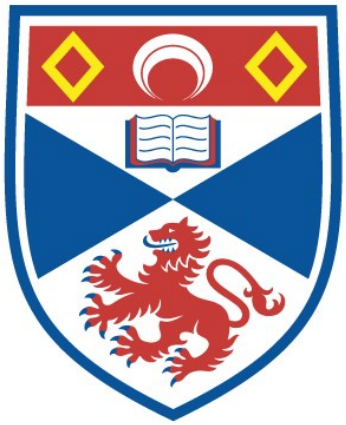
# APPLICATIONS OF ISOTHIOUREA GENERATED AMMONIUM ENOLATES IN ASYMMETRIC SYNTHESIS

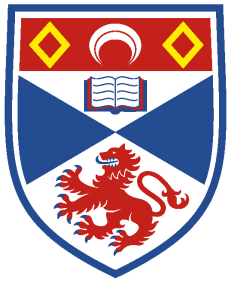
**Siobhan Rose Smith**

**A Thesis Submitted for the Degree of PhD**
**at the**
**University of St Andrews**



**2014**

# Applications of Isothiourea Generated Ammonium Enolates in Asymmetric Synthesis



University of
St Andrews

**Siobhan Rose Smith**

**2014**

This thesis is submitted in partial fulfillment for the degree of PhD at the University of St Andrews

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*For Mum and Dad*

# Acknowledgements

Firstly I must thank Andy for welcoming me into his group and all his support throughout my undergraduate and postgraduate – without his encouragement I wouldn't be where I am today! I've thoroughly enjoyed being part of his research team! Also thanks to my industrial supervisor Pete for welcoming me to GSK Stevenage and for many cheering emails – and of course GSK and the EPSRC for funding.

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# Abstract

This thesis describes expansion of the ability of isothioureas to act as organocatalysts in formal [2+2]-, [3+2]- and [4+2]-cycloadditions between carboxylic acids and various acceptors *via* Type I ammonium enolate intermediates.

**Chapter 2** describes the optimisation and investigation of [2+2]-cycloadditions from ammonium enolates and *N*-sulfonylimines as the two components. The development of this methodology allows successful access to highly stereodefined *β*-lactams and, following *in situ* ring-opening, *β*-aminoesters. The products are obtained from either preformed homoanhydrides or directly from carboxylic acids, using open flask conditions, from simple, bench-stable starting materials and is scalable. A variety of *anti*-*β*-lactams (21 examples, 46-68% yield, up to >95:5 dr, 21->99% ee) and *β*-aminoesters (9 examples, 44-74% yield, up to >95:5 dr, 68-92% ee) were accessed in moderate yield, excellent diastereo- and good enantioselectivity. This represents an improved route to *anti*-*β*-lactams over previously described ketene and *N*-triflyl imine based methods.

**Chapter 3** subsequently describes studies focussed on the use of ester surrogates in the formal [4+2]-cycloaddition reactions of isothiourea generated Type I ammonium enolates. Iso-propylphosphonate **163** proved highly effective as the four-component in this process, which following the *in situ* ring-opening of the initial dihydropyranone product allowed isolation of a range of novel diester products which were previously unobtainable using this methodology. The products were accessed in moderate to excellent yields, excellent diastereo- and enantiocontrol (9 examples, 12-63% yield, up to >95:5 dr, 67-99% ee) with this process also amenable to a large scale. Furthermore, selective reduction and acid-catalysed cyclisation allowed access to *δ*-lactone products in good yield with retention of stereocontrol.

Finally, **Chapter 4** describes work on isothiourea-catalysed formal [3+2]-cycloadditions of oxaziridines and acetic anhydrides gave access to stereodefined five-membered oxazolidin-4-one heterocycles. In this case, the use of preformed homoanhydrides and an inorganic base was imperitive to avoid reduction of the oxaziridine starting material. The oxazolidin-4-one products could be accessed in excellent yield and ee however poor dr (13 examples, 63-96% yield, up to 59:41 dr *anti:syn*, up to >99% ee for both diastereoisomers). Following isolation, reduction of

these heterocycles allowed access to enantioenriched diols with little loss in stereocontrol. Mechanistic analysis has shown that an improvement in diasterocontrol can be obtained by the use of an enantioenriched oxaziridine, demonstrating the stereospecificity of this process.

# Publications

The work described in this thesis has formed the basis of the following peer reviewed publications to date:

1. "Isothiourea-catalyzed asymmetric synthesis of *β*-lactams and *β*-amino esters from arylacetic acid derivatives and *N*-sulfonyl aldimines" S. R. Smith, J. Douglas, H. Prevet, P. Shapland, A. M. Z. Slawin and A. D. Smith *J. Org. Chem.* **2014**, *79*, 1626-1639.
2. "*α*-Ketophosphonates as Ester Surrogates: Isothiourea-Catalyzed Asymmetric Diester and Lactone Synthesis" S. R. Smith, S. M. Leckie, R. Holmes, J. Douglas, C. Fallan, P. Shapland, D. Pryde, A. M. Z. Slawin and A. D. Smith *Org. Lett.* **2014**, *16*, 2506-2509.
3. "Organocatalytic Michael Addition-Lactonisation of Carboxylic Acids using *α*,*β*-Unsaturated Trichloromethyl Ketones as *α*,*β*-Unsaturated Ester Equivalents" L. C. Morrill, D. G. Stark, J. E. Taylor, S. R. Smith, J. A. Squires, A. D'Hollander, C. Simal, P. Shapland, T. J. C. O'Riordan and A. D. Smith *Org. Biomol. Chem.* **2014**, *12*, 9016-9027.

# Abbreviations

| | |
|---|---|
| Ac | Acetyl |
| app. | Apparent |
| ASAP | Atmospheric solids analysis probe |
| aq | Aqueous |
| Ar | Aromatic |
| atm | Atmosphere |
| BEMP | 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine |
| BINAP | 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl |
| Bn | Benzyl |
| Boc | *N*-*tert*-Butoxycarbonyl |
| br | Broad |
| BTM | Benzotetramisole |
| Bu | Butyl |
| BQ | Benzoylquinine |
| BQd | Benzoylquinidine |
| Bs | Bosyl |
| Bz | Benzoyl |
| *c* | Concentration |
| C | Celsius |
| cat. | Catalyst |
| Cy | Cyclohexyl |
| cm | Centimeter |
| d | Doublet |
| DCC | Dicyclohexylcarbodiimide |
| DHPB | 3,4-Dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole |
| DIBAL-H | Di-*iso*-butylaluminium hydride |
| DMAP | 4-Dimethylaminopyridine |
| DMF | Dimethylformamide |
| DMSO | Dimethyl sulfoxide |
| dr | Diasteroisomeric ratio |
| ee | Enantiomeric excess |
| EI | Electron impact |
| Equiv. | Equivalent molar quantity |
| ESI | Electrospray ionisation |
| Et | Ethyl |
| g | Gram(s) |
| GC | Gas chromatography |
| h | Hour(s) |
| HOMO | Highest occupied molecular orbital |
| HBTM | Homobenzotetramisole |
| HPLC | High performance liquid chromatography |
| HRMS | High resolution mass spectrometry |
| Hz | Hertz |
| IPA | Isopropanol |
| IR | Infrared |

| | |
|---|---|
| KHMDS | Potassium hexamethyldisilazide |
| LDA | Lithium di-*iso*-propylamide |
| LRMS | Low resolution mass spectrometry |
| LUMO | Lowest occupied molecular orbital |
| M | Molar (i.e. mol $dm^{-3}$) |
| m | Multiplet |
| *m* | *Meta* |
| Me | Methyl |
| MHz | Megahertz |
| mg | Milligram(s) |
| mL | Millilitre(s) |
| mol | Mole(s) |
| mp | Melting point |
| MS | Mass spectrometry |
| M. S. | Molecular sieves |
| NBS | *N*-Bromosuccinimide |
| NCAL | Nucleophile-catalysed Aldol-lactonisation |
| NHC | N-heterocyclic carbene |
| NMR | Nuclear magnetic resonance |
| nOe | Nuclear Overhauser effect spectroscopy |
| Ns | Nosyl |
| NSI | Nanospray ionisation |
| *o* | *Ortho* |
| *p* | *Para* |
| Ph | Phenyl |
| Piv | Pivaloyl |
| PMP | *p*-Methoxyphenyl |
| ppm | Parts per million |
| PPY | 4-Pyrrolidinopyridine |
| Pr | Propyl |
| PS | Polymer supported |
| q | Quartet |
| R | Alkyl |
| rt | Ambient (room) temperature |
| s | Singlet |
| sat. | Saturated |
| t | Triplet/time |
| *t* | *Tert* |
| T | Temperature |
| TBS | *tert*-Butyldimethylsilyl |
| Tf | Triflyl |
| TFA | Trifluoroacetic acid |
| TFAA | Trifluoroacetic anhydride |
| THF | Tetrahydrofuran |
| tlc | Thin layer chromatography |
| TM | Tetramisole |
| TMS | Trimethylsilyl |
| Ts | Tosyl |

# Contents

# Chapter 1: Introduction

## 1.1 Asymmetric Synthesis

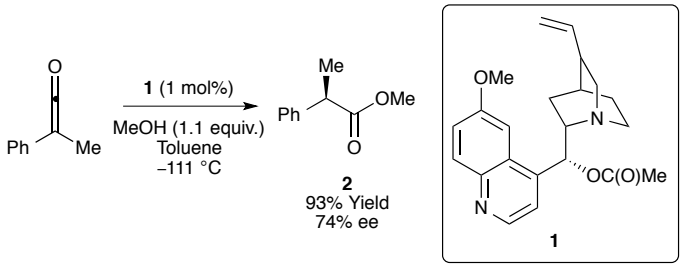
The chiral recognition of biological systems has led to the increased significance of asymmetric synthesis. As two enantiomers of a chiral compound are often recognised as different substances *in vivo*, they can often produce entirely different biological responses. In the best case the undesired enantiomer will be ineffective but it could have negative side effects or even exhibit toxicity. A well documented example of this is the case of thalidomide, which was prescribed as the racemate for severe morning sickness in the 1950's. In 1961 it was removed from the market following the discovery that it was a severe teratogen causing birth defects in thousands of children.[1] In this case, one of the enantiomers was found to be responsible for this detrimental effect and, as the enantiomers interconvert *in vivo* selling an enantiomerically pure drug would be unproductive.[2] However, in many other cases, the synthesis and administration of only the desired enantiomer of a drug would not only potentially reduce costs and increase atom efficiency but also lead to fewer side effects and possibly lower required doses. Indeed, the U.S. Food and Drug Administration agency treat the presence of an undesired enantiomer as an impurity and withhold drug approval unless exclusively one enantiomer is present. Chemical and enzymatic resolution alongside the use of chiral auxiliaries are traditional routes for the synthesis of enantiomerically pure chiral compounds. However, more recently the field of asymmetric catalysis has come to the fore utilising chiral catalysts in sub-stoichiometric quantities to create enantiomerically pure products. The potential economic advantages of this approach has led to the development of this field of synthesis and along with metal and biocatalysis, it has been established that small organic molecules can be highly selective and efficient catalysts.[3] Now considered the "third pillar" of asymmetric catalysis,[4] organocatalysis is the focus of this thesis.

## 1.2 Organocatalysis

In recent years, the ability of small organic molecules to promote synthetic transformations has been investigated extensively. First termed "organocatalysis" by MacMillan in 2000,[5] this field of chemistry is defined as the acceleration of a chemical reaction using sub-stoichiometric amounts of metal-free, low molecular

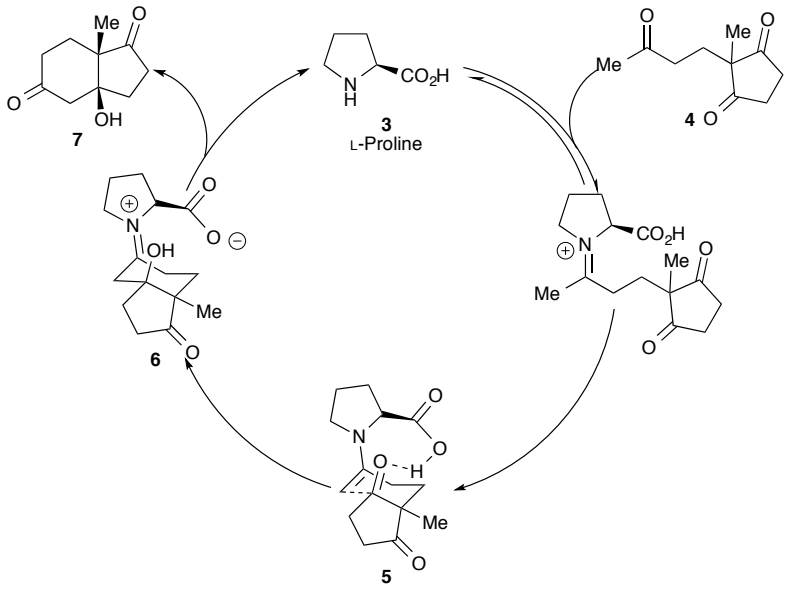
weight organic molecules as catalysts.[6,7] The use of small organic molecules as enantioselective catalysts has many advantages over alternative synthetic strategies including ease of availability and mild, simple reaction conditions.[4] In comparison with metal catalysts, which have been invaluable throughout the history of synthetic chemistry, they often can enable the development of new chemistry. Also, in some cases the development of organocatalytic alternatives to metal-based processes can be highly attractive.[6]

Early work in this area, prior to the acceptance of organocatalytic methods as useful tools in synthetic organic chemistry, began to emerge in the 1960s. Pracejus described the first example of a chiral organic molecule catalysing an organic process when *o*-acetylquinine **1** (1 mol%) was shown to catalyse the addition of methanol to a ketene at low temperature (Scheme 1.1).[8] The enantioenriched ester **2** was isolated in 93% yield and 74% ee.




**Scheme 1.1: Addition of Methanol to a Prochiral Ketene Catalysed by *o*-Acetylquinine 1**

Following this pioneering study, in 1971 the Hajos-Parrish-Eder-Sauer-Wiechert reaction was reported.[9] This process employed the naturally occurring amino acid L-proline **3** to catalyse the intramolecular asymmetric aldol reaction of a triketone (Scheme 1.2). In the reaction mechanism, L-proline **3** reacts the starting ketone **4** to form enamine **5** as the active species. Proton transfer between the carboxylic acid of the enamine nucleophile and the carbonyl electrophile in the proposed intermediate **5** gives the product precursor **6**. Subsequent hydrolysis to release L-proline gives the bicyclic diketone product **7** in high yield and with 95% ee at low catalyst loading (3 mol%).

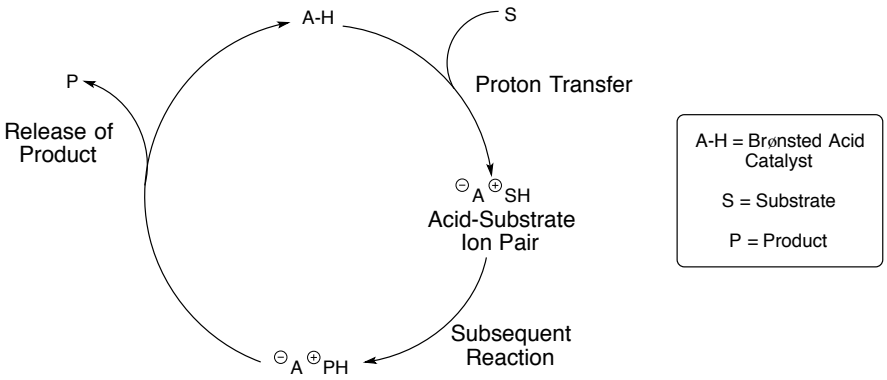



**Scheme 1.2: The Hajos-Parrish-Eder-Sauer-Wiechert Reaction**

Since these early examples of chiral induction, organocatalysis has become increasingly important in asymmetric synthesis due to the possibility of forming multiple new bonds and stereocentres in a one-pot synthesis with a wide variety of activation modes. In 2005, List defined four broad classes of organocatalysis based on the character of the substrate-catalyst interaction:[3] Brønsted acid, Brønsted base, Lewis acid, and Lewis base. These classes will be discussed further in the following sections.

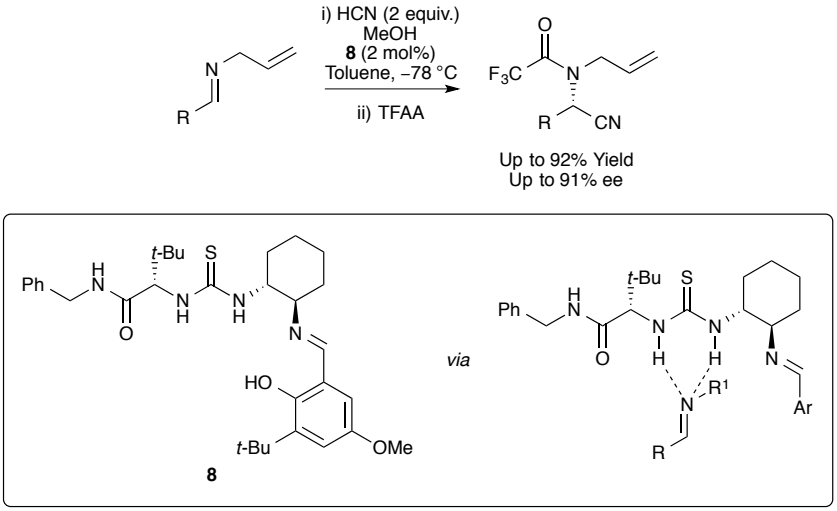
### 1.2.1 Brønsted Acid Organocatalysis

Brønsted acid organocatalysis is defined as a process initiated by protonation or partial protonation to activate an electrophilic substrate - usually a carbonyl or imine[3] - generating a catalyst/substrate complex and allowing reaction to proceed to generate the product (Scheme 1.3). This activation is similar to enzymatic activation where hydrogen-bonding to an enzyme's active site occurs and for this reason, Brønsted acid organocatalysis is also known as hydrogen-bonding catalysis.



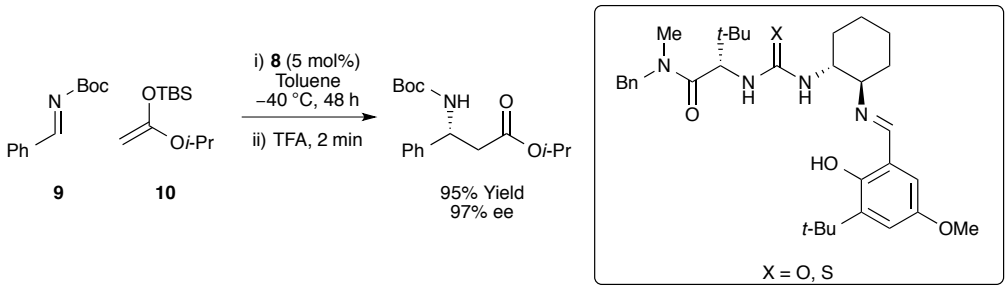

**Scheme 1.3: General Catalytic Cycle for Brønsted Acid Organocatalysis**

This type of organocatalysis was pioneered by Jacøbsen who reported an enantioselective Strecker reaction in 1998 as the first example of Brønsted acid catalysis. The unanticipated discovery that Schiff bases, originally designed for use as ligands in metal catalysed processes, could independently catalyse the asymmetric hydrocyanation reaction of a wide variety of imine substrates initiated this work (Scheme 1.4).[10] Mechanistic investigations showed it was consistent with a double hydrogen-bond activation of the imine by the acidic NH protons of thiourea **8** leading to a lowering in the energy of its LUMO and enhancing its electrophilic nature. Since this work, chiral alcohols such as BINOL[11] and TADDOL[12] derivatives have also been used as catalysts for similar processes.



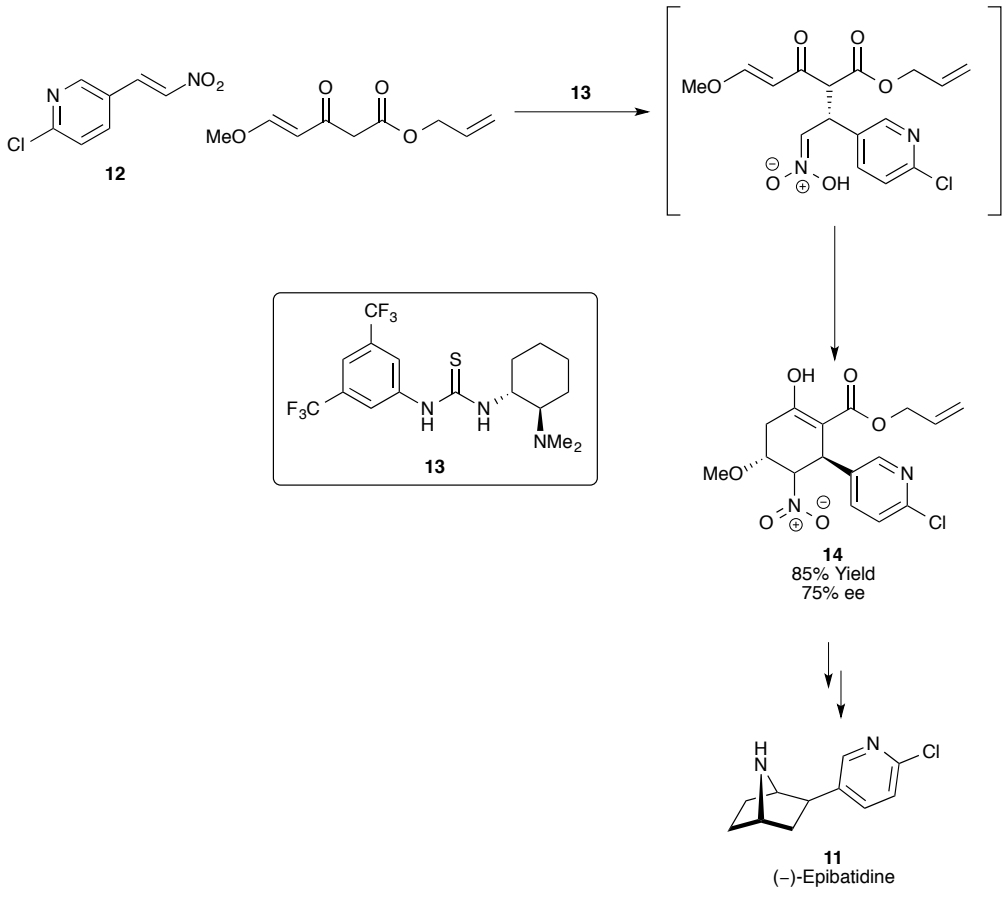

**Scheme 1.4: Jacøbsen's Brønsted Acid Catalysed Asymmetric Strecker Reaction**

Subsequent studies from the same group expanded this concept to include the Mannich reaction between *N*-Boc imine **9** and ketene acetal **10** (Scheme 1.5).[13] Access to the $\beta$-amino ester was achieved in excellent yield and ee and again it is presumed that a double hydrogen-bonding activation allows high reactivity and stereoselectivity in this process.




**Scheme 1.5: Asymmetric Thiourea Catalysed Mannich-Reaction**

Hydrogen-bonding catalysis has been successfully applied to the synthesis of many natural products including that of (–)-epibatidine **11** by Takemoto and co-workers in 2004 (Scheme 1.6).[14] The key step required activation of nitrostyrene **12** for an initial asymmetric intermolecular Michael addition catalysed by their thiourea catalyst **13**, followed by an intramolecular Michael addition which gave the ketoester product **14** in 75% ee.




**Scheme 1.6: Hydrogen-bonding Catalysis in the Synthesis of (–)-Epibatidine 11**

In this case, thiourea **13** acts as as a bifunctional catalyst with Takemoto proposing that the thiourea activates the nitro-olefin through a double hydrogen-bonding interaction whilst the neighbouring tertiary amine forms a hydrogen-bond to the incoming enol, enhancing its nucleophilicity. In this mechanism, the approach of the

nucleophile is also fixed by the chiral catalyst, which accounts for the high levels of enantioselectivity observed (Figure 1.1). Other advances in this area have involved the use of chiral stronger acids such as BINOL derived phosphoric acids.[6]

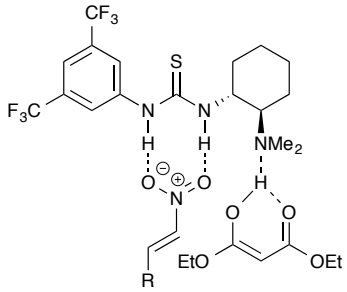
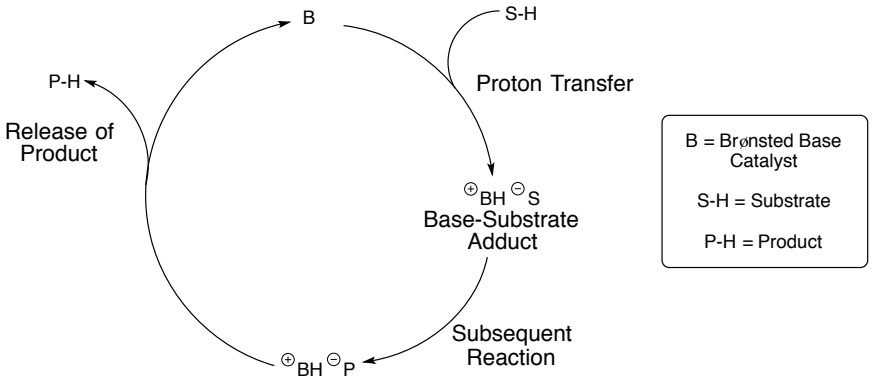



**Figure 1.1: Bifunctionality of Takemoto's Thiourea Catalyst 13**

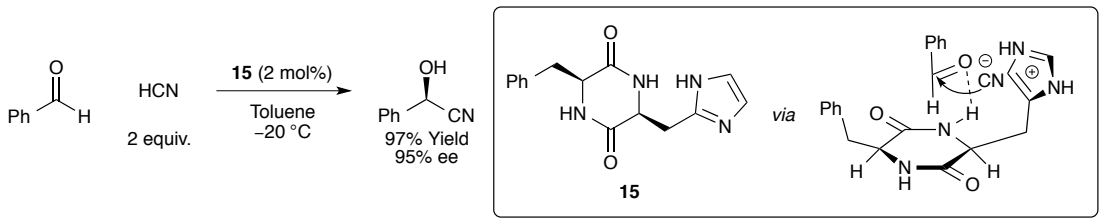
### 1.2.2 Brønsted Base Organocatalysis

A Brønsted base is defined as being as a molecule capable of accepting a proton from an acid and therefore in contrast to Brønsted acid catalysis, the Brønsted base catalytic cycle is initiated by complete or partial deprotonation of a substrate (Scheme 1.7). Typical examples of organic Brønsted base catalysis in asymmetric synthesis are hydrocyanation reactions and Michael additions.[3]



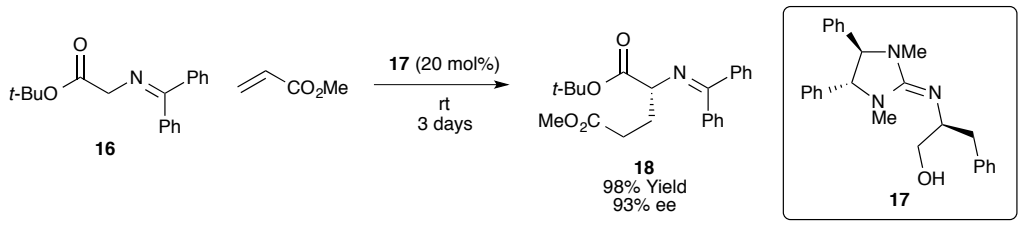

**Scheme 1.7: General Brønsted Base Catalytic Cycle**

Onoue *et al*. described an example of Brønsted base catalysis with use of cyclopeptide **15** as a catalyst in the addition of hydrogen cyanide to various aldehydes (Scheme 1.8).[15] This process produced cyanohydrins in excellent yield and ee, which could be further elaborated to $\alpha$-hydroxy carboxylic acids, $\alpha$-hydroxy esters, and $\beta$-amino alcohols.




**Scheme 1.8: Brønsted Base Catalysed Addition of Hydrogen Cyanide**

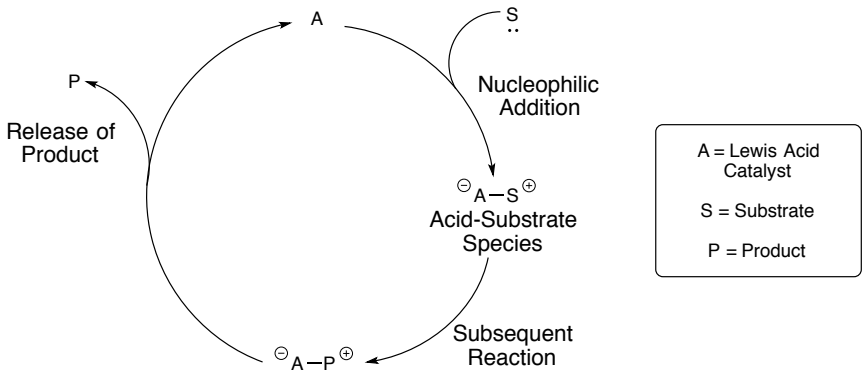
Another example of Brønsted base catalysis was reported by Isobe and co-workers describing the Michael reaction of a prochiral glycine derivative *t*-butyl diphenyliminoacetate **16** with acrylates in the presence of a modified guanidine catalyst **17** under solvent free conditions (Scheme 1.9).[16] Functionalised stereodefined amino esters **18** were isolated in high yield with enhanced enantioselectivity for a range of substrates.




**Scheme 1.9: Isobe's Brønsted Base Catalysed Michael Reaction**

### 1.2.3 Lewis Acid Organocatalysis

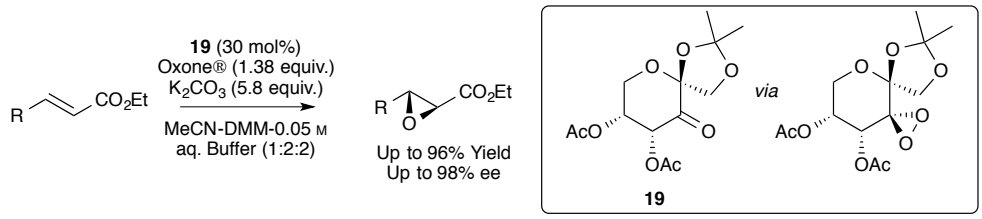
Lewis acid catalysts are defined as having a vacant orbital and activate nucleophilic substrates through accepting a lone pair of electrons (Scheme 1.10). Many examples fall into the class of phase-transfer catalysts in which the reaction of the catalyst and substrate facilitates migration from one phase (usually organic) to another (usually aqueous) where the reaction occurs.




**Scheme 1.10: Lewis Acid Catalysis General Cycle**

The epoxidation of olefins using chiral dioxiranes generated *in situ* is an important example of Lewis Acid organocatalysis. Shi's example utilises D-fructose derived

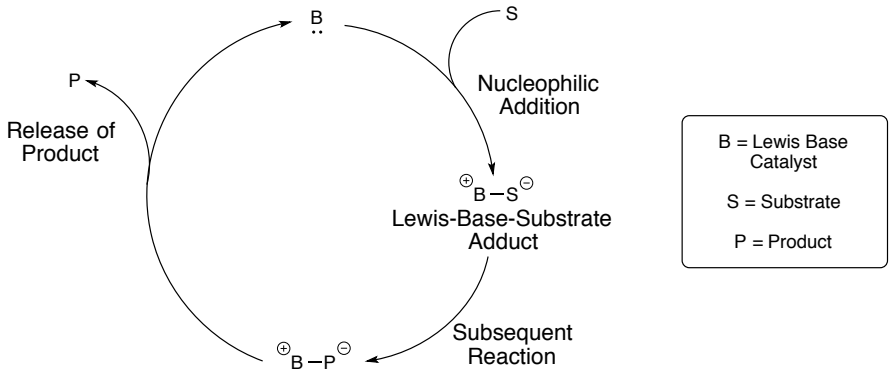
ketone catalyst **19** with Oxone® as a stoichiometric oxidant to generate the epoxide products in excellent ee (Scheme 1.11).[17]




**Scheme 1.11: Lewis Acid Catalysed Epoxidation Reaction**

### 1.2.4 Lewis Base Organocatalysis

In 1923, Gilbert N. Lewis proposed the definition of a Lewis base[18] as a molecule with a lone pair of electrons in its HOMO that can fill the valence shell of a Lewis acid (an electron deficient molecule). Lewis base-mediated catalysis represents the largest area of organocatalysis (Scheme 1.12). In this mode of catalysis, the Lewis base forms an adduct with a Lewis acid substrate *via* nucleophilic addition. This addition changes the reactivity of the substrate, converting it to either an activated nucleophile or electrophile[3] and therefore increases the rate of reaction with another reagent and product formation. The Lewis base is regenerated during this process resulting by definition in a catalytic process.[19]




**Scheme 1.12: Lewis Base Organocatalysis**

The Hajos-Parrish-Eder-Sauer-Wichert reaction is an early example of Lewis base catalysis (previously discussed in Scheme 1.2) and more specifically, enamine catalysis. Lewis base catalysis can be subdivided based upon activation mode into enamine, iminium, NHC catalysis and ammonium enolate catalysis amongst others (Figure 1.2) and representative examples of these selected reaction modes are described in the remainder of this chapter. Asymmetric Lewis base organocatalysis is

the main focus of research within the Smith group and therefore of this thesis, especially utilising isothiourea catalysts to form ammonium enolate intermediates.

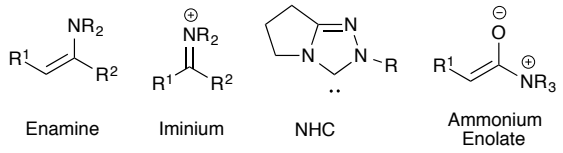
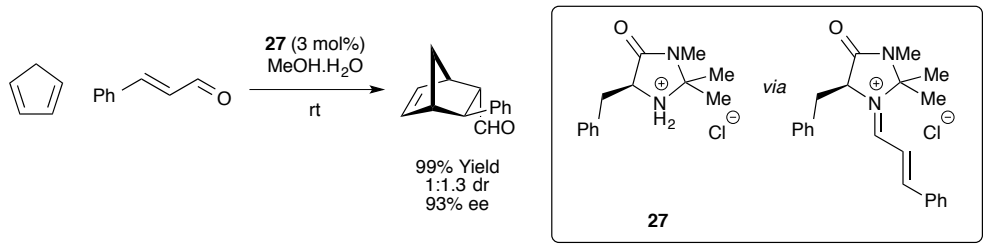



**Figure 1.2: Modes of Lewis Base Activation**

### 1.2.4.1 Iminium Catalysis

In iminium catalysis, reversible reaction of the Lewis basic amine catalyst with a carbonyl substrate forms an activated iminium ion lowering the LUMO. MacMillan's enantioselective Diels-Alder reaction of $\alpha,\beta$-unsaturated aldehydes and ketones, with dienes using a chiral imidazolidinone catalyst **27** was the pioneering example of this principle in modern organocatalysis (Scheme 1.13).[20] Although the diastereoselectivity of this reaction was low, the enantioselectivity was excellent, giving functionalised cyclohexanes in high yields.

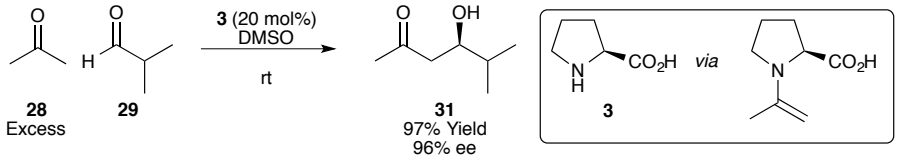



**Scheme 1.13: MacMillan's Enantioselective Diels-Alder Reaction**

This active species has been used to facilitate many asymmetric reactions including Knoevenagel condensations,[21] Diels-Alder reactions,[5] and 1,3-dipolar cycloadditions.[22]

### 1.2.4.2 Enamine Catalysis

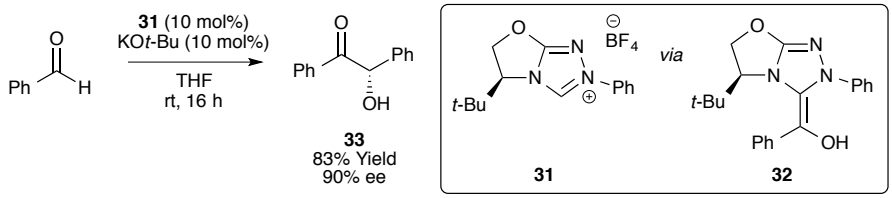
Formation of a catalytically generated iminium ion from a nucleophilic amine catalyst and a carbonyl compound, followed by deprotonation to form a nucleophilic enamine intermediate is the basis of enamine catalysis. This intermediate can then go on to react with various electrophiles or alternatively undergo a pericyclic reaction. List and co-workers developed enamine catalysis, expanding on the previously described Hajos-Parrish reaction, by reporting an intermolecular aldol reaction (Scheme 1.14).[23] They utilised ketone **28** and aldehyde **29** in a L-Proline **3** catalysed process and gave access to the crossed aldol product **30** in excellent enantioselectivity.




**Scheme 1.14: Asymmetric Intermolecular Aldol Reaction**

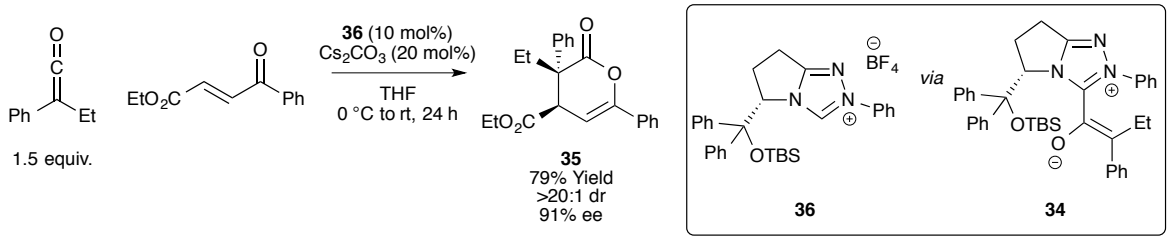
### 1.2.4.3 Carbene Catalysis

Carbene catalysis, particularly N-heterocyclic carbene (NHC) catalysed activation of a substrate can occur in a wide variety of reaction manifolds.[24] The use of NHCs to catalyse the benzoin reaction is well established with Enders and co-workers illustrating the use of a *t*-leucine-derived triazolium NHC **31** to catalyse an asymmetric benzoin reaction in 2002 (Scheme 1.15).[25] In this reaction, salt **31** is deprotonated *in situ* to reveal the carbene. The reaction then proceeds with the carbene adding into an aromatic aldehyde to form the Breslow intermediate **32** *via* an NHC/aldehyde tetrahedral adduct. The Breslow intermediate is nucleophilic and can add to a second molecule of aldehyde. Finally, extrusion of the NHC catalyst affords the benzoin product **33** in excellent yield and ee. The related carbene catalysed Stetter reaction also takes advantage of the reactivity of the Breslow intermediate.[26]




**Scheme 1.15: NHC-Catalysed Asymmetric Benzoin Reaction**

Chiral azolium enolates can be accessed by the reaction of NHCs with ketenes or *via* redox processes with $\alpha$-functionalised aldehydes or enals.[27] Ye and co-workers showed in 2008 that NHCs could catalyse the formal [4+2]-cycloaddition of disubstituted ketenes and enones *via* azolium enolate **34** forming the *anti*-dihydropyranone product **35** in excellent yield, dr and ee (Scheme 1.16).[28]

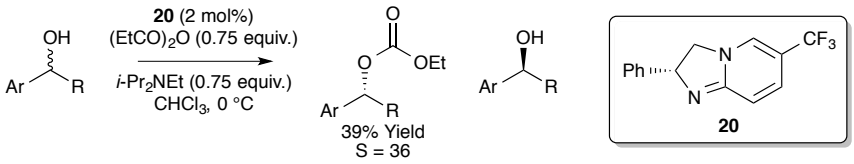



**Scheme 1.16: NHC-Catalysed Formal [4+2]-Cycloaddtion *via* Azolium Enolate 34**

The number of NHC-mediated reactions has vastly increased in recent years and now include reactions such as transesterification, activation of esters and conjugate additions amongst many others.[29]

### 1.2.4.4 Amidines and Isothioureas as Lewis Base Organocatalysts

In the last decade, Birman and co-workers have developed a range of catalysts based on amidine and isothiourea core structures.[30] These catalysts are highly successful in a range of processes such as the use of amidine **20** in the kinetic resolution of secondary alcohols (Scheme 1.17).[31]




**Scheme 1.17: Birman's Kinetic Resolution of Secondary Alcohols**

Following the success of amidine **20** in the resolution of secondary alcohols, the Birman group undertook investigations to optimise the structure of these catalysts (Figure 1.3).[32] The addition of a second aromatic ring led to the development of amidine **21**.[33] This was designed to have greater $\pi$-stacking with the aromatic alcohol substrates. It was found that both the reaction rate and selectivity were improved when compared with **20**. Birman and co-workers made a further improvement by changing to an isothiourea core. It was shown the commercially available isothiourea (–)-tetramisole.HCl **22** and its derivative (*R*)-benzotetramisole **23** were superior in the kinetic resolution.[34] The use of homobenzotetramisole (HBTM, **24**) led to increased levels of enantioselectivity[35] and then simultaneously but independently, Birman[36] and Smith[37] found that an alkyl substituent at the *C*(3) position of HBTM (**25** and **26**) gave an increase in catalytic activity when used in two different systems – the kinetic resolution of secondary alcohols, and *O*- to *C*-carboxyl group transfer of oxazolyl carbonates respectively.

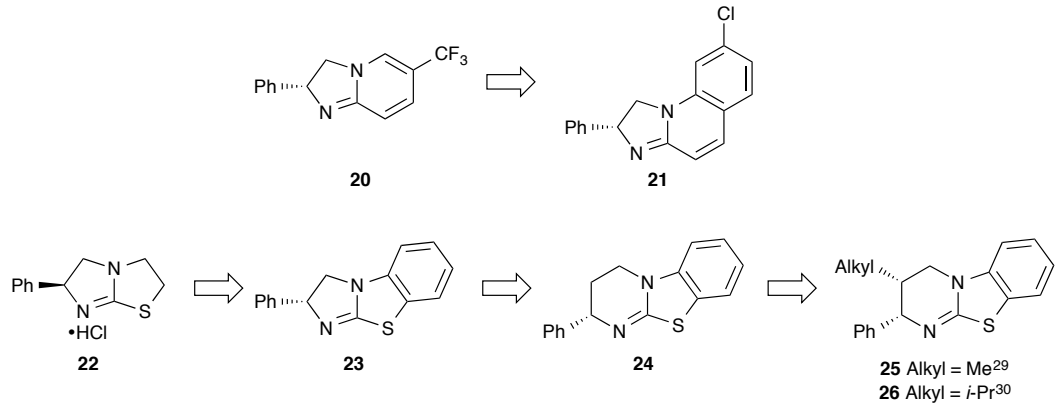



**Figure 1.3: Evolution of Amidine and Isothiourea Catalysts**

### 1.2.4.5 Ammonium Enolate Catalysis

Lewis base catalysis has recently been extended to include ammonium enolates as intermediates in asymmetric organocatalysis. This important and widespread strategy,[38] often explored utilising chiral tertiary amine catalysts, provides a chiral environment for enolate reactions allowing control of enantioselectivity and often result in enhanced reactivity.[39] Ammonium enolates can be subdivided and are classed as Type I, II or III with the number referring to the number of atoms from the enolate oxygen to the ammonium nitrogen (Figure 1.4). Type I enolates are formed directly from the reaction of a nucleophilic amine catalyst with a ketene or alternatively, by the acylation of a tertiary amine followed by deprotonation by a base. Type II ammonium enolates are formed by the $S_N2$ displacement of an $\alpha$ leaving group by an amine and Type III are generated by Michael addition of an amine to an acrylate or vinyl ketone. The ammonium enolate intermediate can then go on to react with a range of electrophiles and their use has been exploited in many areas of organocatalysis including $\beta$-lactone synthesis, $\alpha$-halogenation reactions and [4+2]-cycloaddition type reactions among others.[39]

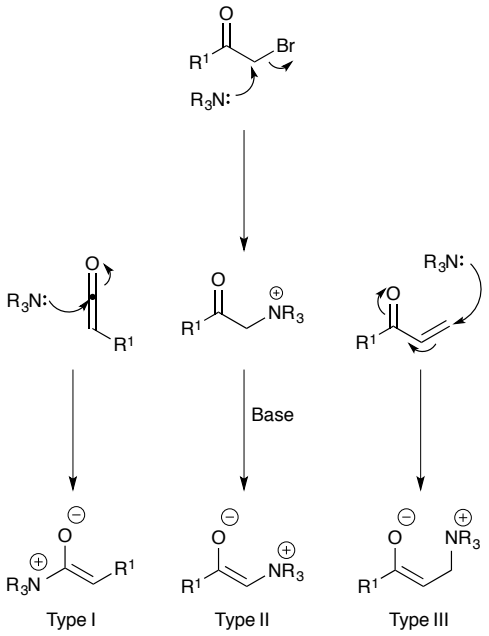
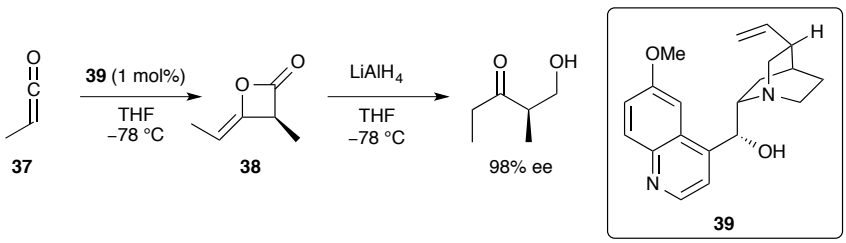


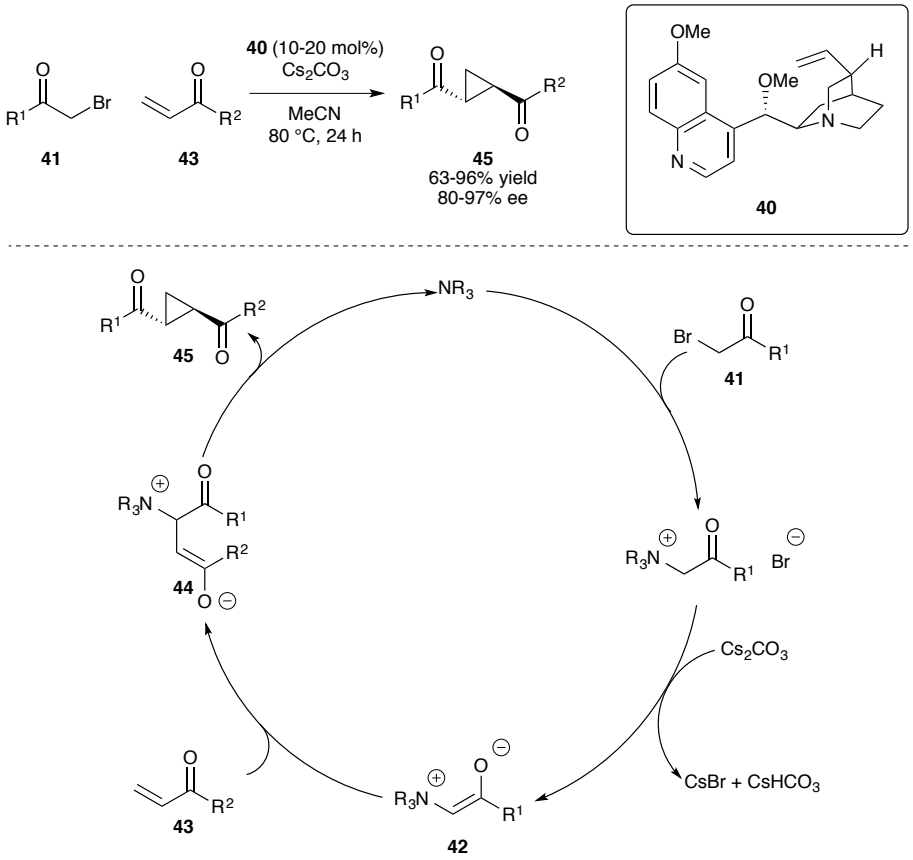

**Figure 1.4: Classes of Ammonium Enolate**

In the synthesis of $\beta$-lactones, Type I ammonium enolates are utilised to promote the asymmetric dimerization of ketenes. Early work by Pracejus and Sauer[40] was expanded by Calter into a method for asymmetric dimerisation of methylketene **37** giving the $\beta$-lactone product **38** in high ee (Scheme 1.18).[41] Subsequent lithium aluminium hydride mediated ring-opening gives access to highly versatile polyketide building blocks with preservation of stereochemistry.



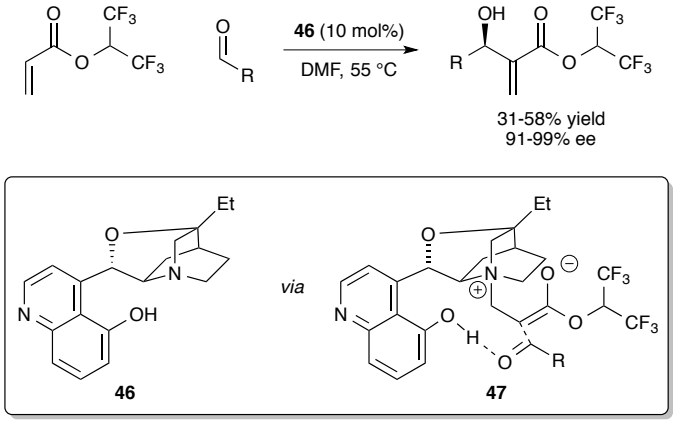

**Scheme 1.18: The Use of Type I Ammonium Enolates in $\beta$-Lactone Synthesis**

Gaunt *et al*. have shown Type II ammonium enolates can react in an intermolecular fashion with electron-deficient olefins to give cyclopropanes in excellent yields and ees (Scheme 1.19).[42] Initial nucleophilic attack of amine catalyst **40** on the alkyl halide **41** at the $\alpha$-position, followed by deprotonation forms ammonium enolate **42** (Type II). This activates the substrate which can then undergo Michael addition onto the vinyl ketone **43**, forming a Type III ammonium enolate species **44**. Nucleophilic attack of the enolate to release the catalyst forms cyclopropane product **45**.




**Scheme 1.19: Gaunt's Cyclopropane Formation and Mechanism**

The use of Type III ammonium enolates can be exemplified by the use of tertiary amine catalyst **46** in the Morita-Baylis-Hillman reaction (Scheme 1.20).[43] It is proposed that in this case the catalyst is "bifunctional" with the hydroxyl group being important in the observed selectivity, forming a hydrogen bond to the aldehyde carbonyl in the proposed transition state **47**, orientating it for attack by the ammonium enolate.

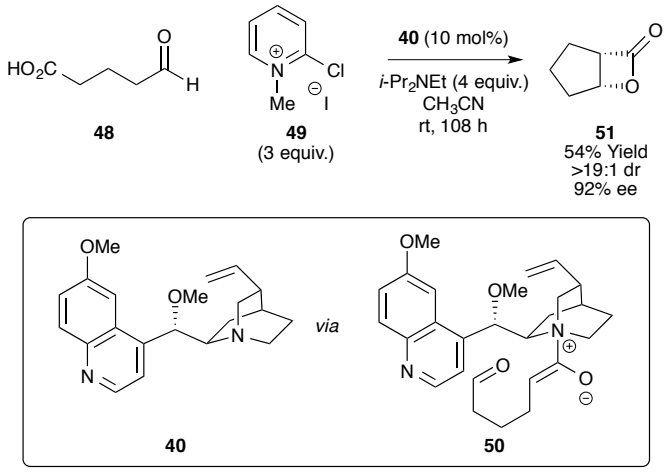



**Scheme 1.20: Type III Ammonium Enolates in a Catalytic Morita-Baylis-Hillman Reaction**

## 1.3 Type I Ammonium Enolates: Generation From Carboxylic Acids

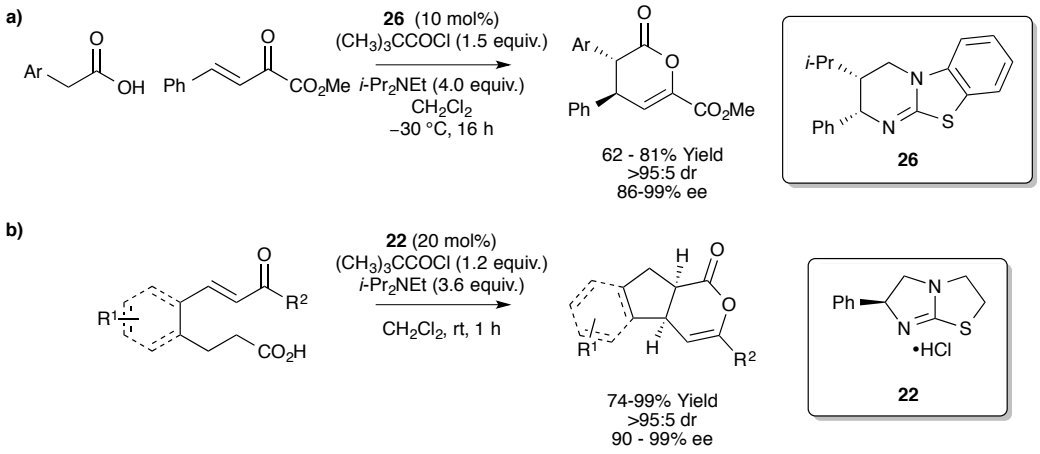
Recent work within the Smith group has focussed on investigating alternatives to the use of ketenes in the generation of Type I ammonium enolates. Ketenes can be difficult substrates to handle due to their high levels of reactivity, which in turn leads to poor long-term stability and often reduced isolated yields. There are also limitations in substrate diversity when using ketenes as starting materials with disubstituted ketenes being the most common.[44]

Activated carboxylic acids have been shown to be an excellent alternative to ketenes in the generation of Type I ammonium enolates. For example, Romo and co-workers reported their nucleophile-catalysed aldol lactonisation (NCAL) reaction in which carboxylic acid **48** undergoes activation by pyridinium salt **49** and in the presence of base and cinchona alkaloid **40** forms Type I ammonium enolate **50**. Intramolecular aldol reaction and lactonisation then occurs to give lactone **51** with excellent levels of stereocontrol (Scheme 1.21).[45]



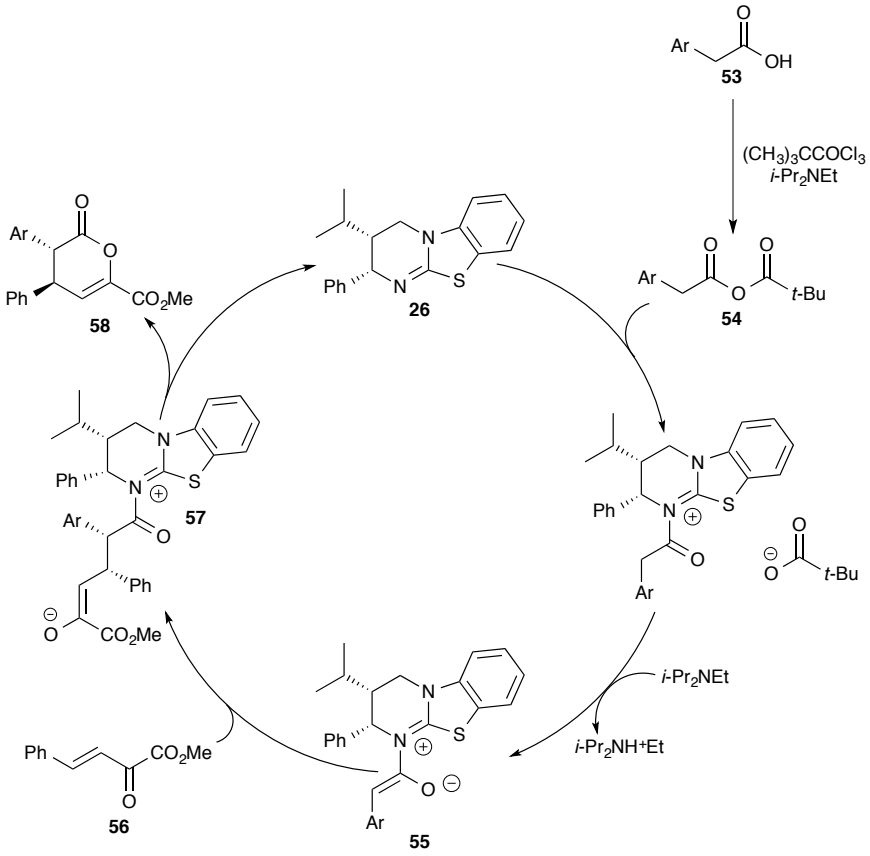

**Scheme 1.21: Organocatalytic β-Lactone Formation from Aldehyde-Acids.**

In 2010, the Smith group expanded the utility of this form of activation in asymmetric inter- and intra-molecular Michael-addition/lactonisation reactions (Scheme 1.22).[38] Using isothiourea catalyst **26** or **22**, the formal [4+2]-cycloaddition products can be accessed in high yield and enantioselectivities.



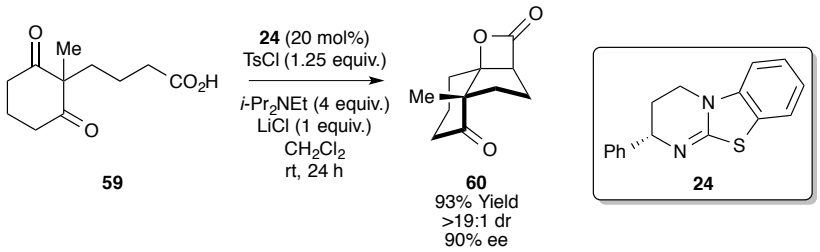

**Scheme 1.22: Isothiourea-Catalysed Asymmetric Inter- and Intramolecular Michael-Addition/Lactonisations**

In the proposed reaction mechanism for these reactions, activation of carboxylic acid **53** using pivaloyl chloride forms mixed anhydride **54** (Scheme 1.23). Nucleophilic addition of the isothiourea catalyst **26** and subsequent deprotonation gives access to the chiral Type I ammonium enolate **55**. The ammonium enolate then undergoes Michael addition to the double bond of the $\alpha,\beta$-unsaturated ketoester **56** to form zwitterionic intermediate **57**, which can then cyclise with release of the catalyst to give lactone product **58**. Following the publication of this work, the scope has been further expanded to further Michael acceptors including *N*-tosyl-$\alpha,\beta$-unsaturated ketimines,[46] *N*-aryl-*N*-aroyldiazenes[47] and trifluoromethylenones.[48]




**Scheme 1.23: Proposed Mechanism for the Isothiourea-Catalysed Intermolecular Michael-Addition/Lactonisation**

Subsequently, Romo has also extended his protocol towards highly enantioselective intramolecular desymmetrising aldol-lactonisation reactions, initially using isothiourea catalyst HBTM **24** (Scheme 1.24).[49] Similarly, this process is initiated by activation of keto-acid **59** with tosyl chloride and in the presence of base and the isothiourea, forms a Type I ammonium enolate that goes on to form tricyclic *β*-lactone **60** in excellent yield and ee.




**Scheme 1.24: Romo's Desymmetrising Aldol/Lactonisation Reaction**

## 1.4 Aims and Objectives

This thesis aims to investigate novel applications for Type I ammonium enolates generated from isothioureas and carboxylic acids in intermolecular cycloaddition reactions. In addition to expansion of their use in formal [4+2]-cycloaddition

reactions, their use in formal [2+2]- and [3+2] reactions will be discussed. The ultimate aim is to create efficient, straight-forward routes to highly stereodefined heterocyclic products and their derivatives using bench stable reagents and in open-flask conditions.

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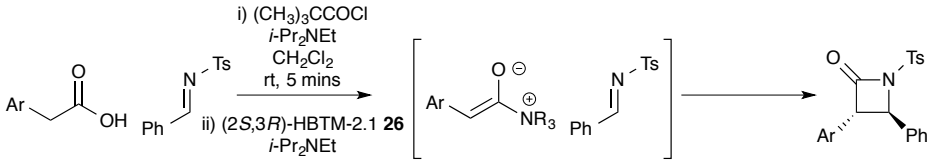
# Chapter 2: Asymmetric Synthesis of β-Lactams and β-Aminoesters using Isothiourea Organocatalysts

## 2.1 Introduction

To expand the scope of previous work within the group, this chapter develops an intermolecular formal [2+2]-cycloaddition based on the [4+2]-intermolecular Michael addition/lactonisation previously discussed. In looking for suitable partners for the [2+2]-cycloaddition, imines were attractive substrates as their use would lead to the formation of β-lactams, a widely recognised pharmacophore in both chemistry and biology, and therefore of great synthetic interest (Scheme 2.1).[1]




**Scheme 2.1: Proposed Route to β-Lactams *via* Isothiourea Generated Ammonium Enolates**

### 2.1.1 β-Lactams

Consisting of a 4-membered cyclic amide with up to two stereocentres in the lactam core, β-lactams are most famously the key structural component in many antibiotics, including the penicillins **61** (Figure 2.1). Since Sir Alexander Fleming, Scottish scientist and Nobel laureate, discovered the antibiotic behaviour of penicillin in 1928[2] and Dorothy Crowfoot-Hodgkin subsequently assigned its structure by X-ray crystallography in 1945,[3] the β-lactam ring has received extensive biological and synthetic investigations.[1] They are also key in a wide variety of other drugs for example Ezetimibe **62**, which is used for the inhibition of cholesterol absorption.[4] This central motif is also prevalent in natural products such as the cephamycins **63**, another family of antibiotic compounds. A large number of methodologies for the synthesis of β-lactams have been developed[5] and their use as synthons for the synthesis of a wide variety of targets has also been extensively studied.[6] Functionalisation of lactams allows access to heterocycles of various sizes, amino(hydroxyl) acid derivatives, β-amino ketones, γ-amino alcohols, and other compounds.[6,7]

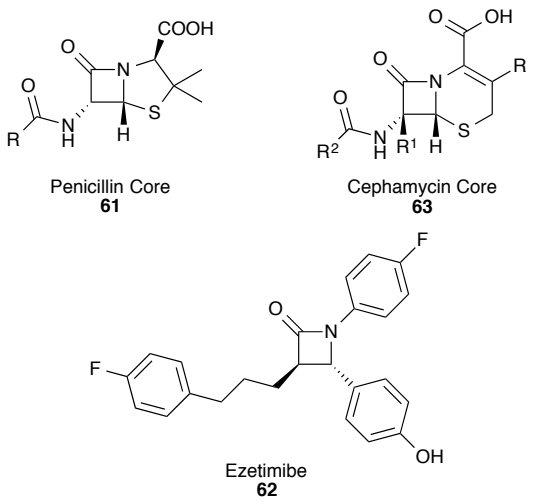
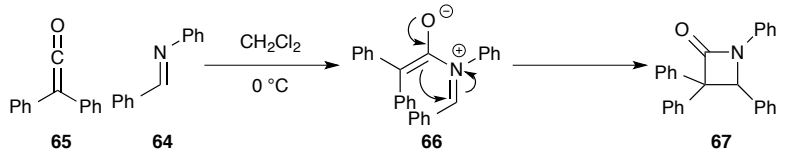



**Figure 2.1: A Range of Molecules Containing the β-Lactam Motif**

The β-lactam ring sets itself apart from other cyclic and acyclic amides with differences in their reactivity owing to changes in the rotational barrier of the carbonyl C-N bond. In an acyclic amide, this barrier is approximately 16-22 kcal $mol^{-1}$ as a consequence of the strong resonance between the nitrogen atom lone pair and the carbonyl π-system.[8] In the case of β-lactams, the strain of the four-membered ring disrupts this resonance making the carbonyl much more electrophilic. In extreme cases the β-lactam can be as reactive as acid chlorides, although in most cases β-lactams can still be isolated.[9] This also alters the IR stretch of the amide carbonyl – whereas acyclic amide carbonyls are typically *ca*. 1660 $cm^{-1}$, β-lactams show a stretch between 1720 and 1815 $cm^{-1}$.[10]

### 2.1.2 Preparation of β-Lactams

There are many routes for the construction of β-lactams including cyclisation reactions, cycloaddition reactions, organometallic-mediated reactions, and other miscellaneous approaches such as ring contraction and radical processes.[5] The first reported synthesis of a β-lactam through a formal [2+2]-cycloaddition of imines to ketenes was reported in 1907 by Staudinger (Scheme 2.2).[11] In this reaction, imine **64** acts as the nucleophile, adding to diphenylketene **65** forming zwitterionic intermediate **66** that undergoes ring-closure to give β-lactam product **67**.[12]

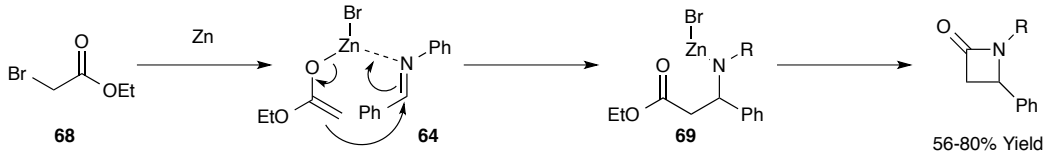



**Scheme 2.2: The Staudinger Reaction**

This synthesis did not receive much attention until the 1940's, but with the elucidation of the structure of the antibiotic penicillin G it has been extensively investigated as the basis of many modern routes into *β*-lactams. Recently these have focussed on the development of asymmetric and specifically catalytic methods.

### 2.1.2.1 Current Methods for *β*-Lactam Synthesis

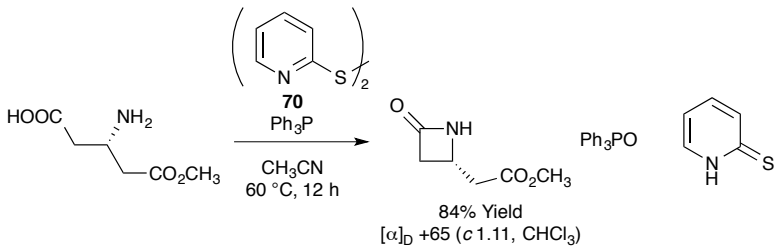
The Staudinger reaction marked the beginning of synthetic chemistry towards *β*-lactams and although many modern methods are based on this approach, there are a number of other existing methodologies for *β*-lactam synthesis. For example, Gilman and Speeter first reported the formation of *β*-lactams *via* condensation of ethyl α-bromoacetate **68** and *N*-phenyl benzaldimine **64** in 1943 as a modification of the Reformatsky reaction (Scheme 2.3).[13]




**Scheme 2.3: The Gilman-Speeter Reaction**

Although this process works reasonably well and is tolerant of a wide range of functional groups, including a range of aryl and alkyl substituents on the nitrogen atom, the yields are often reduced by competitive protonation of intermediate **69**. Grignard addition to the resulting side-product can convert it into the *β*-lactam *via* deprotonation and cyclisation, but this adds additional steps to the synthesis, decreasing the efficiency of this reaction.[14]

Alternatively, Ohno *et al*.[15] used triphenylphosphine and Mukaiyama's 2,2'-dipyridyldisulfide **70** to convert *β*-amino acids into *β*-lactams (Scheme 2.4). This is generally applicable to a wide range of *β*-amino acids with a range of functional groups but with varying yields.



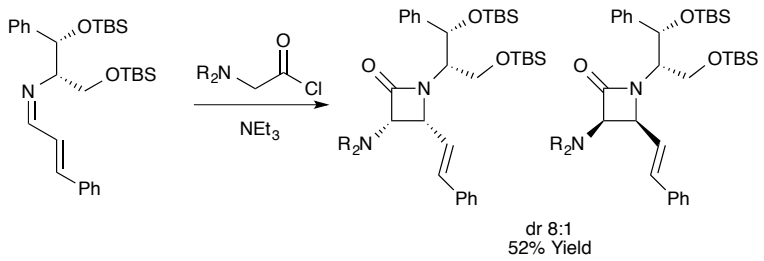

**Scheme 2.4: β-Lactam Formation Using Mukaiyama's Reagent 70**

Other methods towards β-lactams include photo-induced rearrangements[16] and radical cyclisations.[17] However, owing to the need for the effective synthesis of enantioenriched compounds, especially for medicinal chemistry, recent advancements have focussed on the development of stereoselective variants of these established synthetic methods.[10]

### 2.1.2.2 Methods for Asymmetric β-Lactam Synthesis

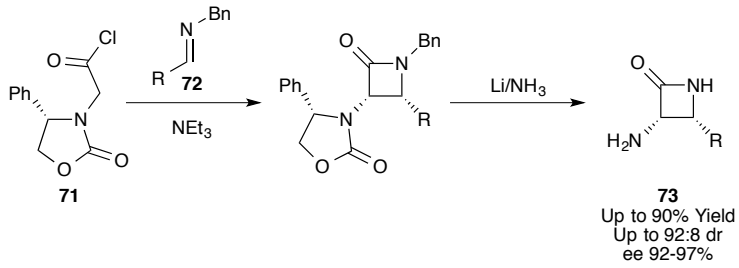
There are two possible stereocentres in the β-lactam core and therefore the possibility of up to four stereoisomers. Consequently, controlling the relative and absolute configuration during synthesis of these products is important in the context of using them as potential pharmaceuticals. In drug molecules different stereoisomers can have differing binding to their biological targets and therefore could possibly have entirely different pharmacological effects.[18] This was the case for Penicillin V, whose unnatural enantiomer has less than 1% of the efficacy of the natural enantiomer.[19] For these reasons, the development of asymmetric routes to enantiopure β-lactams are of great importance.

Much work has been carried out on introducing and controlling stereochemistry through adaption of the Staudinger reaction in which stereoinduction through either of the two components of the reaction is possible. Inducing asymmetry through the imine component can be achieved by utilizing an imine derived from either an enantiomerically enriched aldehyde[20] or the amine.[21] For example, Gunda used an enantioenriched *N*-protecting group on the imine to give the *syn*-β-lactam product in high diastereoselectivity but in only modest yield (Scheme 2.5). In addition, this method required two steps to synthesise the enantiopure imine and a further two steps to remove the *N*-protecting group if required.




**Scheme 2.5: Gunda's Chiral Auxiliary Approach to β-Lactam Synthesis**

Alternatively, Evans *et al*. demonstrated that the use of a stereodirecting group on the ketene could also be effective (Scheme 2.6).[22] Homochiral (4*S*)-phenyloxazolidylacetyl chloride **71** was used as a ketene precursor, with base being used to generate the ketene *in situ*. Following reaction with imine **72** and cleavage of both the chiral oxazolidinone and *N*-protecting groups in one step, β-lactam **73** was isolated in excellent yield and diastereoselectivity. The requisite oxazolidinone could be accessed in two steps from the commercially available amino acid (*S*)-phenylglycine in good overall yield (62%) and the facile, one-step removal is a benefit of this chemistry.



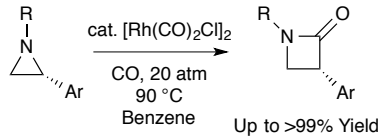

**Scheme 2.6: Evans's Chiral Auxiliary Approach to β-Lactam Synthesis**

However, both of these examples rely on chiral auxiliaries that whilst effective, are required in stoichiometric quantities with added costs and require extra steps for their introduction and removal.[10] It is for this reason that catalytic, asymmetric syntheses of the β-lactam ring have been of increasing interest in recent years.

### 2.1.2.3 Catalytic Asymmetric Synthesis of β-Lactams

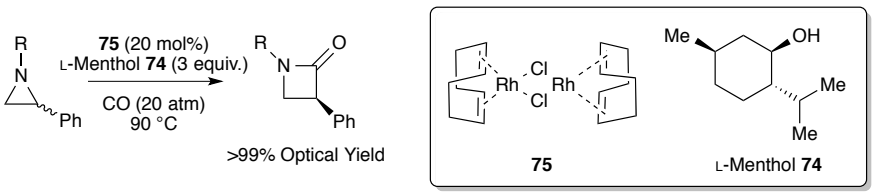
One of the first asymmetric synthesis of β-lactams in conjunction with catalysis was a metal-catalysed carbonylation reaction that produces β-lactam rings by the insertion of carbon monoxide into C-N bonds. Expanding on their 1981 work on the carbonylation of azirines,[23] Alper *et al*. reported the metal-catalysed carbonylation of aziridines to yield β-lactams (Scheme 2.7).[24] Using an enantiopure aziridine starting material, 5 mol% of a rhodium (I) catalyst under 20 atm CO pressure at 90 °C yielded

exclusive insertion of the carbon monoxide into the aryl-substituted C-N bond with complete retention of configuration and quantitative yields.



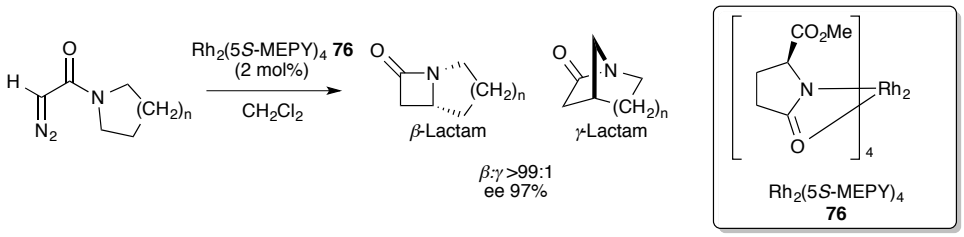

**Scheme 2.7: Rhodium Catalysed Carbonylation to β-Lactams**

This was later expanded to an asymmetric variant using racemic aziridines in a kinetic resolution (Scheme 2.8).[24b] Excess chiral additive L-menthol **74** was employed with a chloro(1,5-cycloctadiene)rhodium(I) dimer **75** as the catalyst to give the (*S*)-β-lactam in excellent optical yield. This gave access to optically enriched β-lactams using an inexpensive, commercially available chiral additive, although owing to the use of excess equivalents this could be seen as less efficient than later methods.




**Scheme 2.8: Kinetic Resolution of Aziridine to give β-Lactams in High Optical Purity**

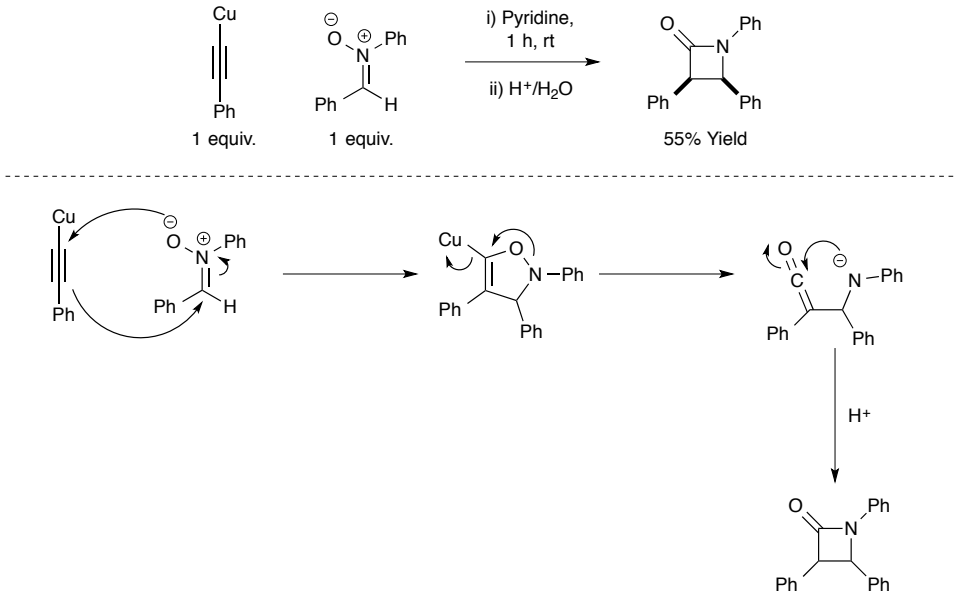
An alternative approach to β-lactam asymmetric synthesis is the intramolecular C-H insertion reaction. This process was first reported by Corey and Felix in 1965[25] and later developed into an asymmetric process by Doyle and co-workers (Scheme 2.9).[26] Using conformationally constrained diazoacetylazacycloalkanes to allow competitive formation of β-lactams over γ-lactams, chiral dirhodium(II) carboxamate catalyst **76** gave the desired β-lactam products in good yields and excellent enantioselectivity whilst using low catalyst loadings (2 mol%).




**Scheme 2.9: Rhodium Catalysed Asymmetric C-H Insertion Reaction**

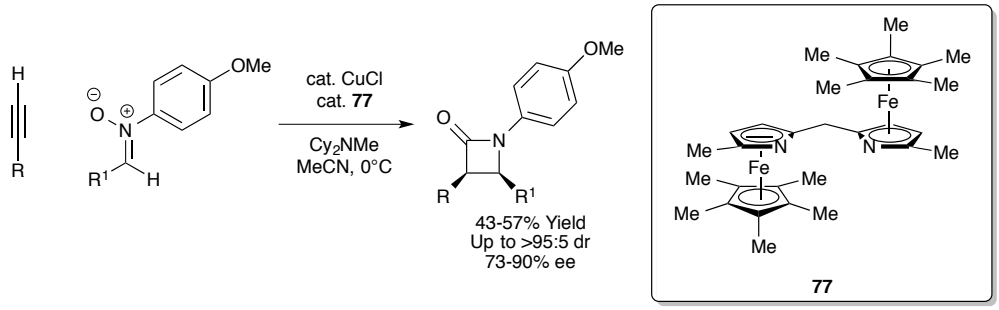
In 1972, Kinugasa and Hashimoto reported the synthesis of *syn*-β-lactams in the reaction between a copper(I) acetylide and a nitrone.[27] This original Kinugasa reaction used preformed stoichiometric copper acetylide, with the mechanism first proposed

by Ding and Irwin in 1976 (Scheme 2.10).[28] It is postulated that [3+2]-cycloaddition of the nitrone and copper acetylide initiates the reaction and following formation of ketene and cyclisation, the β-lactam product is formed. Ding had evidence to support this mechanism including experiments varying the groups on both the nitrone and acetylide, which led to products with the predicted substitution patterns, whilst reaction in the presence of $^{18}O$ labelled water produced no $^{18}O$-labelled products. This indicated that the oxygen in the product was derived from the nitrone.




**Scheme 2.10: Kinugasa Reaction**

The Kinugasa reaction is amenable to catalysis with the first catalytic modification described by Miura in 1993 and later extended to incorporate chiral ligands.[29] However, this reaction is highly sensitive to both the ligand used and the substitution on the nitrone, with the product distribution between β-lactams, azaenynes, imines and carboxylic acids varying and the methodology generally suffers from low enantioselectivities.[51a] In 2002, Fu and co-workers developed the first successful diastereo- and enatioselective catalytic variant in which a variety of nitrones and terminal alkynes were coupled to make *syn*-β-lactams using 1-2.4 mol% of CuCl and a $C_2$-symmetric planar-chiral bis(azaferrocene) ligand **77** (Scheme 2.11).[30] This successful method incorporated a wide scope of nitrones and alkynes with good isolated yields and high ees and drs.

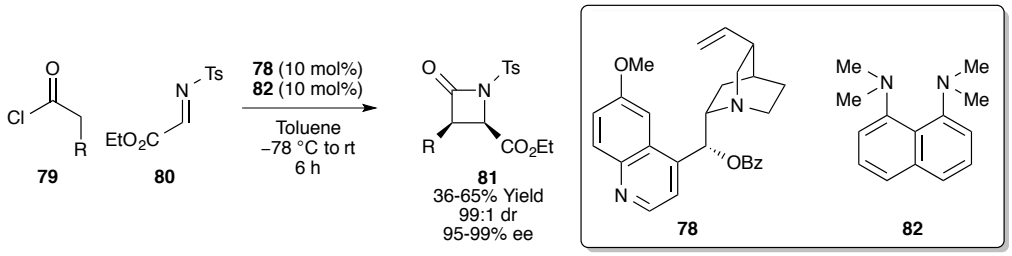



**Scheme 2.11: Fu's Enantioselective Kinugasa Reaction**

### 2.1.2.4 Organocatalytic Asymmetric Synthesis of β-Lactams

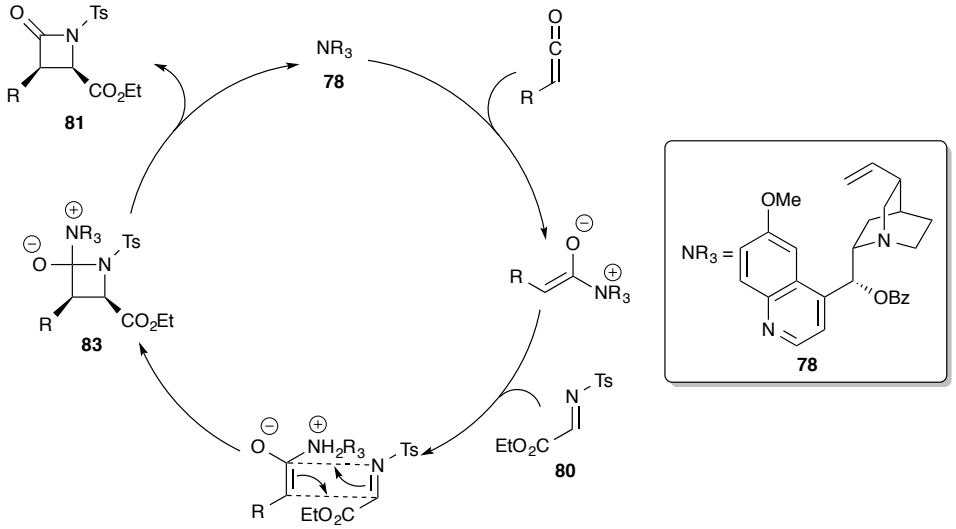
By far the most successful methods for the asymmetric synthesis of β-lactams to date have been based on an organocatalytic umpolung Staudinger approach with nucleophilic addition of a ketene-derived enolate to the imine.[10] Pioneered by Lectka in 2000,[31] examples of asymmetric β-lactam formation have been shown independently by Fu and Lectka using enantioenriched amines and N-heterocyclic carbenes as organocatalysts.

Lectka *et al*. showed that cinchona alkaloid benzoylquinine **78** (BQ) or benzoylquinidine (BQd) could catalyse the addition of a range of mono- and disubstituted ketenes (with the very reactive monosubstituted ketenes formed *in situ* from acid chlorides **79**) to electron-deficient *N*-tosylimino ester **80**. This gives the *syn*-β-lactam product **81** in excellent enantio- and diastereoselectivities but usually with moderate yields (Scheme 2.12).[32] A non-nucleophilic base was required to form the ketene in order to avoid a base catalysed racemic background reaction. In this case, proton sponge **82** was the superior base and, whilst not being able to form the ketene itself, could act as a thermodynamic sink allowing the more kinetically active BQ or BQd to deprotonate the ketene precursor and shuttle the proton to the proton sponge that precipitates as the hydrochloride salt. This leaves the BQ free to catalyse the desired reaction.



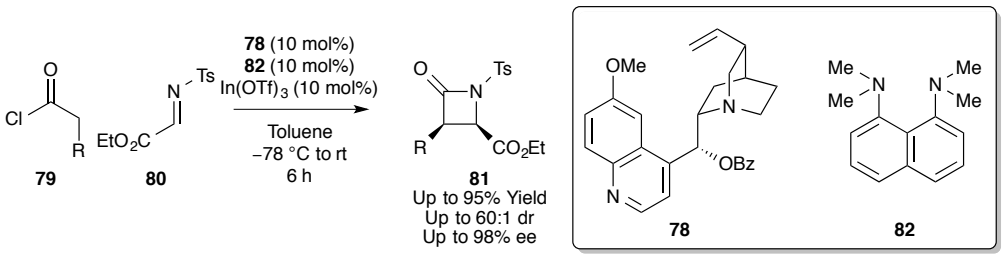

**Scheme 2.12: Asymmetric Organocatalytic Synthesis of β-Lactams Using a Cinchona Alkaloid Catalyst**

The proposed mechanism involves initial attack of the amine catalyst **78** on the carbonyl of the ketene to form the ammonium enolate, followed by formal [2+2]-cycloaddition with the imine acceptor **80** to generate **83**. Release of the catalyst produces the *β*-lactam product **81** (Scheme 2.13).




**Scheme 2.13: Proposed Mechanism for the Organocatalytic Asymmetric Staudinger Reaction**

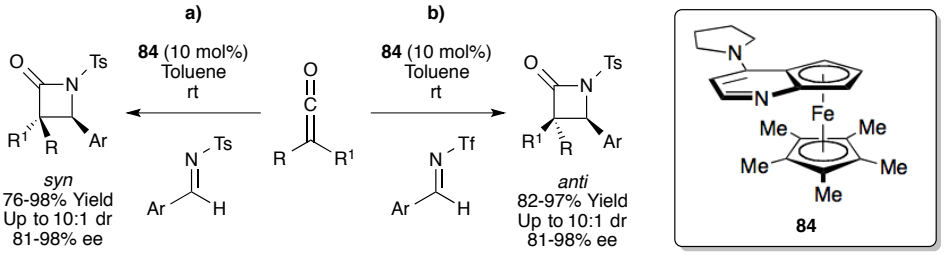
This work was later extended by Lectka to incorporate solid-phase chemistry with the catalyst held on a solid-support resin.[33] This method gave the *β*-lactam products in comparable yields (65%) and high ee (>99%) following recrystallisation. The catalyst-packed columns could be used up to 20 times without sacrificing yield or ee. The yields of the original system were then improved (up to 95%) with the use of a bifunctional catalyst system with 10 mol% $In(OTf)_3$ as a co-catalyst to further activate the imine (Scheme 2.14).[34] These methods, whilst practical and allowing access to the *syn-β*-lactams in high levels of stereoselectivity, were very limited as the scope of the imine is confined almost exclusively to the highly reactive tosyl imino ethyl ester **80**.[10]




**Scheme 2.14: Improved Yields with Use of Indium Triflate Co-catalyst**

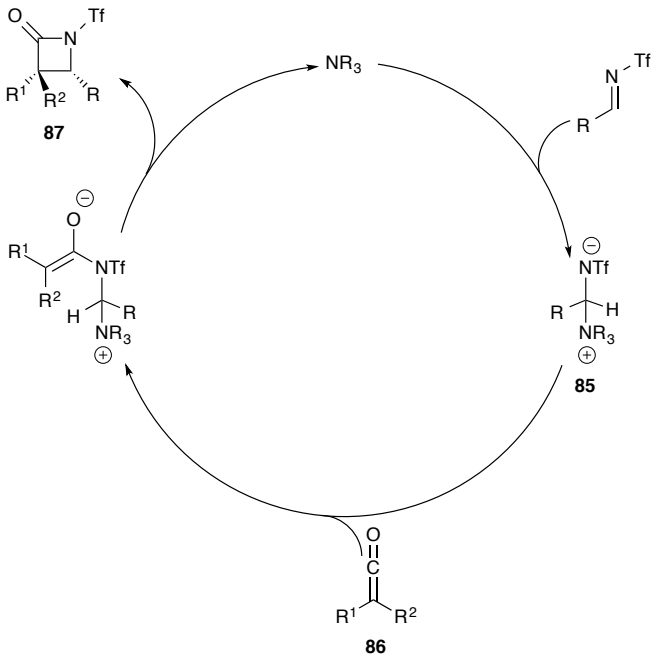
In 2001, Fu showed that a planar-chiral 4-(pyrrolidino)pyridine (PPY) derivative **84** was also a highly efficient catalyst for the umpolung Staudinger reaction (Scheme

2.15a).[35] In the reaction of both symmetrical and unsymmetrical preformed aryl and alkyl ketenes with a wide range of *N*-tosyl imines, the trisubstituted *β*-lactams could be accessed in up to 94:6 dr (*syn:anti*) and up to 98% ee. A drawback of this method is that it is limited to disubstituted ketenes. Mechanistically, this is believed to proceed in a similar manner to the Lectka method. Interestingly, when Fu investigated varying substituents on the imine nitrogen atom, it was found that by changing the nitrogen protecting substituent from tosyl to triflate the diastereoselectivity of the reaction was reversed to favour the *anti*-product, again with good dr and ee (Scheme 2.15b).[36] Unfortunately, the high cost of the synthesis of these imines limits the commercial viability of this route to *anti*-*β*-lactams.



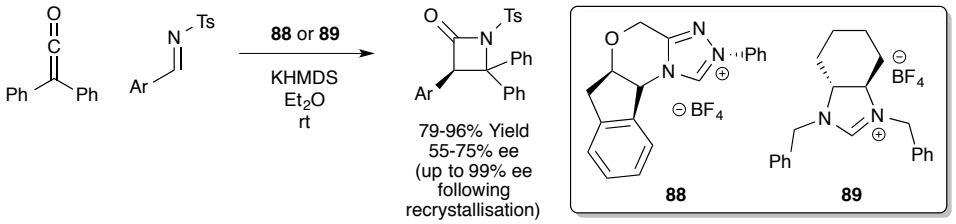

**Scheme 2.15: Fu's Reversal of Diastereoselectivity Using *N*-Trifyl Imines**

It is proposed that the diastereoselectivity is altered owing to a change in mechanism. It has been suggested that with a *N*-triflyl substituent the catalyst preferentially attacks the imine to form zwitterionic intermediate **85** (Scheme 2.16). The anionic nitrogen atom can then add to the carbonyl of the ketene **86** and, following enolate cyclisation, generate *β*-lactam **87** in high diastereo- and enantioselectivities. However, this is purely speculative with no evidence to support this mechanism other than the change in observed diastereoselectivity.



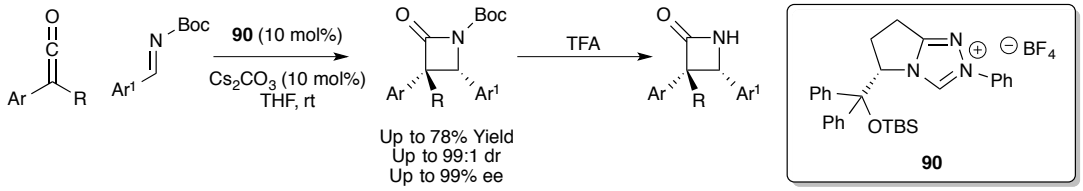

**Scheme 2.16: Proposed Mechanism to Account for the Change in Diastereoselectivity**

In 2008, it was shown by the Smith group that NHCs can also be used as organocatalysts in the Staudinger reaction (Scheme 2.17).[1] They promote the formal [2+2]-cycloaddition of diphenyl ketenes with *N*-tosyl imines to give the *β*-lactam products in excellent yields and when using chiral NHCs modest ees (55-75%) that could be improved by recrystallisation.



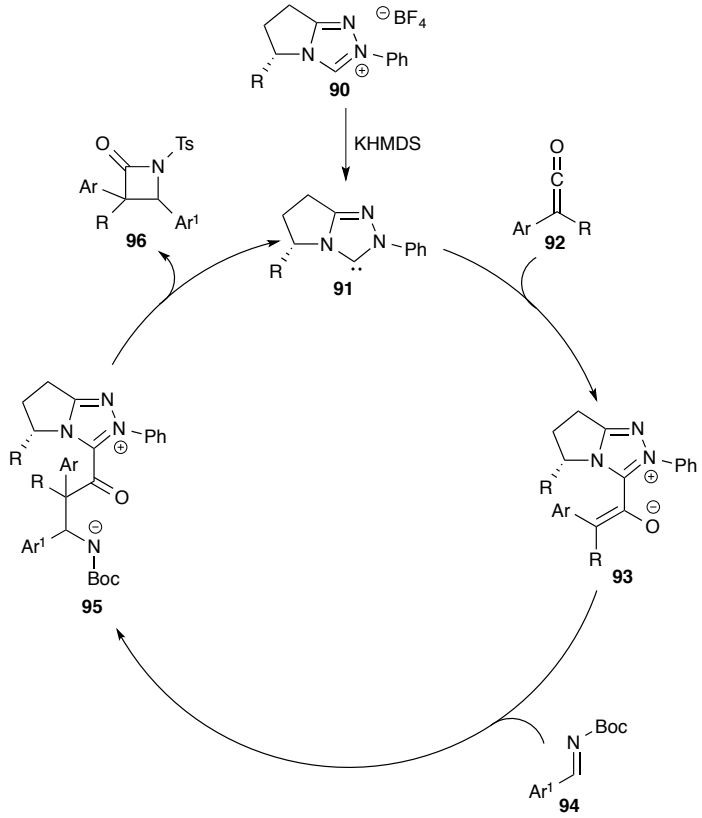

**Scheme 2.17: Asymmetric Formation of *β*-Lactams using N-Heterocyclic Carbenes as Organocatalysts**

Independently in 2008, Ye published a similar route to *β*-lactams using NHCs as organocatalysts in the reaction of disubstituted ketenes and *N*-Boc-substituted imines to form *syn*-*β*-lactams (Scheme 2.18).[37] Although the yields were moderate (53-78%), the ees and drs were generally excellent. This route also gave access to the free *β*-lactam as the Boc group can be removed by TFA without loss of enantiopurity. However, both this and the previous example from the Smith group are limited to disubstituted ketenes.



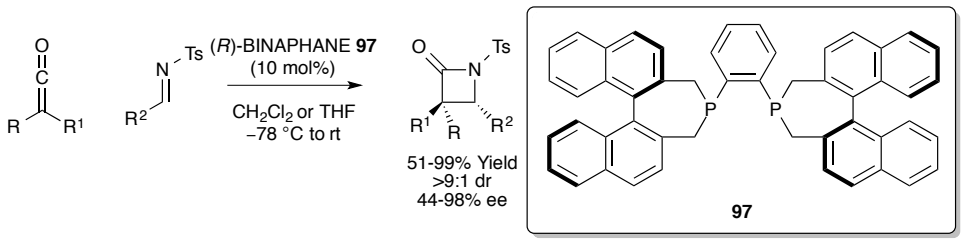

**Scheme 2.18: Ye's Approach to Organocatalytic Asymmetric Formation of β-Lactams**

In the proposed mechanism for these examples (Scheme 2.19), the NHC **91**, generated by deprotonation of the corresponding salt **90**, adds to the carbonyl of the ketene **92** forming zwitterionic intermediate **93**. The enolate then attacks imine **94** to give intermediate **95**, which following intramolecular cyclisation and release of the carbene affords β-lactam product **96**.




**Scheme 2.19: Proposed Mechanism for the use of NHCs as Organocatalysts in the Asymmetric Formation of β-Lactams**

More recently, Kerrigan reported a method that favours the generation of *anti*-β-lactams from disubstituted ketenes, *N*-tosylaryl imines and a nucleophilic phosphine catalyst **97** (Scheme 2.20).[38] The β-lactams are formed in modest to excellent yields (51-99%) and ees (44-98%), and typically excellent drs (*anti:syn* 9:1). A major advantage of this route over Fu's is the use of the less expensive *N*-tosyl instead of *N*-triflyl imines.



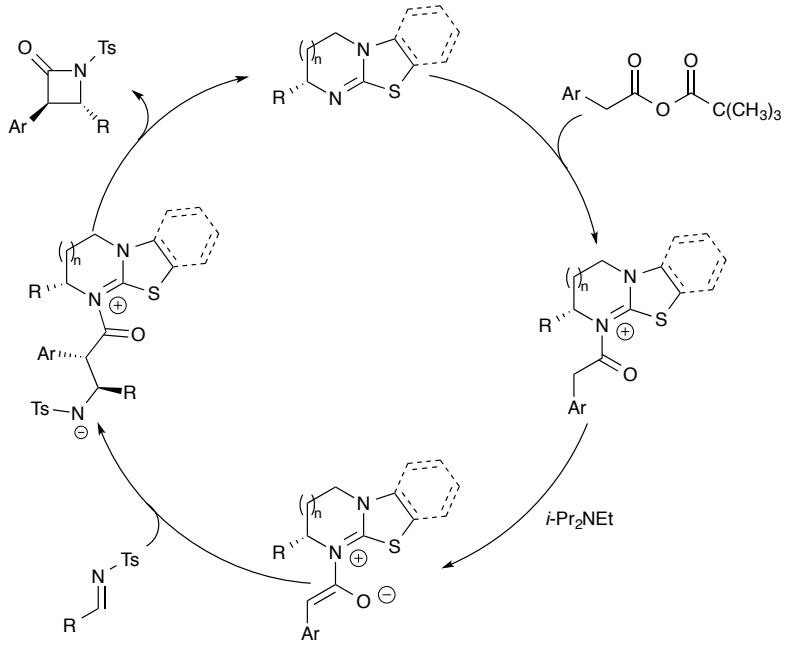

**Scheme 2.20: Kerrigan's Approach to β-Lactam Synthesis**

## 1.1 Aims and Objectives

Although many routes to β-lactams have been reported, organocatalytic methods based on the Staudinger reaction currently rely on the use of ketene starting materials. Although synthetically useful compounds, ketenes are notoriously difficult to work with owing to their high reactivity, poor long-term stability and inconvenient preparation. Therefore we felt there was scope for a new method based on the ammonium enolate chemistry developed within the Smith group as an alternative Staudinger approach.

It was postulated that direct replacement of the α,β-unsaturated keto-esters used as four components in asymmetric Michael additions with an imine two component would lead to β-lactam formation (Scheme 2.21). There is scope for variation of the catalyst (including changes in the ring size and functionalisation), the acid (variation of the aryl group to introduce more steric bulk, electron-donating and withdrawing groups or heteroatoms) and the imine (varying the R-group and the *N*-protecting group).

It was hoped that the *anti*-product would predominate as opposed to the *syn*-products observed previously through the method reported by Lectka. If this were the case, it would give a more convenient and cheaper approach to these highly desired products without the use of expensive *N*-triflyl imines employed by Fu or the difficult to handle ketene starting materials.[39]



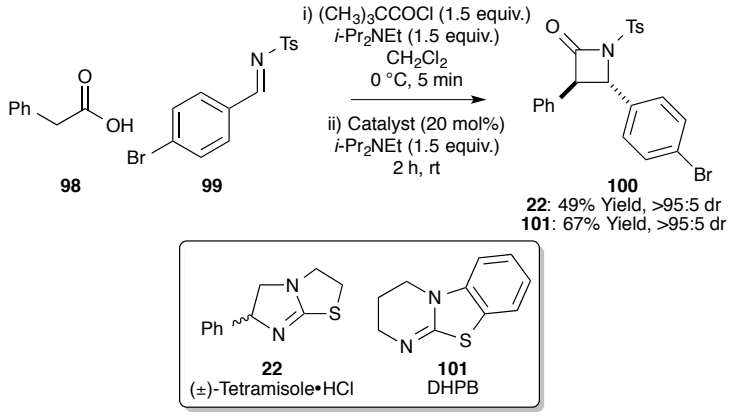

**Scheme 2.21: Postulated Mechanism for Formation of β-Lactams *via* Ammonium Enolates**

## 2.2 Results and Discussion

### 2.2.1 Initial Optimisation of Reaction to β-Lactams

#### 2.2.1.1 Model Reaction

Initial studies focussed on trialling the use of imines under the standard conditions previously optimised within the group for the intermolecular Michael addition/lactonisation reactions using pivaloyl chloride as the carboxylic acid activating agent.[40] Phenylacetic acid **98** and *p*-bromo-*N*-tosyl imine **99** were used for the initial screen using racemic tetramisole **22** as the catalyst. We were pleased to observe the formation of essentially one diastereoisomer (dr >95:5) of the expected β-lactam product **100** in a 49% yield (Scheme 2.22). Under the same reaction conditions achiral DHPB **101** could be used, giving a slightly higher yield of 67% yield of **100** with the dr remaining the same.




**Scheme 2.22: Formation of β-Lactam 100 Using an Isothiourea Catalyst**

### 2.2.1.2 Determination of Stereochemistry

Much study into the coupling constants between the *C*(3) and *C*(4) protons of the *β*-lactam ring has been carried out. Akagi *et al*., reported the coupling constants of the *syn* and *anti* diphenyl *β*-lactams as $^{3}J_{H\text{-}H}$= 6 and 3 Hz, respectively (Figure 2.2).[41] This pattern is a general phenomenon and is widely used to assign the relative stereochemistry in *β*-lactams.

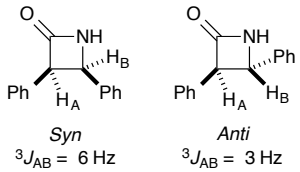



**Figure 2.2: Reported Coupling Constants in β-Lactam Rings**

For example, Gunda *et al*. used the analogy to these coupling constants to assign their *β*-lactam products as predominantly the *syn*-diastereoisomer ($^{3}J$ = 5.6 Hz) (Figure 2.3) and this was later confirmed by nOe analysis.[42]

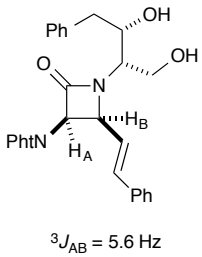
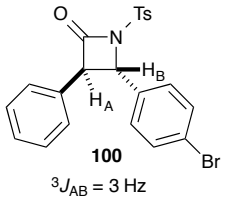



**Figure 2.3: Gunda's β-Lactam Product**

The same analogy was used to assign the major diastereoisomer of *β*-lactam **100** as the *anti* product ($^{3}J$ = 3 Hz) (Figure 2.4) and was also applied to all further products. Following this, nOe analysis showed no transfer of spin from $H_A$ and $H_B$ confirming the *anti* stereochemistry of this *β*-lactam.




**100**

$^3J_{AB}$ = 3 Hz

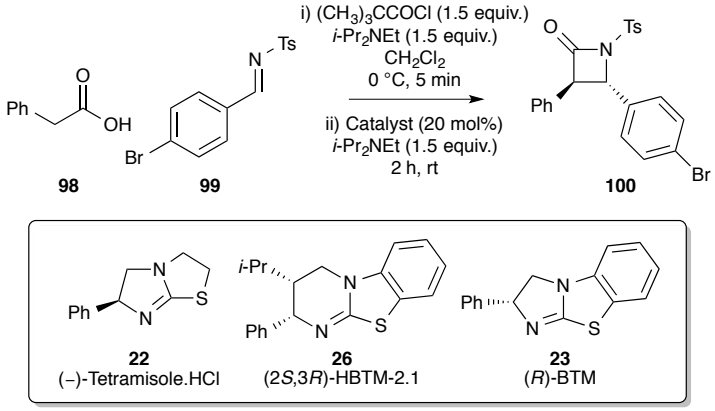
**Figure 2.4: Assignment of Our Major Diastereoisomer**

### 2.2.1.3 Chiral Catalyst Screen

The range of chiral isothiourea catalysts available to us, (–)-tetramisole.HCl **22**, (2*S*,3*R*)-HBTM-2.1 **26** and (*R*)-BTM **23** were then screened under the initial reaction conditions (Table 2.1). All reactions gave high diastereoselectivity for the *anti*-product although with modest ees.

During the course of our studies into the reactivity of this process a test reaction was carried out to investigate the possibility of a racemic background reaction. Under standard reaction conditions with omission of the isothiourea catalyst, formation of the product was observed in relatively good yield (entry 4). The implication is that the *in situ* formed mixed anhydride is sufficiently reactive enough to cyclise with the imine promoted by the base present in the reaction.

A change in procedure was devised in which the mixed anhydride would be formed in the absence of the imine. Following addition of the chiral isothiourea catalyst and base, allowing formation of the chiral ammonium enolate in catalytic amounts, the imine would be added and cyclisation would form the *β*-lactam, hopefully avoiding high levels of the racemic background reaction occurring. Under this new procedure, with (–)-tetramisole.HCl **22** as the catalyst, the ee of product **100** was slightly increased from 57% to 60% (entry 5).

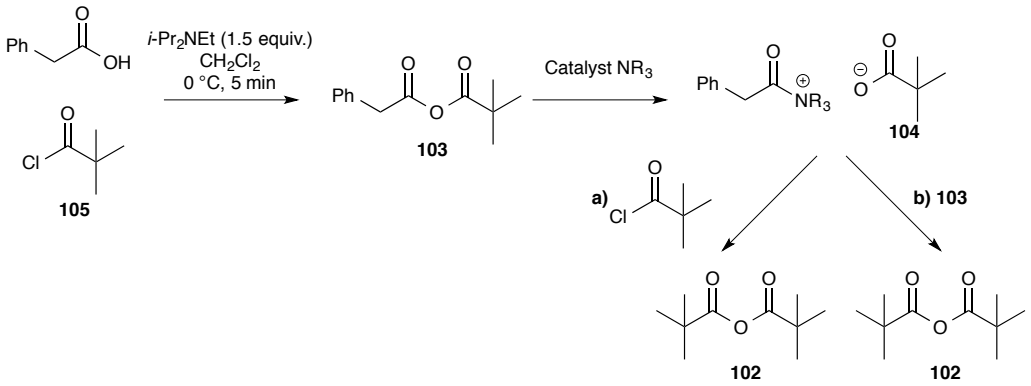



| Entry | Catalyst | Yield (%)[a] | Pivalic Anhydride (%)[a] | dr (*anti:syn*)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | (–)-Tetramisole.HCl **22** | 37 | 5 | >95:5 | 57 |
| 2 | (2*S*,3*R*)-HBTM-2.1 **26** | 89 | 4 | >95:5 | 57 (*ent*) |
| 3 | (*R*)-BTM **23** | 67 | 7 | >95:5 | 66 (*ent*) |
| 4 | None | 39 | 3 | >95:5 | N/A |
| 5 | (–)-Tetramisole.HCl **22** | 67 | 6 | >95:5 | 60 |

[a] As a mixture of β-lactam and pivalic anhydride. [b] Determined by inspection of $^1$H NMR spectrum of crude. [c] Obtained by chiral HPLC analysis.

**Table 2.1: Chiral Isothiourea Catalyst Screen**

However, a major concern with our development of this methodology at this stage were variable yields. Although in all cases the quoted yields contain a majority of the β-lactam product, they also all contained varying amounts of pivalic anhydride that could not be readily separated by chromatography. Considering our proposed mechanism, the pivalic anhydride **102** by-product may arise *in situ* in two ways (Scheme 2.23). Following generation of the mixed anhydride **103** and subsequent reaction with the Lewis base catalyst, the carboxylate leaving group **104** could react with excess pivaloyl chloride **105** to form homoanhydride **102** (Scheme 2.23a). Alternatively, the homoanhydride can be formed *via* reaction of the same anionic leaving group **104** with the mixed anhydride **103** (Scheme 2.23b).

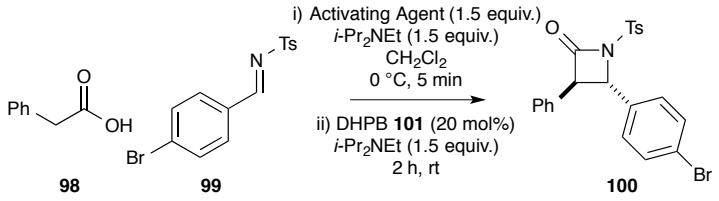



**Scheme 2.23: Proposed Mechanisms for Generation of Homoanhydride 102**

Despite numerous attempts, a suitable purification method could not be found and this contaminant was unable to be removed from the product. It was therefore concluded that it would necessary to screen alternative activating agents for this process.

### 2.2.1.4 Screening of Activating Agents

4-Methoxybenzoic anhydride and tosyl chloride were chosen as possible alternatives to pivaloyl chloride and were screened under the previous racemic reaction conditions (Table 2.2). When using 4-methoxybenzoic anhydride, no conversion into the product was observed (entry 2). Tosyl chloride was more successful, forming the desired *β*-lactam product, again in excellent dr (entry 3) and although the isolated yield remained the same as with pivaloyl chloride, the actual yield of *β*-lactam product was increased as it could now be successfully purified. Therefore, tosyl chloride was selected as our activating agent of choice in further studies.

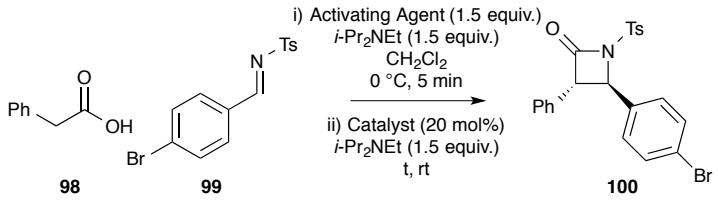



| Entry | Activating Agent | Yield (%) | dr (*anti:syn*)[b] |
|---|---|---|---|
| 1 | Pivaloyl chloride | 67[a] | >95:5 |
| 2 | 4-Methoxybenzoic anhydride | NR | N/A |
| 3 | Tosyl chloride | 68 | >95:5 |

[a] As a mixture of *β*-lactam and pivalic anhydride. [b] Determined by inspection of $^1$H NMR spectrum of crude.

**Table 2.2: Screening of Activating Agents**

A further advantage of changing the activating agent to tosyl chloride was an enhanced enantioselectivity of the reaction compared with pivaloyl chloride (Table 2.3). These results allowed us to select (*R*)-BTM **23** and tosyl chloride as the optimum catalyst and activating agent respectively, with this combination giving *β*-lactam **100** in 77% yield , >95:5 dr and 85% ee (entry 4).




**98** **99** **100**

| Entry | Catalyst | Activating Agent | t (h) | Yield (%) | dr (*anti:syn*)[b] | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | (2*S*,3*R*)-HBTM-2.1 **26** | PivCl | 2.5 | 89[a] | >95:5 | 57 |
| 2 | (2*S*,3*R*)-HBTM-2.1 **26** | TsCl | 4.5 | 32 | >95:5 | 72 |
| 3 | (*R*)-BTM **23** | PivCl | 2.5 | 67[a] | >95:5 | 66 |
| 4 | (*R*)-BTM **23** | TsCl | 3.5 | 77 | >95:5 | 85 |

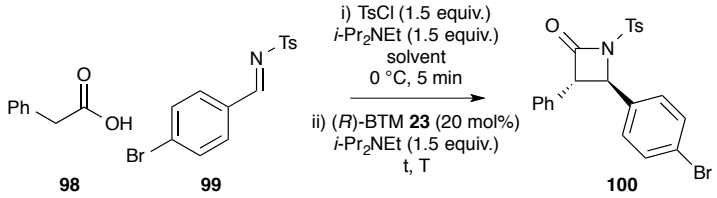
[a] As a mixture of β-lactam and pivalic anhydride. [b] Determined by inspection of $^1$H NMR spectrum of crude. [c] Obtained by chiral HPLC analysis

**Table 2.3: Variation of ee with Activating Agent**

### 2.2.1.5 Screening Solvent and Temperature

Following identification of the optimum catalyst and activating agent for *β*-lactam formation, a solvent screen was carried out to observe any effects on the yield or ee (Table 2.4). In previous work from the group, improvements had been seen when using THF as the solvent,[43] however in this case it led to a reduction in both yield and ee (entry 2). It was proposed that reducing the temperature would further inhibit the racemic background reaction and so screening at lower temperatures was carried out. Although the ee at 0 °C was very high (93%, entry 3), the product was contaminated with an unknown by-product. Further analysis revealed that this was also present in the crude products from the racemic series when catalysed with DHPB **101**, although only a minor component. So far, analysis has not been able to confirm the structure of

this product. Interestingly, lowering the temperature further to −10 °C, the ee was seen to decrease (80%, entry 4). Further lowering the temperature led to a greatly extended reaction times with full conversion never being achieved and so the product was not isolated (entry 5).




| Entry | Solvent | Temperature (°C) | t (h) | Yield (%) | dr (*anti:syn*)[a] | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | rt | 2 | 77 | >95:5 | 85 |
| 2 | THF | rt | 2 | 57 | >95:5 | 59 |
| 3 | $CH_2Cl_2$ | 0 | 5 | 58 | >95:5 | 93 |
| 4 | $CH_2Cl_2$ | −10 | 18 | 17 | >95:5 | 80 |
| 5 | $CH_2Cl_2$ | −30 | 40 | ND | >95:5 | N/A |

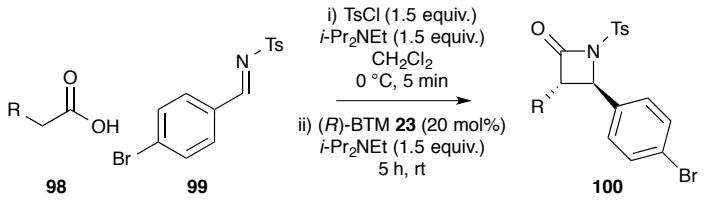
[a] Determined by inspection of $^1$H NMR spectrum of crude. [b] Obtained by chiral HPLC analysis

**Table 2.4: Solvent and Temperature Screen**

### 2.2.2 Variation of Acid

With the optimum conditions in hand, a variety of aryl acetic acids were screened in the newly developed process (Table 2.5). The corresponding β-lactams were isolated in modest to good yield (42-77% yield), excellent diastereoselectivity and in high enantioselectivity (79-88% ee). As yet this effect is unexplained however it is possible that the mixed anhydride is more reactive in this case and so there could be more competition from a racemic background reaction. *o*-Tolylacetic acid showed a slightly reduced diastereoselectivity (entry 4), with the minor diastereoisomer having a much lower ee. It is thought this also may be owing to less discrimination between the faces of the ammonium enolate. Additionally, an non-aryl example, (thiophenyl)acetic acid could also be used in this protocol, generating **105** with moderate diastereo- and enantiocontrol (entry 6). This procedure, although producing the β-lactam products in

excellent dr and ee, often suffered variable product yields that were not representative of reaction conversion. We propose that instability of the β-lactam products towards chromatographic purification is the cause of this.




| Entry | Compound | R | Yield (%) | dr (*anti:syn*)[a] | ee (%, *anti/syn*)[b] |
|---|---|---|---|---|---|
| 1 | **100** | Phenyl | 77 | >95:5 | 85 |
| 2 | **101** | *p*-Tolyl | 42 | >95:5 | 87 |
| 3 | **102** | *m*-Tolyl | 53 | >95:5 | 81 |
| 4 | **103** | *o*-Tolyl | 70[c] | 90:10 | 81/47 |
| 5 | **104** | *p*-Methoxyphenyl | 67 | >95:5 | 83 |
| 6 | **105** | *S*-Phenyl | 42[c] | 85:15 | 61/62 |

[a] Determined by inspection of $^1$H NMR spectrum of crude. [b] Obtained by chiral HPLC analysis. [c] Combined yield to partially separable diastereoisomers.

**Table 2.5: Variation of Acid Component**

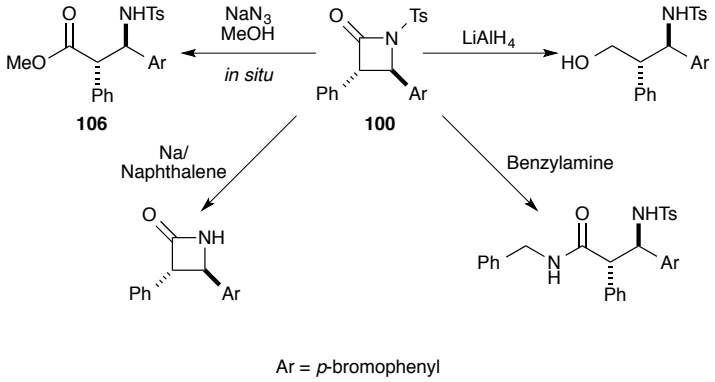
### 2.2.3 Derivatisations

Following the discovery that the β-lactam products formed from our protocol were unsuitable for column chromatography and other purification methods proved ineffective, derivatisations to convert the product into stable, isolable substrates were investigated with the hope that they would be easier to obtain (Scheme 2.24).

Treatment of the β-lactam products with methanol alone afforded none of the expected β-amino ester product. However, the addition of sodium azide led to full consumption of the β-lactam after one hour, with β-aminoester **106** consistently isolated in 42-46% yield with excellent dr (>95:5). Other methods to derivatise the β-lactam were attempted including: reductive ring-opening using lithium aluminium hydride; removal of the *N*-tosyl group using sodium/naphthalene; and ring-opening

using benzylamine. However, all of these methods led to a mixture of products from which the desired products were unable to be isolated.

Therefore, our next step was to optimise the ring-opening using sodium azide and methanol. This derivatisation was convenient and could be carried out *in situ* with no intermediate work up (yield with work up 42%, without 46%).

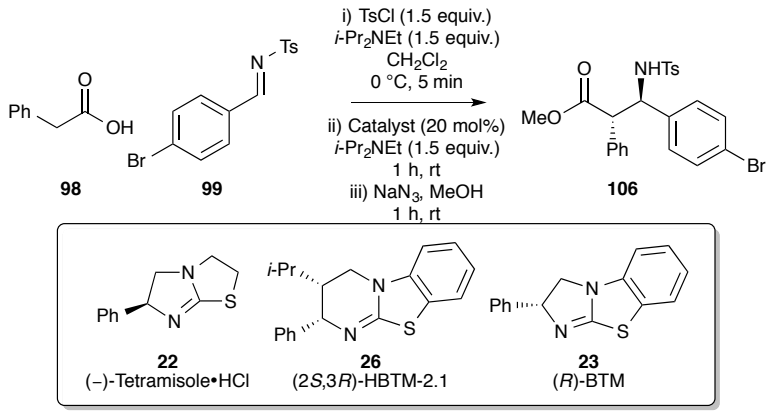



**Scheme 2.24: Derivatisation Routes Investigated**

## 2.2.4 Optimisation of Reaction to β-Aminoesters

### 2.2.4.1 Chiral Catalyst Screen

Literature precedent for the kinetic resolution of β-lactams by isothiourea catalysts led us to be mindful that the catalyst could be involved in the ring-opening step of our process.[44] Therefore, the chiral catalyst screen was repeated for the β-amino ester forming procedure (Table 2.6). All catalysts screened gave excellent dr (>95:5), although the yields were much lower than the racemic reaction. The ee was good in all cases with (2*S*,3*R*)-HBTM-2.1 **26** giving the highest ee of 83% (entry 3). Although this was a different optimum catalyst to the β-lactam forming reactions, it was chosen for all further investigations.




| Entry | Catalyst | Yield (%) | dr (*anti:syn*)[a] | ee (%)[b] |
|---|---|---|---|---|
| 1 | DHPB **101** | 42-46 | >95:5 | N/A |
| 2 | (–)-Tetramisole.HCl **22** | 16 | >95:5 | 70 (*ent*) |
| 3 | (2*S*,3*R*)-HBTM-2.1 **26** | 24 | >95:5 | 83 |
| 4 | (*R*)-BTM **23** | 30 | >95:5 | 74 |

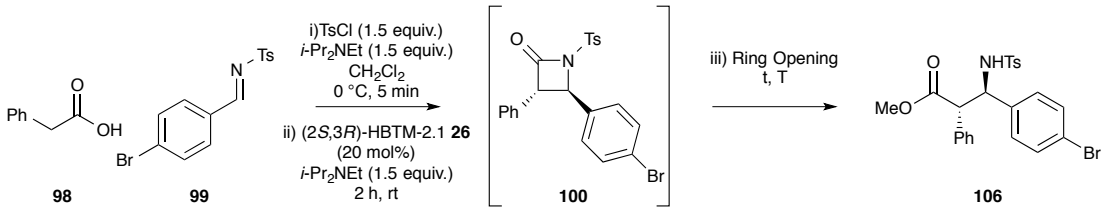
[a] Determined by inspection of $^1$H NMR spectrum of crude. [b] Obtained by chiral HPLC analysis.

**Table 2.6: Chiral Catalyst Screen for Formation of β-Aminoesters**

### 2.2.4.2 Screen of Ring-Opening Conditions

Following further investigation of the literature, other ring-opening methods were investigated to see if the yield could be further improved (Table 2.7). If the ring-opening was carried out using only a catalytic amount of sodium azide (10%) in methanol, the yield increased from 24 to 66% using catalyst **26** (entry 2). However, sodium methoxide in methanol not only increased the yield to 40% but also the ee from 83% to 96%, the reason for which is unclear (entry 3).

Cooling the reaction mixture to 0 °C had no impact on the enantioselectivity of the reaction and cooling further led to no improvement with a much extended reaction time (entries 4 and 5). Following the success of the reactions with sodium methoxide in methanol, formation of methoxide *in situ* from *n*-butyllithium was investigated (entry 6). This led to a further increase in yield to 62% with 93% ee, a superior result to that with catalytic sodium azide, so this method was used for all further examples.



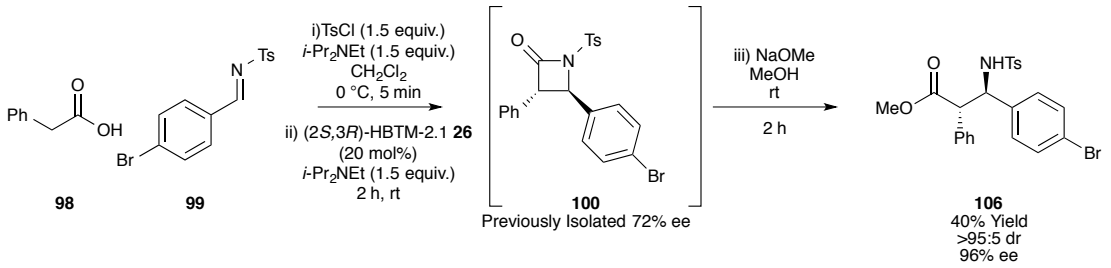

| Entry | Ring Opening Method | t (h) | T (°C) | Yield (%) | dr (*anti:syn*)[a] | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | $NaN_3$/MeOH | 1 | rt | 24 | >95:5 | 83 |
| 2 | $NaN_3$ (10 mol%)/MeOH | 4 | rt | 66 | >95:5 | 85 |
| 3 | NaOMe/MeOH | 2 | rt | 40 | >95:5 | 96 |
| 4 | NaOMe/MeOH | 4 | 0 | 53 | >95:5 | 96 |
| 5 | NaOMe/MeOH | 24 | –30 | 43 | >95:5 | 95 |
| 6 | *n*-BuLi/MeOH | 1 | –78 to rt | 62 | >95:5 | 93 |

[a] Determined by inspection of $^1$H NMR spectrum of crude. [b] Obtained by chiral HPLC analysis

**Table 2.7: Investigation into Ring Opening Methods**

### 2.2.4.3 Investigation into Enantioselectivity of the Ring-Opening Step

It was observed during the catalyst screen that there was a slight enhancement in the ee of β-amino esters when compared with the β-lactams isolated under the same conditions (Scheme 2.25). When using isothiourea (2*S*,3*R*)-HBTM-2.1 **26**, the ee had increased from 72% of the β-lactam to 96% of the β-amino ester. This was thought to be outwith measurement error and given that the kinetic resolution of *syn*-β-lactams using isothioureas was reported in the literature, there was speculation that the isothiourea catalyst maybe involved in the ring-opening step.[44]

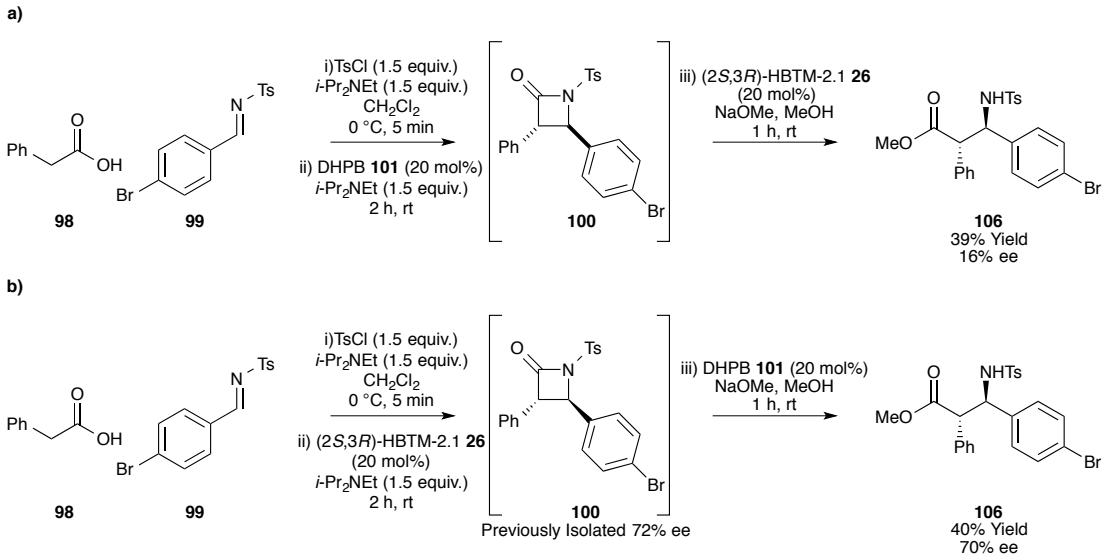



**Scheme 2.25: Comparison of Isolated ees of β-Lactam and β-Aminoester**

To investigate this further, two reactions were carried out, one in which the β-lactam would be formed with the achiral catalyst, DHPB **101** and then following a work-up,

the ring-opening would be carried out in the presence of the chiral catalyst (2*S*,3*R*)-HBTM-2.1 **26** and a second with asymmetric *β*-lactam formation and ring-opening in the presence of the achiral catalyst (Scheme 2.26).

In the first reaction, if no catalyst were involved in the ring-opening step, we would expect to form the racemic *β*-amino ester. However, a modest ee of 16% was obtained from the final product (Scheme 2.28a). In the second reaction, the previously isolated *β*-lactam was found to have an ee of 72%, which was conserved when the ring opening was carried out in the presence of achiral DHPB **101** (Scheme 2.28b). Under our standard reaction conditions, the ee of the isolated aminoester is 10% higher than the *β*-lactam. These results support the theory that the ring-opening is also enantioselective, however, later investigations found that the ee enhancement was not general and so perhaps this phenomenon is not as significant as first thought.

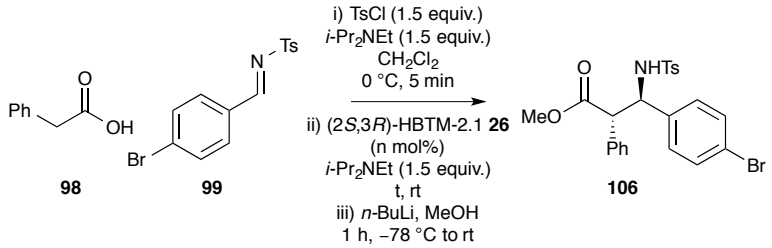



**Scheme 2.26: Kinetic Resolution of Ring-Opening**

### 2.2.4.4 Catalyst Loading

Following optimisation of the yield at 20 mol% of catalyst **26**, the catalyst loading was reduced to investigate its impact on yield and the enantioselectivity of the reaction (Table 2.8). The loading could be reduced to 5 mol% with no significant impact, the yield remained moderate at 65% and the ee was excellent at 92%. However, the time for the *β*-lactam forming step had to be increased from one hour to 2.5 hours to allow full consumption of starting material (entry 3). Further decreasing of the catalyst loading to 1 mol% was not productive as there was a slight drop in ee

to 85% and the starting material was only 85% consumed after 2.5 hours (measured by $^1$H NMR, entry 4).




| Entry | Catalyst Loading (mol%) | Time (h) | Yield (%) | dr (*anti:syn*)[a] | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | 20 | 1 | 60-62 | >95:5 | 89-93 |
| 2 | 10 | 2 | 53 | >95:5 | 95 |
| 3 | 5 | 2.5 | 50 | >95:5 | >99 |
| 4 | 1 | 2.5 | 44 | >95:5 | 85 |

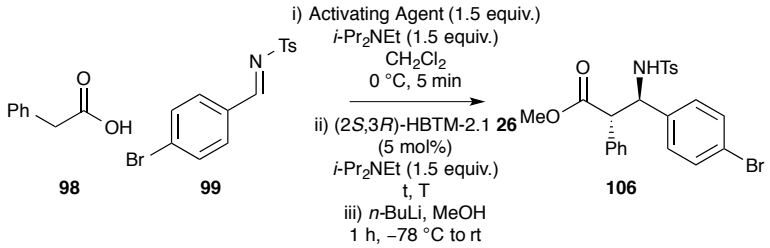
[a] Determined by inspection of $^1$H NMR spectrum of crude. [b] Obtained by chiral HPLC analysis

**Table 2.8: Reduction of Catalyst Loading**

### 2.2.4.5 Screening of Activating Agent

To conclude a thorough optimisation of the ring-opening procedure, other activating agents were screened for the *β*-lactam formation (Table 2.9). Benzoyl chloride gave a comparable ee of 91% however the yield was only 45% (entry 2). Although pivaloyl chloride gave a comparable yield to reactions with tosyl chloride, the ee of the product was only 78% (entry 3). It was decided to cool the reaction using pivolyl chloride during the *β*-lactam formation step to investigate whether the ee could be improved while maintaining the good yield. There was a significant increase in the ee of the product from 78% to 92% when reducing the temperature to 0 °C, however the yield was reduced to 34% (entry 4) and the $^1$H NMR spectrum of the crude material of the reaction at 0 °C revealed that there had not been full consumption of the imine. Additional reduction of the temperature led to no further increase in ee. In fact, at –30 °C the ee decreased to 76% indicating that the catalysed process was also considerably slower at this temperature allowing competition from the racemic

background reaction (entry 6). Therefore, tosyl chloride was kept as the optimum activating agent.




| Entry | Activating Agent | T (°C) | t (h) | Yield (%) | dr (*anti:syn*)[a] | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | TsCl | rt | 1 | 62 | >95:5 | 93 |
| 2 | BzCl | rt | 1 | 45 | >95:5 | 91 |
| 3 | PivCl | rt | 1 | 65 | >95:5 | 78 |
| 4 | PivCl | 0 | 5 | 34 | >95:5 | 92 |
| 5 | PivCl | –10 | 18 | 36 | >95:5 | 90 |
| 6 | PivCl | –30 | 18 | 31 | >95:5 | 76 |

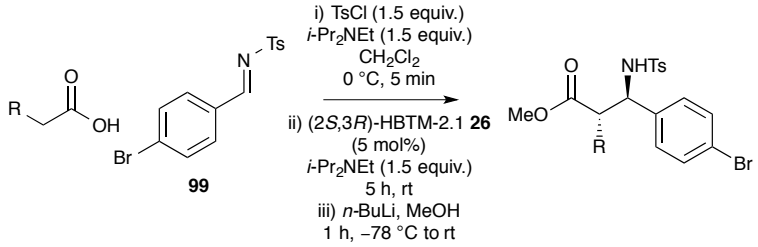
[a] Determined by inspection of $^1$H NMR spectrum of crude. [b] Obtained by chiral HPLC analysis.

**Table 2.9: Investigation into Activating Agent**

### 2.2.5 Variation of the Carboxylic Acid Component

Using the final optimised conditions, the acetic acid component was varied to explore the scope of the reaction. Steric tolerance around the aromatic ring, electron-donating and -withdrawing substituents were all investigated along with the addition of heteroaromatic groups.

In general, the addition of steric bulk was well tolerated (Table 2.10). Some loss of diastereoselectivity was seen with a substituent in the *ortho* position (entries 4 and 5) although the enantioselectivity was not dramatically affected.



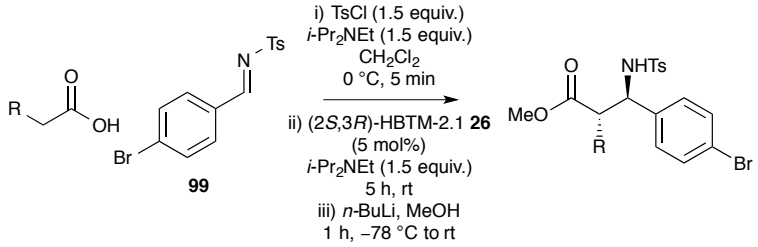

| Entry | Compound | R | Yield (%) | dr (*anti:syn*)[a] | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | **106** | Phenyl | 50 | >95:5 | >99 |
| 2 | **107** | *p*-Tolyl | 46 | >95:5 | 86 |
| 3 | **108** | *m*-Tolyl | 40 | >95:5 | 74 |
| 4 | **109** | *o*-Tolyl | 61 | 90:10 | 76 |
| 5 | **110** | 1-Naphthyl | 46 | 90:10 | 82 |
| 6 | **111** | 2-Naphthyl | 68 | >95:5 | 85 |

[a] Determined by inspection of $^1$H NMR spectrum of crude. [b] Obtained by chiral HPLC analysis.

**Table 2.10: Steric Investigation of Acid Variation**

Further investigations revealed electron-donating and withdrawing substituents were well tolerated (Table 2.11, entries 5 and 7) with no loss of diastereo- or enantiocontrol. However, when a strongly electron-withdrawing acid was used (entry 8) the reaction was slow and less than 5% conversion was seen into the β-lactam overnight. It is thought that this is owing to the decreased nucleophilicity of the ammonium enolate.

Hetereoaromatic groups and (phenylthio)acetic acid (entries 1, 2, 3 and 10) were also tolerated in the reaction conditions and gave product in yields consistent with other examples, however the diastereoselectivity and especially the enantioselectivity was much lower. Pleasingly, the reaction could also be carried out on a gram scale, with 1.3 g (41% yield) of β-amino ester **106** synthesised in 85% ee.




| Entry | Compound | R | Yield (%) | dr (*anti:syn*)[a] | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | **112** | 2-Thiophene | 46 | 85:15 | 21 |
| 2 | **113** | 3-Thiophene | 50 | 91:9 | ND |
| 3 | **114** | 1-Methyl-3-indole | 55 | 56:44 | 23 |
| 4 | **115** | *p*-Bromophenyl | 43 | >95:5 | 98 |
| 5 | **116** | *p*-Methoxyphenyl | 42 | >95:5 | 76 |
| 6 | **117** | *p*-Chlorophenyl | 68 | >95:5 | 78 |
| 7 | **118** | *p*-Fluorophenyl | 56 | >95:5 | 76 |
| 8 | **119** | *p*-Trifluoromethylphenyl | <5% conversion overnight | | |
| 9 | **120** | Diphenyl | 44 | >95:5 | 73 |
| 10 | **121** | *S*-Phenyl | 71 | 75:25 | 57 (*syn*: 57) |

[a] Determined by inspection of $^1$H NMR spectrum of crude. [b] Obtained by chiral HPLC analysis.

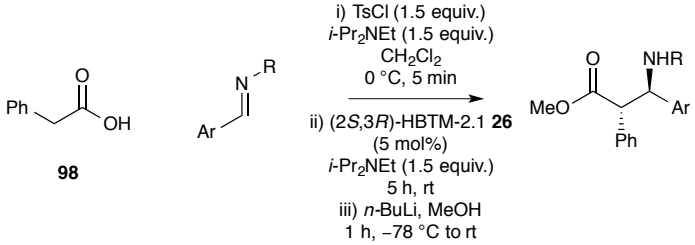
**Table 2.11: Further Acid Variation**

### 2.2.6 Variation of the Imine

Next, a range of imines were synthesised and investigated under the standard reaction conditions to further expand the scope of the reaction (Table 2.12).

Use of phenyl imine (entry 2) gave consistent results with a yield of 49% and an ee of 80%. However, electron-donating groups on the aryl substituent or nitrogen protecting groups were seen to have a detrimental effect on the reaction with less than 5% conversion into the β-lactam observed at extended reaction times (18 h, entries 3 and 10). This is presumably owing to deactivation of the imine to nucleophilic attack

by the ammonium enolate. A furyl group on the imine was also tolerated (entry 4) although with some drop in the diastereo- and enantiocontrol.




| Entry | Compound | R | Ar | Yield (%) | dr (*anti:syn*)[a] | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **106** | Tosyl | *p*-Bromophenyl | 50 | >95:5 | >99 |
| 2 | **122** | Tosyl | Phenyl | 49 | >95:5 | 80 |
| 3 | **123** | Tosyl | *p*-Methoxyphenyl | <5% conversion overnight | | |
| 4 | **124** | Tosyl | Furyl | 55 | 80:20 | 70 |
| 5 | **125** | Tosyl | *p*-Trifluoromethylphenyl | 49 | 92:8 | 44 |
| 6[c] | **125** | Tosyl | *p*-Trifluoromethylphenyl | 36 | 92:8 | 52 |
| 7 | **126** | Tosyl | 1-Naphthyl | 61 | 75:25 | 56 |
| 8 | **127** | Tosyl | 2-Naphthyl | 55 | >95:5 | 95 |
| 9 | **128** | Nosyl | Phenyl | 54 | >95:5 | 80 |
| 10 | **129** | Boc | Phenyl | <5% conversion overnight | | |
| 11 | **130** | PMP | Phenyl | <5% conversion overnight | | |

[a] Determined by inspection of $^1$H NMR spectrum of crude. [b] Obtained by chiral HPLC analysis. PMP = *p*-methoxyphenyl. [c] Reaction carried out at 0 °C.

**Table 2.12: Variation of the Imine Component**

Changing the electronics of the imine seemed to have a much greater effect on the outcome of the reaction than variation of the acid. Using an electron-withdrawing group on the aryl ring (*p*-trifluoromethyl) gave the product in only moderate yield with a significant decrease in dr and ee (entry 5). This is thought to be owing to the increased electrophilicity of the carbonyl increasing the rate of the racemic

background reaction with respect to the catalysed reaction. Decreasing the temperature of the ring-forming step to 0 °C led to a slight increase in ee, which lends some support to this theory (entry 6). Increasing steric bulk was tolerated in good yield (entry 7) but, as seen with the acid variation, increased sterics in the *ortho*-position led to a decrease in the dr and ee of the β-amino ester product. Pleasingly, there was no change in selectivity seen when changing from a *N*-tosyl to a *N*-nosyl protecting group (entry 9) however, changing to either a *N*-Boc or *N*-PMP protecting group again shut down the reaction (entry 10 and 11).

The absolute configuration of *β*-amino ester **106** was determined using X-ray crystallography as (2*S*,3*R*) (Figure 2.5).

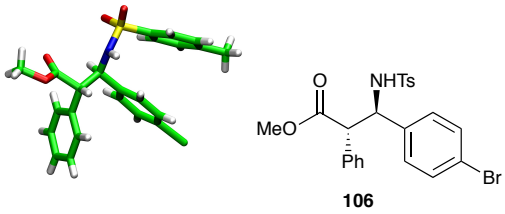
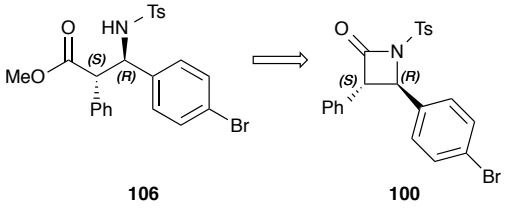



**Figure 2.5: X-Ray Crystal Structure of *β*-Aminoester 106**

By correlation the absolute configuration of *β*-lactam **100** must also be (2*S*,3*R*) (Scheme 2.27). This further confirms the *anti* stereochemistry of the major diastereomer assigned through coupling constant analysis.



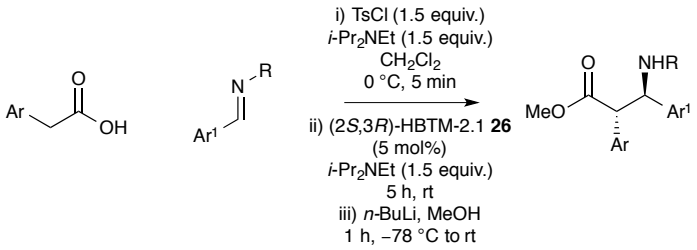

**Scheme 2.27: Assignment of Absolute Configuration of *β*-Lactam 100**

### 2.2.7 Recrystallisation of *β*-Amino Ester Products

Following comparison of the *β*-amino ester ees with those previously obtained for the isolated *β*-lactams, it was noted that only the examples using phenylacetic acid or *p*-bromophenylacetic acid with the *N*-tosyl protected *p*-bromophenyl imine showed an increase in ee. It was postulated that these products may be more crystalline than the others and therefore some racemic product was crystallising during column chromatography giving an enantioenriched product.[45]

To investigate this, the ee of the crude product from the reaction of phenylacetic acid and the *N*-tosyl-protected *p*-bromophenyl imine followed by ring-opening was obtained and found to be 80% ee. This is consistent with the ee of the previously isolated β-lactam and also the other *β*-aminoesters synthesised.

To investigate whether the ee could be enhanced in general, a selection of *β*-amino esters were synthesised on a larger scale, isolated *via* column chromatography and then recrystallised (Table 2.13). The ee was increased in three cases (entries 1, 3 and 4) and mostly without too much loss in yield during the recrystallization. In the case of the *p*-chlorophenylacetic *β*-amino ester, the ee of the recrystallised material was only 20% (entry 2). On analysis of the filtrate, it was found to have an ee of 81% ee. This implies that in this case, the racemic compound is more crystalline than the major enantiomer. Whereas the *N*-nosyl-protected *β*-aminoester **128** resulted in no improvement in the ee (entry 5). However the ability to recrystallize the *β*-amino ester products for enhancement of ee does appear to be a general trend for the tosyl protected *β*-aminoesters.



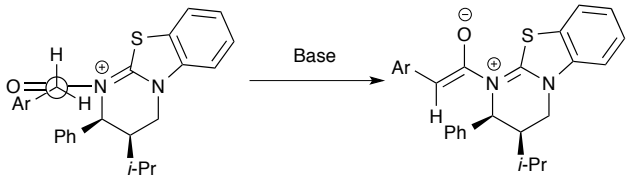

| Entry | R | Ar | Ar[1] | Column Yield (%) | Recrystallisation Yield (%) | ee (previous ee, %)[a] |
|---|---|---|---|---|---|---|
| 1 | Ts | *o*-Tolyl | *p*-Bromophenyl | 58 | 42 | 96 (76) |
| 2 | Ts | *p*-Chlorophenyl | *p*-Bromophenyl | 40 | 13 | 20 (78) |
| 3 | Ts | Phenyl | Phenyl | 54 | 26 | 93 (80) |
| 4 | Ts | 2-Naphthyl | *p*-Bromophenyl | 58 | 41 | >99 (85) |
| 5 | Ns | Phenyl | Phenyl | 45 | 35 | 76 (76) |

[a] Obtained by chiral HPLC analysis.

**Table 2.13: Improvements in ee Following Recrystallisations**

### 2.2.8 Proposed Pre-Transition State Assemblies

The conformation of the ammonium enolate is key to understanding the stereoselectivity of the reaction. Treating the acyl ammonium species **131** with base (Scheme 2.28), deprotonation must occur when the $\sigma_{C\text{-}H}$ orbital is approximately perpendicular to the carbonyl group to allow electron flow into the oxygen $\pi^*$ orbital. When drawn in a Newman-type projection with the large aryl group orientated away from the steric bulk of the catalyst, deprotonation forms (*Z*)-ammonium enolate **55**.




**131** **55**

**Scheme 2.28: Proposed Conformation of the Ammonium Enolate**

There is also evidence that further stabilisation and conformational control in this ammonium enolate could be possible through a 1,5 S-O interaction. This intramolecular non-bonded interaction has been observed in a large number of organosulfur compounds. Nagao *et al*. showed by X-ray crystallographic analysis that in the favoured conformer of **132** (conformer B), the distance between the sulfur and the oxygen atom (2.646 Å) is smaller than the sum of their Van der Waals radii (3.32 Å) and therefore proposed a stabilising S-O interaction (Figure 2.6). They suggested this was owing to an overlap of the carbonyl non-bonding orbital with the $\sigma^*$ orbital of the C-S bond.[46]

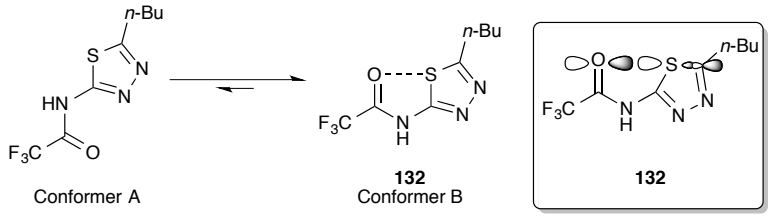
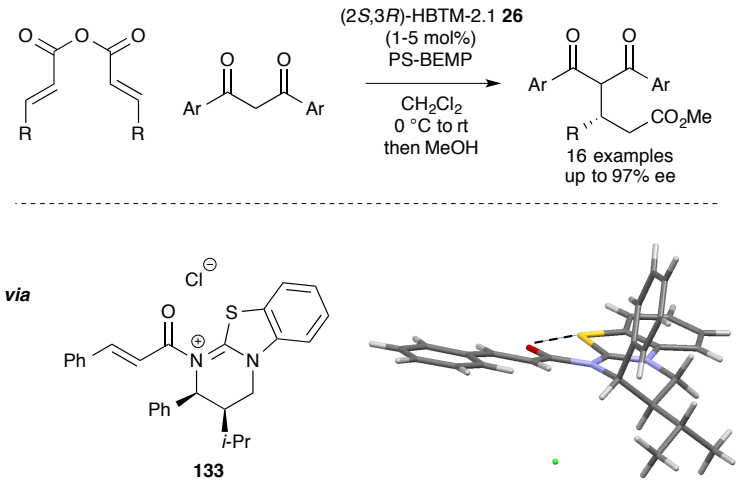



**Figure 2.6: Evidence of a 1-5 S-O Interaction**

Additionally, Birman noted in his work on the design of amidine derivatives as acylation catalysts that introduction of a sulfur atom results in a vast increase in catalytic activity, which he attributed to the non-bonded S-O interaction stabilising *N*-acylated intermediates.[47] Futhermore, Romo accredited the selectivity of his NCAL process to the same non-bonding interaction.[48]

Recent work within the Smith group investigating the mechanism of anhydrides as α,β-unsaturated acyl ammonium precursors led to the isolation of acyl ammonium species **133** (Scheme 2.29).[49] X-ray crystallography confirmed the structure and supported the previously hypothesised stabilising non-bonding S-O interaction by showing *syn* geometry between the carbonyl oxygen and the isothiourea sulfur atom with the O-S distance (2.479 Å) being significantly shorter than that of the calculated Van der Waal's distance (3.620 Å). In this system, **133** could also be used as a pre-catalyst in the reaction, indicating that it is an intermediate in the reaction.




**Scheme 2.29: Isolation of Acyl Ammonium Species 133**

Using this information, a transition state can be proposed that is consistent with the observed *anti* product (assuming it is formed under kinetic control). It is postulated that when the imine approaches enolate **55**, locked in position by the S-O interaction, it would approach *anti* to the stereodirecting group of the catalyst and that the very bulky *N*-protecting group will be furthest from the aryl group of the carboxylic acid (Figure 2.7). Addition of the enolate to the imine *Re*-face followed by cyclisation of this proposed transition state would result in the aryl groups being on opposite faces of the β-lactam and the observed *anti*-β-lactam being formed.

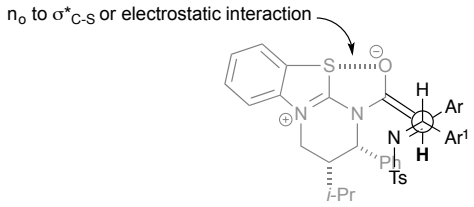
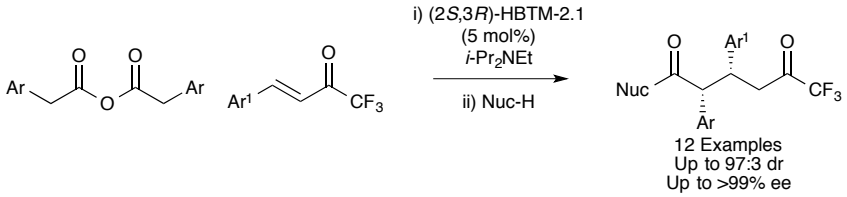



**Figure 2.7: Proposed Transition State**

## 2.3 Reaction from the Preformed Homoanhydride

While an effective procedure for the formation of a range of *anti*-β-amino esters with excellent diastereocontrol and good to excellent enantiocontrol has been described, a process that allows reproducible access to the corresponding β-lactam was still desired. Previous work within the group has shown that preformed homoanhydrides can be used as alternative starting materials for related isothiourea catalysed cyclisations (Scheme 2.30).[50]




**Scheme 2.30: Preformed Homoanhydrides as Starting Materials for Isothiourea-Catalysed Cyclisations Followed by a Ring-Opening Reaction**

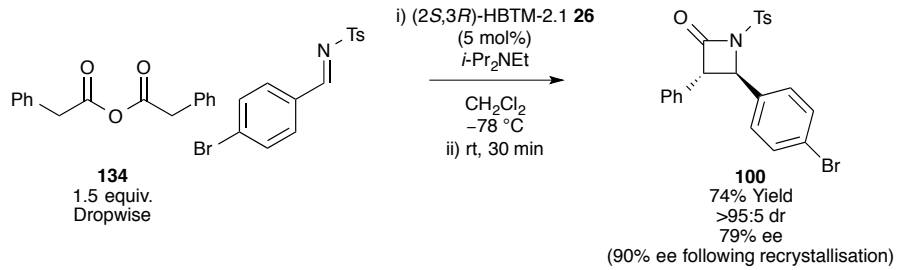
In this case, it was hoped that simplifying the reaction conditions by removing the need for *in situ* acid activation would lead to minimal by-products and ultimately aid purification, allowing for isolation of analytically pure, stereodefined *anti*-β-lactams.

### 2.3.1 Optimisation of Reaction from Preformed Anhydride

Initial work was carried out by project student Hugues Prevet to optimise the process for formation of β-lactams from a preformed anhydride. Treatment of benzoic anhydride and **134** with (2*S*,3*R*)-HBTM-2.1 **26** (5 mol%) and *i*-$Pr_2$NEt (1.5 equiv.) led to formation of the β-lactam **100** that could be consistently isolated as the major reaction product, albeit in low yield (30%).

Dropwise addition of an increased quantity of anhydride (1.5 equivalents over 45 minutes) at a lower reaction temperature (−78 °C) was required in order to eliminate competitive addition of the ammonium enolate to the homoanhydride. This improved the yield to 74% with excellent diastereoselectivity and good enantioselectivity, which following recrystallisation could be isolated in 90% ee (Scheme 2.31).

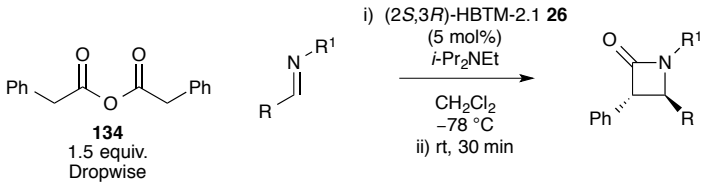
Importantly, as opposed to the original procedure from the arylacetic acid, the use of a preformed homoanhydride allowed isolation of the β-lactam heterocycle in reproducible yields.




**Scheme 2.31: Optimised Conditions for Formation of β-lactams from Preformed Homoanhydrides**

## 2.3.2 Variation of the Imine

A moderate selection of aryl imines were screened under the newly developed conditions and were also tolerated in similar yield (47-60% yield) and enantioselectivity (68-92% ee) but in slightly reduced diastereoselectivity (up to 93:7 dr) (Table 2.14). Similarly to the reaction directly from the carboxylic acid, strongly electron-withdrawing substituents were tolerated although with reduced ee (entry 3) and aldimines with electron-donating groups showed no activity (entry 4). Extended aromatic systems with increased steric bulk were tolerated (entry 5) albeit with reduced dr. Attempted use of an alkyl imine gave complete loss of diastereocontrol (entry 6).

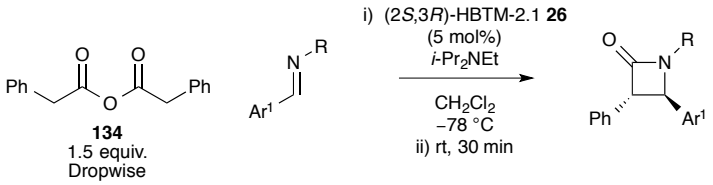



| Entry | Compound | R | $R^1$ | Yield (%) | dr (*anti:syn*)[a] | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **100** | *p*-Bromophenyl | Tosyl | 74 | >95:5 | 79 |
| 2 | **135** | Phenyl | Tosyl | 60 | 90:10 | 82 |
| 3 | **136** | *p*-Trifluoromethylphenyl | Tosyl | 47 | 93:7 | 68 |
| 4 | **137** | *p*-Methoxyphenyl | Tosyl | NR | N/A | N/A |
| 5 | **138** | 2-Naphthyl | Tosyl | 56 | 85:15 | 92 (*syn* 54) |
| 6 | **139** | Isopropyl | Tosyl | ND | 50:50[c] | ND |
| 7 | **140** | Phenyl | Nosyl | 51 | 90:10 | 86 |

[a] Determined by inspection of $^1$H NMR spectrum of crude. [b] Obtained by chiral HPLC analysis. [c] Could not be isolated and therefore not fully characterised.

**Table 2.14: Imine Variation**

Analogous to the β-amino esters, β-lactam formation was performed on a large scale, purified by column chromatography and then the products were recrystallised to investigate if this had a positive effect on the final ee (Table 2.15). In both cases, the ee could be significantly enhanced to greater than 90% ee.



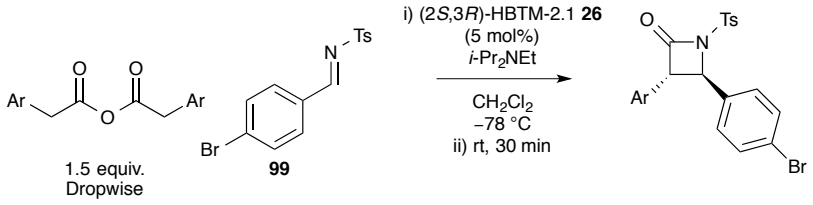

| Entry | $Ar^1$ | R | Column Yield (%) | Recryst Yield (%) | Recryst ee (%) (previous ee)[a] |
|---|---|---|---|---|---|
| 1 | *p*-Bromophenyl | Tosyl | 74 | 56 | 90 (79) |
| 2 | Phenyl | Tosyl | 60 | 34 | >99 (82) |

[a] Obtained by chiral HPLC analysis.

**Table 2.15: Enhancement of ee by Recrystallisation**

### 2.3.3 Variation of the Anhydride

Modification of the anhydride portion provided β-lactams with good to excellent dr and good enantiocontrol incorporating a range of aryl and heteroaryl substitution (Table 2.16). Again, in comparison with reactions directly from the acetic acids, the yields were more consistent, although the dr dropped. The ee of the products was consistent with previously isolated β-lactams from the acid.

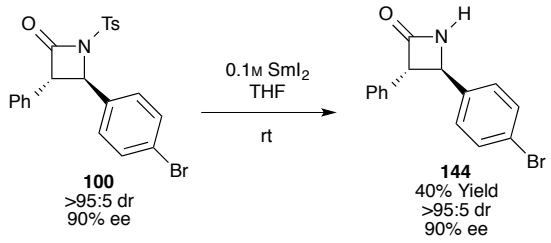



| Entry | Compound | Ar | Yield (%) | dr (*anti:syn*)[a] | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | **141** | *p*-Bromophenyl | 74 | >95:5 | 79 |
| 2 | **104** | *p*-Methoxyphenyl | 72 | >95:5 | 70 |
| 3 | **142** | 3-Thiophene | 47 | 93:7 | 68 |
| 4 | **143** | 2-Naphthyl | 44 | 90:10 | 83 |

[a] Determined by inspection of $^1$H NMR spectrum of crude. [b] Obtained by chiral HPLC analysis

**Table 2.16: Variation of Homoanhydride**

Additionally, removal of the *N*-tosyl substituent of the parent β-lactam was possible by treatment with $SmI_2$ to give **144** without racemisation (Scheme 2.32).

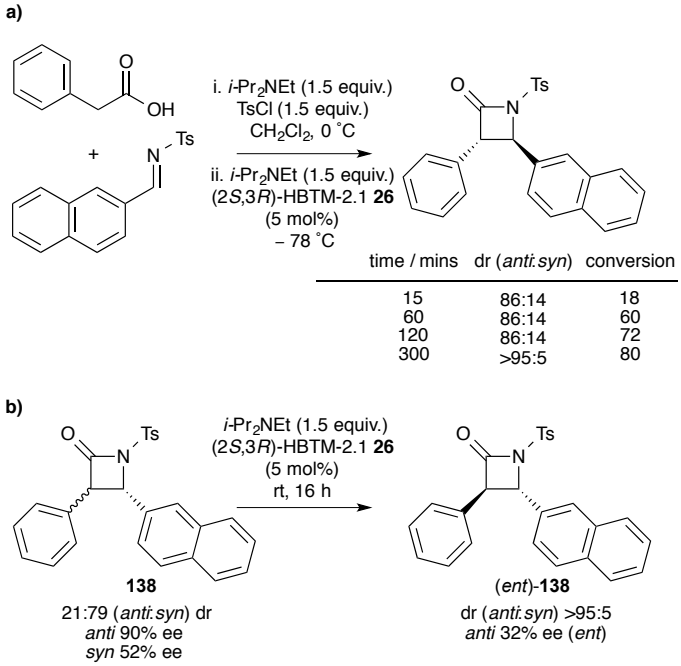



**Scheme 2.32: Detosylation Reaction**

### 2.3.4 Control Studies

As slightly reduced diastereocontrol was observed in formation of the β-lactam products from pre-made arylacetic anhydrides as opposed to directly from the carboxylic acid, a sample of (3*S*,4*R*)-3,4-diphenyl-1-tosylazetidin-2-one **135** was retreated to the reaction conditions for one hour. Following this, the dr was found to have improved from 90:10 to 93:7 implying that epimerisation occurs over time. There is precedent in the literature that *syn*-β-lactams can be readily converted into the more thermodynamically stable *anti*-isomers by a straightforward base-catalysed isomerisation.[51] As reaction from the homoanhydrides requires a shorter time and lower temperature than from the acid, this could explain the lower dr as the rate for epimerisation may be reduced.

This observation prompted us to investigate the possibility of *in situ* product epimerisation leading to enhanced diastereocontrol. To test this hypothesis, the diastereoselectivity of the reaction was analysed at intervals (Scheme 2.33a) with the reaction carried out at −78 ˚C in order to slow down the rate. At modest levels of conversion (<20%) a dr of 85:15 was observed, however, after further reaction time, enhanced diastereocontrol was observed (dr >95:5), consistent with *in situ* epimerisation. To further confirm our theory, an isolated example of β-lactam **138** (dr *anti*:*syn* 21:79; *anti* 90% ee; *syn* 52% ee) was retreated with *i*-$Pr_2NEt$ (1.5 equiv.) and (2*S*,3*R*)-HBTM-2.1 **26** (5 mol%) in $CH_2Cl_2$, generating (*ent*)-*anti*-**138** (>95:5 dr, 32% ee) in quantitative yield (Scheme 2.33b).[52] This is consistent with the *syn*-diastereoisomer having preferentially the (3*S*,4*S*)-configuration, and with *in situ* epimerisation generating *ent*-**138** preferentially. Under identical experimental conditions, a sample of *anti*-**138** (>95:5 dr, 90% ee) showed no change in dr or ee, consistent with no epimerisation of the *anti*-β-lactam under the reaction conditions.

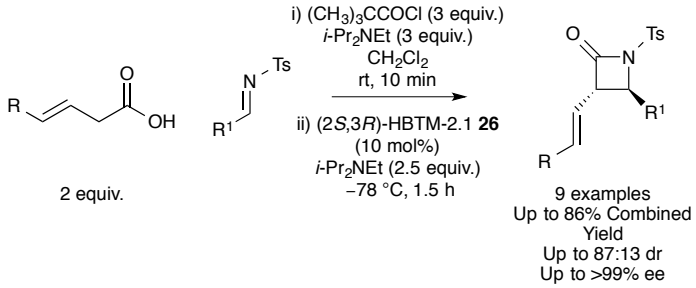



**Scheme 2.33: Diastereoselectivity Investigations**

## 2.4 Conclusions

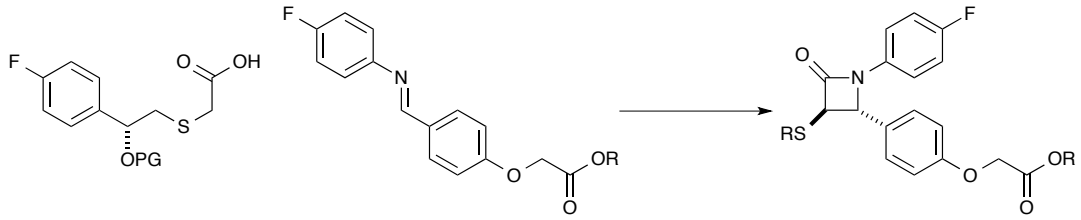
The chemical synthesis of the β-lactam core structure continues to be a very significant field of research.[10] This chapter has discussed our developments in this area, which demonstrate that isothioureas can efficiently catalyse an umpolung Staudinger type reaction in high diastereo- and enantioselective to form the *anti*-β-lactam products from homoanhydrides. An *in situ* ring-opening allows access to the equally synthetically interesting β-amino ester products directly from arylacetic acids with good to excellent enantioselectivity (up to >99% ee). This synthetic route is of particular interest as it involves easy to prepare or commercially available, bench-stable starting materials and the reaction is carried out under mild conditions without the need for anhydrous solvent.

Further work in this area from within the group has shown 3-alkenoic acids to also be effective ammonium enolate precursors that, when coupled with imine partners, form alternatively substituted *anti*-β-lactam products in good dr and excellent ee (Scheme 2.34). As with work described in this thesis, the *syn*-β-lactam products could be readily converted into the *anti*-product under basic conditions.




**Scheme 2.34: Use of Alkenoic Acids for β-Lactam Formation**

This work could potentially lead to future applications such as to a synthetic target for example the cholesterol absorption inhibitor AZD4121.[53] The key intermediate is formed *via* a Staudinger reaction between a chiral carboxylic acid and an imine. However a mixture of diastereoisomers of the β-lactam is obtained and a resolution must be carried out (Scheme 2.35). As our process has thus far proved highly diastereoselective, it is thought that using our catalytic process instead of the standard Staudinger reaction may remove the need for this resolution. However further optimization of our process would be required as thus far, carboxylic acids containing a sulfur atom have resulted in disappointing ees.



**Scheme 2.35: Staudinger Reaction *en route* to AZD4121**

## 2.5 References for Chapter 2

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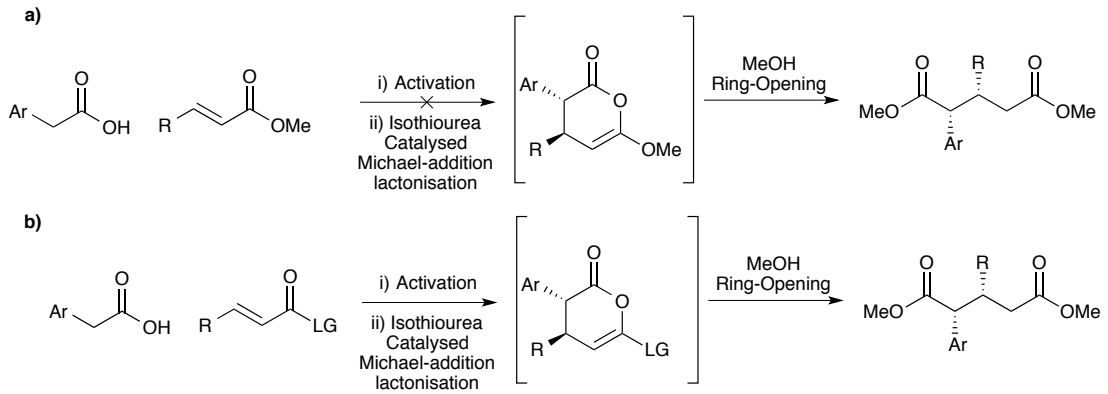
# Chapter 3: Asymmetric Isothiourea-mediated Organocatalytic Formation of Diesters *via* Ammonium Enolates from Ester Surrogates

## 3.1 Introduction

In an effort to expand the scope of previous work within the group, we were interested in developing alternative intermolecular formal [4+2]-cycloadditions based on the intermolecular Michael-addition/lactonisation previously discussed. The use of $\alpha,\beta$-unsaturated esters and amides as Michael acceptors in such processes remains a significant synthetic challenge owing to the decreased electrophilicity of these species (Scheme 3.1a). For example, whilst $\alpha$-keto-$\beta,\gamma$-unsaturated esters work well in this methodology,[1] methyl cinnamate does not. Alternative ester surrogates were sought which were reactive towards the ammonium enolates generated from isothioureas but also contained a leaving group, which could be displaced on ring-opening by an alcohol (Scheme 3.1b). These acceptors could then be used as alternatives to esters in this catalysis leading to the same ring-opened diester products after treatment with alcohols.




**Scheme 3.1: (a) Direct Use of Esters in Isothiourea Catalysed Michael-Addition/Lactonisation Reactions are Unsuccessful (b) Strategy to Overcome This**

### 3.1.1 Esters Surrogates as Michael Acceptors

Various acceptors have proved amenable in the ammonium enolate formal [4+2]-cycloaddition chemistry developed within the group, including $\alpha$-keto-$\beta,\gamma$-unsaturated esters,[1] *N*-tosyl-$\alpha,\beta$-unsaturated ketimines,[2] *N*-aryl-*N*-aroyldiazenes[3] and trifluoromethylenones.[4] However, simple $\alpha,\beta$-unsaturated esters and amides have not been employed successfully owing to their inherent decreased reactivity.

Within the literature, strategies to overcome the typical modest reactivity of $\alpha,\beta$-unsaturated esters problem use ester surrogates such as *N*-acylpyrroles **145**,[5] 2-acylimidazoles **146**[6] and activated imides **147**,[7] and in asymmetric catalysis the use of trichloromethylketones **148** and $\alpha,\beta$-unsaturated phosphonates **149** has been forged (Figure 3.1).[8,9,10] Trichloromethylketones **148** and phosphonates **149** will be further discussed as the basis of this chapter.

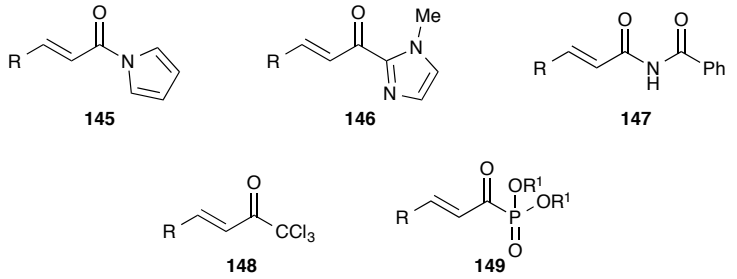
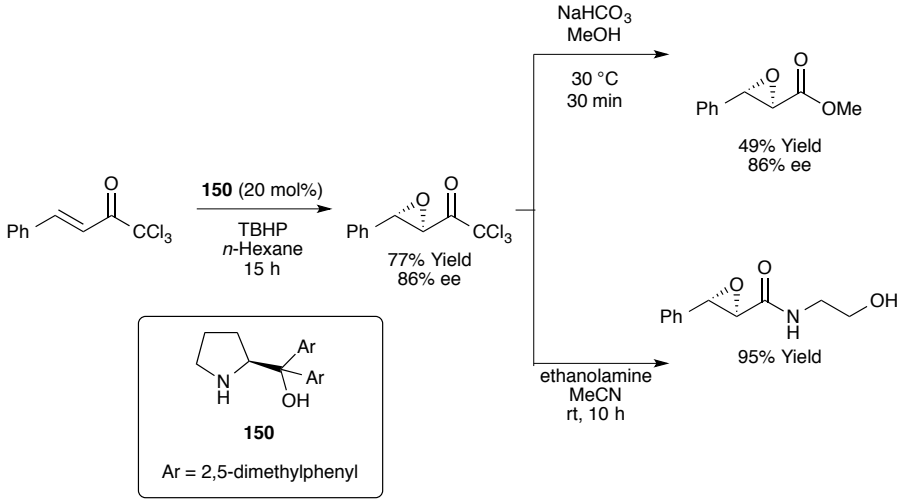



**Figure 3.1: $\alpha,\beta$-Unsaturated Ester Equivalents**

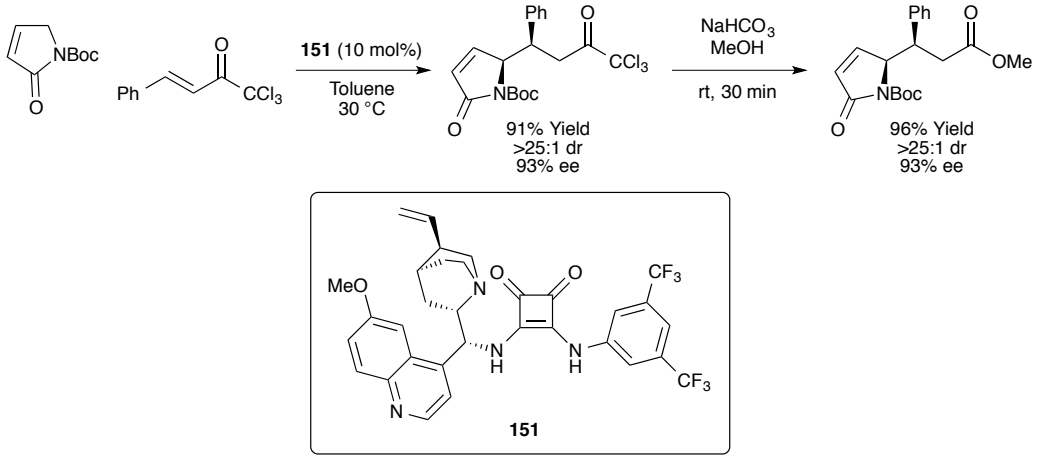
### 3.1.1.1 Trichloromethylketones as Ester Surrogates

The versatility of trichloromethylketones has previously been shown in their use as carboxylic acid, ester and amide equivalents in haloform-type reactions owing to the leaving group ability of the $CCl_3$ group.[11] It has also been previously reported that $\alpha,\beta$-unsaturated trichloromethyl ketones can be used as ester and amide equivalents of Michael acceptors.[12,13] For example, Zhao and co-workers reported an asymmetric epoxidation of $\alpha,\beta$-unsaturated trichloromethylenone using prolinol catalyst **150** (Scheme 3.2).[12] Following isolation of the epoxide, esters and amides could be obtained by displacement of the $CCl_3$ group.




**Scheme 3.2: Zhao's Use of Trichloromethylketones as Ester Mimics**

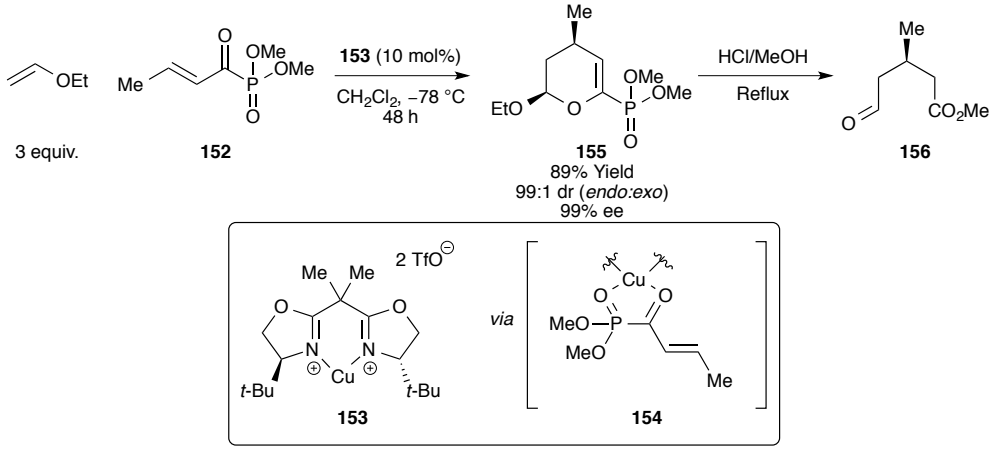
More recently, Wang *et al*. utilised $\alpha,\beta$-unsaturated trichloromethylketones in their squaramide catalysed asymmetric Michael-addition of $\alpha,\beta$-unsaturated $\gamma$-butyrolactams (Scheme 3.3).[13] Methanolysis of the $CCl_3$ group without loss of stereoselectivity demonstrated the utility of their methodology.




**Scheme 3.3: Wang's Use of Trichlormethylketones as Ester Surrogates**

### 3.1.1.2 $\alpha$-Ketophosphonates as Ester Surrogates

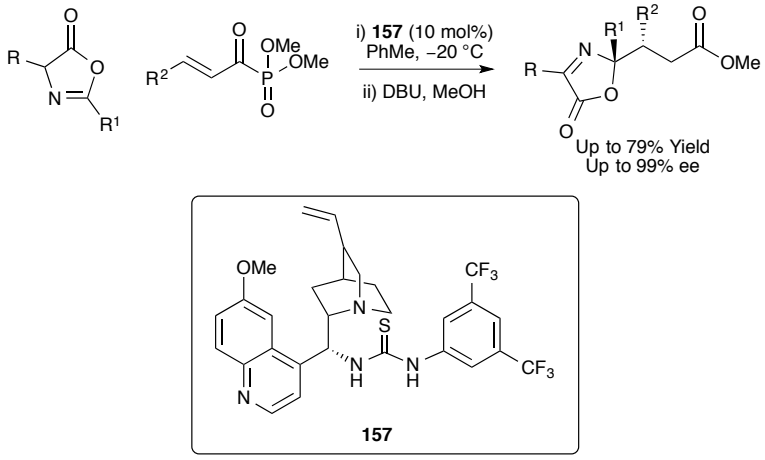
$\alpha$-Ketophosphonates as ester equivalents were first reported by Evans *et al*. in 1998.[6,8,9,14] They utilised ketophosphonate **152** in a stereoselective Lewis acid catalysed hetero Diels-Alder reaction with vinyl ethers (Scheme 3.4). The copper (II) bis(oxazoline) **153** catalyst formed intermediate **154** in which coordination of both the carbonyl and phosphonate oxygens to the copper sufficiently activated them for reaction, forming **155** in excellent yield, dr and ee. Treatment of the product with acidic methanol gave the aldehyde ester **156**.




**Scheme 3.4: First Example of $\alpha$-Ketophosphonates as Ester Surrogates**

Jørgensen later demonstrated an asymmetric thiourea catalysed addition of oxazolone, amongst other nucleophiles, to $\alpha$-ketophosphonates (Scheme 3.5).[10] *In situ*

methanolysis of the ketophosphonate ester equivalent gave access to a range of optically active ester conjugate adducts in excellent enantioselectivity and yield. This process was believed to proceed through activation of the oxazolone by deprotonation along with coordination of the thiourea **157** to the $\alpha$-ketophosphonate. DBU catalysed addition of a second nucleophile leads to formation of the desired ester product.

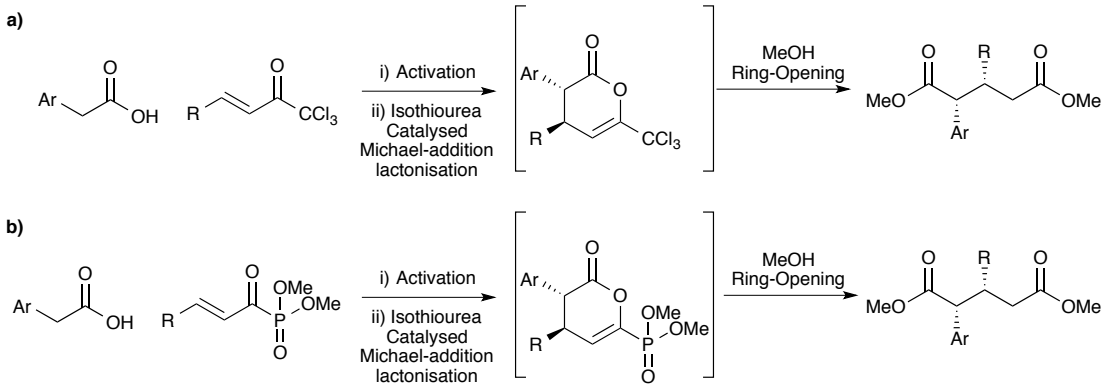



**Scheme 3.5: Jørgensen's Demonstration of $\alpha$-Ketophosphonates as Ester Surrogates**

During these investigations, Jørgensen outlined a set of three characteristics he believed a successful ester surrogate should possess: enhanced activation of the substrate towards nucleophilic attack; improved coordination to the chiral catalyst; and easy replacement of the group, preferably *in situ*.

## 3.2 Aims and Objectives

As part of our on-going research into isothiourea catalysed ammonium enolate chemistry, we wished to investigate the use of trichloromethylketones and $\alpha$-ketophosphonates as ester equivalents to give access to stereodefined diester products (Scheme 3.6). Further derivatisation of these products would be investigated in order to demonstrate the synthetic utility of this methodology.

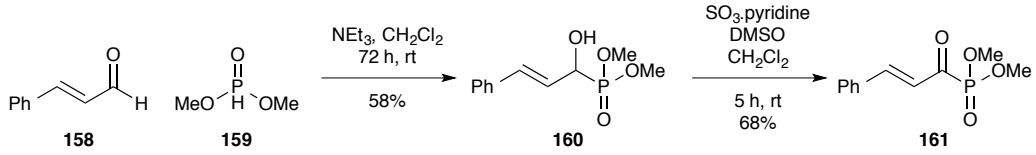



**Scheme 3.6: Use of Trichloromethylketones (a) or α-Ketophosphonates (b) as Ester Surrogates in Isothiourea Catalysed Ammonium Enolate Chemistry**

## 3.3 Results and Discussion

### 3.3.1 Previous Work on [4+2]-cycloadditions of α-Ketophosphonates Within the Smith Group

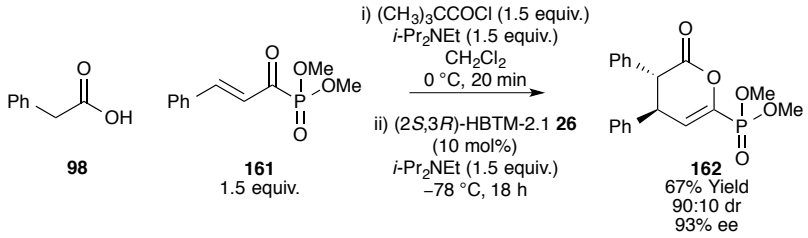
Previous work carried out by Reuben Holmes and Stuart Leckie led to optimisation of the synthesis of the α-ketophosphonate acceptors. Preparation through a modified version of the method published by Spilling,[15] whereby cinnamaldehyde **158** and dimethylphosphite **159** were stirred under Michaelis-Arbuzov conditions with triethylamine at room temperature, gave the allylic alcohol **160** (Scheme 3.7). Oxidation of **160** under Parikh-Doering conditions as described by Evans[16] gave the crude α-ketophosphonate **161**. An observed disadvantage of these acceptors was difficulty of purification – both silica column chromatography and distillation led to degradation of the α-ketophosphonate. In order to avoid the need for purification, the intermediate alcohol was triturated with ether allowing the final compound to be used without further purification.




**Scheme 3.7: Synthesis of *a*-Ketophosphonate Acceptors**

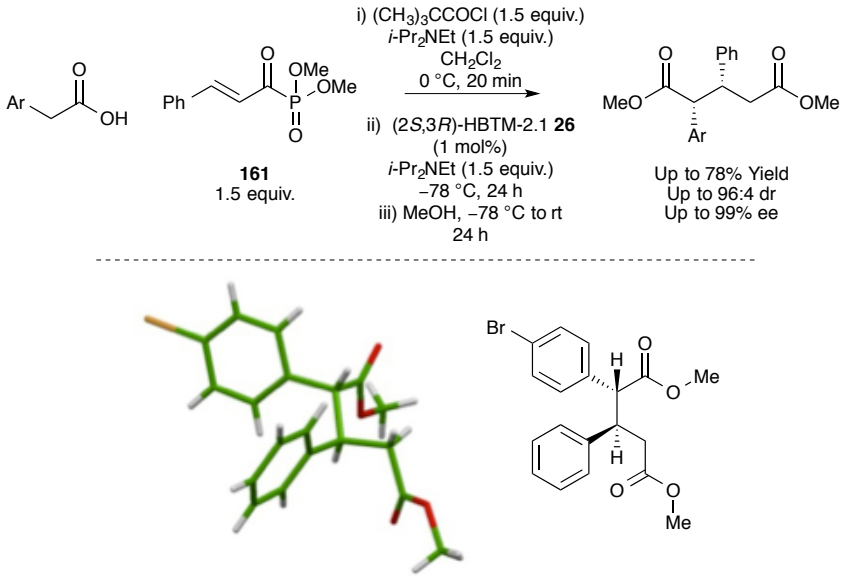
Following optimisation of the starting material synthesis, the enantioselective Michael-addition/lactonisation using arylacetic acids was explored (Scheme 3.8). *In situ* activation of the carboxylic acid **98** to the mixed anhydride was carried out using pivaloyl chloride and Hünig's base at 0 °C for 20 minutes. The reaction mixture was then cooled to –78 °C and (2*S*,3*R*)-HBTM-2.1 **26**, the α-ketophosphonate and further

Hünig's base were added before stirring at –78 °C overnight. This allowed access to the dihydropyranone product **162** in high disatereo- and enantioselectivity and good yields. However, isolation of the products was difficult owing to their instability especially to silica column chromatography – a problem noted with many similar $\delta$-lactones produced within the group.[1,2,3,4]




**Scheme 3.8: Reaction of $\alpha,\beta$-Ketophosphonates to Dihydropyranones**

As the ultimate aim of this work was to use these $\alpha$-phosphonates as masked esters in our reaction, *in situ* alcholysis was investigated and optimised (Scheme 3.9). Pleasingly, the desired diester products were accessed in excellent yields, dr and ee with the absolute configuration confirmed by X-ray crystallography.

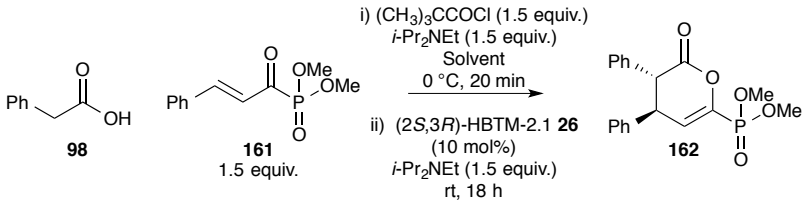



**Scheme 3.9: *In Situ* Methanolysis of Dihydropyranones to the Desired Diester Products**

### 3.3.2 Further Optimisation

Further to this work, my research started with a short investigation into the optimised conditions (Table 3.1). Solvent had not previously been varied from dichloromethane although THF had been shown to give improved stereoselectivities at room temperature in a similar process using *N*-tosyl-$\alpha,\beta$-unsaturated ketimines as acceptors.[2] Although changing the solvent to THF gave improved enantioselectivity at

room temperature (entry 2, dr 89:11, 97% ee compared with previous result of dr 88:12, 86% ee), owing to solubility problems the reaction could not proceed to full conversion and a low yield of 41% was obtained (entry 2). Combinations of solvents ($CH_2Cl_2$/THF) were tried but the reactions failed to reach completion even with extended reaction times.

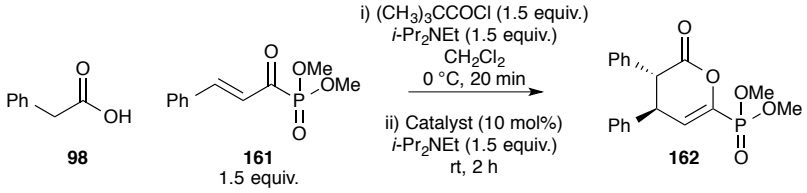



| Entry | Solvent | Yield (%) (conversion)[a] | dr (*anti:syn*)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1[d] | $CH_2Cl_2$ | 51 | 88:12 | 86 |
| 2 | THF | 41 (50) | 89:11 | 97 |
| 3 | THF:$CH_2Cl_2$ (3:1) | (78) | 89:11 | ND |
| 4 | THF: $CH_2Cl_2$ (1:1) | (80) | 89:11 | ND |

[a] Isolated yield of single diastereoisomer, conversion calculated by analysis of $^1$H NMR spectrum of crude. [b] Determined by analysis of $^1$H NMR spectrum of crude. [c] Determined by chiral HPLC analysis. [d] Work carried out by Reuben Holmes

**Table 3.1: Solvent Screen**

During the initial catalyst screen (Table 3.2), (2*S*,3*R*)-HBTM-2.1 **26** had been identified as the optimum catalyst (entry 1) with superior enantioselectivity over HBTM **24** and (–)=tetramisole.HCl **22** (entries 2 and 3). However, (*R*)-benzotetramisole **23** had not been tested in this process. Under the same reaction conditions benzotetramisole gave a lower isolated yield and reduced enantioselectivity (entry 4), therefore (2*S*,3*R*)-HBTM-2.1 **26** was used as the optimum asymmetric catalyst.




| Entry | Catalyst | Yield (%)[a] | dr (*anti:syn*)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1[d] | (2*S*,3*R*)-HBTM-2.1 **26** | 51 | 88:12 | 86 |
| 2[d] | HBTM **24** | 76 | 88:12 | 65 |
| 3[d] | (−)-Tetramisole.HCl **22** | 66 | 84:16 | 60 (*ent*) |
| 4 | (*R*)-BTM **23** | 42 | 74:26 | 56 |

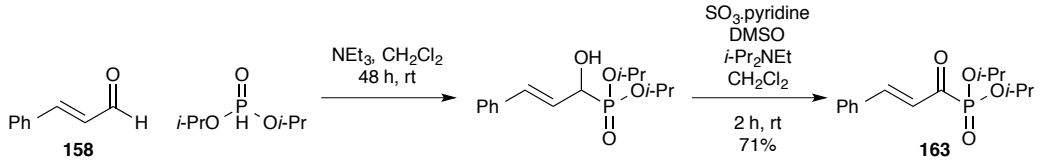
[a] Isolated yield of single diastereoisomer, conversion calculated by analysis of $^1$H NMR spectrum of crude. [b] Determined by analysis of $^1$H NMR spectrum of crude. [c] Determined by chiral HPLC analysis. [d] Work carried out by Reuben Holmes

**Table 3.2: Screen of Asymmetric Isothiourea Catalysts**

However, the long-term stability of the employed dimethoxy ketophosphonates was problematic with degradation occurring very quickly even when stored under an inert atmosphere at low temperature and this was a considerable drawback of this methodology. The starting material significantly degraded over a 3-4 week period and resulted in loss of ultimate yield of our cycloaddition reactions, even when using excess acceptor. Owing to this, an investigation into alternative acceptor substrates was carried out.

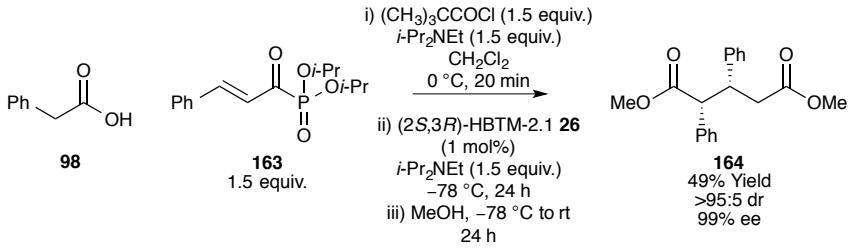
### 3.3.3 *Iso*-Propylphosphonate

It was noted that *iso*-propylphosphonate **163** was easier to prepare than its methoxy counterpart as it was able to be purified by silica gel chromatography. This $\alpha$-ketophosphonate could be stored for several months in the fridge under argon without degradation. This indicates that this phosphonate is more stable and indeed we were able to make it on a large scale (40 mmol, Scheme 3.10) with purification by column chromatography.




**Scheme 3.10: Large Scale Synthesis of $\alpha$-Ketophosphonate 163**

An initial reaction under the previously optimised reaction conditions revealed that the *iso*-propylphosphonate **163** also underwent displacement by methanol to give access to the diester product **164** in excellent diastereo- and enantioselectivity (Scheme 3.11), although in a slightly reduced overall yield.



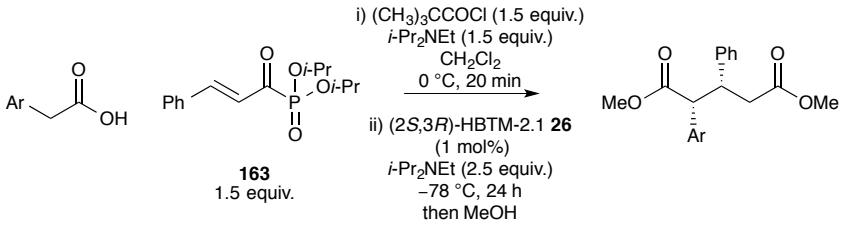

**Scheme 3.11: $\alpha$-Ketophosphonate 163 in Diester Formation**

### 3.3.3.1 Investigation of the Scope

The scope of the reaction was investigated using the preferred di-*iso*-propylphosphonate **163** by variation of the arylacetic acid. A range of diester products were synthesised and isolated in generally good yield, diastereo- and excellent enantioselectivities (Table 3.3).

In the case of the $\alpha$-ketophosphonate acceptors, *ortho*-substituted acids had not previously been investigated. A short investigation into this was carried out using *o*-tolyl acetic acid (entry 2) and the dr appeared to be very poor (56:44) however the products were not isolated and so not fully characterised.

Electron-donating and withdrawing groups were tolerated however with a small decrease in the dr in the case of *p*-fluorophenylacetic acid (entry 4). Notably the substrate scope included heteroarylacetic acids although with varying stereoselectivities with these acids. Diesters **168** and **169** were both isolated in moderate yields and lower ee (entries 5 and 6) however 3-thiophenylacetic acid was well tolerated with **170** isolated in excellent yield, dr and ee (entry 7).

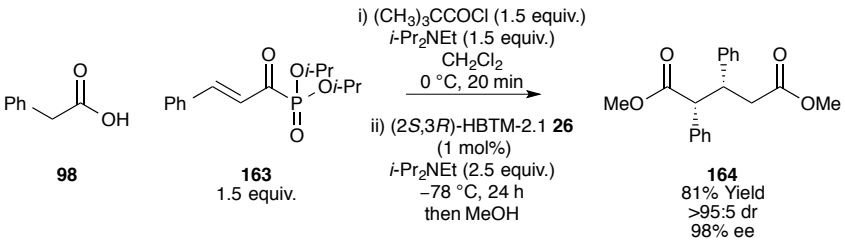



| Entry | Compound | Ar | Yield (%)[a] | dr (*anti:syn*)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **164** | Phenyl | 49 | 90:10 | 99 |
| 2 | **165** | *o*-Tolyl | ND (45% conversion) | 56:44 | ND |
| 3 | **166** | *p*-Methoxyphenyl | 73 | >95:5 | >99 |
| 4 | **167** | *p*-Fluorophenyl | 77 | 85:15 | 99 |
| 5 | **168** | *N*-Methyl-3-indolyl | 62 | 86:14 | 88 |
| 6 | **169** | 2-Thiophene | 51 | >95:5 | 67 |
| 7 | **170** | 3-Thiophene | 86 | >95:5 | >99 |

All reactions carried out on a 0.4 mmol scale. [a] Isolated yield of single diastereoisomer, conversion calculated by analysis of $^1$H NMR spectrum of crude. [b] Determined by analysis of $^1$H NMR spectrum of crude. [c] Determined by chiral HPLC analysis.

**Table 3.3: Variation of Arylacetic acid with *Iso*-Propylphosphonate 163**

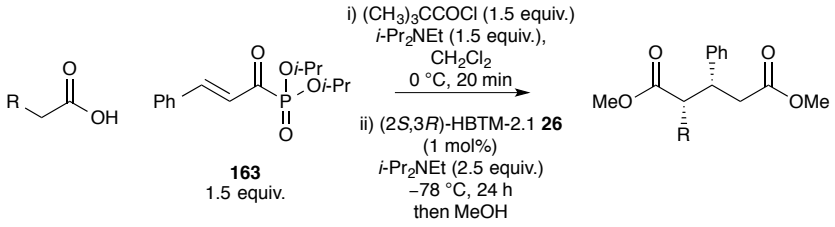
This methodology was shown to be amenable to scale synthesis with reaction on 2 mmol of **98** carried out and the diester **164** was isolated in excellent yield, dr and ee (Scheme 3.12).

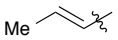
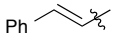
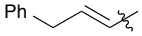



**Scheme 3.12: Large-Scale Synthesis of 164**

Building upon the success of alkenyl acetic acids as suitable ammonium enolate precursors within the group, these acids were also tested under the reaction conditions

with the *iso*-propylketophosphonate acceptor **163** (Table 3.4). Pleasingly, these acids were also tolerated in this system with excellent yields, diastereo- and enatioselectivity except for in the case of styrylacetic acid. Here, a decrease in the dr from >95:5 to 90:10 was observed following column chromatography and also a much lower ee than other examples was obtained (entry 2). The reasons for this are currently unknown.



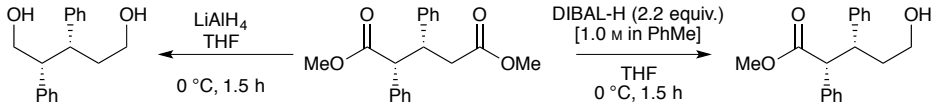

| Entry | Compound | R | Yield (%)[a] | dr (*anti:syn*)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **171** |  | 74 | >95:5 | >99 |
| 2 | **172** |  | 77 | >95:5[e] | 27 |
| 3 | **173** |  | 76 | >95:5 | >99 |

[a] Isolated yield of single diastereoisomer, conversion calculated by analysis of $^1$H NMR spectrum of crude. [b] Determined by analysis of $^1$H NMR spectrum of crude. [c] Determined by chiral HPLC analysis. [e] dr 90:10 following silica gel column chromatography.

**Table 3.4: Screen of Alkenylacetic acids**

### 3.3.3.2 Product Derivatisations

To further demonstrate the utility of this protocol, a series of synthetic transformations of the diester products were investigated. Previous work by Stuart Leckie showed that following isolation of the diester product **164**, it was possible to reduce both esters to give the diol **174** using lithium aluminium hydride or to selectively reduce the less sterically crowded ester using DIBAL-H to give alcohol **175**, both with no erosion of the dr or ee (Scheme 3.13).



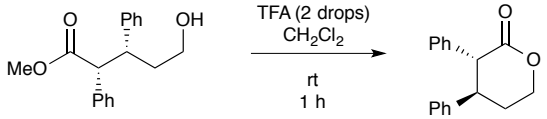

**174**
99% Yield
>95:5 dr
99% ee

**164**
>95:5 dr
99% ee

**175**
91% Yield
>95:5 dr
99% ee

**Scheme 3.13: Reductions of Diester Product 164**

Following isolation of alcohol **175**, subsequent acid-catalysed cyclisation gave access to lactone **176** without the need for purification and again with no effect on the dr or ee (Scheme 3.14).

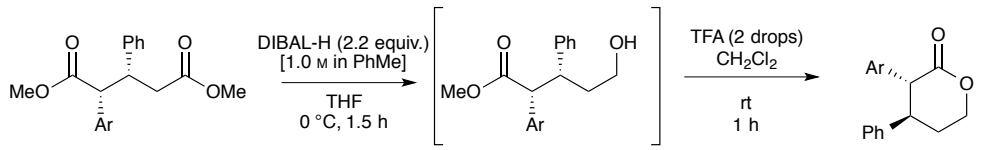


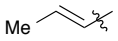
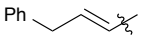

**175**
91% Yield
>95:5 dr
99% ee

**176**
99% Yield
>95:5 dr
99% ee

**Scheme 3.14: Acid-Catalysed Cyclisation of Alcohol 175 to Give New Lactone Scaffold**

With an aim to prove this was a general process, several diesters with a variety of substitution patterns were treated under these reaction conditions. Generally, it was found that this method worked well, with the stereochemistry conserved in all cases. Also, the reaction could be carried out from the diester without the need to purify the intermediate alcohol. However, the alkenyl examples **180** and **181** were only isolated in low yield using this protocol which potentially could be improved by purification of the intermediate (Table 3.5).



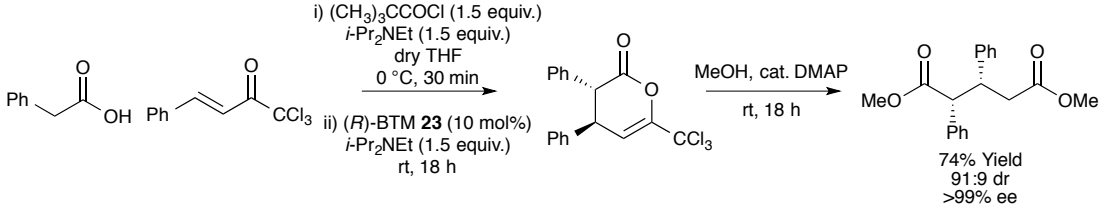

| Entry | Compound | R | Yield (%)[a] | dr (*anti:syn*)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **176** | Phenyl | 54 | >95:5 | 98 |
| 2 | **177** | *p*-Methoxyphenyl | 49 | >95:5 | >99 |
| 3 | **178** | *p*-Fluorophenyl | 63 | >95:5 | >99 |
| 4 | **179** | 2-Thiophenyl | 30 | >95:5 | 70 |
| 5 | **180** |  | 12 | >95:5 | 99 |
| 6 | **181** |  | 29 | >95:5 | 98 |

[a] Isolated yield of single diastereoisomer, conversion calculated by analysis of $^1$H NMR spectrum of crude. [b] Determined by analysis of $^1$H NMR spectrum of crude. [c] Determined by chiral HPLC analysis. [e] dr 90:10 following silica gel column chromatography.

**Table 3.5: Scope of Selective Reduction and Lactonisation**

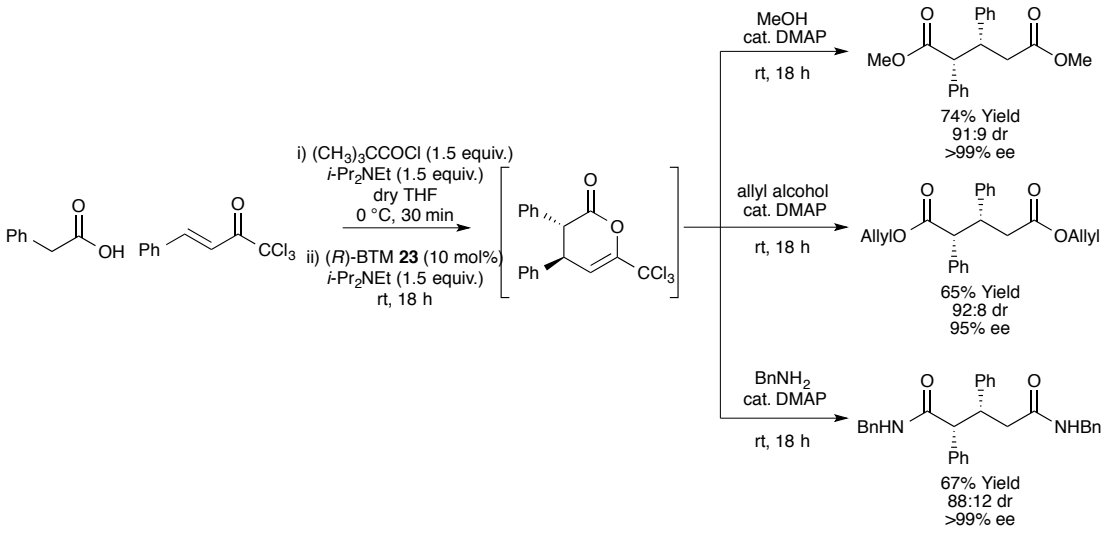
### 3.3.4 Previous Work on [4+2]-cycloadditions of Trichloromethylketones Within the Smith Group

Previous work carried out by Agathe D'Hollander, Carmen Simal and James Squires led to optimisation of the synthesis of the trichloromethylketone acceptors and their enantioselective lactonisation (Scheme 3.15). Following ring-opening with methanol, the same diester products formed from the $\alpha$-ketophosphonates were observed, indicating that trichloromethylketones can also act as ester surrogates in this process. In this case, the trichloromethylketones had an added advantage over the $\alpha$-ketophosphonates in that they were bench stable for over a year.




**Scheme 3.15: Trichloroketones as Ester Surrogates**

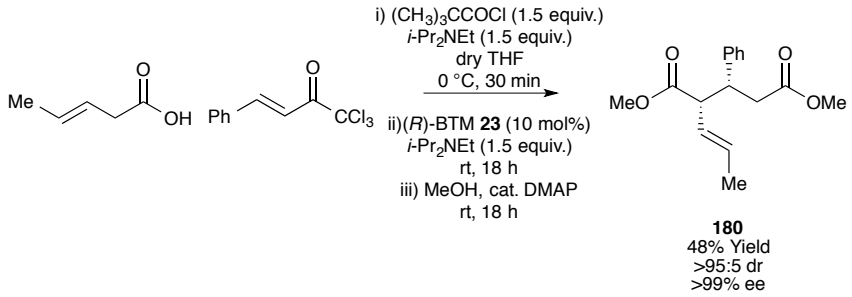
The scope of trichloromethylketones in our Michael-addition/lactonisation reaction was extensively investigated with 15 examples synthesised in up to 74% yield, 91:9 dr and >99% ee. The nucleophile for ring-opening was also varied and shown to be successful (Scheme 3.16).




**Scheme 3.16: Variation of Ring-Opening Nucleophile**

### 3.3.5 Expansion of This Work to Alkenyl Acids

Following the success of alkenyl acids in other processes from our group, an example was carried out with the trichloromethylketone acceptor (Scheme 3.17). The reaction proceeded well with the diester product being isolated in good yield and with excellent diastereo- and enantioselectivity.



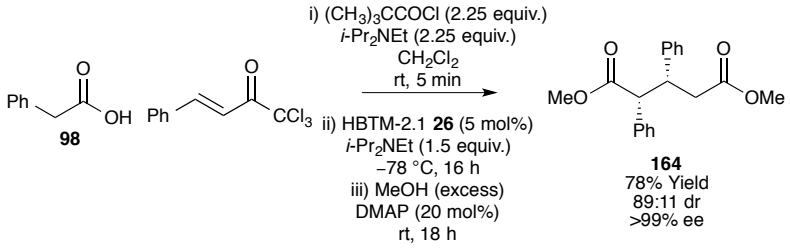

**Scheme 3.17: Example of Alkenyl Acid in Trichloromethylketone Chemistry**

## 3.4 Conclusions

In conclusion, the use of $\alpha,\beta$-unsaturated ketophosphonates as masked ester equivalents in Michael addition/lactonisation reactions with a range of acetic acids has been demonstrated. Difficulty with the purity of the methoxy phosphonate acceptor was overcome by using isopropyl phosphonate as it was amenable to column chromatography and found to be much more stable. A number of diester products

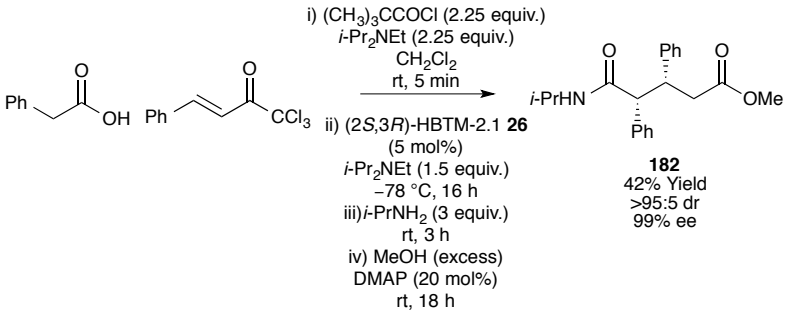
have been isolated from the newly developed reaction in excellent stereoselectivities. Subsequently, the synthetic utility of these diesters was then demonstrated through reduction to the diol and selective reduction to the ester-alcohol, which, following acid-catalysed cyclisation, gives access to new disubstituted lactone products without loss of stereocontrol.

Trichloromethylketones were also found to be useful ester equivalents under similar conditions and in this case have the advantage of being bench stable for over a year. Although initially optimised conditions required dry conditions, continuation of this work by other members of the group has identified conditions under which anhydrous solvent is not required (Scheme 3.18).[17]



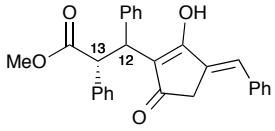

**Scheme 3.18: Final Optimised Conditions for Diester Synthesis from Trichloromethylketones**

Interestingly, recent work has established that using lower equivalents of the nucleophile for ring-opening of the trichlorolactone led to isolation of the monoester where displacement of the trichloromethyl group had not taken place. This led to the possibility of forming differentially protected dicarbonyl derivatives through the sequential addition of two distinct nucleophiles. This theory was proven through the reaction between phenylacetic acid and trichloromethylketone, which was first ring-opened with three equivalents of isopropylamine. Upon the disappearance of the initial dihydropyranone product by TLC analysis, addition of a large excess of methanol and catalytic DMAP (20 mol%) led to formation of $\gamma$-ester amide **182,** which was isolated in 42% yield over the one-pot 3-step reaction sequence as a single diastereoisomer in 99% ee (Scheme 3.19).




**Scheme 3.19: Sequential Addition of Two Nuclephiles to Form γ-Ester Amide 182**

In the future it is hoped this methodology could be applied to the synthesis of a potential bioactive target molecule. Pulveravens A and B have both been shown to have micromolar activity against carcinogen induced precancerous lesion formation (Figure 3.2).[18] They contain a similar substitution pattern as accessed from our methodology and so could be an interesting target for this work.




Pulveraven A (12*R*,13*R*)
Pulveraven B (12*S*,13*R*)

**Figure 3.2: Pulveraven A and B**

## 3.5 References For Chapter 3

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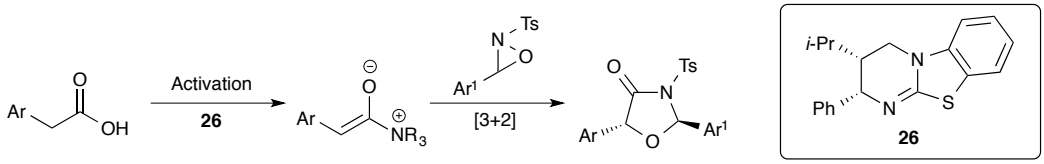
# Chapter 4: An Isothiourea Catalysed Formal [3+2]-Cycloaddition Towards Oxazolidin-4-ones

## 4.1 Introduction

### 4.1.1 Expansion of Isothiourea Ammonium Enolate Chemistry to Formal [3+2]-Cycloadditions

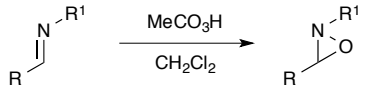
Continuing from previous work in this thesis describing work towards novel [2+2]- and [4+2]-cycloadditions, we now wished to expand this to formal [3+2]-cycloadditions. In the quest to synthesise a range of enantiomerically pure heterocyclic compounds, formal [3+2]-cycloadditions would provide an excellent approach towards five-membered ring systems of various connectivities and substitution patterns.[1] Previous work within the Smith group on ammonium enolate chemistry with various electrophilic partners has proven successful and it was postulated that an oxaziridine would make a good substrate for initial studies into the expansion of this work into [3+2] reactions (Scheme 4.1).




**Scheme 4.1: Premise for Expansion of Ammonium Enolate Chemistry to Incorporate Five-Membered Ring Formation**

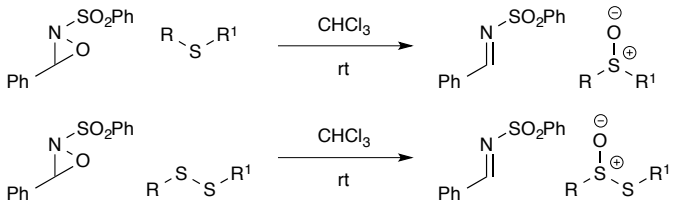
### 4.1.2 Oxaziridines

Oxaziridines, three-membered heterocycles containing an oxygen, nitrogen and carbon atom, were first reported in 1956[2] with Emmons's observation that certain aldimines were readily oxidised using peracetic acid. All analytical and experimental data indicated the formation of an oxygen-nitrogen-carbon ring, now known as an oxaziridine (Scheme 4.2). Their reactivity was similar in many respects to organic peroxides, with an active oxygen atom that allowed assaying by iodometric procedures - analysis by the oxidation of hydrogen iodide into iodine[2] - and initial research into their properties focussed on their use as oxidising agents.[3] Oxiaziridines have increased stability compared to analogous dioxiranes and peroxometal complexes, allowing improved ease of preparation and storage.[4]



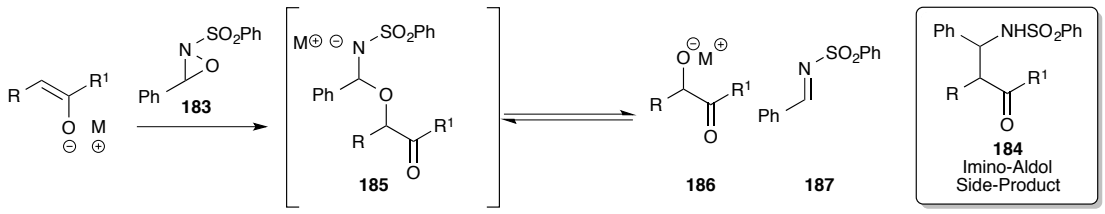

**Scheme 4.2: Oxidation of Imine into Oxaziridine by Peracetic Acid**

Oxaziridines can be classified by their *N*-substituent and varying this has a significant effect on their reactivity. In general, oxaziridines with small groups on the nitrogen atom (H, Me) act as aminating agents, whilst those with larger or electron-withdrawing groups acting as oxidising agents.[5] *N*-Alkyl, *N*-H, *N*-acyl, *N*-phosphinoyl, *N*-silyl and *N*-sulfonyloxaziridines have all been reported, however *N*-sulfonyloxaziridines are the most extensively used class after first being reported in the late 1970's by Davis and co-workers.[6] Their stability, ease of synthesis and superior oxidising ability over other classes facilitates their preparation and use in synthesis.[5] *N*-Sulfonyloxaziridines are characterised by a highly electrophilic oxygen atom and were first shown to selectively oxidise sufides and disulfides into the corresponding sulfoxides and thiolsulfinates (Scheme 4.3).[6] This process was observed to be virtually instantaneous and highly selective for sulfoxide synthesis without formation of the corresponding sulfone.




**Scheme 4.3: Oxidation of Sulfides and Disulfides by *N*-Sulfonyloxaziridines**

In 1984, Davis and co-workers expanded this process to use oxaziridine **183** for the direct hydroxylation of enolates (Scheme 4.4).[7] Efficient methods for the α-hydroxylation of carbonyl compounds are of great synthetic interest owing to the presence of this structural motif in many biologically active natural products[8] and is perhaps the most widely utilised reaction of oxaziridines.[5] Davis observed that the base used to form the enolate (and therefore the enolate counterion) was important and an imino-aldol side-product **184** was formed using lithium enolates but not observed using sodium enolates. He proposed this was due to a difference in the equilibrium between **185** and **186**. With a lithium counterion, this equilibrium lay more to the right allowing enolate **186** to react directly with imine by-product **187** to form imino-aldol product **184**.



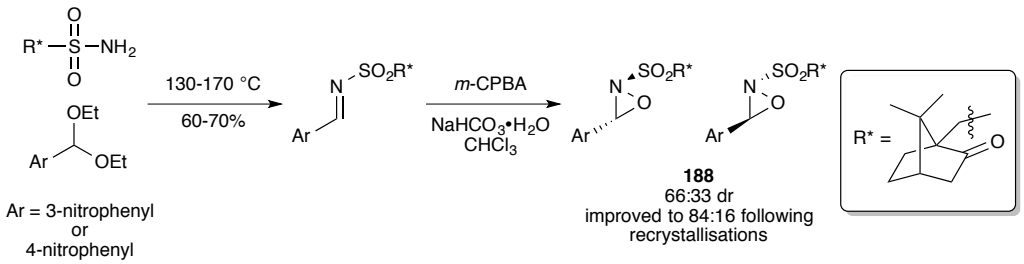

**Scheme 4.4: Direct Hydroxylation of Enolates by *N*-Sulfonyloxaziridines**

Further work in this field has included oxidation of olefins into epoxides,[7] triphenylphosphines into their oxides,[9] hydrogen iodide into iodine and chloride ions into chlorine,[10] organometallics into alcohols,[11] and amines into amine oxides.[3]

### 4.1.3 Oxaziridines in Asymmetric Synthesis

An interesting feature of oxaziridines is their inherent stereochemistry.[2] The stereogenicity of the nitrogen atom and its considerable barrier to inversion allows the synthesis of enantiopure oxaziridines. The barrier to inversion at nitrogen was determined to be 25-32 kcalmol$^{-1}$ for *N*-alkyl oxaziridines,[12] although this varies depending on the *N*-substituent. The transition state for thermal epimerisation also has increased ring strain, which provides a further barrier to nitrogen inversion.[13]

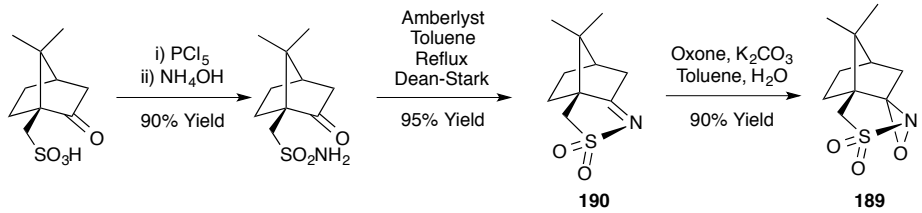
Davis noted that this property could allow for stereospecific transfer of heteroatoms if the starting oxaziridine was of high enantiopurity. In 1979, Davis reported the use of camphor derived oxaziridine **188** as an enantioenriched oxidising agent providing an alternative to chiral peroxy acids.[14] Synthesis of oxaziridine **188** employed a two-step procedure (Scheme 4.5), with the first step requiring heating of (–)-camphor-10-sulfonamide with the diethyl acetals of the requisite nitrobenzaldehydes. Oxidation by *m*-CPBA in the presence of sodium bicarbonate gave the oxaziridines as mixtures of diastereoisomers (66:33). Following several recrystallisations, the diastereomeric ratio was improved to 84:16 and this mixture was used for further experiments.




**Scheme 4.5: Synthesis of Chiral Oxaziridines**

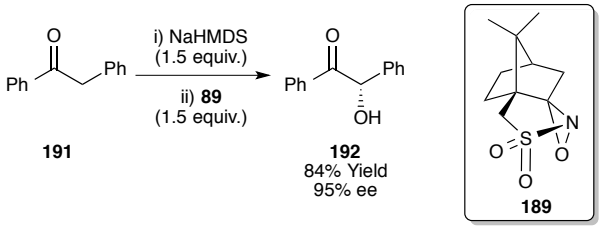
The first synthetically useful approach to reagent-controlled asymmetric oxidation using chiral *N*-sulfonyloxaziridines utilised oxaziridine **189**, formed by the selective oxidation of camphor sulfonic acid derived imine **190** (Scheme 4.6).[15] These

synthetically useful compounds are readily available on kilogram scale as single stereoisomers. As a result of their widespread utility, varients of these compounds are currently commercially available from Sigma Aldrich.[16]



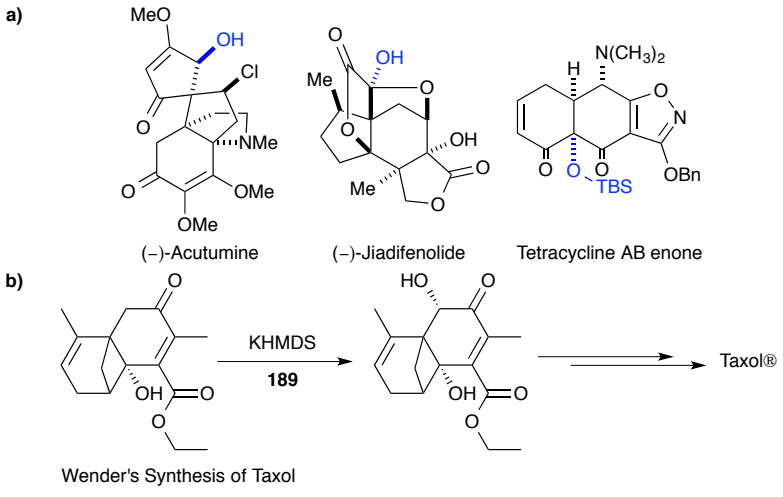

**Scheme 4.6: Synthesis of Davis's Chiral Camphor-Derived Oxaziridine 189**

Davis and co-workers applied (camphorylsulfonyl)oxaziridine **189** to the $\alpha$-oxidation of ketones. For example, treating ketone **191** with NaHMDS followed by oxaziridine **189** gives $\alpha$-hydroxyketone **192** in 84% yield with excellent levels of stereocontrol (Scheme 4.7).[15]



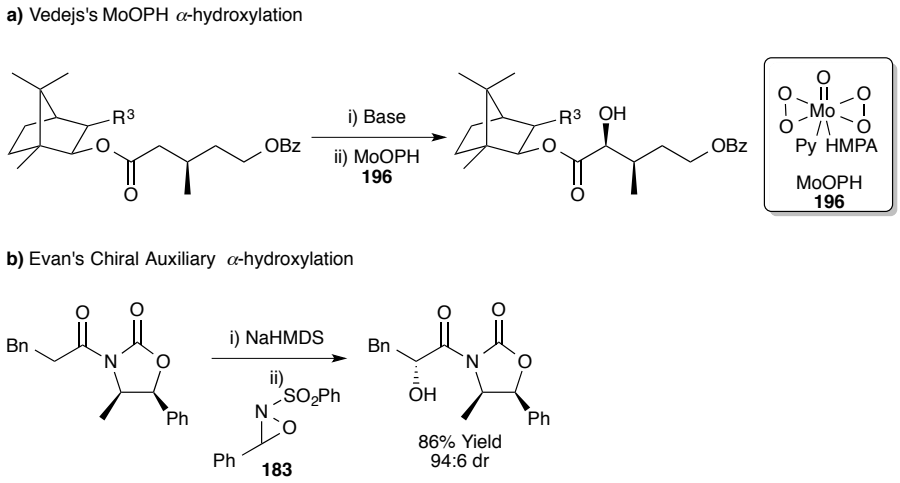

**Scheme 4.7: Davis's Asymmetric Hydroxylation of Ketones**

This process has been used to insert $\alpha$-hydroxyl groups in many total syntheses of biologically important natural products[17] including (–)-acutumine **193**,[18] (–)-jiadifenolide[19] **194** and tetracycline AB enone **195**, a key precursor to tetracycline antibiotics (Scheme 4.8a),[20] and also in two syntheses of Taxol® including Wender's synthesis in 1997 (Scheme 4.8b).[21]




**Scheme 4.8: Use of Davis's Asymmetric Hydroxylation in Total Synthesis**

Alternative methods for the $\alpha$-oxidation of carbonyls include using Vedejs's oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide) (MoOPH) **196** reagent as the electrophilic oxygen source with camphor derived starting materials (Scheme 4.9a),[22] or using Evans's chiral auxiliary with a racemic *N*-sulfonyloxaziridine **183** as the electrophile (Scheme 4.9b).[23] Whilst both these methods give good selectivities they both make use of a chiral auxiliary, a well-documented disadvantage of which is the need to prepare and then remove the auxiliary thereby adding extra steps to the synthetic sequence.

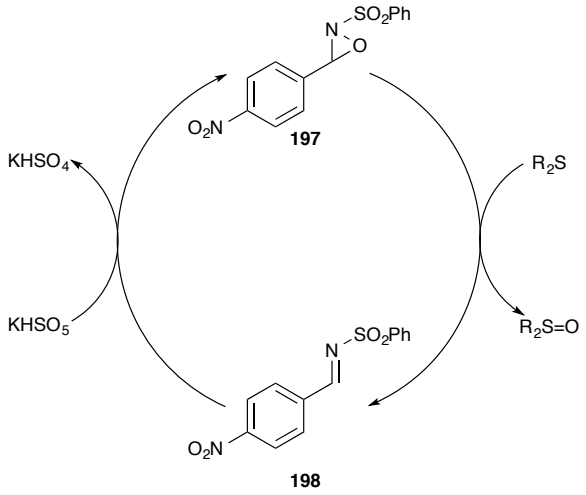



**Scheme 4.9: Alternative Methods for $\alpha$-Hydroxylation**

### 4.1.4 Oxaziridines in Asymmetric Catalysis

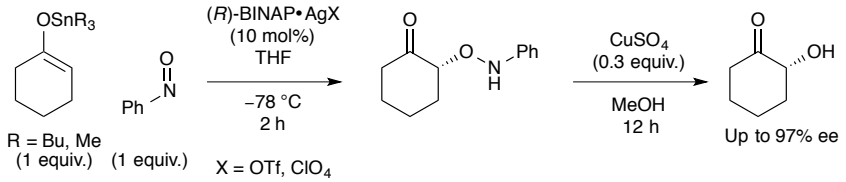
As the historic route for asymmetric oxidation by oxaziridines generally requires either a stoichiometric amount of a chiral oxaziridine or a chiral auxiliary,[24] recently there has been a quest to develop a catalytic asymmetric version of Davis's oxaziridine oxidation reaction, especially for asymmetric $\alpha$-hydroxylation reactions.

Catalytic processes involving oxaziridines were again first investigated by Davis *et al*. who published a process requiring catalytic amounts of oxaziridine and a stoichiometric re-oxidant in 1988 (Scheme 4.10).[25] The oxidation of sulfides into sulfoxides using a catalytic amount of **197** followed by re-oxidation of the sulfonylimine **198** to the oxaziridine was described. *m*-CPBA could not be used as a re-oxidant as under the reaction conditions it would oxidise the desired sulfides into sulfones, however, buffered peroxymonosulfate (Oxone®) was suitable and gave no background oxidation.



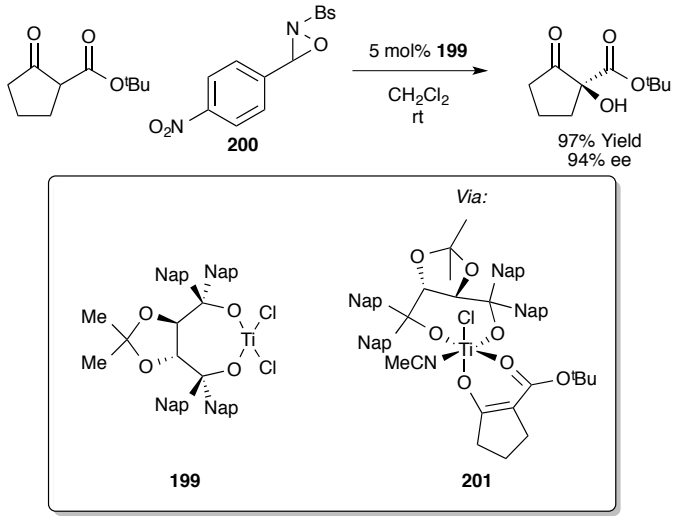

**Scheme 4.10: Oxidation of Sulfides into Sulfoxides Using Catalytic Oxaziridine**

In 2003, Yamamoto *et al*. described the first catalytic enantioselective introduction of an oxy group at the $\alpha$-position of a ketone enolate using nitrosobenzene as an oxaziridine alternative (Scheme 4.11).[26] Using an (*R*)-BINAP-silver complex, the $\alpha$-hydroxy compounds could be isolated in up to 97% ee after N-O bond cleavage using $CuSO_4$, with high regioselectivity for the *O*-adduct over the *N*-adduct.



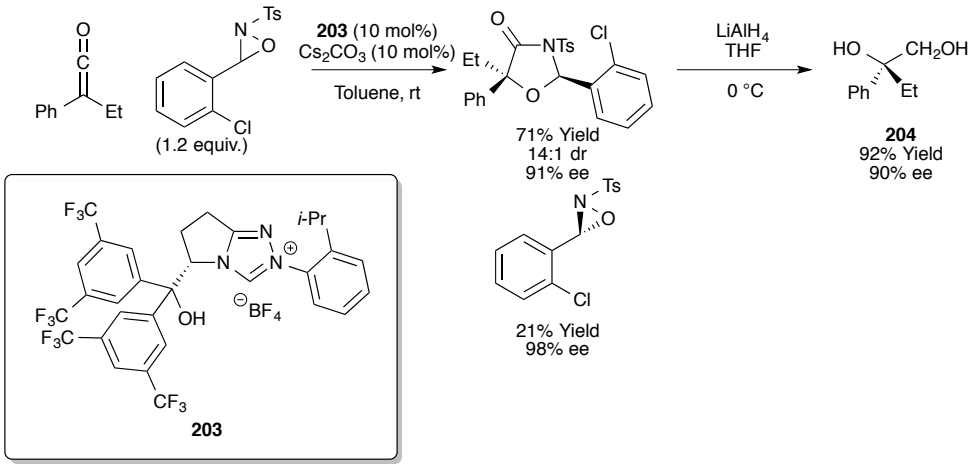

**Scheme 4.11: Nitrosobenzene as an Oxaziridine Alternative for $\alpha$-Hydroxylation**

The use of oxaziridines for the asymmetric hydroxylation of $\beta$-ketoesters was reported by Togni and co-workers in 2004 (Scheme 4.12).[27] This was the first direct asymmetric transition-metal-catalysed $\alpha$-hydroxylation reported. Using a chiral Lewis acid titanium (IV) TADDOLate complex **199** as the catalyst and 2-(phenylsulfonyl)-3-(4-nitrophenyl)oxaziridine **200** as the oxidising agent, products containing a quaternary stereocentre could be isolated in high yields and enantioselectivities. The proposed mechanism involved coordination of the titanium catalyst to the dicarbonyl compound to form a chiral enolate **201**, which is epoxidised by the oxaziridine with subsequent ring-opening giving the observed product.




**Scheme 4.12: Hydroxylation of $\beta$-Ketoesters using Titanium (IV) TADDOLate Complex 199**

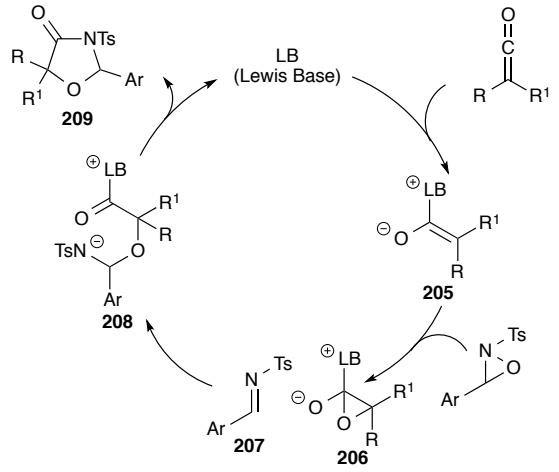
Recently, organocatalytic examples of $\alpha$-hydroxylation have come to the forefront. Lewis base catalysts have been shown to catalyse formal [3+2]-cycloaddition reactions of *N*-sulfonyloxaziridines *via* N-O bond cleavage, giving access to oxazolidin-4-one products. In 2010, Ye *et al*. reported the formal [3+2] cycloaddition of a ketene and an oxaziridine catalysed by NHC **203** (Scheme 4.13).[24] These products are masked $\alpha$-hydroxy carbonyl compounds and Ye demonstrated that reduction of these compounds with $LiAlH_4$ gives access to the enantioenriched diol **204**. Notably, when 1.2 equivalents of racemic oxaziridine was used, the optically active oxaziridine could be recovered in reasonable yield and good to excellent enantiopurity.




**Scheme 4.13: Ye's Synthesis of Oxazolidin-4-ones and Optically Active Diols**

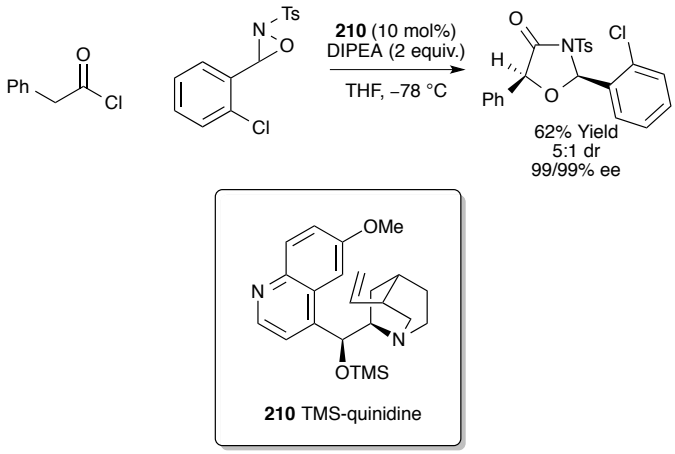
This formal cycloaddition reaction is proposed to proceed through addition of the Lewis base catalyst to the ketene substrate, forming zwitterionic enolate intermediate **205** (Scheme 4.14). Subsequent oxidation by the oxaziridine gives intermediate **206**

and imine **207** which undergo a nucleophilic addition to zwitterionic complex **208**. Following collapse of this intermediate, the final cycloadduct **209** is formed and the Lewis base catalyst regenerated.



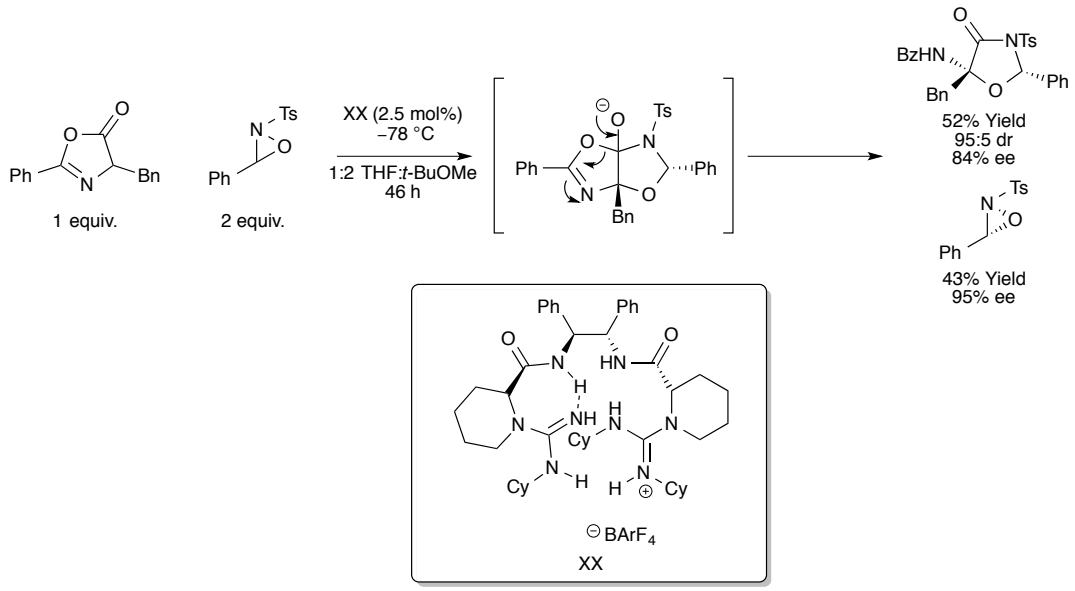

**Scheme 4.14: Proposed Reaction Mechanism for Ye's [3+2]-Cycloaddition**

This method was not suitable for monsubstituted ketenes generated *in situ* from acyl chlorides however, using cinchona alkaloid catalyst TMS-quinidine **210**, the disubstituted *syn*-products could be accessed in moderate to good yields and high enantioselectivities (Scheme 4.15).[24,28]



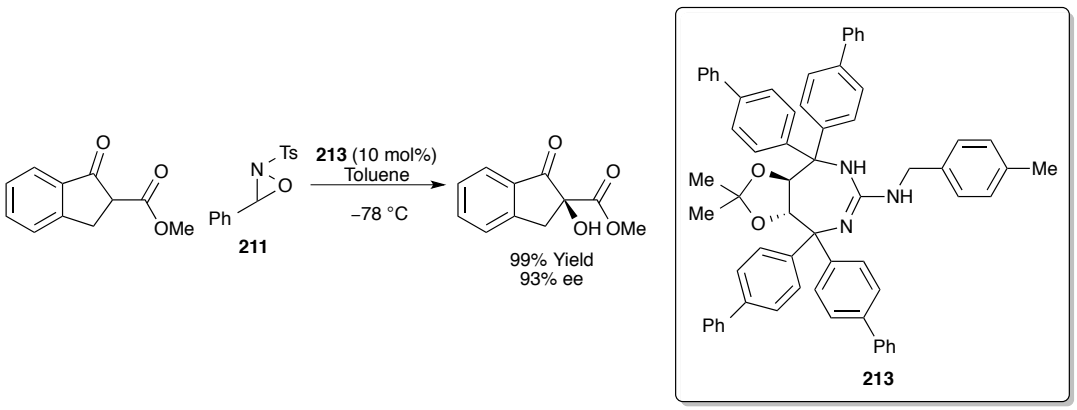

**Scheme 4.15: Formation of Oxazolidin-4-ones from Monosubstituted Ketenes**

In 2013, Lui and Feng reported a similar route to oxazolidin-4-ones *via* the oxyamination of azlactones using oxaziridine **211** catalysed by chiral bis-guanidinium salt **212** (Scheme 4.16).[29] The products were formed in excellent diastereo- and enantioselectivity and the process also results in the kinetic resolution of a range of oxaziridines.




**Scheme 4.16: Oxazolidin-4-ones *via* Oxyamination of Azlactones**

Also in 2013, Zou *et al*. reported that the use of a TADDOL-like chiral guanidine **213** for the $\alpha$-hydroxylation of $\beta$-ketoesters forms products with excellent yields and enantioselectivities (Scheme 4.17).[30] *N*-Tosyloxaziridine **211** was selected as the source of electrophilic oxygen as it was much more selective than other sources screened.




**Scheme 4.17: TADDOL-like Chiral Guanidine 213 for $\alpha$-Hydroxylation of $\beta$-Ketoesters**

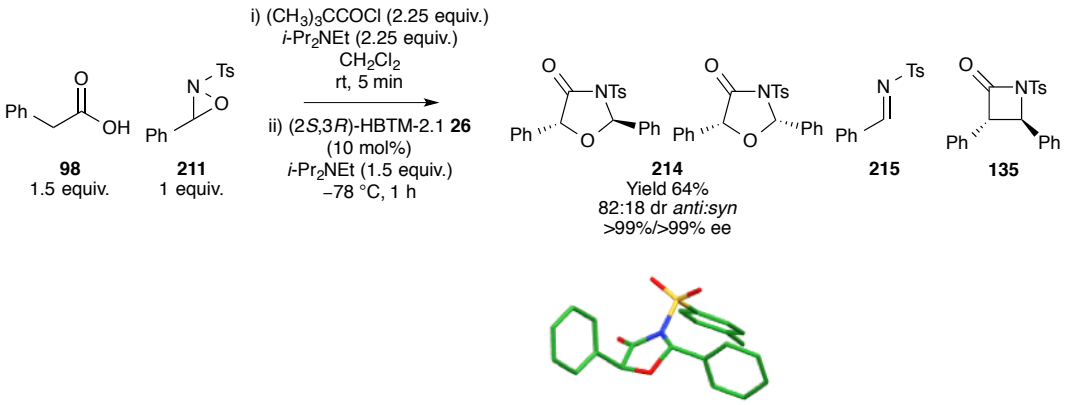
## 4.2 Aim

Expanding our work on isothiourea based chiral ammonium enolates in organocatalysis, it was postulated that these intermediates could be used as an alternative to ketene derived enolates in a similar system to that of Ye.[24,28] Using isothioureas as our Lewis base catalysts to generate ammonium enolates *in situ* from activated carboxylic acids and oxaziridines as electrophiles, we hoped to gain access to enantioenriched oxazolidin-4-ones. A secondary aim was to probe the mechanistic influence of the use of enantioenriched oxaziridines in this system.

## 4.3 Results and Discussion

### 4.3.1 Previous Work on [3+2]-Cycloadditions Within the Smith Group

Initial studies carried out by Louis Morrill identified oxaziridines as suitable partners for formal [3+2]-cycloadditions with isothiourea generated ammonium enolates (Scheme 4.18). The oxazolidin-4-one product **214** was isolated in 64% yield with good diastereoselectivity (86:14 *anti:syn*) and excellent ee (both diastereoisomers >99% ee), however the product containined 6% of an imine contaminant **215** and also trace levels of *β*-lactam **135**. X-ray crystallography of a racemic sample allowed assignment of the relative configuration of the major diastereoisomer as *anti*, however a crystal of the asymmetric sample could not be obtained precluding determination of the absolute configuration by this method. The absolute configuration of both enantiomers was assigned by methods discussed later in this chapter.




**Scheme 4.18: Isothiourea-Catalysed Oxazolidin-4-one Formation**

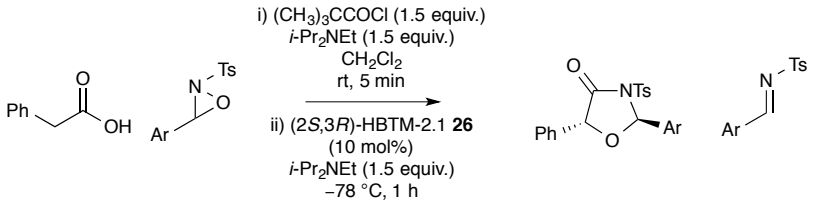
The observation of imine in the product distribution led to the hypothesis that this was the product of an alternative pathway outwith the isothiourea catalysed [3+2]-cycloaddition *via* oxaziridine degradation. Furthermore, as the imine co-eluted with the product during column chromatography, isolation of clean oxazolidin-4-one **214** was not possible.

### 4.3.2 Reaction Optimisation

#### 4.3.2.1 Initial Scope Screen

In continuing this project, our initial work focussed on variation of the aryl unit within the oxaziridine in order to see if this gave any effect on the formation of the imine side-product. In dichloromethane at room temperature to phenylacetic acid **98**, *N*-sulfonyloxaziridine, pivaloyl chloride and Hünig's base were added and the reaction

mixture stirred at room temperature for five minutes. Following cooling to –78 °C, (2*S*,3*R*)-HBTM-2.1 **26** (10 mol%) and further Hünig's base were added and the reaction mixture stirred for 1 hour before quenching with 1M hydrochloric acid. A number of *N*-tosyloxaziridines were screened including the *o*-chlorophenyl example Ye favoured for his chemistry (Table 4.1).[24,28]




| Entry | Compound | Ar | *β*-Lactam[a] (%) | Imine (%)[a] | Yield (%)[b] | dr (*anti:syn*)[c] | ee (%, *anti*/*syn*)[d] |
|---|---|---|---|---|---|---|---|
| 1 | **214** | Phenyl | 5 | 13 | 60 | 69:31 | >99/>99 |
| 2 | **216** | *o*-Chloro phenyl | 9 | 13 | 20 | 74:26 | 96/>99 |
| 3 | **217** | *p*-Bromo phenyl | 0 | 48 | 21 | 78:12 | 94/>99 |
| 4 | **218** | 2-Naphthyl | 0 | 6 | 0 | N/A | N/A |

[a] Percentage of material relative to product from inspection of $^1$H NMR spectrum of crude. [b] As a mixture of diastereomers including imine contaminent. [c] Determined by inspection of $^1$H NMR spectrum of crude. [d] Obtained by chiral HPLC analysis

**Table 4.1: Variation of Oxaziridine**

The results varied considerably in the amounts of imine and *β*-lactam present. This was unsurprising as it has been reported that small structural changes in the oxaziridine can affect their reactivity vastly and, in the case of a more reactive oxaziridine, this could lead to an increase in any background reaction.[5]

Use of *o*-chlorophenyl oxaziridine **219** (entry 2) allowed us to directly compare the $^1$H NMR spectrum of our product with that of Ye's. Evaluation of the chemical shift of the *C*(2) proton of Ye's product **216** showed their major *syn*-oxazolidin-4-one to be at 5.34 ppm and their minor *anti*-oxazolidinone to be at 5.38 ppm (Figure 4.1). The signal for our major diastereoisomer was at 5.38 ppm further confirming its assignment as the *anti* product.

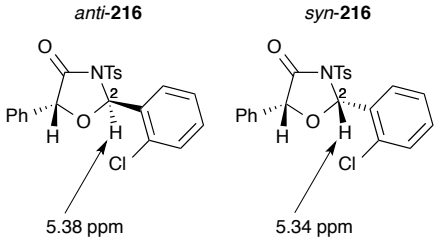



**Figure 4.1: Assignment of Diastereoisomers *via* Chemical Shift**

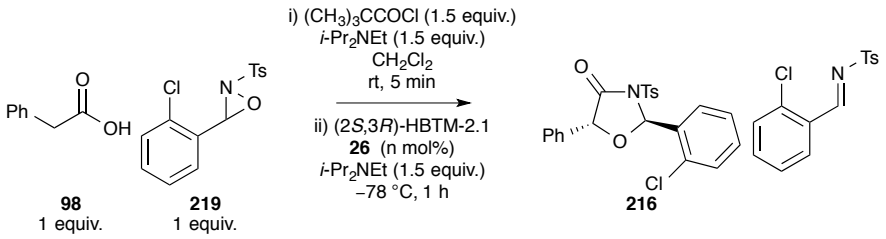
*p*-Bromophenyl oxaziridine **220** (entry 3) showed low conversion to the desired oxazolidin-4-one product with 48% of the undesired imine instead being formed, whereas, the 2-naphthyl substituted oxaziridine **221** (entry 4) had very limited solubility in dichloromethane and no desired product was observed, with only a small amount of imine and starting material observed in the $^{1}$H NMR spectrum of the crude material. This reaction was repeated in tetrahydrofuran in which the oxaziridine dissolved fully, however the results of the reaction were again disappointing with only degradation of the oxaziridine observed.

As none of the alternative oxaziridines gave any improvement in the outcome of the reaction, further investigations were undertaken to optimise the reaction for the synthesis of the desired oxazolidinone products.

#### 4.3.2.2 Lowering of Catalyst Loading

It was postulated that the catalyst **26** could be oxidised by the oxaziridine in a side reaction and that lowering the catalyst loading would lead to less imine side-product. A brief catalyst loading investigation was carried out in order to hopefully minimise imine formation and make the reaction more economical (Table 4.2).

Interestingly, at lower catalyst loadings the dr was seen to increase, although this also increased the levels of imine observed. When using 2 mol% of isothiourea catalyst (entry 3), 28% of $\beta$-lactam side-product was present in the crude reaction mixture. When using 1 mol% of catalyst (entry 4) there was no conversion into product with only degradation of the oxaziridine into imine observed. This implies that the catalyst is not involved in the pathway for imine formation and in fact higher levels of catalyst allows oxazolidinone formation to be competitive with imine formation.




| Entry | mol % | Imine[a] (%) | Yield (%)[b] | dr (*anti:syn*)[c] | ee (%, *anti*/*syn*)[d] |
|---|---|---|---|---|---|
| 1 | 10 | 13 | 60 | 69:31 | >99/>99 |
| 2 | 5 | 16 | 62 | 73:27 | 44/ND |
| 3 | 2 | 50 | ND | 83:17 | ND |
| 4 | 1 | 68 | ND | ND | ND |

[a] Percentage of material relative to product from inspection of $^1$H NMR spectrum of crude. [b] As a mixture of diastereomers. [c] Determined by inspection of $^1$H NMR spectrum of crude. [d] Obtained by chiral HPLC analysis

**Table 4.2: Catalyst Loading Screen**

At 5 mol% catalyst loading (entry 2), similar levels of imine and product were seen as at 10 mol% (entry 1) however there was a small amount of imine left in the purified sample. Disappointingly the ee decreased dramatically from >99% to 44% upon decreased catalyst loading and so 10 mol% was therefore kept as the optimum catalyst loading.

### 4.3.2.3 Attempted Removal of Imine

Alternative purification techniques to column chromatography for removal of the unwanted imine side-product were investigated. A reductive work up with sodium borohydride, which would convert the imine into an amine and hopefully allow easier purification proved unsuccessful in practise as it also caused degradation of the oxazolidin-4-one product.

Trituration of the product following column chromatography yielded only the major diastereoisomer, but in low yields and so was again discounted.

Further lowering of the temperature of the reaction to –100 °C with a dry ice/$Et_2O$ bath in an attempt to stop the side reaction led to very low conversion into the desired product (24%, dr 80:20 *anti:syn*) and a large proportion of imine and aldehyde side products (37% and 13% respectively) were obtained.

#### 4.3.2.4 Side Reaction Investigations

At this point, an evaluation of all results collected highlighted that the degradation of the oxaziridine starting material was the major problem when developing this chemistry as any contamination of the crude product with greater than 5% of imine resulted in the inability to successfully purify the product. In addition, if the imine was formed in a large proportion prior to oxidation of the enolate, competitive *β*-lactam formation ensued and this had a detrimental effect on the yield of the desired product. Additionally, the presence of imine and formation of β-lactam led us to propose that the imine was being formed independently of the desired reaction.

In order to investigate imine formation, we considered possible pathways for its formation through analysis of combinations of the reaction components. A $^{1}$H NMR sample of Hünig's base in deuterated dichloromethane was treated with oxaziridine **211** and the sample re-analysed by $^{1}$H NMR spectroscopy. The results show formation of the *N*-oxide of the base in less than one hour at room temperature, along with formation of imine **215** (Figure 4.2).[31] Evaluation of the literature highlighted the ability for oxaziridines to act as strong oxidising agents not just for enolates[7] but also amines into amine oxides.[3] That the base was so readily oxidised was a major breakthrough in understanding the reaction process and showed we needed to re-evaluate our reaction conditions.

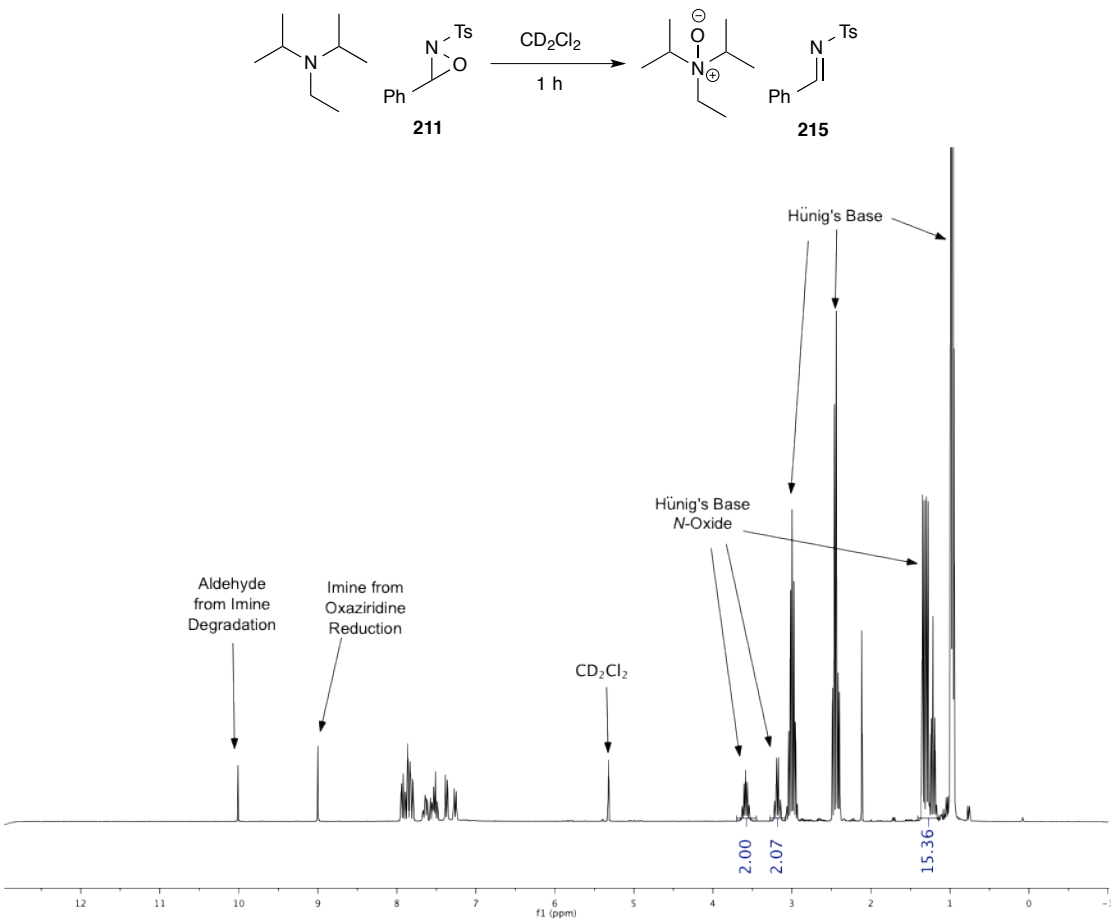
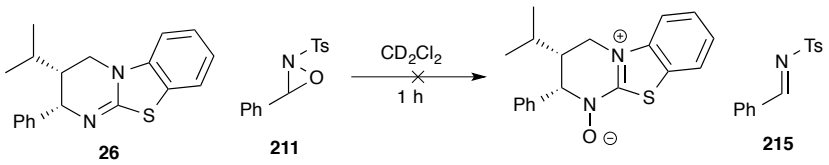


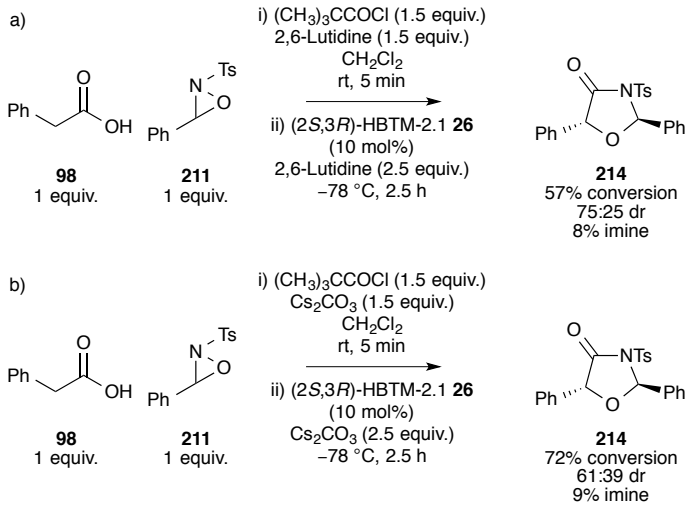

**Figure 4.2: Oxidation of Hünig's Base by the Oxaziridine 211**

In addition, our use of a potentially oxidisable isothiourea catalyst allows another path to imine formation to be proposed – through catalyst oxidation by the oxaziridine acceptor. A similar $^{1}$H NMR experiment to that with Hünig's base was carried out with the isothiourea catalyst (2*S*,3*R*)-HBTM-2.1 **26** (Scheme 4.19). After one hour, one equivalent of oxaziridine **211** and one equivalent of catalyst showed no change. However, over an extended period (>18 hours) the appearance of imine and a shift of the isothiourea's chemical shifts indicated that oxidation had occurred although the product was not isolated. This evidence along with the high levels of enantioselectivity observed in [3+2]-cycloaddition indicates that this pathway would not be highly competitive and we therefore dismissed this as a route to imine formation in our reaction timescale.




**Scheme 4.19: Oxidation of (2*S*,3*R*)-HBTM-2.1 26 by the Oxaziridine**

Following these investigations, a second base screen was carried out with 2,6-lutidine and cesium carbonate being used in $CH_2Cl_2$ at −78 °C. With 2,6-lutidine we hoped the *N*-oxide would be less readily formed and although initial results seemed promising with no imine present in samples taken after one hour, after 2.5 hours 8% of imine was present (Scheme 4.20a). Full conversion of the oxaziridine was not achieved even when left overnight and an exceptionally high level of imine was observed (46%). Although cesium carbonate had initially been dismissed due to poor levels of solubility in THF at low temperatures, it had not yet been evaluated in dichloromethane at −78 °C. This reaction was seen to proceed with good conversion over one hour (71%) however around 10% of imine was also present. After 2.5 hours there was little change (Scheme 4.20b) and after leaving overnight, multiple products were observed.

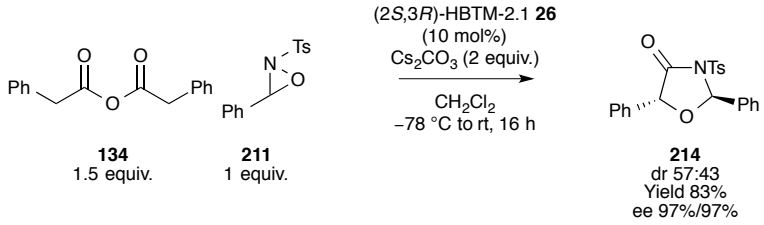



**Scheme 4.20: 2,6-Lutidine and Caesium Carbonate Base Screen**

These results were disappointing and indicated there must be a further route to imine formation that had yet to be investigated. As oxaziridines have been shown to oxidise chloride ions into chlorine,[10] the use of pivaloyl chloride as an activating agent in this process was questioned, as following activation, chloride ions would be formed and need a quenching pathway. This seemed to be an obvious route for competitive reaction of the oxaziridine and formation of imine that we wished to avoid. We

therefore chose to examine the use of homoanhydrides in this reaction, which as shown in previous work in the group, can also be used as ammonium enolate precursors whilst removing the need for the preactivation step (Scheme 4.21).[32]

The use of homoanhydrides proved very effective and we were able to minimise the presence of $\beta$-lactam and imine completely. Using 1.5 equivalents of the homoanhydride **134** under the previous conditions in dichloromethane with cesium carbonate as the base gave the product **214** in poor dr (57:43, *anti:syn*) but excellent yield and ee. These were used as the optimum conditions for further investigations into the scope of the reaction.



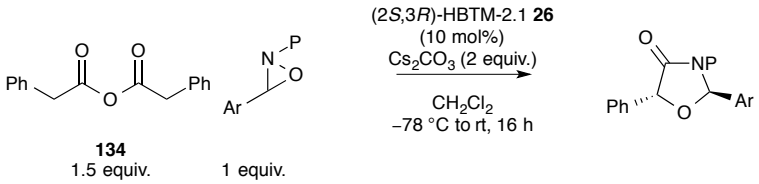

**Scheme 4.21: Homoanhydride 134 as Starting Material for Oxazolidin-4-one 214 Formation**

### 4.3.3 Investigation into the Scope of the Reaction

#### 4.3.3.1 Variation of the Oxaziridine

With the optimum conditions in hand, the scope of the reaction was investigated by first varying the oxaziridine component. As before, the aromatic group was varied, and also the *N*-protecting group was changed to a nosyl group to give a small number of examples (Table 4.3).

In all cases the yield was high (73-83%) but the dr was poor. The ees of both product diastereoisomers were good, although a lot of variation was seen between examples. Surprisingly, in the case of the *o*-chlorophenyl oxaziridine **219** (Entry 2), the ee was seen to be much reduced whereas the reaction directly from the acid had showed high levels of enantiocontrol. As this process should go through the same postulated intermediate, the change in ee is likely to be due to an enhanced racemic background reaction when reacting from a pre-formed homoanhydride.




| Entry | Compound | Ar | P | Yield (%) | dr (*anti:syn*)[c] | ee (%, *anti/syn*)[d] |
|---|---|---|---|---|---|---|
| 1 | **214** | Phenyl | Ts | 83[a] | 57:43 | 97/97 |
| 2 | **215** | *o*-Chlorophenyl | Ts | 78[b] | 55:45 | 78/79 |
| 3 | **216** | *p*-Bromophenyl | Ts | 82[b] | 55:45 | 81/90 |
| 4 | **222** | Phenyl | Ns | 73[b] | 59:41 | 85/80 |

[a] As a mixture of diastereomers. [b] Combined yield of partially separable diastereomers. [c] Determined by inspection of $^1$H NMR spectrum of crude. [d] Obtained by chiral HPLC analysis

**Table 4.3: Variation of the Oxaziridine**

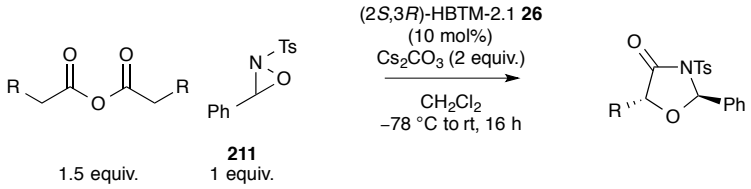
### 4.3.3.2 Variation of the Anhydride

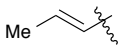
Investigation of the scope of this chemistry continued with variation of the anhydride component. A range of homoanhydrides were synthesised and used in the optimum reaction conditions (Table 4.4). In most cases the results are consistent, with products formed in excellent yields, low diastereomeric ratios but excellent ees.

In the case of 2-naphthylanhydride **223** (entry 4) the yield was significantly lower than other examples, however this was owing to isolation issues and not low reaction conversion. *Ortho*-substituents were well tolerated with *o*-tolylacetic anhydride **224** giving the product in excellent yields, with both diastereoisomers formed in >99% ee (entry 5). The 3-thiopheneacetic anhydride **225** (entry 8) was tolerated with the product being isolated in excellent yield, however the ees of both diastereoisomers were seen to be 10% lower than other examples. This is consistent with previous examples of isothiourea generated ammonium enolate chemistry from 3-thiopheneacetic acid derivatives (see previous chapters) and is thought to be owing to disruption of the favourable interaction between the oxygen non-bonding orbital and the C-S σ* orbital, or electrostatic interaction, within the catalyst ammonium enolate.

Pleasingly, an alkenyl example provided product **234** in excellent yield and ee (entry 9), however *p*-trifluorophenylacetic anhydride **226** (entry 10) gave a low ee of only 43% for the *anti*-diastereoisomer. It is proposed that this highly activated anhydride

undergoes a rapid racemic background reaction that is in competition with the isothiourea catalysed pathway, hence giving a good yield of the product but with reduced ee.




| Entry | Compound | R | Yield (%) | dr (*anti:syn*)[c] | ee (%, *anti*/*syn*)[d] |
|---|---|---|---|---|---|
| 1 | **214** | Phenyl | 83[a] | 57:43 | 97/97 |
| 2 | **227** | *p*-Fluorophenyl | 73[a] | 54:46 | 99/>99 |
| 3 | **228** | *p*-Methoxyphenyl | 89[a] | 55:45 | 97/94 |
| 4 | **229** | 2-Naphthyl | 48[a] | 53:47 | 93/90 |
| 5 | **230** | *o*-Tolyl | 96[b] | 53:47 | >99/>99 |
| 6 | **231** | *m*-Tolyl | 79[b] | 51:49 | 92/94 |
| 7 | **232** | *p*-Tolyl | 88[a] | 53:47 | 97/>99 |
| 8 | **233** | 3-Thiophene | 79[b] | 59:41 | 87/81 |
| 9 | **234** |  | 63[b] | 54:46 | 97/97 |
| 10 | **235** | *p*-Trifluoromethylphenyl | 68[a] | 49:51 | 43/36 |

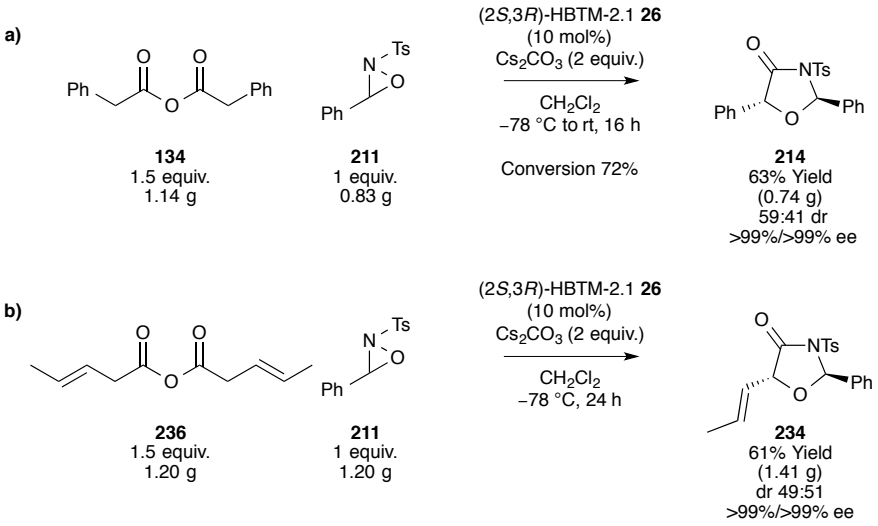
[a] As a mixture of diastereomers. [b] Combined yield of partially separable diastereomers. [c] Determined by inspection of $^1$H NMR spectrum of crude. [d] Obtained by chiral HPLC analysis

**Table 4.4: Variation of the Anhydride**

### 4.3.4 Scale Up

To further show the utility of this reaction, two examples were carried out in increased scale (Scheme 4.22) in an attempt to access gram quantities of the product. Using phenylacetic anhydride on 3 mmol scale, the yield of product **214** decreased considerably, although there was not much change in the diastereo- or enantioselectivity of the reaction (Scheme 4.22a). The low yield was attributed to the

fact that the reaction did not reach full conversion in the reaction time (after 16 hours the conversion was only 72%) and therefore future reactions on a large scale would be left for an extended reaction time. With the alkenyl anhydride **236** (6.5 mmol), the reaction was carried out using a cryostat allowing the reaction temperature to be maintained at –78 ˚C for 24 hours upon which time the reaction was complete by TLC (Scheme 4.22b). The oxazolidin-4-one product **234** was isolated in excellent ee with comparable yield to the smaller scale example, although the dr was slightly worse.




**Scheme 4.22: Large Scale Synthesis of Oxazolidin-4-ones 214 and 234**

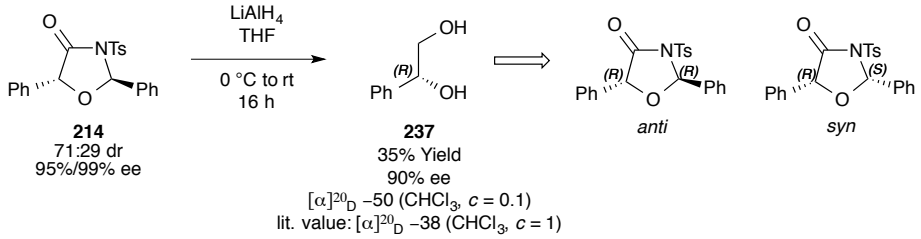
In total, twelve oxazolidin-4-one examples were synthesised, many of which were novel compounds. The reaction exhibits a wide level of scope tolerated within both the oxaziridine and acetic anhydride substituents, including electron-donating and withdrawing groups, steric bulk around the aromatic ring, heterocyclic, and alkenyl examples.

### 4.3.5 Derivatisation of Products

With the scope of the reaction having been thoroughly investigated, our attention turned to derivatisation of the oxazolidin-4-one products in order to demonstrate the utility of the reaction in organic synthesis.

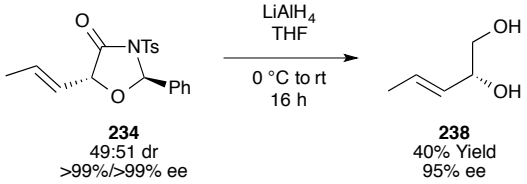
Firstly, reduction of oxazolidin-4-one **214** (dr 71:29 *anti:syn*) with $LiAlH_4$ in order to access diol **237** (Scheme 4.23) was investigated. Pleasingly, the diol was formed and isolated in 35% yield and maintained high levels of enantioenrichment (90% ee) – indicating that the *C*(5) stereochemistry is the same in both diastereoisomers. Although the ee was slightly lower than that expected, this did allow us to assign the absolute configuration of our products *via* comparison of the $[\alpha]_D$ to literature values

($[\alpha]_D$ –50, *c* 0.1; literature of (*R*) diol –38, *c* 1).[24] Therefore, the configuration of the major *anti*-diastereoisomer of our oxazolidin-4-one is (2*R*,5*R*) and the minor *syn*-diastereoisomer is (2*S*,5*R*).



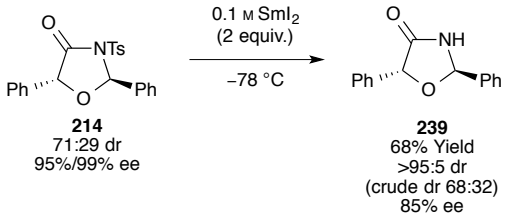

**Scheme 4.23: Reduction of Oxazolidin-4-one to Enantioenriched Diol and Assingment of Stereochemistry**

The reduction was repeated using **234** as the starting material to investigate whether it was a general process (Scheme 4.24). Again a small decrease in ee was observed, however with the pendant alkene still intact, this interesting diol **238** could allow a pathway into many other synthetically interesting products in hopefully high stereoselectivities.




**Scheme 4.24: Reduction of Oxazolidin-4-one 234**

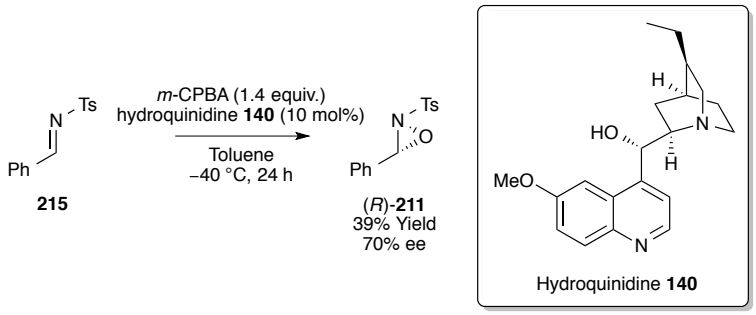
A second derivatisation of interest was the removal of the *N*-protecting group. As seen in our previous work on *β*-lactams, samarium iodide allows mild removal of *N*-tosyl groups without degradation of the starting material or product. In this case, it was again found to be the most reliable method after first having no success with either sodium/naphthalene,[33] magnesium/titanium isopropoxide,[34] or TBAF methods.[35] The product **239** was isolated in good yield though only the *anti* diastereoisomer could be obtained, and with some small loss in ee observed (Scheme 4.25).




**Scheme 4.25: Samarium Iodide Removal of *N*-Tosyl Group**

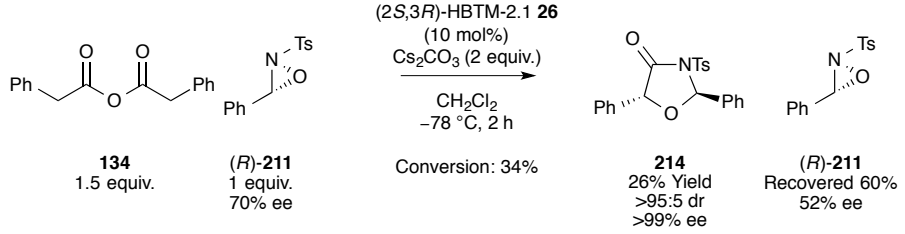
### 4.3.6 Stereoselectivity Investigations

In order to investigate the variations seen in diastereoselectivity between reactions with the *in situ* activated acid and the pre-activated homoanhydride, a study into the matched/mismatched effect between the chiral ammonium enolate and the two enantiomers of the racemic oxaziridine was undertaken. It was therefore necessary to synthesise an enantioenriched oxaziridine. This was accomplished using the method reported by Jørgensen in 2011 using the commercially available hydroquinidine **240**, which had been shown during their optimisation to give good levels of stereoinduction.[36] Oxidation of the imine **215** by *m*-CPBA in the presence of **240** gave the (*R*)-oxaziridine **211** in moderate yields and 70% ee (Scheme 4.26).



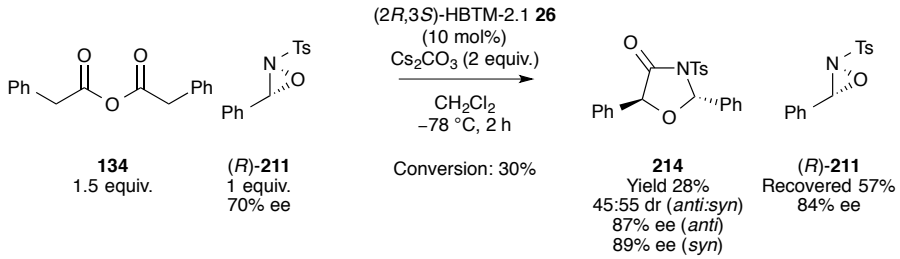

**Scheme 4.26: Synthesis of Enantioenriched Oxaziridine (*R*)-211**

Initial studies, under the standard conditions, used homoanhydride **134** with the enantioenriched oxaziridine (*R*)-**211** in the presence of (2*S*,3*R*)-HBTM-2.1 **26** (Scheme 4.27). After two hours the reaction was quenched to show the level of stereoinduction. At 34% conversion (by $^1$H NMR spectroscopy) the ee determined by chiral HPLC remained high at >99%, however, interestingly the dr was now excellent at >95:5. The high dr suggests that the reaction mechanism occurs without scrambling of the oxaziridine configuration at the carbon stereocentre and that this was a matched case with the ammonium enolate reacting preferentially with the major enantiomer of the oxaziridine. This was further supported by the ee of the recovered oxaziridine being lower (52%) than the starting ee (70%).



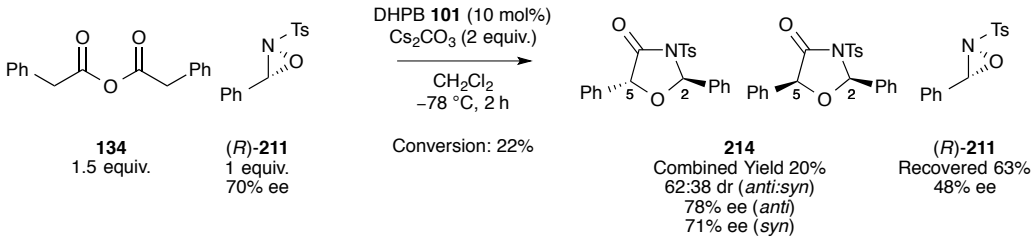

**Scheme 4.27: Reaction of Homoanhydride with Enantioenriched Oxaziridine in Presence of Enantiomerically Pure Catalyst**

In the mis-matched case with the opposite enantiomer of the catalyst, (2*R*,3*S*)-HBTM-2.1 **26**, the opposite major enantiomer of each diastereoisomer was formed as dictated by catalyst stereochemistry. The reaction dr was observed to swing slightly in favour of the *syn*-diastereoisomer and the ees observed were lower (Scheme 4.28). The drop in ee from >99% to 87-89% could be explained by this catalytic pathway being less favoured and therefore a competitive racemic background reaction is possible. The ee of recovered oxaziridine increases which supports the hypothesis that the minor enantiomer of the oxaziridine is reacting preferentially in this case.




**Scheme 4.28: Reaction of Homoanhydride with Enantioenriched Oxaziridine in Presence of Enantiomerically Pure Catalyst in a Mis-matched Case**

A reaction was then carried out using the enantioenriched oxaziridine (*R*)-**211** and the achiral isothiourea DHPB **101** to investigate the level of substrate control on the reaction (Scheme 4.29). In this case, product **214** was formed in a moderate ee (78 %) under substrate control. As the product ee effectively matches that of the starting oxaziridine, this supports that the *C*(2) stereogenic centre is maintained from the oxaziridine without scrambling of the stereochemistry. Through chiral HPLC analysis, we can identify that the major enantiomer of the *syn* diastereoisomer is (2*R*,5*S*), the opposite to that usually observed. This supports that the *C*(5) stereogenic centre is formed under catalyst control – and in this case there is no control from the achiral isothiourea forming a mixture of diastereoisomers at this position.

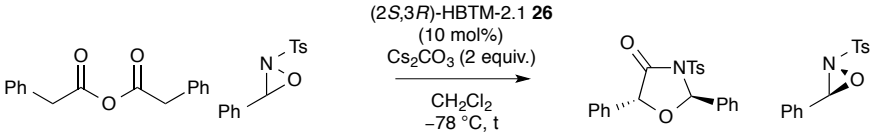



**Scheme 4.29: Reaction of Homoanhydride with Enantioenriched Oxaziridine in Presence of Achiral Catalyst**

From these investigations, it was proposed that when carrying out the reaction with racemic oxaziridine that the "matched" case ((2*S*,3*R*)-HBTM-2.1 **26** and the (*R*)-oxaziridine) would initially be preferential however, as the reaction proceeds to

complete conversion there would be subsequent reaction of the "mis-matched" case. This would explain the near 1:1 dr observed as each enantiomer of the oxaziridine would eventually react completely.

To investigate these hypotheses, reactions were carried out where samples were taken at intervals in an attempt to observe any change in dr or ee. In the first experiment, benzoic anhydride **134** was reacted with racemic oxaziridine using (2*S*,3*R*)-HBTM-2.1 **26** and the dr was monitored by $^{1}$H NMR spectroscopy over time (Table 4.5). It was expected that the dr would start high, as in the 50:50 mix of the two enantiomers of the oxaziridine the ammonium enolate would react preferentially with its matched partner before this effect was overcome by the presence of a higher relative concentration of the "mis-matched" enantiomer. This product distribution was observed, with high dr at the start of the reaction (<1 min dr: 70:30) and lower dr at the end of the reaction (at completion the dr was 53:47). The ee of the *anti* diasteroisomer was high throughout showing that the oxaziridine had little effect on the ee and this was under catalyst control. Purification by preparative tlc allowed determination of the ee in some cases and as expected, a small resolution of the oxaziridine **211** was seen over the course of the reaction with isolated samples having an ee of 10%.



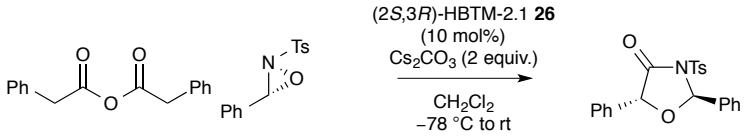

**134** 1.5 equiv. **211** 1 equiv. Racemic **214** (*S*)-**211**

| Entry | Time | Conversion (%)[a] | dr (*anti:syn*)[a] | 214 ee (%, *anti*/*syn*) [b] | 211 ee (%)[b] |
|---|---|---|---|---|---|
| 1 | <1 min | 15 | 70:30 | ND | ND |
| 2 | 5 min | 15 | 72:28 | ND | ND |
| 3 | 15 min | 27 | 68:32 | >99/ND | 10 |
| 4 | 30 min | 32 | 66:34 | ND | ND |
| 5 | 1 hour | 27 | 68:32 | >99/>99 | 10 |
| 6 | 2 hours | 33 | 68:32 | ND | ND |
| 7 | 4 hours | 74 | 57:43 | >99/>99 | ND |
| 8 | 16 hours | 100 | 53:47 | >99/>99 | N/A |

[a] Determined by inspection of $^1$H NMR spectrum of crude. [b] Obtained by chiral HPLC analysis following preparative tlc.

**Table 4.5: Monitoring of Diastereoselectivity and Enantioselectivity Over Time**

In a second reaction, the homoanhydride **134** was reacted again with the enantioenriched oxaziridine, although this time the reaction was allowed to proceed to completion (Scheme 4.30). It was expected that at completion, the dr would match the er of the starting oxaziridine; this was found to be the case with the dr of the reaction being 85:15 corresponding to an er of 85:15 (70% ee) of oxaziridine **211**.




**134** 1.5 equiv. (*R*)-**211** 1 equiv. ee 70% **214** Yield 20% dr 85:15 (*anti:syn*) ee 98%/98%

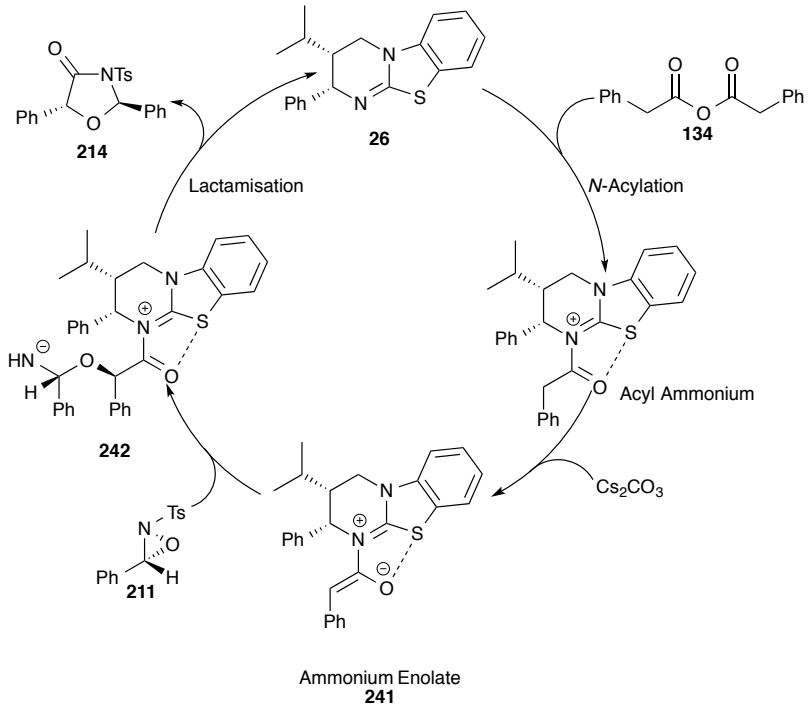
**Scheme 4.30: Repeat of Matched Case with Reaction Completed**

In the case of the reaction directly from the carboxylic acid, an improved dr is observed. From the mechanistic information gathered thus far, it is proposed that this could be due to two possible side reactions. Firstly, the matched case reacting at a relatively higher rate and in turn, competitive oxidation of the base and chloride ions is being carried out preferentially with the slower reacting enantiomer of the

oxaziridine (owing to an increase in its relative concentration), or secondly because of low conversion of the reaction.

### 4.3.7 Proposed Reaction Mechanism and Stereochemical Rationale

The proposed mechanism of the reaction proceeds *via* the *N*-acylation of the catalyst by the homoanhydride and deprotonation to give the ammonium enolate **241**, which has been previously discussed (Scheme 4.31). The stabilising S-O interaction/electrostatic interaction previously described again locks the enolate conformation and oxidation can only occur on the *Re* face. Ye and co-workers[36] then propose oxidation by oxaziridine **211** to form an epoxide and imine, although we prefer an $\alpha$-oxidation to give intermediate **242** followed by lactamisation to form the oxazoldin-4-one product **214** and regenerate the catalyst.



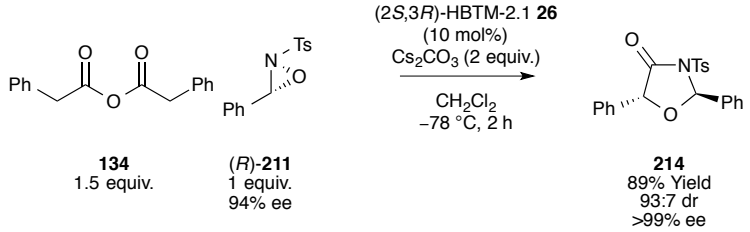

**Scheme 4.31: Proposed General Mechanism for Oxazolidin-4-one Formation**

The reaction mechanism shows the stereochemistry at the *C*(5) position of the oxazolidin-4-one is set by the facial selectivity due to the isothiourea catalyst's substituents. This accounts for the high enantioselectivities observed. When using an enantioenriched oxaziridine, substrate control can come into play at the *C*(2) stereocentre. Assuming the configuration is maintained in intermediate **242** following oxidation, lactamisation would occur to give just one diastereoisomer. However, under our standard reaction conditions, the racemic oxaziridine allows no control of

the *C*(2) centre which accounts for the near 50:50 dr observed in all cases, at high conversion.

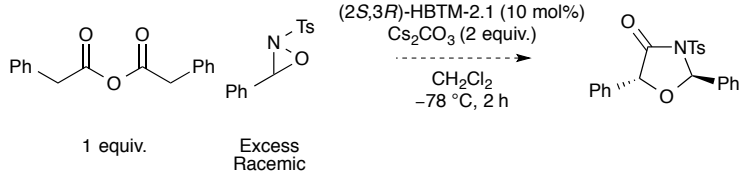
### 4.3.8 **Conclusions**

This chapter has discussed the development of a highly enantioselective route to oxazolidin-4-ones with excellent yields though low drs, which in turn, gives access to synthetically useful diols in ee. This work further expands the chemistry of oxaziridines, which are convenient, bench-stable and neutral sources of electrophilic oxygen[5] and our own work on the uses of isothiourea generated chiral ammonium enolates. Further work in this area would focus on improvement of the diastereoselectivity of the reaction. It was postulated that this could be achieved by the use of enantiopure oxaziridine starting materials, as shown by the positive results in test reactions using an oxaziridine of high enantioselectivity and this work has now been carried out by another group member, Charlene Fallan, with great success (Scheme 4.32). This work could ultimately allow access to both enantiomers of the diol products when using the correct combinations of catalyst and oxaziridine, taking advantage of matched effects.



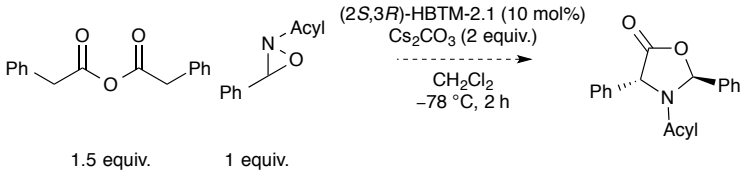

**Scheme 4.32: Potential Use of Enantiopure Oxaziridine (*R*)-211 to Form Products in High Diastereo- and Enantiocontrol**

Alternatively, the use of an excess of oxaziridine with modest ee could be investigated. At completion, with the catalyst only selecting for its matched pair, would return the product in excellent yields, dr and ee. Another possibility would be to investigate the use of excess racemic oxaziridine; in this case the matched effect may be strong enough to allow high levels of diastereoselectivity of the oxazolidin-4-one product (Scheme 4.33).




**Scheme 4.33: Use of Excess Racemic Oxaziridine to Force High Levels of Diastereoselectivity**

Further investigation of other *N*-oxaziridines could also allow access to other products as oxaziridines have high sensitivity to the steric and electronic properties of their substituents, which can allow different chemoselectivities.[5] For example, *N*-unsubstituted or *N*-acyl substituted oxaziridines have been found to have extensive use as electrophilic sources of nitrogen and so may allow us access to enantioenriched α-aminated products (Scheme 4.34).




**Scheme 4.34: Use of Alternative Oxaziridines for Different Substitution Patterns**

## 4.4 References for Chapter 4

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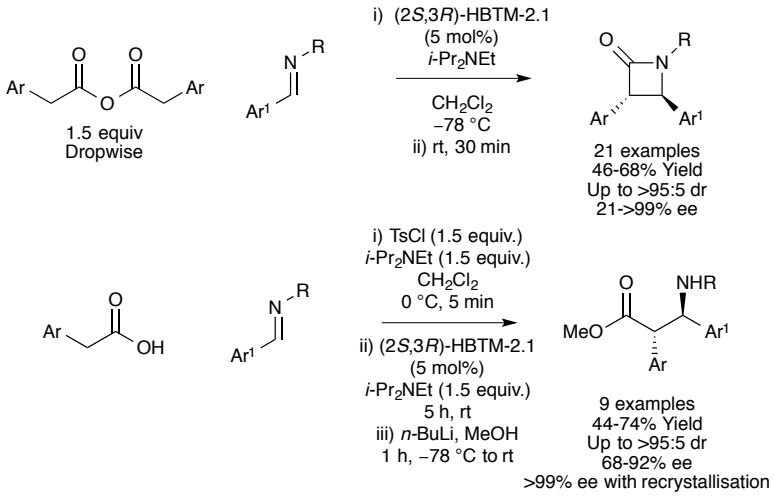
# Chapter 5: Conclusions

This thesis has documented expansion of the use of isothiourea and carboxylic acid generated Type I ammonium enolates in asymmetric synthesis. Further to published methodologies from the Smith group on their use in intermolecular formal [4+2]-cycloaddition reactions, this work has been expanded to include [2+2]- and [3+2]-cycloadditions.

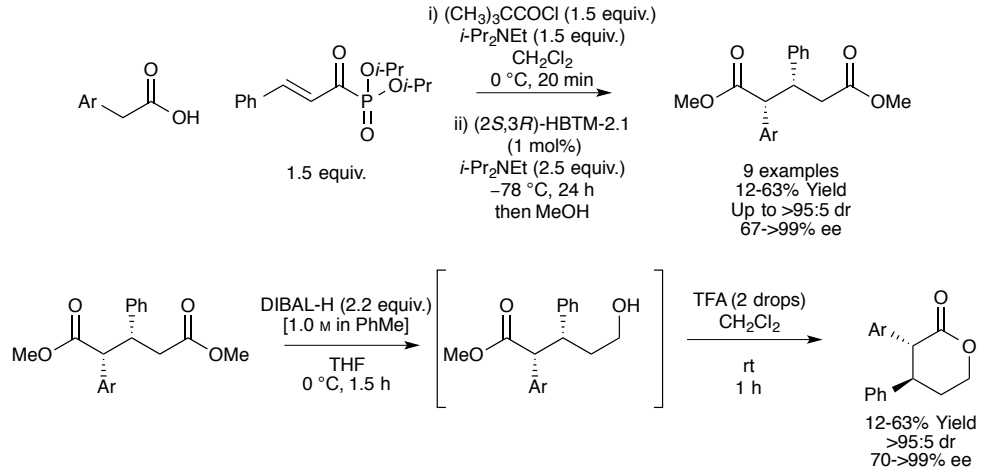
Firstly, asymmetric formal [2+2]-cycloaddition of isothiourea generated Type I ammonium enolates and *N*-sulfonylimines was reported. This methodology allows successful access to highly stereodefined $\beta$-lactams and $\beta$-aminoesters, either from preformed homoanhydrides or directly from carboxylic acids respectively. The protocol is carried out using open flask conditions, from simple, bench-stable starting materials and is also scalable. A variety of *anti*-$\beta$-lactams and $\beta$-aminoesters were accessed in moderate yield, excellent diastereo- and good enantioselectivity (Scheme 5.1). Recrystallisation can allow improvement of the enantioselectivity to excellent levels and represents an improved route to *anti*-$\beta$-lactams over the previous ketene and *N*-triflyl imine based methods reported.




**Scheme 5.1: Summary of $\beta$-Lactam and $\beta$-Aminoester Synthesis**

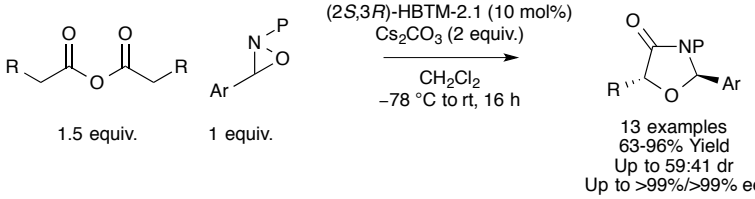
Subsequent studies focussed on the use of ester surrogates in the formal [4+2]-cycloaddition reactions of isothiourea generated Type I ammonium enolates to gain access to diester products which were previously unobtainable using this methodology. The use of *iso*-propylphosphonate **163** in this chemistry proved highly effective in this process, following *in situ* ring-opening of the initial dihydropyranone product isolation of the desired diester products was achieved in moderate to excellent yields and with

excellent diastereo- and enantiocontrol (Scheme 5.2). Furthermore, selective reduction and acid-catalysed cyclisation allowed access to $\delta$-lactone products in good yield with retention of stereocontrol. This process is also amenable to large scale and further work in this area has also shown the use of $\alpha,\beta$-unsaturated trichloroketones in the synthesis of identical diester products.




**Scheme 5.2: Summary of Work on $\alpha$-Ketophosphonates as Ester Surrogates**

Finally, it was shown that isothiourea-catalysed formal [3+2]-cycloadditions of oxaziridines and acetic anhydrides gave access to five-membered oxazolidin-4-one heterocycles. In this case, the use of preformed homoanhydrides and an inorganic base was imperative to avoid reduction of the oxaziridine starting material. The oxazolidin-4-one products could be accessed in excellent yield and ee however poor dr (Scheme 5.3). Investigations using an enantioenriched oxaziridine with two opposite enantiomers of the isothiourea catalyst, into the "matched" and "mis-matched" cases allowed insight into the mechanistic influence of the oxaziridine. This indicated that use of a racemic oxaziridine accounted for the poor diastereoselectivity of the reaction and further work has revealed that when using an enantioenriched oxaziridine in a "matched" case, the diastereoselectivity is much improved (93:7 from an oxaziridine of 94% ee). Synthesis of the oxazolidin-4-one products was amenable to a large scale and following isolation, reduction allowed access to enantioenriched diols with little loss in stereocontrol.




**Scheme 5.3: Formal [3+2]-Cycloaddition Reaction Using Oxaziridine Starting Material**

Prior to the beginning of this thesis, although carboxylic acid starting materials had been shown to be useful ammonium enolate precursors by Romo and co-workers, and isothioureas had been used in the catalytic generation of ammonium enolates by the Smith group, however the scope of these reactions were limited to mainly [4+2]-cycloaddition processes. The work described within this thesis adds to the existing research within the ammonium enolate literature with the development of inter-molecular [2+2]- and [3+2]-cycloaddition reactions. The use of isothioureas in this work has further shown their use as nucleophilic Lewis base organocatalysts for the generation Type I ammonium enolates capable of transferring excellent levels of stereocontrol.

Further research is currently underway within the Smith group to investigate the potential for these ammonium enolates in a range of organocatalytic processes.

# Chapter 6: Experimental

## 6.1 General Information

Reactions involving moisture sensitive reagents were carried out under an argon atmosphere using standard vacuum line techniques in addition to dry solvents. All glassware used was flame dried and cooled under vacuum.

For moisture sensitive reactions, solvents (THF, $CH_2Cl_2$, toluene, hexane and $Et_2O$) were obtained anhydrous and purified by an alumina column (Mbraun SPS-800). Petrol is defined as petroleum ether 40-60 °C. All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise.

Room temperature (rt) refers to 20-25 °C. Temperatures of 0 °C and −78 °C were obtained using ice/water and $CO_2$(s)/acetone baths respectively. Temperatures of 0 °C to −50 °C for overnight reactions were obtained using an immersion cooler (HAAKE EK 90). Reflux conditions were obtained using an oil bath equipped with a contact thermometer. *In vacuo* refers to the use of a Büchi Rotavapor R-2000 rotary evaporator with a Vacubrand $CVC_2$ vacuum controller or a Heidolph Laborota 4001 rotary evaporator with a vacuum controller.

Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 $F_{254}$ silica). TLC visualisation was carried out with ultraviolet light (254 nm), followed by staining with a 1% aqueous $KMnO_4$ solution. Flash column chromatography was performed on Kieselgel 60 silica in the solvent system stated.

$^{1}H$, $^{13}C$ and $^{19}F$ nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (300 MHz, $^{1}H$, 75 MHz $^{13}C\{1H\}$, 282 MHz $^{19}F\{1H\}$), Bruker Avance II 400 (400 MHz, $^{1}H$, 100 MHz $^{13}C\{1H\}$, 376 MHz $^{19}F\{1H\}$) or a Bruker Avance II 400 (500 MHz, $^{1}H$, 125 MHz $^{13}C\{1H\}$, 470 MHz $^{19}F\{1H\}$) spectrometer at ambient temperature in the deuterated solvent stated. All chemical shifts are quoted in parts per million (ppm) relative to the residual solvent as the internal standard. All coupling constants, *J*, are quoted in Hz. Multiplicities are indicated by: s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), ABq (AB quartet), sept (septet), oct (octet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublet of doublets, dt (doublet of triplets), dq (doublet of quartets) and td (triplet of doublets). The

abbreviation Ar is used to denote aromatic, Ph to denote phenyl, Bn to denote benzyl, br to denote broad and *app* to denote apparent. NMR peak assignments were confirmed using 2D 1H correlated spectroscopy (COSY), 2D 1H nuclear Overhauser effect spectroscopy (NOESY), 2D 1H–13C heteronuclear multiple-bond correlation spectroscopy (HMBC), and 2D 1H–13C heteronuclear single quantum coherence (HSQC) where necessary.

Infrared spectra ($\nu_{max}$/cm$^{-1}$) were recorded on either a Perkin-Elmer Spectrum GX FT-IR spectrometer using either thin films on NaCl plates or KBr discs or a Shimadzu IRAffinity-1 using a Pike attenuated total reflectance (ATR) accessory. Only the characteristic peaks are quoted.

Melting points were recorded on an Electrothermal 9100 melting point apparatus and are uncorrected. *Dec* refers to decomposition.

HPLC analyses were obtained on two separate machines; a Gilson HPLC consisting of a Gilson 305 pump, Gilson 306 pump, Gilson 811C dynamic mixer, Gilson 805 manometric module, Gilson 401C dilutor, Gilson 213XL sample injector and sample detection was performed with a Gilson 118 UV/vis detector while the temperature was assumed to be 23 °C; a Shimadzu HPLC consisting of a DGU-20A5 degasser, LC-20AT liquid chromatograph, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven which allowed the temperature to be set from 25-40 °C. Separation was achieved using DAICEL CHIRALCEL OD-H and OJ-H columns or DAICEL CHIRALPAK AD-H, AS-H, IA, IB, IC and ID columns. All chiral HPLC traces were compared to the authentic racemic spectrum prepared in analogous fashion.

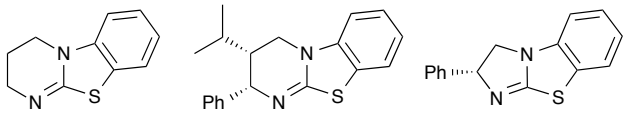
Mass spectrometry (*m/z*) data were acquired by electrospray ionisation (ESI), chemical ionisation (CI), electron impact (EI), atmospheric solids analysis probe (ASAP), atmospheric pressure chemical ionization (APCI) or nanospray ionisation (NSI) either at the University of St Andrews or the EPSRC National Mass Spectrometry Service Centre, Swansea. At the University of St Andrews, low and high resolution ESI MS were carried out on a Micromass LCT spectrometer. At the EPSRC National Mass Spectrometry Service Centre, low resolution NSI MS was

carried out on a Micromass Quattro II spectrometer and high resolution NSI MS on a Thermofisher LTQ Orbitrap XL spectrometer.

Optical rotations were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at rt.

## 6.2 Experimental for Chapter 2

### 6.2.1 Isothiourea Catalysts



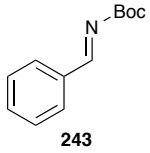
DHPB **101** (2*S*,3*R*) HBTM 2.1 **26** (*R*)-Benzotetramisole **23**

DHPB **101**, (2*R*,3*S*)-HBTM-2.1 **26** and (±)-HBTM-2.1 **26** were made within the group according to literature procedures.[1,2] (–)-Tetramisole.HCl **22** is commercially available

#### 6.2.1.1 Synthesis of (2*S*,3*R*)-HBTM-2.1 26

**26** was prepared using the procedure described by Smith *et al*. as described in the following section.[3]

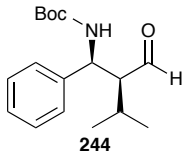
*t*-Butyl benzylidenecarbamate **243**



**243**

*t*-Butyl(phenyl(phenylsulfonyl)methyl)carbamate (20.0 g, 57.57 mmol) was added to a solution of potassium carbonate (47.8 g, 346.0 mmol) and sodium sulfate (60.0 g, 422.0 mmol) in THF (500 mL). The reaction mixture was refluxed for 15 h before allowing to cool to room temperature, filtering and concentrating the filtrate *in vacuo* to afford **243**, a yellow oil (9.8 g, 47.7 mmol, 83% yield) with all data was in accordance with the literature.[3] $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$: 1.54 (9H, s, C(C*H*$_3$)), 7.53-7.58 (2H, m Ar*H*), 7.61-7.77 (1H, m, Ar*H*), 7.92-7.95 (2H, m, Ar*H*), 8.80 (1H, s, C*H*).

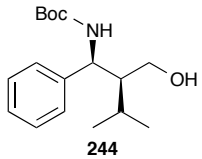
*t*-Butyl (1*S*,2*S*)-2-formyl-3-methyl-1-phenylbutylcarbamate **244**




**244**

*t*-Butyl (1*S*,2*S*)-2-formyl-3-methyl-1-phenylbutylcarbamate **243** (5.0 g, 24.4 mmol) was dissolved in acetonitrile (250 mL) and isovaleraldeyhyde (5.23 mL, 49.8 mmol) was added. The reaction was cooled to 0 ˚C and (*S*)-proline (0.56 g, 4.7 mmol) was added before stirring for 18 h before addition of distilled water (80 mL). The solution was allowed to warm to room temperature whilst stirring vigorously before adding diethyl ether (100 mL) and extracting the aqueous layer (3 × $Et_2O$). The organic extracts were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product, which was triturated with hexane to afford **244** as a white fluffy solid (5.9 g, 20.3 mmol, 83% yield) with all data was in accordance with the literature.[3] mp 130-132 ˚C {lit.[3] mp 141-142 ˚C}; $[\alpha]_D^{20}$ –54.0 (*c* 1.0, $CHCl_3$) {lit.[3] $[\alpha]_D^{20}$ –68.0 (*c* 1.0, $CHCl_3$)}; $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$: 0.93 (3H, d, *J* 6.8, C*H*$_3$), 1.05 (3H, d, *J* 6.9, C*H*$_3$), 1.33 (9H, s, C(C*H*$_3$)$_3$), 1.97-2.07, (1H, m, C(3)*H*), 2.37-2.44 (1H, m, C(2)*H*), 4.83-5.09 (2H, m, C(1)*H* and N*H*), 7.11-7.26 (5H, m, Ar*H*), 9.41 (1H, d, *J* 4.2, C(O)*H*).

*t*-Butyl (1*S*,2*S*)-2-(hydroxylmethyl)-3-methyl-1-phenylbutyl carbamate **245**

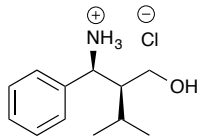



**244**

To a solution of **244** (5.40 g, 18.55 mmol) in methanol (160 mL), sodium borohydride (1.05 g, 27.83 mmol) was added and the reaction mixture stirred at room temperature for 2 h. Saturated aqueous sodium bicarbonate (50 mL) was added and the methanol was removed *in vacuo*. The aqueous layer was extracted with dichloromethane (3× 25 mL), the organic layers combined, dried ($MgSO_4$) and concentrated *in vacuo* to give **245** (4.6 g, 15.9 mmol, 86%), a white solid with all data was in accordance with the

literature.[3] mp 101-110 ˚C {lit.[3] mp 106-108 ˚C}; $[\alpha]_D^{20}$ –25.6 (*c* 1.0, $CHCl_3$) {lit.[3] $[\alpha]_D^{20}$ –26.7 (*c* 0.7, $CHCl_3$)}; $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$: 0.85 (3H, d, *J* 6.9 Hz, C*H*$_3$), 0.99 (3H, d, *J* 6.8 Hz, C*H*$_3$), 1.41 (9H, s, C(C*H*$_3$)$_3$), 1.73 (1H, m, C*H*(CH$_3$)$_2$), 1.86 (1H, m, C*Hi*-Pr), 3.50 (1H, m, C*H*$_A$H$_B$OH), 3.65-3.68 (1H, m, CH$_A$*H*$_B$OH), 5.00-5.04 (1H, m, C*H*NH), 5.47 (1H, br s, N*H*), 7.27-7.37 (5H, m, Ar*H*).

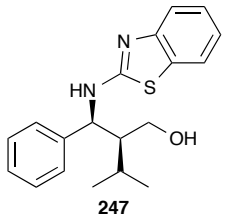
(1*S*)-2-((2*S*)-Amino(phenyl)methyl)-3-methylbutan-1-ol hydrochloride **246**




**246**

**245** (4.6g, 15.9 mmol) was added to a solution of 4 M HCl in dioxane (49.7 mL, 198.8 mmol) and stirred at room temperature for 4 h. The reaction was concentrated *in vacuo* to give **246** as an off-white solid (3.5 g, 15.4 mmol, 97%) with all data was in accordance with the literature.[3] mp 185-190 ˚C; {lit.[3] mp 168-170 ˚C} $[\alpha]_D^{20}$ –23.8 (*c* 1.0, MeOH); {lit.[3] $[\alpha]_D^{20}$ –22.9 (*c* 0.98, MeOH)}; $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$: 0.48 (3H, d, *J* 6.8, C*H*$_3$), 1.13 (3H, d, *J* 6.8, C*H*$_3$), 1.18 (1H, app. oct, *J* 6.8, C*H*(CH$_3$)$_2$), 1.61-1.69 (1H, m, C*Hi*-Pr), 3.13 (1H, dd, *J* 10.4, 9.9, C*H*$_A$H$_B$OH), 3.40 (1H, dd, *J* 10.6, 4.5, CH$_A$*H*$_B$OH), 4.21 (1H, d, *J* 4.3, C*H*NH), 7.09-7.18 (5H, m, ArH).

(3*S*,4*R*)-3-*iso*-Propyl-4-phenyl-3,4-dihydro-2*H*-pyrimido[2,1-b] benzothiazole **247**

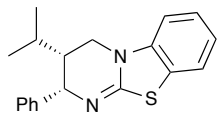



**247**

A sealed vial was charged with **246** (400 mg, 1.75 mmol), Hunig's base (1.16 mL, 6.65 mmol) and purged with nitrogen. The mixture was heated to 135 °C and 2-chlorobenzothiazole (0.24 mL, 1.84 mmol) was added. The reaction was stirred at 135 °C for 3 days then allowed to cool to room temperature. The resulting mixture was applied directly to a silica column for purification (98:2, dichloromethane:ethanol) to

yield **247** as a yellow oil (0.41 g, 1.26 mmol, 73%) with all data was in accordance with the literature.[3] $[\alpha]_D^{20}$ –52.7 (*c* 1.0, $CHCl_3$); {lit.[3] $[\alpha]_D^{20}$ –54.8 (*c* 0.5, $CHCl_3$)}; $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$: 0.85 (3H, t, *J* 6.9, C*H*$_3$), 1.07 (3H, d, *J* 6.8, C*H*$_3$), 1.75-1.84 (1H, m, C*H*$(CH_3)_2$), 2.05-2.10 (1H, m, C*Hi*-Pr), 3.57-3.69 (1H, m, C$H_AH_B$OH), 3.75-3.79 (1H, m, C$H_AH_B$OH), 5.02 (1H, m, C*H*NH), 7.04-7.29 (5H, m, Ar*H*), 7.32-7.51 (4H, m, Ar*H*).

(3*R*,4*S*)-4-Phenyl-3-*iso*-Propyl-3,4-dihydro-2*H*-pyrimido[2,1-b] benzothiazole **26**



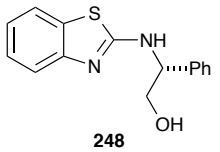

(2*S*,3*R*) HBTM 2.1 **26**

Thionyl chloride (0.48 mL, 6.64 mmol) was added to **247** (1.03 g, 3.16 mmol) in toluene (20 mL) and the reaction heated at reflux for 3 h until complete (aliquots monitored by $^1$H NMR). The reaction was cooled and quenched with methanol (20 mL), concentrated, basified with 10% NaOH solution and extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to give **26** as a light brown solid (0.71 g, 2.29 mmol, 73%) with all data was in accordance with the literature.[3] Chiral HPLC analysis, Chiralcel AD-H (80:20 Hexane:IPA, flow rate 1.0 mL min$^{-1}$, 254 nm, rt) $t_R$ major (2*S*,3*R*) 17.6 min, $t_R$ minor (2*R*,3*S*) 30.7 min, >99% ee; mp 145-151 ˚C, {lit.[3] mp 136-138 ˚C}; $[\alpha]_D^{20}$ +332.4 (*c* 1.0, $CHCl_3$); {lit.[3] $[\alpha]_D^{20}$ +288.4 (*c* 0.5, $CHCl_3$)}; $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$: 0.93 (3H, d, *J* 6.6, C*H*$_3$), 1.19 (3H, d, *J* 5.9, C*H*$_3$), 1.37-1.45 (1H, m, C*H*$(CH_3)_2$), 1.56-1.63 (1H, m, C*Hi*-Pr), 2.10-2.19 (1H, m, C$H_AH_B$), 3.62-3.71 (1H, m, C$H_AH_B$), 4.24-4.29 (1H, m, C*H*Ph), 7.05-7.21 (4H, m, Ar*H*), 7.32-7.71 (5H, m, Ar*H*).

### 6.2.1.2 Synthesis of (*R*)-Benzotetramisole 23

**23** was prepared following the procedure by Birman *et al*. as described in the following section.[1]

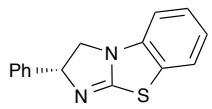
(*R*)-*N*-(Thiazolyl-2)-2-hydroxy-1-phenylethylamine **248**




**248**

2-chlorobenzothiazole (1 mL, 8.08 mmol), (*R*)-(+)-phenylglycinol (1.11 g, 8.08 mmol) and *i*-$Pr_2NEt$ (2.11 mL, 12.1 mmol) were added to a sealed tube, flushed with nitrogen and heated at 130 °C for 19 h. After cooling, the reaction mixture was treated with dichloromethane (5 mL) and left at room temperature to dissolve over 3 h. The diluted reaction mixture was applied directly to a silica column and purified (96:4 $CH_2Cl_2$:IPA) to give **248** as an off-white solid (2.15 g, 7.9 mmol, 99 %) with all data was in accordance with the literature.[1] mp 158-162 ˚C {lit.[1] mp 159-160 ˚C}; $[\alpha]_D^{20}$ +97.4 (*c* 1.0, MeOH); {lit.[1] $[\alpha]_D^{20}$ +98.7 (*c* 0.99, MeOH)}; $^1$H NMR (300 MHz, $CD_3OD$) $\delta_H$: 3.75-3.85 (2H, m), 4.99 (1H, dd, *J* 7.1, 5.2), 7.02 (1H, t, *J* 7.1), 7.20-7.48 (7H, m), 7.56 (1H, d, *J* 8.1).

(*R*)-Benzotetramisole **23**




(*R*)-Benzotetramisole **23**

**248** (5.87 g, 21.71 mmol) was dissolved in anhydrous dichloromethane (200 mL) cooled to 0 °C and treated with triethylamine (9.08 mL, 65.13 mmol) and mesyl chloride (2.52 mL, 32.57 mmol). The mixture was stirred for 1 h and then warmed to room temperature. Methanol (2.5 mL) and then triethylamine (30.3 mL, 217.1 mmol) was added and the mixture refluxed overnight. The mixture was cooled to room temperature, washed with water and dried over $Na_2SO_4$ before removing the solvent *in vacuo*. The crude product was purified by silica chromatography (94:5:1 Hexane:IPA:$NEt_3$) to give a yellow solid which following recrystallization ($Et_2O$:hexane) gave **23** as a white solid (3.55 g, 14.1 mmol, 65%) with all data was in accordance with the literature.[1] mp 91-95 ˚C {lit.[1] mp 94.5-95.0 ˚C}; $[\alpha]_D^{20}$ +251.1 (*c* 1.0 in $CH_3OH$) {lit.[1] $[\alpha]_D^{20}$ +256.7 (*c* 1.00 in $CH_3OH$)}; $^1$H NMR (300 MHz,

$CDCl_3$) $\delta_H$: 3.72 (1H, dd, *J* 8.9, 8.2), 4.28 (1H, dd, *J* 10.1, 8.9), 5.66 (1H, dd, *J* 10.3, 8.1), 6.79 (1H, m), 7.00 (1H, m), 7.23 (1H, m), 7.30-7.39 (6H, m).

### 6.2.2 General Experimental Procedures

#### 6.2.2.1 General Procedure A: Formation of *N*-Sulfonyl Imines

*N*-Sulfonylimines were prepared according to the procedure described by Proctor in 1981.[4] Boron trifluoride diethyletherate (0.016 equiv.) was added to a refluxing solution of the aldehyde (1.0 equiv.) and appropriate sulfonamide (1.0 equiv.) in toluene (150 mL) using Dean-Stark apparatus. The mixture was refluxed overnight until the theoretical amount of water had been collected. The solution was then cooled and washed with 2 M NaOH solution and water. The organic layer was separated, dried ($MgSO_4$) and the solvent was removed *in vacuo*. The resulting solid was purified by recrystallization.

#### 6.2.2.2 General Procedure B: Synthesis of Homoanhydride Starting Materials

To a solution of the appropriate carboxylic acid (1 equiv.) in toluene (0.3 M), DCC (0.50-0.55 equiv.) was added and the solution stirred at room temperature for 15 min. The suspension was filtered and concentrated *in vacuo* to give the crude product, which was used without further purification.

#### 6.2.2.3 General Procedure C: Asymmetric Formal [2+2]-Cycloaddition of Arylacetic Acids and *N*-Sulfonylimines

To a stirred solution of the appropriate carboxylic acid (1 equiv.) in dichloromethane (~1 mL/0.2 mmol) at 0 °C, tosyl chloride (1.5 equiv.) and *i*-$Pr_2NEt$ (1.5 equiv.) were added. The solution was stirred at 0 °C for 20 min. The isothiourea catalyst (20 mol%) and the imine (1 equiv.) were added followed by *i*-$Pr_2NEt$ (1.5 equiv.). The solution was then stirred at room temperature for 5 h, quenched using 1M HCl (~1 mL/0.2 mmol), extracted (3 × EtOAc), the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by column chromatography in the stated conditions to give the *β*-lactam product.

#### 6.2.2.4 General Procedure D: Asymmetric Formal [2+2]-Cycloaddition of Arylacetic Acids and *N*-Sulfonylimines With *In Situ* Ring Opening

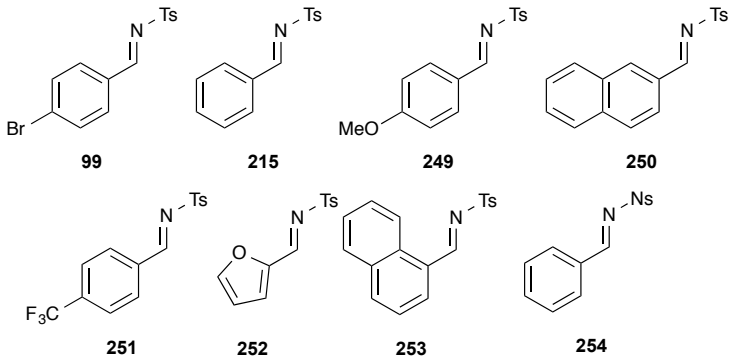
To a stirred solution of the carboxylic acid (1 equiv.) in dichloromethane (~1 mL/0.2 mmol) at 0 °C, tosyl chloride (1.5 equiv.) and *i*-$Pr_2NEt$ (1.5 equiv.) were added. The solution was stirred at 0 °C for 20 min. The isothiourea catalyst (5 mol%) and the imine (1 equiv.) were added followed by *i*-$Pr_2NEt$ (1.5 equiv.) and the solution was stirred at room temperature for 5 h. 2.5 M Butyl lithium solution in hexanes (55 equiv.) was added to methanol (~1 mL/0.2 mmol) at −78°C and this solution was added by canula to the reaction mixture. After 1 h, the reaction was quenched using water (~1 mL/0.2 mmol), extracted (3 × EtOAc), the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* followed by purification by column chromatography in the stated conditions to give the *β*-amino ester product.

#### 6.2.2.5 General Procedure E: Asymmetric Formal [2+2]-cycloaddition of Homoanhydrides and *N*-sulfonylimines

To a stirred solution of the imine (1 equiv.) in dichloromethane (~1 mL/0.2 mmol) at −78 °C, the isothiourea catalyst (5 mol%) and *i*-$Pr_2NEt$ (1.25 equiv.) were added followed by the appropriate anhydride (1.5 equiv.) as a solution in dichloromethane (1.2mL/0.3 mmol) dropwise (2.3mL $h^{-1}$). The solution was then allowed to warm to room temperature and stirred for a further 30 min, quenched using 1M HCl (~1 mL/0.2 mmol), extracted (3 × EtOAc), the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* followed by purification by column chromatography in the stated conditions to give the *β*-lactam product.

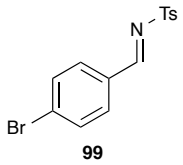
### 6.2.3 Starting Materials Synthesis

#### 6.2.3.1 *N*-sulfonylaldimines



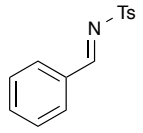

*N*-sulfonylimines **99**, **215** and **249** were all made following literature procedures.[4] All other sulfonylimines (**250-254**) were supplied by other members of the group.

<u>*N*-(4-Bromobenzylidene)-4-methylbenzenesulfonamide **99**</u>




Following *General Procedure A,* 4-bromobenzaldehyde (9.25 g, 50 mmol) and *para*-toluenesulfonamide (8.56 g, 50 mmol) were stirred for 16 h to give the crude product, which was recrystallised (THF/hexane) to give the product **99** as a white solid (11.4 g, 68%) with all data was in accordance with the literature.[4] $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.49 (3H, s, C*H*$_3$), 7.34 (2H, d, *J* 8.2, Ar*H*), 7.68 (2H, d, *J* 8.1, Ar*H*), 7.76 (2H, d, *J* 8.4, Ar*H*), 7.86 (2H, d, *J* 8.4, Ar*H*), 8.99 (1H, s, C*H*).

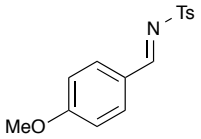
*N*-Benzylidene-4-methylbenzenesulfonamide **215**




**215**

Following *General Procedure A,* benzaldehyde (5.1 mL, 50 mmol) and *para*-toluenesulfonamide (8.56 g, 50 mmol) were stirred for 16 h to give the crude product, which was recrystallised (EtOAc/hexane) to give the product **215** as a white solid (9.65 g, 74%) with all data was in accordance with the literature.[4] $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.45 (3H, s, C*H*$_3$), 7.36 (2H, d, *J* 8.0, Ar*H*), 7.47 (2H, t, *J* 7.6, Ar*H*), 7.61 (2H, tt, *J* 7.4, 2.7, Ar*H*), 7.86-7.97 (4H, m, Ar*H*), 9.02 (1H, s, C*H*).

*N*-(4-methoxybenzylidene)-4-methylbenzenesulfonamide **249**

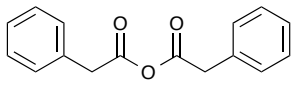



**249**

Following *General Procedure A,* 4-methoxybenzaldehyde (6.1 mL, 50 mmol) and *para*-toluenesulfonamide (8.56 g, 50 mmol) were stirred for 16 h to give the crude product, which was recrystallised (THF/hexane) give the product **249** as a white solid (11.72 g 81.0%) with all data was in accordance with the literature.[4] $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.42 (3H, s, C*H*$_3$), 3.84 (3H, s, C*H*$_3$), 6.95 (2H, d, *J* 8.6, Ar*H*), 7.30 (2H, d, *J* 8.0, Ar*H*), 7.77-7.95 (4H, m, Ar*H*), 8.92 (1H, s, C*H*).

### 6.2.3.2 Anhydrides

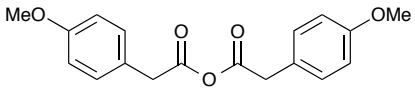
2-Phenylacetic anhydride **134**



**134**

Following *General Procedure B*, phenylacetic acid (0.45 g, 3.33 mmol) and DCC (0.35 g, 1.70 mmol) were stirred in toluene (10 mL) to give product **134** as a white solid (0.43 g, >99%) with data in accordance to the literature.[5] mp 68-70 °C {lit.[5] mp 72-72.5 °C}; $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 3.76 (4H, s, 2 C$H_2$), 7.23-7.25 (4H, m, Ar*H*), 7.32-7.38 (6H, m, Ar*H*).

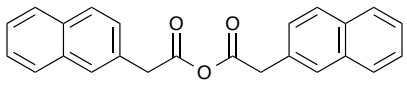
2-(4-Methoxyphenyl)acetic anhydride **255**



**255**

Following *General Procedure B*, 4-methoxyphenylacetic acid (1.00 g, 6.00 mmol) and DCC (0.62 g, 3.00 mmol) were stirred in toluene (25 mL) to give product **255** as a white solid (0.94 g, >99%) with data in accordance with the literature.[6] mp 46-48 °C {Lit.[6] 60-62 °C}; $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$: 3.66 (4H, s, 2 C$H_2$), 3.80 (6H, s, 2 C$H_3$), 6.83-6.86 (4H, m, Ar*H*), 7.10-7.13 (4H, m, Ar*H*).

2-(Naphthalen-2-yl)acetic anhydride **223**

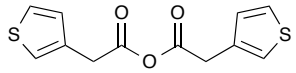


**223**

Following *General Procedure B*, 2-naphthylacetic acid (1.00 g, 5.40 mmol) and DCC (0.56 g, 2.70 mmol) were stirred in toluene (25 mL) to give product **223** as a white solid (0.41 g, 43%) with data in accordance with the literature.[6] mp 100-104 °C {Lit.[6] 104-108 °C}; $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$: 3.88 (4H, s, 2 C$H_2$), 7.27 (2H, d, *J* 7.4,

Ar*H*), 7.47-7.51 (4H, m, Ar*H*), 7.63 (2H, s, 2 Ar*H*), 7.70-7.73 (4H, m, Ar*H*), 7.80-7.83 (2H, m, Ar*H*).

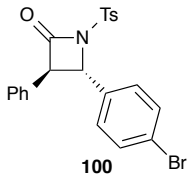
2-(Thiophen-3-yl)acetic anhydride **225**



**225**

Following *General Procedure B*, 3-thiopheneacetic acid (0.47 g, 3.33 mmol) and DCC (0.35 g, 1.70 mmol) were stirred in toluene (10 mL) to give product **225** as a yellow solid (0.44 g, >99%) with data in accordance with the literature.[6] mp 36-38 °C {Lit.[6] 40-42 °C}; $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 3.79 (4H, s, 2 C$H_2$), 6.99 (2H, dd, *J* 5.0, 1.2, Ar*H*), 7.15 (2H, dd, *J* 2.0, 1.0, Ar*H*), 7.31 (2H, dd, *J* 5.0, 3.0, Ar*H*).

### 6.2.4 Optimisation Studies on 100



**100**

*Isothiourea Catalyst Screen:*

The title compound was prepared according to *General Procedure C*, from phenyl acetic acid (27.2 mg, 0.20 mmol), pivaloyl chloride (37 μL, 0.30 mmol), 2 portions of *i*-$Pr_2$NEt (52 μL, 0.30 mmol) and imine **99** (70.8 mg, 0.20 mmol). All reactions at rt for 2 h.

(–)Tetramisole.HCl **22** (9.63 mg, 0.04 mmol, 20 mol%) gave crude **100** (>95:5 dr). Chromatographic purification (5:95-90:10 Petrol:EtOAc) gave **100** (>95:5 dr) as a white solid (33.6 mg, 37%); 57% ee (*ent*).

(2*S*,3*R*)-HBTM-2.1 **26** (12.3 mg, 0.04 mmol, 20 mol%) gave crude **100** (>95:5 dr). Chromatographic purification (5:95-90:10 Petrol:EtOAc) gave **100** (>95:5 dr) as a white solid (80.8 mg, 89%); 57% ee.

(*R*)-BTM **23** (10.0 mg, 0.04 mmol, 20 mol%) gave crude **100** (>95:5 dr). Chromatographic purification (5:95-90:10 Petrol:EtOAc) gave 1**00** (>95:5 dr) as a white solid (80.8 mg, 89%); 57% ee.

*Activating Agent Screen:*

The title compound was prepared according to *General Procedure C*, from phenyl acetic acid (27.2 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2NEt$ (52 μL, 0.30 mmol) and imine **99** (70.8 mg, 0.20 mmol). All reactions at rt

(2*S*,3*R*)-HBTM-2.1 **26** (12.3 mg, 0.04 mmol, 20 mol%) for 4.5 h gave crude **100** (>95:5 dr). Chromatographic purification (5:95-90:10 Petrol:EtOAc) gave **100** (>95:5 dr) as a white solid (29.1 mg, 32%); 72% ee.

(*R*)-BTM **23** (10.0 mg, 0.04 mmol, 20 mol%) for 3.5 h gave crude **100** (>95:5 dr). Chromatographic purification (5:95-90:10 Petrol:EtOAc) gave **100** (>95:5 dr) as a white solid (69.9 mg, 77%); 85% ee.

*Solvent and Temperature Screen:*

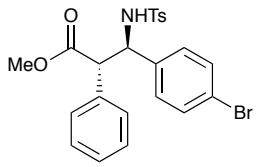
The title compound was prepared according to *General Procedure C*, from phenyl acetic acid (27.2 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2NEt$ (52 μL, 0.30 mmol), (*R*)-BTM **23** (10.0 mg, 0.04 mmol, 20 mol%) and imine **99** (70.8 mg, 0.20 mmol).

Reaction in THF at rt for 2 h gave crude **100** (>95:5 dr). Chromatographic purification (5:95-90:10 Petrol:EtOAc) gave **100** (>95:5 dr) as a white solid (51.7 mg, 57%); 59% ee.

Reaction in $CH_2Cl_2$ at 0 °C for 5 h gave crude **100** (>95:5 dr). Chromatographic purification (5:95-90:10 Petrol:EtOAc) gave **100** (>95:5 dr) as a white solid (52.6 mg, 58%); 93% ee.

Reaction in $CH_2Cl_2$ at –10 °C for 18 h gave crude **100** (>95:5 dr). Chromatographic purification (5:95-90:10 Petrol:EtOAc) gave **100** (>95:5 dr) as a white solid (15.4 mg, 17%); 80% ee.

### 6.2.5 Optimisation Studies on 106




**106**

*Isothiourea Catalyst Screen:*

The title compound was prepared according to *General Procedure D* from phenylacetic acid (27 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2NEt$ (52 μL, 0.30 mmol), imine **99** (70.8 mg, 0.20 mmol) and $NaN_3$ (19.5 mg, 0.30 mmol) and methanol (1 mL). All reactions were carried out for 1 h at rt for the cyclisation and 1 h at rt for the ring-opening.

(–)Tetramisole.HCl **22** (9.63 mg, 0.04 mmol, 20 mol%) gave crude **106** (>95:5 dr). Chromatographic purification (80:20 Petrol:EtOAc) gave **106** (>95:5 dr) as a white solid (14.5 mg, 16%); 70% ee (*ent*).

(2*S*,3*R*)-HBTM-2.1 **26** (12.3 mg, 0.04 mmol, 20 mol%) gave crude **106** (>95:5 dr). Chromatographic purification (80:20 Petrol:EtOAc) gave **106** (>95:5 dr) as a white solid (21.8 mg, 24%); 83% ee.

(*R*)-BTM **23** (10.0 mg, 0.04 mmol, 20 mol%) gave crude **106** (>95:5 dr). Chromatographic purification (80:20 Petrol:EtOAc) gave **106** (>95:5 dr) as a white solid (27.2 mg, 30%); 74% ee.

*Ring Opening Conditions:*

The title compound was prepared according to *General Procedure D* from phenylacetic acid (27 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2NEt$ (52 μL, 0.30 mmol), (2*S*,3*R*)-HBTM-2.1 **26** (12.3 mg, 0.04 mmol, 20 mol%), and imine **99** (70.8 mg, 0.20 mmol). All reactions were carried out for 2 h at rt for the cyclisation.

$NaN_3$ (1.3 mg, 0.02 mmol, 10 mol%) and methanol (1 mL) for 4.5 h at rt gave crude **106** (>95:5 dr). Chromatographic purification (80:20 Petrol:EtOAc) gave **106** (>95:5 dr) as a white solid (60.0 mg, 66%); 85% ee.

NaOMe (excess) and methanol (1 mL) for 2 h at rt gave crude **106** (>95:5 dr). Chromatographic purification (80:20 Petrol:EtOAc) gave **106** (>95:5 dr) as a white solid (36.4 mg, 40%); 96% ee.

NaOMe (excess) and methanol (1 mL) for 4 h at 0 °C gave crude **106** (>95:5 dr). Chromatographic purification (80:20 Petrol:EtOAc) gave **106** (>95:5 dr) as a white solid (48.2 mg, 53%); 96% ee.

NaOMe (excess) and methanol (1 mL) for 24 h at –30 °C gave crude **106** (>95:5 dr). Chromatographic purification (80:20 Petrol:EtOAc) gave **106** (>95:5 dr) as a white solid (39.1 mg, 43%); 95% ee.

2.5 M Butyl lithium solution in hexanes (0.1 mL, 55 equiv, 11 mmol) and methanol (1 mL) for 1 h at –78 °C to rt gave crude **106** (>95:5 dr). Chromatographic purification (80:20 Petrol:EtOAc) gave **106** (>95:5 dr) as a white solid (56.4 mg, 62%); 93% ee.

*Catalyst Loading Screen:*

The title compound was prepared according to *General Procedure D* from phenylacetic acid (27 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2NEt$ (52 μL, 0.30 mmol), 2.5 M Butyl lithium solution in hexanes (0.1 mL, 55 equiv, 11 mmol) and imine **99** (70.8 mg, 0.20 mmol). All reactions were carried out at rt for the cyclisation and –78 °C to rt for the ring-opening.

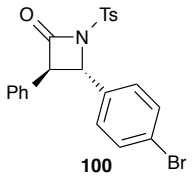
(2*S*,3*R*)-HBTM-2.1 **26** (6.17 mg, 0.02 mmol, 10 mol%) for 2 h gave crude **106** (>95:5 dr). Chromatographic purification (80:20 Petrol:EtOAc) gave **106** (>95:5 dr) as a white solid (48.2 mg, 53%); 95% ee.

(2*S*,3*R*)-HBTM-2.1 **26** (3.08 mg, 0.01 mmol, 5 mol%) for 2.5 h gave crude **106** (>95:5 dr). Chromatographic purification (80:20 Petrol:EtOAc) gave **106** (>95:5 dr) as a white solid (45.5 mg, 50%); >99% ee.

(2*S*,3*R*)-HBTM-2.1 **26** (0.62 mg, 0.002 mmol, 1 mol%) for 2.5 h gave crude **106** (>95:5 dr). Chromatographic purification (80:20 Petrol:EtOAc) gave **106** (>95:5 dr) as a white solid (40.0 mg, 44%); 85% ee.

### 6.2.6 Experimental Procedures

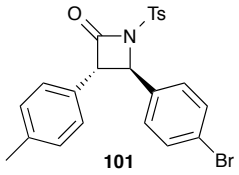
(3*S*,4*R*)-4-(4-Bromophenyl)-3-phenyl-1-tosylazetidin-2-one **100**




**100**

The title compound was prepared according to *General Procedure C*, from phenyl acetic acid (27.2 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2NEt$ (52 μL, 0.30 mmol), **23** (10.0 mg, 20 mol%, 0.04 mmol), imine **99** (70.8 mg, 0.20 mmol) and purified by chromatography (5:95-90:10 Petrol:EtOAc) to afford **100** as a white solid (52.7 mg, 58%); mp 60-64 ˚C; $[\alpha]_D^{22}$ −2.3 (*c* 1.0, $CH_2Cl_2$); chiral HPLC analysis, Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, rt), $t_R$ minor (3*R*,4*S*) 19.4 min, $t_R$ major (3*S*,4*R*) 21.0 min, 88% ee; $\nu_{max}$ (KBr) 1797 (C=O), 1369 (C-N), 1172 (R-$SO_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.48 (3H, s, $SO_2ArCH_3$), 4.22 (1H, d, *J* 3.4, C(3)*H*), 4.92 (1H, d, *J* 3.4, C(4)*H*), 7.04 (2H, m, Ar*H*), 7.18 (2H, m, Ar*H*), 7.32 (5H, m, Ar*H*), 7.47 (2H, m, Ar*H*), 7.75 (2H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.8 ($SO_2ArCCH_3$), 64.4. (*C*(3)), 65.1 (*C*(4)), 123.4 (*C*Br), 127.3 (*Ph*), 127.6 (*Ph*), 128.1 (*Ph*), 128.6, 129.3, 130.0, 132.2 (*Ph*), 132.5 ($C_{ipso}$), 135.2 ($C_{ipso}$), 135.6 ($C_{ipso}$), 145.6 ($CCH_3$), 165.2 (*C*(2)); m/*z* ($NSI^+$) 475 ($[M+NH_4]^+$), 100%); HRMS ($NSI^+$) $C_{22}H_{22}BrN_2O_3S^+$ ($[M+NH_4]^+$), requires 473.0528; found 473.0539 (−0.2 ppm).

(3*S*,4*R*)-4-(4-Bromophenyl)-3-(*p*-tolyl)-1-tosylazetidin-2-one **101**

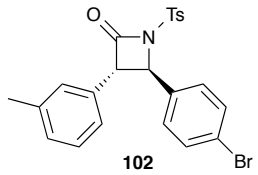



**101**

The title compound was prepared according to *General Procedure C* from *p*-tolylacetic acid (30.0 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of $^iPr_2NEt$ (52 μL, 0.30 mmol), **23** (10 mg, 20 mol%, 0.04 mmol), imine **99**

(70.8 mg, 0.20 mmol) and purified by chromatography (95:5 Petrol:EtOAc) to afford the **101** as a white solid (39.3 mg, 42%); mp 40-44 °C; $[\alpha]_D^{22}$ −2.5 (*c* 1.0, $CH_2Cl_2$); Chiral HPLC analysis, Chiralcel OD-H (80:20 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, rt), $t_R$ major (3*S*,4*R*) 13.6 min, $t_R$ minor (3*R*,4*S*) 16.1 min, 87% ee; $\nu_{max}$ (KBr) 1795 (C=O), 1368 (C-N), 1158 (R-$SO_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.31 (3H, s, C(3)ArC*H*$_3$), 2.47 (3H, s, $NSO_2$ArC*H*$_3$), 4.17 (1H, d, *J* 3.4, C(3)*H*), 4.87 (1H, d, *J* 3.4, C(4)*H*), 6.90 (2H, d, *J* 8.2, C(3)ArC(2)*H*), 7.10 (2H, d, *J* 8.2, C(3)ArC(3)*H*), 7.15 (2H, d, *J* 8.3, $SO_2$ArC(2)*H* ), 7.31 (2H, d, *J* 8.6, C(4)ArC(2)*H*), 7.46 (2H, d, *J* 8.5, C(4)ArC(3)*H*), 7.73 (2H, d, *J* 8.3, $SO_2$ArC(2)*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$:21.3 (C(3)Ar*C*$H_3$), 21.9 ($NSO_2$Ar*C*$H_3$), 64.3 (*C*(3)), 65.4 (*C*(4)), 123.1 (C(4)Ar*C*(4)), 127.3 (Ar*C*), 127.7 (C(3)Ar*C*(2)), 128.2 ($NSO_2$Ar*C*(2)), 129.6 ($C_{ipso}$), 130.0 (Ar*C*), 130.1 (Ar*C*), 132.3 (C(4)Ar*C*(3)), 135.3 (C(3)Ar*C*(1)), 135.7 ($SO_2$Ar*C*(1)), 138.8 (C(3)Ar*C*(4)), 145.7 ($SO_2$Ar*C*(4)), 165.4 (*C*(2)); *m/z* ($NSI^+$) 489 ($[M+NH_4]^+$, 100%); HRMS ($NSI^+$) $C_{23}H_{24}BrN_2O_3S^+$ ($[M+NH_4]^+$), requires 487.0682; found 487.0686 (−0.7 ppm).

(3*S*,4*R*)-4-(4-Bromophenyl)-3-(*m*-tolyl)-1-tosylazetidin-2-one **102**

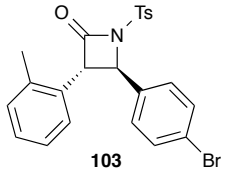


**102**

The title compound was prepared according to *General Procedure C* from *m*-tolylacetic acid (30.0 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of $^i$Pr$_2$NEt (52 μL, 0.30 mmol), **23** (10 mg, 20 mol%, 0.04 mmol), imine **99** (70.8 mg, 0.20 mmol) and purified by chromatography (90:10 Petrol:EtOAc) to afford **102** as a white solid (50.2 mg, 53%); mp 130-134 °C; $[\alpha]_D^{22}$ −2.6 (*c* 1.0, $CH_2Cl_2$); Chiral HPLC analysis, Chiralcel OD-H (80:20 Hexane:IPA, flow rate 0.25 mL $min^{-1}$, 211 nm, rt), $t_R$ minor (3*R*,4*S*) 45.0 min, $t_R$ major (3*S*,4*R*) 51.5 min, 79% ee; $\nu_{max}$ (KBr) 1806 (C=O), 1370 (C-N), 1172 (R-$SO_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.25 (3H,

s, $NSO_2ArCH_3$), 2.47 (3H, s, C(3)Ar$CH_3$) 4.15 (1H, d, *J* 3.4, C(3)*H*) 4.87 (1H, d, *J* 3.4, C(4)*H*), 6.72 (1H, s, Ar*H*), 6.80 (1H, d, *J* 7.7, Ar*H*), 6.71 (1H, d, *J* 7.7, Ar*H*), 7.18 (3H, m, Ar*H*), 7.33 (2H, d, *J* 8.3, Ar*H*), 7.46 (2H, d, *J* 8.4, Ar*H*), 7.76 (2H, d, *J* 8.3, Ar*H*); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.4 ($NSO_2ArCH_3$), 21.9 (C(3)Ar$CH_3$), 64.8 (*C*(3)), 65.3 (*C*(4)), 123.3 (C4)Ar*C*(4)Br), 124.7 (Ar*C*), 127.7 (Ar*C*), 127.8 (Ar*C*), 128.3, 129.2 (Ar*C*), 129.5 (Ar*C*), 130.2 ($C_{ipso}$), 132.3 (Ar*C*), 132.6, 135.4 ($C_{ipso}$), 135.8 ($C_{ipso}$), 139.3 ($C_{ipso}$), 145.7 ($NSO_2ArC(4)CH_3$), 165.5 (*C*(2)); *m/z* ($NSI^+$) 489 ($[M+NH_4]^+$, 100%); HRMS (NSI+) $C_{23}H_{24}BrN_2O_3S^+$ ($[M+NH_4]^+$), requires 487.0683; found 487.0686 (–0.5 ppm).

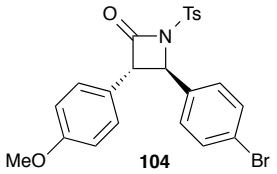
(3*S*,4*R*)-4-(4-Bromophenyl)-3-(*o*-tolyl)-1-tosylazetidin-2-one **103**



**103**

The title compound was prepared according to *General Procedure C* from *o*-tolylacetic acid (60 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2NEt$ (52 μL, 0.30 mmol), **23** (10 mg, 20 mol%, 0.04 mmol), imine **99** (70.8 mg, 0.20 mmol) and purified by chromatography (90:10 Petrol:EtOAc) to afford **103** as a white solid (53.1 mg, 56 %); mp 32-36 ˚C; $[\alpha]_D^{22}$ +4.4 (*c* 0.25, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta_H$: 1.97 (3H, s, $SO_2ArCH_3$), 2.47 (3H, s, Ph$CH_3$), 4.43 (1H, d, *J* 3.4, C(3)*H*), 4.82 (1H, d, *J* 3.4, C(4)*H*), 7.03 (1H, m, Ar*H*), 7.18 (5H, m, Ar*H*), 7.31 (2H, d, *J* 8.6, Ar*H*), 7.47 (2H, d, 7.47, Ar*H*), 7.71 (2H, d, Ph*H*); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta_C$: 20.3 ($SO_2PhMe$), 22.2 (Ph*Me*), 42.1, 62.7 (*C*(3)), 63.3 (*C*(4)), 123.7, 127.1, 127.2, 128.0, 129.0, 130.0 ($C_{ipso}$), 130.3 (*Ph*), 131.3, 132.6 (*Ph*), 135.8 ($C_{ipso}$), 136.6 ($C_{ipso}$), 145.7 ($SO_2C_5H_4CMe$), 165.9 (*C*(2)); *m/z* ($NSI^+$) 489 ($[M+NH_4]^+$, 100%); HRMS (NSI+) $C_{23}H_{24}BrN_2O_3S^+$ ($[M+NH_4]^+$), requires 487.0681; found 487.0686 (-0.9 ppm)

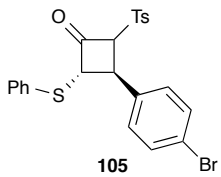
(3*S*,4*R*)-4-(4-Bromophenyl)-3-(4-methoxyphenyl)-1-tosylazetidin-2-one **104**




**104**

The title compound was prepared according to *General Procedure C* from *p*-methoxyphenylacetic acid (33.0 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2NEt$ (52 μL, 0.30 mmol), **23** (10 mg, 20 mol%, 0.04 mmol), imine **99** (70.8 mg, 0.20 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to afford **104** as a white solid (62.0 mg, 67%); mp 32-36 ˚C; $[\alpha]_D^{22}$ −30.0 (*c* 1.0, $CH_2Cl_2$); Chiral HPLC analysis, Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, rt), $t_R$ minor (3*R*,4*S*) 33.4 min, $t_R$ major (3*S*,4*R*) 42.0 min, 83% ee; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.47 (3H, s, $NSO_2ArCH_3$), 3.77 (3H, s, $OCH_3$), 4.19 (1H, d, *J* 3.4, C(3)*H*), 4.85 (1H, d, *J* 3.4, C(4)*H*), 6.01 (2H, d *J* 8.8, Ar*H*), 6.93 (2H, d *J* 8.5, Ar*H*), 7.15 (2H, d, *J* 8.3, Ar*H*), 7.31 (2H, m, Ar*H*), 7.45 (2H, d, *J* 8.5, Ar*H*), 7.73 (2H, d, *J* 8.3, Ar*H*); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.9 ($NSO_2ArCH_3$), 55.5 ($OCH_3$), 64.1 (*C*(3)), 65.6 (*C*(4)), 114.8 (Ar*C*), 123.2, ($C_{ipso}$), 124.6 ($C_{ipso}$), 127.7 (Ar*C*), 128.2 (Ar*C*), 128.6 (Ar*C*), 130.1 (Ar*C*), 132.3 (Ar*C*), 135.4 ($C_{ipso}$), 135.7 ($C_{ipso}$), 145.7 ($NSO_2ArC(4)CH_3$), 159.8 ($C(3)ArC(4)OCH_3$), 165.7 (*C*(2)); *m/z* ($NSI^+$) 505 ($[M+NH_4]^+$, 100%); HRMS ($NSI^+$) $C_{23}H_{21}BrNO_4S^+$ ($[M+H]^+$), requires 486.0368; found 486.0369 (−0.2 ppm).

(3*S*,4*S*)-4-(4-Bromophenyl)-3-(phenylthio)-1-tosylazetidin-2-one **105**




**105**

The title compound was prepared according to *General Procedure C* from (phenylthio)acetic acid (33.6 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2NEt$ (52 μL, 0.30 mmol), **23** (10 mg, 20 mol%, 0.04 mmol), imine **99** (70.8 mg, 0.20 mmol) and purified by chromatography (90:10 Petrol:EtOAc) to afford

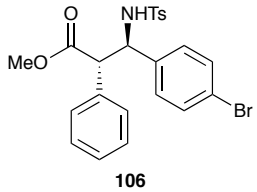
**105** as a white solid (40.7 mg, 42% as a mixture of *anti:syn* 85:15). Careful purification allowed isolation of an analytical sample for characterisation.

Data for the *anti* diastereoisomer: isolated white solid (8.3 mg, 14%); mp 78-84 ˚C; $[\alpha]_D^{22}$ +7.0 (*c* 0.1, $CHCl_3$); Chiral HPLC analysis, Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C), $t_R$ major (3*S*,4*S*) 16.1 min, $t_R$ minor (3*R*,4*R*) 20.8 min, 61% ee; $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.46 (3H, s, $NSO_2ArCH_3$), 4.11 (1H, d, *J* 3.2, C(3)*H*), 4.70 (1H, d, *J* 3.2, C(4)*H*), 7.12-7.24 (2H, m, Ar*H*), 7.21-7.30 (5H, m, Ar*H*), 7.42-7.47 (4H, m, Ar*H*), 7.57-7.59 (2H, m, Ar*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.9 ($NSO_2ArCH_3$), 61.5 (*C*(3)), 63.6 (*C*(4)), 123.5 (*C*Br), 127.9 (*Ph*), 128.1 (*Ph*), 128.6, 129.3, 129.6, 130.1, 132.3, 134.5, 134.5 ($C_{ipso}$), 135.3 ($C_{ipso}$), 145.6 (*C*Me), 163.2 (C(2)); *m/z* (ESI$^+$) 512 ([M+Na]$^+$, 100%); HRMS (NSI$^+$) $C_{22}H_{18}BrNO_3S_2^+$ ([M+Na]$^+$), requires 509.9798; found 509.9804 (−1.1 ppm).

Selected data for the *Syn* diastereoisomer: $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.49 (3H, s, $NSO_2ArCH_3$), 4.79 (2H, d, *J* 6.4, C*H*), 5.35 (2H, d, *J* 6.1, C*H*), 6.99-7.02 (2H, m, Ar*H*), 7.71-7.76 (2H, m, Ar*H*); Chiral HPLC analysis, Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211nm, 24°C), $t_R$ major (3*R*,4*S*) 25.9 min, $t_R$ minor (3*S*,4*R*) 33.6 min, 62% ee.

(2*S*,3*R*)-Methyl-

3-(4-bromophenyl)-3-(4-methylphenylsulfonamido)-2-phenylpropanoate **106**

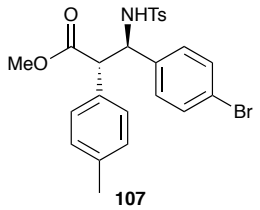



**106**

The title compound was prepared according to *General Procedure D* from phenylacetic acid (27 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of $^i$Pr$_2$NEt (52 μL, 0.30 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), 2.5 M Butyl lithium solution in hexanes (0.1 mL, 55 equiv, 11 mmol), imine **99** (70.8 mg, 0.20 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to **106** as a white

solid (49.0 mg, 50%); mp 156-159°C; $[\alpha]_D^{22}$ –24.3 (*c* 1, $CHCl_3$); chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C), $t_R$ minor (2*R*,3*S*) 29.0 min, $t_R$ major (2*S*,3*R*) 42.7 min, >99% ee; $\nu_{max}$ (neat) 3236.6 (NH), 1739.8 (C=O), 1330.9 (R-$SO_2$N), 1153.4 (R-$SO_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.35 (3H, s, ArC*H*$_3$), 3.61 (3H, s, OC*H*$_3$), 3.92 (1H, d, *J* 6.45, C(2)*H*), 4.80 (1H, dd, *J* 8.82, 6.53, C(3)*H*), 5.98 (1H, d, *J* 8.64, N*H*), 6.89-6.91 (2H, m, C(3)ArC(2)*H*), 7.01 (2H, d, *J* 7.95, C(3)NHS$O_2$ArC(3)*H*), 7.13-7.16 (2H, m, Ar*H*), 7.20-7.23 (5H, m, Ar*H*), 7.33 (2H, d, *J* 8.29, C(3)NHS$O_2$Ar(2)*H*); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta_C$: 21.6 (Ar*C*H$_3$), 52.6 (O*C*H$_3$), 57.5 (*C*(2)), 60.6 (*C*(3)), 121.7 (Ar*C*Br), 127.0 (C(3)NHS$O_2$Ar*C*(2)), 128.1 (Ar*C*), 128.6 (Ar*C*), 128.7 (Ar*C*), 128.9 (C(3)Ar*C*(2)), 129.3 (C(3)NHS$O_2$Ar*C*(3)), 131.5 (Ar*C*), 134.5 (C(2)Ar*C*(1)), 137.5 (C(3)NHS$O_2$Ar*C*(1)), 137.8 (C(3)Ar*C*(1)), 143.1 (C(3)NHS$O_2$Ar*C*(4)), 172.2 (*C*(1)); *m/z* (NSI$^+$) 507 ([M+$NH_4$]$^+$, 100%); HRMS (NSI$^+$) $C_{23}H_{23}BrNO_4S^+$ ([M+H]$^+$), requires 488.0523; found 488.0526 (–0.5 ppm).

(2*S*,3*R*)-Methyl 3-(4-bromophenyl)-3-(4-methylphenylsulfonamido)-2-(p-tolyl)propanoate **107**

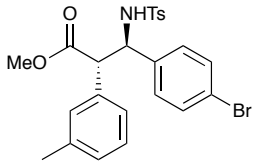


**107**

The title compound was prepared according to *General Procedure D* from *p*-tolylacetic acid (30 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2$NEt (52 μL, 0.30 mmol), **16** (3.1 mg, 5 mol%, 0.01 mmol), 2.5 M butyl lithium solution in hexanes (0.1 mL, 11 mmol), imine **99** (70.8 mg, 0.20 mmol) and purified by chromatography (80:20 Petrol:EtOAc ) to give **107** as a white solid (45.8 mg, 46%); mp 163-168°C; $[\alpha]_D^{22}$ –26.0 (*c* 0.25, $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 0.5 mL $min^{-1}$, 211 nm, 30 °C), $t_R$ major (2*S*,3*R*) 33.9 min, $t_R$ minor (2*R*,3*S*) 38.3 min, 87% ee; $\nu_{max}$ (neat) 3252.0 (NH), 1735.9 (C=O), 1352.1 (R-$SO_2$N), 1159.2 (R-$SO_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.28 (3H, s,

C(2)ArC*H*$_3$), 2.35 (3H, s, C(3)NHSO$_2$ArC*H*$_3$), 3.59 (3H, s, OC*H*$_3$), 3.89 (1H, d, *J* 6.5, C(2)*H*), 4.77 (1H, dd, *J* 8.8, 6.5, C(3)*H*), 6.03 (1H, d, *J* 8.8, N*H*), 6.91 (2H, d, *J* 8.4, C(3)ArC(2)*H*), 6.99-7.02 (6H, m, Ar*H*), 7.22 (2H, d, *J* 8.5, C(3)ArC(3)*H*), 7.33 (2H, d, *J* 8.3, C(3)NHSO$_2$ArC(2)*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.3 (C(2)Ar*C*H$_3$), 21.6 (C(3)NHSO$_2$Ar*C*H$_3$), 52.5 (O*C*H$_3$), 57.1 (C(2)), 60.6 (C(3)), 121.6 (Ar*C*Br), 127.0 (C(3)NHSO$_2$Ar*C*(2)), 128.8 (C(3)Ar*C*(2)), 128.4 (Ar*C*), 129.3 (C(3)NHSO$_2$Ar*C*(3)), 129.6 (Ar*C*), 131.4 (C(2)Ar*C*(1)), 131.5 (C(3)Ar*C*(3)), 137.6 (C(3)NHSO$_2$Ar*C*(1)), 137.9 (C(2)Ar*C*(4)), 138.0 (C(3)Ar*C*(1)), 143.0 (C(3)NHSO$_2$Ar*C*(4)), 172.4 (C(1)); *m/z* (NSI$^+$) 519 ([M+NH4]$^+$, 45%), 526 (100%); HRMS (NSI$^+$) $C_{24}H_{25}BrNO_4S^+$ ([M+H]$^+$), requires 502.0681; found 502.0682 (–0.2 ppm).

(2*S*,3*R*)-Methyl 3-(4-methylphenylsulfonamido)-3-phenyl-2-(*m*-tolyl)propanoate **108**

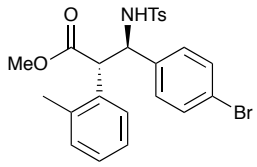



**108**

The title compound was prepared according to *General Procedure D* from *m*-tolylacetic acid (30 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-Pr$_2$NEt (52 μL, 0.30 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), 2.5 M butyl lithium solution in hexanes (0.1 mL, 11 mmol), imine **99** (70.8 mg, 0.20 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **108** as a white solid (40.7 mg, 40%); mp 124-130°C; $[\alpha]_D^{22}$ –25.0 (*c* 0.1, $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 1.0 mL min$^{-1}$, 211 nm, 30 °C), $t_R$ minor (2*R*,3*S*) 39.9 min, $t_R$ major (2*S*,3*R*) 42.8 min, 74% ee; $\nu_{max}$ (neat) 3248.1 (NH), 1735.9 (C=O), 1159.2 (R-SO$_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.23 (3H, s, C(2)ArC(3)C*H*$_3$), 2.34 (3H, s, C(3)NHSO$_2$ArC*H*$_3$), 3.60 (3H, s, OC*H*$_3$), 3.90 (1H, d, *J* 6.6, C(2)*H*), 4.79 (1H, dd, *J* 8.9, 6.7, C(3)*H*), 6.14 (1H, d, *J* 8.9, N*H*), 6.91-6.93 (4H, m, Ar*H*), 7.00 (3H, d, *J* 7.9, Ar*H*), 7.07 (1H, t, *J* 7.9, C(2)ArC(3)*H*), 7.22 (2H, d, *J* 8.5, Ar*H*), 7.32 (2H, d, *J* 8.3, Ar*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.5 (C(2)ArC(3)*C*H$_3$), 21.6

(C(3)NHSO$_2$Ar*C*H$_3$), 52.6 (O*C*H$_3$), 57.4 (C(2)), 60.6 (C(3)), 121.6 (*C*Br), 125.6 (C(3)Ar*C*(2)), 126.9 (Ar*C*), 128.7 (2xAr*C*), 128.8 (Ar*C*), 129.2 (Ar*C*), 129.3 (Ar*C*), 131.4 (Ar*C*), 134.4 (C(2)Ar*C*(1)), 137.6 (C(3)NHSO$_2$Ar*C*(1)), 138.0 (C(3)Ar*C*(1)), 138.5 (C(2)Ar*C*(3)), 143.0 (C(3)NHSO$_2$Ar*C*(4)), 172.3 (C(1)); *m/z* (NSI$^+$) 214(100%), 519 ([M+NH4]$^+$, 40%); HRMS (NSI$^+$) $C_{24}H_{25}BrNO_4S^+$ ([M+H]$^+$), requires 502.0681; found 502.0682 (–0.2 ppm).

(2*S*,3*R*)-Methyl-3-(4-bromophenyl)-3-(4-methylphenylsulfonamido)-2-(*o*-tolyl)propanoate **109**

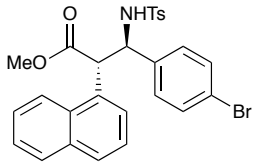



**109**

The title compound was prepared according to *General Procedure D* from *o*-tolylacetic acid (150 mg, 1.0 mmol), tosyl chloride (286.5 mg, 1.50 mmol), 2 portions of *i*-Pr$_2$NEt (260 μL, 1.50 mmol), **26** (15.5 mg, 5 mol%, 0.05 mmol), 2.5 M butyl lithium solution in hexanes (0.5 mL, 55 mmol), imine **99** (354.0 mg, 1.0 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **109** as a white solid (304.5 mg, 61%); mp 124-128°C; $[\alpha]_D^{22}$ −17.2 (*c* 0.25, $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 1.0 mL min$^{-1}$, 211 nm, 30 °C), $t_R$ minor (2*R*,3*S*) 16.7 min, $t_R$ major (2*S*,3*R*) 24.2 min, 76% ee; $\nu_{max}$ (neat) 3246.2 (NH), 1745.6 (C=O),1163.1 (R-SO$_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.20 (3H, s, C(2)ArC*H*$_3$), 2.34 (3H, s, C(3)NHSO$_2$ArC*H*$_3$), 3.59 (3H, s, OC*H*$_3$), 4.20 (1H, d, *J* 6.8 Hz, C(2)*H*), 4.76 (1H, dd, *J* 8.7, 6.8, C(3)*H*), 6.30 (1H, d, *J* 8.8, N*H*), 6.93-6.96 (2H, m, C(3)ArC(2)*H*), 6.99-7.02 (3H, m, Ar*H*), 7.08 (2H, td, *J* 1.9, 6.7, C(2)ArC(4)*H* & C(2)ArC(5)*H*), 7.19-7.21 (2H, m, C(3)ArC(3)*H*), 7.26-7.28 (1H, m, C(2)ArC(6)*H*), 7.33 (2H, d, *J* 8.3, C(3)NHSO$_2$ArC(2)*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 19.7 (C(2)ArC(2)*C*H$_3$), 21.6 (C(3)NHSO$_2$Ar*C*H$_3$), 52.5 (*C*H$_3$O), 52.9 (*C*(2)), 59.5 (*C*(3)), 121.6 (*C*Br), 126.5 (C(3)NHSO$_2$Ar*C*(2)), 126.9 (C(2)Ar*C*(4)), 127.8 (C(2)Ar*C*(6)), 128.0 (C(2)Ar*C*(5)), 128.7 (C(3)Ar*C*(2)), 129.3 (Ar*C*), 130.9 (Ar*C*), 132.9

(C(3)Ar*C*(3)), 133.0 (C(2)Ar*C*(1)), 135.9 (C(2)Ar*C*(2)), 137.4 (C(3)Ar*C*(1)), 138.0 (C(3)NHSO$_2$Ar*C*(1)), 143.0 (C(3)NHSO$_2$Ar*C*(4)), 172.6 (*C*(1)); *m/z* (NSI$^+$) 521 ([M+NH4]$^+$, 100%); HRMS (NSI$^+$) $C_{24}H_{25}BrNO_4S^+$ ([M+H]$^+$), requires 502.0682; found 502.0682 (–0.0 ppm). This was recrystallised from $CH_2Cl_2$/Petrol to **109** as a white solid (209.7 mg, 42%); mp 116-120 ˚C; $[\alpha]_D^{22}$ –12.0° (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (8020 hexane:IPA, flow rate 1.0 mL min$^{-1}$, 211 nm, 30 °C), $t_R$ minor(2*R*,3*S*) 16.7 min, $t_R$ major (2*S*,3*R*) 24.2 min, 96% ee.

(2*S*,3*R*)-Methyl 3-(4-bromophenyl)-3-(4-2-(naphthalene-1-yl)propanoate **110**

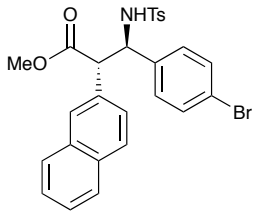



**110**

The title compound was prepared according to *General Procedure D* from 1-naphthylacetic acid (37.2 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-Pr$_2$NEt (52 μL, 0.30 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), 2.5 M butyl lithium solution in hexanes (0.1 mL, 11 mmol), imine **99** (70.8 mg, 0.20 mmol) and purified by chromatography (80:20 hexane:IPA) to give **110** as a white solid (49.8 mg, 46%); mp 122-128°C; $[\alpha]_D^{22}$ –12.2 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 1.0 mL min$^{-1}$, 270 nm, 30 °C), $t_R$ major (2*S*,3*R*) 24.9min, $t_R$ minor (2*R*,3*S*) 30.6 min, 82% ee; $\nu_{max}$ (neat) 3244.3 (NH), 1735.9 (C=O), 1330.9 (R-SO$_2$N), 1157.3 (R-SO$_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.24 (3H, s, ArC*H*$_3$), 3.57 (3H, s, OC*H*$_3$), 4.82 (1H, d, *J* 4.7, C(2)*H*), 4.86-4.89 (1H, m, C(3)*H*), 6.47 (1H, d, *J* 8.7, N*H*), 6.74 (2H, d, *J* 8.0, C(3)NHSO$_2$ArC(3)*H*), 7.07-7.10 (2H, m, C(3)NHSO$_2$ArC(2)*H*), 7.21-7.25 (2H, m, C(3)ArC(2)*H*), 7.27-7.37 (4H, m, Ar*H*), 7.46-7.58 (2H, m, Ar*H*), 7.69 (1H, d, *J* 7.9, Ar*H*), 7.79-7.82 (1H, m, Ar*H*), 7.90 (1H, d, *J* 8.4, Ar*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.5 (Ar*C*H$_3$), 52.2 (*C*(2)), 52.6 (O*C*H$_3$), 58.7 (*C*(3)), 121.8 (*C*Br), 121.82 (Ar*C*), 125.4 (Ar*C*), 125.9 (Ar*C*), 126.1 (Ar*C*), 126.4 (C(3)NHSO$_2$Ar*C*(2)), 127.1 (Ar*C*)), 128.5 (C(3)Ar*C*(2)), 128.9 (Ar*C*), 129.0 (C(3)NHSO$_2$Ar*C*(3)), 129.5 (Ar*C*), 130. 2 (*C*$_{ipso}$), 130.7 (*C*$_{ipso}$), 131.75

(Ar*C*), 134.2 ($C_{ipso}$), 136.9 (C(3)NHSO$_2$Ar*C*(1)), 139.0 (C(3)Ar*C*(1)), 142.6 (Ar*C*(4)CH$_3$), 172.8 (C(1)); *m/z* (NSI$^+$) 555 ([M+NH$_4$]$^+$, 45%), 562 (100%); HRMS (NSI$^+$) $C_{27}H_{25}BrNO_4S^+$ ([M+H]$^+$), requires 538.0680; found 538.0682 (–0.4 ppm).

(2*S*,3*R*)-Methyl 3-(4-bromophenyl)-3-(4-methylphenylsulfonamido)-2-(naphthalen-2-yl)propanoate **111**

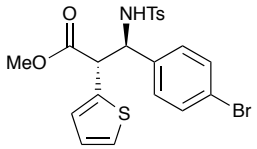



**111**

The title compound was prepared according to *General Procedure D* from 2-naphthylacetic acid (186.0 mg, 1.0 mmol), tosyl chloride (286.5 mg, 1.50 mmol), 2 portions of *i*-Pr$_2$NEt (260 μL, 1.50 mmol), **26** (15.5 mg, 5 mol%, 0.05 mmol), 2.5 M butyl lithium solution in hexanes (0.5 mL, 55 mmol), imine **99** (354.0 mg, 1.0 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **111** as a white solid (368.5 mg, 68%); mp 164-170°C; $[\alpha]_D^{22}$ –35.8 (*c* 0.25, CHCl$_3$); Chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 1.0 mL min$^{-1}$, 220 nm, 30 °C), $t_R$ major (2*S*,3*R*) 24.0 min, $t_R$ minor (2*R*,3*S*) 27.7 min, 85% ee; $\nu_{max}$ (neat) 3209.6 (NH), 1710.9 (C=O), 1336.7 (R-SO$_2$N), 1163.1 (R-SO$_2$N); $^1$H NMR (400 MHz, CDCl$_3$) $\delta_H$: 2.17 (3H, s, ArC*H$_3$*), 3.61 (3H, s, OC*H$_3$*), 4.13 (1H, d, *J* 6.0, C(2)*H*), 4.87 (1H, dd, *J* 9.0, 5.9, C(3)*H*), 6.23 (1H, d, *J* 9.0, N*H*), 6.72 (2H, d, *J* 7.9, C(3)NHSO$_2$ARC(3)*H*), 7.04-7.07 (2H, m, C(3)ArC(2)*H*), 7.20-7.23 (3H, m, Ar*H*), 7.26-7.29 (2H, m, C(3)ArC(3)*H*), 7.46-7.49 (2H, m, Ar*H*), 7.56 (1H, d, *J* 1.2, C(2)ArC(3)*H*), 7.60-7.63 (1H, m, Ar*H*), 7.67-7.70 (1H, m, Ar*H*), 7.74-7.77 (1H, m, Ar*H*); $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$) $\delta_C$: 21.5 (Ar*C*H$_3$), 52.6 (O*C*H$_3$), 57.3 (C(2)), 60.6 (C(3)), 121.8 (*C*Br), 126.0 (Ar*C*), 126.5 (2xAr*C*), 126.6 (C(3)NHSO$_2$Ar*C*(2)), 127.6 (C(2)Ar*C*(3)), 127.7 (Ar*C*), 128.1 (Ar*C*), 128.6 (C(3)Ar*C*(2)), 128.7 (C(3)Ar*C*(2)), 129.1 (C(3)NHSO$_2$Ar*C*(3)), 131.6 (C(3)Ar*C*(3)), 131.9 (C(2)Ar*C*(2)), 132.9 ($C_{ipso}$), 133.2 ($C_{ipso}$), 137.2 (C(3)NHSO$_2$Ar*C*(1)), 138.3 (C(3)Ar*C*(1)), 142.9 (Ar*C*(4)CH$_3$), 172.2

(C(1)); *m/z* HRMS (NSI$^+$) $C_{27}H_{28}BrN_2O_4S^+$ ([M+$NH_4$]$^+$), requires 555.0945; found 555.0948 (–0.5 ppm). This was recrystallised from $CH_2Cl_2$/Petrol to give **111** as a white solid (222.2 mg, 41%); mp 106-112 ˚C; $[\alpha]_D^{22}$ –39.0° (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 1.0 mL min$^{-1}$, 220 nm, 30 °C), $t_R$ major (2*S*,3*R*) 24.0 min, $t_R$ minor (2*R*,3*S*) 27.7 min, 91% ee.

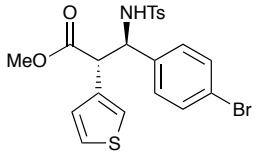
(2*S*,3*R*)-methyl 3-(4-bromophenyl)-3-(4-methylphenylsulfonamido)-2-(thiophen-2-yl)propanoate **112**



**112**

The title compound was prepared according to *General Procedure D* from 2-thiopheneacetic acid (28.4 mg, 0.2 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2NEt$ (52 μL, 0.30 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), 2.5 M butyl lithium solution in hexanes (0.1 mL, 11 mmol), imine **99** (70.8 mg, 0.20 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **112** as a white solid (45.0 mg, 46%). mp 154-160°C; $[\alpha]_D^{22}$ –11.0° (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (90:10 Hexane:IPA, flow rate 1.0 mL min$^{-1}$, 211 nm, rt), $t_R$ (2*R*,3*S*), 53.5 min, $t_R$ *(2S,3R)* 109.2 min, 21% ee; $\nu_{max}$ (neat) 3244.3 (NH), 1734.0 (C=O), 1448.5 (thiophene), 1159.2 (R-$SO_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.34 (3H, s, ArC*H*$_3$), 3.63 (3H, s, OC*H*$_3$), 4.04 (1H, d, *J* 7.0, C(2)*H*), 4.82 (1H, dd, *J* 9.1, 7.0, C(3)*H*), 6.19 (1H, d, *J* 9.1, N*H*), 6.82-6.85 (2H, m, C(3)ArC(2)*H*), 6.87 (1H, dd, *J* 5.0, 1.3, C(2)Ar*H*), 6.98-7.05 (2H, m, C(3)NHSO$_2$ArC(3)*H*), 7.07-7.09 (1H, m, C(2)Ar*H*), 7.12-7.22 (3H, m, Ar*H*), 7.31-7.42 (2H, m, C(3)NHSO$_2$AR(2)*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.6 (Ar*C*H$_3$), 52.6 (O*C*H$_3$), 52.9 (*C*(2)), 60.0 (*C*(3)), 121.8 (*C*Br), 124.0 (C(2)Ar*C*), 126.3 (C(2)Ar*C*), 127.0 (C(3)NHSO$_2$Ar*C*(2)), 127.5 (C(2)Ar*C*), 128.5 (C(3)Ar*C*(2)), 129.4 (C(3)NHSO$_2$Ar*C*(3)), 131.5 (C(3)Ar*C*(3)), 134.3 (C(2)Ar*C*(1)), 137.5 (C(3)NHSO$_2$Ar*C*(1), 137.7 (C(3)Ar*C*(1)), 143.3 (Ar*C*(4)CH$_3$), 172.1 (*C*(1)); *m/z* (NSI$^+$) 513 ([M+$NH_4$]$^+$, 100%); HRMS (NSI$^+$) $C_{21}H_{21}BrNO_4S_2^+$ ([M+H]$^+$), requires 494.0091; found 494.0090 (+0.2 ppm

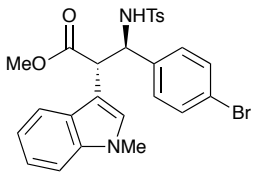
(2*S*,3*R*)-methyl 3-(4-bromophenyl)-3-(4-methylphenylsulfonamido)-2-(thiophen-3-yl)propanoate **113**




**113**

The title compound was prepared according to *General Procedure D* from 3-thiopheneacetic acid (28.4 mg, 0.2 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2NEt$ (52 μL, 0.30 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), 2.5 M butyl lithium solution in hexanes (0.1 mL, 11 mmol), imine **99** (70.8 mg, 0.20 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **113** as a white solid (49.8 mg, 50%); mp 154-160°C; $[\alpha]_D^{22}$ -11.0 (*c* 0.5, $CHCl_3$); $\nu_{max}$ (neat) 3244.3 (NH), 1734.0 (C=O), 1448.5 (thiophene), 1159.2 (R-$SO_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.35 (3H, s, ArC$H_3$), 3.61 (3H, s, OC$H_3$), 4.03 (1H, d, *J* 6.1, C(2)*H*), 4.80 (1H, dd, *J* 8.6, 6.4, C(3)*H*), 5.97 (1H, d, *J* 9.1, N*H*), 6.85-6.87 (2H, m, C(3)ArC(2)*H*), 6.87-6.89 (1H, m, C(2)ArC(4)*H*), 7.02-7.04 (2H, m, C(3)$NHSO_2$ArC(4)*H*), 7.10-7.11 (1H, m, C(2)ArC(2)*H*), 7.16-7.18 ( 1H, m, C(2)ArC(5)*H*), 7.21-7.23 (2H, m, C(3)ArC(3)*H*), 7.36-7.38 (2H, m, C(3)$NHSO_2$ArC(2)*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.6 (Ar*C*$H_3$), 52.6 (O*C*$H_3$), 53.2 (*C*(2)), 60.1 (*C*(3)), 121.6 (*C*Br), 124.0 (C(2)Ar*C*(2)), 126.2 (C(2)Ar*C*(5)), 127.0 (C(3)$NHSO_2$Ar*C*(2)), 127.5 (C(2)Ar*C*(3)), 128.6 (C(3)Ar*C*(2)), 129.3 (C(3)$NHSO_2$Ar*C*(3)), 131.4 (C(3)Ar*C*(3)), 134.3 (C(2)Ar*C*(1)), 137.4 (C(3)Ar*C*(1)), 137.5 (C(3)$NHSO_2$Ar*C*(1)), 143.2 (Ar*C*(4)$CH_3$), 172.2 (*C*(1)); *m/z* ($NSI^+$) 512 ($[M+NH_4]^+$, 65%) 517 (100%); HRMS ($NSI^+$) $C_{21}H_{21}BrNO_4S_2^+$ ($[M+H]^+$), requires 494.0087; found 494.0090 (-0.6 ppm).

(2*S*,3*R*)-methyl 3-(4-bromophenyl)-2-(1-methyl-1*H*-indol-3-yl)-3-(4-methylphenylsulfonamido)propanoate **114**

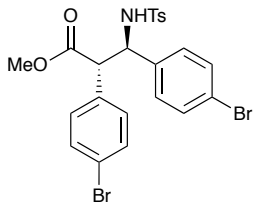



**114**

The title compound was prepared according to *General Procedure D* from 2-thiopheneacetic acid (28.4 mg, 0.2 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2NEt$ (52 μL, 0.30 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), 2.5 M butyl lithium solution in hexanes (0.1 mL, 11 mmol), imine **99** (70.8 mg, 0.20 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **114** as a brown solid (59.6 mg, 55%); mp 58-64°C; $[\alpha]_D^{22}$ –13.0 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 1 mL $min^{-1}$, 211 nm) $t_R$ (2*R*,3*S*) 40.6 min, $t_R$ (2*S*,3*R*) 44.5 min, 23%; $\nu_{max}$ (neat) 3365.8 (NH), 3273.2 (NH), 1558.5 (indole), 1506.4 (indole), 1338.6 (R-$SO_2$N), 1157.3 (R-$SO_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.32 (3H, s, ArC$H_3$), 3.59 (3H, s, OC$H_3$), 3.70 (3H, s, NC$H_3$), 4.30 (1H, d, *J* 4.89 (1H, dd, *J* 8.3, 4.8, C(2)*H*), 6.43 (1H, d *J* 8.3, N*H*), 6.81-6.91 (3H, m, $NHSO_2$ArC(3)*H*), 7.02 (1H, s, C(2)ArC(2)*H*), 7.09-7.19 (3H, m, Ar*H*), 7.20 -7.32 (4H, m, Ar*H*), 7.32-7.42 (2H, m, C(3)$NHSO_2$ArC(2)*H*), 7.46-7.49 (1H, m, Ar*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.6 (Ar*C*$H_3$), 32.9 (N*C*$H_3$), 48.5 (O*C*$H_3$), 52.4 (*C*(2)), 59.1 (*C*(3)), 107.5 ($C_{ipso}$), 109.6 (Ar*C*), 118.2 (Ar*C*), 119.7 (Ar*C*), 121.6 (*C*Br), 122.1 (Ar*C*), 126.5 ($C_{ipso}$), 126.6(Ar*C*), 128.0 (C(2)Ar*C*(2)), 128.4 (Ar*C*), 128.9 (C(2)$NHSO_2$Ar*C*(3)), 131.6 (C(2)$NHSO_2$Ar*C*(2)), 136.8 (C(2)Ar*C*(1)), 137.2 (C(3)$NHSO_2$Ar*C*(1)), 138.9 C(3)Ar*C*(1)), 142.7 (C(3)$NHSO_2$Ar*C*(4)), 173.0 (*C*(1)); *m/z* ($NSI^+$) 559 ($[M+NH_4]^+$, 100%); HRMS ($NSI^+$) $C_{26}H_{26}BrN_2O_4S^+$ ($[M+H]^+$), requires 541.0788; found 541.0791 (-0.6 ppm).

(2*S*,3*R*)-Methyl 2,3-bis(4-bromophenyl)-3-(4-methylphenylsulfonamido)propanoate

**115**

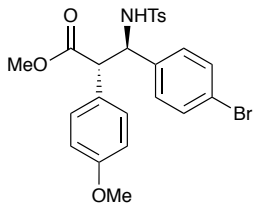



**115**

The title compound was prepared according to *General Procedure D* from 4-bromophenylacetic acid (43.0 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol),

2 portions of *i*-$Pr_2NEt$ (52 μL, 0.30 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), 2.5 M butyl lithium solution in hexanes (0.1 mL, 11 mmol), imine **99** (70.8 mg, 0.20 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **115** as a white solid (49.6 mg, 43%); mp 168-172°C; $[\alpha]_D^{22}$ –28.0 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 220 nm, 30 °C), $t_R$ major (2*S*,3*R*) 15.7 min, $t_R$ minor (2*R*,3*S*) 18.5 min, 98% ee; $\nu_{max}$ (neat) 3367.7 (NH), 3298.3 (NH), 1718.6 (C=O), 1708.9 (C=O), 1338.6 (R-$SO_2$N), 1155.4 (R-$SO_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.38 (3H, s, ArC*H*$_3$), 3.59 (3H, s, OC*H*$_3$), 3.90 (1H, d, *J* 6.3, C(2)*H*), 4.73 (1H, dd, *J* 9.1, 6.3, C(3)*H*), 6.09 (1H, d, *J* 9.1, N*H*), 6.94-6.96 (2H, m, C(3)ArC(2)*H*), 6.99-7.01 (2H, m, C(2)ArC(2)*H*), 7.02-7.05 (2H, m, Ar*H*), 7.24-7.26 (1H, m, Ar*H*), 7.27-7.29 (3H, m, Ar*H*), 7.31-7.33 (2H, m, C(3)NHS$O_2$ArC(2)*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.7 (Ar*C*$H_3$), 52.7 (O*C*$H_3$), 56.7 (C(2)), 60.5 (C(3)), 121.9 (C(3)Ar*C*(4)Br), 122.4 (C(2)Ar*C*(4)Br), 126.8 (C(3)NHS$O_2$Ar*C*(2)), 128.6 (C(3)Ar*C*(2)), 129.4 (C(2)Ar*C*(2)), 130.1 (C(3)NHS$O_2$Ar*C*(3)), 131.7 (C(3)Ar*C*(3)), 131.9 (C(2)Ar*C*(3)), 133.6 (C(2)Ar*C*(1)), 137.4 (C(3)NHS$O_2$Ar*C*(1)), 137.7 (C(3)Ar*C*(1)), 143.4 (Ar*C*(4)$CH_3$), 171.9 (C(1)); *m/z* (NSI$^+$) 582 ([M+NH4]$^+$, 35%), 589 (100%); HRMS (NSI$^+$) $C_{23}H_{22}Br_2NO_4S^+$ ([M+H]$^+$), requires 565.9630; found 565.931 (–0.1 ppm).

(2*S*,3*R*)-Methyl 3-(4-bromophenyl)-2-(4-methoxyphenyl)-3-(4-methylphenylsulfonamido)propanoate **116**



**116**

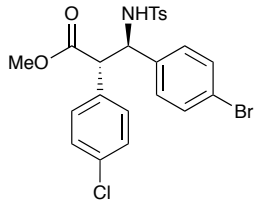
The title compound was prepared according to *General Procedure D* from *p*-methoxyphenylacetic acid (33.0 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2NEt$ (52 μL, 0.30 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), 2.5 M butyl lithium solution in hexanes (0.1 mL, 11 mmol), imine **99** (70.8 mg, 0.20

mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **116** as a white solid (43.2 mg, 42%); mp 168-172°C; $[\alpha]_D^{22}$ –27.6 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 220 nm, 30 °C), $t_R$ major (2*S*,3*R*) 24.1 min, $t_R$ minor (2*R*,3*S*) 27.1 min, 76% ee; $\nu_{max}$ (neat) 3253.9 (NH), 1734.0 (C=O), 1157.3 (R-$SO_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.35 (3H, s, ArC*H*$_3$), 3.60 (3H, s, C(1)(O)OC*H*$_3$), 3.76 (3H, s, ArOC*H*$_3$), 3.86 (1H, d, *J* 6.66, C(2)*H*), 4.73-4.77 (1H, dd, *J* 8.79, 6.49, C(3)*H*), 5.97-5.99 (1H, d, *J* 8.89, N*H*), 6.69 (2H, d, *J* 8.79, C(2)ArC(2)*H*), 6.89 (2H, d, *J* 8.62, C(3)ArC(2)*H*), 6.99-7.01 (2H, m, C(3)NHS$O_2$ArC(3)*H*), 7.04 (2H, d, *J* 8.81, C(2)ArC(3)*H*), 7.21 (2H, d, *J* 8.52, C(3)ArC(3)*H*), 7.32-7.34 (2H, m, C(3)NHS$O_2$ArC(2)*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.6 (Ar*C*$H_3$), 52.5 (C(1)(O)O*C*$H_3$), 55.3 (ArO*C*$H_3$), 56.6 (C(2)), 60.7 (C(3)), 114.2 (C(2)Ar*C*(2)), 121.6 (*C*Br), 126.5 (C(2)Ar*C*(1)), 127.0 (C(3)NHS$O_2$Ar*C*(2)), 128.7 (C(3)Ar*C*(2)), 129.3 (Ar*C*), 129.6 (Ar*C*), 131.5 (C(3)Ar*C*(3)), 137.6 (C(3)NHS$O_2$Ar*C*(1)), 137.9 (C(3)Ar*C*(1)), 143.0 (Ar*C*(4)$CH_3$), 159.4 (Ar*C*(4)$OCH_3$), 172.5 (C(1)); *m/z* (NSI$^+$) 535 ([M+$NH_4$]$^+$, 90%), 542 (100%); HRMS (NSI$^+$) $C_{24}H_{25}BrNO_5S^+$ ([M+H]$^+$), requires 518.0630; found 518.0631 (–0.3 ppm).

(2*S*,3*R*)-Methyl

3-(4-bromophenyl)-2-(4-chlorophenyl)-3-(4-methylphenylsulfonamido)propanoate

**117**

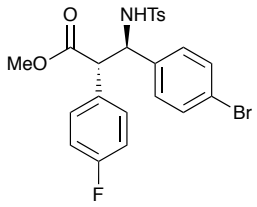



**117**

The title compound was prepared according to *General Procedure D* from 4-chlorophenylacetic acid (34.1mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2$NEt (52 μL, 0.30 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), 2.5 M butyl lithium solution in hexanes (0.1 mL, 11 mmol), imine **99** (70.8 mg, 0.20 mmol)

and purified by chromatography (80:20 Petrol:EtOAc) to give **117** as a white solid (71.3 mg, 68%); mp 120-124°C; $[\alpha]_D^{22}$ –27.2 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C), $t_R$ major (2*S*,3*R*) 15.6 min, $t_R$ minor (2*R*,3*S*) 17.7 min, 78% ee; $\nu_{max}$ (neat) 3304.1 (NH), 3257.8 (NH), 1735.9 (C=O), 1718.6 (C=O), 1153.4 (R-$SO_2$N), 1089.8 (C-Cl); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.37 (3H, s, C*H*$_3$), 3.60 (3H, s, C*H*$_3$OC(1)), 3.91 (1H, d, *J* 6.4, C(2)*H*), 4.74 (1H, dd, *J* 9.2, 6.4, C(3)*H*), 6.13 (1H, d, *J* 9.1, N*H*), 6.90-6.96 (2H, m, C(3)CC*H*), 6.99-7.08 (4H, m, Ar*H*), 7.09-7.15 (2H, m, C(2)CC*H*), 7.23-7.29 (2H, m, C*H*CBr), 7.30-7.36 (2H, m, $SO_2$CC*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.3 (*C*H$_3$), 52.4 (*C*H$_3$C(1)), 56.3 (*C*(2)), 60.2 (*C*(3)), 121.5 (*C*Br), 126.7 ($SO_2$CAr*C*), 128.4 (C(3)CAr*C*H), 128.8 (Ar*C*), 129.2 (C(2)C*C*H), 129.6 (Ar*C*), 131.5 (Ar*C*CBr), 132.7 (C(2)Ar*C*), 133.9 (Ar*C*Cl), 137.1 ($SO_2$*C*), 137.4 (C(3)Ar*C*), 143.0 (Ar*C*$CH_3$), 171.6 (C(1)(O)); *m/z* (NSI$^+$) 522 ([M+$NH_4$]$^+$, 50%), 546 (100%); HRMS (NSI$^+$) $C_{23}H_{22}BrClNO_4S^+$ ([M+H]$^+$), requires 522.0134; found 522.0136 (–0.4 ppm).

(2*S*,3*R*)-Methyl 3-(4-bromophenyl)-2-(4-fluorophenyl)-3-(4-methylphenylsulfonamido)propanoate **118**

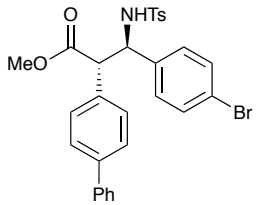



**118**

The title compound was prepared according to *General Procedure D* from 4-fluorophenylacetic acid (30.8 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2$NEt (52 μL, 0.30 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), 2.5 M butyl lithium solution in hexanes (0.1 mL, 11 mmol), imine **99** (70.8 mg, 0.20 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **118** as a white solid (56.5 mg, 56%); mp 138-144°C; $[\alpha]_D^{22}$ –22.2 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralcel OD-H (80:20 hexane:IPA, flow rate 0.5 mL $min^{-1}$, 211 nm, 30 °C), $t_R$ minor (2*R*,3*S*) 17.8 min, $t_R$ major (2*S*,3*R*) 22.4 min, 76% ee; $\nu_{max}$ (neat) 3273.2 (NH), 1718.6

(C=O), 1153.4 (R-$SO_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.35 (3H, s, ArC$H_3$), 3.61 (3H, s, OC$H_3$), 3.91 (1H, d, *J* 6.6, C(2)*H*), 4.75 (1H, dd, *J* 8.8, 6.8, C(3)*H*), 6.05 (1H, d, *J* 9.0, N*H*), 6.85 (2H, t, *J* 8.6, C(2)ArC(3)*H*), 6.90 (2H, d, *J* 8.4, C(3)ArC(2)*H*), 7.02 (2H, d, *J* 8.0, C(3)NHS$O_2$ArC(3)*H*), 7.10 (2H, dd, *J* 8.6, 5.3, C(2)ARC(2)*H*), 7.23 (2H, d, *J* 8.4, C(3)ArC(3)*H*), 7.34 (2H, d, *J* 8.2, NHS$O_2$ARC(2)*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.5 (Ar*C*$H_3$), 52.7 (O*C*$H_3$), 56.6 (*C*(2)), 60.7 (*C*(3)), 115.8 (d, *J* 21.3, C(2)Ar*C*(3)), 121.8 (*C*Br), 126.9 (C(3)NHS$O_2$Ar*C*(2)), 128.6 (C(3)Ar*C*(2)), 129.4 (C(3)NHS$O_2$Ar*C*(3)), 130.2 (d, *J* 7.5, C(2)Ar*C*(2)), 130.3 (d, *J* 3.8, C(2)Ar*C*(1)), 131.6 (C(3)Ar*C*(3)), 137.5 (C(3)Ar*C*1)), 137.7 (C(3)NHS$O_2$*C*(1)), 143.3 (Ar*C*(4)$CH_3$), 162.5 (d, *J* 246.3, Ar*C*F), 172.1 (*C*(1)); $^{19}$F{$^1$H} NMR (470 MHz, $CDCl_3$) $\delta_{F:}$ −114.3 (Ar*F*); *m/z* (NSI$^+$) 524 ([M+$NH_4$]$^+$, 100%); HRMS (NSI$^+$) $C_{23}H_{22}BrFNO_4S^+$ ([M+H]$^+$), requires 506.0430; found 506.0431 (–0.3 ppm).

(2*S*,3*R*)-Methyl 2-([1,1'-biphenyl]-4-yl)-3-(4-bromophenyl)-3-(4-methylphenylsulfonamido)propanoate **120**

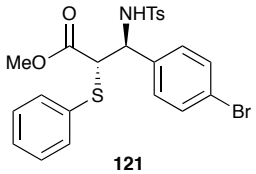


**120**

The title compound was prepared according to *General Procedure D* from biphenylacetic acid (42.4 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2$NEt (52 μL, 0.30 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), 2.5 M butyl lithium solution in hexanes (0.1 mL, 11 mmol), imine **99** (70.8 mg, 0.20 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **120** as a white solid (49.7 mg, 44%); mp 148-154°C; $[\alpha]_D^{22}$ −45.5 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (90:10 hexane:IPA, flow rate 1.0 mL min$^{-1}$, 220 nm, 30 °C), $t_R$ major (2*S*,3*R*) 39.4 min, $t_R$ minor (2*R*,3*S*) 50.3 min, 73% ee; $\nu_{max}$ (neat) 3306.0 (NH), 1718.6 (C=O), 1153.4 (R-$SO_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.20 (3H, s, ArC$H_3$), 3.63

(3H, s, OC*H*$_3$), 4.00 (1H, d, *J* 6.5, C(2)*H*), 4.84 (1H, dd, *J* 9.1, 6.5, C(3)*H*), 6.23 (1H, d, *J* 9.1, N*H*), 6.93-7.01 (4H, m, Ar*H*), 7.16-7.22 (2H, m, C(3)NHSO$_2$ArC(3)*H*), 7.22-7.26 (2H, m, C(3)ArC(3)*H*), 7.31-7.36 (3H, m, Ar*H*), 7.36-7.48 (4H, m, Ar*H*), 7.50-7.57 (2H, m, Ar*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.4 (Ar*C*H$_3$), 52.6 (O*C*H$_3$), 57.1 (*C*(2)), 60.7 (*C*(3)), 121.2 (*C*Br), 127.0 (NHSO$_2$Ar*C*(2)), 127.2 (Ar*C*), 127.4 (Ar*C*), 127.7 (Ar*C*), 128.7 (Ar*C*), 128.9 (Ar*C*), 129.0 (Ar*C*), 129.2 (NHSO$_2$Ar*C*(3)), 131.5 (C(3)Ar*C*(3)), 133.5 (*C*$_{ipso}$), 137.6 (C(3)NHSO$_2$Ar*C*(1)), 138.0 (C(3)Ar*C*(1)), 140.2 (C(2)Ar*C*(1)), 140.8 (*C*$_{ipso}$), 143.1 (Ar*C*(4)CH$_3$), 172.3 (*C*(1)) ; *m/z* (NSI$^+$) 581 ([M+NH$_4$]$^+$, 70%), 588 (100%); HRMS (NSI$^+$) $C_{29}H_{27}BrNO_4S^+$ ([M+H]$^+$), requires 564.0838; found 564.0839 (–0.1 ppm).

(2*S*,3*S*)-Methyl 3-(4-bromophenyl)-3-(4-methylphenylsulfonamido)-2-(phenylthio)propanoate **121**



**121**

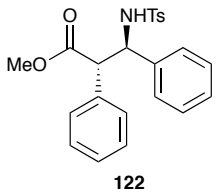
The title compound was prepared according to *General Procedure D* from (phenylthio)acetic acid (33.6 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-Pr$_2$NEt (52 μL, 0.30 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), 2.5 M butyl lithium solution in hexanes (0.1 mL, 11 mmol), imine **99** (70.8 mg, 0.20 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **121** as a white solid and a mixture of diastereoisomers (73.8 mg, 71%). Careful purification allowed an analytical sample of each diastereoisomer to be obtained for characterisation

Data for the *anti* diastereoisomer: isolated white solid (8.3 mg, 14%); mp 120-124°C; $[\alpha]_D^{22}$ +6.0° (*c* 0.2, $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 1.0 mL min$^{-1}$, 220 nm, 30 °C), $t_R$ major (2*S*,3*S*) 20.4 min, $t_R$ minor (2*R*,3*R*) 24.7 min, 61% ee; $\nu_{max}$ (neat) 3288.6 (NH), 1710.9 (C=O), 1338.6 (R-SO$_2$N), 1159.2 (R-SO$_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.37 (3H, s, ArC*H*$_3$), 3.52 (3H, s, OC*H*$_3$), 3.85 (1H, d, *J* 5.3, C(2)*H*), 4.82 (1H, dd, *J* 8.8, 5.3, C(3)*H*), 6.18 ( 1H,

d, *J* 8.8, N*H*), 6.90 (2H, d, *J* 8.4, C(3)ArC(2)*H*), 7.10-7.15 (2H, m, C(3)NHSO$_2$ArC(3)*H*), 7.25-7.31 (7H, m, Ar*H*), 7.53-7.55 (2H, m, C(3)NHSO$_2$ArC(2)*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.6 (Ar*C*H$_3$), 52.7 (O*C*H$_3$), 56.8 (*C*(2)), 58.7 (*C*(3)), 122.2 (*C*Br), 127.3 (C(3)NHSO$_2$Ar*C*(3)), 128.6 (C(3)Ar*C*(2)), 128.8 (Ar*C*), 129.4 (C(3)NHSO$_2$Ar*C*(2)), 129.5 (Ar*C*), 131.7 (C(3)Ar*C*(3)), 132.8, SAr*C*(1)), 133.3 (Ar*C*), 136.8 (C(3)Ar*C*(1), 137.6 (SO$_2$Ar*C*(1)), 143.5 (Ar*C*(4)CH$_3$), 170.9 (*C*(1)); *m/z* (NSI$^+$) 537 ([M+NH$_4$]$^+$, 75%), 544 (100%); HRMS (NSI$^+$) $C_{23}H_{22}BrNO_4S_2Na^+$ ([M+Na]$^+$), requires 542.0060; found 542.0066 (–1.1 ppm).

Selected data for the *syn* diastereoisomer: isolated as a colourless oil (6.2mg, 8%), $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.41 (3H, s, ArC*H*$_3$), 3.50 (3H, s, OC*H*$_3$), 3.80 (1H, d, *J* 9.1, C(2)*H*), 4.55-4.58 (1H, m, C(3)*H*), 5.70-5.75 (1H, m, N*H*), 6.97-7.00 (2H, m, C(3)ArC(2)*H*), 7.13-7.16 (2H, m, C(3)NHSO$_2$ArC(3)*H*), 7.22-7.24 (2H, m, C(3)ArC(3)*H*), 7.32-7.43 (5H, m, Ar*H*), 7.43-7.46 (2H, m, C(3)NHSO$_2$ArC(2)*H*$^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.7 (Ar*C*H$_3$), 52.6 (O*C*H$_3$), 56.9 (*C*(2)), 57.3 (*C*(3)), 122.5 (*C*Br), 127.4 (C(3)NHSO$_2$AR*C*(2)), 129.2 (Ar*C*), 129.5 (C(3)NHSO$_2$Ar*C*(3)), 129.5 (Ar*C*), 129.9 (C(3)Ar*C*(2)), 130.8 (SAr*C*(1)), 131.4 (C(3)Ar*C*(3)), 134.0 (Ar*C*), 135.7 (C(3)Ar*C*(1)), 136.9 (SO$_2$Ar*C*(1)), 143.7 (Ar*C*(4)CH$_3$),169.1 (*C*(1)); Chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 1.0 mL min$^{-1}$, 220 nm, 30°C), $t_R$ major: 30.6 min, $t_R$ minor: 38.4 min, 57% ee.

(2*R*,3*S*)-Methyl 3-(4-methylphenylsulfonamido)-2,3-diphenylpropanoate **122**

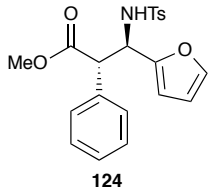



**122**

The title compound was prepared according to *General Procedure D* from phenylacetic acid (136.0 mg, 1.0 mmol), tosyl chloride (286.5 mg, 1.50 mmol), 2 portions of *i*-Pr$_2$NEt (260 μL, 1.50 mmol), **26** (15.5 mg, 5 mol%, 0.05 mmol), 2.5 M

butyl lithium solution in hexanes (0.5 mL, 55 mmol), imine **215** (51.9 mg, 0.2 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **122** as a white solid (219.3 mg, 54%); mp 162-165°C; $[\alpha]_D^{22}$ −25.6° (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (90:10 hexane:IPA, flow rate 0.5 mL $min^{-1}$, 211 nm, 30 °C), $t_R$ minor (2*S*,3*R*) 61.7min, $t_R$ major (2*R*,3*S*) 82.0 min, 80% ee; $\nu_{max}$ (neat) 3282.8 (NH), 1714.7 (C=O), 1159.2 (R-$SO_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.30 (3H, s, ArC$H_3$), 3.59 (3H, s, OC$H_3$), 3.97 (1H, d, *J* 6.5, C(2)*H*), 4.85 (1H, dd, *J* 9.1, 6.5, C(3)*H*), 6.01 (1H, d, *J* 9.1, N*H*), 6.98 (2H, d, *J* 8.0, C(3)NHS$O_2$ArC(3)*H*), 7.00-7.03 (2H, m, Ar*H*), 7.10 (3H, m, Ar*H*), 7.16-7.20 (5H, m, Ar*H*), 7.34-7.36 (2H, m, C(3)NHS$O_2$ArC(2)*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.5 (Ar*C*$H_3$), 52.5 (O*C*$H_3$), 57.8 (*C*(2)), 61.2 (*C*(3)), 126.8 (Ar*C*), 127.0 (C(3)NHS$O_2$Ar*C*(2)), 127.6 (Ar*C*), 127.9 (Ar*C*), 128.4 (Ar*C*), 128.6 (Ar*C*), 128.8 (Ar*C*), 129.2 (C(3)NHS$O_2$Ar*C*(3)), 134.9 (C(2)Ar*C*(1)), 138.8 (C(3)NHS$O_2$*C*(1)), 142.8 (Ar*C*(4)$CH_3$), 151.1 (C(3)Ar*C*(1)), 172.4 (*C*(1)); *m/z* ($NSI^+$) 427 ($[M+NH_4]^+$, 100%); HRMS ($NSI^+$) $C_{23}H_{24}NO_4S^+$ ($[M+H]^+$), requires 410.1422; found 410.1421 (+0.4 ppm). This was recrystallised from $CH_2Cl_2$/Petrol to give **122** as a white solid (105.6 mg, 26%); mp 168-172 ˚C; $[\alpha]_D^{22}$ −30.8° (*c* 0.5 in $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (90:10 hexane:IPA, flow rate 0.5 mL $min^{-1}$, 211 nm, 30 °C), $t_R$ minor (2*S*,3*R*) 61.7min, $t_R$ major (2*R*,3*S*) 82.0 min, 93% ee.

(2*S*,3*R*)-Methyl 3-(furan-2-yl)-3-(4-methylphenylsulfonamido)-2-phenylpropanoate **124**

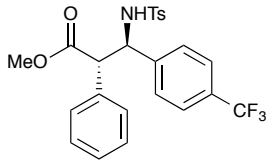



**124**

The title compound was prepared according to *General Procedure D* from phenylacetic acid (27.2 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2$NEt (52 μL, 0.30 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), 2.5 M butyl lithium solution in hexanes (0.1 mL, 11 mmol), imine **252** (53.6 mg, 0.20 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **124** as a white

solid (43.7 mg, 55%); mp 154-160°C; $[\alpha]_D^{22}$ –4.6 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralcel OJ-H (90:10 hexane:IPA, flow rate 0.5 mL $min^{-1}$, 211 nm, 30 °C), $t_R$ major (2*S*,3*R*) 45.3 min, $t_R$ minor (2*R*,3*S*) 53.9 min, 69% ee; $\nu_{max}$ (neat) 3263.6 (NH), 1726.3 (C=O), 1163.1 (R-$SO_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.43 (3H, s, ArC$H_3$), 3.65 (3H, s, OC$H_3$), 4.12 (1H, d, *J* 7.1, C(2)*H*), 4.97 (1H, dd, *J* 9.7, 7.1, C(3)*H*), 5.66 (1H, d, *J* 9.8, N*H*), 5.84 (1H, d, *J* 3.3, C(3)ArC(3)*H*), 6.04 (1H, dd, *J* 3.2, 1.8, C(3)ArC(4)*H*), 7.09 (2H, d, *J* 8.0, $NHSO_2$ArC(3)*H*), 7.13 (3H, dd, *J* 9.3, 1.2, Ar*H*), 7.20 (3H dd, *J* 4.8,2.4, Ar*H*), 7.46 (2H, d, *J* 8.2, $SO_2$ArC(2)*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.6 (Ar*C*$H_3$), 52.5 (O*C*$H_3$), 55.0 (*C*(2)), 55.4 (*C*(3)), 108.4 (Ar*C*), 110.4 (Ar*C*), 127.0 (Ar*C*), 128.0 (Ar*C*), 128.6 (C(3)$NHSO_2$Ar*C*(3)), 128.7 (C(2)Ar*C*(1)), 129.4 (C(3)$NHSO_2$Ar*C*(1)), 134.4 (Ar*C*), 137.7 (C(3)$NHSO_2$Ar*C*(1)), 142.0 (C(3)$NHSO_2$Ar*C*(4)), 143.0 (Ar*C*(4)$CH_3$), 151.1 (C(3)Ar*C*(1)), 172.0 (*C*(1)); *m/z* ($NSI^+$) 229 (100%), 417 ($[M+NH_4]^+$, 55%); HRMS ($NSI^+$) $C_{21}H_{22}NO_5S^+$ ($[M+H]^+$), requires 400.1209; found 400.1213 (–1.0 ppm).

(2*S*,3*R*)-Methyl 3-(4-methylphenylsulfonamido)-2-phenyl-3-(4-(trifluoromethyl)phenyl)propanoate **125**

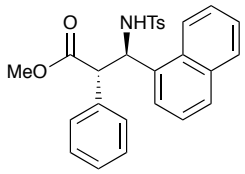



**125**

The title compound was prepared according to *General Procedure D* from phenylacetic acid (27.2 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2$NEt (52 μL, 0.30 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), 2.5 M butyl lithium solution in hexanes (0.1 mL, 11 mmol), imine **251** (65.5 mg, 0.20 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **125** as a white solid (46.4 mg, 49%); mp 118-124°C; $[\alpha]_D^{22}$ –17.6 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C), $t_R$ minor (2*R*,3*S*) 15.9 min, $t_R$ major (2*S*,3*R*) 20.9 min, 47% ee; $\nu_{max}$ (neat) 3236.6 (NH), 1741.7 (C=O), 1323.2 (R-$SO_2$N), 1161.2 (R-$SO_2$N), 1116.8 ($CF_3$); $^1$H NMR

(400 MHz, $CDCl_3$) $\delta_H$: 2.28 (3H, s, ArC$H_3$), 3.64 (3H,s, OC$H_3$), 3.96 (1H, d, *J* 7.3, C(2)*H*), 4.94 (1H, dd, *J* 9.1, 7.3, (C(3)*H*), 6.34 (1H, d, *J* 9.1, N*H*), 6.95 (2H, d *J* 8.3, C(3)NHSO$_2$ArC(3)*H*), 7.07-7.10 (2H, m, Ar*H*), 7.16-7.19 (5H, m, Ar*H*), 7.29-7.34 (4H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.4 (Ar*C*H$_3$), 52.7 (O*C*H$_3$), 57.6 (*C*(2)), 60.8 (*C*(3)), 124.0 (q, *J* 271.3, $CF_3$), 125.2 (q, *J* 5, C(3)Ar*C*(3)), 126.9 (Ar*C*), 127.6 (Ar*C*), 128.2 (Ar*C*), 128.6 (Ar*C*), 128.9 (Ar*C*), 129.3 (Ar*C*), 129.7 (q, *J* 36.6, C(3)Ar*C*(4)$CF_3$), 134.3 (C(2)Ar*C*(1)), 137.4 (C(3)NHSO$_2$Ar*C*(1)), 142.4 (C(3)Ar*C*(1)), 143.2 (C(3)NHSO$_2$Ar*C*(4)$CH_3$), 172.2 (*C*(1)); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) $\delta_{F:}$ −63.2 (C*F*$_3$); *m/z* (NSI$^+$) 495 ([M+$NH_4$]$^+$, 100%); HRMS (NSI$^+$) $C_{24}H_{23}F_3NO_4S^+$ ([M+H]$^+$), requires 478.1289; found 478.1294 (−1.1 ppm).

(2*S*,3*R*)-Methyl 3-(4-methylphenylsulfonamido)-3-(naphthalen-1-yl)-2-phenylpropanoate **126**

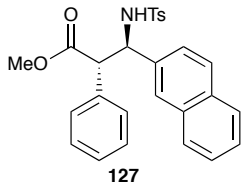



**126**

The title compound was prepared according to *General Procedure D* from phenylacetic acid (27.2 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-Pr$_2$NEt (52 μL, 0.30 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), 2.5 M butyl lithium solution in hexanes (0.1 mL, 11 mmol), imine **253** (61.9 mg, 0.20 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **126** as a white solid (57.6 mg, 63%); mp 122-128°C; $[\alpha]_D^{22}$ −30.4° (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralcel OD-H (95:5 hexane:IPA, flow rate 0.4 mL min$^{-1}$, 211 nm, 30 °C), $t_R$ minor (2*R*,3*S*) 80.1 min, $t_R$ major (2*S*,3*R*) 101.2 min, 56% ee; $\nu_{max}$ (neat) 3286.6 (NH), 1720.5 (C=O), 1161.2 (R-SO$_2$N); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.21 (3H, s, ArC$H_3$), 3.53 (3H, s, OC$H_3$), 4.23 (1H, d, *J* 5.0, C(2)*H*), 5.62 (1H, dd, *J* 9.2, 5.0, C(3)*H*), 6.63 (1H, d, *J* 9.0, N*H*), 6.72-6.86 (2H, m, Ar*H*), 7.15-7.25 (6H, m, Ar*H*), 7.30-7.38 (3H, m, Ar*H*), 7.48 (1H, ddd, *J* 8.0, 6.8, 1.2, Ar*H*), 7.56 (1H, ddd, *J* 8.5, 6.8, 1.5, Ar*H*), 7.64 (1H, d, *J* 8.1, Ar*H*), 7.75-7.83 (1H, m, Ar*H*), 8.00 (1H, d, *J* 8.5,

Ar*H*); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.3 (Ar*C*$H_3$), 52.5 (O*C*$H_3$), 57.6 (*C*(2)), 61.3 (*C*(3)), 124.3 (Ar*C*), 126.2 (Ar*C*), 126.3 (Ar*C*), 126.6 (Ar*C*), 126.9 (Ar*C*), 127.6 (Ar*C*), 127.9 (Ar*C*), 128.0 (Ar*C*), 128.3 (Ar*C*), 128.7 (Ar*C*), 128.8 (Ar*C*), 129.1 (Ar*C*), 132.7 ($C_{ipso}$), 133.0 ($C_{ipso}$), 134.8 ($C_{ipso}$), 135.7 ($C_{ipso}$), 137.6 ($C_{ipso}$), 142.8 (Ar*C*(4)$CH_3$), 172.5 (*C*(1)); *m/z* ($NSI^+$) 477 ($[M+NH_4]^+$, 80%), 482 (100%); HRMS ($NSI^+$) $C_{27}H_{25}NO_4SNa^+$ ($[M+Na]^+$), requires 482.1387; found 482.1397 (–2.0 ppm).

(2*S*,3*R*)-Methyl 3-(4-methylphenylsulfonamido)-3-(naphthalen-2-yl)-2-phenylpropanoate **127**

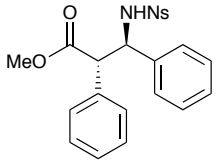



**127**

The title compound was prepared according to *General Procedure D* from phenylacetic acid (27.2 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2NEt$ (52 μL, 0.30 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), 2.5 M butyl lithium solution in hexanes (0.1 mL, 11 mmol), imine **253** (61.9 mg, 0.20 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **127** as a white solid (50.3 mg, 55%) as a white solid; mp 164-170°C; $[\alpha]_D^{22}$ –24.4° (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C), $t_R$ minor (2*R*,3*S*) 18.5 min, $t_R$ major (2*S*,3*R*) 21.2 min, 95% ee; $\nu_{max}$ (neat) 3257.8 (NH), 1722.4 (C=O), 1165.0 (R-$SO_2$N); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.08 (3H, s, ArC$H_3$), 3.61 (3H, s, OC$H_3$), 4.09 (1H, d, *J* 6.7, C(2)*H*), 5.03 (1H, dd, *J* 9.2, 6.7, C(3)*H*), 6.18 (1H, d, *J* 9.2, N*H*), 6.77-6.80 (2H, m, Ar*H*), 7.04-7.26 (5H, m, Ar*H*), 7.27-7.37 (4H, m, Ar*H*), 7.39-7.43 (2H, m, Ar*H*), 7.52-7.64 (2H, m, Ar*H*), 7.69-7.72 (1H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.3 (Ar*C*$H_3$), 52.5 (O*C*$H_3$), 57.7 (*C*(2)), 61.3 (*C*(3)), 124.3 (Ar*C*), 126.1 (Ar*C*), 126.2 (Ar*C*), 126.6 (Ar*C*), 126.9 (Ar*C*), 127.5 (Ar*C*), 127.9 (Ar*C*), 128.0 (Ar*C*), 128.3 (Ar*C*), 128.7 (Ar*C*), 128.8 (Ar*C*), 129.1 (Ar*C*), 132.7 ($C_{ipso}$), 132.9 ($C_{ipso}$), 134.8 ($C_{ipso}$), 135.6 ($C_{ipso}$), 137.6 ($C_{ipso}$), 142.8 (Ar*C*(4)$CH_3$), 172.5 (*C*(1)); *m/z* ($NSI^+$) 477 ($[M+NH_4]^+$,

80%), 482 (100%); HRMS (NSI$^+$) $C_{27}H_{25}NO_4SNa^+$ ([M+Na]$^+$), requires 482.1387; found 482.1397 (–2.0 ppm).

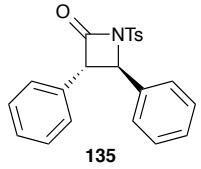
(2*S*,3*R*)-Methyl 3-(4-nitrophenylsulfonamido)-2,3-diphenylpropanoate **128**




**128**

The title compound was prepared according to *General Procedure D* from phenylacetic acid (27.2 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2NEt$ (52 μL, 0.30 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), 2.5 M butyl lithium solution in hexanes (0.1 mL, 11 mmol), imine **254** (58.1 mg, 0.20 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **128** as a white solid (47.4 mg, 54%); mp 158-162°C; $[\alpha]_D^{22}$ –20.8° (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralcel OD-H (90:10 hexane:IPA, flow rate 0.5 mL min$^{-1}$, 211 nm, 30 °C), $t_R$ minor (2*R*,3*S*) 63.7 min, $t_R$ major (2*S*,3*R*) 106.7 min, 75% ee; $\nu_{max}$ (neat) 3240.4 (NH), 1739.8 (C=O), 1390.0 ($NO_2$), 1323.2 ($RSO_2N$), 1161.2 ($RSO_2N$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 3.60 (s, 3H, OC*H*$_3$), 4.02 (1H, d, *J* 5.4, C(2)*H*), 4.86 (1H, dd, *J* 9.2, 5.4, C(3)*H*), 6.59 (1H, d, *J* 9.2, N*H*), 7.09-7.12 (3H, m, Ar*H*), 7.14-7.23 (7H, m, Ar*H*), 7.58 (2H, d, *J* 8.8, $NHSO_2$ArC(2)*H*), 7.98 (2H, d, *J* 8.8, $NHSO_2$ArC(3)*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 52.6 (O*C*H$_3$), 57.1 (*C*(2)), 61.7 (*C*(3)), 123.8 ($NHSO_2$Ar*C*(3)), 126.7 (Ar*C*), 128.0 (Ar*C*), 128.1 (Ar*C*), 128.2 (Ar*C*), 128.3 (Ar*C*), 128.7 (Ar*C*), 129.0 (NHSOAr*C*(2)), 134.8 ($NHSO_2$Ar*C*(1)), 138.5 ($C_{ipso}$), 146.5 ($C_{ipso}$), 149.4 (*C*$NO_2$), 172.6 (*C*(1)); *m/z* (NSI$^+$) 458 ([M+$NH_4$]$^+$, 100%); HRMS (NSI$^+$) $C_{22}H_{24}N_3O_6S^+$ ([M+$NH_4$]$^+$), requires 458.1382; found 458.1380 (+0.4 ppm).

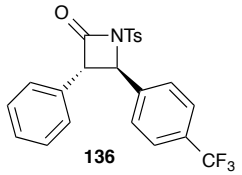
(3*S*,4*R*)-4,3-Diphenyl-1-tosylazetidin-2-one **135**




**135**

The title compound was prepared according to *General Procedure E* from imine **215** (338.0 mg, 1.0 mmol), **26** (15.5 mg, 5 mol%, 0.05 mmol), *i*-$Pr_2NEt$ (215 μL, 1.25 mmol), benzoic anhydride **134** (381.0 mg, 1.5 mmol) and purified by chromatography (90:10 Petrol:EtOAc) to give **135** as a white solid (228.7 mg, 60%); Chiral HPLC analysis, Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 254 nm, 30 °C), $t_R$ major (3*S*,4*R*) 14.8 min, $t_R$ minor (3*R*,4*S*) 19.6 min, 89% ee; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.45 (3H, s, C$H_3$), 4.27 (1H, d, *J* 3.4, C(3)*H*), 4.98 (1H, d, *J* 3.4, C(4)*H*), 7.06 (2H, m, *Ph*), 7.26-7.34 (10H, m, *Ph*), 7.71 (2H, m, *Ph*). All NMR data was in accordance to the literature.[7] This was recrystallised from $CH_2Cl_2$/Petrol to give the **135** as a white solid (129.5 mg, 34%); mp 91-98 ˚C {lit. mp 123-124 ˚C}; $[\alpha]_D^{22}$ +35.6° (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 254 nm, 30 °C), $t_R$ major (3*S*,4*R*) 14.8 min, $t_R$ minor (3*R*,4*S*) 19.6 min, >99% ee.

(3*S*,4*R*)-3-Phenyl-1-tosyl-4-(4-(trifluoromethyl)phenyl)azetidin-2-one **136**

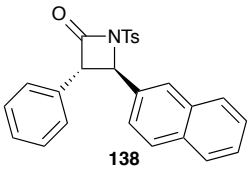



**136**

The title compound was prepared according to *General Procedure E* from imine **251** (65.5 mg, 0.20 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), *i*-$Pr_2Net$ (43.0 μL, 0.25 mmol), benzoic anhydride **134** (76.2 mg, 0.30 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **136** as a white gum (41.9 mg, 47%); $[\alpha]_D^{22}$ +17.2° (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralcel OD-H (95:5 hexane:IPA, flow rate 0.25 mL $min^{-1}$, 211 nm, 30 °C), $t_R$ minor (3*R*,4*S*) 82.7 min, $t_R$ major (3*S*,4*R*) 90.2 min, 68%

ee; $\nu_{max}$ (neat) 1796 (C=O), 1323 (R-$SO_2$N), 1167 (R-$SO_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.47 (3H, s, $NSO_2ArCH_3$), 4.25 (1H, d, *J* 3.4, C(3)*H*), 5.00 (1H, d, *J* 3.4, C(4)*H*), 6.98-7.08 (2H, m, Ar*H*), 7.29-7.37 (5H, m, Ar*H*), 7.40-7.43 (2H, m, Ar*H*), 7.55-7.63 (2H, m, Ar*H*), 7.73-7.76 (2H, m, Ar*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.9 ($NSO_2ArCH_3$), 64.6 (*C*(3)), 65.0 (*C*(4)), 123.9 (q, *J* 217, *C*$F_3$), 126.2 (q, *J* 3, C(4)Ar*C*(3)), 126.9 (Ar*C*), 127.4 (Ar*C*), 127.7 (Ar*C*), 128.8 (Ar*C*), 129.5 (Ar*C*), 130.2 (Ar*C*), 131.5 (q, *J* 26, C(4)Ar*C*(4)$CF_3$), 132.5 (*C*$_{ipso}$), 135.5 (*C*$_{ipso}$), 140.3 (C(4)Ar*C*(1)), 145.9 ($NSO_2ArC(4)CH_3$), 165.1 (*C*(1)); $^{19}$F{$^1$H} (282 MHz, $CDCl_3$) $\delta_F$: 62.7 ($CF_3$); *m/z* (NSI$^+$) 463 ([M+$NH_4$]$^+$, 100%); HRMS (NSI$^+$) $C_{23}H_{19}BF_3NO_3S_1^+$ ([M+H]$^+$), requires 446.1031; found 446.1032 (−0.3 ppm).

(3*S*,4*R*)-4-(Naphthalene-2-yl)-3-phenyl-1-tosylazetidin-2-one **138**



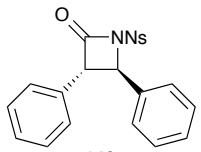

**138**

The title compound was prepared according to *General Procedure E* from imine **250** (61.9 mg, 0.20 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), *i*-$Pr_2$NEt (43.0 μL, 0.25 mmol), benzoic anhydride **134** (76.2 mg, 0.30 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **138** as a white solid (47.8 mg, 56%); mp 38-44 °C; $[\alpha]_D^{22}$ −8.8° (*c* 0.25, $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 1.0 mL min$^{-1}$, 211 nm, 30 °C), $t_R$ major (3*S*,4*R*) 19.3 min, $t_R$ minor (3*R*,4*S*) 41.5 min, 92% ee; $\nu_{max}$ (neat) 2920, 1792 (C=O), 1456 (C-N), 1364 (R-$SO_2$N), 1166 (R-$SO_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.41 (3H, s, $NSO_2ArCH_3$), 4.36 (1H, d, *J* 3.0, C(3)*H*), 5.16 (1H, d, *J* 3.0, C(4)*H*), 7.11-7.14 (2H, m, Ar*H*), 7.16-7.24 (2H, m, Ar*H*), 7.31-7.35 (3H, m, Ar*H*), 7.48-7.57 (2H, m, Ar*H*), 7.69- 7.72 (3H, m, Ar*H*), 7.72-7.76 (2H, m, Ar*H*), 7.80 (1H, d, *J* 8.5, Ar*H*), 7.82-7.89 (1H, m, Ar*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.8 ($NSO_2ArCH_3$), 64.5 (*C*(3)), 66.2 (*C*(4)), 123.3 (Ar*C*), 126.7 (Ar*C*), 126.9 (Ar*C*), 127.0 (Ar*C*), 127.4 (Ar*C*), 127.8 (Ar*C*), 127.9

(Ar*C*), 128.2 (Ar*C*), 128.6 (Ar*C*), 129.2 (Ar*C*), 129.4 (Ar*C*), 130.0 (Ar*C*), 133.0 (*C*$_{ipso}$), 133.1 (*C*$_{ipso}$), 133.3 (*C*$_{ipso}$), 133.6 (*C*$_{ipso}$), 135.8 (C(3)Ar*C*(1)), 145.5 ($NSO_2$Ar*C*(4)$CH_3$), 165.5 (*C*(2)); *m/z* ($NSI^+$) 445 ($[M+NH_4]^+$, 100%); HRMS ($NSI^+$) $C_{26}H_{25}N_2O_3S^+$ ($[M+NH_4]^+$), requires 445.1578; found 445.1580 (-0.5 ppm).

Selected data for the *syn* diastereoisomer: $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.43 (3H, s, $NSO_2$ArC*H*$_3$), 5.04 (1H, *J* 6.8, C*H*), 5.65 (1H, *J* 6.9, C*H*); Chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 1.0 mL min$^{-1}$, 211 nm, 30 °C), $t_R$ major: 18.1 min, $t_R$ minor: 25.6 min, 54% ee.

(3*S*,4*R*)-1-((4-Nitrophenyl)sulfonyl)-3,4-diphenylazetidin-2-one **140**

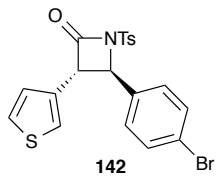



**140**

The title compound was prepared according to *General Procedure E* from imine **251** (58.1 mg, 0.20 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), *i*-$Pr_2$NEt (43.0 μL, 0.25 mmol), benzoic anhydride **134** (72.6 mg, 0.30 mmol) and purified by chromatography (90:10 Petrol:EtOAc) to give **140** as a white solid (41.6 mg, 51%). mp 108-114 ˚C; $[\alpha]_D^{22}$ –2.1° (*c* 0.9, $CHCl_3$); Chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 1.0 mL min$^{-1}$, 211 nm, 30 °C), $t_R$ minor (3*R*,4*S*) 28.3 min, $t_R$ major (3*S*,4*R*) 32.6 min, 85% ee; $\nu_{max}$ (KBr) 1797 (C=O), 1529 ($NO_2$), 1379 (C-N), 1176 (R-$SO_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 4.42 (1H, d, *J* 3.45, C(3)*H*), 5.12 (1H, d, *J* 3.43, C(4)*H*), 7.17-7.20 (2H, m, Ar*H*), 7.24-7.25 (1H, m, Ar*H*), 7.32-7.40 (7H, m, Ar*H*), 7.92-7.97 (2H, m, $NSO_2$ArC(2)*H*), 8.27-8.29 (2H, m, $NSO_2$ArC(3)*H*); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta_C$: 64.2 (*C*(3)), 66.3 (*C*(4)), 124.3 ($NSO_2$Ar*C*(3)), 126.8 (Ar*C*), 127.0 (Ar*C*), 128.6 (Ar*C*), 128.8 ($NSO_2$Ar*C*(2)), 129.1 (Ar*C*), 129.3 (Ar*C*), 129.6 (Ar*C*), 132.2 (C(4)Ar*C*(1)), 135.0 (C(3)Ar*C*(1)), 144.1 ($NSO_2$Ar*C*(1)),

150.7 ($NSO_2ArC$(4)), 164.8 (*C*(2)); *m/z* (APCI$^+$) 409 ([M+H]$^+$,100%); HRMS (APCI+) $C_{21}H_{17}N_2O_5S^+$ ([M+H]$^+$), requires 409.0851; found 409.0853(−0.4 ppm).

(3*S*,4*R*)-4-(4-bromophenyl)-3-(thiophen-3-yl)-1-tosylazetidin-2-one **142**

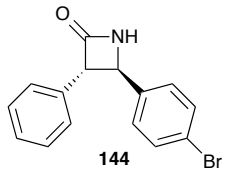


**142**

The title compound was prepared according to *General Procedure E* from imine **99** (70.8 mg, 0.2 mmol), **26** (3.1 mg, 5 mol%, 0.01 mmol), *i*-$Pr_2NEt$ (43.0 μL, 0.25 mmol), anhydride **134** (79.9 mg, 0.3 mmol) and purified by chromatography (80:20 Petrol:EtOAc) to give **142** as a white solid (43.5 mg, 47%); mp 104-106 °C; $[\alpha]_D^{22}$ +20.0° (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.0 mL min$^{-1}$, 220nM, 30°C), $t_R$ minor (3*R*,4*S*) 26.6 min, $t_R$ major (3*S*,4*R*) 34.1 min, 82% ee; $\nu_{max}$ (neat) 3109 (thiophene CH), 1792 (C=O), 1487 (C-N), 1373 (R-$SO_2$N), 1173 (R-$SO_2$N); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.47 (3H, s, $NSO_2ArCH_3$), 4.29 (1H, d, *J* 3.3, C(3)*H*), 4.87 (1H, d, *J* 3.3, C(4)*H*), 6.76 (1H, dd, *J* 1.3, 5.0, C(3)Ar*H*), 7.08 (1H, dt, *J* 0.9, 1.8, C(3)Ar*H*), 7.16-7.18 (2H, m, Ar*H*), 7.31-7.34 (3H, m, Ar*H*), 7.46-7.48 (2H, m, Ar*H*), 7.72-7.74 (2H, m, Ar*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.9 ($NSO_2ArCH_3$), 60.1 (*C*(3)), 64.9 (*C*(4)), 123.4 (C(3)Ar*C*), 125.8 (C(3)Ar*C*), 127.6 (Ar*C*), 127.7 (Ar*C*), 128.2 (Ar*C*), 130.1 (Ar*C*), 132.1 ($C_{ipso}$), 135.2 ($C_{ipso}$), 135.5 ($C_{ipso}$), 145.8 ($NSO_2ArC$(4)$CH_3$), 164.9 (*C*(2)), 185.4 ($C_{ipso}$); *m/z* (NSI$^+$) 579 ([M+$NH_4$]$^+$, 85%), 481 ([M+$NH_4$]$^+$, 100%); HRMS (NSI$^+$) $C_{20}H_{17}BrNO_3S_2^+$ ([M+$NH_4$]$^+$), requires 461.9830; found 461.9828 (+0.5 ppm).

### 6.2.7 Detosylation reaction

(3*S*,4*R*)-4-(4-Bromophenyl)-3-phenylazetidin-2-one **144**




**144**

Using a modified version of the procedure by Lectka *et al.*[8] *N*-tosylazetidinone **100** (54.1 mg, 0.12 mmol, 1 equiv.) was stirred in THF (1mL) at room temperature and $SmI_2$ (7.80 mL, 0.72 mmol, 6 equiv.) was added dropwise until the colour remained consistent. The reaction mixture was stirred for 5 min, quenched with $NaHCO_3$ (5 mL), extracted (3 × EtOAc), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as a yellow oil. Following purification by column chromatography (60:40 Petrol:EtOAc) **144** was isolated as a colourless oil (14.6 mg, 48%). $[\alpha]_D^{22}$ –55.6° (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralcel OD-H (80:20 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211nm, 25°C), $t_R$ major (3*S*,4*R*) 29.2 min, $t_R$ minor (3*R*,4*S*) 38.9 min, 90% ee; $\nu_{max}$ (neat) 3263 (NH), 1751 (C=O); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 4.17 (1H, d, *J* 2.40, C(3)*H*), 4.65 (1H, d, *J* 2.40, C(4)*H*), 6.34 (1H, br s, N*H*), 7.28-7.32 (4H, m, Ar*H*), 7.34-7.39 (2H, m, Ar*H*), 7.53-7.55 (2H, m, Ar*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 59.8 (*C*(3)), 66.4 (*C*(4)), 122.5 (*C*Br), 127.4 (Ar*C*), 127.5 (Ar*C*), 128.1 (Ar*C*), 129.2 (Ar*C*), 132.3 (Ar*C*), 134.5 ($C_{ipso}$), 138.7 ($C_{ipso}$), 168.8 (*C*(2)); *m/z* ($NSI^+$) 324 (100%), 319 ($[M+NH_4]^+$, 85%); HRMS (NSI+) $C_{15}H_{13}BrNO^+$ ($[M+H]^+$), requires 302.0178; found 302.0175 (+1.0 ppm).

### 6.2.8 Control Experiments

#### 6.2.8.1 Control Experiment (a)

*β*-lactam **139** was prepared according to *General Procedure C* from phenyl acetic acid (27.2 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*-$Pr_2NEt$ (52 μL, 0.30 mmol), **26** (10 mg, 20 mol%, 0.04 mmol) and imine **250** (70.8 mg, 0.20 mmol). The reaction was monitored over time using $^1$H NMR for changes in

the diastereomeric ratio. The results are shown in table S1 and from this it was concluded that *syn* product is initially formed in a small quantity however under the reaction conditions it is epimerised to the *anti* product to give the observed ratio of products.

| time / mins | dr (*anti*:*syn*) | conversion |
|---|---|---|
| 15 | 86:14 | 18 |
| 60 | 86:14 | 60 |
| 120 | 86:14 | 72 |
| 300 | >95:5 | 80 |

**Table S1**

### 6.2.8.2 Control Experiment (b)

A sample of β-lactam **139** (3.3 mg, 0.007 mmol) with of a known dr (*anti:syn* 21:79) and ees (*anti* 90%, *syn* 52%) was dissolved in dichloromethane (1 mL) and treated with *i*-$Pr_2Net$ (100 μL, 0.6 mmol) and **26** (3.1 mg, 0.01 mmol). The reaction was stirred at room temperature for 3 h, quenched with 1 M HCl, extracted (3 × $CH_2Cl_2$), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product (dr >95:5) with identical spectroscopic data as previously reported; Chiral HPLC analysis, ChiralPak AD-H (80:20 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C), $t_R$ minor (3*S*,4*R*) 19.3 min, $t_R$ major (3*R*,4*S*) 41.5 min, 32% ee.

Obtaining (*ent*)-*anti*-**139** (>95:5 dr, 32% ee) is consistent with the minor *syn*-diastereoisomer having preferentially the (3*S*,4*S*)-configuration and *in situ* epimerization generating *ent*-**139** preferentially.

## 6.3 Experimental for Chapter 3

### 6.3.1 General Experimental Procedures

#### 6.3.1.1 General Procedure F: Potassium Fluoride Mediated Hydrophosphonation of Cinnamaldehydes

Using a modified version of the procedure described by Texier-Boullet and Foucaud[9] the requisite aldehyde (1.0 equiv.) and desired phosphite (2.0 equiv.) were added to solid potassium fluoride (5.0 equiv.) and stirred vigorously at rt for 16 h before diluting with $CH_2Cl_2$ and stirring vigorously at rt for a further 2 h. The suspension was filtered and the filtrate concentrated *in vacuo* to give the crude product.

#### 6.3.1.2 General Procedure G: Parikh–Doering Oxidation

Following the procedure described by Evans *et al.*,[10] to a solution of the requisite allylic alcohol (1.0 equiv.) in $CH_2Cl_2$ at −10 °C was added a saturated solution of $SO_3$.pyridine (3.0 equiv.) in DMSO and *i*-$Pr_2NEt$ (3.0 equiv.) and the reaction stirred at −10 °C until complete by tlc (warming to rt if necessary). Upon completion the reaction was diluted with $Et_2O$ and washed consecutively with $H_2O$, saturated aqueous $NaHCO_3$, saturated aqueous $CuSO_4$ and brine. The ethereal solution was dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product.

#### 6.3.1.3 General Procedure H: Asymmetric Intermolecular Michael Addition-Lactonisation Followed by In Situ Methanolysis

To a solution of acetic acid (1.0 equiv.) in $CH_2Cl_2$ (0.1M) was added *i*-$Pr_2NEt$ (1.5 equiv.) and pivaloyl chloride (1.5 equiv.) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min. after which the ice bath was replaced with a dry ice/acetone bath and the reaction cooled to −78 °C and (2*S*,3*R*)-HBTM-2.1 (1 mol%), the desired phosphonate acceptor (1.5 equiv.) as a solution in $CH_2Cl_2$ (0.1M) and *i*-$Pr_2NEt$ (2.5 equiv.) were added and the reaction stirred at −78 °C for 24 h. MeOH (0.2M) was added and the reaction stirred at −78 °C warming to room temperature for a further 24 h. 1M HCl was added to quench the reaction. The organic phase was separated and the aqueous phase extracted with $CH_2Cl_2$ (2 ×). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude reaction mixture which was purified by column chromatography.

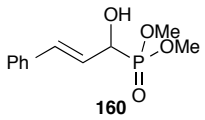
#### 6.3.1.4 General Procedure I: Selective Reduction Followed By Lactonisation

To a solution of the requisite diester (1.0 equiv.) in THF (3 mL) at 0 °C was added DIBAL-H (2.2 equiv.) and the reaction stirred for 90 min. 1 M HCl (5 mL) was added and the biphasic mixture stirred vigorously for 5 min. The organic phase was removed and the aqueous phase was extracted with $CH_2Cl_2$ (5 × 15 mL). The combine organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the intermediate alcohol which was redissolved in $CH_2Cl_2$ and treated with TFA (2 drops). The solution stirred at rt for 1 h before concentration *in vacuo*. The resultant solid was re-dissolved in $CH_2Cl_2$ and washed with sat. aqueous $NaHCO_3$ (2 × 2 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by column chromatography under the described conditions.

### 6.3.2 Starting Material Synthesis

#### 6.3.2.1 α-Ketophosphonates

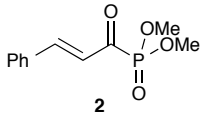
(*E*)-Dimethyl (1-hydroxy-3-phenylallyl)phosphonate **160**



**160**

Following *General Procedure F*, to a solution of cinnamaldehyde **158** (21.0 mL, 167 mmol) and dimethyl phosphite **159** (15.3 mL, 167 mmol) in $CH_2Cl_2$ (220 mL) was added triethylamine (23.3 mL, 167 mmol) and the reaction mixture stirred at rt for 72 h before concentration *in vacuo* gave the crude product. Trituration with $Et_2O$ gave **160** as a colourless solid (23.8 g, 58% yield) with spectroscopic data in accordance with the literature[10] and which was used in the next step without further purification; mp 97-99 °C; {lit.[10] 101-102 °C; $^1$H (300 MHz, $CDCl_3$) $\delta_H$: 3.84 (6H, d, *J* 10.4, OC*H*$_3$), 4.07 (1H, br s, O*H*), 4.73 (1H, ddd, *J* 12.9, 6.3, 1.5, C(OH)*H*), 6.34 (1H, ddd, *J* 15.9, 6.3, 5.4, C(2)*H*), 6.81 (1H, ddd, *J* 15.9, 4.8, 1.5, C(3)*H*), 7.24-7.36 (3H, m, Ar*H*(3,4)), 7.39-7.45 (2H, m, Ar*H*(2)); $^{31}$P{$^1$H} (121 MHz, $CDCl_3$) $\delta_P$: 28.8.

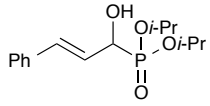
(*E*)-Dimethyl cinnamoylphosphonate **161**



**2**

Following *General Procedure G*, (*E*)-dimethyl (1-hydroxy-3-phenylallyl)phosphonate **160** (12.0 g, 49.5 mmol), $SO_3$.pyridine (23.6 g, 149 mmol), *i*-$Pr_2$NEt (25.9 mL, 149 mmol) and DMSO (100 mL) were stirred in $CH_2Cl_2$ (400 mL) at –10 ºC for 4 h to give **161** as a yellow oil (8.10 g, 68%) with spectroscopic data in accordance to the literature,[10] which was used without further purification; $^1$H (300 MHz, $CDCl_3$) $\delta_H$: 3.90 (6H, d, *J* 10.8, OC*H*$_3$), 7.08 (1H, dd, *J* 16.3, 12.9, C(2)*H*), 7.40-7.47 (3H, m, ArC(3,4)*H*), 7.61-7.67 (2H, m, ArC(2)*H*), 8.12 (1H, d, *J* 16.3, C(3)*H*); $^{31}$P{$^1$H} (121 MHz, $CDCl_3$) $\delta_P$: 0.5.

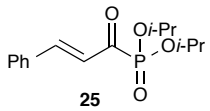
(*E*)-Diisopropyl (1-hydroxy-3-phenylallyl)phosphonate **256**



**256**

Following *General Procedure F*, cinnamaldehyde (2.52 mL, 20 mmol), diisopropyl phosphite (3.34 mL, 17.0 mmol) and potassium fluoride (5.80 g, 50.0 mmol) were stirred at rt for 48 h to gve the crude product **256** as a yellow oil, which was used in the next step without further purification; $^1$H (300 MHz, $CDCl_3$) $\delta_H$: 0.89-1.05 (12H, m, 4 *i*-PrC*H*$_3$), 4.26-4.50 (3H, m, 2 *i*-PrC*H* and C(1)*H*), 5.77 (1H, br s, O*H*), 6.07 (1H, dt, *J* 15.9, 5.4, C(2)*H*), 6.48 (1H, dd, *J* 15.9, 4.7, C(3)*H*), 6.98-7.06 (5H, m, Ar*H*); $^{31}$P{$^1$H} (121 MHz, $CDCl_3$) $\delta_P$: 20.2.

(*E*)-Diisopropyl cinnamoylphosphonate **163**

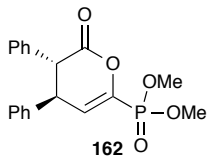


**25**

Following *General Procedure G*, allylic alcohol **256** (5.96 g, 20.0 mmol), $SO_3$.pyridine (4.69 g, 30.0 mmol), *i*-$Pr_2$NEt (5.23 mL, 30.0 mmol) and DMSO (20

mL) were stirred in $CH_2Cl_2$ (100 mL) at –10 ºC for 1 h to give the crude product. Purification *via* column chromatography on silica gel (Petrol:EtOAc 60:40) gave **163** as a yellow oil (2.41 g, 41% over two steps) with spectroscopic data in accordance with the literature;[11] $^1$H (300 MHz, $CDCl_3$) $\delta_H$: 1.34-1.43 (12H, m, 4 *i*-PrC*H*$_3$), 4.67-4.87 (2H, m, 2 *i*-PrC*H*), 7.11 (1H, dd, *J* 16.3, 10.8, C(2)*H*), 7.39-7.46 (3H, m, Ar*H*(3,4)), 7.59-7.66 (2H, m, Ar*H*(2)), 8.09 (1H, d. *J* 16.3, C(3)*H*); $^{31}$P{$^1$H} (121 MHz, $CDCl_3$) $\delta_P$: 3.1.

### 6.3.3 Optimisation Studies on 162



**162**

*Solvent Screen:*

To a solution of phenylacetic acid (54.4 mg, 0.40 mmol, 1 equiv.), was added *i*-Pr$_2$NEt (104.6 µL, 0.60 mmol, 1.5 equiv.) and pivaloyl chloride (74.0 µL, 0.60 mmol, 1.5 equiv.) at 0 °C. The desired phosphonate acceptor **161** (144.1 mg, 0.60 mmol, 1.5 equiv.) as a solution, (2*S*,3*R*)-HBTM-2.1 **26** (1.2 mg, 0.004 mmol, 1 mol%), and *i*-Pr$_2$NEt (174.3 µL, 1 mmol, 2.5 equiv.) were added. All reactions were carried out for 18h at rt.

In $CH_2Cl_2$ (2+2 mL) gave crude **162** (88:12 dr). Chromatographic purification (40:60 Petrol:EtOAc) gave **162** (>95:5 dr) as a yellow oil (73.4 mg, 51%); 86% ee.

In THF (2+2 mL) gave crude **162** (50% conversion, 88:12 dr). Chromatographic purification (40:60 Petrol:EtOAc) gave **162** (>95:5 dr) as a yellow oil (59.0 mg, 41%%); 97% ee.

*Asymmetric Catalyst Screen:*

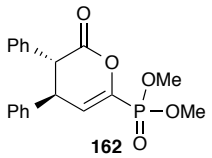
To a solution of phenylacetic acid (54.4 mg, 0.40 mmol, 1 equiv.) in $CH_2Cl_2$ (2 mL), was added *i*-$Pr_2NEt$ (104.6 μL, 0.60 mmol, 1.5 equiv.) and pivaloyl chloride (74.0 μL, 0.60 mmol, 1.5 equiv.) at 0 °C. The desired phosphonate acceptor **161** (144.1 mg, 0.60 mmol, 1.5 equiv.) as a solution in $CH_2Cl_2$ (2 mL) and *i*-$Pr_2NEt$ (174.3 μL, 1 mmol, 2.5 equiv.) were added. All reactions were carried out for 2h at rt.

With (2*S*,3*R*)-HBTM-2.1 **26** (12 mg, 0.04 mmol, 10 mol%) gave crude **162** (88:12 dr). Chromatographic purification (40:60 Petrol:EtOAc) gave **162** (>95:5 dr) as a yellow oil (73.4 mg, 51%); 86% ee.

With (*R*)-BTM **23** (10 mg, 0.04 mmol, 10 mol%) gave crude **162** (74:26 dr). Chromatographic purification (40:60 Petrol:EtOAc) gave **162** (>95:5 dr) as a yellow oil (60.4 mg, 42%); 56% ee.

### 6.3.4 Experimental Procedures

(3*R*,4*S*)-Dimethyl (2-oxo-3,4-diphenyl-3,4-dihydro-2*H*-pyran-6-yl)phosphonate **162**

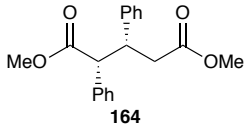


**162**

To a solution of phenylacetic acid **98** (54.4 mg, 0.40 mmol, 1 equiv.), in $CH_2Cl_2$ (2 mL, 0.1M) was added *i*-$Pr_2NEt$ (104.6 μL, 0.60 mmol, 1.5 equiv.) and pivaloyl chloride (74.0 μL, 0.60 mmol, 1.5 equiv.) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min after which the ice bath was replaced with a dry ice/acetone bath and the reaction cooled to −78 °C and (2*S*,3*R*)-HBTM-2.1 **26** (1.2 mg, 0.004 mmol, 1 mol%), the desired phosphonate acceptor **161** (144.1 mg, 0.60 mmol, 1.5 equiv.) as a solution in $CH_2Cl_2$ (2 mL, 0.1M) and *i*-$Pr_2NEt$ (174.3 μL, 1 mmol, 2.5 equiv.) were added and the reaction stirred at −78 °C for 24 h. 1M HCl was added to quench the

reaction. The organic phase was separated and the aqueous phase extracted $CH_2Cl_2$ (2 × 5 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude reaction mixture. Purification *via* column chromatography on silica gel (Petrol:EtOAc 40:60) gave **162** (119.4 mg, 83%) as a yellow oil. $[\alpha]_D^{20}$ –45.0 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.0 mLmin$^{-1}$, 220 nm, 24 °C) $t_R$ (3*R*,4*S*) major 30.4 min, $t_R$ (3*S*,4*R*) minor 33.6 min, 98% ee; $\nu_{max}$ (film) 3029.0 (C-H), 2958.0, 1776.0 (C=O), 1452.0, 1260.0 (P=O), 1050.0 (P-O); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 3.81 (3H, d, *J* 11.2, OC*H*$_3$), 3.89 (3H, d, *J* 11.2, OC*H*$_3$), 3.96 (1H, d, *J* 8.5, C(3)*H*), 4.07 (1H, m, C(4)*H*), 6.53 (1H, dd, *J* 10.2, 3.8, C(5)*H*), 7.04 (2H, m, Ar*H*), 7.11 (2H, m, Ar*H*), 7.22-7.29 (6H, m, Ar*H*); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta_C$: 45.7 (d, *J* 12.6, *C*(4)), 52.7 (*C*(3)), 53.8 (app. t, *J* 6.0, 2 O*C*H$_3$), 123.2 (d, *J* 19.3, *C*(5)), 127.5 (2 Ar*C*), 128.0 (C(4)Ar*C*(4)), 128.1 (Ar*C*), 128.3 (2 Ar*C*), 128.9 (2 Ar*C*), 129.1 (2 Ar*C*), 135.4 (*C*$_{ipso}$), 138.9 (C(4)Ar*C*(1)), 143.4 (d, *J* 232.0, *C*(6)), 167.0 (d, *J* 8.5, *C*(2)); $^{31}$P{$^1$H} NMR (121 MHz, $CDCl_3$) $\delta_P$: + 7.12; HRMS (ASAP) $C_{19}H_{20}O_5P$ $[M+H]^+$, found 359.1043, requires 359.1042 (–0.2 ppm).

(2*R*,3*R*)-Dimethyl 2,3-diphenylpentanedioate **164**

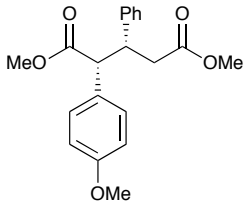


**164**

Following *General Procedure H*, phenylacetic acid **98** (476 mg, 3.50 mmol), *i*-Pr$_2$NEt (0.87 mL, 5.00 mmol) and pivaloyl chloride (0.62 mL, 5.00 mmol) in $CH_2Cl_2$ (4.50 mL) with isothiourea **26** (10.9 mg, 0.05 mmol), (*E*)-diisopropyl cinnamoylphosphonate **163** (1.50 g, 5.00 mmol) in $CH_2Cl_2$ (4.50 mL) and *i*-Pr$_2$NEt (1.45 mL, 8.50 mmol) for 24 h at –78 °C followed by addition of MeOH (9 mL) and a further 24 h at –78 °C gave the crude product (>95:5 dr *anti*:*syn*). Purification *via* column chromatography on silica gel (Petrol:EtOAc 90:10) gave diester **164** (0.95 g, 87%, >95:5 dr) as a colourless solid. mp 62-63 °C; $[\alpha]_D^{20}$ –125.7 (*c* 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flowrate 1 mLmin$^{-1}$, 220 nm, 30 °C) $t_R$(2*S*,3*S*) minor 10.6 min, $t_R$(2*R*,3*R*) major 12.5 min, 98% ee; $\nu_{max}$ (film)

2957 (C–H), 1777 (C=O), 1603, 1508, 1456, 1263, 1225 (C–O), 1113 (C–O), 1016; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.76-2.86 (2H, m, C$H_2$), 3.51 (3H, s, C(5)$O_2$C$H_3$), 3.69 (3H, s, C(1)$O_2$C$H_3$), 3.83-3.93 (2H, m, C(2)*H* and C(3)*H*), 6.98-7.14 (10H, m, Ar*H*); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) $\delta_C$: 39.3 (*C*(4)), 45.6 (*C*(3)), 51.7 (C(5)$O_2$*C*$H_3$), 52.3 (C(1)$O_2$C$H_3$), 57.3 (*C*(2)), 126.8 (Ar*C*(4)), 127.4 (Ar*C*(4)), 128.2 (4 Ar*C*), 128.4 (2 Ar*C*), 128.7 (2 Ar*C*), 136.7 (C(2)Ar*C*(1)), 140.3 (C(3)Ar*C*(1)), 172.0 (*C*(5)), 173.5 (*C*(1)); HRMS (NSI$^+$) $C_{19}H_{21}O_4$ $[M+H]^+$ found 313.1439, requires 313.1434; (+1.5 ppm).

(2*R*,3*R*)-Dimethyl 2-(4-methoxyphenyl)-3-phenylpentanedioate **166**

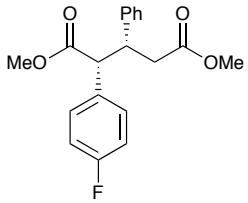


**166**

Following *General Procedure H*, 2-(4-methoxyphenyl)acetic acid (32.0 mg, 0.20 mmol), *i*-$Pr_2$NEt (52.3 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in $CH_2Cl_2$ (2 mL) with isothiourea **26** (6.2 mg, 0.02 mmol), (*E*)-dimethyl cinnamoylphosphonate **163** (72.1 mg, 0.30 mmol) in $CH_2Cl_2$ (2 mL) and *i*-$Pr_2$NEt (87.1 μL, 0.50 mmol) for 24 h at −78 °C followed by addition of MeOH (2 mL) and a further 24 h at −78 °C gave the crude product (93:7 dr *anti*:*syn*). Purification *via* column chromatography on silica gel (Petrol:EtOAc 90:10) gave diester **166** (36.1 mg, 56%, 94:6 dr) as a colourless solid; mp 99-101 °C;$[\alpha]_D^{20}$ −135.1 (*c* 0.2, $CHCl_3$); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flowrate 1 mL min$^{-1}$, 254 nm, RT) $t_R$(2*S*,3*S*) minor 14.8 min, $t_R$(2*R*,3*R*) major 22.3 min, 98% ee; $\nu_{max}$ (film) 2953 (C–H), 1734 (C=O), 1728 (C=O), 1510, 1437, 1246 (C–O), 1178 (C–O); $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta_H$: 2.72-2.84 (2H, m, C$H_2$), 3.51 (3H, s, C(5)$O_2$C$H_3$), 3.67 (3H, s, OC$H_3$), *3*.70 (3H, s, OC$H_3$), 3.75-3.85 (2H, m, C(2)*H* and C(3)*H*), 6.62-6.70 (2H, m, C(2)ArC(3)*H*), 6.96-7.16 (7H, m, C(2)ArC(2)*H* and C(3)ArC*H*); $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$) $\delta_C$: 39.4 (*C*(4)), 45.6 (*C*(3)), 51.7 (C(5)$O_2$*C*$H_3$), 52.2 (O*C*$H_3$), 55.2 (O*C*$H_3$), 56.4 (*C*(2)), 113.8 (2 C(2)Ar*C*(3)), 126.8 (C(3)Ar*C*(4)), 128.3 (4

C(3)Ar*C*(2,3)), 128.8 (C(2)Ar*C*(1)), 129.7 (2 C(2)Ar*C*(2)), 140.4 (C(3)Ar*C*(1)), 158.8 (C(2)Ar*C*(4)), 172.0 (*C*(5)), 173.8 (*C*(1)); HRMS (NSI)$^+$ $C_{20}H_{23}O_5^+$ $[M+H]^+$, found 343.1545, requires 343.1540 (+1.5 ppm).

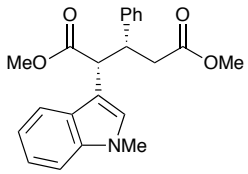
(2*R*,3*R*)-Dimethyl 2-(4-fluorophenyl)-3-phenylpentanedioate **167**




**167**

Following *General Procedure H*, 2-(4-fluorophenyl)acetic acid (30.8 mg, 0.20 mmol), *i*-$Pr_2NEt$ (52.3 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in $CH_2Cl_2$ (2 mL) with isothiourea **26** (0.6 mg, 0.002 mmol), (*E*)-dimethyl cinnamoylphosphonate **163** (72.1 mg, 0.30 mmol) in $CH_2Cl_2$ (2 mL) and *i*-$Pr_2NEt$ (87.1 μL, 0.50 mmol) for 24 h at −78 °C followed by addition of MeOH (2 mL) and a further 24 h at −78 °C gave the crude product (91:9 dr *anti*:*syn*). Purification *via* column chromatography on silica gel (Petrol:EtOAc 90:10) gave diester **167** (46.2 mg, 70%, >98:2 dr) as a colourless solid. mp 86-88 °C; $[\alpha]_D^{20}$ −119.5 (*c* 0.2, $CHCl_3$); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flowrate 1 mL min$^{-1}$, 220 nm, RT) $t_R$(2*S*,3*S*) minor 11.5 min, $t_R$(2*R*,3*R*) major 13.9 min, 98% ee; $\nu_{max}$ (film) 2841 (C–H), 1745 (C=O), 1730 (C=O), 1508, 1435, 1229 (C–O), 1206 (C–O), 1080, 1018; $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$: 2.76-2.81 (2H, m, C$H_2$), 3.51 (3H, s, C(5)$O_2$C$H_3$), 3.70 (3H, s, C(1)$O_2$C$H_3$), 3.80-3.83 (2H, m, C(2)*H* and C(3)*H*), 6.77-6.85 (2H, m, C(2)ArC(3)*H*, 6.95-6.99 (2H, m, Ar*H*), 7.05-7.12 (5H, m, Ar*H*); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta_C$: 39.4 (*C*(4)), 45.7 (*C*(3)), 51.7 (C(5)$O_2$*C*$H_3$), 52.4 (C(1)$O_2$*C*$H_3$), 56.5 (*C*(2)), 115.3 (d, *J* 21.4, 2 C(2)Ar*C*(3)), 126.9 (C(3)Ar*C*(4)), 128.2 (2 Ar*C*), 128.3 (2 Ar*C*), 130.3 (d, *J* 8.1, 2 C(2)Ar*C*(2)), 132.5 (d, *J* 3.3, C(2)Ar*C*(1)), 140.1 (C(3)Ar*C*(1)), 162.1 (d, *J* 246.0, (C(2)Ar*C*(4)), 171.9 (*C*(5)), 173.4 (*C*(1)); $^{19}$F{$^1$H} NMR (282 MHz, $CDCl_3$) $\delta_F$:−115.6; HRMS (NSI)$^+$ $C_{19}H_{20}FO_4^+$ $[M+H]^+$, found 331.1345, requires 331.1340 (+1.5 ppm).

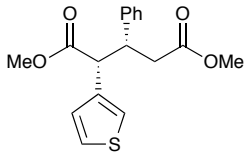
(2*R*,3*R*)-Dimethyl 2-(1-methyl-1*H*-indol-3-yl)-3-phenylpentanedioate **168**




**168**

Following *General Procedure H*, 1-methyl-3-indoleacetic acid (37.8 mg, 0.20 mmol), *i*-$Pr_2NEt$ (52.3 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in $CH_2Cl_2$ (2 mL) with isothiourea **26** (0.6 mg, 0.002 mmol), (*E*)-diisopropyl cinnamoylphosphonate **163** (72.1 mg, 0.30 mmol) in $CH_2Cl_2$ (2 mL) and *i*-$Pr_2NEt$ (87.1 μL, 0.50 mmol) for 24 h at –78 °C followed by addition of MeOH (2 mL) and a further 24 h at –78 °C gave the crude product (86:14 dr *anti*:*syn*). Purification *via* column chromatography on silica gel (Petrol:EtOAc 90:10) gave diester **168** (73.1 mg, 62%, 86:14 dr) as a brown oil. $[\alpha]_D^{20}$ –39.8 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flowrate 1 $mLmin^{-1}$, 220 nm) $t_R$(2*S*,3*S*) minor 23.3 min, $t_R$(2*R*,3*R*) major 49.6 min, 88% ee; $\nu_{max}$ (film) 2951 (C–H), 1732 (C=O), 1717 (C=O), 1612, 1472, 1200 (C–O), 1085, 1013; $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$: 2.87 (2H, d, *J* 7.4, C$H_2$), 3.49 (3H, s, C(5)$O_2$C$H_3$), 3.65 (3H, s, C$H_3$), 3.65 (3H, s, C$H_3$), 3.94-4.03 (1H, m, C(3)*H*), 4.26 (1H, d, *J* 9.1, C(2)*H*), 6.85 (1H, s, indoleC(2)*H*), 7.04-7.25 (8H, m, Ar*H*), 7.60 (1H, dt, *J* 7.9, 1.0, Ar*H*); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta_C$: 32.9 (N*C*$H_3$), 38.5 (*C*(4)), 44.7 (*C*(3)), 48.6 (*C*(2)), 51.6 (C(5)$O_2$*C*$H_3$), 52.1 (C(1)$O_2$*C*$H_3$), 109.3 (indole*C*(7)), 109.6 (indole*C*(3)), 119.3 (Ar*C*), 119.3 (Ar*C*), 121.7 (Ar*C*), 126.8 (Ar*C*(4)), 128.0 (2 Ar*C*), 128.2 (2 Ar*C*), 128.3 (indole*C*(2)), 128.6 (indole*C*(3a)), 136.8 (indole*C*(7a)), 141.2 (Ar*C*(1)), 172.4 (*C*(5)), 173.9 (*C*(1)); HRMS (NSI)$^+$ $C_{22}H_{24}NO_4^+$ $[M+H]^+$, found 366.1703, requires 366.1700 (+0.9 ppm).

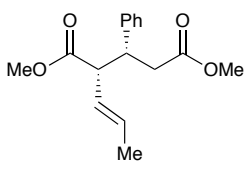
(2*S*,3*R*)-Dimethyl 3-phenyl-2-(thiophen-3-yl)pentanedioate **170**




**170**

Following *General Procedure H*, 3-thiopheneacetic acid (56.9 mg, 0.40 mmol), *i*-$Pr_2NEt$ (104.6 μL, 0.45 mmol) and pivaloyl chloride (74.0 μL, 0.45 mmol) in $CH_2Cl_2$ (2 mL) with **26** (1.24 mg, 0.004 mmol), (*E*)-diisopropyl cinnamoylphosphonate **163** (177.8 mg, 0.60 mmol) in $CH_2Cl_2$ (2 mL) and *i*-$Pr_2NEt$ (174.3 μL, 1.00 mmol) for 24 h at −78 °C followed by addition of MeOH (2 mL) and a further 24 h at −78 °C warming to room temperature gave the crude product (>95:5 dr *anti*:*syn*). Purification *via* column chromatography on silica gel (Petrol:EtOAc 90:10) gave diester **170** (109.6 mg, 86%, >95:5 dr) as a white solid. mp 60-64 °C; $[\alpha]_D^{22}$ −69.0° (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralcel AD-H (90:10 hexane:IPA, flow rate 0.5 $mLmin^{-1}$, 211 nm, 30 °C), $t_R$(2*R*,3*S*) minor 15.4 min, $t_R$(2*S*,3*R*) major 17.7 min, >99% ee; $\nu_{max}$ (film) 2958 (C-H), 2359, 1732 (C=O), 1072; $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$: 2.77-2.80 (2H, m, C*H*$_2$), 3.52 (3H, s, C(5)O$_2$*Me*), 3.71 (3H, s, C(1)O$_2$*Me*), 3.75-3.83 (1H, m, C(3)*H*), 4.00 (1H, d, *J* 10.2, C(2)*H*), 6.85 (1H, dd, *J* 5.0, 1.3, C(2)Ar*H*), 6.91 (1H, dd, *J* 3.0, 1.3, C(2)Ar*H*), 6.99-7.03 (2H, m), 7.08-7.20 (4H, m); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta_C$: 38.8 (*C*(4)), 45.8 (*C*(3)), 51.7 (C(5)O$_2$*C*H$_3$), 52.3 (C(1)O$_2$*C*H$_3$), 52.8 (*C*(2)), 123.2 (C(2)Ar*C*(3)), 125.3 (C(2)Ar*C*), 127.0 (C(3)Ar*C*(4)), 127.6 (C(2)Ar*C*), 128.1 (2 C(3)Ar*C*(2)), 128.3 (2 C(3)Ar*C*(3)), 136.7 (C(2)Ar*C*), 140.4 (C(3)Ar*C*(1)), 172.0 (*C*(5)), 173.2 (*C*(1)); HRMS (NSI)$^+$ $C_{15}H_{15}O_2S^+$ $[M+H]^+$, found 259.0787, requires 259.0790 (+1.1 ppm).

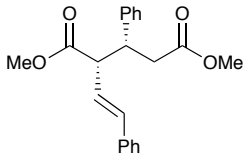
(2*S*,3*R*)-Dimethyl 3-phenyl-2-((*E*)-prop-1-en-1-yl)pentanedioate **171**




**171**

Following *General Procedure H*, 3-pentanoic acid (40.6 μL, 0.40 mmol), *i*-$Pr_2NEt$ (104.6 μL, 0.45 mmol) and pivaloyl chloride (74.0 μL, 0.45 mmol) in $CH_2Cl_2$ (2 mL) with **26** (1.24 mg, 0.004 mmol), (*E*)-diisopropyl cinnamoylphosphonate **163** (177.8 mg, 0.60 mmol) in $CH_2Cl_2$ (2 mL) and *i*-$Pr_2NEt$ (174.3 μL, 1.00 mmol) for 24 h at −78 °C followed by addition of MeOH (2 mL) and a further 24 h at −78 °C warming to room temperature gave the crude product (>95:5 dr *anti*:*syn*). Purification *via* column chromatography on silica gel (Petrol:EtOAc 95:5-80:20) gave diester **171** (81.3 mg, 74%, >95:5 dr) as a colourless oil. $[\alpha]_D^{22}$ −27.8° (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralcel OD-H (97:3 hexane:IPA, flow rate 0.5 $mLmin^{-1}$, 211 nm, RT), $t_R$(2*R*,3*S*) minor 19.5 min, $t_R$(2*S*,3*R*) major 39.8 min, >99% ee; $\nu_{max}$ (film) 3030 (=CH stretch), 1732 (C=O), 963 (C=C); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta_H$: 1.55 (3H, dd, *J* 6.1, 1.3, C(2)C(3')$H_3$), 2.70 (2H, d, *J* 7.5, C(4)$H_2$), 3.28 (1H, t, *J* 8.6, C(2)*H*), 3.53 (3H, s, C(5)$O_2C H_3$), 3.57 (2H, q, *J* 7.7, C(3)*H*), 3.66 (3H, s, C(1)$O_2C H_3$), 5.23-5.32 (1H, ddq, *J* 15.2, 8.8, 1.3, C(2)C(1')*H*)), 5.33-5.44 (1H, dq, *J* 15.2, 6.3, C(2)C(2')*H*)), 7.09-7.14 (2H, m, C(3)ArC(2)*H*), 7.16-7.22 (1H, m, C(3)ArC(4)*H*), 7.23-7.29 (2H, m, C(3)ArC(3)*H*); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta_C$: 17.9 (C(2)*C*(3')$H_3$), 38.4 (*C*(4)), 44.1 (*C*(3)), 51.6 (C(5)$O_2C H_3$), 51.8 (C(1)$O_2C H_3$), 54.4 (*C*(2)), 126.1 (*C*(1')), 127.0 (C(3)Ar*C*(4)), 128.2 (2 C(3)Ar*C*(2)), 128.3 (2 C(3)Ar*C*(3)), 130.0 (*C*(2')), 140.3 (C(3)Ar*C*(1)), 172.1 (*C*(5)), 173.6 (*C*(1)); HRMS $(NSI)^+$ $C_{16}H_{24}O_4N^+$ $[M+NH_4]^+$, found 294.1700, requires 294.1703 (+1.1 ppm).

(2*S*,3*R*)-Dimethyl 3-pheyl-2-((*E*)-styryl)pentanedioate **172**

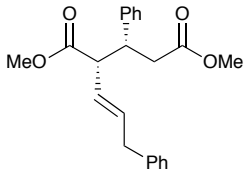



**172**

Following *General Procedure H*, *trans*-styrylacetic acid (64.9 mg, 0.40 mmol), *i*-$Pr_2NEt$ (104.6 μL, 0.45 mmol) and pivaloyl chloride (74.0 μL, 0.45 mmol) in $CH_2Cl_2$ (2 mL) with **26** (1.24 mg, 0.004 mmol), (*E*)-diisopropyl cinnamoylphosphonate **163** (177.8 mg, 0.60 mmol) in $CH_2Cl_2$ (2 mL) and *i*-$Pr_2NEt$ (174.3 μL, 1.00 mmol) for 24 h at −78 °C followed by addition of MeOH (2 mL) and a further 24 h at −78 °C

warming to room temperature gave the crude product (>95:5 dr *anti*:*syn*). Purification *via* column chromatography on silica gel (Petrol:EtOAc 95:5-80:20) gave diester **172** (102.4 mg, 77%, 90:10 dr) as a white solid; mp 62-54 °C; $[\alpha]_D^{22}$ −23.0° (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralcel AD-H (80:20 hexane:IPA, flow rate 1.0 $mLmin^{-1}$, 211 nm, RT), $t_R$(2*S*,3*R*) major 28.4 min, $t_R$(2*R*,3*S*) minor 36.4 min, 27% ee; $\nu_{max}$ (neat) 3028 (=CH stretch), 1732 (C=O), 966 (C=C); $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$: 2.73-2.82 (2H, m, C(4)$H_2$), 3.49 (1H, ddd, *J* 9.3,8.0, 0.8, C(2)*H*), 3.56 (3H, s, C(5)$O_2CH_3$), 3.69 (3H, s, C(1)$O_2CH_3$), 3.74 (1H, m, C(3)*H*), 6.00 (1H, dd, *J* 15.9, 9.4, C(1')*H*), 6.29 (1H, d, *J* 15.9, C(2')*H*), 7.09-7.33 (10H, m, Ar*H*); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta_C$: 38.4 (*C*(4)), 44.5 (*C*(3)), 51.8 (C(5)$O_2CH_3$), 52.2 (C(1)$O_2CH_3$), 54.7 (*C*(2)), 125.0 (*C*(1')), 126.5 (2 Ar*C*), 127.3 (Ar*C*), 127.8 (Ar*C*), 128.3 (2 Ar*C*), 128.6 (4 Ar*C*), 133.9 (*C*(2')), 136.7 (C(2')Ar*C*(1)), 140.1 (C(3)Ar*C*(1)), 172.1 (*C*(5)), 173.2 (*C*(1)); HRMS (NSI)$^+$ $C_{21}H_{23}O_4$ [M], found 339.1592, requires 339.1591 (+0.3 ppm).

(2*S*,3*R*)-Dimethyl3-phenyl-2-((*E*)-3-phenylprop-1-en-1-yl) pentanedioate **173**

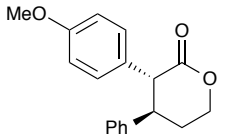


**173**

Following *General Procedure H*, (*E*)-5-phenylpent-3-enoic acid (70.5 mg, 0.40 mmol), *i*-$Pr_2$NEt (104.6 μL, 0.45 mmol) and pivaloyl chloride (74.0 μL, 0.45 mmol) in $CH_2Cl_2$ (2 mL) with **26** (1.24 mg, 0.004 mmol), (*E*)-diisopropyl cinnamoylphosphonate **163** (177.8 mg, 0.60 mmol) in $CH_2Cl_2$ (2 mL) and *i*-$Pr_2$NEt (174.3 μL, 1.00 mmol) for 24 h at −78 °C followed by addition of MeOH (2 mL) and a further 24 h at −78 °C warming to room temperature gave the crude product (>95:5 dr *anti*:*syn*). Purification *via* column chromatography on silica gel (Petrol:EtOAc 95:5-85:15) gave diester **173** (107.7 mg, 76%, >95:5 dr) as a colourless oil. $[\alpha]_D^{22}$ −6.9° (*c* 1.0 in $CHCl_3$); Chiral HPLC analysis, Chiralcel OJ-H (99.5:0.5 hexane:IPA, flow rate 1.5 $mLmin^{-1}$, 211 nm, 40 °C), $t_R$(2*S*,3*R*) major 34.8 min, $t_R$(2*R*,3*S*) minor 40.5 min, >99% ee; $\nu_{max}$ (neat) 3028 (=CH stretch), 1736 (C=O), 974 (C=C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.69 (2H, d, *J* 7.5, C(4)$H_2$), 3.21 (2H, d, *J* 6.5, C(3')$H_2$),

3.33 (1H, t, *J* 9.2, C(2)*H*), 3.53 (3H, s, C(5)$O_2$C$H_3$), 3.53-3.65 (1H, m, C(3)*H*), 3.71 (3H, s, C(1)$O_2$C$H_3$), 5.33 (1H, ddt, *J* 15.3, 9.2, 1.1, C(2)C(1')*H*), 5.47 (1H, dt, *J* 15.4, 6.6, C(2)C(2')*H*), 6.73-6.81 (2H, m, Ar*H*), 7.07-7.22 (5H, m, Ar*H*), 7.22-7.34 (3H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta_C$: 38.7 ($CH_2$), 38.9 ($CH_2$), 44.4 (*C*(3)), 51.7 (C(5)$O_2C$$H_3$), 52.1 (C(1)$O_2C$$H_3$), 54.8 (*C*(2)), 126.1 (*C*(1')), 127.1 (Ar*C*), 127.3 (Ar*C*), 128.3 (2 Ar*C*), 128.4 (2 Ar*C*), 128.5 (2 Ar*C*), 128.6 (2 Ar*C*), 133.7 (*C*(2')), 139.8 (C(3')Ar*C*(1)), 140.5 (C(3)Ar*C*(1)), 172.0 (*C*(5)), 173.6 (*C*(1)); HRMS $(NSI)^+$ $C_{22}H_{25}O_4$ [M], found 353.1747, requires 353.1747 (–0.1 ppm).

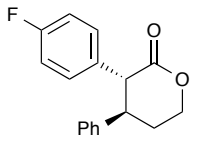
(3*R*,4*R*)-3-(4-Methoxyphenyl)-4-phenyltetrahydro-2*H*-pyran-2-one **177**



**177**

Following *General Procedure I*, **166** (99.9 mg, 0.3 mmol) and DIBAL-H (660 μL, 0.66 mmol) in THF (2 mL) was stirred at 0 °C for 90 min to give the crude intermediate. This was dissolved in $CH_2Cl_2$ (2 mL), treated with TFA (2 drops) and stirred at room temperature for 1 h. The crude product (>95:5 dr *anti:syn*) was purified *via* column chromatography on silica gel (Petrol:EtOAc 80:20-60:40) gave the product **177** (41.9mg, 49%) as a white solid. mp 76-80 °C; $[\alpha]_D^{22}$ –191.2° (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralcel AD-H (90:10 hexane:IPA, flow rate 1 mL $min^{-1}$, 211 nm, 30 °C), $t_R$(3*R*,4*R*) major 27.9 min, $t_R$(3*S*,4*S*) minor 35.2 min, >99% ee; $\nu_{max}$ (film) 1728 (C=O), 1514, 1175 (C-O); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.17-2.39 (2H, m, C(5)$H_2$), 3.24-3.37 (1H, m, C(4)*H*), 3.74 (3H, s, OC$H_3$), 3.81 (1H, d, *J* 10.8, C(3)*H*)), 4.46-4.70 (2H, m, C(6)$H_2$), 6.74 (2H, d, *J* 8.7, C(3)ArC(3)*H*), 6.86-6.95 (2H, m, C(3)ArC(2)*H*), 6.97-7.07 (2H, m, Ar*H*), 7.13-7.24 (3H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) $\delta_C$: 30.9 (*C*(5)), 46.7 ($CH_3$), 54.6 (*C*H), 55.3 (*C*H), 68.7 (*C*(6)), 114.1 (2 C(3)Ar*C*(3)), 127.2 (2 C(3)Ar*C*(2), C(4)Ar*C*(4)), 128.8 (2 C(4)Ar*C*), 129.9 (2 C(4)Ar*C*), 130.0 (C(3)Ar*C*(1)), 142.2 (C(4)Ar*C*(1)), 158.7 (C(3)Ar*C*(1)), 172.5 (*C*(2)); HRMS $(NSI)^+$ $C_{18}H_{19}O_3^+$ $[M+H]^+$, found 283.1330, requires 283.1329 (+0.5 ppm).

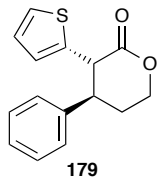
(3*R*,4*R*)-3-(4-Fluorophenyl)-4-phenyltetrahydro-2*H*-pyran-2-one **178**



**178**

Following *General Procedure I*, **167** (87.4 mg, 0.26 mmol) and DIBAL-H (570 μL, 0.57 mmol) in THF (2 mL) was stirred at 0 °C for 90 min to give the crude intermediate. This was dissolved in $CH_2Cl_2$ (2 mL), treated with TFA (2 drops) and stirred at room temperature for 1 h. The crude product (>95:5 dr *anti:syn*) was purified *via* column chromatography on silica gel (Petrol:EtOAc 70:30) gave **178** (44.6 mg, 63%) as a white solid; mp 120-124 °C; $[\alpha]_D^{22}$ –22.8° (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralcel AD-H (95:5 hexane:IPA, flow rate 1 mL $min^{-1}$, 211 nm, 30 °C), $t_R$(3*R*,4*R*) major 28.2 min, $t_R$(3*S*,4*S*) minor 37.3 min, >99% ee; $\nu_{max}$ (film) 1717 (C=O), 1508, 1209 (C-F), 1186 (C-O); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.26-2.34 (2H, m, C(5)$H_2$), 3.22-3.34 (1H, m, C(4)*H*), 3.86 (1H, d, *J* 11.2, C(3)*H*)), 4.60 (1H, ddd, J 11.4, 9.6, 4.0, C(6)$H_AH_B$) 4.67 (1H, dt, *J* 11.4, 4.6, C(6)$H_AH_B$), 6.90-6.94 (2H, m, Ar*H*), 6.94-7.00 (2H, m, Ar*H*), 7.01-7.05 (2H, m, Ar*H*), 7.19-7.30 (3H, m, Ar*H*); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta_C$: 30.9 (*C*(5)), 46.8 (*C*H), 54.7 (*C*H), 68.8 (*C*(6)), 115.5 (d, *J* 21.7, 2 C(3)Ar*C*(3)), 127.2 (2 C(4)Ar*C*), 127.4 (C(4)Ar*C*), 128.9 (2 C(4)Ar*C*), 130.5 (d, *J* 8.1, 2 C(3)Ar*C*(2), 133.6 (d, *J* 2.8, C(3)Ar*C*(1)), 141.8 (C(4)Ar*C*), 162.0 (d, *J* 246.0, C(3)Ar*C*(4)), 172.0 (*C*(2)); $^{19}$F{$^1$H} NMR (376 MHz, $CDCl_3$) $\delta_F$: –115.2; HRMS (NSI)$^+$ $C_{17}H_{16}O_2F^+$ $[M+H]^+$, found 271.1130, requires 271.1129 (+0.4 ppm).

(3*R*,4*R*)-3-(Thiophen-2-yl)-4-phenyltetrahydro-2H-pyran-2-one **179**



**179**

Following *General Procedure I*, **169** (57.3 mg, 0.18 mmol) and DIBAL-H (400 μL, 0.40 mmol) in THF (2 mL) was stirred at 0 °C for 90 min to give the crude intermediate. This was dissolved in $CH_2Cl_2$ (2 mL), treated with TFA (2 drops) and stirred at room temperature for 1 h. The crude product (>95:5 dr *anti:syn*) was purified *via* column chromatography on silica gel (Petrol:EtOAc 70:30) gave the product as a white solid (13.8 mg, 30%). mp 90-96 °C; $[\alpha]_D^{22}$ −82.5° (*c* 0.2, $CHCl_3$); Chiral HPLC analysis, Chiralcel AD-H (95:5 hexane:IPA, flow rate 1 mL $min^{-1}$, 211 nm, 30 ˚C), $t_R$ (2*R*,3*R*) major: 32.1 min, $t_R$ (2*S*,3*S*) minor: 47.4 min, 70% ee; (400 MHz, $CDCl_3$) 2.24-2.32 (2H, m, C(5)$H_2$), 3.36-3.44 (1H, m, C(4)*H*), 4.22 (1H, d, *J* 12, C(3)*H*)), 4.55-4.59 (2H, m, C(6)$H_2$), 6.72-6.74 (1H, m, Ar*H*), 6.82-6.84 (1H, m, Ar*H*), 7.11-7.29 (6H, Ar*H*); HRMS $(NSI)^+$ $C_{15}H_{15}O_2S^+$ $[M+H]^+$, found 259.0796, requires 259.0787 (+1.1 ppm).

## 6.4 Experimental for Chapter 4

### 6.4.1 General Experimental Procedures

#### 6.4.1.1 General Procedure J: Synthesis of *N*-Sulfonyl Oxaziridine Starting Materials

To a solution of saturated aqueous sodium bicarbonate (1 M), benzyltrimethylammonium chloride (0.11 equiv.) and the appropriate *N*-sulfonyl imine (1 equiv.) as a solution in chloroform (1 M) was added. The mixture was cooled to 0 °C and a solution of *m*-CPBA (1.1 equiv.) in chloroform (0.5 M) was added dropwise at 0 °C and stirred for 1 h. The organic layer was separated, washed with water, 10% sodium sulphite solution, water and brine before drying ($MgSO_4$) and concentrating *in vacuo,* keeping the bath temperature below 40 °C. The crude product was recrystallised from ethyl acetate/petrol without heating.

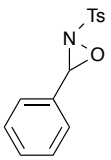
#### 6.4.1.2 General Procedure K: Asymmetric Organocatalytic Formation of Oxazolidin-4-ones

To a solution of the appropriate anhydride (1.5 equiv.) and cesium chloride (2 equiv.) in $CH_2Cl_2$ (0.2 M) at –78 °C, the appropriate oxaziridine (1 equiv.) and (2*S*,3*R*)-HBTM-2.1 (10 mol%) were added. The reaction mixture was stirred at –78 °C allowing to warm to room temperature over 16 h before being quenched with 1 M HCl, extracted with $CH_2Cl_2$ (2×), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified *via* column chromatography on silica gel (eluent petrol:$Et_2O$ 80:20 unless otherwise stated).

### 6.4.2 Starting Materials

#### 6.4.2.1 Oxaziridines

3-Phenyl-2-tosyl-1,2-oxaziridine **211**

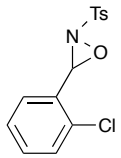



**211**

Following *General Procedure J*, benzyltrimethyammonium chloride (0.28 g, 1.49 mmol), (*E*)-*N*-(benzylidene)-4-methylbenzenesulfonamide **215** (3.5 g, 13.5 mmol)

and *m*-CPBA (3.34 g, 14.9 mmol, <77%) were stirred at 0 °C for 1 h. The resulting yellow solid was recrystallised to give **211** as a white solid (3.82 g, >99%) with data in accordance with the literature. [12] mp 92-94 °C {Lit.[12] 85-85 °C}; $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.49 (3H, s, C*H*$_3$), 5.45 (1H, s, C*H*), 7.31-7.55 (7H, m, Ar*H*), 7.87-7.97 (2H, m, Ar*H*).

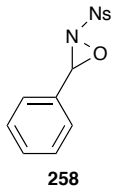
3-(2-Chlorophenyl)-2-tosyl-1,2-oxaziridine **219**




**219**

Following *General Procedure J*, benzyltrimethyammonium chloride (0.23 g, 1.25 mmol), (*E*)-*N*-(2-chlorobenzylidene)-4-methylbenzenesulfonamide **257** (3.34 g, 11.4 mmol) and *m*-CPBA (2.81 g, 12.5 mmol, <77%) were stirred at 0 °C for 1 h. The resulting yellow solid was recrystallised to give **219** as a white solid (2.97 g, 84%) with data in accordance with the literature.[13] mp 92-94 °C {Lit. 105-107 °C[13]}; $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.50 (3H, s, C*H*$_3$), 5.86 (1H, s, C*H*), 7.26-7.29 (2H, m, Ar*H*), 7.37-7.45 (4H, m, Ar*H*), 7.94 (2H, d, *J* 8.4, Ar*H*).

3-Nitro-4-(3-phenyl-1,2-oxaziridin-2-yl)benzenesulfonic acid **258**

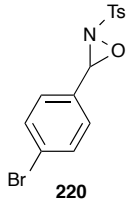



**258**

Following *General Procedure J*, benzyltrimethyammonium chloride (0.08 g, 0.41 mmol), (*E*)-4-(benzylideneamino)-3-nitrobenzenesulfonic acid **254**(1.08 g, 3.72 mmol) and *m*-CPBA (0.92 g, 4.09 mmol, <77%) were stirred at 0 °C for 1 h. The resulting yellow solid was recrystallised to give **258** as a pale yellow solid (0.66 g, 58%) with data in accordance with the literature.[12] mp 84-86 °C {Lit.[12] 94-95 °C}; $^1$H

NMR (400 MHz, $CDCl_3$) $\delta_H$: 5.60 (1H, s, C*H*), 7.39-7.48 (4H, m, Ar*H*), 7.47-7.54 (1H, m, Ar*H*), 8.27 (2H, d, *J* 8.8, $SO_2$Ar*H*), 8.48 (2H, d, *J* 8.8, $SO_2$Ar*H*).

3-(4-Bromophenyl)-2-tosyl-1,2-oxaziridine **220**

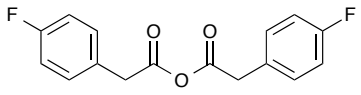



**220**

Following *General Procedure J*, benzyltrimethyammonium chloride (0.22 g, 1.18 mmol), (*E*)-*N*-(4-bromobenzylidene)-4-methylbenzenesulfonamide **99** (3.63 g, 10.7 mmol) and *m*-CPBA (2.64 g, 11.8 mmol, <77%) were stirred at 0 °C for 1 h. The resulting white solid was recrystallised to give **220** as a white solid (2.03 g, 54%) with data in accordance with the literature.[14] mp 98-100 °C {Lit.[14] 92-93 °C}; $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.50 (3H, s, C$H_3$), 5.42 (1H, s, C*H*), 7.28-7.34 (2H, m, Ar*H*), 7.43 (2H, d, *J* 8.1, Ar*H*), 7.54 (2H, d, *J* 8.5, Ar*H*), 7.92 (2H, d, *J* 8.3, Ar*H*).

### 6.4.2.2 Homoanhydrides

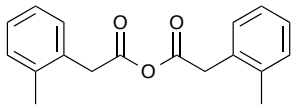
2-(4-Fluorophenyl)acetic anhydride **259**




**259**

Following *General Procedure B*, 4-fluorophenylacetic acid (1.00 g, 6.49 mmol) and DCC (0.74 g, 3.57 mmol) were stirred in toluene (20 mL) to give product **259** as a white solid (0.94 g, >99%) with data in accordance with the literature. mp 46-48 °C {Lit.[6] 36-38 °C}; $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 3.70 (4H, s, 2 C$H_2$), 6.94-7.08 (4H, m, Ar*H*), 7.11-7.22 (4H, m, Ar*H*); $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta_F$: –115.1 (Ar*F*).

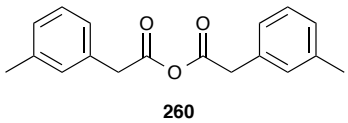
2-(*o*-Tolyl)acetic anhydride **224**



**224**

Following *General Procedure B*, *o*-tolylacetic acid (0.50g, 3.33 mmol) and DCC (0.35 g, 1.70 mmol) were stirred in toluene (10 mL) to give product **224** as a sticky oil (0.47 g, >99%) with data in accordance with the literature.[15] $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.24 (6H, s, 2 C$H_3$), 3.72 (4H, s, 2 × C$H_2$), 7.07-7.11 (2H, m, Ar*H*), 7.11-7.25 (6H, m, Ar*H*); $^{13}$C{$^{1}$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 19.6 (*C*$H_3$), 40.2 (*C*$H_2$), 126.4 (Ar*C*), 128.1 (Ar*C*), 130.5 (Ar*C*), 130.7 (Ar*C*), 130.9 (Ar*C*(1)), 137.1 Ar*C*(2)$CH_3$), 167.0 (*C*=O).

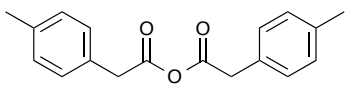
2-(*m*-Tolyl)acetic anhydride **260**



**260**

Following *General Procedure B*, *m*-tolylacetic acid (0.50 g, 3.33 mmol) and DCC (0.35 g, 1.70 mmol) were stirred in toluene (10 mL) to give product **260** as a yellow oil (0.47 g, >99%) with data in accordance with the literature.[15] $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.27 (6H, s, 2 × C$H_3$), 3.54 (4H, s, 2 × C$H_2$), 6.99-7.02 (3H, m, Ar*H*), 7.12-7.18 (5H, m, Ar*H*).

2-(*p*-Tolyl)acetic anhydride **261**

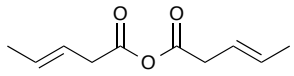


**261**

Following *General Procedure B*, *p*-tolylacetic acid (0.50 g, 3.33 mmol) and DCC (0.35 g, 1.70 mmol) were stirred in toluene (10 mL) to give product **261** as a white solid (0.47 g, >99%) with data in accordance with the literature.[15] mp 46-48 °C {Lit.[15]

56-57 °C}; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 2.39 (6H, s, 2 × C$H_3$), 3.72 (4H, s, 2 × C$H_2$), 7.12-7.19 (8H, m, Ar*H*).

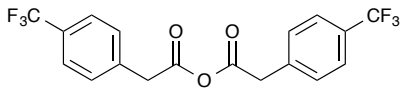
(*E*)-Pent-3-enoic anhydride **236**



**236**

Following *General Procedure B*, 3-pentenoic acid (1.36 mL, 13.3 mmol) and DCC (1.40 g, 6.80 mmol) were stirred in toluene (40 mL) to give product **236** as a pale yellow oil (1.20 g, >99%). $\nu_{max}$ (neat) 3000 (=CH), 2920 (C-H), 1819 (C=O), 1749 (C=O), 1699 (C=C), 1031 (C-O); $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta_H$: 1.69-1.73 (6H, m, 2 × C$H_3$), 3.11-3.20 (4H, m, 2 × C$H_2$), 5.42-5.57 (2H, m, 2 × C*H*), 5.57-5.70 (2H, m, 2 C*H*); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) $\delta_C$: 18.1 (*C*H$_3$), 39.0 (*C*H$_2$), 120.9 (*C*H), 131.2 (*C*H), 167.9 (*C*=O); *m/z* (ASAP$^+$) 200 ([M+NH$_4$]$^+$, 75%); HRMS (ASAP$^+$) $C_{10}H_{18}O_3N^+$ ([M+NH$_4$]$^+$), requires 200.1281; found 200.1277 (–2.1 ppm).

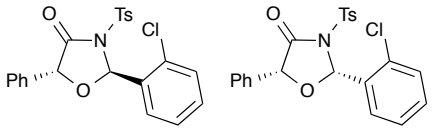
2-(4-(Trifluoromethyl)phenyl)acetic anhydride **226**



**226**

Following *General Procedure B*, *p*-trifluoromethylphenyl acid (0.68g, 3.33 mmol) and DCC (0.35 g, 1.70 mmol) were stirred in toluene (10 mL) to give product **226** as an off white solid (0.65 g, >99%). mp 58-60 °C; $\nu_{max}$ (neat) 2933 (C-H), 1813 (C=O), 1749 (C=O), 1062 (C-O), 766 ($CF_3$); $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 3.80 (4H, s, 2 C$H_2$), 7.33 (4H, d, *J* 8.1, Ar*H*), 7.59 (4H, d, *J* 8.1, Ar*H*); $^{13}$C{$^{1}$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 41.8 (*C*H$_2$), 124.1 (q, $^{1}J_{CF}$ 272.1, *C*F$_3$), 125.9 (q, $^{3}J_{CF}$ 4.1, Ar*C*(3)), 129.9 (Ar*C*(2)), 130.3 (q, $^{2}J_{CF}$ 32.8, Ar*C*(4)), 135.8 (Ar*C*(1)), 166.0 (*C*=O); $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta_F$: –115.1 (Ar*F*); *m/z* HRMS $C_{18}H_{13}F_6O_3^+$ ([M+H]$^+$), requires 391.0763; found 391.0759 (–1.1 ppm)

### 6.4.3 Optimisation Studies on 216




**216**

*Catalyst Loading Screen:*

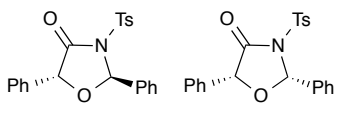
To a solution of phenylacetic acid (27.2 mg, 0.20 mmol, 1 equiv.), was added *i*-$Pr_2NEt$ (52.0 μL, 0.30 mmol, 1.5 equiv.) and pivaloyl chloride (37.0 μL, 0.30 mmol, 1.5 equiv.) at 0 °C and stirred for 20 min. Oxaziridine **219** (62.0 mg, 0.2 mmol), *i*-$Pr_2NEt$ (87.2 μL, 0.50 mmol, 2.5 equiv.) stirred at –78 °C to room temperature for 1 h

(2*S*,3*R*)-HBTM-2.1 **26** (6.17 mg, 0.02 mmol, 10 mol%) gave crude **216** (69:31 dr). Chromatographic purification (80:20 Petrol:$Et_2O$) gave **216** as a white solid and mixture of diastereoisomers (51.2 mg, 60%); >99%/>99% ee. By $^1$H NMR, 13% imine was observed.

(2*S*,3*R*)-HBTM-2.1 **26** (3.08 mg, 0.01 mmol, 5 mol%) gave crude **216** (73:27 dr). Chromatographic purification (80:20 Petrol:$Et_2O$) gave **216** as a white solid and mixture of diastereoisomers (53.0 mg, 62%); 44%/>ND ee. By $^1$H NMR, 16% imine was observed.

### 6.4.4 Experimental Procedures

(2*R*,5*R*)-2,5-Diphenyl-3-tosyloxazolidin-4-one (*anti*-**214**) and (2*S*,5*R*)-2,5-diphenyl-3-tosyloxazolidin-4-one (*syn*-**214**)



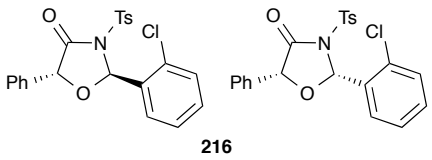

**214**

Following *General Procedure K*, homoanhydride **134** (76.3 mg, 0.3 mmol), cesium carbonate (131.5 mg, 0.4 mmol), oxaziridine **211** (55.1 mg, 0.2 mmol) and (2*S*,3*R*)-HBTM-2.1 **26** (6.2 mg, 0.02 mmol) were stirred in dichloromethane (1 mL) at –78 °C to room temperature for 16 h to give the crude product (57:43 *anti:syn*). Purification yielded the product as a mixture of diastereoisomers (54:46 *anti:syn*) as a white solid (65.2 mg, 83%). mp 154-157 °C; $[\alpha]_D^{22}$ +11.8 (*c* 0.5, $CHCl_3$); $\nu_{max}$ (neat) 1751 (C=O), 1373 (C-N), 1175 (R-$SO_2$N), 1088 (C-O); *m/z* (NSI$^+$) 395 ([M+H]$^+$, 100%); HMRS (NSI$^+$) $C_{22}H_{20}NSO_4^+$ ([M+H]$^+$) requires 394.1108; found 394.1108 (0 ppm).

Data for the *anti* diastereoisomer **214**: Chiral HPLC analysis, Chiralcel AD-H (95:5 hexane:IPA, flow rate 1.5 mL min$^{-1}$, 211 nm, 40 °C) $t_R$ major (2*R*,5*R*): 27.1 min, $t_R$ minor (2*S*,5*S*): 53.9 min, 97% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.41 (3H, s, C$H_3$), 5.44 (1H, d, *J* 1.2, C(5)*H*), 6.71 (1H, d, *J* 1.3, C(2)*H*), 7.17-7.19 (2H, m, $SO_2$ArC(3)*H*), 7.37-7.40 (10H, m, ArC*H*), 7.50-7.55 (2H, m, $SO_2$ArC(2)*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.8 (*C*$H_3$), 77.4 (*C*(5)), 91.3 (*C*(2)), 126.5 (C(5)Ar*C*(2)), 127.5 (C(2)Ar*C*(2)), 128.4 ($SO_2$Ar*C*(2)), 128.8 (Ar*C*), 129.0 (Ar*C*), 129.2 (Ar*C*), 129.6 ($SO_2$Ar*C*(3)), 130.3 (Ar*C*), 134.4 (C(5)Ar*C*(1)), 134.8 (C(2)Ar*C*(1)), 136.6 ($SO_2$Ar*C*(1)), 145.8 ($SO_2$Ar*C*(4)), 168.8 (*C*(4)).

Selected data for the *syn* diastereoisomer **214**: Chiral HPLC analysis, Chiralcel AD-H (95:5 hexane:IPA, flow rate 1.5 mL min$^{-1}$, 211 nm, 40 °C) $t_R$ major (2*S*,5*R*): 25.1 min, $t_R$ minor (2*R*,5*S*): 30.4 min, 94% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.39 (3H, s, C$H_3$), 5.41 (1H, d, *J* 1.3, C(5)*H*), 6.59 (1H, d, *J* 1.4, C(2)*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.8 (*C*$H_3$), 78.7 (*C*(5)), 90.9 (*C*(2)), 126.4 (C(5)Ar*C*(2)), 128.3 (C(2)Ar*C*(2)), 128.4 ($SO_2$Ar*C*(2)), 128.6 (Ar*C*), 128.7 (Ar*C*), 129.6 ($SO_2$Ar*C*(3)), 130.5 (Ar*C*), 134.0 (C(5)Ar*C*(1)), 135.1 (C(2)Ar*C*(1)), 136.4 ($SO_2$Ar*C*(1)), 145.7 ($SO_2$Ar*C*(4)), 168.6 (*C*(4)).

(2*R*,5*R*)-2-(2-Chlorophenyl)-5-phenyl-3-tosyloxazolidin-4-one (*anti*-**216**) and (2*S*,5*R*)-2-(2-chlorophenyl)-5-phenyl-3-tosyloxazolidin-4-one (*syn*-**216**)



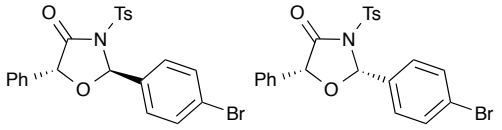

**216**

Following *General Procedure K*, homoanhydride **134** (76.3 mg, 0.3 mmol), cesium carbonate (131.5 mg, 0.4 mmol), oxaziridine **219** (62.0 mg, 0.2 mmol) and (2*S*,3*R*)-HBTM-2.1 **26** (6.2 mg, 0.02 mmol) were stirred at –78 °C to room temperature for 16 h to give the crude product (55:45 *anti:syn*). Purification yielded the product as a mixture of diastereoisomers (56:44 *anti:syn*) as a white solid (66.6 mg, 78%). Careful purification allowed isolation of an analytical sample of each diastereoisomer for full characterisation.

Data for the *anti* diastereoisomer XX: white solid, mp 150-152 °C; $[\alpha]_D^{22}$ –16.6 (c 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralcel AD-H (95:5 hexane:IPA, flow rate 1.5 mL $min^{-1}$, 211 nm, 30 °C) $t_R$ major (2*R*,5*R*): 23.0 min, $t_R$ minor (2*S*,5*S*): 53.2 min, 78% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.43 (3H, s, C$H_3$), 5.38 (1H, d, *J* 1.3, C(5)*H*), 7.02 (1H, d, *J* 1.4, C(2)*H*), 7.14-7.25 (2H, m, $SO_2$ArC(3)*H*), 7.28-7.47 (9H, m, ArC*H*), 7.56-7.69 (2H, m, $SO_2$ArC(2)*H*).

Data for the *syn* diastereoisomer XX: white solid with data in accordance with the literature.[16] 156-158 °C {Lit.[16] 182-184 °C}; $[\alpha]_D^{22}$ +40.2 ($CHCl_3$, *c* 0.5); Chiral HPLC analysis, Chiralcel AD-H (95:5 hexane:IPA, flow rate 1.5 mL $min^{-1}$, 211 nm, 30 °C), $t_R$ major (2*S*,5*R*): 40.4 min, $t_R$ minor (2*R*,5*S*): 46.0 min, 78% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.43 (3H, s, C$H_3$), 5.35 (1H, d, *J* 1.3, C(5)*H*), 7.06 (1H, s, C(2)*H*), 7.23-7.31 (2H, m, $SO_2$ArC(3)*H*), 7.28-7.50 (9H, m), 7.75-7.64 (2H, m, $SO_2$ArC(3)*H*).

(2*R*,5*R*)-2-(4-Bromophenyl)-5-phenyl-3-tosyloxazolidin-4-one (*anti*-**217**) and (2*S*,5*R*)-2-(4-Bromophenyl)-5-phenyl-3-tosyloxazolidin-4-one (*syn*-**217**)




**217**

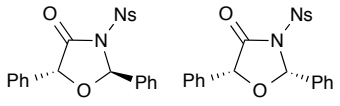
Following *General Procedure K*, homoanhydride **134** (76.3 mg, 0.3 mmol), cesium carbonate (131.5 mg, 0.4 mmol), oxaziridine **220** (70.8 mg, 0.2 mmol) and (2*S*,3*R*)-HBTM-2.1 **26** (6.2 mg, 0.02 mmol) were stirred at –78 °C to room temperature for 16 h to give the crude product (55:45 *anti:syn*). Purification yielded the product as a mixture of diastereoisomers (47:53 *anti:syn*) as a white solid (77.5mg, 82%). Careful purification allowed isolation of an analytical sample of each diastereoisomer for full characterisation.

Data for the *anti* diastereoisomer **217**: white solid, mp 96-100 °C; $[\alpha]_D^{22}$ +8.0 (*c* 0.5, $CHCl_3$); $\nu_{max}$ (neat) 1751 (C=O), 1373 (C-N), 1172 (R-$SO_2$N), 1068 (C-O); Chiral HPLC analysis, Chiralcel OD-H (90:10 hexane;IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C) $t_R$ major (2*R*,5*R*): 17.2 min, $t_R$ minor (2*S*,5*S*): 20.5 min, 99% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.41 (3H, s, C$H_3$), 5.39 (1H, d, *J* 1.4, C(5)*H*), 6.54 (1H, d, *J* 1.4, C(2)*H*), 7.16-7.24 (2H, m, $SO_2$ArC(3)*H*), 7.23-7.30 (3H, m, Ar*H*), 7.30-7.41 (4H, m, Ar*H*), 7.46-7.56 (4H, m, Ar*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.9 (*C*$H_3$), 79.0 (*C*(5)), 90.2 (*C*(2)), 124.8 (C(2)Ar*C*(4)), 126.3 (C(5)Ar*C*(2)), 128.3 (C(2)Ar*C*(2)), 128.8 ($SO_2$Ar*C*(2)), 129.1 (Ar*C*), 129.7 (C(2)Ar*C*(1)), 130.0 ($SO_2$Ar*C*(3)), 131.9 (Ar*C*), 133.8 (C(5)Ar*C*(1)), 134.9 (Ar*C*), 135.6 ($SO_2$Ar*C*(1)), 146.0 ($SO_2$Ar*C*(4)), 168.5 (*C*(4)); *m/z* (NSI$^+$) 472 ([M+$NH_4$]$^+$, 60%); HMRS (NSI$^+$) $C_{22}H_{19}BrNSO_4^+$ ([M+$NH_4$]$^+$) requires 472.0213; found 472.0203 (–2.1 ppm).

Data for the *syn* diastereoisomer **217**: white solid, mp 162-168 °C; $[\alpha]_D^{22}$ –14.0 (*c* 0.5, $CHCl_3$); $\nu_{max}$ (neat) 1751 (C=O), 1375 (C-N), 1170 (R-$SO_2$N), 1090 (C-O); Chiral HPLC analysis, Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C) $t_R$ major (2*R*,5*S*): 15.5 min, $t_R$ minor (2*S*,5*R*): 24.6 min, 89% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.43 (3H, s, C$H_3$), 5.40 (1H, d, *J* 1.2, C(5)*H*), 6.64 (1H, d, *J* 1.2, C(2)*H*), 7.19-7.25 (2H, m, Ar*H*), 7.24-7.31 (4H, m, Ar*H*), 7.31-7.40 (5H, m, Ar*H*),

7.49-7.55 (2H, m, $SO_2$ArC(2)*H*); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.9 (*C*$H_3$), 78.8 (*C*(5)), 90.6 (*C*(2)), 124.6 (C(2)Ar*C*(4)), 126.5 (C(5)Ar*C*(2)), 128.3 (C(2)Ar*C*(2)), 129.0 ($SO_2$Ar*C*(2)), 129.2 (Ar*C*), 129.4 (Ar*C*), 129.7 (Ar*C*), 132.0 ($SO_2$Ar*C*(3)), 134.2 (Ar*C*), 134.8 (C(5)Ar*C*(1)), 135.7 ($SO_2$Ar*C*(1)), 146.0 ($SO_2$-Ar*C*(4)), 168.7 (*C*(4)).

3-Nitro-4-((2*R*,5*R*)-4-oxo-2,5-diphenyloxazolidin-3-yl)benzenesulfonic (*anti*-**222**) acid and 3-nitro-4-((2*S*,5*R*)-4-oxo-2,5-diphenyloxazolidin-3-yl)benzenesulfonic acid (*syn*-**222**)



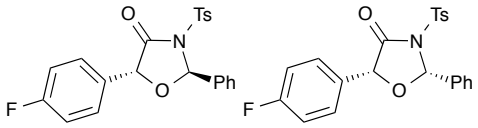

**222**

Following *General Procedure K*, homoanhydride **134** (76.3 mg, 0.3 mmol), cesium carbonate (131.5 mg, 0.4 mmol), oxaziridine **211** (64.5 mg, 0.2 mmol) and (2*S*,3*R*)-HBTM-2.1 **26**(6.2 mg, 0.02 mmol) were stirred at –78 °C to room temperature for 16 h to give the crude product (59:41 *anti:syn*). Purification yielded the product as a mixture of diastereoisomers (52:48 *anti:syn*) as a white solid (62.0 mg, 73%).

Data for the *anti* diastereoisomer **222**: white solid, mp 146-150 °C; $[\alpha]_D^{22}$ +68.2 (*c* 0.5, $CHCl_3$); $\nu_{max}$ (neat) 1751 (C=O), 1531 ($NO_2$), 1384 (C-N), 1180 (R-$SO_2$N), 1086 (C-O); Chiral HPLC analysis, Chiralcel AD-H (80:20 hexane:IPA, flow rate 1.25 mL $min^{-1}$, 211 nm, 40 °C) $t_R$ major (2*R*,5*R*): 27.3 min, $t_R$ minor (2*S*,5*S*): 29.9 min, 85% ee; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta_H$: 5.51 (1H, d, *J* 1.2, C(5)*H*), 6.72 (1H, d, *J* 1.2, C(2)*H*), 7.29-7.45 (9H, m, Ar*H*), 7.45-7.57 (1H, m, Ar*H*) 7.68-7.83 (2H, m, $SO_2$ArC(3)*H*), 8.12-8.26 (2H, m, $SO_2$ArC(2)*H*); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta_C$: 78.9 (*C*(5)), 91.5 (*C*(2)), 124.1 (Ar*C*), 126.3 (C(5)Ar*C*(2)), 127.7 (C(2)Ar*C*(2)), 129.0 ($SO_2$Ar*C*(2)), 129.2 (2 Ar*C*), 129.6 (Ar*C*), 129.6 ($SO_2$Ar*C*(3)), 130.8 (Ar*C*), 133.9 ($C_{ipso}$), 136.1 (C(5)Ar*C*(1)), 143.1 ($SO_2$Ar*C*(1)), 151.0 ($SO_2$Ar*C*(4)), 168.7 (*C*(4)); *m/z* ($NSI^+$) 425 ($[M+H]^+$, 100%); HMRS $C_{21}H_{17}N_2O_6S^+$ ($[M+H]^+$) requires 425.0802; found 425.0801 (–0.2 ppm).

Selected data for the *syn* diastereoisomer **222**: white solid, mp 90-94 °C; $[\alpha]_D^{22}$ –48.0 (*c* 0.1, $CHCl_3$); $\nu_{max}$ (neat) 1749 (C=O), 1533 ($NO_2$), 1386 (C-N), 1182 (R-$SO_2$N), 1087 (C-O); Chiral HPLC analysis, Chiralcel AD-H (80:20 hexane:IPA, flow rate 1.5 mL $min^{-1}$, 211 nm, 30 °C) $t_R$ major (2*S*,5*R*): 18.3 min, $t_R$ minor (2*R*,5*S*): 20.7 min, 80% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 5.49 (1H, d, *J* 1.3, C(5)*H*), 6.62 (1H, d, *J* 1.4, C(2)*H*), 7.30-7.45 (9H, m, Ar*H*), 7.66 (2H, d, *J* 8.9, $SO_2$ArC(3)*H*), 8.16 (2H, d, *J* 8.9 $SO_2$ArC(2)*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 79.0 (*C*(5)), 90.9 (*C*(2)), 124.1 (C(5)Ar*C*(2)), 126.4 (C(2)Ar*C*(2)), 128.7 ($SO_2$Ar*C*(2)), 128.8 (Ar*C*), 128.9 (Ar*C*), 129.3 (Ar*C*), 129.5 ($SO_2$Ar*C*(3)), 131.0 (Ar*C*), 133.4 (C(5)Ar*C*(1)), 135.6 (C(2)Ar*C*(1)), 143.5 ($SO_2$Ar*C*(4)), 168.5 (*C*(4)).

(2*R*,5*R*)-5-(4-Fluorophenyl)-2-phenyl-3-tosyloxazolidin-4-one (*anti*-**227**) and (2*S*,5*R*)-5-(4-fluorophenyl)-2-phenyl-3-tosyloxazolidin-4-one (*syn*-**227**)




**227**

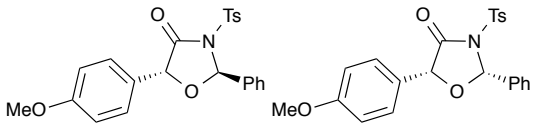
Following *General Procedure K*, homoanhydride **259** (87.1 mg, 0.3 mmol), cesium carbonate (131.5 mg, 0.4 mmol), oxaziridine **211** (55.1 mg, 0.2 mmol) and (2*S*,3*R*)-HBTM-2.1 **26**(6.2 mg, 0.02 mmol) were stirred at –78 °C to room temperature for 16 h to give the crude product (54:46 *anti:syn*). Purification yielded the the product as a mixture of diastereoisomers (55:45 *anti:syn*) as a white solid (60.4 mg, 73%). mp 84-90 °C; $[\alpha]_D^{22}$ +5.6 (*c* 0.5, $CHCl_3$); $\nu_{max}$ (neat) 1749 (C=O), 1508, 1373 (C-N), 1174 (R-$SO_2$N), 1068 (C-O); *m/z* (NSI$^+$) 412 ([M+H]$^+$, 100%); HMRS (NSI$^+$) $C_{22}H_{19}FNSO_4^+$ ([M+H]$^+$) requires 412.1013; found 412.1007 (–1.5 ppm).

Data for the *anti* diastereoisomer **227**: Chiral HPLC analysis, Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C), $t_R$ minor (2*S*,5*S*): 17.0 min, $t_R$ major (2*R*,5*R*): 18.9 min, 99% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.41 (3H, s, C$H_3$), 5.40 (1H, s, C(5)*H*), 6.70 (1H, d, *J* 1.3, C(2)*H*), 6.97-7.14 (2H, m, Ar*H*), 7.13-7.23 (2H, m, Ar*H*), 7.30-7.44 (5H, m, Ar*H*), 7.40-7.52 (2H, m, Ar*H*), 7.49-7.60 (2H, m,

Ar*H*); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.9 (*C*$H_3$), 78.1 (*C*(5)), 91.3 (*C*(2)), 116.0 (d, $^2J_{CF}$ 21.8, C(5)Ar*C*(3)), 127.5 (C(2)Ar*C*(4)), 128.3 (C(2)Ar*C*(2)), 128.4 (Ar*C*), 128.6 ($SO_2$Ar*C*(2)), 129.9 ($SO_2$Ar*C*(3)), 130.3 (d, $^4J_{CF}$ 3.2, C(5)Ar*C*(1)), 130.4 (Ar*C*), 135.0 ($SO_2$Ar*C*(1)), 136.0 (Ar*C*), 145.9 ($SO_2$Ar*C*(4)), 163.3 (d, $^1J_{CF}$ 246, C(5)Ar*C*(4)), 168.6 (*C*(4)). $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) $\delta_F$: –112.3.

Selected data for the *syn* diastereoisomer **227**: Chiral HPLC analysis, Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C) $t_R$ major (2*S*,5*R*): 16.0 min, $t_R$ minor (2*R*,5*S*): 27.6 min, 99% ee; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.39 (3H, s, C$H_3$), 5.38 (1H, s, C(5)*H*), 6.57 (1H, d, *J* 1.4, C(2)*H*); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.9 (*C*$H_3$), 78.5 (*C*(5)), 91.0 (*C*(2)), 116.0 (d, $^2J_{CF}$ 21.9, C(5)Ar*C*(3)), 128.2 (C(2)Ar*C*(2)), 128.5 ($SO_2$Ar*C*(2)), 129.9 (d, $^4J_{CF}$ 3.4, C(5)Ar*C*(1)), 130.6 ($SO_2$Ar*C*(3)), 134.9 (Ar*C*), 136.3 ($SO_2$Ar*C*(1)), 145.8 ($SO_2$Ar*C*(4)), 163.2 (d, $^1J_{CF}$ 246, C(5)Ar*C*(4)), 168.4 (*C*(4)); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$ $\delta_F$: –112.8.

(2*R*,5*R*)-5-(4-Methoxyphenyl)-2-phenyl-3-tosyloxazolidin-4-one and (*anti*-**228**) (2*S*,5*R*)-5-(4-methoxyphenyl)-2-phenyl-3-tosyloxazolidin-4-one (*syn*-**228**)




**228**

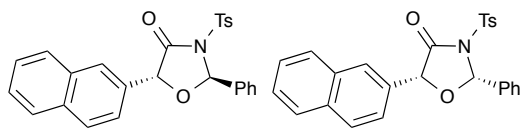
Following *General Procedure K*, homoanhydride **255** (94.3 mg, 0.3 mmol), cesium carbonate (131.5 mg, 0.4 mmol), oxaziridine **211** (55.1 mg, 0.2 mmol) and (2*S*,3*R*)-HBTM-2.1 **26** (6.2 mg, 0.02 mmol) were stirred at –78 °C to room temperature for 16 h to give the crude product (55:45 *anti:syn*). Purification yielded the product as a mixture of diastereoisomers (55:45 *anti:syn*) as a colourless oil (75.4 mg, 89%). $[\alpha]_D^{22}$ +7.8 (*c* 0.5, $CHCl_3$); $\nu_{max}$ (neat) 1749 (C=O), 1373 (C-N), 1175 (R-$SO_2$N), 1088 (C-O); *m/z* (NSI) 424 ($[M+H]^+$, 100%); HMRS (NSI) $C_{23}H_{22}NSO_5^+$ ($[M+H]^+$) requires 424.1213; found 424.1214 (0.2 ppm).

Data for the *anti* diastereoisomer **228**: Chiral HPLC analysis, Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C) $t_R$ minor (2*S*,5*S*): 30.3 min, $t_R$

major (2*R*,5*R*): 33.4 min, 97% ee; $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.41 (3H, s, $SO_2ArCH_3$), 3.80 (3H, s, $OCH_3$), 5.37 (1H, s, C(5)*H*), 6.68 (1H, d, *J* 1.2, C(2)*H*), 6.87-6.92 (2H, m, C(5)Ar*C*(3)*H*), 7.16-7.23 (2H, m, $SO_2$ArC(2)*H*), 7.22-7.29 (2H, m, Ar*H*), 7.36-7.40 (3H, m, Ar*H*), 7.46-7.48 (2H, m, Ar*H*), 7.51-7.58 (2H, m, Ar*H*); $^{13}$C{$^{1}$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.9 (Ar*C*$H_3$), 55.5 (O*C*$H_3$), 78.6 (*C*(5)), 91.1 (*C*(2)), 114.4 (C(5)Ar*C*(3)), 126.5 (C(5)Ar*C*(1)), 127.5 (C(2)Ar*C*(2)), 128.3 (C(5)Ar*C*(2)), 128.4 ($SO_2$Ar*C*(2)), 128.6 (Ar*C*), 128.8 (Ar*C*), 129.6 ($SO_2$Ar*C*(3)), 130.0 (Ar*C*), 134.9 ($SO_2$Ar*C*(1)), 136.7 (C(2)Ar*C*(1)), 145.7 ($SO_2$Ar*C*(4)), 160.4 (C(5)Ar*C*(4)), 169.1 (*C*(4)).

Selected data for the *syn* diastereoisomer **228**: Chiral HPLC analysis, Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.0 mL min$^{-1}$, 211 nm, 30 °C) $t_R$ major (2*S*,5*R*): 25.2 min, $t_R$ minor (2*R*,5*S*): 27.6 min, 94% ee; $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.39 (3H, s, $SO_2ArCH_3$), 3.78 (3H, s, $OCH_3$), 5.35 (1H, s, C(5)*H*), 6.55 (1H, d, *J* 1.4, C(2)*H*), 6.86-6.89 (2H, m, C(5)Ar*C*(3)*H*), 7.15-7.18 (2H, m, $SO_2$ArC(2)*H*); $^{13}$C{$^{1}$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.8 (Ar*C*$H_3$), 55.5 (O*C*$H_3$), 79.0 (*C*(5)), 90.8 (*C*(2)), 114.2 (C(5)Ar*C*(3)), 126.1 (C(5)Ar*C*(1)), 127.5 (C(2)Ar*C*(2)), 128.3 (C(5)Ar*C*(2)), 128.4 ($SO_2$Ar*C*(2)), 128.6 (Ar*C*), 128.8 (Ar*C*), 129.6 ($SO_2$Ar*C*(3)), 130.0 (Ar*C*), 135.2 ($SO_2$Ar*C*(1)), 136.4 (C(2)Ar*C*(1)), 145.6 ($SO_2$Ar*C*(4)), 160.4 (C(5)Ar*C*(4)), 169.0 (*C*(4)).

(2*R*,5*R*)-5-(Naphthalen-2-yl)-2-phenyl-3-tosyloxazolidin-4-one (*anti*-**229**) and (2*S*,5*R*)-5-(naphthalen-2-yl)-2-phenyl-3-tosyloxazolidin-4-one (*syn*-**229**)




**229**

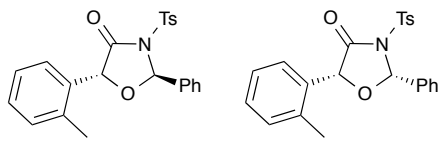
Following *General Procedure K*, homoanhydride **223** (106.3 mg, 0.3 mmol), cesium carbonate (131.5 mg, 0.4 mmol), oxaziridine **211** (55.1 mg, 0.2 mmol) and (2*S*,3*R*)-HBTM-2.1 **26** (6.2 mg, 0.02 mmol) were stirred at –78 °C to room temperature for 16 h to give the crude product (53:47 *anti:syn*). Purification yielded the product as a mixture of diastereoisomers (58:42 *anti:syn*) as a white solid (47.0 mg, 48%). mp

136-140 °C; $[\alpha]_D^{22}$ +31.8 (*c* 0.5, $CHCl_3$); $\nu_{max}$ (neat) 1749 (C=O), 1373 (C-N), 1175 (R-$SO_2$N), 1088 (C-O); *m/z* (NSI$^+$) 461 ([M+$NH_4$]$^+$, 60%); HMRS (NSI$^+$) $C_{26}H_{22}NSO_4^+$ ([M+$NH_4$]$^+$) requires 444.1264; found 444.1254 (–2.3 ppm).

Data for the *anti* diastereoisomer **229**: Chiral HPLC analysis, Chiralcel AD-H (90:10 hexane:IPA, flow rate 1.0 mL min$^{-1}$, 211 nm, 40 °C) $t_R$ major (2*R*,5*R*): 24.3 min, $t_R$ minor (2*S*,5*S*): 57.9 min, 94% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.39 (3H, s, ArC$H_3$), 5.60 (1H, s, C(5)*H*), 6.77 (1H, d, *J* 1.2, C(2)*H*), 7.16-7.20 (2H, m, $SO_2$ArC(2)*H*), 7.35-7.60 (9H, m, Ar*H*), 7.79-7.89 (4H, m, Ar*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.8 (Ar*C*$H_3$), 78.9 (*C*(5)), 91.4 (*C*(2)), 123.7 (Ar*C*), 126.1 (Ar*C*), 126.7 (Ar*C*), 126.8 (Ar*C*), 127.5 (C(2)Ar*C*(2)), 127.9 (Ar*C*), 128.3 (Ar*C*), 128.4 ($SO_2$Ar*C*(2)), 128.7 (Ar*C*), 128.9 (Ar*C*), 129.6 ($SO_2$Ar*C*(3)), 130.3 (Ar*C*), 131.7 (C(5)Ar*C*(1)), 133.1 ($C_{ipso}$), 133.6 ($C_{ipso}$), 134.8 ($SO_2$Ar*C*(1)), 136.7 (C(2)Ar*C*(1)), 145.8 ($SO_2$Ar*C*(4)), 168.8 (*C*(4)).

Selected data for the *syn* diastereoisomer **229**: Chiral HPLC analysis, Chiralcel AD-H (90:10 hexane:IPA, flow rate 1.0 mL min$^{-1}$, 211 nm, 40 °C) $t_R$ major (2*S*,5*R*): 20.9 min, $t_R$ minor (2*R*,5*S*): 32.0 min, 90% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.37 (3H, s, ArC$H_3$), 5.59 (1H, s, C(5)*H*), 6.65 (1H, d, *J* 1.2, C(2)*H*), 7.11-7.16 (2H, m, $SO_2$ArC(2)*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.8 (Ar*C*$H_3$), 79.2 (*C*(5)), 91.1 (*C*(2)), 123.6 (Ar*C*), 125.8 (Ar*C*), 126.5 (Ar*C*), 126.7 (Ar*C*), 127.5 (C(2)Ar*C*(2)), 127.8 (Ar*C*), 128.3 (C(5)Ar*C*(2)), 128.5 ($SO_2$Ar*C*(2)), 128.6 (Ar*C*), 129.0 (Ar*C*), 129.6 ($SO_2$Ar*C*(3)), 130.5 (Ar*C*), 131.5 (C(5)Ar*C*(1)), 133.0 ($C_{ipso}$), 133.5 ($C_{ipso}$), 135.2 ($SO_2$Ar*C*(1)), 136.5 (C(2)Ar*C*(1)), 145.7 ($SO_2$Ar*C*(4)), 168.6 (*C*(4)).

(2*R*,5*R*)-2-Phenyl-5-(*o*-tolyl)-3-tosyloxazolidin-4-one (*anti*-**230**) and (2*S*,5*R*)-2-phenyl-5-(*o*-tolyl)-3-tosyloxazolidin-4-one (*syn*-**230**)




**230**

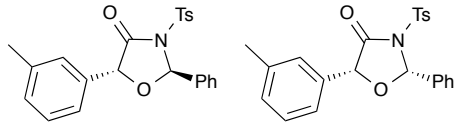
Following *General Procedure K*, homoanhydride **224** (84.7 mg, 0.3 mmol), cesium carbonate (131.5 mg, 0.4 mmol), oxaziridine **211** (55.1 mg, 0.2 mmol) and (2*S*,3*R*)-HBTM-2.1 **26** (6.2 mg, 0.02 mmol) were stirred at –78 °C to room temperature for 16 h to give the crude product (53:47 *anti:syn*). Purification yielded the product as a mixture of diastereoisomers (58:42 *anti:syn*) as a white solid (78.5 mg, 96%). Careful purification allowed isolation of an analytical sample of each diastereoisomer for full characterisation.

Data for the *anti* diastereoisomer **230**: white solid, mp 90-96 °C; $[\alpha]_D^{22}$ +42.8 (c 0.5, $CHCl_3$); $\nu_{max}$ (neat) 1749 (C=O), 1373 (C-N), 1175 (R-$SO_2$N), 1088 (C-O); Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 40 °C) $t_R$ minor (2*S*,5*S*): 22.9 min, $t_R$ major (2*R*,5*R*): 26.5 min, >99% ee; *m/z* ($NSI^+$) 408 ($[M+H]^+$, 100%); HMRS ($NSI^+$) $C_{23}H_{22}NSO_4^+$ ($[M+H]^+$, 100%) requires 408.1264; found 408.1258 (–1.5 ppm); $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.30 (3H, s, C(5)ArC$H_3$), 2.43 (3H, s, $SO_2$ArC$H_3$), 5.60 (1H, d, *J* 1.2, C(5)*H*), 6.70 (1H, d, *J* 1.2, C(2)*H*), 7.14-7.20 (3H, m, Ar*H*), 7.20-7.25 (2H, m, Ar*H*), 7.37-7.47 (5H, m, Ar*H*), 7.58-7.64 (2H, m, Ar*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 19.3 (C(5)Ar*C*$H_3$), 21.9 ($SO_2$Ar*C*$H_3$), 77.4 (*C*(5)), 91.0 (*C*(2)), 126.4 (Ar*C*), 127.4 (C(2)Ar*C*(2)), 127.6 (Ar*C*), 128.5 ($SO_2$Ar*C*(2)), 128.9 (2 Ar*C*), 129.5 (Ar*C*), 129.7 ($SO_2$Ar*C*(3)), 130.2 (Ar*C*), 131.3 (Ar*C*), 132.8 (C(5)Ar*C*(1)), 134.8 ($SO_2$Ar*C*(1)), 136.9 (C(2)Ar*C*(1)), 137.3 (C(5)Ar*C*(2)$CH_3$), 145.8 ($SO_2$Ar*C*(4)), 169.1 (*C*(4)); *m/z* ($NSI^+$) 408 ($[M+H]^+$, 99%) HMRS ($NSI^+$) $C_{23}H_{22}NSO_4^+$ ($[M+H]^+$) requires 408.1264; found 408.1258 (–1.5 ppm).

Data for the *syn* diastereoisomer **230**: white solid, mp 126-132 °C; $[\alpha]_D^{22}$ –56.2 (*c* 0.5, $CHCl_3$); $\nu_{max}$ (neat) 1749 (C=O), 1373 (C-N), 1172 (R-$SO_2$N), 1088 (C-O); Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane: IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 40 °C) $t_R$ minor (2*R*,5*S*): 16.8 min, $t_R$ major (2*S*,5*R*): 18.8 min, >99% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.40 (3H, s, C(5)ArC$H_3$), 2.45 (3H, s, $SO_2$ArC$H_3$), 5.66 (1H, d, *J* 1.6, C(5)*H*), 6.57 (1H, d, *J* 1.6, C(2)*H*), 7.12-7.19 (3H, m, Ar*H*), 7.19-7.25 (2H, m, Ar*H*), 7.29-7.34 (1H, m, Ar*H*), 7.35-7.52 (7H, m, Ar*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 19.7 (C(5)Ar*C*$H_3$), 21.8 ($SO_2$Ar*C*$H_3$), 77.4 (*C*(5)), 90.8 (*C*(2)), 126.3 (Ar*C*), 126.6 (Ar*C*), 128.2 (C(2)Ar*C*(2)), 128.6 ($SO_2$Ar*C*(2)), 128.6 (2 Ar*C*), 129.2

(Ar*C*), 129.6 ($SO_2$Ar*C*(3)), 130.5 (Ar*C*), 131.0 (Ar*C*), 132.2 (C(5)Ar*C*(1)), 135.3 ($SO_2$Ar*C*(1)), 136.1 (C(2)Ar*C*(1)), 137.1 (C(5)Ar*C*(2)$CH_3$), 145.6 ($SO_2$Ar*C*(4)), 168.8 (*C*(4)).

(2*R*,5*R*)-2-Phenyl-5-(*m*-tolyl)-3-tosyloxazolidin-4-one (*anti*-**231**) and (2*S*,5*R*)-2-phenyl-5-(*m*-tolyl)-3-tosyloxazolidin-4-one (*syn*-**231**)




**231**

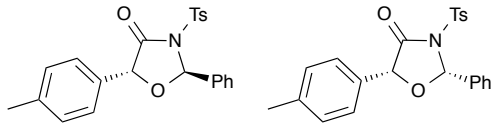
Following *General Procedure K*, homoanhydride **260** (84.7 mg, 0.3 mmol), cesium carbonate (131.5 mg, 0.4 mmol), oxaziridine **211** (55.1 mg, 0.2 mmol) and (2*S*,3*R*)-HBTM-2.1 **26** (6.2 mg, 0.02 mmol) were stirred at –78 °C to room temperature for 16 h to give the crude product (51:49 *anti:syn*). Purification yielded the product as a mixture of diastereoisomers (54.46 *anti:syn*) as a colourless oil (64.4 mg, 79%). $[\alpha]_D^{22}$ +11.6( *c* 0.5, $CHCl_3$); $\nu_{max}$ (neat) 1751 (C=O), 1373 (C-N), 1175 (R-$SO_2$N), 1088 (C-O); *m/z* 408 ($NSI^+$) ($[M+H]^+$, 100%); HMRS ($NSI^+$) $C_{23}H_{22}NSO_4^+$ ($[M+H]^+$) requires 408.1264; found 408.1257 (–1.7 ppm).

Data for the *anti* diastereoisomer **231**: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 40 °C) $t_R$ major (2*R*,5*R*): 20.9 min, $t_R$ minor (2*S*,5*S*): 42.0 min, 92% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.20 (3H, s, C(5)ArC*H*$_3$), 2.27 (3H, s, $SO_2$ArC*H*$_3$), 5.25 (1H, s, C(5)*H*), 6.57 (1H, d, *J* 1.3, C(2)*H*), 6.96-7.08 (4H, m, Ar*H*), 7.08-7.15 (2H, m, Ar*H*), 7.21-7.29 (3H, m, Ar*H*), 7.29-7.38 (2H, m, Ar*H*), 7.37-7.27 (2H, m, Ar*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.5 (C(5)Ar*C*$H_3$), 21.8 ($SO_2$Ar*C*$H_3$), 78.8 (*C*(5)), 91.3 (*C*(2)), 123.8 (Ar*C*), 127.2 (Ar*C*), 127.5 (Ar*C*), 128.4 (C(2)Ar*C*(2)), 128.6 ($SO_2$Ar*C*(2)), 128.8 (2 x Ar*C*), 129.6 ($SO_2$Ar*C*(3)), 130.1 (Ar*C*), 130.3 (Ar*C*), 134.4 (C(5)Ar*C*(1)), 134.9 ($SO_2$Ar*C*(1)), 136.7 (C(2)Ar*C*(1)), 138.8 (C(5)Ar*C*(2)$CH_3$), 145.7 ($SO_2$Ar*C*(4)), 169.0 (*C*(4)).

Selected data for the *syn* diastereoisomer **231**: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 40 °C) $t_R$ major (2*S*,5*R*): 19.1 min, $t_R$ minor (2*R*,5*S*):

26.3 min, 94% ee; $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.18 (3H, s, C(5)ArC$H_3$), 2.25 (3H, s, $SO_2$ArC$H_3$), 5.23 (1H, d, *J* 1.2, C(5)*H*), 6.44 (1H, d, *J* 1.4, C(2)*H*); $^{13}$C{$^{1}$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.6 (C(5)Ar*C*H$_3$), 21.8 ($SO_2$Ar*C*H$_3$), 79.1 (*C*(5)), 90.9 (*C*(2)), 123.4 (Ar*C*), 127.1 (Ar*C*), 127.5 (2 Ar*C*), 128.3 (C(2)Ar*C*(2)), 128.4 ($SO_2$Ar*C*(2)), 128.9 (Ar*C*), 129.6 ($SO_2$Ar*C*(3)), 129.8 (Ar*C*), 130.5 (Ar*C*), 133.9 (C(5)Ar*C*(1)), 135.1 ($SO_2$Ar*C*(1)), 136.5 (C(2)Ar*C*(1)), 138.4 (C(5)Ar*C*(2)CH$_3$), 145.6 ($SO_2$Ar*C*(4)), 168.7 (*C*(4)).

(2*R*,5*R*)-2-Phenyl-5-(*p*-tolyl)-3-tosyloxazolidin-4-one (*anti*-**232**) and (2*S*,5*R*)-2-phenyl-5-(*p*-tolyl)-3-tosyloxazolidin-4-one (*syn*-**232**)




**232**

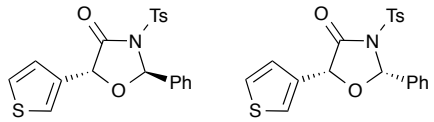
Following *General Procedure K*, homoanhydride **261** (84.7 mg, 0.3 mmol), cesium carbonate (131.5 mg, 0.4 mmol), oxaziridine **211** (55.1 mg, 0.2 mmol) and (2*S*,3*R*)-HBTM-2.1 **26** (6.2 mg, 0.02 mmol) were stirred at –78 °C to room temperature for 16 h to give the crude product (53:47 *anti:syn*). Purification yielded the product as a mixture of diastereoisomers (54.46 *anti:syn*) as a white solid (71.6 mg, 88%). mp 138-142 °C; $[\alpha]_D^{22}$ –3.0 (*c* 0.5, $CHCl_3$); $\nu_{max}$ (neat) 1749 (C=O), 1373 (C-N), 1175 (R-$SO_2$N); *m/z* (NSI$^+$) 408 ([M+H]$^+$, 85%); HMRS (NSI$^+$) $C_{23}H_{22}NSO_4^+$ ([M+H]$^+$) requires 408.1264; found 408.1259 (–1.2 ppm).

Data for the *anti* diastereoisomer **232**: Chiral HPLC analysis, Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.0 mL min$^{-1}$, 211 nm, 30 °C) $t_R$ major (2*R*,5*R*): 17.2 min, $t_R$ minor (2*S*,5*S*): 22.5 min, 97% ee; $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.35 (3H, s, C(5)ArC$H_3$), 2.41 (3H, s, $SO_2$ArC$H_3$), 5.39 (1H, s, C(5)*H*), 6.69 (1H, d, *J* 1.2, C(2)*H*), 7.16-7.21 (4H, m, Ar*H*), 7.24 (2H, d, *J* 8.1, Ar*H*), 7.34-7.43 (3H, m, Ar*H*), 7.40-7.50 (2H, m, Ar*H*), 7.50-7.58 (2H, m, Ar*H*); $^{13}$C{$^{1}$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.3 (C(5)Ar*C*H$_3$), 21.7 ($SO_2$Ar*C*H$_3$), 78.7 (*C*(5)), 91.1 (*C*(2)), 126.5 (C(5)Ar*C*(2)), 127.4 (2 Ar*C*), 128.2 (C(2)Ar*C*(2)), 128.7 ($SO_2$Ar*C*(2)), 129.5 ($SO_2$Ar*C*(3)), 129.6 (2 Ar*C*),

130.1 (Ar*C*), 131.4 (C(5)Ar*C*(1)), 134.8 ($SO_2$Ar*C*(1)), 136.6 (C(2)Ar*C*(1)), 139.2 (C(5)Ar*C*(4)), 145.6 ($SO_2$Ar*C*(4)), 168.9 (*C*(4)).

Selected data for the *syn* diastereoisomer **232**: Chiral HPLC analysis, Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C) $t_R$ major (2*S*,5*R*): 15.3 min, $t_R$ minor (2*R*,5*S*): 26.7 min, 97% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.33 (3H, s, C(5)ArC$H_3$), 2.39 (3H, s, $SO_2$ArC$H_3$), 5.38 (1H, s, C(5)*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.2 (C(5)Ar*C*$H_3$), 21.7 ($SO_2$Ar*C*$H_3$), 79.0 (*C*(5)), 90.7 (*C*(2)), 126.3 (C(5)Ar*C*(2)), 128.1 (C(2)Ar*C*(2)), 128.3 (2 Ar*C*), 128.5 ($SO_2$Ar*C*(2)), 129.3 ($SO_2$Ar*C*(3)), 130.3 (Ar*C*), 131.0 (C(5)Ar*C*(1)), 134.8 ($SO_2$Ar*C*(1)), 136.3 (C(2)Ar*C*(1)), 138.8 (C(5)Ar*C*(4)), 145.4 ($SO_2$Ar*C*(4)), 168.7 (*C*(4)).

(2*R*,5*R*)-2-Phenyl-5-(thiophen-3-yl)-3-tosyloxazolidin-4-one (*anti*-**233**) and (2*S*,5*R*)-2-phenyl-5-(thiophen-3-yl)-3-tosyloxazolidin-4-one (*syn*-**233**)




**233**

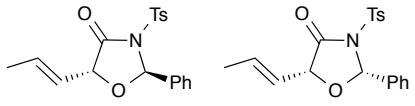
Following *General Procedure K*, homoanhydride **225** (79.9 mg, 0.3 mmol), cesium carbonate (131.5 mg, 0.4 mmol), oxaziridine **211** (55.1 mg, 0.2 mmol) and (2*S*,3*R*)-HBTM-2.1 **26** (6.2 mg, 0.02 mmol) were stirred at –78 °C to room temperature for 16 h to give the crude product (59:41 *anti:syn*). Purification yielded the product as a mixture of diastereoisomers (59:41 *anti:syn*) as a waxy white solid (62.8 mg, 79%). mp 90-96 °C; $[\alpha]_D^{22}$ +32.8 (*c* 0.5, $CHCl_3$); $\nu_{max}$ (neat) 1751 (C=O), 1373 (C-N), 1175 (R-$SO_2$N), 1088 (C-O); *m/z* (NSI$^+$) 400 ([M+$NH_4$]$^+$, 75%); HMRS (NSI$^+$) $C_{20}H_{18}NS_2O_4^+$ ([M+$NH_4$]$^+$) requires 400.0672; found 400.0667 (–1.2 ppm).

Data for the *anti* diastereoisomer **233**: Chiral HPLC analysis, Chiralpak IA (80:20 hexane:IPA, flow rate 1.5 mL $min^{-1}$, 211 nm, 30 °C) $t_R$ major (2*R*,5*R*): 8.7 min, $t_R$ minor (2*S*,5*S*): 13.2 min, 87% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.35 (3H, s, $SO_2$ArC$H_3$), 5.44 (1H, s, C(5)*H*), 6.55 (1H, d, *J* 1.2, C(2)*H*), 6.98-7.02 (1H, m, Ar*H*), 7.11-7.15 (2H, m, $SO_2$Ar*H*), 7.19 (1H, s, C(5)ArC(2)*H*), 7.28 (2H, dd, *J* 1.8, 1.0, Ar*H*) 7.32 (2H, app. s, Ar*H*), 7.33-7.41 (2H, m, Ar*H*), 7.46 (2H, d, *J* 8.4, $SO_2$Ar*H*);

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.7 ($SO_2ArCH_3$), 75.5 (*C*(5)), 91.1 (*C*(2)), 123.7 (C(5)Ar*C*(2)), 125.5 (Ar*C*), 127.1 (Ar*C*), 127.5 (Ar*C*), 128.2 (C(2)Ar*C*(2)), 128.7 ($SO_2ArC$(2)), 129.5 ($SO_2ArC$(3)), 130.9 (C(5)Ar*C*(1)), 134.7 ($SO_2ArC$(1)), 135.0 (C(2)Ar*C*(1)), 136.3 (C(5)Ar*C*(4)), 145.7 ($SO_2ArC$(4)), 168.3 (*C*(4)).

Data for the *syn* diastereoisomer **233**: Chiral HPLC analysis, Chiralpak IA (80:20 hexane:IPA, flow rate 1.5 mL $min^{-1}$, 211 nm, 30 °C) $t_R$ major (2*S*,5*R*): 9.4 min, $t_R$ minor (2*R*,5*S*): 9.8 min, 81% ee; $^{1}H$ NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.32 (3H, s, $SO_2ArCH_3$), 5.43 (1H, d, *J* 1.2 C(5)*H*), 6.49 (1H, d, *J* 1.3, C(2)*H*), 7.04-7.07 (1H, m, Ar*H*), 7.01-7.10 (2H, m, $SO_2ArH$), 7.24 (1H, s, C(5)ArC(2)*H*), 7.33-7.41 (2H, m, $SO_2ArH$); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.7 ($SO_2ArCH_3$), 76.2 (*C*(5)), 91.0 (*C*(2)), 123.2 (C(5)Ar*C*(2)), 126.6 (Ar*C*), 128.1 (2 Ar*C*), 128.2 (C(2)Ar*C*(2)), 128.5 ($SO_2ArC$(2)), 130.3 (2 Ar*C*), 134.6 ($SO_2ArC$(1)), 134.9 (C(2)Ar*C*(1)), 136.3 (C(5)Ar*C*(4)), 145.6 ($SO_2ArC$(4)), 168.0 (*C*(4)).

(2*R*,5*R*)-2-Phenyl-5-((*E*)-prop-1-en-1-yl)-3-tosyloxazolidin-4-one (*anti*-**234**) and (2*S*,5*R*)-2-phenyl-5-((*E*)-prop-1-en-1-yl)-3-tosyloxazolidin-4-one (*syn*-**234**)




**234**

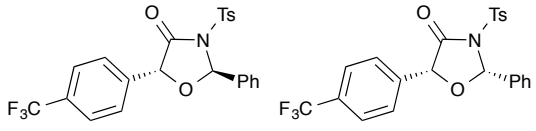
Following *General Procedure K*, homoanhydride **136** (1.20g mg, 6.5 mmol), cesium carbonate (2.8 g, 8.6 mmol), oxaziridine **211** (1.20 g, 4.3 mmol) and (2*S*,3*R*)-HBTM-2.1 **26** (0.13 g, 0.43 mmol) were stirred at –78 °C for 24 h to give the crude product (49:51 *anti:syn*). Purification yielded the product as a mixture of diastereoisomers (54:46 *anti:syn*) as a colourless oil (1.41 g, 61%).

Data for the *anti* diastereoisomer **234**: colourless oil, $[\alpha]_D^{22}$ +10.0 (*c* 0.2, $CHCl_3$); $\nu_{max}$ (neat) 1749 (C=O), 1373 (C-N), 1175 (R-$SO_2$N), 1090 (C-O); Chiral HPLC analysis, Chiralcel OD-H (95:5 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C) $t_R$ minor (2*S*,5*S*): 19.0 min, $t_R$ major (2*R*,5*R*): 22.3 min, >99% ee; $^{1}H$ NMR (500 MHz, $CDCl_3$) $\delta_H$: 1.66-1.71 (3H, m, CHC$H_3$), 2.34 (3H, s, ArC$H_3$), 4.76 (1H, dq, *J* 6.7, 1.1, C(5)*H*), 5.44 (1H, td, *J* 6.8, 1.7, C*H*), 5.83-5.91 (1H, m, C*H*), 6.47 (1H, d, *J* 1.2, C(2)*H*), 7.05-

7.15 (2H, m, $SO_2ArC(3)H$), 7.20-7.31 (3H, m, ArC*H*), 7.31-7.40 (2H, m, ArC*H*), 7.42-7.54 (2H, m, $SO_2ArC(2)H$); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta_C$: 17.9 ($CHCH_3$), 21.7 ($ArCH_3$), 78.0 (*C*(5)), 90.8 (*C*(2)), 123.3 ($CHCHCH_3$), 127.3 (C(5)Ar*C*(2)), 128.0 (Ar*C*), 128.2 (Ar*C*), 128.3 ($SO_2ArC(2)$), 128.4 (Ar*C*), 128.6 (Ar*C*), 129.4 ($SO_2ArC(3)$), 130.0 (Ar*C*), 133.5 ($CHCH_3$), 134.8 (C(2)Ar*C*(1)), 136.6 ($SO_2ArC(1)$), 145.6 ($SO_2ArC(4)$), 169.0 (*C*(4)); *m/z* ($NSI^+$) 358 ($[M+H]^+$, 100%) HMRS ($NSI^+$) $C_{19}H_{20}NSO_4^+$ ($[M+H]^+$) requires 358.1108; found 358.1105 (–0.7 ppm).

Selected data for the *syn* diastereoisomer **234**: colourless oil, $[\alpha]_D^{22}$ +2.6 (*c* 0.1, $CHCl_3$); Chiral HPLC analysis, Chiralcel OD-H (95:5 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C), $t_R$ major (2*S*,5*R*): 21.0 min, $t_R$ minor (2*R*,5*S*): 29.9 min, >99% ee; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.42 (3H, s, $CH_3$), 4.80-4.87 (1H, m, C(5)*H*), 5.47-5.57 (1H, m, C*H*), 5.87-5.99 (1H, m, C*H*), 6.45 (1H, d, *J* 1.2, C(2)*H*); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta_C$: 78.8 (*C*(5)), 90.7 (*C*(2)), 123.7 ($CHCHCH_3$), ($SO_2ArC(3)$), 130.2 (Ar*C*), 134.0 ($CHCH_3$), 135.1 (C(2)Ar*C*(1)), 136.5 ($SO_2ArC(1)$), 145.4 ($SO_2ArC(4)$), 168.9 (*C*(4)).

(2*R*,5*R*)-2-Phenyl-3-tosyl-5-(4-(trifluoromethyl)phenyl)oxazolidin-4-one (*anti*-**235**) and (2*S*,5*R*)-2-phenyl-3-tosyl-5-(4-(trifluoromethyl)phenyl)oxazolidin-4-one (*syn*-**235**)




**235**

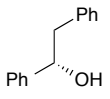
Following *General Procedure K*, homoanhydride **226** (117.1 mg, 0.3 mmol), cesium carbonate (131.5 mg, 0.4 mmol), oxaziridine **211** (55.1 mg, 0.2 mmol) and (2*S*,3*R*)-HBTM-2.1 **26** (6.2 mg, 0.02 mmol) were stirred at –78 °C to room temperature for 16 h to give the crude product (49:51 *anti:syn*). Purification yielded the product as a mixture of diastereoisomers (48:52 *anti:syn*) as a white solid (62.9 mg, 68%).

Data for the *anti* diastereoisomer **235**: colourless oil, $[\alpha]_D^{22}$ +69.0 (*c* 0.1, $CHCl_3$); $\nu_{max}$ (neat) 1749 (C=O), 1489 (C-F); Chiral HPLC analysis, Chiralcel OD-H (90:10

hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C) $t_R$ minor (2*S*,5*S*): 19.8 min, $t_R$ major (2*R*,5*R*): 22.6 min, 43% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.41 (3H, s, C$H_3$), 5.48 (1H, s, C(5)*H*), 6.72 (1H, d, *J* 1.3, C(2)*H*), 7.12-7.23 (2H, m, $SO_2$ArC(3)*H*), 7.32-7.45 (4H, m, ArC*H*), 7.49-7.53 (2H, m, $SO_2$ArC(2)*H*), 7.53-7.57 (3H, m, ArC*H*), 7.64-7.66 (2H, m, ArC*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.9 (*C*$H_3$), 77.9 (*C*(5)), 91.5 (*C*(2)), 125.9 (q, $^3J_{CF}$ 4.0, C(5)Ar*C*(3)), 126.6 (C(2)Ar*C*(2)), 126.9 (q, $^1J_{CF}$ 272.4, *C*$F_3$), 127.5, 128.4 (C(5)Ar*C*(2)), 129.0 ($SO_2$Ar*C*(2)), 129.6 (Ar*C*), 130.5 (Ar*C*), 131.4 (q, $^2J_{CF}$ 32.5, C(5)Ar*C*(4)), 134.6 (C(2)Ar*C*(1)), 136.3 ($SO_2$Ar*C*(1)), 138.2 ($C_{ipso}$), 146.0 ($SO_2$Ar*C*(4)), 168.8 (*C*(4)); $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta_F$: –62.7 (Ar*F*); *m/z* (NSI$^+$) 461 ([M+H]$^+$, 40%); HMRS (NSI$^+$) $C_{23}H_{19}F_3NSO_4^+$ ([M+H]$^+$) requires 462.0976; found 462.0981 (–1.2 ppm).

Selected Data for the *syn* diastereoisomer **235**: colourless oil, Chiral HPLC analysis, Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C) $t_R$ major (2*S*,5*R*): 15.9 min, $t_R$ minor (2*R*,5*S*): 35.9 min, 36% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.38 (3H, s, C$H_3$), 5.48 (1H, s, C(5)*H*), 6.62 (1H, d, *J* 1.3, C(2)*H*), 7.15-7.17 (2H, m, $SO_2$ArC(3)*H*), 7.31-7.35 (2H, m, ArC*H*), 7.35-7.40 (2H, m, Ar*H*), 7.40-7.44 (2H, m, ArC*H*), 7.52-7.58 (2H, m, ArC*H*), 7.58-7.63 (2H, m, ArC*H*); $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$) $\delta_C$: 21.9 (*C*$H_3$), 78.1 (*C*(5)), 91.2 (*C*(2)), 125.6 (q, $^3J_{CF}$ 4.0, C(5)Ar*C*(3)), 126.4 (C(2)Ar*C*(2)), 128.3 (C(5)Ar*C*(2)), 128.8 ($SO_2$Ar*C*(2)), 129.7 (Ar*C*), 130.7 (Ar*C*); $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta_F$: –62.7 (Ar*F*).

(*R*)-1-Phenylethane-1,2-diol **237**

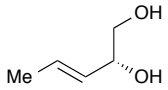



**237**

Following a modified procedure of Ye *et al*.[16] to a solution of oxazolidin-4-one **214** (39.3 mg, 0.1 mmol, 1 equiv.) in dry THF (1 mL, 0.1 M) at 0 °C, 1 M $LiAlH_4$ in THF (0.2 mL, 0.2 mmol, 2 equiv.) was added and the reaction stirred at 0 °C allowing to warm to room temperature over 16 h. The reaction was quenched with 10% NaOH and stirred for 1 h, $CH_2Cl_2$ (1 mL) was added and the organic layer separated, dried

($MgSO_4$) and concentrated *in vacuo* to give the crude product as a colourless oil. Purification by column chromatography using silica gel (Petrol:$Et_2O$ 70:30) gave **237** as a white solid (4.8 mg, 35%) with data in accordance with the literature.[16] mp 46-50 {lit.[16] 66-68 °C}; $[\alpha]_D^{22}$ –50 (*c*, 0.1, $CHCl_3$) {lit.[16] $[\alpha]_D^{22}$ –23.4 (*c* 1, $CHCl_3$)}; Chiral HPLC analysis, Chiralcel OD-H (95:5 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C) $t_R$ major (*R*): 23.4 min, $t_R$ minor (*S*): 26.8 min, 90% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.07 (1H, br. s, O*H*), 2.52 (1H, br. s, O*H*), 3.67 (1H, dd, *J* 11.3, 8.1, C$H_A$H$_B$), 3.76 (1H, t, *J* 2.1, CH$_A$$H_B$), 4.84 (1H, dd, *J* 8.1, 3.6, C*H*), 7.28-7.41 (5H, m, Ar*H*).

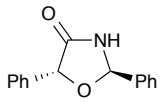
(*R*,*E*)-Pent-3-ene-1,2-diol **238**




**238**

Following a modified procedure of Ye *et al*. to a solution of oxazolidin-4-one **234** (178.7 mg, 0.5 mmol, 1 equiv.) in dry THF (5 mL, 0.1 M) at 0 °C, 1 M $LiAlH_4$ in THF (1 mL, 1 mmol, 2 equiv.) was added and the reaction stirred at 0 °C allowing to warm to room temperature over 16 h. The reaction was quenched with 10% NaOH, stirred for 1 h, $CH_2Cl_2$ (5 mL) was added and the organic layer separated, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as a colourless oil. Purification by column chromatography using silica gel (petrol:$Et_2O$ 70:30) gave **238** as a colourless oil (20.5 mg, 40%) with data in accordance with the literature[17] $[\alpha]_D^{22}$ –10.0 (*c* 0.1, $CHCl_3$) {lit.[17] $[\alpha]_D^{22}$ –23.4 (*c* 1, $CHCl_3$)}; Chiral GC analysis, Agilent Cyclosil B (length: 30 m, thickness: 0.250 mm, film thickness: 0.25 μm), carrier gas: He, linear velocity: 40 cm/sec, initial temperature: 100 °C (hold 2 min), ramp rate: 5 °C/min to 140 °C (hold 2 min), total run time 12 min, $t_R$ minor (*S*) 7.7 min, $t_R$ major (*R*) 7.9 min, 95% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 1.73 (3H, dd, *J* 6.4, 1.7, C$H_3$), 2.38 (2H, br. s, 2 O*H*), 3.49 (1H, ddd, *J* 11.2, 7.6, 1.8, C$H_A$H$_B$), 3.64 (1H, dt, *J* 11.3, 2.6, CH$_A$$H_B$), 4.20 (1H, td, *J* 7.1, 3.2, C*H*OH), 5.48 (1H, ddt, *J* 15.4, 6.7, 1.7, C*H*CH$_3$), 5.69-5.92 (1H, m, C*H*CHCH$_3$).

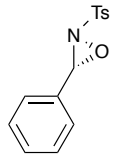
(2*R*,5*R*)-2,5-Diphenyloxazolidin-4-one **239**




**239**

Using a modified version of the procedure by Lectka *et al.*[18] *N*-tosyloxazolidin-4-one **214** (100 mg, 0.25 mmol, 1 equiv.) was stirred in degassed THF (1mL) at –78 °C and $SmI_2$ (5 mL, 0.5 mmol, 2 equiv.) was added dropwise until the colour remained consistent. The reaction mixture was stirred for 5 min, quenched with $NaHCO_3$ (5 mL), extracted (3 × EtOAc), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Following purification by column chromatography (Petrol:$Et_2O$ 50:50) oxazolidin-4-one **239** was isolated as a white solid (40.4 mg, 68%, *anti:syn* >95:5). mp 128-130 °C; $[\alpha]_D^{22}$ –71.8 (*c* 0.5, $CHCl_3$); $\nu_{max}$ (neat) 3207 (NH), 1725 (C=O), 1373 (C-N); Chiral HPLC analysis, Chiralcel AD-H (90:10 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C) $t_R$ major (2*R*,5*R*): 11.5 min, $t_R$ minor (2*S*,3*S*): 15.5 min, 88% ee; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta_H$: 5.42 (1H, d, *J* 2.2, C(5)*H*), 6.32 (1H, d, *J* 2.2, C(2)*H*), 7.31-7.47 (5H, m, ArC*H*), 7.47-7.60 (5H, m, ArC*H*), 7.77 (1H, s, N*H*); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta_C$: 78.6 (*C*(5)), 88.0 (*C*(2)), 126.4 (C(5)Ar*C*(2)), 126.6 (C(2)Ar*C*(2)), 128.8 ($SO_2$Ar*C*(2)), 128.9 (Ar*C*), 129.1 (Ar*C*), 130.1 (Ar*C*), 136.2 (C(5)Ar*C*(1)), 138.4 (C(2)Ar*C*(1)), 173.7 (*C*(4)); *m/z* ($NSI^+$) 262 ($[M+Na]^+$, 100%); HMRS ($NSI^+$) $C_{15}H_{13}NO_2Na^+$ ($[M+Na]^+$) requires 262.0841; found 262.0838 (+1.0 ppm).

(*R*)-3-Phenyl-2-tosyl-1,2-oxaziridine **211**



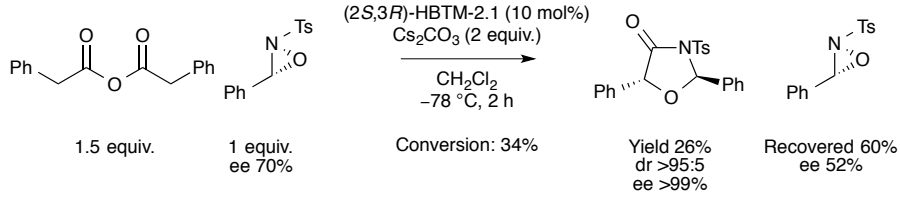

(*R*)-**211**

Using the procedure by Jørgensen *et al*.[19] a flask was charged with the *N*-tosylphenyl imine

(0.52 g, 2.0 mmol), hydroquinidine (65.3 mg, 0.2 mmol) and toluene (20 mL). The mixture was stirred at room temperature until fully dissolved and then cooled to –40 °C. *m*-CPBA (0.63 g, purity 70%, 2.8 mmol) was added and the reaction mixture stirred at –40 °C for 20 h. The crude mixture was loaded directly onto a column packed with silica gel and eluted with the toluene to give **211** as a white solid (0.21g, 39%) with data in accordance with the literature.[19] mp 86-89 °C {lit.[19] 90.4- 91.7 °C}; $[\alpha]_D^{22}$ –40.0 (*c* 0.5, $CH_2Cl_2$) {lit.[19] –49.8 (*c* 0.58, $CH_2Cl_2$)}; Chiral HPLC analysis, Chiralcel OD-H (95:5 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C) $t_R$ major (*R*): 14.7 min, $t_R$ minor (*S*): 21.4 min, 70% ee; $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$: 2.49 (3H, s, C*H*$_3$), 5.46 (1H, s, C*H*), 7.42-7.50 (7H, m, Ar*H*).

### 6.4.5 Stereoselectivity Experiments

#### 6.4.5.1 Reaction of Homoanhydride with Enantioenriched Oxaziridine in Presence of Enantiomerically Pure Catalyst

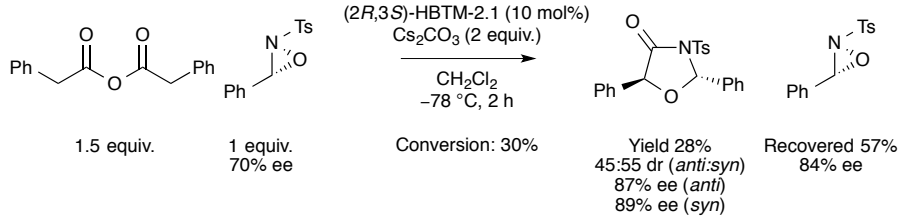



Following *General Procedure C*, homoanhydride **134** (76.3 mg, 0.3 mmol), cesium carbonate (131.5 mg, 0.4 mmol), enantioenriched oxaziridine **211** (55.1 mg, 0.2 mmol, 70% ee) and (2*S*,3*R*)-HBTM-2.1 **26** (6.2 mg, 0.02 mmol) were stirred at –78 °C to room temperature for 2 h to give the crude product (>95:5 *anti:syn*, 34% conversion). Purification yielded the remaining oxaziridine **211** as a white solid (46.1 mg, 60%) and **214** as a white solid (20.7 mg, 26%) with all data in accordance with that previously reported.

Chiral HPLC analysis of oxaziridine **211**: Chiralcel OD-H (95:5 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C) $t_R$ major (*R*): 14.7 min, $t_R$ minor (*S*): 21.4 min, 52% ee

Chiral HPLC analysis of oxazolidin-4-one **214**: Chiralcel AD-H (95:5 hexane:IPA, flow rate 1.5 mL $min^{-1}$, 211 nm, 40 °C) $t_R$ major (2*R*,5*R*): 27.1 min, $t_R$ minor (2*S*,5*S*): 53.9 min, >99%.

### 6.4.5.2 Reaction of Homoanhydride with Enantioenriched Oxaziridine in Presence of Enantiomerically Pure Catalyst in a Mis-matched Case



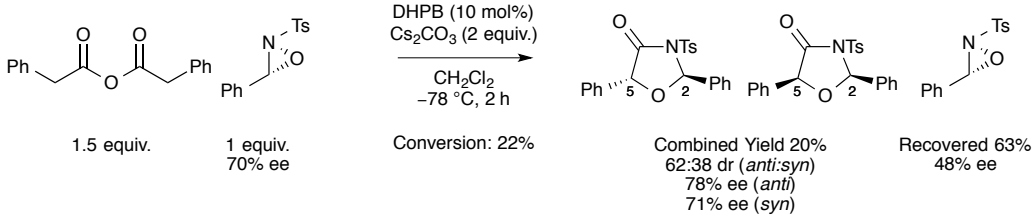

Following *General Procedure C*, homoanhydride **234** (76.3 mg, 0.3 mmol), cesium carbonate (131.5 mg, 0.4 mmol), enantioenriched oxaziridine **211** (55.1 mg, 0.2 mmol, 70% ee) and (2*R*,3*S*)-HBTM-2.1 **26** (6.2 mg, 0.02 mmol) were stirred at –78 °C to room temperature for 2 h to give the crude product **214** (45:55 *anti:syn*, 22% conversion). Purification yielded the remaining oxaziridine **211** as a white solid (31.3 mg, 57%) and **214** as a white solid (22.4 mg, 28%) with all data in accordance with that previously reported.

Chiral HPLC analysis of oxaziridine **211**: Chiralcel OD-H (95:5 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C) $t_R$ major (*R*): 14.7 min, $t_R$ minor (*S*): 21.4 min, 76% ee.

Chiral HPLC analysis of *anti*-oxazolidin-4-one **214**: Chiralcel AD-H (95:5 hexane:IPA, flow rate 1.5 mL $min^{-1}$, 211 nm, 40 °C) $t_R$ minor (2*R*,5*R*): 27.1 min, $t_R$ major (2*S*,5*S*): 53.9 min, 87%.

Chiral HPLC analysis of the *syn*-oxazolidin-4-one **214**: Chiralcel AD-H (95:5 hexane:IPA, flow rate 1.5 mL $min^{-1}$, 211 nm, 40 °C) $t_R$ minor (2*S*,5*R*): 25.1 min, $t_R$ major (2*R*,5*S*): 30.4 min, 89% ee.

### 6.4.5.3 Reaction of Homoanhydride with Enantioenriched Oxaziridine in Presence of Achiral Catalyst



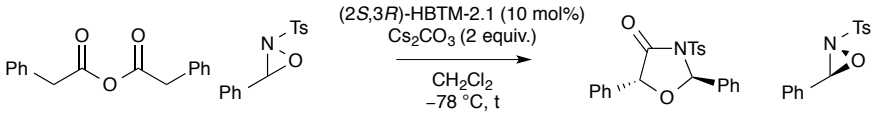

Following *General Procedure C*, homoanhydride **134** (76.3 mg, 0.3 mmol), cesium carbonate (131.5 mg, 0.4 mmol), enantioenriched oxaziridine **211** (55.1 mg, 0.2 mmol, 70% ee) and DHPB **101** (3.8 mg, 0.02 mmol) were stirred at –78 °C to room temperature for 2 h to give the crude product (62:38 *anti:syn*, 14% conversion). Purification yielded the remaining oxaziridine **211** as a white solid (34.9 mg, 63%) and **214** as a white solid (15.5 mg, 20%) with all data in accordance with that previously reported.

Chiral HPLC analysis of oxaziridine **211**: Chiralcel OD-H (95:5 hexane:IPA, flow rate 1.0 mL $min^{-1}$, 211 nm, 30 °C) $t_R$ major (*R*): 14.7 min, $t_R$ minor (*S*): 21.4 min, 48% ee.

Chiral HPLC analysis of *anti*-oxazolidin-4-one **214**: Chiralcel AD-H (95:5 hexane:IPA, flow rate 1.5 mL $min^{-1}$, 211 nm, 40 °C) $t_R$ major (2*R*,5*R*): 27.1 min, $t_R$ minor (2*S*,5*S*): 53.9 min, 78%.

Chiral HPLC analysis of the *syn*-oxazolidin-4-one **214**: Chiralcel AD-H (95:5 hexane:IPA, flow rate 1.5 mL $min^{-1}$, 211 nm, 40 °C) $t_R$ minor (2*S*,5*R*): 25.1 min, $t_R$ major (2*R*,5*S*): 30.4 min, 71% ee.

### 6.4.5.4 Monitoring of Diastereoselectivity and Enantioselectivity Over Time



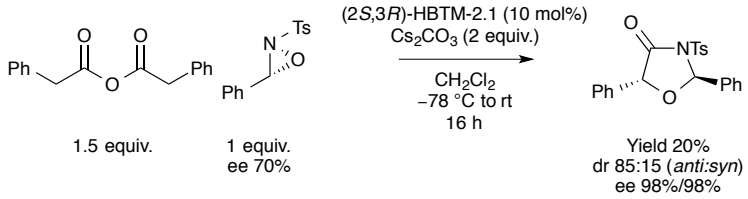

1.5 equiv. 1 equiv. Racemic

| Entry | Time | Conversion (%)[a] | dr (*anti:syn*)[a] | 214 ee (%, *anti*/*syn*)[b] | 211 ee (%)[b] |
|---|---|---|---|---|---|
| 1 | <1 min | 15 | 70:30 | ND | ND |
| 2 | 5 min | 15 | 72:28 | ND | ND |
| 3 | 15 min | 27 | 68:32 | >99/ND | 10 |
| 4 | 30 min | 32 | 66:34 | ND | ND |
| 5 | 1 h | 27 | 68:32 | >99/>99 | 10 |
| 6 | 2 h | 33 | 68:32 | ND | ND |
| 7 | 4 h | 74 | 57:43 | >99/>99 | ND |
| 8 | 16 h | 100 | 53:47 | >99/>99 | N/A |

[a] Determined by inspection of crude $^1$H NMR. [b] Obtained by chiral HPLC analysis following preparative tlc.

Following *General Procedure C*, homoanhydride **134** (187 mg, 0.8 mmol), cesium carbonate (326 mg, 1.0 mmol), oxaziridine **211** (138 mg, 0.5 mmol) and (2*S*,3*R*)-HBTM-2.1 **26** (15.4 mg, 0.05 mmol) were stirred at –78 °C to room temperature for 16 h with 0.2 mL samples taken at intervals to monitor conversion, dr and ee. Samples were purified for HPLC using preparative tlc (50:50 Petrol:$Et_2O$). All data was in accordance to that already reported.

### 6.4.5.5 Repeat of "Matched" Case with Reaction Completed




Following *General Procedure C*, homoanhydride **134** (76.3 mg, 0.3 mmol), cesium carbonate (131.5 mg, 0.4 mmol), enantioenriched oxaziridine **211** (55.1 mg, 0.2 mmol, 70% ee) and (2*S*,3*R*)-HBTM-2.1 **26** (6.2 mg, 0.02 mmol) were stirred at –78 °C to room temperature for 16 h to give the crude product (85:15 *anti:syn*, 100% conversion). Purification yielded the product **214** as a white solid (17.1 mg, 20%) with all data in accordance with that previously reported.

Chiral HPLC analysis of *anti*-oxazolidin-4-one **214**: Chiralcel AD-H (95:5 hexane:IPA flow rate 1.5 mL $min^{-1}$, 211 nm, 40 °C) $t_R$ major (2*R*,5*R*): 27.1 min, $t_R$ minor (2*S*,5*S*): 53.9 min, 98%.

Chiral HPLC analysis of the *syn*-oxazolidin-4-one **214**: Chiralcel AD-H (95:5 hexane:IPA, flow rate 1.5 mL $min^{-1}$, 211 nm, 40 °C) $t_R$ major (2*S*,5*R*): 25.1 min, $t_R$ minor (2*R*,5*S*): 30.4 min, 98% ee.

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