# Enantioselective organocatalytic cycloaddition reactions between enolisable anhydrides and imines

Trinity College Dublin

A thesis submitted to the University of Dublin for the degree of Doctor of Philosophy

by

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Under the supervision of Prof. Stephen Connon

February 2019

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S. A. Cronin, A. Gutiérrez Collar, S. Gundala, C. Cornaggia, E. Torrente, F. Manoni, A. Botte, B. Twamley and S. J. Connon, *Org. Biomol. Chem.*, 2016, **14**, 6955.

A. Gutiérrez Collar, C. Trujillo and S. J. Connon, *Chem. Eur. J.*, Accepted

## Acknowledgements

First and most important, I would like to thank my supervisor Prof. Stephen Connon for giving me the opportunity to join his group and for his constant help and advice.

I would like to thank the members of the Connon group past and present especially to Romain, Ryan and Mili for all their help, support and advice throughout the entire PhD. Special mention to Bruce, with whom I have spent so many laughs in and out of the lab.

I am very grateful to Cristina for helping to improve as a researcher and more important, for listening to all my jokes and all my complaints so patiently.

Thanks to Ruairí, from the Scanlan group for helping me with all his knowledge about chemistry and for trying to make me playing football again. My legs still hurt for that month of football. I would like to extend my gratitude to Josh and Will for his advice and for all the good times in the pub.

I would like thank all the staff in the School of Chemistry, especially to Dr. John O'Brien for his insparing dedication to elucidate molecular structures by NMR analysis and Dr. Manuel Ruether for all his technical knowledge. I would also like to thank Dr. Brendan Twamley for carrying out the X-ray diffraction pattern of my molecules.

To my Spanish friends; Elena who I have known for almost 10 years! Thank you for telling me to get this position and Luis for all those Barça's matches we have seen and all the political debate.

I am etternaly grateful to David, Heather and Harry for caring for me so much. Thank you so much.

Finally, I would like to thank my family for their unconditional love and support regardless of the distance.

**Abstract**

Cycloaddition reactions between enolisable anhydrides and imines have long been known as excellent tools for the synthesis of natural products. The racemic version is well known to be capable of providing products with excellent diastereoselectivity, however, asymmetric variants of these reactions have remained elusive.

The main challenge associated with this chemistry relates to the propensity for the imine to behave as a base. The use of an *N*-mesyl substituent on the imine allows for suppression of the uncatalysed reaction, rendering the reaction amenable to the asymmetric catalysis. Promoting the reaction with a bifunctional organocatalyst has allowed for the first catalytic, asymmetric cycloadditions of imines with homophthalic anhydride, affording products with *ee* up to 82%.

Under the influence of anion-binding bifunctional catalysis a wide range of α,β-unsaturated imines have been shown to undergo reaction with enolisable anhydrides to form highly synthetically useful α-tetralones with excellent enantio- and diastereocontrol. The presence of an *N*-trityl protecting group on the imine diverts the reaction towards the Tamura reaction exclusively. The cycloadducts were converted through a facile 2-step elaboration into an α-haloketone.

The scope of the anhydride component has been extended to various activated arylsuccinic anhydrides to form γ-lactams with excellent levels of enantiocontrol.

## Abbreviations

| | |
|---|---|
| Å | Ångström |
| AcCl | Acetyl chloride |
| ACE | Acetyl cholinesterase |
| AcOH | Acetic acid |
| APCI | Atmospheric Pressure Chemical Ionization |
| app. t | Apparent triplet |
| Alk | Alkyl |
| Boc | Butoxy carbonyl |
| Bz | Benzyl |
| $^{13}$C NMR | Carbon NMR |
| COSY | Homonuclear correlation spectroscopy |
| $CO_2$ | Carbon dioxide |
| *ca.* | circa (approximately) |
| cat. | Catalyst |
| conc. | Concentrated |
| conv. | Conversion |
| CSP | Chiral stationary phase |
| Cy | Cyclohexyl |
| DABCO | 1,4-Diazabicyclo[2.2.2]octane |
| DCC | *N*,*N*'-Dicyclohexaylcarnodiimide |
| DMSO | Dimethyl sulfoxide |
| DMSO-$d_6$ | Dimethyl sulfoxide-$d_6$ |
| *dr* | Diastereomeric ratio |
| d | Days |
| d | Doublet |
| dd | Doublet of doublets |
| ddd | Doublet of doublet of doublets |
| DIBAL-H | Diisobutylaluminium hydride |
| DIAD | Diisopropyl azodicarboxylate |
| DFT | Density functional theory |
| DIPEA | *N*,*N*-Diisopropylethylamine |

| | |
|---|---|
| DMAP | 4-(Dimethylamino)pyridine |
| DMA | *N*,*N*-Dimethylacetamide |
| DME | 1,2-Dimethoxyethane |
| DMF | *N*,*N*-Dimethylformamide |
| DPPA | Diphenylphosphoryl azide |
| *e.g.* | For example |
| *etc* | And so forth |
| EDG | Electron-donating group |
| ESI | Electrospray ionization |
| *ee* | Enantiomeric excess |
| equiv. | Equivalent |
| EWG | Electron-withdrawing group |
| HSQC | Heteronuclear single quantum coherence spectroscopy |
| HMBC | Heteronuclear multiple-bond correlation spectroscopy |
| HOMO | Highest occupied molecular orbital |
| HRMS | High Resolution Mass Spectrometry |
| $^{1}$H NMR | Proton NMR |
| h | Hours |
| HPLC | High Performance Liquid Chromatography |
| $^{i}$Pr | *iso*-propyl |
| $^{i}$PrOH | *iso*-Propanol |
| IR | Infrared |
| *J* | Coupling constant |
| $K_2CO_3$ | Potassium carbonate |
| LUMO | Lowest unoccupied molecular orbital |
| LDA | Lithium di-*iso*-propylamine |
| m | Multiplet |
| *m*- | *meta*- |
| m.p. | Melting point |
| *m*/*z* | Mass/Charge |
| Me | Methyl |
| MeOH | Methanol |

| | |
|---|---|
| MeI | Iodomethane |
| MS | Molecular sieves |
| Ms | Methylsulfonyl |
| MsCl | Methylsulfonyl chloride |
| $MgSO_4$ | Magnesium sulfate |
| min | Minutes |
| MTBE | Methyl-*tert*-butyl ether |
| NBS | *N*-Bromosuccinimide |
| NCS | *N*-Chlorosuccinimide |
| NMR | Nuclear magnetic resonance |
| n.d. | Not determined |
| NHC | *N*-Heterocyclic carbene |
| $NaHCO_3$ | Sodium bicarbonate |
| $NaNO_2$ | Sodium nitrite |
| NOE | Nuclear Overhauser Effect |
| Nu | Nucleophile |
| Ph | Phenyl |
| PhMe | Toluene |
| $PPh_3$ | Triphenylphosphine |
| PhLi | Phenyllithium |
| Pr | Propyl |
| *p*- | *para*- |
| Pd/C | Palladium over activated charcoal |
| q | quartet |
| (q) | quaternary |
| $R_f$ | Retention factor |
| RDS | Rate-determining step |
| Rh | Rhodium |
| rt | Room temperature |
| s | Singlet |
| $SOCl_2$ | Thionyl chloride |
| $S_N$ | Nucleophilic substitution |

| | |
|---|---|
| temp. | Temperature |
| THF | Tetrahydrofuran |
| TLC | Thin layer chromatography |
| TMS | Trimethylsilyl |
| $TMSCHN_2$ | Trimethylsilyl diazomethane |
| Trt | Trityl |
| TS | Transition state |
| Ts | *p*-Toluenesulfonyl |
| TsCl | *p*-Toluenesulfonyl chloride |
| UV | Ultraviolet |

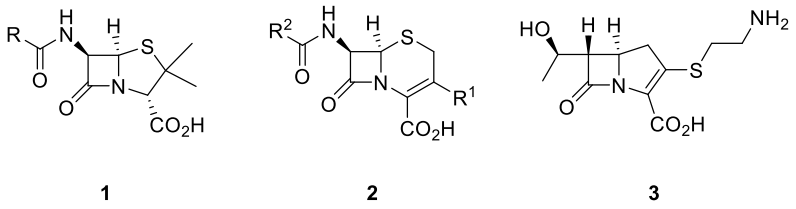
# Introduction

## 1.1 Lactams

Lactams are a large family of compounds containing a cyclic amide that are present in a wide variety of natural products and drugs.[1] There are different types of lactams classified according to the ring size. Hence, we find the β, δ and γ variants amongst the most biologically relevant lactams. The Greek letter refers to the type of amino acid they produce upon hydrolysis, therefore, β-lactams will produce β-aminoacids and so on.

### 1.1.1 Biological and medicinal relevance

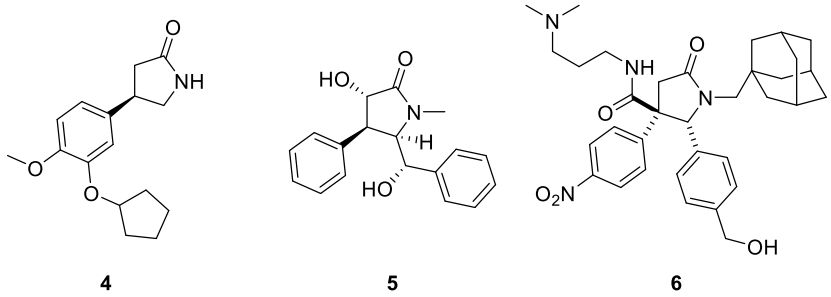
Penicillins (**1**), first discovered by Alexander Fleming in 1928,[2] are the fist β-lactams to be used as antibiotics.[3] After this, β-lactams, such as cephalosporins (**2**) and thienamycin (**3**) among others, have been used to create a new class of broad-spectrum antibiotics (Figure 1.1).[4] As a group, all these drugs are effective against many gram-positive, gram-negative and anaerobic microorganisms, inhibiting the synthesis of the cellular wall, killing the cell.




**1** **2** **3**

**Figure 1.1** Example of natural β-lactam antibiotics.

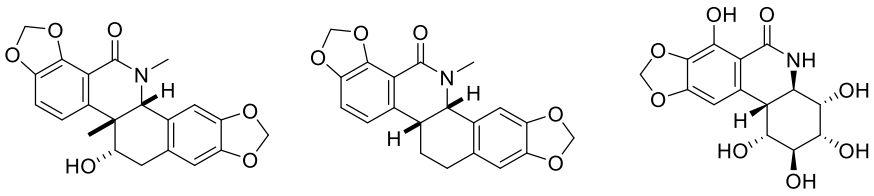
The use of γ-lactams as antibiotics comes from the increasing bacterial resistance to the β-lactam ring. In 1986, Baldwin *et al*. and researchers from Eli Lilly,[5] independently reported the first γ-lactam-based analogues of penems with a superior activity than their β-analogues. However, whereas β-lactams are mainly used as antibiotics, γ-lactams have shown a wider scope of activity. Rolipram (**4**), developed by Schering AG, was used as an antidepressant drug,[6] Clausenamide **5**, a natural product isolated from leaves of *Clausena lansium* by Yang *et al.*[7] that has a strong potential in the treatment of Alzheimer's disease[8] and lactam **6**, a potential transcription-factor inhibitor,[9] are just a few examples of γ-lactams with biological activity (Figure 1.2).




**4** **5** **6**

**Figure 1.2** Example of different γ-lactams with different biological properties.

A wide variety of polycylic natural products present a δ-lactam core. For example, corynoline **7**, that is an acetylcholinesterase (ACE) inhibitor isolated from *Corydalis incise*,[10] Chelidonine **8**, isolated from *Papaveraceae*[11] possessing an ACE and butyrylcholinesterase inhibitory activity, or pancratistatin (**9**), an alkaloid with a powerful anti-cancer activity,[12] all present a polycyclic δ-lactam core (Figure 1.3).




**7** **8** **9**

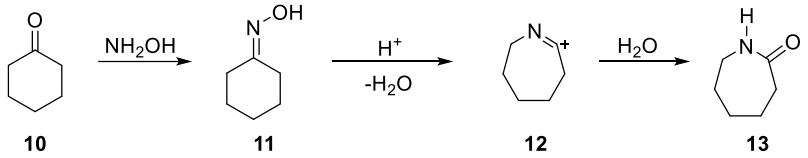
**Figure 1.3** Natural products with a δ-lactam core.

### 1.1.2 Principal methods of synthesis and associated challenges

The most common methodology to obtain bioactive lactams is to extract them from different organisms.[13] Nevertheless, these organisms are limited and the extraction procedures are often tedious and expensive, so in order to reduce the environmental damage or to gain access to a wider range of functionalised lactams, the creation of new methodologies to produce lactams (among other functional groups) is essential. Currently, it is possible to find a wide variety of methods to synthesise lactams[14] that involve palladium chemistry,[15] copper-catalysed 1,3-dipolar cycloaddition of alkynes and nitrones,[16] radically processes,[17] the Biginelli reaction[18] or the direct coupling of amines with carboxylic acids or derivatives. Some of the more common of these are outlined below.

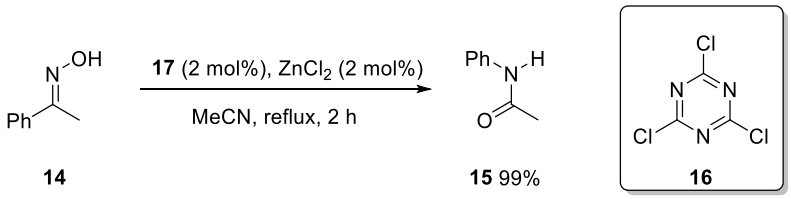
### 1.1.2.1 Beckmann rearrangement

The Beckmann rearrangement involves the conversion of a ketone into an amide. When the ketone is cyclic the product obtained is a lactam with an expansion on the size of the ring.[19] Ketone **10** reacts with hydroxylamine to produce oxime **11** that dehydrates in an acid-catalysed process promoting the migration of the alkyl group at the *trans* position of the oxime to produce **12** that gets hydrated to furnish, after a proton transfer, lactam **13** (Scheme 1.1).




**Scheme 1.1** Mechanism of the transformation of **10** into lactam **13** *via* a Beckmann rearrangement.

Historically, this reaction involved the use of strong acids and high temperatures that led to the formation of a high number of byproducts. To overcome this problem, the use of organocatalysts has been crucial. In 2005, Yamamoto *et al.* reported the first highly effective combined metal (ion) and organocatalytic process[20] to transform oxime **14** into amide **15** in excellent yield promoted by catalyst **16** (Scheme 1.2).

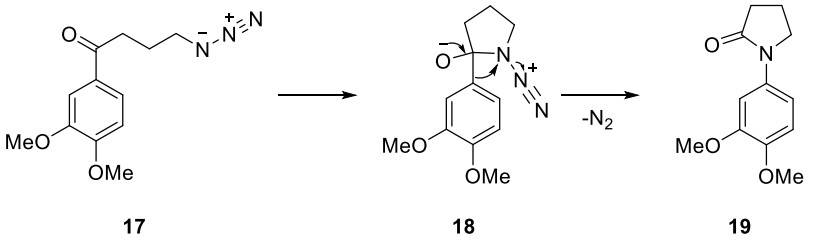



**Scheme 1.2** First organocatalytic Beckmann rearrangement.

The main disadvantage of this methodology to furnish lactams is that the yield decreases significantly when the synthesis of small ring lactams is attempted (6 and below);[21] however, it has been applied to total synthesis[22] and is a stereospecific process.[23]

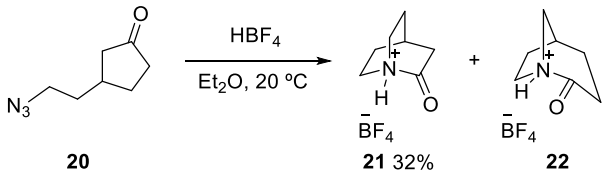
### 1.1.2.2 Schmidt reaction with cyclic ketones

The Schmidt reaction presents some similar aspects to the Beckmann rearrangement, although the latter is thermodynamically favoured by the loss of molecular nitrogen, an entropic driving force for the process. Ketone **17** possess a side chain with an azide group that reacts with the carbonyl to form the tetrahedral alkoxide intermediate **18**. This intermediate collapses to form the lactam promoting the migration of the phenyl ring to the nitrogen atom with concomitant extrusion of molecular nitrogen to afford lactam **19** (Scheme 1.3).[24]




**Scheme 1.3** Mechanism of the intramolecular Schmidt reaction.

This methodology has shown special utility in intramolecular processes involving azides and ketones, especially to make bridged lactams in which the nitrogen is at a bridgehead position.[25] Thereby, Stoltz *et al.* published the synthesis, for the first time, of 2-quinuclidonium tetrafluoroborate (**21**) – a compound that had previously attracted Woodward, as it related to the structure and synthesis of quinine, forming the quinuclidine ring.[26] Catalysed by $HBF_4$, azide **20** cyclised to furnish lactams **21** and **22** in a 76:24 proportion, due to the small differentiation of both α-carbons from a migratory aptitude perspective. Lactam **21** was isolated by recrystallisation (Scheme 1.4).

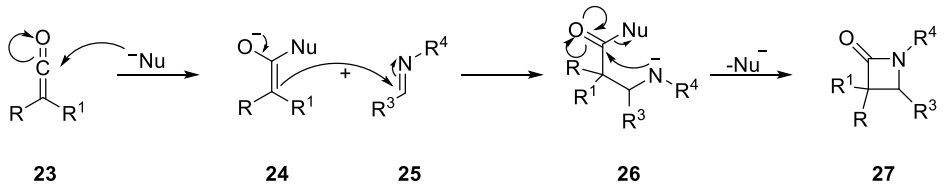



**Scheme 1.4** First synthesis of **21**.

Schmidt synthesis to form lactams has also been used in total synthesis of alkaloids[27] however, as is sometimes the case in the Beckmann rearrangement, the selectivity of the migration has proven problematic, with low yields also often reported.

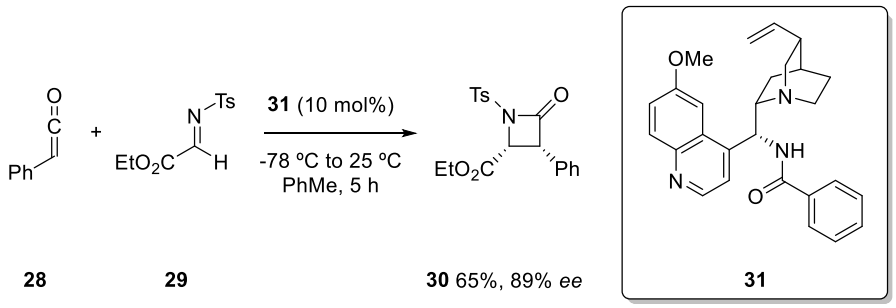
### 1.1.2.3 Staudinger synthesis

Considered as a [2+2] cycloaddition reaction between ketenes and imines, the Staudinger reaction is one of the most important methods that give access to β-lactams.[14] The reaction begins with a nucleophilic catalyst that attacks ketene **23** to produce intermediate **24**, which then reacts with imine **25** *via* Mannich addition to form **26**, that, after a subsequent cyclisation furnishes β-lactam **27** (Scheme 1.5).




**Scheme 1.5** Proposed mechanism of the Staudinger reaction.

A common selectivity problem is due to the nucleophilicty of the imine, which could initiate the reaction, was addressed by Lectka *et al* who proposed a new approach in which they decreased the nucleophilicity of the imine by placing an EWG on the nitrogen atom and employed a chiral tertiary amine **31**. Thus, they catalysed the cycloaddition reaction between ketene **28** and imine **29** to furnish β-lactam **30** with good enantiocontrol (Scheme 1.6).[28]



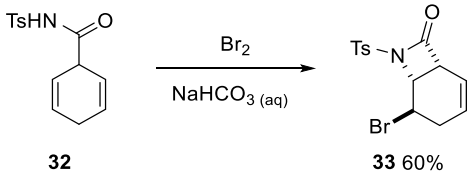

**Scheme 1.6** First highly enantioselective Staudinger reaction.

In 2005, the enantioselectivity of the reaction was increased through the use of a bifunctional catalyst system based on benzoylquinine and indium (III), in which the quinuclidine ring from the benzoylquinine initiates the reaction *via* nucleophilic attack to the ketene, while the imine is activated by coordination to the indium ion.[29]

In 2008, Ye *et al.*[30] reported an organocatalytic version when they carried out the reaction employing NHC chemistry: produced β-lactams in good yields and with excellent enantiocontrol.

### 1.1.2.4 Halolactamisation

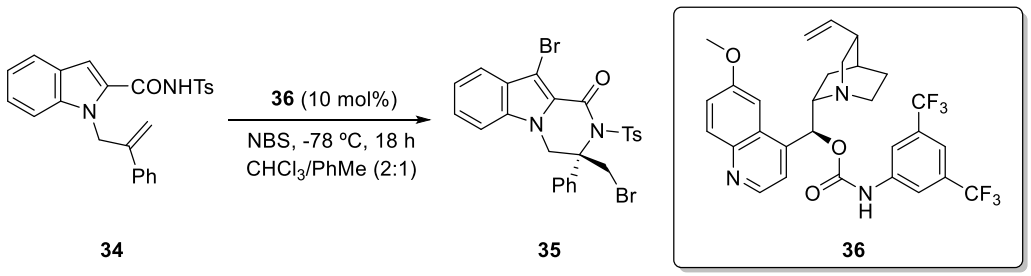
In 1982, Ganem *et al.* reported a novel synthesis of β-lactams employing amides and olefins,[31] in a similar process to halolactonisation; a very well-known reaction at that time.[32] Amides were believed to afford principally lactones, by reaction at the oxygen and then hydrolysis, under the standard reaction conditions.[33] Therefore, efforts were made to explore different forms of reactivity to prevent the amide from forming the lactone. The authors decided to lower the p$K_a$ of the amide, by synthesising tosyl amide **32**, which underwent, in a smooth reaction, the bromocyclisation to furnish bromo β-lactam **33** in a moderate yield (Scheme 1.7).




**Scheme 1.7** The first bromolactamisation reaction.

The reaction is believed to occur *via* formation of a bromonium ion after coordination of the bromine to the olefin. The amide, activated *via* deprotonation by a base, attacks the bromonium species, forming the lactam.

A catalytic enantioselective process remained elusive for decades until 2015, when Yeung *et al.* reported the formation of polycyclic lactam **35** from indole **34** promoted by cinchona alkaloid **36** using NBS as a brominating agent (Scheme 1.8). The authors proposed the interaction of the bromine with the olefin and the carbamate from the catalyst while the quinuclidine moiety concomitantly activated the amide *via* hydrogen bonding.[34] As a consequence of the use of NBS the indole ring was also brominated at the C'-3 position.

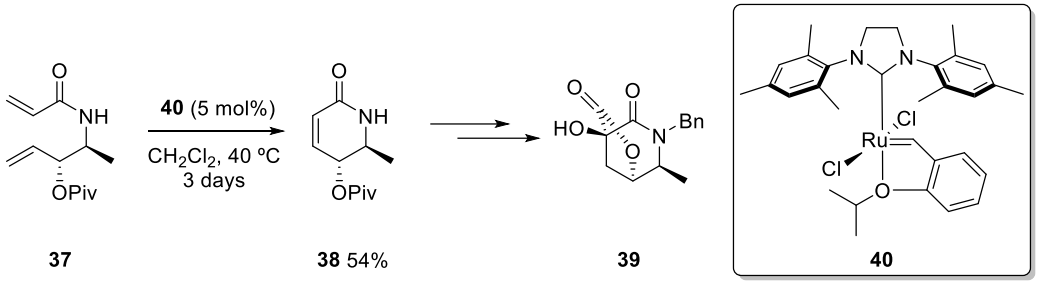



**Scheme 1.8** The first asymmetric catalytic bromolactamisation.

### 1.1.2.5 Ring-closing metathesis (RCM)

So far, all of the examples shown have been focused on the synthesis of lactams *via* C-N bond formation; however, the lactam can also be formed by creating a new C-C bond. An important synthetic methodology is the RCM reaction,[35] which is especially useful when attempting to make macrolactams.[36]

In 2010, Wilden *et al*. employed a Grubbs-Hoveyda 2nd generation catalyst (**40**) to create the lactam core of Awajanomycin (**39**), a natural product with a cytotoxic activity against human lung adenocarcinoma cells. They carried out the RCM from diene **37** to afford the unsaturated lactam **38** with a moderate yield (Scheme 1.9).[37]

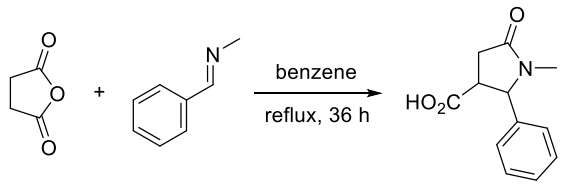



**37** **38** 54% **39** **40**

**Scheme 1.9** RCM to form **38**, an intermediate in the synthesis of Awajanomycin (**39**).

### 1.1.2.6 Cycloaddition reactions between imines and enolisable anhydrides

In 1969, Castagnoli reported the first cycloaddition reaction between imines and enolisable anhydrides while synthesising analogues of nicotine. The reaction involved the cycloaddition reaction of succinic anhydride (**41**) with imine **42** to produce lactam **43** as the mixture of the *cis* and *trans* acids in an 82% yield (Scheme 1.10).[38] In the study he proposed that the reaction proceeded through an iminolysis pathway. This reaction will be discussed in greater detail in Section 1.3.2.

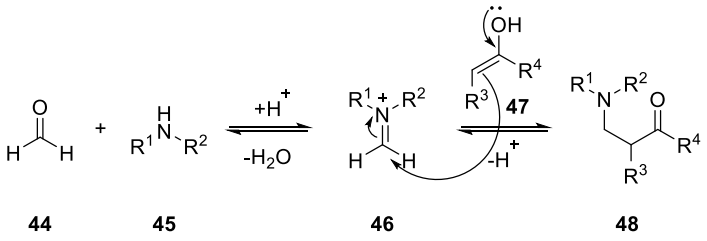



**41** **42** **43** 82%

**Scheme 1.10** Cycloaddition reaction between succinic anhydride and **42**.

## 1.2 Mannich reaction

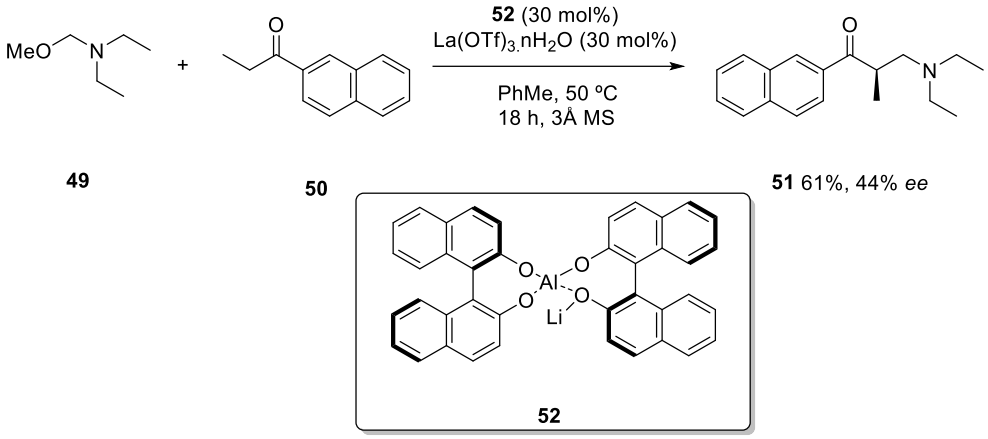
Probably the most notable reaction that imines can undergo is the Mannich reaction, in which a C-nucleophile attacks at the carbon atom of the imine forming a new C-C bond. It is an ideal methodology for the synthesis of β-amino carbonyl compounds.[39] The reaction starts with amine **45** reacting with formaldehyde (**44**) to form iminium ion **46** in a reversible condensation reaction. The enol form of **47** reacts with **46** at the electron deficient carbon to form **48** (Scheme 1.11). A protic solvent is necessary to activate the imine and to facilitate the keto-enol tautomerisation of **47**. The reaction was originally performed in one-pot under reflux conditions in a protic solvent. These conditions did not prove ideal, as the number of side products formed was considerable.[40] Preformed imines,[41] aminals[42] or iminium salts[43] can be used to circumvent this problem.




**Scheme 1.11** The archetypal Mannich reaction.

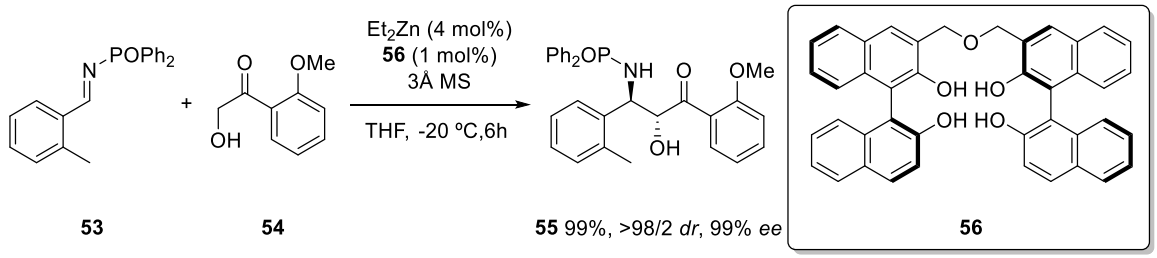
### 1.2.1 Asymmetric Mannich additions employing transition metals

The first direct catalytic asymmetric Mannich addition was reported by Shibasaki *et al.*[44] in 1999. The reaction involved the formation *in situ* of the iminium ion **46** through the use of **49** and the chiral metal complex **50**[45] and $La(OTf)_3 \cdot nH_2O$ as a cocatalyst to form β-amino aryl ketone **51** in moderate yield and low enantioselectivity (Scheme 1.12).




**Scheme 1.12** The first catalytic asymmetric Mannich addition catalysed by a metal complex.

Later, Shibasaki demonstrated that the combination of using zinc, BINOL **56** as a chiral ligand and the *N*-diphenylphosphinoyl protected imine **53** led to the formation of the Mannich adduct **55** as a single diastereomer in excellent yield and enantiocontrol (Scheme 1.13).[46]




**Scheme 1.13** Enantioselective Mannich addition catalysed by a zinc-complex.

The X-ray diffraction pattern analysis indicated that the absolute configuration of the two new formed stereocentres was (*R*,*R*). Hence, the authors proposed the reaction proceed *via* pre-transition state assembly **57**, in which the *re*-face of the imine **53** approached the *re*-face of the Zn-enolate complex. Due to the steric demand of the *N*-diphenylphosphinoyl group the synthesis of the *anti*-diastereomer was favoured (Figure 1.4).

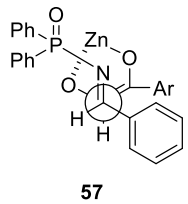
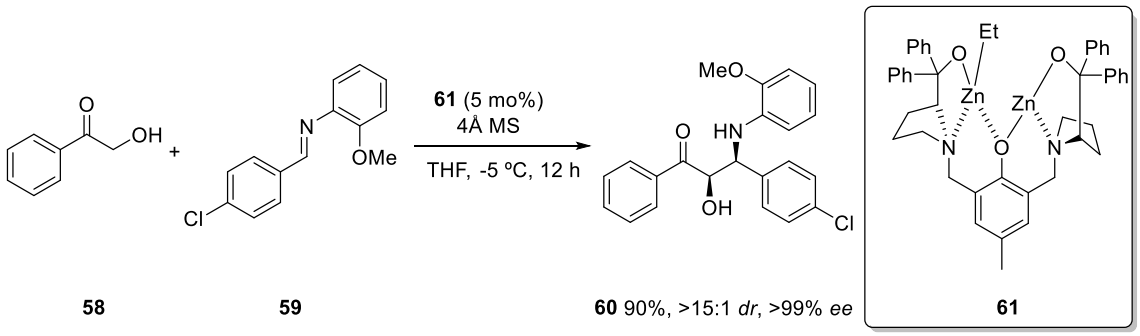



**Figure 1.4** Stereochemical rationalisation proposed by Shibasaki.[46]

At the same time, Trost *et al*. reported the formation of *syn*-β-aminoalcohols employing zinc but with a different ligand. The ligand forms di-nuclear zinc complex **61** that promotes the Mannich addition of **58** to **59** furnishing *syn*-**60** in excellent diastereo- and enantiocontrol (Scheme 1.14).[47]




**Scheme 1.14** Enantioselective formation of *syn*-β-aminoalcohols reported by Trost.

Another metallic-framework widely used is copper(II).[48] Jørgensen *et al*. reported the first asymmetric Mannich reaction of carbonyl compounds and imino esters catalysed by chiral copper complexes. They considered the generation of the enol as a key step of the reaction. They proposed that such step was catalysed by Cu(II).[49] The newly-formed enol coordinated to the Cu(II) in a bidentate fashion. The imine approaches through the *si*-face of the enol and coordinates to the metal in a bidentate fashion (Figure 1.5).[50]

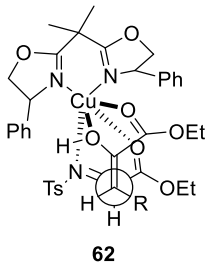
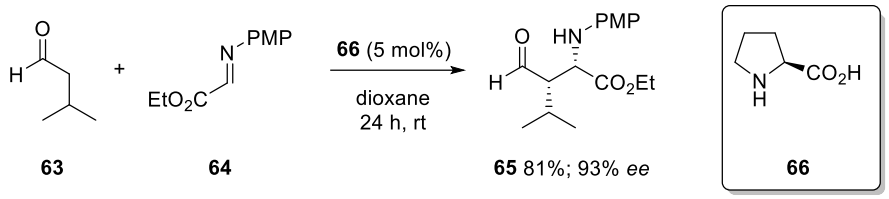



**Figure 1.5** Stereochemical rationalisation proposed by Jørgensen *et al*.[50]

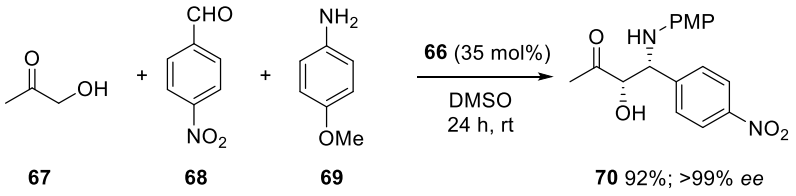
### 1.2.2 Organocatalyatic asymmetric Mannich additions

The first organocatalytic asymmetric Mannich reaction between unmodified aldehydes and imines was reported in 2001 by Barbas *et al.*[51] (*L*)-Proline (**66**) promotes the nucleophilic attack of aldehyde **63**, *via* enamine-based catalysis, on imine **64** (Scheme 1.15).



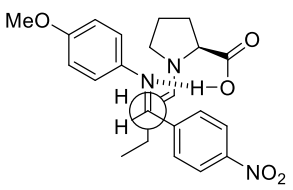

**Scheme 1.15** First enantioselective Mannich reaction with an unmodified aldehyde.

Two years later, List *et al.* reported the first organocatalytic three-component Mannich reaction between aldehyde **68**, anisidine (**69**) and α-hydroxyketone (**67**) to furnish β-aminoketone **70** with excellent enantioselectivity, catalysed by **66** (Scheme 1.16).[52] The highest levels of enantiocontrol are achieved when aromatic imines bearing electron-withdrawing groups are employed.




**Scheme 1.16** First organocatalytic asymmetric one-pot three-component Mannich reaction.

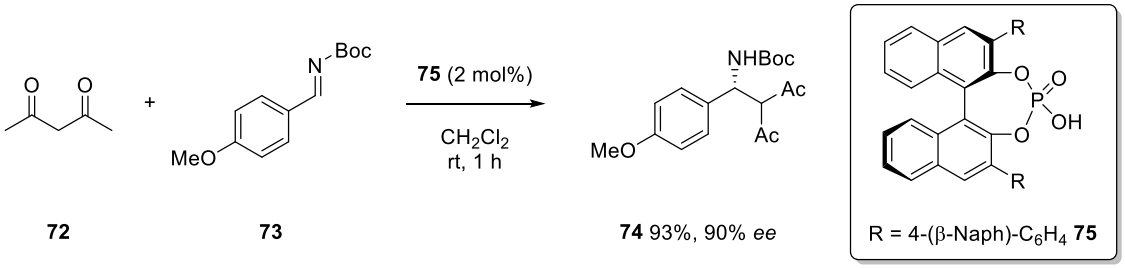
The mechanism of this reaction is believed to proceed *via* enamine formation between the proline and the carbonyl compound. The carboxylic acid from the proline interacts *via* hydrogen-bond with the imine, activating it and accommodating it for the attack by the enamine. Subsequent hydrolysis of the product frees the proline, which re-enters the catalytic cycle. The enantioselectivity is determined in the Mannich addition of the enamine. The *si*-face of the enamine attacks through the *si*-face of the *trans*-imine. The hydrogen-bond between the carboxylic acid and the imine stabilises the transition state (Figure 1.6).[53]




**71**

**Figure 1.6** Pre-transition state assembly proposed by Córdova to explain the stereochemical outcome of the reaction.

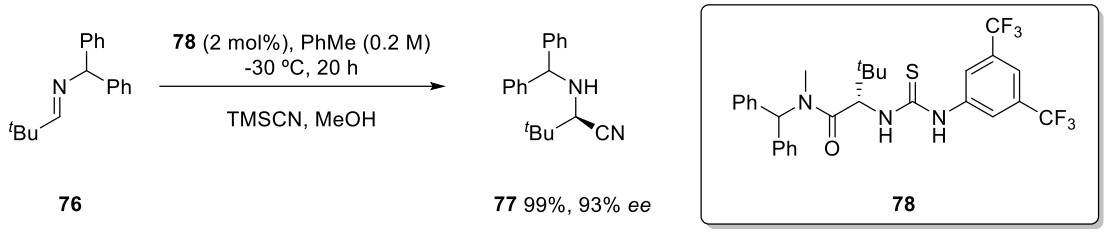
Since, the scope of the Mannich reaction has been widely expanded to include different nucleophiles.[54] Tereda *et al.*[55] reported one of the first examples of the addition of β-dicarbonyl compounds[56] to *N*-boc aldimine **73**. The process was catalysed by chiral phosphoric acid **75** and produced β-aminoketones in excellent optical purity (Scheme 1.17). The chiral phosphoric acid acted as a bifunctional catalyst: its acidity allowed the catalyst to interact with the imine *via* hydrogen-bonding and the phosphoryl oxygen acted as a Lewis basic site.[55]




**72** **73** **74** 93%, 90% *ee*

**Scheme 1.17** Asymmetric Mannich addition of β-dicarbonyl compounds to aldimines.

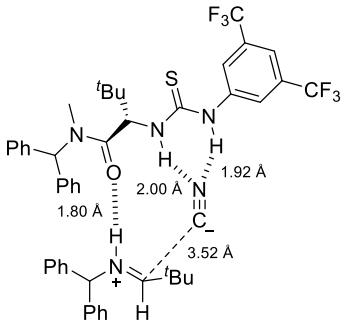
The Mannich addition is an excellent synthetic route to get access to α-amino acid derivatives.[57] Another important reaction that furnishes α-amino acid derivatives is the Strecker reaction. This proceeds *via* addition of cyanide to imines.[58] The reaction can be catalysed by organometallic frameworks[59] or by metal-free organic molecules.[60] The main problem associated with the process was the extremely hazardous sources of cyanide (*i.e.* HCN,[61] $Bu_3SnCN$[62]) which made the scale up of the reaction to an industrial level challenging.[63] However, in recent years safer methods have been developed to produce the cyanide ion.[64] An organocatalytic and safer version was reported in 2009 by Jacobsen[65] to transform imine **76** into the α-cyanoamine **77** (using TMSCN/MeOH) as the cyanide source catalysed by **78** (Scheme 1.18).




**76** **77** 99%, 93% *ee* **78**

**Scheme 1.18** Organocatalytic asymmetric Strecker reaction.

The authors proposed the formation of the transition state **79**, in which the imine is protonated forming an iminium ion whose N-H is interacting *via* hydrogen-bond with the amide unit of the catalyst **78**. The cyanide ion is stabilised by the thiourea *via* hydrogen-bond interactions (Figure 1.7).[66]




**79**

**Figure 1.7** Transition state proposed by Jacobsen *et al.*[66]

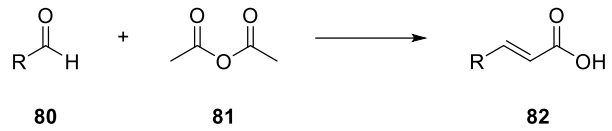
## 1.3 Cycloaddition reactions involving enolisable anhydrides

Historically, anhydrides have been considered as electrophilic acylating agents[67] stronger than esters and weaker than acid chlorides. Nevertheless, some anhydrides can play the role of nucleophiles in the reactions. These enolisable anhydrides can act as *C*-nucleophiles in addition reaction with a wide variety of electrophiles.

### 1.3.1 Reaction of enolisable anhydrides with aldehydes

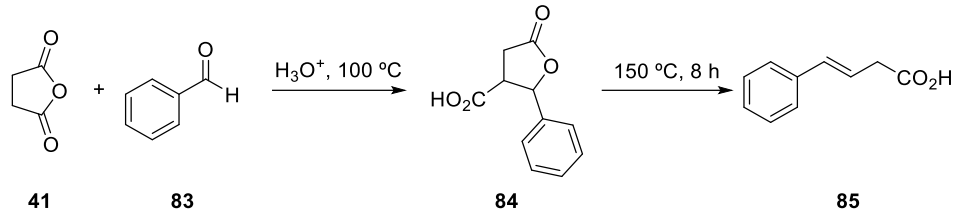
#### 1.3.1.1 Perkin reaction

In 1877, Perkin performed the first reaction in which an anhydride acts as a nucleophile in a condensation reaction (Scheme 1.19).[68] Perkin observed that in the presence of a base, simple aliphatic anhydride, such as acetic anhydride (**81**) underwent a condensation reaction with **80** to afford α,β-unsaturated acid **82**.




**Scheme 1.19** The first example of an anhydride acting as a C-nucleophile.

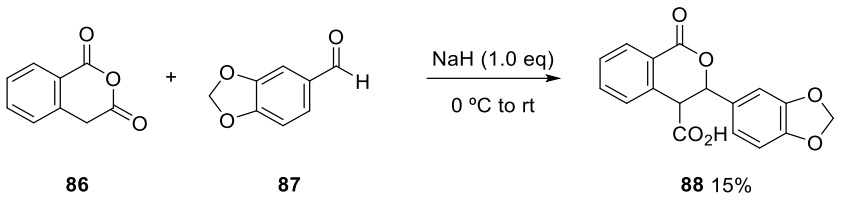
A few years later, Fittig *et al.*[69] reported the formation of γ-butyrolactone **84** from succinic anhydride (**41**) and benzaldehyde (**83**) at high temperature under acidic conditions. When the temperature was increased, product **84** underwent a decarboxylation process to form the Perkin-condensation product **85** (Scheme 1.20).




**Scheme 1.20** Reaction carried out by Fittig *et al.*

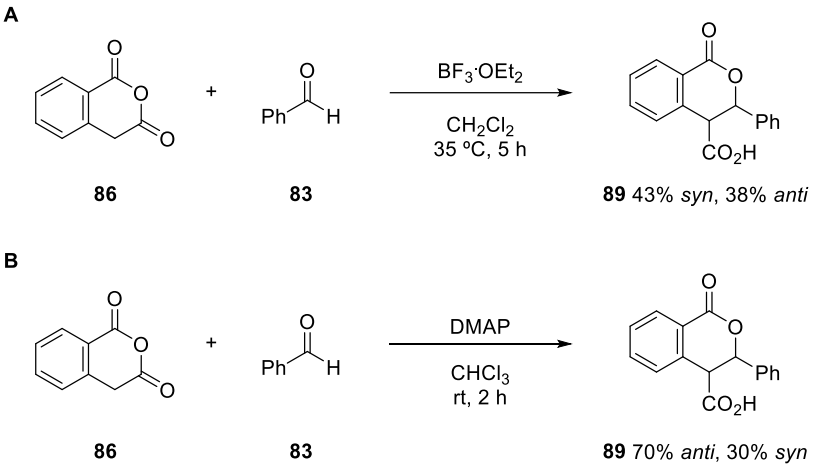
### 1.3.1.2 Pinder reaction

Ninety years after Perkin reported the potential used of enolisable anhydrides as nucleophiles, Pinder reported the first cycloaddition in which homophthalic anhydride behaves as a nucleophile, employing aldehydes as the electrophilic component of the reaction.[70] It was found that a strong base promotes the formal cycloaddition of cyclic anhydride **86** with aldehyde **87** to afford dihydroiocoumarin **88** (Scheme 1.21).




**Scheme 1.21** First example of a cycloaddition between anhydrides and aldehydes.

In 1999, Gesquiere *et al.* reported that the cycloaddition reaction between homophthalic anhydrides and aldehydes and ketones could be catalysed in the presence of a Lewis acid. Borontrifluoroetherate catalyses the tautomerisation of **86**, while activating the aldehyde **83** to form lactone **89** in a *syn*:*anti* ratio of ca. 1:1 (Scheme 1.22,A).[71] Some years later, Palamareva and Bogdanov reported the same transformation but employing DMAP (at stoichiometric level) with selectivity for the *anti* diastereomer (70/30 *dr*) (Scheme 1.22,B).[72]

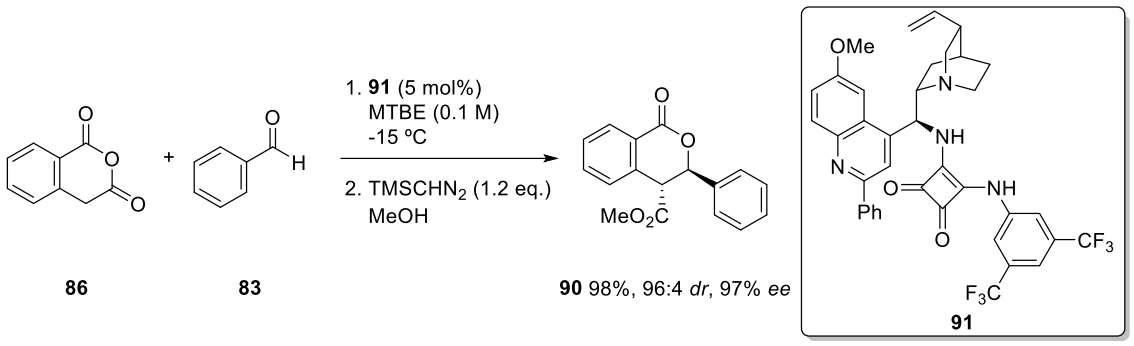



**Scheme 1.22** Cycloaddition reaction between anhydrides and aldehydes under acid or base catalytic conditions.

### 1.3.1.3 Asymmetric organocatalytic processes

The methodology reported by Pinder allows access to different racemic dihydroisocumarins, a core present in a wide range of natural products with phytotoxic,[73] antifungal,[74] antimalarial[75] and anti-inflamatory activity.[76]

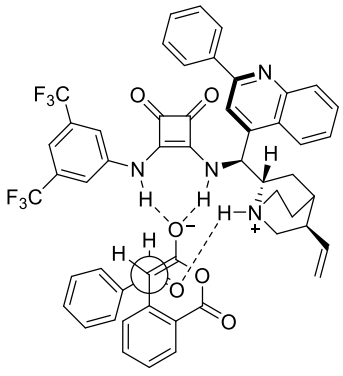
It was hypothesised that if the strong base employed by Pinder could be replaced by a weaker organic one, the process would be amenable to asymmetric induction. Indeed, this proved to be the case when, in 2012, our group reported the first organocatalytic asymmetric cycloaddition reaction between **86** and aldehyde **83** to furnish lactone **90** promoted by the catalyst **91** with excellent enantio- and diastereocontrol (Scheme 1.23). The process proved to be very robust: a wide variety of aldehydes and different variants of the homophthalic anhydride (**86**) were evaluated.[77] Recently, our group has reported that in the presence of a bulkier catalyst the diastereocontrol can be diverted to the *cis*-diastereomer retaining the excellent enantiocontrol.[78]




**86** **83** **90** 98%, 96:4 *dr*, 97% *ee*

**Scheme 1.23** First asymmetric cycloaddition reaction involving enolisable anhydrides.

Some years later, our group published a DFT mechanistic study to understand the mechanism and stereochemical outcome of the reaction.[79] The quinuclidine moiety of **91** deprotonates the anhydride **86**, whose enolate interacts *via* hydrogen-bonding with the catalyst's squaramide moiety. Aldehyde **83** is activated *via* hydrogen-bonding, by the catalyst's protonated ammonium ion, and subsequently attacked by the enolate to form the intermediate that leads to the formation of lactone **90** *via* acylation. The formation of this C-C bond turned out to be the rate-limiting step of the reaction (Figure 1.8). The authors also reported that when the aldehyde is present, the binding mode between the catalyst and the anhydride remains unaltered, meaning that there is only one face of the enolate available to attack the aldehyde.

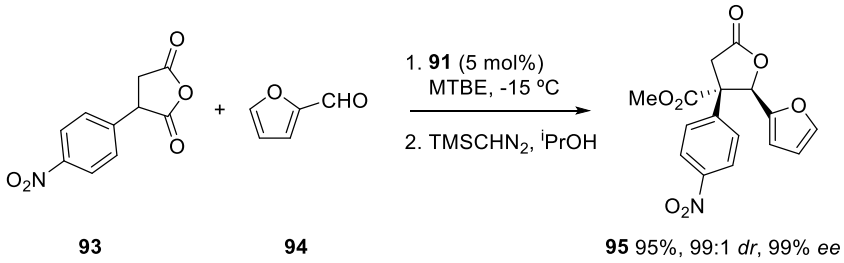



**92**

**Figure 1.8** Pre-transition state assembly of the cycloaddition reaction between **86** and **83**.[79]

Not only homophthalic anhydrides can undergo cycloaddition reaction, but also succinic anhydrides, as seen in Castagnoli's seminal work.[38] The reaction between aldehydes and succinic anhydrides would provide access to γ-lactones, a structural unit present in a large range of natural products.[80]

Preliminary studies found **41** unreactive towards aldehydes under the same catalytic condition previously reported.[80] Therefore, to circumvent this problem, a stabilising group was installed at the α-position of the anhydride. Thus, anhydride **93** was synthesised and reacted with **94**, leading to the highly enantio- and diastereoselective formation of **95** in the presence of catalyst **91** (Scheme 1.24).




**93** **94** **95** 95%, 99:1 *dr*, 99% *ee*

**Scheme 1.24** Cycloaddition reaction between an α-substituted succinic anhydride and an aldehyde.

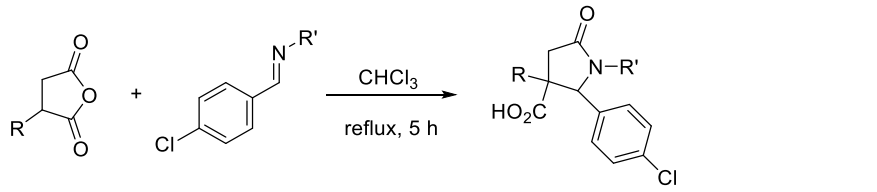
Recently, the scope of the cycloaddition reaction between enolisable anhydrides and aldehydes has been considerably broadened. It is possible now to resolve (*via* cycloaddition with aldehydes) different succinic anhydrides kinetically[81] and dynamically[82] and also to carry out the reaction employing ketones as electrophiles.[83]

### 1.3.2 Reaction of anhydrides with imines

#### 1.3.2.1 Succinic anhydrides

The cycloaddition reaction between enolisable anhydrides and imines has received considerable attention in the chemical literature[84] since Castagnoli published his first findings in 1969.[38] Boucherle reported a similar study to that reported by Castagnoli, in which he performed the reaction with succinic anhydride and different imines yielding only one product diastereomer.[85] The reaction between succinic anhydrides and imines usually requires harsh conditions (elevated temperatures and long reactions times) and it usually offers low yields; factors that have limited the utility of this reaction.

Substituted anhydrides offer a tool to tune the reactivity of the succinic anhydride. Phenyl succinic anhydride (**96**) has proven to be more reactive than the succinic anhydride due to the presence of the enol-stabilising group. Thus, anhydride **96** reacts with *N*-substituted imine **98** faster than succinic anhydride, to afford lactam **100**, albeit with lower diastereoselectivity (23/77, *syn*/*anti*) than when succinic anhydride is used (Scheme 1.25).[86]



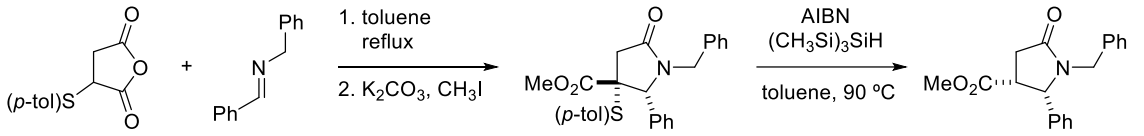

**41** R = H
**96** R = Ph

**97** R' = $^{n}$Bu
**98** R' = Me

**99** R = H; R' = $^{n}$Bu, >99:1 *dr* (*anti*:*syn*)
**100** R = Ph; R' = Me, 77:23 *dr* (*anti*:*syn*)

**Scheme 1.25** The cycloaddition reaction between enolisable anhydrides and imines.

The presence of different enol-stabilising groups at the α-position of the anhydride opens a window to new reagents on this reaction. Thus, the attachment of a thioether group,[87] allows anhydride **101** to react with various imines (**102**) to form tetrasubstituted γ-lactam **103** in good yields and retaining the excellent levels of diastereocontrol achieved with succinic anhydride. Furthermore, the thioether group can be easily removed by using AIBN to furnish **104** with inversion of the stereochemistry of the stereocentre (Scheme 1.26).[88] Therefore, the presence of a cleavable group on the anhydride, that also helps to activate the anhydride, provides access to products formally derived from succinic anhydride.



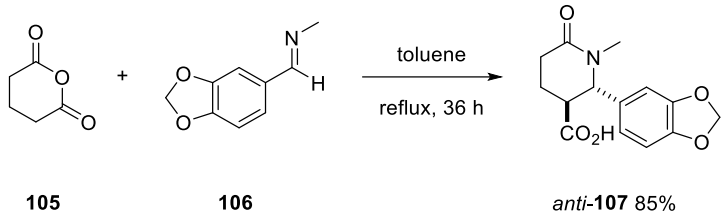

**101** **102** *anti*-**103** 91%, >95:5 *dr* *syn*-**104** 93%, >95:5 *dr*

**Scheme 1.26** The cycloaddition reaction between imines and 'masked' succinic anhydride.

The possibility of tuning the acidity of the α-hydrogen atom of the anhydride allows for the introduction of increased product malleability. Thus, it is possible to produce different lactams bearing different α-substituents such as 3-cyano[89] and 3-sulfonyl.[90]

### 1.3.2.2 Glutaric anhydrides

Glutaric anhydrides react in a similar way to succinic anhydrides, requiring extended reaction times at elevated temperatures.[91] Boucherle *et al.* demonstrated that when reacting glutaric anhydride (**105**) with imine **106**, lactam **107** was obtained in moderated yield (Scheme 1.27). *Anti*-**107** was obtained by recrystallisation, so the diastereoselectivity of the process could not be determined, however the authors argued that the product is isolated in >85% yield, so the diastereoselectivity had to be reasonably high.[85]

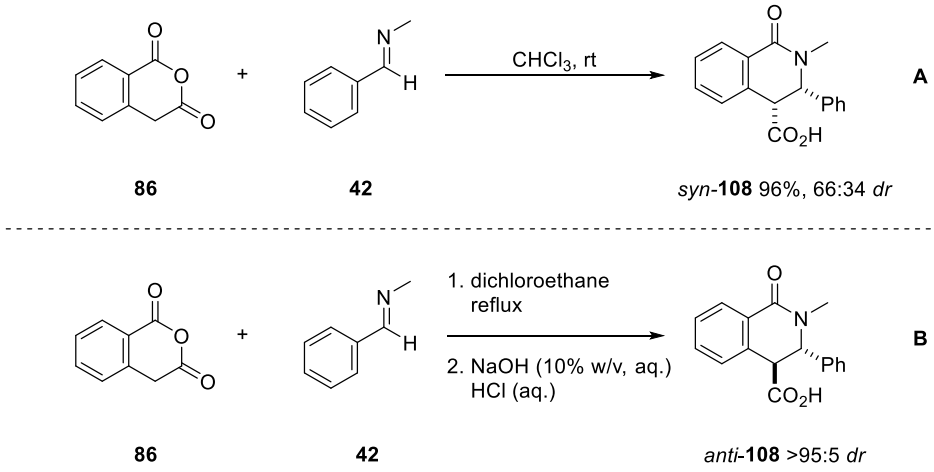



**Scheme 1.27** The cycloaddition reaction between glutaric anhydride and imine **106**.

As seen with the succinic anhydrides, enol-stabilising groups can also be installed at the α-position of the anhydride to increase the reactivity of the anhydride.[90] Another successful strategy is to incorporate fused heteroaromatic rings.[92]

### 1.3.2.3 Homophthalic anhydrides

As was seen with succinic and glutaric anhydrides, the presence of an enol-stabilising group in the anhydride increases the reactivity of the anhydride. Homophthalic anhydrides are more reactive than the other anhydrides discussed previously and reacts with imines at room temperature. Homophthalic anhydride has a p$K_a$ of 8.27[93] and when it is deprotonated at the α-position, the enolate is stabilised by conjugation with the aromatic ring, which accounts for its faster reactivity with imines. Cushman[94] and Haimova[95] published (simultaneously and independently) their results concerning the reaction between homophthalic anhydride (**86**) and imine **42** (Scheme 1.28).

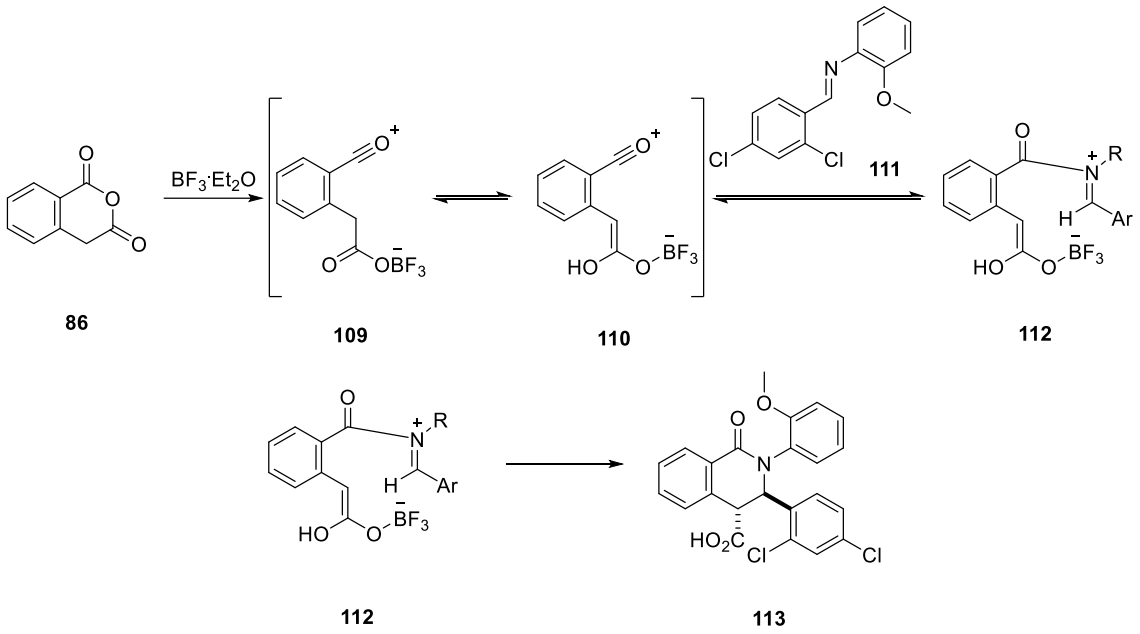



**Scheme 1.28** Comparison of Cushman's (**A**) and Haimova's experiment (**B**).

Cushman reported that the reaction produced *syn*-**108** (Scheme 1.28 A) whereas Haimova's results indicated a preference for *anti*-**108** (Scheme 1.28 B). Cushman reported that the *syn*-diastereomer is the kinetic product and it converts into the *anti* stereoisomer (thermodynamic

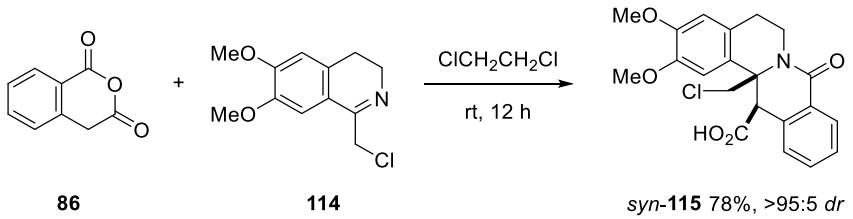
product) upon epimerisation by heating in xylene, acetic acid or during the basic work-up carried out by Haimova.[86]

Gesquiere *et al.* reported that the *anti*-selectivity can be also favoured with the use of Lewis acids.[96] Thus, when the cycloaddition reaction with imine **111** is carried out in the presence of $BF_3{\cdot}Et_2O$, *anti*-**113** is produced as the only diastereomer. The Lewis acid coordinates the endocyclic-oxygen atom of the anhydride, causing ring opening to give **109** which is believed to tautomerise to enolate **110** which is trapped by imine **111** to form adduct **112**. Subsequent cyclisation leads to *anti*-**113** (Scheme 1.29).




**Scheme 1.29** Proposed mechanism for the diastereoselective formation of *anti*-**113** by Gesquiere.[96]

Homophthalic anhydrides have also been reported to react with ketimines (imines derived from ketones). As ketone analogues,[83] ketimines are generally less reactive than aldimines and they require elevated temperatures to react, which often results in lower diastereoselectivity. Another problem that affects the diastereoselectivity is the less steric discrepancy between ketimines faces. However, Haimova reported the reaction of imine **114** with **86** to form lactam **115** as a single diastereomer (Scheme 1.30).[97]




**86** **114** *syn*-**115** 78%, >95:5 *dr*

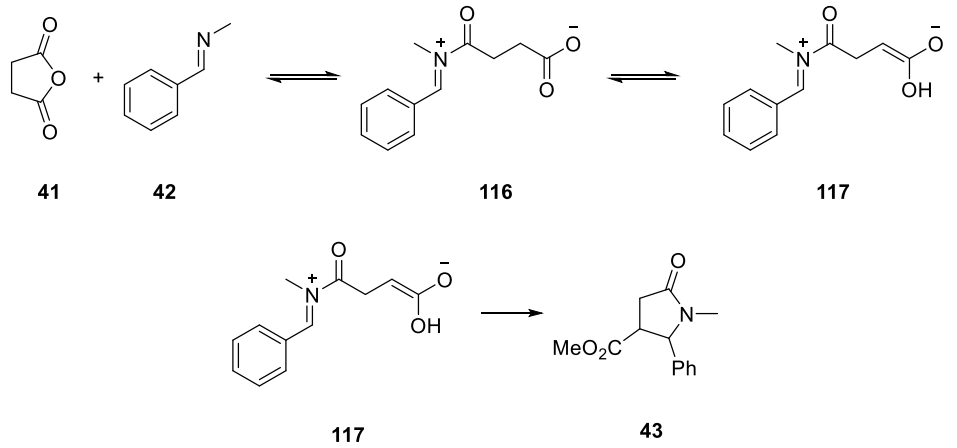
**Scheme 1.30** Cycloaddition reaction between **86** and ketimine **114** with high diastereocontrol.

### 1.3.2.4 Mechanistic proposals

Despite almost 50 years of intense research, the mechanism has yet to be elucidated and still remains a topic of debate.

#### 1.3.2.4.1 Castagnoli's proposal

Castagnoli made his first postulation of the mechanism alongside his original observations.[98] He proposed an iminolysis pathway in which imine **42** opens anhydride **41** generating the acyl iminium carboxylate **116** that (after tautomerisation to the enolate form **117**) cyclises to form **43** (Scheme 1.31). However not enough data was ascertained to support this mechanistic proposal.




**41** **42** **116** **117**

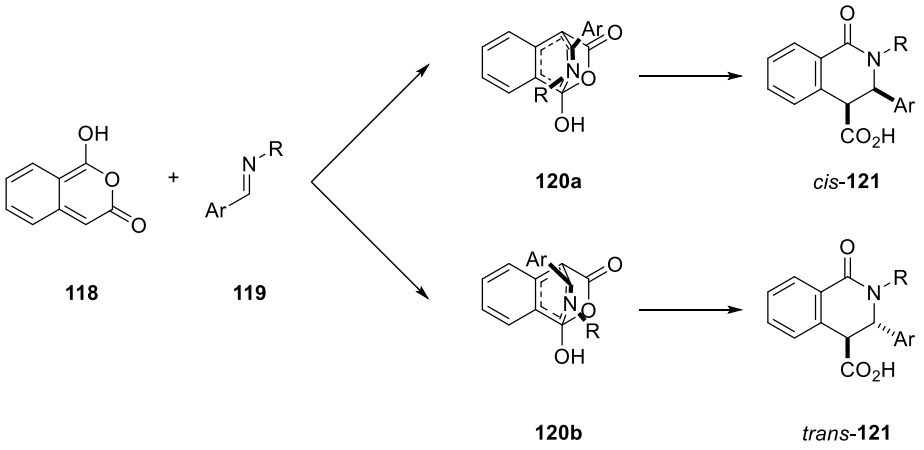
**117** **43**

**Scheme 1.31** Castagonli's proposed mechanism for the synthesis of **43**.

#### 1.3.2.4.2 Cushman's proposal

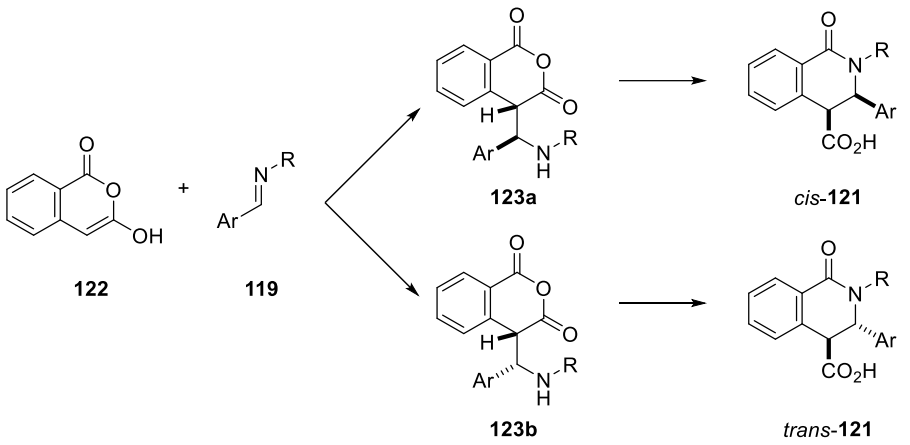
Cushman expanded the scope of the anhydride component of the reaction by employing homophthalic anhydride (**86**) in 1977.[94] Ten years later, he conducted a series of experiments focusing on the influence of the substrate's electronic and steric characteristic in order to elucidate the reaction mechanism.[86] As a result, he proposed three distinct mechanistic possibilities.

The first proposal involves a Diels-Alder cycloaddition between an enol tautomer of homophthalic anhydride (**118**) and imine **119**. Tautomer **118** had been reported as a reactant in the condensation of homophthalic anhydride with dienophiles (the Tamura reaction will be discussed in Section 1.3.3).[99] Although the Tamura reaction required prolonged heating at elevated temperatures (typically 100-200 ºC), the reaction of imines with homophthalic anhydride took place at room temperature in relatively short periods of time. Moreover, analysing the hypothetical adducts of the Diels-Alder reaction **120a** and **120b**, bulky substituents on the nitrogen atom would lead to the formation of *trans*-**121** due to steric clash between the bulky substituent and the aromatic ring in **120a**, however the experimental outcome indicated that bulky groups on the nitrogen atom led to the formation of *cis*-**121** (Scheme 1.32).



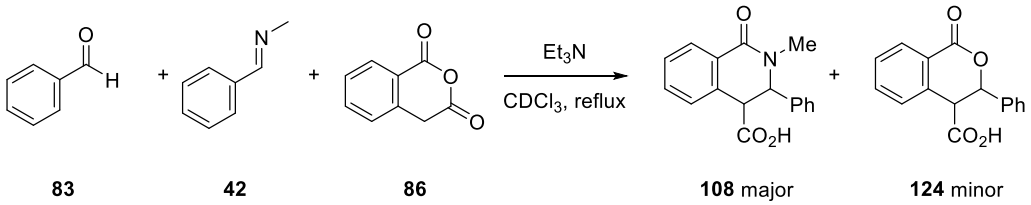

**Scheme 1.32** Cushman's first mechanistic proposal based on a Diels-Alder reaction.

The second proposal was based on the formation of the C-C bond prior to the C-N bond formation: a nitrogeneous analogue of the Perkin reaction.[68] Enol tautomer **122** attacks, *via* Mannich addition, imine **119** to form the intermediates **123a** and **123b** that after an *N*-acylation event, form *cis*-**121** and *trans*-**121** (Scheme 1.33).



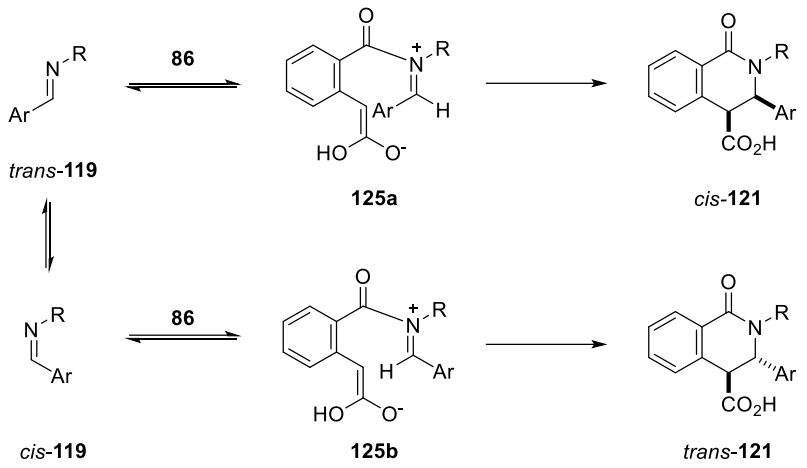

**Scheme 1.33** Mechanistic proposal based on the nucleophilic attack of the anhydride enol tautomer.

To test this hypothesis, imine **42** was allowed to compete with **83** for reaction with **86** in the presence of triethylamine. The mixture of *cis/trans*-**108** lactams were formed predominantly, whereas lactone **124** was a minor product (Scheme 1.34). Thus, this experiment helped to discount the proposed Mannich addition mechanism; as aldehydes are generally more reactive electrophiles than imines, thereby the main product would have been expected to be the lactone, instead of the lactam.




**Scheme 1.34** Competition experiment between imine **42**, aldehyde **83** and anhydride **87**.

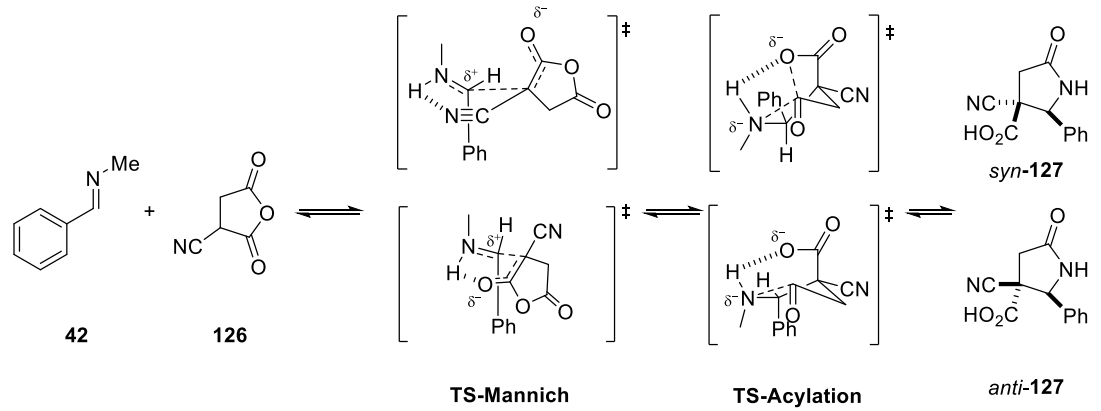
The third mechanism proposal is the iminolysis pathway (Scheme 1.35). It was proposed that the rate-limiting step of the process was the *cis*/*trans* isomerisation of imine **119**. An EDG at the *p*-position of the imine's aromatic ring increases the energy for imine isomerisation and stabilises the developing positive charge in the transition state leading to **125a**. When large groups were placed on the nitrogen atom, the reaction produced *cis*-**121** exclusively, due to – according to the authors – a steric clash between the large substituent and the aromatic ring in *cis*-**119**. This justification also explains why when using imines whose configuration is *cis* (cyclic imines for example) the configuration of the lactam is always *trans*.




**Scheme 1.35** Mechanism based on an iminolysis process.

#### 1.3.2.4.3 Shaw's and Cheong's proposal

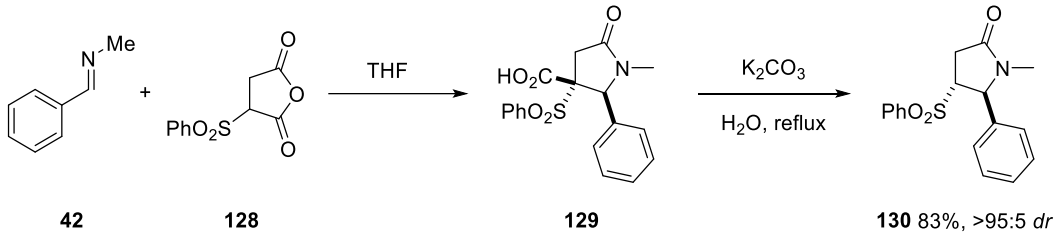
More recently, DFT calculations were utilised to elucidate the mechanism of the reaction. Kaneti *et al*. were the first to report a computational study to elucidate the mechanism of the cycloaddition reaction between enolisable anhydrides and imines. They concluded that the rate-determining step of the reaction is 'a concerted iminolysis and elimination of the carboxylate followed by a charge transference.'[100] In 2013, Shaw and Cheong proposed a stepwise mechanism for the cycloaddition between **42** and anhydride **126**.[101] For the first step, the Mannich addition, *anti*-**127** is slightly favoured as it possesses a stronger hydrogen-bond interaction between the iminium ion and the enolate, whereas *syn*-**127** presents a weaker hydrogen-bond between the iminium ion and the cyano group on the anhydride (the energy difference between both is $\Delta\Delta G$=0.8 kcal/mol, see Scheme 1.36). For the next step, the acylation, the energy difference between the transition state corresponding to *anti* and *syn* diastereomers is bigger and is key to the diastereocontrol; the *anti*-diastereomer exists in an eclipsed configuration (the energy difference is $\Delta\Delta G$=4.4 kcal/mol). The energy barriers to the *syn*-diastereomer are: 13.5 kcal/mol for the Mannich step (**TS-Mannich**) and 10.9 kcal/mol to the acylation step (**TS-Acylation**), and the energy barriers for the *anti*-diastereomer are: 12.7 kcal/mol for the Mannich step (**TS-Mannich**) and 15.3 kcal/mol for the acylation step (**TS-Acylation**). The rate-determining step for the dominant diastereomer (*syn*-**127**) is the Mannich reaction, whereas the rate-determining step of the minor diastereomer (*anti*-**127**) is *N*-acylation. Although the first barrier of the reaction is lower for the *anti* diastereomer, the barrier in its rate-determining step is considerably higher than the energy barrier of the rate-determining step for *syn* (Scheme 1.36).[102]




**Scheme 1.36** Shaw's and Cheong's mechanistic proposal.[102]

### 1.3.2.5 Applications of the cycloaddition reactions of imines with enolisable anhydrides

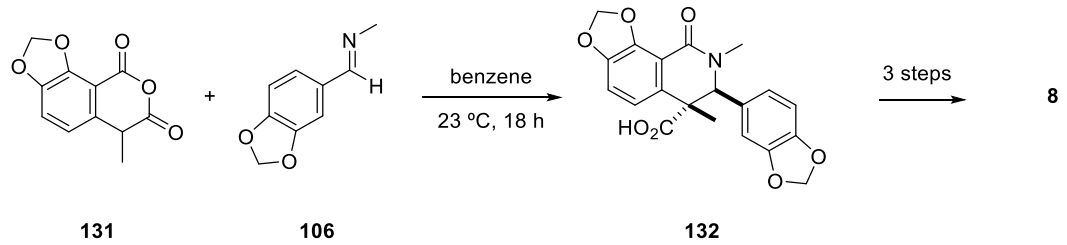
Following his mechanistic proposal, Shaw further investigated the cycloaddition and achieved excellent levels of diastereocontrol in the reaction between imines (**42**) and anhydride **128** (Scheme 1.37).[90] Lactam **129**, formed as the *syn* diastereomer predominantly, decarboxylates in the presence of a base to form lactam **130**.




**Scheme 1.37** Diastereoselective formation of γ-lactams reported by Shaw.[90]

The reaction has been applied to the racemic synthesis of natural products[103] and γ-lactams such as **6**, which exhibit biological activity.[9]

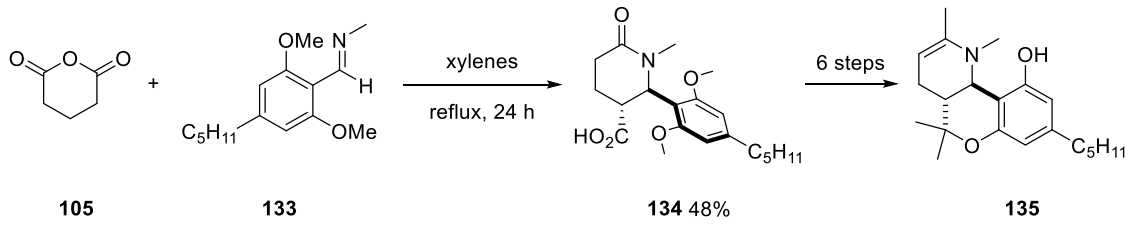
The cycloaddition between homophthalic anhydrides and imines provides a powerful tool for the synthesis of natural products and different alkaloids.[104] Cushman reported the racemic total synthesis of polycyclic 6-oxocorynoline (**8**) in which anhydride **131** underwent a cycloaddition reaction with imine **106** to form lactam **132**, the main core of the natural product, which was synthesised in three additional steps (Scheme 1.38).[105]




**Scheme 1.38** Total synthesis of 6-oxocorynoline (**8**) reported by Cushman.

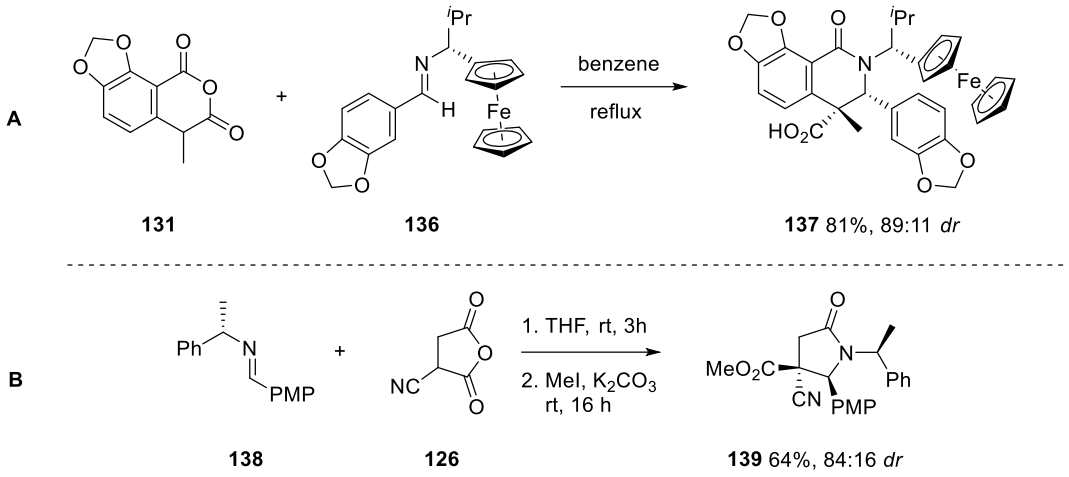
The cycloaddition reaction can be utilised not only for the synthesis of natural products containing lactams, but also as an intermediate step in the synthesis of natural products with polycyclic amine cores by reducing the lactam.[106]

Glutaric anhydrides have been used by Castagnoli in the synthesis of pharmacologically active analogues of tetrahydrocannabinol.[107] The authors employed the cycloaddition reaction between anhydride **105** and imine **133** to synthesise bicyclic lactam **134**, that was converted in six further steps into the corresponding fused-tricyclic amine **135** – an analogue of tetrahydrocannabinol (Scheme 1.39).[108]




**Scheme 1.39** Total synthesis of a tetrahydrocannabinol analogue reported by Castagnoli.

Despite the synthetic utility described previously and the wide variety of products accessible through this route, at the outset of the work described in this thesis, access to enantioenriched cycloaddition products between imines and anhydrides was not possible. There are only two examples of an asymmetric processes involving anhydrides and imines and they both require the use of a chiral auxiliary on the imine. The first process was employed in the asymmetric formal synthesis of corynoline. This used a chiral ferrocene unit attached at the nitrogen atom on the imine: the anhydride **131** underwent cycloaddition with the chiral imine **136** to furnish chiral the lactam **137** in an 89:11 *dr* (Scheme 1.40, A).[109] The other stereoselective process reported in the literature, reacted the chiral imine **138** with **126** to afford lactam **139** with a good diastereomeric ratio (Scheme 1.40, B).[89]

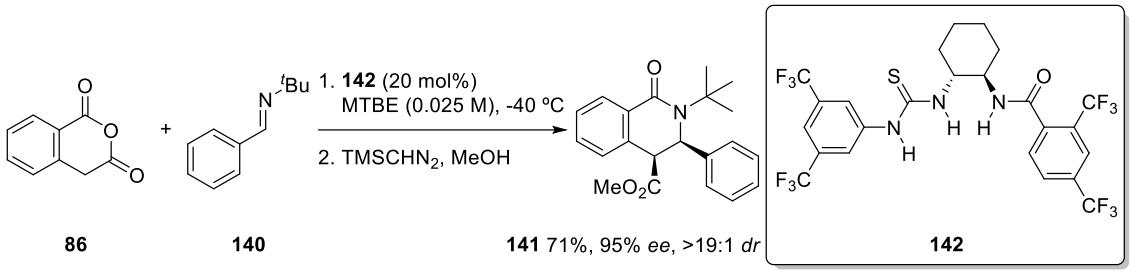



**Scheme 1.40** The only two examples of an asymmetric cycloaddition employing chiral imines and anhydrides.

Although the two asymmetric versions offer enantioenriched lactams in moderate yields with moderate diastereocontrol, the main problem associated with these syntheses is the use of chiral auxiliaries, which are often expensive and that require extra steps to cleave, reducing the overall yield of the reaction. In addition, the cycloaddition reaction provides access to highly functionalised lactams with two contiguous stereocentres. Therefore, the development of an atom-economic, organocatalytic asymmetric process capable of providing access to enantiopure biologically active compounds would be a highly desirable development.

### 1.3.2.6 Current advances in the organocatalytic asymmetric version

As previously mentioned, at the beginning of this research project (4 years ago), there were no examples of an organocatalytic asymmetric version of the cycloaddition reaction between enolisable anhydrides and imines. However two years ago, Seidel *et al.* reported the second (i.e. after the results in Section 2.2 were published) organocatalytic asymmetric process. They reported the conversion of homophthalic anhydride (**86**) and imine **140** to δ-lactam **141** catalysed by **142** with excellent diastereo- and enantiocontrol (Scheme 1.41).[93]




**Scheme 1.41** Enantioselective cycloaddition reaction reported by Seidel two years ago.

Consistent with the hypothesis reported by Shaw and Cheong,[102] a computational study indicated that the imine deprotonates the anhydride; forming an ionic complex with the enolate (Scheme 1.27). Seidel utilised the catalyst to interact with both the iminium ion and the enolate and to create the requisite chiral environment for them to react with enantio- and diastereocontrol. The amide moiety of the catalyst interacts, through the oxygen atom, *via* hydrogen-bonding with the iminium ion N-H, while the enolate interacts *via* hydrogen-bonding with the thiourea unit (Figure 1.9).

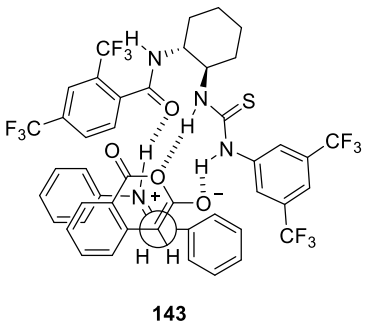
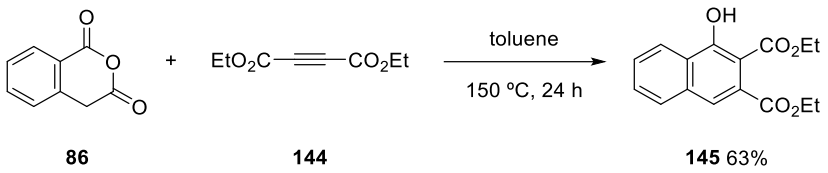



**Figure 1.9** Pre-transition state for the addition step key in the enantiocontrol of the reaction reported by Seidel.[93]

### 1.3.3 Reaction with alkenes/alkynes: the Tamura cycloaddition

#### 1.3.3.1 Double-activated alkenes/alkynes

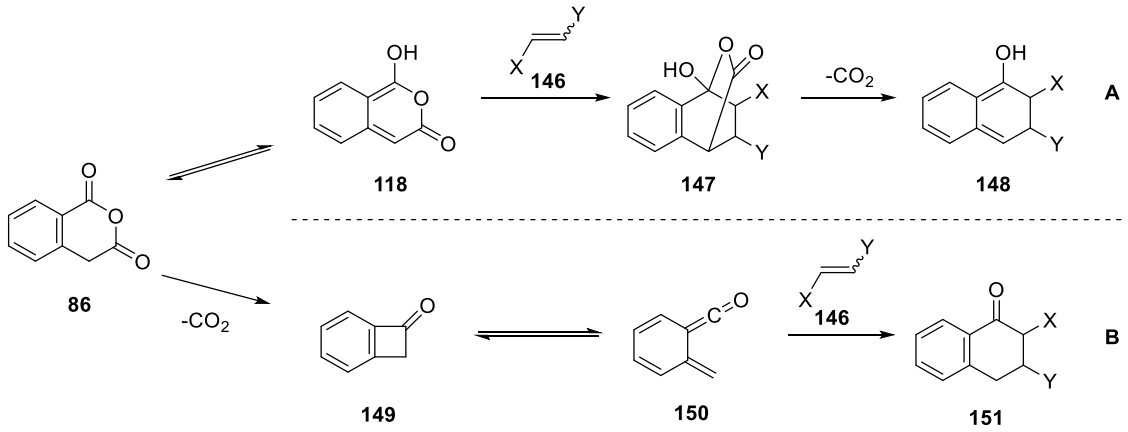
Enolisable anhydrides can also undergo a cycloaddition reaction with activated alkynes/alkenes to produce polycyclic systems. The first example of this reaction was reported by Tamura *et al.*[99] in 1981. They disclosed that when **86** was heated at high temperature (150 ºC in toluene in a sealed tube) for 24 hours with alkyne **144**, naphthol **145** was obtained in a moderate yield (Scheme 1.42).




**Scheme 1.42** The first cycloaddition reaction between enolisable anhydrides and alkynes reported by Tamura in 1981.

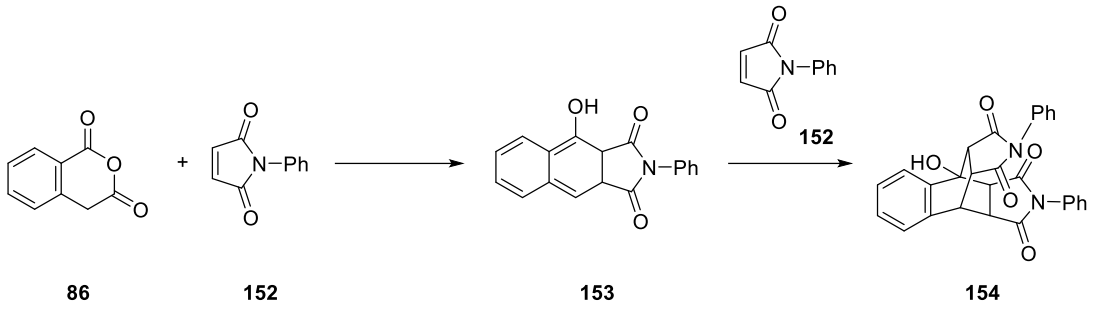
#### 1.3.3.1.1 Mechanistic considerations

Tamura found that the alkyne or alkene must be double activated at both termini to obtained good yields.[99] However, in the seminal publication on the topic, the highest yield obtained was only 65%. Tamura examined the scope of the dienophile substrate and proposed two possible pathways that the reaction could follow. The first of them involves the Diels-Alder reaction between the enol-tautomer form of the anhydride **86** and the dienophile **146** to form the [4+2] Diels-Alder adduct **147** that evolves with extrusion of $CO_2$ to form **148** (Scheme 1.43, A). The other pathway starts with the extrusion of $CO_2$ from **86** to afford four-membered ring ketone **149** that ring-opens to form ketene **150** that undergo the Diels-Alder reaction with **146** to furnish **151**, the keto-tautomer of **147** (Scheme 1.43, B).




**Scheme 1.43** First mechanistic proposals by Tamura in 1981.

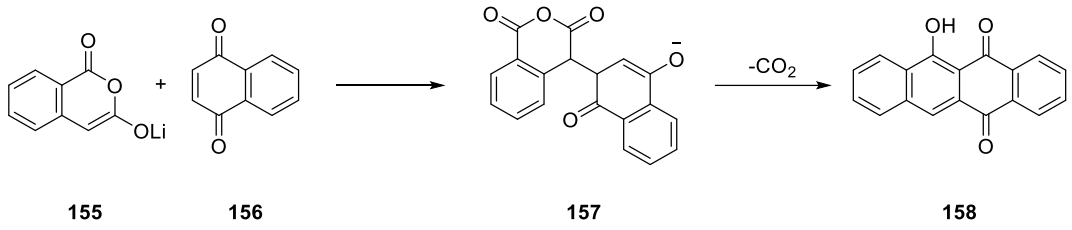
Nevertheless, they argued that not enough data was gathered to confirm either mechanism although, they also proposed that the most likely mechanism was mechanism A, as the treatment of **86** with *N*-phenylmaleimide (**152**) led to the double addition of the *N*-phenylmaleimide in the final product **154**. This could only happened if one equivalent of *N*-phenylmaleimide reacted with **153** – which appeared to support the thesis that **152** initially reacts with **118** (Scheme 1.44).




**Scheme 1.44** Tamura reaction between anhydride **86** and dienophile **152**.

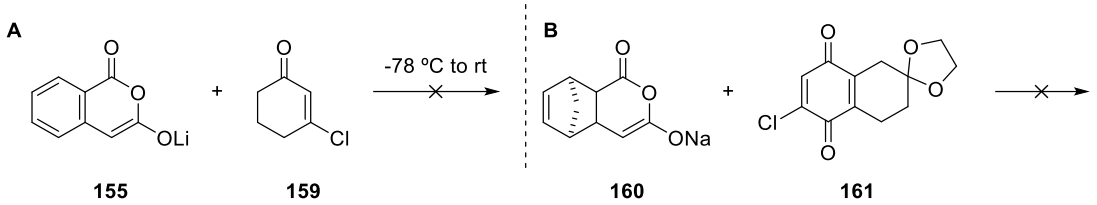
However, the reaction conditions associated with the original Tamura reaction were harsh (long exposure at high temperatures in aromatic solvents) and the yields were not especially high, so a few years later, Tamura improved the process by employing an external base to initiate the reaction. After evaluating several organic bases, they managed to deprotonate the benzylic position of the homophthalic anhydride by using either LDA or NaH. Using this procedure, they managed to improve the generally moderate yields to up to 96% in some cases, under mild reaction conditions (NaH at 0 ºC in THF). Despite this advance, mono-activated alkynes were still producing poor product yields.[110]

The use of a strong base opened another mechanistic possibility – a stepwise process based on a Michael-type reaction. Enolate **155** reacts *via* Michael addition with the dienophile **156**. Michael adduct **157**, after cyclisation and concomitant extrusion of $CO_2$ forms polycyclic compound **158** (Scheme 1.45).



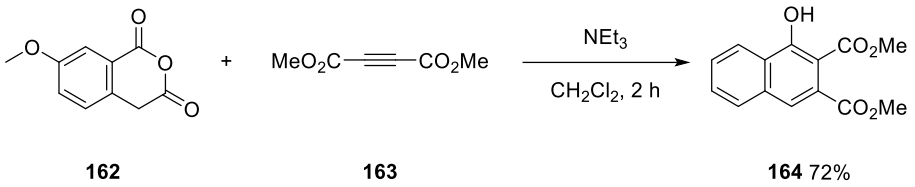

**Scheme 1.45** Proposed mechanism by Tamura based on a Michael addition.

To test this new hypothesis they tried to react enolate **155** with known Michael acceptor **159**, however, the reaction did not proceed (Scheme 1.46, A). Next, they focused their attention on the Michael acceptor **161** by making it react with different C-nucleophile enolate **160** in a Michael reaction, but it failed to afford any product (Scheme 1.46, B). Finally, based on the results gathered, they concluded that the most likely mechanism for the reaction to proceed was the Diels-Alder pathway (Scheme 1.43, A), although they could not discard completely the Michael addition pathway due to the lack of results.




**Scheme 1.46** Reactions between known Michael-acceptors and different C-nucleophile enolates.

Similar to the cycloaddition reaction between imines and enolisable anhydrides, the mechanism of the Tamura reaction has been an object of study for decades and in 1991, Smith *et al*. added more controversy when they carried out the Tamura reaction between anhydride **162** and activated alkyne **163** employing catalytic amounts of $NEt_3$ at room temperature to obtain compound **164** in good yield (Scheme 1.47).[111]



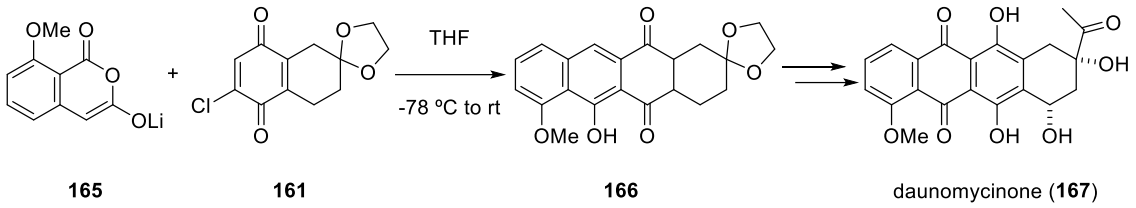

**Scheme 1.47** Tamura reaction catalysed by $NEt_3$ reported by Smith in 1991.

However, not only homophthalic anhydrides undergo Tamura cycloaddition, but also different heteroaromatic enolisable anhydrides[92] and some activated glutaconic anhydrides.[112]

#### 1.3.3.1.2 Application of the cycloaddition to the synthesis of biological active molecules

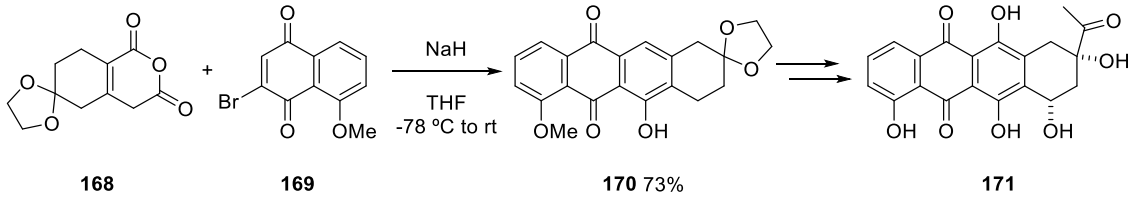
Although the mechanism of the reaction remains uncertain (it has been classified as a Diels-Alder reaction),[84] the reaction possesses considerable potential in the synthesis of natural products, as it allows access to complex polycyclic compounds, the core of a wide variety of natural products.[113] Tamura demonstrated that this strategy could be applied to the synthesis of anthracyclinones, the core of tetracycline antibiotics[114] and many natural products.[115]As a first example, he reported a formal synthesis of (±)-daunomycinone (**167**).[116] Using a base-induced cycloaddition reaction between **165** and **161** he synthesised the polycyclic **166** with excellent regiospecifity. They reported that the yield could be improved through the use of the enolate lithium (Scheme 1.48).[117] The chlorine atom in the dienophile had two important roles in the reaction. Firstly, it controlled the regiochemistry

of the reaction and secondly, it facilitated the aromatisation of the product *via* elimination of hydrogen chloride.



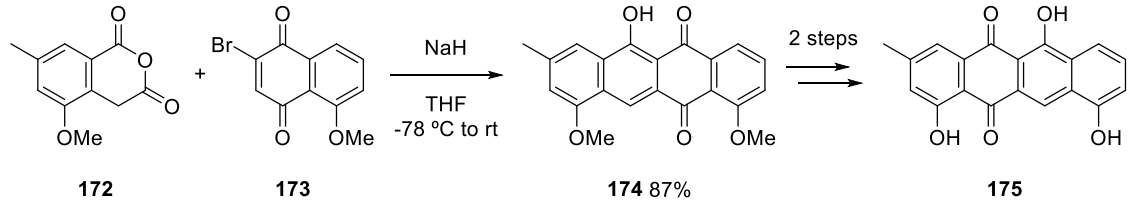

**Scheme 1.48** Formal synthesis of (±)-daunomycinone reported by Tamura.

Some years after Tamura *et al.* initially reported the formal synthesis of (±)-daunomycinone they proposed a new synthetic route in which they used a new anhydride to carry out the reaction. **168** was synthesised and underwent a cycloaddition reaction with **169**, promoted by NaH in THF to furnish tetracycline **170** in good yield (Scheme 1.49).[118] **171** is an intermediate in the total synthesis of 11-deoxycarminomycinone (**171**).[119]



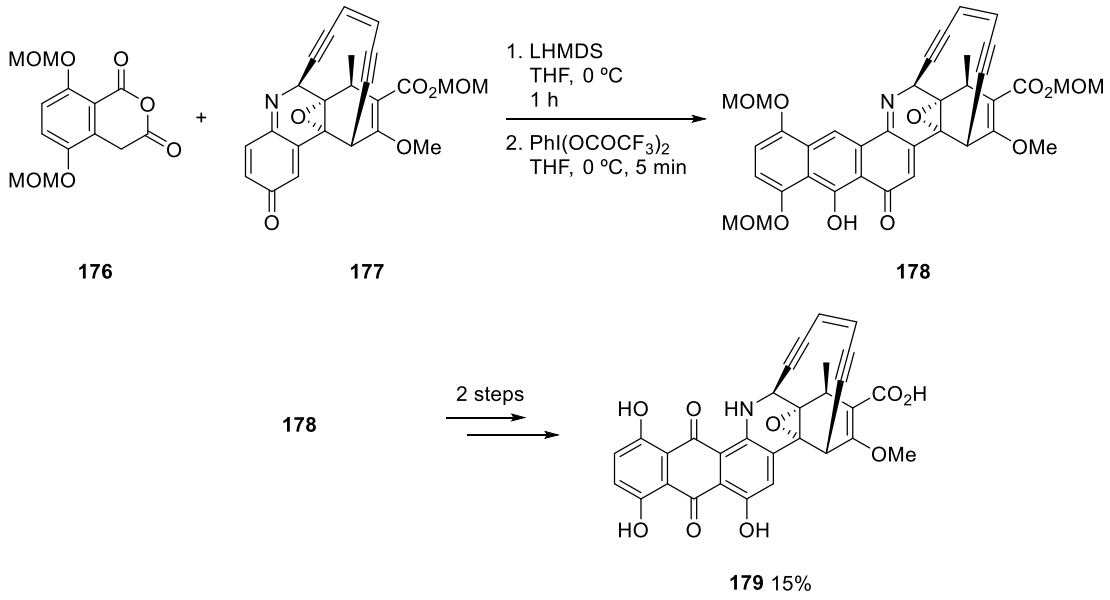

**Scheme 1.49** Formal synthesis of **171** reported by Tamura.

The synthesis of the antibiotic SS-228R (**175**), known to inhibit the growth of Gram-positive bacteria and the enzyme dopamine-β-hydroxylase, was also achieved *via* Tamura cycloaddition between anhydride **172** and electrophile **173**, again requiring the use of a strong base. The intermediate **174** was obtained in good yield and converted into the antibiotic **175** after two further steps (Scheme 1.50).[120] The bromine atom in **173** controlled the regiocontrol of the reaction and facilitated the aromatisation of the product to form **174** *via* elimination of hydrogen bromide.



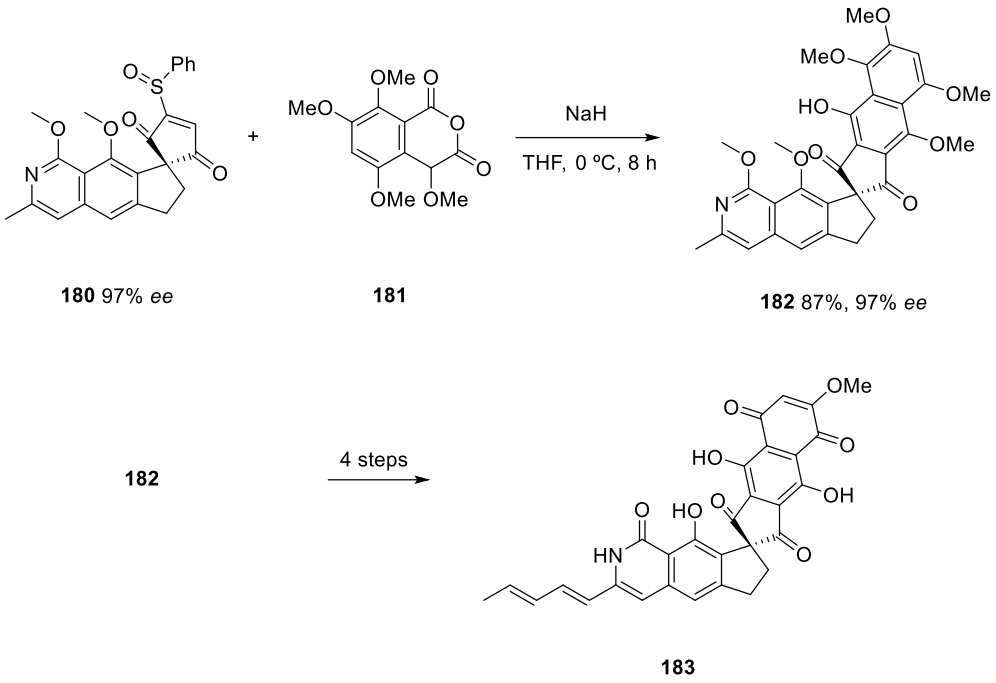

**Scheme 1.50** Total synthesis of **175** reported by Tamura

As seen in the examples above, the reaction presented multiple possibilities, as both the anhydride and the electrophile could be exhaustively modified. This reaction was employed by Danishefsky *et al.* in the total synthesis of (±)-dynemicin A (**179**)[121] which has a challenging structure with a pentacyclic core. After several attempts and different synthetic approaches which were unsuccessful,[122] Danishefsky *et al.* managed to synthesise (±)-dynemicin A employing a Tamura reaction as a key step in the formation of the polycyclic system. The low overall yield of the process (15%) was attributed to the instability of the intermediates of the process and the level of difficulty in the purification of the natural product. Anhydride **176** was treated with LHMDS to form the corresponding enolate that was added to the quinone imine **177**. The product could not be isolated and it was oxidised *in situ* to afford **178**, which was converted into **179** after two more steps (Scheme 1.51).[123]




**Scheme 1.51** Total synthesis of (±)-dynemicin A reported by Danishefsky.

Fredericamycin A, a potent antitumor and antibiotic compound,[124] is another example of a natural product that contains a [4+2]-cycloaddition reaction in its total synthesis. Carried out by Kita *et al.*,[125] they employed enantiomerically pure alkene **180** and anhydride **181**. The transformation was induced by deprotonation of **181** with NaH in THF. Compound **182**, generated in good yield and enantiomeric excess, was converted into Fredericamycin A after four further steps (Scheme 1.52).[126] A sulfoxide group was incorporated into **180** in order to control the regiochemistry of the reaction and its spontaneous elimination facilitates the aromatisation of the product.

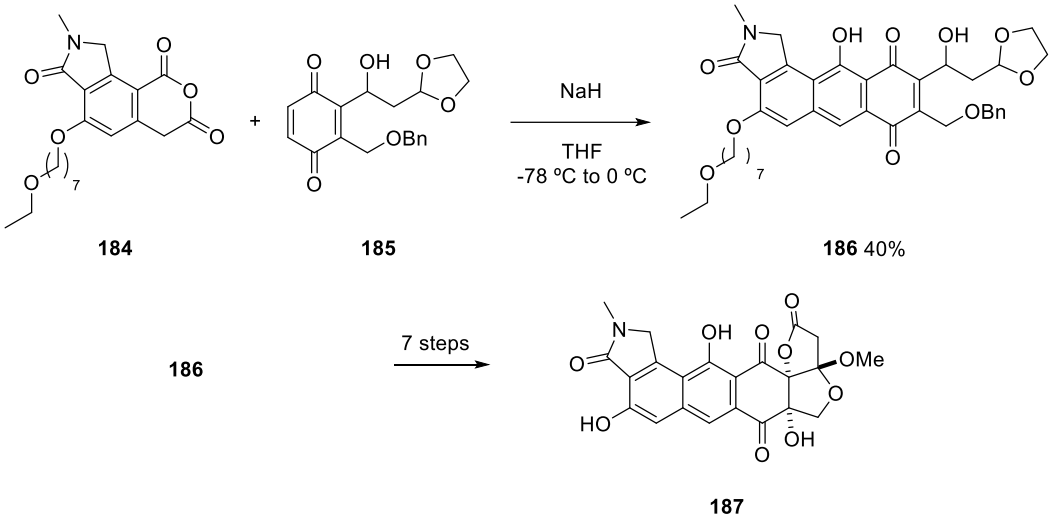



**180** 97% *ee* **181** **182** 87%, 97% *ee*

**182** **183**

**Scheme 1.52** Total synthesis of Fredericamycin A.

Another interesting total synthesis involving the Tamura cycloaddition is the preparation of of Lactonamycinone (**187**). Reported by Danishefsky *et al*.,[127] they employed anhydride **184** and quinone **185**, which in addition to being the electrophile in the reaction, also oxidises the cycloadduct to furnish **186**. Therefore the process required two equivalents of **185**. Furthermore, the hydroxyl group β- to the carbonyl in compound **185** allowed differentiation between the two carbonyls, due to the formation of an intramolecular hydrogen-bond.[128] Cycloadduct **186** was converted into the natural product **187** after 7 more steps (Scheme 1.53).[129]



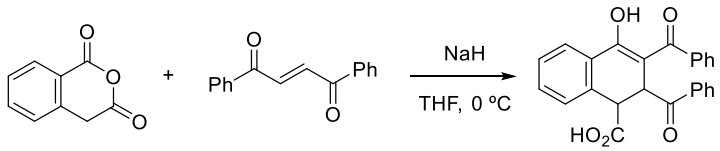

**184** **185** **186** 40%

**186** **187**

**Scheme 1.53** Total synthesis Lactonamycinone reported by Danishefsky.

#### 1.3.3.1.3 Asymmetric organocatalytic processes

The examples reported above highlight that Tamura cycloaddition products are highly susceptible to aromatisation, thereby ablating any stereochemical information within this portion of the molecule. This detracts from the Tamura cycloaddition's utility in asymmetric synthesis. However, in 1984 Tamura reported a cycloaddition reaction in which aromatisation did not occur, between **86** and alkene **188**, to furnish compound **189**, induced by NaH in THF (Scheme 1.54).[110]




**86** **188** **189** 83%

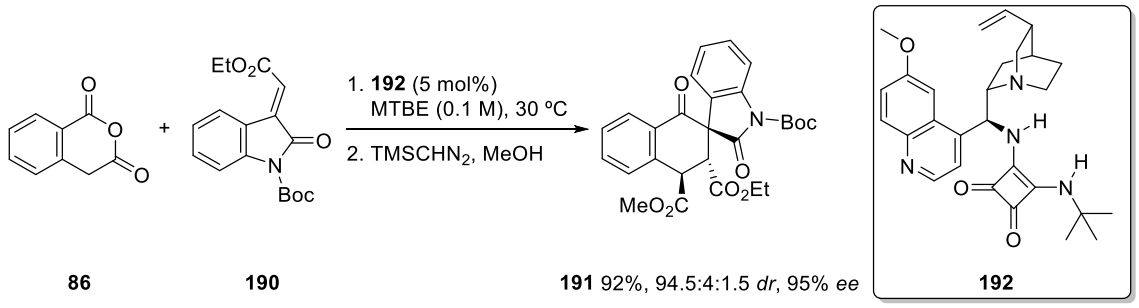
**Scheme 1.54** Example reported by Tamura in which the aromatisation of the system did not occur

The absence of a leaving group on the electrophile and the mild reaction conditions, reduced the propensity aromatisation of the product. Thus, **189** was perfectly stable, and the Tamura cycloaddition had created two new stereocentres.

The examples shown previously, demonstrated the importance and potential of the reaction. Smith demonstrated that homophthalic anhydride could undergo the Tamura cycloaddition in the presence of relatively weak organic bases (Scheme 1.47).[111] Also, homophthalic

anhydrides have been employed in cycloaddition reactions with aldehydes catalysed by cinchona alkaloids (Scheme 1.23).

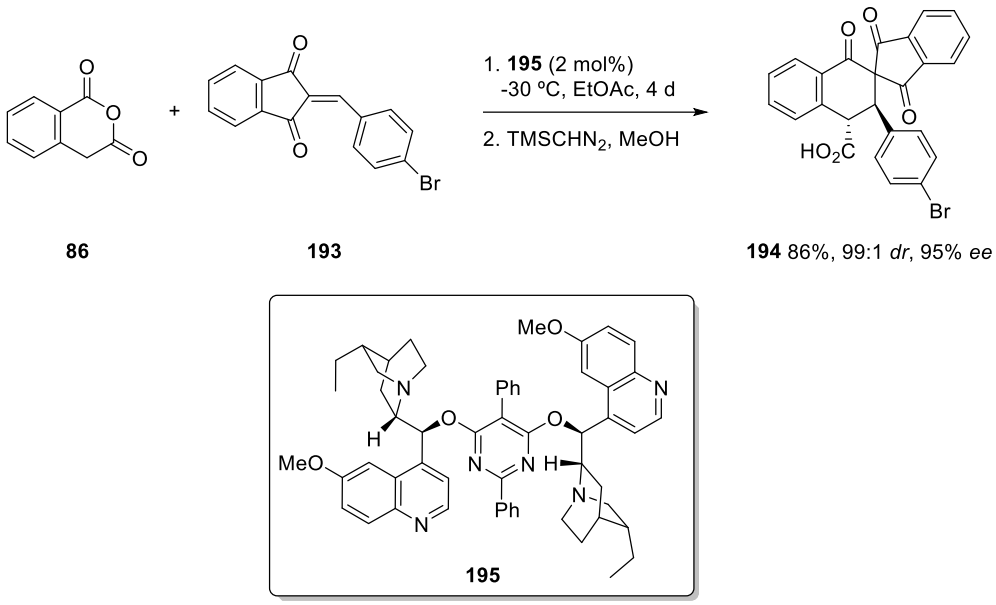
In 2014, our group reported the first catalytic asymmetric Tamura reaction between enolisable anhydrides, such as **86**, and oxindole **190** to afford access to spirooxindoles (e.g. **191**, compounds present in a wide range of natural biological active natural products)[130] catalysed by cinchona alkaloid-derivative **192** (Scheme 1.55).[112] In the process two new C-C bond have been formed along with three stereocentres, one of them quaternary and completely carbogenic. Furthermore, spirooxindol **191** is formed with excellent diasterecontrol and yield in an optically pure manner.




**Scheme 1.55** First catalytic asymmetric Tamura cycloaddition reported by our group.

Different anhydrides like homophthalic derivatives or derivatives from glutaconic anhydride were employed retaining the excellent levels of diastereo- and enantiocontrol. The oxindole component was also modified; leading to excellent levels of enantiocontrol. When the reaction was carried out at -50 ºC the diastereocontrol changed to favour the formation of the *syn* diastereomer with excellent enantiocontrol.

Recently, Wu *et al.* employed an alkene doubly activated on just one termini of the olefin in an attempt to expand the scope of the electrophile component of the reaction. Thus, promoted by catalyst **195**, homophthalic anhydride reacted with 2-arylidene-1,3-dione **193** to furnish spiroo-1,3-indanedione **194**, possessing two contiguous stereocentres, in good yield and diastereocontrol and moderate enantiocontrol (Scheme 1.56).[131]



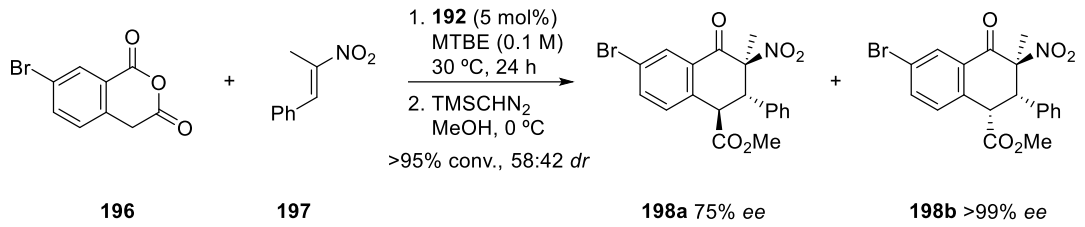

**Scheme 1.56** Catalytic Tamura cycloaddition of diactivated alkene **193**.

### 1.3.3.2 Mono-activated alkenes

#### 1.3.3.2.1 Organocatalytic processes

The previous section outlined that in the Tamura reaction the alkene or alkyne needed to be doubly activated in order to achieve good yields. However, Tamura reported two examples in which the electrophile was monoactivated – the yield achieved under thermal conditions was 19%[99] and when a strong base was used the yield improved to 50%.[110]

Nevertheless, our group became interested in the case in which a single strong electron-withdrawing group was employed to activate the alkene. Therefore, in 2017, our group reported the first highly enantioselective Tamura cycloaddition of mono-activated olefins employing nitrostyrenes.[132] The use of methylnitrostyrenes allowed for the use of less complex but synthetically malleable substrates, while retaining the three contiguous stereocentres in the product, one of them quaternary. Thus, the reaction between anhydride **196** and methylnitrostyrene **197** promoted by catalyst **192** afforded ketones **198a** and **198b** (58:42 *dr*) with good and excellent enantiocontrol respectively (Scheme 1.57).

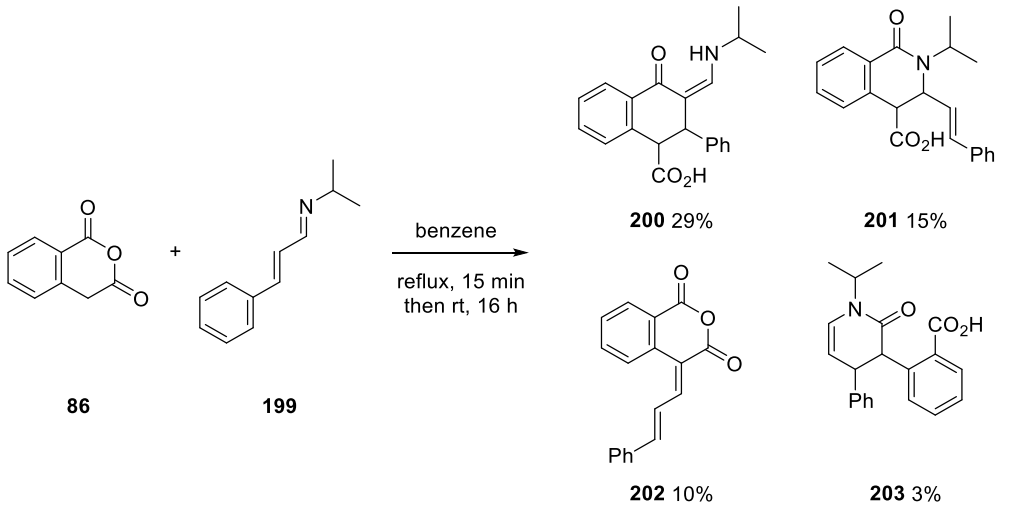



**Scheme 1.57** Catalytic Tamura cycloaddition between homophthalic anhydrides and mono-activated alkenes.

Shortly after, Pan *et al.*[133] reported a similar procedure between homophthalic anhydrides and different α-branched nitroolefins which produced ketones.

#### 1.3.3.2.2 Reaction of homophthalic anhydride with α,β-unsaturated imines

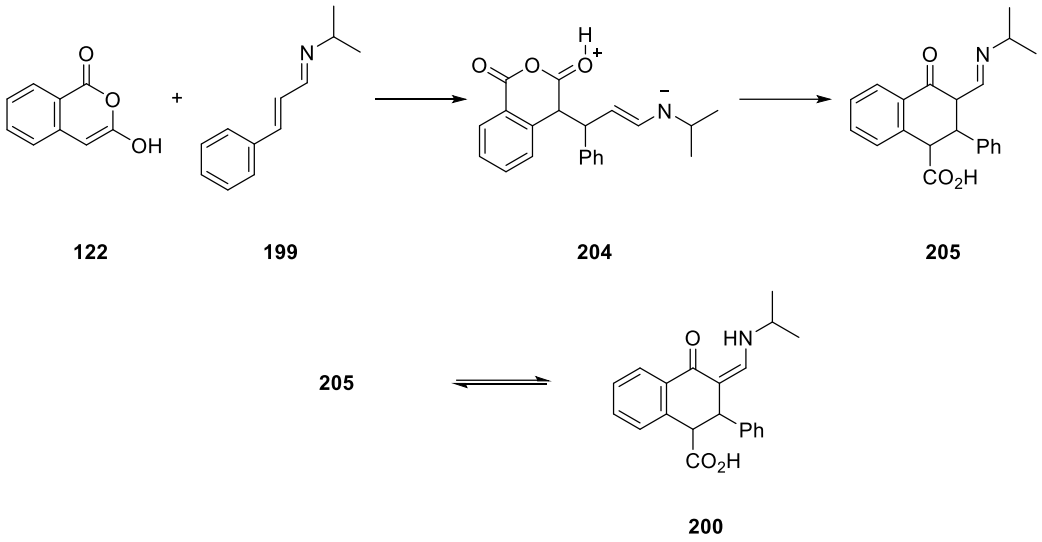
The reaction of enolisable anhydrides and α,β-unsaturated imines is a special case. First reported by Haimova *et al.* in 1995,[134] α,β-unsaturated imines can react with anhydrides at the imine position as standard imines, following the formal [4+2]-cycloaddition reaction reported originally by Castagnoli (hereafter, referred to as the Castagnoli reaction), at the olefin, *via* Tamura cycloaddition, or produce the product of a Perkin type condensation. Thus, when **86** was heated in benzene in the presence of imine **199**, the reaction produced a complex mixture of products (Scheme 1.58).




**Scheme 1.58** Reaction between **86** and α,β-unsaturated imine **199** affording a complex mixture of products.

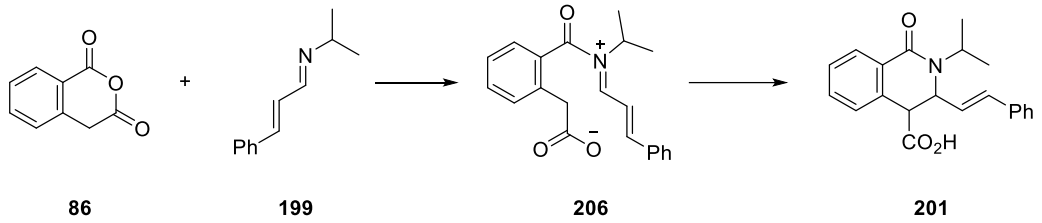
The authors proposed a different pathway for each product of the reaction. The formation of major product **200** was rationalised as a two-step reaction, in which the first step was a Michael-type addition of **122** (enol-tautomer of **86**) to imine **199**,[135] to form Michael adduct

**204**, which cyclised to form **205** that was converted to **200** following tautomerisation (Scheme 1.59).



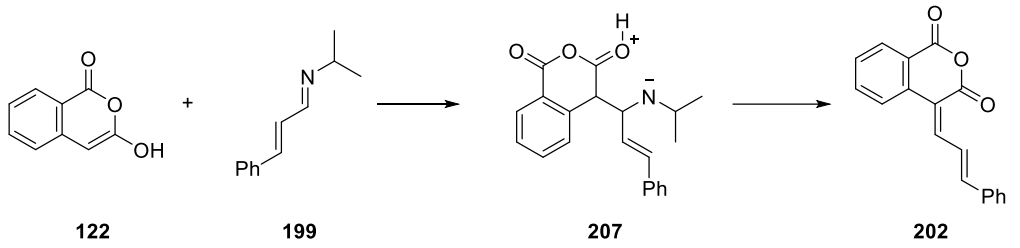

**Scheme 1.59** Proposed pathway for the formation of **200** by Haimova *et al.*

For the formation of **201**, the authors proposed another two-step process similar to the one previously outlined by Cushman (see Section 1.3.2.4.2),[86] in which iminolysis of the anhydride initiated the reaction to form **206** and subsequent ring-closure formed **201** (Scheme 1.60).



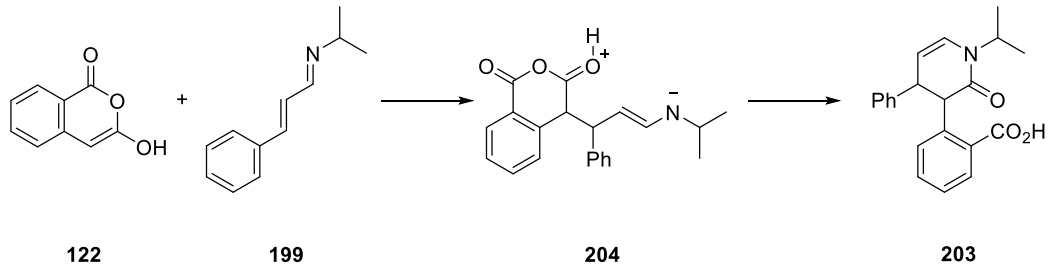

**Scheme 1.60** Proposed pathway for the formation of **201** based on the Castagnoli reaction.

As mentioned previously, **202** was the product of a Perkin type condensation in which the first step was the Mannich addition of **122** to **199** to produce Zwitterionic intermediate **207**, which collapsed with elimination of the amine to form **202** (Scheme 1.61).



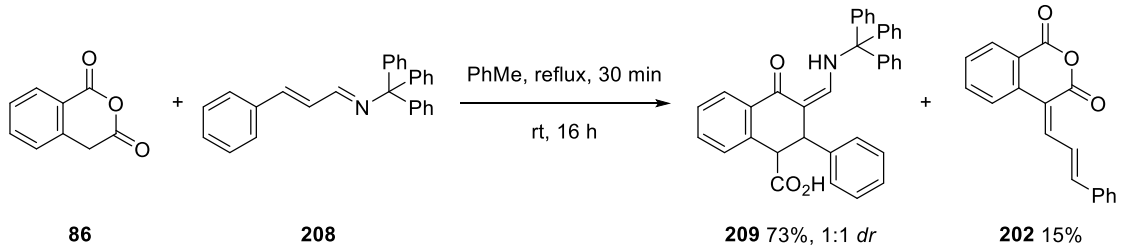

**Scheme 1.61** Formation of **202** *via* addition-elimination.

Finally, **203** was explained *via* a two-step process (1,4-addition) similar to the formation of **200**, differing in that the ring-closure occurred as a result of the nucleophilic ring closure of the nitrogenous anion on to the anhydride to form **203** (Scheme 1.62).




**Scheme 1.63** Proposed mechanism for the formation of **203** based on a 1,4-addition.

The authors found that the ratio of the products could be diverted. Thus, in the presence of acidic catalysts in polar solvents the formation of the Castagnoli product **201** and the Perkin condensation product **202** were favoured. In addition, modifying the nature of the substituents on the imine could also divert the reaction to favour the formation of some products over others. Hence, when bulky groups were substituted on the nitrogen atom, the iminolysis pathway to form **201** was disfavoured as the nitrogen was serically encumbered. In 1997, Georgieva *et al.* reported the reaction between bulky imine **208** and **86** to afford a mixture of *syn*/*anti*-**209** in a moderate yield however, the Perkin condensation product **202** was still being formed (Scheme 1.64).[136]




**Scheme 1.64** Formation of **209** *via* Tamura cycloaddition.

This reaction represents an example in which the Tamura reaction proceeds with moderate yields when the alkene is mono-activated in the absence of catalyst. Unfortunately, due to the high number of products obtained in the reaction and the lower yields in addition as the harsh reaction conditions employed, the reaction has been classified as 'synthetically unattractive'.[137]

## 1.4 Objectives

- To carry out the first enantioselective cycloaddition reaction between homophthalic anhydride and *N*-sulfonylimines, catalysed by bifunctional cinchona alkaloids.
- To carry out a highly enantioselective Tamura reaction between homophthalic anhydrides and α,β-unsaturated imines through an anion-binding catalysis.
- To expand the scope of the catalytic enantioselective Castagnoli reaction to the use of activated succinic anhydrides and *N*-protected imines.

# Results and discussion

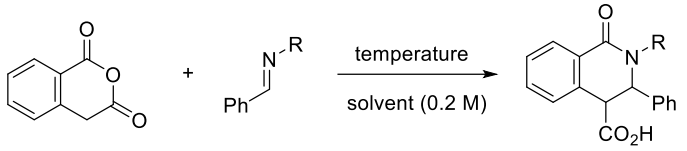
## 2 Cycloaddition reactions between homophthalic anhydride and *N*-sulfonylimines catalysed by cinchona alkaloids

The main problem (from a catalysis standpoint) associated with the cycloaddition reaction between imines and enolisable anhydrides is the nucleophilic/basic character of the imine. As mentioned before, imines can react with enolisable anhydrides *via* formation of the iminium ion complex described by Shaw (see Section 1.3.2.4.3).[102] Therefore, in order to obtain control over the reaction with an enantiopure catalyst, we proposed that the basic character of the imine needed to be eliminated.[28] By doing this, it was thought that a bifunctional catalyst could promote the reaction, activating both anhydride and imine in a similar manner to that observed with aldehydes.[79]

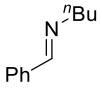
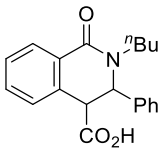
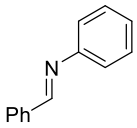
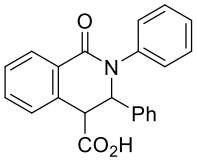
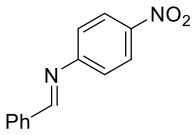
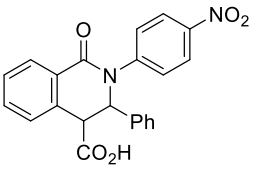
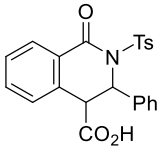
### 2.1 Preliminary results within our group

In order to eradicate the uncatalysed reaction (the reaction due to the basic character of the imine), different substituents were placed at the nitrogen atom on the imine to render it less active (Table 2.1). The presence of the $^{n}$Bu- on the nitrogen atom of the imine **210** did not have the desired effect and lactam **211** was formed quantitatively (independently of the reaction temperature) when the reaction was carried out in THF as solvent (entry 1 and 2) however, the change of solvent to the less polar MTBE decreased the rate of formation of **211** (yet this was still too fast to allow complete catalyst control, entry 3). Imine **212** incorporating a phenyl substituent resulted in a less basic imine; however, lactam **213** was still being formed when **212** was exposed to homophthalic anhydride, albeit with decreased yield (entry 4). When a *p*-nitrophenyl substituent was attached to the nitrogen atom of the imine, the basicity of imine **214** was sufficiently removed and lactam **215** was not formed (entry 5). Finally, the presence of a more malleable tosyl group on imine **216** also allowed the avoidance of the formation of **227** (entry 6).

**Table 2.1** Preliminary study of the effect of different substituents on the nitrogen of the imine within our group.



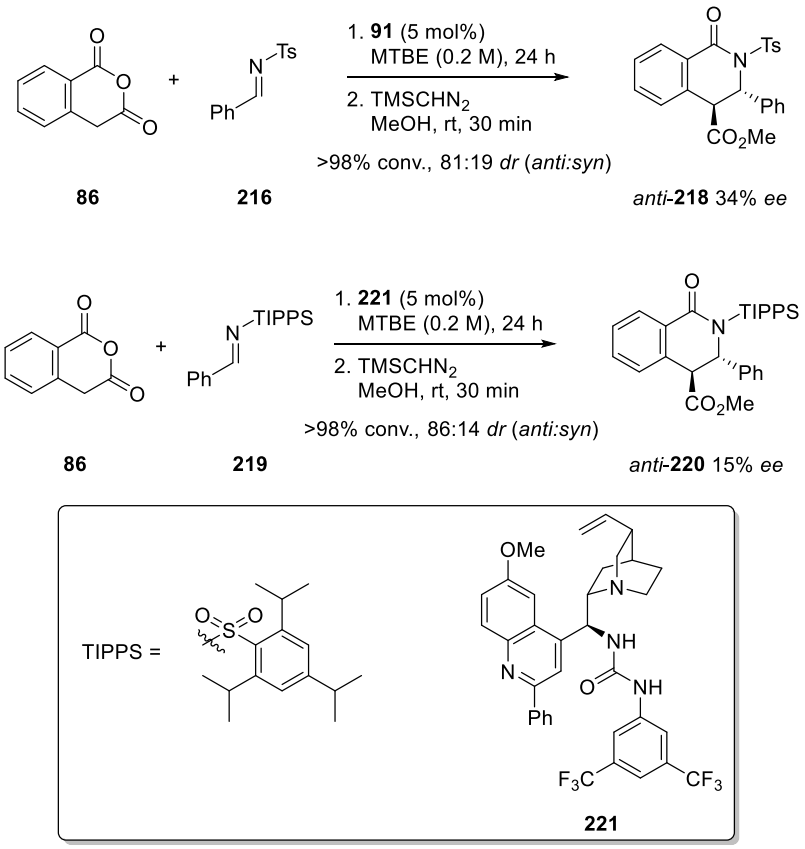

**86**

| Entry | Imine | Product | Solv. | T (ºC) | t (h) | Conv. (%)[a] |
|---|---|---|---|---|---|---|
| 1 |  |  | THF | -30 | 15 | >98 |
| 2 | | | THF | -78 | 15 | >98 |
| 3 | **210** | **211** | MTBE | rt | 24 | 62 |
| 4 |  |  | MTBE | rt | 4 | 39 |
| | **212** | **213** | | | | |
| 5 |  |  | MTBE | rt | 24 | 0 |
| | **214** | **215** | | | | |
| 6 |  |  | MTBE | rt | 24 | 0 |
| | **216** | **217** | | | | |

[a]Determined by $^{1}$H-NMR spectroscopy using *p*-iodoanisole as internal standard.

Imines **214** and **216** proved to be good candidates for the catalytic reaction, as they did not undergo cycloaddition with **86** under those reaction conditions. Therefore, **216** became the substrate for the catalytic reaction as the tosyl group could easily be removed through subsequent reduction.[138]

The new candidate **216** was reacted under the same reaction conditions which furnished good enantiocontrol previously with aldehydes and enolisable anhydrides.[77, 80] However, the results were not satisfactory, as lactam **218** was formed with a lower *ee* than expected. Thus, the group considered the possibility that the cause for the low enantiocontrol was the presence of the substituent on the nitrogen atom of the imine. To test this, a larger group was substituted on imine **219** – which led to the formation of lactam **220** was formed with even less enantiocontrol (Scheme 2.1).



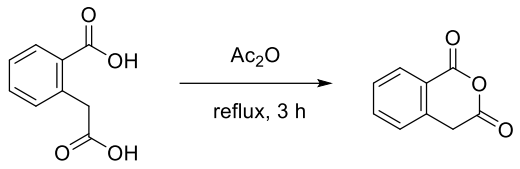

**Scheme 2.1** Preliminary results concerning the cycloaddition of imines with anhydrides in the presence of chiral catalysts

## 2.2 Scope of the reaction

### 2.2.1 Epimerisation problem and development of a new esterification protocol

Bearing in mind that the preliminary results indicated that the bulk of the imine *N*-substituent had an effect on the enantioselectivity of the reaction, we decided to employ a sulfonyl group smaller than tosyl. Hence, we synthesised imine **228**, which incorporates an *N*-mesyl substituent.

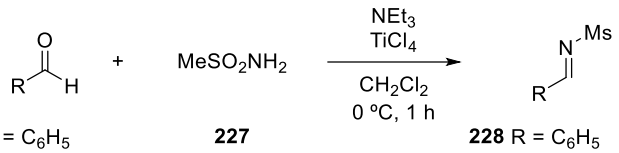
Homophthalic anhydride (**86**) was synthesised in a condensation reaction from the homophthalic acid **222**, which was heated in acetic anhydride at the reflux temperature (Scheme 2.2).




**222** **86** 83%

**Scheme 2.2** Condensation of di-carboxylic acid **222** to afford **86**.

Imines were synthesised through a condensation reaction between the corresponding aldehyde and methylsulfonamide (**227**), and purified by recrystallisation from hexane:$CH_2Cl_2$. The aldehyde was activated using a Lewis acid, in this case $TiCl_4$ was utilised (Scheme 2.3).



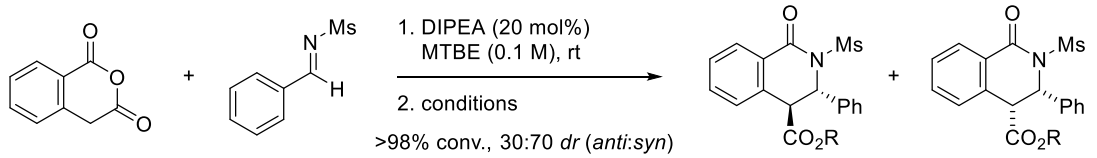

| | | | |
|---|---|---|---|
| **83** R = $C_6H_5$ | **227** | **228** R = $C_6H_5$ | 38% |
| **223** R = 3-MeO-$C_6H_4$ | | **229** R = 3-MeO-$C_6H_4$ | 41% |
| **224** R = 4-MeO-$C_6H_4$ | | **230** R = 4-MeO-$C_6H_4$ | 40% |
| **94** R = 2-furyl | | **231** R = 2-furyl | 39% |
| **225** R = 2-naphthyl | | **232** R = 2-naphthyl | 32% |
| **226** R = $^t$Bu | | **233** R = $^t$Bu | 31% |

**Scheme 2.3** Condensation reaction to afford imines **228**, **229**, **230**, **231**, **232** and **233**.

However, the use of those mesyl imines brought further issues, as we noticed that we could not reproduce the enantiocontrol of the reaction upon repetition. The problem was found during the esterification process; we detected a change in the diasteromeric ratio in the $^1$H-NMR spectra of the crude of the reaction prior to and following esterification. Therefore, we employed a catalytic amount of DIPEA, to promote the reaction between **86** and imine **228**

(the diastereocontrol of the crude racemic reaction was 30:70 (*anti*/*syn*)) and searched for a new set of conditions to carry out the esterification. Such conditions are summarised in Table 2.2. The *syn* diastereomer was transformed into the *anti* diastereomer in less than 30 min when MeOH was used to activate the $TMSCHN_2$ regardless of the temperature, although the rate was lower when less equivalents of MeOH were employed (entries 1, 2, 3 and 4). The exchange of MeOH for $^{i}$PrOH – another alcohol that has been already reported as $TMSCHN_2$-activating for the esterification of acids[80] – did not stop the epimerisation, although it decreased the ratio (entry 5). The conversion also decreased when the esterification was carried out at lower temperatures (entry 6). Steglich esterification led to high conversion of the *syn*-diastereomer into the *anti* (entry 7). The same occurred when the same conditions were applied to produce an amide instead of an ester (entry 8). The use of $K_2CO_3$ as base to deprotonate the acid and methyl iodide to methylate – conditions reported by Shaw to carry out esterifications of acidic lactams[89] – gave full epimerisation (entry 9). Finally, activating $TMSCHN_2$ with EtOH at -30 ºC with only 15 eq. for 30 min allowed us to convert the acid, the product of the catalytic reaction, into the ester without any trace of epimerisation in the products (entry 10).

**Table 2.2** Screening of different esterification procedures.

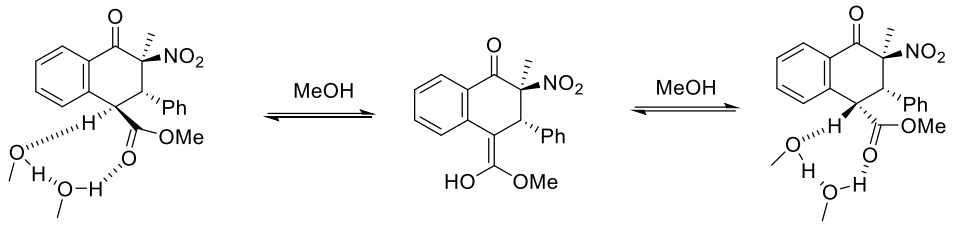



**86** **228** *anti*-**234** *syn*-**234**

| Entry | Reagents | Conditions | *dr*[a] (*anti*:*syn*) |
|---|---|---|---|
| 1 | $TMSCHN_2$/MeOH | 0 ºC / MeOH (30 eq.) | 44:56 |
| 2 | $TMSCHN_2$/MeOH | 0 ºC / MeOH (15 eq.) | 45:55 |
| 3 | $TMSCHN_2$/MeOH | -30 ºC / MeOH (30 eq.) | 43:57 |
| 4 | $TMSCHN_2$/MeOH | -30 ºC / MeOH (15 eq.) | 42:58 |
| 5 | $TMSCHN_2$/$^i$PrOH | 0 ºC / $^i$PrOH (15 eq.) | 45:55 |
| 6 | $TMSCHN_2$/$^i$PrOH | -30 ºC / $^i$PrOH (15 eq.) | 40:60 |
| 7 | DCC, DMAP, $^t$BuOH | 0 ºC | 95:5 |
| 8 | DCC, DMAP, $BzNH_2$ | 0 ºC | 95:5 |
| 9 | $K_2CO_3$, MeI | 0 ºC | 99:1 |
| 10 | $TMSCHN_2$/EtOH | -30 ºC / EtOH (15 eq.) | 30:70 |

[a]Determined by $^1$H-NMR spectroscopy.

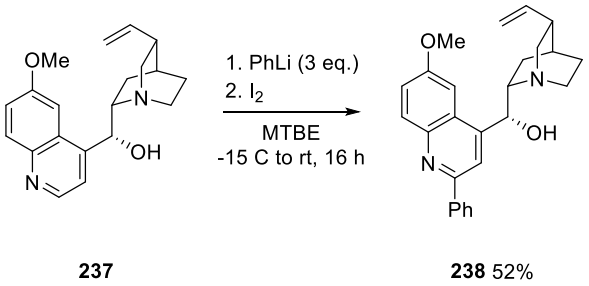
A similar epimerisation process was observed and explained by our group, while working with nitrostyrenes.[132] The process involved the interaction of two molecules of methanol with *anti*-**234** and deprotonation of the α-proton to the ester group by the methanol forming enol **236**. Subsequent protonation of the enol from the other face of the molecule formed the *syn*-**234** (Scheme 2.4). The authors proposed that the presence of the two molecules of methanol interacting with each other, to form a diol complex, was key in the process as they were simultaneously activating both the α-hydrogen and the ester. The replacement of methanol for ethylene glycol, mimicking the diol complex formed by the two molecules of methanol, proved to accelerate the epimerisation. Ethanol possesses an alkyl chain that blocks the space for another molecule of the alcohol to approach and deprotonate the molecule. This corroborates our esterification conditions employing ethanol to activate the $TMSCHN_2$.




**Scheme 2.4** Epimerisation process induced by methanol reported by our group.[132]

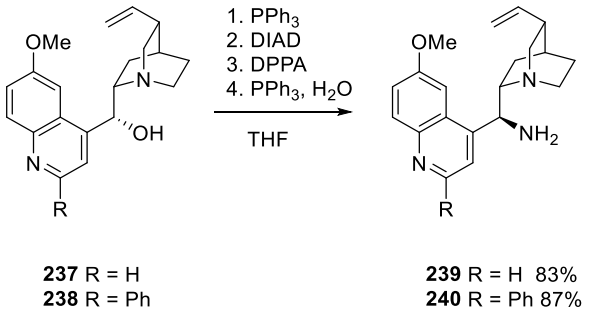
### 2.2.2 Synthesis of catalysts and evaluation

The first step of the synthesis of urea-based catalyst **221**, containing a C-2 substitution on the catalyst quinoline ring, was the introduction of the phenyl group. Towards this end, quinine (**237**) was treated with PhLi to afford **238** (Scheme 2.5).[139]



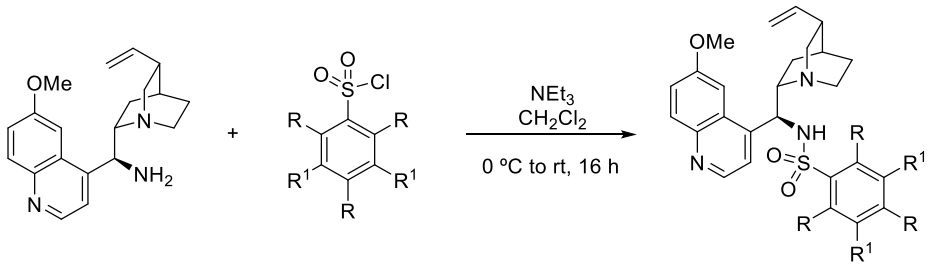

**Scheme 2.5** Treatment of quinine with phenyl lithium.

Quinine (**237**) and its arylated-derivative **238** underwent a Mitsunobu[140] reaction followed by a Staudinger reduction[141] to substitute the hydroxyl group for an amino group with complete inversion of the configuration of the stereocentre (Scheme 2.6).




**Scheme 2.6** Mitsunobu and Staudinger reaction of quinine (**237**) and arylated derivative **238**.

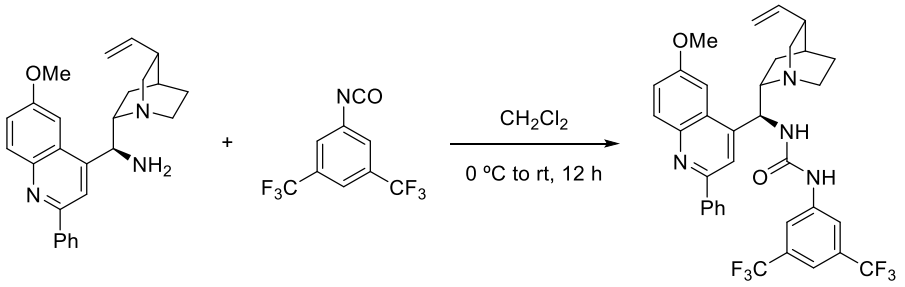
Sulfonamide-based catalysts **243** and **244** (previously synthesised by former member of the group Dr. Aldo Pesculli) were prepared in good yields by a coupling reaction between the corresponding sulfonylchloride derivative and **239** in $CH_2Cl_2$ (Scheme 2.7).




**239** **241** R = $^{i}$Pr; $R^1$ = H; **242** R = H; $R^1$ = $CF_3$ **243** R = $^{i}$Pr; $R^1$ = H 73%; **244** R = H; $R^1$ = $CF_3$ 71%

**Scheme 2.7** Synthesis of catalysts **243** and **244**.

Catalyst **221** was isolated in good yield from an addition reaction between quinine-derivative **240** and 3,5-*bis*(trifluoromethyl)phenyl isocyanate (**245**, Scheme 2.8).

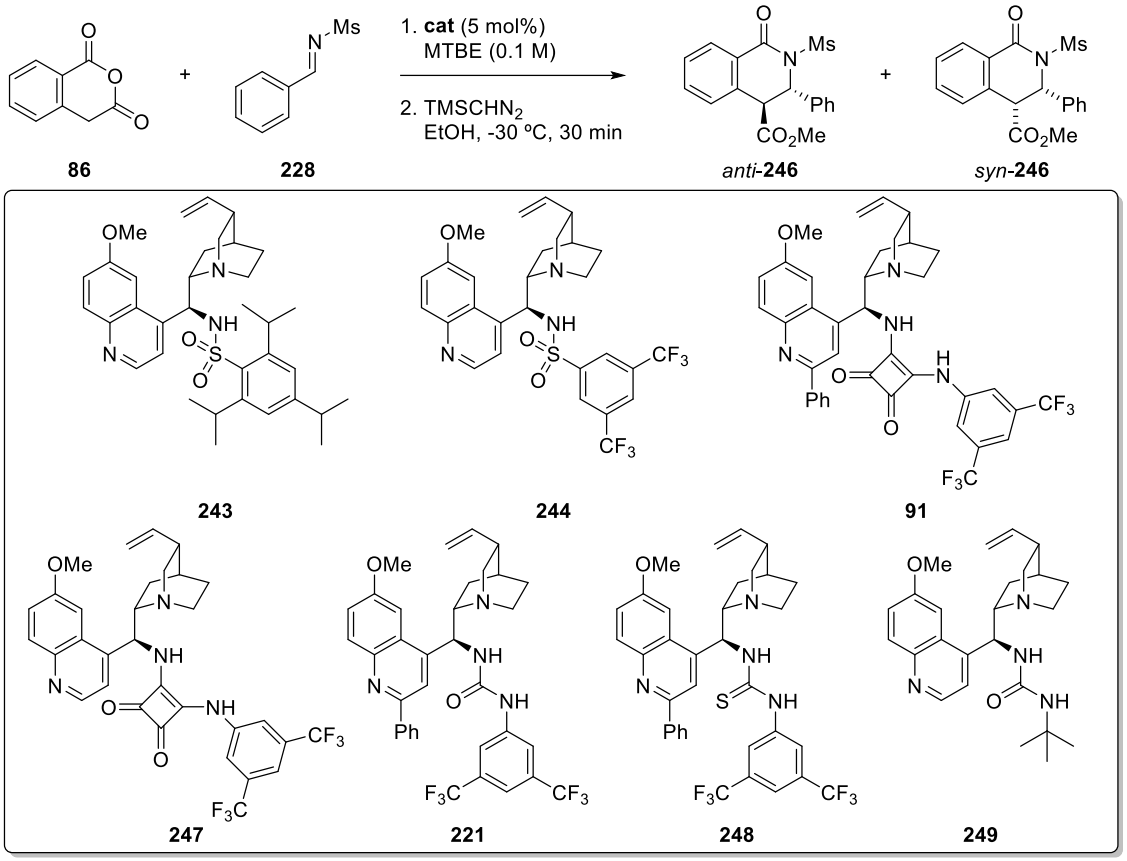



**240** **245** **221** 73%

**Scheme 2.8** Synthesis of catalyst **221**.

Once we found a robust protocol for the esterification of the carboxylic acids that afforded reproducible results, we began the search for an adequate catalyst for this process (Table 2.3).

**Table 2.3** Evaluation of the performance of different organocatalysts.



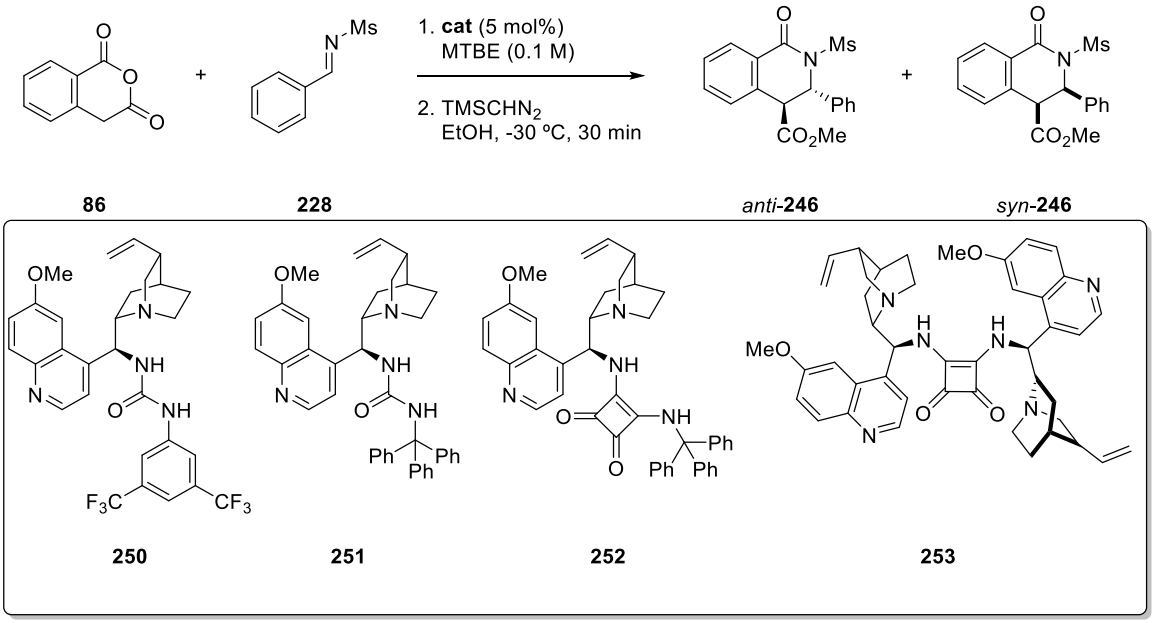

| Entry | Cat. | T (ºC) | t (h) | Conv.[a] (%) | *dr*[b] (*syn*:*anti*) | $ee_{syn}$[c] (%) | $ee_{anti}$[c] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **241** | rt | 24 | >98 | 38:62 | 13 | 47 |
| 2 | **244** | rt | 24 | >98 | 34:66 | 21 | 31 |
| 3 | **91** | rt | 5 | >98 | 26:74 | 0 | 31 |
| 4 | **247** | rt | 16 | >98 | 45:55 | 29 | 33 |
| 5 | **221** | rt | 16 | >98 | 23:77 | 12 | 58 |
| 6 | **248** | rt | 16 | >98 | 26:74 | 43 | 61 |
| 7 | **249** | rt | 16 | >98 | 31:69 | 15 | 46 |
| 8 | **221** | 40 | 5 | >98 | 23:77 | 6 | 53 |
| 9 | **221** | -30 | 48 | 95 | 36:64 | 27 | 70 |
| 10 | **221** | -50 | 72 | 90 | 36:64 | 18 | 51 |
| 11 | **248** | -30 | 66 | >98 | 37:63 | 42 | 65 |

[a]Determined by $^1$H-NMR spectroscopy using *p*-iodoanisole as internal standard. [b]Determined by $^1$H-NMR spectroscopy [c]Determined by CSP-HPLC.

We initiated the search for the optimum catalyst for the reaction with sulfonamide-substituted catalysts **243** and **244**, but the enantiomeric control of the reaction for the major diastereomer was quite low (entries 1 and 2). We decided to modify the hydrogen-bond donor from a sulfonamide to a squaramide, which presents a convergent hydrogen-bond donor to the substrate, with catalyst **91** (which had proven successful with aldehydes), however the enantiocontrol could not be improved (entry 3). Catalyst **91** contains C-2 substitution on the catalyst quinoline ring that increased the steric demand of the catalyst considerably, thus we decided to remove that substitution to increase the reaction pocket for our substrates with catalyst **247**. The enantiocontrol remained low, also the diastereoselectivity decreased (entry 4), which highlights the importance of the C-2 phenyl group of the catalyst on the diastereocontrol. Both catalysts had been synthesised previously by former members of the Connon group. Bearing in mind the importance of the C-2 phenyl group on the diastereocontrol of the reaction, we evaluated urea catalyst **221** and its thiourea analogue **248**: both promoted the reaction with similar moderate enantiocontrol (entries 5 and 6). We decided to evaluate urea-based **249**; unfortunately, it could not outperform **221** (entry 7). In order to elucidate the impact of the temperature on the enantio- and diastereoselectivity, the reaction was carried out at 40 ºC promoted by **221**. Although the enantiocontrol obtained did not differ greatly from the reaction at room temperature (entry 8). However, when the reaction was carried out at -30 ºC, the enantiocontrol of the reaction increased to 70% *ee* (entry 9). Thiourea analogue **248**, that at room temperature had the same efficiency as its urea analogue, failed to equal the enantiocontrol achieved by the urea-based **221** at -30 ºC (entry 10). Encouraged by finding that the enantiocontrol increased when lowering the temperature, we carried out the reaction at -50 ºC, unfortunately the enantiocontrol did not increase (entry 11).

In addition to these results, we had to take into consideration the results obtained by Sarah Cronin. Working together to find the best conditions, her results are summarised in Table 2.4.

**Table 2.4** Screening of catalysts reported by Sarah Cronin.




| Entry | Cat. | T (ºC) | t (h) | Conv.[a] (%) | *dr*[b] *syn*:*anti* | $ee_{syn}$[c] (%) | $ee_{anti}$[c] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **250** | rt | 16 | >98 | 23:77 | 16 | 53 |
| 2 | **251** | rt | 16 | >98 | 31:69 | 15 | 46 |
| 3 | **252** | rt | 24 | >98 | 31:69 | 59 | 15 |
| 4 | **253** | rt | 24 | >98 | 39:61 | 12 | 10 |

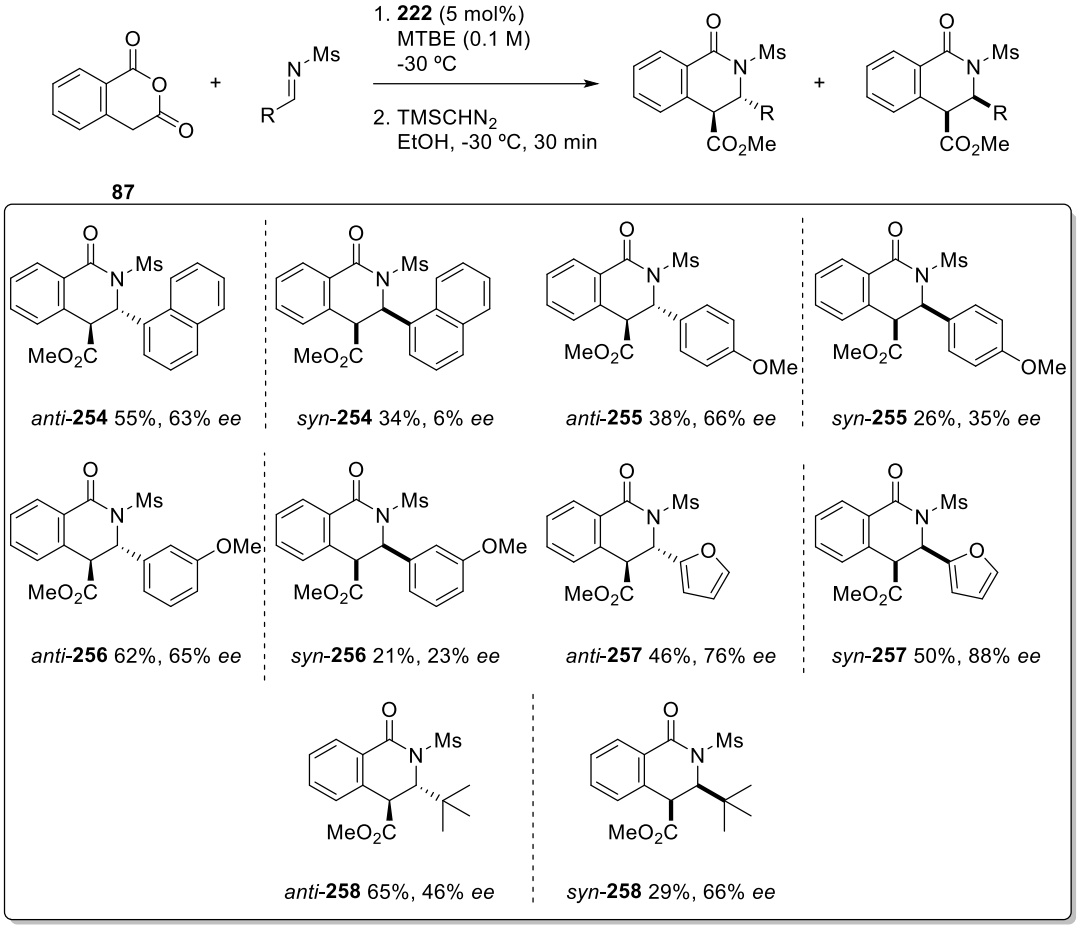
[a]Determined by $^1$H-NMR spectroscopy using *p*-iodoanisole as internal standard. [b]Determined by 1H-NMR spectroscopy. [c]Determined by CSP-HPLC.

From her results, we observed that the use of the urea catalyst bearing an electron-withdrawing group **250** yielded slightly improved enantiocontrol compared to the bulky **251** (entries 1 and 2) which confirmed the importance of the *bis*-(3,4-trifluoromethyl)phenyl ring in the hydrogen-donating unit, also found in the superior catalyst **221**. Two bulky squaramides **252** and **253** were evaluated unfortunately, the enantiocontrol achieved by those catalyst was quite disappointing (entries 3 and 4).

The results outlined in the last two tables, made apparent that the urea **221** was the catalyst that rendered the best control in terms of both diastereo- and enantiocontrol.

### 2.2.3 Expansion of the scope with respect to the electrophilic component: screening of imines

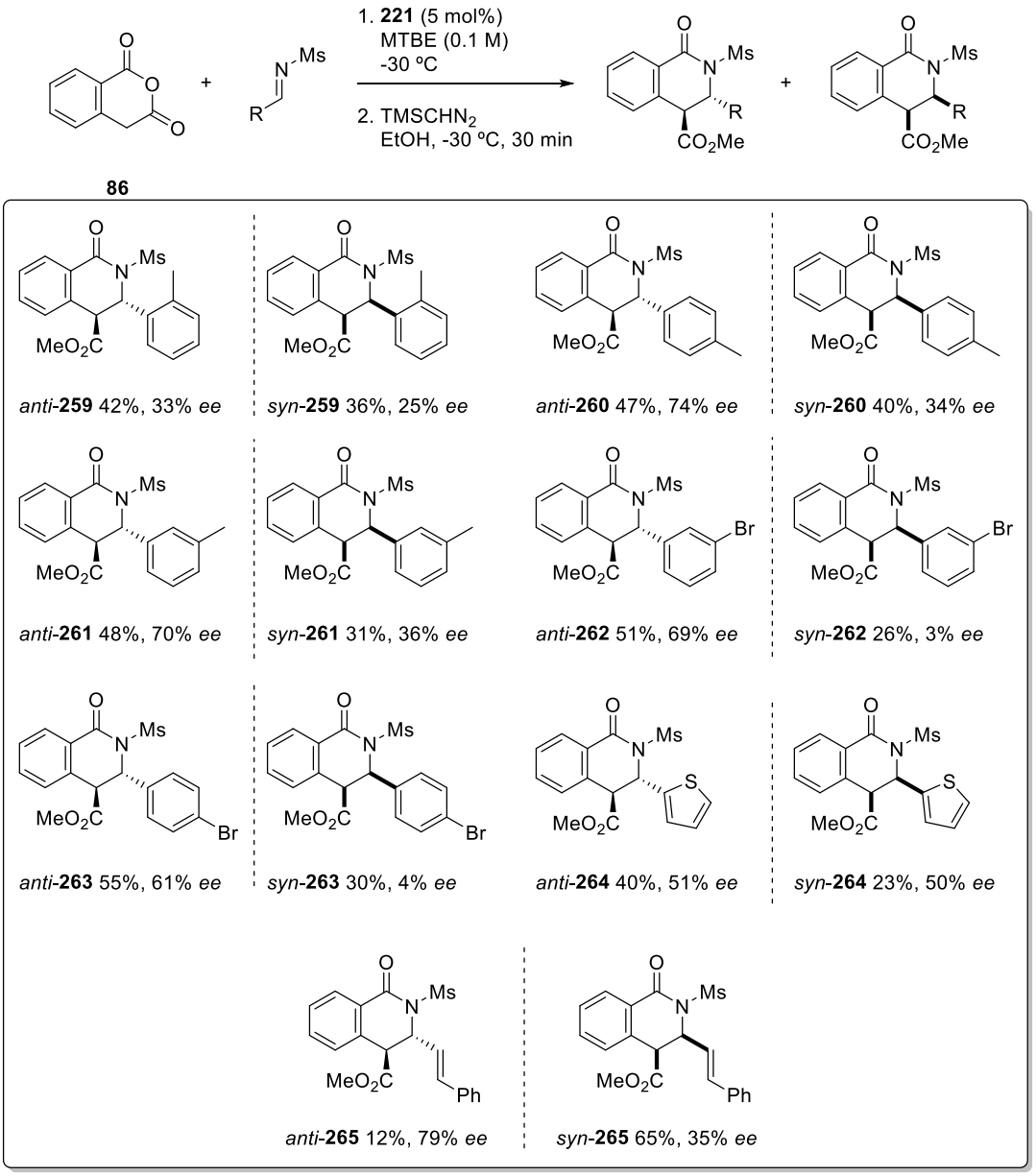
Once the optimal catalytic conditions had been ascertained (catalyst **222** in MTBE at -30 ºC), we decided to focus our efforts on optimising the reaction by modifications of the imine component of the reaction. We wished to examine the influence of the aldehyde-derived substituent on the imine on stereocontrol (Scheme 2.9).




**Scheme 2.9** Scope of the imine component

In almost all of the cases the *anti* diastereomer was the dominant diastereomer formed in the reaction, with the exception of *anti*-**257** and *syn*-**257** that were produced in a 1:1 ratio. Futhermore, bulky substituents or strong electron-donating groups did not have a significant impact on the enantiocontrol: *anti*-**254**, *anti*-**255** and *anti*-**256** were all formed within similar levels of enantiocontrol. The method developed could be applied to aliphatic systems (i.e. **258**), however, here the reaction favoured the formation of the *syn* diastereomer.

This part of the project was also done in collaboration with Sarah Cronin and she evaluated a range of weak electron-donating and electron-withdrawing substituents (Scheme 2.10).




**Scheme 2.10** Results provided by Sarah Cronin on the screening of the imine component.

An X-ray diffraction pattern study of *anti*-**263** was used to assign the absolute (*S*,*S*) configuration of the *anti*-diastereomers by analogy (Figure 2.1).

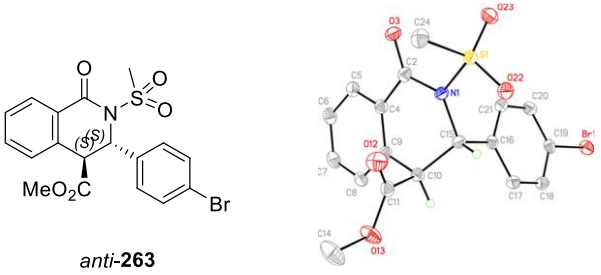
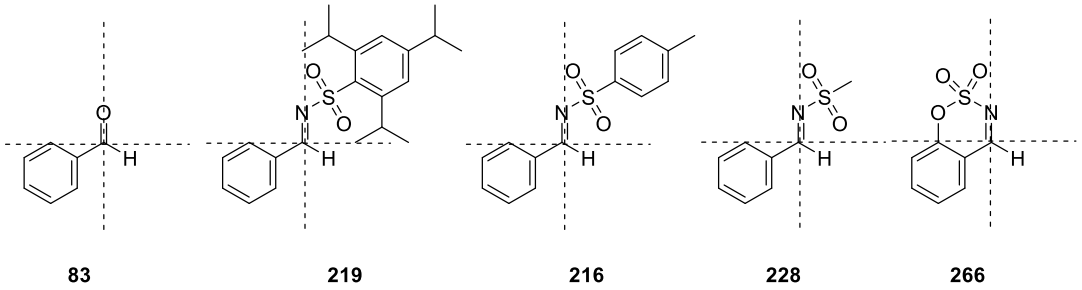



**Figure 2.1** Crystal structure of *anti*-**263**.

## 2.3 A new substrate: cycloaddition reaction employing a cyclic imine

Despite our best efforts outlined in Section 2.2, we realised that the enantiocontrol could not be improved any further. Therefore, we pursued another strategy.

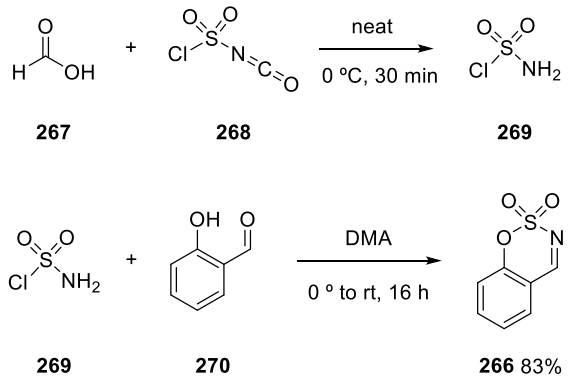
The cycloaddition reaction between anhydrides and aldehydes had been successful and we noted that aldehydes are completely unhindered in one quadrant of the molecule (Figure 2.2). Thus, our attention was brought back to the sulfonyl substituent. We observed a correlation between the enantiocontrol and the size of the sulfonyl substituent. Therefore, we tried to make our imine more 'aldehyde-like' while still supressing the basicity of the imine (**266**).



**83** **219** **216** **228** **266**

**Figure 2.2** Comparison of the bulkiness of the different imines with **83** using a quadrant to divide the space surrounding the molecule.

The synthesis of **266** started with the reaction between formic acid (**267**) and chlorosulfonyl isocyanate (**268**) to form chlorosulfonamide **269**, that, due to its reactivity,[142] was reacted immediately with salicylaldehyde (**270**) to furnish the desired imine **266** in good yield (Scheme 2.11).



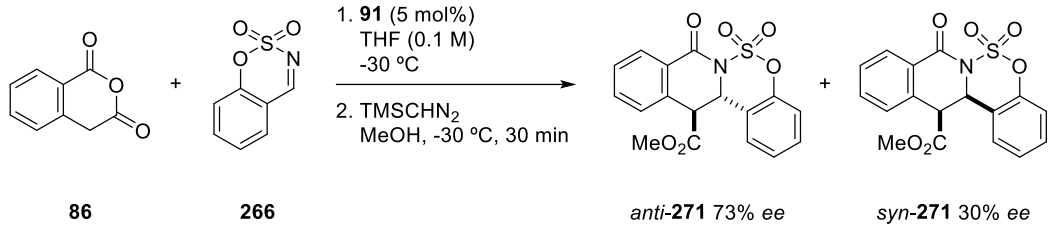

**267** **268** **269**

**269** **270** **266** 83%

**Scheme 2.11** Synthesis of cyclic imine **266**.

Imine **266** was reacted under similar reaction conditions as the acyclic imines. Thus, imine **266** was reacted with **86** in the presence of **91** to afford cycloadduct **271** as a mixture of

diastereomers (*anti*:*syn* 37:67 *dr*), with an observed enantiocontrol of 73% *ee* for *anti*-**271** and 30% *ee* for *syn*-**271** (Scheme 2.12). As was observed with the acyclic imines, the *anti* diastereomer was formed with greater enantiocontrol, however it was not the dominant diastereomer of the reaction.



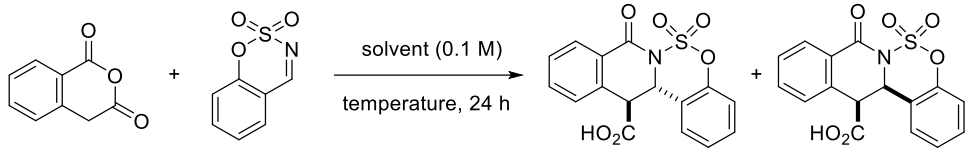

**86** **266** *anti*-**271** 73% *ee* *syn*-**271** 30% *ee*

**Scheme 2.12** Cycloaddition reaction between **266** and anhydride **86** catalysed by **91**.

Nevertheless, we detected that the reaction proceeded in the absence of catalyst, meaning that there was some uncatalysed reaction competing against the catalysed process. Despite the electron-withdrawing sulfonyl group on the imine **266**, it was more reactive than the acyclic analogues **219**, **216** and **228**. We postulated that this was likely related to the *cis* conformation of the imine and the attendant reduced steric hindrance.

Despite the presence of the uncatalysed reaction, promising levels of enantiocontrol were achieved, which confirmed our reasoning that an imine which behaves like an aldehyde should react under catalyst control. Encouraged by this finding, we set out to supress the uncatalysed reaction, initially by varying the solvent and the temperature of the reaction (Table 2.5).

**Table 2.5** Screening of different reaction conditions to eradicate the uncatalysed reaction.

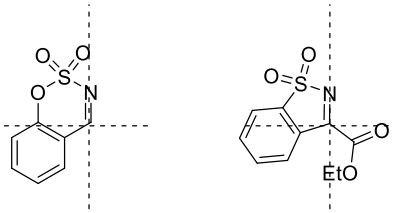



**87** **266** *anti*-**272** *syn*-**272**

| Entry | Solvent | Temperature (ºC) | Conversion (%)[a] |
|---|---|---|---|
| 1 | THF | -30 | 100 |
| 2 | THF | -50 | 100 |
| 3 | MTBE | -30 | 80 |
| 4 | MTBE | -50 | 53 |

[a]Determined by $^1$H-NMR spectroscopy using *p*-iodoanisole as internal standard.

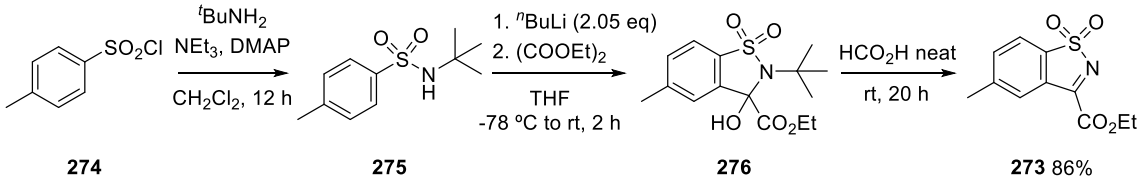
When the reaction was carried out in THF, the mixture of both diastereomers of **272** were formed quantitatively even at low temperatures (entries 1 and 2). However, the change of solvent to the less polar MTBE at -30 ºC slightly reduced the conversion of the reaction, likely due to the lack of solubility of **87** in that solvent (entry 3). Finally, when the reaction was performed at -50 ºC the conversion of the reaction was reduced to 53% after 24 hours (entry 4). However, 53% conversion still represented a too fast background process to be compatible with highly enantioselective catalysed reaction. Therefore we tried to find another imine with a different steric demand as **266**. We decided upon cyclic imine **273**[143] (Figure 2.3).




**266** **273**

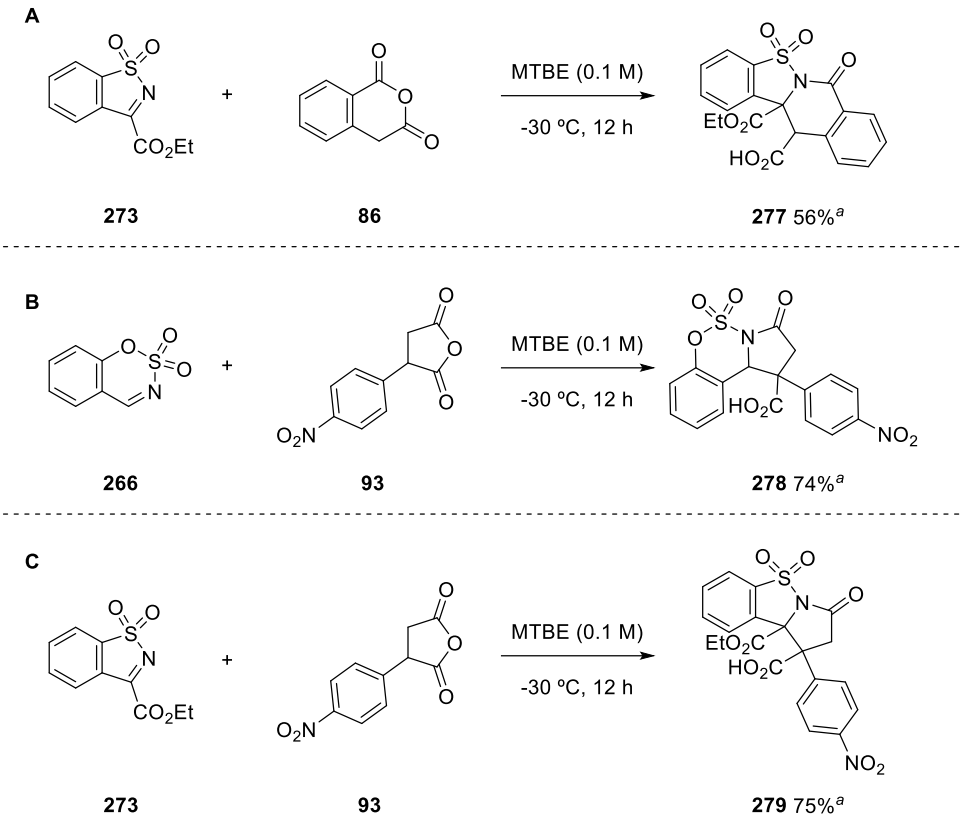
**Figure 2.3** Comparison of imines **266** and **273** in a quadrant to compare the steric bulk of both.

The synthesis of **273** started from tosylchloride (**274**), which underwent coupling with *tert*-butyl amine in the presence of $NEt_3$ and DMAP in $CH_2Cl_2$ to form sulfonamide **275**. Sulfonamide **275** was treated with two equivalents of $^n$BuLi and then quenched with diethyl oxalate to form hemiaminal **276**. Dehydration of **276** with formic acid led to **273** in good yield (Scheme 2.13).




**Scheme 2.13** Synthesis of cyclic imine **273**.

Unfortunately, imine **273** also reacted with **86** in MTBE at low temperature in the absence of catalyst (Scheme 2.14, A). As we were not able to eradicate the uncatalysed reaction by either lowering the temperature or employing a different imine, we decided to evaluate a different enolisable anhydride that we thought could undergo the cycloaddition reaction with imines more slowly. *p*-Nitrophenylsuccinic anhydride (**93**) proved too reactive and it underwent cycloaddition with imines **266** and **273** in the absence of catalyst (Scheme 2.14, B and C).



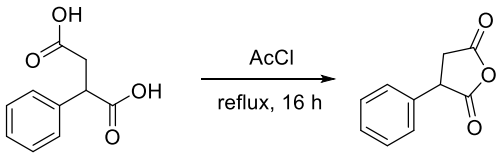

**273** **86** **277** 56%[a]

**266** **93** **278** 74%[a]

**273** **93** **279** 75%[a]

**Scheme 2.14** Different attempts to identify in which no uncatalysed reaction is observed. [a]Conversion determined by $^1$H-NMR spectroscopy using *p*-iodoanisole as internal standard.

Therefore, we investigated the use of a less reactive anhydride – phenylsuccinic anhydride (**96**). Anhydride **96** was synthesised by dehydration of phenyl succinic acid (**280**) in freshly distilled acetyl chloride, followed by purification by trituration with diethyl ether (Scheme 2.15).

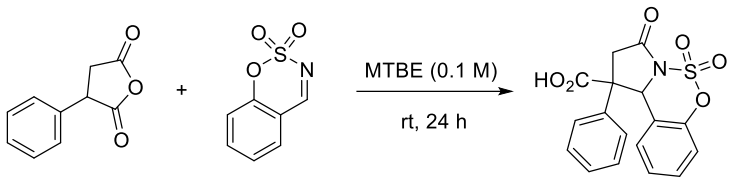



**280** **96** 93%

**Scheme 2.15** Synthesis of phenylsuccinic anhydride (**96**).

Firstly, we attempted to detect any undesired uncatalysed reaction between **96** and imine **266** in the absence of catalyst in MTBE at room temperature (Scheme 2.16). No reaction was observed, which convinced us that the catalytic reaction should be the only reaction taking

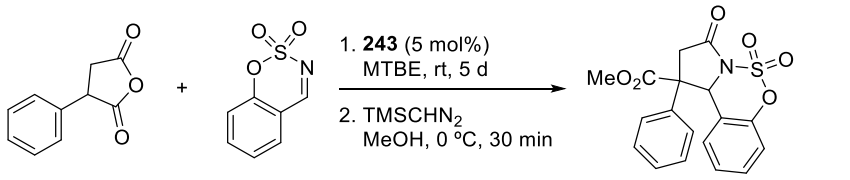
place if product were to be formed, thereby guaranteeing complete control by the catalyst over product formation.




**96** **266** **281** 0%

**Scheme 2.16** Reaction between anhydride **96** and imine **266** in the absence of catalyst.

After confirmation of the absence of background reaction, we initiated the screening of different catalysts available in the laboratory, however more problems arose, as anhydride **96** was less reactive than **86**, the catalytic reaction did not go to completion; this was quenched after five days, with 93% conversion (Scheme 2.17).

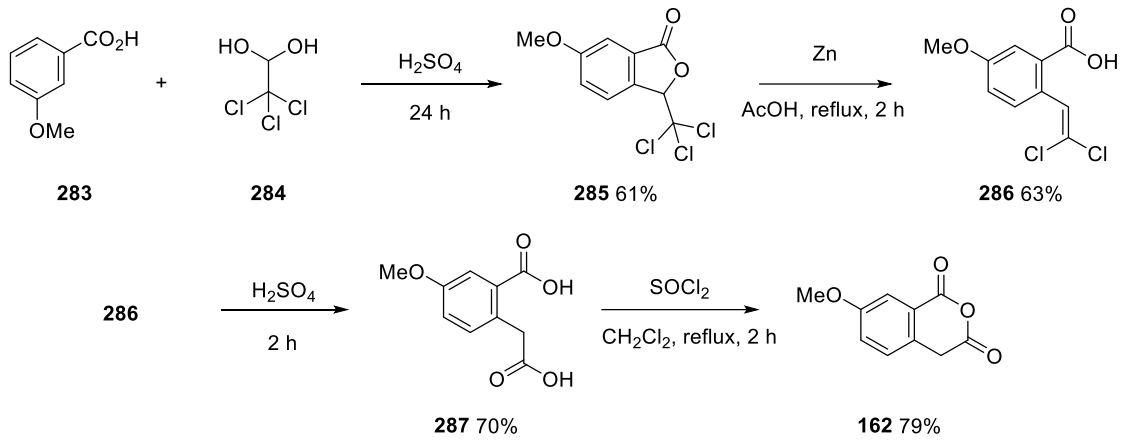



**96** **266** **282** 93% conv. 71:29 *dr*, 57% *ee*

**Scheme 2.17** Catalytic cycloaddition reaction between **96** with **266** catalysed by **243**.

The enantiocontrol achieved at room temperature was not good, and the low reactivity of the anhydride hampered the optimisation of the enantiocontrol by lowering the temperature – 51% conversion at 0 ºC after 15 days using 20 mol% of catalyst.

We knew that an ideal anhydride for our system should have a reactivity somewhere between phenylsuccinic anhydride and homophthalic anhydride. Therefore, anhydride **162** became our new candidate. 3-Methoxybenzoic acid (**283**) reacted with chloral hydrate (**284**) in conc. $H_2SO_4$ to afford **285** in moderate yield. **285** Was then reduced with zinc in acetic acid at reflux to afford styrene **286**, which reacted in sulfuric acid to furnish dicarboxylic acid **287**. Diacid **287** underwent a self-condensation reaction promoted by thionyl chloride in dichloromethane to afford anhydride **162** (Scheme 2.18).

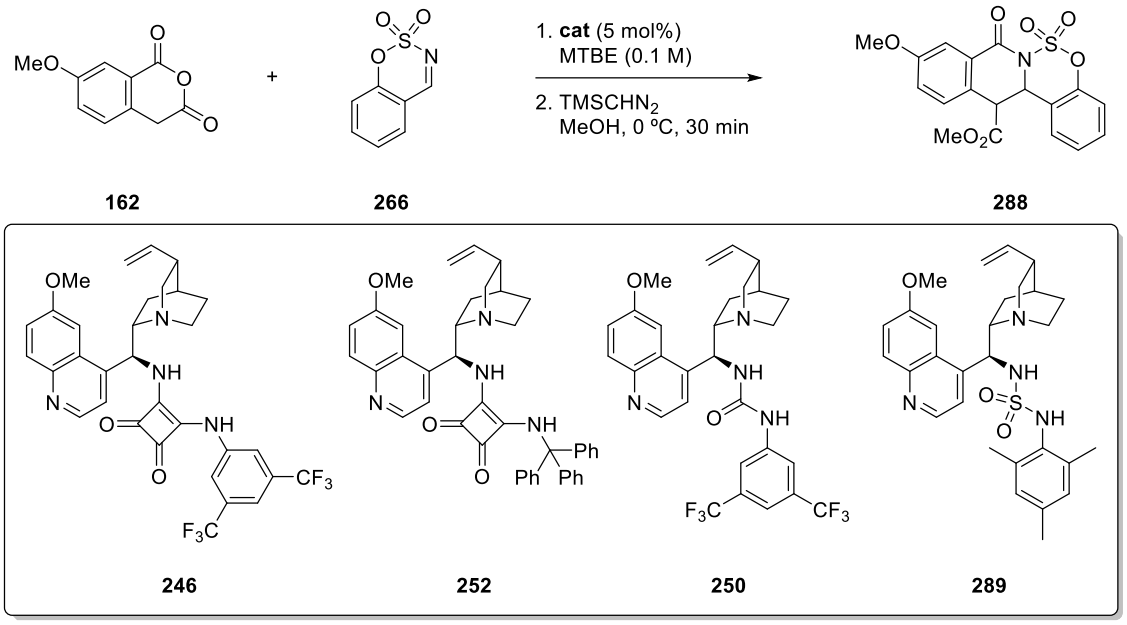



**Scheme 2.18** Synthesis of anhydride **162**.

### 2.3.1 Catalyst screen

Anhydride **162** proved out to be a good candidate, as it did not react with **266** in the absence of a catalyst, and the catalytic reaction proceeded at a convenient rate. Therefore, we started with the evaluation of different catalysts available in the laboratory (Table 2.6).

**Table 2.6** Screening of different catalysts available in the laboratory.



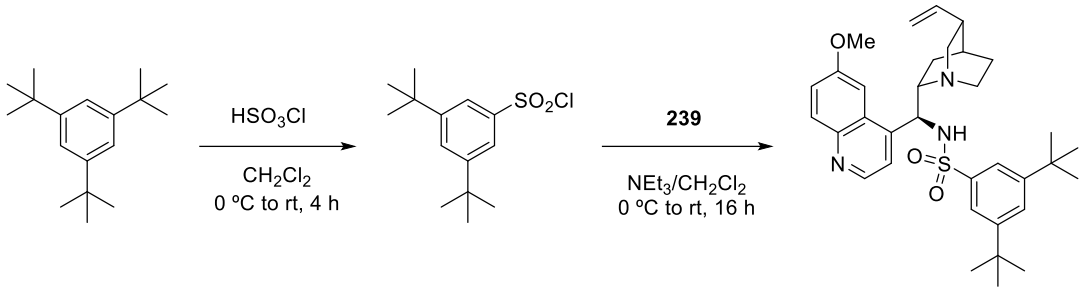

| Entry | **Cat.** | T (ºC) | T (h) | Conv.[a] (%) | *dr* *(anti/syn)*[b] | $ee_{anti}$[c] (%) | $ee_{syn}$[c] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **246** | rt | 4 | >99 | 53:47 | 20 | 35 |
| 2 | **252** | rt | 4 | >99 | 66:34 | 19 | 21 |
| 3 | **250** | rt | 4 | >99 | 43:57 | 8 | 30 |
| 4 | **289** | rt | 4 | >99 | 68:32 | 48 | 7 |

[a]Determined by $^1$H-NMR spectroscopy using *p*-iodoanisole as internal standard. [b]Determined by $^1$H-NMR spectroscopy. [c]Determined by CSP-HPLC.

We began our studies with the squaramide-based catalyst **246** and the bulkier analogue **252**; however, both catalysts promoted the formation of *anti*-**288** with low diastereocontrol and poor enantioselectivity (entries 1 and 2). Substitution of the catalyst's Lewis acidic moiety from squaramide to urea **250** led to the formation of *anti*-**288** in an almost racemic fashion (entry 3). Sulfamide **289**, a new type of catalyst developed by a former member of the Connon group (Dr. Romain Claveau) which possesses an acidic hydrogen-bond donor,[81] promoted the reaction with greater diastereocontrol and enantiocontrol that the other catalysts (entry 4). It seems apparent that more acidic hydrogen-bond donating catalysts are more advantageous from a product enantiomeric excess standpoint, with the sulfamide **289** clearly superior to urea and squaramide variants in this reaction.

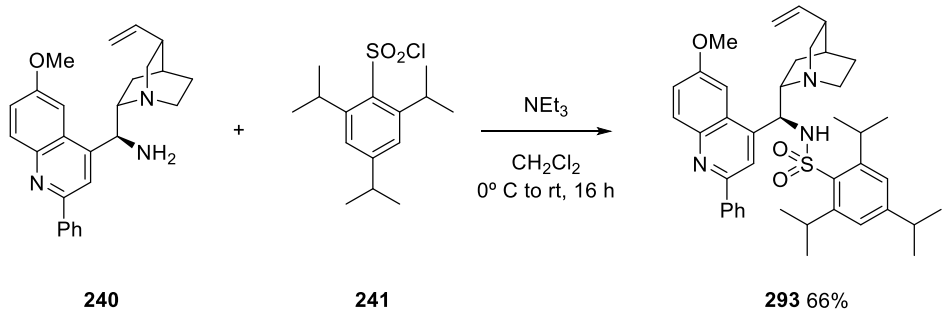
The degree of enantiocontrol was still inferior to the enantioselectivity obtained with the acyclic imines (see Table 2.3), therefore different sulfonamide-based catalysts were considered. The hydrogen-bond donor in the sulfonamide is more acidic than the squaramide (p$K_a$ =11.9[144]) moiety but less acidic than the sulfamide moiety.

The treatment of 1,3,5-tri-*tert*-butylbenzene (**290**) with chlorosulfonic acid in $CH_2Cl_2$ afforded sulfonyl chloride **291** in good yield. Subsequent coupling with **239** afforded catalyst **292** in good yield (Scheme 2.19).




**Scheme 2.19** Synthesis of catalyst **292**.

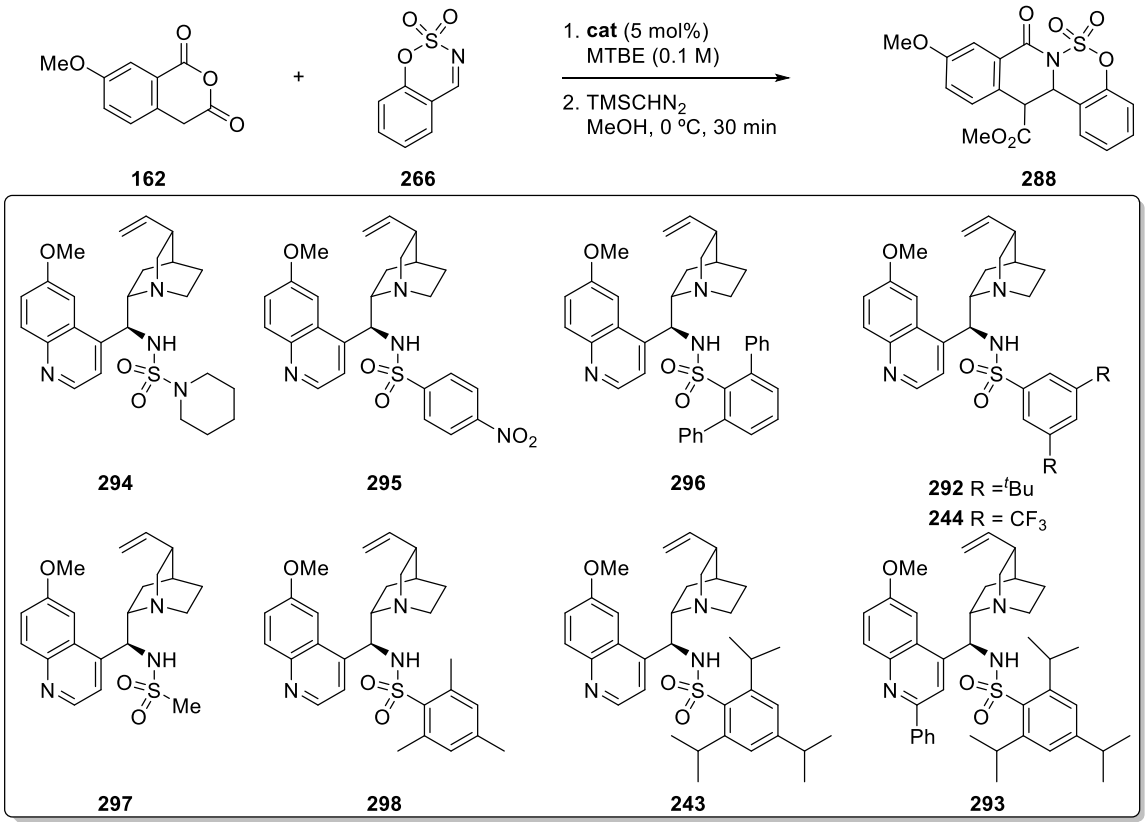
Catalyst **293** was synthesised through reaction of **240** with **241** in dichloromethane in the presence of triethylamine (Scheme 2.).




**Scheme 2.20** Synthesis of catalyst **293**.

Since many different sulfonamide-based chiral bifunctional catalysts of variable steric and electronic characteristics were available in the laboratory, it was decided to evaluate their performance in this reaction (Table 2.7).

**Table 2.7** Screening of different sulfonamide-based catalysts.



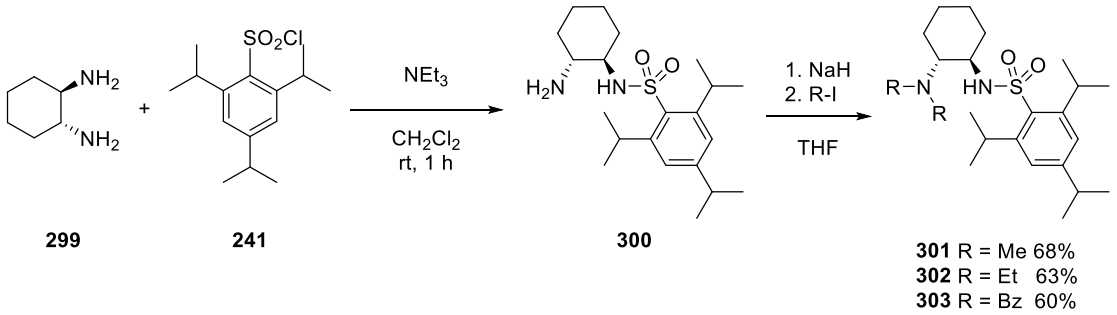

| Entry | **Cat.** | T (ºC) | t (h) | Conv.[a] (%) | *dr* *(anti/syn)*[b] | $ee_{anti}$[c] (%) | $ee_{syn}$[c] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **294** | rt | 6 | >99 | 61:39 | 40 | 10 |
| 2 | **295** | rt | 6 | >99 | 60:40 | 40 | 10 |
| 3 | **296** | rt | 6 | >99 | 61:39 | 45 | 53 |
| 4 | **292** | rt | 6 | >99 | 52:48 | 60 | 37 |
| 5 | **244** | rt | 6 | >99 | 74:26 | 65 | 34 |
| 6 | **297** | rt | 6 | >99 | 68:32 | 19 | 7 |
| 7 | **298** | rt | 6 | >99 | 64:36 | 55 | 13 |
| 8 | **243** | rt | 6 | >99 | 65:35 | 61 | 6 |
| 9 | **293** | rt | 6 | >99 | 18:82 | 17 | 33 |
| 10 | **244** | -30 | 96 | >99 | 80:20 | 70 | 0 |
| 11 | **243** | -30 | 96 | >99 | 75:25 | 82 | 14 |

[a]Determined by $^1$H-NMR spectroscopy using *p*-iodoanisole as internal standard. [b]Determined by $^1$H-NMR spectroscopy. [c]Determined by CSP-HPLC.

We initiated the screening of the sulfamide-based catalyst **294** and sulfonamide-based catalyst **295** (both catalysts were provided by Dr. Astrid Botte) that promoted the formation of **288** with similar low levels of enantiocontrol (entries 1 and 2). We decided to examine the effect of increasing the size of the substituent on the sulfonamide through the use of catalyst **296** (provided by Dr. Romain Claveau) that promoted the reaction with better control than the previous ones (entry 3). We further sought to analyse the effect of bulk on the sulfonamide by changing the position of the bulky substituent. Thus, we synthesised catalyst **292** and we observed that **292** induced the formation of *anti*-**288** with moderate enantioselectivity, albeit with decreased diastereocontrol (entry 4). Encouraged by that result, we decided to retain the same substitution pattern and probe the effect of electron-withdrawing substituents. Therefore, we employed catalyst **244**, which promoted the reaction with a moderate diastereo- and enantiocontrol (entry 5). Similar levels of enantiocontrol were obtained with bulky and electron-withdrawing substituents, so we decided to evaluate the smallest sulfonamide substituent possible by utilising catalyst **297**, which promoted the reaction with poor enantioselectivity (entry 6). Catalyst **298** promoted the reaction with moderate enantiocontrol (entry 7) and the bulkier **243** improved enantiocontrol marginally (entry 8). The installation of a phenyl substituent at the C-2 position on the catalyst quinoline ring to make a more sterically demanding analogue of **243** furnished **293**. Unfortunately, the enantiocontrol of the reaction promoted by **293** reduced dramatically, and reversed the sense of diastereocontrol (entry 9). The impact of the reaction temperature on enantiocontrol was analysed when catalysts **243** and **244** promoted the formation of **288**. When the reaction was conducted at -30 ºC, both catalysts improved the diastereocontrol and the enantiocontrol (entry 10) and in the case of **243** the reaction achieved good levels of enantiocontrol (82% *ee*, entry 11).

That was the best result we had hitherto achieved; however, we were not satisfied, as we were optimistic of improving further the enantiocontrol. Thus, we utilised variants of Takemoto-type catalysts' replacing the thiourea moiety for a sulfonamide. From the results summarised in Tables 2.5 and 2.6, we concluded that the sulfonamide moiety was the most promising hydrogen-bond donor for the reaction, especially the 2,4,6-triisopropylphenylsulfonyl derivatives. Therefore, we decided to retain that moiety and modify the bulkiness around the nitrogenous base, which would allow us to better vary the steric requirement of the catalyst.

The version of the Takemoto's bifunctional catalyst based on sulfonamide **301**, **302** and **303** were synthesised in a two-step process starting from (*R*,*R*)-1,2-diaminocyclohexane (**299**) and **241**. After work up, the crude **300** was dissolved, without further purification, in THF and treated with NaH and the corresponding alkylhalide to furnish catalysts **301**, **302** and **303** (Scheme 2.21).

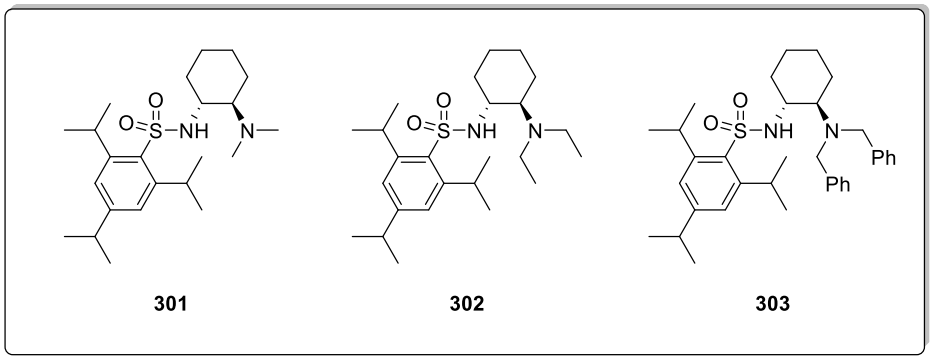



**Scheme 2.21** Synthesis of catalysts **301**, **302** and **303**.

The results of the screening of these new sulfonamide-based catalysts are outlined in Table 2.8.

**Table 2.8** Screening of *N*-sulfonamide-1,2-cyclohexanediamine-based catalysts.


**162** **266** **288**



**301** **302** **303**

| Entry | **Cat.** | T (°C) | t (h) | Conv.[a] (%) | *dr*[a] | *ee*$_{anti}$[b] (%) | *ee*$_{syn}$[b] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **301** | rt | 8 | >99 | 65:35 | 50 | 0 |
| 2 | **302** | -30 | 96 | 0 | - | - | - |
| 3 | **303** | rt | 48 | 0 | - | - | - |

[a]Determined by $^1$H-NMR spectroscopy using *p*-iodoanisole as internal standard. [b]Determined by $^1$H-NMR spectroscopy. [c]Determined by CSP-HPLC.

Starting from the smallest substituent possible (methyl), catalyst **301** induced the formation of *anti*-**288** with moderate enantiocontrol (entry 1). Although catalyst **301** could not outperform the enantiocontrol obtained using catalyst **243**, it was yet a promising result as we considered those catalysts would possess greater versatility from a steric modification standpoint. Unfortunately, when we employed bulkier catalysts **302** and **303** to promote the formation of **288**, the reaction did not proceed; most likely due to the hindrance around the nitrogen atom, thereby either blocking the deprotonation of the anhydride or preventing a pre-transition assembly conducive to enantioselective catalysis (entries 2 and 3).

### 2.3.2 Design of a new sulfonamide-based catalyst

The synthesis of a new catalyst was required if we wanted to optimise the reaction and afford excellent levels of enantiocontrol. We observed that when the size of the substituent on the sulfonamide aromatic ring was decreased ($^i$Pr in catalyst **243** to Me in catalyst **298**) the enantiocontrol diminished: i.e. **243** promoted the formation of *anti*-**288** with 61% *ee* and

catalyst **298** with 55% *ee*. That effect was more pronounced when the whole aromatic ring was substituted for a methyl group – catalyst **297** induced the formation of *anti*-**288** with 19% *ee*. Therefore we hypothesised that if we could synthesise a catalyst bulkier than **243**, the enantiocontrol could potentially be improved to *ca.* 90% *ee* (Figure 2.4).

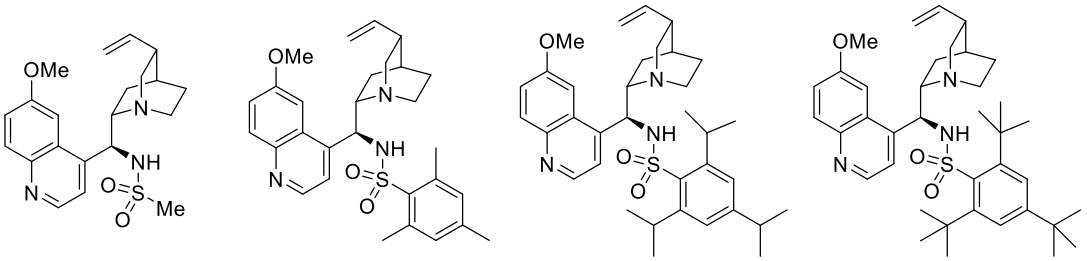
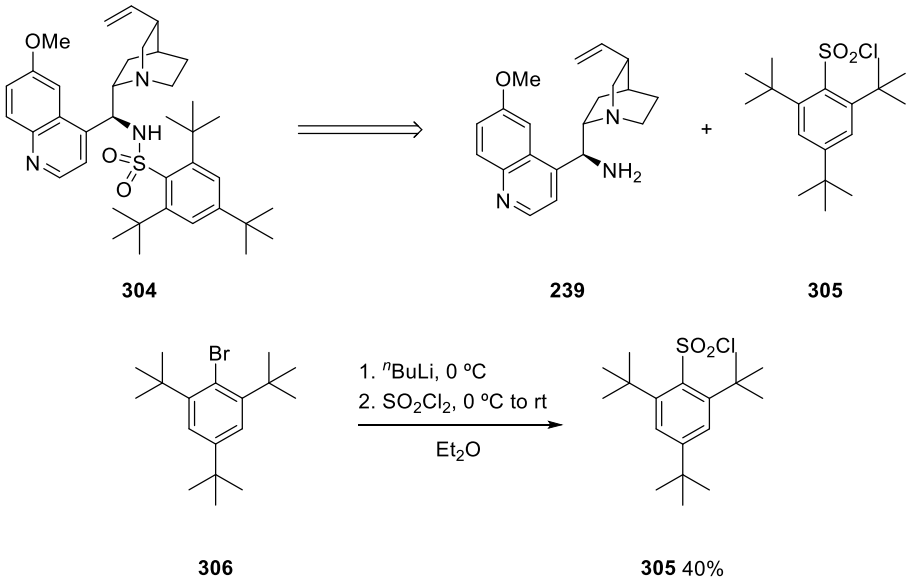



**Figure 2.4** Correlation between the size of the sulfonyl substituent and the enantiocontrol.

We proposed to synthesise catalyst **304** by the reaction between **239** and sulfonyl chloride **305**. The sulfonyl chloride **305** was synthesised through lithiation of **306** and subsequent treatment with sulfuryl chloride in very low yield (Scheme 2.22).



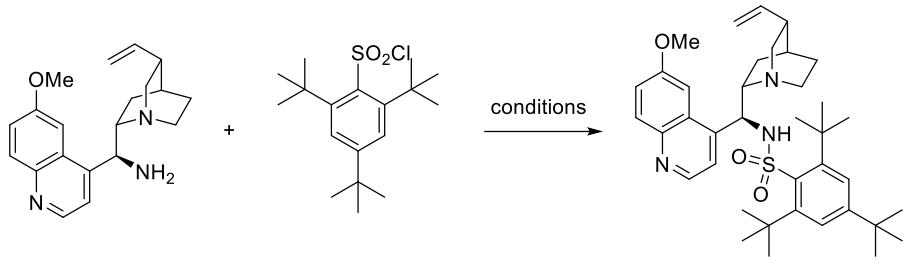

**Scheme 2.22** Retrosynthesis of **304** and synthesis of **305**.

Firstly, we considered that the reason behind the low yield of the reaction was the lithiation step, so we performed the reaction in different solvents (THF, MTBE and $^{i}Pr_2O$) and different temperatures to carry out the lithiation (-78 ºC, -15 ºC and 0 ºC). We realised that the problem was likely during the addition of $SO_2Cl_2$ to the lithium salt, as the $^1$H-NMR

spectra of the crude of the lithiation reaction showed full conversion of the starting material. $SO_2Cl_2$ Was too big to fit properly in the small pocket left by the *tert*-butyl groups.

Despite the low yield afforded on the first step, the next reaction was the coupling of **305** to **239** (Table 2.9). The standard conditions that were successful in the synthesis of the other sulfonamide-based catalysts (**243**, **244** and **293**) failed to furnish any product regardless of the concentration of the reaction (entries 1, 2 and 3). Identical results were obtained when the reaction was performed in THF (entry 4). In order to obtain more insight into the reaction, we performed the coupling in DMSO-$d_6$ using DABCO as base at 70 ºC. Unfortunately, after 5 days no conversion was observed in the $^1$H-NMR spectrum of the crude reaction mixture (entry 5). We used the same set of conditions employed by Dr. Romain Claveau to synthesise catalyst **296** – with considerable congestion in the two *ortho*-positions to the sulfonyl chloride group; however, no conversion was observed after 24 hours (entry 6). Finally, concerned that **239** was not nucleophilic enough to attack the sulfonyl chloride **305**, we decided to deprotonate **239** with $^n$BuLi and add it *via* cannula to a solution of **305** in THF (entry 7). We also attempted on inverted order of addition with **305** being added *via* cannula to the deprotonated **239**. In both cases we did not observe any change in the conversion. When the addition of $^n$BuLi was completed, a change in the colour of the solution was observed, which may indicate the formation of the anion, meaning that the problem was likely related on the addition to the sulfonyl chloride.

**Table 2.9** Reaction conditions for the coupling between **239** and **304**.




**239** **305** **304**

| Entry | Conditions | Conversion (%)[a] |
|---|---|---|
| 1 | $CH_2Cl_2$ (0.1 M) / $NEt_3$, rt | 0 |
| 2 | $CH_2Cl_2$ (0.5 M) / $NEt_3$, rt | 0 |
| 3 | $CH_2Cl_2$ (1.0 M) / $NEt_3$, rt | 0 |
| 4 | THF (1.0 M) / $NEt_3$, rt | 0 |
| 5 | DMSO (1.0 M) / DABCO 70 ºC | 0 |
| 6 | NaOH (2 M, 1 eq.) / $CH_2Cl_2$ 0 ºC to rt | 0 |
| 7 | THF (1.0 M) / $^n$BuLi, -78 ºC | 0 |

[a]Determined by $^1$H-NMR spectroscopy.

In order to prove that **305** could undergo addition of nucleophiles we reacted it with pyrrolidine. After 7 days 70% conversion was observed; however, this is a quite low reaction rate for a good nucleophile such as pyrrolidine.[145] Therefore, we were in a situation in which both nucleophile and electrophile were too bulky to react with each other.

At the moment we reached that conclusion, Seidel *et al.* published their work on the cycloaddition reaction between homophthalic anhydride and imines through a different approach.[93] We were trying to dampen the basic character of the imine and to use a bifunctional catalyst to activate both anhydride and imine, whereas Seidel just used his catalyst to interact with the transition state described by Shaw and placing them in the adequate chiral environment (see Section 1.3.2.4.3).

## 2.4 Conclusions

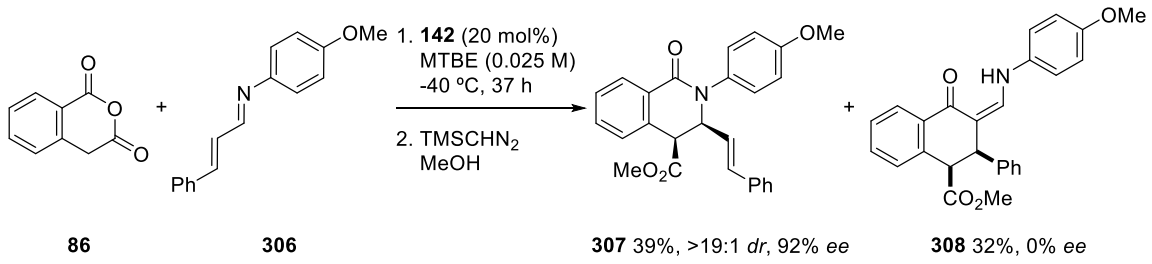
We have reported that through the use of *N*-sulphonamido substituents, the proclivity of *N*-alkyl and *N*-aryl imines to undergo cycloaddition with homophthalic anhydride can be supressed – rendering the reaction amenable to asymmetric catalysis.

Catalyst **221** was found as the most suitable bifunctional organocatalyst for the process, promoting the formation of different disubstituted dihydroisoquinolones with excellent overall yields, poor to moderate diastereoselectivity and levels of enantiocontrol in up to 79% *ee*.

The strategy of making an 'aldehyde like' imine proved to be successful as the enantiocontrol of the promoted reaction was increased up to 82% *ee* for the dominant diastereomer with a 4:1 diastereomeric ratio (the highest enantiocontrol at that moment for that process).

## 3 Asymmetric catalytic Tamura cycloaddition reaction between enolisable anhydrides and α,β-unsaturated imines.

As outlined previously, the reactivity of α,β-unsaturated imines with enolisable anhydrides is widely varied. They can undergo Castagnoli reaction, Tamura cycloaddition, Perkin condensation and 1,4-cycloadditions. Depending on either the conditions of the reaction or the substrates, the ratio of the products can be manipulated. Georgieva *et al*. reported the change in behaviour of an α,β-unsaturated imine when the nature of the group on the imine was modified.[136] When Seidel *et al.*[93] reported the cycloaddition reaction between α,β-unsaturated imine **306** and **86** catalysed by **142**, the reaction was not chemoselective, since the group on the nitrogen atom was of insufficient bulk to prevent the formation of the Tamura-type product. They reported the formation of the Castagnoli product **307** (with low yield but excellent diastereo- and enantiocontrol) and the Tamura cycloaddition product **308** with low yield and in a racemic fashion (Scheme 3.1).

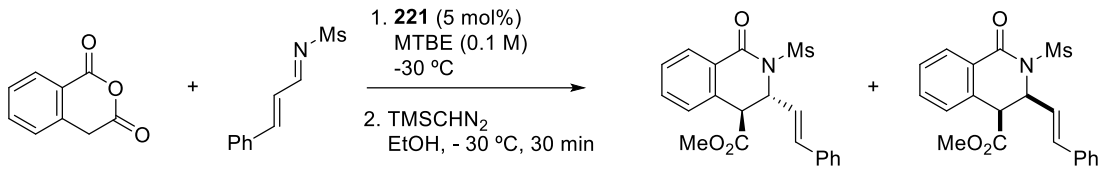



**86** **306** **307** 39%, >19:1 *dr*, 92% *ee* **308** 32%, 0% *ee*

**Scheme 3.1** Cycloaddition reaction between α,β-unsaturated imine **308** and **86** reported by Seidel

Seidel controlled the number of products formed in the reaction from four possibilities to two under the aforementioned reaction conditions.

In the cycloaddition reaction of acyclic imines with **86**, we reported how imine **309** underwent a cycloaddition reaction with **86** to afford the exclusive formation of the Castagnoli-type product **266**. This chemoselectivity is ascribed to the effect of the mesyl group on the imine (Scheme 3.2 and Section 2.2.3).




**Scheme 3.2** Cycloaddition reaction between α,β-unsaturated imine **309** and **86** reported by our group.

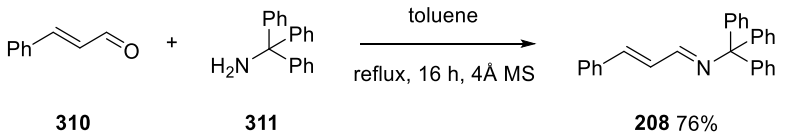
In addition, Georgieva *et al.* reported that a bulky imine substituent is more conducive towards the formation of the Tamura-type product (see Scheme 1.64). Nevertheless, the reaction requires high temperatures and suffers from poor yields and chemoselectivity issues due to the concomitant formation of the Perkin-type condensation product.

The product of the Tamura reaction of α,β-unsaturated imines with enolisable anhydrides is a tetralone containing an enaminone functionality;[146] compounds of vast utility in organic synthesis[147] and important building blocks in the synthesis of natural products.[148] Furthermore, their hydrolysis furnishes carbonyl compounds, which cannot be formed from Tamura cycloadditions between enols and enolisable anhydrides as in these structures reaction occurs exclusively at the carbonyl group.[78]

### 3.1 Preliminary results

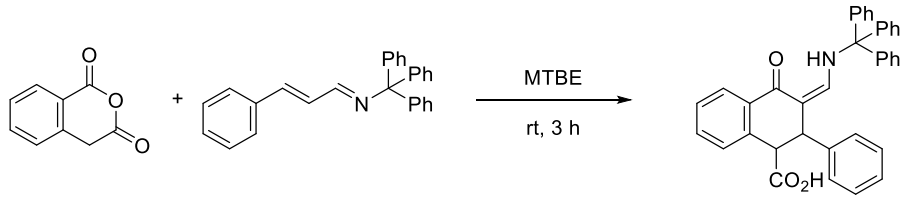
Inspired by Seidel's findings, we applied the same model to the Tamura reaction between α,β-unsaturated imines of augmented steric bulk and enolisable anhydrides. By using a chiral catalyst we could potentially lower the barrier of the reaction (which usually requires high temperatures) while placing the interacting reagents in the requisite chiral environment. If successful, Tamura reactions of broader synthetic scope could be accomplished *via* asymmetric catalysis for the first time.

We began with the synthesis of imine **208** *via* the condensation reaction between cinnamaldehyde (**310**) and tritylamine (**311**) in toluene (Scheme 3.3).




**Scheme 3.3** Condensation reaction to afford imine **208**.

Our initial hypothesis was that the Perkin-type condensation product formed due to the high reaction temperature. We therefore, studied the reaction between anhydride **86** and imine **208** at room temperature to evaluate the ratio of product formation. To our delight we found exclusive formation of the Tamura-type product after 3 hours, in MTBE at room temperature with 56% conversion (Scheme 3.4). However, when the reaction had reached full conversion, formation of the Perkin-type condensation product **202** was detected.



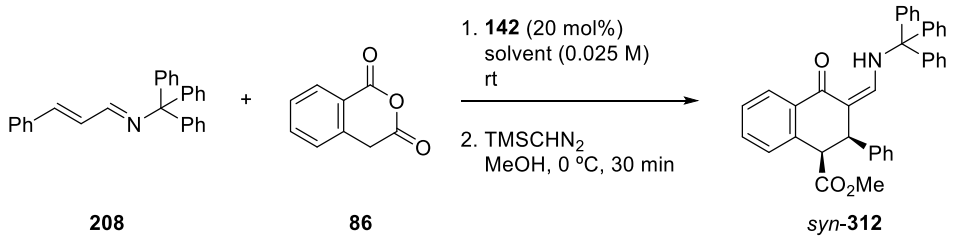

**86** **208** **209** 56%, 1:1 *dr*

**Scheme 3.4** Tamura cycloaddition reaction between **86** and **208** at room temperature.

### 3.2 Screening of the catalytic conditions for the reaction

After finding that the substrates could undergo a Tamura reaction at ambient temperature, an enantiocontrolled variant was our next objective. Our initial efforts in designing an enantiocontrolled variation of the Tamura reaction cuntered upon finding an appropriate solvent (Table 3.1).

**Table 3.1** Screening of solvents.




**208** **86** *syn*-**312**

| Entry | Solvent | t (h) | Conv. (%)[a] | *dr*[b] (*syn*/*anti*) | $ee_{syn}$ (%)[c] |
|---|---|---|---|---|---|
| 1 | MTBE | 2 | >98 | 75:25 | 32 |
| 2 | MeCN | 2 | >98 | 60:40 | 3 |
| 3 | THF | 2 | >98 | 46:54 | 17 |
| 4 | $CH_2Cl_2$ | 2 | >98 | 67:33 | 32 |
| 5 | $Et_2O$ | 2 | >98 | 80:20 | 37 |
| 6 | PhMe | 2 | >98 | 80:20 | 50 |
| 7 | $C_6H_5Cl$ | 2 | >98 | 79:21 | 49 |

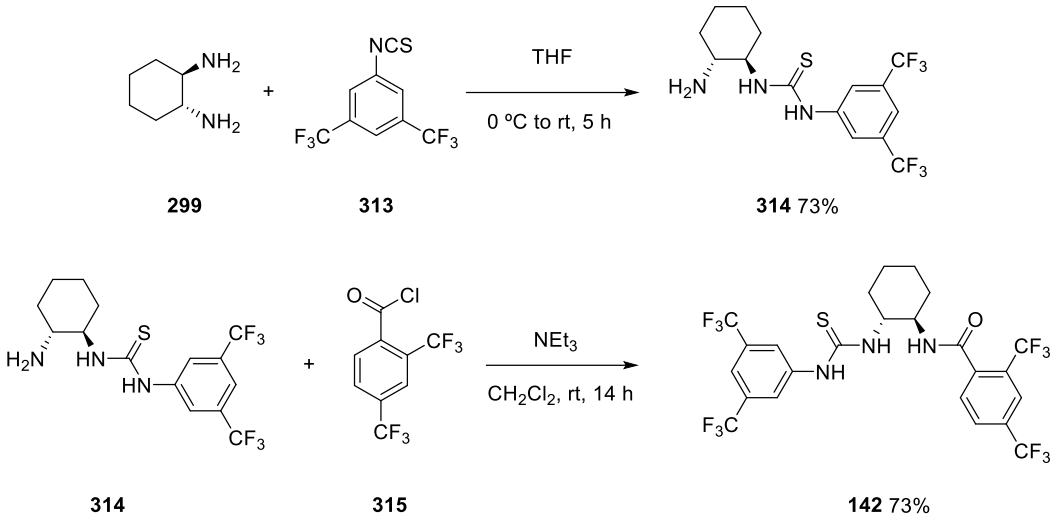
[a]Determined by $^1$H-NMR spectroscopy using *p*-iodoanisole as an internal standard. [b]Determined by $^1$H-NMR spectroscopy. [c]Determined by CSP-HPLC.

We began our studies with the same reaction conditions utilised by Seidel to promote the formation of **141** with 88% *ee*.[93] These conditions resulted in the formation of **312** with low diastereo- and enantiocontrol (entry 1, 32% *ee*). The use of polar solvents did not improve the enantioselectivity; as the reaction occured in an almost racemic fashion (entries 2 and 3). The diminishing enantiocontrol observed with polar solvents indicated that the enantioselectivity could potentially be influenced with more non-polar solvents. Hence, we carried out the reaction in dichloromethane and diethyl ether; however, the results were similar to those observed when the reaction was performed in MTBE (entries 4 and 5). Finally, the use of less polar aromatic solvents facilitated better enantiocontrol, although the results were still far from being synthetically useful (entries 6 and 7).

### 3.2.1 Catalyst design and evaluation

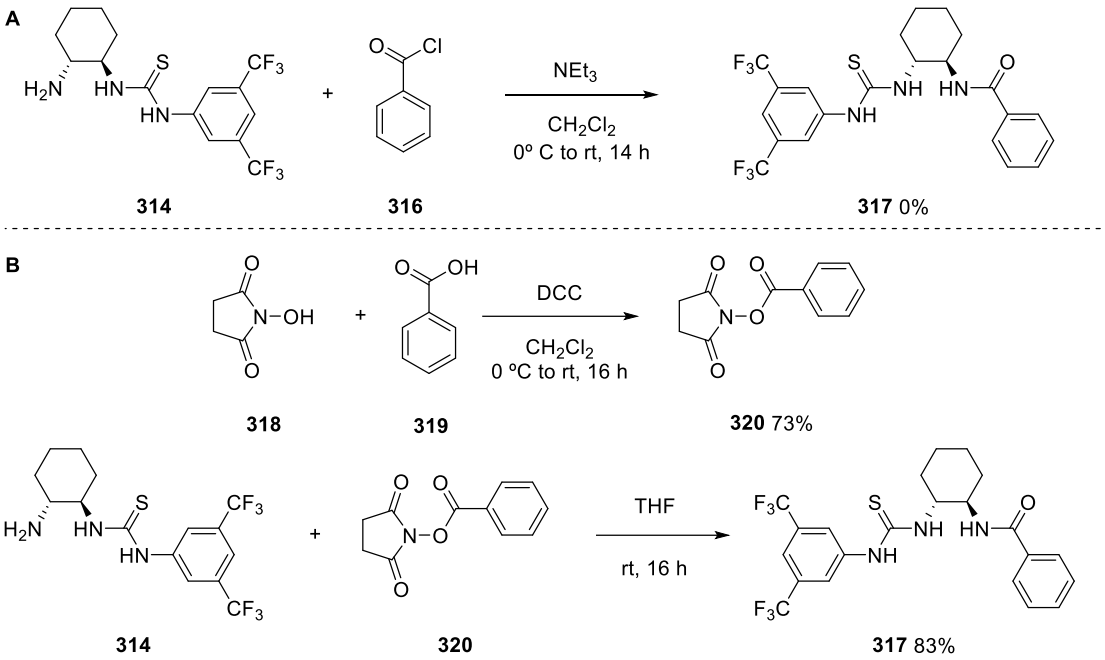
Catalyst **142**, employed by Seidel with excellent enantiocontrol in the cycloaddition between homophthalic anhydride (**86**) and imines,[93] was synthesised in a two-step process. (*R*,*R*)-1,2-Diaminocyclohexane (**299**) was treated with 3,5-*bis*(trifluoromethyl)phenyl isothiocyanate

(**313**) in THF to form **314** in good yield. The mono-thiourea derived **314** was treated with acyl chloride **315** in $CH_2Cl_2$ to afford catalyst **143** in good yield (Scheme 3.5).



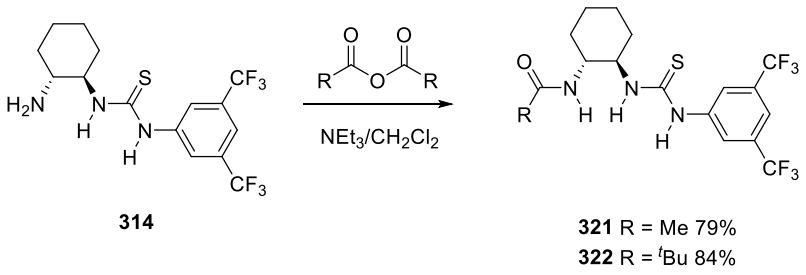

**Scheme 3.5** Synthesis of catalyst **142**.

The same strategy could not be applied to synthesise catalyst **317** as the direct coupling between **314** and benzoyl chloride (**316**) failed to furnish catalyst **317** (Scheme 3.7, A). We had to find another source of the benzoyl group. Thus, we synthesised **320** from *N*-hydroxysuccinimide (**318**) and benzoic acid (**319**) employing DCC. Finally, the reaction between mono-thiourea **314** and **320** in $CH_2Cl_2$ furnished catalyst **317** in good yield (Scheme 3.6, B).



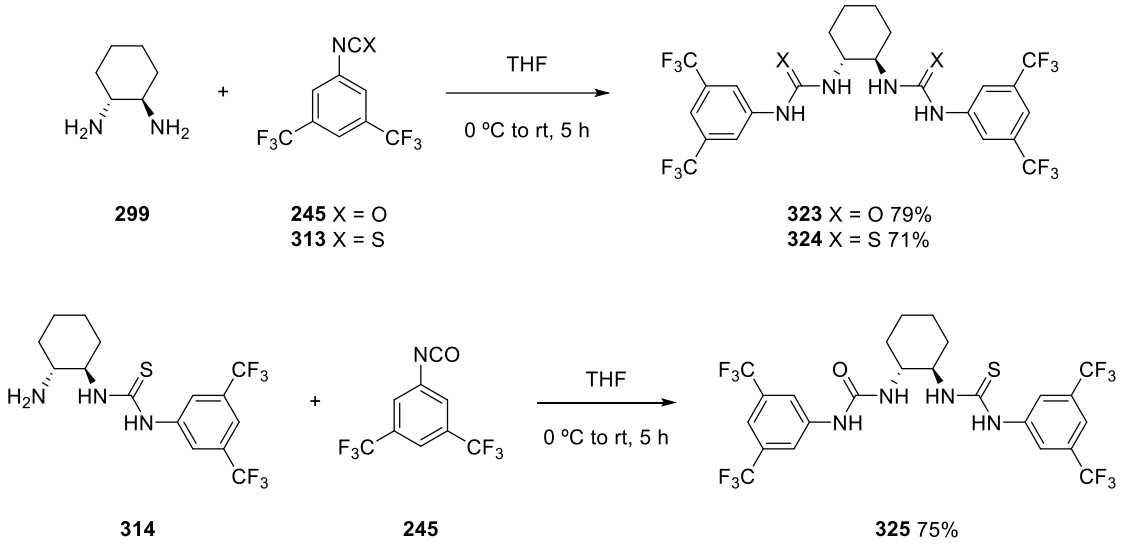

**Scheme 3.6** Synthesis of catalyst **317**.

Catalysts **321** and **322** were also synthesised from **314** and treated with the requisite anhydride to afford the corresponding catalysts in good yields (Scheme 3.7).




**Scheme 3.7** Synthesis of catalysts **321** and **322**.

The Nagasawa-type catalysts were all synthesised in a similar fashion; reaction with two equivalents of the corresponding iso(thio)cyanate and **299** to afford the *bis*-(thio)urea-based catalysts **323** and **324**, and the mixed urea-thiourea **325** was formed by the addition of 3,5-*bis*(trifluoromethyl)phenyl isocyanate (**245**) to **314**. All the catalysts were isolated in good to moderate yields (Scheme 3.8).

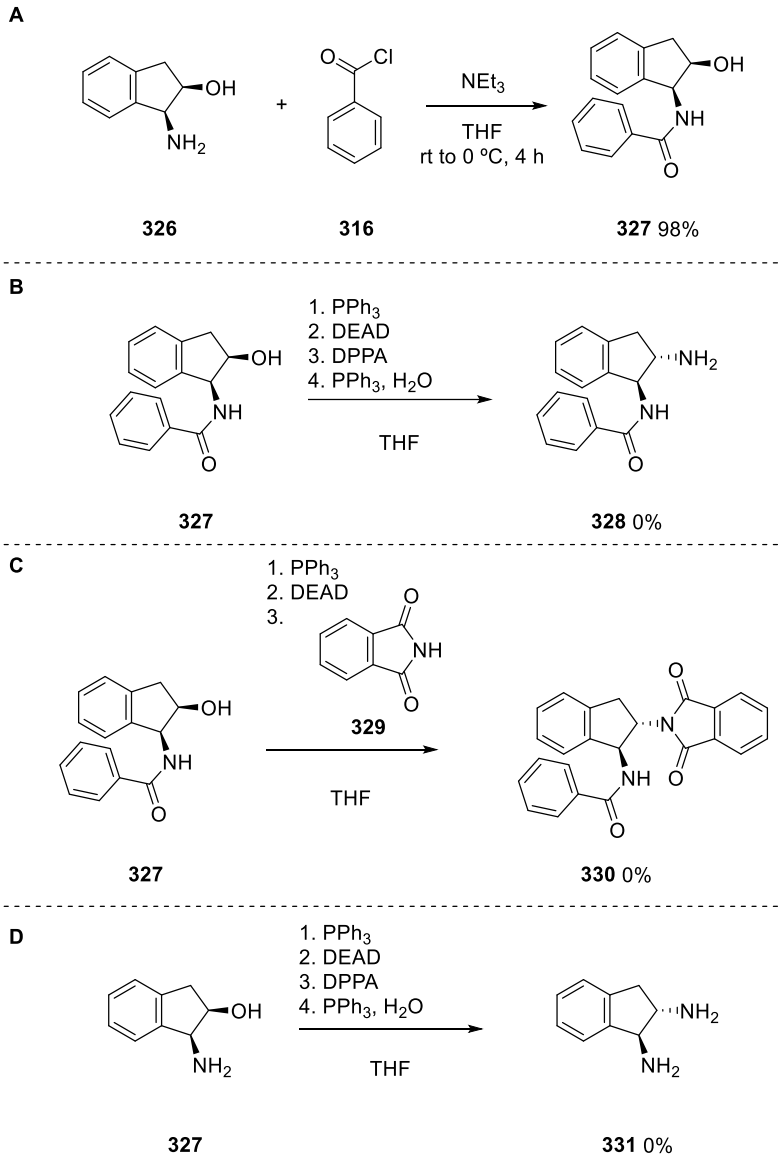



**299** **245** X = O, **313** X = S → **323** X = O 79%, **324** X = S 71%

**314** + **245** → **325** 75%

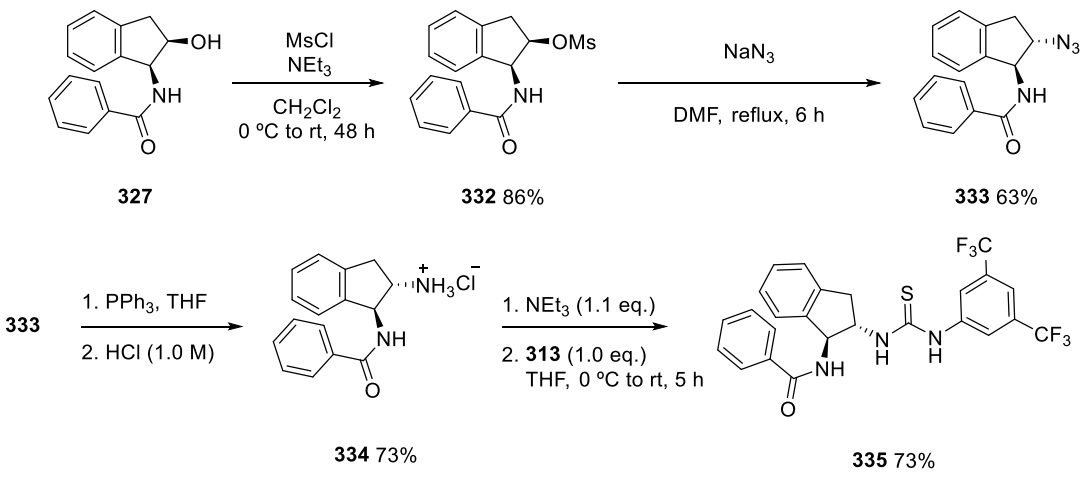
**Scheme 3.8** Synthesis of Nagasawa-type catayst **323**, **324** and **325**

We began the synthesis of catalyst **335** with the reaction between **326** and **316** in the presence of triethylamine to form amide **327** in quantitative amounts (Scheme 3.9, A). To convert the hydroxyl group into an amine, with complete inversion of the configuration, we attempted a Mitsunobu reaction followed by a Staudinger reduction. Unfortunately it failed to produce the corresponding amine **328** (Scheme 3.9, B). We next attempted a Mitsunobu reaction, exchanging the hydroxyl group for phthalamide (**329**) and subsequent reduction to form the amine **328** (Scheme 3.9, C). Unfortunately the desired product was not formed. We hypothesised that the amide could potentially be interfering in the reaction and we therefore carried out a Mitsunobu reaction and a Staudinger reduction on the starting material **327**, however, the desired formation of **331** still remained elusive (Scheme 3.9, D).



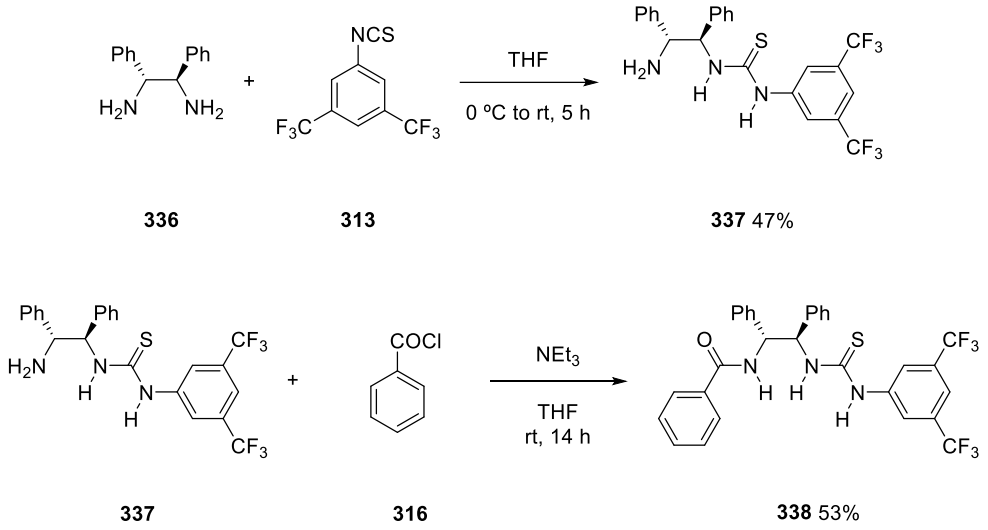

**Scheme 3.9** Synthesis of **327** (**A**) and attempts to obtain the amine functionality (**B**, **C** and **D**).

Finally, converting the hydroxyl group into a leaving group *via* mesylation, an $S_N2$ reaction with **332** employing $NaN_3$ in DMF with complete inversion of the configuration of the stereocentre was possible. Azide **333** was reduced *via* Staudinger reduction to afford the desired amine **328** that was isolated as the hydrochloride salt **334**. In a final step, after deprotonation of the salt **334**, **328** was reacted with **313** to furnish catalyst **335** in good yield (Scheme 3.10).



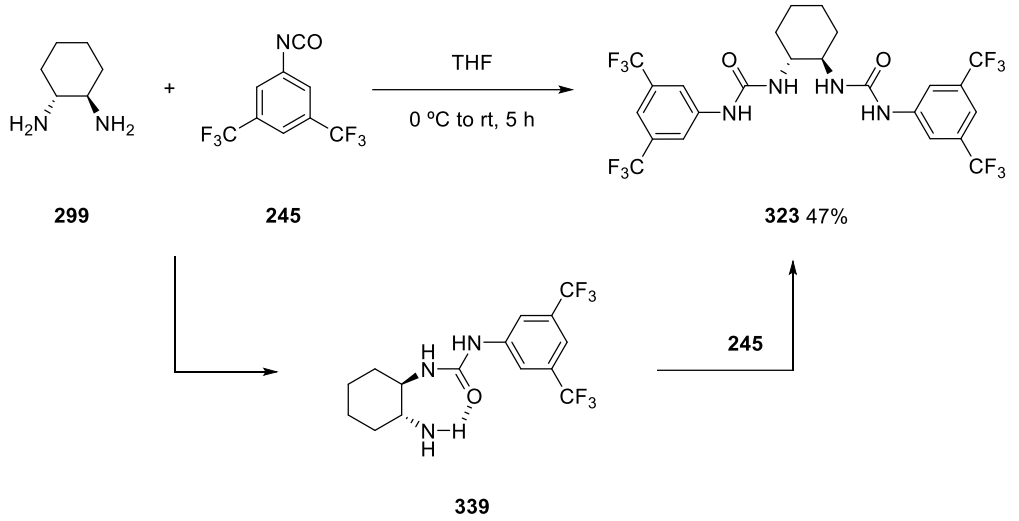

**Scheme 3.10** Synthesis of catalyst **335**.

Following a similar synthetic route employed in the synthesis of catalysts **142** and **317**, (*R*,*R*)-1,2-diphenylethylenediamine (**336**) was treated with **313** to form mono-thiourea **337** in low yield. **337** Was reacted with **316** in $CH_2Cl_2$ to afford catalyst **338** in moderate yield (Scheme 3.11).



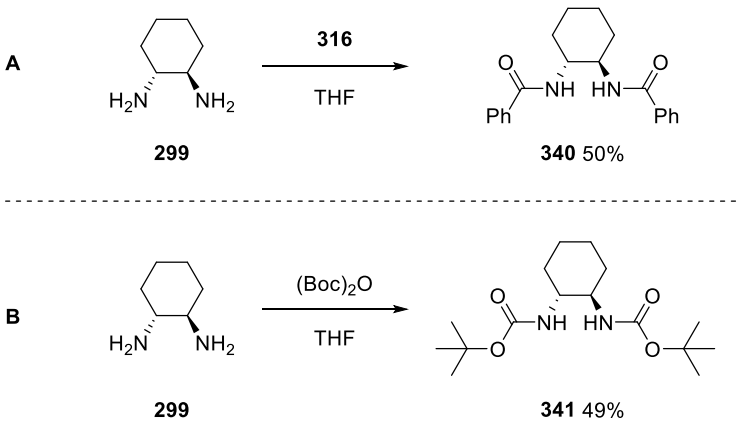

**Scheme 3.11** Synthesis of catalyst **338**.

The synthesis of catalyst **345** was more complicated than its thiourea analogue **313**. The reaction between diamine **299** and **245** did not furnish the corresponding mono-urea compound **339**, instead, it formed the *bis*-urea catalyst **323**. We proposed the reason for this was an intramolecular hydrogen-bonding in **339** between the oxygen atom from the urea and the N-H from the free amine that rendered the amine more nucleophilic than the starting material, leading to the formation of catalyst **323** (Scheme 3.12).



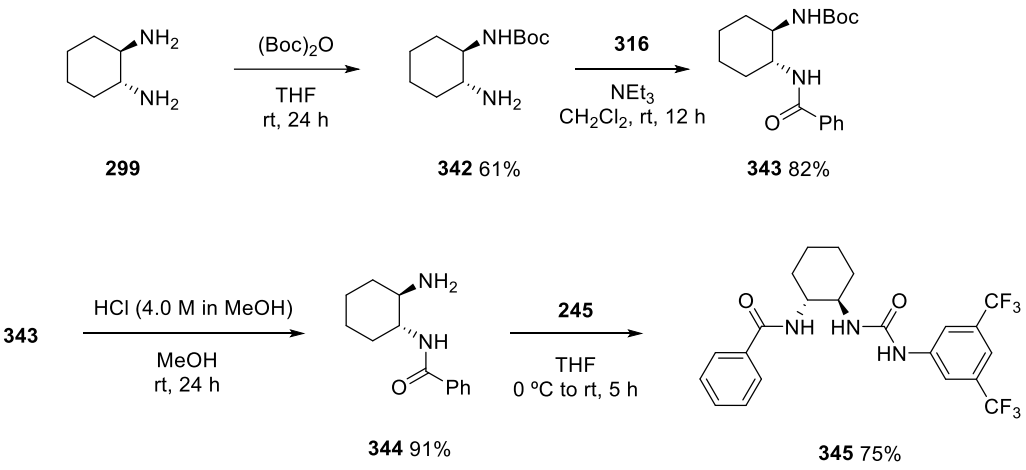

**Scheme 3.12** Stoichiometric reaction between **299** and **245** to furnish only **323**.

The intramolecular hydrogen-bonding hypothesis was supported by the formation of the *bis*-substituted amide **340** in the reaction between **299** and benzoyl chloride (**316**, Scheme 3.13, A) and the formation of the *bis*-Boc-protected amine **341** in the reaction between **299** and di-*tert*-butyl dicarbonate (Scheme 3.13, B) when both reactions were performed in stoichiometric ratios.




**Scheme 3.13** Stoichiometric reactions of **299** with different electrophiles.

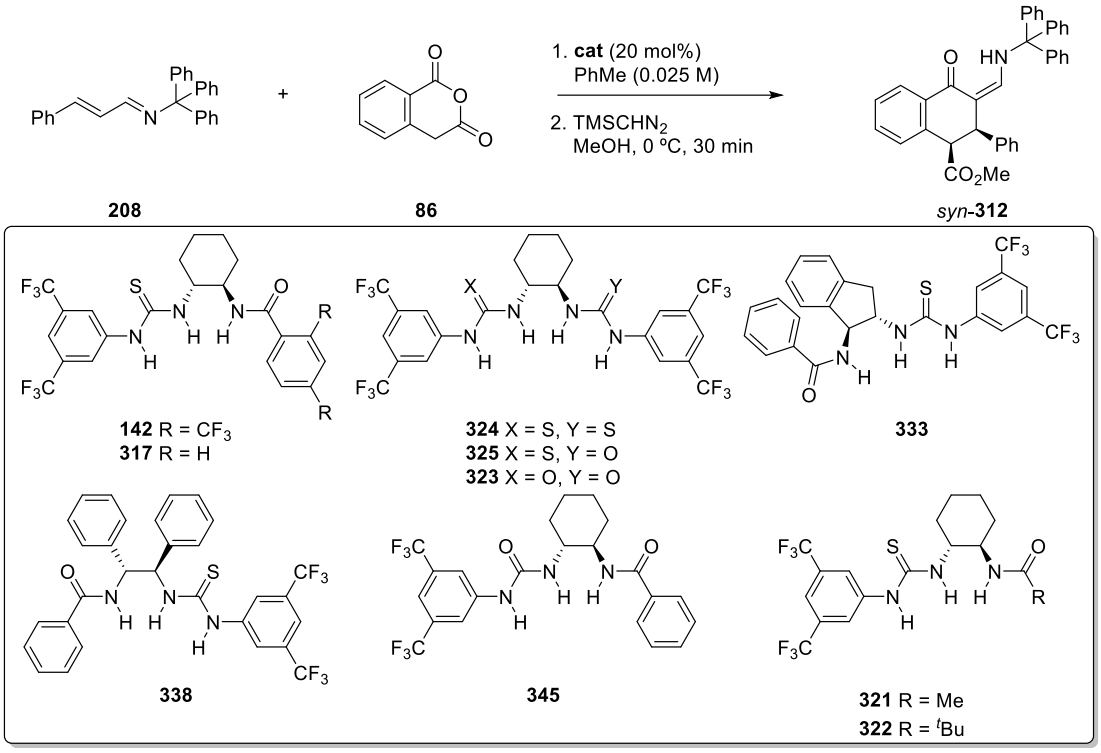
To circumvent this problem, we employed three equivalents of **299** for one of di-*tert*-butyl dicarbonate to furnish mono-Boc-protected amine **342** in moderate yield. The addition of benzoyl chloride (**316**) furnished **343** in good yield and subsequent deprotection yielded mono-amine **344**. Finally amine **344** was reacted with **246** in THF to produce catalyst **345** in good yield (Scheme 3.14).




**Scheme 3.14** Synthesis of catalyst **345**.

These catalysts were evaluated in the reaction between **86** and **208** (Table 3.2).

**Table 3.2** Evaluation of bifunctional catalysts in the asymmetric Tamura cycloaddition.



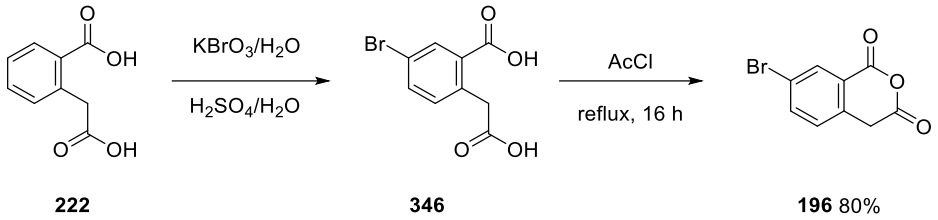

| Entry | **Cat** | T (ºC) | t (h) | Conv. (%)[a] | *dr*[b] (*syn*/*anti*) | *ee*$_{syn}$ (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **142** | rt | 2 | >98 | 80:20 | 50 |
| 2[d] | **317** | rt | 2 | >98 | 80:20 | 83 |
| 3 | **324** | rt | 2 | >98 | 70:30 | 49 |
| 4[d] | **325** | rt | 2 | >98 | 70:30 | 60 |
| 5 | **323** | rt | 2 | >98 | 77:23 | 80 |
| 6 | **142** | -30 | 30 | >98 | 85:15 | 70 |
| 7[d] | **142** | -40 | 30 | >98 | 85:15 | 75 |
| 8 | **323** | -40 | 26 | >98 | 82:18 | 86 |
| 9 | **333** | -40 | 26 | >98 | 87:13 | 63 |
| 10[d,e] | **338** | -40 | 48 | 50 | 50:50 | 0 |
| 11[d] | **317** | -40 | 48 | >98 | 95:5 | 95 |
| 12[d] | **345** | -40 | 30 | >98 | 84:16 | 75 |
| 13[d] | **321** | -40 | 36 | >98 | 86:14 | 79 |
| 14[d,e] | **322** | -40 | 36 | >98 | 93:7 | 96 |

[a]Determined by $^1$H-NMR spectroscopy using *p*-iodoanisole as an internal standard. [b]Determined by $^1$H-NMR spectroscopy. [c]Determined by CSP-HPLC. [d]Catalyst loading of 5 mol%. [e]Reaction concentration of 0.1 M.

The electron-withdrawing groups on the benzoylamide unit of catalyst **142** proved to be a very important factor in achieving enantiocontrol in Seidel's study. In our study, catalyst **142** promoted the formation of **312** with low enantiocontrol (entry 1). The removal of those electron-withdrawing groups improved the enantioselectivity considerably (**317**, entry 2). Next, we switched our attention to the use of Nagasawa-type catalysts[149] – which have proven their worth in anion-binding-mediated enantioselective acyl transfer[150] although they did not show great enantiocontrol in Seidel's study involving cycloadditions with imines.[93] Interestingly, *bis*-thiourea **324** was outperformed by the mixed urea-thiourea **323** while use of the *bis*-urea **323** allowed superior control: increasing the enantiocontrol up to 80% (entries 3, 4 and 5). These series of results highlighted the importance of the catalyst's Lewis-basic iminium ion-binding carbonyl group. The effect that lowering the temperature had on the reaction allowed an improvement in the enantiocontrol of catalysts **142** and **323** over the reaction, reaching a maximum enantiocontrol of 86% (entries 6, 7 and 8). At this point, we decided to examine the impact of the 1,2-cyclohexanediamine core on the efficiency of the catalyst. Firstly, we modified the core to a five-membered ring-based system (*i.e.* catalyst **333**) that imparted less control on the reaction (entry 9). Secondly, we used its acyclic analogue **338** which promoted the reaction in a racemic fashion (entry 10). We therefore returned to the original 1,2-cyclohexanediamino core and evaluated catalyst **317** at low temperature. Catalyst **317** promoted the formation of the product with excellent levels of diastereo- and enantiocontrol (entry 11). We had observed that **323** was clearly superior to **324**, so to take advantage of the superiority of the urea over the thiourea-based system, we synthesised the urea version of **317**. Next, we evaluated the new catalyst **345** in the reaction; however, it could not outperform its thiourea analogue (entry 12). Nevertheless, there were still some possibilities to be studied. Altering the benzoyl unit would allow observing the impact of the sterics of that unit on the stereochemical outcome of the reaction. Hence, we started preparing the smallest version possible; replacing the aromatic amide unit for a methyl amide. Catalyst **321** promoted the formation of **312** in a slightly higher enantiocontrol than **142** (entry 13). Finally, an increase of the size of the aliphatic amide, *via* the use of catalyst **322** bearing a *tert*-butyl group led to the formation of **312** with 96% *ee* utilising only 5 mol% loading of catalyst and a concentration 0.1 M.

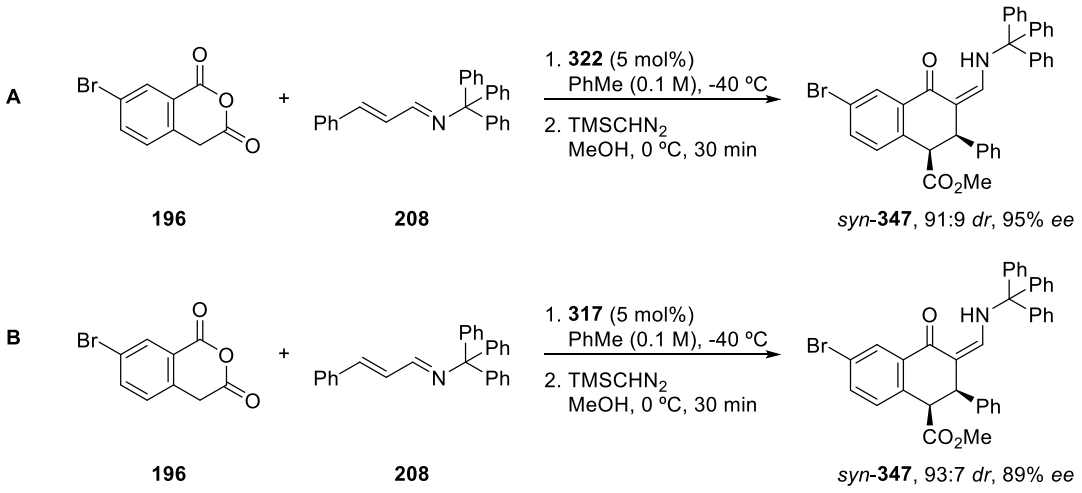
Catalysts **317** and **322** promoted the formation of **312** in excellent enantioselectivity. To differentiate between the two catalysts, we decided to evaluate them with an anhydride with different electronic characteristics than **86**. Anhydride **196** was formed in a two-step

synthesis. Starting from **222**, this was treated with potassium bromate and sulfuric acid in water. Bromo-compound **346** rendered **196** after a self-condensation reaction with acetyl chloride (Scheme 3.15).




**Scheme 3.15** Synthesis of bromoanhydride **196**.

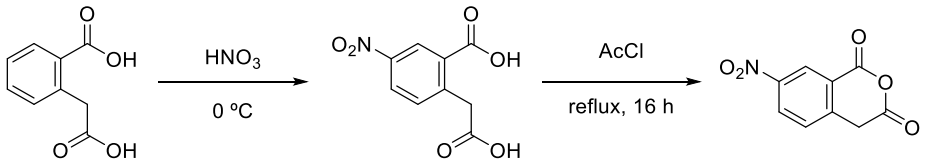
We then carried out the Tamura reaction between imine **208** and anhydride **196** under the optimal reaction conditions, at -40 ºC in toluene with a concentration of 0.1 M. Both catalysts promoted the generation of *syn*-**347** with excellent diastereocontrol, however only the use of catalyst **322** promoted the product formation with excellent enantiocontrol; affording *syn*-**347** in 95% *ee* (Scheme 3.16, A). Under identical conditions, catalyst **317** promoted the reaction with an inferior 89% *ee* (Scheme 3.16, B).




**Scheme 3.16** Cycloaddition between **196** and **208** catalysed by **322** and **317**.

### 3.3 Expanding the scope of the reaction: the anhydride component

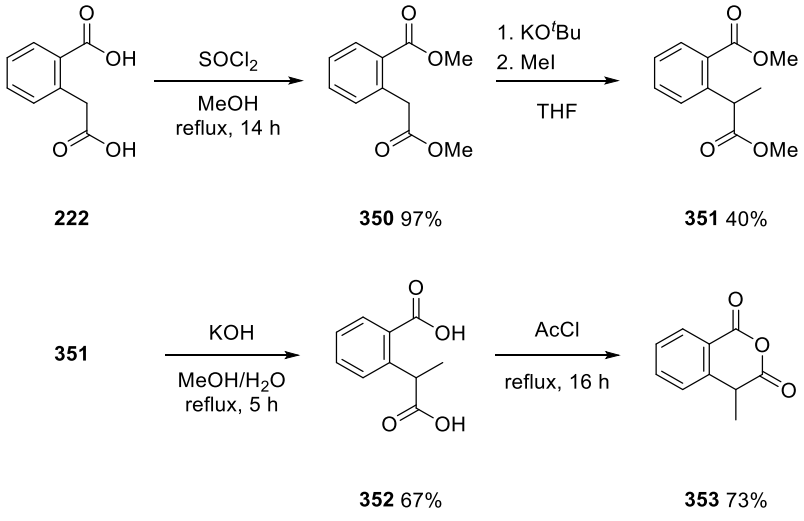
Different homophthalic anhydride derivatives were evaluated in the reaction. Homophthalic acid (**222**) was treated with fuming nitric acid at 0 ºC to furnish dicarboxylic acid **348** in good yield. Through a self-condensation reaction, **348** produced **349** in good yield (Scheme 3.17).




**222** **348** 72% **349** 80%

**Scheme 3.17** Synthesis of anhydride **349**.

Homophthalic acid (**222**) was converted into the methyl ester **350** employing $SO_2Cl_2$ in methanol. Potassium *tert*-butoxide was used to deprotonate the α-position with subsequent methylation using MeI affording **351** in moderate yield. Ester **351** was hydrolysed to furnish acid **352** that, through a self-condensation in acetyl chloride, produced anhydride **353** (Scheme 3.18).



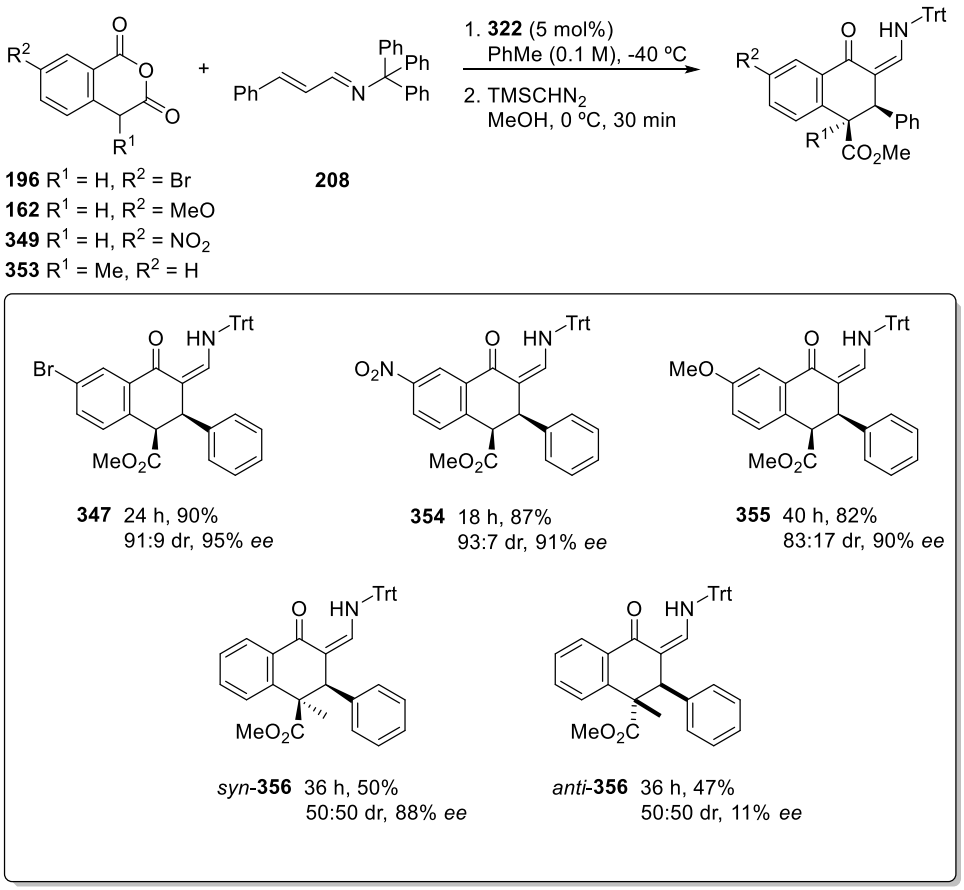

**222** **350** 97% **351** 40%

**351** **352** 67% **353** 73%

**Scheme 3.18** Synthesis of anhydride **353**.

The presence of different electron-withdrawing or electron-donating groups on the homophthalic anhydride did not have a significant impact on the enantiocontrol of the reaction, and tetralones **347**, **354** and **355** were formed with good to excellent diastereocontrol and excellent enantioselectivity in the presence of catalyst **322**. The formation of tetralone **356 –** incorporating a quaternary stereocentre, could not be promoted

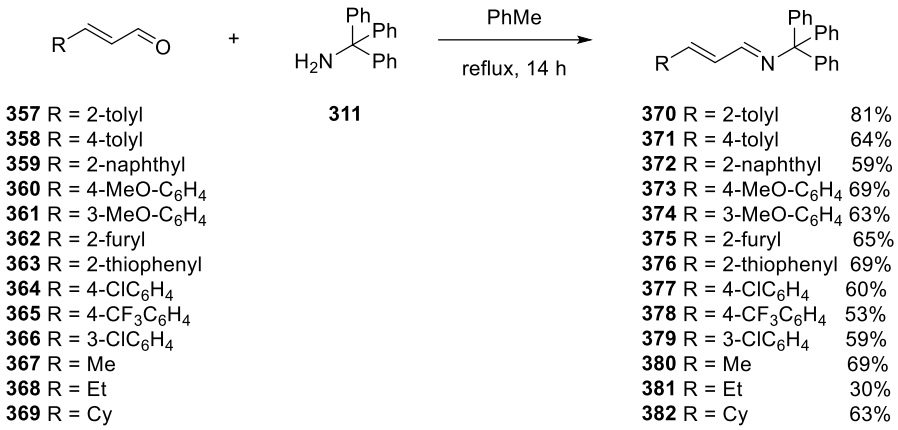
with any diastereocontrol however, the enantiocontrol achieved in the preparation of *syn*-**356** was still synthetically useful (Scheme 3.19).




**Scheme 3.19** Scope of the substrate: the anhydride component.

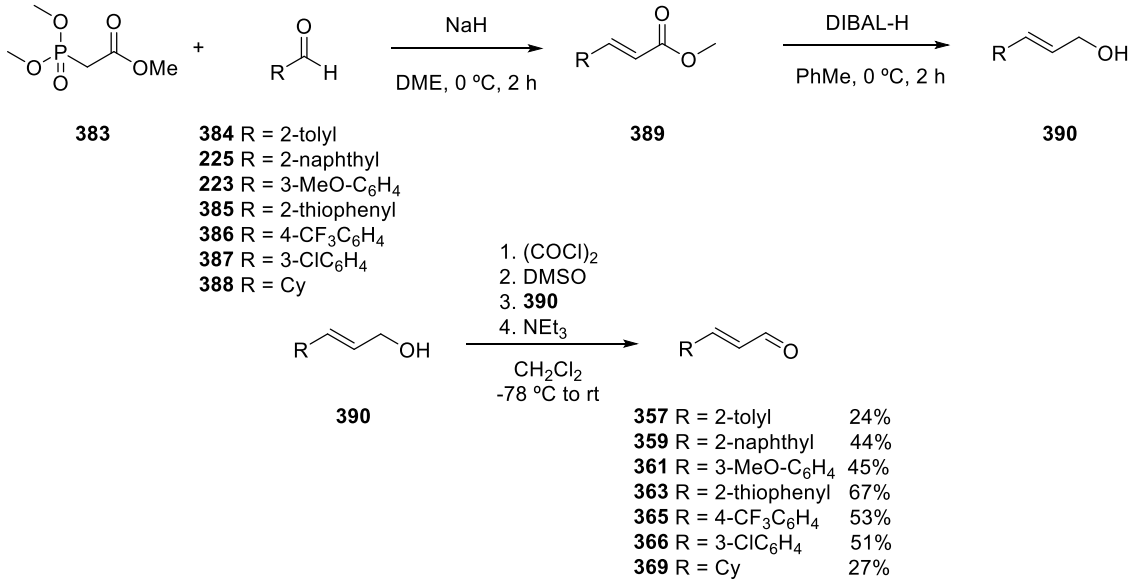
### 3.4 Expanding the scope of the reaction: the imine component

With the catalytic conditions optimised, we focused our attention on expanding the scope of the reaction. All imines were synthesised *via* condensation between the corresponding α,β-unsaturated aldehyde and tritylamine in toluene. The imines were obtained in a moderate yield after trituration with hexanes (Scheme 3.20).



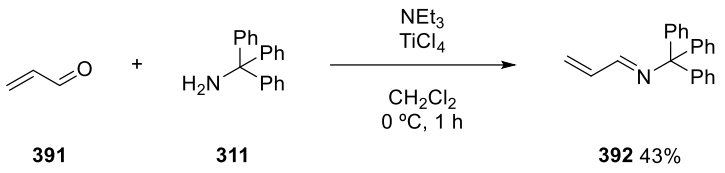

**Scheme 3.20** Synthesis of *N*-tritylimines

Some of the α,β-unsaturated aldehydes starting materials were synthesised from the corresponding aldehyde that underwent a Wittig-Horner reaction with trimethyl phosphonoacetate (**383**) to form esters of general type **389**. The (*E*)-isomer was predominantly formed except when R = Cy (80:20 *trans*:*cis*), however the *cis*-isomer isomerised to the thermodynamically more stable *trans*-isomer during the condensation with trityl amine. Ester **389** was reduced to allyl alcohol **390** using DIBAL-H and **390** underwent a Swern oxidation to furnish the corresponding aldehyde (Scheme 3.21).



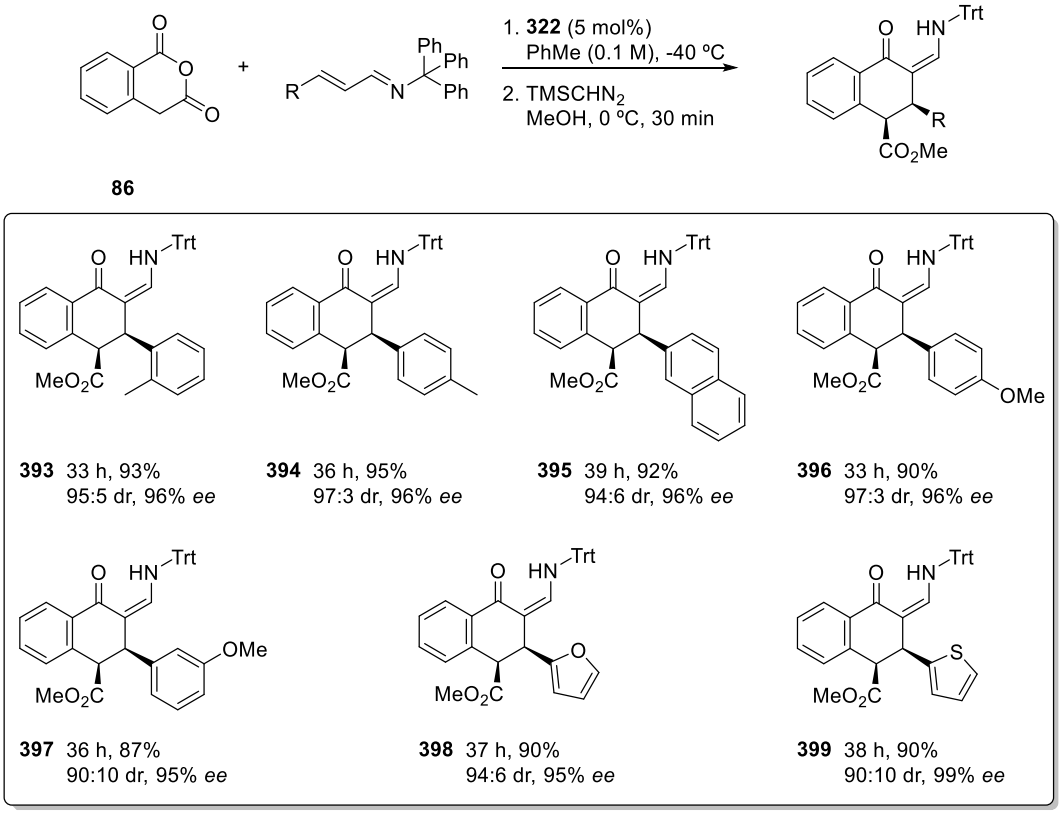

**Scheme 3.21** Synthetic route to form α,β-unsaturated aldehydes.

Imine **392** was synthesised from acrolein (**391**); employing amine **311** in $CH_2Cl_2$ at 0 ºC using $TiCl_4$ to activate the carbonyl group (Scheme 3.22).




**Scheme 3.22** Synthesis of imine **392**.

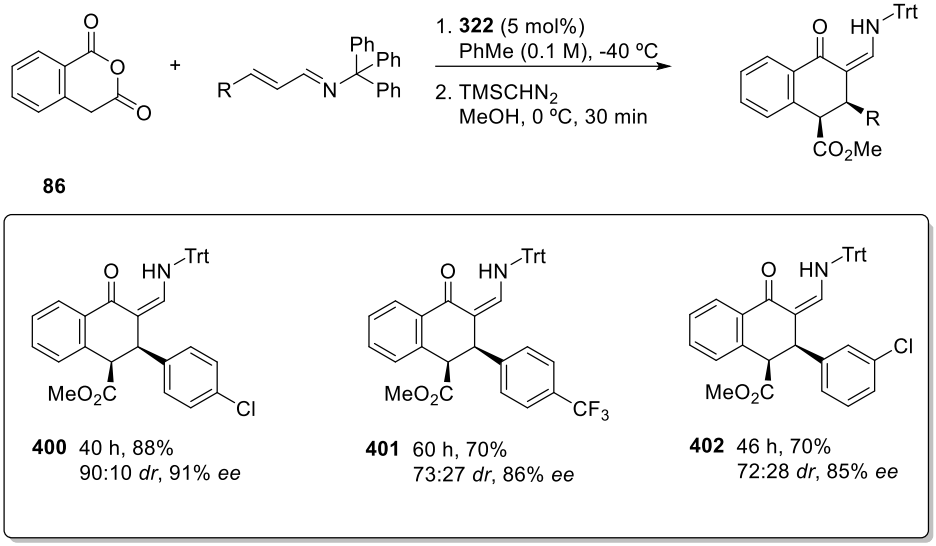
All the synthesised imines were reacted with **86** in toluene (0.1 M) at -40 ºC in the presence of catalyst **322** (Scheme 3.23). A wide variety of tetralones were synthesised in excellent yield and with excellent levels of diastereo- and enantiocontrol, irrespective of the position or the size of the electron-donating group on the aromatic β-substituted associated with the imine (*i.e.* products **393**-**397**). When the substituent is an electron-rich heteroaromatic ring, the diastereo- and enantioselectivity of the process remained excellent (*i.e.* **398** and **399**). This level of control is perhaps best demonstrated by the formation of tetralone **399** bearing a thiophene ring in an almost optically pure fashion.




**Scheme 3.23** Scope of the substrate: imines with different electron-donating groups.

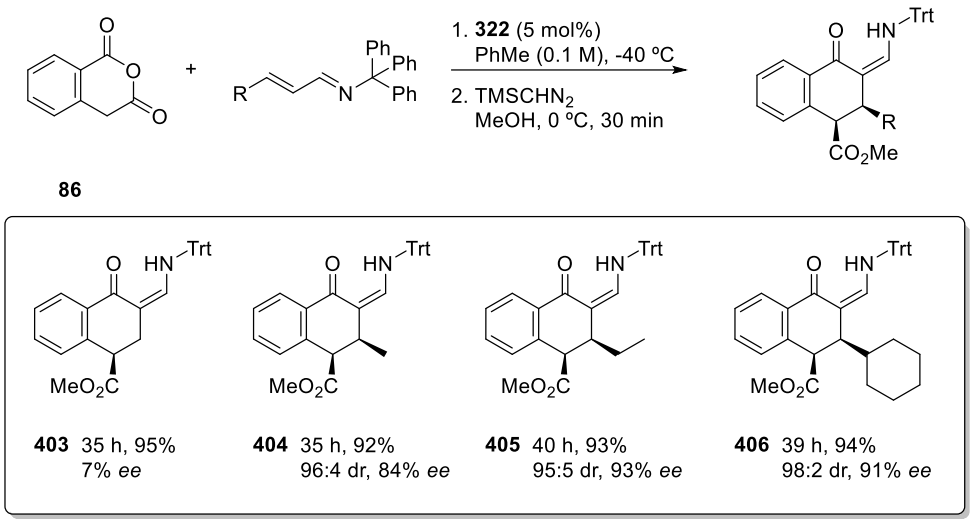
Our next objective was to investigate if imines substituted with different electron-withdrawing groups could offer similar levels of enantiocontrol to their relatively electron-

rich counterparts (Scheme 3.24). The enantiocontrol decreased slightly however, **400**, **401** and **402** were still obtained with good diastereo- and enantioselectivity.




**Scheme 3.24** Scope of the substrate: imines with different electron-withdrawing groups.

Finally, we turned our attention on the effect of aliphatic substituents (Scheme 3.25). Unfortunately tetralone **403** was formed almost as a racemate, as the β-position of the α,β-unsaturated imine was not substituted. This observation offered a potential explaination as to why the promotion of a more enantiocontrolled reaction was possible with a bigger imine-β-substituent. Thus, when a small methyl group was present at the β-position, the enantiocontrol increased drastically: tetralone **404** was generated with 84% *ee*. Further increase in the size of the aliphatic group proved advantageous from an enantioselectivity standpoint (*i.e.* **405** and **406**).




**Scheme 3.25** Scope of the substrate: imine components bearing aliphatic β-subtituents.

### 3.5 Rationalisation of the stereochemistry outcome

In all of the cases, the *syn* diastereomer was formed predominantly, however, the assignment of the *syn*/*anti* conformation was not possible with certainty until an X-ray diffraction pattern study was performed. The reason of this was that the *syn* and *anti* diastereomers exhibited very similar coupling constants – $J_{syn}$ 5.1 Hz and $J_{anti}$ 4.7 (average values of all the products) at the C-3 and C-4 carbon atoms. Also, rather unexpectedly, the *syn* diastereomer has the larger coupling constant. The compounds appear in a *cisoide* conformation in the $^{1}$H-NMR spectra, therefore NOE experiments were inconclusive. The X-ray diffraction pattern study of compound **399** indicated that the absolute configuration of the compound is *R*,*S* (Figure 3.1).

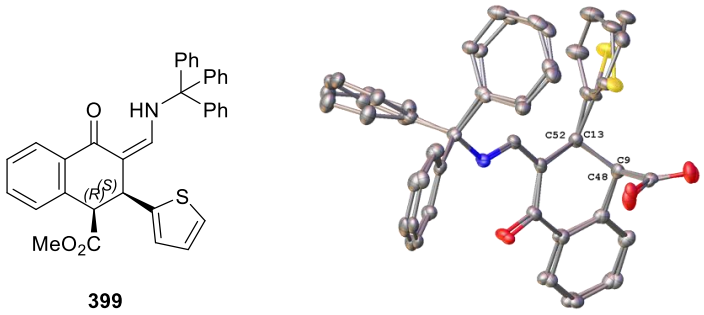



**Figure 3.1** Crystal structure of tetralone **399**.

A DFT study was performed in our group by Dr. Cristina Trujillo to aid us understand the mechanism of the reaction and the stereochemical outcome. The results are summarised below.

The energy profile for the formation of both enantiomers of **399** (Figure 3.2) is interesting in that in the case of the generation of the major enantiomer (*R*,*S*)-**399** cyclisation is rate determining; while the 1,4-conjugate addition reaction is the slow step leading to the formation of the (*S*,*R*)-antipode. The rate-determining step (RDS) barrier height leading to the major enantiomer is calculated to be lower than the RDS associated with the minor. Both pathways pass through a relatively stable 1,4-conjugate addition adduct and the cyclisation step is essentially irreversible under the reaction conditions. Overall barriers are rather low – consistent with smooth cycloaddition at -40 °C.

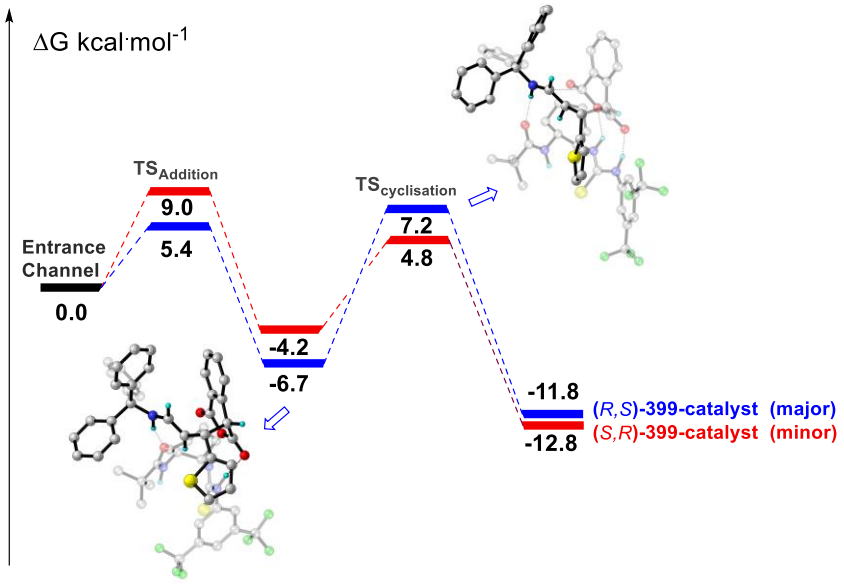



**Figure 3.2** Calculated (DFT) potential energy surface associated with the formation of both enantiomers of **399**.

On examination of TSs associated with the key first stereocentre forming 1,4-conjugate addition reaction step for both major and minor enantiomers, we observed a similar mode of action to that reported by Seidel and Vetticat during catalysis of the Castagnoli reaction.[93] The catalyst stabilises and organises the encounter between the enolate and iminium ion through hydrogen-bonding interactions - namely between the enolate and the thiourea unit and the iminium ion N-H proton and the catalyst's amide group. In the TS associated with the major enantiomer (*R*,*S*)-**399** (Figure 3.3, *left*), the iminium ion is held more tightly (1.79 Å vs 1.91 Å) than calculated previously,[93] consistent with the observed improved performance of more basic amide/urea systems in the Tamura reaction under study not observed in the Castagnoli chemistry. The large trityl moiety, which must avoid steric clashes with both the bound enolate and the catalyst's *t*-butyl group (the exchange of which

for a methyl-unit led to diminished product *ee* - see catalyst **321**, Table 3.2) is directed away from the catalyst bulk and into solvent. In the TS leading to the minor (*S*,*R*)-**399** enantiomer (Figure 3.3, *right*), in order to accommodate the trityl unit and expose the olefin *re*-face to the nucleophile, the anhydride enolate must be bound *via* its less basic oxygen atoms to achieve a Bürgi-Dunitz trajectory. This results in weaker hydrogen bond interactions between both iminium ion/anhydride enolate and the catalyst and a barrier differential ($\Delta\Delta G^{\ddagger}$ = 3.6 kcal mol$^{-1}$) consistent with the 99% *ee* observed.

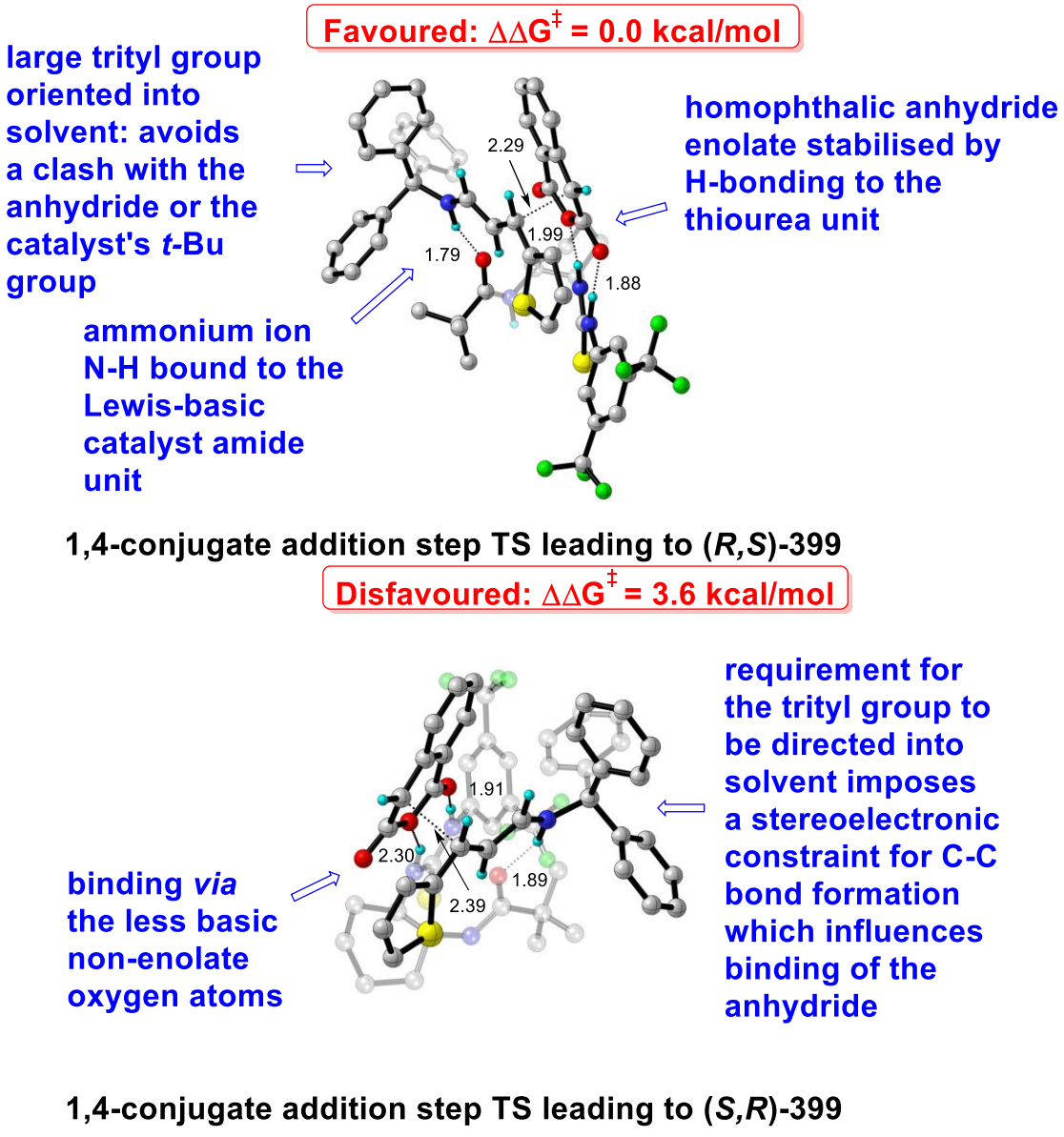
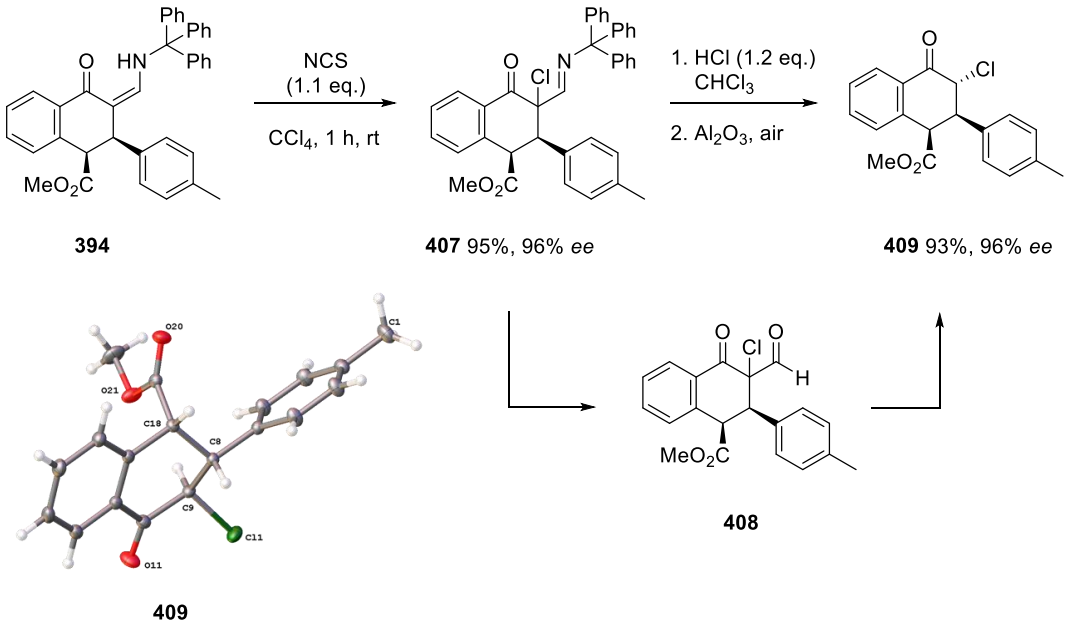



**Figure 3.3** Calculated (DFT) lowest energy transition state structures associated with both enantiomers of **399**.

### 3.6 Functionalisation of the catalytic product

We developed an enantioselective method that gave access to a wide variety of highly functionalised β-enaminones bearing two contiguous stereocentres with excellent yields enantio- and diastereocontrol.

To highlight the synthetic utility of our methodology, we decided to treat product **394** with NCS to chlorinate the α-position to the carbonyl and form β-ketoimine **407** in excellent yield, as a single diastereomer, with complete retention of the enantiocontrol and the incorporation of a new quaternary stereocentre. A mild hydrolysis employing an ethereal solution of HCl led to the formation of aldehyde **408** however, it was not possible to isolate as it was contaminated with tritylalcohol sideproduct of the hydrolysis of the imine – a HMBC experiment of the reaction crude could not find any trace of N-H in the mixture, suggesting the presence of the tritylalcohol. Finally, once the hydrolysis reaction was completed (monitored by $^1$H-NMR spectra), neutral alumina was added and aldehyde **408** underwent an oxidation-β-ketodecarboxylation process to form the α-chlorotetralone **409** as a single diastereomer in excellent yield and retaining the enantioncontrol. The X-ray diffraction pattern identified the compound as the (*R*,*R*,*R*)-**409** (Scheme 3.26). The final product is an α-chloroketone[151] that could be further modified *via* $S_N2$ retaining the enantiocontrol.[152]




**Scheme 3.26** Synthesis of α-chlorotetralone **409** and the crystal structure.

## 3.7 Conclusions

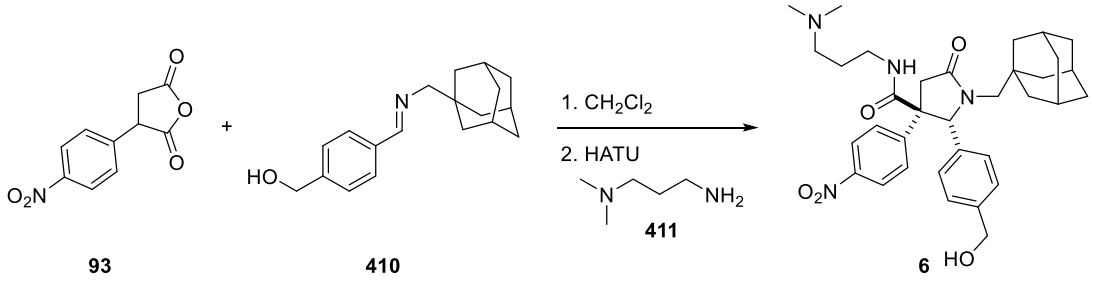
We have reported the reaction between *N*-protected α,β-unsaturated imines and homophthalic anhydrides to selectively form Tamura-type products. Optically pure highly functionalised α-tetralones can be formed through the use of a chiral catalyst that stabilises the enolate and the iminium ion and places them in the adequate chiral environment.

The process allows the formation of α-tetralones with two contiguous stereocentres in excellent yields, enantio- and diastereocontrol (99% *ee* and 9:1 *dr*). Due to the presence of the enaminone unit, the molecule can be widely functionalised. We have reported one example of the chlorination of the enaminone to create a new quaternary stereocentre with complete stereocontrol. Further modifications allow us to convert the β-ketoimine into an α-chlorotetralone, bearing three contiguous with excellent yield and retaining the enantiocontrol.

A DFT study has been carried out to support and provide more knowledge about the origin of the stereoselectivity.

## 4 Cycloaddition reactions between succinic anhydrides and imines

As outlined in Section 1.3.2.1, succinic anhydrides can undergo cycloaddition reactions with imines to form γ-lactam products. This reaction type has a great potential utility in the synthesis of biologically active lactams. For instance, Shaw *et al.* in 2007 reported that the reaction between anhydride **93** and imine **410** afforded lactam **6** after coupling with amine **413** in a separate step (Scheme 4.1).[9]



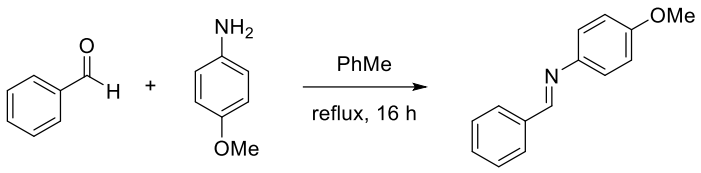

**Scheme 4.1** Synthesis of biologically active γ-lactam reported by Shaw.

HOXA13 is a transcription-factor that regulates the development of the limb and genitourinary tissues[153] and is excessively expressed in tumour cells. Lactam **6** was found to have an $IC_{50}$ of 6.5 μM when screened in an assay of the HOXA13 DNA binding-domain and its target DNA sequence; outlining its potential as an anticancer drug candidate.

Despite the promising inhibitory characteristics of lactam **6** towards HOXA13 described by Shaw *et al.*, asymmetric synthetic methodologies to afford enantiopure γ-lactams were insufficient to establish the relative activity of each enantiomer.[154] We decided to develop a synthetic methodology that allowed access to enantiopure γ-lactams of this type.

### 4.1 Development of the catalytic process

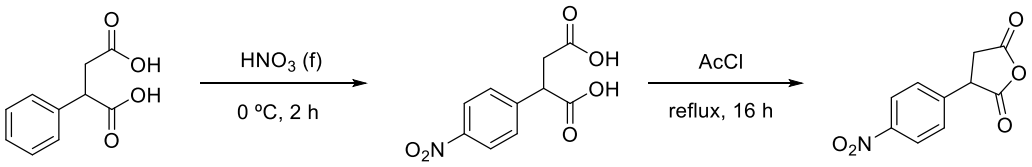
Based on the results outline in Chapter 3, it was expected that a basic imine was needed in order to ensure a sufficient interaction with the catalyst during reaction with the anhydride. Imine **412** was synthesised through a condensation reaction between benzaldehyde (**83**) and amine **69** in moderate yield (Scheme 4.2).




**83** **69** **412** 68%

**Scheme 4.2** Synthesis of imine **412**.

Anhydride **93** was obtained in a two-step process. Nitration of phenyl succinic acid (**280**) afforded acid **413** in moderate yield, which after a self-condensation in acetyl chloride produced anhydride **93** in good yield (Scheme 4.3).

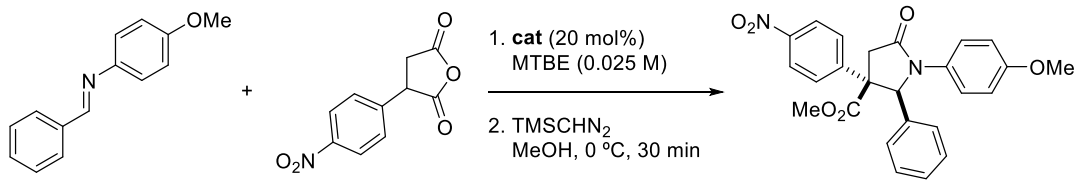



**280** **413** 53% **93** 78%

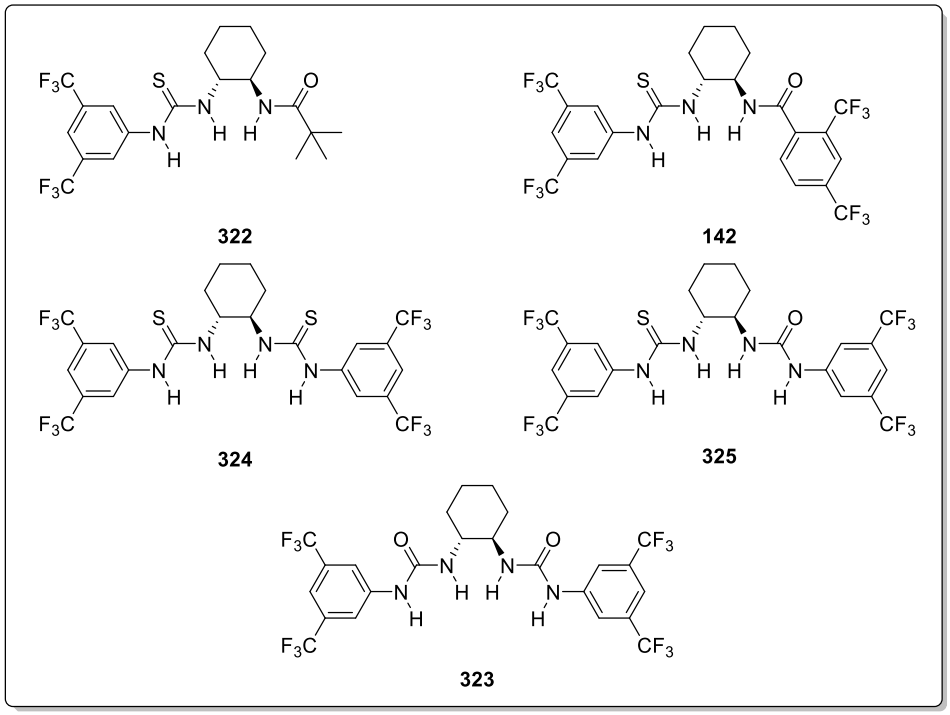
**Scheme 4.3** Synthesis of anhydride **93**.

With substrates in hand, optimisation of the reaction conditions was undertaken (Table 4.01).

**Table 4.1** Screening of catalytic conditions




**412** **93** ***syn*-414**




| Entry | **Cat.** | T (°C) | t (h) | Conv. (%)[a] | *dr*[b] (*syn*/*anti*) | *ee* (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **322** | rt | 20 | >99 | >99:1 | 78 |
| 2 | **143** | rt | 20 | >99 | >99:1 | 80 |
| 3 | **143** | 0 | 24 | >99 | >99:1 | 83 |
| 4 | **324** | rt | 20 | >99 | >99:1 | 69 |
| 5 | **325** | rt | 20 | >99 | >99:1 | 88 |
| 6 | **323** | rt | 20 | >99 | >99:1 | 91 |
| 7 | **323** | 0 | 26 | >99 | >99:1 | 90 |
| 8 | **323** | -15 | 72 | 48 | >99:1 | n.d. |
| 9[d] | **323** | -15 | 47 | >99 | >99:1 | 82 |

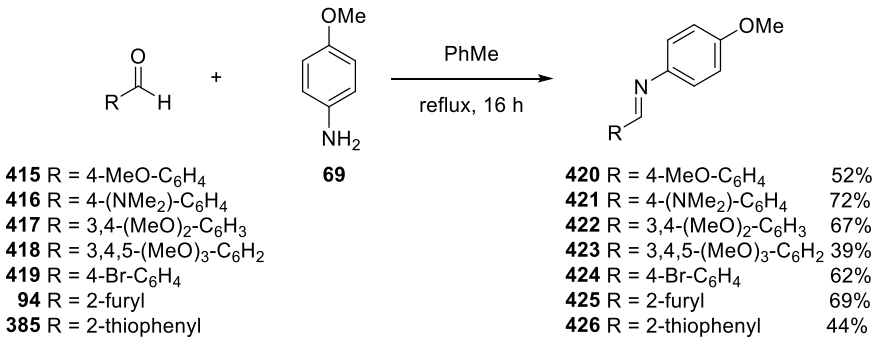
[a]Determined by $^1$H NMR spectroscopy using *p*-iodoanisole as an internal standard. [b]Diastereomeric ratio determined by $^1$H NMR spectroscopy. [c]Determined by CSP-HPLC. [d]Concentration 0.1 M.

Optimisation was initially carried out with catalyst **322** – which had previously been found to catalyse the Tamura reaction between enolisable anhydrides and α,β-unsaturated imines with excellent enantiocontrol (Chapter 3). Catalyst **322** promoted the formation of **414** as a single diastereomer with good enantiocontrol (entry 1). The reaction was also promoted with catalyst **142** that had been employed in the cycloaddition between homophthalic anhydride and imines achieving excellent enantioselectivity.[93] Unfortunately, catalyst **142** promoted the reaction between **93** and **412** with similar enantiocontrol to that promoted by catalyst **322** (entry 2). When the reaction was promoted by catalyst **142** at 0 ºC enantiocontrol improved slightly (entry 3). *bis*-Thiourea **324** induced the formation of **412** with only moderate enantioselectivity (entry 4), despite performing at a similar level to **142** in the aforementioned Tamura reaction (see entries 1 and 3, Table 3.2). Next, the reaction was carried out in the presence of mixed urea-thiourea catalyst **325**; which induced the formation of **414** with good enantiocontrol (entry 5). When *bis*-urea catalyst **323** was employed to promote the reaction between **93** and **412**, **414** was formed with excellent enantioselectivity (entry 6). When catalyst **323** induced the formation of *syn*-**414** at 0 ºC, the enantiocontrol of the reaction remained the same as when the reaction was performed at room temperature (entry 7). In order to further investigate the effect of low temperatures on the enantioselectivity of the process, *bis*-urea catalyst **323** was used to promote the reaction at -15 ºC. Unfortunately, the reaction became too slow, likely due to poor catalyst solubility, it was not possible to determine the enantiocontrol due to lack of product formation (entry 8). The enantiocontrol of the reaction decreased considerably when the concentration of the reaction was increased (entry 9).

### 4.2 Expanding the scope: the imine component

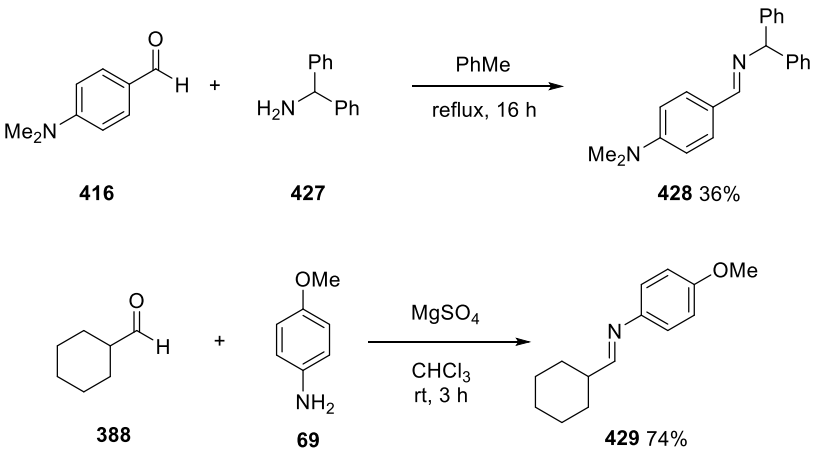
The effect of the steric and electronic characteristics of imine substrates on the enantiocontrol of the reaction with anhydride **93** was investigated under the newly optimised catalytic conditions.

Imines were synthesised using the identical reaction conditions employed for the synthesis of model imine **413**, in a condensation reaction between the corresponding aldehyde and *p*-anisidine (**69**, Scheme 4.4).



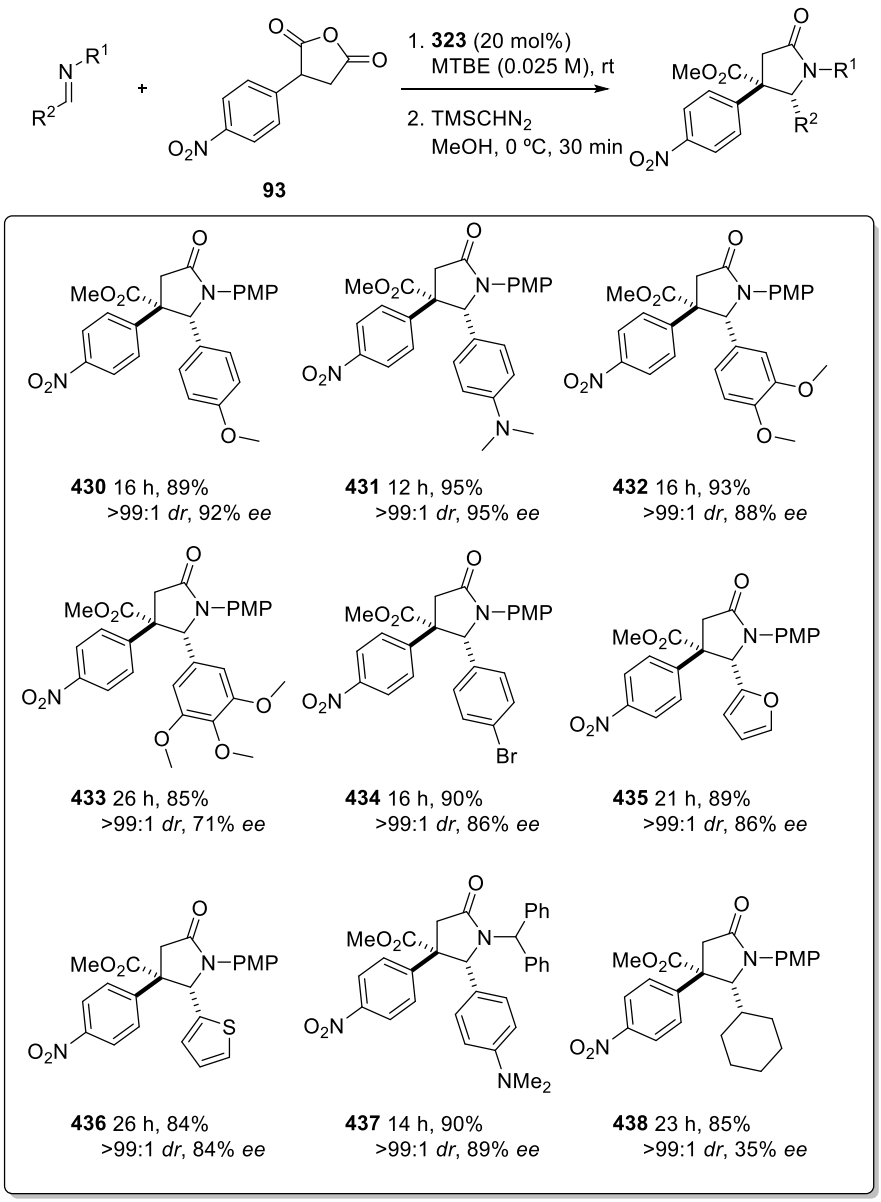

**Scheme 4.4** Synthesis of imines **423-429**.

Imines **428** and **429** were synthesised from **416** and benzhydrylamine (**427**) in toluene at reflux and through condensation of cyclohexanecarboxaldehyde (**388**) with anisidine (**69**) in chloroform at room temperature respectively (Scheme 4.5).




**Scheme 4.5** Synthesis of imines **428** and **429**.

Imines were evaluated under the optimal reaction conditions developed in the previous Section 4.1 – catalyst **323**, 20 mol% loading in MTBE at room temperature (Scheme 4.6).



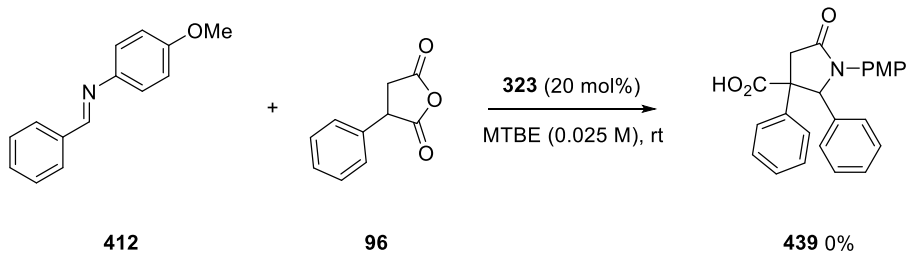

**Scheme 4.6** Expanding the scope of the reaction: the imine component.

The presence of electron-donating substituents on imines **420** and **421** led to increased basicity relative to imine **412**, which improved the enantiocontrol and afforded lactams **430** and **431** as single diastereomers with excellent enantiocontrol. The presence of the *p*-dimethylamino group resulted in a more basic imine in comparison to the *p*-methoxy substituted substrate, suggesting a stronger interaction with the catalyst. The dimethoxy substituted lactam **432** could also be prepared in good, albeit slightly lower *ee*. A decrease in the enantioselectivity of the process was observed with sterically hindered imine **423**, allowing isolation of lactam **433** with only moderate enantiocontrol. We would note that the –I effect of the methoxy groups in the 3- and 5- positions may also be relevant here. The

electron-withdrawing *p*-bromophenyl group on imine **424** led to the formation of lactam **424** in good *ee*. The use of electron-rich heterocyclic imines was also tolerated; leading to formation of lactams **435** and **436** with good enantioselectivity. Protection of the imine nitrogen atom with a benzhydryl group led to the formation of lactam **437** with good enantioselectivity. The enantiocontrol obtained in the reaction furnishing lactam **431** was greater than the enantiocontrol achieved in the formation of lactam **439** – which highlights the superiority of the *N*-*p*-methoxyphenyl substituent over the *N*-benzhydryl substituent in influencing selectivity. Unfortunately, aliphatic imine **429** was not well tolerated by catalyst **323**; lactam **438** was afforded with low enantiocontrol, albeit as a single diastereomer.

### 4.3 Expanding the scope of the reaction: the anhydride component

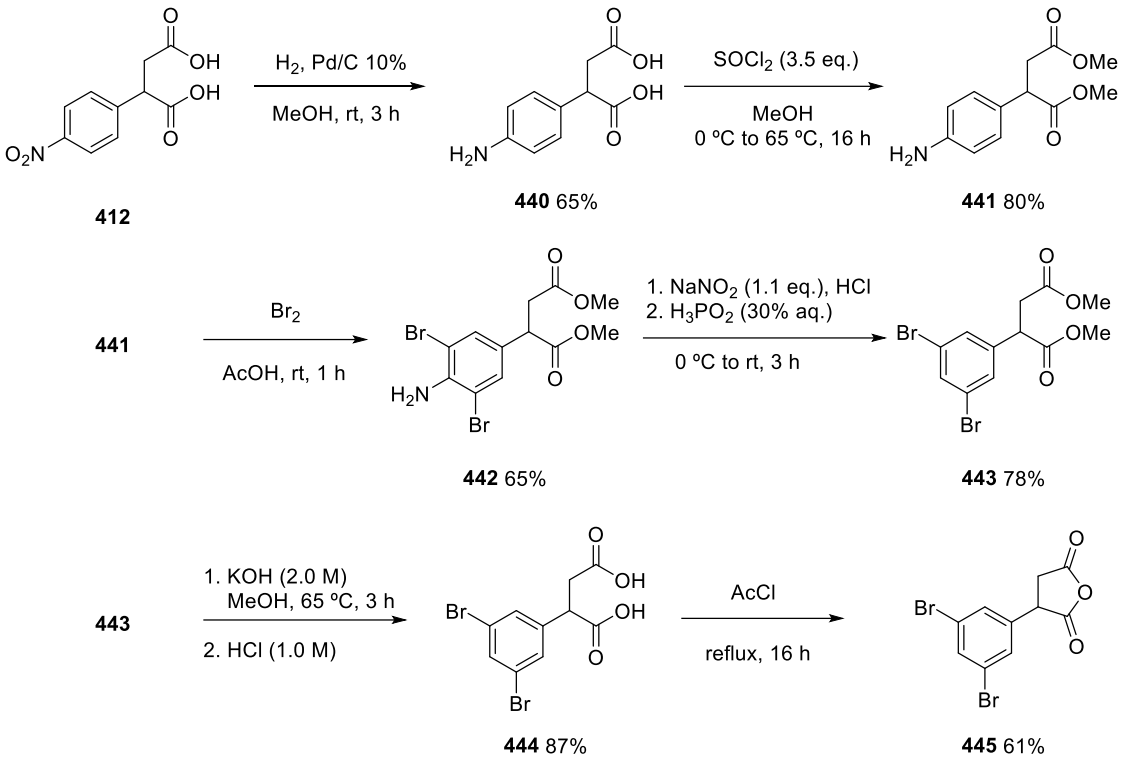
We attempted to expand the scope of the reaction to different anhydrides, starting with the reaction between imine **412** and phenylsuccinic anhydride (**96**) promoted by catalyst **323**. Unfortunately, no conversion was observed after 24 hours (Scheme 4.7).




**412** **96** **439** 0%

**Scheme 4.7** Reaction between imine **412** and anhydride **96**.

The failure of **96** to react with **412**, under the same conditions in which **412** proved to be an excellent substrate was likely due to the relatively low concentration of the enolate of **96** necessary to interact with the catalyst **323**. By that rationale, we envisaged that by installing an enol-stabilising group on the aryl unit of the anhydride this issue may be circumvented. Thus, we synthesised anhydride **446** from *p*-nitrosuccinic acid (**413**). Reduction of the nitro group by hydrogen over palladium/carbon led to aniline **440**. Esterification of **440** with thionyl chloride in methanol furnished ester **441** in good yield, which underwent a bromination in acetic acid to form dibromoaniline **442**. Compound **442** was reduced *via* diazonium salt formation to **443**. Subsequent hydrolysis of the ester groups afforded dicarboxylic acid **444** in good yield. Diacid **444** underwent a self-condensation reaction in acetyl chloride to yield anhydride **445** (Scheme 4.8).




**Scheme 4.8** Synthesis of 3,5-dibromophenylsuccinic anhydride (**445**).

Mr. Bruce Lockett-Walters kindly provided arylsuccinic anhydrides with different enol-stabilising groups in order to probe the scope of the reaction further (Figure 4.1).

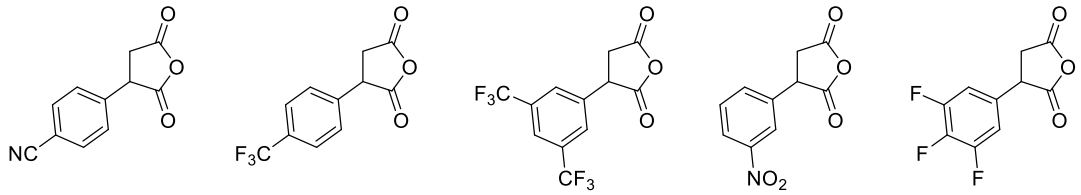
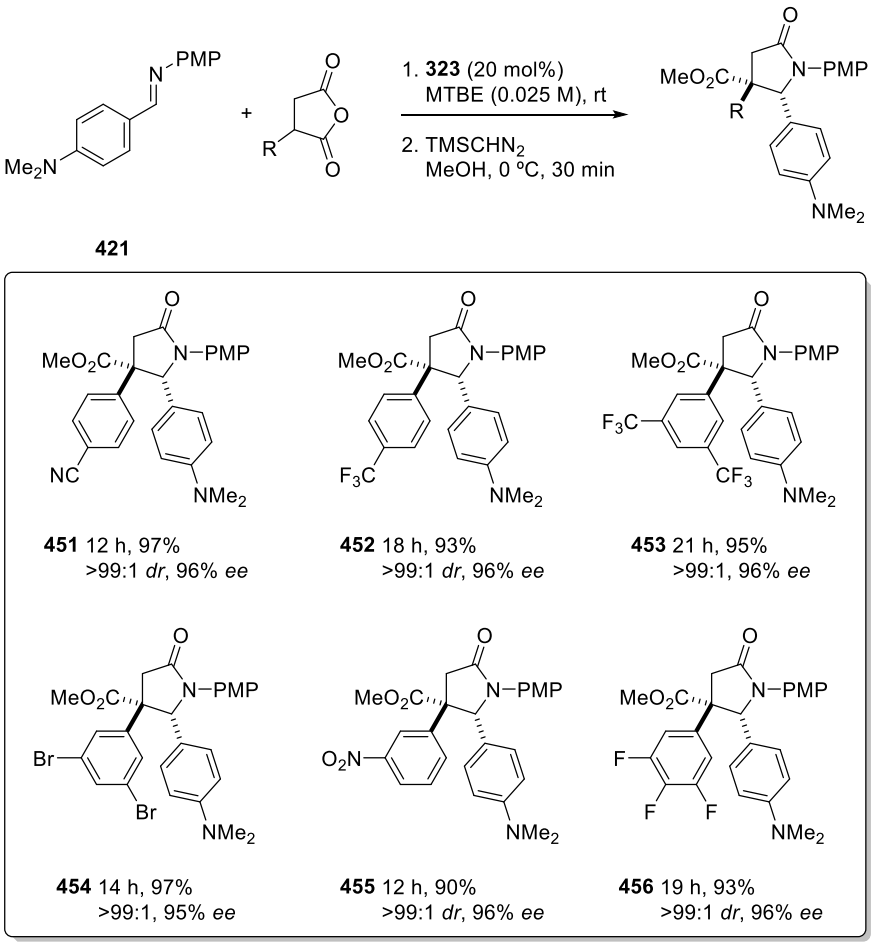



**Figure 4.1** Anhydrides provided by Mr. Bruce Lockett-Walters.

We then evaluated the anhydrides with imine **421** under the optimal reaction conditions previously established (Table 4.3).




**Scheme 4.9** Expanding the scope: the anhydride component.

Regardless of the electronic and steric characteristics of the anhydrides, all lactams (**453-458**) were formed in excellent yields, as single diastereomers and with excellent enantiocontrol.

The relative configuration was assigned based on a NOE experiment. When the δ-hydrogen of the lactam ring was irradiated, it showed an interaction with the *ortho*-hydrogens from the aromatic ring in the β-position of the lactam (Figure 4.2).

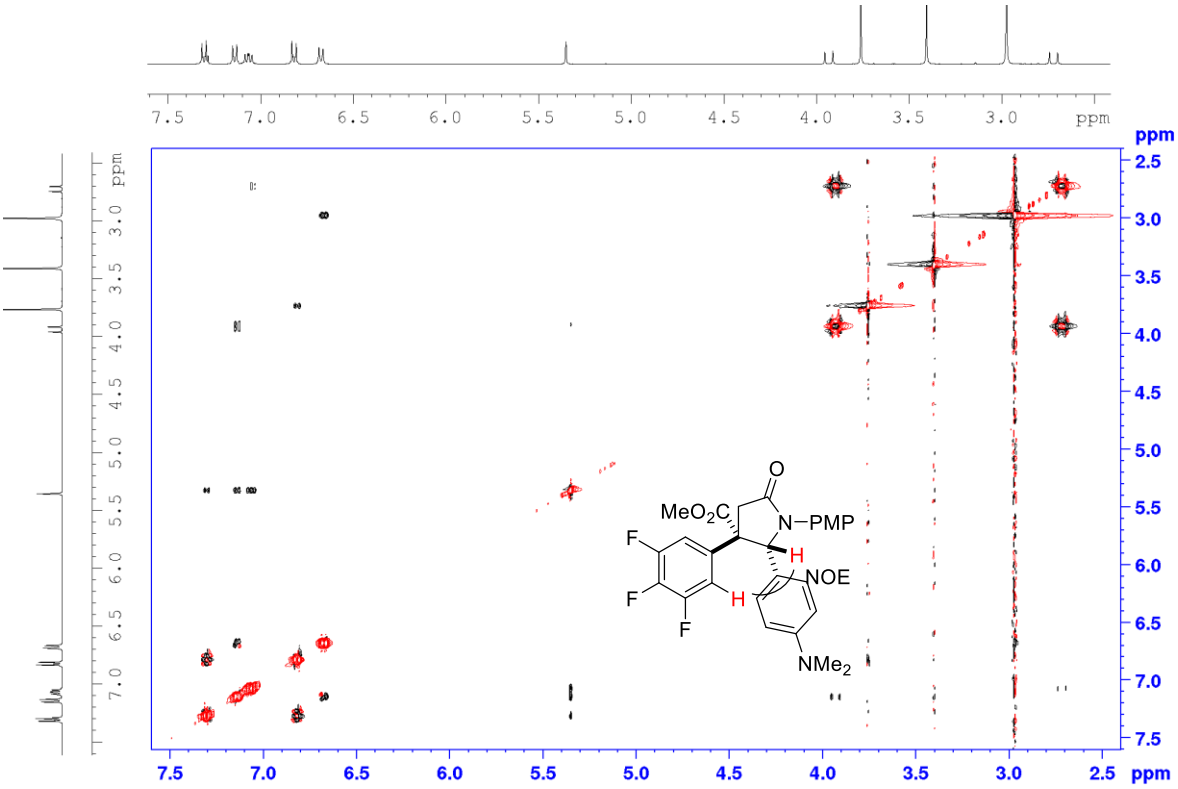



**Figure 4.2** NOE experiment of compound **456**.

## 4.4 Conclusions

This work details the development of the first catalytic enantioselective cycloaddition reaction between imines and activated arylsuccinic anhydrides. This methodology provides access to highly enantioselective *N*-protected γ-lactams with two contiguous stereocentres (one of them quaternary). The furnished lactams possess the same substitution pattern as the biologically active lactam **6**.

In all of the cases lactams are formed as a single diastereomer. The basicity of the imines has an important role on the enantiocontrol; imines bearing electron-donating substituents are better tolerated than those with electron-withdrawing groups. Bulky substituents on the imine are not well tolerated by the catalyst. The anhydride component do not have a significant effect on the enantiocontrol of the catalyst than the imine component.

A DFT based computational study is being carried out to clarify the mechanism of the reaction and to explain the origin of the stereochemistry observed.

X-ray diffraction pattern analysis is ongoing to determine the absolute configuration of the lactams afforded.

# 5 Experimental procedure and data

## 5.1 General information

Proton Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker DPX 400 MHz and Bruker Avance II 600MHz spectrometers, using as solvent CDCl3, DMSO-d6 or $D_2O$ and referenced relative to residual $CHCl_3$ ($\delta$ = 7.26 ppm) DMSO ($\delta$ = 2.50 ppm) or $H_2O$ ($\delta$ = 4.79 ppm). Chemical shifts are reported in ppm and coupling constants (J) in Hertz. Carbon NMR spectra were recorded on the same instruments (100.6 MHz and 150.9 MHz respectively) with total proton decoupling. Fluorine NMR spectra were recorded on the Bruker DPX400 machine (376.5 MHz). HSQC, HMBC, TOCSY NOE and ROESY NMR experiments were used to aid assignment of NMR peaks when required. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. ESI mass spectra were acquired using a Waters Micromass LCT- time of flight mass spectrometer (TOF), interfaced to a Waters 2690 HPLC. The instrument was operated in positive or negative mode as required. EI mass spectra were acquired using a GCT Premier Micromass time of flight mass spectrometer (TOF). The instrument was operated in positive mode. Chemical Ionization (CI) mass spectra were determined using a GCT Premier Micromass mass spectrometer in CI mode utilising methane as the ionisation gas. APCI experiments were carried out on a Bruker microTOF-Q III spectrometer interfaced to a Dionex UltiMate 3000 LC or direct insertion probe. The instrument was operated in positive or negative mode as required. Agilent tuning mix APCI-TOF was used to calibrate the system. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualized by UV irradiation and $KMnO_4$ staining. Optical rotation measurements are quoted in units of $10^{-1}$deg $cm^2g^{-1}$. Toluene was distilled over calcium hydride and stored under argon. Anhydrous acetonitrile ($CH_3CN$), dichloromethane ($CH_2Cl_2$), tetrahydrofuran (THF) and diethyl ether ($Et_2O$) were obtained by using Pure Solv MD-4EN Solvent Purification System. Methanol (MeOH) and isopropyl alcohol (i-PrOH) were dried over activated 3Å molecular sieves. Commercially available anhydrous t-butyl methyl ether (MTBE) and EtOH were used. Analytical CSP-HPLC was performed on Daicel Chiralpak, AD, AD-H, IA, or Chiralcel OD, OD-H, OJ-H (4.6 mm x 25 cm) columns or ACQUITY UPC2 on chiral Trefoil AMY1, CEL1, CEL2 (2,5 µm, 3.0 x 150mm) columns.

## 5.2 Experimental data for Chapter 2

### 5.2.1 General procedures

**General procedure A: synthesis of anhydrides**

An oven-dried round-bottomed flask was charged with the corresponding di-carboxylic acid (1 eq) and dissolved in freshly distilled acetyl chloride. The reaction was heated at 60 ºC for 16 hours. After completion, the solvent was removed and the solid obtained was triturated in diethyl ether to afford the corresponding anhydride.

**General procedure B: synthesis of *N*-mesylimines**

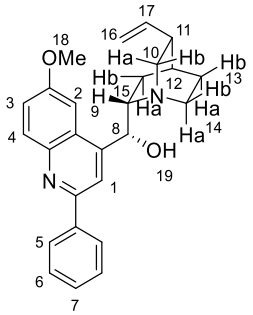
An oven-dried round-bottomed flask was charged with methanesulfonamide (1 equiv.) fitted with a septum and placed under an atmosphere of argon. Dry $CH_2Cl_2$ was then added via syringe followed by $NEt_3$ (3 equiv.) and the appropriate aldehyde (1 equiv.). The resulting solution was cooled to 0 ºC. $TiCl_4$ (0.5 equiv.) was then added drop-wise to the solution at 0 ºC and it was allowed to stir for 1 h at this temperature. The reaction mixture was filtered through celite and washed with $CH_2Cl_2$. The filtrate was concentrated in vacuo and the resulting solid was suspended in toluene and then filtered to remove $NEt_3$.HCl. The filtrate was then concentrated in vacuo to afford the desired imine which was purified by recrystallisation.

**General procedure C: catalytic reaction between homophthalic anhydride and imines**

An oven dried 10 mL reaction vessel containing a stirring bar was charged with anhydride 4 (39.9 mg, 0.25 mmol) then placed under an argon atmosphere. Anhydrous MTBE (2.5 mL) was added via syringe and the reaction mixture was then cooled to -30 °C. The appropriate imine (0.25 mmol) was added followed by catalyst 30 (0.01 mmol, 5 mol%) and the reaction was stirred at -30 °C until completion. The conversion of the reaction was determined by $^1$H NMR spectroscopic analysis using p-iodoanisole (28.8 mg, 0.12 mmol) as an internal standard. To the reaction mixture containing the diastereomeric mixture of carboxylic acid lactam products, anhydrous EtOH (220 μL), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150 μL, 0.30 mmol) were added via syringe and the reaction was allowed to stir for exactly 30 min at -30 ºC. The solvent was then removed *in vacuo* at room temperature and the crude mixture of diastereomeric esters was purified immediately by column chromatography.

### 5.2.2 Synthesis of catalysts

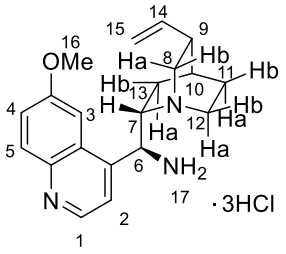
**(*R*)-(6-Methoxy-2-phenylquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanol (238)**




To a suspension of quinine (**237**, 3.88 g, 11.9 mmol) in anhydrous MTBE (75 mL) placed at -10 ºC was added phenyl lithium (1.8 M in THF, 20 mL, 35.7 mmol) *via* syringe. The mixture was stirred for 30 min at that temperature and then warm at room temperature for 16 h. The mixture was placed at 0 ºC and acetic acid (15 mL) was added, followed by water (50 mL) and ethyl acetate (50 mL). The reaction was warmed at room temperature and iodine was added until a brown colouration persisted. An aqueous solution (50 mL) of sodium thiosulfate (3.00 g) was added, followed by an aqueous ammonia (35 %, 30 mL). The mixture was stirred for 10 min at room temperature. The organic phase was washed with brine and the aqueous phase extracted with dicloromethane. The organic fractions were dried over $MgSO_4$ and the solvent removed in *vacuo*. The crude oil was purified by flash column chromatography to furnish 2.50 g of a white solid (2.50 g, 6.24 mmol, 52 %). M.p. 157-160 ºC (lit.[155] m. p. 151 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.07 (1 H, d, *J* 9.2, H-4), 7.97 (2 H, m, H-5), 7.85 (1 H, s, H-1), 7.45-7.37 (3 H, m, H-6 and H-7), 7.33 (1 H, dd, *J* 9.2, 2.2, H-3), 7.17 (1 H, d, *J* 2.2, H-2), 5.74 (1 H, ddd, *J* 17.2, 10.1, 7.7, H-16), 5.42 (1 H, d, *J* 2.9, H-8), 4.94 (2 H, dd, *J* 17.2, 10.1, H-17), 3.90 (3 H, s, H-18), 3.50-3.38 (1 H, m, H-10b), 3.14-3.02 (2 H, m, H-9 and H-14a), 2.69-2.57 (2 H, m, H-14b and H-10a), 2.31-2.21 (1 H, m, H-11), 1.86-1.67 (3 H, m, H-13b, H-15b and H-12), 1.59-1.42 (2 H, m, H-13a, H-15a).

**(*S*)-(6-methoxy-2-phenylquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanamine·3HCl (239·3HCl)**

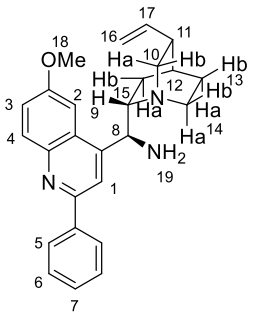



A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with quinine (**237**, 79, 5.00 g, 15.4 mmol), triphenylphosphine (4.85 g, 2.42 mmol) and dry THF (70 mL). Diisopropyl azodicarboxylate (DIAD) (3.6 mL, 18.5 mmol) was added via syringe at 0 °C under an argon atmosphere and the reaction mixture was stirred at 0 °C for 30 min. A solution of diphenylphosphoryl azide (DPPA, 4.0 mL, 18.5 mmol) in dry THF (32 mL) was then added dropwise. The reaction mixture was allowed to stir for 12 h at room temperature and then heated at 50 °C for an additional 2 h. After cooling the reaction mixture to room temperature, triphenylphosphine (5.30 g, 20.0 mmol) was added portionwise. The reaction was then heated at 50 °C for 2 h after which time, the resultant mixture was cooled to room temperature, diluted with water (5 mL) and allowed to stir for 4 h. The organic volatiles were removed under reduced pressure and the residue was dissolved in an aqueous solution of HCl (2.0 N, 20 mL). The aqueous layer was washed with CH2Cl2 (3 x 20 mL) and concentrated in vacuo to afford **239·3HCl** as a yellow solid (5.53 g, 12.8 mmol, 83%). M.p. 218-222 °C, (lit.[156] m.p. 220-222 °C).

**$\delta_H$ (400 MHz, D2O)*** 9.03 (1 H, d, J 5.8, H-1), 8.27 (1 H, d, J 9.4, H-5), 8.12 (1 H, d, J 5.8, H-2), 7.96 (1 H, dd, J 2.4, 9.4 H-4), 7.83 (1 H, bs, H-3), 5.90 (1 H, ddd, J 6.8, 10.5, 17.2, H-14), 5.53 (1 H, d, J 10.6, H-6), 5.32-5.18 (2 H, m, H-15), 4.34-4.22 (1 H, m, H-7), 4.11 (3 H, s, H-16), 4.04-3.92 (1 H, m, H-12a), 3.85 (1 H, dd, J 10.6, 13.3, H-8b), 3.59-3.45 (2 H, m, H-12b and H-8a), 3.02-2.93 (1 H, m, H-9), 2.17-2.00 (3 H, m, H-11b, H-11a and H-10), 1.96-1.84 (1 H, m, H-13b), 1.18 (1 H, dd, J 7.2, 14.2, H-13a).

* The protic signal (H-17) is not visible in $D_2O$.

**(*S*)-(6-methoxy-2-phenylquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanamine (240)**

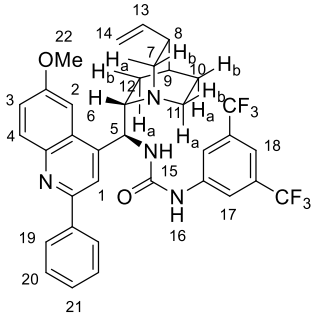



To a solution of **238** (2.40 g, 5.99 mmol) and triphenylphosphine (1.89 g, 7.19 mmol) in dry THF (50 mL), at 0 ºC, was added diisopropyl azodicarboxylate (DIAD) (1.41 mL, 7.19 mmol) dropwise *via* syringe. 30 min later, diphenylphosphoryl azide (DPPA) (1.55 mL, 7.19 mmol) was added dropwise *via* syringe and the mixture was warmed at room temperature and stirred for 16 h, then heated at 50 ºC for 2 h. At the same temperature, triphenylphosphine (1.89 g, 7.19 mmol) was added and stirred for 2 additional hours. The reaction was cooled down at room temperature and water (10 mL) was added and stirred for 4 h. THF was removed *in vacuo* and the residue was treated with HCl (2 N, 20.0 mL) and washed with $CH_2Cl_2$. The aqueous layer was basify using 1.0 N NaOH and extracted with $CH_2Cl_2$. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to afford **240** as a pale orange oil (2.04 g, 5.21 mmol, 87%).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.16-8.06 (3 H, m, H-5 and H-4), 7.97 (1 H, bs, H-1), 7.83-7.60 (1 H, m, H-2), 7.53-7.46 (2 H, m, H-6), 7.46-7.33 (2 H, m, H-7 and H-3), 5.78 (1 H, ddd, *J* 17.7, 10.4, 7.8, H-16), 5.02-4.91 (2 H, m, H-17), 4.71-4.60 (1 H, m, H-8), 3.96 (3 H, s, H-18), 3.34-3.05 (3 H, m, H-14a, H-10b and H-9), 2.88-2.75 (2 H, m, H-14b and H-10a), 2.35-2.23 (1 H, m, H-11), 2.14-1.87 (2 H, m, H-19), 1.71-1.52 (3 H, m, H-13b, H-13a and H-12), 1.48-1.37 (1 H, m, H-15b), 0.92-0.78 (1 H, m, H-15a).

**HRMS (*m/z* – ESI)** Found: 400.2382 $(M+H)^+$ $C_{26}H_{30}N_3O$ Requires: 400.2389.

**1-(3,5-*Bis*(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxy-2-phenylquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)urea (221)**



A round-bottomed flask containing a stirring bar under argon atmosphere was charged with **240** (1 g, 2.5 mmol) followed by dry $CH_2Cl_2$ (20 mL) and the reaction mixture was cooled in an icebath. 3,5-bis-(Trifluoromethyl)phenyl isocyanate (**245**, 520 μL, 3.00 mmol) was added via syringe and the reaction was stirred at 0 ºC to room temperature for 16 h. The solvent was removed in vacuo and the crude residue was purified by flash chromatography ($CH_2Cl_2$:MeOH 95:5) to yield **221** as a white solid (1.2 g, 1.82 mmol, 73%), M.p. 152-153 °C. $[\alpha]_D^{20}$ +14.8 (c 0.6 $CHCl_3$).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.79 (1 H, br. s, H-18), 8.19-8.14 (3 H, m, H-19 and H-4), 7. 93 (1 H, s, H-18), 7.78-7.75 (3 H, m, H-17 and H-1), 7.53-7.43 (4 H, m, H-21, H-20 and H-3), 7.34 (1 H, br. s, H-15), 6.98 (1 H, br. s, H-5), 5.83 (1 H, br. s, H-15), 5.64-5.53 (1 H, m, H-13), 4.99-4.96 (2 H, m, H-14), 4.00 (3 H, s, H-22), 3.83-3.64 (2 H, m, H-11a and H-6), 3.21 (1 H, m, H-7b), 2.81-2.72 (2 H, m, H-11b and H-7a), 2.42 (1 H, m, H-8), 1.84-1.77 (4 H, m, H-12b, H-10b, H-10a and H-9), 1.12 (1 H, br. s, H-12a).

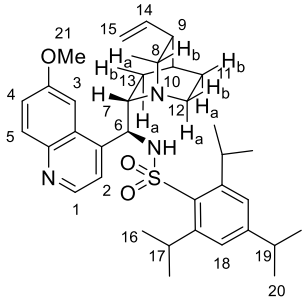
**$\delta_C$ (100 MHz, $CDCl_3$)** 158.4 (q), 154.7 (q), 154.6 (q), 145.0 (q), 143.7 (q), 140.8 (q), 139.2, 139.1 (q), 132.2, 131.7 (q, $J_{C-F}$ 33), 129.2, 128.8, 127.3, 127.2, 123.3 (q, $J_{C-F}$ 272.9), 121.7, 117.8, 116.7, 115.4, 115.3, 101.5, 60.2, 55.8, 54.8, 49.6, 41.2, 37.4, 29.6, 26.7, 26.1

**$\delta_F$ (376 MHz, $CDCl_3$)** -63.1.

**$\nu_{max}$ ($cm^{-1}$)** 2988, 1670, 1630, 1555, 1469, 1349, 1250, 1171, 1009, 876.

**HRMS (*m/z* - ESI)** [M+H]+ found 655.2498. $C_{35}H_{33}N_4O_2F_6$ requires 655.2508.

**2,4,6-Triisopropyl-*N*-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)benzenesulfonamide (243)**



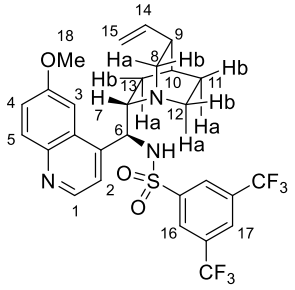
To a suspension of **239** (0.300 g, 0.928 mmol) in dry $CH_2Cl_2$ (12.5 mL), was added freshly distilled triethylamine (0.711 mL, 5.10 mmol). Once the suspension got into solution, the flask was placed in an ice bath at 0 ºC and 2,4,6-triisopropylbenzenesulfonyl chloride (**241**, 0.281 g, 0.928 mmol) in dry $CH_2Cl_2$ (mL) was added dropwise. The mixture was allowed to stir at room temperature for 16 h. The solvent was removed in *vacuo* and the crude purified by column chromatography, affording **243** as a white solid (0.400 g, 0.677 mmol, 73%). M.p. 111-114 ºC (lit.[157] 115-118 ºC).

$^1$H-NMR showed the presence of two rotamers in a 78:22 ratio.

Major romater:

$\delta_H$ (400 MHz, DMSO) 8.51 (1 H, d, *J* 4.3, H-1), 7.92 (1 H, d, *J* 9.7, H-5), 7.49-7.39 (2 H, m, H-4 and H-3), 7.37 (1 H, d, *J* 4.4, H-2), 6.97 (2 H, s, H-18), 5.77-5.65 (1 H, m, H-14), 5.15 (1 H, d, *J* 10.5, H-6), 4.99-4.80 (2 H, m, H-15), 3.93 (3 H, s, H-21), 3.90-3.85 (3 H, m, H-17 and H-9), 3.12-3.00 (1 H, m, H-8a), 2.99-2.74 (3 H, m, H-20, H-12a and H-7), 2.68-2.61 (1 H, m, H-8b), 2.50-2.40 (1 H, m, H-12b), 2.25-2.15 (1 H, m, H-10), 1.55-1.30 (3 H, m, H-13a, H-11b and H-11a), 1.20-0.86 (18 H, m, H-20 and H-16), 0.76-0.70 (1 H, m, H-13b).

**_N_-((_S_)-(6-methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)-3-5-_bis_(trifluoromethyl)benzenesulfonamide (244)**



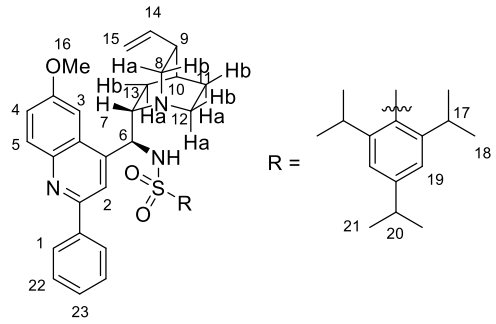

To a suspension of **239** (0.300 g, 0.928 mmol) in dry $CH_2Cl_2$ (12.5 mL), was added freshly distilled triethylamine (0.711 mL, 5.10 mmol). Once the suspension got into solution, the flask was placed in an ice bath at 0 ºC and 3,5-*bis*(trifluoromethyl)benzenesulfonyl chloride (**242**, 0.290 g, 0.928 mmol) in dry $CH_2Cl_2$ (mL) was added dropwise. The mixture was allowed to stir at room temperature for 16 h. The solvent was removed in *vacuo* and the crude purified by column chromatography, furnishing **245** as a white solid (0.395 g, 0.659 mmol, 71%). M.p. 148-150 °C (lit.[158] 155-156 ºC).

$^1$H-NMR showed the presence of two rotamers in a 1:1 ratio.

Both rotamers are reported:

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.62 (1 H, d, *J* 4.5, H-1), 8.39 (1 H, d, *J* 4.5, H-1), 7.95 (1 H, d, *J* 9.0, H-5), 7.81 (1 H, d, *J* 9.0, H-5), 7.76 (2 H, s, H-16), 7.73 (1 H, s, H-17), 7.68 (2 H, s, H-16), 7.47 (1 H, s, H-17), 7.49-7.43 (2 H, m, H-4 and H-3), 7.26 (1 H, d, *J* 4.5, H-2), 7.18 (1 H, dd, *J* 9.0,2.2, H-4), 7.07 (1 H, d, *J* 4.5, H-2), 5.71 (1 H, ddd, *J* 17.3, 10.5, 7.5, H-14), 5.63 (1 H, ddd, *J* 17.3, 10.5, 7.5, H-14), 5.14 (1 H, d, *J* 10.7, H-6), 5.05-4.89 (2 H, m, H-15), 4.53 (1 H, d, *J* 10.7, H-6), 4.05 (3 H, s, H-18), 3.84 (3 H, s, H-18), 3.40 (1 H, dd, *J* 17.7, 9.4, H-7), 3.36-3.27 (2 H, m, H-8b), 3.16-3.03 (2 H, m, H-12a), 2.92 (1 H, dd, *J* 17.7, 9.4, H-7), 2.87-2.71 (4 H, m, H-12b and H-8a), 2.40-2.33 (2 H, m, H-9), 1.80-1.62 (6 H, m, H-11b, H-11a and H-10), 1.44-1.34 (2 H, m, H-13b), 0.98 (1 H, dd, *J* 13.7, 7.5, H-13a), 0.86 (1 H, dd, *J* 13.7, 7.5, H-13a).

**2,4,6-triisopropyl-*N*-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)benzenesulfonamide (293)**



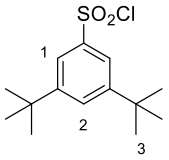

To a suspension of **240** (0.300 g, 0.588 mmol) in dry $CH_2Cl_2$ (12.5 mL), was added freshly distilled triethylamine (0.450 mL, 3.23 mmol). Once the suspension got into solution, the flask was placed in an ice bath at 0 ºC and 2,4,6-triisopropylbenzenesulfonyl chloride (0.178 g, 0.588 mmol) in dry $CH_2Cl_2$ (mL) was added dropwise. The mixture was allowed to stir at room temperature for 16 h. The solvent was removed in *vacuo* and the crude purified by column chromatography, obtaining **293** as a white solid (0.237 g, 0.364 mmol, 62%). $^1$H-NMR showed the presence of two rotamers in a 89:11 ratio.

Major rotamer:

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.04 (1 H, d, J 9.2, H-5), 7.67 (2 H, d, J 6.9, H-1), 7.62 (1 H, s, H-2), 7.51 (1 H, s, H-3), 7.41-7.37 (4 H, m, H-23, H-22 and H-4), 6.87 (2 H, H-19), 5.67-5.58 (1 H, m, H-14), 5.43 (1 H, d, J 10.5, H-6), 4.94-4.87 (2 H, m, H-15), 4.02 (3 H, s, H-16), 3.83-3.74 (2 H, m, H-17), 3.30-3.24 (2 H, m, H-8a and H-7), 2.85-2.72 (2 H, m, H-20 and H-12a), 2.68-2.60 (2 H, m, H-9 and H-8b), 2.34-2.24 (1 H, m, H-12b), 1.71-1.61 (3 H, m, H-13a, H-11b and H-11a), 1.29-1.23 (2 H, m, H-13b and H-10), 1.21-0.98 (12 H, m, H-18), 0.74 (6 H, d, J 6.6, H-21).

**HRMS (*m/z* – ESI)** $[M+H]^+$ Found: 666.3730. $C_{41}H_{52}N_3O_3S$ Requires: 666.3729.

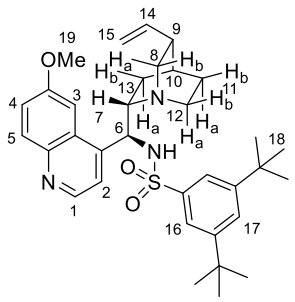
**3,5-Di-*tert*-butylbenzenesuflonyl chloride (291)**




1,3,5-Tri-*tert*-butylbenzene (**290**) (0.739 g, 3.00 mmol) was dissolved in dry $CH_2Cl_2$ (30 mL) and placed in an ice bath. Chlorosulfonic acid (0.874 mL, 13.2 mmol) was added dropwise and the mixture was stirred at room temperature for 4 h. The reaction was quenched with a saturated solution of $NaHCO_3$ and extracted with $CH_2Cl_2$. The organic phase was dried over $MgSO_4$ and the solvent removed under reduce pressure. The crude was purified by column chromatography to afford compound **291** as a white solid (0.806 g, 2.79 mmol, 93%). M.p. 87-89 ºC (lit.[159] 81-83 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 7.83 (2 H, d, *J* 1.8, H-1), 7.76 (1 H, t, *J* 1.8, H-2), 1.36 (18 H, s, H-3).

**3,5-Di-*tert*-butyl-*N*-((S)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)benzenesulfonamide (292)**




To a suspension of **239** (0.300 g, 0.928 mmol) in dry $CH_2Cl_2$ (12.5 mL), was added freshly distilled triethylamine (0.711 mL, 5.10 mmol). Once the suspension got into solution, the flask was placed in an ice bath at 0 ºC and 3,5-*bis*-*tert*-butylbenzenesulfonyl chloride (**292**, 0.268 g, 0.928 mmol) in dry $CH_2Cl_2$ (mL) was added dropwise. The mixture was allowed to stir at room temperature for 16 h. The solvent was removed in *vacuo* and the crude purified by column chromatography, obtaining **292** as a white solid (0.406 g, 0.705 mmol, 71%). M.p. 90-92 °C.

$^1$H-NMR showed the presence of two rotamers in a 3:2 ratio.

Major rotamer

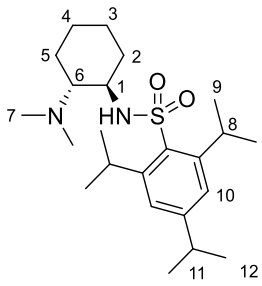
**$\delta_H$ (400 MHz, $CDCl_3$** 8.42 (1 H, d, *J* 4.5, H-1), 7.94 (1 H, d, *J* 9.4, H-5), 7.46 (1 H, d, *J* 2.5, H-3), 7.38 (1 H, d, *J* 9.4, 2.5, H-4), 7.34 (1 H, d, *J* 1.7, H-17), 7.31 (2 H, d, *J* 1.7, H-16), 7.21 (1 H, d, *J* 4.5, H-2), 5.66 (1 H, ddd, *J* 17.7, 10.4, 7.3, H-14), 5.05 (1 H, d, *J* 10.4, H-6), 4.99-4.90 (2 H, m, H-15), 4.01 (3 H, s, H-19), 3.29-3.20 (1 H, m, H-8a), 3.06-2.97 (1 H, m, H-12a), 2.81-2.61 (3 H, m, H-12b, H-8b and H-7), 2.33-2.24 (1 H, m, H-9), 1.72-1.51 (2 H, m, H-13b and H-13a), 1.30-1.19 (1 H, m, H-11b), 1.14 (18 H, s, H-18), 0.92-0.82 (1 H, m, H-11a).

**$\delta_C$ (100 MHz, $CDCl_3$)** 157.9 (q), 151.4 (q), 147.2, 144.2 (q), 142.8 (q), 141.1, 138.9 (q), 131.8, 128.7 (q), 126.9, 121.4, 121.0, 120.3, 114.7, 101.4, 61.6, 55.7 (x2), 52.8, 40.3, 39.5, 34.8 (q), 31.0, 27.9, 27.3, 25.0.

**$\nu_{max}$ ($cm^{-1}$)** 2954, 2874, 1622, 1509, 1475, 1308, 1242, 1159, 853.

**HRMS (*m/z* - ESI)** $[M-H]^-$ Found 574.3105. $C_{34}H_{44}N_3O_3S$ Requires 574.3108.

***N*-((1*R*,2*R*)-2-(Dimethylamino)cyclohexyl)-2,4,6-triisopropylbenzenesulfonamide (301)**




To a solution of (1*R*,2*R*)-cyclohexanediamine (**299**, 0.228 g, 2.00 mmol) and triethylamine (0.278 mL, 2.00 mmol) in dichloromethane (15.0 mL) was added 2,4,6-triisopropylbenzenesulfonyl chloride (**241**, 0.606 g, 2.00 mmol) in dichloromethane (5.00 mL) at room temperature. The reaction was stirred at room temperature. After 1 hour, 1.0 M NaOH (aq) was added and the mixture was extracted with $CH_2Cl_2$. The organic phase was dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The residue was dissolve in THF (20.0 mL) and NaH (0.120 g, 2.00 mmol) followed by MeI (0.311 mL, 5.00 mmol)

were added at room temperature. The mixture was heated at the reflux temperature for 1 hour. The suspension was cooled at room temperature and $H_2O$ was added to quench the unreacted NaH. The mixture was extracted with $CH_2Cl_2$ and the organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified on silica gel column chromatography to afford catalyst **301** as a white solid (0.556 g, 1.36 mmol, 68%). M.p. 54-55 °C.

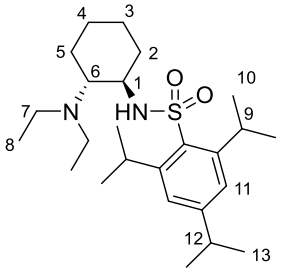
**$\delta_H$ (400 MHz, $CDCl_3$)** 7.17 (2 H, s, H-10), 4.32-4.21 (2 H, m, H-8), 3.14-3.05 (1 H, m, H-1), 2.95-2.85 (1 H, m, H-11), 2.29-2.12 (2 H, m, H-6 and H-2eq), 2.04 (6 H, s, H-7), 1.85-1.72 (2 H, m, H-5eq and H-3eq), 1.68-1.54 (1 H, m, H-2eq), 1.34-1.03 (22 H, m, H-12, H-9, H-5a, H-4a, H-3a and H-2a).

**$\delta_C$ (100 MHz, $CDCl_3$)** 152.4 (q), 149.9 (q), 133.9 (q), 123.7, 66.1, 53.9, 39.5, 34.1, 33.1, 29.7, 25.2 (x2), 24.5, 24.3, 23.7, 23.6, 21.1.

**$\nu_{max}$ ($cm^{-1}$)** 2930, 1602, 1451, 1331, 1267, 1035, 889, 555.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 409.2885. $C_{23}H_{41}N_2O_2S$ Requires 409.2883.

***N*-((1*R*,2*R*)-2-(diethylamino)cyclohexyl)-2,4,6-triisopropylbenzenesulfonamide (302)**




To a solution of (1*R*,2*R*)-cyclohexanediamine (**299**, 0.300 g, 2.63 mmol) and triethylamine (0.366 mL, 2.63 mmol) in dichloromethane (20.0 mL) was added 2,4,6-triisopropylbenzenesulfonyl chloride (**241**, 0.796 g, 2.63 mmol) in dichloromethane (6.00 mL) at room temperature. The reaction was stirred at room temperature. After 1 hour, 1.0 M NaOH (aq) was added and the mixture was extracted with $CH_2Cl_2$. The organic phase was dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The residue was dissolve in THF (26.0 mL) and NaH (0.158 g, 6.58 mmol) followed by EtI (0.528 mL, 6.58 mmol) were added at room temperature. The mixture was heated at the reflux temperature for 1 hour. The suspension was cooled at room temperature and $H_2O$ was added to quench the unreacted

NaH. The mixture was extracted with $CH_2Cl_2$ and the organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified on silica gel column chromatography to afford catalyst **302** as a white solid (0.724 g, 1.66 mmol, 63%). M.p. 60-62 °C.

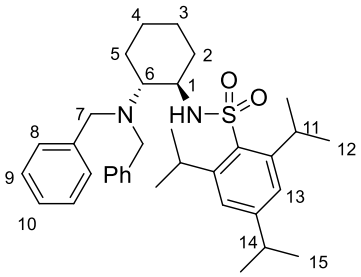
**$\delta_H$ (400 MHz, $CDCl_3$)** 7.15 (2 H, s, H-11), 6.15 (1 H, br. s, N-H), 4.37-4.26 (2 H, m, H-9), 3.39-3.29 (1 H, m, H-1), 2.96-2.85 (1 H. m, H-12), 2.69-2.55 (2 H, m, H-7), 2.39-2.23 (3 H, m, H-7 and H-6), 2.06-1.96 (1 H, m, H-2eq), 1.88-1.71 (2 H, m, H-5eq and H-3eq), 1.66-1.49 (1 H, m, H-4eq), 1.33-1.08 (21 H, m, H-13, H-10, H-5a, H-4a and H-3a), 1.06-0.89 (7 H, m, H-8 and H-2a).

**$\delta_C$ (100 MHz, $CDCl_3$)** 152.3 (q), 149.8 (q), 134.8 (q), 123.6, 62.3, 53.9, 42.8, 34.1, 32.6, 29.5, 25.6, 25.0, 24.5, 24.2, 23.6, 23.4, 14.2.

**$\nu_{max}$ ($cm^{-1}$)** 2956, 2928, 1602, 1448, 1325, 1298, 1147, 87, 656.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 437.320267. $C_{25}H_{45}N_2O_2S$ Requires 437.319626.

***N*-((1*R*,2*R*)-2-(Dibenzylamino)cyclohexyl)-2,4,6-triisopropylbenzenesulfonamide (303)**




To a solution of (1*R*,2*R*)-cyclohexanediamine (**299**, 0.300 g, 2.63 mmol) and triethylamine (0.366 mL, 2.63 mmol) in dichloromethane (20.0 mL) was added 2,4,6-triisopropylbenzenesulfonyl chloride (**241**, 0.796 g, 2.63 mmol) in dichloromethane (6.00 mL) at room temperature. The reaction was stirred at room temperature. After 1 hour, 1M NaOH (aq) was added and the mixture was extracted with $CH_2Cl_2$. The organic phase was dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The residue was dissolve in THF (26.0 mL) and NaH (0.158 g, 6.58 mmol) followed by benzyl bromide (0.779 mL, 6.58 mmol) were added at room temperature. The mixture was heated at the reflux temperature for 1 hour. The suspension was cooled at room temperature and $H_2O$ was added to quench

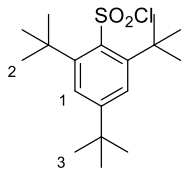
the unreacted NaH. The mixture was extracted with $CH_2Cl_2$ and the organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified on silica gel column chromatography to afford catalyst **303** as a white solid (0.885 g, 1.58 mmol, 60%). M.p. 109-111 ºC.

**$\delta_H$ (600 MHz, $CDCl_3$)** 7.32-7.13 (14 H, m, H-13, H-10, H-9 and H-7), 4.39 (2 H, s, H-7), 4.13-4.04 (2 H, m, H-11), 3.71-3.60 (1 H, m, H-1), 3.52 (1 H, d, *J* 13.4, H-7a), 3.04 (1 H, d, *J* 13.4, H-7b), 2.96-2.87 (1 H, m, H-14), 2.39-2.28 (1 H, m, H-6), 2.13-2.05 (1 H, m, H-2eq), 1.91-1.83 (1 H, m, H-5eq), 1.70-1.52 (2 H, m, H-4eq and H-3eq), 1.32-0.94 (22 H, m, H-15, H-12, H-5a, H-4a, H-3a and H-2a).

**$\delta_C$ (151 MHz, $CDCl_3$)** 152.9 (q), 151.1 (q), 140.9 (q), 138.6 (q), 132.7 (q), 128.4, 128.3, 128.2, 128.1, 127.4, 126.6, 124.1, 57.2, 53.4, 49.9, 34.1, 32.4, 30.0, 25.9, 25.1, 24.9, 24.3, 23.6.

**$\nu_{max}$ ($cm^{-1}$)** 2930, 1674, 1473, 1381, 1276, 1168, 681.

**2,4,6-Tri-*tert*-butylbenzenesulfonyl chloride (305)**

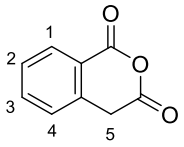



To a solution of **306** (0.360 g, 1.11 mmol) in dry diethyl ether (2.00 mL) at 0 ºC $^n$BuLi (0.532 mL, 2.5 M) was added dropwise. After the addition the reaction was stirred for 3 h at 0 ºC. $SO_2Cl_2$ (0.150 mL, 1.84 mmol) was added dropwise to the reaction and it was allowed to warm at room temperature. The reaction was stirred overnight at room temperature. Water was added and the organic phase was extracted with $CH_2Cl_2$ and dried over $MgSO_4$. The solvent was removed under reduce pressure and the product was purified by column chromatography to furnish compound **305** as a white solid (0.150 g, 0.44 mmol, 40%). M.p. 139-142 ºC (lit.[160] 142 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 7.45 (2 H, s, H-1), 1.59 (18 H, s, H-2), 1.29 (9 H, s, H-3).

### 5.2.3 Synthesis of anhydrides

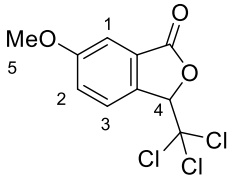
**Homophthalic anhydride (86)**




An oven-dried 100 mL round-bottom flask was charged with homophthalic acid (**222**, 3.00 g, 18.3 mmol) and acetic anhydride (20 mL). The solution was stirred at 80 ºC for 3 h. After cooling down at room temperature the solvent was removed and the crude was triturated with diethyl ether. The product was filtrated to obtain **86** as a white solid (2.46 g, 15.2 mmol, 83 %). M.p. 143-145 ºC (lit.[77] 144-145 ºC).

**$\delta_H$ (400 MHz, DMSO-$d_6$)** 8.05 (1 H, d, *J* 8.2, H-1), 7.75 (1 H, app. t, H-3), 7.52 (1 H, app. t., H-2), 7.44 (1 H, d, *J* 7.8, H-4), 4.27 (2 H, s, H-5).

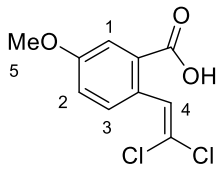
**6-Methoxy-3-(trichloromethyl)isobenzofuran-1(3*H*)-one (285)**




To a 25 mL round-bottomed flask containing 3-Methoxybenzoic acid (**283**, 5.00 g, 33.1 mmol) with a drying tube ($CaCl_2$) attached, chloral hydrate (**284**, 5.47 g, 33.1 mmol) was added. Concentrated $H_2SO_4$ (25 mL) was added and the mixture was stirred at room temperature for 24 h. The mixture was poured onto ice and the precipitated formed was isolated by filtration and recrystallised from ethanol. The product was isolated as a white solid (5.68 g, 20.2 mmol, 61%). M.p. 135-137 ºC (lit.[77] 136-137 ºC).

**$\delta_H$ (400 MHz, DMSO-$d_6$)** 7.85 (1 H, d, *J* 8.8, H-3), 7.45-7.37 (2 H, m, H-2 and H-1), 6.50 (1 H, s, H-4), 3.87 (3 H, s, H-5).

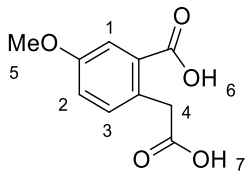
**2-(2,2-Dichlorovinyl)-5-methoxybenzoic acid (286)**




Compound (**285**, 3.00 g, 11.1 mmol) was placed in a 100 mL round-bottomed flask and dissolved in glacial acetic acid (33 mL). Zinc dust (2.90 g, 44.4 mmol) was added portionwise over a period of 30 min. The mixture was stirred at room temperature for further 30 min and then it was placed at reflux for 1 h. The suspension was filtered hot over a pad of Celite and the filtrates were diluted with water. The precipitate formed was collected by filtration and purified by recrystallisation from EtOH/$H_2O$ to afford product **286** as a white solid (1.72 g, 6.99 mmol, 63%). M.p. 166-167 ºC (lit.[77] 167-168 ºC).

**$\delta_H$ (400 MHz, DMSO-$d_6$)** 7.48 (1 H, d, *J* 9.0, H-3), 7.43-7.37 (2 H, m, H-4 and H-1), 7.17 (1 H, dd, *J* 9.0, 2.9, H-2), 3.79 (3 H, s, H-5).

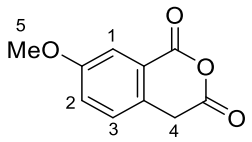
**2-(Carboxymethyl)-5-methoxybenzoic acid (287)**




An oven-dried 25 mL round-bottomed flask fitted with a drying tube ($CaCl_2$) was charged with concentrated $H_2SO_4$ (25 mL). Compound **286** (1.70 g, 6.99 mmol) was added portionwise over 20 min. Once the addition was completed, the reaction was stirred at room temperature for 2 h. and then it was poured onto ice. The precipitate was filtered and washed with cold water. Compound **287** was isolated as a white solid (1.03 g, 4.89 mmol, 70%). M.p. 173-175 ºC (lit.[77] 180.182 ºC).

**$\delta_H$ (400 MHz, DMSO-$d_6$)** 7.38 (1 H, d, *J* 2.6, H-1), 7.24 (1 H, d, *J* 8.3, H-3), 7.08 (1 H, dd, *J* 8.3, 2.6, H-2), 3.84 (2 H, s, H-4), 3.28 (3 H, s, H-5).

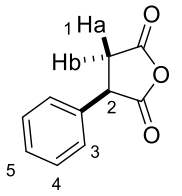
**7-Methoxyisochromane-1,3-dione**[77] **(162)**




Diacid **287** (1.00 g, 4.76 mmol) was placed in a 50 mL round-bottom flask with $CH_2Cl_2$ (18 mL). Freshly distilled $SOCl_2$ (1.03 mL, 14.1 mmol) was added and the reaction was heated at reflux until the complete dissolution of the acid. The reaction was cooled to room temperature and the solvent and the excess of $SOCl_2$ were removed *in vacuo*. The crude solid was triturated with diethyl ether and filtered to afford anhydride **162** as a yellow solid (0.758 g, 3.95 mmol, 83%). M.p. 141-144 ºC. (lit.[77] 144-145 ºC).

**$\delta_H$ (400 MHz, DMSO-$d_6$)** 7.48 (1 H, d, *J* 1.4, H-1), 7.38-7.30 (2 H, m, H-3 and H-2), 4.19 (2 H, s, H-4), 3.82 (3 H, s, H-5).

**Phenylsuccinic anhydride (96)**

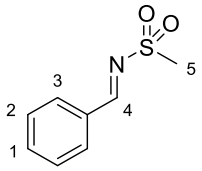



Prepared according to general procedure A, an oven-dried 100 mL round-bottom flask containing phenyl succinic acid (**280**, 4.00 g, 22.5 mmol) freshly acetyl chloride (30 mL) was added and was stirred at reflux. After 16 h acetyl chloride was removed and the product was triturated with diethyl ether. The product was filtered as a white solid (3.80 g, 21.6 mmol, 96 %). M.p. 52-54 ºC (lit.[161] 53-54 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 7.43-7.33 (3 H, m, H-5 and H-4), 7.28-7.22 (2 H, m, H-3), 4.33 (1 H, dd, *J* 10.2, 6.5, H-2), 3.45 (1 H, dd, *J* 18.7, 10.2, H-1a), 3.11 (1 H, dd, *J* 18.7, 6.5, H-1b).

### 5.2.4 Synthesis of imines

**(*E*)-*N*-Benzylidenemethanesulfonamide (228)**

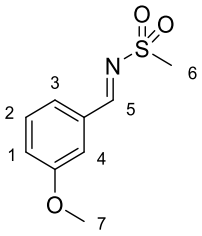



Prepared according to general procedure **B** using methanesulfonamide (**227**, 0.950 g, 10.0 mmol), $NEt_3$ (4.20 mL, 30.0 mmol), benzaldehyde (**83**, 1.20 mL, 10.0 mmol) in dry $CH_2Cl_2$ (25.0 mL) and $TiCl_4$ (0.547 mL, 0.50 mmol). The product was purified by recrystallization from $CH_2Cl_2$:hexane to afford **228** as an off-white solid (695 mg, 38%). NMR spectral data of **228** matches with the literature data.[162]

**$\delta_H$ (400 MHz, $CDCl_3$)** 9.04 (1 H, s, H-4), 7.96 (2 H, d, *J* 7.4, H-3), 7.68-7.64 (2 H, m, H-2), 7.55 (1 H, t, *J* 7.4, H-1), 3.14 (3 H, s, H-5).

**HRMS (*m/z* - ESI)** $[M+H]^+$ found 184.0430. $C_8H_{10}NO_2S$ requires 184.0432.

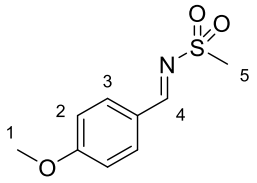
**(*E*)-*N*-(3-methoxybenzylidene) methanesulfonamide (229)**




Prepared according to general procedure **B** using methanesulfonamide (**227**, 0.780 g, 8.20 mmol), $NEt_3$ (3.40 mL, 25.0 mmol), *m*-anisaldehyde (**223**, 1.00 mL, 8.20 mmol) and $TiCl_4$ (0.442 mL, 4.10 mmol) in dry $CH_2Cl_2$ (25 mL). The product was purified by recrystallisation from $CH_2Cl_2$:hexane to afford **229** as a white solid (717 mg, 41%). Mp. 87-88 ºC (lit. 88-90 ºC) NMR spectral data of **229** matches with the literature data.

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.98 (1 H, s, H-5), 7.52-7.45 (2 H, m, H-4 and H-3), 7.42 (1 H, app. t, H-2), 7.19 (1 H, ddd, *J* 8.1, 2.6, 1.2, H-1), 3.83 (3 H, s, H-7), 3.13 (3 H, s, H-6).

**(*E*)-*N*-(4-methoxybenzylidene) methanesulfonamide (230)**

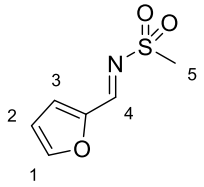


Prepared according to general procedure **B** using methanesulfonamide (**227**, 0.95 mg, 10.0 mmol), $NEt_3$ (4.20 mL, 30.0 mmol), 4-methoxybenzaldehyde (**224**, 1.20 mL, 10.0 mmol) and $TiCl_4$ (0.547 mL, 0.50 mmol) in dry $CH_2Cl_2$ (25.0 mL). The product was purified by recrystallisation from $CH_2Cl_2$:hexane to afford **230** as a pale yellow solid (0.852 mg, 40%). NMR spectral data of **230** matches with the literature data.[163]

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.91 (1 H, s, H-4), 7.90 (2 H, d, *J* 8.6, H-3), 7.00 (2 H, d, *J* 8.6, H-2), 3.89 (3 H, s, H-1), 3.09 (3 H, s, H-5)

**HRMS (*m/z* - ESI)** $[M+H]^+$ found 214.0538. $C_9H_{12}NO_3S$ requires 214.0538.

**(*E*)-*N*-(furan-2-ylmethylene) methanesulfonamide (231)**



Prepared according to general procedure **B** using methanesulfonamide (**227**, 1.51 g, 12.1 mmol), $NEt_3$ (5.10 mL, 36.3 mmol), furfuraldehyde (**94**, 1.00 mL, 12.1 mmol) and $TiCl_4$ (0.663 mL, 6.05 mmol) in dry $CH_2Cl_2$ (25.0 mL). The product was purified by recrystallisation from $CH_2Cl_2$:hexane to afford **231** as a white solid (0.819 mg, 39%). Mp. 93-94 ºC.

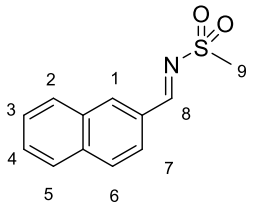
**$\delta_H$ (400 MHz, CDCl3)** 8.77 (1 H, s, H-4), 7.80-7.77 (1 H, m, H-1), 7.36 (1 H, d, *J* 3.6, H-3), 6.67 (1 H, dd, *J* 3.6, 1.8, H-2), 3.12 (3 H, s, H-5).

**$\delta_C$ (100MHz, CDCl3)** 156.7, 150.0 (q), 148.9, 125.2, 113.9, 40.5.

**$\nu_{max}$ ($cm^{-1}$)** 3029, 2916, 1648, 1543, 1474, 1341, 1141, 1030, 964, 813.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 174.0221 $C_6H_8NO_3S$ requires 174.0225.

**(*E*)-*N*-(Naphthalen-2-ylmethylene) methanesulfonamide (232)**

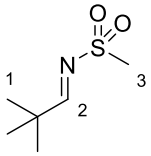



Prepared according to general procedure **B** using methanesulfonamide (**227**, 0.950 g, 10.0 mmol), $NEt_3$ (4.20 mL, 30.0 mmol), 2-naphthaldehyde (**225**, 1.56 g, 10.0 mmol) and $TiCl_4$ (0.547 mL, 0.500 mmol) in dry $CH_2Cl_2$ (25.0 mL). The product was purified by recrystallisation from $CH_2Cl_2$:hexane to afford **232** as a pale yellow solid (0.746 g, 32%). NMR spectral data of **232** matches with the literature data.[164]

$\delta_H$ (400 MHz, $CDCl_3$) 9.17 (1 H, s, H-8), 8.36-8.34 (1 H, m, H-1), 8.08-8.05 (1 H, m, H-7), 7.99-7.89 (3 H, m, H-6, H-5 and H-2), 7.62-7.57 (2 H, m, H-4 and H-3), 3.18 (3 H, s, H-9).

**HRMS (*m/z* - ESI)** $[M+H]^+$ found 234.0590. $C_{12}H_{12}NO_2S$ requires 234.0589.

**(*E*)-N-(2,2-dimethylpropylidene) methanesulfonamide (233)**




Prepared according to general procedure **B** using methanesulfonamide (**227**, 0.802 g, 8.43 mmol), $NEt_3$ (3.90 mL, 27.6 mmol), pivalaldehyde (**226**, 0.915 mL, 8.43 mmol) and $TiCl_4$ (0.799 mL, 4.21 mmol) in dry $CH_2Cl_2$ (25.0 mL). The product was purified by recrystallisation from $CH_2Cl_2$:hexane to afford **233** as a brown solid (427 mg, 31%). Mp. 67-68 °C.

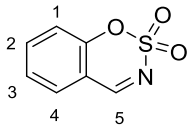
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.45 (1 H, s, H-2), 3.02 (3 H, s, H-3), 1.56 (9 H, s, H-1).

**$\delta_C$ (100MHz, $CDCl_3$)** 185.6, 40.0, 38.0, 25.9 (q).

**$\nu_{max}$ ($cm^{-1}$)** 2972, 1632, 1301, 114, 963, 804, 784.

**HRMS (*m/z* - ESI)** [M+H] Found 164.0740 $C_6H_{14}NO_2S$ requires 164.0745.

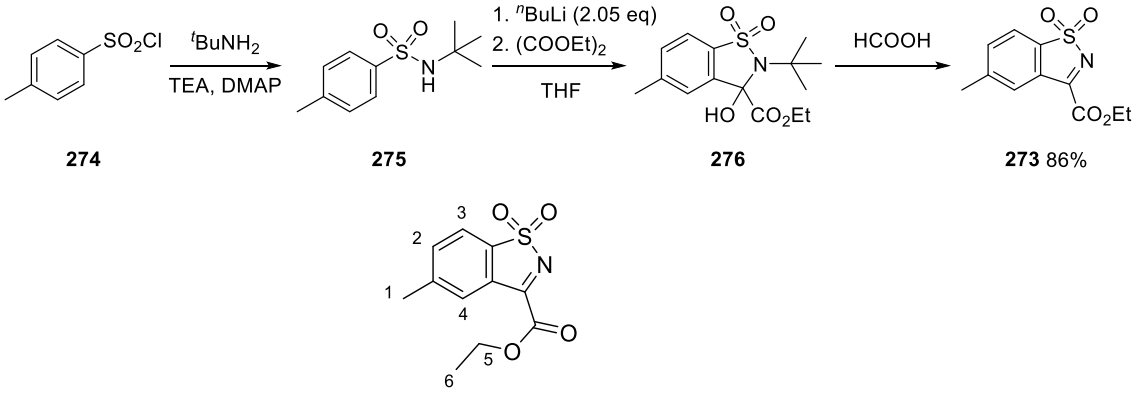
**Benzo [e][1,2,3]oxathiazine 2,2-dioxide (266)**



To an oven-dried 50 mL round-bottom flask was added chlorosulfonyl isocyanate (**268**, 4.97 mL, 57.3 mmol) and cooled at 0 ºC. Formic acid (**267**, 2.16 mL, 57.3 mmol) was added dropwise (exothermic reaction) and the mixture was allowed to stir at the same temperature. After 30 min, chlorosulfonamide **269** was formed as a white solid and it was added, without further purification, portionwise to an oven-dried 100 mL round-bottom flask containing freshly distilled salicylaldehyde **270** (2.00 mL, 19.10 mmol) in 25 mL of *N*,*N*-dimethyl acetamide at 0 ºC. The reaction was left stirring for 16 h at room temperature until TLC analysis indicated completion of the reaction. A mixture of water-ice (10.0 mL and 10.0 g) was added carefully and extracted with $CH_2Cl_2$, the organic layer was washed with a 10% $NaHCO_3$ solution and dried over $MgSO_4$. The solution was filtered to remove the drying agent and concentred under reduce pressure to furnish an oil that was purified in a flash column using silica gel as stationary phase and hexane : ethyl acetate (7:3) as eluent. The product **75** was purified as a white solid (2.80 g, 83 %). Mp. 88-91 ºC (lit.[165] m.p. 92-94 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.66 (1 H, s, H-5), 7.75 (1 H, m, H-2), 7.67 (1 H, dd, *J* 7.7, 1.6, H-4), 7.42 (1 H, m, H-3), 7.26 (1 H, d, *J* 8.2, H-1).

**Ethyl 5-methylbenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (273)**




A solution of $^t$butylamine (0.662 mL, 6.30 mmol) and triethylamine (1.17 mL, 8.40 mmol) in dichloromethane (40.0 mL) was cooled at 0 ºC. *p*-Toluenesulfonyl chloride (0.800 g, 4.20 mmol) in dichloromethane (10.0 mL) was added dropwise and the reaction was stirred

overnight. The reaction was extracted with a saturated solution of sodium carbonate and brine. The organic layer was separated and dried over $MgSO_4$. The solvent was removed and compound **275** was used in the next step without further purification.

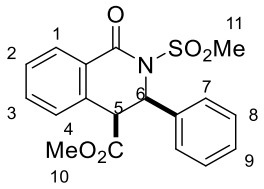
Compound **275** was dissolved in dry THF (25.0 mL) and $^n$BuLi (4.5 mL, 1.6 M) was added dropwise over a 20 min period at 0 ºC. Once the addition was completed the reaction was stirred for further 25 min at 0 ºC. The suspension was cooled to -78 ºC and diethyl oxalate (1.42 mL, 9.45 mmol) was added. The suspension was allowed to warm at room temperature and it was stirred for 2 h. The reaction was quenched with 1.0 M HCl and water was added. The mixture was extracted with diethyl ether and then washed with brine. The organic phase was dried over $MgSO_4$ and the solvent was removed to afford compound **276** that was used in the next step without further purification.

Formic acid (1.00 mL) was added to the crude product obtained previously and the suspension was stirred at room temperature. The reaction was stirred at that temperature for 20 h. The formic acid was removed *via* azeotropic distillation with $CH_2Cl_2$. The crude obtained was purified by column chromatography to afford imine **273** as a white solid (0.915 g, 3.61 mmol, 86%). NMR spectral data of **273** matches with the literature data.[143]

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.07 (1 H, s, H-4), 7.82 (1 H, d, *J* 7.7, H-3), 7.57 (1 H, d, *J* 7.7, H-2), 4.54 (2 H, q, *J* 7.7, H-5), 2.53 (3 H, s, H-1), 1.48 (3 H, t, *J* 7.7, H-6).

### 5.2.5 Catalytic cycloaddition reactions between enolisable anhydrides and imines

**_syn_-Methyl 2-(methylsulfonyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (_syn_-246)**




Prepared according to general procedure **C** using anhydride **86** (39.9 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **228** (48.5 mg, 0.25 mmol) and catalyst **221** (8.2 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 48 h to give a diastereomeric mixture of carboxylic acids in a 64:36 ratio (anti:syn). After esterification, the diastereomer

*syn*-**246** was purified by column chromatography. The product was isolated as a white solid (24 mg, 27 %). M.p. 156-158 °C. $[\alpha]^{20}_{D}$ -34.0 (c 0.05, acetone).

CSP-HPLC analysis, Chiralcel AD (4.6 mm x 25 cm), hexane/IPA: 70/30, 1 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 8.9 min (major enantiomer) and 10.1 min (minor enantiomer).

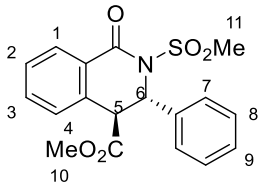
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.30 (1 H, d, *J* 7.9, H-1), 7.62-7.49 (3 H, m, H-4, H-3 and H-2), 7.27-7.17 (3 H, m, H-9 and H-8), 7.01 (2 H, d, *J* 7.2, H-7), 6.07 (1 H, d, *J* 6.2, H-6), 4.88 (1 H, d, *J* 6.2, H-5), 3.67 (3 H, s, H-10), 3.07 (3 H, s, H-11).

**$\delta_C$ (100 MHz, $CDCl_3$)** 168.7 (C=O), 163.6 (C=O), 135.5 (q), 134.4 (q), 133.5, 129.2, 129.1, 128.8 (q), 128.6, 128.3, 127.5, 127.4, 59.8, 52.3, 48.9, 41.1.

**$\nu_{max}$ ($cm^{-1}$)** 3019, 2924, 1732, 1060, 1599, 1499, 1340, 1235, 1155, 1027, 967, 767, 692.

**HRMS (*m/z* - ESI)** $[M+H]^+$ found 360.0896. $C_{18}H_{18}NO_5S$ requires 360.0900.

**Methyl (3*S*,4*S*)-2-(methylsulfonyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*anti*-246)**




Prepared according to general procedure **C** using anhydride **86** (39.9 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **228** (48.5 mg, 0.25 mmol) and catalyst **221** (8.2 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 48 h to give a diastereomeric mixture of carboxylic acids in a 64:36 ratio (anti:syn). After esterification, the diastereomer *anti*-**246** was purified by column chromatography. The product was isolated as a white solid (42 mg, 47 %). M.p. 130-135 °C. $[\alpha]^{20}_{D}$ 15.3 (c 0.15, acetone).

CSP-HPLC analysis, Chiralcel AD (4.6 mm x 25 cm), hexane/IPA: 70/30, 1 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 18.2 min (major enantiomer) and 30.1 min (minor enantiomer).

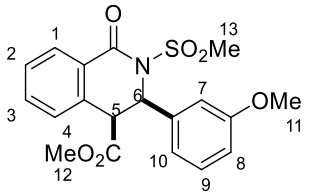
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.18 (1 H, d, *J* 7.9, H-1), 7.51-7.45 (2 H, m, H-3 and H-2), 7.25-7.14 (6 H, m, H-9, H-8, H-7 and H-4), 6.22 (1 H, s, H-6), 4.12 (1 H, s, H-5), 3.74 (3 H, s, H-10), 3.45 (3 H, s, H-11).

**$\delta_C$ (100 MHz, $CDCl_3$)** 170.4 (C=O), 163.6 (C=O), 138.0 (q), 134.1, 133.0 (q), 129.4, 129.0 (q), 128.9, 128.8, 128.1, 128.0, 125.9, 59.0, 53.0, 50.7, 41.8.

**$\nu_{max}$ ($cm^{-1}$)** 3011, 2931, 1736, 1682, 1602, 1458, 1320, 1245, 1158, 1010, 959, 839, 718.

**HRMS (*m/z* - ESI)** $[M+H]^+$ found 360.0908. $C_{18}H_{18}NO_5S$ requires 360.0900.

***syn*-Methyl 3-(3-methoxyphenyl)-2-(methylsulfonyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4- carboxylate (*syn*-256)**




Prepared according to general procedure **C** using anhydride **86** (39.9 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **229** (48.9 mg, 0.25 mmol) and catalyst **221** (8.2 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 60 h to give a diastereomeric mixture of carboxylic acids in a 60:40 ratio (anti:syn). After esterification, the diastereomer *syn*-**256** was purified by column chromatography as a white solid (19 mg, 21%). Mp. 125-127 ºC. $[\alpha]^{20}_D$ 11.5 (c = 0.20, acetone).

CSP-HPLC analysis, Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 80/20, 1 mL min-1 , RT, UV detection at 254 nm, retention times: 12.8 min (major enantiomer) and 14.3 min (minor enantiomer).

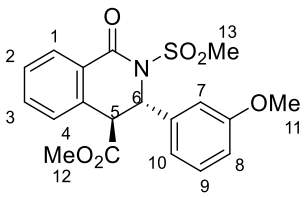
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.28 (1 H, d, *J* 7.4, H-1), 7.64-7.56 (2 H, m, H-3 and H-2), 7.52-7.46 (1 H, m, H-4), 7.09 (1 H, app. t, H-9), 6.76 (1 H, dd, *J* 8.2, 2.3, H-8), 6.57 (1 H, d, *J* 7.7, H-10), 6.52 (1 H, app. t, H-7), 6.03 (1 H, d, *J* 6.2, H-6), 4.85 (1 H, d, *J* 6.2, H-5), 3.69 (3 H, s, H-12), 3.61 (3 H, s, H-11), 3.10 (3 H, s, H-13).

**$\delta_C$ (100 MHz, $CDCl_3$)** 168.7 (C=O), 163.6 (C=O), 159.5 (q), 137.0 (q), 134.4, 133.6 (q), 129.9, 129.0, 128.6 (q), 128.3, 127.4, 119.7, 114.2, 113.6, 59.7, 55.0, 52.3, 48.9, 42.2.

**$\nu_{max}$ ($cm^{-1}$)** 3063, 2951, 1740, 1678, 1601, 1458, 1345, 1320, 1249, 1151, 1117, 970, 766, 696.

**HRMS (m/z - ESI)** $[M+H]^+$ Found 390.1010. $C_{19}H_{20}NO_6S$ requires 390.1006.

**Methyl (3*S*,4*S*)-3-(3-methoxyphenyl)-2-(methylsulfonyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4- carboxylate (*anti*-256)**




Prepared according to general procedure **C** using anhydride **86** (39.9 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **229** (48.9 mg, 0.25 mmol) and catalyst **221** (8.2 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 60 h to give a diastereomeric mixture of carboxylic acids in a 60:40 ratio (anti:syn). After esterification, the diastereomer *anti*-**256** was purified by column chromatography as a white solid (60 mg, 62%). Mp. 140-142 ºC. $[\alpha]^{20}_D$ 6.0 (c = 0.20, acetone).

CSP-HPLC analysis, Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 80/20, 1 mL min-1 , RT, UV detection at 254 nm, retention times: 25.6 min (major enantiomer) and 32.0 min (minor enantiomer).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.14 (1 H, dd, *J* 7.5, 1.3, H-1), 7.52-7.39 (2 H, m, H-3 and H-2), 7.21 (1 H, d, *J* 7.3, H-4), 7.12 (1 H, app. t, H-9), 6.74-6.65 (3 H, m, H-10, H-8 and H-7), 6.17 (1 H, s, H-6), 4.12 (1 H, s,

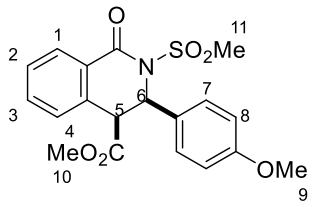
H-5), 3.72 (3 H, s, H-12), 3.67 (3 H, s, H-11), 3.43 (3 H, s, H-13).

**$\delta_C$ (100 MHz, $CDCl_3$)** 170.3 (C=O), 163.6 (C=O), 159.9 (q), 139.7 (q), 134.1, 133.1 (q), 130.0, 129.4, 129.0, 128.8 (q), 128.0, 118.1, 113.5, 111.9, 59.0, 55.1, 53.0, 50.6, 41.8.

**$\nu_{max}$ ($cm^{-1}$)** 3059, 2949, 1736, 1677, 1600, 1458, 1341, 1248, 1152, 1117, 971, 767, 735.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 390.1010. $C_{19}H_{20}NO_6S$ requires 390.1006.

**syn-Methyl 3-(4-methoxyphenyl)-2-(methylsulfonyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4- carboxylate (*syn*-256)**




Prepared according to general procedure **C** using anhydride **86** (39.9 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **230** (48.9 mg, 0.25 mmol) and catalyst **221** (8.2 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 168 h to give a diastereomeric mixture of carboxylic acids in a 56:44 ratio (anti:syn). After esterification, the diastereomer *syn*-**256** was purified by column chromatography as a colourless oil (20 mg, 26%). [α]20 D = 21.9 (c = 0.19, acetone).

CSP-HPLC analysis, Chiralcel AD (4.6 mm x 25 cm), hexane/IPA: 60/40, 1 mL min-1, RT, UV detection at 254 nm, retention times: 8.5 min (minor enantiomer) and 9.6 min (major enantiomer).

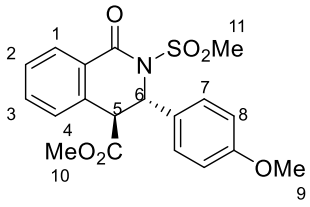
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.29 (1 H, dd, *J* 7.8, 1.7, H-1), 7.62-7.56 (2 H, m, H-3 and H-2), 7.50 (1 H, m, H-4), 6.94 (2 H, d, *J* 7.6, H-7), 6.69 (2 H, d, *J* 7.6, H-8), 6.03 (1 H, d, *J* 6.6, H-6), 4.85 (1 H, d, *J* 6.6, H-5), 3.70 (3 H, s, H-10), 3.68 (3 H, s, H-9), 3.06 (3 H, s, H-11).

**$\delta_C$ (100 MHz, $CDCl_3$)** 168.8 (C=O), 163.6 (C=O), 159.9 (q), 134.4 (q), 133.7 (q), 129.0 (q), 128.7, 128.3, 127.5, 127.3, 114.1, 59.4, 55.1, 52.3, 48.9, 42.1.

**$\nu_{max}$ ($cm^{-1}$)** 2961, 2918, 1735, 1678, 1604, 1459, 1320, 1254, 1176, 1063, 962, 767.

**HRMS (*m/z* - ESI)** $[M+H]^+$ found 390.1009. $C_{19}H_{20}NO_6S$ requires 390.1006.

**Methyl (3*S*,4*S*)-3-(4-methoxyphenyl)-2-(methylsulfonyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4- carboxylate (*anti*-255)**




Prepared according to general procedure **C** using anhydride **86** (39.9 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **230** (48.9 mg, 0.25 mmol) and catalyst **221** (8.2 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 168 h to give a diastereomeric mixture of carboxylic acids in a 56:44 ratio (*anti:syn*). After esterification, the diastereomer *anti*-**255** was purified by column chromatography as a colourless oil (36 mg, 38%, 66% ee). [α]20 D = 24.2 (c = 0.32, acetone).

CSP-HPLC analysis, Chiralcel AD (4.6 mm x 25 cm), hexane/IPA: 60/40, 1 mL min-1, RT, UV detection at 254 nm, retention times: 21.3 min (major enantiomer) and 30.3 min (minor enantiomer).

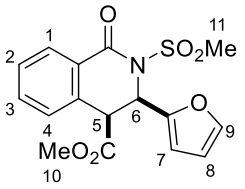
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.16 (1 H, d, *J* 8.0, H-1), 7.52-7.43 (2 H, m, H-3 and H-2), 7.23-7.23 (1 H, m, H-4), 7.05 (2 H, d, *J* 7.8, H-7), 6.74 (2 H, d, *J* 7.8, H-8), 6.16 (1 H, s, H-6), 4.08 (1 H, s, H-5), 3.72 (3 H, s, H-10), 3.70 (3 H, s, H-9), 3.41 (3 H, s, H-11).

**$\delta_C$ (100 MHz, $CDCl_3$)** 170.4 (C=O), 163.6 (C=O), 159.3 (q), 134.1 (q), 133.2, 130.1 (q), 129.4, 129.0 (q), 128.9, 127.5, 127.2, 114.2, 58.6, 55.1, 53.0, 50.7, 41.8.

**$\nu_{max}$ (cm$^{-1}$)** 2984, 2956, 1733, 1688, 1604, 1499, 1350, 1254, 1166, 1039, 962, 769.

**HRMS (m/z - ESI)** $[M+H]^+$ found 390.1009. $C_{19}H_{20}NO_6S$ requires 390.1006.

***syn*-Methyl 3-(furan-2-yl)-2-(methylsulfonyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*syn*-257)**




Prepared according to general procedure **C** using anhydride **86** (39.9 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **231** (42.6 mg, 0.25 mmol) and catalyst **221** (8.2 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 48 h to give a diastereomeric mixture of carboxylic acids in a 41:59 ratio (*anti:syn*). After esterification, the diastereomer *syn*-**257** was purified by column chromatography as a pale yellow oil (45 mg, 50%, 88% ee). $[\alpha]^{20}_D$ 50.0 (c = 0.20, acetone).

CSP-HPLC analysis, Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 95/5, 1 mL min-1, RT, UV detection at 254 nm, retention times: 33.7 min (major enantiomer) and 37.9 min (minor enantiomer).

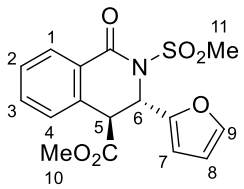
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.20 (1 H, dd, *J* 7.7, 0.8, H-1), 7.68-7.57 (2 H, m, H-4 and H-4), 7.46 (1 H, app. t, H-2), 7.18 (1 H, d, *J* 1.5, H-9), 6.17 (1 H, dd, *J* 3.3, 1.5, H-8), 6.15 (1 H, d, *J* 5.5, H-6), 6.04 (1 H, d, *J* 3.3, H-7), 4.75 (1 H, d, *J* 5.5, H-5), 3.77 (3 H, s, H-10), 3.20 (3 H, s, H-11).

**$\delta_C$ (100 MHz, $CDCl_3$)** 168.6 (C=O), 163.7 (C=O), 149.0 (q), 143.2, 134.2, 134.0 (q), 129.2, 128.2, 127.8, 127.4 (q), 110.3, 109.8, 53.7, 52.6, 47.8, 41.8.

**$\nu_{max}$ (cm$^{-1}$)** 3052, 2953, 1742, 1685, 1602, 1457, 1348, 1316, 1159, 964, 735.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 350.0688. $C_{16}H_{16}NO_6S$ requires 350.0693.

**Methyl (3*S*,4*S*)-3-(furan-2-yl)-2-(methylsulfonyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4- carboxylate (*anti*-257)**




Prepared according to general procedure **C** using anhydride **86** (39.9 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **231** (42.6 mg, 0.25 mmol) and catalyst **221** (8.2 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 48 h to give a diastereomeric mixture of carboxylic acids in a 41:59 ratio (*anti:syn*). After esterification, the diastereomer *anti*-**257** was purified by column chromatography as a white solid (39 mg, 46%, 76% ee). Mp. 154-155 ºC. $[\alpha]^{20}_D$ 48.0 (c 0.12, acetone).

CSP-HPLC analysis, Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 85/15, 1 mL min-1, RT, UV detection at 254 nm, retention times: 20.5 min (major enantiomer) and 30.1 min (minor enantiomer).

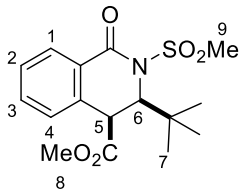
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.09 (1 H, d, *J* 7.5, H-1), 7.55 (1 H, app. t, H-3), 7.43 (1 H, app. t, H-2), 7.35 (1 H, d, *J* 7.5, H-4), 7.21 (1 H, s, H-9), 6.23 (1 H, d, *J* 1.4, H-6), 6.16 (1 H, dd, *J* 3.1, 1.4, H-8), 6.10 (1 H, d, *J* 3.1, H-7), 4.31 (1 H, d, *J* 1.4, H-5), 3.73 (3 H, s, H-10), 3.45 (3 H, s, H-11).

**$\delta_C$ (100 MHz, $CDCl_3$)** 169.7 (C=O), 163.0 (C=O), 150.8 (q), 142.7, 134.1 (q), 133.7, 129.3, 129.1, 128.9 (q), 127.5, 110.5, 108.6, 53.6, 53.1, 47.2, 41.8.

**$\nu_{max}$ ($cm^{-1}$)** 3055, 2950, 1735, 1678, 1600, 1458, 1344, 1250, 1152, 972, 766, 737.

**HRMS (m/z - ESI)** $[M+H]^+$ Found 350.0700. $C_{16}H_{16}NO_6S$ requires 350.0693.

**_syn_-Methyl 3-(tert-butyl)-2-(methylsulfonyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (_syn_-258)**




Prepared according to general procedure **C** using anhydride **86** (39.9 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **233** (40.1 mg, 0.25 mmol) and catalyst **221** (16.4 mg, 0.02 mmol, 10 mol%). The reaction was stirred at room temperature for 120 h to give a diastereomeric mixture of carboxylic acids in a 61:39 ratio (*anti:syn*). After esterification, the diastereomer *syn*-**258** was purified by column chromatography as a colourless oil (25 mg, 29%). $[\alpha]^{20}_{D}$ 47.1 (c = 0.20, acetone).

CSP-HPLC analysis, Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1 mL min-1, RT, UV detection at 254 nm, retention times: 12.1 min (minor enantiomer) and 14.3 min (major enantiomer).

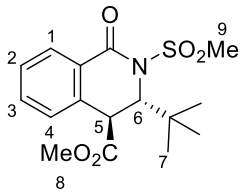
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.12-8.05 (2 H, m, H-3 and H-1), 7.63-7.56 (1 H, m, H-4), 7.41 (1 H, app. t, H-2), 5.06 (1 H, d, *J* 4.7, H-6), 4.53 (1 H, d, *J* 4.7, H-5), 3.83 (3 H, s, H-8), 3.54 (3 H, s, H-9), 0.81 (9 H, s, H-7).

**$\delta_C$ (100 MHz, $CDCl_3$)** 170.1 (C=O), 164.8 (C=O), 135.1 (q), 134.2, 128.7, 128.5 (q), 127.9, 126.9, 63.7 (q), 52.0, 46.8, 43.1, 37.8, 28.8.

**$\nu_{max}$ ($cm^{-1}$)** 3064, 2956, 1741, 1680, 1457, 1343, 1159, 965, 765.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 340.1213. $C_{16}H_{22}NO_5S$ requires 340.1213.

**Methyl (3*S*,4*S*)-3-(tert-butyl)-2-(methylsulfonyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4- carboxylate (*anti*-258)**




Prepared according to general procedure **C** using anhydride **86** (39.9 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **233** (40.1 mg, 0.25 mmol) and catalyst **221** (16.4 mg, 0.02 mmol, 10 mol%). The reaction was stirred at room temperature for 120 h to give a diastereomeric mixture of carboxylic acids in a 61:39 ratio (*anti:syn*). After esterification, the diastereomer *anti*-**258** was purified by column chromatography eluting with 70/30 hexane/EtOAc and isolated as a white solid (55mg, 65%). Mp. 153-155 ºC. $[\alpha]^{20}_{D}$ 10.5 (c = 0.20, acetone).

CSP-HPLC analysis, Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1 mL min-1, RT, UV detection at 254 nm, retention times: 17.6 min (major enantiomer) and 21.7 min (minor enantiomer).

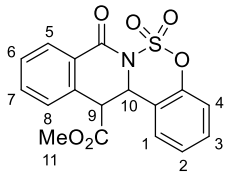
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.08 (1 H, dd, *J* 7.5, 0.8, H-1), 7.58-7.51 (1 H, m, H-3), 7.47-7.40 (1 H, m, H-2), 7.32 (1 H, d, *J* 7.5, H-4), 4.73 (1 H, d, *J* 1.1, H-6), 4.08 (1 H, d, *J* 1.1, H-5), 3.68 (3 H, s, H-8), 3.45 (3 H, s, H-9), 0.84 (9 H, s, H-7).

**$\delta_C$ (100 MHz, $CDCl_3$)** 171.5 (C=O), 164.1 (C=O), 135.0 (q), 134.1, 128.8 (x2), 128.7 (q), 128.2, 64.0 (q), 52.8, 44.2, 41.0, 36.7, 27.9.

**$\nu_{max}$ ($cm^{-1}$)** 3060, 2972, 1732, 1685, 1465, 1340, 1249, 1157, 1027, 962, 768, 733.

**HRMS (m/z - ESI)** $[M+H]^+$ Found 340.1216. $C_{16}H_{22}NO_5S$ requires 340.1213.

**Methyl 8-oxo-13,13a-dihydro-8*H*-benzo[5,6][1,2,3]oxathiazino[3,4-*b*]isoquinoline-13-carboxylat 6,6-dioxide (272)**




To an oven-dried 10 mL round-bottom flask, imine **266** (45.1 mg, 0.246 mmol), homophthalic anhydride **86** (39.9 g, 0.246 mmol) and catalyst **91** (9.1 g, 0.0123 mmol) were placed under argon at -30 ºC. Anhydrous THF (2.5 mL) was added *via* syringe. After completion of the reaction, dry MeOH (0.500 mL) was added followed by $TMSCH_2$ (0.147 mL, 0.295 mmol). After 1 h stirring at -30 ºC, the solvent was removed under reduced pressure and the crude was purified by a flash column. Both diastereomers were isolated together, as a white solid (0.063 g, 71%)

CSP-HPLC analysis. Chiralpak IA, hexane/IPA: 90/10, 1.0 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 43.99 min (major diastereomer, major enantiomer) 64.13 min (minor diastereomer, minor enantiomer), 72.89 min (major diastereomer, minor enantiomer), 108.31 (minor diastereomer, major enantiomer)

**$\delta_H$ (400 MHz, $CDCl_3$)** *syn*-**271**: 8.30 (1 H, dd, *J* 7.7, 1.4, H-5), 7.67 (1 H, app. td, H-7), 7.57 (1 H, app. td, H-6), 7.51-7.36 (4 H, m, H-8, H-4, H-1 and H-3), 7.26-7-18 (1 H, m, H-2), 5.72 (1 H, d, *J* 3.3, H-10), 4.33 (1 H, d, *J* 3.3, H-9), 3.55 (3 H, s, H-11)

*anti*-**271**: 8.16 (1 H, dd, *J* 7.8, 1.4, H-5), 7.65 (1 H, app. td, H-7), 7.52-7.35 (4 H, m, H-6, H-8, H-1 and H-3), 7.27-7-19 (2 H, m, H-4 and H-2), 6.21 (1 H, d, *J* 5.1, H-10), 4.70 (1 H, d, *J* 5.1 H-9), 3.84 (3 H, s, H-11)

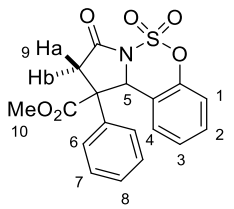
**$\delta_C$ (100 MHz, $CDCl_3$)** *syn*-**271**: 167.9 (C=O), 162.0 (C=O), 148.9 (q), 135.3 (q), 134.4, 130.6, 130.4, 129.5, 128.4, 127.1, 126.5 (q), 126.4, 121.2 (q), 119.4, 61.2, 52.8, 50.9

*anti*-**271**: 169.7 (C=O), 161.4 (C=O), 150.9 (q), 134.7, 133.9 (q), 140.0, 130.1, 129.3, 128.4, 127.0 (q), 126.6, 125.3, 122.1 (q), 120.0, 60.6, 53.4, 47.1

**$\nu_{max}$ ($cm^{-1}$)** 2954, 1732, 1702, 1405, 1195, 1178, 1127, 831, 763, 660.

**HRMS (*m/z* – ESI)** Found: 382.0366 $(M+Na)^+$ $C_{17}H_{13}NO_6SNa$ Required: 382.0361.

**Methyl 3-oxo-1-phenyl-1,2,3,10b-tetrahydobenzo[*e*]pyrrolo[1,2-*c*]oxathiazine-1-carboxylate 5,5-dioxide (282)**




To an oven-dried 10 mL round-bottom flask, imine **266** (45.1 mg, 0.246 mmol) and phenylsuccinic anhydride **96** (43.3 g, 0.246 mmol) were added and dissolved in anhydrous MTBE (2.0 mL) and placed under argon. Catalyst **243** (8.9 g, 0.012 mmol) was added dissolved in anhydrous MTBE (0.5 mL) *via* syringe. Once the reaction was completed, the flask was place in an ice bath and dry MeOH (0.500 mL) was added followed by $TMSCH_2$ (0.147 mL, 0.295 mmol). After 1 h stirring at that temperature, the solvent was removed under reduced pressure and the crude was purified by a flash column. Both diastereomers were isolated together, as a white solid (0.066 g, 72 %).

CSP-HPLC analysis. Chiralpak AD, hexane/IPA: 90/10, 1.0 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 19.03 (major diastereomer, minor enantiomer) 27.53 min (major diastereomer, major enantiomer), 36.00 (minor diastereomer, major enantiomer), 39.84 (minor diastereomer, major enantiomer).

**$\delta_H$ (600 MHz, $CDCl_3$)** *syn*-**282:** 7.54-7.50 (2 H, m, H-7), 7.49-7.45 (1 H, m, H-4), 7.44-7.37 (3 H, m, H-8 and H-6), 7.19-7.14 (2 H, m, H-3 and H-2), 7.10 (1 H, d, *J* 7.6, H-1), 6.17 (1 H, s, H-5), 3.46 (3 H, s, H-10), 3.41 (1 H, d, *J* 17.0, H-9a), 3.02 (1 H, d, *J* 17.0, H-9b).

*anti*-**282:** 7.65 (1 H, d, *J* 8.0, H-4), 7.22-7.7.12 (5 H, m, H-2, H-3 , H-7 and H-8), 6.96-6.91 (2 H, m, H-6), 6.77 (1 H, dd, *J* 8.0, 1.3, H-1), 6.25 (1 H, s, H-5), 3.93 (3 H, s, H-10), 3.34 (1 H, d, *J* 17.8, H-9a), 3.27 (1 H, d, *J* 17.8, H-9b)

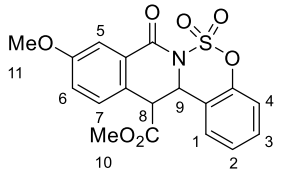
**$\delta_C$ (100 MHz, $CDCl_3$)** *syn*-**282:** 170.9 (C=O), 166.6 (C=O), 149.7 (q), 136.9 (q), 130.4, 129.3, 128.8, 127.2, 127.0, 126.2, 120.4 (q), 119.2, 64.8, 57.4, 52.9, 44.8

*anti*-**282:** 172.9 (C=O), 167.2 (C=O), 150.0 (q), 135.7 (q), 129.9, 128.8, 128.7, 128.5, 126.5, 126.1, 119.6, 118.9, 66.5, 56.9 (q), 53.5, 42.0

**$\nu_{max}$ ($cm^{-1}$)** 2964, 1732, 1702, 1406, 1253, 1168, 833, 761, 691

**HRMS (*m/z* - ESI)** Found: 374.0694 $(M+H)^+$ $C_{18}H_{16}NO_6S$ Required: 374.0698.

**Methyl 10-methoxy 8-oxo-13,13a-dihydro-8*H*-benzo[5,6][1,2,3]oxathiazino[3,4-*b*]isoquinoline-13-carboxylate 6,6-dioxide (288)**




Prepared according to general procedure **C** using anhydride **162** (47.3 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **266** (45.1 mg, 0.25 mmol) and catalyst **243** (5.90 mg, 0.01 mmol, 5 mol%). The reaction was stirred at room temperature for 120 h to give a diastereomeric mixture of carboxylic acids in a 61:39 ratio (anti:syn). After esterification, the diastereomers were isolated together (86.6 mg, 0.22 mmol 89%). Mp. 153-155 ºC.

**$\delta_H$ (400 MHz, $CDCl_3$)** *anti*-**288**: 7.57 (1 H, d, *J* 2.0, H-5), 7.45-7.30 (1 H, m, H-7, 7.33-7.07 (5 H, m, H-6, H-4, H-3, H-2 and H-1), 6.14 (1 H, d, *J* 4.8, H-9), 4.59 (1 H, d, *J* 4.8, H-8), 3.80 (3 H, s, H-10), 3.77 (3 H, s, H-11).

s*yn*-**288**: 7.74 (1 H, d, *J* 3.0, H-5), 7.47-7.40 (1 H, m, H-7), 7.39-7.29 (3 H, m, H-3, H-2 and H-1), 7.22-7.14 (2 H, m, H-6 and H-4), 5.66 (1 H, d, *J* 3.5, H-9), 4.21 (1 H, d, *J* 3.5, H-8), 3.88 (3 H, s, H-10), 3.51 (3 H, s, H-11).

**$\delta_C$ (100 MHz, $CDCl_3$)** *anti*-**288**: 169.9 (C=O), 161.3 (C=O), 160.1 (q), 150.8 (q), 130.9, 129.7, 127.7 (q), 126.6, 125.9 (q), 125.3, 122.4, 122.3 (q), 119.7, 112.8, 60.7, 55.7, 53.4, 46.2.

| | |
|---|---|
| | *syn*-**288**: 168.1 (C=O), 162.0 (C=O), 160.3 (q), 148.8 (q), 130.6, 129.7, 127.6 (q), 127.4 (q), 127.1, 126.4, 122.1, 121.5 (q), 119.3, 113.0, 61.4, 55.8, 52.7, 50.1. |
| **$\nu_{max}$ ($cm^{-1}$)** | 2949, 1734, 1709, 1409, 1187, 1169, 1116, 829, 754, 660. |

## 5.3 Experimental data for Chapter 3

### 5.3.1 General procedures

**General procedure D: synthesis of α,β-unsaturated aldehydes**

To a 100 mL round-bottomed flask containing NaH (0.192 g, 8.00 mmol, 50% dispersed in mineral oil, 2.0 eq.) DME (6.00 mL) was added and the solution was cooled at 0 ºC. Trimethyl phosphonoacetate (1.30 mL, 8.00 mmol, 1.0 eq.) was added and stirred at 0 ºC for 15 min. The corresponding aldehyde (4.00 mmol, 1.0 eq.) dissolved in DME (2.00 mL) was added dropwise and the reaction was stirred at 0 ºC for 30 min. EtOAc (x2) and water (x2) were added and the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the obtained compound was used in the next step without further purification.

The ester obtained previously (4.00 mmol) was dissolved in anhydrous toluene (8.00 mL) and cooled at 0 ºC. DIBAL-H (8.00 mL, 8.00 mmol, 1.0 M in toluene, 2.0 eq.) was added dropwise. The reaction was stirred for 30 min at 0 ºC and it was quenched with 10% Rochelle's salt solution. The reaction was stirred for an additional hour. EtOAc and water were added (2 times) and the combined organic fractions washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the product was used in the next step without further purification.

To a 100 mL round-bottomed flask containing anhydrous $CH_2Cl_2$ (4.00 mL), oxalyl chloride (2.00 mL, 2.0 M in $CH_2Cl_2$, 4.00 mmol, 1.0 eq.) was added and the reaction was cooled to -78 ºC. DMSO (0.625 mL, 8.80 mmol) was added and the reaction was stirred for 10 min. The alcohol obtained in the last step (4.00 mmol) was dissolved in anhydrous $CH_2Cl_2$ (9.00 mL) and added dropwise to the reaction and stirred for another 20 min at -78 ºC. Freshly distilled $Et_3N$ (3.03 mL, 20.0 mmol, 5.0 eq.) was added dropwise at -78 ºC and the reaction was allowed to warm up to room temperature and stirred for 3 h. Water was added to the reaction and then the reaction was extracted with diethyl ether (4 times). The combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed and the compound was purified by column chromatography.

**General procedure E: synthesis of *N*-tritylimines**

Triphenylmethylenamine (1 eq) and 4 Å molecular sieves were placed in an RBF and charge with dry toluene. The corresponding aldehyde (1 eq) was added and the reaction was heated at reflux for 16 h. The reaction mixture was filtered through celite and the solvent removed. The crude was triturated with hexane and filtered to afford the corresponding imine.

**General procedure F: evaluation of the imine component in the cycloaddition reaction between anhydride 87 and imines.**

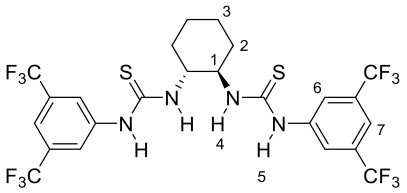
An oven-dried 10 mL reaction vessel was charged with the corresponding imine (0.20 mmol) and placed under an argon atmosphere. Dry toluene (2.0 mL) was added and the vessel was placed at -40 ºC. Catalyst **322** (4.7 mg, 0.01 mmol, 5 mol%) was added followed by **86** (32.4 mg, 0.20 mmol). The conversion of the reaction was determined by $^{1}$H-NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. After completion, the solvent was removed and the acid were purified by column chromatography. The *cis*-acid was then esterified with MeOH (15 eq) and trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 1.2 eq) in dry toluene (0.1 M) and stirred at 0 ºC for 1 h. The solvent was removed and the ester was purified by column chromatography.

**General procedure G: evaluation of the anhydride component in the cycloaddition reaction between imine 209 and anhydrides.**

An oven-dried 10 mL reaction vessel was charged with imine **208** (74.7 mg, 0.20 mmol) and placed under an argon atmosphere. Dry toluene (2.0 mL) was added and the vessel was placed at -40 ºC. Catalyst **322** (4.7 mg, 0.01 mmol, 5 mol%) was added followed by the corresponding anhydride (0.20 mmol). The conversion of the reaction was determined by $^{1}$H-NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. After completion, the solvent was removed and the acid was isolated by column chromatography. The acid was esterified using trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 1.2 eq) and MeOH (15 eq) in dry toluene (0.1 M) and stirred at 0 ºC for 1 h. The solvent was removed and the ester was purified by column chromatography.

### 5.3.2 Synthesis of catalysts

**1,1'-((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea (324)**

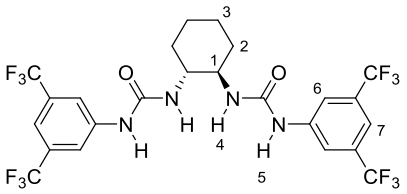


3,5-Bis(trifluoromethyl)phenyl isothiocyanate (1.00 mL, 5.90 mmol) was added dropwise stirred solution of cyclohexanediamine (0.300 g, 2.63 mmol) in $CH_2CL_2$ (20.00 mL) over 30 min at 0 ºC and then the mixture was left stirring at room temperature for 5 h. The product was purified by column chromatography (1.22 g, 1.87 mmol, 71%). NMR spectral data of **324** matches with the literature data.[149]

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.16 (2 H, s, H-5), 7.81 (4 H, s, H-6), 7.67 (2 H, s, H-7), 7.05 (2 H, s, H-4), 4.46-4.32 (2 H, m, H-1), 2.27-2.12 (2 H, m, H-2eq), 1.87-1.72 (2 H, m, H-3eq), 1.44-1.29 (4 H, m, H-2a and H-3a).

**HRMS (*m/z* – ESI)** $[M+H]^+$ Found 655.0878. $C_{24}H_{19}F_{12}N_4S_2$ Requires 655.0865.

**1,1'-((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea (323)**



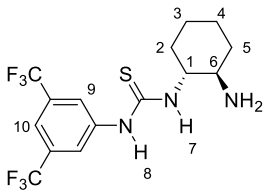
3,5-Bis(trifluoromethyl)phenyl isocyanate (0.691 mL, 4.00 mmol) was added dropwise stirred solution of cyclohexanediamine (0.228 g, 2.00 mmol) in THF (5.00 mL) over 30 min at 0 ºC and then the mixture was left stirring at room temperature for 5 h. The product was isolated by filtration (0.987 g, 1.58 mmol, 79%). NMR spectral data of **323** matches with the literature data.[166]

**$\delta_H$ (600 MHz, DMSO)** 9.21 (2 H, s, H-5), 7.90 (4 H, s, H-6), 7.36 (2 H, s, H-7), 6.24 (2 H, d, *J* 8.5, H-4), 3.54-3.45 (2 H, m, H-1), 1.95-1.85 (2 H,

m, H-2eq), 1.76-1.66 (2 H, m, H-3eq), 1.37-1.24 (4 H, m, H-2a and H-3a)

**HRMS (*m/z* – ESI)** $[M-H]^-$ Found 623.1330. $C_{24}H_{19}F_{12}N_4O_2$ Requires 623.1321.

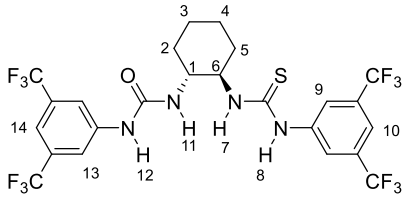
**1-((1*R*,2*R*)-2-aminocyclohexyl)-3-(3,5-*bis*(trifluoromethyl)phenylthiourea (314)**



3,5-Bis(trifluoromethyl)phenyl isothiocyanate (0.480 mL, 2.63 mmol) was added dropwise stirred solution of cyclohexanediamine (0.300 g, 2.63 mmol) in THF (20.00 mL) over 30 min at 0 ºC and then the mixture was left stirring at room temperature for 5 h. The product was purified by column chromatography (0.740 g, 1.92 mmol, 73%). M.p. 65-68 ºC (lit.[167] 69-71 ºC).

**$\delta_H$ (400 MHz, DMSO)** 8.20 (2 H, s, H-9), 7.64 (1 H, s, H-10), 3.83 (1 H, br. s, H-1), 2.59-2.43 (1 H, m, H-6), 2.12-1.95 (1 H, m, H-2eq), 1.89-1.74 (1 H, m, H-5eq), 1.70-1.50 (2 H, m, H-4eq and H-3eq), 1.30-0.94 (4 H, H-5a, H-4a, H-3a and H-2a).

**1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*R*,2*R*)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)urea (325)**



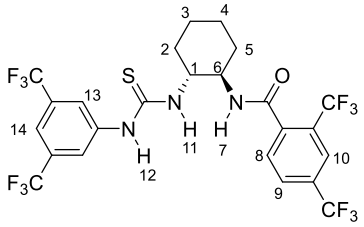
3,5-Bis(trifluoromethyl)phenyl isocyanate (0.134 mL, 0.778 mmol) was added dropwise to a stirred solution of **314** (0.300 g, 0.778 mmol) in THF (5.00 mL) over 30 min at 0 ºC and then the mixture was left stirring at room temperature for 5 h. The product was isolated by filtration (0.373 g, 0.583 mmol, 75%).

**$\delta_H$ (400 MHz, DMSO)** 8.30 (1 H, br. s, H-8), 7.83-7.58 (5 H, m, H-13, H-10 and H-9), 7.41 (1 H, s, H-14), 7.27-7.04 (1 H, m, H-7), 5.86 (1 H, d, *J* 6.5, H-11), 4.46-4.31 (1 H, m, H-6), 3.84-3.62 (1 H, m, H-

1), 2.34-2.21 (1H, m, H-5eq), 2.19-2.08 (1 H, m, H-2eq), 1.92-1.77 (2 H, m, H-4eq and H-3eq), 1.50-1.26 (4 H, m, H-5a, H-4a, H-3a and H-2a).

**HRMS (*m/z* – ESI)** $[M-H]^-$ Found 623.1330. $C_{24}H_{19}F_{12}N_4O_2$ Requires 623.1321.

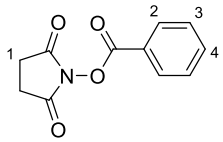
***N*-((1*R*,2*R*)-2-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)benzamide (142)**



To an oven-dried 50 mL round-bottom flask containing monothiourea **314** (0.400 g, 1.04 mmol) was added dry $CH_2Cl_2$ (10 mL) and triethylamine (0.291 mL, 2.08 mmol). The flask was placed in an ice bath and acyl chloride **315** (0.315 g, 1.14 mmol) was added dropwise and the mixture was stirred at room temperature for 16 h. The solvent was removed and the crude was purified by silica gel chromatography. Catalyst **142** was isolated as a white powder (0.475 g, 0.759 mmol, 73%). M.p. 210-212 ºC (lit.[93] 212-213 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.95 (1 H, s, H-12), 7.86 (1 H, s, H-10), 7.76 (1 H, d, *J* 7.9, H-8), 7.69-7.58 (3 H, m, H-13 and H-9), 7.57-7.43 (2 H, m, H-14 and H-11), 7.31 (1 H, d, *J* 7.4, H-7), 4.81-4.65 (1 H, m, H-1), 4.02-3.89 (1 H, m, H-6), 2.40-2.20 (2 H, m, H-5eq and H-2eq), 2.02-1.87 (2 H, m, H-4eq and H-3eq), 1.60-1.32 (4 H, m, H-5a, H-4a, H-3a and H-2a).

**2,5-Dioxopyrrolidin-1-yl benzoate (320)**

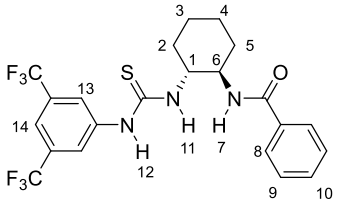


Benzoic acid (**319**, 0.611 g, 5.00 mmol) was dissolved in 10.0 mL of $CH_2Cl_2$ and it was added to a 50 mL round-bottomed flask containing *N*-hydroxysuccinimide (**318**, 0.604 g, 5.25 mmol). The flask was cooled at 0 ºC and a solution of DCC (2.01 g, 9.75 mmol) in $CH_2Cl_2$ (10.0 mL) was added dropwise. Upon complete addition the reaction was allowed to warm up at room temperature and it was stirred for 16 h. The reaction was filtered and the

filtrate was dried *in vacuum*. The residue was suspended in $Et_2O$ and filtrated. The compound was dried and product **320** was obtained as a white solid (0.801 g, 3.65 mmol, 73%). M.p. 137-140 ºC (lit.[168] 139-140 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.14 (2 H, d, *J* 7.6, H-2), 7.68 (1 H, t, *J* 7.3, H-4), 7.51 (2 H, app. t, H-3), 2.90 (4 H, s, H-1).

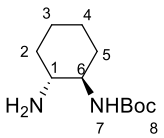
***N*-((1*R*,2*R*)-2-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)benzamide (317)**




To an oven-dried 50 mL round-bottom flask containing monothiourea **314** (0.200 g, 0.520 mmol) and **320** (0.171 g, 0.780 mmol) were added. Dry THF (5.00 mL) was added and the reaction was stirred at room temperature for 16 h. The solvent was removed and the crude was purified by silica gel chromatography. Catalyst **317** was isolated as a white powder (0.211 g, 0.432 mmol, 83%). M.p. 80-83 ºC (lit.[169] 83-85 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.85 (1 H, s, H-12), 7.79-7.66 (5 H, m, H-13, H-11 and H-8), 7.76 (1 H, s, H-14), 7.46 (1 H, t, *J* 7.3, H-10), 7.34 (2 H, app. t, H-9), 7.18 (1 H, d, *J* 5.5, H-7), 4.81-4.65 (1 H, m, H-1), 4.05-3.93 (1 H, m, H-6), 2.43-2.15 (2 H, m, H-5eq and H-2eq), 2.00-166 (2 H, m, H-4eq and H-3eq), 1.73-1.40 (4 H, m, H-5a, H-4a, H-3a and 2a).

***tert*-Butyl ((1*R*,2*R*)-2-aminocyclohexyl)carbamate (342)**

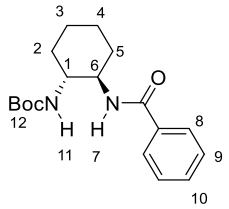



To an oven-dried 50 mL round-bottomed flask containing (*R*,*R*)-1,2-cyclohexanediamine (**299**, 0.343 g, 3.00 mmol) dissolved in $CH_2Cl_2$ (7.5 mL), a solution of di-*tert*-butyl carbonate (0.218 g, 1.00 mmol) in $CH_2Cl_2$ (2.50 mL) was added at 0 ºC. The reaction was stirred at room temperature for 24 h. Water (5.0 mL) and $CH_2Cl_2$ (7.0 mL) were added and the organic phase separated and the solvent removed *in vacuo*. The residue was dissolved in diethyl ether

(15 mL) and water (20 mL). 1.0 M HCl was added until pH = 5. The aqueous phase was collected and alkalified with 1.0 M NaOH to pH = 11 and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduce pressure to afford compound **342** (0.131 g, 0.611 mmol, 61%) that was used in the next step without further purification. NMR spectral data of **342** matches with the literature data.[170]

**$\delta_H$ (400 MHz, $CDCl_3$)** 4.56 (1 H, m, H-7), 3.13 (1 H, m, H-6), 2.29 (1 H, m, H-1), 2.07-1.93 (2 H, m, H-5eq and H-2eq), 1.67-1.50 (2 H, m, H-4eq and H-3eq), 1.43 (9 H, s, H-8), 1.10-0.97 (4 H, m, H-5a, H-4a, H-3a and H-2a).

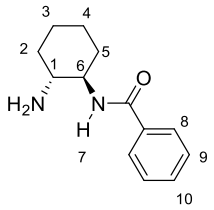
***tert*-Butyl ((1*R*,2*R*)-2-benzamidocyclohexyl)carbamate (343)**




Compound **342** (0.131 g, 0.611 mmol) was placed in a 25 mL round-bottomed flask and it was dissolved in $CH_2Cl_2$ (6.00 mL) and $NEt_3$ (0.102 mL, 0.730 mmol) was added. The flak was placed on an ice bath and benzoyl chloride (**316**, 0.100 mL, 0.611 mmol) was added dropwise. The reaction was allowed to warm at room temperature and stirred for 12 h. The solvent was removed and the product was purified by column chromatography. Product **343** was isolated as a white solid (0.160 g, 0.502 mmol, 82%).

**$\delta_H$ (400 MHz, $CDCl_3$)** 7.83 (2 H, d, *J* 7.5, H-8), 7.46 (1 H, t, *J* 7.5, H-10), 7.39 (2 H, app. t, H-9), 7.06 (1 H, d, *J* 6.9, H-7), 4.65 (1 H, d, *J* 9.1, H-11), 3.81-3.70 (1 H, m, H-6), 3.59-3.46 (1 H, m, H-6), 2.31-2.21 (1 H, m, H-5eq), 2.06-1.98 (1 H, m, H-2eq), 1.87-1.69 (2 H, m, H-4eq and H-3eq), 1.46-1.16 (13 H, m, H-12, H-5a, H-4a, H-3a, H-2a).

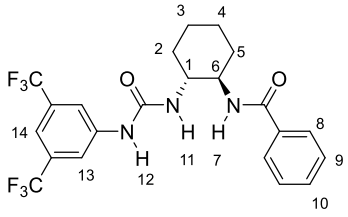
***N*-((1*R*,2*R*)-2-Aminocyclohexyl)benzamide (344)**



Compound **343** (0.160 g, 0.50 mmol) was dissolved in MeOH (5.00 mL) and HCl-MeOH (0.130 mL, 4.0 M), was added. The reaction was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the crude was dissolved in $CH_2Cl_2$. The organic solution was treated with 1.0 M HCl and the aqueous phase extracted and basified with 1.0 M NaOH. The aqueous phase was extracted with $CH_2Cl_2$. The organic phase was dried over $MgSO_4$ and the solvent removed to afford compound **344** (0.100 g, 0.458 mmol, 91%). M.p. 180-181 ºC (lit.[171] 176.5-179.8 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 7.73 (2 H, d, *J* 7.3, H-8), 7.40 (1 H, t, *J* 7.3, H-10), 7.33 (2 H, app. t, H-9), 6.51 (1 H, d, *J* 7.7, H-7), 3.70-3.58 (1 H, m, H-6), 2.50-2.40 (1 H, m, H-1), 2.06-1.93 (2 H, m, H-5eq and H-2eq), 1.73-1.60 (2 H, m, H-4eq and H-3eq), 1.27-1.09 (4 H, m, H-5a, H-4a, H-3a and H-2a).

***N*-((1*R*,2*R*)-2-(3,5-bis(trifluoromethyl)phenyl)ureido)cyclohexyl)benzamide (345)**



To a 10 mL round-bottomed flask containing amide **344** (0.100 g, 0.458 mmol), THF (2.0 mL) was added and placed at 0 ºC. 3,5-*Bis*(trifluoromethyl)phenyl isocyanate (**245**, 74.6 μL, 0.458 mmol) was added dropwise and the flask was stirred at room temperature for 5 h. The solvent was removed and the product purified by a column chromatography to afford catalyst **345** as a white solid (0.163 g, 0.343 mmol, 75%).

**$\delta_H$ (600 MHz, DMSO)** 9.24 (1 H, s, H-12), 8.29 (1 H, d, *J* 8.5, H-11), 7.98 (2 H, s, H-13), 7.78 (2 H, dd, *J* 1.3, 8.5, H-8), 7.49 (1 H, s, H-14), 7.45 (1 H, app. t, H-10), 7.35 (2 H, app. t, H-9), 6.34 (1 H, d, *J* 8.3, H-

7), 3.86-3.78 (1 H, m, H-6), 3.66-3.59 (1 H, m, H-1), 2.02-1.95 (1 H, m, H-2eq), 1.91-1.85 (1 H, m, H-5eq), 1.75-1.69 (2 H, m, H-4eq and H-3eq), 1.50-1.41 (1 H, m, H-5a), 1.36-1.21 (3 H, m, H-4a, H-3a and H-2a).

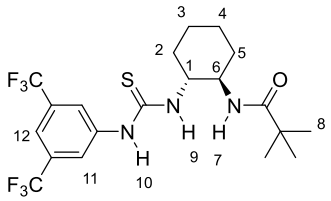
**$\delta_C$ (151 MHz, DMSO)** 166.2 (C=O), 154.9 (C=O), 142.4 (q), 134.7 (q), 130.9, 130.5 (q, $J_{C-F}$ 33.4, q), 127.9, 127.1, 123.3 (q, $J_{C-F}$ 274.1, q), 117.1, 113.4, 53.0 (x2), 32.3, 31.8, 24.6, 24.5.

**$\delta_F$ (376 MHz, DMSO)** -61.8.

**$\nu_{max}$ (neat)/cm$^{-1}$** 3289, 2922, 1630, 1525, 1498, 1394, 1275, 1140, 987, 767, 699.

**HRMS (*m/z* – APCI)** $[M+H]^+$ Found. 474.1612. $C_{22}H_{22}F_6N_3O_2$ Requires 474.1610.

***N*-((1*R*,2*R*)-2-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)pivalamide (322)**




To an oven-dried 50 mL round-bottom flask containing monothiourea **314** (0.400 g, 1.04 mmol) was added dry THF (10 mL) and triethylamine (0.291 mL, 2.08 mmol). The flask was placed in an ice bath and pivaloyl anhydride (0.232 mL, 1.14 mmol) was added dropwise and the mixture was stirred at room temperature for 16 h. The solvent was removed and the crude was purified by silica gel chromatography. Catalyst **322** was isolated as a white powder (0.335 g, 0.759 mmol, 73%). M. p. 145-147 ºC. $[\alpha]^{20}_D$ = +107.5 (c 0.1, MeOH).

**$\delta_H$ (600 MHz, DMSO)** 10.14 (1 H, s, H-10), 8.17 (2 H, s, H-11), 7.98 (1 H, d, *J* 8.0, H-9), 7.74 (1 H, s, H-12), 7.26 (1 H, d, *J* 7.9, H-7), 4.36-4.26 (1 H, m, H-1), 3.74-3.67 (1 H, m, H-6), 2.06-1.96 (1 H, m, H-5eq), 1.85-1.77 (1 H, m, H-2eq), 1.75-1.63 (2 H, m, H-4eq and H-3eq), 1.45-1.20 (4 H, m, H-5a, H-4a, H-3a and H-2a), 1.06 (9 H, s, H-8).

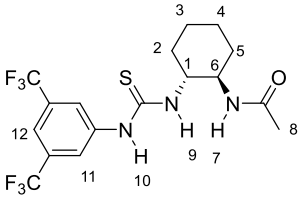
**$\delta_C$ (100 MHz, $CDCl_3$)** 181.9 (q), 180.4 (C=O), 140.5 (q), 131.7 (q, $J_{C-F}$ 33.1, q), 124.4, 123.2 (q, $J_{C-F}$ 272.3, q), 118.4, 56.8, 54.9, 38.8, 32.5, 27.3, 25.1, 24.7.

**$\delta_F$ (376 MHz, $CDCl_3$)** -63.1.

**$\nu_{max}$ ($cm^{-1}$)** 3293, 2938, 1619, 1527, 1473, 1383, 1275, 1171, 1126, 969, 890, 681.

**HRMS (*m/z* - ESI)** $[M-H]^-$ Found 468.1561. $C_{20}H_{24}F_6N_3OS$ requires 468.1549.

***N*-((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)acetamide (321)**




To an oven-dried 50 mL round-bottom flask containing monothiourea **314** (0.150 g, 0.389 mmol) was added dry THF (10 mL) and triethylamine (0.112 mL, 0.856 mmol). The flask was placed in an ice bath and acetic anhydride (0.040 mL, 0.428 mmol) was added dropwise and the mixture was stirred at room temperature for 16 h. The solvent was removed and the crude purified by silica gel chromatography. Catalyst **321** was isolated as a white powder (0.152 g, 0.355 mmol, 83%). M. p. 203-204 ºC. $[\alpha]^{20}_D$ = +49 (c 0.1, MeOH).

**$\delta_H$ (600 MHz, DMSO)** 10.17 (1 H, s, H-10), 8.27 (2 H, s, H-11), 8.02-7.87 (2 H, m, H-9 and H-7), 7.75 (1 H, s, H-12), 4.12-4.01 (1 H, m, H-1), 3.77-3.68 (1 H, m, H-6), 2.28-2.18 (1 H, m, H-5eq), 1.90-1.78 (4 H, m, H-8 and H-2eq), 1.75-1.65 (2 H, m, H-4eq and H-3eq), 1.36-1.14 (4 H, m, H-5a, H-4a, H-3a and H-2a).

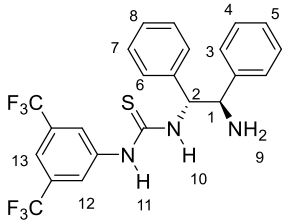
**$\delta_C$ (151 MHz, DMSO)** 180.4 (q), 170.0 (C=O), 142.3 (q), 130.6 (q, $J_{C-F}$ 33.2, q), 123.7 (q, $J_{C-F}$ 275.1, q), 122.3, 116.5, 79.6, 79.4, 79.2, 58.2, 51.6, 32.4, 31.5, 24.8, 24.6, 23.2.

**$\delta_F$ (376 MHz, DMSO)** -61.6.

**$\nu_{max}$ (cm$^{-1}$)** 3296, 3102, 2928, 1625, 1600, 1545, 1473, 1389, 1270, 1133, 879, 678.

**HRMS (*m/z* – ESI$^-$)** $[M+H]^+$ Found. 428.1210. $C_{17}H_{19}F_6N_3OS$ Requires. 428.1225.

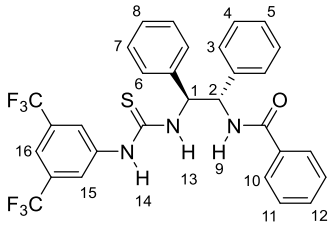
**1-((1*R*,2*R*)-2-Amino-1,2-diphenylethyl)-3-(3,5-*bis*(trifluoromethyl)phenyl)thiourea (337)**



3,5-*bis*(Trifluoromethyl)phenyl isothiocyanate (**313**, 0.182 mL, 0.271 mmol) was added to a stirred solution of **336** (0.212 g, 1.00 mmol) in THF (10.0 mL) at 0 ºC over a period of 30 min. After the addition the solution was warmed up at room temperature and stirred for 5 h. The solvent was removed *in vacuo* and the crude was purified by column chromatography to afford chiral amine **337** (0.227 g, 0.47 mmol, 47%). M.p. 89-91 ºC (lit.[167] 91-93 ºC)

**$\delta_H$ (400 MHz, DMSO)** 10.40 (1 H, s, H-11), 8.08 (2 H, s, H-12), 7.49 (1 H, s, H-113), 7.49-7.00 (10 H, m, H-8, H.7, H-6, H-5, H-4 and H-3), 5.25 (1 H, s, H-2), 4.13 (1 H, s, H-1), 2.91 (3 H, br s, H-10 and H-9).

***N*-((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-1,2-diphenylethyl)benzamide (338)**



To an oven-dried 50 mL round-bottom flask containing monothiourea **337** (0.200 g, 0.417 mmol) was added dry THF (5.00 mL) and triethylamine (0.127 mL, 0.917 mmol). The flask was placed in an ice-bath and freshly distilled benzoyl chloride (**316**, 0.050 mL, 0.417 mmol) was added dropwise and the mixture was stirred at room temperature for 14 h. The solvent removed and the crude purified by silica gel chromatography. Catalyst **338** was isolated as a white powder (0.147 g, 0.250 mmol, 53%). M. p. 80-83 ºC. $[\alpha]^{20}_D$ = +30 (c 0.1, MeOH).

**$\delta_H$ (600 MHz, DMSO)** 8.09 (2 H, s, H-15), 8.06 (1 H, s, H-16), 7.54-7.11 (18 H, m, H-14, H-13, H-12, H-11, H-10, H-9, H-8, H-7, H-6, H-5, H-4 and H-3), 5.15 (1 H, d, *J* 5.2, H-1), 4.94 (1 H, br s, H-2).

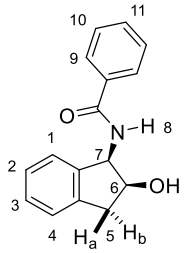
**$\delta_C$ (151MHz, DMSO)** 170.2 (q), 168.9 (C=O), 153.5 (q), 143.0 (q), 140.8 (q), 135.1 (q), 133.8, 132.4, 132.2, 131.5 (q, $J_{C-F}$ 33.1, q), 129.4, 129.2, 128.8, 128.6, 128.5, 128.0, 127.1, 123.2 (q, $J_{C-F}$ 274.0, q), 121.4, 75.2, 72.8.

**$\delta_F$ (376 MHz, DMSO)** -61.6.

**$\nu_{max}$ ($cm^{-1}$)** 3020, 1677, 1630, 1449, 1377, 1321, 1278, 1132, 696.

**HRMS (*m/z* – ESI)** $[M-H_3S]^-$ Found 552.153768. $C_{30}H_{20}F_6N_3O$ Requires 552.151605.

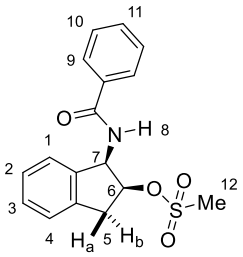
***N*-((1*R*,2*S*)-2-Hydroxy-2,3-dihydro-1*H*-inden-1-yl)benzamide (327)**




To an oven-dried 100 mL round-bottom flask containing **326** (1.00 g, 6.70 mmol) and THF (60 mL), $NEt_3$ (1.03 mL, 7.36 mmol) was added *via* syringe. The flask was placed in ice-bath and benzoyl chloride (**316**, 0.778 mL, 6.70 mmol) was added dropwise *via* syringe. The mixture was stirred at room temperature for 4 h. The solvent was removed and the mixture was triturated with EtOAc (15 mL) and then with $H_2O$. Compound **327** was isolated by filtration as a white solid (1.66 g, 6.57 mmol, 98%). NMR spectral data of **327** matches with the literature data.[172]

**$\delta_H$ (400 MHz, $CDCl_3$)** 7.86 (2 H, d, *J* 7.3, H-9), 7.53 (1 H, app. t, H-11), 7.46 (2 H, app. t, H-10), 7.37 (1 H, d, *J* 6.9, H-1), 7.31-7.26 (3 H, m, H-4, H-3 and H-2), 6.81 (1 H, br. s, H-8), 5.64 (1 H, dd, *J* 5.1, 8.0, H-7), 4.80-4.74 (1 H, m, H-6), 3.37 (1 H, dd, *J* 5.1, 16.2, H-5a), 3.01 (1 H, dd, *J* 1.6, 16.2, H-5b).

**(1*R*,2*S*)-1-Benzamido-2,3-dihydro-1*H*-inden-2-yl methanesulfonate (332)**

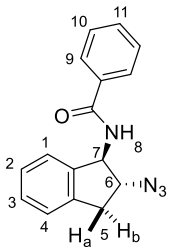


Compound **327** (1.38 g, 5.44 mmol) was placed in a 50 mL round-bottomed flask and dissolved in $CH_2Cl_2$ (15.0 mL). Triethylamine (2.27 mL, 16.3 mmol) was added and the flask was placed at 0 ºC. Mesylchloride (0.632 mL, 8.16 mmol) was added and the mixture was warmed at room temperature and stirred for 48 h. The resulting solution was diluted with $CH_2Cl_2$ and washed consecutively with 1.0 M HCl, 10% (w/v) $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo* to afford compound **332** (1.54 g, 5.44 mmol, 86%) that was used without further purification.

**$\delta_H$ (400 MHz, DMSO)** 8.89 (1 H, d, *J* 8.0, H-8), 7.96 (2 H, d, *J* 6.9, H-9), 7.60-7.15 (7 H, m, H-11, H-10, H-4, H-3, H-2 and H-1), 5.84-5.72 (1 H, m, H-7), 5.51-5.39 (1 H, m, H-6), 3.39 (1 H, dd, *J* 17.4, 4.3, H-5a), 3.21 (1 H, d, *J* 17.4, H-5b), 3.09 (3 H, s, H-12).

**HRMS (*m/z* – ESI$^-$)** Found 354.0764 $[M+Na]^+$ $C_{17}H_{17}NO_4NaS$ Requires 354.0770.

***N*-((1*R*,2*R*)-2-Azido-2,3-dihydro-1*H*-inden-1-yl)benzamide (333)**



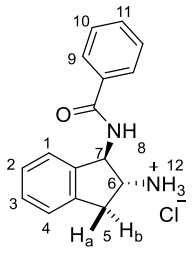
To a 100 mL round-bottomed flask containing compound **332** (1.00 g, 3.02 mmol) in DMF (30.0 mL), sodium azide (0.210 g, 3.23 mmol) was added and the reaction was placed at 60 ºC for 22 h. The resulting solution was allowed to cool down at room temperature and it was diluted with EtOAc and washed with cold water. The organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified by column chromatography to

afford compound **333** (0.531 g, 1.91 mmol, 63%). NMR spectral data of **333** matches with the literature data.[173]

**$\delta_H$ (400 MHz, DMSO)** 8.99 (1 H, d, *J* 9.7, H-8), 7.91 (2 H, d, *J* 7.9, H-9), 7.59-7.44 (3 H, m, H-11 and H-10), 7.30-7.13 (4 H, m, H-4, H-3, H-2 and H-1), 5.51 (1 H, app. t, H-7), 4.39 (1 H, app. q, H-6), 3.37-3.25 (1 H, m, H-5a (under H2O resonance)), 2.84 (1 H, dd, *J* 15.3, 8.1, H-5b).

**HRMS (*m/z* – ESI$^-$)** Found. 301.1056 $[M+Na]^+$ $C_{16}H_{14}N_4NaO$ Requires. 301.1059.

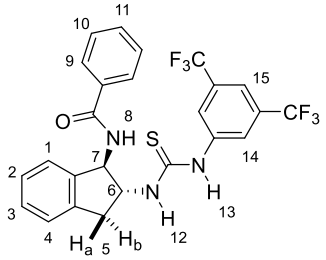
**(1*R*,2*R*)-1-Benzamido-2,3-dihydro-1*H*-inden-2-aminium chloride (334)**




Triphenylphosphine (0.498 g, 1.90 mmol) and compound **333** (0.530 g, 1.90 mmol) were placed in a 50 mL round-bottomed flask and dissolved in anhydrous THF (16.0 mL). The reaction was stirred at 45 ºC for 14 h. Deionised water (3.00 mL) was added and the reaction was stirred at 45 ºC for an additional 24 h. The solvent was reduced under reduce pressure and the oil obtained dissolved $CH_2Cl_2$ and 1.0 M HCl. The aqueous layer was extracted, washed with $CH_2Cl_2$ and the water removed to afford the hydrochloride salt **334** (0.400 g, 1.39 mmol, 73%). M.p. 283-285 ºC (lit.[173] 285-287 ºC).

**$\delta_H$ (400 MHz, DMSO)** 9.00 (1 H, d, *J* 8.4, H-8), 8.50 (3 H, br. s, H-12), 7.96 (2 H, d, *J* 7.3, H-9), 7.56 (1 H, t, *J* 7.2, H-11), 7.53-7.45 (2 H, app. t, H-10), 7.33-7.15 (4 H, m, H-1, H-2, H-3 and H-4), 5.73-5.65 (1 H, app. t, H-7), 4.03-3.87 (1 H, app. q, H-6), 3.35 (1 H, dd, *J* 15.8, 8.2 H-5a), 2.99 (1 H, dd, *J* 15.8, 8.9, H-5b).

**_N_-((1_R_,2_R_)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-2,3-dihydro-1_H_-inden-1-yl)benzamide (335)**




Salt **334** (0.200 g, 0.693 mmol) was placed in an oven-dried 25 mL round-bottom flask and suspended in THF (7 mL). Triethylamine (0.144 mL, 1.04 mmol) was added and the mixture was stirred for 10 min. The flask was placed in an ice-bath and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**313**, 0.126 mL, 0.693 mmol) was added dropwise and the mixture was stirred at room temperature for 14 h. The reaction was diluted with $H_2O$ and extracted with ethyl acetate. The organic phase was washed with brine and dried over magnesium sulphate. The solvent was removed and the crude was purified by silica gel chromatography. Catalyst **335** was obtained as a white solid (0.264 g, 0.506 mmol, 73%). M.p. 188-191 ºC. $[\alpha]^{20}_D$ = -64.7 (c 0.1, MeOH).

**$\delta_H$ (400 MHz, DMSO)** 10.20 (1 H, s, H-12), 9.02 (1 H, d, *J* 8.7, H-8), 8.72 (2 H, s, H-14), 7.96 (2 H, d, *J* 6.8, H-9), 7.73 (1 H, s, H-15), 7.55 (1 H, app. t, H-11), 7.52-7.44 (2 H, m, H-10), 7.33-7.13 (4 H, m, H-4, H-3, H-2 and H-1), 5.83-5.67 (1 H, m, H-7), 5.25-5.09 (1 H, m, H-6), 3.63-3.51 (1 H, m, H-5a), 2.91-2.74 (1 H, m, H-5b).

**$\delta_C$ (151 MHz, DMSO)** 181.4 (q), 167.3 (C=O), 142.3 (q), 142.1 (q), 140.0 (q), 134.6 (q), 131.8, 130.7 (q, $J_{C-F}$ 31.3, q), 128.7, 128.3, 128.0, 127.3, 125.2, 124.1, 123.7 (q, $J_{C-F}$ 274.0, q) 122.4, 61.8, 58.7, 36.4.

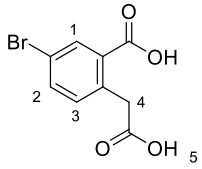
**$\delta_F$ (376 MHz, DMSO-*d*$_6$)** -61.6.

**$\nu_{max}$ (cm$^{-1}$)** 3275, 2959, 1638, 1523, 1473, 1381, 1274, 1127, 884, 680

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 524.1230. $C_{25}H_{20}F_6N_3OS$ requires 524.1225.

### 5.3.3 Synthesis of anhydrides

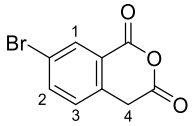
**5-Bromo-2-(carboxymethyl)benzoic acid (346)**




A 100 mL round-bottomed flask equipped with a condenser was charged with homophthalic acid (**222**, 5.00 g, 27.0 mmol), potassium bromate (6.60 g, 40.0 mmol) and water (30 mL). The reaction was heated at 90 ºC and conc. $H_2SO_4$ (25 mL) dissolved in water (40 mL) was added over a period of 30 min. After the addition, the reaction was stirred for 2 h at that temperature. The reaction was cooled down at room temperature and the precipitate formed was filtered and washed with water (25 mL). The solid was recrystallised from EtOAc to furnish compound **346** as a white solid (3.15 g, 12.1 mmol, 45%). M.p. 209-210 ºC (lit.[174] 210-211 ºC).

**$\delta_H$ (400 MHz, DMSO-$d_6$)** 7.97 (1 H, d, *J* 2.1, H-1), 7.70 (1 H, dd, *J* 8.1, 2.1, H-2), 7.29 (1 H, d, *J* 8.1, H-3), 3.90 (2 H, s, H-4).

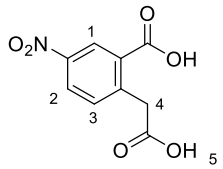
**7-Bromoisochromane-1,3-dione (196)**




Following general procedure **A**, 5-Bromo-2-(carboxymethyl)benzoic acid (**346**, 0.500 g, 1.93 mmol) was dissolved in freshly distilled acetyl chloride (5.0 mL). After purification, Anhydride **196** was isolated as a white solid (0.370 g, 1.54 mmol, 80%). M.p. 174-175 °C (lit.[77] 171-173 °C).

**$\delta_H$ (400 MHz, DMSO-$d_6$)** 8.11 (1 H, d, *J* 1.9, H-1), 7.92 (1 H, dd, *J* 8.4, 1.9, H-2), 7.40 (1 H, d, *J* 8.4, H-3), 4.21 (2 H, s, H-4).

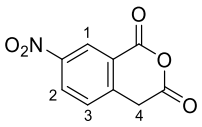
**2-(Carboxymethyl)-5-nitrobenzoic acid (348)**



A 100 mL round-bottomed flask containing fuming $HNO_3$ (15.0 mL) was cooled to 0 ºC. Homophthalic acid (**222**, 2.00 g, 11.1 mmol) was added portionwise, keeping the temperature of the reaction below 15 ºC. After the addition, the mixture was stirred at 0 ºC for 2 h. Crushed ice (15.0 g) and water (20 mL) were added to the mixture and the white precipitate collected by filtration. The product was recrystallised from $H_2O$ and the product was obtained as a white solid (1.82 g, 8.10 mmol, 73%). M.p. 231-232 ºC (lit.[175] 235 ºC).

**$\delta_H$ (400 MHz, DMSO-$d_6$)** 13.58 (1 H, br. s, H-6), 12.43 (1 H, br. s, H-5), 8.60 (1 H, d, *J* 3.1, H-1), 8.34 (1 H, dd, *J* 8.4, 3.1, H-2), 7.65 (1 H, d, *J* 8.4, H-3), 4.08 (2 H, s, H-4).

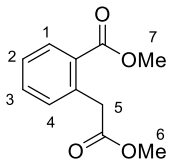
**7-Nitroisochromane-1,3-dione (349)**



Following general procedure **A**, using 2-(Carboxymethyl)-5-nitrobenzoic acid (**328**, 0.500 g, 2.22 mmol) in freshly distilled acetyl chloride (5.0 mL) After purification anhydride **349** (0.370 g, 1.79 mmol, 80%) was isolated by filtration as a white solid. M.p. 153-155 °C (lit.[77] 154-155 °C)

**$\delta_H$ (400 MHz, DMSO-$d_6$)** 8.11 (1 H, d, *J* 1.9, H-1), 7.92 (1 H, dd, *J* 8.4, 1.9, H-2), 7.40 (1 H, d, *J* 8.4, H-3), 4.21 (2 H, s, H-4).

**Methyl 2-(2-methoxy-2-oxoethyl)benzoate (350)**

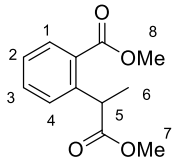


Homophthalic acid (**222**, 4.00 g, 22.2 mmol) was placed in a 100 mL round-bottomed flask and MeOH (70.0 mL) was added. $SOCl_2$ (4.80 mL, 66.6 mmol) was added at 0 ºC and the

reaction was heated under reflux for 14 h. The reaction was cooled at room temperature and the excess of $SOCl_2$ was quenched with a saturated aqueous solution of $NaHCO_3$. The volatiles were removed under pressure and the mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to afford compound **350** as a white solid (4.48 g, 21.6 mmol, 97%). M.p. 57-59 ºC (lit.[176] 52-56 ºC)

**$\delta_H$ (400 MHz, $CHCl_3$)** 8.02 (1 H, dd, *J* 7.8, 1.2, H-1), 7.51-7.46 (1 H, m, H-3), 7.40-7.33 (1 H, m, H-2), 7.25 (1 H, d, *J* 7.4, H-4), 4.01 (2 H, s, H-5), 3.87 (3 H, s, H-7), 3.70 (3 H, s, H-6).

**Methyl 2-(1-methoxy-1-oxopropan-2-yl)benzoate[176] (351)**

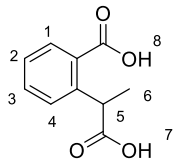



An oven-dried 100 mL round-bottomed flask was charged with **350** (3.00 g, 14.4 mmol) in anhydrous THF (15.0 mL). Potassium *tert*-butoxide (1.62 g, 14.4 mmol) was added at 0 ºC and the reaction was allowed to stir at that temperature for 30 min. MeI (0.965 mL, 15.8 mmol) was added and the reaction was stirred at room temperature for 12 h. The reaction was quenched with $Na_2S_2O_3$ and extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. The organic solvent was removed *in vacuo* and the crude was purified by column chromatography to afford compound **351** (1.25 g, 5.62 mmol, 40%).

**$\delta_H$ (400 MHz, $CHCl_3$)** 7.91 (1 H, dd, *J* 7.9, 1.3, H-1), 7.49 (1 H, m, H-3), 7.38 (1 H, d, *J* 8.0, H-4), 7.32 (1 H, m, H-2), 4.65 (1 H, q, *J* 7.1, H-5), 3.89 (3 H, s, H-8), 3.65 (3 H, s, H-7), 1.53 (3 H, d, *J* 7.1).

**HRMS (*m/z* – ESI)** $[M+H]^+$ Found 223.0890. $C_{12}H_{15}O_4$ Requires 223.0891.

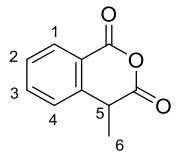
**2-(1-Carboxyethyl)benzoic acid (352)**




To a solution of compound **351** (1.25 g, 5.62 mmol) in a mixture $H_2O$:MeOH (20 mL, 1:1) KOH (3.16 g, 56.2 mmol) was added and the mixture was heated at 80 ºC for 5 h. The reaction was cooled at room temperature and the volatiles were removed under reduce pressure to afford compound **352** as a white solid (0.730 g, 3.76 mmol, 67%). M.p. 143-146 ºC (lit.[177] 149-150 ºC).

**$\delta_H$ (400 MHz, DMSO)** 12.58 (2 H, br. s, H-8 and H-7), 7.79 (1 H, d, *J* 8.0, H-1), 7.51 (1 H, m, H-3), 7.40-7.27 (2 H, m, H-4 and H-2), 4.55 (1 H, q, *J* 7.0, H-5), 1.37 (3 H, d, *J* 7.0, H-6).

**4-Methylisochromane-1,3-dione (353)**

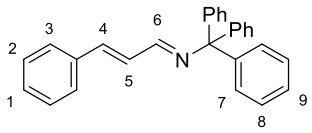



Following general procedure **A**, 2-(1-Carboxyethyl)benzoic acid (**352**, 730 g, 3.76 mmol) was dissolved in acetyl chloride (10 mL). After purification anhydride **353** was isolated as a white powder (0.483 g, 2.74 mmol, 73%). M.p. 170-170 ºC (lit.[79] 171-173 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.20 (1 H, d, *J* 7.9, H-1), 7.72 (1 H, app. t, H-3), 7.51 (1 H, app. t, H-2), 7.40 (1 H, d, *J* 7.9, H-4), 4.07 (1 H, q, *J* 7.4, H-5) 1.74 (3 H, d, *J* 7.4, H-6).

### 5.3.4 Synthesis of imines

**(1*E*,2*E*)-3-Phenyl-*N*-tritylprop-2-en-1-imine[136] (208)**

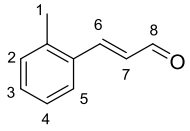



Following general procedure **E**, triphenylmethylenamine (**311**, 2.06 g, 7.93 mmol), cinnamaldehyde (**310**, 1.00 mL, 7.93 mmol) and toluene (20 mL) were heated at reflux for 16 h. After purification **208** was isolated as a white solid (2.25 g, 6.03 mmol, 76%).

**$\delta_H$ (400 MHz, $CDCl_3$)** 7.70 (1 H, d, *J* 8.7, H-6), 7.49 (2 H, m, H-3), 7.40-7.15 (19 H, m, H-1, H-2, H-7, H-8 and H-9), 6.86 (1 H, d, *J* 15.9, H-4).

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 374.1906. $C_{28}H_{24}N$ requires 374.1903.

**(*E*)-3-(*o*-Tolyl)acrylaldehyde (357)**

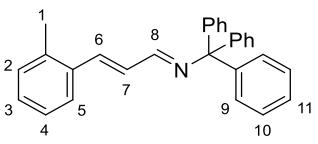



Following general procedure **D**, starting from *o*-tolualdehyde (**384**, 0.463 mL, 4.00 mmol). Compound **357** was isolated as a colourless oil (0.140 g, 0.958 mmol, 24%). NMR spectral data of **357** matches with the literature data.

**$\delta_H$ (400 MHz, $CDCl_3$)** 9.73 (1 H, d, *J* 7.7, H-8), 7.78 (1 H, d, *J* 15.8, H-6), 7.60 (1 H, m, H-5), 7.37-7.30 (1 H, m, H-3), 7.29-7.22 (2 H, m, H-4 and H-2), 6.67 (1 H, dd, *J* 15.8, 7.7, H-7), 2.48 (3 H, s, H-1).

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 147.0832. $C_{10}H_{11}O$ Requires 147.0833

**(1*E*,2*E*)-3-(*o*-Tolyl)-*N*-tritylprop-2-en-1-imine (S4)**




Following general procedure **E**, **357** (0.140 g, 0.958 mmol), triphenylmethylenamine (0.248 g, 0.958 mmol) were dissolved in toluene (25 mL) and heated at reflux for 16 h. The

compound **370** was obtained as a white solid (0.114 g, 0.780 mmol, 81%). M. p. 109-110 ºC.

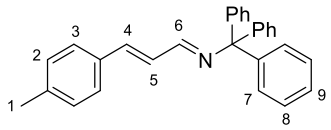
**$\delta_H$ (400 MHz, $CDCl_3$)** 7.72 (1 H, d, *J* 7.7, H-8), 7.65-7.60 (1 H, m, H-5), 7.35-7.08 (20 H, m, H-11, H-10, H-9, H-7, H-6, H-4, H-3, H-2), 2.35 (3 H, s, H-1).

**$\delta_C$ (100 MHz, $CDCl_3$)** 162.2, 145.8 (q), 139.8, 136.5 (q), 134.6, 130.6 (q), 129.8, 128.9, 127.8, 126.8, 126.3, 125.9, 78.7 (q), 19.9.

**$\nu_{max}$ ($cm^{-1}$)** 2981, 1534, 1454, 1382, 1252, 1162, 980, 818.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 388.2050. $C_{29}H_{26}N$ requires 388.2059.

**(1*E*,2*E*)-3-(*p*-Tolyl)-*N*-tritylprop-2-en-1-imine (371)**




Following general procedure **E**, 4-methylcinnamaldehyde (**358**, 0.439 g, 3.00 mmol), tritphenylmethylenamine (0.778 g, 3.00 mmol) were dissolved in toluene (25 mL) and heated at reflux for 16 h. The compound **371** was obtained as a white solid (0.750 g, 1.93 mmol, 64%). M.p. 160-161 ºC.

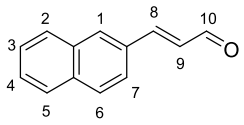
**$\delta_H$ (400 MHz, $CDCl_3$)** 7.68 (1 H, d, *J* 8.7, H-6), 7.37 (2 H, d, *J* 7.8, H-3), 7.34-7.11 (18 H, m, H-9, H-8, H-7, H-5 and H-2), 6.82 (1 H, d, *J* 16.2, H-4), 3.26 (3 H, s, H-1).

**$\delta_C$ (100 MHz, $CDCl_3$)** 162.2, 145.8 (q), 142.4, 139.3 (q), 133.1 (q), 129.8, 129.5, 128.1, 127.7, 127.2, 126.7, 78.6 (q), 21.4.

**$\nu_{max}$ ($cm^{-1}$)** 3029, 1629, 1605, 1490, 1444, 1145, 1003, 973, 752, 703.

**HRMS (*m/z* - APCI)** $[M+H]^+$ Found 388.2055. $C_{29}H_{26}N$ requires 388.2059.

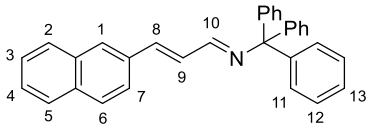
**(*E*)-3-(Naphthalen-2-yl)acrylaldehyde (359)**




Following general procedure **D**, starting from 2-naphthaldehyde (**226**, 0.625 g, 4.00 mmol). Compound **359** was isolated as a white solid (0.320 g, 1.76 mmol, 44%). M.p. 118-119 ºC (lit.[178] 118-119 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 9.77 (1 H, d, *J* 7.7, H-10), 8.00 (1 H, br. s, H-1), 7.92-7.84 (3 H, m, H-6, H-5 and H-2), 7.69 (1 H, dd, *J* 8.2, 1.3, H-7), 7.65 (1 H, d, *J* 15.9, H-8), 7.59-7.51 (2 H, m, H-4 and H-3), 6.84 (1 H, dd, *J* 15.9, 7.7, H-9).

**(1*E*,2*E*)-3-(Naphthalen-2-yl)-*N*-tritylprop-2-en-1-imine (372)**




Following general procedure **E**, (*E*)-3-(naphthalene-2-yl)acrylaldehyde (**359**, 0.320 g, 1.76 mmol), triphenylmethylenamine (0.456 g, 1.76 mmol) were dissolved in toluene (25 mL) and heated at reflux for 16 h. The compound **372** was obtained as a white solid (0.440 g, 1.04 mmol, 59%). M. p. 194-195 ºC.

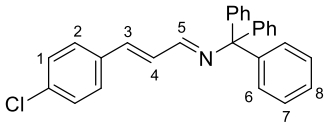
**$\delta_H$ (400 MHz, $CDCl_3$)** 7.86-7.78 (4 H, m, H-6, H-5, H-2 and H-1), 7.75 (1 H, d, *J* 8.7, H-10), 7.70 (1 H, dd, *J* 8.6, 1.5, H-7), 7.52-7.44 (2 H, m, H-4 and H-3), 7.38-7.21 (16 H, m, H-13, H-12, H-11 and H-9), 7.02 (1 H, d, *J* 15.9, H-8).

**$\delta_C$ (100 MHz, $CDCl_3$)** 162.1, 145.7 (q), 142.4, 133.7 (q), 133.4 (q), 129.8, 129.3, 128.6, 128.3, 128.2, 127.8, 127.7, 126.8, 126.7 (q), 126.5, 123.5, 78.8 (q).

**$\nu_{max}$ ($cm^{-1}$)** 2981, 1638, 1616, 1442, 1000, 810, 757, 698.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 424.2059. $C_{32}H_{26}N$ requires 424.2059.

**(1*E*,2*E*)-3-(4-Chlorophenyl)-*N*-tritylprop-2-en-1-imine (377)**



Following general procedure **E**, 4-chlorocinnamaldehyde (**364**, 0.500 g, 3.00 mmol), triphenylmethylenamine (0.778 g, 3.00 mmol) were dissolved in toluene (25 mL) and heated at reflux for 16 h. The compound **377** was obtained as a white solid (0.740 g, 1.81 mmol, 60%). M.p. 147-149 ºC.

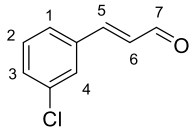
**$\delta_H$ (400 MHz, $CDCl_3$)** 7.68 (1 H, d, *J* 8.6, H-5), 7.41 (2 H, d, *J* 7.7, H-2), 7.36-7.15 (18 H, m, H-8, H-7, H-6, H-4, H-1), 6.81 (1 H, d, *J* 16.0, H-3).

**$\delta_C$ (151 MHz, $CDCl_3$)** 161.7, 145.6 (q), 140.9, 134.9 (q), 134.4 (q), 129.8, 129.6, 129.1, 128.4, 127.8, 126.8, 78.8 (q).

**$\nu_{max}$ ($cm^{-1}$)** 2981, 1634, 1588, 1489, 1406, 1090, 809, 655.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 408.1512. $C_{28}H_{23}ClN$ requires 408.1513.

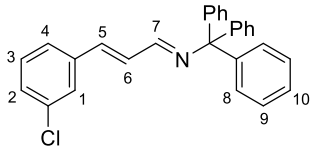
**(*E*)-3-(3-chlorophenyl)acrylaldehyde (364)**



Following general procedure **D**, starting from *m*-chlorobenzaldehyde (**387**, 0.453 mL, 4.00 mmol). Compound **364** was obtained as a white solid (0.342 g, 2.06 mmol, 51%). M.p. 37-39 ºC (lit.[179] 38.5-39.5 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 9.71 (1 H, d, *J* 7.5, H-7), 7.54 (1 H, s, H-4), 7.48-7.33 (4 H, m, H-5, H-3, H-2 and H-1), 6.70 (1 H, dd, *J* 15.8, 7.5, H-6).

**(1*E*,2*E*)-3-(3-Chlorophenyl)-*N*-tritylprop-2-en-1-imine (379)**



Following general procedure **E**, 3-chlorocinnamaldehyde (**366**, 0.342 g, 2.06 mmol), triphenylmethilenamine (0.533 g, 2.06 mmol) were dissolved in toluene (25 mL) and heated

at reflux for 16 h. The compound **379** was obtained as a white solid (0.493 g, 1.21 mmol, 59%). M.p. 119-120 ºC

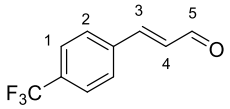
**$\delta_H$ (400 MHz, $CDCl_3$)** 7.67 (1 H, d, *J* 8.5, H-7), 7.46 (1 H, s, H-1), 7.37-7.14 (19 H, m, H-10, H-9, H-8, H-6, H-4, H-3 and H-2), 6.78 (1 H, d, *J* 16.1, H-5).

**$\delta_C$ (100 MHz, $CDCl_3$)** 161.4, 145.6 (q), 140.6, 137.7, 134.8 (q), 130.0 (q), 128.9, 128.1, 127.9, 127.1, 126.8, 125.2, 78.8 (q).

**$\nu_{max}$ ($cm^{-1}$)** 3024, 1626, 1601, 1511, 1190, 1173, 1026, 753, 699.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 408.1506. $C_{28}H_{23}ClN$ requires 408.1513.

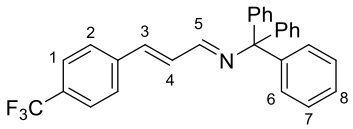
***(*E)-3-(4-(trifluoromethyl)phenyl)acrylaldehyde (365)**




Following general procedure **D**, starting from 4-(trifluoromethyl)benzaldehyde (**386**, 0.546 mL, 4.00 mmol). Compound **365** was isolated as a colourless oil (0.428 g, 2.14 mmol, 53%). NMR spectral data of **365** matches with the literature data.[180]

**$\delta_H$ (400 MHz, $CDCl_3$)** 9.75 (1 H, d, *J* 7.6, H-5), 7.72-7.65 (4 H, m, H-2 and H-1), 7.50 (1 H, d, *J* 16.0, H-3), 6.78 (1 H, dd, *J* 16.0, 7.6, H-4).

**(1*E*,2*E*)-3-(4-(Trifluoromethyl)phenyl)-*N*-tritylprop-2-en-1-imine (378)**




Following general procedure **E**, 4-(trifluoromethyl)cinnamaldehyde (**365**, 0.428 g, 2.14 mmol), triphenylmethylenamine (0.554 g, 2.14 mmol) were dissolved in toluene (25 mL) and heated at reflux for 16 h. The compound **378** was obtained as a white solid (0.620 g, 1.40 mmol, 66%). M. p. 149-150 ºC.

**$\delta_H$ (400 MHz, $CDCl_3$)** 7.70 (1 H, d, *J* 8.7, H-5), 7.61 (2 H, d, *J* 8.4, H-1), 7.57 (2 H, d, *J* 8.4, H-2), 7.32-7.18 (16 H, m, H-8, H-7, H-6 and H-4), 6.87 (1 H, d, *J* 16.1, H-3).

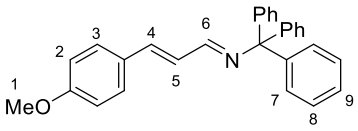
**$\delta_C$ (151 MHz, $CDCl_3$)** 161.4, 145.5 (q), 140.4, 139.3, 131.4 (q), 130.6 (q, $J_{C-F}$ 31.9, q), 129.8, 127.8, 127.3, 126.9, 125.8 (q, $J_{C-F}$ 4.1), 124.0 (q, $J_{C-F}$ 272.7, q), 78.9 (q).

**$\delta_F$ (376 MHz, $CDCl_3$)** -62.7.

**$\nu_{max}$ ($cm^{-1}$)** 2926, 1617, 1488, 1443, 1330, 1067, 999, 757, 703.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 442.1779. $C_{29}H_{23}F_3N$ requires 442.1777.

**(1*E*,2*E*)-3-(4-Methoxyphenyl)-*N*-tritylprop-2-en-1-imine (373)**




Following general procedure **E**, 4-methoxycinnamaldehyde (**360**, 0.487 g, 3.00 mmol), triphenylmethylenamine (0.778 g, 3.00 mmol) were dissolved in toluene (25 mL) and heated at reflux for 16 h. The compound **373** was obtained as a white solid (0.835 g, 2.07 mmol, 69%). M. p. 139-140 ºC.

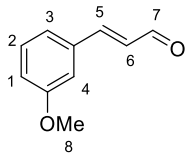
**$\delta_H$ (400 MHz, $CDCl_3$)** 7.67 (1 H, d, *J* 8.6, H-6), 7.42 (2 H, d, *J* 8.6, H-3), 7.35-7.20 (15 H, m, H-9, H-8 and H-7), 7.08 (1 H, dd, *J* 15.7, 8.6, H-5), 6.89 (2 H, d, *J* 8.6, H-2), 6.80 (1 H, d, *J* 15.7, H-4), 3.83 (3 H, s, H-1).

**$\delta_C$ (100 MHz, $CDCl_3$)** 162.3, 160.4 (q), 145.9 (q), 142.1, 129.8, 128.7 (x2), 127.7, 126.9 (q), 126.7, 114.2, 78.6 (q), 55.3.

**$\nu_{max}$ ($cm^{-1}$)** 3023, 1630, 1601, 1511, 1412, 1261, 1174, 1027, 999, 754, 699.

**HRMS (*m/z* - APCI)** $[M+H]^+$ Found 404.2009. $C_{29}H_{26}NO$ Requires 404.2008.

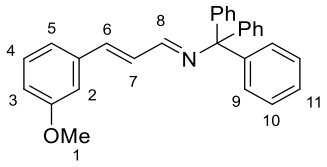
**(*E*)-3-(3-Methoxyphenyl)acrylaldehyde (361)**




Following general procedure **D**, starting from *m*-anisaldehyde (**223**, 0.518 mL, 4.00 mmol). Compound **361** was isolated as a white solid (0.291 g, 1.80 mmol, 45%). M.p. 35-37 ºC (lit. M.p. 37 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 9.71 (1 H, d, *J* 7.8, H-7), 7.45 (1 H, d, 15.9, H-5), 7.35 (1 H, m, H-2), 7.16 (1 H, d, *J* 7.7, H-3), 7.08 (1 H, br. s, H-4), 7.00 (1 H, d, *J* 7.8, H-1), 6.71 (1 H, dd, *J* 15.9, 7.8, H-6), 3.85 (3 H, s, H-8).

**(1*E*,2*E*)-3-(3-Methoxyphenyl)-*N*-tritylprop-2-en-1-imine (374)**




Following general procedure **E**, 3-methoxycinnamaldehyde (**361**, 0.291 g, 1.80 mmol), triphenylmethylenamine (0.467 g, 1.80 mmol) were dissolved in toluene (25 mL) and heated at reflux for 16 h. The compound **374** was obtained as a white solid (0.458 g, 1.13 mmol, 63%). M. p. 155-157 ºC.

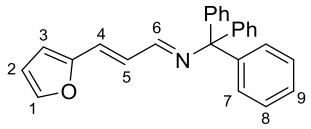
**$\delta_H$ (400 MHz, $CDCl_3$)** 7.71 (1 H, d, *J* 8.8, H-8), 7.36-7.17 (17 H, m, H-11, H-10, H-9, H-7 and H-4), 7.10-7.02 (2 H, m, H-5 and H-2), 6.91-6.80 (2 H, m, H-4 and H-3), 3.83 (3 H, s, H-1).

**$\delta_C$ (100 MHz, $CDCl_3$)** 162.0, 159.9 (q), 145.7 (q), 142.3, 137.3 (q), 129.8, 129.8, 129.3, 127.8, 126.8, 120.1, 115.2, 111.8, 78.8 (q), 55.2.

**$\nu_{max}$ ($cm^{-1}$)** 2981, 1633, 1588, 1489, 1406, 1091, 809, 698.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 404.2008. $C_{29}H_{26}NO$ requires 404.2008.

**(1*E*,2*E*)-3-(Furan-2-yl)-*N*-tritylprop-2-en-1-imine (375)**




Following general procedure **E**, *trans*-3-(2-furyl)acrolein (**362**, 0.366 g, 3.00 mmol), triphenylmethylenamine (0.778 g, 3.00 mmol) were dissolved in toluene (25 mL) and heated at reflux for 16 h. The compound **375** was obtained as a beige solid (0.710 g, 65%). M. p. 145-146 ºC.

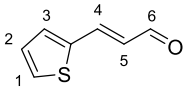
**$\delta_H$ (400 MHz, $CDCl_3$)** 7.60 (1 H, d, *J* 8.9, H-6), 7.45 (1 H, br s, H-1), 7.34-7.20 (15 H, m, H-9, H-8 and H-7), 7.08 (1 H, dd, *J* 15.9, 8.9, H-5), 6.64 (1 H, d, *J* 15.9, H-4), 6.46-6.41 (2 H, m, H-3 and H-2).

**$\delta_C$ (100 MHz, $CDCl_3$)** 161.4, 152.1 (q), 145.8 (q), 143.7, 129.8, 129.0, 127.7, 127.2, 126.7, 112.0, 111.6, 78.6 (q).

**$\nu_{max}$ ($cm^{-1}$)** 2981, 1618, 1481, 1442, 1144, 998, 963, 749, 698.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 364.1687. $C_{26}H_{22}NO$ requires 364.1696.

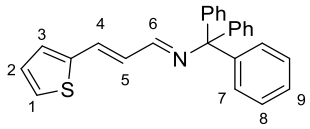
**(*E*)-3-(thiophen-2-yl)acrylaldehyde (363)**




Following general procedure **D**, starting from 2-thiophenecarboxaldehyde (**385**, 0.647 g, 4.00 mmol). Compound **363** was isolated as a colourless oil (0.275 g, 2.70 mmol, 67%). NMR spectral data of **363** matches with the literature data.[181]

**$\delta_H$ (400 MHz, $CDCl_3$)** 9.63 (1 H, d, *J* 7.7, H-6), 7.58 (1 H, d, *J* 15.8, H-4), 7.50 (1 H, d, *J* 4.4, H-1), 7.36 (1 H, d, *J* 3.3, H-3), 7.11 (1 H, dd, *J* 4.4, 3.3, H-2), 6.52 (1 H, dd, *J* 15.8, 7.7, H-5).

**(1*E*,2*E*)-3-(Thiophen-2-yl)-*N*-tritylprop-2-en-1-imine (376)**




Following general procedure **E**, (*E*)-3-(thiophen-2-yl)acrylaldehyde (**363**, 0.375 g, 2.70 mmol), triphenylmethylenamine (0.710 g, 2.82 mmol) were dissolved in toluene (25 mL) and heated at reflux for 16 h. The compound **376** was obtained as a yellow solid (0.360 g, 1.87 mmol, 69%). M. p. 147-148 ºC.

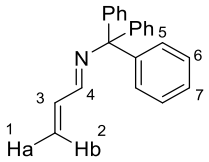
**$\delta_H$ (400 MHz, $CDCl_3$)** 7.65 (1 H, dd, *J* 7.0, 1.0, H-6), 7.38-7.22 (16 H, m, H-9, H-8, H-7 and H-3), 7.12 (1 H, dd, *J* 3.7, 1.0, H-1), 7.08-6.98 (3 H, m, H-5, H-4 and H-2).

**$\delta_C$ (100 MHz, $CDCl_3$)** 161.5, 145.7 (q), 141.2 (q), 134.8, 129.8, 128.4, 127.9, 127.0, 126.8, 78.7 (q).

**$\nu_{max}$ ($cm^{-1}$)** 2981, 1620, 1490, 1443, 960, 752, 698.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 380.1466. $C_{26}H_{22}NS$ requires 380.1467.

**(*E*)-*N*-Tritylprop-2-en-1-imine (392)**




An oven-dried 50 mL round-bottom flask was charged with triphenylmethilenamine (2.70 g, 10.6 mmol) fitted with a septum and placed under an atmosphere of argon. Dry $CH_2Cl_2$ (50 mL) was then added *via* syringe followed by $NEt_3$ (4.44 mL, 31.8 mmol) and acrolein (**391**, 0.500 mL, 10.6 mmol). The resulting solution was cooled to 0 ºC and $TiCl_4$ (0.580 mL, 5.30 mmol) was added dropwise to the solution at 0 ºC and it was allowed to stir, at same temperature for 1 h. The reaction mixture was filtered through celite and washed with $CH_2Cl_2$. The filtrate was concentrated *in vacuo* and the resulting solid was suspended in toluene and filtered to remove $NEt_3$.HCl. The filtrate was then concentrated *in vacuo* to afford **392** that was purified by recrystallisation from hexane and dichloromethane (0.630 g, 20%). M. p. 135-137 ºC.

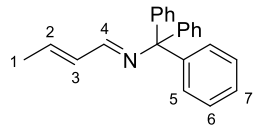
**$\delta_H$ (400 MHz, $CDCl_3$)** 7.54 (1 H, d, *J* 8.8, H-4), 7.36-7.18 (15 H, m, H-7, H-6 and H-5), 6.80 (1 H, ddd, *J* 17.3, 10.3, 8.8, H-3), 5.82 (1 H, d, *J* 10.3, H-1a), 5.61 (1 H, d, *J* 17.3, H-1b).

**$\delta_C$ (151 MHz, $CDCl_3$)** 162.2, 145.5 (q), 137.9, 129.8, 127.8, 127.4, 126.8, 78.5 (q).

**$\nu_{max}$ ($cm^{-1}$)** 2981, 1687, 1442, 1342, 1108, 658, 696.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 298.1585. $C_{22}H_{20}N$ requires 298.1590.

**(1*E*,2*E*)-*N*-Tritylbut-2-en-1-imine (380)**




Following general procedure **E**, crotonaldehyde (**367**, 0.500 mL, 6.03 mmol), triphenylmethylenamine (1.56 g, 6.03 mmol) were dissolved in toluene (50 mL) and heated at reflux for 16 h. The compound **380** was obtained as a beige solid (1.24 g, 4.16 mmol, 69%). M. p. 117-118 ºC.

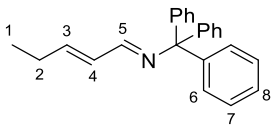
**$\delta_H$ (400 MHz, $CDCl_3$)** 7.47 (1 H, d, *J* 8.7, H-4), 7.32-7.15 (15 H, m, H-7, H-6 and H-5), 6.15 (1 H, ddq, *J* 15.5, 8.7, 1.7, H-3), 6.09 (1 H, dd, *J* 15.5, 6.7, H-2), 1.88 (3 H, dd, *J* 6.7, 1.7, H-1).

**$\delta_C$ (100 MHz, $CDCl_3$)** 162.0, 145.8 (q), 141.2, 132.9, 129.8, 127.7, 126.6, 78.2 (q), 18.4.

**$\nu_{max}$ ($cm^{-1}$)** 3019, 2932, 1654, 1616, 1499, 1441, 961, 756, 698

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 312.1744. $C_{23}H_{22}N$ requires 312.1747.

**(1*E*,2*E*)-*N*-Tritylpent-2-en-1-imine (381)**




Following general procedure **E**, *trans*-2-pentenal (**368**, 0.500 mL, 2.56 mmol), triphenylmethylenamine (1.33 g, 2.56 mmol) were dissolved in toluene (25 mL) and heated at reflux for 16 h. The product was purified by column chromatography on silica gel to afford **381** as a white solid (0.240 g, 0.737 mmol, 30%). M. p. 105-106 ºC.

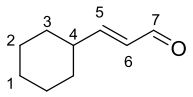
**$\delta_H$ (400 MHz, $CDCl_3$)** 7.48 (1 H, d, *J* 8.7, H-5), 7.32-7.16 (15 H, m, H-8, H-7 and H-6), 6.50 (1 H, ddt, *J* 15.7, 8.7, 1.6, H-4), 6.13 (1 H, dt, *J* 15.7, 6.4, H-3), 2.27-2.18 (2 H, m, H-2), 1.06 (3 H, t, *J* 7.4, H-1).

**$\delta_C$ (100 MHz, $CDCl_3$)** 162.2, 147.9, 145.8 (q), 130.4, 129.8, 127.7, 126.6, 77.2 (q), 25.7, 12.6.

**$\nu_{max}$ ($cm^{-1}$)** 3055, 2966, 1648, 1616, 1489, 1444, 964, 756, 698.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 326.189. $C_{24}H_{24}N$ requires 326.1903.

**(*E*)-3-Cyclohexylacrylaldehyde (369)**

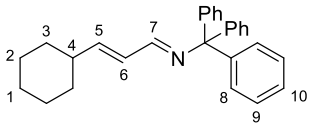



Following general procedure **D**, starting from cyclohexanecarboxaldehyde (**388**, 0.485 mL, 4.00 mmol). Compound **369** was isolated as a colourless oil (0.150 g, 1.10 mmol, 27%). NMR spectral data of **369** matches with the literature data.[182] $^1$H-NMR shows a mixture of *cis*/*trans* isomers 15:85.

Only *trans* isomer is reported.

**$\delta_H$ (400 MHz, $CDCl_3$)** 9.50 (1 H, d, *J* 7.8, H-7), 6.77 (1 H, dd, *J* 15.6, 6.5, H-6), 6.07 (1 H, dd, *J* 15.6, 7.8, H-6, 2.34-2.20 (1 H, m, H-4), 1.90-1.62 (5 H, m, H-3eq, H-2eq and H-1eq), 1.43-1.08 (5 H, m, H-3a, H-2a, H-1a).

**(1*E*,2*E*)-3-(Cyclohexyl)-*N*-tritylprop-2-en-1-imine (382)**




Following general procedure **E**, (*E*)-3-cyclohexylacrilaldehyde (**369**, 0.150 g, 1.10 mmol) and triphenylmethylenamine (0.285 g, 1.10 mmol) were dissolved in toluene (15 mL) and heated at reflux for 16 h. Compound **382** was isolated as a white solid (0.264 g, 0.696 mmol, 63%). M. p. 132-133 ºC.

**$\delta_H$ (400 MHz, $CDCl_3$)** 7.46 (1 H, d, *J* 8.9, H-7), 7.31-7.16 (15 H, m, H-10, H-9 and H-8), 6.45 (1 H, ddd, *J* 15.7, 8.9, 1.3, H-6), 6.02 (1 H, dd, *J*

15.7, 8.8, H-5), 2.19-2.07 (1 H, m, H-4), 1.82-1.62 (5 H, m, H-3eq, H-2eq and H-1eq), 1.36-1.04 (5 H, m, H-3a, H-2a, H-1a).

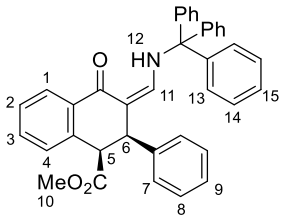
**$\delta_C$ (100 MHz, $CDCl_3$)** 162.5, 151.9, 145.8 (q), 129.8, 128.9, 127.7, 126.6, 78.2 (q), 40.8, 32.1, 26.0, 25.9.

**$\nu_{max}$ ($cm^{-1}$)** 2925, 2851, 1649, 1623, 1488, 1442, 999, 757, 699.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 380.2367. $C_{28}H_{30}N$ requires 380.2373.

### 5.3.5 Catalytic Tamura reaction between enolisable anhydrides and α,β-unsaturated imines

**Methyl (1*R*,2*R*,*Z*)-4-oxo-2-phenyl-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (312)**



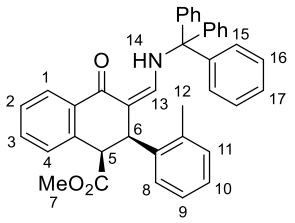

Prepared following general procedure **G**, using **86** (32.4 mg, 0.20 mmol). After purification and esterification, enamine **312** was isolated as a yellow solid (98.0 mg, 0.18 mmol, 89%). Spectral data for this compound were consistent with those reported in the literature.[136] $[\alpha]^{20}_D$ = +244.2 (c 0.1, MeOH).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 7.19 min (minor enantiomer) and 7.77 (major enantiomer)

**$\delta_H$ (400 MHz, $CDCl_3$)** 12.11 (1 H, d, *J* 12.5, H-12), 8.21-8.14 (1 H, m, H-1), 7.46-7.39 (2 H, m, H-3 and H-2), 7.33-7.20 (9 H, m, H-15 and H-14), 7.19-7.01 (10 H, m, H-13, H-9, H-7 and H-4), 6.94-6.89 (2 H, m, H-8), 6.47 (1 H, d, *J* 12.5, H-11), 4.31 (1 H, d, *J* 5.5, H-6), 4.05 (1 H, d, *J* 5.5, H-5), 3.51 (3 H, s, H-10).

**HRMS (*m/z* - ESI)** $[M-H]^-$ Found 548.2232. $C_{38}H_{30}NO_3$ requires 548.2231.

**Methyl (1*R*,2*R*,*Z*)-4-oxo-2-(*o*-tolyl)-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (393)**




Prepared following general procedure **F**, using imine **370** (77.5 mg, 0.20 mmol). After purification and esterification, enamine **393** was isolated as a yellow solid (105 mg, 0.19 mmol, 93%) M.p. 102-105 ºC. $[\alpha]^{20}_{D}$ = +204.0 (c 0.1, MeOH).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.7 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 9.35 min (minor enantiomer) and 9.95 (major enantiomer)

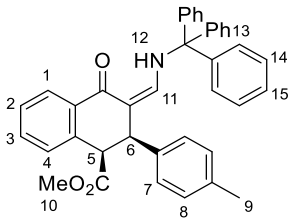
**$\delta_H$ (400 MHz, $CDCl_3$)** 12.04 (1 H, d, *J* 12.2, H-14), 8.21-8.16 (1 H, m, H-1), 7.49-7.38 (2 H, m, H-3 and H-2), 7.31-7.07 (16 H, m, H-17, H-16, H-15 and H-4), 7.02-6.76 (4 H, m, H-11, H-10, H-9 and H-8) 6.30 (1 H, d, *J* 12.2, H-13), 4.67 (1 H, d, *J* 5.1, H-6), 3.92 (1 H, d, *J* 5.1, H-5), 3.49 (3 H, s, H-7), 2.17 (3 H, s, H-12).

**$\delta_C$ (100 MHz, $CDCl_3$)** 186.2 (C=O), 172.0 (C=O), 151.7 (q), 144.7 (q), 137.8, 137.5, 136.0 (q), 128.8 (q), 128.2 (q), 128.1, 127.5, 127.3, 127.2, 126.6, 125.9, 102.8 (q), 73.0 (q), 51.6, 50.7, 41.7, 19.6.

**$\nu_{max}$ ($cm^{-1}$)** 2989, 1740, 1629, 1599, 1322, 1227, 1000, 697.

**HRMS (*m/z* - ESI)** $[M+Na]^+$ Found 586.2378. $C_{39}H_{33}NNaO_3$ Requires 586.2353.

**Methyl (1*R*,2*R*,*Z*)-4-oxo-2-(*p*-tolyl)-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (394)**




Prepared following general procedure **F**, using imine **371** (77.5 mg, 0.20 mmol). After purification and esterification, enamine **394** was isolated as a yellow solid (107 mg, 0.19 mmol, 95%). M.p. 98-102 ºC. $[\alpha]^{20}_{D}$ = +258.3 (c 0.1, MeOH).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 6.12 min (minor enantiomer) and 6.68 (major enantiomer)

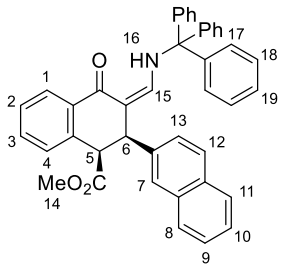
**$\delta_H$ (400 MHz, $CDCl_3$)** 12.07 (1 H, d, *J* 12.5, H-12), 8.19-8.14 (1 H, m, H-1), 7.45-7.38 (2 H, m, H-3 and H-2), 7.31-7.21 (9 H, m, H-15 and H-14), 7.17-7.11 (6 H, m, H-13), 6.86 (2 H, d, *J* 8.0, H-8), 6.78 (2 H, d, *J* 8.0, H-7), 6.43 (1 H, d, *J* 12.5, H-11), 4.26 (1 H, d, *J* 5.3, H-6), 4.02 (1 H, d, *J* 5.3, H-5), 3.53 (3 H, s, H-10), 2.23 (3 H, s, H-9).

**$\delta_C$ (100 MHz, $CDCl_3$)** 185.8 (C=O), 171.9 (C=O), 151.9 (q), 144.6 (q), 137.2 (q), 136.8, 136.4, 135.2 (q), 131.6 (q), 129.0, 128.9, 128.3, 128.1, 128.0, 127.6, 127.3, 127.0, 103.6 (q), 73.1 (q), 52.0, 51.6, 47.0, 21.0.

**$\nu_{max}$ ($cm^{-1}$)** 3025, 1736, 1629, 1596, 1442, 1239, 1001, 697.

**HRMS (*m/z* - ESI)** $[M+Na]^+$ Found 586.2369. $C_{39}H_{33}NNaO_3$ Requires 586.2353.

**Methyl (1*R*,2*R*,*Z*)- 4-oxo-3-((tritylamino)methylene)-1,2,3,4-tetrahydro-[2,2'-binaphthalene]-1-carboxylate (395)**




Prepared following general procedure **F**, using imine **372** (84.7 mg, 0.20 mmol). After purification and esterification, enamine **395** was isolated as a yellow solid (110 mg, 0.19 mmol, 92%). M.p. 155-157 ºC. $[\alpha]^{20}_{D}$ = +133.0 (c 0.1, MeOH).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.7 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 13.18 min (minor enantiomer) and 14.05 (major enantiomer).

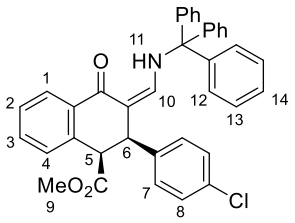
**$\delta_H$ (400 MHz, $CDCl_3$)** 12.13 (1 H, d, *J* 12.2, H-16), 8.24-8.18 (1 H, m, H-1), 7.66-7.60 (2 H, m, H-10 and H-9), 7.54-7.38 (6 H, m, H-11, H-8, H-12, H-7, H-3 and H-2), 7.32-6.98 (17 H, m, H-19, H-18, H-17, H-13 and H-4), 6.44 (1 H, d, *J* 12.2, H-15), 4.48 (1 H, d, *J* 5.2, H-6), 4.13 (1 H, d, *J* 5.2, H-5) 3.50 (3 H, s, H-14).

**$\delta_C$ (100 MHz, $CDCl_3$)** 185.7 (C=O), 171.9 (C=O), 152.1 (q), 144.5 (q), 138.1 (q), 136.7 (q), 135.2, 133.3 (q), 132.6 (q), 131.7, 128.8, 128.1 (x2), 128.0, 127.8, 127.6 (x2), 127.5, 127.3, 127.1, 126.2, 125.8, 125.6, 103.4 (q), 73.1 (q), 51.9, 51.6, 47.5.

**$\nu_{max}$ ($cm^{-1}$)** 2926, 1735, 1629, 1598, 1546, 1414, 1247, 1151, 698.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 600.2529. $C_{42}H_{34}NO_3$ Requires 600.2533.

**Methyl (1*R*,2*R*,*Z*)-2-(4-chlorophenyl)-4-oxo-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (400)**




Prepared following general procedure **F**, using imine **377** (81.6 mg, 0.20 mmol). After purification and esterification, enamine **400** was isolated as a yellow solid (103 mg, 0.18 mmol, 88%). M.p. 98-100 ºC. $[\alpha]^{20}_{D}$ = +177 (c 0.1, MeOH).

CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.7 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 8.70 min (minor enantiomer), 9.52 min (major enantiomer).

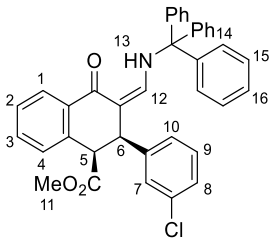
**$\delta_H$ (400 MHz, $CDCl_3$)** 12.07 (1 H, d, *J* 12.1, H-11), 8.20-8.15 (1 H, m, H-1), 7.46-7.41 (2 H, m, H-3 and H-2), 7.32-7.23 (10 H, m, H-14, H-13 and H-4), 7.19-7.11 (6 H, m, H-12), 7.03 (2 H, d, *J* 8.4, H-8), 6.84 (2 H, d, *J* 8.4, H-7), 6.37 (1 H, d, *J* 12.1, H-10), 4.27 (1 H, d, *J* 5.3, H-6), 4.05 (1 H, d, *J* 5.3, H-5), 3.53 (3 H, s, H-9).

**$\delta_C$ (100 MHz, $CDCl_3$)** 185.6 (C=O), 171.6 (C=O), 151.9 (q), 144.5 (q), 139.1 (q), 136.3 (q), 135.0, 132.7, 131.8 (q), 129.8, 128.8, 128.2 (x2), 127.6, 127.4, 127.0, 103.1 (q), 73.2 (q), 51.7, 51.6, 46.7.

**$\nu_{max}$ ($cm^{-1}$)** 2963, 1735, 1631, 1599, 1323, 1445, 1087, 699.

**HRMS (*m/z* - APCI)** $[M-H]^-$ Found 582.1835. $C_{38}H_{29}ClNO_3$ Requires 582.1841.

**Methyl (1*R*,2*R*,*Z*)-2-(3-chlorophenyl)-4-oxo-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (402)**




Prepared following general procedure **F** using imine **379** (81.6 mg, 0.20 mmol). After purification and esterification, enamine **402** was purified as a yellow solid (81.6 mg, 0.14 mmol, 70%). M.p. 180-182 ºC. $[\alpha]^{20}_{D}$ = +155.0 (c 0.1, MeOH).

CSP-HPLC analysis. Chiralpak ODH (4.6 mm x 25 cm), hexane/IPA: 83/17, 0.3 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 25.29 min (major enantiomer) and 28.48 min (minor enantiomer).

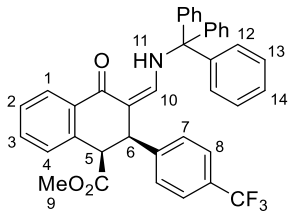
**$\delta_H$ (400 MHz, $CDCl_3$)** 12.14 (1 H, d, *J* 12.3, H-13), 8.20-8.15 (1 H, m, H-1), 7.46-7.40 (2 H, m, H-3 and H-2), 7.33-7.18 (10 H, m, H-16, H-15 and H-4), 7.17-7.06 (7 H, m, H-14 and H-9), 7.05-6.92 (2 H, m, H-9 and H-7), 6.81 (1 H, d, *J* 7.7, H-10), 6.42 (1 H, d, *J* 12.3, H-12), 4.27 (1 H, d, *J* 5.3, H-6), 4.05 (1 H, *J* 5.3, H-5), 3.54 (3 H, s, H-11).

**$\delta_C$ (100 MHz, $CDCl_3$)** 185.5 (C=O), 171.6 (C=O), 151.8 (q), 144.4 (q), 142.8 (q), 136.2 (q), 135.0, 134.0 (q), 131.7, 129.6, 128.8, 128.6, 128.2 (x2), 127.6, 127.4, 127.2, 127.0, 126.7, 102.8 (q), 73.2 (q), 51.7 (x2), 47.0.

**$\nu_{max}$ ($cm^{-1}$)** 2923, 1748, 1634, 1545, 1140, 999, 702.

**HRMS (*m/z* - APCI)** $[M-H]^-$ Found 582.1840. $C_{38}H_{29}ClNO_3$ Requires 582.1841.

**Methyl (1*R*,2*R*,*Z*)-2-(4-trifluoromethylphenyl)-4-oxo-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (401)**




Prepared following general procedure **F**, using imine **379** (88.3 mg, 0.20 mmol). After purification and esterification, enamine **401** was purified as a yellow solid (86.5 mg, 0.14 mmol, 70%). M.p. 170-173 ºC $[\alpha]^{20}_{D}$ = +285.0 (c 0.2, MeOH)

CSP-HPLC analysis. Chiralpak ODH (4.6 mm x 25 cm), hexane/IPA: 83/17, 0.3 mL $min^{-1}$, RT, UV detection at 254 nm, retention times 25.29 min (major enantiomer) and 28.48 (minor enantiomer).

**$\delta_H$ (400 MHz, $CDCl_3$)** 12.09 (1 H, d, *J* 12.9, H-11), 8.22-8.15 (1 H, m, H-1), 7.49-7.40 (2 H, m, H-3 and H-2), 7.34-7.08 (18 H, m, H-14, H-13, H-12, H-8 and H-4), 7.03 (2 H, d, *J* 9.1, H-7), 6.31 (1 H, d, *J* 12.9, H-10), 4.36 (1 H, d, *J* 5.1, H-6), 4.08 (1 H, d, *J* 5.1, H-5), 3.53 (3 H, s, H-9).

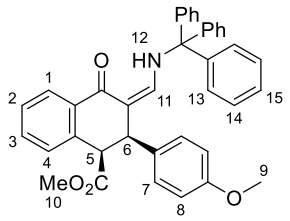
**$\delta_C$ (100 MHz, $CDCl_3$)** 185.5 (C=O), 171.5 (C=O), 151.8 (q), 144.4 (q), 136.1 (q), 135.0, 131.8 (q), 128.9, 128.8, 128.5, 128.3, 128.2, 128.0, 127.6, 127.5, 127.1, 125.3 (q, $J_{C-F}$ 3.8), 124.5 (q, $J_{C-F}$ 272.2, q), 102.8 (q), 73.2 (q), 51.7, 51.4, 47.1.

**$\delta_F$ (376 MHz, $CDCl_3$)** -62.6.

**$\nu_{max}$ ($cm^{-1}$)** 2949, 1734, 1633, 1599, 1552, 1445, 1324, 1154, 757, 699.

**HRMS (*m/z* - ESI)** $[M+Na]^+$ Found 640.2071. $C_{39}H_{30}F_3NNaO_3$ Requires 640.2070.

**Methyl (1*R*,2*R*,*Z*)-2-(4-methoxyphenyl)-4-oxo-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (396)**




Prepared following general procedure **F**, using imine **373** (80.7 mg, 0.20 mmol). After purification and esterification, enamine **396** was isolated as a yellow solid (104 mg, 0.18 mmol, 90%). M.p. 155-157 ºC. $[\alpha]^{20}_{D}$ = +337.5 (c 0.4, MeOH).

CSP-HPLC analysis. Chiralpak ODH (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.5 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 38.85 min (minor enantiomer) and 52.45 (major enantiomer).

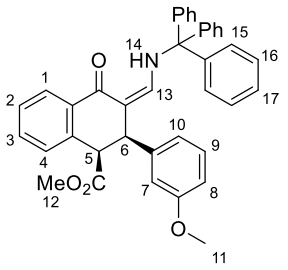
**$\delta_H$ (400 MHz, $CDCl_3$)** 12.07 (1 H, d, *J* 12.3, H-12), 8.21-8.14 (1 H, m, H-1), 7.46-7.38 (2 H, m, H-3 and H-2), 7.32-7.11 (16 H, m, H-15, H-14, H-13 and H-4), 6.83 (2 H, d, *J* 8.9, H-7), 6.59 (2 H, d, *J* 8.9, H-8), 6.46 (1 H, d, *J* 12.3, H-11), 4.27 (1 H, d, *J* 5.4, H-6), 4.01 (1 H, d, *J* 5.4, H-5), 3.73 (3 H, s, H-9), 3.53 (3 H, s, H-10).

**$\delta_C$ (100 MHz, $CDCl_3$)** 185.9 (C=O), 171.9 (C=O), 158.3 (q), 152.0 (q), 144.7 (q), 136.8 (q), 135.1 (q), 132.3, 131.6, 129.5, 129.5, 128.9, 128.2, 128.1, 127.6, 127.3, 127.0, 113.7, 103.6 (q), 73.0 (q), 55.1, 52.2, 51.6, 46.6.

**$\nu_{max}$ ($cm^{-1}$)** 2950, 1734, 1631, 1599, 1242, 1153, 698.

**HRMS (*m/z* - ESI)** $[M+Na]^+$ Found 602.2328. $C_{39}H_{33}NNaO_4$ Requires 602.2302.

**Methyl (1*R*,2*R*,*Z*)-2-(3-methoxyphenyl)-4-oxo-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (397)**




Prepared following general procedure **F**, using imine **374** (80.7 mg, 0.2 mmol). After purification and esterification, enamine **397** was isolated as a yellow solid (101 mg, 0.17 mmol, 87%). M. p. 90-93 ºC. $[\alpha]^{20}_{D}$ = +376.0 (c 0.1, MeOH).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.7 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 13.40 min (minor enantiomer) and 14.41 min (major enantiomer).

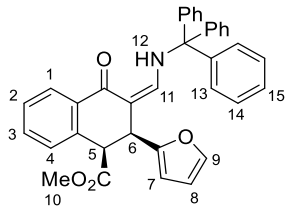
**$\delta_H$ (400 MHz, $CDCl_3$)** 12.13 (1 H, d, *J* 12.2, H-14), 8.21-8.15 (1 H, m, H-1), 7.47-7.38 (2 H, m, H-3 and H-2), 7.34-7.11 (16 H, m, H-17, H-16, H-15 and H-4), 6.98 (1 H, app. t, H-9), 6.64 (1 H, dd, *J* 8.3, 2.1, H-10), 6.55-6.44 (3 H, m, H-13, H-8 and H-7), 4.28 (1 H, d, *J* 5.4, H-6), 4.06 (1 H, d, *J* 5.4, H-5), 3.64 (3 H, s, H-11), 3.54 (3 H, s, H-12).

**$\delta_C$ (100 MHz, $CDCl_3$)** 185.7 (C=O), 171.8 (C=O), 159.4 (q), 151.9 (q), 144.6 (q), 142.0, 136.7, 135.1 (q), 131.6, 129.3, 128.9, 128.1 (x2), 127.6, 127.3, 127.0, 120.7, 114.0, 112.6, 103.4 (q), 73.1 (q), 54.9, 51.8, 51.6, 47.4.

**$\nu_{max}$ ($cm^{-1}$)** 2947, 1734, 1630, 1599, 1447, 1257, 1152, 1001, 697.

**HRMS (*m/z* - APCI)** $[M-H]^-$ Found 578.2341. $C_{39}H_{32}NO_4$ Requires 578.2337.

**Methyl (1*R*,2*S*,*Z*)- 2-(furan-2-yl)-4-oxo-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (398)**




Prepared following general procedure **F**, using imine **275** (72.7 mg, 0.20 mmol). After purification and esterification, enamine **398** was isolated as a yellow solid (97.5 mg, 0.18 mmol, 90%). M.p. 103-105 ºC. $[\alpha]^{20}_{D}$ = +79.0 (c 0.1, MeOH).

CSP-HPLC analysis. Chiralpak ODH (4.6 mm x 25 cm), hexane/IPA: 99/1, 1.0 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 39.41 min (minor enantiomer) and 43.20 min (major enantiomer).

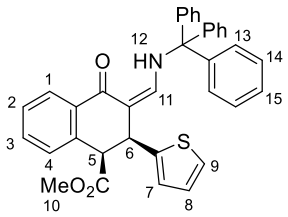
**$\delta_H$ (400 MHz, $CDCl_3$)** 12.00 (1 H, d, *J* 12.4, H-12), 8.16-8.09 (1 H, m, H-1), 7.45-7.12 (16 H, m, H-15, H-14, H-13 and H-4), 7.07 (1 H, s, H-9), 6.47 (1 H, d, *J* 12.4, H-11), 6.08-6.03 (1 H, m, H-8), 5.79 (1 H, d, *J* 3.4, H-7), 4.39 (1 H, d, *J* 5.1, H-6), 4.11 (1 H, d, *J* 5.1, H-5), 3.63 (3 H, s, H-10).

**$\delta_C$ (100 MHz, $CDCl_3$)** 185.3 (C=O), 171.5 (C=O), 153.7 (q), 151.4 (q), 144.5 (q), 141.4, 136.3, 134.9 (q), 131.6, 128.9, 128.3, 128.2, 128.0, 127.6, 127.4, 127.0, 109.9, 107.5, 101.8 (q), 73.2 (q), 51.9, 49.7, 40.6.

**$\nu_{max}$ ($cm^{-1}$)** 2922, 1732, 1630, 1594, 1440, 1346, 1239, 1155, 750, 697.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 540.2165. $C_{36}H_{30}NO_4$ Requires 540.2169.

**Methyl (1*R*,2*S*,*Z*)-4-oxo-2-(thiophen-2-yl)-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (399)**




Prepared following general procedure **F**, using imine **376** (75.8 mg, 0.20 mmol). After purification and esterification, enamine **399** was isolated as a yellow solid (99.9 mg, 0.18 mmol, 90%). M.p. 128-129 ºC. $[\alpha]^{20}_{D}$ = +40.0 (c 0.1, MeOH).

CSP-HPLC analysis. Chiralpak ODH (4.6 mm x 25 cm), hexane/IPA: 99/1, 0.7 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 65.20 min (major enantiomer).

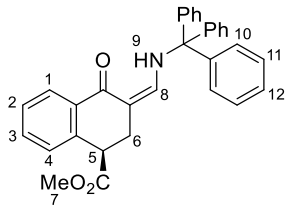
**$\delta_H$ (400 MHz, $CDCl_3$)** 12.04 (1 H, d, *J* 12.5, H-12), 8.19-8.11 (1 H, m, H-1), 7.47-7.13 (18 H, m, H-15, H-14, H-13, H-4, H-3 and H-2), 6.97 (1 H, d, *J* 4.9, H-9), 6.71 (1 H, dd, *J* 4.9, 3.6, H-8), 6.60-6.53 (2 H, m, H-11 and H-7), 4.59 (1 H, d, *J* 5.2, H-6), 4.17 (1 H, d, *J* 5.2, H-5), 3.63 (3 H, s, H-10).

**$\delta_C$ (100 MHz, $CDCl_3$)** 185.0 (C=O), 171.5 (C=O), 151.7 (q), 144.5 (q), 136.2 (q), 135.0, 131.7, 129.7 (q), 128.9, 128.2, 128.1, 127.8, 127.4, 127.0, 126.3, 125.7, 124.2, 104.6 (q), 73.2 (q), 51.8 (x2), 42.4.

**$\nu_{max}$ ($cm^{-1}$)** 2923, 1742, 1630, 1599, 1431, 1156, 1001, 697.

**HRMS (*m/z* - ESI)** $[M+Na]^+$ Found 578.1784. $C_{36}H_{29}NNaO_3S$ Requires 578.1760.

**Methyl (1*R*, *Z*)-4-oxo-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (403)**




Prepared following general procedure **F**, using imine **392** (59.5 mg, 0.20 mmol). After purification and esterification, enamine **403** was isolated as yellow oil (90.0 mg, 0.19 mmol, 95%). $[\alpha]^{20}_{D}$ = -5.0 (c 0.1, MeOH).

CSP-HPLC analysis. Chiralpak ODH (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 7.65 min (minor enantiomer) and 8.67 min (major enantiomer).

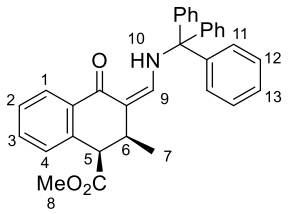
**$\delta_H$ (400 MHz, $CDCl_3$)** 11.79 (1 H, d, *J* 12.1, H-9), 8.08 (1 H, dd, *J* 7.0, 1.8, H-1), 7.46-7.37 (2 H, m, H-3 and H-2), 7.36-7.18 (17 H, m, H-12, H-11, H-10 and H-4), 6.70 (1 H, d, *J* 12.1, H-8), 3.83 (1 H, app. t, H-5), 3.65 (3 H, s, H-7), 2.86-2.72 (2 H, m, H-6).

**$\delta_C$ (100 MHz, $CDCl_3$)** 185.7 (C=O), 173.2 (C=O), 150.7 (q), 144.7 (q), 137.9, 135.3 (q), 131.5, 128.9, 128.2, 128.0, 127.9, 127.5, 126.7, 99.7 (q), 72.9 (q), 52.1, 45.6, 31.0.

**$\nu_{max}$ ($cm^{-1}$)** 2947, 1730, 1632, 1600, 1551, 1444, 1154, 986, 697.

**HRMS (*m/z* - ESI)** $[M+Na]^+$ Found 496.1889. $C_{32}H_{27}NNaO_3$ Requires 496.1883.

**Methyl (1*R*,2*S*,*Z*)-2-methyl-4-oxo-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (404)**




Prepared following general procedure **F**, using imine **380** (62.3 mg, 0.20 mmol). After purification and esterification, enamine **404** was isolated as a yellow solid (89.7 mg, 0.18 mmol, 92%). M.p. 115-117 ºC. $[\alpha]^{20}_{D}$ = +32.0 (c 0.1, MeOH).

CSP-HPLC analysis. Chiralpak ODH (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 6.77 min (minor enantiomer) and 7.95 min (major enantiomer).

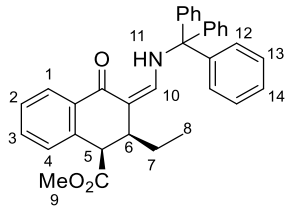
**$\delta_H$ (400 MHz, $CDCl_3$)** 11.89 (1 H, d, *J* 11.8, H-10), 8.14-8.04 (1 H, m, H-1), 7.46-7.16 (18 H, m, H-13, H-12, H-11, H-4, H-3 and H-2), 6.62 (1 H, d, *J* 11.8, H-9), 3.86 (1 H, d, *J* 4.6, H-5), 3.62 (3 H, s, H-8), 3.12-3.02 (1 H, m, H-6), 0.96 (3 H, d, *J* 7.1, H-7).

**$\delta_C$ (100 MHz, $CDCl_3$)** 186.1 (C=O), 171.8 (C=O), 149.3 (q), 144.8 (q), 137.6, 135.0 (q), 131.5, 128.9, 128.2, 127.8, 127.7, 127.4, 126.9, 105.4 (q), 73.0 (q), 51.6, 51.4, 34.8, 17.0.

**$\nu_{max}$ ($cm^{-1}$)** 2923, 1742, 1630, 1599, 1545, 1431, 1156, 1001, 697.

**HRMS (*m/z* - ESI)** $[M+Na]^+$ Found 510.2062. $C_{33}H_{29}NNaO_3$ Requires 510.2040.

**Methyl (1*R*,2*S*,*Z*)-2-ethyl-4-oxo-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (405)**




Prepared following general procedure **F**, using imine **381** (65.1 mg, 0.20 mmol). After purification and esterification, enamine **405** was isolated as a yellow solid (93.3 mg, 0.19 mmol, 93%). M.p. 131-134 ºC. $[\alpha]^{20}_{D}$ = + 72.7 (c 0.1, MeOH).

CSP-HPLC analysis. Chiralpak ODH (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 5.51 min (minor enantiomer) and 7.03 min (major enantiomer).

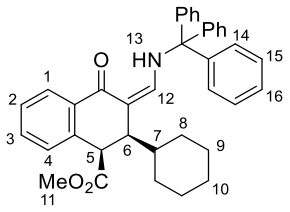
**$\delta_H$ (400 MHz, $CDCl_3$)** 11.94 (1 H, d, *J* 12.6, H-11), 8.10-8.03 (1 H, m, H-1), 7.47-7.15 (18 H, m, H-14, H-13, H-12, H-4, H-3 and H-2), 6.62 (1 H, d, *J* 12.6, H-10), 4.11 (1 H, d, *J* 3.9, H-5), 3.68 (3 H, s, H-9), 2.66-2.58 (1 H, m, H-6), 1.46-1.31 (1 H, m, H-7a), 1.29-1.14 (1 H, m, H-7b), 0.70 (3 H, app. t, H-8).

**$\delta_C$ (100 MHz, $CDCl_3$)** 186.0 (C=O), 172.2 (C=O), 150.2 (q), 144.7 (q), 137.2 (q), 134.8, 131.5, 128.9, 127.6, 127.4, 126.8, 103.9 (q), 73.0 (q), 51.7, 49.4, 42.4, 22.9, 11.7.

**$\nu_{max}$ ($cm^{-1}$)** 2948, 1734, 1634, 1598, 1323, 1153, 1086, 965, 700.

**HRMS (*m/z* - ESI)** $[M+Na]^+$ Found 524.2207. $C_{34}H_{31}NNaO_3$ Requires 524.2196.

**Methyl (1*R*,2*S*,*Z*)-2-cyclohexyl-4-oxo-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (406)**




Prepared following general procedure **F**, using imine **382** (75.9 mg, 0.20 mmol). After purification and esterification, enamine **406** was isolated as a yellow solid (104 mg, 0.19 mmol, 94%). M.p. 177-179 ºC. $[\alpha]^{20}_{D}$ = +3.0 (c 0.1, MeOH).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 4.43 min (major enantiomer) and 6.03 min (minor enantiomer).

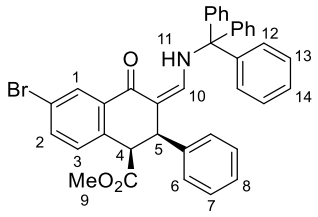
**$\delta_H$ (400 MHz, $CDCl_3$)** 12.03 (1 H, d, *J* 12.3, H-13), 8.06 (1 H, d, *J* 7.6, H-1), 7.45-7.20 (18 H, m, H-16, H-15, H-14, H-4, H-3 and H-2), 6.60 (1 H, d, *J* 12.3, H-12), 4.20 (1 H, d, *J* 4.6, H-5), 3.71 (3 H, s, H-11), 2.60 (1 H, app. t, H-6), 1.63-0.48 (11 H, m, H-10, H-9, H-8 and H-7).

**$\delta_C$ (100 MHz, $CDCl_3$)** 172.6 (C=O), 151.5 (C=O), 144.8 (q), 137.9 (q), 135.1 (q), 131.5, 129.0, 128.3, 127.5, 127.4, 127.3, 126.5, 101.7 (q), 73.1 (q), 51.7, 48.2, 46.1, 30.9, 26.5, 26.2.

**$\nu_{max}$ ($cm^{-1}$)** 2923, 1742, 1630, 1599, 1545, 1431, 1156, 1001, 697.

**HRMS (*m/z* - ESI)** $[M+Na]^+$ Found 578.2664. $C_{38}H_{37}NNaO_3$ Requires 578.2666.

**Methyl (1*R*,2*R*,*Z*)-6-bromo-4-oxo-2-phenyl-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (347)**




Prepared following general procedure **G**, using anhydride **196** (48.2 mg, 0.20 mmol). After purification and esterification, enamine **347** was isolated as a yellow solid (113 mg, 0.18 mmol, 90%). M. p. 154-155 ºC. $[\alpha]^{20}_{D}$ = +40 (c 0.1, MeOH).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 6.24 min (major enantiomer) and 7.06 min (minor enantiomer).

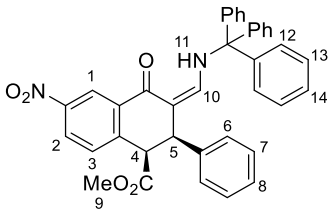
**$\delta_H$ (400 MHz, $CDCl_3$)** 12.21 (1 H, d, *J* 12.7, H-11), 8.33 (1 H, d, *J* 2.0, H-1), 7.52 (1 H, dd, *J* 8.1, 2.0, H-2), 7.33-7.03 (19 H, m, H-14, H-13, H-12, H-8, H-7 and H-3), 6.94-6.86 (2 H, m, H-6), 6.53 (1 H, d, *J* 12.7, H-10), 4.28 (1 H, d, *J* 5.5, H-5), 4.03 (1 H, d, *J* 5.5, H-4), 3.51 (3 H, s, H-9).

**$\delta_C$ (100 MHz, $CDCl_3$)** 184.0 (C=O), 171.4 (C=O), 152.7 (q), 144.4 (q), 142.0 (q), 136.9 (q), 135.2 (q), 134.3, 130.0, 129.5, 128.8, 128.4 (x2), 128.3, 128.2, 127.5, 127.1, 122.5, 103.0 (q), 73.3 (q), 51.7, 51.3, 47.1.

**$\nu_{max}$ ($cm^{-1}$)** 2921, 1719, 1626, 1550, 1444, 1323, 1233, 1204, 1028, 697.

**HRMS (*m/z* - APCI)** $[M+H]^+$ Found 626.1316. $C_{38}H_{29}BrNO_3$ requires 626.1325.

**Methyl (1*R*,2*R*,*Z*)-6-nitro-4-oxo-2-phenyl-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (354)**




Prepared following general procedure **G**, using anhydride **349** (41.4 mg, 0.20 mmol). After purification and esterification, enamine **354** was isolated as a yellow solid (103 mg, 0.17 mmol, 87%). M. p. 128-130 ºC. $[\alpha]^{20}_{D}$ = +224.7 (c 0.3, MeOH).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 10.17 min (major enantiomer) and 11.22 min (minor enantiomer).

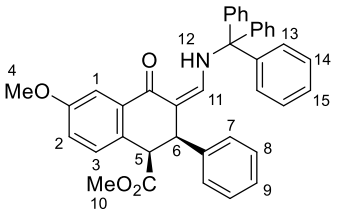
**$\delta_H$ (400 MHz, $CDCl_3$)** 12.34 (1 H, d, *J* 12.5, H-11), 9.02 (1 H, d, *J* 2.5, H-1), 8.24 (1 H, dd, *J* 8.5, 2.5, H-2), 7.52 (1 H, d, *J* 8.5, H-3), 7.34-7.05 (17 H, m, H-14, H-13, H-12, H-8 and H-7), 6.89 (2 H, d, *J* 6.8, H-6), 6.62 (1 H, d, *J* 12.5, H-10), 4.33 (1 H, d, *J* 5.5, H-5), 4.20 (1 H, d, *J* 5.5, H-4), 3.54 (3 H, s, H-9).

**$\delta_C$ (100 MHz, $CDCl_3$)** 182.6 (C=O), 170.6 (C=O), 153.4 (q), 148.1 (q), 144.1, 142.6 (q), 139.8 (q), 136.7 (q), 129.1, 128.8, 128.5, 128.3, 128.2, 127.6, 127.3, 125.6, 122.1, 102.7 (q), 73.5 (q), 51.9, 51.6, 46.8.

**$\nu_{max}$ ($cm^{-1}$)** 2925, 1732, 1629, 1548, 1523, 1441, 2263, 1153, 697.

**HRMS (*m/z* - ESI)** $[M-H]^-$ Found 593.2077. $C_{38}H_{29}N_2O_5$ Requires 593.2082.

**Methyl (1*R*,2*R*,*Z*)-6-methoxy-4-oxo-2-phenyl-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (355)**




Prepared following general procedure **G**, using anhydride **162** (38.4 mg, 0.2 mmol). After purification and esterification, enamine **355** was isolated as a yellow solid (95.1 mg, 0.16 mmol, 82%). M. p. $[\alpha]^{20}_{D}$ = +123 (c 0.1, MeOH).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 6.78 min (major enantiomer) and 7.63 min (minor enantiomer).

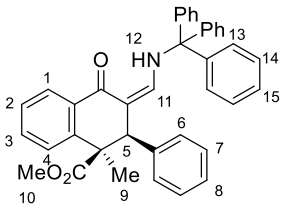
**$\delta_H$ (400 MHz, $CDCl_3$)** 12.08 (1 H, d, *J* 12.2, H-12), 7.72 (1 H, d, *J* 3.0, H-1), 7.32-7.04 (19 H, m, H-15, H-14, H-13, H-9, H-8 and H-3), 6.99 (1 H, dd, *J* 8.4, 3.0, H-2), 6.95-6.90 (2 H, m, H-7), 6.49 (1 H, d, *J* 12.2, H-11), 4.29 (1 H, d, *J* 5.4, H-6), 4.01 (1 H, d, *J* 5.4, H-5), 3.90 (3 H, s, H-4), 3.51 (3 H, s, H-10).

**$\delta_C$ (100 MHz, $CDCl_3$)** 185.6 (C=O), 172.1 (C=O), 159.6 (q), 152.1 (q), 144.6 (q), 140.5 (q), 136.3 (q), 129.2, 128.9, 128.4, 128.2, 127.6, 127.3, 126.9, 119.2, 109.9, 103.4 (q), 73.1 (q), 55.6, 51.5, 51.3, 47.5.

**$\nu_{max}$ ($cm^{-1}$)** 2924, 1726, 1623, 1523, 1434, 1273, 1160, 1026, 697.

**HRMS (*m/z* - APCI)** $[M-H]^-$ Found 578.2331. $C_{39}H_{32}NO_4$ Requires 578.2337.

**Methyl (1*R*,2*R*,*Z*)-1-methyl-4-oxo-2-phenyl-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (*syn*-356)**




Prepared following general procedure **G** using anhydride **353** (35.2 mg, 0.20 mmol). After purification and esterification, enamine *syn*-**356** was isolated as a yellow oil (56.4 mg, 0.10 mmol, 50%). $[\alpha]^{20}_{D}$ = +44 (c 0.1, MeOH).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 4.92 min (minor enantiomer) and 5.67 min (major enantiomer).

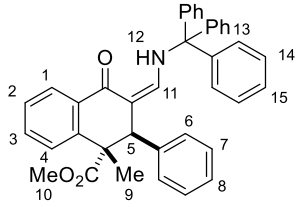
**$\delta_H$ (400 MHz, $CDCl_3$)** 12.08 (1 H, d, *J* 12.5, H-12), 8.24 (1 H, dd, *J* 7.3, 1.6, H-1), 7.49-7.40 (2 H, m, H-3 and H-2), 7.37 (1 H, dd, *J* 7.7, 1.6, H-4), 7.32-7.25 (9 H, m, H-15 and H-14), 7.16-7.04 (9 H, m, H-13, H-8 and H-7), 6.89-6.82 (2 H, m, H-6), 6.49 (1 H, d, *J* 12.5, H-11), 3.81 (1 H, s, H-5), 3.40 (3 H, s, H-10), 1.63 (3 H, s, H-9).

**$\delta_C$ (100 MHz, $CDCl_3$)** 184.7 (C=O), 174.5 (C=O), 153.1 (q), 144.5 (q), 142.1 (q), 141.9 (q), 134.3, 131.2, 128.9, 128.3, 128.2, 128.1, 127.6, 127.4 (x2), 126.8, 126.7, 103.7 (q), 73.2 (q), 55.2 (q), 52.1, 51.6, 27.2.

**$\nu_{max}$ ($cm^{-1}$)** 2923, 1726, 1627, 1599, 1446, 1235, 1005, 697.

**HRMS (*m/z* - APCI)** $[M-H]^-$ Found 562.2374. $C_{39}H_{32}NO_3$ Requires 562.2388.

**Methyl (*Z*)-1-methyl-4-oxo-2-phenyl-3-((tritylamino)methylene)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (*anti*-356)**




Prepared following general procedure **G** using anhydride **353** (35.2 mg, 0.20 mmol). After purification and esterification, enamine *anti*-**356** was isolated as a yellow oil (56.4 mg, 0.10 mmol, 50%). $[\alpha]^{20}_{D}$ = +44 (c 0.1, MeOH).

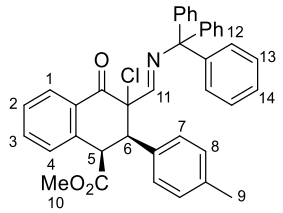
**$\delta_H$ (400 MHz, $CDCl_3$)** 12.17 (1 H, d, *J* 12.2, H-12), 8.21-8.11 (1 H, m, H-1), 7.48-7.39 (2 H, m, H-3 and H-2), 7.35-6.89 (19 H, m, H-15, H-14, H-13, H-8, H-7 and H-4), 6.79 (2 H, d, *J* 6.9, H-6), 6.70 (1 H, d, *J* 12.2, H-11), 4.16 (1 H, s, H-5), 3.56 (3 H, s, H-10), 1.44 (3 H, s, H-9).

**$\delta_C$ (100 MHz, $CDCl_3$)** 185.1 (C=O), 173.3 (C=O), 153.3 (q), 144.4 (q), 140.9 (q), 140.8 (q), 129.5, 129.1, 128.9, 128.7, 128.5, 128.2, 127.9, 127.6 127.5, 127.0, 126.3, 104.8 (q), 73.2 (q), 52.6, 52.5, 51.4, 31.2.

**$\nu_{max}$ ($cm^{-1}$)** 2979, 1619, 1487, 1439, 1144, 980, 963, 777, 687.

**HRMS (*m/z* - APCI)** $[M-H]^-$ Found 562.2373. $C_{39}H_{32}NO_3$ Requires 562.2388.

**Methyl (1*R*,2*R*)-3-chloro-4-oxo-2-(*p*-tolyl)-3-((*E*)-(tritylamino)methyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (407)**




Enamine **394** (100 mg, 0.177 mmol) was placed in a 10 mL round-bottom flask and dissolved in $CCl_4$ (1.00 mL). *N*-chlorosuccinamide (26 mg, 0.195 mmol) was added and the mixture was stirred at room temperature for 1 hour. Once the reaction was completed the solvent was

removed *in vacuo* and the crude was purified by column chromatography to afford imine **407** as a yellow solid (100 mg, 0.168 mmol, 95%). M.p. 52-55 ºC. $[\alpha]^{20}_{D}$ 72 º (c 0.3, Acetone).

CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 4.05 min (major enantiomer) and 4.90 min (minor enantiomer).

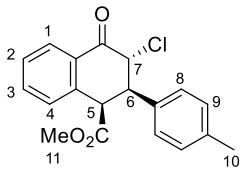
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.19 (1 H, d, *J* 7.8, H-1), 7.64 (1 H, app. t, H-2), 7.54 (1 H, s, H-11), 7.52-7.42 (2 H, m, H-4 and H-2), 7.22-7.14 (9 H, m, H-14 and H-13), 7.02-6.94 (6 H, m, H-12), 6.74 (2 H, d, *J* 7.8, H-8), 6.66 (2 H, d, *J* 7.8, H-7), 5.11 (1 H, d, *J* 6.1,H-6), 4.60 (1 H, d, *J* 6.1, H-5), 3.53 (3 H, s, H-10), 2.18 (3 H, s, H-9).

**$\delta_C$ (100 MHz, $CDCl_3$)** 189.5 (C=O), 171.4 (C=O), 159.0 (q), 144.8 (q), 137.6 (q), 137.0 (q), 134.5 (q), 132.2, 130.6, 130.4, 129.6, 129.1, 128.0 (x2), 127.6, 126.7, 78.9 (q), 68.3 (q), 53.8, 52.0, 47.3, 21.0.

**$\nu_{max}$ ($cm^{-1}$)** 2922, 2853, 1747, 1691, 1599, 1446, 1304, 1160, 1002, 698.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 598.2148. $C_{39}H_{33}ClNO_3$ requires 598.2143.

**Methyl (1*R*,2*R*,3*R*)-3-chloro-4-oxo-2-(*p*-tolyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (409)**




Imine **407** (94 mg, 0.157 mmol) was placed in a 25 mL round-bottomed flask and dissolved in chloroform (5.00 mL). HCl (1.0 N in diethyl ether, 0.190 mL.) was added and the reaction was left stirred overnight at room temperature. Neutral alumina (700 mg approx.) was added and the reaction was stirred at room temperature. Once the reaction was completed the solvent was removed *in vacuo* and the alumina/crude was purified by column chromatography on silica gel (dry loading) to afford compound **409** as a yellow solid (48 mg, 0.146 mmol, 93%). M.p. 137-140 ºC. $[\alpha]^{20}_{D}$ 216 º (c 0.15, Acetone).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL $min^{-1}$, RT, UV detection at 254 nm, retention times: 12.31 min (major enantiomer) and 14.35 min (minor enantiomer).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.20 (1 H, d, *J* 7.4, H-1), 7.62-7.55 (1 H, m, H-2), 7.49 (1 H, app. t, H-3), 7.34 (1 H, d, *J* 7.7, H-4), 7.19 (2 H, d, *J* 8.3, H-9), 7.16 (2 H, d, *J* 8.3, H-8), 5.83 (1 H, d, *J* 12.7, H-7), 4.25 (1 H, d, *J* 4.7, H-5), 3.85 (1 H, dd, *J* 12.7, 4.7, H-6), 3.52 (3 H, s, H-11), 2.36 (3 H, s, H-10).

**$\delta_C$ (151 MHz, $CDCl_3$)** 191.0 (C=O), 171.5 (C=O), 138.7 (q), 137.8 (q), 134.9 (q), 134.4, 131.0 (q), 129.6, 129.2, 128.9, 128.3, 127.7, 60.5, 52.9 52.4, 51.3, 21.2.

**$\nu_{max}$ ($cm^{-1}$)** 2920, 2851, 1718, 1686, 1594, 1453, 1439, 1352, 1170, 971, 814, 733, 705.

**HRMS (*m/z* - ESI)** $[M+Na]^+$ Found 351.0765. $C_{19}H_{17}ClNaO_3$ requires 351.0758.

## 5.4 Experimental data for Chapter 4

### General procedure H: condensation reaction between aldehydes and amines

The corresponding amine (1 eq) and 4 Å molecular sieves were placed in an RBF and charged with dry toluene. The corresponding aldehyde (1 eq) was added and the reaction was heated at reflux for 16 h. The reaction mixture was filtered through celite and the solvent removed. The crude was recrystallised to afford the corresponding imine.

### General procedure I: evaluation of the imine component in the cycloaddition reaction between anhydride 94 and imines

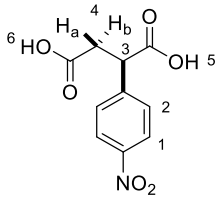
A 20 mL round-bottom flask was charged with **93** (44.2 mg, 0.20 mmol), catalyst **323** (25.0 mg, 0.04 mmol) and the corresponding imine (0.20 mmol). MTBE was added (8.00 mL) and the reaction was left to stir at room temperature. The conversion of the reaction was determined by $^{1}$H-NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. Once the reaction was completed the reaction was placed in an ice-bath and MeOH (0.20 mL, 3.00 mmol) was added followed by $TMSCHN_2$ (0.12 mL, 0.24 mmol). The reaction was stirred for 30 min, the solvent removed and the crude purified by column chromatography to afford the corresponding lactam.

### General procedure J: evaluation of the anhydride component in the cycloaddition reaction between imine 421 and anhydrides

A 20 mL round-bottom flask was charged with imine **421** (50.9 mg, 0.20 mmol), catalyst **323** (25.0 mg, 0.04 mmol) and the corresponding anhydride (0.20 mmol). MTBE was added (8.00 mL) and the reaction was left to stir at room temperature. The conversion of the reaction was determined by $^{1}$H-NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. Once the reaction was completed the reaction was placed in an ice-bath and MeOH (0.20 mL, 3.00 mmol) was added followed by $TMSCHN_2$ (0.12 mL, 0.24 mmol). The reaction was stirred for 30 min, the solvent removed and the crude purified by column chromatography to afford the corresponding lactam.

### 5.4.1 Synthesis of anhydrides

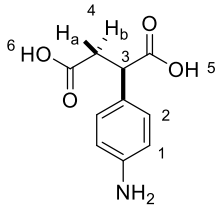
**2-(4-Nitrophenyl)succinic acid (413)**




A 100 mL round-bottomed flask containing fuming $HNO_3$ (15.0 mL) was cooled to 0 ºC. Phenylsuccinic acid (**280**, 2.00 g, 25.7 mmol) was added portionwise, keeping the temperature of the reaction below 15 ºC. After the addition, the mixture was stirred at 0 ºC for 2 h. Crushed ice (15.0 g) and water (20 mL) were added to the mixture and the white precipitate collected by filtration. The product was recrystallised from $H_2O$ and the product was obtained as a white solid (3.26 g, 13.6 mmol, 53%). M.p. 228-230 ºC (lit.[80] 233-235 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.16 (2 H, d, *J* 8.9, H-1), 7.57 (2 H, d, *J* 8.9, H-2), 4.07 (1 H, dd, *J* 9.8, 5.5, H-3), 2.97 (1 H, dd, *J* 16.9, 9.8, H-4a), 2.61 (1 H, dd, *J* 16.9, 5.5, H-4b).

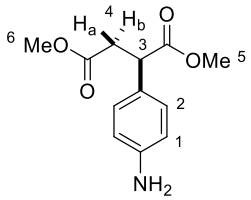
**2-(4-Aminophenyl)succinic acid (440)**




An oven-dried 100 mL round-bottomed flask, was charged with **413** (4.50 g, 18.8 mmol) followed by 10% Pd/C (2 mol%) and suspended in MeOH (25 mL). The flask was evacuated and placed under a hydrogen atmosphere and stirred for 3 h at room temperature. The flask was evacuated filled with argon and water (25 mL) was added. The reaction was heated at 70 ºC for 15 min and then filtered hot through a pad of Celite and washed with hot water. The filtrate was allowed to cool at room temperature and the precipitate was collected by filtration and dried *in vacuo* to afford compound **440** (2.00 g, 9.58 mmol, 51%) as a pale yellow solid. M.p. 201-203 ºC (lit.[80] 202-204 ºC).

**$\delta_H$ (400 MHz, DMSO)** 6.91 (2 H, d, *J* 8.2, H-2), 6.48 (2 H, d, *J* 8.2, H-1), 3.66 (1 H, dd, *J* 10.4, 5.1, H-3), 2.85 (1 H, dd, *J* 16.7, 10.4, H-4a), 2.42 (1 H, dd, *J* 16.7, 5.1, H-4b)

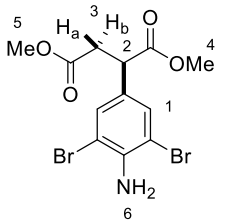
**Dimethyl 2-(4-aminophenyl)succinate (441)**




To a 100 mL round-bottomed flask containing **440** (2.0 g, 9.56 mmol), anhydrous MeOH (10 mL) was added. Freshly distilled $SO_2Cl_2$ (2.44 mL, 33.5 mmol) was added dropwise *via* syringe at 0 ºC. After addition, the flask was fitted with a condenser and the reaction was heated at 70 ºC for 16 h. The reaction was allowed to cool at room temperature and the excess of thionyl chloride was quenched with a saturated aqueous solution of $NaHCO_3$. The solvent was removed *in vacuo* and the mixture obtained extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduce pressure. Compound **441** was obtained as a peach coloured solid (1.81 g, 7.65 mmol, 80%). M.p. 110-112 ºC (lit.[80] 110-112 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 7.03 (2 H, d, *J* 8.5, H-2), 6.61 (2 H, d, *J* 8.5, H-1), 3.95 (1 H, dd, *J* 9.8, 4.9, H-3), 3.64 (6 H, s, H-6 and H-5), 3.13 (1 H, dd, *J* 17.0, 9.8, H-4a), 2.60 (1 H, dd, *J* 17.0, 4.9, H-4b).

**Dimethyl 2-(4-amino-3,5-dibromophenyl) succinate (442)**



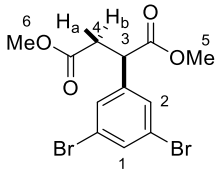

A 50 mL round-bottomed flask was charged with **441** (1.50 g, 6.30 mmol) and acetic acid (15 mL). Bromine (0.798 mL, 15.5 mmol) was added dropwise at room temperature and the mixture was allowed to stir for 1 h. The excess of bromine was quenched by addition of a saturated aqueous solution of $Na_2S_2O_3$, followed by addition of a 10% aqueous solution of $NaHCO_3$ until pH = 8.The mixture was extracted with $CH_2Cl_2$ and the combined organic

layers were dried over $MgSO_4$. The solvent was removed *in vacuo* and the product was obtained as a yellow oil (1.62 g, 4.09 mmol, 65%).

**$\delta_H$ (400 MHz, $CDCl_3$)** 7.30 (2 H, s, H-1), 4.54 (2 H, br. s, H-6), 3.90 (1 H, dd, *J* 9.8, 5.5, H-2), 3.66 (3 H, s, H-4), 3.64 (3 H, s, H-5), 3.13 (1 H, dd, *J* 17.0, 9.8, H-3a), 2.63 (1 H, dd, *J* 17.0, 5.5, H-3b).

**HRMS (*m/z* – ESI)** $[M+Na]^+$ Found 415.9126. $C_{12}H_{13}Br_2NO_4Na$ Requires 415.9109.

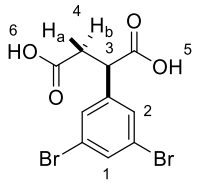
**Dimethyl 2-(3,5-dibromophenyl)succinate (443)**




A three-necked oven-dried 100 mL round-bottomed flask equipped with a thermometer was charged with **442** (1.5 g, 3.80 mmol) and a conc. HCl (15 mL). The flasked was cooled at 0 ºC and a solution of $NaNO_2$ (0.288 g, 4.1 mmol) in water (10 mL) was added slowly keeping the temperature of the reaction mixture below 5 ºC. The resulting mixture was stirred for 20 min at 0 ºC and a solution of $H_3PO_2$ (45 mL, 30% *w/v* in water) was added at that temperature. The reaction was allowed to warm up to room temperature and it was stirred for 3 h after which time water (25 mL) was added. The reaction mixture was extracted with $CH_2Cl_2$ and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduce pressure and the crude was purified by column chromatography to afford product **443** as a white solid (1.13 g, 2.96 mmol, 78%). M.p. 88-90 ºC (lit.[80] 89-91 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 7.57 (1 H, t, *J* 1.8, H-1), 7.35 (2 H, d, *J* 1.8, H-2), 4.00 (1 H, dd, *J* 9.6, 5.4, H-3), 3.69 (3 H, s, H-5), 3.67 (3 H, s, H-6), 3.14 (1 H, dd, *J* 17.1, 9.6, H-4a), 2.63 (1 H, dd, *J* 17.1, 5.4, H-4b).

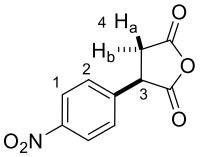
**2-(3,5-Dibromophenyl)succinic acid (444)**




A 2.0 M aqueous solution of KOH (20 mL) was added to a stirred solution of **443** (1.00 g, 2.64 mmol) in MeOH (20 mL). The reaction mixture was heated under reflux for 3 h and then cooled to room temperature. The organic solvent was removed under reduce pressure and the solution was acidified to pH = 2 by addition of 2.0 M HCl. The white precipitate was collected by suction filtration and dried to furnish **444** as a white solid (0.810 g, 2.30 mmol, 87%). M.p. 225-228 ºC (lit.[80] 227-229 ºC).

**$\delta_H$ (400 MHz, DMSO)** 12.4 (2 H, br. s, H-6 and H-5), 7.72 (1 H, d, *J* 1.7, H-1), 7.50 (2 H, d, *J* 1.7, H-2), 3.92 (1 H, dd, *J* 9.6, 5.7, H-3), 2.93 (1 H, dd, *J* 17.0, 9.6, H-4a), 2.60 (1 H, dd, *J* 17.0, 5.7, H-4b).

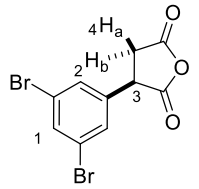
**3-(4-Nitrophenyl)dihydrofuran-2,5-dione (93)**




Following general procedure **A**, dicarboxylic acid **412** (3.00 g, 12.5 mmol) was dissolved in freshly distilled acetyl chloride (15.0 mL) and heated at reflux temperature for 16 h. After purification and several azeotropic distillations with $CHCl_3$ on a rotary evaporator, anhydride **94** was obtained as a white solid (2.16 g, 9.75 mmol, 78%). M.p. 68-70 ºC. Spectral data for this compound were consistent with those reported in the literature.[80]

**$\delta_H$ (400 MHz, DMSO)** 8.22 (2 H, d, *J* 9.0, H-1), 7.75 (2 H, d, *J* 9.0, H-2), 4.84 (1 H, dd, *J* 9.7, 8.4, H-3), 3.44 (1 H, dd, *J* 18.0, 9.7, H-4a), 3.32 (1 H, dd, *J* 18.0, 8.4, H-4b).

**3-(3,5-Dibromophenyl)dihydrofuran-2,5-dione (445)**

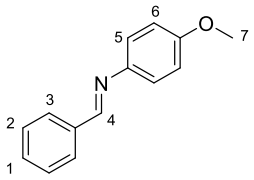



Prepared according to general procedure **A**, using dicarboxylic acid **444** (2.80 g, 7.96 mmol) and freshly distilled acetyl chloride to afford **447** as a white solid (1.97 g, 74%). Spectral data for this compound were consistent with those found in the literature.[80] M.p. 110-112 °C (lit.[80]112-115 °C).

**$\delta_H$ (400 MHz, $CDCl_3$)** 7.69 (1 H, s, H-1), 7.38 (2 H, s, H-2), 4.31 (1 H, dd, *J* 10.3, 7.2, H-3), 3.48 (1 H, dd, *J* 18.9, 10.3, H-4a), 3.11 (1 H, dd, *J* 18.9, 7.2, H-4b).

### 5.4.2 Synthesis of imines

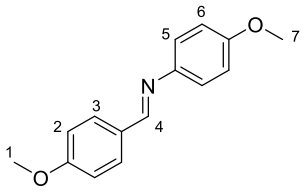
**(*E*)-*N*-(4-Methoxyphenyl)-1-phenylmethanimine (412)**




Following general procedure **H**, benzaldehyde (**84**, 1.00 mL, 9.84) and anisidine (1.21 g, 9.84 mmol) were reacted in dry toluene (20.0 mL). The product was recrystallised from hexane/ethyl acetate to afford imine **412** (1.41 g, 6.69 mmol, 68%) as a white solid. M.p. 70-71 ºC. (lit.[183] 66-68 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.49 (1 H, s, H-4), 7.96-7.85 (2 H, m, H-3), 7.50-7.43 (3 H, m, H-2 and H-1), 7.25 (2 H, d, *J* 8.8, H-5), 6.94 (2 H, d, *J* 8.8, H-6), 3.84 (3 H, s, H-7).

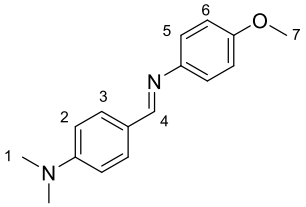
**(*E*)-*N*, 2-Bis(4-methoxyphenyl)methanimine (420)**




Following general procedure **H**, *p*-anisaldehyde (**415**, 1.00 mL, 8.22 mmol) and *p*-anisidine (1.01 g, 8.22 mmol) were reacted in dry toluene (20.0 mL). The product was recrystallised from hexane/ethyl acetate to afford imine **420** (1.03 g, 4.27 mmol, 52%). M.p. 137-140 ºC (lit.[184] 145-146 ºC)

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.40 (1 H, s, H.4), 7.83 (2 H, d, *J* 8.6, H-3), 7.21 (2 H, d, *J* 8.9, H-5), 6.97 (2 H, d, *J* 8.6, H-2), 6.92 (2 H, d, *J* 8.9, H-6), 3.87 (3 H, s, H-1), 3.83 (3 H, s, H-7).

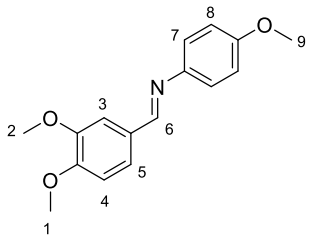
**(*E*)-4-(((4-Methoxyphenyl)imino)methyl)-*N*,*N*-dimethylaniline (421)**




Following general procedure **H**, 4-dimethylaminobenzaldehyde (**416**, 1.00 g, 6.70 mmol) and *p*-anisidine (0.825 g, 6.70 mmol) were reacted in dry toluene (20.0 mL). The product was recrystallised from hexane/ethyl acetate to afford imine **421** (1.23 g, 4.84 mmol, 72%). M.p. 137-139 ºC (lit.[185] 140-141 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.34 (1 H, s, H-4), 7.75 (2 H, d, *J* 8.7, H-3), 7.19 (2 H, d, *J* 8.9, H-5), 6.91 (2 H, d, *J* 8.9, H-6), 6.73 (2 H, d, *J* 8.7, H-2), 3.82 (3 H, s, H-7), 3.05 (6 H, s, H-1).

**(*E*)-1-(3,4-Dimethoxyphenyl)-*N*-(4-methoxyphenyl)methanimine (422)**

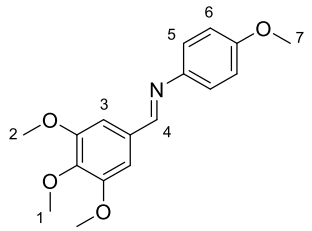



Following general procedure **H**, 3,4-dimethoxybenzaldehyde (**417**, 0.831 g, 5.00 mmol) and *p*-anisidine (0.616 g, 5.00 mmol) were reacted in dry toluene (20.0 mL). The product was recrystallised from hexane/ethyl acetate to afford imine **422** (0.917 g, 3.38 mmol, 67%).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.38 (1 H, s, H-6), 7.61 (1 H, d, *J* 1.7, H-3), 7.29 (1 H, dd, *J* 8.2, 1.7, H-5), 7.21 (2 H, d, *J* 8.9, H-7), 6.95-6.90 (3 H, m, H-8 and H-4), 3.99 (3 H, s, H-1), 3.95 (3 H, s, H-2), 3.83 (3 H, s, H-9).

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 272.1291. $C_{16}H_{18}NO_3$ Requires 272.1281.

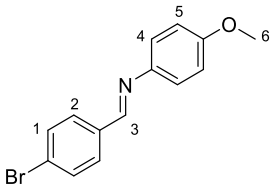
**(*E*)-*N*-(4-Methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)methanimine (423)**




Following general procedure **H**, 3,4,5-trimethoxybenzaldehyde (**418**, 0.981 g, 5.00 mmol) and *p*-anisidine (0.616 g, 5.00 mmol) were reacted in dry toluene (20.0 mL). The product was recrystallised from hexane/ethyl acetate to afford imine **423** (0.578 g, 1.92 mmol, 39%). M.p 109-111 ºC (lit.[186] 108 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.37 (1 H, s, H-4), 7.22 (2 H, d, *J* 9.0, H-5), 7.14 (2 H, s, H.3), 6.93 (2 H, d, *J* 9.0, H-6), 3.95 (6 H, s, H-2), 3.91 (3 H, s, H-1), 3.84 (3 H, s, H-7).

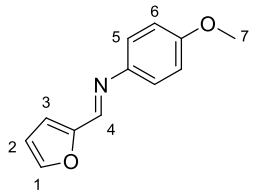
**(*E*)-1-(4-Bromophenyl)-*N*-(4-methoxyphenyl)methanimine (424)**




Following general procedure **H**, *p*-bromobenzaldehyde (**419**, 0.556 g, 3.00 mmol) and *p*-anisidine (0.369 g, 3.00 mmol) were reacted in dry toluene (20.0 mL). The product was recrystallised from hexane/ethyl acetate to afford imine **424** (0.540 g, 1.86 mmol, 62%). M.p. 139-140 ºC (lit.[187] 146 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.43 (1 H, s, H-3), 7.75 (2 H, d, *J* 8.4, H-2), 7.59 (2 H, d, *J* 8.4, H-1), 7.24 (2 H, d, *J* 8.9, H-4), 6.93 (2 H, d, *J* 8.9, H-5), 3.83 (3 H, s, H-6).

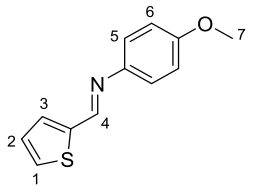
**(*E*)-1-(Furan-2-yl)-*N*-(4-methoxyphenyl)methanimine (425)**




Following general procedure **H**, furfural (**94**, 0.500 mL, 6.04 mmol) and *p*-anisidine (0.743 g, 6.04 mmol) were reacted in dry toluene (20.0 mL). The product was recrystallised from hexane/ethyl acetate to afford imine **425** (0.834 g, 4.14 mmol, 69%). M.p. 68-70 ºC (lit.[188] 71-72 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.31 (1 H, s, H-4), 7.60 (1 H, d, *J* 1.7, H-1), 7.29-7.23 (2 H, m, H-5), 6.96-6.88 (3 H, m, H-6 and H-3), 6.55 (1 H, dd, *J* 3.5, 1.7, H-2), 3.83 (3 H, s).

**(*E*)-*N*-(4-Methoxyphenyl)-1-(thiophen-2-yl)methanimine (426)**

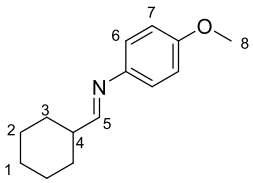



Following general procedure **H**, 2-thiophenecarboxaldehyde (**385**, 0.500 mL, 5.35 mmol) and *p*-anisidine (0.659 g, 5.35 mmol) were reacted in dry toluene (20.0 mL). The product was recrystallised from hexane/ethyl acetate to afford imine **426** (0.515 g, 2.37 mmol, 44%).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.58 (1 H, s, H-4), 7.48 (1 H, d, *J* 5.2, H-1), 7.45 (1 H, d, *J* 3.5, H-3), 7.22 (2 H, d, *J* 8.9, H-5), 7.12 (1 H, dd, *J* 5.2, 3.5, H-2), 6.91 (2 H, d, *J* 8.9, H-6), 3.83 (3 H, s, H-7).

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 218.0637. $C_{12}H_{12}NOS$ Requires 218.0634.

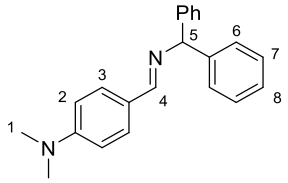
**(*E*)-1-Cyclohexyl-*N*-(4-Methoxyphenyl)methanimine (429)**




Cyclohexanecarboxaldehyde (**388**, 1.00 mL, 8.25 mmol) and *p*-anisidine (1.02 g, 8.25 mmol) were reacted in chloroform (20.0 mL). $MgSO_4$ was added and the mixture was stirred at room temperature for 3 h. The reaction was filtered through a short pad of Celite and the solvent removed *in vacuo* to furnish imine **429** as a yellow oil (1.33 g, 6.12 mmol, 74%).

**$\delta_H$ (400 MHz, $CDCl_3$)** 7.71 (1 H, d, *J* 4.9, H-5), 7.01 (2 H, d, *J* 8.7, H-6), 6.86 (2 H, d, *J* 8.7, H-7), 3.78 (3 H, s, H-8), 2.30-1.00 (11 H, m, H-4, H-3, H-2 and H-1).

**(*E*)-4-((Benzhydrylimino)methyl)-*N*,*N*-dimethylaniline (428)**

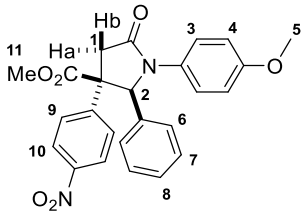



Following general procedure **H**, *p*-dimethylaminobenzaldehyde (**416**, 0.432 g, 2.90 mmol) and benzhydrylamine (0.500 mL, 2.90 mmol) were reacted in dry toluene (20.0 mL). The product was recrystallised from hexane/ethyl acetate to afford imine **428** (0.330 g, 1.05 mmol, 36%). M.p. 137-139 ºC (lit.[189] 140-141 ºC).

**$\delta_H$ (400 MHz, $CDCl_3$)** 8.28 (1 H, s, H-4), 7.71 (2 H, d, *J* 8.9, H-3), 7.39 (4 H, d, *J* 7.3, H-6), 7.33-7.27 (4 H, m, H-7), 7.20 (2 H, t, *J* 7.3, H-8), 6.69 (2 H, d, *J* 8.9, H-2), 5.53 (1 H, s, H-5), 3.01 (6 H, s, H-1).

### 5.4.3 Catalytic reactions between anhydrides and imines to afford lactams

**Methyl 1-(4-methoxyphenyl)-3-(4-nitrophenyl)-5-oxo-2-phenylpyrrolidine-3-carboxylate (414)**




Prepared following general procedure **I**, using imine **412** (42.2 mg, 0.20 mmol). After esterification and purification, lactam **414** was isolated as a brown solid (80.4 mg, 0.18 mmol, 90%). M.p. 98-100 ºC. $[\alpha]^{20}_D$ = -2.36 (c 0.11, Acetone).

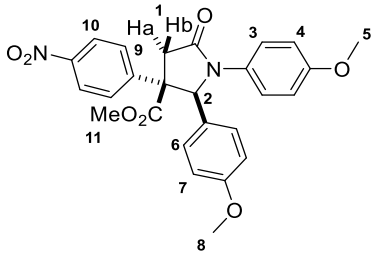
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.26 (2 H, d, *J* 8.8, H-10), 7.55 (2 H, d, *J* 8.8, H-9), 7.41-7.26 (7 H, m, H-8, H-7, H-6 and H-3), 6.80 (2 H, d, *J* 9.1, H-4), 5.57 (1 H, s, H-2), 4.00 (1 H, d, *J* 17.4, H-1a), 3.74 (3 H, s, H-5), 3.32 (3 H, s, H-11), 2.75 (1 H, d, *J* 17.4, H-1b)

**$\delta_C$ (100 MHz, $CDCl_3$)** 170.6 (C=O), 170.3 (C=O), 157.4 (q), 148.9 (q), 147.4 (q), 135.6 (q), 130.4 (q), 129.3, 128.9, 127.6, 127.0, 124.4, 123.5, 114.4, 70.3, 58.3 (q), 55.4, 52.5, 41.8

**$\nu_{max}$ ($cm^{-1}$)** 2951, 1736, 1678, 1615, 1510, 1391, 1350, 1242, 1031, 828

**HRMS (*m/z* - APCI)** $[M+H]^+$ Found 447.1558. $C_{25}H_{23}N_2O_6$ Requires 447.1550.

**Methyl 1,2-bis(4-methoxyphenyl)-3-(4-nitrophenyl)-5-oxopyrrolidine-3-carboxylate (430)**




Prepared following general procedure **I**, using imine **420** (48.4 mg, 0.20 mmol). After esterification and purification, lactam **430** was isolated as a brown solid (84.8 mg, 0.18 mmol, 89%). M.p. 100-103 ºC. $[\alpha]^{20}_D$ = -2.34 (c 0.1, Acetone).

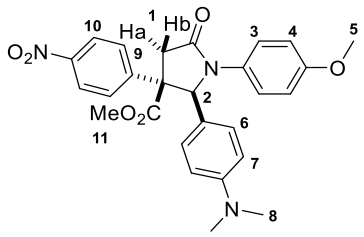
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.25 (2 H, d, *J* 8.9, H-10), 7.53 (2 H, d, *J* 8.9, H-9), 7.29 (2 H, d, *J* 9.0, H-3), 7.23 (2 H, d, *J* 8.7, H-6), 6.89 (2 H, d, *J* 8.7, H-7), 6.81 (2 H, d, *J* 9.0, H-4), 5.53 (1 H, s, H-2), 3.97 (1 H, d, *J* 17.5, H-1a), 3.80 (3 H, s, H-8), 3.75 (3 H, s, H-5), 3.36 (3 H, s, H-11), 2.72 (1 H, d, *J* 17.5, H-1b).

**$\delta_C$ (100 MHz, $CDCl_3$)** 170.6 (C=O), 170.4 (C=O), 160.1 (q), 157.4 (q), 149.0 (q), 147.3 (q), 130.5 (q), 128.9, 127.3 (q), 127.0, 124.3, 123.5, 114.3 (x2), 69.8, 58.4 (q), 55.4, 55.3, 52.6. 41.8.

**$\nu_{max}$ ($cm^{-1}$)** 2952, 1733, 1693, 1607, 1515, 1433, 1347, 1243, 1056, 829.

**HRMS (*m/z* - APCI)** $[M+H]^+$ Found 477.1656. $C_{26}H_{25}N_2O_7$ Requires 477.1656.

**Methyl 2-(4-(dimethylamino)phenyl)-1-(4-methoxyphenyl)-3-(4-nitrophenyl)-5-oxopyrrolidine-3-carboxylate (431)**




Prepared following general procedure **I**, using imine **421** (50.9 mg, 0.20 mmol). After esterification and purification, lactam **431** was isolated as an orange solid (93.0 mg, 0.19 mmol, 95%). M.p. 140-143 ºC. $[\alpha]^{20}_D$ = -2.11 (c 0.1, Acetone).

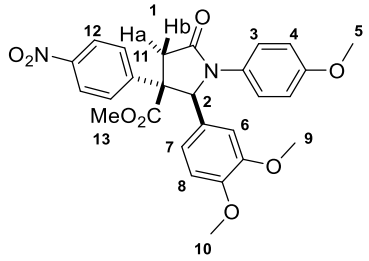
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.24 (2 H, d, *J* 8.9, H-10), 7.52 (2 H, d, *J* 8.9, H-9), 7.32 (2 H, d, *J* 9.0, H-4), 7.13 (2 H, d, *J* 8.8, H-6), 6.80 (2 H, d, *J* 9.0, H-4), 6.66 (2 H, d, *J* 8.8, H-7), 5.48 (1 H, s, H-2), 3.99 (1 H, d, *J* 17.4, H-1a), 3.74 (3 H, s, H-5), 3.40 (3 H, s, H-11), 2.95 (6 H, s, H-8), 2.70 (1 H, d, *J* 17.4, H-1b).

**$\delta_C$ (100 MHz, $CDCl_3$)** 170.7 (C=O), 170.5 (C=O), 157.3 (q), 150.7 (q), 149.3 (q), 147.2 (q), 130.7 (q), 128.4, 127.1, 124.3, 123.5, 122.0 (q), 114.3, 112.1, 69.9, 58.6 (q), 55.4, 52.5, 41.9, 40.2.

**$\nu_{max}$ ($cm^{-1}$)** 2952, 1733, 1693, 1607, 1515, 1347, 1244, 1057, 828, 728.

**HRMS (*m/z* - APCI)** $[M+H]^+$ Found 490.1968. $C_{27}H_{28}N_3O_6$ Requires 456.1417.

**Methyl 2-(3,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-3-(4-nitrophenyl)-5-oxopyrrolidine-3-carboxylate (432)**




Prepared following general procedure **I**, using imine **422** (54.3 mg, 0.20 mmol). After esterification and purification, lactam **432** was isolated as a white solid (94.2 mg, 0.19 mmol, 93%). M.p. 109-110 ºC. $[\alpha]^{20}_{D}$ = -2.19 (c 0.12, Acetone).

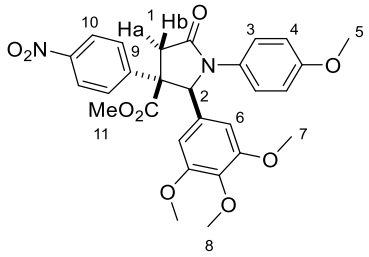
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.26 (2 H, d, *J* 8.9, H-12), 7.53 (2 H, d, *J* 8.9, H-11), 7.29 (2 H, d, *J* 9.1, H-3), 6.91-6.75 (5 H, m, H-8, H-7, H-6 and H-4), 5.51 (1 H, s, H-2), 3.98 (1 H, d, *J* 17.4, H-1a), 3.88 (3 H, s, H-9), 3.85 (3 H, s, H-10), 3.75 (3 H, s, H-5), 3.39 (3 H, s, H-13), 2.74 (1 H, d, *J* 17.4, H-1b).

**$\delta_C$ (100 MHz, $CDCl_3$)** 170.5 (C=O), 170.4 (C=O), 157.4 (q), 149.6 (q), 149.2 (q), 148.9 (q), 147.3 (q), 130.4 (q), 127.7, 127.0, 124.3, 123.5, 120.1 (q), 114.4, 111.2, 110.6, 70.1, 58.4 (q), 56.0, 55.8, 55.4, 52.7, 41.9

**$\nu_{max}$ ($cm^{-1}$)** 2954, 1732, 1693, 1606, 1513, 1443, 1348, 1246, 1140, 1027, 856.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 507.1767. $C_{27}H_{27}N_2O_8$ Requires 507.1762.

**Methyl 1-(4-methoxyphenyl)-3-(4-nitrophenyl)-5-oxo-2-(3,4,5-trimethoxyphenyl)pyrrolidine-3-carboxylate (433)**




Prepared following general procedure **I**, using imine **423** (60.3 mg, 0.20 mmol). After esterification and purification, lactam **433** was isolated as a white solid (91.2 mg, 0.17 mmol, 85%). M.p. 165-166 ºC. $[\alpha]^{20}_{D}$ = -2.14 (c 0.12, Acetone).

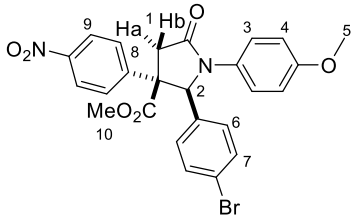
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.25 (2 H, d, *J* 8.9, H-10), 7.53 (2 H, d, *J* 8.9, H-9), 7.30 (2 H, d, *J* 9.1, H-3), 6.84 (2 H, d, *J* 9.1, H-4), 6.50 (2 H, s, H-6), 5.49 (1 H, s, H-2), 3.97 (1 H, d, *J* 17.4, H-1a), 3.84 (3 H, s, H-8), 3.82 (6 H, s, H-7), 3.76 (3 H, s, H-5), 3.40 (3 H, s, H-11), 2.74 (1 H, d, *J* 17.4, H-1b).

**$\delta_C$ (100 MHz, $CDCl_3$)** 170.5 (C=O), 170.2 (C=O), 157.5 (q), 153.5 (q), 148.8 (q), 147.4 (q), 138.6 (q), 131.0 (q), 130.4 (q), 127.0, 124.3, 123.4, 114.4, 104.7, 70.4, 60.9, 58.4 (q), 56.2, 55.4, 52.7, 41.9

**$\nu_{max}$ ($cm^{-1}$)** 2938, 1728, 1703, 1590, 1512, 1460, 1329, 1234, 1122, 698

**HRMS (*m/z* - ESI)** $[M+Na]^+$ Found 559.1676. $C_{28}H_{28}N_2NaO_9$ Requires 559.1687.

**Methyl 2-(4-bromophenyl)-1-(4-methoxyphenyl)-3-(4-nitrophenyl)-5-oxopyrrolidine-3-carboxylate (434)**




Prepared following general procedure **I**, using imine **424** (58.0 mg, 0.20 mmol). After esterification and purification, lactam **434** was isolated as a white solid (94.6 mg, 0.18 mmol, 90%). M.p. 127-130 ºC. $[\alpha]^{20}_D$ = -1.93 (c 0.12, Acetone).

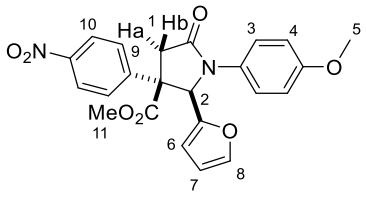
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.26 (2 H, d, *J* 8.9, H-9), 7.57-7.49 (4 H, m, H-8 and H-7), 7.28-7.23 (2 H, m, H-3), 7.20 (2 H, d, *J* 8.5, H-6), 6.81 ( 2 H, d, *J* 9.0, H-4), 5.53 (1 H, s, H-2), 3.93 (1 H, d, *J* 17.4, H-1a), 3.75 (3 H, s, H-5), 3.38 (3 H, s, H-10), 2.77 (1 H, d, *J* 17.4, H-1b).

**$\delta_C$ (100 MHz, $CDCl_3$)** 170.4 (C=O), 170.1 (C=O), 157.5 (q), 148.5 (q), 147.4 (q), 134.8 (q), 132.2, 130.1 (q), 129.3 (q), 126.9, 124.4, 123.5, 114.5, 69.8, 58.1 (q), 55.4, 52.7, 41.6.

**$\nu_{max}$ ($cm^{-1}$)** 2951, 1735, 1694, 1607, 1515, 1347, 1242, 1031, 856, 697.

**HRMS (*m/z* - ESI)** $[M-H]^-$ Found 523.0514. $C_{25}H_{20}BrN_2O_6$ Requires 523.0510.

**Methyl 2-(furan-2-yl)-1-(4-methoxyphenyl)-3-(4-nitrophenyl)-5-oxopyrrolidine-3-carboxylate (435)**




Prepared following general procedure **I**, using imine **425** (40.2 mg, 0.20 mmol). After esterification and purification, lactam **435** was isolated as a white solid (77.7 mg, 0.18 mmol, 89%). M.p. 150-153 ºC. $[\alpha]^{20}_D$ = -1.78 (c 0.17, Acetone).

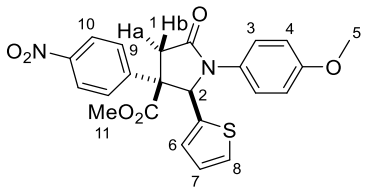
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.27 (2 H, d, *J* 8.8, H-10), 7.61 (2 H, d, *J* 8.8, H-9), 7.44 (1 H, d, *J* 0.9, H-8), 7.12 (2 H, d, *J* 9.1, H-3), 6.84 (2 H, d, *J* 9.1, H-4), 6.38-6.31 (2 H, m, H-7 and H-6), 5.50 (1 H, s, H-2), 4.01 (1 H, d, *J* 17.1, H-1a), 3.77 (3 H, s, H-5), 3.51 (3 H, s, H-11), 2.86 (1 H, d, *J* 17.1, H-1b).

**$\delta_C$ (100 MHz, $CDCl_3$)** 170.8 (C=O), 170.3 (C=O), 158.0 (q), 149.4 (q), 147.7 (q), 147.5 (q), 143.5, 129.9 (q), 126.9, 124.8, 124.4, 114.5, 110.9, 110.5, 64.6, 57.0 (q), 55.4, 53.0, 41.5.

**$\nu_{max}$ ($cm^{-1}$)** 2931, 1741, 1688, 1596, 1511, 1235, 1119, 728.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 437.1350. $C_{23}H_{21}N_2O_7$ Requires 437.1343.

**Methyl 1-(4-methoxyphenyl)-3-(4-nitrophenyl)-5-oxo-2-(thiophen-2-yl)pyrrolidine-3-carboxylate (436)**




Prepared following general procedure **I**, using imine **426** (43.5 mg, 0.20 mmol). After esterification and purification, lactam **436** was isolated as a white solid (76.0 mg, 0.17 mmol, 84%). M.p. 140-143 ºC. $[\alpha]^{20}_D$ = -2.11 (c 0.2, Acetone).

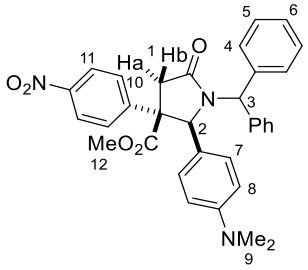
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.26 (2 H, d, *J* 8.9, H-10), 7.58 (2 H, d, *J* 8.9, H-9), 7.33 (1 H, dd, *J* 5.1, 1.0, H-8), 7.28 (2 H, d, *J* 9.1, H-3), 7.06 (1 H, d, *J* 3.2, H-6), 7.00 (1 H, dd, *J* 5.1, 3.2, H-7), 6.83 (2 H, d, *J* 9.1, H-4), 5.83 (1 H, s, H-2), 4.02 (1 H, d, *J* 17.3, H-1a), 3.76 (3 H, s, H-5), 3.48 (3 H, s, H-11), 3.82 (1 H, d, *J* 17.3, H-1b).

**$\delta_C$ (100 MHz, $CDCl_3$)** 170.1 (C=O), 170.0 (C=O), 157.6 (q), 147.8 (q), 147.5 (q), 139.1 (q), 130.0 (q), 127.8, 127.2, 127.0, 126.7, 124.4, 123.7, 114.4, 66.2, 58.3 (q), 55.4, 52.8, 41.2.

**$\nu_{max}$ ($cm^{-1}$)** 2953, 1732, 1682, 1606, 1514, 1433, 1348, 1246, 1028, 725.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 453.1119. $C_{23}H_{21}N_2O_6S$ Requires 453.1115.

**Methyl 1-benzhydryl-2-(4-(dimethylamino)phenyl)-3-(4-nitrophenyl)-5-oxopyrrolidine-3-carboxylate (437)**




Prepared following general procedure **I**, using imine **428** (62.9 mg, 0.20 mmol). After esterification and purification, lactam **437** was isolated as a yellow solid (98.9 mg, 0.18 mmol, 90%). M.p. 147-150 ºC. $[\alpha]^{20}_{D}$ = -1.56 (c 0.1, Acetone).

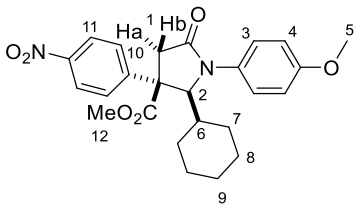
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.11 (2 H, d, *J* 9.1, H-11), 7.39 (2 H, d, *J* 9.1, H-10), 7.24-7.10 (8 H, m, H-7, H-6 and H-5), 7.03-6.95 (4 H, m, H-4), 6.59 (2 H, d, *J* 8.6, H-8), 5.79 (1 H, s, H-2), 4.94 (1 H, s, H-3), 3.95 (1 H, d, *J* 17.3, H-1a), 3.22 (3 H, s, H-12), 2.95 (6 H, s, H-9), 2.75 (1 H, d, *J* 17.3, H-1b).

**$\delta_C$ (100 MHz, $CDCl_3$)** 171.5 (C=O), 170.7 (C=O), 150.7 (q), 148.6 (q), 147.2 (q), 138.3 (q), 138.2 (q), 129.4, 129.2, 128.4, 128.2, 128.0, 127.7, 127.5, 127.4, 123.8, 122.7 (q), 111.9, 69.5, 62.5, 58.5 (q), 52.4, 41.0, 40.3.

**$\nu_{max}$ ($cm^{-1}$)** 2949, 1736, 1694, 1612, 1519, 1447, 1347, 1239, 1058, 700.

**HRMS (*m/z* - APCI)** $[M+H]^+$ Found 550.2344. $C_{33}H_{32}N_3O_5$ Requires 550.2336.

**Methyl 2-cyclohexyl-1-(4-methoxyphenyl)-3-(4-nitrophenyl)-5-oxopyrrolidine-3-carboxylate (438)**




Prepared following general procedure **I**, using imine **429** (43.5 mg, 0.20 mmol). After esterification and purification, lactam **438** was isolated as a white solid (76.9 mg, 0.17 mmol, 85%). M.p. 147-150 ºC. $[\alpha]^{20}_D$ = 0.22 (c 0.1, Acetone).

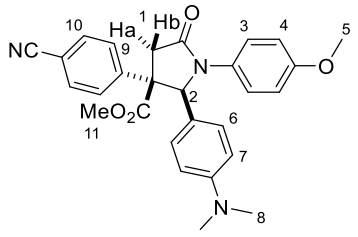
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.24 (2 H, d, *J* 9.0, H-11), 7.67 (2 H, d, *J* 9.0, H-10), 7.18 (2 H, d, *J* 9.0, H-3), 6.88 (2 H, d, *J* 9.0, H-4), 4.52 (1 H, d, *J* 2.0, H-2), 3.79 (3 H, s, H-5), 3.77 (3 H, s, H-12), 3.69 (1 H, d, *J* 17.4, H-1a), 2.84 (1 H, d, *J* 17.4, H-1b), 1.99-1.89 (1 H, m, H-6), 1.81-0.47 (10 H, m, H-9, H-8 and H-7).

**$\delta_C$ (100 MHz, $CDCl_3$)** 171.5 (C=O), 170.5 (C=O), 157.6 (q), 149.3 (q), 147.3 (q), 131.4 (q), 127.0, 125.0, 124.2, 114.4, 72.9, 56.0 (q), 55.4, 53.0 42.4, 41.8, 33.0, 27.6, 27.1, 26.3, 25.8.

**$\nu_{max}$ ($cm^{-1}$)** 2933, 2852, 1733, 1688, 1511, 1404, 1128, 853, 732.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 453.2020. $C_{25}H_{29}N_2O_6$ Requires 453.2020.

**Methyl 3-(4-cianophenyl)-2-(4-(dimethylamino)phenyl)-1-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylate (451)**




Prepared following general procedure **J**, using anhydride **446** (40.2 mg, 0.20 mmol). After esterification and purification, lactam **451** was isolated as a white solid (91.1 mg, 0.19 mmol, 96%). M.p. 163-165 ºC. $[\alpha]^{20}_D$ = -2.31 (c 0.15, Acetone).

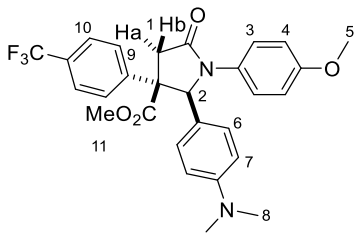
**$\delta_H$ (400 MHz, $CDCl_3$)** 7.68 (2 H, d, *J* 8.5, H-10), 7.46 (2 H, d, *J* 8.5, H-9), 7.31 (2 H, d, *J* 9.0, H-3), 7.12 (2 H, d, *J* 8.8, H-6), 6.80 (2 H, d, *J* 9.0, H-4), 6.65 (2 H, d, *J* 8.8, H-7), 5.45 (1 H, s, H-2), 3.96 (1 H, d, *J* 17.3, H-1a), 3.74 (3 H, s, H-5), 3.37 (3 H, s, H-11), 2.95 (6 H, s, H-8), 2.67 (1 H, d, *J* 17.3, H-1b).

**$\delta_C$ (100 MHz, $CDCl_3$)** 170.7 (C=O), 170.6 (C=O), 157.2 (q), 150.6 (q), 147.3 (q), 132.9, 130.8 (q), 128.4 (q), 126.8, 123.4, 122.0 (q), 118.2, 114.2, 112.1, 111.8 (q), 69.8, 58.6 (q), 55.4, 52.5, 41.9, 40.2.

**$\nu_{max}$ ($cm^{-1}$)** 2939, 2230, 1729, 1702, 1609, 1590, 1510, 1330, 1234, 1123, 963, 790.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 70.2078. $C_{28}H_{28}N_3O_4$ Requires 470.2074.

**Methyl 2-(4-(dimethylamino)phenyl)-1-(4-methoxyphenyl)-5-oxo-3-(4-(trifluoromethyl)phenyl)pyrrolidine-3-carboxylate (452)**




Prepared following general procedure **J**, using anhydride **447** (48.8 mg, 0.20 mmol). After esterification and purification, lactam **452** was isolated as a white solid (95.3 mg, 0.19 mmol, 93%). M.p. 183-185 ºC. $[\alpha]^{20}_D$ = -1.97 (c 0.1, Acetone).

**$\delta_H$ (400 MHz, $CDCl_3$)** 7.64 (2 H, d, *J* 8.8, H-10), 7.47 (2 H, d, *J* 8.8, H-9), 7.33 (2 H, d, *J* 9.1, H-3), 7.14 (2 H, d, *J* 8.8, H-6), 6.80 (2 H, d, *J* 9.1, H-4), 6.66 (2 H, d, *J* 8.8, H-7), 5.49 (1 H, s, H-2), 3.97 (1 H, d, *J* 17.3, H-1a), 3.74 (3 H, s, H-5), 3.37 (3 H, s, H-11), 2.95 (6 H, s, H-8), 2.70 (1 H, d, *J* 17.3, H-1b).

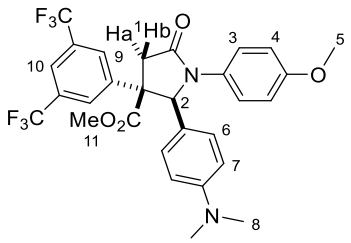
**$\delta_C$ (100 MHz, $CDCl_3$)** 171.0 (x2) (C=O), 157.2 (q), 150.6 (q), 146.1 (q, $J_{C-F}$ 1.5, q), 130.9 (q), 130.0 (q, $J_{C-F}$ 33.5, q), 128.4, 126.3, 126.1 (q, $J_{C-F}$ 3.6), 123.8 (q, $J_{C-F}$ 271.8, q), 122.4 (q), 114.2, 112.1, 69.9, 58.4 (q), 55.4, 52.4, 42.1, 40.2.

**$\delta_F$ (376 MHz, $CDCl_3$)** -62.7.

**$\nu_{max}$ ($cm^{-1}$)** 2932, 1735, 1679, 1618, 1513, 1438, 1325, 1249, 1173, 800.

**HRMS (*m/z* - APCI)** $[M+H]^+$ Found 513.2000. $C_{28}H_{28}F_3N_2O_4$ Requires 456.1417.

**Methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2-(4-(dimethylamino)phenyl)-1-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylate (453)**




Prepared following general procedure **J**, using anhydride **448** (62.4 mg, 0.20 mmol). After esterification and purification, lactam **453** was isolated as a white solid (110 mg, 0.19 mmol, 95%). M.p. 155-158 ºC. $[\alpha]^{20}_D$ = -1.3 (c 0.1, Acetone).

**$\delta_H$ (400 MHz, $CDCl_3$)** 7.89 (1 H, s, H-10), 7.83 (2 H, s, H-9), 7.25 (2 H, d, *J* 9.0, H-3), 7.17 (2 H, d, *J* 8.8, H-6), 6.83 (2 H, d, *J* 9.0, H-4), 6.70 (2 H, d, *J* 8.8, H-7), 5.45 (1 H, s, H-2), 4.02 (1 H, d, *J* 17.1, H-1a), 3.77 (3 H, s, H-11), 3.42 (3 H, s, H-5), 2.99 (6 H, s, H-8), 2.72 (1 H, d, *J* 17.1, H-1b).

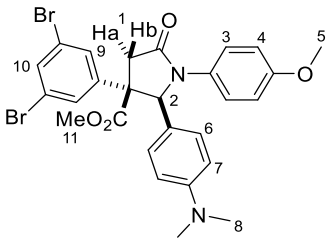
**$\delta_C$ (100 MHz, $CDCl_3$)** 170.6 (C=O), 170.4 (C=O), 157.6 (q), 150.8 (q), 144.8 (q), 132.5 (q, $J_{C-F}$ 33.4, q), 130.4 (q), 128.5, 126.4, 124.3, 123.1 (q, $J_{C-F}$ 273.2, q), 121.9 (q), 121.8 (q), 114.4, 112.1, 70.4, 58.6, 55.4, 52.7, 41.7, 40.2.

**$\delta_F$ (376 MHz, $CDCl_3$)** -62.8.

**$\nu_{max}$ ($cm^{-1}$)** 2953, 1732, 1682, 1607, 1518, 1433, 1348, 1246, 1031, 856, 696.

**HRMS (*m/z* - ESI)** $[M+H]^+$ Found 581.1869. $C_{29}H_{27}F_6N_2O_4$ Requires 581.1869.

**Methyl 3-(3,5-dibromophenyl)-2-(4-(dimethylamino)phenyl)-1-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylate (454)**




Prepared following general procedure **J**, using anhydride **445** (66.4 mg, 0.20 mmol). After esterification and purification, lactam **454** was isolated as a white solid (113 mg, 0.19 mmol, 97%). M.p. 107-110 ºC. $[\alpha]^{20}_D$ = -1.23 (c 0.1, Acetone).

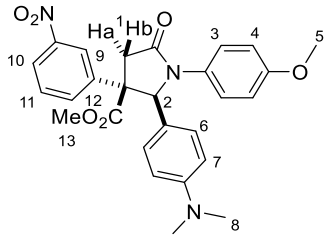
**$\delta_H$ (400 MHz, $CDCl_3$)** 7.62 (1 H, t, *J* 1.4, H-10), 7.43 (2 H, d, *J* 1.4, H-9), 7.24 (2 H, d, *J* 9.0, H-3), 7.10 (2 H, d, *J* 8.7, H-6), 6.79 (2 H, d, *J* 9.0, H-4), 6.63 (2 H, d, *J* 8.7, H-7), 5.35 (1 H, s, H-2), 3.91 (1 H, d, *J* 17.3, H-1a), 3.72 (3 H, s, H-5), 3.35 (3 H, s, H-11), 2.93 (6 H, s, H.8), 2.67 (1 H, d, *J* 17.3, H-1b).

**$\delta_C$ (100 MHz, $CDCl_3$)** 170.8 (C=O), 170.5 (C=O), 157.4 (q), 150.6 (q), 145.8 (q), 133.5 (q), 130.6 (q), 128.5, 128.0, 124.2, 123.6, 122.1 (q), 114.3, 112.0, 70.8, 58.1 (q), 55.3, 52.5, 41.7, 40.2.

**$\nu_{max}$ ($cm^{-1}$)** 2951, 1735, 1678, 1509, 1435, 1243, 1184, 1034, 828.

**HRMS (*m/z* - APCI)** $[M+H]^+$ Found 601.0330. $C_{27}H_{27}Br_2N_2O_4$ Requires 601.0332.

**Methyl 2-(4-(dimethylamino)phenyl)-1-(4-methoxyphenyl)-3-(3-nitrophenyl)-5-oxopyrrolidine-3-carboxylate (455)**




Prepared following general procedure **J**, using anhydride **449** (44.2 mg, 0.20 mmol). After esterification and purification, lactam **455** was isolated as a pale yellow solid (88.1 mg, 0.18 mmol, 90%). M.p. 165-166 ºC. $[\alpha]^{20}_D$ = -2.26 (c 0.14, Acetone).

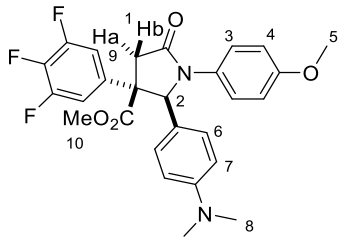
**$\delta_H$ (400 MHz, $CDCl_3$)** 8.35 (1 H, app. t, H-9), 8.20 (1 H, dd, *J* 8.1, 1.1, H-10), 7.67 (1 H, dd, *J* 8.0, 1.1, H-12), 7.57 (1 H, app. t, H-11), 7.30 (2 H, d, *J* 9.1, H-3), 7.15 (2 H, d, *J* 8.8, H-6), 6.81 (2 H, d, *J* 9.1, H-4), 6.66 (2 H, d, *J* 8.8, H-7), 5.49 (1 H, s, H-2), 3.99 (1 H, d, *J* 17.3, H-1a), 3.74 (3 H, s, H-5), 3.38 (3 H, s, H-13), 2.95 (6 H, s, H-8), 2.73 (1 H, d, *J* 17.3, H-1b).

**$\delta_C$ (100 MHz, $CDCl_3$)** 170.8 (C=O), 170.6 (C=O), 157.4 (q), 150.7 (q), 148.7 (q), 144.2 (q), 132.2 (q), 130.6 (q), 130.1, 128.5, 124.1, 122.8, 122.0, 121.2, 114.3, 112.1, 70.3, 58.3 (q), 55.4, 52.5, 41.8, 40.2.

**$\nu_{max}$ ($cm^{-1}$)** 2953, 1732, 1681, 1518, 1433, 1348, 1246, 1057, 856, 727.

**HRMS (*m/z* - APCI)** $[M+H]^+$ Found 490.1984. $C_{27}H_{28}N_3O_6$ Requires 490.1973.

**Methyl 2-(4-(dimethylamino)phenyl)-1-(4-methoxyphenyl)-5-oxo-3-(3,4,5-trifluorophenyl)pyrrolidine-3-carboxylate (456)**




Prepared following general procedure **J**, using anhydride **450** (46.0 mg, 0.20 mmol). After esterification and purification, lactam **456** was isolated as a white solid (93.5 mg, 0.19 mmol, 93%). M.p. 87-90 ºC. $[\alpha]^{20}_D$ = -1.87 (c 0.11, Acetone).

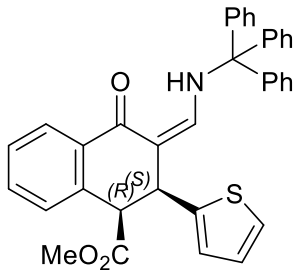
**$\delta_H$ (400 MHz, $CDCl_3$)** 7.27 (2 H, d, *J* 8.9, H-3), 7.10 (2 H, d, *J* 8.4, H-6), 7.06-6.96 (2 H, m, H-9), 6.78 (2 H, d, *J* 8.9, H-4), 6.63 (2 H, d, *J* 8.4, H-7), 5.31 (1 H, s, H-2), 3.89 (1 H, d, *J* 17.1, H-1a), 3.72 (3 H, s, H-5), 3.36 (3 H, s, H-10), 2.93 (6 H, s, H-8), 2.67 (1 H, d, *J* 17.1, H-1b).

**$\delta_C$ (100 MHz, $CDCl_3$)** 170.8 (C=O), 170.4 (C=O), 157.3 (q), 151.3 (ddd, $J_{C-F}$ 251.2, 9.80, 3.6, q), 150.7 (q), 139.2 (dt, $J_{C-F}$ 253.8, 15.1, q), 138.4

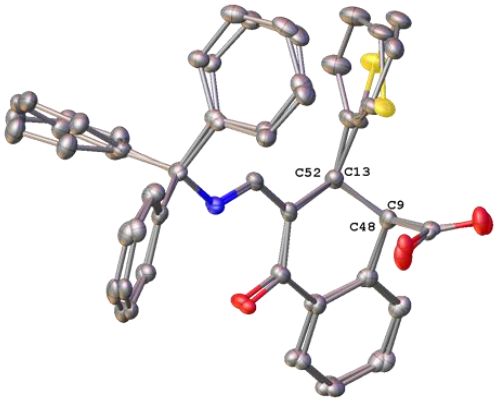
| | |
|---|---|
| | (m, q), 130.7 (q), 128.4, 123.6 (q), 122.0, 114.3, 112.1, 110.8 (dd, $J_{C\text{-}F}$ 22.3, 5.8), 70.5, 57.8 (q), 55.4, 52.5, 41.6, 40.2. |
| **$\delta_F$ (376 MHz, $CDCl_3$)** | -132.3 (2 F, d, *J* 20.6), -160.6 (1 F, t, *J* 20.6). |
| **$\nu_{max}$ ($cm^{-1}$)** | 2952, 1739, 1696, 1613, 1525, 1510, 1433, 1343, 1244, 1039, 949, 917, 799. |
| **HRMS (*m/z* - ESI)** | $[M+H]^+$ Found 499.1836. $C_{27}H_{26}F_3N_2O_4$ Requires 499.1839. |

## 5.5 X-ray crystallography data

### 5.5.1 X-ray crystallography data for 399




**399**




A specimen of $C_{36}H_{29}Cl_2NO_3S$, approximate dimensions 0.012 mm x 0.060 mm x 0.320 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 100(2)K on a Bruker B8 Quest Eco with an Oxford Cryostream low temperature device using a MiTeGen micromount. Bruker APEX software was used to correct for Lorentz and polarization effects.

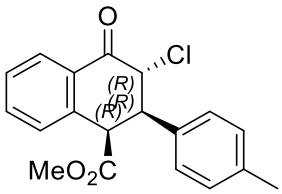
The integration of the data using a monoclinic unit cell yielded a total of 56100 reflections to a maximum θ angle of 26.94° (0.78 Å resolution), of which 13278 were independent (average redundancy 4.225, completeness = 99.4%, $R_{int}$ = 6.53%, $R_{sig}$ = 5.27%) and 10867 (81.84%) were greater than $2\sigma(F^2)$. The final cell constants of a = 14.2410(6) Å, b = 9.0056(4) Å, c = 24.3961(10) Å, β = 99.8657(13)°, volume = 3082.5(2) $Å^3$, are based upon the refinement of the XYZ-centroids of reflections above 20 σ(I). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.6831 and 0.7454.

The structure was solved with the XT structure solution program using Intrinsic Phasing and refined with the XL refinement package using Least Squares minimisation with Olex2[8], using the space group $P2_1$, with Z = 4 for the formula unit, $C_{36}H_{29}Cl_2NO_3S$. The final anisotropic full-matrix least-squares refinement on $F^2$ with 811 variables converged at R1 = 4.33%, for the observed data and wR2 = 10.40% for all data. The goodness-of-fit was 1.034. The largest peak in the final difference electron density synthesis was 0.494 $e^-/Å^3$ and the largest hole was -0.362 $e^-/Å^3$ with an RMS deviation of 0.056 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.350 $g/cm^3$ and F(000), 1304 $e^-$.

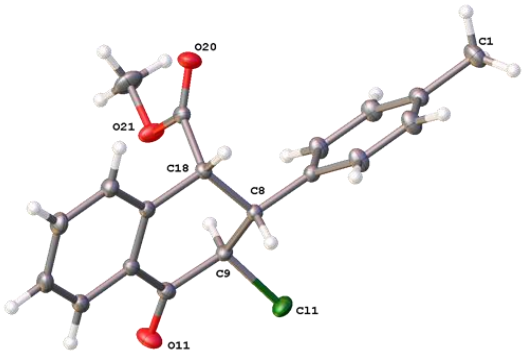
**Table 5.1** Crystal data and structure refinement parameters of **399**

| | | |
|---|---|---|
| Empirical formula | $C_{36}H_{29}Cl_2NO_3S$ | |
| Formula weight | 626.56 | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | $P2_1$ | |
| Unit cell dimensions | a = 14.2410(6) Å | α= 90°. |
| | b = 9.0056(4) Å | β= 99.8657(13)°. |
| | c = 24.3961(10) Å | γ = 90°. |
| Volume | 3082.5(2) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.350 $Mg/m^3$ | |
| Absorption coefficient | 0.316 $mm^{-1}$ | |
| F(000) | 1304 | |
| Crystal size | 0.32 x 0.06 x 0.012 $mm^3$ | |
| Theta range for data collection | 2.688 to 26.936°. | |
| Index ranges | $-18\leq h\leq 18$, $-11\leq k\leq 11$, $-31\leq l\leq 31$ | |
| Reflections collected | 56100 | |
| Independent reflections | 13278 [R(int) = 0.0653] | |
| Completeness to theta = 25.242° | 99.8 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.7454 and 0.6831 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 13278 / 191 / 811 | |
| Goodness-of-fit on $F^2$ | 1.034 | |
| Final R indices [$I>2\sigma(I)$] | R1 = 0.0433, wR2 = 0.0953 | |
| R indices (all data) | R1 = 0.0623, wR2 = 0.1040 | |
| Absolute structure parameter | 0.02(2) | |
| Largest diff. peak and hole | 0.494 and -0.362 $e.Å^{-3}$ | |

### 5.5.2 X-ray crystallography data for 411




**411**




A clear colourless fragment-like specimen of $C_{19}H_{17}ClO_3$, approximate dimensions 0.260 mm x 0.290 mm x 0.440 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 100(2)K on a Bruker D8 Quest ECO with an Oxford Cryostream low temperature device using a MiTeGen micromount. Bruker APEX software was used to correct for Lorentz and polarization effects.

The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a trigonalunit cell yielded a total of 27780 reflections to a maximum θ angle of 30.62° (0.70 Å resolution), of which 5005 were independent (average redundancy 5.550, completeness = 99.9%, $R_{int}$ = 2.74%, $R_{sig}$ = 2.08%) and 4797(95.84%) were greater than $2\sigma(F^2)$. The final cell constants of a = 9.2635(3) Å, b = 9.2635(3) Å, c = 16.4534(6) Å, volume = 1222.75(9) $Å^3$, are based upon the refinement of the XYZ-centroids of 9900 reflections above 20 σ(I) with 5.649° < 2θ < 61.24°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.933. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.6963 and 0.7461.

The structure was solved with the XT structure solution program using Intrinsic Phasing and refined with the XL refinement package using Least Squares minimisation with Olex2, using the space group $P3_1$, with Z = 3 for the formula unit, $C_{19}H_{17}ClO_3$. The final anisotropic full-matrix least-squares refinement on $F^2$ with 210 variables converged at R1 = 2.62%, for the observed data and wR2 = 6.87% for all data. The goodness-of-fit was 1.032. The largest peak in the final difference electron density synthesis was 0.243 $e^-/Å^3$ and the largest hole was -0.220 $e^-/Å^3$ with an RMS deviation of 0.045 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.339 $g/cm^3$ and F(000), 516 $e^-$.

**Refinement Note:** Model has Chirality at C8, C9, C18 = R.

**Table 5.2** Crystal data and structure refinement parameters of **411**

| | | |
|---|---|---|
| Empirical formula | $C_{19}H_{17}ClO_3$ | |
| Formula weight | 328.77 | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Trigonal | |
| Space group | $P3_1$ | |
| Unit cell dimensions | a = 9.2635(3) Å | α= 90°. |
| | b = 9.2635(3) Å | β= 90°. |
| | c = 16.4534(6) Å | γ = 120°. |
| Volume | 1222.75(9) $Å^3$ | |
| Z | 3 | |
| Density (calculated) | 1.339 $Mg/m^3$ | |
| Absorption coefficient | 0.246 $mm^{-1}$ | |
| F(000) | 516 | |
| Crystal size | 0.44 x 0.29 x 0.26 $mm^3$ | |
| Theta range for data collection | 2.539 to 30.620°. | |
| Index ranges | $-13 \leq h \leq 13$, $-13 \leq k \leq 13$, $-23 \leq l \leq 23$ | |
| Reflections collected | 27780 | |
| Independent reflections | 5005 [R(int) = 0.0274] | |
| Completeness to theta = 25.242° | 100.0 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.7461 and 0.6963 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 5005 / 1 / 210 | |
| Goodness-of-fit on $F^2$ | 1.032 | |
| Final R indices [$I>2\sigma(I)$] | R1 = 0.0262, wR2 = 0.0672 | |
| R indices (all data) | R1 = 0.0283, wR2 = 0.0687 | |
| Absolute structure parameter | 0.006(12) | |
| Largest diff. peak and hole | 0.243 and -0.220 $e.Å^{-3}$ | |

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