Organocatalysed transformations of enolisable cyclic anhydrides

Trinity College Dublin

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

Doctor of Philosophy

by

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Under the supervision of

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Declaration

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Astrid Botte


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Abstract

Herein is reported our attempts at the first formal cycloaddition reaction involving either glutaric anhydride derivatives or cyclic anhydrides including an endocyclic electron-withdrawing heteroatom with different electrophiles promoted by cinchona alkaloid derived catalysts. Despite the promising advantages of employing anhydrides bearing enol-stabilising groups, the optimisation of the synthetic pathway proved difficult.

The use of cinchona alkaloid-derived bifunctional organocatalysts to promote the dynamic kinetic resolution of cyclic anhydrides by alcoholysis was investigated. Initial studies were aimed at evaluating the regioselectivity of the nucleophilic addition using phenylsuccinic anhydride. Experiments aimed towards the development of optimal reaction conditions have been conducted and several bifunctional cinchona alkaloid substituted organocatalysts were evaluated. Although the novel sulfonamide-based organocatalysts failed to promote a potential DKR strategy, they proved to be excellent catalysts for highly efficient PKR of enolisable cyclic anhydrides with unprecedent enantiocontrol.

Evaluation of the steric properties of the alcohols nucleophiles was also undertaken but did not give the desired results, while varying their electronic properties was found to influence the resulting regio- and enantioselectivity of the reactions under scrutiny.

Furthermore, the enantioselective resolution of cyclic anhydrides with variable substituents was also explored. The results obtained demonstrated the feasibility of the process; which allows for the PKR of substituted succinic anhydrides with a regioselectivity which depends on the steric bulk of the anhydride.

Finally, the possibility of using iminophosphorane bifunctional catalysts to promote the enantioselective cycloaddition reaction of enolisable anhydrides with various aldehydes to form annulated structures was investigated. The first example of a cycloaddition reaction between phenylglutaconic anhydride and aromatic aldehydes has been demonstrated. The evaluation of several aldehydes as substrates was also studied and the expansion of the substrate scope with regard to the anhydrides was also reported.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>Ac</td>
<td>Acetyl</td>
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<tr>
<td>AcOH</td>
<td>Acetic acid</td>
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<td>AD</td>
<td>Asymmetric dihydroxylation</td>
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<td>APCI</td>
<td>Atmospheric-pressure chemical ionization</td>
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<tr>
<td>app. d</td>
<td>Apparent doublet</td>
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<tr>
<td>app. s</td>
<td>Apparent singlet</td>
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<td>Apparent triplet</td>
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<td>Base</td>
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<td>Boiling point</td>
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<td>tert-Butyloxycarbonyl</td>
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<td>bs</td>
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<td>Diphenylphosphoryl azide</td>
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<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
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<tr>
<td>E</td>
<td>Electrophile</td>
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<td>Description</td>
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</tr>
<tr>
<td>EDG</td>
<td>Electron donating group</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
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<td>Electron ionisation</td>
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<td>Electrospray ionization</td>
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<td>EWG</td>
<td>Electron withdrawing group</td>
</tr>
<tr>
<td>h</td>
<td>Hours</td>
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<td>His</td>
<td>Histidine</td>
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<tr>
<td>HMPA</td>
<td>Hexamethyl phosphoramide</td>
</tr>
<tr>
<td>HNEt&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Diethyl amine</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest occupied molecular orbital</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>High-resolution mass spectrometry</td>
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<tr>
<td>i-IPA</td>
<td>iso-Propyl alcohol</td>
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<td>i-Pr</td>
<td>Isopropyl</td>
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<tr>
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<td>N,N’-Diisopropylethylamine (Hünig’s base)</td>
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<td>2-propanol</td>
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<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>IUPAC</td>
<td>International Union of Pure and Applied Chemistry</td>
</tr>
<tr>
<td>KHMDS</td>
<td>Potassium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>LA</td>
<td>Lewis acid</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>L-DOPA</td>
<td>L-3,4-DIHYDROXYPHENYLALANINE</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>Lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>lit.</td>
<td>Literature</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet</td>
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<td>m-</td>
<td>meta-</td>
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<td>m.p.</td>
<td>Melting point</td>
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<tr>
<td>MTBE</td>
<td>Methyl-&lt;i&gt;tert&lt;/i&gt;-butyl ether</td>
</tr>
<tr>
<td>MW</td>
<td>Microwave</td>
</tr>
<tr>
<td>n-</td>
<td>normal-</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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</tr>
<tr>
<td>NAD⁺/NADH</td>
<td>Nicotinamide adenine dinucleotide</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>Sodium bis(trimethylsilyl)amide</td>
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<tr>
<td>NEt₃</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
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<td>NOE</td>
<td>Nuclear Overhauser Effect</td>
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<tr>
<td>Nu</td>
<td>Nucleophile</td>
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<td>o-</td>
<td>ortho-</td>
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<td>OAc</td>
<td>Acetate</td>
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<tr>
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<td>Quantitative</td>
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<tr>
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<td>Triplet</td>
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<td>tert-Butyl alcohol</td>
</tr>
<tr>
<td>temp.</td>
<td>Temperature</td>
</tr>
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<td>tert-</td>
<td>tertiary-</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAAA</td>
<td>Trifluoroacetic anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
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<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
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<td>TMS</td>
<td>Trimethylsilyl</td>
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<tr>
<td>TMSCHN₂</td>
<td>Trimethylsilyl diazomethane</td>
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<tr>
<td>TMSCN</td>
<td>Trimethylsilyl cyanide</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>v/v</td>
<td>Volume/Volume</td>
</tr>
<tr>
<td>w/v</td>
<td>Weight/Volume</td>
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</table>
Chapter 1

Introduction
Chapter 1

Introduction

1.1 Asymmetric synthesis: an overview

“...do not let your left hand know what your right hand is doing, so that your giving may be a secret...”
Matthew 6:3

One of the most fundamental, yet most intriguing aspects of the universe is ‘chirality’. Derived from the Greek ‘χείρ’ (cheir, hand), chirality is a geometric property of an object whereby it is non-superimposable on its mirror image. The simple example of chirality in nature is human hands; the right hand is the mirror image of the left, but they are non-superimposable.

The concept of tetrahedral chirality was introduced by J. H. van’t Hoff\(^1\) and J. A. Le Bel\(^2\) in 1874 following the experiment of L. Pasteur in 1848, when he observed that crystalline deposits that formed in wine barrels during fermentation were composed of sodium and ammonium tartrates. After separating them, he recognised that they rotated plane polarised light.\(^3\)

The importance of chirality in chemistry since the turn of the nineteenth century cannot be understated. An increasing industrial demand for enantiomerically pure molecules led to a substantial growth in research and development of asymmetric synthesis.\(^4\) As the three-dimensional structure of chiral molecules is a fundamental feature for their interactions with biological systems, the control of stereochemistry has become an important aspect for the food and pharmaceutical industries.\(^5,6\) Different stereoisomers that are non-superimposable mirror images (enantiomers), despite having identical physical properties, can have disparate pharmacology.\(^7\) The importance of enantiopurity is demonstrated by the tragic case of thalidomide, an highly publicised drug in 1950s and 1960s in Germany. Only one of the two enantiomers of thalidomide had sedative effects, the other was a potent teratogen, causing birth defects and malformations of the newborn child. A more benign example is that of limonene, an aromatic substance present in lemons and oranges. In this case the difference is clearly perceptible from smell, one enantiomer smells like lemons, while the other smells of oranges.\(^8\)
1.1.1 Early approaches to the synthesis of enantiopure compounds

Overall, the four strategies for the synthesis of enantiomerically-pure compounds are:

1. The resolution of a racemic mixture
2. Chiral pool
3. The use of a chiral auxiliary
4. Asymmetric synthesis

Industrially, the resolution of racemates is used for the production of more than 50% of the optically active drugs. The resolution of a racemic mixture is in most cases achieved by conversion of a racemic mixture into a mixture of separable diastereomeric salts by derivatisation with an optically pure resolving agent. Some significant drawbacks are that the process is time consuming due to the necessity for extra steps for the formation and the cleavage of the diastereomeric pairs and the yield is limited to 50% as the unwanted enantiomer remains at the end of the process.

The chiral pool approach technique uses enantiopure molecules (chiral building block) mostly derived from natural products. Common chiral starting materials include carbohydrates, amino acids, and amines. These natural compounds have some advantages, they are readily available, cheap and multifunctional but also many drawbacks should also be considered. In this synthetic method, the efficacy of the chiral pool in synthesis depends on the structural similarity between the target molecule and the chiral natural molecule available otherwise there would be an excessive number of synthetic steps resulting in a low yield, a high cost and low environmental sustainability.

One of the first pharmaceutical applications of chiral pool synthesis dates to 1980, when Salzmann and co-workers used L-aspartic acid as chiral pool member in the synthesis of the β-lactam antibiotic imipenem (Merck).

The chiral auxiliary strategy requires that an enantiomerically pure chiral group is covalently linked to the achiral substrate and is released when the desired product is obtained. An example is the 3-step asymmetric synthesis of the pheromone frontalin (5) developed by Whitesell and co-workers in 1986 using 8-phenylmenthol as chiral auxiliary (Scheme 1.1).
Asymmetric catalysis can use enzymes, organometallic catalysts or small, low molecular weight chiral organic molecules (organocatalysts).\textsuperscript{14,15} Asymmetric catalysis concerns the use of sub-stoichiometric amounts of a chiral catalyst. These compounds form reversible complexes with the substrate molecule and are functional for more catalytic cycles.

Can a catalyst determine the stereochemical outcome of a reaction with excellent enantiocontrol? The first to definitely answer this question using de-novo designed catalysts was Knowles (Nobel Prize in Chemistry in 2001): in the 1970s, he developed a method for one of the first enantioselective hydrogenations reporting one of the first examples of asymmetric metal-catalysis. Following Wilkinson’s studies, on catalytic hydrogenation with triphenylphosphine complex of rhodium chloride,\textsuperscript{16} he observed that by using chiral bisphosphine ligands (DIPAMP \textsuperscript{8}), stereochemical information was transferred from the rhodium centre to the olefinic substrate \textsuperscript{6}, leading to the formation of \textsuperscript{7} in excellent enantiomeric excess (Scheme 1.2).\textsuperscript{17}

\begin{equation*}
\text{Scheme 1.1} \quad \text{Example of enantioselective synthesis promoted by chiral auxiliary.}
\end{equation*}

\begin{equation*}
\text{Scheme 1.2} \quad \text{Enantioselective metal-catalysed hydrogenation.}
\end{equation*}

Until recently, the field of asymmetric catalysis was dominated by chiral transition metal catalysts, however, the use of heavy and often toxic metals requires high purification
costs, some metals can be very expensive and rare and can be highly sensitive to atmospheric agents such as oxygen and humidity.

Biocatalysis is a synthetic strategy based on the use of enzymes, antibodies or microbes as catalysts. For many years humans utilised enzymes in fermentation to produce and preserve food, in the first half of 20th century scientists began to use such molecules in various biocatalytic processes. In 1913, Ludwig Rosenthaler reported the preparation of (R)-mandelonitrile (11) by treating benzaldehyde (9) with HCN (10) in presence of emulsin extracted from bitter almonds (Scheme 1.3). 

Scheme 1.3 Enzyme-catalysed asymmetric synthesis of (R)-mandelonitrile (11).

Biocatalysis, has become a valuable alternative to asymmetric synthesis, not only for the lower environmental impact that derives from their application, but also for the economic advantages.

1.2 The development of organocatalysis

Organocatalysis is the branch of asymmetric catalysis that uses chiral natural or synthetic organic molecules as catalysts. These compounds are usually stable to moisture and air, non toxic, readily available and low-cost. Since the beginning of organic synthesis, chemists tried to prepare molecules with the elegance and efficiency found in nature. In 1928 the German chemist W. Langenbeck published "Analogies in the catalytic action of enzymes and defined organic substances". It is curious that the same author coined the term "organic catalysts" but still more surprising is that in 1949 he published the second edition (!) of the book "Organic catalysts and their relationship with enzymes".

In 1971 Hajos-Parrish-Eder-Sauer-Wiechert reported the first asymmetric intramolecular aldol reaction of triketone 12, using (L)-proline (13) as catalyst, to give 14. In a second step, acid catalysed dehydration furnished the Wieland-Miescher ketone (WMK, 15, Scheme 1.4), an important intermediate in steroid synthesis.
Later, in the 1980s, Inoue and co-workers demonstrated that a cyclic dipeptide prepared from \((L)-\)phenylalanine and \((L)-\)histidine (16), was able to catalyse the addition of 10 to benzaldehyde (9) with the creation of chiral cyanohydrin 11 (Scheme 1.5).\(^\text{27}\)

**Scheme 1.5** Enantioselective aldehyde hydrocyanation.

1.2.1 Organocatalysis: principal modes of action

Organocatalysis is still a rather new and popular field that only came to prominence at the start of the 21\(^{\text{st}}\) century. Before that only sporadic mentioning of chemical transformations promoted by organic catalysts were reported. It was List, Lerner and Barbas who reported the first example of an intermolecular asymmetric aldol reaction between an excess of acetone (18) with aldehydes \((i.e.\) 19) catalysed by \((L)-\)proline (13, Scheme 1.6).\(^\text{28}\)

**Scheme 1.6** Proline catalysed intermolecular asymmetric reaction.

Shortly after this seminal publication, MacMillan \textit{et al.} used secondary amines such as 23 to catalyse the Diels-Alder reaction between dienes \((i.e.\) 21) and \(\alpha,\beta\)-unsaturated
aldehydes such as 22 generating a new class of catalysts known as MacMillan's imidazolidinones\(^{29}\) (Scheme 1.7).

\[
\begin{align*}
\text{Scheme 1.7} & \quad \text{Asymmetric organocatalysed Diels-Alder reaction.}
\end{align*}
\]

These methods for the asymmetric formation of C-C bonds at the time represented a previously unseen general method of catalytic activation of carbonyl compounds based on enamine-iminium catalysis. Both of these activation methods are based on the generation of intermediates via condensation of cyclic chiral amines with a carbonyl group, consequently generating a positively charged iminium ion with concurrent lowering of LUMO energy.\(^{30,31}\) In case of \(\pi\)-conjugated systems, the electronic delocalisation induced by iminium ions facilitates nucleophilic additions (LUMO-activation, Scheme 1.8a) while for isolated \(\pi\)-systems, this electronic delocalisation can induce a rapid deprotonation event at the \(\alpha\)-carbon leading to the generation of an enamine of greater nucleophillic character (HOMO-activation, Scheme 1.8b). This phenomenon can be seen in proline-catalysed asymmetric reactions.\(^{28}\)

\[
\begin{align*}
\text{Figure 1.1} & \quad \text{Iminium-enamine catalysis.}
\end{align*}
\]

The efficiency and synthetic applications of these catalytic modes of action can be significantly improved when they work in tandem with each other, which facilitates “one pot” reactions. The reaction of the nucleophile with the iminium ion 1a, resulting in the
formation of an enamine, enables electrophilic addition 1b thereby creating two stereocenters in the process (1c, Scheme 1.8).

Scheme 1.8  Combination of iminium-enamine catalytic cycles.

The first tandem iminium-enamine catalysis reaction was reported by List, Yang and Fonseca in 2005. The authors described a Michael cyclisation in which an enal enone such as 25 in the presence of Hantzsch ester 27 and imidazolidinone salt 26, successfully promoted the formation of keto aldehydes (i.e. 28) in high yield and enantioselectivity (Scheme 1.9).32

Scheme 1.9  Imidazolidinone-catalysed Michael cyclisation.

H-bonding is frequently used by biological systems for molecular recognition, substrate binding, orientation and activation.33 In view of the ubiquity of hydrogen bonds in nature, non-covalent interaction-based catalysis mimicking enzymatic functions has emerged as a powerful catalytic method in contemporary organic synthesis.34,35 One of the first examples appeared in the early 1980s when Hine et al. recognised the ability of biphenyldiols to promote the aminolysis of epoxides through double hydrogen bond catalysis.36,37 He reported the superiority of 1,8-biphenylenediol (30) to phenol itself in the addition of diethylamine to phenyl glycidyl ether (29) to furnish 31 (Scheme 1.10).
Scheme 1.10 Epoxide-opening reaction promoted by biphenylenediol.

An extension of this concept came in the following years, when Kelly and co-workers demonstrated Diels-Alder reactions with superior rates, by establishing a bis-hydrogen bond interaction between biphenyldiols such as 34 and dienophiles (i.e. 33, Scheme 1.11)\(^3\)

Scheme 1.11 Bis-hydrogen bond promoted Diels-Alder reaction.

1.2.2 (Thio)ureas in asymmetric organocatalysis

In the late 1980s, asymmetric synthesis based on electrophile activation by small molecules H-bond donors gained considerable attention.\(^3\) The observation by Etter and co-workers that electron poor diarylureas co-crystallised with a wide variety of Lewis bases (e.g. sulfoxides) due to their high H-bond donating ability should be considered noteworthy.\(^4\)\(^5\) In 1994, inspired by Kelly’s work and the elucidation of m-nitrodiarylurea’s crystal structure by Etter, Curran et al. reported the first example of a general acid catalysed reaction using urea derivatives (i.e. 37) as catalysts. In particular, he found that catalytic amounts of 37 were able to catalyse the allylation of cyclic \(\alpha\) sulfinyl radicals observing very small rate accelerations but improved diastereoselectivity.\(^6\) Shortly afterwards, the same group reported how these catalysts, bearing a trifluoromethyl group and a lipophilic octyl ester on each phenyl ring were also used to increase the rate of the Claisen rearrangement of 36 (Scheme 1.12).\(^7\)
Scheme 1.12 Claisen rearrangement catalysed by N,N-diaryl urea.

Control experiments demonstrated that by replacing N,N-dimethyl urea 37 with 38 (no hydrogen bonds available) resulted in complete inhibition of the aforementioned accelerated reaction rate. Further proof of the important effect of hydrogen bonds was provided when benzanilide (41, one hydrogen bond available) resulted in only a slightly decreased rate of reaction. These studies suggested that the acceleration of Claisen rearrangement was due in large part to the formation of hydrogen bonds in the transition state 39 between the substrate 36 and catalyst 37.

In 2000, Schreiner and co-workers inspired by the results obtained by Etter, Curran et al. used thiourea derivatives as catalysts for Diels-Alder reactions. The idea of using a catalyst bearing a thiourea was ascribed to the several advantages thioureas presented in comparison to the urea counterparts such as: enhanced differences in acidities (pKa thiourea 21.0; pKa urea 26.9), more solubility in a variety of solvents, easier synthesis and lower electronegativity of sulfur and less propensity towards dimerisation. A series of computational studies revealed similarities between H-bonded complex of an N-acyloxazolidinone (i.e. 42) and the corresponding Lewis acid complex. These studies were then substantiated by a significant rate acceleration of the Diels-Alder reaction between cyclopentadiene (43) and 42 to furnish products 44a and 44b (Scheme 1.13).
The catalytic effectiveness of a series of symmetrically substituted thioureas was then investigated by the same group. As expected, the choice of catalyst was crucial for controlling the outcome of the reaction. While the alkyl-substituted thioureas and 1,3-diphenylthiourea (49) resulted in only a minimal enhancement of reaction rate, the accelerating effect of thioureas bearing electron-withdrawing groups (i.e. 46) was more pronounced. Scheme 1.15 depicts an example of N,N-disubstituted thioureas such as 46 promoting the [4+2] cycloaddition reactions of cyclopentadiene (43) with α,β-unsaturated ketones such as 47. The superiority of catalyst 46 compared to 45 was ascribed to the enhanced acidity of the NH bonds provided by the CF$_3$ substituent which theoretically, can lead to an increased level of hydrogen bond donating ability, and secondly by facilitating hydrogen bonding interactions between the sulfur atom of the thiourea and the ortho protons of the aniline units, subsequently generating a more rigid structure (Scheme 1.14).

![Scheme 1.13](image1)

**Scheme 1.13** Diels-Alder reaction promoted by diarylthioureas.

![Scheme 1.14](image2)

**Scheme 1.14** [4 + 2] cycloaddition reactions catalysed by diarylthioureas.
In subsequent studies, Schreiner’s catalyst 46 was shown to be an efficient promoter in a wide range of organic transformations such as Corey-Chaykovsky epoxidations, epoxide ring opening reactions, and Baylis-Hillman reactions.

In 2003, Takemoto and co-workers reported 46 as an efficient catalyst for the promotion of the addition of cyanide (TMSCN) and ketene silyl acetics to various nitrones in high yield with fast reaction rates. Almost simultaneously, Ricci et al. reported the use of diaryl(thio)ureas as catalysts capable of accelerating the addition of aromatic substrates to electron deficient alkenes (Friedel-Crafts-type alkylation). They observed that the presence of an electron donating functionality on the aryl ring of the dimethylaniline, resulted in enhanced reactivity with compounds such as nitroolefin 51 (Scheme 1.15). The authors proposed a catalyst mode of action via interactions between the thiourea catalyst (46) and the nitro group of the nitroolefin (A Scheme 1.15).

![Scheme 1.15](image)

**Scheme 1.15** Friedel–Crafts Alkylation catalysed by thiourea 46.

Inspired by biological redox transformations, and in particular by Hantzsch esters as biomimetic reductants, Zhang and Schreiner developed a biomimetic procedure for reduction of nitroolefins. Thiourea 46 was efficiently employed in reduction of nitrostyrene (51) using Hantzsch ester 30 as a NADPH analogue to give 53 in good yield (Scheme 1.16).
Scheme 1.16 Thiourea promoted biomimetic reduction of nitrostyrene (51).

Among the variety of reactions catalysed by (thio)urea derivatives, the dual activation of the Morita-Baylis-Hillman reaction using a combination of DABCO and various H-bonding catalysts was found particularly efficient by Connon et al. in 2004. Unexpectedly, the urea analogue (i.e. 56) was superior to the more acidic 46 in terms of efficiency in the reaction between methyl acrylate (54) and benzaldehyde (9). This enhanced efficiency was postulated to be due to thiourea’s partial decomposition under the reaction conditions (Scheme 1.17).

Scheme 1.17 Baylis-Hillman reaction promoted by (thio)urea derivatives.

Shortly after, Connon and co-workers reported that substituted N,N-diarylureas (i.e. 56) are capable of the efficient catalysis of the Corey–Chaykovsky reaction involving the inexpensive trimethylsulfonium iodide (58) and several aldehydes such as 57 (Scheme 1.18).

Scheme 1.18 Corey-Chaykovsky reaction promoted by a N,N-diarylurea.
In the following years, the same group introduced the first transthioesterification reaction catalysed by urea-based hydrogen bond donors. A binary catalyst system consisting of urea \(56\) and a promoter (DIPEA) was able to promote the reaction between bulky chiral thioesters and unhindered achiral thiols.\(^{54}\)

### 1.2.3 Chiral (thio)ureas as organocatalysts

In the course of studies involving asymmetric metal-catalysed cyanide addition to the C=\(\text{N}\) double bond (Strecker reaction), in 1998 Jacobsen \textit{et al.} reported the first example of an asymmetric reaction promoted by chiral (thio)ureas.\(^{55}\) As a chiral precursor for the preparation of these catalysts, enantiomerically pure 1,2-diaminocyclohexane was used in addition to an optically active alkyl \(\alpha\)-amino acid. On the basis of computational and mechanistic studies, these new types of organocatalysts were found to be highly suitable for the formation of two hydrogen bonds with the nitrogen atom of the (\(Z\))-isomer of imines, promoting the reaction with a higher degree of enantioselectivity than the comparable metal-catalysed analogous process. After a series of experiments aimed at optimising the catalyst structure, \(62\) was the superior Strecker catalyst prepared to date\(^{56,57}\). The use of aliphatic as well as aromatic aldimines (\textit{i.e.} \(61\)), in presence of 1 mol\% of catalyst \(62\) affording the \(\alpha\)-aminonitrile \(63\) was completed in excellent enantioselectivity (Scheme 1.19).

![Scheme 1.19 Asymmetric Strecker reaction with optimised Jacobsen-type organocatalyst 62.](image)

In the next few years, Jacobsen \textit{et al.} explored the use of this new family of chiral (thio)urea organocatalysts, utilising them in a large range of chemical transformations such as Mannich-\(^{58}\), nitro-Mannich-\(^{59}\), and hydrophosphonylation reactions.\(^{60}\)

### 1.2.4 Bifunctional asymmetric (thio)urea-based organocatalysts
Over the past decade, bifunctional compounds, bearing both a thiourea moiety and an amine group on a chiral scaffold have emerged as a powerful tool in asymmetric organocatalysis.\textsuperscript{61,62,63} Chiral catalysts containing both an acidic and basic/nucleophilic structural units were first reported by Takemoto and co-workers in 2003.\textsuperscript{64} They demonstrated that use of the thiourea catalyst 66, led to an efficient Michael addition reaction of malonates such as 65 to nitroolefins (\textit{i.e.} 64). These organocatalysts brought about the simultaneous activation of both the nucleophilic and electrophilic components in a chiral environment, introducing the concept of bifunctionality (68, Scheme 1.20).\textsuperscript{39}

![Scheme 1.20 Michael-type reaction catalysed by bifunctional thiourea 66.](image)

Shortly afterwhard, Takemoto \textit{et al.} used the bifunctional thiourea 66 to promote the Michael addition of malonitrile to a wide range of $\alpha,\beta$-unsaturated imides\textsuperscript{65} and also revealed its capability of promoting a highly enantio- and diastereoselective aza-Henry reaction of $N$-Boc imines with nitroalkanes.\textsuperscript{66,67}

In 2007, subsequent studies by the same group led to the development of a new amino-alcohol-type thiourea 71, reporting the first asymmetric catalytic Petasis reaction of quinolines (69) and vinyl boronic acids (\textit{i.e.} 70) in which the thiourea moiety could activate the $N$-acylated quinolinium salt as a Brønsted acid (73, Scheme 1.21).\textsuperscript{68}
Scheme 1.21 Asymmetric Petasis reaction catalysed by thiourea 71.

1.3 Introduction of natural cinchona alkaloids in organocatalysis

Cinchona alkaloids, were brought to Europe as a treatment for malaria in the early 17th century by Jesuit priests returning from Peru. Linnaeus in 1742 named the tree, cinchona, from which they derived, although the bark was more commonly known as Jesuit’s powder or Peruvian bark. They were commercialised after the discovery of the anti-malarial properties of an active compound known as quinine (74) from P. J. Pelletier, J. Bienaim and Caventou in 1820. Today, about seven hundred tons of alkaloids are extracted from the bark of Cinchona Ledgeriana, nearly half of it ends up in the food industry as an additive and the second part is used as an antimalarial drug (quinine 74) and as a relaxant of cardiac muscles (quinidine 76). These inexpensive and readily prepared natural products exist in two pseudoenantiomeric forms, exemplified by quinine and quinidine. They, possess a relatively rigid structure containing a basic quinuclidine nitrogen atom and an acidic hydroxyl group positioned in close proximity to each other in a well defined chiral environment (Figure 1.2).74,75

Figure 1.2 Nomenclature and main examples of cinchona alkaloids.
The first use of cinchona alkaloids in asymmetric synthesis appeared in 1912, when Bredig and Fiske reported the addition of HCN (10) to benzaldehyde (9) in presence of quinine (74) or quinidine (76) as organocatalysts. Despite the enantioselectivity being unremarkable, they demonstrated the possibility to obtain products (i.e. 78 and 79) with opposite chirality in reactions catalysed by cinchona alkaloids pseudoenantiomers (Scheme 1.22).

Scheme 1.22 Addition of HCN (10) to benzaldehyde (9) promoted by cinchona alkaloids.

In the early 1980s, H. Wynberg reported the first studies involving the use of cinchona alkaloids as catalysts in the enantioselective addition between aromatic thiols and cyclic enones. Their inherent bifunctionality allowed the simultaneous activation of the cycloalkenone 80 and the thiol 81 by the hydroxyl and amine groups respectively, obtaining opposite enantiomers when using either quinidine or cinchonine (Scheme 1.23).
Scheme 1.23 Cinchona alkaloid-catalysed addition of thiols to $\alpha,\beta$-unsaturated ketones.

Recently, the bifunctional nature of cinchona alkaloid-derived organocatalysts was recognised by numerous other groups, with their status as one of the most important chiral backbones in organic synthesis set, their application in a myriad of chemical transformations soon followed.\textsuperscript{78,79,80}

### 1.3.1 Cinchona alkaloid organocatalysts functionalisation

In order to improve the catalytic activity of cinchona alkaloids, the most common structural modification are made at the C-9 position. In addition, the presence of different chiral centres makes them easily tunable, with the possibility of developing a series of extremely versatile and functionalised alkaloids, capable of catalysing a series of different synthetic transformations (Scheme 1.24).

**Scheme 1.24** Active sites of functionalisation in cinchona alkaloids and their derivatives.
1.3.2 (Thio)urea-substituted cinchona alkaloids

In 1989, Dijkstra and co-workers shown that the conformation of cinchona alkaloids in solution is largely influenced by the nature of substituents on the C-9 position. These studies were then recently substantiated by Melchiorre and co-workers in 2009, who demonstrated that the substitution of the OH with an O-benzoyl group, results in a depreciable level of stereoselectivity.

Recently, the derivatisation of cinchona alkaloids by substituting the OH group with (thio)ureas became a common strategy adopted by several research groups working in the field of organocatalysis. A number of thiourea and urea derivatives were developed from natural cinchona alkaloids and successfully employed in asymmetric synthesis.

Connon and co-workers deduced that the absolute configuration at C-9 of the cinchona structure was crucial in order to reach high levels of selectivity. In 2005, they found that the use of the pseudoenantiomeric hydroquinine-based catalyst led to a very efficient reaction but with an opposite sense of asymmetric induction to that observed for the hydroquinidine-based compound. This catalyst promoted Michael-type additions of dimethyl malonate to nitrostyrene allowing the generation of product in high yields and enantioselectivity (Scheme 1.25).

![Scheme 1.25](image)

Scheme 1.25 Michael addition promoted by thiourea-substituted cinchona alkaloids.

In the same year, Soós et al. found a similar trend for the asymmetric addition of nitromethane to chalcones, confirming the importance of thiourea-based cinchona alkaloids catalysts of possessing the correct relative orientation. Independently but simultaneously, Dixon and co-workers used a cinchonidine-derived organocatalyst lacking the methoxy group on the quinoline ring. Like the Connon-Soós catalysts, this
epi-dehydroquinine-derived thiourea catalyst 86 promoted the addition of 51 to dimethyl malonate (83) giving 87 in excellent yield and enantioselectivity (Scheme 1.26).\(^{85}\)

![Scheme 1.26 Michael addition reaction promoted by thiourea cinchona catalyst 86 reported by Dixon et al.](image)

**Scheme 1.26** Michael addition reaction promoted by thiourea cinchona catalyst 86 reported by Dixon et al.

### 1.3.3 Squaramide-substituted cinchona alkaloids

The introduction of a chiral framework within the backbone of compounds possessing an H-bond donor *motif* has become a productive strategy that enables the realization of organocatalysts used in a wide range of transformations with high efficiency and stereoselectivity. In particular, bifunctional cinchona alkaloids bearing (thio)ureas in their structural core played a leading role as a result of their ability to act as double hydrogen bonding donors from which several functionalities, such as carbonyl, nitro and imine groups, have been successfully activated.\(^{63}\) Recently, Rawal *et al.* described the development of a new family of H-bonding catalysts based on the squaramide functional group, which have emerged as an effective alternative to the previously investigated (thio)urea-based catalysts.\(^{86}\)

Crucial to the development of squaramide-based organocatalysts is the understanding and characterisation of their H-bonding patterns and capabilities as well as the structural differences to the analogous thioureas. Squaramides are remarkable four-membered ring systems derived from squaric acid also known as “quadratic acid”, which was first synthesised by Cohen *et al.* in 1959.\(^{87}\) The amide derivatives of squaric acids offer the potential to hydrogen bond to acceptors, donors (behavior close to that observed for (thio)ureas) and depending upon the conformational preference to mixed acceptor–donor groups (Figure 1.3a).
In both thioureas and squaramides the lone pair on the nitrogen atom is delocalised however, the dianion form of squaric acid is characterised by an unusually high double acidity ($\text{pK}_a^1 = 0.54$; $\text{pK}_a^2 = 3.58$) due to the stability of the negative charge by delocalisation.\textsuperscript{88,89} A concomitant higher aromaticity of the ring (according to the Huckel rule $4n+2$; $n=0$) obtained upon H-bond formation, is significant for the superior H-bond donating capacity of squaramides compared to (thio)urea (Figure 1.3b).\textsuperscript{88,89}

Finally, Rawal reported that the distance between the two NH groups in the case of squaramides (2.72 Å) is about one third further than (thio)ureas (2.13 Å) and the difference of the dihedral angles of the N–H bonds about 8°, which could influence the strength of the H-bonding and the relative catalytic competence (Figure 1.3c).\textsuperscript{85,86}

As mentioned above, in 2008 Rawal and co-workers applied a chiral squaramide-based organocatalyst derived from cinchona alkaloids (\textit{i.e.} 90) in the Michael-type addition of 1,3-dicarbonyl compounds such as 89 to nitroolefins (\textit{i.e.} 88, Scheme 1.27).\textsuperscript{86}
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Scheme 1.27  Michael addition promoted by squaramide-based cinchona alkaloid organocatalysts.

Since the publication of seminal work from the Rawals group,\textsuperscript{86} squaramide-substituted cinchona alkaloids can be viewed as highly functional catalysts capable of promoting a plethora of structurally unrelated synthetic transformations.\textsuperscript{89}

1.3.4 Modification at C-6’

The ability of C-6’OH substituted cinchona alkaloids to activate Michael acceptors in enantioselective transformations was first demonstrated in 2002.\textsuperscript{90} Shortly afterwards, Deng and co-workers reported that the employment of demethylated phenolic cinchona alkaloid as the catalyst in a 1,4-addition of malonates to nitroalkenes resulted in significantly higher enantioselectivity and a faster rate than the methoxy substituted variant. In his attempt to rationalise these results, the author proposed that both the phenolic-OH and the quinuclidine functionalities participate in the stabilisation and organisation of the transition state.\textsuperscript{91}

In 2006, Hiemstra \textit{et al.}\textsuperscript{92} demonstrated that the substitution of the methoxy group on C-6’ with a thiourea moiety and benzylation of the C-9 hydroxy substituent proved highly advantageous with regards to the promotion of a more enantioselective variant of the catalytic asymmetric Henry reaction between nitromethane and aldehydes such as \textsuperscript{92}, to afford \textsuperscript{94} (Scheme 1.28).
Scheme 1.28  Henry reaction promoted by 93 bearing a thiourea group at C-6’.

Other examples of C-6’ substituted cinchona alkaloid organocatalysts have been reported in the literature such as in the catalysis enantioselective aza Morita-Baylis-Hillman reactions,93 annulation reactions94 and the asymmetric conjugate addition of thiols by Deng et al in 2009.95

1.3.5 Modification at C-2’

C-2’ modified cinchona alkaloids were first introduced by Gaunt and co-workers in 2006 who developed an organocatalytic enantioselective intramolecular cyclopropanation reaction via ammonium ylide intermediates.96 The authors observed that the attempt to catalyse the asymmetric intramolecular cyclopropanation of alkenyl chloroketones (i.e. 95) in presence of quinine derivatives such as 96 resulted in high enantioselectivity but poor yield. They attributed this to a alkylative side reaction occurring at the quinoline nitrogen with the formation of an unreactive ammonium ylide intermediate, leading to the consumption of both catalyst and starting material. They therefore synthesised a C-2’ methyl substituted cinchona alkaloid 97 that may act by a steric hindrance preventing the alkylation of the quinoline nitrogen atom in order to possibly inhibit the undesired interaction with the α-haloketone. Employing catalyst 97 the reaction furnished the desired product 98 in higher yield and excellent enentioselectivity (Scheme 1.29).
Scheme 1.29 Cyclopropanation promoted by C-2’ modified cinchona catalysts.

In 2012, Deng et al tested the efficacy of several modified cinchona alkaloids as catalysts in the asymmetric synthesis of trifluoromethylated amines via the isomerisation of imines. Extensive catalyst screening highlighted the positive effect, with regards to enantioselectivity, by the introduction of substituents at the C-2’ position of the quinoline ring. Interestingly, the electronic nature of the 2’-substituent proved crucial in influencing the levels of asymmetric induction achievable. A 2’-Me substitution pattern furnished a catalyst capable of promoting a reaction with low enantiocontrol, whilst 2’-Br substitution resulted in significant amelioration of product ee. Further electronic manipulations furnished catalyst 103, complete with a 2’ chloro substituent, which proved to be the most effective from an enantioselectivity standpoint. Catalyst 103 was employed in the reaction with imines such as 99, providing the product 100 in high yield and enantioselectivity, which readily underwent hydrolysis to give the desired chiral trifluoromethylated amines 101 (Scheme 1.30). Subsequently, the authors carefully evaluated the effect of different reaction conditions and observed that decreasing the temperature (from rt to -20 °C) and concentration (from 1.0 to 0.1 M) had positive effects on the enantiomeric excess of the products.
Scheme 1.30 Asymmetric isomerisation of imines promoted by C-2’ substituted cinchona alkaloids.

More recent reports of C-2’ substituted cinchona alkaloid derivatives have emerged, however their use has been limited to different areas of asymmetric catalysis such as aminocatalysis, phase-transfer catalysis and organometallic chemistry (where they are used as ligands).

1.4 Use of enolisable anhydrides as nucleophiles in formal cycloaddition reactions: historical overview

The synthetic utility of anhydrides as electrophilic acyl transfer agents has been studied for over a century. The concept of using enolisable anhydrides as nucleophiles in formal cycloaddition reactions is a rather recent development.

The first example of this type of reactivity was reported by Perkin in 1868. His work reported the use of enolisable anhydrides as carbon-based nucleophiles at high temperature in presence of weak carboxylate bases. He found that an aliphatic enolisable anhydride such as 105 when treated with salicylaldehyde (106) at high temperature, using sodium acetate as a weak base, allowed for the formation of coumarins (i.e. 107 Scheme 1.31).

Scheme 1.31 Reaction between enolisable aliphatic anhydride 105 and salicylic aldehydes to form coumarins 107.
Later on, during his study, Perkin also reported that the reaction between succinic anhydride (108) and benzaldehyde (9) in the presence of sodium succinate (109) when heated at 180 °C furnished the product 110 as a result of a decarboxylation reaction (Scheme 1.32 A). After a short period Fittig and co-workers carried out Perkin’s reaction at a lower temperature (i.e. 100 °C) and concluded that the mechanism is similar to an aldol condensation involving a β-hydroxy intermediate that leads to the product after dehydration. In his experiment Fittig observed the formation of the lactone 111 which would decarboxylate furnishing the product 110, originally reported by Perkin (Scheme 1.32 B).

Scheme 1.32 Anhydride addition to benzaldehyde (9) reported by Perkin (A) and Fittig (B).

In 1931, Müller reported the condensation between the sodium enolate of homophthalic anhydride (112) and benzaldehyde (9) that furnished a dihydroisocoumarin adduct, with a cycloaddition process similar to the cycloaddition of succinic anhydride (108) to benzaldehyde (9).

Shortly afterwards, Pinder performed the same reaction using piperonaldehyde (113) to form the cycloadduct 114, confirming the reactivity previously reported by Müller (Scheme 1.33).

Scheme 1.33 Cycloaddition between homophthalic anhydride sodium enolate (112) and piperonaldehyde (113).
In relation to the synthetic utility of lactams as intermediates for the synthesis of a wide variety of heterocycles, including many analogues of natural alkaloids, in 1971, Castagnoli et al. reported the first cycloaddition reaction between succinic anhydride (108) and different aromatic imines such as 115 to give γ-lactam 116 (Scheme 1.34).

\[
\begin{align*}
\text{108} + \text{115} & \xrightarrow{\text{C}_6\text{H}_6, 80^\circ\text{C}, 36\text{ h}} \text{116}
\end{align*}
\]

Scheme 1.34 Cycloaddition reaction of succinic anhydride (108) to imines.

Due to the apparent increase in reactivity of imines when substituted with an electron-donating group, a new mechanism was proposed, characterised by the initial iminolysis of the anhydride by nucleophilic attack of the nitrogen atom of the imines on the electrophilic anhydride. This process contradicted the Perkin-type mechanism based on the nucleophilic attack of the anhydride enol tautomer on the electrophile and the first Diels-Alder theory that involved the use of imine as dienophile. An expansion of the study to glutaric anhydride was shortly after reported by the same group. The application of the cycloaddition reaction on glutaric anhydride became a strategy for the synthesis of natural product analogues.

In the late 1980s, Cushman and co-workers reported a series of studies on the cycloaddition reaction between homophthalic anhydride (117) and a range of para-substituted imines of general structure 118 with a particular emphasis on the effect that different substituents on the imines could have on the stereochemistry of the product 119 (Scheme 1.35).

\[
\begin{align*}
\text{117} + \text{118} & \xrightarrow{\text{CHCl}_3, \text{rt}} \text{119}
\end{align*}
\]

119a R\(^1\) = Me, R\(^2\) = NO\(_2\)  
119b R\(^1\) = Me, R\(^2\) = H  
119c R\(^1\) = Me, R\(^2\) = N(CH\(_3\))\(_2\)  
119d R\(^1\) = t-Bu, R\(^2\) = H

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</table>

Scheme 1.35 Cycloaddition of homophthalic anhydride (117) to imines.
A similar transformation involving phenylsuccinic anhydride was described later by Shaw et al. with a discussion on the effect that electron-withdrawing substituents (e.g. NO$_2$) may have on the outcome of the cycloaddition.$^{116,117,118}$

The cycloaddition reaction involving homophthalic anhydride was later expanded by Tamura et al. to include different types of electrophiles. In 1981 this group reported the regioselective cycloaddition reaction between 117 and compounds containing carbon-carbon multiple bonds (i.e. 120) under thermal conditions to furnish 121 (Scheme 1.36).$^{113}$

![Scheme 1.36 Cycloaddition of homophthalic anhydride (117) to an alkyne.](image)

In order to optimise the yields of cycloaddition products, the same group reported a base-promoted variant of the reaction involving a strong base such as lithium diisopropylamide (LDA) or sodium hydride (NaH) under milder conditions.$^{119}$ A similar strong-base mediated strategy was described by Danishefsky and co-workers in the cycloaddition reaction of homophthalic anhydride to dienophiles.$^{120}$

1.4.1 Cycloaddition reactions with aldehydes

Cycloaddition reactions between an anhydride and an aldehyde has received less attention than the imine variants. Generally, the reaction involves the homophthalic anhydride (117) and aromatic aldehydes. The mechanism proceeds through the enolisation of the anhydride promoted by either a base$^{121,122,123}$ or a Lewis$^{124}$ acid moiety followed by its addition to the aldehyde generating the tetrahedral intermediate which then lactonises in an intramolecular process to form the dihydroisocoumarin product, with trans-configuration generally favoured (Scheme 1.37).$^{125}$
Scheme 1.37 Proposed mechanism of addition of homophthalic anhydride (117) to aldehydes.

Kita and co-workers in 1991 experimented for the first time with the use of a strong base in the cycloaddition reaction of homophthalic anhydride (117) to aldehydes.\textsuperscript{122} The attention focused on the effect of temperature on the reaction between 117 and 9 using different bases (Scheme 1.38).

Scheme 1.38 Cycloaddition between homophthalic anhydride (117) and benzaldehyde (9) promoted by various bases.

As previously reported by Nakajima, the use of Na$_2$CO$_3$ provided the cycloadduct product, which upon functionalisation with diazomethane furnished the methyl ester 125. Further studies were aimed at evaluating the use of stronger bases. In particular, they observed that, at low temperatures, the reaction carried out using sodium hydride mainly provided the cycloadduct 125 kinetic product while higher temperatures favoured the formation of the methylene C-4 adduct 126 thermodynamic product.

<table>
<thead>
<tr>
<th>Base</th>
<th>Temperature</th>
<th>125 Yield (%)</th>
<th>126 Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na$_2$CO$_3$</td>
<td>rt</td>
<td>35</td>
<td>43</td>
</tr>
<tr>
<td>NaH</td>
<td>0 °C to rt</td>
<td>83</td>
<td>-</td>
</tr>
<tr>
<td>NaH</td>
<td>50 °C</td>
<td>5</td>
<td>82</td>
</tr>
</tbody>
</table>
Shortly afterwards, Gesquiere et al experimented on cycloaddition reactions involving aldehydes and ketones as electrophiles activated by the Lewis acid boron trifluoride-diethyl ether complex (128). They presented a new strategy for the synthesis of isocoumarin-4-carboxylic acid derivatives (i.e. 129) in which the addition of benzaldehyde (9) and enolate formation from anhydride 127 were simultaneously mediated by an excess of 128 (Scheme 1.39).

Scheme 1.39  Cycloaddition reaction of anhydrides to aldehydes proposed by Gesquiere.

An extension of the substrate scope towards the use of ketones was then examined by the same group who reported a decrease in product yields, postulated to be due to the lower reactivity of these functional groups in comparison with aldehydes. In 2004 Palamavera et al. described the reaction using a series of aromatic aldehydes mediated by 4-dimethylaminopyridine (DMAP) under mild conditions. 

Cycloaddition reactions involving aldehydes has generally been limited to the use of homophthalic anhydride. As a consequence of the proposed reaction mechanism, the stability of the reactive enolate species is a fundamental requirement in order to positively influence the diastereoselectivity of the reaction. For this reason homophthalic anhydride (117), in which the negative charge is highly stabilised on the aromatic ring was the most well-developed substrate for this reaction. An example of expansion of the substrate scope to succinic anhydride with a series of aldehydes was reported in the late 1980s by Lawlor and co-workers. They described a new synthetic strategy based on the associated use of a Lewis acid such as ZnCl₂ and a base (i.e. triethylamine). The reaction between succinic anhydride (108) and aldehydes such as 130 proved useful for the formation of paraconic acid derivatives 133 via putative 131 and 132. There was lack of details regarding the stereochemistry of the cycloaddition products provided (Scheme 1.40).
Another example of succinic anhydrides (i.e. 134) being employed in cycloaddition reactions with 2,4-methoxybenzaldehyde (130) reported the use of stronger bases such as KHMDS (Scheme 1.41). In this case the deprotonation by the highly hindered base occurs at the methylene instead of the substituted CH carbon, however the desired cycloadduct products 135 and 136 were formed with high yield and good ee.
1.5 Development of asymmetric cycloaddition reactions involving enolisable anhydrides

Formal cycloaddition reactions between enolisable anhydrides and electron deficient π-systems have received considerable attention in the past. A catalytic asymmetric approach to these reactions was less explored despite the synthetic utility of products containing the dihydroisocoumarin core structure known for a wide range of medicinal applications.

Since the seminal work reported in 1868 by Perkin, it is well-known that enolisable anhydrides can react with aldehyde electrophiles either thermally or in the presence of Lewis acids or Brønsted bases. Our research group has recently developed an efficient diastereo- and enantioselective protocol involving the use of cinchona alkaloid-derived bifunctional organocatalysts. We reported that a range of aldehydes can participate in a clean cycloaddition with homophthalic anhydride (117) under the influence of cinchona alkaloid-based organocatalysts, to yield substituted lactones with excellent yield and enantiocontrol. Preliminary studies on cycloaddition reactions between 117 and benzaldehyde (9) were first conducted using Hünig’s base as catalyst. The reaction furnished (in 95% yield) a cis/trans-diastereomeric mixture in a 36/67 ratio. The subsequent use of N,N-diaryl urea (56) inhibited the reaction with a lower yield and lower diastereoselectivity. Connon et al., later reported the use of a bifunctional C-9’ urea substituted cinchona alkaloid organocatalyst which resulted in the promotion of a higher yielding reaction with enhanced levels of diastereoocontrol. Conversion of the carboxylic acid substituent of 137 to the methyl ester derivative followed by purification by flash chromatography on silica gel permitted the isolation of the products and the evaluation of the enantioselectivity of the process. As previously mentioned, Rawal recently designed a class of squaramide-substituted catalysts as an alternative to (thio)urea-based materials. Use of novel squaramide by our group, upon installation of a phenyl substituent at C-2' led to better yields and superior enantio- and diastereoocontrol (Scheme 1.42).
The results obtained in these preliminary experiments prompted our group to focus on the substrate scope. Electron-deficient, electron-rich, hindered and heterocyclic aromatic aldehydes were well tolerated by catalysts at 5 mol% loading. Aliphatic aldehydes, both straight-chain and more hindered anhydrides could undergo the annulation reaction. Substitution at the aromatic ring is a feature of several of the medicinally relevant dihydroisocoumarin compounds. Connon and co-workers evaluated the effect of the installation of electron-withdrawing and -donating groups on the homophthalic anhydride pronucleophile (117). In particular, the observation of a retardation of rate in the presence of an electron-donating methoxy substituent confirmed that the formation of the anhydride keto-enol tautomer is a key factor influencing reaction rate.

Recently, our group reported the first computational study of the mechanism of the cycloaddition between homophthalic anhydride (117) and benzaldehyde (9) promoted by the C-2’ phenyl substituted squaramide-based catalyst 140. DFT methods revealed an unambiguous preference for a ‘specific catalysis-like’ pathway involving initial (highly favourable) anhydride deprotonation by the catalyst to give a bound enolate, which reacts with aldehyde with activation by the ammonium ion of the catalyst in the key, stereocentre forming step (Figure 1.4). The previously proposed mechanism based on general base

Scheme 1.42 Cycloaddition reaction between homophthalic anhydride (117) and benzaldehyde (9).

<table>
<thead>
<tr>
<th>cat</th>
<th>yield (%)</th>
<th>dr (trans:cis)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>138</td>
<td>97</td>
<td>86:14</td>
<td>66</td>
</tr>
<tr>
<td>139</td>
<td>89</td>
<td>84:16</td>
<td>90</td>
</tr>
<tr>
<td>140</td>
<td>95</td>
<td>91:9</td>
<td>96</td>
</tr>
</tbody>
</table>

\[
\text{Ar} = \text{3,5-(CF}_3\text{)}_2\text{-C}_6\text{H}_3
\]

\[
\begin{align*}
\text{Ar} &= \text{3,5-(CF}_3\text{)}_2\text{-C}_6\text{H}_3 \\
\text{MeO} &= \text{3,5-(CF}_3\text{)}_2\text{-C}_6\text{H}_3 \\
\text{R} &= \text{H, C}_6\text{H}_5
\end{align*}
\]
catalysis of the addition of the enol of the anhydride to the aldehyde was unambiguously refuted.

![Figure 1.4](image)

**Figure 1.4** Stereochemical rationale: summary.

### 1.5.1 Enolisable succinic anhydrides in organocatalysed cycloaddition reactions with aldehydes

Preliminary experiments using succinic anhydride (108) and benzaldehyde (9) were not successful. Shaw and co-workers explained the failure of this reaction as a result of recalcitrant anhydride enolisation. Our research group began analysing the reactivity of anhydrides substituted with an enol-stabilising group such as arylsuccinic anhydrides with benzaldehyde (9). The reaction is assumed to proceed via a similar pre-transition state assembly as proposed for the reaction involving homophthalic anhydride (117). Our group evaluated the influence of thiourea and squaramide-based cinchona alkaloid catalysts. A significant decrease in performance associated with the squaramide variant 139 lacking the C-2’ phenyl substituent and the corresponding thiourea-based catalyst 138 suggested the importance of such substitution in the catalysis process (Scheme 1.43).
Scheme 1.43  Cycloaddition reaction of arylsuccinic anhydrides with benzaldehyde (9).

The evaluation of two more enolisable anhydrides 142 and 143 was later reported. The presence of a 3,5-dibromophenyl group increased the rate of reaction although the diastereoselectivity diminished compared to the unsubstituted aryl anhydride 141, while excellent yield and ee were obtained using the powerful enol-stabilising p-nitro substituted variant 143.146

1.5.2  The asymmetric cycloaddition reaction between enolisable anhydrides and alkylidene-2-oxindoles

Connon et al. carried out a range of preliminary studies involving homophthalic anhydride (117) and different electrophiles, as Tamura and co-workers147 had described previously. The initial reaction considered was an annulation between 117 and N-alkyl imines. The observation that the reaction occurred spontaneously without any catalyst prompted our group to introduce electron-withdrawing substituents at the nitrogen atom. This strategy was successful providing a diastereomeric mixture of lactams with the cis-isomer as the predominant product. Shortly afterwards, a range of preliminary studies involving common Michael acceptors as pronucleophiles were reported.148 The reaction involving both ethyl acrylate and acrylonitrile failed while (E)-chalcone and (E)-nitrostyrene provided good yields of the corresponding products. Complications during the esterification procedure prompted the use of Michael acceptors with trisubstituted double bonds such as the commercially available β-methyl-(E)-nitrostyrene which produced products as a mixture of two diastereomers. Furthermore, homophthalic anhydride (117) was reacted with N-Boc oxindoles 147 in the presence of squaramide-substituted cinchona alkaloids. The novel tert-butyl squaramide catalyst 148 proved very
active. The Tamura cycloaddition proceeded rapidly producing the tetracyclic
spiroadduct 149 complete with a quaternary stereocentre, with excellent diastereo- and
enanto-control (Scheme 1.44).

**Scheme 1.44** Organocatalytic cycloaddition of homophthalic anhydride (117) to
oxindoles.

After these encouraging results, our group reported catalytic asymmetric Tamura
cycloaddition reactions using glutaconic acid derivatives. The phenylglutaconic
anhydride 150 and its methyl substituted variant 151 represented the first examples of the
expansion of enantioselective cycloadditions involving enolisable anhydrides beyond
either homophthalic or arylsuccinic analogues. Interestingly, the cycloaddition products
formed were not the expected compounds, due to a decarboxylation process occurring
during the esterification process. All the reactions involving this new class of anhydrides
proceeded smoothly, producing the *trans*-isomers 152 and 153 in high yield and excellent
*ee* (Scheme 1.45).\(^1\)

**Scheme 1.45** Organocatalytic cycloaddition of glutaconic anhydride derivatives to
oxindole 147.
1.6 Organocatalytic desymmetrisation of meso cyclic anhydrides: historical overview

In the presence of a chiral catalyst one of the carbonyl groups of a meso cyclic anhydride substrate can theoretically be selectively converted into an hemiester containing either single or multiple stereocentres. The first example of desymmetrisation of meso-anhydrides promoted by natural cinchona alkaloids as organocatalysts was reported by Oda in 1985. He reported the asymmetric alcoholysis of different cyclic anhydrides focusing on meso-glutaric and succinic anhydrides. After the evaluation of various catalysts, methanolysis of 2,4-dimethylglutaric anhydride (154) in the presence of 10 mol% of (+)-cinchonine was performed in almost quantitative yield and good ee (Scheme 1.46 a). Comparable results were obtained shortly later by Aitken, who demonstrated that the chiral quinuclidine moiety of the alkaloid was responsible for the observed stereocontrol only when present as a free base. Aitken reported related studies focusing on the methanolysis of the tetracyclic anhydrides (i.e. 156), in the presence of a considerable loading of (-)-quinine, and also obtained moderate enantioselectivity of the hemiester product 157 (Scheme 1.46 b).

Scheme 1.46 Cinchona alkaloid catalysed desymmetrisation of meso-cyclic anhydrides reported by Oda (a) and Aitken (b).

A very efficient process for the desymmetrisation of meso anhydrides was reported by Bolm et al. in 1999. The desymmetrisation of several meso-anhydrides was achieved by methanolysis at -55 °C using 110 mol% of either quinine or quinidine with excellent enantioselectivity. Scheme 1.48 depicts a selected example in which the tricyclic
anhydride \( \text{158} \) is converted to both its hemiesters \( \text{159} \) and \( \text{ent-159} \) with an excess of methanol, in the presence of a stoichiometric amount of \((-\)-quine, and \((+\)-quinidine.\(^{154}\)

![Scheme 1.47](image)

**Scheme 1.47** Highly enantioselective desymmetrisation of meso-anhydrides by Bolm.

A further screening of different alcohol nucleophiles was carried out. Benzyl alcohol was found to furnish the requisite product with relatively high enantiomeric excess in reactions promoted by both catalysts even in the absence of \( \text{CCl}_4 \) as co-solvent.

Later Deng and co-workers reported an highly enantioselective alcoholysis of succinic anhydride derivatives using the commercially available modified cinchona alkaloid Sharpless’ ligand \((\text{DHQD})_2\text{AQN} \ (\text{160})\) and its quinine-derived pseudoenantiomer \((\text{DHQ})_2\text{AQN} \) at 5-20% loading.\(^{155}\) It was found that the anthraquinone-bridged dimers of these catalysts were able to catalyse the reaction with a wide range of substrates (Scheme 1.48). Deng used \((\text{DHQD})_2\text{AQN} \ (\text{160})\) to promote the enantioselective desymmetrisation of meso-bicyclic glutaric acid anhydride derivatives which resulted in the formation hemiesters \((i.e. \text{162})\) in excellent ee.

![Scheme 1.48](image)

**Scheme 1.48** Meso-glutaric anhydride desymmetrisation promoted by Sharpless’s catalysts.
In the following years, Hamersak et al., while attempting the synthesis of pregabalin, reported an interesting and unexpected inversion of enantioselectivity based on the degree of quinine loading during the desymmetrisation of glutaric anhydrides.\textsuperscript{156} Consistent with Oda and Aitken’s previous related studies,\textsuperscript{149,150,151} the chiral quinuclidine moiety of the cinchona alkaloid (only when present as the free-base) was responsible for the enantiocontrol of the reaction. Indeed, desymmetrisation reactions involving succinic anhydrides reported a negative effect on the enantiomeric excess of the hemiester products when decreased catalyst loadings were implemented. In contrast, Hamersak observed that by decreasing the amount of quinine from 60\% to 10\% in the alcoholysis of 3-substituted glutaric anhydrides with benzyl alcohol, the sense of asymmetric induction was inverted from 40\% R to 40\% S. The inversion of configuration suggested a probable switch of mechanism occurring under certain conditions, however a full explanation has not been reported yet.

1.6.1 Bifunctional cinchona alkaloid derivatives as catalysts in desymmetrisation reactions of meso-anhydrides

Chiral bases derived from either cinchona alkaloids or proline have been shown to be efficient catalysts for stereoselective alcoholysis of anhydrides. The possibility to achieve the formation of hemiesters that can be applied in the synthesis of many bioactive compounds made this catalytic reaction extremely attractive.\textsuperscript{157,158} Previously, cinchona-derived (thio)urea and squaramide catalysts, in particular, have displayed exceptional potential as their \textit{bis}-hydrogen bonding donors can be used to activate electrophilic carbonyl groups and imines. Consequently, the development of bifunctional cinchona alkaloid organocatalysts capable of promoting desymmetrisation reactions of cyclic meso-anhydrides has become particularly attractive. The main advantage associated with this strategy is the inherent ability of the bifunctional catalysts to simultaneously activate the pro-nucleophile (alcohol) \textit{via} a general base mechanism and the electrophile \textit{via} hydrogen bond interactions with the thiourea moiety.\textsuperscript{154} Difficulties related to the high catalyst loading required and the prohibitively low temperature required to reach high levels of enantiocontrol reported by Bolm and Deng,\textsuperscript{153,155} prompted our group, to develop an unprecedented protocol in which the reaction was promoted by a bifunctional thiourea organocatalyst. In 2008, Connon and co-workers reported the first highly enantioselective desymmetrisation of several meso anhydrides promoted by bifunctional
thiourea-based organocatalyst 163 (Scheme 1.49). In order to improve the efficiency of the desymmetrisation protocol, they analysed the effect of the concentration of reactants in solution to determine if this could influence the enantiomeric excess of the hemiester products. More dilute conditions led to less catalyst aggregation and therefore, higher ee. By using catalyst loading of 1 mol%, glutaric anhydride derivatives such as 164 and 165 were converted to the corresponding hemiesters with excellent ee (Scheme 1.49). Desymmetrisation reactions were generally conducted using methanol although its replacement with allyl alcohol did not compromise the enantioselectivity.\textsuperscript{159}

\begin{equation}
\text{Scheme 1.49} \quad \text{Catalytic desymmetrisation of meso-glutaric anhydrides by Connon et al.}
\end{equation}

Shortly after our group published this work, Song \textit{et al.} also independently investigated the use of two thiourea-based cinchona alkaloid catalysts (\textit{i.e.} 163 and 84) in the desymmetrisation reaction of meso-cyclic anhydrides.\textsuperscript{160} In Scheme 1.50 is shown the asymmetric methanolsysis of cis-1,2-cyclohexane dicarboxylic anhydride (168) in dioxane by 10 mol\% of thiourea-substituted cinchona alkaloids 163 and 84 respectively. As a comparison, the same desymmetrisation reaction was carried out in the presence of the naturally occurring quinine and hydroquinine as catalysts. The catalysts lacking the thiourea functional group afforded the corresponding hemiester with notably diminished product ee, which provided substantial evidence that the hydrogen bonding moiety was a key driver of catalysis.
Song and co-workers then found that the highest enantioselectivities were observed in aprotic $H$-bond accepting solvents while the lowest enantioselectivity was obtained with protic solvents like methanol. These effects were attributed to the tendency of the catalyst to aggregate via inter and intramolecular acid-base interactions under specific reaction conditions. According to the results obtained, polar protic solvents such as methanol are able to weaken the hydrogen bonding interaction between the catalyst and the substrates due to its ability to act as both hydrogen bond donor/acceptor decreasing the overall enantioselectivity of the reaction.

### 1.6.2 Novel bifunctional cinchona alkaloid organocatalysts: introduction of the sulfonamide moiety

Urea- and thiourea-based bifunctional organocatalysts proved to be effective in promoting several useful organic reactions\(^8\). However, from observing an unusual decrease in enantioselectivity with higher concentrations and lower temperatures, it was assumed that due to their bifunctional nature, thiourea-based organocatalysts tend to aggregate via inter and intramolecular acid-base interactions through hydrogen bonding between the (thio)urea NH groups and the (thio)urea sulfur or oxygen atom. In 2008, Soós and co-workers reported a series of $^1$H NMR spectroscopic studies demonstrating that (thio)urea catalysts actually exist as dimers, even in solution\(^{161}\). Furthermore, the same group observed the instability of (thio)urea catalysts under thermal conditions\(^{162}\). For these reasons, they explored the development of novel bifunctional organocatalysts endowed with a sulfonamide moiety. In 2008, Soós \textit{et al.}, hypothesizing that the incorporation of N-sulfonamides could prevent this self-aggregation problem, developed the first example of a thermally robust sulfonamide-based bifunctional organocatalyst.
Chapter 1

Introduction

170. The desymmetrisation reaction of meso-anhydride 168 by methanol in the presence of catalyst 170 proceeded smoothly, furnishing the hemiester product 171 in high yield and excellent enantioselectivity (Scheme 1.51).

\[
\text{\begin{align*}
168 & \xrightarrow{170 \; (10\, \text{mol\%})} 170 & \xrightarrow{\text{CH}_3\text{OH} \; (10.0 \, \text{equiv.})} 171 + \text{ent-171} \\
\end{align*}}
\]

<table>
<thead>
<tr>
<th>[168]/M</th>
<th>T (°C)</th>
<th>main isomer yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>20</td>
<td>171</td>
<td>84</td>
</tr>
<tr>
<td>0.05</td>
<td>20</td>
<td>171</td>
<td>91</td>
</tr>
<tr>
<td>0.2</td>
<td>20</td>
<td>171</td>
<td>82</td>
</tr>
<tr>
<td>0.1</td>
<td>0</td>
<td>171</td>
<td>80</td>
</tr>
<tr>
<td>0.1</td>
<td>-20</td>
<td>171</td>
<td>82</td>
</tr>
<tr>
<td>0.1</td>
<td>-40</td>
<td>171</td>
<td>78</td>
</tr>
</tbody>
</table>

Scheme 1.51 Enantioselective desymmetrisation of meso-anhydride 168 promoted by sulfonamide-base organocatalysts.

Further evaluation at different temperatures and concentrations demonstrated that catalyst 170 was not sensitive to the reaction conditions. They observed that changing these parameters did not compromise the enantioselectivity of the reaction, confirming the postulate that sulfonamide-based catalysts possessed a low tendency to form self-aggregates. The computational studies recently reported by Soós and co-workers to explain the stereoselectivity associated with the methanolytic desymmetrisation of meso-anhydrides with the bifunctional thiourea-based organocatalyst\textsuperscript{160} were also used to clarify the mechanism involving a sulfonamide-based catalyst. The authors claimed that the quinuclidine group acts as a general base, accepting a hydrogen bond from the incoming methanol nucleophile while the sulfonamide group stabilises the oxyanionic group of the transition-state as a hydrogen-bond donor (172, Scheme 1.51).\textsuperscript{163}

Shortly afterwards, the same group reported an optimised protocol using the sulfonamide catalyst 170 for the desymmetrisation of several 3-substituted glutaric anhydrides.
obtaining good yields and excellent enantioselectivities and its practicality was also demonstrated in a concise three step synthesis of pregabalin.163

1.7 General concepts of kinetic resolution (KR)

Many strategies have been used for obtaining enantiopure materials, one of the most common used is kinetic resolution (KR).165,166 It represents a strategy to obtain enantiopure compounds from a racemic mixture (Scheme 1.52).

\[
\begin{align*}
RC^* & \xrightarrow{k_R} C^* \xrightarrow{k_S} R + S \xrightarrow{C^*} SC^* \\
\end{align*}
\]

\(k_R, k_S = \text{specific rate constants for reaction of R and S respectively}
\)

\(C^* = \text{chiral catalyst}
\)

Scheme 1.52 Kinetic resolution.

In the case where \(k_R\) is different from \(k_S\) and the reaction is stopped between 0% and 100% conversion, the process can be described as a kinetic resolution.

Enantiomers have identical chemical properties and, as such, are inseparable from one another in an achiral environment, but in the presence of a chiral agent (i.e. the chiral catalyst) two diastereomeric transition states are created. The preferential reaction of one enantiomer over the other depends on the difference in transition state energies (\(\Delta \Delta G^{TS}\), Figure 1.5).167 It is, therefore, theoretically possible to convert one undesired enantiomer to the desired enantiomer of the product in the presence of a chiral catalyst, while leaving the other unchanged.

\[\Delta \Delta G^{TS} = \Delta G^{TS}_R - \Delta G^{TS}_S\]

Figure 1.5 Potential energy diagram for kinetic resolution
For chemical processes, the efficiency of kinetic resolution is generally defined by the S factor (selectivity) of a reaction, (the ratio of competing rate constants). It is directly correlated to $\Delta \Delta G_{TS}$ and depends on the reaction rate constant relative to the formation of each enantiomer on reaction with the chiral agent according to the Equation 1.1

$$S = \frac{k_{rel}}{k_{slow}} = e^{\Delta \Delta G_{RT}}$$

Equation 1.1 Correlation between S factor and reaction rate constants.

Generally, the selectivity can be calculated by equations 1.2 and 1.3 reported in Figure 1.6, where $C$ stands for conversion ($0 \leq C \leq 1$) while $ee$ and $ee'$ ($0 \leq ee$ and $ee' \leq 1$) are the enantiomeric excesses of unreacted recovered starting material and product, respectively.

$$S = \frac{\ln[1-C(1-eC)]}{\ln[1-C(1+ee)]}$$

$$S = \frac{\ln[1-C(1+ee')]}{\ln[1-C(1-eC)]]}$$

Equation 1.2

Equation 1.3

Figure 1.6 Stereoselectivity factors calculated with respect to reactant and product.

In kinetic resolution the $ee$ of both starting material and product changes during the reaction and is associated with the conversion. As the reaction proceeds the $ee$ of the starting material increases while the $ee$ of the products decrease. The isolation of the unreacted substrate in 98% $ee$ means an S factor = 10 and is generally considered economically attractive to the chemical industries because it allows the recovery of at least 30% of reactant. Ideally, the S factor should be very high, if S is more than 50, a significant amount of enantioenriched materials (>98% ee, 45% yield) can be obtained (Figure 1.7).
The main advantage of kinetic resolution process is the possibility of recovering both enantiomers of the racemic mixture. By stopping the reaction at a certain conversion point, one can obtain the desired enantiomers either transformed into products or as unreacted starting materials. On the other hand, the major limitation of conventional kinetic resolution is that the maximum theoretical yield of a pure enantiomer obtainable is limited to 50%.\textsuperscript{169}

1.7.1 KR and desymmetrisation of cyclic anhydrides via modified cinchona alkaloid-catalysed alcoholysis and thiolysis

In 2001, Deng \textit{et al.} reported an efficient kinetic resolution of $N$-carboxy cyclic anhydrides (UNCAs)\textsuperscript{170} when treated at low temperature with alcohols in presence of the dimeric cinchona alkaloid (DHQD)$_2$AQN (\textit{160}) previously investigated in the asymmetric alcoholysis of \textit{meso}-cyclic anhydrides.\textsuperscript{155} The $N$-carboxy anhydride such as \textit{174}, was easily prepared in high yields from the corresponding racemic amino acid \textit{173} in a two-step procedure based on cyclisation with diphosgene followed by $N$-protection with Cbz or Fmoc. The kinetic resolution of \textit{174} carried out using 10 mol\% of catalyst \textit{160} in the presence of methanol, afforded the $N$-protected methyl ester \textit{175} and the unreacted UNCA \textit{S-174} in excellent enantioselectivity (S = 114) which was then hydrolysed to furnish the corresponding $N$-protected aminoacid \textit{176} (Scheme 1.53).

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{Scheme1.53}

\textbf{Scheme 1.53} Kinetic resolution of \textit{174} via modified cinchona alkaloid-catalysed methanolysis.
\end{scheme}
This kinetic resolution procedure was then extended to a wide variety of alkyl and aryl substituted UNCAs which were efficiently resolved at low temperature with high enantioselectivity (selectivity factors up to 170).

In 2008, Connon et al. performed the acylative KR of a sec-thiol (i.e. 177) with glutaric anhydride in the presence of bifunctional thiourea- and sulfonamide-based cinchona alkaloid organocatalysts, respectively, which resulted in a very modest selectivity. The reaction carried out using 3-substituted achiral glutaric anhydrides such as 178, in the presence of sulfonamide-based catalyst 170 resulted in a KR of thiol 177 with better enantioselectivity and with concomitant anhydride desymmetrisation (Scheme 1.54). The authors claimed that additional substituents played a key role in controlling the interactions between the catalyst and a single carbonyl group of the incoming anhydride simultaneously thereby improving the enantioselective resolution of the thiol.

![Scheme 1.54](image)

**Scheme 1.54** Kinetic resolution of thiol 177 with simultaneous desymmetrisation of achiral anhydride 178 promoted by sulfonamide-based cinchona alkaloids.

A further evaluation of the steric and electronic characteristics of sulfonamide-based catalysts revealed the superiority of hindered catalysts and in particular, 185 with a selectivity of 8.5 was found to be very synthetically useful.
1.8 General concepts of dynamic kinetic resolution (DKR)

As mentioned above, the maximum theoretical yield of KR is limited to 50%. An efficient strategy that allows one to overcome this yield limit is known as dynamic kinetic resolution (DKR, Scheme 1.55).\textsuperscript{160,172}

\begin{center}
\begin{tikzpicture}

\node at (0,0) {Racemic mixture};
\node at (0.5,0) {\textit{R} \rightleftharpoons \textit{S}};
\node at (2,0) {C\*};
\node at (2.5,0) {RC\*};

\end{tikzpicture}
\end{center}

\textit{C\*} = chiral catalyst

\textbf{Scheme 1.55} Dynamic kinetic resolution (DKR).

In an ideal dynamic or second order kinetic resolution process 100\% of one product enantiomer can be obtained from the continual racemisation of the unreactive substrate enantiomer. In order to obtain an highly selective DKR, the racemisation of the substrate should occur more quickly than the interaction of the slower reacting substrate (\textit{S}_s) with the chiral agent (\textit{i.e.} \(k_{\text{fast}} \gg k_{\text{slow}}\) and \(k_{\text{rac}} \gg k_{\text{slow}}\), Figure 1.8).

\begin{center}
\begin{tikzpicture}

\node at (0,0) {$\textit{S}_R$};
\node at (1,0) {\(k_R = k_{\text{fast}}\)};
\node at (2,0) {$\textit{P}_R$};
\node at (0,-1) {$\textit{S}_S$};
\node at (1,-1) {\(k_s = k_{\text{slow}}\)};
\node at (2,-1) {$\textit{P}_S$};
\node at (0,-0.5) {$k_{\text{rac}}$};

\end{tikzpicture}
\end{center}

\textbf{Figure 1.8} Correlation between rate constants and efficiency of DKR process.

The starting material will be racemic for the entire reaction and the enantiomeric excess of the product will not be sensitive to the extent of reaction (Figure 1.9).
Figure 1.9  Correlation between % enantiomeric excess of product and % conversion in DKR process.

1.8.1 DKR of racemic cyclic anhydrides promoted by bifunctional cinchona alkaloid organocatalysts

The synthesis of optically active $\alpha$-hydroxy acids has received considerable attention in the past as this structural motif exists in many biological compounds.\cite{173} The majority of catalytic synthetic strategies involved the use of chiral transition metal complexes\cite{174,175,176} as a catalytic valid alternative to the well-developed enzymatic approaches.\cite{177,178,179} However, no examples of metal-free cinchona alkaloid-catalysed kinetic resolutions of $\alpha$-hydroxy acids have been reported. In addition, the acidic nature of the $\alpha$-proton of dioxolanediones 187 easily prepared from the corresponding $\alpha$-hydroxy acids 186 treated with diphosgene, prompted Deng et al. to investigate the possibility of developing an efficient DKR. In 2002, they reported the reaction of racemic dioxolanediones 187 with ethanol in the presence of the bifunctional cinchona alkaloid organocatalyst 160. The reaction proceeded smoothly furnishing the product 188 with excellent enantioselectivity (Scheme 1.56).\cite{180} The enantiomeric excess of the product and the starting material were analysed at different reaction times, and were found to be 95% and 0% respectively. The control experiment performed using optically pure 187, also showed the formation of a racemic mixture. The authors found that the catalyst 160 acted in a dual role, mediating the racemisation of the starting material and promoting the conversion of both the enantiomers to a single optically active ester product 188 via an highly efficient dynamic kinetic resolution process.
Scheme 1.56  DKR of dioxolanediones 187 with ethanol promoted by the Sharpless catalyst 160.

Shortly afterwards, Deng and co-workers extended the scope of this dual function catalysis of modified cinchona alkaloids, reporting an efficient DKR of α-aryl UNCA s at room temperature. The reaction performed using both α-aryl and α-heteroaryl UNCA s 189 with allyl alcohol (190) in the presence of the modified cinchona alkaloid catalyst 160 provided the corresponding allyl amino esters 191 in high yield and excellent enantioselectivity (Scheme 1.57). 181 The optically active esters 191 were generally converted to the α-aryl and heteroaryl amino acids 192 without influencing the optical purity via room temperature Pd-catalysed deallylation.

Scheme 1.57  DKR of UNCA s with allyl alcohol (190) promoted by modified cinchona alkaloid organocatalyst 160.

Interestingly, Deng’s previous studies had demonstrated that at low temperature (-78 °C) the alcoholysis of UNCA s promoted by organocatalyst 160 occurred via conventional
kinetic resolution. The authors attributed these results to a general base catalysis mechanism. The rate-determining step of the alcoholysis catalysed by modified cinchona alkaloids involved a termolecular pre-transition state assembly 195a, while the racemisation of UNCA had a bimolecular transition state 195b. It was shown that the epimerisation could be significantly accelerated by increasing the temperature from -78 to 0 °C (Scheme 1.58).

![Cinchona alkaloid-catalysed DKR of UNCAs: proposed mechanism.](image)

**Scheme 1.58** Cinchona alkaloid-catalysed DKR of UNCAs: proposed mechanism.

### 1.8.2 DKR of azalactones promoted by bifunctional organocatalysts

Chiral α-amino acids have been widely utilised as intermediates for the synthesis of pharmaceuticals, ligands and organocatalysts. The alcoholytic dynamic kinetic resolution of azalactones became an attractive strategy to provide enantiomerically pure α-amino acid derivatives.

In 2005, Berkessel reported the alcoholytic ring opening of azalactones via a DKR process promoted by the bifunctional amine urea catalyst 202. 1H NMR spectroscopic studies demonstrated that the catalyst resulted in successful activation of the azalactone by hydrogen bonding interactions of the urea moiety with the carbonyl group. Scheme 1.59 depicts the reactions of several azalactones derived from both α-aromatic and aliphatic α-amino acids with 190, in the presence of catalyst 202 which furnished products in good enantioselectivity (72-87% ee).
Soon after, the same group demonstrated that both the efficiency and the enantioselectivity could be improved with the use of thiourea-based catalysts. The evaluation of bifunctional Takemoto-type organocatalysts suggested that catalysts bearing hindered substituents were more efficient in promoting this process. Therefore, they synthesised several tert-leucine amide-derived catalysts which proved successful in promoting the DKR of azalactones with excellent levels of enantioselectivity of up to 95%.

In 2008, Connon and co-workers investigated the use of (thio)urea-based cinchona alkaloids in promoting DKR with allyl alcohol of several azalactones. Interestingly, it was observed that urea derivatives were more efficient than thioureas and, in particular, the dihydroquinine-derived urea catalyst gave the best results. The results obtained by these preliminary experiments prompted our group to extend the substrate scope towards the use of thiol nucleophiles. The use of bifunctional urea-based cinchona alkaloid promoted the asymmetric ring opening of the azalactone with cyclohexyl thiol to give the corresponding thioester with high yield and moderate enantiomeric excess (Scheme 1.60).

**Scheme 1.59** DKR of azalactones with promoted by catalyst 202.

**Scheme 1.60** DKR of azalactones with thiols promoted by urea-based cinchona alkaloid 210.
The catalytic DKR of azalactones promoted by (thio)urea organocatalysts has been extensively explored,\textsuperscript{187,188} however, the use of squaramide-based catalysts has not been widely reported. In 2009, Song \textit{et al}. described a novel squaramide-based organocatalytic DKR of racemic azalactones with various alcohols. The reaction carried out using bifunctional squaramide-substituted dimeric cinchona alkaloid \textsuperscript{212} promoted the DKR of the azalactone \textsuperscript{198}; affording the \textit{S}-\textit{\alpha}-amino allyl ester \textsuperscript{213} in almost quantitative yields and excellent \textit{ee} (Scheme 1.61).\textsuperscript{189}

\[ 
\begin{array}{c}
\text{N} \quad \text{O} \\
\text{Ph} \quad \text{Pr} \\
\text{198} \quad \text{190 (2.0 equiv.)} \\
\end{array} 
\xrightarrow{\text{212 (10 mol\%)} \text{CH}_2\text{Cl}_2, rt} 
\begin{array}{c}
\text{HN} \quad \text{O} \\
\text{Ph} \\
\text{S-213 99\%, 93\% ee} \\
\end{array} + 
\begin{array}{c}
\text{HN} \quad \text{O} \\
\text{Ph} \\
\text{R-213} \\
\end{array}
\]

\textbf{Scheme 1.61} DKR of azalactones promoted by squaramide-substituted dimeric cinchona alkaloids.

1.9 General concepts of parallel kinetic resolution (PKR)

One of the major strategies for the preparation of enantiomerically pure chiral compounds is still the kinetic resolution of racemic mixtures \textit{via} chemical\textsuperscript{168,190} or enzymatic\textsuperscript{191} procedures. Unfortunately, at conversions close to 50\% there is a decrease in the \textit{ee} of the product due to the continuous increase of the relative concentration of the less reactive substrate enantiomer. To avoid this limitation, parallel kinetic resolution (PKR) is a strategy that allows for the formation of distinct products with improved \textit{ee} as well as up to 50\% theoretical yield.\textsuperscript{192} The concept of parallel resolution was first introduced by Vedejs and Chen\textsuperscript{193} in 1997 although some examples had already been known.\textsuperscript{194} In 1987, Brooks \textit{et al}. described that baker’s yeast was capable of reducing one enantiomer of a \textit{\beta}-keto ester to a chiral alcohol and decarboxylate the other to form an achiral ketone. Despite the enzymatic selectivity that, in this case, was already efficient and the parallel decarboxylation reaction that did not give advantages in terms of enantiomeric excess,
this experiment demonstrated the potential of different products being formed in competing reactions.

In an ideal situation, the 1:1 substrate ratio is maintained by a competing parallel reaction that removes the slower reacting substrate at similar rate, $P_{1R}/P_{2S}$ and $S_R/S_S$ are constant during the course of resolution (Scheme 1.62).

Scheme 1.62  Ideal PKR process.

In PKR, the selectivity factor can be lower than in KR but it achieves higher enantioselectivity. For example, in a PKR reaction using two simultaneous transformations with $S = 49$ (100% conversion), to achieve the same result in a simple kinetic resolution $S$ should be 200 at 50% conversion. Theoretically, both parallel experiments of the PKR process allow the recovery of each enantiomer with 96% ee.\textsuperscript{190,191}

PKR is classified into three different groups depending on the structural relationship between the two products $P_{1R}$ and $P_{1S}$.

- Chemodivergent PKR: two non-isomeric compounds, in some cases, completely different and one of them can be useless, since it is not chiral.
- Regiodivergent PKR: single functional group leads to two regioisomeric compounds or a substrate with the same active functional group but at different positions on the molecule.
- Stereodivergent PKR: Wittig-type reactions with the formation of geometric isomers ($Z$ and $E$) and those reactions in which in both enantiomers of the molecule are formed a new chiral centre, furnishing two different diastereomers.

1.9.1 PKR of cyclic anhydrides

In 2001, Uozomi and co-workers reported the first example of parallel kinetic resolution of cyclic anhydrides promoted by proline-derived organocatalysts. The reaction between
the racemic mixture of anhydride rac-214 and methanol, in the presence of the hydroxyl proline derivative 215 as catalyst provided the resulting hemiester products 216 and 217 with high enantioselectivity, despite the poor yield obtained (Scheme 1.63).

Soon after, Deng et al. reported the highly efficient parallel kinetic resolution of substituted succinic anhydrides promoted by the dimeric cinchona alkaloid (DHDQ)$_2$AQN 160. Initial studies using 2-methyl succinic anhydride (218a) demonstrated the importance of the alcohol in determining the enantioselectivity. The use of 2,2,2-trifluoroethanol (219) resulted in a more enantioselective process, in contrast with the observation by Bolm and co-workers that this alcohol nucleophile afforded racemic products in the desymmetrisation of meso anhydrides catalysed by modified-cinchona alkaloids. Having established the best nucleophile, in the presence of 160 as catalyst, a series of 2-alkyl succinic and 2-aryl substituted variants with electron-rich and electron-poor aromatic rings (i.e. 218) were effectively resolved via PKR furnishing the hemiester products 220 and 221 in high yields and excellent enantiomeric excess (Scheme 1.65). While the regioisomers of the alkyl hemiesters were separated using normal chromatographic separation, the aryl succinates were converted to β- and α-aryl-γ-butyrolactones 222 and 223, respectively.
Scheme 1.64 Parallel kinetic resolution of succinic anhydrides by Deng et al.

The same group reported the formation of lactone 222 derived from the anhydride 218g, with a significant selectivity corresponding to an S factor of at least 112 in conventional kinetic resolution, as an important intermediate in the enantioselective synthesis of the GABA receptor antagonist baclofen (Scheme 1.64).
1.10 Organosuperbases as catalysts: a promising tool in asymmetric synthesis

Over the past years, asymmetric catalysis has become a rapidly developing field of research. As mentioned before (Section 1.1.1), the three principal promoters of various enantio differentiating transformations are generally considered metals, enzymes and organocatalysts. Among them, the latter, have been deeply studied only over the last two decades and nowadays are considered to be one of the most constantly growing field of research. In particular, after the renaissance of organocatalysis, the chiral scaffold of cinchona alkaloids has become a pillar of several modern organocatalytic strategies and several research groups started to focus their attention on the development of different bifunctional modified-cinchona alkaloids. Recently, the introduction of chiral bases with guanidine 226, cyclopropenimine 227 and iminophosphorane 228 structural motifs are receiving increasing attention (Figure 1.10).

Figure 1.10 From traditional Brønsted base catalysis to organosuperbases in organocatalysis.

Guanidines are neutral nitrogen compounds and they are widely used as strong bases in synthetic organic chemistry. Their application in asymmetric catalysis has recently been the subject of reviews and includes a wide range of transformations such as Henry, Michael, Diels-Alder and Mannich reactions. The strong basicity of cyclopropenimines has been reported since 1999 however, the first application of
bis(dialkylamino)cyclopropenimines as Brønsted base catalysts in Michael and Mannich reactions\textsuperscript{206,207,208} appeared only in 2012.

In 1987, Schwesinger and co-workers introduced for the first time the concept of compounds derived from iminophosphoric acid, bearing three aminoalkyl groups linked to a phosphorus atom.\textsuperscript{209} They have been employed as very strong non-ionic bases in many organic chemical transformations\textsuperscript{210} and recently their application in asymmetric synthesis as organosuperbases is gaining significant consideration. Commonly, iminophosphoranes are divided into three main groups depending on their structural features. As shown in Figure 1.11, type 1 (a) includes compounds with a spirocyclic system bearing the iminophosphorane as a central atom. This class of catalysts can be prepared \textit{in situ} starting from the corresponding salt treated with a strong inorganic base.

The second type (b) includes bifunctional iminophosphoranes generally bearing a (thio)urea moiety capable of H-bonding interactions. They allow the activation of the pronucleophile via deprotonation simultaneously activating the electrophile through hydrogen bonding interactions. The last type (c), includes excessively strong basic iminophosphoranes (pK\textsubscript{BH+} = 35-37) in which the amide moieties (P-N bonds) are fundamental for the catalytic activity.\textsuperscript{198}

![Figure 1.11](image-url)  
\textbf{Figure 1.11} Classification of iminophosphorane organocatalysts.
1.10.1 Concept, design and applications of bifunctional iminophosphorane organocatalysts (BIMP)

Over the last ten years, the bifunctional Brønsted base/H-bond donor organocatalysts that generally possess both a tertiary amine and a H-bond donor group have received significant attention and have been employed in a wide range of enantioselective addition reactions.\textsuperscript{211} Despite the utility of their synthetic applications, this family of organocatalysts has limitations. For example, the relatively weak basicity of the tertiary amine could prove challenging in the activation of the pronucleophile and often long reaction times are required.

In 2013, Dixon and co-workers became interested in developing a new class of strongly basic and tunable bifunctional Brønsted base/H-bond donor organocatalysts. The authors introduced a bifunctional iminophosphorane catalyst bearing a triaryliminophosphorane functionality readily available from a direct Staudinger-type reaction between the corresponding azide (1-\textit{t}ert leucine derived azide) and triphenylphosphine.\textsuperscript{212,213} The additional functionality enhanced the Brønsted basicity of this novel class of catalysts relative to the more weakly basic tertiary amine moiety. Interestingly, it was found that the basicity of triaryliminophosphorane can be easily modified through the introduction of substituents on the aryl rings with different electronic properties, for instance, the basicity of the tris(4-methoxyphenyl)phosphine-derived is three orders of magnitude greater than the unsubstituted variant. Dixon \textit{et al.} reported the first general enantioselective organocatalytic nitro-Mannich reaction of nitromethane (234) with unactivated ketimines such as 233. The simultaneous activation of 234 (via deprotonation) and the ketimines (233, via H-bonding interactions), by bifunctional iminophosphorane organocatalysts led to the formation of the addition products (235) in high conversion (up to 99\%) and good enantiomeric excess (up to 85\%, Scheme 1. 65).\textsuperscript{213}
Scheme 1.65 Nitro-Mannich addition of 234 to ketimine 233 promoted by BIMP organocatalysts.

The same reaction was then carried out in the presence of cinchonine-derived bifunctional catalyst 138 as a direct comparison. The absence of products was a clear demonstration of the enhanced basicity of BIMPs compared to that of a cinchona-based catalyst containing tertiary amines.\textsuperscript{213} Shortly after, Dixon and co-workers developed an analogue of these catalysts by immobilisation on a solid polystyrene support.\textsuperscript{214} Despite their efficacy in promoting the aza-Henry reaction previously investigated, their catalytic activity was comparable to the non-immobilised variants. However, the easy recovery of the catalysts after the reaction by a simple filtration and the possibility to utilise them up to eleven times with the same catalytic activity resulted in a useful strategy. The utility of the nitro-Mannich products as chiral building blocks with nitrogen atoms was then confirmed by the reductive synthesis of the corresponding amines.\textsuperscript{198}
Two years later, the same group hypothesised that the enhanced basicity of iminophosphorane organosuperbases could succeed in dealing with the poor reactivity of unactivated methacrylate esters to the addition of nucleophiles. Therefore, they decided to investigate the sulfa-Michael addition of aliphatic thiol pronucleophiles, in view of the synthetic utility of chiral sulfides and the absence of metal-free catalytic enantioselective additions to unactivated α-substituted acrylate esters. Based on the enhanced basicity of tris (p-methoxyphenyl)phosphine and inspired by Jacobsen and Takemoto’s cyclohexanediamine-derived organocatalyst, they developed a 2nd generation of bifunctional iminophosphorane organosuperbases (Scheme 1.67).

![Figure 1.12](image)

**Figure 1.12** 2nd generation BIMP organocatalysts screened for performance in the sulfa-Michael addition reaction.

The sulfa-Michael addition of 1-propanethiol (245) to methyl methacrylate (246) as Michael acceptor in presence of BIMP organocatalysts proceeded smoothly, furnishing the addition products 247 in excellent yields and enantioselectivities (Scheme 1.66).
Scheme 1.66 Sulf-Michael addition of thiol 245 to 246 promoted by 2nd generation BIMP organocatalysts.

The authors attributed the excellent catalytic performance of 244 to the activation of the alkyl-thiol by the strong Brønsted basicity of the catalyst while the two tert-leucine residues surrounding the hydrogen bond donor thiourea, facilitated the enantiofacial selectivity in the protonation of the enolate intermediate.

Next, this protocol was expanded to different $\alpha$-substituted $\alpha,\beta$-unsaturated methyl or phenyl esters. The use of methyl ester Michael acceptors $\alpha$-substituted with electron withdrawing groups led to significantly improved results (up to 93% ee).\(^{215}\)

The synthetic utility of $\alpha$-aminophosphonic acid derivatives as important peptide mimics has been exploited in the synthesis of compounds with a wide range of biological activities such as anti-HIV,\(^{216,217}\) antibacterial\(^{218,219}\) and protease inhibition.\(^{220,221}\) As a result, the asymmetric phospha-Mannich reaction between phosphite pro-nucleophiles and imine electrophiles derived from aldehydes has been widely studied in the past. The enantioselective approaches reported in the literature are commonly based on the use of both metal-rich\(^{222,223}\) and metal-free catalysts.\(^{224}\) A similar 1,2-addition to imines derived from ketones (ketimine) has received much less attention in the past due to their reduced electrophilicity. In 2016, Dixon et al., based on the recent developments of nitro-Mannich reactions of ketimine,\(^{213}\) reported the enantioselective phospha-Mannich reaction of diethyl phosphite (248) to unactivated $N$-DPP-protected ketimines 249 promoted by a bifunctional iminophosphorane (BIMP) superbase organocatalyst 239. The reactions have been carried out with a series of ketimines with both electron-rich and electron-poor
substituents furnishing the corresponding addition products 250 with excellent yields and moderate enantioselectivities (Scheme 1.67).\(^{225}\)

\[
\begin{align*}
\text{EtO}^- & \quad \text{H} \\
\text{OEt} & \quad \text{P(O)Ph}_2 \\
248 & \quad 249 \quad \text{R}^1 \quad \text{R}^2 \\
& \quad 239 (10 \text{ mol}%) \\
\text{O} & \quad \text{P(O)Ph}_2 \\
250 & \quad \text{R}^1 \quad \text{R}^2 \\
\end{align*}
\]

\[
\begin{array}{ccc}
249a & \text{R}^1 = \text{Ph}, \text{R}_2 = \text{CH}_3 \\
249b & \text{R}^1 = 4-\text{OMe-C}_6\text{H}_4, \text{R}_2 = \text{CH}_3 \\
249c & \text{R}^1 = 3-\text{OMe-C}_6\text{H}_4, \text{R}_2 = \text{CH}_3 \\
249d & \text{R}^1 = 4-\text{Cl-C}_6\text{H}_4, \text{R}_2 = \text{CH}_3 \\
249e & \text{R}^1 = 4-\text{F-C}_6\text{H}_4, \text{R}_2 = \text{CH}_3 \\
249f & \text{R}^1 = \text{Ph}, \text{R}_2 = \text{CH}_2\text{CH}_3 \\
\end{array}
\]

<table>
<thead>
<tr>
<th>\text{250}</th>
<th>\text{yield} (%)</th>
<th>\text{ee} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>99</td>
<td>58</td>
</tr>
<tr>
<td>b</td>
<td>90</td>
<td>62</td>
</tr>
<tr>
<td>c</td>
<td>&gt;99</td>
<td>58</td>
</tr>
<tr>
<td>d</td>
<td>&gt;99</td>
<td>54</td>
</tr>
<tr>
<td>e</td>
<td>98</td>
<td>56</td>
</tr>
<tr>
<td>f</td>
<td>&gt;99</td>
<td>71</td>
</tr>
</tbody>
</table>

**Scheme 1.67** Phospha-Mannich addition of 248 to ketimines catalysed by bifunctional iminophosphorane organocatalyst 239.

In 2017, Dixon and co-workers, inspired by the successful use of bifunctional iminophosphorane organocatalysts in promoting the sulfa-Michael addition of alkyl thiols to \(\alpha\)-substituted acrylate esters,\(^{216}\) described the first organocatalytic sulfa-Michael addition of thiols \((\text{i.e. 245})\) to unactivated \(\beta\)-substituted-\(\alpha,\beta\)-unsaturated esters. The reaction of the commercially available methyl crotonate (251a) and 245 in the presence of the newly synthesised bifunctional iminophosphorane organocatalyst 253 furnished the addition product 252a in almost quantitative yield and a modest enantioselectivity (Scheme 1.68).\(^{226}\) The effect of changing the ester group of the crotonate was also investigated. They observed that the use of tert-butyl crotonate (251e) resulted in a significant increase in enantiomeric excess of the product 252e.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
251 & \quad 245 \quad \text{R}^1 \\
& \quad 253 (10 \text{ mol}%) \\
\text{O} & \quad \text{O} \\
252 & \quad \text{R}^1 \\
\end{align*}
\]

\[
\begin{array}{ccc}
252 & \text{yield} (%) & \text{er} \\
\text{a} & >99 & 81:19 \\
\text{b} & 95 & 84:16 \\
\text{c} & >99 & 85:15 \\
\text{d} & >99 & 81:19 \\
\text{e} & 94 & 92:8 \\
\end{array}
\]

**Scheme 1.68** Sulfa-Michael addition of thiols to \(\beta\)-substituted-\(\alpha,\beta\)-unsaturated esters promoted by 2\(^{nd}\) generation BIMP organocatalyst 253.
1.11 Objectives

We aimed to:

- Explore the reactivity of different enolisable anhydride nucleophiles in the cycloaddition reaction with benzaldehyde.
- Investigate the feasibility of using cinchona alkaloid-derived catalysts to promote the dynamic kinetic resolution of enolisable cyclic anhydrides.
- Analyse the possibility of developing a new protocol for the annulation reaction by using iminophosphorane organosuperbases as alternative catalysts.
Chapter 2

Results and Discussion: The asymmetric organocatalytic formal cycloaddition of enolisable cyclic anhydrides
2.1 The asymmetric organocatalytic formal cycloaddition of enolisable cyclic anhydrides: expansion of the substrate scope

Aldehydes, ketones and Michael acceptors have been employed in asymmetric cycloaddition reactions with enolisable cyclic anhydrides.\textsuperscript{136,146,148} As discussed in Section 1.5.1, the cycloaddition reaction between aldehydes and homophthalic anhydride can result in the formation of the annulation products with high yields and excellent enantiomeric excess in the presence of stoichiometric amounts of either (thio)urea or squaramide-based bifunctional cinchona alkaloid organocatalysts. This work revealed that, in principle, any enolisable anhydride can be employed as a nucleophile in asymmetric catalysis. The attempt to expand the substrate scope has been generally limited to succinic and substituted glutaconic anhydrides. Our group reasoned that the absence of more catalytic asymmetric variants of this reaction was due to the difficulties related to anhydrides lacking the enol-stabilising benzo-fused ring. Our group demonstrated that the use of succinic anhydride (108) with benzaldehyde (9) in the presence of catalyst 140 (Scheme 1.42) was unsuccessful. They attributed the failure of succinic anhydride to act as an effective substrate to impractically low concentrations of the reacting enol in solution. Accordingly, we became interested in exploring the possibility of using other anhydrides, focusing on the enhancement of the enol-forming capacity of the anhydride component. Despite the promising advantages of employing anhydrides bearing enol-stabilising groups, the optimisation of the synthetic pathway proved difficult. Due to the failure of the annulation reaction with 108, we lost interest in the use of glutaric anhydride and became directly interested in the aryl-substituted variants. The anhydrides that were chosen for the expansion of the substrate scope were those containing five and especially six-membered rings, in order to investigate the influence that the ring size may have on the outcome of the asymmetric cycloaddition. Glutaric anhydride derivatives and anhydrides including an electron-withdrawing heteroatom in their cyclic structure (254-263 Figure 2.1) were selected as models for this investigation.
2.1.1 Synthesis of enolisable glutaric anhydride derivatives

It was previously investigated by our group that the inclusion of a bromine atom on the five-membered anhydride 108 could facilitate the formation of a reactive enolate, but no examples of six-membered cyclic anhydrides have been reported. It was initially decided to evaluate 2-bromoglutaric anhydride (254). This anhydride could be synthesised potentially starting from the commercially available racemic glutamic acid monosodium salt monohydrate (264). The first step of the synthesis consists of the formation of the 2-bromoglutaric acid (265) via a Sandmeyer-type reaction. However, a considerable quantity of 266 as a by-product was also detected (Scheme 2.1).

Scheme 2.1 Attempted synthesis of anhydride 254.
Chapter 2

Results and discussion

In order to facilitate the isolation of the desired product 265, the mixture of products obtained was, upon extraction, esterified with methanol heated under reflux in the presence of sulfuric acid to give the bis-ester 267 in moderate yield (53%) and traces of by-product 268. The purification of 267 by flash chromatography on silica gel, was followed by its hydrolysis with 0.1 M NaOH furnishing the bis-acid 265. The cyclisation reaction of 265 was attempted with acetic anhydride and acetyl chloride respectively, however, \(^1\)H NMR spectroscopic analysis of the reaction mixture revealed mainly unreacted starting material and only 5% yield of the desired product. Simultaneously, as shown in Scheme 2.2, the same synthetic pathway was followed for the 2-chloro-substituted variant 255. Unfortunately, the cyclisation reaction of the bis-acid 269 also failed to produce the desired anhydride leading us to temporarily abandon the synthesis of 2-halogen-substituted glutaric anhydrides.

Scheme 2.2  Attempted synthesis of anhydride 255.

The cyano-substituted glutaric anhydride (256) was not reported at the beginning of this work and its synthesis proved to be very complicated. The alkylation of ethyl cyanoacetate (272) with ethyl acrylate (273) using sodium ethoxide as base in ethanol furnished complex mixtures of unreacted 272, the desired mono-alkylated compound 274, and considerable quantities of bis-alkylated compound. The isolation of pure 274 by Kugelrohr distillation proved problematic, contributing to the low isolated yield of the reaction (26%). The hydrolysis of the diester 274 was performed using LiOH in a THF/water mixture at room temperature for 3 hours. \(^{228}\) The cyclisation of the bis-
carboxylic acid 275 to form anhydride 256 using either AcCl or Ac₂O failed, therefore, the reaction was performed with trifluoroacetic anhydride and this furnished the desired product in very poor yield (Scheme 2.3).

Scheme 2.3  Synthesis of anhydride 256.

Anhydride 256 was evaluated in the asymmetric cycloaddition reaction with benzaldehyde (9) promoted by catalyst 140 at room temperature (Scheme 2.4). The desired product 276 could only be obtained in low yield. A longer reaction time (120 h) and increased concentration (0.2 M) did not prove effective for enhancing the yield, therefore, the reaction using this type of anhydride was deemed to be too slow to be considered synthetically useful.

Scheme 2.4  Evaluation of anhydride 256 in the asymmetric annulation reaction with 9.
2.1.2 Synthesis and evaluation of aryglutaric anhydrides in the asymmetric annulation reaction with benzaldehyde

Our group has demonstrated the successful employment of enolisable arylsuccinic anhydrides in the asymmetric annulation reaction with benzaldehyde \(^{(9)}\). We therefore, became interested in the synthesis and evaluation of aryglutaric derivatives under the optimum conditions previously reported in literature.\(^{(136)}\) The synthesis of 2-phenyl glutaric anhydride \((\text{257})\) was achieved in moderate yield via the four step synthetic pathway described in Scheme 2.5. The first step of the synthesis consists of the formation of the ester \((\text{278})\) in 98% yield which, was then reacted with methyl acrylate \((\text{279})\) in a Michael addition, furnishing the bis-ester \((\text{280})\) as a yellow oil. Ester \((\text{280})\) was hydrolysed with sodium hydroxide in methanol to the corresponding bis-carboxylic acid \((\text{281})\) which was cyclised to form the desired anhydride \((\text{257})\).

\[ \begin{align*}
\text{277} & \xrightarrow{\text{CH}_3\text{OH, H}_2\text{SO}_4, \text{reflux, 3 h}} \text{278 98\%} \\
\text{278} & \xrightarrow{i\text{BuOK, THF -78 °C, 1 h}} \text{280 33\%} \\
\text{280} & \xrightarrow{\text{1. NaOH, CH}_3\text{OH, reflux, 4 h} \hspace{1cm} 2. \text{H}_3\text{O}^+} \text{281 79\%} \\
\text{281} & \xrightarrow{\text{AcCl, reflux 12 h}} \text{257 80\%}
\end{align*} \]

Scheme 2.5 The synthesis of aryglutaric anhydride \((\text{257})\).

In accordance with the increased enol-stabilisation associated with \(p\)-\(\text{NO}_2\)-phenylsuccinic anhydride, the next step was the installation of the \(\text{NO}_2\) electron-withdrawing group to the aryl moiety of anhydride \((\text{257})\). The synthesis began with the formation of 2-(4-nitrophenyl)acetic acid \((\text{283})\). The Michael addition between ester \((\text{284})\) and \((\text{279})\) using sodium methoxide in methanol furnished the bis-ester \((\text{285})\) followed by hydrolysis with \(\text{NaOH}\) to afford the bis-acid \((\text{286})\). The obtained residue was then reacted with acetyl chloride at reflux for 12 hours to give \((\text{258})\) (Scheme 2.6).
Scheme 2.6  The synthesis of arylglutaric anhydride 258.

Now, in possession of the optimal reaction conditions,136,146,148 these anhydrides 257 and 258 were evaluated in the asymmetric cycloaddition reaction with 9 promoted by catalysts 139 and 140 respectively at room temperature (Scheme 2.7). Unfortunately, the asymmetric annulation reaction failed to produce the desired lactones with both of these anhydrides. Analysis of the crude mixture by $^1$H NMR spectroscopy indicated only the presence of completely unreacted starting material.

Scheme 2.7  Evaluation of anhydride 257 (A) and anhydride 258 (B) in the asymmetric annulation reaction with 9.
2.1.3 Synthesis and evaluation of anhydrides bearing electron-withdrawing heteroatoms in the asymmetric annulation reaction with benzaldehyde

Since the installation of enol-stabilising groups on enolisable glutaric anhydrides proved unsuccessful in promoting the reactivity in annulation reactions with benzaldehyde, we became interested in anhydrides containing electron-withdrawing heteroatoms within the ring, that, to the best of our knowledge, have never been explored before.

The ready commercial availability of iminodiacetic acid (289) prompted us to synthesise and evaluate anhydride 260 bearing a nitrogen heteroatom within the ring that enhances the acidity of the α-hydrogen and may enhance the enolisation ability of the anhydride. The first step of the synthesis was the introduction of di-tert-butyl dicarbonate ((Boc)$_2$O) as a protecting group, yielding N-Boc-iminodiacetic acid (290). The attempted cyclisation of 290 using dicyclohexylcarbodiimide (DCC) proved unsuccessful (due to a difficult purification) and led us to use a polystyrene-bound variant which gave the desired product 259 in good yield (Scheme 2.8).

Scheme 2.8 The synthesis of anhydride 259.

The tosyl-substituted iminodiacetic anhydride 260 was also prepared by reaction of the bis-acid 291, synthesised according to the known literature one step synthetic procedure, with acetyl chloride (Scheme 2.9).

Scheme 2.9 The synthesis of anhydride 260.

The evaluation of these new substrates in the reaction with 9 promoted by a catalytic amount of 5 mol% of 140 was the next step in this study. Disappointingly, analysis of the crude reaction mixture by $^1$H NMR spectroscopy revealed that the starting materials were completely unreactive under the reaction conditions employed (Scheme 2.10A, B).
Scheme 2.10 Evaluation of anhydride \textbf{259} (A) and anhydride \textbf{260} (B) in the asymmetric annulation reaction with \textbf{9}.

The synthesis of the \(N\)-benzoyl substituted anhydride \textbf{261} was not known at the beginning of this investigation and its synthesis proved to be very problematic. However we envisaged that this substrate could be obtained via a similar synthetic route to that used in the synthesis of the \(N\)-Boc and \(N\)-Ts variants (\textbf{259} and \textbf{260} respectively). Iminodiacetic acid (\textbf{289}) was subjected to esterification to obtain the bis-ester \textbf{294} which was subsequently reacted with benzoyl chloride to form the product \textbf{295}. The attempted hydrolysis of \textbf{295} with either NaOH or KOH proved ineffective, therefore, the hydrolysis was carried out using LiOH in THF/water 3:1 and afforded compound \textbf{296} in moderate yield. Unfortunately, the bis-carboxylic acid \textbf{296} failed to cyclise to form anhydride \textbf{262}. Reagents such as acetyl chloride, acetic anhydride and polymer supported-DCC which are commonly employed for this type of transformation, proved ineffective here; furnishing an excess of acid (70\%) which could not be isolated from the desired product. When we later became aware of the methodology employed by Charton \textit{et al.} for the cyclisation of \textbf{296} (\textit{i.e.} TFAA 2\% and \textbf{Ac}_2\text{O} for 4 h at room temperature)\textsuperscript{230} we reasoned that our lack of success could have been due to the use of non-forcing reaction conditions (Scheme 2.11).
Due to the lack of success, the synthesis and evaluation of anhydrides with this type of structure seemed futile, was therefore temporarily abandoned.

2.1.4 Synthesis and evaluation of sulfone-substituted anhydrides in the asymmetric annulation reaction with benzaldehyde

Inspired by the diastereoselective synthesis of \( \gamma \) - and \( \delta \) -lactams from imines and sulfone-substituted anhydrides reported by Shaw et al., we decided to evaluate these substrates in the mechanistically unrelated formal cycloaddition with aldehydes. Two anhydrides bearing this moiety were prepared: 262 and 263. According to the known literature procedures, the commercially available benzenesulfinic acid sodium salt (297) was reacted with maleic anhydride (298) to obtain the dicarboxylic acid 299. The cyclisation reactions to form the desired anhydride 262 was accomplished by treating the bis-acid 299 with acetic anhydride (Scheme 2.12).

The synthesis of the sulfone-substituted glutaric variant 263 was achieved in good yield over a three step procedure. The commercially available benzenesulfinic acid sodium salt (297) was treated with tert-butyl bromoacetate (300) to furnish 301. The alkylation of 301 with tert-butyl acrylate (302) in the presence of caesium carbonate in acetonitrile afforded the bis-ester 303. Anhydride 263 was subsequently obtained by reacting 303
with trifluoroacetic acid for 1 h at room temperature, followed by the cyclisation reaction with trifluoroacetic anhydride (Scheme 2.13).

Scheme 2.13 The synthesis of anhydride 263.

These anhydrides were evaluated in the asymmetric cycloaddition reaction with 9 promoted by 5 mol% of catalyst 140 at room temperature as shown in Scheme 2.14 A, B.

Scheme 2.14 Evaluation of anhydride 262 (A) and anhydride 263 (B) in the asymmetric annulation reaction with 9.

Unfortunately, the desired lactone could not be obtained. Analysis by $^1$H NMR spectroscopy of the crude product obtained upon removal of the solvent in vacuo revealed that the corresponding ring-opened acids had formed. We proposed that the observed instability of anhydrides 262 and 263 is due to the main to the likely strong acidity of the $\alpha$-proton on these compounds conferred by the presence of the powerfully electron-withdrawing sulfone groups on the $\alpha$-carbon atom.
2.1.5 Use of other electrophiles in the asymmetric annulation reaction with enolisable cyclic anhydrides

In view of the disappointing results obtained with the use of aldehyde 9 in annulation reactions, we decided to evaluate other electrophiles. It has been reported by our group that ketones and 2-alkylidene oxindoles were successfully employed in enantioselective cycloadditions with enolisable anhydrides promoted by cinchona alkaloid organocatalysts. We therefore became interested in the development of a similar process that involved the reaction of our new set of enolisable anhydrides as nucleophiles. In order to study the feasibility of the process, the substituted oxindole 147 had to be prepared (Scheme 2.15). According to the literature procedure, the synthesis started with the reaction between ethyl bromoacetate (306) and triphenylphosphine (307) to furnish the intermediate phosphonium salt (308) which is deprotonated by sodium hydroxide solution and extracted to provide the ylide 309. The formation of the oxindole 311 was then achieved via a Wittig reaction between the ylide 309 and isatin (310). Subsequently, 311 was, upon purification by column chromatography on silica gel, protected at the nitrogen atom by reaction with di-tert-butyl dicarbonate ((Boc)₂O) in the presence of a catalytic amount of DMAP giving the desired product 147 in excellent overall yield.

Scheme 2.15 Synthesis of the substituted oxindole 147.

Now, in possession of a number of different anhydrides (257, 258, 259, 260, 262 and 263) and the optimal reaction conditions, the evaluation of these substrates promoted by catalysts 138, 140 and 148 was the next step in the study. We considered the annulation reaction with 2,2,2-trifluoroacetophenone (312, Scheme 2.16A) and alkylidene 2-oxindole (147, Scheme 2.16B) respectively at room temperature.
Scheme 2.16 Evaluation of 312 (A) and 147 (B) in the asymmetric annulation reaction with enolisable anhydrides.

We were rather disappointed to observe that the annulation reactions failed even when using different electrophiles.

2.2 Conclusions

As described in the previous section, with regards to Connon’s protocol,\textsuperscript{136,146,148} modified cinchona alkaloids could be used at 5 mol\% loading for the promotion of the enantioselective cycloaddition involving homophtalic or arylsuccinic anhydrides and different electrophiles. Disappointingly, the possibility of using six-membered ring anhydrides or anhydrides bearing an electron-withdrawing heteroatom in their structural core resulted unsuccessful. In conclusion, faced with these results, despite the intensive efforts devoted to this project, we assumed that attempting to expand the asymmetric protocol recently developed by our group\textsuperscript{136,146,148} with these anhydrides was not promising and no further attention was given to this work.
Chapter 3

Results and Discussion: Towards the development of asymmetric dynamic kinetic resolution of cyclic anhydrides
3.1 Towards the development of asymmetric dynamic kinetic resolution of cyclic anhydrides

The racemisation of compounds with a stereogenic centre containing an acidic proton in the α position to a carbonyl group is considered an effective strategy to equilibrate the two reactive enantiomers (Scheme 3.1).\(^{235,236}\)

Scheme 3.1 Enol intermediate formation via racemisation.

Tang and Deng\(^{198}\) observed that in the presence of the modified cinchona alkaloid (DHQD)\(_2\)AQN (160), alcoholysis of mono substituted succinic anhydrides underwent rapid parallel kinetic resolution of the two enantiomers of the cyclic anhydride (see Section 1.9.1). However, no examples of organocatalytic dynamic kinetic resolution of succinic anhydrides by alcoholysis have been reported.

Our group, inspired by Deng’s studies, considered the development of a DKR strategy, promoted by thiourea sulfonamide and squaramide-substituted cinchona alkaloids, involving racemisation of enolisable succinic anhydrides enantiomers \((R)\)- and \((S)\)-313. This would require us to be able to develop a catalytic reaction in which the catalyst can guide the incoming alcohol \(R'\text{OH}\) to a single face of a single carbonyl group on the anhydride, while exchanging interaction with the other carbonyl. In addition, it must be able to facilitate the racemisation of the anhydride enantiomers at an appreciable rate (Scheme 3.2).

Scheme 3.2 Dynamic kinetic resolution of monosubstituted succinic anhydrides.
3.1.1 Alcoholysis of phenylsuccinic anhydrides promoted by cinchona alkaloid derivatives

Our group\textsuperscript{160} was recently engaged in the use of cinchona alkaloid-derived bifunctional organocatalysts to promote the enantioselective desymmetrisation of cyclic \textit{meso} anhydrides \textit{via} asymmetric nucleophilic additions of alcohols and thiols. The bifunctional catalysts employed were thought to activate the anhydride electrophiles through hydrogen bond donation and the pronucleophiles \textit{via} general-base catalysis (Figure 3.1).

![Figure 3.1](image)

\textbf{Figure 3.1} Dual activation mode using bifunctional (thio)urea-modified cinchona alkaloids.

Cinchona-alkaloid derived bifunctional organocatalysts were also successfully employed by our group for the asymmetric thiolysis of achiral anhydrides and the concomitant kinetic resolution of secondary thiol nucleophiles.\textsuperscript{171} Prompted by the excellent results obtained with the use of these catalysts to promote asymmetric openings of cyclic anhydrides, we decided to explore the feasibility of using cinchona alkaloid-derived catalysts to promote the dynamic kinetic resolution of phenylsuccinic anhydride (141).

3.1.2 Preliminary experiments

To test the hypothesis laid out in Section 3.1 we decided to evaluate the regioselectivity of the nucleophilic addition to anhydride 141, using various alcohols (R’OH) as nucleophiles in the presence of a catalytic amount of the thiourea-based organocatalyst 163. The anhydride 141 was easily synthesised by reaction of the commercially available phenylsuccinic acid (316) with acetyl chloride under reflux (Scheme 3.3).
Scheme 3.3  Synthesis of phenylsuccinic anhydride (141).

Using MTBE as solvent, 141 and R’OH were reacted together in the presence of 5 mol% of 163 at room temperature under the conditions shown in Table 3.1 to furnish the corresponding hemiesters.

Table 3.1  Alcoholysis of phenylsuccinic anhydride: preliminary experiments.

<table>
<thead>
<tr>
<th>entry</th>
<th>ROH</th>
<th>Time (h)</th>
<th>conv (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ratio 317:318&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH (319)</td>
<td>24</td>
<td>98</td>
<td>49:51</td>
</tr>
<tr>
<td>2</td>
<td>EtOH (320)</td>
<td>24</td>
<td>98</td>
<td>46:54</td>
</tr>
<tr>
<td>3</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;=CHCH&lt;sub&gt;2&lt;/sub&gt;OH (190)</td>
<td>24</td>
<td>97</td>
<td>45:55</td>
</tr>
<tr>
<td>4</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;OH (321)</td>
<td>24</td>
<td>98</td>
<td>45:55</td>
</tr>
<tr>
<td>5</td>
<td>i-PrOH (322)</td>
<td>72</td>
<td>47</td>
<td>47:53</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using p-iodoanisole as an internal standard.

The alcoholysis of anhydride 141 using methanol (319, Table 3.2, entry 1) led to the formation of almost equal amounts of product 317 and 318. By reacting anhydride 141 with other primary alcohols such as ethanol (320), allyl alcohol (190) and benzyl alcohol (321), only marginally superior product ratios were reported (Table 3.1, entries 2, 3 and 4 respectively). It was observed that when the reaction was carried out using isopropanol (322) as the nucleophile (entry 5), the product ratio remained virtually unchanged, however significantly lower conversion was observed even after 72 h.
At this point, we decided to evaluate the regioselectivity of our reaction using two squaramide-based cinchona alkaloid as reaction promoters. The protocol used involved the reaction of anhydride 141 with either alcohol 190, 319 or 321 in the presence of catalytic amounts of 140 or 148 in MTBE (0.1 M) at room temperature (Table 3.2).

**Table 3.2** Alcoholysis of anhydride 141: preliminary catalyst screening.

<table>
<thead>
<tr>
<th>entry</th>
<th>ROH</th>
<th>cat.</th>
<th>conv (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ratio 317:318&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>319</td>
<td>140</td>
<td>98</td>
<td>50:50</td>
</tr>
<tr>
<td>2</td>
<td>319</td>
<td>148</td>
<td>98</td>
<td>50:50</td>
</tr>
<tr>
<td>3</td>
<td>190</td>
<td>140</td>
<td>97</td>
<td>50:50</td>
</tr>
<tr>
<td>4</td>
<td>190</td>
<td>148</td>
<td>97</td>
<td>50:50</td>
</tr>
<tr>
<td>5</td>
<td>321</td>
<td>140</td>
<td>98</td>
<td>45:55</td>
</tr>
<tr>
<td>6</td>
<td>321</td>
<td>148</td>
<td>98</td>
<td>45:55</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis using <i>p</i>-iodoanisole as an internal standard.

Unfortunately, in all cases evaluated, the use of squaramide-based catalysts did not influence the regioselective outcome of the reaction compared to the thiourea catalyst 163 previously investigated.

Kinetic studies, involving monitoring the reaction over time, were then carried out (Table 3.3). The reaction between 141 and methanol 319 in the presence of catalyst 163 revealed that high conversion to the hemiester products can be obtained in a short reaction time (entry 1 and 2). It was also observed that regioselectivity was independent of conversion (entries 1, 2 and 3).
Table 3.3  Alcoholysis of anhydride 141: kinetic studies.

![Reaction scheme](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>Time (h)</th>
<th>conv (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ratio 323:324&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>72</td>
<td>49:51</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>86</td>
<td>49:51</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>98</td>
<td>49:51</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using p-iodoanisole as an internal standard.

It is clear from these data that either the catalyst is not promoting the racemisation of anhydride 141 fast enough relative to the rate of addition, or that no KR is taking place. In an attempt to improve the regioselectivity of our protocol, we decided to use smaller amounts of alcohol (i.e. 1 equiv.) so that racemisation is given a chance to occur (slow addition step), and to lower the temperature from rt to -30 °C. The addition step requires three species to cooperate in the transition state (catalyst, alcohol and anhydride), while the racemisation only requires two species (catalyst and anhydride). Therefore, at lower temperature, addition has a less entropically favourable transition state and should slow relative to racemisation. The sets of reaction previously mentioned were repeated at lower temperature and using equimolar amounts of anhydride 141 and ROH in the presence of catalysts 163 and the results are presented in Table 3.4.
Results and discussion

Table 3.4  Alcoholysis of anhydride 141 performed at -30 °C.

In all cases evaluated, a lower temperature of -30 °C did not result in substantial improvement in hemiester product ratio but did result in lower conversion when compared to the reaction performed at room temperature (entries 1, 2 and 3).

At this point, we decided to carry out further screening of different alcohols. Since it was perceived that the steric properties of the pronucleophiles were not responsible for the regioselective outcome of the alcoholysis of anhydride 141, it was decided to analyse whether the use of alcohols having different electronic properties could affect the hemiester ratio (Table 3.5).

Table 3.5  Alcoholysis of anhydride 141: preliminary alcohol screening.

---

**Table 3.4**  Alcoholysis of anhydride 141 performed at -30 °C.

<table>
<thead>
<tr>
<th>entry</th>
<th>ROH</th>
<th>temp (°C)</th>
<th>conv (%)</th>
<th>ratio 317:318</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH (319)</td>
<td>-30</td>
<td>78</td>
<td>50:50</td>
</tr>
<tr>
<td>2</td>
<td>C2H5OH (190)</td>
<td>-30</td>
<td>45</td>
<td>45:55</td>
</tr>
<tr>
<td>3</td>
<td>PhCH2OH (321)</td>
<td>-30</td>
<td>48</td>
<td>45:55</td>
</tr>
</tbody>
</table>

* Determined by ¹H NMR spectroscopic analysis using p-iodoanisole as an internal standard.

<table>
<thead>
<tr>
<th>entry</th>
<th>ROH</th>
<th>time (h)</th>
<th>conv (%)</th>
<th>ratio 317:318</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CF3CH2OH (219)</td>
<td>48</td>
<td>98</td>
<td>38:62</td>
</tr>
<tr>
<td>2</td>
<td>CCl3CH2OH (323)</td>
<td>48</td>
<td>96</td>
<td>32:68</td>
</tr>
</tbody>
</table>

* Determined by ¹H NMR spectroscopic analysis using p-iodoanisole as an internal standard.

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Chapter 3

Results and discussion

Gratifyingly, the use of electron-deficient alcohols such as 2,2,2 trifluoroethanol (219) and 2,2,2-trichloroethanol (323, Table 3.1, entry 1 and 2 respectively) led to quantitative conversions and markedly improved hemiester ratio with product 318 being formed in a two-fold excess compared to 317.

We therefore decided to evaluate the reaction between anhydride 141 and these alcohols at lower temperature (0 °C) in the presence of catalyst 163 (Table 3.6).

**Table 3.6** Alcoholsysis of anhydride 141 performed at 0 °C.

<table>
<thead>
<tr>
<th>entry</th>
<th>ROH</th>
<th>temp (°C)</th>
<th>conv (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ratio 317:318&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH (219)</td>
<td>0</td>
<td>83</td>
<td>40:60</td>
</tr>
<tr>
<td>2</td>
<td>CCl&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH (323)</td>
<td>0</td>
<td>79</td>
<td>34:66</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using <sup>p</sup>-iodoanisole as an internal standard.

Unfortunately, reducing the temperature to 0 °C using either 219 or 323 (entries 1 and 2, Table 3.6) gave a product ratio marginally inferior to that obtained at room temperature.

3.1.3 Preliminary evaluation of alternative cyclic anhydrides as electrophiles

In light of the poor regioselectivities obtained, it was decided to employ anhydrides with an electron withdrawing group in order to increase the enolisation proclivity of the anhydride to allow subsequent rapid racemisation of the substrate. We decided to employ 4-nitrophenylsuccinic anhydride (143), which was synthesised according to a literature procedure (Scheme 3.4).<sup>237</sup>

**Scheme 3.4** Synthesis of 4-nitrophenylsuccinic anhydride (143).
Anhydride 143 was reacted with several alcohols (ROH) catalysed by thiourea-substituted cinchona alkaloid catalyst 163 (Table 3.7).

**Table 3.7** Preliminary evaluation of the substrates scope: phenylsuccinic anhydride component.

<table>
<thead>
<tr>
<th>entry</th>
<th>ROH</th>
<th>temp (°C)</th>
<th>conv (%)</th>
<th>ratio 325:326&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>(320)</td>
<td>98</td>
<td>47:53</td>
</tr>
<tr>
<td>2</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH (219)</td>
<td>25</td>
<td>98</td>
<td>42:58</td>
</tr>
<tr>
<td>3</td>
<td>CCl&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH (323)</td>
<td>25</td>
<td>98</td>
<td>38:62</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using p-iodoanisole as an internal standard.

Disappointingly, the use of anhydride 143 in the organocatalytic alcoholysis with different alcohols such as ethanol (320), 2,2,2-trifluoroethanol (219) and 2,2,2-trichloroethanol (323) promoted by catalyst 163 at room temperature failed to improve the product ratio (entries 1, 2 and 3 respectively) significantly, giving results even slightly inferior to those obtained with 141.

Shortly after, the sulfone substituted succinic anhydride (262) and the sulfone-substituted glutaric anhydride (263) were employed in the reaction promoted by catalyst 163 at room temperature for 48 h using MTBE as solvent and in the presence of an equimolar amount of 323 as the nucleophile (Scheme 3.5).

**Scheme 3.5** Alcoholysis of anhydrides 262 (A) and 263 (B).
When anhydrides 262 and 263 were evaluated, the presence of two products in the reaction mixture was identified. Initial $^1$H NMR spectroscopic analysis of the structures obtained supported the original alcoholysis hypothesis, however, the products formed were ultimately determined not to be those expected. A mixture of the two hemiesters 327a/327b (Scheme 3.5A) and 328a/328b (Scheme 3.5B) were found, along with significant amounts of their corresponding acids 299 and 329 respectively. It was assumed that even a minimum amount of water may compete with the nucleophilic attack of the alcohol interfering with our reaction scope. We reasoned that a strategy which could allow us to circumvent this inconvenience would be necessary in order to clearly evaluate DKR efficiency. We therefore decided to carefully dry the reaction conditions using molecular sieves and freshly distilled alcohol under an argon atmosphere. Unfortunately, this procedure proved ineffective in avoiding the formation of acid; demonstrating the extreme instability of anhydrides 262 and 263 compared to anhydride 141.

3.2 Preliminary (thio)urea and squaramide-based catalyst evaluation and optimisation studies for the regio/enantioselective alcoholysis of phenylsuccinic anhydride

Since the preliminary investigations were directed towards the regioselectivity, our attention will now focus on the evaluation of the catalyst capability in promoting both the racemisation and the enantioselective ring-opening. Our protocol involved the reaction of equimolar amounts of 141 and alcohol 323 (which provided the best product ratio previously) promoted by 5 mol% of catalyst at room temperature in MTBE (0.1 M, Scheme 3.6A). After 48 h, conversions achieved in the reaction was determined by $^1$H NMR spectroscopic analysis of the crude mixture, using p-iodoanisole as an internal standard. Evaluation of the enantioselectivity of the process by chiral stationary phase high performance liquid chromatography (CSP-HPLC) was then required. In order to achieve this, we converted the mixture of phenyl succinates 330 and 331 to β- and α-aryl-γ-butyrolactones following the procedure reported by Deng.197 Reduction with lithium triethylborohydride solution followed by acidification with hydrochloric acid solution and second extraction with organic solvent allowed for the isolation of β- and α-aryl-γ-butyrolactones 332 and 333 which were then purified by flash column chromatography on silica gel (Scheme 3.6B).
**Scheme 3.6** Conversion of the phenyl succinate products 330 and 331 to β- and α-aryl-γ-butyrolactones 332 and 333.

Accordingly, we decided to evaluate several cinchona-based organocatalysts which were previously made by fellow researchers in our group and were readily available in our laboratory. For this reason, it was possible to evaluate a wide range of catalysts in the reaction between 141 and alcohol 323 (Table 3.8).
Table 3.8  Preliminary catalyst evaluation in the enantioselective alcoholsysis of 141.

\[
\begin{align*}
\text{141} & \xrightarrow{\text{cat. (5.0 mol%) 323 (1.0 equiv.) MTBE (0.1 M), rt, 48 h}} \text{330} + \text{331} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>conv (%)(^a)</th>
<th>ratio</th>
<th>ee (%)(^b)</th>
<th>yield (%)(^c)</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
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<td>330:331(^a)</td>
<td>332</td>
<td>333</td>
</tr>
<tr>
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<td>98</td>
<td>34:66</td>
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<td>31:69</td>
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<td>334</td>
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<td>32:68</td>
<td>84</td>
<td>63</td>
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<td>139</td>
<td>80</td>
<td>50:50</td>
<td>90</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>148</td>
<td>95</td>
<td>37:63</td>
<td>90</td>
<td>72</td>
</tr>
</tbody>
</table>

\(^a\)Determined by \(^1\)H NMR spectroscopic analysis using \(p\)-iodoanisole as an internal standard. \(^b\) Determined by CSP-HPLC. \(^c\) Isolated yield.

The reaction promoted by catalyst 163 led to the formation of hemiester in moderate regioselectivity and good ee (entry 1). The use of catalysts 138 or 334 in which the thiourea moiety of catalyst 163 has been exchanged for an urea moiety, proved comparable: a marginal increase in regioselectivity compared to the analogous reaction promoted by catalyst 163 was reported (entries 2 and 3), however, lower ee was observed.

The substitution of the thiourea moiety with a squaramide unit in catalysts 139 and 148 resulted in a slower reaction time and was unhelpful in improving the regioselective alcoholsysis reaction (entries 4 and 5 respectively), but led to a reaction with excellent enantioselectivity (especially in terms of the formation of the minor lactone product 332).
At this point, the same catalyst screening was repeated using allyl alcohol (190) as the nucleophile, in order to evaluate the enantioselective alcoholysis of 141 with an alcohol which had proved less efficacious in terms of regioselectivity compared to alcohol 323 in previous studies (Section 3.1.2).

Table 3.9 Catalyst evaluation in the enantioselective alcoholysis 141 with 9.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>conv (%)</th>
<th>ratio</th>
<th>ee (%)</th>
<th>yield (%)</th>
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</thead>
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<tr>
<td></td>
<td></td>
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<td>332</td>
<td>333</td>
</tr>
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<td>163</td>
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<td>45:55</td>
<td>67</td>
<td>73</td>
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<td>98</td>
<td>45:55</td>
<td>85</td>
<td>68</td>
</tr>
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<td>3</td>
<td>334</td>
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<td>45:55</td>
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<td>4</td>
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<td>5</td>
<td>148</td>
<td>96</td>
<td>50:50</td>
<td>79</td>
<td>75</td>
</tr>
</tbody>
</table>

*a Determined by $^1$H NMR spectroscopic analysis using $\rho$-iodoanisole as an internal standard. *b Determined by CSP-HPLC. *c Isolated yield.

As shown in Table 3.9, catalyst 163 promoted the formation of almost equal amount of products in low ee (entry 1). Unfortunately, the use of urea-based catalysts 138 and 334 did not improve the regioselectivity of the alcoholysis reaction of 141 (entries 2 and 3) compared to the reaction promoted by the thiourea-substituted variant 163, although better enantiocontrol, which provided lactone 332 with superior ee was notable. The bifunctional squaramide-based catalysts 139 and 148 afforded the formation of equal amounts of hemiester products (entries 4 and 5) and comparable enantioselectivity.

This data demonstrated the superiority of trichloroethanol (323) with respect to allyl alcohol (190) as the nucleophile in the alcoholysis of anhydride 141 promoted by (thio)urea- and squaramide-based cinchona alkaloids. Gratifyingly this alcohol proved successful in giving improved hemiester product ratios with concomitant efficient
interactions with the catalysts, furnishing the mixture of lactones in considerably higher ee.

3.2.1 Squaramide-based catalyst evaluation for the regio/enantioselective alcoholyis of phenylsuccinic anhydride

Having established 2,2,2-trichloroethanol (323) as the best nucleophile for the alcoholysis of 141, the next goal was to further increase regio- and enantioselectivity; this was attempted through further screening of squaramide-substituted cinchona alkaloids catalysts. The catalytic activity of C-2’ phenyl-substituted squaramide–based cinchona alkaloids 140 and 337 was subsequently evaluated and compared with that of the less sterically hindered derivatives previously investigated (Table 3.10).

Table 3.10 Catalyst evaluation in the enantioselective alcoholyis of anhydride 141 with 323.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>conv (%)$^a$</th>
<th>ratio</th>
<th>ee (%)$^b$</th>
<th>yield (%)$^c$</th>
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</thead>
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<td></td>
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<td>330:331$^a$</td>
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<td>333</td>
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<td>73</td>
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<td>337</td>
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<td>50:50</td>
<td>98</td>
<td>74</td>
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<td>3</td>
<td>338</td>
<td>96</td>
<td>37:63</td>
<td>98</td>
<td>90</td>
</tr>
</tbody>
</table>

$^a$Determined by $^1$H NMR spectroscopic analysis using $p$-iodoanisole as an internal standard. $^b$ Determined by CSP-HPLC. $^c$ Isolated yield.
Chapter 3

Results and discussion

The regioselectivity of the reaction was not affected by the introduction of a phenyl substituent on the catalyst, while a notably higher ee of the lactone 332 was produced using the phenyl-substituted catalysts 140 and 337 (entries 1 and 2). The exchange of an alkyl group, such as the tert-butyl on 337, for the bulky trityl on 338 of the squaramide moiety resulted in superior regioselectivity and promoted the formation of the lactone products with good yield and exceptionally high enantioselectivity (entry 3).

3.2.1.1 Optimisation studies for the regio/enantioselective alcoholysis of phenylsuccinic anhydride

Prompted by the results obtained with catalyst 338, we decided to optimise the reaction conditions. The influence of temperature, concentration and catalyst loading were assessed using catalyst 338, the results of this study are reported in Table 3.11.

Table 3.11 Effect of temperature, concentration and catalyst loading on the catalytic performance of 338.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp.</th>
<th>Conc.</th>
<th>338 Loading</th>
<th>Conv.</th>
<th>Ratio&lt;sup&gt;a&lt;/sup&gt;</th>
<th>EE&lt;sup&gt;b&lt;/sup&gt; (%)</th>
<th>Yield&lt;sup&gt;c&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(°C)</td>
<td>[M]</td>
<td>(mol %)</td>
<td>(%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>330:331</td>
<td>332:333</td>
<td>332:333</td>
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<tr>
<td>[3] previous</td>
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<td>0.1</td>
<td>5</td>
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<td>37:63</td>
<td>98</td>
<td>90</td>
</tr>
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<td>0.1</td>
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<td>32:68</td>
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<td>32:68</td>
<td>94</td>
<td>82</td>
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</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using p-iodoanisole as an internal standard. <sup>b</sup>Determined by CSP-HPLC. <sup>c</sup>Isolated yield.

We were pleased to observe that lowering the temperature and the concentration respectively (entries 1 and 2), caused a significant improvement in the regiocontrol, furnishing the hemiesters 330 and 331 in an excellent ratio and high enantioselectivity, although longer reaction times were required. Higher concentration and catalyst loading
(entries 3 and 4 respectively) led to slightly lower regioselectivities and furnished the lactone products with marginally inferior enantiomeric excess.

### 3.3 Squaramide-based catalyst screening in the regio/enantioselective alcoholysis of phenylsuccinic anhydride

The efficiency of the alcoholysis approach using catalyst 338 had proven superior to that observed with all other catalysts tested in our preliminary screening. Encouraged by such results we, therefore, decided to further investigate the performance of squaramide-substituted catalysts in the reaction under scrutiny. For this reason, we employed a set of newly synthesised squaramide-based catalysts which were prepared and kindly provided by the fellow researcher Dr. Umar Farid in our group (Figure 3.2).

**Figure 3.2** Squaramide-substituted cinchona alkaloids evaluated as catalysts for the alcoholysis of 141 with 323.

The $N$-alkyl squaramide catalyst 339 promoted the reaction with moderate regioselectivity and high ee (Table 3.12, entry 1). Comparable results were obtained with the use of catalyst 340 bearing an additional chiral centre via the inclusion of the unnatural amino acid D-phenyl glycine (protected as the pyrrolidinamide), however a decrease in conversion was observed (entry 2, Table 3.12). It was noteworthy that catalyst 341, containing the unnatural amino acid L-phenyl glycine promoted a significantly more regioselective alcoholysis of anhydride 141, albeit with a decrease in enantiomeric excess of the major lactone 333 (entry 3, Table 3.12).
Table 3.12  New squaramide-based catalyst evaluation in the enantioselective alcoholysis of phenylsuccinic anhydride (141) with 323.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>conv (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ratio</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
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<tr>
<td>2</td>
<td>340</td>
<td>87</td>
<td>36:64</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>341</td>
<td>84</td>
<td>23:77</td>
<td>92</td>
<td>79</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using <sup>p</sup>-iodoanisole as an internal standard.  
<sup>b</sup>Determined by CSP-HPLC.  
<sup>c</sup>Isolated yield.

Next, we became interested in exploring the catalytic activity of <i>C</i><sub>2</sub>-symmetric analogue 342 and 343 which were prepared by Dr. Seàn Tallon and had previously proved to be excellent catalysts for the addition of alcohols to azlactones<sup>238</sup> (Table 3.13).

Table 3.13  <i>C</i><sub>2</sub>-symmetric catalyst evaluation in the enantioselective alcoholysis of anhydride 141 with 323.
Gratifyingly, in the reaction catalysed by 342 and 343, anhydride 141 underwent conversion to the corresponding hemiesters 330 and 331 with the highest regioselectivity observed so far in this study, probably due to the highly sterically hindered nature of the catalyst. However, the use of bulky structures failed to promote an enhancement of product ee. Despite the poor ee, these reactions proved to be useful as we observed that, at room temperature under these reaction conditions, the selective interaction of the alcohol nucleophile with a single carbonyl group of the anhydride was improved. Therefore, we decided to evaluate the catalytic performance of the C$_2$-symmetric catalyst 342; varying the reaction conditions as outlined in Table 3.14.

Table 3.14 Attempted optimisation of the reaction conditions for the regio/enantioselective alcoholyis of anhydride 141 with 323 promoted by catalyst 342.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>conv (%)$^a$</th>
<th>ratio</th>
<th>ee (%)$^b$</th>
<th>yield (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>330:331$^a$</td>
<td>332 333 332 333</td>
</tr>
<tr>
<td>1</td>
<td>342</td>
<td>87</td>
<td>20:80</td>
<td>68 66</td>
<td>13 66</td>
</tr>
<tr>
<td>2</td>
<td>343</td>
<td>90</td>
<td>16:84</td>
<td>87 67</td>
<td>11 69</td>
</tr>
</tbody>
</table>

$^a$Determined by $^1$H NMR spectroscopic analysis using p-iodoanisole as an internal standard. $^b$ Determined by CSP-HPLC. $^c$ Isolated yield.

Initially, anhydride 141 was treated with alcohol 323 in the presence of catalyst 342 at
-30 °C. Unfortunately, the attempted variation of temperature did not lead to an improvement in hemiester ratio and also promoted the formation of the corresponding lactones with lower enantiomeric excess. The use of a different solvent (i.e. THF) at room temperature did not result in substantial improvement of both regio- and enantioselectivity but did result in lower conversion (entry 2). As a result it was decided that this class of catalyst was not suitable for further investigation.

3.4 Preliminary screening of sulfonamide-based catalysts and optimisation studies for the regio/enantioselective alcoholyisis of phenylsuccinic anhydride

As discussed in Section 1.6.1, it has been demonstrated that C-9-(thio)urea-substituted cinchona alkaloids (i.e. 163, Scheme 3.1) promote the desymmetrisation of meso-anhydrides via the simultaneous activation of both the electrophile and the nucleophile.\textsuperscript{159,160} Shortly afterwards, our group, had described the introduction of a sulfonamide moiety into the cinchona alkaloid framework and the successful application of such derivatives in promoting the kinetic resolution of thiols and the desymmetrisation of substituted-glutaric anhydrides.\textsuperscript{171} As a result, we envisaged that catalysts bearing such a dual hydrogen-bond donating moiety at C-9 could be effective in promoting an efficient DKR of cyclic anhydrides. Therefore, we decided to carry out a preliminary screening of sulfonamide-substituted cinchona alkaloids 344 and 345 in the alcoholysis of anhydride 141 with the alcohol 323 (Table 3.15).
Table 3.15 Sulfonamide-based catalyst evaluation in the enantioselective alcoholsysis of anhydride 141 with 323.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>conv (%)^a</th>
<th>ratio</th>
<th>ee (%)^b</th>
<th>yield (%)^c</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1</td>
<td>344</td>
<td>93</td>
<td>33:67</td>
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<td>91</td>
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<tr>
<td>2</td>
<td>345</td>
<td>87</td>
<td>37:63</td>
<td>95</td>
<td>87</td>
</tr>
</tbody>
</table>

^a Determined by ^1^H NMR spectroscopic analysis using p-iodoanisole as an internal standard. ^b Determined by CSP-HPLC. ^c Isolated yield.

The use of catalyst 344 proved to be comparable to the thiourea-based catalyst 163 tested at the beginning of our screening (see Table 3.8, Section 3.1.2); with product 331 being formed in a two-fold excess over 330, however markedly higher enantioselectivity was obtained (Table 3.15, entry 1). The introduction of a phenyl substituent at the C-2' position of catalyst 345 (provided by fellow researcher Mr. Romain Claveau) promoted the reaction with lower level of regioselectivity while affording the minor lactone 332 with marginally higher enantiomeric excess (entry 2).

3.5 Preliminary expansion of the substrate scope: the alcohol component

As a result of the excellent ee achieved, we decided to evaluate the substrate scope of this reaction by evaluating the catalytic activity of 344 and 345 in promoting the alcoholsysis of 141 with the commercially available neopentyl alcohol (346) as the nucleophile.
Table 3.16 Enantioselective alcoholysis of 141 with 346 promoted by sulfonamide-based catalysts.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>conv (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ratio</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>347:348&lt;sup&gt;a&lt;/sup&gt;</td>
<td>332</td>
<td>333</td>
</tr>
<tr>
<td>1</td>
<td>344</td>
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<td>50:50</td>
<td>64</td>
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<td>50:50</td>
<td>66</td>
<td>51</td>
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</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using <sup>p</sup>-iodoanisole as an internal standard. <sup>b</sup>Determined by CSP-HPLC. <sup>c</sup>Isolated yield.

Disappointingly, when the alcohol 346 was employed as the nucleophile, anhydride 141 was converted to its hemiesters in a significantly low conversion and in exactly equal amounts. In addition, the resulting lactone products 332 and 333 were isolated in poor enantiomeric excess (Table 3.16, entries 1 and 2). It is likely that the hindered nature of 346 makes its activation by the catalyst (via the tertiary amine) less favourable in a controlled enantioselective addition to the anhydride, therefore, no further attention was given to this alcohol.

With a preliminary evaluation of three different classes of catalysts (i.e. thiourea-, squaramide- and sulfonamide-subsituted cinchona alkaloids) in hand, we decided to select the best results in terms of catalyst efficacy, obtained using alcohol 323 as the nucleophile, and expand the substrate scope to the 2,2,2-trifluoro and 2,2,2-tribromo-substituted variants (219 and 349, respectively).
Table 3.17 Catalysts evaluation in the enantioselective alcoholysis of 141 with 219.

As reported in Table 3.17, in the reaction of anhydride 141 with 219, the regioselectivity obtained through the use of the thiourea-based alkaloid 163 (entry 1) proved to be comparable to the trityl-substituted squaramide variant 338 (entry 2), however, the optical purity of the lactone products was significantly improved. The reaction performed in the presence of the sulfonamide-based catalyst 344 led to the formation of the phenyl succinates with a higher level of regioselectivity but did not influence the ee (entry 3).

Despite the fact that the use of alcohol 219 did not improve the results, we felt it opportune to evaluate the alcoholysis of anhydride 141 using 2,2,2-tribromoethanol (349) since no example of enantioselective opening of cyclic anhydrides with this alcohol has been reported (Table 3.18).
In the presence of the thiourea catalyst 163, the reaction proceeded at slightly slower rates, allowing the formation of the hemiesters in a ratio comparable to that obtained with the previous alcohol nucleophiles, however, poor enantiomeric excess was obtained (Table 3.18, entry 1). Gratifyingly, the squaramide-based catalyst 338 promoted the reaction with better regioselectivity and good ee (entry 2), on the other hand, catalyst 344 proved to be inefficient; promoting the formation of the lactone products with the lowest regio/enantioselectivity (entry 3).

### 3.5.1 Substrate scope: thiols as nucleophiles

The outcome of the reactions carried out in presence of both 219 and 349 was unfortunate: both substrates failed to improve the regio/enantioselective outcome of the reaction under scrutiny. Given the lack of encouraging results, on the basis of what we had previously observed in the desymmetrisation reaction of 3-methylglutaric anhydride by thiolysis (Section 1.7.1), the focus of the methodology was directed towards the use of thiols as nucleophiles. In preliminary experiments, it was decided to evaluate the thiolysis of 141 in the presence of the thiourea catalyst 163 with the use of both alkyl and aryl primary thiols i.e. 354 and 210 respectively in order to investigate the efficiency of nucleophiles with different electronic properties (Table 3.19).

#### Table 3.18  Catalyst evaluation in the enantioselective alcoholysis of 141 with 349.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>conv (%)</th>
<th>ratio 352:353</th>
<th>ee (%)</th>
<th>yield (%)</th>
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<tr>
<td>3</td>
<td>344</td>
<td>96</td>
<td>39:61</td>
<td>73</td>
<td>86</td>
</tr>
</tbody>
</table>

*a* Determined by $^1$H NMR spectroscopic analysis using $p$-iodoanisole as an internal standard. *b* Determined by CSP-HPLC. *c* Isolated yield from 141.
Table 3.19  Regio/enantioselective thiolysis of 141.

<table>
<thead>
<tr>
<th>entry</th>
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<th>conv (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ratio 355:356&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
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</thead>
<tbody>
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<td>95</td>
<td>34:66</td>
<td>21</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>cyclohexyl SH 210</td>
<td>52</td>
<td>35:65</td>
<td>-</td>
<td>-</td>
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</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using <i>p</i>-iodoanisole as an internal standard. <sup>b</sup>Determined by CSP-HPLC. <sup>c</sup>Isolated yield.

The reaction involving 4-<i>tert</i>-butylnbenzyl mercaptan (354) with anhydride 141 yielded the hemiester 356a in a two fold excess compared to the minor hemiester 355a, however, very poor enantioselectivity was observed (Table 3.19, entry 1). Unfortunately, the use of cyclohexyl thiol (210, entry 2) resulted in a low conversion, and allowing the reaction to proceed for a longer period of time did not influence the result. Despite the fact that the use of thiols was unsuccessful with catalyst 163, we decided to repeat the reaction in the presence of squaramide- and sulfonamide-based catalysts such as 344 and 345.
Table 3.20  Sulfonamide-based catalysts evaluation in the thiolysis of 141 with 354.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>conv (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ratio 357:358&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>344</td>
<td>88</td>
<td>38:62</td>
<td>2 63</td>
<td>22 46</td>
</tr>
<tr>
<td>2</td>
<td>345</td>
<td>91</td>
<td>42:58</td>
<td>48 60</td>
<td>36 31</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using p-iodoanisole as an internal standard.  
<sup>b</sup>Determined by CSP-HPLC.  
<sup>c</sup>Isolated yield.

Disappointingly, as described in Table 3.20, the use of catalysts 344 and 345 promoted the reaction, furnishing thioesters with low regioselectivity and with only slight enantiomeric excess (2% ee, entry 1). In summary, these experiments were considered sufficient to prove alcohols as superior nucleophiles and the possibility of extending the resolution strategy to thiols was disregarded.

### 3.6 Evaluation of sulfonamide-based cinchona alkaloids for the regio/enantioselective alcoholysis of phenylsuccinic anhydride

In preliminary experiments, we attempted the DKR of anhydride 141 with alcohol 323 in the presence of several substituted cinchona alkaloid organocatalysts. Among them, the sulfonamide-based catalysts 344 and 345 (see Section 3.4) have been demonstrated to be capable of promoting the addition of alcohol nucleophiles to cyclic anhydrides with good levels of regioselectivity and excellent enantiomeric excess. With a view toward finding the optimum catalyst, we decided to concentrate our efforts on the further evaluation of a wide range of sulfonamide-substituted cinchona alkaloids. These catalysts (synthesised by colleagues and acquired within the laboratory, Figure 3.3) had different steric and electronic characteristics which would allow us to better understand their role in promoting the DKR process.
As reported in Table 3.21, the methyl-substituted catalyst 359 was able to promote the formation of hemiesters in a moderate 29:71 ratio and good ee (entry 1). The use of the more hindered catalyst 360 led to an increased ratio of products but similar enantioselectivity was obtained (entry 2). Catalyst 361, bearing electron-withdrawing substituents, promoted a more efficient regio/enantioselective addition of the alcohol nucleophile to the anhydride 141 which, after derivatisation, led to the formation of the corresponding lactones in excellent enantiomeric excess (entry 3, 97% ee). The use of the electron-deficient pentafluoro-substituted catalyst 362 could further enhance the regioselectivity (entry 4, 24:76 ratio) and promote the formation of both products in excellent ee. Unfortunately, the reaction performed in the presence of catalysts 363 and 364 led to decreased product ratio and enantioselectivity (entries 5 and 6, respectively). The adamantane-substituted sulfonamide catalyst 365 and the tert-butyl-substituted variant 366 promoted the formation of products in 24:76 ratios (entries 7 and 8), albeit with product ee lower than previously reported using electron-deficient sulfonamide analogues (i.e. entries 3 and 4, Table 3.21).
Table 3.21  Evaluation of sulfonamide-substituted cinchona alkaloids in the alcoholysis of 141.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>conv (%)(^a)</th>
<th>ratio</th>
<th>ee (%)(^b)</th>
<th>yield (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>330:331(^a)</td>
<td>332</td>
<td>333</td>
</tr>
<tr>
<td>1</td>
<td>359</td>
<td>91</td>
<td>29:71</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>360</td>
<td>87</td>
<td>25:75</td>
<td>93</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>361</td>
<td>96</td>
<td>27:73</td>
<td>97</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>362</td>
<td>96</td>
<td>24:76</td>
<td>97</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>363</td>
<td>69</td>
<td>33:67</td>
<td>81</td>
<td>73</td>
</tr>
<tr>
<td>6</td>
<td>364</td>
<td>96</td>
<td>29:71</td>
<td>77</td>
<td>57</td>
</tr>
<tr>
<td>7</td>
<td>365</td>
<td>93</td>
<td>24:76</td>
<td>88</td>
<td>89</td>
</tr>
<tr>
<td>8</td>
<td>366</td>
<td>88</td>
<td>24:76</td>
<td>84</td>
<td>84</td>
</tr>
</tbody>
</table>

\(^a\)Determined by \(^1\)H NMR spectroscopic analysis using p-iodoanisole as an internal standard. \(^b\)Determined by CSP-HPLC. \(^c\)Isolated yield.

3.6.1 Optimisation of the reaction conditions

The promising results involving the pentafluoro-substituted sulfonamide catalysed alcoholysis of 141 (Table 3.21, entry 4) prompted us to investigate the factors affecting the reaction. As an initial evaluation, the same reaction was monitored under various conditions and these are summarised in Table 3.22.
Table 3.22 Optimisation of the pentafluoro-substituted sulfonamide-catalysed alcoholsysis of 141.

<table>
<thead>
<tr>
<th>entry</th>
<th>conc. [M]</th>
<th>solvent</th>
<th>temp. (°C)</th>
<th>loading (%)</th>
<th>conv (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ratio 330:331&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td>MTBE</td>
<td>25</td>
<td>5</td>
<td>91</td>
<td>28:72</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>MTBE</td>
<td>25</td>
<td>5</td>
<td>96</td>
<td>32:68</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>THF</td>
<td>25</td>
<td>5</td>
<td>61</td>
<td>24:76</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>0.1</td>
<td>MTBE</td>
<td>30</td>
<td>5</td>
<td>97</td>
<td>24:76</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>0.1</td>
<td>MTBE</td>
<td>0</td>
<td>5</td>
<td>93</td>
<td>24:76</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>0.1</td>
<td>MTBE</td>
<td>25</td>
<td>10</td>
<td>93</td>
<td>25:75</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>0.1</td>
<td>MTBE</td>
<td>25</td>
<td>20</td>
<td>96</td>
<td>29:71</td>
<td>96</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using p-iodoanisole as an internal standard. <sup>b</sup>Determined by CSP-HPLC.

A decrease in concentration from 0.1 M to 0.05 M resulted in only marginally diminished conversion after 48 h, although furnishing products with less regioselectivity and slightly inferior ee (entry 1). When repeated at a higher concentration, (i.e 0.2 M) the reaction exhibited a significant decrease in regioselectivity while the ee remained practically unchanged (entry 2). The use of THF as solvent seemed to be responsible for a drastic reduction of reaction rate (entry 3, 61% conversion in 48 h), however, the hemiester ratio and the enantiomeric excess of the products were not affected.

The reaction temperature was the next parameter to be evaluated. Increasing the temperature to 30 °C did not influence either the regio- or the enantioselectivity compared to that obtained at room temperature (entry 4), while the reaction performed at 0 °C provided products with slightly lower optical purity (entry 5).
Subsequently, it was decided to increase the catalyst loading from 5 mol% to 10 and 20 mol% (entries 6 and 7 respectively). In all cases evaluated, the regioselectivity was marginally decreased, however, products were furnished in good enantiomeric excess.

### 3.6.2 Evaluation of the substrate scope: the alcohol component

Following the preliminary catalyst screening and the optimisation of the reaction conditions, it emerged that the sulfonamide derivative 362 was the most promising candidate as promoter for the reaction under scrutiny. To further optimise the method, the effect of either hindered or electron-deficient nucleophiles on the reaction was examined. The target was to find a suitable trend that would allow us to clarify their role in promoting an efficient regio/enantioselective alcoholysis of anhydride 141. With the aim to see if we could hit a “sweet spot” in terms of acidity, the effect of several alcohol nucleophiles with a \( \text{p}K_a \) range between 10 and 16 was investigated. Most likely related to general base catalysis of the reaction, in order for the catalyst to influence the transition state, proton transfer should be hopefully 50% complete at that stage. In addition, in view of the preliminary results obtained with the use of nucleophiles such as neopentyl alcohol bearing hindered 1‘Bu substituent (see Table 3.16, Section 3.5), a study of the steric properties of the alcohols based on the evaluation of their Taft \( E_s \) values was carried out.

**Table 3.23** Evaluation of the substrate scope: the alcohol component.

<table>
<thead>
<tr>
<th>entry</th>
<th>ROH</th>
<th>( \text{p}K_a ) (( \text{H}_2\text{O} ))</th>
<th>( E_s^a ) (log ( k/k_0 ))</th>
<th>conv (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ratio</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>332</th>
<th>333</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>319</td>
<td>-1.24</td>
<td>98</td>
<td>45:55</td>
<td>72</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>EtOH</td>
<td>320</td>
<td>-1.31</td>
<td>98</td>
<td>45:55</td>
<td>82</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;OH</td>
<td>321</td>
<td>-1.62</td>
<td>98</td>
<td>35:65</td>
<td>86</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>
As reported in Table 3.23, the alcoholysis reaction of anhydride 141 with this set of alcohols was investigated under previously identified optimum conditions. It was found that the less hindered alcohols *i.e.* 319 and 320 led to the formation of the corresponding hemiesters with the lowest level of regioselectivity and moderate ee (entries 1 and 2). The use of 321 and 190 resulted in a slightly more selective resolution process (entries 3 and 4) and higher enantioselectivity. The variation of the electronic properties of the alcohol nucleophile using 219, 323 and 349 respectively, was well tolerated by the catalyst which

<table>
<thead>
<tr>
<th>Table 3.23 Results and discussion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>190</td>
</tr>
<tr>
<td>5</td>
<td>219</td>
</tr>
<tr>
<td>6</td>
<td>323</td>
</tr>
<tr>
<td>7</td>
<td>349</td>
</tr>
<tr>
<td>8</td>
<td>369</td>
</tr>
<tr>
<td>9</td>
<td>370</td>
</tr>
<tr>
<td>10</td>
<td>371</td>
</tr>
<tr>
<td>11</td>
<td>372</td>
</tr>
<tr>
<td>12</td>
<td>373</td>
</tr>
</tbody>
</table>

<sup>a</sup> Taft E<sub>s</sub> values.<sup>239</sup> <sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis using p-iodoanisole as an internal standard. <sup>c</sup> Determined by CSP-HPLC. * Revised Taft steric constant.<sup>239</sup>

---

As reported in Table 3.23, the alcoholysis reaction of anhydride 141 with this set of alcohols was investigated under previously identified optimum conditions. It was found that the less hindered alcohols *i.e.* 319 and 320 led to the formation of the corresponding hemiesters with the lowest level of regioselectivity and moderate ee (entries 1 and 2). The use of 321 and 190 resulted in a slightly more selective resolution process (entries 3 and 4) and higher enantioselectivity. The variation of the electronic properties of the alcohol nucleophile using 219, 323 and 349 respectively, was well tolerated by the catalyst which
promoted the reaction with an enormous improvement in the regioselectivity and enantiomeric excess of the products (entries 5, 6 and 7 respectively). When secondary alcohols such as diphenylmethanol (369, entry 8) and 370 (entry 9) were employed, significantly reduced conversion was observed, furnishing products in low ratios and remarkably lower ee. The use of furfuryl alcohol (371) and the electron-deficient pentafluorobenzyl alcohol (372) maintained good levels of regioselectivity and relatively high ee of the minor lactone 367 (entries 10 and 11, respectively). Use of different alcohols, such as in 373 bearing an ester functional group, led to conversion to the corresponding hemiester products with slightly higher regioselectivity, albeit in poor ee (entry 12).

In summary, these results demonstrated that the steric properties of the alcohol nucleophile are not playing a prominent role in determining the selective attack of one carbonyl of the anhydride over the other, while allowing the formation of the products in poor enantiomeric excess. On the other hand, we observed the benefits deriving from the employment of more acidic alcohols (such as 349), leading to the improvement of the regio/enantioselective alcoholysis of anhydride 141.

3.7 Synthesis and evaluation of novel sulfonamide-based cinchona alkaloid catalysts

With a view towards finding the optimum catalyst structure, it was decided to carry out a systematic investigation concerning the use of novel sulfonamide-substituted cinchona alkaloids. On the basis of successful results previously observed in the preliminary evaluation of sulfonamide-based catalysts (Section 3.6), the synthesis of mostly electron-deficient sulfonamide-substituted cinchona alkaloid derivatives and their evaluation in the promotion of the DKR reaction of 141 was the next logical step (Figure 3.4).
According to the literature procedure, we initially prepared the amine starting from readily available quinine. The alkaloid was transformed via a Mitsunobu reaction into the azido intermediate with inverted configuration at C-9. The following in situ Staudinger reduction with an excess of PPh₃ and acidic water furnished the hydrochloride salt (Scheme 3.7).

Scheme 3.7 Synthesis of 9-epi-quinine amine hydrochloride salt 380.

Sulfonamide-modified organocatalysts 374-378 were prepared in good yields by the reaction of 9-epi-quinine amine hydrochloride salt (380) with the relevant sulfonyl chloride (381-385) in the presence of a large excess of triethylamine (Scheme 3.8).
Scheme 3.8 Synthesis of sulfonamide-substituted cinchona alkaloid catalysts 374-378.

We evaluated the catalytic performance of these newly synthesised sulfonamide-substituted catalysts as promoters of the DKR of anhydride 141 with alcohol 323 (Table 3.24).

Table 3.24 Evaluation of new sulfonamide-based catalysts in the asymmetric resolution of 141 with 323.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>conv (%)$^a$</th>
<th>ratio</th>
<th>ee (%)$^b$</th>
<th>yield (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>374</td>
<td>59</td>
<td>23:77</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>375</td>
<td>96</td>
<td>26:74</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>376</td>
<td>95</td>
<td>29:71</td>
<td>97</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>377</td>
<td>95</td>
<td>26:74</td>
<td>95</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>378</td>
<td>94</td>
<td>26:74</td>
<td>96</td>
<td>93</td>
</tr>
</tbody>
</table>

$^a$ Determined by $^1$H NMR spectroscopic analysis using $p$-iodoanisole as an internal standard. $^b$ Determined by CSP-HPLC. $^c$ Isolated yield.
The less hindered electron-deficient catalyst 374 promoted the formation of the hemiester products in high regioselectivity (Table 3.24, entry 1, 23:77 ratio) and good enantiomeric excess, albeit with low conversion after 48 h. The piperidine-substituted derivative 375 was also able to promote the resolution of 141; furnishing products with a slightly inferior hemiester ratio, however, the enantioselectivity remained unchanged (entry 2). The introduction of a p-NO₂-phenyl substituent in the sulfonamide framework in catalyst 376 led to the formation of products in moderate regioselectivity although with excellent enantioselectivity (ee up to 97%, entry 3). Catalysts bearing thiophene-substituted units such as in 377 which is similar in structure to 378, were deemed highly suitable for the promotion of the reaction under scrutiny, as the desired hemiester products were formed in a good ratio, excellent ee and increased yields (entries 4 and 5 respectively).

3.7.1 Thiophene-substituted sulfonamide catalysts as promoters of the regio/enantioselective alcoholysis of phenylsuccinic anhydride: optimisation studies

Satisfied that the thiophene-based sulfonamides 377 and 378 were excellent catalysts for the alcoholytic DKR of anhydride 141 with alcohol 323 (see Table 3.24, Section 3.7), the next step was to evaluate them using 2,2,2-tribromoethanol (349), which proved to be an efficient nucleophile in the alcohol screening previously reported (see Table 3.23, Section 3.6.2).
As reported in Table 3.25, it was found that the enantioselective alcoholysis of 141 promoted by 377 and 378 in the presence of alcohol 349 led to the formation of products in slightly higher levels of regioselectivity (entries 1 and 2) compared to the same reaction carried out in the presence of alcohol 323 (Table 3.24, Section 3.1.12). Gratifyingly, the corresponding major lactone 333 was formed in good yield and excellent optical purity up to 94% (entry 2).

We therefore decided to perform the optimisation of the alcoholysis of 141 with 349 in the presence of catalyst 378 varying the reaction conditions, as outlined in Table 3.26.
Table 3.26  Attempted optimisation of the reaction conditions for the alcoholyis of 141 with 349 promoted by sulfonamide catalyst 378.

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>entry</th>
<th>temp.</th>
<th>loading 378 (%)</th>
<th>conc. [M]</th>
<th>solvent</th>
<th>conv (%)a</th>
<th>ratio 386:387a</th>
<th>ee (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rt</td>
<td>5</td>
<td>0.1</td>
<td>MTBE</td>
<td>98</td>
<td>24:76</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>5</td>
<td>0.1</td>
<td>MTBE</td>
<td>98</td>
<td>26:74</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>5</td>
<td>0.1</td>
<td>MTBE</td>
<td>70</td>
<td>29:71</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>rt</td>
<td>15</td>
<td>0.1</td>
<td>MTBE</td>
<td>98</td>
<td>26:74</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>rt</td>
<td>5</td>
<td>0.2</td>
<td>MTBE</td>
<td>98</td>
<td>28:72</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>rt</td>
<td>5</td>
<td>0.05</td>
<td>MTBE</td>
<td>98</td>
<td>24:76</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>rt</td>
<td>5</td>
<td>0.1</td>
<td>THF</td>
<td>35</td>
<td>28:72</td>
<td>--</td>
</tr>
<tr>
<td>8</td>
<td>rt</td>
<td>5</td>
<td>0.1</td>
<td>Diisopropyl ether</td>
<td>87</td>
<td>30:70</td>
<td>85</td>
</tr>
</tbody>
</table>

a Determined by $^1$H NMR spectroscopic analysis using $p$-iodoanisole as an internal standard.
b Determined by CSP-HPLC.

Generally, the attempted variation of temperature, catalyst loading, concentration and solvent did not improve the regioselectivity of the hemiester products (Table 3.26, entries 2-5) compared to the reaction accomplished in MTBE as the solvent at a concentration of 0.1 M with 5 mol% of catalyst 378 and at room temperature (entry 1). Gratifyingly, by decreasing the concentration to 0.05 M (entry 6) we were able to obtain the lactone products with excellent enantioselectivity (up to 97% ee). The use of THF as solvent again led to a significant decrease in the reaction rate (35% conversion in 48 h, entry 7), while the reaction performed in diisopropyl ether resulted in an erosion of product ratio and ee (entry 8).

3.8 Investigation into the enantioselective outcome of the reaction
By analogy with the recent studies concerning the alcoholysis of meso-anhydrides with sulfonamide-based catalysts reported by Song et al. (see Section 1.6.2) we proposed that the addition of alcohol to the anhydride given high energy tetrahedral intermediates that are both a strong H-bond acceptor (oxyanion) and a strong H-bond donor (protonated ether). These complexes may be regarded as transition state analogues for the rate and enantio-determining step of the catalytic process. The catalyst operates through a bifunctional mechanism in which the stabilisation of the developing positive charge on the alcohol oxygen atom is mediated by the basic quinuclidine ring that acts as a general base, while developing the negative charge on the anhydride carbonyl unit undergoing nucleophilic attack is stabilised by the H-bond-donating sulfonamide moiety. The absolute configuration was established by comparison of the optical rotation of the lactones and to those reported in the literature, indicating that the two hemiesters formed were (S)-386 and (R)-387. Therefore, based on the binding mode previously mentioned, in agreement with the experimentally observed enantioselectivity ((S)-386 and (R)-387, 94% ee, Table 3.26 entry 1), we proposed two schematic representations of the catalyst-transition-state-analogue complex, which gave the major products (Figure 3.5). The backside nucleophilic attack on the more hindered carbonyl of the anhydride (binding mode A) is postulated to occur to avoid clashing between the phenyl substituent and the quinuclidine ring; this is not a feature of the alcohol-binding assembly involving the less hindered carbonyl which undergoes instead the nucleophilic attack on the top face (binding mode B).

![Binding mode A leading to (S)-386 and Binding mode B leading to (R)-387](image)

**Figure 3.5** Binding mode leading to (S)-386 and (R)-387.

**3.9 Expansion of the substrate scope: the anhydride component**
While the scope of the process with respect to the alcohol nucleophile component was widely explored, the next logical step was to expand the substrate scope towards the use of different anhydrides. We therefore, decided to select and prepare a set of enolisable cyclic anhydrides with different electronic and steric characteristics for the evaluation of the substrate scope (Figure 3.6).

![Selection of a set of anhydrides prepared for the evaluation of substrate scope.](image)

**Figure 3.6** Selection of a set of anhydrides prepared for the evaluation of substrate scope.

### 3.9.1 Synthesis and evaluation of alternative cyclic anhydrides as electrophiles

As mentioned in Section 1.5.1, our group, in a series of studies involving the asymmetric cycloaddition reaction between phenylsuccinic anhydride (141) and benzaldehyde (9) have demonstrated that the replacement of the phenyl unit with electron poor analogues (*i.e.* 142 and 143) resulted in improved enolisation ability of the anhydride; thereby leading to a more efficient annulation reaction. Therefore, the variation of the electronic features of the phenyl ring of 141 has been explored and the electron deficient \( p\)-NO\(_2\)-phenylsuccinic anhydride (143) was evaluated as a substrate for the alcoholysis reaction with 349 in the presence of catalyst 378 in MTBE as solvent for 48 h at room temperature (Scheme 3.9).
Scheme 3.9 Enantioselective alcoholysis of anhydride 142 with 349 promoted by catalyst 378.

Unfortunately, the alcoholysis of anydride 142 provided a diastereomer ratio slightly inferior to that obtained with the anhydride lacking the $p$-NO$_2$ substituent on the phenyl ring 141. The subsequent reduction with lithium triethylborohydride solution failed to afford the desired lactones 396 and 397. By using the enantiopure $(R)$-$(+)$-α-methylbenzylamine (398) in the presence of thionyl chloride and excess of a base (i.e. triethylamine) we were able to afford the corresponding chiral amides; with the minor product 399 formed in excellent diastereomeric excess (98% $de$, Scheme 3.9) while $^1$H-NMR spectroscopic analysis showed the major product 400 in only 20% $de$. We postulated that an epimerisation process may be taking place during the derivatisation reaction. Deprotonation in the α position in the presence of an excess of base (i.e. triethylamine) and the subsequent formation of a ketene stabilised by the phenyl group could cause loss of $ee$ (Scheme 3.10).

Scheme 3.10 Proposed epimerisation mechanism.
Shortly after, the substituted phenylsuccinic anhydride possessing a deactivating group (-OMe, 388, kindly provided by fellow researcher Ms. Maria Luisa Aiello) was evaluated under the same reaction conditions (Scheme 3.11).

![Scheme 3.11](image)

Scheme 3.11 Enantioselective alcoholysis of anhydride 388 with 349 promoted by catalyst 378.

Use of anhydride 388 resulted in significantly inferior regioselectivity, thus demonstrating that, in this case, the enol is less stable due to the destabilising electronic effect of the methoxy group on the phenyl ring (407), making the DKR process less efficient; however, high enantioselectivity was still reported.

Shortly after, we decided to evaluate different α-heteroatom-substituted succinic anhydrides. In particular, the synthesis of anhydride 389 which would form amino acid derivatives as products, was accomplished starting from the reaction between the readily available racemic aspartic acid (409) and phthalic anhydride (410), followed by the cyclisation of the bis-acid 411 to furnish 389 in excellent yield (Scheme 3.12).

![Scheme 3.12](image)

Scheme 3.12 Synthesis of anhydride 389.

Disappointingly, the reaction between anhydride 389 and alcohol 349 afforded the hemiester products with low conversion in 48 h and in almost equal amounts. The turbid appearance of the product mixture prompted us to monitor the crude reaction by 1H-NMR.
spectroscopy, revealing the presence of the hemiester adducts in a ratio not constant with time. It was, therefore, assumed that the low solubility of this substrate in MTBE may interfere with our reaction scope. In addition, the attempted derivatisation of 412 and 413 to form either lactones or amides proved ineffective, however, the esterification using diazomethane in MeOH was successful, which furnished the desired product in moderate enantiomeric excess (entry 1, Table 3.27). We therefore decided to optimise the reaction conditions in order to improve the regio/enantioselective outcome of the reaction. Unfortunately, the use of THF as solvent proved ineffective, $^1$H NMR spectroscopic analysis of the crude reaction mixture revealed completely unreacted starting materials (entry 2).

**Table 3.27** Enantioselective alcoholysis of anhydride 389 with 349 promoted by catalyst 378.

![Diagram](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>temp. (°C)</th>
<th>solvent</th>
<th>conv (%)$^a$</th>
<th>ratio</th>
<th>ee (%)$^b$</th>
<th>412:413$^c$</th>
<th>414</th>
<th>415</th>
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<tr>
<td>1</td>
<td>rt</td>
<td>MTBE</td>
<td>41</td>
<td>45:55</td>
<td>79</td>
<td>76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>rt</td>
<td>THF</td>
<td>0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$Determined by $^1$H NMR spectroscopic analysis using $p$-iodoanisole as an internal standard.  
$^b$Determined by CSP-HPLC.

The slow conversion obtained in the evaluation of anhydride 389 led us to postulate that a kinetic resolution process may occur. In order to clarify the possible kinetic mechanism behind this reaction we decided to open the unreacted anhydride substrate by reacting it with the enantiopure (R)-(+)-$\alpha$-methylbenzylamine (398). Subsequently, a solution of
diazomethane in MeOH was added to afford, upon isolation by flash chromatography, the product 416 in only 3% ee (Scheme 3.13).

**Scheme 3.13** DKR of anhydride 389: kinetic process evaluation.

We, therefore, reasoned that no significant KR is occurring and that the solubility issue could be a plausible explanation for the low reactivity of this substrate.

The synthesis of benzyloxy-substituted succinic anhydride 390 was accomplished over four steps as described in Scheme 3.14. The esterification of the commercially available racemic malic acid 417 using thionyl chloride in methanol afforded the bis-ester 418. The alkylation of 418 using benzyl bromide (419) in the presence of Ag₂O furnished the desired product 420 which was, upon purification by column chromatography, hydrolysed under basic conditions to the corresponding bis-acid 421. The cyclisation to give 390 was accomplished by treating 421 with acetyl chloride.

**Scheme 3.14** Synthesis of anhydride 390.
Anhydride 390 was evaluated in the enantioselective addition of 349 in the presence of catalyst 378 at room temperature for 48 h as shown in Scheme 3.15. Gratifyingly, the alkoxy-substituted substrate led to the formation of only one hemiester (423), favouring the addition to the most hindered carbonyl of the anhydride, however, in very poor optical purity. Speculating as to the reason for the high regioselectivity of this substrate, we postulated that the incoming alcohol pronucleophile is deprotonated by the tertiary amine of the catalyst via general base catalysis with the concomitant stabilisation by the lone pair of the alkoxy substituent of the catalyst which would also increase the electrophilicity of the α-carbonyl undergoing the nucleophilic attack.

**Scheme 3.15** Enantioselective alcoholysis of anhydride 390 with 349 promoted by catalyst 378.

Next, we moved towards the evaluation of α-bromosuccinic anhydride. Despite the fact that our group has recently described the lack of success of this substrate in the asymmetric annulation reaction with aldehydes due to an elimination process competing with the reaction scope, we envisaged that, in our case, the addition of the alcohol nucleophile could occur more quickly than the elimination thereby allowing the resolution process to occur. The synthesis of 2-bromosuccinic anhydride (391) was accomplished over two steps. Starting from the racemic aspartic acid (409) we formed α-bromo-substituted bis-acid 426 (via a Sandmeyer-type reaction) which was then cyclised using acetic anhydride to afford anhydride 391 in excellent yield (Scheme 3.16, A).

**Scheme 3.16** Synthesis of anhydride 391 (A) and its evaluation in the enantioselective alcoholysis with 349 promoted by 378 (B).
Chapter 3

Results and discussion

Unfortunately, as shown in Scheme 3.16B, the use of anhydride 391 in the asymmetric alcoholysis with 349 promoted by catalyst 378 at room temperature failed to produce the desired hemiesters 427. Analysis of the crude mixture by $^1$H NMR spectroscopy showed the formation of maleic anhydride (428) via an elimination process.

Shortly after, we decided to investigate the regio/enantioselective alcoholysis of thioaryl-substituted succinic anhydrides; with the intention of improving the enolisability but also increasing the malleability of the product. Their syntheses were achieved in good yields over two steps from the reaction between the correspondig thiophenols (429-431) with the commercially available maleic acid (432) to give the bis-acids 433-435 which were then cyclised with acetic anhydride to afford anhydrides 392-394 (Scheme 3.17).

Scheme 3.17 Synthesis of anhydrides 392-394.

Interestingly, as outlined in Table 3.28, when the phenylsulfide anhydride 392 was employed in the asymmetric alcoholysis with 349 promoted by catalyst 378, a 3:1 ratio of products was obtained in moderate enantiomeric excess (entry 1). Surprisingly, the regioselective addition occurred in favour of reaction at the more hindered carbonyl group. Studies related to compounds such as 2-acetylthiophene, characterised by the simultaneous presence of sulfur and carbonyl groups, demonstrated a preference for the syn conformation over the anti. The stabilisation of the syn form was attributed to the delocalisation of the in-plane lone pair of the exocyclic carbonyl oxygen atom into the C-S $\sigma^*$ orbital (Figure 3.7).

Figure 3.7 Oxygen-sulfur orbital interactions.

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Attractive interactions between sulfur atoms and lone pairs of oxygen atoms present in alcohols, ethers (sp$^3$ systems) or the carbonyl moieties of amides, esters, or ketones, are present in a range of structural contexts. In particular, in medicinal chemistry, these types of interactions can contribute favourably to the augmentation of drug-target binding energies and are widely utilised in drug design.$^{243,244,245}$ Taking our cue from such reports, with a view toward the eventual explanation of the regioselectivity obtained in the reaction under scrutiny, we envisaged that an intramolecular delocalisation involving the lone pair of electrons of the α-carbonyl oxygen into the proximal C-S σ* orbital ($^{437a}$, Table 3.28) would be possible, this would therefore contribute to favour nucleophilic addition at that position.

The use of the more hindered anhydride 393 led to the formation of hemiesters in an almost 1:1 ratio, although in marginally higher enantiomeric excess (entry 2). We believe that the preferential alcoholysis of the thio-aryl succinic anhydrides at the most hindered carbonyl is now more difficult due to the steric bulk of the ortho-methyl substituents on the phenyl ring of anhydride 393 which could prevent the incoming alcohol from attacking efficiently, thereby leading to an erosion of the regiocontrol. When the phenyl ring was substituted in the para position with an electron-withdrawing halogen such as chloride in anhydride 394, the formation of products was observed in a significantly improved ratio (24:76) and good ee (entry 3).
Table 3.28 Evaluation of thioaryl anhydrides in the enantioselective alcoholysis with 349 promoted by catalyst 378.

<table>
<thead>
<tr>
<th>entry</th>
<th>anhydride</th>
<th>conv (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ratio</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>436:437</td>
<td>438</td>
<td>439</td>
</tr>
<tr>
<td>1</td>
<td>392</td>
<td>97</td>
<td>32:68</td>
<td>80</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>393</td>
<td>73</td>
<td>42:58</td>
<td>85</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>394</td>
<td>74</td>
<td>28:72</td>
<td>86</td>
<td>90</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by 1H NMR spectroscopic analysis using p-iodoanisole as an internal standard. <sup>b</sup> Determined by CSP-HPLC. <sup>c</sup> Isolated yield.

It was then considered opportune to verify whether we could improve the regio/enantiocontrol of these reactions by lowering the temperature to -15 °C (Table 3.29).

Table 3.29 Evaluation of the effect of temperature in the enantioselective alcoholysis of thioaryl anhydrides with 349 promoted by catalyst 378.

<table>
<thead>
<tr>
<th>entry</th>
<th>anhydride</th>
<th>temp. (°C)</th>
<th>conv (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ratio</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
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<td></td>
<td>436:437</td>
<td>438</td>
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<tr>
<td>1</td>
<td>392</td>
<td>-15</td>
<td>68</td>
<td>32:68</td>
<td>80</td>
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<tr>
<td>2</td>
<td>393</td>
<td>-15</td>
<td>56</td>
<td>44:56</td>
<td>72</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>394</td>
<td>-15</td>
<td>44</td>
<td>24:76</td>
<td>70</td>
<td>75</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by 1H NMR spectroscopic analysis using p-iodoanisole as an internal standard. <sup>b</sup> Determined by CSP-HPLC. <sup>c</sup> Isolated yield from 141.
These experiments were not able to induce an increase in the hemiester ratio, which remained practically unchanged compared to those carried out at room temperature, while affording the products with significantly diminished conversion and lower ee values (entries 1, 2 and 3).

Taking as an example the reaction between anhydride 394 and 349 at room temperature in the presence of catalyst 378, which gave us the higher product ratio, we envisioned that by carrying out a one pot experiment in which the catalyst promotes a Michael addition followed by DKR, the regio/enantioselective outcome of the reaction under scrutiny could be improved (Scheme 3.18).

Scheme 3.18  Evaluation of “one pot” experiment involving the asymmetric alcoholysis of 394 with 349 promoted catalyst 378.

Unfortunately, the one pot alcoholysis experiment proved ineffective and was accompanied by a notable drop in regioselectivity and poor product enantiomeric excess.

Once the evaluation of several aryl-substituted succinic anhydrides was completed, it also seemed prudent to move towards the use of a set of succinic anhydrides incorporating alkyl substituents.

Inspired by the use of methyl and allyl-substituted succinic anhydrides (218a and 218d, respectively) in parallel kinetic resolution with alcohols reported by Deng et al. (see Section 1.9.1) we employed them in the alcoholysis reaction promoted by the sulfonamide-based catalyst 378 under the optimised reaction conditions in hand (Table 3.30). When the simple methyl and allyl-substituted anhydrides 218a and 218d were used, an almost 1:1 mixture of products was observed. Subsequent derivatisation with the
chiral amine 398 showed the formation of products in excellent ee up to 99% (444a and 444b, entries 1 and 2, respectively).

**Table 3.30** Evaluation of 218a and 218d in the enantioselective alcoholysis with 349 promoted by catalyst 378.

<table>
<thead>
<tr>
<th>entry</th>
<th>anhydride</th>
<th>conv (%)</th>
<th>ratio 442:443</th>
<th>ee (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>218a</td>
<td>98</td>
<td>45:55</td>
<td>99&lt;sup&gt;d&lt;/sup&gt;</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>218d</td>
<td>98</td>
<td>46:54</td>
<td>99</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>444a</td>
<td>99&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>38</td>
<td></td>
</tr>
<tr>
<td></td>
<td>444b</td>
<td>90</td>
<td></td>
<td>52</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using p-iodoanisole as an internal standard. <sup>b</sup>Determined by CSP-HPLC. <sup>c</sup>Isolated yield from 141. <sup>d</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis.

It is interesting to note that the methyl- and allyl-substituted anhydrides 218a and 218d were less selectively attacked than their phenyl analogues (141 and 143). Since it seemed clear that the steric properties of the anhydride are responsible for the regioselective outcome of the reaction, we decided to analyse the installation of a bulky isopropyl substituent. The synthesis of 395 was accomplished via a 5 step synthetic route as described in Scheme 3.19. The commercially available isopropyl maleic acid (446) was subjected to an esterification process to furnish 447 which was subsequentially alkylated by reacting with methyl bromoacetate (448) in the presence of sodium hydride as a base in THF to afford the product 449. The hydrolysis of the *tris*-ester 449 was achieved using NaOH in a MeOH/THF mixture. The decarboxylation reaction of 450 at 150 °C gave the *bis*-acid 451 which was then cyclised using acetyl chloride to furnish the desired anhydride 395.
Scheme 3.19 Synthesis of anhydride 395.

Anhydride 395 was employed in the asymmetric alcoholysis with 349 promoted by catalyst 370 at room temperature in MTBE. Pleasantly, we observed the formation of hemiesters 452 and 453 in improved ratios (35:65, Scheme 3.20) with the larger isopropyl group compared to the less hindered anhydrides 218a and 218d. To our disappointment, following derivatisation reaction to amides in the presence of 398 we failed to isolate the major product. This inconvenience suggested that the presence of a bulky substituent in \( \alpha \)-position to the carbonyl undergoing the derivatisation may prevent the reaction from occurring, however, the minor product was obtained in an excellent enantiomeric excess up to 94% ee.

Scheme 3.20 Evaluation of 395 in the enantioselective alcoholysis with 349 promoted by catalyst 378.

Since the expansion of the substrate scope was only carried out using succinic anhydride derivatives, it was decided to investigate the feasibility of employing 6-membered anhydrides and the role that the ring size may have on the outcome of the reaction. Studies related to anhydride 257 interestingly showed a massive improvement in terms of
regioslectivity (a 4:96 ratio) with the formation of almost one hemiester 456 exclusively (Scheme 3.21).

Scheme 3.21 Enantioselective alcoholysis of anhydride 257 with 349 promoted by catalyst 378.

In order to explain the regioselective outcome of this reaction, we postulated that anhydride 257 (Figure 3.8a) shows a bigger discrepancy in reactivity between the two carbonyls that make the alcoholysis of the substrate more sensitive to the steric effect of the phenyl substituent, favouring therefore the nucleophilic attack on the less hindered position. On the other hand, in anhydride 141 the electronic effect (inductive and field effects) of one carbonyl over the other is predominant, resulting in an activation of both the positions towards the nucleophilic attack with the consequent reduction of regioselectivity (Figure 3.8b).

Figure 3.8 Steric and electronic effects of anhydride 257 (a) and 141 (b).

Despite the excellent regiocontrol, the desired hemiester 457 was obtained in very low conversion (40% after 5 days) and poor ee (20% ee, Scheme 3.21).
3.10 Investigation of the mechanistic aspects involved in the resolution process

Some experiments were aimed at evaluating the possible mechanism responsible for our resolution strategy. Taking as an experimental model the reaction between anhydride 141 and alcohol 323 in the presence of catalyst 378, we stopped the reaction at 20, 50 and 80% conversion respectively and, subsequently, the unreacted anhydride was isolated.

### Table 3.31 DKR of anhydride 141: preliminary experiments on mechanism evaluation.

<table>
<thead>
<tr>
<th>entry</th>
<th>conv (%)a</th>
<th>ratio 330:331a</th>
<th>ee (%)b</th>
<th>ee (%)b</th>
<th>332</th>
<th>333</th>
<th>141c</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>24:76</td>
<td>93</td>
<td>93</td>
<td></td>
<td></td>
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<td>50</td>
<td>24:76</td>
<td>97</td>
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<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>24:76</td>
<td>97</td>
<td>92</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Determined by 1H NMR spectroscopic analysis using p-iodoanisole as an internal standard. b Determined by CSP-HPLC. c unreacted anhydride 141.

As outlined in Table 3.31, the regio and enantioselectivity remained practically constant for the duration of the reaction (entries 1, 2 and 3) and the remaining unreacted starting material isolated after 50% conversion and purified by flash chromatography was found to be racemic. These experimental results obtained for the reaction under scrutiny would suggest the absence of a kinetic resolution process, however either a dynamic or parallel kinetic resolution could not be ruled out. However, as we mentioned in Section 3.1, for an efficient DKR, the racemisation of the two reactive enantiomers of the cyclic anhydride should occur more quickly than the interaction of the slower substrate with the catalyst. Disappointingly, in accordance with the previous experiment, our results indicated that racemisation is too slow, the mono esters 330 and 331 were formed at a similar rate throughout the course of the reaction and so enantiocontrol is mostly likely due to PKR.
3.11 Conclusions

In summary, our attempts to develop a DKR of enolisable cyclic anhydrides was unsuccessful. However, an highly efficient PKR has been described. Interestingly, the evaluation of the substrate scope with regards to the nucleophile revealed that the regio and enantioselectivity of the PKR process was influenced by the electronic and steric characteristics of the alcohol. In particular, by employing alcohols with a pkₐ between 11 and 13 (i.e. 323 and 349) we were able to afford the products in ratios of 24:76 and high enantiomeric excess while by increasing the size of the R group we afforded mono esters in significantly lower ee. Furthermore, the method was shown to be applicable to several cyclic anhydrides with different substituents. Our results suggested that the regioselectivity of the PKR of the reaction under scrutiny tended to increase depending on the steric hindrance of the anhydride as highlighted in Scheme 3.22.

![Scheme 3.22 Steric effect in the PKR of enolisable cyclic anhydrides.](image)

Interestingly, by varying the electronic properties of the anhydride (i.e. α-heteroatom-substituted anhydrides), thioaryl succinic anhydrides (392, 393 and 394, Table 3.28) underwent alcoholysis mainly at the most hindered carbonyl while by employing the alkoxy-substituted variant 390 (Scheme 3.15) we were able to form only one mono ester product, albeit in low ee.
Finally, a wide range of modified-cinchona alkaloid catalysts were evaluated. In particular, the use of sulfonamide-based cinchona alkaloid organocatalysts carried out PKR of both aliphatic and aromatic-substituted succinic anhydrides with unprecedented enantiocontrol.
Chapter 4

Results and Discussion: Towards the development of an asymmetric formal cycloaddition of enolisable cyclic anhydrides to benzaldehyde promoted by iminophosphorane organosuperbase catalysts
Chapter 4

Results and discussion

4.1 Towards the development of an asymmetric formal cycloaddition of enolisable cyclic anhydrides to benzaldehyde promoted by iminophosphorane organosuperbase catalysts

Over the years, organocatalysis has been involved in the development of organocatalysts with H-bond donating abilities capable of promoting several enantioselective chemical transformations. For this reason, the investigation of catalysts with new H-bond donating moieties has become prominent in the field of organocatalysis. As mentioned in Section 1.10, Dixon and co-workers described a new class of strongly basic and tunable bifunctional organocatalysts based on the introduction of iminophosphorane moieties. However, the concept of organosuperbase as bifunctional catalysts is a rather recent development and their promising potential has been confined to Michael-type reactions.

Recently, our group, among others, has been focused on the design and preparation of chiral bifunctional (thio)urea and squaramide-derived catalysts successfully employed in the enantioselective formal cycloaddition reaction between cyclic anhydrides and different electrophiles. Due to the lack of success of our attempt to expand the substrate scope towards the use of different enolisable cyclic anhydride (See section 2.1) we became intrigued by the possibility of developing a new protocol for the annulation reaction by using iminophosphorane organosuperbases as alternative catalysts.

4.1.2 Synthesis of iminophosphorane bifunctional catalysts

To investigate this hypothesis, the bifunctional iminophosphorane catalyst was synthesised following the general procedure reported by Dixon, as shown in Scheme 4.1. The first step of the synthesis consists of the formation of the L-tert-leucinol in 88% yield by reduction of the commercially available L-tert-leucine in the presence of iodine and sodium borohydride in THF according to the known literature procedure. The product was then protected using Boc anhydride to give 462, which was reacted with phthalimide and triphenylphosphine in THF followed by the addition of a solution of DIAD to afford 464 in 85% yield. This compound, after purification by column chromatography on silica gel, was reacted with an excess of hydrazine monohydrate in ethanol, furnishing the desired diamine 465. The product so obtained was then reacted with the diazotransfer reagent N\textsubscript{3}SO\textsubscript{2}Im. HCl in the presence of
potassium carbonate and copper (II) sulfate pentahydrate in methanol at rt for 16 h to yield 467. The aminazide 467 was, upon purification, firstly deprotected by adding trifluoroacetic acid and then reacted with 3,5-bis(trifluoromethyl)phenyl isothiocyanate (468) to afford the azide 469. The subsequent reaction between 469 and tris(4-methoxyphenyl)phospine (470) at room temperature for 24 h furnished the desired catalyst 239 in 85% yield.

Scheme 4.1 Synthesis of iminophosphorane catalyst 239.

4.1.3 Evaluation of the asymmetric cycloaddition reaction of enolisable anhydrides with benzaldehyde promoted by iminophosphorane organocatalysts

As discussed in Section 1.5.1, the asymmetric cycloaddition reaction between phenylsuccinic anhydride (141) and benzaldehyde (9) can be promoted by squaramide-based catalyst 140 in high diastereo- and enantioselectivity, however, a significant decrease in yield (44% at room temperature), compared to those obtained with homophthalic anhydride (117), has been reported. Inspired by these results, we decided therefore to investigate whether the use of iminophosphorane organosuberbases as catalysts for such a reaction could enhance the yield. Preliminary studies were aimed at
evaluating the reaction between anhydride 141 and aldehyde 9 in the presence of catalyst 239 under the optimised reaction condition previously reported by our group.\textsuperscript{136,146,148}

Scheme 4.2 Asymmetric cycloaddition reaction between 141 and 9 promoted by iminophosphorane catalyst 239.

As shown in Scheme 4.2, in the reaction catalysed by iminophosphorane catalyst 239, 141 underwent the formation of the corresponding products at room temperature in 24 h in 43\% yield with moderate diastereocontrol, albeit with poor enantioselectivity. Unfortunately, catalyst 239 proved ineffective in efficiently improving the asymmetric cycloaddition reaction protocol previously developed. Although the first attempt was unsuccessful, we decided to evaluate the feasibility of catalyst 239 in the annulation reactions involving different enolisable cyclic anhydrides previously found to be recalcitrant substrates using more traditional organocatalyst systems (Scheme 4.3).

Scheme 4.3 Evaluation of enolisable anhydrides in the asymmetric cycloaddition with 9 promoted by iminophosphorane catalyst 239.
Initial experiments using phenylglutaric anhydride (257, Scheme 4.3, A) and anhydride 389 (Scheme 4.3, B) failed to afford the desired cycloaddition products. The thioaryl-substituted succinic anhydrides 392 and 394 (Scheme 4.3, C) underwent the asymmetric cycloaddition reaction with 9 in the presence of catalyst 239 with the formation of lactone products in low yield after 24 h. Longer reaction times afforded only marginally increased yields.

### 4.1.4 Synthesis and evaluation of substituted glutaconic anhydrides in the formal cycloaddition reaction with aldehydes promoted by iminophosphorane catalysts

The disappointing results obtained from the evaluation of enolisable 5-membered cyclic anhydrides in the asymmetric reaction with 9 catalysed by 239 prompted us to investigate the use of alternative cyclic anhydrides. Inspired by the recent successful employment of phenyl glutaconic anhydride (150) in the formal cycloaddition reaction with benzaldehyde (reported by fellow researcher Ms Maria Luisa Aiello) we became interested in the evaluation of this substrate as the nucleophile in the organocatalytic reaction with both aromatic and aliphatic aldehydes.

The synthesis of 150 was accomplished *via* a three step synthetic route as outlined in Scheme 4.4. The reaction between ethyl phenylpropiolate (473) and ethyl acetoacetate (474) in presence of sodium hydroxide in 1,4-dioxane furnished the lactone 475 which was then, upon purification by column chromatography on silica gel, hydrolysed using sodium hydroxide in water to give the bis-acid 476. The cyclisation reaction with acetyl chloride afforded the desired anhydride 150 in moderate yield.

![Scheme 4.4](image-url)  
**Scheme 4.4** Synthesis of anhydride 150.
Preliminary experiments aimed at evaluating 150 with hydrocinnamaldehyde (477) in the presence of catalyst 239 were carried out in conjunction with Ms. Maria Luisa Aiello who was experimenting on the use of these substrates in the asymmetric cycloaddition reaction promoted by (thio)urea and squaramide-based cinchona alkaloid organocatalysts.

**Table 4.1 Organocatalyst evaluation in the asymmetric cycloaddition between 150 and 477.**

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>solvent</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>dr (trans:cis)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee&lt;sub&gt;trans&lt;/sub&gt; (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ee&lt;sub&gt;cis&lt;/sub&gt; (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>138</td>
<td>THF</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>163</td>
<td>THF</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>139</td>
<td>THF</td>
<td>66</td>
<td>38:62</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>140</td>
<td>THF</td>
<td>77</td>
<td>43:57</td>
<td>95</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>239</td>
<td>MTBE</td>
<td>46</td>
<td>75:25</td>
<td>68</td>
<td>80</td>
</tr>
</tbody>
</table>

<sup>a</sup>Yield of combined diastereomers determined by<sup>1</sup>H NMR spectroscopic analysis using p-iodoanisole as an internal standard. <sup>b</sup>Diastereomeric ratio determined by<sup>1</sup>H NMR spectroscopic analysis. <sup>c</sup>Determined by CSP-HPLC. <sup>d</sup>Reaction executed by Ms. Maria Luisa Aiello.

The evaluation of the catalysts in the asymmetric cycloaddition of 150 with 477 is displayed in Table 4.1 above. Fellow researcher Ms. Maria Luisa Aiello observed that the reaction performed using (thio)urea-based catalysts 138 and 163 failed to afford the desired products (entries 1 and 2), while the use of squaramide-based catalysts 139 and 140 promoted the reaction in moderate yields (entries 3 and 4). The same researcher also reported that the products were formed in low diastereoselectivity with the predominance
of the cis diastereomer in an excellent enantiocontrol. Interestingly, the iminophosphorane catalyst 239 promoted the reaction with opposite diastereocontrol (entry 5, 75:25 dr) and moderate ee, albeit in low yield. Given the poor yield obtained in the enantioselective cycloaddition reaction catalysed by 239, the optimisation of the reaction condition was the next avenue to be investigated (Table 4.2).

**Table 4.2** Attempted optimisation of the reaction conditions in the asymmetric cycloaddition reaction between 150 and 477 promoted by iminophosphorane catalyst 239.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>239 loading (mol%)</th>
<th>yield (%)</th>
<th>dr (trans: cis)</th>
<th>ee&lt;sub&gt;trans&lt;/sub&gt; (%)</th>
<th>ee&lt;sub&gt;cis&lt;/sub&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MTBE</td>
<td>5</td>
<td>46</td>
<td>75:25</td>
<td>68</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>5</td>
<td>40</td>
<td>71:29</td>
<td>73</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>MTBE</td>
<td>5+5</td>
<td>46</td>
<td>75:25</td>
<td>66</td>
<td>80</td>
</tr>
</tbody>
</table>

* Yield of combined diastereomers determined by 1H NMR spectroscopic analysis using p-iodoanisole as an internal standard. b Diastereomeric ratio determined by 1H NMR spectroscopic analysis. c Determined by CSP-HPLC.

The use of THF as solvent did not prove effective in improving the yield of the reaction providing the corresponding lactone-esters in 40% yield after 24 h (entry 2) and slightly decreasing dr, however, the trans diastereomer was formed in marginally higher optical purity. Speculating on the possible degradation of the catalyst during the reaction contributing to the overall low yield, we assumed that by increasing the catalyst loading by a further 5 mol% after 24 h this problem could be overcome but unfortunately this strategy failed (entry 3).
4.1.4.1 Evaluation of the substrate scope: the aldehyde component

The moderate diastereomeric and enantiomeric control observed in the formation of the lactones using aldehyde 477 prompted the investigation into the use of different aldehydes with both aromatic and alkyl substituents. The results are summarised in Table 4.3.

**Table 4.3** Evaluation of different aldehydes in the asymmetric cycloaddition reaction with 150 promoted by 239.

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>yield (%)</th>
<th>dr (trans: cis)</th>
<th>ee&lt;sub&gt;trans&lt;/sub&gt; (%)</th>
<th>ee&lt;sub&gt;cis&lt;/sub&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Product Image" /></td>
<td>49</td>
<td>87:13</td>
<td>66</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Product Image" /></td>
<td>60</td>
<td>95:5</td>
<td>31</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Product Image" /></td>
<td>59</td>
<td>89:11</td>
<td>16</td>
<td>--</td>
</tr>
</tbody>
</table>

1. 239 (5 mol%) MTBE (0.1 M), 24 h, rt
2. TMSCHN₂ (1.2 equiv.) i-PrOH (5.0 equiv.) THF (0.1 M) 0 °C to rt, 1 h

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>yield (%)</th>
<th>dr (trans: cis)</th>
<th>ee&lt;sub&gt;trans&lt;/sub&gt; (%)</th>
<th>ee&lt;sub&gt;cis&lt;/sub&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Product Image" /></td>
<td>49</td>
<td>87:13</td>
<td>66</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Product Image" /></td>
<td>60</td>
<td>95:5</td>
<td>31</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Product Image" /></td>
<td>59</td>
<td>89:11</td>
<td>16</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Yield of combined diastereomers determined by $^1$H NMR spectroscopic analysis using p-iodoanisole as an internal standard.</td>
<td>Diastereomeric ratio determined by $^1$H NMR spectroscopic analysis.</td>
<td>Diastereomeric ratio determined by CSP-HPLC.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----</td>
<td>---------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------</td>
<td>------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>60 90:10 20 --</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>49 99 42 --</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>37 76:24 94 99</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>42 55:45 94 30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>36 70:30 95 50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

It was found that by employing the hindered branched aromatic aldehyde 479 the cycloaddition products were obtained in moderate *dr* and *ee*, albeit in lower yields (49%, entry 1). Next, the effects resulting from the introduction of electron-rich and electron-poor substituents on the benzaldehyde substrate were investigated and aldehydes 480-483 were evaluated. Use of these compounds resulted in an improvement in the product yields up to 60% and excellent diastereocontrol with the formation of only the trans-diastereomer in almost all cases evaluated (entries 2, 3, 4 and 5). Despite the moderate
product yields and the high $dr$ achieved, the influence of the substituted aromatic ring on enantioselectivity was deleterious: a significant loss in product $ee$ was obtained. Interestingly, by switching the aromatic aldehydes with the aliphatic variants, we observed the opposite trend. While the yields and $drs$ of the products was significantly lower, the use of these substrates in the cycloaddition reaction with anhydride 150 promoted by 239 led to the formation of the trans-diastereomer in excellent $ee$ up to 95% (entries 6, 7 and 8).

4.1.4.2 Evaluation of the substrate scope: the anhydride component

The most promising result obtained previously in the asymmetric cycloaddition reaction between 150 and aldehyde 484 (entry 6, Table 4.3) promoted by the iminophosphorane catalyst 239 prompted us to evaluate different anhydride nucleophiles in this reaction. Accordingly, it was decided to evaluate the methyl-substituted glutaric anhydride 151 and its methoxy-substituted variant 496 as shown in Scheme 4.5.

**Scheme 4.5** Evaluation of anhydrides 151 and 496 in the asymmetric cycloaddition reaction with 484 promoted by 239.

In the presence of anhydride 151, the reaction proceeded with the formation of the desired products in a slightly improved yield and $dr$ compared to the phenyl-substituted variant 470 previously evaluated, however, with unsatisfactory enantioselectivity (Scheme 4.5, A), while 496 completely failed to undergo the asymmetric cycloaddition reaction under scrutiny (Scheme 4.5, B).
4.1.5 Conclusions

In this project it has been demonstrated that iminophosphorane catalyst 239 can be employed in the asymmetric cycloaddition reaction of phenylsuccinic anhydride (141) with benzaldehyde (9) albeit with unsatisfactory yield and stereocontrol. However, in collaboration with Ms Maria Luisa Aiello, the first asymmetric cycloaddition reaction between phenylglutaconic anhydride (150) and 9 catalysed by iminophosphorane catalyst 239 has been described. The method was demonstrated to be applicable to a range of aromatic aldehydes, with the product being formed in high diastereoselectivity but with only modest enantiocontrol. Gratifyingly, the substrate scope could be further extended to aliphatic aldehydes which allowed the formation of enantioenriched products in up to 95% ee. In addition, the employment of different glutaconic anhydride derivatives has been reported.
Chapter 5

Experimental section
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 solvents CDCl₃, DMSO-d₆ or D₂O and referenced relative to residual CHCl₃ (δ = 7.26 ppm), DMSO (δ = 2.50 ppm) or H₂O (δ = 4.79 ppm). Chemical shifts are reported in ppm and coupling constants (J) in Hertz. Carbon NMR spectra were recorded on the same instruments (100.6 MHz) with total proton decoupling. Fluorine and phosphorus NMR spectra were recorded on the Bruker DPX400 machine (376.5 and 202 MHz respectively). COSY, HSQC, HMBC, and TOCSY NMR experiments were used to aid assignment of NMR peaks when required. All melting points are uncorrected. Infrared spectra were obtained using neat samples on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. ESI mass spectra were acquired using a Waters Micromass LCT-time of flight mass spectrometer (TOF), interfaced to a Waters 2690 HPLC. APCI experiments were carried out on a Bruker microTOF-Q III spectrometer interfaced to a Dionex UltiMate 3000 LC or direct insertion probe. The instrument was operated in positive or negative mode as required. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated 60F₂₅₄ slides, and visualised by UV irradiation or KMnO₄ staining. Optical rotation measurements were made on a Rudolph Research Analytical Autopol IV instrument, and are quoted in units of 10⁻¹ deg cm² g⁻¹. Anhydrous tetrahydrofuran (THF), CH₂Cl₂ and Et₂O were obtained by using a Pure Solv MD4EN Solvent Purification System. Methanol (MeOH) was dried over activated 3Å molecular sieves. Ethanol (EtOH) was dried over magnesium and iodine. Commercially available anhydrous t-butyl methyl ether (MTBE), 1,4-dioxane, diisopropyl ether were used. Analytical CSP-HPLC was performed on Daicel Chiralpak, AD, AD-H, AS, IA, OD, OD-H, OJ-H (4.6 mm x 25 cm) columns and using ACQUITY UPC², Trefoil CEL1, CEL2, 2.5μm (3.0 x 150 mm).

5.1 Experimental procedures and data for Chapter 2

5.1.1 Procedure A: general procedure for the organocatalysed cycloaddition reaction between the relevant anhydride and benzaldehyde

An oven-dried 10 mL reaction vessel containing a magnetic stirring bar under argon atmosphere was charged with the relevant anhydride (0.246 mmol) and the relevant catalyst (0.0123 mmol - 5 mol%). Anhydrous MTBE (2.5 mL, 0.1 M) was added via
syringe and the reaction mixture was stirred at room temperature. Freshly distilled benzaldehyde (23, 25 µL, 0.246 mmol) was then added via syringe and the resulting mixture was allowed to stir for 48 h.

2-Bromopentanedioic acid (265)\textsuperscript{247}

\[
\text{HO} - \text{C} - \text{O} - \text{OH}
\]

A round-bottomed flask containing a magnetic stirring bar was charged with racemic glutamic acid monosodium salt monohydrate (264, 5.00 g, 26.7 mmol) followed by NaBr (22.4 g, 218 mmol) in HBr (1 M, 150 mL) and the reaction mixture was cooled to -5 °C. A solution of NaNO\textsubscript{2} (5.50 g, 80.0 mmol) in water (25 mL) was added dropwise over 1 hour and stirred for 7 h. Then concentrated sulfuric acid (3.6 mL) was slowly added to the solution and extracted with ether (150 mL x 3). The combined organic phases were washed with brine (100 mL x 2), dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and the solvent was removed \textit{in vacuo} to afford 265 as a white solid (675 mg, 12%). M.p 47 °C, (lit.,\textsuperscript{248} m.p 40 °C).

\[\delta_H\ (400\ MHz,\ \text{CDCl}_3):\ 9.40\ (2\ H,\ bs,\ H-1),\ 4.39\ (1\ H,\ app.\ t,\ H-2),\ 2.69-2.53\ (3\ H,\ m,\ H-3,\ H-4a),\ 2.47-2.27\ (1\ H,\ m,\ H-4b).\]

Dimethyl 2-bromopentanedioate (267)\textsuperscript{248}

\[
\text{HO} - \text{C} - \text{O} - \text{O} - \text{Br}
\]

A round-bottomed flask containing a magnetic stirring bar was charged with 265 (650 mg, 2.71 mmol), sulfuric acid (1 ml) and methanol (15 mL). The reaction mixture was refluxed for 12 h, the solvent was then evaporated \textit{in vacuo} to furnish a yellow oil, the residue was purified by column chromatography (hexanes:EtOAc 9:1 v/v) to give 267 (343 mg, 53%) as a yellow oil.

\[\delta_H\ (400\ MHz,\ \text{CDCl}_3):\ 4.36\ (1\ H,\ dd,\ J\ 6.0,\ 8.6,\ H-4),\ 3.77\ (3\ H,\ s,\ H-5),\ 3.67\ (3\ H,\ s,\ H-1),\ 2.64-2.45\ (2\ H,\ m,\ H-2),\ 2.40-2.32\ (1\ H,\ m,\ H-3a),\ 2.32-2.20\ (1\ H,\ m,\ H-3b).\]

HRMS (m/z – ESI): Found: 236.9803 (M-H) \textsuperscript{+} \text{C}_7\text{H}_{10}\text{BrO}_4 \text{ Requires: } 236.9896.
2-Chloropentanedioic acid (269)\textsuperscript{249}

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Cl} & \quad \text{2a,b} \\
\text{HO} & \quad \text{OH}
\end{align*}
\]

A round-bottomed flask containing a magnetic stirring bar was charged with racemic glutamic acid monosodium salt monohydrate (264, 5.00 g, 26.7 mmol) followed by NaCl (12.7 g, 218 mmol) in HCl (1.0 M, 150 mL) and reaction mixture was cooled at -5 °C. A solution of NaNO\textsubscript{2} (5.5 g, 80 mmol) in water (25 mL) was added dropwise over 4 h and stirred for 7 h. Then concentrated sulfuric acid (3.6 mL) was slowly added to the solution and extracted with diethyl ether (150 mL x 3). The combined organic phases were washed with brine (100 mL x 2), dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and the solvent was removed \textit{in vacuo} to afford 269 as a white solid (1.0 g, 23%). M.p. 86 °C, (lit.\textsuperscript{249} m.p 99 °C).

\[
\delta_H \; (400 \text{ MHz, CDCl}_3): \quad 4.96 \; (1 \text{ H, app. t, H-1}), \quad 2.67-2.50 \; (3 \text{ H, m, H-2, H-3a}), \quad 2.42-2.37 \; (1 \text{ H, m, H-3b}).
\]

\textbf{Dimethyl 2-chloropentanedioate (270)\textsuperscript{249}}

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Cl} & \quad \text{3} \\
\text{HO} & \quad \text{HO}
\end{align*}
\]

A round-bottomed flask containing a magnetic stirring bar was charged 269 (1.00 g, 6.00 mmol), sulfuric acid (1 mL) and methanol (25 mL). The reaction mixture was refluxed for 12 h, the solvent was then evaporated \textit{in vacuo} to furnish a yellow oil, the residue was purified by column chromatography (hex:EtOAc 9:1 v/v) to give 270 as a yellow solid (538 mg, 46%).

\[
\delta_H \; (400 \text{ MHz, CDCl}_3): \quad 4.40 \; (1 \text{ H, dd, J 5.1, 8.4, H-1}), \quad 3.77 \; (3 \text{ H, s, H-2}), \quad 3.67 \; (3 \text{ H, s, H-3}), \quad 2.52 \; (2 \text{ H, t, J 7.2, H-5}), \quad 2.40-2.31 \; (1 \text{ H, m, H-4a}), \quad 2.26-2.16 \; (1 \text{ H, m, H-4b}).
\]

\textbf{HRMS (m/z – ESI)}: Found: 193.0380 (M-H)\textsuperscript{-} C\textsubscript{7}H\textsubscript{10}ClO\textsubscript{4} Requires: 193.0389.
Diethyl 2-cyanopentanedioate (274)\textsuperscript{228}

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{CN}
\end{array}
\]

A round-bottomed flask containing a magnetic stirring bar was charged with ethyl cyanooacetate (272, 1 mL, 8.80 mmol) in ethanol (30 mL) and the solution was cooled at -78 °C. Sodium ethoxide (718 mg, 10.5 mmol) was added and the solution reaction mixture stirred for 10 min, after which time 273 (1 mL, 8.80 mmol) was added dropwise via syringe over 15 min. The reaction mixture was stirred for 1 h then acetic acid (0.4 mL) and water (1 mL) were added. The solution was concentrated under reduced pressure, then the residue was extracted with diethyl ether (50 mL), washed with brine and dried over MgSO\textsubscript{4}. After the removal of the solvent in vacuo, the oily residue was purified by Kugelrohr distillation to yield pure 274 (488 mg, 26%).

\[\delta_H (400 \text{ MHz, CDCl}_3): \quad 4.23 (2 \text{ H, q, } J 7.1, \text{ H-1'}), 4.09 (2 \text{ H, q, } J 7.3, \text{ H-1''}), 3.75 (1 \text{ H, app. t, H-2}), 2.51 (2 \text{ H, t, } J 7.2, \text{ H-3}), 2.04-2.36 (2 \text{ H, m, H-4}), 1.36 (3 \text{ H, t, } J 7.1, \text{ H-2'}), 1.13 (3 \text{ H, t, } J 7.3, \text{ H-2''}).\]

HRMS (\textit{m/z} -ESI): Found: 212.1066. [M-H] C\textsubscript{10}H\textsubscript{14}NO\textsubscript{4} Requires: 212.1066.

2-Cyanopentanedioic acid (275)\textsuperscript{228}

\[
\begin{array}{c}
\text{OH} \\
\text{CN} \\
\text{OH}
\end{array}
\]

A round-bottomed flask containing a magnetic stirring bar was charged with 274 (400 mg, 1.87 mmol) in a mixture of THF/water 3:1 (20 mL). Lithium hydroxide monohydrate (470 mg, 11.2 mmol) was added and the solution was stirred at room temperature for 3 h. The reaction mixture was acidified by adding concentrated aqueous HCl (5 mL) and extracted with EtOAc (15 mL x 3) to furnish 275 as a white solid (220 mg, 75%). M.p. 140-145 °C.

\[\delta_H (400 \text{ MHz, DMSO-}d_6): \quad 4.06 (1 \text{ H, dd, } J 5.9, 8.1, \text{ H-1}), 2.37 (2 \text{ H, t, } J 7.4, \text{ H-2}), 2.13-2.05 (1 \text{ H, m, H-3a}), 2.03-1.96 (1 \text{ H, m, H-3b}).\]
2,6-Dioxotetrahydro-2H-pyran-3-carbonitrile (256) \(^{228}\)

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{CN}
\end{array}
\]

A 25 mL round-bottomed flask containing a magnetic stirring bar was charged with \(275\) (200 mg, 1.27 mmol) and trifluoroacetic anhydride (8.5 mL). The reaction mixture was stirred at room temperature for 12 h, trifluoroacetic anhydride was removed under reduced pressure and the residue was washed with toluene (10 mL x 3). Hexane (10 mL) was added and the mixture was filtered to yield \(256\) as a white solid (19.5 mg, 11%). M.p. 88-90 °C.

\(\delta_H\) (400 MHz, CDCl\(_3\)): 3.81 (1 H, dd, \(J = 5.1, 10.2\), H-1), 3.07 (1 H, ddd, \(J = 5.3, 11.5, 18.1\) H-2a), 2.88-2.79 (1 H, m, H-2b), 2.49-2.35 (2 H, m, H-3).

**Methyl 2-phenylacetate (278)\(^{250}\)**

A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with 2-phenylacetic acid (277, 5.00 g, 36.7 mmol). Sulfuric acid (1 mL) and methanol (75 mL) were added and the reaction mixture was heated at reflux temperature for 3 h. The solvent was evaporated and the residue was dissolved in diethyl ether (30 mL) and then washed with a saturated aqueous solution of NaHCO\(_3\) (3 x 15 mL) and H\(_2\)O (2 x 15 mL). The organic phase was dried over MgSO\(_4\) and filtered. The solvent was evaporated to give the product \(278\) as an oily residue (5.40 g, 98%). Spectral data for this compound were consistent with those in the literature.\(^{250}\)

\(\delta_H\) (400 MHz, CDCl\(_3\)): 7.33-7.25 (5 H, m, H-1, H-2 and H-3), 3.68 (3 H, s, H-5), 3.62 (2 H, s, H-4),

HRMS (m/z – ESI): Found: 149.0685 (M-H) \(\text{C}_9\text{H}_9\text{O}_2\) Requires: 149.0685.
Dimethyl-2-phenylpentanedioate (280)$^{251}$

An oven dried 250 mL round-bottomed flask containing a magnetic stirring bar was charged with potassium tert-butoxide (586 mg, 5.2 mmol) in toluene (35 mL). A solution of methyl 2-phenylacetate 278 (3.50 g, 19.9 mmol) in toluene (35 mL) was added dropwise under an argon atmosphere at -78 °C and stirred for 15 min. Then methyl acrylate (279, 1.57 mL, 17.6 mmol) solution in toluene (35 mL) was added dropwise and stirred for 10 min. The reaction mixture was poured into a saturated aqueous solution of NH$_4$Cl (25 mL), extracted with ethyl acetate (25 mL) and dried over MgSO$_4$. After the removal of the solvent in vacuo, the residue was purified by column chromatography (hexanes:EtOAc 9:1 v/v) to give 280 as a white solid (1.44 g, 33%).

Spectral data for this compound were consistent with those in the literature.$^{251}$

\[
\delta_H (400 \text{ MHz, CDCl}_3): \quad 7.35-7.32 (5 \text{ H, m, H-1, H-2, H-3}), 3.68 (3 \text{ H, s, H-7}), 3.67 (3 \text{ H, s, H-8}), 3.65 (1 \text{ H, t, J } 8.0, \text{ H-4}), 2.42-2.36 (1 \text{ H, m, H-5a}), 2.29 (2 \text{ H, t, J } 7.44, \text{ H-6}), 2.18-2.11 (1 \text{ H, m, H-5b}).
\]

HRMS (m/z – ESI): Found: 236.1057 (M-H)$^+$ C$_{13}$H$_{16}$O$_4$ Requires: 236.1049.

2-Phenylpentanedioic acid (281)$^{252}$

A 50 mL round-bottomed flask containing a magnetic stirring bar was charged with 280 (1.00 g, 4.2 mmol) and methanol (33 mL). A solution of NaOH in water (0.1 N) was added and the reaction mixture was refluxed for 4 h. After cooling, the PH of the solution was partially neutralised by adding a solution of HCl (3.0 N). The solvent was removed in vacuo and the residue was dissolved in water and acidified to pH = 1.5 (3.0 N) with HCl. The aqueous mixture was extracted with diethyl ether (15 mL x 3) and dried with sodium sulfate to give 281 (690 mg, 79%).$^{252}$
\[ \delta_H (400 \text{ MHz, CDCl}_3)^* : 7.35-7.27 (5 \text{ H, m, H-1, H-2 and H-3}), 3.65 (1 \text{ H, t, } J 7.14, \text{ H-4}), 2.45-2.33 (3 \text{ H, m, H-5a and H-6}), 2.14-2.08 (1 \text{ H, m, H-5b}). \]

HRMS (m/z – ESI): Found: 207.0655 (M-H) \text{ C}_{11}\text{H}_{11}\text{O}_4 \text{ Requires: } 207.0657

*The proton signals (H-7 and H-8) are not visible in CDCl\text{3}.

3-Phenyldihydro-2H-pyran-2,6(3H)-dione (257)\textsuperscript{253}

![Diagram of 3-Phenyldihydro-2H-pyran-2,6(3H)-dione](image)

A 25 mL round-bottomed flask containing a magnetic stirring bar was charged with 281 (500 mg, 2.40 mmol) and freshly distilled acetyl chloride (10 mL). The apparatus was then equipped with a condenser and a septum and kept under an argon atmosphere. The reaction mixture was heated at reflux temperature for 12 h, then concentrated in vacuo to afford 257 as an off-white solid (360 mg, 79\%). M.p 89 °C (lit.,\textsuperscript{253} m.p. 96 °C).

\[ \delta_H (400 \text{ MHz, DMSO-}d_6) : 7.39-7.34 (2 \text{ H, m, H-2}), 7.33-7.30 (2 \text{ H, m, H-1}), 7.27-7.23 (1 \text{ H, m, H-3}), 4.17 (1 \text{ H, dd, } J 5.3, 13.0, \text{ H-4}), 3.01-2.95 (1 \text{ H, m, H-6a}), 2.88-2.83 (1 \text{ H, m, H-6b}), 2.40-2.38 (1 \text{ H, m, H-5a}), 2.05-2.03 (1 \text{ H, m, H-5b}). \]

2-(4-Nitrophenyl)acetic acid (283)\textsuperscript{251}

![Diagram of 2-(4-Nitrophenyl)acetic acid](image)

A 50 mL round-bottomed flask containing a magnetic stirring bar was charged with water (10 mL) and concentrated sulfuric acid (10 mL). 4-nitrophenylacetonitrile (282, 3.00 g, 18.5 mmol) was added to this mixture. The reaction mixture was refluxed for 2 h, diluted with water (150 mL) and cooled to 0 °C when a colourless crystalline solid separated.
The solid was filtered off, washed with ice-cold water to remove traces of acid and dried to yield 283 (3.00 g, 90%). M.p. 138 °C, (lit., 254 m.p. 150 °C).

\[ \delta_H (400 \text{ MHz, CDCl}_3): \]

8.21 (2 H, d, J 8.6, H-1), 7.47 (2 H, d, J 8.6, H-2), 3.79 (2 H, s, H-3).

**Methyl 2-(4-nitrophenyl)acetate (284)**

\[ \text{O} \]

\[ \begin{array}{c}
3 \\
\text{O} \\
1 \\
\text{O} \\
2
\end{array} \]

\[ \text{NO}_2 \]

Prepared according to the esterification reaction procedure described for the synthesis of 278, using 283 (3.00 g, 16.5 mmol) sulfuric acid (0.5 mL) and methanol (40 mL). Product 284 was isolated as an amorphous solid (3.17 g, 98%). M.p. 50 °C.

\[ \delta_H (400 \text{ MHz, CDCl}_3): \]


**Dimethyl 2-(4-nitrophenyl)pentanedioate (285)**

\[ \text{O} \]

\[ \begin{array}{c}
6 \\
\text{O} \\
\text{O} \\
5 \\
\text{O} \\
1 \\
\text{O} \\
2
\end{array} \]

\[ \text{NO}_2 \]

An oven dried 25 mL round-bottomed flask containing a magnetic stirring bar was charged with sodium methoxide (250 mg, 4.6 mmol) in dry methanol (5 mL). A methanolic (5 mL) solution of 285 (1.10 g, 5.60 mmol) was added dropwise under an argon atmosphere at -78 °C and stirred for 15 min. Methyl acrylate (279, 0.42 mL, 4.60 mmol) solution in methanol (35 mL) was added dropwise and stirred at reflux for 4 h. The reaction mixture was poured into a saturated aqueous solution of NH₄Cl (25 mL), extracted with EtOAc (25 mL) and dried over MgSO₄. After the removal of the solvent in vacuo, the residue was purified by column chromatography (hexanes:EtOAc 9:1) to give 285 as a yellow oil (450 mg, 35%).
$\delta_H$ (400 MHz, CDCl$_3$): 8.18 (2 H, d, $J$ 8.5, H-2), 7.45 (2 H, d, $J$ 8.5 H-1), 3.77 (1 H, t, $J$ 7.5, H-3), 3.67 (3 H, s, H-7), 3.64 (3 H, s, H-6), 2.45-2.36 (1 H, m, H-4a), 2.27 (2 H, t, $J$ 7.1, H-5), 2.14-2.07 (1 H, m, H-4b).

HRMS (m/z – ESI): Found: 280.0906 (M-H) $\text{C}_{13}\text{H}_{14}\text{NO}_6$ Requires: 280.0899.

2-(4-Nitrophenyl)pentanedioic acid (286)

Prepared according to the hydrolysis reaction procedure described for the synthesis of 281, using 285 (450 mg, 1.60 mmol), methanol (15 mL) and aqueous NaOH solution (15 mL). Product 286 was isolated as an oily residue (260 mg, 64%).

$\delta_H$ (400 MHz, DMSO-$d_6$): 8.20 (2 H, d, $J$ 8.8, H-2), 7.56 (2 H, d, $J$ 8.8, H-1), 3.78 (1 H, t, $J$ 6.8, H-3), 2.23-2.08 (3 H, m, H-4a, H-5), 1.95-1.88 (1 H, m H-4b).

HRMS (m/z – ESI): Found: 252.0577 (M-H) $\text{C}_{11}\text{H}_{10}\text{NO}_6$ Requires: 252.0586

3-(4-Nitrophenyl)dihydro-2H-pyran-2,6(3H)-dione (258)

An oven dried 50 mL round-bottomed flask containing a magnetic stirring bar was charged with 286 (260 mg, 1.27 mmol). Freshly distilled acetyl chloride (7 mL) was added, the flask was fitted with a condenser and the reaction mixture was heated at reflux temperature under an argon atmosphere for 12 h. Acetyl chloride was then removed in vacuo to obtain 258 as pale yellow needles (135 mg, 42%). M.p. 135 °C, (lit.$^{255}$ m.p. 136 °C).
Experimental procedures and data

δ_H (400 MHz, DMSO-d_6): 8.24 (2 H, d, J 8.8, H-2), 7.62 (2 H, d, J 8.8, H-1), 4.38 (1 H, dd, J 5.4, 13.2, H-3), 3.04-2.94 (1 H, m, H-5a), 2.92-2.86 (1 H, m, H-5b), 2.48-2.43 (1 H, m, H-4a), 2.07-2.01 (1 H, m, H-4b).

2,2'-(tert-Butoxycarbonyl)azanediyl)diacetic acid (290)\(^{256}\)

A 250 mL round-bottomed flask containing a magnetic stirring bar was charged with iminodiacetic acid (289, 2.55 g, 19.1 mmol) in 50% (v/v) aqueous THF (50 mL). Sodium bicarbonate (6.38 g, 76 mmol) was slowly added and the solution was stirred for 10 min. Then di-tert-butyl dicarbonate (5.0 g, 23 mmol) was added. The reaction mixture was stirred for 2 days. The solvent was then removed under reduced pressure, the aqueous layer was washed with ether (2 x 15 mL), acidified with HCl (6 N, 15 mL) to pH = 1 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to give 290 (1.20 g, 26%). M.p 130 °C, (lit.,\(^{256}\) m.p 144-145 °C).

Spectral data for this compound were consistent with those in the literature.\(^{257}\)

δ_H (400 MHz, CDCl_3): 4.16 (2 H, s, H-1), 4.01 (2 H, s, H-2), 1.46 (9 H, s, H-3).

tert-Butyl 2,6-dioxomorpholine-4-carboxylate (259)\(^{257}\)

An oven dried 25 mL round-bottomed flask containing a magnetic stirring bar was charged with N-cyclohexylcarbodiimide, N'-methyl polystyrene (373 mg, 0.857 mmol). Freshly distilled CH_2Cl_2 (6 mL) was added and the suspension was gently stirred for 10 min. 290 (100 mg, 0.428 mmol) was added, the flask was fitted with a condenser and the reaction mixture was stirred under an argon atmosphere for 16 h. The resin was filtered
and the resulting solution was concentrated in vacuo yielding an off-white solid (70.0 mg, 76%). M.p 126 °C, (lit.,\textsuperscript{257} m.p. 110-111 °C).

Spectral data for this compound were consistent with those in the literature.\textsuperscript{257}

\[ \delta_H (400 \text{ MHz, CDCl}_3): \quad 4.42 (4 \text{ H, s, H-1}), 1.49 (9 \text{ H, s, H-2}). \]

2,2'-(Tosylazanediyl)diacetic acid (291)

\[
\begin{align*}
\text{O}_2\text{S} &\quad \text{N} \quad \text{CO}_2\text{H} \\
1 &\quad 2 &\quad 3 \\
\end{align*}
\]

A 250 mL round-bottomed flask containing a magnetic stirring bar was charged with an aqueous solution of NaOH (2 N, 45 mL). Iminodiacetic acid (289, 3.00 g, 22.5 mmol) was added and the solution was stirred for 15 min. A solution of tosyl chloride (6.42 g, 33.7 mmol) in diethyl ether (40 mL) was added over the course of 2 h and the mixture was stirred for 4 h. The ether layer was discarded, the aqueous layer was acidified to pH = 1 with concentrated HCl and the precipitate was separated, dried over Na\textsubscript{2}SO\textsubscript{4} and crystallised from water to give 291 (3.14 g, 47%). M.p. 172 °C.

\[ \delta_H (400 \text{ MHz, DMSO-}d_6): \quad 7.68 (2 \text{ H, d } J 7.9, \text{ H-1}), 7.35 (2 \text{ H, d, } J 7.9, \text{ H-2}), 4.12 (4 \text{ H, s, H-4}), 2.37 (3 \text{ H, s, H-3}). \]

4-Tosylmorpholine-2,6-dione (260)

\[
\begin{align*}
\text{O}_2\text{S} &\quad \text{N} \quad \text{O} \\
1 &\quad 2 &\quad 3 \\
\end{align*}
\]

A 25 mL round-bottomed flask containing a magnetic stirring bar was charged with 291 (500 mg, 1.74 mmol). Freshly distilled acetyl chloride (7 mL) was added, the flask was fitted with a condenser and the reaction mixture was stirred at reflux under an argon atmosphere for 16 h. The acetyl chloride was then removed in vacuo to obtain 260 as a white solid (220 mg, 47%). M.p. 142-145 °C.
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Experimental procedures and data

\[ \delta_H (400 \text{ MHz, CDCl}_3): \quad 7.68 (2 \text{ H, d, } J 7.8, \text{ H-1}), 7.40 (2 \text{ H, d, } J 7.8, \text{ H-2}), 4.22 (4 \text{ H, s, H-4}), 2.46 (3 \text{ H, s, H-3}). \]

\[ \delta_C (100 \text{ MHz, CDCl}_3): \quad 160.7 (\text{C=O}), 146.2 (q), 131.7 (q), 130.9, 127.7, 46.4, 21.8. \]

\[ \nu_{\text{max}} (\text{neat})/\text{cm}^{-1}: \quad 1830, 1774, 1596, 1429, 1354, 1240, 1168, 1106, 950, 872, 814. \]

**Dimethyl 2,2'-azanediyl diacetate (294)**

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{O}
\end{align*}
\]

An oven dried 100 mL round-bottomed flask containing a magnetic stirring bar was charged with a solution of thionyl chloride (8.8 mL) in methanol (80 mL). 289 (3.00 g, 22.5 mmol) was added and the solution was stirred for 12 h at reflux. The solvent was then removed *in vacuo* to give 294 as a white solid (2.00 g, 57%). M.p. 122-127 °C.

Spectral data for this compound were consistent with those in the literature.

\[ \delta_H (400 \text{ MHz, CDCl}_3): \quad 3.72 (6 \text{ H, s, H-1}), 3.46 (4 \text{ H, s, H-2}), 2.04 (1 \text{ H, s, H-3}). \]

**Dimethyl 2,2'-(benzoylazanediyl) diacetate (295)**

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{O}
\end{align*}
\]

A 250 mL round-bottomed flask containing a magnetic stirring bar was charged with 294 (2.00 g, 12.4 mmol) in anhydrous CH\(_2\)Cl\(_2\) (60 mL) followed by freshly distilled triethylamine (2.0 mL, 14.88 mmol) and the mixture was cooled at 0 °C. A solution of benzoyl chloride (1.6 mL, 13.6 mmol) in anhydrous CH\(_2\)Cl\(_2\) (10 mL) was added dropwise *via* syringe and the reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated and the residue was dissolved in diethyl ether (30 mL) and then washed with a saturated aqueous solution of NaHCO\(_3\) (3 x 15 mL) and H\(_2\)O (2 x 15 mL). The organic phase was dried over MgSO\(_4\) and filtered. The solvent was concentrated *in vacuo* to give 295 as a white solid (1.70 g, 52%). M.p. 80-85 °C., (lit.,\(^{299}\) m.p. 73-76 °C).
δ_H (400 MHz, CDCl₃): 7.44-7.36 (5 H, m, H-1, H-2, H-3), 4.32 (2 H, s, H-4), 4.13 (2 H, s, H-5), 3.76 (3 H, s, H-6), 3.73 (3 H, s, H-7).

2,2′-(Benzoylanediyldiacetic acid (296)

A round-bottomed flask containing a magnetic stirring bar was charged with 295 (1.00 g, 3.76 mmol) in a mixture of THF/water 3:1 (20 mL). Lithium hydroxide monohydrate (788 mg, 18.8 mmol) was added and the solution stirred at room temperature for 3 h. The reaction mixture was acidified by adding concentrated aqueous solution of HCl (5 mL) and extracted with EtOAc (15 mL x 3) to furnish 296 as a white solid (446 mg, 50%). M.p. 83-85 °C. (lit., 260 m.p 88-90 °C).

Spectral data for this compound were consistent with those in the literature.

δ_H (400 MHz, CDCl₃): 7.46-7.40 (5 H, m, H-1, H-2, H-3), 4.35 (2 H, s, H-4), 4.18 (2 H, s, H-5).

2-(Phenylsulfonyl)succinic acid (299)

A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with benzenesulfinic sodium salt (289, 4.35 g, 26.5 mmol) and dissolved in water (44 mL) at 0 °C. Maleic anhydride (298, 2.60 g, 26.5 mmol) was added. The reaction mixture was allowed to warm slowly to room temperature overnight. Then 10% aqueous solution of HCl was added and the mixture was extracted with EtOAc (2 x 15 mL). The combined organic layers were dried over MgSO₄ and the solvent was removed in vacuo to yield 299 as a brown solid (5.50 g, 80%).
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Experimental procedures and data

δ_H (400 MHz, CDCl_3):

HRMS (m/z – ESI):
Found: 281.0103 (M+Na)^+ C_{10}H_{10}O_{6}NaS Requires: 281.0096.

3-(Phenylsulfonyl)dihydrofuran-2,5-dione (262)_{231}

An oven dried 100 mL round-bottomed flask containing a magnetic stirring bar was charged with 299 (5.50 g, 21.3 mmol) and freshly distilled toluene (22 mL). Acetic anhydride (28 mL 7.95 mmol) was added, and the reaction mixture was heated at reflux for 3 h. The solvent was evaporated in vacuo and the resulting brown solid was washed several times with cold CH_2Cl_2 and collected in fritted funnel, yielding a white to light brown solid 262 (2.00 g, 39%). M.p. 130-132 °C, (lit.,_{231} m.p. 132-133 °C).

δ_H (400 MHz, CDCl_3):

Tert-butyl 2-(phenylsulfonyl)acetate (301)_{231}

An oven dried 100 mL round-bottomed flask containing a magnetic stirring bar was charged with benzenesulfinic acid sodium salt (289, 2.70 g, 16.1 mmol) and ethanol (90 mL). Tert-butyl bromoacetate (302, 2 mL, 13.4 mmol) was added to the solution. The reaction mixture was refluxed for 4 h and then concentrated in vacuo. The crude mixture was suspended in diethyl ether (75 mL) and washed with water (2 x 75 mL) and brine (75
mL). The organic layer was dried over MgSO$_4$ and concentrated in vacuo to yield 301 (2.60 g, 76%) as a clear oil.

Spectral data for this compound were consistent with those in the literature.$^{231}$

$\delta_H$ (400 MHz, CDCl$_3$): 7.59 (2 H, d, $J$ 8.0, H-1), 7.68 (1 H, t, $J$ 7.8, H-3), 7.58, (2 H, app. t, H-2), 4.03 (2 H, s, H-4), 1.36 (9 H, s, H-5).

HRMS ($m/z$ – ESI): Found: 279.0677 (M+Na)$^+$ C$_{12}$H$_{16}$O$_4$NaS Requires: 279.0667.

Di-tert-butyl 2-(phenylsulfonyl)pentanedioate (303)$^{231}$

An oven dried 100 mL round-bottomed flask containing a magnetic stirring bar was charged with 301 (2.60 g, 10.1 mmol), cesium carbonate (165 mg, 0.50 mmol), tert-butyl acrylate (302, 1.49 mL, 10.1 mmol) and acetonitrile (35 mL). The reaction mixture was heated at 50 °C overnight and then diluted with water (40 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexanes:EtOAc 8:2) to yield 303 (2.00 g, 51%).

Spectral data for this compound were consistent with those in the literature.$^{231}$

$\delta_H$ (400 MHz, CDCl$_3$): 7.90 (2 H, d, $J$ 7.9, H-1), 7.67 (1 H, t, $J$ 7.3, H-3), 7.56 (2 H, app. t, H-2), 4.00 (1 H, dd, $J$ 4.1, 10.3, H-4), 2.41-2.10 (4 H, m, H-5, H-6), 1.42 (9 H, s, H-8), 1.35 (9 H, s, H-7).

HRMS ($m/z$ – ESI): Found: 407.1504 (M+Na)$^+$ C$_{19}$H$_{28}$O$_6$NaS Requires: 407.1504.
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3-(Phenylsulfonyl)dihydro-2H-pyran-2,6(3H)-dione (263)\textsuperscript{231}

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{S} & \quad \text{O}
\end{align*}
\]

An oven dried 50 mL round bottom flask containing a magnetic stirring bar was charged with 303 (2 g, 5.2 mmol), CH\textsubscript{2}Cl\textsubscript{2} (22 mL) and trifluoroacetic acid (22 mL). The reaction mixture was stirred for 1 h and then concentrated \textit{in vacuo} and azeotropically distilled with CH\textsubscript{2}Cl\textsubscript{2}. Trifluoroacetic anhydride was added to the crude mixture and stirred overnight. The reaction mixture was concentrated \textit{in vacuo} and azeotroped with toluene. Filtering the off-white solid with diethyl ether yielded 263 (900 mg, 68%) as a white solid. M.p 138 °C (lit.\textsuperscript{231} m.p 122.2-122.8 °C).

Spectral data for this compound were consistent with those in the literature.\textsuperscript{231}

\[\delta_H (400 \text{ MHz, CDCl}_3): \quad 7.93 (2 \text{ H, d, } J \text{ 7.76, H-1}) 7.80 (1 \text{ H, } J \text{ 7.49, H-3}), 7.66 (2 \text{ H, t, } J \text{ 7.92, H-2}), 4.17 (1 \text{ H, app dd, H-4}), 3.35-3.25 (1 \text{ H, m, H-6a}), 2.91-2.84 (2 \text{ H, m, H-6b and H-5a}), 2.48-2.33 (1 \text{ H, m, H-5b}).\]

(2-Ethoxy-2-oxoethyl)triphenylphosphonium bromide (308)\textsuperscript{262}

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Br}
\end{align*}
\]

A round-bottomed flask containing a magnetic stirring bar was charged with triphenylphosphine (307, 6.50 g, 25.0 mmol) and toluene (65 mL). To the mixture was then added \textit{via} syringe ethyl bromoacetate (2.75 mL, 25.0 mmol), the flask was fitted with a condenser and the reaction was heated at 90 °C for 15 h. The mixture was cooled to room temperature and the solid formed was filtered, washed with diethyl ether (3 x 20 mL) and dried \textit{in vacuo} to give product 308 as a white solid (9.6 g, 90%). M.p. 150-152 °C, (lit.,\textsuperscript{261} m.p. 155-156 °C).

Spectral data for this compound were consistent with those in the literature.\textsuperscript{262}
\( \delta_H (400 \text{ MHz, CDCl}_3) \):

7.89 (6 H, dd, J 7.7, 13.4, H-1), 7.77 (3 H, t, J 7.7, H-3),
7.73-7.60 (6 H, m, H-2), 5.54 (2 H, d, J 13.7, H-4), 4.01 (2 H, q, J 7.2, H-5), 1.04 (3 H, t, J 7.2, H-6).

(E)-Ethyl 2-(2-oxindolin-3-ylidene)acetate (311)\(^{263}\)

A round-bottomed flask containing a magnetic stirring bar was charged with 308 (6.0 g, 14.0 mmol) and CH\(_2\)Cl\(_2\) (50 mL). To the mixture was then added an aqueous solution of NaOH (1.0 M, 50 mL) and the reaction was allowed to stir vigorously at room temperature for 15 min. The organic layer was separated and the aqueous phase was extracted with CH\(_2\)Cl\(_2\) (3 x 30 mL). The combined organic layers were dried over anhydrous MgSO\(_4\), filtered and concentrated \textit{in vacuo} to give a residue of the crude ylide (309, 4.8 g, 99%) that was then dissolved in toluene. To the reaction mixture was added isatin (310, 1.87 g, 12.7 mmol) and the reaction was stirred at room temperature for 12 h. The solvent was then removed under reduced pressure and the residue obtained was purified by flash column chromatography, (hexanes:EtoAc 8:2), to give 311 as an orange solid (2.45 g, 89%). M.p. 160 °C, (lit.\(^{263}\) m.p. 164-165 °C); TLC (hexanes:EtoAc, 8:2 v/v): \(R_f = 0.22\).

Spectral data for this compound were consistent with those in the literature.\(^{263}\)

\( \delta_H (400 \text{ MHz, CDCl}_3) \):

8.55 (1 H, d, J 7.7, H-1), 8.22 (1 H, bs, H-8), 7.31 (1 H, app. t, H-3), 7.04 (1 H, app. t, H-2), 6.87 (1 H, s, H-5), 6.84 (1 H, d, J 7.8, H-4), 4.32 (2 H, q, J 7.2, H-6), 1.36 (3 H, t, J 7.2, H-7).
(E)-**tert-**Butyl 3-(2-ethoxy-2-oxoethylidene)-2-oxindoline-1-carboxylate (147)<sup>263</sup>

A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with 311 (1.50 g, 6.91 mmol), DMAP (84.4 mg, 0.691 mmol – 10 mol%) and acetonitrile (30 ml) was added via syringe. To the mixture was then added a solution of (Boc)<sub>2</sub>O (1.81 g, 8.29 mmol) in acetonitrile (8 mL) dropwise via syringe over 20 min, and the reaction was stirred at room temperature for 15 h. The solvent was then removed under reduced pressure and the residue obtained was purified by flash column chromatography, (hexanes:EtOAc 8:2), to yield 147 as a yellow solid (1.96 g, 90%). M.p. 61-63 °C, (lit.,<sup>263</sup> m.p. 65-67 °C); TLC (hexanes:EtOAc, 9:1 v/v): R<sub>f</sub> = 0.50.

Spectral data for this compound were consistent with those in the literature.<sup>263</sup>

δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>): 8.68 (1 H, d, J 7.7, H-1), 7.90 (1 H, d, J 8.1, H-4), 7.42 (1 H, app. t, H-3), 7.17 (1 H, app. t, H-2), 6.90 (1 H, s, H-5), 4.33 (2 H, q. J 7.2, H-6), 1.66 (9 H, s, H-8), 1.35 (3 H, t, J 7.2, H-7).
5.2 Experimental procedures and data for Chapter 3

5.2.1 Procedure B: general procedure for the organocatalysed alcoholysis of phenylsuccinic anhydride at room temperature and conversion of the corresponding hemiesters to β- and α-aryl-γ-butyrolactones (Scheme 3.6)

A 10 mL reaction vial containing a magnetic stirring bar was charged with phenylsuccinic anhydride (141, 0.20 mmol) and the relevant catalyst (0.01 mmol - 5 mol%). The reaction vial was flushed with argon and fitted with a septum. MTBE (2 mL) was added via syringe followed by the appropriate alcohol (0.20 mmol). The solution was then allowed to stir at room temperature. When full conversion was detected by $^1$H-NMR spectroscopic analysis the solvent was removed under reduced pressure. In cases where conversion was not complete, the reaction was quenched by adding HCl (0.1 N, 2 mL) and the aqueous phase was extracted with EtOAc (3 x 2 mL). The organic phases were combined, dried over MgSO$_4$, and concentrated in vacuo to provide the desired hemiesters 330 and 331. To a solution of hemiesters (0.2 mmol) in THF (3.0 mL) was added dropwise via syringe a solution of LiBEt$_3$H in THF (1.0 mL, 1.0 mmol). The reaction mixture was allowed to stir at 0 °C for 30 min then at room temperature for additional 2.5 h under argon atmosphere. Water (1 mL) and HCl (1 N, 2 mL) were added and the mixture was stirred for another 4 h. The reaction mixture was extracted with diethyl ether (5 mL x 3) and combined organic phase were dried over MgSO$_4$ and filtered. The solvent was then removed in vacuo and the crude mixture was purified by flash chromatography (diethyl ether/hexanes 7:3 v/v) to afford lactones 332 and 333.

5.2.2 Procedure C: general procedure for the organocatalysed alcoholysis of the relevant anhydride at room temperature and conversion of the corresponding hemiesters to amides

A 10 mL reaction vial containing a magnetic stirring bar was charged with the relevant anhydride (0.20 mmol) and the relevant catalyst (0.01 mmol - 5 mol%). The reaction vial was flushed with argon and fitted with a septum. MTBE (2.0 mL) was added via syringe followed by the appropriate alcohol (0.20 mmol). The solution was then allowed to stir at room temperature. When full conversion was detected by $^1$H-NMR spectroscopic analysis the solvent was removed under reduced pressure. In cases where conversion was not complete, the reaction was quenched by adding HCl (0.1 N, 2 mL) and the aqueous phase
was extracted with EtOAc (3 x 5 mL). The organic phases were combined, dried over 
MgSO₄, and concentrated in vacuo to provide the desired hemiesters. A mixture of 
hemiesters (0.2 mmol) in anhydrous CH₂Cl₂ (4.0 mL) was cooled at 0 °C, a solution of 
thionyl chloride (17.7 µL, 0.2 mmol) in CH₂Cl₂ (2.0 mL) was then added and the reaction 
mixture was allowed to stir for 10 min under argon atmosphere. Freshly distilled Et₃N 
(70.0 µL, 0.5 mmol) and (R)-(+)-α-methylbenzylamine (398, 25.8 µL, 0.2 mmol) were 
added and the mixture was allowed to stir at 0 °C for 1 h and then at room temperature 
for an additional 1 h. The solvent was removed under reduced pressure and the residue 
was dissolved in EtOAc (10 mL). The solution was washed successively with 1.0 M 
aqueous solution of HCl (10 mL), saturated aqueous NaHCO₃ (10 mL) and saturated 
aqueous NaCl (10 mL). The organic layer was dried over MgSO₄ and filtered. The solvent 
was then removed in vacuo and the crude mixture was purified by flash chromatography 
(hexanes/EtOAc 1:1 v/v) to afford pure amide-esters.

5.2.3 Procedure D: general procedure for the synthesis of sulfonamide-derived 
cinchona alkaloid organocatalysts

A suspension of 9-epi-QA·3HCl (328, 1.15 mmol) in dry CH₂Cl₂ (12 mL) was stirred at 
room temperature. Triethylamine (5.0 equiv.) was then added via syringe and the 
resulting clear solution was cooled to 0° C. The relevant sulfonyl chloride (1.0 equiv.) 
was then slowly injected and the solution was allowed to warm up to room temperature 
and stirred for 15 h. After evaporation of the solvent, the crude residue was purified by 
flash chromatography affording the desired sulfonamide catalyst.

(S)-(6-Methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-
yl)methanamine·3HCl (380)²⁶⁴
A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with quinine (74, 5.00 g, 15.4 mmol), triphenylphosphine (4.85 g, 2.42 mmol) and dry THF (70 mL). Diisopropyl azodicarboxylate (DIAD) (3.6 mL, 18.5 mmol) was added via syringe at 0 °C under an argon atmosphere and the reaction mixture was stirred for 30 min. A solution of diphenylphosphoryl azide (DPPA, 4.0 mL, 18.5 mmol) in dry THF (30 mL) was then added dropwise. The reaction mixture was stirred for 12 h at room temperature and then heated at 50 °C for 2 h. Triphenylphosphine (5.3 g, 20 mmol) was added portionwise and the reaction was heated at 50 °C for 2 h. Water (5 mL) was then added at room temperature and the mixture was stirred for 4 h. The organic volatiles were removed in vacuo and the residue was dissolved in a 2.0 M aqueous solution of HCl (15 mL). The aqueous layer was washed with CH$_2$Cl$_2$ (3 x 15 mL) and concentrated in vacuo to afford 380 as yellow solid (5.73 g, 86%). M.p. 216-220 °C, (lit.,$^{265}$ m.p. 220-222 °C).

$\delta$H (400 MHz, D$_2$O):* 
9.04 (1 H, d, J 5.8, H-1), 8.29 (1 H, d, J 9.4, H-5), 8.15 (1 H, d, J 5.8, H-2), 7.94 (1 H, dd, J 2.4, 9.4 H-4), 7.84 (1 H, bs, H-3), 5.90 (1 H, ddd, J 6.8, 10.5, 17.2, H-14), 5.56 (1 H, d, J 10.6, H-6), 5.32-5.18 (2 H, m, H-15), 4.35-4.23 (1 H, m, H-7), 4.13 (3 H, s, H-16), 4.04-3.92 (1 H, m, H-12a), 3.85 (1 H, dd, J 10.6, 13.3, H-8b), 3.59-3.45 (2 H, m, H-8a, H-12b), 3.00-2.90 (1 H, m, H-9), 2.17-2.00 (3 H, m, H-10, H-11a and H-11b), 1.96-1.84 (1 H, m, H-13b), 1.18 (1 H, dd, J 7.2, 14.2, H-13a).

* The protic signal (H-17) is not visible in D$_2$O.

1,1,1-Trifluoro-N-((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)methanesulfonamide (374)
General procedure D was followed using trifluoromethanesulfonyl chloride (122.4 μL, 1.15 mmol) to afford 374 as a white solid (408.6 mg, 78%) after flash chromatography. M.p. 106-108 °C, [α]_D^20 = +25.8 (c = 0.86, CHCl₃).

δ_H (600 MHz, CDCl₃):
8.78 (0.8 H, d, J 4.4, H-1), 8.70 (0.2 H, d, J 4.4, H-1), 8.22 (0.2 H, d, J 2.3, H-3), 8.09 (1 H, d, J 9.1, H-5), 7.75 (0.8 H, d, J 4.3, H-2), 7.47-7.42 (1.8 H, m, 0.8 H-3, H-4), 7.26 (0.2 H, d, J 4.3, H-2), 5.71-5.61 (1 H, m, H-14), 5.35 (0.8 H, d, J 10.1, H-6), 5.18-5.10 (2 H, m, H-15), 4.74 (0.2 H, d, J 10.1, H-6), 4.14 (0.8 H, dd, J 9.2, 17.1, H-7), 4.01 (2.4 H, s, H-16), 3.91 (0.6 H, s, H-16), 3.84 (0.2 H, dd, J 9.2, 17.1, H-7), 3.77-3.70 (2 H, m, H-8a, H-12a), 3.50-3.40 ( 2H, m, H-9), 2.0-1.97 (3 H, m, H-11a, H-11b, H-10), 1.60-1.55 (1 H, m, H-13b), 1.25-1.22 (0.8 H, m, H-13a), 0.92-0.87 (0.2 H, m, H-13a).

δ_C (150 MHz, CDCl₃):
158.2 (q, major), 157.3 (q, minor), 148.1 (major), 147.1 (minor), 145.4 (q, major), 144.4 (q, major), 144.3 (q, minor), 141.4 (q, minor), 137.4 (minor), 136.7 (major), 132.0 (major), 131.8 (minor), 127.6 (q, major), 127.3 (q, minor), 121.8 (minor), 121.4 (q, J_CF 267, CF₃) 121.3 (major), 120.9 (minor), 120.6 (major), 117.4 (major), 117.2 (minor), 104.9 (minor), 101.0 (major), 64.8 (minor), 63.4 (major), 60.3 (minor), 55.8 (minor), 55.7 (major), 54.3 (major), 54.1 (minor), 53.5 (major), 41.1 (major), 40.6 (minor), 37.3 (minor), 36.9 (major), 29.7 (minor), 29.3 (minor), 27.0 (major), 24.9 (minor), 24.8 (major), 23.2 (major).

δ_F (376 MHz, CDCl₃):
-77.5 (major), -77.7 (minor).

ν_max (neat)/cm⁻¹:
2955, 1621, 1509, 1348, 1242, 1160, 1029, 853, 606.

HRMS (m/z - ESI):
General procedure D was followed using piperidine-1-sulfonyl chloride (161.5 μL, 1.15 mmol) to afford 375 as a yellow solid (336 mg, 62%) after flash chromatography. M.p. 88-90 °C, [α]D20 = +15 (c = 1.3, CHCl3).

δH (600 MHz, CDCl3):
- 8.84 (0.5, d, J 4.9, H-1), 8.70 (0.5 H, d, J 4.9, H-1), 8.07 (0.5 H, d, J 9.1, H-5), 8.05 (0.5 H, d, J 9.1, H-5), 7.86 (0.5 H, d, J 2.7, H-3), 7.64 (0.5 H, d, J 4.4, H-2), 7.58 (0.5 H, d, J 2.7, H-3), 7.43 (0.5 H, dd, J 2.4, 8.9, H-4), 7.41 (0.5 H, dd, J 2.4, 8.9, H-4), 7.29 (0.5 H, d, J 4.4, H-2), 5.74 (0.5 H, ddd, J 7.5, 10.1, 17.5, H-14), 5.66 (0.5 H, ddd, J 7.5, 10.1, 17.5, H-14), 4.14 (0.5 H, d, J 10.7, H-6), 5.07-4.93 (2 H, m, H-15), 4.47 (0.5 H, d, J 10.7, H-6), 4.01 (1.5 H, s, H-16), 3.98 (1.5 H, s, H-16), 3.56-3.53 (0.5 H, m, H-8b), 3.48-3.43 (0.5 H, m, H-8b), 3.40 (0.5 H, dd, J 10.0, 17.6, H-7), 3.33 (0.5 H, dd, J 10.0, 17.6, H-7), 3.30-3.23 (1 H, m, H-12a), 2.95-2.76 (2 H, m, H-8a, H-12b), 2.72-2.63 (4 H, m, H-17), 2.44-2.35 (1 H, m, H-9), 1.81-1.65 (3 H, m, H-11a, H-11b, H-10), 1.76-1.71 (2 H, m, H-18a), 1.48-1.37 (2 H, m, H-18b), 1.06 (0.5 H, dd, J 5.5, 12.9, H-13a), 0.87 (0.5 H, dd, J 5.5, 12.9, H-13a), 0.76-0.72 (2 H, m, H-19).

δC (150 MHz, CDCl3):
- 158.2 (q), 157.2 (q), 147.7, 147.1, 145.3 (q), 144.5 (q), 144.4 (q), 144.2 (q), 141.6, 140.2, 132.0, 131.8, 129.2 (q), 127.2 (q), 123.8, 121.9, 121.7, 119.8, 116.6, 115.3, 115.1, 164
114.9, 103.1, 100.8, 63.1, 56.1, 55.7, 55.3, 52.8, 46.2, 46.0, 40.5, 40.0, 39.3, 38.8, 27.4, 27.3, 27.2, 26.4, 25.1, 24.4, 24.3, 24.2, 23.1, 23.0.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3675, 2969, 1620, 1473, 1432, 1252, 1141, 774, 564.

HRMS ($m/z$ - ESI): Found: 471.2430 (M+H)\textsuperscript{+} C\textsubscript{25}H\textsubscript{35}N\textsubscript{4}O\textsubscript{3}S Requires: 471.2430.

N-((S)-(6-Methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinluclidin-2-yl)methyl)-4-nitrobenzenesulfonamide (376)

General procedure D was followed using 4-nitrobenzene sulfonyl chloride (255 mg, 1.15 mmol) to afford 376 as a yellow solid (433 mg, 74%) after flash chromatography. M.p. 120-122 °C, $[\alpha]_{D}^{20} = +30$ ($c = 1.2$, CHCl\textsubscript{3}).

$\delta$\textsubscript{H} (600 MHz, CDCl\textsubscript{3}): 8.70 (0.5 H, d, J 4.3, H-1), 8.48 (0.5 H, d, J 4.3, H-1), 8.01 (0.5 H, d, J 8.9, H-5), 7.94 (1 H, d, J 8.2, H-18), 7.83 (0.5 H, d, J 8.9, H-5), 7.68 (0.5 H, d, J 8.2, H-18), 7.53 (1 H, d, J 8.2, NH), 7.46 (0.5 H, dd, J 3.0, 9.5, H-4), 7.44 (0.5 H, d, J 2.7, H-3), 7.38 (1 H, d, J 8.2, H-19), 7.34 (0.5 H, d, J 2.7, H-3), 7.30 (0.5 H, d, J 4.1, H-2), 7.25 (0.5 H, d, J 4.1, H-2), 7.20 (0.5 H, dd, J 3.0, 9.5, H-4), 5.74-5.61 (1 H, m, H-14), 5.16 (0.5 H, d, J 10.7, H-6), 5.05-4.92 (2 H, m, H-15), 4.52 (0.5 H, d, J 10.7, H-6), 4.05 (1.5 H, s, H-16), 3.86 (1.5 H, s, H-16), 3.43 (0.5 H, dd, J 9.3, 17.2, H-7), 3.39-3.31 (1 H, m, H-8b), 3.19-3.09 (1 H, m, H-12a), 3.04 (0.5 H, dd, J 9.3, 17.2, H-7), 2.92-2.75 (2 H, m, H-8a, H-12b), 2.40-2.37 (1
H, m, H-9), 1.80-1.68 (3 H, m, H-11a, H-11b, H-10), 1.45-1.39 (1 H, m, H-13b), 1.02 (0.5 H, dd, J 7.9, 13.4, H-13a), 0.91 (0.5 H, dd, J 7.9, 13.4, H-13b).

δC (150 MHz, CDCl₃): 158.3 (q), 156.9 (q), 149.6 (q), 149.1 (q), 147.2, 146.9, 145.7 (q), 144.8 (q), 144.7 (q), 144.4 (q), 141.4 (q), 140.8, 140.2, 138.1 (q), 132.0, 131.9, 128.4 (q), 128.2, 127.8, 126.5 (q), 124.5, 123.3, 122.7, 121.6, 120.6, 120.3, 115.3, 115.0, 62.8, 60.8, 55.9, 55.8, 55.7, 55.5, 55.3, 52.7, 40.5, 40.1, 39.9, 39.4, 27.5, 27.4, 27.3, 27.2, 26.1, 24.9.

νmax (neat)/cm⁻¹: 3675, 2970, 1717, 1621, 1527, 1347, 1158, 734, 571.


2,5-Dichloro-N-((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)thiophene-3-sulfonamide (377)

General procedure D was followed using 2,5-dichlorothiophene-3-sulfonyl chloride (171 μL, 1.15 mmol) to afford 377 as a colorless solid (495 mg, 80%) after flash chromatography. M.p. 110-112 °C, [α]D²⁰ = +34 (c = 1.1, CHCl₃).

δH (600 MHz, CDCl₃): 8.71 (0.5 H, d, J 4.5, H-1), 8.69 (0.5 H, d, J 4.5, H-1), 8.04 (0.5 H, d, J 9.0, H-5), 8.0 (0.5 H, d, J 9.0, H-5), 7.59 (0.5 H, d, J 2.7, H-3), 7.53 (0.5 H, d, J 4.4, H-2), 7.44 (0.5 H, dd, J 2.5, 9.0, H-4), 7.39 (0.5 H, d, J 2.7, H-3), 7.35 (0.5 H, dd, J 2.5, 9.0, H-4), 7.29 (0.5 H, d, J 4.4, H-2), 6.36 (0.5 H, s,
H-17), 6.21 (0.5, s, H-17), 5.76-5.61 (1 H, m, H-14), 5.12 (0.5 H, d, J 10.5, H-6), 5.07-4.93 (2 H, m, H-15), 4.51 (0.5 H, d, J 10.5, H-6), 4.03 (1.5 H, s, H-16), 3.96 (1.5 H, s, H-16), 3.55 (0.5 H, dd, J 9.4, 17.7, H-7), 3.44-3.19 (2 H, m, H-8b, H-12a), 3.07 (0.5 H, dd, J 9.4, 17.7, H-7), 2.95-2.77 (2 H, m, H-8a, H-12b), 2.45-2.33 (1 H, m, H-9), 1.82-1.65 (3 H, m, H-11a, H-11b, H-10), 1.37-1.51 (1 H, m, H-13b), 1.01 (0.5 H, dd, J 7.5, 13.7, H-13a), 0.93 (0.5 H, dd, J 7.5, 13.7, H-13-a).

\( \delta_{C} (150 \text{ MHz, CDCl}_3): \)

158.2 (q), 157.1 (q), 147.5, 146.8, 145.0 (q), 144.5 (q), 141.4 (q), 141.2 (q), 140.7, 139.9, 138.4 (q), 135.8 (q), 135.2 (q), 132.0, 131.8, 130.5 (q), 128.1 (q), 126.8 (q), 126.4, 126.2 (q), 125.9 (q), 125.7, 124.5, 121.6, 121.5, 119.9, 115.5, 115.1, 102.1, 100.6, 62.8, 60.5, 55.8, 55.7, 55.6, 55.3, 55.2, 52.6, 40.6, 40.1, 39.3, 38.7, 27.7, 27.4, 27.3, 27.2, 26.1, 24.8.

\( \nu_{\text{max}} \text{ (neat)/cm}^{-1}: \)

2971, 1621, 1474, 1242, 1194, 1030, 879, 580.

HRMS (m/z - ESI):

Found: 538.0797 (M+H)

C\(_{24}\)H\(_{26}\)Cl\(_2\)N\(_3\)O\(_3\)S\(_2\)

Requires: 538.0787.

5-Chloro-N-((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)-4-nitrothiophene-2-sulfonamide (378)
Chapter 5

Experimental procedures and data

General procedure D was followed using 5-chloro-4-nitrothiophene-2-sulfonyl chloride (301 mg, 1.15 mmol) to afford 378 as a yellow solid (493 mg, 78%) after flash chromatography. M.p. 100-102 °C. \([\alpha]_D^{20} = +23 \quad (c = 1.0, \text{CHCl}_3)\).

\[\delta_H(600 \text{ MHz, CDCl}_3):\]
- 8.75 (0.5 H, d, J 4.4, H-1), 8.67 (0.5 H, d, J 4.4, H-1), 8.04 (0.5 H, d, J 9.3, H-5), 7.97 (0.5 H, d, J 9.3, H-5), 7.47-7.42 (2 H, m, H-3), (0.5) H-4, (0.5) H-2), 7.33-7.30 (1.5 H, m, (0.5) H-3, (0.5) H-4, (0.5) H-17), 7.14 (0.5 H, s, H-17), 5.76-5.61 (1 H, m, H-14), 5.17 (0.5 H, d, J 10.8, H-6), 5.08-4.92 (2 H, m, H-15), 4.52 (0.5 H, d, J 10.8, H-6), 4.04 (1.5 H, s, H-16), 3.92 (1.5 H, s, H-16), 3.48 (0.5 H, dd, J 9.6, 18.8, H-7), 3.44-3.19 (2 H, m, H-8b, H-12a), 3.03 (0.5 H, dd, J 9.6, 18.8, H-7), 2.97-2.75 (2 H, m, H-8a, H-12a), 2.46-2.36 (1 H, m, H-9), 1.80-1.67 (3 H, m, H-11a, H-11b, H-10), 1.54-1.42 (0.5 H, dd, J 7.3, 13.6, H-13a), 0.95 (0.5 H, dd, J 7.3, 13.6, H-13b).

\[\delta_C(150 \text{ MHz, CDCl}_3):\]
- 158.6 (q), 157.2 (q), 154.1 (q), 147.3, 147.2, 144.7 (q), 144.3 (q), 141.3 (q), 141.2 (q), 140.7, 139.8, 137.7 (q), 136.7 (q), 135.3 (q), 132.2, 132.1, 130.4 (q), 128.3 (q), 127.6, 126.9, 126.5 (q), 124.8, 121.6, 120.4, 120.2, 115.6, 115.1, 106.6, 103.3, 100.7, 62.9, 60.5, 55.9, 55.7, 55.6, 55.1, 53.0, 50.0, 40.6, 40.1, 39.4, 38.7, 27.6, 27.5, 27.2, 27.1, 26.1, 24.8.

\[\nu_{\text{max}} \text{ (neat)/cm}^{-1}:\]
- 2945, 1620, 1539, 1362, 1170, 1148, 920, 835, 563.

HRMS (m/z - ESI): Found: 549.1031 (M+H)+ \(\text{C}_{24}\text{H}_{26}\text{N}_{4}\text{O}_{5}\text{S}_{2}\text{Cl}\) Requires: 549.1033.
3-Phenyldihydrofuran-2,5-dione (Phenylsuccinic anhydride 141)

A 50 mL round-bottomed flask containing a magnetic stirring bar was charged with phenylsuccinic acid (316, 2.00 g, 10.3 mmol). Freshly distilled acetyl chloride (15 mL) was added, the flask was fitted with a condenser and the reaction mixture was heated at reflux temperature under an argon atmosphere for 16 h. The acetyl chloride was then removed in vacuo to obtain 141 as a white solid (1.81 g, 100%). M.p. 50-53 °C, (lit.266 m.p. 51-53 °C).

Spectral data for this compound were consistent with those in the literature.267


2-(4-Nitrophenyl)succinic acid (p-Nitrophenyl succinic acid, 324)

A three-necked oven-dried round-bottomed flask fitted with a thermometer and containing a magnetic stirring bar was charged with fuming HNO3 (15 mL) and cooled to 0 °C. Phenylsuccinic acid (316, 5.00 g, 25.7 mmol) was added portionwise while keeping the temperature below 20 °C. The solution was allowed to stir at 0 °C for 2 h, then crushed ice (15 g) and water (10 mL) were added to the reaction mixture. The white precipitate formed was filtered, washed with water and then recrystallised from water to obtain 324 as a white solid (3.60 g, 58%). M.p. 227-230 °C.
Experimental procedures and data

\( \delta_H (400 \text{ MHz, DMSO-d}_6) \): 12.5 (2 H, bs, H-5 and H-6), 8.20 (2 H, d, J 8.8, H-4), 7.61 (2 H, d, J 8.8, H-3), 4.08 (1 H, dd, J 5.6, 9.7, H-2), 3.01 (1 H, dd, J 9.7, 17.0, H-1b), 2.65 (1 H, dd, J 5.6, 17.0, H-1a).

\( \delta_C (100 \text{ MHz, DMSO-d}_6) \): 173.2 (C=O), 172.5 (C=O), 146.6 (q), 146.2 (q), 129.6, 123.5, 46.7, 36.8.

\( \nu_{\text{max}} \) (neat)/cm\(^{-1}\): 2860, 2578, 1700, 1598, 1520, 1435, 1344, 1257, 925, 730.

HRMS (m/z - ESI): Found: 238.0353 (M-H) \( \cdot \text{C}_{10}\text{H}_8\text{NO}_6 \) Requires: 238.0352.

3-(4-Nitrophenyl)dihydrofuran-2,5-dione (143)

A round-bottomed flask containing a magnetic stirring bar was charged with 324 (2.00 g, 8.36 mmol). Freshly distilled acetyl chloride (15 mL) was added, the flask was fitted with a condenser and the reaction mixture was heated at reflux under an argon atmosphere for 16 h. Acetyl chloride was then removed \textit{in vacuo} to obtain a brown oil that was purified by flash chromatography (hexanes:EtOAc 1:1) to furnish 143 as a viscous yellow oil (1.25 g, 68%).

Spectral data for this compound were consistent with those in the literature\(^{268}\)

\( \delta_H (400 \text{ MHz, CDCl}_3) \): 8.33 (2 H, d, J 8.8, H-4), 7.50 (2 H, d, J 8.8, H-3), 4.51 (1H, dd, J 7.2, 10.4, H-2), 3.55 (1 H, dd, J 10.4, 18.8, H-1a), 3.18 (1 H, J 7.2, dd, 18.8, H-1b).

HRMS (m/z - ESI): Found: 220.0243 (M-H) \( \cdot \text{C}_{10}\text{H}_8\text{NO}_5 \) Requires: 220.0246.
(S)-4-Phenylidihydrofuran-2(3H)-one (332, Table 3.25, entry 2)

Prepared according to general procedure B using phenylsuccinic anhydride (141, 35.3 mg, 0.20 mmol) and the catalyst 378 (5.60 mg, 0.01 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 330 and 331 (24:76 ratio, 0.2 mmol) was dissolved in THF (3.0 mL), LiBEt₃H in THF (1.0 mL, 1.0 mmol) was added. The reaction mixture was allowed to stir at 0 °C for 30 min then at room temperature for additional 2.5 h under an argon atmosphere. Water (1 mL) and aqueous solution of HCl (1 N, 2 mL) were added and the mixture was stirred for another 4 h. Upon purification by flash column chromatography eluting with 70:30 diethyl ether:hexanes, lactone 332 (obtained from hemiester 330) was isolated as a white solid (7.00 mg, 21%). M.p. 56–58 °C, (lit.,²⁶⁸ m.p. 60-62 °C); TLC (diethyl ether:hexanes, 7:3 v/v): Rₖ = 0.56, [α]₅⁺²₀ = +1.8 (c = 0.09, CHCl₃), (lit.¹⁹⁸ [α]₅⁺²₀ = -45.9 (c = 3.3, CHCl₃) for (R)-enantiomer).

CSP-HPLC analysis. Chiralpak AS (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min⁻¹, rt, UV detection at 254 nm, retention times: 27.7 min (minor enantiomer) and 30.8 min (major enantiomer).
Spectral data for this compound were consistent with those in the literature.²⁶⁹

δ_H (400 MHz, CDCl₃): 7.39-7.29 (3 H, m, H-1 and H-2), 7.29-7.23 (2 H, m, H-3), 4.65 (1 H, dd, J 7.9, 8.9, H-4a), 4.25 (1 H, dd, J 7.9, 9.0, H-4b), 3.77 (1 H, quint, J 8.6, H-5), 2.91 (1 H, dd, J 8.6, 17.4, H-6a), 2.66 (1 H, dd, J 9.2, 17.4, H-6b).
(R)-3-Phenyldihydrofuran-2(3H)-one (333, Table 3.25, entry 2)

Prepared according to general procedure B using phenylsuccinic anhydride (141, 35.3 mg, 0.20 mmol) and the catalyst 378 (5.6 mg, 0.01 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 330 and 331 (24:76 ratio, 0.2 mmol) was dissolved in THF (3.0 mL), LiBEt$_3$H in THF (1.0 mL 1.0 mmol) was added. The reaction mixture was allowed to stir at 0 °C for 30 min then at room temperature for additional 2.5 h under an argon atmosphere. Water (1 mL) and an aqueous solution of HCl (1 N, 2 mL) were added and the mixture was stirred for another 4 h. Upon purification by flash column chromatography eluting, with 70:30 diethyl ether:hexanes, lactone 332 (obtained from hemiester 331) was isolated as a white solid (22.0 mg, 68%). M.p. 45-46 °C, TLC (diethyl ether:hexanes, 7:3 v/v): R$_f$ = 0.40, [α]$_D^{20}$ = +1.3 (c = 0.12, CHCl$_3$). (lit. $^{197}$ [α]$_D^{20}$ = -4.4 (c =1.3, CHCl$_3$) for (S)-enantiomer).

CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 96/4, 0.8 mL min$^{-1}$, rt, UV detection at 254 nm, retention times: 22.3 min (major enantiomer) and 26.3 min (minor enantiomer).

δ$_H$ (400 MHz, CDCl$_3$): 7.38-7.25 (5 H, m, H-1, H-2, H-3), 4.47 (1 H, td, J 3.4, 9.0, H-4a), 4.34 (1 H, td, J 6.7, 9.0, H-4b), 3.80 (1 H, dd, J 3.8, 10.2, H-5), 2.75-2.67 (1H, m, H-6a), 2.48-2.38 (1 H, m, H-6b).

2,2,2-Tribromoethyl-2-(4-nitrophenyl)-4-oxo-4-(((R)-1-phenylethyl)amino)butanoate (399, Scheme 3.9)

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Prepared according to general procedure C using anhydride (143, 44.2 mg, 0.200 mmol) and the catalyst 378 (5.60 mg, 0.010 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.200 mmol). The mixture of hemiesters 396 and 397 (26:74 ratio, 0.200 mmol) was dissolved in anhydrous CH₂Cl₂ (4.0 mL), was cooled to 0 °C, a solution of thionyl chloride (17.7 μL, 0.2 mmol) in CH₂Cl₂ (2.0 mL) was then added and the reaction mixture was allowed to stir for 10 min under an argon atmosphere. Freshly distilled Et₃N (70.0 μL, 0.5 mmol) and (R)-(+)
-α-methylbenzylamine (398, 25.8 μL, 0.2 mmol) were added and the mixture was allowed to stir at 0 °C for 1 h and then at room temperature for an additional 1 h. Upon purification by flash column chromatography eluting with 50:50 hexanes:EtOAc, amide 399 (obtained from hemiester 396) was isolated as a white solid (18.0 mg, 15%). M.p. 112-114 °C, TLC (hexane/EtOAc, 1:1 v/v): Rf = 0.32; [α]D²⁰ = +2.1 (c = 0.015, CHCl₃).

δH (400 MHz, CDCl₃): 8.23 (2 H, d, J 8.9, H-1), 7.58 (2 H, d, J 8.9, H-2), 7.38-7.35 (3 H, m, H-9, H-11), 7.31 (2 H, d, J 6.8, H-10), 5.75 (1 H, d, J 7.9, H-6), 5.15-5.11 (1 H, m, H-7), 4.96 (1 H, d, J 12.2, H-5a), 4.81 (1 H, d, J 12.2, H-5b), 4.51 (1 H, dd, J 5.8, 8.8, H-3), 3.17 (1 H, dd, J 8.8, 15.2, H-4a), 2.69 (1 H, dd, J 5.8, 15.2, H-4b), 1.45 (3 H, d, J 6.4, H-8).

δC (100 MHz, CDCl₃): 170.1 (C=O), 168.1 (C=O), 147.5 (q), 144.3 (q), 142.6 (q), 129.3, 128.7, 127.6, 126.1, 124.0, 77.1, 49.1, 47.5, 39.1, 34.7 (q), 21.6.

νmax (neat)/cm⁻¹: 3665, 2297, 1754, 1540, 1413, 1245, 1070, 920, 717, 569.

2,2,2-Tribromoethyl-3-(4-nitrophenyl)-4-oxo-4-(((R)-1-phenylethyl)amino)butanoate (400, Scheme 3.9)

Prepared according to general procedure C using anhydride (143, 44.2 mg, 0.20 mmol) and the catalyst 378 (5.06 mg, 0.01 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 396 and 397 (26:74 ratio, 0.2 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (4.0 mL) and cooled to 0°C. Thionyl chloride (17.7 µL, 0.20 mmol) in CH$_2$Cl$_2$ (2.0 mL) was then added and the reaction mixture was allowed to stir for 10 min under an argon atmosphere. Freshly distilled Et$_3$N (70.0 µL, 0.5 mmol) and (R)-(++)-α-methylbenzylamine (398, 25.8 µL, 0.20 mmol) were added and the mixture was allowed to stir at 0°C for 1 h and then at room temperature for an additional 1 h. Upon purification by flash column chromatography eluting with 50:50 hexane:EtOAc, amide 400 (obtained from hemiester 397) in a diastereomeric ratio 60:40 was isolated as a white solid (70.5 mg, 58%). M.p. 112-114°C, TLC (hexanes/EtOAc, 1:1 v/v): R$_f$ = 0.45; [α]$_D^{20}$ = +1.7 (c = 0.03, CHCl$_3$).

Major diastereomer:

δ$_H$ (400 MHz, CDCl$_3$): 8.20 (2 H, d, J 7.7 H-1), 7.50 (2 H, d, J 7.7, H-2), 7.28-7.23 (3 H, m, H-8, H-10), 7.10 (2 H, d, J 6.68, H-9), 5.74 (1 H, d, J 7.7 NH), 5.15-5.10 (1 H, m, H-6), 4.96 (1 H, d, J 12.2, H-5a), 4.81 (1 H, d, J 12.2, H-5b), 4.08 (1 H, dd, J 5.6, 8.8, H-3), 3.51 (1 H, dd, J 8.8, 17.2, H-4a), 2.87 (1 H, dd, J 5.6, 17.2, H-4b), 1.51 (3 H, d, J 6.9, H-7).

δ$_C$ (100 MHz, CDCl$_3$): 169.7 (C=O), 169.3 (C=O), 147.5 (q), 145.4 (q), 142.5 (q), 128.9, 128.6, 127.5, 125.8, 124.2, 77.1, 49.5, 48.2, 37.6, 35.1 (q), 21.6.
HRMS (m/z - ESI):  

Minor diastereomer:

δ_H (400 MHz, CDCl₃): 8.20 (2 H, d, J 7.7 H-1), 7.55 (2 H, d, J 7.7, H-2), 7.34-7.25 (5 H, m, H-8, H-9, H-10), 5.76 (1 H, d, J 7.7 NH), 5.05 (1 H, m, H-6), 5.01 (1 H, d, J 12.0, H-5a), 4.90 (1 H, d, J 12.2, H-5b), 4.02 (1 H, dd, J 5.7, 9.0, H-3), 3.43 (1 H, dd, J 9.0, 17.3, H-4a), 2.83 (1 H, dd, J 5.7, 17.3, H-4b), 1.36 (3 H, d, J 6.9, H-7).

δ_C (100 MHz, CDCl₃): 169.6 (C=O), 169.5 (C=O), 147.0 (q), 145.4 (q), 142.5 (q), 128.9, 128.6, 127.8, 125.9, 124.0, 77.5, 49.8, 48.5, 37.5, 35.1 (q), 21.5.

4-(4-Methoxyphenyl)dihydrofuran-2(3H)-one (405, Scheme 3.11)

Prepared according to general procedure B using p-methoxy phenylsuccinic anhydride (388, 41.2 mg, 0.20 mmol) and the catalyst 378 (5.60 mg, 0.010 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 403 and 404 (32:68 ratio, 0.2 mmol) was dissolved in THF (3.0 mL), LiBEt₃H in THF (1.0 mL, 1.0 mmol) was added. The reaction mixture was allowed to stir at 0 °C for 30 min then at room temperature for additional 2.5 h under an argon atmosphere. Water (1 mL) and an aqueous solution of HCl (1 N, 2 mL) were added and the mixture was stirred for another 4 h. Upon purification by flash column chromatography eluting with 70:30 diethyl ether:hexanes, lactone 405 (obtained from hemiester 403) was isolated as a pale yellow solid (10.0 mg, 27%). M.p. 72-74 °C, (lit., ᵃᵣ,D = +36.8 (c =0.60, CHCl₃), (lit., ᵃᵣ,D = +36.8 (c =0.60, CHCl₃).
CSP-HPLC analysis. Chiralpak AS (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min\(^{-1}\), rt, UV detection at 254 nm, retention times: 46.3 min (major enantiomer) and 59.4 min (minor enantiomer).

\[\delta_H (400 \text{ MHz, CDCl}_3): 7.23 \ (2 \ H, \ d, \ J 8.7, \ H-1), 6.89 \ (2 \ H, \ d, \ J 8.7 \ H-2), 4.58 \ (1 \ H, \ dd, \ J 7.5, 8.9, \ H-3a), 4.31 \ (1 \ H, \ dd, \ J 6.8, 8.9, \ H-3b), 3.80 \ (3 \ H, \ s, \ H-4), 3.5 \ (1 \ H, \ quint, \ J 7.5, \ H-5), 2.89 \ (1 \ H, \ dd, \ J 7.5, 17.2, \ H-6a), 2.64 \ (1 \ H, \ dd, \ J 9.0, 17.2, \ H-6b).\]

**3-(4-Methoxyphenyl)dihydrofuran-2(3H)-one (406, Scheme 3.11)**

Prepared according to general procedure B using \(p\)-methoxy phenylsuccinic anhydride (388, 41.2 mg, 0.20 mmol) and the catalyst 378 (5.60 mg, 0.010 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 401 and 402 (32:68 ratio, 0.2 mmol) was dissolved in THF (3.0 mL), LiBE\(\text{t}_3\)H in THF (1.0 mL, 1.0 mmol) was added. The reaction mixture was allowed to stir at 0 \(^\circ\)C for 30 min then at room temperature for additional 2.5 h under an argon atmosphere. Water (1 mL) and an aqueous solution of HCl (1 N, 2 mL) were added and the mixture was stirred for another 4 h. Upon purification by flash column chromatography eluting with 70:30 diethyl ether:hexane, lactone 406 (obtained from hemisteer 404) was isolated as a pale yellow solid (10.0 mg, 27%). M.p. 68-70 \(^\circ\)C, TLC (diethyl ether:hexanes, 7:3 v/v): \(R_f = 0.42\), [\(\alpha\)]\(_D\)\(^{20}\) = +2.7 (c = 0.03, CHCl\(_3\)).

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: 16.0 min (major enantiomer) and 18.5 min (minor enantiomer).

\[\delta_H (400 \text{ MHz, CDCl}_3): 7.28 \ (2 \ H, \ d, \ J 8.5, \ H-1), 7.01 \ (2 \ H, \ d, \ J 8.5 \ H-2), 4.52 \ (1 \ H, \ m, \ H-3a), 4.38 \ (1 \ H, \ ddd, \ J 6.5, 9.1, 9.1, \ H-3b), 3.81 \ (3\]
H, s, H-4), 3.79 (1 H, q, J 8.4, H-5), 2.75 (1 H, m, H-6a), 2.54 (1 H, m, H-6b).

$\delta_C$ (100 MHz, CDCl$_3$): 176.2 (C=O), 156.9 (q), 139.5 (q), 128.6, 128.4, 69.7, 56.2, 44.2, 31.8.


2-(1,3-Dioioisoindolin-2-yl)succinic acid (411)

A 100 mL round-bottomed flask containing a stirring bar was charged with phthalic anhydride (410) (1.10 g, 7.42 mmol), D,L-aspartic acid (409) (1.00 g, 7.51 mmol) and acetic acid (15 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 in vacuo, water (5 mL) was added to the residue and the solid formed was filtered, washed with cold water and recrystallised from H$_2$O to give 411 (1.62 g, 82%) as a white solid. Spectral data for this compound were consistent with those in the literature. M.p. 220-224 °C, (lit., 271 m.p. 227-230 °C).

$\delta_H$ (400 MHz, DMSO-$d_6$): 12.51 (2 H, bs, COOH), 7.93-7.88 (4 H, m, H-1 and H-2), 5.13 (1 H, app. t, H-3), 3.13 (1 H, dd, J 7.4, 16.8, H-4a), 2.93 (1 H, dd, J 7.1, 16.8, H-4b).

2-(2,5-Dioxotetrahydrofuran-3-yl)isoindoline-1,3-dione (389)

A 50 mL round-bottomed flask containing a stirring bar was charged with 411 (1.00 g, 3.80 mmol). Acetic anhydride (13 mL) was added, the flask was fitted with a condenser and the reaction mixture was heated at reflux temperature for 2 h. Acetic anhydride was
removed under reduced pressure and the residue obtained was triturated with diethyl ether (5 mL), filtered and dried to obtain 389 as a white solid (838 mg, 90%). Spectral data for this compound were consistent with those in the literature.\textsuperscript{272} M.p. 222-225 °C (lit.,\textsuperscript{273} m.p. 227 °C).

\[ \delta_H (400 \text{ MHz, DMSO-}d_6): \quad 7.97-7.83 \text{ (4 H, m, H-1 and H-2), } 5.55 \text{ (1 H, dd, } J 6.5, 9.7, \text{ H-3), } 3.49-3.31 \text{ (2 H, m, H-4a, H-4b).} \]

4-Methyl 1-(2,2,2-tribromoethyl)2-(1,3-dioxoisooindolin-2-yl)succinate (414, Table 3.27, entry 1)

Prepared according to the general procedure C using anhydride 389 (49.9 mg, 0.2 mmol) and the catalyst 378 (5.60 mg, 0.010 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 412 and 413 (40:60 ratio) was dissolved in MeOH (5.0 equiv.), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 1.2 equiv.) 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 diesters was purified by flash chromatography eluting with 50:50 hexane:EtOAc, diester 415 (obtained from hemiester 412) was isolated as a white solid (13.4 mg, 11%). M.p. 175-177 °C, TLC (hexane/EtOAc, 1:1 v/v): \( R_f = 0.49 \), \([\alpha]_D^{20} = +0.9 \) (c = 0.018, CHCl\textsubscript{3}).

CSP-HPLC analysis. Chiralpak ODH (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min\textsuperscript{-1}, rt, UV detection at 254 nm, retention times: 27.0 min (major enantiomer) and 42.4 min (minor enantiomer).

\[ \delta_H (400 \text{ MHz, CDCl}_3): \quad 7.91 \text{ (2 H, dd, } J 3.1, 5.6, \text{ H-1), } 7.78 \text{ (2 H, dd, } J 3.1, 5.6, \text{ H-2), } 5.61 \text{ (1 H, dd, } J 6.1, 8.4, \text{ H-3), } 4.91 \text{ (2 H, s, H-4), } 3.73 \text{ (3 H, s, H-5), } 3.52 \text{ (1 H, dd, } J 6.1, 16.7, \text{ H-6a), } 3.27 \text{ (1 H, dd, } J 8.4, 16.7, \text{ H-6b).} \]
Experimental procedures and data

\[ \delta_c (100 \text{ MHz, CDCl}_3): \]

170.2 (C=O), 167.1 (2 x C=O), 166.7 (C=O), 134.4, 131.7 (q), 131.5 (q), 123.7, 52.3, 48.2, 33.6 (q), 29.7, 22.6.

\[ \nu_{\text{max}} (\text{neat})/\text{cm}^{-1}: \]

3664, 2971, 1745, 1549, 1411, 1243, 1065, 922, 718, 566.

HRMS (m/z - ESI):  Found: 561.8229 (M+Na)\(^+\) \(\text{C}_{15}\text{H}_{12}\text{Br}_3\text{NNaO}_6\) Requires: 561.8225.

**1-Methyl 4-(2,2,2-tribromoethyl)2-(1,3-dioxoisindolin-2-yl)succinate (415, Table 3.27, entry 1)**

Prepared according to general procedure C using anhydride 389 (49.9 mg, 0.20 mmol) and the catalyst 378 (5.60 mg, 0.010 mmol). MTBE (2 mL) was added *via* syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 412 and 413 (40:60 ratio) was dissolved in MeOH (5.0 equiv.), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 1.2 equiv.) 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 diesters was purified by flash chromatography eluting with 50:50 hexane:EtOAc, diester 416 (obtained from hemiester 413) was isolated as a brown solid (18.5 mg, 17%). M.p. 172-175°C, TLC (hexane/EtOAc, 1:1 v/v): R\(_f\) = 0.51, [\(\alpha\)]\(_D\)\(^{20}\) = +1.5 (c = 0.020, CHCl\(_3\)).

CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 70/30, 1.0 mL min\(^{-1}\), rt, UV detection at 254 nm, retention times: 18.6 min (minor enantiomer) and 37.4 min (major enantiomer).

\[ \delta_h (400 \text{ MHz, CDCl}_3): \]

7.90 (2 H, dd, J 3.1, 5.6, H-1), 7.78 (2 H, dd, J 3.1, 5.6, H-2), 5.48 (1 H, dd, J 5.8, 8.9, H-3), 4.95 (2 H, s, H-4), 3.79 (3 H, s, H-5), 3.59 (1 H, dd, J 5.8, 17.1, H-6a), 3.36 (1 H, dd, J 8.9, 17.1, H-6b).
\( \delta_{C} (100 \text{ MHz, CDCl}_3): 170.1 (C=O), 168.4 (2 \times C=O), 167.2 (C=O), 134.4, 131.7 (q), 131.6 (q), 123.7, 53.2, 48.1, 33.8 (q), 29.7, 22.7 \).

HRMS (m/z - ESI): Found: 561.8227 (M+Na)\(^+\) \( \text{C}_{15}\text{H}_{12}\text{Br}_3\text{NNaO}_6 \) Requires: 561.8226.

**Dimethyl 2-hydroxysuccinate (418)**

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{O} \quad \text{OH} \\
\end{align*}
\]

An oven dried 100 mL round-bottomed flask containing a stirring bar was fitted with a septum and then placed under an argon atmosphere (balloon). Racemic malic acid (417) (2.50 g, 18.6 mmol) and MeOH (15 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 was removed \textit{in vacuo} and the residue was washed with EtOAc (30 mL), then extracted with a saturated aqueous solution of NaHCO\(_3\) (3 x 20 mL), dried over MgSO\(_4\), filtered and the solvent was removed \textit{in vacuo} to yield 418 (2.32 g, 77%) as a colourless oil.

Spectral data for this compound were consistent with those in the literature.\(^{274}\)

\( \delta_{H} (400 \text{ MHz, CDCl}_3): 4.51 (1 \text{ H, app. t, H-3}), 3.80 (3 \text{ H, s, H-2}), 3.70 (3 \text{ H, s, H-1}), 3.25 (1 \text{ H, bs, OH}), 2.92-2.74 (2 \text{ H, m, H-4}). \)

**Dimethyl 2-(benzyloxy)succinate (420)**

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

A 100 mL round-bottomed flask containing a stirring bar was charged with 418 (1.50 g, 9.26 mmol) in EtOAc (20 mL). Silver (I) oxide (3.20 g, 13.8 mmol) and benzyl bromide (1.35 mL, 11.1 mmol) were added and the reaction mixture was allowed to stir at room
temperature for 16 h. The solution was filtered through a celite pad and the crude residue was purified by flash chromatography eluting in gradient from 100% hexane to 10% EtOAc in hexane and isolated 420 (1.49 g, 64%) as a yellow oil.

\[ \delta_H (400 \text{ MHz, CDCl}_3): \]
- 7.35-7.29 (5 H, m, H-1, H-2, H-3),
- 4.71 (H, d, J 11.5 H-4a),
- 4.60 (1 H, d, J 11.5, H-4b),
- 4.38 (1 H, dd J 5.1, 7.6, H-5),
- 3.75 (3 H, s, H-6),
- 3.66 (3 H, s, H-7),
- 2.79 (2 H, m, H-8).

HRMS (m/z - ESI):
- Found: 251.0906 (M-H) \text{C}_{13}\text{H}_{15}\text{O}_5 \text{Requires: 251.0910.}

2-(Benzyloxy)succinic acid (421)

\[
\text{HO} \quad \text{O} \quad \text{OH} \\
\text{O} \quad \text{4a,b} \quad \text{4a,b} \\
3 \quad 2 \quad 1
\]

A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with 420 (1.00 g, 4.46 mmol) and THF/MeOH 1:1 (50 mL). A solution of NaOH (0.1 N) in water (50 mL) was added and the reaction mixture was refluxed for 24 h. The solution was partially neutralised with an aqueous solution of HCl (3 N). The aqueous mixture was extracted with diethyl ether (3 x 15 mL) and dried with Na$_2$SO$_4$ to give 421 (670 mg, 67%) as a pale yellow oil.

\[ \delta_H (400 \text{ MHz, CDCl}_3): \]
- 7.35-7.28 (5 H, m, H-1, H-2, H-3),
- 4.72 (1 H, d, J 11.3, H-4a),
- 4.65 (1 H, d, J 11.3, H-4b),
- 4.38 (1 H, dd, J 5.1, 7.3, H-5),
- 2.91-2.84 (2 H, m, H-6a, H-6b)

HRMS (m/z - ESI):
- Found: 223.0707 (M-H) \text{C}_{11}\text{H}_{11}\text{O}_5 \text{Requires: 223.0710.}

3-(Benzyloxy)dihydrofuran-2,5-dione (390)

\[
\text{O=O} \quad \text{O} \\
\text{6b} \quad \text{4a,b} \\
\text{6a} \quad \text{2} \\
3
\]
An oven dried round-bottomed flask containing a stirring bar was charged with 421 (500 mg, 2.23 mmol) and freshly distilled acetyl chloride (10 mL). The apparatus was fitted with a condenser and a septum, placed under an argon atmosphere and the reaction mixture was stirred at room temperature for 24 h. The excess acetyl chloride in excess was removed in vacuo and the residue was triturated with diethyl ether (5 mL) and filtered to obtain 390 (156 mg, 34%) as a pale yellow solid. M.p. 108-110 °C.

δH (400 MHz, CDCl3): 7.38-7.29 (5 H, m, H-1, H-2, H-3), 4.79 (1 H, m, H-5), 4.76 (1 H, d, J 12.4, H-4a), 4.94 (1 H, d, J 12.4, H-4b), 3.24 (1 H, dd, J 10.5, 19.9, H-6b), 3.07 (1 H, dd, J 6.5, 19.9, H-6a).

3-(Benzyloxy)dihydrofuran-2(3H)-one (423, Scheme 3.15)

Prepared according to general procedure B using anhydride 390 (41.2 mg, 0.20 mmol) and the catalyst 378 (5.60 mg, 0.010 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The hemiesters 422 was dissolved in THF (3.0 mL), LiBEt₃H in THF (1.0 mL, 1.0 mmol) was added. The reaction mixture was allowed to stir at 0 °C for 30 min then at room temperature for additional 2.5 h under an argon atmosphere. Water (1 mL) and an aqueous solution of HCl (1 N, 2 mL) were added and the mixture was stirred for another 4 h. Upon purification by flash column chromatography eluting with 70:30 diethyl ether:hexanes, lactone 423 was isolated as a white solid (32.2 mg, 84%). M.p. 75-77 °C, (lit.,275 m.p 70-71 °C); TLC (diethyl ether:hexanes, 7:3 v/v): Rf = 0.45, [α]D²⁰ = +8.0 (c = 0.20, CHCl₃), (lit.,276 [α]D²⁰ = -28.7 (c =0.95, CHCl₃) for (S)-enantiomer).

CSP-HPLC analysis. Chiralpak AS (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min⁻¹, rt, UV detection at 254 nm, retention times: 60.3 min (major enantiomer) and 77.1 min (minor enantiomer).
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Experimental procedures and data

\[ \delta_H (400 \text{ MHz, CDCl}_3): \]

- 7.41-7.32 (5 H, m, H-1, H-2, H-3), 4.56 (1 H, d, J 11.7, H-4a), 4.52 (1 H, d, J 11.7, H-4b), 4.44-4.37 (3 H, m, H-5, H-7), 2.71-2.68 (2 H, m, H-6).

\[ \delta_C (100 \text{ MHz, CDCl}_3): \]

- 176.4 (C=O), 136.9 (q), 128.6, 128.2, 127.7, 73.8, 73.1, 71.2, 34.9.


2-Bromosuccinic acid (426)

\[
\begin{align*}
\text{HO} & \\
\text{Br} & \\
\text{O} & \\
\end{align*}
\]

A three neck round-bottomed flask containing a stirring bar and fitted with a thermometer was charged with racemic aspartic acid (409, 5.0 g, 37.5 mmol) and KBr (20.1 g, 169 mmol). A 3.0 M aqueous solution of \( \text{H}_2\text{SO}_4 \) (100 mL) was added and the reaction mixture was cooled to -5 °C. A solution of \( \text{NaNO}_2 \) (4.41 g, 63.8 mmol) in water (15 mL) was added dropwise to the reaction mixture over 1 h under vigorous stirring while maintaining the temperature below 5 °C. The solution was stirred for 2 h at a temperature between 0 °C and -5 °C. The reaction mixture was then extracted with AcOEt (4 x 50 mL), the combined organic extracts were washed with a half saturated aqueous solution of NaCl (50 mL), dried over \( \text{MgSO}_4 \), and concentrated \textit{in vacuo} to obtain 426 pure as a white solid (6.21 g, 84%). Spectral data for this compound were consistent with those in the literature.277 M.p. 174-177 °C, (lit.,278 m.p. 163-164 °C).

\[ \delta_H (400 \text{ MHz, DMSO-d}_6): \]

- 12.81 (2 H, bs, COOH), 4.51 (1 H, app. t, H-2), 3.09 (1 H, dd, J 8.5, 17.0, H-3a), 2.88 (1 H, dd, J 6.3, 17.0, H-3b).

3-Bromodihydrofuran-2,5-dione (391)

\[
\begin{align*}
\text{H} & \\
\end{align*}
\]
An oven dried round-bottomed flask containing a stirring bar was charged with 426 (1.00 g, 5.08 mmol) and acetic anhydride (10 mL). The apparatus was fitted with a condenser and a septum, placed under an argon atmosphere and the reaction mixture was heated at reflux temperature for 2 h. The excess acetic anhydride was removed in vacuo to obtain 391 (873 mg, 96%) as a yellow oil.

$$\delta_H (400 \text{ MHz, CDCl}_3):$$ 4.83 (1 H, dd, $J$ 4.1, 9.1, H-1), 3.71 (1 H, dd, $J$ 9.1, 19.7, H-2a), 3.29 (1 H, $J$ 4.1, 19.7, H-2b).

2-(Phenylthio)succinic acid (433)

An oven dried round-bottomed flask containing a stirring bar was charged with maleic acid (1.5 g, 12.9 mmol) anhydrous THF (25 mL) and freshly distilled triethylamine (4.5 mL, 32.3 mmol). Thiophenol (429) (1.5 mL, 14.2 mmol) was added via syringe and the reaction mixture was heated at reflux temperature for 16 h. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (15 mL), washed with a 2 M aqueous NaOH solution (2 x 25 mL). The aqueous phase was acidified with concentrated HCl (8 mL), the precipitate formed was filtered, washed with diethyl ether (5 mL) and dried to furnish 433 (2.63 g, 90%) as a white solid. M.p. 108-110 °C.

$$\delta_H (400 \text{ MHz, DMSO}-d_6):$$ 12.60 (2 H, bs, COOH), 7.46 (2 H, d, $J$ 7.8, H-4), 7.40-7.33 (3 H, m, H-5 and H-6), 3.90 (1 H, dd, $J$ 5.3, 9.4, H-2), 2.66 (1 H, dd, $J$ 9.4, 16.9, H-3a), 2.63 (1 H, dd, $J$ 5.3, 16.9, H-3b).

$$\delta_C (100 \text{ MHz, DMSO}-d_6):$$ 172.5 (C=O), 171.9 (C=O), 132.8, 132.6 (q), 129.7, 128.6, 45.5, 36.9.

$$\nu_{\text{max}} \text{ (neat)/cm}^{-1} :$$ 2887, 2642, 2539, 1694, 1412, 1295, 1170, 929, 740, 695.

3-(Phenylthio)dihydrofuran-2,5-dione (392)

An oven dried round-bottomed flask containing a stirring bar was charged with 433 (2.00 g, 8.85 mmol) and acetic anhydride (15 mL). The apparatus was equipped with a condenser and a septum and kept under an argon atmosphere (balloon). The reaction mixture was heated at reflux for 2 h, then concentrated under reduced pressure to give anhydride 392 (1.71 g, 93%) pure as a brown oil.

δ_H (400 MHz, DMSO-d_6): 7.55 (2 H, d, J 6.2, H-4), 7.41-7.31 (3 H, m, H-5 and H-6), 4.71 (1 H, dd, J 5.1, 9.8, H-2), 3.57 (1 H, dd, J 9.8, 18.6, H-3a), 3.03 (1 H, dd, J 5.1, 18.6, H-3b).

δ_C (100 MHz, DMSO-d_6): 171.5 (C=O), 169.6 (C=O), 134.5 (q), 132.3, 129.6 128.8, 44.5, 36.1.

ν_max (film)/cm⁻¹: 2989, 2938, 1869, 1780, 1210, 1127, 1057, 910, 744, 696.

HRMS (m/z -ESI): Found: 207.0118 [M-H] C_{10}H_7O_3S Requires: 207.0116.

3-(Phenylthio)dihydrofuran-2(3H)-one (438a)

Prepared according to general procedure B using anhydride 392 (41.6 mg, 0.20 mmol) and the catalyst 378 (5.6 mg, 0.010 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 436a and 437a (32:68 ratio) was dissolved in THF (3.0 mL) and LiBEt₃H in THF (1.0 mL, 1.0 mmol) was added. The reaction mixture was allowed to stir at 0 °C for 30 min then at room temperature for additional 2.5 h under an argon atmosphere. Water (1 mL) and an aqueous solution of HCl (1 N, 2 mL) were added and the mixture was stirred for another 4 h. Upon
purification by flash column chromatography eluting with 70:30 diethyl ether:hexane, lactone 438a (obtained from hemiester 436a) was isolated as a colorless oil (8.70 mg, 21%), TLC (diethyl ether:hexane, 7:3 v/v): \( R_f = 0.38, [\alpha]_D^{20} = +46 \) (c = 0.30, CHCl₃).

CSP-HPLC analysis. Chiralpak 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: 19.5 min (minor enantiomer) and 21.3 min (major enantiomer).

\( \delta_H (400\text{ MHz, CDCl}_3): \) 7.54 (2 H, d, J 8.8, H-1), 7.30-7.34 (3 H, m, H-2, H-3), 4.26-4.18 (2 H, m, H-4), 3.84 (1 H, dd, J 6.1, 8.7, H-5), 2.61-2.70 (1 H, m, H-6a), 2.31-2.22 (1 H, m, H-6b).

4-(Phenylthio)dihydrofuran-2(3H)-one (439a)

Prepared according to general procedure B using anhydride 392 (41.6 mg, 0.20 mmol) and the catalyst 378 (5.60 mg, 0.010 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 436a and 437a (32:68 ratio) was dissolved in THF (3.0 mL), and LiBEt₃H in THF (1.0 mL, 1.0 mmol) was added. The reaction mixture was allowed to stir at 0 °C for 30 min then at room temperature for additional 2.5 h under an argon atmosphere. Water (1 mL) and an aqueous solution of HCl (1 N, 2 mL) were added and the mixture was stirred for another 4 h. Upon purification by flash column chromatography eluting with 70:30 diethyl ether:hexanes, lactone 439a (obtained from hemiester 437a) was isolated as a colorless oil (21.2 mg, 51%), TLC (diethyl ether:hexane, 7:3 v/v): \( R_f = 0.32, [\alpha]_D^{20} = +1.5 \) (c = 0.03, CHCl₃). (lit.\(^{279} [\alpha]_D^{20} = +36.6 \) (c =1.16, CHCl₃).

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: 15.2 min (major enantiomer) and 34.4 min (minor enantiomer).
\( \delta_H \) (400 MHz, CDCl_3): 7.41 (2 H, d, \( J \) 7.6, H-1), 7.30-7.36 (3 H, m, H-2, H-3), 4.52 (1 H, dd, \( J \) 7.1, 9.8, H-4a), 4.19 (1 H, dd, \( J \) 5.5, 9.8, H-4b), 3.99 (1 H, quint, \( J \) 5.5 H-5), 2.88 (1 H, dd, \( J \) 8.0, 17.4 H-6a), 2.52 (1 H, dd, \( J \) 5.5, 17.4 H-6b).

2-((2,6-Dimethylphenyl)thio)succinic acid (434)

An oven dried round-bottomed flask containing a stirring bar was charged with maleic acid (1.50 g, 12.9 mmol) anhydrous THF (25 mL) and freshly distilled triethylamine (4.50 mL, 32.3 mmol). 2,2-dimethylthiophenol (430) (1.9 mL, 14.2 mmol) was added via syringe and the reaction mixture was heated at reflux temperature for 16 h. The solvent was removed under reduced pressure and the residue was extracted with EtOAc (15 mL), washed with a 2.0 M aqueous solution of NaOH (2 x 25 mL). The aqueous phase was acidified with concentrated HCl, the precipitate formed was filtered, washed with diethyl ether (5 mL) and dried to furnish 434 (2.9 g, 88%) as a white solid. M.p. 192-194 °C.

\( \delta_H \) (400 MHz, DMSO-\( \text{d}_6 \)): 7.21-7.14 (3 H, m, H-1, H-2), 4.58 (1 H, dd, \( J \) 4.7, 10.4, H-3), 2.74 (1 H, dd, \( J \) 10.4, 16.9 H-4a), 2.57 (1 H, dd \( J \) 4.7, 16.9, H-4b), 2.46 (6 H, s, H-5).

\( \delta_C \) (100 MHz, DMSO-\( \text{d}_6 \)): 172.4 (C=O), 171.8 (C=O), 143.5 (q), 130.7 (q), 129.3, 128.3, 45.1, 36.2, 21.6.

\( \nu_{\text{max}} \) (neat)/cm\(^{-1}\): 3675, 2971, 1691, 1540, 1363, 1066, 920, 773, 564.

HRMS (m/z -ESI): Found: 277.0515 [M+Na]\(^+\) \( \text{C}_{12}\text{H}_{14}\text{O}_4\text{NaS} \) Requires: 277.0505.
Chapter 5

Experimental procedures and data

3-((2,6-Dimethylphenyl)thio)dihydrofuran-2,5-dione (393)

An oven dried round-bottomed flask containing a stirring bar was charged with 434 (2.25 g, 8.85 mmol) and acetic anhydride (15 mL). The apparatus was equipped with a condenser and a septum and kept under an argon atmosphere (balloon). The reaction mixture was heated at reflux for 2 h, then concentrated under reduced pressure to give anhydride 393 (1.81 g, 87%) pure as a dark brown oil.

δ_H (400 MHz, DMSO-d_6): 7.26-7.16 (3 H, m, H-1, H-2), 4.22 (1 H, dd, J 5.3, 9.5, H-3), 3.50 (1 H, dd, J 9.5, 18.8, H-4a), 2.97 (1 H, dd, J 5.3, 18.8, H-4b), 2.48 (6 H, s, H-5).

δ_C (100 MHz, DMSO-d_6): 171.3 (C=O), 170.1 (C=O), 143.2 (q), 130.5 (q), 129.7, 128.4, 44.2, 36.1, 21.6.

ν_{max} (neat)/cm^{-1}: 2985, 2938, 1867, 1780, 1210, 1126, 1050, 914, 745, 696.

HRMS (m/z -ESI): Found: 259.0390 [M+Na]^+ C_{12}H_{12}O_3NaS Requires: 259.0399.

3-((2,6-Dimethylphenyl)thio)dihydrofuran-2(3H)-one (438b)

Prepared according to general procedure B using anhydride 393 (47.3 mg, 0.20 mmol) and the catalyst 378 (5.60 mg, 0.010 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 436b and 437b (45:55 ratio) was dissolved in THF (3.0 mL) and LiBEt_3H in THF (1.0 mL, 1.0
mmol) was added. The reaction mixture was allowed to stir at 0 °C for 30 min then at room temperature for additional 2.5 h under an argon atmosphere. Water (1 mL) and an aqueous solution of HCl (1 N, 2 mL) were added and the mixture was stirred for another 4 h. Upon purification by flash column chromatography eluting with 70:30 diethyl ether:hexanes, lactone 438b (obtained from hemiesters 436b) was isolated as a white solid (11.5 mg, 26%). M.p 50-52 °C, TLC (diethyl ether:hexane, 7:3 v/v): Rf = 0.40, [α]D = +106 (c = 0.30, CHCl₃).

CSP-HPLC analysis. Chiralpak 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: 10.1 min (major enantiomer) and 13.0 min (minor enantiomer).

δH (400 MHz, CDCl₃): 7.11-7.19 (3 H, m, H-2, H-3), 4.34 (1 H, td, J 6.8, 8.8, H-4a), 4.31 (1 H, td, J 3.8, 8.8, H-4b), 3.69 (1 H, dd, J 4.3, 8.1, H-5), 2.61 (6 H, s, H-1), 2.59-2.56 (1 H, m, H-6a), 2.22-2.17 (1 H, m, H-6b).

δC (100 MHz, CDCl₃): 174.6 (C=O), 143.8 (q), 130.8 (q), 129.9, 129.4, 128.7 (q), 67.9, 65.1, 42.6, 30.1, 21.9.

νmax (neat)/cm⁻¹: 2987, 1869, 1740, 1200, 1120, 1069, 910, 756, 599.


4-((2,6-Dimethylphenyl)thio)dihydrofuran-2(3H)-one (239b)

Prepared according to general procedure B using anhydride 393 (47.3 mg, 0.20 mmol) and the catalyst 378 (5.60 mg, 0.010 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 436b and 437b (45:55 ratio) was dissolved in THF (3.0 mL) and LiBEt₃H in THF (1.0 mL, 1.0
mmol) was added. The reaction mixture was allowed to stir at 0 °C for 30 min then at room temperature for additional 2.5 h under an argon atmosphere. Water (1 mL) and an aqueous solution of HCl (1 N, 2 mL) were added and the mixture was stirred for another 4 h. Upon purification by flash column chromatography eluting with 70:30 diethyl ether:hexanes, lactone 439b (obtained from hemiester 437b) was isolated as a white solid (13.3 mg, 30%). M.p 48–50 °C; (lit.279 m.p 50.0–50.8), TLC (diethyl ether:hexane, 7:3 v/v): R_t = 0.35, [α]_D^20 = +87 (c = 0.9, CHCl_3), (lit.,277 [α]_D^20 = +29.7 (c =3.11, CHCl_3).

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: 12.1 min (major enantiomer) and 14.2 min (minor enantiomer).

δ_H (400 MHz, CDCl_3): 7.16-7.09 (3 H, m, H-2, H-3), 4.37 (1 H, dd, J 6.1, 9.8, H-4a), 4.06 (1 H, dd, J 4.3, 9.8, H-4b), 3.79 (1 H, quint, J 4.3 H-5), 2.81 (1 H, dd, J 8.1, 17.4, H-6a), 2.58 (6 H, s, H-1), 2.45 (1 H, dd, J 4.3, 17.4 H-6b).

δ_C (100 MHz, CDCl_3): 175.2 (C=O), 143.6 (q), 130.2 (q), 129.5, 128.5, 128.4 (q), 72.2, 66.8, 41.4, 35.2, 22.1.

2-((4-Chlorophenyl)thio)succinic acid (435)

An oven dried round-bottomed flask containing a stirring bar was charged with maleic acid (1.50 g, 12.9 mmol), anhydrous THF (25 mL) and freshly distilled triethylamine (4.5 mL, 32.3 mmol). 4-Chlorothiophenol (431) (2.05 g, 14.21 mmol) was added via syringe and the reaction mixture was heated at reflux temperature for 16 h. The solvent was removed under reduced pressure and the residue was extracted with EtOAc (15 mL), washed with a 2.0 M aqueous solution of NaOH (2 x 25 mL). The aqueous phase was acidified with concentrated HCl, the precipitate formed was filtered, washed with diethyl
ether (5 mL) and dried to furnish 435 (2.5 g, 75%) as a white solid. M.p 135-137 °C, (lit.\textsuperscript{280} m.p 165 °C).

δ\textsubscript{H} (400 MHz, DMSO-\textit{d}\textsubscript{6}): 7.46 (2 H, d, \textit{J} 7.2, H-1), 7.40 (2 H, d, \textit{J} 7.2, H-2), 3.91 (1 H, dd, \textit{J} 5.8, 9.2, H-3), 2.72-2.57 (2 H, m, H-4).

3-((4-Chlorophenyl)thio)dihydrofuran-2,5-dione (394)

An oven dried round-bottomed flask containing a stirring bar was charged with 435 (2.50 g, 9.58 mmol) and acetic anhydride (15 mL). The apparatus was equipped with a condenser and a septum and kept under an argon atmosphere (balloon). The reaction mixture was heated at reflux for 2 h, then concentrated under reduced pressure. The residue was then triturated in diethyl ether (5 mL) and filtered to give anhydride 394 (1.83 g, 79%) pure as a dark brown solid. M.p. 98-100 °C, (lit.,\textsuperscript{275} m.p. 96-98 °C).

δ\textsubscript{H} (400 MHz, DMSO-\textit{d}\textsubscript{6}): 7.51 (2 H, d, \textit{J} 8.6, H-1), 7.44 (2 H, d, \textit{J} 8.6, H-2), 4.70 (1 H, dd, \textit{J} 5.2, 9.6, H-3), 3.52 (1 H, dd, \textit{J} 9.6, 18.9, H-4a) 3.01 (1 H, dd, \textit{J} 5.2, 18.9, H-4b).

3-((4-Chlorophenyl)thio)dihydrofuran-2(3H)-one (438c)

Prepared according to general procedure B using anhydride 394 (48.5 mg, 0.20 mmol) and the catalyst 378 (5.60 mg, 0.010 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 436c and 437c (24:76 ratio) was dissolved in THF (3.0 mL) and LiBE\textsubscript{t}H in THF (1.0 mL, 1.0 mmol) was added. The reaction mixture was allowed to stir at 0 °C for 30 min then at room temperature for additional 2.5 h under an argon atmosphere. Water (1 mL) and an
aqueous solution of HCl (1 N, 2 mL) were added and the mixture was stirred for another 4 h. Upon purification by flash column chromatography eluting with 70:30 diethyl ether:hexane, lactone 438c (obtained from hemiester 436c) was isolated as a white solid (4.1 mg, 9%), $[\alpha]_D^{20} = +116$ (c = 0.10, CHCl$_3$).

CSP-HPLC analysis. Chiralpak 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: 19.3 min (major enantiomer) and 20.9 min (minor enantiomer).

$\delta_H$ (400 MHz, CDCl$_3$): 7.48 (2 H, J 8.2, H-1), 7.30 (2 H, d, J 8.2 H-2), 4.28-4.24 (2 H, m, H-3), 3.80 (1 H, dd, J 6.4, 8.7, H-4), 2.71-2.62 (1 H, m, H-5a), 2.27-2.20 (1 H, m, H-5b).


4-((4-Chlorophenyl)thio)dihydrofuran-2(3H)-one (439c)

Prepared according to general procedure B using anhydride 394 (48.5 mg, 0.20 mmol) and the catalyst 378 (5.6 mg, 0.010 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 436c and 437c (24:76 ratio) was dissolved in THF (3.0 mL), LiBEt$_3$H in THF (1.0 mL, 1.0 mmol) was added. The reaction mixture was allowed to stir at 0 $^\circ$C for 30 min then at room temperature for additional 2.5 h under an argon atmosphere. Water (1 mL) and an aqueous solution of HCl (1 N, 2 mL) were added and the mixture was stirred for another 4 h. Upon purification by flash column chromatography eluting with 70:30 diethyl ether:hexanes, lactone 439c (obtained from hemiester 437c) was isolated as a white solid (24.2 mg, 53%). M.p. 62-64 $^\circ$C, (lit. 281 m.p 60-61$^\circ$C); $[\alpha]_D^{20} = +116$ (c = 0.10, CHCl$_3$).

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: 14.7 min (major enantiomer) and 16.5 min (minor enantiomer).

192
δ_H (400 MHz, CDCl_3):  
7.35 (2 H, d, J 8.4, H-1), 7.31 (2 H, J 8.4, H-2), 4.51 (1 H, dd, J 7.4, 9.9, H-4a), 4.17 (1 H, dd, J 5.3, 9.9, H-4b), 3.96 (1 H, quint, J 5.3, H-3), 2.88 (1 H, dd, J 8.1, 17.7 H-5a), 2.50 (1 H, dd, J 5.3, 17.7 H-5b).

2,2,2-Tribromoethyl 2-methyl-4-oxo-4-(((R)-1-phenylethyl)amino)butanoate (444a)

Prepared according to general procedure C using methylsuccinic anhydride (218a, 28.8 mg, 0.20 mmol) and the catalyst 378 (5.60 mg, 0.010 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 442a and 443a (45:55 ratio, 98% conversion) was dissolved in anhydrous CH_2Cl_2 (4.0 mL) and the mixture was cooled to 0 °C. Thionyl chloride (17.7 µL, 0.20 mmol) in CH_2Cl_2 (2.0 mL) was then added and the reaction mixture was allowed to stir for 10 min under an argon atmosphere. Freshly distilled Et_3N (70.0 µL, 0.50 mmol) and (R)-(+)-α-methylbenzylamine (398, 25.8 µL, 0.20 mmol) were added and the mixture was allowed to stir at 0 °C for 1 h and then at room temperature for an additional 1 h. Upon purification by flash column chromatography eluting with 70:30 hexane:EtOAc, amide 444a (obtained from hemiesters 442a) was isolated as a white solid (14.5 mg, 32%), M. p. 70-72 °C, [α]_D^20 = +1.5 (c = 0.025, CHCl_3).

δ_H (400 MHz, CDCl_3):  
7.38-7.31 (5 H, m, H-1, H-2, H-3), 5.83 (1 H, d, J 6.7, NH), 5.18-5.12 (1 H, m, H-4), 4.97 (1 H, d, J 11.6, H-5a), 4.82 (1 H, d, J 11.6, H-5b), 3.20 (1 H, m, H-6), 2.71 (1 H, dd, J 8.3, 15.0, H-7a), 2.37 (1 H, dd, J 5.9, 15.0, H-7b), 1.53 (3 H, d, J 6.2, H-8), 1.38 (3 H, d, J 6.8, H-9).

δ_C (100 MHz, CDCl_3):  
173.8 (C=O), 169.4 (C=O), 142.9 (q), 128.7, 127.4, 126.2, 76.7, 48.9, 39.6, 36.3, 35.7 (q), 21.7, 17.2.

ν_max (neat)/cm:\:  
3662, 2970, 1720, 1445, 1150, 1080, 880, 569.
HRMS (m/z - ESI): Found: $519.8730 \ [\text{M}+\text{Na}]^+$ C$_{15}$H$_{18}$Br$_3$NNaO$_3$ Requires: 519.8729.

2,2,2-Tribromoethyl 3-methyl-4-oxo-4-((R)-1-phenylethyl)amino)butanoate (445a)

Prepared according to general procedure C using methylsuccinic anhydride (218a, 28.8 mg, 0.20 mmol) and the catalyst 378 (5.6 mg, 0.01 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 442a and 443a (45:55 ratio, 98% conversion) was dissolved in anhydrous CH$_2$Cl$_2$ (4.0 mL) and the reaction mixture was cooled to 0°C. Thionyl chloride (17.7 μL, 0.20 mmol) in CH$_2$Cl$_2$ (2.0 mL) was then added and the reaction mixture was allowed to stir for 10 min under an argon atmosphere. Freshly distilled Et$_3$N (70.0 μL, 0.5 mmol) and (R)-(+)-$\alpha$-methylbenzylamine (398, 25.8 μL, 0.2 mmol) were added and the mixture was allowed to stir at 0°C for 1 h and then at room temperature for an additional 1 h. Upon purification by flash column chromatography eluting with 70:30 hexane:EtOAc, amide 445a (obtained from hemiesters 443a) was isolated as a white solid (21.0 mg, 38%), M. p. 68-70 ºC, $[\alpha]_D^{20} = +1.12$ ($c = 0.03$, CHCl$_3$).

$\delta$$_H$ (400 MHz, CDCl$_3$): 7.39-7.32 (5 H, m, H-1, H-2, H-3), 5.90 (1 H, d, J 6.7, NH), 5.19-5.14 (1 H, m, H-4), 5.01 (1 H, d, J 12.6, H-5a), 4.92 (1 H, d, J 12.6, H-5b), 3.03 (1 H, dd, J 8.7, 17.2, H-7a), 2.79 (1 H, m, H-6), 2.59 (1 H, dd, J 5.9, 17.2, H-7b), 1.52 (3 H, d, J 6.2, H-8), 1.26 (3 H, d, J 6.8, H-9).

$\delta$$_C$ (100 MHz, CDCl$_3$): 173.6 (C=O), 170.7 (C=O), 143.1 (q), 128.7, 127.4, 126.1, 76.9, 48.8, 37.7, 37.0, 35.5 (q), 21.7, 17.9.

$\nu$$_{_{_{_{max}}}}$ (neat)/cm$^{-1}$: 3663, 2970, 1718, 1446, 1152, 1080, 878, 611.
HRMS (m/z -ESI): Found: 519.8726 [M+Na]+ \( \text{C}_{15}\text{H}_{16}\text{Br}_{3}\text{NNaO}_{3} \) Requires: 519.8729.

2,2,2-Tribromoethyl 2-(2-oxo-2-(((R)-1-phenylethyl)amino)ethyl)hex-5-enoate (444b)

Prepared according to general procedure C using allylsuccinic anhydride (218d, 28.0 mg, 0.20 mmol) and the catalyst 378 (5.60 mg, 0.01 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 442b and 443b (46:54 ratio, 98% conversion) was dissolved in anhydrous CH\(_2\)Cl\(_2\) (4.0 mL) and the reaction mixture was cooled to 0 °C. Thionyl chloride (17.7 µL, 0.2 mmol) in CH\(_2\)Cl\(_2\) (2.0 mL) was then added and the reaction mixture was allowed to stir for 10 min under argon atmosphere. Freshly distilled Et\(_3\)N (70.0 µL, 0.5 mmol) and (R)-(+)\(-\)α-methylbenzylamine (398, 25.8 µL, 0.2 mmol) were added and the mixture was allowed to stir at 0 °C for 1 h and then at room temperature for an additional 1 h. Upon purification by flash column chromatography eluting with 70:30 hexanes:EtOAc, amide 444b (obtained from hemiesters 442b) was isolated as a white solid (18.5 mg, 38%). TLC (hexanes/EtOAc, 7:3 v/v): R\(_f\) = 0.41, \([\alpha]\)\(_D\) = +1.8 (c = 0.025, CHCl\(_3\)), M.p. 78-80 °C.

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min\(^{-1}\), rt, UV detection at 254 nm, retention times: 9.95 min (major enantiomer), 99% ee.

\(\delta\)\(_H\) (400 MHz, CDCl\(_3\)): 7.38-7.30 (5 H, m, H-1, H-2, H-3), 5.86-5.75 (2 H, m, NH, H-4), 5.16-5.11 (3 H, m, H-5a, H-5b, H-6), 4.93 (1 H, d, \(J\) 12.0, H-7a), 4.79 (1 H, d, \(J\) 12.0, H-7b), 3.26 (1 H, m, H-8), 2.64 (1 H, dd, \(J\) 9.0, 15.1, H-9a), 2.59-2.53 (1 H, m, H-10a), 2.50-2.40 (2 H, H-9b, H-10b), 1.51 (3 H, d, \(J\) 7.2, H-11).

\(\delta\)\(_C\) (100 MHz, CDCl\(_3\)): 172.6 (C=O), 169.4 (C=O), 142.9 (q), 134.2, 128.7, 127.5, 126.2, 118.2, 76.9, 48.8, 41.1, 36.9, 35.9, 35.4 (q), 21.7.
\[ \nu_{\text{max}} \text{ (neat)/cm}^{-1}: \quad 3664, 2971, 1749, 1541, 1411, 1242, 1066, 921, 716, 563. \]

HRMS (m/z -ESI): Found: 545.8878 \([\text{M}+\text{Na}]^+\) \(\text{C}_{17}\text{H}_{20}\text{Br}_3\text{N}\text{NaO}_3\) Requires: 545.8885.

2,2,2-Tribromoethyl 3-((\((R)-1\)-phenylethyl)carbamoyl)hex-5-enoate (445b)

Prepared according to general procedure C using allylsuccinic anhydride (218d, 28.0 mg, 0.20 mmol) and the catalyst 378 (5.60 mg, 0.01 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 442b and 443b (46:54 ratio, 98% conversion) was dissolved in anhydrous CH\(_2\)Cl\(_2\) (4.0 mL) and the reaction mixture was cooled to 0 °C. Thionyl chloride (17.7 \(\mu\)L, 0.2 mmol) in CH\(_2\)Cl\(_2\) (2.0 mL) was then added and the reaction mixture was allowed to stir for 10 min under an argon atmosphere. Freshly distilled Et\(_3\)N (70.0 \(\mu\)L, 0.5 mmol) and \((R)-(\pm)\)-\(\alpha\)-methylbenzylamine (398, 25.8 \(\mu\)L, 0.2 mmol) were added and the mixture was allowed to stir at 0 °C for 1 h and then at room temperature for an additional 1 h. Upon purification by flash column chromatography eluting with 70:30 hexane:EtOAc, amide 444b (obtained from hemiesters 443b) was isolated as a white solid (29.5 mg, 52%). TLC (hexanes/EtOAc, 7:3 v/v): \(R_f = 0.42\), \([\alpha]_D^{20} = +1.1\) (c = 0.035, CHCl\(_3\)), M.p. 85-87 °C.

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min\(^{-1}\),rtT, UV detection at 254 nm, retention times: 9.9 min (minor enantiomer) and 11.9 min (major enantiomer).

\(\delta_H\) (400 MHz, CDCl\(_3\)): 7.38-7.30 (5 H, m, H-1, H-2, H-3), 5.92 (1 H, d, \(J = 7.3\) Hz), 5.76-5.65 (1 H, m, H-4), 5.15-5.05 (3 H, m, H-5a, H-5b, H-6), 5.0 (1 H, d, \(J = 12.2\) Hz), 4.90 (1 H, d, \(J = 12.2\) Hz), 2.99 (1 H, dd, \(J = 8.6, 16.7\) Hz), 2.75-2.62 (2 H, m, H-8,
H-9b), 2.47-2.38 (1 H, m, H-10a), 2.30-2.22 (1 H, m, H-10b), 1.51 (3 H, d, J 7.2, H-11).

$\delta_C$ (100 MHz, CDCl$_3$): 172.4 (C=O), 170.7 (C=O), 143.0 (q), 134.6, 128.6, 127.3, 126.2, 118.1, 77.2, 48.8, 42.3, 36.6, 35.7, 35.5 (q), 21.5.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3664, 2971, 1751, 1537, 1412, 1242, 1066, 920, 711, 574.

HRMS ($m/z$ -ESI): Found: 545.8874 [M+Na]$^+$ C$_{17}$H$_{20}$Br$_3$NaO$_3$ Requires: 545.8885.

**Dimethyl 2-isopropylmalonate (447)**

A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with 2-isopropyl acid (277, 5.00 g, 34.2 mmol). Concentrated sulfuric acid (1 mL) and methanol (75 mL) were added and the reaction mixture was heated at reflux temperature for 16 h. The solvent was evaporated and the residue was dissolved in diethyl ether (30 mL) and then washed with a saturated aqueous solution of NaHCO$_3$ (3 x 15 mL) and H$_2$O (2 x 15 mL). The organic phase was dried over MgSO$_4$ and filtered. The solvent was removed *in vacuo* to give the product 447 as an oily residue (5.54 g, 93%). Spectral data for this compound were consistent with those in the literature.$^{282}$

$\delta_H$ (400 MHz, CDCl$_3$): 3.70 (6 H, s, H-1), 3.13 (1 H, d, J 8.7, H-2), 2.37 (1 H, m, H-3), 0.96 (6 H, d, J 6.8, H-4).

HRMS ($m/z$ -ESI): Found: 197.0984 (M+Na)$^+$ C$_8$H$_{14}$O$_4$Na Requires: 197.0984.

**Trimethyl 3-methylbutane-1,2,2-tricarboxylate (449)**

197
An oven dried 100 mL round-bottomed flask containing a magnetic stirring bar was charged with sodium hydride (442 mg, 11.0 mmol) in dry THF (25 mL). A THF (5 mL) solution of 447 (1.60 g, 9.20 mmol) was added dropwise under an argon atmosphere at room temperature and stirred for 15 min. Methylbromoacetate (448, 960 µL, 10.12 mmol) was added dropwise and stirred at reflux for 2 h. After the removal of the solvent in vacuo, the residue was purified by column chromatography (hexane:EtOAc 9:1) to give 449 as a yellow oil (1.51 g, 67%).

\[ \delta_H (400 \text{ MHz, CDCl}_3): \]
\[ 3.71 (6 \text{ H, s, H-1}), 3.63 (3 \text{ H, s, H-2}), 2.87 (2 \text{ H, s, H-3}), 2.34 (1 \text{ H, m, H-4}), 0.96 (3 \text{ H, d, J 6.9, H-5}) 0.92 (3 \text{ H, d, J 6.9, H-6}). \]

\[ \delta_C (100 \text{ MHz, CDCl}_3): \]
\[ 174.4 (\text{C=O}), 171.8 (2 \times \text{C=O}), 58.1 (\text{q}), 53.4, 53.2, 51.8, 33.9, 22.8, 16.2. \]

\[ \nu_{\text{max}} (\text{neat})/\text{cm}^{-1}: \]
\[ 2886, 2628, 1742, 1684, 1310, 1244, 1185, 1134, 1014, 863. \]

HRMS (m/z -ESI): Found: 269.1088 (M+Na)+ \text{C}_{11}\text{H}_{18}\text{O}_{6}\text{Na} Requires: 269.1091.

### 3-Methylbutane-1,2,2-tricarboxylic acid (450)

A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with 449 (1.54 g, 6.23 mmol) and THF/MeOH 1:1 (66 mL). An aqueous solution of NaOH in water (0.1 N) was added and the reaction mixture was refluxed for 24 h. The mixture was partially neutralised with an aqueous solution of HCl (3 N). The aqueous mixture was extracted with diethyl ether (3 x 15 mL) and dried with Na$_2$SO$_4$ to give 450 (522 mg, 41%) as a yellow oil.

\[ \delta_H (400 \text{ MHz, CDCl}_3): \]
\[ 9.44 (3 \text{ H, bs, H-1}), 2.19 (1 \text{ H, m, H-2}), 2.08 (2 \text{ H, s, H-3}), 1.05 (3 \text{ H, d, J 6.9, H-4}), 1.02 (3 \text{ H, d, J 6.9, H-5}). \]
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δC (100 MHz, CDCl₃):  177.1 (2 x C=O), 176.3 (C=O), 59.9 (q), 37.1, 22.8, 16.3.

νₘₐₓ (neat)/cm⁻¹:  2978, 1742, 1684, 1308, 1295, 1180, 1026, 904.


2-isoPropylsuccinic acid (451)

A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with 449 (1.50 g, 7.34 mmol) and heated at 150 °C for 2 h to give 451 as a dark brown solid (1.10 g, 94%), M.p. 105-107 ºC, (lit.,²⁸³ m.p 110-111 ºC)

δH (400 MHz, DMSO-d₆):  12.11 (2 H, bs, H-1), 2.43 (2 H, dd, H-2, H-3a), 2.27 (1 H, dd, J 3.4, 15.9, H-3b), 1.86 (1 H, m, H-4), 0.99 (3 H, d, J 7.0, H-5), 0.95 (3 H, d, J 7.0, H-6).

3-isoPropyldihydropyran-2,5-dione (395)

An oven dried round-bottomed flask containing a stirring bar was charged with 451 (1.00 g, 6.24 mmol) and freshly distilled acetyl chloride (15 mL), The apparatus was equipped with a condenser and a septum and kept under an argon atmosphere (balloon). The reaction mixture was heated at reflux overnight, then concentrated under reduced pressure to give anhydride 395 (781 mg, 88%) pure as a dark brown oil.

δH (400 MHz, DMSO-d₆):  3.13 (1 H, ddd, J 5.9, 9.6, 15.7, H-1), 2.96 (1 H, dd, J 9.6, 18.3, H-2b), 2.82 (1 H, dd, J 5.9, 18.3, H-2a), 2.07 (1 H, sept, J 6.5, H-3), 0.92 (3 H, d, J 6.9, H-4), 0.85 (3 H, d, J 6.9, H-5).

HRMS (m/z -ESI):  Found: 143.0708 (M+H)+  C₇H₁₀O₃  Requires: 143.0703.

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2,2,2-Tribromoethyl 2-isopropyl-4-oxo-4-(((R)-1-phenylethyl)amino)butanoate (454, Scheme 3.20)

Prepared according to general procedure C using isopropylsuccinic anhydride (451, 28.4 mg, 0.20 mmol) and the catalyst 378 (5.60 mg, 0.01 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 452 and 453 (35:65 ratio, 41% conversion) was dissolved in anhydrous CH₂Cl₂ (4.0 mL) and the reaction was cooled to 0 °C. Thionyl chloride (17.7 μL, 0.20 mmol) in CH₂Cl₂ (2.0 mL) was then added and the reaction mixture was allowed to stir for 10 min under an argon atmosphere. Freshly distilled Et₃N (70.0 μL, 0.5 mmol) and (R)-(+)α-methylbenzylamine (398, 25.8 μL, 0.20 mmol) were added and the mixture was allowed to stir at 0 °C for 1 h and then at room temperature for an additional 1 h. Upon purification by flash column chromatography eluting with 70:30 hexanes:EtOAc, amide 454 (obtained from hemiester 452) was isolated as a white solid (15.16 mg, 14%). TLC (hexane/EtOAc, 7:3 v/v): Rₛ = 0.32; [α]D²⁰ = +2.5 (c = 0.0020, CHCl₃), M. p. 92-94 °C.

δ_H (400 MHz, CDCl₃): 7.37-7.33 (5 H, m, H-1, H-2, H-3), 5.86 (1 H, d, J 6.7, NH), 5.17-5.16 (1 H, m, H-4), 5.01 (1 H, d, J 12.7, H-5a), 4.88 (1 H, d, J 12.7, H-5b), 3.01 (1 H, dd, J 10.4, 17.4, H-6a), 2.65 (1 H, dd, J 3.3, 17.4, H-6b), 2.39, (1 H, m, H-7), 1.94 (1 H, m, H-8), 1.51 (3 H, d, J 6.9, H-9), 0.94 (3 H, d, J, 7.0, H-10), 0.83 (3 H, d, J 7.0, H-11).

δ_C (100 MHz, CDCl₃): 172.6 (C=O), 171.3 (C=O), 143.2 (q), 128.6, 127.3, 126.3, 77.2, 49.4, 48.8, 35.6 (q), 33.7, 30.4, 21.5, 20.5, 19.8.

ν_max (neat)/cm⁻¹: 3663, 2971, 1716, 1446, 1153, 1078, 878, 564.

HRMS (m/z -ESI): Found: 547.9046 (M+Na)⁺ C₁₇H₂₂Br₃NNaO₃ Requires: 547.9042.
2,2,2-Tribromoethyl 5-oxo-4-phenyl-5-(((R)-1-phenylethyl)amino)pentanoate (457)

Prepared according to general procedure C using phenylglutaric anhydride (257, 38.0 mg, 0.20 mmol) and the catalyst 378 (5.60 mg, 0.010 mmol). MTBE (2 mL) was added via syringe followed by the alcohol 349 (56.5 mg, 0.20 mmol). The mixture of hemiesters 455 and 456 (4:96 ratio, 0.2 mmol) was dissolved in anhydrous CH₂Cl₂ (4.0 mL) and the reaction mixture was cooled to 0 °C. Thionyl chloride (17.7 µL, 0.20 mmol) in CH₂Cl₂ (2.0 mL) was then added and the reaction mixture was allowed to stir for 10 min under an argon atmosphere. Freshly distilled Et₃N (70.0 µL, 0.5 mmol) and (R)-(+)-α-methylbenzylamine (398, 25.8 µL, 0.2 mmol) were added and the mixture was allowed to stir at 0 °C for 1 h and then at room temperature for an additional 1 h. Upon purification by flash column chromatography eluting with 70:30 hexanes:EtOAc, diastereomeric mixture of amides (R,R)-457 and (S,R)-457 (obtained from hemiester 456) was isolated as a white solid (33.4 mg, 29%). TLC (hexane/EtOAc, 7:3 v/v): Rᵣ = 0.39, [α]D²₀ = +28.5 (c = 0.26, CHCl₃), M. p. 155-158 °C.

Major diastereomer:

\[
\begin{align*}
\delta_H (400 MHz, CDCl₃): & \quad 7.35-7.23 (10 H, m, H-1, H-1’, H-2, H-2’, H-3, H-3’), 5.63 (1 H, d, J 7.1, NH), 5.08-5.05 (1H, m, H-4), 4.88 (2 H, s, H-5), 3.50 (1 H, app.t, H-6), 2.55-2.39 (3 H, m, H-7, H-8a), 2.19-2.09 (1 H, m, H-8b), 1.33 (3 H, d, J 6.7, H-9). \\
\delta_C (100 MHz, CDCl₃): & \quad 173.8 (C=O), 171.2 (C=O), 141.9 (q), 137.3 (q), 128.8, 128.4, 127.9, 127.7, 126.9, 126.5, 79.8, 53.5, 45.8, 34.2 (q), 30.9, 24.2, 21.3. \\
\nu_{max} (neat)/cm⁻¹: & \quad 3660, 2968, 1724, 1445, 1149, 1065, 865, 670.
\end{align*}
\]
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HRMS (m/z -ESI):  Found: 595.9178 (M+Na)\(^+\) \(\text{C}_{21}\text{H}_{22}\text{Br}_3\text{NNaO}_3\)  Requires: 595.9185.

Minor diastereomer:

\[ \delta_H (400\text{ MHz, CDCl}_3): 7.33-7.12 (10\text{ H, m, H-1, H-1', H-2, H-2', H-3, H-3'}), 5.62 (1\text{ H, d, J 7.1, NH}), 5.06-5.04 (1\text{ H, m, H-4}), 4.90 (2\text{ H, s, H-5}), 3.52 (1\text{ H, app.t, H-6}), 2.55-2.45 (3\text{ H, m, H-7, H-8a}), 2.16-2.11 (1\text{ H, m, H-8b}), 1.40 (3\text{ H, d, J 6.7, H-9}). \]

\[ \delta_C (100\text{ MHz, CDCl}_3): 173.6 (\text{C=O}), 171.1 (\text{C=O}), 141.7 (\text{q}), 137.4 (\text{q}), 128.8, 128.4, 127.9, 127.7, 126.9, 126.8, 79.7, 53.2, 45.9, 34.7 (\text{q}) 30.9, 24.3, 21.3 (\text{q}). \]

\(^*\)[\(\alpha\)\(^{20}\)]\(^D\) refers to a mixture of \((R,R)-457\) and \((S,R)-457\) (60:40).

5.3  Experimental procedures and data for Chapter 4

5.3.1  Procedure E: general procedure for the organocatalysed cycloaddition of phenylsuccinic anhydride and substituted glutaric anhydrides to aldehydes

An oven-dried 10 mL reaction flask containing a magnetic stirring bar under an argon atmosphere was charged with the relevant anhydride (1.0 equiv.), catalyst 239 (5 mol\%) and anhydrous MTBE (0.1 M). The relevant aldehyde (1 equiv.) was added via syringe. The reaction was allowed to stir at room temperature for 72 h. The yield and diastereomeric ratio of the carboxylic acids were determined by \(^1\text{H NMR spectroscopic analysis using p-iodoanisole (0.5 equiv.) as an internal standard. To a solution of the corresponding carboxylic acids in dry THF (0.1 M) were added via isopropyl alcohol (5.0 equiv.) and trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 1.2 equiv.) at -15 °C. The reaction was allowed to stir for 30 minutes. The solvent was then evaporated in vacuo and the crude mixture of diastereomeric esters was purified by flash chromatography eluting with 80:20 hexane:EtOAc. The enantiomeric excesses of the products were determined by CSP-HPLC.}
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**(S)-2-Amino-3,3-dimethylbutan-1-ol (461)**

![Chemical structure of (S)-2-Amino-3,3-dimethylbutan-1-ol](image)

An oven-dried 100 mL reaction flask containing a magnetic stirring bar under an argon atmosphere was charged with sodium borohydride (1.38 g, 36.4 mmol) in THF (0.4 M), and L-tert-leucine (460, 2.00 g, 15.2 mmol). The reaction mixture was cooled at 0 °C and a solution of iodine (3.86 g, 15.2 mmol) in THF (0.35 M) was added dropwise over 30 min, then the reaction mixture was warmed to room temperature for 15 min and then refluxed for 24 h. The reaction mixture was cooled to room temperature and MeOH was added until a clear solution was obtained then the solvent was removed under reduced pressure. The white paste was dissolved in a 20% aqueous solution of KOH (20 mL) and stirring was maintained for 4 h and the reaction mixture was extracted with CH$_2$Cl$_2$ (3 x 60 mL), washed with brine, dried over MgSO$_4$ and the volatiles removed in vacuo to afford the crude amino alcohol **461** (1.56 g, 88%) as a colourless liquid.$^{284}$

\[\delta_H (400 \text{ MHz, CDCl}_3 precious):\]

- 3.62 (1 H, dd, J 3.6, 11.1, H-1a),
- 3.14 (1 H, app. t, H-1b),
- 2.44 (1 H, dd J 3.6, 9.7, H-2),
- 0.81 (9 H, s, H-3).

**HRMS (m/z -ESI):**

- Found: 116.1203 (M-H)
- C$_6$H$_{14}$NO
- Requires: 116.1206.

*The signals NH$_2$ and OH were not visible in CDCl$_3$.

**tert-Butyl (S)-(1-hydroxy-3,3-dimethylbutan-2-yl)carbamate (462)**

![Chemical structure of tert-Butyl (S)-(1-hydroxy-3,3-dimethylbutan-2-yl)carbamate](image)

An oven-dried 100 mL reaction flask containing a magnetic stirring bar under an argon atmosphere was charged with **461** (1.50 g, 12.8 mmol) in CH$_2$Cl$_2$ (0.4 M), then triethylamine (2.1 mL, 15.1 mmol) was added and the reaction mixture was cooled to 0 °C using an ice bath. Boc anhydride (15.1 mmol) was added and stirring was maintained at 0 °C for 1 h and then 24 h at room temperature. The reaction mixture was washed with...
water (20 mL), brine, dried over MgSO\textsubscript{4} and volatiles were removed \textit{in vacuo}. The crude mixture was purified by flash column chromatography eluting in a gradient from 100% hexane to 30% EtOAc in hexanes obtaining 462 as colourless solid (2.22 g, 80%), M. p. 108-110 °C, (lit.\textsuperscript{285} m.p 105 °C).

\[ \delta_{H} (400 \text{ MHz, CDCl}_3): \]

- 4.62 (1 H, bs, NH),
- 3.87-3.84 (1 H, m, H-1a),
- 3.51-3.49 (2 H, m, H-1b, H-2),
- 2.64 (1 H, bs, OH),
- 1.45 (9 H, s, H-3),
- 0.95 (9 H, s, H-4).

\textit{tert-Butyl (S)-(1,(1,3-dioxoisooindolin-2-yl)-3,3-dimethylbutan-2-yl)carbamate} (464)\textsuperscript{285}

An oven-dried 100 mL reaction flask containing a magnetic stirring bar under an argon atmosphere was charged with 462 (1.83 g, 8.43 mmol), phtalimide (463, 1.24 g, 8.43 mmol) and triphenylphospine (2.20 g, 8.43 mmol) in THF (0.2 M). Under a N\textsubscript{2} atmosphere at room temperature DIAD (1.8 mL, 8.85 mmol) was added dropwise \textit{via} syringe and stirred for 24 h. The reaction was concentrated under reduced pressure and the residue was purified by flash column chromatography eluting in a gradient from 100% hexane to 20% EtOAc in hexanes to afford 464 (2.48, 85%) as a colourless solid. M.p. 145-147 °C; (lit.\textsuperscript{285} m.p 146-147 °C).

\[ \delta_{H} (400 \text{ MHz, CDCl}_3): \]

- 7.83 (2 H, dd, J 3.0, 5.5, H-1),
- 7.69 (2 H, dd, J 3.0, 5.5, H-2),
- 4.47 (1 H, d, J 10.5, NH),
- 3.88-3.74 (2 H, m, H-3, H-4a),
- 3.65 (1 H, dd, J 1.5, 14.4, H-4b),
- 1.11 (9 H, s, H-5),
- 1.01 (9 H, s, H-6).
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**tert-Butyl (S)-(1-amino-3,3-dimethylbutan-2-yl)carbamate (465)**

An oven-dried 100 mL reaction flask containing a magnetic stirring bar under an argon atmosphere was charged with 464 (1.80 g, 5.19 mmol) in EtOH (30 mL) and under a N₂ atmosphere at room temperature was added hydrazine monohydrate (0.40 mL, 7.78 mmol). The reaction mixture was heated to reflux and stirred for 5 h, then cooled to room temperature and filtered. The precipitate was washed with CH₂Cl₂ (3 x 20 mL), and the filtrate was concentrated in vacuo. The crude product was purified by recrystallisation from hexanes to afford 465 as a colourless solid (797 mg, 71%). M.p 88-90 °C. (lit. m.p 84 °C)

δ_H (400 MHz, CDCl₃): 4.49 (1 H, d, J 10.0, NH), 3.35 (1 H, td, J 3.0, 10.5, H-1), 2.95 (1 H, dd, J 3.0, 13.5, H-2a), 2.41 (1 H, dd, J 10.5, 13.5, H-2b), 1.83 (2 H, bs, NH₂), 1.44 (9 H, s, H-3), 0.91 (9 H, s, H-4).

**1H-imidazole-1-sulfonyl azide hydrogen chloride (466)**

A 250 mL round bottomed flask containing a magnetic stirring bar was charged with NaN₃ (5.0 g, 77.0 mmol) and CH₃CN (77 mL). Sulfuryl chloride (6.2 mL, 77.0 mmol) was added dropwise via syringe at 0°C and the reaction mixture was allowed to stir for 16 h at room temperature. Imidazole (10.0 g, 146 mmol), was then added portionwise to the ice-cooled solution and the resulting mixture stirred for 3 h at room temperature. The reaction was diluted with EtOAc (150 mL), washed with H₂O (2 x 150 mL) followed by a saturated aqueous solution of NaHCO₃ (2 x 100 mL). The combined organic phases were dried over MgSO₄ and filtered. To the filtrate a solution of HCl in EtOH (8.2 mL,
115 mmol) at 0°C was added dropwise, and the resulting suspension was then filtered. The residue obtained was then washed with EtOAc (3 x 100 mL) to furnish 439 as colourless solid (5.25 g, 30 %). M.p. 98-100 °C, (lit., m.p. 100-102 °C)

δ\textsubscript{H} (400 MHz, D\textsubscript{2}O): 9.11 (1 H, s, H-3), 7.86 (1 H, s, H-2), 7.42 (1 H, s, H-1).

**tert-Butyl (S)-(1-azido-3,3-dimethylbutan-2-yl)carbamate (467)**

\[ \begin{align*}
\text{O} & \text{NH} \\
\text{O} & \text{N}_3
\end{align*} \]

An oven-dried 100 mL reaction flask containing a magnetic stirring bar under an argon atmosphere was charged with 464 (1.80 g, 5.19 mmol), K\textsubscript{2}CO\textsubscript{3} (1.22 g, 8.82 mmol) and CuSO\textsubscript{4}.5H\textsubscript{2}O (0.013 g, 0.052 mmol) in MeOH (0.2 M) under argon atmosphere. The reaction mixture was cooled to 0 °C, 466 (1.04 g, 5.0 mmol) was added to the solution and then stirred at room temperature for 16 h. The reaction was diluted with water (20 mL) and Et\textsubscript{2}O (20 mL). The aqueous layer was extracted with Et\textsubscript{2}O (20 mL) and the combined organics were washed with brine and dried over MgSO\textsubscript{4}, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting in gradient from 100% hexane to 10% EtOAc in hexane to obtain 467 as a colourless solid (994 mg, 79%). M.p. 65-67 °C, (lit., m.p. 58-60 °C).

δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}): 4.54 (1 H, d, J 9.5, NH), 3.64-3.59 (1 H, m, H-1), 3.48 (1 H, dd, J 3.0, 12.5, H-2a), 3.22 (1 H, dd, J 8.0, 12.5, H-2b), 1.46 (9 H, H-3), 0.94 (9 H, s, H-4).

**(S)-1-(1-azido-3,3-dimethylbutan-2-yl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (469)**

\[ \begin{align*}
\text{F}_3\text{C} & \text{S} \\
\text{F}_3\text{C} & \text{N}_3
\end{align*} \]
A 100 mL reaction flask containing a magnetic stirring bar under an argon atmosphere was charged with 467 (750 mg, 3.1 mmol) and cooled to 0 °C. TFA (3 mL) was added dropwise and the solution was stirred at room temperature for 3 h. TFA was evaporated under reduced pressure and the residue dissolved in diethyl ether (10 mL), a 2.0 M aqueous solution of NaOH was added until pH 14. The aqueous phase was extracted with diethyl ether (2 x 20 mL) and the combined organics were dried over MgSO₄, filtered and concentrated under a stream of N₂. The crude aminoazide was dissolved in THF (12 mL), 468 (0.68 mL, 3.72 mmol) was added dropwise and the solution was stirred at room temperature for 12 h. Upon purification by flash column chromatography eluting in gradient from 100% hexane to 10% EtOAc in hexanes 469 was afforded as a colourless solid (961 mg, 75%). M.p 175-177 °C, (lit., 213 m.p 164-166 °C).

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexanes/IPA: 95:5, 1.0 mL min⁻¹, rt, UV detection at 254 nm, retention times: 6.4 min (minor enantiomer), and 7.7 (major enantiomer).

δ_H (400 MHz, MeOD-d4): 8.23 (2 H, s, H-1), 7.64 (1 H, s, H-2), 4.69-4.50 (1 H, m, H-3), 3.62 (1 H, dd, J 4.0, 13.0, H-4a), 3.42 (1 H, dd, J 8.0, 13.0, H-4b), 0.95 (9 H, s, H-5).

(S)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(3,3-dimethyl-1-((triphenyl-l5-phosphanylidene)amino)butan-2-yl)thiourea (239)²¹⁵

To a 25 mL round bottomed flask containing a magnetic stirring bar was added 469 (500 mg, 1.21 mmol), followed by diethyl ether (3.0 mL) and tris(4-methoxyphenyl)phosphine (426 mg, 1.21 mmol) under an argon atmosphere. The reaction mixture was allowed to stir at room temperature for 24 h, after which time pentane (1 mL) was added and the resulting suspension was stirred vigorously for 2 h. The thick precipitate formed was
filtered, washed with pentane:EtO (1:1) and dried \textit{in vacuo} to give \textbf{239} as an off white solid (759 mg, 85\%) as a colourless solid. M.p. 146-148 °C, (lit.,\textsuperscript{215} m.p 148-150 °C).

\[\delta\text{H (400 MHz, CDCl}_3\text{)}: 7.57 (2 \text{H, s, H-1}), 7.52-7.43 (6 \text{H, m, H-2}), 7.32 (1 \text{H, s, H-3}), 7.05-6.95 (6 \text{H, m, H-4}), 3.87 (9 \text{H, s, H-5}), 4.08 (1 \text{H, bs, H-6}), 3.23 (1 \text{H, dd, J 5.5, 8.7, H-7a}), 2.90 (1 \text{H, app. q, H-7b}), 0.95 (9 \text{H, s, H-8}).\]

\textbf{(2S,3S)-Methyl 5-oxo-2,3-diphenyltetrahydrofuran-3-carboxylate (trans-144, Scheme 4.2)}

Prepared according to general procedure E using phenylsuccinic anhydride (\textbf{140}, 43.3 mg, 0.492 mmol), anhydrous MTBE (4.9 mL, 0.1 M), freshly distilled benzaldehyde (50 \muL, 0.492 mmol) and catalyst \textbf{239} (18.2 mg, 0.0246 mmol - 5 mol\%). The reaction was allowed to stir for 24 h at room temperature to give a diastereomeric mixture of carboxylic acids in a 83:17 (\textit{trans}:\textit{cis}) ratio. After esterification, the major diastereomer (\textit{trans-144}) was isolated and purified by flash column chromatography, eluting in gradient from 100\% hexane to 20\% EtOAc in hexanes to give a colourless oil (62.1 mg, 43\%). TLC (hexane:EtOAc, 8:2 v/v): R\textsubscript{f} = 0.35, [\alpha]_{D}^{20} = -94.2 (c = 0.50, CHCl\textsubscript{3}).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min\textsuperscript{-1}, rt, UV detection at 254 nm, retention times: 18.3 min (minor enantiomer) and 31.1 min (major enantiomer).

\[\delta\text{H (400 MHz, CDCl}_3\text{)}: 7.20-7.01 (6 \text{H, m, H-4, H-5, H-7 and H-8}), 6.97 (2 \text{H, d, J 7.3, H-3}), 6.81 (2 \text{H, d, J 7.3, H-6}), 6.30 (1 \text{H, s, H-2}), 3.78 (3 \text{H, s, H-9}), 3.42 (1 \text{H, d, J 17.6, H-1b}), 3.34 (1 \text{H, d, J 17.6, H-1a}).\]

\[\delta\text{C (100 MHz, CDCl}_3\text{)}: 174.1 (C=O), 172.9 (C=O), 134.9 (q), 134.5 (q), 128.5, 128.4, 128.1, 127.8, 127.0, 126.8, 85.6, 59.7 (q), 53.3, 38.3.\]
\[ \nu_{\text{max}} \text{(neat)}/\text{cm}^{-1}: \quad 3039, 2954, 1782, 1731, 1499, 1435, 1235, 1178, 1008, 898, 753, 695. \]

HRMS \((m/z - \text{ESI})\): Found: 319.0941 \((\text{M+Na})^+\) \(\text{C}_{18}\text{H}_{16}\text{O}_4\text{Na}\) Requires: 319.0946.

**Ethyl 6-methyl-2-oxo-4-phenyl-2H-pyran-5-carboxylate (475)\(^{\text{288}}\)**

A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with ethyl 3-phenylpropiolate (474, 1.4 mL, 8.60 mmol) followed by ethyl 3-oxobutanoate (473, 1.0 mL, 8.60 mmol) and 1,4-dioxane (16.5 mL). \(\text{NaOH} (68.8 \text{ mg, 1.72 mmol})\) was added to the solution and the reaction mixture was heated at 90 °C for 16 h. The mixture was then cooled to room temperature, diluted with water (30 mL) and extracted with \(\text{EtOAc} (3 \times 15 \text{ mL})\). The combined organic extracts were dried over \(\text{MgSO}_4\), filtered and concentrated \textit{in vacuo} to give a pale yellow solid which was purified by trituration with hexane (5 mL) furnishing 475 as a white solid (1.20 g, 57%). M.p. 90-92 °C (lit.,\(^{\text{289}}\) m.p. 95-96 °C).

\[ \delta_H (400 \text{ MHz, CDCl}_3) : \quad 7.44-7.36 (3 \text{ H, m, H-2 and H-4}), 7.32-7.25 (2 \text{ H, m, H-3}), 6.14 (1 \text{ H, s, H-1}), 3.95 (2 \text{ H, q, } J 7.1, \text{ H-6}), 2.45 (3 \text{ H, s, H-5}), 0.86 (3 \text{ H, t, } J 7.1, \text{ H-7}). \]

**\((E)\)-3-Phenylpent-2-enedioic acid (476)\(^{\text{148}}\)**

A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with 475 (1.0 g, 3.8 mmol), water (15 mL) and \(\text{NaOH} (760 \text{ mg, 19.0 mmol})\). The flask was fitted with a condenser and the reaction mixture was heated at 80 °C for 5 h. The mixture was then cooled to room temperature and diluted with diethyl ether (2 x 10 mL). HCl conc.
was then added to adjust the pH = 2 and the mixture was extracted with diethyl ether (3 x 10 mL). The combined organic phases were dried over MgSO₄, filtered and the solvent was evaporated under reduced pressure to afford a residue that was triturated with Et₂O (5 mL) to give 476 as a white solid (587 mg, 75%). M.p. 136-138 °C, (lit.²⁸⁹ m.p. 128-130 °C).

δ_H (400 MHz, DMSO-d₆): 12.36 (2 H, bs, H-6 and H-7), 7.54-7.48 (2 H, m, H-3), 7.45-7.35 (3 H, m, H-2 and H-4), 6.22 (1 H, s, H-1), 4.11 (2 H, s, H-5).

**Phenyl-2H-pyran-2,6(3H)-dione (150)²⁹⁰**

A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with 476, (250 mg, 1.21 mmol) then followed by acetyl chloride (5 mL). The flask was fitted with a condenser and the reaction mixture was heated at reflux for 16 h. After purification, 150 was obtained as a white solid (108 mg, 47%). M.p. 190-192 °C, (lit.,²⁹¹ m.p. 193-195 °C).

δ_H (400 MHz, DMSO-d₆): 7.79 (2 H, d, J 6.7, H-2), 7.55-7.41 (3 H, m, H-3, H-4), 6.78 (1 H, s, H-1), 4.15 (2 H, s, H-5).

**Ethyl 4,6-dimethyl-2-oxo-2H-pyran-5-carboxylate (497)²⁹²**

A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with H₂SO₄ conc. (20 mL) and the reaction was cooled to 10 °C. Ethyl 3-oxobutanoate (473, 26.0 mL, 204 mmol) was added dropwise via syringe while keeping the reaction temperature below 15 °C. The resultant mixture was allowed to stir at room temperature
for 72 h after which time the reaction was poured into ice (60 g) and extracted with Et₂O (3 x 100 mL). The combined organic layers were washed with a 10% aqueous solution of Na₂CO₃ (1 x 100 mL), dried over MgSO₄, filtered and concentrated in vacuo. The residue obtained was then purified by flash column chromatography eluting in gradient from 100% hexane to 20% EtOAc in hexane to furnish 497 as a yellow oil (16.3 g, 20%).

δ_H (400 MHz, CDCl₃): 6.01 (1 H, s, H-1), 4.32 (2 H, q, J 7.0, H-4), 2.40 (3 H, s, H-3), 2.21 (3 H, s, H-2), 1.35 (3 H, t, J 7.0, H-5).


3-Methylpent-2-enedioic acid (498)

A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with 497 (3.00 g, 15.2 mmol), water (40 mL) and NaOH (3.00 mg, 76.0 mmol). The flask was fitted with a condenser and the reaction mixture was heated at 80 °C for 5 h. The mixture was then cooled to room temperature and diluted with Et₂O (2 x 20 mL). The pH of the aqueous solution was adjusted to pH = 2 by the addition of HCl conc. The mixture was then extracted with diethyl ether (3 x 20 mL). The combined organic phases were dried over MgSO₄, filtered and the solvent removed under reduced pressure to furnish a residue that was triturated with Et₂O (6 mL) to afford (E/Z)-498 in a 72:28 ratio (1.32 g, 60%). M.p. 108-110 °C (lit., 289 m.p. 101-105 °C).

(E)-498:

δ_H (400 MHz, DMSO-d₆): 12.23 (2 H, bs, H-4, H-5), 5.70 (1 H, s, H-1), 3.12 (2 H, s, H-3), 2.10 (3 H, s, H-2).

(Z)-498:

δ_H (400 MHz, DMSO-d₆): 12.23 (2 H, bs, H-4, H-5), 5.75 (1 H, s, H-1), 3.63 (2 H, s, H-3), 1.89 (3 H, s, H-2).
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4-Methyl-2H-pyran-2,6(3H)-dione (151)\textsuperscript{289}

\begin{center}
\includegraphics[width=0.3\textwidth]{image.png}
\end{center}

A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with 498, (250 mg, 1.73 mmol), then followed by acetyl chloride (5 mL). The flask was fitted with a condenser and the reaction mixture was heated at reflux for 16 h. After purification, 151 was obtained as a white solid (96.8 mg, 30\%). M.p. 76-78 °C (lit., 289 m.p. 79-83 °C).

$\delta_H$ (400 MHz, DMSO-d$_6$): 6.09 (1 H, s, H-1), 3.64 (2 H, s, H-3), 1.97 (3 H, s, H-2).

(Z)-Dimethyl 3-methoxypent-2-enedioate (499)\textsuperscript{233}

\begin{center}
\includegraphics[width=0.45\textwidth]{image.png}
\end{center}

A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with dimethyl-1,3-acetonedicarboxylate (3.20 g, 22.9 mmol) in MeOH (50.0 mL). Trimethyl orthoformate (5.0 mL, 45.9 mmol) and p-toluenesulfonic acid (196 mg, 1.14 mmol) were then added. The flask was fitted with a condenser and the reaction mixture was heated at reflux temperature for 72 h under an argon atmosphere. The solvent was then removed under reduced pressure to give a yellow oil that was purified by flash column chromatography eluting in gradient from 100% hexane to 20% EtOAc in hexane, to furnish 499 as a pale yellow oil (1.66 g, 38\%).

$\delta_H$ (400 MHz, CDCl$_3$): 5.19 (1 H, s, H-1), 3.84 (2 H, s, H-2), 3.71 (3 H, s, H-3), 3.69 (3 H, s, H-4), 3.68 (3 H, s, H-5).

HRMS (m/z -EI): 

\begin{itemize}
  \item Found: 211.0581 [M+Na]$^+$
  \item $C_8H_{12}O_5Na$ Requires: 211.0582.
\end{itemize}
(Z)-3-Methoxypent-2-enedioic acid (500)\textsuperscript{291}

\[
\begin{array}{c}
\text{HO} \\
\text{O} \\
\text{O} \\
\text{C} \\
\text{C} \\
\end{array}
\]

A 100 mL round-bottomed flask containing a magnetizing stirring bar was charged with 499 (875 mg, 4.64 mmol), water (14.5 mL) and KOH (1.04 g, 18.5 mmol). The flask was fitted with a condenser and the reaction mixture was heated at 50 °C for 12 h. The pH of the solution was then adjusted to pH = 2 by the addition of HCl conc. The mixture was then extracted with Et₂O (3 x 30 mL). The combined organic phases were dried over MgSO₄, filtered and concentrated \textit{in vacuo}. The resultant residue was triturated with Et₂O (5 mL) to give 500 as an off white solid (614 mg, 50%). M.p. 175-177 °C, (lit.,\textsuperscript{291} 180 °C).

δ\textsubscript{H} (400 MHz, DMSO-\textsubscript{d₆}): 12.05 (2 H, s, H-4), 5.12 (1 H, s, H-1), 3.68 (2 H, s, H-2), 3.61 (3 H, s, H-3).

4-Methoxy-2H-pyran-2,6(3H)-dione (496)\textsuperscript{293}

A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with 500, (250 mg, 1.56 mmol), then followed by acetyl chloride (5 mL). The flask was fitted with a condenser and the reaction mixture was heated at reflux for 16 h. After purification, 496 was obtained as a white solid (66.4 mg, 30%). M.p. 85-87 °C. (lit.,\textsuperscript{294} 85-87 °C)

δ\textsubscript{H} (400 MHz, DMSO-\textsubscript{d₆}): 5.55 (1 H, s, H-1), 3.78 (3 H, s, H-2), 3.72 (2 H, s, H-3).
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Methyl 6-oxo-2-phenethyl-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate (*trans-478 and cis-478, Table 4.1 entry 5*)

Prepared according to general procedure E using anhydride 150 (46.3 mg, 0.246 mmol), anhydrous MTBE (2.5 mL, 0.1 M), freshly distilled hydrocinnamaldehyde 477 (32.4 µL, 0.246 mmol) and catalyst 239 (9.10 mg, 0.0123 mmol - 5 mol%). The reaction was stirred for 24 hours at room temperature to give a diastereomeric mixture of carboxylic acids in a 75:25 ratio (*trans:cis*). After esterification the diastereomeric mixture was purified by flash column chromatography eluting with 75:25 hexanes:EtOAc, *trans-478* and *cis-478* were isolated together as a pale yellow oil (38.0 mg, 46%). TLC (hexanes/EtOAc, 8:2 v/v): \( R_f 0.65, [\alpha]_D^{20} = -3.2 \) (c = 0.003, CHCl₃).*

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10. 1.0 mL min⁻¹, rt, UV detection at 254 nm, retention times: *trans-478* 14.7 min (major enantiomer) and 21.4 min (minor enantiomer), *cis-478* 17.4 min (major enantiomer) and 23.2 min (minor enantiomer).

*trans-478:*

\[ \delta^H (400 \text{ MHz, CDCl}_3): \]
7.56-7.52 (2 H, m, H-9), 7.48-7.42 (3 H, m, H-10 and H-11), 7.35-7.30 (2 H, m, H-6), 7.27-7.20 (3 H, m, H-7 and H-8), 6.43 (1 H, s, H-1), 4.96-4.90 (1 H, m, H-3), 3.83 (1 H, d, \( J = 4.0 \), H-2), 3.65 (3 H, s, H-12), 2.97-2.93 (1 H, m, H-5a), 2.84-2.77 (1 H, m, H-5b), 2.30-2.22 (1 H, m, H-4a), 2.02-1.93 (1 H, m, H-4b).

\[ \delta^C (100 \text{ MHz, CDCl}_3): \]
169.9 (C=O), 163.0 (C=O), 151.7 (q), 140.3 (q), 134.7 (q), 130.6, 129.2, 128.8, 128.5, 126.6, 126.1, 116.9, 78.5, 52.9, 47.3, 35.6, 31.6.
\( \nu_{\text{max}} \) (neat)/\text{cm}^{-1}: 2927, 2855, 1725, 1457, 1261, 1237, 1158, 1110, 1086, 1030, 993, 709, 645.

HRMS (\( m/z \) - ESI): Found: 337.1443 [M+H]\(^+\) \( \text{C}_{21}\text{H}_{21}\text{O}_{4} \) Requires: 337.1434.

cis-478:

\( \delta \)\(_{\text{H}} \) (400 MHz, CDCl\(_3\)): 7.56-7.52 (2 H, m, H-9), 7.48-7.42 (3 H, m, H-10 and H-11), 7.35-7.30 (2 H, m, H-6), 7.27-7.20 (3 H, m, H-7 and H-8), 6.54 (1 H, s, H-1), 4.61-4.53 (1 H, m, H-3), 3.77 (1 H, d, \( J = 3.5 \), H-2), 3.74 (3 H, s, H-12), 3.06-2.94 (1 H, m, H-5a), 2.94-2.83 (1 H, m, H-5b), 2.25-2.14 (1 H, m, H-4a), 2.13-2.03 (1 H, m, H-4b).

\( \delta \)\(_{\text{C}} \) (100 MHz, CDCl\(_3\)): 168.4 (C=O), 164.6 (C=O), 151.6 (q), 140.4 (q), 134.6 (q), 131.0, 129.2, 128.7, 128.6, 126.3, 126.0, 116.6, 67.9, 52.9, 47.0, 34.2, 31.2.

* \([\alpha]_{D}^{20}\) refers to a mixture of trans-478: cis-478 (75:25)

Methyl 2-benzhydryl-6-oxo-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate (trans-487 and cis-487, Table 4.3 entry 1)

Prepared according to general procedure E using anhydride 150 (46.3 mg, 0.246 mmol), anhydrous MTBE (2.5 mL, 0.1 M), freshly distilled diphenylacetaldehyde (479, 43.6 \( \mu \)L, 0.246 mmol) and catalyst 239 (9.10 mg, 0.0123 mmol - 5 mol\%). The reaction was stirred for 24 hours at room temperature to give a diastereomeric mixture of carboxylic acids in a 87:13 ratio (trans:cis). After esterification the diastereomeric mixture was purified by flash column chromatography eluting with 75:25 hexane:EtOAc, trans-487 and cis-487 were isolated together as a pale yellow oil (48.0 mg, 49\%). TLC (hexane/EtOAc, 8:2 \( \nu/\nu \)): \( R_f \) 0.67, \([\alpha]_{D}^{20}\) = - 23.0 (\( c = 0.05, \text{CHCl}_{3} \))*.
CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min⁻¹, rt, UV detection at 254 nm, retention times: \textit{trans-487} 2.98 min (major enantiomer) and 3.5 min (minor enantiomer), \textit{cis-487} 3.2 min (major enantiomer), 3.9 min (minor enantiomer).

\textit{trans-487}:

\[ \begin{array}{l}
\delta_H (400 \text{ MHz, CDCl}_3): \quad 7.49-7.45 (2 \text{ H, m, H-11}), 7.44-7.39 (5 \text{ H, m, H-5, H-12 and H-13}), 7.38-7.35 (4 \text{ H, m, H-8 and H-9}), 7.35-7.29 (3 \text{ H, m, H-6 and H-10}), 7.21-7.19 (1 \text{ H, m, H-7}), 6.53 (1 \text{ H, s, H-1}), 5.83 (1 \text{ H, dd, J 2.9, 10.4, H-3}), 4.34 (1 \text{ H, d, J 10.4, H-4}), 3.83 (1 \text{ H, d, J 2.9, H-2}), 3.67 (3 \text{ H, s, H-14}). \\
\delta_C (100 \text{ MHz, CDCl}_3): \quad 169.7 (\text{ C=O}), 162.4 (\text{ C=O}), 150.3 (\text{ q}), 140.6 (\text{ q}), 139.5 (\text{ q}), 135.7 (\text{ q}), 130.7, 129.4, 129.0, 128.8, 128.4, 128.1, 127.6, 127.2, 126.3, 116.9, 80.6, 54.4, 53.1, 44.3. \\
\nu_{\text{max}} (\text{ neat})/\text{cm}^{-1}: \quad 3088, 2971, 2923, 1660, 1592, 1506, 1472, 1311, 1217, 1072, 998, 768, 642. \\
HRMS (m/z -ESI): \quad \text{Found: } 421.1407 \quad [\text{M+Na}]^+ \quad \text{C}_{26}\text{H}_{22}\text{O}_{4}\text{Na} \quad \text{Requires: } 421.1410.
\end{array} \]

\textit{cis-487}:

\[ \begin{array}{l}
\delta_H (400 \text{ MHz, CDCl}_3): \quad 7.49-7.45 (2 \text{ H, m, H-11}), 7.44-7.39 (5 \text{ H, m, H-5, H-12 and H-13}), 7.38-7.35 (4 \text{ H, m, H-8 and H-9}), 7.35-7.29 (3 \text{ H, m, H-6 and H-10}), 7.21-7.19 (1 \text{ H, m, H-7}), 6.55 (1 \text{ H, s, H-1}), 5.37 (1 \text{ H, dd, J 1.4, 10.6, H-3}), 4.33 (1 \text{ H, d, J 10.6, H-4}), 3.82 (1 \text{ H, d, J 1.4, H-2}), 3.67 (3 \text{ H, s, H-14}). \\
\delta_C (100 \text{ MHz, CDCl}_3): \quad 168.1 (\text{ C=O}), 164.4 (\text{ C=O}), 152.3 (\text{ q}), 140.2 (\text{ q}), 139.9 (\text{ q}), 134.6 (\text{ q}), 130.9, 129.2, 129.1, 128.6, 128.2, 128.23, 127.5, 126.9, 126.3, 116.7, 79.7, 53.7, 52.8, 44.9. 
\end{array} \]

* \([\alpha]^{20}_D\) refers to a mixture of \textit{trans-487: cis-487} (87:13)
Methyl 2-(4-chlorophenyl)-6-oxo-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate
\((\text{trans}-488, \text{Table 4.3, entry 2})\)

![Chemical structure](image)

Prepared according to general procedure E using anhydride 150 (46.3 mg, 0.246 mmol), anhydrous MTBE (2.5 mL, 0.1 M), recrystallised 4-chlorobenzaldehyde (480, 34.6 mg, 0.246 mmol) and catalyst 239 (9.10 mg, 0.0123 mmol - 5 mol%). The reaction was stirred for 24 hours at room temperature to give a diastereomeric mixture of carboxylic acids in a 95:5 ratio (\text{trans}:\text{cis}). After esterification by flash column chromatography eluting with 75:25 hexane:EtOAc, \text{trans}-487 was isolated as a pale yellow oil (50.6 mg, 60%). TLC (hexane/EtOAc, 8:2 v/v): \(R_t\) 0.6, \([\alpha]^{20}_D = -17\) (\(c = 0.03, \text{CHCl}_3\)).

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min\(^{-1}\), rt, UV detection at 254 nm, retention times: 20.3 min (major enantiomer), 26.7 min (minor enantiomer).

\[\delta_H\ (400\ \text{MHz, CDCl}_3):\]
7.46 (5 H, m, H-2, H-3, H-4), 7.39-7.29 (4 H, m, H-7, H-8), 6.44 (1 H, s, H-1), 5.97 (1 H, d, \(J 5.4\), H-6), 4.23 (1 H, d, \(J 5.4\), H-5), 3.65 (3 H, s, H-9).

\[\delta_C\ (100\ \text{MHz, CDCl}_3):\]
169.3 (C=O), 162.9 (C=O), 151.3 (q), 135.6 (q), 135.5 (q), 134.8 (q), 130.7, 129.1, 129.0, 127.4, 126.0, 117.5, 79.4, 53.1, 49.1.

\(v_{\text{max}}\) (neat)/cm\(^{-1}\):
2952, 2925, 2861, 1735, 1708, 1601, 1458, 1260, 1002, 825, 741.

HRMS (m/z -ESI):
Methyl 2-(2-chlorophenyl)-6-oxo-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate (trans-489, Table 4.3, entry 3)

Prepared according to general procedure E using anhydride 150 (46.3 mg, 0.246 mmol), anhydrous MTBE (2.5 mL, 0.1 M), freshly distilled 2-chlorobenzaldehyde (481, 28.1 µL, 0.246 mmol) and catalyst 239 (9.10 mg, 0.0123 mmol - 5 mol%). The reaction was stirred for 24 hours at room temperature to give a diastereomeric mixture of carboxylic acids in a 89:11 ratio (trans:cis). After esterification by flash column chromatography eluting with 75:25 hexane:EtOAc, trans-489 was isolated as a pale yellow oil (49.7 mg, 59%). TLC (hexane/EtOAc, 8:2 v/v): Rf 0.6, [α]D20 = - 4.0 (c = 0.01, 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: 22.7 min (major enantiomer), 35.7 (minor enantiomer).

δH (400 MHz, CDCl3):
7.48-7.43 (5 H, m, H-2, H-3, H-4), 7.36-7.30 (4 H, m, H-7, H-8, H-9, H-10), 6.45 (1 H, s, H-1), 4.45 (1 H, d, J 5.5, H-6), 3.77 (1 H, d, J 5.5, H-5), 3.75 (3 H, s, H-11).

δC (100 MHz, CDCl3):
169.1 (C=O), 163.3 (C=O), 150.14, (q), 135.6 (q), 134.6 (q), 131.7 (q), 130.7, 130.3, 130.0, 129.1, 127.2, 126.1, 116.8, 77.6, 53.1, 46.8.

νmax (neat)/cm⁻¹:
2952, 2925, 2861, 1732, 1708, 1601, 1458, 1268, 1002, 825, 744.

HRMS (m/z -ESI):
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Methyl 2-(4-nitrophenyl)-6-oxo-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate  
(*trans*-490, Table 4.3, entry 4)

Prepared according to general procedure E using anhydride 150 (46.3 mg, 0.246 mmol), anhydrous MTBE (2.5 mL, 0.1 M), recrystallised 4-nitrobenzaldehyde (482, 37.1 mg, 0.246 mmol) and catalyst 239 (9.10 mg, 0.0123 mmol - 5 mol%). The reaction was stirred for 24 hours at room temperature to give a diastereomeric mixture of carboxylic acids in a 90:10 ratio (*trans*: *cis*). After esterification by flash column chromatography eluting with 75:25 hexanes:EtOAc, *trans*-490 was isolated as a pale yellow oil (52.2 mg, 60%). TLC (hexane/EtOAc, 8:2 v/v): Rf 0.58, $[\alpha]_D^{20} = -36 (c = 0.05, CHCl_3)$.

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 80/20, 1.0 mL min$^{-1}$, rt, UV detection at 254 nm, retention times: 21.1 min (major enantiomer), 31.8 min (minor enantiomer).

$\delta$H (400 MHz, CDCl$_3$): 8.27 (2 H, d, $J$ 8.8, H-8), 7.58 (2 H, d, $J$ 8.8, H-7), 7.47-7.42 (5 H, m, H-2, H-3, H-4), 6.46 (1 H, s, H-1), 6.11 (1 H, d, $J$ 5.1, H-6), 4.26 (1 H, d, $J$ 5.1, H-5), 3.68 (3 H, s, H-9).

$\delta$C (100 MHz, CDCl$_3$): 168.9 (C=O), 162.3 (C=O), 151.1 (q), 148.1 (q), 144.1 (q), 135.2 (q), 131.0, 129.2, 127.0, 126.0, 124.1, 117.4, 78.9, 53.3, 48.9.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 2968, 1715, 1601, 1453, 1420, 1287, 1253, 1119, 1002, 862, 824, 731, 720.

Methyl 2-(4-methoxyphenyl)-6-oxo-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate (trans-491, Table 4.3, entry 5)

Prepared according to general procedure E using anhydride 150 (46.3 mg, 0.246 mmol), anhydrous MTBE (2.5 mL, 0.1 M), freshly distilled 4-methoxybenzaldehyde (483, 30 µl, 0.246 mmol) and catalyst 239 (9.10 mg, 0.0123 mmol - 5 mol%). The reaction was stirred for 24 hours at room temperature to give a diastereomeric mixture of carboxylic acids in a 99:1 ratio (trans: cis). After esterification by flash column chromatography eluting with 75:25 hexane:EtOAc, trans-491 was isolated as a pale yellow oil (40.8 mg, 49%). TLC (hexane/EtOAc, 8:2 v/v): Rf 0.6, $[\alpha]_{D}^{20} = -30$ (c = 0.01, CHCl$_3$).

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min$^{-1}$, rt, UV detection at 254 nm, retention times: 30.6 min (major enantiomer), 44.2 min (minor enantiomer).

$\delta$H (400 MHz, CDCl$_3$): 7.46-7.43 (5 H, m, H-2, H-3, H-4), 7.30 (2 H, d, J 8.6, H-7), 6.90 (2 H, d, J 8.6, H-8), 6.43 (1 H, s, H-1), 5.94 (1 H, d, J 5.3, H-6), 4.27 (1 H, d, J 5.3, H-5), 3.81 (3 H, s, H-9), 3.62 (3 H, s, H-10).

$\delta$C (100 MHz, CDCl$_3$): 169.6 (C=O), 163.3 (C=O), 159.9 (q), 151.5 (q), 135.8 (q), 130.5 (q), 129.0, 127.5, 126.0, 117.7, 114.1, 79.9, 77.2, 55.3, 52.9, 49.2.

$\nu$max (neat)/cm$^{-1}$: 3012, 2959, 2930, 2834, 1710, 1604, 1518, 1248, 990, 734.

HRMS (m/z -ESI): Found: 361.1049 [M+Na]$^+$ C$_{20}$H$_{18}$NaO$_5$ Requires: 361.1046.
Methyl 6-oxo-2-(pentan-3-yl)-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate (*trans*-492 and *cis*-492, (Tabl4 4.3, entry 6)

Prepared according to general procedure E using anhydride 150 (46.3 mg, 0.246 mmol), anhydrous MTBE (2.5 mL, 0.1 M), 2-ethylbutaraldehyde (484, 30.4 µL, 0.246 mmol) and catalyst 239 (9.10 mg, 0.0123 mmol - 5 mol%). The reaction was stirred for 24 hours at room temperature to give a diastereomeric mixture of carboxylic acids in a 76:24 ratio (*trans*: *cis*). After esterification the diastereomeric mixture was purified by flash column chromatography eluting with 75:25 hexane:EtOAc, *trans*-492 and *cis*-492 were isolated together as a pale yellow oil (27.52 mg, 37%). TLC (hexane/EtOAc, 8:2 v/v): Rf 0.59, . \([\alpha]_D^{20} = -36.0 (c = 0.04, \text{CHCl}_3)\)*.

CSP-HPLC analysis. Chiralcel OD (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.3 mL min\(^{-1}\), rt, UV detection at 254 nm, retention times: *trans*-492 36.6 min (minor enantiomer), 52.1 min (major enantiomer); *cis*-492 32.5 min (major enantiomer, 99% ee).

*trans*-492:

\[\delta_H \text{ (400 MHz, CDCl}_3\text{):}\]

7.60-7.59 (2 H, m, H-10), 7.50-7.47 (3 H, m, H-9 and H-11), 6.42 (1 H, s, H-1), 4.83 (1 H, dd, J 4.4, 7.3, H-3), 4.03 (1 H, d, J 4.4, H-2), 3.61 (3 H, s, H-12), 1.84,1.69 (3 H, m, H-4, H-5a, H-6a), 1.70-1.62 (1 H, m, H-5b), 1.53-1.44 (1 H, m, H-6b), 0.98-0.94 (6 H, m, H-7 and H-8).

\[\delta_C \text{ (100 MHz, CDCl}_3\text{):}\]

170.0 (C=O), 163.4 (C=O), 152.3 (q), 135.9 (q), 130.5, 129.1, 126.0, 117.3, 81.0, 53.1, 44.9, 43.1, 22.0, 21.0, 10.7, 10.5.

\[\nu_{\text{max}} \text{ (neat)/cm}^{-1}:\]

3086, 2965, 2877, 1721, 1696, 1624, 1446, 1353, 1269, 1245, 1086, 1012, 990, 893, 777, 689, 602, 576.
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**cis-492:**

δ_H (400 MHz, CDCl₃):

7.63-7.54 (2 H, m, H-10), 7.48-7.44 (3 H, m, H-9 and H-11), 6.55 (1 H, s, H-1), 4.44 (1 H, dd, J 3.1, 9.1, H-3), 3.93 (1 H, d, J 3.1, H-2), 3.73 (3 H, s, H-12), 1.84-1.69 (3 H, m, H-4, H-5a, H-6a), 1.70-1.54 (1 H, m, H-6b), 0.98-0.94 (6 H, m, H-7 and H-8).

δ_c (100 MHz, CDCl₃):

168.7 (C=O), 165.0 (C=O), 152.1 (q), 134.9 (q), 130.9, 129.2, 126.2, 116.8, 79.9, 52.9, 45.2, 41.7, 20.2, 19.7, 9.9, 9.6.

*[α]_D^{20}_{20} refers to a mixture of trans-492; cis-492 (76:24)*

**Methyl 2-heptyl-6-oxo-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate (trans-493 and cis-493, Table 4.3, entry 7)**

![Chemical Structure](image)

Prepared according to general procedure E using anhydride 150 (46.3 mg, 0.246 mmol), anhydrous MTBE (2.5 mL, 0.1 M), freshly distilled octanal (485, 38.4 µL, 0.246 mmol) and catalyst 239 (9.10 mg, 0.0123 mmol - 5 mol%). The reaction was stirred for 24 hours at room temperature to give a diastereomeric mixture of carboxylic acids in a 55:45 ratio (trans: cis). After esterification the diastereomeric mixture was purified by flash column chromatography eluting with 75:25 hexanes:EtOAc. trans-493 and cis-493 were isolated together as a pale yellow oil (34.1 mg, 42%). TLC (hexane/EtOAc, 8:2 v/v): R_f 0.59.

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.5 mL min⁻¹, rt. UV detection at 254 nm. Retention times: trans-493 17.1 min (major enantiomer), 24.1 min (minor enantiomer); cis-493 22.5 min (major enantiomer), 25.7 min (minor enantiomer).
**trans-493:**

δ_H (600 MHz, CDCl_3):

7.42-7.33 (5 H, m, H-2, H-3, H-4), 6.42 (1 H, s, H-1), 4.96-4.88 (1 H, m, H-6), 3.83 (1 H, d, J 3.9, H-5), 3.69 (3 H, s, H-14), 1.96-1.89 (1 H, m, H-7a), 1.73-1.64 (1 H, m, H-7b), 1.61-1.51 (1 H, m, H-8a), 1.50-1.42 (1 H, m, H-8b), 1.40-1.23 (8 H, m, H-9, H-10, H-11 and H-12), 0.94-0.86 (3 H, m, H-13).

δ_C (151 MHz, CDCl_3):

171.1 (C=O), 163.2, 150.9 (q), 134.7 (q), 130.6, 129.1, 126.0, 117.0, 79.2, 53.0, 47.1, 33.8, 31.6, 29.1, 29.03, 25.4, 22.61, 14.0.

ν_max (neat)/cm⁻¹:

2927, 2856, 1712, 1624, 1447, 1350, 1242, 1161, 1020, 875, 772, 726, 686.

HRMS (m/z - APCI):

Found: 331.1913 [M+H]^+ C_{20}H_{27}O_4 Requires: 331.1903.

**cis-493:**

δ_H (600 MHz, CDCl_3):

7.52-7.45 (2 H, m, H-2), 7.42-7.33 (3 H, m, H-3, H-4), 6.46 (1 H, s, H-1), 4.60 (1 H, ddd, J 3.5, 5.1, 8.3, H-6), 3.71 (1 H, d, J 3.5, H-5), 3.65 (3 H, s, H-14), 1.88-1.83 (1 H, m, H-7a), 1.84-1.73 (1 H, m, H-7b), 1.70-1.62 (1 H, m, H-8a), 1.58-1.48 (1 H, m, H-8b), 1.40-1.23 (8 H, m, H-9, H-10, H-11 and H-12), 0.94-0.86 (3 H, m, H-13).

δ_C (151 MHz, CDCl_3):

168.5 (C=O), 164.8 (C=O), 151.6 (q), 134.8 (q), 130.9, 129.2, 126.1, 116.7, 78.2, 52.9, 47.0, 32.6, 31.7, 29.2, 29.08, 25.3, 22.63, 14.1.
Methyl-2-(4-methylpent-3-en-1-yl)-6-oxo-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate (*trans*-494 and *cis*-494, Table 4.3, entry 8)

![Diagram of the compound](image.png)

Prepared according to general procedure E using anhydride 150 (46.3 mg, 0.246 mmol), anhydrous MTBE (2.5 mL, 0.1 M), freshly distilled 4-pentenal (486, 24.3 µL, 0.246 mmol) and catalyst 239 (9.10 mg, 0.0123 mmol - 5 mol%). The reaction was stirred for 24 hours at room temperature to give a diastereomeric mixture of carboxylic acids in a 70:30 ratio (*trans*: *cis*). After esterification the diastereomeric mixture was purified by flash column chromatography eluting with 75:25 hexane:EtOAc, *trans*-*494* and *cis*-494 were isolated together as a pale yellow oil (25.4 mg, 36%). TLC (hexane/EtOAc, 8:2 v/v): R<sub>f</sub> 0.72, [α]<sub>D</sub><sup>20</sup> = - 45.0 (c = 0.01, CHCl<sub>3</sub>)<sup>*</sup>.

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.5 mL min<sup>-1</sup>, rt, UV detection at 254 nm, retention times: *trans*-494 19.0 min (minor enantiomer), 24.2 min (major enantiomer); *cis*-494 21.0 min (minor enantiomer), 34.2 (major enantiomer).

**trans*-494:**

δ<sub>H</sub> (600 MHz, CDCl<sub>3</sub>):

7.53-7.41 (5 H, m, H-2, H-3 and H-4), 6.44 (1 H, s, H-1), 5.86-5.77 (1 H, m, H-9), 5.12 (1 H, dd, J 1.5, 17.1, H-10a), 5.06 (1 H, dd, J 1.5, 10.1, H-10b), 4.98-4.93 (1 H, m, H-6), 3.86 (1 H, d, J 4.1, H-5), 3.69 (3 H, s, H-11), 2.40-2.33 (1 H, m, H-8a), 2.32-2.23 (1 H, m, H-8b), 2.12-1.98 (1H, m, H-7a), 1.82-1.70 (1 H, m, H-7b).

δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>):

169.9 (C=O), 162.9 (C=O), 150.9 (q), 136.5, 135.8 (q), 130.7, 129.4, 126.0, 117.0, 116.21, 78.4, 53.1, 47.2, 33.1, 29.4.
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$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 2952, 1710, 1641, 1447, 1352, 1255, 1118, 1055, 973, 909, 878, 774, 683, 603.


cis-494:

$\delta$H (600 MHz, CDCl$_3$): 7.61-7.54 (2 H, m, H-2), 7.53-7.41 (3 H, m, H-3 and H-4), 6.56 (1 H, s, H-1), 5.95-5.76 (1 H, m, H-9), 5.15 (1 H, dd, $J$ 1.5, 17.6, H-10a), 5.07 (1 H, dd, $J$ 1.5, 10.2, H-10b), 4.62 (1 H, ddd, $J$ 4.9, 8.7, H-6), 3.80 (1 H, d, $J$ 3.4, H-5), 3.75 (3 H, s, H-11), 2.48-2.39 (1 H, m, H-8a), 2.40-2.31 (1 H, m, H-8b), 2.02-1.93 (1H, m, H-7a), 1.93-1.84 (1 H, m, H-7b).

$\delta$C (100 MHz, CDCl$_3$): 169.4 (C=O), 164.6 (C=O), 151.5 (q), 136.7, 134.7 (q), 131.1, 129.1, 126.1, 116.7, 116.2, 77.2, 52.9, 46.9, 31.7, 29.3.

* $[\alpha]_{D}^{20}$ refers to a mixture of trans-494: cis-494 (70:30)

Methyl 4-methyl-6-oxo-2-(pentan-3-yl)-3,6-dihydro-2H-pyran-3-carboxylate (trans-495, Scheme 4.5)

Prepared according to general procedure E using anhydride 151 (31.0 mg, 0.246 mmol), anhydrous MTBE (2.5 mL, 0.1 M), 2-ethylbutaraldehyde (484, 30.4 µL, 0.246 mmol) and catalyst 239 (9.10 mg, 0.0123 mmol - 5 mol%). The reaction was stirred for 24 hours at room temperature to give a diastereomeric mixture of carboxylic acids in a 87:13 ratio (trans:cis). After esterification by flash column chromatography eluting with 75:25 hexane:EtoAc, trans-495 was isolated as a pale yellow oil (24.8 mg, 42%). TLC (hexane/EtoAc, 8:2 v/v): $R_t$ 0.7, $[\alpha]_{D}^{20} = - 23.3 \ (c = 0.02, \text{CHCl}_3)$. 
CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.5 mL min\(^{-1}\), RT, UV detection at 254 nm, retention times: 14.5 min (major enantiomer), 16.3 min (minor enantiomer).

$$\delta_H (400 \text{ MHz, CDCl}_3): \quad 5.93 (1 \text{ H, s, H-1}), 4.73 (1 \text{ H, dd, } J 4.5, 8.4, \text{ H-3}), 3.49 (1 \text{ H, d, } J 8.4, \text{ H-2}), 3.81 (3 \text{ H, s, H-9}), 2.01 (3 \text{ H, s, H-10}), 1.78-1.61 (3 \text{ H, m, H-4, H-5a, H-6a}), 1.56-1.41 (2 \text{ H, H-5b, H-6b}), 0.97-0.91 (6 \text{ H, m, H-7, H-8}).$$

$$\delta_C (100 \text{ MHz, CDCl}_3): \quad 172.9 (\text{C=O}), 164.2 (\text{C=O}), 161.3 (\text{q}), 116.4, 78.3, 52.3, 45.5, 44.8, 23.7, 22.6, 20.2, 11.4, 10.9.$$  

$$\nu_{\text{max}} \text{ (neat)/cm}^{-1}: \quad 2965, 1721, 1695, 1624, 1446, 1350, 1245, 1055, 1018, 893, 777, 689, 602, 576.$$  

HRMS (m/z -ESI): Found: 263.1249 [M+Na]\(^{+}\) \(C_{13}H_{20}NaO_4\) Requires: 263.1253.
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