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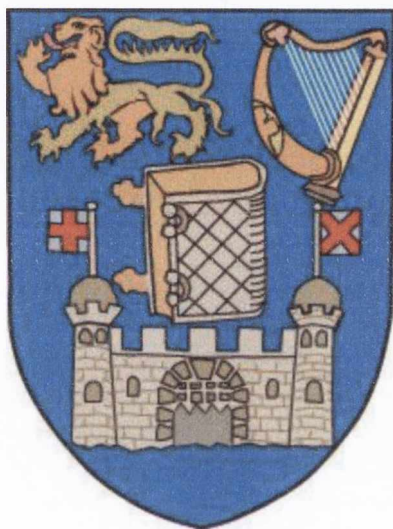
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Novel biomimetic organocatalysts and asymmetric formal cycloaddition reactions using enolisable anhydrides as nucleophiles



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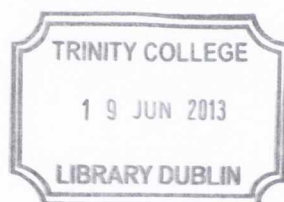
A thesis submitted to the University of Dublin for the degree of Doctor of Philosophy

by

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Under the supervision of Prof. Stephen Connon

February 2013



Thesis 10108

Declaration

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ite, S. Tallon and S. J. Connon, *Org. Lett.*, 2012, **14**,

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Abstract

The synthesis of a biomimetic organocatalyst bearing functional groups mimicking the active residues in the active site of the oxidoreductase enzyme non-phosphorylating glyceraldehyde-3-phosphate dehydrogenase (GAPN) has been undertaken. Analogues of GAPN having a Cys-mimicking thiol group, a Asn- mimicking amide functionality but devoid of a NAD^+ -mimicking pyridinium ion were prepared and evaluated in the reaction with aldehydes to form hemithioacetal species, which is the first step of the overall oxidation reaction catalysed by the natural enzyme GAPN. For the first time the reactivity of a Cys-mimicking thiol group was exploited in a biomimetic oxidation and we could observe that in our enzyme mimics, acid catalysis (in the form of hydrogen-bond donation) was not involved in the hemithioacetal-forming step. Attempts to imitate the hydride transfer step of the biochemical pathway failed repeatedly due to the instability of the enzyme mimic under the reaction conditions.

It has been demonstrated that cinchona alkaloid-derived organocatalysts are able to promote the reaction involving either homophthalic anhydrides or arylsuccinic anhydrides and a wide range of aldehydes. By using a novel *ad hoc*-designed squaramide-derived bifunctional organocatalyst, we were able to develop the first asymmetric catalytic protocol for formal cycloaddition reactions involving enolisable anhydrides and aldehydes. The synthesis of chiral 3,4-dihydroisocoumarins and paraconic acid derivatives bearing a quaternary stereocentre was achieved in good yields with excellent diastereo- and enantiocontrol (up to 99% *ee*) over the formation of two adjacent chiral centres. It was demonstrated that the reactivity of anhydrides in annulation reactions with aldehydes is directly dependant on their enolisability, and the possibility of using imines bearing electron-withdrawing groups on the nitrogen atom as the electrophilic component in asymmetric annulation reactions has been demonstrated for the first time.

Novel *N*-alkyl urea-substituted cinchona alkaloids have been prepared and used to promote highly asymmetric annulation reactions between enolisable anhydrides and a wide range of prochiral activated ketones. It was possible to access *via* a one-pot reaction chiral densely functionalised lactone products inclusive of the naturally occurring 3,4-dihydroisocoumarins and spirooxindoles motifs and bearing up to 2

contiguous quaternary stereocentres in good yields and with good to excellent diastereo- and enantiocontrol (up to 99% *ee*).

Abbreviations

Å	Angstrom
Ac	Acetyl
AcOH	Acetic acid
ADH	Alcohol dehydrogenase
AIBN	Azobisisobutyronitrile
ALDH	Aldehyde dehydrogenase
Ar	Aryl
ASADH	L-aspartate-β-semialdehyde dehydrogenase
Asn	Asparagine
atm	Atmosphere
BINAP	2,2'-Diamino-1,1'-binaphthalene
[bmim]	1-Butyl-3-methylimidazolium
Bn	Benzyl
Boc	<i>tert</i> -Butoxycarbonyl
Bz	Benzoyl
<i>c</i> -	<i>cyclo</i>
cat.	Catalyst
CSP	Chiral stationary phase
Cys	Cysteine
DAST	Diaminoethylsulfur trifluoride
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DCE	Dichloroethane
<i>de</i>	Diastereomeric excess
DIAD	Diisopropyl azodicarboxylate
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulphoxide
DPPA	Diphenylphosphoryl azide
<i>dr</i>	Diastereomeric ratio
EDG	Electron donating group
<i>ee</i>	Enantiomeric excess
equiv.	Equivalent
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
EWG	Electron withdrawing group
HPLC	High Performance Liquid Chromatography
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
GAPN	Non-phosphorylating glyceraldehyde-3-phosphate dehydrogenase
Glu	Glutamic acid
His	Histidine
ⁱ Pr	Isopropyl
ⁱ Pr ₂ NEt	<i>N,N'</i> -Diisopropylethylamine (Hünig's base)
ⁱ PrOH	2-propanol
IR	Infra red
LDH	Lactate dehydrogenase
<i>m</i>	<i>meta</i>
Me	Methyl

MeCN	Acetonitrile
MeOH	Methanol
mimNADH	NADH mimic
MTBE	Methyl- <i>tert</i> -butyl ether
NAD ⁺ /NADH	Nicotinamide adenine dinucleotide
NADP ⁺ /NADPH	Nicotinamide adenine dinucleotide phosphate
ⁿ Bu	<i>normal</i> -Butyl
NEt ₃	Triethylamine
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
Nu	Nucleophile
<i>o</i> -	<i>ortho</i>
<i>p</i> -	<i>para</i>
Pg	Protecting group
Ph	Phenyl
Piv	Pivaloyl
PhMe	Toluene
PMB	<i>p</i> -Methoxy benzyl
PMP	<i>p</i> -Methoxy phenyl
Pro	Proline
PTSA	<i>p</i> -Toluenesulfonic acid
<i>rac</i>	Racemic
rt	Room temperature
^t Bu	<i>tert</i> -Butyl
^t BuOH	<i>tert</i> -Butyl alcohol
TBAB	Tetrabutylammonium bromide
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
Thr	Threonine
TMS	Trimethylsilyl
TMSCHN ₂	Trimethylsilyl diazomethane
Ts	Tosyl

1.0 Introduction

1.1 Chirality: general remarks

The term chirality (derived from the Greek word for hand, $\chi\epsilon\iota\rho$) first appeared as a neologism coined in 1894 by Lord Kelvin, who stated as follows: “*I call any geometrical figure, or group of points, chiral, and say that it has chirality if its image in a plane mirror, ideally realised, cannot be brought to coincide with itself.*”¹ From a chemist’s perspective however, chirality had been already observed and described several decades earlier, when Pasteur in 1848² -inspired by the seminal work by Biot³- described molecular chirality as the ability by a chiral enantioenriched molecule (such as tartaric acid) to rotate the plan of a beam of polarised light. That decisive piece of evidence proved that chiral molecules behave differently in an asymmetric environment and sparked the interest of chemists in the study of the chemical properties of natural chiral molecules. Almost two centuries of continuous discoveries in the field have shaped our knowledge of the concepts behind stereochemistry and asymmetric synthesis. It is nowadays well established that enantiomers possess indistinguishable physical and chemical properties in a symmetric environment and that they only differ between each other when they interact with chiral substrates.

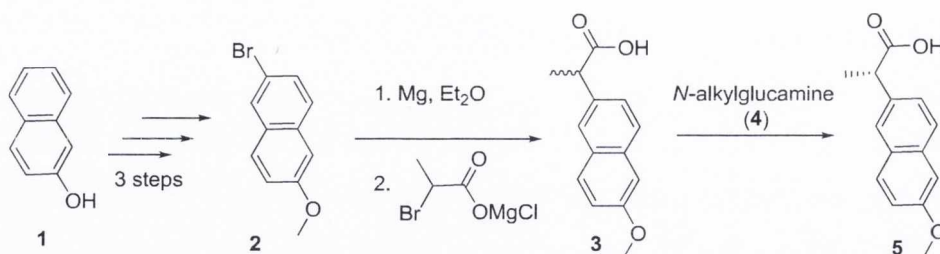
This fact is of crucial importance if we consider that chirality is ubiquitous in nature. Chiral molecules such as primary metabolites (*e.g.* sugars, amino acids) and secondary metabolites (*e.g.* alkaloids, terpenoids) are produced by nature in pure enantiomeric forms and can react at different rates with the enantiomers of either chiral molecule. Given this, it is not surprising that the efficient and selective synthesis of enantiopure molecules remains a current, tantalising and challenging concept for chemists not only for its intellectual reward, but also because of its inherent financial value.

1.1.1 Approaches to the synthesis of enantiopure compounds

Enantiopure molecules can be synthesised using three different strategies:⁴ (a) the separation of two enantiomers from a racemic mixture using chemical, physical or enzymatic means; (b) the synthesis using naturally occurring chiral molecules (the so-called ‘chiral pool’) as starting materials or chiral auxiliaries; (c) asymmetric catalysis using prochiral starting materials and a chiral catalyst or enzyme. Each of the three

methods present intrinsic advantages and drawbacks and normally the choice of one strategy over the others for the synthesis of enantiopure compounds on an industrial scale is driven by the cost-effectiveness of the overall procedure and its practicality.⁵

The resolution of a racemic mixture in most cases involves the reaction with an optically pure resolving agent (*e.g.* a base or a carboxylic acid) that leads to the formation of physically distinct and thus separable (*e.g.* by crystallisation) diastereomeric pairs. The main drawback associated with this methodology is that a maximum yield of 50% can be obtained if only one of the two enantiomers is desired. Half of the product is generally discarded or chemically converted into the racemate and subjected to another cycle.⁶ Two additional steps are required for the formation of the diastereomeric pair and the subsequent recovery of the separated pure enantiomer and finally the quantitative recovery of an optically pure (thus potentially expensive) resolving agent. Enzymatic or chemical kinetic resolution may be employed, however yields are also limited to a maximum of 50%. In Scheme 1.1 is a depiction of the large-scale manufacturing process for the synthesis of (*S*)-naproxen (**5**) by Syntex between 1976 and 1993. The production of the desired enantiomer was achieved by the resolution of the racemic mixture of carboxylic acids **3** by the separation of diastereomeric salts formed by reaction with an enantiomerically pure base *N*-alkylglucamine (**4**).⁵



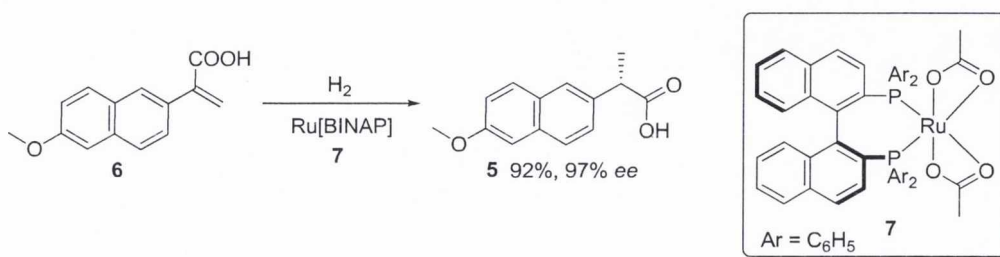
Scheme 1.1 Synthesis of (*S*)-naproxen (**5**) by resolution of a racemic mixture

While it is theoretically possible to achieve quantitative yields of enantiopure compounds *via* asymmetric synthesis using prochiral substrates and enantiomerically pure reagents or chiral auxiliaries belonging to the ‘chiral pool’ (*e.g.* sugars, amino acids, terpenes), one significant drawback is the need for stoichiometric quantities of these reagents. Furthermore, since it is usually challenging to access both optically active forms of a natural compound this synthetic methodology, by virtue of asymmetric induction, usually only leads to chiral products in one enantiomerically pure

form.⁴ An additional operational drawback arises when a chiral auxiliary-based strategy is employed. Two extra steps are required to install and remove the chiral moiety, which normally leads to an increase in cost and a decrease in yield of the overall synthesis.⁷

Asymmetric catalysis normally allows a more efficient synthesis of enantiomerically pure compounds by reacting prochiral starting materials and chiral catalysts. The main advantages of this strategy are that a quantitative yield is theoretically achievable and that low loadings (normally in the range of 0.1 to 20 mol%) of an enantiomerically pure catalyst can be used provided that it is readily regenerated at the end of every catalytic cycle.⁸ Enzymes, organometallic catalysts and organocatalysts have found widespread use in asymmetric synthesis. Enzymes are natural catalysts able to promote highly regio-, chemo- and enantioselective reactions, nonetheless they often exhibit a limited substrate scope and their complex three-dimensional structure may render their use impractical in industrial processes.⁹

Synthetically derived catalysts, such as organometallic catalysts and organocatalysts present the advantage of being designable and tuneable *ad hoc* according to the reaction under examination and to the substrates employed. Therefore these synthetic strategies are extremely versatile and virtually limitless with regard to their catalytic potentials.^{4,10} Asymmetric organometallic catalysis normally relies on a transition-metal (*e.g.* Rh, Ir, Pd, Ru) bound to enantiomerically pure ligands (*e.g.* phosphines, amino alcohols, diamines). Very low catalyst loadings may be employed, nonetheless these metals generally require an oxygen-free inert atmosphere and ultra-dry conditions in order to be functional. Their high price and toxicity are factors that potentially cause several limitations in their use for the synthesis of compounds whose regulatory requirements restricts metal contamination.¹¹ The asymmetric synthesis of (*S*)-naproxen (**5**) developed by Noyori *et al.*¹² using a ruthenium (II) (*S*)-BINAP complex (**7**) as catalyst is depicted in Scheme 1.2.



Scheme 1.2 Metal-catalysed asymmetric synthesis of (*S*)-naproxen (**5**)

It is remarkable that this one-step asymmetric synthesis of the blockbuster drug **5** in 92% yield and 97% *ee* was never implemented by Syntex, the pharmaceutical company holding the patent for **5**. Even though at the time two thirds of the cost of the total naproxen production was associated with the resolution-racemisation step, the 135 atm needed for the hydrogenation combined with a higher cost of **6** compared to **2** rendered this procedure too costly and impractical.⁵

During the last decade, there has been a tremendous development of organocatalysis for asymmetric synthesis, bridging the gap between enzyme-mediated biocatalysis and organometallic catalysis. Organocatalysis employs organic molecules as catalytic species. This strategy has shown to be a valid, powerful, versatile and reliable alternative to the already existing methodologies for the stereoselective synthesis of chiral compounds.¹³ Many of the catalysts used are derived from cheap and readily available natural compounds (*e.g.* proline, cinchona alkaloids) and as such they tend to be stable, non-toxic, environmentally friendly and relatively insensitive to air and moisture.¹³ Since its inception, the field of enantioselective organocatalysis has had a significant impact in stereoselective target-oriented synthesis and has developed into a practical synthetic concept. Although this field is still in its infancy, the breadth of different reactions that can be catalysed make it a complementary discipline to conventional metal catalysis.¹⁴ Catalysts having multifaceted modes of action have gradually appeared, with the result that their catalytic potential has increased dramatically over the years.^{15,16,17,18,19,20}

1.2 Enzymes: catalysts provided by nature

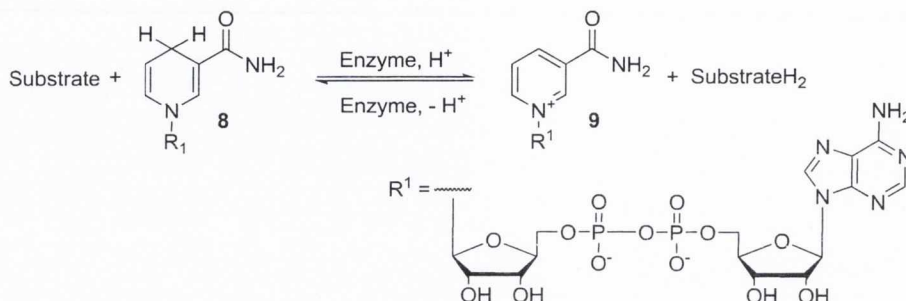
Even though the very existence of living organisms would be impractical without enzymes, their crucial biocatalytic role in a trivial yet vital process such as fermentation was discovered by Pasteur only in the 19th century.²¹ His pioneering studies on living yeast cells were followed by the observation of Buchner - which earned him the 1907 Nobel Prize in chemistry - that the catalytic activity of enzymes is expressed independently from the presence of a living organism.²² While a detailed and specific dissertation on enzymes is beyond the scope of this thesis, it is certainly worth pointing out briefly some basic concepts regarding this vast topic.

Enzymes are a particular type of protein designed by nature to catalyse a diverse range of biochemical reactions occurring in living cells. Enzymes are considerably larger than the substrates they act upon, and as proteins, they possess highly complex three-dimensional structures that are determined both by the linear sequence of amino acids and their folding in space. Functional enzymes may require the association of several proteins and the presence of non-protein species (cofactors) such as coenzymes, prosthetic groups or metal ions to exert their catalytic activity. Despite their size, they display exceptional substrate specificity due to the fact that the catalytic activity of enzymes is confined in a small region called the active site. Usually only a few amino acids in the active site are responsible for the binding of and subsequent reaction with substrates *via* both reversible non-covalent interactions and discrete covalent intermediates.²³ The model that best describes the interaction between the active site and the substrate is based on 'induced-fit'.²⁴ The mechanisms involved in the catalytic reactions vary depending on the active amino acids and usually entails a combination of different types of catalyses. Enzymes possess excellent substrate affinity and remarkable catalytic activity (they normally accelerate reactions by a factor of 10^9 - 10^{10}),²³ furthermore by virtue of the chiral environment of the active site, enzymes exhibit excellent chemo-, regio- and stereoselectivity which makes them outstanding asymmetric catalysts.

1.2.1 Enzyme-mediated catalysis of redox reactions

Redox reactions are ubiquitous in biological systems and are catalysed by a class of enzymes called oxidoreductases. Among the important reactions catalysed by these enzymes are: epoxidations of alkenes, hydroxylations, sulfoxidations, oxidation/reductions of carbonyls, peroxidations, reduction of activated double bonds and even Baeyer-Villiger reactions.⁹ The activity of some of these types of enzymes, (*e.g.* dehydrogenases) are dependent on the presence of stoichiometric cofactors. These are usually organic molecules (coenzymes) that act in the redox process as electron-transferring agents (in the form of hydride anions). Nicotinamide adenine dinucleotide (NADH, **8**), its oxidised form NAD^+ (**9**) and their phosphate derivatives NADPH/ NADP^+ are the coenzymes most extensively used by oxidoreductases.²³ Their structures include an adenine, two ribose molecules linked by two phosphate groups and a nicotinamide unit. The reactive site of the coenzyme is the nicotinamide moiety that

can be reduced to a dihydropyridine or oxidised to a pyridinium ring. As with the majority of biological processes, enzymatic NAD(P)H-dependent redox reactions are reversible as depicted in Scheme 1.3.



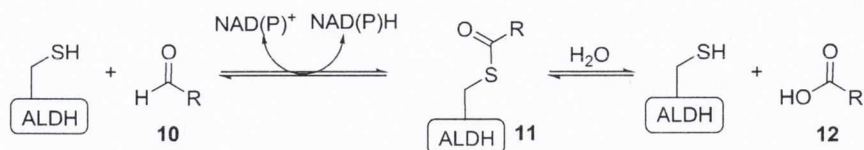
Scheme 1.3 NADH/NAD⁺-mediated reductions: general reaction scheme

In order to sustain a redox balance inside the cell, the equilibrium between the oxidised and reduced forms is continuously maintained in biological systems through a series of coupled reactions.²⁵

1.2.2 Aldehyde dehydrogenases

Aldehyde dehydrogenases (ALDHs) are a superfamily of NAD(P)⁺-dependant enzymes – widely distributed, from bacteria to humans – which oxidise a plethora of endogenous and exogenous aldehydes into the corresponding carboxylic acids.²⁶ Endogenous aldehydes are formed during the metabolism of amino acids, carbohydrates, lipids, biogenic amines, vitamins, and steroids, while exogenous aldehydes arise from the biotransformation of a large number of drugs and environmental agents.²⁷ Due to the electrophilicity and high reactivity of aldehydes, metabolites containing this functional group may lead to cytotoxic effects,²⁸ therefore ALDHs play a crucial role in their selective elimination by mean of oxidation into more water-soluble carboxylic acids which can be more readily eliminated.³⁴ Despite the wide variety of enzymes that constitute this superfamily, ALDHs share a number of highly conserved residues necessary for their catalytic activity and the binding of the cofactor.²⁹ The active site of enzymes belonging to the ALDH family includes an invariant cysteine residue responsible for triggering the catalytic mechanism.^{30,31} The general reaction scheme for

the ALDH-mediated oxidation of aldehydes **10** into carboxylic acids **12** is presented in Scheme 1.4.

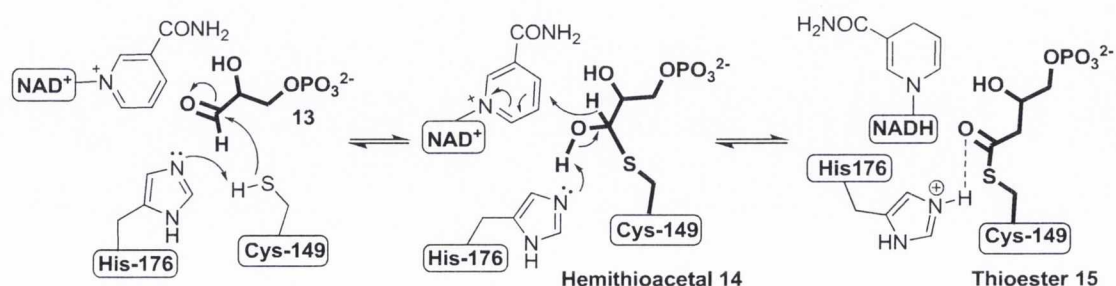


Scheme 1.4 ALDH-mediated oxidation of aldehydes: general reaction scheme

The overall reaction proceeds *via* a thioester intermediate (*i.e.* **11**) formed after the attack of the aforementioned cysteine residue on the carbonyl group and oxidation of the resulting hemithioacetal. Different amino acids in the active site cooperate with the invariant cysteine in the catalytic reaction, however hemithioacetals and thioester intermediates are a common feature among this class of enzymes. In order to gain a more thorough insight into the multifaceted mode of action associated with these enzymes, selected examples of ALDHs will be discussed in the following sections while stressing the differences implied in their catalytic mechanisms.

1.2.2.1 Mode of action associated with phosphorylating glyceraldehyde-3-phosphate dehydrogenase (GAPDH)

Phosphorylating glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is an enzyme involved in glycolysis and gluconeogenesis processes. The enzyme is responsible for the catalysis of the reversible oxidative phosphorylation of glyceraldehyde-3-phosphate (**13**) into 1,3-bisphosphoglycerate *via* hemithioacetal **14** and thioester **15** intermediates as shown in Scheme 1.5.²³

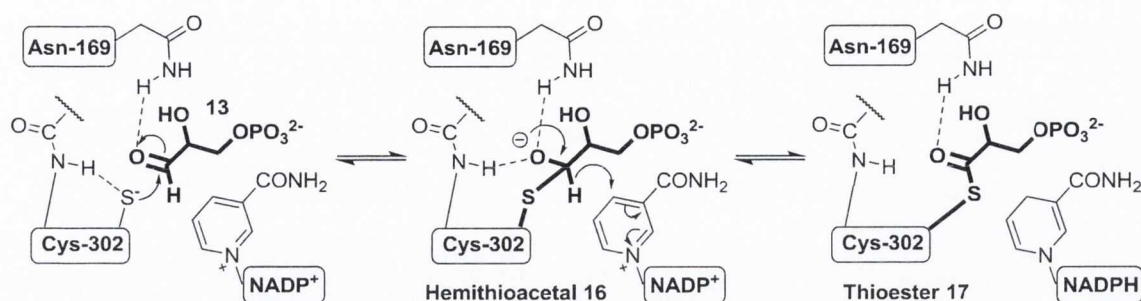


Scheme 1.5 Mode of action associated with GAPDH

The activity of GAPDH is dependent on the cofactor NAD^+ and inorganic phosphate. Studies involving site-direct mutagenesis by Branlant *et al.* on isolated GAPDH from *Escherichia coli* and *Bacillus stearothermophilus* provided supporting evidence for the key roles of Cys-149 and His-176 in the catalytic activity of the enzyme.^{32,33,34} The binding of the cofactor NAD^+ triggers the catalysis by generating conformational changes within the active site. This accounts for the creation of anion binding areas which favours the interactions with the negatively charged phosphate group on **13**.³⁵ His-176 exerts a multiple role in the catalytic activity of the enzyme.³² The imidazole ring is responsible for the formation of the active thiolate on Cys-149, which attacks the carbonyl group of **13** and generates hemithioacetal **14**,³³ and His-176 also favours the hydride transfer to a NAD^+ molecule by deprotonation (*i.e.* base catalysis) of the hydroxyl group present on **14**. Finally, the imidazolium ring on His-176 is involved in the stabilisation of the tetrahedral species forming upon the subsequent attack of the inorganic phosphate onto thioester **15** and in the base catalysis of the deacylation which is the rate-determining step of the overall reaction.³⁴

1.2.2.2 Mode of action associated with non-phosphorylating glyceraldehyde-3-phosphate dehydrogenase (GAPN)

Non-phosphorylating glyceraldehyde-3-phosphate dehydrogenase (GAPN) -found in plants and bacteria- catalyses the NADP-mediated irreversible oxidation of **13** to 3-phosphoglycerate. Sequence analysis revealed that GAPN is not related to GAPDH, but is a member of the aldehyde dehydrogenase family.³⁶ The mode of action associated with GAPDH and GAPN has in common a cysteine residue triggering the catalytic reaction and covalently-bound hemithioacetal and thioester intermediates. Nonetheless, the two enzymes have different key amino acids involved in the catalytic cycle. GAPN exhibits the same affinity for **13** as GAPDH, however the product formed by GAPN is the carboxylic acid which arises following the nucleophilic attack by H_2O on the thioester intermediate **17**. A series of critical studies by Branlant *et al.*^{37,38,39,40,41} involving site-directed mutagenesis on GAPN from *Streptococcus mutans* culminated with the isolation of thioester intermediate **17** (in the mutant E268A),⁴² which allowed for the proposal of a scenario accounting for the catalysis of GAPN (Scheme 1.6).



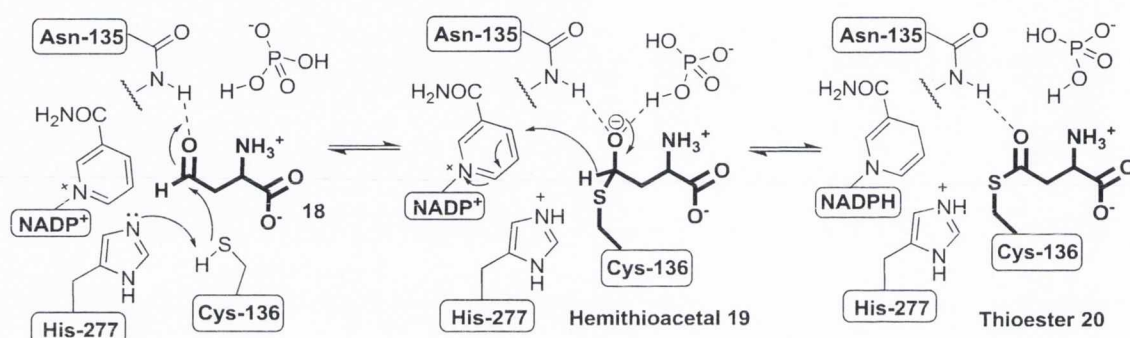
Scheme 1.6 Mode of action associated with GAPN

The essential Cys-302 needs to be both accessible and in the thiolate form to attack the aldehyde group at a physiological pH. The activation of Cys-302 arises from a conformational change in the active site induced by the binding of NADP⁺. This reorganisation results in the repositioning of the active residues Glu-268 and Cys-302 and the lowering of their pK_a which leads to the deprotonation of the latter to form a thiolate. This is believed to benefit from stabilisation by both the backbone amides of Cys-302 (and possibly Thr-303) together with the positive charge on the pyridinium ring of NADP⁺.^{37,38} The thiolate attack on **13** leads to the formation of hemithioacetal **16** which is stabilised by hydrogen-bond donation (*i.e.* acid catalysis) from the amide side-chain of Asn-169 and the backbone amide of Cys-302 in a sort of oxyanion hole. The ensuing deprotonation allows an efficient hydride transfer to NADP⁺ without the assistance of base catalysis.^{38,40} The thioester **17** is eventually hydrolysed by H₂O in what is proposed to be the rate-determining step of the reaction.³⁹ The nucleophilic character of the attacking molecule of H₂O is enhanced by Glu-238 and the reaction benefits from the stabilisation of the tetrahedral intermediate in the oxyanion hole provided by (at least) hydrogen bond donation by Asn-169.^{38,49}

1.2.2.3 Mode of action associated with L-aspartate- β -semialdehyde dehydrogenase (ASADH)

Aspartate semialdehyde dehydrogenase (ASADH) is an enzyme involved in the biosynthesis of essential amino acids in bacteria. The products of the aspartate pathway are essential in microorganisms and its absence in mammals makes this enzyme an attractive target for antibiotic development.⁴³ Similar to GAPDH this enzyme is part of the NAD(P)⁺-dependent dehydrogenase class and is responsible for the catalysis of a

reductive phosphorylation *via* the formation of hemithioacetal **19** and thioester **20** as intermediates.⁴⁴ Both were isolated within the active site of crystallised ASADH from *Haemophilus influenza* which helped to gain a deeper insight into the mode of action associated with this enzyme.^{43,45} The natural substrate for ASADH is β -aspartyl phosphate (**18**) which is reduced and phosphorylated to L-aspartate- β -semialdehyde. The proposed mode of action is shown in Scheme 1.7; in reverse biological direction in order to facilitate the comparison with GAPDH and GAPN.



Scheme 1.7 Mode of action associated with ASADH

Studies by Viola *et al.* on isolated ASADH involving site-directed mutagenesis proved that the catalytic event is triggered by the deprotonation of Cys-136 by the adjacent His-277 residue and the nucleophilic attack of the formed thiolate on **18** to form **19**.⁴³ With the capture of the tetrahedral intermediate **19**, Viola *et al.* were responsible for the discovery that this transient species was embedded and stabilised in a distinctive binding pocket reminiscent of the oxyanion hole found in serine protease.⁴⁵ In ASADH, the backbone amide of Asn-135 and the enzyme-bound inorganic phosphate are responsible for stabilising the oxyanion formed in **19** by hydrogen bond-donation (*i.e.* by acid catalysis) similarly to the mode of action associated with GAPN (Scheme 1.6). Electrostatic repulsions force the newly formed thioester **20** to assume an orientation more favourable towards nucleophilic attack by the inorganic phosphate, which leads to the formation of β -aspartyl phosphate. This second attack is also promoted by acid catalysis since the generated tetrahedral intermediate benefits from the stabilisation by hydrogen-bond donation from a structural molecule of H₂O.^{43,45}

1.3 Biomimetic chemistry, artificial enzymes and NAD⁺/NADH mimics

Chemists have learnt from the outstanding catalytic performances of enzymes and have exploited the principles which underpin enzymatic catalysis in synthetic chemistry. Biocatalysis represents a green alternative to traditional methods and a wide range of reactions requiring high degrees of regio-, chemo- and enantioselectivity have been successfully accomplished using enzymes as heterogeneous catalysts.¹⁶ The employment of enzymes for asymmetric catalysis in preparative organic chemistry on a laboratory scale is not usually considered as a first-choice option mainly because enzymes are very specific with regard to their substrate compatibility while their use also involves relevant operational drawbacks.^{9,46}

The potential advantages associated with the exploitation of nature's chemical know-how and the interest in gaining an insight into the mechanisms of biocatalysis have prompted chemists to develop the concepts of 'biomimetic chemistry' and 'artificial enzymes'.^{47,48} This last term was coined by Breslow,⁴⁹ who has been responsible for the initial development and further advancement of this new approach in synthetic chemistry.⁴⁸ It is evident that the only way to achieve the catalytic efficacy of enzymes, while avoiding their use, is by synthesising smaller, less sophisticated and hence less complex molecules that can act as models. This has the advantage of providing a better understanding of biocatalytic processes, whilst creating more robust and versatile catalysts that possess the potential to exhibit enzyme-like selectivity but lack their intrinsic operational drawbacks. Examples of the concept of biomimetic chemistry include the use of aminoacids or other natural molecules as chiral catalysts, the concoction of redox reactions mediated by hydride transfer synthesis and the integration of a synthetic methodology into a process involving cascade reactions. In addition to these concepts, the synthesis and development of artificial enzymes is also an important achievement for synthetic chemists as they endeavour to understand, imitate and exploit biochemical reactions.

The chemical activity of artificial enzymes involves the concepts of molecular recognition of a substrate and biomimetic catalysis by using functional groups that model the structural features of an enzyme's active-site residues.^{50,51,52,53,54} Since its inception this field has grown enormously over the years. Its detailed coverage is

beyond the scope of this thesis, however some examples regarding biomimetic redox reactions promoted by synthetic mimics of the naturally occurring NAD and NADH will be dealt with in the following Sections.

1.3.1 Dihydropyridines as NADH analogues in biomimetic asymmetric reductions

Enzymatic systems in nature regularly use NADH as a stoichiometric cofactor in reduction reactions. The chiral environment within the active site of the enzyme where these reactions occur combined with the natural and renewable source of hydride ions equivalents, (*i.e.* the 1,4-dihydronicotinamide moiety contained in NADH) account for the efficacy and high enantioselectivity encountered in biocatalysed reduction reactions *in vivo*. To attain such a degree of stereocontrol in synthetic chemistry is extremely desirable, (particularly due to the utility of asymmetric reductions in synthesis) and has been inspired the development for the successful design of a wide array of new molecules which are able to bring about asymmetric catalytic reductions with levels of enantioselectivity comparable to those achievable by enzymes. Historically speaking, the benchmark catalysts for these reactions were based on transition metal complexes, however the appealing prospect of developing a metal-free, chemoselective, asymmetric and biomimetic alternative to these catalysts has encouraged the synthesis of organocatalysts able to mimic the reactivity of NADH.

Due to the similarity of their structural features with naturally occurring NADH, synthetic dihydropyridines such Hantzsch esters of general type **21** and 1,4-dihydronicotinamides **22** (or derivatives thereof) have been broadly employed as bioinspired ‘catalysts’ (most often employed in stoichiometric amounts) for the asymmetric reduction reactions of a wide range of electron deficient π -systems.

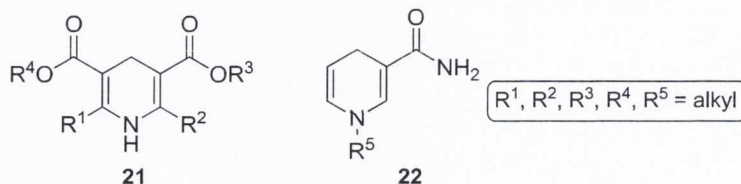
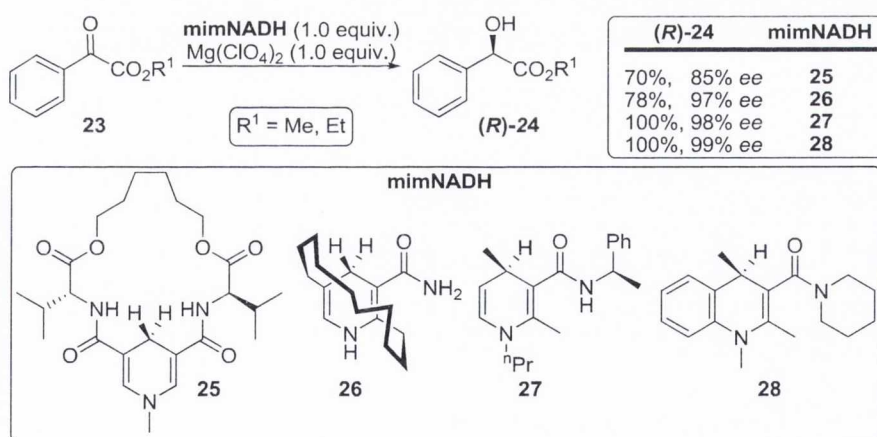


Figure 1.1 General structure of Hantzsch esters and 1,4-dihydronicotinamides

Driven by the aromatisation energy gained upon oxidation (*i.e.* the loss of a hydride ion), 1,4-dihydropyridines are efficient reducing agents. Despite being a legacy of the late 19th century,⁵⁵ Hantzsch esters and related systems saw their first employment as mild reducing agents only in the second half of the last century.⁵⁶ The development of NADH analogues as reagents in asymmetric reductions originated more recently.⁵⁷ In this field, the applications of NADH mimics can be categorised as being exploited in either asymmetric reductions induced by using chiral NADH analogues activated by metal ions - mainly Mg²⁺ - both at stoichiometric loadings, or asymmetric catalytic reductions employing a chiral organocatalyst and a NADH mimic as a sacrificial hydride donor.⁵⁸

In the first category there has been wide interest in designing chiral dihydropyridines (or derivatives thereof) for the asymmetric reduction of (mainly) activated ketones. As far as the implementation of an element of chirality is concerned, two strategies have been primarily pursued: the installation of a chiral centre on the reactive C-4 position or the introduction of a chiral side chain on the dihydropyridine ring. Selected examples^{59,60,61,62} employed in the asymmetric reduction of benzoyl formates into mandelates are depicted in Scheme 1.8.

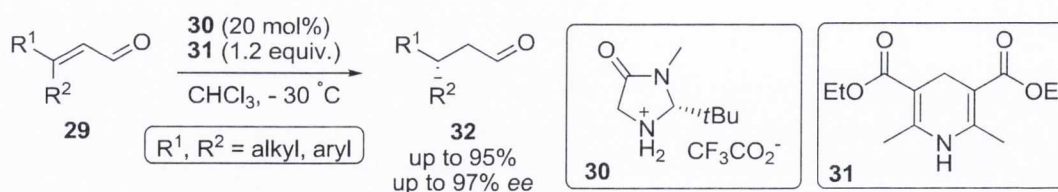


Scheme 1.8 Asymmetric reduction of benzoyl formates using chiral NADH mimics

The use of Mg(II) ions plays a crucial role in the stereospecific transfer of hydride, which is believed to be mediated by the formation of a ternary complex between substrate, Mg(II) and chiral NADH mimic. Some of the main flaws associated with

these chiral reagents are their stoichiometric loading, their reliance on source of Mg(II) ions and, in some cases, their complicated multi-step syntheses.

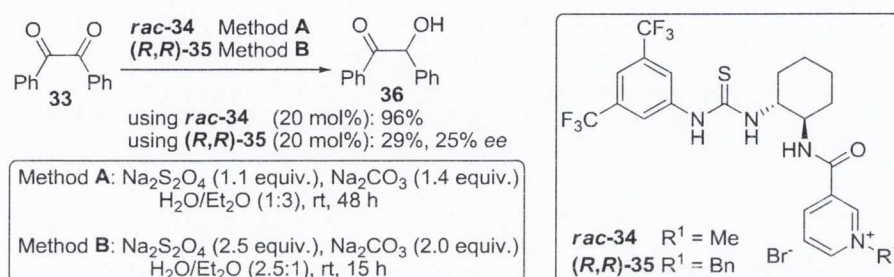
The undesirable use of metal ions and chiral reagents in stoichiometric loading has prompted the development of strategies for asymmetric biomimetic reduction reactions. These rely on the combination of a chiral organocatalyst or organometallic catalyst and a stoichiometric achiral hydride donor such as a Hantzsch ester. This approach has spawned much interest recently thanks to the emergence of the concept of iminium catalysis, resulting in a wide variety of chiral catalysts.^{58,63,64} By using this type of strategy, the reduction of electron-deficient olefins, imines and activated ketones for instance – either alone or coupled with other reactions in a cascade process – was achieved with excellent degrees of enantioselectivity.⁶⁴ A mechanism reminiscent of the mode of action of enzymes is a common feature of this strategy. The chiral organocatalyst (*e.g.* amine, phosphoric acid, thiourea) interacts with the prochiral electrophile and generates an activated species (*i.e.* lowers its LUMO) in an asymmetric environment. The achiral hydride donor (*e.g.* Hantzsch ester) then delivers a hydride ion in a stereospecific fashion. An example of asymmetric biomimetic reduction reported by MacMillan *et al.*⁶⁵ is depicted in Scheme 1.9. The authors described the asymmetric reduction of α,β -unsaturated aldehydes (*i.e.* **29**) using organocatalyst **30** *via* the formation of a chiral iminium ion as the activated species that was subsequently reduced by Hantzsch ester **31** (Scheme 1.9)



Scheme 1.9 Examples of asymmetric reductions using chiral organocatalysts

The combined use of organocatalysts and NADH analogues to accomplish biomimetic asymmetric reductions presents the benefit of reducing the waste of a precious chiral component, nevertheless this strategy is still incapable of competing with the efficiency of nature's oxidoreductases. However, it should be noted that biocatalysts all require the presence of a stoichiometric cofactor.

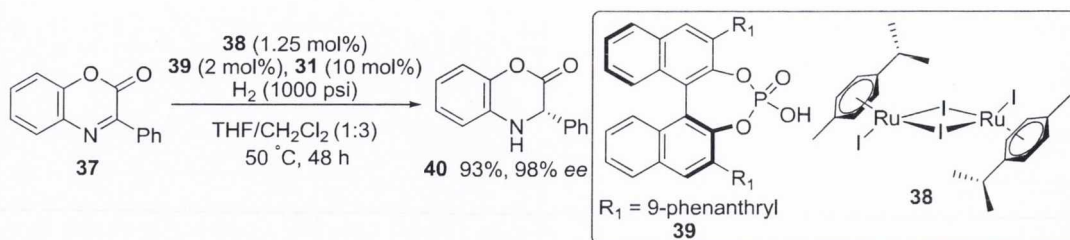
Only a handful of biomimetic asymmetric reductions have been reported involving the use of a chiral organocatalyst and the synchronous regeneration of the source of hydride ions. Our group has been involved in dealing with this challenging task and has developed a bifunctional catalyst (***rac*-34**) which incorporates the chiral activating moiety (*i.e.* thiourea) and the dihydropyridine group on the same entity (Scheme 1.10).⁶⁶



Scheme 1.10 Reduction of 1,2-diketones using a chiral NADH regenerated *in situ*

The use of substoichiometric loadings of the reducing agent are feasible due to its parallel regeneration by using an inexpensive co-reductant such as sodium dithionite ($\text{Na}_2\text{S}_2\text{O}_4$) in a biphasic system. The elusive biomimetic organocatalytic reduction of ketones (a functional group known to be recalcitrant for this type of transformation)⁶⁴ could be accomplished by using ***rac*-34**, which led to the synthesis of the α -hydroxy ketone **36** in good to excellent yields from **33**. The asymmetric reaction has also been attempted by using the enantiomerically pure catalyst **(*R,R*)-35**, however the degree of enantioselectivity achieved was moderate by virtue of the reaction conditions including a base which was responsible for the racemisation of the product.

Very recently, Zhou *et al.*⁶⁷ were able for the first time to achieve high enantioselectivities in a biomimetic organocatalytic asymmetric reduction with simultaneous regeneration of the NADH mimic (Scheme 1.11). A chiral phosphoric acid **39** and Hanzsch ester **31** were employed in catalytic loadings for the reduction of benzoxazinone **37**. The use of a commercially available Ru(II) species as a co-catalyst **38** and hydrogen gas as the co-reductant in the reaction mixture, allowed for the regeneration *in situ* of **31** and thus rendered the overall process truly catalytic.



Scheme 1.11 Asymmetric reduction with parallel regeneration of a NADH mimic

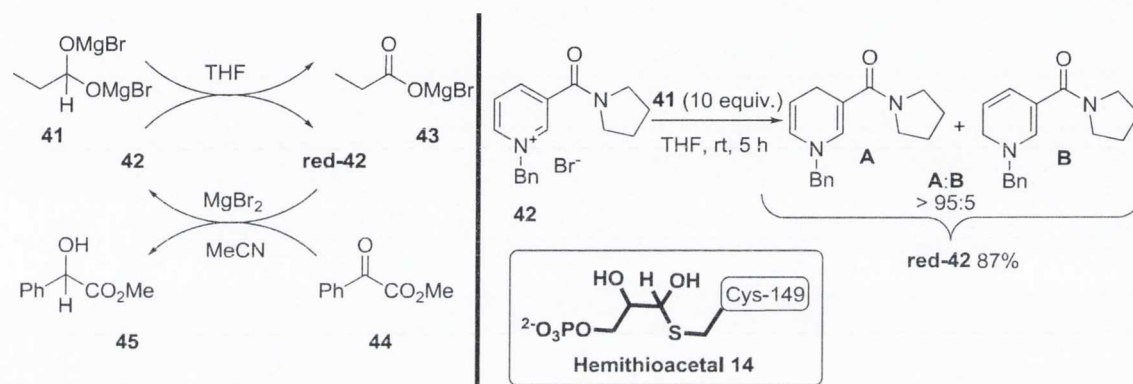
1.3.2 Pyridinium and acridinium salts as NAD^+ analogues in biomimetic oxidations

The possibility of discovering a mild and biomimetic alternative to oxidation reactions (which are often metal ion-based), together with the opportunity of gaining an insight into the mode of action of NAD^+ -dependent oxidoreductases is undoubtedly fascinating. The use of NAD^+ analogues in biomimetic oxidations has seen very few applications compared to reductions by NADH mimics. This is arguably due to the fact that artificial NADH-mediated reductions generally introduce new stereocentres and are therefore more interesting due to their potential asymmetric nature. The vast majority of NAD^+ mimics structurally resemble the naturally occurring NAD^+ in being *N*-alkyl pyridinium salts substituted at C-3 with an amide, however *N*-aryl pyridinium ions,⁶⁸ pyridopyrimidines,⁶⁹ 9-phenylxanthilium ions⁷⁰ and *N*-acridinium ions⁷¹ have also been sporadically employed.

Early examples of pyridinium salts acting as NAD^+ analogues in the oxidation of alcohols to aldehydes (*i.e.* mimicking alcohol dehydrogenases—ADHs) were ambiguous: while the formation of oxidised products speculatively formed *via* hydride-transfer was proved, no evidence for the formation of dihydropyridines was provided.^{72,73} The mimicry of ADHs by using reactive metal alcoholates (Mg,⁷⁴ Zn,⁷⁵ Na and Li⁶⁸ salts) and pyridinium ions as NAD^+ analogues (*i.e.* hydride acceptors) has been most preponderant over the years, though biomimetic oxidations *e.g.* formate dehydrogenase⁷⁶ and GAPDH⁷⁷ mimics have also been reported.

The first observation of a biomimetic oxidation of an aldehyde to a carboxylate species in a process reminiscent of the mode of action of GAPDH was accomplished by

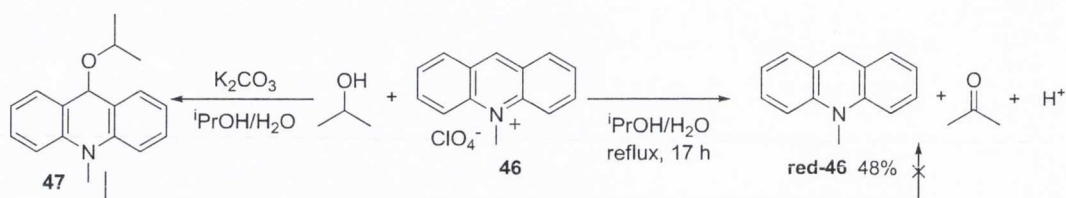
Kanomata *et al.* in 1998⁷⁷ and still remains the only example of its type known in the literature to date. It is noteworthy that the reagent employed was not an aldehyde, but the *in situ* formed diolate **41**⁷⁸ (Scheme 1.12) which resembles the hemithioacetal intermediate **14** formed during the oxidative phosphorylation catalysed by GAPDH (see Scheme 1.5). The NAD⁺ mimic of choice was the *N*-benzylpyridinium salt **42** bearing a tertiary amide, which provided superior yields of the dihydropyridine species **red-42** and enhanced regioselectivity (with regard to the hydride-transfer) to form predominantly the desired 1,4-dihydropyridine (*i.e.* the regioisomer naturally formed by GAPDH).



Scheme 1.12 Biomimetic oxidation reported by Kanomata *et al.*

When used in excess (5 to 10 equivalents), diolate **41** was oxidised by **42** to the carboxylate species **43**, with moderate to excellent yields of **red-42** also formed. Isotope-labeling experiments were conducted by using a deuterated version of **41** which unequivocally proved that the regioselectivity of the hydride attack on the pyridinium ring was the result of kinetic control. As well as the remarkable achievement of having accomplished the unprecedented mimicking of GAPDH, what is truly outstanding about this study is the possibility of regenerating the NAD⁺ mimic **42** *in situ*. Indeed, crude **red-42** did reduce α -ketoester **44** to alcohol **45** in moderate yields in the presence of MgBr₂ (formed as the byproduct of the first reaction) and was consequently re-oxidised to **42**. This second reaction mimics the enzyme activity of lactate dehydrogenase (LDH). By coupling these two reactions, Kanomata *et al.* created a full catalytic cycle (*albeit* in a step-wise manner) formally equivalent to those associated with oxidoreductase enzymes.

The general drawback intrinsic to the use of pyridinium ions as NAD^+ mimics is the regioselectivity of the nucleophilic attack of the hydride: a mixture of 1,4- and 1,6-dihydropyridines was always observed; as opposed to the naturally occurring regioselective reduction which typically occurs at C-4. The more recent use of acridinium ions as NAD^+ analogues in a ADH mimicking reaction by Lu *et al.*⁷¹ has circumvented this issue: the central pyridinium ring of the acridinium salt has the C-2 and C-6 positions blocked by fused benzene rings. Lu *et al.* employed acridinium ion **46** for the thermal oxidation of 2-propanol to acetone as illustrated in Scheme 1.13.



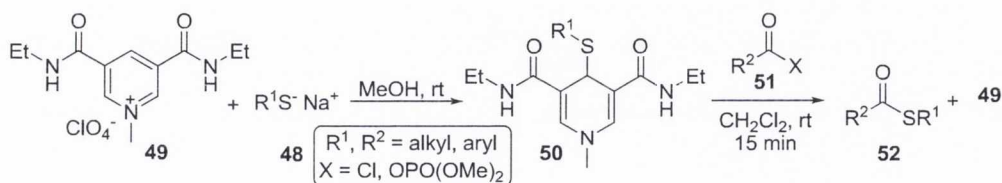
Scheme 1.13 Biomimetic oxidation of $i\text{PrOH}$ observed by Lu *et al.*

The reduced dihydroacridine **red-46** was obtained in moderate yield by heating at reflux temperature the acridinium ion **46** in a dark oxygen-free atmosphere in $i\text{PrOH}/\text{H}_2\text{O}$ (95:5 v:v). The regioselective hydride-transfer occurred exclusively at C-9 and 2-propanol was concomitantly oxidised to acetone. When a base was added to the reaction mixture, the adduct **47** was formed quantitatively and no **red-46** could be detected even after 20 h, thereby excluding an intramolecular hydride-transfer. In a subsequent study by the same lead author, unequivocal evidence for an intermolecular mechanism was produced.⁷⁹ Another remarkable observation that was made in this study was the beneficial effect of a protic solvent: when either 2-propanol or water were replaced with acetonitrile, the rate of the reaction decreased considerably. The author postulated that in the transition state of the reaction, hydrogen-bond donation was involved which was crucial in favouring the hydride-transfer. This observation suits well to what is believed to occur in the active site of ADHs, where an extended network of hydrogen-bonded amino acids and a zinc ion are involved in the redox event.⁸⁰

1.3.3 Pyridinium salts as catalysts in nucleophilic addition reactions

It is well established that certain pyridines (*e.g.* DMAP) behave as nucleophilic catalysts for a variety of reactions.⁸¹ Conversely, the use of pyridinium salts to promote nucleophilic addition reactions has had very few applications. Diverse nucleophiles have been reported to add to pyridinium salts,⁸² nonetheless only a handful of examples accounting for their use as carriers of nucleophiles other than hydride ions have been reported in the literature.

With a series of seminal studies, Kellogg *et al.*⁸³ were involved in the development and implementation of the concept of NAD⁺ mimics acting as transfer reagents for nucleophilic additions. In a preliminary investigation^{83a} (Scheme 1.14) it was demonstrated that at room temperature, a variety of alkyl and aryl thiolates **48** regioselectively added to the pyridinium ion **49** having amide groups installed at the C-3 and C-5 positions to afford near quantitative yields of adduct **50**. Kellogg *et al.* reacted the *in situ*-formed adduct **50** with an activated carboxylic acid **51** (*i.e.* acyl chlorides or phosphates) at room temperature and obtained thioester **52** together with the initial pyridinium salt **49**. The methodology proved to be extremely versatile in terms of both the thiolate and the activated acid employed: aliphatic, aromatic and sterically hindered substrates all afforded thioesters in good to excellent yields. This represents a useful protocol for the preparation of thioesters by virtue of the mild and neutral reaction conditions employed which is desirable due to their intrinsic reactivity.⁸⁴



Scheme 1.14 Pyridinium ions acting as reagents for the transfer of thiolates

It is noteworthy that the same author was also able to monitor the formation of a hemithioacetal intermediate (*albeit* in a NMR tube) by using a thiolate adduct similar to **50** and salicylaldehyde.^{83c} This observation was remarkable, since such a species is implicated in the mode of action associated with GAPDH: however, no further details on this finding were provided.

1.4 Hydrogen-bonding catalysis promoted by (thio)ureas and squaramides: from molecular recognition to organocatalysis

It is well established that molecular recognition (such as that between substrates and enzymes for example) is the basis of a wide variety of biologically important reactions and represents a crucial aspect of many fields from supramolecular chemistry to drug design.⁸⁵ The recognition and interaction between two molecules that are considered complementary to each other is usually based on a series of non-covalent interactions such as coordinative, electrostatic, π -stacking, hydrophobic, van der Waals and hydrogen-bonding.⁸⁵ Detailed investigations into the mode of action of enzymes have identified the pivotal role of hydrogen-bonding interactions (*e.g.* stabilisation of oxoanionic tetrahedral intermediates) in biocatalytic processes⁸⁶ which was also emphasised in earlier Sections (*i.e.* Sections 1.2.2.1 to 1.2.2.3) when discussing the activity of different ALDH enzymes.

Independently, the catalytic competence of small organic molecules bearing a well-defined hydrogen-bond donating moiety in their structure was discovered.⁸⁷ It was observed that such a structural feature was able to act as a Lewis acid by establishing an interaction with a Lewis base (*e.g.* electron-rich heteroatom) *via* hydrogen-bond donation.⁸⁸ In pioneering studies, Hine *et al.*⁸⁹ identified that biphenyldiols such as **53** were able to catalyse the aminolysis of epoxides and proposed that the enhanced reactivity observed, resulted from the simultaneous formation of two strong hydrogen bonds to the epoxide oxygen atom. This theory was further developed by Kelly *et al.*⁹⁰ with their observation that biphenyldiols bearing electron-withdrawing groups at the *para*-positions (*i.e.* **54**) were capable of promoting the Diels-Alder reaction by establishing a double hydrogen bond with the dienophile. The seminal studies involving biphenyldiols as catalysts led to the now accepted premise that general acid catalysis by conformationally restricted metal-free diprotic Lewis acids is a effective strategy upon which to base the design of novel organocatalysts. Since then, the bioinspired concept of catalysis by hydrogen-bonding and its application in promoting a wide variety of reactions has grown immensely and has assumed a key role in contemporary organic synthesis and organocatalytic processes.⁹¹ The initial observations of catalysis by hydrogen-bonding evolved into asymmetric processes and, taking their cue from enzymatic systems, have consequently developed into the concept of bifunctional

53: Hine *et al.* (1984)
54: Kelly *et al.* (1990)
55: Etter *et al.* (1990)
56: Curran *et al.* (1994)
57: Schreiner *et al.* (2002)
58: Jacobsen *et al.* (1998)
59: Wynberg *et al.* (1981)
60: Takemoto *et al.* (2003)
61: Rawal *et al.* (2008)
62: Sakai *et al.* (2008)

Importance of hydrogen-bonding in catalysis

Co-crystallisation of an H-bonded complex:
 (thio)urea has hydrogen-bonding abilities

Electron-deficient (thio)ureas:
 catalysis by hydrogen-bonding

Asymmetric catalysis by hydrogen-bonding

Trifunctional catalysis

Hydrogen-bonding catalysis by squaramides

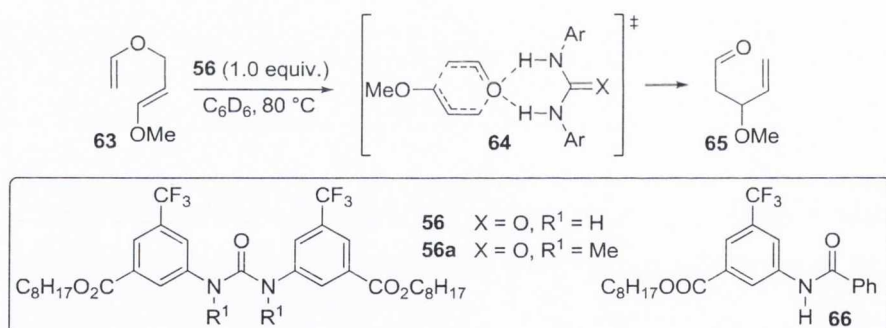
Bifunctional catalysis.
 Use of cinchona alkaloids

In the following Sections the concept of hydrogen-bonding-based catalysis by the urea, thiourea and squaramide moieties will be compared and discussed in more detail. Some of the applications of catalysts bearing these functionalities will also be presented.

1.4.1 *N,N'*-Diaryl (thio)urea based catalysis

The observation by Etter *et al.*⁹³ that electron-deficient *N,N'*-diaryl ureas (particularly **55**) acted as bidentate hydrogen-bond donors and were able to co-crystallise with compounds incorporating a Lewis basic functional groups, (*e.g.* ketones), can certainly be regarded (with hindsight) as significant. The binding mode was characterised by each urea donating two hydrogen bonds to the Lewis base. In Scheme 1.15 is depicted the first application of (thio)ureas in a general acid-promoted transformation reported by Curran *et al.*⁹⁴ (detailing their use of *N,N'*-diaryl urea **56** for the catalysis of a Claisen rearrangement).

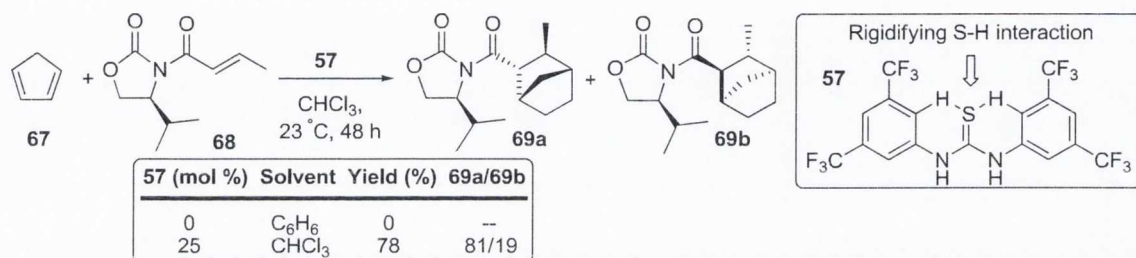
In the presence of a stoichiometric amount of **56**, bearing a trifluoromethyl group and a lipophilic octyl ester in the *meta*- position of each phenyl ring, a 22-fold acceleration in the reaction rate of the Claisen rearrangement of **63** (relative to the rate of the uncatalysed process) was observed.



Scheme 1.15 *N,N'*-Diaryl urea mediated Claisen rearrangement as reported by Curran.

The presence of a double hydrogen-bond interaction in the transition state **64** was proposed as an explanation for the catalytic effect and, in agreement with this model, dialkylurea **56a** and amide **66** failed to promote the reaction. While the need for **56** in stoichiometric loading in order to achieve satisfactory results rendered this methodology inefficient, this study had the merit of discovering the importance of electron-withdrawing substituents (*i.e.* trifluoromethyl groups) in the *meta*- position of the aromatic rings in *N,N'*-diaryl (thio)ureas. Such groups were responsible for the augmentation of the N-H acidity of the catalyst which resulted in its enhanced hydrogen-bond donating ability. Schreiner *et al.* built upon Curran's findings and

developed thiourea **57**, which was capable of promoting the Diels-Alder reaction between cyclopentadiene **67** and the α,β -unsaturated amide **68** in a fashion comparable to weak Lewis acids such as AlCl_3 and TiCl_4 (Scheme 1.16).⁹⁵ By using a combination of NMR and IR spectroscopy and *ab initio* calculations, the authors were able to postulate that thiourea **57** was able to form hydrogen-bond interactions with the dienophile.



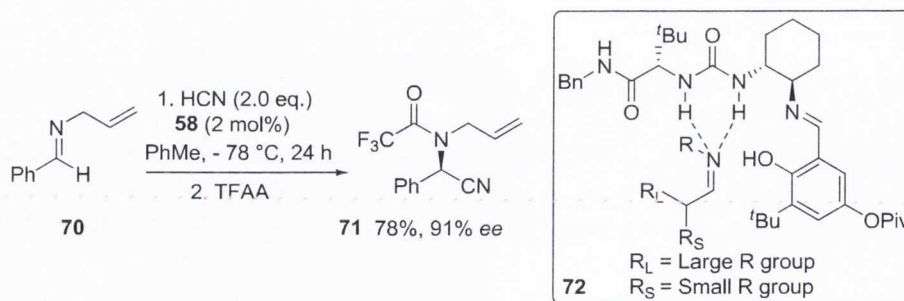
Scheme 1.16 An *N,N'*-diaryl-thiourea mediated Diels-Alder reaction

The efficacy of thiourea organocatalysts such as **57** was further explained by the same authors.⁹⁶ The thiourea moiety was preferred over urea for a number of reasons including greater solubility in a range of organic solvents, ease of preparation and reduced proclivity for self-association due to the lower electronegativity of the sulfur atom compared to the oxygen present in ureas.⁹⁶ Furthermore, the ability of thiourea derivatives as hydrogen-bond donors was generally deemed superior due to their greater acidity compared to urea analogues ($\text{p}K_{\text{a}}$ thiourea = 21.0; $\text{p}K_{\text{a}}$ urea = 26.9).⁹⁷ From this study, the importance of installing electron-deficient aromatic moieties to the thiourea core in order to maximise the catalytic activity also emerged; indeed, *N,N'*-dialkyl thiourea and electron-rich *N,N'*-diaryl thiourea derivatives exhibited inferior catalytic performance. The choice of trifluoromethyl (*i.e.* CF_3) as the electron-withdrawing group was based on their lack of Lewis-basicity (as opposed to other groups such as nitro, esters, *etc.*) which reduced the possibility of self-association. In addition, computational studies suggested that trifluoromethyl groups in *meta*-position rigidified the internal interaction between the Lewis-basic sulfur atom and the *ortho*-hydrogen atoms which resulted in a hindered rotation of the thiourea moiety hence the minimisation of the entropic penalty upon complexation (see Scheme 1.16).⁹⁶

Since these groundbreaking findings, *N,N'*-diarylthiourea **57** and its urea counterpart have been used as catalysts in a wide range of mechanistically unrelated transformations such as (*inter alia*) Friedel-Craft alkylations,⁹⁸ biomimetic reductions by Hantzsch esters,⁹⁹ epoxide openings,¹⁰⁰ Baylis-Hillman reactions¹⁰¹ and Corey-Chaykovsky¹⁰² reactions. Furthermore, the electron-deficient *meta*-CF₃-substituted diaryl (thio)urea motif has been incorporated in various asymmetric (bifunctional) organocatalysts.

1.4.2 Chiral (thio)ureas in asymmetric organocatalysis

The first example of an asymmetric reaction catalysed by chiral (thio)ureas was reported by Jacobsen *et al.*, who were studying the Strecker reaction of aromatic *N*-allyl aldimines **70** (Scheme 1.17).¹⁰³ The chiral thiourea-containing Schiff base **58** was initially designed as a member of a library of ligands for the metal-catalysed version of the reaction. However, rather serendipitously, **58** alone in the absence of metal additives was capable of promoting the formation of the desired products with higher levels of enantioselectivity. Mechanistic studies exhibited that the (thio)urea catalyst is capable of reversibly binding to the imine by double hydrogen-bond donation to the nitrogen lone pair. Furthermore, it was demonstrated that the catalyst binds preferentially to the (*Z*)-isomer of the imine in order to minimise steric interactions between the catalyst and large imine substituents (as depicted in **72** for a catalyst structurally analogous to **58**). This interaction activates the substrate in a chiral environment and allows the addition of HCN to occur in a face-selective manner.¹⁰⁴



Scheme 1.17 Asymmetric Strecker reactions catalysed by a chiral thiourea

Aside from the benefits associated with the discovery of an excellent protocol for the enantioselective synthesis of α -amino nitriles -which, being the precursors of α -amino acids, have a high synthetic value- the development of catalysts such as **58** represented

an important advancement in hydrogen-bond-mediated catalysis. It was demonstrated that (thio)urea derivatives incorporating chiral substituents are capable of transferring their stereochemical information to prochiral substrates in addition reactions.

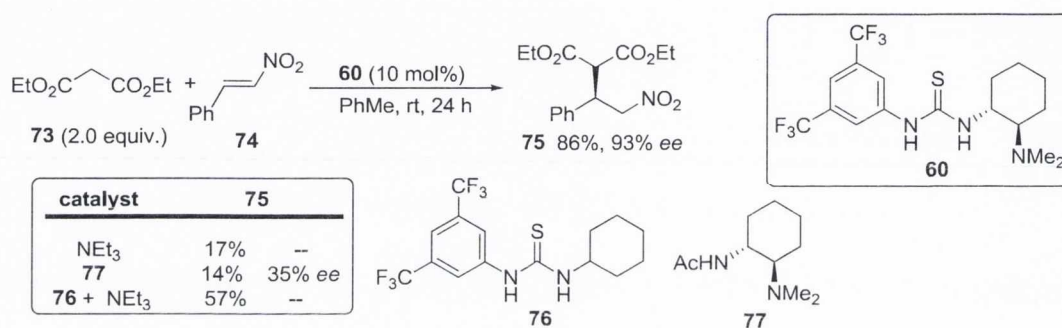
Subsequent studies by the same author confirmed the general versatility of the molecular framework present in **58** by building a library of related catalysts which widened considerably the potentialities in terms of reaction scope. A diverse array of transformations have been promoted by catalysts related to **58** such as (*inter alia*) Mannich reactions,¹⁰⁵ Pictet-Spengler reactions¹⁰⁶ and nitro-Mannich reactions.¹⁰⁷

1.4.3 Bifunctional asymmetric organocatalysis using (thio)ureas

The introduction of chiral bifunctional (thio)urea catalysts represented a further advancement in the field of hydrogen-bond-mediated asymmetric catalysis. Bifunctional catalysts exert their catalytic activity by simultaneously activating both the nucleophile and the electrophile in a given reaction in a way reminiscent to biocatalysis by some natural enzymatic systems. While adding an increased level of complexity (structurally speaking), such catalysts hold the potential to create a tighter chiral environment during the encounter of the nucleophile and the electrophile by simultaneously interacting with both reactants, which eventually allows for significantly improved catalytic activity and enhanced stereocontrol over the addition event. The structure of the vast majority of bifunctional (thio)urea catalysts includes a combination of tuneable aromatic functionality at one (thio)urea nitrogen atom (to maximise the catalysts's rigidity and hydrogen-bond donating ability) and a chiral functionality (often a Lewis base) at the other nitrogen atom. While a *N*-aryl (thio)urea moiety having electron-withdrawing groups (most frequently CF₃ groups at the *meta*-positions) is generally employed in the hydrogen-bond donating moiety, the chiral functionality set to activate the nucleophile reagent can bear a higher variety of Lewis bases. Indeed, the excellent functional group tolerance reported by thio(urea) catalysts (which stems from their relatively weak enthalpic binding with organic Lewis basic nucleophiles), has allowed for the development of catalysts bearing a wide range of functionalities.⁸⁸

Takemoto *et al.* were the first to develop a bifunctional thiourea catalyst when they discovered that **60** was able to promote the Michael addition of diethyl malonate **73** to

β -nitrostyrenes such as **74** with excellent enantioselectivity (Scheme 1.18).¹⁰⁸ They proposed that the thiourea moiety was activating the nitroolefin (by hydrogen-bond donation) while the chiral tertiary amine was responsible for the activation of the pronucleophile. Moreover, they established that both processes were occurring simultaneously in the transition state. They observed that by replacing bifunctional catalyst **60** with either triethylamine (NEt₃), a combination of triethylamine and thiourea **76** or the chiral amine **77**, the reaction occurred with poor yields and moderate levels of enantioselectivity.



Scheme 1.18 Use of thioureas as bifunctional organocatalysts as reported by Takemoto

The scope of Takemoto's catalyst **60** has been further widened by the same author and other research groups to encompass asymmetric reactions in which both the nucleophile and electrophile differ substantially from those for which it was initially developed (*i.e.* malonate esters and nitrostyrenes).^{109,110}

The mechanism and the structure of a plausible transition state for the reaction was a debated question. Takemoto *et al.* proposed that the reactants were activated simultaneously by the catalyst as shown in Figure 1.3, A.¹⁰⁸ The tertiary amine was responsible for the deprotonation of the malonate ester and the generation of a nucleophilic enolate anion by general base catalysis. This species would stereoselectively attack one face of the nitroolefin electrophile which was activated by dual hydrogen-bonding donation from the thiourea moiety. However, an alternative mechanism was later proposed by Soès *et al.*¹¹¹ in which it was speculated that the enolate nucleophile was held in place by hydrogen-bonding to the thiourea moiety whereas the activation of the nitroolefin is achieved *via* interaction with the protonated tertiary amine as depicted in Figure 1.3, B.

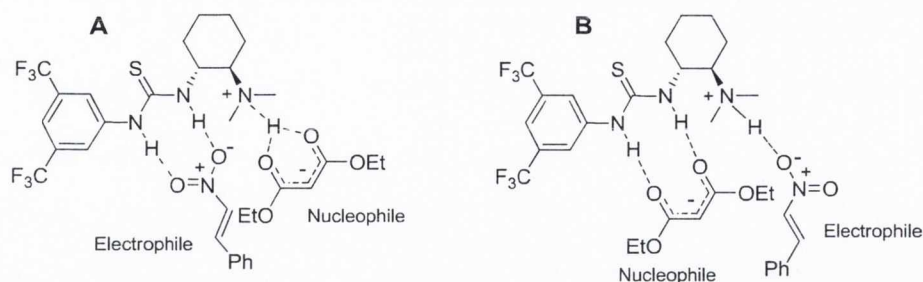


Figure 1.3 Proposed transition states involved in the Michael addition reaction promoted by Takemoto's catalyst

Less than a decade has passed since the strong potential of bifunctional (thio)urea organocatalysts were unveiled to the scientific community.¹⁰⁸ Since then, considerable progress has been made in this field and a wide variety of novel bifunctional molecules have appeared which can bring about the catalysis of a multitude of transformations.^{87,88} Furthermore, the concept of the incorporation of (thio)urea moieties into cinchona alkaloids has also been developed. A wide variety of catalysts were created using this privileged chiral scaffolding providing excellent enantioselectivities.¹¹²

1.4.4 Bifunctional asymmetric organocatalysis using squaramides

Despite having entered the scene of asymmetric catalysis as late as 1998, thioureas and ureas have become protagonists in this field and over the years have been extensively implemented as a versatile and effective hydrogen-bond donating moiety. Inasmuch as (thio)ureas have proven to be a gold mine for catalyst discovery, other hydrogen-bond donor motifs have been much less explored.⁹² In this field, the latest addition to the catalytic arsenal available to organic chemists is the squaramide functionality. The synthesis of squaramides was first achieved in 1966¹¹³ (compared to the synthesis of urea which appeared as early as 1828¹¹⁴); and their rather unusual structure has been studied in detail, however their application has been mainly limited to the fields of medicinal chemistry and supramolecular chemistry thanks to their abilities as ion receptors.¹¹⁵

Squaramides possess some rather peculiar structural features and hydrogen-bond donating abilities compared to ureas and thioureas (Figure 1.4).^{115,116} They are four-membered ring systems derived from squaric acid that possess a duality in hydrogen-

bonding and are able to form up to four hydrogen-bonds. The two nitrogen bound hydrogen atoms can effectively act as two-fold hydrogen-bond donors and the presence of two carbonyl unit makes it a dual hydrogen-bond acceptor as well, which also leads to the possibility of the formation of dimeric species due to self-association (Figure 1.4, A).¹¹⁶

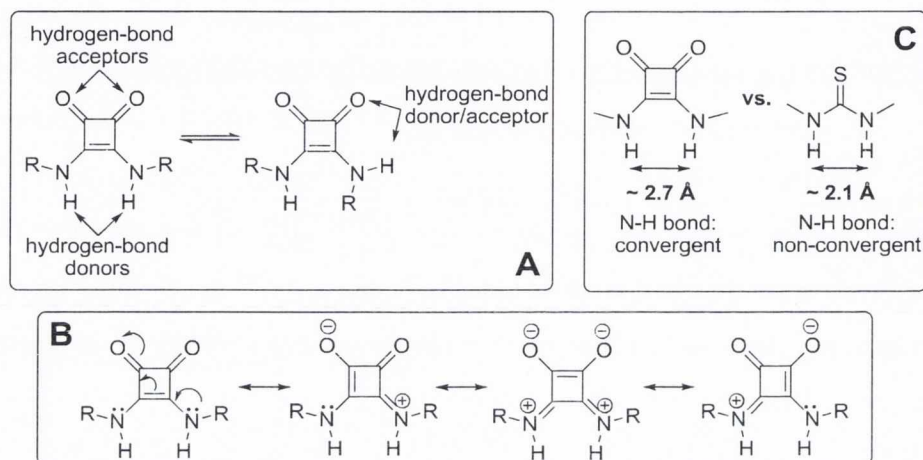
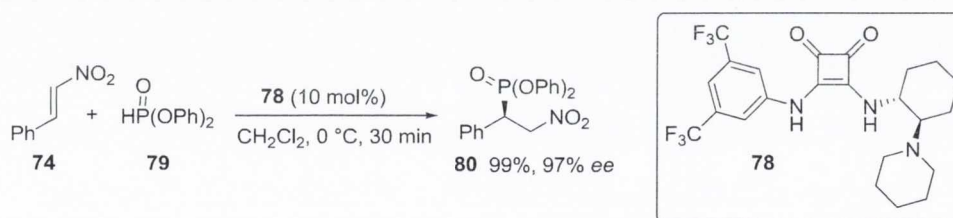


Figure 1.4 Structural features of squaramides

The high hydrogen-bond acceptor and donor capabilities of squaramides, (significantly higher compared to urea and thiourea) can be explained by virtue of an enhancement in their aromaticity upon binding.¹¹⁷ Indeed, the formal build up of negative charge upon hydrogen-bond donation can be delocalised on the two carbonyls and leads to the formation of a formal double positive charge in the cyclobutenedione system, which acquires aromatic character according to Hückel rule (*i.e.* $4n + 2$, $n = 0$).¹¹⁵ Squaramides are considered vinylogous amides and are structurally rigid (like their urea and thiourea counterparts). However, only in the case of squaramides is there the possibility of delocalising both lone pairs on the nitrogen atoms, thereby restricting the rotation of the two C-N bonds and causing both the carbonyl and amine groups to be coplanar (Figure 1.4, B).¹¹⁶ Another difference between (thio)ureas and squaramides is the relative distance and spacing of the two N-H groups. The distances for *N,N'*-dimethylthiourea and *N,N'*-dimethylsquaramide have been calculated to be 2.13 Å and 2.72 Å respectively by Rawal *et al.*⁹² Moreover, the structure of the cyclobutanedione ring induces a convergent orientation of the N-H bonds (approximately 6°), a property that cannot be found in (thio)ureas (Figure 1.4, C).⁹² Even considering these differences, squaramides and (thio)ureas share some striking structural similarities which renders

quite astonishing the fact that the former have not been considered as an alternative to the highly successful (thio)urea-based systems at an earlier stage. Notwithstanding their unique structural properties, squaramide-based catalysts have the additional advantage of a generally straightforward preparation starting from dialkoxysquaric esters following a modular synthesis under relatively mild conditions (often devoid of purification by column chromatography).¹¹⁶

Catalyst **78** was synthesised by Rawal *et al.*¹¹⁸ and was successfully employed in the Michael addition of diphenylphosphite **79** to nitroalkenes such as **74** (Scheme 1.19). The β -nitro phosphonate **80**, which is a precursor to biologically active β -amino phosphonic acids, was formed in high yields and excellent *ee*. Catalyst **78** outperformed thiourea analogues which were previously considered the benchmark catalysts for this transformation (providing only low yields of **80** and moderate enantioselectivities).¹¹⁹ Catalyst **78** was subsequently chosen as the most proficient for a number of other reactions.^{120,121,122}



Scheme 1.19 Bifunctional squaramide-promoted asymmetric Michael addition

Other novel bifunctional squaramide catalysts have been developed in this short period of time since the seminal studies of Rawal *et al.* and have been successfully employed in a number of mechanistically unrelated reactions.^{123,124,125} The vast knowledge acquired in the field of (thio)urea organocatalysis and its rather straightforward inclusion into squaramide catalysis combined with the outstanding levels of stereocontrol that have been achieved thus far with squaramides, promises for further impressive developments in this field in the coming years.

1.5 Cinchona alkaloids: a privileged scaffold in bifunctional organocatalysis

The motivations that set most Spanish *conquistadores* to embark and establish a vast colony in South America in the 16th century were most certainly fuelled by the pursuit of wealth in the form of immense gold reserves. For centuries Spanish settlers, while in their hunt for *El Dorado*, heavily exploited the territory and the indigenous population and produced the simultaneous funneling of an inestimable treasure to Europe in the form of well sought-after gold and other native natural products. In the following centuries up to contemporary times the majority of the world's population have benefited from these products and so did the scientific community, to a lesser extent, with the use of cinchona alkaloids. These natural products, with quinine as a prominent member, are extracted from the bark of the South American tree *Cinchona officinalis*. The broad medicinal history of quinine is the main reason for its notoriety today, however its catalytic properties have also contributed to the privileged position held by cinchona alkaloids.¹²⁸ Quinine (**81**), quinidine (**82**), cinchonine (**59**) and cinchonidine (**83**) are major constituents of the bark extract of trees belonging to the Cinchona class and are small yet complex molecules. They contain five stereogenic centers (N-1, C-3, C-4, C-8 and C-9), a basic and nucleophilic quinuclidine ring, a quinoline unit, a secondary alcohol, a methyl ether (in the case of **81** and **82**) and a terminal olefin as shown in Figure 1.5.

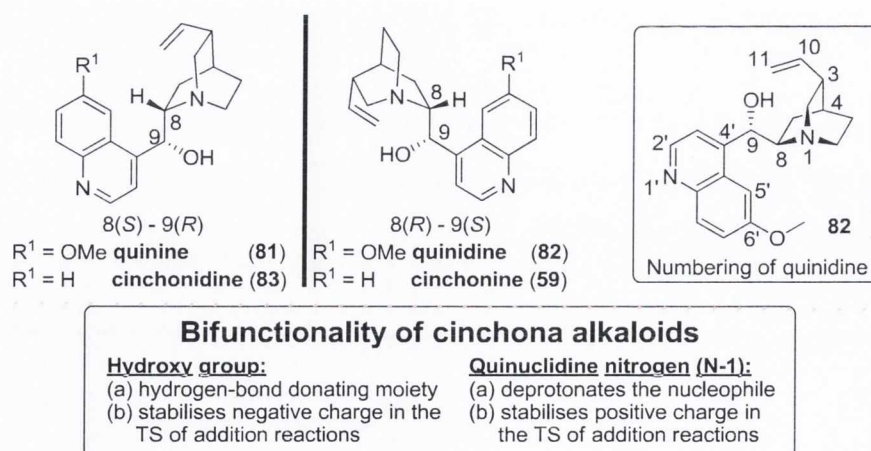


Figure 1.5 Structure of natural cinchona alkaloids

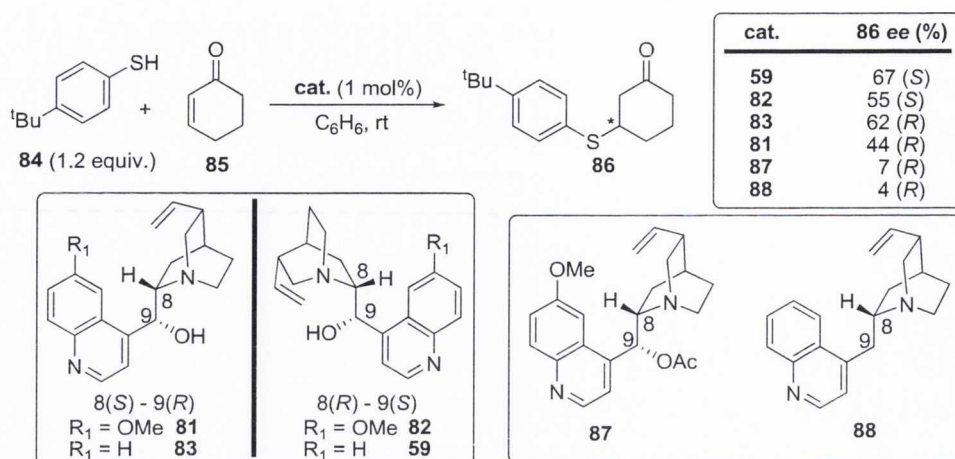
Cinchona alkaloids possess a relatively rigid structure¹²⁶ and yet are flexible molecules in solution: by rotating along the C-9-C-4' and the C-8-C-9 bonds they can adopt

several conformations. These molecules make an efficient natural bifunctional scaffold in organocatalytic applications since the basic quinuclidine nitrogen and the Lewis acidic hydroxy group functionalities are positioned in close proximity to each other in a well defined chiral environment. Cinchona alkaloids are always referred to as being pairs of *pseudoenantiomers* since, of the five stereocenters, only the ones at C-8 and C-9 have opposite configurations. As a result, when quinines or quinidines (or derivatives thereof) are used as organocatalysts in an asymmetric reaction, they usually provide the same product in opposite enantiomeric forms.¹¹²

1.5.1 Natural cinchona alkaloids as organocatalysts

At the time when the concept of bifunctionality in thiourea-based organocatalysis was officially formalised with the discovery of Takemoto's catalyst **60** in 2003 (*vide supra*), cinchona alkaloids had already been known to promote asymmetric reactions. In this field, the first application of cinchona alkaloid was reported by Bredig and Fiske as early as 1912 albeit with low optical yields.¹²⁷ However it was not until the late 1970s early 1980s - thanks to Wynberg *et al.*¹²⁸ - when a new era in asymmetric catalysis driven by cinchona alkaloids began.¹²⁹

In 1981, Hiemstra and Wynberg released a landmark publication reporting the results of their thorough studies on the influence of natural cinchona alkaloids in the Michael addition reaction between aromatic thiols and cyclic enones (Scheme 1.20).¹²⁸ They observed the formation of Michael adduct **86** from *p*-*tert*-butylthiophenol (**84**) and 2-cyclohexen-1-one (**85**) in quantitative yield and with an enantiomeric excess of up to 67% when cinchonine (**59**) was employed as the catalyst. Derivatives devoid of the hydroxy group (such as **87** and **88**) were synthesised and evaluated in this reaction. The results obtained pointed out that the hydroxy functionality was essential to obtain products with appreciable levels of enantioselectivity. In addition, it was observed that products arising from the use of quinine and quinidine had opposite absolute configurations. These pieces of evidence led the author to speculate that cinchona alkaloids exerted their catalytic activity *via* the simultaneous activation of the thiol (*i.e.* nucleophile) and the cyclohexenone (*i.e.* electrophile) by the hydroxy and the amine groups respectively and thus formally acted as bifunctional catalysts.¹²⁸



Scheme 1.20 Michael addition promoted by natural and modified cinchona alkaloids

In the following years, Wynberg *et al.* extensively explored the use of cinchona alkaloids as catalysts in a variety of other transformations and obtained products with good to excellent stereocontrol.¹³⁰ However, aside from the establishment of some useful synthetic protocols, the main merit of these studies was to unveil the huge potential of cinchona alkaloids as natural bifunctional catalysts. Notwithstanding the major advancements in the field of bifunctional catalysis and hydrogen-bonding catalysis which led to the design of more active cinchona alkaloid-derived catalytic species,^{112,131} the natural molecules are still being used by chemists in organocatalytic processes and in some cases their catalytic activity is still unsurpassed.¹¹² It is therefore not surprising that nowadays cinchona alkaloids are considered ‘privileged’ structures.¹³²

1.5.2 Functionalisation of cinchona alkaloids and fine tuning of their bifunctional catalytic activity

In the conclusions section of his seminal publication of 1981, Wynberg stated that: “*the scope of the utility of hydroxy amines can perhaps be extended by constructing a catalyst containing a stronger base or a better hydrogen bond donor. Not only are hydroxy amines capable of exerting bifunctional catalysis but also other combinations of functional groups can in principle exhibit such behavior.*”¹²⁸ In view of the precedent set by Wynberg and despite the ready availability of cinchona alkaloid it is somewhat surprising that this field did not undergo immediate growth, however the farsightedness of Wynberg’s assertion was eventually acknowledged. The scientific interest in

cinchona alkaloids was ignited in a time just prior to the flourishing of the concept of hydrogen-bonding catalysis and, when this became solidly established among the chemists community, the two fields accordingly merged. The committed pursuit of creating catalysts with a stronger base and a better hydrogen bond donor, as envisaged by Wynberg, has led over the years to widespread modifications to the structures of cinchona alkaloids. The structural richness of cinchona alkaloids has been extensively exploited for the facile modification of the naturally occurring alkaloids to develop synthetic, tailor-made compounds for specific applications.¹¹² In organocatalytic processes promoted by bifunctional cinchona catalysts the quinuclidine moiety is normally involved in the activation of the nucleophile, therefore its position is predetermined by the structure of the alkaloids. Conversely, the nature (*e.g.* hydroxy group, (thio)urea, amide *etc.*) and position of the hydrogen-bond donating moiety is far more flexible and its relative location with regard to the quinuclidine ring together with the degree of hydrogen-bonding established with the electrophile is crucial for the promotion of a catalytic process with good stereocontrol. Some of the possible modifications on the structure of natural cinchona alkaloids that have been reported over the years are depicted in Figure 1.6.^{112,131}

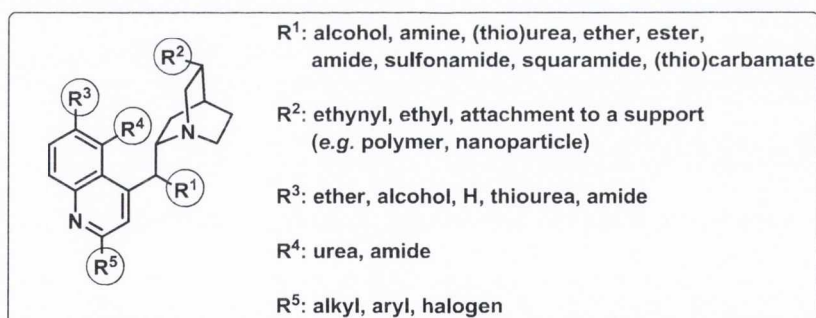


Figure 1.6 Reported modifications of cinchona alkaloids

1.5.2.1 (Thio)urea- and squaramide-substituted cinchona alkaloids

Following the studies by Takemoto *et al.*, it was envisaged that the inclusion of a (thio)urea moiety in the structure of cinchona alkaloids, as well as accessing a dual hydrogen-bond donating motif, had the advantage of allowing fine tuning of the Lewis acidity (*i.e.* binding ability) by altering the substitution on the (thio)urea-moiety and an overall greater structural rigidity (due to the increased bulk of a (thio)urea group relative

to a hydroxy moiety). Thus far, (thio)-urea units have been included at the C-9, C-6' and C-5' positions of natural cinchona alkaloids.

1.5.2.1.1 (Thio)urea and squaramide moieties introduced at C-9

Despite the fact that the strategy of substituting the hydroxyl group at C-9 with a urea moiety appeared in the literature as early as 2003,¹³³ it was not until 2005 when bifunctional C-9-substituted (thio)urea cinchona catalysts were thoroughly examined and successfully employed in asymmetric transformations. Four different authors independently and almost simultaneously reported the use of this strategy.^{134,135,136,137} An advantage associated with this approach, is the accessibility of (thio)urea derivatives of cinchona alkaloids with both natural and unnatural absolute configurations at C-9, thus allowing the elucidation of the effect of the stereochemistry at C-9 on the organocatalytic competence of cinchona alkaloids.¹³¹

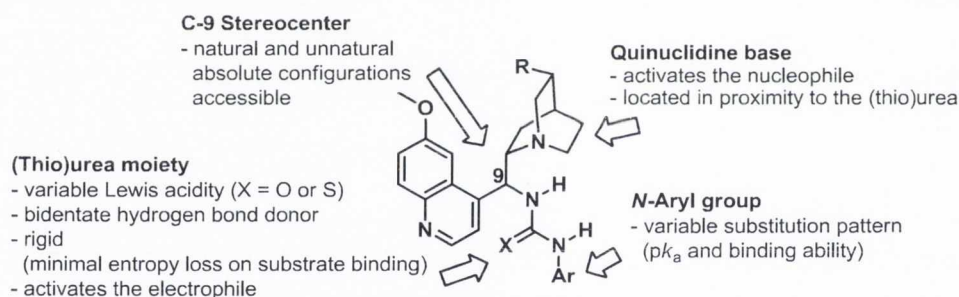
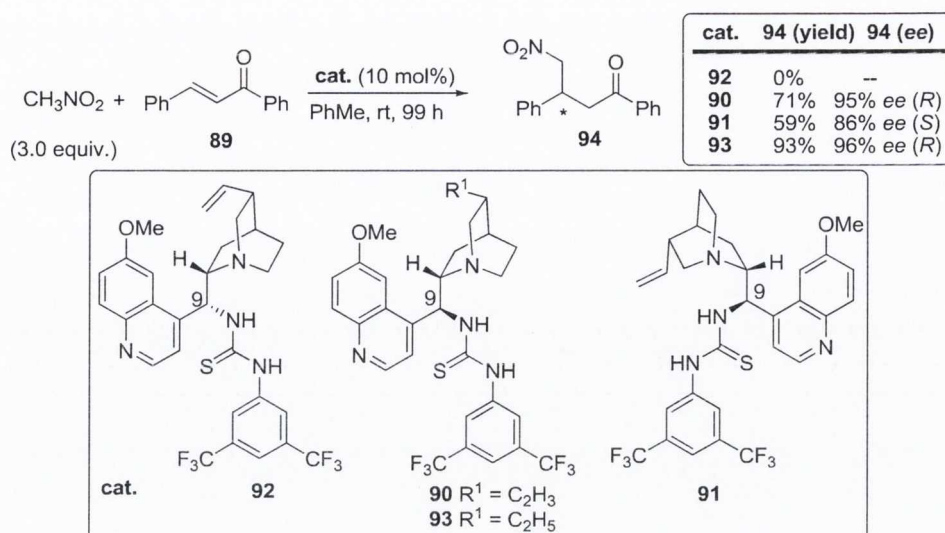


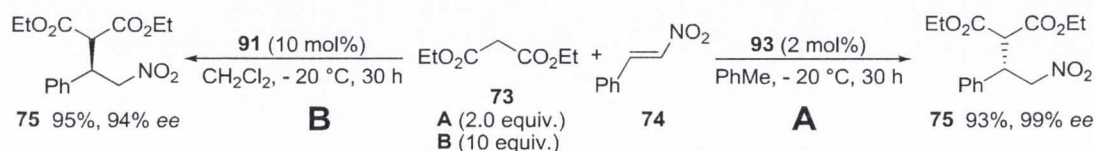
Figure 1.7 (Thio)urea-modified cinchona alkaloid catalysts: design rationale.

Soès *et al.*¹³⁵ explored the use of C-9 thiourea-substituted cinchona alkaloids in the asymmetric addition of nitromethane to chalcones (*i.e.* **89**). Starting from quinine (**81**) and quinidine (**82**), the author synthesised a small library of thiourea catalysts. The synthesis of catalysts **90** and **91** from the parent alkaloids **81** and **82** respectively was accomplished in two steps with overall epimerisation of the C-9 stereocentre. Surprisingly, organocatalyst **92** – the thiourea derivative of quinine with natural stereochemistry at C-9 – exhibited no activity. Conversely, both *epi*-thiourea catalyst **90** and its *pseudoenantiomer* **91** could promote the Michael addition reaction and afforded products with inverted absolute configuration with excellent levels of enantiocontrol when employed at 10 mol% loading. Enantioselectivity could be further improved by using the dehydroquinine-derived catalyst **93** (Scheme 1.21).



Scheme 1.21 Addition of nitromethane to chalcones catalysed by thiourea-substituted cinchona alkaloids.

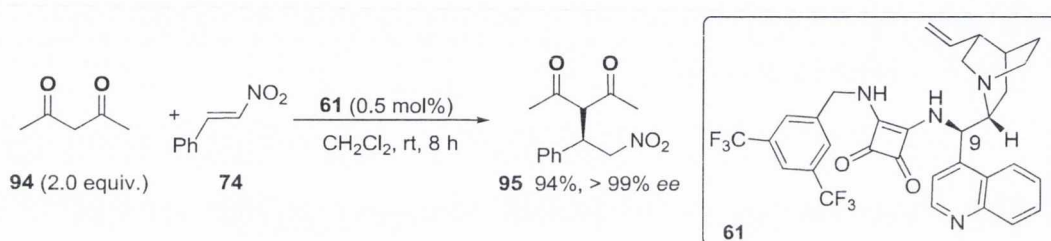
Shortly afterwards, Connon *et al.*¹³⁶ and Dixon *et al.*¹³⁷ almost simultaneously reported the use of these catalysts for the Michael addition of dimethyl malonate **73** to nitroolefins such as **74**. Our group reported that the configuration at C-9 of dehydroquinine derivatives was an important factor affecting the catalyst performances and observed increased enantioselectivity when the urea moiety at C-9 was replaced with the more Lewis acidic thiourea. It was found that *epi*-dehydroquinine-derived thiourea catalyst **93** in loadings as low as 0.5 mol% could promote the reaction and allowed the formation of Michael adducts **75** in high yields and excellent enantioselectivities (Scheme 1.22, A).¹³⁶ At the same time, Dixon *et al.* - while screening catalysts bearing different hydrogen-bond donating moieties - also observed that the thiourea motif was the most effective and eventually discovered that the use of *epi*-cinchonine-derived thiourea catalyst **91** in 10 mol% loading could afford Michael adduct **75** with yields and enantioselectivity comparable to those obtained by Connon *et al.*, albeit with inverted absolute configurations (Scheme 1.22, B).¹³⁷



Scheme 1.22 Michael addition reaction promoted by thiourea cinchona catalyst **76** reported by Connon *et al.* (**A**) and Dixon *et al.* (**B**)

Since the report of these seminal studies, 9-*epi*-cinchona alkaloids bearing a (thio)urea moiety on C-9 have been extensively used as catalysts for a plethora of mechanistically unrelated reactions, and excellent reviews have documented their applications.^{112,131}

A more recent expansion to this class of catalysts was impelled by Rawal *et al.* in 2008 with their elegant substitution of the (thio)urea moiety with a squaramide (*i.e.* catalyst **77**).⁹² Its catalytic activity was evaluated in the Michael addition reaction of 2,4-dicarbonyl compounds such as **94** to nitroolefins as in **74** (Scheme 1.23). It was observed that Michael adduct **95** could be formed in high yield and excellent enantioselectivity when **77** was employed in loadings as low as 0.5 mol%.



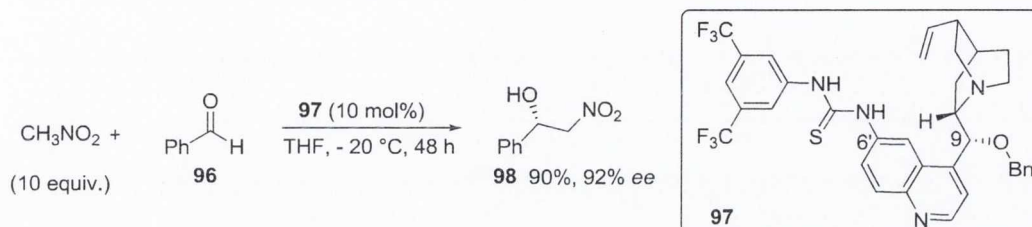
Scheme 1.23 Michael addition reaction promoted by squaramide cinchona catalyst **61**

After Rawal's recent seminal breakthrough, the inclusion of squaramides on the backbone of cinchona alkaloids has become more widespread, several successful applications have been reported.¹¹⁶

1.5.2.1.2 Thiourea moiety introduced at C-6'

Shortly after the reports demonstrating the efficacy of C-9-substituted thiourea cinchona alkaloids as catalysts in Michael addition reactions (*vide supra*), researchers began to be intrigued by the possibility of exploring the 'catalytic space' around these catalysts, *i.e.*, to evaluate other possible substitution patterns. Previous studies demonstrated that the installation of a hydrogen-bond donating moiety (*i.e.* hydroxy group) at the C-6' position of cinchona alkaloids could result in active catalysts for asymmetric reactions.¹³⁸ Learning from these observations, Hiemstra *et al.*¹³⁹ demonstrated in 2006 that C-9 is not the sole position on the cinchona alkaloid backbone where a thiourea functionality can be installed with advantage. Substitution of the methoxy group on C-6' with a thiourea moiety and benzylation of the C-9 hydroxy substituent without

disturbing the stereochemical configuration of the natural alkaloid, resulted in a powerful catalyst for the asymmetric Henry reaction. The quinine-derived catalyst **97** was shown to promote the attack of nitromethane on a variety of aromatic and heteroaromatic aldehydes (*e.g.* **96**) affording adduct **98** products in excellent yield and enantiomeric excess (Scheme 1.24).

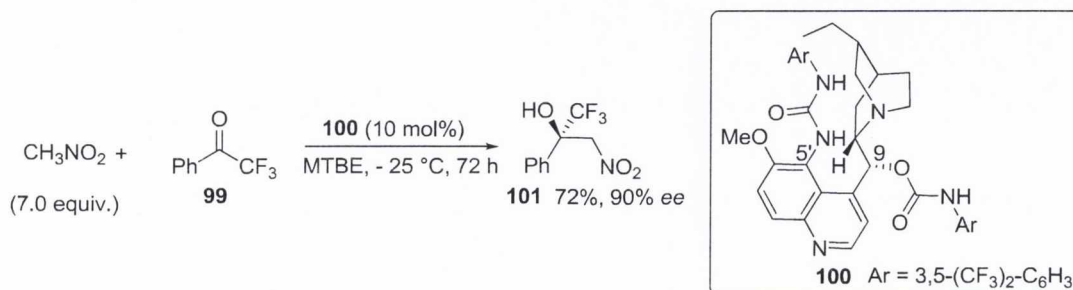


Scheme 1.24 Henry reaction catalysed by **97** bearing a thiourea group at C-6'

Since the report of Hiemstra *et al.* only two other studies have emerged in which a C-6' thiourea-substituted cinchona alkaloid bearing an ether group at C-9 proved to be the optimal catalyst for an asymmetric reaction.^{140,141}

1.5.2.1.3 Urea moiety introduced at C-5'

More recently our group, intrigued by Hiemstra's work on the Henry reaction, was prompted to investigate other possible sensitive positions along the backbone of cinchona alkaloids for the installation of (thio)urea moieties that could result in active catalysts. During this investigation it was demonstrated that the introduction of a urea moiety at C-5' of the quinoline moiety could result in molecules bearing a catalytic activity. When used at 10 mol% loading, dihydroquinine-derived catalyst **100**, bearing a urea moiety at C-5' and a carbamoyl group at C-9 could promote the Henry reaction between nitromethane and trifluoromethylketones such as **99** affording products in high yield and excellent enantioselectivities (Scheme 1.25).¹⁴²



Scheme 1.25 Henry reaction catalysed by **100** bearing a thiourea group on C-5'

Since this first report, our group has been actively involved in the development of other C-5' urea-substituted catalysts. A library of such catalysts was built and one of these proved to be successful in promoting the Michael addition reaction of aliphatic thiols to nitroalkenes.¹⁴³

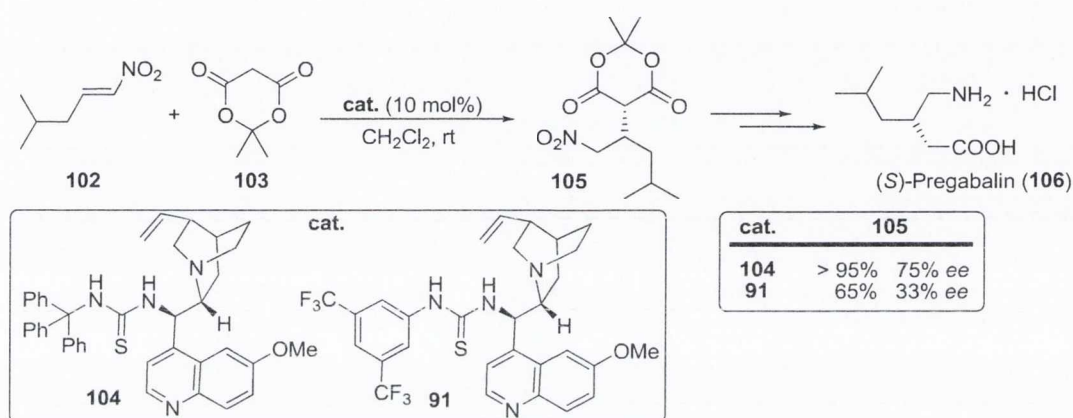
1.5.2.1.4 *N*-Alkyl thiourea-substituted cinchona alkaloids

The privileged role of the 3,5-bis(trifluoromethyl)phenyl moiety on (thio)urea-based organocatalysts has been rationalised by its ability to confer specific stereoelectronic properties to the (thio)urea functionality which are beneficial for its dual hydrogen-bond donating capabilities (*vide supra*). The pK_a (*i.e.* Lewis acidity) of bifunctional (thio)urea organocatalysts has been considered to be a crucial parameter to take into account in catalyst design^{144,145} as a predictor of the hydrogen-bond donating capabilities of the system. Nonetheless, pK_a alone is not sufficient to predict the levels of stereinduction provided by a (thio)urea-based organocatalyst in a given reaction, and often the catalysts screening phase of a study is based on a trial-and-error approach.

The rigidity and increased Lewis acidity intrinsic to electron-deficient aryl (thio)ureas, combined with their relatively low steric hindrance, are highly desirable properties for the formation of strong hydrogen-bond interactions in the stabilisation of the transition state of a given addition reaction. Examples of *N*-alkyl thiourea-substituted cinchona alkaloids outperforming their *N*-aryl counterparts have been sporadically reported in recent times.¹⁴⁶ Conversely, no examples of an *N*-alkyl urea-based cinchona alkaloid-derived catalyst has been documented thus far.¹⁴⁷ The substitution of an electron-deficient aryl group with an alkyl group on the (thio)urea functionality results in the increase of its pK_a and in the decrease of its hydrogen-bond donating abilities. Nonetheless, the introduction of elements of steric hindrance, additional hydrogen-bond donating functionalities, chiral moieties and other functional groups on the organocatalyst in the near vicinity of the (thio)urea unit, which are more easily installed as part of an alkyl substituent, may result in an enhancement of the overall catalytic performance. This makes *N*-alkyl (thio)ureas potentially more tunable platforms for bifunctional cinchona organocatalysts relative to their *N*-aryl counterparts, where

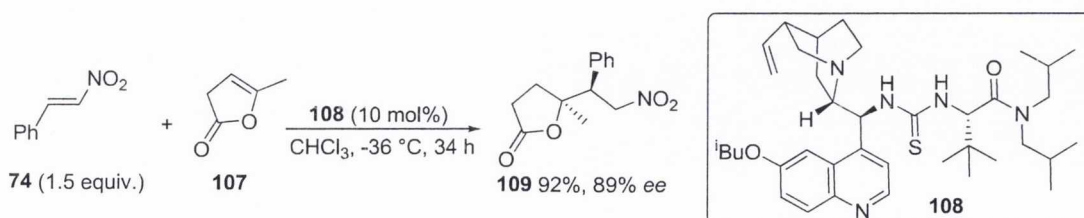
structural changes are generally limited to the introduction of functional groups altering the electronic character of the aromatic ring.

In Scheme 1.26 is depicted the use of a C-9 thiourea-substituted cinchona alkaloid bearing a bulky trityl group (*i.e.* **104**) as a catalyst promoting the key asymmetric Michael addition reaction in the synthesis of the drug Pregabalin (**106**). Koskinen *et al.* synthesised a library of thiourea cinchona catalysts and reported that **104** outperformed the widely employed *N*-aryl thiourea catalyst **91**.¹⁴⁸



Scheme 1.26 Synthesis of (*S*)-Pregabalin using catalyst **104** to promote the key asymmetric Michael addition

More recently, Mukherjee *et al.*,¹⁴⁹ inspired by the pioneering work of Jacobsen (Section 1.4.2), prepared a new family of cinchona catalysts bearing a *tert*-leucine-derived *tert*-butyl moiety and an additional stereocentre on the thiourea motif. The author reported that catalyst **108** (at 10 mol% loading) could promote the vinylogous Michael addition reaction between the lactone **107** and nitroolefin **74** to afford products bearing a quaternary stereocentre such as **109** in high yield and excellent enantioselectivity (Scheme 1.27).

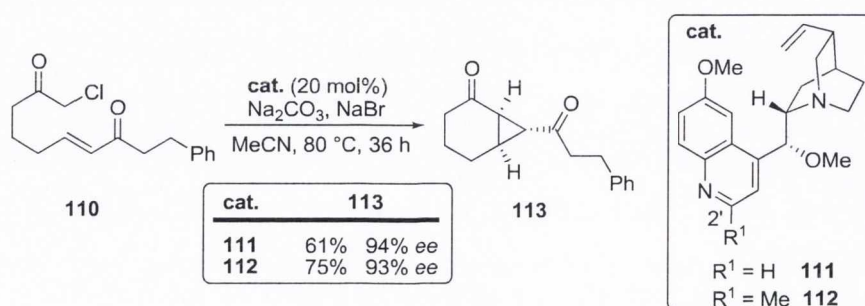


Scheme 1.27 A vinylogous Michael addition promoted by the *N,N*-dialkyl thiourea-based catalyst **108**

1.5.2.2 Cinchona-based organocatalysts modified at C-2'

The fine tuning of the catalytic performance of cinchona alkaloids can also be achieved *via* the modification of their carbon skeleton at the C-2' position. The insertion of alkyl and aryl groups at C-2' has been documented in several studies and very recently the introduction of a halogen atom was also reported. The substitution at C-2' leads to changes in the steric and electronic properties of cinchona alkaloids, leading to interference with the conformational equilibria of these species in solution and, being adjacent to the nitrogen atom of the quinoline moiety, may result in the impairment of its reactivity as a nucleophile.¹⁵⁰ Of all the known organocatalytic applications of such modified molecules, only two involve their use as bifunctional catalysts, the rest of the examples reports the use of C-2' substituted cinchona alkaloids as chiral amines either involving the reactivity of the quinuclidine ring nitrogen or the presence of a primary amino group at C-9.

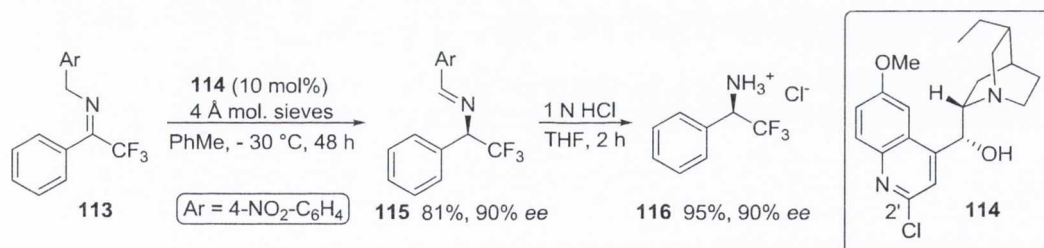
Gaunt *et al.* were the first to use a C-2' modified cinchona alkaloid as a catalyst developed through a mechanism-guided design strategy.¹⁵⁰ The authors had observed that the use of a chiral amine such as quinine-derived **111** to promote the asymmetric intramolecular cyclopropanation of alkenyl chloroketones such as **110** generated products with excellent enantioselectivities albeit only in moderate yields (which could not be improved by the optimisation of the reaction conditions) as depicted in Scheme 1.28.¹⁵¹ The author speculated that the unsatisfactory yields were due to the catalyst being poisoned *via* the alkylation of the quinoline nitrogen with **110**. In order to obviate the effects of such deleterious reactivity a methyl group at C-2' was introduced which provided **112**. Its use eventually led to excellent enantioselectivities and slightly improved yields due to the impairment of the nucleophilicity of the quinoline nitrogen.



Scheme 1.28 Asymmetric intramolecular cyclopropanation promoted by **112**

Following this report and the disclosure of a breakthrough publication by Hintermann *et al.*¹⁵² who reported a protocol for the straightforward synthesis of C-2' substituted cinchona alkaloids, several applications of such catalysts acting as chiral amines have appeared in the literature.^{153,154,155}

Another example of a C-2' substituted bifunctional cinchona catalyst was recently reported by Deng *et al.*¹⁵⁶ The authors noted that the introduction of substituents at C-2' had a dramatic effect on the enantioselectivity of the asymmetric isomerisation of trifluoromethyl ketimines such as **113**. The study reported that the stereocontrol of the transformation was strongly reliant on the electronic nature of the substituent at C-2' more than on its steric requirements. Accordingly, the exchange from a methyl group to a bromine and to a chlorine atom provided a steady enhancement in the *ee*'s of the products. The use of catalyst **114** (at 10 mol% loading) promoted the isomerisation of *N*-benzyl trifluoromethyl ketimine **113** to afford product **115** in excellent yield and enantioselectivity. Aromatic and aliphatic ketimines were well tolerated and the products formed could be further manipulated to afford trifluoromethylated amines such as **116** (Scheme 1.29).



Scheme 1.29 Isomerisation of imines promoted by a C-2' substituted cinchona alkaloid

1.5.2.3 Other substitutions

Urea, thiourea and squaramide have not been the only hydrogen-bond donating moieties introduced on the backbone of cinchona alkaloids. Other functional groups (such as amides,¹⁵⁷ alcohols,¹⁵⁸ sulphonamides,¹⁵⁹ *etc.*) have been used as the electrophile-activating components for a wide array of reactions.¹¹² Cupreines and cupreidines (*i.e.* **117**, **118**) derivatives as bifunctional organocatalysts have been successfully employed in numerous applications.^{112,160} These molecules utilise the phenolic hydroxy group arising from the demethylation of the ether at C-6' as a hydrogen-bond donating motif and have the secondary alcohol at C-9 functionalised. This class of molecules was also

inspirational for our group and led to the recent development of a small library of catalysts bearing a phenolic hydroxy group on aromatic moieties installed at C-9 (*i.e.* **119**).¹⁶¹ Amides and sulphonamides (such as **120** and **121**) as single hydrogen-bond donating moieties on cinchona alkaloids, have also been reported. Excellent reviews have appeared which cover in detail the widespread employment of cinchona alkaloids and derivative thereof as organocatalysts.^{112,131} Representative examples of bifunctional cinchona catalysts using hydrogen-bond donating moieties other than (thio)urea and squaramide are depicted in the upper part of Figure 1.8 (*i.e.* **117-121**).

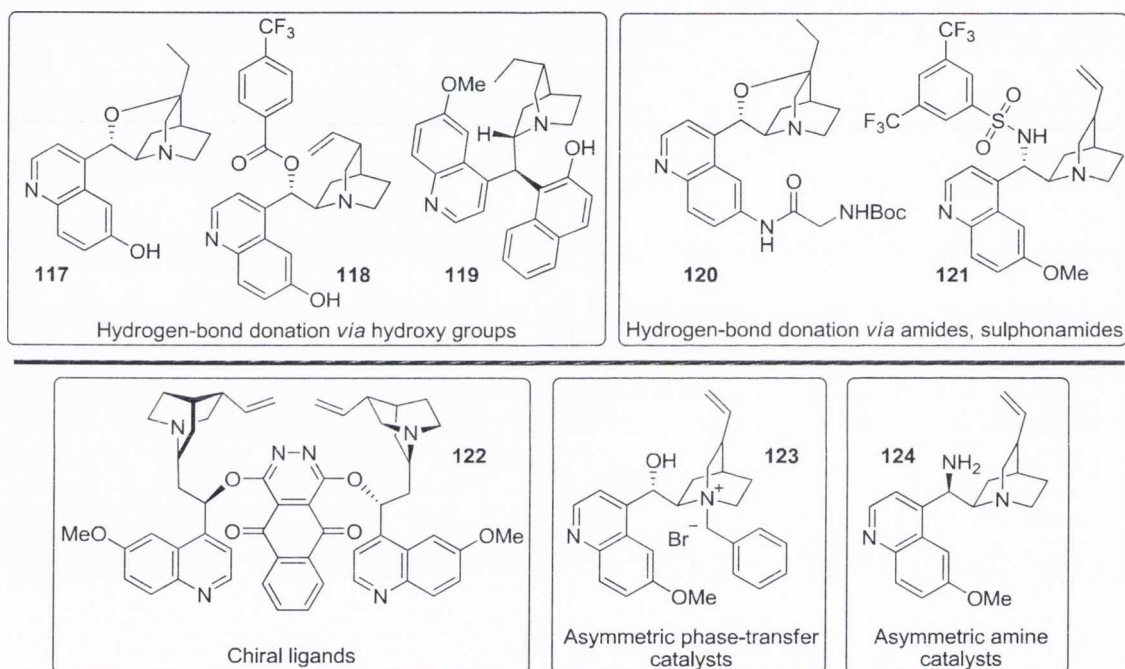


Figure 1.8 Structures of selected cinchona-based molecules devoid of the (thio)urea and squaramide units

Applications of cinchona-based molecules as either chiral ligands, phase transfer catalysts or monofunctional organocatalysts (*i.e.* chiral bases) have not been thoroughly discussed in this thesis. The ligand for Sharpless asymmetric dihydroxylations, chiral cinchoninium salts formed *via* alkylation of the nitrogen on the quinuclidine ring and deoxy cinchona alkaloids bearing a primary amine at C-9 (**122**, **123** and **124** respectively, in the lower part of Figure 1.8) are examples of such compounds. The applications of these molecules in asymmetric processes have been covered in several excellent reviews.^{112,162,163}

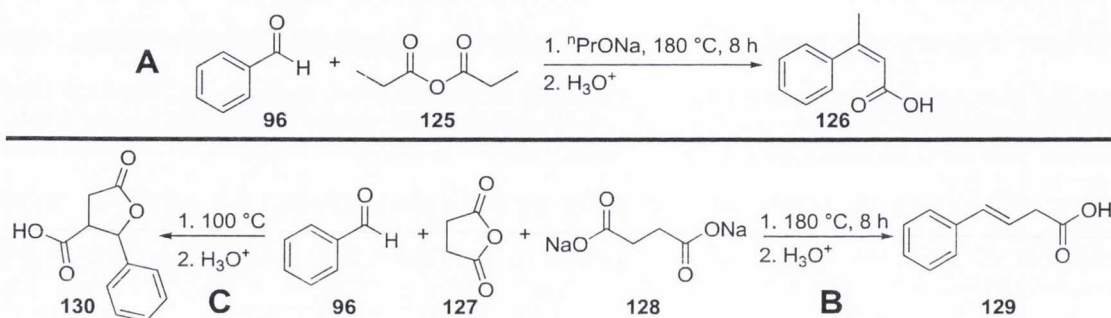
1.6 Cyclic anhydrides in formal cycloaddition reactions

Even in the contemporary era, where the concepts of *umpolung* reactivity and cascade reaction sequences which can lead to an inversion of functional group reactivity are firmly embedded in the mind of the chemist, many functional groups remain associated with a single reactivity mode. Carboxylic acid anhydrides belong to this category. Anhydrides are of enormous synthetic significance, as they (in general terms) occupy territory conveniently positioned between the highly reactive acyl halides and the more stable but considerably less reactive carboxylic acid ester electrophiles, and as such they have been used as electrophilic acyl transfer agents¹⁶⁴ for over a century.¹⁶⁵ While their chemistry is almost completely dominated by their electrophilicity, a relatively small number of cases involving the participation of enolisable anhydrides as carbon-based nucleophiles in aldol-like coupling processes have been reported.¹⁶⁶ Even though reactions involving the use of enolisable anhydrides as nucleophiles in formal cycloadditions are rather unexplored, they are extremely useful as they allow the efficient one-step synthesis of polysubstituted heterocyclic molecules - ubiquitous motifs in a broad spectrum of natural products - with (in most instances) the simultaneous creation of two new stereocentres.

1.6.1 Anhydrides acting as carbon-based nucleophiles: historical perspective

Enolisable anhydrides have been known to react as carbon-based nucleophiles with electron deficient π -systems such as aldehydes, imines, ketones and alkenes or alkynes.¹⁶⁶ Early examples of this type of reactivity date back to the late 19th century. In 1868, William H. Perkin was investigating the action of acetic anhydride on aromatic aldehydes.¹⁶⁷ Perkin observed for the first time that enolisable aliphatic anhydrides can behave as carbon-based nucleophiles at elevated temperatures in the presence of weak carboxylate bases.¹⁶⁸ This reaction was thoroughly studied by Perkin; it led to the first synthesis of coumarin (when using *o*-salicyl aldehyde) and it was later named in his honour as the 'Perkin reaction', an important transformation to prepare α,β -unsaturated carboxylic acids from aromatic and aliphatic aldehydes (Scheme 1.30, A).¹⁶⁹ During his investigations, Perkin observed that if benzaldehyde (**96**) and succinic anhydride (**127**) were heated at 180 °C in the presence of sodium succinate (**128**), a product would form (*i.e.* **129**) which was a structural isomer of **126** produced from the same reaction using

propionic anhydride (**125**) and sodium propionate (Scheme 1.30, B). He speculated that such discrepancy was the result of a decarboxylation reaction. Some years later, Fittig and co-workers, made important contributions toward the elucidation of the mechanism of the Perkin reaction and ultimately concluded that the reaction is an addition process, similar to an aldol condensation, involving an intermediate β -hydroxy compound that forms the α,β -unsaturated acid upon loss of a water molecule.¹⁷⁰

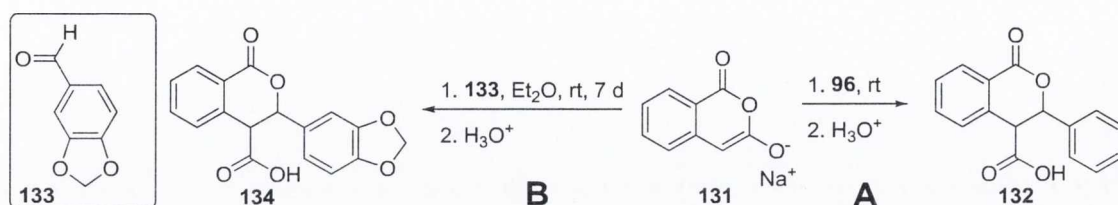


Scheme 1.30 Reactivity of anhydrides as carbon-based nucleophiles reported by Perkin (**A**, **B**) and Fittig (**C**)

Fittig repeated Perkin's experiment using succinic anhydride (**127**) and benzaldehyde (**96**) albeit at a lower temperature (*i.e.* 100 °C) and observed that, under those conditions, the major product formed was lactone **130** (Scheme 1.30, C), which would undergo decarboxylation upon heating to afford the product firstly observed by Perkin (*i.e.* **129**).^{170,171} Shortly after, in agreement with the reactivity reported by Fittig, Erdmann *et al.* also observed the formation of γ -lactones when succinic anhydride and aromatic aldehydes were heated in the presence of sodium acetate.¹⁷²

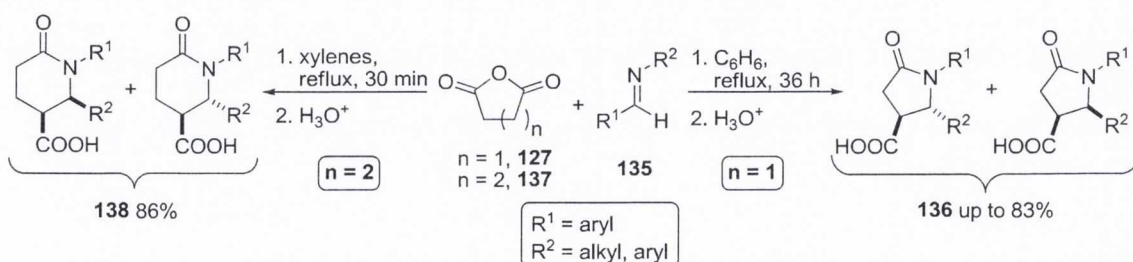
In 1931, Müller reported for the first time the use of homophthalic anhydride for the same type of cyclisation reactions. He observed that the sodium enolate of homophthalic anhydride **131** reacted readily with aldehyde **96** at room temperature and lead to the formation of a bicyclic dihydroisocoumarin **132**.¹⁷³ This reaction (depicted in Scheme 1.31, A) was analogous to the syntheses of γ -lactones involving succinic anhydride, reported by his predecessors. He also corroborated the concept that formal cycloaddition reactions between cyclic anhydrides and aldehydes occurred *via* the enolisation of the former, which was still debated at the time.¹⁷⁰ Much later, Pinder *et al.*¹⁷⁴ confirmed the reactivity observed by Müller when they reacted the sodium enolate

of homophthalic anhydride with piperonal (**133**) at room temperature to obtain the dihydroisocoumarin derivative **134** (as shown in Scheme 1.31, B).



Scheme 1.31 Homophthalic anhydride in a formal cycloaddition reaction with aldehydes as reported by Müller (A) and Pinder *et al.* (B)

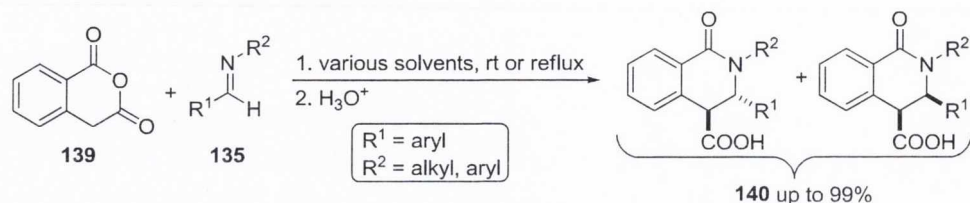
The first examples of formal cycloaddition reactions between cyclic anhydrides and imines were reported by Castagnoli and are depicted in Scheme 1.32. In 1969 he discovered that succinic anhydride (**127**) reacted under thermal conditions with aromatic *N*-alkyl and *N*-aryl imines (*i.e.* **135**) to form γ -lactams bearing a carboxylic acid **136**.¹⁷⁵ With this study, the author had the merit of a more thorough analysis of the stereochemistry of the products formed. Using NMR spectroscopic techniques, Castagnoli was able to establish that the annulation with imines afforded a mixture of *cis-trans* diastereomeric mixtures. The substrate scope of the reaction was further broadened when the same author reported that glutaric anhydride (**137**) was also able to undergo thermal annulations with imines to form a diastereomeric mixture of δ -lactams **138**.¹⁷⁶



Scheme 1.32 Succinic and glutaric anhydrides in a formal cycloaddition reaction with imines as reported by Castagnoli.

These discoveries were later paired with independent and almost simultaneous observations by Cushman¹⁷⁷ and Haimova,¹⁷⁸ who reported that the reaction between homophthalic anhydride (**139**) and imines such as **135** at room temperature afforded

diastereomeric mixtures of dihydroisoquinolonic acids **140** as shown in Scheme 1.33. Cushman was also responsible for proposing the mechanism of the reaction in a subsequent study.¹⁷⁹



Scheme 1.33 Homophthalic anhydride in formal cycloaddition reactions with imines as reported by Cushman and Haimova.

The reaction scope was further widened by Tamura,¹⁸⁰ who reported that homophthalic anhydrides reacted as formal dienes with alkenes and alkynes to produce fused aromatic products reminiscent of a Diels-Alder cycloaddition. This transformation was later called the ‘Tamura reaction’.¹⁶⁶

Our present knowledge of formal cycloaddition reactions between enolisable anhydrides and electron deficient π -systems has been shaped by these seminal discoveries. The highly substituted heterocyclic compounds formed as a result of this type of reactivity have been used in several syntheses of natural products and other molecules of biological interest.¹⁶⁶ The utility of cyclic anhydrides in formal cycloaddition reactions has been greatly enhanced recently thanks to the development of multicomponent reactions.¹⁶⁶ In the following Sections the formal cycloaddition with imines, aldehydes and ketones will be presented. The aspects related to the annulation reaction as reported by Tamura *et al.* will not be analysed in this thesis, however a excellent review has appeared which summarises this topic.¹⁶⁶

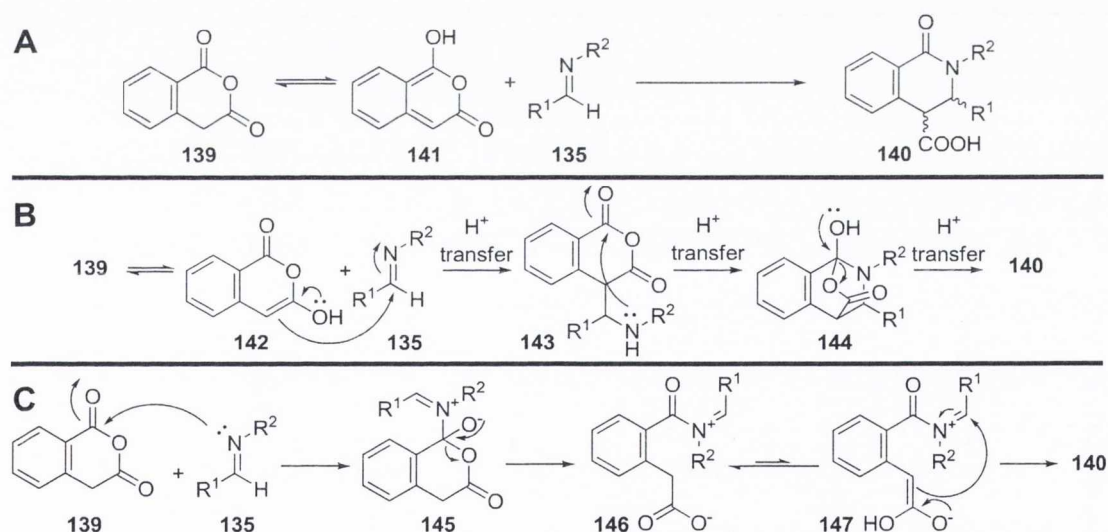
1.6.2 Reaction mechanism: current thinking

The reaction mechanism of the annulation reaction between cyclic anhydrides and electron deficient π -systems has never been directly confirmed, however pieces of evidence have been produced which favour one of the two mechanistic pathways depending on whether the substrate is either an aldehyde or an imine. As the name suggests, formal cycloadditions proceed with an apparent degree of synchronicity which

differ according to the substrates involved. While there has been tendency in the literature to consider the reaction with aldehydes to proceed *via* an asynchronous mechanism, the annulation with imines has been described as being both a concerted cycloaddition and a stepwise process.¹⁶⁶

1.6.2.1 Formal cycloaddition reaction with imines

The nature of the mechanism of the formal cycloaddition reaction between cyclic anhydrides and imines has been controversial. Historically, three different mechanisms have been invoked for this transformation. The three proposed pathways for the reaction with homophthalic anhydride (**139**) are depicted in Scheme 1.34: (A) a concerted [4+2] aza Diels-Alder reaction; (B) a stepwise process involving the attack of the enolised anhydride on the electrophilic imine and (C) the asynchronous iminolysis of the anhydride.



Scheme 1.34 Postulated mechanisms of the annulation reaction between homophthalic anhydride and imines

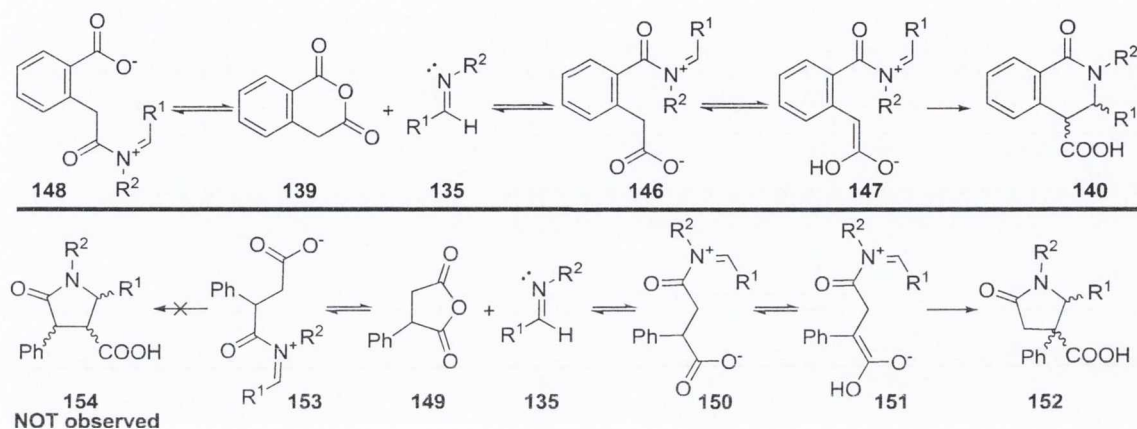
Current thinking regarding the mechanism of the reaction strongly supports the involvement of stepwise anhydride iminolysis (Scheme 1.34, C) as advanced by Cushman *et al.* in a seminal study.¹⁷⁹ The authors investigated the reaction between homophthalic anhydride (**139**) and a wide range of differently substituted aldimines **135** and rationalised the influence of electronic effects on both the rate and the

stereochemistry of the reaction. Cushman *et al.* postulated that the reaction between imines and cyclic anhydrides is triggered by the nucleophilic attack of the lone pair of the imine nitrogen on the anhydride, and that it proceeds in a stepwise fashion *via* ionic intermediates. The attack of the imine on the anhydride forms the internal *N*-acyl iminium carboxylate zwitterion **146** which is in a disfavoured equilibrium and undergoes the rate-limiting tautomerisation to enolate **147**. This species subsequently attacks the electrophilic iminium group and yields the lactam product **140** following an *endo*-trig cyclisation.

With a series of elegant experiments and thoughtful considerations, Cushman *et al.* were also responsible of ruling out the plausibility of the other two possible mechanisms. The concerted Diels-Alder reaction between imines and the dienol tautomer **141** of homophthalic anhydride (which has been proposed by Tamura *et al.* to be the reactant in the cycloaddition with a variety of dienophiles)¹⁸⁰ was deemed implausible because of (*inter alia*) the discrepancy observed in the reaction conditions for the Tamura reaction and the annulation with imines. Indeed, the fact that Tamura *et al.* reported the necessity of either high temperatures and long reaction times^{180a} or the presence of a strong base (*e.g.* LDA, sodium hydride)^{180c} even with very reactive dienophiles, was incompatible with experimental data showing that homophthalic anhydride and imines (*i.e.* a much weaker dienophile) readily reacted at room temperature and under neutral conditions. The second possible pathway (involving nucleophilic attack of the enolised anhydride **142** on the imine) was also considered improbable. Benzaldehyde (**96**) and an imine such as **135** were concurrently reacted with homophthalic anhydride (**139**) in the presence of triethylamine. It was reasonable to expect, on the basis of the enhanced electrophilicity of aldehydes compared to *N*-alkyl imines, that if both reactions were occurring by the same mechanism, lactone **132** would be the predominant species formed. However, since lactam **140** was the major product of the reaction, this assumption was proved inaccurate.¹⁷⁹

The reaction between aldimines and either homophthalic anhydride (**139**) or phenyl succinic anhydride (**149**) afforded diastereomeric mixtures of lactams such as **140** and **152** exclusively whereas other byproducts such as **154** were not reported. This observation is compatible with either a regioselective iminolysis of the anhydrides or at least, as Shaw *et al.*¹⁸¹ proposed for substituted succinic anhydrides, indicates the

reversibility of the nucleophilic attack of the imine as it is shown in Scheme 1.35. The presence of equilibria interconverting the two ionic species **153** and **150**, ultimately leads to the formation of **151** (stabilised by the phenyl ring) which subsequently causes the formation of the observed γ -lactams **152**.



Scheme 1.35 Regioselectivity of the anhydride iminolysis

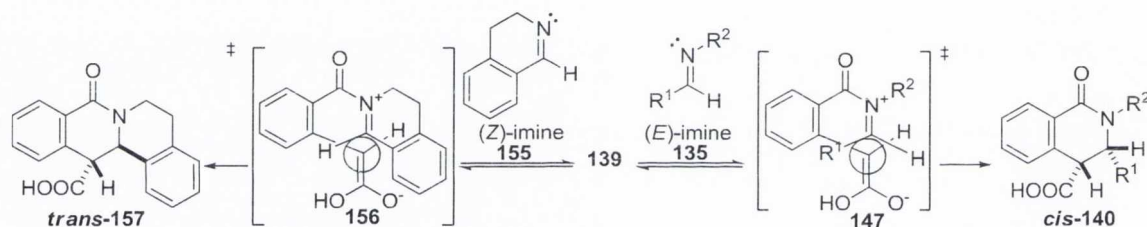
More recently Kaneti *et al.*,¹⁸² as part of a computational study of a model reaction involving MO and DFT calculations, suggested that the mechanism of the reaction would better fit the concerted cycloaddition model since ionic intermediate **147** was not observed as an energy minimum. Nonetheless, due to the fact that experimental results produced by this type of reaction have always been in accordance with the asynchronous mechanism proposed by Cushman, the theoretical hypothesis of Kaneti has not been widely accepted.¹⁶⁶

1.6.2.1.1 Stereochemical considerations

The almost simultaneous reports of the reaction between imines and homophthalic anhydrides (**139**) by Cushman *et al.*¹⁷⁷ and Haimova *et al.*,¹⁷⁸ produced ambiguous results regarding the selectivity of the reaction for the formation of either *cis*- or *trans*-diastereomers. While the former group of authors observed the preferential formation of *cis*-isomers (albeit with moderate diastereoselectivities), the latter reported the predominance of lactones possessing a *trans*-configuration. A similar inconsistency was also observed by the two authors for the reaction of cyclic imines such as

dihydroisoquinoline **155**: *trans*-isomers were reported by Cushman while Haimova observed the formation of *cis*-products.

Cushman *et al.* decisively explained this discrepancy and demonstrated that *cis*-isomers were kinetically favoured and would epimerise upon heating in either xylene or acetic acid or as a consequence of the basic extraction employed by Haimova *et al.* in their study.¹⁷⁹ The use of the cyclic imine **155** afforded preferentially *trans*-isomers, which could similarly epimerise. The author asserted that the origin of the selectivity relied on the geometry of the attacking imine. If the more thermodynamically stable (*E*)-isomer was responsible for the opening of the anhydride, an antiperiplanar attack of the enolate caused the formation of the lactone with a *cis*-geometry. This explanation, reported in Scheme 1.36, would also account for the opposite kinetic selectivity observed when using dihydroisoquinoline (*i.e.* an imine locked in the (*Z*)-configuration).^{166,179}



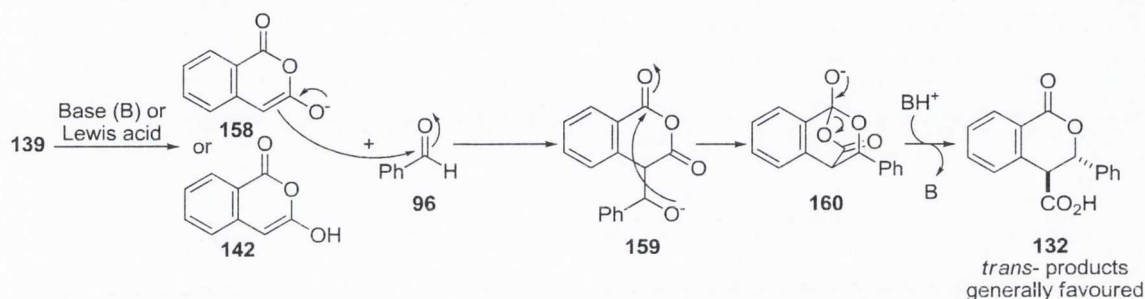
Scheme 1.36 Rationale behind the stereochemical outcome of the formal cycloaddition between homophthalic anhydride and imines

This hypothesis was further supported by the observation of lower *cis/trans* ratios when imines having smaller substituents on the nitrogen atom were employed. Indeed, with these substrates (*E*)- and (*Z*)-isomers can more easily interconvert. The preferential formation of *cis*-isomers could also be observed with the use of phenylsuccinic anhydride (**149**), albeit with a lower selectivity.¹⁷⁹

1.6.2.2 Formal cycloaddition reaction with aldehydes

The mechanism of the formal cycloaddition between cyclic anhydrides and aldehydes has generally been less controversial and, since the preliminary reports by Fittig, Erdmann, Müller and Pinder (*vide supra*), the reaction is generally deemed to proceed *via* the enolisation of the anhydride and its attack on the carbonyl group.¹⁶⁶ Aldehydes

are not nucleophilic enough to attack the anhydride, and thus a mechanism similar to the one postulated for imines had been ruled out *a priori*.¹⁶⁶ In Scheme 1.37 is depicted the reaction between homophthalic anhydride (**139**) and benzaldehyde (**96**). The initial enolisation of the anhydride followed by its addition to the aldehyde electrophile, generates the tetrahedral intermediate **159**, which then rapidly lactonises to form the dihydroisocoumarin species **132** in an intramolecular process.



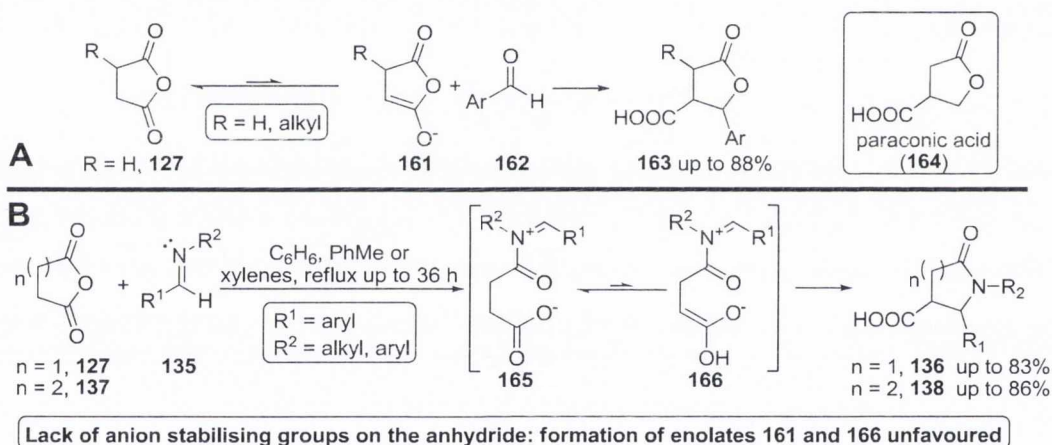
Scheme 1.37 Proposed mechanism of the annulation between homophthalic anhydride and aldehydes

This hypothesis is supported by (*inter alia*) the observation that homophthalic anhydride – the enol form of which (*i.e.* **142**) is stabilised by conjugation with the aromatic ring – is considerably more reactive substrates than simpler, non-benzo fused analogues (*i.e.* succinic anhydride). The formation of products having a *trans*- configuration, where phenyl group and carboxylic acid are both pseudoequatorial, is generally favoured.

1.6.3 Relationship between structure and anhydride reactivity

Imines and aldehydes have been employed in formal cycloaddition reactions in conjunction with several cyclic anhydrides, however the substrate scope of these reactions is generally limited to succinic, glutaric and homophthalic anhydrides. The postulation of reaction mechanisms for these annulation reactions involving enolisation has led to the introduction of moieties able to stabilise the reactive enolate species. This has had a beneficial effect on the rate of these annulation reactions, thereby allowing milder reaction conditions, higher yields and enhanced diastereoselectivities in the formation of both lactams and lactones.

The formal cycloaddition between succinic anhydride (**127**) and aromatic aldehydes such as **162** has been known since the late 19th century and has been sporadically reported since. The rate-limiting enolisation step to form **161** is disfavoured by the lack of a stabilising group on the anhydride (*e.g.* aromatic ring, electron-withdrawing group) and therefore the reaction generally requires either strong reagents or harsh reaction conditions. Among the reagents employed to promote these reactions are: strong bases (such as Na-, K- or LiHMDS) to cleanly deprotonate the anhydride,¹⁸³ a strong Lewis acid and triethylamine both in stoichiometric loadings^{184,185,186} or a weak base (*e.g.* sodium acetate) and high temperatures.^{171,172,187,188,189} The products, which are γ -butyrolactones (*i.e.* **163**) derivatives of paraconic acid (**164**), are formed in moderate to high yields and poor to excellent diastereoselectivities, depending on the reaction conditions employed (Scheme 1.38, A).

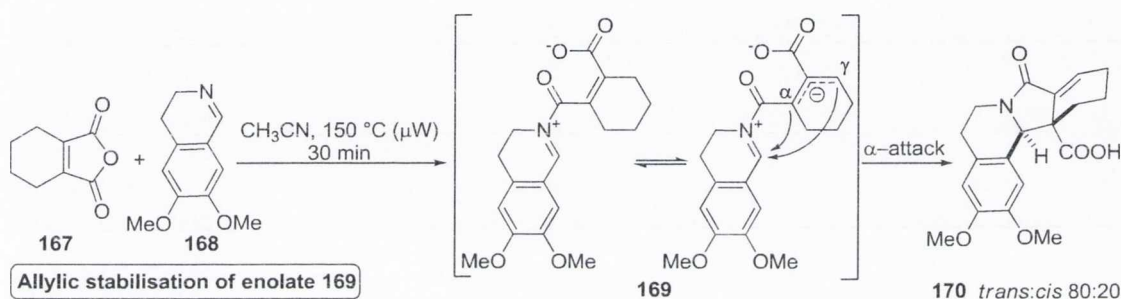


Scheme 1.38 Reaction between succinic anhydride and aldehydes (**A**) or imines (**B**)

Aromatic *N*-alkyl and *N*-aryl aldimines have been employed in the formal cycloaddition with either **127**^{175,190,191,192,193} or **137**.^{176,291,194,195} The rate-limiting tautomerisation to enolate **166** is unfavourable; thus high temperatures and long reaction times are required. The products, γ - and δ -lactams respectively, are generally formed in variable yields and diastereoselectivities (Scheme 1.38, B).¹⁶⁶

Shaw *et al.*¹⁹⁶ recently employed alkyl-substituted maleic anhydrides such as **167** in formal cycloadditions with aromatic (*Z*)-*N*-alkyl aldimines (*e.g.* **168**). In contrast to succinic and glutaric anhydrides, which lacked any anion stabilising groups, the author

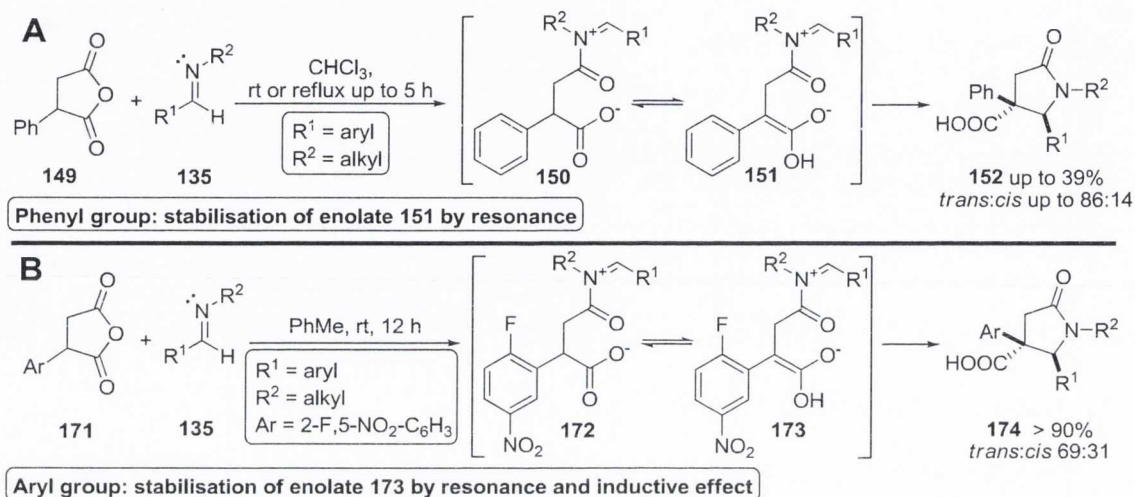
envisaged that the zwitterion enolate **169** formed upon iminolysis of anhydride **167** could benefit from allylic stabilisation (*i.e.* prototropic shift). Simultaneously, the nucleophilic attack from either the α - or γ - position of enolate **169** on the iminium ion, could generate products with diverse structural frameworks. From their study it is not clear whether allylic stabilisation played a significant role in promoting the reactivity of anhydride **167** since the reaction conditions involved high temperatures and microwave irradiation and only products arising from the attack from the α - position were obtained (*i.e.* **170**), as shown in Scheme 1.39. However, the presence of an olefin in **167** allowed, in some cases, the formation of unexpected compounds *via* reaction pathways different from that involved in formal cycloadditions.



Scheme 1.39 Reaction between substituted maleic anhydrides and imine **168**

Substituted succinic anhydrides such as phenylsuccinic anhydride (**149**), thioether-substituted and cyano-substituted succinic anhydrides have also been employed in the formal cycloaddition with imines. The presence of an aromatic ring, a thioether moiety or an electron-withdrawing group on the anhydride, accelerates the rate-limiting tautomerisation equilibrium by stabilising the reactive enolate. Phenylsuccinic anhydride (**149**) was initially employed by Cushman *et al.*¹⁷⁹ in conjunction with aromatic *N*-alkyl aldimines as shown in Scheme 1.40, A. The enhanced stabilisation of enolate **151** rendered **149** a more reactive anhydride than succinic anhydride (**127**): allowing the formation of γ -lactams **152** using milder reaction conditions than was otherwise possible. The yields and distereoselectivities of products **152** were low (with a preference for the *trans*-diastereomer) and highly dependant on both the substituent on the nitrogen atom and on the aromatic ring of the imine. In a subsequent study, Shaw *et al.*¹⁹⁷ detailed the importance of electronic factors on the reactivity of the anhydride component. The authors observed that the reactivity of phenylsuccinic anhydrides could be further enhanced by introducing electron-withdrawing substituents on the aromatic

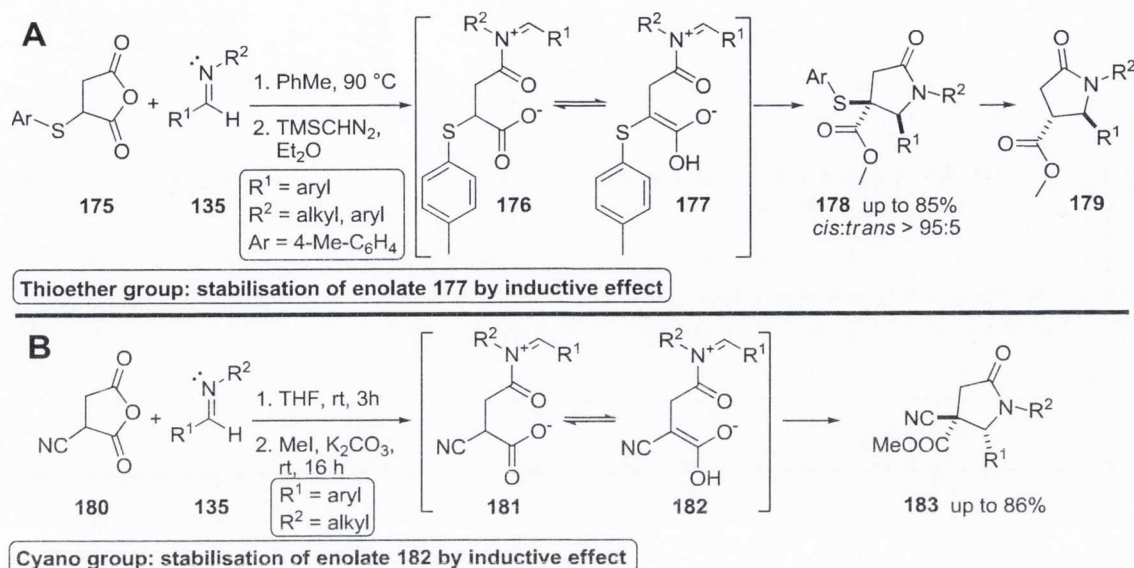
ring (e.g. nitro group, halogen atoms), by virtue of their ability to stabilise enolate **173**. The reaction with aromatic *N*-alkyl aldimines and 2-fluoro-5-nitrophenylsuccinic anhydride (**171**), (depicted in Scheme 1.40, B) could be accomplished at room temperature; γ -lactams **174** were produced in good yields and moderate diastereoselectivities with a preference for the *trans*-product.



Scheme 1.40 Reaction between phenylsuccinic anhydrides and imines as reported by Cushman *et al.* (A) and Shaw *et al.* (B)

After their preliminary report, Shaw *et al.* were also responsible for the evaluation of heteroatom-substituted succinic anhydrides in the annulation reaction with aromatic *N*-alkyl and *N*-aryl imines.¹⁸¹ The author envisaged that a thioether moiety on succinic anhydride could enhance its reactivity by increasing its acidity (*i.e.* stabilising enolate **177**). Indeed, thioether-substituted succinic anhydrides such as **175** (easily prepared from maleic anhydride and the corresponding thiol) reacted with aromatic aldimines to provide γ -lactams (which were esterified *in situ*) in good yields and unprecedented diastereoselectivities favouring the formation of *cis*-isomers **178** (Scheme 1.41, A).¹⁸¹ The use of a thioether moiety had the additional advantage of offering the practitioner the option of either a radical or a reductive cleavage of the carbon-sulfur bond to form the corresponding succinic anhydride-derived γ -lactams **179**, which can be accessed in either diastereomeric form if an additional epimerisation step is performed.¹⁸¹ Very recently, Shaw *et al.*¹⁹⁸ reported the use of cyano-substituted succinic anhydride **180** in the annulation reaction with aromatic *N*-alkyl aldimines. By virtue of the electron-withdrawing nature of this functional group, enolate **182** was stabilised and the formal

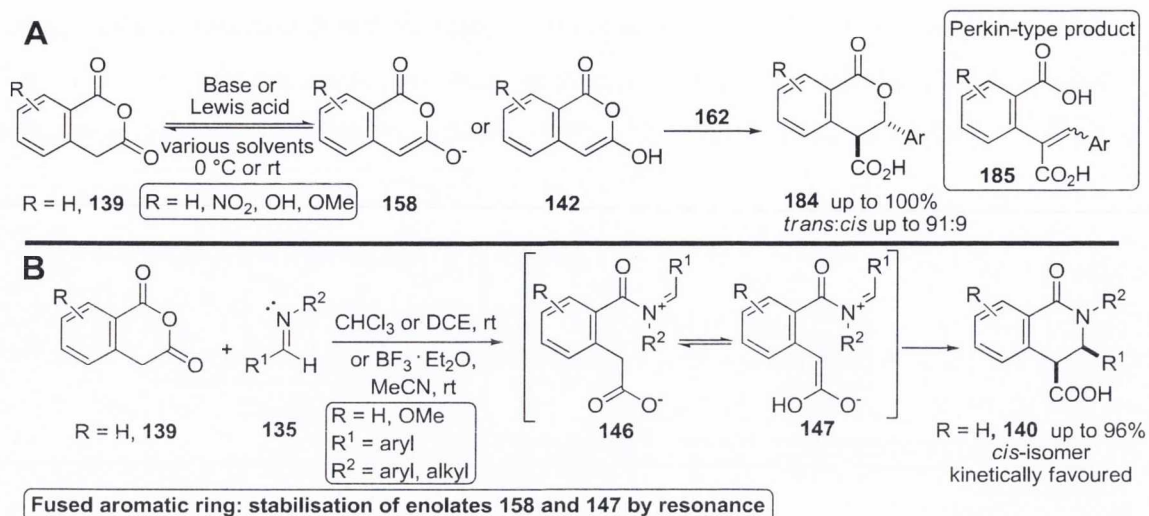
cycloaddition occurred readily at room temperature to afford γ -lactams (which were esterified *in situ*) in good yields as shown in Scheme 1.41, B.



Scheme 1.41 Reaction between thioether-substituted (**A**) and cyano-substituted (**B**) anhydrides and imines

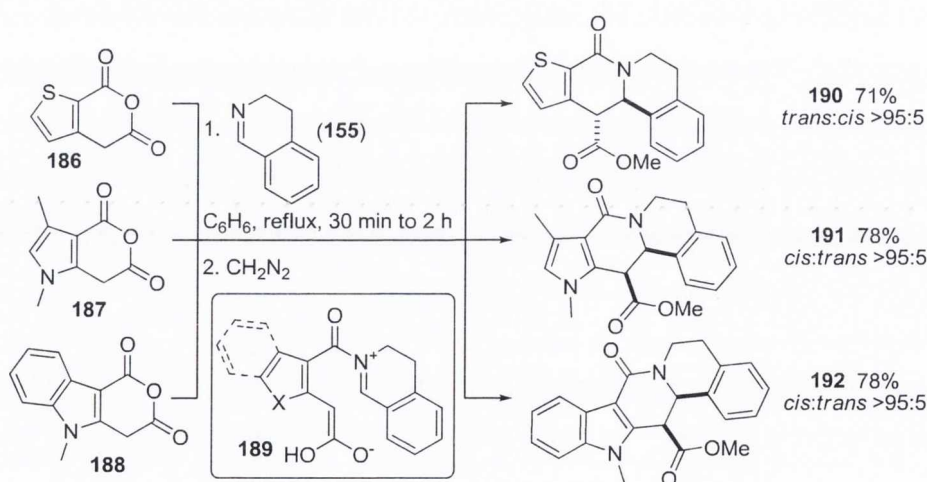
Homophthalic anhydrides have been widely employed in formal cycloadditions with both aromatic aldehydes and imines. The presence of the aromatic ring on the anhydride is beneficial for its reactivity with both aldehydes and imines since intermediates **142**, **147** and **158** are stabilised by resonance. Annulation reactions between homophthalic anhydrides and aromatic aldehydes **162** have been promoted by either bases^{199,200,201,202} or Lewis acid²⁰³ and occurred readily even at low temperatures (Scheme 1.42, A). Regardless of the type of catalysis employed, products **184** were generally formed in good to excellent yields and diastereoselectivities. In some cases, when a base (*e.g.* sodium hydride, sodium carbonate or DMAP) was used to promote the reaction, Perkin-type reactivity was observed and α,β -unsaturated carboxylic acids (*i.e.* **185**) were formed.

The annulation between homophthalic anhydrides with aldimines and ketimines is depicted in Scheme 1.42, B. The stabilisation of the reactive enolate **147** by resonance, renders homophthalic anhydrides much more reactive than simpler, non-benzo fused analogues and allows the formal cycloaddition with imines to occur readily at room temperature in good to excellent yields; often in the absence of a catalyst.



Scheme 1.42 Reaction between **139** and aldehydes (A) or imines (B)

Heteroaromatic analogues of homophthalic (*i.e.* **186**, **187** and **188**) have been employed by Tamura *et al.*²⁰⁴ in annulation reactions with dihydroisoquinoline (**155**). The presence of a heteroaromatic moiety can stabilise the reactive enolates **189**; nonetheless, the reaction conditions employed are significantly more harsh than those reported for the analogous reaction with homophthalic anhydride (**139**). This fact is most likely due to the electron-rich nature of the heteroaromatic systems employed which reduces the stabilisation potential of enolates such as **189**. The products (which were esterified *in situ*) could be prepared in good yields and high diastereoselectivities (Scheme 1.43). The observation in some cases of the formation of *trans*-diastereomers (*i.e.* **190**) is likely consistent with an *in situ* epimerisation of the initially formed *cis*-isomer.¹⁶⁶

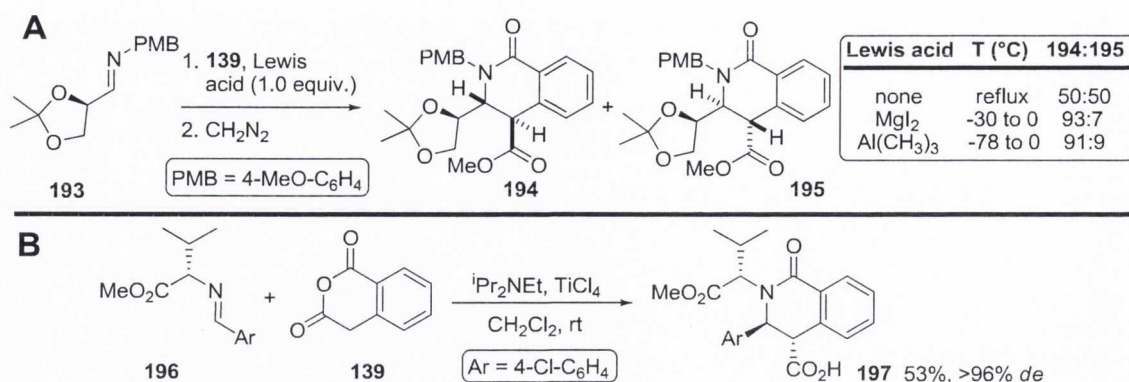


Scheme 1.43 Reaction between heteroaromatic analogues of homophthalic anhydride and a (*Z*)-imine

1.6.4 Diastereo- and enantioselective variants of the reaction

Formal cycloaddition reactions have been employed as key transformations in the total synthesis of numerous natural products and drug leads. In this field, the imine-based methodology and the Tamura reaction have received considerably more attention than the aldehyde-based variant. Despite the fact that these annulation reactions normally lead to the creation of two stereocentres (not in the Tamura reaction) and in spite of the high synthetic potential of the densely functionalised heterocyclic products formed (whose structural units are present in a broad spectrum of chiral natural products), no asymmetric variant of formal cycloaddition reactions with either imines or aldehydes has been reported. Even though, in some instances, outstanding diastereoselectivities have been described (*i.e.* diastereomeric excesses beyond 90%) arising from reactions employing either imines and anhydrides, these selectivities are most often resulting from a combination of fortuitous circumstances, the optimisation of reaction conditions (*e.g.* temperature, solvent), the variation of substituents on the reagents and the involvement of epimerisation reactions. Studies aimed to develop a diastereo- and enantioselective protocol for formal cycloaddition synthesis have been only sporadically reported.^{205,206,207}

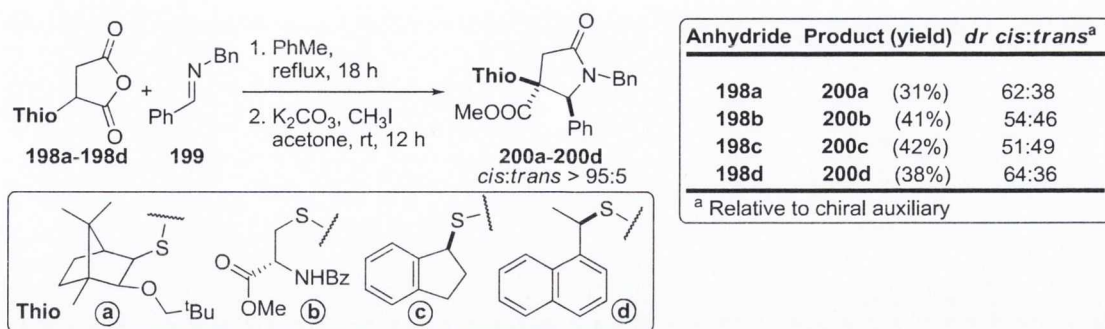
In a study aimed at preparing the core structure of a natural product, Clark *et al.*²⁰⁵ employed an imine derived from a chiral aldehyde (*i.e.* **193**) and evaluated its performance in the formal cycloaddition with homophthalic anhydride (**139**), as shown in Scheme 1.44, A. Preliminary results indicated that the desired product **194** was formed (after the esterification of the carboxylic acid with diazomethane), albeit with no diastereocontrol. The authors envisaged that the introduction of a Lewis acid that could form a chelate complex with the nitrogen and the α -alkoxy group on the imine could possibly enhance the stereoselectivity in the formation of the desired *cis*-isomer **194**. The author observed that the use of a Lewis acid additive such as MgI₂ or Al(CH₃)₃ at low temperatures was beneficial to the diastereoselectivity of the process and the ratio of **194**:**195** was increased up to 93:7. However, the simultaneous dramatic change of the reaction conditions does not allow us to draw any conclusions on the impact of the Lewis acid on the mechanism and the stereochemical outcome of this reaction.¹⁶⁶



Scheme 1.44 Evaluation of the asymmetric induction provided by a chiral imine

Cossío *et al.*²⁰⁶ discovered a protocol to prepare lactams products having the unusual *trans*- stereochemistry *via* formal cycloaddition between homophthalic anhydride (**139**) and imines which involved the use of stoichiometric amounts of a base ($i\text{Pr}_2\text{NEt}$) and a Lewis acid (TiCl_4) and were able to achieve products in high diastereoselectivity with two selected imine substrates. These reaction conditions, combined with the use of an enantiopure imine derived from a chiral amine (*i.e.* **196**), allowed the authors to access product **197** with excellent distereoselection (Scheme.1.44, B); conversely the use of an imine derived from a chiral aldehyde in the same transformation afforded *trans*-lactams with low *de*'s.

Very recently Shaw *et al.*²⁰⁷ evaluated the effect of chiral sulfide-substituted anhydrides on the diastereoselective synthesis of γ -lactams as depicted in Scheme 1.45. The author, inspired by the unprecedented diastereoselectivities obtained with the use of thioether-substituted succinic anhydrides in annulation reactions with imines (*vide supra*), was prompted to analyse the feasibility of accessing enantiomerically enriched products by using thiols as chiral auxiliaries. The assessment of the diastereoselectivity of the reaction was accomplished using imine **199** and thioether-substituted succinic anhydrides **198a-d**.



Scheme 1.45 Evaluation of the use of thiols as chiral auxiliaries in annulation reactions

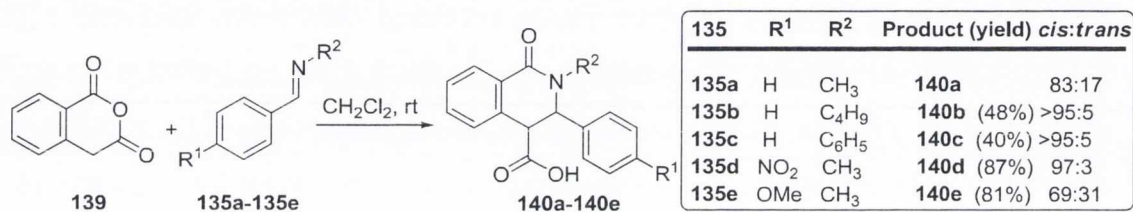
Even though the *cis:trans* ratio of the products formed **200a-d** was uniformly high (>95:5), the diastereomeric ratios relative to the chiral thiol auxiliaries were very modest and the yields of γ -lactams obtained were poor; irrespective of the structure of the thiol auxiliary employed.

At the outset of this work, no methodology for the catalytic asymmetric cycloaddition of either aldehydes or imines was known. The lack of such an enantioselective protocol for the formal cycloaddition of cyclic anhydrides with imines and aldehydes represents a significant drawback for the implementation of these methodologies in the synthesis of enantiomerically pure natural products.

1.6.5 Formal cycloaddition reactions between imines and enolisable anhydrides

The annulation reaction between cyclic anhydrides and a wide range of imines has been reported: aromatic aldimines have been predominantly employed for this reaction and sporadic examples involving ketimines have also been described. Aliphatic aldimines derived from enolisable aldehydes have proven to be problematic substrates because of the potential formation of enamides after the iminolysis of the anhydride and the formation of iminium ions.¹⁶⁶ The most seminal study in this field was carried out by Cushman *et al.*¹⁷⁹ who evaluated a wide range of different aromatic aldimines in the formal cycloaddition reaction with homophthalic anhydride (**139**) and phenylsuccinic anhydride (**149**) and noted the influence on products diastereomeric excesses of the substituents on the imine component. Higher diastereomeric ratios were observed with the use of imines derived from benzaldehydes bearing electron-deficient (Scheme

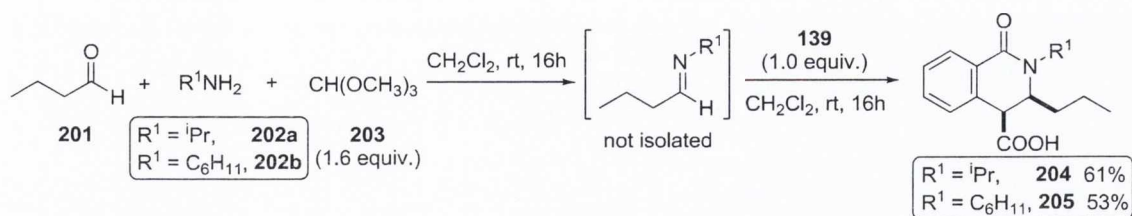
1.46). The steric bulk of the substituent on the nitrogen atom contributes to both the reactivity of the imine and the diastereoselectivity of the transformation. A small group (such as the methyl) on **135a** generated lactam **140a** in moderate diastereoselectivity, however, in a subsequent experiment, **135a** reacted much faster than **135b** bearing the bulkier *tert*-butyl group. Conversely, the latter substrate led to improved diastereoselectivities and the exclusive formation of **140b** as the *cis*-isomer. Electronic effects were also observed to play an important role: imine **135b** was found to be more reactive (despite its steric hindrance) than the less bulky, but also less nucleophilic imine **135c**.¹⁷⁹



Scheme 1.46 Annulation between **139** and aromatic aldimines: influence of the imine substituents on the reactivity and diastereoselectivity of the reaction

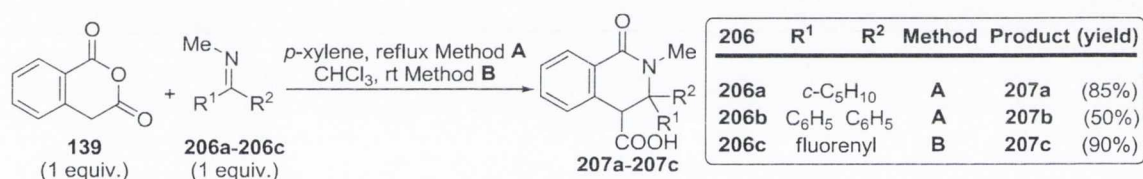
Lewis acids (*e.g.* BF₃·Et₂O) have been reported to act as catalysts for the annulation reaction of imines and homophthalic anhydride.²⁰⁸ The preferential formation of *trans*-isomers has been described in these reactions, however this phenomenon is most likely caused by an *in situ* acid-promoted epimerisation of the kinetically favoured *cis*-products.¹⁶⁶

The use of aliphatic imine for the annulation with homophthalic anhydride has been recently described by Gesquiere *et al.*,²⁰⁹ who used aldehyde **201**, primary amines **202a** or **202b** and trimethyl orthoformate (**203**) to form imines *in situ*. The reaction with homophthalic anhydride (**139**) led to the formation of δ -lactams **204** and **205** selectively as *cis*-isomers (Scheme 1.47). The product yields were modest, however this study was the first and currently only one known to date where linear aliphatic aldehydes have been successfully used in this reaction.



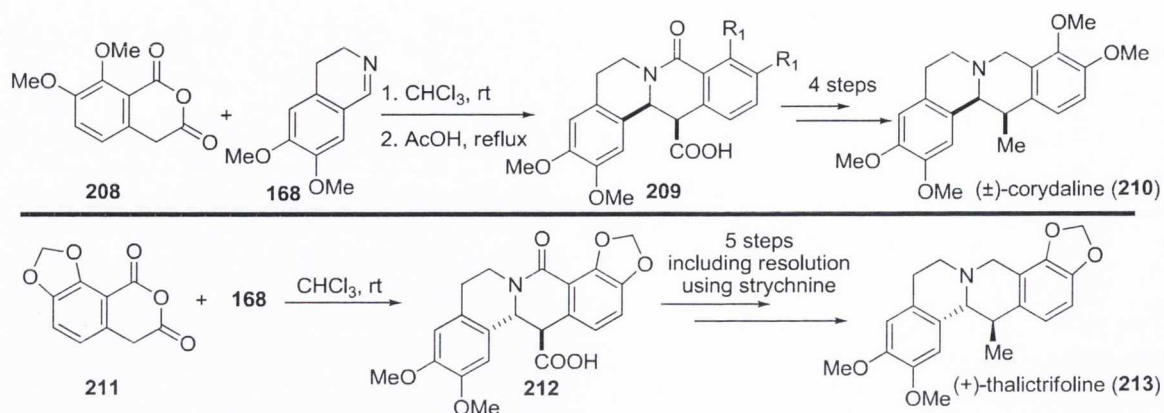
Scheme 1.47 *In situ* formation of aliphatic aldimines for annulation reactions with **139**.

Examples of formal cycloaddition reactions involving ketimines and homophthalic anhydride (**139**) have been described.^{177,210,211,212} The creation of products having a quaternary stereocenter could be achieved using ketimines, however the reduced reactivity of these substrates compared to aldimines, resulted in either longer reaction times and higher temperatures or the formation of lactams in lower yields. Cushman *et al.*¹⁷⁷ reported a preliminary study employing both aromatic and aliphatic ketimines in annulation reactions with **139** (Scheme 1.48).



Scheme 1.48 Annulation reaction between anhydride **139** and ketimines

The formal cycloaddition reactions between imines and cyclic anhydrides have been employed as key transformation for the synthesis of drug leads and natural products, especially alkaloids. Diastereoselective syntheses could be achieved using these transformations, however the lack of an enantioselective methodology, resulted in the synthesis of natural products in their racemic form, unless a chiral agent (*e.g.* strychnine) was employed to resolve the mixture of carboxylic acids formed upon formal cycloaddition. The structures of some of these molecules are shown in Scheme 1.49. A more detailed presentation of these types of application is beyond the scope of this thesis, however a recent review thoroughly covers this field.¹⁶⁶



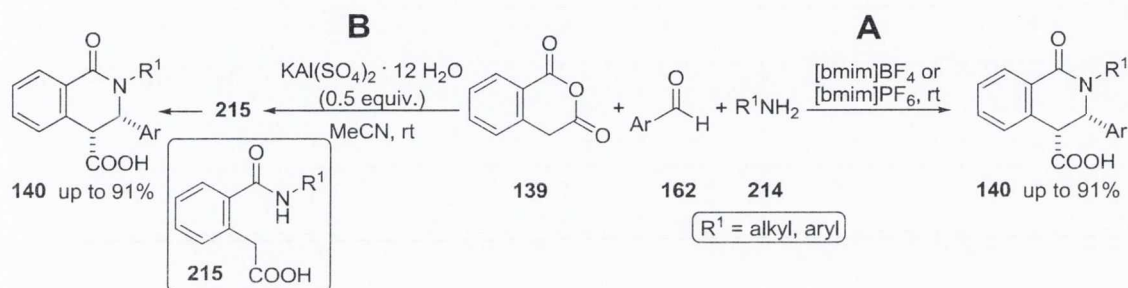
Scheme 1.49 Annulation reactions using imines for the synthesis of natural products

1.6.5.1 Cyclic anhydrides and imines in multicomponent reactions

Multicomponent reactions (MCRs) are important transformations that, starting from three or more reactants, allow the highly atom economical, one-pot synthesis of products. These reactions differ from ‘cascade’ or ‘domino’ processes, since in MCRs the components are combined simultaneously and their order of addition does not influence the outcome of the reactions. Furthermore, the components are, to a certain extent, independently variable; which maximises the potential structural diversity of the products formed.²¹³ These transformations have been known for over a century, and their use has recently gained prominence with the surge of combinatorial chemistry, diversity-oriented synthesis and high throughput screening techniques.²¹³

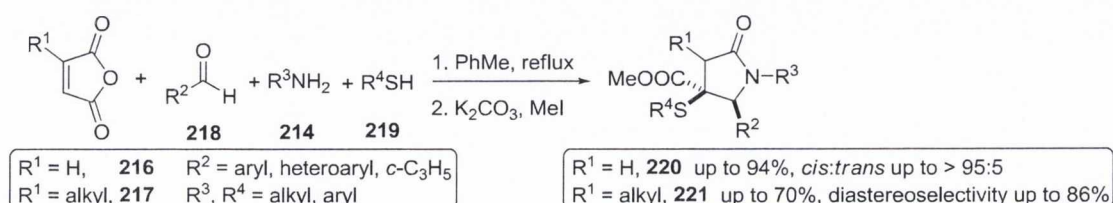
Recently, MCRs have been developed for the synthesis of dihydroisoquinolonic acids such as **140**. Yadav *et al.*²¹⁴ devised the use of a three component condensation reaction (depicted in Scheme 1.50, A) in which homophthalic anhydride (**139**), an aromatic aldehyde **162** and a primary amine **214** allowed the one-pot formation of δ -lactams structurally equivalent to those obtained *via* annulation reaction of imines and **139**. The reaction proceeded under mild conditions: the three components were mixed and reacted in an imidazolium-based ionic liquid at room temperature to form lactams **140** in high yields exclusively as *cis*-isomers. Yadav *et al.* did not postulate a mechanism for this process, however, in a subsequent study Azizian *et al.*²¹⁵ developed an analogous Lewis acid-promoted MCR and analysed the intermediates of this transformation by NMR spectroscopy. The author reacted **139**, an aromatic aldehyde **162**, a primary amine

214 and alum ($\text{KAl}(\text{SO}_4)_2 \cdot 12 \text{H}_2\text{O}$) as a Lewis acid in acetonitrile at room temperature as shown in Scheme 1.50, B. Analysis of the reaction by ^1H -NMR spectroscopy ruled out the involvement of an *in situ* formed imine as the reaction intermediate and pointed out the regioselective opening of **139** to form emiamide **215** which could be detected and isolated. This intermediate was speculated to subsequently react with the aldehyde component and cyclise *via* the iminium ion postulated by Cushman *et al.* (*vide supra*) to form *cis*-isomers of dihydroisoquinolonic acids **140**.



Scheme 1.50 Three component reactions for the synthesis of dihydroisoquinolonic acids (*i.e.* **140**)

Shaw *et al.*¹⁸¹ developed a four component reaction for the one-pot synthesis of tetra- and penta-substituted γ -lactams (**220** and **221** respectively) possessing either two or three adjacent stereocenters. The thermal reaction of maleic anhydrides **216** or **217**, an aldehyde **218**, a primary amine **214** and a thiol **219**, followed by the *in situ* esterification of the carboxylic acid products, allowed the synthesis of lactams **220** and **221** equivalent to those formed by annulation reaction between an imine and a thioether-substituted succinic anhydrides (*vide supra*). Aromatic and aliphatic amines and aromatic aldehyde were well tolerated by this methodology. Aromatic and sterically-hindered thiols provided the best results in terms of diastereoselectivity, with the predominant formation of *cis*-isomers. The use of a 3-alkyl-substituted maleic anhydride (*i.e.* **217**) allowed the synthesis of penta-substituted γ -lactams in moderate to good yields and good diastereoselectivity. The overall reaction is shown in Scheme 1.51.

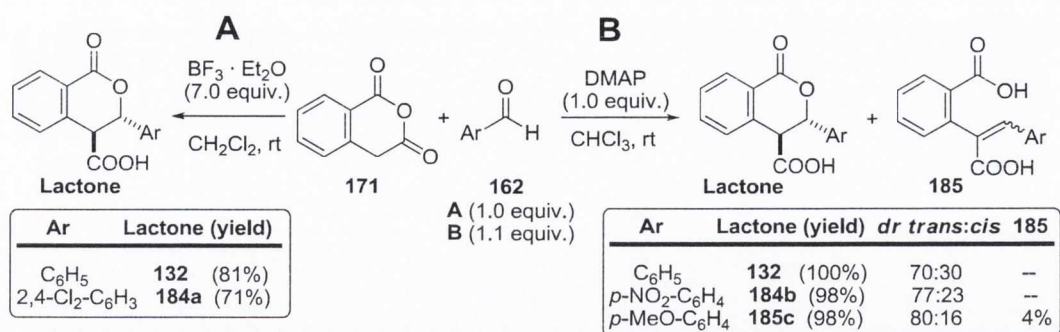


Scheme 1.51 Four component reaction for the synthesis of γ -lactams

Since its discovery, this versatile MCR has been further expanded by Shaw *et al.*²¹⁶ and implemented in the synthesis of natural products.²¹⁷

1.6.6 Formal cycloaddition reactions between aldehydes and enolisable anhydrides

Despite the historical importance held by aldehydes in formal cycloaddition reaction with anhydrides, transformations involving this functional group as the electrophilic species have received significantly less attention than those where imines are employed. Similarly, the substrate scope for annulation reactions with aldehydes is also considerably more limited and is restricted to aromatic aldehydes and succinic or homophthalic anhydrides. Without considering the early examples of this reaction,¹⁷¹⁻¹⁷³ the majority of other studies have been aimed to the specific synthesis of products containing the lactone moiety as intermediates along the synthetic pathways leading to other target molecules.^{174,183,185-189,199} Formal studies which thoroughly examined this type of reaction and its mechanism have not been produced and only a handful of reports dealing specifically with the formation of lactones *via* this transformation have been published.^{184,200-203} Among these, perhaps the most known and complete studies have been reported by Gesquiere *et al.*²⁰³ and Palamareva *et al.*,²⁰² these examine the possibility of promoting the reaction between aromatic aldehydes **162** and homophthalic anhydride (**139**) by either Lewis acid or base catalysis. Gesquiere *et al.* reported that the annulation reaction could benefit from acid catalysis and used boron trifluoride etherate (*i.e.* $\text{BF}_3 \cdot \text{Et}_2\text{O}$) in excess (Scheme 1.52, A). Probably the Lewis acid played a dual role in the catalysis and induced the enolisation of **139** and activated the carbonyl of the aromatic aldehyde in the nucleophilic addition step. The products were formed in good to excellent yields, with the electron-deficient aldehyde **162a** showing a reduced reactivity than benzaldehyde (**96**) possibly because of weaker interactions with the Lewis acid. Data provided on the diastereoselectivity of the transformation were ambiguous since the analysis of the crude mixture was not reported and yields of the single diastereomers are provided after their purification by crystallisation.²⁰³



Scheme 1.52 Annulation reaction between **139** and aromatic aldehydes as reported by Gesquiere *et al.* (**A**) and Palamareva *et al.* (**B**)

Palamareva *et al.* investigated the catalytic performance of 4-dimethylaminopyridine (DMAP) under mild reaction conditions.²⁰² The authors evaluated the reaction between **139**, DMAP in stoichiometric loadings and a range of aromatic aldehydes at room temperature and observed that the annulation reaction occurred promptly and afforded δ -lactones in excellent yields irrespective of the electronic nature of the electrophile (Scheme 1.52, B). Electron-rich and electron-deficient aldehydes were compatible with this methodology as well as heteroaromatic aldehydes. The diastereoselectivities, which were analysed prior to purification of the products by crystallisation, ranged from moderate to excellent; with a general preference for the formation of *trans*-isomers. It is noteworthy that in some cases – predominantly when electron-rich and heteroaromatic aldehydes were employed – unsaturated products (*i.e.* **185**) formed *via* aldol condensation (Perkin-type reactivity) were reported.²⁰²

1.6.6.1 Dihydroisocoumarins and γ -butyrolactones: important frameworks in natural products

The bicyclic 3,4-dihydroisocoumarin structural unit (*i.e.* **222**) is present in a broad range of chiral natural products (and derivatives) possessing a remarkable range of (*inter alia*) cytotoxic/antiproliferative,^{218,219,220} phytotoxic,²²¹ antimicrobial,^{222,223} antifungal,²²⁴ antiulcer,^{225,226} antimalarial,²²⁷ anti-inflammatory,^{225,226} antioxidant²²⁸ and antiallergic²²⁹ properties. These natural products generally possess a hydroxy group at C-8 and an aryl or alkyl substituent at C-3 which is sometimes accompanied by a moiety appended on C-4 *via* a carbon-oxygen bond. This substitution pattern accounts for the presence of at

least one stereocentre on the dihydroisocoumarin core. The molecular structures of some of the members belonging to this class of compounds are depicted in Figure 1.9.

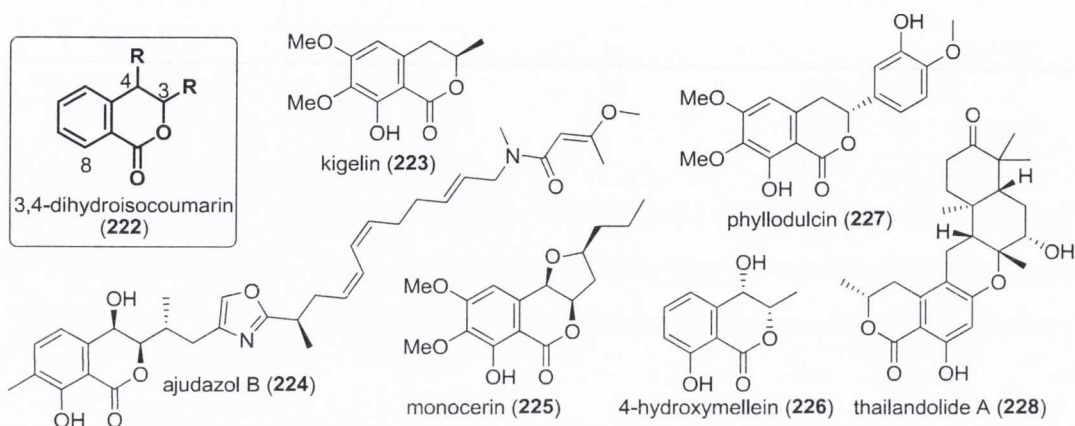


Figure 1.9 Natural products containing the 3,4-dihydroisocoumarin unit

Due to the relevance of optically active natural 3,4-dihydroisocoumarins, significant effort has been devoted over the past decades to their synthesis²³⁰ which includes the development of asymmetric strategies. In this field, commonly employed key transformations used include asymmetric *ortho*-lithiations of *o*-toluic acids protected with a chiral oxazoline²³¹ and the asymmetric Sharpless dihydroxylation of alkenes.^{232,233,234} Other methodologies have been successfully employed for the synthesis of chiral 3,4-dihydroisocoumarins such as (*inter alia*), rhodium-catalyzed intermolecular [4+2] annulations,²³⁵ alkylations of enantiomerically pure terminal epoxides,²³⁶ enzyme-promoted dynamic kinetic resolutions,²³⁷ chiral hypervalent iodine-mediated oxylactonisations²³⁸ and asymmetric organocatalytic bromocyclisations.²³⁹ Chiral dihydroisocoumarins could be accessed with excellent levels of enantioselectivity using these methodologies, however common drawbacks encountered in some of these processes include the involvement of complex multistep procedures, poor versatility, harsh reaction conditions and low yields due to the formation of byproducts.

The γ -butyrolactone structural unit is another important structural feature which is abundantly found in a wide range of natural products.^{240,241} Among these the carboxylic acid group-bearing paraconic acid derivatives are lichen-sourced molecules of particular interest which exhibit antitumour, antifungal and antibiotic properties.²⁴² The molecular

structure of these natural products generally includes an alkyl chain at C-4, a carboxylic acid group at C-3 and most often presents an *exo*-methylene substituent or a methyl group at C-2. The structures of some of the natural products containing the paraconic acid unit are depicted in Figure 1.10.

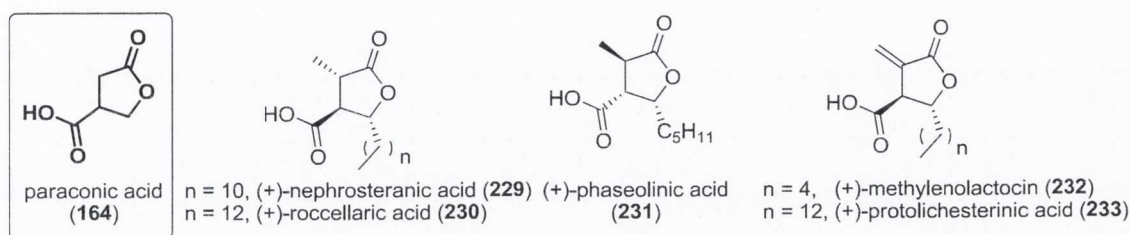
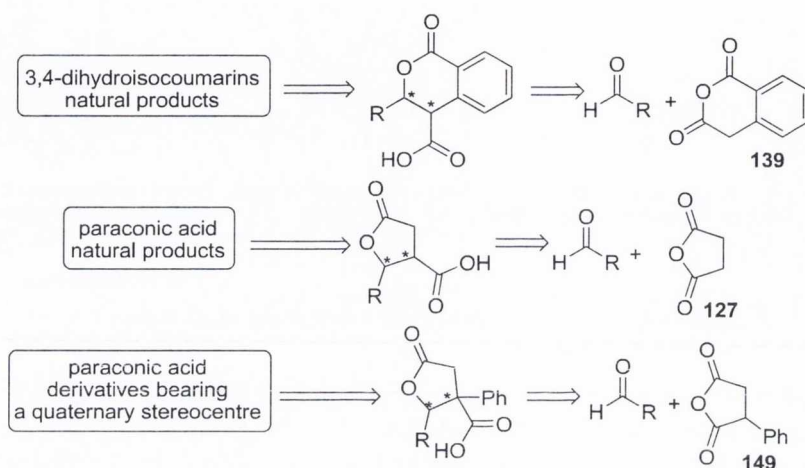


Figure 1.10 Natural products containing the paraconic acid unit

A number of syntheses have been developed for the preparation of paraconic acids either in racemic or enantioenriched form. Asymmetric strategies have been developed which involve the use of chiral auxiliaries (*e.g.* oxazolines),²⁴³ synthons from the chiral pool (*e.g.* mannitol, tartaric acid)^{244,245} or catalytic methodologies such as (*inter alia*) Sharpless epoxidations,²⁴⁶ copper(I)-catalysed asymmetric cyclopropanations²⁴⁷ and Sharpless dihydroxylations.²⁴⁸ A wide range of natural paraconic acids could be afforded in excellent optical purities using these methodologies, however, analogously to what has been described for the synthesis of 3,4-dihydrodcoumarins, these strategies often have the drawback of involving long multistep procedures.

A retrosynthetic analysis of molecules belonging to these two important class of natural compounds, confirms that formal cycloadditions between cyclic anhydrides and aldehydes is a desirable key transformation. The annulation using readily available homophthalic anhydride (**139**) allows for the mild and potentially high-yielding one-step synthesis of 3,4-dihydroisocoumarins bearing two adjacent tertiary stereocenters and represents a remarkable shortcut compared to the known methodologies used to access this class of molecules. Likewise, the formal cycloaddition reaction with succinic anhydride (**127**) has the appealing potential to afford paraconic acid derivatives bearing two stereocentres *via* a one-pot procedure. In addition, the use of a substituted succinic anhydride (*e.g.* **149**), will generate molecules with a quaternary stereocentre (this class of compounds have recently been evaluated as antitumour agents and one candidate possessed sub-micromolar activity against multiple cancer cell lines²⁴⁹). However,

despite these intrinsic advantages, the lack of an asymmetric protocol for this transformation and the limitations imposed by the narrow substrate scope of the racemic version (limited to the use of aromatic aldehydes), has prevented the use of this reaction for the synthesis of chiral natural compounds and analogous molecules.

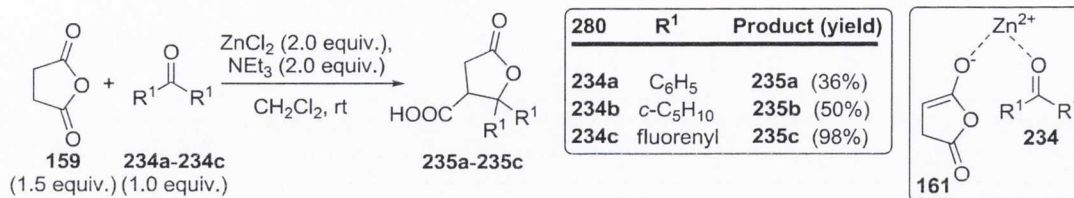


Scheme 1.53 Formal cycloaddition reactions with aldehydes as potential key transformations for the synthesis of natural products

1.6.7 Formal cycloaddition reactions between ketones and enolisable anhydrides

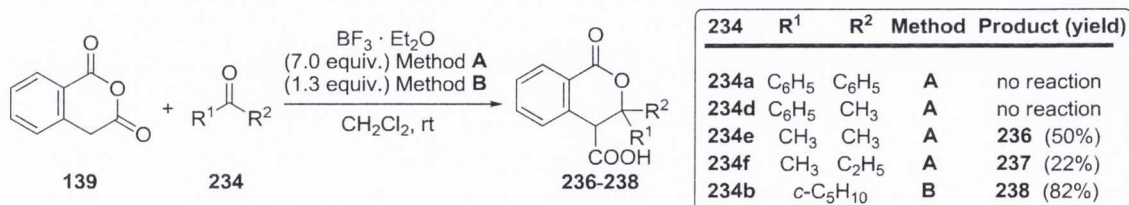
Formal cycloaddition reactions using ketones as substrates have received considerably less attention. Despite the intrinsic advantage of creating lactones bearing a quaternary stereocentre (when asymmetrically substituted ketones are employed), the reduced electrophilicity of non-activated alkyl and aryl ketones when compared to aldehydes has prevented their widespread use. Symmetric ketones have been employed for the first time by Lawlor *et al.*¹⁸⁴ in a formal cycloaddition reaction with succinic anhydride (**127**) promoted by triethylamine and a Lewis acid such as zinc chloride (Scheme 1.54). The proposed mechanism for this reaction involves the deprotonation of succinic anhydride by triethylamine and leading to enolate **161** which benefits from the stabilisation provided by the Lewis acidity of the zinc atom that is able to form bidentate complexes with both **161** and the ketone component **234**. A subsequent attack on the carbonyl leads to a cyclisation reaction and the formation of lactones **235a-c**. Benzophenone (**234a**), and cyclohexan-1-one (**234b**) reacted under these conditions to afford γ -lactones albeit in yields that were considerably lower than those obtained with

aldehydes. Conversely, the use of fluorenone (**234c**) as the ketone component afforded products in excellent yields, perhaps because of its flat structure which removed much of the steric hindrance and facilitated its reactivity with enolate **161**.



Scheme 1.54 Formal cycloaddition between succinic anhydride and ketones

In a subsequent report, Gesquiere *et al.*²⁰³ used ketones in annulation reactions with homophthalic anhydride (**139**) promoted by a Lewis acid (*i.e.* BF₃·Et₂O) as shown in Scheme 1.55 (Method A). Aromatic ketones such as benzophenone (**234a**) and acetophenone (**234d**) failed to react with **139**, whereas aliphatic ketones such as acetone (**234e**) and butan-2-one (**234f**) afforded δ -lactones (**236** and **237** respectively) in low to moderate yields. It is noteworthy that the use of butan-2-one by Gesquiere *et al.* represents the only known example of the use of an asymmetric ketone in these transformations. More recently, Palamareva *et al.*²⁵⁰ employed a similar Lewis acid-promoted methodology for the formal cycloaddition between **139** and cyclohexan-1-one (**234b**). The spiro-substituted δ -lactone **238** was formed in excellent yields as described in Scheme 1.55 (Method B) and was subsequently derivatised with a range of amines to form a small library of amides which were evaluated for their antimicrobial properties.



Scheme 1.55 Annulation reaction between homophthalic anhydride and ketones

The three aforementioned studies are the only reported examples of the use of ketones in annulation reactions with cyclic anhydrides.

1.7 Quaternary stereocenters: fighting against steric congestion

In the past decades the field of asymmetric synthesis has witnessed impressive developments and a broad range of chiral auxiliaries, reagents and catalysts have been devised for the enantioselective preparation of complex chiral molecules. In this field, the challenging task of creating asymmetric carbon-carbon bonds with excellent stereocontrol is perhaps the most crucial and its intrinsic difficulty is further exacerbated when the targeted chiral centre is a quaternary carbon atom. Indeed, despite the flourishing of novel asymmetric methods and the tremendous progress made, significantly few catalytic asymmetric protocols (often having narrow substrate scopes) have been described for the efficient creation of chiral quaternary stereocentres²⁵¹ and the synthesis of these structural features often represents the most challenging step of a synthetic procedure.²⁷⁴ Chiral quaternary stereocenters are ubiquitous in natural products²⁷⁶ and thus the development of reliable methods to access them is crucial for synthetic organic chemists. The extensive coverage of such a broad and important topic is beyond the scope of this thesis, however some general remarks will be briefly discussed together with few examples of syntheses of quaternary stereocentres with a particular emphasis on asymmetric organocatalytic methods for their preparation. Several excellent reviews^{252,253,254,255,256,257,258,259} and a book²⁶⁰ have been published which encompass in more detail this topic.

1.7.1 General remarks on the synthesis of all-carbon quaternary stereocentres

The term ‘quaternary stereocentre’ is often misleading because it can be used to address two types of chiral carbon atom: one bonded to four different carbon substituents and also, more generally, a carbon atom which is quaternary-substituted which allows for the presence of one carbon-heteroatom bond (*e.g.* tertiary alcohols). In order to avoid any source of confusion, those chiral carbon atoms which are bound to four different carbon substituents are generally named ‘all-carbon quaternary stereocentres’.²⁶⁰

While quaternary-substituted carbon stereocentres are significantly easier to access *via*, for instance, the face-selective addition of carbon-based nucleophiles to asymmetrically substituted carbonyl compounds, all-carbon quaternary stereocentres are intrinsically

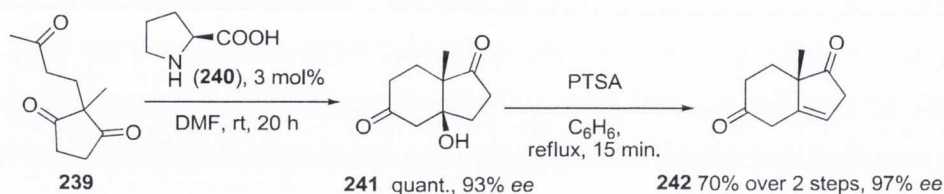
more difficult to synthesise mainly because of the steric repulsion between the carbon substituents encountered during the asymmetric carbon-carbon bond forming event. This impediment becomes even more challenging for the enantioselective synthesis of all-carbon stereogenic centres in acyclic systems²⁵⁹ (which are more complicated to access due to the degrees of freedom associated with these structures) and for the synthesis of multiple adjacent quaternary stereocentres,^{255b} where steric clashes are further exacerbated. The lack of hydrogen atoms and the relative stability and strength of carbon-carbon bonds, means that when a quaternary stereocentre is formed, its configuration becomes difficult (or impossible) to invert (*e.g.* by means of epimerisation reactions or bond cleavage). This phenomenon may be seen as an advantage since racemisation phenomena are generally undesired, however it also means that the overall efficiency of a synthetic protocol is determined by the level of stereoselectivity achieved in the transformation leading to the creation of the quaternary stereocentre.²⁶⁰

Frequently used carbon-carbon bond forming asymmetric reactions employed for the synthesis of quaternary stereocentres are (*inter alia*) cycloaddition reactions (*e.g.* Diels-Alder), Michael additions, Pd-mediated allylations, alkylations, cyclopropanations, aldol reactions and cascade cyclisations.²⁵²⁻²⁵⁹ Both chiral auxiliary- and catalyst-based methodologies have been employed for the synthesis of these types of stereocentres, nevertheless, the assembly of quaternary stereocentres still remains a considerably underdeveloped research area. The need for more general and versatile procedures for the synthesis of all-carbon quaternary stereocentres in order to access complex molecular structures has prompted the research of novel asymmetric transformations and chiral (organo)catalysts and the progress witnessed in this field in the past decades have been resumed in detail in the aforementioned reviews.²⁵²⁻²⁵⁹

1.7.2 Organocatalysis as a tool for the synthesis of quaternary stereocentres

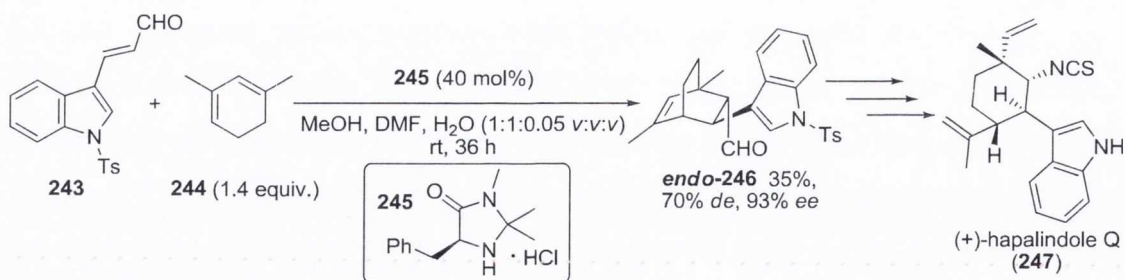
One of the first examples of asymmetric organocatalytic transformations, the Hajos-Parrish-Eder-Sauer-Wiechert reaction, was employed for the creation of molecules bearing two quaternary stereocentres (albeit only one of the 'all-carbon' type) *via* a proline-catalysed asymmetric intramolecular aldol reaction (Scheme 1.56).²⁶¹ Achiral triketone **239** was reacted with the natural amino acid L-proline (**240**) in loadings as low as 3 mol% and cyclised to form the quaternary stereocentre-containing **241** in

quantitative yield and excellent enantioselectivity (Scheme 1.60). This molecule could be further dehydrated to form the Robinson annulation product **242** (*i.e.* Wieland-Miescher ketone) in high yields.



Scheme 1.56 The proline-catalysed Hajos–Parrish–Eder–Sauer–Wiechert reaction

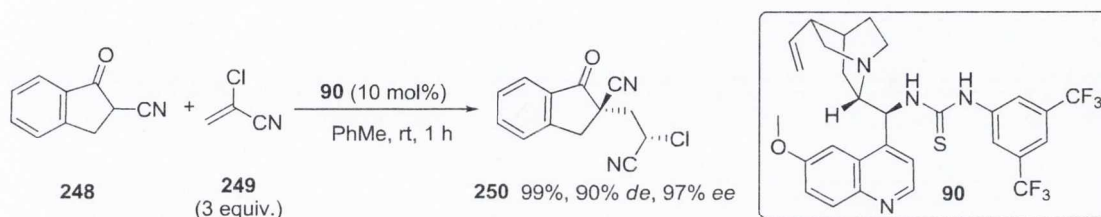
More recently, the enantioselective organocatalysed Diels–Alder reaction has been employed for the asymmetric synthesis of the marine alkaloid (+)-hapalindole Q (**247**) as shown in Scheme 1.57.²⁶² Kerr *et al.* built upon the observation by MacMillan *et al.*²⁶³ that imidazolidinone **245** could promote the Diels–Alder reaction using a α,β -unsaturated aldehyde as the dienophile and used the same catalyst in an analogous reaction using **243** and **244** as the dienophile and diene respectively. This transformation led to the synthesis of the highly complex adduct *endo*-**246** bearing four contiguous chiral centres (one of which was an all-carbon quaternary stereocentre) with excellent stereocontrol, albeit in poor yields. Adduct *endo*-**246** was further modified to access the desired (+)-hapalindole Q in six additional steps.



Scheme 1.57 Synthesis of **247** via an asymmetric organocatalytic Diels–Alder reaction

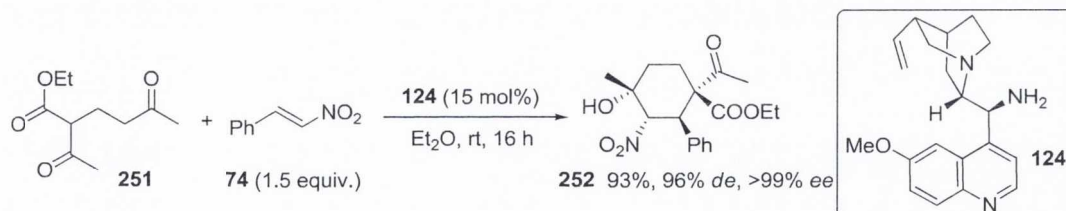
The asymmetric organocatalytic conjugate addition of activated carbonyl compounds to Michael acceptors have been reported by many authors as a powerful transformation to generate molecules having a quaternary stereocentre; often with the simultaneous creation of additional stereocentres.²⁵⁸ Deng *et al.*²⁶⁴ described the Michael addition

reaction between 2-cyanoindanone (**248**) and α -chloroacrylonitrile (**249**) promoted by the thiourea-substituted cinchona alkaloid (**90**) and accessed Michael adducts such as **250** bearing two stereocentres (whereof one of the ‘all-carbon quaternary’ type) in high yields and excellent diastereo- and enantiocontrol (Scheme 1.58). The methodology proved to be extremely robust and a diverse array of α -cyano-substituted ketones and esters were compatible as Michael donors providing enantioselectivities of >94%.



Scheme 1.58 Asymmetric catalytic Michael addition reaction catalysed by **90**

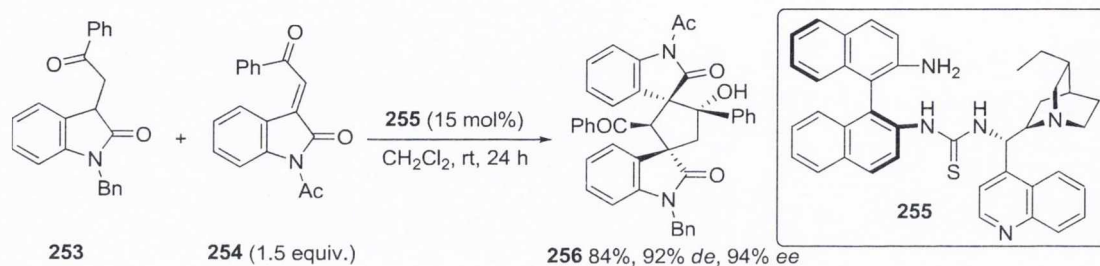
The quinine-derived catalyst **124** was employed by Zhong *et al.*²⁶⁵ to promote the asymmetric tandem Michael addition-Henry reaction between trans- β -nitrostyrene (**74**) and diketoester **251** as shown in Scheme 1.59. This cascade process afforded highly-functionalised cyclohexanes such as **252** bearing four contiguous stereocentres including two quaternary centres.



Scheme 1.59 Asymmetric tandem Michael addition-Henry reaction catalysed by **124**

More recently Barbas *et al.*²⁶⁶ described an impressive asymmetric organocatalytic cascade reaction for the synthesis of spiroxindoles (a common unit embedded in a multitude of drugs and natural products) with the simultaneous creation of three quaternary stereocentres (two of these of the ‘all-carbon’ type). The preliminary evaluation of the catalytic activity of more common cinchona alkaloid-based molecules in the tandem Michael-addition-Henry reaction between 3-substituted oxindoles such as **253** and methyleneindolinones as in **254**, induced the authors to prepare the new catalyst **255** bearing a binaphthyl primary amine and a thiourea hydrogen-bond donor

on the cinchona alkaloid scaffold. This species could bring about the efficient asymmetric catalysis of this transformation under convenient reaction conditions and afforded the targeted highly-substituted bispiroindole products (*i.e.* **256**) in high yields and excellent diastereo- and enantioselectivities (Scheme 1.60).



Scheme 1.60 Simultaneous creation of three quaternary stereocentres mediated by **255**

While this succinct list of examples gives the reader a flavour regarding the powerful potential of organocatalysis for the synthesis of complex structures bearing a single or multiple quaternary stereocentres, a multitude of other protocols have been reported; especially in the last decade.²⁵⁸ The variety of reactions employed to achieve the synthesis of these stereocentres is generally limited to a handful of transformations (*e.g.* Michael additions, Diels-Alder reactions), however the use of different combinations of nucleophile and electrophile components have generated the creation of highly diversified molecules which are potentially useful for the synthesis of a wide array of drug candidates and natural products.

2.0 Results and discussion

2.1 Towards the synthesis of a ALDH mimic: rationale for catalyst synthesis

The rationale behind the design of molecules mimicking a ALDH enzyme is to introduce biomimetic catalysis as a valuable alternative for the oxidation of aldehydes (including their oxidative esterification and amidation). Simultaneously, if the enzyme mimics are appropriately designed, they would provide insight into the catalytic mechanisms used in nature by enzymes. In Section 1.2.1 the main biochemical principles involved in the catalytic competency of enzymes promoting redox reactions were presented. The role of enzymes belonging to the ALDH superfamily was emphasised in Section 1.2.2 and the importance of the cysteine-derived thiol group in their active site as the moiety initiating the catalytic oxidation of aldehydes was discussed.

The enzyme glyceraldehyde-3-phosphate dehydrogenase was chosen as the representative of the ALDH superfamily to be mimicked. This enzyme catalyse the oxidation of glceraldehyde-3-phosphate *via* a hemithioacetal species and a thioester intermediate. Two different types of this enzyme exist in nature, the phosphorylating GAPDH and the non-phosphorylating GAPN. Their catalytic activity stems from the involvement of multifunctional catalysis provided by the action of different residues in their active sites as described by Branlant *et al.* (see Sections 1.2.2.1 and 1.2.2.2). The proposed catalytic mechanism of the enzyme is based on nucleophilic catalysis by a cysteine residue and either general base catalysis by an histidine residue (in GAPDH)³²⁻³⁴ or general acid catalysis by an asparagine residue (in GAPN).³⁷⁻⁴² In addition to this, the activity of the enzyme is dependent on the presence of NAD(P)⁺ as a cofactor.

2.1.1 Miniaturisation of the active site of glyceraldehyde-3-phosphate dehydrogenase

In order to synthesise mimics of GAPDH and GAPN a strategy had to be devised which allowed the miniaturisation of their active sites and the installation of the functional groups of the active amino acids into a molecule having an easily accessible structural framework. Taking inspiration from the seminal studies by Kanomata *et al.* and Kellogg

et al. (see Sections 1.3.2 and 1.3.3), it was decided to design the structure of the targeted mimics so as to include a pyridinium salt (the NAD(P)⁺-mimicking moiety) bearing at the C-3 and C-5 positions functional groups acting as analogues of the catalytically relevant amino acids in the enzyme active site. One of these two side chains had to include a thiol group mimicking a cysteine residue, while the other was intended to facilitate either acid or base catalysis by incorporating either an amide acting as hydrogen-bond donating group (Asn mimic) or an amine (His mimic). In order to introduce an element of structural rigidity, a spacer composed of a proline-derived moiety was chosen to incorporate the functionalities exerting either acid or base catalysis. This spacer had the advantage of being readily available in both enantiomeric forms (allowing for the evaluation of different spatial conformations of the mimic) and in addition it shared a similar structure with the tertiary amide present on the NAD⁺ mimic **42** prepared by Kanomata *et al.*⁷⁷

Two types of molecules were devised as outlined in Figure 2.1; one was designed to mimic GAPN (*i.e.* **257**), while the other was devised to mimic GAPDH (*i.e.* **258**). The author undertook the task of investigating the effects of general acid catalysis using enzyme mimics such as **257**, while my colleague Mr. Séan Tallon focused on the synthesis of molecules such as **258**, which possess a basic moiety.

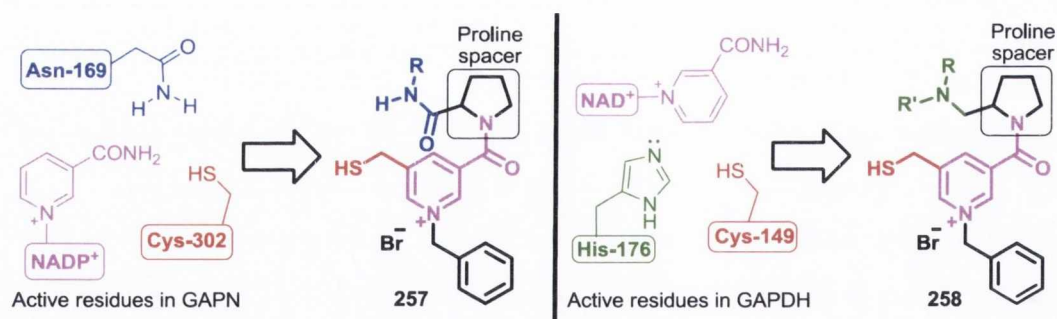
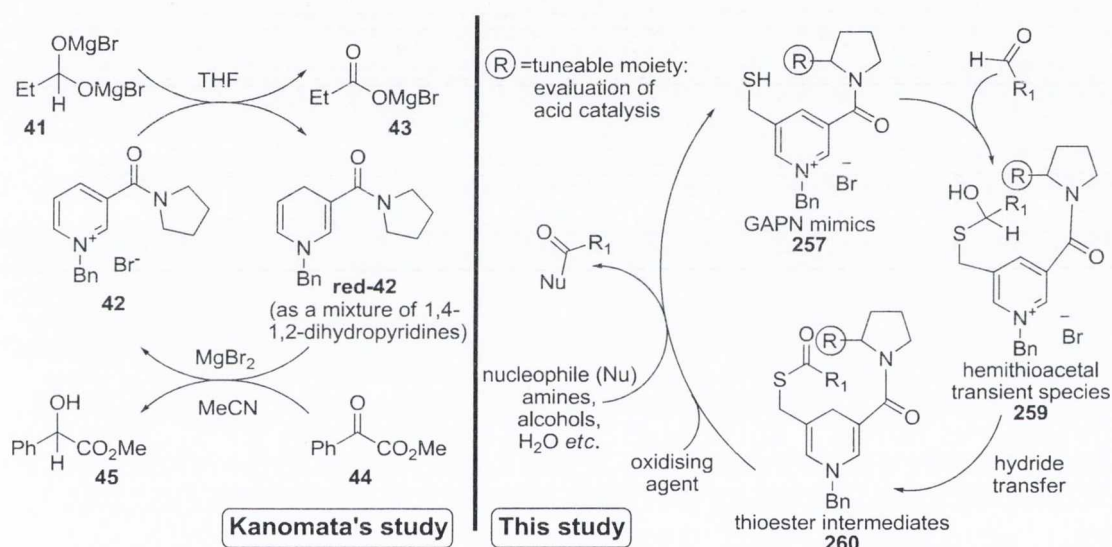


Figure 2.1 Miniaturisation of the active site of GAPN into mimic **257** and GAPDH into mimic **258**

The study by Kanomata *et al.*⁷⁷ which described the viability of pyridinium salt **42** as a NAD⁺ mimic (see Section 1.3.2) represented an impressive breakthrough in the field. Nonetheless, despite the described efficacy of **42** as the promoter of a biomimetic oxidation, the lack of moieties able to form hemithioacetal and thioester intermediates

meant that **42** could not be considered *per se* as a ALDH mimic. On the contrary, the aim of this investigation is the development of a functional GAPN mimic exhibiting a mode of action similar to the natural enzyme and thus encompassing the formation of hemithioacetal transient species and thioester intermediates. This strategy presents several advantages such as: (a) the creation of species exploiting the reactivity of thiols in its mode of action (as observed for cysteine residues in dehydrogenase enzymes) and (b) a better understanding of the role of general acid catalysis in promoting the crucial steps involved in the overall catalytic reaction (from hemithioacetal formation to nucleophilic attack on the thioester intermediate). The aim of our investigation is outlined in Scheme 2.1 and compared to Kanomata's study.



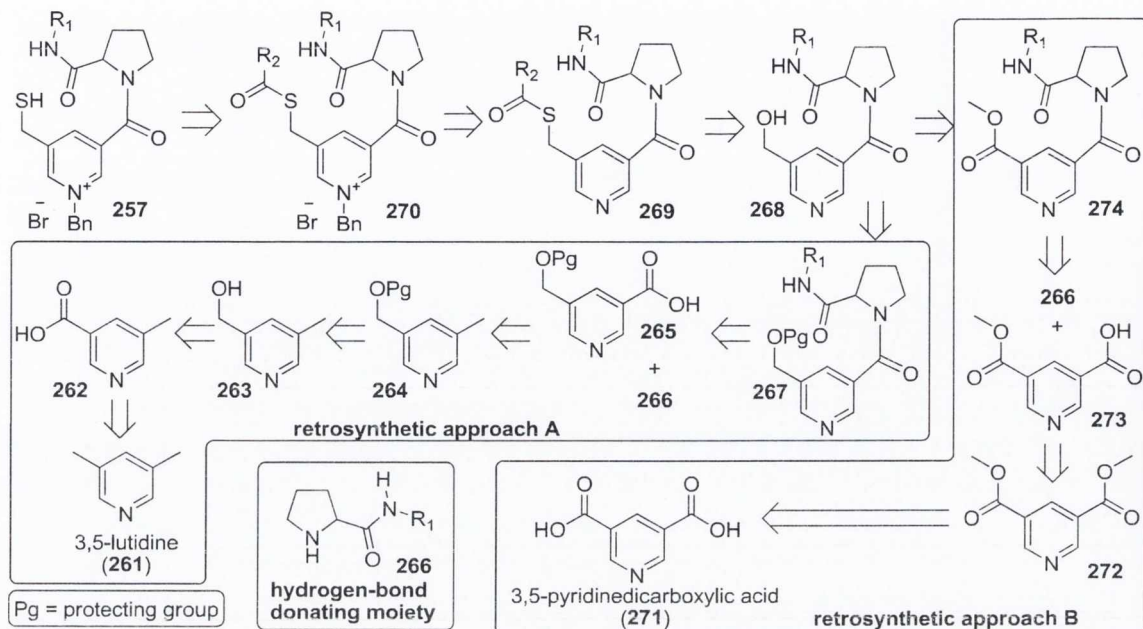
Scheme 2.1 Aim of this study: synthesis and evaluation of GAPN mimics

In order to assess the influence of general acid catalysis on the catalytic performance of these molecules in each of the three steps involved in the overall reaction (*i.e.* hemithioacetal formation, hydride transfer and nucleophilic attack on the thioester intermediate), the evaluation of GAPN mimics will be accomplished one step (of the catalytic cycle) at a time.

2.2 Proposed catalyst synthesis: retrosynthetic analysis

The synthesis of GAPN mimics such as **257** was devised following a retrosynthetic approach. Several crucial factors had to be taken into consideration to achieve a sensible and concise synthetic route. For practical reasons it was decided that GAPN mimics would be synthesised and stored as thioester 'promimics' (*i.e.* **270**) in order to avoid oxidation of the thiol group by adventitious oxygen. Therefore, it was planned to access the GAPN mimics in their active form as thiols *in situ* by deprotection of thioesters **270** only immediately prior to their use. It was also deemed desirable to install the NAD⁺-mimicking moiety at the latest possible stage by alkylation of the pyridine ring on thioester **269**. This decision was taken in order to avoid the impractical handling of pyridinium salts which are intrinsically difficult to purify. In order to achieve a versatile synthetic procedure that could be potentially employed for the creation of a library of GAPN mimics possessing different hydrogen-bond donating moieties, it was determined that the proline-derived Asn-mimicking moiety **266** would be synthesised separately and subsequently installed on the pyridine ring. By using this approach it was deemed possible to maximise the differentiation and tuneability of the hydrogen-bond donating abilities of the mimics with a minimal interference on the main synthetic route. Another desirable feature for the synthesis and evaluation of a library of GAPN mimics was the employment of a concise procedure with the possibility of preparing a common precursor on relatively large scale (*i.e.* **265** and **273**) which could be subsequently derivatised with the diverse hydrogen-bond donating moieties.

Two possible retrosynthetic approaches were considered (A and B respectively, as depicted in Scheme 2.2) which implied the use of readily available symmetric compounds as starting materials (*i.e.* **261** and **271**) and differed from one another only by the way these precursors were desymmetrised.



Scheme 2.2 Retrosynthetic approaches to the synthesis of GAPN mimics

2.3 Synthesis of thioester precursors devoid of the NAD^+ -mimicking moiety

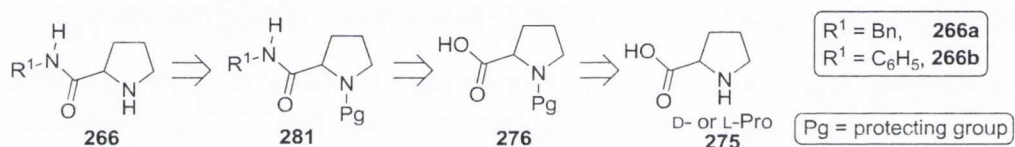
Since we desired to pursue the *stepwise* evaluation of GAPN mimics, thioester precursors lacking a pyridinium ring (thus unable to be reduced *via* hydride transfer) such as **269** were first synthesised and employed in the investigation of the first step of the overall oxidation reaction: hemithioacetal formation.

2.3.1 Synthesis of the Asn-109-mimicking moiety

The formation of a hemithioacetal transient species in the active site of GAPN is believed to benefit from acid catalysis in the form of hydrogen-bond donation provided by (*inter alia*) the primary amide group present on the active residue Asn-109 (see Section 1.2.2.2).³⁷⁻⁴² Therefore, in order to evaluate if a similar beneficial effect was also achievable in GAPN mimics, it was decided that the preliminary hydrogen-bond donating moiety to be assessed would incorporate an amide group. The choice of using a proline-derived spacer to accommodate the Asn-mimicking moiety on the GAPN mimic led us to synthesise the prolinamide derivatives **266a** – **266b**. These structures were chosen as it was envisaged that they would afford us the opportunity to investigate

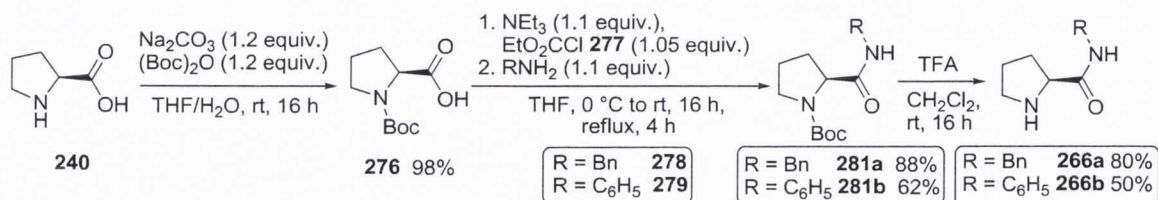
the influence of the pK_a of the amide N-H proton on the efficacy of the mimic in stabilising the putative hemithioacetal intermediate.

The retrosynthetic approach for the L-prolinamide derivatives **266a** – **266b** bearing hydrogen-bond donating ability resulted in a possible three-step sequence starting from the readily available amino acid proline (**275**) in its natural configuration (*i.e.* L-Pro, **240**) as depicted in Scheme 2.3. The preliminary step was the synthesis of an amino protected proline (**276**). This compound would subsequently be reacted with a primary amine in the presence of an activating agent to form a protected prolinamide derivative as in **281**, which would eventually undergo a deprotection step to access the free amino group present on derivatives such as **266** which allows their installation at a later stage on the pyridine core of the GAPN mimics.



Scheme 2.3 Retrosynthetic approach for the hydrogen-bond donating moiety

A carbamate group such as *tert*-butoxy carbonyl (Boc) was initially chosen as the *N*-protecting group for L-proline. The *N*-Boc protection was readily accomplished by reacting L-proline (**240**) and di-*tert*-butyl-dicarbonate (Boc_2O) under standard conditions to afford **276** in excellent yield. The amide group on **281** was installed *via* the *in situ* formation of a reactive mixed anhydride species. The reaction between **276** and ethyl chloroformate (**277**) in the presence of triethylamine afforded the mixed anhydride species, which was subsequently treated with the appropriate primary amine **278–279**. The *N*-Boc-protected L-prolinamide derivatives **281a–281b** were purified by column chromatography and could be achieved in good to excellent isolated yields (Scheme 2.4).



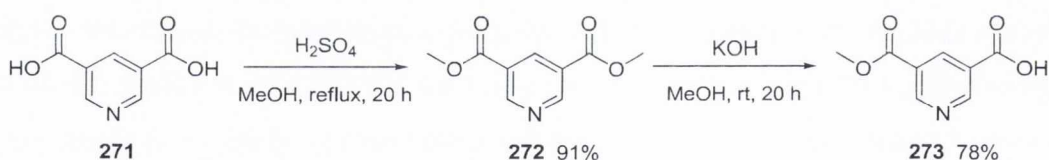
Scheme 2.4. Three-step synthesis of L-prolinamide derivatives

The deprotection of the prolinamides derivatives **281a–281b** was accomplished under acidic conditions at room temperature using trifluoroacetic acid (TFA) in CH₂Cl₂ followed by a basic aqueous work-up in order to isolate the free bases **266a–266b**. The removal of the Boc group on **281a** resulted in good yields of the desired amide **266a**, whereas the deprotections of **281b** and **281c** proved to be more problematic. The conversion of **281b** to **266b** could be accomplished albeit in moderate yields; this reaction was not optimised and it was decided to temporarily disregard the use of **266b** as the hydrogen-bond donating moiety.

2.3.2 Desymmetrisation of the pyridine moiety

The analysis of the retrosynthetic approach to GAPN mimics led us to identify two possible complementary strategies for the desymmetrisation of pyridine-based starting material (Scheme 2.2). It was initially envisaged to pursue the synthesis of GAPN mimics following the retrosynthetic approach **A** and using commercially available 3,5-lutidine (**261**) as the starting material. An early desymmetrisation step involving a regioselective KMnO₄-mediated benzylic oxidation was chosen to access the desired *mono*-carboxylic acid **262** following the procedure described by Forn *et al.*²⁶⁷ The yields achieved were mediocre (up to 36%) and, most importantly, the reaction lacked the desired regioselectivity. The corresponding dicarboxylic acid was obtained (7 to 12%) as a by-product together with **262**. The separation of these acids by means of precipitation (varying the pH or by recrystallisation) was extremely laborious and not always reproducible on variable scales. The addition of pyridine to the reaction mixture as a co-solvent was investigated in order to enhance the solubility of **261** in water, however no improvement could be appreciated either in terms of yields or regioselectivity of the transformation. In order to separate **262** from the dicarboxylic acid an additional step along the synthetic pathway was required leading to the formation of the corresponding ethyl esters which could be separated by column chromatography. The lack of selectivity of the proposed desymmetrisation protocol, the poor yields and the impractical purification of **262** led to a reconsideration of the entire synthetic strategy.

The retrosynthetic approach **B** was therefore considered, which consisted of the use of commercially available 3,5-pyridinedicarboxylic acid (**271**) as the starting material and a desymmetrisation step using a regioselective *mono*-hydrolysis. The dicarboxylic acid **271** was converted to its corresponding methyl ester **272** in excellent yields *via* a Fischer esterification. The diester **272** was desymmetrised by a selective *mono*-hydrolysis reaction as described by Kass *et al.*:²⁶⁸ basic hydrolysis using a 0.1 M solution of methanolic KOH at room temperature furnished **273** in good yield (Scheme 2.5). None of the unwanted *bis*-carboxylate species was observed and it was possible to partially recover the unreacted starting material **272** *via* a simple extraction. The chemoselectivity of this reaction is due to the initial formation of the *mono*-carboxylate salt in a basic environment. By virtue of its weakly electron-donating character, this group deactivates the second hydrolysis by making the remaining ester group less electrophilic.²⁶⁹ The carboxylic acid **273** was effectively isolated as the free base from the aqueous phase during the extractive work-up by means of precipitation, lowering the pH to the range 3 to 5.



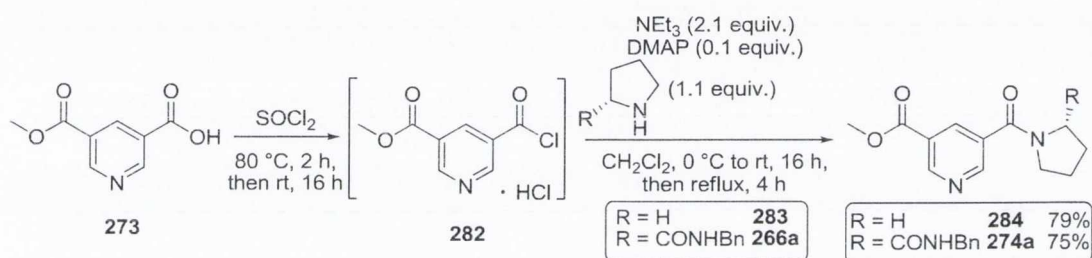
Scheme 2.5 Desymmetrisation of the pyridine moiety

This synthetic strategy proved to be reliable and effective in terms of selectivity; in addition it allowed for the large-scale synthesis over two steps of a precursor (*i.e.* **273**) that could be functionalised with different hydrogen-bond donating moieties.

2.3.3 Coupling of the pyridine core to the Asn-109-mimicking moiety

In order to assess the role of general acid catalysis in the formation of hemithioacetal species, it was deemed necessary to compare GAPN mimics with a compound which possessed a similar structural framework but which lacked any hydrogen-bond donating abilities. In order to achieve the synthesis of such a simplified model it was decided to derivatise the carboxylic acid on **273** and to access tertiary amide **284** by using pyrrolidine (**283**) as the amine component (Scheme 2.6).

Initially, the synthesis of **284** was accomplished in good yields (up to 70%) *via* the formation of a mixed anhydride following a procedure analogous to the one already employed for the synthesis of Asn-mimicking moieties. However, the absence of acid-sensitive functional groups prompted the investigation of the synthesis of **284** *via* the *in situ* formation of acyl chloride **282** by using SOCl_2 . This protocol resulted in slightly improved yields of **284**, the lack of by-products and an easier purification by column chromatography. It was therefore selected as the synthetic methodology for the coupling of Asn-mimicking moieties to compound **273** as shown in Scheme 2.6. The coupling *via* acyl chloride **282** of L-prolinamide derivative **266a** resulted in good yields of the desired amide **274a**.



Scheme 2.6 Coupling of the pyridine core to the Asn-mimicking moiety

2.3.4 Synthesis of thioacetate precursors

Once the Asn-mimicking moiety was installed on the pyridine core at the C-3 position, the synthesis of GAPN mimics consisted of the inclusion of a thiol group protected as a thioester at the C-5 position. The first step involved the chemoselective reduction of the methyl ester on the pyridine ring to a benzylic alcohol. Various nucleophilic reducing agents were used to accomplish the synthesis of alcohols **268a** and **285** from esters **274a** and **284** respectively. Initially the reduction reaction was accomplished using NaBH_4 at reflux temperature in a protic solvent, however the yields obtained for both **268a** and **285** were mediocre and deemed unacceptable for such a late step in the synthetic route. In addition, it was believed that the aqueous work-up employed caused a significant loss of the relatively water-soluble alcohols **268a** and **285**. The presence of literature precedents for reductions of methyl esters at the C-3 and C-5 positions of the pyridine ring using LiAlH_4 at $-78\text{ }^\circ\text{C}$ ²⁷⁰ prompted the investigation of the use of these conditions in the reduction of **274a** and **284**. This strategy proved to be more successful and

provided reproducible results. After the optimisation of the reaction conditions and the work-up, a LiAlH₄-based reduction methodology was established which could provide alcohols **268a** and **285** in good yields, as outlined in Table 2.1. Alcohols **268a** and **285** were subsequently transformed into thioesters **269a** and **286** following a Mitsunobu reaction in the presence of thioacetic acid as shown in Table 2.1. The reaction yielded the desired thioesters in good yields.

Table 2.1 Reduction of the methyl ester group and installation of a thioester moiety

$\text{R} = \text{H}$ 284 $\text{R} = \text{CONHBn}$ 274a $\text{R} = \text{H}$ 285 $\text{R} = \text{CONHBn}$ 268a $\text{R} = \text{H}$ 286 85% $\text{R} = \text{CONHBn}$ 269a 76%						
Entry	substrate	product	reducing agent (red.)	solvent	T (°C)	yield (%) ^a
1	284	285	NaBH ₄	EtOH	70	52
2	274a	268a	NaBH ₄	EtOH	70	33
3	284	285	LiAlH ₄	THF	-78	83
4	274a	268a	LiAlH ₄	THF	-78	77

^a Refers to isolated yields after purification by column chromatography.

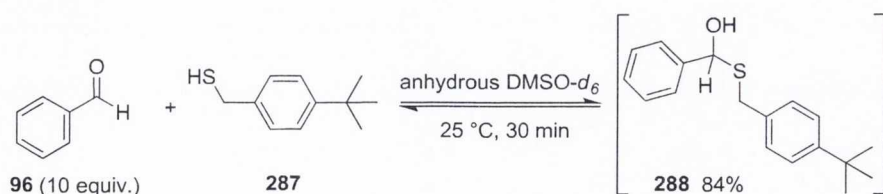
2.4 Preliminary evaluation of GAPN mimics lacking a pyridinium ring in the formation of hemithioacetals

In order to evaluate the GAPN mimics lacking a pyridinium ring and assess the role of acid catalysis in the formation of hemithioacetal species, it was necessary to remove the thioester group on the precursors **269a** and **286** in order to generate the Cys-302-mimicking thiol moiety. It was decided to form the thiol group on GAPN mimics *in situ* immediately prior to their reaction with aldehydes *via* the removal of the acetate protecting group in quantitative yields. We envisaged that this type of protocol would have the advantage of eliminating the purification step and thus minimising the manipulations on the thiol-bearing mimics which could lead to the formation of inactive disulfides species by oxidation. Furthermore this strategy could in principle be implemented for the use of GAPN mimics bearing a NAD⁺-mimicking moiety whose purification as thiols would be even more complex. In order to gain a preliminary

insight into the formation of hemithioacetals and to evaluate possible strategies for the quantitative generation of thiols from thioacetates, less complex model compounds were initially employed.

2.4.1 Use of model compounds to develop a strategy for the generation of thiols from thioacetates and preliminary observations of hemithioacetal species

The commercially available thiol 4-*tert*-butylbenzyl mercaptan (**287**) in conjunction with benzaldehyde (**96**) were first employed for the observation of hemithioacetal **288** in solution. We were prompted to use deuterated DMSO (DMSO- d_6) and an internal standard (*i.e.* 2,5-diphenyl furan) in order to monitor and quantify the formation of hemithioacetal species. The use of this solvent was dictated by preliminary studies conducted by a colleague, Dr. Linda Cronin, which pointed out that hemithioacetal species could not be detected by ^1H NMR when using deuterated chloroform (CDCl_3). Gratifyingly the reaction between thiol **287** and an excess of benzaldehyde (**96**) allowed the rapid formation of reasonable amounts of hemithioacetal **288** (Scheme 2.7). It was observed that the yield of **288** was dependant on the amount of water present in DMSO- d_6 and that thorough drying of the solvent using molecular sieves facilitated the formation of **288** in higher yields (up to 84%). We investigated the addition of catalytic amounts (10 mol%) of an additive such as benzoic acid in order to assess the influence of acid catalysis on the formation of hemithioacetal **288**, however no beneficial effect could be observed.

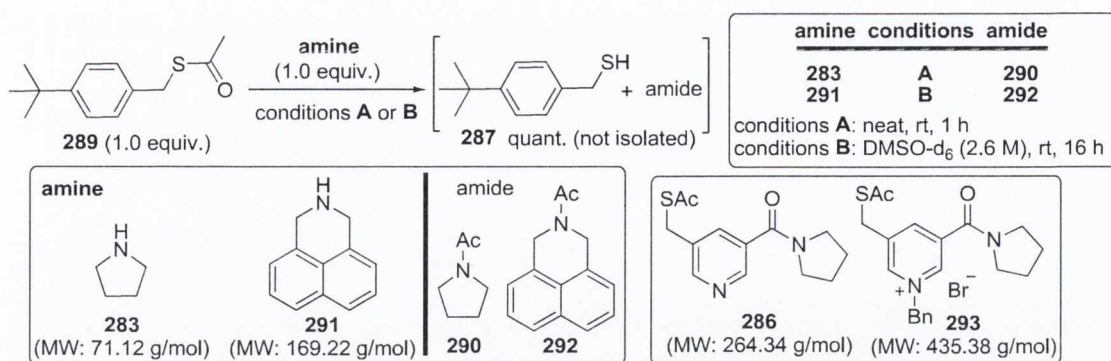


Scheme 2.7 Preliminary observations of hemithioacetal species by ^1H NMR spectroscopy

The need for a common strategy for the quantitative *in situ* generation of thiols on both alkylated and non-alkylated GAPN mimics led us to discard the most widely used protocols²⁷¹ (*e.g.* reductive methods or basic solvolysis) for the cleavage of thioacetates. A previous study by Yelm,²⁷² which described that thiols could be obtained *via* a

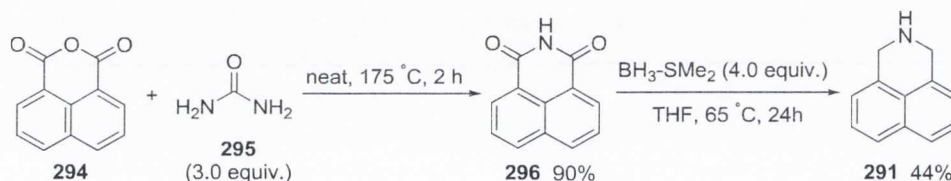
pyrrolidine-promoted aminolysis of thioacetates and could be reacted *in situ* with electrophiles such as Michael acceptors and alkyl halides, was inspirational for the application of a similar methodology to thioacetates **269a** and **286**. The mild reaction conditions, quantitative yields of thiols obtained by Yelm and the formation of an amide (*i.e.* **290**) as the sole by-product from this reaction (a molecule which would neither interfere with nor promote the formation of hemithioacetals) rendered this protocol particularly attractive. Therefore this methodology was initially evaluated using thioacetate **289**, which was used as a model compound for precursors **269a** and **286**.

A series of preliminary experiments demonstrated that the pyrrolidine-promoted aminolysis of thioacetate **289** was a viable option, and prompted the optimisation of the reaction conditions which led to the development of a protocol which entailed the use of **289** and pyrrolidine (**283**) in equivalent quantities without the addition of solvent. Using these conditions, thiol **287** was rapidly formed in quantitative yield (measured by ^1H NMR spectroscopy using an internal standard) and without the observation of any disulfide species (Scheme 2.8). This preliminary result was extremely positive, however the implementation of an aminolysis-based procedure for the deacetylation of **269a** and **286** and their benzylated derivatives required us to investigate into a more appropriate protocol. It was reasoned that a major practical drawback of the use of pyrrolidine (**283**) for the aminolysis of bigger thioester precursors (more closely resembling GAPN mimics) resided in the significant difference in their molecular weights. A protocol requiring neat reaction conditions and exactly stoichiometric loading of the volatile pyrrolidine was predicted to lead to either a significant margin of error or the use of unacceptably high quantities of thioacetate precursors (*e.g.* **286**, **293**). In order to obviate this practical issue, it was decided to use a heavier nucleophilic amine (*i.e.* **291**) otherwise similar in its nucleophilicity to pyrrolidine. Gratifyingly, the use of amine **291** provided satisfactory results for the removal of the acetyl group on **289** and the generation of thiol **287** could be achieved in quantitative yield, albeit after longer reaction times (Scheme 2.8).



Scheme 2.8 Preliminary investigation into the aminolysis of thioacetates

The synthesis of amine **291** could be accomplished over two steps: initially 1,8-naphthalic anhydride (**294**) and urea (**295**) were reacted to form imide **296** in excellent yield.²⁷³ This compound was subsequently reduced with borane in THF at refluxing temperature to afford the desired amine **291** (Scheme 2.9).

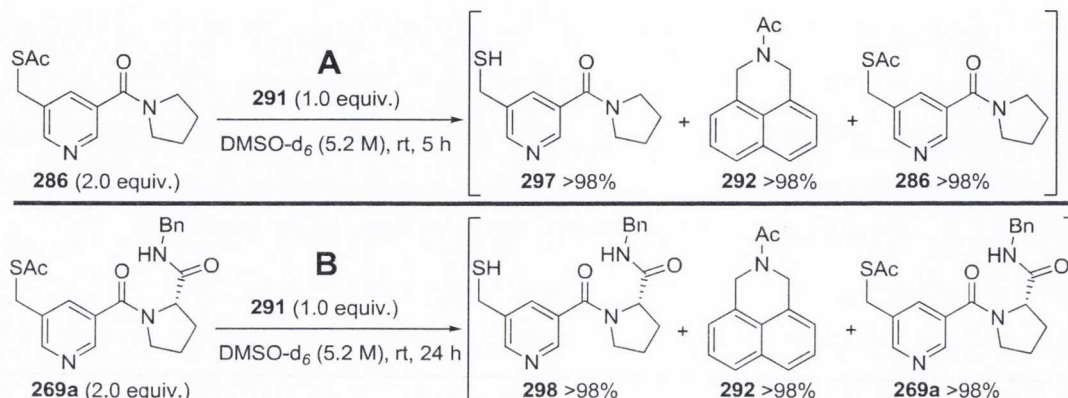


Scheme 2.9 Synthesis of amine **291**

2.4.2 Aminolysis of thioacetate precursors and assessment of acid catalysis in the formation of hemithioacetals

The protocol developed for the deprotection of thioacetate **289** using amine **291** was evaluated on the model thioester **286**. Some additional precautions were taken: the deuterated DMSO used in the transformation was thoroughly dried (with molecular sieves) and degassed using a freeze-thaw methodology in order to avoid the formation of disulfide species *via* oxidation by adventitious oxygen. Preliminary experiments using thioacetate **286** and amine **291** in equal stoichiometric proportions failed to afford the desired thiol **297** in quantitative yields. It was therefore decided that an excess of thioacetate **286** was needed in order to obtain complete conversion. Gratifyingly, the use of two equivalents of thioacetate **286** and amine **291** led to the formation of thiol **297** in quantitative yields (determined by ^1H NMR spectroscopy using styrene as an

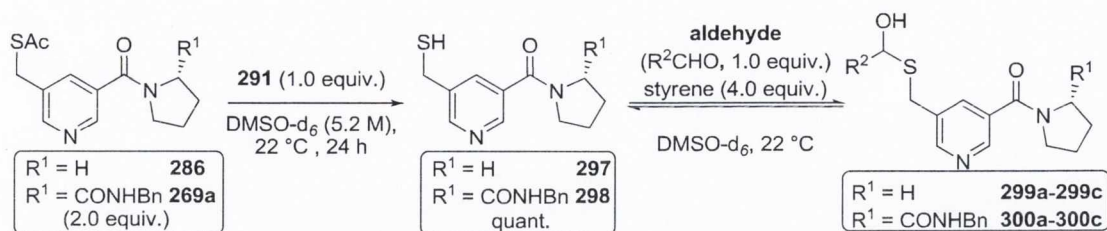
internal standard) as shown in Scheme 2.10, A. The use of a more sterically hindered thioacetate such as **269a** was compatible with this protocol, and thiol **298** could also be obtained quantitatively, however longer reaction times were required (Scheme 2.10, B).



Scheme 2.10 Deprotection of thioacetates **286** and **269a** using amine **291**

Having a protocol for the deacetylation of thioesters in hand, it was decided to develop a one-pot procedure which could allow the observation of hemithioacetal species immediately after the deprotection step. The methodology used to monitor the formation of hemithioacetals **299a-c** and **300a-c** is illustrated in Table 2.2. For clarity, the other products formed upon aminolysis using **291** (*i.e.* the excess of thioacetate species and amide **292**) have been omitted from the reaction scheme. Three types of aldehydes were employed in order to determine the role of the aldehyde component in the formation of hemithioacetals. Compound **286** and the hydrogen-bond donating group-bearing **269a** were evaluated in order to assess the influence of acid catalysis. Since the formation of hemithioacetals is a reversible process, the reaction mixture was analysed twice by $^1\text{H-NMR}$, 30 minutes and 24 hours after the addition of the aldehyde component in order to monitor the kinetics of the transformation. In addition, the use of styrene as an internal standard allowed the quantification of the hemithioacetal species formed.

Table 2.2 Formation of hemithioacetals and assessment of acid catalysis



entry	substrate	aldehyde (R^2)	product	yield (%) ^a	
				after 30 min.	after 24 h
1	286		299a	21	21
2	269a		300a	14	14
3	286		299b	69	69
4	269a		300b	62	62
5	286		299c	15	64
6	269a		300c	8	26

^a Determined by ^1H NMR spectroscopy using styrene as an internal standard.

The use of 2-naphthaldehyde (Table 2.2, entries 1 and 2) led to the formation of hemithioacetals **299a** and **300a** in poor yields and the ratios did not change with time, indicating that the equilibrium was reached rapidly. The thiol derived from **286** (unable to promote the reaction by acid catalysis) afforded hemithioacetal **299a** in yields slightly higher than those obtained with the use of a GAPN mimic bearing a hydrogen-bond donating moiety. This preliminary result most possibly stemmed from the enhanced steric hindrance provided by the amide moiety on the thiol derived from **269a**, which inhibited the formation of hemithioacetal **300a**. Disappointingly, it appeared that hydrogen-bond donation (*i.e.* acid catalysis) was not involved in the hemithioacetal-forming step, however it was deemed necessary to evaluate other aldehydes. The more activated *p*-nitro benzaldehyde was employed (Table 2.2, entries 3 and 4) and, as expected, higher yields of hemithioacetals were obtained due to the enhanced

electrophilicity of the carbonyl group. The results arising from the use of this aldehyde were in accordance with those obtained with 2-naphthaldehyde: the equilibrium was reached rapidly and hydrogen-bond donation did not seem to favour the formation of hemithioacetals, since yields obtained using **299b** were higher than those observed using **300b**. An attempted experiment using 2D ^1H -NMR techniques aimed at the observation of a spatial correlation between the hydroxyl group of hemithioacetal **300b** and the hydrogen-bond donating moiety, failed to confirm an interaction between the two moieties. The last aldehyde that was evaluated was the aliphatic hydrocinnamaldehyde. The results stemming from the use of this compound were significantly different than those obtained with aromatic aldehydes since the equilibration of the reaction required much longer times. However, excluding this phenomenon, derivatives lacking a hydrogen-bond donating moiety outperformed those able to exert acid catalysis and significantly higher yields of **299c** were obtained with respect to **300c**.

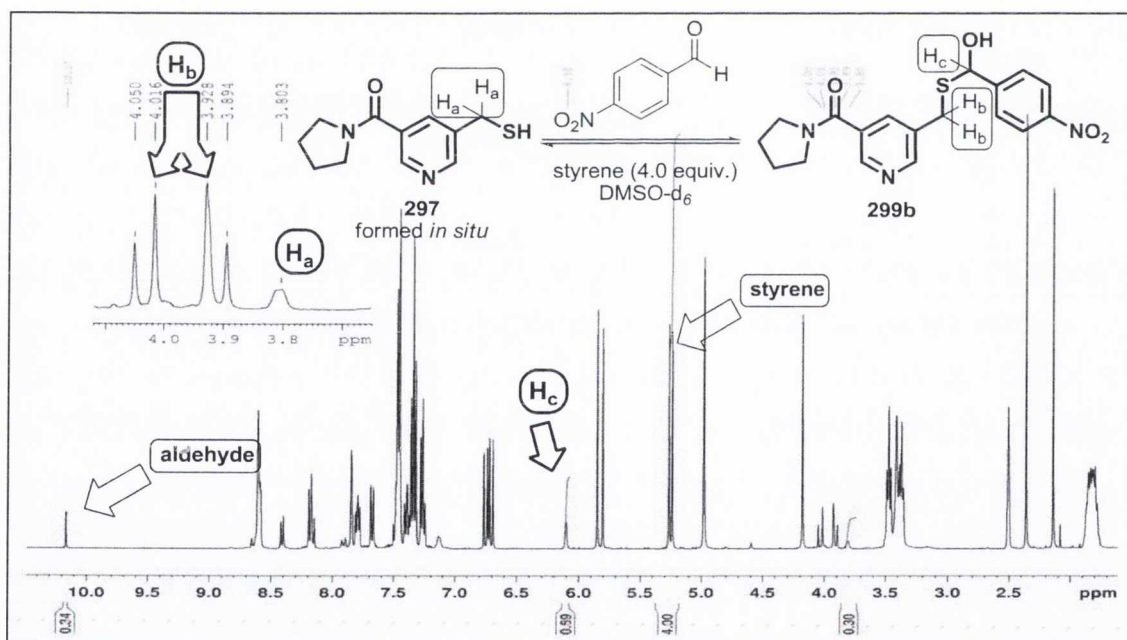


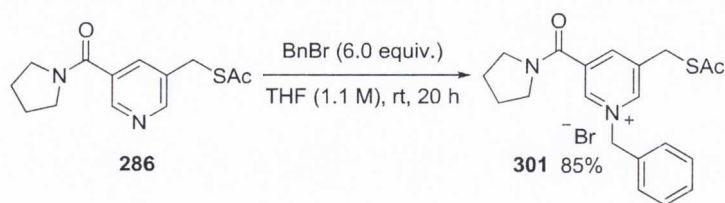
Figure 2.2 ^1H -NMR spectrum of hemithioacetal **299b**

This preliminary evaluation was a qualified success as it allowed us to clearly observe the formation of hemithioacetals using molecules closely resembling the targeted GAPN mimics (the ^1H NMR spectrum of **299b** is shown in Figure 2.2). In addition it was discovered that the formation of hemithioacetals derived from aromatic aldehydes was rapid and that aliphatic aldehydes reacted considerably more slowly. To the

author's disappointment it was also found that, in contrast to what is believed to occur in the active site of the natural GAPN, acid catalysis as exerted by the evaluated GAPN mimic did not seem to be involved in the promotion of the hemithioacetal formation in our model system. It was noteworthy that the GAPDH mimics synthesised and evaluated by my colleague Mr. Séan Tallon (which were able to exert general base catalysis), could in one case (using hydrocynnamaldehyde) promote the hemithioacetal formation and allowed for the equilibration of this reaction to occur after 30 minutes. This observation seemed to prove the involvement of base catalysis, however it was reasoned that acid catalysis could be involved in the second step of the transformation (*i.e.* hydride transfer) and therefore GAPN mimics bearing a NAD^+ -mimicking moiety were synthesised and evaluated.

2.5 Synthesis of a thioester precursor bearing a NAD^+ -mimicking moiety and investigation towards the *in situ* formation of a thiol group

In order to evaluate the role of GAPN mimics and acid catalysis in the step involving hydride transfer it was necessary to install a NAD^+ -mimicking moiety in the form of a pyridinium ring. It was decided to initially use thioacetate **286**, (which was more easily accessible than **269a**) to develop a synthetic procedure that would provide the desired pyridinium salts. The alkylation of the pyridine ring on **286** was achieved in high yields by using an excess of benzyl bromide and compound **301** (whose structure is reminiscent of Kanomata's NAD^+ mimic, *i.e.* **42**) could be isolated pure by its precipitation using diethyl ether followed by the removal of the supernatant containing the alkylating reagent in excess (Scheme 2.11).



Scheme 2.11 Benzylation of thioester **286**

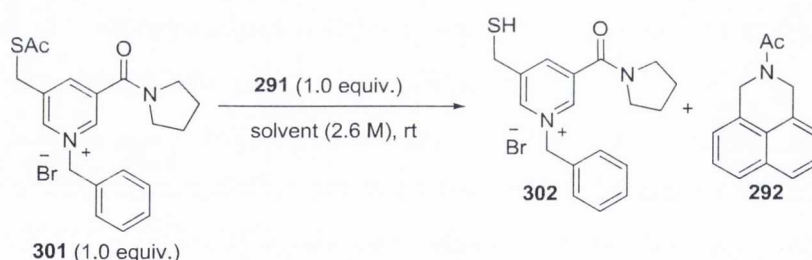
In order to evaluate the feasibility of hemithioacetal formation and intramolecular hydride transfer using GAPN mimics, a thiol moiety needed to be generated *in situ*. It

was therefore decided to react thioacetate **301** with amine **291** to assess the viability of the aminolysis methodology successfully employed for thioacetate **286**.

2.5.1 Formation of thiol species *via* aminolysis of thioacetate precursors having a NAD⁺-mimicking moiety

It was reasoned that the installation on **301** of an electron-withdrawing positively charged moiety could enhance the lability of the thioester protecting group. It was therefore envisaged that the aminolysis reaction and the formation of thiol **302** *in situ* could have occurred more rapidly with the use of equivalent quantities of thioester precursors and amine **291**. However, the methodology which was successfully employed for thioesters **286** and **269a** disappointingly failed to afford quantitative yields of thiol **302** (Table 2.3).

Table 2.3 Aminolysis of thioester **301** using amine **291**



entry	solvent	time (h)	Yield of thiol 302 (%) ^a
1	DMSO- <i>d</i> ₆	2.5	80
2	DMSO- <i>d</i> ₆	5	80
3 ^b	DMSO- <i>d</i> ₆	5	80
4	CH ₃ CN	5	79
5	MeOH	5	70

^a Determined by ¹H-NMR using styrene as an internal standard. ^b 2.0 equiv. of thioester **286** were used.

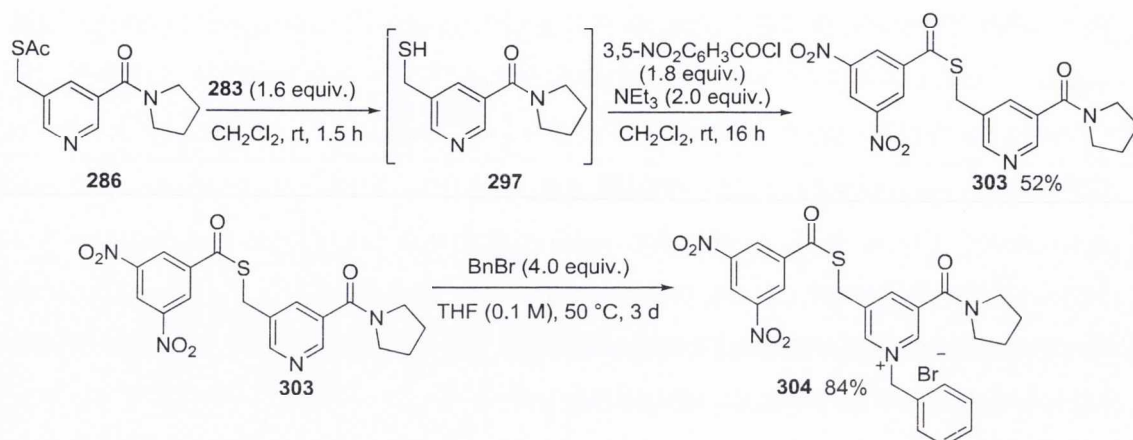
As expected, the reaction proceeded rapidly even using the thioester and amine in equivalent loadings, however the analysis by ¹H NMR spectroscopy revealed that the transformation was not quantitative and that unidentified by-products were formed in most cases. The aminolysis reaction was attempted in several solvents and was also

thoroughly examined by my colleague Mr. Séan Tallon, who attempted to enhance the yields of thiol **302** by varying the reaction conditions. The reaction in DMSO-*d*₆ afforded the highest yields of thiol **302** (Table 2.3, entries 1, 2 and 3), however neither the addition of an excess of thioester **301** nor longer reaction times afforded quantitative conversion. The aminolysis reaction with pyrrolidine (**283**) was also attempted in various solvents, however lower yields of **302** were obtained, together with the presence of by-products which increased in concentration with longer reaction times. Alternative nucleophiles such as *N*-amino-morpholine and sodium methoxide in DMSO-*d*₆ were evaluated, however their use generated either lower yields of **302** or the formation of by-products.

Fellow researcher Mr. Séan Tallon was also unable to develop a protocol leading to quantitative yields of thiol **302** *via* the aminolysis of **301**. It was considered that one of the possible reasons accounting for the apparent establishment of an equilibration process, was the protonation (thus inactivation) of amine **291** by thiol **302** whose pK_a was thought of having being lowered by the presence of a pyridinium moiety.

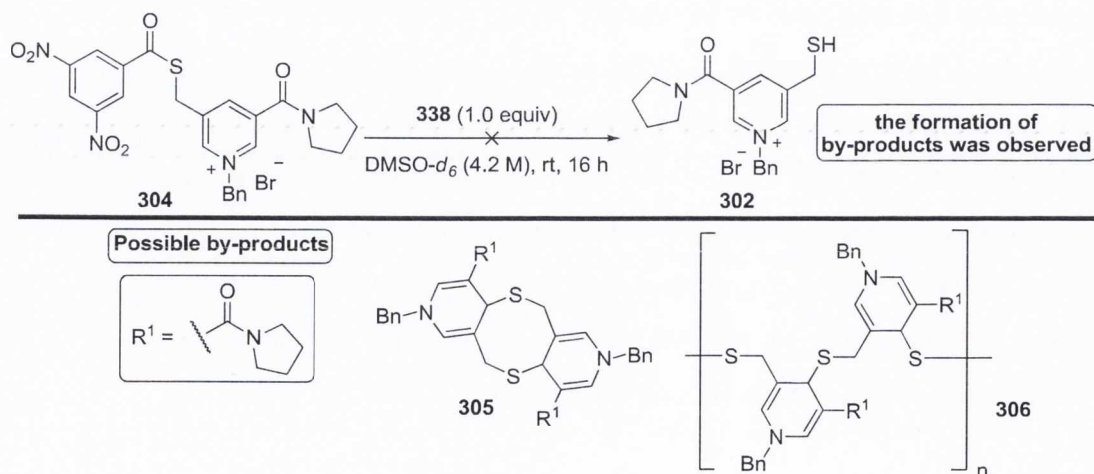
2.5.2 Synthesis of a more activated thioester precursor and evaluation of its deprotection by aminolysis

In order to promote the quantitative formation of thiol **302**, it was decided to install a more activated thioester as the protecting group and it was envisaged that this could be achieved by adding an extra step to the planned synthetic route to GAPN mimics. Thioacetate **286** was used as the starting material in a one-pot reaction involving the deacetylation using pyrrolidine (**283**) to form thiol **297** *in situ*. This species was subsequently reacted with 3,5-dinitrobenzoyl chloride in the presence of triethylamine to generate thioester **303** which could be obtained in moderate yield after purification by column chromatography (Scheme 2.12). We then introduced the NAD⁺-mimicking moiety by alkylation of the pyridine ring using an excess of benzyl bromide (Scheme 2.12). Compound **304** was purified by precipitation with diethyl ether using the same protocol employed for the thioacetate analogue **301**.



Scheme 2.12 Synthesis of a more labile thioester precursor and installation of the NAD^+ -mimicking moiety

The choice of using a 3,5-dinitro benzoate group stemmed from preliminary studies conducted by Mr. Séan Tallon which indicated that a quantitative generation of thiols could be achieved (albeit using simpler model compounds) by the removal of this protecting group *via* aminolysis using the conditions previously employed (Scheme 2.13). Disappointingly the removal of the protecting group on **304** using amine **291** failed to produce quantitative yields of thiol **302** and led to the formation of an insoluble product that prevented the exact interpretation of the crude reaction mixture by ^1H NMR spectroscopy. The experiment was also attempted in the absence of light, however this did not affect the outcome of the reaction. Mr. Séan Tallon was further involved in the study of the aminolysis of **304** however, to our disappointment, a protocol allowing the clean and quantitative generation of thiol **302** could not be developed.

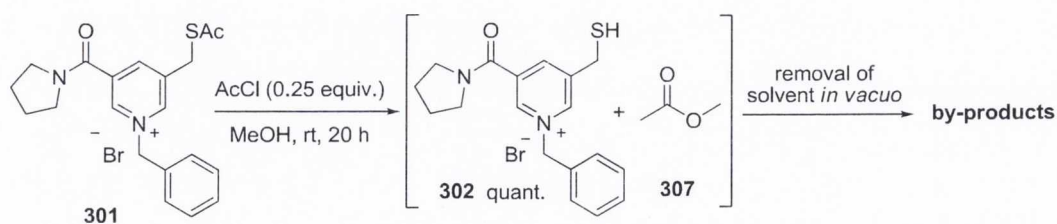


Scheme 2.13 Attempted aminolysis of thioester **304**

It was reasoned that the formation of substantial amounts of by-products which were observed exclusively with the use of thioesters on pyridinium salts could stem from the reaction of the thiol group formed *in situ* with the electrophilic C-4 (or C-2) position of the pyridinium ring as reported by Kellog *et al.* (see section 1.3.3). This type of reactivity could potentially lead to the formation of dimeric and polymeric adducts (Scheme 2.13, **305** and **306** respectively) lacking the ability of forming hemithioacetals and thus unable to act as GAPN mimics. The most likely establishment of an acid/base equilibrium generating unacceptable yields of thiol **302** together with the formation of considerable amount of by-products indicated that the aminolysis of thioesters was not a viable option for the formation of GAPN mimics

2.5.3 Evaluation of an alternative methodology for the deprotection of thioacetates

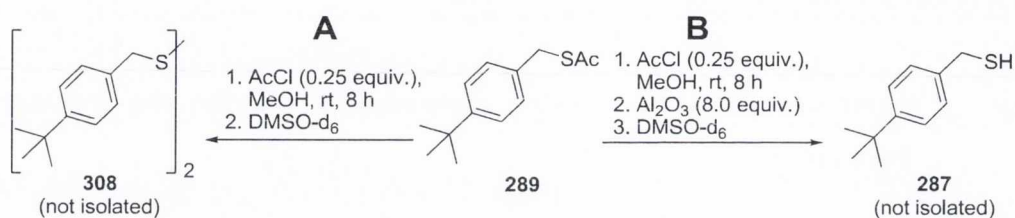
The impossibility of achieving a clean and quantitative deacetylation of thioester **301** *via* aminolysis prompted the investigation of alternative deprotection methodologies. Prasad *et al.*²⁷⁴ reported the formation of thiols from thioacetates by the generation of HCl *in situ* using catalytic amounts of acetyl chloride in methanol. It was envisaged that this protocol represented a viable option for the deprotection of thioester **301** because it could generate thiols without the establishment of acid/base reactions and with the formation of the volatile methyl acetate (**307**) as the only byproduct. It was therefore decided to evaluate this methodology (Scheme 2.14).



Scheme 2.14 Attempted methanolysis of thioester **301**

Preliminary experiments revealed that the use of acetyl chloride in methanol led to a quantitative formation of thiol **302** (as monitored by ¹H NMR spectroscopy), however the removal of the solvent during the work-up procedure led to the formation of an unidentifiable insoluble by-product (possibly a mixture of dimeric or polymeric species

as it was also speculated to occur in the aminolysis reaction). The removal of the solvent *in vacuo* at room temperature produced the same result, which seemed to indicate that the reactivity of thiol **302** was mainly dependent on its concentration in solution. This hypothesis prompted the investigation of a protocol which involved a work-up procedure where the concentration of **302** in solution could be maintained unaltered. It was therefore decided to add the high boiling solvent DMSO- d_6 to the reaction mixture prior to the removal of excess methanol and methyl acetate. However, rather unexpectedly, the addition of this solvent to the reaction mixture immediately after the deacetylation led to the quantitative formation of disulfide species.

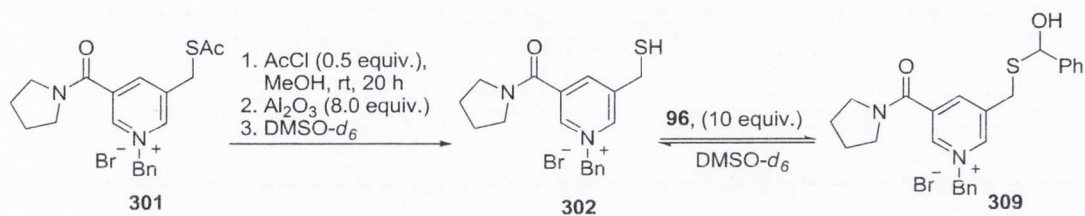


Scheme 2.15 Development of a work-up protocol using model **289**

It was hypothesised that the generation of disulfide **308** from thiol **287** proceeded *via* a Swern-type oxidation upon the formation of an electrophilic species from the reaction between DMSO- d_6 and the residual acid in solution (*i.e.* HCl) with the simultaneous formation of the easily detectable dimethyl sulfide. This assumption was indirectly validated by the observation of the same type of reactivity using thioacetate **289** (shown in Scheme 2.15, A). This compound was therefore employed to develop a useful protocol for the quantitative generation of thiols *in situ*. It was envisaged that the use of a heterogeneous base (*i.e.* basic alumina) could neutralise the residual HCl and was at the same time removable from the reaction mixture prior to the evaluation of **302** in the formation of hemithioacetals and in the hydride transfer step. A procedure involving the use of basic alumina was initially developed for the generation of thiol **287** and proved to be successful in avoiding the formation of inactive disulfide species (Scheme 2.15, B).

This encouraging result prompted the implementation of this novel methodology for the deacetylation of thioester **301** and the one-pot evaluation of the GAPN mimic **302** in the presence of an excess of aldehyde. The use of anhydrous degassed methanol and freshly distilled acetyl chloride afforded the methanolysis of thioacetate **301** (Scheme 2.16).

Basic alumina was added to the crude reaction mixture and the supernatant containing thiol **302** was subsequently removed by decanting the solution which was then added to DMSO-*d*₆. Removal of the lower boiling solvent *in vacuo* at room temperature afforded thiol **302** in DMSO-*d*₆, the presence of which could be directly confirmed by ¹H NMR spectroscopy (shown in Figure 2.3, A). The addition of an excess of benzaldehyde (**96**), led to the instantaneous formation of hemithioacetal **309** (the ¹H NMR spectrum is depicted in Figure 2.3, B). It is noteworthy that this species did not evolve into a thioester and the formation of a dihydropyridine species *via* hydride transfer was not observed.



Scheme 2.16 Methanolysis of **301** and formation of hemithioacetal **309** *in situ*

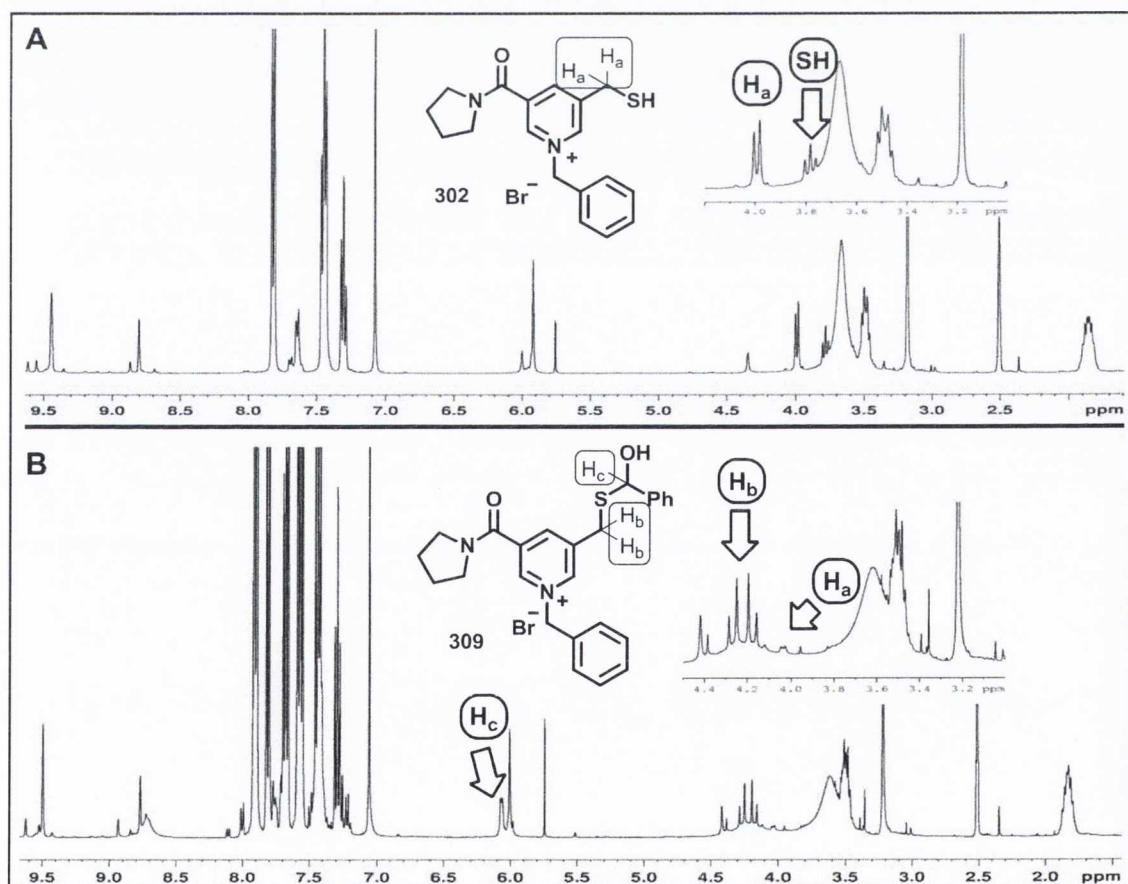
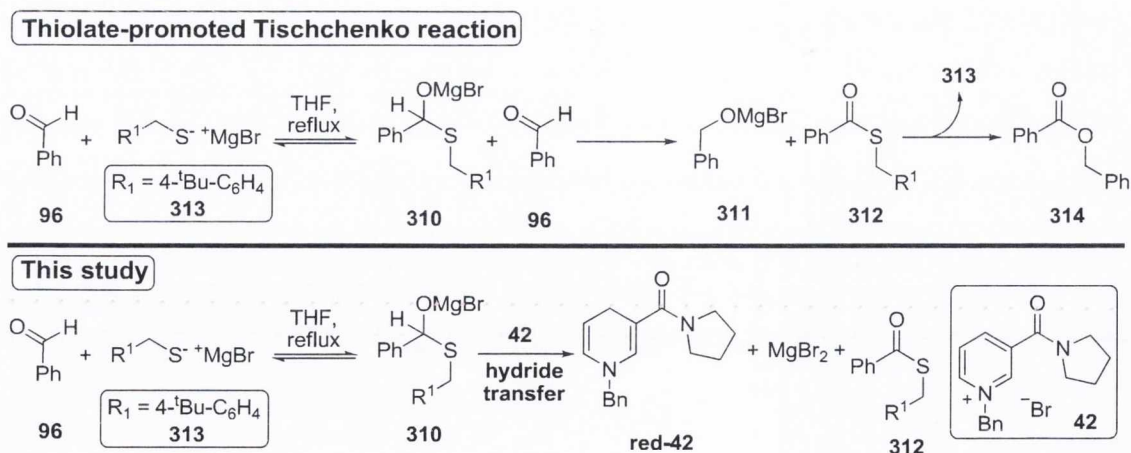


Figure 2.3 ¹H NMR spectrum of thiol **302** formed *in situ* (A) and of hemithioacetal **309** (B).

The observation of hemithioacetal **309** proved that GAPN mimics were able to promote the first step of the catalytic reaction, however the use of such a laborious and complicated protocol inevitably led to a consistent and unacceptable loss of compound **302** and its partial oxidation to disulfide by adventitious oxygen. The impracticality of this methodology, stemming mainly from the multiple obligated manipulations in the work-up procedure, prompted its discard for future investigations.

2.6 Synthesis and evaluation of pyridinium salts as NAD⁺ mimics

The investigation on GAPN mimics indicated that these species were able to react with aldehydes and form hemithioacetals (albeit using inefficient protocols), however the intramolecular hydride transfer step could not be observed and in addition the intrinsic instability of molecules bearing thiol groups on pyridinium moieties was noted. It was therefore decided to evaluate the feasibility of an intermolecular hydride transfer between hemithioacetal species formed *in situ* and compounds having an electrophilic pyridinium ring. The rationale of this study was inspired by the NAD⁺ mimicry described by Kanomata *et al.*⁷⁷ (see Section 1.3.2) and the observation that thiolate salts were excellent catalysts for the Tischchenko reaction (*i.e.* the disproportionation of an aldehyde) by our group.²⁷⁵

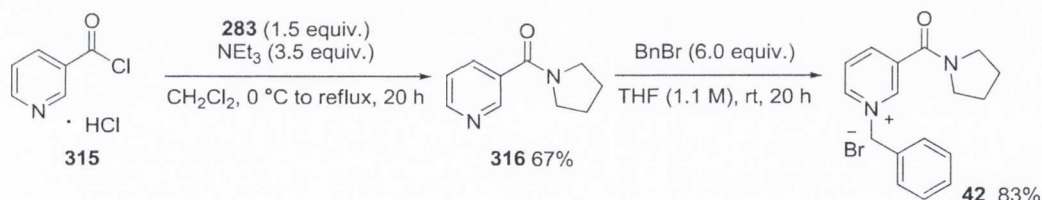


Scheme 2.17 Rationale for the investigation of an intermolecular hydride transfer

It was previously observed that the reaction between thiol **287** and a Grignard reagent generated a thiolate salt (*i.e.* **313**) which reacted with benzaldehyde (**96**) and formed the

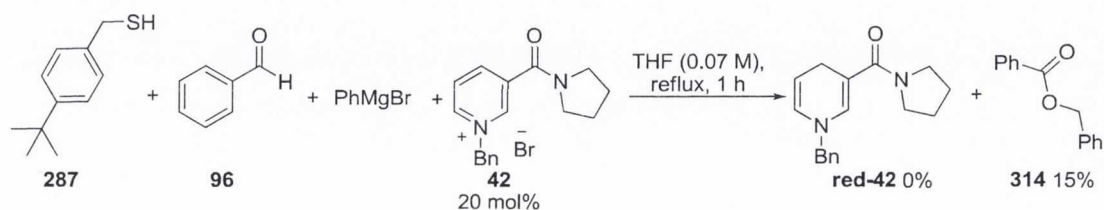
hemithioacetal conjugate base **310** in a reversible process. This species was able to transfer a hydride ion to aldehyde **96** leading to the formation of alkoxide **311** and thioester **312** which could subsequently react to form ester **314** with the simultaneous regeneration of the thiolate catalyst **313** (Scheme 2.17). It was therefore envisaged that the presence of a thiolate species and an electrophile other than benzaldehyde (*i.e.* a pyridinium salt) could lead to a different reactive pathway and form dihydropyridine **red-42** via an intermolecular hydride transfer reminiscent of the biomimetic process reported by Kanomata *et al.*

Initially it was decided to synthesise and evaluate compound **42**, which was previously employed as a NAD⁺ mimic by Kanomata *et al.* The synthesis of **42** was accomplished in two steps starting from the commercially available acid chloride **315** which was reacted with pyrrolidine (**283**) in the presence of an excess of triethylamine to afford the amide **316** in moderate yields. This compound was subsequently alkylated with an excess of benzyl bromide to form the desired **42** in excellent yields (Scheme 2.18).



Scheme 2.18 Synthesis of NAD⁺ mimic **42**

The hygroscopic pyridinium salt **42** was thoroughly dried prior to its evaluation according to the protocol reported by Kanomata *et al.*, which entailed the use of an excess (5 equivalents) of hydride donor (*i.e.* **313**, formed *in-situ* by reacting **287**, **96** and PhMgBr) and refluxing temperatures (Scheme 2.19).



Scheme 2.19 Evaluation of NAD⁺ mimic **42** in a thiolate-promoted intramolecular hydride transfer

The analysis of the reaction mixture by ^1H NMR spectroscopy disappointingly indicated the absence of dihydropyridine species and the formation of ester **314**, albeit in low yields. The stoichiometry of the reaction was varied, however the use of either equimolar loadings of **313** and **42** or an excesses of **42** (up to 3 equivalents) did not alter the outcome of the reaction. The hydride transfer did not occur under these reaction conditions and neither a dihydropyridine species nor ester **314** could be detected. The limited solubility of **42** in THF was noted and was believed to be a factor impeding the hydride transfer to occur. However, the previous study reporting the effective use of pyridinium salts such as **42** as NAD^+ mimics which could be reduced by diolates under identical reaction conditions, was indicative that the lack of solubility of **42** was not impeding its reactivity in that process. It was therefore reasoned that the lack of reactivity of **42** when thiolate salts such as **313** were employed as hydride donors stemmed from the presence of a reversible reaction leading to their formation which generated large amounts of benzaldehyde (**96**) in solution. The presence of two concurrent nucleophiles caused the hydride transfer to occur preferentially on the carbonyl group rather than on the pyridinium ring which accounted for the lack of dihydropyridine species and the presence of ester **314**.

2.7 Conclusions

Our attempts to develop a GAPN mimic have revealed that the proposed structural framework is not of an appropriate design to furnish a stable and functional species able to catalyse the biomimetic oxidation of aldehydes (including their oxidative esterification and amidation). The ambitious strategy of miniaturising the active site of the natural enzyme GAPN and incorporating on a single molecule the functional groups associated with its mode of action has proven unsuccessful. In this regard it was acknowledged that the presence on the same molecule of a cysteine-mimicking thiol group and a pyridinium moiety acting as a NAD^+ analogue is problematic. However, despite the goals of this investigation not being achieved, it was possible to obtain some important results.

We were able to synthesise GAPN mimics devoid of a pyridinium moiety and evaluate them in the formation of hemithioacetal species, which is the first step of the overall oxidation reaction catalysed by the natural enzyme GAPN. In this regard it was possible

to observe the remarkable difference in reactivity associated with aliphatic aldehydes compared to aromatic analogues. Preliminary results in this area seemed to exclude the involvement of acid catalysis since the control molecule **286** outperformed **269a**, which had hydrogen-bond donating capabilities.

The generation of a GAPN mimic devoid of a hydrogen-bond donating moiety was achieved (albeit using a labourious and impractical procedure) *via* the deprotection of a thioester precursor. It was possible to observe the formation of a hemithioacetal using this mimic, however the intramolecular hydride transfer step did not occur and it was not possible to observe the formation of a dihydropyridine species.

Finally it was proved that the intermolecular hydride transfer using thiolate ions and pyridinium salts was not a viable process, since the formation of dihydropyridine species could not be observed. In this regard, it was demonstrated that the pyridinium ring is a relatively weak electrophile.

3.1 Towards the development of asymmetric formal cycloaddition reactions using enolisable anhydrides

As described in previous Sections in the introductory chapter (see Sections 1.6 to 1.6.7), the formal cycloaddition reaction between enolisable anhydrides and electron deficient π -systems is an important transformation that allows the one-pot synthesis of densely functionalised lactams and lactones with the simultaneous formation of up to two new stereocentres. Despite an extensive body of work has been devoted to the study of these annulation reactions (in particular those using imines as electrophiles), a crucial drawback is the lack of an effective asymmetric methodology.

Thanks to the work by Cushman *et al.*,¹⁷⁹ it is now established that formal cycloaddition reactions between enolisable anhydrides and (*E*)-imines provide diastereomeric mixtures of lactams with a preference for the *cis*-diastereomer (see Sections 1.6.2.1.1 and 1.6.5), whereas experimental results indicated the predominant formation of *trans*-diastereomers (Sections 1.6.2 and 1.6.6) when aldehydes are the electrophilic component of the reaction.²⁰² Only three studies involving chiral substrates have been reported so far (see Section 1.6.4). Two of these used an enantiopure imine (reported by Clark *et al.*²⁰⁵ and Cossío *et al.*²⁰⁶) while the other involved chiral sulfide-substituted anhydrides (described by Shaw *et al.*).²⁰⁷ The first two allowed for the formation of products in excellent diastereoselectivities (up to 86% and 96% *de* respectively) and good yields (up to 60%), however they either failed to provide a plausible stereochemical rationale,²⁰⁵ or they lacked a broad applicability²⁰⁶ while the third produced only modest levels of *de* and low product yields. No catalytic asymmetric methodologies had been reported at the outset of this project.

The intrinsic utility of formal cycloadditions with enolisable anhydrides, their relative underdevelopment and the lack of an efficient and versatile diastereo- and enantioselective methodology prompted us to begin an investigation aimed at conceiving and implementing an asymmetric organocatalytic protocol for these reactions. In order to achieve this goal, the author was closely cooperating with fellow researcher Mr. Francesco Manoni since the beginning of this investigation. Unless otherwise specified, the data reported in the following Sections are resulting from experimental work carried out by the author alone.

3.1.1 Rationale for the use of a cinchona alkaloid-based bifunctional organocatalyst to promote asymmetric annulation reactions with enolisable anhydrides

The formal cycloaddition reaction between enolisable anhydrides and imines can be promoted by Lewis acids (see Section 1.6.5), whereas the reaction with aldehydes has been performed using either Lewis acids or bases as additives to promote the enolatisation of anhydrides (see Sections 1.6.3 and 1.6.6). These reports established that annulation reactions could benefit from either acid or base catalysis, however the Lewis acid or base additives were always employed as reagents at either stoichiometric or super-stoichiometric loadings.

We reasoned that this absence of catalytic methodologies, at least in the case of the reaction with aldehydes, (which are considered the electrophilic components) was related to the obvious difficulty in persuading an inherently electrophilic species (*i.e.* anhydride) to attack an aldehyde as a nucleophile, without either reacting with itself (an anhydride is usually regarded as a more reactive electrophile than an aldehyde) or the putative catalyst in a deleterious fashion. In addition, the formation of products bearing a carboxylic acid rendered the use of bases in catalytic loadings problematic because of potential product inhibition of catalysis *via* protonation.

Our group (among others^{276,277,278,279,280,281,282}) have recently been engaged in the use of cinchona alkaloid-derived bifunctional organocatalysts to promote the asymmetric addition of alcohol²⁸³ and thiol^{284,285} nucleophiles to cyclic anhydrides. These catalysts rely on the confluence of relatively weak synergistic catalyst-substrate interactions (mostly the donation of hydrogen bonds to the anhydride electrophile and general-base catalysis of the nucleophilic addition of the pronucleophile), they are compatible with cyclic anhydride substrates (hitherto only when the anhydrides are being employed as electrophiles), and have been known (in isolated cases) to activate aldehyde and ketone electrophiles.^{139,142} Therefore, it was proposed (somewhat counter intuitively) that in the absence of a powerful pronucleophile (*e.g.* alcohols, thiols) these bifunctional catalysts could be employed to bring about the activation of an enolisable anhydride as a nucleophile through the equilibrium between it and its enol form *via* general base catalysis (with concomitant suppression of the anhydride's propensity to act as an

electrophile), while simultaneously activating the electrophile through hydrogen bond donation (*i.e.* general acid catalysis) in a controlled chiral environment.

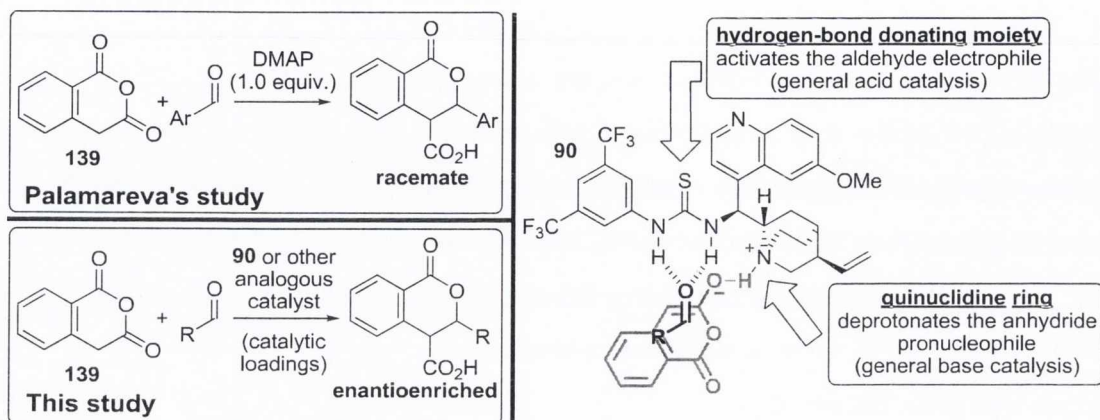


Figure 3.1 Rationale for the development of bifunctional organocatalysts-promoted asymmetric annulations between enolisable anhydrides and aldehydes

The rationale for the promotion of the asymmetric annulation reaction between homophthalic anhydride (**139**) and aldehydes by a cinchona alkaloid-derived bifunctional organocatalyst (*e.g.* **90**) is depicted in Figure 3.1 and is compared to Palamareva's study,²⁰² which reported the use of DMAP in stoichiometric loadings to promote analogous racemic reactions. It is noteworthy that the same catalyst (*i.e.* **90**) which was employed by our group to promote nucleophilic additions to cyclic anhydrides,^{283,284} could in principle promote the additions of anhydrides to other species, even relatively weak electrophiles such as aldehydes.

3.2 Preliminary investigations towards the development of an asymmetric organocatalytic protocol

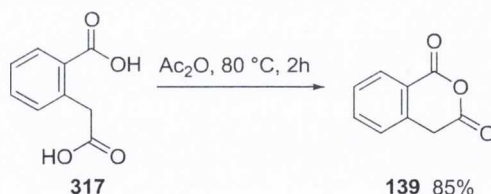
To verify the plausibility of creating an asymmetric catalytic methodology for annulation reactions involving cinchona alkaloid derivatives as bifunctional organocatalysts, it was initially decided to evaluate the transformation between anhydrides and aldehydes. The sporadic nature of reports describing the annulation with aldehydes and the reduced substrate scope for this transformation compared to its imine counterpart (only aromatic aldehydes and succinic or homophthalic anhydrides had

been reported), rendered the potential improvement achievable by the development of a versatile asymmetric methodology very appealing.

3.2.1 Preliminary evaluation of the involvement of bifunctional catalysis in the annulation reaction with aldehydes

Initially a series of preliminary experiments aimed at assessing the influence of bifunctional catalysis on the annulation reaction between homophthalic anhydride (**139**) and benzaldehyde (**96**) were carried out in cooperation with Mr. Francesco Manoni. The combined data are reported in Table 3.1 in order to allow for more complete analysis (the experiments accomplished by the author are highlighted).

Homophthalic anhydride (**139**) was easily prepared from the commercially available homophthalic acid (**317**) and acetic anhydride by heating the reaction mixture at 80 °C for two hours (or until the carboxylic acid had dissolved). The crude homophthalic anhydride obtained after the removal of the acetic anhydride could be purified by trituration with ether (Scheme 3.1).



Scheme 3.1 Synthesis of homophthalic anhydride (**139**)

The formal cycloaddition reaction between **139** and benzaldehyde (**96**) was initially performed using THF as the solvent. This choice was motivated by previous observations in our group that reported the use of ethereal solvents as key in the bifunctional catalysis of reactions which form acids from anhydrides.^{283,284} It is believed that the pK_a of the acid product is higher in ethers than in other solvents, which prevents the inhibition of catalysis *via* protonation of the quinuclidine moiety. The yields of the products could be easily determined by ¹H NMR spectroscopy of the crude mixture by using an internal standard (*i.e.* *p*-iodoanisole). In addition, by using the data reported by Palamareva *et al.*,²⁰² it was possible to discern the resonances corresponding to the

protons on C-3 and C-4 in **trans-132** and **cis-132** by ^1H NMR spectroscopy due to their different chemical shifts and 3J values.

Table 3.1 Preliminary evaluation of bifunctional catalysis in formal cycloaddition reactions

entry	cat.	conc. (M)	yield of combined diastereomers (%) ^a	<i>dr</i> ^b <i>trans:cis</i>
1	--	0.4	49	71:29
2	--	0.2	20	75:25
3	ⁱ Pr ₂ NEt	0.2	94	75:25
4	ⁱ Pr ₂ NEt + 318	0.2	93	69:31
5	318	0.2	32	75:25
6	319	0.2	96	86:14

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

^b Diastereomeric ratio: determined by ^1H NMR spectroscopy (400 MHz).

It was observed that the uncatalysed reaction occurred with moderate diastereoselectivity in favour of **trans-132** (entry 1). The rate of the background reaction (the suppression of which would be crucial for the development of an asymmetric protocol) could be significantly reduced (and the diastereoselectivity enhanced) by lowering the concentration (entry 2). The use of Hünig's base as a catalyst (entry 3) led to considerably faster reactions with no improvement in diastereoselectivity, however it was pleasing to observe that sub-stoichiometric catalysis of this reaction by an amine base was possible. Hünig's base and *N,N*-diaryl urea **318** were used in order to simulate the bifunctional catalysis provided by a urea-substituted cinchona alkaloid-derived organocatalyst; albeit in an achiral environment. The combination of these two catalysts afforded equally high yields as those observed using a base alone, however the diastereoselectivity obtained was marginally lower (entry 4). The author observed that the use of urea **318** as a catalyst, actually inhibited the reaction: low yields were detected and the diastereoselectivity was unchanged relative to the uncatalysed reaction

(entry 5). Most gratifyingly, excellent yields of lactone **312** were obtained when the urea-substituted cinchona alkaloid-derived organocatalyst **319** (previously synthesised by Dr. Aldo Pesciulli)²⁸⁶ was employed to promote the reaction (entry 6). The diastereoselectivity was also significantly higher than that observed with the combined use of an amine and urea **318** (compare entries 4 and 6) which was indicative of the importance of the chiral scaffolding provided by the molecular framework of cinchona alkaloids, and suggested a possible synergy between the two catalyst functional groups capable of facilitating general base catalysis and hydrogen-bond donation.

In a second series of experiments, the catalysis of the reaction provided by bifunctional catalyst **319** was further investigated by the author and the results are reported in Table 3.2.

Table 3.2 The reaction of **139** with **96** promoted by catalyst **319**: the influence of reaction time and solvent

entry	solvent	time (h)	yield of combined diastereomers (%) ^a	<i>dr</i> ^b <i>trans</i> : <i>cis</i>
1	THF	1	85	86:14
2	THF	2	91	86:14
3	THF	18	96	86:14
4	MTBE	2	93	87:13

^a Determined by ¹H-NMR spectroscopy using *p*-iodoanisole as an internal standard. ^b Diastereomeric ratio: determined by ¹H NMR spectroscopy (400 MHz).

It was observed that the annulation occurred rapidly at room temperature and excellent yields of lactones could be achieved even after short times at room temperature (entry 1). The *dr* was constant throughout the transformation, therefore excluding the participation of product epimerisation reactions (entries 1, 2 and 3). The reaction was performed using another less polar ethereal solvent (MTBE) and resulted in slightly

lower product yields (over 2 hours) and practically unchanged *dr* (compare entries 2 and 4). However, both anhydride **139** and catalyst **319** – which were fully soluble in THF – did not completely solubilise in MTBE and therefore it was decided to temporarily abandon the use of this solvent.

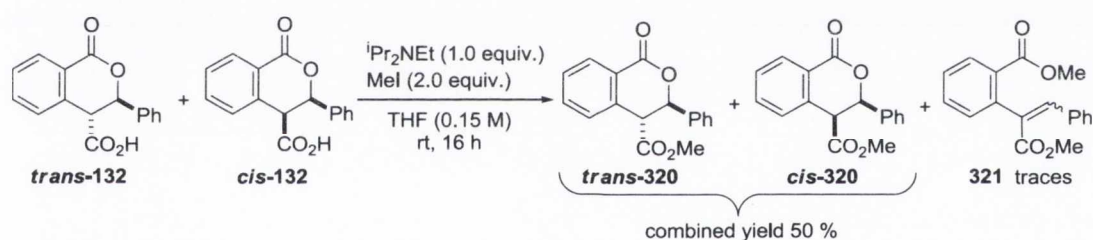
Palamareva *et al.*²⁰² described the possibility of separating the diastereomeric carboxylic acids products **132** by means of a double extraction (using a NaHCO₃ solution followed by a HCl solution) and recorded the *dr* of the reactions only after this extractive work-up. In an attempt to verify whether this procedure was affecting the diastereoselectivity of the reaction (*e.g. via* epimerisation reactions, lactone opening or reduced solubility of either diastereomer), the *dr* was recorded both before and after the extractive work-up. It was observed that the ratio of diastereomeric products *trans*-**132**:*cis*-**132** remained unchanged.

The results obtained by this series of preliminary experiments indicated that the development of an asymmetric catalytic protocol for annulation reactions between homophthalic anhydride (**139**) and aldehydes using cinchona alkaloid-derived organocatalysts was feasible. It was therefore decided, in cooperation with Mr. Francesco Manoni, to establish a methodology that would allow for the evaluation of the enantioselectivity provided by these catalysts.

3.2.2 Esterification of the carboxylic acids products prior to the assessment of their enantiomeric excesses

The diastereomeric lactones formed *via* annulation reaction between anhydride **139** and benzaldehyde **96** possess a carboxylic acid group which renders their separation and purification by column chromatography on silica gel problematic. Likewise, the separation of the diastereomeric pair *via* crystallisation was deemed incompatible with an unbiased assessment of the enantiomeric excesses of the carboxylic acid-bearing products; the diastereomers may co-crystallise, or an enhancement of the enantiomeric purity of the crystals formed could result.²⁸⁷ It seemed therefore logical to functionalise the carboxylic acid groups on *trans*-**132** and *cis*-**132** as methyl esters and subsequently separate the diastereomeric esters by column chromatography.

Palamareva *et al.*²⁰² reported that the esterification of these types of carboxylic acids (albeit only on *trans*-isomers which they obtained by crystallisation) could be achieved by using a combination of K_2CO_3 and methyl iodide. This protocol was attempted and was successful in affording *trans*-**320**, however *cis*-**320** could not be observed and compound **321** was formed instead; prompting us to discard this methodology. It was reasoned that the formation of **321** occurred *via* deprotonation at C-4 of the esters **320** and subsequent opening of the lactone, followed by esterification of the carboxylic acid formed. The use of a mixed anhydride method using a combination of ethyl chloroformate (**282**), triethylamine and methanol was also deemed inadequate, since it afforded a mixture of *trans*-**320**, *cis*-**320** and product **321**. On the contrary, the use of an organic base and methyl iodide afforded a diastereomeric mixture of esters **320** and only traces of product **321** (Scheme 3.2). In this regard, it was reported that the use of Hünig's base (iPr_2NEt) afforded higher yields of esters **320** than those obtained employing triethylamine as the base.



Scheme 3.2 Esterification of racemic carboxylic acids **132**

It was observed that *trans*-**320** and *cis*-**320** could be separated by column chromatography, however it was initially decided to analyse the diastereomeric mixture by CSP-HPLC. The task of separating the four stereoisomers by using CSP-HPLC proved complicated, however it was eventually possible to obtain conditions that could enable the assessment of enantiomeric excesses for both diastereomers. The chromatogram associated with a racemic mixture of esters **320** is reported in Figure 3.2.

With a general procedure and analysis protocol in hand, it was decided to evaluate several cinchona-alkaloid derived organocatalysts in this transformation.

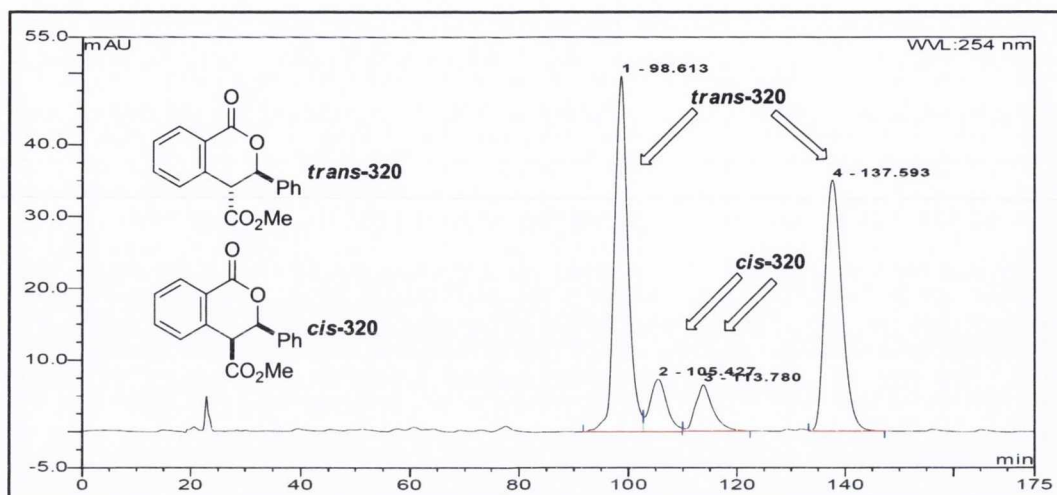


Figure 3.2 CSP-HPLC chromatogram of a racemic mixture of diastereomeric esters *trans*-320 and *cis*-320

3.3 Evaluation of cinchona alkaloid-derived organocatalysts in the formal cycloaddition between homophthalic anhydride and benzaldehyde

Our group has been involved in the past years in the development of novel bifunctional cinchona-based organocatalysts which have seen numerous successful applications in a wide range of mechanistically unrelated reactions. A relatively large library of these catalysts was available at the outset of this investigation, and therefore we were in a privileged position to evaluate and compare the catalytic performance of several cinchona-based organocatalysts in the annulation reaction between homophthalic anhydride (**139**) and benzaldehyde (**96**). The structure of the catalysts used (which were kindly provided by fellow researchers) are reported in Figure 3.3, while the results stemming from their evaluation are reported in Table 3.3. In this phase, Mr. Francesco Manoni assessed the catalytic activity of cinchona-based organocatalysts different to those shown in Figure 3.3, allowing a more precise picture of the optimal steric and electronic properties required to bring about the enantioselective catalysis of this transformation.

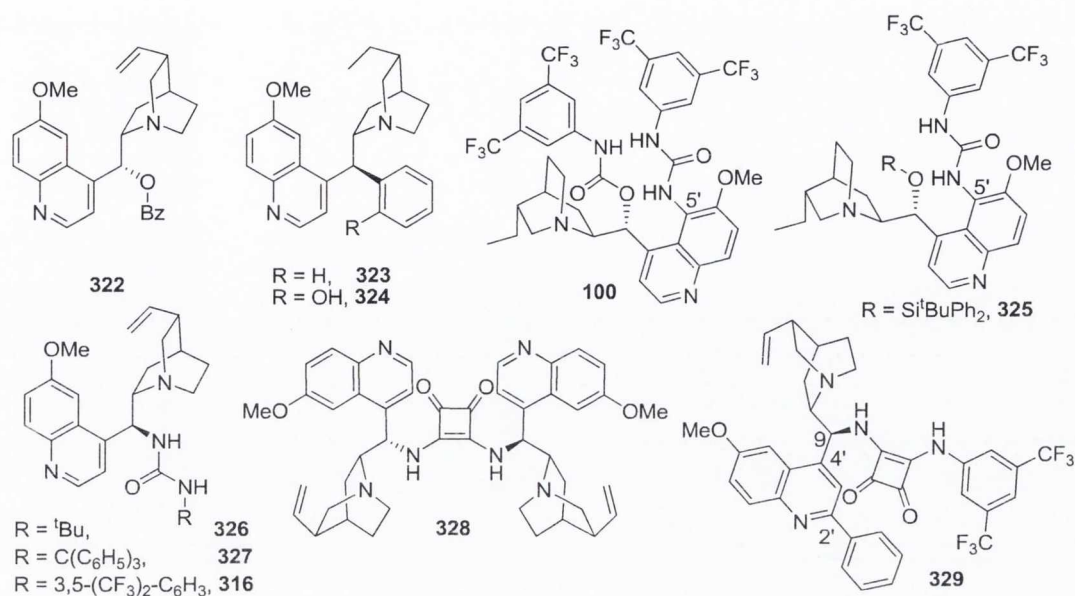


Figure 3.3 Structures of cinchona alkaloid-derived organocatalysts evaluated

Table 3.3 Evaluation of the catalytic activity of several cinchona alkaloid-derived organocatalysts

entry	cat.	yield of combined diastereomers (%) ^a	<i>dr</i> ^b <i>trans</i> : <i>cis</i>	<i>ee</i> _{<i>trans</i>} (%) ^c	<i>ee</i> _{<i>cis</i>} (%) ^c
1	322	93	83:17	-28	-1
2	323	>95	68:32	1	-3
3	324	93	78:22	-21	-3
4	100	82	85:15	10	-20
5	325	>95	83:17	23	-39
6	326	96	86:14	72	40
7	327	>95	76:24	58	51
8	316	97	86:14	66	70
9	328	86	78:22	40	32
10 ^d	329	96	91:9	93	65

^a Determined by ¹H NMR spectroscopy using *p*-iodoanisole as an internal standard. ^b Diastereomeric ratio: determined by ¹H NMR spectroscopy (400 MHz).

^c Determined by CSP-HPLC. ^d Reaction time: 24 h.

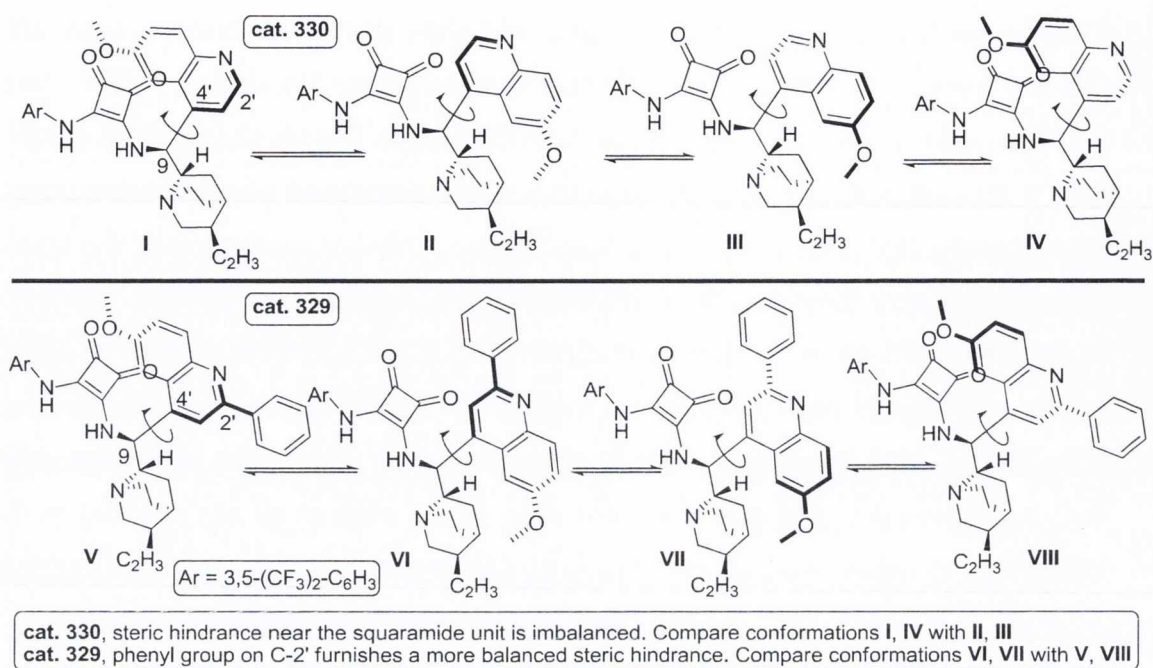
Both monofunctional and bifunctional catalysts were evaluated and different hydrogen-bond donating moiety were compared. In every case the crude reaction mixture was treated using the aforementioned extractive work-up procedure and the diastereomeric mixture of carboxylic acids obtained was analysed by ^1H NMR to determine the *dr*. The carboxylic acids were subsequently esterified and purified by column chromatography to obtain a diastereomeric mixture of esters **320**, the enantiomeric excesses of which could be determined by CSP-HPLC. Some general trends could be observed in every catalysed reaction irrespective of the catalysts' structure: excellent product yields were obtained and a preference for the formation of the *trans*-isomer was observed. The enantioselectivities for the minor *cis*-isomer seemed to benefit to a certain extent from the presence of a dual hydrogen-bond donating moiety (compare entries 1-3 with 4-10).

It was observed that the monofunctional *O*-benzoylated derivative of quinine **322** promoted the reaction – probably acting as a chiral base – with marginally lower diastereoselectivity compared to the previously evaluated bifunctional catalyst **319**, however with product enantiomeric excesses which were inadequate (entry 1). The recently developed mono- and bifunctional C-9 arylated alkaloids **323** and **324** (kindly provided by Mr. Cormac Quigley),¹⁶¹ afforded products with poor enantiomeric excesses (entries 2 and 3), however the comparison of their performance was indicative for the importance of a bifunctional mode of action (*i.e.* the presence of a hydrogen-bond donating moiety). In this regard, the comparison between catalyst **324** and **319** clearly stressed the superiority of the urea moiety compared to the hydroxy group as a hydrogen-bond donor (compare entries 3 and 8). The quinidine-derived catalysts **100** and **325**, which possess a urea moiety at the C-5' position, were developed in our group and recently proved to be excellent catalysts for Henry reactions¹⁴² and Michael additions¹⁴³ respectively (see Section 1.5.2.1.3). These catalysts were provided by fellow researcher Ms. Carole Palacio, however they promoted the reaction with low levels of product *ee* (entries 4 and 5).

The catalytic performance of C-9-*N,N*-dialkyl urea-substituted cinchona alkaloids **326** and **327** was subsequently evaluated and compared with that of the less sterically hindered *N*-aryl urea derivative **319** (the three catalysts were previously synthesised by Dr. Aldo Pesciulli).²⁸⁶ The exchange of an electron-deficient aryl group on the urea moiety in **319** for alkyl groups such as the *tert*-butyl on **326** or the trityl on **327** most

likely caused a perturbation of the hydrogen-bond interactions (see Section 1.5.2.1.4), however this did not influence the *dr* of the transformation. The optical purity of the *trans*-product was affected by the change: a slightly higher *ee* was produced using *N,N*-dialkyl urea catalyst **326**, however the enantiocontrol diminished when the increasingly bulky catalyst **327** was used, which was indicative of the importance of the steric hindrance in the vicinity of the hydrogen-bond donating moiety (entries 6-8).

In order to explore the catalytic performance of catalysts bearing a different dual hydrogen-bond donating moiety at C-9, it was decided to evaluate squaramide-substituted cinchona alkaloids, which were prepared and kindly provided by Mr. Séan Tallon. The C₂-symmetric analogue **328**, which is an excellent catalyst for the addition of alcohols to azlactones,²⁸⁸ was unsuitable for use in the reaction currently under study (entry 9). Simultaneously, Mr. Francesco Manoni made the crucial observation that the use of a squaramide-substituted cinchona alkaloid (*i.e.* **330**, Scheme 3.3) afforded excellent products *ee* (*i.e.* 90% *ee* for the *trans*-isomer) albeit still with unsatisfactory *dr* (*i.e.* *trans:cis* 84:16). This was possibly due to the unique features of the squaramide moiety in terms of hydrogen-bond donation (see Section 1.4.4) which improved the interaction either with homophthalic anhydride (**139**) or benzaldehyde (**96**) during the transition state of the reaction. Prompted by this promising result it was decided to modify catalyst **330** in order to obtain a species capable of promoting the reaction with increased asymmetric induction. It was envisaged that the installation of a moiety at the C-2' position of the quinoline ring could be beneficial to catalytic performance by balancing the steric requirement of the quinoline when this unit rotates around the C-4'–C-9 axis, which we proposed would render catalyst performance less dependent on the orientation of this heterocyclic substituent (Scheme 3.4). In order to verify our hypothesis, catalyst **329** (prepared by Mr. Séan Tallon) was evaluated in the reaction under scrutiny, and gratifyingly provided products with excellent diastereoselection and *ee* (entry 10).



Scheme 3.3 Rationale for the development of a C-2' substituted cinchona alkaloid-derived organocatalyst

3.3.1 Further optimisation of the reaction conditions

Prompted by the discovery that cinchona alkaloid-derived organocatalyst **329** outperformed all of the other candidates (including those evaluated separately by Mr. Francesco Manoni), it was decided to optimise the reaction conditions. The influence of solvent and concentration were assessed using catalyst **329**, the results of this study are reported in Table 3.4.

The reaction was initially attempted in THF at concentrations lower than those employed in previous evaluation studies (*i.e.* 0.2 M, entry 1). This choice was motivated by the significant inhibition of the uncatalysed reaction by lowering the concentration, as observed by Mr. Francesco Manoni (see Table 3.1). The reaction performed at 0.01 M led to the formation of the major isomer in lower *ee* and *dr* with an unexpected simultaneous improvement of the enantiomeric excess of the minor product (entry 2). A halving of the concentration from the initial conditions (*i.e.* 0.1 M) led to the formation of *trans*-products with slightly improved enantio- and diastereocontrol (entry 3). The use of MTBE was evaluated, since preliminary experiments with catalysts **319** indicated

that slightly improved diastereocontrol could be achieved in this solvent (see Table 3.2). The reaction in MTBE was heterogeneous, however *trans*-**320** could be obtained with improved *dr* and *ee* (entry 4). The use of more polar solvents such as dichloromethane and acetonitrile led to lower yields and diastereoselectivity (entries 5 and 7). Possibly in these solvents the pK_a of the carboxylic acids formed is lower than in ethereal solvents causing the protonation of the quinuclidine nitrogen and the inhibition of the catalysis. Finally, toluene was evaluated, however despite the excellent product yields and *dr* obtained, the optical purity of the products was inferior in this solvent. This short study seemed to confirm the hypothesis that the use of ethereal solvents is crucial for reactions catalysed by bifunctional organocatalysts in which a carboxylic acid product is formed; MTBE was considered the solvent of choice for further studies.

Table 3.4 Effect of both concentration and solvent on the catalytic performance of **329**

entry	time (h)	solvent	conc. (M)	temp. (°C)	yield (%) ^a	<i>dr</i> ^b <i>trans</i> : <i>cis</i>	<i>ee</i> _{<i>trans</i>} (%) ^c	<i>ee</i> _{<i>cis</i>} (%) ^c
1	24	THF	0.2	rt	96	91:9	93	65
2	20	THF	0.01	rt	97	82:18	91	92
3	18	THF	0.1	23	98	91:9	94	73
4	18	MTBE	0.1	23	>95	92:8	95	61
5	36	CH ₂ Cl ₂	0.1	23	57	82:18	n.d. ^d	n.d. ^d
6	18	PhMe	0.1	23	>95	90:10	87	26
7	36	MeCN	0.1	23	65	72:28	n.d. ^d	n.d. ^d

^a Yield of the combined diastereoisomers; determined by ¹H NMR spectroscopy using *p*-iodoanisole as an internal standard. ^b Diastereomeric ratio; determined by ¹H NMR spectroscopy (400 MHz). ^c Determined by CSP-HPLC. ^d Not determined.

3.4 Evaluation of the substrate scope: the aldehyde component

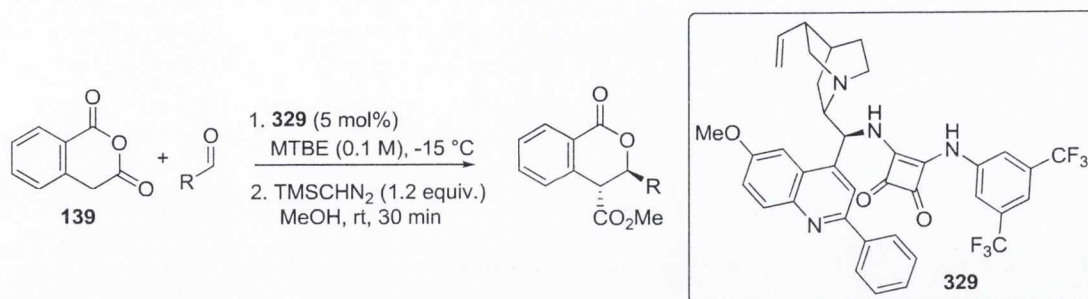
With a synthetically useful protocol in hand, it was decided to evaluate the substrate scope of this reaction by using different aldehydes. A major drawback was the low-

yielding esterification methodology involving the use of methyl iodide and Hünig's base which allowed the analysis by CSP-HPLC but at the expense of the overall isolated yield of pure major *trans*-diastereomer. It was therefore decided to exchange this methodology with a more efficient protocol involving the treatment of the crude mixture of carboxylic acids with trimethylsilyl diazomethane (TMSCHN₂) and methanol. A wide range of aromatic and aliphatic aldehydes were evaluated in the annulation reaction with homophthalic anhydride (**139**) promoted by catalyst **329** (at 5 mol% loading) in MTBE and -15 °C (at this temperature improved product *ee* were obtained by Mr. Francesco Manoni); the results are reported in Table 3.5.

The methodology proved extremely robust: electron-deficient- (entries 1 and 2), hindered- (entry 3) and heterocyclic aromatic (entry 4) aldehydes were well tolerated by the catalyst. Yields and enantiomeric excesses of the isolated *trans*-diastereomers **331**-**334** were generally excellent ($\geq 90\%$ yield and $\geq 96\%$ *ee* respectively). Aliphatic aldehydes were used for the first time in this type of transformation and were found to be compatible with catalyst **329**, providing product *trans*-**336** in high yields and excellent enantiomeric excess albeit over longer reaction times (entry 6). While the *dr* was uniformly excellent in the case of aromatic aldehydes, the use of an aliphatic aldehyde led to acceptable but elevated levels of the *cis*-diastereomer, which could be slightly reduced by performing the reaction at a lower temperature (*i.e.* -30 °C). The separation of the diastereomeric esters by column chromatography was not feasible in this case, however this drawback was somewhat mitigated by the fact that both *trans*- and *cis*-diastereomers were formed in near optical purity.

The use of 3-pyridinecarboxaldehyde led to the formation of *trans*-**335** in lower diastereocontrol and mediocre *ee* (entry 5). This result may be due to the basic pyridine nitrogen interfering with the catalytic activity of **329**. Indeed, even considering the higher basicity of the quinuclidine nitrogen on **329**, the presence of a large excess of 3-pyridinecarboxaldehyde (relative to **329**) at the beginning of the reaction might have led to the formation of the active enolate of homophthalic anhydride *via* a pyridine-promoted deprotonation in an achiral environment. In this regard, it was reported by Aitken *et al.* that in cinchona alkaloid-catalysed addition reactions on cyclic anhydrides the enantioselective catalysis provided by the quinuclidine nitrogen may be in competition with non-selective catalysis by the quinoline nitrogen.²⁸⁹

Table 3.5 Evaluation of the substrate scope: the aldehyde component



entry	Product	time (h)	yield (%) ^a	<i>dr</i> ^b <i>trans:cis</i>	<i>ee</i> _{trans} (%) ^c
1	 <i>trans</i> -331	48	93	97:3	96
2	 <i>trans</i> -332	48	93	95:5	97
3	 <i>trans</i> -333	48	95	97:3	99
4	 <i>trans</i> -334	48	90	93:7	98
5	 <i>trans</i> -335	22	82	84:16	64
6 ^d	 <i>trans</i> -336	93	98 ^e	78:22	98 (97) ^f

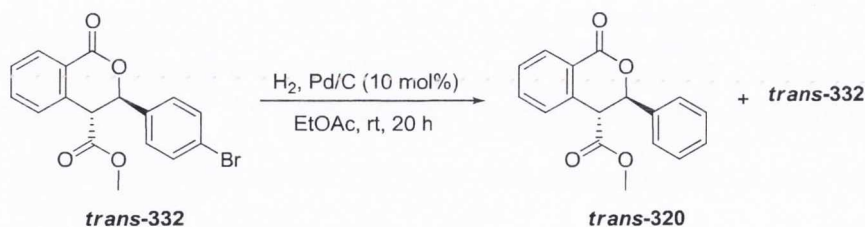
^a Isolated yield of the *trans*-diastereomer after column chromatography.

^b Diastereomeric ratio: determined by ^1H NMR spectroscopy (400 MHz). ^c Determined by CSP-HPLC. ^d Reaction performed at $-30\text{ }^{\circ}\text{C}$. ^e Diastereomers inseparable: combined isolated yield. ^f *ee* of *cis*-isomer in parenthesis.

3.4.1 Assignment of the absolute stereochemistry of *trans*-332 by X-ray crystal diffraction analysis and of *trans*-320 via reductive debromination

The lack of asymmetric protocols for the annulation reaction between enolisable anhydrides and aldehydes prompted us to assign the absolute stereochemistry of the products we obtained. We decided to obtain a crystal of *trans*-332, since the presence of a heavy atom (*i.e.* bromine) was a desirable feature for a more accurate determination of the absolute configuration. Most gratifyingly, recrystallisation of *trans*-332 from a mixture of ethyl acetate and hexane afforded a crystal that could be analysed using X-ray diffraction. The molecular structure obtained (see the Appendix at the end of this thesis for experimental details) could be used to unequivocally assign the absolute stereochemistry as (3*R*,4*R*).

We subsequently assigned the configuration also to *trans*-320 (derived from the addition of homophthalic anhydride to benzaldehyde in the presence of catalyst 329). A reductive debromination of *trans*-332 was accomplished on a small scale (*i.e.* 0.06 mmol) *via* catalytic hydrogenation at room temperature and atmospheric pressure using Pd on charcoal (10 mol%) in order to obtain *trans*-320 (Scheme 3.4). The crude mixture was purified by column chromatography. Even though it was not possible to separate the desired *trans*-320 from the unreacted *trans*-332, the CSP-HPLC chromatogram associated with the mixture could be compared with that of pure *trans*-320, which allowed the assignment of the absolute configuration of *trans*-320 as (3*R*,4*R*). Accordingly, we assigned the absolute configuration of *trans*-331–336 by analogy.



Scheme 3.4 Reductive debromination of *trans*-332 to form *trans*-320

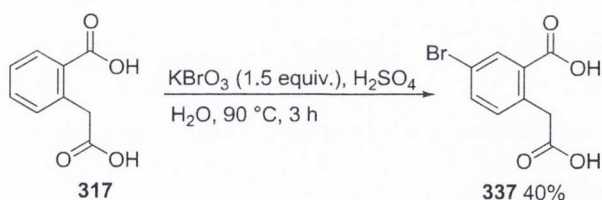
3.5 Evaluation of the substrate scope: the anhydride component

The substrate scope of the annulation reaction using homophthalic anhydride and aldehydes was proved to be broad with regard to the aldehyde component, therefore it was decided to explore the possibility of using enolisable anhydrides other than **139**.

3.5.1 Evaluation of substituted homophthalic anhydrides

It was initially decided to evaluate substituted homophthalic anhydrides in annulation reactions with benzaldehyde using the asymmetric methodology previously employed for the screening of aldehydes. Substitution at the aromatic ring is a feature of several of the medically relevant bicyclic dihydroisocoumarin compounds²¹⁸⁻²²⁹ (see Section 1.6.6.1) and with this regard we were prompted to investigate the effect of electron-withdrawing and electron-donating functionality on the aromatic ring of homophthalic anhydride (**139**).

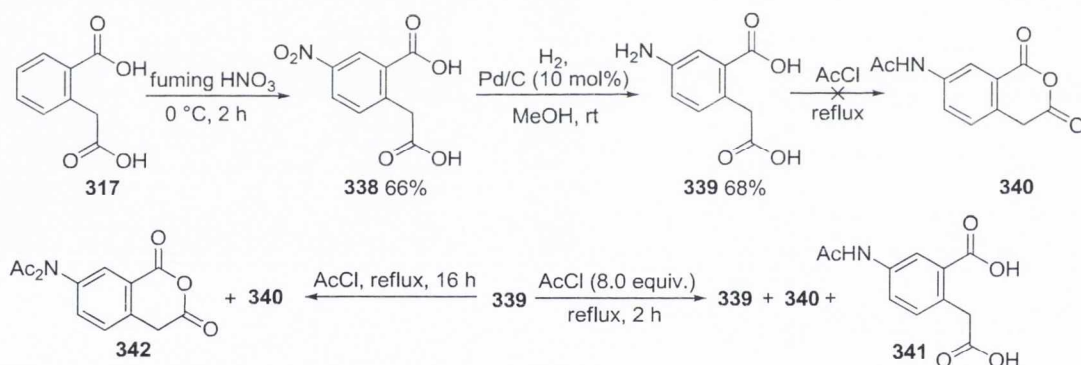
The synthesis of the bromo-substituted dicarboxylic acid **337** was achieved in moderate yields by a regioselective bromination of homophthalic acid **317** using potassium bromate and H₂SO₄ as described by Balci *et al.*²⁹⁰ (Scheme 3.5). The dicarboxylic acid **337** was converted into the corresponding bromo-substituted homophthalic anhydride by Mr. Francesco Manoni who was also responsible for its evaluation.



Scheme 3.5 Synthesis of 5-bromo-2-(carboxymethyl)benzoic acid (**337**)

The synthesis of an amide-substituted homophthalic anhydride (*i.e.* **340**) from homophthalic acid **317** over three steps had been previously reported (Scheme 3.6).²⁹¹ We were interested in preparing and evaluating this substrate in order to assess the effects of a moderately electron-donating group on the reactivity of homophthalic anhydrides. The regioselective nitration of homophthalic acid (**317**) using fuming nitric

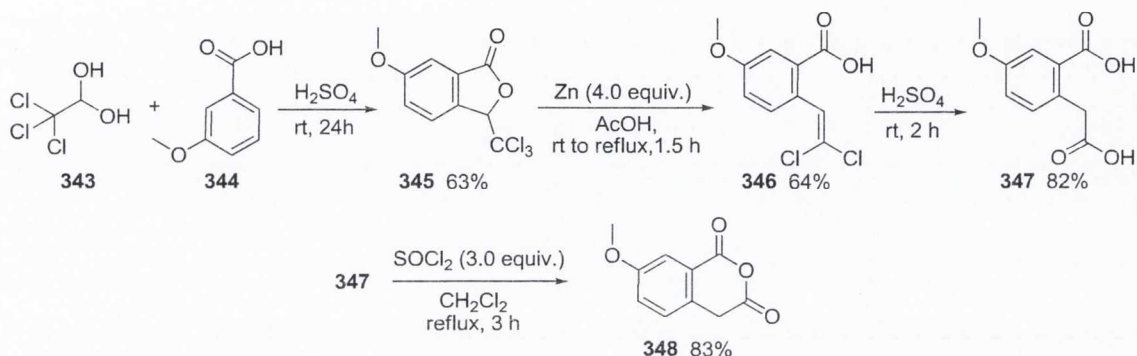
acid at low temperatures led to the formation of the dicarboxylic acid **338** in good yields. The subsequent catalytic hydrogenation of the nitro group using Pd on charcoal (10 mol%) at atmospheric pressure afforded the amine-substituted homophthalic acid **339**, which could be purified by recrystallisation from water. The formation of anhydride **340** was described as a one-pot reaction which involved heating at refluxing temperature for 2 hours the dicarboxylic acid **339** and a slight excess of acetyl chloride.²⁹¹ This methodology was attempted, however, ¹H NMR spectroscopic analysis of the crude product obtained revealed the presence of a mixture of unreacted **339**, anhydride **340** and **341**. Longer reaction times afforded a combination of **340** and **341** in a 9:1 ratio, however **341** could not be obtained pure by column chromatography. The use of acetyl chloride in larger excess led to the formation of a mixture of anhydrides **340** and **342**, which could not be purified either by recrystallisation or by column chromatography. Faced with these unexpected difficulties, we decided to temporarily abandon the synthesis and evaluation of anhydride **340**.



Scheme 3.6 Attempted synthesis of anhydride **340**

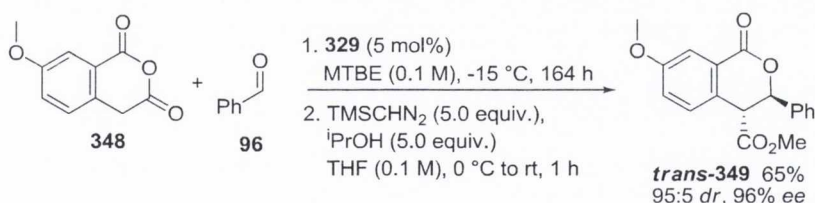
The observation that the most common substituents on the aromatic ring of naturally occurring 3,4-dihydroisocoumarins are methoxy- and hydroxy groups (see Section 1.6.6.1), prompted us to prepare and evaluate a methoxy-substituted homophthalic anhydride (*i.e.* **348**). The dicarboxylic acid **347** (which is the precursor of anhydride **348**) was prepared over three steps following a procedure based on the reports by Hill *et al.*²⁹² and Usgaonkar *et al.*²⁹³ Chloral hydrate (**343**) was reacted with *m*-methoxybenzoic acid (**344**) in concentrated sulphuric acid to afford the lactone **345** bearing a trichloromethyl group. The reductive dechlorination of **345** using zinc in acetic acid led to the formation of carboxylic acid **346** which, upon reaction with concentrated

sulphuric acid, was converted to methoxy-substituted homophthalic acid **347**. This compound was subsequently transformed into the desired anhydride **348** on a reaction with thionyl chloride, as previously reported by Balci *et al.*²⁹⁴ The anhydride could be obtained pure in good yield by trituration in diethyl ether (Scheme 3.7).



Scheme 3.7 Synthesis of the methoxy-substituted homophthalic anhydride **348**

The methoxy-substituted homophthalic anhydride **348** was evaluated in the annulation reaction with benzaldehyde (**96**) using the optimised protocol previously employed for the screening of aldehydes (Scheme 3.8).



Scheme 3.8 Asymmetric annulation reaction between anhydride **348** and benzaldehyde promoted by catalyst **329**

The electron-donating methoxy group was found to be compatible with catalyst **329**: *trans*-**349** could be prepared in good yield and excellent *ee*. This observation was very appealing since it potentially enables the asymmetric synthesis of methoxy-substituted naturally occurring 3,4-dihydroisocoumarins. The reaction was slower than the analogous transformation involving homophthalic anhydride (**139**); most likely due to the electron-rich aromatic ring which, being conjugated with the enol form of the anhydride, disfavoured its formation. The esterification of the carboxylic acids was accomplished using a slightly modified protocol, which was previously optimised by

Mr. Francesco Manoni following his observation that lactones formed from substituted homophthalic anhydrides were more prone to deleterious ring opening by methanol.

3.5.2 Synthesis and evaluation of enolisable succinic anhydride derivatives in the asymmetric annulation reaction with benzaldehyde

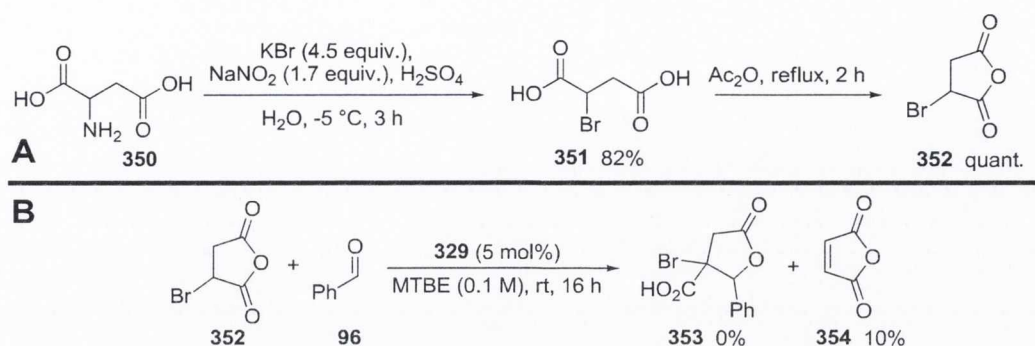
While it was established that our novel asymmetric protocol was of broad scope with respect to the aldehyde component and was compatible with homophthalic anhydrides bearing substituents on the aromatic ring, the requirement for a enol-stabilising benzo-fused structure was perceived as a restriction. It was envisaged that in principle any enolisable anhydride could undergo this reaction if catalysts such as **329** could catalyse the equilibrium between the keto and enol form of the anhydride.

The uncatalysed annulation reaction with aldehydes had been reported using succinic anhydride (and alkylated derivatives thereof), albeit using either harsh reaction conditions involving the use of Lewis acids or strong bases (see Sections 1.6.1 and 1.6.3). The use of succinic anhydride (**127**) in conjunction with benzaldehyde was ruled out because of early experiments by Mr. Francesco Manoni which highlighted the incompatibility of this anhydride with catalyst **329**. It appeared likely that the failure of succinic anhydride to serve as an effective substrate was due to impractically low concentrations of the reacting enol in solution.

Cushman¹⁷⁹ and Shaw^{181,197,198} reported that the presence of an enol-stabilising group on the succinic anhydride structural framework enabled the imine-based annulation reactions (which are not thought to proceed *via* the same mechanism, but which are likely to involve a similar rate-determining enolisation step) to occur under milder conditions (see Section 1.6.3). Along these lines it was decided to synthesise succinic anhydrides bearing enol-stabilising substituents and evaluate them in the annulation reaction with benzaldehyde promoted by catalyst **329**.

It was envisaged that the inclusion of a halogen atom on succinic anhydride could facilitate the formation of a reactive enolate. The synthesis of 2-bromosuccinic acid (**351**) was achieved in excellent yields from the commercially available racemic aspartic

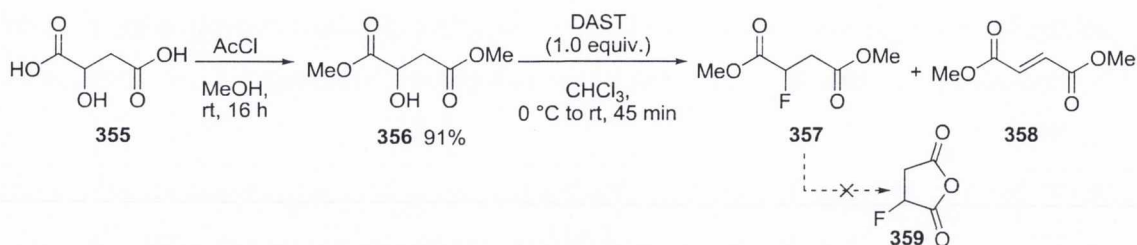
acid (**350**) *via* a Sandmeyer-type reaction.²⁹⁵ Anhydride **352** was subsequently obtained by heating the dicarboxylic acid **351** in acetic anhydride²⁹⁶ (Scheme 3.7, A).



Scheme 3.7 (A) Synthesis of 2-bromosuccinic anhydride (**352**) (B) its evaluation in the asymmetric annulation reaction with benzaldehyde

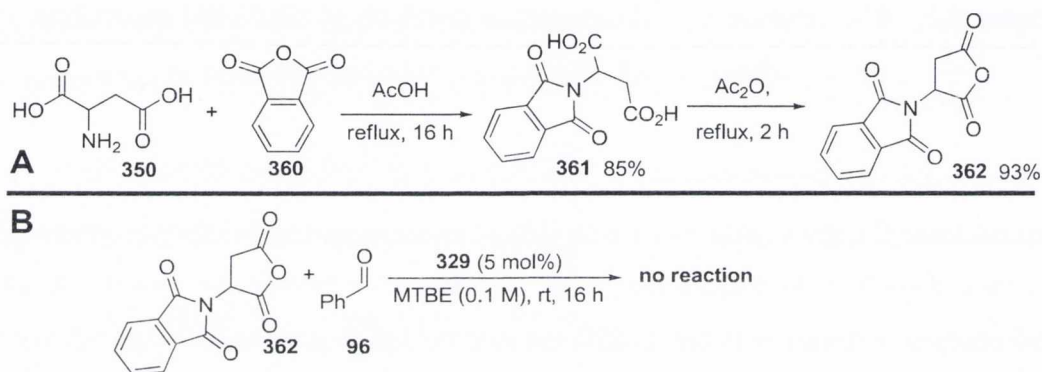
Unfortunately, the use of anhydride **352** in the asymmetric annulation reaction with benzaldehyde (**96**) promoted by catalyst **329** at room temperature failed to produce the desired lactone **353**. Analysis of the crude mixture by ¹H NMR spectroscopy indicated the formation of maleic anhydride (**354**) *via* an elimination process (Scheme 3.7, B).

This result prompted us to investigate the synthesis of 2-fluorosuccinic anhydride (**359**), which had the advantage of possessing a electron-withdrawing halogen atom with a decreased propensity to undergo elimination reactions. The commercially available malic acid (**355**) was reacted with acetyl chloride in methanol to form the corresponding *bis*-methylester (**356**), which was subsequently treated with the fluorinating agent diethylaminosulfur trifluoride (DAST) under reaction conditions previously described in the literature.²⁹⁷ ¹H NMR spectroscopic analysis of the crude mixture revealed the formation of the desired fluorinated product (**357**), however the presence of dimethyl fumarate (**358**) as a by-product was also detected (Scheme 3.8). The attempted purification of **357** either by Kugelrohr distillation or *via* fractional distillation proved unsuccessful (due to the tendency of **358** to sublime). These difficulties, combined with the lack of literature precedent describing the purification of either **357** or analogous derivatives, led us to temporarily abandon the synthesis of 2-fluorosuccinic anhydride (**359**).



Scheme 3.8 Attempted synthesis of anhydride **359**

The ready availability of aspartic acid (**350**) prompted us to evaluate the synthesis of anhydride **362** which was accomplished over two steps starting from the racemic amino acid **350** and the commercially available phthalic anhydride (**360**), Scheme 3.9, A.



Scheme 3.9 (A) Synthesis of anhydride **362** (B) its evaluation in the asymmetric annulation reaction with benzaldehyde

Disappointingly, the reaction between anhydride **362** and benzaldehyde failed to afford the desired lactone products. Analysis of the crude reaction mixture by ^1H NMR spectroscopy revealed that **362** was completely unreactive under the reaction conditions employed (Scheme 3.9, B).

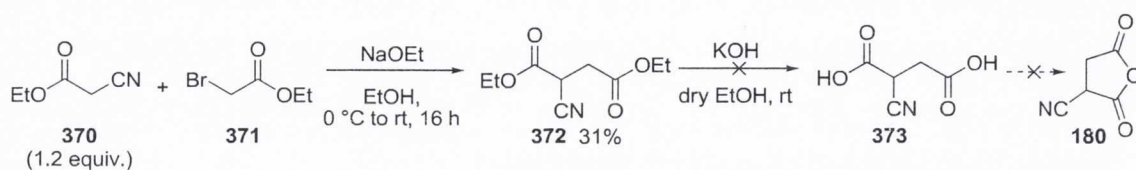
We decided to prepare anhydrides bearing more powerful electron-withdrawing groups. The synthesis of the trifluoromethyl-substituted succinic anhydride **369** had not been reported, however we envisaged that this substrate could be obtained *via* a reasonably straightforward synthetic route (Scheme 3.10). Diethyl malonate (**73**) was subjected to a *mono*-hydrolysis process to obtain the carboxylic acid **363**²⁹⁸ which was subsequently reacted with ketoester **364** in pyridine to form the product **365** *via* a decarboxylation reaction. This compound was subsequently transformed into alkene **366**.²⁹⁹ The catalytic hydrogenation of **366** using Pd on charcoal (10 mol%) at a pressure of 3 atm.

proved ineffective (the starting material could be quantitatively recovered). Therefore a reduction using NaBH₄ was employed, which afforded compound **367** which was subsequently hydrolysed under acidic conditions to afford the diacid **368**. Unfortunately, despite considerable experimentation, the *bis*-carboxylic acid failed to cyclise cleanly to form anhydride **369**. Reagents such as acetyl chloride, acetic anhydride and trifluoroacetic anhydride (TFAA), which are commonly employed for this type of transformations, proved ineffective here. Analysis by ¹H NMR and ¹⁹F NMR spectroscopy indicated the formation of the desired anhydride, together with multiple by-products which could not be identified.

Scheme 3.10 Attempted synthesis of anhydride **369**

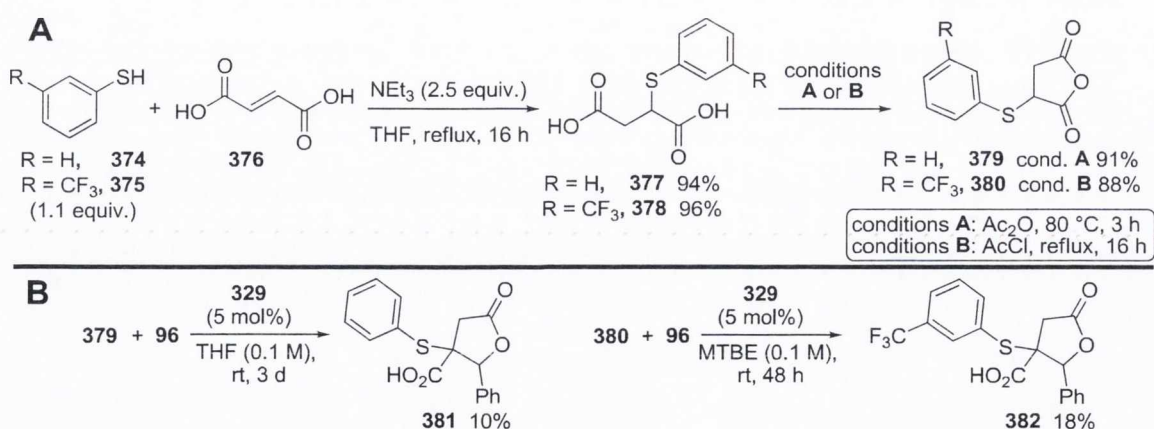
The cyano-substituted succinic anhydride **180** was not known at the beginning of this investigation and its synthesis proved to be very problematic (as later also acknowledged by Shaw *et al.*,¹⁹⁸ see Section 1.6.3). The alkylation of ethyl cyanoacetate (**370**) with ethyl bromoacetate (**371**) using sodium ethoxide in ethanol afforded complex mixtures of the desired *mono*-alkylated compound **372**, unreacted **369** and considerable quantities of *bis*-alkylated compound. The isolation of pure **372** by Kugelrohr distillation proved troublesome, contributing to the low yield of the reaction. The hydrolysis of the diester **372** was attempted using KOH in anhydrous ethanol. This choice was motivated by a previous study on a structurally related compound,³⁰⁰ however the analysis by ¹H NMR spectroscopy of the crude product obtained upon removal of the solvent *in vacuo* revealed that other unidentifiable products had formed.

but not the target material **373**. When we later became aware of the methodology employed by Shaw *et al.* for the hydrolysis of **372** (*i.e.* LiOH in a THF/water mixture at room temperature for 2.5 hours) we reasoned that our lack of success could have been ascribed to the use of a significantly stronger base and anhydrous reaction conditions which could have led to the formation of other by-products (Scheme 3.11).



Scheme 3.11 Attempted synthesis of anhydride **180**

Inspired by the use of thioaryl-substituted succinic anhydrides in annulation reactions with imines reported by Shaw *et al.*¹⁸¹ (see Section 1.6.3) we decided to evaluate these substrates in the mechanistically unrelated formal cycloaddition with aldehydes. Two anhydrides bearing this moiety were prepared: **381** and **382**. Their syntheses were accomplished over two steps: either thiophenol (**374**) or the commercially available thiol **375** were reacted with maleic acid (**376**) in the presence of triethylamine to obtain dicarboxylic acids **377** and **378** respectively. The cyclisation reactions to form the desired anhydrides **379** and **380** were accomplished by treating either of the corresponding diacids with either acetic anhydride or acetyl chloride (Scheme 3.12, A).



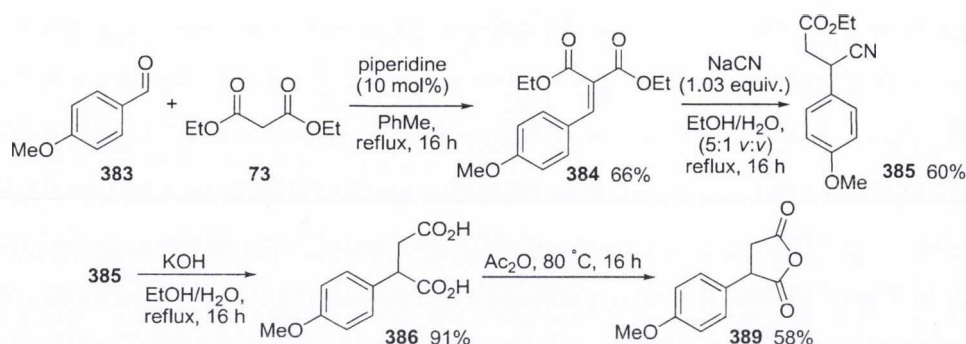
Scheme 3.12 (A) Synthesis of thioaryl-substituted anhydrides (B) their evaluation in the annulation reaction with benzaldehyde

These anhydrides were evaluated in the asymmetric cycloaddition reaction with benzaldehyde (**96**) promoted by catalyst **329** at room temperature as shown in Scheme 3.12, B. The desired lactones **381** and **382** could be obtained, albeit in low yields. An increase in concentration (*i.e.* 0.2 M) and refluxing temperatures proved ineffective in enhancing the yields of lactone **381**, and much longer reaction times afforded only slightly increased yields. We were pleased to observe the improved reactivity (relative to succinic anhydride and **379**) of anhydride **380** bearing a thioether moiety with an increased electron-withdrawing character, nonetheless the reactions using this type of anhydrides proved to be too slow to be considered synthetically useful.

3.5.3 Synthesis and evaluation of arylsuccinic anhydrides

Since the installation of enol-stabilising groups on enolisable anhydrides proved unsuccessful in increasing their reactivity, we became interested in arylsuccinic anhydrides, which were reported to react in annulation reactions with imines (see Section 1.6.3). My co-worker Mr. Francesco Manoni was more directly involved in the preliminary evaluation of these types of anhydrides, which he found were compatible with catalyst **329** and reacted with benzaldehyde (Table 3.6) to form substituted paraconic acids (see Section 1.6.6.1). Mr. Manoni found that the reactivity of arylsuccinic anhydrides improved with the introduction of electron-withdrawing groups on the pendant aromatic ring (compare entries 1 and 2). The author then also became involved in this investigation. Since it was noted that the enhanced reactivity of anhydrides relied on the presence of enol-stabilising substituents, we sought the confirmation of this reactivity trend by using an anhydride bearing an enol-destabilising electron rich aryl unit (*i.e.* **389**).

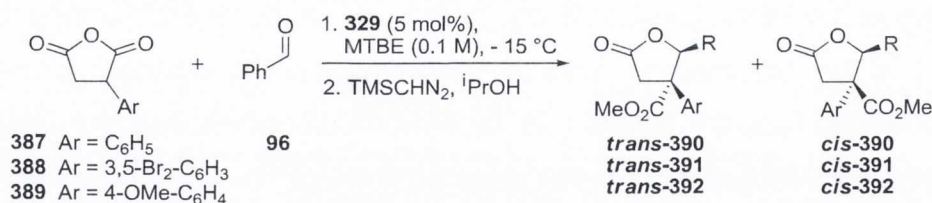
The synthesis of anhydride **387** was accomplished over four steps (Scheme 3.13). A Knoevenagel condensation between *p*-anisaldehyde (**383**) and diethyl malonate (**73**) afforded the α,β -unsaturated derivative **384**, which upon addition of NaCN and decarboxylation was transformed into compound **385**. The basic hydrolysis of both ester and nitrile functionalities provided diacid **386**, which was subsequently cyclised with acetic anhydride to afford the *p*-methoxy-substituted phenylsuccinic anhydride **389**.



Scheme 3.13 Synthesis of anhydride **389**

The annulation reaction between anhydride **389** and benzaldehyde provided very low yields of lactone product **392** (Table 3.6, entry 3) which allowed us to establish the principle of electronic control over the activity of anhydrides. In the interests of full disclosure, all of the data relative to this preliminary study are reported in Table 3.6; it is important to stress that the author only contributed the experiment outlined in entry 3 (highlighted) entries 1 and 2 stem from experimental work accomplished by Mr. Manoni.

Table 3.6 Evaluation of arylsuccinic anhydrides as substrates for the asymmetric annulation reaction with benzaldehyde



Entry	product	time (h)	yield (%) ^a	<i>dr</i> ^b	<i>ee</i> _{trans}
				(<i>trans</i> : <i>cis</i>)	(%) ^c
1	390	110	34	97:3	83
2	391	97	76	94:6	76
3	392	93	7 ^d	n.d. ^e	n.d. ^e

^a Yield of the combined diastereoisomers: determined by ¹H NMR spectroscopy using either *p*-iodoanisole or styrene as an internal standard.

^b Diastereomeric ratio: determined by ¹H NMR spectroscopy (400 MHz).

^c Determined by CSP-HPLC. ^d Yield of the carboxylic acid precursor of *trans*-**392**. ^e Not determined.

3.5.3.1 Evaluation of the substrate scope for the asymmetric annulation reaction using arylsuccinic anhydride **393**: the aldehyde component

Mr. Manoni observed that the introduction of an increasingly electron-withdrawing group on the aryl moiety of the anhydride component (*i.e.* NO₂, $\sigma_p = 0.81$), allowed the formation of γ -lactones products in excellent yields, enantio- and diastereoselectivities. Anhydride **393** was therefore chosen as the optimal substrate to be evaluated in annulation reactions (carried out by the author) using a wide range of aldehydes (Table 3.7).

Table 3.7 Evaluation of the substrate scope by changing the aldehyde component

393 Ar = 4-NO₂-C₆H₄

entry	product	time (h)	yield (%) ^a	<i>dr</i> ^b <i>trans:cis</i>	<i>ee</i> _{trans} (%) ^c
1	 MeO ₂ C Ar <i>trans</i> -394	100	93	95:5	82
2	 MeO ₂ C Ar <i>trans</i> -395	164	71	92:8	73
3	 MeO ₂ C Ar <i>trans</i> -396	161	63	95:5	91
4 ^d	 MeO ₂ C Ar <i>trans</i> -397	98	56	88:12	95

^a Isolated yield of the *trans*-diastereomer after column chromatography.

^b Diastereomeric ratio: determined by ¹H NMR spectroscopy (400 MHz). ^c Determined by CSP-HPLC. ^d Catalyst loading: 20 mol%

Compared to homophthalic anhydride (**139**), the reactions using arylsuccinic anhydride **393** under otherwise identical conditions proved to be significantly slower (compare Tables 3.5 and 3.7). One of the reasons for this reduced reactivity was most likely due

to the greater enol-stabilisation potential of the *p*-nitro phenyl group; nonetheless, the methodology using anhydride **393** was found to be extremely robust. Both electron-deficient (entry 1) and electron-rich aldehydes (entry 2) reacted with anhydride **393** to give the isolated *trans*-butyrolactones **394** and **395** with excellent diastereocontrol. As expected the less electrophilic *p*-anisaldehyde required longer reaction times and afforded lower (albeit synthetically useful) yields (entry 2). The levels of enantiomeric excess of these products were good to moderate, with the use of a deactivated aldehyde leading to product *trans*-**395** with slightly lower *ee*. The use of a hindered aldehyde (entry 3) resulted in reduced product yields but a sharp increase in enantioselectivity, which allowed the isolation of *trans*-**396** with excellent *ee*. An aliphatic aldehyde (entry 4) was also tolerated: *trans*-**397** could be formed in moderate yields using higher loadings of catalyst **329** in higher loadings. The product was formed with excellent enantiocontrol but lower diastereocontrol.

Other aldehydes were evaluated by Mr. Francesco Manoni and provided products with excellent diastereo- and enantioselectivities, among them heterocyclic aromatic aldehydes also proved to be compatible with this asymmetric methodology. In addition, the analysis by X-ray diffraction of a crystal obtained by my co-worker, allowed the unequivocal assignment of the absolute stereochemistry as (2*R*,3*S*). This configuration was subsequently assigned by analogy to all of the major diastereomers obtained *via* this methodology.

3.6 Asymmetric annulation reactions with aldehydes promoted by catalyst **329**: a proposed mechanism

In the absence of computational studies which could indicate the lowest energy transition state involved in the asymmetric annulation reactions under scrutiny and the lack of spectroscopic evidence suggesting the conformation adopted by the catalytic species, our proposal of a mechanism describing how a cinchona alkaloid-derived organocatalyst organises the encounter between the aldehyde and anhydride substrates is essentially speculative but fits the experimental data obtained.

It is generally accepted that in formal cycloaddition reactions between anhydrides and aldehydes the former are the nucleophiles while the latter represent the electrophilic

component. The mechanism is generally deemed to proceed *via* the enolisation of the anhydride and its attack on the carbonyl group (see Section 1.6.2.2). The experimental results obtained from this investigation seems to confirm this mechanism; we noticed that electronic effects play a significant role in these reactions and determine both the reactivity of anhydrides as nucleophiles (by promoting or disfavoured their enolisation) and that of aldehydes as electrophiles (by influencing the electrophilic character of the carbonyl group).

If we consider the reaction between homophthalic anhydride (**139**) and benzaldehyde (**96**) promoted by catalyst **329**, the knowledge of the absolute stereochemistry of the major lactone formed (*i.e.* (3*R*,4*R*)-**trans**-**320**) allows us to unequivocally establish that the *si*-face of the enolate interacted with the *re*-face of the aldehyde component (Figure 3.4, A). It is plausible that a degree of π -stacking between the aldehyde and homophthalic anhydride aromatic rings in reactions involving aromatic substrates may contribute to the high diastereocontrol, which would go some way towards explaining the lower diastereoselectivity observed in the corresponding reactions involving aliphatic aldehydes.

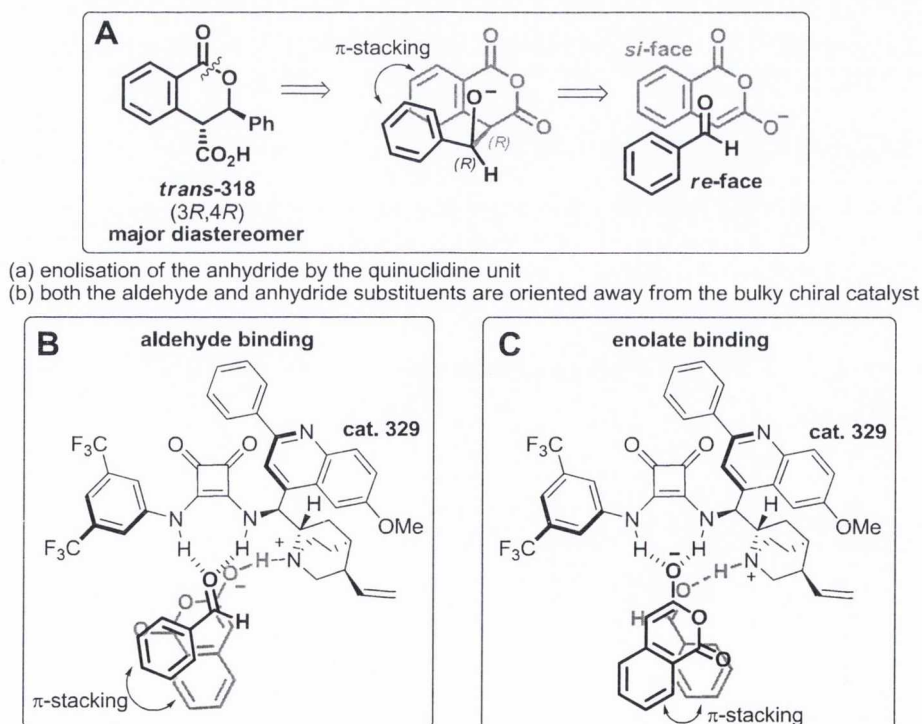


Figure 3.4 Proposed mechanism for annulation reactions promoted by catalyst **329**

It appears obvious that in the bifunctional catalysis exerted by **329** the chiral quinuclidine moiety is involved in the deprotonation of the anhydride pronucleophile and the formation of a reactive enolate species *via* base catalysis, the role of the hydrogen-bond donating moiety (*i.e.* the squaramide unit) seems more ambiguous. As it was the case with Takemoto's catalyst, the bifunctional catalytic activity of which could be described by two possible transition states (see Section 1.4.3), similarly with catalyst **329** two types of hydrogen-bond interactions are plausible: a binding with the aldehyde (Figure 3.4, B) and a binding with the enolate (Figure 3.4, C). Both of the binding modes account for the observed stereochemistry of the products and in both we suggested that the substrates are oriented in such a fashion to avoid steric clashes with the bulky chiral catalyst groups.

While it is imprudent to assume the exclusivity of one type of hydrogen-bond interaction on the basis of such a limited number of experimental results, we nonetheless reasoned that the 'aldehyde binding mode' could be more likely involved in this transformation as this transition state was in accordance with the data obtained. The most relevant observation supporting this hypothesis was the different levels of product *ee* obtained when *trans*-**320** was formed under the influence of either catalyst **319** (Table 3.3, entry 8) or **327** (Table 3.3, entry 7), which differ only by their steric character in the vicinity of the urea moiety. By using molecular models, we noted that, while maintaining the orientation of the substituents of both aldehyde and anhydride away from the bulky chiral catalyst, the 'aldehyde-binding' *pre*-transition state assembly involving the bulky catalyst **327** is characterised by an unavoidable steric clash (Figure 3.5, B), which is not a feature of either the corresponding assembly involving the less hindered catalyst **319** (Figure 3.5, A) or the 'enolate-binding' assemblies involving either **319** or **327** (Figure 3.5, C and D).

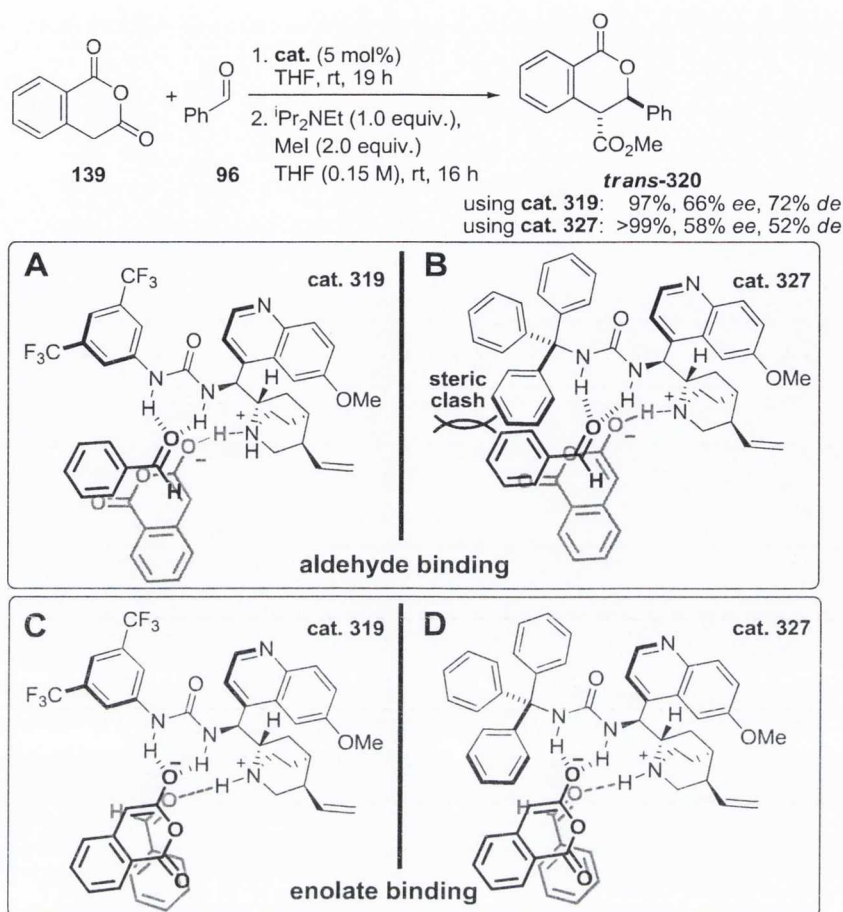


Figure 3.5 Formal cycloaddition reaction promoted by catalysts **319** or **327**: a comparison between different *pre*-transition state assemblies

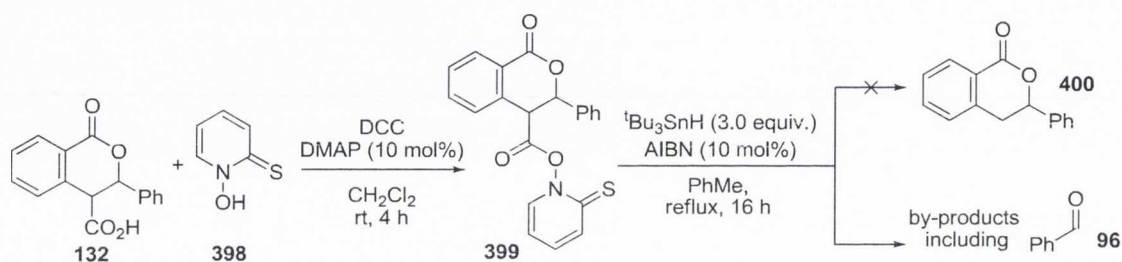
Since the reaction catalysed by **327** provided **trans-320** with lower enantio- and diastereocontrol than the corresponding reaction promoted by **319**, we would tentatively suggest that the *pre*-transition state assembly shown in Figure 3.5 A most accurately represents the catalyst-controlled encounter of the aldehyde and the anhydride.

3.7 Modification of the carboxylic acid group formed upon annulation reaction: towards the synthesis of natural products

The 3,4-dihydroisocoumarin motif is present in a wide range of natural products and is easily accessible in a one-pot procedure *via* the formal cycloaddition reaction between aldehydes and homophthalic anhydrides (see Section 1.6.6.1). Following the discovery of an asymmetric protocol which allowed the efficient high-yielding formation of 3,4-dihydroisocoumarins with excellent diastereo- and enantiocontrol, we became intrigued

by the possibility of exploiting this methodology for the synthesis of natural products. All of the reported natural 3,4-dihydroisocoumarins possessed either a single stereocentre at C-3 or a carbon-oxygen bond at C-4.

A Barton decarboxylation reaction was attempted on the crude diastereomeric mixture of carboxylic acid **132** in order to obtain product **400** with the simultaneous loss of a stereocentre. The reaction was carried out under standard conditions which involved the formation of 'Barton ester' **399** *in situ*, followed by its radical reductive decarboxylation (Scheme 3.14).



Scheme 3.14 Attempted Barton decarboxylation of the 3,4-dihydroisocoumarin **132**

Disappointingly, ^1H NMR spectroscopic analysis of the crude product, failed to detect the formation of the desired **400**. Multiple by-products were formed including considerable quantities of benzaldehyde, whose formation was most likely due to a cycloreversion reaction in competition with the desired reductive decarboxylation. Following this observation we reasoned that the Barton decarboxylation reaction of compounds such as **132** was not a viable option to prepare naturally occurring 3,4-dihydroisocoumarins.

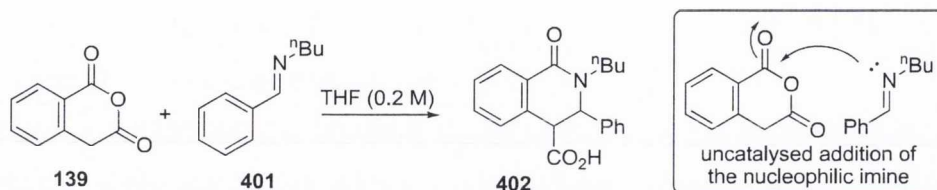
3.8 Evaluation of the substrate scope for annulation reactions with homophthalic anhydride by using different electrophiles

Intrigued by the excellent results obtained in the asymmetric annulation reaction between homophthalic anhydrides and aldehydes, we were encouraged to evaluate our newly established methodology using different electrophiles.

3.8.1 Use of imines in the asymmetric annulation reaction with homophthalic anhydride

It was initially decided to use imines as the electrophilic component in our asymmetric protocol. The mechanism for annulations involving imines is widely accepted to proceed *via* initial iminolysis of the anhydride (see Section 1.6.2.1), a fact that apparently seems incompatible with the proposed mode of action of cinchona alkaloid-derived bifunctional organocatalysts; nonetheless, numerous examples of the use of hydrogen-bond donating bifunctional organocatalysts to promote reaction additions to imines are known. In addition, Cossío *et al.*²⁰⁶ have reported diastereoselective formal cycloaddition reactions promoted by a Lewis acid and a base and invoked a reactivity in which the imine component acts as an electrophile, therefore we speculated that perhaps the use of a bifunctional organocatalyst could divert the annulation reaction mechanism involving imines away from initial iminolysis (as the catalyst would be expected to activate the imine towards electrophilic attack and simultaneously reduce its nucleophilicity) and towards a mechanism analogous to that proposed to occur using aldehyde substrates.

Initially we considered the annulation reaction between homophthalic anhydride (**139**) and the *N*-alkyl imine **401** (Table 3.8). We were rather disappointed to observe that this reaction occurred spontaneously in the absence of catalyst even at temperatures as low as -78 °C. Faced with this rapid uncatalysed reaction, we envisaged that attempting to implement our newly established asymmetric protocol with these substrates would be futile.

Table 3.8 Uncatalysed annulation reactions using *N*-alkyl aldimine **401**

entry	T (°C)	time (h)	yield of combined diastereomers (%) ^a
1	-30	15	>95
2	-78	15	>95
3	-78	0.5	70

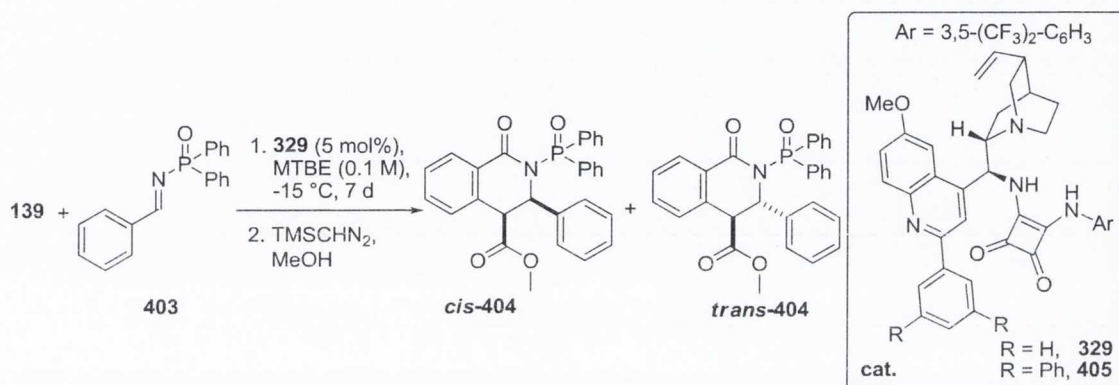
^a Determined by ¹H NMR spectroscopy using *p*-iodoanisole as an internal standard

We reasoned that a strategy which could allow us to circumvent this inconvenient reactivity would be the introduction of electron-withdrawing substituents at the nitrogen atom which would render it less nucleophilic and simultaneously enhance the electrophilicity of the carbonyl-derived carbon atom. We envisaged that this strategy could render the mechanism of the annulation reaction with imines more similar to that involved in the analogous transformation with aldehydes and thus more suitable to the promotion by bifunctional cinchona alkaloid-derived organocatalysts. Most gratifyingly, our hypothesis was confirmed when Dr. Esther Torrente reported that the uncatalysed reaction between homophthalic anhydride (**139**) and *N*-diphenylphosphinoyl aldimine **403** did not occur. Having proved this, we decided to evaluate the use of imine **403** as a substrate using our newly established asymmetric protocol (Table 3.9).

We were pleased to observe that the asymmetric annulation reaction between homophthalic anhydride and imine **403** provided a diastereomeric mixture of lactams (*i.e.* **404**), with the *cis*-isomer being the predominant product. The use of activated imines bearing electron-withdrawing groups appended at the nitrogen atom in formal cycloaddition reactions with enolisable anhydrides was unprecedented. The preliminary results obtained with these types of imines demonstrated that by lowering the nucleophilicity of the nitrogen atom it was possible to obtain lactam products which were more likely formed *via* the attack of the enolised **139**. The reaction proved significantly slower than the aldehyde-based methodology, and the enantio- and

diastereoselectivity reported with the use of catalyst **329** were moderate (Table 3.9, entry 1). The use of catalyst **405** (provided by Mr. Séan Tallon) bearing a bulkier group at the C-2' position provided increased diastereocontrol, however the *ee* for the major isomer *cis*-**403** was still modest (entry 2) which prompted the temporarily suspension of this investigation.

Table 3.9 Annulation reactions using *N*-diphenylphosphinoyl aldimine **402**



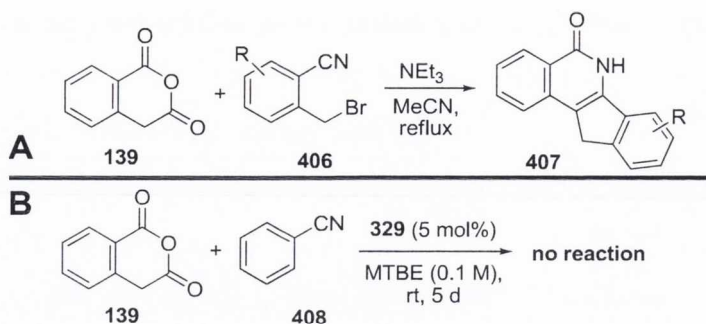
entry	cat.	yield of combined diastereomers (%) ^a	<i>dr</i> ^b (<i>cis</i> - 403 : <i>trans</i> - 403)	<i>ee</i> _{<i>cis</i>} (%) ^c
1	329	70	60:40	50
2	405	75	85:15	64

^a Determined by ¹H NMR spectroscopy using *p*-iodoanisole as an internal standard. ^b Diastereomeric ratio: determined by ¹H NMR spectroscopy (400 MHz).

^c Determined by CSP-HPLC.

3.8.2 Use of other electrophiles in the asymmetric annulation reaction with homophthalic anhydride

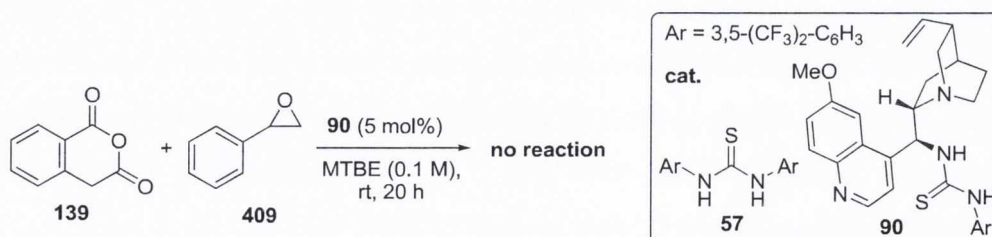
In view of the modest results obtained with the use of imines in annulation reactions, we decided to evaluate other electrophiles. Jagtap *et al.*³⁰¹ reported an interesting transformation involving the use of homophthalic anhydride (**139**) and *o*-cyanobenzyl bromides (*i.e.* **406**) which, upon heating at refluxing temperature in the presence of triethylamine, form tetracyclic compounds (*i.e.* **407**) *via* a presumed base-promoted alkylation-cyclisation-decarboxylation cascade process (Scheme 3.15, A).



Scheme 3.15 (A) The reaction between **139** and **406** reported by Jagtap *et al.* (B) An attempted annulation reaction between **139** and benzonitrile (**408**)

Due to the formation of a lactam product this transformation was appealing. We envisaged that the use of catalytic quantities of base and lower temperatures could have prevented the stereocentre-destroying decarboxylation pathway. Disappointingly, homophthalic anhydride (**139**) and benzonitrile (**408**) were found to be completely unreactive under the conditions employed (Scheme 3.15, B).

The alcoholysis^{100a} and aminolysis^{100b} of epoxides has been reported to benefit from catalysis provided by thiourea-based species (*i.e.* **57**) acting as hydrogen-bond donating moieties. The use of epoxides as electrophiles in annulation reactions with enolisable anhydrides is unprecedented, however it was hypothesised that (despite their lower electrophilicity compared to aldehydes) the reactivity of the enol of homophthalic anhydride combined with the release of the epoxide strain energy could have led to a bifunctional organocatalyst-promoted nucleophilic opening of the oxirane ring and the formation of lactone products. It was decided to evaluate the commercially available styrene oxide (**409**) as electrophile in the annulation reaction with homophthalic anhydride promoted by catalyst **90** which was preferred over other analogues due to its closer resemblance to catalyst **57** (Scheme 3.16).



Scheme 3.16 Attempted annulation reaction using styrene oxide as the electrophile

Disappointingly the analysis of the crude reaction mixture by ^1H NMR spectroscopy using *p*-iodoanisole as an internal standard revealed that the nucleophilic opening of epoxide **409** did not occur. Styrene oxide was found to be completely unreactive under the reaction conditions employed.

3.9 Conclusions

The goal of developing the first asymmetric catalytic protocol for formal cycloaddition reactions involving enolisable anhydrides has been successfully achieved. In this regard we demonstrated that cinchona alkaloid-derived organocatalysts are able to promote the reaction involving either homophthalic anhydrides or arylsuccinic anhydrides and a wide range of aldehydes. By using the novel *ad hoc*-designed bifunctional organocatalyst **329**, we were able to synthesise – under convenient conditions – 3,4-dihydroisocoumarins and paraconic acid derivatives bearing a quaternary stereocentre in good yields with excellent diastereo- and enantiocontrol over the formation of two chiral centres. In addition, it was demonstrated for the first time the possibility of using aliphatic aldehydes in annulation reactions with enolisable anhydrides. A *pre*-transition state assembly for the transformation involving organocatalyst **329** has been formulated, which accounts for the stereochemical outcome of the process.

It was demonstrated that the reactivity of anhydrides in annulation reactions is directly dependant on their enolisability in the presence of catalyst **329**. The synthesis of several non-benzofused cyclic anhydrides bearing enol-stabilising groups has been accomplished, and these substrates have been assessed in annulation reactions with benzaldehyde. The substituted succinic anhydrides which have been evaluated were found to be either unreactive or only marginally reactive under the reaction conditions employed, which is indicative for the necessity of installing a strongly enol-stabilising group on the structural framework of the anhydride component.

While bifunctional organocatalysts can effectively promote the asymmetric annulation with aldehydes, the use of other electrophiles in this transformation was less successful. However, it was demonstrated for the first time that imines bearing electron-withdrawing groups on the nitrogen atom could behave as the electrophilic component

in asymmetric annulation reactions and led to the formation of enantioenriched lactams, albeit in moderate yields and enantiomeric excess.

4.1 Towards the development of asymmetric formal cycloaddition reactions between enolisable anhydrides and ketones

It has been reported (in three unrelated studies) that ketones react with enolisable anhydrides in the presence of a Lewis acid additive in super-stoichiometric loadings to form lactone products *via* annulation reactions.^{184,203,250} Similarly to aldehydes, ketones are considered to be the electrophilic component in these transformations and are believed to undergo nucleophilic attack by the anhydride in its reactive enol(ate) form (see Section 1.6.7). The substrate scope of these annulation reactions is extremely narrow: the pronucleophile is limited to either succinic or homophthalic anhydrides and the electrophiles employed are mainly symmetrical aromatic and cyclic aliphatic ketones. Only one example has been reported for the use of an asymmetrical ketone (*i.e.* 2-butanone) and no catalytic asymmetric methodologies had been described at the outset of this investigation.

The existence of few literature precedents accounting for the use of ketones in (racemic) annulation reactions encouraged us to evaluate the compatibility of these substrates with our newly developed asymmetric protocol. The possibility of creating lactones bearing a quaternary stereocentre (when asymmetrically substituted ketones are employed) rendered this investigation even more appealing.

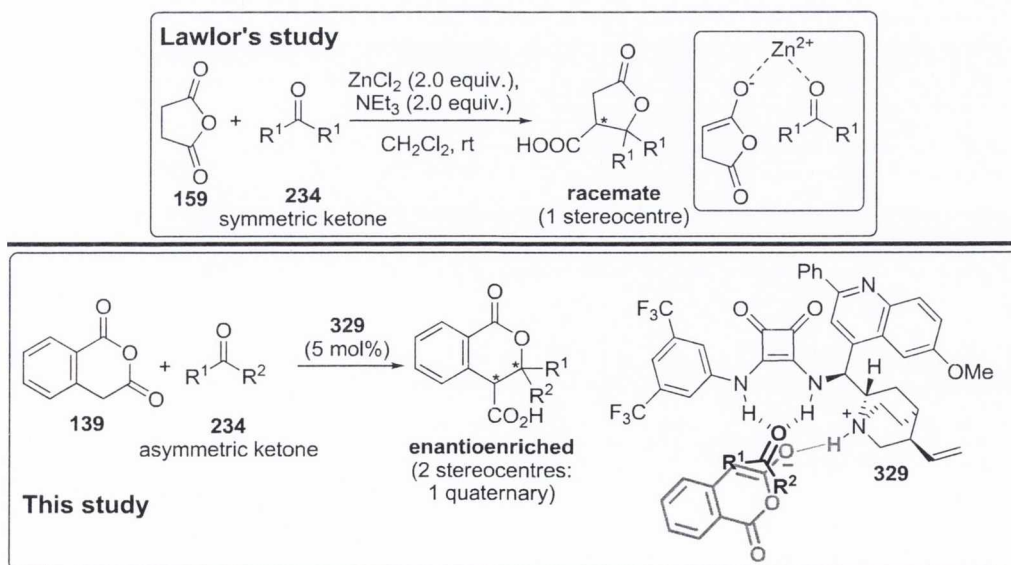


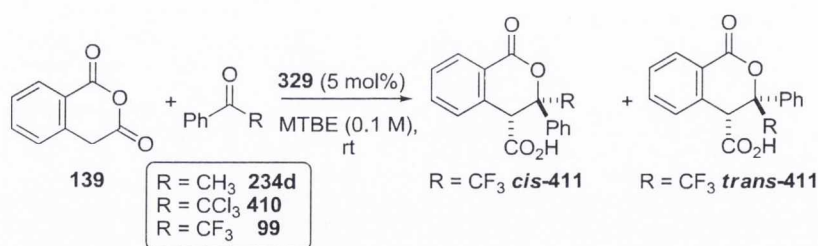
Figure 4.1 Rationale for the development of bifunctional organocatalyst-promoted asymmetric annulations between enolisable anhydrides and ketones

The study by Lawlor and co-workers¹⁸⁴ was particularly intriguing, since it reported that the combined use of an organic base and a Lewis acid could bring about the catalysis of annulation reactions with ketones; a result that rendered the use of a bifunctional cinchona alkaloid-derived organocatalyst (*i.e.* **329**) a reasonable alternative (Figure 4.1).

4.2 Preliminary evaluation of acetophenone derivatives in the asymmetric annulation reaction with homophthalic anhydride

We reasoned that the reduced electrophilicity of non-activated alkyl and aryl ketones when compared to aldehydes was a major drawback for the use of our asymmetric methodology; which was previously found incompatible with weakly electrophilic substrates (*i.e.* nitriles, epoxides). We initially decided to evaluate the asymmetric annulation reaction between homophthalic anhydride (**139**) and acetophenone derivatives promoted by catalyst **329** (Table 4.1). The choice of these ketones was motivated by their structural similarity with benzaldehyde; in addition these substrates allowed for the introduction of electron-withdrawing moieties that could enhance the electrophilicity of the carbonyl group if needed.

Table 4.1 Evaluation of acetophenone derivatives in the annulation reaction with homophthalic anhydride



entry	ketone	time (h)	yield of combined diastereomers (%) ^a
1	234d	40	0
2	410	96	14
3	99	20	98

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

As expected, an enhancement in electrophilicity of the carbonyl group in acetophenone derivatives was crucial to produce synthetically useful yields of lactone products. Acetophenone (**234d**) was completely unreactive under the reaction conditions employed (entry 1); the introduction of a trichloromethyl moiety on the ketone (*i.e.* **410**) led to a marginal increase of its reactivity (entry 2) while the installation of the highly electron-withdrawing trifluoromethyl group led to the formation of lactone products **411** in excellent yields (entry 3).

4.2.1 Preliminary optimisation of the reaction conditions

The promising result obtained from this preliminary set of experiments prompted us to further investigate the annulation reaction between homophthalic anhydride (**139**) and 2,2,2-trifluoroacetophenone (**99**). This transformation appeared particularly useful as it allowed the generation of trifluoromethylated chiral products which are of general interest due to their unique properties and pharmaceutical relevance.^{302,303} We were pleased to find that the previously employed extractive work-up and the esterification of the carboxylic acid products using trimethylsilyl diazomethane and methanol were compatible with asymmetric annulations using 2,2,2-trifluoroacetophenone (**99**) and that the major ester product could be isolated pure by column chromatography. While the *dr* of products *cis*-**411**:*trans*-**411** could be determined by ¹H NMR spectroscopy using the resonance associated with the proton at C-4, the formation of a quaternary stereocentre complicated the assignment of the relative stereochemistry of the major lactone diastereomer. On the basis of ¹H NMR NOE experiments on the pure ester product **412**, we were able to determine a *cis* stereochemistry for the major diastereomer since the resonances associated with the proton at C-4 (H_a) and to the *o*-protons (H_b) on the aromatic ring at C-3 showed a NOE contact thus indicating their close proximity to each other (Figure 4.1).

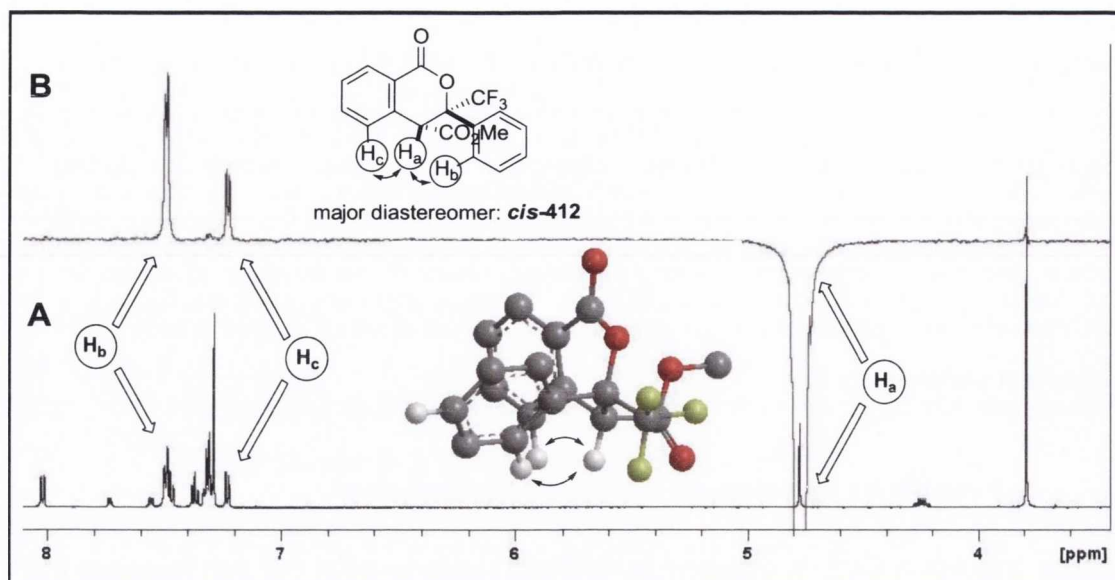


Figure 4.2 ^1H NMR spectrum of *cis*-412 (A) and ^1H NMR NOE experiment proving the proximity of proton H_a , H_b and H_c (B).

We performed a preliminary evaluation of catalysts (depicted in Figure 4.3) and reaction conditions aimed to establish an optimal asymmetric protocol for this transformation (Table 4.2).

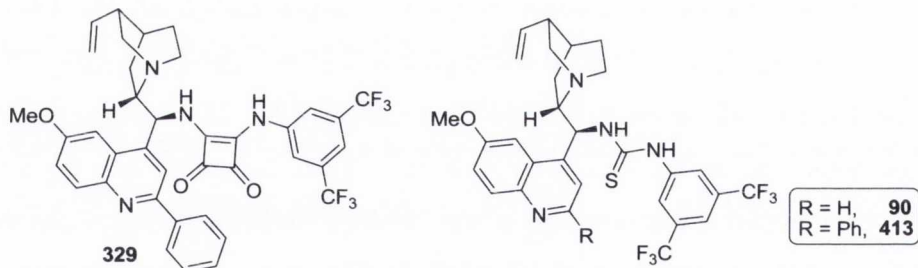
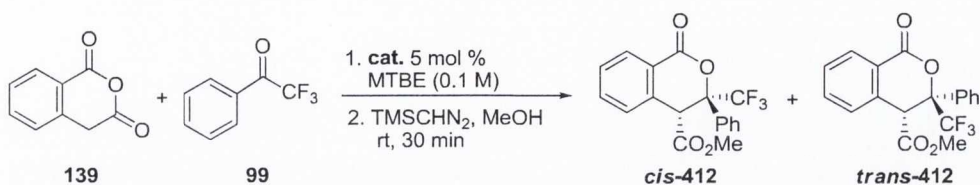


Figure 4.3 Squaramide- and thiourea-substituted cinchona alkaloids evaluated as catalysts for the annulation between anhydride 139 and ketone 99

Table 4.2 The reaction of **139** with **99**: the influence of the hydrogen-bond donating moiety and temperature



entry	cat.	temp. (°C)	time (h)	yield (%) ^a	<i>dr</i> ^b <i>cis:trans</i>	<i>ee</i> _{cis} (%) ^c
1	329	20	20	98	85:15	64
2	329	-15	63	53	88:12	61
3 ^d	329	-15	120	73	90:10	54
4	90	20	47	>95	91:9	48
5	413	20	47	>95	91:9	56
6	413	-15	66	71	94:6	70

^a Yield of the combined diastereoisomers: determined by ¹H NMR spectroscopy using *p*-iodoanisole as an internal standard. ^b Diastereomeric ratio: determined by ¹H NMR spectroscopy (400 MHz). ^c Determined by CSP-HPLC. ^d Reaction in THF.

Catalyst **329**, which outperformed all of the other evaluated cinchona-alkaloid analogues in promoting annulation reactions with aldehydes, was initially evaluated (entries 1-3). Lactone products were formed in excellent yield at room temperature, albeit with moderate *ee* (entry 1). The lowering of the temperature to -15 °C led to significantly slower reactions and practically unchanged enantiomeric excesses (entry 2). It was decided to change the reaction solvent from MTBE to THF (entry 3), however this led to inferior enantioselectivities and yields which did not exceed 73% even after 5 days. It was reasoned that the moderate enantiocontrol observed with the use of catalyst **329** could indicate the inappropriateness of the catalyst's squaramido group, thus we decided to evaluate other cinchona alkaloid derivatives bearing different hydrogen-bond donating moieties which were kindly provided by Mr. Séan Tallon. The thiourea derivative **90** appeared to be an unsuitable candidate (entry 4), as was catalyst **413** (entry 5) since their use provided products in low optical purity, however it was encouraging to observe that the installation of a phenyl group at the C-2' position of the quinoline moiety seemed to be crucial in obtaining enhanced enantiocontrol in the transformation under scrutiny. To shed some light on the influence of the temperature

on catalyst efficacy, we evaluated the thiourea derivative **413** at $-15\text{ }^{\circ}\text{C}$ and were pleased to observe that its catalytic performance considerably improved (entry 6): the enantiomeric induction sharply increased at the expense of product yield, which was however still synthetically useful.

4.3 Evaluation of cinchona alkaloid-derived organocatalysts in the annulation reaction between homophthalic anhydride and 2,2,2-trifluoroacetophenone

The inferiority of the squaramide derivative **329** compared to the thiourea analogue **413** in the formal cycloaddition reaction between homophthalic anhydride (**139**) and 2,2,2-trifluoroacetophenone (**99**) at $-15\text{ }^{\circ}\text{C}$ seemed indicative of different steric and electronic requirements of this transformation compared to the analogous annulation reaction with aldehydes. We were convinced that the *pre*-transition state assembly of this reaction was analogous to either of those hypothesised for the transformation with aldehydes (see Figure 3.4, B and C) and we envisaged that a dual hydrogen-bond donating moiety at the C-9 position provided the most appropriate binding with either the enolate or the ketone. This fact prompted us to assess different cinchona alkaloid-derived organocatalysts able to provide this type of interaction, in particular urea derivatives such as those shown in Figure 4.4.

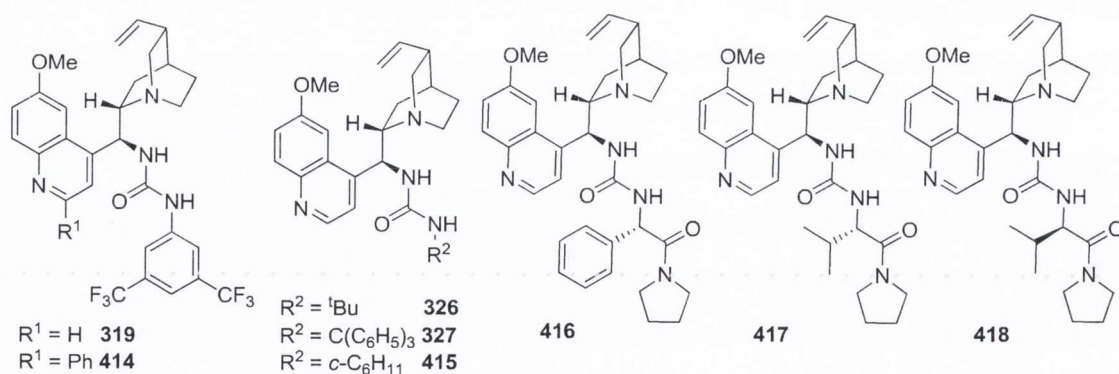
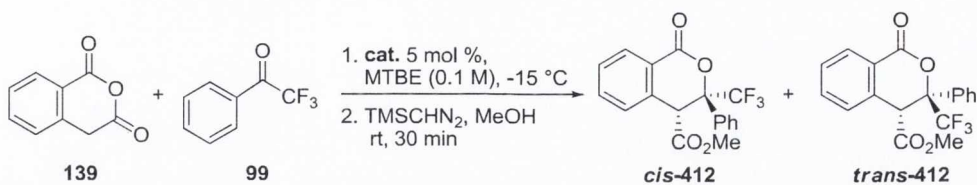


Figure 4.4 Urea-substituted cinchona alkaloids evaluated as catalysts for the reaction between anhydride **139** and 2,2,2-trifluoroacetophenone (**99**)

Table 4.3 Evaluation of the catalytic activity of several urea-substituted cinchona alkaloid-derived organocatalysts



entry	cat.	time (h)	yield (%) ^a	<i>dr</i> ^b <i>cis:trans</i>	<i>ee</i> _{<i>cis</i>} (%) ^c
1	319	63	81	90:10	56
2	414	55	76	90:10	71.5
3	326	64	85	93:7	84
4	327	64	65	97:3	84
5	415	64	84	94:6	74
6	416	69	64	96:4	62
7	417	69	71	97:3	84
8	418	69	58	97:3	-38

^a Yield of the combined diastereoisomers: determined by ¹H NMR spectroscopy using *p*-iodoanisole as an internal standard.

^b Diastereomeric ratio: determined by ¹H NMR spectroscopy (400 MHz).

^c Determined by CSP-HPLC.

A wide range of bifunctional urea-substituted cinchona alkaloid-derived organocatalysts (*i.e.* **319**, **326**, **327** and **415-418**) were previously synthesised by Dr. Aldo Pesciulli²⁸⁶ and proved crucial in allowing a thorough evaluation of the optimal steric and electronic requirements of a catalytic species for the reaction under scrutiny. In addition, the use of catalyst **414** (provided by Mr. Séan Tallon), enabled the assessment of the influence of a phenyl group at the C-2' position. Since none of the catalysed reactions afforded quantitative yields of lactone products, in every case the crude reaction mixture was treated using the extractive work-up previously reported for annulations with aldehydes. The *dr* of the products formed was generally excellent (>90:10) irrespective of the catalyst structure, and a preference for the formation of the *cis*-isomer was always observed.

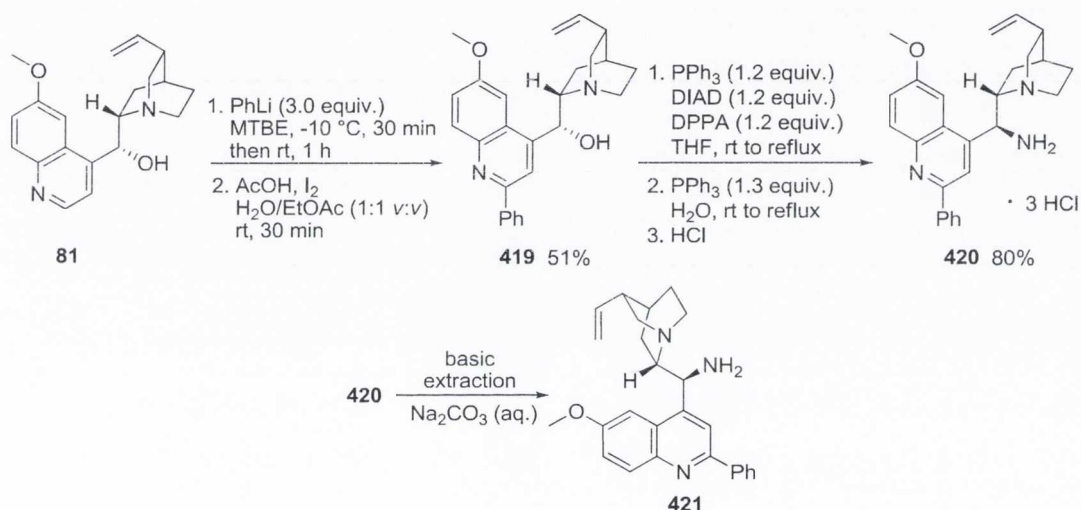
The *N*-aryl urea catalyst **319** promoted the reaction with moderate enantioselectivities and was deemed inadequate (entry 1). The use of catalyst **414** led to a sharp increase in *ee* for the major diastereomer (entry 2), a result that was once more indicative of the key

importance of a substituent on the C-2' position of the quinoline ring for an optimal catalytic performance in these types of annulation reactions. The transformation catalysed by urea **414** provided enhanced enantiocontrol in the formation of *cis*-**412** when compared to the thiourea analogue **413** which suggested the superiority of the hydrogen-bond donation provided by the urea moiety (Table 4.2 entry 6 compared to Table 4.3 entry 2). The evaluation of a series of *N*-alkyl urea catalysts (*i.e.* **326**, **327** and **417**, entries 3-5) unexpectedly afforded the major *cis*-**412** in higher *ee* than when generated in the presence of the *N*-aryl analogue **319** (entry 1); these results implied the importance of a sterically hindered urea moiety. In this regard, the *tert*-butyl- and the trityl-substituted catalysts **326** and **327** provided slightly superior enantiocontrol compared to that obtained with **415**, which bears a cyclohexyl urea moiety. It was possible to assess the catalytic performance of *N*-alkyl urea analogues bearing an additional chiral centre *via* the inclusion of catalysts incorporating a *C*-protected α -amino acid; the use of catalyst **416** bearing the unnatural amino acid L-phenyl glycine led to product enantiomeric excesses which were inadequate for synthetic utility. It was noteworthy that both catalysts **417** and **418** (containing a valine residue in its natural L- or unnatural D-configuration respectively) led to the formation of *cis*-**412** with high diastereoselection, albeit with opposite asymmetric inductions (entries 7 and 8).

4.4 Synthesis and evaluation of novel C-2'-substituted cinchona alkaloid-derived organocatalysts bearing a *N*-alkyl urea moiety

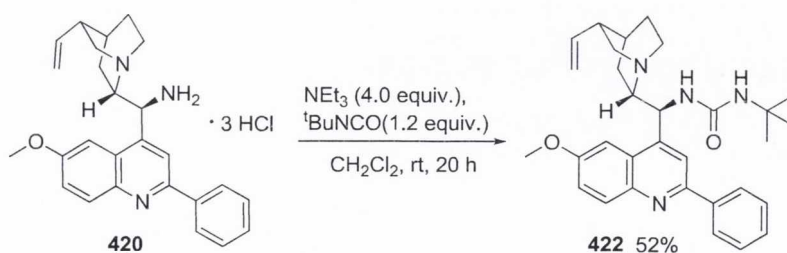
Following the preliminary catalyst screening it emerged that the urea derivatives **326** and **327** were the most promising candidates as promoters for the reaction under scrutiny, yet it was clear that they did not represent an optimal catalytic solution. Crucial information had surfaced from the evaluation of bifunctional catalysts which allowed us to speculate on a possible ideal structural framework for the optimum catalytic species; in particular the importance of a phenyl group at the C-2' position of the quinoline ring and a sterically demanding *N*-alkyl urea as the hydrogen-bond donating moiety were acknowledged. Accordingly, we decided to synthesise and prepare two novel C-2'-substituted urea derivatives, (*i.e.* **422**, **426**), structurally similar to **326** and **327**.

The alkylation of the quinoline ring at C-2' was accomplished by treating the readily available quinine (**81**) with an excess of phenyl lithium followed by an *in situ* oxidation of the 1,2-dihydroadduct using iodine.¹⁵² The relatively low yields of **419** obtained are mainly due to the difficult purification of the product and its separation from the unreacted quinine by means of column chromatography. The C-2'-alkylated alkaloid **419** was transformed into the hydrochloride salt **420** via a Mitsunobu reaction immediately followed by a Staudinger reduction of the *in situ* formed azido intermediate and a work-up involving an acid wash; the overall transformation caused the inversion of configuration at C-9. The free amine **421** could be obtained via a basic extraction as shown in Scheme 4.1.



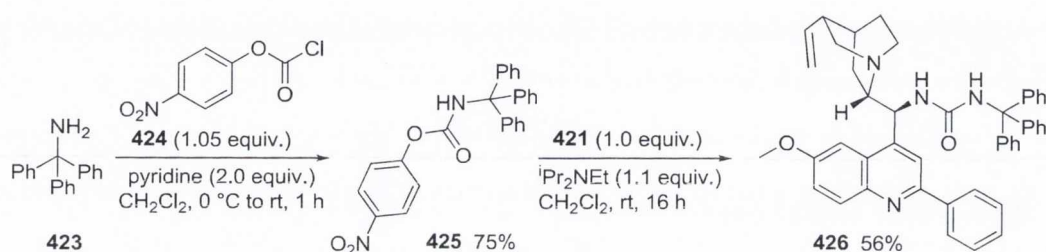
Scheme 4.1 Synthesis of the C-2'-phenyl-substituted 9-amino-*epi*-quinine **421**

Treatment of **420** with excess triethylamine and subsequent reaction of the free amine with the commercially available *tert*-butyl isocyanate in dichloromethane yielded the urea-substituted catalyst **422** which could be purified by column chromatography (Scheme 4.2).



Scheme 4.2 Synthesis of *tert*-butyl-substituted 9-*epi*-quinine urea **422**.

The unavailability of trityl isocyanate prompted us to explore an alternative synthetic protocol to install the *N*-trityl urea moiety and prepare catalyst **426**. Triphenylmethyl amine (**423**) was initially reacted with 4-nitrophenyl chloroformate (**424**) and a two fold excess of freshly distilled pyridine in anhydrous dichloromethane to form the carbamate **425** which could be purified by column chromatography.³⁰⁴ This was subsequently reacted with **421** in the presence of a small excess of anhydrous Hünig's base to form catalyst **426** in moderate yields (Scheme 4.3).

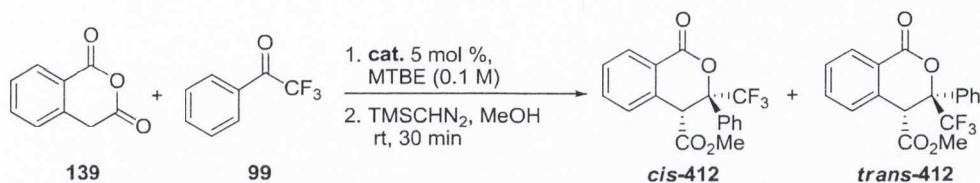


Scheme 4.3 Synthesis of trityl-substituted 9-*epi*-quinine urea **426**

We decided to evaluate the catalytic activity of both **422** and **426** in the annulation reaction between homophthalic anhydride and 2,2,2-trifluoroacetophenone and to further optimise the reaction conditions. The results obtained from this study are summarised in Table 4.4.

The enhancement of product *ee* reported with the use of **426** confirmed that the structural framework of this catalyst was better suited for the transformation under scrutiny (entry 1). The reaction was performed at -30 °C which led to an additional small enhancement of diastereo- and enantioselection for *cis*-**412** (entry 2); however increasingly lower temperatures caused a considerable erosion of product yields and were therefore deemed impractical (entry 3). Catalyst **422** was evaluated at -30 °C and led to the formation of the major diastereomer *cis*-**412** in marginally higher yields, at the expense of enantio- and diastereocontrol (entry 4). Finally, we were pleased to observe that the yields obtained with the use of catalyst **426** could be substantially improved by using an excess (*i.e.* 1.5 equivalents) of homophthalic anhydride (entry 5).

Table 4.4 Evaluation of catalysts **422** and **426** in the asymmetric annulation between **139** and **99**



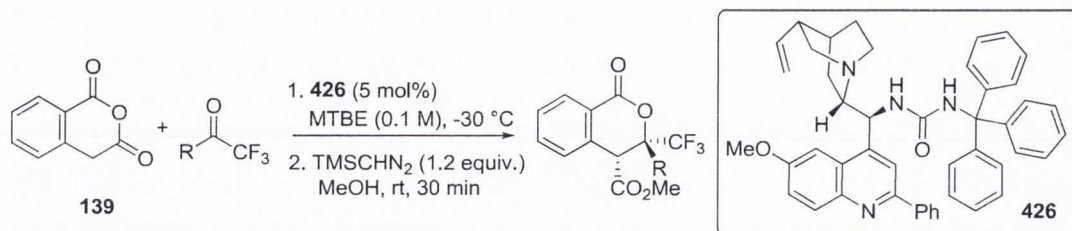
entry	cat.	temp. (°C)	time (h)	yield (%) ^a	<i>dr</i> ^b <i>cis:trans</i>	<i>ee</i> _{<i>cis</i>} (%) ^c
1	426	-15	64	78	95:5	90
2	426	-30	63	79	96:4	92
3	426	-60	63	32	98:2	n.d.
4	422	-30	61	88	91:9	88
5 ^d	426	-30	64	>95	97:3	92

^a Yield of the combined diastereoisomers: determined by ¹H NMR spectroscopy using *p*-iodoanisole as an internal standard. ^b Diastereomeric ratio: determined by ¹H NMR spectroscopy (400 MHz). ^c Determined by CSP-HPLC. ^d 1.5 equivalents of anhydride **139**.

4.5 Evaluation of the substrate scope: the trifluoromethyl ketone component

With a synthetically useful protocol in hand and **426** identified as the optimal catalyst for the annulation reaction between homophthalic anhydride (**139**) and 2,2,2-trifluoroacetophenone (**99**), it was decided to evaluate the substrate scope by using different trifluoromethyl ketones (Table 4.5).

Table 4.5 Evaluation of the substrate scope: the trifluoromethyl ketone component



entry	Product	time (h)	Yield (%) ^a	<i>dr</i> ^b <i>cis:trans</i>	<i>ee</i> _{cis} (%) ^c
1 ^d		64	93	97:3	92
2		61	85	98:2	95
3		95	89	97:3	92
4		94	79	97:3	92
5 ^d		94	61	88:12	91

^a Isolated yield. ^b Diastereomeric ratio: determined by ^1H NMR spectroscopy (400 MHz). ^c Determined by CSP-HPLC. ^d 1.5 equivalents of anhydride **139**.

We were pleased to observe that, in addition to 2,2,2-trifluoroacetophenone (**99**) (entry 1) *para*- and *meta*-substituted electron-deficient aryl trifluoromethyl ketones (entries 2–4) were found to be compatible with catalyst **426** and reacted with anhydride **139** to form lactones having a *cis*-configuration which could be isolated pure in excellent yields and enantiomeric excess. The use of the somewhat electron-rich 4'-methyl-2,2,2-

trifluoroacetophenone (entry 5) led to the formation of *cis*-**430** in equally excellent *ee*, albeit in lower yield and *dr*.

Recrystallisation of *cis*-**412** from a mixture of ethyl acetate and hexane afforded a crystal that could be analysed using X-ray diffraction. Despite the absence of a heavy atom in the crystal of *cis*-**412**, X-ray analysis using a diffractometer equipped with a copper source allowed to obtain a molecular structure (see the Appendix at the end of this thesis for experimental details) having a low Flack parameter (0.07) which could be used to unequivocally assign the absolute stereochemistry as (3*R*,4*R*). Accordingly, we assigned the absolute configuration of *cis*-**427–430** by analogy.

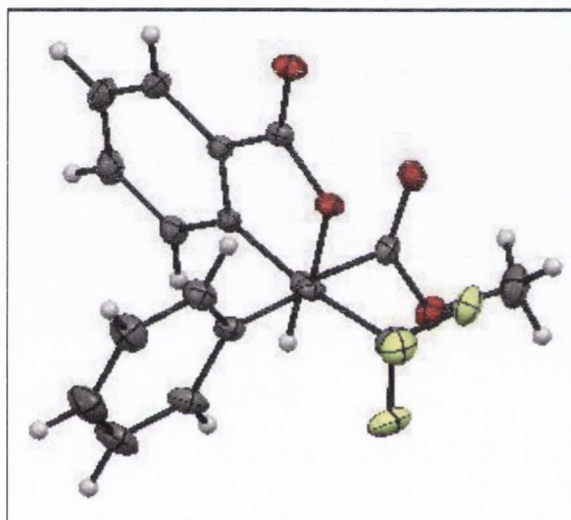


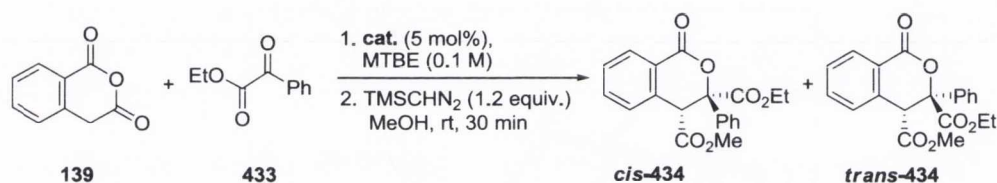
Figure 4.5 Structure of *cis*-**412** determined by X-ray diffraction analysis

4.6 Evaluation of α -ketoesters as substrates for the annulation reaction with homophthalic anhydride

While we demonstrated the feasibility of asymmetric annulation reactions with 2,2,2-trifluoroacetophenone derivatives, we became interested in a more versatile methodology that could encompass activated ketones bearing electron-withdrawing moieties other than the trifluoromethyl group. We therefore turned our attention towards α -ketoesters. In particular, we evaluated the compatibility of the commercially available ethyl benzoylformate (**433**) in the asymmetric annulation reaction with homophthalic anhydride (**139**).

We were pleased to observe that ethyl benzoylformate reacted with homophthalic anhydride in a formal cycloaddition to form a diastereomeric mixture of carboxylic acids which were esterified *in situ*. The major diastereomer could be purified and isolated by column chromatography. The *dr* of the carboxylic acids could be determined by ^1H NMR spectroscopy using the different chemical shift for the resonance of the proton at C-4, while ^1H NMR NOE experiments involving the major diastereomeric ester product allowed us to assign a *cis* stereochemistry to the major product.

Table 4.6 Preliminary evaluation of α -ketoester **433** in the annulation reaction with anhydride **139** promoted by *N*-alkyl urea-substituted cinchona alkaloids



entry	cat.	temp. (°C)	time (h)	yield (%) ^a	<i>dr</i> ^b <i>cis:trans</i>	<i>ee</i> _{<i>cis</i>} (%) ^c
1	327	20	64	81	78:22	77
2	327	-15	72	78	81:19	79
3	422	-15	61	94	97:3	86
4	426	-15	64	>95	80:20	88
5	426	-30	64	72	84:16	84

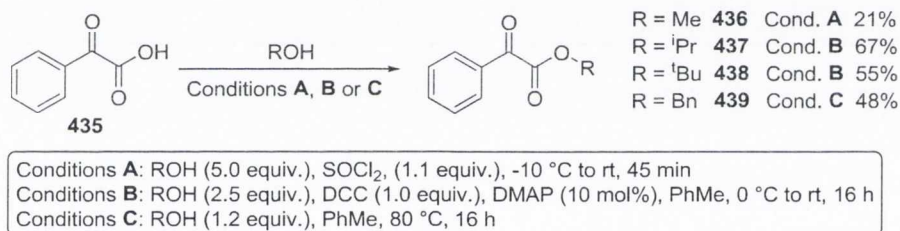
^a Yield of the combined diastereoisomers: determined by ^1H NMR spectroscopy using *p*-iodoanisole as an internal standard. ^b Diastereomeric ratio: determined by ^1H NMR spectroscopy (400 MHz). ^c Determined by CSP-HPLC.

The yields for annulation reactions using α -ketoester **433** promoted by cinchona alkaloid-derived organocatalysts were generally good to excellent. The use of catalyst **327** devoid of a phenyl group at C-2' to promote the reaction under scrutiny afforded the major diastereomer *cis*-**434** in good optical purity and moderate *dr* (entry 1) which were enhanced by lowering the reaction temperature to -15 °C (entry 2). The novel catalyst **422** under equivalent reaction conditions provided an increased asymmetric induction (entry 3) which were surpassed by using catalyst **426** whose catalytic capabilities could afford *cis*-**434** in up to 88% *ee* at -15 °C (entry 4). Finally, a lowering

of the reaction temperature to -30 °C did not lead to an improvement of the optical purity of *cis*-**434** (entry 5).

4.6.1 Synthesis and evaluation of other α -ketoesters in the asymmetric annulation reaction with homophthalic anhydride

Encouraged by these preliminary results obtained with ethyl benzoylformate (**433**) in annulation reactions with homophthalic anhydride, we decided to evaluate the use of benzoylformate substrates bearing different ester groups. The commercially available phenylglyoxylic acid (**435**) was treated with the appropriate alcohol to form a set of α -ketoesters (*i.e.* **436-439**)^{305,306} in low to moderate yields (Scheme 4.4) which were subsequently reacted with homophthalic anhydride at -15 °C in the presence of catalyst **426** (Table 4.7).



Scheme 4.4 Synthesis of alkyl benzoylformate substrates **436-439**

From the screening of α -ketoesters **434-437** it was possible to observe that the steric hindrance of the ester group was influential on both product yields and stereocontrol of the annulation reaction promoted by catalyst **426**, (Table 4.7). In general, good diastereocontrol was observed with the formation of *cis*-lactones as the major diastereomer. The use of ketoester **436** with the smallest methyl ester moiety provided the best diastereoselectivity (entry 2), however the highest *ee*'s were attained with the use of ethyl and *iso*-propyl ketoesters **433** and **437** (88% *ee* and 84% *ee* respectively, entries 1, 3). Lower product yields were obtained with substrates bearing a more sterically hindered ester group (*i.e.* **438**, **439**, entries 4 and 5).

Table 4.7 Evaluation of various alkyl benzoylformates in the annulation with **139**: the influence of the ester group

entry	α -ketoester	R	product	time (h)	yield (%) ^a	<i>dr</i> ^b <i>cis:trans</i>	<i>ee</i> _{<i>cis</i>} (%) ^c
1	433	Et	434	64	>95	80:20	88
2	436	Me	440	38	85	89:11	79
3	437	ⁱ Pr	441	38	>95	82:18	84
4	438	^t Bu	442	94	75	80:20	73
5	439	Bn	443	67	68	88:12	80

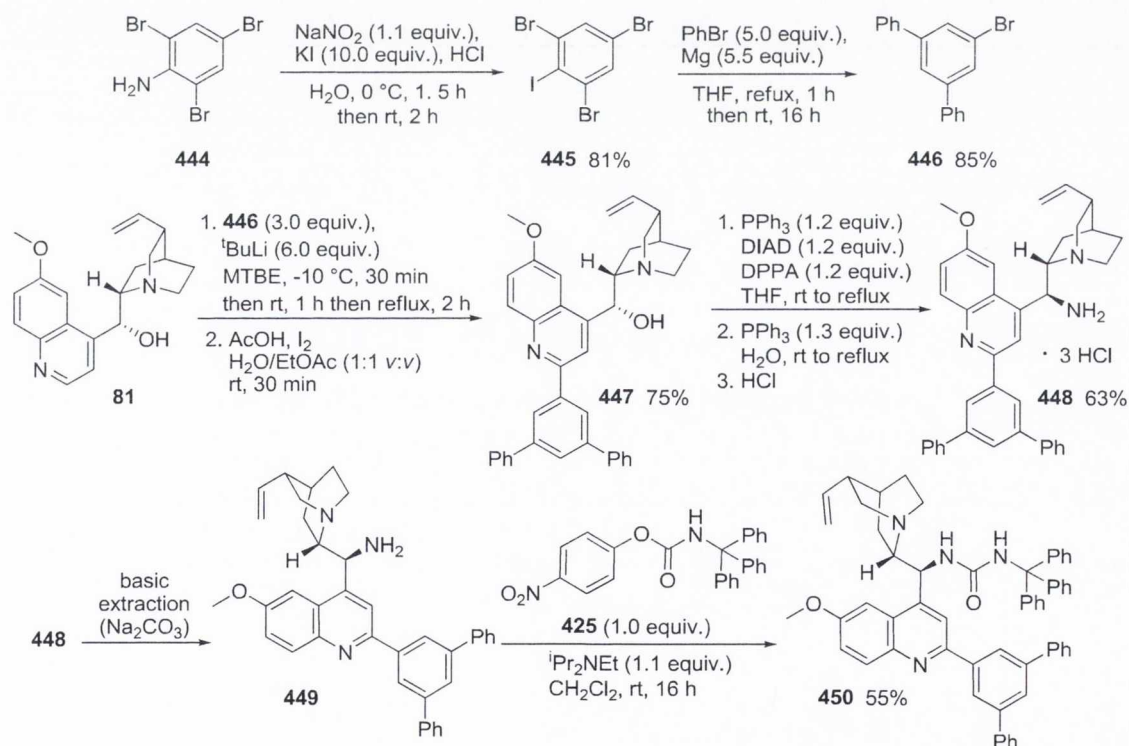
^a Yield of the combined diastereoisomers: determined by ¹H NMR spectroscopy using *p*-iodoanisole as an internal standard. ^b Diastereomeric ratio: determined by ¹H NMR spectroscopy (400 MHz). ^c Determined by CSP-HPLC.

4.6.2 Synthesis and evaluation of a novel C-2'-terphenyl-substituted cinchona alkaloid-derived organocatalyst bearing a *N*-trityl urea moiety

While we identified α -ketoesters **433** and **437** as the two most promising candidates for the development of a synthetically useful asymmetric protocol, we were still dissatisfied with the levels of asymmetric induction associated with the use of catalyst **426**.

Since we previously reported that the introduction of an element of steric hindrance at the C-2' position of the quinoline ring was beneficial for the asymmetric induction provided by bifunctional organocatalysts in annulations with both aldehydes (Section 3.3) and trifluoromethyl ketones (*vide supra*), we envisaged that, by creating a novel organocatalyst structurally similar to **426** but bearing a bulkier moiety at the C-2' position, we could enhance the diastereo- and enantiocontrol in annulations with α -ketoesters. In order to confirm our hypothesis, we decided to prepare catalyst **450** bearing a *m*-terphenyl moiety at C-2', as shown in Scheme 4.5.

The synthesis of the *m*-terphenyl group was accomplished in good yields over two steps: the commercially available 2,4,6-tribromoaniline (**444**) was initially transformed into 1,3,5-tribromo-2-iodobenzene (**445**) via a Sandmeyer-type reaction,³⁰⁷ this compound was subsequently treated with an excess of phenylmagnesium bromide in THF to yield 1-bromo-3,5-diphenylbenzene (**446**).³⁰⁸ The alkylation of quinine (**81**) with **446** was achieved in the presence of *tert*-butyl lithium via a halogen-lithium exchange and the 1,2-dihydroquinoline adduct formed was oxidised *in situ* with iodine following a methodology already employed for the synthesis of a C-2'-phenyl-substituted analogue (*i.e.* **419**, Scheme 4.1). The so-formed alcohol **447** underwent a Mitsunobu reaction-Staudinger reduction sequence to form the hydrochloride salt **448**. A subsequent extraction with a saturated aqueous carbonate solution led to the formation of the free amine **449** which, upon reaction with carbamate **425**, was transformed into catalyst **450**.

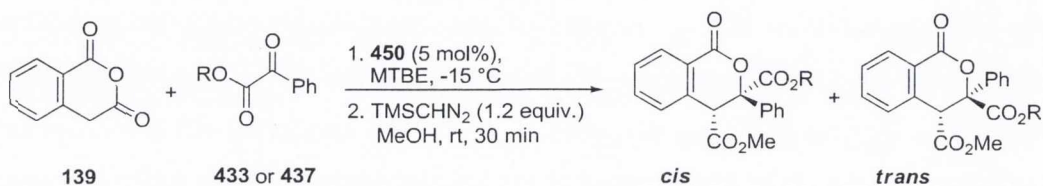


Scheme 4.5 Synthesis of the C-2'-*m*-terphenyl-substituted *N*-trityl-urea 9-*epi*-quinine **450**

The catalytic activity of **450** was subsequently evaluated in the annulation reaction between homophthalic anhydride (**139**) and either of the two most promising α -

ketoester candidates (*i.e.* **433** and **437**); the results of this study are reported in Table 4.8.

Table 4.8 Evaluation of catalyst **450** in the annulation reaction between **139** and either **433** or **437**



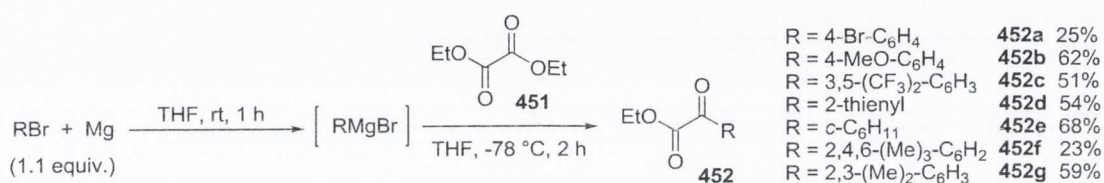
entry	α -ketoester	R	conc. (M)	time (h)	yield (%) ^a	<i>dr</i> ^b <i>cis:trans</i>	<i>ee</i> _{<i>cis</i>} (%) ^c
1	437	ⁱ Pr	0.1	91	>95	93:7	89
2	433	Et	0.1	94	>95	86:14	90
3	437	ⁱ Pr	0.02	67	91	98:2	88
4	433	Et	0.02	64	>95	93:7	92
5	433	Et	0.01	64	87	96:4	91

^a Yield of the combined diastereoisomers: determined by ¹H NMR spectroscopy using *p*-iodoanisole as an internal standard. ^b Diastereomeric ratio: determined by ¹H NMR spectroscopy (400 MHz). ^c Determined by CSP-HPLC.

Most gratifyingly we found that the diastereo- and enantiocontrol provided by catalyst **450** were slightly superior than those obtained with the use of catalyst **426** (compare entries 1 and 2 with Table 4.7, entries 1 and 3); and, while the *dr* of the lactone products was higher by using ketoester **437**, the use of substrate **433** led to slightly increased enantiomeric excesses. The reaction concentration proved to be a crucial parameter in these reactions: its decrease from 0.1 M to 0.02 M led to the formation of lactone products in excellent diastereo- and enantioselectivities and simultaneously revealed the superiority of ketoester **433** for this transformation (entries 3 and 4). A further decrease of the concentration (*i.e.* 0.01 M, entry 5) was not considered beneficial since the major diastereomer was formed with practically unchanged *ee* albeit in lower yield.

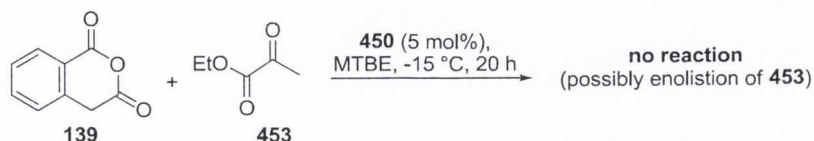
4.7 Synthesis and evaluation of ethyl α -ketoesters in the asymmetric annulation reaction with homophthalic anhydride

Having discovered that catalyst **450** in conjunction with ethyl α -ketoesters provided the best enantioselectivities in the asymmetric annulation reaction with homophthalic anhydride (**139**) and α -ketoesters under optimised reaction conditions, we decided to widen the substrate scope by preparing and evaluating other ethyl α -ketoesters as substrates. These substrates (*i.e.* **452a-g**) were synthesised in good yields *via* the dropwise addition of Grignard reagents to diethyl oxalate (**451**) at $-78\text{ }^{\circ}\text{C}$ ³⁰⁹ following a procedure similar to that previously reported by Nakamura *et al.*³¹⁰ (Scheme 4.6).



Scheme 4.6 Synthesis of a set of ethyl α -ketoesters

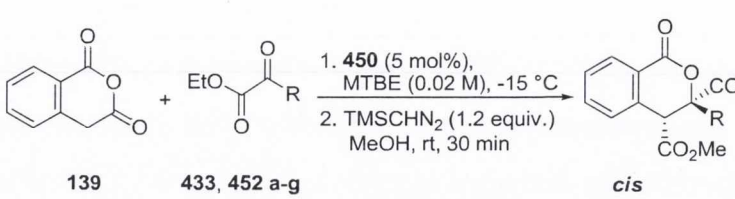
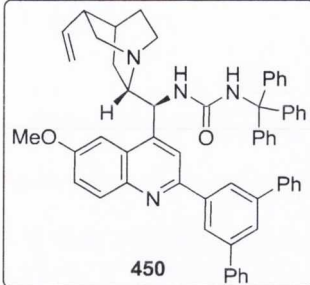
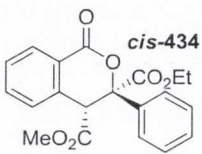
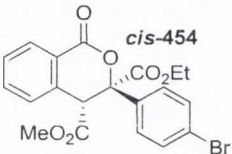
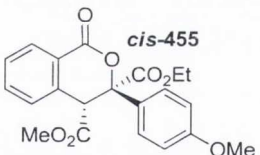
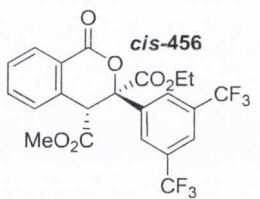
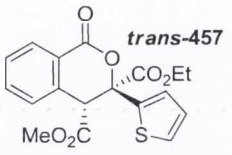
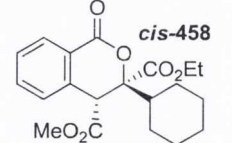
Due to its ready availability ethyl pyruvate (**453**) was initially evaluated (Scheme 4.7); however ¹H NMR spectroscopic analysis of the crude mixture using *p*-iodoanisole as an internal standard revealed that the annulation reaction with homophthalic anhydride (**139**) did not occur. The observation that the resonance associated with the methyl group of **453** had disappeared seemed to indicate the preferential enolisation of **453** promoted by catalyst **450**, which left the anhydride pronucleophile unreacted.



Scheme 4.7 Attempted annulation using ethyl pyruvate as the ketone component

The ethyl α -ketoesters **433** and **452a-g** were evaluated in the same transformation; the results are reported in Table 4.9

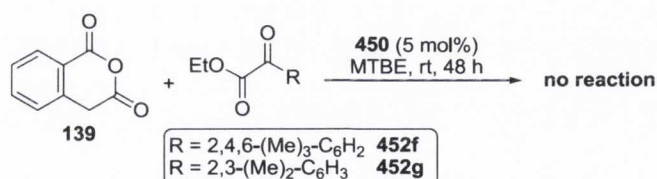
Table 4.9 Evaluation of the substrate scope: the ethyl α -ketoester component

 139 433, 452 a-g <i>cis</i>  450						
entry	α -ketoester	product	time (h)	yield (%) ^a	<i>dr</i> ^b <i>cis:trans</i>	<i>ee</i> _{<i>cis</i>} (%) ^c
1	433	 <i>cis</i> -434	36	89	93:7	92
2	452a	 <i>cis</i> -454	41	94 ^d	97:3	95 (91) ^e
3 ^f	452b	 <i>cis</i> -455	72	61	81:19	87
4 ^g	452c	 <i>cis</i> -456	94	92	97:3	85
5	452d	 <i>trans</i> -457	86	75	94:6	86
6	452e	 <i>cis</i> -458	72	85	90:10	66

^a Isolated yield. ^b Diastereomeric ratio: determined by ¹H NMR spectroscopy (400 MHz). ^c Determined by CSP-HPLC. ^d Diastereomers inseparable: combined isolated yield. ^e *ee* of *cis*-isomer in parenthesis. ^f Catalyst loading 10 mol%. ^g Reaction performed at -50 °C

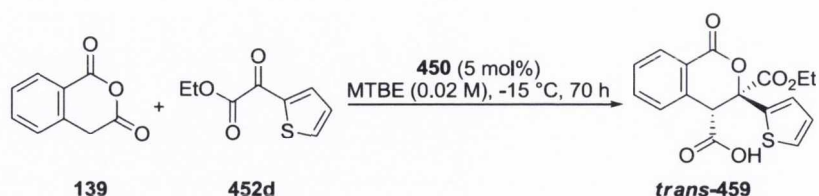
The use of ethyl α -ketoesters led to the formation of products having good to excellent diastereoselectivities. The methodology proved robust and in addition to ethyl benzoylformate (entry 1), electron-deficient- (entries 2 and 4), electron-rich- (entry 3) and heterocyclic aromatic (entry 5) ethyl ketoesters were well tolerated by the catalyst. Excellent yields and enantiomeric excesses were obtained for the *cis*-diastereoisomers **434** and **454** (entries 1 and 2) and, while for the latter case it was not possible to separate the diastereomeric esters, the minor *trans*-**454** was also formed in excellent optical purity. As expected, the use of less electrophilic ethyl α -ketoesters led to lower (albeit still synthetically useful) product yields (entries 3 and 5). While ethyl pyruvate (**453**) was found to be incompatible with the annulation reaction catalysed by **450**, the use of a less enolisable aliphatic ethyl ketoester was tolerated and led to the formation of *cis*-**458** in excellent yields and *dr*, albeit only moderate *ee*. Despite considerable experimentation and the variation of temperature, catalyst loading and concentration, the optical purity of this compound could not be increased.

Sterically hindered ethyl α -ketoesters such as **452f** and **452g** were found to be incompatible with catalyst **450** and completely unreactive even at room temperature (Scheme 4.8).



Scheme 4.8 Attempted annulation using sterically hindered α -ketoesters **452f-g**

We decided to obtain and analyse a crystal of one of the products obtained by the formal cycloaddition using α -ketoesters. Our attempts in recrystallising *trans*-**457** (bearing sulfur as the heavy atom) failed, however we were able to obtain a crystal of the corresponding carboxylic acid *trans*-**459** (from a mixture of diethyl ether and ethyl acetate) that could be analysed by X-ray diffraction. The molecular structure obtained (see the Appendix at the end of this thesis for experimental details) could be used to unequivocally assign the absolute stereochemistry as (3*S*,4*R*). Accordingly, we assigned the absolute configuration of *cis*-**434**, *cis*-**454-456** and *cis*-**458** as (3*R*,4*R*) by analogy.



Scheme 4.9 Synthesis of *trans*-**459** the crystal of which was used to assign the absolute stereochemistry by X-ray diffraction analysis

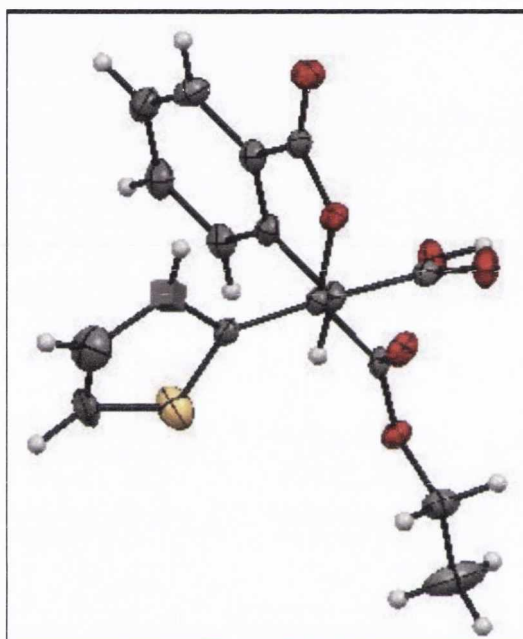


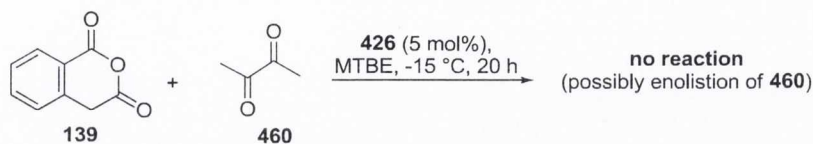
Figure 4.6 Structure of *trans*-**459** determined by X-ray diffraction analysis

4.8 Evaluation of α -diketones in the asymmetric annulation reaction with homophthalic anhydride

Encouraged by the results obtained in the asymmetric annulation reaction using α -ketoesters, we decided to widen the substrate scope even further by using 1,2-diketones. We decided to use C_2 -symmetric 1,2-diketones in order to equally balance the reactivity of the carbonyl groups.

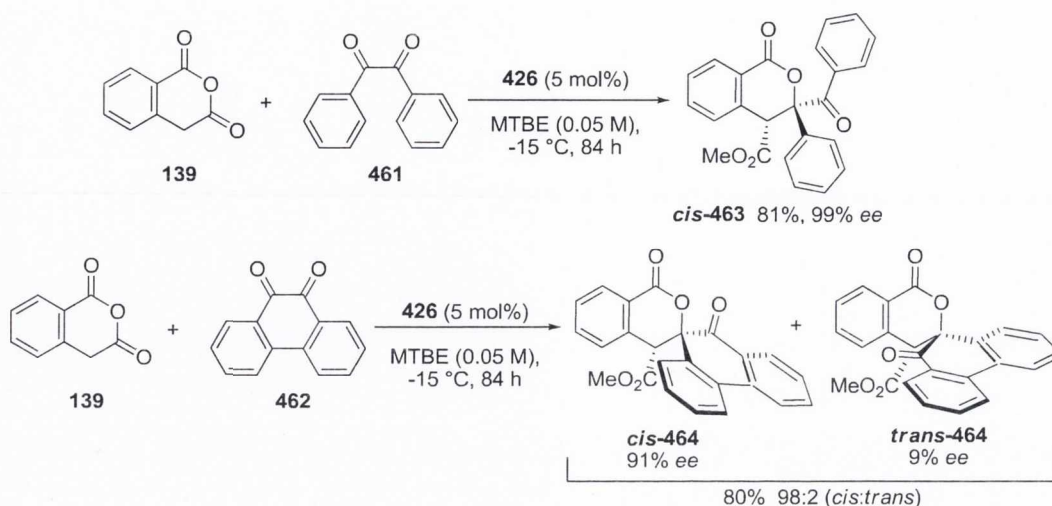
We initially used 2,3-butanedione (**460**) in the asymmetric annulation with homophthalic anhydride (**139**) promoted by catalyst **426** (Scheme 4.10). ^1H NMR spectroscopic analysis of the crude reaction mixture using *p*-iodoanisole as an internal standard revealed that **139** had not reacted and that the resonance relative to **460** had

disappeared, possibly indicating the preferential enolisation of the 1,2-diketone component (and possible self-condensation).



Scheme 4.10 Attempted annulation using 2,3-butanedione (**460**)

While we were not surprised to notice a lack of reactivity using **460** as the substrate – which we already observed in the attempted annulation with ethyl pyruvate (**453**) – we decided to evaluate aromatic 1,2-diketones lacking enolisable protons such as the commercially available benzil (**461**) and 9,10-phenanthrenequinone (**462**) in the same transformation (Scheme 4.11). Benzil (**461**) had previously been used in conjunction with homophthalic anhydride (**139**) to form at elevated temperatures isobenzofuranone derivatives *via* a reactivity reminiscent of formal cycloadditions followed by a decarboxylation.³¹¹ This substrate seemed particularly interesting because of its peculiar structural features; in fact the presence of bulky phenyl groups on **461** determines its unusual molecular structure which, unlike the less sterically hindered 2,3-butanedione (**460**), is not planar *anti* but is characterised by having a long central carbon-carbon bond (1.546 Å)³¹² and the bicarbonyl system out of plane with a torsion angle between the two carbonyls that had been reported to vary in solution (depending on the solvent used)³¹³ and had been measured as either 117° (in the gas phase)³¹² or 108° (in the solid state).³¹⁴ On the other side, the use of 9,10-phenanthrenequinone (**462**), was appealing since it potentially allowed for the formation of spirocyclic lactone products.



Scheme 4.11 Evaluation of 1,2-diketones **461** and **462** in the asymmetric annulation reaction with **139** promoted by catalyst **426**

The annulation reactions between either **461** or **462** and anhydride **139** were carried out using catalyst **426** at -15 °C; the concentration used was 0.05 M, since we noted that at higher concentrations (*i.e.* 0.1 M) the ketones were almost completely insoluble. We were pleased to observe that both substrates were compatible with catalyst **426** and that they reacted with homophthalic anhydride (**139**) to afford lactone products in good yields and excellent enantioselectivity. The reactions using 1,2-diketones proved slower than the analogous transformation with α -ketoesters, however lactone products were formed in remarkably higher *ee*'s, possibly due to the different structural framework of **461** (*i.e.* non planar) and **462** (*i.e.* cyclic).

The relative stereochemistry of the major diastereomers **463** and **464** was initially assigned *via* ^1H NMR NOE experiments; these indicated the preferential formation of *cis*-diastereoisomers in both reactions since NOE contacts were observed between the resonance relative to the proton at C-4 and the *o*-protons of the aromatic ring appended at C-3. A crystal was obtained for *cis*-**463** which could be used to establish the absolute stereochemistry of the product to be (3*R*,4*R*) *via* X-ray diffraction analysis (Figure 4.7).

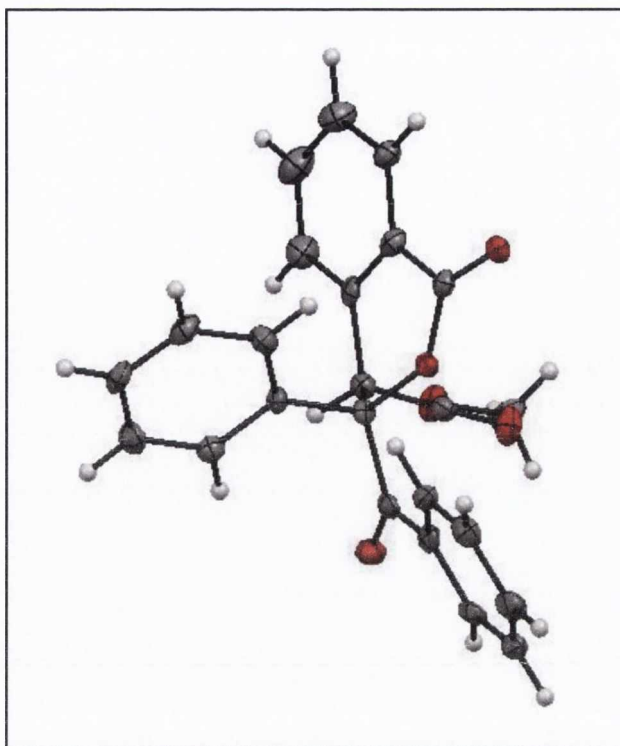
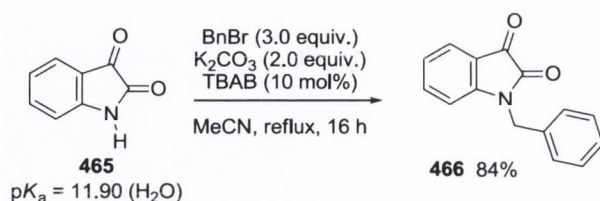


Figure 4.7 Structure of *cis*-**463** determined by X-ray diffraction analysis

4.9 Evaluation of α -ketoamides in the asymmetric annulation reaction with homophthalic anhydride

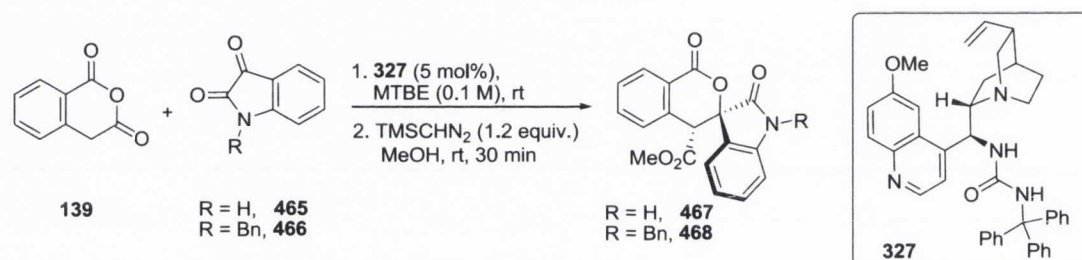
The successful implementation of our newly developed asymmetric protocol in annulation reactions using α -ketoesters and 1,2-diketones prompted us to evaluate α -ketoamides as the electrophilic component. We were particularly intrigued by the possibility of using the readily available isatin (**465**) as a substrate for annulation reactions, since it potentially allowed the formation of chiral products incorporating the spirooxindole structural motif, which is commonly found in a wide range of natural products and drug leads.^{315,316,317}

We envisaged that a possible inconvenience associated with the use of isatin (**465**) in annulation reactions with homophthalic anhydride (**139**) was the acidity of the amide hydrogen, whose pK_a in water had been calculated as 11.90.³¹⁸ Therefore, we prepared the *N*-benzyl protected analogue **466** as depicted in Scheme 4.12 and evaluated it alongside **465** in the annulation reaction with **139** promoted by catalyst **327** (Table 4.10).



Scheme 4.12 Synthesis of *N*-benzyl isatin (**466**)

Table 4.10 Preliminary evaluation of isatin and *N*-benzyl isatin in the annulation reaction with homophthalic anhydride



entry	isatin	R	time (h)	conversion (%) ^a	<i>ee</i> _{cis} (%) ^b
1	465	H	22	90	13
2	466	Bn	67	>95	43

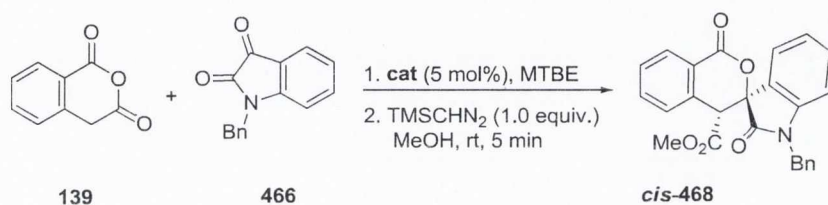
^a Determined by ¹H NMR spectroscopy. ^b Determined by CSP-HPLC.

While we were pleased to observe that both isatin (**465**) and its *N*-benzylated derivative **466** reacted with homophthalic anhydride to form the desired lactone products *cis*-**467** (entry 1) and *cis*-**468** respectively (entry 2) as the major diastereomers, we reported a remarkable increase in product *ee* with the use of **466**, which we ascribed to the lack of the acidic amide hydrogen. The optical purity obtained for *cis*-**468** at room temperature was modest, nonetheless it inspired us to evaluate catalysts **426** and **450** and optimise the reaction conditions in order to obtain synthetically useful enantioselectivities (Table 4.11).

The annulation reaction using *N*-benzyl isatin (**466**) proved to be much faster than analogous transformations using other activated ketones, which we reasoned was due to the increased electrophilic character of the carbonyl group in **466**. A drawback was the unsuitability of using either *p*-iodoanisole or styrene as an internal standard to

determine the yield by ^1H NMR spectroscopy since their resonances overlapped with those of the lactone products; the conversion for these reactions were therefore measured by monitoring the disappearance of the resonance of the benzylic protons of **466**.

Table 4.11 Optimisation of the reaction conditions for the asymmetric annulation between **466** and **139**

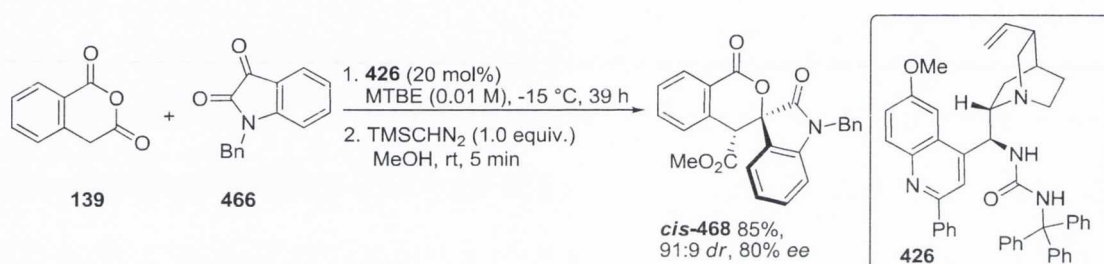
						
entry	cat.	temp (°C)	conc. (M)	time (h)	conversion (%) ^a	<i>ee</i> _{cis} (%) ^b
1	327	20	0.1	67	>95	43
2	327	-15	0.1	63	>95	24
3	426	20	0.1	24	>95	42
4	426	-15	0.1	63	>95	59
5	450	-15	0.1	60	>95	33
6	426	-15	0.01	61	>95	73
7	426	-50	0.01	60	>95	69
8 ^c	426	-15	0.01	39	>95	80

^a Determined by ^1H NMR spectroscopy. ^b Determined by CSP-HPLC.

^c Catalyst loading: 20 mol%

We initially evaluated catalyst **327** and we noticed that the modest *ee* obtained for *cis*-**468** at room temperature (entry 1) could not be increased by lowering the temperature to -15 °C (entry 2). Catalyst **426** promoted the formation of *cis*-**468** at room temperature in optical purity practically equivalent than when generated in the presence of **327** (compare entry 3 and 1), nevertheless, a decrease of the reaction temperature was in this case conducive to an enhancement of the optical purity of *cis*-**468** (entry 4). Catalyst **450** was found to be an unsuitable promoter of the reaction under scrutiny under equivalent reaction conditions (entry 5). The poor solubility of **466** in MTBE and the presence of the racemic background reaction, prompted us to a lowering of the concentration to 0.01 M: this proved extremely beneficial for the asymmetric induction

provided by catalyst **426** and the now homogeneous reaction led to the formation of *cis*-**468** in higher enantioselectivity (entry 6). The reaction at -50 °C afforded *cis*-**468** in equally high yields, albeit slightly lower *ee* (entry 7), while we found that increasing the catalyst loading (*i.e.* 20 mol%) at -15 °C led to the improvement of the product enantiomeric excess up to 80%. Despite considerable experimentation, we were unable to bring about further improvement in the optical purity of *cis*-**468**. While the degree of product enantiomeric excess using **466** was lower compared to that reported with the use of other ketone substrates, we were nonetheless satisfied to achieve the synthesis of a chiral spirooxindole in good *ee* using our asymmetric protocol.



Scheme 4.13 Organocatalysed asymmetric annulation between **466** and **139** under optimised reaction conditions

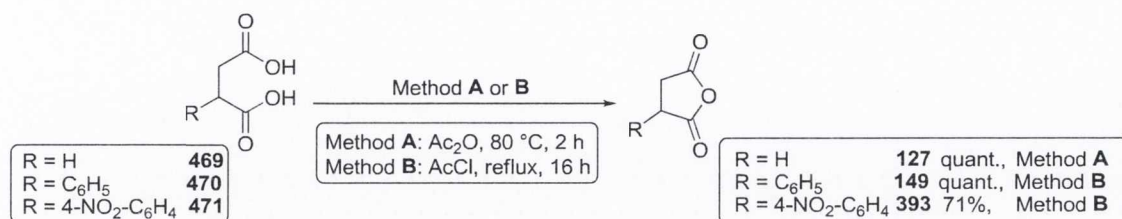
With a synthetically useful protocol in hand, we repeated the reaction in order to measure the *dr* and determine the isolated yield of *cis*-**468** (Scheme 4.13). The *dr* could be determined by ^1H NMR spectroscopic analysis of the crude mixture of carboxylic acids using the resonance of the proton at C-4, while the relative stereochemistry of the major ester diastereomer could be established using ^1H NMR NOE experiments.

4.10 Evaluation of the substrate scope: the anhydride component

Cinchona-derived organocatalysts proved to be extremely versatile and promoted the catalytic asymmetric annulation reactions using a wide range of activated ketones, however the sole use of the benzo-fused homophthalic anhydride (**139**) as the pronucleophile species was perceived as a limitation.

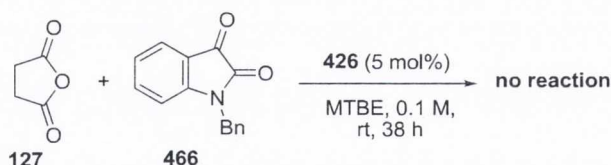
Succinic anhydride (**127**) and aryl succinic anhydrides (*i.e.* **149** and **393**) could be readily synthesised in excellent yields by treating the corresponding *bis*-carboxylic

acids (*i.e.* **469**, **470** and **471**) with either acetic anhydride or acetyl chloride as depicted in Scheme 4.14.



Scheme 4.14 Synthesis of anhydrides **127**, **149** and **393**

Succinic anhydride was previously found to be unreactive in annulations with aldehydes in the presence of cinchona-derived catalysts and we ascribed this lack of reactivity to the low concentration in solution of the enol reactive species. We hoped that the use of the highly electrophilic *N*-benzyl isatin (**466**) could compensate for the ineffective enolisation of succinic anhydride (**127**) promoted by bifunctional organocatalysts such as **426**. Most disappointingly, ¹H NMR spectroscopic analysis of the crude reaction mixture indicated that the annulation between **127** and **466** did not occur even at room temperature (Scheme 4.15).

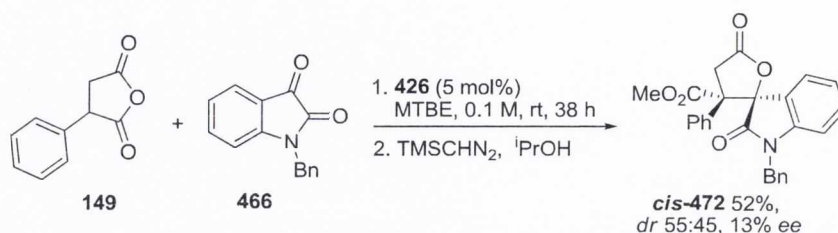


Scheme 4.15 Attempted organocatalysed annulation reaction using succinic anhydride and **466**

Encouraged by the excellent results obtained with the use of arylsuccinic anhydrides in annulations with aldehydes (see Section 3.5.3) and inspired by the potential one-pot asymmetric synthesis of complex and highly functionalised spirooxindole derivatives bearing two consecutive quaternary stereocentres, we decided to explore their use in the formal cycloaddition with **466**.

We were pleased to observe that phenylsuccinic anhydride (**149**) reacted at room temperature with *N*-benzyl isatin, however the major product *cis*-**472** was formed in poor diastereomeric excesses and low optical purity (Scheme 4.16). While it seemed

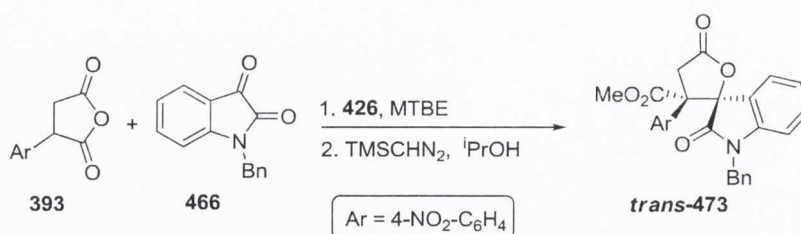
clear that the use of a more enolisable anhydride (with respect to succinic anhydride) was crucial to obtain annulated products, we deemed the enantiomeric excess obtained with the use of anhydride **149** to be too low to attempt an optimisation of this reaction.



Scheme 4.16 Annulation between phenyl succinic anhydride and *N*-benzyl isatin

We next turned our attention to 4-nitrophenylsuccinic anhydride (**393**) and performed the annulation reactions with **466** at lower reaction temperatures (which in our experience were beneficial for the asymmetric induction in reactions promoted by catalyst **426**). The annulation between **393** and **466** promoted by catalyst **426** occurred at -15 °C to afford excellent yields of the lactone product **trans-473** in a moderate but promising 74% ee (Table 4.12, entry 1). Further modification of the reaction conditions (entry 2) allowed access to **cis-473** in excellent enantiomeric excess and high yields.

Table 4.12 Optimisation of the reaction conditions for the asymmetric annulation between **393** and **466**



entry	cat. loading (mol%)	temp (°C)	conc. (M)	time (h)	yield (%) ^a	ee _{cis} (%) ^b
1	5	-15	0.02	240	88	74
2	20	-30	0.01	21	91	98

^a Isolated yield of the major diastereomer. ^b Determined by CSP-HPLC.

A crystal of **trans-473** was obtained which was suitable for X-ray diffraction analysis; the molecular structure obtained (see the Appendix at the end of this thesis for

experimental details) could be used to unequivocally assign the absolute stereochemistry as (2*R*,3*S*).

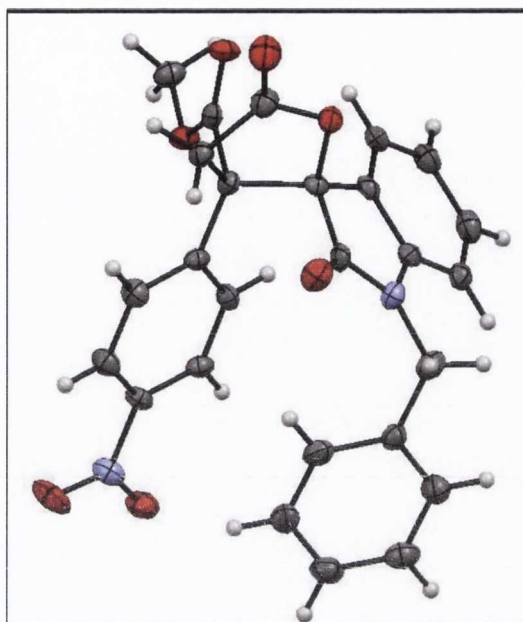


Figure 4.8 Structure of *trans*-473 determined by X-ray diffraction analysis

4.11 Asymmetric annulation reactions with ketones: a proposed mechanism

At the outset of this investigation, the knowledge of formal cycloaddition reactions between anhydrides and ketones was extremely limited, and the only postulated mechanism for this reaction was advanced by Lawlor *et al.*¹⁸⁴ who suggested that anhydrides are the pronucleophile species, which, upon enolisation, attack the ketone carbonyl group. The experimental results obtained from this investigation seem to confirm this hypothesis, in particular we noticed that electronic effects are important in determining the reactivity of anhydrides as nucleophiles (as observed in cycloadditions using succinic and arylsuccinic anhydrides) and of ketones as electrophiles.

Regardless of the nature of the activated ketone component (*i.e.* trifluoromethyl ketones, α -ketoesters, 1,2-diketones), we noticed that the nucleophilic attack of the enolised homophthalic anhydride occurred from its *si*-face selectively on the *si*-face of the ketone carbonyl group (Figure 4.5). The lactone products formed shared the same absolute configuration (determined by X-ray diffraction analysis) which, despite the

different structure of the catalysts used to promote the reaction, was also equivalent to that of products obtained *via* formal cycloaddition reactions with aldehydes.

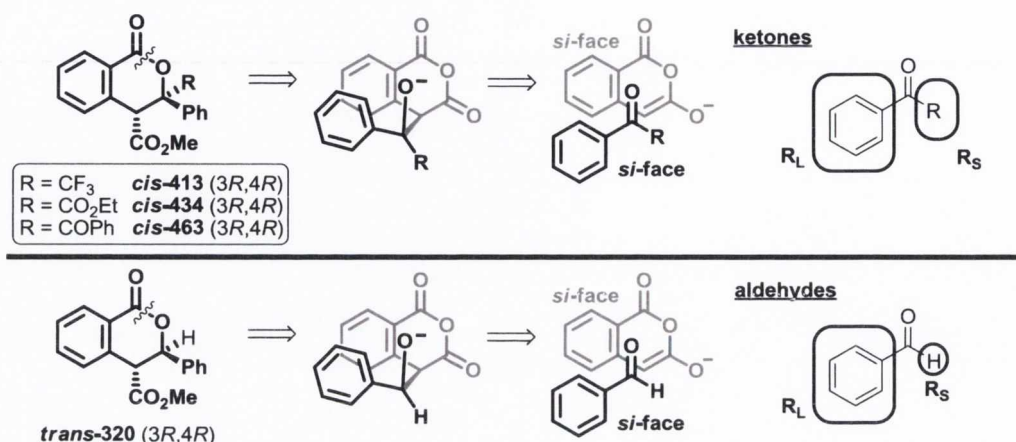


Figure 4.5 Stereochemical outcome of cycloaddition reactions between homophthalic anhydride and activated ketones and aldehydes

We assume that in the *pre*-transition state of the reaction the compound bound to the hydrogen-bond donating moiety (*i.e.* urea) will orient its large substituent in a way to avoid steric clashes with the backbone of cinchona alkaloid-derived catalysts. The use of ketones having substituents (R_L and R_S respectively) appended on the carbonyl group comparable in size, poses a greater challenge in predicting an optimal assembly in the *pre*-transition state compared to the equivalent reaction using aldehydes where the R_L (*i.e.* aryl, alkyl group) and R_S (hydrogen atom) can be clearly indentified.

In an effort to elucidate a possible mode of action for catalyst **426** in the formal cycloaddition between anhydride **139** and ketone **99** and advance a mechanism which fits the experimental results obtained, we built and analysed molecular models representing the *pre*-transition state assemblies of the reaction. The preliminary analysis of these models (for catalysts **426** and **450**) led us to consider the cinchona alkaloid-derived moiety of these catalytic species to be the more sterically demanding even considering the presence of a bulky *N*-trityl urea group. Therefore, if we consider the CF_3 group in **99** to be smaller (*i.e.* R_S) than the phenyl moiety (as reported by several studies^{319,320,321}), we are induced to think that the substrate will orient the R_S group towards the cinchona alkaloid backbone in the *pre*-transition state of the reaction. We

proposed two different assemblies: a ‘ketone binding’ (Figure 4.9) and an ‘enolate binding’ (Figure 4.10) which account for the observed stereochemistry of the major lactone products and the stereoelectronic requirements of both the stereocentre-forming step (Bürgi-Dunitz approach) and the catalyst-substrate binding interactions.

Ketone binding

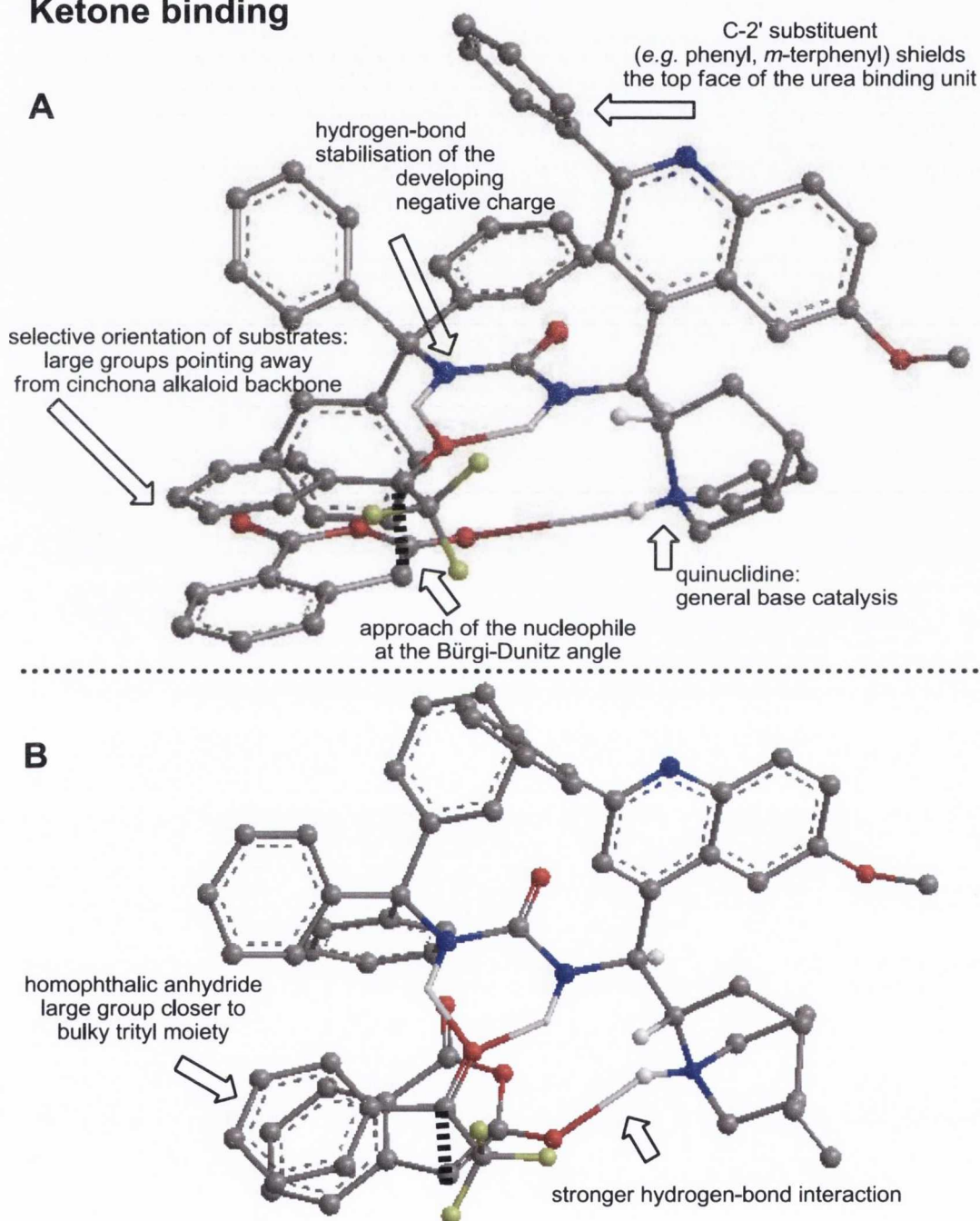


Figure 4.9 “Ketone-binding” pre-transition state assemblies in the reaction between 139 and 99:

Enolate binding

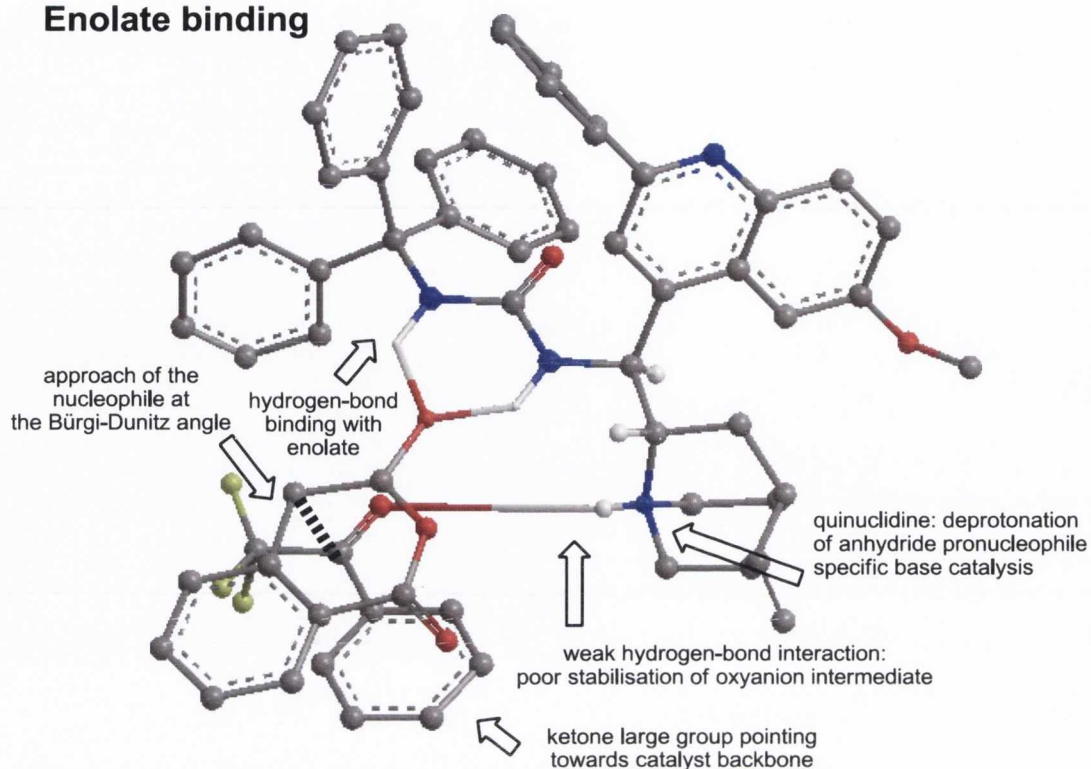


Figure 4.10 “Enolate-binding” pre-transition state assembly in the reaction between **139** and **99**:

It is possible to observe that in a ‘ketone-binding’ assembly all of the steric and electronic prerequisites are encompassed: the quinuclidine moiety generates the reactive enol form of the anhydride pronucleophile which subsequently attacks the *si*-face of ketone **99** while the oxyanion intermediate on the carbonyl is stabilised by the dual hydrogen-bond donation of the urea moiety. While in the assembly **A** both substrates are oriented in a way to avoid steric clashes with the catalyst, a seemingly weak interaction between the quinuclidine moiety and the enolised **139** can be observed; however, this interaction is strengthened if we consider an orientation of the anhydride in which its large group is slightly closer to the bulky trityl unit on catalyst **426** (assembly **B**). On the other hand, in an ‘enolate-binding’ assembly, the quinuclidine amine deprotonates anhydride **139** to form an enolate reactive species (bound to the urea unit) which attacks the *si*-face of **99** from a Bürgi-Dunitz trajectory. The fact that the ketone large group (*i.e.* phenyl) is pointing towards the catalyst backbone combined with the marginal stabilisation of the oxyanion intermediate by hydrogen-bond donation from the protonated quinuclidine (which in this *pre*-transition state scenario is exceedingly distant from the reacting substrates) induce us to suggest that a *pre*-

transition state assembly involving a ‘ketone binding’ (either **A** or **B**) most accurately represents the catalyst-controlled encounter of the ketone and the anhydride.

With regard to the catalyst structure, we would speculate that the bulky moiety at C-2’ is crucial for optimal asymmetric induction not only by balancing the steric requirement of the catalytic species along the C-4’ – C-9 rotational axis, but also by shielding one of the faces of the hydrogen-bond donating unit. The bulky trityl-urea moiety, despite having a lower hydrogen-bond donation potential, outperformed both *N*-aryl squaramides and thioureas possibly by providing a more sterically congested binding pocket in which ketones having substituents (R_S and R_L) relatively similar in size (compared to those in aldehydes) are oriented in a tighter *pre*-transition state assembly.

4.12 Conclusions

We were able to develop the first asymmetric catalytic protocol for annulation reactions between enolisable anhydrides and asymmetric ketones and we demonstrated that cinchona alkaloid-derived organocatalysts are able to promote the reactions involving either homophthalic anhydrides or arylsuccinic anhydrides and a wide range of ketones. We synthesised novel *ad hoc*-designed bifunctional *N*-alkyl urea substituted cinchona alkaloids which were able to promote the formation of chiral 3,4-dihydroisocoumarins and spirooxindoles bearing up to 2 contiguous quaternary stereocentres in good yields and with good to excellent diastereo- and enantiocontrol. While the use of *N*-alkyl thiourea cinchona alkaloid-derived organocatalysts as optimal catalysts for a given reaction has been documented, to our knowledge, this investigation represents the first example where *N*-alkyl urea derivatives (*i.e.* **426** and **450**) have outperformed (in terms of asymmetric induction) *N*-aryl urea analogues and other similar catalytic species.

The substrate scope for the transformation under scrutiny has been considerably expanded: arylsuccinic anhydrides were used for the first time and also prochiral aromatic ketones bearing functionalities different than alkyl groups, which has allowed the synthesis of densely functionalised lactone products. The excellent versatility of our newly developed asymmetric protocol has allowed the proficient use of structurally diverse activated ketones. In addition, a possible (tentative) mechanistic explanation for

the mode of action of **426** has been provided, which fits with the experimental results obtained.

5.0 General experimental data

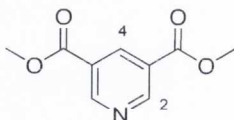
Proton Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker DPX 400 MHz and Bruker Avance II 600MHz spectrometers, using as solvent CDCl_3 , DMSO-d_6 or CD_3OD and referenced relative to residual CHCl_3 ($\delta = 7.26$ ppm) DMSO ($\delta = 2.50$ ppm) or CH_3OH ($\delta = 3.31$ ppm). Chemical 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. 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. A Waters micromass LCT-tof mass spectrometer was used in ESI positive and ESI negative modes for electrospray ionization mass spectrometry. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated 60F₂₅₄ slides, and visualized by UV irradiation and KMnO_4 staining. Optical rotation measurements are quoted in units of $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. Acetonitrile, toluene and methylene chloride (CH_2Cl_2) were distilled over calcium hydride and stored under argon. Tetrahydrofuran (THF) and diethyl ether were distilled over sodium-benzophenone and stored under argon. Methanol (MeOH) and isopropyl alcohol ($i\text{PrOH}$) were dried over activated 3Å molecular sieves. Commercially available anhydrous *t*-butyl methyl ether (MTBE) was used. Analytical CSP-HPLC was performed on Daicel CHIRALPAK, AD, AD-H, OJ-H, or Chiralcel OD-H (4.6 mm x 25 cm) columns. The X-ray crystallography data for crystal sample ***trans*-332** were collected on a Rigaku Saturn 724 CCD diffractometer. A suitable crystal from each compound was selected and mounted on a glass fibre tip and placed on the goniometer head in a 150K N_2 gas stream. The data sets were collected using Crystalclear-SM 1.4.0 software and, for each crystal, 1246 diffraction images, of 0.5° per image, were recorded. Data integration, reduction and correction for absorption and polarisation effects were all performed using Crystalclear-SM 1.4.0 software. Space group determination, structure solution and refinement were obtained using Crystalstructure ver. 3.8 and Bruker Shelxtl Ver. 6.14 software. The data for the crystal structures ***cis*-412**, ***trans*-459**, ***cis*-463** and ***trans*-473** were collected on a Bruker Smart Apex2 CCD Diffractometer. For each dataset, a suitable crystal was selected and mounted using inert oil on a 0.3mm MiTeGen loop and placed on the goniometer head in a 100K N_2 gas

stream. The datasets were collected using Bruker APEX2 v2011.8-0 software. Data integrations, reductions and corrections for absorption and polarization effects were all performed using APEX2 v2011.8-0 software. Space group determination, structure solution and refinement were obtained using Bruker Shelxtl* Ver. 6.14 software. The structures were solved with Direct Methods using the SHELXTL program and refined against IF^2I with the program XL from SHELX-97 using all data. Non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were placed into geometrically calculated positions and refined using a riding model. (*Software Reference Manual, version 5.625; Bruker Analytical X-Ray Systems Inc.: Madison, WI, 2001. Sheldrick, G. M. SHELXTL, An Integrated System for Data Collection, Processing, Structure Solution and Refinement; Bruker Analytical X-Ray Systems Inc.: Madison, WI, 2001.)

5.1 Experimental data for Chapter 2

5.1.1 Synthesis of the pyridine core of GAPN mimics

5.1.1.1 Dimethyl pyridine-3,5-dicarboxylate (**272**)

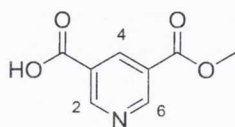


A 500 mL round-bottomed flask containing a stirring bar was charged with 3,5-pyridinedicarboxylic acid (**271**) (10.00 g, 59.84 mmol). MeOH (100 mL) followed by conc. H_2SO_4 (3 mL) were added, the flask was fitted with a condenser and the resulting suspension was stirred under reflux for 20 h after which time a solution was obtained. The solution was concentrated under reduced pressure and to the resulting oil, Et_2O (150 mL) was added followed by a saturated solution of $NaHCO_3$ until pH 8 was reached. The mixture was extracted using Et_2O (4 x 150 mL), the combined organic fractions were dried over $MgSO_4$ and the solvent was removed *in vacuo* to give **272** (10.60 g, 91%) as a white solid. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³²² M.p 87-90 °C (lit.,³²² 85.5-86.3 °C).

δ_{H} (400 MHz, CDCl_3): 9.39 (2 H, d, J 2.1, H-2 and H-6), 8.90 (1 H, t, J 2.1, H-4), ,
4.02 (6 H, s, $(\text{OCH}_3)_2$),

δ_{C} (100 MHz, CDCl_3): 164.9 (C=O), 154.2, 138.1, 126.0 (q), 52.8.

5.1.1.2 5-(Methoxycarbonyl)nicotinic acid (**273**)



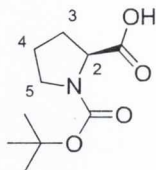
In a 1 L round-bottomed flask containing a stirring bar, **272** (10.00 g, 51.24 mmol) was dissolved in a 0.1 M solution of KOH (3.09 g, 55.07 mmol) in MeOH (550 mL). The solution was stirred at room temperature for 20 h, then it was separated into two portions of 275 mL each. To each batch, Et_2O (300 mL) and H_2O (200 mL) were added and the mixtures were extracted with Et_2O (3 x 200 mL). The combined organic fractions were dried over MgSO_4 and the solvent was removed *in vacuo* to afford the unreacted starting material **272** (1.68 g, 8.71 mmol). Conc. HCl was added dropwise to the combined aqueous layers until pH 5 was reached, then concentrated under reduced pressure to a volume of 50 mL. The precipitated white solid was filtered and washed with toluene (30 mL), then transferred to a 250 mL round-bottomed flask followed by a further addition of toluene (30 mL). The solvent was removed *in vacuo* to afford **273** (7.24 g, 78%) as a white solid. M.p 218–221 °C (lit.,³²³ 216–218 °C).

δ_{H} (400 MHz, $\text{DMSO}-d_6$): 13.81 (1 H, bs, CO_2H), 9.26 (2 H, app. t, H-2 and H-6), 8.63
(1 H, app. t, H-4), 3.93 (3 H, s, OCH_3).

δ_{C} (100 MHz, $\text{DMSO}-d_6$): 165.4 (C=O), 164.5 (C=O), 153.8, 153.2, 137.2, 126.8 (q),
125.7 (q), 52.7.

5.1.2 Synthesis of the Asn-109-mimicking moieties

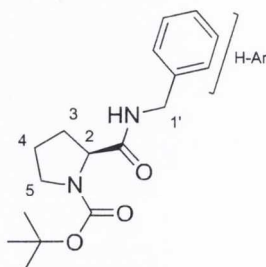
5.1.2.1 *N*-(*tert*-Butoxycarbonyl)-L-proline (**276**)



A 500 mL round-bottomed flask containing a stirring bar was charged with L-proline (**240**) (14.00 g, 121.60 mmol) and Na_2CO_3 (15.50 g, 146.24 mmol). A 50% mixture of THF/ H_2O (300 mL) was added and the resulting suspension was stirred at room temperature for 30 min. Di-*tert*-butyl dicarbonate (32.00 g, 146.62 mmol) was added and the solution was stirred at room temperature for 16 h after which time a white suspension was obtained. The THF was removed under reduced pressure, the mixture was extracted with EtOAc (2 x 20 mL), then 0.5 M HCl was added to the aqueous layer until pH 4 was reached. The mixture was extracted using CH_2Cl_2 (3 x 100 mL), the combined organic fractions were dried over MgSO_4 and the solvent was removed *in vacuo* to give **276** (25.75 g, 98%) as a white solid. The ^1H NMR analysis of this compound indicated the presence of 2 rotameric species at room temperature in CDCl_3 . The isolated compound exhibited identical spectroscopic data to those reported in the literature.³²⁴ M.p 130-132 °C (lit.,³²⁴ 135-137 °C). $[\alpha]_{\text{D}}^{20} = -74.2$ (*c* 1.00, CHCl_3).

δ_{H} (400 MHz, CDCl_3): 10.99 (1 H, bs, CO_2H), 4.45-4.16 (1 H, m, H-2), 3.64-3.28 (2 H, m, H-5), 2.40-1.81 (4 H, m, H-3 and H-4), 1.46 (9 H, s, $\text{C}(\text{CH}_3)_3$).

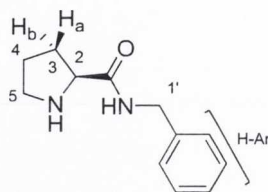
5.1.2.2 *N*^{*α*}-(*tert*-Butoxycarbonyl)-*N*-benzyl-(*S*)-prolinamide (**281a**)



An oven dried 250 mL round-bottomed flask containing a stirring bar was charged with **276** (6.00 g, 27.88 mmol). The apparatus was flushed with argon, then fitted with a septum and placed under an argon atmosphere (balloon). Dry THF (80 mL) followed by freshly distilled triethylamine (4.30 mL, 30.85 mmol) were added *via* syringe and the resulting solution was cooled to 0 °C and stirred for 30 min. Freshly distilled ethyl chloroformate (**277**) (2.80 mL, 29.30 mmol) was added dropwise *via* syringe to the reaction mixture at 0 °C resulting in the formation of a white suspension. The reaction was stirred at 0 °C for 1 h and subsequently freshly distilled benzylamine (**278**) (3.40 mL, 31.04 mmol) was added dropwise *via* syringe. After the addition, the flask was allowed to warm to room temperature and the reaction was stirred for 16 h, then a condenser was fitted and the reaction mixture was stirred for further 4 hours at reflux. The suspension was then cooled to room temperature, filtered and the filtrate was washed with EtOAc (3 x 10 mL). The solution was concentrated *in vacuo* to give a viscous yellow oil that was taken up with CH₂Cl₂ (50 mL), treated with a saturated aqueous solution of NaHCO₃ (20 mL) and subsequently extracted with CH₂Cl₂ (3 x 50 mL). The combined organic fractions were dried over MgSO₄ and the solvent was removed under reduced pressure. Purification by flash chromatography (7:3 hexane-EtOAc) of the crude product afforded **281a** (7.44 g, 88%) as a white solid. The ¹H NMR analysis of this compound indicated the presence of 2 rotameric species at room temperature in DMSO-*d*₆ and the ratio was found to be 2:3. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³²⁵ M.p 125-128 °C (lit.,³²⁵ 121-122 °C). Major rotamer assigned for ¹H NMR. [α]_D²⁰ = -83.5 (*c* 1.00, CHCl₃).

δ_{H} (400 MHz, DMSO-*d*₆): 8.38 (1 H, bs, CONH), 7.35-7.17 (5 H, m, H-Ar), 4.39-4.29 (1 H, m, H-2), 4.26-4.05 (2 H, m, H1'), 3.46-3.23 (2 H, m, H-5), 2.21-1.68 (4 H, m, H-3 and H-4), 1.35 (9 H, s, C(CH₃)₃).

5.1.2.3 (S)-N-Benzylpyrrolidine-2-carboxamide (266a)

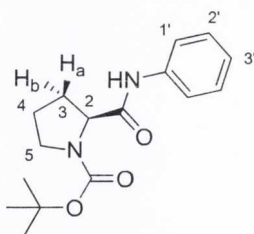


In a 100 mL round-bottomed flask containing a stirring bar, **281a** (1.00 g, 3.29 mmol) was dissolved in CH_2Cl_2 (40 mL). TFA (20.0 mL) was added to the solution *via* syringe and the reaction mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure, then a 2 M solution of NaOH (7 mL) was added. Ground NaOH was then added to the residue until alkaline pH was reached. The resulting solution was extracted with CH_2Cl_2 (4 x 40 mL). The combined organic fractions were dried over MgSO_4 and the solvent was removed *in vacuo* to give **266a** (538 mg, 80%) as a viscous pale yellow oil. $[\alpha]_{\text{D}}^{20} = -50.8$ (*c* 1.10, CHCl_3).

δ_{H} (600 MHz, $\text{DMSO}-d_6$): 8.42 (1 H, bs, CONH), 7.41-7.17 (5 H, m, H-Ar), 4.36-4.22 (2 H, m, H-1'), 3.66-3.55 (1 H, m, H-2), 3.35 (NH coincident with the H_2O resonance), 2.92-2.77 (2 H, m, H-5), 2.04-1.93 (1 H, m, H-3a), 1.77-1.66 (1 H, m, H-3b), 1.66-1.57 (2 H, m, H-4).

HRMS (m/z -ESI): $[\text{M}+\text{Na}]^+$ found 227.1167. $\text{C}_{12}\text{H}_{16}\text{N}_2\text{ONa}$ Requires 227.1160.

5.1.2.5 (S)-tert-Butyl 2-(phenylcarbamoyl)pyrrolidine-1-carboxylate (281b)

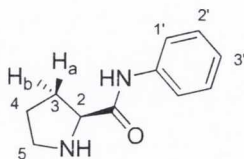


An oven dried 250 mL round-bottomed flask containing a stirring bar was charged with **276** (3.00 g, 13.94 mmol). The apparatus was flushed with argon, then fitted with a

septum and placed under an argon atmosphere (balloon). Dry THF (50 mL) followed by freshly distilled triethylamine (2.30 mL, 16.72 mmol) were added *via* syringe and the resulting solution was cooled to 0 °C and stirred for 30 min. Freshly distilled ethyl chloroformate (**277**) (1.60 mL, 16.72 mmol) was added dropwise *via* syringe to the reaction mixture at 0 °C resulting in the formation of a white suspension. The reaction was stirred at 0 °C for 1 h and subsequently freshly distilled aniline (**279**) (1.50 mL, 16.72 mmol) was added dropwise *via* syringe. After the addition, the flask was allowed to warm to room temperature and the reaction was stirred for 16 h, then a condenser was fitted and the reaction mixture was stirred for further 4 hours at reflux. The suspension was then cooled to room temperature, filtered and the filtrate was washed with EtOAc (3 x 10 mL). The solution was concentrated *in vacuo* to give a viscous yellow oil that was taken up with CH₂Cl₂ (50 mL), treated with a saturated aqueous solution of NaHCO₃ (20 mL) and subsequently extracted with CH₂Cl₂ (3 x 50 mL). The combined organic fractions were dried over MgSO₄ and the solvent was removed under reduced pressure. Purification by flash chromatography (9:1 hexane-EtOAc) of the crude product afforded **281b** (2.51 g, 62%) as a white solid. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³²⁶ M.p 183-186 °C (lit.,³²⁷ 185-188 °C). $[\alpha]_D^{20} = -140.2$ (c 0.5, CHCl₃).

δ_H (400 MHz, CDCl₃): 9.49 (1 H, bs, NH), 7.51 (2 H, d, *J* 8.2, H-1'), 7.38-7.22 (2 H, m, H-2'), 7.17-6.98 (1 H, m, H-3'), 4.64-4.19 (1 H, m, H-2), 3.71-3.14 (2 H, m, H-5), 2.68-2.43 (1 H, m, H-3a), 2.09-1.75 (3 H, m, H-3b and H-4), 1.49 (9 H, s, (CH₃)₃).

5.1.2.6 (S)-N-Phenylpyrrolidine-2-carboxamide (**266b**)



In a 100 mL round-bottomed flask containing a stirring bar, **281b** (1.20 g, 4.13 mmol) was dissolved in CH₂Cl₂ (20 mL). TFA (10.0 mL) was added to the solution *via* syringe and the reaction mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure, then a 2 M solution of NaOH (7 mL) was added.

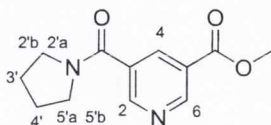
Ground NaOH was then added to the residue until alkaline pH was reached. The resulting solution was extracted with CH₂Cl₂ (4 x 40 mL). The combined organic fractions were dried over MgSO₄ and the solvent was removed *in vacuo* to give **266b** (784 mg, 50%) as a white solid. M.p 77-78 °C (lit.,³²⁷ 76-77 °C). $[\alpha]_D^{20} = -71.5^\circ$ (*c* 1.0, CHCl₃).

δ_H (400 MHz, DMSO-*d*₆): 9.94 (1 H, bs, CONH), 7.63 (2 H, d, *J* 8.0, H-1'), 7.29 (2 H, app. t, H-2'), 7.07-6.99 (1 H, m, H-3'), 3.71-3.64 (1 H, m, H-2), 3.35 (NH coincident with the H₂O resonance), 2.88 (2 H, app. t, H-5), 2.10-2.96 (1 H, m, H-3a), 1.82-1.70 (1 H, m, H-3b), 1.69-1.58 (2 H, m, H-4).

5.1.3 Procedure A: general protocol for the coupling of **273** with the Asn-mimicking moiety

An oven dried 100 mL round-bottomed flask containing a stirring bar was charged with **273** (2.00 g, 11.04 mmol, 1.0 equiv.). The apparatus was fitted with a condenser, flushed with argon, then fitted with a septum and placed under an argon atmosphere (balloon). Freshly distilled SOCl₂ (50 mL) was added *via* syringe and the suspension was heated at reflux for 2 h or until the complete dissolution of **273**. The solution was allowed to cool to room temperature and was stirred for 16 h. The SOCl₂ in excess was removed by distillation, then toluene (4 mL) was added *via* syringe to the resulting off-white solid and the solvent was subsequently removed under reduced pressure. The residue was dissolved in dry CH₂Cl₂ (50 mL) and cooled to 0 °C. Dry triethylamine (2.1 equiv.) was added dropwise *via* syringe to the reaction mixture, followed by DMAP (10 mmol%) and subsequently the appropriate amine (1.1 equiv.) was added *via* syringe. The reaction mixture was stirred at room temperature for 16 h, then a condenser was fitted and the reaction was heated at reflux for 4 h. The reaction was allowed to cool to room temperature, then a saturated aqueous solution of NaHCO₃ (25 mL) was added and the mixture was extracted using CH₂Cl₂ (3 x 50 mL). The combined organic fractions were dried over MgSO₄ and the solvent was removed *in vacuo*. The crude product was obtained as a brown viscous oil and was purified by flash chromatography.

5.1.3.1 Methyl 5-(pyrrolidine-1-carbonyl)nicotinate (**284**)



Prepared as per procedure A using **273** (2.00 g, 11.04 mmol), dry triethylamine (3.2 mL, 23.18 mmol), DMAP (135 mg, 1.10 mmol) and freshly distilled pyrrolidine (**283**) (1.0 mL, 11.98 mmol). Flash chromatography (100% EtOAc) afforded **284** (2.04 g, 79%) as a white solid. M.p 94-96 °C.

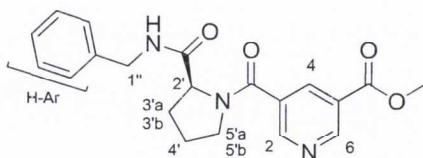
δ_{H} (400 MHz, CDCl_3): 9.26 (1 H, s, H-6), 8.96 (1 H, s, H-2), 8.47 (1 H, s, H-4), 3.98 (3 H, s, OCH_3), 3.69 (2 H, app. t, H-2'b, H-5'b), 3.47 (2 H, app. t, H-2'a, H-5'a), 2.09-1.90 (4 H, m, H-3' and H-4').

δ_{C} (100 MHz, CDCl_3): 165.6 (C=O), 164.6 (C=O), 151.3, 151.1, 135.4, 132.3 (q), 125.2 (q), 52.2, 49.1, 46.1, 26.0, 23.9.

ν_{max} (film)/ cm^{-1} : 2953, 1728, 1617, 1415, 1285, 1205, 1105, 828, 736.

HRMS (m/z -ESI): $[\text{M}+\text{H}]^+$ found 235.1077. $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}_3$ Requires 235.1083.

5.1.3.2 (*S*)-Methyl 5-(2-(3-phenylpropanoyl)pyrrolidine-1-carbonyl)nicotinate (**274a**)



Prepared as per procedure A using **273** (2.42 g, 13.35 mmol), freshly distilled triethylamine (4.0 mL, 28.70 mmol), DMAP (163 mg, 1.34 mmol) and a solution of *N*-benzyl-L-prolinamide (**266a**) (3.00 g, 14.69 mmol) in dry CH_2Cl_2 (5 mL). Flash

chromatography (100% EtOAc) afforded **274a** (3.69 g, 75%) as an off-white solid. M.p 128-133 °C. $[\alpha]_D^{20} = -68.9$ (c 0.70, CHCl₃).

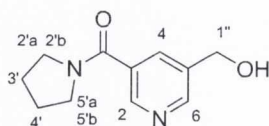
δ_H (400 MHz, CDCl₃): 9.29 (1 H, s, H-6), 8.94 (1 H, s, H-2), 8.46 (1 H, s, H-4), 7.39-7.23 (5 H, m, H-Ar), 7.15 (1 H, m, NH), 4.78 (1 H, dd, J 5.5, 8.0, H-2'), 4.50 (2 H, dd, J 6.0, 15.0, H-1''), 3.99 (3 H, s, OCH₃), 3.72-3.59 (1 H, m, H-5'b), 3.56-3.42 (1 H, m, H-5'a), 1.99-1.83 (1 H, m, H-3'a), 2.26-2.07 (2 H, m, H-4'), 2.58-2.43 (1 H, m, H-3'b).

δ_C (100 MHz, CDCl₃): 170.1 (C=O), 166.9 (C=O), 164.4 (C=O), 151.5, 151.2, 137.7 (q), 135.5, 131.4, (q), 128.2, 127.1, 126.9, 125.3 (q), 59.9, 52.3, 49.9, 43.2, 27.2, 25.1.

ν_{max} (film)/cm⁻¹: 3280, 1731, 1654, 1627, 1425, 1281, 1238, 1199.

HRMS (m/z -ESI): $[M+H]^+$ found 368.1605. C₂₀H₂₂N₃O₄ Requires 368.1610.

5.1.4.1 (5-(Hydroxymethyl)pyridin-3-yl)(pyrrolidin-1-yl)methanone (**285**)



An oven dried 100 mL round-bottomed flask containing a stirring bar was charged with **284** (3.34 g, 14.26 mmol), flushed with argon, then fitted with a septum and placed under an argon atmosphere (balloon). Dry THF (50 mL) was added *via* syringe and the mixture was immersed in an ultrasonic bath at room temperature until **284** was fully dissolved. The solution was cooled to -78 °C and stirred for 15 min. LiAlH₄ (750 mg, 20.04 mmol) was added to the reaction mixture at -78 °C in two equal portions 15 min. apart. The reaction mixture was stirred at -78 °C for 20 h and then H₂O (2 mL) was added. The reaction mixture was stirred at -78 °C for further 30 min and subsequently diluted with EtOAc (3 mL). The flask was allowed to warm to room temperature, and the reaction was stirred for additional 15 min then MgSO₄ was added. The resulting

suspension was filtered through a sintered glass funnel and the filtrate was washed with EtOAc (4 x 20 mL). The washings were concentrated under reduced pressure to give the crude product as a viscous yellow oil. The remaining salts were further washed with MeOH (3 x 10 mL), the washings were concentrated *in vacuo* and the resulting yellow residue, was suspended in 5 mL of a saturated solution of Rochelle salt (potassium sodium tartrate). The suspension was stirred for 2 h at room temperature and subsequently extracted with EtOAc (4 x 20 mL). The combined organic fractions were dried over MgSO₄ and the solvent was removed *in vacuo* providing the crude product as a yellow oil. The two portions of crude product were combined and purified by flash chromatography (eluting in gradient from 100% EtOAc to 10% MeOH in EtOAc) to afford **285** (2.45 g, 83%) as a pale yellow oil.

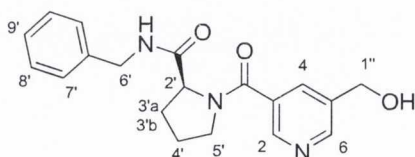
δ_{H} (400 MHz, CDCl₃): 8.58 (1 H, s, H-2), 8.53 (1 H, s, H-6), 7.81 (1 H, s, H-4), 4.73 (2 H, s, H-1''), 4.36 (1 H, bs, OH), 3.62 (2 H, app. t, H-2'b and H-5'b), 3.41 (2 H, app. t, H-2'a and H-5'a), 2.04-1.85 (4 H, m, H-3' and H-4').

δ_{C} (100 MHz, CDCl₃): 166.8 (C=O), 148.8, 145.9, 136.6 (q), 133.0, 132.0 (q), 61.3, 49.1, 46.0, 25.9, 23.9.

ν_{max} (film)/cm⁻¹: 3345, 2877, 1611, 1419, 1191, 1027.

HRMS (*m/z* -ESI): [M+H]⁺ found 207.1128. C₁₁H₁₅N₂O₂ Requires 207.1134.

5.1.4.2 (S)-1-(1-(5-(Hydroxymethyl)nicotinoyl)pyrrolidin-2-yl)-3-phenylpropan-1-one (268a)



An oven dried 100 mL round-bottomed flask containing a stirring bar was charged with **274a** (2.51 g, 6.83 mmol), flushed with argon, then fitted with a septum and placed

under an argon atmosphere (balloon). Dry THF (50 mL) was added *via* syringe and the mixture was immersed in an ultrasonic bath at room temperature until **274a** was fully dissolved. The solution was cooled to -78 °C and stirred for 15 min. LiAlH₄ (383 mg, 10.24 mmol) was added to the reaction mixture at -78 °C in two equal portions 15 min apart. The reaction mixture was stirred at -78 °C for 20 h and then Na₂SO₄ · 10 H₂O (3.28 g, 10.18 mmol) was added. The reaction mixture was stirred at -78 °C for further 30 min and subsequently diluted with EtOAc (2.2 mL). The flask was allowed to warm to room temperature and the reaction was stirred for additional 15 min. The resulting suspension was filtered through a sintered glass funnel and the filtrate was washed with EtOAc (4 x 20 mL). The washings were dried over MgSO₄ and the solvent was removed under reduced pressure to give the crude product as a viscous yellow oil. The remaining salts were further washed with MeOH (3 x 10 mL) and the washings were concentrated *in vacuo* and the resulting yellow residue, was suspended in 5 mL of a saturated solution of Rochelle salt (potassium sodium tartrate). The suspension was stirred for 2 h at room temperature and subsequently extracted with EtOAc (4 x 20 mL). The combined organic fractions were dried over MgSO₄ and the solvent was removed *in vacuo* providing the crude product as a yellow oil. The two portions of crude product were combined and purified by flash chromatography (9:1 EtOAc-MeOH) to afford **56** (1.78 g, 77%) as a pale yellow oil. The ¹H NMR analysis of this compound indicates the presence of 2 rotameric species at room temperature in DMSO-*d*₆ and the ratio was found to be 7:3. Major rotamer assigned for ¹³C NMR. [α]_D²⁰ = -45.4 (*c* 0.70, CHCl₃).

δ_H (600 MHz, DMSO-*d*₆): **major rotamer** 8.47 (1 H, bt, CONH), 8.64 (1 H, bs, H-2), 8.59 (1 H, bs, H-6), 7.93 (1 H, bs, H-4), 7.35-7.19 (5 H, m, H-7', H-8' and H-9'), 5.46 (1 H, t, *J* 5.7, OH), 4.59 (2 H, d, *J* 5.7, H-1''), 4.54-4.48 (1 H, m, H-2'), 4.39-4.29 (2 H, m, 1.7H, H-6'), 3.64-3.61 (2 H, m, H-5'), 2.28-2.19 (1 H, m, H-3'b), 1.97-1.78 (m, 3H, H-3'a and H-4').

minor rotamer 8.56 (1 H, s, H-2), 8.43 (1 H, s, H-6), 8.31 (1 H, bt, CONH), 7.69 (1 H, bs, H-4), 7.35-7.19 (3 H, m, H-8' and H-9'), 6.93 (2 H, d, *J* 7.2, H-7'), 5.41 (1 H, t, *J* 5.7, OH), 4.54-4.48 (2 H, m, H-1''), 4.39-4.29 (1 H, m, H-2'),

4.16-4.03 (2 H, m, H-6'), 3.50-3.44 (2 H, m, H-5'), 2.28-2.19 (1 H, m, H-3'b), 1.97-1.78 (3 H, m, H-3'a and H-4'y).

δ_C (100 MHz, DMSO- d_6): 171.5 (C=O), 166.7 (C=O), 149.5 (q), 149.1, 148.5 (q), 146.4, 133.1, 132.5 (q), 128.2, 126.8, 126.6, 60.3, 59.8, 49.8, 41.8, 29.9, 24.9.

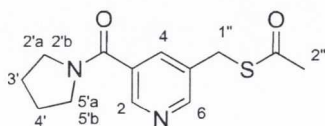
$\nu_{\max}$ (film)/ cm^{-1} : 3280, 1736, 1614, 1413, 1237, 1027.

HRMS (m/z -ESI): $[M+H]^+$ found: 340.1658. $C_{19}H_{22}N_3O_3$ Requires 340.1661.

5.1.5 Procedure B: general protocol for the synthesis of thioacetate intermediates *via* a Mitsunobu reaction.

An oven dried 100 mL round-bottomed flask containing a stirring bar was charged with PPh_3 (2.05 equiv.), flushed with argon, then fitted with a septum and placed under an argon atmosphere (balloon). Dry THF (40 mL) was added *via* syringe and the solution was cooled to 0 °C and stirred for 15 min. DIAD (2.05 equiv.) was then added dropwise *via* syringe and the solution was stirred at 0 °C for a further 30 min after which time a white precipitate had formed. A solution of the appropriate alcohol (1.80 mmol) in dry THF (20 mL) followed by thioacetic acid (2.05 equiv.) were then added *via* syringe to the reaction mixture at 0 °C. The flask was allowed to warm to room temperature and the solution was stirred for 16 h. The resulting orange solution was concentrated *in vacuo* and the crude product obtained as an orange oil was purified by flash chromatography.

5.1.5.1 *S*-(5-(Pyrrolidine-1-carbonyl)pyridin-3-yl)methyl ethanethioate (286)



Prepared as per procedure B using PPh_3 (2.18 g, 8.30 mmol), DIAD (1.70 mL, 8.30 mmol), a solution of **285** (835 mg, 4.05 mmol) in dry THF (20 mL) and thioacetic acid

(0.620 mL, 8.25 mmol). Flash chromatography (100% EtOAc) afforded **286** (902 mg, 85%) as a viscous dark yellow oil.

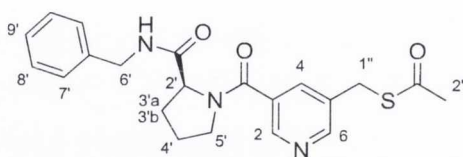
δ_{H} (400 MHz, DMSO- d_6): 8.60 (2 H, app. t, H-2 and H-6), 7.85 (1 H, t, J 2.1, H-4), 4.18 (2 H, s, H-1''), 3.48 (2 H, app. t, H-2'b and H-5'b), 3.39 (2 H, app. t, H-2'a and H-5'a), 2.38 (3 H, s, H-2''), 1.93-1.78 (4 H, m, H-3' and H-4').

δ_{C} (100 MHz, DMSO- d_6): 194.8 (C=O), 165.7 (C=O), 150.6 (CH), 146.4, 134.9 (q), 133.9, 132.5 (q), 48.8, 46.1, 30.3, 29.5, 25.9, 23.9.

ν_{max} (film)/ cm^{-1} : 2977, 1690, 1619, 1411, 1229, 1132, 1104, 1027.

HRMS (m/z -ESI): $[\text{M}+\text{H}]^+$ found 265.1008. $\text{C}_{13}\text{H}_{17}\text{N}_2\text{O}_2\text{S}$ Requires 265.1011.

5.1.5.2 (S)-S-(5-(2-(3-Phenylpropanoyl)pyrrolidine-1-carbonyl)pyridin-3-yl)methyl ethanethioate (**269a**)



Prepared as per procedure B using PPh_3 (970 mg, 3.70 mmol), DIAD (0.800 mL, 3.86 mmol), a solution of **268a** (612 mg, 1.80 mmol) in dry THF (20 mL) and thioacetic acid (0.270 mL, 3.78 mmol). Flash chromatography (eluting in gradient from 100% EtOAc to 10% MeOH in EtOAc) afforded **269a** (607 mg, 76%) as an off-white foamy solid. The ^1H NMR analysis of this compound indicates the presence of 2 rotameric species at room temperature in DMSO- d_6 and the ratio was found to be 7:3. Major rotamer assigned for ^{13}C NMR. $[\alpha]_{\text{D}}^{20} = -61.7$ (c 1.10, CHCl_3).

δ_{H} (600 MHz, DMSO- d_6): **major rotamer** 8.67 (1 H, d, J 2.1, H-2), 8.62 (1 H, d, J 2.1, H-6), 8.52 (1 H, t, J 6.4, CONH), 7.91 (1 H, app. t, H-4), 7.37-7.19 (5 H, m, H-7', H-8', and H-9'), 4.55-4.46 (1

H, m, H-2'), 4.40-4.31 (2 H, m, H-6'), 4.25 (2 H, s, H-1''), 3.68-3.56 (2 H, m, H-5'), 2.38 (3 H, s, H-2''), 2.37-2.19 (1 H, m, H-3'b), 1.98-1.77 (3 H, m, H-3'a, H-3'ay and H-4').

minor rotamer 8.57 (1 H, d, *J* 2.1, H-2), 8.44 (1 H, d, *J* 2.1, H-6), 8.36 (1 H, t, *J* 6.4 CONH), 7.67 (1 H, app. t, H-4y), 7.37-7.19 (3 H, m, H-8' and H-9'), 6.95 (2 H, d, *J* 6.9, H-7'), 4.40-4.31 (1 H, m, H-2'), 4.16-4.01 (4 H, m, H-1'' and H-6'), 3.53-3.42 (2 H, m, H-5'), 2.35 (3 H, s, H-2''), 2.37-2.19 (1 H, m, H-3'b), 1.98-1.77 (3 H, m, H-3'a and H-4').

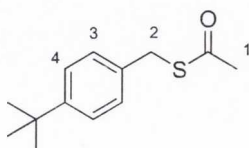
δ_C (151 MHz, DMSO-*d*₆): 194.2 (C=O), 171.0 (C=O), 167.7 (C=O), 151.9, 151.3 (q), 146.7, 146.0 (q), 135.3, 130.8 (q), 128.4, 127.4, 127.2, 60.3, 50.0, 43.5, 30.2, 30.0, 28.1, 25.4.

$\nu_{\max}$ (film)/cm⁻¹: 3281, 2976, 1731, 1626, 1557, 1412, 1280, 1237, 1026, 1106.

HRMS (*m/z* -ESI): [M+H]⁺ found 398.1532. C₂₁H₂₄N₃O₃S Requires 398.1538.

5.1.6 Synthesis of of model compounds to develop a strategy for the generation of thiols from thioacetates

5.1.6.1 *S*-4-*tert*-Butylbenzyl ethanethioate (289)



A 100 mL round-bottomed flask containing a stirring bar was charged with freshly distilled **287** (5.0 mL, 26.62 mmol). CH₂Cl₂ (20 mL) and cooled to 0 °C. Triethylamine (7.40 mL, 53.24 mmol) was added *via* syringe followed by DMAP (326 mg, 2.66

mmol). Acetic anhydride (3.0 mL, 31.95 mmol) was added dropwise *via* syringe to the solution and after the addition the reaction was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was treated with a saturated aqueous solution of NaHCO₃ (20 mL) and was subsequently extracted with CH₂Cl₂ (4 x 30 mL). The combined organic fractions were dried over MgSO₄ and the solvent was removed *in vacuo* to give the crude product as a yellow oil. Purification of the crude product by flash chromatography (95:5 Hexane-EtOAc) provided **289** (4.48 g, 76%) as a colourless oil.

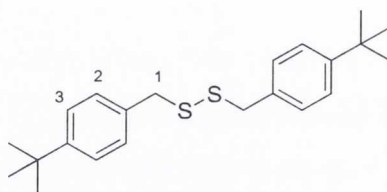
δ_{H} (400 MHz, DMSO-*d*₆): 7.31 (2 H, d, *J* 8.2, H-4), 7.20 (2 H, d, *J* 8.2, H-3), 4.07 (2 H, s, H-2), 2.34 (3 H, s, H-1), 1.25 (9 H, s, C(CH₃)₃).

δ_{C} (100 MHz, DMSO-*d*₆): 194.8 (C=O), 149.5 (q), 134.7 (q), 128.4, 125.3, 34.2 (q), 32.1, 31.1, 30.2.

ν_{max} (film)/cm⁻¹: 2961, 1738, 1637, 1364, 1130, 1102, 955.

HRMS (*m/z* -ESI): [M+Na]⁺ Found: 245.0965. C₁₃H₁₈OSNa Requires: 245.0976.

5.1.6.2 1,2-bis(4-*tert*-Butylbenzyl)disulfane (308)



A 25 mL round-bottomed flask containing a stirring bar was charged with **287** (480 μ L, 2.77 mmol). CH₂Cl₂ (5 mL) together with triethylamine (390 μ L, 2.78 mmol) were added *via* syringe to **287** followed by I₂ (703 mg, 2.77 mmol). The solution was stirred at room temperature for 16 h, then washed with a saturated aqueous solution of Na₂S₂O₃ (5 mL). A 2 M solution of NaOH (8 mL) was added and the solution was subsequently extracted with CH₂Cl₂ (3 x 10 mL). The combined organic fractions were dried over MgSO₄ and the solvent was removed *in vacuo* to give the crude product as a yellow oil.

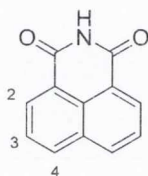
Purification of the crude product by flash chromatography (95:5 Hexane-EtOAc) provided **308** (191 mg, 53%) as a light brown solid. M.p. 64-65 °C. (lit.,³²⁸ 65-66 °C).

δ_{H} (400 MHz, DMSO-*d*₆): 7.35 (4 H, d, *J* 8.2, H-3), 7.18 (4 H, d, *J* 8.2, H-2), 3.69 (4 H, s, H-1), 1.27 (18 H, s, C(CH₃)₃),

δ_{C} (100 MHz, DMSO-*d*₆): 149.8 (q), 134.1 (q), 129.1, 125.1, 41.3, 34.2, 31.1.

5.1.7 Synthesis of amine **291** for the aminolysis of thioacetates

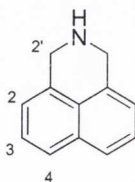
5.1.7.1 1,8-Naphthalimide (**296**)



A 50 mL round-bottomed flask was charged with anhydride **294** (3.00 g, 15.14 mmol) and urea (**295**) (2.75 g, 45.42 mmol) and fitted with a condenser. The reaction mixture was heated at 175 °C for 2 h, then cooled to room temperature. The solid residue was transferred to a Buchner funnel, washed with hot water (3 x 10 mL) and dried to obtain **296** as a white solid (2.69 g, 90%). M.p. 297-299 °C. (lit.,³²⁹ 301-303 °C).

δ_{H} (400 MHz, DMSO-*d*₆): 11.70 (1 H, bs, NH), 8.48-8.41 (4 H, m, H-2 and H-4), 7.86 (2 H, app. t, H-3).

5.1.7.2 2,3-Dihydro-1H-benzo[*de*]isoquinoline (**291**)



An oven dried 250 mL round-bottomed flask containing a stirring bar was charged with **296** (2.00 g, 10.14 mmol). The apparatus was fitted with a condenser, flushed with

argon, then fitted with a septum and placed under an argon atmosphere (balloon). Anhydrous THF (60 mL) was added *via* syringe and the reaction mixture was cooled to 0 °C. A solution of $\text{BH}_3 \cdot \text{SMe}_2$ (1.0 M in THF, 40.56 mmol, 40.5 mL) was added dropwise to the mixture *via* syringe and the reaction was heated at reflux temperature for 24 h. After being cooled to room temperature, the borane in excess was quenched by dropwise addition of MeOH (20 mL). The solution was concentrated under reduced pressure and the residue was purified by column chromatography (100% AcOEt) to afford **291** (755.1 mg, 44%) as a brown solid. M.p. 57-60 °C. (lit.,³³⁰ 58-60 °C).

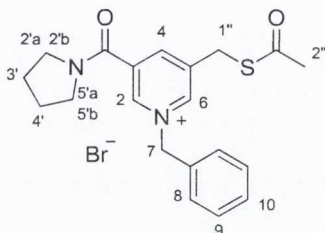
δ_{H} (400 MHz, CDCl_3): 7.70 (2 H, d, J 8.5, H-4), 7.40 (2 H, app. t, H-3), 7.18 (2 H, d, J 7.5, H-2), 4.33 (4 H, s, H-2'), 1.91 (1 H, bs, NH).

5.1.8 Procedure C: general protocol for the evaluation of GAPN mimics lacking a pyridinium ring in the formation of hemithioacetals

An oven dried 2 mL reaction vial was degassed, flushed with argon, then fitted with a septum and placed under an argon atmosphere (balloon). Thioacetate **269a** or **286** (0.105 mmol, 2.0 equiv.) and amine **291** (8.8 mg, 0.052 mmol, 1.0 equiv.) were added to the vial followed by anhydrous deoxygenated DMSO- d_6 (20 μL , 5.2 M). The balloon was removed, the vial was capped and the reaction mixture was maintained at 22 °C for 24 h. Styrene (24 μL , 20.88 mmol, 4.0 equiv.) and DMSO- d_6 were then added to the reaction mixture *via* syringe followed by the relevant aldehyde (0.052 mmol, 1.0 equiv.). The solution was mixed and transferred *via* syringe into an oven dried NMR tube that was previously flushed with argon, fitted with a septum and placed under argon atmosphere (balloon). The reaction mixture was analysed by ^1H NMR spectroscopy after 30 min to record the formation of hemithioacetal species, then kept at 22 °C and analysed again after 24 h.

5.1.9 Synthesis of thioester precursors bearing a NAD⁺-mimicking moiety

5.1.9.1 3-(Acetylthiomethyl)-1-benzyl-5-(pyrrolidine-1-carbonyl)pyridinium bromide (**301**)



An oven dried 100 mL round-bottomed flask containing a stirring bar was charged with **286** (584 mg, 2.21 mmol), flushed with argon, then fitted with a septum and placed under an argon atmosphere (balloon). Dry THF (2.0 mL) followed by benzyl bromide (1.60 mL, 13.44 mmol) was added *via* syringe and the solution was stirred at room temperature for 20 h. The reaction was concentrated under reduced pressure to give the crude product as a viscous oil. To remove the unreacted starting material and the reactant in excess, the residue was added with Et₂O (10 mL), the resulting precipitate was then decanted and the organic layer was removed. The procedure was repeated 6 times until TLC analysis indicated the complete disappearance of benzyl bromide from the reaction mixture. The residue was dried *in vacuo* to obtain **301** (815.1 mg, 85%) as a hygroscopic foamy white solid.

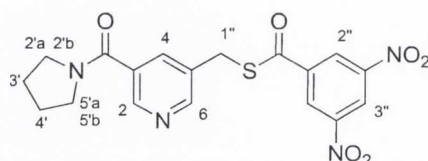
δ_{H} (400 MHz, CDCl₃): 9.81 (1 H, s, H-2), 9.47 (1 H, s, H-6), 8.47 (1 H, s, H-4), 7.80-7.65 (2 H, m, H-8), 7.42-7.31 (3 H, m, H-9 and H-10), 6.31 (2 H, s, H-7), 4.32 (2 H, s, H-1''), 3.76-3.62 (2 H, app. t, H-2'a and H-5'a), 3.60-3.50 (2 H, app. t, H-2'b and H-5'b), 2.30 (3 H, s, H-2''), 2.03-1.86 (4 H, m, H-3' and H-4').

δ_{C} (100 MHz, CDCl₃): 194.3 (C=O), 161.2 (C=O), 145.3, 143.5, 141.1, 140.3 (q), 136.4 (q), 132.1 (q), 129.7, 129.4, 129.2, 63.9, 49.3, 46.6, 29.9, 29.4, 26.0, 23.7.

ν_{max} (film)/ cm^{-1} : 3396, 2977, 1690, 1622, 1411, 1229, 1132, 1104, 1027, 912

HRMS (m/z -ESI): $[\text{M}+\text{H}]^+$ found: 355.1476. $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_2\text{S}$ Requires: 355.1480.

5.1.9.2 S-(5-(Pyrrolidine-1-carbonyl)pyridin-3-yl)methyl-3,5-dinitrobenzothioate (**303**)



An oven dried 10 mL round-bottomed flask containing a stirring bar was charged with **286** (400 mg, 1.51 mmol), flushed with argon, fitted with a septum and kept under an Ar atmosphere (balloon). Anhydrous deoxygenated CH_2Cl_2 (1.5 mL) was added *via* syringe followed by freshly distilled pyrrolidine (200.0 μL , 2.42 mmol) and the reaction was stirred at room temperature for 90 min. A solution of 3,5-dinitrobenzoyl chloride (83.1 mg, 2.72 mmol) in anhydrous deoxygenated CH_2Cl_2 (2 mL) was added *via* syringe immediately followed by triethylamine (420.0 μL , 3 mmol) and the reaction mixture was stirred for 16 h. The solvent was then removed *in vacuo* and the residue was purified by column chromatography (100% EtOAc) to obtain **303** (326.9 mg, 52%) as a thick yellow oil.

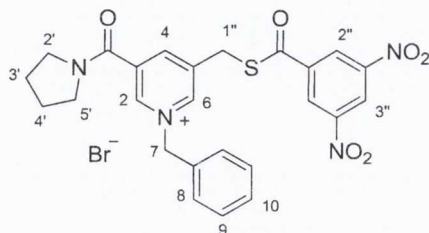
δ_{H} (400 MHz, $\text{DMSO}-d_6$): 9.25 (1 H, s, H-3''), 9.06 (2 H, s, H-2''), 8.71 (2 H, bs, H-2 and H-6), 7.95 (1 H, s, H-4), 4.45 (2 H, s, H-1''), 3.66 (2 H, app. t, H-2'b and 5'b), 3.47 (2 H, app. t, H-2'a and H-5'a), 2.08-1.87 (4 H, m, H-3' and H-4').

δ_{C} (100 MHz, CDCl_3): 186.5 (C=O), 167.9 (C=O), 150.5, 148.3 (q), 146.8, 138.6 (q), 135.4, 132.5 (q), 131.9 (q), 126.6, 122.2, 49.1, 46.1, 30.5, 26.0, 23.9.

ν_{max} (film)/ cm^{-1} : 3095, 2973, 2878, 2361, 1619, 1540, 1455, 1413, 1341, 1222, 1109, 840, 684

HRMS (m/z -ESI): $[M+H]^+$ found: 417.0862. $C_{18}H_{17}N_4O_4S$ Requires: 417.10869.

5.1.9.3 1-Benzyl-3-((3,5-dinitrobenzoylthio)methyl)-5-(pyrrolidine-1-carbonyl)pyridinium bromide (**304**)



An oven dried 25 mL round-bottomed flask containing a stirring bar was charged with **303** (300.0 mg, 0.72 mmol), anhydrous THF (7 mL) and benzyl bromide (340.0 μ L, 2.88 mmol). The apparatus was fitted with a condenser and a septum, kept under an argon atmosphere (balloon) and the reaction was stirred at 50 °C for 3 days. The reaction was concentrated under reduced pressure to give the crude product as a viscous oil. To remove benzyl bromide in excess, the residue was added with Et₂O (5 x 5 mL), the resulting precipitate was decanted and the supernatant was removed. The residue was dried *in vacuo* to obtain **304** (355.3 mg, 84%) as a hygroscopic foamy dark yellow solid.

δ_H (400 MHz, CDCl₃): 9.98 (1 H, s, H-2), 9.22 (1 H, s, H-3''), 9.18 (1 H, s, H-6), 8.97 (2 H, s, H-2''), 8.66 (1 H, s, H-4), 7.69-7.66 (2 H, m, H-8), 7.49-7.42 (3 H, m, H-9 and H-10), 6.28 (2 H, s, H-7), 4.74 (2 H, s, H-1''), 3.75-3.59 (4 H, m, H-2' and H-5'), 2.08-1.96 (4 H, m, H-3' and H-4').

δ_C (100 MHz, CDCl₃): 187.6 (C=O), 161.7 (C=O), 148.5 (q), 146.3, 144.3, 141.9, 139.4 (q), 138.5 (q), 136.7 (q), 132.5 (q), 130.1, 129.9, 129.6, 127.2, 122.8, 64.6, 49.7, 47.1, 30.5, 26.4, 24.1.

ν_{max} (film)/ cm^{-1} : 3395, 2975, 1620, 1539, 1447, 1341, 1223, 1185, 1110, 994, 912, 717.

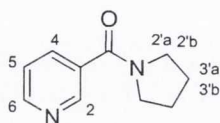
HRMS (m/z -ESI): $[\text{M}+\text{H}]^+$ found: 585.0440. $\text{C}_{25}\text{H}_{22}\text{N}_4\text{O}_6\text{SBr}$ Requires: 585.0443.

5.1.10 Procedure D: methanolysis of thioacetate **301** and formation of a hemithioacetal species *in situ*

A oven dried 1 mL reaction vial containing a stirring bar was degassed, then flushed with argon, fitted with a septum and placed under an atmosphere of Ar (balloon). Thioacetate **301** (110.2 mg, 0.25 mmol) was added and was dissolved in anhydrous and deoxygenated MeOH (210 μL), then acetyl chloride (9 μL , 0.126 mmol, 0.5 equiv.) was added dropwise *via* syringe to the solution. The balloon was removed, the vial was capped and the reaction was stirred at room temperature for 20 h. Basic Al_2O_3 (206 mg, 2.02 mmol, 8.0 equiv.) was added and the reaction mixture was stirred at room temperature for 30 min. The liquid was decanted and transferred *via* syringe to a oven dried 5 mL round-bottomed flask that was placed under an atmosphere of Ar. The solid residue was washed with anhydrous CH_2Cl_2 (3 x 600 μL) and the washings were added *via* syringe to the previously decanted liquid immediately followed by a solution of 2,5-diphenyl furan (55.7 mg, 0.253 mmol, 1.0 equiv.) in anhydrous and deoxygenated DMSO-d_6 (600 μL). The solvent was removed *in vacuo* at room temperature and the residue was transferred *via* syringe into an oven dried NMR tube that was fitted with a septum and placed under an atmosphere of Ar (balloon). The quantity of thiol **302** present in solution was determined by ^1H NMR spectroscopic analysis using 2,5-diphenyl furan as an internal standard, and was used to determine the amount of pyridine (1.0 equiv.) and freshly distilled benzaldehyde (**96**) (10.0 equiv.) that were added to the NMR tube *via* syringe. The solution was then mixed and ^1H NMR spectroscopic analysis of the reaction mixture was used to determine the formation of hemithioacetal intermediate **309**.

5.1.11 Synthesis of NAD⁺ mimic 42

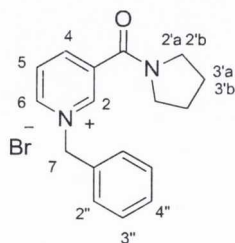
5.1.11.1 Pyridin-3-yl(pyrrolidin-1-yl)methanone (316)



An oven dried 100 mL round-bottomed flask containing a stirring bar was charged with **315** (1.50 g, 8.43 mmol) and anhydrous CH₂Cl₂ (50 mL). The apparatus was then fitted with a septum, placed under an Ar atmosphere (balloon) and cooled to 0 °C. Freshly distilled triethylamine (4.1 mL, 29.49 mmol) was added *via* syringe followed by anhydrous pyrrolidine (1.0 mL, 12.65 mmol). The apparatus was fitted with a condenser and the reaction was heated at reflux temperature for 20 h. The resulting solution was then cooled to room temperature and washed with an aqueous saturated solution of NaHCO₃ (3 x 30 mL) and brine, the organic phase was dried over MgSO₄, filtered and the solvent was removed *in vacuo* to obtain a residue that was purified by column chromatography (100% EtOAc) to afford **316** (995 mg, 67%). The isolated compound exhibited identical spectroscopic data to those reported in the literature.³³¹

δ_{H} (400 MHz, CDCl₃): 8.76 (1 H, s, H-2), 8.68 (1 H, dd, *J* 4.5, 1.5, H-6), 7.89 (1 H, dd, *J* 8.0, 1.5, H-4), 7.39-7.36 (1 H, m, H-5), 3.69 (2 H, app. t, H-2'a), 3.48 (2 H, app. t, H-2'b), 2.05-1.91 (4 H, m, H-3'a and H-3'b).

5.1.11.2 1-Benzyl-3-(pyrrolidine-1-carbonyl)pyridinium bromide (42)

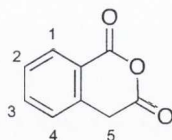


An oven dried 10 mL round-bottomed flask containing a stirring bar was charged with **316** (800 mg, 4.54 mmol), flushed with argon, then fitted with a septum and placed under an argon atmosphere (balloon). Anhydrous THF (4.1 mL) followed by benzyl bromide (3.2 mL, 27.24 mmol) were added *via* syringe and the solution was stirred at room temperature for 20 h. The reaction was concentrated under reduced pressure to give the crude product as a viscous oil which was washed with Et₂O (6 x 10 mL), the resulting precipitate was then decanted and the organic layer was removed. The solid residue was dried *in vacuo* to obtain **42** (1.31 g, 83%) as a white solid. The isolated compound exhibited identical spectroscopic data to those reported in the literature.⁷⁷ M.p 171-174 °C (lit.,⁷⁷ 172-175 °C).

δ_{H} (400 MHz, CDCl₃): 9.65 (1 H, d, *J* 5.5, H-6), 9.48 (1 H, s, H-2), 8.60 (1 H, d, *J* 8.0, H-4), 8.19-8.15 (1 H, m, H-5), 7.70-7.68 (2 H, m, H-2''), 7.41-7.37 (3 H, m, H-3'' and H-4''), 6.39 (2 H, s, H-7), 3.67 (2 H, app. t, H-2'a), 3.61 (2 H, app. t, H-2'b), 1.99-1.94 (4 H, m, H-3'a and H-3'b).

5.2 Experimental data for Chapter 3

5.2.1 Homophthalic anhydride (139)



A 100 mL round-bottomed flask containing a stirring bar was charged with homophthalic acid (**317**) (2.00 g, 11.10 mmol). Acetic anhydride (25 mL) was added, the flask was fitted with a condenser and the reaction mixture was heated at 80 °C for 2 h. The excess acetic anhydride was removed *in vacuo* and the solid obtained was triturated with Et₂O (10 mL), filtered and dried to obtain homophthalic anhydride as an off white solid (1.53 g, 85%). The isolated compound exhibited identical spectroscopic data to those reported in the literature.³³² M.p. 140-144 °C (lit.,³³³ m.p. 140-145 °C)

δ_{H} (400 MHz, DMSO-*d*₆): 8.05 (1 H, d, *J* 8.2, H-1), 7.75 (1 H, app. t, H-2), 7.52 (1 H, app. t, H-3), 7.44 (1 H, d, *J* 7.8, H-4), 4.27 (2 H, s, H-5).

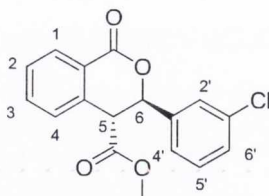
5.2.2.1 Procedure E: general protocol for the preparation of racemic dihydroisocoumarins *trans*-320 and *trans*-331–*trans*-336

A oven-dried 10 mL reaction vessel containing a stirring bar under argon atmosphere was charged with anhydride **139** (39.9 mg, 0.25 mmol). Anhydrous MTBE (2.4 mL, 0.1 M) was added *via* syringe followed by the relevant aldehyde (0.25 mmol). *N,N*-Diisopropylethylamine (8.6 μ L, 0.049 mmol, 20 mol%) was added *via* syringe and the resulting mixture was stirred for 20 h at room temperature. To the reaction mixture containing the corresponding carboxylic acids, anhydrous MeOH (750.0 μ L), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150.0 μ L, 0.30 mmol) were added *via* syringe and the reaction was allowed to stir for 30 min. at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash chromatography to isolate the major diastereomer. In the case of the racemic synthesis *trans*-336 and *cis*-336, both diastereomers were recovered combined after purification by column chromatography.

5.2.2.2 Procedure F: general protocol for asymmetric cycloaddition reactions between anhydride **139** and aldehydes (Table 3.5)

An oven dried 10 mL reaction vessel containing a stirring bar under argon atmosphere was charged with anhydride **139** (39.9 mg, 0.25 mmol) and catalyst **329** (8.7 mg, 0.012 mmol, 5 mol%). Anhydrous MTBE (2.4 mL, 0.1 M) was added *via* syringe and the suspension was then cooled to -15 °C. The relevant aldehyde (0.246 mmol) was added *via* syringe and the reaction mixture was stirred for the time indicated in Table 3.5. The yield and diastereomeric ratio of the products were subsequently monitored by ¹H-NMR spectroscopic analysis using *p*-iodoanisole (28.8 mg, 0.12 mmol) as an internal standard. To the reaction mixture containing the corresponding carboxylic acids, anhydrous MeOH (750.0 μL), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150.0 μL, 0.30 mmol) were added *via* syringe and the reaction was allowed to stir for 30 min. at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash chromatography eluting in gradient from 100% hexane to 5% EtOAc in hexane to isolate the major diastereomer. The enantiomeric excess of the products was determined by CSP-HPLC using the conditions indicated for each case.

5.2.2.2.1 3*R*,4*R*)-Methyl 3-(3-chlorophenyl)-1-oxoisochroman-4-carboxylate (*trans*-**331**, Table 3.5, entry 1)



Prepared according to general procedure F using freshly distilled 3-chlorobenzaldehyde (27.8 μL, 0.25 mmol). The reaction was stirred for 48 h to give a diastereomeric mixture of carboxylic acids in a 97:3 ratio (*trans*:*cis*). After esterification, the major diastereomer (*trans*-**331**) was isolated and purified by column chromatography to give an off-white solid (72.5 mg, 93%, 96% *ee*). M.p. 70-72 °C. $[\alpha]_D^{20} = +31.0$ (*c* 0.20, CHCl₃).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 83/17, 0.5 mL min⁻¹, RT, UV detection at 254 nm, retention times: 31.6 min (minor enantiomer) and 46.0 min (major enantiomer).

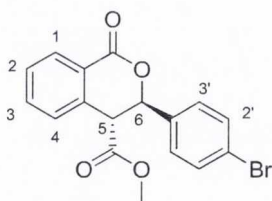
δ_{H} (400 MHz, CDCl₃): 8.18 (1 H, d, J 7.5, H-1), 7.62 (1 H, app. t, H-2), 7.50 (1 H, app. t, H-3), 7.41 (1 H, s, H-2'), 7.37-7.24 (3 H, m, H-4', H-5' and H-6'), 7.21 (1 H, d, J 7.5, H-4), 5.82 (1 H, d, J 8.5, H-6), 4.30 (1 H, d, J 8.5, H-5), 3.72 (3 H, s, CO₂CH₃).

δ_{C} (100 MHz, CDCl₃): 170.0 (C=O), 163.8 (C=O), 138.7 (q), 135.9 (q), 134.9 (q), 134.7, 130.9, 130.2, 129.5, 129.1, 127.1, 126.8, 125.1, 124.4 (q), 79.9, 52.9, 50.8.

ν_{max} (film)/cm⁻¹: 3063, 2958, 2925, 2853, 1730, 1603, 1437, 1261, 1155, 1119, 1081, 784, 737, 708.

HRMS (m/z -ESI): [M+H]⁺ found: 317.0588. C₁₇H₁₄O₄Cl Requires: 317.0581.

5.2.2.2.2 (3*R*,4*R*)-Methyl 3-(4-bromophenyl)-1-oxoisochroman-4-carboxylate (*trans*-332, Table 3.5, entry 2)



Prepared according to general procedure F using recrystallised *p*-bromobenzaldehyde (45.5 mg, 0.25 mmol). The reaction was stirred for 48 h to give a diastereomeric mixture of carboxylic acids in a 95:5 ratio (*trans*:*cis*). After esterification, the major diastereomer (*trans*-332) was isolated and purified by column chromatography to give a white solid (82.8 mg, 93%, 97% *ee*). M.p. 138-140 °C. $[\alpha]_{\text{D}}^{20} = +8.0$ (c 0.20, CHCl₃)

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 99/1, 1.0 mL min⁻¹, RT, UV detection at 254 nm, retention times: 83.3 min (major enantiomer) and 102.6 min (minor enantiomer).

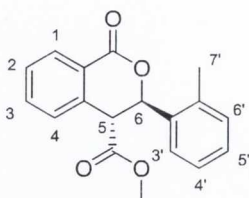
δ_{H} (400 MHz, CDCl₃): 8.18 (1 H, d, *J* 7.8, H-1), 7.65-7.57 (1 H, app. t, H-2), 7.55-7.45 (3 H, m, H-3 and H-2'), 7.28 (2 H, d, *J* 7.2, H-3'), 7.19 (1 H, d, *J* 7.5, H-4), 5.81 (1 H, d, *J* 8.4, H-6), 4.29 (1 H, d, *J* 8.4, H-5), 3.71 (3 H, s, CO₂CH₃).

δ_{C} (100 MHz, CDCl₃): 169.1 (C=O), 163.8 (C=O), 135.9 (q), 135.7 (q), 134.6, 132.0, 130.8, 129.1, 128.6, 126.7, 124.4 (q), 123.3 (q), 80.0, 52.9, 50.7.

ν_{max} (film)/cm⁻¹: 3071, 3018, 2953, 1726, 1601, 1490, 1258, 1009, 822, 736, 692.

HRMS (*m/z* -ESI): [M-H] found 358.9910. C₁₇H₁₂O₄Br Requires 358.9909.

5.2.2.2.3 (3*R*,4*R*)-Methyl 1-oxo-3-*o*-tolylisochroman-4-carboxylate (*trans*-333,
Table 3.5, entry 3)



Prepared according to general procedure F using freshly distilled 2-methylbenzaldehyde (28.4 μ L, 0.25 mmol). The reaction was stirred for 48 h to give a diastereomeric mixture of carboxylic acids in a 97:3 ratio (*trans*:*cis*). After esterification, the major diastereomer (*trans*-333) was isolated and purified by column chromatography to give a white solid (69.4 mg, 95%, 99% *ee*). M.p. 114-116 °C. [α]_D²⁰ = -20.0 (*c* 0.20, CHCl₃).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 83/17, 0.5 mL min⁻¹, RT, UV detection at 254 nm, retention times: 20.7 min (minor enantiomer) and 31.8 min (major enantiomer).

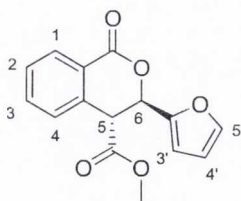
δ_H (400 MHz, CDCl₃): 8.20 (1 H, d, *J* 7.7, H-1), 7.62 (1 H, app. t, H-2), 7.51 (1 H, app. t, H-3), 7.31 (1 H, d, *J* 7.3, H-4) 7.28-7.13 (4 H, m, H-3', H-4', H-5' and H-6'), 6.08 (1 H, d, *J* 8.7, H-6), 4.48 (1 H, d, *J* 8.7, H-5), 3.68 (3 H, s, CO₂CH₃), 2.45 (3 H, s, H-11).

δ_C (100 MHz, CDCl₃): 169.7 (C=O), 163.8 (C=O), 136.1 (2x q), 133.9, 133.7 (q), 130.6, 130.3, 128.7, 128.4, 126.4, 126.2, 125.9, 124.1 (q), 77.1, 52.2, 48.7, 18.9.

$\nu_{\max}$ (film)/cm⁻¹: 3073, 3027, 2955, 2932, 2846, 1720, 1602, 1459, 1434, 1253, 1003, 918, 741.

HRMS (*m/z* -ESI): [M+Na]⁺ found 319.0946. C₁₈H₁₆O₄Na Requires 319.0946.

5.2.2.2.4 (3*R*,4*R*)-Methyl 3-(furan-2-yl)-1-oxoisochroman-4-carboxylate (*trans*-334, Table 3.5, entry 4)



Prepared according to general procedure F using freshly distilled furan-2-carboxaldehyde (20.4 μ L, 0.25 mmol). The reaction was stirred for 48 h to give a diastereomeric mixture of carboxylic acids in a 93:7 ratio (*trans*:*cis*). After esterification, the major diastereomer (*trans*-334) was isolated and purified by column chromatography to give a yellow solid (61.4 mg, 90%, 98% *ee*). M.p. 112-114 °C. $[\alpha]_D^{20} = -70.0$ (*c* 0.20, CHCl₃).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min⁻¹, RT, UV detection at 254 nm, retention times: 23.3 min (major enantiomer) and 31.4 min (minor enantiomer).

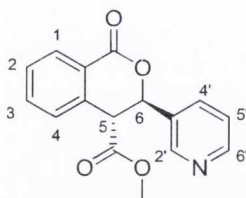
δ_{H} (400 MHz, CDCl₃): 8.14 (1 H, d, *J* 7.8, H-1), δ 7.62 (1 H, app. t, H-2), 7.49 (1 H, app. t, H-3), 7.35 (1 H, s, H-5'), 7.31 (1 H, d, *J* 7.4, H-4), 6.34-6.24 (2 H, m, H-3' and H-4'), 6.00 (1 H, d, *J* 5.9, H-6), 4.46 (1 H, d, *J* 5.9, H-5), 3.76 (3 H, s, CO₂CH₃).

δ_{C} (100 MHz, CDCl₃): 169.8 (C=O), 163.5 (C=O), 149.7 (q), 143.4, 135.5 (q), 134.4, 130.7, 129.1, 127.7, 124.6 (q), 110.7, 109.8, 73.9, 53.2, 47.1.

ν_{max} (film)/cm⁻¹: 3141, 3120, 2951, 2853, 1737, 1715, 1601, 1462, 1435, 1258, 1121, 1004, 930, 745, 690.

HRMS (*m/z* -ESI): [M+H]⁺ found 273.0774. C₁₅H₁₃O₅ Requires 273.0763.

5.2.2.2.5 (3*R*,4*R*)-Methyl 1-oxo-3-(pyridin-2-yl)isochroman-4-carboxylate (*trans*-335, Table 3.5, entry 5)



Prepared according to general procedure F using freshly distilled pyridin-3-carboxaldehyde (23.5 μ L, 0.25 mmol). The reaction was stirred for 22 h to give a diastereomeric mixture of carboxylic acids in a 84:16 ratio (*trans*:*cis*). After esterification, the major diastereomer (*trans*-334) was isolated and purified by column chromatography to give a thick oil (57.1 mg, 82%, 64% *ee*).

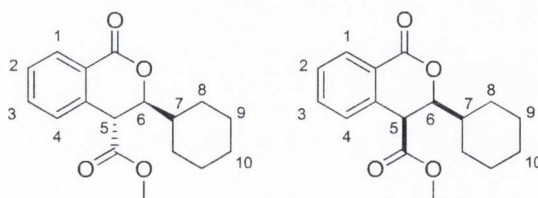
CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min⁻¹, RT, UV detection at 254 nm, retention times: 21.1 min (major enantiomer) and 43.4 min (minor enantiomer).

δ_{H} (400 MHz, CDCl₃): 8.48 (1 H, d, *J* 3.0, H-2'), δ 8.09 (1 H, d, *J* 7.8, H-1), 7.65 (1 H, app. t, H-2), 7.57-7.45 (2 H, m, H-3 and H-6'), 7.40 (1 H, app. t, H-5'), 7.30 (1 H, d, *J* 7.6, H-4), 7.17 (1 H, dd, *J* 5.0, 7.2, H-4'), 6.14 (1 H, d, *J* 5.1, H-5), 4.86 (1 H, d, *J* 5.1, H-6), 3.77 (3 H, s, CO₂CH₃).

δ_{C} (100 MHz, CDCl₃): 170.7 (C=O), 163.8 (C=O), 156.4 (q), 149.2, 137.2, 135.3 (q), 134.4, 130.3, 128.8, 128.5, 124.6 (q), 123.3, 121.4, 80.0, 53.0, 47.1.

HRMS (*m/z* -ESI): [M-H] found 282.0777. C₁₆H₁₂NO₄ Requires 282.0766.

5.2.2.2.6 Methyl 3-cyclohexyl-1-oxoisochroman-4-carboxylate (*trans*-336 – *cis*-336, Table 3.5, entry 6)



Prepared according to general procedure F using freshly distilled cyclohexanecarboxyaldehyde (29.8 μ L, 0.25 mmol). The reaction was stirred for 93 h at -30 °C to give a diastereomeric mixture of carboxylic acids in a 78:22 ratio (*trans*:*cis*). After esterification, both diastereomers (*trans*-336 and *cis*-336) were purified by column chromatography to give a pale yellow oil (69.5 mg, 98%, combined yield for both diastereoisomers). The diastereomeric ratio of the esters was found to be 79:21 (*trans*-336:*cis*-336) by ¹H-NMR spectroscopic analysis. The enantiomeric excesses for *trans*-336 and *cis*-336 were found to be 98% *ee* and 97% *ee* respectively.

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 60/40, 0.1 mL min⁻¹, RT, UV detection at 254 nm, retention times: **trans-336** 47.1 min (major enantiomer) and 57.7 min (minor enantiomer); **cis-336** 55.4 min (minor enantiomer) and 62.8 min (major enantiomer).

δ_H (600 MHz, CDCl₃): **trans-336**: 8.13 (1 H, d, *J* 6.9, H-1), 7.58 (1 H, app. t, H-2), 7.46 (1 H, app. t, H-3), 7.22 (1 H, d, *J* 7.7, H-4), 4.66 (1 H, app. t, H-6), 4.06 (1 H, d, *J* 5.8, H-5), 3.77 (3 H, s, CO₂CH₃), 1.97-1.88 (1 H, m, H-7), 1.87-1.08 (10 H, m, H-8, H-9 and H-10).

δ_C (100 MHz, CDCl₃): **trans-336**: 171.2 (C=O), 164.1 (C=O), 136.1 (q), 134.2, 130.4, 128.8, 127.6, 125.1 (q), 83.5, 52.9, 45.7, 40.5, 29.4, 27.9, 26.1, 26.0, 25.9.

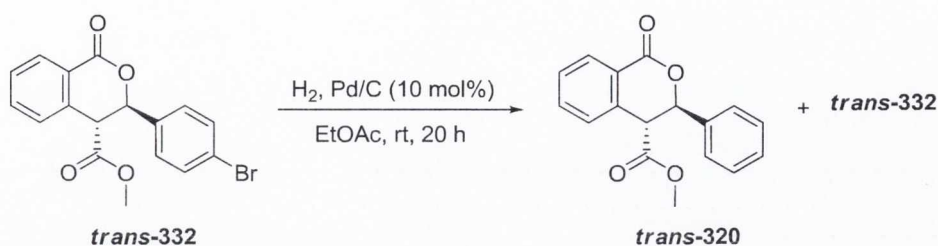
δ_H (600 MHz, CDCl₃): **cis-336**: 8.14 (1 H, d, *J* 6.9, H-1), 7.56 (1 H, app. t, H-2), 7.47 (1 H, app. t, H-3), 7.31 (1 H, d, *J* 7.5, H-4), 4.24 (1 H, dd, *J* 3.0, 9.9, H-6), 4.00 (1 H, d, *J* 3.0, H-5), 3.66 (3 H, CO₂CH₃), 2.41-2.23 (1 H, m, H-7), 2.03-1.08 (8 H, m, H-8 and H-9), 1.08-0.95 (2 H, m, H-10).

δ_C (100 MHz, CDCl₃): **cis-336**: 169.5 (C=O), 165.1 (C=O), 137.1 (q), 133.8, 130.8, 129.1, 127.4, 125.8 (q), 83.3, 52.7, 46.0, 40.0, 29.6, 28.5, 26.3, 25.7, 25.3.

$\nu_{\max}$ (film)/cm⁻¹: 2927, 2854, 1723, 1604, 1459, 1240, 1160, 1113, 1082.

HRMS (*m/z* -ESI): [M+H]⁺ found 289.1435. C₁₇H₂₁O₄ Requires 289.1440.

5.2.3 Reductive debromination of *trans*-332 and assignment of the absolute configuration of *trans*-320

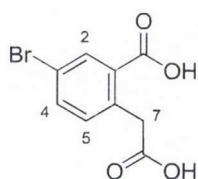


A 25 mL round-bottomed flask containing a stirring bar was charged with *trans*-332 (20.2 mg, 0.056 mmol) and EtOAc (10 mL). 10% Pd/C (1.2 mg, 2 mol%) was added, the flask was evacuated, placed under an atmosphere of hydrogen gas at atmospheric pressure and stirred for 20 h at room temperature. The flask was then evacuated and filled with an inert atmosphere. The reaction mixture was filtered through a pad of Celite and washed with EtOAc as the eluent. The solvent was removed *in vacuo* and the residue was purified by column chromatography (10% EtOAc in hexane) to afford a mixture of *trans*-332 and *trans*-320.

Since the absolute configuration of *trans*-332 was known, this allowed the assignment of the absolute configuration of *trans*-320 as (*R,R*) through comparison of the HPLC chromatogram from the reaction above with that of pure *trans*-320 derived from the addition of anhydride **139** to benzaldehyde **96** in the presence of catalyst **329**.

5.2.4 Synthesis of substituted homophthalic acids and anhydride **348**

5.2.4.1 5-Bromo-2-(carboxymethyl)benzoic acid (**337**)

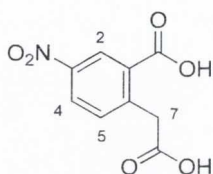


A 250 mL round-bottomed flask containing a stirring bar was charged with acid **317** (5.00 g, 27.75 mmol) and potassium bromate (6.65 g, 39.82 mmol) and fitted with a condenser, then water (30 mL) was added and the reaction mixture was heated at 90 °C.

A solution of concentrated H₂SO₄ (24 mL) in water (40 mL) was added slowly to the reaction mixture at 90 °C *via* dropping funnel over a period of 30 min. The reaction was stirred for 2 h at 90 °C, then cooled to room temperature; the solid formed was filtered, washed with water (3 x 50 mL), dried and recrystallised from EtOAc to give **337** as a white solid (2.87 g, 40%). The isolated compound exhibited identical spectroscopic data to those reported in the literature.²⁹⁰ M.p 214-217 °C (lit.,²⁹⁰ 216-217 °C).

δ_{H} (400 MHz, DMSO-*d*₆): 12.72 (2 H, bs, COOH), 7.98 (1 H, d, *J* 2.2, H-2), 7.72 (1 H, dd, *J* 2.2, 8.3, H-4), 7.31 (1 H, d, *J* 8.3, H-5), 3.91 (2 H, s, H-7).

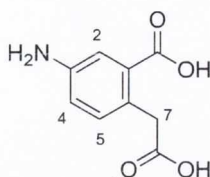
5.2.4.2.1 2-(Carboxymethyl)-5-nitrobenzoic acid (**338**)



A 100 mL three neck round-bottomed flask containing a large stirring bar and fitted with a thermometer was charged with fuming nitric acid (15 mL) and was cooled to 0 °C (inner temperature) using an ice bath acid **317** (5.00 g, 27.75 mmol) was added portionwise over 30 min so that the temperature was maintained below 20 °C. The reaction mixture was stirred at 0 °C for 2 h, then it was poured onto ice and left stirring vigorously until the ice was dissolved. The precipitate was filtered, washed with water and recrystallised from water to yield **338** as an off-white solid (4.12 g, 66%). The isolated compound exhibited identical spectroscopic data to those reported in the literature.²⁹¹ M.p 230-223 °C (lit.²⁹¹ 235 °C).

δ_{H} (400 MHz, DMSO-*d*₆): 12.78 (2 H, bs, COOH), 8.63 (1 H, d, *J* 2.1, H-2), 8.38 (1 H, dd, *J* 2.1, 8.4, H-4), 7.69 (1 H, d, *J* 8.4, H-5), 4.18 (2 H, s, H-7).

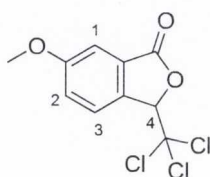
5.2.4.2.2 5-Amino-2-(carboxymethyl)benzoic acid (**339**)



A 100 mL round-bottomed flask containing a stirring bar was charged with **338** (3.00 g, 13.32 mmol) and MeOH (20 mL). 10% Pd/C (283 mg, 2 mol%) was added, the flask was evacuated, placed under an atmosphere of hydrogen gas at atmospheric pressure and the reaction was stirred for 48 h at room temperature. The flask was then evacuated and filled with an inert atmosphere. Water (50 mL) was added, the mixture was heated at reflux temperature for 10 min, then filtered hot through a pad of Celite. The filtrates were cooled to room temperature and the crystals formed were filtered, washed with cold water and recrystallised a second time from water to obtain **339** as a pale yellow solid (1.77 g, 68%). The isolated compound exhibited identical spectroscopic data to those reported in the literature.²⁹¹ M.p 215-217 °C (lit.,²⁹¹ 218 °C).

δ_{H} (400 MHz, DMSO- d_6): 12.10 (2 H, bs, COOH), 7.14 (1 H, d, J 2.4, H-2), 6.92 (1 H, d, J 8.2, H-5), 6.66 (1 H, dd, J 2.4, 8.2, H-4), 5.30 (2 H, bs, NH₂), 3.70 (2 H, s, H-7).

5.2.4.3.1 6-Methoxy-3-(trichloromethyl)isobenzofuran-1(3H)-one (**345**)

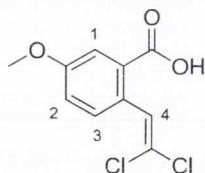


An oven dried 25 mL three neck round-bottomed flask containing a stirring bar was fitted with a drying tube (CaCl₂) and was charged with *m*-methoxybenzoic acid (**344**) (5.04 g, 17.91 mmol) followed by chloral hydrate (**343**) (2.96 g, 17.91 mmol). Concentrated H₂SO₄ (12 mL) was added and the reaction mixture was left stirring at room temperature for 24 h. It was then poured onto ice, a thick precipitate formed and the mixture was left stirring vigorously until the ice was dissolved. The precipitate was filtered, washed with water and dried. The solid was recrystallised from ethanol, the

crystals were then filtered and dried to yield **345** as off-white needles (3.16 g, 63%). The isolated compound exhibited identical spectroscopic data to those reported in the literature.²⁹² M.p. 134-136 °C (lit.,²⁹² m.p. 136-137 °C).

δ_{H} (400 MHz, DMSO-*d*₆): 7.88 (1 H, d, *J* 8.3, H-3), 7.49-7.39 (2 H, m, H-1 and H-2), 6.54 (1 H, s, H-4), 3.90 (3 H, s, OCH₃).

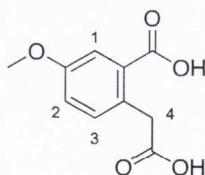
5.2.4.3.2 2-(2,2-dichlorovinyl)-5-Methoxybenzoic acid (**346**)



A 100 mL round-bottomed flask containing a stirring bar was charged with **345** (3.09 g, 10.94 mmol) and glacial acetic acid (40 mL). Zinc dust (2.86 g, 43.76 mmol) was added in small portions over 30 min. to the stirred reaction mixture. The reaction was left stirring at room temperature for further 30 min. and then heated at reflux for 1h. It was filtered hot over a pad of Celite and the filtrates were diluted with water. The precipitate formed was collected by filtration and recrystallised from EtOH/H₂O to give **346** as white needles (1.74 g, 64%). The isolated compound exhibited identical spectroscopic data to those reported in the literature.²⁹² M.p. 164-166 °C (lit.²⁹² m.p. 167-168 °C).

δ_{H} (400 MHz, DMSO-*d*₆): 13.31 (1 H, bs, COOH), 7.51 (1 H, d, *J* 8.7, H-3), 7.47-7.39 (2 H, m, H-1 and H-4), 7.21 (1 H, dd, *J* 8.7, 2.2, H-2), 3.82 (3 H, s, OCH₃).

5.2.4.3.3 2-(Carboxymethyl)-5-methoxybenzoic acid (**347**)

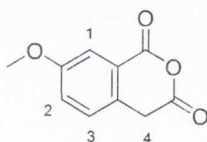


A oven-dried 25 mL three neck round-bottomed flask containing a stirring bar was fitted with a drying tube (CaCl₂) and charged with concentrated H₂SO₄ (12 mL).

Compound **346** (1.69 g, 6.83 mmol) was added portionwise to the stirred solution over 20 min. so that each additional portion was added only after the previous one was completely dissolved. After the addition was complete the reaction was left stirring at room temperature for 2 h and then it was poured onto ice. A precipitate formed and the mixture was stirred until the ice was dissolved. The precipitate was filtered, washed with cold water and dried to give **347** as an off-white solid (1.18 g, 82%). The isolated compound exhibited identical spectroscopic data to those reported in the literature.²⁹² M.p. 175-177 °C (lit.²⁹² m.p. 180-182 °C).

δ_{H} (400 MHz, DMSO-*d*₆): 12.36 (2 H, bs, COOH), 7.39 (1 H, d, *J* 2.6, H-1), 7.24 (1 H, d, *J* 8.4, H-3), 7.08 (1 H, dd, *J* 2.6, 8.4, H-2), 3.84 (2 H, s, H-4), 3.78 (3 H, s, OCH₃).

5.2.4.3.4 7-Methoxyisochroman-1,3-dione (**348**)

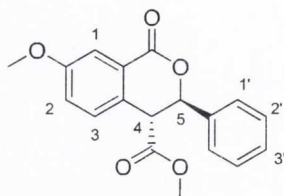


An oven dried 50 mL round-bottomed flask containing a stirring bar was charged with **347** (1.14 g, 5.42 mmol) and CH₂Cl₂ (20 mL). The apparatus was fitted with a condenser, flushed with argon, then fitted with a septum and placed under an argon atmosphere (balloon). Freshly distilled SOCl₂ (1.2 mL) was added *via* syringe and the suspension was heated at reflux for 2 h or until the complete dissolution of **347**. The reaction mixture was cooled to room temperature and the solvent and excess SOCl₂ were removed *in vacuo*. The crude product obtained was purified by trituration with Et₂O to afford **348** as a yellow solid (861 mg, 83%). The isolated compound exhibited identical spectroscopic data to those reported in the literature.²⁹⁴ M.p. 138-140 °C (lit.,³³⁴ m.p. 144-145 °C).

δ_{H} (400 MHz, DMSO-*d*₆): 7.49 (1 H, d, *J* 2.1, H-1), 7.40-7.30 (2 H, m, H-2 and H-3), 4.19 (2 H, s, H-4), 3.84 (3 H, s, OCH₃).

5.2.5 Synthesis of dihydroisocoumarin *trans*-349 using the substituted homophthalic anhydride 348

5.2.5.1 (3*R*,4*R*)-Methyl 7-methoxy-1-oxo-3-phenylisochroman-4-carboxylate (*trans*-349)



An oven dried 10 mL reaction vessel containing a stirring bar under argon atmosphere was charged with **348** (47.3 mg, 0.25 mmol). Anhydrous MTBE (2.4 mL, 0.1 M) was added *via* syringe and the suspension was then cooled to -15 °C. Freshly distilled benzaldehyde (**96**) (25.0 µL, 0.25 mmol) was added *via* syringe followed by catalyst **329** (8.7 mg, 0.012 mmol, 5 mol%) and the resulting mixture was stirred for 164 h to give a diastereomeric mixture of carboxylic acids in a 95:5 ratio (*trans*:*cis*). The reaction was then diluted with EtOAc (15 mL) and extracted with an aqueous solution of NaHCO₃ (10% w/v, 3 x 15 mL). The combined aqueous extracts were acidified with HCl (2.0 N), a white precipitate formed and the mixture was then extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over MgSO₄ and the solvent was removed *in vacuo* to yield the crude diastereomeric mixture of carboxylic acids as an off-white solid. The acids were then dissolved in THF (2.4 mL) and the solution was cooled to 0 °C. Anhydrous isopropyl alcohol (96.0 µL, 1.25 mmol) immediately followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 620.0 µL, 1.24 mmol) were added *via* syringe and the reaction was allowed to stir for 1 h at room temperature. The solvent was then removed *in vacuo* at room temperature and the crude mixture of diastereomeric esters was purified by flash chromatography eluting in gradient from 100% hexane to 10% EtOAc in hexane to give the major diastereomer *trans*-349 as a white solid (52.3 mg, 68%). M.p. 124-126 °C. $[\alpha]_D^{20} = +28.0$ (*c* 0.20, CHCl₃).

CSP-HPLC analysis. Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min⁻¹, RT, UV detection at 254 nm, retention times: 33.0 min (minor enantiomer) and 47.5 min (major enantiomer).

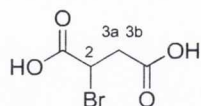
δ_{H} (400 MHz, CDCl_3):	7.66 (1 H, d, J 2.5, H-1), 7.43-7.30 (5 H, m, H-2, H-3, H-2' and H-3'), 7.20-7.06 (2 H, m, H-1'), 5.86 (1 H, d, J 8.0, H-5), 4.28 (1 H, d, J 8.0, H-4), 3.87 (3 H, s, OCH_3), 3.69 (3 H, s, CO_2CH_3).
δ_{C} (100 MHz, CDCl_3):	170.5 (C=O), 164.3 (C=O), 159.9 (q), 136.9 (q), 129.2, 128.9, 128.29 (q), 128.27, 126.8, 125.7 (q), 122.3, 113.4, 80.9, 55.8, 52.8, 50.1.
ν_{max} (film)/ cm^{-1} :	2957, 2924, 2853, 1720, 1612, 1496, 1433, 1284, 1267, 1222, 1163, 1074, 1014, 877, 814, 740, 701.
HRMS (m/z -ESI):	[M-H] found 311.0919. $\text{C}_{18}\text{H}_{15}\text{O}_5$ Requires 311.0919.

5.2.5.2 Synthesis of (*rac*)-*trans*-349

An oven dried 10 mL reaction vessel containing a stirring bar under argon atmosphere was charged with **348** (0.25 mmol). Anhydrous MTBE (2.4 mL, 0.1 M) was added *via* syringe followed by benzaldehyde (25 μL , 0.25 mmol). The reaction was cooled to 0 °C and *N,N*-diisopropylethylamine (8.6 μL , 0.049 mmol, 20 mol%) was added *via* syringe. The reaction was stirred for 20 h at room temperature then it was diluted with EtOAc (15 mL) and extracted with an aqueous solution of NaHCO_3 (10% w/v, 3 x 15 mL). The combined aqueous extracts were acidified with HCl (2.0 N), a white precipitate formed and the mixture was then extracted with EtOAc (3 x 15 mL). The organic extracts were dried over MgSO_4 and the solvent was removed *in vacuo* to yield the diastereomeric mixture of carboxylic acids as an off-white solid. The acids were then dissolved in THF (2.4 mL, 0.1 M) and the solution was cooled to 0 °C. Anhydrous isopropyl alcohol (96 μL) immediately followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 620 μL , 1.25 mmol) were added *via* syringe and the reaction was allowed to stir for 1 h at room temperature. The solvent was then removed *in vacuo* at room temperature and the crude mixture of diastereomeric esters was purified by flash chromatography to isolate the major diastereomer.

5.2.6 Synthesis and evaluation of enolisable succinic anhydride derivatives in the asymmetric annulation reaction with benzaldehyde

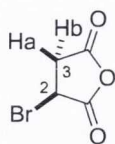
5.2.6.1.1 2-Bromosuccinic acid (**351**)



A 500 mL three neck round-bottomed flask containing a large stirring bar and fitted with a thermometer was charged with racemic aspartic acid (10.00 g, 75.13 mmol) and KBr (40.23 g, 338.08 mmol). A 2.5 M aqueous solution of H_2SO_4 (200 mL) was added and the reaction mixture was cooled to $-5\text{ }^\circ\text{C}$ (inner temperature) using an ice bath. A solution of NaNO_2 (8.82 g, 127.72 mmol) in water (30 mL) was added dropwise to the reaction mixture over 1 h under vigorous stirring while maintaining the temperature below $5\text{ }^\circ\text{C}$. After completion of the addition, the dark solution was stirred for 2 h at a temperature between $0\text{ }^\circ\text{C}$ and $-5\text{ }^\circ\text{C}$. The reaction mixture was then extracted with AcOEt (4 x 100 mL), the combined organic extracts were washed with a half saturated aqueous solution of NaCl (100 mL), dried over MgSO_4 , and concentrated *in vacuo* to obtain **351** pure as a white solid (12.14 g, 82%). The isolated compound exhibited identical spectroscopic data to those reported in the literature.³³⁵ M.p. $175\text{--}177\text{ }^\circ\text{C}$ (lit.³³⁶ m.p. $163\text{--}164\text{ }^\circ\text{C}$).

δ_{H} (400 MHz, $\text{DMSO-}d_6$): 12.82 (2 H, bs, COOH), 4.52 (1 H, app. t, H-2), 3.08 (1 H, dd, J 8.5, 17.0, H-3a), 2.89 (1 H, dd, 6.3, 17.0, H-3b).

5.2.6.1.2 3-Bromodihydrofuran-2,5-dione (**352**)

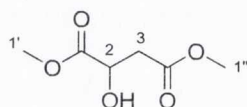


An oven dried 25 mL round-bottomed flask containing a stirring bar was charged with **351** (1.00 g, 5.08 mmol) and acetic anhydride (10 mL). The apparatus was fitted with a condenser and a septum, placed under an Ar atmosphere (balloon) and the reaction

mixture was heated at reflux temperature for 2 h. The acetic anhydride in excess was removed *in vacuo* to obtain **352** (908 mg, 100%) as a thick beige oil.

δ_{H} (400 MHz, CDCl_3): 4.83 (1 H, dd, J 4.1, 9.1, H-2), 3.71 (1 H, dd, J 9.1, 19.7, H-3a), 3.29 (1 H, J 4.1, 19.7, H-3b).

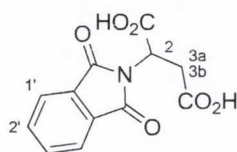
5.2.6.2.1 Dimethyl 2-hydroxysuccinate (**356**)



An oven dried 50 mL round-bottomed flask containing a stirring bar was flushed with argon, fitted with a septum and then placed under an argon atmosphere (balloon). Racemic malic acid (**355**) (5.00 g, 37.29 mmol) and MeOH (30 mL) were added and the solution was cooled to 0 °C. Freshly distilled acetyl chloride (2 mL) was added dropwise *via* syringe at 0 °C, then the balloon was removed, the flask was stoppered and the reaction mixture was stirred at room temperature for 16 h. The solvent and excess acetyl chloride were removed *in vacuo* and the residue was taken up with AcOEt (30 mL), then extracted with a saturated aqueous solution of NaHCO_3 (3 x 20 mL). The organic extract was dried over MgSO_4 , filtered and the solvent was removed *in vacuo* to yield **356** (5.50 g, 91%) as a colourless oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³³⁷

δ_{H} (400 MHz, CDCl_3): 4.50 (1 H, app. t, H-2), 3.81 (3 H, s, H-1'), 3.71 (3 H, s, H-1''), 3.25 (1 H, bs, OH), 2.91-2.75 (2 H, m, H-3).

5.2.6.3.1 2-(1,3-Dioxoisindolin-2-yl)succinic acid (**361**)

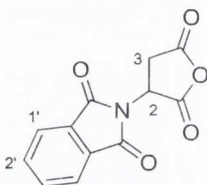


A 100 mL round-bottomed flask containing a stirring bar was charged with phthalic anhydride (**360**) (2.20 g, 14.85 mmol), D,L-aspartic acid (**350**) (2.00 g, 15.03 mmol) and

acetic acid (25 mL). The apparatus was equipped with a condenser and the reaction mixture was heated at reflux temperature for 16 h. The solvent was then removed under reduced pressure, cold water (5 mL) was added to the residue and the solid formed was filtered, washed with cold water and recrystallised from H₂O to yield **361** (3.32 g, 85%) as a white solid. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³³⁸ref M.p. 223-227 °C (lit.,³³⁸ m.p. 227-230 °C).

δ_{H} (400 MHz, DMSO-*d*₆): 12.50 (2 H, bs, COOH), 7.94-7.87 (4 H, m, H-1' and H-2'), 5.15 (1 H, app. t, H-2), 3.13 (1 H, dd, *J* 7.5, 16.8, H-3a), 2.93 (1 H, dd, *J* 7.2, 16.8, H-3b).

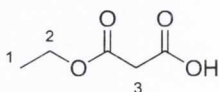
5.2.6.3.2 2-(2,5-Dioxotetrahydrofuran-3-yl)isoindoline-1,3-dione (**362**)



A 50 mL round-bottomed flask containing a stirring bar was charged with **361** (2.00 g, 7.60 mmol). Acetic anhydride (25 mL) was added, the flask was fitted with a condenser and the reaction mixture was heated at reflux temperature for 2 h. The excess acetic anhydride was removed *in vacuo* and the solid obtained was triturated with Et₂O (10 mL), filtered and dried to obtain **362** as a white solid (1.73 g, 93%). The isolated compound exhibited identical spectroscopic data to those reported in the literature.³³⁹ref M.p. 218-222 °C (lit.,³⁴⁰ m.p. 227°C).

δ_{H} (400 MHz, DMSO-*d*₆): 7.99-7.85 (4 H, m, H-1' and H-2'), 5.57 (1 H, dd, *J* 6.5, 9.7, H-2), 3.47-3.31 (2 H, m, H-3).

5.2.6.4.1 3-Ethoxy-3-oxopropanoic acid (**363**)

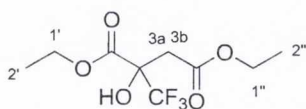


A 250 mL round-bottomed flask equipped with a stirring bar was charged with diethyl malonate (**73**) (19.0 mL, 124.55 mmol), MeCN (5 mL) and H₂O (50 mL) and the solution was cooled to 0 °C. A solution of KOH (7.00 g, 124.75 mmol) in water (25 mL) was added dropwise over 15 min with a dropping funnel to the stirred reaction mixture at 0 °C. Upon completion of the addition, the flask was stoppered and the solution was stirred at 0 °C for 1 h. The reaction mixture was acidified by adding concentrated aqueous HCl (19 mL) and saturated with NaCl, then it was extracted with EtOAc (5 x 100 mL). The organic extracts were washed with brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo* to afford a oily residue which was distilled under reduced pressure to yield **363** (12.30 g, 75%) as a colourless oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.²⁹⁸

δ_{H} (400 MHz, CDCl₃): 10.62 (1 H, bs, CO₂H), 4.23 (2 H, *J* 7.1, H-2), 3.42 (2 H, s, H-3), 1.28 (2 H, *J* 7.1, H-1).

HRMS (*m/z* -ESI): [M-H] found 131.0344. C₅H₇O₄ Requires 131.0344.

5.2.6.4.2 Diethyl 2-hydroxy-2-(trifluoromethyl)succinate (**365**)



A 50 mL round-bottomed flask equipped with a stirring bar was charged with **363** (4.08 g, 30.93 mmol) and **364** (3.9 mL, 29.40 mmol) then fitted with a condenser. Pyridine (20 mL) was slowly added with a dropping funnel to the stirred mixture of reagents and after the evolution of CO₂ ceased, the reaction was stirred at 30 °C for 16 h. Ether (50 mL) was added to the reaction mixture which was then extracted with an aqueous solution of CuSO₄ (10 x 20 mL). The organic extracts were washed with a saturated aqueous solution of NaHCO₃ (2 x 20 mL), brine (2 x 20 mL), then dried over MgSO₄ and filtered. The solvent was removed *in vacuo* to obtain **365** (6.07 g, 80%) as a colourless oil.

δ_{H} (400 MHz, CDCl_3): 4.43-4.34 (2 H, m, H-1'), 4.23-4.06 (3 H, m, OH and H-1''), 3.16, (1 H, d, J 16.6, H-3a), 2.93 (1 H, d, J 16.6, H-3b), 1.33 (3 H, app. t, H-2'), 1.25 (3 H, t, J 7.1, H-2'').

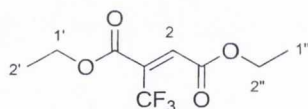
δ_{C} (100 MHz, CDCl_3): 168.6 (C=O), 168.5 (C=O), 123.1 (q, $J_{\text{C-F}}$, 286.3) (q), 75.4 (q, $J_{\text{C-F}}$ 30.0) (q), 64.1, 61.6, 37.2 (q, $J_{\text{C-F}}$ 1.2), 14.2, 14.0.

δ_{F} (376 MHz, CDCl_3): -79.13

ν_{max} (film)/ cm^{-1} : 3474, 2989, 1742, 1308, 1240, 1188, 1136, 1015, 861.

HRMS (m/z -ESI): $[\text{M}+\text{Na}]^+$ found 281.0611. $\text{C}_9\text{H}_{13}\text{O}_5\text{NaF}_3$ Requires 281.0613.

5.2.6.4.3 Diethyl 2-(trifluoromethyl)but-2-enedioate (366)



An oven dried 250 mL round-bottomed flask containing a stirring bar was charged with **365** (5.00 g, 19.36 mmol). Anhydrous CH_2Cl_2 (50 mL) was added *via* syringe and the apparatus was fitted with a condenser and a septum and placed under an argon atmosphere (balloon). Freshly distilled SOCl_2 (2.1 mL, 29.04 mmol) was added *via* syringe and the reaction mixture was stirred for 30 min at room temperature, then triethylamine (8.1 mL, 58.08 mmol) was added *via* syringe over 10 min and the resulting dark brown solution was heated at reflux temperature for 16 h. The reaction mixture was cooled to room temperature, washed with a concentrated aqueous solution of NaHCO_3 (3 x 20 mL) and brine (3 x 20 mL) and the organic extracts were dried over MgSO_4 and filtered. The solvent was removed *in vacuo* to obtain a dark oil which was purified by column chromatography (CH_2Cl_2 :hexane 7:3) to yield **366** (3.02 g, 65%) as a dark yellow oil.

δ_{H} (400 MHz, CDCl_3): 6.66 (1 H, q, $J_{\text{H-F}}$ 1.2, H-2), 4.35 (2 H, q, J 7.1 H-1'), 4.29 (2 H, q, J 7.1, H-1''), 1.39-1.29 (6 H, m, H-2' and H-2'').

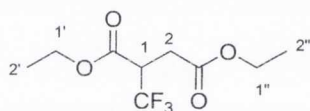
δ_C (100 MHz, $CDCl_3$): 163.1 (C=O), 161.0 (C=O), 133.5 (q, J_{C-F} 33.0) (q), 120.8 (q, J_{C-F} 274.9) (q), 129.8 (J_{C-F} 5.6), 62.6, 62.1, 13.9, 13.7.

δ_F (376 MHz, $CDCl_3$): -65.58

ν_{max} (film)/ cm^{-1} : 2989, 1742, 1308, 1240, 1188, 1136, 1015, 1026, 904.

HRMS (m/z -ESI): [M-H] found 239.0535. $C_9H_{10}O_4F_3$ Requires 239.0531.

5.2.6.4.4 Diethyl 2-(trifluoromethyl)succinate (367)



An oven dried 50 mL round-bottomed flask containing a stirring bar was charged with **366** (693 mg, 2.88 mmol), anhydrous THF (9 mL) and EtOH (6 mL) it was then fitted with a septum and kept under an argon atmosphere. The solution was cooled to 0 °C, then $NaBH_4$ (76.3 mg, 2.02 mmol) was added in four portions and the reaction mixture was stirred at 0 °C for 2 h. The $NaBH_4$ in excess was quenched by slow addition of a saturated solution of NH_4Cl (10 mL) at 0 °C, the reaction was stirred for 15 min then it was concentrated *in vacuo* to about a half of its volume and extracted with $CHCl_2$ (3 x 10 mL). The organic extracts were washed with brine, dried over $MgSO_4$, the solvent was evaporated under reduced pressure to afford a liquid residue which was purified by column chromatography (CH_2Cl_2 :hexane 7:3) to afford **367** (467.3 mg, 67%) as a pale yellow liquid.

δ_H (400 MHz, $CDCl_3$): 6.66 (1 H, q, J_{H-F} 1.2, H-2), 4.35 (2 H, q, J 7.1 H-1'), 4.29 (2 H, q, J 7.1, H-1''), 3.68-3.54 (1 H, m, H-1), 1.39-1.29 (6 H, m, H-2' and H-2'').

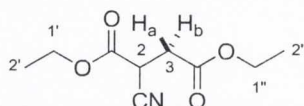
δ_C (100 MHz, $CDCl_3$): 163.1 (C=O), 161.0 (C=O), 133.5 (q, J_{C-F} 33.0) (q), 120.8 (q, J_{C-F} 274.9) (q), 129.8 (J_{C-F} 5.6), 62.6, 62.1, 13.9, 13.7.

δ_F (376 MHz, $CDCl_3$): -65.58

ν_{max} (film)/ cm^{-1} : 2987, 1741, 1310, 1219, 1163, 1111, 1023

HRMS (m/z -EI): $[M-C_2H_5O]$ found 197.0416. $C_9H_{10}O_4F_3$ Requires 197.0426.

5.2.6.5.1 Diethyl 2-cyanosuccinate (**372**)

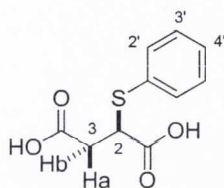


An oven dried 250 mL round-bottomed flask containing a stirring bar was charged with **370** (5.0 mL, 72.05 mmol) and EtOH (50 mL) and the solution was cooled to 0 °C. Sodium ethoxide (4.08 g, 60.05 mmol) was added and the reaction mixture was stirred for 10 min, then **371** (6.6 mL, 60.05 mmol) was added dropwise *via* syringe over 15 min. The reaction mixture was stirred at 0 °C for 30 min, then the flask was stoppered and the solution was stirred at room temperature for 16 h. Water (20 mL) was added to the reaction, the solution was concentrated under reduced pressure, then the residue was taken up with diethyl ether (50 mL), washed with brine and dried over $MgSO_4$. After the removal of the solvent in vacuo, the oily residue was purified by Kugelrohr distillation to afford pure **372** (3.70 g, 31%) as a colourless oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.¹⁹⁸

δ_H (400 MHz, $CDCl_3$): 4.30 (2 H, q, J 7.1, H-1'), 4.21 (2 H, q, J 7.3, H-1''), 3.92 (1 H, app. t, H-2), 3.03, (1 H, dd, J 6.7, 17.2, H-3a), 2.92 (1 H, dd, J 6.1, 17.2, H-3b), 1.34 (3 H, t, J 7.1, H-2'), 1.28 (3 H, t, J 7.3, H-2'').

HRMS (m/z -ESI): $[M-H]$ found 198.0766. $C_9H_{12}NO_4$ Requires 198.0766.

5.2.6.6.1 2-(Phenylthio)succinic acid (**377**)



An oven dried 100 mL round-bottomed flask containing a stirring bar was charged with maleic acid (3.00 g, 25.85 mmol) anhydrous THF (50 mL) and freshly distilled triethylamine (9.0 mL, 64.62 mmol). The apparatus was then equipped with a condenser and a septum and kept under an argon atmosphere (balloon). Thiophenol (**374**) (2.9 mL, 28.43 mmol) was added *via* syringe and the reaction mixture was heated at reflux temperature for 16 h. The solvent was removed *in vacuo* and the residue was taken up with EtOAc (20 mL), then washed with a 2 M aqueous NaOH solution (2 x 20 mL). The aqueous phase was acidified with concentrated HCl, the precipitate formed was filtered, washed with diethyl ether (5 mL) and dried to yield **377** (5.49 g, 94%) as a white solid. M.p. 109-112 °C.

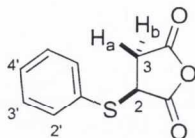
δ_{H} (400 MHz, DMSO- d_6): 12.61 (2 H, bs, COOH), 7.47 (2 H, d, J 7.8, H-2'), 7.41-7.30 (3 H, m, H-3' and H-4'), 3.92 (1 H, dd, J 5.4, 9.3, H-2), 2.67 (1 H, dd, J 9.3, 16.9, H-3a), 2.63 (1 H, dd, J 5.4, 16.9, H-3b).

δ_{C} (100 MHz, DMSO- d_6): 172.4 (C=O), 172.1 (C=O), 132.9, 132.8 (q), 129.6, 128.5, 45.4, 36.8.

ν_{max} (film)/ cm^{-1} : 2886, 2642, 2529, 1684, 1412, 1295, 1180, 925, 744, 692.

HRMS (m/z -ESI): [M-H] found 225.0220. $\text{C}_{10}\text{H}_9\text{O}_4\text{S}$ Requires 225.0222.

5.2.6.6.2 3-(Phenylthio)dihydrofuran-2,5-dione (379)



An oven dried 50 mL round-bottomed flask containing a stirring bar was charged with **376** (2.00 g, 8.85 mmol) and acetic anhydride (15 mL). The apparatus was then equipped with a condenser and a septum and kept under an argon atmosphere (balloon). The reaction mixture was heated at 90 °C for 2 h, then concentrated *in vacuo* to afford anhydride **379** (1.68 g, 91%) pure as a dark brown oil.

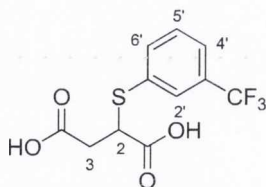
δ_{H} (400 MHz, DMSO- d_6): 7.53 (2 H, d, J 6.1, H-2'), 7.44-7.34 (3 H, m, H-3' and H-4'), 4.72 (1 H, dd, J 5.2, 9.7, H-2), 3.57 (1 H, dd, J 9.7, 18.5, H-3a), 3.03 (1 H, dd, J 5.2, 18.5, H-3b).

δ_{C} (100 MHz, DMSO- d_6): 171.6 (C=O), 169.8 (C=O), 134.3 (q), 132.4, 129.5, 128.6, 44.4, 36.0.

ν_{max} (film)/ cm^{-1} : 2991, 2936, 1863, 1782, 1207, 1124, 1057, 908, 746, 692.

HRMS (m/z -ESI): [M-H] found 207.0117. $\text{C}_{10}\text{H}_7\text{O}_3\text{S}$ Requires 207.0116.

5.2.6.7.1 2-(3-(Trifluoromethyl)phenylthio)succinic acid (378)



An oven dried 50 mL round-bottomed flask containing a stirring bar was charged with maleic acid (1.00 g, 8.62 mmol) anhydrous THF (20 mL) and freshly distilled triethylamine (3.0 mL, 21.54 mmol). The apparatus was then equipped with a condenser and a septum and kept under an argon atmosphere (balloon). Thiol **375** (1.2 mL, 9.05 mmol) was added *via* syringe and the reaction mixture was heated at reflux temperature

for 16 h. The solvent was removed *in vacuo* and the residue was taken up with EtOAc (20 mL), then washed with a 2 M aqueous NaOH solution (2 x 20 mL). The aqueous phase was acidified with concentrated HCl, then extracted with CH₂Cl₂ (4 x 20 mL). The organic extracts were dried over MgSO₄, filtered and the solvent was removed *in vacuo* to yield **378** (2.43 g, 96%) as an off-white solid. M.p. 140-142 °C

δ_{H} (400 MHz, DMSO-*d*₆): 12.66 (2 H, bs, COOH), 7.76 (1 H, bs, H-2'), 7.73 (2 H, d, *J* 7.9, H-6'), 7.64 (1 H, d, *J* 7.7, H-4'), 7.56 (1 H, app. t, H-5'), 4.03 (1 H, dd, *J* 5.9, 8.8, H-2), 2.77-2.59 (2 H, m, H-3).

δ_{C} (100 MHz, DMSO-*d*₆): 171.8 (C=O), 171.5 (C=O), 135.6, (q, *J*_{C-F} 1.3), 134.8 (q), 130.1, 129.8 (q, *J*_{C-F} 31.9) (q), 127.8 (q, *J*_{C-F} 3.9), 124.4 (q, *J*_{C-F} 3.9), 123.7 (q, *J*_{C-F} 273.2) (q) 44.8, 36.2.

δ_{F} (376 MHz, DMSO-*d*₆): -61.32

ν_{max} (film)/cm⁻¹: 2855, 2642, 1693, 1416, 1324, 1303, 1163, 1126, 1068, 805, 696.

HRMS (*m/z* -ESI): [M-H] found 293.0092. C₁₁H₈O₄F₃S Requires 293.0095.

5.2.6.7.2 3-(3-(Trifluoromethyl)phenylthio)dihydrofuran-2,5-dione (**380**)



An oven dried 50 mL round-bottomed flask containing a stirring bar was charged with **376** (2.00 g, 6.80 mmol) and freshly distilled acetyl chloride (15 mL). The apparatus was then equipped with a condenser and a septum and kept under an argon atmosphere (balloon). The reaction mixture was heated at reflux temperature for 16 h, then concentrated *in vacuo* to give an oil that solidified upon standing at room temperature. This was triturated with Et₂O and filtered to afford **380** (1.65 g, 88%) as an off-white solid. M.p. 44-46 °C

δ_{H} (400 MHz, DMSO- d_6): 7.87 (1 H, bs, H-2'), 7.81 (1 H, d, J 7.6, H-6'), 7.71 (1 H, d, J 7.6, H-4'), 7.63 (1 H, app. t, H-5'), 4.90 (1 H, dd, J 5.8, 9.8, H-2), 3.57 (1 H, dd, J 9.8, 18.7, H-3a), 3.11 (1 H, J 5.8, 18.7, H-3b).

δ_{C} (100 MHz, DMSO- d_6): 171.6 (C=O), 169.6 (C=O), 134.9, 134.7 (q), 130.4, 130.1 (q, $J_{\text{C-F}}$ 32.0) (q), 127.2 (q, $J_{\text{C-F}}$ 3.8), 124.6 (q, $J_{\text{C-F}}$ 3.8), 123.7 (q, $J_{\text{C-F}}$ 272.5) (q) 44.1, 35.8.

δ_{F} (376 MHz, DMSO- d_6): -61.38

ν_{max} (film)/ cm^{-1} : 2945, 1863, 1785, 1408, 1324, 1221, 1173, 1128, 1064, 925, 803, 694.

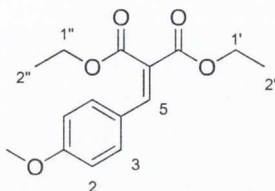
HRMS (m/z -ESI): [M-H] found 274.9997. $\text{C}_{11}\text{H}_6\text{O}_3\text{F}_3\text{S}$ Requires 274.9990.

5.2.6.8 Procedure G: general protocol for the evaluation of enolisable succinic anhydride derivatives in the asymmetric annulation with benzaldehyde

An oven dried 10 mL round-bottomed flask containing a stirring bar was flushed with argon, fitted with a septum and then placed under argon atmosphere (balloon). The relevant anhydride was added (0.25 mmol, 1.0 equiv.) followed by anhydrous MTBE (2.40 mL, 0.1 M) and catalyst **329** (8.7 mg, 0.012 mmol, 5 mol%). Benzaldehyde (**96**) (25 μL , 0.25 mmol, 1.0 equiv.) was added *via* syringe and the resulting mixture was stirred at room temperature for the time indicated in each case. The yield of the products was monitored by ^1H NMR spectroscopic analysis using either *p*-iodoanisole or styrene (0.5 equiv.) as an internal standard.

5.2.7 Synthesis and evaluation of anhydride **387** in the asymmetric annulation reaction with benzaldehyde

5.2.7.1.1 Diethyl 2-(4-methoxybenzylidene)malonate (**384**)

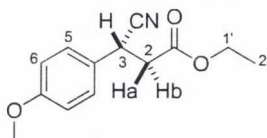


A three neck oven dried 100 mL round-bottomed flask containing a stirring bar was fitted with a Dean-Stark apparatus and charged with **73** (9.50 mL, 62.28 mmol). Toluene (50 mL) followed by piperidine (620.0 μ L, 6.26 mmol) and *p*-anisaldehyde (**383**) (7.60 mL, 62.48 mmol) were added *via* syringe. The reaction was heated under reflux for 16 h with continuous removal of water. The reaction was then cooled to room temperature and toluene was removed *in vacuo*. The oily residue was taken up in EtOAc (50 mL) and then washed with an aqueous solution of HCl (2.0 N, 15 mL) and with a saturated aqueous solution of NaHCO₃ (20 mL). The organic phase was dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The crude oil was distilled by Kugelrohr to remove impurities and to leave **384** as a pale yellow oil (11.5 g, 66%). The isolated compound exhibited identical spectroscopic data to those reported in the literature.³⁴¹

δ_{H} (400 MHz, CDCl₃): 7.67 (1 H, s, H-5), 7.42 (2 H, d, *J* 8.8, H-3), 6.89 (2 H, d, *J* 8.8, H-2), 4.44-4.26 (4 H, m, H1' and H-1''), 3.83 (3 H, s, OCH₃), 1.37-1.28 (6 H, m, H-2' and H-2'').

HRMS (*m/z* -ESI): [M+Na]⁺ found 301.1067. C₁₅H₁₈O₅Na Requires 301.1052.

5.2.7.1.2 Ethyl 3-cyano-3-(4-methoxyphenyl)propanoate (**385**)



A 100 mL round-bottomed flask fitted with a condenser and containing a stirring bar was charged with **384** (8.50 g, 30.54 mmol) and a mixture of EtOH (50 mL) and water (10.0 mL). NaCN (1.54 g, 31.4 mmol) was added portionwise to the solution and the reaction was heated under reflux for 16 h. The reaction mixture was then cooled to room temperature, filtered and EtOH was then removed *in vacuo*. The residue was partitioned between EtOAc (50 mL) and brine (20 mL) and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extracts were then dried over MgSO₄, filtered and the solvent was removed *in vacuo*. A yellow oil was obtained which was purified by Kugelrohr distillation to obtain **385** as a pale yellow oil (4.26 g, 60%).

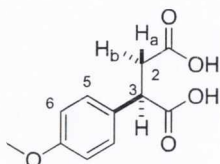
δ_{H} (400 MHz, CDCl₃): 7.28 (2 H, d, *J* 8.7, H-5), 6.90 (2 H, d, *J* 8.7, H-6), 4.24 (1 H, app. t, H-3), 4.17 (2 H, q, *J* 7.1, H-1'), 3.81 (3 H, s, OCH₃), 2.98 (1 H, dd, *J* 8.1, 16.5, H-2b), 2.80 (1 H, dd, *J* 7.0, 16.5, H-2a), 1.24 (3 H, t, *J* 7.1, H-2').

δ_{C} (100 MHz, CDCl₃): 169.4 (C=O), 159.8 (q), 128.7, 126.5 (q), 120.4 (C≡N), 114.7, 61.6, 55.5, 40.3, 32.6, 14.2.

ν_{max} (film)/cm⁻¹: 2982, 2940, 2840, 2247, 1732, 1612, 1512, 1373, 1250, 1179, 1028, 832

HRMS (*m/z* -ESI): [M+Na]⁺ found 256.0949. C₁₃H₁₅NO₃Na Requires 256.0950.

5.2.7.1.3 2-(4-Methoxyphenyl)succinic acid (**386**)



A 100 mL round-bottomed flask fitted with a condenser and containing a stirring bar was charged with **385** (1.96 g, 8.40 mmol) and a mixture of EtOH (30 mL) and water (20 mL). KOH (2.12 g, 37.86 mmol) was added to the solution and the reaction was

heated under reflux for 16 h. The reaction mixture was then cooled to room temperature and EtOH was removed *in vacuo*. The residue was acidified with conc. HCl and the precipitate formed was collected by suction filtration, washed with water (10 mL) and dried *in vacuo*. The crude solid was then recrystallised from H₂O/EtOH and dried to yield **386** as an off-white solid (1.72 g, 91%). M.p. 199-202 °C (lit.³⁴² m.p. 197-199 °C).

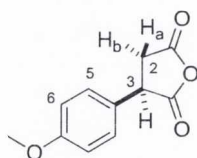
δ_{H} (400 MHz, CDCl₃): 12.30 (2 H, 2bs, COOH), 7.20 (2 H, d, *J* 8.6, H-5), 6.88 (2 H, d, *J* 8.6, H-6), 3.82 (1 H, dd, *J* 5.1, 10.2, H-3), 3.72 (3H, s, OCH₃), 2.93 (1 H, dd, *J* 10.2, 16.9, H-2a), 2.55-2.40 (1 H, m, H-2b)

δ_{C} (100 MHz, CDCl₃): 174.3 (C=O), 172.8 (C=O), 158.4 (q), 130.6 (q), 128.8, 114.0, 55.1, 46.0, 37.6.

ν_{max} (film)/cm⁻¹: 2892, 2602, 1689, 1611, 1514, 1426, 1324, 1242, 1179, 1027, 917, 820.

HRMS (*m/z* -ESI): [M-H] found 223.0606. C₁₁H₁₁O₅ Requires 223.0606.

5.2.7.1.4 3-(4-Methoxyphenyl)dihydrofuran-2,5-dione (**387**)



A 25 mL round-bottomed flask containing a stirring bar was charged with **386** (600 mg, 2.68 mmol). Acetic anhydride (15 mL) was added, the flask was fitted with a condenser and the reaction mixture was heated at 80 °C under an argon atmosphere for 16 h. The acetic anhydride was then removed *in vacuo* to obtain a yellow oil. Et₂O (5 mL) was added and the mixture was stirred for 1 h at room temperature. The precipitate formed was collected by suction filtration, washed with Et₂O (2 x 2 mL) and dried *in vacuo* to afford **14c** as a white solid (320 mg, 58%). M.p. 88-90 °C (lit.³⁴³ m.p. 91-92 °C).

δ_{H} (400 MHz, CDCl_3): 7.19 (2 H, d, J 8.7, H-5), 6.93 (2 H, d, J 8.7, H-6), 4.29 (1 H, dd, J 6.6, 10.2, H-2), 3.81 (3 H, s, OCH_3), 3.44 (1 H, dd, J 10.2, 18.9, H-2a), 3.09 (1 H, dd, J 6.6, 18.9, H-2b).

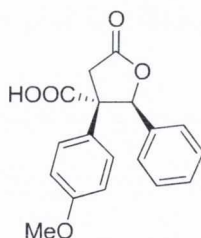
δ_{C} (100 MHz, CDCl_3): 172.0 (C=O), 169.7 (C=O), 159.9 (q), 128.6, 126.6 (q), 115.0, 55.5, 46.0, 36.9.

ν_{max} (film)/ cm^{-1} : 3062, 3019, 2972, 2891, 2843, 1854, 1763, 1619, 1518, 1228, 1026, 900, 843, 796.

HRMS (m/z -ESI): [M-H] found 205.0500. $\text{C}_{11}\text{H}_9\text{O}_4$ Requires 205.0501.

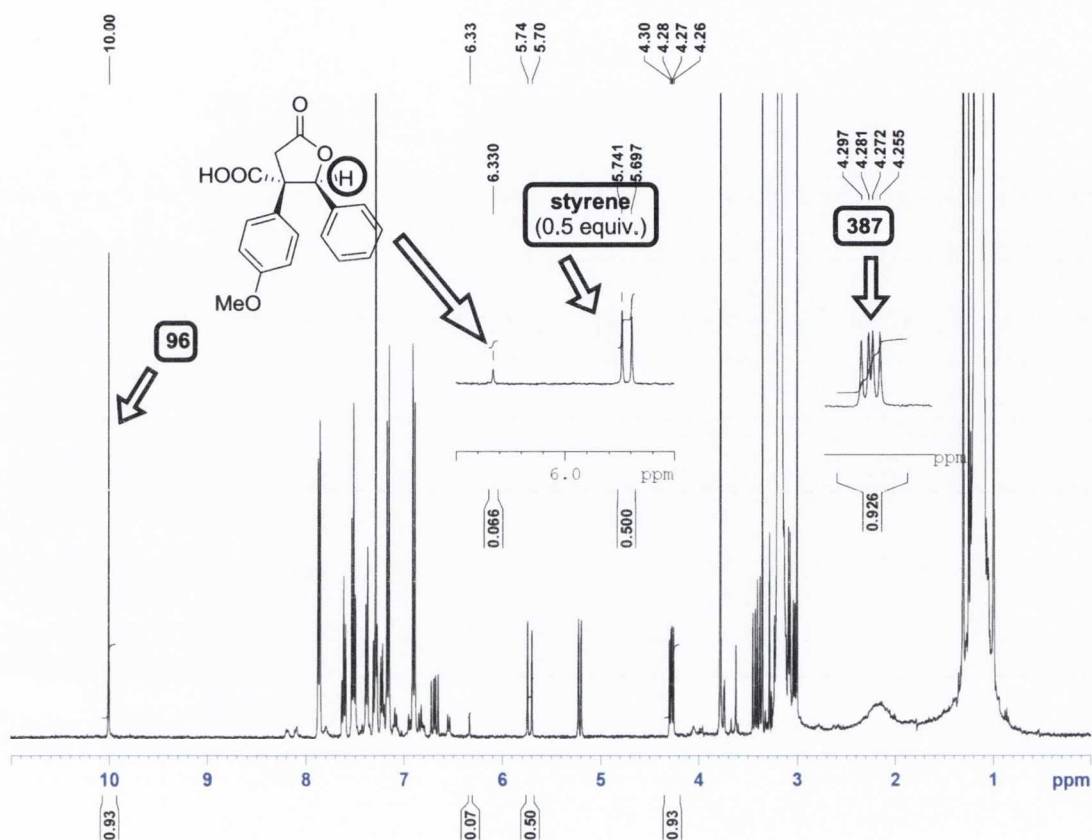
5.2.7.2 Reaction of anhydride **387** with benzaldehyde (**96**) promoted by catalyst **329**

5.7.2.1 (2*S*,3*S*)-3-(4-Methoxyphenyl)-5-oxo-2-phenyltetrahydrofuran-3-carboxylic acid (precursor of *trans*-**392**, Table 3.6, entry 3)



A oven-dried 10 mL reaction vessel containing a stirring bar under argon atmosphere was charged with **387** (50.7 mg, 0.25 mmol). Anhydrous MTBE (0.1 M, 2.4 mL) was added *via* syringe and the reaction mixture was then cooled to $-15\text{ }^{\circ}\text{C}$. Freshly distilled benzaldehyde (**96**) (25.0 μL , 0.25 mmol) was added *via* syringe to the reaction mixture followed by catalyst **329** (5 mol%, 8.7 mg) and the resulting mixture was stirred at $-15\text{ }^{\circ}\text{C}$ for 93 h. The yield of the products was monitored by ^1H NMR spectroscopic analysis using styrene (14.3 μL , 1.2 mmol) as an internal standard. The carboxylic acid precursor of *trans*-**392** was formed in 7% yield after 93 h, (see ^1H NMR spectrum that follows) while the yield of the precursor of *cis*-**392** was not quantifiable by ^1H NMR spectroscopic analysis.

Due to the low conversion of the reaction, esterification was not carried out and *trans*-**392** was not isolated.



5.2.8 Evaluation of the substrate scope for the asymmetric annulation using anhydride **393**

5.2.8.1 Procedure H: general protocol for the synthesis of racemic γ -butyrolactones *trans*-**394**–*trans*-**397**

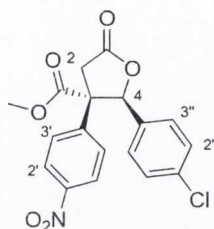
An oven dried 10 mL reaction vessel containing a stirring bar under argon atmosphere was charged with anhydride **393** (1.0 equiv.). Anhydrous MTBE (0.1 M) was added *via* syringe and the reaction mixture was then cooled to 0 °C. The relevant aldehyde (1.0 equiv.) was added to the reaction mixture followed by *N,N*-diisopropylethylamine (5 mol%) and the resulting mixture was allowed to warm to room temperature and stirred for 20 h. To the reaction mixture containing the corresponding carboxylic acids, anhydrous isopropyl alcohol (5.0 equiv.), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 1.2 equiv.) were added *via* syringe at 0 °C and the reaction

was allowed to stir for 1 h at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash chromatography to isolate the major diastereomer.

5.2.8.2 Procedure I: general protocol for asymmetric cycloaddition reactions between anhydride **393 and aldehydes (Table 3.7)**

An oven dried 10 mL reaction vessel containing a stirring bar under argon atmosphere was charged with anhydride **393** (1.0 equiv.) Anhydrous MTBE (0.1 M) was added *via* syringe and the reaction mixture was then cooled to -15 °C. The relevant aldehyde (1.0 equiv.) was added to the reaction mixture followed by catalyst **329** (5 mol%) and the resulting mixture was stirred at -15 °C for the time indicated in Table 3.7. The yield and diastereomeric ratio of the products were monitored by ¹H-NMR spectroscopic analysis using either *p*-iodoanisole or styrene (0.5 equiv.) as an internal standard. The reaction was then diluted with EtOAc (15 mL) and extracted with an aqueous solution of NaHCO₃ (10% w/v, 3 x 15 mL). The combined aqueous extracts were acidified with HCl (2.0 N), a white precipitate formed and the mixture was then extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over MgSO₄ and the solvent was removed *in vacuo* to yield the diastereomeric mixture of carboxylic acids. The acids were then dissolved in dry THF (0.1 M) and the solution was cooled to 0 °C, anhydrous isopropyl alcohol (5.0 equiv.), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 1.2 equiv.) were added *via* syringe at 0 °C and the reaction was allowed to stir for 1 h at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash chromatography to isolate the major diastereomer. The enantiomeric excess of the products was determined by CSP-HPLC using the conditions indicated for each case.

5.2.8.2.1 (2*S*,3*S*)-Methyl 2-(4-chlorophenyl)-3-(4-nitrophenyl)-5-oxotetrahydrofuran-3-carboxylate (*trans*-394**, Table 3.7, entry 1)**



An oven dried 10 mL reaction vessel containing a stirring bar under argon atmosphere was charged with anhydride **393** (59.6 mg, 0.27 mmol). Anhydrous MTBE (2.7 mL, 0.1 M) was added *via* syringe and the reaction mixture was then cooled to -15 °C. Recrystallised 4-chlorobenzaldehyde (37.8 mg, 0.27 mmol) was added to the reaction mixture followed by catalyst **329** (9.5 mg 0.014 mmol, 5 mol%) and reaction was stirred at -15 °C for 100 h to give a diastereomeric mixture of carboxylic acids in a 95:5 ratio (*trans*:*cis*). After esterification, the major diastereomer (*trans*-**394**) was isolated and purified by column chromatography eluting in gradient from 100% hexane to 20% EtOAc in hexane to give a white solid (93.8 mg, 93%). TLC (hexane:EtOAc, 8:2 *v/v*): R_f = 0.12. M.p. 60-63 °C. $[\alpha]_D^{20}$ = -59.0° (*c* 0.20, CHCl₃).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 85/15, 1.0 mL min⁻¹, RT, UV detection at 254 nm, retention times: 76.3 min. (minor enantiomer) and 87.4 min. (major enantiomer).

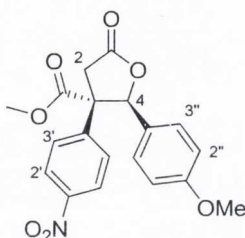
δ_H (400 MHz, CDCl₃): 8.02 (2 H, d, *J* 8.8, H-2'), 7.11 (2 H, d, *J* 8.5, H-2''), 7.03-6.92 (4 H, m, H-3' and H-3''), 6.28 (1 H, s, H-4), 3.82 (3 H, s, CO₂CH₃), 3.41 (2 H, s, H-2).

δ_C (100 MHz, CDCl₃): 172.7 (C=O), 171.7 (C=O), 147.5 (q), 142.0 (q), 135.0 (q), 132.2 (q), 128.5, 128.2, 128.1, 123.7, 84.5, 59.6 (q), 53.8, 38.7.

ν_{max} (film)/cm⁻¹: 2956, 2934, 2855, 1790, 1734, 1568, 1522, 1349, 1243, 1176, 1091, 1010, 853, 737, 621.

HRMS (m/z -ESI): [M-H] found 374.0418. $C_{18}H_{13}NO_6Cl$ Requires 374.0431.

5.2.8.2.2 (2*S*,3*S*)-Methyl 2-(4-methoxyphenyl)-3-(4-nitrophenyl)-5-oxotetrahydrofuran-3-carboxylate (*trans*-395**, Table 3.7, entry 2)**



Prepared according to general procedure I using **393** (53.5 mg, 0.24 mmol), anhydrous MTBE (0.1 M, 2.4 mL), freshly distilled 4-methoxybenzaldehyde (29.4 μ L, 0.24 mmol) and catalyst **329** (8.6 mg, 0.012 mmol, 5 mol%). The reaction was stirred for 164 h to give a diastereomeric mixture of carboxylic acids in a 92:8 ratio (*trans*:*cis*). After esterification, the major diastereomer (*trans*-**395**) was isolated and purified by column chromatography eluting in gradient from 100% hexane to 20% EtOAc in hexane to give a beige solid (64.1 mg, 71%). TLC (hexane:EtOAc, 8:2 v/v): R_f = 0.10. M.p. 62-64 $^{\circ}C$. $[\alpha]_D^{20}$ = -47.0 $^{\circ}$ (c 0.10, $CHCl_3$).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 85/15, 1.0 mL min^{-1} , RT, UV detection at 254 nm, retention times: 85.0 min. (minor enantiomer) and 115.2 min. (major enantiomer).

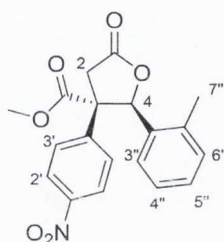
δ_H (400 MHz, $CDCl_3$): 8.01 (2 H, d, J = 8.7, H-2'), 7.01 (2 H, d, J 8.7, H-3'), 6.89 (2 H, d, J 8.5, H-3''), 6.64 (2 H, d, J 8.5, H-2''), 6.29 (1 H, s, H-4), 3.80 (3 H, s, OCH_3), 3.71 (3 H, s, CO_2CH_3), 3.41 (2 H, s, H-2).

δ_C (100 MHz, $CDCl_3$): 173.1 (C=O), 171.9 (C=O), 160.0 (q), 147.4 (q), 142.4 (q), 128.3, 128.2, 125.6 (q), 123.5, 113.6, 85.3, 59.8 (q), 55.3, 53.7, 38.3.

ν_{max} (film)/ cm^{-1} : 2956, 2844, 1785, 1733, 1608, 1516, 1436, 1349, 1249, 1173, 1005, 854, 737, 702.

HRMS (m/z -ESI): [M-H] found 370.0910. $\text{C}_{19}\text{H}_{16}\text{NO}_7$ Requires 370.0927.

5.2.8.2.3 (2*S*,3*S*)-Methyl 3-(4-nitrophenyl)-5-oxo-2-(*o*-tolyl)tetrahydrofuran-3-carboxylate (*trans*-396**, Table 3.7, entry 3)**



Prepared according to general procedure I using **393** (55.5 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), freshly distilled 2-methylbenzaldehyde (29.0 μL 0.25 mmol) and catalyst **329** (8.9 mg, 0.013 mmol, 5 mol%). The reaction was stirred for 161 h to give a diastereomeric mixture of carboxylic acids in a 95:5 ratio (*trans*:*cis*). After esterification, the major diastereomer (*trans*-**396**) was isolated and purified by column chromatography eluting in gradient from 100% hexane to 20% EtOAc in hexane to give an off-white solid (56.1 mg, 63%). TLC (hexane:EtOAc, 8:2 *v/v*): R_f = 0.18. M.p. 61-64 $^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{20} = -73.5^{\circ}$ (c 0.20, CHCl_3).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 85/15, 1.0 mL min^{-1} , RT, UV detection at 254 nm, retention times: 33.6 min. (minor enantiomer) and 44.7 min. (major enantiomer).

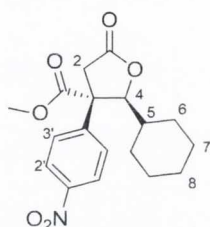
δ_{H} (400 MHz, CDCl_3): 7.97 (2 H, d, J 8.8, H-2'), 7.12 (1 H, app. t, H-5''), 7.07-6.91 (4 H, m, H-3' and H-4''), 6.74-6.63 (2 H, m, H-3'' and H-6''), 3.87 (3 H, s, CO_2CH_3), 3.55 (1 H, d, J 17.6, H-2a), 3.45 (1 H, d, J 17.6, H-2b), 2.20 (3 H, s, H-7'').

δ_{C} (100 MHz, CDCl_3): 173.3 (C=O), 172.2 (C=O), 147.4 (q), 141.9 (q), 136.4 (q), 132.4 (q), 131.1, 129.2, 128.7, 126.5, 126.1, 123.2, 82.8, 60.4 (q), 54.1, 38.3, 19.7.

ν_{max} (film)/ cm^{-1} : 2957, 2929, 2857, 1772, 1737, 1597, 1522, 1349, 1239, 1177, 1000, 852, 731, 701.

HRMS (m/z -ESI): [M-H] found 354.0970. $\text{C}_{19}\text{H}_{16}\text{NO}_6$ Requires 354.0978.

5.2.8.2.4 (2*S*,3*S*)-Methyl 2-cyclohexyl-3-(4-nitrophenyl)-5-oxotetrahydrofuran-3-carboxylate (*trans*-**397**, Table 3.7, entry 4)



Prepared according to general procedure I using **393** (47.4 mg, 0.21 mmol), anhydrous MTBE (0.1 M, 2.1 mL), freshly distilled cyclohexanecarboxaldehyde (25.9 μL , 0.21 mmol) and catalyst **329** (30.2 mg, 0.043 mmol, 20 mol%). The reaction was stirred for 98 h to give a diastereomeric mixture of carboxylic acids in a 88:12 ratio (*trans*:*cis*). After esterification, the major diastereomer (*trans*-**397**) was purified by column chromatography eluting in gradient from 100% hexane to 20% EtOAc in hexane to give an off-white solid (41.6 mg, 56%). TLC (hexane:EtOAc, 8:2 v/v): R_f = 0.19. M.p. 49-51 $^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{20}$ = -100.7 $^{\circ}$ (c 0.15, CHCl_3).

CSP-HPLC analysis. Chiralcel OD (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1} , RT, UV detection at 254 nm, retention times: 27.1 min. (minor enantiomer) and 29.6 min. (major enantiomer).

δ_{H} (400 MHz, CDCl_3): 8.26 (2 H, d, J 8.8, H-2'), 7.46 (2 H, d, J 8.8, H-3'), 5.20 (1 H, d, J 3.4, H-4), 3.75 (3 H, s, CO_2CH_3), 3.37 (1 H, d, J

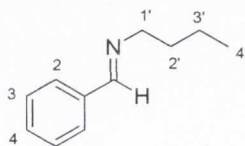
17.4, H-2a), 3.19 (1 H, d, J 17.4, H-2b), 1.79-0.70 (11 H, m, H-5, H-6, H-7 and H-8).

δ_{C} (100 MHz, CDCl_3): 173.5 (C=O), 172.3 (C=O), 147.7 (q), 142.8 (q), 128.5, 124.0, 88.2, 58.3 (q), 54.0, 39.2, 37.8, 30.2, 26.3, 26.0, 25.6, 25.5.

ν_{max} (film)/ cm^{-1} : 2929, 2855, 1779, 1734, 1602, 1521, 1449, 1348, 1245, 1172, 988, 853, 704.

5.2.9 Synthesis of aldimines as the electrophile components in annulation reactions with homophthalic anhydride

5.2.9.1 (*E*)-*N*-Benzylidenebutan-1-amine (401)

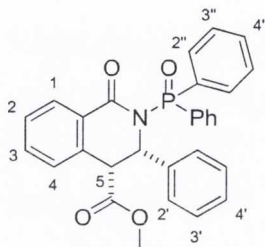


An oven dried 50 mL round-bottomed flask containing a stirring bar was charged with, dry CH_2Cl_2 (25 mL) and anhydrous MgSO_4 (5.00 g, 41.54 mmol). Freshly distilled benzaldehyde (2.0 mL, 19.69 mmol) and *n*-butyl amine (2.4 mL, 24.28 mmol) were added *via* syringe, the flask was stoppered and the reaction mixture was stirred at room temperature for 16 h. The MgSO_4 was removed by filtration over a pad of Celite and the filtrates were concentrated *in vacuo* to afford imine **401** (3.11 g, 98%) as a colourless oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³⁴⁴

δ_{H} (400 MHz, CDCl_3): 8.27 (1 H, s, N=CH), 7.77-7.69 (2 H, m, H-2), 7.45-7.37 (3 H, m, H-3 and H-4), 3.62 (2 H, t, J 7.2, H-1'), 1.69 (2 H, app. quint., H-2'), 1.39 (2 H, sext., J 7.4, H-3'), 0.95 (3 H, t, J 7.4, H-4').

HRMS (m/z -ESI): $[\text{M}+\text{H}]^+$ found 162.1279. $\text{C}_{11}\text{H}_{16}\text{N}$ Requires 162.1283.

5.2.10 Methyl 2-(diphenylphosphoryl)-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*cis*-404, Table 3.9 entry 2)



An oven dried 10 mL reaction vessel containing a stirring bar was charged with anhydride **139** (40.0 mg, 0.25 mmol) then placed under an argon atmosphere (balloon). Anhydrous MTBE (2.4 mL) was added *via* syringe and the reaction mixture was then cooled to -15 °C. Imine **403** (75.1 mg, 0.25 mmol) was added followed by catalyst **405** (10.6 mg, 0.012 mmol, 5 mol%) and the reaction was stirred at -15 °C for 7 days. The conversion of the reaction was determined by ^1H NMR spectroscopic analysis using *p*-iodoanisole (28.8 mg, 0.123 mmol) as an internal standard and monitoring the disappearance of imine **403**. To the reaction mixture containing the corresponding carboxylic acids, anhydrous MeOH (750 μL), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150 μL , 0.300 mmol) were added *via* syringe and the reaction was allowed to stir for 30 min. at room temperature. The solvent was then removed *in vacuo* at room temperature and the crude mixture of diastereomeric esters was purified by column chromatography ($\text{CH}_2\text{Cl}_2\text{:EtOAc}$ 3:1) to give *cis*-**404** (58.0 mg, 49%, 64% *ee*) as a white solid. M.p. 159-161 °C. $[\alpha]_{\text{D}}^{20} = 40.0^\circ$ (*c* 0.05, CHCl_3).

δ_{H} (600 MHz, CDCl_3): 8.05 (1 H, d, *J* 7.5, H-1), 7.86 (2 H, dd, *J* 7.3, 13.6, H-2'), 7.75 (2 H, dd, *J* 7.3, 13.6, H-2'), 7.62-7.31 (8 H, m, H-2, H-3, H-4 and H-Ar), 7.25-7.00 (6 H, m, H-3' and H-4'), , 6.34-6.30 (1 H, app. d, H-6), 4.17 (1 H, app. s, H-5), 3.71 (3 H, s, CO_2CH_3).

δ_{C} (150 MHz, CDCl_3): 171.2 (q), 166.5 (q), 139.9, 133.7, 133.6, 132.8 (d, $J_{\text{C-P}}$ 11.0 Hz), 132.3 (d, $J_{\text{C-P}}$ 6.7), 132.2 (d, $J_{\text{C-P}}$ 6.6), 131.9 (d, $J_{\text{C-P}}$ 12.0), 131.1 (d, $J_{\text{C-P}}$ 126.7), 130.5 (d, $J_{\text{C-P}}$ 126.9), 129.0,

128.9, 128.8, 128.7, 128.5, 128.3 (d, J_{C-P} 14.0), 127.9 (d, J = 13.6 Hz), 127.8, 126.8, 57.2 (d, J_{C-P} 2.6), 53.0, 51.2 (d, J = 3.6 Hz)

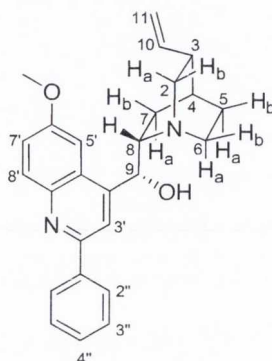
^{31}P NMR (162 MHz, CDCl_3): 31.4 ppm.

HRMS (m/z - ESI): $[\text{M}+\text{H}]^+$ found, 482.1504. $\text{C}_{29}\text{H}_{25}\text{NO}_4\text{P}$ Requires 482.1521;.

5.3 Experimental data for Chapter 4

5.3.1 Synthesis of C-2'-substituted quinine derivatives

5.3.1.1 (R)-(6-Methoxy-2-phenylquinolin-4-yl)((2S,4S,8R)-8-vinylquinuclidin-2-yl)methanol (**419**)

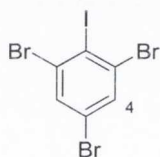


An oven dried 500 mL round-bottomed flask containing a large stirring bar was charged with quinine (**81**) (6.50 g, 20.03 mmol) fitted with a septum and placed under an argon atmosphere. Anhydrous MTBE (120 mL) was added *via* syringe and the suspension was cooled to -10 °C. A solution of phenyl lithium (1.8 M in THF, 34.0 mL, 61.20 mmol) was added *via* syringe in two equal portions to the vigorously stirred suspension and the reaction mixture was stirred at -10 °C for 30 min then warmed to room temperature and stirred for 2 h. Acetic acid (15 mL) is added dropwise *via* syringe to the reaction at 0 °C, followed by H₂O (50 mL) and EtOAc (50 mL). The reaction is allowed to room temperature, then solid iodine is added in several portions to the vigorously stirred mixture until the appearance of a persistent deep brown coloration. A solution of sodium thiosulfate (Na₂S₂O₃, 3.00 g) in water (50 mL) is added, followed by a concentrated solution of aqueous ammonia (35%, 30 mL) and the mixture is stirred vigorously for 10 min. The organic phase is then washed with brine and the aqueous phase is extracted with CH₂Cl₂ (3 x 40 mL), the combined organic extracts are then dried over MgSO₄, filtered and the solvent removed *in vacuo*. The crude oily residue is purified by column chromatography eluting in gradient from 100% EtOAc to 5% MeOH in AcOEt to EtOAc:NEt₃:MeOH 90:5:5 (TLC is better visualised using PhMe:MeOH:NEt₃ 10:1:1 which allows for a better separation of the product from the starting alkaloid) to obtain **419** (4.10 g, 51%) as a white amorphous solid. The isolated

compound exhibited identical spectroscopic data to those reported in the literature.¹⁵² M.p 96-100 °C (lit.,¹⁵² 140 °C). $[\alpha]_D^{20} = -18.7$ (c 0.25, CHCl₃).

δ_H (400 MHz, CDCl₃): 8.08-7.96 (3 H, m, H-8' and H-2''), 7.85 (1 H, s, H-3'), 7.46-7.35 (3 H, m, H-7', H-3'' and H-4''), 7.31 (1 H, dd, J 9.2, 2.5, H-7'), 7.13 (1 H, d, J 2.5, H-5'), 5.72 (1 H, ddd, J 7.7, 10.1, 17.5, H-10), 5.45 (1 H, d, J 3.1, H-9), 4.99-4.85 (2 H, m, H-11), 3.87 (3 H, s, OCH₃), 3.49-3.35 (1 H, m, H-2b), 3.16-3.01 (2 H, m, H-6a and H-8), 2.72-2.57 (2 H, m, H-2a and H-6b), 2.31-2.19 (1 H, m, H-3), 1.84-1.65 (3 H, m, H-4, H-5b and H-7b), 1.59-1.39 (2 H, m, H-5a and H-7a).

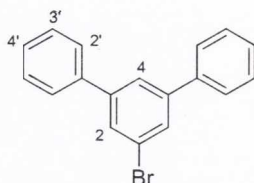
5.3.1.2.1 1,3,5-Tribromo-2-iodobenzene (**445**)



A 250 mL three neck round-bottomed flask containing a stirring bar and fitted with a thermometer was charged with 2,4,6-tribromoaniline (**444**) (10.00 g, 30.32 mmol) and concentrated aqueous HCl (20 mL) and the suspension was cooled to 0 °C. A solution of NaNO₂ (2.30 g, 33.35 mmol) in water (10 mL) was added dropwise to the reaction mixture while keeping its temperature below 10 °C and upon completion of the addition the reaction was stirred at 0 °C for 30 min. A solution of KI (50.33 g, 303.20 mmol) in H₂O (75 mL) was added dropwise to the vigorously stirred reaction mixture at 0 °C, then it was warmed to room temperature and stirred for 2 h. An aqueous 0.5 M solution of Na₂SO₃ (20 mL) and CH₂Cl₂ (50 mL) were added, the organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts were washed with a 2 M aqueous solution of NaOH (50 mL), H₂O (50 mL) and brine (50 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The solid residue obtained was recrystallised from CH₂Cl₂/hexane to yield **445** (10.82 g, 81%) as pale yellow needles. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³⁰⁷ M.p. 105-109 °C (lit.,³⁰⁷ 101-103 °C).

δ_{H} (400 MHz, CDCl_3): 7.71 (2 H, s, H-4).

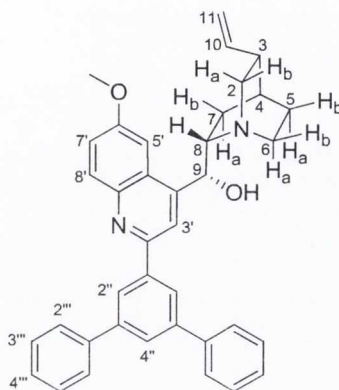
5.3.1.2.2 1-Bromo-3,5-diphenylbenzene (446)



An oven dried 250 mL round-bottomed flask equipped with a stirring bar was charged with freshly ground magnesium (2.74 g, 112.76 mmol) and anhydrous THF (20 mL), then it was fitted with a condenser and placed under an argon atmosphere (balloon). Bromobenzene (11.8 mL, 112.76 mmol) was added *via* syringe in two portions at room temperature, then the reaction mixture was heated at reflux temperature for 1 h. The reaction was cooled to room temperature, then a solution of **445** (9.92 g, 22.51 mmol) in anhydrous THF (70 mL) was added *via* syringe and the reaction mixture was heated at reflux for 1 h, then stirred at room temperature for 16 h. A 2 M aqueous solution of HCl (50 mL) was added slowly to the reaction, followed by CH_2Cl_2 (50 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried over MgSO_4 , filtered and the solvent removed *in vacuo*. The residue was purified by flash chromatography (100% hexane) to yield **446** (5.92 g, 85%) as a white solid. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³⁰⁸ M.p. 113-114 °C (lit.,³⁰⁸ 107-109 °C).

δ_{H} (400 MHz, CDCl_3): 7.71 (3 H, bs, H-2 and H-4), 7.61 (4 H, d, J 7.8, H-2'), 7.47 (4 H, app. t, H-3'), 7.40 (2 H, t, J 7.7, H-4').

5.3.1.2.3 (R)-(6-Methoxy-2-*m*-terphenylquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methanol (447)



An oven dried 250 mL round-bottomed flask containing a large stirring bar was charged with **446** (4.63 g, 14.98 mmol) fitted with a septum and placed under an argon atmosphere. Anhydrous diethyl ether (10 mL) was added *via* syringe and the suspension was cooled to -10 °C. A solution of *tert*-butyl lithium (1.7 M in pentane, 17.0 mL, 28.90 mmol) was added *via* syringe in one portion and the reaction mixture was stirred at -10 °C for 30 min then warmed to room temperature and stirred for 1 h. The reaction was cooled to 0 °C, then anhydrous MTBE (30 mL) was added *via* syringe followed by quinine (1.62 g, 4.99 mmol) and the reaction mixture was stirred at 0 °C for 30 min, then at room temperature for 1 h, then heated at reflux temperature for 2 h. Acetic acid (5 mL) is added dropwise *via* syringe to the reaction at 0 °C, followed by H₂O (20 mL) and EtOAc (20 mL). The reaction is allowed to room temperature, then solid iodine is added in several portions to the vigorously stirred mixture until the appearance of a persistent deep brown coloration. A solution of sodium thiosulfate (Na₂S₂O₃, 1.00 g) in water (20 mL) is added, followed by a concentrated solution of aqueous ammonia (35%, 20 mL) and the mixture is stirred vigorously for 10 min. The organic phase is then washed with brine and the aqueous phase is extracted with CH₂Cl₂ (3 x 20 mL), the combined organic extracts are then dried over MgSO₄, filtered and the solvent removed *in vacuo*. The crude oily residue is purified by column chromatography eluting in gradient from 100% EtOAc to 2% MeOH in AcOEt to EtOAc:MeOH:NEt₃ 95:5:1 to obtain **447** (2.07 g, 75%) as an off-white amorphous solid. M.p 126-128 °C. $[\alpha]_D^{20} = +11.0$ (*c* 0.20, CHCl₃).

δ_{H} (400 MHz, CDCl_3):	8.29 (2 H, s, H-2''), 8.11 (1 H, d, J 9.1, H-8'), 8.06 (1 H, s, H-3'), 7.83 (1 H, s, H-4''), 7.73 (4 H, d, J 7.8, H-2'''), 7.49 (4 H, app. t, H-3'''), 7.44-7.33 (3 H, m, H-7' and H-4'''), 7.20 (1 H, d, J 2.3, H-5'), 5.74 (1 H, ddd, J 7.7, 10.3, 17.2, H-10), 5.61 (1 H, bs, H-9), 4.96 (1 H, d, J 17.2, H-11), 4.91 (1 H, d, J 10.3, H-11), 3.91 (3 H, s, OCH_3), 3.57-3.44 (1 H, m, H-6a), 3.25-3.07 (2 H, m, H-2b and H-8), 2.79-2.65 (2 H, m, H-2a and H-6b), 2.37-2.22 (1 H, m, H-3), 1.89-1.76 (3 H, m, H-4, H-5b and H-7b), 1.65-1.42 (2 H, m, H-5a and H-7a).
δ_{C} (100 MHz, CDCl_3):	157.9 (q), 154.5 (q), 148.2 (q), 144.6 (q), 142.4 (q), 141.8, 141.3 (q), 140.9 (q), 132.1, 129.0, 127.7, 127.6, 127.0, 125.8 (q), 125.3, 122.0, 116.5, 114.7, 101.3, 72.3, 60.3, 57.2, 56.0, 43.6, 40.1, 28.1, 27.7, 21.8.
ν_{max} (film)/ cm^{-1} :	3256, 3062, 2932, 2865, 1620, 1595, 1500, 1361, 1231, 1029, 878, 827, 758, 696.
HRMS (m/z -ESI):	$[\text{M}+\text{H}]^+$ found 553.2863. $\text{C}_{38}\text{H}_{37}\text{N}_2\text{O}_2$ Requires 553.2855.

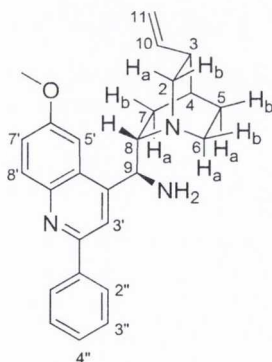
5.3.2 Procedure J: general protocol for the preparation of 9-*epi*-amine-derivatives (3HCl salts) of quinine-derived alkaloids

A oven dried 250 mL round-bottomed flask containing a stirring bar was charged with triphenylphosphine (1.2 equiv.) and the appropriate quinine derivative (10 mmol), fitted with a septum and placed under an argon atmosphere. Anhydrous THF (65 mL) was added *via* syringe and the resulting solution was cooled to 0 °C. Diisopropyl azodicarboxylate (DIAD, 1.2 equiv) was added dropwise *via* syringe followed by diphenylphosphoryl azide (DPPA, 1.2 equiv.), the resulting mixture was allowed to warm up to room temperature and stirred for 16 h, then heated at reflux temperature for 2 h. The so-formed azido species was reduced *in situ* *via* a Staudinger reduction: the reaction mixture was cooled to room temperature, then triphenylphosphine (1.2 equiv.)

was added and the solution was heated at reflux temperature for 5 hours. After cooling the reaction to room temperature, H₂O (20 mL) was added and the reaction was stirred at room temperature for 20 h, it was then concentrated *in vacuo* and the residue dissolved in CH₂Cl₂ (30 mL). A 2 M aqueous solution of HCl (30 mL) was added, the aqueous phase was separated and washed with CH₂Cl₂ (3 x 20 mL). The aqueous layer was then concentrated under reduced pressure to obtain the hydrochloride salt of the 9-*epi*-amine-derivative of the quinine-derived alkaloid as pale yellow salts.

The 9-*epi*-quinine-derived alkaloids bearing an amino group at C-9 could be generated by dissolving the relative hydrochloride salt in a mixture of CH₂Cl₂ (20 mL) and a saturated aqueous solution of Na₂CO₃. The basic aqueous layer was extracted with CH₂Cl₂ (4 x 20 mL), the organic extracts were dried over MgSO₄, filtered and the solvent removed *in vacuo* to obtain the relevant free amine base in quantitative yields.

5.3.2.2 (S)-[6-Methoxy-2-phenylquinolin-4-yl][(2S,4S,8R)-8-vinylquinuclidin-2-yl]methanamine (421)

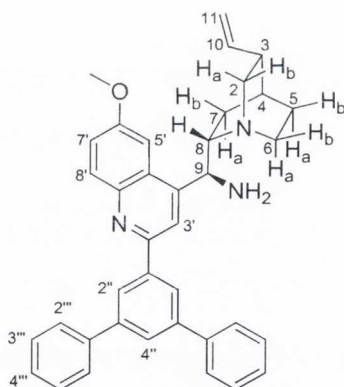


Prepared according to general procedure J, using **419** (4.05 g, 10.11 mmol), PPh₃ (3.18 g, 12.12 mmol), DIAD (2.4 mL, 12.19 mmol) and DPPA (2.6 mL, 12.11 mmol) in THF (65 mL). The Staudinger reduction was performed using PPh₃ (3.45 g, 13.15 mmol) and deionised H₂O (20 mL) to obtain the hydrochloride salt **420** (4.12 g, 80%) as a pale yellow solid. After a basic extraction using CH₂Cl₂ (3 x 20 mL) and a saturated aqueous solution of Na₂CO₃, compound **421** could be obtained as a thick oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.¹⁵³ $[\alpha]_D^{20} = +26.4$ (*c* 0.25, CHCl₃).

δ_{H} (400 MHz, CDCl_3): 8.15 (2 H, d, J 7.4, H-2''), 8.11 (1 H, d, J 9.1, H-8'), 7.98 (1 H, bs, H-3'), 7.68 (1 H, bs, H-5'), 7.52 (2 H, app. t, H-3''), 7.44 (1 H, t, J 7.4 H-4''), 7.40 (1 H, dd, J 2.7, 9.4 H-7'), 5.79 (1 H, ddd, J 7.8, 10.1, 17.0, H-10), 5.04-4.89 (2 H, m, H-11), 4.67 (1 H, bs, H-9), 3.98 (3 H, s, OCH_3), 3.36-3.06 (3 H, m, H-8, H-6a and H-2b), 2.90-2.76 (2 H, m, H-2a and H-6b), 2.34-2.24 (1 H, m, H-3), 2.05 (2 H, bs, NH_2), 1.70-1.51 (3 H, m, H-4, H-5a and H-5b), 1.50-1.36 (1 H, m, H-7b), 0.92-0.78 (1 H, m, H-7a)

HRMS (m/z -ESI): $[\text{M}+\text{H}]^+$ found 400.2391. $\text{C}_{26}\text{H}_{30}\text{N}_3\text{O}$ Requires 400.2389.

5.3.2.3 (*S*)-[6-Methoxy-2-*m*-terphenylquinolin-4-yl][(2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl]methanamine (**445**)

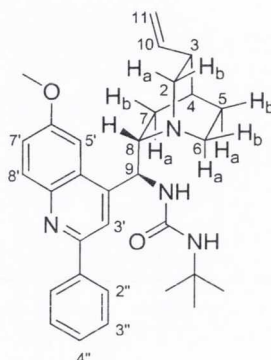


Prepared according to general procedure J, using **443** (1.84 g, 3.33 mmol), PPh_3 (1.05 g, 4.00 mmol), DIAD (790 μL , 4.00 mmol) and DPPA (870 μL , 4.04 mmol) in THF (25 mL). The Staudinger reduction was performed using PPh_3 (1.13 g, 4.33 mmol) and deionised H_2O (10 mL). The residue obtained after removal of the solvent *in vacuo* was taken up with CHCl_2 (10 mL) and Et_2O (10 mL), concentrated HCl was added and the precipitate formed was filtered and dried to obtain the hydrochloride salt **444** (1.39 g, 63%) as a pale yellow solid. After a basic extraction using CH_2Cl_2 (3 x 20 mL) and a saturated aqueous solution of Na_2CO_3 , compound **445** could be obtained as a tan solid. M.p 124-126 $^\circ\text{C}$. $[\alpha]_{\text{D}}^{20} = +31.2^\circ$ (c 0.20, CHCl_3).

δ_{H} (400 MHz, CDCl_3):	8.35 (2 H, s, H-2''), 8.15 (1 H, d, J 9.3, H-8'), 8.08 (1 H, bs, H-3'), 7.89 (1 H, s, H-4''), 7.77 (4 H, d, J 7.6, H-2'''), 7.53-7.49 (5 H, m, H-7' and H-3'''), 7.46-7.40 (3 H, m, H-5', H-4'''), 5.82-5.75 (1 H, m, H-10), 5.02-4.93 (2 H, m, H-11), 4.69 (1 H, bs, H-9), 3.98 (3 H, s, OCH_3), 3.32-3.25 (3 H, m, H-8, H-6a and H-2b), 2.88-2.82 (2 H, m, H-2a, H-6b), 2.30 (1 H, m, H-3), 1.65-1.47 (4 H, m, H-4, H-5a, H-5b, H-7b), 0.91-0.88 (1 H, m, H-7a).
δ_{C} (100 MHz, CDCl_3):	157.7 (q), 154.6 (q), 147.6 (q), 144.9 (q), 142.4 (q), 141.6, 141.2 (q), 140.9 (q), 132.2, 128.8 (2 x C), 127.8 (q), 127.6, 127.5, 126.8, 125.3, 121.4, 118.1, 114.4, 101.8, 77.3, 56.1, 55.6, 41.0, 39.7, 28.1, 27.6, 26.0.
ν_{max} (film)/ cm^{-1} :	2933, 2098, 1620, 1595, 1480, 1230, 1031, 907, 829, 759, 696
HRMS (m/z -ESI) :	[M+H] ⁺ found 552.3009. $\text{C}_{38}\text{H}_{38}\text{N}_3\text{O}$ Requires 552.3015.

5.3.3 Synthesis of urea-substituted *epi*-cinchona alkaloid catalysts **327**, **422**, **426** and **450**

5.3.3.1 1-*tert*-Butyl-3-((*S*)-(6-methoxy-2-phenylquinolin-4-yl))((2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)urea (**422**)



An oven dried 25 mL reaction vessel containing a stirring bar under argon atmosphere was charged with **420** (500.0 mg, 0.98 mmol). Anhydrous CH₂Cl₂ (10 mL) was added *via* syringe and the reaction was cooled to 0 °C. Freshly distilled triethylamine (685.0 μL, 4.91 mmol) was added *via* syringe and, when the solid had dissolved *tert*-butyl isocyanate (125.0 μL, 1.09 mmol) was added. The resulting solution was warmed to room temperature and stirred for 20 h. The mixture was then transferred into a separating funnel, washed with water (2 x 10 mL), the organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (100% EtOAc) to obtain urea **422** (254.1 mg, 52% yield) as an amorphous white solid. M.p. 131-134 °C. $[\alpha]_D^{20} = -16.5^\circ$ (*c* 0.20, CHCl₃).

δ_H (400 MHz, CDCl₃): 8.16-8.06 (3 H, m, H-8' and H-2''), 7.84 (1 H, s, H-3'), 7.76 (1 H, *J* 1.9, H-5'), 7.52 (2 H, app. t, H-3''), 7.48-7.36 (2 H, m, H-7' and H-4''), 6.27 (1 H, bs, NH), 5.70 (1 H, ddd, *J* 7.2, 10.2, 16.6, H-10), 5.42 (1 H, bs, H-9), 5.11-5.02 (2 H, m, H-11), 4.88 (1 H, bs, NH), 4.02 (3 H, s, OCH₃), 3.66-3.48 (2 H, m, H-6a and H-8), 3.46 (1 H, dd, *J* 10.5, 13.6, H-2b), 3.08-2.87 (2 H, m, H-2a and H-6b), 2.57-2.44 (1 H, m, H-3), 1.97-1.72 (3 H, m, H-4, H-5a and H-5b),

1.64 (1 H, app. t, H-7b), 1.26 (9 H, s, (CH₃)₃), 1.24-1.14 (1 H, m, H-7a).

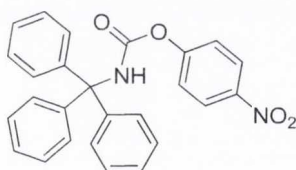
δ_{C} (150 MHz, CDCl₃):* 158.1 (q), 157.2 (q), 154.8 (q), 145.2 (q), 139.7 (q), 139.3, 132.3, 129.1, 128.9, 127.5, 127.2 (q), 122.1, 117.9 (q), 116.1, 102.1, 60.2, 56.0, 55.2, 50.6, 41.1, 38.4, 29.5, 27.3, 26.5, 25.6.

* The resonance of a quaternary C could not be identified in the spectrum

ν_{max} (film)/cm⁻¹: 3311, 2962, 1667, 1621, 1545, 1500, 1353, 1221, 1029, 916, 829, 771, 694.

HRMS (m/z -ESI): [M-H] found 497.2928. C₃₁H₃₇N₄O₂ Requires 497.2917.

5.3.3.2.1 4-Nitrophenyl tritylcarbamate (**425**)



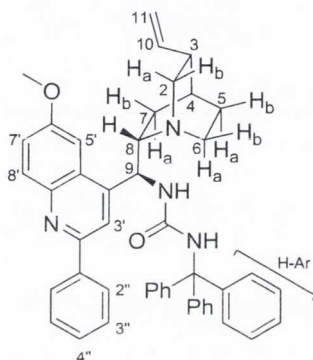
A 50 mL oven dried round-bottomed flask containing a stirring bar was charged with amine **423** (1.50 g, 5.78 mmol) and anhydrous CH₂Cl₂ (5 mL), then it was fitted with a septum, kept under an argon atmosphere (balloon) and cooled to 0 °C. A solution of **424** (1.22 g, 6.07 mmol) in anhydrous CH₂Cl₂ (20 mL) was added *via* syringe at 0 °C, immediately followed by freshly distilled pyridine (935.0 μ L, 11.57 mmol). The resulting solution was stirred for 16 h at room temperature, then concentrated *in vacuo*. The residue was purified by column chromatography (6:4 CH₂Cl₂:hexane) to afford **425** (1.85 g, 75%) as a white solid. M.p. 140-142 °C.

δ_{H} (400 MHz, CDCl₃): 8.17 (2 H, d, J 8.4, H-2), 7.44-7.16 (17 H, m, H-3 and H-Ar), 6.43 (1 H, bs, CONH).

δ_C (100 MHz, $CDCl_3$): 155.6 (q), 151.5 (C=O), 144.1 (2 x q), 128.7, 128.3, 127.6, 125.1, 121.9.

ν_{max} (film)/ cm^{-1} : 3310, 3058, 1726, 1514, 1481, 1243, 1207, 1101, 1008, 858, 699.

5.3.3.2.3 1-Trityl-3-((*S*)-(6-methoxy-2-phenylquinolin-4-yl)((2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)urea (**426**)



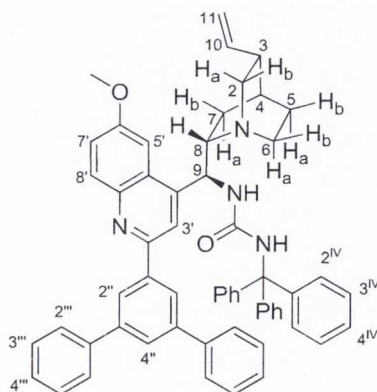
A 50 mL oven dried round-bottomed flask containing a stirring bar was charged with the free amine **421** (936.5 mg, 2.35 mmol) and anhydrous CH_2Cl_2 (10 mL), then it was fitted with a septum and kept under an argon atmosphere (balloon) and cooled to 0 °C. A solution of **425** (1.00 g, 2.36 mmol) in anhydrous CH_2Cl_2 (20 mL) was added *via* syringe, immediately followed by anhydrous diisopropylethylamine (450.0 μ L, 2.59 mmol) and the reaction mixture was stirred at room temperature for 20 h. The yellow solution was transferred to a separating funnel, and washed with a 2 M aqueous solution of NaOH (6 x 30 mL) until the aqueous washings were almost colourless. The organic extracts were then washed with brine, dried over $MgSO_4$ filtered and the solvent was removed *in vacuo* to afford a residue which was purified by column chromatography eluting in gradient from 10% hexane in EtOAc to 100% EtOAc to yield **426** (901.3 mg, 56%) as an amorphous white solid. Alternatively **426** could also be purified by recrystallisation from CH_2Cl_2 . M.p. 126-130 °C. $[\alpha]_D^{20} = -23.0^\circ$ (c 0.20, $CHCl_3$).

δ_H (600 MHz, CD_3OD): 8.04 (2 H, d, *J* 7.8, H-2''), 8.02 (1 H, d, *J* 9.3, H-8'), 7.81 (1 H, bs, NH) 7.66 (1 H, bs, H-5'), 7.54 (2 H, app. t, H-3''), 7.48 (1 H, t, *J* 7.4, H-4''), 7.39 (1 H, dd, *J* 2.0, 9.1, H-7'),

δ_{C} (150 MHz, CD_3OD):* 158.4 (q), 158.0 (q), 155.4 (q), 148.1, 145.8 (q), 144.6 (q), 141.6, 139.9, 130.8, 129.2, 128.9, 128.8, 127.6, 126.7, 122.6, 113.9, 102.3, 69.8 (q), 65.9, 59.8, 55.8, 55.3, 41.2, 39.7, 27.9, 27.5, 26.3, 26.2.

$$v_{\max} \text{ (film)}/\text{cm}^{-1}: \quad 3311, 3059, 2924, 1621, 1596, 1494, 1444, 1348, 1230, \\ 1028, 910, 826, 696.$$

5.3.3.2.4 1-Trityl-3-((*S*)-(6-methoxy-2-*m*-terphenylquinolin-4-yl)((*2S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)urea (450)



251

A solution of **425** (876.2 mg, 2.06 mmol) in anhydrous CH_2Cl_2 (10 mL) was added *via* syringe, immediately followed by anhydrous diisopropylethylamine (395.0 μL , 2.27 mmol) and the reaction mixture was stirred at room temperature for 20 h. The yellow solution was transferred to a separating funnel, and washed with a 2 M aqueous solution of NaOH (6 x 30 mL) until the aqueous washings were almost colourless. The organic extracts were then washed with brine, dried over MgSO_4 filtered and the solvent was removed *in vacuo* to afford a residue which was purified by column chromatography eluting in gradient from 10% hexane in EtOAc to 100% EtOAc to yield **450** (948.4 mg, 55%) as an amorphous yellow solid. M.p. 98-102 °C. $[\alpha]_{\text{D}}^{20} = +17.5^\circ$ (*c* 0.20, CHCl_3).

δ_{H} (600 MHz, CDCl_3): 8.33 (2 H, d, *J* 1.6, H-2''), 8.17 (1 H, d, *J* 9.3, H-8'), 7.94-7.82 (2 H, m, H-3' and H-4''), 7.81-7.70 (6 H, m, H-2''', H-7' and H-5'), 7.63-7.33 (12 H m, H-3''', H-4''', H-2^{IV}), 7.26-6.94 (9 H, m, H-3^{IV} and H-4^{IV}) 5.75 (1 H, ddd, *J* 7.0, 9.9, 17.4, H-10), 5.07, (1 H, d, *J* 11.2, H-9), 5.04-4.89 (2 H, m, H-11), 3.99 (3 H, s, OCH_3), 3.52-3.17 (3 H, m, H-8, H-6a and H-2b), 2.99-2.79 (2 H, m, H-2a and H-6b), 2.20-2.35 (1 H, m, H-3), 1.75-1.36 (4 H, m, H-4, H-5a, H-5b and H-7b), 0.92-0.76 (1 H, m, H-7a).

δ_{C} (150 MHz, CDCl_3): 171.1 (q), 158.0 (q), 154.2 (q), 145.1 (q), 142.4 (q), 142.2 (q), 141.3, 141.1 (q), 140.9 (q), 140.2 (q), 132.5, 132.4, 132.3, 128.9, 128.7, 128.6, 128.5, 128.4, 127.8, 127.5, 127.4, 127.3, 127.31, 126.9, 126.88, 125.3, 125.1, 122.0, 114.4, 69.6 (q), 55.9, 55.6, 40.9, 39.3, 29.5, 27.9, 27.1, 26.1.

ν_{max} (film)/ cm^{-1} : 3315, 3058, 2928, 2861, 2095, 1621, 1593, 1493, 1360, 1230, 1028, 914, 757, 696.

HRMS (*m/z* -ESI): $[\text{M}+\text{H}]^+$ found 837.4157. $\text{C}_{58}\text{H}_{53}\text{N}_4\text{O}_2$ Requires 837.4169.

5.3.4.1 Procedure K: general protocol for the preparation of racemic dihydroisocoumarins by annulation reactions between anhydride **139** and ketones (*i.e.* trifluoromethyl ketones, α -ketoesters, 1,2-diketones and α -ketoamides)

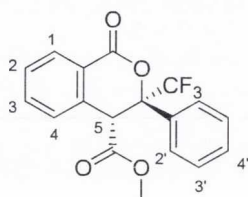
An oven dried 10 mL round-bottomed flask containing a stirring bar under argon atmosphere was charged with the relevant ketone (0.25 mmol) and anhydrous MTBE (2.4 mL, 0.1 M). Anhydride **139** (39.9 mg, 0.25 mmol) was then added to the reaction followed by *N,N*-diisopropylethylamine (8.6 μ L, 0.049 mmol, 20 mol%) and the resulting mixture was stirred for 20 h at room temperature. To the reaction mixture containing the corresponding carboxylic acids, anhydrous MeOH (750.0 μ L), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150.0 μ L, 0.30 mmol) were added *via* syringe and the reaction was allowed to stir for 30 min at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash chromatography to isolate the major diastereomer.

5.3.4.2 Procedure L: general protocol for asymmetric cycloaddition reactions between anhydride **139** and trifluoromethyl ketones (Table 4.5)

An oven dried 10 mL reaction vessel containing a stirring bar under argon atmosphere was charged with anhydride **139** (0.25 mmol, 1.0 equiv.) and catalyst **426** (5 mol%). Anhydrous MTBE (0.1 M) was added *via* syringe and the suspension was then cooled to -30 °C. The relevant trifluoromethyl ketone (1.0 equiv.) was added *via* syringe and the reaction mixture was stirred for the time indicated in Table 4.5. The yield was monitored by ^1H NMR spectroscopic analysis using *p*-iodoanisole (0.5 equiv.) as an internal standard. The reaction was then diluted with EtOAc (15 mL) and extracted with an aqueous solution of NaHCO_3 (10% w/v, 3 x 10 mL). The combined aqueous extracts were acidified with HCl (2.0 N) and the mixture was then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over MgSO_4 and the solvent was removed *in vacuo* to yield the diastereomeric mixture of carboxylic acids. The diastereomeric ratio of the products was determined *via* ^1H NMR spectroscopic analysis of the crude mixture, the carboxylic acids were then suspended in anhydrous MTBE (0.1 M). Dry MeOH (750.0 μ L), followed by trimethylsilyldiazomethane (2.0 M

solution in diethyl ether, 1.2 equiv.) were added *via* syringe and the reaction was allowed to stir for 30 min at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash chromatography to isolate the major diastereomer. The enantiomeric excess of the products was determined by CSP-HPLC using the conditions indicated for each case.

5.3.4.2.1 (3*R*,4*R*)-Methyl 1-oxo-3-phenyl-3-(trifluoromethyl)isochroman-4-carboxylate (*cis*-**413**, Table 4.5, entry 1)



Prepared according to general procedure L using anhydride **139** (30.0 mg, 0.18 mmol), anhydrous MTBE (1.2 mL), 2,2,2-trifluoroacetophenone (17.3 μ L, 0.12 mmol) and catalyst **426** (4.2 mg, 0.0061 mmol). The reaction was stirred for 64 h at -30 °C to give a diastereomeric mixture of carboxylic acids in a 97:3 ratio (*cis:trans*). After esterification, the major diastereomer (*cis*-**413**) was purified by column chromatography eluting in gradient from 100% hexane to 5% EtOAc in hexane and isolated as a white solid (39.1 mg, 93%, 92% *ee*). M.p. 138-140 °C. $[\alpha]_D^{20} = -170.0$ (*c* 0.15, CHCl₃)

CSP-HPLC analysis. Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 85/15, 0.5 mL min⁻¹, RT, UV detection at 254 nm, retention times: 27.2 min (major enantiomer) and 37.7 min (minor enantiomer).

δ_H (400 MHz, CDCl₃): 7.99 (1 H, d, *J* 7.5, H-1), 7.50-7.41 (3 H, m, H-2 and H-2'), 7.34 (1 H, app. t, H-3), 7.32-7.23 (3 H, m, H-3' and H-4'), 7.20 (1 H, d, *J* 7.5, H-4), 4.75 (1 H, s, H-5), 3.76 (3 H, s, CO₂CH₃).

δ_C (100 MHz, CDCl₃): 168.3 (C=O), 162.0 (C=O), 134.5, 134.1 (q), 133.7 (q), 130.8, 129.9, 129.5, 129.0, 127.4, 126.6 (q, *J*_{C-F} 0.8), 125.3

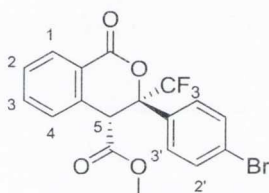
(q), 122.6 (q, $J_{\text{C-F}}$ 284.6) (q), 84.2 (q, $J_{\text{C-F}}$ 30.2) (q), 53.5, 47.9.

δ_{F} (376 MHz, CDCl_3): -76.87.

ν_{max} (film)/ cm^{-1} : 2959, 1744, 1733, 1328, 1228, 1178, 1106, 1076, 1033, 961, 711, 647.

HRMS (m/z -ESI): $[\text{M}+\text{H}]^+$ found 351.0852. $\text{C}_{18}\text{H}_{14}\text{O}_4\text{F}_3$ Requires 351.0844.

5.3.4.2.2 (3*R*,4*R*)-Methyl 3-(4-bromophenyl)-1-oxo-3-(trifluoromethyl)isochroman-4-carboxylate (*cis*-427**, Table 4.5, entry 2)**



Prepared according to general procedure L using anhydride **139** (60.0 mg, 0.37 mmol), anhydrous MTBE (3.6 mL), 4'-bromo-2,2,2-trifluoroacetophenone (56.0 μL , 0.37 mmol) and catalyst **426** (12.6 mg, 0.018 mmol, 5 mol%). The reaction was stirred at -30°C for 61 h to give a diastereomeric mixture of carboxylic acids in a 98:2 ratio (*cis:trans*). After esterification, the major diastereomer (*cis*-**427**) was purified by column chromatography eluting in gradient from 100% hexane to 10% EtOAc in hexane and isolated as a white solid (134.0 mg, 85%, 95% ee) M.p. $58\text{--}60^\circ\text{C}$. $[\alpha]_{\text{D}}^{20} = -166.4$ (c 0.28, CHCl_3).

CSP-HPLC analysis. Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.5 mL min^{-1} , RT, UV detection at 254 nm, retention times: 28.8 min (minor enantiomer) and 30.9 min (major enantiomer).

δ_{H} (400 MHz, CDCl_3): 8.01 (1 H, d, J 7.7, H-1), 7.48 (1 H, app. t, H-2), 7.43 (2 H, d, J 8.7, H-2'), 7.38 (1 H, app. t, H-3), 7.33 (1 H, d, J 8.7,

H-3'), 7.20 (1 H, d, J 7.6, H-4), 4.68 (1 H, s, H-5), 3.76 (3 H, s, CO₂CH₃).

δ_C (100 MHz, CDCl₃): 168.0 (C=O), 161.6 (C=O), 134.8, 133.8 (q), 132.9 (q), 132.3, 131.0, 129.7, 128.3, 127.4, 125.1 (q), 124.5 (q), 122.3 (q, J_{C-F} 283.8) (q), 83.9 (q, J_{C-F} 30.7) (q), 53.6, 47.7.

δ_F (376 MHz, CDCl₃): -76.93.

$\nu_{\max}$ (film)/cm⁻¹: 2958, 2924, 2852, 1741, 1600, 1460, 1330, 1245, 1179, 1103, 1070, 961, 819, 723.

HRMS (m/z -ESI): [M-H] found 426.9803. C₁₈H₁₁O₄F₃Br Requires 426.9793.

5.3.4.2.3 (3*R*,4*R*)-Methyl 3-(3-fluorophenyl)-1-oxo-3-(trifluoromethyl)isochroman-4-carboxylate (*cis*-428, Table 4.5, entry 3)



Prepared according to general procedure L using anhydride **139** (39.9 mg, 0.25 mmol), anhydrous MTBE (2.4 mL), 2,2,2,3'-tetrafluoroacetophenone (34.5 μ L, 0.25 mmol) and catalyst **426** (8.4 mg, 0.012 mmol). The reaction was stirred at -30 °C for 95 h to give a diastereomeric mixture of carboxylic acids in a 97:3 ratio (*cis:trans*). After esterification, the major diastereomer (*cis*-428) was purified by column chromatography eluting in gradient from 100% hexane to 5% EtOAc in hexane and isolated as a white solid (80.6 mg, 89%, 92% *ee*). M.p. 125-127 °C. $[\alpha]_D^{20} = -176.6$ (c 0.15, CHCl₃).

CSP-HPLC analysis. Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 98/2, 0.7 mL min⁻¹, RT, UV detection at 254 nm, retention times: 29.3 min (minor enantiomer) and 31.5 min (major enantiomer).

δ_{H} (400 MHz, CDCl_3): 8.01 (1 H, d, J 7.6, H-1), 7.48 (1 H, app. t, H-2), 7.37 (1 H, app. t, H-3), 7.32-7.13 (4 H, m, H-4, H-2', H-4' and H-6'), 7.02-6.94 (1 H, m, H-5'), 4.68 (1 H, s, H-5), 3.76 (3 H, s, CO_2CH_3).

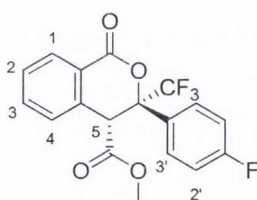
δ_{C} (100 MHz, CDCl_3): 167.8 (C=O), 162.7 (d, $J_{\text{C-F}}$ 248.5) (q), 161.4 (C=O), 136.1 (d, $J_{\text{C-F}}$ 6.9) (q), 134.5, 133.5 (q), 130.7, 130.6 (d, $J_{\text{C-F}}$, 8.3), 129.5, 127.3, 124.9 (q), 122.2 (q, $J_{\text{C-F}}$ 284.4) (q), 122.2 (d, $J_{\text{C-F}}$ 2.2), 117.0 (d, $J_{\text{C-F}}$ 20.9), 114.1 (d, $J_{\text{C-F}}$ 24.4), 83.6 (q, $J_{\text{C-F}}$ 30.9) (q), 53.4, 47.7.

δ_{F} (376 MHz, CDCl_3): -76.79 (CF_3), -110.61 (F).

ν_{max} (film)/ cm^{-1} : 2953, 2920, 1748, 1595, 1438, 1331, 1215, 1185, 1153, 1116, 1061, 1024, 828, 784, 707.

HRMS (m/z -ESI): [M-H] found 367.0602. $\text{C}_{18}\text{H}_{11}\text{O}_4\text{F}_4$ Requires 367.0593.

5.3.4.2.4 (3*R*,4*R*)-Methyl 3-(4-fluorophenyl)-1-oxo-3-(trifluoromethyl)isochroman-4-carboxylate (*cis*-**429**, Table 4.5, entry 4)



Prepared according to general procedure L using anhydride **139** (39.9 mg, 0.25 mmol), anhydrous MTBE (2.4 mL), 2,2,2,4'-tetrafluoroacetophenone (34.5 μL , 0.25 mmol) and catalyst **426** (8.4 mg, 0.012 mmol). The reaction was stirred at $-30\text{ }^{\circ}\text{C}$ for 94 h to give a diastereomeric mixture of carboxylic acids in a 97:3 ratio (*cis:trans*). After esterification, the major diastereomer (*cis*-**429**) was purified by column chromatography eluting in gradient from 100% hexane to 5% EtOAc in hexane and isolated as a white solid (71.6 mg, 79%, 92% *ee*). M.p. $77\text{--}79\text{ }^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{20} = -200.0$ (c 0.20, CHCl_3).

CSP-HPLC analysis. Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 1.0 mL min⁻¹, RT, UV detection at 254 nm, retention times: 12.9 min. (minor enantiomer) and 15.6 min. (major enantiomer).

δ_{H} (400 MHz, CDCl₃): 8.00 (1 H, d, *J* 7.7, H-1), 7.51-7.42 (3 H, m, H-2 and H-3'), 7.37 (1 H, app. t, H-3), 7.21 (1 H, d, *J* 7.6, H-4), 7.03-6.94 (2 H, m, H-2'), 4.70 (1 H, s, H-5), 3.76 (3 H, s, CO₂CH₃).

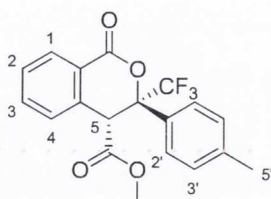
δ_{C} (100 MHz, CDCl₃): 168.1 (C=O), 163.3 (d *J*_{C-F} 250.9) (q), 161.7 (C=O), 134.7, 133.9 (q), 130.9, 129.63, 129.62 (q), 128.8 (d, *J*_{C-F} 8.7), 127.4, 125.1 (q), 122.5 (q *J*_{C-F} 284.1) (q), 116.2 (d, *J*_{C-F} 21.3), 83.9 (q, *J*_{C-F} 32.7) (q), 53.6, 47.9.

δ_{F} (376 MHz, CDCl₃): -77.08 (CF₃), -110.91 (F).

ν_{max} (film)/cm⁻¹: 2958, 2928, 1791, 1605, 1512, 1460, 1332, 1223, 1173, 1096, 1070, 964, 834, 725, 703.

HRMS (*m/z* -ESI): [M-H] found 367.0598. C₁₈H₁₁O₄F₄ Requires 367.0593.

5.3.4.2.5 (3*R*,4*R*)-Methyl 1-oxo-3-*p*-tolyl-3-(trifluoromethyl)isochroman-4-carboxylate (*cis*-**430**, Table 4.5, entry 5)



Prepared according to general procedure L using anhydride **139** (30.0 mg, 0.18 mmol), anhydrous MTBE (1.2 mL), 2,2,2,4'-tetrafluoroacetophenone (18.7 μ L, 0.12 mmol) and catalyst **426** (4.2 mg, 0.0061 mmol). The reaction was stirred at -30 °C for 86 h to give a diastereomeric mixture of carboxylic acids in a 88:12 ratio (*cis:trans*). After esterification, the major diastereomer (*cis*-**430**) was purified by column chromatography

eluting in gradient from 100% hexane to 5% EtOAc in hexane and isolated as a white solid (26.7 mg, 61%, 91% *ee*). M.p. 112-114 °C.

CSP-HPLC analysis. Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 1.0 mL min⁻¹, RT, UV detection at 254 nm, retention times: 19.4 min (major enantiomer) and 29.6 min (minor enantiomer).

δ_{H} (400 MHz, CDCl₃): 7.99 (1 H, d, *J* 7.7, H-1), 7.45 (1 H, dd, *J* 1.2, 7.7, H-2), 7.38-7.30 (3 H, m, H-3 and H-2'), 7.20 (1 H, d, *J* 7.5, H-4), 7.08 (2 H, d, *J* 8.3, H-3'), 4.73 (1 H, s, H-5), 3.75 (3 H, s, CO₂CH₃), 2.24 (3 H, s, H-5').

δ_{C} (100 MHz, CDCl₃): 168.4 (C=O), 162.1 (C=O), 140.0, 134.5, 134.2 (q), 130.8, 130.7 (q), 129.8, 129.4, 127.4, 126.5, 125.3 (q), 122.7 (q, *J*_{C-F} 284.9) (q), 84.2 (q, *J*_{C-F} 31.2) (q), 53.5, 47.9, 21.1.

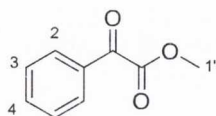
δ_{F} (376 MHz, CDCl₃): -81.77

ν_{max} (film)/cm⁻¹: 2926, 2852, 1737, 1433, 1331, 1277, 1233, 1187, 1177, 1103, 1074, 962, 810, 723.

HRMS (*m/z* -ESI): [M-H] found 363.0847. C₁₉H₁₄O₄F₃ Requires 363.0844.

5.3.5 Synthesis of α -ketoesters from phenylglyoxylic acid (435)

5.3.5.1 Methyl 2-oxo-2-phenylacetate (436)



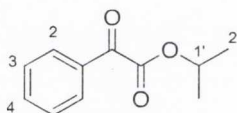
An oven dried 5 mL round-bottomed flask containing a stirring bar was charged with **435** (500.0 mg, 3.33 mmol), then fitted with a septum and kept under an argon atmosphere (balloon). Anhydrous methanol (675 μ L, 16.66 mmol) was added *via* syringe and the reaction mixture was cooled to 0 °C. Freshly distilled SOCl₂ (266 μ L

,3.66 mmol) was added dropwise *via* syringe, the reaction was allowed to warm to room temperature and it was stirred for an additional 45 min. The solvent and excess SOCl_2 was removed *in vacuo* and the residue was purified by column chromatography (hexane:diethyl ether 10:1) to yield **436** (114.8 mg, 21%) as a colourless oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³⁴⁵

δ_{H} (400 MHz, CDCl_3): 8.02 (2 H, d, J 7.5, H-2), 7.67 (1 H, t, J 7.5, H-4), 7.52 (2 H, app. t, H-3), 3.99 (3 H, s, OCH_3).

HRMS (m/z -EI): [M] found 164.0473. $\text{C}_9\text{H}_8\text{O}_3$ Requires 164.0473.

5.3.5.2 Isopropyl 2-oxo-2-phenylacetate (**437**)

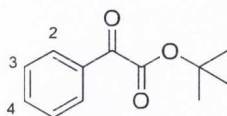


An oven dried 25 mL round-bottomed flask containing a stirring bar was charged with **435** (500.0 mg, 3.33 mmol), then fitted with a septum and kept under an argon atmosphere (balloon). Toluene (8 mL) was added *via* syringe and the solution was cooled to 0 °C. DMAP (42.6 mg 0.35 mmol) and DCC (686.0 mg, 3.32 mmol) were added, followed by anhydrous 2-propanol (640 μL , 8.37 mmol) and the reaction mixture was stirred at room temperature for 16 h. The mixture was filtered through a pad of Celite, washed with ether (5 mL), the filtrates were then concentrated *in vacuo* and the residue was purified by column chromatography (hexane:diethyl ether 10:1) to afford **437** (427.5 mg, 67%) as a colourless oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³⁴⁸

δ_{H} (400 MHz, CDCl_3): 8.00 (2 H, d, J 7.5, H-2), 7.66 (1 H, d, J 7.4, H-4), 7.52 (2 H, app. t, H-3), 5.33 (1 H, sept., J 6.3, H-1'), 1.42 (6 H, d, J 6.3, H-2')

HRMS (m/z -EI): [M] found 192.0793. $\text{C}_{11}\text{H}_{12}\text{O}_3$ Requires 192.0786.

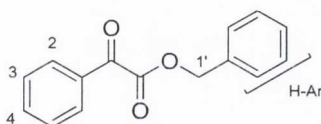
5.3.5.3 *Tert*-butyl 2-oxo-2-phenylacetate (**438**)



An oven dried 25 mL round-bottomed flask containing a stirring bar was charged with **435** (500.0 mg, 3.33 mmol), then fitted with a septum and kept under an argon atmosphere (balloon). Toluene (8 mL) was added *via* syringe and the solution was cooled to 0 °C. DMAP (42.6 mg 0.35 mmol) and DCC (686.0 mg, 3.32 mmol) were added, followed by *tert*-butyl alcohol (800 μ L, 8.36 mmol) and the reaction mixture was stirred at room temperature for 16 h. The mixture was filtered through a pad of Celite, washed with ether (5 mL), the filtrates were then concentrated *in vacuo* and the residue was purified by column chromatography (hexane:diethyl ether 10:1) to afford **438** (377.7 mg, 55%) as a colourless oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³⁴⁸

δ_{H} (400 MHz, CDCl_3): 7.97 (2 H, d, J 8.0, H-2), 7.64 (1 H, t, J 7.4, H-4), 1.63 (9 H, s, $(\text{CH}_3)_3$).

5.3.5.4 Benzyl 2-oxo-2-phenylacetate (**439**)



An oven dried 10 mL round-bottomed flask containing a stirring bar was charged with **435** (500.0 mg, 3.33 mmol), toluene (3 mL) and benzyl alcohol (450 μ L, 4.34 mmol), it was fitted then with a condenser and the reaction mixture was heated at 80 °C for 16 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (hexane:diethyl ether 10:1) to yield **439** (384.1 mg, 48%) as a pale yellow oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³⁴⁶

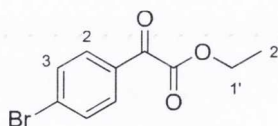
δ_{H} (400 MHz, CDCl_3): 7.97 (2 H, d, J 7.8, H-2), 7.65 (1 H, t, J 7.4, H-4), 7.55-7.32 (7 H, m, H-3 and H-Ar), 5.42 (2 H, s, H-1').

HRMS (m/z -ESI): [M-H] found 239.0707. $\text{C}_{15}\text{H}_{11}\text{O}_3$ Requires 239.0708.

5.3.6 Procedure M: general protocol for the synthesis of ethyl α -ketoesters by addition of Grignard reagents to diethyl oxalate (447)

An oven dried 25 mL round-bottomed flask containing a stirring bar was charged with freshly ground magnesium (1.2 equiv.) and anhydrous THF (2 mL), it was then fitted with a condenser and kept under an argon atmosphere (balloon). The relevant aryl bromide (1.1 equiv.) was added dropwise *via* syringe down the condenser and the reaction mixture was then heated at reflux temperature for 1 h. The resulting solution of Grignard reagent was taken up with a syringe and added dropwise over 1 h using a syringe pump to a solution of **447** (680 μL , 5.05 mmol, 1.0 equiv.) in dry THF (10 mL) at $-78\text{ }^\circ\text{C}$. Upon completion of the addition, the reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1 h, then warmed to room temperature. A 2 M aqueous solution of HCl (10 mL) and H_2O (10 mL) were added and the solution was extracted with Et_2O (4 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO_4 , filtered, the solvent was removed *in vacuo* and the residue was purified either by column chromatography or by distillation at reduced pressure to afford the corresponding ethyl α -ketoester.

5.3.6.1 Ethyl 2-(4-bromophenyl)-2-oxoacetate (448a)

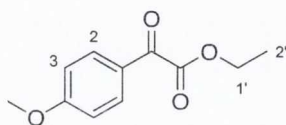


Prepared according to general procedure M using 1,4-dibromobenzene (1.30 mg, 5.51 mmol), magnesium (145.8 mg, 6.00 mmol), diethyl oxalate (680 μL , 5.05 mmol) and THF (15 mL). The crude product was purified by Kugelrohr distillation to yield α -ketoester **448a** (324.6 mg, 25%) as a colourless oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³¹⁰

δ_{H} (400 MHz, CDCl_3): 7.90 (2 H, d, J 8.6, H-2), 7.66 (2 H, d, J 8.6, H-3), 4.45 (2 H, q, J 7.2, H-1'), 1.42 (3 H, t, J 7.2, H-2').

HRMS (m/z -EI): [M] found 255.9728. $\text{C}_{10}\text{H}_9\text{O}_3\text{Br}$ Requires 255.9735.

5.3.6.2 Ethyl 2-(4-methoxyphenyl)-2-oxoacetate (448b)

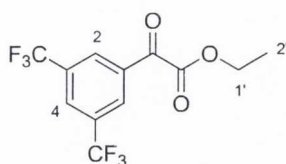


Prepared according to general procedure M using 4-bromoanisole (1.3 mL, 10.36 mmol), magnesium (274.6 mg, 11.30 mmol), diethyl oxalate (1.3 mL, 9.57 mmol) and THF (25 mL). The crude product was purified by column chromatography (hexane:EtOAc 20:1) to yield α -ketoester **448b** (1.23 g, 62%) as a colourless oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³¹⁰

δ_{H} (400 MHz, CDCl_3): 8.01 (2 H, d, J 8.9, H-2), 6.98 (2 H, d, J 8.9, H-3), 4.44 (2 H, q, J 7.1, H-1'), 3.90 (3 H, s, OCH_3), 1.42 (3 H, t, J 7.1, H-2').

HRMS (m/z -EI): [M] found 208.0732. $\text{C}_{11}\text{H}_{12}\text{O}_4$ Requires 208.0736.

5.3.6.3 Ethyl 2-(3,5-bis(trifluoromethyl)phenyl)-2-oxoacetate (488c)



Prepared according to general procedure M using the commercially available 3,5-bis(trifluoromethyl)phenylmagnesium bromide (0.5 M in THF, 6.0 mL, 3.00 mmol), diethyl oxalate (370 μL , 2.73 mmol) and THF (10 mL). The crude product was purified

by column chromatography (hexane:EtOAc 20:1) to yield α -ketoester **448c** (437.4 mg, 51%) as a light yellow oil.

δ_{H} (400 MHz, CDCl_3): 8.55 (2 H, s, H-2), 8.15 (1 H, s, H-4), 4.50 (2 H, q, J 7.2, H-1'), 1.46 (3 H, t, J 7.2, H-2').

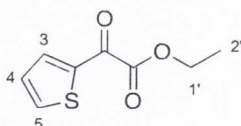
δ_{C} (100 MHz, CDCl_3): 182.9 (C=O), 161.9 (C=O), 134.6 (q), 132.9 (q, $J_{\text{C-F}}$ 34.2) (q), 130.4 (q, $J_{\text{C-F}}$ 3.8), 128.0 (sept., $J_{\text{C-F}}$ 3.5), 122.9 (q, $J_{\text{C-F}}$ 272.4) (q), 63.5, 14.3.

δ_{F} (376 MHz, CDCl_3): -63.13

ν_{max} (film)/ cm^{-1} : 3096, 2991, 1735, 1705, 1276, 1171, 1130, 1033, 913, 847, 698, 681.

HRMS (m/z -EI): $[\text{M}-\text{C}_2\text{H}_5\text{O}_2]$ found 241.0080. $\text{C}_9\text{H}_3\text{OF}_6$ Requires 241.0088.

5.3.6.4 Ethyl 2-oxo-2-(thiophen-2-yl)acetate (**448d**)

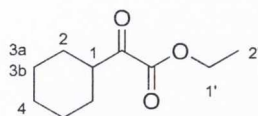


Prepared according to general procedure M using 2-bromothiophene (1.7 mL, 10.86 mmol), magnesium (287.8 mg, 11.84 mmol), diethyl oxalate (1.3 mL, 9.57 mmol) and THF (25 mL). The crude product was purified by distillation at reduced pressure to yield α -ketoester **448d** (951.9 mg, 54%) as a dark yellow oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³⁴⁷

δ_{H} (400 MHz, CDCl_3): 8.14 (1 H, d, J 3.8, H-5), 7.82 (1 H, d, J 4.9, H-3), 7.20 (1 H, app. t, H-4), 4.44 (2 H, q, J 7.2, H-1'), 1.43 (3 H, t, J 7.2, H-2').

HRMS (m/z -EI): $[\text{M}]$ found 184.0188. $\text{C}_8\text{H}_8\text{O}_3\text{S}$ Requires 184.0194.

5.3.6.5 Ethyl 2-cyclohexyl-2-oxoacetate (**448e**)

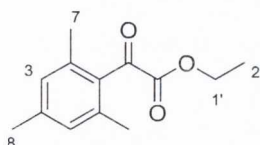


Prepared according to general procedure M using the commercially available cyclohexylmagnesium chloride (2.0 M in Et₂O, 3.0 mL, 6.00 mmol), diethyl oxalate (740 μ L, 5.45 mmol) and THF (15 mL). The crude product was purified by column chromatography (hexane:EtOAc 20:1) to yield α -ketoester **448e** (682.8 mg, 68%) as a colourless oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³¹⁰

δ_{H} (400 MHz, CDCl₃): 4.31 (2 H, q, J 7.1, H-1'), 3.10-2.96 (1 H, m, H-1), 1.99-1.58 (6 H, m, H-2 and H-3a), 1.45-1.06 (7 H, m, H-3b, H-4 and H-2').

HRMS (m/z -ESI): $[M+H]^+$ found 185.1178. C₁₀H₁₇O₃ Requires 185.1178.

5.3.6.6 Ethyl 2-mesityl-2-oxoacetate (**448f**)

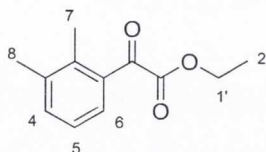


Prepared according to general procedure M using the commercially available 2-mesitylmagnesium bromide (1.0 M in THF, 5.0 mL, 5.00 mmol) diethyl oxalate (620 μ L, 4.55 mmol) and THF (15 mL). The crude product was purified by column chromatography (hexane:EtOAc 20:1) to yield α -ketoester **448f** (225.5 mg, 23%) as a colourless oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³⁴⁷

δ_{H} (400 MHz, CDCl₃): 6.88 (2 H, s, H-3), 4.37 (2 H, q, J 7.2, H-1'), 2.30 (3 H, s, H-8), 2.25 (6 H, s, H-7), 1.37 (3 H, t, J 7.2, H-2').

HRMS (m/z -ESI): $[M+Na]^+$ found 243.0995. $C_{13}H_{16}O_3Na$ Requires 243.0997.

5.3.6.7 Ethyl 2-(2,3-dimethylphenyl)-2-oxoacetate (**448g**)



Prepared according to general procedure M using 1-bromo-2,3-dimethylbenzene (1.0 mL, 7.38 mmol), magnesium (195.5 mg, 8.05 mmol), diethyl oxalate (910 μ L, 6.71 mmol) and THF (20 mL). The crude product was purified by column chromatography (hexane:EtOAc 20:1) to yield α -ketoester **448g** (816.5 mg, 59%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$): 7.46 (1 H, d, J 7.8, H-6), 7.38 (1 H, d, J 7.4, H-4), 7.21 (1 H, app. t, H-5), 4.42 (2 H, q, J 7.2, H-1'), 2.46 (3 H, s, H-7), 2.34 (3 H, s, H-8), 1.41 (3 H, t, J 7.2, H-2').

δ_C (100 MHz, $CDCl_3$): 189.8 (C=O), 164.7 (C=O), 139.1 (q), 138.9 (q), 135.2, 132.8 (q), 129.6, 125.6, 62.5, 20.6, 16.7, 14.3.

ν_{max} (film)/ cm^{-1} : 2983, 1733, 1685, 1454, 1308, 1215, 1197, 1092, 1013, 971, 682.

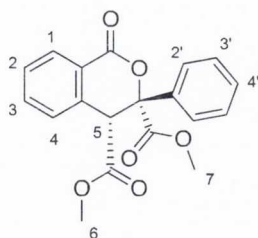
HRMS (m/z -EI): $[M]$ found 206.0935. $C_{12}H_{14}O_3$ Requires 206.0943.

5.3.7 Procedure N: general protocol for asymmetric cycloaddition reactions between anhydride **139** and α -ketoesters (Table 4.7 and Table 4.9)

An oven dried 20 mL reaction vessel containing a stirring bar under argon atmosphere was charged with the relevant α -ketoester (0.246 mmol, 1.0 equiv.). Anhydrous MTBE (0.1 M or 0.02 M) was added *via* syringe and the solution was cooled to -15 $^{\circ}C$. Anhydride **139** (1.0 equiv.) was added to the reaction immediately followed by the cinchona-based catalyst (either **426** or **450**, 5 mol%) and the reaction mixture was

stirred for the time indicated in Table 4.7 or Table 4.9. The yield was monitored by ^1H NMR spectroscopic analysis using *p*-iodoanisole (0.5 equiv.) as an internal standard. The reaction was then diluted with EtOAc (15 mL) and extracted with an aqueous solution of NaHCO_3 (10% w/v, 3 x 10 mL). The combined aqueous extracts were acidified with HCl (2.0 N) and the mixture was then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over MgSO_4 and the solvent was removed *in vacuo* to yield the diastereomeric mixture of carboxylic acids. The diastereomeric ratio of the products was determined via ^1H NMR spectroscopic analysis of the crude mixture, the carboxylic acids were then suspended in anhydrous MTBE (0.1 M). Dry MeOH (750.0 μL), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 1.2 equiv.) were added *via* syringe and the reaction was allowed to stir for 30 min at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash chromatography to isolate the major diastereomer. The enantiomeric excess of the products was determined by CSP-HPLC using the conditions indicated for each case.

5.3.7.1 (3*R*,4*R*)-Dimethyl 1-oxo-3-phenylisochroman-3,4-dicarboxylate (*cis*-440, Table 4.7, entry 2)



Prepared according to general procedure N using anhydride **139** (20.0 mg, 0.12 mmol), anhydrous MTBE (1.2 mL), α -ketoester **436** (17.5 μL , 0.12 mmol) and catalyst **426** (4.2 mg, 0.0061 mmol). The reaction was stirred at $-15\text{ }^\circ\text{C}$ for 38 h to give a diastereomeric mixture of carboxylic acids in a 89:11 ratio (*cis:trans*). After esterification, the major diastereomer (*cis*-440) was purified by column chromatography eluting in gradient from 100% hexane to 10% EtOAc in hexane and isolated as a white solid (28.6 mg, 70%, 79% *ee*). M.p. 155-156 $^\circ\text{C}$

CSP-HPLC analysis. Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min⁻¹, RT, UV detection at 254 nm, retention times: 47.7 min (minor enantiomer) and 73.5 min (major enantiomer).

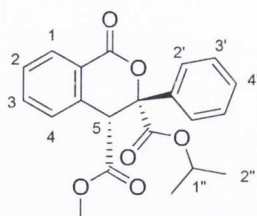
δ_{H} (400 MHz, CDCl₃): 8.00 (1 H, d, *J* 7.7 Hz, H-1), 7.55-7.45 (3 H, m, H-3 and H-2'), 7.42 (1 H, d, *J* 7.6 Hz, H-4), 7.35 (1 H, app. t, H-2), 7.30-7.18 (3 H, m, H-2' and H-3'), 4.95 (1 H, s, H-5), 3.81 (3 H, s, H-7), 3.71 (3 H, s, H-6).

δ_{C} (100 MHz, CDCl₃): 169.7 (C=O), 169.4 (C=O), 162.9 (C=O), 136.7 (q), 134.6, 133.7 (q), 130.5, 129.3, 129.15, 129.12, 129.08, 125.6, 124.4 (q), 84.4 (q), 53.7, 53.2, 50.5.

ν_{max} (film)/cm⁻¹: 2958, 1736, 1727, 1600, 1434, 1270, 1222, 1158, 1112, 1081, 972, 739, 722.

HRMS (*m/z* -ESI): [M-H] found 339.0872. C₁₉H₁₅O₆ Requires 339.0869.

5.3.7.2 (3*R*,4*R*)-3-Isopropyl 4-methyl 1-oxo-3-phenylisochroman-3,4-dicarboxylate (*cis*-**441**, Table 4.7, entry 3)



Prepared according to general procedure N using anhydride **139** (20.0 mg, 0.12 mmol), anhydrous MTBE (1.2 mL), α -ketoester **437** (22.3 μ L, 0.12 mmol) and catalyst **426** (4.2 mg, 0.0061 mmol). The reaction was stirred at -15 °C for 38 h to give a diastereomeric mixture of carboxylic acids in a 82:18 ratio (*cis:trans*). After esterification, the major diastereomer (*cis*-**441**) was purified by column chromatography eluting in gradient from 100% hexane to 10% EtOAc in hexane and isolated as a white solid (33.1 mg, 75%, 84% *ee*). M.p. 138-140 °C. $[\alpha]_{\text{D}}^{20} = -81.0$ (*c* 0.10, CHCl₃)

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 98/2, 0.7 mL min⁻¹, RT, UV detection at 254 nm, retention times: 46.2 min (minor enantiomer) and 51.7 min (major enantiomer).

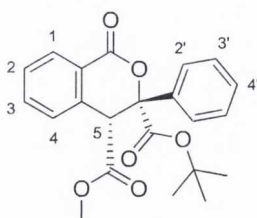
δ_{H} (400 MHz, CDCl₃): 7.98 (1 H, d, *J* 7.7, H-1), 7.53-7.44 (3 H, m, H-3 and H-2'), 7.42 (1 H, d, *J* 7.4, H-4), 7.33 (1 H, app. t, H-2), 7.28-7.15 (3 H, m, H-3' and H-4'), 5.05 (1 H, app. sept., H-1''), 4.93 (1 H, s, H-5), 3.69 (3 H, s, CO₂CH₃), 1.25 (6 H, app. d, H-2'').

δ_{C} (100 MHz, CDCl₃): 169.5 (C=O), 168.1 (C=O), 163.1 (C=O), 137.0 (q), 134.5, 133.8 (q), 130.4, 129.2, 129.0, 128.94, 128.92, 125.6, 124.5 (q), 81.1 (q), 70.6, 53.0, 50.1, 29.8.

ν_{max} (film)/cm⁻¹: 2922, 2853, 1758, 1741, 1720, 1599, 1459, 1265, 1223, 1172, 1121, 1100, 1086, 974, 733.

HRMS (*m/z* -ESI): [M-H] found 367.1190. C₂₁H₁₉O₆ Requires 367.1182.

5.3.7.3 (3*R*,4*R*)-3-Tert-butyl 4-methyl 1-oxo-3-phenylisochroman-3,4-dicarboxylate (*cis*-**442**, Table 4.7, entry 4)



Prepared according to general procedure N using anhydride **139** (20.0 mg, 0.12 mmol), anhydrous MTBE (1.2 mL), α -ketoester **438** (24.0 μ L, 0.12 mmol) and catalyst **426** (4.2 mg, 0.0061 mmol). The reaction was stirred at -15 °C for 94 h to give a diastereomeric mixture of carboxylic acids in a 80:20 ratio (*cis:trans*). After esterification, the major diastereomer (*cis*-**442**) was purified by column chromatography eluting in gradient from 100% hexane to 10% EtOAc in hexane and isolated as a white solid (25.2 mg, 55%, 73% *ee*).

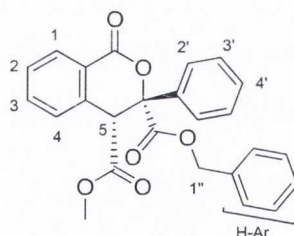
CSP-HPLC analysis. Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min⁻¹, RT, UV detection at 254 nm, retention times: 24.2 min (minor enantiomer) and 35.9 min (major enantiomer).

δ_{H} (400 MHz, CDCl₃): 8.00 (1 H, d, *J* 7.7, H-1), 7.54-7.38 (4 H, m, H-3, H-4 and H-2'), 7.34 (1 H, app. t, H-3), 7.29-7.17 (3 H, m, H-3' and H-4'), 4.87 (1 H, s, H-5), 3.71 (3 H, s, CO₂CH₃), 1.42 (9 H, s, C(CH₃)₃).

δ_{C} (100 MHz, CDCl₃): 169.5 (C=O), 167.0 (C=O), 163.0 (C=O), 137.1 (q), 134.3, 133.8 (q), 130.3, 129.0, 128.74, 128.69, 128.6, 125.4, 124.5 (q), 84.1 (q), 83.6 (q), 52.8, 50.1, 27.6.

HRMS (*m/z* -ESI): [M-H] found 381.1326. C₂₂H₂₁O₆ Requires 381.1338.

5.3.7.4 (3*R*,4*R*)-3-Benzyl 4-methyl 1-oxo-3-phenylisochroman-3,4-dicarboxylate (*cis*-**443**, Table 4.7, entry 5)



Prepared according to general procedure N using anhydride **139** (20.0 mg, 0.12 mmol), anhydrous MTBE (1.2 mL), α -ketoester **439** (24.4 μ L, 0.12 mmol) and catalyst **426** (4.2 mg, 0.0061 mmol). The reaction was stirred at -15 °C for 67 h to give a diastereomeric mixture of carboxylic acids in a 88:12 ratio (*cis:trans*). After esterification, the major diastereomer (*cis*-**433**) was purified by column chromatography eluting in gradient from 100% hexane to 10% EtOAc in hexane and isolated a white solid (32.8 mg, 52%, 80% *ee*). [α]_D²⁰ = -82.0 (*c* 0.05, CHCl₃).

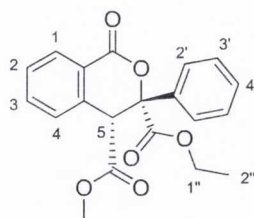
CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min⁻¹, RT, UV detection at 254 nm, retention times: 36.4 min (minor enantiomer) and 46.7 min (major enantiomer).

δ_{H} (400 MHz, CDCl₃): 7.99 (1 H, d, *J* 7.8, H-1), 7.54-7.44 (3 H, m, H-3 and H-2'), 7.41 (1 H, d, *J* 7.4, H-4), 7.34 (1 H, app. t, H-2), 7.32-7.18 (8 H, m, H-3', H-4' and H-Ar), 5.27 (1 H, d, *J* 12.2, H-1''a), 5.17 (1 H, d, *J* 12.2, H-1''b), 4.93 (1 H, s, H-5), 3.54 (3 H, s, CO₂CH₃).

δ_{C} (100 MHz, CDCl₃): 169.3 (C=O), 168.5 (C=O), 162.9 (C=O), 136.7 (q), 135.1 (q), 134.6, 133.8 (q), 130.5, 129.2, 129.1, 129.07, 129.0, 128.6, 128.5, 128.4, 125.7, 124.5 (q), 84.3 (q), 68.1, 53.0, 50.2.

HRMS (*m/z* -ESI): [M-H] found 415.1198. C₂₅H₁₉O₆ Requires 415.1182.

5.3.7.5 (3*R*,4*R*)-3-Ethyl 4-methyl 1-oxo-3-phenylisochroman-3,4-dicarboxylate (*cis*-**434**, Table 4.9, entry 1)



Prepared according to general procedure N using anhydride **139** (39.9 mg, 0.25 mmol), anhydrous MTBE (0.02 M, 12.0 mL), α -ketoester **433** (39.1 μ L, 0.25 mmol) and catalyst **450** (10.2 mg, 0.012 mmol). The reaction was stirred at -15 °C for 36 h to give a diastereomeric mixture of carboxylic acids in a 93:7 ratio (*cis:trans*). After esterification, the major diastereomer (*cis*-**434**) was purified by column chromatography eluting in gradient from 100% hexane to 10% EtOAc in hexane and isolated as a white solid (77.5 mg, 89%, 92% *ee*). M.p. 132-134 °C. [α]_D²⁰ = -82.0 (*c* 0.10, CHCl₃).

CSP-HPLC analysis. Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min⁻¹, RT, UV detection at 254 nm, retention times: 35.9 min (minor enantiomer) and 44.0 min (major enantiomer).

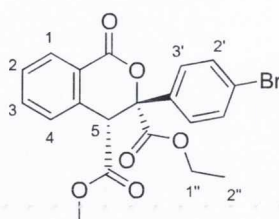
δ_{H} (400 MHz, CDCl₃): 8.00 (1 H, d, *J* 7.7, H-1), 7.54-7.45 (3 H, m, H-3 and H-2'), 7.42 (1 H, d, *J* 7.5, H-4), 7.35 (1 H, app. t, H-2), 7.30-7.18 (3 H, m, H-3' and H-4'), 4.95 (1 H, s, H-5), 4.26 (2 H, q, *J* 7.2, H-1''), 3.70 (3 H, s, CO₂CH₃), 1.26 (3 H, t, *J* 7.2, H-2'').

δ_{C} (100 MHz, CDCl₃): 169.5 (C=O), 168.9 (C=O), 163.0 (C=O), 136.9 (q), 134.6, 133.8 (q), 130.5, 129.2, 129.1, 129.03, 129.01, 125.6, 124.5 (q), 84.3 (q), 62.8, 53.1, 50.4, 14.0.

ν_{max} (film)/cm⁻¹: 2949, 2924, 2852, 1759, 1738, 1722, 1460, 1276, 1259, 1218, 1147, 1084, 1048, 721, 690.

HRMS (*m/z* -ESI): [M+Na]⁺ found 377.0996. C₂₀H₁₈O₆Na Requires 377.1001.

5.3.7.5.1 3-Ethyl 4-methyl 3-(4-bromophenyl)-1-oxoisochroman-3,4-dicarboxylate (*cis*-**454** – *trans*-**454**, Table 4.9, entry 2)



Prepared according to general procedure N using anhydride **139** (40.9 mg, 0.25 mmol), anhydrous MTBE (0.02 M, 12.0 mL), α -ketoester **452a** (64.9 mg, 0.25 mmol) and catalyst **450** (10.2 mg, 0.012 mmol). The reaction was stirred at -15 °C for 41 h to give a diastereomeric mixture of carboxylic acids in a 97:3 ratio (*cis:trans*). After esterification, both diastereomers (*cis*-**454** and *trans*-**454**) were purified by column chromatography eluting in gradient from 100% hexane to 10% EtOAc in hexane and isolated as a pale yellow solid (99.0 mg, 94%, combined yield for both

diastereoisomers, **cis-454**: 95% *ee*, **trans-454**: 91% *ee*. M.p. 145-147 °C. $[\alpha]_D^{20} = -96.6$ (*c* 0.15, CHCl₃). * Major diastereomer assigned for ¹H NMR and ¹³C NMR.

* $[\alpha]_D^{20}$ referred to a mixture of **cis-454:trans-454** in a 97:3 ratio

CSP-HPLC analysis. Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min⁻¹, RT, UV detection at 254 nm, retention times: 34.9 min (major enantiomer) and 58.1 min (minor enantiomer).

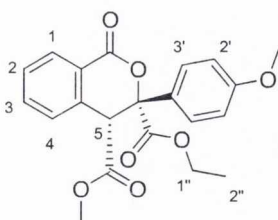
δ_H (400 MHz, CDCl₃): 8.00 (1 H, d, *J* 7.7, H-1), 7.53 (1 H, app. t, H-3), 7.45-7.31 (6 H, H-2, H-4, H-2' and H-3'), 4.88 (1 H, s, H-5), 4.26 (2 H, q, *J* 7.1, H-1''), 3.70 (3 H, s, CO₂CH₃), 1.26 (3 H, t, *J* 7.1, H-2'').

δ_C (100 MHz, CDCl₃): 169.2 (C=O), 168.6 (C=O), 162.7 (C=O), 136.1 (q), 134.8, 133.5 (q), 132.2, 130.6, 129.4, 129.1, 127.4, 124.3 (q), 123.5 (q), 83.9 (q), 63.0, 53.2, 50.2, 14.0.

$\nu_{\max}$ (film)/cm⁻¹: 2991, 2953, 2926, 2852, 1758, 1735, 1724, 1602, 1457, 1273, 1222, 1119, 1041, 1005, 971, 786, 728.

HRMS (*m/z* -ESI): [M-H] found 383.1129. C₂₁H₁₉O₇ Requires 383.1131.

5.3.7.5.2 (3*R*,4*R*)-3-Ethyl 4-methyl 3-(4-methoxyphenyl)-1-oxisochroman-3,4-dicarboxylate (**cis-455**, Table 4.9, entry 3)



Prepared according to general procedure N using anhydride **139** (27.6 mg, 0.17 mmol), anhydrous MTBE (0.02 M, 8.5 mL), α -ketoester **452b** (35.4 mg, 0.17 mmol) and catalyst **450** (14.2 mg, 0.017 mmol, 10 mol%). The reaction was stirred at -15 °C for 72 h to give a diastereomeric mixture of carboxylic acids in a 81:19 ratio (*cis:trans*). After

esterification, the major diastereomer (*cis*-**455**) was purified by column chromatography eluting in gradient from 100% hexane to 20% EtOAc in hexane and isolated as a white solid (39.9 mg, 61%, 87% *ee*). M.p. 132-134 °C. $[\alpha]_D^{20} = -93.3$ (*c* 0.15, CHCl₃).

CSP-HPLC analysis. Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 80/20, 1.0 mL min⁻¹, RT, UV detection at 254 nm, retention times: 25.0 min. (major enantiomer) and 44.7 min. (minor enantiomer).

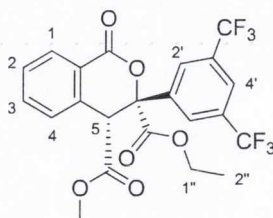
δ_H (400 MHz, CDCl₃): 7.98 (1 H, d, *J* 7.6, H-1), 7.50 (1 H, app. t, H-3), 7.45-7.30 (4 H, m, H-2, H-4 and H-3'), 6.74 (2 H, d, *J* 8.9, H-2'), 4.90 (1 H, s, H-5), 4.24 (2 H, q, *J* 7.1 H-1''), 3.69 (3 H, s, CO₂CH₃), 3.68 (3 H, s, OCH₃), 1.24 (3 H, t, *J* 7.1, H-2'').

δ_C (100 MHz, CDCl₃): 169.6 (C=O), 169.2 (C=O), 163.2 (C=O), 160.0 (q), 134.7, 134.1 (q), 130.6, 129.3, 129.2, 128.8 (q), 127.2, 124.7 (q), 114.4, 84.1 (q), 62.8, 55.4, 53.2, 50.3, 14.2.

$\nu_{\max}$ (film)/cm⁻¹: 2966, 2924, 2853, 1742, 1723, 1604, 1510, 1246, 1225, 1188, 1114, 1089, 1022, 853, 730.

HRMS (*m/z* -ESI): [M-H] found 431.0115. C₂₀H₁₆O₆Br Requires 431.0130.

5.3.7.5.3 (3*R*,4*R*)-3-Ethyl 4-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-1-oxoisochroman-3,4-dicarboxylate (*cis*-**456**, Table 4.9, entry 4)



Prepared according to general procedure N using anhydride **139** (43.6 mg, 0.27 mmol), anhydrous MTBE (0.02 M, 13.5 mL), α -ketoester **452c** (84.4 mg, 0.27 mmol) and catalyst **450** (11.2 mg, 0.017 mmol). The reaction was stirred at -50 °C for 94 h to give a diastereomeric mixture of carboxylic acids in a 97:3 ratio (*cis:trans*). After

esterification, the major diastereomer (*cis*-**456**) was purified by column chromatography eluting in gradient from 100% hexane to 20% EtOAc in hexane and isolated as a white solid (121.8 mg, 92%, 85% *ee*). M.p. 147-149 °C. $[\alpha]_D^{20} = -64.4$ (*c* 0.25, CHCl₃).

CSP-HPLC analysis. Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.3 mL min⁻¹, RT, UV detection at 254 nm, retention times: 20.7 min (minor enantiomer) and 36.3 min (major enantiomer).

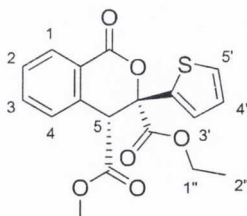
δ_H (400 MHz, CDCl₃): 8.03 (1 H, dd, *J* 1.0, 7.7, H-1), 7.95 (2 H, s, H-2'), 7.76 (1 H, s, H-4'), 7.57 (1 H, app. t, H-3), 7.46 (1 H, d, *J* 7.6, H-4), 7.41 (1 H, app. t, H-2), 4.93 (1 H, s, H-5), 4.31 (2 H, app. q, H-1''), 3.73 (3 H, s, CO₂CH₃), 1.29 (3 H, t, *J* 7.1, H-2'').

δ_C (100 MHz, CDCl₃): 168.6 (C=O), 167.9 (C=O), 161.9 (C=O), 140.1 (q), 135.2, 132.9 (q), 132.6 (q, *J*_{C-F} 33.8) (q), 130.8, 129.9, 129.0, 126.1 (m), 124.0 (q), 122.8 (q, *J*_{C-F} 273.6) (q), 83.4 (q), 63.6, 53.4, 50.2, 14.0.

$\nu_{\max}$ (film)/cm⁻¹: 2966, 2924, 1761, 1734, 1375, 1276, 1227, 1169, 1127, 1072, 899, 681.

HRMS (*m/z* -ESI): [M-H] found 489.0773. C₂₂H₁₅O₆F₆ Requires 489.0773.

5.3.7.5.4 (3*S*,4*R*)-3-Ethyl 4-methyl 1-oxo-3-(thiophen-2-yl)isochroman-3,4-dicarboxylate (*cis*-**457**, Table 4.9, entry 4)



Prepared according to general procedure N using anhydride **139** (39.0 mg, 0.24 mmol), anhydrous MTBE (0.02 M, 12.0 mL), α -ketoester **452d** (44.0 mg, 0.24 mmol) and catalyst **450** (10.0 mg, 0.012 mmol). The reaction was stirred at -15 °C for 86 h to give

a diastereomeric mixture of carboxylic acids in a 94:6 ratio (*cis:trans*). After esterification, the major diastereomer (**cis-457**) was purified by column chromatography eluting in gradient from 100% hexane to 10% EtOAc in hexane and isolated as a white solid (64.9 mg, 75%, 86% *ee*). M.p. 108-112 °C. $[\alpha]_D^{20} = -105.2$ (*c* 0.25, CHCl₃).

CSP-HPLC analysis. Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min⁻¹, RT, UV detection at 254 nm, retention times: 28.4 min (major enantiomer) and 47.8 min. (minor enantiomer).

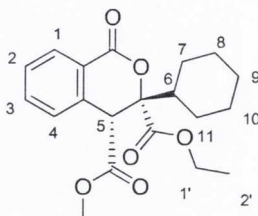
δ_H (400 MHz, CDCl₃): 8.03 (1 H, d, *J* 7.8, H-1), 7.56 (1 H, app. t, H-3), 7.49 (1 H, d, *J* 7.6, H-4), 7.40 (1 H, app. t, H-2), 7.17 (1 H, d, *J* 4.8, H-5'), 7.09 (1 H, d, *J* 3.4 H-3'), 6.83 (1 H, app. t, H-4'), 4.87 (1 H, s, H-5), 4.39-4.24 (2 H, m, H-1''), 3.69 (3 H, s, CO₂CH₃), 1.30 (3 H, app. t, H-2'').

δ_C (100 MHz, CDCl₃): 169.0 (C=O), 168.2 (C=O), 162.3 (C=O), 140.4 (q), 134.7, 133.7 (q), 130.6, 129.3, 129.2, 127.2, 127.00, 126.98, 124.1 (q), 82.7 (q), 63.0, 53.1, 51.3, 14.0.

$\nu_{\max}$ (film)/cm⁻¹: 3105, 2962, 2924, 1734, 1601, 1459, 1432, 1254, 1218, 1112, 1078, 727.

HRMS (*m/z* -ESI): [M-H] found 359.0585. C₁₈H₁₅O₆S Requires 359.0589.

5.3.7.5.5 (3*S*,4*R*)-3-Ethyl 4-methyl 3-cyclohexyl-1-oxoisochroman-3,4-dicarboxylate (**cis-458**, Table 4.9, entry 5)



Prepared according to general procedure N using anhydride **139** (23.1 mg, 0.14 mmol), anhydrous MTBE (0.02 M, 7.4 mL), α -ketoester **452e** (26.3 mg, 0.14 mmol) and

catalyst **450** (10.0 mg, 0.012 mmol). The reaction was stirred at -15 °C for 72 h to give a diastereomeric mixture of carboxylic acids in a 90:10 ratio (*cis:trans*). After esterification, the major diastereomer (*cis*-**458**) was purified by column chromatography eluting in gradient from 100% hexane to 10% EtOAc in hexane and isolated as a white solid (42.9 mg, 85%, 66% *ee*). M.p. 99-102 °C.

CSP-HPLC analysis. Chiralcel OJ-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.7 mL min⁻¹, RT, UV detection at 254 nm, retention times: 20.3 min (major enantiomer) and 32.9 min (minor enantiomer).

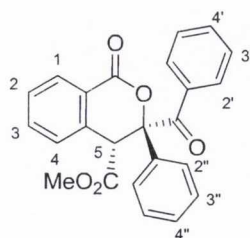
δ_{H} (400 MHz, CDCl₃): 8.06 (1 H, d, *J* 7.6, H-1), 7.50 (1 H, app. t, H-3), 7.42 (1 H, app. t, H-2), 7.26 (1 H, d, *J* 7.6, H-4), 4.50 (1 H, s, H-5), 4.04-3.88 (2 H, m, H-1'), 3.66 (3 H, s, CO₂CH₃), 2.34-2.23 (1 H, m, H-6), 2.10-1.90 (4 H, m, H-7), 1.88-1.72 (4 H, m, H-8), 1.73-1.61 (1 H, m, H-9).

δ_{C} (100 MHz, CDCl₃): 169.4 (C=O), 169.0 (C=O), 163.9 (C=O), 134.9 (q), 133.9, 130.3, 129.4, 127.8, 125.8 (q), 87.9 (q), 62.1, 52.9, 48.5, 44.3, 29.8, 27.5, 27.1, 26.5, 26.24, 16.6.

ν_{max} (film)/cm⁻¹: 2929, 2853, 1730, 1605, 1466, 1224, 1189, 1167, 1074, 1018, 998, 730, 696.

HRMS (*m/z* -ESI): [M-H] found 359.1495. C₂₀H₂₃O₆ Requires 359.1495.

5.3.7.8.1 (3*R*,4*R*)-Methyl 3-benzoyl-1-oxo-3-phenylisochroman-4-carboxylate



An oven dried 10 mL reaction vessel containing a stirring bar under argon atmosphere was charged with the anhydride **139** (40.0 mg, 0.25 mol). Anhydrous MTBE (4.8 mL)

was added *via* syringe and the solution was cooled to -15 °C. Ketone **461** (51.7 mg, 0.25 mmol) was added to the reaction immediately followed by catalyst **426** (8.4 mg, 0.012 mmol, 5 mol%) and the reaction mixture was stirred at -15 °C for 84 h. The reaction was then diluted with EtOAc (15 mL) and extracted with an aqueous solution of NaHCO₃ (10% w/v, 3 x 10 mL). The combined aqueous extracts were acidified with HCl (2.0 N) and the mixture was then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over MgSO₄ and the solvent was removed *in vacuo* to yield the diastereomeric mixture of carboxylic acids which were suspended in anhydrous MTBE (0.1 M). Dry MeOH (750.0 µL), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150.0 µL) were added *via* syringe and the reaction was allowed to stir for 30 min at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash chromatography eluting in gradient from 100% hexane to 20% EtOAc in hexane. The major diastereomer *cis*-**463** was isolated pure (78.2 mg, 81%, 99% *ee*) as an off-white solid. M.p. 138-140 °C. $[\alpha]_D^{20} = 82.5$ (*c* 0.20, CHCl₃).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 98/2, 1.0 mL min⁻¹, RT, UV detection at 254 nm, retention times: 24.6 min (minor enantiomer) and 30.1 min (major enantiomer).

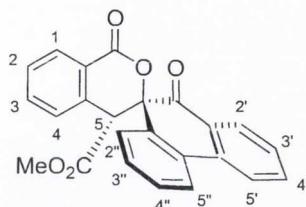
δ_H (400 MHz, CDCl₃): 8.10 (1 H, d, *J* 7.7, H-1), 8.03 (2 H, d, *J* 7.4, H-2'), 7.53-7.43 (4 H, m, H-3, H-4' and H-2''), 7.42-7.32 (4 H, m, H-2, H-4 and H-3'), 7.30-7.23 (2 H, m, H-3''), 7.22-7.15 (1 H, m, H-4''), 4.91 (1 H, s, H-5), 3.66 (3 H, s, CO₂CH₃).

δ_C (100 MHz, CDCl₃): 196.7 (C=O), 170.3 (C=O), 163.4 (C=O), 136.8 (q), 134.7, 134.5 (q), 133.7 (q), 133.3, 130.6, 130.4, 129.3, 129.2, 129.1, 128.9, 128.4, 125.4, 124.5 (q), 90.7 (q), 53.1, 52.9.

ν_{max} (film)/cm⁻¹: 2921, 2853, 1725, 1609, 1492, 1366, 1346, 1256, 1171, 1072, 1034, 997, 754.

HRMS (*m/z* -ESI): [M+Na]⁺ found 409.1043. C₂₄H₁₈O₅Na Requires 409.1052.

5.3.8.2 Methyl 3-benzoyl-3-(2-ethylphenyl)-1-oxoisochroman-4-carboxylate



An oven dried 10 mL reaction vessel containing a stirring bar under argon atmosphere was charged with the anhydride **139** (40.0 mg, 0.25 mol). Anhydrous MTBE (4.8 mL) was added *via* syringe and the solution was cooled to -15 °C. Ketone **462** (51.2 mg, 0.25 mmol) was added to the reaction immediately followed by catalyst **426** (8.4 mg, 0.012 mmol, 5 mol%) and the reaction mixture was stirred at -15 °C for 84 h. The reaction was then diluted with EtOAc (15 mL) and extracted with an aqueous solution of NaHCO₃ (10% w/v, 3 x 10 mL). The combined aqueous extracts were acidified with HCl (2.0 N) and the mixture was then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over MgSO₄ and the solvent was removed *in vacuo* to yield the diastereomeric mixture of carboxylic acids which were suspended in anhydrous MTBE (0.1 M). Dry MeOH (750.0 µL), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150.0 µL) were added *via* syringe and the reaction was allowed to stir for 30 min at room temperature. After esterification, the solvent was removed *in vacuo* and both diastereomers (*cis*-**464** and *trans*-**464**) were purified by column chromatography eluting in gradient from 100% hexane to 20% EtOAc in hexane and obtained in a 98:2 ratio (*cis:trans*) as a pale yellow solid (82.8 mg, 80%, combined yield for both diastereoisomers, *cis*-**464**: 91% *ee*, *trans*-**464**: 9% *ee*. M.p. 176-179 °C. $[\alpha]_D^{20} = +150.0$ (*c* 0.10, CHCl₃). * Major diastereomer assigned for ¹H NMR and ¹³C NMR..

* $[\alpha]_D^{20}$ referred to a mixture of *cis*-**464:trans**-**464** in a 98:2 ratio

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: 24.6 min (minor enantiomer) and 30.1 min (major enantiomer).

δ_H (600 MHz, CDCl₃): 8.33 (1 H, dd, *J* 2.6, 7.3, H-1), 7.97 (1 H, d, *J* 8.0, H-5'), 7.94 (1 H, d, *J* 7.2, H-5''), 7.87 (1 H, dd, *J* 1.2, 7.7, H-2'), 7.75 (1 H, dd, *J* 1.1, 7.8, H-2''), 7.71 (1 H, app. t, H-4'),

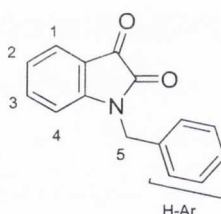
7.57-7.50 (3 H, m, H-2, H-3 and H-4''), 7.49-7.40 (2 H, m, H-3' and H-3''), 6.98-6.93 (1 H, m, H-4), 4.68 (1 H, s, H-5), 3.23 (3 H, s, CO₂CH₃).

δ_C (150 MHz, CDCl₃): 193.9 (C=O), 168.3 (C=O), 164.1 (C=O), 136.2 (q), 135.5 (q), 135.3, 134.0, 131.93 (q), 131.9 (q), 130.3 (q), 130.2, 129.7, 129.6, 129.2, 129.1, 128.1, 128.0, 126.8, 125.4 (q), 124.2, 123.1, 84.9 (q), 58.4, 52.4.

$\nu_{\max}$ (film)/cm⁻¹: 2958, 2924, 2852, 1734, 1689, 1599, 1451, 1256, 1209, 1163, 1117, 997, 765, 745, 692.

HRMS (*m/z* -ESI): [M+Na]⁺ found 407.0897. C₂₄H₁₆O₅Na Requires 407.0895.

5.3.9.1 1-Benzylindoline-2,3-dione (463)

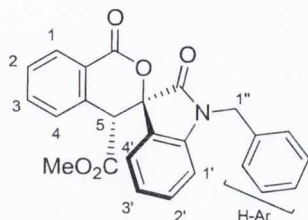


A 50 mL round-bottomed flask containing a stirring bar was charged with isatin (**461**) (1.00 g, 6.80 mmol), K₂CO₃ (1.88 g, 13.59 mmol), TBAB (219.2 mg, 0.68 mmol) and MeCN (25 mL). Benzyl bromide (2.5 mL, 20.61 mmol) was added *via* syringe, the apparatus was fitted with a condenser and the reaction mixture was heated at reflux temperature for 16 h. The solvent was then removed in vacuo and the residue was recrystallised from EtOH to afford pure **463** (1.35 g, 84%) as orange needles. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³⁴⁸ M.p. 128-130 °C (lit.,³⁵¹ 129-131 °C).

δ_H (400 MHz, CDCl₃): 7.60 (1 H, d, *J* 7.3, H-1), 7.46 (1 H, app. t, H-2), 7.38-7.28 (5 H, m, H-Ar), 7.07 (1 H, app. t, H-3), 6.77 (1 H, d, *J* 7.8, H-4), 4.93, (2 H, s, H-5).

HRMS (m/z -ESI): $[M+H]^+$ found 238.0860. $C_{15}H_{12}NO_2$ Requires 238.0868.

5.3.9.2 (3*R*,4'*R*)-Methyl 1-benzyl-1',2-dioxospiro[indoline-3,3'-isochroman]-4'-carboxylate (*cis*-468)



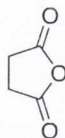
An oven dried 20 mL reaction vessel containing a stirring bar under argon atmosphere was charged with anhydride **139** (20.0 mg, 0.12 mol) and catalyst **426** (5.1 mg, 0.0061 mmol, 5 mol%). Anhydrous MTBE (12.0 mL) was added *via* syringe and the solution was cooled to -15 °C. Ketone **463** (29.2 mg, 0.12 mmol) was added to the reaction and the mixture was stirred at -15 °C for 39 h. The reaction was then diluted with EtOAc (15 mL) and extracted with an aqueous solution of $NaHCO_3$ (10% w/v, 3 x 10 mL). The combined aqueous extracts were acidified with HCl (2.0 N) and the mixture was then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo* to yield the diastereomeric mixture of carboxylic acids. 1H NMR spectroscopic analysis of the crude mixture allowed to establish the *dr* of the products to be 91:9 (*cis:trans*). The carboxylic acids were suspended in anhydrous MTBE (0.1 M). Dry MeOH (350.0 μ L), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 75.0 μ L) were added *via* syringe and the reaction was allowed to stir for 5 min at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash chromatography eluting in gradient from 100% hexane to 25% EtOAc in hexane. The major diastereomer *cis*-**468** was isolated pure (42.2 mg, 85%, 80% *ee*) as an off-white solid. M.p. 140-142 °C. $[\alpha]_D^{20} = -52.0$ (*c* 0.10, $CHCl_3$).

CSP-HPLC analysis. Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1} , RT, UV detection at 254 nm, retention times: 66.8 min (minor enantiomer) and 33.8 min (major enantiomer).

δ_{H} (400 MHz, CDCl_3):	8.26 (1 H, d, J 7.1, H-1), 7.65 (1 H, app. t, H-2), 7.57 (1 H, app. t, H-3), 7.40-7.20 (7 H, m, H-4, H-2' and H-Ar), 6.97-6.89 (2 H, m, H-3' and H-4'), 6.73 (1 H, d, J 7.9, H-1'), 4.92 (1 H, J 15.7, H-1''a), 4.82, (1 H, J 15.7, H-1''b), 4.54 (1 H, s, H-5), 3.67 (3 H, s, CO_2CH_3).
δ_{C} (150 MHz, CDCl_3):	171.1 (C=O), 168.4 (C=O), 163.3 (C=O), 143.2 (q), 135.1 (q), 134.5, 133.7 (q), 131.6, 130.5, 129.4, 129.0, 128.0, 127.7, 126.7, 125.9 (q), 125.4 (q), 124.3, 123.4, 110.1, 80.4 (q), 53.0, 50.5, 44.4.
ν_{max} (film)/ cm^{-1} :	2928, 2852, 1739, 1662, 1597, 1447, 1254, 1216, 1156, 1118, 1080, 834, 754, 728, 685.
HRMS (m/z -ESI):	$[\text{M}+\text{Na}]^+$ found 436.1158. $\text{C}_{25}\text{H}_{19}\text{NO}_5\text{Na}$ Requires 436.1161.

5.3.10 Synthesis of succinic and arylsuccinic anhydrides

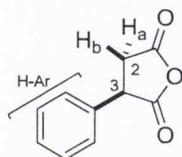
5.3.10.1 Succinic anhydride (**127**)



A 50 mL round-bottomed flask containing a stirring bar was charged with succinic acid (2.00 g, 16.94 mmol). Acetic anhydride (25 mL) was added, the flask was fitted with a condenser and the reaction mixture was heated at 80 °C for 2 h. The excess acetic anhydride was removed *in vacuo* to obtain **127** as a white solid (1.69 g, 100%). M.p. 118-120 °C (lit.³⁴⁹ m.p. 117-119 °C).

δ_{H} (400 MHz, $\text{DMSO}-d_6$): 2.89 (s, 4H).

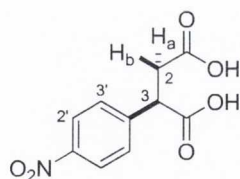
5.3.10.2 3-Phenyldihydrofuran-2,5-dione (149)



An oven dried 50 mL round-bottomed flask containing a stirring bar was charged with **470** (2.00 g, 10.30 mmol). Freshly distilled acetyl chloride (15 mL) was added, the flask was fitted with a condenser, then flushed with argon, fitted with a septum and placed under an atmosphere of Ar (balloon). The reaction mixture was heated at reflux temperature for 16 h. The acetyl chloride was then removed *in vacuo* to obtain **149** as a white solid (1.81 g, 100%). The isolated compound exhibited identical spectroscopic data to those reported in the literature.³⁵⁰ M.p. 50-52 °C (lit.³⁵² m.p. 51-53 °C).

δ_{H} (400 MHz, DMSO- d_6): 7.48-7.29 (5 H, m, H-Ar), 4.61 (1 H, dd, J 7.8, 10.0, H-3), 3.43 (1 H, dd, J 10.0, 18.3, H-2a), 3.13 (1 H, dd, J 7.8, 18.3, H-2b).

5.3.10.3.1 2-(4-Nitrophenyl)succinic acid (471)



A three-neck oven dried 100 mL round-bottomed flask fitted with a thermometer and containing a stirring bar was charged with fuming HNO_3 (30.0 mL) and cooled to 0 °C. **470** (5.00 g, 25.75 mmol) was added portionwise while keeping the temperature below 20 °C. The solution was stirred at 0 °C for 2 h, then crushed ice and H_2O (10 mL) were added to the reaction mixture. The white precipitate formed was filtered, washed with water, dried, and then recrystallised three times from water to obtain **471** as a white solid (7.2 g, 58%). M.p. 233-235 °C.

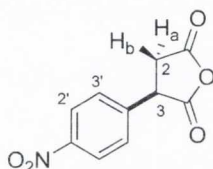
δ_{H} (400 MHz, DMSO- d_6): 12.45 (2 H, bs, CO₂H), 8.16 (2 H, d, J 8.6, H-2'), 7.56 (2 H, d, J 8.6, H-3'), 4.07 (1 H, dd, J 5.6, 9.6, H-3), 2.97 (1 H, dd, J 9.6, 17.0, H-2a), 2.61 (1 H, dd, J = 5.6, 17.0, H-2b).

δ_{C} (100 MHz, DMSO- d_6): 173.1 (C=O), 172.4 (C=O), 146.7 (q), 146.4 (q), 129.4, 123.7, 46.7, 36.9.

ν_{max} (film)/cm⁻¹: 2862, 2576, 1703, 1596, 1520, 1435, 1347, 1255, 926, 732.

HRMS (m/z -ESI): [M-H] found 238.0353. C₁₀H₈NO₆ Requires 238.0352.

5.3.10.3.2 3-(4-Nitrophenyl)dihydrofuran-2,5-dione (393)



An oven dried 25 mL round-bottomed flask containing a stirring bar was charged with **471** (1.00 g, 4.18 mmol). Freshly distilled acetyl chloride (8.0 mL) was added, the flask was fitted with a condenser and a septum and the reaction mixture was heated at reflux temperature under an atmosphere of Ar (balloon) for 16 h. The acetyl chloride was then removed *in vacuo* to obtain a dark yellow oil that was purified by passing it through a plug of silica eluting with hexane:EtOAc 1:1 *v/v* to obtain **393** as a thick yellow oil (656.1 mg, 71%).³⁵⁰

δ_{H} (400 MHz, CDCl₃): 8.30 (2 H, d, J 8.9, H-2'), 7.51 (2 H, d, J 8.9, H-3'), 4.49 (1 H, dd, J 7.2, 10.4, H-3), 3.55 (1 H, dd, J 10.4, 18.8, H-2b), 3.17 (1 H, dd, J 7.2, 18.8, H-2a).

HRMS (m/z -ESI): [M-H] found 220.0243. C₁₀H₈NO₆ Requires 220.0246.

5.3.11 (2*R*,3*S*)-methyl 1'-benzyl-3-(4-nitrophenyl)-2',5-dioxo-4,5-dihydro-3*H*-spiro[furan-2,3'-indoline]-3-carboxylate (*trans*-473)



An oven dried 10 mL reaction vessel containing a stirring bar under argon atmosphere was charged with anhydride **393** (37.2 mg, 0.17 mmol). Anhydrous MTBE (17.0 mL) was added *via* syringe and the solution was cooled to -15 °C. Catalyst **426** (23.0 mg, 0.033 mmol, 20 mol%) was added to the reaction, immediately followed by ketone **463** (39.9 mg, 0.17 mmol) and the reaction mixture was stirred at -15 °C for 21 h. The reaction was then diluted with EtOAc (15 mL) and extracted with an aqueous solution of NaHCO₃ (10% w/v, 3 x 10 mL). The combined aqueous extracts were acidified with HCl (2.0 N) and the mixture was then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over MgSO₄ and the solvent was removed *in vacuo* to obtain a diastereomeric mixture of carboxylic acids which was suspended in anhydrous MTBE (0.1 M). Dry ¹PrOH (64.0 μL), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150.0 μL) were added to the suspension *via* syringe and the reaction was allowed to stir for 30 min at room temperature. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash chromatography eluting in gradient from 100% hexane to 20% EtOAc in hexane. The major diastereomer *trans*-**473** was isolated pure (70.6 mg, 88%, 98% *ee*) as an off-white solid. M.p. 191-193 °C. $[\alpha]_D^{20} = +41.6$ (c 0.18, CHCl₃).

CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 75/25, 1.0 mL min⁻¹, RT, UV detection at 254 nm, retention times: 22.3 min (minor enantiomer) and 56.3 min (major enantiomer).

δ_H (600 MHz, CDCl₃): 7.87 (2 H, d, *J* 8.9, H-2'), 7.48 (1 H, app. t, H-3''), 7.32-7.13 (5 H, m, H-2'', H-4'', H-3''' and H-4'''), 4.8 (1 H, *J*

14.9, H-2a), 4.30 (2 H, app. t, H-3), 3.82 (3 H, 2, CO₂CH₃), 3.33 (1 H, d, *J* 14.9, H-2b).

δ_{C} (150 MHz, CDCl₃): 172.4 (C=O), 171.6 (C=O), 169.8 (C=O), 147.6 (q), 144.3 (q), 141.8 (q), 140.8 (q), 134.2 (q), 132.5, 128.7, 128.3, 128.0, 125.9, 124.0, 123.3, 122.3, 110.2, 85.3 (q), 60.3 (q), 53.6, 44.3, 36.6.

ν_{max} (film)/cm⁻¹: 3021, 2958, 2924, 2857, 1808, 1723, 1608, 1520, 1467, 1350, 1259, 1171, 997, 865, 759, 745.

HRMS (*m/z* -ESI): [M+H]⁺ found 473.1341. C₂₆H₂₁N₂O₇ Requires 473.1349.

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7.0 Appendix

X-ray crystallography data for lactones (3*R*,4*R*)-412, (3*R*,4*R*)-463

(3*R*,4*R*)-412

A specimen of C₁₈H₁₃F₃O₄ was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

The integration of the data using a hexagonal unit cell yielded a total of 16841 reflections to a maximum θ angle of 66.55° (0.84 Å resolution), of which 2290 were independent (average redundancy 7.354, completeness = 98.8%, $R_{\text{int}} = 2.69\%$, $R_{\text{sig}} = 2.71\%$) and 2288 (99.91%) were greater than $2\sigma(F^2)$. The final cell constants of $\underline{a} = 9.0807(3)$ Å, $\underline{b} = 9.0807(3)$ Å, $\underline{c} = 33.7042(11)$ Å, volume = 2406.87(14) Å³, are based upon the refinement of the XYZ-centroids of reflections above 20 $\sigma(I)$. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 61, with $Z = 6$ for the formula unit, C₁₈H₁₃F₃O₄. The final anisotropic full-matrix least-squares refinement on F^2 with 228 variables converged at $R1 = 2.28\%$, for the observed data and $wR2 = 6.74\%$ for all data. The goodness-of-fit was 1.463. The largest peak in the final difference electron density synthesis was 0.178 e⁻/Å³ and the largest hole was -0.134 e⁻/Å³ with an RMS deviation of 0.032 e⁻/Å³. On the basis of the final model, the calculated density was 1.450 g/cm³ and $F(000)$, 1080 e⁻.

Table 1. Sample and crystal data for (3*R*,4*R*)-412.

Identification code	cc1vket44	
Chemical formula	C ₁₈ H ₁₃ F ₃ O ₄	
Formula weight	350.28	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	hexagonal	
Space group	P 61	
Unit cell dimensions	$a = 9.0807(3)$ Å	$\alpha = 90^\circ$
	$b = 9.0807(3)$ Å	$\beta = 90^\circ$
	$c = 33.7042(11)$ Å	$\gamma = 120^\circ$
Volume	2406.87(14) Å ³	
Z	6	
Density (calculated)	1.450 g/cm ³	

Absorption coefficient	1.081 mm ⁻¹
F(000)	1080

Table 2. Data collection and structure refinement for (3*R*,4*R*)-412.

Theta range for data collection	5.63 to 66.55°
Index ranges	-10 ≤ h ≤ 10, -10 ≤ k ≤ 10, -39 ≤ l ≤ 28
Reflections collected	16841
Independent reflections	2290 [R(int) = 0.0269]
Structure solution technique	direct methods
Structure solution program	SHELXS-97 (Sheldrick, 2008)
Refinement method	Full-matrix least-squares on F ²
Refinement program	SHELXL-97 (Sheldrick, 2008)
Function minimized	$\sum w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	2290 / 69 / 228
Goodness-of-fit on F²	1.463
Δ/σ_{max}	0.001
Final R indices	2288 data; I > 2σ(I) R1 = 0.0228, wR2 = 0.0674 all data R1 = 0.0228, wR2 = 0.0674
Weighting scheme	w = 1/[σ ² (F _o ²) + (0.0414P) ² + 0.0000P] where P = (F _o ² + 2F _c ²)/3
Absolute structure parameter	0.1(1)
Extinction coefficient	0.0014(3)
Largest diff. peak and hole	0.178 and -0.134 eÅ ⁻³
R.M.S. deviation from mean	0.032 eÅ ⁻³

Table 3. Atomic coordinates and equivalent isotropic atomic displacement parameters ($\text{\AA}^2$) for *trans*-412.

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
F001	0.52612(11)	0.11140(10)	0.11101(3)	0.0274(2)
F002	0.28089(10)	0.97184(10)	0.08346(3)	0.0280(2)
O003	0.45502(10)	0.80670(10)	0.08091(3)	0.0167(2)
O10	0.43167(11)	0.55818(11)	0.09233(3)	0.0225(2)
O005	0.16726(12)	0.89306(11)	0.00215(3)	0.0237(2)
F006	0.48024(13)	0.19253(10)	0.05426(3)	0.0351(2)
O007	0.14369(11)	0.65994(12)	0.03160(3)	0.0218(2)
C008	0.45606(13)	0.66438(15)	0.06791(4)	0.0162(3)
C009	0.22880(14)	0.79779(15)	0.01703(4)	0.0165(3)
C00A	0.47254(13)	0.76261(14)	0.99792(4)	0.0153(3)
C00B	0.70381(15)	0.04914(14)	0.05141(4)	0.0188(3)
C00C	0.48618(14)	0.65395(15)	0.02511(4)	0.0168(3)
C00D	0.44831(19)	0.05694(16)	0.07604(5)	0.0227(3)
C00E	0.49727(15)	0.74763(16)	0.95787(4)	0.0201(3)
C00F	0.50925(15)	0.94837(14)	0.05421(4)	0.0161(3)
C00G	0.42285(14)	0.88794(13)	0.01331(4)	0.0155(3)
C00H	0.52259(16)	0.52989(15)	0.01193(5)	0.0232(3)
C00I	0.80052(17)	0.02688(16)	0.08017(5)	0.0235(3)
C00J	0.54531(18)	0.51476(17)	0.97203(5)	0.0279(3)
C00K	0.53267(16)	0.62277(17)	0.94482(5)	0.0256(3)
C00L	0.97745(19)	0.12353(19)	0.07924(5)	0.0322(4)
C00M	0.78528(18)	0.16866(16)	0.02143(5)	0.0266(3)
C00N	0.05722(18)	0.24118(19)	0.04943(6)	0.0348(4)
C00O	0.9617(2)	0.26415(18)	0.02065(5)	0.0343(4)
C00P	0.98585(19)	0.8218(2)	0.00740(5)	0.0326(3)

Table 4. Bond lengths (Å) for (3*R*,4*R*)-412.

F001-C00D	1.3355(19)	F002-C00D	1.3402(18)
O003-C008	1.3692(16)	O003-C00F	1.4402(15)
O10-C008	1.2012(17)	O005-C009	1.3400(16)
O005-C00P	1.4483(17)	F006-C00D	1.3347(17)
O007-C009	1.1991(16)	C008-C00C	1.480(2)
C009-C00G	1.5325(15)	C00A-C00E	1.3861(19)
C00A-C00C	1.3968(19)	C00A-C00G	1.5104(16)
C00B-C00I	1.389(2)	C00B-C00M	1.3940(19)
C00B-C00F	1.5333(16)	C00C-C00H	1.3957(18)
C00D-C00F	1.5379(17)	C00E-C00K	1.395(2)
C00F-C00G	1.5447(18)	C00H-C00J	1.378(2)
C00I-C00L	1.394(2)	C00J-C00K	1.389(2)
C00L-C00N	1.379(3)	C00M-C00O	1.389(2)
C00N-C00O	1.385(3)		

Table 5. Bond angles (°) for (3*R*,4*R*)-412.

C008-O003-C00F	118.84(10)	C009-O005-C00P	114.46(11)
O10-C008-O003	116.94(13)	O10-C008-C00C	125.61(12)
O003-C008-C00C	117.45(11)	O007-C009-O005	124.61(11)
O007-C009-C00G	124.05(11)	O005-C009-C00G	111.33(10)
C00E-C00A-C00C	119.58(11)	C00E-C00A-C00G	122.17(11)
C00C-C00A-C00G	118.19(12)	C00I-C00B-C00M	119.41(12)
C00I-C00B-C00F	119.60(12)	C00M-C00B-C00F	120.92(13)
C00H-C00C-C00A	120.13(13)	C00H-C00C-C008	119.18(12)
C00A-C00C-C008	120.65(11)	F006-C00D-F001	108.24(10)
F006-C00D-F002	107.17(11)	F001-C00D-F002	106.64(12)
F006-C00D-C00F	110.27(12)	F001-C00D-C00F	111.49(11)
F002-C00D-C00F	112.81(10)	C00A-C00E-C00K	120.08(13)
O003-C00F-C00B	110.42(10)	O003-C00F-C00D	101.63(10)
C00B-C00F-C00D	108.87(10)	O003-C00F-C00G	110.75(9)
C00B-C00F-C00G	112.72(11)	C00D-C00F-C00G	111.90(10)
C00A-C00G-C009	108.82(9)	C00A-C00G-C00F	106.51(10)
C009-C00G-C00F	111.15(11)	C00J-C00H-C00C	119.92(13)
C00B-C00I-C00L	120.42(13)	C00H-C00J-C00K	120.31(12)
C00J-C00K-C00E	119.98(14)	C00N-C00L-C00I	119.87(16)
C00O-C00M-C00B	119.81(14)	C00L-C00N-C00O	120.07(14)
C00N-C00O-C00M	120.42(14)		

Table 6. Torsion angles (°) for (3*R*,4*R*)-412.

C00F-O003-C008-O10	170.54(10)	C00F-O003-C008-C00C	-9.75(13)
C00P-O005-C009-O007	4.2(2)	C00P-O005-C009-C00G	-175.46(12)
C00E-C00A-C00C-C00H	-0.72(18)	C00G-C00A-C00C-C00H	176.48(10)
C00E-C00A-C00C-C008	-178.43(10)	C00G-C00A-C00C-C008	-1.23(15)
O10-C008-C00C-C00H	-13.24(17)	O003-C008-C00C-C00H	167.08(10)
O10-C008-C00C-C00A	164.50(12)	O003-C008-C00C-C00A	-15.19(15)
C00C-C00A-C00E-C00K	1.09(18)	C00G-C00A-C00E-C00K	-175.99(10)
C008-O003-C00F-C00B	-77.74(12)	C008-O003-C00F-C00D	166.86(9)
C008-O003-C00F-C00G	47.83(13)	C00I-C00B-C00F-O003	-16.86(16)
C00M-C00B-C00F-O003	166.13(12)	C00I-C00B-C00F-C00D	93.91(13)
C00M-C00B-C00F-C00D	-83.10(16)	C00I-C00B-C00F-C00G	-141.31(12)
C00M-C00B-C00F-C00G	41.68(15)	F006-C00D-C00F-O003	-176.71(10)
F001-C00D-C00F-O003	63.02(13)	F002-C00D-C00F-O003	-56.94(14)
F006-C00D-C00F-C00B	66.75(14)	F001-C00D-C00F-C00B	-53.51(15)
F002-C00D-C00F-C00B	-173.47(12)	F006-C00D-C00F-C00G	-58.51(14)
F001-C00D-C00F-C00G	-178.77(10)	F002-C00D-C00F-C00G	61.27(15)
C00E-C00A-C00G-C009	93.94(14)	C00C-C00A-C00G-C009	-83.19(13)
C00E-C00A-C00G-C00F	-146.16(11)	C00C-C00A-C00G-C00F	36.72(13)
O007-C009-C00G-C00A	45.77(18)	O005-C009-C00G-C00A	-134.57(12)
O007-C009-C00G-C00F	-71.21(15)	O005-C009-C00G-C00F	108.45(12)
O003-C00F-C00G-C00A	-59.02(12)	C00B-C00F-C00G-C00A	65.25(12)
C00D-C00F-C00G-C00A	-171.65(10)	O003-C00F-C00G-C009	59.36(12)
C00B-C00F-C00G-C009	-176.37(9)	C00D-C00F-C00G-C009	-53.27(13)
C00A-C00C-C00H-C00J	0.08(18)	C008-C00C-C00H-C00J	177.82(11)
C00M-C00B-C00I-C00L	0.3(2)	C00F-C00B-C00I-C00L	-176.77(13)
C00C-C00H-C00J-C00K	0.20(19)	C00H-C00J-C00K-C00E	0.2(2)
C00A-C00E-C00K-C00J	-0.82(19)	C00B-C00I-C00L-C00N	-0.5(2)
C00I-C00B-C00M-C00O	-0.1(2)	C00F-C00B-C00M-C00O	176.92(13)
C00I-C00L-C00N-C00O	0.5(2)	C00L-C00N-C00O-C00M	-0.3(2)
C00B-C00M-C00O-C00N	0.1(2)		

Table 7. Anisotropic atomic displacement parameters (Å²) for (3*R*,4*R*)-412.

The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
F001	0.0409(4)	0.0284(4)	0.0143(5)	-0.0083(3)	-0.0031(4)	0.0184(3)
F002	0.0334(4)	0.0382(4)	0.0208(5)	-0.0079(3)	-0.0002(3)	0.0242(4)
O003	0.0226(4)	0.0153(4)	0.0110(5)	0.0023(3)	0.0021(3)	0.0087(3)
O10	0.0259(4)	0.0203(4)	0.0194(5)	0.0056(4)	-0.0021(4)	0.0102(3)
O005	0.0264(5)	0.0308(4)	0.0204(6)	0.0024(4)	-0.0016(4)	0.0191(4)

F006	0.0659(6)	0.0259(4)	0.0245(5)	0.0015(3)	0.0010(4)	0.0313(4)
O007	0.0226(4)	0.0236(4)	0.0182(5)	0.0012(4)	0.0043(4)	0.0107(4)
C008	0.0153(5)	0.0143(5)	0.0163(7)	0.0017(5)	-0.0020(5)	0.0055(4)
C009	0.0222(6)	0.0218(5)	0.0091(6)	-0.0029(5)	-0.0005(5)	0.0137(5)
C00A	0.0140(5)	0.0141(5)	0.0154(7)	-0.0006(5)	0.0006(4)	0.0053(4)
C00B	0.0237(6)	0.0142(5)	0.0141(7)	-0.0023(5)	0.0008(5)	0.0062(4)
C00C	0.0149(5)	0.0147(5)	0.0191(7)	0.0007(5)	-0.0004(5)	0.0061(4)
C00D	0.0377(6)	0.0225(5)	0.0121(7)	-0.0026(5)	-0.0035(5)	0.0181(5)
C00E	0.0209(5)	0.0201(6)	0.0169(7)	-0.0006(5)	0.0007(5)	0.0085(4)
C00F	0.0246(5)	0.0140(5)	0.0090(7)	0.0016(4)	0.0015(5)	0.0091(4)
C00G	0.0195(5)	0.0167(5)	0.0108(6)	0.0000(4)	0.0004(4)	0.0095(4)
C00H	0.0229(6)	0.0196(5)	0.0301(9)	-0.0008(5)	0.0009(5)	0.0128(5)
C00I	0.0273(6)	0.0222(6)	0.0166(8)	-0.0001(5)	-0.0002(5)	0.0090(5)
C00J	0.0279(6)	0.0240(6)	0.0347(9)	-0.0082(6)	0.0029(6)	0.0152(5)
C00K	0.0249(6)	0.0278(6)	0.0214(8)	-0.0075(6)	0.0032(5)	0.0111(5)
C00L	0.0266(6)	0.0336(7)	0.0296(9)	-0.0032(6)	-0.0056(6)	0.0100(5)
C00M	0.0341(7)	0.0162(5)	0.0177(8)	0.0016(5)	-0.0008(6)	0.0036(5)
C00N	0.0255(6)	0.0284(7)	0.0310(10)	-0.0077(7)	0.0006(6)	-0.0012(5)
C00O	0.0368(7)	0.0231(6)	0.0210(9)	0.0002(6)	0.0044(6)	-0.0014(5)
C00P	0.0313(7)	0.0512(8)	0.0269(9)	0.0021(7)	0.0000(6)	0.0295(7)

Table 8. Hydrogen atomic coordinates and isotropic atomic displacement parameters ($\text{\AA}^2$) for (3*R*,4*R*)-412.

	x/a	y/b	z/c	U(eq)
H00E	0.4901	0.8225	-0.0607	0.024
H00G	0.4639	0.9867	-0.0052	0.019
H00H	0.5317	0.4560	0.0305	0.028
H00I	0.7457	0.9453	0.1006	0.028
H00J	0.5697	0.4300	-0.0369	0.033
H00K	0.5481	0.6117	-0.0827	0.031
H00L	1.0429	1.1084	0.0991	0.039
H00M	0.7203	1.1848	0.0016	0.032
H00N	1.1778	1.3065	0.0486	0.042
H00O	1.0172	1.3457	0.0002	0.041
H00A	-0.0748	0.7111	-0.0059	0.049
H00B	-0.0490	0.8987	-0.0041	0.049
H00C	-0.0414	0.8072	0.0358	0.049

(3*R*,4*R*)-463

A specimen of $C_{73}H_{55}O_{14}$ was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

The total exposure time was 10.34 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 10677 reflections to a maximum θ angle of 60.00° (0.89 Å resolution), of which 6705 were independent (average redundancy 1.592, completeness = 98.1%, $R_{\text{int}} = 3.45\%$, $R_{\text{sig}} = 5.25\%$) and 6259 (93.35%) were greater than $2\sigma(F^2)$. The final cell constants of $a = 8.7392(3)$ Å, $b = 21.6452(9)$ Å, $c = 14.8615(5)$ Å, $\beta = 91.550(2)^\circ$, volume = $2810.20(18)$ Å³, are based upon the refinement of the XYZ-centroids of 4235 reflections above $20\sigma(I)$ with $7.217^\circ < 2\theta < 129.4^\circ$. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.821.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P 1 2 1 1$, with $Z = 2$ for the formula unit, $C_{73}H_{55}O_{14}$. The final anisotropic full-matrix least-squares refinement on F^2 with 788 variables converged at $R1 = 6.93\%$, for the observed data and $wR2 = 18.88\%$ for all data. The goodness-of-fit was 1.029. The largest peak in the final difference electron density synthesis was $1.582\text{ e}^-/\text{\AA}^3$ and the largest hole was $-0.553\text{ e}^-/\text{\AA}^3$ with an RMS deviation of $0.091\text{ e}^-/\text{\AA}^3$. On the basis of the final model, the calculated density was 1.366 g/cm^3 and $F(000)$, 1210 e^- .

Table 1. Sample and crystal data for (3*R*,4*R*)-463.

Identification code	k181	
Chemical formula	$C_{73}H_{55}O_{14}$	
Formula weight	1156.17	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	monoclinic	
Space group	$P 1 2 1 1$	
Unit cell dimensions	$a = 8.7392(3)$ Å	$\alpha = 90^\circ$
	$b = 21.6452(9)$ Å	$\beta = 91.550(2)^\circ$
	$c = 14.8615(5)$ Å	$\gamma = 90^\circ$
Volume	$2810.20(18)$ Å ³	
Z	2	
Density (calculated)	1.366 g/cm^3	
Absorption coefficient	0.773 mm^{-1}	
$F(000)$	1210	

Table 2. Data collection and structure refinement for (3*R*,4*R*)-463.

Theta range for data collection	3.61 to 60.00°		
Index ranges	-9<=h<=8, -21<=k<=24, -16<=l<=16		
Reflections collected	10677		
Independent reflections	6705 [R(int) = 0.0345]		
Coverage of independent reflections	98.1%		
Absorption correction	multi-scan		
Structure solution technique	direct methods		
Structure solution program	SHELXS-97 (Sheldrick, 2008)		
Refinement method	Full-matrix least-squares on F ²		
Refinement program	SHELXL-97 (Sheldrick, 2008)		
Function minimized	Σ w(F _o ² - F _c ²) ²		
Data / restraints / parameters	6705 / 1 / 788		
Goodness-of-fit on F ²	1.029		
Δ/σ _{max}	0.020		
Final R indices	6259 data; I>2σ(I)	R1 = 0.0693, wR2 = 0.1841	
	all data	R1 = 0.0736, wR2 = 0.1888	
	w=1/[σ ² (F _o ²)+(0.1269P) ² +4.1964P] where P=(F _o ² +2F _c ²)/3		
Weighting scheme			
Absolute structure parameter	0.0(3)		
Extinction coefficient	0.0018(4)		
Largest diff. peak and hole	1.582 and -0.553 eÅ ⁻³		
R.M.S. deviation from mean	0.091 eÅ ⁻³		

Table 3. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å²) for (3*R*,4*R*)-463.

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
O1	0.5608(4)	0.49844(17)	0.5904(2)	0.0163(8)
O4	0.6195(4)	0.49483(17)	0.4482(2)	0.0195(8)
O5	0.2363(4)	0.64576(18)	0.6087(3)	0.0254(9)
O8	0.2525(4)	0.54529(19)	0.5739(3)	0.0290(9)
O11	0.3377(4)	0.52148(18)	0.7756(2)	0.0228(8)
C3	0.6333(5)	0.5935(3)	0.5169(3)	0.0187(11)
C4	0.6043(5)	0.5263(2)	0.5135(3)	0.0165(11)
C7	0.3071(6)	0.5914(3)	0.6078(3)	0.0194(11)
C10	0.4255(5)	0.4936(3)	0.7280(3)	0.0178(11)

C11	0.4665(5)	0.5962(2)	0.6497(3)	0.0162(11)
C15	0.9617(6)	0.5324(3)	0.7434(4)	0.0255(12)
C16	0.2985(6)	0.3938(3)	0.7522(3)	0.0202(12)
C18	0.4288(6)	0.4251(3)	0.7254(3)	0.0198(12)
C19	0.9567(6)	0.5577(3)	0.8279(4)	0.0228(12)
C20	0.5699(5)	0.6292(3)	0.5846(3)	0.0175(11)
C22	0.5371(5)	0.5329(2)	0.6721(3)	0.0135(10)
C23	0.7258(6)	0.6208(3)	0.4521(4)	0.0226(12)
C24	0.6869(6)	0.5410(2)	0.7274(3)	0.0154(10)
C25	0.5558(6)	0.3904(3)	0.6980(3)	0.0195(11)
C27	0.4158(7)	0.2968(3)	0.7217(3)	0.0265(13)
C28	0.8276(6)	0.5245(2)	0.6921(3)	0.0187(11)
C29	0.6833(6)	0.5651(3)	0.8142(3)	0.0192(11)
C33	0.5479(7)	0.3267(3)	0.6967(4)	0.0257(13)
C38	0.5988(6)	0.6925(3)	0.5877(4)	0.0244(12)
C42	0.2908(6)	0.3301(3)	0.7495(3)	0.0237(13)
C45	0.7554(6)	0.6836(3)	0.4575(4)	0.0276(13)
C46	0.8165(6)	0.5735(3)	0.8642(4)	0.0246(12)
C50	0.0884(6)	0.6486(3)	0.5607(4)	0.0288(13)
C51	0.6910(7)	0.7184(3)	0.5245(4)	0.0331(14)
O2	0.7970(4)	0.41988(17)	0.2662(2)	0.0191(8)
O3	0.5052(4)	0.35541(18)	0.4635(2)	0.0206(8)
O6	0.5807(4)	0.28692(18)	0.2168(2)	0.0230(8)
O7	0.8961(4)	0.50627(17)	0.3206(2)	0.0219(8)
O9	0.4826(4)	0.39606(18)	0.3248(2)	0.0207(8)
C2	0.7139(5)	0.3394(2)	0.3685(3)	0.0174(11)
C5	0.8260(5)	0.3645(3)	0.4394(3)	0.0169(11)
C6	0.5550(6)	0.3681(2)	0.3817(3)	0.0167(11)
C8	0.7714(5)	0.3547(2)	0.2751(3)	0.0165(11)
C9	0.8671(5)	0.4536(3)	0.3354(3)	0.0171(11)
C13	0.8586(6)	0.3347(3)	0.5196(3)	0.0221(12)
C14	0.8976(5)	0.4206(2)	0.4214(3)	0.0170(11)
C17	0.9170(5)	0.3184(2)	0.2553(3)	0.0153(11)
C26	0.0297(6)	0.4161(3)	0.5640(4)	0.0258(13)
C32	0.6459(6)	0.3361(3)	0.2036(3)	0.0196(12)
C36	0.6128(6)	0.3721(3)	0.1200(3)	0.0214(12)
C37	0.3585(6)	0.3827(3)	0.4841(3)	0.0201(11)
C39	0.0017(6)	0.4461(3)	0.4835(4)	0.0218(12)
C43	0.9595(6)	0.3599(3)	0.5822(3)	0.0264(13)
C55	0.9137(7)	0.2546(3)	0.2514(4)	0.0270(13)

C56	0.0555(6)	0.3488(3)	0.2456(5)	0.0385(16)
C57	0.1833(7)	0.2523(3)	0.2238(4)	0.0351(16)
C61	0.0461(7)	0.2208(3)	0.2347(4)	0.0346(15)
C62	0.5276(9)	0.4340(3)	0.9643(4)	0.0437(17)
C64	0.1891(7)	0.3147(4)	0.2301(5)	0.047(2)
C67	0.5913(9)	0.3387(5)	0.0425(6)	0.061(2)
C69	0.5481(10)	0.3702(5)	0.9618(6)	0.066(2)
C70	0.590(2)	0.4615(6)	0.0276(8)	0.166(9)
C71	0.630(2)	0.4313(6)	0.1092(9)	0.169(10)
O10	0.9011(4)	0.22029(18)	0.7924(2)	0.0252(9)
O12	0.8281(5)	0.2143(2)	0.6493(3)	0.0364(10)
O13	0.1396(4)	0.2043(2)	0.9774(3)	0.0382(11)
O14	0.1809(6)	0.1645(3)	0.7617(4)	0.0605(16)
C1	0.2425(5)	0.0854(3)	0.8512(4)	0.0243(14)
C12	0.7786(5)	0.1889(2)	0.9312(3)	0.0168(11)
C21	0.9266(6)	0.1912(2)	0.8784(4)	0.0206(12)
C30	0.8503(6)	0.1871(3)	0.7193(4)	0.0242(12)
C31	0.7176(6)	0.0892(3)	0.6742(4)	0.0244(12)
C34	0.7402(6)	0.9990(3)	0.7645(4)	0.0258(13)
C35	0.6807(6)	0.0288(3)	0.6898(4)	0.0281(13)
C40	0.8434(6)	0.0292(3)	0.8231(4)	0.0261(12)
C41	0.8822(5)	0.0897(3)	0.8073(4)	0.0195(11)
C44	0.6390(6)	0.2076(3)	0.8928(4)	0.0233(12)
C47	0.8171(6)	0.1203(3)	0.7330(3)	0.0201(12)
C48	0.9930(6)	0.1260(3)	0.8664(4)	0.0228(12)
C49	0.0394(6)	0.2315(3)	0.9330(4)	0.0289(14)
C52	0.7856(6)	0.1672(3)	0.0187(4)	0.0254(13)
C53	0.1516(7)	0.1294(3)	0.8184(5)	0.0359(16)
C54	0.5070(7)	0.2024(3)	0.9416(4)	0.0356(15)
C58	0.0271(9)	0.2997(3)	0.9380(4)	0.0389(17)
C59	0.5120(7)	0.1795(3)	0.0280(4)	0.0364(15)
C60	0.6518(7)	0.1623(3)	0.0682(4)	0.0336(15)
C63	0.9325(7)	0.3361(3)	0.8859(5)	0.0383(16)
C65	0.9255(11)	0.3996(3)	0.8953(5)	0.055(2)
C66	0.3837(8)	0.0789(6)	0.8031(7)	0.089(4)
C68	0.1558(12)	0.3258(5)	0.9926(7)	0.068(2)
C72	0.1632(13)	0.3903(5)	0.9982(8)	0.083(3)
C73	0.020(3)	0.4256(5)	0.9597(7)	0.158(9)

Table 4. Bond lengths (Å) for (3*R*,4*R*)-463.

O1-C4	1.356(6)	O1-C22	1.445(6)
O4-C4	1.197(6)	O5-C7	1.330(7)
O5-C50	1.461(6)	O8-C7	1.210(7)
O11-C10	1.217(6)	C3-C20	1.394(8)
C3-C23	1.405(8)	C3-C4	1.478(8)
C7-C11	1.513(7)	C10-C18	1.484(8)
C10-C22	1.552(7)	C11-C20	1.520(7)
C11-C22	1.534(7)	C11-H11	1.0
C15-C19	1.372(8)	C15-C28	1.391(7)
C15-H15	0.95	C16-C42	1.381(8)
C16-C18	1.391(8)	C16-H16	0.95
C18-C25	1.409(8)	C19-C46	1.395(8)
C19-H19	0.95	C20-C38	1.393(8)
C22-C24	1.536(7)	C23-C45	1.384(9)
C23-H23	0.95	C24-C29	1.392(7)
C24-C28	1.396(7)	C25-C33	1.379(8)
C25-H25	0.95	C27-C42	1.382(9)
C27-C33	1.384(8)	C27-H27	0.95
C28-H28	0.95	C29-C46	1.376(8)
C29-H29	0.95	C33-H33	0.95
C38-C51	1.375(9)	C38-H38	0.95
C42-H42	0.95	C45-C51	1.381(9)
C45-H45	0.95	C46-H46	0.95
C50-H50A	0.98	C50-H50B	0.98
C50-H50C	0.98	C51-H51	0.95
O2-C9	1.390(6)	O2-C8	1.436(7)
O3-C6	1.330(6)	O3-C37	1.452(6)
O6-C32	1.226(7)	O7-C9	1.191(7)
O9-C6	1.206(6)	C2-C5	1.519(7)
C2-C8	1.524(7)	C2-C6	1.538(7)
C2-H2	1.0	C5-C13	1.379(8)
C5-C14	1.395(8)	C8-C17	1.531(7)
C8-C32	1.559(7)	C9-C14	1.482(7)
C13-C43	1.377(8)	C13-H13	0.95
C14-C39	1.392(7)	C17-C55	1.382(8)
C17-C56	1.389(8)	C26-C39	1.377(8)
C26-C43	1.391(9)	C26-H26	0.95
C32-C36	1.487(8)	C36-C71	1.301(13)

C36-C67	1.369(11)	C37-H37A	0.98
C37-H37B	0.98	C37-H37C	0.98
C39-H39	0.95	C43-H43	0.95
C55-C61	1.396(8)	C55-H55	0.95
C56-C64	1.405(9)	C56-H56	0.95
C57-C64	1.354(10)	C57-C61	1.392(10)
C57-H57	0.95	C61-H61	0.95
C62-C70	1.228(12)	C62-C69	1.393(13)
C62-H62	0.95	C64-H64	0.95
C67-C69	1.421(12)	C67-H67	0.95
C69-H69	0.95	C70-C71	1.412(12)
C70-H70	0.95	C71-H71	0.95
O10-C30	1.366(7)	O10-C21	1.437(7)
O12-C30	1.206(7)	O13-C49	1.232(8)
O14-C53	1.168(9)	C1-C53	1.324(9)
C1-C66	1.449(9)	C1-H1	0.95
C12-C52	1.381(8)	C12-C44	1.394(7)
C12-C21	1.531(7)	C21-C49	1.532(8)
C21-C48	1.538(8)	C30-C47	1.491(8)
C31-C35	1.368(9)	C31-C47	1.391(8)
C31-H31	0.95	C34-C35	1.374(8)
C34-C40	1.398(8)	C34-H34	0.95
C35-H35	0.95	C40-C41	1.375(8)
C40-H40	0.95	C41-C47	1.395(8)
C41-C48	1.509(7)	C44-C54	1.384(8)
C44-H44	0.95	C48-C53	1.577(9)
C48-H48	1.0	C49-C58	1.482(9)
C52-C60	1.403(8)	C52-H52	0.95
C54-C59	1.376(9)	C54-H54	0.95
C58-C63	1.367(10)	C58-C68	1.481(12)
C59-C60	1.395(9)	C59-H59	0.95
C60-H60	0.95	C63-C65	1.383(10)
C63-H63	0.95	C65-C73	1.369(14)
C65-H65	0.95	C66-H66A	0.98
C66-H66B	0.98	C66-H66C	0.98
C68-C72	1.399(15)	C68-H68	0.95
C72-C73	1.56(2)	C72-H72	0.95
C73-H73	0.95		

Table 5. Bond angles (°) for (3*R*,4*R*)-463.

C4-O1-C22	121.9(4)	C7-O5-C50	116.0(4)
C20-C3-C23	120.6(5)	C20-C3-C4	119.9(5)
C23-C3-C4	119.5(5)	O4-C4-O1	118.1(5)
O4-C4-C3	124.5(5)	O1-C4-C3	117.5(4)
O8-C7-O5	123.7(5)	O8-C7-C11	125.1(5)
O5-C7-C11	111.0(5)	O11-C10-C18	121.5(5)
O11-C10-C22	117.0(5)	C18-C10-C22	121.4(4)
C7-C11-C20	109.1(4)	C7-C11-C22	112.9(4)
C20-C11-C22	108.4(4)	C7-C11-H11	108.8
C20-C11-H11	108.8	C22-C11-H11	108.8
C19-C15-C28	120.2(5)	C19-C15-H15	119.9
C28-C15-H15	119.9	C42-C16-C18	121.1(5)
C42-C16-H16	119.4	C18-C16-H16	119.4
C16-C18-C25	118.7(5)	C16-C18-C10	117.5(5)
C25-C18-C10	123.8(5)	C15-C19-C46	120.2(5)
C15-C19-H19	119.9	C46-C19-H19	119.9
C38-C20-C3	119.6(5)	C38-C20-C11	123.5(5)
C3-C20-C11	116.9(5)	O1-C22-C11	110.1(4)
O1-C22-C24	111.6(4)	C11-C22-C24	110.3(4)
O1-C22-C10	105.8(4)	C11-C22-C10	110.5(4)
C24-C22-C10	108.3(4)	C45-C23-C3	118.9(5)
C45-C23-H23	120.5	C3-C23-H23	120.5
C29-C24-C28	119.1(5)	C29-C24-C22	119.9(4)
C28-C24-C22	121.1(4)	C33-C25-C18	119.8(5)
C33-C25-H25	120.1	C18-C25-H25	120.1
C42-C27-C33	120.5(6)	C42-C27-H27	119.7
C33-C27-H27	119.7	C15-C28-C24	120.0(5)
C15-C28-H28	120.0	C24-C28-H28	120.0
C46-C29-C24	120.7(5)	C46-C29-H29	119.6
C24-C29-H29	119.6	C25-C33-C27	120.3(5)
C25-C33-H33	119.8	C27-C33-H33	119.8
C51-C38-C20	119.2(5)	C51-C38-H38	120.4
C20-C38-H38	120.4	C16-C42-C27	119.4(5)
C16-C42-H42	120.3	C27-C42-H42	120.3
C51-C45-C23	119.9(5)	C51-C45-H45	120.0
C23-C45-H45	120.0	C29-C46-C19	119.8(5)
C29-C46-H46	120.1	C19-C46-H46	120.1
O5-C50-H50A	109.5	O5-C50-H50B	109.5

H50A-C50-H50B	109.5	O5-C50-H50C	109.5
H50A-C50-H50C	109.5	H50B-C50-H50C	109.5
C38-C51-C45	121.8(6)	C38-C51-H51	119.1
C45-C51-H51	119.1	C9-O2-C8	120.9(4)
C6-O3-C37	114.9(4)	C5-C2-C8	109.4(4)
C5-C2-C6	109.5(4)	C8-C2-C6	110.5(4)
C5-C2-H2	109.1	C8-C2-H2	109.1
C6-C2-H2	109.1	C13-C5-C14	119.3(4)
C13-C5-C2	123.1(5)	C14-C5-C2	117.6(4)
O9-C6-O3	124.5(5)	O9-C6-C2	124.8(5)
O3-C6-C2	110.6(4)	O2-C8-C2	110.7(4)
O2-C8-C17	110.7(4)	C2-C8-C17	111.1(4)
O2-C8-C32	107.4(4)	C2-C8-C32	108.8(4)
C17-C8-C32	108.0(4)	O7-C9-O2	117.2(4)
O7-C9-C14	125.9(5)	O2-C9-C14	116.9(4)
C43-C13-C5	120.8(5)	C43-C13-H13	119.6
C5-C13-H13	119.6	C39-C14-C5	120.5(5)
C39-C14-C9	118.7(5)	C5-C14-C9	120.8(4)
C55-C17-C56	119.1(5)	C55-C17-C8	120.2(5)
C56-C17-C8	120.6(5)	C39-C26-C43	120.8(5)
C39-C26-H26	119.6	C43-C26-H26	119.6
O6-C32-C36	120.5(5)	O6-C32-C8	115.8(5)
C36-C32-C8	123.5(5)	C71-C36-C67	115.4(8)
C71-C36-C32	126.8(6)	C67-C36-C32	116.4(6)
O3-C37-H37A	109.5	O3-C37-H37B	109.5
H37A-C37-H37B	109.5	O3-C37-H37C	109.5
H37A-C37-H37C	109.5	H37B-C37-H37C	109.5
C26-C39-C14	119.1(5)	C26-C39-H39	120.5
C14-C39-H39	120.5	C13-C43-C26	119.5(5)
C13-C43-H43	120.3	C26-C43-H43	120.3
C17-C55-C61	120.9(6)	C17-C55-H55	119.6
C61-C55-H55	119.6	C17-C56-C64	119.9(6)
C17-C56-H56	120.1	C64-C56-H56	120.1
C64-C57-C61	120.7(5)	C64-C57-H57	119.6
C61-C57-H57	119.6	C57-C61-C55	119.0(6)
C57-C61-H61	120.5	C55-C61-H61	120.5
C70-C62-C69	116.5(9)	C70-C62-H62	121.7
C69-C62-H62	121.7	C57-C64-C56	120.3(6)
C57-C64-H64	119.8	C56-C64-H64	119.8
C36-C67-C69	118.9(8)	C36-C67-H67	120.5

C69-C67-H67	120.5	C62-C69-C67	119.0(8)
C62-C69-H69	120.5	C67-C69-H69	120.5
C62-C70-C71	121.8(9)	C62-C70-H70	119.1
C71-C70-H70	119.1	C36-C71-C70	122.4(9)
C36-C71-H71	118.8	C70-C71-H71	118.8
C30-O10-C21	121.1(4)	C53-C1-C66	113.5(8)
C53-C1-H1	123.2	C66-C1-H1	123.2
C52-C12-C44	120.0(5)	C52-C12-C21	118.5(4)
C44-C12-C21	121.5(5)	O10-C21-C12	111.0(4)
O10-C21-C49	107.6(4)	C12-C21-C49	106.7(4)
O10-C21-C48	110.4(4)	C12-C21-C48	110.9(4)
C49-C21-C48	110.2(4)	O12-C30-O10	118.1(5)
O12-C30-C47	124.3(5)	O10-C30-C47	117.5(5)
C35-C31-C47	120.1(5)	C35-C31-H31	120.0
C47-C31-H31	120.0	C35-C34-C40	120.5(5)
C35-C34-H34	119.7	C40-C34-H34	119.7
C31-C35-C34	120.0(5)	C31-C35-H35	120.0
C34-C35-H35	120.0	C41-C40-C34	119.8(5)
C41-C40-H40	120.1	C34-C40-H40	120.1
C40-C41-C47	119.3(5)	C40-C41-C48	123.6(5)
C47-C41-C48	117.0(5)	C54-C44-C12	119.7(5)
C54-C44-H44	120.2	C12-C44-H44	120.2
C31-C47-C41	120.2(5)	C31-C47-C30	120.3(5)
C41-C47-C30	119.5(5)	C41-C48-C21	107.9(4)
C41-C48-C53	108.6(4)	C21-C48-C53	110.4(5)
C41-C48-H48	110.0	C21-C48-H48	110.0
C53-C48-H48	110.0	O13-C49-C58	120.0(6)
O13-C49-C21	116.7(5)	C58-C49-C21	123.2(6)
C12-C52-C60	120.2(5)	C12-C52-H52	119.9
C60-C52-H52	119.9	O14-C53-C1	126.3(7)
O14-C53-C48	124.7(6)	C1-C53-C48	109.0(6)
C59-C54-C44	120.8(5)	C59-C54-H54	119.6
C44-C54-H54	119.6	C63-C58-C68	122.0(6)
C63-C58-C49	126.1(6)	C68-C58-C49	110.6(7)
C54-C59-C60	120.1(5)	C54-C59-H59	120.0
C60-C59-H59	120.0	C59-C60-C52	119.2(5)
C59-C60-H60	120.4	C52-C60-H60	120.4
C58-C63-C65	122.9(7)	C58-C63-H63	118.6
C65-C63-H63	118.6	C73-C65-C63	116.9(9)
C73-C65-H65	121.6	C63-C65-H65	121.6

C1-C66-H66A	109.5	C1-C66-H66B	109.5
H66A-C66-H66B	109.5	C1-C66-H66C	109.5
H66A-C66-H66C	109.5	H66B-C66-H66C	109.5
C72-C68-C58	116.5(9)	C72-C68-H68	121.8
C58-C68-H68	121.8	C68-C72-C73	115.5(10)
C68-C72-H72	122.2	C73-C72-H72	122.2
C65-C73-C72	121.2(11)	C65-C73-H73	119.4
C72-C73-H73	119.4		

Table 6. Torsion angles (°) for (3*R*,4*R*)-463.

C22-O1-C4-O4	-178.9(4)	C22-O1-C4-C3	2.5(6)
C20-C3-C4-O4	160.4(5)	C23-C3-C4-O4	-20.1(7)
C20-C3-C4-O1	-21.1(6)	C23-C3-C4-O1	158.4(4)
C50-O5-C7-O8	-3.8(7)	C50-O5-C7-C11	173.1(4)
O8-C7-C11-C20	102.8(6)	O5-C7-C11-C20	-74.1(5)
O8-C7-C11-C22	-17.8(7)	O5-C7-C11-C22	165.4(4)
C42-C16-C18-C25	-2.1(7)	C42-C16-C18-C10	178.3(4)
O11-C10-C18-C16	22.1(7)	C22-C10-C18-C16	-159.6(4)
O11-C10-C18-C25	-157.6(5)	C22-C10-C18-C25	20.8(7)
C28-C15-C19-C46	2.5(9)	C23-C3-C20-C38	0.0(7)
C4-C3-C20-C38	179.5(4)	C23-C3-C20-C11	177.8(4)
C4-C3-C20-C11	-2.7(6)	C7-C11-C20-C38	94.7(6)
C22-C11-C20-C38	-142.0(5)	C7-C11-C20-C3	-83.0(5)
C22-C11-C20-C3	40.3(5)	C4-O1-C22-C11	36.4(6)
C4-O1-C22-C24	-86.5(5)	C4-O1-C22-C10	155.9(4)
C7-C11-C22-O1	65.1(5)	C20-C11-C22-O1	-55.8(5)
C7-C11-C22-C24	-171.2(4)	C20-C11-C22-C24	67.9(5)
C7-C11-C22-C10	-51.4(5)	C20-C11-C22-C10	-172.4(4)
O11-C10-C22-O1	-148.0(4)	C18-C10-C22-O1	33.6(5)
O11-C10-C22-C11	-28.8(6)	C18-C10-C22-C11	152.8(4)
O11-C10-C22-C24	92.1(5)	C18-C10-C22-C24	-86.3(5)
C20-C3-C23-C45	1.2(7)	C4-C3-C23-C45	-178.3(5)
O1-C22-C24-C29	-170.6(4)	C11-C22-C24-C29	66.6(6)
C10-C22-C24-C29	-54.5(6)	O1-C22-C24-C28	9.2(7)
C11-C22-C24-C28	-113.6(5)	C10-C22-C24-C28	125.3(5)
C16-C18-C25-C33	1.2(7)	C10-C18-C25-C33	-179.2(5)
C19-C15-C28-C24	-1.5(8)	C29-C24-C28-C15	-0.3(8)
C22-C24-C28-C15	179.8(5)	C28-C24-C29-C46	1.1(8)
C22-C24-C29-C46	-179.0(5)	C18-C25-C33-C27	0.3(8)

C42-C27-C33-C25	-0.9(8)	C3-C20-C38-C51	-0.7(8)
C11-C20-C38-C51	-178.4(5)	C18-C16-C42-C27	1.5(8)
C33-C27-C42-C16	0.0(8)	C3-C23-C45-C51	-1.7(8)
C24-C29-C46-C19	-0.1(8)	C15-C19-C46-C29	-1.7(8)
C20-C38-C51-C45	0.2(9)	C23-C45-C51-C38	1.0(9)
C8-C2-C5-C13	-144.3(5)	C6-C2-C5-C13	94.5(6)
C8-C2-C5-C14	36.0(6)	C6-C2-C5-C14	-85.2(5)
C37-O3-C6-O9	-5.3(7)	C37-O3-C6-C2	177.5(4)
C5-C2-C6-O9	124.0(5)	C8-C2-C6-O9	3.4(7)
C5-C2-C6-O3	-58.8(5)	C8-C2-C6-O3	-179.4(4)
C9-O2-C8-C2	42.4(5)	C9-O2-C8-C17	-81.2(5)
C9-O2-C8-C32	161.1(4)	C5-C2-C8-O2	-55.2(5)
C6-C2-C8-O2	65.4(5)	C5-C2-C8-C17	68.2(5)
C6-C2-C8-C17	-171.1(4)	C5-C2-C8-C32	-173.0(4)
C6-C2-C8-C32	-52.3(5)	C8-O2-C9-O7	174.0(4)
C8-O2-C9-C14	-6.6(6)	C14-C5-C13-C43	0.6(7)
C2-C5-C13-C43	-179.1(5)	C13-C5-C14-C39	0.4(7)
C2-C5-C14-C39	-179.9(4)	C13-C5-C14-C9	179.1(5)
C2-C5-C14-C9	-1.2(7)	O7-C9-C14-C39	-17.6(7)
O2-C9-C14-C39	163.1(4)	O7-C9-C14-C5	163.7(5)
O2-C9-C14-C5	-15.6(6)	O2-C8-C17-C55	-173.6(4)
C2-C8-C17-C55	63.0(6)	C32-C8-C17-C55	-56.3(6)
O2-C8-C17-C56	9.7(7)	C2-C8-C17-C56	-113.7(6)
C32-C8-C17-C56	127.0(5)	O2-C8-C32-O6	-161.1(4)
C2-C8-C32-O6	-41.3(6)	C17-C8-C32-O6	79.4(5)
O2-C8-C32-C36	23.6(6)	C2-C8-C32-C36	143.4(5)
C17-C8-C32-C36	-95.9(6)	O6-C32-C36-C71	155.2(13)
C8-C32-C36-C71	-29.7(14)	O6-C32-C36-C67	-38.5(7)
C8-C32-C36-C67	136.6(6)	C43-C26-C39-C14	2.2(8)
C5-C14-C39-C26	-1.8(7)	C9-C14-C39-C26	179.5(5)
C5-C13-C43-C26	-0.2(8)	C39-C26-C43-C13	-1.2(8)
C56-C17-C55-C61	-2.3(8)	C8-C17-C55-C61	-179.0(5)
C55-C17-C56-C64	1.4(9)	C8-C17-C56-C64	178.1(6)
C64-C57-C61-C55	0.7(10)	C17-C55-C61-C57	1.3(9)
C61-C57-C64-C56	-1.6(11)	C17-C56-C64-C57	0.6(11)
C71-C36-C67-C69	-16.8(14)	C32-C36-C67-C69	175.3(6)
C70-C62-C69-C67	20.7(15)	C36-C67-C69-C62	-0.6(12)
C69-C62-C70-C71	-23.(3)	C67-C36-C71-C70	16.(2)
C32-C36-C71-C70	-177.7(15)	C62-C70-C71-C36	5.(3)
C30-O10-C21-C12	-86.0(5)	C30-O10-C21-C49	157.6(4)

C30-O10-C21-C48	37.3(6)	C52-C12-C21-O10	-174.4(5)
C44-C12-C21-O10	6.0(7)	C52-C12-C21-C49	-57.4(6)
C44-C12-C21-C49	123.0(6)	C52-C12-C21-C48	62.5(6)
C44-C12-C21-C48	-117.0(6)	C21-O10-C30-O12	178.6(5)
C21-O10-C30-C47	2.1(7)	C47-C31-C35-C34	1.0(8)
C40-C34-C35-C31	-2.6(8)	C35-C34-C40-C41	2.0(8)
C34-C40-C41-C47	0.2(8)	C34-C40-C41-C48	-179.7(5)
C52-C12-C44-C54	-2.1(9)	C21-C12-C44-C54	177.4(5)
C35-C31-C47-C41	1.2(8)	C35-C31-C47-C30	-176.3(5)
C40-C41-C47-C31	-1.8(7)	C48-C41-C47-C31	178.1(5)
C40-C41-C47-C30	175.7(5)	C48-C41-C47-C30	-4.3(7)
O12-C30-C47-C31	-19.1(8)	O10-C30-C47-C31	157.2(5)
O12-C30-C47-C41	163.4(5)	O10-C30-C47-C41	-20.4(7)
C40-C41-C48-C21	-138.0(5)	C47-C41-C48-C21	42.1(6)
C40-C41-C48-C53	102.3(6)	C47-C41-C48-C53	-77.6(6)
O10-C21-C48-C41	-57.7(5)	C12-C21-C48-C41	65.7(6)
C49-C21-C48-C41	-176.4(4)	O10-C21-C48-C53	60.9(5)
C12-C21-C48-C53	-175.7(4)	C49-C21-C48-C53	-57.8(6)
O10-C21-C49-O13	-138.8(5)	C12-C21-C49-O13	102.1(5)
C48-C21-C49-O13	-18.4(7)	O10-C21-C49-C58	44.6(7)
C12-C21-C49-C58	-74.5(6)	C48-C21-C49-C58	165.1(5)
C44-C12-C52-C60	1.8(9)	C21-C12-C52-C60	-177.8(6)
C66-C1-C53-O14	-6.5(10)	C66-C1-C53-C48	171.9(5)
C41-C48-C53-O14	81.7(8)	C21-C48-C53-O14	-36.4(8)
C41-C48-C53-C1	-96.7(5)	C21-C48-C53-C1	145.2(5)
C12-C44-C54-C59	0.5(10)	O13-C49-C58-C63	172.8(6)
C21-C49-C58-C63	-10.7(10)	O13-C49-C58-C68	5.8(8)
C21-C49-C58-C68	-177.7(6)	C44-C54-C59-C60	1.4(11)
C54-C59-C60-C52	-1.7(11)	C12-C52-C60-C59	0.1(10)
C68-C58-C63-C65	-15.4(11)	C49-C58-C63-C65	179.0(7)
C58-C63-C65-C73	0.6(14)	C63-C58-C68-C72	8.6(12)
C49-C58-C68-C72	176.2(8)	C58-C68-C72-C73	9.9(15)
C63-C65-C73-C72	19.2(19)	C68-C72-C73-C65	-25.2(2)

Table 7. Anisotropic atomic displacement parameters ($\text{\AA}^2$) for (3*R*,4*R*)-463.

The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.0164(17)	0.019(2)	0.0134(17)	-0.0005(15)	0.0000(13)	0.0008(14)

O4	0.0216(18)	0.022(2)	0.0153(18)	-0.0018(17)	0.0002(14)	-0.0019(15)
O5	0.0168(18)	0.025(2)	0.034(2)	-0.0032(17)	-0.0040(15)	0.0066(16)
O8	0.0227(19)	0.029(2)	0.035(2)	-0.0051(18)	-0.0084(16)	0.0000(17)
O11	0.0178(18)	0.030(2)	0.0207(18)	0.0017(17)	0.0035(15)	0.0016(16)
C3	0.013(2)	0.018(3)	0.025(3)	0.005(2)	-0.003(2)	0.001(2)
C4	0.013(2)	0.016(3)	0.021(3)	-0.002(2)	-0.0027(19)	0.001(2)
C7	0.023(3)	0.020(3)	0.015(2)	0.001(2)	0.001(2)	0.000(2)
C10	0.015(2)	0.027(3)	0.012(2)	-0.001(2)	-0.0029(19)	0.001(2)
C11	0.015(2)	0.017(3)	0.016(3)	0.000(2)	0.0002(19)	0.004(2)
C15	0.011(2)	0.029(3)	0.036(3)	0.002(3)	-0.001(2)	-0.001(2)
C16	0.017(3)	0.032(3)	0.012(2)	0.009(2)	-0.0016(18)	0.004(2)
C18	0.017(3)	0.023(3)	0.018(3)	0.005(2)	-0.008(2)	-0.001(2)
C19	0.017(3)	0.019(3)	0.032(3)	0.003(2)	-0.008(2)	-0.005(2)
C20	0.012(2)	0.019(3)	0.021(3)	0.001(2)	-0.0089(19)	0.000(2)
C22	0.013(2)	0.012(3)	0.015(2)	-0.004(2)	0.0008(18)	0.004(2)
C23	0.016(3)	0.027(3)	0.024(3)	0.001(2)	0.001(2)	-0.002(2)
C24	0.016(2)	0.013(3)	0.017(2)	-0.001(2)	-0.0028(19)	0.000(2)
C25	0.019(3)	0.021(3)	0.019(3)	0.002(2)	-0.001(2)	-0.004(2)
C27	0.041(3)	0.018(3)	0.020(3)	0.006(2)	-0.003(2)	-0.003(3)
C28	0.021(3)	0.017(3)	0.017(2)	0.002(2)	-0.001(2)	0.006(2)
C29	0.016(2)	0.019(3)	0.022(3)	0.000(2)	0.002(2)	0.003(2)
C33	0.029(3)	0.027(4)	0.021(3)	0.000(2)	-0.002(2)	0.004(2)
C38	0.026(3)	0.016(3)	0.031(3)	0.001(2)	0.000(2)	0.006(2)
C42	0.021(3)	0.032(4)	0.018(3)	0.005(2)	-0.002(2)	-0.005(2)
C45	0.023(3)	0.021(3)	0.038(3)	0.011(3)	0.002(2)	0.005(2)
C46	0.031(3)	0.023(3)	0.020(3)	0.001(2)	-0.005(2)	0.000(2)
C50	0.013(3)	0.031(3)	0.042(3)	0.007(3)	-0.001(2)	0.001(2)
C51	0.028(3)	0.021(3)	0.051(4)	0.001(3)	0.000(3)	0.000(2)
O2	0.0279(19)	0.016(2)	0.0135(17)	-0.0021(14)	-0.0036(14)	-0.0014(15)
O3	0.0124(16)	0.029(2)	0.0200(18)	0.0009(16)	0.0024(13)	0.0002(15)
O6	0.0196(18)	0.022(2)	0.027(2)	-0.0034(16)	-0.0016(14)	-0.0029(16)
O7	0.0224(19)	0.016(2)	0.0272(19)	-0.0022(16)	0.0028(15)	-0.0042(15)
O9	0.0170(17)	0.024(2)	0.0213(18)	-0.0015(16)	-0.0014(14)	0.0044(15)
C2	0.016(2)	0.017(3)	0.019(3)	-0.003(2)	-0.004(2)	0.000(2)
C5	0.011(2)	0.024(3)	0.016(2)	-0.006(2)	0.0020(18)	-0.001(2)
C6	0.020(2)	0.010(3)	0.020(3)	0.002(2)	-0.001(2)	-0.002(2)
C8	0.019(2)	0.015(3)	0.016(2)	0.001(2)	-0.003(2)	-0.002(2)
C9	0.010(2)	0.020(3)	0.021(3)	-0.004(2)	0.0002(19)	0.002(2)
C13	0.016(2)	0.029(3)	0.021(3)	0.001(2)	0.002(2)	0.005(2)
C14	0.015(2)	0.019(3)	0.017(2)	-0.005(2)	0.0010(19)	0.004(2)

C17	0.015(2)	0.014(3)	0.017(2)	-0.003(2)	0.0006(19)	-0.001(2)
C26	0.022(3)	0.037(4)	0.019(3)	-0.008(2)	-0.002(2)	0.006(2)
C32	0.019(3)	0.020(3)	0.020(3)	-0.006(2)	0.002(2)	0.003(2)
C36	0.020(3)	0.028(3)	0.016(3)	-0.005(2)	-0.0015(19)	0.004(2)
C37	0.015(2)	0.023(3)	0.022(3)	-0.002(2)	0.004(2)	0.001(2)
C39	0.014(2)	0.024(3)	0.027(3)	-0.004(2)	0.004(2)	0.004(2)
C43	0.026(3)	0.040(4)	0.014(2)	0.003(3)	0.002(2)	0.011(3)
C55	0.029(3)	0.020(3)	0.032(3)	0.004(3)	0.007(2)	0.000(2)
C56	0.017(3)	0.038(4)	0.060(4)	-0.022(3)	0.000(3)	-0.002(3)
C57	0.028(3)	0.040(4)	0.037(3)	-0.013(3)	-0.007(2)	0.020(3)
C61	0.039(3)	0.023(3)	0.043(4)	-0.006(3)	0.011(3)	0.009(3)
C62	0.066(5)	0.035(4)	0.029(3)	0.005(3)	-0.020(3)	-0.001(3)
C64	0.008(3)	0.053(5)	0.080(5)	-0.040(4)	0.005(3)	0.001(3)
C67	0.048(4)	0.070(6)	0.067(5)	0.005(5)	0.004(4)	-0.001(4)
C69	0.069(5)	0.078(7)	0.051(5)	-0.002(4)	-0.007(4)	-0.002(5)
C70	0.32(2)	0.083(9)	0.087(8)	0.070(7)	-0.146(12)	-0.123(12)
C71	0.29(2)	0.098(10)	0.112(9)	0.080(8)	-0.155(12)	-0.141(12)
O10	0.034(2)	0.023(2)	0.0187(18)	-0.0015(16)	0.0090(15)	-0.0065(17)
O12	0.056(3)	0.034(3)	0.020(2)	0.0072(19)	0.0054(18)	0.000(2)
O13	0.020(2)	0.048(3)	0.047(2)	-0.022(2)	-0.0037(18)	0.0011(19)
O14	0.041(3)	0.052(4)	0.090(4)	-0.016(3)	0.038(3)	-0.015(2)
C1	0.005(2)	0.043(4)	0.024(3)	-0.023(3)	-0.0127(19)	0.025(2)
C12	0.015(2)	0.014(3)	0.022(3)	0.004(2)	0.002(2)	0.000(2)
C21	0.020(3)	0.015(3)	0.027(3)	-0.004(2)	0.001(2)	-0.004(2)
C30	0.024(3)	0.027(3)	0.022(3)	-0.003(3)	0.008(2)	0.000(2)
C31	0.020(3)	0.029(3)	0.024(3)	-0.008(2)	-0.003(2)	0.000(2)
C34	0.025(3)	0.019(3)	0.033(3)	-0.010(3)	0.001(2)	-0.005(2)
C35	0.018(3)	0.029(4)	0.037(3)	-0.009(3)	-0.007(2)	-0.005(2)
C40	0.027(3)	0.022(3)	0.030(3)	0.001(3)	0.000(2)	0.005(2)
C41	0.016(2)	0.017(3)	0.025(3)	-0.009(2)	0.004(2)	-0.001(2)
C44	0.024(3)	0.024(3)	0.022(3)	0.004(2)	0.000(2)	0.010(2)
C47	0.022(3)	0.017(3)	0.021(3)	-0.006(2)	0.005(2)	0.000(2)
C48	0.018(3)	0.020(3)	0.031(3)	-0.008(2)	-0.009(2)	0.006(2)
C49	0.025(3)	0.030(4)	0.033(3)	-0.007(3)	0.013(3)	-0.011(3)
C52	0.017(3)	0.034(4)	0.025(3)	0.006(3)	0.000(2)	0.005(2)
C53	0.029(3)	0.028(4)	0.050(4)	-0.021(3)	-0.007(3)	-0.011(3)
C54	0.019(3)	0.050(4)	0.037(3)	0.000(3)	-0.003(2)	0.003(3)
C58	0.079(5)	0.019(4)	0.019(3)	-0.001(3)	0.004(3)	-0.019(3)
C59	0.019(3)	0.050(4)	0.041(4)	0.008(3)	0.010(2)	-0.007(3)
C60	0.028(3)	0.051(4)	0.022(3)	0.013(3)	0.008(2)	-0.003(3)

C63	0.031(3)	0.029(4)	0.056(4)	-0.022(3)	0.010(3)	-0.007(3)
C65	0.099(6)	0.025(4)	0.040(4)	-0.003(3)	0.009(4)	-0.009(4)
C66	0.012(3)	0.153(10)	0.102(7)	-0.086(7)	0.012(4)	0.008(4)
C68	0.075(6)	0.055(6)	0.075(6)	-0.008(5)	0.004(5)	0.000(5)
C72	0.092(7)	0.068(7)	0.089(7)	-0.002(6)	-0.013(6)	-0.002(6)
C73	0.39(3)	0.024(5)	0.053(6)	0.005(4)	-0.090(10)	-0.033(9)

Table 8. Hydrogen atomic coordinates and isotropic atomic displacement parameters ($\text{\AA}^2$) for (3*R*,4*R*)-463.

	x/a	y/b	z/c	U(eq)
H11	0.4615	0.6210	0.7063	0.019
H15	1.0571	0.5202	0.7198	0.031
H16	0.2135	0.4167	0.7727	0.024
H19	1.0490	0.5646	0.8617	0.027
H23	0.7674	0.5967	0.4054	0.027
H25	0.6465	0.4107	0.6806	0.023
H27	0.4110	0.2530	0.7197	0.032
H28	0.8318	0.5078	0.6331	0.022
H29	0.5880	0.5757	0.8391	0.023
H33	0.6337	0.3033	0.6785	0.031
H38	0.5553	0.7174	0.6331	0.029
H42	0.2003	0.3094	0.7666	0.028
H45	0.8200	0.7026	0.4152	0.033
H46	0.8129	0.5900	0.9233	0.029
H50A	0.1020	0.6387	0.4971	0.043
H50B	0.0458	0.6903	0.5658	0.043
H50C	0.0181	0.6187	0.5869	0.043
H51	0.7108	0.7616	0.5269	0.04
H2	0.7067	0.2936	0.3751	0.021
H13	0.8109	0.2963	0.5318	0.027
H26	1.0978	0.4339	0.6076	0.031
H37A	0.3665	0.4278	0.4817	0.03
H37B	0.3293	0.3701	0.5446	0.03
H37C	0.2806	0.3687	0.4401	0.03
H39	1.0527	0.4837	0.4706	0.026
H43	0.9811	0.3391	0.6374	0.032
H55	0.8200	0.2334	0.2601	0.032
H56	1.0600	0.3925	0.2494	0.046
H57	1.2737	0.2298	0.2117	0.042

H61	1.0426	0.1770	0.2309	0.041
H62	0.4686	0.4552	-0.0806	0.052
H64	1.2840	0.3355	0.2241	0.057
H67	0.6051	0.2952	0.0425	0.074
H69	0.5334	0.3481	-0.0930	0.079
H70	0.6116	0.5043	0.0216	0.2
H71	0.6705	0.4552	0.1579	0.203
H1	1.2177	0.0606	0.9014	0.029
H31	0.6751	0.1099	0.6230	0.029
H34	0.7109	-0.0424	0.7765	0.031
H35	0.6139	0.0075	0.6491	0.034
H40	0.8867	0.0079	0.8736	0.031
H44	0.6344	0.2238	0.8334	0.028
H48	1.0062	0.1053	0.9263	0.027
H52	0.8813	0.1556	1.0453	0.031
H54	0.4117	0.2149	0.9152	0.043
H59	0.4203	0.1754	1.0603	0.044
H60	0.6562	0.1475	1.1284	0.04
H63	0.8688	0.3169	0.8412	0.046
H65	0.8582	0.4240	0.8587	0.065
H66A	1.3639	0.0553	0.7476	0.133
H66B	1.4593	0.0570	0.8410	0.133
H66C	1.4231	0.1198	0.7880	0.133
H68	1.2294	0.3001	1.0223	0.082
H72	1.2496	0.4112	1.0237	0.1
H73	0.9984	0.4659	0.9813	0.189