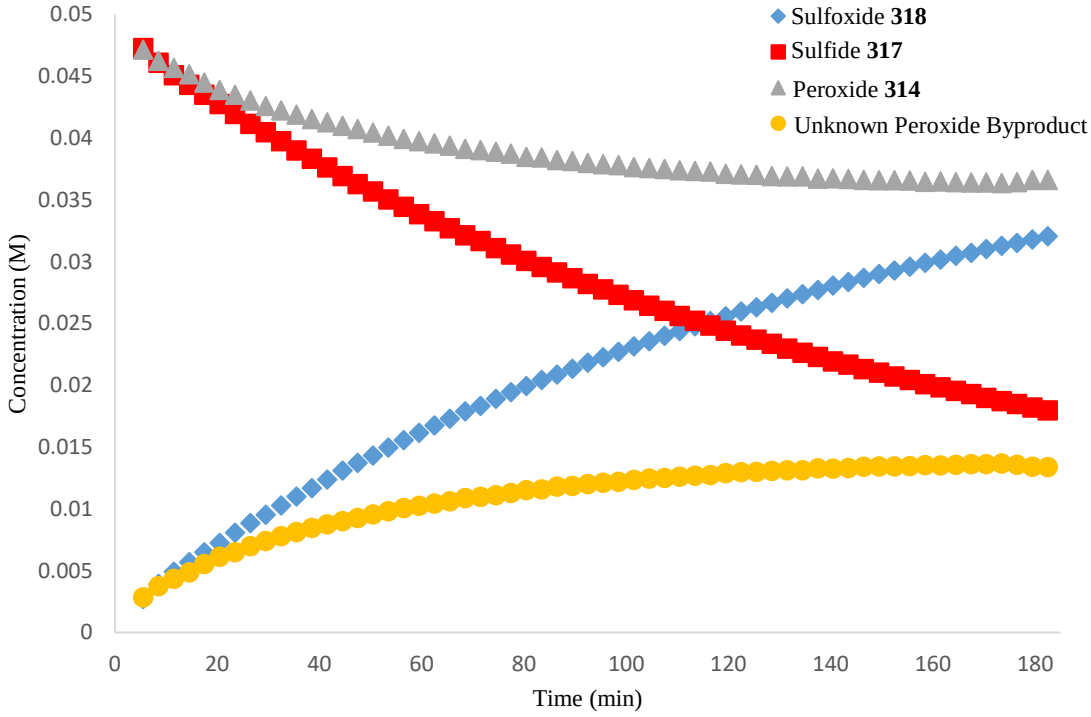


Figure 2-58. Reaction profile of stoichiometric sulfoxidation of sulfide **317** using peroxide **314**.

Homogenous solutions of sulfide **317** and peroxide **314** were monitored over time using ^{1}H NMR spectroscopy with dimethylterephthalate **444** as an internal standard. Sulfide **317** was cleanly converted into sulfoxide **318**, however, the rate of

consumption of sulfide **317** was roughly half that of peroxide **314**. Similarly, the rate of formation of an unidentified byproduct, believed to be related to peroxide **314**, was found to be roughly half that of the rate of formation of sulfoxide **318**. This suggests that peroxide **314** was responsible for the conversion of two equivalents of sulfide **317** into sulfoxide **318**.

The kinetic order in sulfide **317** was determined using an excess of peroxide **314** (3 equiv.), monitored in $CDCl_3$ by ^1H NMR spectroscopy (**Figure 2-59**).

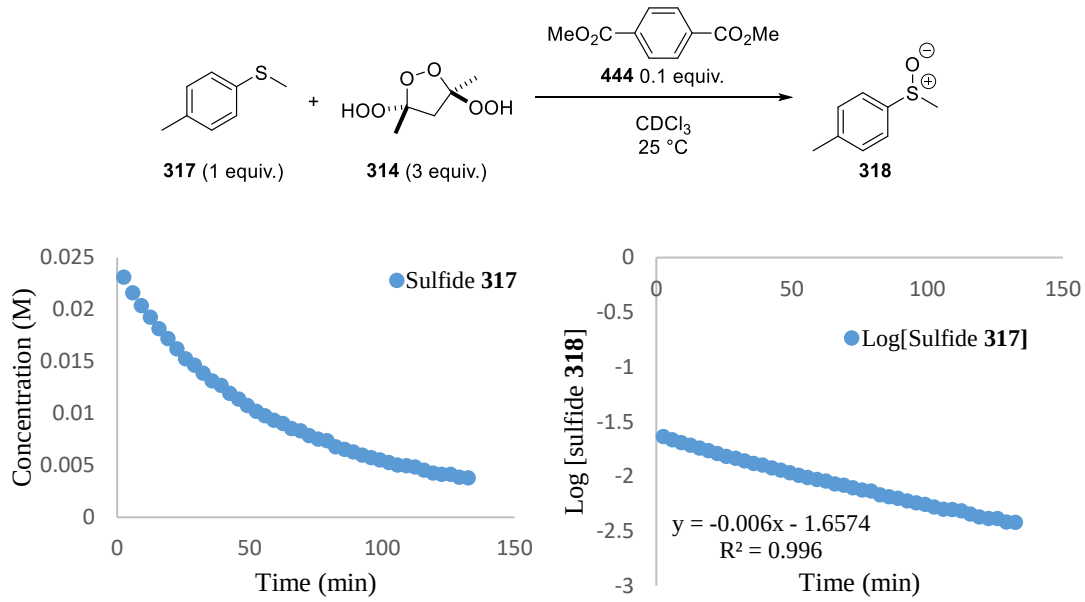


Figure 2-59. Reaction coordinates of sulfide **317** consumption in the presence of excess peroxide **314** and the logarithmic plot of concentration versus time, showing a first-order dependence in sulfide **317**.

A linear correlation was observed in the logarithmic plot of sulfide **317** concentration against time, thus indicating a first-order dependence in sulfide **317**. A similar method was used to determine the kinetic order of peroxide **314**, with the consumption of peroxide **314** being monitored by ^1H NMR spectroscopy in $CDCl_3$ and an excess of sulfide **317** (3 equiv.) (**Figure 2-60**).

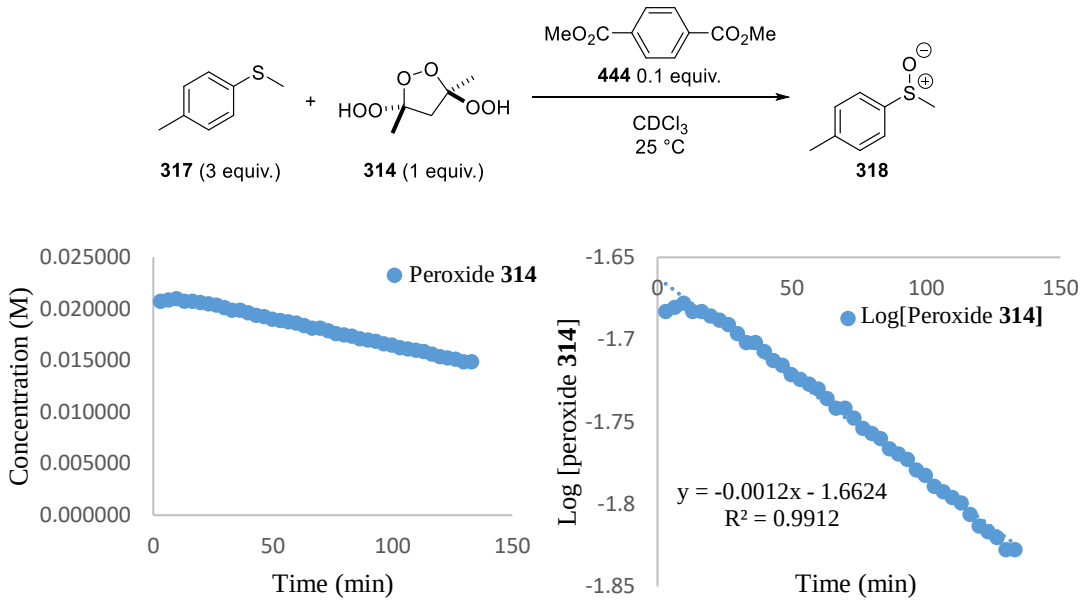


Figure 2-60. Reaction coordinates of peroxide **314** consumption in the presence of excess peroxide **314** and the logarithmic plot of concentration versus time, showing an apparent first-order dependence in peroxide **314**.

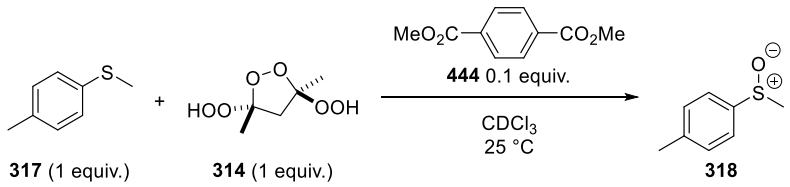
A mostly linear correlation was observed in the logarithmic plot of peroxide **314** concentration against time, thus indicating a first-order dependence in peroxide **314**. The accuracy of this data is debatable, given that peroxide **314** was clearly shown to react to produce another reactive species. However, the data suggested an overall second-order process for the reaction, being first-order in both sulfide **317** and peroxide **318**, as shown in **Equation 1**.

$$\text{Rate} = k[\text{sulfide } \mathbf{317}][\text{peroxide } \mathbf{318}] \qquad \textbf{Equation 1}$$

In the case of the initial reaction, where [sulfide **317**] and [peroxide **318**] are initially equivalent, **Equation 2** can be rewritten as:

$$\text{Rate} = \text{k}[\text{sulfide } \mathbf{317}]^2 \qquad \textbf{Equation 2}$$

In order to confirm the proposed second-order process, a plot of 1/[sulfide **317**] for the initial reaction was conducted (**Figure 2-61**).



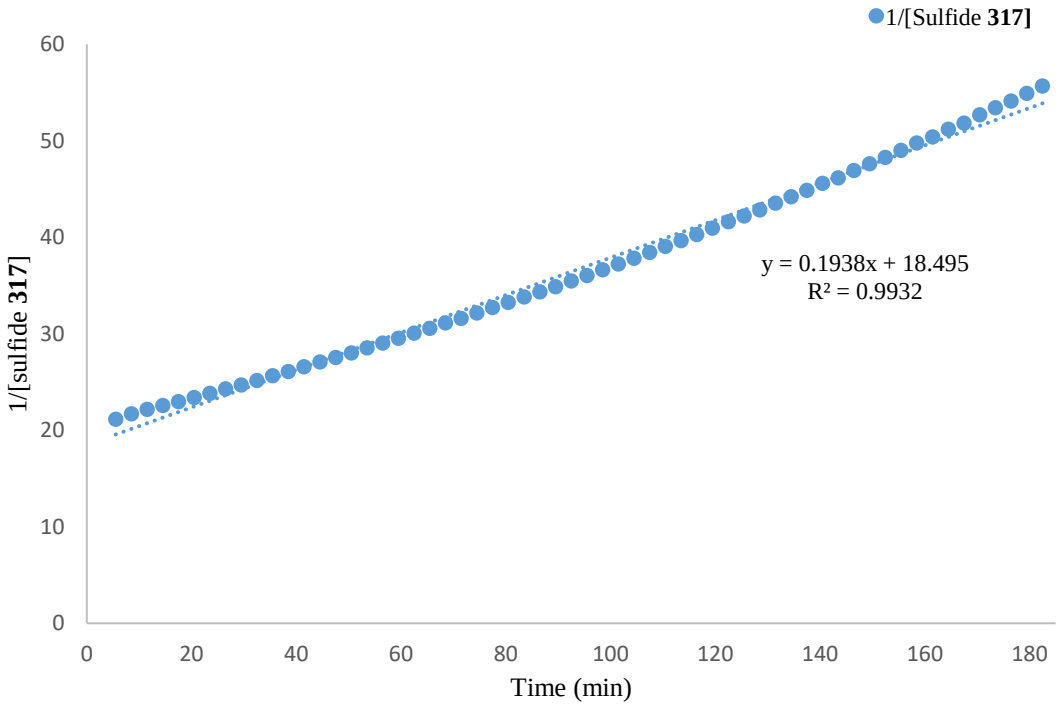


Figure 2-61. Plot of 1/[sulfide **317**] versus time, showing the reaction to be second-order.

The linear correlation observed in the plot of 1/[sulfide **317**] versus time confirmed the belief that the reaction was indeed second-order with a rate constant of k = 0.19 M^{-1} min^{-1} (or 3.17 M^{-1} s^{-1}).

2.3.6.2 Transition State Investigation

Most of the evidence gathered thus far had shown that peroxide **314** was responsible for the transfer of two equivalents of oxygen atom to sulfide **270**. Because of these observations we were confident that the *exo*-peroxides were responsible for the transfer of oxygen and not the *endo*-peroxide moieties. We therefore became interested in determining a transition state barrier for the reaction. In order to examine this, computational chemistry was employed.

DFT calculations have been used previously been used in the investigation of a number of stoichiometric procedures featuring the use of organic peroxides. Within our own group, DFT studies using the B3LYP functional and a 6-31 +G** basis set were used

to study the transition state of the *syn*-dihydroxylation of alkenes with malonoyl peroxides.[17] Similarly, work carried out by Houk, Siegel and co-workers showed the use of the B3LYP functional in the study of the phthaloyl peroxide mediated oxidation of arenes.[128] It was therefore our belief that it should be possible to use the B3LYP functional with a 6-31 +G* basis set to deteremine potential transition states for the reaction. Assuming an ionic process, it was postulated that three reasonable mechanisms may exist for the transfer of oxygen to sulfide **270** (**Figure 2-62**).

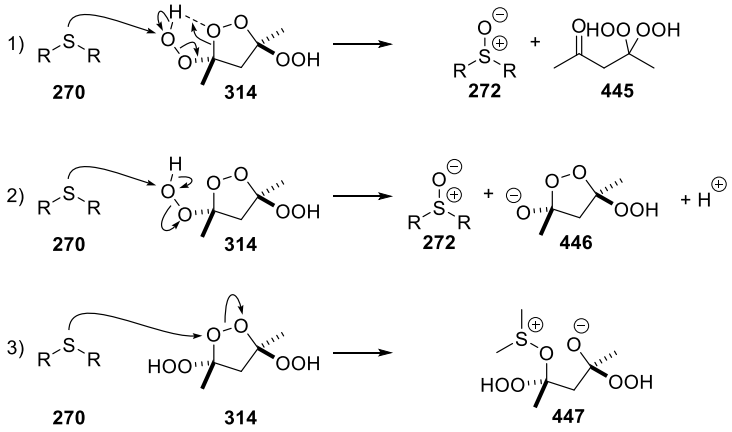


Figure 2-62. Proposed ionic mechanisms for stoichiometric oxidation.

A sulfide could potentially react with the *exo*-peroxide moiety in either a concerted mechanism featuring ring opening of the dioxolane ring **314** to give gem peroxide **445** and sulfoxide **272** (**Mechanism 1**). The reaction with the *exo*-peroxide moiety could also proceed to furnish sulfoxide **272** with dioxolane **446** and a proton as co-products (**Mechanism 2**). Despite the wealth of evidence that suggested a reaction with the *exo*-peroxide moieties rather than the *endo*-peroxide moiety, we felt that it was worth considering this as a possibility as it was postulated that insight into the difference in activation energies between the two peroxide environmentss may improve future reagent and catalyst design (**Mechanism 3**). Using the Gaussian09 suite of programmes, an attempt to locate transition states for each of these proposed mechanisms was made. A transition state was found for **Mechanism 1** (**Figure 2-63**).

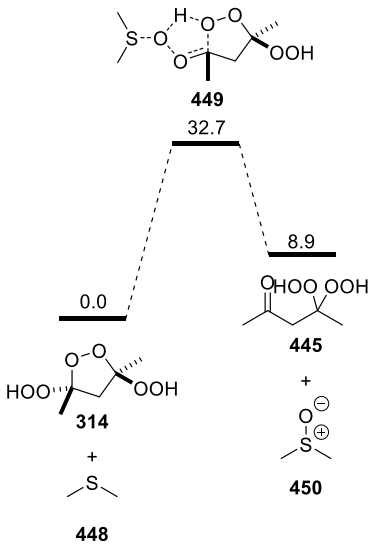


Figure 2-63. Transisition state calculated for reaction **Mechanism 1**.

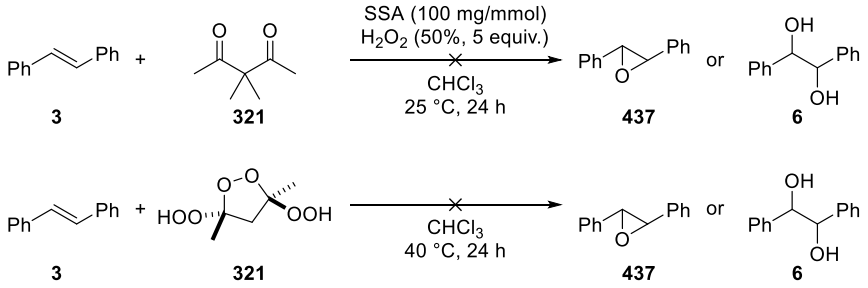
A transition state with an energy of 32.7 kcal mol^{-1} was discovered for a concerted mechanism involving the ring opening of dioxolane **314**. Unfortunately attempts to model the two other postulated mechanisms for the process proved unsuccessful. As the expertise needed to complete these studies was out with the experience within the group, these studies were abandoned due to time constraints.

In conclusion, mechanistic studies of the stoichiometric process have revealed a second order reaction, which appears to be first order in both sulfide and peroxide, with a rate constant of $k = 0.19\ M^{-1}\ min^{-1}$ (or $3.17\ M^{-1}\ s^{-1}$). Initial DFT studies revealed a transition state of 32.7 kcal mol^{-1} for one of three postulated mechanisms.

2.3.7 Reacting Alternative Nucleophiles

2.3.7.1 Reagent Design

Ultimately, the catalytic sulfoxidation process was originally envisioned as an attempt to render the malonoyl peroxide mediated dihydroxylation a catalytic procedure. Unfortunately, neither the catalytic nor the stoichiometric procedure using ketone **321** and peroxide **314** respectively produced any evidence of *trans*-stilbene **3** oxidation (**Scheme 2-59**).



Scheme 2-58. Both the catalytic and stoichiometric processes failed to produce oxidised products from alkene **3**.

It was clear from these results that dioxolane **314** was simply not reactive enough to interact with these weak nucleophiles such as alkenes. It was proposed that a change in the design of the reagent could allow an increase in reactivity. In order to address this, it was suggested that a "hybrid" of the dioxolane and malonoyl peroxide motifs might allow an increase in the reactivity of the peroxide whilst maintaining the catalytic activity developed for the sulfoxidation process. It was suggested this hybrid compound **451** could be accessed from carboxylic acid **452**, which could be prepared from ethyl acetoacetate **365** (**Figure 2-64**).

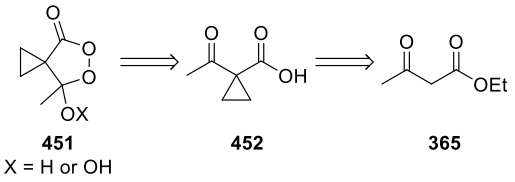
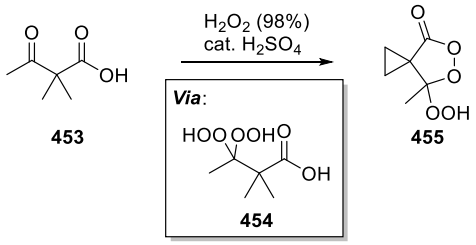


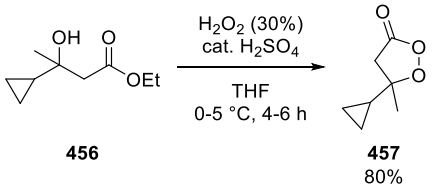
Figure 2-64. Retrosynthetic analysis of hybrid compound **451**.

Upon investigating the literature we were pleased to find two examples of the synthesis of peroxy lactone moieties such as **455**. Work carried out by Gibson and co-workers revealed that treatment of ethyl-2,2-dimethylacetoacetate **453** with 98% hydrogen peroxide and catalytic H_2SO_4 yielded peroxy lactone **455**, believed to be a product of cyclisation of the *gem*-peroxide **454** on the carboxylic acid (**Scheme 2-60**).[129]



Scheme 2-59. The synthesis of peroxy lactone **455** was reported by Gibson.[129]

Using much milder conditions, Singh and co-workers were able to synthesise peroxy lactone **457** from the corresponding tertiary alcohol **456** in an 80% yield (**Scheme 2-61**).[130]



Scheme 2-60. The synthesis of peroxy lactone **457** was reported by Singh.[130]

Based on these results we proposed the synthesis of three compounds that we believed could possibly form peroxy lactones under similar conditions as the catalytic sulfoxidation process (**Figure 2-65**).

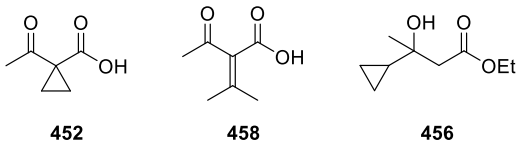
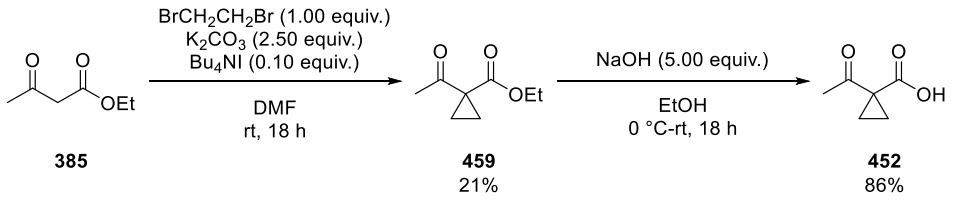


Figure 2-65. Target compounds **452**, **456** and **458**.

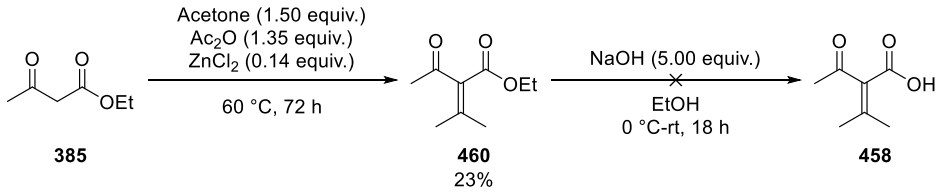
2.3.7.2 Synthesis of Target Compounds 452, 456 and 458

The synthesis of target compound **452** was achieved by the alkylation of ethyl acetoacetate **385** followed by hydrolysis (**Scheme 2-62**).



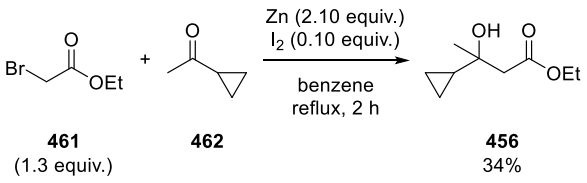
Scheme 2-61. Synthesis of target compound **452**.

The synthesis of target compound **452** was achieved in an unoptimised overall yield of 18%. Although the alkylation step resulted in an undesirably low yield of 21% the optimisation of this step was deemed unimportant due to time constraints, however, could **452** could potentially be achieved directly from **385** using a process similar to the synthesis of **141** (**Page 37-38**). An attempt was then made to synthesise target compound **458**. It was proposed that the synthesis of **458** could be achieved *via* Knoevenagel condensation[131] and subsequent hydrolysis (**Scheme 2-63**).



Scheme 2-62. Attempted synthesis of target compound **458**.

Although the synthesis of ester **460** was achieved by Knoevenagel condensation in an unoptimised 23% yield, the subsequent hydrolysis attempt failed to yield target compound **458**. Due to time constraints, further hydrolysis attempts were abandoned, however, ester **460** was retained to attempt peroxide formation. Finally, target compound **456** was synthesised *via* a literature procedure from α-bromoethyl acetate **461** (**Scheme 2-64**).[132]

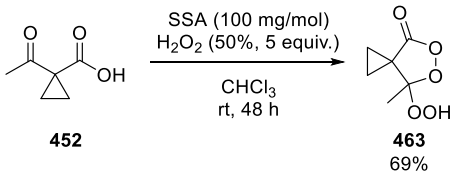


Scheme 2-63. Synthesis of target compound **456**.

Target compound **456** was synthesised in a 34% yield. With all three compounds available, attention turned to the attempted synthesis of the corresponding peroxides.

2.3.7.3 Peroxy Lactone Synthesis

Initially, we were interested in attempting to use the catalytic sulfoxidation conditions to prepare peroxy lactone **463** from target compound **452** (**Scheme 2-65**).



Scheme 2-64. Synthesis of peroxy lactone 463.

To our delight, peroxy lactone **463** was synthesised in a high unoptimised yield of 69% using very mild conditions. The identity of peroxy lactone **463** was confirmed *via* single crystal X-Ray structure (**Figure 2-66**).

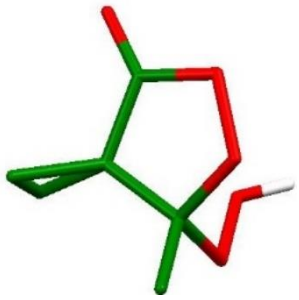
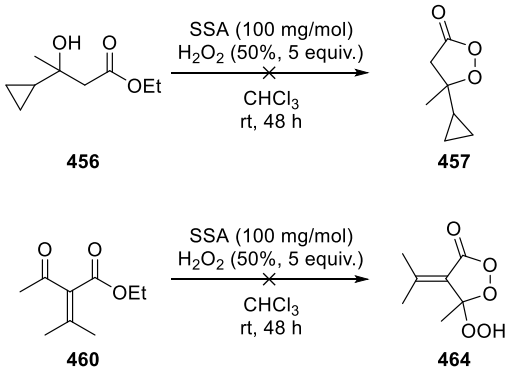


Figure 2-66. Single crystal X-Ray structure of peroxy lactone **463**.

Unfortunately, similar success was not observed for peroxy lactones **457** and **464** whose attempted synthesis were unsuccessful (**Scheme 2-66**).

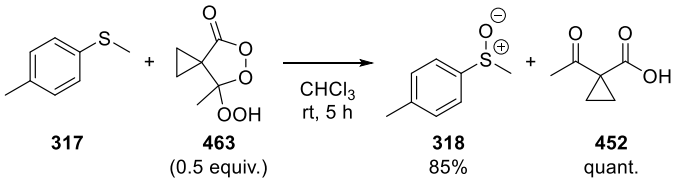


Scheme 2-65. Attempted synthesis of peroxy lactones **457** and **464**.

Although other conditions may have been (and should have been in the case of **457**)[130] successful for the synthesis of peroxy lactones **457** and **464**, their synthesis was abandoned due to time constraints.

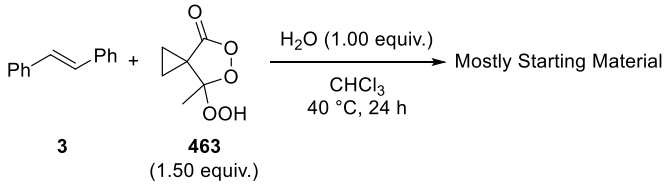
2.3.7.4 Reactivity of Peroxy Lactone 463

Initially, we were interested in testing the reactivity of peroxy lactone **463** with sulfide **317** (**Scheme 2-67**).



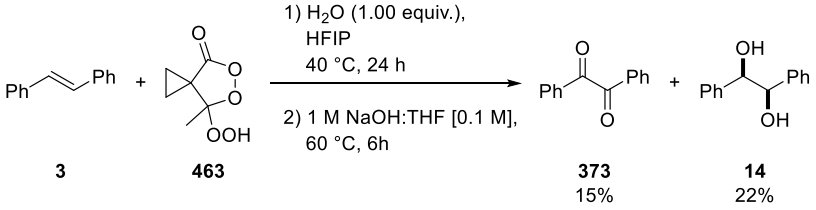
Scheme 2-66. Reaction of peroxy lactone **463** with sulfide **317**.

Pleasingly, half an equivalent of peroxy lactone **463** reacted with sulfide **317** to produce sulfoxide **318** in an 85% yield returning carboxylic acid **452** in a quantitative yield. Interestingly, when reacting the two reagents in a 1:1 ratio, the ^{1}H NMR spectra of the crude reaction mixture suggested that only half of peroxy lactone **452** had reacted with sulfide **317**, which had been converted into carboxylic acid **452**. Unfortunately this result gleaned little in the way of insight into the relative reactivity of the two peroxide moieties. Having reacted the peroxy lactone **463** with a sulfide to show its potential as an oxidant, an initial attempt was made to examine its reactivity towards stilbene **3** was made (**Scheme 2-68**).



Scheme 2-67. First attempted reaction of peroxy lactone **463** and stilbene **3**.

Peroxy lactone **463** and stilbene **3** were stirred under the standard *syn*-dihydroxylation reaction conditions resulting mostly in recovered starting material. However, new peaks in the ^{1}H NMR spectra of the crude material were present suggesting a low level of reactivity. In order to further probe this, HFIP was chosen as the solvent for the reaction based on previous successes within the group[70,78] (**Scheme 2-69**).



Scheme 2-68. Reaction of peroxy lactone **463** and stilbene **3** in HFIP.

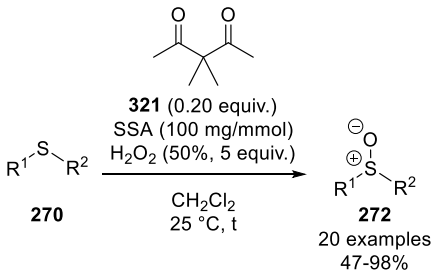
Following the hydrolysis of the crude reaction material with sodium hydroxide, benzil **373** and *syn*-hydrobenzoin **14** were recovered from the reaction in a 15% and 22% yield respectively. Despite the low yields of both products this was a breakthrough for the project showing that peroxides formed under the relatively mild conditions used for the catalytic sulfoxidation procedure could in fact be used for alkene oxidation with the recovery of the starting materials for peroxide synthesis. Unfortunately, due to time constraints the project could not be taken any further.

In conclusion, a group of novel peroxide structures was proposed to overcome the reactivity difficulties encountered when trying to react trisperoxide **314** with alkenes. To that end, peroxy lactone **463** was synthesised in 3 steps from ethyl acetoacetate **385**. Peroxy lactone **463**, whose structure was confirmed by X-Ray crystal structure, has shown reactivity in the oxidation of both sulfides and alkenes.

2.4 Conclusions and Future Work

Catalysis had been considered a challenge for the malonoyl peroxide mediated dihydroxylation of alkenes due to a mismatch between the peroxide formation

conditions and the hydrolysis conditions used to liberate the diacid and diol products. 1,3-Diketones were proposed as a potential alternative for a catalytic system and after some optimisation a successful and novel catalytic system was developed for the selective oxidation of sulfides to sulfoxides (**Scheme 2-70**).



Scheme 2-69. Catalytic sulfoxidation with diketone **321**.

The optimal conditions were applied to a substrate scope and 21 varied substrates were successfully converted into their corresponding sulfoxides in average to excellent yield (47–98%).

The mechanism of the reaction was subsequently investigated. Isolation of the reaction intermediates implicated a variety of dioxolane structures as potential catalytic species. This work was further supported through the use of tool compounds which showed that dioxolane structures such as **314** had the same levels of catalytic activity as the corresponding ketones. This work also revealed that the *exo*-peroxide (**red**) moieties and not the *endo*-peroxide (**blue**) moieties were exclusively responsible for oxidation (**Figure 2-67**).

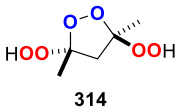
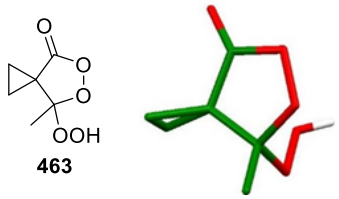


Figure 2-67. Dioxolanes such as **314** were shown to be catalytically compitent and reactive through the **exo**-peroxide moieties and not **endo**-peroxide moieties.

Following this, a mechanistic investigation on the stoichiometric reaction revealed a second-order reaction with a reaction with a rate constant of k = 0.19 M^{-1} min^{-1} (or 3.17 M^{-1} s^{-1}) and a potential transition state for the reaction between **314** and a sulfide was calculated using DFT.

Although this methodology was shown to be ineffective in the oxidation of alkenes, a proposal for a new "hybrid" peroxy lactone resulted in the synthesis and characterisation of **463**. Peroxy lactone **463** was shown to be reactive to both sulfides and alkenes (**Figure 2-68**).



463

Figure 2-68. Peroxy lactone **463**.

It is proposed that there are three main aims for the future of the project. First and foremost it is suggested that the further development of peroxy lactone **463** both as a reagent for alkene oxidation and as part of a catalytic oxidation process should be undertaken.

Secondly, several attempts were made to synthesise chiral ketones during the optimisation of the catalytic sulfoxidation process. Despite a lack of success in this area, it is proposed that the ability to use a chiral diketone may allow for the synthesis of chiral sulfoxides.

Finally, maintaining the biphase of the catalytic sulfoxidation reaction was found to be important in supressing the background, uncatalysed process. However, we believe that the biphase might also play an important role in the catalytic process as well. We suggest that in order to become the reactive dioxolane **466** species, ketone **321** must first transfer across the phase barrier to the aqueous layer. Upon becoming active species **466** the peroxide transfers across the phase barrier to the organic layer where the oxidation reaction can take place (**Figure 2-69**). Unfortunately, we have been unable to develop a set of experiments to probe this hypothesis within the timescale available, however, it is hoped that this can be addressed in future work.

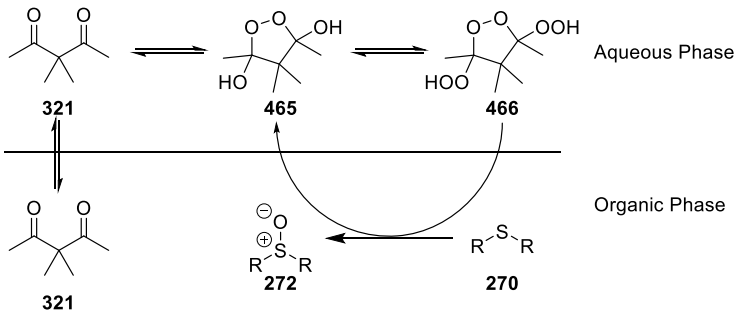


Figure 2-69. It is proposed that the biphase may be important to the catalytic process.

Chapter 3: Experimental

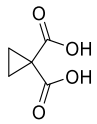
Chapter 3. Experimental

General Procedures: Commercially available solvents and reagents were used without further purification unless otherwise stated. Anhydrous THF, dichlromethane and diethyl ether were obtained from a SPS system at the University of Strathclyde. Petrol refers specifically to the 40–60 °C fraction of petroleum ether. Flash chromatography was carried out using Merck Kieselgel 60 H silica. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF_{254} that were visualised under UV light (at 254 and/or 360 nm) or via $KMnO_4$ or anisaldehyde solutions. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III or a Bruker Avance spectrometer operating at 400 MHz (^1H) and 101 MHz (^{13}C) respectively, or a Bruker Avance DRX spectrometer, operating at 500 MHz (^1H) and 125 MHz (^{13}C) in $CDCl_3$ at 27 °C unless stated otherwise and were reported in ppm; *J* values were recorded in Hz and multiplicities were expressed by the usual conventions. Low-resolution mass spectra (LRMS) were recorded on an Agilent 6130 single quadrupole with APCI/ESI dual score, on a ThermoQuest Finnigan LCQ DUO electrospray, or on an Agilent 7890A GC system equipped with a 30 m DB5MS column connected to a 5975C inert XL CI MSD with Triple-Axis Detector and were determined using atmospheric pressure chemical ionization (APCI) unless otherwise stated. ESI refers to electrospray ionization, CI refers to chemical ionization (methane) and EI refers to electron ionization. High-resolution mass spectra were obtained courtesy of the EPSRC Mass Spectrometry Service at University of Wales, Swansea, U.K. using the ionization methods specified. *In vacuo* refers to evaporation at reduced pressure using a rotary evaporator and diaphragm pump, followed by the removal of trace volatiles using a vacuum (oil) pump Infrared spectra were recorded on a Shimadzu IRAffinity-1 equipped with an ATR (Attenuated Total Reflectance) probe and were reported in cm^{-1}. Melting points were obtained on a Stuart SMP11 device and were uncorrected. **Caution**: Peroxides are particularly dangerous. These procedures should be carried out by knowledgeable laboratory workers using Teflon coated, plastic or bone spatulas; parafilm wrapped glassware or plastic containers; blast shields; and Kevlar undergloves.

3.1 Chapter 1 – *Anti*-Dihydroxylation

3.1.1 Peroxide Formation

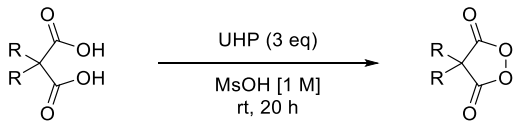
3.1.1.1 Cyclopropane-1,1-dicarboxylic acid 141[71]



Benzyltriethylammonium chloride (56.5 g, 248 mmol) was suspended in a 50% NaOH solution (250 g in 500 mL of water) and the solution was stirred vigorously with a mechanical stirrer. A premixed solution of diethyl malonate (37.5 mL, 248 mmol) and 1,2-dibromoethane (31.9 mL, 334 mmol) was added to the heterogeneous mixture and the resulting solution was stirred at room temperature for 2 hours. The reaction mixture was then transferred to a 2 L flask and the residual contents of the reaction flask were washed over with water (3 × 50 mL). The mixture was cooled in an ice bath and slowly quenched with conc. HCl (12 M, 500 mL) over 1.5 hours, maintaining a temperature of >15 °C. The aqueous layer was then extracted with diethyl ether (3 × 300 mL). Combined organic extracts were washed with brine (500 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude material was then washed with petrol to afford the *title compound* (15.5 g, 119 mmol, 48%) as a colourless solid.

Colourless solid; **MP** 132–134 °C [Lit: 137–140 °C]; **IR** (ATR)/cm^{-1}: 3118, 2981, 1710, 1215; **^{1}H NMR** (400 MHz, *d6*-DMSO) δ 1.31 (s, 4H); **^{13}C NMR** (101 MHz, *d6*-DMSO) δ 171.7, 27.2, 16.2; **LRMS** (LCMS-ESI) *m/z* 131 $[M+H]^+$. Spectroscopic data matches literature.

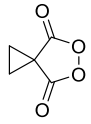
3.1.1.2 General Procedure A: Synthesis of Malonoyl Peroxides.



Malonic acid (3.00 g, 23.0 mmol) was dissolved in MsOH (25 mL) and stirred at room temperature for 2 minutes. UHP (6.51 g, 69.0 mmol) was added to the solution in three portions. The resulting solution was then stirred at room temperature for 18 hours. The reaction mixture was diluted with iced water:EtOAc (1:1) and the layers were separated. The aqueous layer was further extracted with EtOAc (2 × 50 mL). The

combined organic extracts were washed with sat. $NaHCO_3$ solution (3 × 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford product.

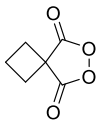
3.1.1.2.1 5,6-Dioxaspiro[2.4]heptane-4,7-dione 13[16]



Cyclopropane-1,1-dicarboxylic acid **141** (4.00 g, 30.8 mmol) and UHP (8.74 g, 93.0 mmol) were reacted in MsOH (30 mL) according to **General Procedure A** affording the *title compound* (3.09 g, 24.1 mmol), 79%) as a colourless solid.

Colourless solid; **MP** 89–90 °C [Lit: 90 °C]; **IR** (ATR)/cm^{-1}: 2918, 1789, 1147; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.10 (s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.3, 23.7, 19.9; unable to obtain low or high resolution mass spec for malonyl peroxides. Spectroscopic data matches literature.

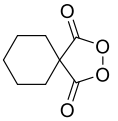
3.1.1.2.2 6,7-Dioxaspiro[3.4]octane-5,8-dione 11[15]



Cyclobutane-1,1-dicarboxylic acid (4.00 g, 28.0 mmol) and UHP (7.84 g, 83.5 mmol) were reacted in MsOH (30 mL) according to **General Procedure A** affording the *title compound* (3.28 g, 23.1 mmol, 83%) as a colourless solid.

Colourless solid; **MP** 62–63 °C [Lit: 63 °C]; **IR** (ATR)/cm^{-1}: 2958, 1799, 1712, 1257; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.71 (t, J = 8.1 Hz), 2.42–2.32 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.1, 40.6, 29.1, 16.5; unable to obtain low or high resolution mass spec for malonyl peroxides. Spectroscopic data matches literature.

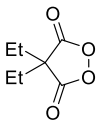
3.1.1.2.3 2,3-Dioxaspiro[4.5]decane-1,4-dione 145[72]



Cyclohexane-1,1-dicarboxylic acid (2.00 g, 11.6 mmol) and UHP (3.27 g, 34.8 mmol) were reacted in MsOH (15 mL) according to **General Procedure A** affording the *title compound* (1.13 g, 6.7 mmol, 57%) as a colourless solid.

Colourless solid; **MP** 38–39 °C [Lit: 41–42 °C]; **IR** (ATR)/cm^{-1}: 2941, 1701, 1240; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.99–1.94 (m, 4H), 1.85–1.78 (m, 4H), 1.63–1.57 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.1, 41.9, 30.7, 24.2, 19.4; unable to obtain low or high resolution mass spec for malonyl peroxides. Spectroscopic data matches literature.

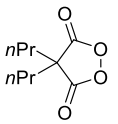
3.1.1.2.4 4,4-Diethyl-1,2-dioxolane-3,5-dione 148[72]



2,2-Diethylmalonic acid (2.00 g, 12.5 mmol) and UHP (3.50 g, 37.5 mmol) were reacted in MsOH (25 mL) according to **General Procedure A** affording the *title compound* (1.88 g, 11.9 mmol, 95%) as a colourless oil.

Colourless oil; **IR** (ATR)/$cm^{-1:}$ 2978, 1790, 1239, 1127, 1058; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.97 (q, *J* = 7.5 Hz, 4H), 1.00 (t, *J* = 7.5 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.2, 51.2, 28.9, 9.0; unable to obtain low or high resolution mass spec for malonyl peroxides. Spectroscopic data matches literature.

3.1.1.2.5 4,4-Dipropyl-1,2-dioxolane-3,5-dione 149[72]



2,2-Di-*n*-propylmalonic acid (2.00 g, 10.6 mmol) and UHP (3.00 g, 31.7 mmol) were reacted in MsOH (20 mL) according to **General Procedure A** affording the *title compound* (1.92 g, 10.3 mmol, 97%) as a colourless oil.

Colourless oil; **IR** (ATR)/cm^{-1}: 2968, 1790, 1225, 1131, 1061; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.91–1.85 (m, 4H), 1.42–1.31 (m, 4H), 0.95 (t, *J* = 7.3 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.4, 49.8, 37.8, 18.2, 13.7; unable to obtain low or high resolution mass spec for malonyl peroxides. Spectroscopic data matches literature.

3.1.2 Reagent Preparation for *Anti*-Dihydroxylation

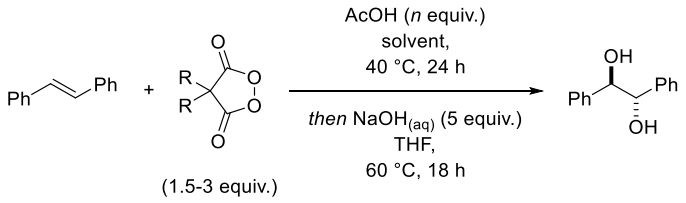
3.1.2.1 Activation of 3 Å Molecular Sieves

3 Å molecular sieves were decanted into a round bottomed flask and heated to ~270 °C under reduced pressure (~0.1 Torr) for 2 hours. The sieves were then cooled to room temperature under reduced pressure and the round bottom flask was filled with N_2. These sieves were then used immediately. Sieves were always dried immediately prior to any experiment being undertaken.

3.1.2.2 Standard Procedure for Drying Acetic Acid

Activated molecular sieves (20% *w/v*) were placed into a flame-dried round bottom flask containing commercial acetic acid ≥ 99.99% (25 mL) under N_2. Acetic acid was stored this way for a minimum of 2 hours prior to use. Storage over 3Å molecular sieves for >48 hours provided acetic acid of a consistent quality for the experiments performed in these studies.

3.1.3 Early Reaction Optimisation

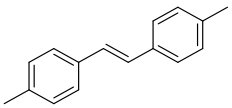


Peroxide (1.5 equiv. for **13**, 2 equiv. for **11** and 3 equiv. for **147–149**) and AcOH (x equiv) in solvent (2 mL) were dried in a PTFE sealed vial over activated 3 Å molecular sieves (200 mg per 2mL solvent) for 2 hours at room temperature, under N_2. The solution was transferred to a PTFE sealed vial containing *trans*-stilbene **3** (180 mg, 1 mmol) and stirred at 40 °C for 24 hours. The solvent was removed *in vacuo* and the crude material dissolved in a mixture of 1 M $NaOH_{(aq)}$:THF (1:1 (0.1 M)). The resulting solution was stirred at 60 °C for 18 hours. The reaction was cooled to room temperature and diluted with H_2O:EtOAc (1:1). The layers were separated and the aqueous was further extracted with EtOAc (× 2). The combined organic extracts were

washed with brine, dried over $MgSO_4$ and filtered. A sample of the crude material was then analysed by ^1H NMR spectroscopy in $CDCl_3$. Details of the conditions and results are given in **Table 1-4** on **Page 43**.

3.1.4 Alkene Synthesis

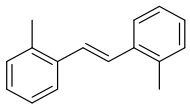
3.1.4.1 (*E*)-1,2-Di-*p*-tolylethene 159[133]



1-Methyl-4-vinylbenzene **156** (2.23 mL, 16.9 mmol) was added to a solution of Grubbs' 2nd generation catalyst (72 mg, 0.09 mmol) in anhydrous CH_2Cl_2 (28 mL) under N_2. The resulting solution was heated to reflux for 5 hours. The reaction was then allowed to cool to room temperature and filtered through a plug of Celite. The solvent was removed *in vacuo* and the crude material purified by silica gel chromatography (petrol) to afford the title compound (1.55 g, 7.47 mmol, 88%) as a colourless solid.

Colourless solid; **MP** 174–176 °C [Lit: 184–185 °C]; **IR** (ATR)/cm^{-1}: 3020, 2910, 817; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.1 Hz, 4H), 7.17 (d, *J* = 7.9 Hz, 4H), 7.05 (s, 2H), 2.37 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.4, 134.8, 129.5,127.7, 126.4, 21.3; **LRMS** (GCMS-CI) *m/z* 209 $[M+H]^+$. Spectroscopic data matches literature.

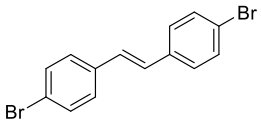
3.1.4.2 (*E*)-1,2-Di-*o*-tolylethene 160[134]



1-Methyl-2-vinylbenzene **157** (2.23 mL, 16.9 mmol) was added to a solution of Grubbs' 2nd generation catalyst (72 mg, 0.09 mmol) in anhydrous CH_2Cl_2 (28 mL) under N_2. The resulting solution was heated to reflux for 24 hours. The reaction was then allowed to cool to room temperature and filtered through a plug of Celite. The solvent was removed *in vacuo* and the crude material purified by silica gel chromatography (petrol) and trituration from EtOAc to afford the title compound (1.048 g, 5.03 mmol, 60%) as a colourless solid.

Colourless solid; **MP** 85-87 °C [Lit: 83–84 °C]; **IR** (ATR)/cm^{-1}: 3061, 3014, 2968, 761 ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.0 Hz, 2H), 7.26–7.18 (m, 8H), δ 2.44 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.9, 135.9, 130.5, 128.1, 127.6, 126.3, 125.7, 20.0; **LRMS** (GCMS-CI) *m/z* 209 $[M+H]^+$. Spectroscopic data matches literature.

3.1.4.3 (*E*)-1,2-Bis(4-bromophenyl)ethene 161[135]

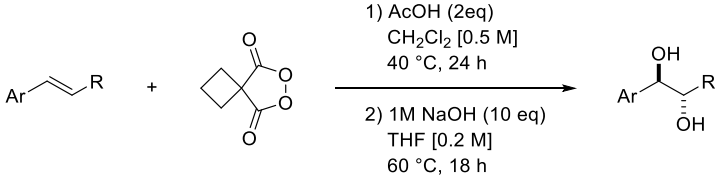


NEt_3 (2.34 mL, 16.8 mmol), 1-bromo-4-vinylbenzene **158** (1.10 mL, 8.42 mmol) and MeCN (90 mL) were added to a flame-dried, three-necked flask containing 1-bromo-4-iodobenzene **162** (2.40 g, 8.48 mmol), palladium acetate (19 mg, 1 mol%) and tri-*o*-tolyl phosphine (52 mg, 2 mol %) under N_2. The resulting solution was stirred at reflux for 48 hours. The reaction was cooled to room temperature and filtered through a plug of Celite, which was subsequently washed with EtOAc (3 × 100 mL). The solvent was removed *in vacuo* and the crude material was purified by trituration with MeOH, which afforded the *title compound* (1.07 g, 3.17 mmol, 75%) as a light brown solid.

Light brown solid; **MP** 214-216 °C [Lit: 210 °C]; **IR** (ATR)/cm^{-1}: 3012, 2941, 821; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.5 Hz, 4H), 7.36 (d, *J* = 8.5 Hz, 4H), 7.02 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.0, 132.0, 128.3, 128.1, 121.8; **LRMS** (GCMS-CI) *m/z* 336 $[M(Br^{79})]^+$. Spectroscopic data matches literature.

3.1.5 Substrate Scope with 6,7-Dioxaspiro[3.4]octane-5,8-dione 11

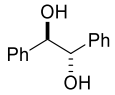
3.1.5.1 General Procedure B: *Anti*-Dihydroxylation Using 6,7-Dioxaspiro[3.4]octane-5,8-dione 11



6,7-Dioxaspiro[3.4]octane-5,8-dione **11** (2 equiv) and AcOH (3 equiv) in CH_2Cl_2 (0.5 M) were dried in a PTFE sealed vial over activated 3 Å molecular sieves (200 mg per 2mL solvent) for 2 hours at room temperature, under N_2. The solution was transferred

to a PTFE sealed vial containing alkene (1 equiv) and stirred at 40 °C for 24 hours. After competition was determined by TLC, the solvent was removed *in vacuo* and the crude material dissolved in a mixture of 1 M $NaOH_{(aq)}$:THF (1:1 (0.1 M)). The resulting solution was stirred at 60 °C for 18 hours. The reaction was cooled to room temperature and diluted with H_2O:EtOAc (1:1). The layers were separated and the aqueous was further extracted with EtOAc (× 2). The combined organic extracts were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude material was purified by silica gel column chromatography to afford the target compounds.

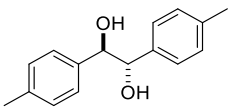
3.1.5.1.1 *rel*-(*1R*,*2S*)-1,2-Diphenylethane-1,2-diol 150[74]



The reaction of *trans*-stilbene **3** (180 mg, 1 mmol), AcOH (170 µL, 3 mmol) and 6,7-dioxaspiro[3.4]octane-5,8-dione **11** (284 mg, 2 mmol) in CH_2Cl_2 (2 mL) at 40 °C for 24 hours, followed by hydrolysis in 1 M $NaOH_{(aq)}$ (10 mL) and THF (10 ml) at 60 °C for 18 hours (crude diol 7.2:1, *anti*:*syn*) according to **General Procedure B** gave *title compound* (144 mg, 0.67 mmol, 67%) as a colourless solid, after silica gel chromatography (petrol:Et_2O, 1:1).

Colourless solid; **MP** 128–131 °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), 4.84 (s, 2H), 2.15 (bs, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.9, 128.3, 128.2, 127.2, 78.2; **LRMS** (GCMS-CI) *m/z* 197.1 $[M\text{-}OH]^+$. Spectroscopic data matches literature.

3.1.5.1.2 *rel*-(*1R*,*2S*)-1,2-Di-*p*-tolylethane-1,2-diol 165[74]

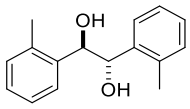


The reaction of (*E*)-1,2-di-*p*-tolylethene **159** (208 mg, 1 mmol), AcOH (170 µL, 3 mmol) and 6,7-dioxaspiro[3.4]octane-5,8-dione **11** (284 mg, 2 mmol) in CH_2Cl_2 (2 mL) at 40 °C for 24 hours, followed by hydrolysis in 1 M $NaOH_{(aq)}$ (10 mL) and THF (10 mL) at 60 °C for 18 hours (crude diol 7.5:1 *anti*:*syn*) according to **General**

Procedure B gave the *title compound* (164 mg, 0.68 mmol, 68%) as a yellow solid, after silica gel chromatography (petrol:EtOAc, 3:1).

Colourless solid; **MP** 140–142 °C [lit: 140–142 °C]; **IR** (ATR)/cm^{-1}:3533, 3469, 3024, 2889, 1512, 1018; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.1 Hz, 4H), 7.14 (d, *J* = 7.9 Hz, 4H), 4.75 (s, 2H), 2.34 (s, 6H), 2.03 (bs, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.0, 137.1, 129.2, 127.2, 78.2, 21.32; **LRMS** (GCMS-CI) *m/z* 225.1 $[M\text{-}OH]^+$; **HRMS** (NSI) calculated for $C_{16}H_{18}O_2Na$ $[M+Na]^+$ 265.1199, found 265.1201. Spectroscopic data matches literature.

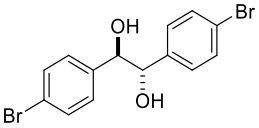
3.1.5.1.3 *rel*-(*1R*,*2S*)-1,2-Di-*o*-tolylethane-1,2-diol 166[74]



The reaction of (*E*)-1,2-di-*o*-tolylethene **160** (208 mg, 1 mmol), AcOH (170 µL, 3 mmol) and 6,7-dioxaspiro[3.4]octane-5,8-dione **11** (284 mg, 2 mmol) in CH_2Cl_2 (2 mL) at 40 °C for 24 hours, followed by hydrolysis in 1 M $NaOH_{(aq)}$ (10 mL) and THF (10 mL) at 60 °C for 18 hours (crude diol 7.4:1 *anti*:*syn*) according to **General Procedure B** gave the *title compound* (204 mg, 0.85 mmol, 85%) as a white solid, after silica gel chromatography (petrol:EtOAc, 3:1).

Colourless solid; **MP** 100–101 °C [lit: 111–116 °C]; **IR** (ATR)/cm^{-1}:3321, 2922, 2854, 1460, 1060, 1028; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.34 (m, 2H), 7.21–7.17 (m, 4H), 7.10–7.08 (m, 2H), 5.20 (app s, 2H), 2.19 (s, 6H), 2.13–2.11 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.3, 136.3, 130.2, 127.9, 126.8, 126.3, 73.5, 19.3; **LRMS** (GCMS-CI) *m/z* 225.1 $[M\text{-}OH]^+$; **HRMS** (NSI) calculated for $C_{16}H_{18}O_2Na$ $[M+Na]^+$ 265.1199, found 265.1200. Spectroscopic data matches literature.

3.1.5.1.4 *rel*-(*1R*,*2S*)-1,2-Bis(4-bromophenyl)ethane-1,2-diol 167[74]



a) The reaction of (*E*)-1,2-bis(4-bromophenyl)ethene **161** (169 mg, 0.5 mmol), AcOH (90 µL, 1.5 mmol) and 6,7-dioxaspiro[3.4]octane-5,8-dione **11** (142 mg, 1 mmol) in CH_2Cl_2 (1 mL) at 40 °C for 24 hours, followed by hydrolysis in 1 M $NaOH_{(aq)}$ (10 mL)

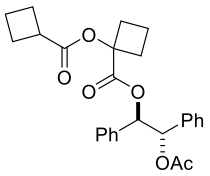
and THF (10 mL) at 60 °C for 18 hours (crude diol 3.5:1 *anti*:*syn*) according to **General Procedure B** gave the *title compound* (70 mg, 0.19 mmol, 38%) as a white solid, after silica gel chromatography (petrol:EtOAc 2:1).

b) The reaction of (*E*)-1,2-bis(4-bromophenyl)ethene **161** (85 mg, 0.25 mmol), AcOH (90 µL, 1.5 mmol) and 6,7-dioxaspiro[3.4]octane-5,8-dione **11** (142 mg, 1 mmol) in CH_2Cl_2 (1 mL) at 40 °C for 24 hours, followed by hydrolysis in 1 M $NaOH_{(aq)}$ (10 mL) and THF (10 mL) at 60 °C for 18 hours (crude diol 8:1 *anti*:*syn*) according to **General Procedure B** gave the *title compound* (65 mg, 0.18 mmol, 70%) as a white solid, after silica gel chromatography (petrol:EtOAc 2:1).

Pale brown solid; **MP** 126–129 °C [Lit: 134–135 °C]; **IR** (ATR)/cm^{-1}: 3290, 2922, 1487, 1006, 800; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (dt, *J* = 8.5, 2.4 Hz, 4H), 7.06 (dt, *J* = 8.5, 2.4 Hz, 4H), 4.83 (s, 2H), 2.27 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.4, 131.4, 128.8, 122.2, 78.7; **LRMS** (GCMS-CI) *m/z* 368.8 $[M-H]^+$; **HRMS** (NSI) calculated for $C_{14}H_{12}Br_2O_2Na$ $[M+Na]^+$ 394.9076, found 394.9078. Spectroscopic data matches literature.

3.1.6 Peroxide 11 Mechanistic Investigation

3.1.6.1 *rel*-(*1R,2S*)-2-acetoxy-1,2-diphenylethyl 1-((cyclobutanecarbonyl)oxy)cyclobutane-1-carboxylate 173

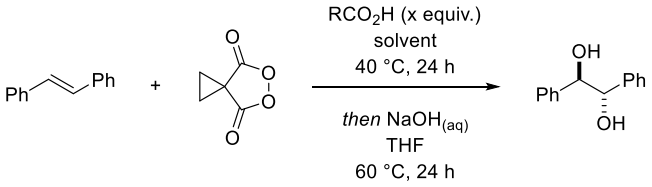


6,7-dioxaspiro[3.4]octane-5,8-dione **11** (284 mg, 2 mmol), AcOH (170 µL, 3 mmol) and CH_2Cl_2 (2 mL) were dried over activated 3 Å molecular sieves in a PTFE sealed vial for 2 hours under N_2. The solution was added to *trans*-stilbene **3** (180 mg, 1 mmol) in a PTFE sealed vial under N_2 and the resulting solution was stirred at 40 °C for 24 hours. The reaction was cooled to room temperature and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography (petrol:EtOAc, 5:1) to afford the *title compound* (115 mg, 0.26 mmol, 26%) as a clear colourless oil.

Colourless oil; **IR** (ATR)/cm^{-1}: 2949, 1735, 1228, 1134; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30–7.26 (m, 6H), 7.22–7.16 (m, 4H), 6.20 (d, *J* = 5.7 Hz, 1H), 6.11 (d, *J* = 5.7 Hz,

1H), 3.17–3.07 (m, 1H), 2.56–2.44 (m, 2H), 2.32–2.12 (m, 7H), 2.02 (s, 3H), 2.00–1.81 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.0, 170.3, 169.7, 135.9, 135.8, 128.6, 128.5, 128.2, 128.2, 128.0, 127.4, 78.3, 77.1, 76.7, 37.8, 32.3, 32.1, 25.1, 25.0, 21.0, 18.5, 14.6; **LRMS** (GCMS-CI) *m/z* 377 $[M\text{-}OAc]^+$; **HRMS** (NSI) calculated for $C_{26}H_{32}O_5N$ $[M+NH_4]^+$ 454.2224, found 454.2220.

3.1.7 Reaction Optimisation

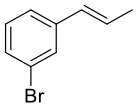


5,6-Dioxaspiro[2.4]heptane-4,7-dione **13** (x equiv.) and RCO_2H (x equiv.) in solvent (2 mL) were dried in a PTFE sealed vial over activated 3 Å molecular sieves (200 mg per 2mL solvent) for 2 hours at room temperature, under N_2. The solution was transferred to a PTFE sealed vial containing *trans*-stilbene **3** (180 mg, 1 mmol) and stirred at 40 °C for 24 hours. After competition was determined by TLC, the solvent was removed *in vacuo* and the crude material dissolved in a mixture of 1 M $NaOH_{(aq)}$:THF (1:1 (0.1 M)). The resulting solution was stirred at 60 °C for 18 hours. The reaction was cooled to room temperature and diluted with H_2O:EtOAc (1:1). The layers were separated and the aqueous was further extracted with EtOAc (× 2). The combined organic extracts were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude material was purified by silica gel column chromatography to afford diol **150**. Details of the conditions and results are given in **Table 1-6** on **Page 51**.

3.1.8 Substrate Scope with 5,6-Dioxaspiro[2.4]heptane-4,7-dione 13

3.1.8.1 Alkene Synthesis

3.1.8.1.1 (*E*)-1-Bromo-3-(prop-1-en-1-yl)benzene 180[77]

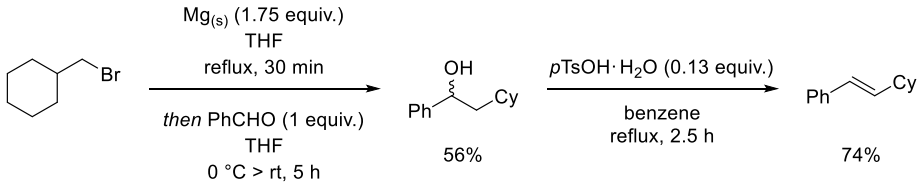


$BF{\cdot}OEt_2$ (860 μL, 7.00 mmol) was added to a mixture of pentan-3-one **193** (1.05 mL, 10.0 mmol), 3-bromobenzaldehyde **192** (1.30 mL, 11.0 mmol) and hexane (20 mL) under N_2. The reaction was heated to reflux and stirred for 3 hours. The reaction was

quenched by the addition of water (10 mL) and the aqueous solution was extracted with Et_2O (3 × 30 mL). The combined organics were dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude material was purified by silica gel chromatography (100% petrol) to afford the *title compound* (855 mg, 4.40 mmol, 44%) as a colourless oil.

Colourless oil; **IR** (ATR)/cm^{-1}: 3020, 2910, 1589, 1560, 958; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (t, *J* = 1.8 Hz, 1H), 7.31 (ddd, *J* = 7.8, 1.8, 1.2 Hz, 1H), 7.23 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 6.33 (d, *J* = 16.8 Hz, 1H), 6.25 (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, 127.6, 124.6, 122.8, 18.6; **LRMS** (GCMS-CI) *m/z* 196.9 $[M(Br^{79})+H]^+$. Spectroscopic data matches literature.

3.1.8.1.2 (*E*)-(2-Cyclohexylvinyl)benzene 15[136]

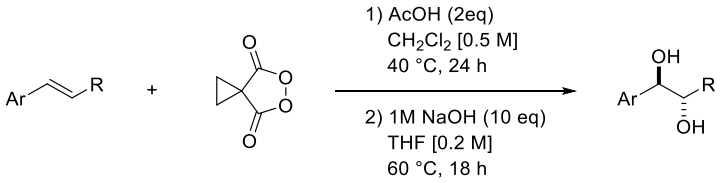


Magnesium turnings (790 mg, 32.9 mmol) were scratched with magnetic stirrer bar in a 3-necked flask fitted with a reflux condenser under N_2. THF (15 mL) and then (bromomethyl)cyclohexane **194** (3.90 mL, 28.2 mmol) was added dropwise. The resulting solution was heated to reflux for 30 minutes. The solution was cooled to 0 °C and a solution of benzaldehyde (1.90 mL, 18.8 mmol) in THF (20 mL) was added dropwise. The reaction was then allowed to warm to rt and stirred for 5 hours. The solvent was evaporated and the crude reaction material was partitioned between water (100 mL) and EtOAc (75 mL) with EDTA (30 mg) and the resulting biphasic solution was stirred at rt for 1 hour. The layers were separated and the aqueous was further extracted with EtOAc (3 × 30 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude material purified by silica gel chromatography (petrol:EtOAc, 9:1>4:1) to give 2-cyclohexyl-1-phenylethan-1-ol **195** (2.14 g, 10.5 mmol, 56%). 2-Cyclohexyl-1-phenylethan-1-ol **195** (2.04 g, 10.0 mmol) and *p*TsOH·H_2O (247 mg, 0.13 mmol) were dissolved in benzene in a round bottomed flask fitted with a Dean-Stark condenser. The solution was heated to reflux and stirred for 2.5 h. The reaction was cooled to rt

and five drops of NEt_3 were added to the reaction. Water (30 mL) and the aqueous was extracted with EtOAc (3 × 30 mL). The combined organics were washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvents were removed *in vacuo* to afford *the title compound* (1.32 g, 7.40 mmol, 74%) as a colourless oil.

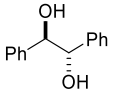
Colourless oil; **IR** (ATR)/cm^{-1}: 3022, 2918. 2847, 1448, 744 ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.3 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.21–7.16 (m, 1H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.19 (dd, *J* = 16.0, 6.9 Hz, 1H), 2.17–2.09 (m, 1H), 1.86–1.74 (m, 4H), 1.73–1.65 (m, 1H), 1.40–1.27 (m, 2H), 1.26–1.13 (m, 3H); **^{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** (GCMS-EI) *m/z* 186.2 $[M]^+$. Spectroscopic data matches literature.

3.1.8.2 General Procedure C: *Anti*-dihydroxylaion Using 5,6-Dioxaspiro[2.4]heptane-4,7-dione 13



5,6-Dioxaspiro[2.4]heptane-4,7-dione **13** (1.5 equiv) and AcOH (2 equiv) in CH_2Cl_2 (0.5 M) were dried in a PTFE sealed vial over activated 3 Å molecular sieves (200 mg per 2mL solvent) for 2 hours at room temperature, under N_2. The solution was transferred to a PTFE sealed vial containing alkene (1 equiv) and stirred at 40 °C for 24 hours. After competition was determined by TLC, the solvent was removed *in vacuo* and the crude material dissolved in a mixture of 1 M $NaOH_{(aq)}$:THF (1:1 (0.1 M)). The resulting solution was stirred at 60 °C for 18 hours. The reaction was cooled to room temperature and diluted with H_2O:EtOAc (1:1). The layers were separated and the aqueous was further extracted with EtOAc (× 2). The combined organic extracts were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude material was purified by silica gel column chromatography to afford the target compounds.

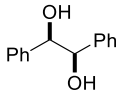
3.1.8.2.1 *rel*-(*1R,2S*)-1,2-Diphenylethane-1,2-diol 150[74]



The reaction of *trans*-stilbene **3** (180 mg, 1.00 mmol), AcOH (115 µL, 2.00 mmol) and 5,6-dioxaspiro[2.4]heptane-4,7-dione **13** (192 mg, 2 mmol) in CH_2Cl_2 (2 mL) at 40 °C for 24 hours, followed by hydrolysis in 1 M $NaOH_{(aq)}$ (10 mL) and THF (10 ml) at 60 °C for 18 hours (crude diol 5:1, *anti*:*syn*) according to **General Procedure C** gave *title compound* (144 mg, 0.67 mmol, 67%) as a colourless solid.

Characterisation previously reported on **Page 175**.

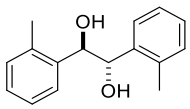
3.1.8.2.2 (*1R*,*2R*)-1,2-diphenylethane-1,2-diol 14[74]



The reaction of *cis*-stilbene **177** (180 mg, 1.00 mmol), AcOH (115 µL, 2.00 mmol) and 5,6-dioxaspiro[2.4]heptane-4,7-dione **13** (192 mg, 2 mmol) in CH_2Cl_2 (2 mL) at 40 °C for 24 hours, followed by hydrolysis in 1 M $NaOH_{(aq)}$ (10 mL) and THF (10 ml) at 60 °C for 18 hours (crude diol 5:1, *anti*:*syn*) according to **General Procedure C** gave *title compound* (169 mg, 0.79 mmol, 79%) as a colourless solid.

Colourless solid; **MP** 108–110 °C [lit: 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** (GCMS-CI) *m/z* 197.0 $[M\text{-}OH]^+$; **HRMS** (NSI) calculated for $C_{14}H_{14}O_2Na$ $[M+Na]^+$ 237.0886, found 237.0883. Spectroscopic data matches literature.

3.1.8.2.3 *rel*-(1*R*,2*S*)-1,2-Di-*o*-tolylethane-1,2-diol 166[74]

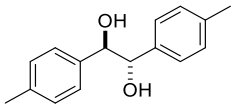


The reaction of (*E*)-1,2-di-*o*-tolylethene **159** (208 mg, 1.00 mmol), AcOH (115 µL, 2.00 mmol) and 5,6-dioxaspiro[2.4]heptane-4,7-dione **13** (192 mg, 2 mmol) in CH_2Cl_2 (2 mL) at 40 °C for 24 hours, followed by hydrolysis in 1 M $NaOH_{(aq)}$ (10 mL) and THF (10 ml) at 60 °C for 18 hours (crude diol 5:1, *anti*:*syn*) according to **General Procedure C**. The crude material was purified by silica gel chromatography

(petrol:EtOAc, 3:1) to give the *title compound* (203 mg, 0.84 mmol, 84%) as a colourless solid.

Characterisation previously reported on **Page 176**.

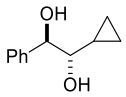
3.1.8.2.4 *rel*-(1*R*,2*S*)-1,2-Di-*p*-tolylethane-1,2-diol 165[74]



The reaction of (*E*)-1,2-di-*p*-tolylethene **159** (208 mg, 1.00 mmol), AcOH (115 µL, 2.00 mmol) and 5,6-dioxaspiro[2.4]heptane-4,7-dione **13** (192 mg, 2 mmol) in CH_2Cl_2 (2 mL) at 40 °C for 24 hours, followed by hydrolysis in 1 M $NaOH_{(aq)}$ (10 mL) and THF (10 ml) at 60 °C for 18 hours (crude diol 4:1, *anti*:*syn*) according to **General Procedure C** gave the *title compound* (221 mg, 0.91 mmol, 91%) as a colourless solid.

Characterisation previously reported on **Page 176**.

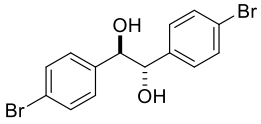
3.1.8.2.5 *rel*-(1*R*,2*S*)-1-Phenyl-2-cyclopropylethane-1,2-diol 201[74]



The reaction of (*E*)-(2-cyclopropylvinyl)benzene **178** (144 mg, 1.00 mmol, 3:1 *E*:*Z*), AcOH (115 µL, 2.00 mmol) and 5,6-dioxaspiro[2.4]heptane-4,7-dione **13** (192 mg, 2 mmol) in CH_2Cl_2 (2 mL) at 40 °C for 24 hours, followed by hydrolysis in 1 M $NaOH_{(aq)}$ (10 mL) and THF (10 ml) at 60 °C for 18 hours (crude diol 3:1, *anti*:*syn*) according to **General Procedure C**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 2:1) to give the *title compound* (165 mg, 0.92 mmol, 92%) as an off-white solid.

Off-white solid; **MP** 62–64 °C; **IR** (ATR)/cm^{-1}:3379, 3282, 3006, 2878, 1431, 1020; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45–7.27 (m, 5H), 4.83 (t, *J* = 3.3 Hz, 1H), 3.16–3.09 (m, 1H), 2.53 (d, *J* = 3.5 Hz, 1H), 1.90 (d, *J* = 3.7 Hz, 1H), 0.92–0.77 (m, 1H), 0.53–0.38 (m, 2H), 0.34–0.23 (m, 1H), 0.11–0.01 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.3, 128.3, 127.9, 127.1, 80.1, 77.0, 13.0, 3.2, 2.3; **LRMS** (GCMS-CI) *m/z* 161.0 $[M\text{-}OH]^+$; **HRMS** (NSI) calculated for $C_{11}H_{14}O_2Na$ $[M+Na]^+$ 201.0886, found 201.0884. Spectroscopic data matches literature.

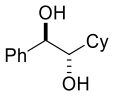
3.1.8.2.6 *rel*-(1*R*,2*S*)-1,2-Di-4-bromophenylethane-1,2-diol 167[74]



The reaction (*E*)-1,2-bis(4-bromophenyl)ethene **161** (169 mg, 0.50 mmol), AcOH (57.0 µL, 1.00 mmol) and 5,6-dioxaspiro[2.4]heptane-4,7-dione **13** (96 mg, 0.75 mmol) in CH_2Cl_2 (1 mL) at 40 °C for 24 hours, followed by hydrolysis in 1 M $NaOH_{(aq)}$ (5 mL) and THF (5 ml) at 60 °C for 18 hours (crude diol 4:1, *anti*:*syn*) according to **General Procedure C**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 2:1) to give the *title compound* (123 mg, 0.33 mmol, 66%) as a pale brown solid.

Characterisation previously reported on **Page 177**.

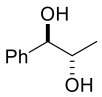
3.1.8.2.7 *rel*-(1*R*,2*S*)-1-Phenyl-2-cyclohexylethane-1,2-diol 203[74]



The reaction (*E*)-2-(cyclohexylvinyl)benzene **15** (186 mg, 1.00 mmol), AcOH (115 µL, 2.00 mmol) and 5,6-dioxaspiro[2.4]heptane-4,7-dione **13** (192 mg, 1.50 mmol) in CH_2Cl_2 (2 mL) at 40 °C for 24 hours, followed by hydrolysis in 1 M $NaOH_{(aq)}$ (10 mL) and THF (10 ml) at 60 °C for 18 hours (crude diol 4:1, *anti*:*syn*) according to **General Procedure C**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 4:1) to give the *title compound* (171 mg, 0.77 mmol, 77%) as a colourless solid.

Colourless solid; **MP** 92–96 °C; **IR** (ATR)/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** (GCMS-CI) *m/z* 203.1 $[M\text{-}OH]^+$; **HRMS** (EI) calculated for $C_{14}H_{24}O_2N_1$ $[M+NH_4]^+$ 238.1802, found 238.1798 $[M+NH_4]^+$. Spectroscopic data matches literature.

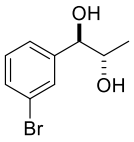
3.1.8.2.8 *rel*-(1*R*,2*S*)-1-Phenylpropane-1,2-diol 202[74]



The reaction (*E*)-prop-1-en-1-ylbenzene **76** (118 mg, 1.00 mmol), AcOH (115 μL, 2.00 mmol) and 5,6-dioxaspiro[2.4]heptane-4,7-dione **13** (192 mg, 1.50 mmol) in CH_2Cl_2 (2 mL) at 40 °C for 24 hours, followed by hydrolysis in 1 M $NaOH_{(aq)}$ (10 mL) and THF (10 ml) at 60 °C for 18 hours (crude diol 4:1, *anti*:*syn*) according to **General Procedure C**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 4:1) to give the *title compound* (136 mg, 0.89 mmol, 89%) as an off-white solid.

Off-white solid; **MP** 90–92 °C; **IR** (thin film)/cm^{-1}: 3403, 3245, 2893, 1457, 1020; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5H), 4.67 (d, *J* = 4.3 Hz, 1H), 4.06–3.97 (m, 1H), 2.54 (bs, 1H), 2.02 (bs, 1H), 1.08 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.4, 128.5, 128.0, 126.8, 77.6, 71.4, 17.4; **LRMS** (GCMS-CI) *m/z* 135.0 $[M\text{-}OH]^+$; **HRMS** (NSI) calculated for $C_9H_{12}O_2Na$ $[M+Na]^+$ 175.0730, found 175.0728. Spectroscopic data matches literature.

3.1.8.2.9 *rel*-(1*R*,2*S*)-1-(2-Bromophenyl)propane-1,2-diol 205[74]

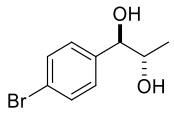


The reaction (*E*)-1-bromo-3-(prop-1-en-1-yl)benzene **180** (197 mg, 1.00 mmol), AcOH (115 μL, 2.00 mmol) and 5,6-dioxaspiro[2.4]heptane-4,7-dione **13** (192 mg, 1.50 mmol) in CH_2Cl_2 (2 mL) at 40 °C for 24 hours, followed by hydrolysis in 1 M $NaOH_{(aq)}$ (10 mL) and THF (10 ml) at 60 °C for 18 hours (crude diol 3:1, *anti*:*syn*) according to **General Procedure C**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 2:1) to give the *title compound* (176 mg, 0.76 mmol, 76%) as a pale yellow solid.

Pale yellow solid; **MP** 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 (t, *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** (100 MHz, $CDCl_3$) δ 142.8, 131.0, 130.0,

129.8, 125.4, 122.7, 71.3, 17.3; **LRMS** (GCMS-CI) *m/z* 212.9 $[M\text{-}OH]^+$; **HRMS** (NSI) calculated for $C_9H_{11}BrO_2Na$ $[M+Na]^+$ 252.9835, found 252.9838. Spectroscopic data matches literature.

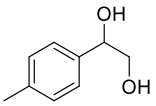
3.1.8.2.10 *rel*-(1*R*,2*S*)-1-(4-Bromophenyl)propane-1,2-diol 204[74]



The reaction (*E*)-1-bromo-4-(prop-1-en-1-yl)benzene **179** (197 mg, 1.00 mmol), AcOH (115 μL, 2.00 mmol) and 5,6-dioxaspiro[2.4]heptane-4,7-dione **13** (192 mg, 1.50 mmol) in CH_2Cl_2 (2 mL) at 40 °C for 24 hours, followed by hydrolysis in 1 M $NaOH_{(aq)}$ (10 mL) and THF (10 ml) at 60 °C for 18 hours (crude diol 4:1, *anti*:*syn*) according to **General Procedure C**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 2:1) to give the *title compound* (183 mg, 0.79 mmol, 79%) as a pale yellow solid.

Pale yellow solid; **MP** 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** (100 MHz, $CDCl_3$) δ 139.4, 131.6, 128.5, 121.8, 76.9, 71.2, 17.2; **LRMS** (GCMS-CI) *m/z* 212.9 $[M\text{-}OH]^+$; **HRMS** (NSI) calculated for $C_9H_{11}BrO_2Na$ $[M+Na]^+$ 252.9835, found 252.9838. Spectroscopic data matches literature.

3.1.8.2.11 1-(*p*-Tolyl)ethane-1,2-diol 210[74]

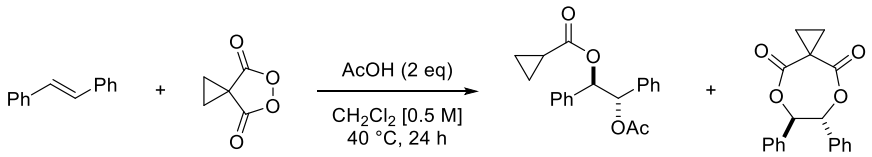


The reaction 1-methyl-4-vinylbenzene **185** (132 μL, 1.00 mmol), AcOH (115 μL, 2.00 mmol) and 5,6-dioxaspiro[2.4]heptane-4,7-dione **13** (192 mg, 1.50 mmol) in CH_2Cl_2 (2 mL) at 40 °C for 24 hours, followed by hydrolysis in 1 M $NaOH_{(aq)}$ (10 mL) and THF (10 ml) at 60 °C for 18 hours according to **General Procedure C**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 2:1) to give the *title compound* (100 mg, 0.66 mmol, 66%) as a colourless solid.

Colourless solid; **MP** 70–72 °C [lit. 76–77 °C]; **IR** (ATR)/cm^{-1}: 3269, 3016, 2923, 2889, 1085, 1062; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 4.80 (dd, *J* = 7.9, 2.9 Hz, 1H), 3.79 – 3.71 (m, 1H), 3.71 – 3.62 (m, 1H), 2.44 (bs, 1H), 2.35 (s, 3H), 2.04 (bs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.9, 137.7, 129.4, 126.2, 74.7, 68.2, 21.3; **LRMS** (GCMS-EI) *m/z* 152.1 $[M]^+$; **HRMS** (EI) calculated for $C_9H_{12}O_2$ $[M]^+$ 152.0837, found 152.0840. Spectroscopic data matches literature.

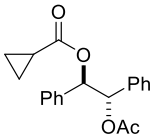
3.1.9 Mechanistic Investigation

3.1.9.1 Isolation of *anti*-dihydroxylation intermediates from the reaction of *trans*-stilbene 3 and 5,6-dioxaspiro[2.4]heptane-4,7-dione 13.



5,6-Dioxaspiro[2.4]heptane-4,7-dione **13** (384 mg, 3 mmol), AcOH (350 µL, 6 mmol) and CH_2Cl_2 (6 mL) were dried over activated 3 Å molecular sieves in a PTFE sealed vial for 2 hours under N_2. The solution was added to *trans*-stilbene **3** (360 mg, 2 mmol) in a PTFE sealed vial under N_2 and the resulting solution was stirred at 40 °C for 24 hours. The reaction was cooled to room temperature and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography (4:1 petrol:Et_2O) to afford *rel*-(*1R,2S*)-2-acetoxy-1,2-diphenylethyl cyclopropanecarboxylate **226** (448 mg, 1.38 mmol, 69%) and *rel*-(*6R,7R*)-6,7-diphenyl-5,8-dioxaspiro[2.6]nonane-4,9-dione **21** (62 mg, 0.20 mmol, 10%) as products.

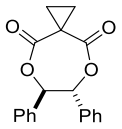
3.1.9.1.1 *rel*-(*1R,2S*)-2-acetoxy-1,2-diphenylethyl cyclopropanecarboxylate 226[74]



White solid; **MP** 123–125 °C [Lit: 113-114 °C]; **IR** (ATR)/cm^{-1}: 2924, 1737, 1714, 1226, 1031; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30–7.26 (m, 6H), 7.22–7.17 (m, 4H), 6.10 (d, *J* = 5.8 Hz, 1H), 6.07 (d, *J* = 5.8 Hz, 1H), 2.01 (s, 3H), 1.63–1.56 (m, *J* = 8.0 Hz, 4.7 Hz, 1H), 0.95–0.76 (m, 4H).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.5, 169.7, 136.4, 136.2, 128.5, 128.4, 128.2, 128.2, 127.8, 127.6, 76.8, 76.4, 21.1, 13.2, 8.7, 8.5;

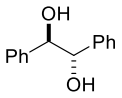
LRMS (GCMS-CI) *m/z* 265 $[M\text{-}OAc]^+$; **HRMS** (APCI) calculated for $C_{20}H_{24}O_4N$ $[M+NH_4]^+$ 342.1700, found 342.1694. Spectroscopic data matches literature.

3.1.9.1.2 *rel*-(*6R,7R*)-6,7-diphenyl-5,8-dioxaspiro[2.6]nonane-4,9-dione 21[74]



White solid; **MP** 144–146 °C [Lit: 122–124 °C]; **IR** (ATR)/cm^{-1}: 2922, 1716, 1307, 1184; **^{1}H NMR** (400 MHz, $CDCl_3$) δ7.25–7.18 (m, 6H, Ar-H), 7.08–7.03 (m, 4H, Ar-H), 5.81 (s, 2H, ArCHO), 2.12–2.06 (m, 2H, $C(CH_2)_2$), 1.89–1.84 (m, 2H, $C(CH_2)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ169.3, 134.8, 129.3, 128.7, 127.4, 84.8, 29.8, 23.3; **LRMS** (GCMS-CI) *m/z* 309 $[M+H]^+$. Spectroscopic data matches literature.

3.1.9.1.3 *rel*-(*1R,2S*)-1,2-diphenylethane-1,2-diol 150 from hydrolysis of isolated *rel*-(*1R,2S*)-2-acetoxy-1,2-diphenylethyl cyclopropanecarboxylate 226

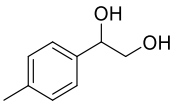


rel-(*1R,2S*)-2-acetoxy-1,2-diphenylethyl cyclopropanecarboxylate **226** (416 mg, 1.28 mmol) was dissolved in THF:1 M $NaOH_{aq}$ (1:1, 20 mL) and stirred at 60 °C for 18 hours. The aqueous was then extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated to afford the *title compound* (271 mg, 1.27 mmol, 99%) as a colourless solid with a *dr* of 35:1 *anti*:*syn*.

Characterisation previously reported on **Page 175**.

3.1.9.2 Regioselectivity of Dioxonium Opening.

3.1.9.2.1 1-(*p*-Tolyl)ethane-1,2-diol 210 by *syn*-dihydroxylation

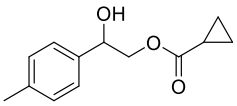


1-Methyl-4-vinylbenzene **185** (660 µL, 5 mmol) was added to a solution of 5,6-dioxaspiro[2.4]heptane-4,7-dione **13** (770 mg, 6 mmol) and water (90 µL, 5 mmol) in $CHCl_3$ (10 mL) at room temperature. The resulting solution was heated to 40 °C and

stirred for 20 hours. The solvent was removed *in vacuo* and the residue was dissolved in 1 M $NaOH_{(aq)}$ (25 mL) and THF (25 mL). The resulting solution was stirred at 60 °C for 20 hours. The reaction was cooled to room temperature and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to afford the *title compound* (635 mg, 4.18 mmol, 84%) as a colourless solid.

Characterisation previously reported on **Page 185**.

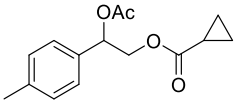
3.1.9.2.2 2-Hydroxy-2-(*p*-tolyl)ethyl cyclopropanecarboxylate 232[74]



Pyridine (162 µL, 2 mmol) and then cyclopropane carbonyl chloride **231** (91 µL, 1 mmol) were added to a solution of 1-(*p*-tolyl)ethane-1,2-diol **210** (152 mg, 1 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The resulting solution was allowed to warm to room temperature and then stirred for 3 hours. The reaction was quenched with 2 M $HCl_{(aq)}$ (20 mL) and the aqueous was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography (petrol:EtOAc, 3:1) to afford the *title compound* (143 mg, 0.65 mmol, 65%) as a clear oil.

Clear oil; **IR** (ATR)/cm^{-1}: 3435, 3014, 2924, 1724, 1707, 1168; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 4.94 (d, *J* = 8.1 Hz, 1H), 4.28 (dd, *J* = 11.6, 3.3 Hz, 1H), 4.16 (dd, *J* = 11.6, 8.4 Hz, 1H), 2.49 (s, 1H), 2.35 (s, 3H), 1.70–1.64 (m, 1H), 1.06–0.99 (m, 2H), 0.93–0.86 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.3, 138.1, 137.0, 129.4, 126.3, 72.6, 69.6, 21.3, 13.0, 8.9, 8.9; **LRMS** (GCMS-CI) *m/z* 203.1 $[M\text{-}OH]^+$. Spectroscopic data matches literature.

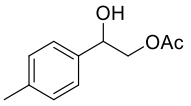
3.1.9.2.3 2-Acetoxy-2-(p-tolyl)ethyl cyclopropanecarboxylate 228[74]



Pyridine (105 µL, 1.32 mmol) and then AcCl **233** (47 µL, 0.66 mmol) were added to a solution of 2-hydroxy-2-(*p*-tolyl)ethyl cyclopropanecarboxylate **232** (120 mg, 0.55 mmol) in CH_2Cl_2 (2.75 mL) at 0 °C. The resulting solution was allowed to warm to room temperature and then stirred for 20 hours. The solution was diluted with CH_2Cl_2 (18 mL) and then washed with 2M $HCl_{(aq)}$ (3 × 20 mL) and brine (50 mL). The combined organic extracts were dried with $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude material was purified by silica gel chromatography (9:1 petroleum ether(40–60 °C):ethyl acetate) to afford the *title compound* (78 mg, 0.29 mmol, 53%) as a yellow oil.

Yellow oil; **IR** (ATR)/cm^{-1}:2980, 2924, 1730, 1371, 1228, 1163; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.5 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 5.99 (app t, *J* = 5.9 Hz, 1H), 4.30 (app d, *J* = 6.8 Hz, 2H), 2.34 (s, 3H), 2.11 (s, 3H), 1.63–1.57 (m, 1H), 1.00–0.97 (m, 2H), 0.89–0.84 (m, 2H) ; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.6, 170.2, 138.5, 133.7, 129.4, 126.8, 73.4, 66.2, 21.3, 21.2, 12.9, 8.7; **LRMS** (GCMS-CI) *m/z* 203.0 $[M\text{-}OAc]^+$; **HRMS** (NSI) calculated for $C_{15}H_{18}O_4Na$ $[M+Na]^+$ 285.1097, found 285.1095. Spectroscopic data matches literature.

3.1.9.2.4 2-Hydroxy-2-(*p*-tolyl)ethyl acetate 234[74]

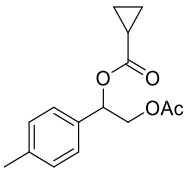


Pyridine (170 µL, 2mmol) and then AcCl **233** (71 µL, 1 mmol) were added to a solution of 1-(*p*-tolyl)ethane-1,2-diol **210** (152 mg, 1 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The resulting solution was allowed to warm to room temperature and then stirred for 3 hours. The reaction was quenched with 2 M $HCl_{(aq)}$ (25 mL) and the aqueous was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude material was purified by silica gel chromatography (petrol:EtOAc, 3:1) to afford the *title compound* (125 mg, 0.64 mmol, 64%) as a clear oil.

Clear oil; **IR** (ATR)/cm^{-1}: 3433, 2924, 1735, 1722, 1230, 1035; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 4.92 (d, *J* = 8.2 Hz, 1H), 4.26 (dd, *J* = 11.6, 3.4 Hz, 1H), 4.15 (dd, *J* = 11.6, 8.4 Hz, 1H), 2.48 (bs, 1H), 2.35 (s, 3H), 2.10 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.3, 138.2, 137.0, 129.4, 129.4,

126.3, 126.2, 72.4, 69.5, 21.3, 21.0; **LRMS** (GCMS-CI) *m/z* 177.0 $[M\text{-}OH]^+$. Spectroscopic data matches literature.

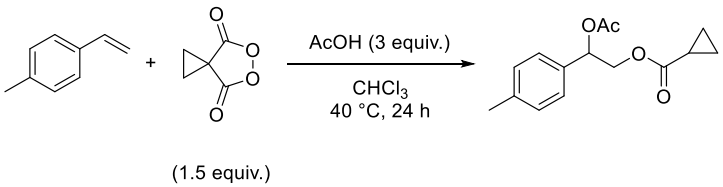
3.1.9.2.5 2-Acetoxy-1-(*p*-tolyl)ethyl cyclopropanecarboxylate 229[74]



Pyridine (95 µL, 1.18 mmol) and then cyclopropane carbonyl chloride **231** (55 µL, 0.59 mmol) were added to a solution of 2-hydroxy-2-(*p*-tolyl)ethyl acetate **234** (95 mg, 0.49 mmol) in CH_2Cl_2 (2 mL). The resulting solution was stirred at room temperature for 20 hours. The solution was diluted with CH_2Cl_2 (18 mL) and then washed with 2 M $HCl_{(aq)}$ (3 × 20 mL) and brine (50 mL). The organics were dried with $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the crude material was then purified by silica gel chromatography (petrol:EtOAc, 9:1) to give the *title compound* (41 mg, 0.16 mmol, 33%) as a yellow oil.

Yellow oil; **IR** (ATR)/cm^{-1}: 2980, 2924, 1730, 1227, 1161; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 5.98 (dd, *J* = 7.0, 5.0 Hz, 1H), 4.31 (d, *J* = 2.7 Hz, 1H), 4.30 (s, 1H), 2.34 (s, 3H), 2.05 (s, 3H), 1.68 (tt, *J* = 8.0, 4.6 Hz, 1H), 1.07–0.95 (m, 2H), 0.93–0.81 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.1, 170.8, 138.5, 133.8, 129.5, 126.8, 73.3, 66.3, 21.3, 20.9, 13.2, 8.8, 8.7; **LRMS** (GCMS-CI) *m/z* 203.0 $[M\text{-}OAc]^+$; **HRMS** (NSI) calculated for $C_{15}H_{18}O_4Na$ $[M+Na]^+$ 285.1097, found 285.1096. Spectroscopic data matches literature.

3.1.9.2.6 *Anti*-dihyroxylation of 185 for crude HMBC comparison

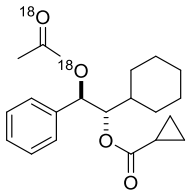


5,6-Dioxaspiro[2.4]heptane-4,7-dione **13** (192 mg, 1.50 mmol) and AcOH (115 µL, 2.00 mmol) in CH_2Cl_2 (2 mL) were dried in a PTFE sealed vial over activated 3 Å molecular sieves (200 mg per 2mL solvent) for 2 hours at room temperature, under N_2. The solution was transferred to a PTFE sealed vial containing 1-methyl-4-vinylbenzene **185** (132 µL, 1.00 mmol) and stirred at 40 °C for 24 hours.

After competition was determined by TLC, the solvent was removed *in vacuo* and a sample of the crude material was dissolved in $CDCl_3$ for analysis by ^{1}H, ^{13}C and HMBC NMR spectroscopy.

3.1.9.3 ^{18}O-Labelling Experiments

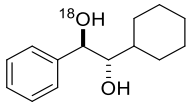
3.1.9.3.1 *rel*-(1*S*,2*R*)-2-(^{18}O-Acetoxy)-1-cyclohexyl-2-phenylethyl cyclopropanecarboxylate 235[74]



5,6-Dioxaspiro[2.4]heptane-4,7-dione **13** (50 mg, 0.39 mmol) was dissolved in a solution of ^{18}O-AcOH in CH_2Cl_2 (0.5 mL of a 1.5 mL solution containing 100 mg of ^{18}O-AcOH, effectively 33 mg, 0.52 mmol) in a PTFE sealed vial and dried over activated 3 Å molecular sieves under N_2 for 2 hours at room temperature. The solution was added to a PTFE sealed vial containing (*E*)-(2-cyclohexylvinyl)benzene **15** (48 mg, 0.26 mmol). The resulting solution was stirred for 24 h at 40 °C. The solvent was removed *in vacuo* and the crude material purified by silica gel chromatography (petrol:EtOAc, 19:1) to afford the *title compound* (18 mg, 0.054 mmol, 21%) as a colourless solid. Regiochemistry of esters determined by HMBC correlations and further functionalization.

Colourless solid; **MP** 80–82 °C; **IR** (ATR)/cm^{-1}: 2926, 2850, 1738, 1725, 1377, 1174, 1027; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5H), 5.92 (d, *J* = 6.0 Hz, 1H), 5.18 (t, *J* = 6.2 Hz, 1H), 2.05 (s, 3H), 1.77–1.74 (m, 4H), 1.63 (bs, 1H), 1.59–1.45 (m, 3H), 1.23–1.03 (m, 5H), 0.92–0.85 (m, 1H), 0.81–0.76 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.1, 169.9, 136.9, 128.4, 128.3, 128.1, 76.8, 74.2, 38.6, 29.9, 27.6, 26.4, 26.1, 25.9, 21.3, 13.0, 8.4, 8.1; **LRMS** (GCMS-CI) *m/z* 333.1 $[M-H]^+$ **HRMS** (NSI) calculated for $C_{20}H_{26}O_2{}^{18}O_2Na$ $[M+Na]^+$ 357.1808, found 357.1808. Spectroscopic data matches literature.

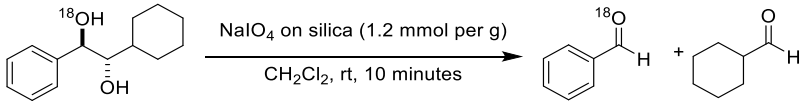
3.1.9.3.2 *rel*-(1*S*,2*R*)-1-Cyclohexyl-2-phenylethane-1,2-diol-^{18}O 236



Methylamine in ethanol (33 wt%, 560 µL, 4.6 mmol) was added to a sealed vial containing *rel*-(1*S*,2*R*)-2-(^{18}O-acetoxy)-1-cyclohexyl-2-phenylethyl cyclopropanecarboxylate **235** (10 mg, 0.03 mmol) and stirred for 72 h at 40 °C. The solvent was removed and methylamine in ethanol (33 wt%, 560 µL, 4.6 mmol) was added again to the sealed vial containing crude material. The resulting solution was stirred for an additional 96 h at 40 °C, after which time the solvent was removed. A GCMS of the crude material was obtained and the crude material was then purified by silica gel chromatography (petrol:EtOAc, 4:1) and filtration through a silica plug (washed with petrol, liberated with EtOAc) to afford the *title compound* (single diastereomer, 4 mg, 0.02 mmol, 66%) as a white solid.

White solid; **MP** and **IR** as unlabelled compound **203** (see **Page 183**); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42–7.29 (m, 5H), 4.74 (app bd, *J* = 3.0 Hz, 1H), 3.61 (app q, *J* = 3.3 Hz, 1H), 2.24 (bd, *J* = 3.1 Hz, 1H), 1.89 (bd, *J* = 9.2 Hz, 1H), 1.81–1.59 (m, 5H), 1.46–1.06 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.1, 128.7, 128.2, 127.5, 79.2, 74.9, 39.3, 30.2, 27.5, 26.6, 26.3, 26.1; **LRMS** (GCMS-CI) *m/z* 203 [M-^{18}OH]$^+$; **HRMS** (CI) calculated for $C_{14}H_{24}O^{18}ON$ [M+NH_4]$^+$ 240.1855, found 240.1855. Spectroscopic data matches literature.

3.1.9.3.3 Oxidative cleavage of rel-(1S,2R)-1-Cyclohexyl-2-phenylethane-1,2-diol-18O 236



3.1.9.3.3.1 Preparation of $NaIO_4$ on Silica

$NaIO_4$ (514 mg, 2.4 mmol) was heated to 75 °C with stirring in H_2O (1 mL) until fully dissolved. Silica powder (2g) was added at 75 °C and crushed manually with a spatula until free flowing. The silica was then dried under high vacuum (3 mbar, 100 °C) for 4 hours.

3.1.9.3.3.2 Oxidative Cleavage

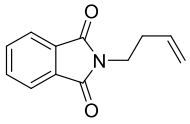
$NaIO_4$ on silica (1.2 mmol per g, 15 mg, 0.018 mmol) was suspended in anhydrous CH_2Cl_2 (50 µL) under N_2. A solution of *rel*-(1*S*,2*R*)-1-cyclohexyl-2-phenylethane-1,2-diol-^{18}O **236** (1 mg, 0.005 mmol) in anhydrous CH_2Cl_2 was added to the suspension and the mixture was stirred for 10 minutes at room temperature. Reaction completion was confirmed by TLC against

benzaldehyde. The suspension was filtered through a sinter and a GCMS was taken immediately. The presence of ^{18}O-benzaldehyde **18** and cyclohexane carbaldehyde **19** were confirmed with retention times of 7.674 and 7.340 and **LRMS** of *m/z* 113.1 $[M+H]^+$ and 109.0 $[M+H]^+$ respectively.

3.1.10 Oxyamination Work

3.1.10.1 Synthesis of (*E*)-4-methyl-N-(4-phenylbut-3-en-1-yl)benzenesulfonamide 253

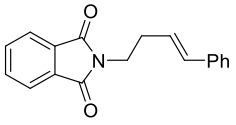
3.1.10.1.1 2-(But-3-en-1-yl)isoindoline-1,3-dione 250[137]



4-Bromobut-1-ene **248** (1.50 mL, 14.8 mmol) was added dropwise to a solution of potassium phthalimide **249** (3.55 g, 19.2 mmol) in DMF (12 mL). The solution was stirred at rt for 8 hours and then heated to reflux and stirred for 16 hours. The reaction was cooled to rt and poured onto ice (30 g) which was allowed to melt. The resulting aqueous solution was extracted with CH_2Cl_2 (4 × 30 mL). The combined organics were washed with 0.2 M KOH (50 mL) and water (50 mL) and the solvents were removed *in vacuo*. The crude material was dissolved in Et_2O (100 mL) and washed with water (4 × 100 mL). The organics were dried over $MgSO_4$, filtered and the solvents were removed *in vacuo* to afford *the title compound* (2.92 g, 14.5 mmol, 98%) as an off-white solid.

Off-white solid; **MP** 54–56 °C [Lit: 52–53 °C]; **IR** (ATR)/cm^{-1}: 3455, 3064, 2941, 1696, 1400; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.84–5.74 (m, 1H), 5.13–4.98 (m, 1H), 3.77 (t, *J* = 7.1 Hz, 2H), 2.48–2.42 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 134.6, 134.0, 132.3, 123.4, 117.7, 37.5, 33.0; **LRMS** (LCMS-ESI) *m/z* 202.1 $[M+H]^+$. Spectroscopic data matches literature.

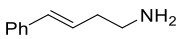
3.1.10.1.2 (*E*)-2-(4-phenylbut-3-en-1-yl)isoindoline-1,3-dione 251[138]



Acetonitrile (100 mL) was added to a mixture of 2-(But-3-en-1-yl)isoindoline-1,3-dione **250** (1.00 g, 4.98 mmol), phenyl iodide (0.61 mL, 5.48 mmol), tri(*o*-tolyl)phosphine (152 mg, 0.50 mmol), NEt_3 (1.37 mL, 10.0 mmol) and palladium acetate (56.0 mg, 0.25 mmol) under N_2. The resuting solution was heated to reflux and stirred for 16 hours. The reaction was cooled to rt and filtered through a pad of celite. The celite was washed with EtOAc (3 × 50 mL) and the solvent was removed *in vacuo*. The residue was dissolved in EtOAc (50 mL) and washed with 2M HCl (2 × 50 mL), water (50 mL) and brine (50 mL). The organics were dried over $MgSO_4$, filtered and the solvents were removed *in vacuo*. The crude material was purified by silica gel chromatography (petrol:EtOAc, 9:1) and subsequent recrystalisation from MeOH to afford the *title compound* (605 mg, 2.18 mmol, 43%) as a light brown solid. Spectroscopic data matches literature.

Light brown solid; **MP** 140–142 °C [Lit: 145–146 °C]; **IR** (ATR)/cm^{-1}: 3460, 3027, 2934, 1705; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.33–7.15 (m, 5H), 6.43 (d, *J* = 15.8 Hz, 1H), 6.17 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.85 (t, *J* = 7.1 Hz, 2H), 2.61 (ddd, *J* = 15.8, 7.2, 1.3 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.5, 137.6, 137.4, 134.1, 132.8, 128.6, 127.4, 127.4, 126.3, 123.4, 37.7, 32.4; **LRMS** (LCMS-ESI) *m/z* 278.0 $[M+H]^+$.

3.1.10.1.3 (*E*)-4-Phenylbut-3-en-1-amine 252

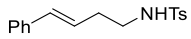


Hydrazine hydrate (710 μL, 14.4 mmol) was added to a solution of (*E*)-2-(4-phenylbut-3-en-1-yl)isoindoline-1,3-dione **251** (2.00 g, 7.22 mmol) in EtOH (29 mL). The resulting solution was heated to reflux and stirred for 35 minutes. The reaction was cooled to rt, 1 M NaOH (30 mL) was added and the EtOH was removed *in vacuo*. The aqueous solution was extracted with EtOAc (2 × 30 mL). The combined organics were washed with water (60 mL), dried over $MgSO_4$ and filtered. The solvents were removed in vacuo to afford the *title compound* (996 mg, 6.77 mmol, 94%) as a brown oil.

Brown oil; **IR** (ATR)/cm^{-1}: 3263, 3025, 2924, 1495, 1450; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.19 (m, 5H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.19 (dt, *J* = 15.8, 7.1 Hz, 1H), 2.85 (t, *J* = 6.6 Hz, 2H), 2.37 (dddz, *J* = 13.7, 6.8, 1.3 Hz, 2H); **^{13}C NMR** (101 MHz,

$CDCl_3$) δ 133.6, 132.1, 128.7, 128.1, 127.2, 126.2, 41.9, 37.5; **LRMS** (LCMS-ESI) *m/z* 148.1 $[M+H]^+$.

3.1.10.1.4 (*E*)-4-Methyl-N-(4-phenylbut-3-en-1-yl)benzenesulfonamide 253[139]

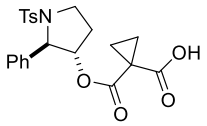


Tosyl chloride (780 mg, 4.10 mmol) then NEt_3 (550 μL, 6.80 mmol) were added to a solution of (*E*)-4-phenylbut-3-en-1-amine **252** (500 mg, 3.40 mmol) in CH_2Cl_2 (27 mL) at 0 °C. The solution was warmed to rt and stirred for 24 hours. The solution was diluted with CH_2Cl_2 (23 mL) and the reaction was washed with 2 M HCl (2 × 50 mL), water (50 mL) and brine (50 mL). The organics were dried over $MgSO_4$ and filtered. The solvents were removed in vacuo and the crude material was purified by silica gel chromatography (petrol:EtOAc, 9:1>5:1) to afford the *title compound* (349 mg, 1.16 mmol, 34%) as white solid.

White solid; **MP** 52–54 °C; **IR** (ATR)/cm^{-1}: 3360, 3030, 2937, 1329, 1154; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.34–7.20 (m, 7H), 6.36 (d, *J* = 15.9 Hz, 1H), 5.97 (dt, *J* = 15.8, 7.1 Hz, 1H), 4.39 (t, *J* = 6.0 Hz, 1H), 3.11 (q, *J* = 6.5 Hz, 2H), 2.43 (s, 3H), 2.37 (ddd, *J* = 15.8, 6.8, 1.3 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.6, 137.1, 133.5, 129.9, 128.7, 127.7, 127.3, 126.3, 125.6, 42.7, 33.2, 21.7; **LRMS** (LCMS-ESI) *m/z* 302.0 $[M+H]^+$. Spectroscopic data matches literature.

3.1.10.2 Oxidation of 253 with 5,6-dioxaspiro[2.4]heptane-4,7-dione 13

3.1.10.2.1 1-(((*rel*-(2R,3S)-2-Phenyl-1-tosylpyrrolidin-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid 254

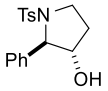


5,6-Dioxaspiro[2.4]heptane-4,7-dione **13** (63.0 mg, 0.50 mmol) was added to a solution of (*E*)-4-methyl-N-(4-phenylbut-3-en-1-yl)benzenesulfonamide **253** (100 mg, 0.33 mmol) in HFIP (660 μL). The resulting solution was stirred at rt for 24 hours. The solvent was removed *in vacuo* and the crude material was purified by silica gel chromatography (EtOAc:AcOH, 100:0>95:5) to afford the title compound (105 mg, 0.24 mmol, 74%) as an amorphous solid.

Amorphous solid; **IR** (ATR)/cm^{-1}: 2924, 1759, 1675, 1349, 1161; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.47–7.15 (m, 7H), 5.00 (d, *J* = 3.5 Hz, 1H), 4.89 (s, 1H), 3.84 (t, *J* = 8.6 Hz, 1H), 3.39–3.32 (m, 1H), 2.45 (s, 3H), 2.22–2.11 (m,

1H), 1.94–1.84 (m, 1H), 1.72–1.67 (m, 1H), 1.58–1.51 (m, 1H), 1.31–1.26 (m, 2H), 1.00–0.94 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.6, 169.9, 144.4, 138.4, 134.3, 130.1, 128.9, 128.3, 127.8, 126.3, 83.4, 68.3, 47.0, 28.5, 25.2, 23.1, 21.7; **LRMS** (LCMS-ESI) *m/z* 430.0 $[M+H]^+$.

3.1.10.2.2 *rel*-(2R,3S)-2-Phenyl-1-tosylpyrrolidin-3-ol 255[140]



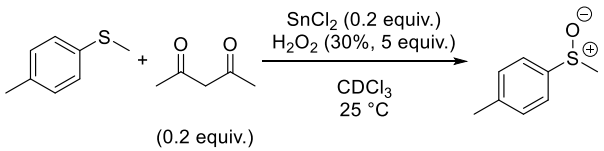
1-(((*rel*-(2R,3S)-2-Phenyl-1-tosylpyrrolidin-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid **254** (260 mg, 0.61 mmol) was dissolved in a solution of 33% methylamine in EtOH (6.10 mL, 48.8 mmol). The resulting solution was heated to 40 °C and stirred for 18 hours. After cooling to rt, the solvent was removed *in vacuo* and the crude material purified by silica gel chromatography (petrol:EtOAc, 2:1>1:1) to afford the title compound (133 mg, 0.42 mmol, 69%) as a white solid.

White Solid; **MP** 148–149 °C [Lit: 155–156 °C]; **IR** (ATR)/cm^{-1}: 3509, 2988, 2882, 1154; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.36–7.26 (m, 7H), 4.66 (s, 1H), 4.18 (s, 1H), 3.75–3.70 (m, 1H), 3.57–3.50 (m, 1H), 2.43 (s, 3H), 2.11–1.98 (m, 1H), 1.78–1.71 (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** (LCMS-ESI) *m/z* 318.0 $[M+H]^+$. Spectroscopic data matches literature.

3.2 Chapter 2 – Organocatalytic Sulfoxidation

3.2.1 Initial Results

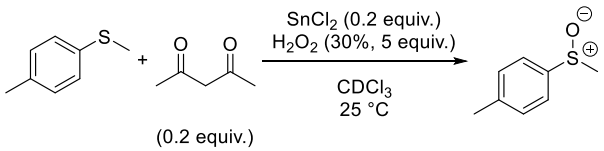
3.2.1.1 NMR Experiment



$H_2O_{2(aq)}$ (30%, 500 µL, 5.00 mmol) was added to a solution of methyl(*p*-tolyl)sulfane **317** (135 µL, 1.00 mmol), acetylacetone **313** (20 µL, 0.20 mmol) and $SnCl_2$ (38 mg, 0.20 mmol) in $CDCl_3$ (5 mL). The resulting biphasic solution was stirred at 25 °C and analysed by ^1H NMR (50 µL sample diluted to 600 µL with $CDCl_3$) at 1, 3, 6 and 24 hours.

The results can be found on **Page 99–101**.

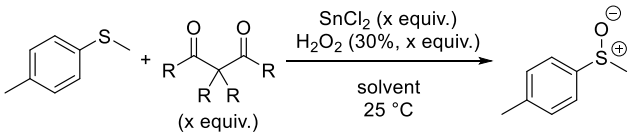
3.2.1.2 HPLC Experiment



$H_2O_{2(aq)}$ (30%, 500 µL, 5.00 mmol) was added to a solution of methyl(*p*-tolyl)sulfane **317**(135 µL, 1.00 mmol), acetylacetone **313** (20 µL, 0.20 mmol) and $SnCl_2$ (38 mg, 0.20 mmol) in $CDCl_3$ (5 mL). The resulting biphasic solution was stirred at 25 °C and analysed by HPLC (10 µL sample diluted to 1 mL with MeCN) at 1, 3, 6 and 24 hours.

The results can be found on **Page 99–101**.

3.2.2 Optimisation of Reaction Conditions: $SnCl_2$ Method



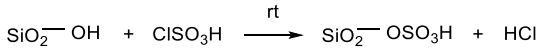
$H_2O_{2(aq)}$ (30%, x equiv.) was added to a solution of methyl(*p*-tolyl)sulfane **317** (135 µL, 1.00 mmol), ketone (x equiv.) and $SnCl_2$ (x equiv.) in solvent (x mL). The resulting

solution was stirred at 25 °C and analysed by HPLC (2.5,5, or 10 μL sample diluted to 1 mL with MeCN) at regular intervals.

The results can be found on **Page 101–111**.

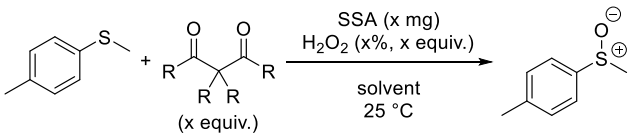
3.2.3 Optimisation of Reaction Conditions: SSA Method

3.2.3.1 Synthesis of SSA 324



Chlorosulfonic acid **323** (13.5 mL, 203 mmol) was added *via* dropping funnel, under a constant flow of N_2, over 1.5 hours to stirred silica **322** (60 g). The exhaust from the reaction vessel was run through 4 M NaOH to quench the HCl gas generated. The silica was allowed to stir for a further hour to ensure completition giving silica sulfuric acid (77 g). Titration with NaOH gave a H^+ concentration of 5.6 mmol/g.

3.2.3.2 Optimsation Reaction Conditions

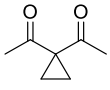


$H_2O_{2(aq)}$ (x%, x equiv.) was added to a solution of methyl(*p*-tolyl)sulfane (135 μL, 1.00 mmol), ketone (x equiv.) and SSA (x mg) in solvent (x mL). The resulting solution was stirred at 25 °C and analysed by HPLC (2.5,5, or 10 μL sample diluted to 1 mL with MeCN) at regular intervals.

The results can be found on **Page 111–132**.

3.2.3.3 Synthesis of Ketones

3.2.3.3.1 1,1'-(Cyclopropane-1,1-diyl)bis(ethan-1-one) 325[141]

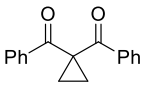


DMSO (50 mL) then acetylacetone **313** (2.00 mL, 20.0 mmol) were added to K_2CO_3 (5.52 g, 40.0 mmol) under N_2 and the resulting solution was stirred at 30 °C for 30 minutes. 1,2-Dibromoethane **140** (1.90 mL, 22.0 mmol) was added in one portion. The temperature was increased to 60 °C and the reaction was stirred for 3 hours. After

cooling to rt, water (200 mL) was added. The aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organics were washed with 2 M HCl (2 × 50 mL) and brine (50 mL). The organics were dried over $MgSO_4$, filtered and the solvents were removed *in vacuo*. The crude material was purified by distillation (54–60 °C, 4 mbar) to afford the *title compound* (742 mg, 5.89 mol, 29%) as a colourless oil.

Colourless oil; **IR** (ATR)/cm^{-1}: 3010, 1588; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 6H), 1.46 (s, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.0, 43.4, 27.9, 17.6; **LRMS** (LCMS-ESI) *m/z* 127.1 $[M+H]^+$. Spectroscopic data matches literature.

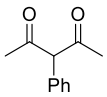
3.2.3.3.2 Cyclopropane-1,1-diylbis(phenylmethanone) 327[118]



DMSO (20 mL) was added to 1,3-diphenylpropane-1,3-dione **326** (2.24 g, 10.0 mmol) and K_2CO_3 (2.76 g, 20 mmol) and the resulting solution was stirred at 30 °C for 30 minutes. 1,2-Dibromoethane **140** (3.50 mL, 40.0 mmol) was added in one portion. The temperature was increased to 60 °C and the reaction was stirred for 16 hours. After cooling to rt, water (200 mL) was added. The aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organics were washed with 2 M HCl (2 × 50 mL) and brine (50 mL). The organics were dried over $MgSO_4$, filtered and the solvents were removed *in vacuo*. The crude material was purified by silica gel chromatography (petrol:Et_2O, 19:1) to afford the title compound (1.03 g, 4.13 mmol, 41%) as a colourless solid.

Colourless solid; **MP** 90–92 °C [Lit: 98–100 °C]; **IR** (ATR)/cm^{-1}: 3068, 3029, 2920, 1662; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76–7.72 (m, 4H), 7.40–7.34 (m, 2H), 7.29–7.23 (m, 4H), 2.05 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 197.6, 137.8, 133.0, 128.7, 128.6 16.7; **LRMS** (LCMS-ESI) *m/z* 251.1 $[M+H]^+$. Spectroscopic data matches literature.

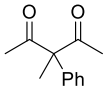
3.2.3.3.3 3-Phenylpentane-2,4-dione 328[142]



Phenyl iodide (2.25 mL, 20.0 mmol) then acetylacetone **313** (4.10 mL, 40.0 mmol) were added to a stirred suspension of copper (I) iodide (380 mg, 2.00 mmol) and K_2CO_3 (11.0 g, 80.0 mmol) in DMSO (50 mL) under N_2. The reaction was heated to 120 °C and stirred for 20 hours. After cooling to rt, the solution was diluted with 1 M HCl (200 mL) and extracted with Et_2O (4 × 100 mL). The combined organics were washed with water (2 × 100 mL) and brine (2 × 100 mL). The organics were dried over $MgSO_4$, filtered and the solvents were removed *in vacuo*. The crude material was purified by silica gel chromatography (petrol:EtOAc, 9:1) to afford the *title compound* (275 mg, 1.56 mmol, 8%) as an amorphous yellow solid.

Amorphous yellow solid; **IR** (ATR)/cm^{-1}: 3058, 3019, 1573, 1403, 1327; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41–7.36 (m, 2H), 7.35–7.30 (m, 1H), 7.19–7.15 (m, 2H), 1.89 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.1, 137.1, 131.3, 129.0, 127.6, 115.4, 24.3; **LRMS** (GCMS-EI) *m/z* 176.1 $[M+H]^+$. Spectroscopic data matches literature.

3.2.3.3.4 3-Methyl-3-phenylpentane-2,4-dione 329[143]

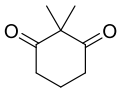


A solution of 3-phenylpentane-2,4-dione **329** (176 mg, 1.00 mmol) in THF (2.5 mL) was added dropwise to a suspension of NaH (48 mg, 2.00 mmol) in THF (2.5 mL) under N_2. The solution was stirred at rt for 30 minutes. MeI (125 μL, 2.00 mmol) was added in one portion and the reaction was stirred for 20 hours, heated to 60 °C and stirred for a further 20 hours. The reaction was cooled to rt and water (10 mL) was added. The aqueous was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics were dried over $MgSO_4$, filtered and removed *in vacuo*. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:0>9:1) to afford the *title compound* (81 mg, 0.43 mmol, 43%) as a yellow oil.

Yellow oil; **IR** (ATR)/cm^{-1}: 2984, 2926, 1699, 701; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42–7.37 (m, 2H), 7.36–7.31 (m, 1H), 7.26–7.22 (m, 2H), 2.12 (s, 6H), 1.77 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.5, 138.2, 129.1, 128.1, 127.7, 70.2, 27.6, 19.8; **LRMS** (GCMS-EI) *m/z* 191.1 $[M+H]^+$; **HRMS** (NSI) calculated for $C_{12}H_{15}O_2$ $[M+NH_4]^+$ 191.1067, found 191.1066. Spectroscopic data matches literature.

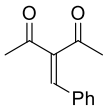
3.2.3.3.5 2,2-Dimethylcyclohexane-1,3-dione 332[119]



MeI (3.60 mL, 58.0 mmol) was added to cyclohexane-1,3-dione **331** (2.24 g, 20.0 mmol) and K_2CO_3 (5.52 g, 40 mmol) in acetone (14 mL) under N_2. The reaction was heated to reflux and stirred for 2.5 hours. After cooling to rt, the solvent was removed *in vacuo* and the crude material was dissolved in $CHCl_3$ (50 mL). 2 M HCl (50 mL) was slowly added to the organics and the layers were separated after the K_2CO_3 had been neutralised. The layers were separated and the organics were further washed with 2 M HCl (2 × 50 mL), water (50 mL) and brine (50 mL). The organics were dried over $MgSO_4$, filtered and remved *in vacuo*. The crude material was purified with silica gel chromatography (petrol:EtOAc, 19:1) to afford the *title compound* (124 mg, 0.80 mmol, 4%) as a colourless oil.

Colourless oil; **IR** (ATR)/cm^{-1}: 2938, 1692; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.68 (app t, *J* = 6.8 Hz, 4H), 1.94 (app p, *J* = 7 Hz, 2H), 1.30 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.5, 61.8, 37.4, 22.3, 18.1; **LRMS** (GCMS-EI) *m/z* 140.2 $[M]^+$. Spectroscopic data matches literature.

3.2.3.3.6 3-Benzylidenepentane-2,4-dione 335[144]

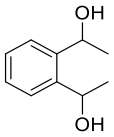


Benzaldehyde **333** (5.10 mL, 50.0 mmol) was added *via* syringe pump over 20 minutes to a solution of acetylacetone **313** (5.10 mL, 50.0 mmol) and piperidine **334** (0.30 mL, 3.00 mmol) in PhMe (50 mL) under N_2. The resulting solution was then heated to reflux and stirred for 4 hours. After cooling to rt, the reaction was washed with sat. $NaHCO_3$ (50 mL), 5% $AcOH_{(aq)}$ (50 mL) and brine (50 mL). The organics were dried over $MgSO_4$, filtered and removed *in vacuo*. The crude material was purified by silica

gel chromatography (petrol:EtOAc, 9:1). To afford the title compound (3.54 g, 18.8 mmol, 38%) as a brown oil.

Brown oil; **IR** (ATR)/cm^{-1}: 3053, 3020, 1707, 1657; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.42–7.37 (m, 5H), 2.42 (s, 3H), 2.28 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.7, 196.6, 143.0, 139.9, 133.0, 130.8, 129.8, 129.1, 31.8, 26.6; **LRMS** *m/z* 189.1 $[M+H]^+$. Spectroscopic data matches literature.

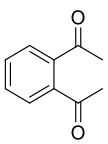
3.2.3.3.7 1,1'-(1,2-phenylene)bis(ethan-1-ol) 337[120]



MeMgCl (3 M in THF, 13.3 mL, 40.0 mmol) was added dropwise to a stirred solution of phthaldialdehyde **336** (1.34 g, 10.0 mmol) in anhydrous THF (13 mL) under N_2 at -78 °C. The resulting solution was stirred at -78 °C for 1 hour, heated to 20 °C and then stirred at 20 °C for 18 hours. The reaction was quenched by dropwise addition of saturated $NH_4Cl_{(aq)}$ (25 mL) at 0 °C. H_2O (20 mL) was added and the aqueous was extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude material was purified by silica gel chromatography (petrol:EtOAc, 3:1>1:1) to afford the *title compound* (1.21 g, 7.29 mmol, 73%) as a colourless oil in an unassigned mixture of diastereomers.

Colourless oil; **IR** (ATR)/cm^{-1}: 3302, 2973, 2928, 1450, 1068, 761; **^{1}H NMR** (400 MHz, $CDCl_3$, major isomer) δ 7.55–7.41 (m, 2H), 7.32–7.28 (m, 2H), 5.21–5.20 (m, 2H), 2.86 (bs, 1H), 2.48 (bs, 1H), 1.58–1.45 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$, major isomer) δ 142.3, 128.0, 125.4, 67.2, 24.6; **LRMS** (LCMS-ESI) *m/z* 147.1 $[M-H_3O]^+$. Spectroscopic data matches literature.

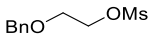
3.2.3.3.8 1,1'-(1,2-Phenylene)bis(ethan-1-one) 338[120]



MnO_2 (7.83 g, 90.0 mmol) was added to a solution of 1,1'-(1,2-phenylene)bis(ethan-1-ol) **337** (1.00 g, 6.02 mmol) in CH_2Cl_2 (20 mL). The resulting suspension was heated to reflux and stirred for 18 hours. After cooling to room temperature, the solution was filtered through a plug of Celite® and washed with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were evaporated to give the *title compound* (776 mg, 4.73 mmol, 79%) as an orange oil.

Orange oil; **IR** (ATR)/cm^{-1}: 3004, 2963, 2924, 1681, 1284; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58–7.53 (m, 4H), 2.54 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.9, 139.7, 131.2, 127.9, 28.9; **LRMS** (LCMS-ESI) *m/z* 163.1 $[M+H]^+$. Spectroscopic data matches literature.

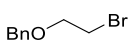
3.2.3.3.9 2-(Benzyloxy)ethyl methanesulfonate 340[145]



MsCl (850 μL, 11.0 mmol) was added dropwise to a solution of 2-(benzyloxy)ethan-1-ol **339** (1.45 mL, 10.0 mmol) in anhydrous pyridine (4 mL) under N_2 at 0 °C. The resulting solution was stirred at 0 °C for 1.5 hours and then rt for 1.5 hours. The reaction was diluted with water (30 mL). The aqueous solution was extracted with Et_2O (3 × 20 mL) and the combined organics were washed with 2 M HCl (2 × 20 mL) and sat. $NaHCO_3$ (2 × 30 mL). The organics were dried over $MgSO_4$, filtered and removed *in vacuo* to give the title compound (2.20 g, 9.56 mmol, 96%) as a colourless oil.

Colourless oil; **IR** (ATR)/cm^{-1}: 3030, 2939, 2865, 1349; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 4.58 (s, 2H), 4.44–4.36 (m, 2H), 3.79–3.69 (m, 2H), 3.03 (s, 3H);^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 128.7, 128.1, 127.9, 73.5, 69.3, 68.0, 37.8; **LRMS** (LCMS-ESI) *m/z* 248.0 $[M+NH_4]^+$; **HRMS** (NSI) calculated for $C_{10}H_{18}O_4NS$ $[M+NH_4]^+$ 248.0951, found 248.0951. Spectroscopic data matches literature.

3.2.3.3.10 ((2-Bromoethoxy)methyl)benzene 341[146]

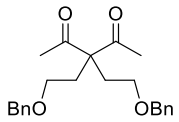


Lithium bromide (1.50 g, 17.4 mmol) was added in one portion to a solution of 2-(benzyloxy)ethyl methanesulfonate **340** (1.00 g, 4.34 mmol) in acetone (13 mL). The solution was heated to reflux and stirred for 18 hours. After cooling to rt, the

acetone was removed *in vacuo* and the residue was dissolved in water (20 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the *title compound* (840 mg, 3.93 mmol, 91%) as a colourless oil.

Colourless oil; **IR** (ATR)/cm^{-1}: 3027, 2854, 1104; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 4.60 (s, 2H), 3.80 (t, *J* = 6.2 Hz, 2H), 3.50 (t, *J* = 6.2 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.9, 128.6, 128.0, 127.9, 73.3, 70.1, 30.6.; **LRMS** (LCMS-ESI) *m/z* 214.1 $[M(^{79}Br)]^+$. Spectroscopic data matches literature.

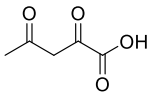
3.2.3.3.11 3,3-bis(2-(Benzyloxy)ethyl)pentane-2,4-dione 342



Acetylacetone **313** (510 μL, 5.00 mmol) was added to K_2CO_3 (1.74 g, 10.5 mmol) in DMSO (5 mL) under N_2. Simultaneously, ((2-Bromoethoxy)methyl)benzene **341** (2.25 g, 10.5 mmol) was added to a solution of potassium iodide (1.45 g, 10.5 mmol) in DMSO (5 mL) under N_2. Both solutions were stirred at 30 °C for 30 minutes. The second solution was added to the first and the resulting solution was heated up to 60 °C and stirred for 18 hours. After cooling to rt, the reaction was diluted with sat. $NaHCO_3$ (100 mL) and the aqueous solution was extracted with Et_2O (5 × 50 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvents removed in vacuo. The crude material was purified by silica gel chromatography (petrol:EtOAc, 5:1) to afford the *title compound* (1.27 g, 3.46, 70%) as an colourless oil.

Colourless oil; **IR** (ATR)/cm^{-1}: 2983, 2888, 1698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.23 (m, 10H), 4.37 (s, 4H), 3.39 (t, *J* = 6.2 Hz, 4H), 2.31 (t, *J* = 6.2 Hz, 4H), 2.10 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 206.6, 138.1, 128.5, 127.8, 73.4, 67.7, 66.0, 30.9, 27.0; LRMS (LCMS-ESI) *m/z* 369.1 $[M+H]^+$; **HRMS** (NSI) calculated for $C_{23}H_{29}O_4$ $[M+H]^+$ 369.2060, found 369.2062.

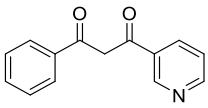
3.2.3.3.12 2,4-Dioxopentanoic acid 345[147]



$NaOH_{(aq)}$ (5 M, 8.00 mL, 40.0 mmol) was added dropwise to a solution of ethyl 2,4-dioxopentanoate **344** (2.80 mL, 20.0 mmol) in MeOH (40 mL) at 0 °C. The resulting solution was warmed to room temperature and stirred for 1 h. MeOH (20 mL) was added to the slurry that had formed to allow it to continue to stir, and it was stirred for a further hour. The precipitate was then filtered, washed with MeOH (3 × 30 mL), dissolved in $H_2SO_{4(aq)}$ (2 N, 50 mL) and extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts were dried with $MgSO_4$ and filtered. The solvents were removed *in vacuo* afford the *title compound* (1.02 g, 7.85 mmol, 39%) as an orange solid.

Orange solid; **MP** 97–99 °C [Lit: 98–100 °C]; **IR** (ATR)/cm^{-1} 3178, 3111, 1733, 1592 **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.47 (s, 1H), 2.28 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.4, 169.0, 164.1, 101.4, 26.8; **LRMS** (LCMS-ESI) *m/z* 129.1 $[M-H]^-$. Spectroscopic data matches literature.

3.2.3.3.13 1-Phenyl-3-(pyridin-3-yl)propane-1,3-dione 348[121]

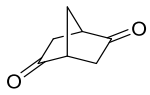


$NaNH_2$ (1.25 g, 32.0 mmol) and methyl nicotinate **347** (5.48 g, 40.0 mmol) were dissolved in benzene (50 mL) under N_2. The resulting solution was heated to 50 °C and acetophenone **346** (2.40 mL, 20.0 mmol) in benzene (2.5 mL) was added dropwise. The reaction was then heated to 80 °C and stirred for 7 hours after which a precipitate had formed. The precipitate was filtered and suspended in 5% $AcOH_{(aq)}$ (40 mL). The aqueous was extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvents were removed *in vacuo* and the crude material was purified by recrystalisation in hot ethanol which gave the *title compound* (361 mg, 1.6 mmol, 8%) as an off-white solid.

Off-white solid; **MP** 119–121 °C [Lit: 121–121.5 °C]; **IR** (ATR)/cm^{-1} 3107; 3055; 1590; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.19 (d, *J* = 1.9 Hz, 1H), 8.77 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.27 (dt, *J* = 8.0, 2.0 Hz, 1H), 8.04–7.95 (m, 2H), 7.61–7.56 (m, 1H), 7.54–7.47 (m, 2H), 7.44 (ddd, *J* = 8.0, 4.8, 0.4 Hz, 1H), 6.86 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 186.6, 183.6, 153.0, 148.7, 135.2, 134.7, 133.0, 131.4, 129.0, 127.5, 123.7,

93.6; **LRMS** (LCMS-ESI) *m/z* 226.1 $[M+H]^+$; **HRMS** (NSI) calculated for $C_{14}H_{11}NO_2$ $[M+H]^+$ 226.0863, found 226.0865. Spectroscopic data matches literature.

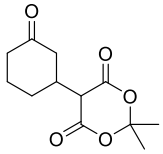
3.2.3.3.14 *rel*-(*1R*,*4R*)-Bicyclo[2.2.1]heptane-2,5-dione 350[122]



Norbornadiene **349** (3.05 mL, 30.0 mmol) was added in one potion to formic acid (17 mL) under N_2. The reaction was heated to reflux and stirred for 24 hours. After cooling to rt, the solvent was removed *in vacuo*. Half of the crude material was dissolved in THF (21 mL) and NaOH (6.00 g, 150 mmol) in water (8.5 mL) was added dropwise at 0 °C. The resulting solution was warmed to rt and stirred for 18 hours. Water (30 mL) and EtOAc (30 mL) were added. The layers were separated and the resulting aqueous solution was further extracted with EtOAc (2 × 30 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude material was vacuum dried for 4 hours. DMSO (4.25 mL, 60.0 mmol) was added under N_2. The solution was diluted with CH_2Cl_2 (15 mL). P_2O_5 (8.52 g, 30 mmol) was added in one portion and the resulting suspension was mechanically stirred for 1 hour at rt. The reaction was cooled to 0 °C and NEt_3 (12.5 mL, 90.0 mmol) was added dropwise over 1 hour. The resulting solution was then stirred at 0 °C for a further hour. After warming to rt, the reaction was quenched *via* the addition of 2 M HCl (30 mL). The aqueous was then extracted with CH_2Cl_2 (4 × 30 mL). The combined organics were then dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The crude material was purified by silica gel chromatography (petrol:EtOAc, 3:1) to afford the title compound (242 mg, 1.95 mmol, 13%) as an amorphous solid.

Amorphous solid; **MP** <30 °C; **IR** (ATR)/cm^{-1} 2996, 2959, 2921, 1731; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.00–2.97 (m, 2H), 2.40-2.34 (m, 2H), 2.18–2.11 (m, 2H), 2.11–2.08 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 212.4, 48.7, 39.1, 36.6; **LRMS** (LCMS-ESI) *m/z* 125.1 $[M+H]^+$; **HRMS** (NSI) calculated for $C_7H_9O_2$ $[M+H]^+$ 125.0594, found 125.0597. Spectroscopic data matches literature.

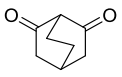
3.2.3.3.15 4,4-Dimethyl-[1,1'-bi(cyclohexane)]-2,3',6-trione 353[123]



A solution of Meldrum's acid **352** (11.2 g, 77.5 mmol) in MeCN (20 mL) was added to a solution of Li_2CO_3 (5.73 g, 77.5 mmol) and $BnNEt_3Cl$ (11.4 g, 50.0 mmol) in MeCN (10 mL) under N_2. The resulting solution was stirred at rt for 30 minutes. A solution of cyclohexanone **351** (4.80 mL, 50.0 mmol) in MeCN (20 mL) was added and the solution was stirred at rt for 24 hours. The reaction was then heated to 40 °C and stirred for a further 24 hours. The reaction was diluted with water (150 mL) and the aqueous solution was extracted with Et_2O (100 mL) and the ether was discarded. The aqueous was then acidified to pH 1 with 2 M HCl and extracted with EtOAc (2 × 150 mL). The combined organics dried over $MgSO_4$, filtered and the solvents were removed *in vacuo*. The crude material was purified by crystalisation from EtOAc to give the title compound (4.55 g, 19.3 mmol, 38%) as a colourless solid.

Colourless solid; **MP** 138–140 °C [Lit: 148–153 °C] **IR** (ATR)/cm^{-1} 3009, 2959, 2882, 1733, 1705, 1060; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.43 (d, *J* = 2.7 Hz, 1H), 2.99–2.88 (m, 1H), 2.89–2.78 (m, 1H), 2.46–2.25 (m, 3H), 2.16–2.07 (m, 1H), 2.06–1.95 (m, 1H), 1.83–1.79 (m, 1H), 1.79 (s, 1H), 1.77 (s, 3H), 1.73–1.60 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.5, 164.4, 164.2, 105.3, 49.9, 44.7, 41.0, 37.7, 28.5, 27.3, 27.1, 25.0; **LRMS** (LCMS-ESI) *m/z* 258.1 $[M+NH_4]^+$; **HRMS** (NSI) calculated for $C_{12}H_{17}O_5$ $[M+H]^+$ 241.1071, found 241.1072. Spectroscopic data matches literature.

3.2.3.3.16 Bicyclo[2.2.2]octane-2,6-dione 354[123]

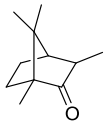


AcOH (10 mL) was added to 4,4-dimethyl-[1,1'-bi(cyclohexane)]-2,3',6-trione **353** (2.40 g, 10.0 mmol) and polyphosphoric acid (12.4 g) under N_2. The resulting solution was heated to 100 °C and stirred for 1 hour. After cooling to rt, brine (200 mL) was added. The aqueous solution was extracted with PhMe (5 × 100 mL). The combined organics were washed with sat. $NaHCO_3$ (4 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude material was

purified by silica gel chromatography (petrol:EtOAc, 5:1) to afford the title compound (361 mg, 2.60 mmol, 26%) as an amorphous solid.

Amorphous solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.18 (t, *J* = 2.9 Hz, 1H), 2.68–2.63 (m, 1H), 2.55–2.47 (m, 2H), 2.42–2.33 (m, 2H), 2.14–2.10 (m, 2H), 1.91–1.83 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 206.9, 64.0, 44.2, 28.2, 23.8, 22.3; **LRMS** (LCMS-ESI) *m/z* 139.1 $[M+H]^+$; **HRMS** (NSI) calculated for $C_8H_{11}O_2$ $[M+H]^+$ 139.0754, found 139.0750. Spectroscopic data matches literature.

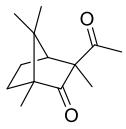
3.2.3.3.17 (*1S,4R*)-1,3,7,7-Tetramethylbicyclo[2.2.1]heptan-2-one 356



n-BuLi solution (2.5 M in hexanes, 4.00 mL, 10.0 mmol) was added dropwise to diisopropylamine (1.40 mL, 10.0 mmol) in anhydrous THF (10 mL) at -78 °C under N_2. The resulting solution was stirred at -78 °C for 30 minutes. A solution of (+)-camphor **356** (1.52 g, 10.0 mmol) in THF (2 mL) was added dropwise at -78 °C and the resulting solution was stirred for 30 min. The reaction was then warmed to 0 °C and MeI (2.50 mL, 40.0 mmol) was added dropwise. The resulting solution was stirred at 0 °C for 1 hour. The reaction was then quenched with 1 M $HCl_{(aq)}$ (20 mL). The aqueous was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with H_2O (3 × 30 mL) and brine (30 mL), dried over $MgSO_4$ and filtered. The solvents were removed *in vacuo* and the crude material was purified by silica gel chromatography (petrol (30–40 °C):Et_2O, 50:1) to afford the *title compound* (890 mg, 5.40 mmol, 54%) as a yellow oil in a 3.5:1 (exo:endo) mixture of diastereoisomers.

Yellow oil; **IR** (ATR)/cm^{-1} 2960, 2932, 2876, 1740; **^{1}H NMR** (400 MHz, $CDCl_3$, major isomer) δ 2.02–1.92 (m, 2H), 1.85 (d, *J* = 4.0 Hz, 1H), 1.68–1.57 (m, 1H), 1.52–1.43 (m, 1H), 1.39–1.33 (m, 1H), 1.20 (d, *J* = 7.6 Hz, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.85 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$, major isomer) δ 222.8, 57.6, 49.4, 48.9, 44.2, 29.5, 29.3, 21.9, 20.7, 16.3, 9.6; **LRMS** (GCMS-EI) *m/z* 166.1 $[M]^+$.

3.2.3.3.18 (*1S,3S,4S*)-3-Acetyl-1,3,7,7-tetramethylbicyclo[2.2.1]heptan-2-one 357



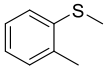
n-BuLi solution (2.30 M in hexanes, 1.31 mL, 3.01 mmol) was added dropwise to a solution of diisoproylamine (420 μL, 3.01 mmol) in THF (3 mL) at -78 °C. The resulting solution was stirred at -78 °C for 30 minutes. A solution of (1S,4R)-1,3,7,7-tetramethylbicyclo[2.2.1]heptan-2-one **356** (500 mg, 3.01 mmol) in THF (2 mL) was added dropwise at -78 °C and stirred for 30 minutes. Distilled and degassed AcCl (430 μL, 6.02 mmol) was then added to the solution at -78 °C. The solution was warmed to 0 °C and stirred for 1 hour. The reaction was quenched *via* the slow addition of 1 M $HCl_{(aq)}$ (30 mL) and the aqueous was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (3 × 30 mL) and brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude material was then purified by silica gel chromatography (petrol:Et_2O, 50:1) to afford the *title compound* (247 mg, 1.19 mmol, 40%) as a colourless oil.

Colourless oil; **IR** (ATR)/cm^{-1} 2952, 2872, 1755, 1368, 1197, 1128; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.09 (d, *J* = 3.7 Hz, 1H), 1.85–1.78 (m, 1H), 1.61–1.52 (m, 1H), 1.53 (s, 3H), 1.47–1.39 (m, 1H), 1.12–1.06 (m, 1H), 0.95 (s, 3H), 0.87 (s, 3H), 0.73 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.3, 149.7, 125.3, 55.5, 55.0, 54.2, 32.9, 25.2, 20.6, 19.8, 19.5, 11.1, 10.3; **LRMS** (GCMS-EI) *m/z* 208.1 $[M]^+$; **HRMS** (NSI) calculated for $C_{13}H_{21}O_2$ $[M+H]^+$ 209.1536, found 209.1530.

3.2.4 Reaction Scope and Limitations

3.2.4.1 Substrate Synthesis

3.2.4.1.1 Methyl(*o*-tolyl)sulfane 379[148]

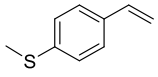


2-Methylbenzenethiol **385** (1.20 mL, 10.0 mmol) was added to solution of NaOH (600 mg, 15.0 mmol) in EtOH (12 mL) and the reaction was stirred at rt for 30 minutes. MeI (0.93 mL, 15.0 mmol) was added dropwise and the resulting solution was stirred at rt for 3 hours. Ice-cold water (50 mL) was added and the aqueous was extracted with

CH_2Cl_2 (3 × 30 mL). The combined organics were washed with brine (3 × 30 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to afford the *title compound* (968 mg, 7.01 mmol, 70%) as a clear oil.

Clear oil; **IR** (ATR)/cm^{-1}: 3055, 3007, 2972, 2916, 1469; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24–7.14 (m, 3H), 7.08 (t, *J* = 7.1 Hz, 1H), 2.48 (s, 3H), 2.36 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.8, 135.9, 129.9, 126.6, 124.8, 124.7, 20.1, 15.4; **LRMS** (LCMS-ESI) *m/z* 138.1 $[M]^+$. Spectroscopic data matches literature.

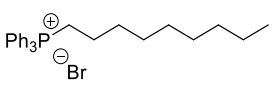
3.2.4.1.2 Methyl(4-vinylphenyl)sulfane 380[149]



n-BuLi solution (2.38 M in hexanes, 5.00 mL, 12.0 mmol) was added dropwise to a suspension of methyltriphenylphosphonium bromide (4.00 g, 11.2 mmol) in THF (25 mL) at 0 °C. The resulting solution was stirred at 0 °C for 30 minutes. 4-Methylthiobenzaldehyde **386** (1.33 mL, 10 mmol) was then added to the now orange solution dropwise at 0 °C causing the formation of a yellow precipitate. The reaction was warmed to room temperature and stirred for 16 hours. The reaction was quenched with saturated $NH_4Cl_{(aq)}$ (25 mL) and the aqueous was extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude material was purified by silica gel chromatography (petrol (30–40 °C)) to afford the *title compound* (1.04 g, 6.90 mmol, 69%) as a glassy solid that melted under the influence of body heat at room temperature.

Glassy solid; **MP** <30 °C; **IR** (ATR)/cm^{-1} 3075, 2986, 2922, 1495; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.31 (m, 2H), 7.23–7.20 (m, 2H), 6.67 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.71 (dd, *J* = 17.6, 0.9 Hz, 1H), 5.21 (dd, *J* = 10.9, 0.8 Hz, 1H), 2.49 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.1, 136.3, 134.7, 126.8, 113.4, 16.0; **LRMS** (GCMS-EI) *m/z* 150.0 $[M]^+$. Spectroscopic data matches literature.

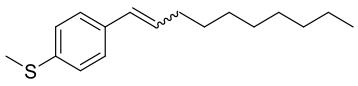
3.2.4.1.3 Nonyltriphenylphosphonium bromide 388



1-Bromononane **387** (5.70 mL, 30 mmol) was added dropwise to a solution of triphenylphosphine (7.86 g, 30 mmol) in toluene (18 mL). The resulting solution was heated to reflux and stirred for 40 hours. The reaction was cooled to room temperature and the solvent was removed *in vacuo*. The residue was dissolved in MeOH (40 mL) and washed with with hexane (3 × 30 mL). The solvent was removed *in vacuo* and the residue dried at 1.5 torr for 24 hours to afford the *title compound* as a highly viscous, colourless oil (12.5 g, 26.7 mmol, 85%).

Colourless oil; **IR** (ATR)/cm^{-1} 2924, 2855, 1439, 1115; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78–7.69 (m, 9H), 7.67–7.60 (m, 6H), 3.66–3.54 (m, 2H), 1.61–1.48 (m, 4H), 1.22–1.05 (m, 10H), 0.74 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.0 (d, *J* = 3 Hz), 133.5 (d, *J* = 10 Hz), 130.5 (d, *J* = 13 Hz), 118.2 (d, *J* = 85 Hz), 31.6, 30.4, 30.3, 29.1, 29.0, 23.0, 22.5, 22.5, 14.0; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 24.1; **LRMS** (GCMS-EI) *m/z* 483.8 $[M+CH_3]^+$; **HRMS** (NSI) calculated for $C_{27}H_{34}P$ $[M\text{-}Br]^+$ 389.2393, found 389.2396.

3.2.4.1.4 (4-(Dec-1-en-1-yl)phenyl)(methyl)sulfane 381



n-BuLi solution (2.38 M in hexanes, 5.5 mL, 13 mmol) was added dropwise to a solution of nonyltriphenylphosphonium bromide **388** (5.53 g, 11.8 mmol) in THF (25 mL) at 0 °C under N_2. The solution was stirred at 0 °C for 30 minutes. 4-Methylthiobenzaldehyde **386** (1.33 mL, 10 mmol) was added dropwise, the resulting solution was warmed to room temperature and stirred for 16 hours. The solution was then heated to 40 °C and stirred for 6 hours. The reaction was quenched by the addition of saturated $NH_4Cl_{(aq)}$ (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude material was then purified by silica gel chromatography (petrol) to afford the *title compound* (1.62 g, 6.19 mmol, 62%) as a colourless oil which was a 1:1 mixture of *cis*:*trans* alkenes.

44 mg of the *cis* alkene (colourless oil) and 342 mg of the *trans* alkene (colourless waxy solid) were separated for characterisation purposes.

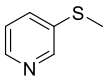
Data for the *cis* alkene:

Colourless oil; **IR** (ATR)/cm^{-1} 2949, 2916, 2843, 1465; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24–7.19 (m, 4H), 6.34 (dt, *J* = 11.6, 1.7 Hz, 1H), 5.64 (dt, *J* = 11.7, 7.3 Hz, 1H), 2.49 (s, 3H), 2.31 (ddd, *J* = 14.9, 7.4, 1.8 Hz, 2H), 1.49–1.40 (m, 2H), 1.35–1.21 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.5, 135.0, 133.3, 129.4, 128.2, 126.6, 32.0, 30.1, 29.6, 29.5, 29.4, 28.9, 22.8, 16.1, 14.3; **LRMS** (GCMS-EI) *m/z* 262.1 $[M]^+$; **HRMS** (ASAP) calculated for $C_{17}H_{27}S$ $[M+H]^+$ 283.1833, found 283.1837.

Data for the *trans* alkene:

Colourless waxy solid; **IR** (ATR)/cm^{-1} 2949, 2916, 2843, 1465; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28–7.24 (m, 2H), 7.21–7.17 (m, 2H), 6.32 (d, *J* = 15.8 Hz, 1H), 6.19 (dt, *J* = 15.8, 6.8 Hz, 1H), 2.47 (s, 3H), 2.23–2.14 (m, 2H), 1.50–1.42 (m, 2H), 1.35–1.24 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.6, 135.3, 131.0, 129.2, 127.1, 126.48, 33.2, 32.0, 29.6, 29.5, 29.4, 29.4, 22.8, 16.3, 14.2; **LRMS** (GCMS-EI) *m/z* 262.1 $[M]^+$; **HRMS** (ASAP) calculated for $C_{17}H_{27}S$ $[M+H]^+$ 283.1833, found 283.1834.

3.2.4.1.5 3-(Methylthio)pyridine 382[150]

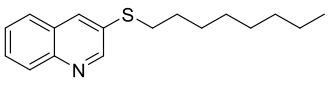


t-BuLi solution (1.52 M in pentane, 13.5 mL, 20.0 mmol) was added dropwise to THF (30 mL) at -95 °C under N_2. A solution of 3-bromopyridine **389** (960 μL, 10.0 mmol) in THF (5 mL) was added dropwise and the resulting solution was stirred at -95 °C for 30 minutes. Dimethyldisulfide (2.20 mL, 25 mmol) was then added dropwise and the solution was stirred at -95 °C for a further hour. The reaction was warmed to -20 °C and H_2O (20 mL) was added dropwise. The solution was then warmed to room temperature and extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried with $MgSO_4$ and filtered. The solvents were removed *in vacuo* and the crude material was purified by silica gel chromatography (petrol:EtOAc, 5:1) to afford the *title compound* (971 mg, 7.76 mmol, 78%) as a colourless oil.

Colourless oil; **IR** (ATR)/cm^{-1} 3036, 2989, 2922, 1562, 1470, 1405, 1111, 1020; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 2.1 Hz, 1H), 8.37 (dd, *J* = 4.7, 1.3, 1H), 7.56 (ddd, *J* = 8.0, 2.4, 1.6, 1H), 7.20 (ddd, *J* = 8.0, 4.8, 0.7, 1H), 2.50 (s, 3H); **^{13}C NMR**

(101 MHz, $CDCl_3$) δ 148.1, 146.4, 135.6, 134.5, 123.6, 16.0; **LRMS** (LCMS-ESI) *m/z* 126.1 $[M+H]^+$; **HRMS** (ASAP) calculated for C_6H_8NS $[M+H]^+$ 126.0377, found 126.0374. Spectroscopic data matches literature.

3.2.4.1.6 3-(Octylthio)quinoline 383[124]

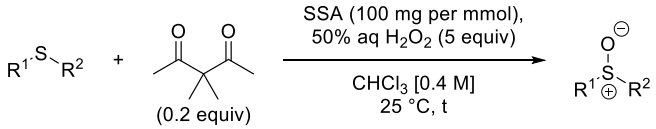


3-Bromoquinoline **390** (1.36 mL, 10.0 mmol), DIPEA (1.91 mL, 11.0 mmol) and then 1-octanethiol (1.73 mL, 10.0 mmol) were added to a solution of $Pd_2(dba)_3$ (92 mg, 0.10 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (111 mg, 0.20 mmol) in anhydrous, degassed PhMe (10 mL) under N_2. The resulting solution was heated to reflux and stirred for 3 hours. The reaction was cooled to room temperature and quenched by the addition of H_2O (30 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvents were removed *in vacuo* and the crude material was purified by silica gel chromatography (petrol:EtOAc, 9:1) and recrystalisation in ice-cold MeOH to afford the *title compound* (1.90 g, 6.95 mmol, 70%) as an amorphous solid.

Amorphous solid; **IR** (ATR)/cm^{-1} 2945, 2919, 2852, 1582; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 2.3 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 2.2 Hz, 1H), 7.73 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.68–7.63 (m, 1H), 7.56–7.51 (m, 1H), 3.02 (t, *J* = 7.3 Hz, 2H), 1.75–1.64 (m, 2H), 1.50–1.40 (m, 2H), 1.33–1.21 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.7, 146.4, 134.7, 131.3, 129.5, 129.1, 128.4, 127.3, 127.0, 34.0, 31.9, 29.3, 29.2, 28.9, 22.8, 14.2; **LRMS** (LCMS-ESI) *m/z* 274.1 $[M+H]^+$. Spectroscopic data matches literature.

3.2.4.2 Substrate Scope

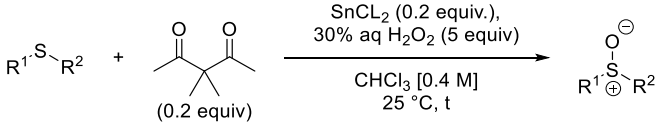
3.2.4.2.1 General Procedure D: Organocatalytic Sulfoxidation with SSA



$H_2O_{2(aq)}$ (50%, 285 µL, 5.00 mmol, 5 equiv) was added to a solution of sulfide (1.00 mmol, 1 equiv), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol, 02 equiv) and

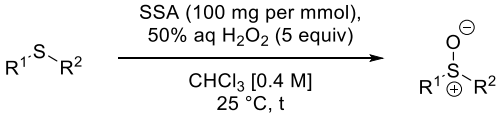
SSA (100 mg) in $CHCl_3$ (2.5 mL). The resulting biphasic solution was stirred at 25 °C for the required time as indicated by TLC or HPLC. The reaction was filtered into saturated $Na_2S_2O_{5(aq)}$ (2 mL) and H_2O (10 mL) and the filtrand was washed with EtOAc (3 × 5 mL). The layers were separated and the aqueous was extracted with EtOAc (2 × 15 mL). The combined organics were then washed with brine (10 mL), dried with $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude material was then purified by silica gel chromatography (petrol:EtOAc) to obtain the target products. All oxidations were run in duplicate and presented results are an average of 2 runs.

3.2.4.2.2 General Procedure E: Organocatalytic Sulfoxidation with $SnCl_2$



$H_2O_{2(aq)}$ (30%, 500 µL, 5.00 mmol, 5 equiv.) was added to a solution of sulfide (1.00 mmol, 1 equiv.), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol, 0.2 equiv.) and $SnCl_2$ (38 mg, 0.20 mmol, 0.2 equiv.) in $CHCl_3$ (2.5 mL). The resulting biphasic solution was stirred at 25 °C for the required time as indicated by TLC or HPLC. The reaction was filtered into saturated $Na_2S_2O_{5(aq)}$ (2 mL) and H_2O (10 mL) and the filtrand was washed with EtOAc (3 × 5 mL). The layers were separated and the aqueous was extracted with EtOAc (2 × 15 mL). The combined organics were then washed with brine (10 mL), dried with $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude material was then purified by silica gel chromatography (petrol:EtOAc) to obtain the target products. All oxidations were run in duplicate and presented results are an average of 2 runs.

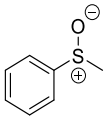
3.2.4.2.3 General Procedure F: Organocatalytic Sulfoxidation Without Ketone



$H_2O_{2(aq)}$ (50%, 285 µL, 5.00 mmol, 5 equiv) was added to a solution of sulfide (1.00 mmol, 1 equiv) and 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol, 0.2 equiv) in $CHCl_3$ (2.5 mL). The resulting biphasic solution was stirred at 25 °C for the required time as indicated by TLC or HPLC. The reaction was filtered into saturated $Na_2S_2O_{5(aq)}$

(2 mL) and H_2O (10 mL) and the filtrand was washed with EtOAc (3 × 5 mL). The layers were separated and the aqueous was extracted with EtOAc (2 × 15 mL). The combined organics were then washed with brine (10 mL), dried with $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude material was then purified by silica gel chromatography (petrol:EtOAc) to obtain the target products.

3.2.4.2.3.1 (Methylsulfinyl)benzene 394[151]

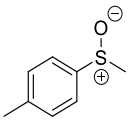


The reaction of thioanisole (117 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 4 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (**Run 1**: 139 mg, 0.99 mmol, 99%, **Run 2**: 136 mg, 0.97 mmol, 97%, **Average Yield**: 98%) as a yellow oil.

The reaction of thioanisole (117 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), $SnCl_2$ (38 mg, 0.20 mmol) and $H_2O_{2(aq)}$ (30% aq, 500 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 6 hours according to **General Procedure E**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (**Run 1**: 96 mg, 0.69 mmol, 69%, **Run 2**: 101 mg, 0.72 mmol, 72%, **Average Yield**: 71%) as a yellow oil.

Yellow oil; **IR** (ATR)/cm^{-1} 3055, 2997, 1444, 1035; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67–7.62 (m, 2H), 7.56–7.47 (m, 3H), 2.72 (s, 3H).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.8, 131.2, 129.5, 123.6, 44.0; **LRMS** (GCMS-CI) *m/z* 140.9 $[M+H]^+$. Spectroscopic data matches literature.

3.2.4.2.3.2 1-Methyl-4-(methylsulfinyl)benzene 318[152]



The reaction of methyl(*p*-tolyl)sulfane (135 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00

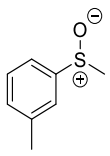
mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 2.5 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (**Run 1**: 152 mg, 0.99 mmol, 99%, **Run 2**: 153 mg, 0.99 mmol, 99%, **Average Yield**: 99%) as an orange oil which crystalised to a yellow solid upon cooling.

The reaction of methyl(*p*-tolyl)sulfane (135 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), $SnCl_2$ (38 mg, 0.2 mmol) and $H_2O_{2(aq)}$ (30% aq, 500 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 6 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (**Run 1**: 150 mg, 0.97 mmol, 97%, **Run 2**: 138 mg, 0.91 mmol, 91%, **Average Yield**: 94%) as an orange oil which crystalised to a yellow solid upon cooling.

The reaction of methyl(*p*-tolyl)sulfane (135 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione (26 µL, 0.20 mmol), and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 2.5 hours according to **General Procedure F**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (15 mg, 0.10 mmol, 10%,) as an orange oil which crystalised to a yellow solid upon cooling.

Yellow solid; **MP** 40–42 °C [Lit = 52–54 °C] **IR** (ATR)/cm^{-1} 2991, 2922, 1496, 1040; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.70 (s, 3H), 2.41 (s, 3H).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.7, 141.6, 130.2, 123.7, 44.1, 21.5; **LRMS** (GCMS-CI) *m/z* 154.9 $[M+H]^+$. Spectroscopic data matches literature.

3.2.4.2.3.3 1-Methyl-3-(methylsulfinyl)benzene 395



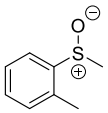
The reaction of methyl(*m*-tolyl)sulfane (138 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 4 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to

give the *title compound* (**Run 1**: 152 mg, 0.99 mmol, 99%, **Run 2**: 144 mg, 0.94 mmol, 94%, **Average Yield**: 97%) as a colourless oil.

The reaction of methyl(*m*-tolyl)sulfane (138 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), $SnCl_2$ (38 mg, 0.2 mmol) and $H_2O_{2(aq)}$ (30% aq, 500 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 8 hours according to **General Procedure E**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (**Run 1**: 132 mg, 0.86 mmol, 86%, **Run 2**: 122 mg, 0.80 mmol, 80%, **Average Yield**: 83%) as a colourless oil.

Colourless oil; **IR** (ATR)/cm^{-1} 2993, 2921, 1415, 1042; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.40 (app d, *J* = 5.1 Hz, 2H), 7.32–7.28 (m, 1H), 2.71 (s, 3H), 2.43 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.6, 139.8, 132.0, 129.3, 123.9, 120.7, 44.1, 21.6; **LRMS** (GCMS-CI) *m/z* 154.9 $[M+H]^+$; **HRMS** (ASAP) calculated for $C_8H_{11}OS$ $[M+H]^+$ 155.0531, found 155.0532.

3.2.4.2.3.4 1-Methyl-2-(methylsulfinyl)benzene 396



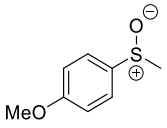
The reaction of methyl(*o*-tolyl)sulfane (138 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 6 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (**Run 1**: 139 mg, 0.90 mmol, 90%, **Run 2**: 137 mg, 0.89 mmol, 89%, **Average Yield**: 90%) as a colourless oil.

The reaction of methyl(*o*-tolyl)sulfane (138 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), $SnCl_2$ (38 mg, 0.2 mmol) and $H_2O_{2(aq)}$ (30% aq, 500 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 9 hours according to **General Procedure E**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (**Run 1**: 141 mg, 0.92 mmol, 92%, **Run 2**: 133 mg, 0.86 mmol, 86%, **Average Yield**: 89%) as a colourless oil.

Colourless oil; **IR** (ATR)/cm^{-1} 3051, 2978, 1474, 1035; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.45 (app td, *J* = 7.6, 0.8 Hz, 1H), 7.39 (td, *J* = 7.4,

1.5 Hz, 1H), 7.20 (app d, *J* = 7.4 Hz, 1H), 2.68 (s, 3H), 2.37 (s, 3H).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.0, 134.1, 130.9, 130.8, 127.6, 123.1, 42.2, 18.2; **LRMS** (GCMS-CI) *m/z* 154.9 $[M+H]^+$; **HRMS** (ASAP) calculated for $C_8H_{11}OS$ $[M+H]^+$ 155.0531, found 155.0532.

3.2.4.2.3.5 1-Methyl-4-(methylsulfinyl)benzene 397[153]

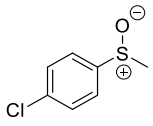


The reaction of (4-methoxyphenyl)(methyl)sulfane (154 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 2 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (EtOAc) to give the *title compound* (**Run 1**: 165 mg, 0.97 mmol, 97%, **Run 2**: 161 mg, 0.95 mmol, 95%, **Average Yield**: 96%) as a colourless solid.

The reaction of (4-methoxyphenyl)(methyl)sulfane (154 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), $SnCl_2$ (38 mg, 0.2 mmol) and $H_2O_{2(aq)}$ (30% aq, 500 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 4 hours according to **General Procedure E**. The crude material was purified by silica gel chromatography (EtOAc) to give the *title compound* (**Run 1**: 149 mg, 0.89 mmol, 89%, **Run 2**: 147 mg, 0.86 mmol, 86%, **Average Yield**: 88%) as a colourless solid.

Colourless solid; **MP** 47–49 °C [Lit = 43–47 °C]; **IR** (ATR)/cm^{-1} 2989, 2958, 1249, 1022; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (dt, *J* = 8.9, 2.9 Hz, 2H), 7.03 (dt, *J* = 8.9, 2.9 Hz, 2H), 3.86 (s, 3H), 2.70 (s, 3H). ; **^{13}C NMR** 13C NMR (101 MHz, $CDCl_3$) δ 162.1, 136.8, 125.6, 115.0, 55.7, 44.2; **LRMS** (GCMS-CI) *m/*z 171.0 $[M+H]^+$. Spectroscopic data matches literature.

3.2.4.2.3.6 1-Chloro-4-(methylsulfinyl)benzene 398[153]



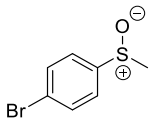
The reaction of (4-chlorophenyl)(methyl)sulfane (130 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50%

aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 7 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (**Run 1**: 164 mg, 0.94 mmol, 94%, **Run 2**: 165 mg, 0.95 mmol, 95%, **Average Yield**: 95%) as a colourless oil.

The reaction of (4-chlorophenyl)(methyl)sulfane (130 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), $SnCl_2$ (38 mg, 0.2 mmol) and $H_2O_{2(aq)}$ (30% aq, 500 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 8 hours according to **General Procedure E**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (**Run 1**: 148 mg, 0.85 mmol, 85%, **Run 2**: 136 mg, 0.78 mmol, 78%, **Average Yield**: 75%) as a colourless oil.

Colourless oil; **IR** (ATR)/cm^{-1} 3081, 2913, 1478, 1040, 742; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (dt, *J* = 8.9, 2.3 Hz, 2H), 7.51 (dt, *J* = 8.9, 2.2 Hz, 2H), 2.72 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.4, 137.4, 129.8, 125.1, 44.2; **LRMS** (GCMS-CI) *m/z* 174.9 $[M+H]^+$.Spectroscopic data matches literature.

3.2.4.2.3.7 1-Bromo-4-(methylsulfinyl)benzene 399

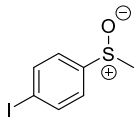


The reaction of (4-bromophenyl)(methyl)sulfane (203 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 7 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (**Run 1**: 188 mg, 0.86 mmol, 86%, **Run 2**: 180 mg, 0.83 mmol, 83%, **Average Yield**: 85%) as a colourless solid.

The reaction of (4-bromophenyl)(methyl)sulfane (203 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), $SnCl_2$ (38 mg, 0.2 mmol) and $H_2O_{2(aq)}$ (30% aq, 500 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 16 hours according to **General Procedure E**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (**Run 1**: 179 mg, 0.82

mmol, 82%, **Run 2**: 187 mg, 0.86 mmol, 86%, **Average Yield**: 84%) as a colourless solid.

Colourless solid; **MP** 89–91 °C; **IR** (ATR)/cm^{-1} 2989, 2911, 1422, 1038, 817; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (dt, *J* = 8.9, 2.3 Hz, 2H), 7.52 (dt, *J* = 9.0, 2.2 Hz, 2H), 2.72 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.1, 132.7, 125.6, 125.3, 44.1.; **LRMS** (GCMS-CI) *m/z* 218.9 [M(Br^{79})+H]; **HRMS** (ASAP) calculated for $C_7H_8OS(Br^{79})$ $[M+H]^+$ 218.9475, found 218.9479.**1-Iodo-4-(methylsulfinyl)benzene 400**

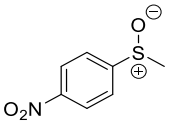


The reaction of (4-iodophenyl)(methyl)sulfane (250 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 7 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (**Run 1**: 230 mg, 0.86 mmol, 86%, **Run 2**: 231 mg, 0.87 mmol, 87%, **Average Yield**: 87%) as a colourless solid.

The reaction of (4-iodophenyl)(methyl)sulfane (250 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), $SnCl_2$ (38 mg, 0.2 mmol) and $H_2O_{2(aq)}$ (30% aq, 500 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 16 hours according to **General Procedure E**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (**Run 1**: 191 mg, 0.72 mmol, 72%, **Run 2**: 191 mg, 0.72 mmol, 72%, **Average Yield**: 72%) as a colourless solid.

Colourless soild; **MP** 117–119 °C; **IR** (ATR)/cm^{-1} 2989, 2911, 1422, 1033, 811; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (dt, *J* = 8.8, 2.1 Hz, 2H), 7.39 (dt, *J* = 8.8, 2.2 Hz, 2H), 2.71 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.9, 138.6, 125.3, 97.5, 44.1; **LRMS** (GCMS-CI) *m/z* 266.9 $[M+H]^+$; **HRMS** (ASAP) calculated for C_7H_8OSI $[M+H]^+$ 266.9341, found 266.9344.

3.2.4.2.3.9 1-(Methylsulfinyl)-4-nitrobenzene 401[151]

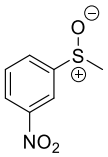


The reaction of methyl(4-nitrophenyl)sulfane (169 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 48 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (EtOAc) to give the *title compound* (**Run 1**: 147 mg, 0.79 mmol, 79%, **Run 2**: 142 mg, 0.76 mmol, 76%, **Average Yield**: 78%) as an off-white solid.

The reaction of methyl(4-nitrophenyl)sulfane (169 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), $SnCl_2$ (38 mg, 0.2 mmol) and $H_2O_{2(aq)}$ (30% aq, 500 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 48 hours according to **General Procedure E**. The crude material was purified by silica gel chromatography (EtOAc) to give the *title compound* (**Run 1**: 115 mg, 0.62 mmol, 62%, **Run 2**: 102 mg, 0.55 mmol, 55%, **Average Yield**: 59%) as an off-white solid.

Off-white solid; **MP** 156–158 °C [Lit = 153–155°C]; **IR** (ATR)/cm^{-1} 3101, 2922, 1517, 1342, 1048; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.40 (dt, *J* = 9.1, 2.2 Hz, 2H), 7.84 (dt, *J* = 9.1, 2.3 Hz, 2H), 2.79 (s, 3H).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.4, 149.7, 124.8, 124.6, 44.0.; **LRMS** (GCMS-CI) *m/z* 185.9 $[M+H]^+$.Spectroscopic data matches literature.

3.2.4.2.3.10 1-(Methylsulfinyl)-3-nitrobenzene 402

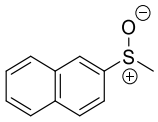


The reaction of methyl(3-nitrophenyl)sulfane (169 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 30 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (EtOAc) to give the *title compound* (**Run 1**: 154 mg, 0.83 mmol, 83%, **Run 2**: 153 mg, 0.83 mmol, 83%, **Average Yield**: 83%) as a pale yellow solid.

The reaction of methyl(3-nitrophenyl)sulfane (169 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), $SnCl_2$ (38 mg, 0.2 mmol) and $H_2O_{2(aq)}$ (30% aq, 500 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 40 hours according to **General Procedure E**. The crude material was purified by silica gel chromatography (EtOAc) to give the *title compound* (**Run 1**: 137 mg, 0.74 mmol, 74%, **Run 2**: 125 mg, 0.68 mmol, 68%, **Average Yield**: 71%) as a pale yellow solid.

Pale yellow solid; **MP** 122–124 °C; **IR** (ATR)/cm^{-1} 3094, 2922, 1521, 1348, 1072; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.49 (app t, *J* = 1.9 Hz, 1H), 8.36 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H), 8.01 (ddd, *J* = 7.8, 1.5, 1.1 Hz, 1H), 7.76 (t, *J* = 7.9 Hz, 1H), 2.80 (s, 3H).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.9, 148.8, 130., 129.41, 125.9, 119.1, 44.2.; **LRMS** (GCMS-CI) *m/z* 185.9 $[M+H]^+$; **HRMS** (ASAP) calculated for $C_78_7NO_3S$ $[M+H]^+$ 186.0225, found 186.0222.

3.2.4.2.3.11 1-Methyl-4-(methylsulfinyl)benzene 403[153]



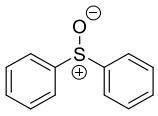
The reaction of methyl(naphthalen-2-yl)sulfide (174 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 6 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (**Run 1**: 170 mg, 0.89 mmol, 89%, **Run 2**: 182 mg, 0.96 mmol, 96%, **Average Yield**: 93%) as a colourless solid.

The reaction of methyl(naphthalen-2-yl)sulfide (174 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), $SnCl_2$ (38 mg, 0.2 mmol) and $H_2O_{2(aq)}$ (30% aq, 500 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 8 hours according to **General Procedure E**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (**Run 1**: 154 mg, 0.81 mmol, 81%, **Run 2**: 168 mg, 0.88 mmol, 88%, **Average Yield**: 85%) as a colourless solid.

Colourless solid; **MP** 113–115 °C [Lit = 92–99 °C]; **IR** (ATR)/cm^{-1} 3058, 2991, 1420, 1035; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 1.4 Hz, 1H), 7.99 (d, *J* = 8.6 Hz,

1H), 7.97–7.89 (m, 2H), 7.63–7.58 (m, 3H), 2.80 (s, 3H).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.9, 134.6, 133.1, 129.8, 128.7, 128.2, 128.0, 127.5, 124.2, 119.6, 44.0; **LRMS** (LCMS-ESI) *m/z* 191.0 $[M+H]^+$. Spectroscopic data matches literature.

3.2.4.2.3.12 Sulfinyldibenzene 404[152]

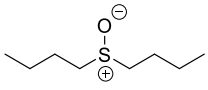


The reaction of diphenylsulfide (165 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 48 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 3:1) to give the *title compound* (**Run 1**: 182 mg, 0.90 mmol, 90%, **Run 2**: 192 mg, 0.95 mmol, 95%, **Average Yield**: 93%) as a colourless solid.

The reaction of diphenylsulfide (165 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), $SnCl_2$ (38 mg, 0.2 mmol) and $H_2O_{2(aq)}$ (30% aq, 500 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 28 hours according to **General Procedure E**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 3:1) to give the *title compound* (**Run 1**: 146 mg, 0.72 mmol, 72%, **Run 2**: 144 mg, 0.71 mmol, 71%, **Average Yield**: 72%) as a colourless solid.

Colourless solid; **MP** 71–73 °C [Lit = 67–68 °C]; **IR** (ATR)/cm^{-1} 3051, 1442, 1024; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68–7.62 (m, 4H), 7.50–7.42 (m, 6H).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.73, 131.21, 129.48, 124.94, 77.16.; **LRMS** (GCMS-CI) *m/z* 203.0 $[M+H]^+$. Spectroscopic data matches literature.

3.2.4.2.3.13 1-(Butylsulfinyl)butane 405[152]



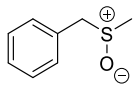
The reaction of di-*n*-butylsulfide (175 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 1 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title*

compound (**Run 1**: 155 mg, 0.96 mmol, 96%, **Run 2**: 154 mg, 0.95 mmol, 95%, **Average Yield**: 96%) as a colourless oil.

The reaction of di-*n*-butylsulfide (175 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), $SnCl_2$ (38 mg, 0.2 mmol) and $H_2O_{2(aq)}$ (30% aq, 500 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 3 hours according to **General Procedure E**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (**Run 1**: 89 mg, 0.55 mmol, 55%, **Run 2**: 84 mg, 0.52 mmol, 52%, **Average Yield**: 54%) as a colourless oil.

Colourless oil; **IR** (ATR)/cm^{-1} 2960, 2932, 1022; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.72–2.57 (m, 4H), 1.80–1.68 (m, 4H), 1.56–1.39 (m, 4H), 0.95 (t, *J* = 7.4 Hz, 6H).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 52.3, 24.7, 22.2, 13.8.; **LRMS** (GCMS-CI) *m/z* 163.0 $[M+H]^+$. Spectroscopic data matches literature.

3.2.4.2.3.14 ((Methylsulfinyl)methyl)benzene 406[153]



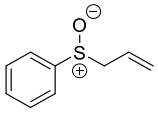
The reaction of benzyl(methyl)sulfane (135 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 2 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (EtOAc) to give the *title compound* (**Run 1**: 120 mg, 0.78 mmol, 78%, **Run 2**: 126 mg, 0.82 mmol, 82%, **Average Yield**: 80%) as a colourless solid.

The reaction of benzyl(methyl)sulfane (135 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), $SnCl_2$ (38 mg, 0.2 mmol) and $H_2O_{2(aq)}$ (30% aq, 500 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 3 hours according to **General Procedure E**. The crude material was purified by silica gel chromatography (EtOAc) to give the *title compound* (**Run 1**: 122 mg, 0.79 mmol, 79%, **Run 2**: 116 mg, 0.75 mmol, 75%, **Average Yield**: 77%) as a colourless solid.

Colourless solid; **MP** 61–63 °C [Lit = 53–59 °C]; **IR** (ATR)/cm^{-1} 3034, 2967, 1498, 1037; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41–7.27 (m, 5H), 4.06 (d, *J* = 12.8 Hz, 1H), 3.92 (d, *J* = 12.8 Hz, 1H), 2.45 (s, 3H).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.3, 130.2,

129.2, 128.6, 60.5, 37.5.; **LRMS** (LCMS-ESI) *m/z* 155.1 $[M+H]^+$.Spectroscopic data matches literature.

3.2.4.2.3.15 (Allylsulfinyl)benzene 407[152]

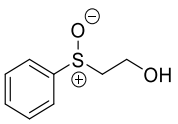


The reaction of allyl(phenyl)sulfane (150 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 4.5 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 3:1) to give the *title compound* (**Run 1**: 141 mg, 0.85 mmol, 85%, **Run 2**: 139 mg, 0.84 mmol, 84%, **Average Yield**: 85%) as a colourless oil.

The reaction of allyl(phenyl)sulfane (150 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), $SnCl_2$ (38 mg, 0.2 mmol) and $H_2O_{2(aq)}$ (30% aq, 500 µL, 5.00 mmol) at 25 °C for 7 hours according to **General Procedure E**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 3:1) to give the *title compound* (**Run 1**: 130 mg, 0.78 mmol, 85%, **Run 2**: 126 mg, 0.76 mmol, 76%, **Average Yield**: 77%) as a colourless oil.

Colourless oil; **IR** (ATR)/cm^{-1} 3055, 2980, 1636, 1446, 1040; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62–7.58 (m, 2H), 7.55–7.47 (m, 3H), 5.65 (ddt, *J* = 17.6, 10.2, 7.5 Hz, 1H), 5.33 (app d, *J* = 10.1, 1H), 5.19 (dq, J = 17.0, 1.2 Hz, 1H), 3.57 (ddq, *J* = 12.8, 7.5, 0.5 Hz, 1H), 3.51 (ddq, *J* = 12.8, 7.5, 0.8 Hz, 1H); **^{13}C NMR** (101 MHz, CDCl3) δ 143.1, 131.2, 129.2, 125.4, 124.5, 124.0, 61.0; **LRMS** (LCMS-ESI) *m/z* 167.0 $[M+H]^+$. Spectroscopic data matches literature.

3.2.4.2.3.16 2-(Phenylsulfinyl)ethan-1-ol 408

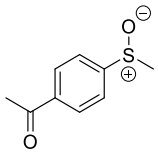


The reaction of of 2-(phenylthio)ethan-1-ol (135 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 2 hours according to **General**

Procedure D. The crude material was purified by silica gel chromatography (EtOAc) to give the *title compound* (**Run 1**: 74 mg, 0.44 mmol, 44%, **Run 2**: 84 mg, 0.49 mmol, 49%, **Average Yield**: 47%) as a colourless oil.

The reaction of of 2-(phenylthio)ethan-1-ol (135 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), $SnCl_2$ (38 mg, 0.2 mmol) and $H_2O_{2(aq)}$ (30% aq, 500 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 3 hours according to **General Procedure E**. The crude material was purified by silica gel chromatography (EtOAc) to give the *title compound* (**Run 1**: 68 mg, 0.40 mmol, 40%, **Run 2**: 74 mg, 0.44 mmol, 44%, **Average Yield**: 42%) as a colourless oil.

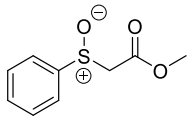
Colourless oil; **IR** (ATR)/cm^{-1} 3341, 2924, 1446, 1020; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67–7.63 (m, 2H), 7.58–7.50 (m, 3H), 4.17 (ddd, *J* = 11.8, 8.7, 2.9 Hz, 1H), 4.04 (ddd, *J* = 12.3, 5.4, 3.9 Hz, 1H), 3.27 (bs, 1H), 3.19 (ddd, *J* = 13.6, 8.7, 3.8 Hz, 1H), 2.87 (ddd, *J* = 13.6, 5.7, 3.0 Hz, 1H).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.1, 131.4, 129.6, 124.1, 57.9, 57.5; **LRMS** (LCMS-ESI) *m/z* 171.0 $[M+H]^+$. **1-(4-(Methylsulfinyl)phenyl)ethan-1-one 409**



The reaction of 1-(4-(methylthio)phenyl)ethan-1-one (166 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 7 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (EtOAc) to give the *title compound* (**Run 1**: 148 mg, 0.81 mmol, 81%, **Run 2**: 150 mg, 0.82 mmol, 82%, **Average Yield**: 82%) as a white solid.

White solid; **MP** 114–116 °C; **IR** (ATR)/cm^{-1} 2986, 2919, 2850, 1671, 1266, 1046; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13–8.09 (dt, *J* = 8.6, 1.8 Hz, 2H), 7.76–7.72 (dt, *J* = 8.6, 1.7 Hz, 2H), 2.76 (s, 3H), 2.65 (s, 3H).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 197.1, 151.1, 139.2, 129.3, 123.9, 44.0, 26.9; **LRMS** (GCMS-EI) *m/z* 182.1 $[M+H]^+$; **HRMS** (ASAP) calculated for $C_9H_{11}O_2S$ $[M+H]^+$ 183.0480, found 183.0476.

3.2.4.2.3.18 Methyl 2-(phenylsulfinyl)acetate 410

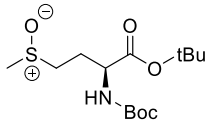


The reaction of methyl 2-(phenylthio)acetate (155 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 32 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (**Run 1**: 190 mg, 0.96 mmol, 96%, **Run 2**: 183 mg, 0.92 mmol, 92%, **Average Yield**: 94%) as a colourless oil.

The reaction of methyl 2-(phenylthio)acetate (155 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), $SnCl_2$ (38 mg, 0.2 mmol) and $H_2O_{2(aq)}$ (30% aq, 500 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 24 hours according to **General Procedure E**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (**Run 1**: 147 mg, 0.74 mmol, 74%, **Run 2**: 161 mg, 0.81 mmol, 81%, **Average Yield**: 78%) as a colourless oil.

Colourless oil; **IR** (ATR)/cm^{-1} 3058, 2954, 1733, 1437, 1264, 1046; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71–7.66 (m, 2H), 7.57–7.52 (m, 2H), 3.85 (d, *J* = 13.7 Hz, 1H), 3.71 (s, 3H), 3.67 (d, *J* = 13.7 Hz, 1H).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.3, 143.2, 132.0, 129.6, 124.3, 61.8, 52.9; **LRMS** (GCMS-CI) *m/z* 198.9 $[M+H]^+$.

3.2.4.2.3.19 *t*-Butyl(*2S*)-2-((*t*-butoxycarbonyl)amino)-4-(methylsulfinyl)butanoate 411

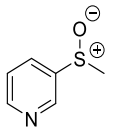


The reaction of *t*-butyl(*t*-butoxycarbonyl)-*L*-methioninate (305 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 2 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (EtOAc) to give the *title compound* (**Run 1**: 285 mg, 0.89 mmol, 89%, **Run 2**: 294 mg, 0.92

mmol, 92%, **Average Yield**: 91%) as a viscous yellow oil which was a 1:1 mixture of diastereomers.

Viscous yellow oil; all data is reported as a 1:1 mixture of diastereomers; **IR** (ATR)/cm^{-1} 3253, 2973, 2926, 1708, 1366, 1151, 1020; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.31–5.15 (m, 1H), 4.36–4.20 (m, 1H), 2.85–2.64 (m, 2H), 2.57 (app d, J = 2.0 Hz, 3H), 2.38–2.25 (m, 1H), 2.10–1.98 (m, 1H), 1.47 (app d, J = 1.2 Hz, 9H), 1.44 (s, 9H).; **^{13}C NMR** (101 MHz, $CDCl_3$) some signals split as a result of 1:1 mixture of diastereomers δ 170.8, 155.6, 83.0, 82.9, 80.2, 53.4, 53.0, 51.0, 50.7, 38.9, 38.8, 28.4, 28.1, 26.4; **LRMS** (LCMS-ESI) *m/z* 344.0 $[M+Na]^+$.

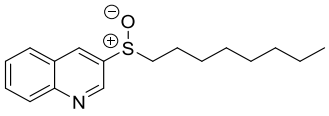
3.2.4.2.3.20 3-(Methylsulfinyl)pyridine 412[154]



The reaction of 3-(methylthio)pyridine (125 mg, 1.00 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 2.5 hours according to **General Procedure F**. The crude material was purified by silica gel chromatography (3% MeOHin CH_2Cl_2) to give the *title compound* (58 mg, 0.41 mmol, 41%) as a yellow oil.

Yellow oil; **IR** (ATR)/cm^{-1} 3043, 2999, 2915, 1575, 1413; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 1.3 Hz, 1H), 8.74 (d, *J* = 3.8 Hz, 1H), 8.08 (app dt, *J* = 8.0, 1.8 Hz, 1H), 7.50 (ddd, *J* = 8.0, 4.8, 0.6 Hz, 1H), 2.79 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.2, 145.5, 142.4, 131.7, 124.5, 44.1; **LRMS** (LCMS-ESI) *m/z* 143.0 $[M+H]^+$. Spectroscopic data matches literature.

3.2.4.2.3.21 3-(octylsulfinyl)quinoline 413



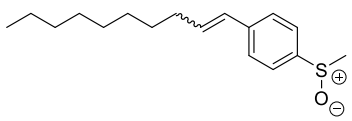
The reaction of 3-(octylthio)quinoline (273 mg, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 2 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 3:1) to

give the *title compound* (**Run 1**: 213 mg, 0.74 mmol, 74%, **Run 2**: 220 mg, 0.76 mmol, 76%, **Average Yield**: 75%) as a yellow oil.

The reaction of 3-(octylthio)quinoline (273 mg, 1.00 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 2 hours according to **General Procedure F**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 3:1) to give the *title compound* (230 mg, 0.79 mmol, 79%) as a yellow oil.

Yellow oil; **IR** (ATR)/cm^{-1} 2947, 2916, 2847, 1497; **^{1}H NMR** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, *J* = 2.2 Hz, 1H), 8.56 (d, *J* = 2.1 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.87–7.79 (m, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 3.03–2.84 (m, 2H), 1.92–1.76 (m, 1H), 1.76–1.57 (m, 1H), 1.55–1.36 (m, 2H), 1.34–1.13 (m, 8H), 0.86 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.2, 145.1, 137.6, 133.3, 131.4, 129.8, 128.5, 128.1, 127.6, 57.3, 31.8, 29.2, 29.1, 28.8, 22.7, 22.1, 14.2; **LRMS** (LCMS-ESI) *m/z* 291.0 $[M+H]^+$; **HRMS** (ASAP) calculated for $C_{17}H_{24}NOS$ $[M+H]^+$ 290.1573, found 290.1574.

3.2.4.2.3.22 1-(Dec-1-en-1-yl)-4-(methylsulfinyl)benzene 415

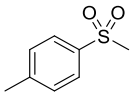


The reaction of (4-(dec-1-en-1-yl)phenyl)(methyl)sulfane (262 mg, 1 mmol, 1:1 mixture of *E*:*Z*), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 4 hours according to **General Procedure D**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 2:1) to give the *title compound* (**Run 1** 226 mg, 0.81 mmol, 81%, **Run 2**: 243 mg, 0.87 mmol, 87%, **Average Yield**: 84%) as a viscous yellow oil which was a 1:1 mixture of diastereomers.

Viscous yellow oil; **^{1}H NMR** (600 MHz, $CDCl_3$, mixture of diastereomers) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 6.43–6.39 (m, 2H), 6.34 (dt, *J* = 15.8, 6.6 Hz, 1H), 5.77 (dt, *J* = 11.7, 7.3 Hz, 1H), 2.73 (s, 3H), 2.71 (s, 3H), 2.31 (qd, *J* = 7.5, 1.7 Hz, 2H), 2.23 (q, *J* = 6.8 Hz, 2H), 1.50–1.43 (m, 4H), 1.37–1.21 (m, 20H), 0.89–0.86 (m, 4H); **^{13}C NMR** (151 MHz,

$CDCl_3$) δ 143.7, 143.5, 141.2, 141.0, 135.6, 134.1, 129.7, 128.7, 127.7, 126.9, 124.0, 123.6, 44.1, 44.1, 33.2, 32.0, 32.0, 30.0, 29.6, 29.6, 29.5, 29.4, 29.4, 29.3, 28.9, 22.8, 14.2; **LRMS** (LCMS-ESI) *m/z* 295.0 $[M+NH_4]^+$; **HRMS** (NSI) calculated for $C_{17}H_{27}OS$ $[M+H]^+$ 279.1777, found 279.1775.

3.2.4.2.4 1-Methyl-4-(methylsulfonyl)benzene 319[155]

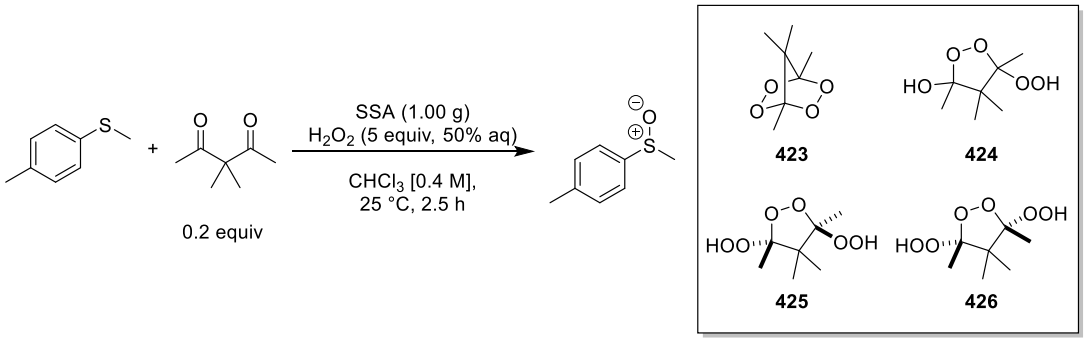


The reaction of methyl(*p*-tolyl)sulfane (135 µL, 1.00 mmol), 3,3-dimethylpentane-2,4-dione **321** (26 µL, 0.20 mmol), SSA (100 mg) and $H_2O_{2(aq)}$ (50% aq, 285 µL, 5.00 mmol) in $CHCl_3$ (2.5 mL) at 25 °C for 7 days according to **General Procedure D**. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:1) to give the *title compound* (145 mg, 0.85 mmol, 85%) as an amorphous solid.

Amorphous solid; **IR** (ATR)/cm^{-1}: 2926, 1286, 1143; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 3.03 (s, 3H), 2.46 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.1, 137.6, 130.1, 127.6, 44.8; **LRMS** (GCMS-CI) *m/z* 171 $[M+H]^+$. Spectroscopic data matches literature.

3.2.5 Mechanistic Insight

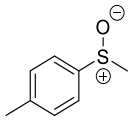
3.2.5.1 Gram synthesis of 1-Methyl-4-(methylsulfinyl)benzene 318 and isolation of reaction intermediates



$H_2O_{2(aq)}$ (50%, 2.85 mL, 50.0 mmol, 5 equiv) was added to a solution of methyl(*p*-tolyl)sulfane **317** (1.35 mL, 10.0 mmol, 1 equiv), 3,3-dimethylpentane-2,4-dione **321** (260 µL, 2.00 mmol, 0.2 equiv) and SSA (1.00 g) in $CHCl_3$ (25 mL). The resulting biphasic solution was stirred at 25 °C for 2.5 hours. The reaction was quenched by

addition of $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude material was immediately purified by silica gel chromatography (petrol:EtOAc, 9:1>5:1>3:1>0:1) to obtain 1-methyl-4-(methylsulfinyl)benzene **317** (1.47 g, 9.55 mmol, 96%), 1,4,7,7-tetramethyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane **423** (36 mg, 0.23 mmol, 11%), 5-hydroperoxy-3,4,4,5-tetramethyl-1,2-dioxolan-3-ol **424** (27 mg, 0.15 mmol, 8%), *rel*-(*3R*,*5R*)-3,5-dihydroperoxy-3,4,4,5-tetramethyl-1,2-dioxolane **425** and *rel*-(3R,5S)-3,5-dihydroperoxy-3,4,4,5-tetramethyl-1,2-dioxolane **426** (144 mg, 0.74 mmol, 37%).

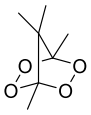
3.2.5.1.1 1-Methyl-4-(methylsulfinyl)benzene 317



Title compound obtained as described above (1.471 g, 9.55 mmol, 96%) as an orange oil which solidified to a yellow solid on standing.

Characterisation previously reported on **Page 216**.

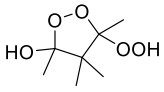
3.2.5.1.2 1,4,7,7-Tetramethyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane 423



Title compound obtained as described above (36 mg, 0.23 mmol, 11%) as a white solid.

White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.42 (s, 6H), 1.19 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 111.9, 56.7, 16.7, 8.2.

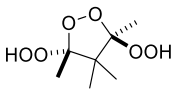
3.2.5.1.3 5-Hydroperoxy-3,4,4,5-tetramethyl-1,2-dioxolan-3-ol 424



Title compound obtained as described above (27 mg, 0.15 mmol, 8%) as a white solid.

White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.46 (bs, 1H), 4.87 (bs, 1H), 1.55 (s, 3H), 1.39 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 114.5, 107.7, 59.0, 27.0, 23.2, 18.5, 16.7, 13.9.

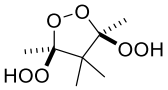
3.2.5.1.4 *rel*-(*3R*,*5R*)-3,5-Dihydroperoxy-3,4,4,5-tetramethyl-1,2-dioxolane 425



Title compound obtained as described above (27 mg, 0.14 mmol, 7%) as a colourless oil.

Colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.40 (bs, 2H), 1.48 (s, 6H), 1.09 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 114.5, 59.1, 19.9, 15.0.

3.2.5.1.5 *rel*-(*3R*,*5S*)-3,5-Dihydroperoxy-3,4,4,5-tetramethyl-1,2-dioxolane 426

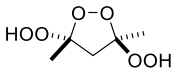


Title compound obtained as described above (144 mg, 0.74 mmol, 37%) as a white solid.

White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.58 (s, 2H), 1.62 (s, 6H), 1.25 (s, 3H), 1.10 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 113.7, 59.9, 24.1, 16.1, 15.0.

3.2.5.2 Synthesis of Tool Compounds

3.2.5.2.1 3,5-Dihydroperoxy-3,5-dimethyl-1,2-dioxolane 314[113c]



$H_2O_{2(aq)}$ (30%, 10.0 mL, 100 mmol) was added to a solution of acetylacetone **313** (2.00 mL, 20 mmol) and SSA (2 g) in MeCN (80 mL) at room temperature. The resulting solution was stirred at room temperature for 18 hours. The reaction was diluted with H_2O (50 mL) and the aqueous was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give the *title compound* as a white solid (2.52 g, 15.2 mmol, 76%).

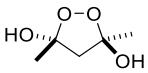
White solid; **MP** 100–102 °C [Lit: 98–100 °C]; **IR** (ATR)/cm^{-1} 3338, 3004, 2952, 1433, 1381, 1165; **^{1}H NMR** (400 MHz, CD_3CN) δ 9.64 (bs, 2H), 2.59 (s, 2H), 1.50 (s, 6H); **^{13}C NMR** (101 MHz, CD3CN) δ 113.1, 52.2, 18.1.; unable to obtain mass spectrometry data for reactive peroxides. Spectroscopic data matches literature.

3.2.5.2.2 1,4-Dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane 433[156]

$H_2O_{2(aq)}$ (50%, 2.85 mL, 50 mmol) was added to a solution of acetylacetone **313** (200 µL, 2 mmol) and SSA (1.00 g) in $CHCl_3$ (25 mL). The resulting biphasic solution was stirred at room temperature for 18 hours. Saturated $Na_2S_2O_{5(aq)}$ (25 mL) was added dropwise at 0 °C. The resulting layers were separated and the aqueous was further extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in* vacuo and the crude material was purified by silica gel chromatography (petrol:EtOAc, 5:1) to afford the *title compound* as a white solid (50 mg, 0.38 mmol, 19%).

White solid; **MP** 121–123 °C [Lit: 123–125 °C]; **IR** (ATR)/cm^{-1} 2956, 2919, 2852, 1467, 1368; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.74 (s, 2H), 1.67 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 110.0, 50.7, 10.8; unable to obtain mass spectrometry data for reactive peroxides. Spectroscopic data matches literature.

3.2.5.2.3 3,5-Dihydroxy-3,5-dimethyl-1,2-dioxolane 432[127]

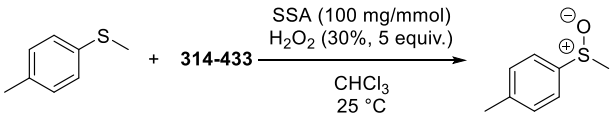


$H_2O_{2(aq)}$ (50%, 0.57 mL, 10.0 mmol) was added every 5 minutes in 0.1 mL portions to acetylacetone **313** (1.00 mL, 10.0 mmol) which was cooled to 0 °C with regular shaking. The vessel was maintained at 0 °C for 4 hours with regular shaking. After warming to rt, the now crystalline material was vacuum dried over P_2O_5 over night giving the *title compound* (1.27 g, 9.62 mmol, 96%) as a white solid.

White solid; **MP** 89–91 °C [Lit: 90–91 °C]; **IR** (ATR)/cm^{-1} 3350, 2931, 2864; **^{1}H NMR** (400 MHz, CD_3CN) δ 2.57 (s, 2H), 2.38 (bs, 2H), 1.46 (s, 6H); **^{13}C NMR** (101 MHz, CD_3CN) δ 106.4, 59.4, 23.3; **LRMS** unable to obtain mass spectrometry data for reactive peroxides. Spectroscopic data matches literature.

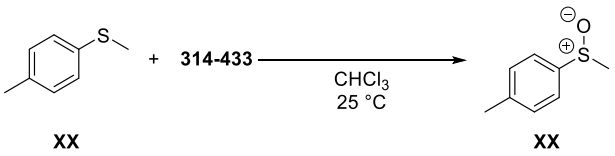
3.2.5.3 HPLC Experiments with Tool Compounds 314-433

3.2.5.3.1 Catalytic Process



$H_2O_{2(aq)}$ (50%, 285 µL, 5.00 mmol) was added to a solution of methyl(*p*-tolyl)sulfane **317** (135 µL, 1.00 mmol), peroxide (0.2 equiv.) and SSA (100 mg) in $CHCl_3$ (2.5 mL). The resulting solution was stirred at 25 °C and analysed by HPLC (5 µL sample diluted to 1 mL with MeCN) at regular intervals.

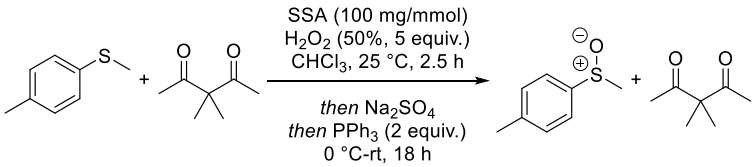
3.2.5.3.2 Sub-stoichiometric



Peroxide (0.2 equiv.) was added to a solution of methyl(*p*-tolyl)sulfane **317** (135 µL, 1.00 mmol), and SSA (100 mg) in $CHCl_3$ (2.5 mL). The resulting solution was stirred at 25 °C and analysed by HPLC (5 µL sample diluted to 1 mL with MeCN) at regular intervals.

3.2.5.4 Catalyst Recovery

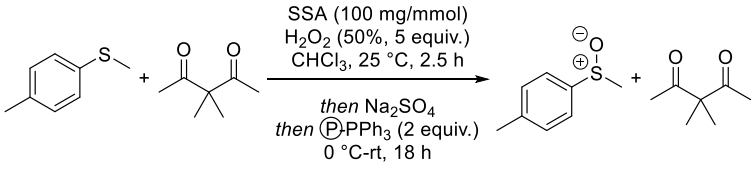
3.2.5.4.1 With PPh_3



$H_2O_{2(aq)}$ (50%, 285 mL, 50.0 mmol) was added to a solution of methyl(*p*-tolyl)sulfane **317** (1.35 mL, 10.0 mml), 3,3-dimethylpentane-2,4-dione **321** (260 µL, 2.00 mmol) and SSA (1.00 g) in $CHCl_3$ (25 mL). The resulting biphasic solution was stirred at 25 °C for 2.5 hours. The reaction was quenched by addition of $MgSO_4$, filtered and diluted with $CHCl_3$ (75 mL). PPh_3 (5.24 g, 20.0 mmol) was added portion wise at 0 °C. The reaction was stirred for 1 hour at rt. The solvent was removed *in vacuo* and hexane (100 mL) was added. The reaction was stirred for 18 hours at rt. The reaction was filtered at the solvent removed *in vacuo*. The crude material was purified by silica gel

chromatography (petrol:EtOAc, 9:1>3:1) to obtain 1-methyl-4-(methylsulfinyl)benzene **318** (1.47 g, 9.55 mmol, 96%) and 3,3-dimethylpentane-2,4-dione **321** (123 mg, 0.98 mmol, 49%).

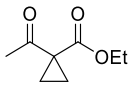
3.2.5.4.2 With Polymer Supported PPh_3



$H_2O_{2(aq)}$ (50%, 285 mL, 50.0 mmol) was added to a solution of methyl(*p*-tolyl)sulfane **317** (1.35 mL, 10.0 mml), 3,3-dimethylpentane-2,4-dione **321** (260 µL, 2.00 mmol) and SSA (1.00 g) in $CHCl_3$ (25 mL). The resulting biphasic solution was stirred at 25 °C for 2.5 hours. The reaction was quenched by addition of $MgSO_4$, filtered and diluted with $CHCl_3$ (75 mL). Polymer supported PPh_3 (10.0 g, 20.0 mmol) was added portion wise at 0 °C. The reaction was stirred for 18 hour at rt. The polymer supported PPh_3 was filtered and the solvent was removed *in vacuo*.The crude material was purified by silica gel chromatography (petrol:EtOAc, 9:1>3:1) to obtain 1-methyl-4-(methylsulfinyl)benzene **318** (1.49 g, 9.70 mmol, 97%) and 3,3-dimethylpentane-2,4-dione **321** (130 mg, 1.02 mmol, 51%).

3.2.6 Achieving Other Nucleophiles

3.2.6.1 Ethyl 1-acetylcyclopropane-1-carboxylate 459

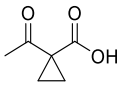


Ethyl acetylacetate **365** (6.30 mL, 50.0 mmol) and 1,2-dibromoethane **140** (4.3 mL, 50.0 mmol) were added dropwise to a stirred suspension of K_2CO_3 (17.3 g, 125 mmol) and TBAI (1.85 g, 5.00 mmol) in dry DMF (125 mL) under N_2. The resulting solution was stirred at room temperature for 18 hours. The mixture was cooled to 0 °C and brine (250 mL) was added to quench the reaction. The resulting aqueous solution was extracted with Et_2O (4 × 100 mL). The combined organic extracts were washed with saturated $Na_2S_2O_{5(aq)}$ (100 mL) and water (2 × 100 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude material was then purified

by silica gel chromatography (PhMe:CH_2Cl_2, 2:1) to afford the *title compound* (1.60 g, 10.2 mmol, 20%) as a yellow oil.

Yellow oil; **IR** (ATR)/cm^{-1}: 2982, 1697, 1117; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.20 (q, *J* = 7.1 Hz, 2H), 2.46 (s, 3H), 1.46 (s, 4H), 1.28 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.3, 171.2, 61.4, 35.2, 30.0, 19.3, 14.2; **LRMS** (GCMS-EI) *m/z* 156.1 $[M]^+$; **HRMS** (NSI) calculated for $C_8H_{13}O_3$ $[M+H]^+$ 157.0859, found 157.0858.

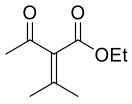
3.2.6.2 1-Acetylcyclopropane-1-carboxylic acid 452



4 M $NaOH_{(aq)}$ (11.4 mL) was added dropwise to a solution of Ethyl 1-acetylcyclopropane-1-carboxylate **459** (1.42 g, 9.11 mmol) in ethanol (3 mL) at 0 °C. The resulting solution was warmed to room temperature and stirred for 18 hours. The aqueous was extracted with Et_2O (2 × 20 mL) and then acidified with 2 M $HCl_{(aq)}$ (35 mL). The resulting aqueous solution was extracted with CH_2Cl_2 (4 × 25 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to afford the *title compound* (900 mg, 7.03 mmol, 78%) as a yellow oil.

Yellow oil; **IR** (ATR)/cm^{-1} 3013, 2926, 1688, 1121; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.99 (bs, 1H), 2.21 (s, 3H), 1.81 (dd, *J* = 8.1, 4.2 Hz, 2H), 1.66 (dd, *J* = 8.0, 4.3 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.2, 173.6, 33.8, 26.5, 21.5; **LRMS** (LCMS-ESI) *m/z* 129.1 $[M+H]^+$; **HRMS** (NSI) calculated for $C_6H_9O_3$ $[M+H]^+$ 129.0546, found 129.0542.

3.2.6.3 Ethyl 2-acetyl-3-methylbut-2-enoate 460

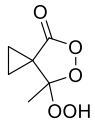


Ethyl acetylacetate **365** (2.60 mL, 20 mmol), acetone (2.20 mL, 30 mmol) and Ac_2O (2.60 mL, 27 mmol) were added to $ZnCl_2$ (381 mg, 2.8 mmol) under N_2. The resulting solution was heated to 60 °C and stirred for 72 hours. The reaction was then cooled to room temperature, diluted with hexane (100 mL), washed with H_2O (4 × 50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude material

was then purified by column chromatography (petrol:Et_2O, 9:1) to afford the *title compound* (769 mg, 4.52 mmol, 23%) as a yellow oil.

Yellow oil; **IR** (ATR)/cm^{-1} 2982, 2937, 1693, 1227; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.23 (q, *J* = 7.1 Hz, 2H), 2.28 (s, 3H), 2.09 (s, 3H), 1.94 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.9, 165.4, 152.8, 131.8, 60.3, 30.1, 22.8, 22.5, 13.6; **LRMS** (LCMS-ESI) *m/z* 170.1 $[M]^+$; **HRMS** (NSI) calculated for $C_9H_{15}O_3$ $[M+H]^+$ 171.1016, found 171.1012.

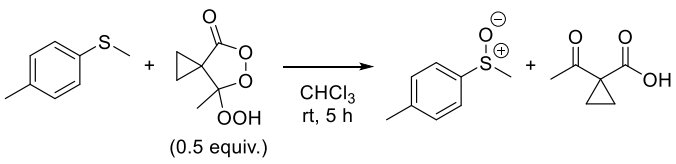
3.2.6.4 7-Hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one 463



H_2O_2 (50%, 285 μL, 5.00 mmol) was added to a solution of acetylcyclopropane-1-carboxylic acid **452** (128 mg, 1.00 mmol) and SSA (100 mg) in $CDCl_3$. Stirred at rt for 72 hours. The reaction was diluted with water (15 mL) and the aqueous was extracted with CH_2Cl_2 (3 ×15 mL). The combined organics were washed with sat. $NaHCO_3$ (3 × 15 mL) and brine (30 mL). The organics were dried over $MgSO_4$, filtered and the solvents were removed *in vacuo* to afford the *title compound* (111 mg, 0.69 mmol, 69%) as a colourless solid.

Colourless solid;; **IR** (ATR)/cm^{-1}: 3436, 2917, 2848, 1760, 1329; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.59 (bs, 1H), 1.57–1.52 (m, 1H), 1.48–1.44 (m, 1H), 1.43 (s, 3H), 1.41–1.31 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.6, 114.4, 28.2, 17.0, 15.9, 12.2; unable to obtain mass spectrometry data for reactive peroxides.

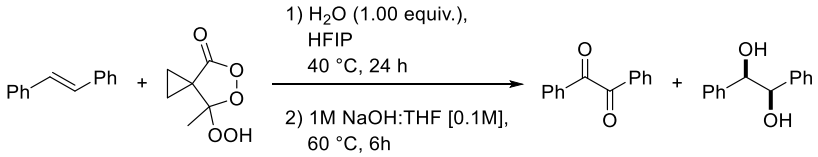
3.2.6.5 Reaction of 7-hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one 463 and methyl(*p*-tolyl)sulfane 317



7-hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **463** (80 mg, 0.50 mmol) was added in one portion to a solution of methyl(p-tolyl)sulfane **317** (135 μL, 1.00 mmol) in $CHCl_3$ (5 mL). The reaction was stirred at rt for 5 hours. The solvent was

removed in vacuo and the crude material was purified by silica gel chromatography (petrol:EtOAc:AcOH, 50:50:1) to afford 1-methyl-4-(methylsulfinyl)benzene **317** (131 mg, 0.85 mmol, 85%) and 1-acetylcyclopropane-1-carboxylic acid **452** (64 mg, 0.50 mmol, quant.).

3.2.6.6 Reaction of 7-hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one 463 and *trans*-stilbene 3



7-hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **463** (90.0 mg, 0.60 mmol) was added in one portion to a solution of *trans*-stilbene **3** (80.0 mg, 0.5 mmol) and water (9 μL, 0.50 mmol) in HFIP (1 mL). The resulting solution was stirred at 40 °C for 24 hours. The reaction was cooled to rt and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography (petrol:EtOAc, 1:0>9:1>3:1) to afford benzil **373** (16 mg, 0.08 mmol, 15%) and *rel*-(1*R*,2*R*)-1,2-diphenylethane-1,2-diol **14** (24 mg, 0.11 mmol, 22%).

Appendix

VI. Appendix

1) X-Ray data for *rel*-(1*S*,2*R*)-2-(acetoxy)-1-cyclohexyl-2-phenylethyl cyclopropanecarboxylate **235**

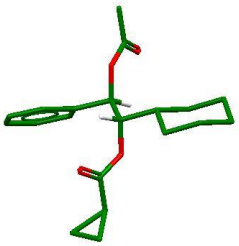
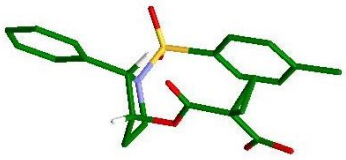


Table **VI-1**. Crystal data and structure refinement for **235**

Identification code	tom_diast_reduced	
Empirical formula	C20 H26 O4	
Formula weight	330.41	
Temperature	123(2) K	
Wavelength	1.54180 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 5.4976(4) Å	α= 100.728(6)°.
	b = 9.0443(7) Å	β= 93.854(6)°.
	c = 18.7581(16) Å	γ = 101.174(6)°.
Volume	893.84(12) $Å^3$	
Z	2	
Density (calculated)	1.228 Mg/m^3	
Absorption coefficient	0.678 mm^{-1}	
F(000)	356	
Crystal size	0.35 x 0.06 x 0.04 mm^3	
Theta range for data collection	4.83 to 74.92°.	
Index ranges	-6<=h<=4, -8<=k<=11, -23<=l<=22	
Reflections collected	5934	
Independent reflections	3437 [R(int) = 0.0382]	
Completeness to theta = 70.00°	97.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.70462	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3437 / 0 / 218	
Goodness-of-fit on F^2	1.065	
Final R indices [I>2sigma(I)]	R1 = 0.0536, wR2 = 0.1457	
R indices (all data)	R1 = 0.0769, wR2 = 0.1726	
Largest diff. peak and hole	0.241 and -0.265 $e.Å^{-3}$	

2) X-Ray crystal data for 1-(((rel-(2R,3S)-2-Phenyl-1-tosylpyrrolidin-3-yl)oxy)carbonyl)cyclopropane-1-carboxylic acid **254**

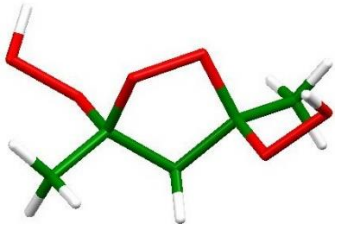
Table **VI-2**. Crystal data and structure refinement for **254**.



Identification code	tom_stuart_needles	
Empirical formula	C24 H27 N O8 S	
Formula weight	489.52	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 2_1/n	
Unit cell dimensions	a = 14.2564(10) Å	α= 90°.
	b = 7.5171(5) Å	β= 92.211(7)°.
	c = 21.4885(16) Å	γ = 90°.
Volume	2301.1(3) Å^3	
Z	4	
Density (calculated)	1.413 Mg/m^3	
Absorption coefficient	0.192 mm^{-1}	
F(000)	1032	
Crystal size	0.33 x 0.16 x 0.05 mm^3	
Theta range for data collection	3.234 to 27.995°.	
Index ranges	-18<=h<=17, -9<=k<=9, -27<=l<=27	
Reflections collected	15728	
Independent reflections	5410 [R(int) = 0.0285]	
Completeness to theta = 27.000°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.86786	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5410 / 0 / 315	
Goodness-of-fit on F^2	1.110	
Final R indices [I>2sigma(I)]	R1 = 0.0541, wR2 = 0.1081	
R indices (all data)	R1 = 0.0691, wR2 = 0.1166	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.429 and -0.441 e.Å^{-3}	

3) X-Ray crystal data for 3,5-Dihydroperoxy-3,5-dimethyl-1,2-dioxolane **314**

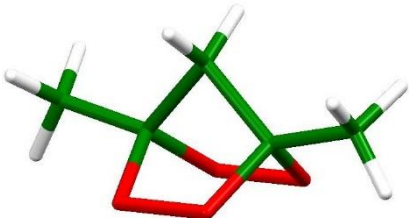
Table **VI-3**. Crystal data and structure refinement for **314**.



Identification code	shelx	
Empirical formula	C5 H10 O6	
Formula weight	166.13	
Temperature	123(2) K	
Wavelength	1.5418 Å	
Crystal system	Orthorhombic	
Space group	P b c n	
Unit cell dimensions	a = 8.8656(6) Å	α= 90°.
	b = 5.5525(5) Å	β= 90°.
	c = 15.4304(10) Å	γ = 90°.
Volume	759.58(10) $Å^3$	
Z	4	
Density (calculated)	1.453 Mg/m^3	
Absorption coefficient	1.201 mm^{-1}	
F(000)	352	
Crystal size	? x ? x ? mm^3	
Theta range for data collection	5.735 to 73.011°.	
Index ranges	-11<=h<=6, -6<=k<=6, -17<=l<=18	
Reflections collected	3122	
Independent reflections	748 [R(int) = 0.0358]	
Completeness to theta = 70.000°	99.7 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	748 / 0 / 56	
Goodness-of-fit on F^2	1.073	
Final R indices [I>2sigma(I)]	R1 = 0.0656, wR2 = 0.1972	
R indices (all data)	R1 = 0.0692, wR2 = 0.2036	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.381 and -0.221 $e.Å^{-3}$	

4) X-Ray crystal data for 1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane **433**

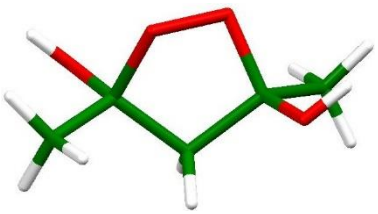
Table **VI-4**. Crystal data and structure refinement for **433**.



Identification code	shelx	
Empirical formula	C5 H8 O4	
Formula weight	132.11	
Temperature	123(2) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P b c n	
Unit cell dimensions	a = 7.1485(2) Å	α= 90°.
	b = 8.5639(2) Å	β= 90°.
	c = 9.7179(3) Å	γ = 90°.
Volume	594.92(3) $Å^3$	
Z	4	
Density (calculated)	1.475 Mg/m^3	
Absorption coefficient	1.123 mm^{-1}	
F(000)	280	
Crystal size	0.30 x 0.24 x 0.04 mm^3	
Theta range for data collection	10.372 to 72.987°.	
Index ranges	-4<=h<=8, -10<=k<=9, -11<=l<=10	
Reflections collected	1967	
Independent reflections	585 [R(int) = 0.0218]	
Completeness to theta = 70.000°	99.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.68549	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	585 / 0 / 43	
Goodness-of-fit on F^2	1.072	
Final R indices [I>2sigma(I)]	R1 = 0.0350, wR2 = 0.0968	
R indices (all data)	R1 = 0.0366, wR2 = 0.0982	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.268 and -0.224 $e.Å^{-3}$	

5) X-Ray crystal data for 3,5-dihydroxy-3,5-dimethyl-1,2-dioxolane **432**

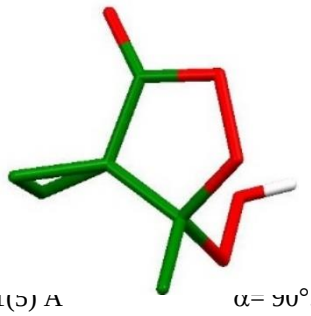
Table **VI-5**. Crystal data and structure refinement for **432**.



Identification code	peroxide	
Empirical formula	C5 H10 O4	
Formula weight	134.13	
Temperature	133(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	$P4_12_12$	
Unit cell dimensions	a = 8.9904(2) Å	α= 90°.
	b = 8.9904(2) Å	β= 90°.
	c = 8.4837(3) Å	γ = 90°.
Volume	685.71(3) $Å^3$	
Z	4	
Density (calculated)	1.299 Mg/m^3	
Absorption coefficient	0.113 mm^{-1}	
F(000)	288	
Crystal size	0.30 x 0.25 x 0.04 mm^3	
Theta range for data collection	3.20 to 28.97°.	
Index ranges	-12<=h<=11, -12<=k<=12, -11<=l<=11	
Reflections collected	6471	
Independent reflections	902 [R(int) = 0.0255]	
Completeness to theta = 27.00°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.49784	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	902 / 0 / 47	
Goodness-of-fit on F^2	1.064	
Final R indices [I>2sigma(I)]	R1 = 0.0338, wR2 = 0.0755	
R indices (all data)	R1 = 0.0385, wR2 = 0.0790	
Absolute structure parameter	0.0(16)	
Largest diff. peak and hole	0.217 and -0.167 $e.Å^{-3}$	

6) X-Ray crystal data for 7-hydroperoxy-7-methyl-5,6-dioxaspiro[2.4]heptan-4-one **463**

Table **VI-6**. Crystal data and structure refinement for **463**.



Identification code	tom_sd_jan2017	
Empirical formula	C6 H8 O5	
Formula weight	160.12	
Temperature	123(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclini	
Space group	Cc	
Unit cell dimensions	a = 6.6061(5) Å	α= 90°.
	b = 11.2152(7) Å	β= 103.133(7)°.
	c = 9.8627(6) Å	γ = 90°.
Volume	711.60(8) Å^3	
Z	4	
Density (calculated)	1.495 Mg/m^3	
Absorption coefficient	1.161 mm^{-1}	
F(000)	336	
Crystal size	0.5 x 0.35 x 0.25 mm^3	
Theta range for data collection	7.94 to 72.78°.	
Index ranges	-8<=h<=6, -13<=k<=13, -10<=l<=12	
Reflections collected	2227	
Independent reflections	1101 [R(int) = 0.0154]	
Completeness to theta = 70.00°	98.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.52047	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1101 / 2 / 105	
Goodness-of-fit on F^2	1.053	
Final R indices [I>2sigma(I)]	R1 = 0.0280, wR2 = 0.0748	
R indices (all data)	R1 = 0.0280, wR2 = 0.0748	
Absolute structure parameter	-0.1(2)	
Largest diff. peak and hole	0.207 and -0.151 e.Å^{-3}	

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