Lancaster University

Palladium-Catalysed Decarboxylative Asymmetric Allylic Alkylation of Thietane-1,1-Dioxides for the Synthesis of Enantioenriched Spirocycles

by

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Declaration

This thesis has not been submitted in support of an application for another degree at this or any other university. It is the result of my own work and includes nothing that is the outcome of work done in collaboration except where specifically indicated. Any section of this thesis which has been published will be clearly identified.

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Abstract

Structurally novel stereofunctionalised heterocyclic building blocks are becoming increasingly important in the field of medicinal chemistry as a means of facilitating drug discovery through improved physicochemical properties. As such, asymmetric synthetic methods to access previously unexplored enantiopure heterocycles are highly sought after. The work disclosed in this thesis involves the development of a palladium-catalysed decarboxylative asymmetric allylic alkylation (Pd-DAAA) of thietane-1,1-dioxides bearing a carbonyl side-chain to afford novel enantioenriched building blocks. Unlike the stereoselective allylic alkylation of cyclic enolates with a fixed alkene geometry, this approach necessitated the alkylation of linear enolate intermediates, which is substantially more difficult to achieve enantioselectively due to the implication of *E*/*Z* enolate isomers. The reaction process was successfully optimised to install an α-sulfonyl tetrasubstituted centre with high levels of enantioselectivity from racemic starting materials. In addition, an extensive substrate scope investigation of ketone and ester enolates bearing aromatic, heteroaromatic and alkyl groups illustrated broad utility of this method, enabling access to a range of products with up to 96% ee. This investigation revealed that esters were slightly more successful substrates than ketones in terms of enantioselectivity, and that substitution of the allylic ester was not well tolerated.

The geometry of the acyclic enolate intermediate was probed to determine its impact on the sense and magnitude of the enantioselectivity in the Pd-DAAA reaction. It was found that a palladium-mediated interconversion of enolate intermediates takes place, furnishing products with high ee from racemic β-ketoester starting materials without the need for pre-formed geometrically pure enolate precursors. Several studies were performed to gain more insight into the mechanism of the reaction. An enolate crossover experiment showed significant enolate exchange, tentatively suggesting that an outer-sphere alkylation mechanism is in operation.

Finally, the utility of this Pd-DAAA methodology was demonstrated in the transformation of one of the enantioenriched thietane-1,1-dioxide building blocks into a novel spirocycle. This spirocycle was proven amenable to various transformations, further demonstrating its potential in medicinal chemistry applications.

Contents

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Throughout my PhD I have been lucky enough to work alongside great people at Lancaster University. I would like to especially thank Eleanor Bowen, Jack Kaufman, Jack Lowe, Bec Spicer and Bette Beament for all the wonderful memories.

My warmest thanks go to my Mum, Dad and brother, Fraser, for their unwavering love and support. Finally, this PhD would not have been possible without my partner Steven by my side. I can't wait to move onto the next chapter with you.

Abbreviations

3D	3-dimensional
λ	lambda (wavelength)
δ	chemical shift (NMR)
Å	angstrom
AAA	asymmetric allylic alkylation
Ac	acetyl
acac	acetylacetonate anion
Ad	adamantyl
ADME	administration, distribution, metabolism and excretion
ANDEN	Bis[2′-(diphenylphosphino)benzamido]-9,10-dihydro-9,10-ethanoanthracene
APCI	atmospheric pressure chemical ionisation
aq.	aqueous
Ar	unspecified aryl group
B	unspecified base
BBN	borabicyclo[3.3.1]nonane
Bzh	benzhydryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
c	concentration
C	Celsius
cat.	catalytic
Cbz	benzyloxycarbonyl
CDI	1,1'-carbonyldiimidazole
COSY	correlated spectroscopy (NMR)
m-CPBA	*meta*-chloroperoxybenzoic acid
CYP450	cytochrome P450
DAAA	decarboxylative asymmetric allylic alkylation
DACH	*trans*-1,2-diaminocyclohexane
DCC	*N*,*N*'-dicyclohexylcarbodiimide

dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DEPT-135	distortionless enhancement by polarization transfer
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMEA	*N*,*N*-dimethylethylamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
E	unspecified electrophile
EC_{50}	half maximal effective concentration
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
ESI	electrospray ionisation
Et	ethyl
FTIR	fourier-transform infrared spectroscopy
gem	geminal
h	hour(s)
HMBC	heteronuclear multiple bond correlation (NMR)
HMDS	bis(trimethylsilyl)amide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence (NMR)
i	*iso*
IC_{50}	half maximal inhibitory concentration
IR	infrared
L_n	ligand
LDA	lithium diisopropylamide
LG	unspecified leaving group
M	molar
M^+	unspecified metal cation
Me	methyl
min	minutes

MOM	methoxymethyl
Ms	methanesulfonyl
M.S.	molecular sieves
MTBE	methyl *tert*-butyl ether
mtdba	1,5-bis-[3-(triethylsilyl)phenyl]penta-1,4-dien-3-one
mp	melting point
m/*z*	mass/charge
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect (NMR)
Ns	2-nitrophenylsulfonyl
Nu	unspecified nucleophile
p	*para*
PG	unspecified protecting group
Ph	phenyl
PHOX	phosphinoxazoline
PMB	*para*-methoxybenzyl
pmdba	1,5-bis-[4-methoxyphenyl]penta-1,4-dien-3-one
PMI	principle moment of inertia
Pr	propyl
py	pyridine
R	unspecified alkyl group
R_f	retention factor
RT	room temperature
TBA	tetrabutylammonium cation
TBDMS	tert-butyldimethylsilyl
tert	tertiary
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	toluenesulfonyl
VT	variable temperature (NMR)
X^-	unspecified counter-anion

1. Introduction

1.1 Spirocycles in Medicinal Chemistry

1.1.1 Structural Complexity in Drug Discovery

Protein receptors within the body consist of complex three-dimensional amino acid structures which selectively allow drug molecules to bind through hydrogen-bonding, electrostatic, π-stacking, and other interactions leading to a pharmacological effect.[1,2] The available space within the receptor must be fully utilised to ensure good ligand-protein binding in order to achieve high potency. Whereas unsaturated sp^2-rich, aromatic and heteroaromatic compounds are planar and largely 2-dimensional in shape, saturated sp^3-rich compounds possess much more varied, 3-dimensional shape.[3] For this reason, 3D structures, similar to natural products that contain several chiral centres, are often better drug candidates[4-9] than planar, aromatic systems.[3,10-13] Indeed, in 2009, Lovering *et al.* detailed the importance of overall molecular complexity in drug candidates, showcasing that increased saturation and the presence of stereocentres were more likely to result in higher success rates in clinical development.[14] It was argued that saturated molecules inherently possess greater shape diversity when compared to flat, unsaturated systems. In addition, compounds with a high proportion of sp^3-carbon atoms can have improved physicochemical properties, such as higher aqueous solubility and lower lipophilicity, resulting in improved oral bioavailability.[14] Alongside the selectivity and potency of binding a drug to the receptor, chirality must also be considered as different enantiomers of drugs can exhibit different binding profiles. Where one enantiomer can efficiently bind and produce the desired effect, its mirror image could be completely ineffective or potentially even toxic.[15] Given that toxicity is one of the leading causes of attrition in clinical trials,[16] compounds with greater specificity and selectivity are often expected to show less toxicity due to improved binding and reduced off-target effects. Despite the advantages of the use of sp^3-rich building blocks in drug discovery, two-dimensional heterocycles continue to dominate compound screening libraries due to the efficiency and robustness of $C(sp^2)$–$C(sp^2)$ cross-coupling methods, such as Suzuki-Miyaura couplings, which are amongst the most commonly used reactions in industry.[17] In fact, the Suzuki-Miyaura reaction is responsible for the formation of 40% of all C–C bonds in the pharmaceutical industry.[17,18]

To visualise the 3-dimensionality of molecules within a screening library, a principle moment of inertia (PMI) plot can be used (Figure 1).[3,11] More specifically, this 2-dimensional triangular chart is a description of the overall molecular 3-dimensional shape without considering any other property, such as molecular weight. The three corners of the triangular map represent linear shapes, such as acetylene (top-left corner), disc-like shapes, such as benzene (bottom corner), and spherical shapes, such as adamantane (top-right corner). This PMI plot clearly depicts the over-populated nature of the linear and disc-like structures contained in the ChEMBL database—a large database containing information on the structures, ADME (administration, distribution, metabolism and excretion) and binding properties for drug-like bioactive compounds.[19] In contrast, molecules occupying overall spherical shapes are sparse and underexplored.[17]

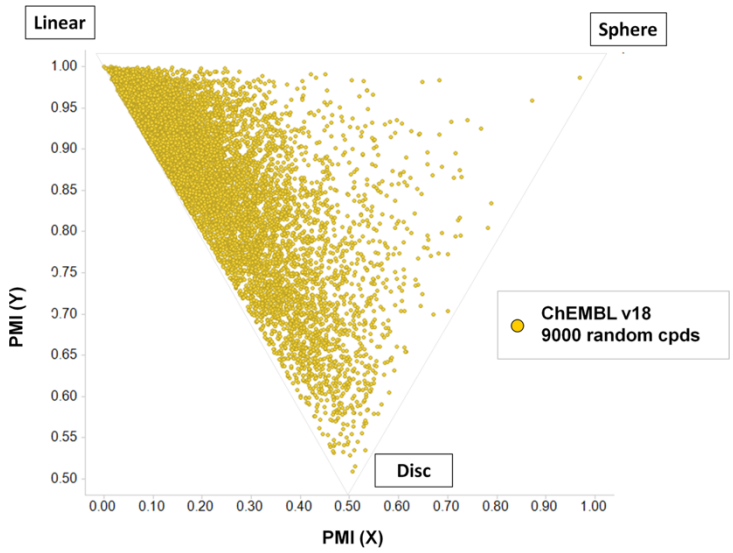


Figure 1: PMI chart depicting structural diversity in a pharmaceutical database. (*ChEMBL = database of bioactive molecules with drug like properties*). Reproduced from Brown *et al.*[17]

With this knowledge, the pharmaceutical industry is actively seeking to diversify their libraries by incorporating novel, non-planar structures that are rich in sp^3 centres, are chiral, and are able to explore new regions of 3D chemical space.[20,21] These structures have the potential to tackle an ever-increasing range of biological targets, including those that had previously been deemed undruggable. However, in contrast to the availability of $C(sp^2)$–$C(sp^2)$ coupling methodologies, the synthesis of enantiopure sp^3-rich building blocks remains to be substantially more challenging.

1.1.2 Four-Membered Heterocycles in Medicinal Chemistry

Four-membered rings, such as cyclobutanes,[22] azetidines,[23] oxetanes,[24] thietanes,[25] and thietane-1,1-dioxides (Figure 2), possess unique three-dimensional structures due to their limited flexibility. The incorporation of small heteroaliphatic rings into lead compounds has become a popular approach to improve the physicochemical properties of drug candidates.[26] These strained, rigid scaffolds offer a number of additional benefits, including structural novelty, access to previously untapped 3D exit vectors, and resistance to metabolic oxidation by enzymes, such as cytochrome P450, due to the structural incompatibility of small rings within the active site of the enzyme.[26]

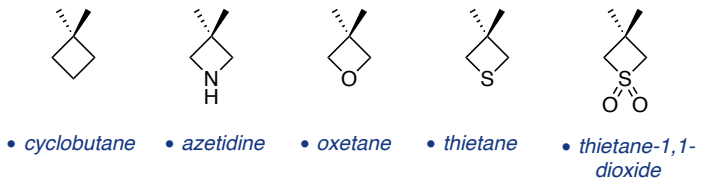


Figure 2: Biologically interesting saturated four-membered carbo- and heterocycles.

In the late 2000s, oxetanes were found to offer a solution to several challenges encountered within the drug development process.[27,28] As oxetanes possess a similar dipole to a carbonyl functionality, replacement of this metabolically labile group with an oxetane afforded molecules with improved ADME properties.[24] More specifically, carbonyl groups, such as aldehydes and ketones do not often feature in drug candidates due to their metabolic instability and possibility of α-deprotonation, with the latter potentially causing epimerisation of any labile α-stereogenic centres. While the C=O bond length of carbonyl **1** is shorter than the corresponding width of oxetane structure **2** (Figure 3), the lone pairs on the oxygen atom remain in the same spatial orientation.[27] The main difference in these structures is the presence of the methylene groups in oxetane **2**, which are positioned above and below the plane of carbonyl **1**. These structural features of **2** allow the molecule to access new regions of chemical space, while maintaining similar hydrogen bond acceptor interactions.

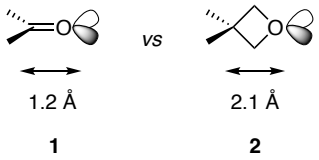


Figure 3: Comparison of carbonyl and oxetane structures.

One area of the application of oxetanes as bioisosteres for carbonyls lies in peptide drugs that are becoming increasingly popular within the pharmaceutical industry, with over 50 marketed compounds and an estimated revenue of $13 billion in 2010.[29,30] While peptide drugs are often highly specific and potent, they suffer from several shortcomings, including fast metabolism by hydrolytic enzymes, leading to short half-life within the stomach and plasma.[30] By replacing the amide carbonyl group in **3** with an oxetane ring (Figure 4), oxetanyl amines **4** are inert to hydrolysis, thus enhancing their stability while maintaining similar hydrogen-bond donor/acceptor interactions present in the parent peptide.[30]

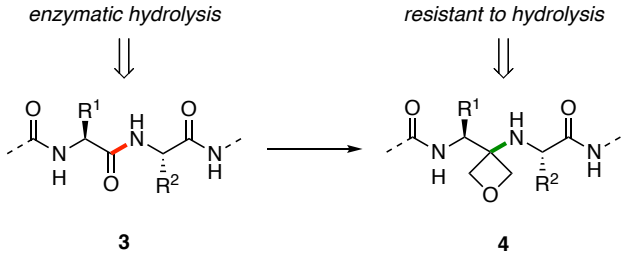


Figure 4: Oxetanyl amines exhibit increased stability *in vivo*.

Another factor responsible for shortening the half-life of medicinally active compounds are the high levels of oxidative metabolism by CYP450 enzymes in the liver that leads to faster excretion and, hence, reduced levels of the drug entering systemic circulation and reaching the target. A common method in the pharmaceutical industry to block oxidation at vulnerable sites in the molecule is to introduce a *gem*-dimethyl unit (**6** to **5**, Figure 5),[31] with more than 10% of marketed drugs containing at least one *gem*-dimethyl group.[27] This strategy can also have its disadvantages. For example, exchanging hydrogen atoms for methyl groups on small compounds may lead to an undesirable increase in the lipophilicity of **5**, whereas the methyl groups can often themselves be vulnerable to oxidation. In contrast, the introduction of an oxetane ring

in **7** not only reduces the lipophilicity of the molecule, but also decreases its affinity for oxidation.[27]

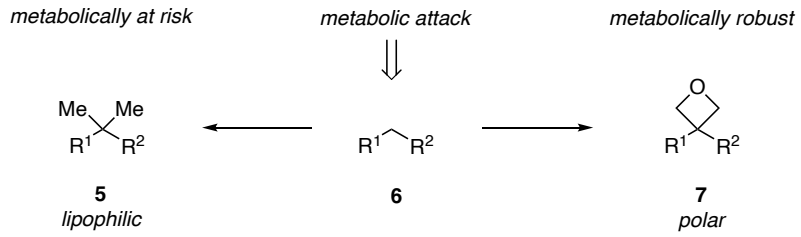
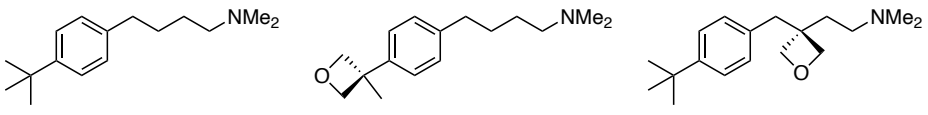


Figure 5: Attachment of an oxetane increases metabolic stability.

To demonstrate the benefits of the oxetane moiety as a polar and metabolically stable isostere for *gem*-dimethyl substituents, Carreira and co-workers carried out a study in which oxetanes were incorporated at different positions in compounds **9** and **10**, and their properties were compared (Figure 6).[31] In this study, *N*,*N*-dimethyl-4-(*p*-*tert*-butylphenyl)butylamine (**8**) was chosen as the model substrate due to its hydrophobic tail and polar head group. In its neutral form, **8** is essentially insoluble in water and contains several positions that are liable to oxidation. Therefore, this compound would be undesirable in drug development and was used for comparison purposes only. Upon modification, substitution of the two methyl groups in **8** with oxetane **9** resulted in reduced lipophilicity, increased aqueous solubility, and enhanced metabolic stability as observed in the reduced intrinsic clearance rates (CLint). Similarly, incorporation of an oxetane in the hydrophobic alkyl chain (**10**) also led to overall improvements in the ADME profile of this compound.



8 **9** **10**

Lipophilicity (log P)	5.0	3.3	3.5
Solubility (mg mL^{-1})	<4	4400	4100
hCLint (min^{-1} mL)	16	0	6
mCLint (min^{-1} mL)	420	44	13

Figure 6: Improved properties with oxetane incorporation (h) measured in human; (m) measured in mouse.

Despite the advantages of incorporating oxetanes into drug candidates, there are currently only 3 marketed drugs containing an oxetane ring. All of them are taxane derivatives used in cancer chemotherapy and are derived from paclitaxel, an oxetane-containing natural product.[27] However, in 2021, there were a further 28 compounds in phase I-III in clinical trials possessing an oxetane unit, illustrating the growing popularity of oxetanes in medicinal chemistry.[26]

In addition to oxetane structures in drug discovery, azetidines can also offer improved physicochemical properties and can act as replacements for nitrogen-containing ring systems, such as piperidine, pyrrolidine and pyrazine.[26] While azetidines are currently less common than oxetanes in drug discovery, they are growing in popularity as they become subjects of more intensive research.[32] However, four-membered sulfur-containing heterocycles, such as thietane-1,1-dioxide, are even less commonly found in medicinal chemistry projects.

1.1.3 Four-Membered Ring-Containing Spirocycles

Spirocycles are structures with two rings linked perpendicular to each other by one common atom, known as the spiroatom (**11**, Figure 7). For clarity, the IUPAC nomenclature of naming spirocycles is the following:

Prefix-spiro[no. of atoms in smaller ring . no. of atoms in larger ring]root name.

The spiroatom is not included within the square brackets; however, it is included in the root name. Numbering of spirocycles within the square brackets starts with the atom adjacent to the spiroatom in the smallest ring until it reaches the junction, and then starts with the larger ring.[33] Examples of spirocycles **12**–**14**, along with their names, are shown in Figure 7.

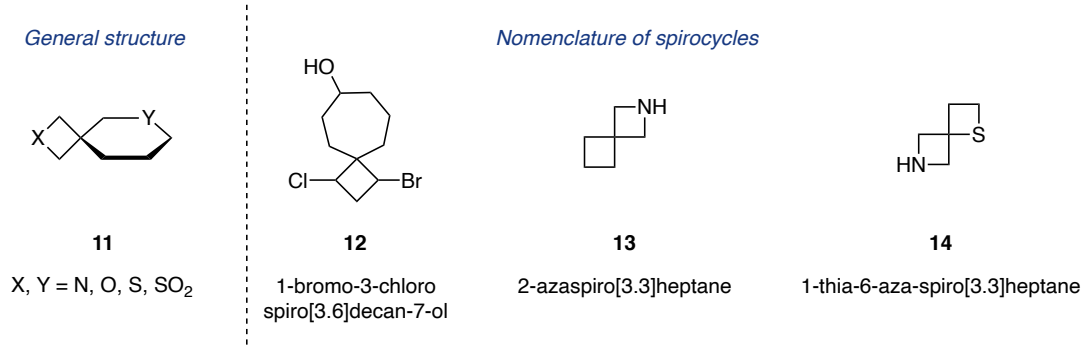


Figure 7: Nomenclature of spirocycles.

Spirocycles are structurally dense and rigid motifs which lower the overall flexibility of the molecule, potentially influencing its binding potency and selectivity.[34] These scaffolds possess desirable properties, including high sp^3-carbon atom count and 3-dimensional shape for pharmaceutical applications, whilst simultaneously offering novel binding interactions due to the unique arrangement of functional groups in space.[35] In addition, four-membered ring-containing spirocycles can often exhibit lower lipophilicity, increased aqueous solubility, as well as higher metabolic stability, leading to more promising ADME properties for the drug candidate.[36]

Spirocycles can also act as mimics for their heterocyclic counterparts. For example, they provide greater opportunities to modify and fine-tune their structures by varying the ring size and creating alternative exit vectors in 3D space that are not available to the saturated heterocyclic congener. For example, while 1,4-heteroatom substituted saturated 6-membered rings, such as morpholine and piperazine, are metabolically stable and are often employed in medicinal chemistry, the corresponding 1,3-heteroatom substituted 6-membered ring systems **15** are unstable *in vivo* and are rarely found within drug molecules due to their fast metabolism (Figure 8). To overcome this problem, spirocycles of type **16** could in principle act as structurally similar, yet more stable alternative.[37]

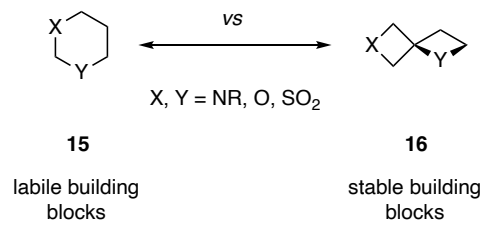


Figure 8: Novel and structurally stable 1,6-heteroatom-substituted spirocycle.

The calculated N–N bond distances of piperazine (**19**) and 2,6-diazaspiro[3.3]heptane (**17**) are 2.86 Å and 3.94 Å, respectively (Figure 9).[36] This slight difference explains why spirocycles are often described as "mimics", and not exact substitutes, of conventional heterocycles.[38] Although spirocycles possessing elongated linear exit vectors, such as **17** and **18**, can be functionalised at the nitrogen atoms in opposing directions, diamine spirocycles can also contain angular exit vectors, such as in **20**–**22**, which enable functionalisation in a broader range of directions in ways that are unachievable for conventional saturated heterocycles.[36]

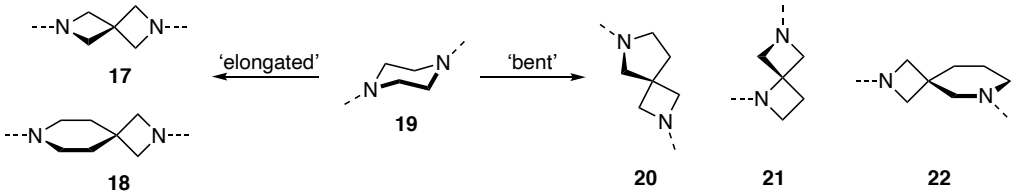


Figure 9: Elongated and bent spirocycles.

1.1.4 Synthetic Routes to Achiral and Racemic Four-Membered Ring-Containing Spirocycles

In the absence of other chiral centres, four-membered ring containing spirocycles can possess either an achiral spirocentre (**11**, 3-substituted, Figure 10) or a chiral spirocentre (**23**, 2-substituted). In the case of a chiral spiroatom, the spirocycle can be racemic, *rac*-**23**, or enantioenriched, **23**, the latter of which requires chiral pool starting materials or asymmetric synthesis to generate one enantiomer of product.

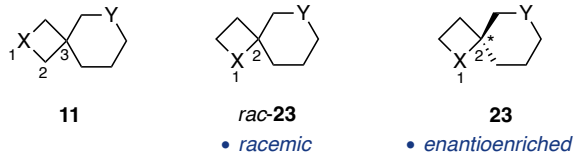
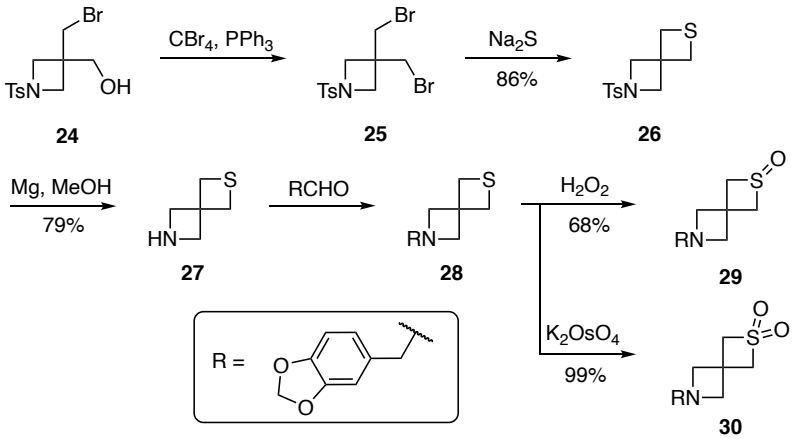


Figure 10: Achiral and chiral spirocycles.

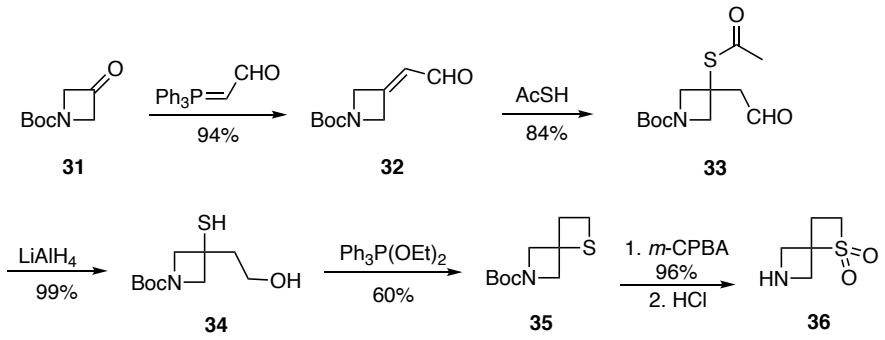
3-Substituted four-membered ring containing spirocycles are the most common as they are achiral and, thus, synthetically more tractable. For example, the synthesis of a thiomorpholine mimic, 2-thia-6-aza-spiro[3.3]heptanes (**28**), was communicated in 2010 by Carreira and co-workers (Scheme 1).[36] Alcohol **24** underwent an Appel

reaction to produce 3,3-dibromomethylazetidine **25**. Reaction of **25** with sodium sulfide created the second four-membered ring in **26** *via* a double substitution reaction. The *N*-tosyl protecting group was removed by reductive cleavage using magnesium in methanol, and the free amine in **27** was functionalised by means of reductive amination to afford **28**. To modify thioether **28** further, selective oxidation was achieved using hydrogen peroxide or potassium osmate to produce sulfoxide **29** and sulfone **30**, respectively.



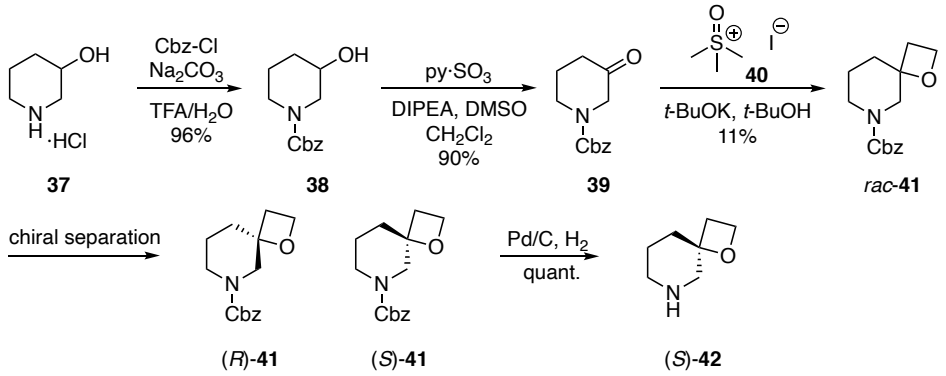
Scheme 1: Synthetic route to 2-thia-6-aza-spiro[3.3]heptanes and derivatives.

To create the "bent" spirocyclic analogue **36**, an alternative synthetic route was devised (Scheme 2). Starting with olefination of Boc-azetidinone **31**, the resulting α,β-unsaturated aldehyde **32** underwent Michael addition with thioacetic acid to afford **33**. Efficient reduction of both the thioester and aldehyde functionalities in **33** with lithium aluminium hydride revealed the free thiol and alcohol in **34**, cyclisation of which using diethoxytriphenylphosphorane furnished spirocyclic scaffold **35**. Oxidation of thietane **35** using *m*-CPBA was achieved in 96% yield, and Boc-deprotection with hydrochloric acid produced **36** in racemic form. Coupling reactions were then reported to pave the way to a variety of *N*-acylated and *N*-arylated spirocycles in high yields.[37]



Scheme 2: Synthesis of achiral 1-thia-6-aza-spiro[3.3]heptane derivatives.

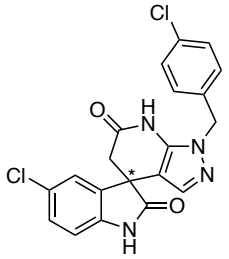
Synthetic routes to *chiral* 2-substituted spirocycles, and more specifically, *enantiopure* spirocycles, are underexplored due to their more challenging synthesis. Scheme 3 depicts access to enantiopure spirocycle **42** *via* racemic synthesis and separation of enantiomers using chiral HPLC.[39] 3-Hydroxypiperidine hydrochloride (**37**) was protected as carbamate **38**, followed by Parikh-Doering oxidation to produce ketone **39** in 90% yield. The oxetane ring was formed using sulfoxonium ylide **40** to generate the chiral but racemic spirocycle **41** in low yield. The enantiomers were separated using chiral HPLC, and the desired enantiomer (*S*)-**41** was deprotected *via* hydrogenolysis to reveal 1-oxa-6-azaspiro[3.5]nonane (**42**).



Scheme 3: Isolation of enantiopure spirocycles using chiral separation.

Preparative separation of enantiomers by chiral HPLC on scale can be useful in some scenarios. For example, in 2015, Zou *et al.* developed a novel dengue virus (DENV) inhibitor **43** (Figure 11). The racemate of this spirocyclic molecule was identified as a 'hit' through a high throughput screening process. To probe the binding of this molecule further, the enantiomers were separated by chiral HPLC and, when screened again, it

was discovered that the (*R*)-enantiomer was 225-fold more potent *in vitro* than the (*S*)-enantiomer.[40]



43

rac-**43** DENV-2 EC_{50} = 51 nM
(*R*)-**43** DENV-2 EC_{50} = 12 nM
(*S*)-**43** DENV-2 EC_{50} = 2710 nM

Figure 11: Difference in potency of *R* and *S* enantiomers of **43**.

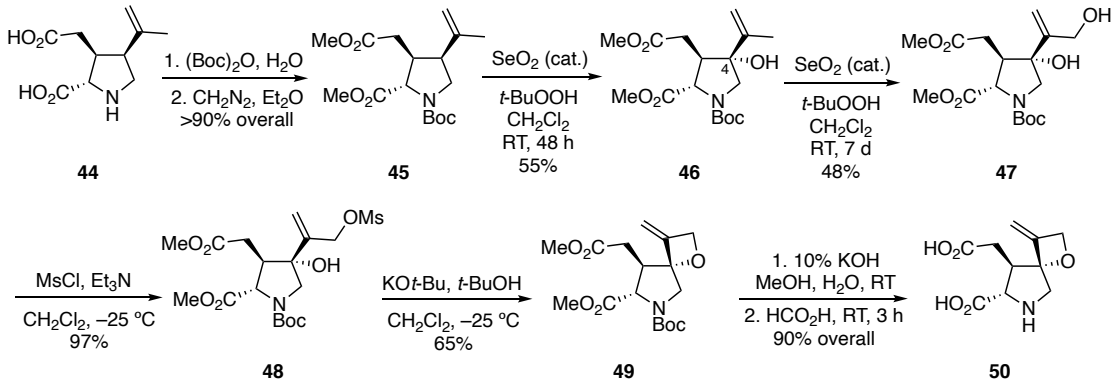
However, on pharmaceutical process scale, separation by chiral HPLC is an inefficient, expensive and time-consuming process. Chiral separation also limits the maximum yield of product to 50%, and while the undesired enantiomer can sometimes be recycled for another purpose, it is often discarded making the overall synthesis uneconomical and wasteful.

Overall, various syntheses of achiral and chiral racemic four-membered ring-containing spirocycles have been widely reported in the literature and in patents.[36,41-43] However, despite the importance of, and desire for, enantiomerically pure compounds in screening libraries, the synthesis of enantioenriched four-membered ring-containing spirocycles remains challenging and elusive due to the requirement for asymmetric synthesis.[44]

1.1.5 Synthetic Routes to Enantioenriched Four-Membered Ring-Containing Spirocycles

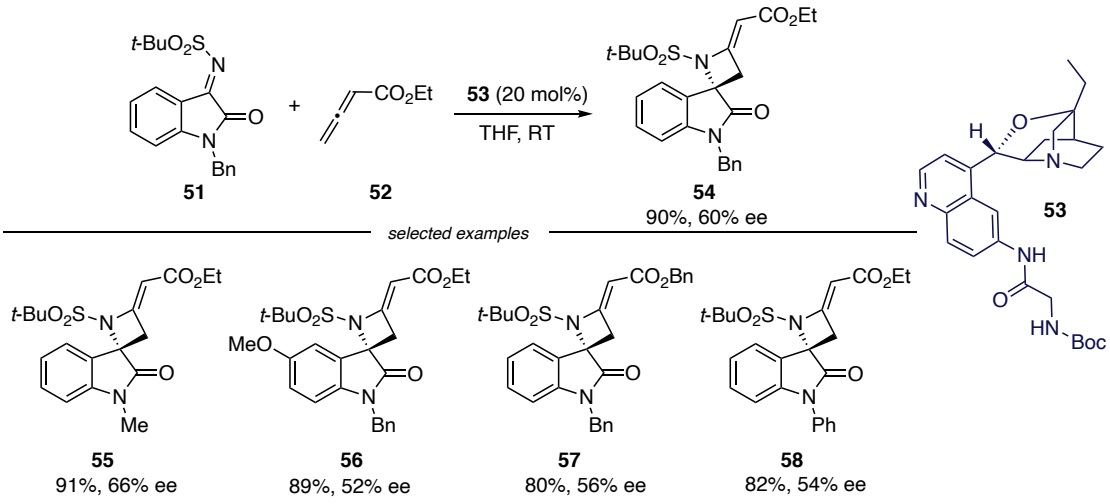
There are limited examples of enantioenriched four-membered ring-containing spirocycles in the literature. An example of a diastereoselective synthesis of kainic-acid-derived oxetane spirocycle **50** is depicted in Scheme 4.[45] This synthesis began with naturally occurring kainic acid (**44**), which was fully protected to **45**. Allylic oxidation with selenium dioxide furnished **46** in a 55% yield. This step proceeded regioselectively and with complete retention of stereochemistry at the C4 position. This intermediate was then re-exposed to selenium dioxide to form diol **47**. Mesylation of the terminal

alcohol to **48**, followed by an intramolecular substitution furnished oxetane-containing spirocycle **49**, which was subsequently deprotected to **50**. Spirocycle **50** possesses several points of functionalisation for analogue synthesis and utilises readily available kainic acid (**44**) from the chiral pool.



Scheme 4: Synthesis of kainic acid derived spirocycle.

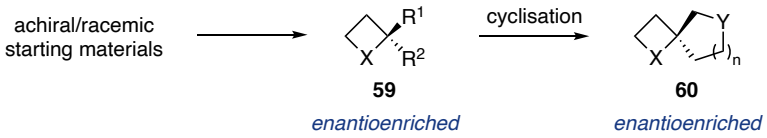
In 2017, Rainoldi and co-workers reported the enantioselective synthesis of azetidine-containing spirocycle **54** *via* a formal [2+2] annulation of isatin-derived *N-tert*-butylsulfonyl ketimine **51** and allenoate **52**, mediated by organocatalyst **53** (Scheme 5). This methodology furnished products **54**–**58** in high yields; however, the enantioselectivity of this transformation was moderate (52–66%).[46]



Scheme 5: Azetidine-containing spirocycles from [2+2] annulation.

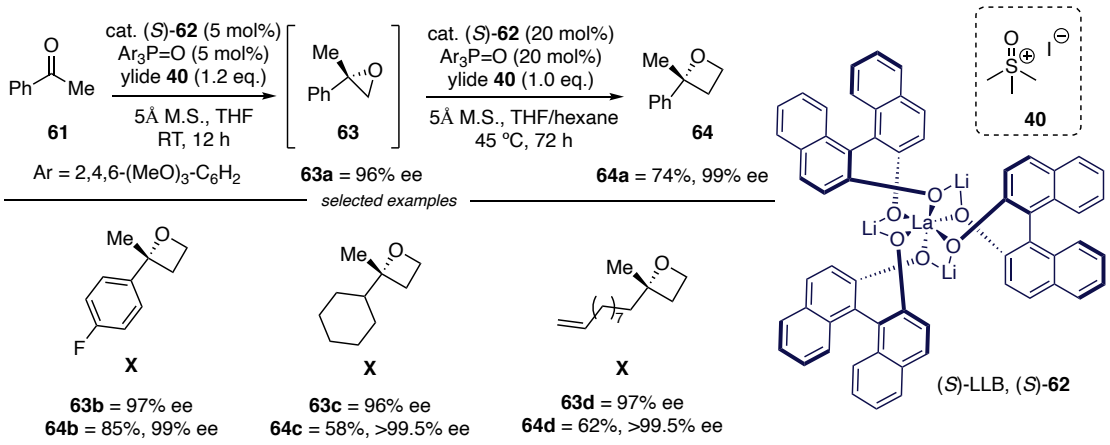
1.1.6 Synthetic Routes to Enantioenriched Four-Membered Saturated Heterocycles

An alternative approach to the synthesis of enantioenriched spirocycles is to first use asymmetric methods to furnish the four-membered heterocycle in enantioenriched form (**59**, Scheme 6), and then derivatise the functional handles in **59** into the enantioenriched spirocycle **60**.



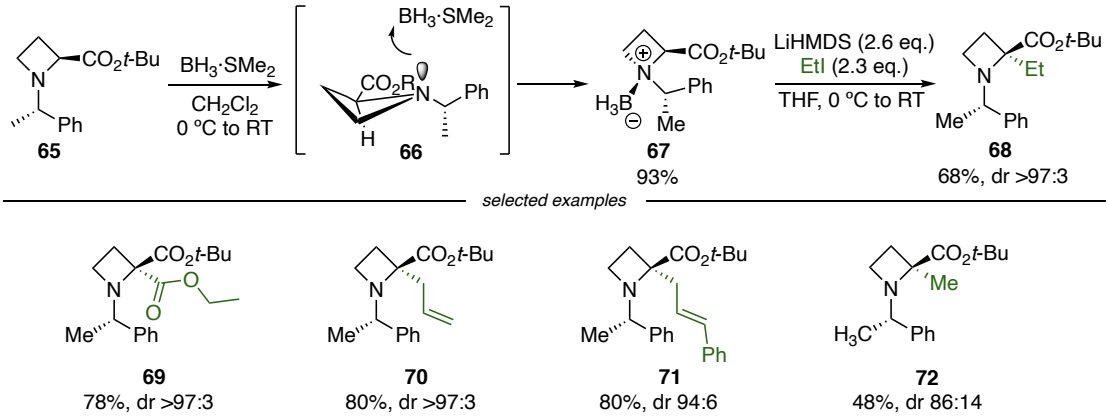
Scheme 6: Alternative approach to enantioenriched spirocyles.

In this context, in 2009, Shibasaki *et al*. reported the one-pot catalytic asymmetric synthesis of 2,2-disubstituted oxetanes **64** (Scheme 7).[47] Using lanthanum-based catalyst (*S*)-**62**, a phosphorus oxide additive and dimethyloxosulfonium methylide (**40**), ketone **61** underwent sequential addition to intermediate epoxide **63**, then to oxetane **64**. This process also benefited from chiral amplification, enabling very high levels of enantioselectivity to be achieved. This methodology was successfully applied to the synthesis of tetrasubstituted α-oxetanes **64a**–**d** bearing aryl and alkyl substituents with excellent ee; however, a more diverse substrate scope that encompases groups compatible with subsequent cyclisation would be required if this methodology was to be used in the synthesis of enantiopure spirocycles.



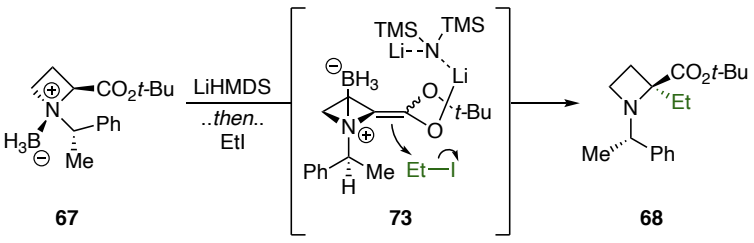
Scheme 7: Enantioenriched oxetane structures.

Azetidine-2-carboxylic acid is a four-membered amino acid analogue of proline. Several synthetic routes to this compound have been reported,[48] and, in 2018, Tayama *et al.* communicated the synthesis of 2-disubstituted azetidines **68**–**72** *via* diastereoselective α-alkylation using diastereomerically pure borane complexes **67** (Scheme 8).[49] This route begins with *N*-boration of **65** in which the substituents at the 2- and *N*-positions are pseudoequatorial (**66**), whereas the axial lone pair on the nitrogen atom co-ordinates to the borane to furnish **67** as a single diastereoisomer. In the final step, enolate alkylation proceeds with high diastereoselectivity to give **68**.



Scheme 8: Diastereoselective azetidine synthesis using diastereomerically pure borane complexes.

This alkylation reaction proceeds through a planar enolate intermediate **73** (Scheme 9). Therefore, in the alkylation step to azetidine **68**, the LiHMDS complex is bound to the enolate oxygen in **73**, which results in the lithium complex and the borane blocking one face of the enolate, and directs alkylation almost exclusively to the opposite face of the enolate.

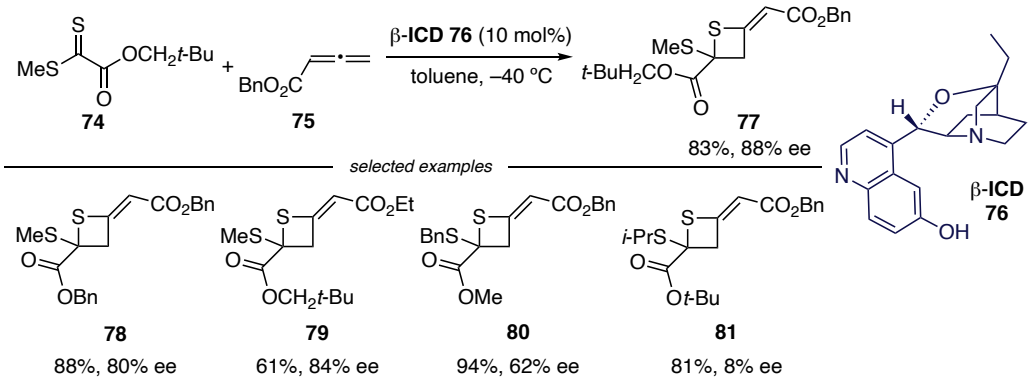


Scheme 9: *N*- to *C*- chirality transfer.

The *N*-(*S*)-1-phenylethyl substituent on the nitrogen atom in **68** can be removed by hydrogenolysis to reveal the enantioenriched azetidine. The *tert*-butyl ester could also

be hydrolysed to furnish the carboxylic acid, which could be utilised in the subsequent synthesis of chiral, enantiopure azetidine spirocycles.

Compared to oxetanes and azetidines, thietanes and their oxidised analogues are underexplored in screening libraries. In 2015, Shi and co-workers reported the reaction of dithioester **74** and allenoate **75** in a [2+2] cycloaddition to yield enantioenriched, 2-disubstituted thietane **77** (Scheme 10).[50] **78** and **79** were achieved in high yields and good enantioselectivity (80% and 84% ee, respectively). Larger substituents on the sulfur atom at the 2-position were less well-tolerated as seen in benzyl example **80**, and isopropyl example **81** (62% and 8% ee, respectively). These scaffolds also provide reactive handles for further functionalisation.

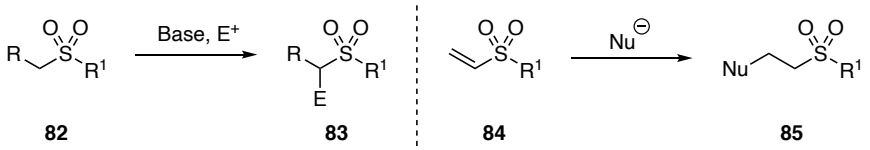


Scheme 10: [2+2] cycloaddition for substituted thietane scaffolds.

Overall, the development of methodologies to generate enantioenriched, 2-tetrasubstituted four-membered heterocycles could provide a way to create enantioenriched spirocycles *via* functionalisation of these building blocks. These structures must possess the requisite functional handles to enable derivatisation and cyclisation into spirocycles. In addition, more research is required to broaden the types of four-membered heterocycles that can be accessed in a catalytic asymmetric fashion.

1.1.7 Sulfones in Medicinal Chemistry

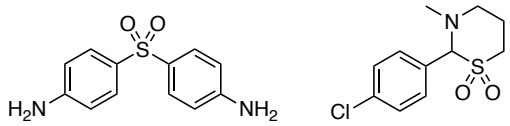
A sulfone is a common functional group that is often accessed by the oxidation of sulfides. The sulfone moiety is considered a carbonyl bioisostere due to its hydrogen-bond acceptor ability.[51] As a versatile functional group, a sulfone can act as a nucleophile when treated with a base *via* deprotonation at the α-position (**82** to **83**, Scheme 11), and also as an electrophile in the form of a Michael acceptor (**84** to **85**).[52]



82 **83** **84** **85**

Scheme 11: Reactivity of sulfones.

Sulfones are found in several drug scaffolds including dapsone (**86**), an antibiotic used in the treatment of leprosy, and chlormezanone (**87**), a muscle relaxant (Figure 12).[53,54]

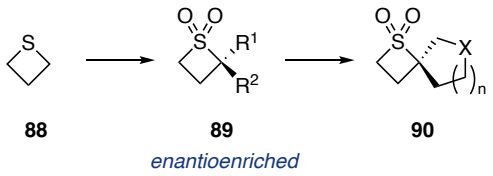


86
dapsone

87
chlormazanone

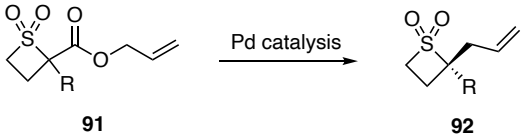
Figure 12: Sulfone-containing drug compounds.

Cyclic sulfones, such as thietane-1,1-dioxide, are of great interest in medicinal chemistry as they are considered a novel and under-investigated analogue to oxetane;[51] however, there has been a significant lack of research into this motif compared to azetidines and oxetanes. Indeed, currently there are no synthetic routes to enantioenriched 2-disubstituted thietane-1,1-dioxide **89** (Scheme 12), or spirocycles thereof (**90**). We, therefore, propose to develop an asymmetric methodology to access enantioenriched building blocks **89** from commercially available thietane (**88**). Following this, derivatisation of the functional handles (R^1 and R^2) in **89** would enable construction of spirocycle **90**.



Scheme 12: Route to thietane-1,1-dioxide containing spirocycles.

More specifically, we sought to develop an enantioselective palladium-catalysed decarboxylative allylic alkylation of thietane-1,1-dioxide substrates **91** to create enantioenriched α-sulfonyl building blocks **92** (Scheme 13).



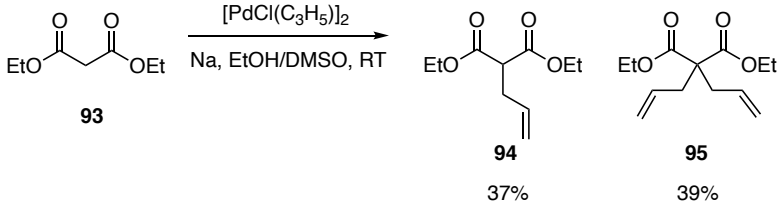
Scheme 13: Palladium-catalysed decarboxylative asymmetric allylic alkylation of thietane-1,1-dioxides.

Therefore, before discussing the specifics of our project aims, a more detailed analysis of the palladium-catalysed asymmetric allylic alkylation process is warranted. This discussion follows in the next section.

1.2 The Tsuji-Trost Reaction for C–C Bond Formation

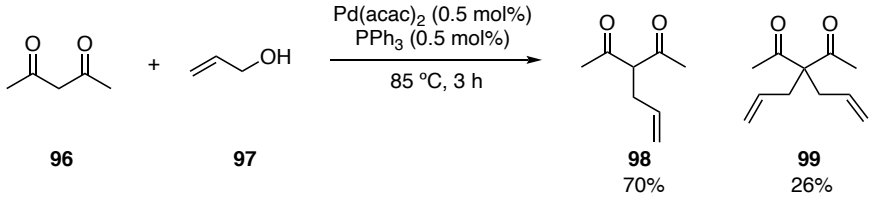
1.2.1 Original Reports

The Tsuji-Trost reaction was first reported by Tsuji and co-workers in 1965, who performed the reaction of π-allylpalladium(II) chloride ($[PdCl(C_3H_5)]_2$) with the sodium salt of diethyl malonate (**93**, Scheme 14). This reaction furnished diethyl allylmalonate (**94**) in 37% yield, and the dialkylated by-product, diethyl diallylmalonate (**95**), in 39% yield.[55]



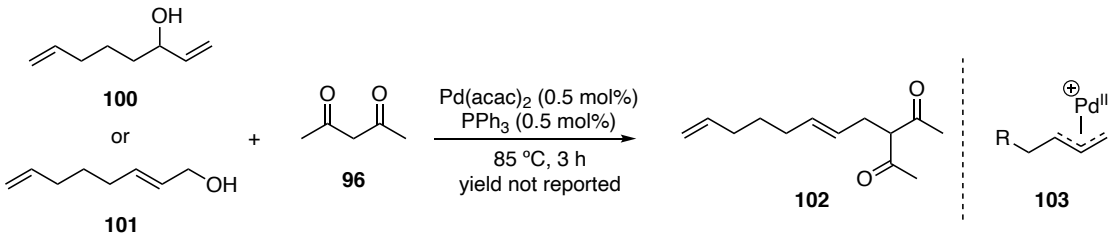
Scheme 14: First palladium-mediated allylic alkylation.

The use of stoichiometric amounts of palladium curbed the utility of this reaction in scaled-up synthesis due to the high cost of palladium and the production of a stoichiometric quantity of waste. Therefore, in 1970, attention turned to exploiting the catalytic nature of palladium to alleviate these problems.[56] Catalytic conditions were successfully reported for the alkylation of acetylacetone (**96**) with allyl alcohol (**97**) using a 0.5 mol% catalyst loading of palladium(II) acetylacetonate, alongside triphenylphosphine as the ligand (Scheme 15). These catalytic conditions produced monoalkylated **98** as the major product in 70% yield, and dialkylated product **99** in 26% yield.



Scheme 15: First allylic alkylation using catalytic quantities of palladium.

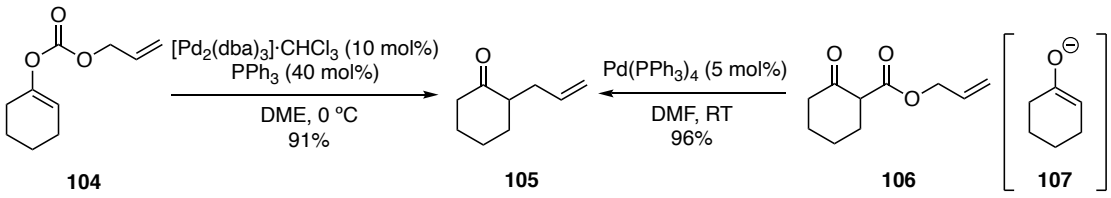
The regioselectivity of this reaction was further probed using isomeric allylic alcohols **100** and **101** (Scheme 16).[56] Interestingly, alkylation of each of these substrates yielded product **102** as a single isomer, suggesting the reaction proceeded *via* common π-allylpalladium(II) intermediate **103** and resulted in preferential alkylation of acetoacetone (**96**) at the least hindered terminus of **103**.



Scheme 16: Investigation of regioselectivity of alkylation in the Tsuji-Trost reaction.

These original reports focused on the *direct* allylic alkylation between an independent nucleophile and an independent allylic electrophile.

In the early 1980s, Tsuji[57] and Saegusa[58] independently developed the analogous palladium-catalysed *decarboxylative* allylic alkylation (Scheme 17). This reaction involved tethering the nucleophile and the electrophile together as either allyl enol carbonate **104** or β-ketoester **106** (Scheme 17), in order to generate the enolate nucleophile **107** *in situ* after the loss of carbon dioxide. More specifically, when allyl enol carbonate **104** and β-ketoester **106** were independently reacted under catalytic palladium conditions, each afforded **105** as the single product, arising from the allylic alkylation of common enolate intermediate **107**.



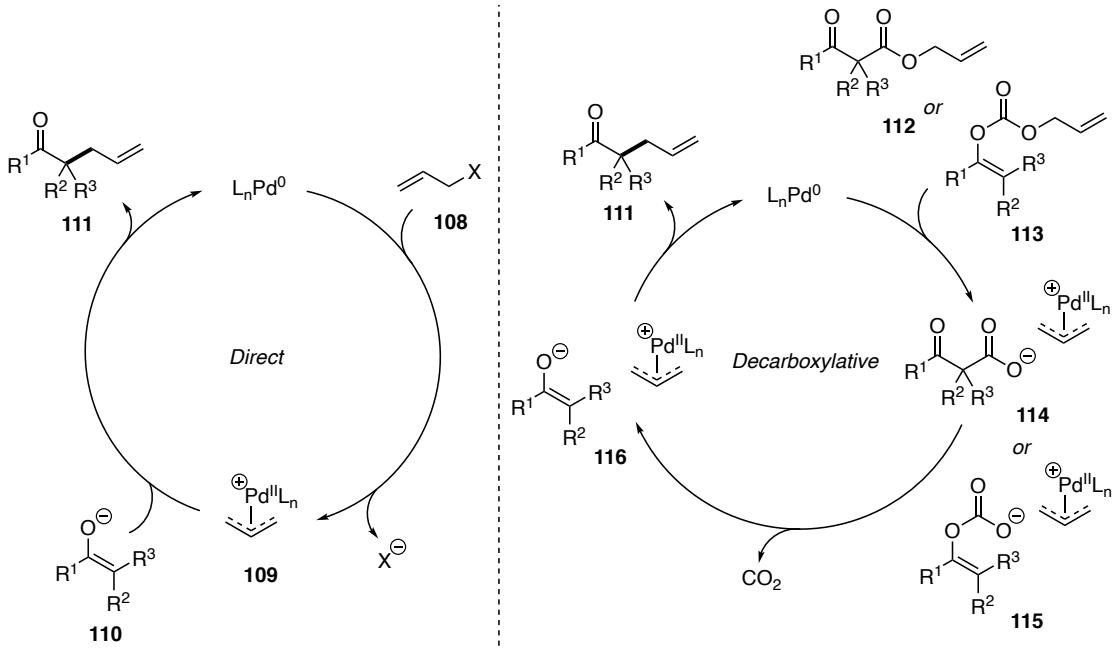
Scheme 17: Early reports of palladium-catalysed decarboxylative allylic alkylation.

Since these seminal reports, the direct and decarboxylative Tsuji-Trost alkylation has become an extremely well-developed reaction for a range of heteroatom and carbon nucleophiles.[59-68] However, this thesis focuses specifically on carbon nucleophiles due to our interest in C–C bond formation. Therefore, a more detailed discussion of the allylic alkylation of *C*-nucleophiles, predominantly enolates, follows in the next few sections.

1.2.2 Direct vs Decarboxylative Allylic Alkylation of Enolates

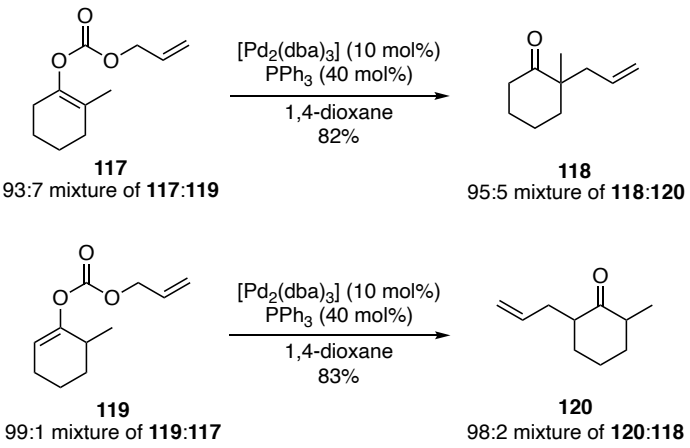
A comparison of the mechanisms of the direct and decarboxylative allylic alkylation of enolates is shown in Scheme 18. Direct allylic alkylation involves the reaction of the electrophile and nucleophile as independent species.[59] An ionisation *via* oxidative addition of palladium(0) to electrophile **108** generates π-allylpalladium(II) complex **109**, which then reacts with enolate nucleophile **110** to form alkylated product **111**. In contrast, in the decarboxylative allylic alkylation reaction, both the nucleophile and allylic electrophile are tethered in β-ketoester **112** or allyl enol carbonate **113**. Substrates **112** and **113** initially undergo oxidative addition to form **114** and **115**. Subsequent decarboxylation of either intermediate releases carbon dioxide to reveal the

common enolate nucleophile and π-allylpalladium(II) complex **116**. Allylic alkylation then releases product **111** and regenerates the palladium(0) catalyst.[66]



Scheme 18: Comparison of the direct and decarboxylative allylic alkylation mechanisms.

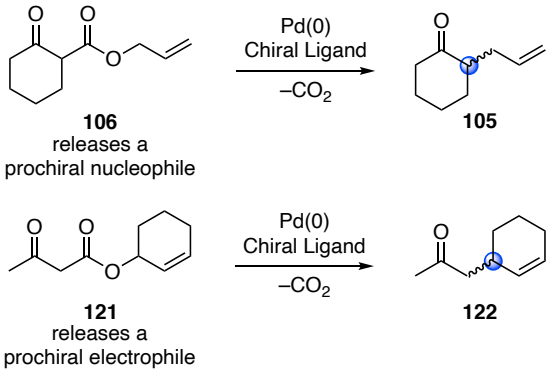
The decarboxylative allylic alkylation process occurs under mild, neutral conditions due to facile decarboxylation to form the requisite enolate. In contrast, the direct alkylation pathway necessitates the use of either a strong base to form the enolate nucleophile, or a preformed specific enol equivalent. In both cases, regioselectivity must be controlled in the presence of more than one enolisable position. The decarboxylative method overcomes this challenge by generating the enolate regiospecifically at the site of decarboxylation. To demonstrate this concept, enol carbonate isomers **117** and **119** were reacted under identical conditions to ascertain whether enolate scrambling occurred during the allylic alkylation reaction (Scheme 19).[57] Products **118** and **120** were formed in a ratio almost identical to that of the starting materials with no isomerisation of the enolate, illustrating the site-selective nature of decarboxylative allylic alkylation. In contrast, selective formation of **118** and **120** *via* a direct allylic alkylation would be much more challenging due to the need to selectively pre-form the requisite thermodynamic or kinetic enolate or specific enol equivalent.



Scheme 19: High regiochemical fidelity of the decarboxylative allylic alkylation.

1.2.3 Development of the Palladium-Catalysed Decarboxylative Asymmetric Allylic Alkylation (Pd-DAAA)

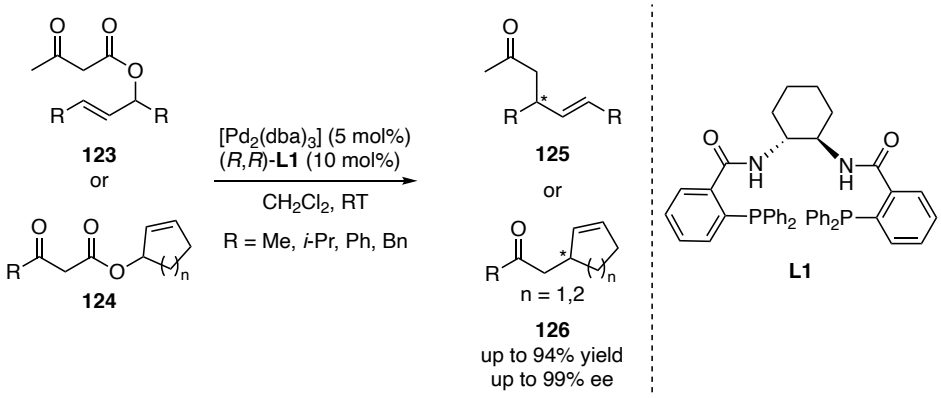
The enantioselectivity of the palladium-catalysed decarboxylative asymmetric allylic alkylation reaction can be imparted using either a prochiral nucleophile or a prochiral electrophile (Scheme 20). Asymmetric alkylation of a prochiral nucleophile, an enolate formed *in situ* from **106**, would afford **105** with a ketone α-stereogenic centre. In contrast, a prochiral electrophile, such as a π-allylpalladium(II) cation derived from **121**, could result in the construction of a stereogenic centre at the allylic centre in **122**.[69]



Scheme 20: Enantioselectivity using prochiral nucleophiles and electrophiles.

The first palladium-catalysed decarboxylative asymmetric allylic alkylation was reported in 2004 by Tunge and co-workers.[70] In this work, substrates **123** and **124**,

bearing a prochiral allylic electrophile, underwent the desired allylic alkylation of ketone enolates in the presence of chiral DACH phenyl-Trost ligand (*R*,*R*)-**L1**, resulting in high enantioselectivity in the formation of alkylated products **125** and **126** (Scheme 21).

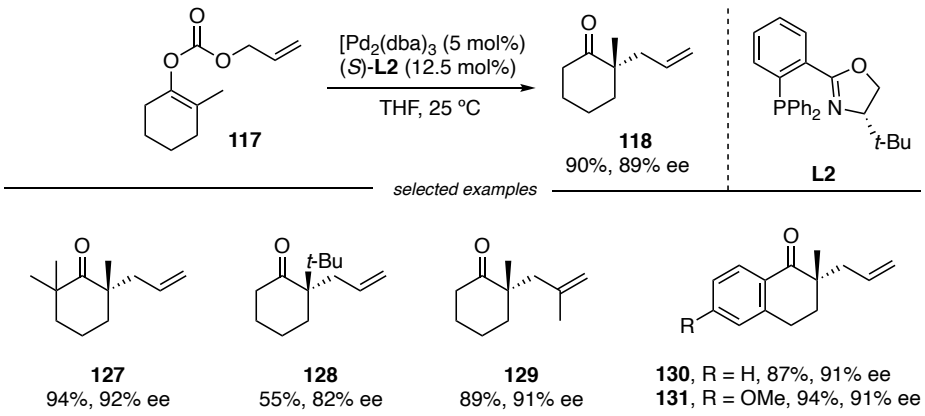


Scheme 21: First Pd-DAAA of a prochiral electrophile.

In addition to prochiral electrophiles, prochiral nucleophiles can also be used to install α-stereogenic all-carbon quaternary centres stereoselectively by preferential alkylation of one of the two prochiral faces of the nucleophilic enolate. It is in this context that the asymmetric decarboxylative allylic alkylation has been most widely investigated.

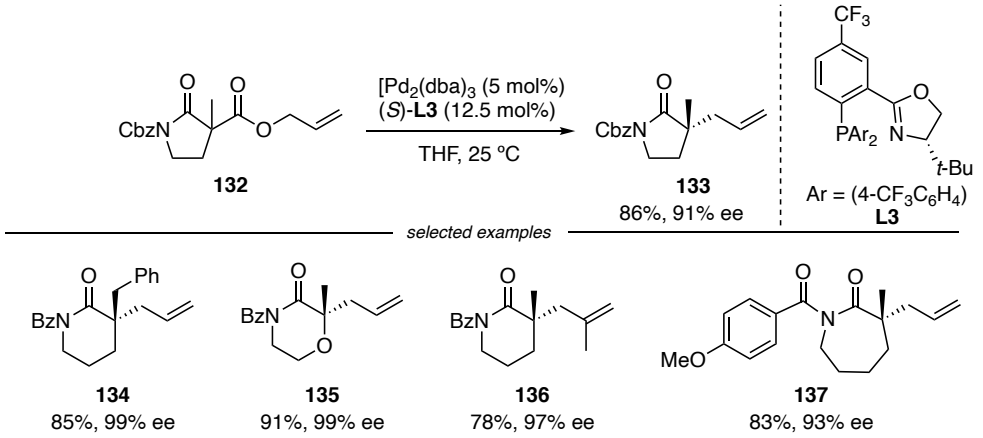
1.2.4 Pd-DAAA of Cyclic Ketone Enolates

The first decarboxylative asymmetric allylic alkylation of prochiral ketone enolates was reported by Stoltz and co-workers in 2004 using allyl enol carbonate **117** in the presence of (*S*)-*t*-Bu-PHOX (**L2**) as the ligand (Scheme 22).[71] This reaction proceeded with high efficiency and enantioselectivity to generate an α-chiral quaternary all-carbon centre in **118**. Alongside methyl-substituted product **118**, *gem*-dimethyl **127**, *tert*-butyl **128**, substituted allyl fragment **129**, and tetralone derivatives **130** and **131** were all compatible with this reaction to form products with high levels of enantioselectivity. Following this development, prochiral ketone enolates have become the most commonly studied substrate type in the context of the Pd-DAAA methodology.[72-91]



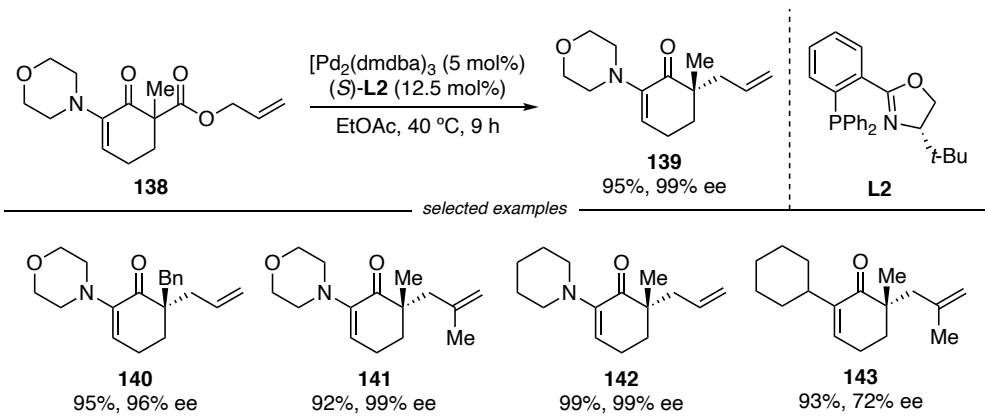
Scheme 22: First Pd-DAAA of prochiral cyclic enolate nucleophiles.

Saturated nitrogen heterocycles are ubiquitous in biologically active natural products and drug compounds. Stereoselective functionalisation of these scaffolds is extremely desirable and, therefore, the DAAA of lactam enolates was reported in 2011 by Stoltz and co-workers (Scheme 23).[92] With β-allylester lactams **132** as substrates, the reaction was probed by investigating the *N*-substituent effect on enantioselectivity. Preliminary results in this study revealed that electron-rich protecting groups gave poor results in the decarboxylative asymmetric allylic alkylation reactions, and hence, electron-withdrawing *N*-substituents were used instead. (*S*)-*t*-Bu-PHOX (**L2**) and (*S*)-$(CF_3)_3$-*t*-Bu-PHOX (**L3**) ligands were compared, with the latter, electron-deficient ligand, giving superior enantioselectivities for all the lactam substrates. The substrate scope was investigated to emphasise the utility of this reaction by varying the lactam ring size and *N*-substituents. Specifically, benzyl carbamates **133** maintained high yields, but achieved slightly lower enantioselectivity than benzoyl amides **134**–**136**. Five-, six- and seven-membered lactams were well tolerated in this reaction (**133**, **134** and **137**), as well as substitution at the allyl group in **136**. The Stoltz group in particular went on to successfully develop the Pd-DAAA reaction of several other *N*-heterocycles,[93] including diazaheterocycles,[94] 1,4-diazepan-5-ones,[95] and 4-imidazolidinones.[96]



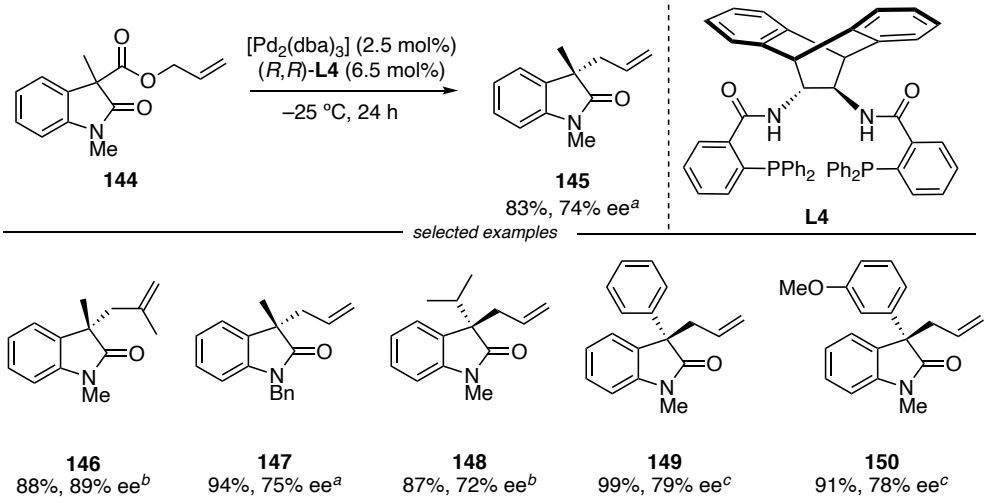
Scheme 23: Pd-DAAA of lactams.

More recently, in 2020, Stoltz and co-workers reported the Pd-DAAA of α-enaminones (Scheme 24).[76] The authors were interested in studying the electronics of the enolate, as well as potential chelation of a heteroatom on the enolate nucleophile to the palladium centre. The DAAA reaction of **138** using (*S*)-*t*-Bu-PHOX (**L2**) as the ligand furnished alkylated product **139** in 99% ee. This reaction was tolerant to α-substituents (**140**) and allyl substituents (**141**), forming products in 96% and 99% ee, respectively. To probe the impact of heteroatom chelation on the enantioselectivity of the reaction, piperidine (**142**) and cyclohexyl (**143**) substrates were subjected to the Pd-DAAA reaction. There was no observable impact on the enantioselectivity when the piperidine substrate was used (99% ee of **142**); however, interestingly, the cyclohexyl substituent led to a significant drop in enantioselectivity, giving only 72% ee of **143**. Therefore, the authors postulated that the high enantioselectivity resulted from a favourable chelation of the nitrogen atom to the palladium centre during alkylation.



Scheme 24: Pd-DAAA of α-enaminones.

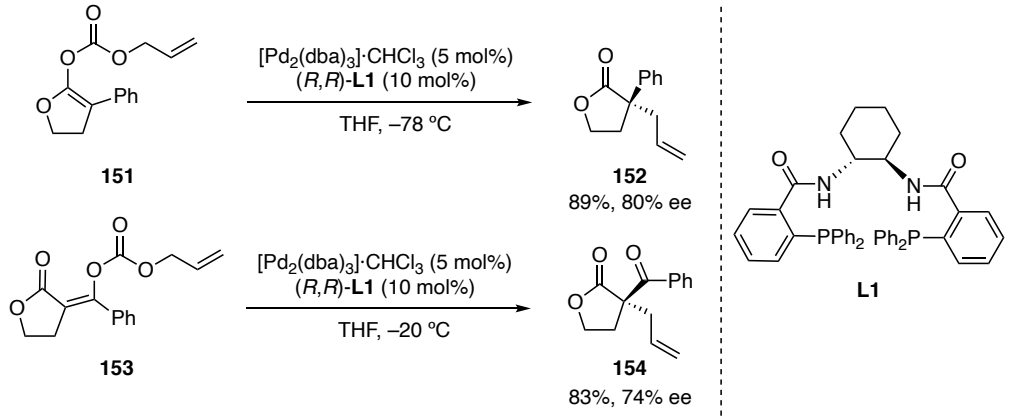
In 2011, Taylor and co-workers reported the Pd-DAAA of alkyl- and aryl-substituted oxindoles (Scheme 25).[97] Interestingly, the steric size of the substituent at the 3-position dictated the sense of enantioselectivity when using (*R*,*R*)-**L4** as the ligand. Small alkyl substituents, such as **145** and **146**, furnished the *S* major enantiomer of product. An alternative *N*-benzyl substituent in **147** did not appear to influence the enantioselectivity of the reaction. In contrast, larger *iso*-propyl (**148**) and phenyl (**149** and **150**) substituents furnished the opposite absolute stereochemical configuration at the α-position of product while maintaining similar levels of enantioselectivity. The switch in the sense of enantioselectivity was rationalised by steric interactions within the chiral ligand sphere, resulting in the opposite faces of the enolate being favourably alkylated.



Reaction solvent: [a] DME; [b] THF; [c] PhMe

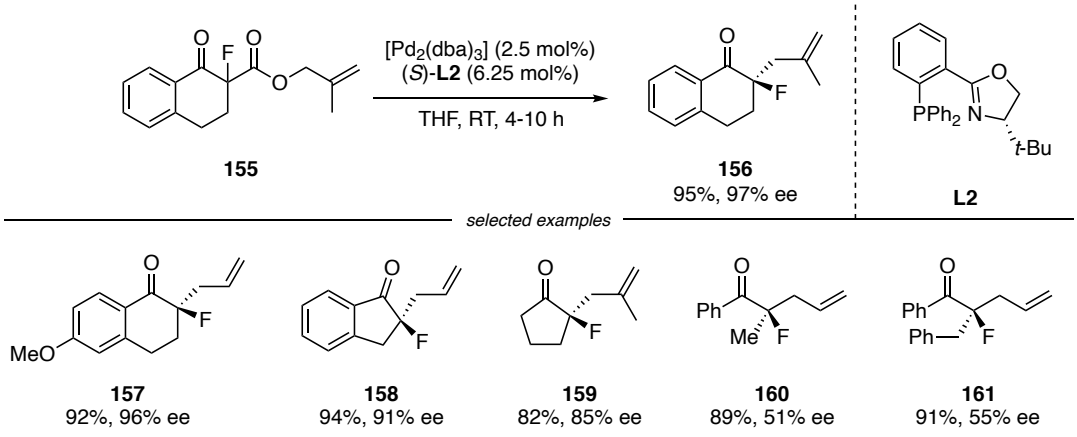
Scheme 25: Pd-DAAA of oxindoles.

In 2016, Cossy and co-workers reported the Pd-DAAA of both cyclic and acyclic allyl enol carbonates derived from γ-butyrolactones to generate α,α'-disubstituted γ-butyrolactones (Scheme 26).[98] The Pd-DAAA reaction of enol carbonate **151** at –78 ºC formed butyrolactone **152** in high yield and enantioselectivity. To generate the α-acyl derivative, enol carbonate (*Z*)-**153** was used as the achiral precursor in the reaction. This substrate was found to be less reactive than **151**, requiring a higher temperature of –20 ºC. Similarly, Cossy and co-workers also reported the decarboxylative asymmetric allylic alkylation of γ-butenolides to furnish unsaturated analogues of **154**.[99]



Scheme 26: Pd-DAAA to enantioenriched α,α'-disubstituted γ-butyrolactones.

Incorporation of fluorine in medicinally relevant compounds is highly desirable, and Pd-DAAA represents a useful method to generate α-fluoro ketones asymmetrically, as reported in 2005 by Nakamura and co-workers (Scheme 27).[77] The reaction of α-fluoro-β-ketoester **155** in the presence of (*S*)-*t*-Bu-PHOX (**L2**) in THF furnished alkylated product **156** in excellent 95% yield and 97% ee. Similarly, cyclic ketones furnished the desired products **157**–**159** in good to excellent enantioselectivities (85–96% ee). While the acyclic examples **160** and **161** maintained high yields, these substrates suffered a significant drop in enantioselectivity (51% and 55% ee, respectively). This outcome is likely caused by the acyclic nature of the enolate intermediate. Indeed, the challenges associated with the asymmetric allylic alkylation of acyclic ketone enolates are discussed in the next section.



Scheme 27: Pd-DAAA of α-fluoro-β-ketoesters.

1.2.5 Pd-DAAA of Acyclic Ketone Enolates

The decarboxylative asymmetric allylic alkylation reaction has mainly been studied on cyclic ketones, such as **106** (Figure 13), as the geometry of the enolate remains fixed, ensuring high levels of stereocontrol. Acyclic β-ketoesters **162** are inherently more challenging as they can form a mixture of enolate geometries following decarboxylation, which could in turn lead to a loss of stereocontrol. However, allyl enol carbonates can be used as sources of geometrically pure acyclic enolates, provided that in the formation of *E*-**163** or *Z*-**163** either the enolate is generated stereoselectively or the enol carbonates are purified chromatographically.

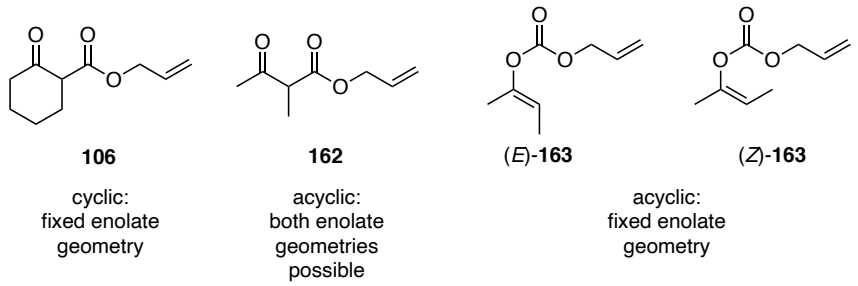
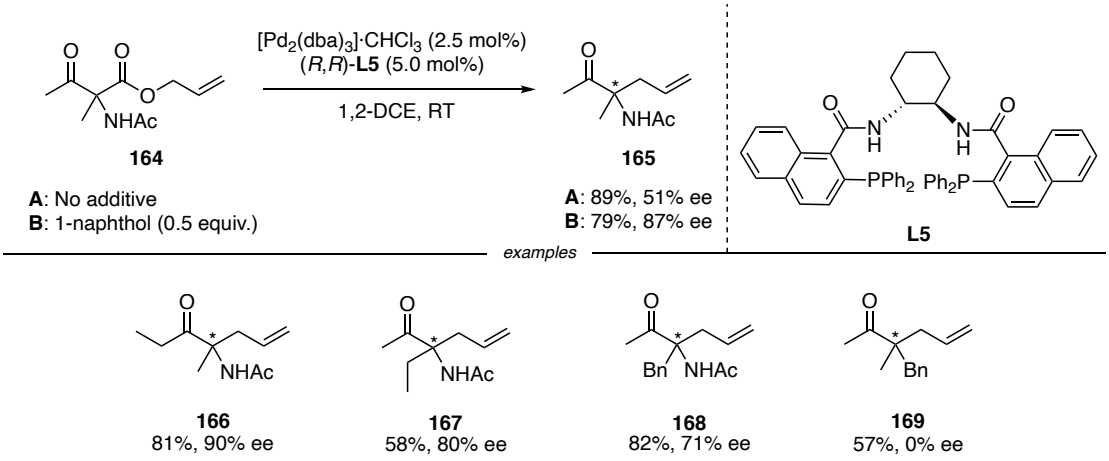


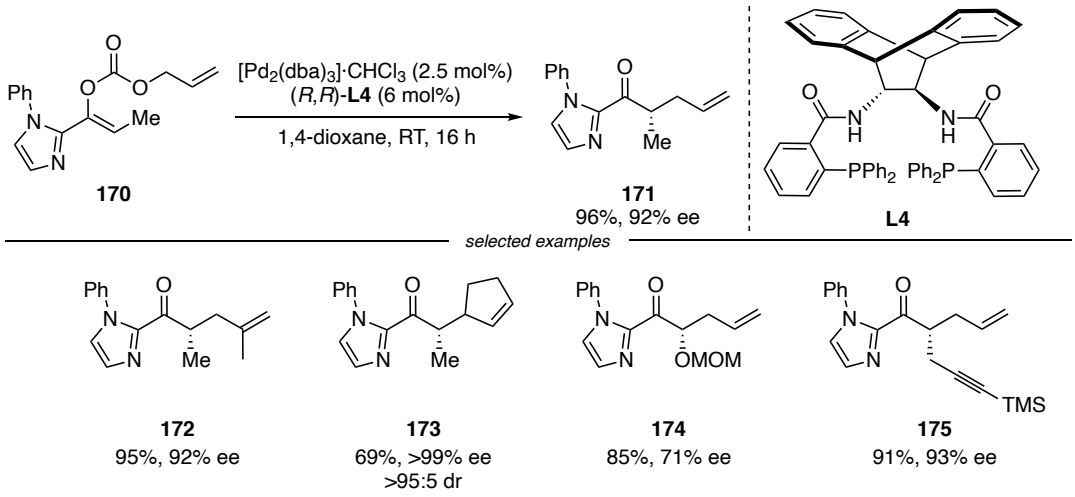
Figure 13: Stereocontrol of enolate geometry using β-ketoesters and enol carbonates.

In 2005, Murakami and co-workers reported the Pd-DAAA of acyclic allyl α-acetamido-β-keto carboxylates **164** (Scheme 28).[100] To achieve higher levels of enantioselectivity of product **165**, this reaction required the addition of a 1-naphthol additive (51% compared to 87% ee) and products containing alkyl substituents, such as methyl (**166**), ethyl (**167**) and benzyl (**168**), were formed with moderate to high enantioselectivities (71–90% ee). The authors postulated the enhancement of enantioselectivity using the 1-naphthol additive was caused by hydrogen-bonding between the additive and the acetamido group, leading to a favoured conformation within the chiral ligand sphere resulting in one enolate being preferred. This argument was strengthened by the reaction to form **169**, which lacks the acetamido group, ultimately leading to racemic product.



Scheme 28: Pd-DAAA of acyclic allyl α-acetamido-β-keto carboxylates.

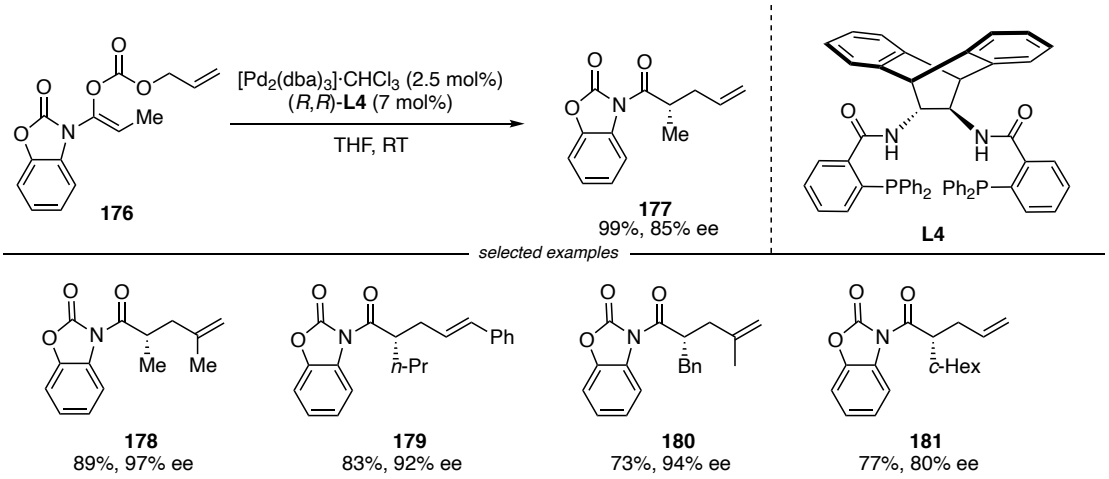
The Pd-DAAA of 2-acylimidazoles was reported by Trost and co-workers in 2010 (Scheme 29).[101] Acyclic *Z*-enol carbonate **170** was transformed into alkylated product **171** in 96% yield and 92% ee. This reaction was tolerant of substitution at the allyl position in **172** and **173**, as well as the OMOM and silyl protected alkyne group at the α-position in **174** and **175**.



Scheme 29: Pd-DAAA of 2-acylimidazoles.

The following year, Trost and co-workers reported the Pd-DAAA of *N*-acyloxazolidines (Scheme 30).[102] Enol carbonate **176** successfully underwent asymmetric alkylation to furnish **177** in excellent yield with good enantioselectivity (99% yield and 85% ee, respectively). This methodology was applicable to substrates

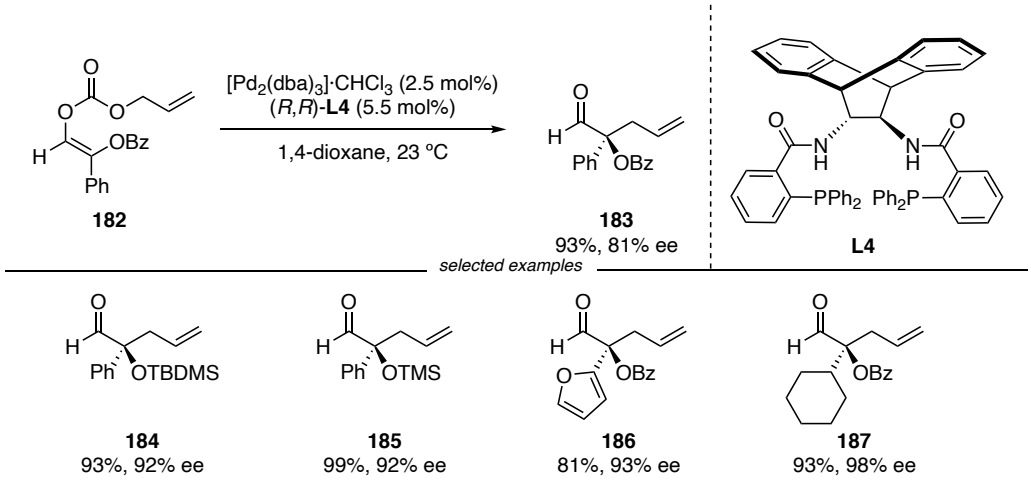
bearing substituted allyl fragments and various alkyl substituents at the reacting centre in **178**–**181**; however, there were no examples of aryl substituents at the α-position.



Scheme 30: Pd-DAAA of *N*-acyloxazolidines.

Both of these transformations (*vide supra*, Schemes 29 and 30) were reported with *Z*-configured enol carbonate precursors **170** and **176** to furnish products **171** and **177** respectively, with high enantioselectivity. However, the authors did not study the impact of *E*-enol carbonate substrates on the efficiency and, crucially, the stereoselectivity of alkylation.

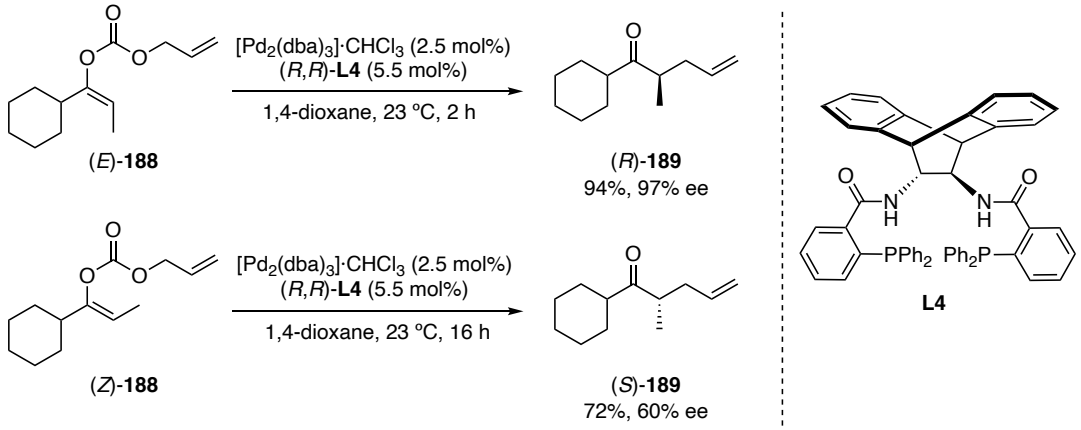
In addition to ketone enolates, acyclic aldehyde-derived enolates can also undergo the Pd-DAAA reaction to generate products with comparable enantioselectivity to acyclic ketone enolates (Scheme 31).[103] Allyl enol carbonate **182** underwent decarboxylative allylic alkylation using (*R*,*R*)-**L4** as the chiral ligand to furnish alkylated **183** in 93% yield and 81% ee. Alternative alcohol protecting groups such as TBDMS and TMS achieved improved enantioselectivities (92% ee of **184** and **185**). Similarly, furyl (**186**) and cyclohexyl (**187**) substituted products were formed in 93% and 98% ee, respectively.



Scheme 31: Pd-DAAA of α-tertiary hydroxyaldehydes.

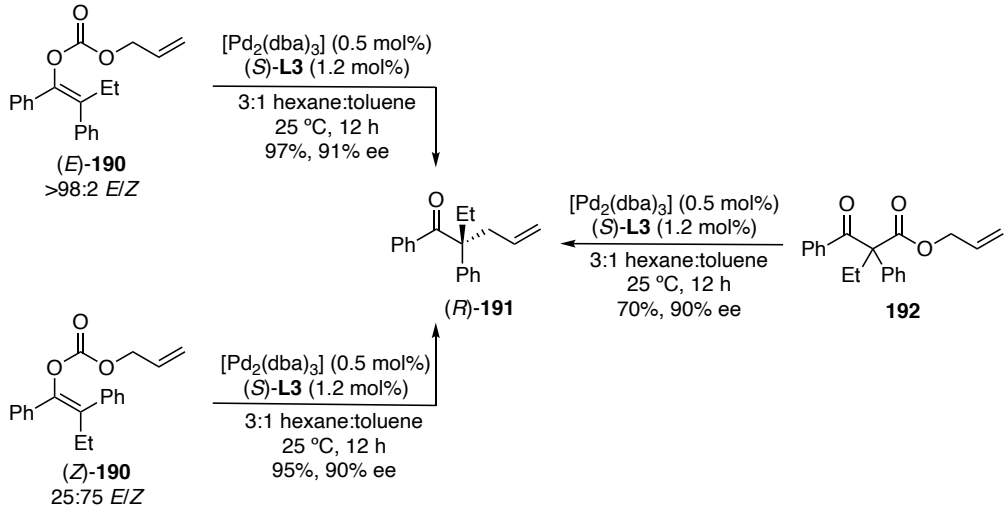
1.2.6 Influence of Enolate Geometry on Stereoselectivity

Trost and co-workers sought to establish the influence of enolate geometry on the enantioselectivity of alkylation for acyclic enol carbonate **188** (Scheme 32). Both *E*-and *Z*-isomers of **188** were reacted under identical Pd-DAAA conditions using the same enantiomer of catalyst (*R*,*R*)-**L4**.[104] Interestingly, the *E* isomer was found to be more reactive, with the reaction going to completion in only 2 h, and achieving a 94% yield and 97% ee of (*R*)-**189**. On the other hand, the reaction of the *Z* isomer required 16 h to reach completion, affording a diminished 72% yield and 60% ee of the opposite enantiomer of product, (*S*)-**189**. These results confirmed that enolate geometry is indeed important in both attaining high levels of stereoselectivity and controlling the sense of stereoinduction of alkylation. It is, therefore, apparent that the additional challenge of accessing geometrically pure allyl enol carbonates needs to be overcome in order to obtain high stereoselectivity of alkylation.



Scheme 32: The effect of enolate geometry on the Pd-DAAA reaction.

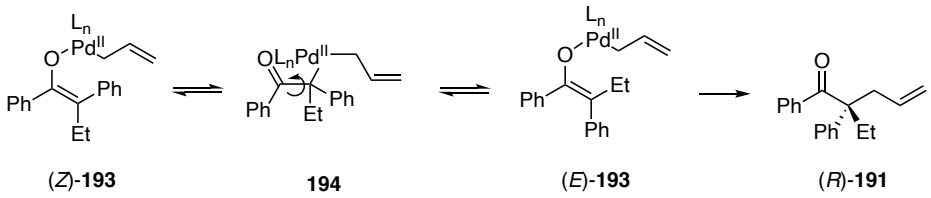
In 2018, the decarboxylative asymmetric allylic alkylation of fully substituted acyclic enol carbonates was reported, in which the importance of enolate geometry was also probed (Scheme 33).[105] Stoltz and co-workers prepared enol carbonates **190** in a >98:2 and 25:75 *E*/*Z* ratio. Under the DAAA conditions using (*S*)-**L3** as the chiral ligand, both isomers afforded (*R*)-**191** as the major enantiomer in almost identical yields and enantioselectivity. The corresponding β-ketoester **192** was also subjected to the palladium conditions and formed (*R*)-**191** as the major enantiomer with identical ee, albeit in a slightly lower yield (70%).



Scheme 33: Inconsequential starting geometry for DAAA to (*R*)-**191**.

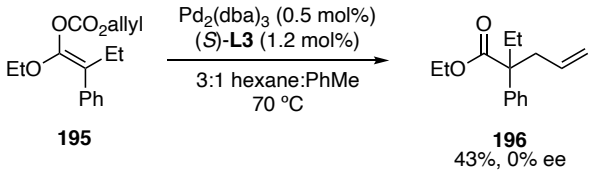
In contrast to the findings by Trost (*vide supra*, Scheme 32), the enolate geometry in this system was inconsequential to the overall stereochemical outcome of the reaction.

This observation can be explained by a palladium-mediated interconversion of the two enolate isomers *via* an equilibrium of the oxygen- and carbon-bound palladium enolates **193** and **194** (Scheme 34). It was postulated that the rate of *E*/*Z* enolate isomerisation is faster than the rate of alkylation of (*Z*)-**193**, resulting in stereoselective alkylation of (*E*)-**193** to give (*R*)-**191** as the major isomer. This process can be thought of as being analogous to a dynamic kinetic resolution.



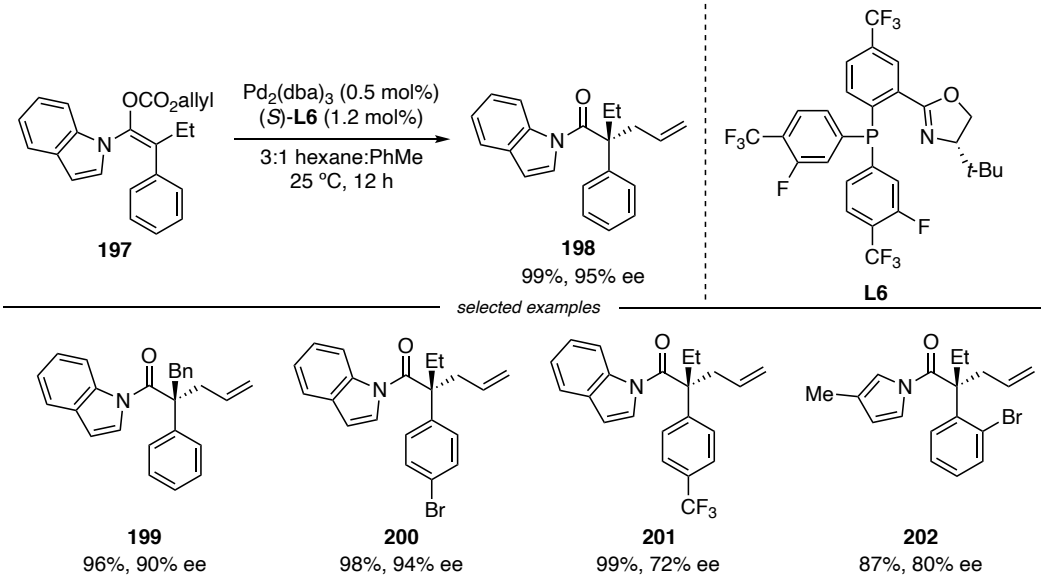
Scheme 34: Palladium-mediated interconversion of enolates.

To extend the methodology of the DAAA reaction to ester enolates, Stoltz and co-workers attempted the DAAA reaction of ester-derived enol carbonate **195** (>98:2 *E*/*Z*) to form a quaternary α-stereogenic centre in **196** (Scheme 35).[106] Despite extensive optimisation, enol carbonate **195** was found to be incompatible with this reaction, furnishing racemic product **196** in 43% yield in the presence of chiral ligand (*S*)-**L3**.



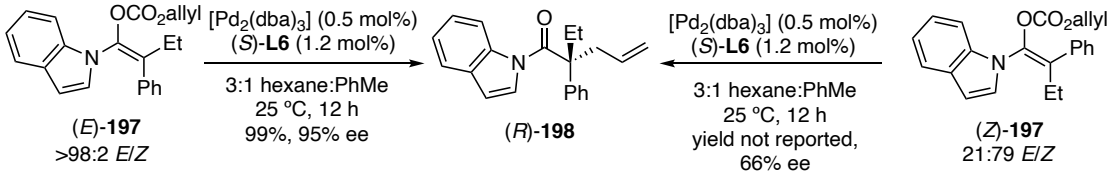
Scheme 35: Unsuccessful Pd-DAAA of ester enolates.

Instead, ester enolate surrogates were attempted in the form of *N*-acyl heterocycles (Scheme 36), such as indole-derived enol carbonate **197**. All starting enol carbonates were used in essentially geometrically pure form (*E*/*Z* ratios of >95:5). Alkylated products **198**–**202** were formed in excellent yields, with phenyl-substituted **199** and *p*-bromophenyl-substituted **200** giving >90% ee. Electron-withdrawing *p*-CF_3 phenyl group and smaller *N*-acyl 3-methyl pyrrole substituent furnished products **201** and **202** in a lower 72% and 80% ee, respectively.



Scheme 36: Pd-DAAA of ester enolate equivalents, *N*-acyl heterocycles.

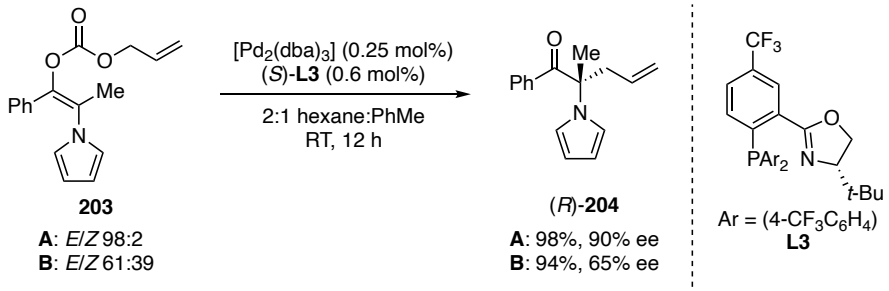
As these *N*-acyl indole-derived enol carbonates **197** are acyclic, the enolate geometry was probed further. Mixtures of >95:5 and 21:79 *E*/*Z* enol carbonates were reacted under palladium conditions (Scheme 37). Although the *R* enantiomer of **198** was the major stereoisomer obtained using both enol carbonates **197**, enantioselectivity of alkylation of the *Z*-enol carbonate (*Z*)-**197** was substantially lower than that of (*E*)-**197** (66% compared to 95% ee, respectively). The reaction outcome suggested that, while an enolate equilibrium was present, it did not occur to the same extent as that found in the Pd-DAAA of ketone-derived enol allyl carbonates **190** (*vide supra*, Scheme 33).



Scheme 37: Partial enolate equilibrium for *N*-acyl indole-derived substrates.

Stoltz and co-workers recently reported the Pd-DAAA reaction of acyclic α-*N*-pyrrolyl ketones using very low catalyst and ligand loading (Scheme 38).[107] To probe the importance of enolate geometry in this system, enol carbonate **203** was synthesised in both a 98:2 and 61:39 *E*/*Z* ratio and reacted independently under Pd-DAAA conditions using (*S*)-**L3** as the ligand. It was found that the (*E*)-**203** isomer led to 90% ee of (*R*)-

204, whereas an *E*/*Z* mixture of **203** resulted in a lower 65% ee of (*R*)-**204**. This study also suggested that a palladium-mediated enolate interconversion had occurred, albeit not to the full extent.

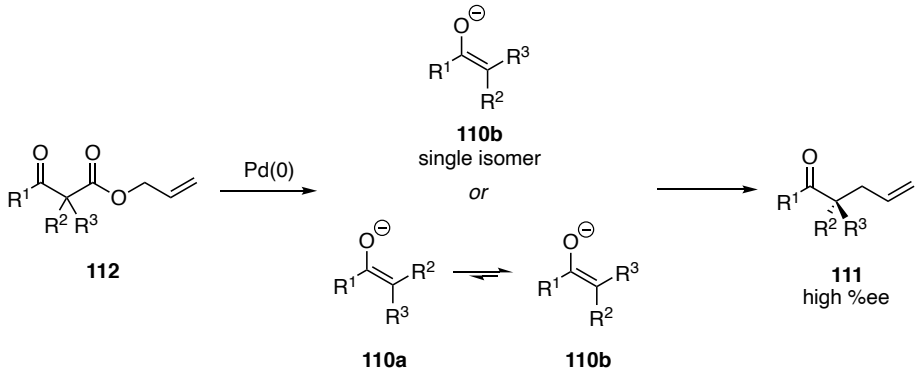


203
A: *E*/*Z* 98:2
B: *E*/*Z* 61:39

(*R*)-**204**
A: 98%, 90% ee
B: 94%, 65% ee

Scheme 38: Partial enolate equilibrium for α-*N*-Pyrrolyl enol carbonate **203**.

Based on these examples, and others,[108,109] it is apparent that the geometry of the allyl enol carbonate precursors must be considered for acyclic substrates, and that often these substrates must be reacted in their geometrically pure form in order to furnish products with high enantioselectivity. However, the use of β-ketoester precursors **112** in a Pd-DAAA reaction is likely to be more challenging unless either decarboxylation results in selective enolate **110b** formation *in situ*, or a fast enolate interconversion of **110a** to **110b** takes place to enable alkylation of one of the enolates and achieve a high ee of **111** (Scheme 39).



112

110b
single isomer

110a

110b

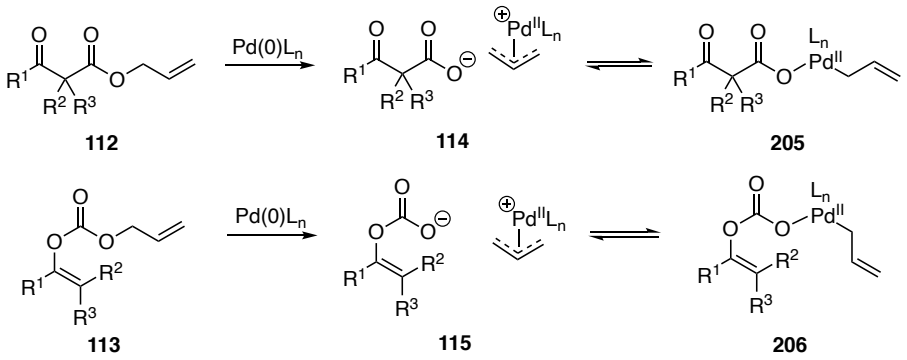
111
high %ee

Scheme 39: Selective enolate formation from β-ketoester.

To gain a deeper understanding of the mechanism of the Pd-DAAA reaction, selected examples and mechanistic studies of this process are discussed in the next section.

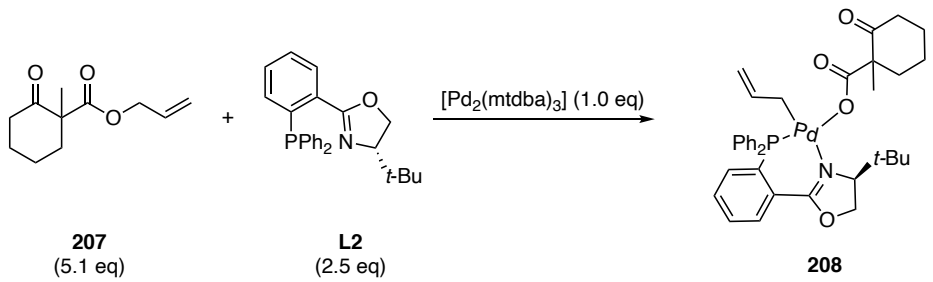
1.2.7 Mechanistic Studies of the Pd-DAAA Reaction

In the first step of the Pd-DAAA mechanism (Scheme 40), ionisation of ester **112** or carbonate **113** occurs by oxidative addition of a palladium(0) catalyst to form palladium-carboxylate ion pair **114** or **115**, which is likely to be in equilibrium with the covalently bound σ-allyl complex **205** or **206**.[66]



Scheme 40: Oxidative addition step.

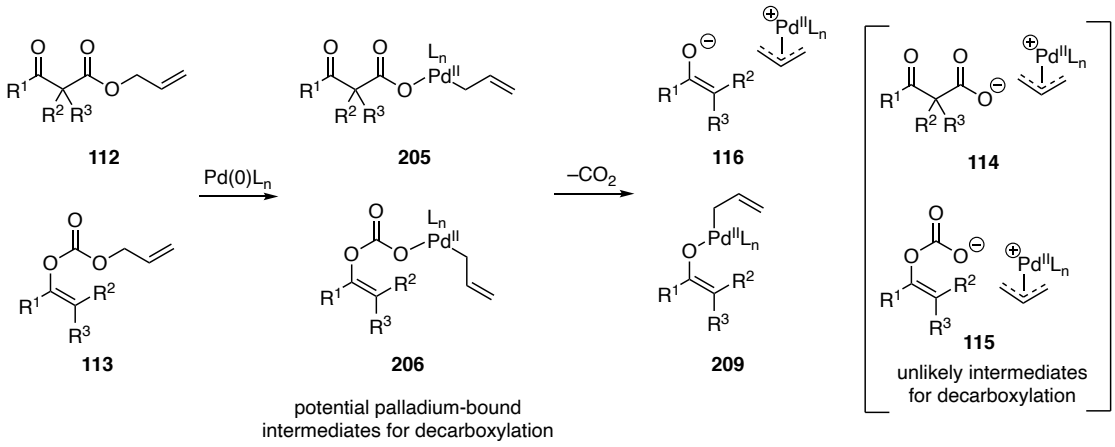
The (σ-allyl)palladium-β-ketocarboxylate intermediate **208** was identified by the Stoltz group using ^{31}P NMR and X-ray crystallography to be the resting catalytic state when using a Pd(PHOX) system for β-ketoester **207** (Scheme 41).[110] This resting state suggests that, in this example, decarboxylation is the rate determining step of the reaction. Despite this observation, decarboxylation remains less studied than the other steps of the mechanism.[66]



Scheme 41: Catalytic resting state in the reaction of β-ketoester **207** with PHOX **L2**.

Following oxidative addition, decarboxylation proceeds to reveal the enolate nucleophile **116** or **209** *in situ* (Scheme 42). In 1980, Saegusa and co-workers reported evidence that decarboxylation only occurs in the presence of palladium.[58] Therefore, it

is believed that decarboxylation to enolate **116** or **209** occurs from palladium-bound intermediate **205** or **206** rather than ion-pair **114** or **115**.



Scheme 42: Decarboxylation in the presence of palladium.

More recently, alternative mechanisms A–C for the decarboxylation of β-ketoallyl ester substrates have been postulated using the knowledge of decarboxylation from other systems/metals (Figure 14).[111] In a theory that contradicts Saegusa, mechanism A was postulated following reports by Darensbourg *et al.* in which decarboxylation of malonic acids with alternative metals, such as Cu(I) and Zn(II), proceeds by ionisation of the metal carboxylate bond.[112] Decarboxylation *via* mechanism B has been suggested due to its similarity to the cyclic decarboxylation of β-ketoacids.[113] Mechanism C suggests that it is the co-ordination of the palladium to the ketone oxygen which encourages decarboxylation by forming a metal-bound, rather than a 'free', enolate.[114]

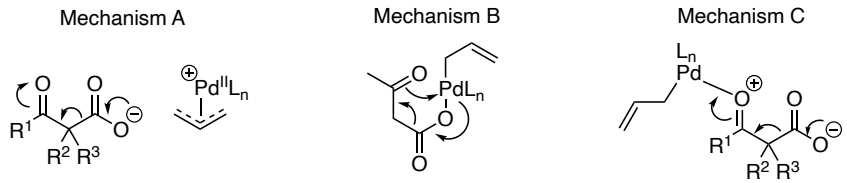
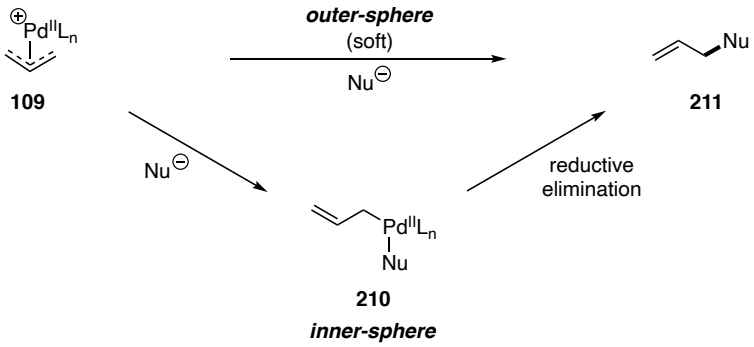


Figure 14: Proposed mechanisms for the decarboxylation step.

1.2.8 Alkylation Pathway: Inner-sphere vs Outer-sphere

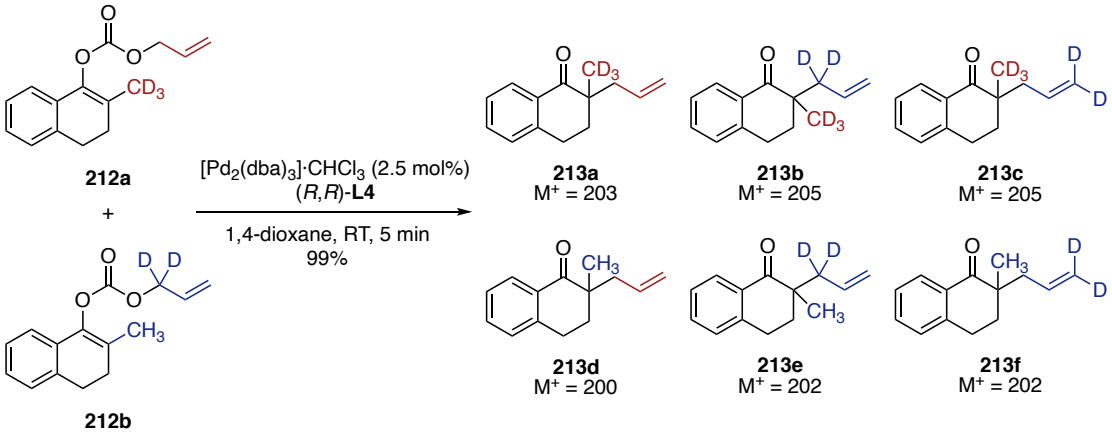
The nature of the nucleophile used in the palladium-catalysed DAAA process is known to influence the mechanism of the reaction. The type of nucleophile can be divided into two broad categories with respect to their pK_a. Stabilised 'soft' nucleophiles (pK_a typically <20), such as enolates of malonates, undergo outer-sphere alkylation, with the nucleophile directly attacking the allyl terminus in **109** to give alkylated **211** (Scheme 43). In contrast, unstabilised 'hard' nucleophiles (pK_a typically >20), such as enolates of simple carbonyls, tend to undergo inner-sphere alkylation, where alkylation occurs within the palladium co-ordination sphere (**210**), *via* reductive elimination to release alkylated product **211**. However, there are also several exceptions to these generalisations, and the exact mode of alkylation is strongly dependent on the ligand used and nature of the nucleophile.[66]



Scheme 43: Comparison of outer- and inner-sphere alkylation.

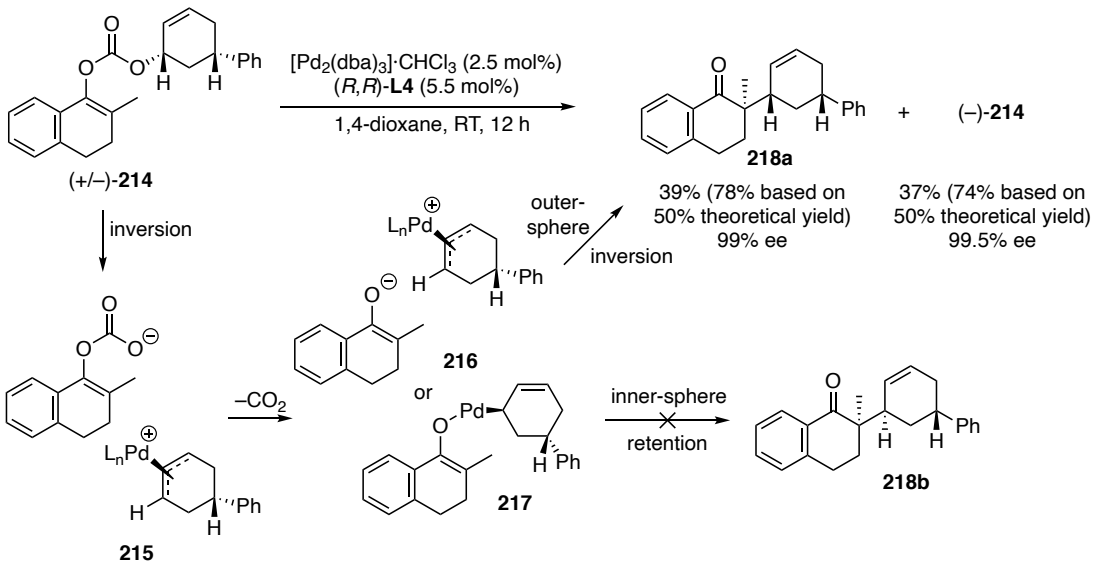
Several strategies have been developed to ascertain which alkylation mechanism dominates. In a report by Trost and co-workers in 2009, a 1:1 mixture of deuterated substrates **212a** and **212b** were reacted under the Pd-DAAA conditions to observe if crossover of the enolates had occurred in the reaction (Scheme 44).[104] Mass spectroscopic analysis of the reaction mixture confirmed that four signals were present (*m*/*z* 200, 202, 203 and 205) at almost equal intensity, correlating to the 6 potential products **213a**–**f**. This scrambling of enolates suggests that the π-allylpalladium(II) complex and the enolate are not tightly bound, and are able to dissociate from each other and exchange before undergoing irreversible alkylation. Although this result did not provide conclusive evidence for the mechanism of alkylation, the observed crossover

does suggest that the enolate and π-allylpalladium(II) complex are not closely associated and, therefore, tentatively hints at an outer-sphere allylic alkylation process.



Scheme 44: Crossover study using deuterium-labelled enol carbonates to determine enolate scrambling.

A separate study to definitively elucidate the allylic alkylation mechanism for this substrate was subsequently performed. To determine whether an inner- or outer-sphere mechanism was in operation, a chiral allylic electrophile **214** was used in the reaction and the resultant stereochemistry of product **218** evaluated (Scheme 45).[104] The oxidative addition of the palladium(0) catalyst to **214** proceeds with stereochemical inversion. Decarboxylation of **215** produces a nucleophilic enolate either in an ion pair **216** or covalently-bound **217**. In the case of an outer-sphere alkylation, the enolate would approach the electrophile from the opposite face of the palladium, i.e. with inversion, and therefore an overall retention of the stereochemistry at the allylic position in **218a** would be observed. On the other hand, an inner-sphere mechanism would involve the reductive elimination from the palladium centre in **217** with retention, giving product **218b** with net inversion of stereochemical configuration of the allylic centre. X-ray crystallography and ^{1}H NMR analysis confirmed **218a** to be the major product formed with 99% ee, and therefore, it was concluded that an outer-sphere alkylation mechanism was in operation. Interestingly, an almost perfect kinetic resolution was observed in which the (–)-**214** enantiomer remained unreacted and was recovered in 37% yield (74% based on 50% theoretical yield, 99.5% ee).



Scheme 45: Stereochemical labelling study.

1.2.9 Origins of Enantioselectivity

The origins of enantioselectivity in the palladium-catalysed asymmetric allylic alkylation can be complex with a number of factors at play. For example, there are two possible pathways for ionisation, *exo*-**219** and *endo*-**219** (Figure 15).[115] *Exo* ionisation is the favoured pathway as it involves the nucleophile approaching at 180º to the leaving group. This reaction can be compared to an S_N2 nucleophilic substitution, in which the nucleophile also approaches at 180º to the leaving group. In this case, Pd(0) is considered the nucleophile in the ionisation step, and the leaving group in the alkylation step. *Endo* ionisation is the unfavoured pathway, as this process occurs at an angle <180º, leading to unfavourable orbital overlap.

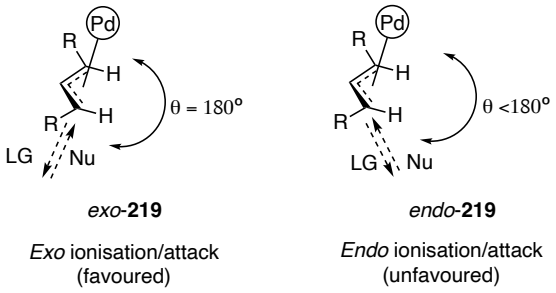
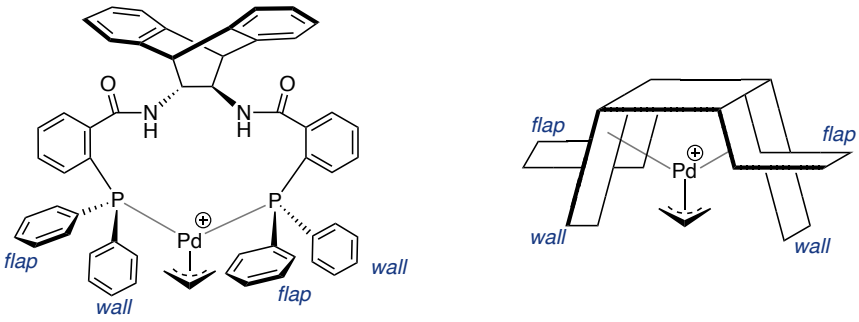


Figure 15: Comparison of *exo* and *endo* ionisation/attack.

In 1999, Trost and co-workers reported an in-depth working model for this reaction in which the authors explored the regio- and enantioselective allylic alkylation of unsymmetrical substrates. In this work, Trost *et al.* proposed a cartoon model of the C_2-symmetric ligand **L4** which can be used to explain the observed regio- and stereoselectivity (Figure 16).[115,116] This 'wall-and-flap' cartoon model represents the ground state structure of the ligand-π-allylpalladium(II) complex and is very useful in predicting and rationalising the stereochemical outcome of the Pd-DAAA processes using Trost ligands.[79]



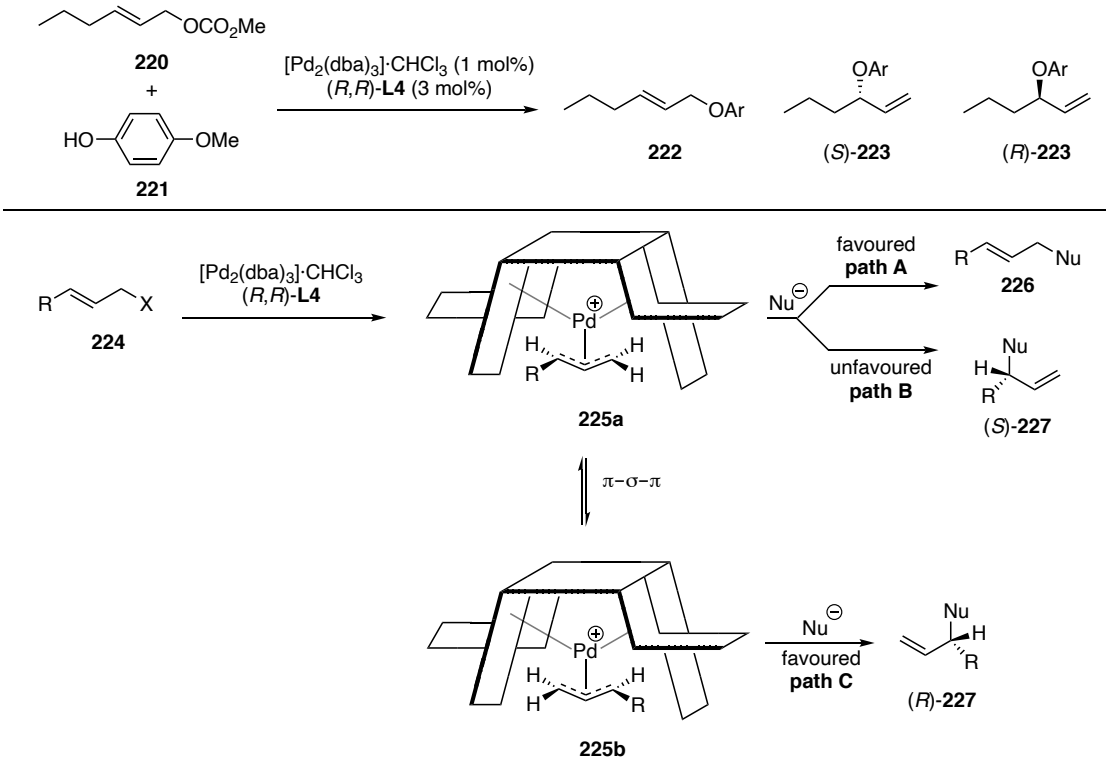
(*R*,*R*)-ANDEN Trost Ligand (**L4**) Cartoon representation

Figure 16: 'Wall-and-flap' cartoon model.

In this structure, the phosphorus-linked phenyl groups adopt pseudoaxial 'walls' and pseudoequatorial 'flaps' which create a chiral environment and direct the nucleophilic attack.[115] The 'walls' are rigid and immobile, pointing approximately perpendicular to the allyl moiety, preventing alkylation of the allyl terminus that is in close proximity to them. In contrast, the 'flaps' are open and parallel to the allyl group, allowing the alkylation to occur at the proximal allyl terminus. Despite this ligand possessing C_2 symmetric character, only one of the four quadrants is favoured for alkylation. The rear quadrants in Figure 16 are ruled out as alkylation would occur by an *endo* process ($\theta < 180^{o}$). The two front quadrants could enable alkylation *via exo* nucleophilic attack. However, as one quadrant is blocked by a 'wall', this leaves only the favoured quadrant (*exo* and sterically unhindered) for nucleophilic attack.

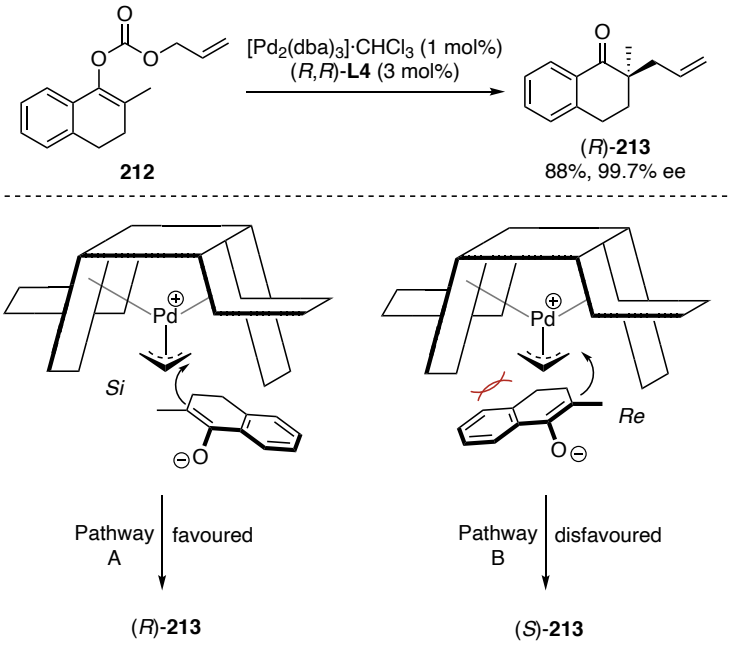
This model can also be used to rationalise the preferred alignment of an unsymmetrical monosubstituted π-allyl group within the ligand sphere (Scheme 46).[116] Ionisation of **224** results in two possible orientations of the planar chiral π-allyl ligand, **225a** and

225b. π-Allylpalladium(II) complex **225a** is kinetically preferred for the ionisation step due to the leaving group dissociating at 180º from the palladium and from under the flap. For the same reason, path A should dominate over path B to favour linear alkylation product **226** over branched **227**. However, complex **225b**, formed by a π-σ-π isomerisation, is more stable than complex **225a** as there is no steric interaction between the R group and the wall of the ligand. As such, *exo* alkylation under the 'flap' would give branched (*R*)-**227**, the enantiomer of (*S*)-**227**. In practice, using monosubstituted electrophile **220** and phenol nucleophile **221**, it was found that the selectivity can be governed by the reaction solvent.[116] In toluene, path A dominates to form mostly linear product **222**. Where small amounts of branched product is formed, (*S*)-**223** is favoured over (*R*)-**223**. When this reaction is performed in a more polar solvent, such as acetonitrile, the charged intermediates are stabilised, slowing the rate of nucleophilic attack, increasing the rate of π-σ-π interconversion and causing path C to dominate.



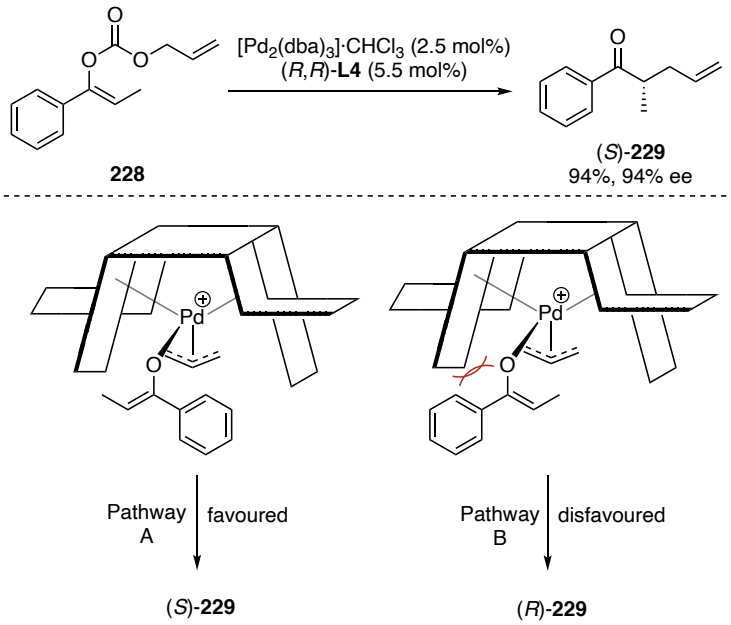
Scheme 46: 'Wall-and-flap' model to rationalise the regio- and enantioselectivity of monosubstituted unsymmetrical allyl group **224**.

In 2009, Trost *et al*. reported the decarboxylative allylic alkylation of the enol carbonate of 2-methyl-1-tetralone (**212**) using (*R*,*R*)-ANDEN Trost (**L4**) as the chiral ligand to form *R*-(**213**) in 88% yield and 99.7% ee (Scheme 47).[117] The observed enantioselectivity of alkylation of the pro-chiral enolate was explained using the 'wall-and-flap' model *via* an outer-sphere alkylation mechanism. In pathway A, the enolate approaches the π-allyl complex with its *Si* face. This is the favoured orientation as the large phenyl group resides under the flap, resulting in alkylation to form the *R* enantiomer of **213**. In contrast, pathway B is disfavoured as the phenyl group experiences steric interactions within the chiral backbone of the ligand.



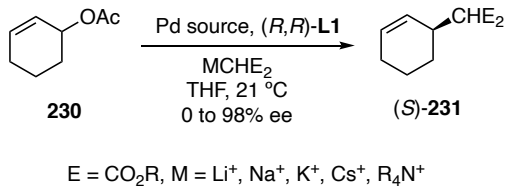
Scheme 47: Preferred orientation of pro-chiral nucleophiles within the chiral ligand structure.

The Trost 'wall-and-flap' model is most commonly used to depict outer-sphere alkylations.[104,115,118] However, in 2005, Trost and co-workers used this cartoon to explain the favourable orientation of the palladium-bound enolate for a transformation that was determined to undergo an inner-sphere alkylation (Scheme 48).[108] In this example, the oxygen-bound palladium enolate aligns the substrate in two orientations for *exo* alkylation. In pathway A, steric interactions of the substrate with the wall of the ligand are minimised, resulting in major enantiomer (*S*)-**229**. The transition state in pathway B is disfavoured due to the steric interactions of the phenyl group with the wall of the Trost ligand.



Scheme 48: Prediction of stereoselectivity of an acyclic enolate with inner-sphere reactivity.

The Trost 'wall-and-flap' model is undeniably useful in explaining the stereochemical outcome of the reaction. However, to gain further information about the selectivity of this ligand, an in-depth mechanistic study of outer-sphere asymmetric allylic alkylation using various metal counter-ions was carried out using deuterium labelling and DFT computational studies (Scheme 49).[119] Lloyd-Jones and co-workers established that there are three factors that result in the observed regio- and enantioselectivity of alkylation of pro-chiral allylic electrophile **230** with a malonate when using Trost ligand (*R*,*R*)-**L1**.



Scheme 49: Pd-AAA transformation studied by Lloyd-Jones and co-workers.

Through NMR studies, the authors discovered that **L1**, originally believed to be C_2 symmetric, was in fact C_1 symmetric, as the ligand formed a 13-membered chelate with a concave shape in which one of the amide N–H bonds of the ligand backbone protrudes into the concave face, close to one of the terminal carbon atoms of the allyl electrophile

(Figure 17). The other amide protrudes in the opposite direction causing the carbonyl to be close to the opposite allyl terminus. This N–H is able to hydrogen-bond with the oxygen atom of the malonate anion and deliver the nucleophile to the pro-*S* terminus of the electrophile. The second factor to be considered when using this ligand is the torquoselective bias. This is caused by a phenyl ring of the ligand interacting with one of the allyl termini, leading to a slight rotation of the allyl unit and, hence, activation of the pro-*S* terminus. The final factor depends on the metal counter-ion, derived from the base utilised in the deprotonation of malonate. Therefore, additives (X^-) of varying binding strength were used in this study to observe how they interact with the metal ion and, thus, how they influence the stereochemical outcome. In the presence of a strongly binding additive X^-, chelation to the metal cation results in a more 'naked' enolate that can hydrogen-bond to the N–H of the ligand backbone and give pro-*S* selectivity. If a metal ion is present with no, or a weakly binding, counter-ion additive X^-, then this metal ion, now more strongly associated with the enolate, will bind to the amide carbonyl, favouring pro-*R* selectivity. The size of the escort M^+ ion, therefore, affects the stereochemical outcome of the reaction. Smaller metal ions, such as Li^+, bind tightly to the enolate and interact with the carbonyl group of the amide for pro-*R* delivery, however, larger escort ions M^+, such as R_4N^+, bind more strongly to the counterion X^- than the enolate and, hence the nucleophile is still able to hydrogen bond with the N–H of the amide for pro-*S* delivery. The understanding of this mechanism is of great importance as it can direct new catalyst design for asymmetric allylic alkylation reactions which may benefit from an activating hydrogen bond for incoming nucleophiles.

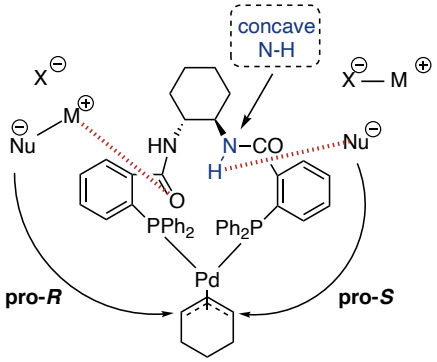
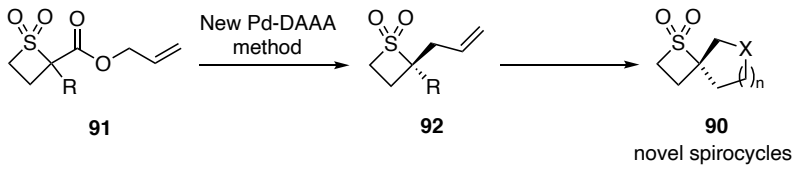


Figure 17: Stereochemical model of outer-sphere AAA of pro-chiral electrophile using standard Trost ligand.

1.2.10 Asymmetric Allylic Alkylation of α-Sulfonyl Anions

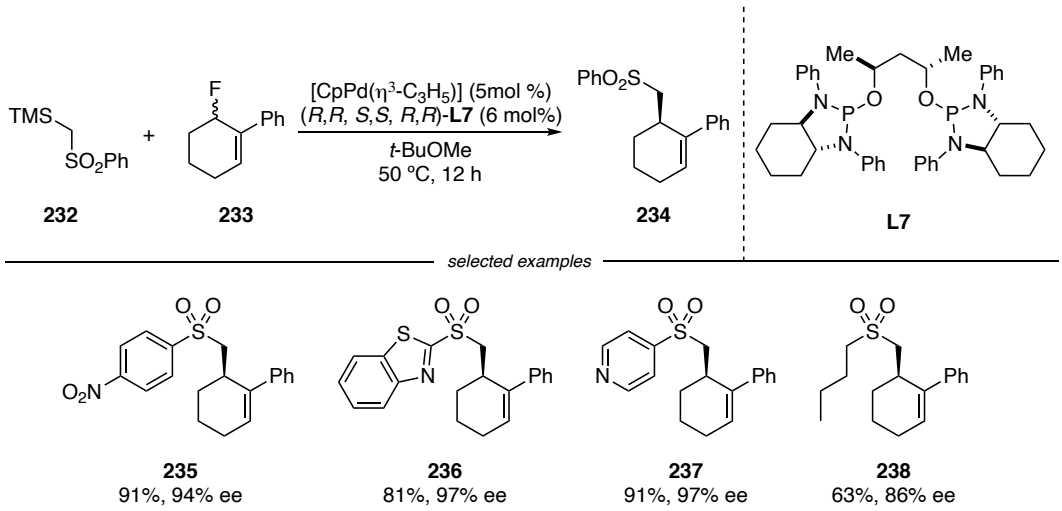
A broad variety of sulfur-based functional groups can be found within drug compounds, including sulfoxides, sulfones, thioethers, sulfonamides,[120] sulfoximines,[121] amongst others. As such, sulfur-containing compounds are often featured in new FDA approved drugs.[122] Our research group is interested in the allylic alkylation of sulfones towards the synthesis of novel chiral building blocks for drug discovery. As previously mentioned in Section 1.1.7 (page 16), we wanted to synthesise chiral, enantioenriched thietane-1,1-dioxide containing spirocycles **90** by developing a Pd-DAAA reaction of racemic starting materials **91** to give enantioenriched thietane-1,1-dioxides **92** that possess the functional handles required for functionalisation to spirocycles **90** (Scheme 50).



Scheme 50: Pd-DAAA for synthesis of enantioenriched thietane-1,1-dioxide containing spirocycles.

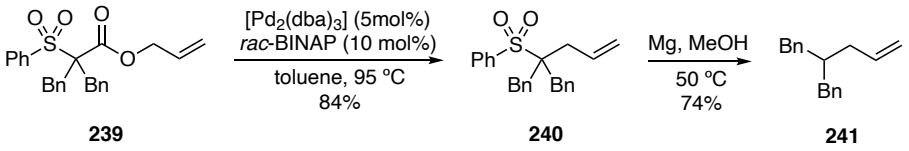
Unlike the highly developed Pd-catalysed DAAA reactions of enolates, the analogous allylic alkylation processes of sulfones are much less common. What is, therefore, necessary is a brief overview of the reactivity of α-sulfonyl anions in allylic alkylation reactions.

In 2021, Trost and co-workers reported the direct palladium-catalysed asymmetric allylic alkylation of α-sulfonyl nucleophiles **232** and prochiral electrophiles **233** (Scheme 51).[123] The authors used an allylic fluoride as the leaving group to promote desilylation, thus revealing the α-sulfonyl anion nucleophile *in situ* under mild conditions. This reaction proceeded with high efficiency and enantioselectivity to give homoallylic aryl sulfones appended with *p*-nitro (**235**), benzothiazoyl (**236**) and heterocyclic pyridyl (**237**) groups. Simple alkyl sulfones, such as **238**, furnished lower yields and enantioselectivity compared to their aryl analogues.



Scheme 51: Pd-AAA using α-sulfonyl nucleophiles.

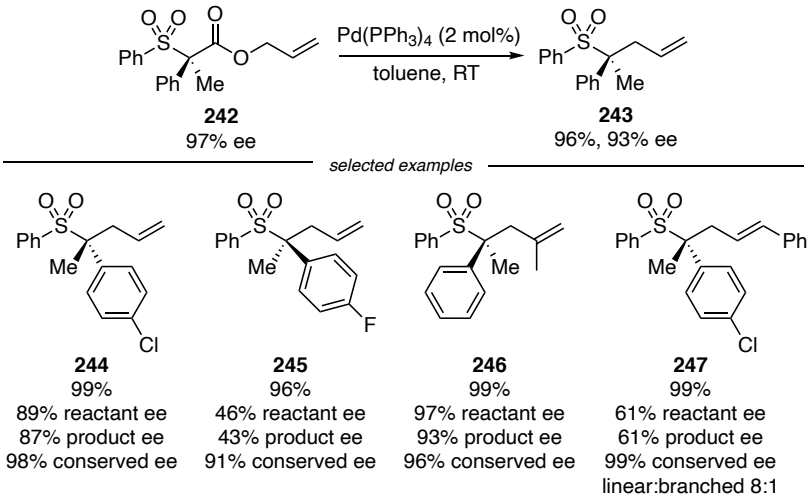
In 2008, Tunge and co-workers reported the decarboxylative allylation of sulfones to give α-tetrasubstituted centres (Scheme 52).[124] This methodology was developed with the intention of using sulfones as a 'traceless activating group' to generate products, such as **241**, which are challenging to synthesise by other means. Incorporation of the sulfonyl functionality in **239** was necessary in order to increase the propensity of decarboxylation and give rise to achiral product **240**. The sulfonyl group can be subsequently cleaved using magnesium in methanol to give a tertiary carbon centre in **241**.



Scheme 52: Decarboxylative allylic alkylation of α-sulfonyl anions.

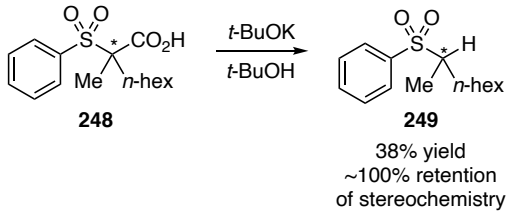
Building on this work, the first stereoretentive decarboxylative allylic alkylation of α-sulfonyl anions using enantioenriched precursors **242** was reported by Tunge and co-workers in 2010 (Scheme 53).[125] This decarboxylative allylic alkylation would usually require elevated temperatures; however, the reaction was found to proceed at room temperature due to the use of the highly active $Pd(PPh_3)_4$ catalyst. Several chiral precursors were used to explore the scope of this reaction. Products bearing α-aryl

substituents **243**–**247** were afforded with high yields and high levels of conservation of ee. Unfortunately, due to the stereoretentive nature of the reaction, low stereoenrichment of the starting materials resulted in low ee of the product, such as in **245** and **247** (43% ee and 61% ee, respectively).



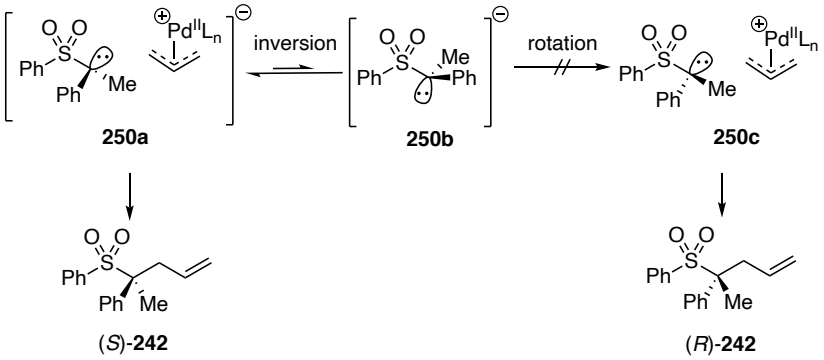
Scheme 53: Stereospecific decarboxylation allylic alkylation of chiral sulfone precursors.

The question that arises is whether racemic sulfones could be used in an enantioconvergent Pd-DAAA reaction to give enantioenriched product. Stabilised and non-stabilised carbanion intermediates act very differently in enantioconvergent reactions. Where stabilised carbanions, such as enolates, are planar, unstabilised carbanions would be required to undergo racemisation by inversion that is faster than allylic alkylation. It was already known that decarboxylative protonation of **248** occurs with retention of stereochemistry to form **249** (Scheme 54);[126] however, C–C bond forming reactions had not been previously studied.



Scheme 54: Stereoretentive protonation of α-sulfonyl anion.

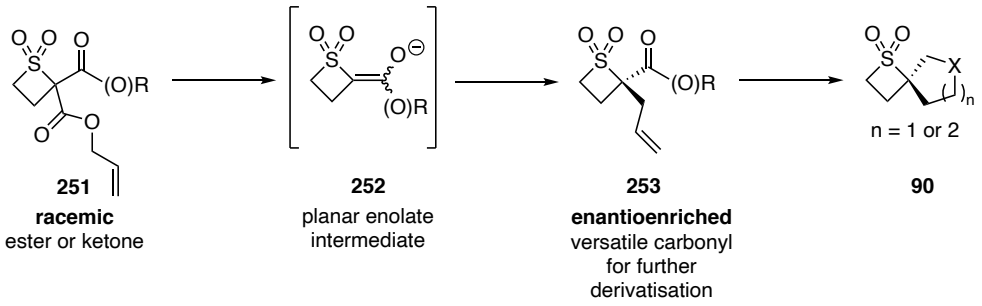
A mechanistic study of the allylation of α-sulfonyl anions was performed by the authors, in which a stereochemical labelling experiment, as seen in Section 1.2.8 (page 37), proved that an outer-sphere alkylation mechanism was in operation. Therefore, the α-sulfonyl anion should exist as part of an ion-pair with the π-allylpalladium(II) complex **250a**, and alkylate to form (*S*)-**242** (Scheme 55). It was found that there is no racemisation of this anion **250a**, even at a high temperature, as it is already in its most stable conformation with the lone pair antiperiplanar to the Ph–S bond and, hence, the C–C bond formation occurs with high level of retention of enantiopurity. The success of stereospecific decarboxylation of sulfones can also be attributed to the rate of C–C bond formation. More specifically, the reactive α-sulfonyl anion and electrophilic π-allylpalladium(II) complex **250a** reacts on a quicker timescale than inversion (**250b**) and rotation (**250c**) of the C–S bond, resulting in retention of stereochemistry. Although a significant advantage of decarboxylative asymmetric allylic alkylation is the ability to produce enantiopure products under mild catalytic conditions from *achiral* or *racemic* precursors, the lack of racemisation of anion **250a** makes the development of the enantioselective allylic alkylation of racemic α-sulfonyl anions challenging.



Scheme 55: Conformational and configurational stability of sulfonyl α-anion.

1.3 Project Aims

The palladium-catalysed decarboxylative asymmetric allylic alkylation reaction has been widely studied and utilised in a number of applications, from natural product synthesis[127,128] to drug discovery.[95] To date, there have been no reports of the Pd-DAAA of sulfones that can install an α-sulfonyl stereogenic centre with high levels of enantioselectivity. To access novel thietane-1,1-dioxide containing building blocks, we envisioned incorporating a carbonyl substituent at the α-position of **251** (Scheme 56), which would serve three functions. Firstly, it would create a stable enolate to facilitate decarboxylation at room temperature or less. Secondly, it would provide a planar nucleophile **252** upon decarboxylation, allowing a stereoablative enantioconvergent process from racemic starting material **251**. Thirdly, the carbonyl present in enantioenriched product **253** would act as a functional handle for subsequent functionalisation towards novel spirocycle **90** synthesis. However, the alkylation of linear enolate intermediate **252** is likely to pose challenges: for the development of an enantioselective DAAA to be viable, either an *in situ* enolate interconversion would be required (*vide supra*, Section 1.2.6, page 30), or geometrically pure allyl enol carbonate precursors would need to be utilised.



Scheme 56: Project concept and strategy.

In the first instance, thietane-1,1-dioxide allyl ester precursors **254** with ketone and ester side-chains (aryl, alkyl, heterocyclic) will be made in a bid to create tetrasubstituted α-sulfonyl carbon centres with high levels of enantioselectivity (Figure 18). Due to the acyclic nature of the enolate intermediate following decarboxylation, a palladium-mediated interconversion of enolates will be required. If such a process does not take

place, the selective synthesis of analogous *Z* or *E* allyl enol carbonates *Z*-**255** or *E*-**255**, with a fixed alkene geometry, as the achiral precursor will need to be developed.

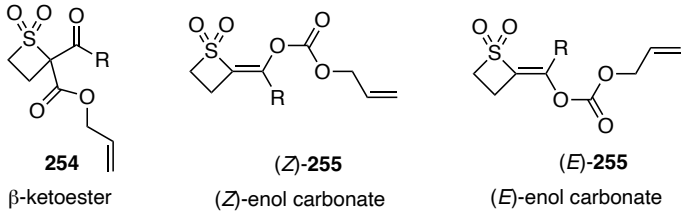


Figure 18: Consideration of enolate geometry in precursors for Pd-DAAA.

With access to the requisite precursors established, the development of the Pd-DAAA reaction will be carried out. Using a test substrate, several reaction parameters will be probed, including chiral ligands for palladium, to find the optimal conditions for high enantioselectivity. Once identified, a full substrate scope investigation will be carried out to determine the successes and limitations of this methodology. This will involve the testing of ketone and ester side-chains containing a range of aryl, heterocyclic and aliphatic substituents. This study will enable us to establish the effect of electronics and sterics on the enantioselectivity of the reaction. A mechanistic study will then follow to gain a deeper understanding of the individual steps of the DAAA reaction.

Finally, the ester- and ketone-containing alkylated products **257** and **260** formed by the Pd-DAAA reaction will be functionalised and derivatised into spirocycles **256**, **258**, **259** and **261** with varying ring size and position of the nitrogen atom to provide novel exit vectors for incorporation into compound libraries within the pharmaceutical industry (Figure 19).

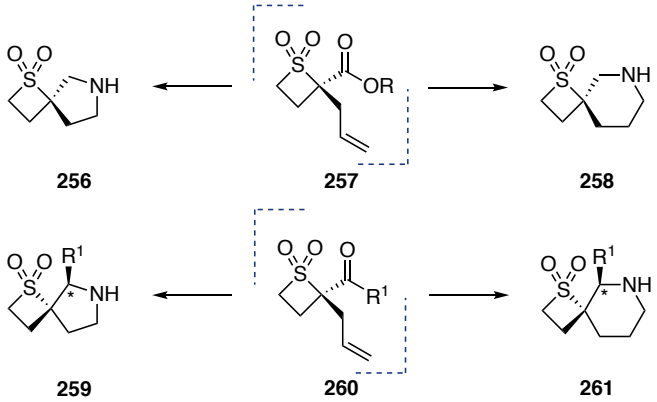


Figure 19: Spirocycles derived from enantioenriched thietane-1,1-dioxide building blocks.

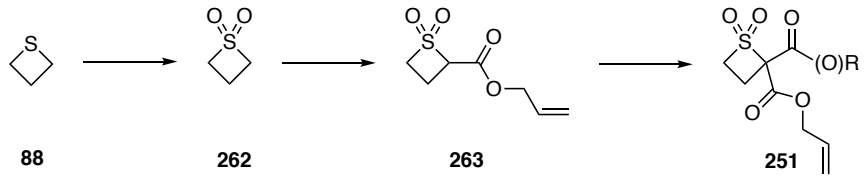
The results emanating from these original project aims are described in the next chapter.

2. Results and Discussion

The work presented within this section has been published in part as: Laidlaw, G.; Franckevičius, V., *Org. Lett.* **2022**, 24, 400–405.[129]

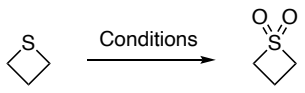
2.1 Synthesis of Test Substrates

A route to β-ketoester precursors was devised from commercially available thietane (**88**, Scheme 57). Oxidation of thietane (**88**) to thietane-1,1-dioxide (**262**), followed by allyl ester installation would furnish intermediate **263**. The enolate intermediate of **263** could then be transformed into ketone- and ester-substituted substrates **251** in a divergent manner using acid chloride and chloroformate electrophiles, respectively.



Scheme 57: Synthetic route to β-ketoester precursors, **251**.

Thietane-1,1-dioxide (**262**) was synthesised by the oxidation of thietane (**88**). Sulfides are often oxidised using peroxides and peracids and, therefore, these reagents were initially attempted for this substrate (Table 1). Two equivalents of oxidant were required to generate the sulfone rather than the sulfoxide functionality.



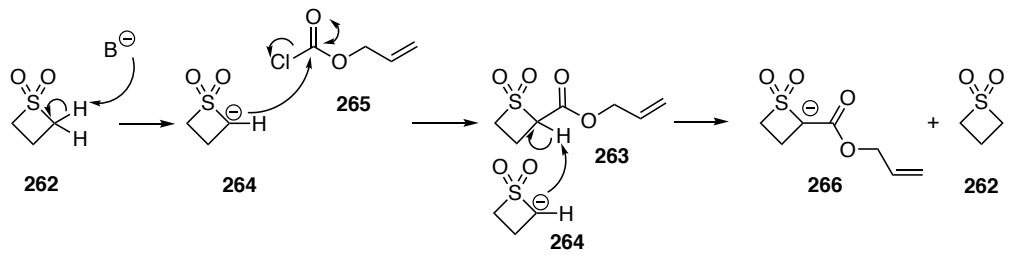
Entry[a]	Conditions	Time (h)	Yield (%)[b]
1	H_2O_2/WO_3, AcOH, H_2O, 0 ºC	1	45
2	*m*-CPBA, CH_2Cl_2, RT	18	49
3	*m*-CPBA/$NaHCO_3$, CH_2Cl_2, RT	18	56
4	$KMnO_4$, H_2O/CH_2Cl_2, RT	18	89 (94[c])

[a] 1.4 mmol (102 mg) of **88**; [b] isolated yield; [c] 54 mmol (4.0 g) of **88**

Table 1: Oxidation of thietane to thietane-1,1-dioxide.

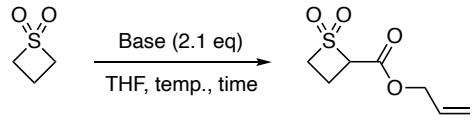
Initial attempts of the oxidation of **88** using tungstic acid and hydrogen peroxide furnished product **262** in a moderate 45% yield (Table 1, entry 1).[130] *m*-CPBA afforded product **262** in 49% yield (entry 2).[131] The use of a sodium bicarbonate buffer to neutralise the benzoic acid by-product led to a marginal increase in yield to 56% (entry 3). Finally, oxidation of **88** with potassium permanganate ($KMnO_4$) resulted in the formation of product in an excellent 89% yield (entry 4).[132] Pleasingly, this reagent is inexpensive, easy-to-handle and furnishes clean sulfone after work-up with no requirement for further purification, even on 54 mmol scale (94% yield).

In the next step, an allylic ester side-chain was to be appended to thietane-1,1-dioxide (*vide supra*, **262** to **263**, Scheme 57). This strategy enables a divergent synthesis for the subsequent attachment of a variety of ketone and ester side-chains to this common intermediate **263**. An important consideration for this reaction is the amount of base used, whereby 2.1 equivalents of base are necessary in order to ensure full conversion (Scheme 58). Specifically, one equivalent of base would deprotonate thietane-1,1-dioxide (**262**) to form α-sulfonyl anion **264** that then reacts with allyl chloroformate (**265**) to give desired product **263**. However, **263** now contains a significantly more acidic proton than that in **262**, which would prematurely quench the unreacted α-sulfonyl anion **264**, regenerating starting material **262**. The addition of two equivalents of base circumvents this problem by deprotonating product **263**, thus allowing α-sulfonyl anion **264** to react fully with allyl chloroformate (**265**).



Scheme 58: Regeneration of **262** using only one equivalent of base.

The reaction conditions were studied and optimised by varying the base, temperature, and duration of the reaction (Table 2). These optimisation studies revealed that LDA was an unsuitable base for this reaction and led to no observable product **263** formation (Table 2, entry 1). NaHMDS and KHMDS as bases did lead to the formation of **263** but the yields were generally low (entries 2 and 3). Interestingly, the reaction with KHMDS as the base at low temperature for 2 h gave a higher yield of 46%. Thus, decomposition was suspected to occur if the reaction was allowed to warm to room temperature, and shorter reaction times were preferred. By using LiHMDS as the base and quenching the reaction at –78 °C (entry 4), the yield of **263** was almost doubled (65%) when the reaction time was reduced from 4 h to 2 h. The efficiency of this process was maintained on 1.5 g scale, affording **263** in 68% isolated yield.



262 **263**

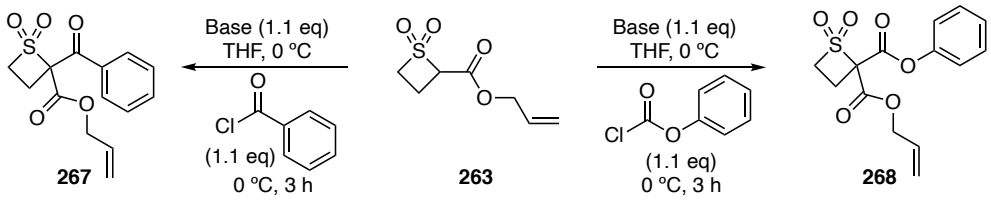
Entry[a]	Base	–78 °C - RT, 24 h (%)[b]	–78 °C, 4 h (%)[b]	–78 °C, 2 h (%)[b]
1	LDA	0	-	-
2	NaHMDS	17	21	-
3	KHMDS	19	29	46
4	LiHMDS	15	36	65 (68[c])

[a] 0.47 mmol (50 mg) of **262**; [b] isolated yield; [c] 14.1 mmol (1.5 g) of **262**.

Table 2: Optimisation study to generate allyl ester **263**.

The final step in the synthesis of racemic test substrates **267** and **268** for the Pd-DAAA reaction was the installation of phenyl ketone and phenyl ester side-chains at the α-position using benzoyl chloride and phenyl chloroformate, respectively (Table 3). Optimisation studies for both ketone and ester precursors were carried out to discover the most suitable base for this reaction. Internal standard, 1,3,5-trimethoxybenzene, was used to quantify the reaction outcome by ^{1}H NMR and all reactions were performed in THF at 0 °C for 4 hours. The most suitable base for the reaction with benzoyl chloride to produce ketone-containing **267** was found to be NaHMDS (entry 2). The use of this base achieved an 85% NMR yield and a 70% isolated yield of **267**. The highest yield of ester-containing **268** was obtained when KHMDS was used as the base, giving a 94%

NMR yield and 77% isolated yield of **268**. When these reactions were scaled up to 250 mg of **263**, **267** and **268** were isolated in 73% and 78% yield, respectively.



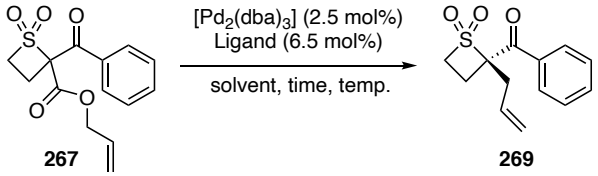
Entry[a]	Base	Yield (%)[b] (ketone 267)	Yield (%)[b] (ester 268)
1	NaH	25	25
2	NaHMDS	85 (70)[c]	72
3	KHMDS	64	94 (77)[c]
4	LiHMDS	79	48

[a] 0.26 mmol (50 mg) of **263**; [b] determined by ^{1}H NMR spectroscopy of the crude product mixture using 1,3,5-trimethoxybenzene as the internal standard; [c] isolated yield

Table 3: Ketone and ester side-chain installation.

2.2 Optimisation of the Pd-DAAA Reaction

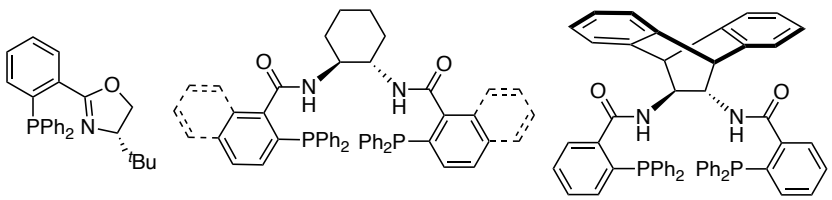
The investigation of the key enantioselective palladium-catalysed allylic alkylation process began with test ketone substrate **267** (Table 4). The effect of the chiral ligand, solvent, temperature and concentration on the enantioselectivity and efficiency of the reaction was probed.



267 **269**

Entry[a]	Ligand	Solvent	Temp. (°C)	Conc. (M)	Time (h)	Yield (%)[b]	ee (%)[c]
1	-	1,4-dioxane	RT	0.04	6	0	-
2	**L1**	1,4-dioxane	RT	0.04	6	80	34
3	**L2**	1,4-dioxane	RT	0.04	6	38	8
4	**L5**	1,4-dioxane	RT	0.04	6	80	24
5	**L4**	**1,4-dioxane**	**RT**	**0.04**	**6**	**74**	**83**
6	**L4**	1,4-dioxane	RT	0.1	6	84	79
7	**L4**	1,4-dioxane	RT	0.2	6	80	75
8	**L4**	MeCN	RT	0.04	6	71	1
9	**L4**	MTBE	RT	0.04	6	82	20
10	**L4**	PhMe	RT	0.04	6	78	22
11	**L4**	Et_2O	RT	0.04	6	71	38
12	**L4**	DME	RT	0.04	6	71	42
13	**L4**	THF	RT	0.04	6	70	41
14	**L4**	CH_2Cl_2	RT	0.04	6	98	65
15	**L4**	$CHCl_3$	RT	0.04	6	82	74
16	**L4**	1,4-dioxane:THF (2:1)	0	0.04	8	80	74
17	**L4**	1,4-dioxane:THF (3:1)	0	0.04	8	75	78
18	**L4**	1,4-dioxane:CH_2Cl_2 (3:1)	0	0.04	8	82	81

[a] 0.17 mmol (50 mg) of **267**; [b] isolated yield; [c] enantiomeric excess determined by chiral HPLC

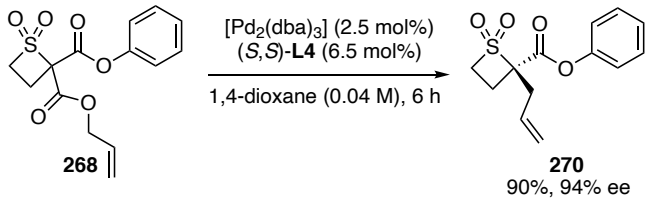


L2 **L1** (phenyl) **L5** (naphthyl) **L4**

Table 4: Optimisation of the palladium-catalysed decarboxylative asymmetric allylic alkylation.

In the first instance, a control experiment was run to ensure that $Pd_2(dba)_3$ does not on its own catalyse the racemic background reaction (Table 4, entry 1). PHOX and Trost ligands are widely reported in the literature for their use in asymmetric allylic alkylation, and as such, four ligands, **L1**, **L2**, **L4** and **L5**, were tested to evaluate the most suitable ligand for this substrate. The use of PHOX, as well as DACH phenyl and naphthyl Trost ligands, **L2**, **L1** and **L5**, respectively, resulted in poor ee of product **269** (8% ee, 34% ee and 24% ee respectively, entries 2-4). Remarkably, despite the possibility of the formation of a mixture of enolates after decarboxylation, (*S*,*S*)-ANDEN Trost ligand **L4** gave a high ee of 84% (entry 5). The concentration of the reaction was also probed, and it was found that, at higher concentrations, the enantioselectivity was lower (entries 6 and 7). The next variable for optimisation was the choice of solvent (entries 8-15). Reaction in acetonitrile afforded racemic product (entry 8). Toluene (entry 10), as well as ethers, such as MTBE (entry 9), diethyl ether (entry 11), DME (entry 12) and tetrahydrofuran (entry 13), all afforded product **269** with low enantioselectivity (20–42% ee). On the other hand, chlorinated solvents, such as dichloromethane (entry 14) and chloroform (entry 15), furnished **269** with higher enantioselectivity (66 and 74% ee, respectively). Nevertheless, 1,4-dioxane remained optimal (84% ee, entry 5). Enantioselectivity can often be improved by performing the reaction at a lower temperature. Unfortunately, given that 1,4-dioxane freezes at 11 °C, this reaction could not be attempted at temperatures much lower than room temperature in this solvent. To overcome this problem and explore the Pd-DAAA reaction at a lower temperature, the use of different ratios of 1,4-dioxane with suitable, low melting point solvents, such as tetrahydrofuran (entries 16 and 17), and dichloromethane (entry 18), were investigated at 0 °C. Although product **269** was obtained with good enantioselectivites (74–82% ee), the original reaction in 1,4-dioxane at room temperature was still superior. Therefore, the reaction conditions of ligand **L4** in 1,4-dioxane as the solvent at room temperature with a concentration of 0.04 M (entry 5) were chosen for the ketone substrate scope investigation.

Remarkably, when phenyl ester **268** was subjected to these optimised conditions, product **270** was isolated in an excellent 90% yield and 94% ee (Scheme 59). Therefore, these conditions were also used in the substrate scope study of ester substituted substrates without further optimisation.

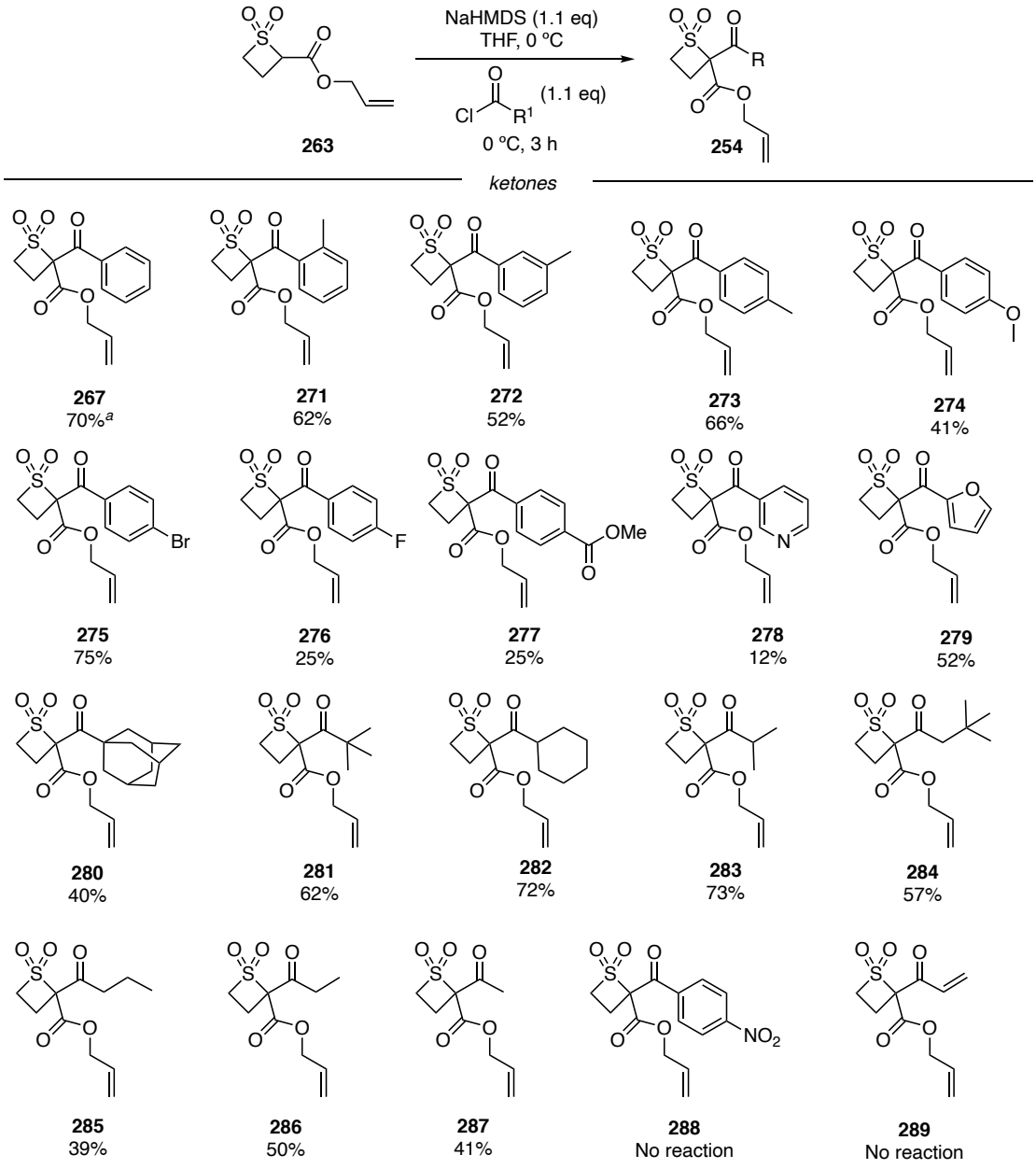


Scheme 59: Pd-DAAA of phenyl ester **268** using optimised conditions.

2.3 Substrate Scope Investigation

2.3.1 Synthesis of Substrates: Ketones

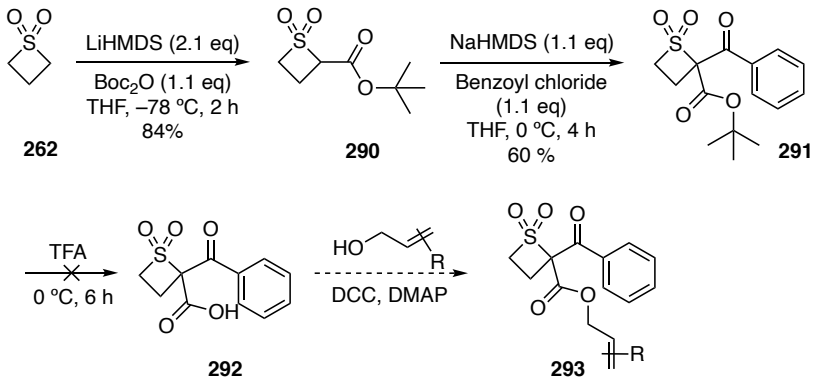
With the conditions for substrate synthesis already optimised (*vide supra*, page 55), various ketone precursors **254** bearing aromatic, aliphatic and heterocyclic substituents were prepared in order to determine the factors that affect the enantioselectivity in the subsequent allylic alkylation step (Table 5). Overall, acylation of allyl ester **263** took place with varying levels of success (12–75% yield). A range of aromatic ketones were prepared, including *ortho*-, *meta*- and *para*-toluoyl containing **271**, **272** and **273**, *p*-methoxy, *p*-bromo and *p*-fluoro substituted **274**, **275** and **276**, as well as pyridyl and furyl ketones **278** and **279**. Large aliphatic ketone substrates, such as adamantanyl, *tert*-butyl, cyclohexyl and isopropyl (**280**–**283**), and compounds bearing smaller linear ethyl and methyl (**286** and **287**) substituents were all successfully synthesised under the optimised reaction conditions. Several attempts to make the *para*-nitro phenyl substrate **288** and vinyl ketone **289** were unsuccessful, resulting in the recovery of starting material even when heated at 80 °C overnight.



[a] isolated yields

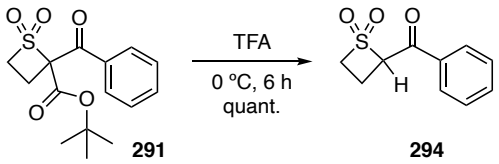
Table 5: Racemic ketone substrates.

The use of allylic electrophiles with substitution at the internal or terminal position of the allyl group has been widely reported in the literature.[72,101,102] In order to study them in our system, a divergent synthesis of substituted allylic esters **293** from common precursor **292** was devised (Scheme 60).



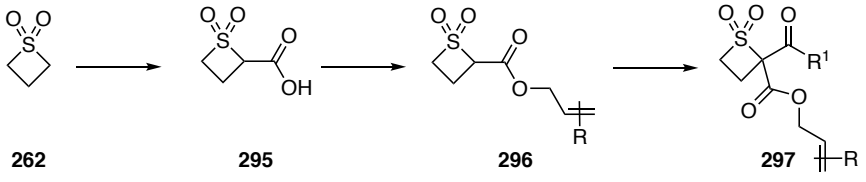
Scheme 60: Divergent synthesis of substituted allyl substrates.

Starting from thietane-1,1-dioxide (**262**), the *tert*-butyl ester substituent was attached using Boc anhydride to produce **290**. The phenyl ketone substituent was then installed in precursor **291** in a moderate 60% yield. The *tert*-butyl group in **291** was chosen as it could be easily removed to reveal carboxylic acid **292**, which in turn could be esterified to give **293**. Unfortunately, due to the electron-withdrawing nature of the ketone functional group, **291** was found to immediately decarboxylate to **294** in the presence of TFA (Scheme 61).



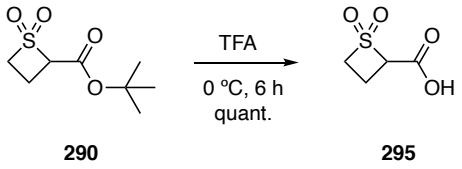
Scheme 61: Decarboxylation of **291** using TFA.

Due to the fast decarboxylation of β-ketoacid **292**, the order of steps was reversed (Scheme 62): the substituted allyl ester **296** was to be made first from acid **295**, followed by the introduction of the ketone side-chain in **297**.



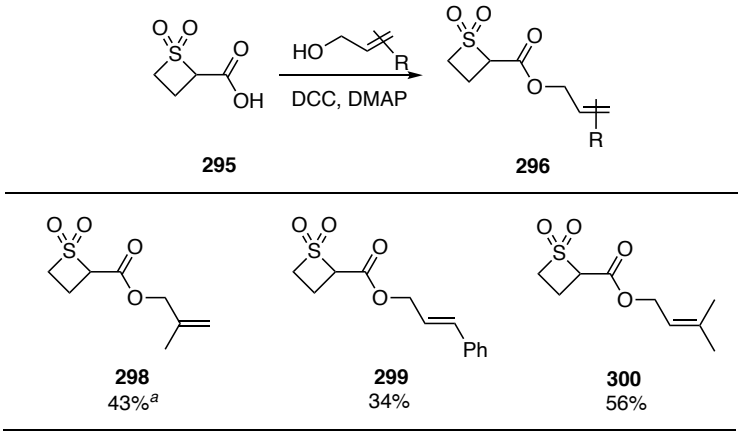
Scheme 62: Alternative route to substituted allyl fragments **297**.

Pleasingly, carboxylic acid **295** could be successfully isolated and stored in the freezer without undergoing decarboxylation (Scheme 63).



Scheme 63: Thietane-1,1-dioxide carboxylic acid.

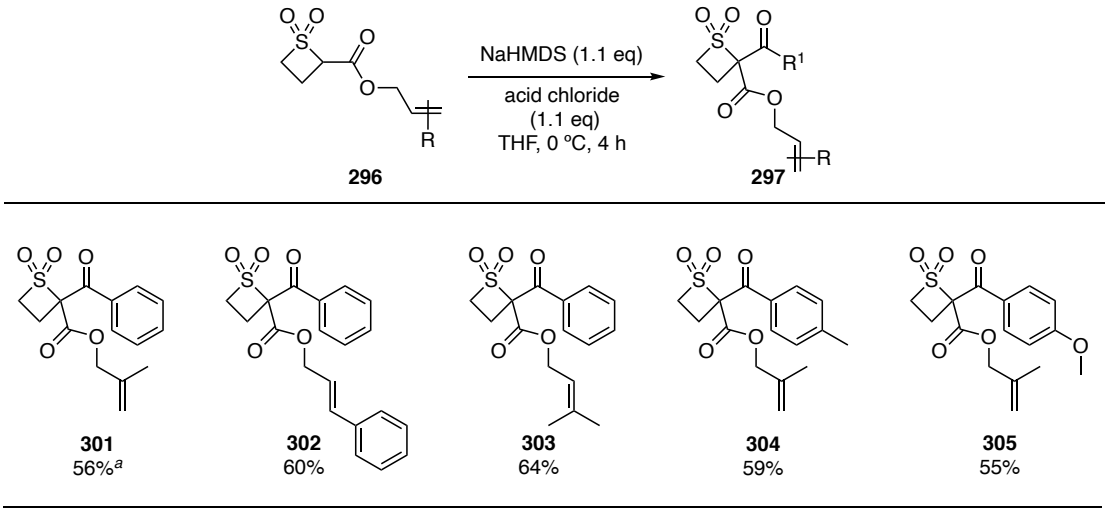
Carboxylic acid **295** was coupled to three allylic alcohols with varying substitution patterns in 34–56% yield of **298**–**300** (Table 6).



[a] isolated yields

Table 6: Preparation of substituted allyl esters.

Finally, installation of the aryl ketone substituent was performed to furnish substituted allyl ester precursors **301**–**305** in moderate yields from **296** (55–64%, Table 7).

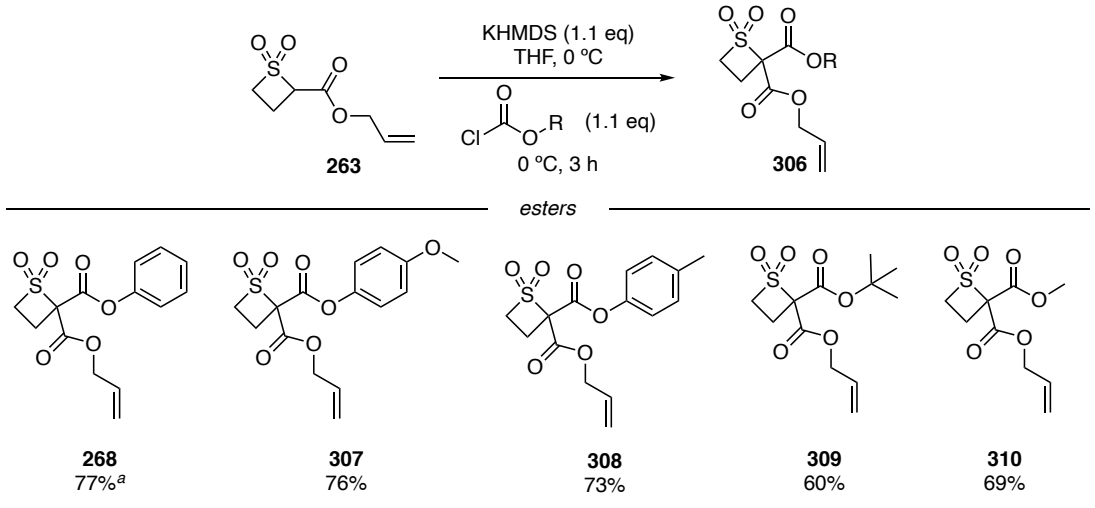


[a] isolated yields

Table 7: Racemic substituted allyl ester ketone substrates.

2.3.2 Synthesis of Substrates: Esters

In addition to the ketone precursors, ester substrates bearing aromatic and aliphatic side-chains (**268, 307**–**310**) were also synthesised from allyl ester **263** in good yields using the optimised reaction conditions (Table 8). Electron-donating (**307** and **308**) and sterically bulky substituent (**309**) were also to be tested.



[a] isolated yields

Table 8: Racemic ester substrates.

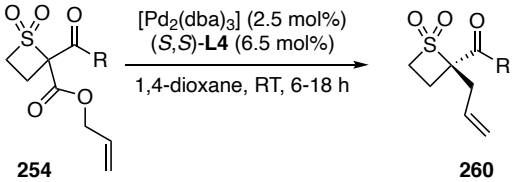
Overall, all substrates were carefully selected to test a range of functionalities, as well as their steric and electronic properties, and to gain an insight into the main factors affecting the enantioselectivity of the Pd-DAAA reaction.

2.3.3 Substrate Scope Investigation: Ketones

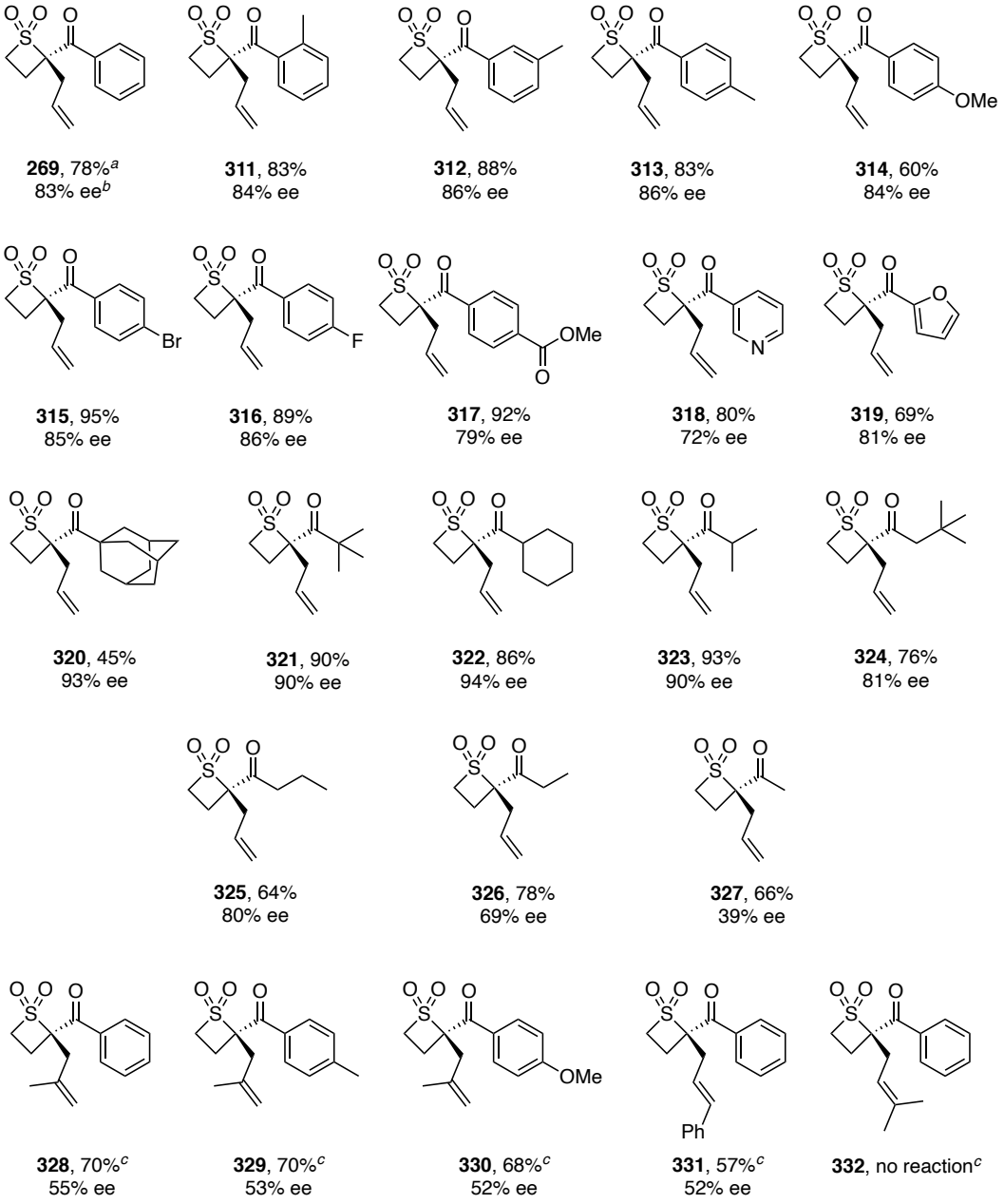
Following the optimisation of the palladium-catalysed DAAA reaction (*vide supra*, Section 2.2), all ketone precursors **254** were subjected to these reaction conditions, the products isolated, and the enantiomeric excess determined by chiral HPLC (Table 9). All products shown in Table 9 were also synthesised in racemic form using 10 mol% $Pd(PPh_3)_4$ as the catalyst for the purposes of HPLC analysis.

Aryl ketone products **269**, **311**–**316** resulted in high enantioenrichment (84–86% ee). The substitution on the phenyl ring did not appear to influence the enantioselectivity, with the exception of methyl ester **317** which gave a slightly lower 79% ee. In spite of the *o*-toluoyl substituent in **311**, likely twisting the benzene ring out of conjugation, there was no impact on the enantioselectivity. The strong electron-donating group, *p*-methoxyphenyl in **314**, also did not exhibit unusual electronic effects and achieved enantioenrichment comparable to that of unsubstituted phenyl ketone product **269**. Interestingly, the *p*-bromo substituted benzene ring in **315** did not undergo oxidative addition at the aryl bromide and alkylated product was formed with 86% ee. This substrate should, therefore, enable further functionalisation of the aryl halide through subsequent coupling reactions. Heterocyclic ketones, namely pyridyl **318** and furyl **319**, furnished products with a lower 72% and 81% ee, suggesting that lone pair availability may impact the selectivity. Ketone products **320**–**324**, bearing bulky alkyl substituents, including tertiary, secondary and branched primary groups, were obtained with high enantioselectivity of >90% ee. However, as the aliphatic substituent decreases in size in **325**–**327**, the ee also decreases, as seen with methyl ketone **327**, which gave a low 39% ee. It is, therefore, feasible that large substituents are necessary to impart sufficient steric differentiation for high enantioselectivity to be obtained.

Despite the success in the literature for the asymmetric allylic alkylation of substituted allyl fragments,[72,101,102] we found substitution to significantly impede the rate of the reaction. As such, the catalyst and ligand loading for the Pd-DAAA reaction was doubled to 5 mol% $Pd_2(dba)_3$ and 13 mol% (*S,S*)-ANDEN Trost Ligand **L4**. Prenylated **332** was not formed even when subjected to double the catalyst loading for 4 days. ^{1}H NMR analysis of the crude reaction mixture revealed a mixture of starting material and decarboxylated/non-alkylated product in a 1:1.7 ratio. On the other hand, the internal methyl and terminal phenyl substituted allyl substrates underwent the catalytic reaction in 4 h with very little to no decarboxylated side-product formation (<10%). Unfortunately, HPLC analysis revealed only modest levels of stereoselectivity: methyl-substituted **328**–**330** were isolated in 52–55% ee, whereas phenyl-substituted **331** was formed with 52% ee.



substrate scope: ketones



269, 78%[a] 83% ee[b]; **311**, 83% 84% ee; **312**, 88% 86% ee; **313**, 83% 86% ee; **314**, 60% 84% ee

315, 95% 85% ee; **316**, 89% 86% ee; **317**, 92% 79% ee; **318**, 80% 72% ee; **319**, 69% 81% ee

320, 45% 93% ee; **321**, 90% 90% ee; **322**, 86% 94% ee; **323**, 93% 90% ee; **324**, 76% 81% ee

325, 64% 80% ee; **326**, 78% 69% ee; **327**, 66% 39% ee

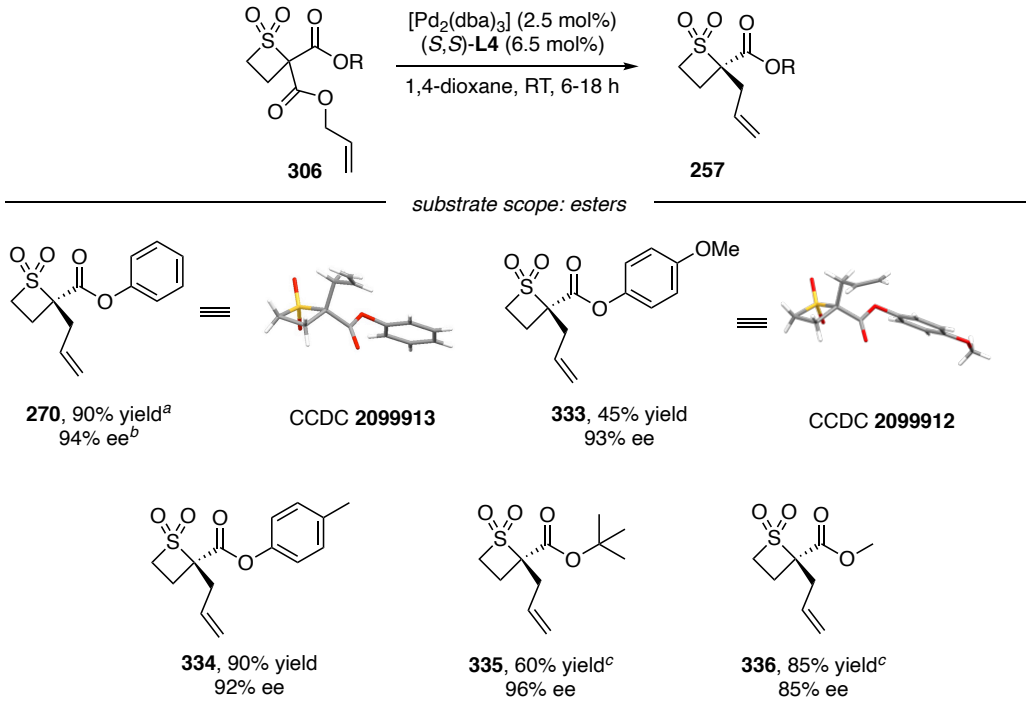
328, 70%[c] 55% ee; **329**, 70%[c] 53% ee; **330**, 68%[c] 52% ee; **331**, 57%[c] 52% ee; **332**, no reaction[c]

[a] isolated yields; [b] enantiomeric excess determined by chiral HPLC; [c] $[Pd_2(dba)_3]$ (5 mol%), (*S*,*S*)-**L4** (13 mol%)

Table 9: Pd-DAAA of thietane-1,1-dioxides bearing ketone side-chains.

2.3.4 Substrate Scope Investigation: Esters

Ester substrates **306** were also subjected to the catalytic conditions and were found to give enantioselectivity that was superior to the ketone examples (Table 10). In this context, aryl esters **270, 333** and **334** were isolated with >90% ee, and, as with the ketones, the substitution on the phenyl ring did not appear to impact the enantioselectivity of the reaction. Pleasingly, *tert*-butyl ester **335** was furnished with 96% ee, the highest of our products. However, the smaller methyl ester **336** was formed with a lower 85% ee.



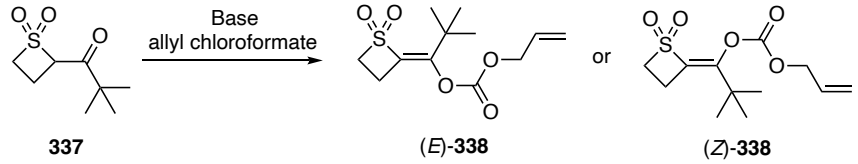
[a] isolated yield; [b] enantiomeric excess determined by chiral HPLC; [c] $[Pd_2(dba)_3]$ (5 mol%), (*S*,*S*)-**L4** (13 mol%)

Table 10: Pd-DAAA of thietane-1,1-dioxides bearing ester side-chains.

We were able to obtain X-ray crystal structures of **270** and **333** to conclusively confirm that the major enantiomer of product contains the *S* absolute stereochemical configuration when using (*S*,*S*)-ANDEN Phenyl Trost ligand **L4**. By extension, this stereochemical outcome was assumed for the other ketone and ester products.

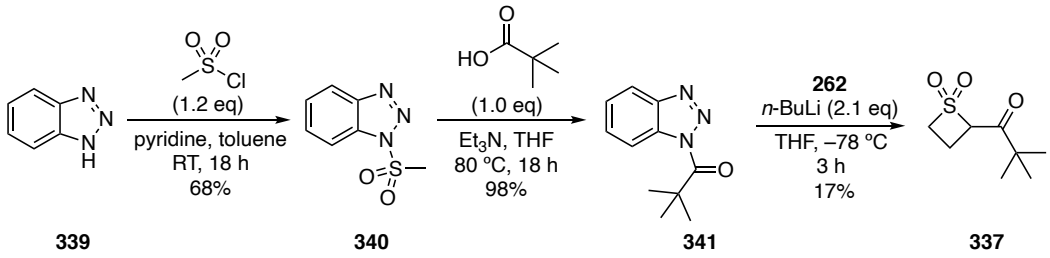
2.4 Enolate Geometry Study

Given the importance of alkene geometry on the enantioselectivity of alkylation of acyclic enolates (*vide supra*, Section 1.2.6), we sought to explore the effect of the enolate geometry in our system. As β-ketoesters are likely to result in a mixture of *E*/*Z* enolates upon decarboxylation, we wanted to individually prepare the *E*- and *Z*-enol carbonates **338** (Scheme 64), and subject them to the standard palladium-catalysed DAAA conditions to gain insight into the importance of enolate geometry on reaction selectivity. We proposed to make allyl enol carbonates **338** from ketone **337** by deprotonation and reaction with allyl chloroformate, followed by chromatographic separation of the two isomers.



Scheme 64: Allyl enol carbonate synthesis from *tert*-butyl ketone **337**.

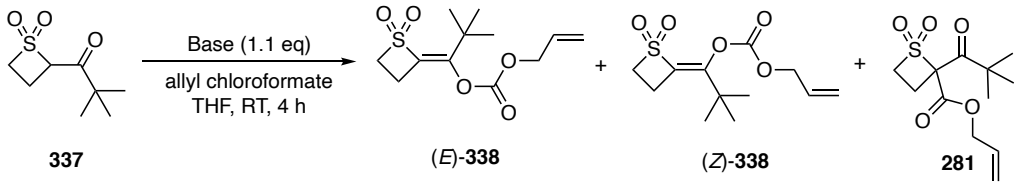
To make ketone **337** (Scheme 65), benzotriazole (**339**) was mesylated to **340**, followed by a reaction with pivalic acid to give amide **341**.[133] Thietane-1,1-dioxide (**262**) was deprotonated using *n*-BuLi, and reacted with electrophile **341**, achieving a disappointing 17% yield of **337**.



Scheme 65: Synthetic route to *tert*-butyl ketone **337** for allyl enol carbonate synthesis.

A base screen for allyl enol carbonate formation revealed varying ratios of *E* and *Z* alkene geometry (Table 11). A mixture of LiHMDS/DMEA (DMEA = *N*,*N*-dimethylethylamine) was found to favour the *Z* enol carbonate geometry in a 1:8.3

E:*Z* ratio (entry 1).[134] LiHMDS, NaHMDS and KHMDS resulted in a more equal mixture of enol carbonates (entries 2–4), albeit KHMDS showed a slight preference for (*E*)-**338**. NaHMDS (entry 3) also led to the formation of a significant amount of β-ketoester **281**. In all cases, substantial quantities of starting material **337** remained. As the reaction with KHMDS was the most efficient in terms of conversion and gave both isomers of **338** in near-equal amounts (entry 4), (*E*)-**338** and (*Z*)-**338** were isolated by chromatography in 34% and 17% yield, respectively.

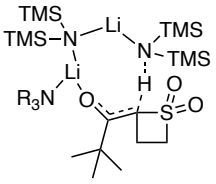


Entry	Base	**337 : *E* : *Z* : 281**[a]
1	LiHMDS[b]/DMEA[b]	5.6 : 1 : 8.3 : 0
2	LiHMDS	7.0 : 1 : 2.4 : 0
3	NaHMDS	4.9 : 1 : 2.1 : 1
4	KHMDS	1 : 1.7 (34%)[c] : 1 (17%)[c] : trace

[a] ratio determined by ^{1}H NMR analysis of the crude product mixture; [b] 2 equivalents used; [c] isolated yield of **338**

Table 11: Synthesis of *E*- and *Z*-enol carbonates **338**.

Based on the work by Collum and co-workers on selective enolisation of acyclic ketones using LiHMDS and trialkylamines,[134] the use of *N*,*N*-dimethylethylamine (DMEA) alongside LiHMDS is believed to promote *Z*-selectivity as it can create a larger aggregate **342** (Figure 20), in which two molecules of LiHMDS are involved. The *E*-selectivity is disfavoured due to the steric interactions between the sulfone and the *tert*-butyl group in the transition state of deprotonation.



R_3N = DMEA

342

Figure 20: Proposed LiHMDS and LiHMDS/DMEA aggregates for enol carbonate synthesis.

The alkene geometry in **338** was determined using selective 1D nOe NMR experiments. The nOe enhancement between the methylene and *tert*-butyl protons was observed in (*Z*)-**338** and not in (*E*)-**338** (Figure 21).

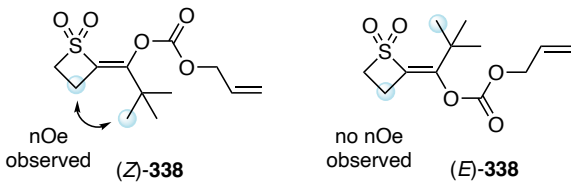
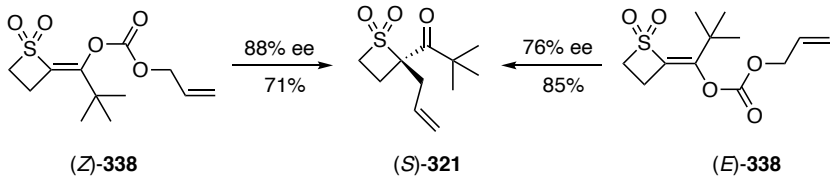


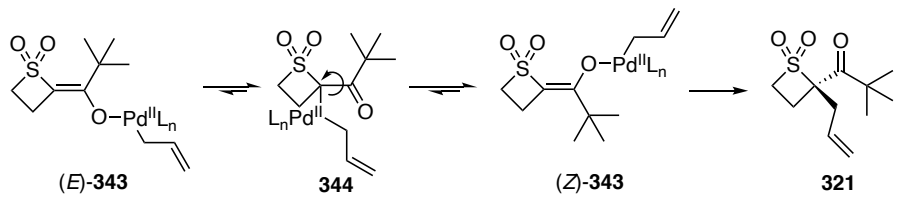
Figure 21: Nuclear Overhauser effect to determine the alkene geometry.

Finally, *E*-(**338**) and *Z*-(**338**) were subjected to the standard palladium-catalysed DAAA reaction conditions, and chiral HPLC analysis confirmed the enantioselectivity of each reaction (Scheme 66). Interestingly, both isomers of **338** afforded (*S*)-**321** as the major enantiomer, with (*E*)-**338** forming **321** in 76% ee and (*Z*)-**338** giving **321** in 88% ee. The level of enantioselectivity of the reaction of (*E*)-**338** was slightly lower when compared to that of β-ketoester **281** (90% ee of (*S*)-**321**, *vide supra*, Table 9, page 65).



Scheme 66: Pd-DAAA of (*Z*)-**338** and (*E*)-**338**.

From these results, we postulate that a palladium-mediated interconversion of the *E*-and *Z*-enolates **343** operates (Scheme 67). This process works by the tautomerisation of the palladium-oxygen enolate (*E*)-**343** to the palladium-carbon bound enolate **344**. Rotation around the C–C single bond in **344** enables the formation of oxygen-bound (*Z*)-**343**. Given that the enantioselectivities of the reaction of (*Z*)-**338** and β-ketoester **281** are very similar (88% and 90% ee, respectively), it is likely that only the *Z*-enolate (*Z*)-**343** undergoes alkylation to **321** within the chiral ligand sphere, akin to a dynamic kinetic resolution.



Scheme 67: Palladium-mediated interconversion *via* Pd–O and Pd–C bound enolate.

2.5 Rationale for the Origin of Stereocontrol

A further rationale for the *E*/*Z* enolate equilibrium using the Trost model is shown below (Figure 22).

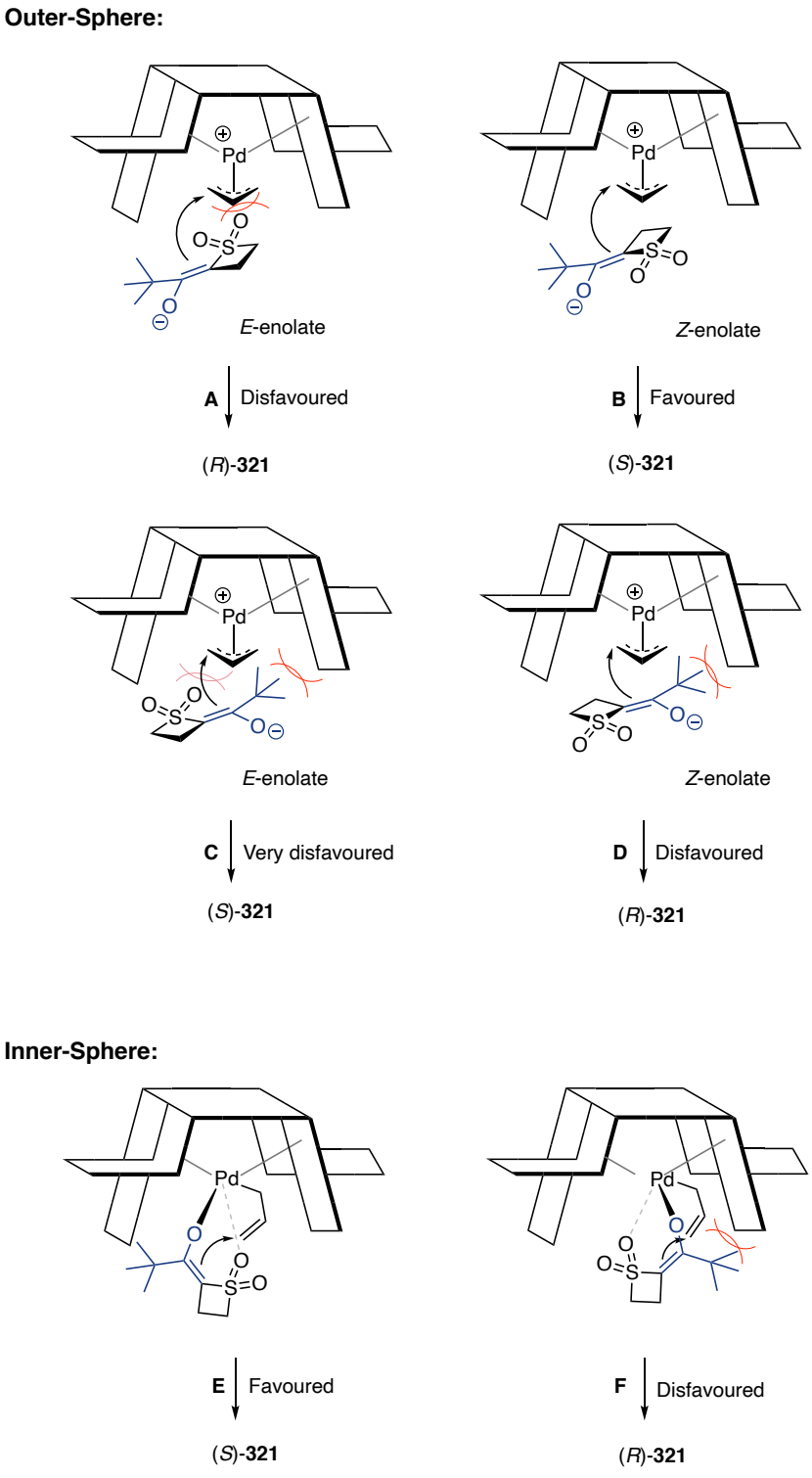


Figure 22: Rationale of observed stereochemical outcome using Trost 'Wall-and-Flap' model.

In an outer-sphere alkylation mechanism, the enolate would prefer to approach the π-allyl system with the large *tert*-butyl substituent residing under the open 'flap'. As this leads to a steric clash between the ligand backbone and the sulfone when in *E*-geometry (pathway A), the *E*-enolate equilibrates to the *Z*-enolate, resulting in reduced steric interactions in the transition state of alkylation (pathway B), affording the major enantiomer (*S*)-**321**. The approach from the opposite face of the enolate is disfavoured due to steric interactions of the *tert*-butyl group with the 'wall' of the ligand for both the *E*- and *Z*-enolates (pathways C and D). As the enolate exclusively alkylates *via* pathway B, the (*S*)-enantiomer is formed with high enantioselectivity. In principle, an inner-sphere alkylation mechanism could also be invoked when the enolate geometry is *Z* due to the stabilising interaction between the oxygen atom of the sulfone and the palladium centre.[135] Pathway E would be favoured over pathway F by minimising the steric clash between the *tert*-butyl substituent and the 'wall' of the ligand in the transition state, also leading to (*S*)-**321** as the major enantiomer. For more details concerning whether outer- or inner-sphere alkylation is preferred in this reaction, see Section 2.6, page 78.

As observed in the substrate scope investigation (*vide supra,* Section 2.3.3), the large steric size of the ketone and ester side-chains is crucial to obtain products with high enantioenrichment. For example, the methyl ketone substrate **287** formed product **327** in 39% ee, which was substantially lower than the selectivity for all other ketones, including ethyl ketone **326** (69% ee). We postulate that this low ee arises due to the lack of steric differentiation between the two faces of the enolate, which can be rationalised using the 'Wall-and-Flap' model (Figure 23). In pathway A, the ketone substituent resides under the flap and alkylation occurs to form (*S*)-**327**, as seen previously. However, due to the similarity in size between the methyl enolate and the thietane-1,1-dioxide, this substrate could also approach the π-allyl system with the four-membered ring residing under the flap, as depicted in pathway B. This pathway would give (*R*)-**327**. It is likely that both transition states are energetically viable and lead to a lower level of enantioselectivity.

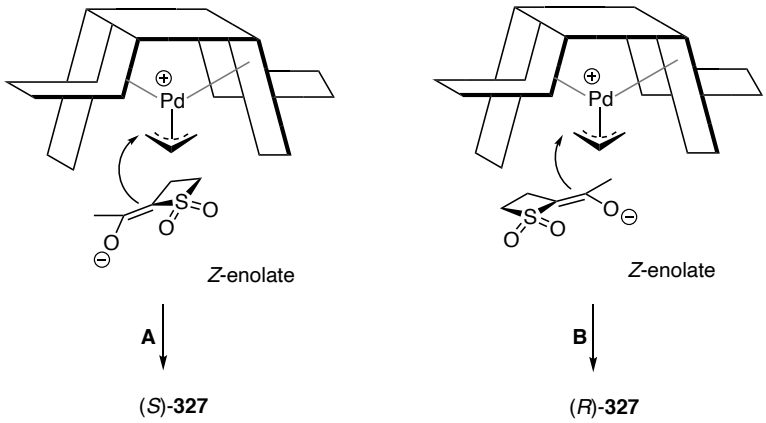
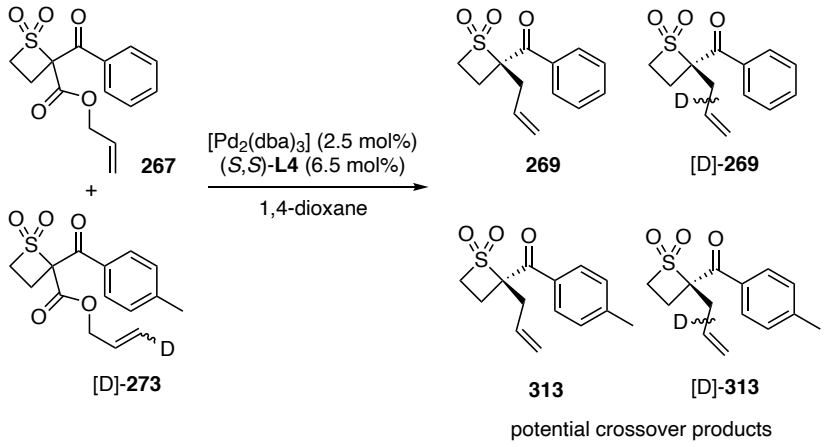


Figure 23: Two potential transition states of alkylation to explain the low enantioselectivity for **327**.

2.6 Mechanistic Study

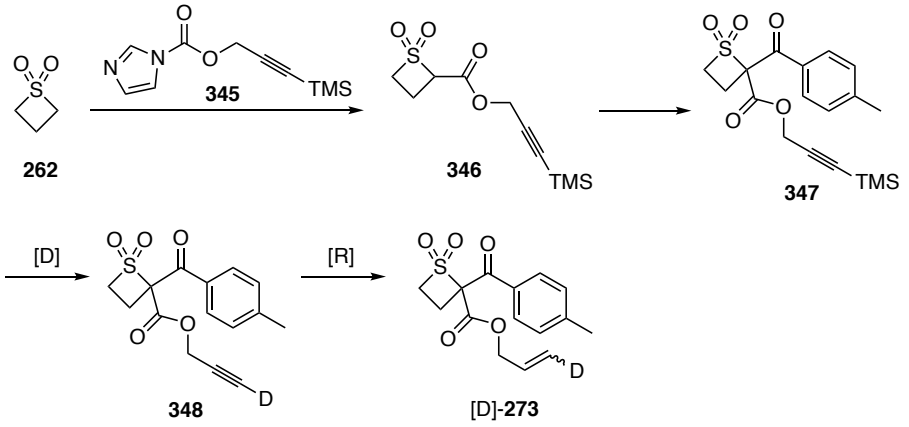
2.6.1 Enolate Crossover

To gain further insight into the mechanism of the Pd-DAAA reaction, an enolate crossover experiment using **267** and a ^{2}H-labelled allylic ester substrate, [D]-**273**, was to be performed (Scheme 68). These substrates were chosen due to their similarity in reactivity. Crossover would be confirmed if products **269**, **313**, [D]-**269** and [D]-**313** were observed in the product mixture. The presence of crossover could potentially suggest an outer-sphere alkylation mechanism as the enolate and the π-allylpalladium(II) complex can freely dissociate from each other. On the other hand, no crossover would be confirmed by the presence of **269** and [D]-**313** only, giving some evidence for an inner-sphere alkylation mechanism.



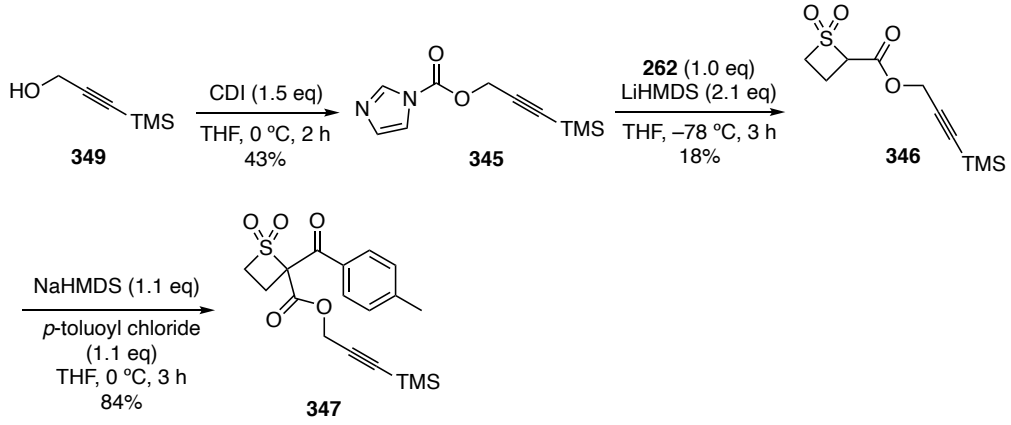
Scheme 68: Enolate crossover using ^{2}H-labelled allylic ester.

To synthesise [D]-**273** (Scheme 69), carbamate **345** would be used to append the TMS-protected propargyl ester onto thietane-1,1-dioxide (**262**) to generate **346**. Installation of the *p*-toluoyl ketone in **347** would be followed by a silyl deprotection and deuteration to give **348**. Finally, reduction of the alkyne to the alkene would furnish crossover substrate [D]-**273**.



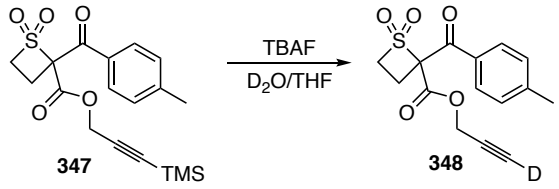
Scheme 69: Proposed synthesis of crossover substrate [D]-**273**.

The first step of this route was to prepare carbamate **345** (Scheme 70). To achieve this, commercially available TMS-protected propargyl alcohol **349** was reacted with CDI to form carbamate **345** in 43% yield. Thietane-1,1-dioxide (**262**) was then reacted with carbamate **345** to furnish **346** in a disappointingly low 18% yield. **346** was further reacted with NaHMDS and *p*-toluoyl chloride to access β-ketoester **347** in 84% yield.



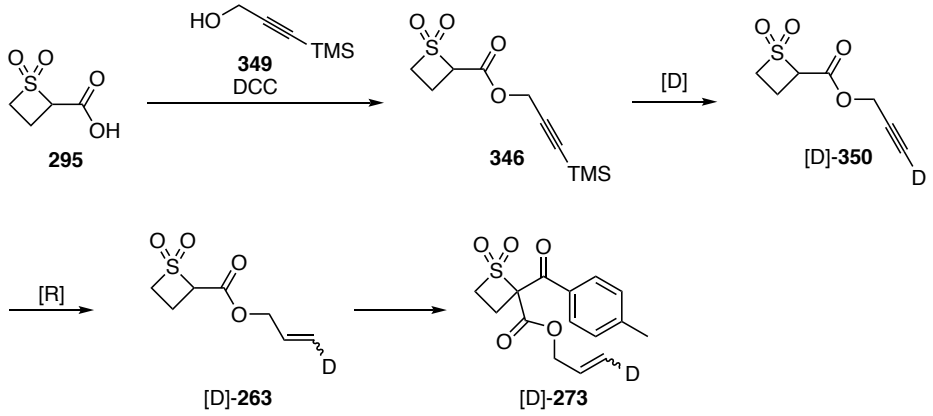
Scheme 70: Synthesis of TMS-protected propargylic substrate **347**.

Deuterium incorporation at the terminal alkyne position was attempted *via* silyl deprotection using TBAF in a D_2O/THF solvent mixture (Scheme 71). Unfortunately, alongside desired product **348**, a significant, unidentified impurity was also formed, which was inseparable from product **348**.



Scheme 71: Silyl deprotection and deuterium quench of **347**.

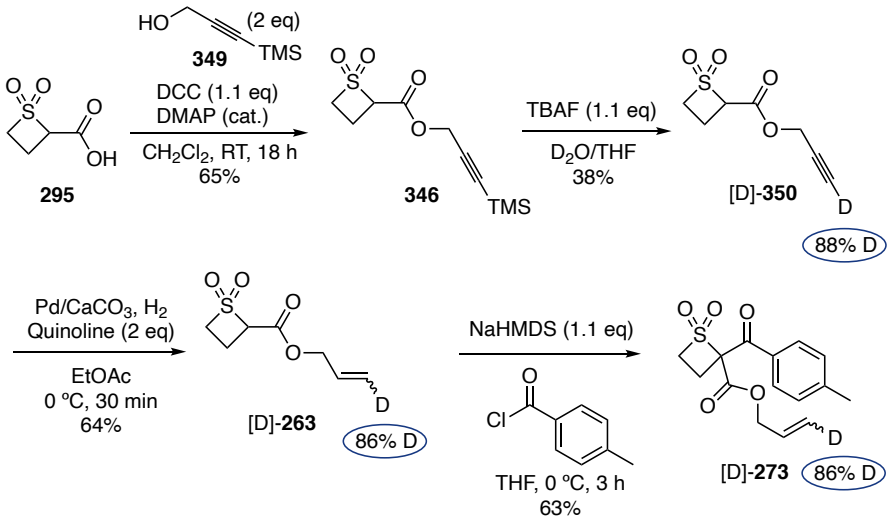
Ultimately, the presence of a large amount of the unknown impurity forced us to abandon this route in favour of an alternative approach (Scheme 72). More specifically, an esterification of carboxylic acid **295** with TMS-protected propargyl alcohol (**349**) may result in a higher yield of **346** compared to the previous route using carbamate **345**. At this stage, the sequence of steps would be reversed, in which alkyne deuteration and reduction would precede ketone installation. As such, desilylation of **346** and a deuterium quench would give [D]-**350**, while Lindlar reduction should give rise to deuterated allyl ester [D]-**263**. Finally, installation of the ketone side-chain using *p*-toluoyl chloride would then furnish the requisite crossover substrate [D]-**273**.



Scheme 72: Route B to crossover substrate [D]-**273**.

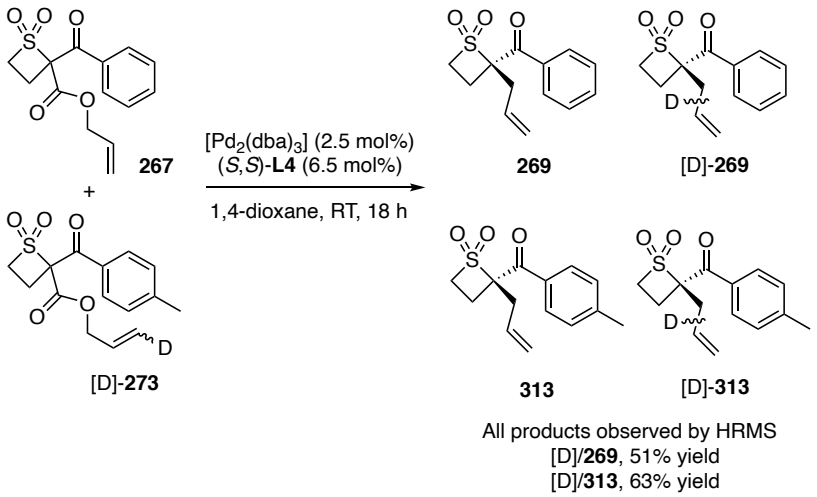
Using Steglich esterification conditions, TMS-protected propargyl ester **346** was obtained in 65% yield from carboxylic acid **295** (Scheme 73), in a much more efficient process than the direct functionalisation of thietane-1,1-dioxide (**262**) with carbamate

345 (18% yield). With **346** in hand, we attempted to deprotect and deuterate the alkyne at this stage, leading to the successful 88% D incorporation at the terminal alkyne in [D]-**350**. Reduction of deuterated alkyne [D]-**350** was performed using Lindlar's catalyst and quinoline (2 eq) under a hydrogen atmosphere in ethyl acetate at 0 ºC for 30 minutes. The reaction proceeded cleanly, furnishing alkene [D]-**263** in 64% yield and with 86% D incorporation without any over-reduction. The final step in the synthesis to make deuterated β-ketoester [D]-**273** was the acylation of [D]-**263** using the previously optimised reaction conditions (*vide supra*, section 2.1, page 55), affording [D]-**273** in 63% yield.



Scheme 73: Synthesis of [D]-**273** for enolate crossover study.

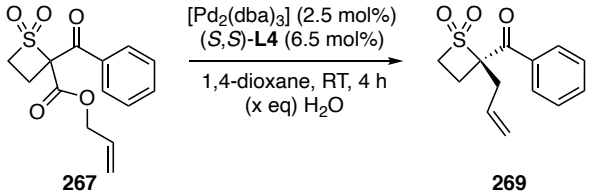
With [D]-**273** and **267** in hand, the crossover reaction was performed (Scheme 74). ^{1}H NMR analysis of the crude product mixture proved difficult due to overlapping signals, whereas column chromatography was ineffective as the products could not be separated due to their similar R_f values. Therefore, the product mixture was analysed by mass spectrometry and revealed the presence of all four crossover products **269**, **313**, [D]-**269** and [D]-**313** in significant amounts. This experiment reveals that the enolate and π-allyl palladium(II) ion pairs undergo exchange faster than alkylation, and may suggest an outer-sphere alkylation mechanism.



Scheme 74: Evidence for enolate crossover.

2.6.2 Water Tolerance Study

In addition to the crossover study, we performed a water tolerance experiment to test whether the enolate ion was a long-lived intermediate in this reaction (Table 12). Due to the similarities in pKa of the enolate and water, we expected the water to quench the enolate at least to some extent and, therefore, impact the yield and, potentially, the ee of **269**.



Entry	H_2O (eq)	Yield (%)[a]	ee (%)[b]
1	0	78	84
2	0.5	78	84
3	1	82	81
4	5	82	80
5	10	78	76
6	20	78	73

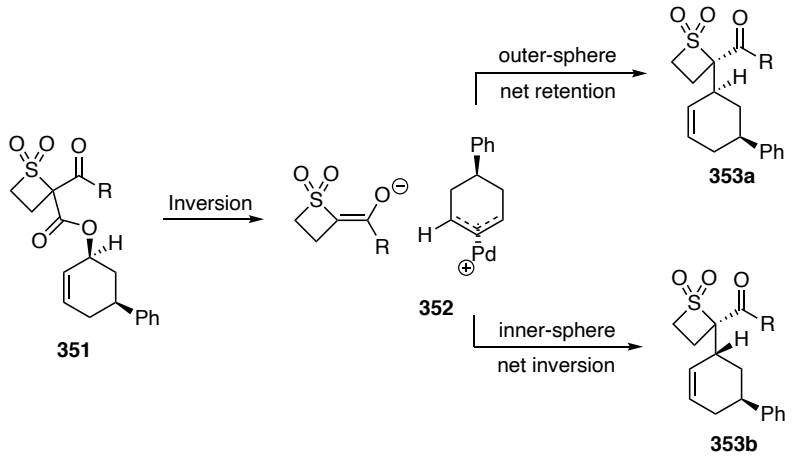
[a] isolated yield; [b] enantiomeric excess determined by chiral HPLC

Table 12: Water tolerance study.

From the results shown in Table 12, the addition of water to the reaction did not appear to impact the yield, and had only a slight impact on the enantioselectivity, even when 20 equivalents of water were used. These results suggest that the free enolate nucleophile is an unlikely species in this allylic alkylation reaction.

2.6.3 Stereochemical Labelling

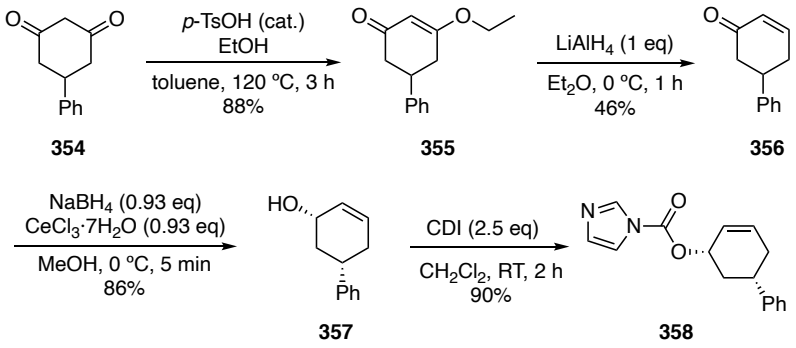
To conclusively elucidate the alkylation mechanism of these carbonyl-stabilised α-sulfonyl anions, the Pd-DAAA reaction using a stereochemical probe was to be performed (Scheme 75). As such, oxidative addition of the palladium catalyst to allylic electrophile **351** would be expected to occur with inversion of stereochemistry at the allylic centre to give **352**. The products of the outer- and inner-sphere alkylation **353a** and **353b** should then be distinguishable due to the diastereomeric relationship between them. For example, outer-sphere alkylation should proceed with a second inversion, causing net retention of the stereochemistry at the allylic centre **353a**. On the other hand, an inner-sphere alkylation should proceed by reductive elimination with retention and, therefore, overall inversion of the allylic site in **353b**.



Scheme 75: Stereochemical probe to indicate an outer- or inner-sphere alkylation.

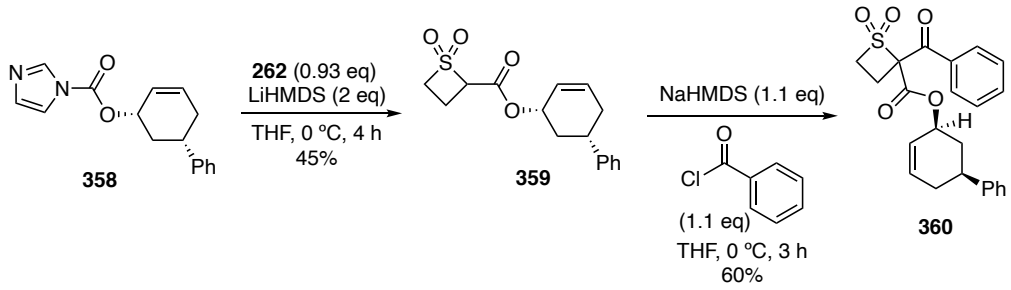
Synthesis of the stereochemical probe began with commercially available 5-phenyl-1,3-cyclohexanedione (**354**) using a literature method (Scheme 76).[136] Ethoxy-substituted enone **355** was synthesised from **354** using *p*-toluenesulfonic acid and ethanol, achieving an 88% yield. Conjugate reduction of **355** using lithium aluminium hydride

furnished enone **356** in 46% yield, and finally, a Luche reduction of **356** afforded a single diastereoisomer of **357** in 86% yield. Allylic alcohol **357** was then transformed into carbamate **358** using CDI in 90% yield.



Scheme 76: Synthesis of stereodefined allylic carbamate **358**.

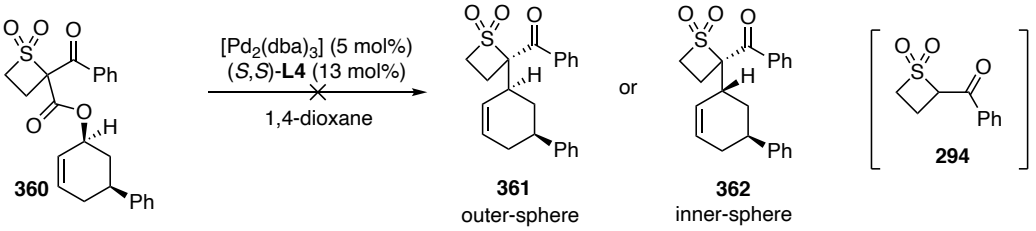
Carbamate **358** was reacted with thietane-1,1-dioxide (**262**) to afford allylic ester **359** in 45% yield (Scheme 77). Finally, acylation with benzoyl chloride afforded **360**, the substrate to be employed in the stereochemical labelling experiment to elucidate whether an inner- or outer-sphere alkylation pathway dominates.



Scheme 77: Synthesis of stereochemical probe **360**.

Allylic ester **360** was subjected to the palladium-catalysed decarboxylative asymmetric allylic alkylation conditions as a mixture of diastereoisomers (Table 13). Due to the substituted nature of the allyl moiety, the catalyst and ligand loading were doubled to 5 mol% Pd and 13 mol% **L4**, and the reaction was run at room temperature for 24 h (entry 1). Unfortunately, this reaction was unsuccessful in forming **361** or **362**, giving only starting material **360** that had failed to undergo oxidative addition. This reaction was attempted under increasingly forcing conditions, including heating to 40 °C and 80 °C for an extended period of time (entries 2 and 3, respectively). At higher temperatures,

there was increased formation of non-alkylated product **294**. From these results, it was apparent that **360** was too sterically hindered to undergo the desired alkylation, making it challenging to definitively ascertain the nature of the alkylation step in the mechanism.

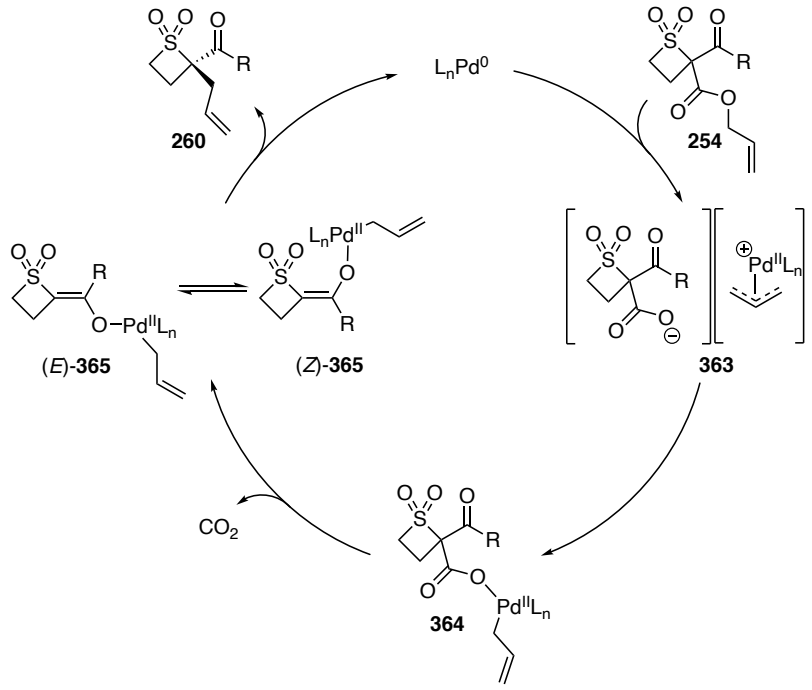


Entry	Conditions	Observations[a]
1	RT, 24 h	**360** only
2	40 °C, 5 days	**360** : **294** (1 : 1.6)
3	80 °C, 48 h	**360** : **294** (1 : 11)

[a] ratio determined by ^{1}H NMR analysis of the crude product mixture

Table 13: Unsuccessful Pd-DAAA of **360**.

Despite this setback, the mechanistic investigations performed thus far provided crucial information about the reaction and, therefore, the following catalytic cycle for the Pd-DAAA of thietane-1,1-dioxides has been proposed (Scheme 78). Following ionisation of **254**, palladium-carboxylate ion pair **363** is formed. We believe this intermediate is relatively long-lived and does not decarboxylate readily to give the enolate as indicated by the tolerance of the reaction to significant amounts of water. We also believe that it is at this stage that crossover occurs. In the presence of palladium,[58] decarboxylation of **364** occurs to reveal *E* and *Z* enolates **365**, which undergo a palladium-mediated interconversion. Alkylation of **365** bearing the *Z*-alkene geometry furnishes enantioenriched **260** and releases the palladium(0) catalyst to continue the cycle.

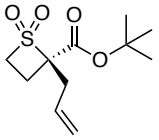


Scheme 78: Proposed catalytic cycle of Pd-DAAA of thietane-1,1-dioxides.

2.7 [3.5] Spirocycle Synthesis

2.7.1 Racemic [3.5] Spirocycle Synthesis

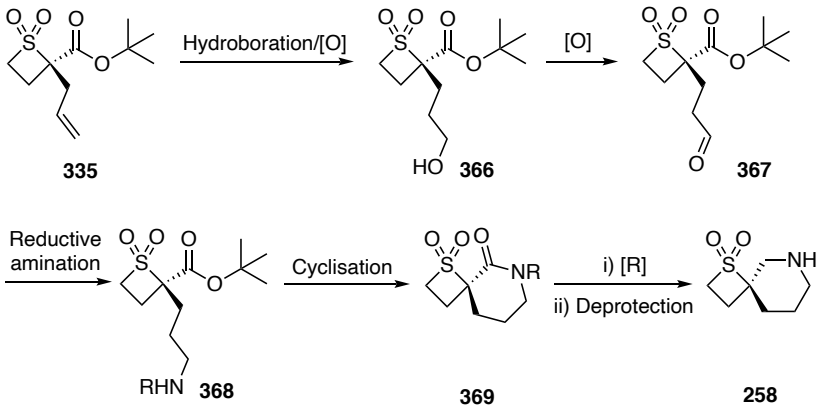
Following the development of the asymmetric methodology to generate enantioenriched thietane-1,1-dioxides, the transformation of these building blocks into novel spirocycles was undertaken. The *tert*-butyl ester product **335** was initially chosen to be explored for two main reasons (Figure 24). Firstly, this compound should furnish the corresponding spirocycle in 96% ee, the highest selectivity we have obtained when developing this chemistry. Secondly, the *tert*-butyl group should be easily removable using TFA to reveal the carboxylic acid, making it a highly useful handle for further functionalisation.



335
96% ee

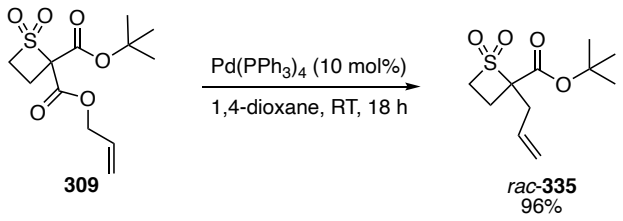
Figure 24: *tert*-Butyl ester substrate **335**.

A route was devised for the synthesis of [3.5] spirocycle **258** from ester **335** (Scheme 79). The first step was to subject the alkene in **335** to hydroboration/oxidation conditions to form primary alcohol **366**. Subsequent oxidation to aldehyde **367** would allow reductive amination to introduce an amine functionality in **368**. Cyclisation of amine **368** onto the *tert*-butyl ester would furnish **369**. Finally, a reduction of the lactam and deprotection would form desired spirocycle **258** bearing an amine as a versatile reactive handle for library generation.



Scheme 79: Proposed synthetic route to [3.5] spirocycle **258**.

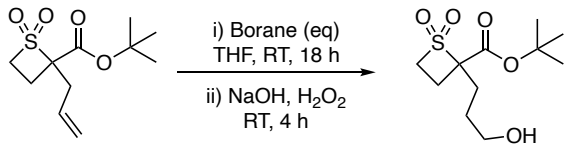
For the purposes of optimisation of the route to spirocycle **258**, ester **335** was made in racemic form on 3 g scale using 10 mol% $Pd(PPh_3)_4$ (Scheme 80), and a racemic synthesis was first investigated.



Scheme 80: Racemic synthesis of **335**.

Initially, hydroboration conditions were screened using BH_3·THF and 9-BBN (Table 14). Hydroboration using BH_3·THF was attempted at increasing borane loadings (entries 1–3); however, even with 5 equivalents of the reagent, the yield of alcohol **366** remained low (43%). 9-BBN was also investigated in the same increments of equivalents used (entries 4-6), and was found to give superior yields of **366**. In

particular, the use of 5 equivalents of 9-BBN, followed by oxidation with hydrogen peroxide furnished alcohol **366** in 71% yield. When the reaction was scaled up to 1.3 g, the yield of **366** remained high (75%).



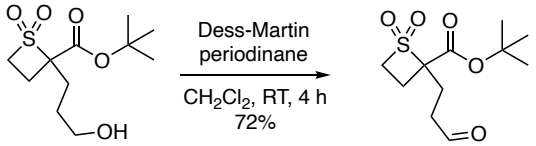
rac-**335** *rac*-**366**

Entry[a]	Conditions	Yield (%)[b]
1	BH_3·THF (1.1 eq)	19
2	BH_3·THF (2.5 eq)	29
3	BH_3·THF (5.0 eq)	43
4	9-BBN (1.1 eq)	14
5	9-BBN (2.5 eq)	38
6	9-BBN (5.0 eq)	71 (75[c])

[a] 0.08 mmol (20 mg) of *rac*-**335**; [b] isolated yield; [c] 5.28 mmol (1.3 g) of *rac*-**335**

Table 14: Hydroboration/oxidation of **335**.

Alcohol **366** was then successfully oxidised to aldehyde **367** using Dess-Martin periodinane in 67% on small scale, and 72% yield on 1 g scale (Scheme 81).

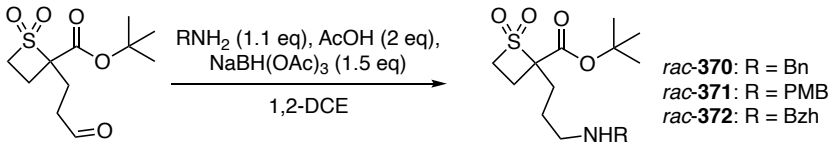


rac-**366** *rac*-**367**

Scheme 81: Dess-Martin periodinane oxidation to aldehyde **367**.

Reductive amination of aldehyde **367** to amine **368** was trialled using ammonia and several primary amines (Table 15). Our initial attempt to produce the primary amine using ammonium hydroxide at 70 ºC was unsuccessful and resulted in reduction of **367** to alcohol **366** (entry 1). Unfortunately, the reaction of allyl amine at room temperature overnight resulted in the double reductive amination product (entry 2). An attempt to prevent over-reaction by lowering the temperature to 0 ºC and using a shorter reaction time was futile (entry 3). Use of 2,4-dimethoxybenzylamine also resulted in the double

reductive amination product (entry 4). Benzylamine and 4-methoxybenzylamine were successful in forming desired amines **370** and **371** (entry 5 and 6), albeit in low yields (26% and 24%, respectively). Benzhydrylamine formed **372** in a 47% yield and benefitted from purification by trituration rather than column chromatography (entry 7). The synthesis of **372** was, therefore, scaled up to 1.1 g in 57% yield.



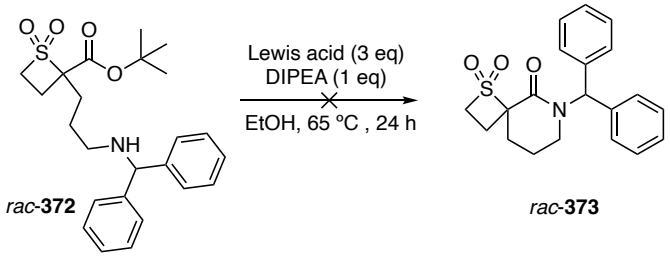
rac-**367** *rac*-**368**

Entry[a]	Amine (RNH_2)	Temp. (°C)	Time (h)	Yield (%)[b]	Product	Observations/Notes
1[c]	NH_3OH	70	4	N/A	-	**366** only[d]
2	allylamine	RT	18	N/A	-	Double reductive amination[d]
3	allylamine	0	20 min	N/A	-	Double reductive amination[d]
4	2,4-dimethoxybenzylamine	RT	18	N/A	-	Double reductive amination[d]
5	benzylamine	RT	18	26	**370**	-
6	4-methoxybenzylamine	RT	18	24	**371**	-
7	benzhydrylamine	RT	18	47 (57[e])	**372**	-

[a] 0.08 mmol (20 mg) of *rac*-**367**; [b] isolated yield; [c] $NaCNBH_3$ and EtOH were used in place of $NaBH(OAc)_3$ and 1,2-DCE; [d] determined by ^1H NMR of the crude product mixture; [e] 2.66 mmol (1.1 g) of *rac*-**367**

Table 15: Reductive amination of **367**.

With **372** in hand, the direct cyclisation of amine **372** to lactam **373** was attempted using several Lewis acids (Table 16). Unfortunately, $CaCl_2$, $AlCl_3$ and $MgCl_2$ all proved unsuccessful in promoting the cyclisation, with starting material being recovered in all cases (entries 1–3). Acetic acid also resulted in no reaction (entry 4). The large steric size of the *tert*-butyl ester and benzhydrylamine were the likely reason for the lack of desired cyclisation.

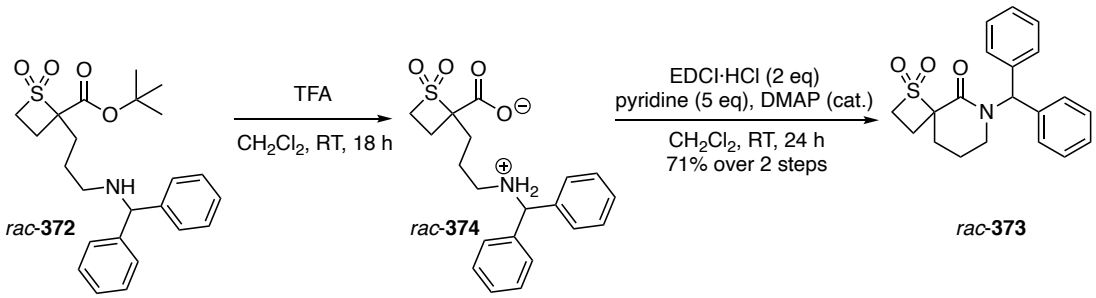


Entry	Lewis Acid
1	$CaCl_2$
2	$AlCl_3$
3	$MgCl_2$
4	AcOH[a]

[a] reaction run in toluene at 90 °C

Table 16: Unsuccessful intramolecular cyclisation onto *tert*-butyl ester to **373**.

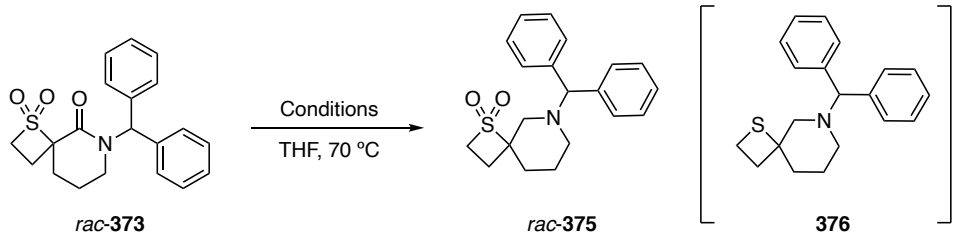
Since cyclisation could not be achieved directly from **372**, an alternative two-step lactamisation was performed by TFA removal of the *tert*-butyl group in **372** (Scheme 82), followed by an intramolecular amide coupling in the presence of EDCI. This reaction sequence afforded spirocycle **373** in 51% yield on 50 mg scale, and an improved 71% yield on 650 mg scale.



Scheme 82: TFA ester removal to amino acid **374**, followed by intramolecular amide coupling.

With spirocycle **373** in hand, reduction of lactam **373** to amine **375** was attempted (Table 17). Lithium aluminium hydride proved too powerful a reducing agent (entry 1) and resulted in over-reduced sulfide **376**. The use of two equivalents of Lewis acid $AlCl_3$, creating a less powerful mixed hydride, successfully impeded the reduction of the sulfone; however, the reaction was slow and did not go to completion after 2 or 4 h (entries 2 and 3). Surprisingly, an attempt using a 1 M solution of $LiAlH_4$ with $AlCl_3$ furnished over-reduced **376** (entry 4). Due to concerns about over-reduction, BH_3·THF

was attempted as a milder reducing agent (entries 5–8). This reagent proved more successful as over-reduction was not observed, even with 10 equivalents of BH_3·THF at reflux (entry 5). Reducing the loading to 5 and 3 equivalents led to an incomplete reaction after 3 h (entries 6 and 7). However, doubling the reaction time to 6 h using only 3 equivalents of borane resulted in full conversion and furnished product **375** in 88% isolated yield (entry 8).



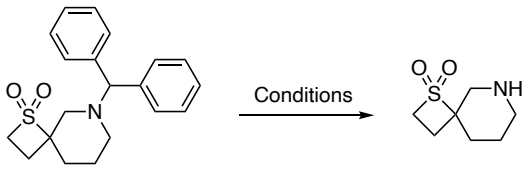
rac-**373** *rac*-**375** **376**

Entry[a]	Conditions	Time (h)	373 : 375[b]	Yield of 375 (%)[c]	Notes
1	$LiAlH_4$ powder (3 eq)	4	-	-	**376** only[d]
2	$LiAlH_4$ powder (2 eq), $AlCl_3$ (2 eq)	2	2.5 : 1	15	
3	$LiAlH_4$ powder (2 eq), $AlCl_3$ (2 eq)	4	1 : 2.5	44	
4	$LiAlH_4$ (1 M in THF) (2 eq), $AlCl_3$ (2 eq)	4	-	-	**376** only[d]
5	BH_3·THF (1 M in THF) (10 eq)	3	**375** only	76	
6	BH_3·THF (1 M in THF) (5 eq)	3	1 : 20	64	
7	BH_3·THF (1 M in THF) (3 eq)	3	1 : 10	61	
8	BH_3·THF (1 M in THF) (3 eq)	6	**375** only	88	

[a] 0.06 mmol (20 mg) of *rac*-**373**; [b] ratio determined by ^{1}H NMR analysis of the crude product mixture; [c] isolated yield; [d] determined by ^{1}H NMR analysis and high-resolution mass spectrometry

Table 17: Reduction of lactam **373** to amine **375**.

The final stage of spirocycle synthesis was deprotection of benzhydrylamine **375** to **258** (Table 18). Several reagents were tried to no avail, including 1-chloroethylchloroformate (entry 1), 4 N hydrochloric acid (entry 2), and triethylsilane (entry 3). Hydrogenolysis using palladium hydroxide in MeOH appeared promising after 2 h (entry 4), however reaction in EtOH yielded no product (entry 5). Pleasingly, hydrogenolysis of **375** in EtOH in the presence of TFA cleanly afforded desired spirocycle **258** in 91% yield (entry 6).



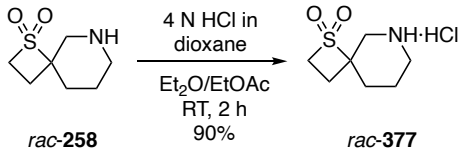
rac-**375** *rac*-**258**

Entry[a]	Conditions	Observations
1	1-chloroethylchloroformate, MeOH, 80 ºC	No reaction
2	4N HCl/1,4-dioxane, MeOH, 70 ºC	No reaction
3	Et_3SiH, TFA, RT	No reaction
4	$Pd(OH)_2/H_2$, MeOH, 2 h, RT	1 : 4 **375** : **258**[b]
5	$Pd(OH)_2/H_2$, EtOH, 2 h, RT	No reaction
6	$Pd(OH)_2/H_2$, EtOH, TFA, 2 h, RT	**258** only (91%)[c]

[a] 0.03 mmol (10 mg) of *rac*-**375**; [b] ratio determined by ^1H NMR analysis of the crude product mixture; [c] isolated yield

Table 18: Deprotection of benzhydryl amine.

Finally, the spirocycle was turned into the hydrochloride salt using 4 N HCl in 1,4-dioxane to furnish racemic **377** in 90% yield (Scheme 83).



rac-**258** *rac*-**377**

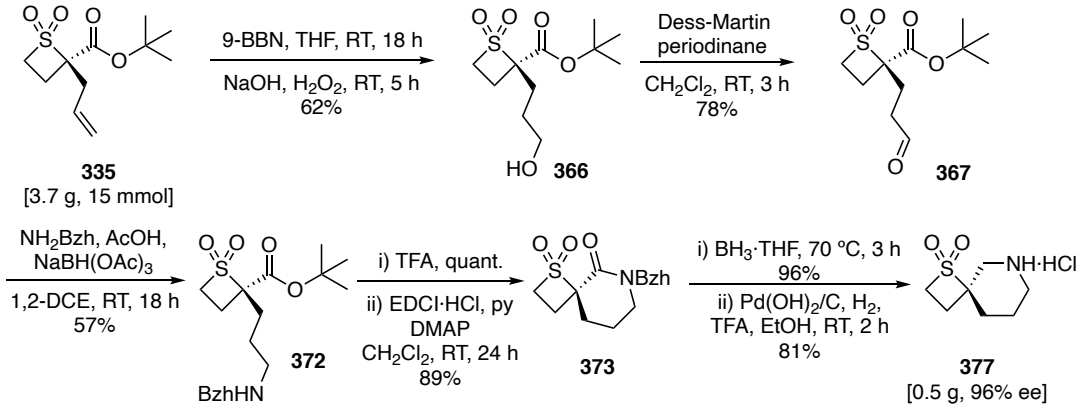
Scheme 83: Formation of the HCl salt of spirocycle **258**.

2.7.2 Enantioenriched [3.5] Spirocycle Synthesis

With the synthesis of racemic spirocycle **258** successfully mapped out, the stage was set to prepare spirocycle **258** in enantioenriched form on scale. The Pd-DAAA of **309** was performed on 5 g scale and furnished enantioenriched **335** in 86% yield (Scheme 84). Chiral HPLC analysis confirmed a consistent enantioenrichment of 96% ee.

Scheme 84: Scale up of the Pd-DAAA reaction of **309**.

Ester **335** was utilised in enantioenriched spirocycle synthesis (Scheme 85). The conditions and yields were mostly reproducible compared to the racemic synthesis, with the amide coupling forming **373** and lactam **373** reduction giving even higher yields when carried out on a larger scale. In total, 0.5 g of **377** as the hydrochloride salt was prepared.



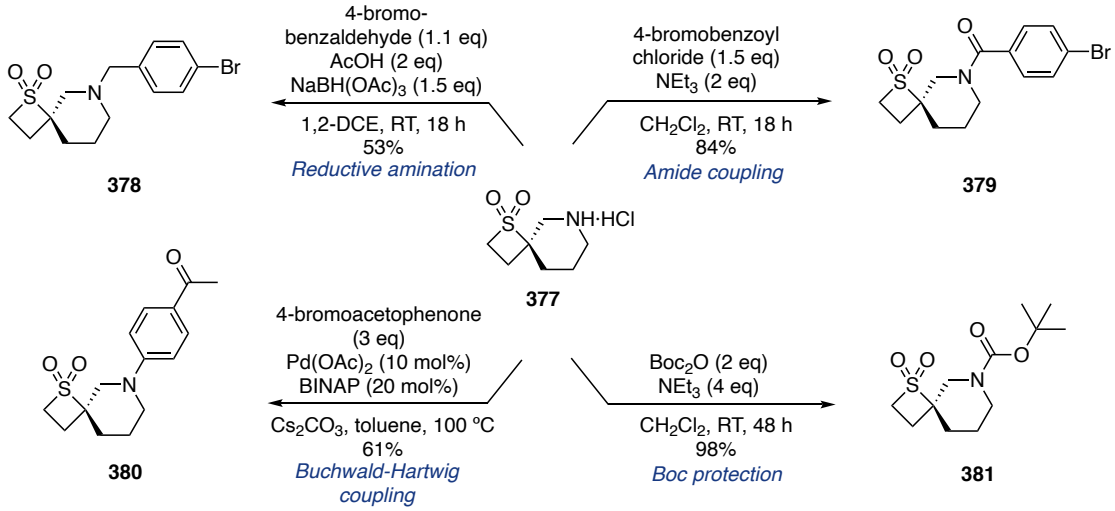
Scheme 85: Synthesis of enantioenriched spirocycle **377**.

Due to the novelty of enantioenriched thietane-1,1-dioxide spirocycles in pharmaceutical screening libraries, **377** has been sent to AstraZeneca for incorporation into screening collections.

2.8 Functionalisations of Spirocycle 377

To demonstrate the utility of spirocycle **377** in compound library synthesis, a series of functionalisations, which are amongst the most commonly used in industry, were performed (Scheme 86). The first derivatisation was the reductive amination of spirocycle **377** with 4-bromobenzaldehyde to form **378** in 53% yield. A simple amide coupling using 4-bromobenzoyl chloride gave rise to **379** in 84% yield. A

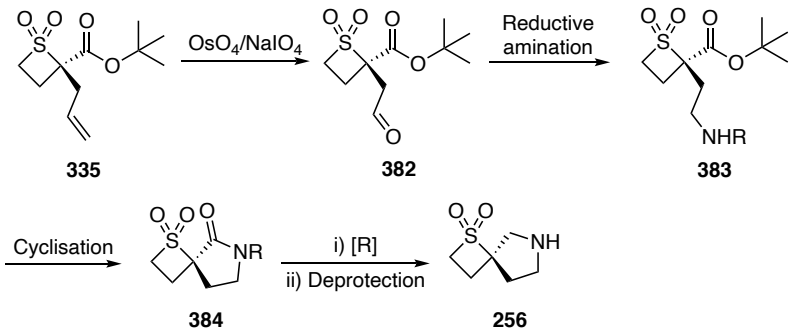
Buchwald-Hartwig coupling proceeded to afford **380** in 61% yield. Finally, protection of amine **377** to carbamate **381** was also attempted in order to confirm the enantioenrichment of spirocycle **377** by chiral HPLC analysis. The ee of **381** was found to be 96%, indicating that, as expected, no erosion of stereoenrichment occurs in the synthesis of spirocycle **377**.



Scheme 86: Functionalisations of spirocycle **377**.

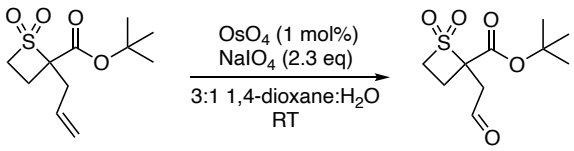
2.9 [3.4] Spirocycle Synthesis

In addition to [3.5] ester-derived spirocycle **258**, a similar route to [3.4] spirocycle **256** was proposed from **335** (Scheme 87), in which an oxidative cleavage step would be used to shorten the carbon chain in **382**, where the analogous reductive amination (**383**), lactamisation (**384**), lactam reduction and deprotection would afford spirocycle **256**.



Scheme 87: Proposed synthesis of [3.4] ester-derived spirocycle **256**.

Lemieux-Johnson oxidation of the alkene in racemic product **335** and *in situ* diol cleavage to aldehyde **382** was attempted (Table 19). Osmium tetroxide and sodium periodate conditions were screened. The non-nucleophilic base 2,6-lutidine is often used in this reaction to suppress side reactions and, therefore, improve yields of the aldehyde product. We attempted the reaction with 2 equivalents of 2,6-lutidine for 4 h which formed a mixture of **335** and **382** in a 1:2 ratio (entry 1). Increasing the reaction time to 7 h only marginally improved the ratio to 1:3 (entry 2). Unfortunately, the isolated yields of **382** were significantly lower than expected, giving just 20% and 25% of **382** for the 4- and 7-hour reaction, respectively, potentially due to decomposition of aldehyde **382** during column chromatography. In the absence of 2,6-lutidine and by running the reaction overnight, ^{1}H NMR analysis of the crude product mixture showed complete conversion of alkene **335** to aldehyde **382** (entry 3). Under these conditions, aldehyde **382** was formed cleanly after work-up, and was used in the next step without further purification.



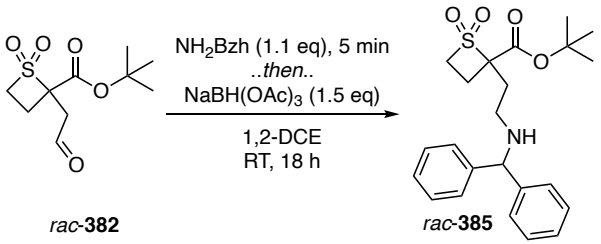
rac-**335** *rac*-**382**

Entry[a]	Conditions	335 : 382[b]	Yield (%)	Observations/Notes
1	2,6-lutidine (2 eq), 4 h	1:2	20[c]	-
2	2,6-lutidine (2 eq), 7 h	1:3	25[c]	-
3	No 2,6-lutidine, 18 h	**382** only	quant.[d]	$NaIO_4$ added after 5 min

[a] 0.08 mmol (20 mg) of *rac*-**335**; [b] ratio determined by ^{1}H NMR analysis of crude product mixture; [c] isolated yield; [d] based on the mass of crude product

Table 19: Dihydroxylation and diol cleavage of **335**.

Due to the suspected instability of **382**, it was immediately reacted as crude material in the reductive amination to form **385** (Table 20). Variations of the previous reductive amination conditions were attempted. In the absence of an acetic acid additive, and with the reducing agent being added after imine formation (entry 1), there was no formation of **385**. This reaction was also unsuccessful in the presence of an acetic acid additive, regardless of the amount added (entries 2 and 3). In all cases, decomposition of aldehyde **382** took place. Interestingly, in the absence of acetic acid and by adding the reducing agent alongside the amine and aldehyde (entry 4), product **385** was indeed formed, albeit in a very low 11% yield.



rac-**382** *rac*-**385**

Entry[a]	Conditions	Yield (%)[b]
1	as stated	-
2	AcOH additive (0.5 eq)	-
3	AcOH additive (2 eq)	-
4	$NaBH(OAc)_3$ was added simultaneously with the amine and aldehyde	11%

[a] 0.09 mmol (25 mg) of *rac*-**382**; [b] isolated yield

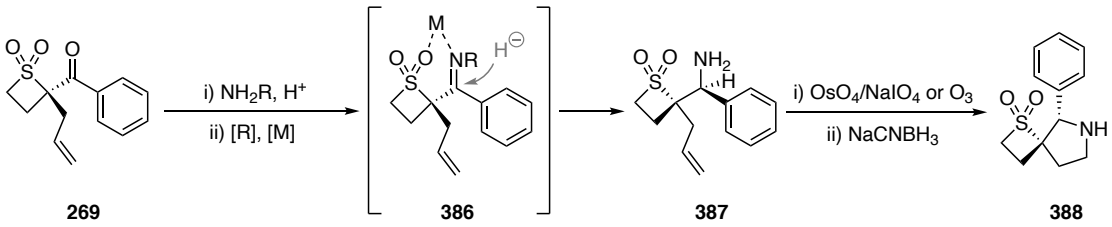
Table 20: Reductive amination of aldehyde **382**.

Although some progress towards [3.4] spirocycle synthesis has been made, optimisation of the reductive amination step to achieve higher yields of amine product is required. Specifically, lower reaction temperatures, different solvents and other amine reagents could be attempted in a bid to improve the yield of amine product. Once this has been overcome, the remaining steps to spirocycle **256** will mirror those used in spirocycle **258** synthesis. Other future avenues to be explored in this project are discussed in the next section.

3. Future Work

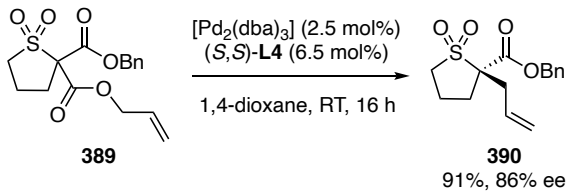
Alongside ester-derived spirocycles, spirocycles arising from ketone products are of particular interest as the ketone side-chain provides alternative exit vectors for functionalisation, as well as two contiguous stereocentres in **388** (Scheme 88). They could be synthesised by conversion of aryl ketone **269** to the corresponding imine **386**, followed by a Lewis acid mediated reduction, in which the Lewis acid should chelate both the sulfone and the imine functionalities. Cyclic stereocontrol could then potentially be invoked to deliver hydride selectively to one face of the imine (**386**). To form the desired spirocycle, the alkene would be transformed into the aldehyde by $OsO_4/NaIO_4$ or ozonolysis, upon which an intramolecular reductive amination to **388** could occur. In this way, spirocycle **388** would contain two contiguous stereocentres,

creating molecular complexity while possessing several exit vectors and points of functionalisation.



Scheme 88: Proposed [3.4] spirocycle synthesis from enantioenriched ketone substrate **269**.

In addition to thietane-1,1-dioxides, this methodology is currently being extended within the group to five-membered sulfolanes and six-membered thiane-1,1-dioxides. Following optimisation, the Pd-DAAA reaction conditions for sulfolane substrate **389** were found to be almost identical to the ones used for thietane-1,1-dioxide substrates in this project (Scheme 89), whereby $Pd_2(dba)_3$ as the source of palladium(0), chiral ligand **L4**, and 1,4-dioxane as the solvent were found to mediate the reaction most efficiently.



Scheme 89: Pd-DAAA of sulfolane substrate **389**.

A selected substrate scope study is shown below (Table 21). Phenyl ester **391** achieved similar enantioselectivity to four-membered ring example **270**; however, it was surprising that *tert*-butyl ester **392**, analogous to the best performing four-membered ring product **335**, was isolated in a low 38% ee. The enantioselectivities of bulky alkyl isopropyl (**393**) and cyclohexyl (**394**) ketones were found to be consistent to those achieved with the thietane-1,1-dioxide substrates (88% and 89% ee, respectively), whereas phenyl ketone **395** was formed in a slightly lower ee of 72%. On the other hand, thiane-1,1-dioxide substrates appeared to have lower reactivity and resulted in poorer enantioselectivities compared to the thietane-1,1-dioxide analogues. For example, the Pd-DAAA reaction to access *tert*-butyl ester **397** and ketone **398** was unsuccessful, likely due to the steric size of the substituent, and resulted in the recovery

of starting material. While cyclohexyl ketone **399** achieved high ee (89%), phenyl ester **396** and *p*-bromo ketone **400** were furnished in a lower 64% and 76% ee, respectively. An extension of this substrate scope is required to fully investigate the successes and limitations of the larger cyclic sulfones.

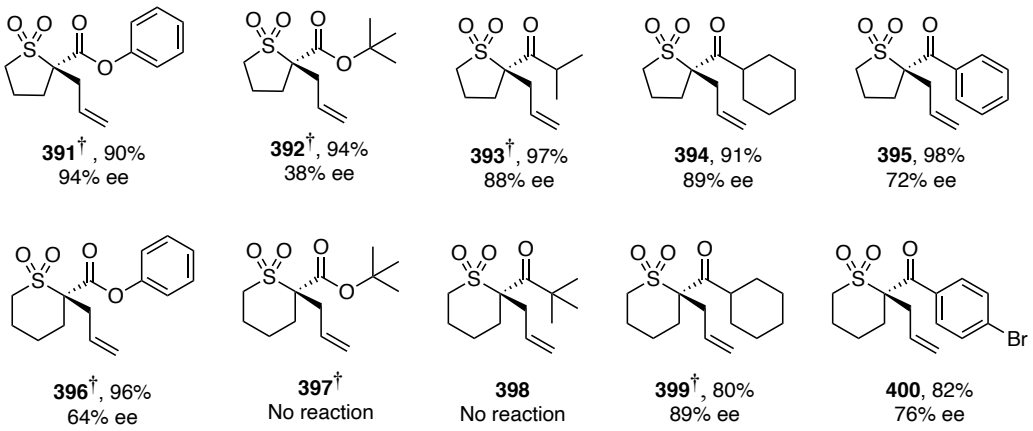
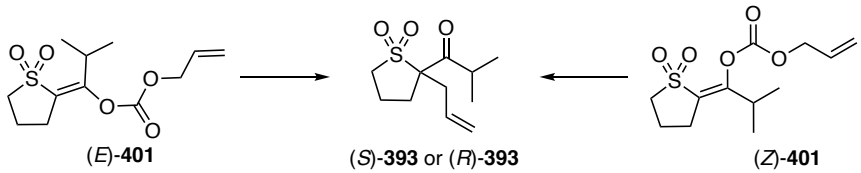


Table 21: Initial substrate scope of sulfolane and thiane substrates. † reaction carried out by a colleague.

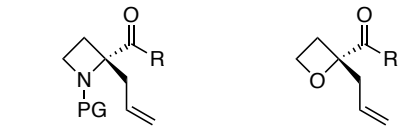
In addition to the extension of the substrate scope for the allylic alkylation of larger-ring sulfones, an enolate geometry study will also be required to assess the importance of the alkene geometry in this system (Scheme 90). Specifically, the synthesis of (*E*)-**401** and (*Z*)-**401** will enable us to ascertain whether enolate isomerisation occurs in the formation of **393** in an analogous manner to the Pd-DAAA of thietane-1,1-dioxides.



Scheme 90: Enolate geometry study on sulfolane substrate **393**.

Our research group are also interested in extending the Pd-DAAA methodology of thietane-1,1-dioxides to azetidine and oxetane systems (**402** and **403**, respectively, Figure 25). As previously discussed, these strained rings are particularly useful in biological and pharmaceutical applications. Current syntheses of enantioenriched azetidine- and oxetane-containing spirocycles are sparse and present many problems in relation to industrial scale synthesis. We envision expanding upon the methodology we

have developed by utilising the ketone and ester carbonyl group strategy to enable a stereoablative enantioconvergent process. Specifically, for the azetidine system, the choice of *N*-protecting group may significantly impact the enantioselectivity of the reaction and, therefore, permit the exploration of this variable. In both cases the challenges associated with the linear nature of the enolate intermediate will need to be overcome.



PG = Ts, Ns, Boc, PMB

402 **403**

Figure 25: Alternative strained ring systems for Pd-DAAA.

4. Conclusions

The aims of this project were to develop the palladium-catalysed decarboxylative asymmetric allylic alkylation of thietane-1,1-dioxides for the synthesis of novel, enantioenriched spirocycles.

The palladium-catalysed DAAA of thietane-1,1-dioxides bearing a carbonyl side-chain was successfully developed despite the challenges associated with stereoselective alkylation of acyclic enolates. The substrate scope investigation demonstrated the successes and limitations of ketone and ester substrates to suitably facilitate a stereoablative enantioconvergent process, generating products with up to 96% ee. It revealed that aryl and large alkyl ketone substituents were successful in achieving high enantioselectivity in the reaction. In contrast, smaller ketone substituents, as well as substitution on the allyl ester resulted in substantially lower enantioselectivity of products. Pleasingly, the ester substrates furnished superior enantioenrichment compared to the ketones counterparts. The importance of the enolate geometry in this acyclic system was probed, suggesting that a palladium-mediated interconversion of *E/Z* enolates takes place in a process that is analogous to a dynamic kinetic resolution, avoiding the need for pre-formed geometrically pure allyl enol carbonate substrates.

Several studies were performed to gain more insight into the mechanism of the reaction. Deuterium-labelled allylic esters were used in enolate crossover studies in which we observed crossover, potentially indicating an outer-sphere alkylation mechanism. This result, alongside a water tolerance study, revealed that the ion-pair formed after oxidative addition to palladium could readily dissociate, and that a free enolate was not a long-lived intermediate in this reaction. Unfortunately, while the stereochemical allylic probe was successfully synthesised, the exact nature of the alkylation pathway could not be determined due to the low reactivity of substituted allyl substrates.

Finally, these enantioenriched thietane-1,1-dioxide building blocks were derivatised and transformed into a novel [3.5] spirocycle in 96% ee. The utility of this spirocycle in compound library generation was also demonstrated by its compatibility with commonly used reactions for further functionalisation.

5. Experimental Section

5.1 General Information

5.1.1 Solvents, Reagents and Starting Materials

Oven-dried glassware and an argon atmosphere was used for all reactions. Dry solvents were obtained from commercial sources or obtained from an Innovative Technologies PureSolv solvent drying system. All reagents and solvents were used as supplied. All reactions conducted above room temperature were heated using a heating block on a stirrer hotplate. Petrol refers to the fraction of petroleum that boils between 40 ºC and 60 ºC. Aqueous solutions were saturated unless otherwise stated. Removal of solvents under vacuum refers to the use of a rotary evaporator at 40 °C, with further drying on a high vacuum line. VWR Chemicals silica gel (40–63 μm particle size) was used for flash column chromatography. Thin layer chromatography (TLC) was carried out using Merck KgaA silica gel 60 F254 aluminium-backed plates. Ultraviolet irradiation (254 nm) and staining with potassium permanganate solution or acidic ammonium molybdate as appropriate were used to visualise TLC plates. Crystals **270** and **333** were obtained by vapor diffusion using hexane/EtOAc.

5.1.2 Instrumentation

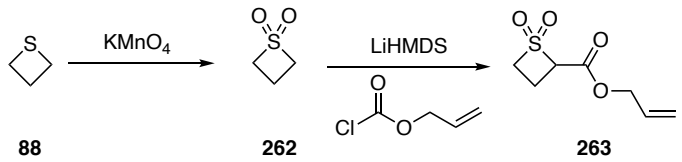
^{1}H NMR spectra were obtained using either a Bruker AVANCE III 400 spectrometer or a Bruker FOURIER 300 spectrometer. ^{13}C NMR spectra were recorded on the same spectrometers at 100 MHz or 75 MHz, respectively. For ^{1}H NMR spectra recorded in $CDCl_3$, the residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) was used as the internal reference. For ^{13}C NMR spectra, the central resonance of $CDCl_3$ (δ_C = 77.2 ppm) was used as the internal reference. For ^{1}H NMR spectra recorded in DMSO-d_6, the residual protic solvent (δ_H = 2.50 ppm) was used as the internal reference. For ^{13}C NMR spectra, the central resonance of DMSO-d_6 (δ_C = 39.5 ppm) was used as the internal reference. For ^{1}H NMR spectra recorded in benzene-d_6, the residual protic solvent (δ_H = 7.16 ppm) was used as the internal reference. For ^{13}C NMR spectra, the central resonance of benzene-d_6 (δ_C = 128.1 ppm) was used as the internal reference. NMR data are reported as follows: chemical shift, δ_H (in parts per million, ppm), (number of protons,

multiplicity, coupling constant, *J* in Hertz, assignment). Couplings are expressed as one, or a combination of: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sextet; septet and m, multiplet. NMR assignments were made using two-dimensional NMR spectroscopy (COSY, DEPT-135, HSQC and HMBC). When coincidental couplings constants were observed in the NMR spectra, the apparent multiplicity of the proton resonance in these cases was reported. The numbering of atoms in NMR assignments do not correspond to IUPAC nomenclature.

High resolution mass spectra (HRMS) were recorded using a Shimadzu LCMS-IT-TOF instrument using ESI or APCI conditions. Infra-red spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer. Melting points were measured on a Sanyo Gallenkamp capillary melting point apparatus. Enantiomeric excesses were determined by chiral HPLC on a Shimadzu NEXERA X2 UHPLC instrument equipped with a UV detector, using either a CHIRALCEL OD-H or CHIRALPAK AD-H column. Optical rotations were measured using an AA-65 Automatic Polarimeter. Where crystals were obtained, single crystals were selected and mounted, on a Mitegen loop using Paratone-N oil, on a SuperNova, Dual, Cu at zero, AtlasS2 diffractometer. The crystals were kept at 100 K during data collection, and data reduction was performed using CrysAlisPro1.171.38.44a (Rigaku Oxford Diffraction, 2015). Compound names are those generated by BIOVIA Draw software, following the IUPAC nomenclature.

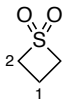
5.2. Experimental Procedures and Characterisation Data

5.2.1 Synthesis of Allyl Ester Starting Material 263



Trimethylene sulfide (thietane, **88**) was purchased from Sigma Aldrich or Alfa Aesar and used without further purification.

Thietane 1,1-dioxide (262)



Using a modified literature procedure,[132] thietane (**88**, 3.9 mL, 54 mmol) and potassium permanganate (17.0 g, 108 mmol) were added to a 1:1 mixture of CH_2Cl_2:H_2O (300 mL). The reaction mixture was stirred vigorously at room temperature overnight. The mixture was filtered and the aqueous layer was extracted with CH_2Cl_2 (200 mL). The organic phase was separated, and the aqueous phase was extracted further with CH_2Cl_2 (3 x 100 mL). The combined organic phases were washed with aq. $Na_2S_2O_3$ (10%, 100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford thietane-1,1-dioxide **262** (5.38 g, 94%) as a colourless solid.

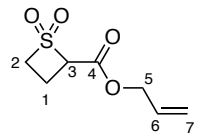
^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.16 – 4.12 (4H, m, **H2**), 2.21 – 2.12 (2H, m, **H1**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 65.7 (**C2**), 6.0 (**C1**).

IR: ν_{max} (neat/cm^{-1}): 2968 (C–H), 1302 (S=O), 1127 (S=O).

All characterisation data are consistent with those reported in the literature.[132]

Allyl 1,1-dioxothietane-2-carboxylate (263)



263

A solution of thietane-1,1-dioxide **262** (1.50 g, 14.1 mmol) in THF (15 mL) was added to a solution of LiHMDS (1 M in THF, 29.6 mL, 29.6 mmol) in THF (60 mL) at –78 °C. The reaction mixture was stirred at –78 ºC for 1 h. Allyl chloroformate (1.65 mL, 15.5 mmol) was added dropwise and the mixture was stirred at –78 ºC for 2 h. The reaction was quenched at –78 °C with aq. HCl (1 N, 10 mL), allowed to warm to room temperature and diluted with water (20 mL). The mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2 deactivated with 2% NEt_3; 12:1 hexane:EtOAc] afforded allylic ester **263** (1.81 g, 68%) as a colourless solid. $\boldsymbol{R_f}$ = 0.22 [3:1 petrol:EtOAc]. **mp**: 40 – 42 ºC.

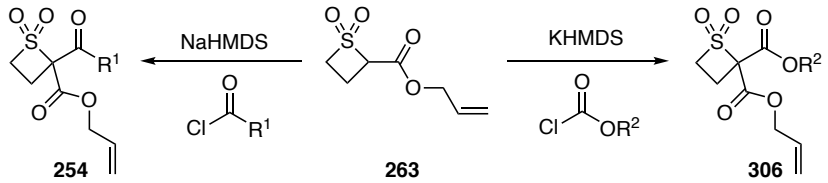
^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.98 – 5.87 (1H, m, **H6**), 5.39 (1H, dq, *J* = 17.2, 1.4 Hz, **H7a**), 5.29 (1H, dq, *J* = 10.4, 1.2 Hz, **H7b**), 5.11 – 5.06 (1H, m, **H3**), 4.76 – 4.71 (2H, m, **H5**), 4.25 – 4.14 (2H, m, **H2**), 2.65 – 2.53 (1H, m, **H1a**), 2.37 – 2.26 (1H, m, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 164.0 (**C4**), 131.1 (**C6**), 119.6 (**C7**), 79.8 (**C3**), 67.3 (**C5**), 65.8 (**C2**), 9.7 (**C1**).

HRMS: (ESI-TOF) *m/z*: $[M–H]^-$ calcd for $C_7H_9O_2S$ 189.0227; found 189.0232.

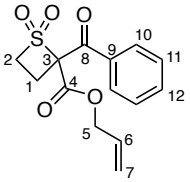
IR: ν_{max} (neat/cm^{-1}): 3035 (C–H), 2959 (C–H), 1742 (C=O), 1312 (S=O), 1125 (S=O).

5.2.2 Synthesis of β-Keto Ester and Malonate Precursors



Acid chlorides and chloroformates were purchased from Sigma Aldrich and used without further purification.

Allyl 2-benzoyl-1,1-dioxo-thietane-2-carboxylate (267)



267

A solution of NaHMDS (1 M in THF, 1.2 mL, 1.2 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (200 mg, 1.05 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. Benzoyl chloride (160 μL, 1.15 mmol) was added dropwise and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 10:1 hexane:EtOAc] afforded **267** (220 mg, 70%) as a colourless oil. $\boldsymbol{R_f}$ = 0.40 [3:1 petrol:EtOAc].

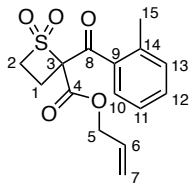
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.01 – 7.96 (2H, m, **H10**), 7.62 (1H, tt, *J* = 7.4, 1.2 Hz, **H12**), 7.53 – 7.47 (2H, m, **H11**), 5.77 (1H, ddt, *J* = 17.4, 10.2, 5.8 Hz, **H6**), 5.22 (1H, dq, *J* = 5.8, 1.2 Hz, **H7a**), 5.20 – 5.18 (1H, m, **H7b**), 4.73 (1H, ddt, *J* = 13.1, 5.8, 1.4 Hz, **H5a**), 4.67 (1H, ddt, *J* = 13.1, 5.8, 1.4 Hz, **H5b**), 4.47 (1H, dt, *J* = 12.4, 10.2 Hz, **H2a**), 4.08 (1H, ddd, *J* = 12.5, 10.2, 3.4 Hz, **H2b**), 2.95 (1H, dt, *J* = 12.4, 10.1 Hz, **H1a**), 2.77 (1H, ddd, *J* = 12.5, 10.4, 3.4 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 187.6 (**C8**), 164.5 (**C4**), 134.8 (**C9**), 134.5 (**C12**), 130.3 (**C6**), 129.7 (**C10**), 128.8 (**C11**), 120.0 (**C7**), 95.7 (**C3**), 67.9 (**C5**), 63.6 (**C2**), 17.5 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{15}O_5S$ 295.0635; found 295.0621.

IR: ν_{max} (neat/cm^{-1}): 3032 (C–H), 2970 (C–H), 1733 (C=O), 1682 (C=O), 1332 (S=O), 1138 (S=O).

Allyl 2-(2-methylbenzoyl)-1,1-dioxo-thietane-2-carboxylate (271)



271

A solution of NaHMDS (1 M in THF, 1.2 mL, 1.2 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (200 mg, 1.05 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. *o*-Toluoyl chloride (151 μL, 1.15 mmol) was added dropwise and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 12:1 hexane:EtOAc] afforded **271** (201 mg, 62%) as a colourless solid. $\boldsymbol{R_f}$ = 0.70 [3:2 petrol:EtOAc]. **mp**: 46 – 48 ºC.

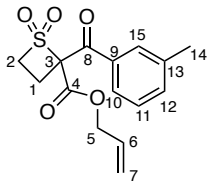
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.59 (1H, dd, *J* = 8.4, 1.4 Hz, **H10**), 7.43 (1H, td, *J* = 7.5, 1.2 Hz, **H12**), 7.32 – 7.27 (2H, m, **H11** and **H13**), 5.72 (1H, ddt, *J* = 17.2, 10.4, 5.8 Hz, **H6**), 5.27 – 5.18 (2H, m, **H7**), 4.70 (1H, ddt, *J* = 13.0, 5.8, 1.3 Hz, **H5a**), 4.62 (1H, ddt, *J* = 13.0, 5.8, 1.3 Hz, **H5b**), 4.36 (1H, ddd, *J* = 12.5, 10.2, 8.7 Hz, **H2a**), 4.12 (1H, ddd, *J* = 12.5, 9.9, 4.9 Hz, **H2b**), 2.87 – 2.72 (2H, m, **H1**), 2.51 (3H, s, **H15**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 189.9 (**C8**), 164.6 (**C4**), 140.2 (**C14**), 134.5 (**C9**), 132.7 (**C12**), 132.4 (**C11** or **C13**), 130.4 (**C6**), 129.0 (**C10**), 125.9 (**C11** or **C13**), 120.0 (**C7**), 97.5 (**C3**), 67.9 (**C5**), 63.6 (**C2**), 21.5 (**C15**), 18.1 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{17}O_5S$ 309.0791; found 309.0779.

IR: ν_{max} (neat/cm^{-1}): 3039 (C–H), 2970 (C–H), 1727 (C=O), 1679 (C=O), 1332 (S=O), 1136 (S=O).

Allyl 2-(3-methylbenzoyl)-1,1-dioxo-thietane-2-carboxylate (272)



272

A solution of NaHMDS (1 M in THF, 1.2 mL, 1.2 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (200 mg, 1.05 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. *m*-Toluoyl chloride (151 μL, 1.15 mmol) was added dropwise and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 12:1 hexane:EtOAc] afforded **272** (168 mg, 52%) as a colourless oil. $\boldsymbol{R_f}$ = 0.45 [2:1 petrol:EtOAc].

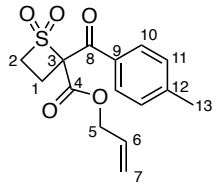
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.83 – 7.76 (2H, m, **H10** and **H15**), 7.47 – 7.38 (2H, m, **H11** and **H12**), 5.80 (1H, ddt, *J* = 17.2, 10.5, 5.8 Hz, **H6**), 5.26 (1H, dq, *J* = 9.0, 1.2 Hz, **H7a**), 5.23 – 5.22 (1H, m, **H7b**), 4.77 (1H, ddt, *J* = 13.0, 5.7, 1.4 Hz, **H5a**), 4.69 (1H, ddt, *J* = 13.0, 5.7, 1.4 Hz, **H5b**), 4.49 (1H, dt, *J* = 12.2, 10.3 Hz, **H2a**), 4.10 (1H, ddd, *J* = 12.6, 10.2, 3.5 Hz, **H2b**), 2.97 (1H, dt, *J* = 12.4, 10.1 Hz, **H1a**), 2.79 (1H, ddd, *J* = 12.5, 10.4, 3.4 Hz, **H1b**), 2.44 (3H, s, **H14**).

^{13}C NMR: (100 MHz, $CDCl_3$) 187.6 (**C8**), 164.5 (**C4**), 138.6 (**C9**), 135.3 (**C11** or **C12**), 134.7 (**C13**), 130.2 (**C6**), 129.9 (**C10** or **C15**), 128.6 (**C11** or **C12**), 126.8 (**C10** or **C15**), 119.9 (**C7**), 95.7 (**C3**), 67.8 (**C5**), 63.5 (**C2**), 21.4 (**C14**), 17.6 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{17}O_5S$ 309.0791, found 309.0794.

IR: ν_{max} (neat/cm^{-1}): 3030 (C–H), 2967 (C–H), 1735 (C=O), 1675 (C=O), 1333 (S=O), 1128 (S=O).

Allyl 2-(4-methylbenzoyl)-1,1-dioxo-thietane-2-carboxylate (273)



273

A solution of NaHMDS (1 M in THF, 1.2 mL, 1.2 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (200 mg, 1.05 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. *p*-Toluoyl chloride (151 μL, 1.15 mmol) was added dropwise and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 12:1 hexane:EtOAc] afforded **273** (214 mg, 66%) as a colourless solid. $\boldsymbol{R_f}$ = 0.70 [3:2 petrol:EtOAc]. **mp**: 59 – 61 ºC.

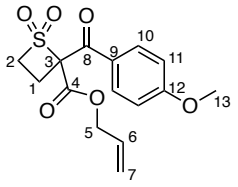
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* = 8.3 Hz, **H10**), 7.30 (2H, d, *J* = 8.6 Hz, **H11**), 5.79 (1H, ddt, *J* = 17.1, 10.4, 5.8 Hz, **H6**), 5.23 (1H, dq, *J* = 8.8, 1.3 Hz, **H7a**), 5.21 – 5.19 (1H, m, **H7b**), 4.74 (1H, ddt, *J* = 13.0, 5.7, 1.4 Hz, **H5a**), 4.68 (1H, ddt, *J* = 13.0, 5.7, 1.4 Hz, **H5b**), 4.45 (1H, dt, *J* = 12.4, 10.2 Hz, **H2a**), 4.07 (1H, ddd, *J* = 13.6, 10.2, 3.4 Hz, **H2b**), 2.95 (1H, dt, *J* = 12.5, 10.1 Hz, **H1a**), 2.77 (1H, ddd, *J* = 13.8, 10.4, 3.4 Hz, **H1b**), 2.42 (3H, s, **H13**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 187.1 (**C8**), 164.6 (**C4**), 145.8 (**C12**), 132.3 (**C9**), 130.4 (**C6**), 129.9 (**C10**), 129.6 (**C11**), 120.0 (**C7**), 95.8 (**C3**), 67.9 (**C5**), 63.5 (**C2**), 22.0 (**C13**), 17.6 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{17}O_5S$ 309.0791; found 309.0780.

IR: ν_{max} (neat/cm^{-1}): 3035 (C–H), 2980 (C–H), 1735 (C=O), 1685 (C=O), 1336 (S=O), 1138 (S=O).

Allyl 2-(4-methoxybenzoyl)-1,1-dioxo-thietane-2-carboxylate (274)



274

A solution of NaHMDS (1 M in THF, 1.2 mL, 1.2 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (200 mg, 1.05 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. *p*-Anisoyl chloride (156 μL, 1.15 mmol) was added dropwise and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 16:1 hexane:EtOAc] afforded **274** (140 mg, 41%) as a colourless oil. $\boldsymbol{R_f}$ = 0.18 [3:1 petrol:EtOAc].

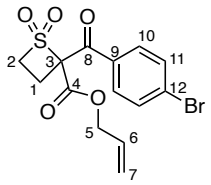
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.02 (2H, d, *J* = 9.0 Hz, **H10**), 6.99 (2H, d, *J* = 9.1 Hz, **H11**), 5.82 (1H, ddt, *J* = 17.2, 10.5, 5.8 Hz, **H6**), 5.27 (1H, dq, *J* = 9.4, 1.2 Hz, **H7a**), 5.24 – 5.22 (1H, m, **H7b**), 4.79 – 4.67 (2H, m, **H5**), 4.46 (1H, dt, *J* = 12.4, 10.1 Hz, **H2a**), 4.08 (1H, ddd, *J* = 12.5, 10.2, 3.4 Hz, **H2b**), 3.90 (3H, s, **H13**), 2.98 (1H, dt, *J* = 12.4, 10.1 Hz, **H1a**), 2.79 (1H, ddd, *J* = 12.5, 10.4, 3.4 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 185.7 (**C8**), 164.6 (**C4**), 164.5 (**C12**), 132.2 (**C10**), 130.3 (**C6**), 127.7 (**C9**), 119.8 (**C7**), 114.0 (**C11**), 95.7 (**C3**), 67.8 (**C5**), 63.3 (**C2**), 55.6 (**C13**), 17.4 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{17}O_6S$ 325.0740; found 325.0725.

IR: ν_{max} (neat/cm^{-1}): 3035 (C–H), 2950 (C–H), 1736 (C=O), 1662 (C=O), 1319 (S=O), 1138 (S=O).

Allyl 2-(4-bromobenzoyl)-1,1-dioxo-thietane-2-carboxylate (275)



275

A solution of NaHMDS (1 M in THF, 1.2 mL, 1.2 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (200 mg, 1.05 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. 4-Bromobenzoyl chloride (250 mg, 1.15 mmol) in THF (5 mL) was added dropwise and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 7:1 hexane:EtOAc] afforded **275** (291 mg, 75%) as a colourless oil. $\boldsymbol{R_f}$ = 0.55 [2:1 petrol:EtOAc].

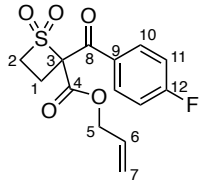
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.87 (2H, d, *J* = 8.8 Hz, **H10**), 7.65 (2H, d, *J* = 8.8 Hz, **H11**), 5.79 (1H, ddt, *J* = 17.4, 10.2, 5.9 Hz, **H6**), 5.27 – 5.21 (2H, m, **H7**), 4.74 (1H, ddt, *J* = 13.0, 5.8, 1.3 Hz, **H5a**), 4.68 (1H, ddt, *J* = 12.9, 6.0, 1.3 Hz, **H5b**), 4.48 (1H, dt, *J* = 12.5, 10.2 Hz, **H2a**), 4.09 (1H, ddd, *J* = 13.6, 10.3, 3.4 Hz, **H2b**), 2.94 (1H, dt, *J* = 12.5, 10.1 Hz, **H1a**), 2.77 (1H, ddd, *J* = 13.8, 10.4, 3.4 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 186.9 (**C8**), 164.3 (**C4**), 133.6 (**C9**), 132.2 (**C11**), 131.2 (**C10**), 130.2 (**C6**), 130.1 (**C12**), 120.4 (**C7**), 95.6 (**C3**), 68.1 (**C5**), 63.7 (**C2**), 17.3 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{14}O_5S^{79}Br$ 372.9731; found 372.9740.

IR: ν_{max} (neat/cm^{-1}): 3084 (C–H), 2963 (C–H), 1735 (C=O), 1681 (C=O), 1323 (S=O), 1138 (S=O).

Allyl 2-(4-fluorobenzoyl)-1,1-dioxo-thietane-2-carboxylate (276)



276

A solution of NaHMDS (1 M in THF, 0.6 mL, 0.6 mmol) in THF (5 mL) was cooled to 0 ºC. A solution of allyl ester **263** (100 mg, 0.53 mmol) in THF (10 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. 4-Fluorobenzoyl chloride (71 μL, 0.6 mmol) was added dropwise and the mixture stirred at 0 ºC for 3 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 10:1 hexane:EtOAc] afforded **276** (41 mg, 25%) as a colourless oil. $\boldsymbol{R_f}$ = 0.31 [2:1 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.07 – 8.02 (2H, m, **H10**), 7.21 – 7.15 (2H, m, **H11**), 5.79 (1H, ddt, *J* = 17.6, 10.0, 5.6 Hz, **H6**), 5.27 – 5.21 (2H, m, **H7**), 4.75 (1H, ddt, *J* = 12.8, 6.0, 1.2 Hz, **H5a**), 4.68 (1H, ddt, *J* = 12.8, 6.0, 1.2 Hz, **H5b**), 4.48 (1H, dt, *J* = 12.8, 10.0 Hz, **H2a**), 4.10 (1H, ddd, *J* = 12.4, 10.0, 3.2 Hz, **H2b**), 2.96 (1H, dt, *J* = 12.8, 10.0 Hz, **H1a**), 2.78 (1H, ddd, *J* = 12.4, 10.4, 3.6 Hz, **H1b**).

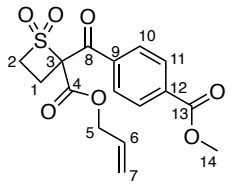
^{13}C NMR: (100 MHz, $CDCl_3$) δ 186.2 (**C8**), 166.6 (d, *J* = 255.2 Hz, **C12**), 164.4 (**C4**), 132.7 (d, *J* = 9.5 Hz, **C10**), 131.3 (d, *J* = 4.0 Hz, **C9**), 130.2 (**C6**), 120.3 (**C7**), 116.1 (d, *J* = 22.0 Hz, **C11**), 95.6 (**C3**), 68.1 (**C5**), 63.6 (**C2**), 17.4 (**C1**).

^{19}F{^{1}H} NMR: (376 MHz, $CDCl_3$) δ –102.3.

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{14}O_5FS$ 313.0540; found 313.0531.

IR: ν_{max} (neat/cm^{-1}): 3035 (C–H), 1733 (C=O), 1697 (C=O), 1334 (S=O), 1138 (S=O).

Allyl 2-(4-(methoxycarbonyl)benzoyl)-1,1-dioxo-thietane-2-carboxylate (277)



277

A solution of NaHMDS (1 M in THF, 0.6 mL, 0.6 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (100 mg, 0.53 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. A solution of methyl 4-(chlorocarbonyl)benzoate (120 mg, 0.6 mmol) in THF (5 mL) was added dropwise and the mixture stirred at 0 ºC for 3 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 10:1 hexane:EtOAc] afforded **277** (46 mg, 25%) as a colourless solid. $\boldsymbol{R}_\mathbf{f}$ = 0.41 [2:1 petrol:EtOAc]. **mp**: 120 – 122 ºC.

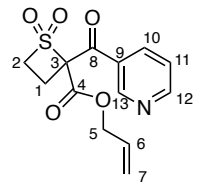
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.19 – 8.16 (2H, m, **H11**), 8.07 – 8.04 (2H, m, **H10**), 5.77 (1H, ddt, *J* = 17.4, 10.3, 5.9 Hz, **H6**), 5.26 – 5.23 (1H, m, **H7a**), 5.22 – 5.19 (1H, m, **H7b**), 4.74 (1H, ddt, *J* = 12.8, 5.9, 1.2 Hz, **H5a**), 4.67 (1H, ddt, *J* = 12.9, 6.0, 1.3 Hz, **H5b**), 4.50 (1H, dt, *J* = 12.4, 10.3 Hz, **H2a**), 4.12 (1H, ddd, *J* = 13.7, 10.2, 3.4 Hz, **H2b**), 3.95 (3H, s, **H14**), 2.96 (1H, dt, *J* = 12.5, 10.1 Hz, **H1a**), 2.78 (1H, ddd, *J* = 12.5, 10.4, 3.4 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 187.5 (**C8**), 166.1 (**C13**), 164.3 (**C4**), 138.0 (**C9**), 135.0 (**C12**), 131.1 (**C6**), 129.9 (**C11**), 129.6 (**C10**), 120.4 (**C7**), 95.7 (**C3**), 68.1 (**C5**), 63.9 (**C2**), 52.7 (**C14**), 17.4 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{17}O_7S$ 353.0690; found 353.0677.

IR: ν_{max} (neat/cm^{-1}): 2978 (C–H), 1731 (C=O), 1686 (C=O), 1334 (S=O), 1138 (S=O).

Allyl 1,1-dioxo-2-(pyridine-3-carbonyl)thietane-2-carboxylate (278)



278

According to a literature procedure,[137] to a suspension of nicotinic acid (175 mg, 1.42 mmol) in oxalyl chloride (1.75 mL, 20.6 mmol) was added DMF (1 drop), and the mixture was stirred at room temperature for 30 minutes. Oxalyl chloride was removed under reduced pressure and an aliquot of product was quenched with MeOH. TLC analysis confirmed methyl ester formation. Crude acid chloride was used in the next step without further analysis or purification.

A solution of NaHMDS (1 M in THF, 1.2 mL, 1.2 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (200 mg, 1.05 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 45 minutes. A solution of freshly prepared nicotinoyl chloride (1.42 mmol) in THF (10 mL) was added dropwise and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 9:1 hexane:EtOAc] afforded **278** (55 mg, 17%) as a sticky colourless oil. $\boldsymbol{R_f}$ = 0.41 [3:2 petrol:EtOAc].

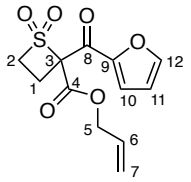
^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.19 (1H, s, **H13**), 8.80 (1H, d, *J* = 3.8 Hz, **H12**), 8.29 – 8.25 (1H, m, **H10**), 7.45 (1H, dd, *J* = 7.8, 4.7 Hz, **H11**), 5.77 (1H, ddt, *J* = 16.4, 9.8, 6.4 Hz, **H6**), 5.27 – 5.23 (1H, m, **H7a**), 5.22 – 5.20 (1H, m, **H7b**), 4.76 – 4.65 (2H, m, **H5**), 4.48 (1H, dt, *J* = 12.4, 10.2 Hz, **H2a**), 4.12 (1H, ddd, *J* = 13.8, 10.3, 3.5 Hz, **H2b**), 2.96 (1H, dt, *J* = 12.5, 9.9 Hz, **H1a**), 2.79 (1H, ddd, *J* = 14.0, 10.5, 3.6 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 187.1 (**C8**), 163.8 (**C4**), 154.2 (**C12**), 150.8 (**C13**), 150.1 (**C9**), 137.2 (**C10**), 130.1 (**C6**), 123.5 (**C11**), 120.5 (**C7**), 95.6 (**C3**), 68.2 (**C5**), 64.0 (**C2**), 16.7 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{14}NO_5S$ 296.0587; found 296.0575.

IR: ν_{max} (neat/cm^{-1}): 3039 (C–H), 2976 (C–H), 1735 (C=O), 1321 (S=O), 1183 (S=O).

Allyl 2-(furan-2-carbonyl)-1,1-dioxo-thietane-2-carboxylate (279)



279

A solution of NaHMDS (1 M in THF, 1.2 mL, 1.2 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (200 mg, 1.05 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. 2-Furoyl chloride (115 μL, 1.15 mmol) was added dropwise and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 9:1 – 5:1 hexane:EtOAc] afforded **279** (155 mg, 52%) as a colourless oil. $\boldsymbol{R_f}$ = 0.23 [3:1 petrol:EtOAc].

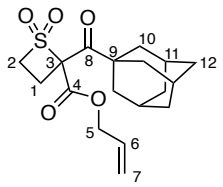
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.68 (1H, dd, *J* = 1.7, 0.8 Hz, **H12**), 7.44 (1H, dd, *J* = 3.7, 0.8 Hz, **H10**), 6.62 (1H, dd, *J* = 3.7, 1.7 Hz, **H11**), 5.85 – 5.75 (1H, m, **H6**), 5.25 (1H, dq, *J* = 6.6, 1.2 Hz, **H7a**), 5.21 (1H, t, *J* = 1.3 Hz, **H7b**), 4.76 (1H, ddt, *J* = 13.2, 5.6, 1.4 Hz, **H5a**), 4.67 (1H, ddt, *J* = 13.2, 5.8, 1.4 Hz, **H5b**), 4.52 – 4.43 (1H, m, **H2a**), 4.10 (1H, ddd, *J* = 12.6, 10.3, 3.4 Hz, **H2b**), 2.93 (1H, dt, *J* = 12.4, 10.0 Hz, **H1a**), 2.68 (1H, ddd, *J* = 12.6, 10.4, 3.4 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 175.8 (**C8**), 164.1 (**C4**), 151.1 (**C9**), 148.0 (**C12**), 130.4 (**C6**), 120.5 (**C10**), 119.7 (**C7**), 113.2 (**C11**), 95.4 (**C3**), 67.8 (**C5**), 64.4 (**C2**), 16.2 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{13}O_6S$ 285.0427; found 285.0436.

IR: ν_{max} (neat/cm^{-1}): 3035 (C–H), 2953 (C–H), 1740 (C=O), 1668 (C=O), 1330 (S=O), 1138 (S=O).

Allyl 2-(adamantane-1-carbonyl)-1,1-dioxo-thietane-2-carboxylate (280)



280

A solution of NaHMDS (1 M in THF, 1.2 mL, 1.2 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (200 mg, 1.05 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. 1-Adamantanecarbonyl chloride (230 mg, 1.15 mmol) in THF (5 mL) was added dropwise and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 10:1 hexane:EtOAc] afforded **280** (145 mg, 40%) as a colourless oil. $\boldsymbol{R_f}$ = 0.53 [2:1 petrol:EtOAc].

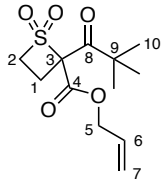
^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.00 – 5.89 (1H, m, **H6**), 5.42 (1H, dq, *J* = 17.2, 1.3 Hz, **H7a**), 5.34 (1H, dq, *J* = 10.4, 1.0 Hz, **H7b**), 4.77 (2H, dq, *J* = 6.2, 1.1 Hz, **H5**), 4.32 (1H, dt, *J* = 12.4, 10.0 Hz, **H2a**), 3.95 (1H, ddd, *J* = 13.2, 10.1, 3.1 Hz, **H2b**), 2.85 (1H, dt, *J* = 12.4, 10.0 Hz, **H1a**), 2.47 (1H, ddd, *J* = 12.4, 10.2, 3.1 Hz, **H1b**), 2.06 – 2.00 (3H, m, **H11**), 1.99 – 1.96 (6H, m, **H10**), 1.73 – 1.68 (6H, m, **H12**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 203.1 (**C8**), 165.0 (**C4**), 130.4 (**C6**), 121.1 (**C7**), 97.0 (**C3**), 67.9 (**C5**), 62.8 (**C2**), 47.4 (**C9**), 38.3 (**C10**), 36.5 (**C12**), 28.1 (**C11**), 18.3 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{25}O_5S$ 353.1417; found 353.1403.

IR: ν_{max} (neat/cm^{-1}): 2905 (C–H), 2851 (C–H), 1733 (C=O), 1697 (C=O), 1332 (S=O), 1136 (S=O).

Allyl 2-(2,2-dimethylpropanoyl)-1,1-dioxo-thietane-2-carboxylate (281)



281

A solution of NaHMDS (1 M in THF, 1.2 mL, 1.2 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (200 mg, 1.05 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. Trimethylacetyl chloride (141 μL, 1.15 mmol) was added dropwise and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 10:1 hexane:EtOAc] afforded **281** (179 mg, 62%) as a colourless solid. $\boldsymbol{R_f}$ = 0.39 [3:1 petrol:EtOAc]. **mp**: 74 – 76 ºC.

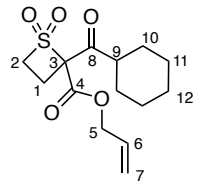
^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.99 – 5.88 (1H, m, **H6**), 5.42 (1H, dq, *J* = 17.2, 1.3 Hz, **H7a**), 5.34 (1H, dq, *J* = 10.4, 1.1 Hz, **H7b**), 4.76 (2H, dq, *J* = 6.1, 1.2 Hz, **H5**), 4.34 (1H, dt, *J* = 12.4, 10.0 Hz, **H2a**), 4.00 (1H, ddd, *J* = 13.3, 10.1, 3.2 Hz, **H2b**), 2.84 (1H, dt, *J* = 12.4, 10.0 Hz, **H1a**), 2.51 (1H, ddd, *J* = 13.5, 10.3, 3.2 Hz, **H1b**), 1.27 (9H, s, **H10**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 204.1 (**C8**), 164.9 (**C4**), 130.3 (**C6**), 121.0 (**C7**), 97.2 (**C3**), 67.9 (**C5**), 62.9 (**C2**), 44.9 (**C9**), 27.5 (**C10**), 18.4 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{19}O_5S$ 275.0948; found 275.0949.

IR: ν_{max} (neat/cm^{-1}): 3041 (C–H), 2976 (C–H), 2875 (C–H), 1733 (C=O), 1701 (C=O), 1332 (S=O), 1136 (S=O).

Allyl 2-(cyclohexanecarbonyl)-1,1-dioxo-thietane-2-carboxylate (282)



282

A solution of NaHMDS (1 M in THF, 1.2 mL, 1.2 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (200 mg, 1.05 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. Cyclohexane carbonyl chloride (154 μL, 1.15 mmol) was added dropwise and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 9:1 hexane:EtOAc] afforded **282** (227 mg, 72%) as a colourless oil. $\boldsymbol{R_f}$ = 0.39 [3:1 petrol:EtOAc].

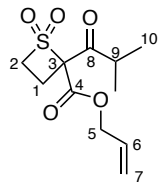
^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.01 – 5.91 (1H, m, **H6**), 5.44 (1H, dq, *J* = 17.2, 1.3 Hz, **H7a**), 5.36 (1H, dq, *J* = 10.4, 1.1 Hz, **H7b**), 4.79 (2H, dq, *J* = 6.2, 1.2 Hz, **H5**), 4.13 – 3.99 (2H, m, **H2**), 3.07 – 2.98 (1H, m, **H9**), 2.86 (1H, ddd, *J* = 16.2, 9.9, 6.2 Hz, **H1a**), 2.56 (1H, ddd, *J* = 18.1, 10.1, 7.8 Hz, **H1b**), 2.05 – 1.16 (10H, m, **H10**, **H11** and **H12**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 199.3 (**C8**), 162.9 (**C4**), 130.5 (**C6**), 120.8 (**C7**), 98.7 (**C3**), 68.1 (**C5**), 63.6 (**C2**), 49.7 (**C9**), 30.4 and 28.5 (**C10**), 25.7 (**C11a** and **C12**), 25.4 (**C11b**), 14.8 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{21}O_5S$ 301.1104; found 301.1101.

IR: ν_{max} (neat/cm^{-1}): 2929 (C–H), 2853 (C–H), 1735 (C=O), 1699 (C=O), 1328 (S=O), 1132 (S=O).

Allyl 2-(2-methylpropanoyl)-1,1-dioxo-thietane-2-carboxylate (283)



283

A solution of NaHMDS (1 M in THF, 1.2 mL, 1.2 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (200 mg, 1.05 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. Isobutyryl chloride (119 μL, 1.15 mmol) was added dropwise and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 9:1 hexane:EtOAc] afforded **283** (198 mg, 73%) as a colourless oil. $\boldsymbol{R_f}$ = 0.56 [3:1 petrol:EtOAc].

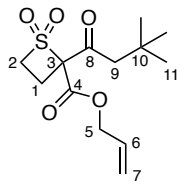
^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.99 – 5.88 (1H, m, **H6**), 5.41 (1H, dq, *J* = 17.2, 1.3 Hz, **H7a**), 5.32 (1H, dq, *J* = 10.4, 1.2 Hz, **H7b**), 4.83 – 4.71 (2H, m, **H5**), 4.14 – 3.99 (2H, m, **H2**), 3.26 (1H, sept, *J* = 6.7 Hz, **H9**), 2.83 (1H, ddd, *J* = 12.4, 10.1, 6.3 Hz, **H1a**), 2.56 (1H, ddd, *J* = 12.3, 10.3, 7.6 Hz, **H1b**), 1.18 (3H, d, *J* = 6.8 Hz, **H10a**), 1.07 (3H, d, *J* = 6.8 Hz, **H10b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 200.8 (**C8**), 162.9 (**C4**), 130.5 (**C6**), 120.6 (**C7**), 98.5 (**C3**), 68.0 (**C5**), 63.7 (**C2**), 39.6 (**C9**), 20.0 and 18.8 (**C10**), 15.0 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{17}O_5S$ 261.0791; found 261.0782.

IR: ν_{max} (neat/cm^{-1}): 3032 (C–H), 2980 (C–H), 1736 (C=O), 1710 (C=O), 1332 (S=O), 1138 (S=O).

Allyl 2-(3,3-dimethylbutanoyl)-1,1-dioxo-thietane-2-carboxylate (284)



284

A solution of NaHMDS (1 M in THF, 1.2 mL, 1.2 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (200 mg, 1.05 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. *tert*-Butyl acetyl chloride (154 μL, 1.15 mmol) was added dropwise and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 10:1 hexane:EtOAc] afforded **284** (184 mg, 57%) as a colourless oil. $\boldsymbol{R_f}$ = 0.55 [3:1 petrol:EtOAc].

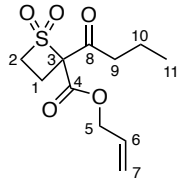
^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.95 (1H, ddt, *J* = 17.2, 10.4, 6.0 Hz, **H6**), 5.42 (1H, dq, *J* = 17.2, 1.3 Hz, **H7a**), 5.34 (1H, dq, *J* = 10.4, 1.1 Hz, **H7b**), 4.78 (2H, dt, *J* = 6.0, 1.2 Hz, **H5**), 4.12 (1H, ddd, *J* = 12.6, 10.4, 6.6 Hz, **H2a**), 4.02 (1H, ddd, *J* = 12.6, 10.4, 6.8 Hz, **H2b**), 2.92 – 2.77 (3H, m, **H1a** and **H9**), 2.57 (1H, ddd, *J* = 12.4, 10.4, 6.8 Hz, **H1b**), 1.04 (9H, s, **H11**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 194.8 (**C8**), 162.9 (**C4**), 130.6 (**C6**), 120.6 (**C7**), 99.0 (**C3**), 68.0 (**C5**), 63.5 (**C9**), 53.7 (**C2**), 31.1 (**C10**), 29.5 (**C11**), 14.9 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{21}O_5S$ 289.1104, found 289.1094.

IR: ν_{max} (neat/cm^{-1}): 2955 (C–H), 2871 (C–H), 1736 (C=O), 1718 (C=O), 1334 (S=O), 1135 (S=O).

Allyl 1,1-dioxo-2-butanoyl-thietane-2-carboxylate (285)



285

A solution of NaHMDS (1M in THF, 0.6 mL, 0.6 mmol) in THF (5 mL) was cooled to 0 °C. A solution of allyl ester **263** (100 mg, 0.53 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 °C for 30 minutes. Butyryl chloride (63 μL, 0.6 mmol) was added dropwise at 0 °C and the mixture stirred at 0 °C for 4 h. The reaction was quenched with aq. HCl (1 N, 0.5 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 10:1 hexane:EtOAc] afforded **285** (54 mg, 39%) as a colourless oil. $\boldsymbol{R_f}$ = 0.64 [2:1 petrol:EtOAc].

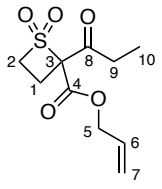
^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.02 – 5.91 (1H, m, **H6**), 5.44 (1H, dd, *J* = 17.2, 1.3 Hz, **H7a**), 5.37 (1H, dd, *J* = 10.4, 1.0 Hz, **H7b**), 4.81 (2H, dd, *J* = 6.0, 1.0 Hz, **H5**), 4.18 (1H, ddd, *J* = 12.7, 10.5, 6.6 Hz, **H2a**), 4.08 (1H, ddd, *J* = 12.7, 10.4, 6.8 Hz, **H2b**), 2.96 – 2.81 (3H, m, **H1a** and **H9**), 2.64 (1H, ddd, *J* = 12.4, 10.5, 6.8 Hz, **H1b**), 1.70 (2H, m, **H10**), 0.97 (3H, t, *J* = 7.4 Hz, **H11**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 196.2 (**C8**), 162.7 (**C4**), 130.4 (**C6**), 120.4 (**C7**), 98.3 (**C3**), 67.9 (**C5**), 63.7 (**C2**), 43.9 (**C9**), 17.1 (**C1**), 14.7 (**C10**), 13.4 (**C11**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{17}O_5S$ 261.0791, found 261.0789.

IR: ν_{max} (neat/cm^{-1}): 2967 (C–H), 2877 (C–H), 1735 (C=O), 1712 (C=O), 1332 (S=O), 1138 (S=O).

Allyl 1,1-dioxo-2-propanoyl-thietane-2-carboxylate (286)



286

A solution of NaHMDS (1 M in THF, 0.6 mL, 0.6 mmol) in THF was cooled to 0 °C. A solution of allyl ester **263** (100 mg, 0.53 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 °C for 30 minutes. Propionyl chloride (53 μL,

0.6 mmol) was added dropwise and the mixture stirred at 0 °C for 3 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 10:1 hexane:EtOAc] afforded **286** (64 mg, 50%) as a colourless oil. $\boldsymbol{R}_\mathbf{f}$ = 0.49 [2:1 petrol:EtOAc].

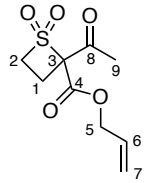
^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.95 (1H, ddt, *J* = 17.2, 10.4, 5.9 Hz, **H6**), 5.41 (1H, dq, *J* = 17.2, 10.3 Hz, **H7a**), 5.34 (1H, dq, *J* = 10.4, 1.1 Hz, **H7b**), 4.79 (2H, dq, *J* = 6.0, 1.6 Hz, **H5**), 4.16 (1H, ddd, *J* = 12.7, 10.4, 6.7 Hz, **H2a**), 4.06 (1H, ddd, *J* = 12.7, 10.3, 6.9 Hz, **H2b**), 3.03 – 2.79 (3H, m, **H1a** and **H9**), 2.62 (1H, ddd, *J* = 12.4, 10.4, 6.9 Hz, **H1b**), 1.15 (3H, t, *J* = 7.1 Hz, **H10**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 197.2 (**C8**), 162.9 (**C4**), 130.5 (**C6**), 120.5 (**C7**), 98.4 (**C3**), 68.1 (**C5**), 63.9 (**C2**), 35.8 (**C9**), 14.8 (**C1**), 8.0 (**C10**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{15}O_5S$ 247.0635; found 247.0638.

IR: ν_{max} (neat/cm^{-1}): 3030 (C–H), 2983 (C–H), 2944 (C–H), 1738 (C=O), 1712 (C=O), 1332 (S=O), 1138 (S=O).

Allyl 2-acetyl-1,1-dioxo-thietane-2-carboxylate (287)



287

A solution of NaHMDS (1 M in THF, 1.2 mL, 1.2 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (200 mg, 1.05 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. Acetyl chloride (82 μL, 1.15 mmol) was added dropwise and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 0.5 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3

x 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 10:1 hexane:EtOAc] afforded **287** (100 mg, 41%) as a colourless oil. $\boldsymbol{R_f}$ = 0.42 [3:1 petrol:EtOAc].

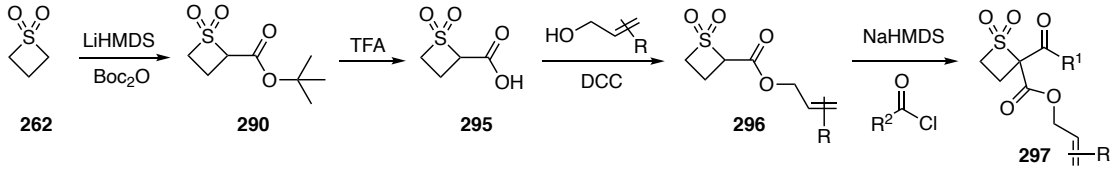
^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.00 – 5.89 (1H, m, **H6**), 5.41 (1H, dq, *J* = 17.2, 1.4 Hz, **H7a**), 5.34 (1H, dq, *J* = 10.4, 1.1 Hz, **H7b**), 4.81 – 4.78 (2H, m, **H5**), 4.17 (1H, ddd, *J* = 12.7, 10.5, 6.7 Hz, **H2a**), 4.06 (1H, ddd, *J* = 12.8, 10.5, 6.7 Hz, **H2b**), 2.83 (1H, ddd, *J* = 12.4, 10.5, 6.8 Hz, **H1a**), 2.63 (1H, ddd, *J* = 12.5, 10.6, 6.7 Hz, **H1b**), 2.56 (3H, s, **H9**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 194.0 (**C8**), 162.6 (**C4**), 130.5 (**C6**), 120.5 (**C7**), 98.6 (**C3**), 68.1 (**C5**), 64.0 (**C2**), 29.8 (**C9**), 14.5 (**C1**).

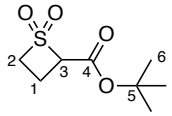
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_9H_{13}O_5S$ 233.0478; found 233.0473.

IR: ν_{max} (neat/cm^{-1}): 3030 (C–H), 2980 (C–H), 1736 (C=O), 1710 (C=O), 1332 (S=O), 1136 (S=O).

5.2.3 Synthesis of Substituted β-Keto Allyl Esters 297



***tert*-Butyl 1,1-dioxothietane-2-carboxylate (290)**



290

A solution of thietane-1,1-dioxide (**262**, 5.30 g, 50 mmol) in THF (100 mL) was added dropwise to a solution of LiHMDS (1 M in THF, 105 mL, 105 mmol) cooled to –78 ºC, and the reaction was stirred at –78 ºC for 1 h. Di-*tert*-butyl dicarbonate (12.6 mL, 55 mmol) was added dropwise and the mixture was stirred at –78 ºC for 3 h. The reaction was quenched at –78 ºC with aq. HCl (1 N, 50 mL) and was allowed to warm to room

temperature. The mixture was diluted with water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, 9:1 hexane:EtOAc] afforded **290** (8.62 g, 84%) as a colourless solid. $\boldsymbol{R}_\mathbf{f}$ = 0.41 [2:1 petrol:EtOAc]. **mp**: 56 – 57 ºC.

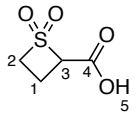
^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.00 – 4.95 (1H, m, **H3**), 4.20 – 4.11 (2H, m, **H2**), 2.59 – 2.49 (1H, m, **H1a**), 2.29 – 2.19 (1H, m, **H1b**), 1.52 (9H, s, **H6**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 163.2 (**C4**), 84.2 (**C5**), 80.8 (**C3**), 65.1 (**C2**), 28.1 (**C6**), 9.6 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M–H]^–$ calcd for $C_8H_{13}O_4S$ 205.0540; found 205.0546.

IR: ν_{max} (neat/cm^{-1}): 2987 (C–H), 2942 (C–H), 1725 (C=O), 1313 (S=O), 1129 (S=O).

1,1-Dioxothietane-2-carboxylic acid (295)



295

A solution of **290** (250 mg, 1.22 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 ºC. Trifluoroacetic acid (0.94 mL, 12.2 mmol) was added dropwise and the reaction was stirred at 0 ºC for 6 h. The mixture was allowed to warm to room temperature, then concentrated under reduced pressure to afford **295** (175 mg, 98%) as a brown solid, which was used in the next step without further purification. **mp**: 118 – 119 ºC.

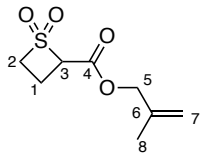
^{1}H NMR: (400 MHz, DMSO-d_6) δ 13.50 (1H, br s, **H5**), 5.40 – 5.33 (1H, m, **H3**), 4.27 – 4.18 (1H, m, **H2a**), 4.14 – 4.06 (1H, m, **H2b**), 2.27 – 2.18 (2H, m, **H1**).

^{13}C NMR: (100 MHz, DMSO-d_6) δ 165.2 (**C4**), 79.4 (**C3**), 64.9 (**C2**), 9.5 (**C1**).

HRMS: (ESI-TOF) *m/z*: $[M–H]^–$ calcd for $C_4H_5O_4S$ 148.9914; found 148.9921.

IR: ν_{max} (neat/cm^{-1}): 3239 (O–H), 2991 (C–H), 1710 (C=O), 1304 (S=O), 1172 (S=O).

2-Methylallyl 1,1-dioxothietane-2-carboxylate (298)



298

To a suspension of **295** (150 mg, 1.0 mmol) in CH_2Cl_2 (2 mL) was added a solution of 2-methyl-2-propen-1-ol (162 μL, 2.0 mmol) and a few crystals of 4-dimethylaminopyridine in CH_2Cl_2 (3 mL). The mixture was cooled to 0 ºC. A solution of *N*,*N*'-dicyclohexylcarbodiimide (227 mg, 1.1 mmol) in CH_2Cl_2 (2 mL) was added. The mixture was allowed to warm to room temperature and stirred at ambient temperature for 18 h. The reaction mixture was filtered through Celite twice, then concentrated under reduced pressure. Purification using flash column chromatography [SiO_2; 7:1 hexane:EtOAc] afforded **298** (88 mg, 43%) as a yellow oil. $\boldsymbol{R_f}$ = 0.26 [3:1 petrol:EtOAc].

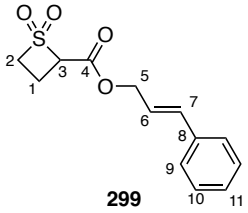
^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.13 – 5.07 (1H, m, **H3**), 5.06 – 5.04 (1H, m, **H7a**), 5.00 – 4.97 (1H, m, **H7b**), 4.71 (1H, d, *J* = 12.7 Hz, **H5a**), 4.62 (1H, d, *J* = 12.8 Hz, **H5b**), 4.23 – 4.15 (2H, m, **H2**), 2.65 – 2.55 (1H, m, **H1a**), 2.37 – 2.27 (1H, m, **H1b**), 1.79 (3H, d, *J* = 0.4 Hz, **H8**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 164.0 (**C4**), 139.0 (**C6**), 114.6 (**C7**), 79.8 (**C3**), 70.1 (**C5**), 65.3 (**C2**), 19.5 (**C8**), 9.7 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_8H_{12}O_4S$ 205.0529; found 205.0521.

IR: ν_{max} (neat/cm^{-1}): 2976 (C–H), 1735 (C=O), 1317 (S=O), 1131 (S=O).

(*E*)-Cinnamyl 1,1-dioxothietane-2-carboxylate (299)



299

To a suspension of **295** (150 mg, 1.0 mmol) in CH_2Cl_2 (2 mL) was added a solution of 3-phenyl-2-propen-1-ol (260 μL, 2.0 mmol) and a few crystals of 4-dimethylaminopyridine in CH_2Cl_2 (3 mL). The mixture was cooled to 0 ºC. A solution of *N*,*N*'-dicyclohexylcarbodiimide (227 mg, 1.1 mmol) in CH_2Cl_2 (2 mL) was added. The mixture was allowed to warm to room temperature and stirred at ambient temperature for 18 h. The reaction mixture was filtered through Celite twice, then concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 10:1 hexane:EtOAc] afforded **299** (89 mg, 34%) as a colourless solid. $\boldsymbol{R_f}$ = 0.29 [3:1 petrol:EtOAc]. **mp**: 128 – 130 ºC.

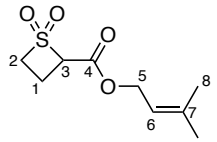
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.42 – 7.38 (2H, m, **H9**), 7.35 – 7.31 (2H, m, **H10**), 7.29 – 7.27 (1H, m, **H11**), 6.72 (1H, d, *J* = 15.9 Hz, **H7**), 6.29 (1H, dt, *J* = 15.9, 6.5 Hz, **H6**), 5.11 (1H, ddt, *J* = 9.9, 6.8, 0.9 Hz, **H3**), 4.91 (2H, dt, *J* = 6.6, 1.6 Hz, **H5**), 4.26 – 4.15 (2H, m, **H2**), 2.67 – 2.57 (1H, m, **H1a**), 2.38 – 2.29 (1H, m, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 164.1 (**C4**), 135.9 (**C8**), 135.5 (**C7**), 128.8 (**C9**), 128.5 (**C11**), 126.9 (**C10**), 122.0 (**C6**), 79.8 (**C3**), 67.4 (**C5**), 65.3 (**C2**), 9.8 (**C1**).

HRMS: molecular ion not detected for $C_{13}H_{14}O_4S$.

IR: ν_{max} (neat/cm^{-1}): 3049 (C–H), 2976 (C–H), 2929 (C–H), 1735 (C=O), 1312 (S=O), 1127 (S=O).

3-Methylbut-2-enyl 1,1-dioxothietane-2-carboxylate (300)



300

To a suspension of **295** (100 mg, 0.67 mmol) in CH_2Cl_2 (2 mL) was added a solution of 3-methyl-2-buten-1-ol (271 μL, 2.67 mmol) and a few crystals of 4-dimethylaminopyridine in CH_2Cl_2 (3 mL). The mixture was cooled to 0 ºC. A solution of *N*,*N*'-dicyclohexylcarbodiimide (153 mg, 0.74 mmol) in CH_2Cl_2 (2 mL) was added. The mixture was allowed to warm to room temperature and stirred at ambient temperature for 18 h. The reaction mixture was filtered through Celite twice, then

concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 9:1 hexane:EtOAc] afforded **300** (82 mg, 56%) as a colourless solid. $\boldsymbol{R_f}$ = 0.68 [3:2 petrol:EtOAc]. **mp**: 44 – 46 ºC.

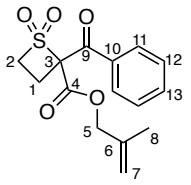
^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.40 – 5.34 (1H, m, **H6**), 5.04 (1H, ddt, *J* = 9.8, 6.8, 1.1 Hz, **H3**), 4.77 (1H, dd, *J* = 12.2, 7.4 Hz, **H5a**), 4.71 (1H, dd, *J* = 12.1, 7.4 Hz, **H5b**), 4.22 – 4.13 (2H, m, **H2**), 2.64 – 2.54 (1H, m, **H1a**), 2.29 (1H, ddd, *J* = 12.4, 9.8, 6.7 Hz, **H1b**), 1.77 (3H, s, **H8a**), 1.73 (3H, s, **H8b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 164.3 (**C4**), 140.8 (**C7**), 117.7 (**C6**), 79.9 (**C3**), 65.3 (**C5**), 63.7 (**C2**), 25.9 and 18.2 (**C8**), 9.8 (**C1**).

HRMS: molecular ion not detected for $C_9H_{14}O_4S$.

IR: ν_{max} (neat/cm^{-1}): 3043 (C–H), 2980 (C–H), 2929 (C–H), 1729 (C=O), 1315 (S=O), 1127 (S=O).

2-Methylallyl 2-benzoyl-1,1-dioxo-thietane-2-carboxylate (301)



301

A solution of NaHMDS (1 M in THF, 0.33 mL, 0.33 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **298** (50 mg, 0.25 mmol) in THF (5 mL) was added and the reaction mixture was stirred at 0 ºC for 15 minutes. Benzoyl chloride (40 μL, 0.33 mmol) was added dropwise and the mixture stirred at 0 ºC for 3 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 9:1 hexane:EtOAc] afforded **301** (43 mg, 56%) as a colourless oil. $\boldsymbol{R_f}$ = 0.48 [2:1 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.02 – 7.98 (2H, m, **H11**), 7.63 (1H, tt, *J* = 7.4, 1.2 Hz, **H13**), 7.53 – 7.48 (2H, m, **H12**), 4.89 – 4.84 (2H, m, **H7**), 4.65 (1H, d, *J* = 12.7 Hz,

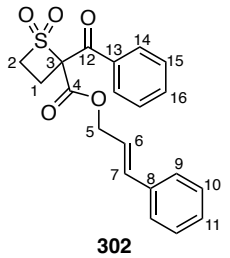
H5a), 4.59 (1H, d, *J* = 12.7 Hz, **H5b**), 4.48 (1H, dt, *J* = 12.4, 10.2 Hz, **H2a**), 4.10 (1H, ddd, *J* = 12.6, 10.2, 3.4 Hz, **H2b**), 2.97 (1H, dt, *J* = 12.5, 10.1 Hz, **H1a**), 2.78 (1H, ddd, *J* = 12.5, 10.4, 3.4 Hz, **H1b**), 1.56 (3H, s, **H8**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 187.6 (**C9**), 164.6 (**C4**), 138.3 (**C10**), 134.8 (**C6**), 134.5 (**C11**), 129.7 (**C13**), 128.9 (**C12**), 115.1 (**C7**), 95.8 (**C3**), 70.9 (**C5**), 63.6 (**C2**), 19.3 (**C8**), 17.6 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{17}O_5S$ 309.0791; found 309.0779.

IR: ν_{max} (neat/cm^{-1}): 3035 (C–H), 2976 (C–H), 1731 (C=O), 1682 (C=O), 1332 (S=O), 1138 (S=O).

(*E*)-Cinnamyl 2-benzoyl-1,1-dioxo-thietane-2-carboxylate (302)



302

A solution of NaHMDS (1 M in THF, 0.30 mL, 0.30 mmol) in THF (5 mL) was cooled to 0 ºC. A solution of allyl ester **299** (60 mg, 0.23 mmol) in THF (5 mL) was added and the reaction mixture was stirred at 0 ºC for 15 minutes. Benzoyl chloride (38 μL, 0.30 mmol) was added dropwise and the reaction mixture was stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 10:1 – 6:1 hexane:EtOAc] afforded **302** (51 mg, 60%) as a colourless oil. $\boldsymbol{R_f}$ = 0.37 [2:1 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.02 – 7.98 (2H, m, **H14**), 7.60 (1H, tt, *J* = 7.4, 1.2 Hz, **H16**), 7.51 – 7.45 (2H, m, **H15**), 7.34 – 7.26 (5H, m, **H9**, **H10** and **H11**), 6.53 (1H, d, *J* = 15.9 Hz, **H7**), 6.10 (1H, dt, *J* = 15.9, 6.5 Hz, **H6**), 4.90 (1H, ddd, *J* = 12.7, 6.4, 1.3

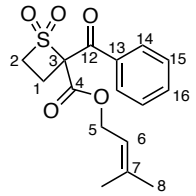
Hz, **H5a**), 4.83 (1H, ddd, *J* = 12.6, 6.5, 1.3 Hz, **H5b**), 4.48 (1H, dt, *J* = 12.2, 10.3 Hz, **H2a**), 4.10 (1H, ddd, *J* = 12.6, 10.2, 3.6 Hz, **H2b**), 2.99 (1H, dt, *J* = 12.4, 10.1 Hz, **H1a**), 2.78 (1H, ddd, *J* = 12.5, 10.4, 3.5 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 187.6 (**C12**), 164.7 (**C4**), 135.9 (**C7**), 135.8 (**C13**), 134.8 (**C8**), 134.5 (**C16**), 129.7 (**C14**), 128.9 (**C15**), 128.8 (**C10**), 128.6 (**C11**), 126.9 (**C9**), 121.0 (**C6**), 95.8 (**C3**), 67.9 (**C5**), 63.7 (**C2**), 17.5 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{18}O_5SNa$ 393.0767; found 393.0773.

IR: ν_{max} (neat/cm^{-1}): 3058 (C–H), 2965 (C–H), 1735 (C=O), 1675 (C=O), 1338 (S=O), 1138 (S=O).

3-Methylbut-2-enyl 2-benzoyl-1,1-dioxo-thietane-2-carboxylate (303)



303

A solution of NaHMDS (1 M in THF, 0.25 mL, 0.25 mmol) in THF (5 mL) was cooled to 0 ºC. A solution of allyl ester **300** (40 mg, 0.18 mmol) in THF (5 mL) was added and the reaction mixture was stirred at 0 ºC for 15 minutes. Benzoyl chloride (30 μL, 0.25 mmol) was added dropwise and the reaction mixture was stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 10:1 hexane:EtOAc] afforded **303** (37 mg, 64%) as a yellow oil. $\boldsymbol{R_f}$ = 0.69 [3:2 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.77 – 7.72 (2H, m, **H11**), 7.39 (1H, tt, *J* = 7.4, 1.2 Hz, **H13**), 7.29 – 7.24 (2H, m, **H12**), 4.99 – 4.93 (1H, m, **H6**), 4.50 (1H, dd, *J* = 12.0, 7.3 Hz, **H5a**), 4.42 (1H, dd, *J* = 12.0, 7.4 Hz, **H5b**), 4.27 – 4.18 (1H, m, **H2a**), 3.81 (1H,

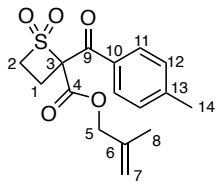
ddd, J = 12.5, 10.2, 3.5 Hz, **H2b**), 2.72 (1H, dt, J = 12.4, 10.1 Hz, **H1a**), 2.51 (1H, ddd, J = 12.4, 10.4, 3.5 Hz, **H1b**), 1.45 (3H, s, **H8a**), 1.35 (3H, s, **H8b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 187.7 (**C9**), 164.8 (**C4**), 141.7 (**C10**), 134.9 (**C7**), 134.4 (**C13**), 129.7 (**C11**), 128.7 (**C12**), 116.8 (**C6**), 95.8 (**C3**), 64.3 (**C5**), 63.6 (**C2**), 25.8 and 18.1 (**C8**), 17.5 (**C1**).

HRMS: (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{18}O_5SNa$ 345.0767; found 345.0758.

IR: ν_{max} (neat/cm^{-1}): 3032 (C–H), 2974 (C–H), 2935 (C–H), 1727 (C=O), 1684 (C=O), 1334 (S=O), 1138 (S=O).

2-Methylallyl 2-(4-methylbenzoyl)-1,1-dioxo-thietane-2-carboxylate (304)



304

A solution of NaHMDS (1 M in THF, 0.80 mL, 0.80 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **298** (125 mg, 0.60 mmol) in THF (5 mL) was added and the reaction mixture was stirred at 0 ºC for 30 minutes. *p*-Toluoyl chloride (105 μL, 0.80 mmol) was added dropwise and the mixture stirred at 0 ºC for 3 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 9:1 hexane:EtOAc] afforded **304** (114 mg, 59%) as a colourless oil. $\boldsymbol{R_f}$ = 0.66 [2:1 petrol:EtOAc].

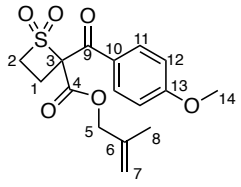
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.90 (2H, d, J = 8.4 Hz, **H11**), 7.29 (2H, d, J = 8.0 Hz, **H12**), 4.89 – 4.86 (2H, m, **H7**), 4.65 (1H, d, J = 12.8 Hz, **H5a**), 4.59 (1H, d, J = 12.8 Hz, **H5b**), 4.45 (1H, dt, J = 12.5, 10.2 Hz, **H2a**), 4.08 (1H, ddd, J = 12.5, 10.1, 3.4 Hz, **H2b**), 2.96 (1H, dt, J = 12.5, 10.1 Hz, **H1a**), 2.76 (1H, ddd, J = 12.5, 10.4, 3.4 Hz, **H1b**), 2.42 (3H, s, **H14**), 1.59 (3H, s, **H8**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 187.1 (**C9**), 164.7 (**C4**), 145.8 (**C13**), 138.3 (**C6**), 132.3 (**C10**), 129.9 (**C11**), 129.6 (**C12**), 114.9 (**C7**), 95.8 (**C3**), 70.8 (**C5**), 63.5 (**C2**), 22.0 (**C14**), 19.4 (**C8**), 17.7 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}O_5S$ 323.0948; found 323.0936.

IR: ν_{max} (neat/cm^{-1}): 3035 (C–H), 2974 (C–H), 1731 (C=O), 1677 (C=O), 1332 (S=O), 1138 (S=O).

2-Methylallyl 2-(4-methoxybenzoyl)-1,1-dioxo-thietane-2-carboxylate (305)



305

A solution of NaHMDS (1 M in THF, 0.40 mL, 0.40 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **298** (75 mg, 0.36 mmol) in THF (5 mL) was added and the reaction mixture was stirred at 0 ºC for 15 minutes. 4-Methoxybenzoyl chloride (60 μL, 0.40 mmol) was added dropwise and the mixture stirred at 0 ºC for 3 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 10:1 hexane:EtOAc] afforded **305** (66 mg, 55%) as a colourless oil. $\boldsymbol{R_f}$ = 0.43 [2:1 petrol:EtOAc].

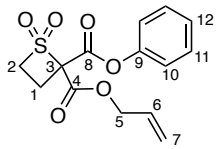
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.99 (2H, d, *J* = 9.1 Hz, **H11**), 6.97 (2H, d, *J* = 9.0 Hz, **H12**), 4.91 – 4.85 (2H, m, **H7**), 4.65 (1H, d, *J* = 17.0 Hz, **H5a**), 4.60 (1H, d, *J* = 17.0 Hz, **H5b**), 4.44 (1H, dt, *J* = 12.5, 10.3 Hz, **H2a**), 4.06 (1H, ddd, *J* = 12.6, 10.2, 3.4 Hz, **H2b**), 3.87 (3H, s, **H14**), 2.96 (1H, dt, *J* = 12.5, 10.1 Hz, **H1a**), 2.77 (1H, ddd, *J* = 12.5, 10.4, 3.4 Hz, **H1b**), 1.60 (3H, s, **H8**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 185.9 (**C9**), 164.7 (**C4**), 164.7 (**C13**), 138.3 (**C6**), 132.3 (**C11**), 127.8 (**C10**), 114.9 (**C7**), 114.4 (**C12**), 95.8 (**C3**), 70.8 (**C5**), 63.3 (**C2**), 55.7 (**C14**), 19.4 (**C8**), 17.6 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}O_6S$ 339.0897; found 339.0883.

IR: ν_{max} (neat/cm^{-1}): 2972 (C–H), 2939 (C–H), 1731 (C=O), 1683 (C=O), 1332 (S=O), 1136 (S=O).

2-Allyl 2'-phenyl 1,1-dioxothietane-2,2-dicarboxylate (268)



268

A solution of KHMDS (0.5 M in toluene, 2.4 mL, 1.2 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (200 mg, 1.05 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. Phenyl chloroformate (170 μL, 1.15 mmol) was added dropwise and the mixture was stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 6:1 hexane:EtOAc] afforded **268** (268 mg, 77%) as a colourless solid. $\boldsymbol{R_f}$ = 0.48 [2:1 petrol:EtOAc]. **mp**: 58 – 60 ºC.

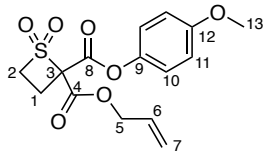
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (2H, m, **H11**), 7.29 (1H, tt, *J* = 7.6, 1.2 Hz, **H12**), 7.19 – 7.16 (2H, m, **H10**), 5.98 (1H, ddt, *J* = 17.2, 10.4, 5.6 Hz, **H6**), 5.46 (1H, dq, *J* = 17.2, 1.2 Hz, **H7a**), 5.34 (1H, dq, *J* = 10.4, 1.2 Hz, **H7b**), 4.87 (2H, dt, *J* = 5.6, 1.6 Hz, **H5**), 4.43 – 4.26 (2H, m, **H2**), 2.83 (2H, ddd, *J* = 13.6, 8.0, 6.8 Hz, **H1**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 162.8 (**C4**), 162.1 (**C8**), 150.4 (**C9**), 130.6 (**C6**), 129.8 (**C11**), 126.9 (**C12**), 121.3 (**C10**), 120.0 (**C7**), 92.6 (**C3**), 68.2 (**C5**), 65.2 (**C2**), 17.2 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{15}O_6S$ 311.0584; found 311.0588.

IR: ν_{max} (neat/cm^{-1}): 3030 (C–H), 2939 (C–H), 2972 (C–H), 1742 (C=O), 1332 (S=O), 1177 (S=O).

2-Allyl 2'-(4-methoxyphenyl) 1,1-dioxothietane-2,2-dicarboxylate (307)



307

A solution of KHMDS (0.5 M in toluene, 2.4 mL, 1.2 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (200 mg, 1.05 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. 4-Methoxyphenyl chloroformate (160 μL, 1.15 mmol) was added dropwise and the mixture was stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 20:1 – 10:1 hexane:EtOAc] afforded **307** (271 mg, 76%) as a colourless oil. $\boldsymbol{R_f}$ = 0.20 [3:2 petrol:EtOAc].

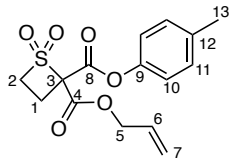
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.11 (2H, dt, *J* = 9.2, 3.0 Hz, **H10**), 6.92 (2H, dt, *J* = 9.2, 3.0 Hz, **H11**), 5.99 (1H, ddt, *J* = 17.2, 10.4, 5.8 Hz, **H6**), 5.47 (1H, dq, *J* = 17.2, 1.4 Hz, **H7a**), 5.35 (1H, dq, *J* = 10.5, 1.2 Hz, **H7b**), 4.87 (2H, dt, *J* = 5.7, 1.4 Hz, **H5**), 4.42 – 4.28 (2H, m, **H2**), 3.83 (3H, s, **H13**), 2.90 – 2.77 (2H, m, **H1**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 162.9 (**C4**), 162.4 (**C8**), 158.1 (**C12**), 143.9 (**C9**), 130.6 (**C6**), 122.1 (**C10**), 120.0 (**C7**), 114.7 (**C11**), 92.6 (**C3**), 68.1 (**C5**), 65.2 (**C2**), 55.8 (**C13**), 17.2 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{17}O_7S$ 341.0690; found 341.0687.

IR: ν_{max} (neat/cm^{-1}): 3002 (C–H), 2955 (C–H), 1736 (C=O), 1340 (S=O), 1176 (S=O).

2-Allyl 2'-(*p*-tolyl) 1,1-dioxothietane-2,2-dicarboxylate (308)



308

A solution of KHMDS (0.5 M in toluene, 2.4 mL, 1.2 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (200 mg, 1.05 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. *p*-Toluoyl chloroformate (165 μL, 1.15 mmol) was added dropwise and the mixture was stirred at 0 ºC for 4 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 10:1 hexane:EtOAc] afforded **308** (250 mg, 73%) as a colourless solid. $\boldsymbol{R_f}$ = 0.57 [2:1 petrol:EtOAc]. **mp**: 58 – 59 ºC.

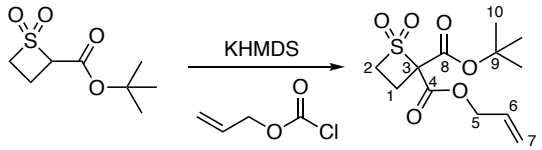
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.22 – 7.17 (2H, m, **H11**), 7.05 (2H, d, *J* = 8.4 Hz, **H10**), 5.96 (1H, ddt, *J* = 17.2, 10.5, 5.7 Hz, **H6**), 5.45 (1H, dq, *J* = 17.2, 1.5 Hz, **H7a**), 5.33 (1H, dq, *J* = 10.4, 1.2 Hz, **H7b**), 4.86 (2H, dt, *J* = 5.7, 1.3 Hz, **H5**), 4.40 – 4.26 (2H, m, **H2**), 2.88 – 2.76 (2H, m, **H1**), 2.34 (3H, s, **H13**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 162.9 (**C4**), 162.2 (**C8**), 148.2 (**C9**), 136.7 (**C12**), 130.6 (**C6**), 130.3 (**C11**), 120.9 (**C10**), 120.0 (**C7**), 92.6 (**C3**), 68.1 (**C5**), 65.2 (**C2**), 21.1 (**C13**), 17.2 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{17}O_6S$ 325.0740; found 325.0749.

IR: ν_{max} (neat/cm^{-1}): 3047 (C–H), 2994 (C–H), 2950 (C–H), 1735 (C=O), 1334 (S=O), 1190 (S=O).

2-Allyl 2'-*tert*-butyl 1,1-dioxothietane-2,2-dicarboxylate (309)



A solution of KHMDS (0.5 M in toluene, 64.1 mL, 32.0 mmol) in THF (180 mL) was cooled to 0 ºC. A solution of *tert*-butyl ester **290** (6.0 g, 29.1 mmol) in THF (20 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 15 minutes. Allyl chloroformate (3.41 mL, 32.0 mmol) was added dropwise and the reaction mixture was stirred at 0 ºC for 3 h. The reaction was quenched with aq. HCl (1 N, 30 mL), allowed to warm to room temperature and diluted with water (100 mL). The mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 19:1 – 9:1 hexane:EtOAc] afforded **309** (5.50 g, 60%) as a colourless oil. $\boldsymbol{R_f}$ = 0.70 [2:1 petrol:EtOAc].

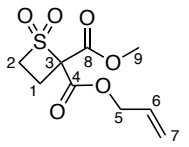
^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.98 – 5.88 (1H, m, **H6**), 5.41 (1H, dq, *J* = 17.2, 1.4 Hz, **H7a**), 5.30 (1H, dd, *J* = 10.4, 1.2 Hz, **H7b**), 4.77 (2H, dt, *J* = 5.8, 1.3 Hz, **H5**), 4.23 – 4.15 (2H, m, **H2**), 2.73 – 2.57 (2H, m, **H1**), 1.52 (9H, s, **H10**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 163.4 (**C4**), 161.8 (**C8**), 130.9 (**C6**), 119.6 (**C7**), 93.3 (**C3**), 85.5 (**C9**), 67.6 (**C5**), 64.5 (**C2**), 27.9 (**C10**), 17.2 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{18}O_6SNa$ 313.0716; found 313.0719.

IR: ν_{max} (neat/cm^{-1}): 2981 (C–H), 2937 (C–H), 1735 (C=O), 1340 (S=O), 1138 (S=O).

2'-Allyl 2-methyl 1,1-dioxothietane-2,2-dicarboxylate (310)



310

A solution of KHMDS (0.5 M in toluene, 1.2 mL, 0.60 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of allyl ester **263** (100 mg, 0.53 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 30 minutes. Methyl chloroformate (48 μL, 0.60 mmol) was added dropwise and the mixture was stirred at 0 ºC for 3 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 5:1 hexane:EtOAc] afforded **310** (90 mg, 69%) as a colourless oil. $\boldsymbol{R_f}$ = 0.31 [3:1 petrol:EtOAc].

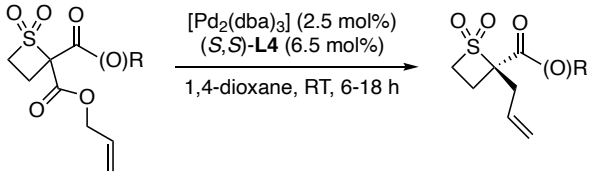
^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.92 (1H, ddt, *J* = 17.2, 10.5, 5.7 Hz, **H6**), 5.40 (1H, dq, *J* = 17.2, 1.4 Hz, **H7a**), 5.30 (1H, dq, *J* = 10.5, 1.2 Hz, **H7b**), 4.78 (2H, dt, *J* = 5.7, 1.4 Hz, **H5**), 4.27 – 4.21 (2H, m, **H2**), 3.90 (3H, s, **H9**), 2.75 – 2.68 (2H, m, **H1**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 163.6 (**C8**), 162.8 (**C4**), 130.7 (**C6**), 119.6 (**C7**), 92.5 (**C3**), 67.9 (**C5**), 64.8 (**C2**), 54.2 (**C9**), 17.1 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_9H_{13}O_6S$ 249.0427; found 249.0428.

IR: ν_{max} (neat/cm^{-1}): 3035 (C–H), 2957 (C–H), 1735 (C=O), 1340 (S=O), 1142 (S=O).

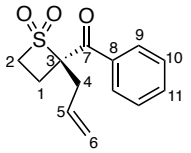
5.2.4 Palladium-Catalysed Decarboxylative Asymmetric Allylic Alkylation



251 **253**

For the purposes of chiral HPLC analysis, all racemic products were prepared using 10 mol% $Pd(PPh_3)_4$ in 1,4-dioxane at RT for 18 h.

(2*S*)-[2-Allyl-1,1-dioxo-thietan-2-yl]-phenyl-methanone (269)



269

A vial was charged with substrate **267** (50 mg, 0.17 mmol), $Pd_2(dba)_3$ (3.5 mg, 0.004 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (8.9 mg, 0.011 mmol) and 1,4-dioxane (4 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 6:1 hexane:EtOAc] afforded **269** (33 mg, 78%) as a colourless oil. $\boldsymbol{R_f}$ = 0.59 [2:1 petrol: EtOAc].

^{1}H NMR: (400 MHz, C_6H_6) δ 8.14 – 8.09 (2H, m, **H9**), 7.02 – 6.95 (3H, m, **H10** and **H11**), 5.19 (1H, ddt, *J* = 17.2, 9.6, 7.2 Hz, **H5**), 4.76 – 4.72 (1H, m, **H6a**), 4.61 (1H, dq, *J* = 16.8, 1.6 Hz, **H6b**), 3.13 – 3.03 (2H, m, **H2**), 3.02 – 2.96 (1H, m, **H4a**), 2.75 – 2.67 (2H, m, **H1a** and **H4b**), 1.30 (1H, ddd, *J* = 12.4, 10.0, 5.2 Hz, **H1b**).

^{13}C NMR: (100 MHz, C_6H_6) δ 192.4 (**C7**), 134.7 (**C8**), 133.6 (**C11**), 129.7 (**C5**), 129.6 (**C9**), 128.9 (**C10**), 120.3 (**C6**), 92.5 (**C3**), 59.7 (**C2**), 39.7 (**C4**), 15.1 (**C1**).

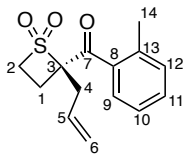
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{15}O_3S$ 251.0742; found 251.0736.

IR: ν_{max} (neat/cm^{-1}): 3065 (C–H), 2974 (C–H), 1675 (C=O), 1313 (S=O), 1127 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 224 nm, 30.0 ºC) t_R = 11.6 min (minor), 14.1 min (major). 83% ee.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +27.5 (*c* = 0.20, $CHCl_3$).

(2*S*)-[2-Allyl-1,1-dioxo-thietan-2-yl]-(*o*-tolyl)methanone (311)



311

A vial was charged with substrate **271** (50 mg, 0.16 mmol), $Pd_2(dba)_3$ (3.6 mg, 0.004 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (8.1 mg, 0.010 mmol) and 1,4-dioxane (4 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 6:1 hexane:EtOAc] afforded **311** (36 mg, 83%) as a colourless solid. $\boldsymbol{R_f}$ = 0.70 [3:2 petrol:EtOAc]. **mp**: 52 – 53 ºC.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.67 (1H, dd, *J* = 7.8, 1.2 Hz, **H9**), 7.42 (1H, td, *J* = 7.5, 1.4 Hz, **H11**), 7.36 – 7.27 (2H, m, **H10** and **H12**), 5.51 – 5.41 (1H, m, **H5**), 5.11 (1H, dq, *J* = 10.1, 1.3 Hz, **H6a**), 4.95 (1H, dq, *J* = 16.9, 1.4 Hz, **H6b**), 4.12 – 4.00 (2H, m, **H2**), 3.12 – 3.01 (2H, m, **H1a** and **H4a**), 2.94 (1H, ddt, *J* = 14.5, 7.2, 1.2 Hz, **H4b**), 2.44 (3H, s, **H14**), 2.03 (1H, ddd, *J* = 15.8, 10.3, 5.6 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 194.6 (**C7**), 140.0 (**C13**), 134.0 (**C8**), 132.5 (**C12**), 132.1 (**C11**), 129.3 (**C5**), 128.5 (**C9**), 125.9 (**C10**), 121.0 (**C6**), 93.8 (**C3**), 60.8 (**C2**), 39.2 (**C4**), 21.4 (**C14**), 15.4 (**C1**).

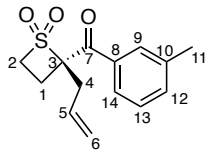
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}O_3S$ 265.0893; found 265.0888.

IR: ν_{max} (neat/cm^{-1}): 3039 (C–H), 2972 (C–H), 1679 (C=O), 1332 (S=O), 1138 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 224 nm, 30.0 ºC) t_R = 12.6 min (minor), 16.9 min (major). 84% ee.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +182.4 (*c* = 0.26, $CHCl_3$).

(2*S*)-[2-Allyl-1,1-dioxo-thietan-2-yl]-(*m*-tolyl)methanone (312)



312

A vial was charged with substrate **272** (50 mg, 0.16 mmol), $Pd_2(dba)_3$ (3.6 mg, 0.004 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (8.1 mg, 0.010 mmol) and 1,4-dioxane (4 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 6:1 hexane:EtOAc] afforded **312** (37 mg, 88%) as a colourless oil. $\boldsymbol{R_f}$ = 0.70 [3:2 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.81 – 7.77 (2H, m, **H9** and **H14**), 7.47 – 7.40 (2H, m, **H12** and **H13**), 5.55 – 5.44 (1H, m, **H5**), 5.15 (1H, dq, *J* = 10.2, 1.3 Hz, **H6a**), 5.07 (1H, dq, *J* = 16.9, 1.4 Hz, **H6b**), 4.10 (1H, ddd, *J* = 13.0, 10.5, 8.9 Hz, **H2a**), 4.00 (1H, ddd, *J* = 12.9, 10.7, 4.6 Hz, **H2b**), 3.20 (1H, ddq, *J* = 14.4, 6.6, 1.1 Hz, **H4a**), 3.10 – 3.00 (2H, m, **H1a** and **H4b**), 2.45 (3H, s, **H11**), 2.09 (1H, ddd, *J* = 12.4, 10.5, 4.6 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 192.3 (**C7**), 138.8 (**C8**), 134.8 (**C12** or **C13**), 133.9 (**C10**), 129.7 (**C9** or **C14**), 129.2 (**C5**), 128.7 (**C12** or **C13**), 126.5 (**C9** or **C14**), 121.1 (**C6**), 92.7 (**C3**), 60.0 (**C2**), 39.6 (**C4**), 21.4 (**C11**), 15.2 (**C1**).

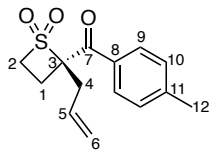
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}O_3S$ 265.0893, found 265.0881.

IR: ν_{max} (neat/cm^{-1}): 3091 (C–H), 2965 (C–H), 1669 (C=O), 1323 (S=O), 1129 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 224 nm, 30.0 ºC) t_R = 10.8 min (minor), 13.1 min (major). 86% ee.

$\boldsymbol{[\alpha]_D^{20}}$ = +79.8 (*c* = 0.16, $CHCl_3$).

(2*S*)-[2-Allyl-1,1-dioxo-thietan-2-yl]-(*p*-tolyl)methanone (313)



313

A vial was charged with substrate **273** (50 mg, 0.16 mmol), $Pd_2(dba)_3$ (3.6 mg, 0.004 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (8.1 mg, 0.010 mmol) and 1,4-dioxane (4 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 6:1 hexane:EtOAc] afforded **313** (35 mg, 83%) as a colourless oil. $\boldsymbol{R_f}$ = 0.70 [3:2 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.92 – 7.88 (2H, m, **H9**), 7.31 (2H, dd, *J* = 8.6, 0.5 Hz, **H10**), 5.53 – 5.42 (1H, m, **H5**), 5.12 (1H, dq, *J* = 10.1, 1.4 Hz, **H6a**), 5.05 (1H, dq, *J* = 16.9, 1.4 Hz, **H6b**), 4.07 (1H, ddd, *J* = 12.9, 10.5, 8.9 Hz, **H2a**), 3.97 (1H, ddd, *J* = 12.9, 10.7, 4.6 Hz, **H2b**), 3.17 (1H, ddq, *J* = 14.4, 6.6, 1.2 Hz, **H4a**), 3.06 – 2.97 (2H, m, **H1a** and **H4b**), 2.43 (3H, s, **H12**), 2.07 (1H, ddd, *J* = 12.5, 10.6, 4.6 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 191.5 (**C7**), 145.0 (**C11**), 132.8 (**C8**), 130.8 (**C10**), 129.5 (**C9**), 128.9 (**C5**), 121.4 (**C6**), 92.7 (**C3**), 60.1 (**C2**), 39.9 (**C4**), 21.9 (**C12**), 15.4 (**C1**).

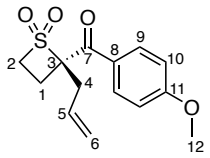
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}O_3S$ 265.0893; found 265.0892.

IR: ν_{max} (neat/cm^{-1}): 3030 (C–H), 2976 (C–H), 1671 (C=O), 1313 (S=O), 1123 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 224 nm, 30.0 ºC) t_R = 16.8 min (minor), 22.2 min (major). 86% ee.

$\boldsymbol{[\alpha]_D^{20}}$ = +52.3 (*c* = 0.22, $CHCl_3$).

(2*S*)-[2-Allyl-1,1-dioxo-thietan-2-yl]-(4-methoxyphenyl)methanone (314)



314

A vial was charged with substrate **274** (40 mg, 0.12 mmol), $Pd_2(dba)_3$ (3.0 mg, 0.003 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (6.4 mg, 0.008 mmol) and 1,4-dioxane (3 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 10:1 hexane:EtOAc] afforded **314** (20 mg, 60%) as a colourless oil. $\boldsymbol{R_f}$ = 0.41 [2:1 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.97 (2H, d, *J* = 8.8 Hz, **H9**), 6.99 (2H, d, *J* = 9.2 Hz, **H10**), 5.55 – 5.43 (1H, m, **H5**), 5.13 (1H, dq, *J* = 10.1, 0.9 Hz, **H6a**), 5.07 (1H, dq, *J* = 16.9, 1.4 Hz, **H6b**), 4.06 (1H, ddd, *J* = 12.9, 10.5, 9.1 Hz, **H2a**), 3.94 (1H, ddd, *J* = 12.9, 10.7, 4.4 Hz, **H2b**), 3.89 (3H, s, **H12**), 3.16 (1H, ddq, *J* = 14.4, 6.6, 1.2 Hz, **H4a**), 3.06 – 2.96 (2H, m, **H1a** and **H4b**), 2.07 (1H, ddd, *J* = 12.5, 10.5, 4.4 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 190.5 (**C7**), 164.4 (**C11**), 131.9 (**C9**), 129.4 (**C5**), 126.9 (**C8**), 121.1 (**C6**), 114.3 (**C10**), 92.6 (**C3**), 60.0 (**C2**), 55.7 (**C12**), 40.1 (**C4**), 15.5 (**C1**).

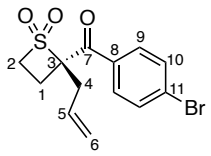
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}O_4S$ 281.0842; found 281.0828.

IR: ν_{max} (neat/cm^{-1}): 3032 (C–H), 2965 (C–H), 1680 (C=O), 1318 (S=O), 1130 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 224 nm, 30.0 ºC) t_R = 29.0 min (minor), 37.2 min (major). 84% ee.

$\boldsymbol{[\alpha]_D^{20}}$ = +69.4 (*c* = 0.12, $CHCl_3$).

(2*S*)-[2-Allyl-1,1-dioxo-thietan-2-yl]-(4-bromophenyl)methanone (315)



315

A vial was charged with substrate **275** (50 mg, 0.13 mmol), $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (7.3 mg, 0.009 mmol) and 1,4-dioxane (4 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 6:1 hexane:EtOAc] afforded **315** (42 mg, 95%) as a colourless solid. $\boldsymbol{R}_\mathbf{f}$ = 0.35 [3:1 petrol:EtOAc]. **mp**: 71 – 73 ºC.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.83 (2H, d, *J* = 8.8 Hz, **H9**), 7.66 (2H, d, *J* = 8.4 Hz, **H10**), 5.53 – 5.40 (1H, m, **H5**), 5.13 (1H, dq, *J* = 10.1, 1.3 Hz, **H6a**), 5.04 (1H, dq, *J* = 16.9, 1.4 Hz, **H6b**), 4.09 (1H, ddd, *J* = 13.0, 10.6, 8.8 Hz, **H2a**), 3.98 (1H, ddd, *J* = 13.0, 10.7, 4.7 Hz, **H2b**), 3.11 (1H, ddq, *J* = 14.5, 6.8, 1.1 Hz, **H4a**), 3.06 – 2.97 (2H, m, **H1a** and **H4b**), 2.08 (1H, ddd, *J* = 15.2, 10.6, 4.7 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 191.5 (**C7**), 132.8 (**C8**), 132.4 (**C10**), 130.8 (**C9**), 129.5 (**C11**), 128.9 (**C5**), 121.4 (**C6**), 92.6 (**C3**), 60.3 (**C2**), 39.6 (**C4**), 15.3 (**C1**).

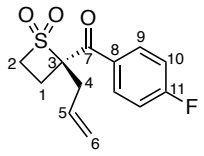
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{14}O_3S^{79}Br$ 328.9842; found 328.9850.

IR: ν_{max} (neat/cm^{-1}): 3032 (C–H), 2965 (C–H), 1675 (C=O), 1313 (S=O), 1127 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 224 nm, 30.0 ºC) t_R = 16.6 min (minor), 18.1 (major). 85% ee.

$\boldsymbol{[\alpha]_D^{20}}$ = +31.8 (*c* = 0.29, $CHCl_3$).

(2*S*)-[2-Allyl-1,1-dioxo-thietan-2-yl]-(4-fluorophenyl)methanone (316)



316

A vial was charged with substrate **276** (25 mg, 0.08 mmol), $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (4.2 mg, 0.005 mmol) and 1,4-dioxane (2 mL). The reaction mixture was stirred at room temperature for 6 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 9:1 hexane:EtOAc] afforded **316** (19 mg, 89%) as a colourless oil. $\boldsymbol{R_f}$ = 0.44 [2:1 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.04 – 7.98 (2H, m, **H9**), 7.22 – 7.16 (2H, m, **H10**), 5.52 – 5.41 (1H, m, **H5**), 5.13 (1H, m, **H6a**), 5.04 (1H, dq, *J* = 16.8, 1.6 Hz, **H6b**), 4.09 (1H, ddd, *J* = 13.2, 10.8, 8.8 Hz, **H2a**), 3.98 (1H, ddd, *J* = 12.8, 10.4, 4.4 Hz, **H2b**), 3.16 – 3.08 (1H, m, **H4a**), 3.07 – 2.97 (2H, m, **H1a** and **H4b**), 2.09 (1H, ddd, *J* = 12.4, 10.4, 4.4 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 190.5 (**C7**), 166.1 (d, *J* = 255.6 Hz, **C11**), 132.1 (d, *J* = 9.5 Hz, **C9**), 130.4 (d, *J* = 3.0 Hz, **C8**), 128.9 (**C5**), 121.3 (**C6**), 116.2 (d, *J* = 21.9 Hz, **C10**), 92.4 (**C3**), 60.1 (**C2**), 39.6 (**C4**), 15.3 (**C1**).

^{19}F{^{1}H} NMR: (376 MHz, $CDCl_3$) δ –103.0.

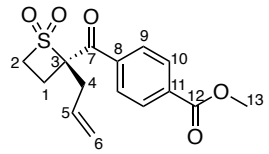
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{14}O_3FS$ 269.0642; found 269.0630.

IR: ν_{max} (neat/cm^{-1}): 3030 (C–H), 2976 (C–H), 1677 (C=O), 1315 (S=O), 1159 (S=O).

Chiral HPLC: (AD-H, hexane/*i*-PrOH = 90/10, flow rate = 1.0 mL/min, λ = 254 nm, 30.0 ºC) t_R = 20.6 min (minor), 21.3 min (major). 86% ee.

$\boldsymbol{[\alpha]_D^{22}}$ = +62.5 (*c* = 0.12, $CHCl_3$).

(2*S*)-[2-Allyl-1,1-dioxo-thietan-2-yl]-(4-methylbenzoate)methanone (317)



317

A vial was charged with substrate **277** (15 mg, 0.04 mmol), $Pd_2(dba)_3$ (1.0 mg, 0.001 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (3.0 mg, 0.003 mmol) and 1,4-dioxane (1 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 5:1 – 2:1 heptane:EtOAc] afforded **317** (12 mg, 92%) as a yellow solid. $\boldsymbol{R_f}$ = 0.23 [2:1 petrol:EtOAc]. **mp**: 78 – 80 ºC.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.17 (2H, dt, *J* = 8.7, 2.0 Hz, **H10**), 8.00 (2H, dt, *J* = 8.8, 2.0 Hz, **H9**), 5.45 (1H, ddt, *J* = 17.0, 9.8, 7.3 Hz, **H5**), 5.11 (1H, dd, *J* = 10.1, 1.2 Hz, **H6a**), 4.99 (1H, dq, *J* = 16.9, 1.4 Hz, **H6b**), 4.11 (1H, ddd, *J* = 13.0, 10.5, 8.6 Hz, **H2a**), 4.01 (1H, ddd, *J* = 13.0, 10.7, 4.9 Hz, **H2b**), 3.95 (3H, s, **H13**) 3.16 – 3.08 (1H, m, **H4a**), 3.07 – 2.97 (2H, m, **H1a** and **H4b**), 2.09 (1H, ddd, *J* = 12.4, 10.5, 4.8 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 192.2 (**C7**), 166.1 (**C12**), 137.5 (**C8**), 134.6 (**C11**), 130.1 (**C10**), 129.3 (**C9**), 128.8 (**C5**), 121.4 (**C6**), 92.7 (**C3**), 60.5 (**C2**), 52.7 (**C13**), 39.4 (**C4**), 15.3 (**C1**).

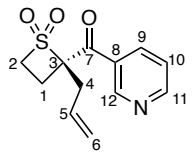
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{17}O_5S$ 309.0791; found 309.0786.

IR: ν_{max} (neat/cm^{-1}): 2953 (C–H), 1720 (C=O), 1681 (C=O), 1317 (S=O), 1108 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 254 nm, 30.0 ºC) t_R = 25.7 min (minor), 33.9 min (major). 79% ee.

$\boldsymbol{[\alpha]_D^{23}}$ = +33.3 (*c* = 0.06, $CHCl_3$).

(2-Allyl-1,1-dioxo-thietan-2-yl)-(3-pyridyl)methanone (318)



318

A vial was charged with substrate **278** (30 mg, 0.10 mmol), $Pd_2(dba)_3$ (2.3 mg, 0.003 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (5.3 mg, 0.007 mmol) and 1,4-dioxane (3 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 10:1 hexane:EtOAc] afforded **318** (20 mg, 80%) as a yellow oil. $\boldsymbol{R_f}$ = 0.13 [3:1 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.17 (1H, s, **H12**), 8.84 (1H, s, **H11**), 8.24 (1H, dd, *J* = 8.0, 1.9 Hz, **H9**), 7.48 (1H, dd, *J* = 7.9, 4.9 Hz, **H10**), 5.52 – 5.41 (1H, m, **H5**), 5.14 (1H, dd, *J* = 10.1, 1.0 Hz, **H6a**), 5.02 (1H, dd, *J* = 16.9, 1.3 Hz, **H6b**), 4.12 (1H, ddd, *J* = 13.2, 10.4, 8.4 Hz, **H2a**), 4.03 (1H, ddd, *J* = 12.8, 10.8, 5.2 Hz, **H2b**), 3.13 – 3.02 (3H, m, **H1a** and **H4**), 2.10 (1H, ddd, *J* = 15.7, 10.6, 5.2 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 191.7 (**C7**), 154.0 (**C11**), 150.6 (**C12**), 136.6 (**C9** and **C10**), 128.6 (**C5**), 123.8 (**C8**), 121.6 (**C6**), 92.7 (**C3**), 60.7 (**C2**), 39.3 (**C4**), 15.1 (**C1**).

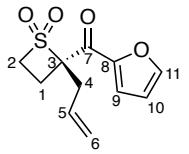
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{14}NO_3S$ 252.0689; found 252.0680.

IR: ν_{max} (neat/cm^{-1}): 3034 (C–H), 2970 (C–H), 1736 (C=O), 1319 (S=O), 1131 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 214 nm, 30.0 ºC) t_R = 40.5 min (minor), 49.8 min (major). 72% ee.

$\boldsymbol{[\alpha]_D^{21}}$ = +36.7 (*c* = 0.15, $CHCl_3$).

(2*S*)-[2-Allyl-1,1-dioxo-thietan-2-yl]-(2-furyl)methanone (319)



319

A vial was charged with substrate **279** (25 mg, 0.09 mmol), $Pd_2(dba)_3$ (2.0 mg, 0.002 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (4.6 mg, 0.006 mmol) and 1,4-dioxane (2 mL). The reaction mixture was stirred at room temperature for 6 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 6:1 hexane:EtOAc] afforded **319** (15 mg, 69%) as a colourless oil. $\boldsymbol{R_f}$ = 0.59 [3:2 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.70 (1H, dd, *J* = 1.7, 0.7 Hz, **H11**), 7.40 (1H, dd, *J* = 3.6, 0.7 Hz, **H9**), 6.61 (1H, dd, *J* = 3.7, 1.7 Hz, **H10**), 5.61 – 5.50 (1H, m, **H5**), 5.18 – 5.09 (2H, m, **H6**), 4.05 (1H, ddd, *J* = 13.0, 10.6, 8.5 Hz, **H2a**), 3.95 (1H, ddd, *J* = 13.0, 10.8, 4.9 Hz, **H2b**), 3.33 (1H, ddq, *J* = 14.5, 6.8, 0.9 Hz, **H4a**), 3.03 (1H, ddt, *J* = 14.5, 7.6, 1.0 Hz, **H4b**), 2.99 – 2.90 (1H, m, **H1a**), 2.05 (1H, ddd, *J* = 12.5, 10.6, 4.9 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 180.7 (**C7**), 151.0 (**C8**), 147.7 (**C11**), 129.5 (**C5**), 121.1 (**C6**), 120.0 (**C9**), 113.1 (**C10**), 92.7 (**C3**), 61.1 (**C2**), 38.7 (**C4**), 14.9 (**C1**).

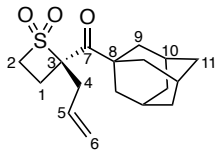
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{13}O_4S$ 241.0529; found 241.0518.

IR: ν_{max} (neat/cm^{-1}): 3134 (C–H), 2968 (C–H), 1662 (C=O), 1313 (S=O), 1127 (S=O).

Chiral HPLC: (AD-H, hexane/*i*-PrOH = 90/10, flow rate = 1.0 mL/min, λ = 224 nm, 30.0 ºC) t_R = 12.5 min (minor), 13.1 min (major). 81% ee.

$\boldsymbol{[\alpha]_D^{20}}$ = –105.7 (*c* = 0.03, $CHCl_3$).

(2*S*)-1-Adamantyl-[2-Allyl-1,1-dioxo-thietan-2-yl]methanone (320)



320

A vial was charged with substrate **280** (30 mg, 0.08 mmol), $Pd_2(dba)_3$ (2.3 mg, 0.004 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (4.9 mg, 0.010 mmol) and 1,4-dioxane (2 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 6:1 hexane:EtOAc] afforded **320** (12 mg, 45%) as a colourless solid. $\boldsymbol{R_f}$ = 0.67 [2:1 petrol:EtOAc]. **mp**: 136 – 137 ºC.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.59 – 5.48 (1H, m, **H5**), 5.25 (1H, br s, **H6a**), 5.22 (1H, dq, *J* = 6.3, 1.2 Hz, **H6b**), 3.89 (1H, dt, *J* = 12.8, 10.3 Hz, **H2a**), 3.76 (1H, ddd, *J* = 12.9, 10.5, 3.1 Hz, **H2b**), 3.17 (1H, ddq, *J* = 15.0, 6.1, 1.3 Hz, **H4a**), 2.90 (1H, ddt, *J* = 15.0, 7.8, 1.0 Hz, **H4b**), 2.77 – 2.68 (1H, m, **H1a**), 2.09 – 1.97 (10H, m, **H1b**, **H9** and **H10**), 1.74 (6H, br s, **H11**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 207.9 (**C7**), 130.2 (**C5**), 121.3 (**C6**), 94.9 (**C3**), 58.9 (**C2**), 47.0 (**C8**), 38.4 (**C9**), 37.9 (**C4**), 36.5 (**C11**), 28.1 (**C10**), 16.5 (**C1**).

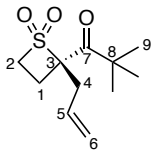
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{25}O_3S$ 309.1519; found 309.1510.

IR: ν_{max} (neat/cm^{-1}): 3013 (C–H), 2905 (C–H), 1677 (C=O), 1315 (S=O), 1131 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 214 nm, 30.0 ºC) t_R = 8.9 min (minor), 10.0 min (major). 93% ee.

$\boldsymbol{[\alpha]_D^{20}}$ = –41.7 (*c* = 0.06, $CHCl_3$).

(2*S*)-1-[2-Allyl-1,1-dioxo-thietan-2-yl]-2,2-dimethyl-propan-1-one (321)



321

A vial was charged with substrate **281** (50 mg, 0.18 mmol), $Pd_2(dba)_3$ (3.6 mg, 0.004 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (10.0 mg, 0.012 mmol) and 1,4-dioxane (4 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 6:1 hexane:EtOAc] afforded **321** (37 mg, 90%) as a colourless oil. $\boldsymbol{R_f}$ = 0.34 [2:1 petrol: EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.60 – 5.49 (1H, m, **H5**), 5.26 – 5.24 (1H, m, **H6a**), 5.22 (1H, dq, *J* = 7.2, 1.4 Hz, **H6b**), 3.95 – 3.86 (1H, m, **H2a**), 3.79 (1H, ddd, *J* = 14.0, 10.6, 3.4 Hz, **H2b**), 3.12 (1H, ddq, *J* = 15.0, 6.3, 1.3 Hz, **H4a**), 2.91 (1H, ddt, *J* = 15.0, 7.6, 1.2 Hz, **H4b**), 2.80 – 2.70 (1H, m, **H1a**), 2.00 (1H, ddd, *J* = 13.8, 10.4, 3.4 Hz, **H1b**), 1.31 (9H, s, **H9**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 208.6 (**C7**), 130.0 (**C5**), 121.3 (**C6**), 95.0 (**C3**), 59.2 (**C2**), 44.3 (**C8**), 37.7 (**C4**), 27.7 (**C9**), 16.5 (**C1**).

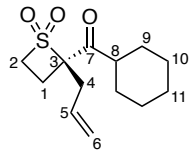
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{19}O_3S$ 231.1049; found 231.1044.

IR: ν_{max} (neat/cm^{-1}): 3084 (C–H), 2974 (C–H), 1725 (C=O), 1317 (S=O), 1127 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 220 nm, 30.0 ºC) t_R = 9.7 min (minor), 10.3 min (major). 90% ee.

$\boldsymbol{[\alpha]_D^{20}}$ = –83.3 (*c* = 0.21, $CHCl_3$).

(2*S*)-[2-Allyl-1,1-dioxo-thietan-2-yl]-cyclohexyl-methanone (322)



322

A vial was charged with substrate **282** (50 mg, 0.17 mmol), $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (9.0 mg, 0.011 mmol) and 1,4-dioxane (4 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 6:1 hexane:EtOAc] afforded **322** (37 mg, 86%) as a colourless oil. $\boldsymbol{R_f}$ = 0.63 [3:1 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.58 – 5.47 (1H, m, **H5**), 5.21 (1H, dq, *J* = 5.6, 1.2 Hz, **H6a**), 5.18 (1H, dq, *J* = 12.1, 1.2 Hz, **H6b**), 3.97 – 3.85 (2H, m, **H2**), 3.10 – 3.03 (1H, m, **H4a**), 2.96 (1H, ddt, *J* = 15.2, 7.7, 1.1 Hz, **H4b**), 2.82 – 2.74 (1H, m, **H1a**), 2.68 (1H, tt, *J* = 11.3, 3.0 Hz, **H8**), 1.87 (1H, ddd, *J* = 16.6, 10.0, 6.6 Hz, **H1b**), 2.05 – 1.97 (1H, m, **H10**), 1.82 – 1.74 (3H, m, **H9**), 1.72 – 1.64 (1H, m, **H10**), 1.43 – 1.19 (5H, m, **H9**, **H10** and **H11**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 205.5 (**C7**), 129.8 (**C5**), 120.9 (**C6**), 95.2 (**C3**), 61.5 (**C2**), 48.9 (**C8**), 36.6 (**C4**), 30.1 (**C9**), 28.4 (**C10**), 25.7 (**C11**), 14.6 (**C1**).

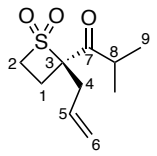
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{21}O_3S$ 257.1206; found 257.1206.

IR: ν_{max} (neat/cm^{-1}): 2929 (C–H), 2853 (C–H), 1720 (C=O), 1306 (S=O), 1127 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 214 nm, 30.0 ºC) t_R = 7.8 min (minor), 8.9 min (major). 94% ee.

$\boldsymbol{[\alpha]_D^{20}}$ = –88.5 (*c* = 0.21, $CHCl_3$).

(2*S*)-1-[2-Allyl-1,1-dioxo-thietan-2-yl]-2-methyl-propan-1-one (323)



323

A vial was charged with substrate **283** (50 mg, 0.19 mmol), $Pd_2(dba)_3$ (4.4 mg, 0.005 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (10.0 mg, 0.012 mmol) and 1,4-dioxane (4 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 6:1 hexane:EtOAc] afforded **323** (38 mg, 93%) as a colourless oil. $\boldsymbol{R_f}$ = 0.28 [3:1 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.60 – 5.49 (1H, m, **H5**), 5.24 – 5.21 (1H, m, **H6a**), 5.19 (1H, dq, *J* = 11.1, 1.2 Hz, **H6b**), 3.99 – 3.87 (2H, m, **H2**), 3.12 – 3.05 (1H, m, **H4a**), 3.02 – 2.92 (2H, m, **H4b** and **H8**), 2.85 – 2.77 (1H, m, **H1a**), 1.90 (1H, ddd, *J* = 12.3, 10.1, 6.5 Hz, **H1b**), 1.21 (3H, d, *J* = 6.7 Hz, **H9a**), 1.15 (3H, d, *J* = 6.7 Hz, **H9b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 206.8 (**C7**), 129.7 (**C5**), 121.0 (**C7**), 95.2 (**C3**), 61.5 (**C2**), 38.7 (**C8**), 36.6 (**C4**), 20.0 and 19.0 (**C9**), 14.8 (**C1**).

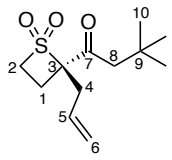
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{17}O_3S$ 217.0893; found 217.0885.

IR: ν_{max} (neat/cm^{-1}): 3097 (C–H), 2980 (C–H), 1716 (C=O), 1302 (S=O), 1123 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 214 nm, 30.0 ºC) t_R = 9.9 min (minor), 10.8 min (major). 90% ee.

$\boldsymbol{[\alpha]_D^{20}}$ = –96.9 (*c* = 0.19, $CHCl_3$).

(2*S*)-1-[2-Allyl-1,1-dioxo-thietan-2-yl]-3,3-dimethyl-butan-1-one (324)



324

A vial was charged with substrate **284** (50 mg, 0.17 mmol), $Pd_2(dba)_3$ (3.6 mg, 0.004 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (9.0 mg, 0.011 mmol) and 1,4-dioxane (4 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 6:1 hexane:EtOAc] afforded **324** (31 mg, 76%) as a colourless oil. $\boldsymbol{R_f}$ = 0.67 [2:1 petrol: EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.60 – 5.49 (1H, m, **H5**), 5.22 – 5.20 (1H, m, **H6a**), 5.18 (1H, dq, *J* = 7.4. 1.2 Hz, **H6b**), 3.97 – 3.84 (2H, m, **H2**), 3.05 – 2.98 (1H, m, **H4a**), 2.93 (1H, ddt, *J* = 15.1, 7.0, 1.3 Hz, **H4b**), 2.89 – 2.80 (1H, m, **H1a**), 2.62 (1H, d, *J* = 18.6 Hz, **H8a**), 2.51 (1H, d, *J* = 18.6 Hz, **H8b**), 1.85 (1H, ddd, *J* = 17.0, 9.7, 7.3 Hz, **H1b**), 1.06 (9H, s, **H10**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 200.2 (**C7**), 129.4 (**C5**), 120.8 (**C6**), 94.6 (**C3**), 61.6 (**C2**), 52.6 (**C8**), 37.4 (**C4**), 30.7 (**C9**), 29.6 (**C10**), 15.1 (**C1**).

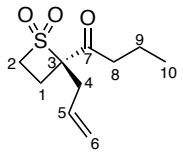
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{21}O_3S$ 245.1206; found 245.1200.

IR: ν_{max} (neat/cm^{-1}): 3084 (C–H), 2953 (C–H), 2871 (C–H), 1714 (C=O), 1319 (S=O), 1131 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 214 nm, 30.0 ºC) t_R = 6.5 min (minor), 7.7 min (major). 81% ee.

$\boldsymbol{[\alpha]_D^{20}}$= –16.6 (*c* = 0.08, $CHCl_3$).

(2*S*)-1-[2-Allyl-1,1-dioxo-thietan-2-yl]butan-1-one (325)



325

A vial was charged with substrate **285** (20 mg, 0.08 mmol), $Pd_2(dba)_3$ (2.0 mg, 0.002 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (4.1 mg, 0.005 mmol) in 1,4-dioxane (2 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure and purification by flash chromatography [SiO_2; 5:1 hexane:EtOAc] afforded **325** (11 mg, 64%) as a colourless oil. $\boldsymbol{R_f}$ = 0.48 [2:1 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.62 – 5.47 (1H, m, **H5**), 5.23 – 5.15 (2H, m, **H6**), 3.96 (2H, t, *J* = 8.8 Hz, **H8**), 3.07 (1H, dd, *J* = 15.1, 6.8 Hz, **H2a**), 3.01 – 2.97 (1H, m, **H2b**), 2.96 – 2.83 (1H, m, **H4a**), 2.74 – 2.51 (2H, m, **H4b** and **H1a**), 1.94 – 1.83 (1H, m, **H1b**), 1.70 (2H, sextet, *J* = 7.4 Hz, **H9**), 0.96 (3H, t, *J* = 7.4 Hz, **H10**).

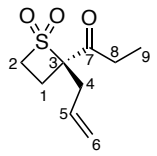
^{13}C NMR: (100 MHz, $CDCl_3$) δ 201.3 (**C7**), 129.2 (**C5**), 120.6 (**C6**), 94.3 (**C3**), 61.7 (**C2**), 42.4 (**C4**), 37.0 (**C8**), 16.7 (**C9**), 15.0 (**C1**), 13.6 (**C10**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{17}O_3S$ 217.0893; found 217.0896.

IR: ν_{max} (neat/cm^{-1}): 2967 (C–H), 2935 (C–H), 2877 (C–H), 1712 (C=O), 1319 (S=O), 1133 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 220 nm, 30.0 ºC) t_R = 9.4 min (minor), 10.5 min (major). 80% ee.

(2*S*)-1-[2-Allyl-1,1-dioxo-thietan-2-yl]propan-1-one (326)



326

A vial was charged with substrate **286** (40 mg, 0.16 mmol), $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (8.1 mg, 0.010 mmol) and 1,4-dioxane (4 mL). The reaction mixture was stirred at room temperature for 6 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 9:1 hexane:EtOAc] afforded **326** (25 mg, 78%) as a colourless oil. $\boldsymbol{R_f}$ = 0.50 [2:1 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.58 – 5.48 (1H, m, **H5**), 5.21 – 5.19 (1H, m, **H6a**), 5.16 (1H, dq, *J* = 5.3, 1.3 Hz, **H6b**), 3.95 (2H, t, *J* = 8.3 Hz, **H2**), 3.10 – 3.02 (1H, m, **H4a**), 2.94 (1H, dt, *J* = 6.9, 1.3 Hz, **H4b**), 2.93 – 2.85 (1H, m, **H1a**), 2.72 (1H, dq, *J* = 18.3, 7.1 Hz, **H8a**), 2.59 (1H, dq, *J* = 18.3, 7.1 Hz, **H8b**), 1.92 – 1.83 (1H, m, **H1b**), 1.14 (3H, t, *J* = 7.1 Hz, **H9**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 202.1 (**C7**), 129.4 (**C5**), 120.7 (**C6**), 94.5 (**C3**), 61.9 (**C2**), 37.1 (**C4**), 34.0 (**C8**), 15.3 (**C1**), 7.7 (**C9**).

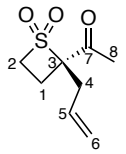
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_9H_{15}O_3S$ 203.0736; found 203.0744.

IR: ν_{max} (neat/cm^{-1}): 3082 (C–H), 2981 (C–H), 2942 (C–H), 1712 (C=O), 1317 (S=O), 1131 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 97/3, flow rate = 1.0 mL/min, λ = 214 nm, 30.0 ºC) t_R = 13.8 min (minor), 14.7 min (major). 69% ee.

$\boldsymbol{[\alpha]_D^{22}}$ = –25.0 (*c* = 0.14, $CHCl_3$).

(2*S*)-1-[2-Allyl-1,1-dioxo-thietan-2-yl]ethanone (327)



327

A vial was charged with substrate **287** (50 mg, 0.21 mmol), $Pd_2(dba)_3$ (5.0 mg, 0.006 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (11.6 mg, 0.014 mmol) and 1,4-dioxane (5 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 6:1 hexane:EtOAc] afforded **327** (26 mg, 66%) as a colourless oil. $\boldsymbol{R_f}$ = 0.65 [3:2 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.62 – 5.51 (1H, m, **H5**), 5.23 – 5.18 (2H, m, **H6**), 3.98 (1H, t, *J* = 8.9 Hz, **H2a**), 3.97 (1H, t, *J* = 13.0 Hz, **H2b**), 3.09 – 3.03 (1H, m, **H4a**), 2.97 (1H, ddt, *J* = 15.0, 6.7, 1.2 Hz, **H4b),** 2.92 – 2.84 (1H, m, **H1a**), 2.35 (3H, s, **H8**), 1.94 – 1.86 (1H, m, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 199.2 (**C7**), 129.2 (**C5**), 120.8 (**C6**), 94.6 (**C3**), 61.9 (**C2**), 37.1 (**C4**), 28.1 (**C8**), 15.1 (**C1**).

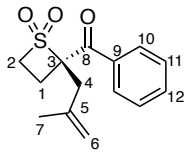
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_8H_{13}O_3S$ 189.0580; found 189.0576.

IR: ν_{max} (neat/cm^{-1}): 3084 (C–H), 2970 (C–H), 1710 (C=O), 1312 (S=O), 1120 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 210 nm, 30.0 ºC) t_R = 13.9 min (minor), 14.6 min (major). 39% ee.

$\boldsymbol{[\alpha]_D^{20}}$ = +21.4 (*c* = 0.07, $CHCl_3$).

(2*S*)-[2-(2-Methylallyl)-1,1-dioxo-thietan-2-yl]-phenyl-methanone (328)



328

A vial was charged with substrate **301** (20 mg, 0.07 mmol), $Pd_2(dba)_3$ (2.9 mg, 0.003 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (6.5 mg, 0.008 mmol) and 1,4-dioxane (2 mL). The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 5:1 hexane:EtOAc] afforded **328** (12 mg, 70%) as a colourless oil. $\boldsymbol{R_f}$ = 0.56 [2:1 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.94 – 7.90 (2H, m, **H10**), 7.60 (1H, tt, *J* = 7.4, 1.3 Hz, **H12**), 7.53 – 7.48 (2H, m, **H11**), 4.79 (1H, t, *J* = 1.4 Hz, **H6a**), 4.57 (1H, t, *J* = 1.0 Hz, **H6b**), 4.12 (1H, ddd, *J* = 13.0, 10.5, 8.0 Hz, **H2a**), 4.05 (1H, ddd, *J* = 13.0, 10.7, 5.7 Hz, **H2b**), 3.25 (1H, d, *J* = 15.2 Hz, **H4a**), 3.23 – 3.19 (1H, m, **H1a**), 3.09 (1H, d, *J* = 15.2 Hz, **H4b**), 2.17 (1H, ddd, *J* = 12.3, 10.5, 5.6 Hz, **H1b**), 1.49 (3H, s, **H7**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 193.1 (**C8**), 138.4 (**C9**), 134.5 (**C5**), 133.6 (**C10**), 129.3 (**C12**), 128.8 (**C11**), 116.2 (**C6**), 92.9 (**C3**), 60.8 (**C2**), 42.5 (**C4**), 23.1 (**C7**), 15.1 (**C1**).

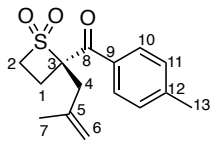
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}O_3S$ 265.0893; found 265.0885.

IR: ν_{max} (neat/cm^{-1}): 3026 (C–H), 2972 (C–H), 2922 (C–H), 1675 (C=O), 1317 (S=O), 1131 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 224 nm, 30.0 ºC) t_R = 13.8 min (minor), 16.9 min (major). 55% ee.

$\boldsymbol{[\alpha]_D^{20}}$ = +81.3 (*c* = 0.08, $CHCl_3$).

(2*S*)-[2-(2-Methylallyl)-1,1-dioxo-thietan-2-yl]-(*p*-tolyl)-methanone (329)



329

A vial was charged with substrate **304** (10 mg, 0.03 mmol), $Pd_2(dba)_3$ (1.4 mg, 0.002 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (3.3 mg, 0.004 mmol) and 1,4-dioxane (1 mL). The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 9:1 hexane:EtOAc] afforded **329** (6 mg, 70%) as a yellow solid. $\boldsymbol{R_f}$ = 0.59 [2:1 petrol:EtOAc]. **mp**: 67 – 68 ºC.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.3 Hz, **H10**), 7.30 (2H, d, *J* = 8.0 Hz, **H11**), 4.80 (1H, t, *J* = 1.4 Hz, **H6a**), 4.59 (1H, br s, **H6b**), 4.10 (1H, ddd, *J* = 13.0, 10.4, 8.1 Hz, **H2a**), 4.02 (1H, ddd, *J* = 12.9, 10.5, 5.6 Hz, **H2b**), 3.26 (1H, d, *J* = 15.2 Hz, **H4a**), 3.20 (1H, m, **H1a**), 3.08 (1H, d, *J* = 15.2 Hz, **H4b**), 2.42 (3H, s, **H13**), 2.16 (1H, ddd, *J* = 12.4, 10.4, 5.6 Hz, **H1b**), 1.49 (3H, s, **H7**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 192.5 (**C8**), 144.7 (**C12**), 138.5 (**C5**), 131.9 (**C9**), 129.5 (**C11**), 129.5 (**C10**), 116.2 (**C6**), 92.9 (**C3**), 60.7 (**C2**), 43.3 (**C4**), 23.1 (**C7**), 21.7 (**C13**), 15.1 (**C1**).

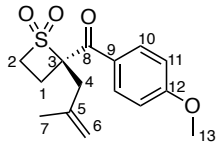
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{19}O_3S$ 279.1049; found 279.1043.

IR: ν_{max} (neat/cm^{-1}): 3032 (C–H), 2970 (C–H), 2924 (C–H), 1671 (C=O), 1315 (S=O), 1131 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 97/3, flow rate = 1.0 mL/min, λ = 224 nm, 30.0 ºC) t_R = 17.7 min (minor), 24.0 min (major). 53% ee.

$\boldsymbol{[\alpha]_D^{22}}$ = +75.0 (*c* = 0.04, $CHCl_3$).

(2*S*)-[2-(2-Methylallyl)-1,1-dioxo-thietan-2-yl]-(4-methoxyphenyl)-methanone (330)



330

A vial was charged with substrate **305** (10 mg, 0.03 mmol), $Pd_2(dba)_3$ (1.4 mg, 0.002 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (3.2 mg, 0.004 mmol) and 1,4-dioxane (1 mL). The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 9:1 hexane:EtOAc] afforded **330** (6 mg, 68%) as a yellow oil. $\boldsymbol{R_f}$ = 0.50 [2:1 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.93 (2H, d, *J* = 9.0 Hz, **H10**), 6.98 (2H, d, *J* = 9.0 Hz, **H11**), 4.81 (1H, t, *J* = 1.4 Hz, **H6a**), 4.61 (1H, br s, **H6b**), 4.09 (1H, ddd, *J* = 13.0, 10.4, 8.3 Hz, **H2a**), 3.99 (1H, ddd, *J* = 12.9, 10.6, 5.4 Hz, **H2b**), 3.88 (3H, s, **H13**), 3.25 (1H, d, *J* = 12.8 Hz, **H4a**), 3.19 – 3.12 (1H, m, **H1a**), 3.09 (1H, d, *J* = 14.8 Hz, **H4b**), 2.17 (1H, ddd, *J* = 12.4, 10.5, 5.4 Hz, **H1b**), 1.50 (3H, s, **H7**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 191.3 (**C8**), 164.1 (**C12**), 138.7 (**C5**), 131.9 (**C10**), 127.4 (**C9**), 116.5 (**C6**), 114.2 (**C11**), 92.9 (**C3**), 60.7 (**C2**), 55.7 (**C13**), 43.1 (**C4**), 23.2 (**C7**), 15.3 (**C1**).

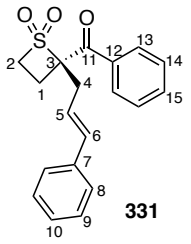
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{19}O_4S$ 295.0999; found 295.0998.

IR: ν_{max} (neat/cm^{-1}): 3076 (C–H), 2970 (C–H), 2842 (C–H), 1665 (C=O), 1310 (S=O), 1129 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 97/3, flow rate = 1.0 mL/min, λ = 224 nm, 30.0 ºC) t_R = 32.7 min (minor), 43.5 min (major). 52% ee.

$\boldsymbol{[\alpha]_D^{22}}$ = –50.0 (*c* = 0.01, $CHCl_3$).

(2*S*)-[2-[(*E*)-Cinnamyl]-1,1-dioxo-thietan-2-yl]-phenyl-methanone (331)



331

A vial was charged with substrate **302** (20 mg, 0.05 mmol), $Pd_2(dba)_3$ (2.5 mg, 0.003 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (5.7 mg, 0.007 mmol) and 1,4-dioxane (1 mL). The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 5:1 hexane:EtOAc] afforded **331** (10 mg, 57%) as a colourless oil. $\boldsymbol{R_f}$ = 0.50 [2:1 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.02 – 7.98 (2H, m, **H13**), 7.64 (1H, tt, *J* = 7.3, 1.3 Hz, **H15**), 7.57 – 7.52 (2H, m, **H14**), 7.30 – 7.20 (5H, m, **H8**, **H9** and **H10**), 6.33 (1H, d, *J* = 15.8 Hz, **H6**), 5.86 – 5.78 (1H, m, **H5**), 4.15 – 4.07 (1H, m, **H2a**), 4.00 (1H, ddd, *J* = 12.9, 10.7, 4.6 Hz, **H2b**), 3.31 (1H, dd, *J* = 14.6, 7.1 Hz, **H4a**), 3.12 (1H, dd, *J* = 14.4, 1.2 Hz, **H4b**), 3.10 – 3.02 (1H, m, **H1a**), 2.15 (1H, ddd, *J* = 12.5, 10.4, 4.6 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 192.4 (**C11**), 136.2 (**C12**), 136.0 (**C5**), 134.1 (**C7**), 134.0 (**C13**), 129.5 (**C15**), 129.1 (**C14**), 128.7 (**C8**), 128.2 (**C9**), 126.5 (**C10**), 120.1 (**C6**), 93.0 (**C3**), 60.3 (**C2**), 39.0 (**C4**), 15.4 (**C1**).

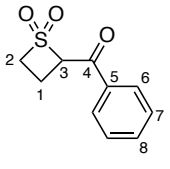
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{19}O_3S$ 327.1049; found 327.1059.

IR: ν_{max} (neat/cm^{-1}): 3058 (C–H), 3028 (C–H), 2965 (C–H), 1675 (C=O), 1315 (S=O), 1131 (S=O).

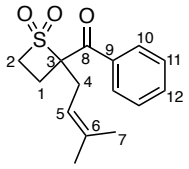
Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 250 nm, 30.0 ºC) t_R = 45.8 min (minor), 57.3 min (major). 52% ee.

$\boldsymbol{[\alpha]_D^{20}}$ = –66.7 (*c* = 0.09, $CHCl_3$).

(1,1-Dioxothietan-2-yl)-phenyl-methanone (294) and **[2-(3-Methylbut-2-enyl)-1,1-dioxo-thietan-2-yl]-phenyl-methanone (332)**



294



332

A vial was charged with substrate **303** (40 mg, 0.12 mmol), $Pd_2(dba)_3$ (5.6 mg, 0.006 mmol) and (*S*,*S*)-ANDEN Trost ligand **L4** (5.7 mg, 0.016 mmol) and 1,4-dioxane (3 mL). The reaction mixture was stirred at room temperature for 4 days. The mixture was concentrated under reduced pressure. Purification by column chromatography [SiO_2; 5:1 hexane:EtOAc] afforded a mixture of starting material **303** and non-alkylated product **294** in a 1:1.7 ratio, corresponding to starting material **303** (15 mg, 39%) and non-alkylated product **294** (15 mg, 60%) as a colourless solid.

294: $\boldsymbol{R_f}$ = 0.28 [2:1 petrol:EtOAc]. **mp**: 70 – 72 ºC.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.09 – 8.04 (2H, m, **H6**), 7.68 (1H, tt, *J* = 7.4, 1.9 Hz, **H8**), 7.59 – 7.52 (2H, m, **H7**), 5.99 – 5.92 (1H, m, **H3**), 4.33 – 4.12 (2H, m, **H2**), 3.07 – 2.93 (1H, m, **H1a**), 2.38 – 2.24 (1H, m, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 187.1 (**C4**), 135.4 (**C5**), 134.7 (**C6**), 129.2 (**C8**), 128.7 (**C7**), 82.3 (**C3**), 64.2 (**C2**), 7.7 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{11}O_3S$ 211.0423; found 211.0419.

IR: ν_{max} (neat/cm^{-1}): 3065 (C–H), 3047 (C–H), 2968 (C–H), 1677 (C=O), 1313 (S=O), 1123 (S=O).

Instead, **332** was prepared in racemic form. A vial was charged with substrate **303** (10 mg, 0.03 mmol), $Pd(PPh_3)_4$ (3.5 mg, 0.003 mmol) and 1,4-dioxane (2 mL). The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure and purification by flash column chromatography [SiO_2; 5:1 hexane:EtOAc] afforded **332** (7 mg, 84%) as a colourless oil. $\boldsymbol{R_f}$ = 0.59 [2:1 petrol:EtOAc].

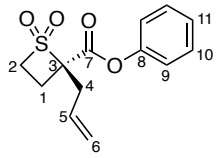
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.97 – 7.95 (2H, m, **H10**), 7.60 (1H, tt, *J* = 7.4, 1.3 Hz, **H12**), 7.53 – 7.48 (2H, m, **H11**), 4.82 – 4.76 (1H, m, **H5**), 4.08 (1H, ddd, *J* = 12.9, 10.5, 8.9 Hz, **H2a**), 3.97 (1H, ddd, *J* = 12.9, 10.7, 4.5 Hz, **H2b**), 3.13 (1H, dd, *J* = 14.8, 7.5 Hz, **H4a**), 3.07 – 2.96 (2H, m, **H1a** and **H4b**), 2.02 (1H, ddd, *J* = 12.4, 10.6, 4.5 Hz, **H1b**), 1.61 (3H, d, *J* = 1.0 Hz, **H7a**), 1.35 (3H, s, **H7b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 192.7 (**C8**), 138.2 (**C9**), 134.2 (**C6**), 133.9 (**C10**), 129.3 (**C12**), 128.9 (**C11**), 114.5 (**C5**), 93.4 (**C3**), 60.1 (**C2**), 34.2 (**C4**), 26.0 and 17.9 (**C7**), 15.6 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{19}O_3S$ 279.1049; found 279.1040.

IR: ν_{max} (neat/cm^{-1}): 3026 (C–H), 2968 (C–H), 2916 (C–H), 1675 (C=O), 1312 (S=O), 1129 (S=O).

(2*S*)-Phenyl 2-allyl-1,1-dioxo-thietane-2-carboxylate (270)



270

A vial was charged with substrate **268** (50 mg, 0.16 mmol), $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (9.0 mg, 0.010 mmol) and 1,4-dioxane (4 mL). The reaction mixture was stirred at room temperature for 6 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 5:1 hexane:EtOAc] afforded **270** (38 mg, 90%) as a colourless solid. $\boldsymbol{R}_\mathbf{f}$ = 0.51 [2:1 petrol:EtOAc]. **mp**: 58 – 60 ºC.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.43 – 7.37 (2H, m, **H10**), 7.28 (1H, tt, *J* = 7.4, 1.1 Hz, **H11**), 7.16 – 7.12 (2H, m, **H9**), 5.77 (1H, ddt, *J* = 17.1, 10.1, 7.0 Hz, **H5**), 5.36 – 5.27 (2H, m, **H6**), 4.22 (1H, ddd, *J* = 13.1, 10.7, 7.1 Hz, **H2a**), 4.12 (1H, ddd, *J* = 13.0, 10.5, 6.2 Hz, **H2b**), 3.31 (1H, dd, *J* = 14.4, 6.8 Hz, **H4a**), 2.95 (1H, ddt, *J* = 14.4, 7.2, 1.1 Hz, **H4b**), 2.92 – 2.84 (1H, m, **H1a**), 2.13 (1H, ddd, *J* = 17.6, 10.5, 7.2 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 165.8 (**C7**), 150.6 (**C8**), 129.8 (**C10**), 129.6 (**C5**), 126.7 (**C11**), 121.5 (**C9**), 121.0 (**C6**), 89.6 (**C3**), 63.2 (**C2**), 37.2 (**C4**), 16.8 (**C1**).

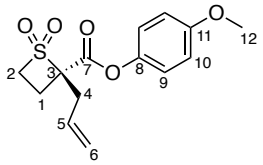
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{15}O_4S$ 267.0686; found 267.0686.

IR: ν_{max} (neat/cm^{-1}): 3054 (C–H), 2970 (C–H), 1751 (C=O), 1315 (S=O), 1138 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 214 nm, 30.0 ºC) t_R = 18.0 min (major), 21.0 min (minor). 94% ee.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +25.8 (*c* = 0.31, $CHCl_3$).

(2*S*)-(4-Methoxyphenyl) 2-allyl-1,1-dioxo-thietane-2-carboxylate (333)



333

A vial was charged with substrate **307** (50 mg, 0.15 mmol), $Pd_2(dba)_3$ (3.4 mg, 0.004 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (7.9 mg, 0.010 mmol) and 1,4-dioxane (4 mL). The reaction mixture was stirred at room temperature for 6 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 12:1 hexane:EtOAc] afforded **333** (20 mg, 45%) as a colourless solid. $\boldsymbol{R_f}$ = 0.49 [3:2 petrol:EtOAc]. **mp**: 50 – 51 °C.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.05 (2H, d, *J* = 9.1 Hz, **H9**), 6.89 (2H, d, *J* = 9.2 Hz, **H10**), 5.75 (1H, ddt, *J* = 17.0, 10.1, 7.0 Hz, **H5**), 5.35 – 5.25 (2H, m, **H6**), 4.21 (1H, ddd, *J* = 13.3, 10.8, 7.2 Hz, **H2a**), 4.10 (1H, ddd, *J* = 13.1, 10.5, 6.2 Hz, **H2b**), 3.80 (3H, s, **H12**), 3.29 (1H, dd, *J* = 14.4, 6.9 Hz, **H4a**), 2.93 (1H, ddt, *J* = 14.3, 7.2, 1.1 Hz, **H4b**), 2.87 (1H, ddd, *J* = 16.9, 10.8, 6.1 Hz, **H1a**), 2.12 (1H, ddd, *J* = 17.6, 10.4, 7.1 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 166.1 (**C7**), 157.9 (**C11**), 144.1 (**C8**), 129.7 (**C5**), 122.3 (**C9**), 120.9 (**C6**), 114.7 (**C10**), 89.6 (**C3**), 63.2 (**C2**), 55.8 (**C12**), 37.2 (**C4**), 16.8 (**C1**).

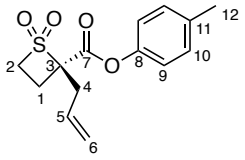
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}O_5S$ 297.0791; found 297.0803.

IR: ν_{max} (neat/cm^{-1}): 3006 (C–H), 2957 (C–H), 1750 (C=O), 1325 (S=O), 1190 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 90/10, flow rate = 1.0 mL/min, λ = 230 nm, 30.0 ºC) t_R = 18.5 min (major), 25.0 min (minor). 93% ee.

$[\alpha]_D^{20}$ = –12.7 (*c* = 0.06, $CHCl_3$).

(2*S*)-*p*-Tolyl 2-allyl-1,1-dioxo-thietane-2-carboxylate (334)



334

A vial was charged with substrate **308** (50 mg, 0.15 mmol), $Pd_2(dba)_3$ (3.5 mg, 0.004 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (7.9 mg, 0.010 mmol) and 1,4-dioxane (4 mL). The reaction mixture was stirred at room temperature for 6 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 5:1 hexane:EtOAc] afforded **334** (38 mg, 90%) as a colourless solid. R_f = 0.54 [3:2 petrol:EtOAc]. **mp**: 83 – 85 ºC.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.21 – 7.17 (2H, m, **H10**), 7.01 (2H, d, *J* = 8.5 Hz, **H9**), 5.76 (1H, ddt, *J* = 17.1, 10.0, 7.0 Hz, **H5**), 5.35 – 5.26 (2H, m, **H6**), 4.21 (1H, ddd, *J* = 13.0, 10.6, 7.1 Hz, **H2a**), 4.10 (1H, ddd, *J* = 13.2, 10.8, 6.4 Hz, **H2b**), 3.30 (1H, dd, *J* = 14.3, 6.8 Hz, **H4a**), 2.94 (1H, ddt, *J* = 14.4, 7.2, 1.0 Hz, **H4b**), 2.87 (1H, ddd, *J* = 17.0, 10.9, 6.2 Hz, **H1a**), 2.35 (3H, s, **H12**), 2.12 (1H, ddd, *J* = 17.5, 10.5, 7.2 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 166.0 (**C7**), 148.4 (**C8**), 136.4 (**C11**), 130.2 (**C10**), 129.7 (**C5**), 121.1 (**C6**), 120.9 (**C9**), 89.6 (**C3**), 63.2 (**C2**), 37.2 (**C4**), 21.1 (**C12**), 16.8 (**C1**).

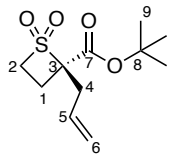
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}O_4S$ 281.0842; found 281.0849.

IR: ν_{max} (neat/cm^{-1}): 3034 (C–H), 2965 (C–H), 2927 (C–H), 1746 (C=O), 1321 (S=O), 1190 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 234 nm, 30.0 ºC) t_R = 16.1 min (major), 24.2 min (minor). 92% ee.

$[\alpha]_D^{20}$ = +13.7 (*c* = 0.31, $CHCl_3$).

(2*S*)-*tert*-Butyl 2-allyl-1,1-dioxo-thietane-2-carboxylate (335)



335

A vial was charged with substrate **309** (50 mg, 0.17 mmol), $Pd_2(dba)_3$ (7.4 mg, 0.009 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (17.8 mg, 0.020 mmol) and 1,4-dioxane (4 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 9:1 hexane:EtOAc] afforded **335** (25 mg, 60%) as a colourless solid.

*Scale Up Procedure for **335**.* To $Pd_2(dba)_3$ (798 mg, 0.871 mmol) and (*S*,*S*)-ANDEN Trost ligand **L4** (1.84 g, 2.26 mmol) was added 1,4-dioxane (435 mL) and the mixture was stirred for 30 min. A solution of substrate **309** (5.05 g, 17.41 mmol) in 1,4-dioxane (10 mL) was added and the mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure and purification by flash chromatography [SiO_2; 49:1 – 19:1 – 9:1 hexane:EtOAc] afforded **335** (3.70 g, 86%) as a colourless solid. R_f = 0.62 [2:1 petrol:EtOAc]. **mp**: 56 – 57 ºC.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.68 – 5.57 (1H, m, **H5**), 5.24 – 5.16 (2H, m, **H6**), 4.07 (1H, ddd, *J* = 13.0, 10.7, 7.0 Hz, **H2a**), 3.99 (1H, ddd, *J* = 13.0, 10.4, 6.4 Hz, **H2b**), 3.06 (1H, dd, *J* = 14.2, 6.6 Hz, **H4a**), 2.80 – 2.67 (2H, m, **H1a** and **H4b**), 1.95 (1H, ddd, *J* = 17.4, 10.4, 7.0 Hz, **H1b**), 1.52 (9H, s, **H9**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 165.4 (**C7**), 130.0 (**C5**), 120.3 (**C6**), 90.1 (**C3**), 84.1 (**C8**), 62.6 (**C2**), 37.4 (**C4**), 28.0 (**C9**), 16.5 (**C1**).

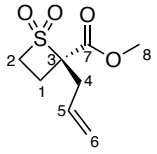
HRMS: (APCI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{11}H_{18}O_4SNa$ 269.0818; found 269.0818.

IR: ν_{max} (neat/cm^{-1}): 2980 (C–H), 2935 (C–H), 1727 (C=O), 1321 (S=O), 1148 (S=O).

Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 220 nm, 30.0 ºC) t_R = 6.6 min (minor), 7.5 min (major). 96% ee.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +77.8 (*c* = 0.09, $CHCl_3$).

(2*S*)-Methyl 2-allyl-1,1-dioxo-thietane-2-carboxylate (336)



336

A vial was charged with substrate **310** (20 mg, 0.08 mmol), $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (8.1 mg, 0.011 mmol) and 1,4-dioxane (2 mL). The reaction mixture was stirred at room temperature for 6 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 10:1 hexane:EtOAc] afforded **336** (14 mg, 85%) as a colourless oil. $\boldsymbol{R_f}$ = 0.45 [2:1 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.68 – 5.56 (1H, m, **H5**), 5.24 – 5.17 (2H, m, **H6**), 4.12 (1H, ddd, *J* = 13.0, 10.8, 7.2 Hz, **H4a**), 4.04 (1H, ddd, *J* = 13.0, 10.4, 6.4 Hz, **H4b**), 3.86 (3H, s, **H8**), 3.10 (1H, dd, *J* = 14.3, 6.5 Hz, **H2a**), 2.84 – 2.72 (2H, m, **H1a** and **H2b**), 2.03 (1H, ddd, *J* = 12.3, 10.3, 7.1 Hz, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 167.1 (**C7**), 129.8 (**C5**), 120.7 (**C6**), 89.6 (**C3**), 62.8 (**C2**), 53.7 (**C8**), 37.1 (**C4**), 16.6 (**C1**).

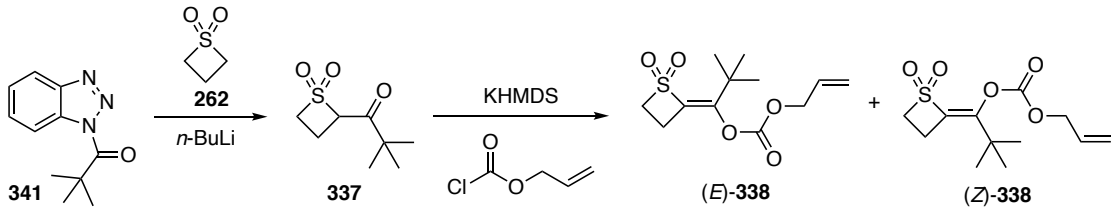
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_8H_{13}O_4S$ 205.0529; found 205.0520.

IR: ν_{max} (neat/cm^{-1}): 3082 (C–H), 2970 (C–H), 1735 (C=O), 1319 (S=O), 1127 (S=O).

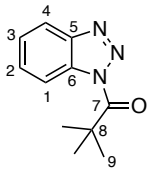
Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 214 nm, 30.0 ºC) t_R = 13.3 min (minor), 13.9 min (major). 85% ee.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +88.9 (*c* = 0.09, $CHCl_3$).

5.2.5 Enolate Geometry Study



1-(Benzotriazol-1-yl)-2,2-dimethyl-propan-1-one (341)



341

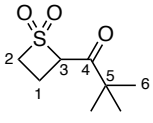
341 was prepared using a literature procedure.[133]

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.30 (1H, dt, *J* = 8.3, 0.9 Hz, **H1**), 8.11 (1H, dt, *J* = 8.2, 0.9 Hz, **H4**), 7.66 – 7.61 (1H, m, **H3**), 7.52 – 7.45 (1H, m, **H2**), 1.64 (9H, s, **H9**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 177.6 (**C7**), 145.1 (**C5**), 132.4 (**C6**), 130.4 (**C3**), 126.1 (**C2**), 120.1 (**C4**), 115.2 (**C1**), 42.7 (**C8**), 27.9 (**C9**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{14}N_3O$ 204.1131; found 204.1122.

1-(1,1-Dioxothietan-2-yl)-2,2-dimethyl-propan-1-one (337)



337

A solution of **262** (365 mg, 3.45 mmol) in THF (20 mL) was cooled to 0 ºC. *n*-BuLi (1.51 M in hexanes, 4.8 mL, 7.24 mmol) was added dropwise and the mixture was stirred at 0 ºC for 1 h. The mixture was cooled to –78 ºC. A solution of **341** (700 mg, 3.45 mmol) in THF (6 mL) was added dropwise and the mixture was stirred at –78 ºC for 3 h. The reaction was quenched at –78 ºC with aq. NH_4Cl (3 mL) and allowed to warm to room temperature. The mixture was diluted with water (10 mL), extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 7:1 – 4:1 hexane:EtOAc] afforded **337** (113 mg, 17%) as a colourless oil. $\boldsymbol{R_f}$ = 0.29 [2:1 petrol:EtOAc].

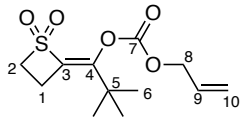
^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.56 – 5.51 (1H, m, **H3**), 4.19 – 4.08 (2H, m, **H2**), 2.73 – 2.61 (1H, m, **H1a**), 2.15 – 2.06 (1H, m, **H1b**), 1.22 (9H, s, **H6**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 203.1 (**C4**), 80.7 (**C3**), 64.5 (**C2**), 43.9 (**C5**), 25.7 (**C6**), 8.2 (**C1**).

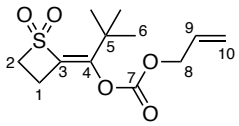
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_8H_{15}O_3S$ 191.0736; found 191.0733.

IR: ν_{max} (neat/cm^{-1}): 2972 (C–H), 2875 (C–H), 1709 (C=O), 1325 (S=O), 1138 (S=O).

Allyl [(1*Z*)-1-(1,1-dioxothietan-2-ylidene)-2,2-dimethyl-propyl] carbonate (*Z*-338) and **Allyl [(1*E*)-1-(1,1-dioxothietan-2-ylidene)-2,2-dimethyl-propyl] carbonate (*E*-338)**



(*Z*)-**338**



(*E*)-**338**

A solution of **337** (25 mg, 0.13 mmol) in THF (2 mL) was added to a solution of KHMDS (0.5 M in toluene, 0.36 mL, 0.18 mmol) in THF (1 mL), and the mixture was stirred at room temperature for 1 h. Allyl chloroformate (20 μL, 0.18 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched with aq. HCl (1N, 3 mL) and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with

brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 9:1 hexane:EtOAc] afforded (*Z*)-**338** (12 mg, 34%) as a colourless solid, and (*E*)-**338** (6 mg, 17%) as a colourless oil.

(*Z*)-338:

R_f = 0.29 [2:1 petrol:EtOAc]. **mp**: 61 – 63 ºC.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.97 (1H, ddt, *J* = 17.2, 10.4, 5.8 Hz, **H9**), 5.40 (1H, dq, *J* = 17.2, 1.4 Hz, **H10a**), 5.31 (1H, dq, *J* = 10.4, 1.2 Hz, **H10b**), 4.72 (2H, dt, *J* = 5.8, 1.3 Hz, **H8**), 4.02 – 3.96 (2H, m, **H2**), 3.04 – 2.99 (2H, m, **H1**), 1.22 (9H, s, **H6**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 156.6 (**C4**), 152.3 (**C7**), 142.9 (**C3**), 131.1 (**C9**), 119.7 (**C10**), 70.0 (**C8**), 62.4 (**C2**), 37.4 (**C5**), 27.6 (**C6**), 16.7 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{19}O_5S$ 275.0948; found 275.0954.

IR: ν_{max} (neat/cm^{-1}): 2978 (C–H), 1768 (C=O), 1313 (S=O), 1142 (S=O).

(*E*)-338:

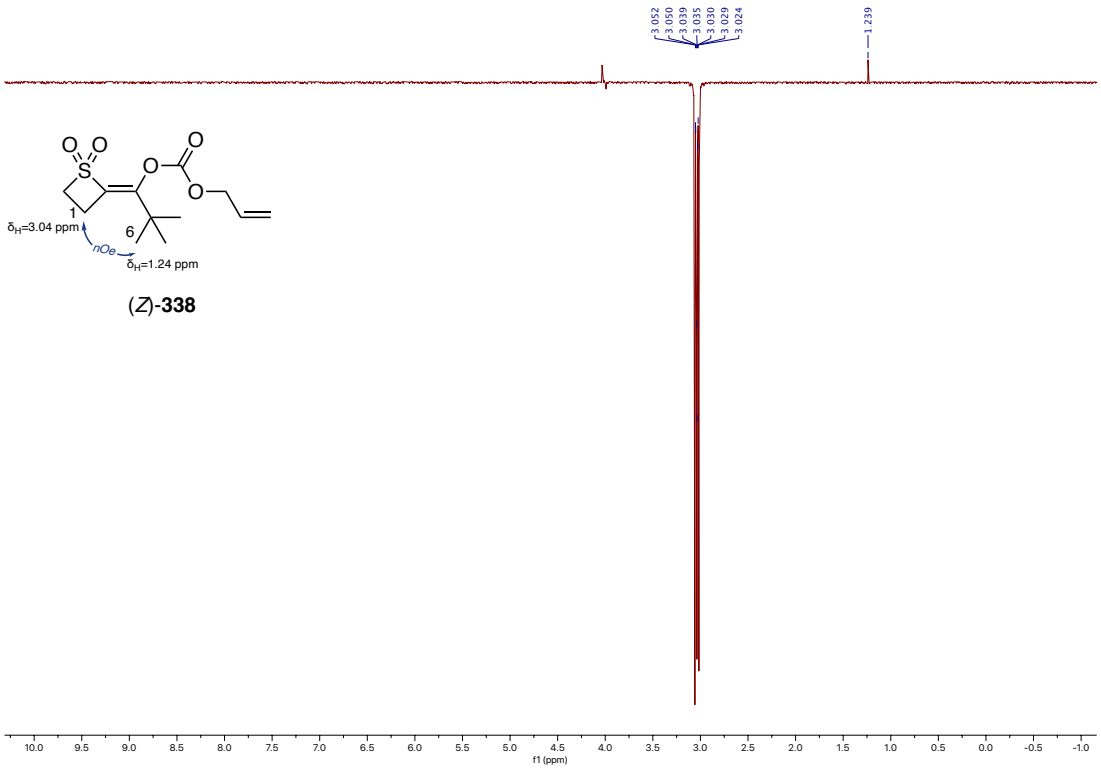
R_f = 0.62 [2:1 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.95 (1H, ddt, *J* = 17.2, 10.4, 5.9 Hz, **H9**), 5.41 (1H, dq, *J* = 17.2, 1.4 Hz, **H10a**), 5.34 (1H, dq, *J* = 10.4, 1.2 Hz, **H10b**), 4.70 (2H, dt, *J* = 5.8, 1.3 Hz, **H8**), 3.95 – 3.86 (2H, m, **H2**), 2.68 – 2.59 (2H, m, **H1**), 1.28 (9H, s, **H6**).

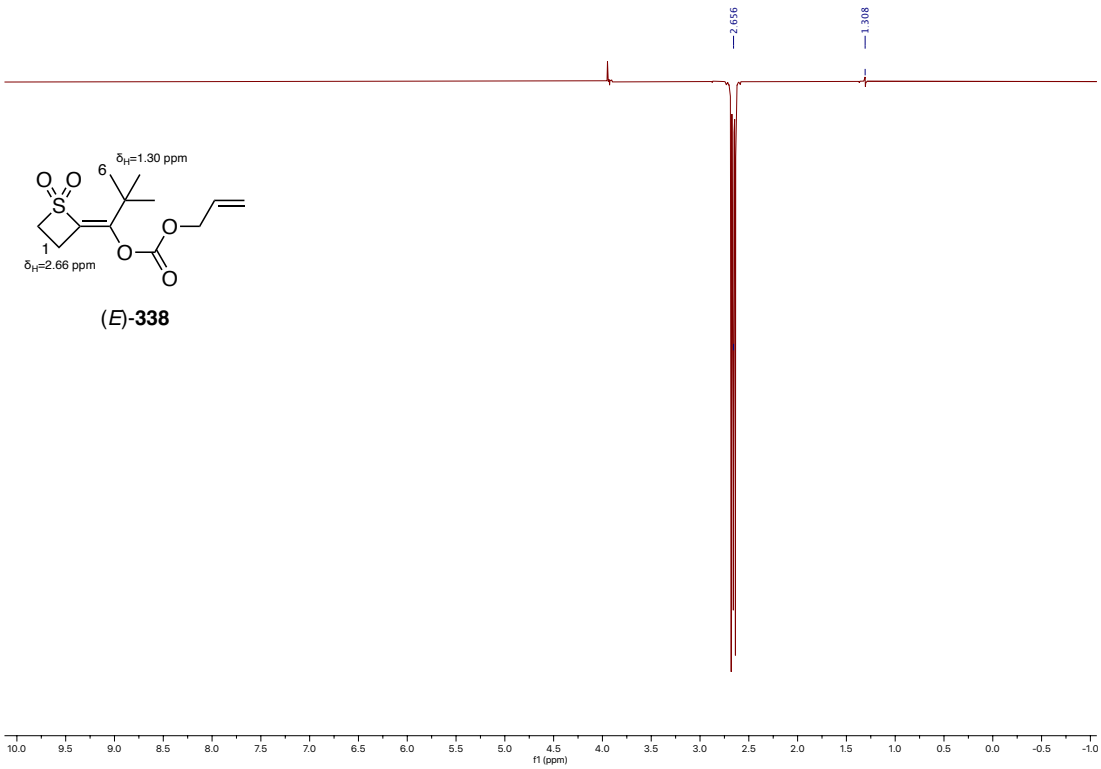
^{13}C NMR: (100 MHz, $CDCl_3$) δ 158.7 (**C4**), 150.8 (**C7**), 143.3 (**C3**), 130.9 (**C9**), 120.1 (**C10**), 69.7 (**C8**), 59.3 (**C2**), 37.6 (**C5**), 27.0 (**C6**), 14.3 (**C1**).

IR: ν_{max} (neat/cm^{-1}): 2970 (C–H), 1763 (C=O), 1317 (S=O), 1127 (S=O).

Selected 1D nOe enhancement was observed between H1 and H6 in (*Z*)-**338** and not in (*E*)-**338**.

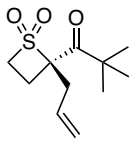

3.052
3.050
3.039
3.035
3.030
3.029
3.024
1.239
δH=3.04 ppm
nOe
δH=1.24 ppm
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

(*Z*)-**338**


2.656
1.308
δH=1.30 ppm
δH=2.66 ppm
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

(*E*)-**338**

(2*S*)-1-[2-Allyl-1,1-dioxo-thietan-2-yl]-2,2-dimethyl-propan-1-one (321)



321

A vial was charged with (*Z*)-**338** (20 mg, 0.073 mmol), $Pd_2(dba)_3$ (1.7 mg, 0.0018 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (3.8 mg, 0.047 mmol) and 1,4-dioxane (1.8 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 5:1 hexane:EtOAc] afforded **321** (12.0 mg, 71%) as a colourless oil. $\boldsymbol{R_f}$ = 0.34 [2:1 petrol: EtOAc].

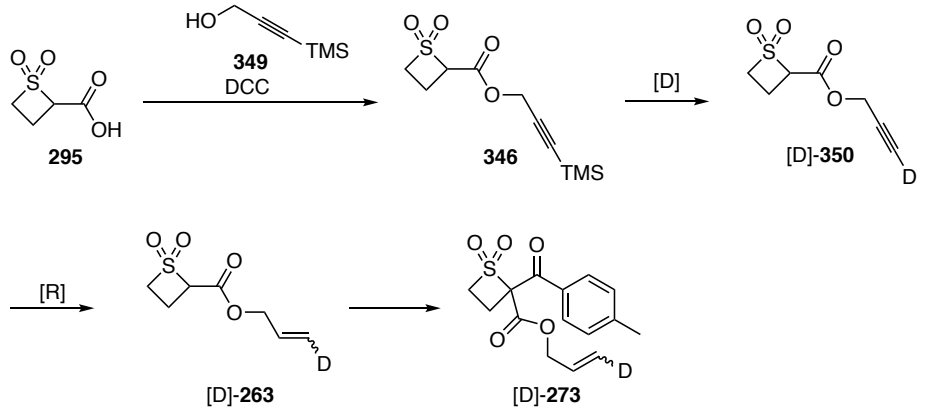
Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 220 nm, 30.0 ºC) t_R = 9.7 min (minor), 10.3 min (major). 88% ee.

A vial was charged with (*E*)-**338** (20 mg, 0.073 mmol), $Pd_2(dba)_3$ (1.7 mg, 0.0018 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (3.8 mg, 0.047 mmol) and 1,4-dioxane (1.8 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by flash chromatography [SiO_2; 5:1 hexane:EtOAc] afforded **321** (14.2 mg, 85%) as a colourless oil. $\boldsymbol{R_f}$ = 0.34 [2:1 petrol: EtOAc].

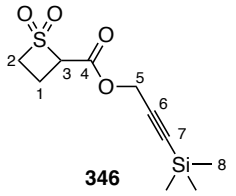
Chiral HPLC: (OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 220 nm, 30.0 ºC) t_R = 9.7 min (minor), 10.3 min (major). 76% ee.

5.2.6 Mechanistic Study

Crossover Study



3-Trimethylsilylprop-2-ynyl 1,1-dioxothietane-2-carboxylate (346)



A solution of **295** (1.0 g, 6.66 mmol), 3-(trimethylsilyl)propargyl alcohol **349** (1.97 mL, 13.3 mmol) and a few crystals of 4-dimethylaminopyridine in CH_2Cl_2 (15 mL) was cooled to 0 ºC. A solution of *N*,*N*'-dicyclohexylcarbodiimide (1.51 g, 7.32 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was allowed to warm to room temperature and stirred at ambient temperature for 18 h. The reaction mixture was filtered through Celite twice, then concentrated under reduced pressure. Purification using flash column chromatography [SiO_2; 10:1 – 4:1 hexane:EtOAc] afforded **346** (1.13 g, 65%) as a colourless solid. $\boldsymbol{R_f}$ = 0.18 [4:1 petrol:EtOAc]. **mp**: 86 – 87 ºC.

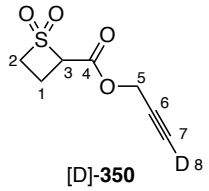
^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.14 –5.08 (1H, m, **H3**), 4.93 (1H, d, *J* = 15.6 Hz, **H5a**), 4.74 (1H, d, *J* = 15.6 Hz, **H5b**), 4.27 – 4.15 (2H, m, **H2**) 2.65 – 2.55 (1H, m, **H1a**), 2.38 – 2.28 (1H, m, **H1b**), 0.19 (9H, s, **H8**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 163.7 (**C4**), 97.7 (**C6**), 93.7 (**C7**), 79.6 (**C3**), 65.5 (**C2**), 54.8 (**C5**), 9.7 (**C1**), –0.3 (**C8**).

HRMS: (APCI-TOF) *m/z*: $[M–H]^-$ calcd for $C_{10}H_{15}O_4SiS$ 259.0466; found 259.0466.

IR: ν_{max} (neat/cm^{-1}): 2972 (C–H), 1735 (C=O), 1317 (S=O), 1127 (S=O).

[D]-Prop-2-ynyl 1,1-dioxothietane-2-carboxylate ([D]-350)



[D]-**350**

346 (400 mg, 1.54 mmol) was dissolved in THF (6 mL). Deuterium oxide (8 mL) was added, followed by tetrabutylammonium fluoride (1 M in THF, 1.70 mL, 1.70 mmol), and the reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with water, extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 5:1 hexane:EtOAc] afforded [D]-**350** (109 mg, 38%, 88% D) as a colourless oil. $\boldsymbol{R}_f$ = 0.22 [3:1 petrol:EtOAc].

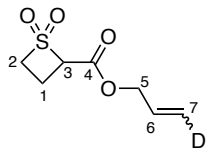
^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.13 – 5.08 (1H, m, **H3**), 4.91 (1H, d, *J* = 15.6 Hz, **H5a**), 4.78 (1H, d, *J* = 15.6 Hz, **H5b**), 4.27 – 4.16 (2H, m, **H2**), 2.66 – 2.57 (1H, m, **H1a**), 2.54 (0.12H, t, *J* = 2.4 Hz, **H8**), 2.39 – 2.29 (1H, m, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 163.7 (**C4**), 79.5 (**C3**), 65.5 (**C2**), 54.0 (**C5**), 9.7 (**C1**). **C6** and **C7** signals were not observed.

HRMS: (APCI-TOF) *m/z*: $[M–H]^-$ calcd for $C_7H_6DO_4S$ 188.0133; found 188.0149.

IR: ν_{max} (neat/cm^{-1}): 2970 (C–H), 1740 (C=O), 1317 (S=O), 1131 (S=O).

[D]-Allyl 1,1-dioxothietane-2-carboxylate ([D]-263)



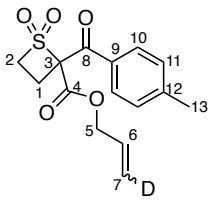
[D]-**263**

A suspension of [D]-**350** (100 mg, 0.53 mmol), $Pd/CaCO_3$ (10mg) and quinoline (125 μL, 1.06 mmol) in EtOAc (7 mL) was degassed with argon. The mixture was cooled to 0 ºC, and then stirred under a hydrogen atmosphere for 30 minutes. The suspension was filtered through a pad of celite, washed with aq. HCl (1 N, 5 mL), brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 4:1 hexane:EtOAc] afforded [D]-**263** (65 mg, 64%, 86% D) as an orange oil. $\boldsymbol{R_f}$ = 0.26 [3:1 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.99 – 5.88 (1H, m, **H6**), 5.42 – 5.35 (0.30H, m, **H7a**), 5.32 – 5.27 (0.84H, m, **H7b**), 5.12 – 5.06 (1H, m, **H3**), 4.80 – 4.69 (2H, m, **H5**), 4.25 – 4.14 (2H, m, **H2**), 2.66 – 2.54 (1H, m, **H1a**), 2.37 – 2.27 (1H, m, **H1b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 164.0 (**C4**), 131.0 (**C6**), 119.4 (t, *J* = 23.8 Hz, **C7**), 79.8 (**C3**), 67.3 (**C5**), 65.3 (**C2**), 9.7 (**C1**).

[D]-Allyl 2-(4-methylbenzoyl)-1,1-dioxo-thietane-2-carboxylate ([D]-273)



[D]-**273**

A solution of NaHMDS (1 M in THF, 0.35 mL, 0.35 mmol) in THF (5 mL) was cooled to 0 ºC. A solution of allyl ester [D]-**263** (60 mg, 0.31 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 ºC for 20 minutes. *p*-Toluoyl chloride (47 μL, 0.35 mmol) was added dropwise and the mixture stirred at 0 ºC for 3 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 15 mL).

The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 4:1 hexane:EtOAc] afforded [D]-**273** (61 mg, 63%, 86% D) as a colourless oil. $\boldsymbol{R_f}$ = 0.58 [3:1 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.89 (2H, dt, *J* = 8.4, 2.0 Hz, **H10**), 7.32 – 7.28 (2H, m, **H11**), 5.84 – 5.74 (1H, m, **H6**), 5.26 – 5.22 (0.23H, m, **H7a**), 5.22 – 5.18 (0.91H, m, **H7b**), 4.71 (2H, dddd, *J* = 18.8, 13.2, 5.6, 1.2 Hz, **H5**), 4.45 (1H, dt, *J* = 12.4, 10.4 Hz, **H2a**), 4.07 (1H, ddd, *J* = 12.4, 10.0, 3.2 Hz, **H2b**), 2.95 (1H, dt, *J* = 12.4, 10.4 Hz, **H1a**), 2.77 (1H, ddd, *J* = 12.4, 10.4, 3.2 Hz, **H1b**), 2.42 (3H, s, **H13**).

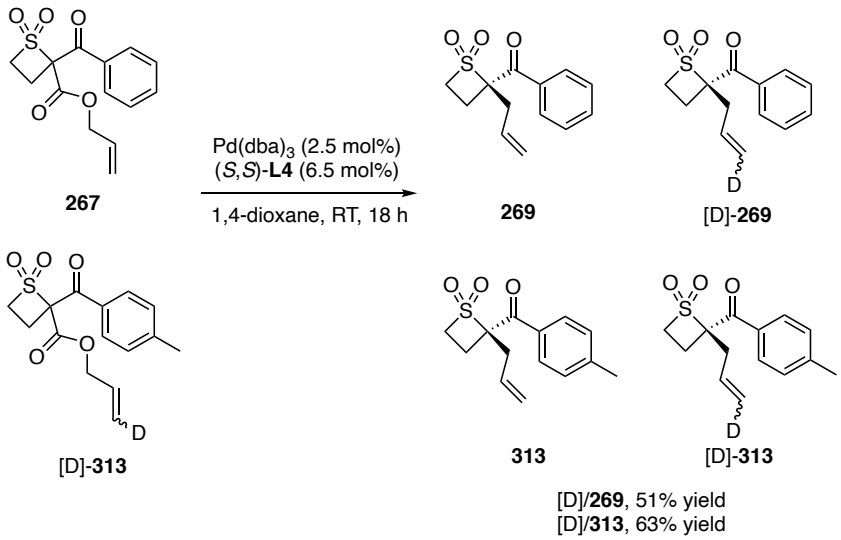
^{13}C NMR: (100 MHz, $CDCl_3$) δ 187.1 (**C8**), 164.6 (**C4**), 145.8 (**C12**), 132.3 (**C9**), 130.3 (**C6**), 129.9 (**C11**), 129.6 (**C10**), 119.7 (**C7**), 95.8 (**C3**), 67.9 (**C5**), 63.5 (**C2**), 22.0 (**C13**), 17.6 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{16}DO_5S$ 310.0854; found 310.0853.

IR: ν_{max} (neat/cm^{-1}): 3034 (C–H), 2959 (C-H), 1731 (C=O), 1677 (C=O), 1332 (S=O), 1140 (S=O).

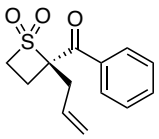
Crossover experiment:

A vial was charged with **267** (25 mg, 0.085 mmol), [D]-**273** (26 mg, 0.084 mmol), $Pd_2(dba)_3$ (3.5 mg, 0.004 mmol), (*S*,*S*)-ANDEN Trost ligand **L4** (8.9 mg, 0.011 mmol) and 1,4-dioxane (4 mL). The reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 7:1 hexane:EtOAc] afforded an inseparable mixture of [D]/**269** and [D]/**313** (29 mg) in a 1:1.2 ratio, corresponding to 12.8 mg, 51% yield of [D]/**269** and 16.2 mg, 63% yield of [D]/**313**.



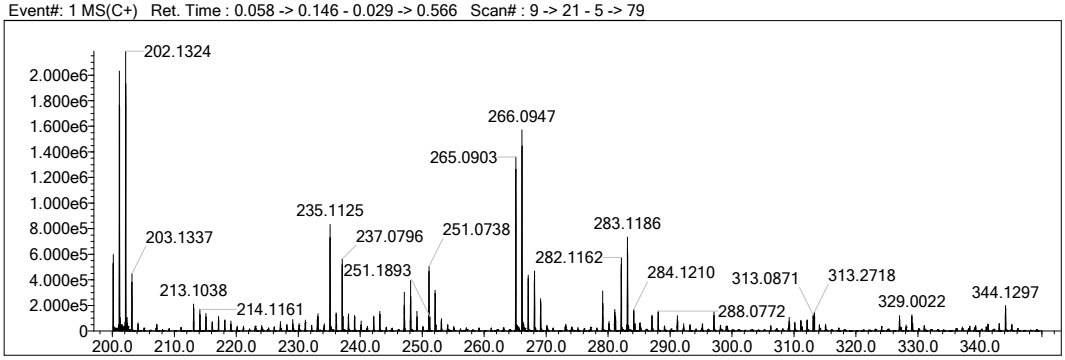
The presence of **269**, [D]-**269**, **313** and [D]-**313** was confirmed by high resolution mass spectrometry.

Enolate Crossover High Resolution Mass Spectrometry Data

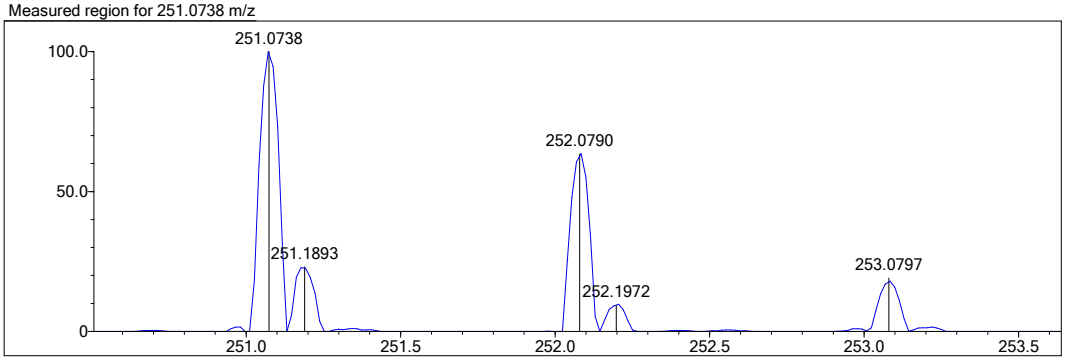


269

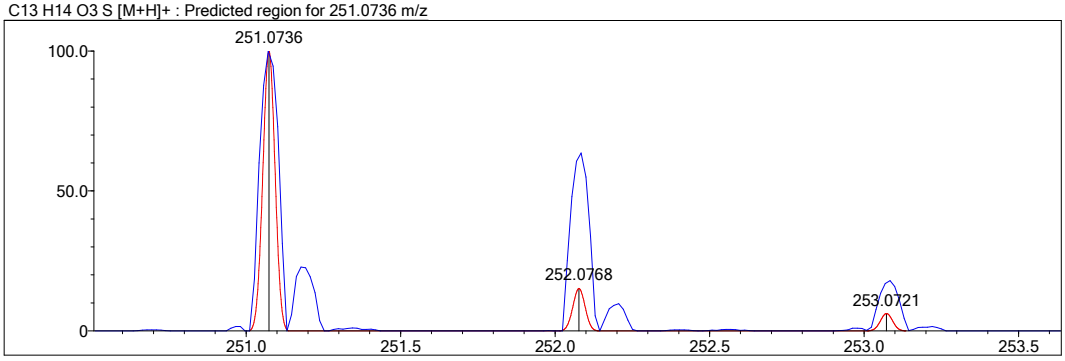
Event#: 1 MS(C+) Ret. Time : 0.058 -> 0.146 - 0.029 -> 0.566 Scan# : 9 -> 21 - 5 -> 79



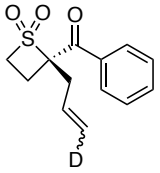
Measured region for 251.0738 m/z



C13 H14 O3 S [M+H]+ : Predicted region for 251.0736 m/z

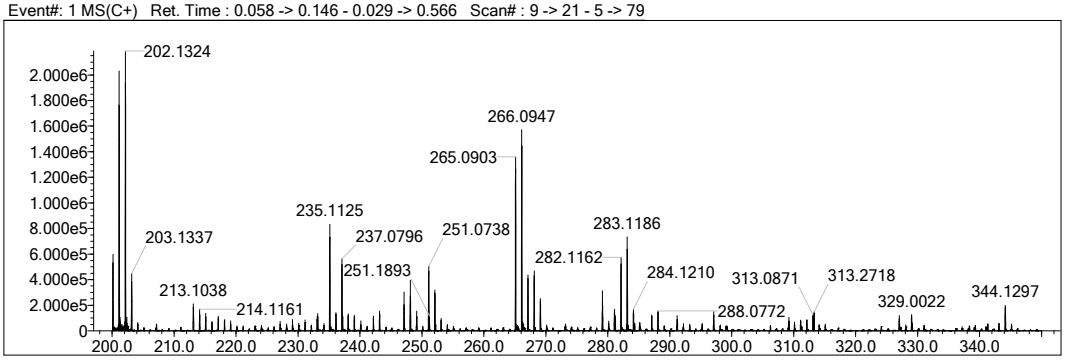


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	41.87	C13 H14 O3 S	[M+H]+	251.0738	251.0736	0.2	0.80	41.87	7.0

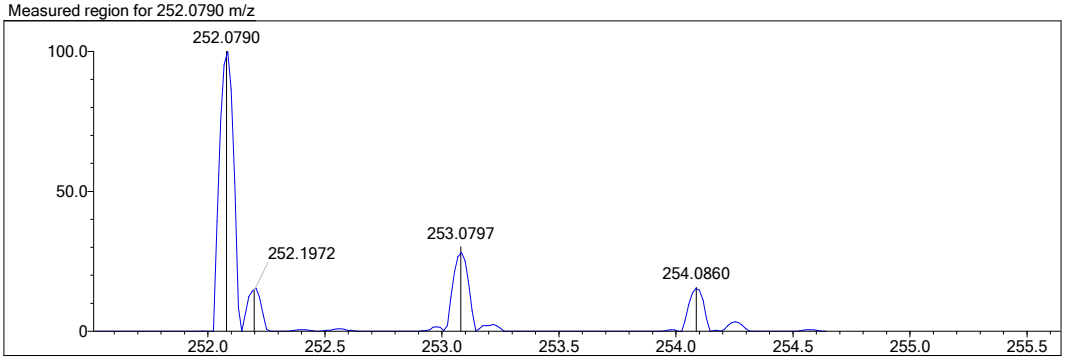


[D]-**269**

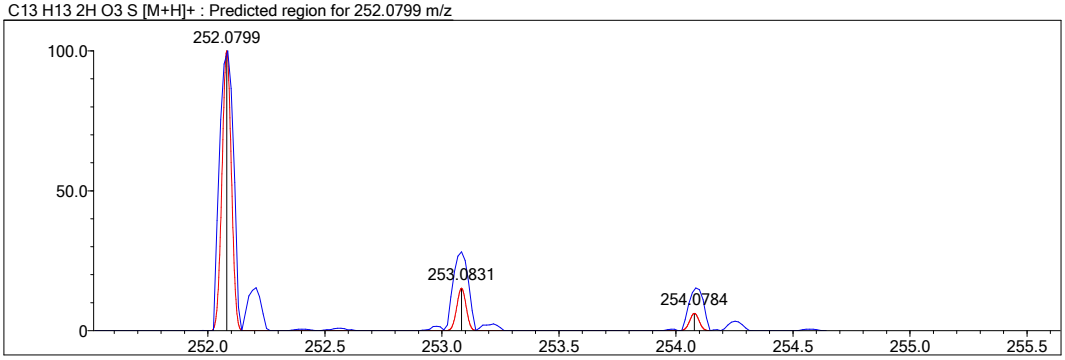
Event#: 1 MS(C+) Ret. Time : 0.058 -> 0.146 - 0.029 -> 0.566 Scan# : 9 -> 21 - 5 -> 79



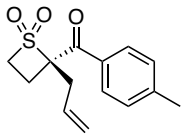
Measured region for 252.0790 m/z



C13 H13 2H O3 S [M+H]+ : Predicted region for 252.0799 m/z

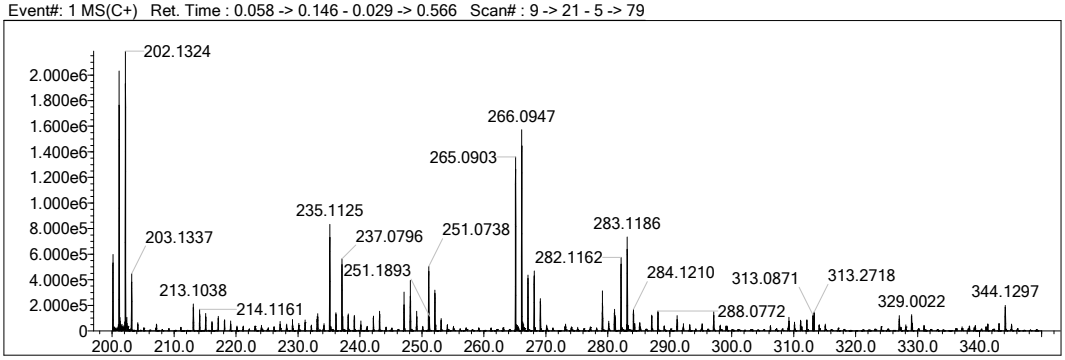


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	49.83	C13 H13 2H O3 S	[M+H]+	252.0790	252.0799	-0.9	-3.57	53.25	7.0

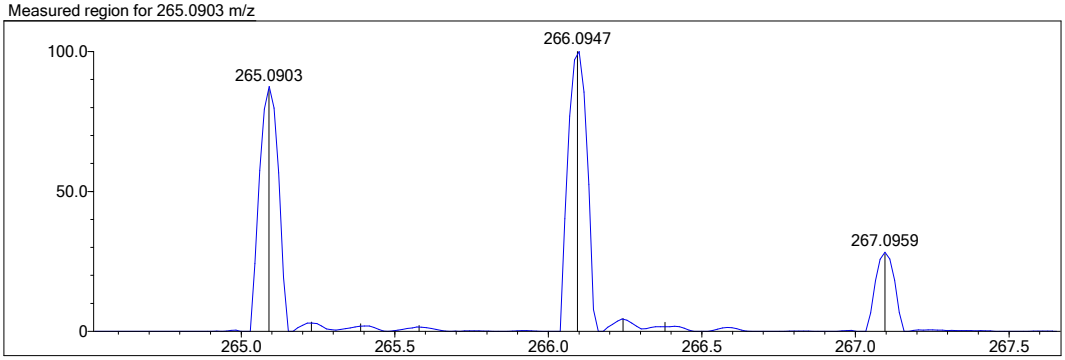


313

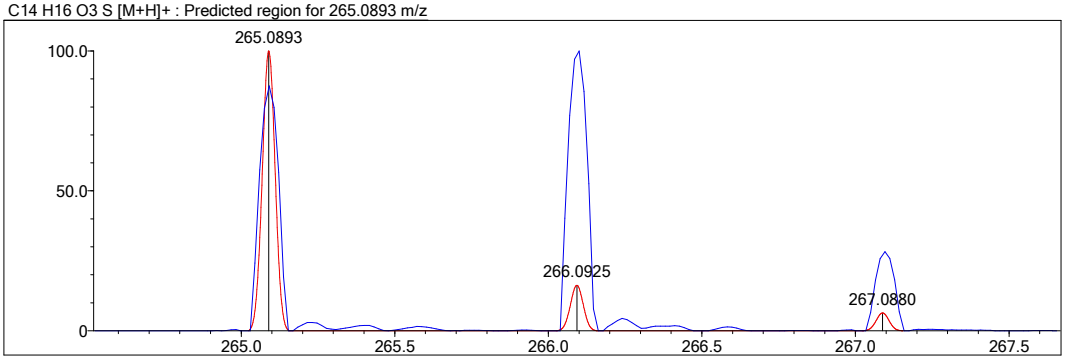
Event#: 1 MS(C+) Ret. Time : 0.058 -> 0.146 - 0.029 -> 0.566 Scan# : 9 -> 21 - 5 -> 79



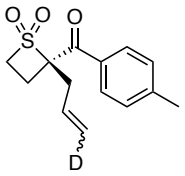
Measured region for 265.0903 m/z



C14 H16 O3 S [M+H]+ : Predicted region for 265.0893 m/z

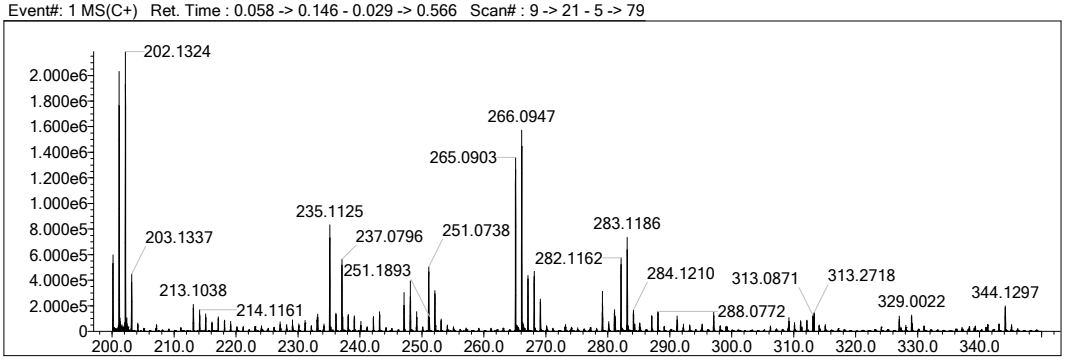


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	38.40	C14 H16 O3 S	[M+H]+	265.0903	265.0893	1.0	3.77	41.26	7.0

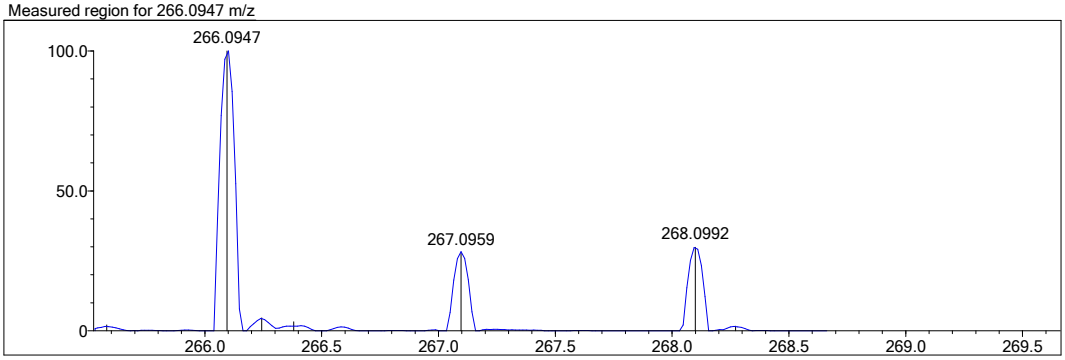


[D]-**313**

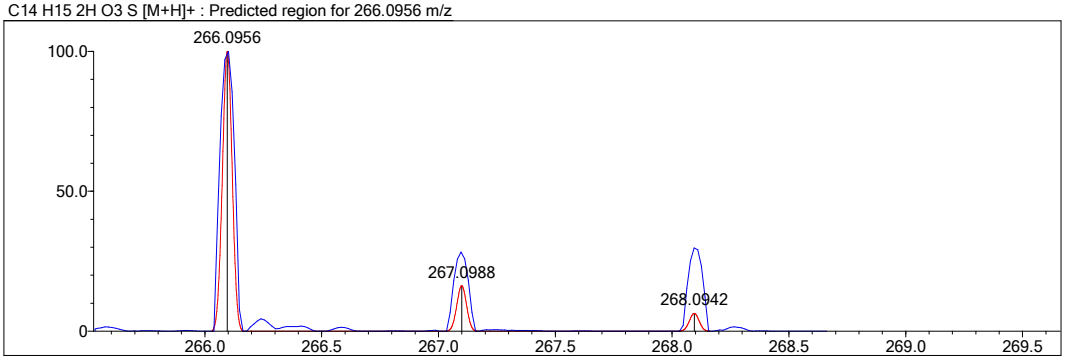
Event#: 1 MS(C+) Ret. Time : 0.058 -> 0.146 - 0.029 -> 0.566 Scan# : 9 -> 21 - 5 -> 79



Measured region for 266.0947 m/z

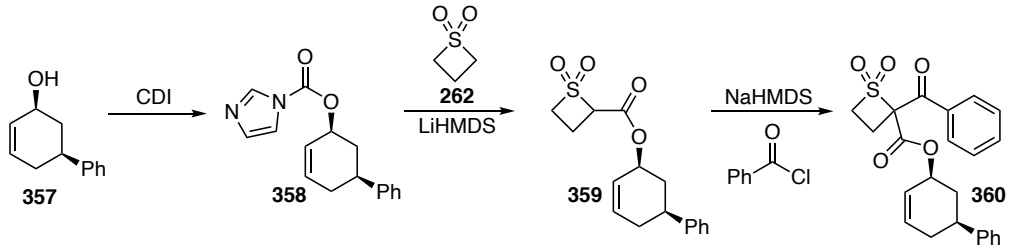


C14 H15 2H O3 S [M+H]+ : Predicted region for 266.0956 m/z



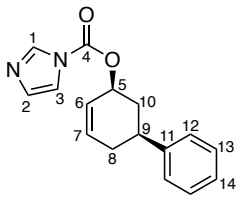
Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
2	45.06	C14 H15 2H O3 S	[M+H]+	266.0947	266.0956	-0.9	-3.38	47.91	7.0

Stereochemical Labelling



357 was prepared by a literature procedure.[136]

(*cis*-5-Phenylcyclohex-2-en-1-yl) imidazole-1-carboxylate (358)



358

357 (400 mg, 2.30 mmol) was dissolved in CH_2Cl_2 (20 mL). 1,1'-Carbonyldiimidazole (932 mg, 5.75 mmol) was added in portions. The suspension was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography [3:1 Petrol:EtOAc] gave **358** (536 mg, 90%) as a colourless solid. $\boldsymbol{R_f}$ = 0.24 [3:1 petrol:EtOAc]. **mp**: 104 – 106 ºC.

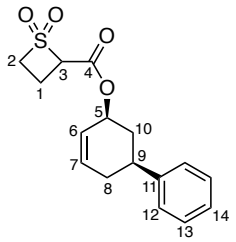
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.10 (1H, br s, **H1**), 7.40 (1H, t, *J* = 1.2 Hz, **H2**), 7.34 – 7.30 (2H, m, **H12**), 7.26 – 7.22 (3H, m, **H13** and **H14**), 7.07 (1H, dd, *J* = 2.0, 0.8 Hz, **H3**), 6.11 – 6.05 (1H, m, **H7**), 5.84 – 5.79 (1H, m, **H6**), 5.78 – 5.72 (1H, m, **H5**), 3.05 (1H, dddd, *J* = 12.9, 10.4, 5.1, 2.6 Hz, **H9**), 2.52 – 2.36 (2H, m, **H8a** and **H10a**), 2.35 – 2.23 (1H, m, **H8b**), 2.05 (1H, td, *J* = 12.6, 9.8 Hz, **H10b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 148.4 (**C4**), 144.5 (**C11**), 137.2 (**C1**), 132.4 (**C7**), 130.2 (**C3**), 128.8 (**C12**), 126.9 (**C13**), 126.9 (**C14**), 125.3 (**C6**), 117.1 (**C2**), 75.5 (**C5**), 38.7 (**C9**), 35.0 (**C10**), 33.2 (**C8**).

HRMS: Molecular ion not observed for $C_{16}H_{16}N_2O_2$.

IR: ν_{max} (neat/cm^{-1}): 3157 (C–H), 2950 (C–H), 2931 (C–H), 1741 (C=O).

(*cis*-5-Phenylcyclohex-2-en-1-yl) 1,1-dioxothietane-2-carboxylate (359)



359

A solution of LiHMDS (1 M in THF, 2.94 mL, 2.94 mmol) in THF (10 mL) was cooled to –78 ºC. A solution of **262** (148 mg, 1.40 mmol) in THF (3 mL) was added and the reaction mixture was stirred at –78 ºC for 30 minutes. A solution of **359** (400 mg, 1.50 mmol) in THF (3 mL) was added dropwise. The mixture was stirred at –78 ºC for 3 h, then allowed to warm to room temperature and stirred at ambient temperature for a further 1 h. The reaction was quenched with aq. HCl (1 N, 0.5 mL) and diluted with water (5 mL). The mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 10:1 hexane:EtOAc] afforded **359** (193 mg, 45%) as a colourless oil. $\boldsymbol{R_f}$ = 0.37 [2:1 petrol:EtOAc].

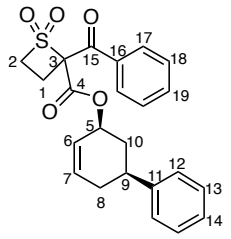
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (2H, m, **H12**), 7.24 – 7.19 (3H, m, **H13** and **H14**), 6.02 – 5.94 (1H, m, **H6**), 5.78 – 5.67 (2H, m, **H5** and **H7**), 5.10 – 5.01 (1H, m, **H3**), 4.27 – 4.12 (2H, m, **H2**), 3.04 – 2.92 (1H, m, **H9**), 2.64 – 2.53 (1H, m, **H1a**), 2.45 – 2.14 (4H, m, **H1b**, **H8** and **H10a**), 1.99 – 1.88 (1H, m, **H10b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 163.9 (**C4**), 144.8 (**C11**), 131.6 (**C6**), 131.2 (**C12**), 128.5 (**C13**), 126.7 (**C14**), 126.2 (**C7**), 80.0 (**C3**), 74.1 (**C5**), 65.4 (**C2**), 39.1 (**C9**), 35.0 (**C10**), 33.5 (**C8**), 9.7 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{18}O_4SNa$ 329.0818; found 329.0826.

IR: ν_{max} (neat/cm^{-1}): 3030 (C–H), 2963 (C–H), 2927 (C–H), 1731 (C=O), 1326 (S=O), 1190 (S=O).

(*cis*-5-Phenylcyclohex-2-en-1-yl) 2-benzoyl-1,1-dioxo-thietane-2-carboxylate (360)



360

A solution of NaHMDS (1 M in THF, 0.4 mL, 0.40 mmol) in THF (10 mL) was cooled to 0 ºC. A solution of **359** (100 mg, 0.33 mmol) in THF (2 mL) was added and the reaction mixture was stirred at 0 ºC for 15 minutes. Benzoyl chloride (56 µL, 0.40 mmol) was added dropwise and the mixture stirred at 0 °C for 3 h. The reaction was quenched with aq. HCl (1 N, 1 mL), allowed to warm to room temperature and diluted with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 7:1 hexane:EtOAc] afforded **360** (82 mg, 60%) as a colourless oil. $\boldsymbol{R}_\mathbf{f}$ = 0.58 [2:1 petrol:EtOAc].

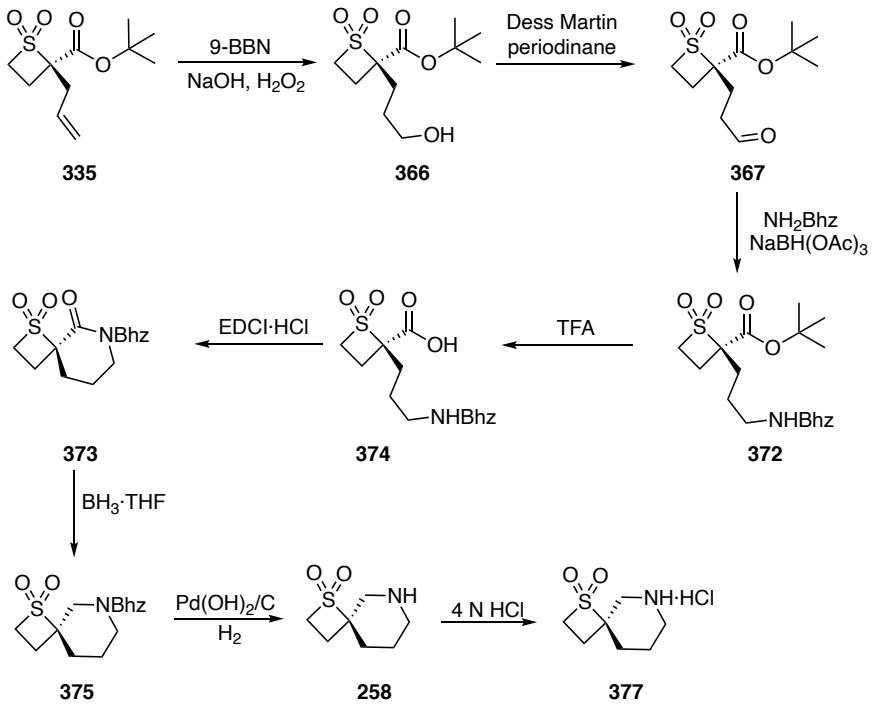
^{1}H NMR: (400 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers) δ 7.71 – 7.42 (5H, m, **H17**, **H18** and **H19**), 7.36 – 7.13 (5H, m, **H12**, **H13** and **H14**), 5.95 – 5.87 (1H, m, **H6**), 5.71 – 5.63 (1H, m, **H5**), 5.60 – 5.52 (1H, m, **H7**), 4.44 – 4.40 (1H, m, **H2a**), 4.09 – 4.05 (1H, m, **H2b**), 2.97 – 2.87 (2H, m, **H1a** and **H9**), 2.75 (1H, ddd, *J* = 12.5, 10.4, 3.5 Hz, **H1b**), 2.35 – 2.09 (3H, m, **H8** and **H10a**), 1.79 – 1.68 (1H, m, **H10b**).

^{13}C NMR: (100 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers) δ 187.9 and 187.8 (**C15**), 164.5 and 164.4 (**C4**), 144.6 and 144.6 (**C11**), 134.9 and 134.9 (**C16**), 134.4 and 134.4 (**C19**), 134.2 and 134.2 (**C6**), 129.7 and 129.7 (**C17**), 129.1 (**C18**), 128.8 and 128.8 (**C12**), 126.9 and 126.8 (**C14**), 126.8 and 126.7 (**C13**), 125.4 and 125.3 (**C7**), 97.4 and 96.0 (**C3**), 74.9 and 74.9 (**C5**), 63.7 and 63.6 (**C2**), 38.8 and 38.8 (**C9**), 34.6 and 34.6 (**C10**), 33.2 and 33.2 (**C8**), 17.5 and 17.4 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{23}H_{22}O_5SNa$ 433.1080; found 433.1078.

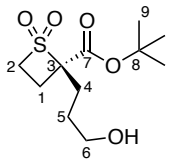
IR: ν_{max} (neat/cm^{-1}): 3054 (C–H), 3028 (C–H), 2953 (C–H), 1727 (C=O), 1682 (C=O), 1338 (S=O), 1138 (S=O).

5.2.7 Synthesis of Spirocycle 377



For the purposes of chiral HPLC analysis, **335** was made in racemic form from **309** using 10 mol% $Pd(PPh_3)_4$ in 1,4-dioxane and used in the synthesis of *rac*-**377**.

(2*S*)-*tert*-Butyl-2-(3-hydroxypropyl)-1,1-dioxo-thietane-2-carboxylate (366)



366

9-BBN monomer (0.5 M in THF, 150 mL, 75.0 mmol) was cooled to 0 ºC. A solution of **335** (3.69 g, 15.0 mmol) in THF (35 mL) was added dropwise and the mixture was stirred at 0 ºC for 30 min, the mixture was allowed to warm to room temperature and stirred at ambient temperature overnight. The mixture was cooled to 0 ºC and a solution of aq. NaOH (3 N, 35 mL) was added dropwise. The mixture was stirred at 0 ºC for 30 min, then H_2O_2 (30% w/w in H_2O, 35 mL) was added dropwise. The mixture was allowed to warm to room temperature and stirred at ambient temperature for 5 h. The

reaction was quenched slowly with aq. $Na_2S_2O_3$ (20 mL), diluted with water (500 mL), and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 4:1 – 2:1 hexane:EtOAc] afforded **366** (2.45 g, 62%) as an opaque oil. R_f = 0.51 [EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.08 (1H, ddd, *J* = 13.0, 10.6, 7.0 Hz, **H2a**), 4.00 (1H, ddd, *J* = 13.0, 10.4, 6.2 Hz, **H2b**), 3.76 – 3.60 (2H, m, **H6**), 2.75 (1H, ddd, *J* = 11.8, 10.7, 6.2 Hz, **H1a**), 2.39 (1H, ddd, *J* = 13.6, 11.2, 5.4 Hz, **H4a**), 2.14 (1H, ddd, *J* = 13.6, 11.2, 4.9 Hz, **H4b**), 1.95 (1H, ddd, *J* = 12.1, 10.4, 7.1 Hz, **H1b**), 1.70 – 1.61 (1H, m, **H5a**), 1.59 – 1.45 (1H, m, **H5b**), 1.52 (9H, s, **H9**).

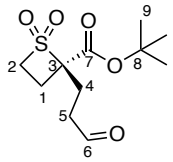
^{13}C NMR: (100 MHz, $CDCl_3$) δ 165.8 (**C7**), 91.2 (**C3**), 84.2 (**C8**), 62.6 (**C2**), 62.1 (**C6**), 29.4 (**C4**), 28.0 (**C9**), 27.4 (**C5**), 17.3 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{11}H_{20}O_5SNa$ 287.0924; found 287.0916.

IR: ν_{max} (neat/cm^{-1}): 3548 (O–H), 2935 (C–H), 2873 (C–H), 1723 (C=O), 1319 (S=O), 1151 (S=O).

$[\alpha]_D^{22}$ = +60.0 (*c* = 0.05, $CHCl_3$).

(2*S*)-*tert*-Butyl-1,1-dioxo-2-(3-oxopropyl)thietane-2-carboxylate (367)



367

To a solution of **366** (2.45 g, 9.28 mmol) in CH_2Cl_2 (180 mL) was added $NaHCO_3$ (7.80 g, 92.8 mmol), followed by Dess-Martin periodinane (7.14 g, 16.8 mmol) portionwise. The reaction mixture was stirred at room temperature for 3 h. The reaction was quenched with aq. $Na_2S_2O_3$ (10%, 100 mL) and stirred for 30 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with aq. $NaHCO_3$ (400 mL), brine (500 mL),

dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 3:1 – 2:1 hexane:EtOAc] afforded **367** (1.90 g, 78%) as a colourless solid. $\boldsymbol{R_f}$ = 0.20 [2:1 petrol:EtOAc]. **mp**: 56 – 57 ºC.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.78 (1H, t, *J* = 0.9 Hz, **H6**), 4.10 (1H, ddd, *J* = 13.0, 10.6, 7.4 Hz, **H2a**), 4.03 (1H, ddd, *J* = 12.9, 10.3, 6.0 Hz, **H2b**), 2.73 (1H, ddd, *J* = 12.1, 10.6, 6.0 Hz, **H1a**), 2.61 – 2.54 (3H, m, **H4a** and **H5**), 2.48 – 2.41 (1H, m, **H4b**), 1.92 (1H, ddd, *J* = 12.1, 10.3, 7.3 Hz, **H1b**), 1.53 (9H, s, **H9**).

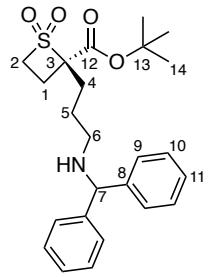
^{13}C NMR: (100 MHz, $CDCl_3$) δ 199.5 (**C6**), 165.3 (**C7**), 90.3 (**C3**), 84.7 (**C8**), 62.8 (**C2**), 39.0 (**C5**), 28.0 (**C9**), 25.5 (**C4**), 17.8 (**C1**).

HRMS: (APCI-TOF) m/z: $[M–H]^-$ calcd for $C_{11}H_{17}O_5S$ 261.0802; found 261.0808.

IR: ν_{max} (neat/cm^{-1}): 2980 (C–H), 2939 (C–H), 1720 (C=O), 1317 (S=O), 1131 (S=O).

$\boldsymbol{[\alpha]_D^{22}}$ = +66.7 (*c* = 0.45, $CHCl_3$).

(2*S*)- *tert*-Butyl-2-[3-(benzhydrylamino)propyl]-1,1-dioxo-thietane-2-carboxylate (372)



372

A solution of **367** (1.85 g, 7.06 mmol), benzhydrylamine (1.34 mL, 7.77 mmol) and acetic acid (0.81 mL, 14.12 mmol) in 1,2-DCE (100 mL) was stirred at room temperature for 6 h. Sodium triacetoxyborohydride (2.25 g, 10.4 mmol) was added and the reaction was stirred at room temperature overnight. The reaction was quenched with aq. $NaHCO_3$ (100 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (5 x 100 mL). The combined organic layers were washed with brine (500 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The oily

residue was triturated with MeOH (25 mL). The resulting solid was isolated by suction filtration, washed with cold MeOH (10 mL) and dried *in vacuo* to afford **372** (1.19 g). The filtrate was concentrated and purified by flash column chromatography [SiO_2, 4:1 hexane:EtOAc + 1% Et_3N] to afford an extra 0.54 g of **372**. Product from both purifications were combined to give **372** (1.73 g, 57%) as a colourless solid. $\boldsymbol{R_f}$ = 0.54 [1:1 petrol:EtOAc]. **mp**: 131 – 133 ºC.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.40 (4H, d, *J* = 8.0 Hz, **H9**), 7.32 (4H, t, *J* = 7.8 Hz, **H10**), 7.25 – 7.21 (2H, m, **H11**), 4.80 (1H, s, **H7**), 4.08 (1H, ddd, *J* = 13.0, 10.6, 7.0 Hz, **H2a**), 3.99 (1H, ddd, *J* = 12.9, 10.4, 6.3 Hz, **H2b**), 2.78 – 2.70 (1H, m, **H1a**), 2.64 (2H, t, *J* = 6.8 Hz, **H6**), 2.39 (1H, ddd, *J* = 13.6, 11.6, 5.2 Hz, **H4a**), 2.11 (1H, ddd, *J* = 13.5, 11.7, 4.8 Hz, **H4b**), 1.90 (1H, ddd, *J* = 12.0, 10.4, 7.0 Hz, **H1b**), 1.56 – 1.53 (1H, m, **H5a**), 1.51 (9H, s, **H14**), 1.47 – 1.40 (1H, m, **H5b**).

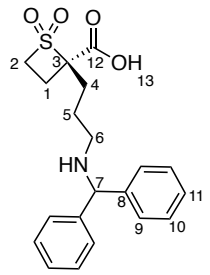
^{13}C NMR: (100 MHz, $CDCl_3$) δ 165.8 (**C12**), 144.1 (**C8**), 128.7 (**C10**), 127.4 (**C9**), 127.2 (**C11**), 91.5 (**C3**), 84.0 (**C13**), 67.6 (**C7**), 62.5 (**C2**), 47.7 (**C6**), 30.8 (**C4**), 28.0 (**C14**), 25.1 (**C5**), 17.2 (**C1**).

HRMS: (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{32}NO_4S$ 430.2047; found 430.2050.

IR: ν_{max} (neat/cm^{-1}): 3322 (N–H), 2935 (C–H), 2806 (C–H), 1716 (C=O), 1313 (S=O), 1123 (S=O).

$\boldsymbol{[\alpha]_D^{22}}$ = +55.0 (*c* = 0.1, $CHCl_3$).

(2*S*)-2-[3-(Benzhydrylamino)propyl]-1,1-dioxo-thietane-2-carboxylic acid (374)



374

To a solution of **372** (1.73 g, 4.03 mmol) in CH_2Cl_2 (40 mL) was added TFA (10 mL) and the mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated under reduced pressure to afford **374** (1.51 g, quant.) as a colourless solid which was used without further purification.

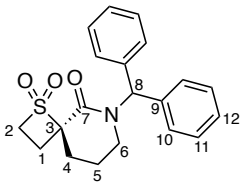
^{1}H NMR: (400 MHz, DMSO-d_6) δ 9.58 (1H, s, **H13**), 7.57 (4H, d, J = 7.4 Hz, **H9**), 7.47 (4H, t, J = 7.6 Hz, **H10**), 7.43 – 7.37 (2H, m, **H11**), 5.60 (1H, s, **H7**), 4.19 (1H, ddd, J = 13.2, 10.4, 7.6 Hz, **H2a**), 4.10 (1H, ddd, J = 13.2, 10.5, 5.6 Hz, **H2b**), 2.90 (2H, br s, **H6**), 2.54 – 2.45 (1H, m, **H1a**), 2.14 (1H, td, J = 12.8, 4.8 Hz, **H4a**), 2.08 – 1.96 (2H, m, **H1b** and **H4b**), 1.81 – 1.66 (1H, m, **H5a**), 1.65 – 1.51 (1H, m, **H5b**).

^{13}C NMR: (100 MHz, DMSO-d_6) δ 167.7 (**C12**), 136.4 (**C8**), 129.1 (**C10**), 128.8 (**C11**), 127.6 (**C9**), 89.1 (**C3**), 64.5 (**C7**), 62.1 (**C2**), 43.8 (**C6**), 29.2 (**C4**), 20.7 (**C5**), 16.2 (**C1**).

HRMS: (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{24}NO_4S$ 374.1421; found 374.1439.

IR: ν_{max} (neat/cm^{-1}): 3228 (O–H), 3076 (C–H), 2849 (C–H), 1306 (S=O), 1140 (S=O).

(4*S*)-8-Benzhydryl-1,1-dioxo-1-thia-8-azaspiro[3.5]nonan-9-one (373)



373

A suspension of crude **374** (1.51 g, 4.03 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 ºC. *N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.54 g, 8.06 mmol), pyridine (1.63 mL, 20.2 mmol) and 4-dimethylaminopyridine (54 mg, 0.04 mmol) were added sequentially. The reaction mixture was stirred at 0 ºC for 30 min, then allowed to warm to room temperature and stirred at ambient temperature for 24 h. The reaction was quenched with aq. HCl (1 N, 100 mL). The mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (300 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 3:1 – 2:1 hexane:EtOAc] afforded **373** (1.27 g, 89%) as a colourless solid. $\boldsymbol{R_f}$ = 0.19 [2:1 petrol:EtOAc]. **mp**: 144 – 145 ºC.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.40 – 7.32 (5H, m, **H10** and **H11a**), 7.32 – 7.27 (3H, m, **H11b**), 7.26 – 7.22 (2H, m, **H12**), 7.20 (1H, s, **H8**), 4.43 (1H, ddd, *J* = 12.4, 10.6, 9.8 Hz, **H2a**), 3.96 (1H, ddd, *J* = 12.8, 10.0, 3.0 Hz, **H2b**), 3.29 – 3.22 (1H, m, **H6a**), 3.05 – 2.96 (1H, m, **H6b**), 2.91 (1H, td, *J* = 11.3, 2.9 Hz, **H1a**), 2.87 – 2.79 (1H, m, **H4a**), 1.98 – 1.88 (2H, m, **H4b** and **H5a**), 1.85 – 1.76 (2H, m, **H1b** and **H5b**).

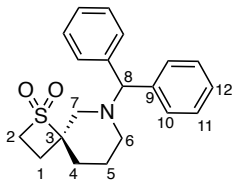
^{13}C NMR: (100 MHz, $CDCl_3$) δ 165.2 (**C7**), 138.4 and 137.7 (**C9**), 129.8 and 128.8 (**C11**), 128.7 and 128.1 (**C10**), 128.1 and 127.5 (**C12**), 88.7 (**C3**), 64.3 (**C2**), 61.4 (**C8**), 44.0 (**C6**), 28.7 (**C4**), 21.3 (**C5**), 19.2 (**C1**).

HRMS: (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{22}NO_3S$ 356.1315; found 356.1315.

IR: ν_{max} (neat/cm^{-1}): 3030 (C–H), 2935 (C–H), 2870 (C–H), 1627 (C=O), 1310 (S=O), 1123 (S=O).

$\boldsymbol{[\alpha]_D^{22}}$ = +151.6 (*c* = 0.32, $CHCl_3$).

(4*S*)-8-Benzhydryl-1-thia-8-azaspiro[3.5]nonane 1,1-dioxide (375)



375

To a solution of **373** (1.23 g, 3.46 mmol) in THF (25 mL) was added BH_3·THF (1 M in THF, 10.4 mL, 10.4 mmol) and the mixture was heated at reflux for 3 h. A fresh portion of BH_3·THF (1 M in THF, 10.4 mL, 10.4 mmol) was added and the mixture was stirred at reflux for a further 2 h. The mixture was allowed to cool to room temperature, quenched dropwise with water (15 mL), and basified with aq. NaOH (10%, 100 mL). The mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (300 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 4:1 hexane:EtOAc] afforded **375** (1.13 g, 96%) as a colourless solid. $\boldsymbol{R_f}$ = 0.30 [2:1 petrol:EtOAc]. **mp**: 163 ºC (decomposition).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.48 – 7.38 (4H, m, **H10**), 7.31 – 7.27 (4H, m, **H11**), 7.22 – 7.16 (2H, m, **H12**), 4.35 (1H, s, **H8**), 3.89 (1H, ddd, *J* = 13.1, 10.4, 7.3 Hz, **H2a**), 3.77 (1H, ddd, *J* = 13.1, 10.5, 5.7 Hz, **H2b**), 3.10 (1H, d, *J* = 11.5 Hz, **H7a**), 2.56 – 2.45 (2H, m, **H6a** and **H7b**), 2.32 – 2.25 (1H, m, **H4a**), 2.24 – 2.14 (1H, m, **H6b**), 2.01 (1H, td, *J* = 11.6, 7.4 Hz, **H1a**), 1.90 – 1.71 (3H, m, **H1b**, **H4b** and **H5a**), 1.68 – 1.57 (1H, m, **H5b**).

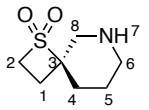
^{13}C NMR: (100 MHz, $CDCl_3$) δ 142.2 and 141.8 (**C9**), 128.7 and 128.6 (**C11**), 128.4 and 128.0 (**C10**), 127.3 (**C12**), 84.0 (**C3**), 76.1 (**C8**), 59.6 (**C2**), 56.1 (**C7**), 51.3 (**C6**), 31.5 (**C4**), 23.2 (**C5**), 20.7 (**C1**).

HRMS: (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{24}NO_2S$ 342.1522; found 342.1509.

IR: ν_{max} (neat/cm^{-1}): 3058 (C–H), 2940 (C–H), 2785 (C–H), 1304 (S=O), 1120 (S=O).

$\boldsymbol{[\alpha]_D^{22}}$ = +39.1 (*c* = 0.32, $CHCl_3$).

(4*S*)-1-Thia-8-azaspiro[3.5]nonane 1,1-dioxide (258)



258

To a suspension of **375** (1.09 g, 3.20 mmol) in EtOH (50 mL) was added TFA (5 mL) and $Pd(OH)_2$ (20 wt% on carbon, 220 mg). The reaction was stirred under a hydrogen atmosphere for 2.5 h. The reaction mixture was filtered through a plug of Celite and concentrated. The residue was suspended between EtOAc (75 mL) and aq. HCl (1 N, 25 mL). The aqueous layer was basified with 3 N NaOH (250 mL) to pH >10 and extracted with CH_2Cl_2 (5 x 100 mL). The combined organic phase was washed with brine (500 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give **258** (451 mg, 81%) as a yellow oil. $\boldsymbol{R_f}$ = baseline [EtOAc].

^{1}H NMR: (400 MHz, DMSO-d_6) δ 4.06 (2H, t, J = 8.7 Hz, **H2**), 3.44 (1H, d, J = 13.2 Hz, **H8a**), 3.32 (1H, br s, **H7**), 3.23 (1H, d, J = 13.2 Hz, **H8b**), 2.91 – 2.80 (2H, m, **H6**), 2.23 – 2.15 (1H, m, **H4a**), 2.09 – 1.99 (1H, m, **H1a**), 1.94 – 1.87 (2H, m, **H1b** and **H4b**), 1.68 (2H, quint, J = 5.8 Hz, **H5**).

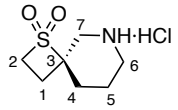
^{13}C NMR: (100 MHz, DMSO-d_6) δ 79.8 (**C3**), 60.0 (**C2**), 46.6 (**C7**), 43.2 (**C6**), 28.4 (**C4**), 20.9 (**C5**), 19.2 (**C1**).

HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_7H_{14}NO_2S$ 176.0740; found 176.0744.

IR: ν_{max} (neat/cm^{-1}): 3330 (N–H), 2942 (C–H), 2855 (C–H), 1297 (S=O), 1121 (S=O).

$\boldsymbol{[\alpha]_D^{22}}$ = +30.0 (c = 0.05, $CHCl_3$).

(4*S*)-1-Thia-8-azaspiro[3.5]nonane 1,1-dioxide hydrochloride (377)



377

258 (449 mg, 2.56 mmol) was dissolved in a mixture of Et_2O (150 mL) and EtOAc (30 mL). HCl in 1,4-dioxane (4 N, 1.28 mL, 5.12 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. The precipitate was isolated by centrifuge to provide salt **377** (512 mg, 95%) as a colourless solid.

^{1}H NMR: (400 MHz, DMSO-d_6) δ 9.92 (1H, br s, **NH**), 9.41 (1H, br s, **NH**), 4.23 – 4.13 (2H, m, **H2**), 3.52 – 3.45 (1H, m, **H7a**), 3.43 – 3.35 (1H, m, **H7b**), 3.06 – 2.96 (1H, m, **H6a**), 2.94 – 2.84 (1H, m, **H6b**), 2.38 – 2.28 (1H, m, **H1a**), 2.14 – 2.06 (1H, m, **H4a**), 2.03 – 1.92 (2H, m, **H1b** and **H4b**), 1.82 – 1.71 (2H, m, **H5**).

^{13}C NMR: (100 MHz, DMSO-d_6) δ 78.5 (**C3**), 60.5 (**C2**), 44.5 (**C7**), 42.0 (**C6**), 27.2 (**C4**), 19.5 (**C1**), 18.9 (**C5**).

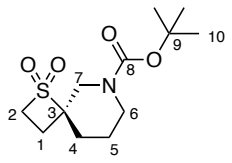
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_7H_{14}NO_2S$ 176.0740; found 176.0731.

IR: ν_{max} (neat/cm^{-1}): 2924 (C–H), 2786 (C–H), 2719 (C–H), 1295 (S=O), 1123 (S=O).

$[\alpha]_D^{21}$ = +5.6 (*c* = 0.27, MeOH).

*To determine the ee of **377**, amine **258** was converted to carbamate **381**:*

(4*S*)-*tert*-Butyl -1,1-dioxo-1-thia-8-azaspiro[3.5]nonane-8-carboxylate (381)



381

A solution of **377** (14 mg, 0.07 mmol), triethylamine (40 μL, 0.28 mmol), di-*tert*-butyl dicarbonate (60 μL, 0.13 mmol) and a few crystals of 4-dimethylaminopyridine in CH_2Cl_2 (5 mL) was stirred at room temperature for 48 h. The reaction was quenched with aq. HCl (1 N, 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 1:1 – 0:1 hexane:EtOAc] afforded **381** (19 mg, 98%) as a colourless oil. $\boldsymbol{R_f}$ = 0.72 [EtOAc].

^{1}H NMR: (400 MHz, DMSO-d_6, VT, 75 ºC) δ 4.06 – 3.93 (3H, m, **H2** and **H7a**), 3.51 (1H, d, J = 13.6 Hz, **H7b**), 3.47 – 3.39 (1H, m, **H6a**), 3.31 – 3.15 (1H, m, **H6b**), 2.26 – 2.18 (1H, m, **H4a**), 1.94 – 1.84 (3H, m, **H1** and **H4b**), 1.62 – 1.53 (2H, m, **H5**), 1.42 (9H, s, **H10**).

^{13}C NMR: (100 MHz, DMSO-d_6, VT, 75 ºC) δ 153.3 (**C8**), 81.2 (**C3**), 78.8 (**C9**), 59.3 (**C2**), 46.5 (**C6**), 42.1 (**C7**), 29.5 (**C4**), 27.7 (**C10**), 21.7 (**C5**), 18.6 (**C1**).

HRMS: (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{21}NO_4SNa$ 298.1084, found 298.1061.

IR: ν_{max} (neat/cm^{-1}): 2974 (C–H), 2862 (C–H), 1688 (C=O), 1310 (S=O), 1125 (S=O).

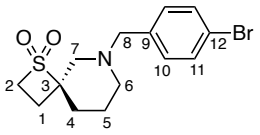
Chiral HPLC: (AD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, λ = 212 nm, 30.0 ºC) t_R = 9.4 min (minor), 24.1 min (major). 96% ee.

$\boldsymbol{[\alpha]_D^{22}}$ = –12.5 (c = 0.12, $CHCl_3$).

For the purposes of HPLC analysis, *rac*-**377** was Boc-protected to *rac*-**381** using the same procedure.

5.2.8 Functionalisations of Spirocycle 377

(4*S*)-8-[(4-Bromophenyl)methyl]-1-thia-8-azaspiro[3.5]nonane 1,1-dioxide (378)



378

A solution of **377** (28 mg, 0.15 mmol), acetic acid (17 μL, 0.30 mmol), and 4-bromobenzaldehyde (31 mg, 0.17 mmol) in 1,2-DCE (4 mL) was stirred at room temperature for 15 minutes. Sodium triacetoxyborohydride (48 mg, 0.23 mmol) was added and the reaction was stirred at room temperature overnight. The reaction was quenched with aq. $NaHCO_3$ (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The organic extracts were combined, washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 2:1 pentane:EtOAc] afforded **378** (27 mg, 53%) as a colourless oil. $\boldsymbol{R_f}$ = 0.71 [EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.43 (2H, d, *J* = 8.4 Hz, **H11**), 7.22 (2H, d, *J* = 8.5 Hz, **H10**), 3.91 (1H, ddd, *J* = 13.2, 10.4, 7.4 Hz, **H2a**), 3.84 (1H, ddd, *J* = 13.2, 10.5, 6.0 Hz, **H2b**), 3.51 (2H, s, **H8**), 3.01 (1H, d, *J* = 11.6 Hz, **H7a**), 2.53 (1H, d, *J* = 11.8 Hz, **H7b**), 2.51 – 2.42 (1H, m, **H6a**), 2.34 – 2.16 (2H, m, **H4a** and **H6b**), 2.00 – 1.92 (1H, m, **H1a**), 1.90 – 1.75 (3H, m, **H1b**, **H4b** and **H5a**), 1.68 – 1.61 (1H, m, **H5b**).

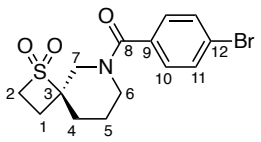
^{13}C NMR: (100 MHz, $CDCl_3$) δ 136.9 (**C9**), 131.4 (**C11**), 130.5 (**C10**), 121.0 (**C12**), 83.3 (**C3**), 62.0 (**C8**), 59.6 (**C2**), 57.2 (**C7**), 52.6 (**C6**), 30.9 (**C4**), 22.8 (**C5**), 20.4 (**C1**).

HRMS: (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{19}NO_2S^{79}Br$ 344.0314; found 344.0302.

IR: ν_{max} (neat/cm^{-1}): 2942 (C–H), 2789 (C–H), 1302 (S=O), 1120 (S=O).

$\boldsymbol{[\alpha]_D^{22}}$ = –3.8 (*c* = 0.26, $CHCl_3$).

(4*S*)-(4-Bromophenyl)-[1,1-dioxo-1-thia-8-azaspiro[3.5]nonan-8-yl]methanone (379)



379

A solution of **377** (14 mg, 0.07 mmol) and triethylamine (20 mL, 0.14 mmol) in CH_2Cl_2 (3 mL) was cooled to 0 ºC. A solution of 4-bromobenzoyl chloride (22 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) was added. The reaction was stirred at 0 ºC for 10 minutes, then allowed to warm to room temperature and stirred at ambient temperature overnight. The reaction was quenched with aq. $NaHCO_3$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 1:1 – 0:1 hexane:EtOAc] afforded **379** (21 mg, 84%) as a colourless sticky oil. $\boldsymbol{R_f}$ = 0.34 [EtOAc].

^{1}H NMR: (400 MHz, DMSO-d_6, VT, 130 ºC) δ 7.63 (2H, d, *J* = 8.4 Hz, **H10**), 7.33 (2H, d, *J* = 8.4 Hz, **H11**), 4.14 (1H, d, *J* = 13.8 Hz, **H7a**), 4.05 – 3.93 (2H, m, **H2**), 3.68 (1H, d, *J* = 13.8 Hz, **H7b**), 3.60 (1H, br s, **H6a**), 3.22 – 3.13 (1H, m, **H6b**), 2.38 – 2.29 (1H, m, **H4a**), 2.00 – 1.85 (3H, m, **H1** and **H4b**), 1.69 – 1.59 (2H, m, **H5**).

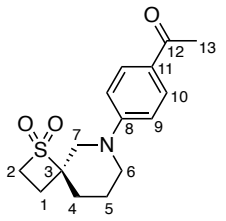
^{13}C NMR: (100 MHz, DMSO-d_6, VT, 130 ºC) δ 168.1 (**C8**), 134.7 (**C9**), 130.6 (**C10**), 128.3 (**C11**), 122.2 (**C12**), 81.3 (**C3**), 59.3 (**C2**), 46.9 (**C6**), 43.6 (**C7**), 29.4 (**C4**), 21.5 (**C5**), 18.6 (**C1**).

HRMS: (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}NO_3S^{79}Br$ 358.0107; found 358.0111.

IR: ν_{max} (neat/cm^{-1}): 2950 (C–H), 2862 (C–H), 1634 (C=O), 1306 (S=O), 1123 (S=O).

$\boldsymbol{[\alpha]_D^{22}}$ = –21.9 (*c* = 0.16, $CHCl_3$).

(4*S*)-1-[4-[1,1-Dioxo-1-thia-8-azaspiro[3.5]nonan-8-yl]phenyl]ethanone (380)



380

A solution of **377** (28 mg, 0.15 mmol) and 4-bromoacetophenone (90 mg, 0.45 mmol) in toluene (2 mL) was added to a flask containing $Pd(OAc)_2$ (3.5 mg, 0.02 mmol), BINAP (19 mg, 0.03 mmol) and Cs_2CO_3 (75 mg, 0.23 mmol). The mixture was stirred at room temperature for 30 minutes, then heated to 100 ºC overnight. The mixture was allowed to cool to room temperature, filtered through a plug of celite and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 3:2 pentane:EtOAc] afforded **380** (27 mg, 61%) as a colourless oil. $\boldsymbol{R_f}$ = 0.56 [EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* = 8.8 Hz, **H10**), 7.00 (2H, d, *J* = 8.8 Hz, **H9**), 4.05 (1H, d, *J* = 13.2 Hz, **H7a**), 4.03 – 3.96 (2H, m, **H2**), 3.46 – 3.41 (1H, m, **H6a**), 3.38 (1H, d, *J* = 13.2 Hz, **H7b**), 3.15 – 3.08 (1H, m, **H6b**), 2.52 (3H, s, **H13**), 2.50 – 2.43 (1H, m, **H4a**), 2.07 – 1.90 (4H, m, **H1**, **H4b** and **H5a**), 1.87 – 1.79 (1H, m, **H5b**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 196.8 (**C12**), 154.4 (**C8**), 130.4 (**C10**), 129.0 (**C11**), 115.4 (**C9**), 82.7 (**C3**), 60.0 (**C2**), 53.6 (**C7**), 47.6 (**C6**), 31.0 (**C4**), 26.4 (**C13**), 22.9 (**C5**), 20.3 (**C1**).

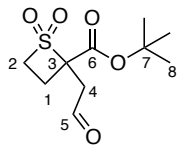
HRMS: (APCI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{20}NO_3S$ 294.1158; found 294.1144.

IR: ν_{max} (neat/cm^{-1}): 2946 (C–H), 2823 (C–H), 1664 (C=O), 1304 (S=O), 1118 (S=O).

$\boldsymbol{[\alpha]_D^{22}}$ = –137.5 (*c* = 0.04, $CHCl_3$).

5.2.9 Synthesis of [3.4] Spirocycle

tert-Butyl-1,1-dioxo-2-(3-oxoethyl)thietane-2-carboxylate (*rac*-382)



382

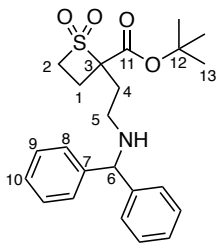
To a solution of *rac*-**335** (100 mg, 0.41 mmol) in a 3:1 1,4-dioxane:H_2O (6 mL) mixture was added osmium tetroxide (2.5wt% in *tert*-butanol, 0.1 mL, 0.008 mmol), and the mixture stirred at room temperature for 5 minutes. Sodium periodate (201 mg, 0.943 mmol) was added and the mixture was stirred at room temperature for 18 h. The reaction mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford *rac*-**382** (101 mg, quant.) as a brown oil which was used without further purification. $\boldsymbol{R_f}$ = 0.51 (1:1 petrol:EtOAc).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.75 (1H, s, **H5**), 4.38 – 4.29 (1H, m, **H2a**), 4.09 (1H, ddd, *J* = 14.4, 10.3, 4.1 Hz, **H2b**), 3.58 (1H, d, *J* = 18.8 Hz, **H4a**), 3.30 (1H, d, *J* = 18.8 Hz, **H4b**), 2.99 (1H, ddd, *J* = 14.8, 10.8, 4.1 Hz, **H1a**), 1.94 – 1.86 (1H, m, **H1b**), 1.51 (9H, s, **H8**).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 196.6 (**C5**), 164.5 (**C6**), 86.7 (**C3**), 84.5 (**C8**), 64.7 (**C2**), 46.7 (**C4**), 27.7 (**C8**), 18.4 (**C1**).

HRMS: molecular ion not detected for $C_{10}H_{16}O_5S$.

***tert*-Butyl-2-[3-(benzhydrylamino)ethyl]-1,1-dioxo-thietane-2-carboxylate (*rac*-385)**



385

To a solution of *rac*-**382** (23 mg, 0.09 mmol) in 1,2-DCE (2 mL) was added benzhydrylamine (18 μL, 0.10 mmol) and sodium triacetoxyborohydride (36 mg, 0.17 mmol). The reaction mixture was stirred at room temperature for 18 h. The reaction was quenched with aq. $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (5 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2; 3:1 hexane:EtOAc] afforded *rac*-**385** (4 mg, 11%) as a colourless oil. $\boldsymbol{R_f}$ = 0.64 [1:1 petrol:EtOAc].

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (7H, m, **H8**, **H9a**, **H9b** and **H9c**), 7.26 – 7.19 (3H, m, **H9d** and **H10**), 4.77 (1H, s, **H6**), 4.13 (1H, ddd, *J* = 12.8, 10.7, 7.7 Hz, **H2a**), 4.01 – 3.93 (1H, m, **H2b**), 2.85 – 2.76 (1H, m, **H1a**), 2.76 – 2.69 (1H, m, **H5a**), 2.63 – 2.54 (2H, m, **H4a** and **H5b**), 2.33 – 2.25 (1H, m, **H4b**), 1.94 (1H, ddd, *J* = 12.2, 10.4, 7.7 Hz, **H1b**), 1.43 (9H, s, **H13**).

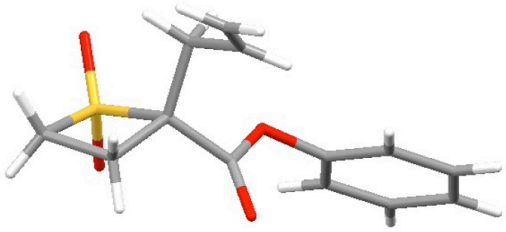
^{13}C NMR: (100 MHz, $CDCl_3$) δ 165.8 (**C11**), 143.6 (**C7**), 128.5 (**C8** or **C9**), 127.3 (**C10**), 127.2 (**C8** or **C9**), 90.8 (**C3**), 83.3 (**C12**), 67.7 (**C6**), 62.9 (**C2**), 43.4 (**C5**), 32.5 (**C4**), 27.8 (**C13**), 16.8 (**C1**).

HRMS: (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{30}NO_4S$ 416.1890; found 416.1892.

IR: ν_{max} (neat/cm^{-1}): 3325 (N–H), 3030 (C–H), 2928 (C–H), 2806 (C–H), 1719 (C=O), 1315 (S=O), 1123 (S=O).

5.3 X-ray Crystallography Data

X-Ray Crystal Structure of 270: CCDC **2099913**



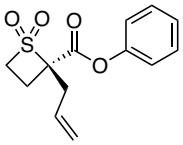


Figure 26. Crystal Structure of **270**

Empirical formula	$C_{13}H_{14}O_4S$
Formula weight	266.30
Temperature/K	100.01(10)
Crystal system	trigonal
Space group	$P3_1$
a/Å	13.07541(6)
b/Å	13.07541(6)
c/Å	6.55984(4)
α/°	90
β/°	90
γ/°	120
Volume/Å^3	971.259(11)
Z	3
ϱ_{calc}g/cm^3	1.366
μ/mm^{-1}	2.275
F(000)	420.0
Crystal size/mm^3	0.406 × 0.176 × 0.093
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.808 to 152.984
Index ranges	-16 ≤ h ≤ 16, -16 ≤ k ≤ 16, -8 ≤ l ≤ 7
Reflections collected	52146
Independent reflections	2663 [R_{int} = 0.0371, R_{sigma} = 0.0110]
Data/restraints/parameters	2663/1/163
Goodness-of-fit on F^2	1.101
Final R indexes [I>=2σ (I)]	R_1 = 0.0244, wR_2 = 0.0673
Final R indexes [all data]	R_1 = 0.0244, wR_2 = 0.0673
Largest diff. peak/hole / e Å^{-3}	0.22/-0.21
Flack parameter	0.005(11)

Table 22. Crystal data and structure refinement for **270**

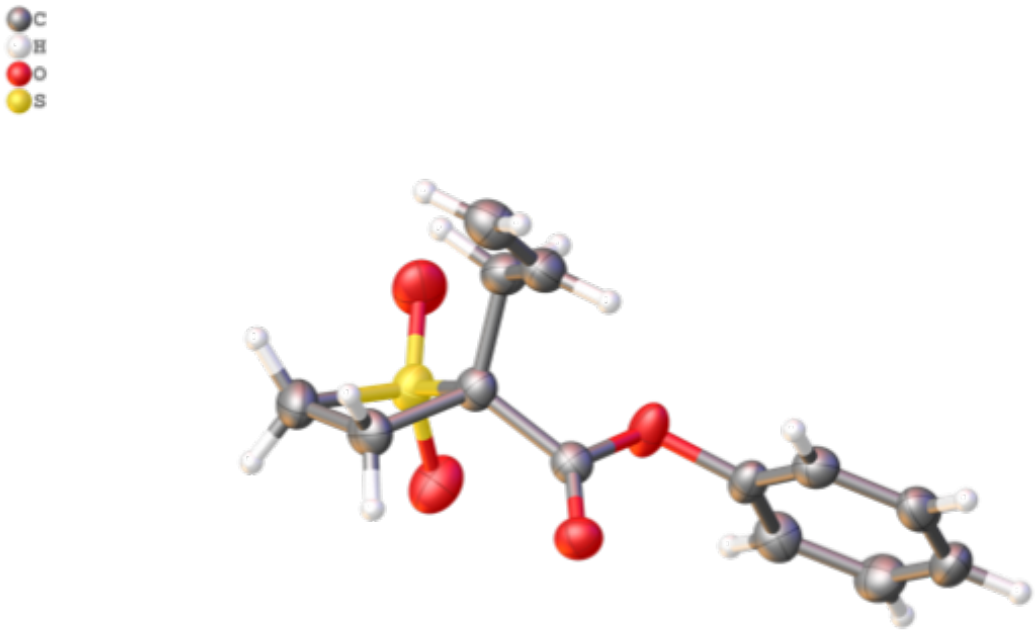
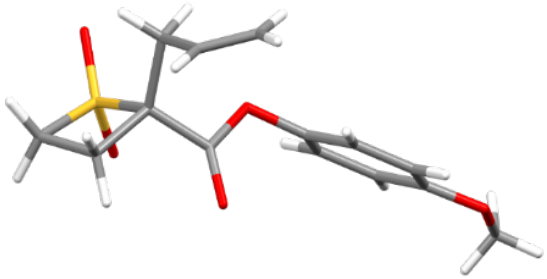


Figure 27: Structure **270** with 70% probability thermal ellipsoids.

X-Ray Crystal Structure of 333: CCDC **2099912**



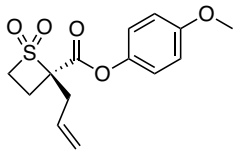


Figure 28. Crystal Structure of **333**

Empirical formula	$C_{14}H_{16}O_5S$
Formula weight	296.33
Temperature/K	99.9(3)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	6.29014(5)
b/Å	11.77074(11)
c/Å	9.67164(8)
α/°	90
β/°	102.3332(7)
γ/°	90
Volume/Å^3	699.558(10)
Z	2
ρ_{calc}g/cm^3	1.407
μ/mm^{-1}	2.218
F(000)	312.0
Crystal size/mm^3	0.1 × 0.1 × 0.08
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.36 to 152.9
Index ranges	$-7 \leq h \leq 7$, $-13 \leq k \leq 14$, $-12 \leq l \leq 12$
Reflections collected	29945
Independent reflections	2769 [R_{int} = 0.0327, R_{sigma} = 0.0108]
Data/restraints/parameters	2769/1/182
Goodness-of-fit on F^2	1.061
Final R indexes [I>=2σ (I)]	R_1 = 0.0249, wR_2 = 0.0682
Final R indexes [all data]	R_1 = 0.0249, wR_2 = 0.0682
Largest diff. peak/hole / e Å^{-3}	0.22/-0.28
Flack parameter	-0.004(8)

Table 23. Crystal data and structure refinement for **333**

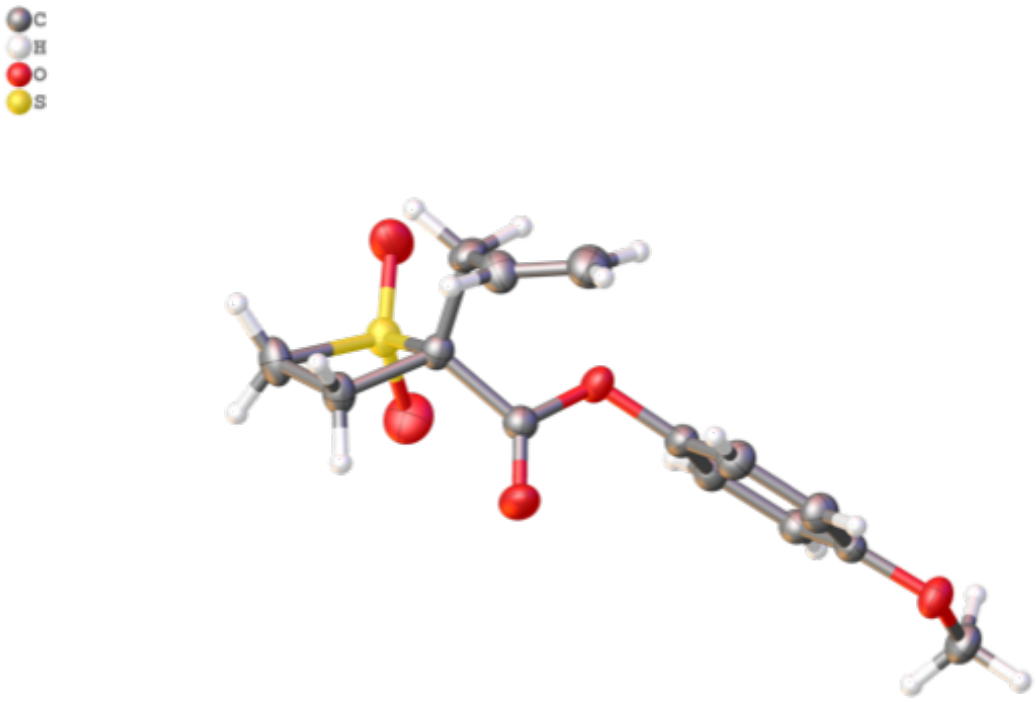


Figure 29: Structure **333** with 70% probability thermal ellipsoids.

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