# Organocatalysed transformations of enolisable cyclic anhydrides

Trinity College Dublin

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Doctor of Philosophy

by

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Under the supervision of

Prof. Stephen Connon

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## Declaration

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

C. Trujillo, I. Rozas, A. Botte and S. J. Connon, *Chem. Commun.*, 2017, **53**, 8874.

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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.

# Abbreviations

| | |
|---|---|
| Ac | Acetyl |
| AcOH | Acetic acid |
| AD | Asymmetric dihydroxylation |
| APCI | Atmospheric-pressure chemical ionization |
| app. d | Apparent doublet |
| app. s | Apparent singlet |
| app. t | Apparent triplet |
| Ar | Aryl |
| B | Base |
| b.p. | Boiling point |
| Bn | Benzyl |
| Boc | *tert*-Butoxycarbonyl |
| bs | Broad singlet |
| *c*- | *cyclo*- |
| cat. | Catalyst |
| CI | Chemical ionisation |
| CIP | Cahn–Ingold–Prelog |
| COD | 1,5-Cyclooctadiene |
| conc. | Concentrated |
| conv. | Conversion |
| CSP | Chiral stationary phase |
| Cys | Cysteine |
| d | Days |
| d | Doublet |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| dd | Doublet of doublets |
| ddd | Doublet of doublet of doublets |
| DIAD | Diisopropyl azodicarboxylate |
| DIP | Direct insertion probe |
| DIPAMP | Ethane-1,2-diylbis[(2-methoxyphenyl)phenylphosphane] |
| DIPEA | *N*,*N*-Diisopropylethylamine |
| DMAP | 4-(Dimethylamino)pyridine |
| DMC | 2-Chloro-l,3-dimethylimidazolinium chloride |
| DMF | Dimethylformamide |
| DMSO | Dimethyl sulfoxide |
| DPPA | Diphenylphosphoryl azide |
| *dr* | Diastereomeric ratio |
| E | Electrophile |

| | |
|---|---|
| EDG | Electron donating group |
| *ee* | Enantiomeric excess |
| EI | Electron ionisation |
| equiv. | Equivalent |
| ESI | Electrospray ionization |
| Et | Ethyl |
| EtOAc | Ethyl acetate |
| EtOH | Ethanol |
| EWG | Electron withdrawing group |
| h | Hours |
| His | Histidine |
| HMPA | Hexamethyl phosphoramide |
| $HNEt_2$ | Diethyl amine |
| HOMO | Highest occupied molecular orbital |
| HPLC | High Performance Liquid Chromatography |
| HRMS | High-resolution mass spectrometry |
| *i*- | *iso*- |
| IPA | *iso*-Propyl alcohol |
| *i*-Pr | Isopropyl |
| *i*-$Pr_2NEt$ | *N,N'*-Diisopropylethylamine (Hünig's base) |
| *i*-PrOH | 2-propanol |
| IR | Infrared |
| IUPAC | International Union of Pure and Applied Chemistry |
| KHMDS | Potassium bis(trimethylsilyl)amide |
| LA | Lewis acid |
| LDA | Lithium diisopropylamide |
| L-DOPA | L-3,4-DIHYDROXYPHENYLALANINE |
| LiHMDS | Lithium bis(trimethylsilyl)amide |
| lit. | Literature |
| LUMO | Lowest unoccupied molecular orbital |
| m | Multiplet |
| *m*- | *meta*- |
| m.p. | Melting point |
| *m*/*z* | Mass/Charge |
| Me | Methyl |
| MeOH | Methanol |
| min | Minutes |
| mol. sieves | Molecular sieves |
| MTBE | Methyl-*tert*-butyl ether |
| MW | Microwave |
| *n*- | *normal*- |

| | |
|---|---|
| $NAD^+$/NADH | Nicotinamide adenine dinucleotide |
| NaHMDS | Sodium bis(trimethylsilyl)amide |
| $NEt_3$ | Triethylamine |
| NMR | Nuclear magnetic resonance |
| NOE | Nuclear Overhauser Effect |
| Nu | Nucleophile |
| *o*- | *ortho*- |
| OAc | Acetate |
| *p*- | *para*- |
| Ph | Phenyl |
| Pr | Propyl |
| prod. | Product |
| q | Quartet |
| quant. | Quantitative |
| rt | Room temperature |
| s | Singlet |
| t | Triplet |
| *t*- | *tert*- |
| *t*-Bu | *tert*-Butyl |
| *t*-BuOH | *tert*-Butyl alcohol |
| temp. | Temperature |
| *tert*- | *tertiary*- |
| TFA | Trifluoroacetic acid |
| TFAA | Trifluoroacetic anhydride |
| THF | Tetrahydrofuran |
| TLC | Thin layer chromatography |
| TMS | Trimethylsilyl |
| $TMSCHN_2$ | Trimethylsilyl diazomethane |
| TMSCN | Trimethylsilyl cyanide |
| UV | Ultraviolet |
| *v*/*v* | Volume/Volume |
| *w*/*v* | Weight/Volume |

# 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-superimposible 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

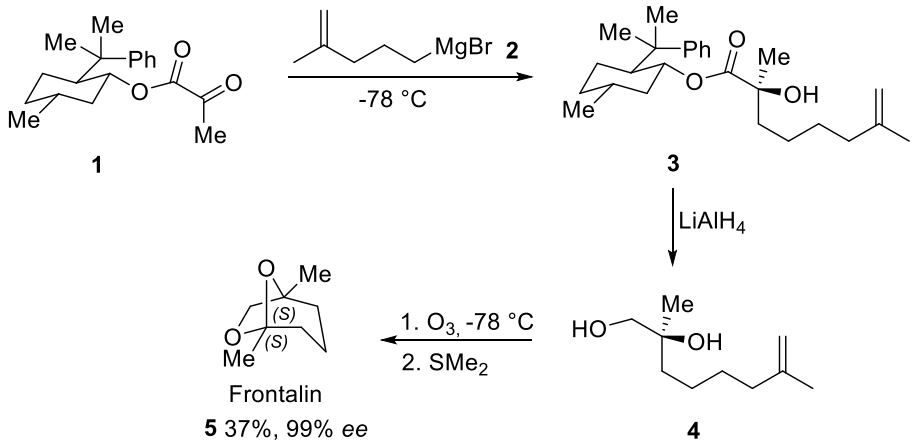
Overall, the four strategies[9] for the synthesis of enantiomerically-pure compounds are:

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.[10] 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.[11] 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).[12]

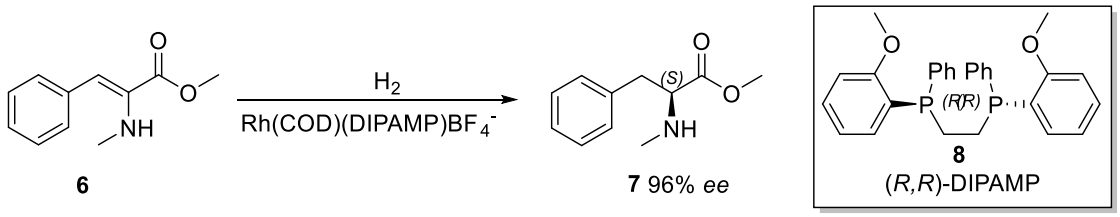
The chiral auxiliary strategy requires that an enantiomerically pure chiral group is covalently linked to the achiral substrate and is realeased when the desired product is obtained. An example is the 3-step asymmetric synthesis of the pherormone frontalin (**5)** developed by Whitesell and co-workers in 1986 using 8-phenylmenthol as chiral auxiliary (Scheme1.1).[13]




**Scheme 1.1** Example of enantioselective synthesis promoted by chiral auxiliary.

Asymmetric catalysis can use enzymes, organometallic catalysts or small, low molecular weight chiral organic molecules (organocatalysts).[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 definetly 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 triphenilphosphine complex of rhodium chloride,[16] he observed that by using chiral bisphosphine ligands (DIPAMP **8**), stereochemical information was transferred from the rhodium centre to the olefinic substrate **6**, leading to the formation of **7** in excellent enantiomeric excess (Scheme 1.2).[17]

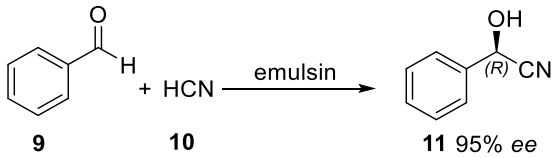



**Scheme 1.2** Enantioselective metal-catalysed hydrogenation.

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.[18,19] 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).[20]



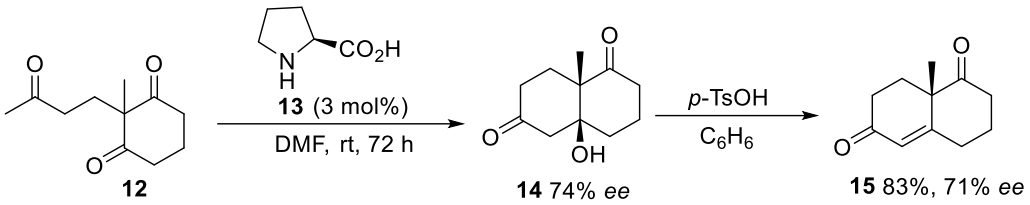

**Scheme 1.3** Enzyme-catalysed asymmetric synthesis of (*R*)-mandelonitrile (**11**).

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.[21]

## 1.2 The development of organocatalysis

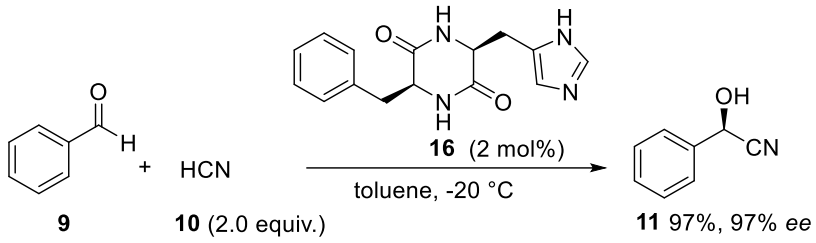
Organocatalysis is the branch of asymmetric catalysis that uses chiral natural or synthetic organic molecules as catalysts. These compounds are usually stable to moisture and air, non toxic, readily available and low-cost. Since the beginning of organic synthesis, chemists tried to prepare molecules 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*".[22,23]

In 1971 Hajos-Parrish[24]-Eder-Sauer-Wiechert[25] 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.[26]




**Scheme 1.4** *L*-Proline mediated annulation.

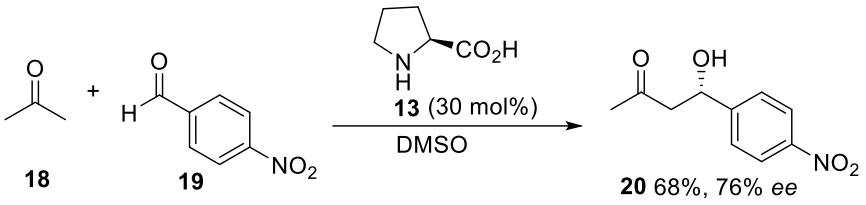
Later, in the 1980s, Inoue and co-workers demonstrated that a cyclic dipeptide prepared from (*L*)-phenylalanine and (*L*)-histidine (**16**), was able to catalyse the addition of **10** to benzaldehyde (**9)** with the creation of chiral cyanohydrin **11** (Scheme 1.5).[27]




**Scheme 1.5** Enantioselective aldehyde hydrocyanation.

### 1.2.1 Organocatalysis: principal modes of action

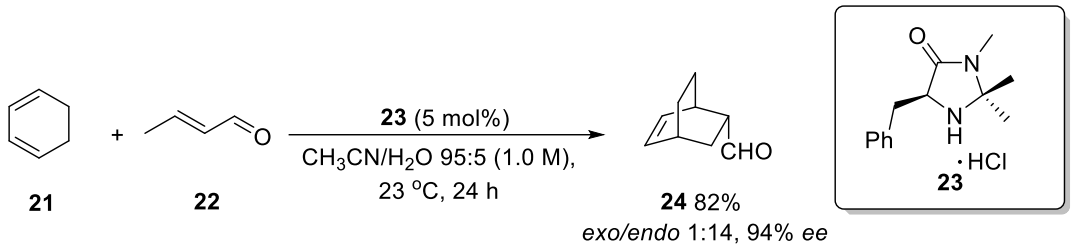
Organocatalysis is still a rather new and popular field that only came to prominence at the start of the 21st century. Before that only sporadic mentioning of chemical transformations promoted by organic catalysts were reported. It was List, Lerner and Barbas who reported the first example of an intermolecular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




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

Shortly after this seminal publication, MacMillan *et al.* used secondary amines such as **23** to catalyse the Diels-Alder reaction between dienes (*i.e.* **21**) and α,β-unsaturated

aldehydes such as **22** generating a new class of catalysts known as MacMillan's imidazolidinones[29] (Scheme 1.7).




**Scheme 1.7** Asymmetric organocatalysed Diels-Alder reaction.

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 π-conjugated systems, the electronic delocalisation induced by iminium ions facilitates nucleophilic additions (LUMO-activation, Scheme 1.8a) while for isolated π- systems, this electronic delocalisation can induce a rapid deprotonation event at the α-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]

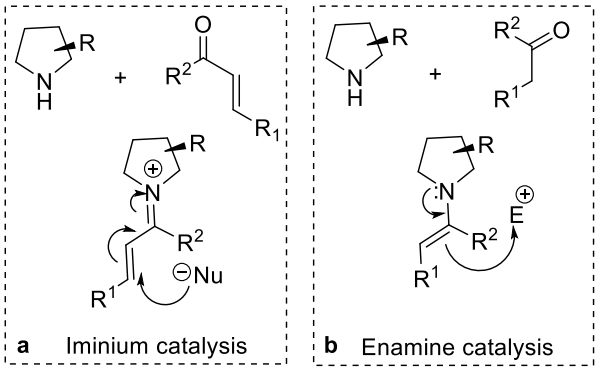
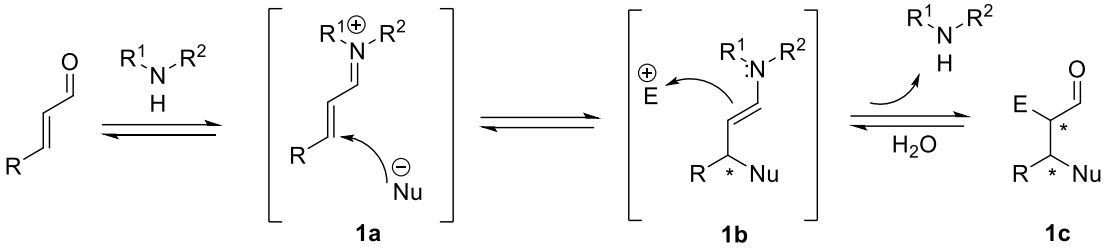



**Figure 1.1** Iminium-enamine catalysis.

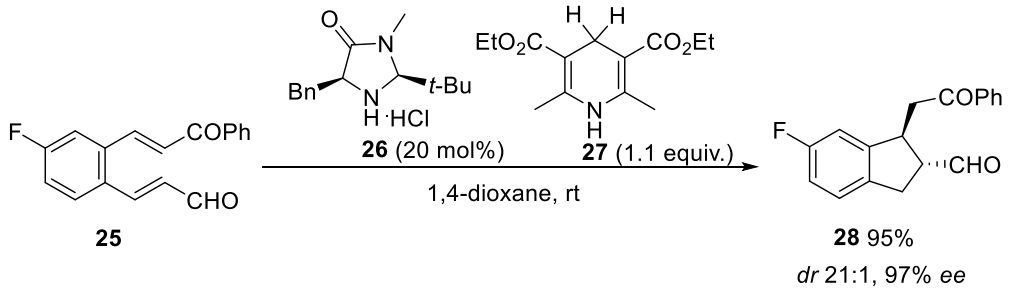
The efficiency and synthetic applications of these catalytic modes of action can be significantly improved when they work in tandem with each other, which facilitates "one pot" reactions. The reaction of the nucleophile with the iminium ion **1a**, resulting in the

formation of an enamine, enables electrophilic addition **1b** thereby creating two stereocenters in the process (**1c**, Scheme 1.8).



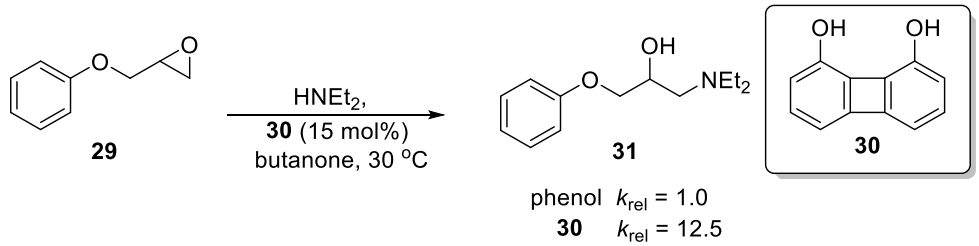

**Scheme 1.8** Combination of iminium-enamine catalytic cycles.

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]



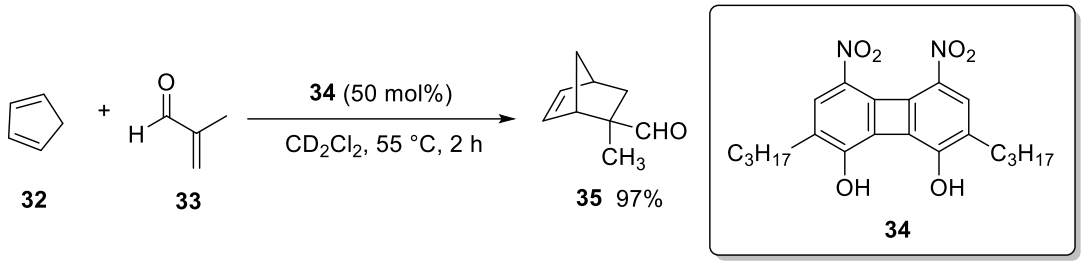

**Scheme 1.9** Imidazolidinone-catalysed Michael cyclisation.

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.

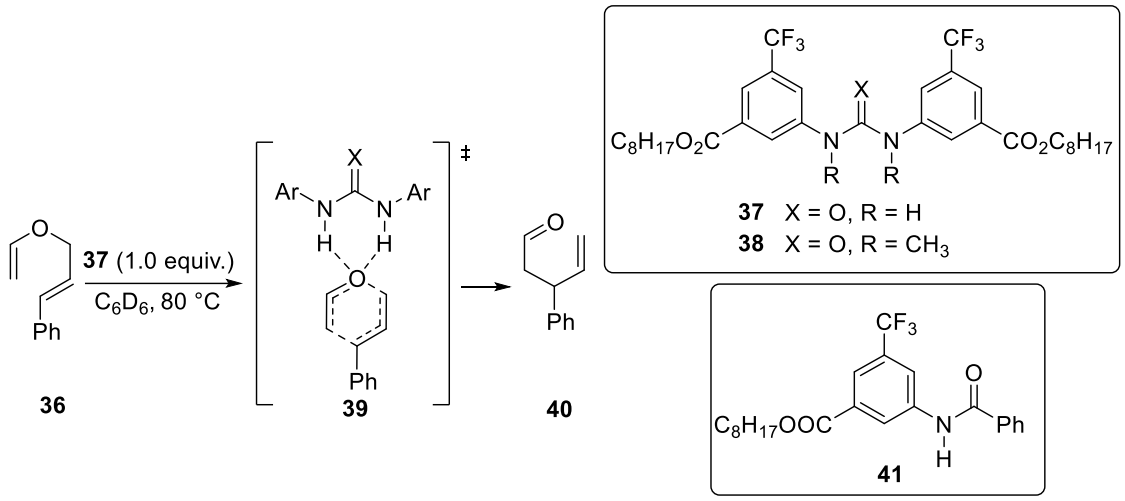
An extension of this concept came in the following years, when Kelly and co-workers demonstrated Diels-Alder reactions with superior rates, by establishing a *bis*-hydrogen bond interaction between biphenyldiols such as **34** and dienophiles (*i.e.* **33**, Scheme 1.11)[38]




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

### 1.2.2 (Thio)ureas in asymmetric organocatalysis

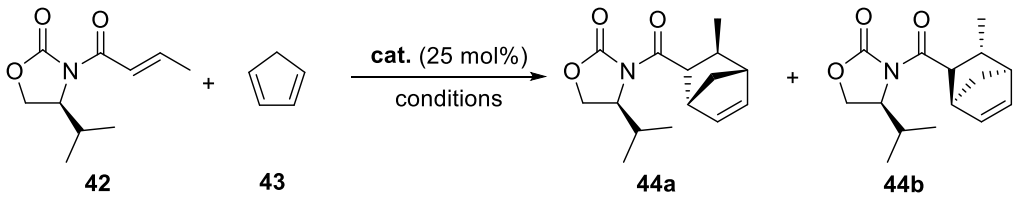
In the late 1980s, asymmetric synthesis based on electrophile activation by small molecules H-bond donors gained considerable attention.[39] The observation by Etter and co-workers that electron poor diarylureas co-crystallised with a wide variety of Lewis bases (*e.g* sulfoxides) due to their high H-bond donating ability should be considered noteworthy.[40,41] 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.[42] 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).[43]

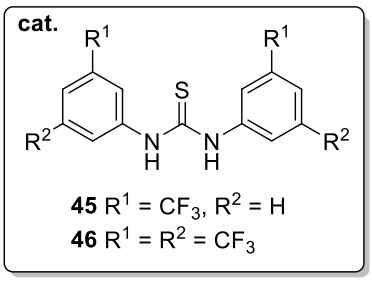



**Scheme 1.12** Claisen rearrangement catalysed by *N,N*-diaryl urea.

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 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.[44] 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).

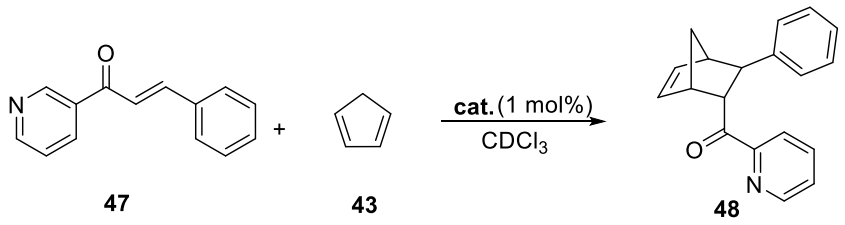


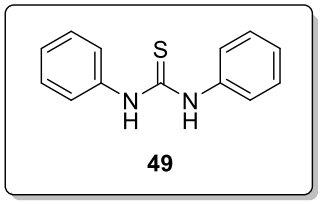




| cat. | yield (%) | dr (44a : 44b) |
|---|---|---|
| - | 55 | 36 : 64 |
| $AlCl_3$ | 95 | 92 : 8 |
| **45** | 74 | 77 : 23 |
| **46** | 78 | 81 : 19 |

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

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 raction. 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).[45]



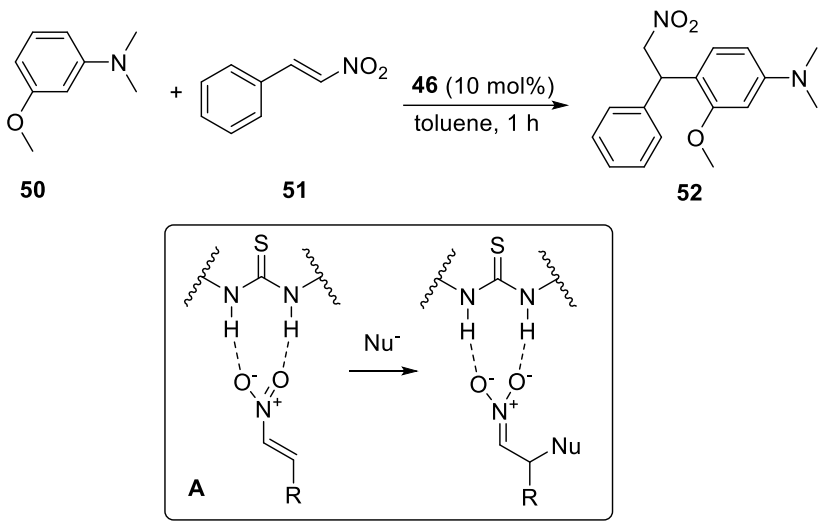




| cat. | $K_{rel}$ |
|---|---|
| **45** | 2.2 |
| **46** | 5.3 |
| **49** | 1.3 |

**Scheme 1.14** [4 + 2] cycloaddition reactions catalysed by diarylthioureas.

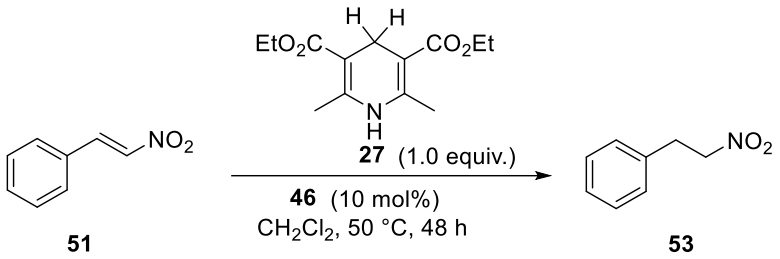
In subsequent studies, Schreiner's catalyst **46** was shown to be an efficient promoter in a wide range of organic transformations such as Corey-Chaykovsky epoxidations,[46] epoxide ring opening reactions,[47] and Baylis-Hillman reactions.[48]

In 2003, Takemoto and co-workers reported **46** as an efficient catalyst for the promotion of the addition of cyanide (TMSCN) and ketene silyl acetals to various nitrones in high yield with fast reaction rates.[49] 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).[50]



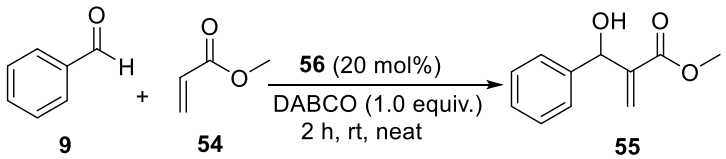

**Scheme 1.15** Friedel–Crafts Alkylation catalysed by thiourea **46**.

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.[51] 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).

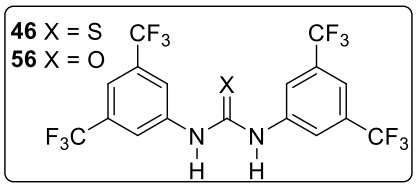



**Scheme 1.16** Thiourea promoted biomimetic reduction of nitrostyrene (**51**).

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.[52] 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).

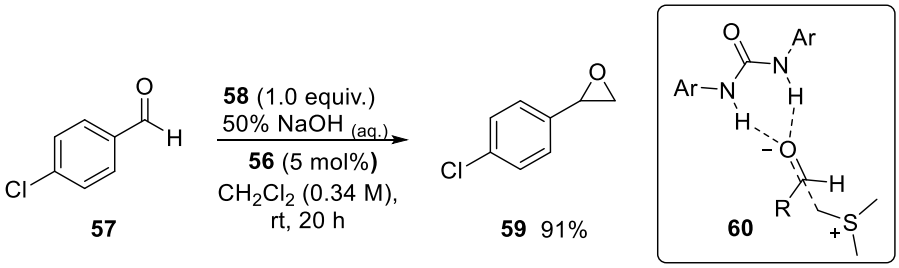



| cat. | $k_{rel}$ |
|---|---|
| **46** | 3.7 |
| **56** | 6.7 |




**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** (Scheme1.18).[53]

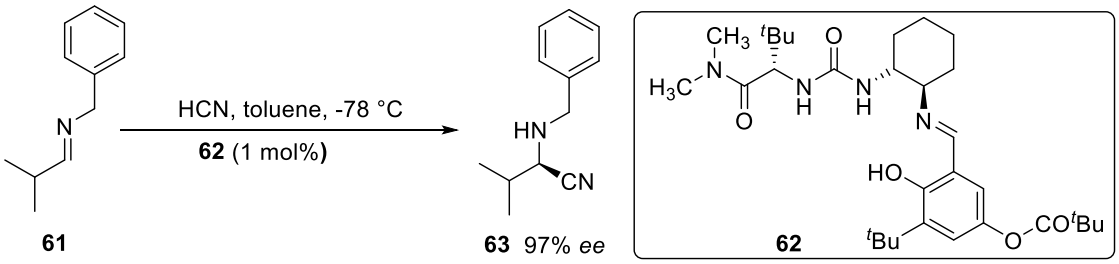



**Scheme 1.18** Corey-Chaykovsky reaction promoted by a *N,N*-diarylurea.

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=N double bond (Strecker reaction), in 1998 Jacobsen *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 (*i.e.* **61**), in presence of 1 mol% of catalyst **62** affording the $\alpha$-aminonitrile **63** was completed in excellent enantioselectivity (Scheme 1.19).

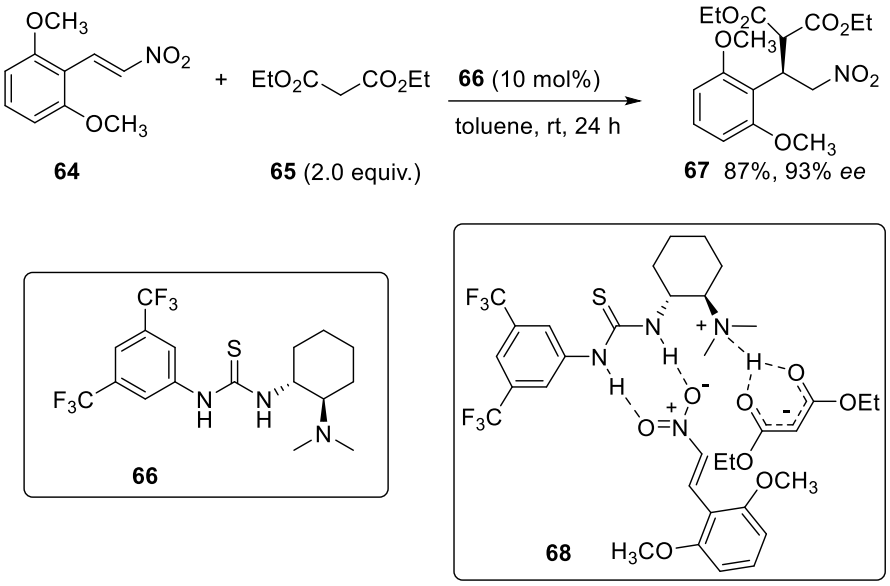



**Scheme 1.19** Asymmetric Strecker reaction with optimised Jacobsen-type organocatalyst **62**.

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

### 1.2.4 Bifunctional asymmetric (thio)urea-based organocatalysts

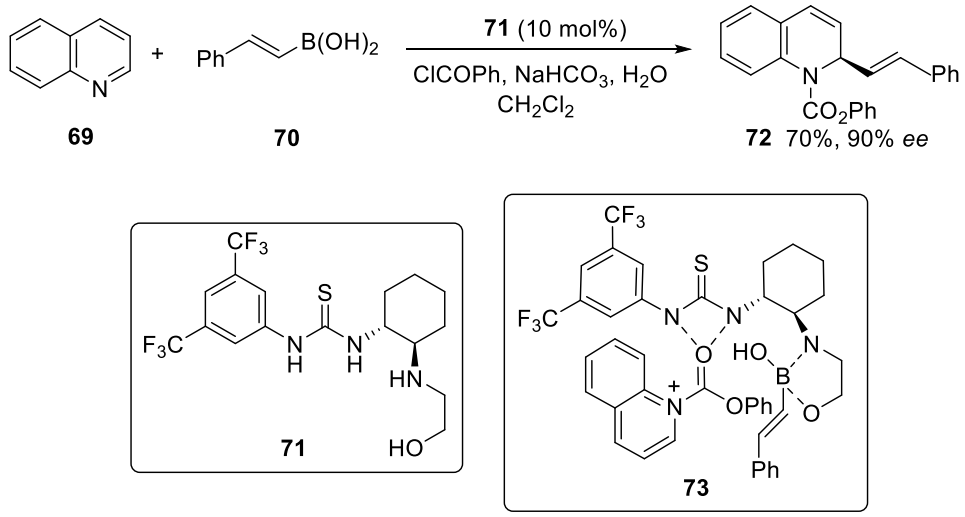
Over the past decade, bifunctional compounds, bearing both a thiourea moiety and an amine group on a chiral scaffold have emerged as a powerful tool in asymmetric organocatalysis.[61,62,63] Chiral catalysts containing both an acidic and basic/nucleophilic structural units were first reported by Takemoto and co-workers in 2003.[64] They demonstrated that use of the thiourea catalyst **66**, led to an efficient Michael addition reaction of malonates such as **65** to nitroolefins (*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).[39]




**Scheme 1.20** Michael-type reaction catalysed by bifunctional thiourea **66**.

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

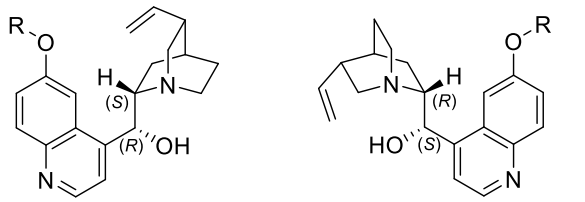
In 2007, subsequent studies by the same group led to the development of a new amino-alcohol-type thiourea **71**, reporting the first asymmetric catalytic Petasis reaction of quinolines (**69**) and vinyl boronic acids (*i.e.* **70**) in which the thiourea moiety could activate the *N*-acylated quinolinium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




**Scheme 1.21** Asymmetric Petasis reaction catalysed by thiourea **71**.

## 1.3 Introduction of natural cinchona alkaloids in organocatalysis

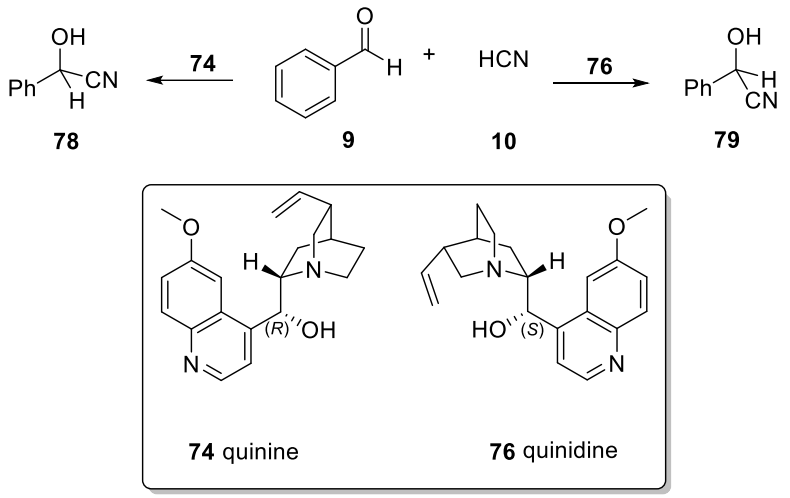
Cinchona alkaloids, were brought to Europe as a treatment for malaria in the early 17th century by Jesuit priests returning from Peru.[69,70] Linnaeus in 1742 named the tree, cinchona, from which they derived, although the bark was more commonly known as Jesuit's powder or Peruvian bark.[71] They were 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.[72] 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**).[73] These inexpensive and readily prepared natural products exist in two *pseudo*enantiomeric 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]




**74** R = Me (-)-quinine
**75** R = H (-)-cinchonidine
**76** R = Me (+)-quinidine
**77** R = H (+)-cinchonine

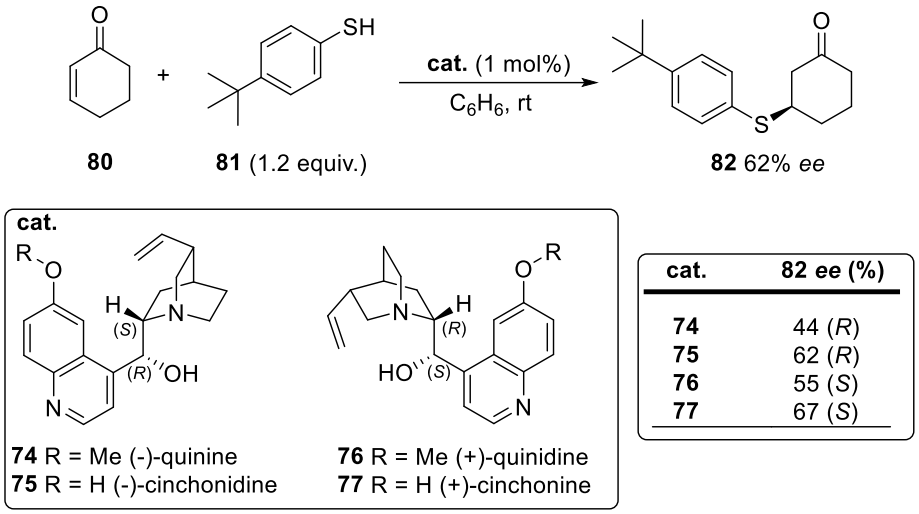
**Figure 1.2** Nomenclature and main examples of cinchona alkaloids.

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 *pseudo*enantiomers (Scheme 1.22).[76]




**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).[34,77]

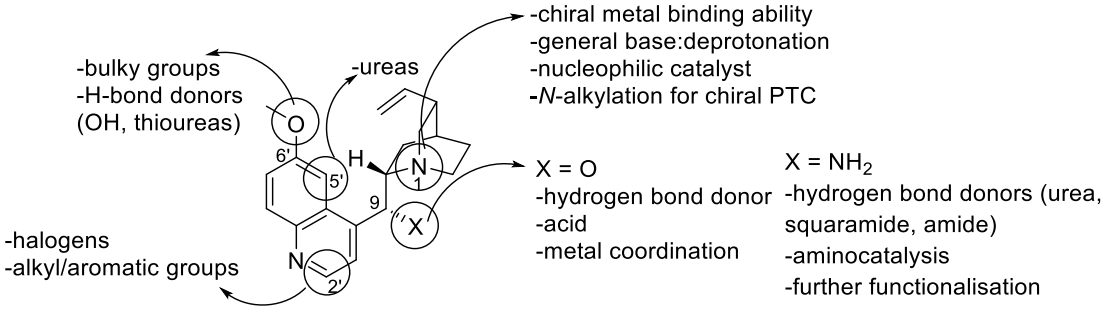



**Scheme 1.23** Cinchona alkaloids-catalysed addition of thiols to $\alpha,\beta$-unsaturated ketones.

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.[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 easly 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).



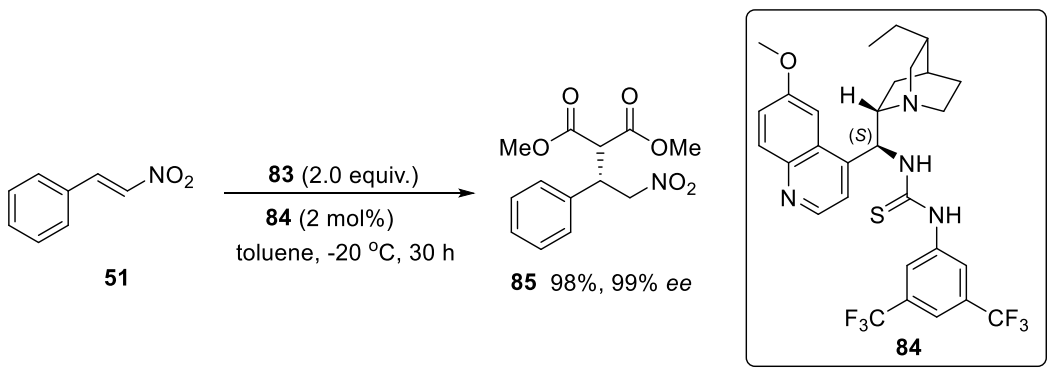

**Scheme 1.24** Active sites of functionalisation in cinchona alkaloids and their derivatives.

### 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.[81] 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.[82]

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.

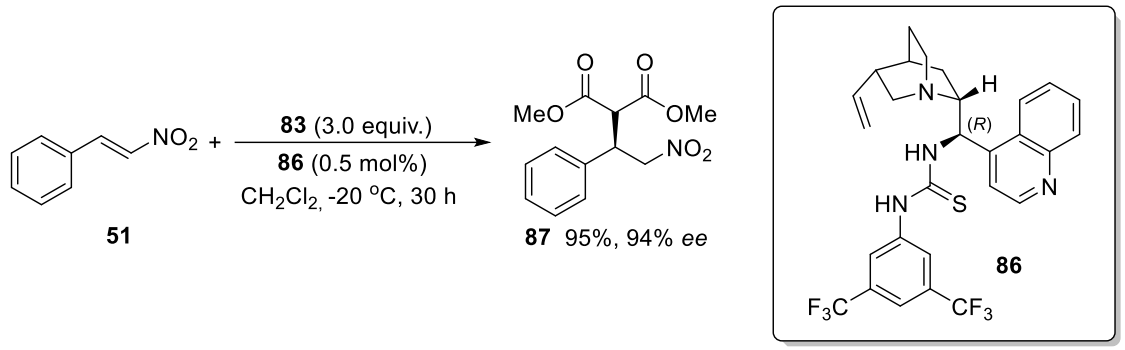
Connon and co-workers deduced that the absolute configuration at *C*-9 of the cinchona structure was crucial in order to reach high levels of selectivity.[83] In 2005, they found that the use of the *pseudo*enantiomeric hydroquinine-based catalyst **84** led to a very efficient reaction but with an opposite sense of asymmetric induction to that observed for the hydroquinidine-based compound. This catalyst promoted Michael-type additions of dimethyl malonate (**83**) to nitrostyrene (**51**) allowing the generation of product **85** in high yields and enantioselectivity (Scheme 1.25).




**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.[84] 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*.

### 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).

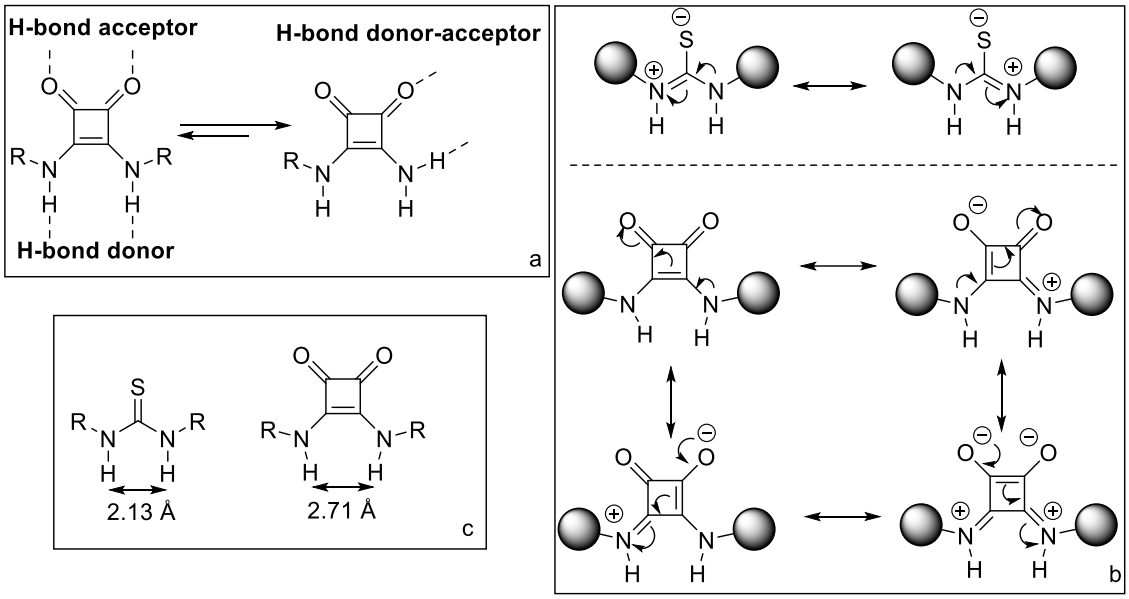
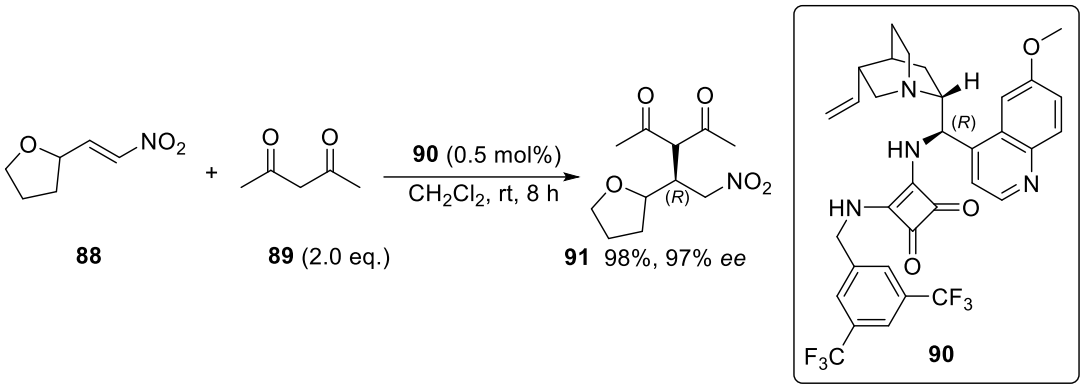



**Figure 1.3** Structural characteristics of squaramide.

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 ($pKa_1$ = 0.54; $pKa_2$ = 3.58) due to the stability of the negative charge by delocalisation.[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).[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).[85,86]

As mentioned above, in 2008 Rawal and co-workers applied a chiral squaramide-based organocatalyst derived from cinchona alkaloids (*i.e.* **90)** in the Michael-type addition of 1,3-dicarbonyl compounds such as **89** to nitroolefins (*i.e.* **88**, Scheme 1.27).[86]



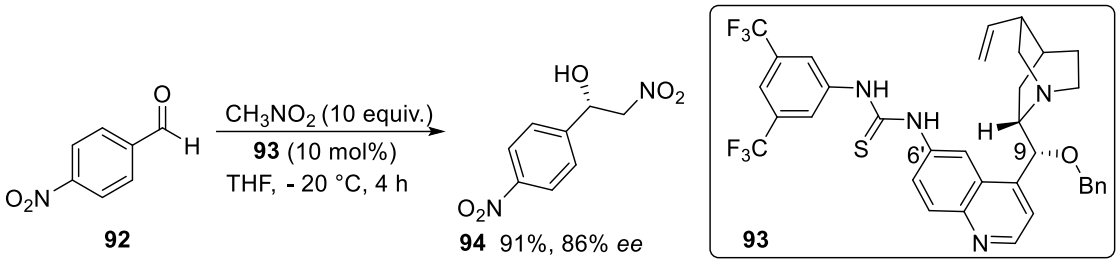

**Scheme 1.27** Michael addition promoted by squaramide-based cinchona alkaloid organocatalysts.

Since the publication of seminal work from the Rawals group,[86] squaramide-substituted cinchona alkaloids can be viewed as highly functional catalysts capable of promoting a plethora of structurally unrelated synthetic transformations.[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.[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.[91]

In 2006, Hiemstra *et al*.[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 **92**, to afford **94** (Scheme 1.28).

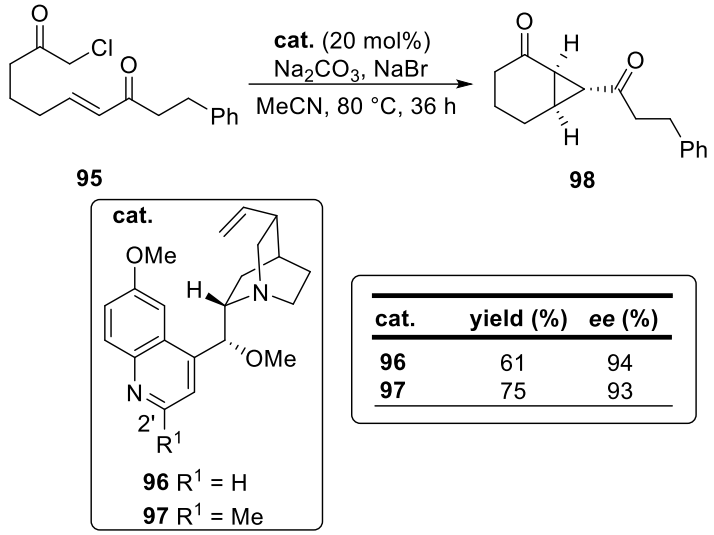



**Scheme 1.28** Henry reaction promoted by **93** bearing a thiourea group at *C*-6'.

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 reactions[94] and the asymmetric conjugate addition of thiols by Deng *et al* in 2009.[95]

### 1.3.5 Modification at C-2'

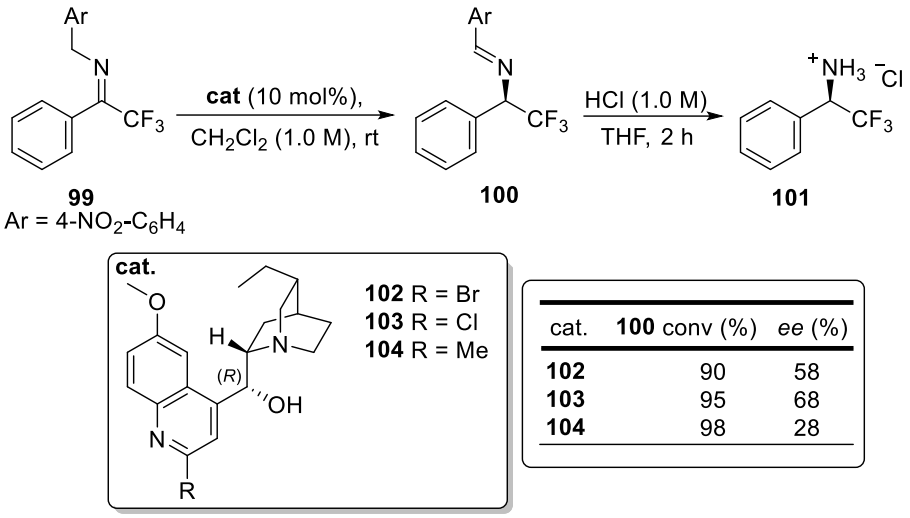
*C*-2' modified cinchona alkaloids were first introduced by Gaunt and co-workers in 2006 who developed an organocatalytic enantioselective intramolecular cyclopropanation reaction *via* ammonium ylide intermediates.[96] The authors observed that the attempt to catalyse the asymmetric intramolecular cyclopropanation 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).




| cat. | yield (%) | *ee* (%) |
|---|---|---|
| **96** | 61 | 94 |
| **97** | 75 | 93 |

**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.[97] 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 substitutent, 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.




| cat. | **100** conv (%) | *ee* (%) |
|---|---|---|
| **102** | 90 | 58 |
| **103** | 95 | 68 |
| **104** | 98 | 28 |

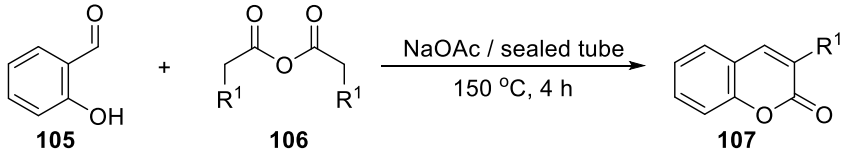
**Scheme 1.30** Asymmetric isomerisation of imines promoted by *C*-2' substituted cinchona alkaloids.

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,[98] phase-transfer catalysis[99] and organometallic chemistry (where they are used as ligands).[100]

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

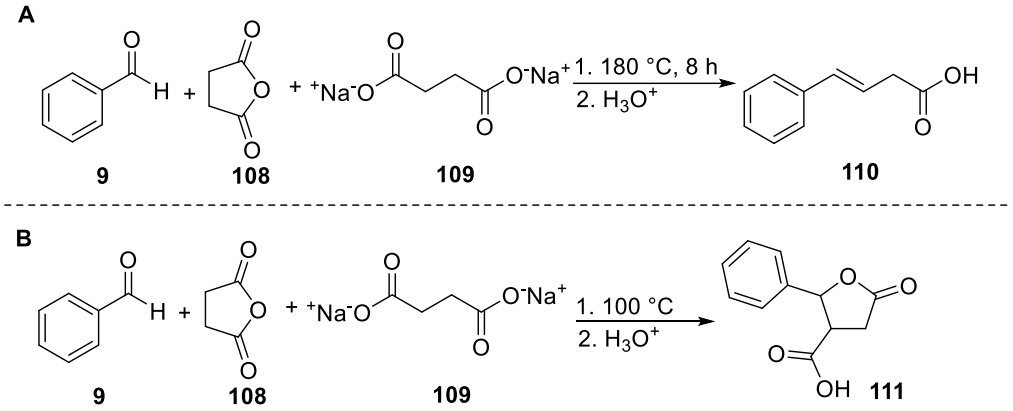
The synthetic utility of anhydrides as electrophilic acyl transfer agents has been studied for over a century.[101,102] The concept of using enolisable anhydrides as nucleophiles in formal cycloaddition reactions is a rather recent development.

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. [103,104,105] 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).[106]




**Scheme 1.31** Reaction between enolisable aliphatic anhydride **105** and salicylic aldehydes to form coumarins **107**.

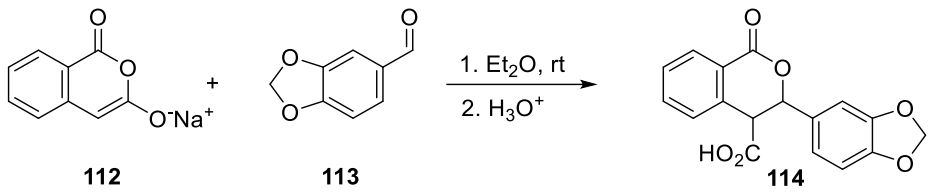
Later on, during his study, Perkin also reported that the reaction between succinic anhydride (**108**) and benzaldehyde (**9**) in the presence of sodium succinate (**109**) when heated at 180 °C furnished the product **110** as a result of a decarboxylation reaction (Scheme 1.32 A). After a short period 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).[107]




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

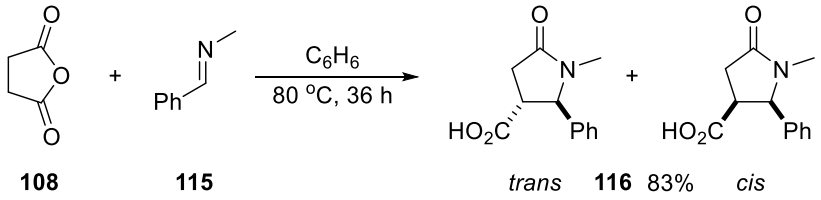
In 1931, Müller reported the condensation between the sodium enolate of homophthalic anhydride (**112**) and benzaldehyde (**9**) that furnished a dihydroisocoumarin adduct,[108] with a cycloaddition process similar to the cycloaddition of succinic anhydride (**108**) to benzaldehyde (**9**).

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).[109]

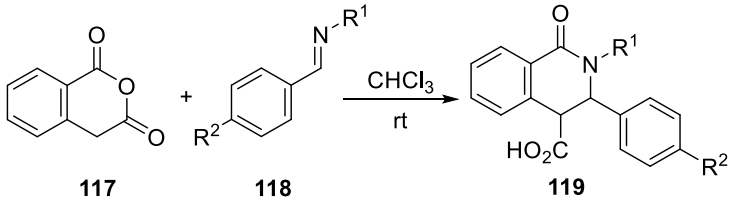



**108** **115** **116** 83%

**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.[110] 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.[111] 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.[112,113]

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).[114,115]




**117** **118** **119**

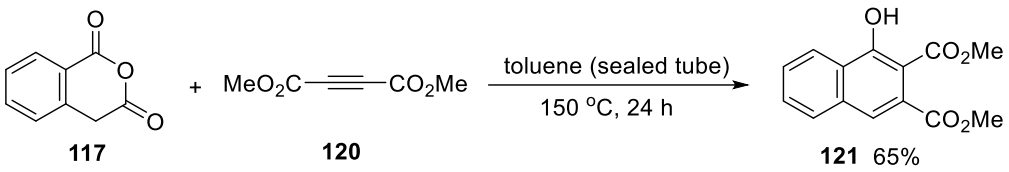
**118a** $R^1$ = Me, $R^2$ = $NO_2$
**118b** $R^1$ = Me, $R^2$ = H
**118c** $R^1$ = Me, $R^2$ = $N(CH_3)_2$
**118d** $R^1$ = *t*-Bu, $R^2$ = H

| **119** | **dr (*trans*:*cis*)** |
|---|---|
| **a** | 97:3 |
| **b** | 83:17 |
| **c** | 20:80 |
| **d** | 0:100 |

**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]

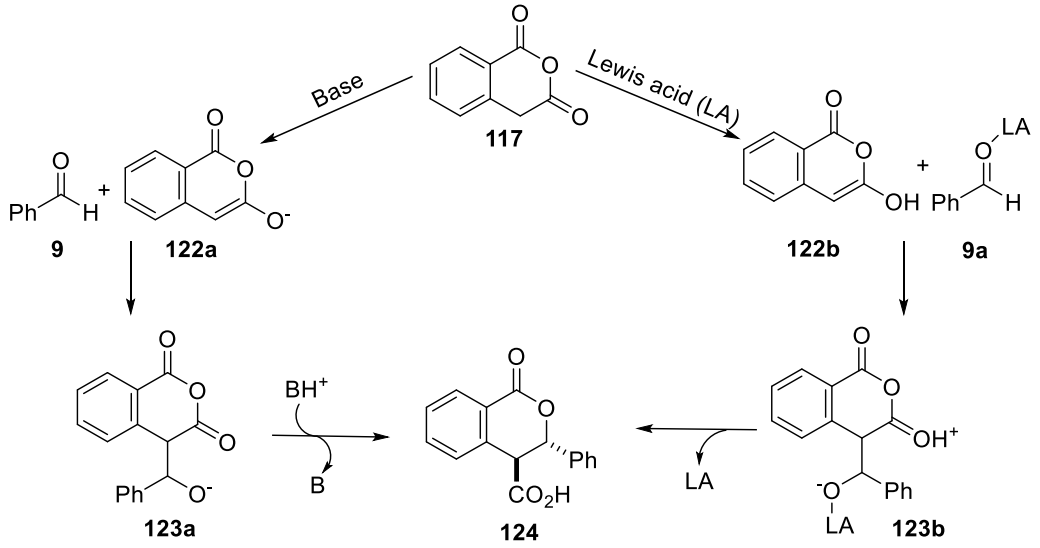



**Scheme 1.36** Cycloaddition of homophtalic anhydride (**117**) to an alkyne.

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]

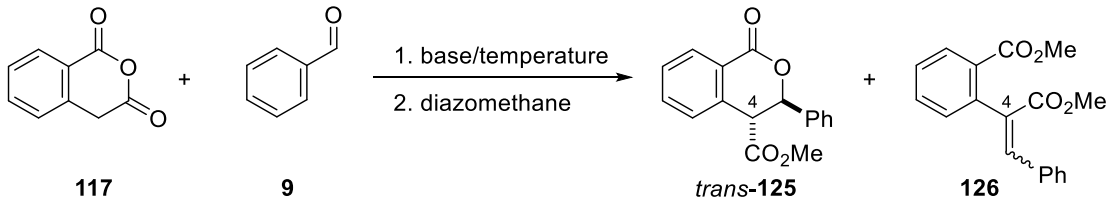
### 1.4.1 Cycloaddition reactions with aldehydes

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.[122] The attention focused on the effect of temperature on the reaction between **117** and **9** using different bases (Scheme 1.38).

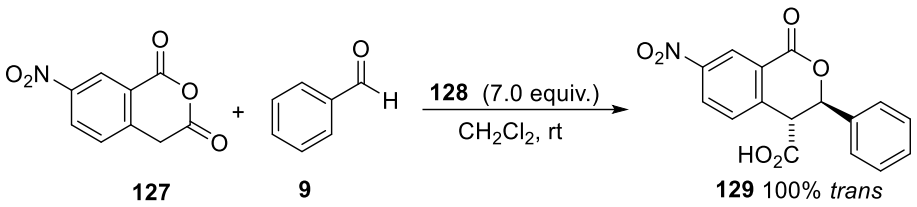



| base | temperature | 125 yield (%) | 126 yield (%) |
|---|---|---|---|
| $Na_2CO_3$ | rt | 35 | 43 |
| NaH | 0 °C to rt | 83 | - |
| NaH | 50 °C | 5 | 82 |

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

As previously reported by Nakajima, the use of $Na_2CO_3$ 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.

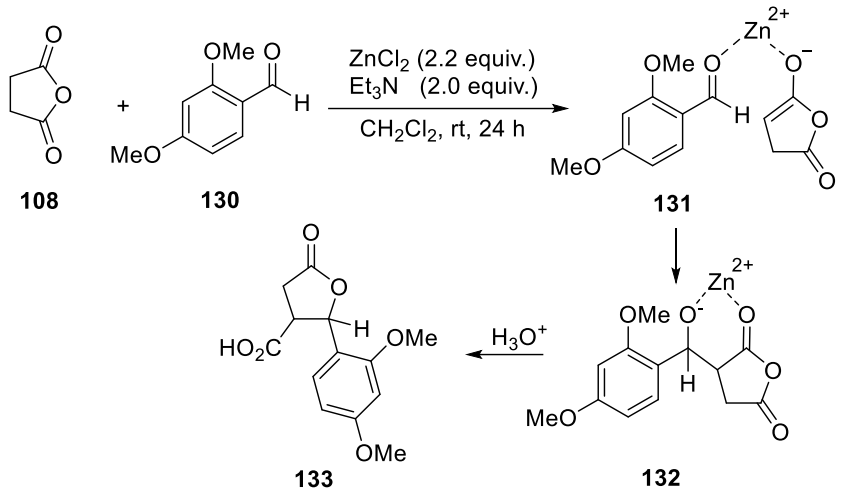
Shortly afterwards, Gesquiere *et al* experimented on cycloaddition reactions involving aldehydes and ketones as electrophiles activated by the Lewis acid boron trifluoride-diethyl ether complex (**128**).[124] They presented a new strategy for the synthesis of isocoumarin-4-carboxylic acid derivatives (*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.

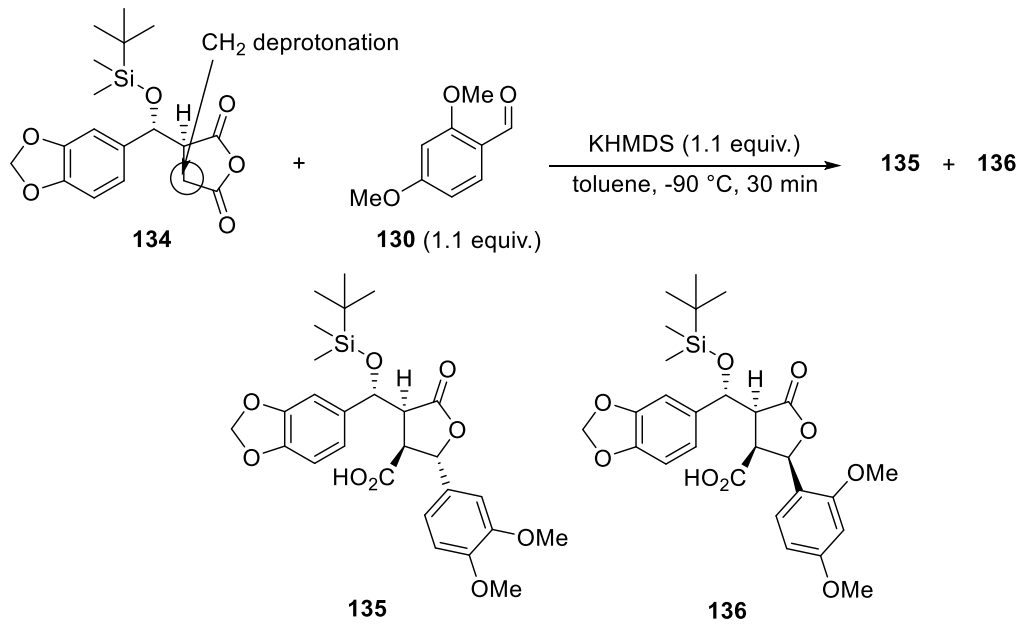
An extension of the substrate scope towards the use of ketones was then examined by the same group who reported a decrease in product yields, postulated to be due to the lower reactivity of these functional groups in comparison with aldehydes.[124] In 2004 Palamavera *et al*. described the reaction using a series of aromatic aldehydes mediated by 4-dimethylaminopyridine (DMAP) under mild conditions.[123]

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.[126] They described a new synthetic strategy based on the associated use of a Lewis acid such as $ZnCl_2$ 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).




**Scheme 1.40** Cycloaddition reaction of succinic anhydride (**108**) with an aldehyde promoted by Lewis acid/base.

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).[127,128,129] 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*.

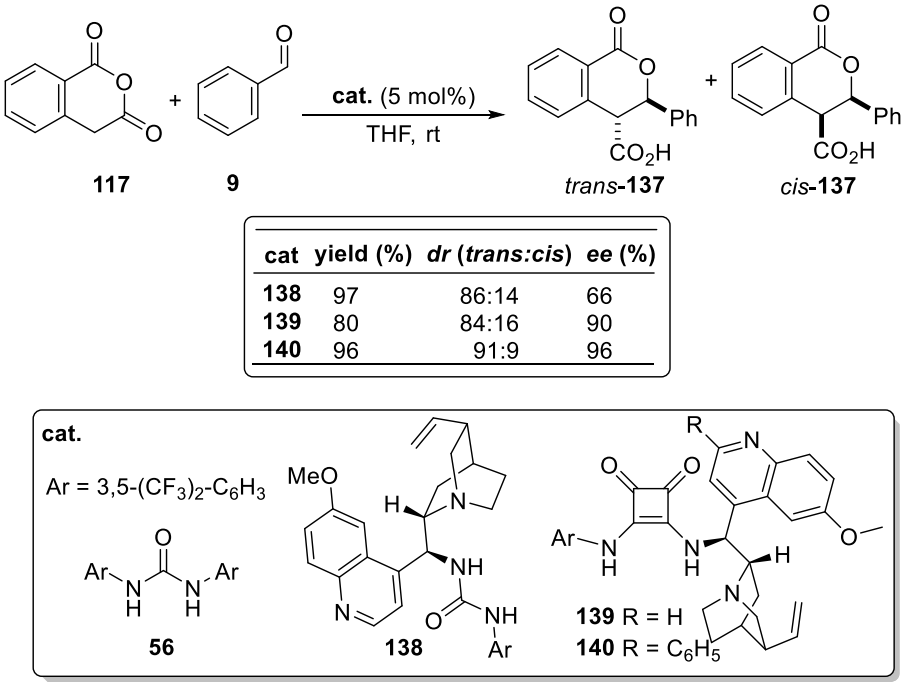



**Scheme 1.41** Cycloaddition reaction of substituted succinic anhydride (**134**) to aldehydes catalysed by KHMDS.

## 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.[125,130] 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.[131,132,133,134]

Since the seminal work reported in 1868 by Perkin,[135] 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[136] 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.[137] 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 **138** which resulted in the promotion of a higher yielding reaction with enhanced levels of diastereocontrol. 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[86,138] recently designed a class of squaramide-substituted catalysts as an alternative to (thio)urea-based materials. Use of novel squaramide **140** by our group, upon installation of a phenyl substituent at *C*-2'[139] led to better yields and superior enantio- and diastereocontrol (Scheme 1.42).




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

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.[140,141,142] Connon and co-workers evaluated the effect of the installation of electron-withdrawing and -donating groups on the homophthalic anhydride pronucleophile (**117**).[136] 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).[137] The previously proposed mechanism based on general base

catalysis of the addition of the enol of the anhydride to the aldehyde was unambiguously refuted.

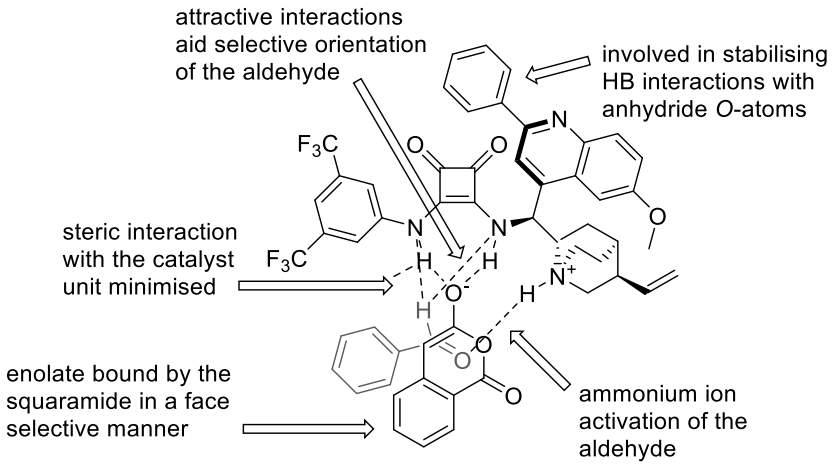
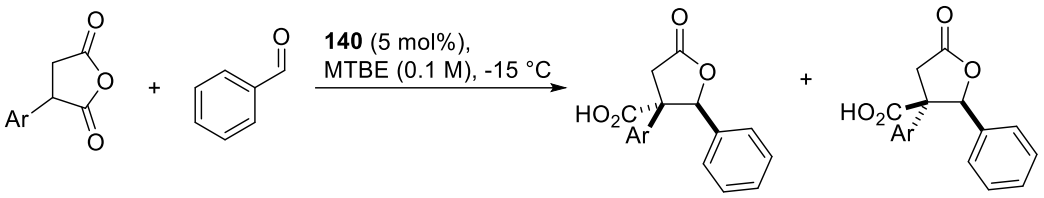



**Figure 1.4** Stereochemical rationale: summary.

### 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.[143,144,145] 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**).[137] 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).




**141** Ar = $C_6H_5$ **9**
**142** Ar = 3,5-$Br_2$-$C_6H_3$
**143** Ar = 4-$NO_2$-$C_6H_4$

*trans*-**144** Ar = $C_6H_5$ *cis*-**144** Ar = $C_6H_5$
*trans*-**145** Ar = 3,5-$Br_2$-$C_6H_3$ *cis*-**145** Ar = 3,5-$Br_2$-$C_6H_3$
*trans*-**146** Ar = 4-$NO_2$-$C_6H_4$ *cis*-**146** Ar = 4-$NO_2$-$C_6H_4$

| product | yield (%) | dr (*trans:cis*) | $ee_{trans}$ (%) |
|---|---|---|---|
| **144** | 34 | 97:3 | 83 |
| **145** | 76 | 94:6 | 76 |
| **146** | 96 | 97:3 | 86 |

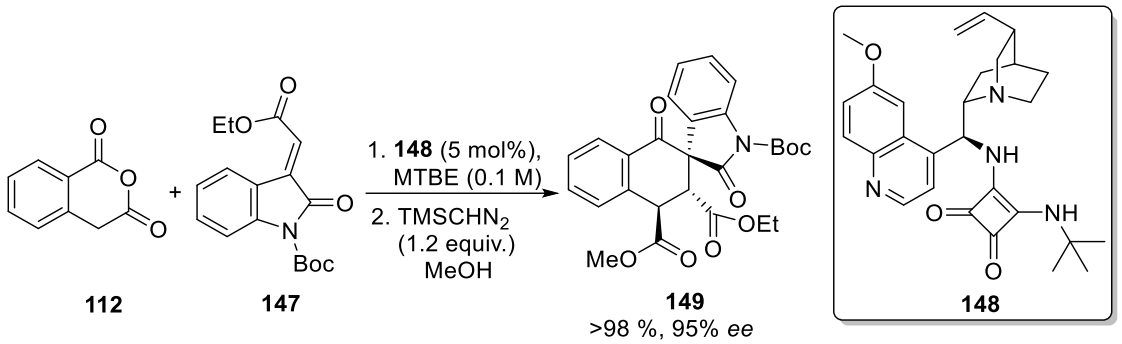
**Scheme 1.43** Cycloaddition reaction of arylsuccinic anhydrides with benzaldehyde (**9**).

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 diasteroselectivity 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

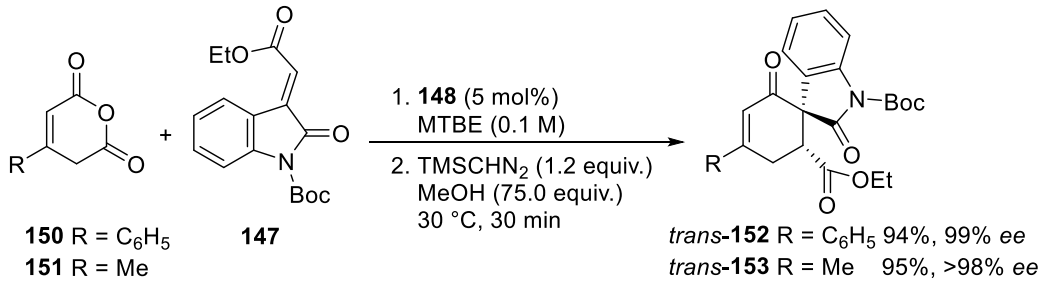
Connon *et al*. carried out a range of preliminary studies involving homophthalic anhydride (**117**) and different electrophiles, as Tamura and co-workers[147] had described previously. The initial reaction considered was an annulation between **117** and *N*-alkyl imines. The observation that the reaction 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 enantio-control (Scheme 1.44).




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

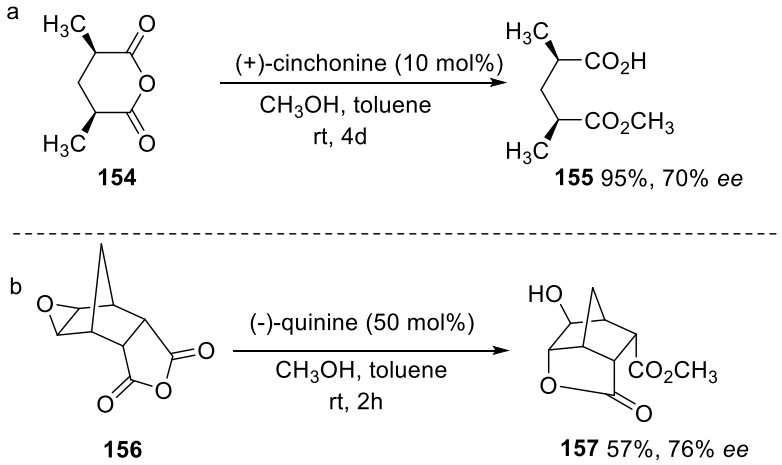
After these encouraging results, our group reported catalytic asymmetric Tamura cycloaddition reactions using glutaconic acid derivatives. The phenylglutaconic anhydride **150** and its methyl substituted variant **151** represented the first examples of the expansion of enantioselective cycloadditions 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).[149]




**Scheme 1.45** Organocatalytic cycloaddition of glutaconic anhydride derivatives to oxindole **147**.

## 1.6 Organocatalytic desymmetrisation of *meso* cyclic anhydrides: historical overview

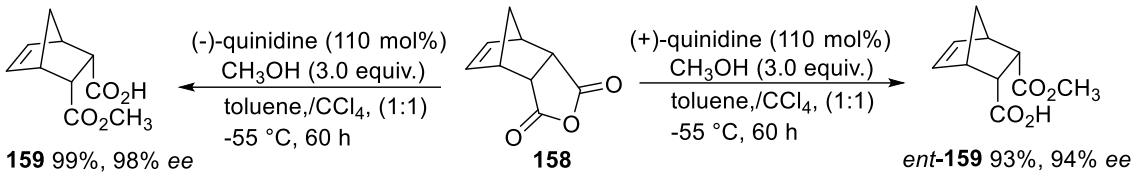
In the presence of a chiral catalyst one of the carbonyl groups of a *meso* cyclic anhydride substrate can theoretically be selectively converted into an hemiester containing either single or multiple stereocentres.The first example of desymmetrisation of *meso*-anhydrides promoted by natural cinchona 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.[149] 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.[150,151] 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.[152,153] Scheme 1.48 depicts a selected example in which the tricyclic

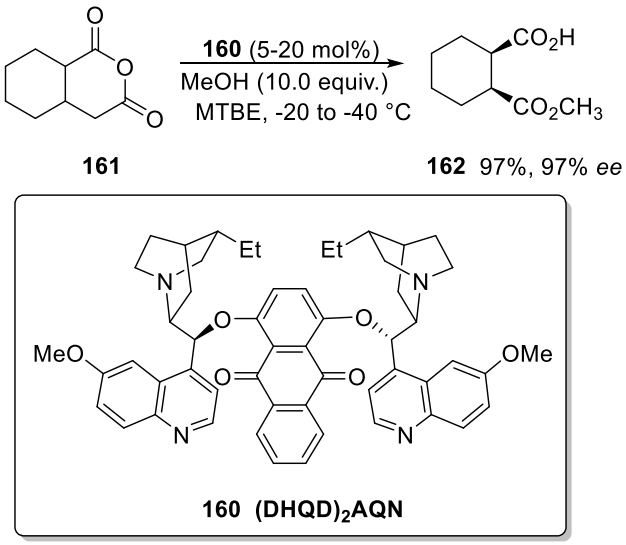
anhydride **158** is converted to both its hemiesters **159** and *ent*-**159** with an excess of methanol, in the presence of a stoichiometric amount of (-)-quinine, and (+)-quinidine.[154]




**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 $CCl_4$ 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 $(DHQD)_2AQN$ (**160**) and its quinine-derived *pseudo*enantiomer $(DHQ)_2AQN$ 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 $(DHQD)_2AQN$ (**160**) to promote the enantioselective desymmetrisation of *meso*-bicyclic glutaric acid anhydride derivatives which resulted in the formation hemiesters (*i.e.* **162**) in excellent *ee*.



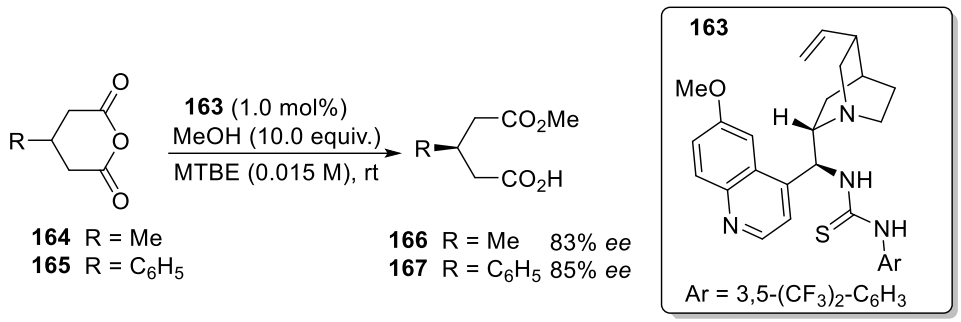

**Scheme 1.48** *Meso*-glutaric anhydride desymmetrisation promoted by Sharpless's catalysts.

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.[156] Consistent with Oda and Aitken's previous related studies,[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

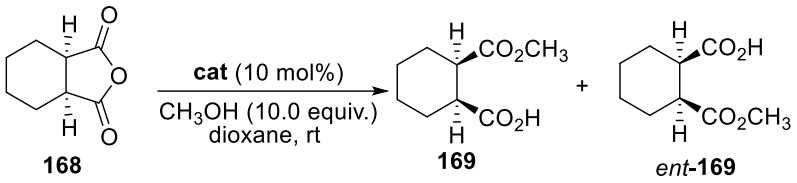
Chiral bases derived from either cinchona alkaloids or proline have been shown to be efficient catalysts for stereoselective alcoholysis of anhydrides. The possibility to achieve the formation of hemiesters that can be applied in the synthesis of many bioactive compounds made this catalytic reaction extremely attractive.[157,158] Previously, cinchona-derived (thio)urea and squaramide catalysts, in particular, have displayed exceptional potential as their *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) *via* a general base mechanism and the electrophile *via* hydrogen bond interactions with the thiourea moiety.[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,[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.[159]




**Scheme 1.49** Catalytic desymmetrisation of *meso*-glutaric anhydrides by Connon *et al*.

Shortly after our group published this work, Song *et al*. also independently investigated the use of two thiourea-based cinchona alkaloid catalysts (*i.e.* **163** and **84**) in the desymmetrisation reaction of *meso*-cyclic anhydrides.[160] In Scheme 1.50 is shown the asymmetric methanolysis 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.




| cat. | main isomer | yield (%) | *ee* (%) |
|---|---|---|---|
| **163** | **169** | 85 | 97 |
| **84** | **169** | 85 | 95 |
| **quinine** | **169** | 81 | 55 |
| **hydroquinine** | **169** | 82 | 53 |

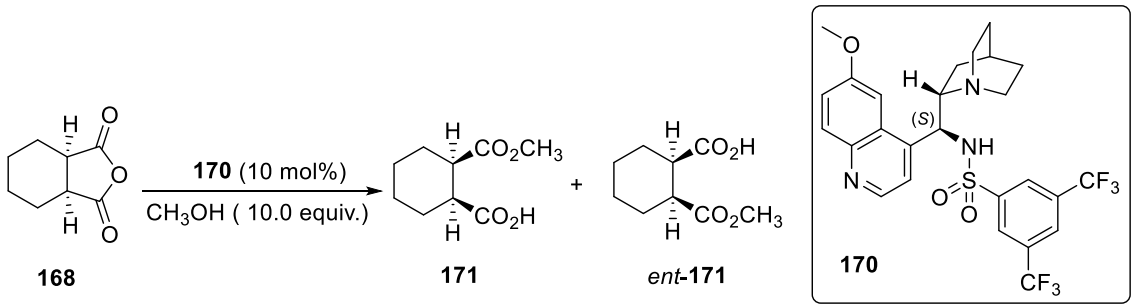
**Scheme 1.50** Catalytic enantioselective ring opening of **168** with methanol reported by Song *et al.*

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.[80] 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, Soòs 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, Soòs *et al.*, hypothesising that the incorporation of *N*-sulfonamides could prevent this self-aggregation problem, developed the first example of a thermally robust sulfonamide-based bifunctional organocatalyst

**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).[163,164]




| [168]/M | T (°C) | main isomer | yield (%) | ee (%) |
|---|---|---|---|---|
| 0.1 | 20 | **171** | 84 | 96 |
| 0.05 | 20 | **171** | 91 | 97 |
| 0.2 | 20 | **171** | 82 | 95 |
| 0.1 | 0 | **171** | 80 | 96 |
| 0.1 | -20 | **171** | 82 | 97 |
| 0.1 | -40 | **171** | 78 | 96 |

**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 Soòs and co-workers to explain the stereoselectivity associated with the methanolytic desymmetrisation of *meso*-anhydrides with the bifunctional thiourea-based organocatalyst[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).[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 obtainig 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).


$k_R$, $k_S$ = specific rate constants for reaction of R and S respectively
C* = 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.

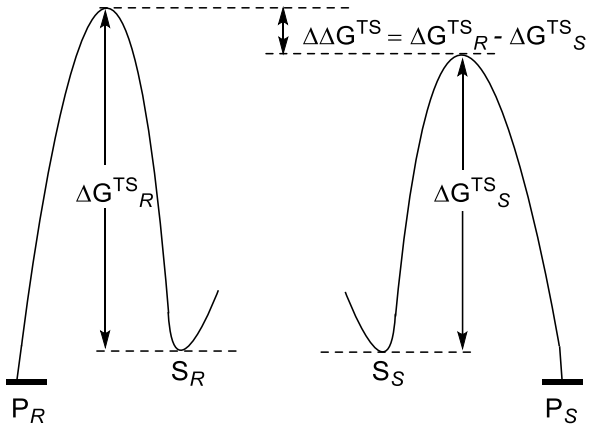



**Figure 1.5** Potential energy diagram for kinetic resolution

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

$$S = k_{rel} = k_{fast}/k_{slow} = e^{\Delta\Delta G/RT}$$

**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.[168]

equation 1.2

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

equation 1.3

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

**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).[169]

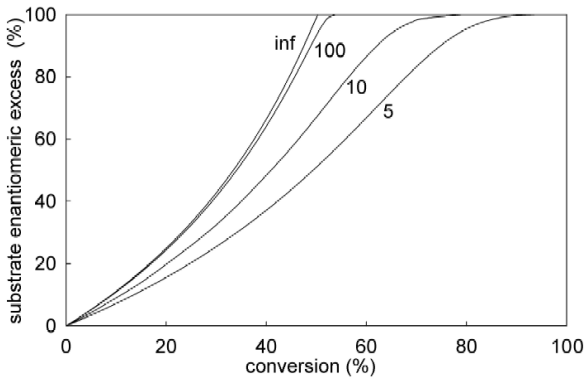
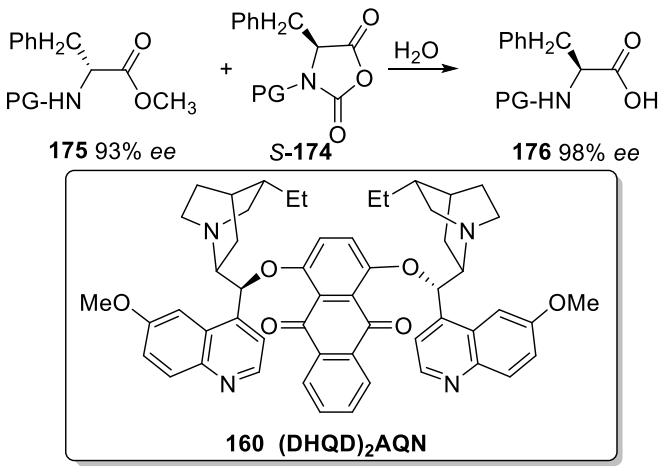



**Figure 1.7** Correlation between enantiomeric eccess (%) of the starting material and conversion (%) with different S values in the KR process.[168]

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%.[169]

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

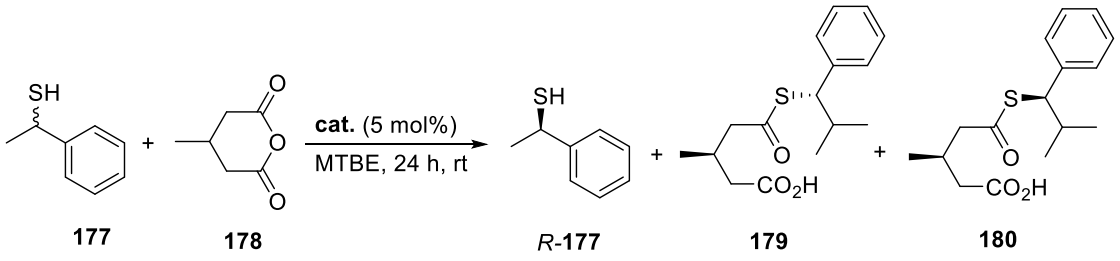
In 2001, Deng *et al*. reported an efficient kinetic resolution of *N*-carboxy cyclic anhydrides (UNCAs)[170] when treated at low temperature with alcohols in presence of the dimeric cinchona alkaloid $(DHQD)_2AQN$ (**160**) previously investigated in the asymmetric alcoholysis of *meso*-cyclic anhydrides.[155] The *N*-carboxy anhydride such as **174**, was easily prepared in high yields from the corresponding racemic amino acid **173** in a two-step procedure based on cyclisation with diphosgene followed by *N*-protection with Cbz or Fmoc. The kinetic resolution of **174** carried out using 10 mol% of catalyst **160** in the presence of methanol, afforded the *N*-protected methyl ester **175** and the unreacted UNCA *S*-**174** in excellent enantioselectivity (S = 114) which was then hydrolysed to furnish the corresponding *N*-protected aminoacid **176** (Scheme 1.53).

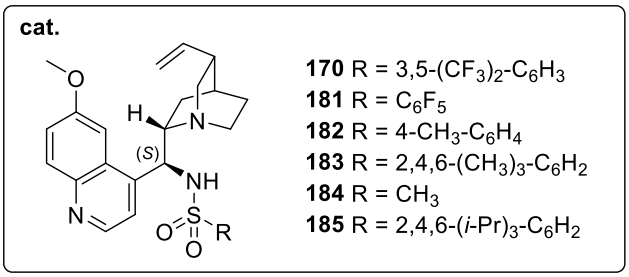



**Scheme 1.53** Kinetic resolution of **174** *via* modified cinchona alkaloid-catalysed methanolysis.

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).[171] 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.



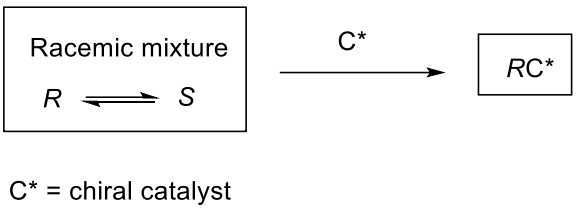

| cat. | dr (179 +*ent*-179:180 + *ent*-180) | 179 *ee* (%) | 180 *ee* (%) | desym. *ee* (%) | *R*-177 *ee* (%) | S |
|---|---|---|---|---|---|---|
| **170** | 66.5:33.5 | 95 | 91 | 92 | 33 | 2.7 |
| **181** | 70:30 | 97 | 87 | 94 | 41 | 3.9 |
| **182** | 73:27 | 97 | 93 | 96 | 41 | 4.0 |
| **183** | 79:21 | 97 | 90 | 96 | 45 | 5.6 |
| **184** | 75:25 | 95 | 84 | 92 | 44 | 4.3 |
| **185** | 89:11 | 95 | 68 | 90 | 60 | 8.5 |

**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).[169,172]




**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 ($S_s$) with the chiral agent (*i.e.* $k_{fast} >> k_{slow}$ and $k_{rac} >> k_{slow}$, Figure 1.8).

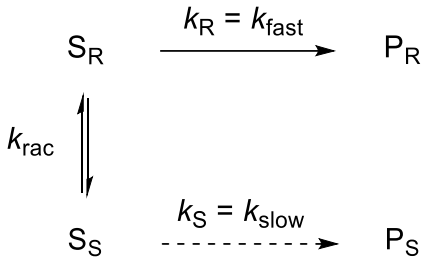



**Figure 1.8** Correlation between rate constants and efficiency of DKR process.

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).

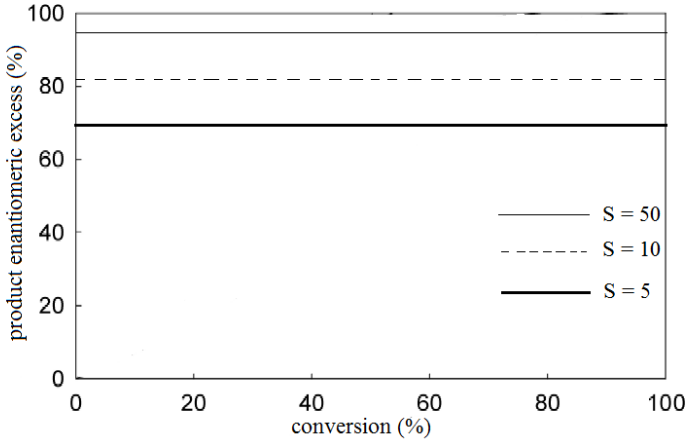
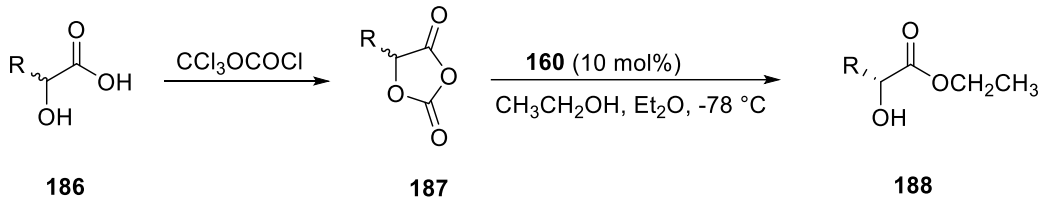



**Figure 1.9** Correlation between % enantiomeric eccess of product and % conversion in DKR process.

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

The synthesis of optially active $\alpha$-hydroxy acids has received considerable attention in the past as this structural motif exists in many biological compounds.[173] The majority of catalytic synthetic strategies involved the use of chiral transition metal complexes[174,175,176] as a catalytic valid alternative to the well-developed enzymatic approaches.[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).[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.



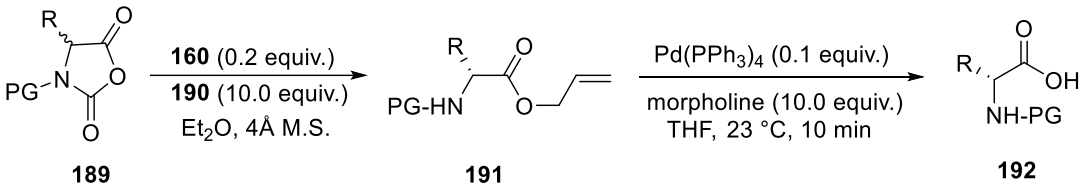

**186** **187** **188**

**186a** R = Ph
**186b** R = 4-Cl-$C_6H_4$
**186c** R = 4-Br-$C_6H_4$
**186d** R = 4-$CF_3$-$C_6H_4$
**186e** R = 3,4-$(F)_2$-$C_6H_3$

| 188 | yield (%) | *ee* (%) |
|---|---|---|
| **a** | 71 | 95 |
| **b** | 70 | 96 |
| **c** | 80 | 96 |
| **d** | 85 | 93 |
| **e** | 65 | 94 |

**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 $\alpha$-aryl UNCAs at room temperature. The reaction performed using both $\alpha$-aryl and $\alpha$-heteroaryl UNCAs **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.




**189** **191** **192**

**189a** R = Ph
**189b** R = 4-F-$C_6H_4$
**189c** R = 4-Cl-$C_6H_4$
**189d** R = thiophenyl
**189e** R = furanyl

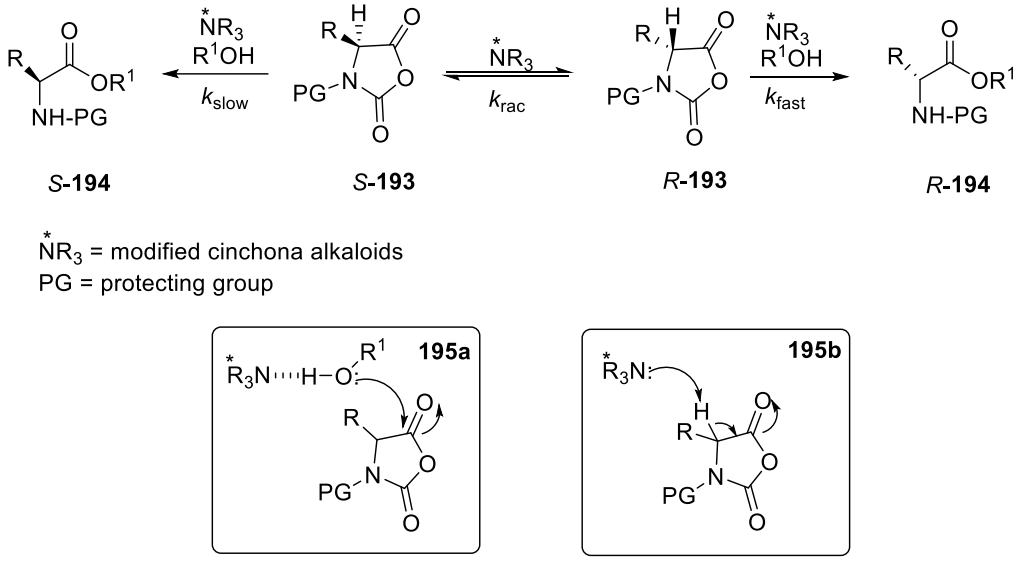
PG = protecting group

| | 191 | | 192 | |
|---|---|---|---|---|
| | yield (%) | *ee* (%) | yield (%) | *ee* (%) |
| **a** | 97 | 91 | 91 | 90 |
| **b** | 96 | 90 | 93 | 90 |
| **c** | 97 | 92 | 92 | 92 |
| **d** | 95 | 91 | 94 | 91 |
| **e** | 98 | 91 | 86 | 89 |

**Scheme 1.57** DKR of UNCAs 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 UNCAs promoted by organocatalyst **160** occurred *via* conventional

kinetic resolution.[170] 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).[182]

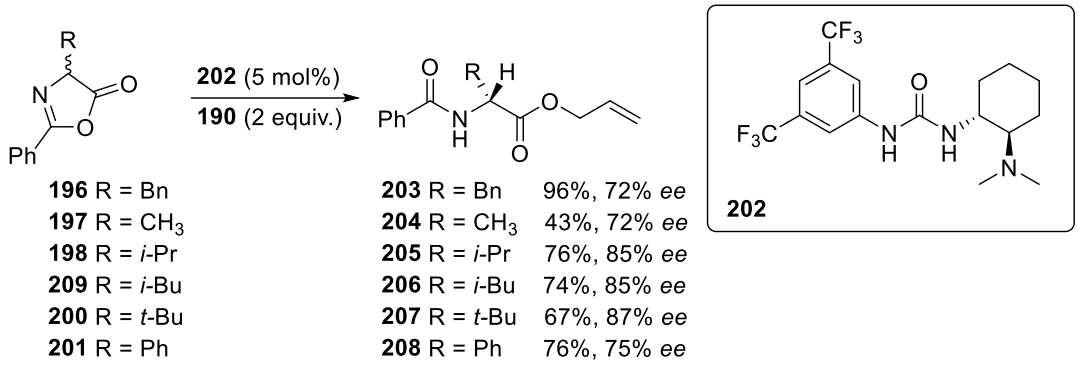



**Scheme 1.58** Cinchona alkaloid-catalysed DKR of UNCAs: proposed mechanism.

### 1.8.2 DKR of azalactones promoted by bifunctional organocatalysts

Chiral $\alpha$-amino acids have been widely utilised as intermediates for the synthesis of pharmaceuticals, ligands and organocatalysts.[183,184,185] 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**. $^1$H 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 $\alpha$-aromatic and aliphatic $\alpha$-amino acids with **190**, in the presence of catalyst **202** which furnished products in good enantioselectivity (72-87% *ee*).[186]

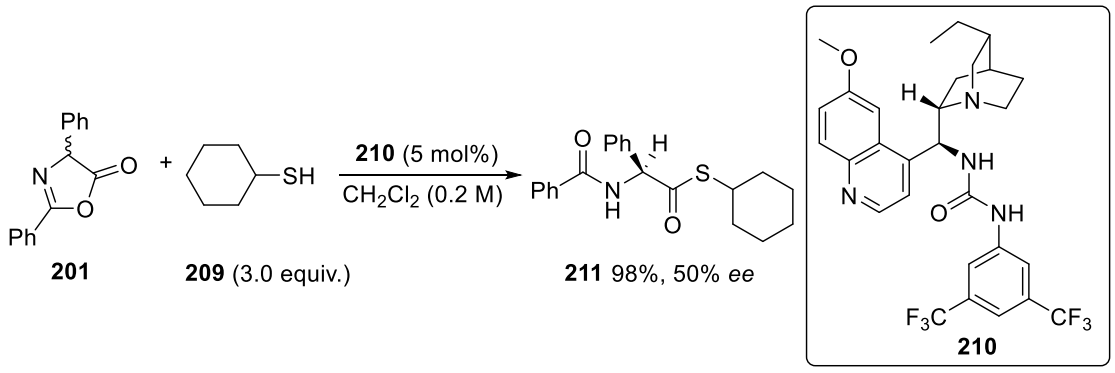



| | | | |
|---|---|---|---|
| **196** R = Bn | **203** R = Bn | 96%, 72% *ee* |
| **197** R = $CH_3$ | **204** R = $CH_3$ | 43%, 72% *ee* |
| **198** R = *i*-Pr | **205** R = *i*-Pr | 76%, 85% *ee* |
| **209** R = *i*-Bu | **206** R = *i*-Bu | 74%, 85% *ee* |
| **200** R = *t*-Bu | **207** R = *t*-Bu | 67%, 87% *ee* |
| **201** R = Ph | **208** R = Ph | 76%, 75% *ee* |

**Scheme 1.59** DKR of azalactones with **190** promoted by catalyst **202**.

Soon after, the same group demonstrated that both the efficiency and the enantioselectivity could be improved with the use of thiourea-based catalysts.[187] The evaluation of bifunctional Takemoto-type organocatalysts[49,50] 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%.

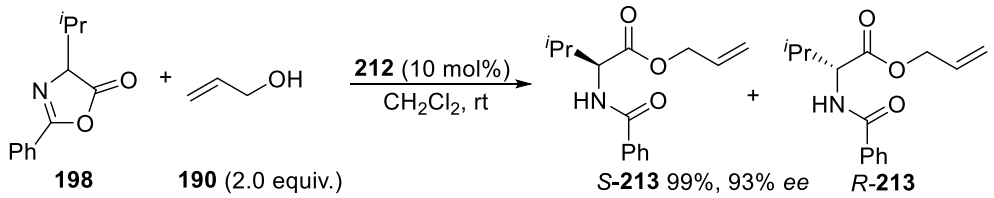
In 2008, Connon and co-workers investigated the use of (thio)urea-based cinchona alkaloids in promoting DKR with allyl alcohol of several azalactones. Interestingly, it was observed that urea derivatives were more efficient than thioureas and, in particular, the dihydroquinine-derived urea catalyst **210** 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 **84** promoted the asymmetric ring opening of the azalactone **201** with cyclohexyl thiol (**209**) to give the corresponding thioester **211** with high yield and moderate enantiomeric excess (Scheme 1.60).[188]

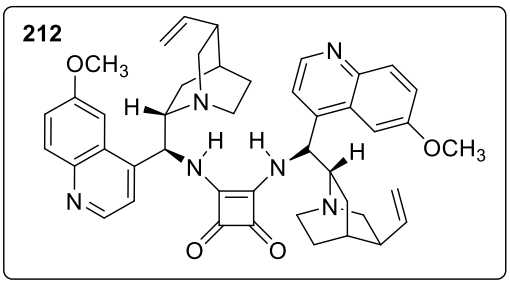



**201** **209** (3.0 equiv.) **211** 98%, 50% *ee*

**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,[187,188] however, the use of squaramide-based catalysts has not been widely reported. In 2009, Song *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 **212** promoted the DKR of the azalactone **198**; affording the *S*-*α*-amino allyl ester **213** in almost quantitative yields and excellent *ee* (Scheme 1.61).[189]



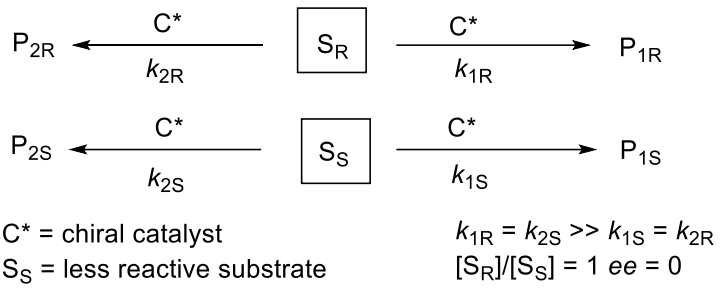

**Scheme 1.61** DKR of azalactones promoted by squaramide-substituted dimeric cinchona alkaloids.

## 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 *via* chemical[168,190] or enzymatic[191] procedures. Unfortunately, at conversions close to 50% there is a decrease in the *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 *ee* as well as up to 50% theoretical yield.[192] The concept of parallel resolution was first introduced by Vedejs and Chen[193] in 1997 although some examples had already been known.[194] In 1987, Brooks *et al*. described that baker's yeast was capable of reducing one enantiomer of a *β*-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*.[190,191]

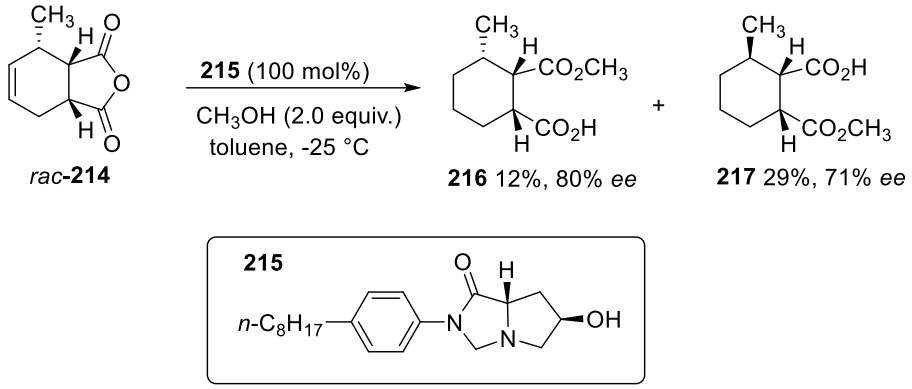
PKR is classified into three different groups depending on the structural relationship between the two products $P_{1R}$ and $P_{1S}$.

- 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

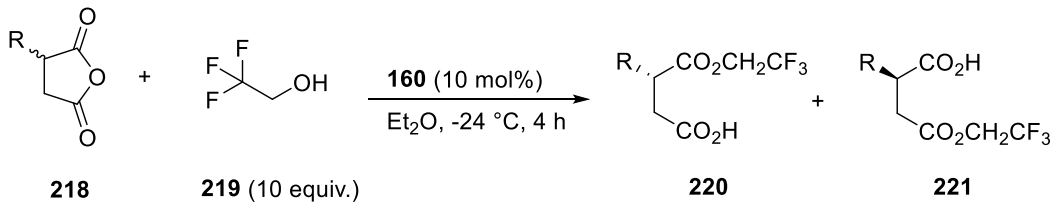
In 2001, Uozomi and co-workers reported the first example of parallel kinetic resolution of cyclic anhydrides promoted by proline-derived organocatalysts. The reaction between

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).[195]




**Scheme 1.63** PKR of cyclic anhydrides promoted by proline-based organocatalysts.

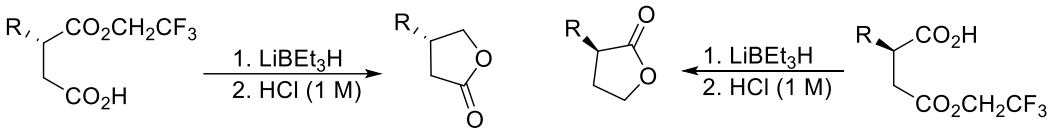
Soon after, Deng *et al*. reported the highly efficient parallel kinetic resolution of substituted succinic anhydrides promoted by the dimeric cinchona alkaloid $(DHDQ)_2AQN$ **160**. Initial studies using 2-methyl succinic anhydride (**218a**) demonstrated the importance of the alcohol in determining 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.[196] 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).[197] While the regioisomers of the alkyl hemiesters were separated using normal chromatographic separation, the aryl succinates were converted to $\beta$- and $\alpha$-aryl-$\gamma$-butyrolactones **222** and **223**, respectively.




**218** **219** (10 equiv.) **220** **221**

| | | ee (%) | | yield (%) | | ee (%) | | yield (%) | |
|---|---|---|---|---|---|---|---|---|---|
| | **R** | **220** | **221** | **220** | **221** | **222** | **223** | **222** | **223** |
| **218a** | $CH_3$ | 93 | 80 | 36 | 41 | --- | | --- | |
| **218b** | $CH_3CH_2$ | 91 | 70 | 38 | 50 | --- | | --- | |
| **218c** | *n*-octyl | 98 | 66 | 38 | 41 | --- | | --- | |
| **218d** | allyl | 96 | 82 | 40 | 49 | --- | | --- | |
| **218e** | Ph | 95 | 87 | | | 95 | 82 | 44 | 32 |
| **218f** | 3-MeO-Ph | 96 | 83 | | | 95 | 83 | 45 | 30 |
| **218g** | 4-Cl-Ph | 96 | 76 | | | 96 | 63 | 44 | 29 |

For R = Ph, 3-MeO-Ph or 4-Cl-Ph:




**220** **222** **223** **221**

**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).[198]

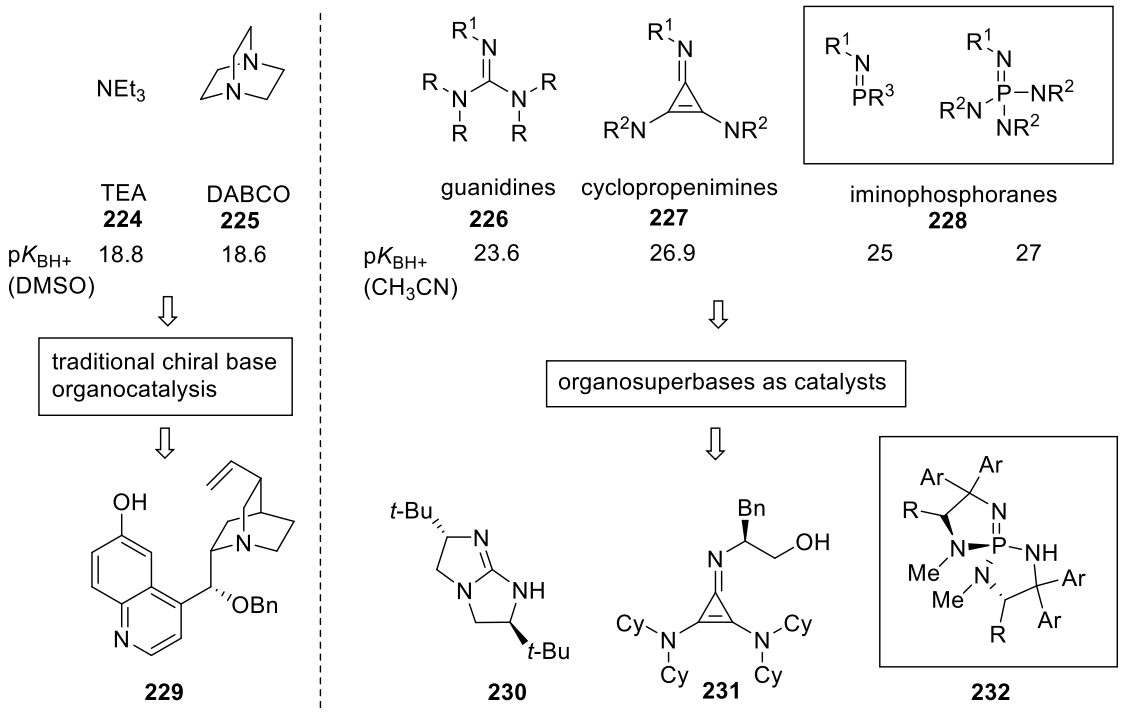



**Figure 1.10** From traditional Brønsted base catalysis to organosuperbases in organocatalysis.

Guanidines are neutral nitrogen compounds and they are widely used as strong bases in synthetic organic chemistry.[199] Their application in asymmetric catalysis has recently been the subject of reviews and includes a wide range of transformations such as Henry,[200] Michael,[201] Diels-Alder[202] and Mannich reactions.[203,204] The strong basicity of cyclopropenimines has been reported since 1999,[205] however, the first application of

bis(dialkylamino)cyclopropenimines as Brønsted base catalysts in Michael and Mannich reactions[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.[209] They have been employed as very strong non-ionic bases in many organic chemical transformations[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 *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 iminophosporanes ($pK_{BH+}$ = 35-37) in which the amide moieties (P-N bonds) are fundamental for the catalytic activity.[198]

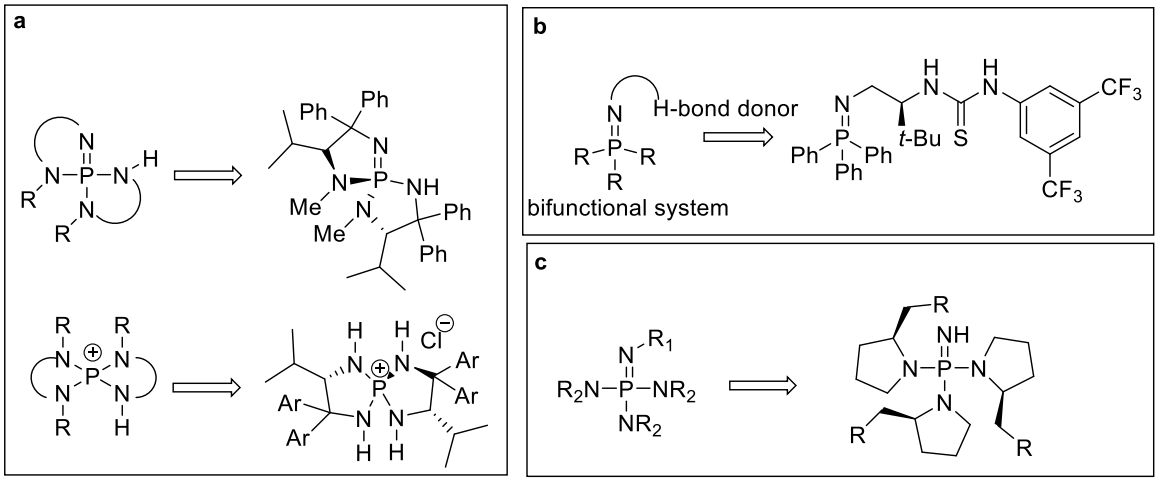
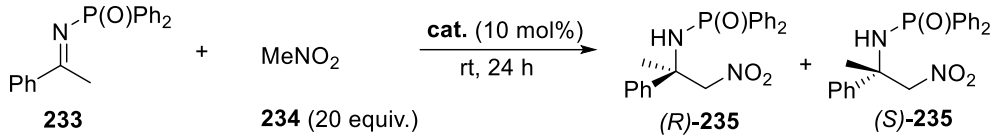


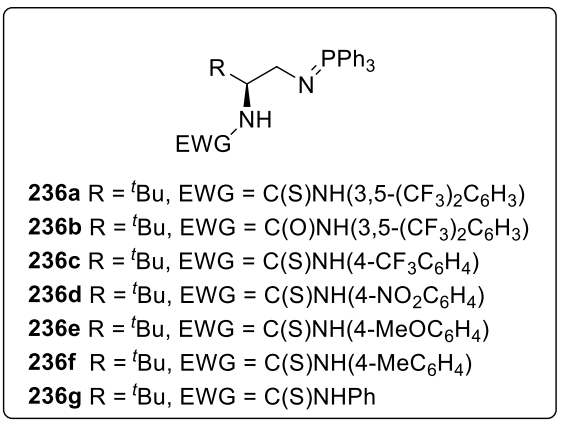

**Figure 1.11** Classification of iminophosphorane organocatalysts.

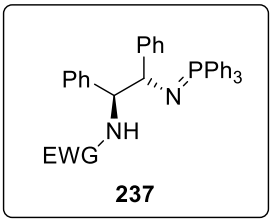
### 1.10.1 Concept, design and applications of bifunctional iminophosphorane organocatalysts (BIMP)

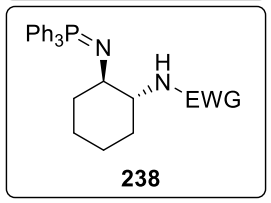
Over the last ten years, the bifunctional Brønsted base/H-bond donor organocatalysts that generally possess both a tertiary amine and a H-bond donor group have received significant attention and have been employed in a wide range of enantioselective addition reactions.[211] Despite the utility of their 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 triarylaminophosphorane functionality readily available from a direct Staudinger-type reaction between the corresponding azide (L-*tert* leucine derived azide) and triphenylphosphine.[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 triaryliminophosporane 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 *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).[213]




| cat. | product | conv. (%) | *ee* (%) |
|---|---|---|---|
| **236a** | *(R)*-235 | 98 | 85 |
| **236b** | *(R)*-235 | 97 | 79 |
| **236c** | *(R)*-235 | 98 | 79 |
| **236d** | *(R)*-235 | 98 | 84 |
| **236e** | *(R)*-235 | 98 | 70 |
| **236f** | *(R)*-235 | 99 | 68 |
| **236g** | *(R)*-235 | 98 | 73 |
| **237** | *(S)*-235 | 48 | 34 |
| **238** | *(S)*-235 | 98 | 20 |

**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.[213] Shortly after, Dixon and co-workers developed an analogue of these catalysts by immobilisation on a solid polystyrene support.[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.[198]

Two years later, the same group hypothesised that the enhanced basicity of iminophosporane 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 $\alpha$-substituted acrylate esters. Based on the enhanced basicity of *tris* (*p*-methoxyphenyl)phosphine and inspired by Jacobsen and Takemoto's cyclohexanediamine-derived organocatalyst[55,64] , they developed a 2nd generation of bifunctional iminophosphorane organosuperbases (Scheme 1.67) [215]

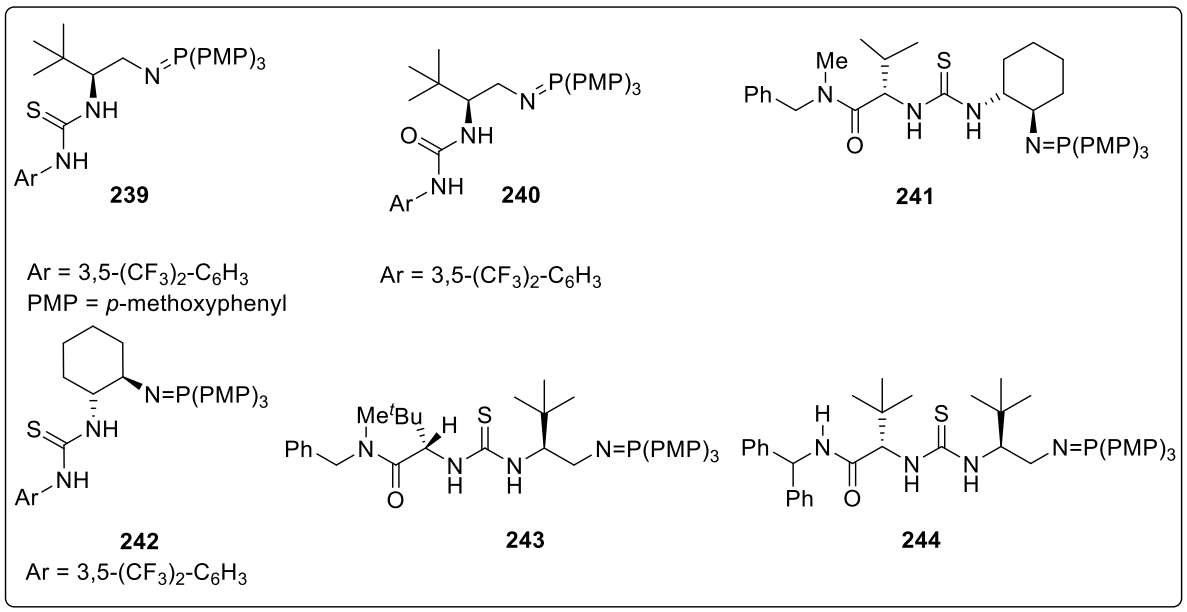
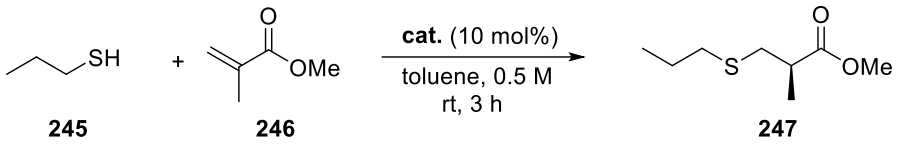



**Figure 1.12** 2nd generation BIMP organocatalysts screened for performance in the sulfa-Michael addition reaction.

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).




**245** **246** **247**

| cat. | yield (%) | *ee* (%) |
|---|---|---|
| **239** | >99 | 72 |
| **240** | >99 | 57 |
| **241** | 91 | 9 |
| **242** | 40 | 6 |
| **243** | 97 | 76 |
| **244** | >99 | 87 |

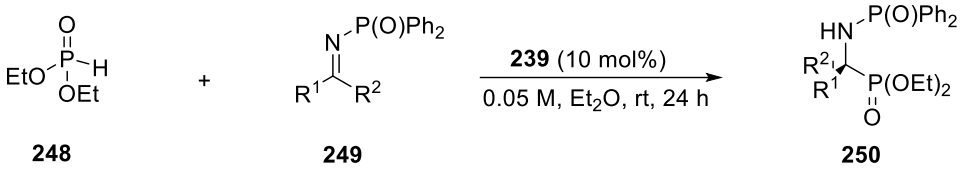
**Scheme 1.66** Sulfa-Michael addition of thiol **245** to **246** promoted by 2nd generation BIMP organocatalysts.

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]



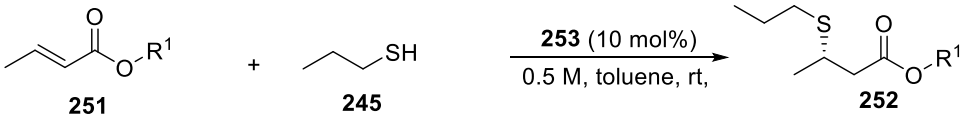

**248** **249** **250**

**249a** $R^1$ = Ph, $R_2$ = $CH_3$
**249b** $R^1$ = 4-OMe-$C_6H_4$, $R_2$ = $CH_3$
**249c** $R^1$ = 3-OMe-$C_6H_4$, $R_2$ = $CH_3$
**249d** $R^1$ = 4-Cl-$C_6H_4$, $R_2$ = $CH_3$
**249e** $R^1$ = 4-F-$C_6H_4$, $R_2$ = $CH_3$
**249f** $R^1$ = Ph, $R_2$ = $CH_2CH_3$

| 250 | yield (%) | *ee* (%) |
|---|---|---|
| **a** | 99 | 58 |
| **b** | 90 | 62 |
| **c** | >99 | 58 |
| **d** | >99 | 54 |
| **e** | 98 | 56 |
| **f** | >99 | 71 |

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

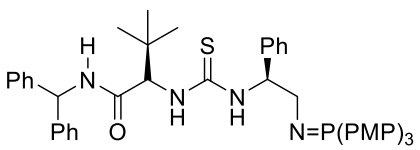
In 2017, Dixon and co-workers, inspired by the successful use of bifunctional iminophosphorane organocatalysts in promoting the sulfa-Michael addition of alkyl thiols to $\alpha$-substituted acrylate esters,[216] described the first organocatalytic sulfa-Michael addition of thiols (*i.e.* **245**) to 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**.




**251** **245** **252**

**251a** $R^1$ = $CH_3$
**251b** $R^1$ = $CH_2CH_3$
**251c** $R^1$ = $^i$Pr
**251d** $R^1$ = Bn
**251e** $R^1$ = $^t$Bu

| 252 | yield (%) | *er* |
|---|---|---|
| **a** | >99 | 81:19 |
| **b** | 95 | 84:16 |
| **c** | >99 | 85:15 |
| **d** | >99 | 81.19 |
| **e** | 94 | 92:8 |




**253**

**Scheme 1.68** Sulfa-Michael addition of thiols to $\beta$-substituted-$\alpha,\beta$-unsaturated esters promoted by 2nd 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.[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 unsuccesful. 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.

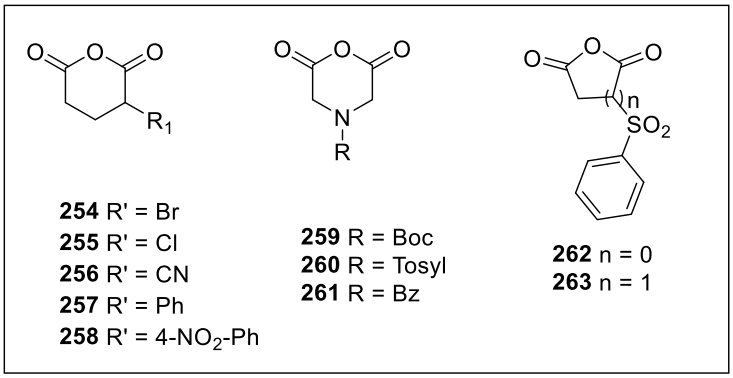
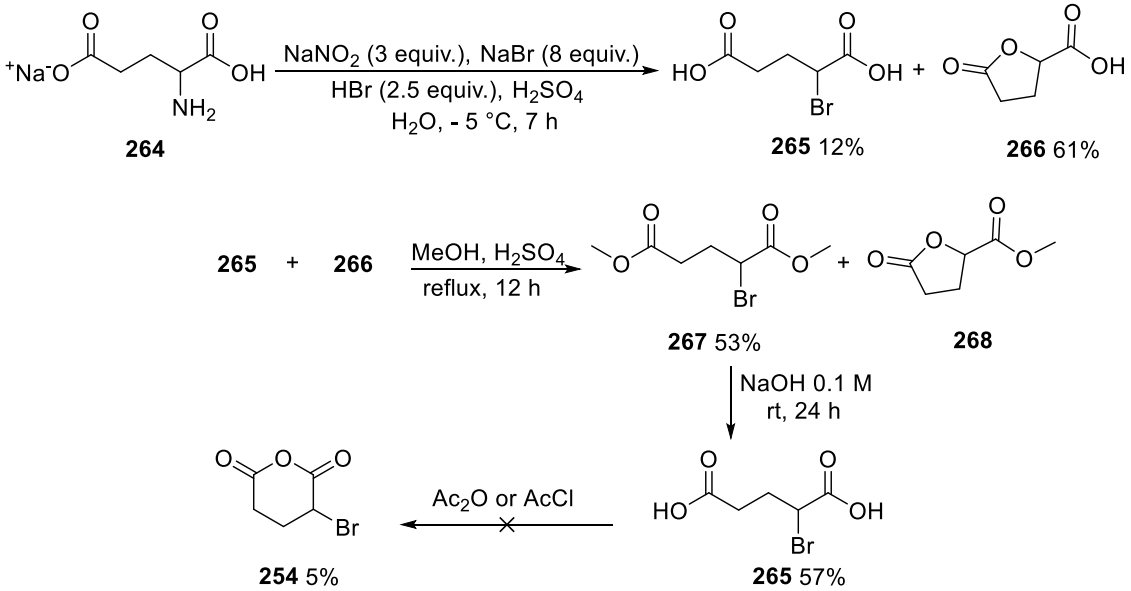



**Figure 2.1** Anhydrides synthesised for the evaluation of the substrate scope.

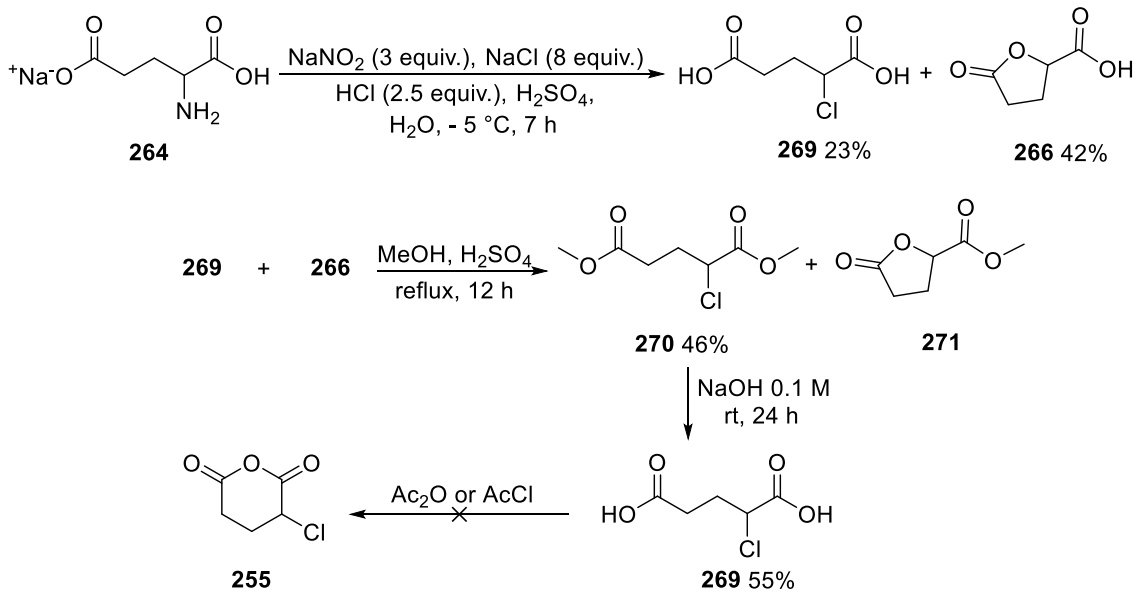
### 2.1.1 Synthesis of enolisable glutaric anhydride derivatives

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.[227] However, a considerable quantity of **266** as a by-product was also detected (Scheme 2.1).




**Scheme 2.1** Attempted synthesis of anhydride **254**.

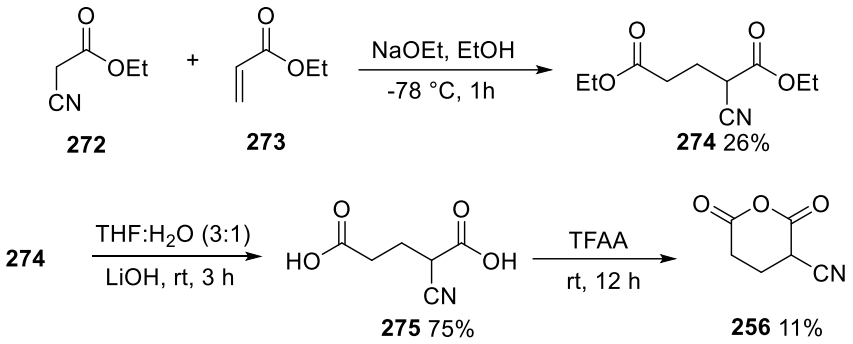
In order to facilitate the isolation of the desired product **265**, the mixture of products obtained was, upon extraction, esterified with methanol heated under reflux in the presence of sulfuric acid to give the *bis*-ester **267** in moderate yield (53%) and traces of by-product **268** . The purification 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**.

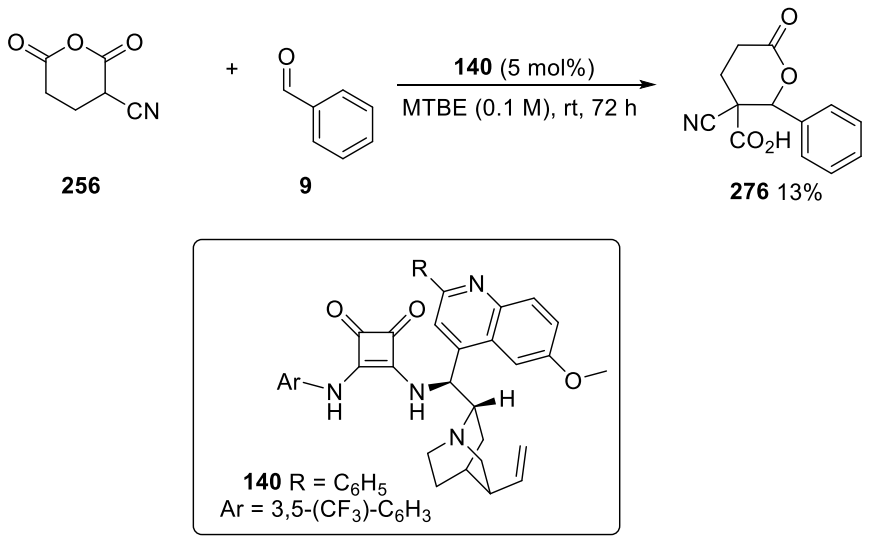
The cyano-substituted glutaric anhydride (**256**) was not reported at the beginning of this work and its synthesis proved to be very complicated. The alkylation of ethyl cyanoacetate (**272**) with ethyl acrylate (**273**) using sodium ethoxide as base in ethanol furnished complex mixtures of unreacted **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 $Ac_2O$ 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**.

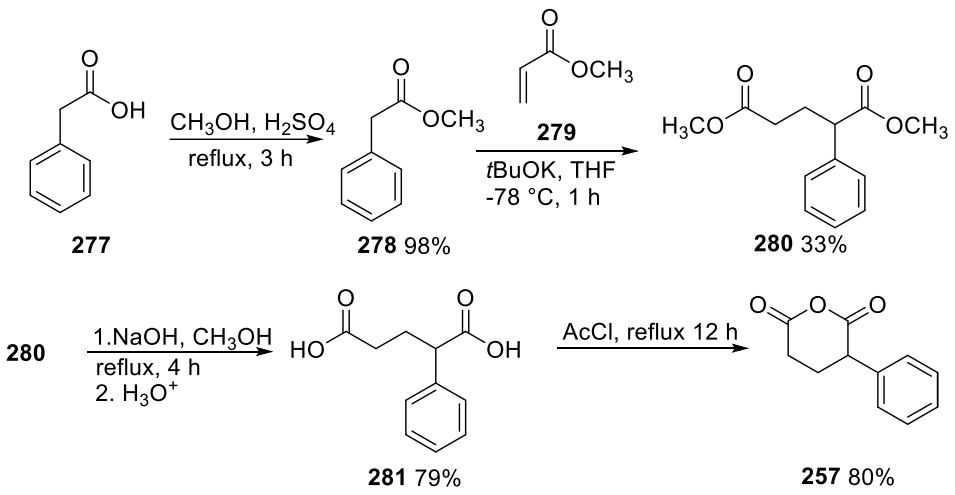
Anhydride **256** was evaluated in the asymmetric cycloaddition reaction with benzaldehyde (**9**) promoted by catalyst **140** at room temperature (Scheme 2.4). The desired product **276** could only be obtained in low yield. A longer reaction time (120 h) and increased concentration (0.2 M) did not 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**.

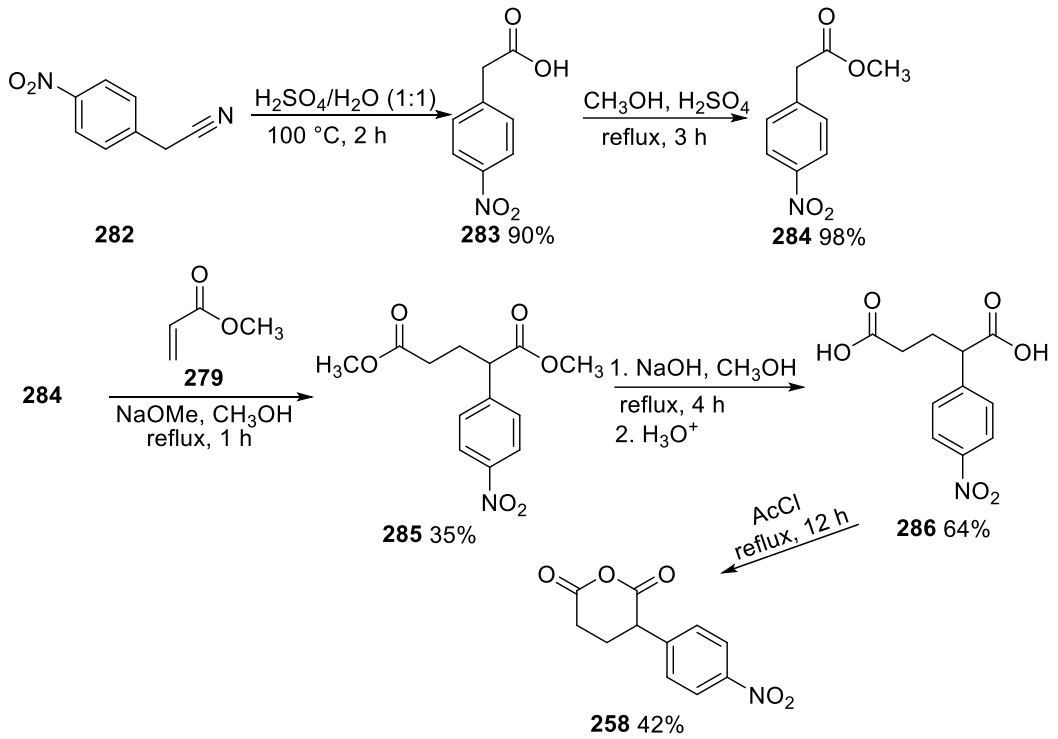
### 2.1.2 Synthesis and evaluation of arylglutaric anhydrides in the asymmetric annulation reaction with benzaldehyde

Our group has demonstrated the successful employment of enolisable arylsuccinic anhydrides in the asymmetric annulation reaction with benzaldehyde (**9**).[146] We therefore, became interested in the synthesis and evaluation of arylglutaric derivatives under the optimum conditions previously reported in literature.[136] The synthesis of 2-phenyl glutaric anhydride (**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 **278** in 98% yield which, was then reacted with methyl acrylate (**279**) in a Michael addition, furnishing the *bis*-ester **280** as a yellow oil. Ester **280** was hydrolysed with sodium hydroxide in methanol to the corresponding *bis*-carboxylic acid **281** which was cyclised to form the desired anhydride **257**.



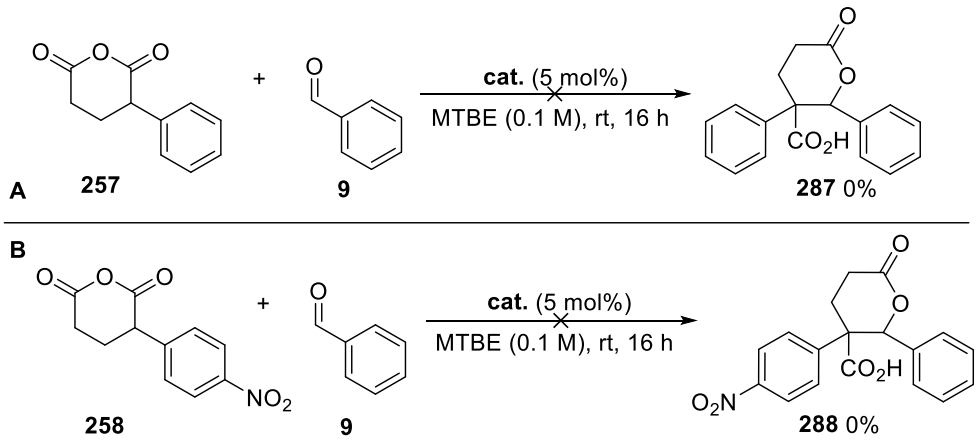

**Scheme 2.5** The synthesis of arylglutaric anhydride **257**.

In accordance with the increased enol-stabilisation associated with *p*-$NO_2$-phenylsuccinic anhydride, the next step was the installation of the $NO_2$ electron-withdrawing group to the aryl moiety of anhydride **257**. The synthesis began with the formation of 2-(4-nitrophenyl)acetic acid (**283**). The Michael addition between ester **284** and **279** using sodium methoxide in methanol furnished the *bis*-ester **285** followed by hydrolysis with NaOH to afford the *bis*-acid **286**. The obtained residue was then reacted with acetyl chloride at reflux for 12 hours to give **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.

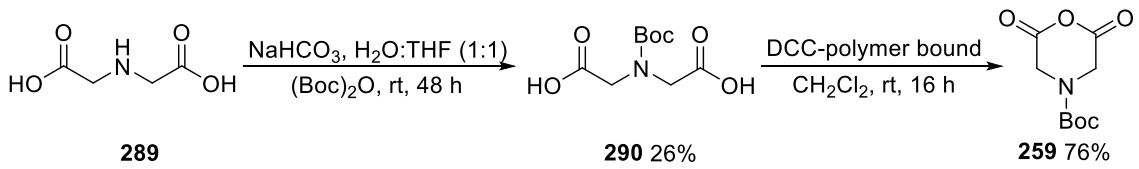



**Scheme 2.7** Evaluation of anhydride **257** (A) and anhydride **258** (B) in the asymmetric annulation reaction with **9**.

### 2.1.3 Synthesis and evaluation of anhydrides bearing electron-withdrawing heteroatoms in the asymmetric annulation reaction with benzaldehyde

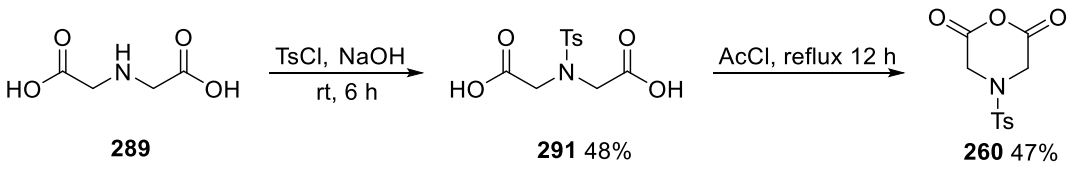
Since the installation of enol-stabilising groups on enolisable glutaric anhydrides proved unsuccessful in promoting the reactivity in annulation reactions with benzaldehyde (**9**), we became interested in anhydrides containing electron-withdrawing heteroatoms within the ring, that, to the best of our 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 $\alpha$-hydrogen and may enhance the enolisation ability of the anhydride. The first step of the synthesis was the introduction of di-*t*-butyl dicarbonate ($(Boc)_2O$) 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).



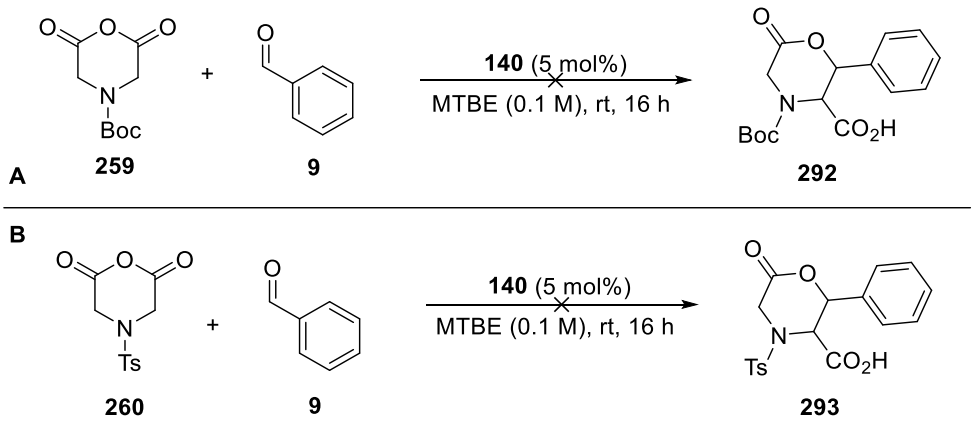

**Scheme 2.8** The synthesis of anhydride **259**.

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,[229] with acetyl chloride (Scheme 2.9).



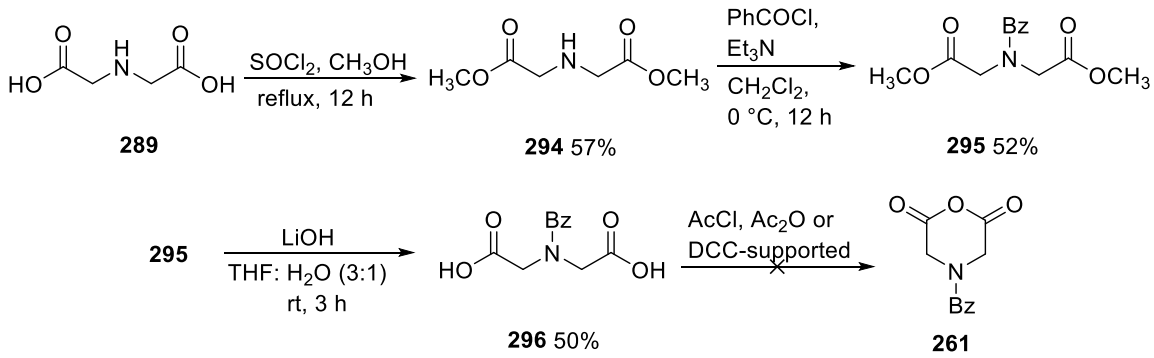

**Scheme 2.9** The synthesis of anhydride **260**.

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 **259** (A) and anhydride **260** (B) in the asymmetric annulation reaction with **9**.

The synthesis of the *N*-benzoyl substituted anhydride **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 (**259** and **260** respectively). Iminodiacetic acid (**289**) was subjected to esterification to obtain the *bis*-ester **294** which was subsequently reacted with benzoyl chloride to form the product **295**. The attempted hydrolysis of **295** with either NaOH or KOH proved ineffective, therefore, the hydrolysis was carried out using LiOH in THF/water 3:1 and afforded compound **296** in moderate yield. Unfortunately, the *bis*-carboxylic acid **296** failed to cyclise to form anhydride **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 *et al*. for the cyclisation of **296** (*i.e.* TFAA 2% and $Ac_2O$ for 4 h at room temperature)[230] we reasoned that our lack of success could have been due to the use of non-forcing reaction conditions (Scheme 2.11).

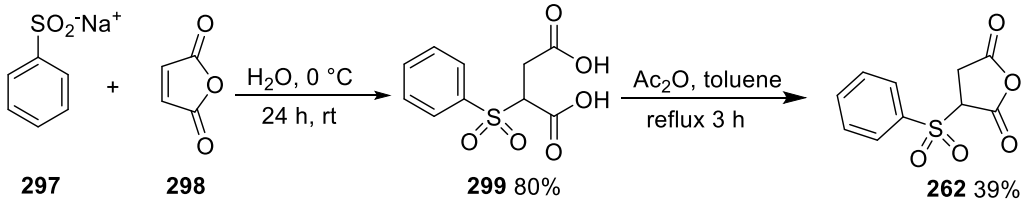



**Scheme 2.11** Attempted synthesis of anhydride **261**.

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

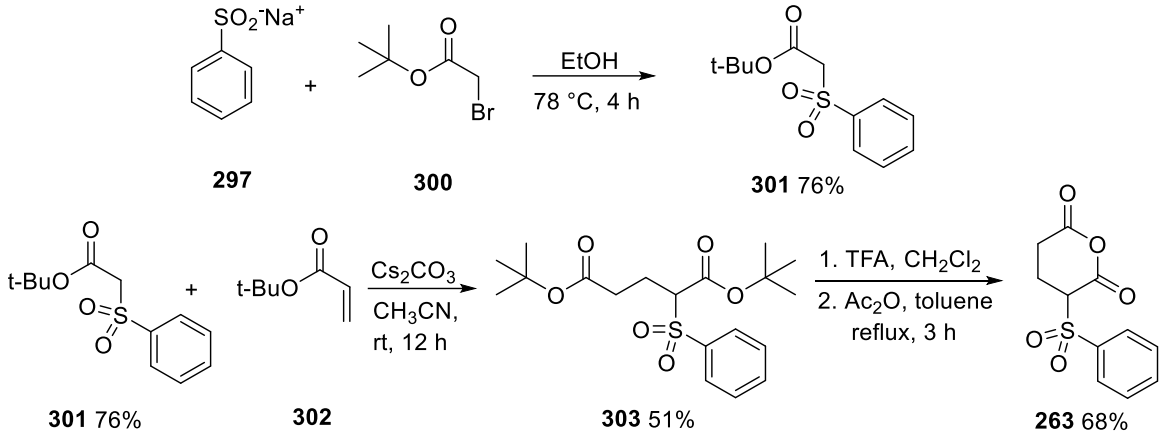
Inspired by the diastereoselective synthesis of $\gamma$- and $\delta$-lactams from imines and sulfone-substituted anhydrides reported by Shaw *et al.*[231] we decided to evaluate these substrates in the mechanistically unrelated formal cycloaddition with aldehydes. Two anhydrides bearing this moiety were prepared: **262** and **263**. According to the known literature procedures,[232] 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).




**Scheme 2.12** The synthesis of anhydride **262**.

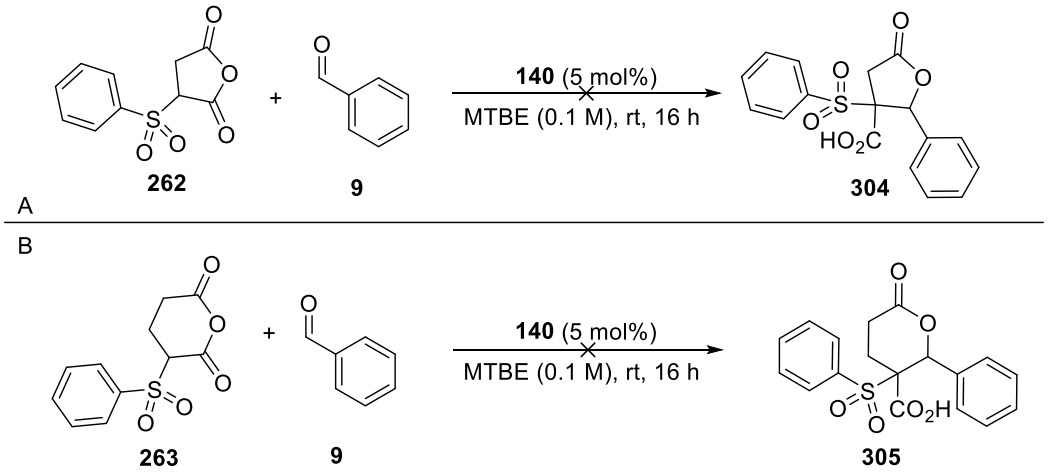
The synthesis of the sulfone-substituted glutaric variant **263** was achieved in good yield over a three step procedure. The commercially avalilable benzenesulfinic acid sodium salt (**297**) was treated with *tert*-butyl bromoacetate (**300**) to furnish **301**. The alkylation of **301** with *tert*-butyl 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.

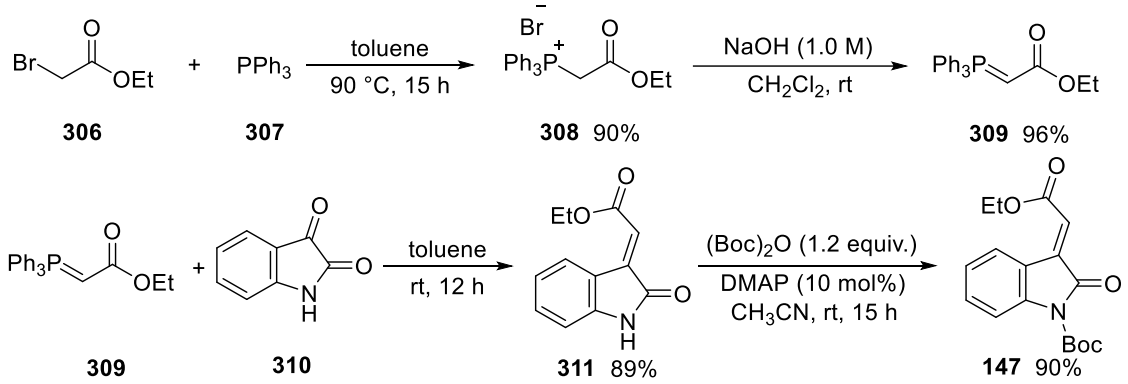



**Scheme 2.14** Evaluation of anhydride **262** (A) and anhydride **263** (B) in the asymmetric annulation reaction with **9**.

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 in 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.

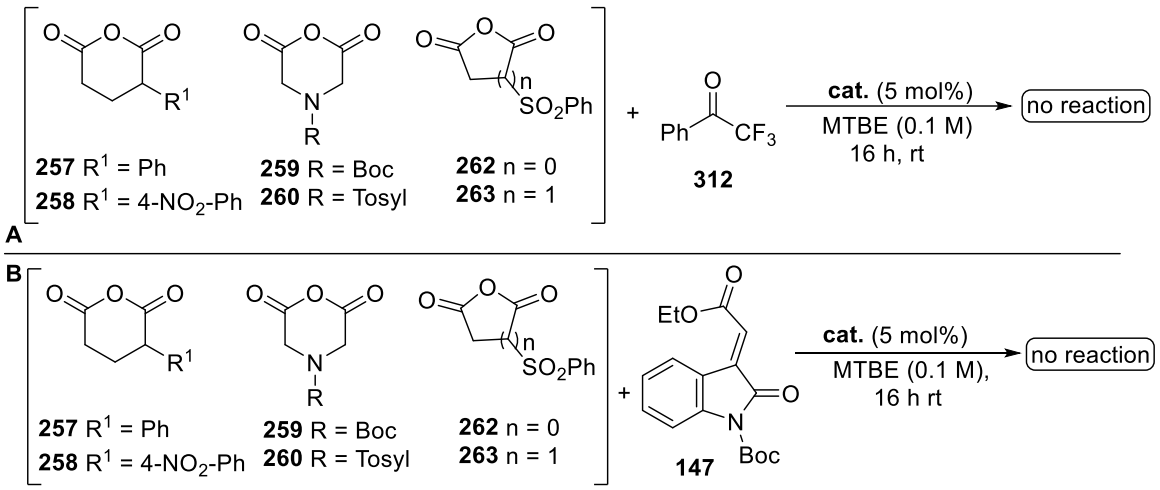
### 2.1.5 Use of other electrophiles in the asymmetric annulation reaction with enolisable cyclic anhydrides

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[233] and 2-alkylidene oxindoles[148] 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,[234] 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**). Subsequentially, **311** was, upon purification by column chromatography on silica gel, protected at the nitrogen atom by reaction with di-*t*-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,[83] the evaluation of these substrates promoted by catalysts **138**, **140** and 1**48** 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

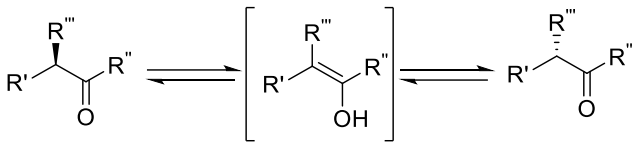
As described in the previous section, with regards to Connon's protocol,[136,146,148] modified cinchona alkaloids could be used at 5 mol% loading for the promotion of the enantioselective cycloaddition involving homophtalic or arylsuccinic anhydrides and different electrophiles. Disappointigly, the possibility 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[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

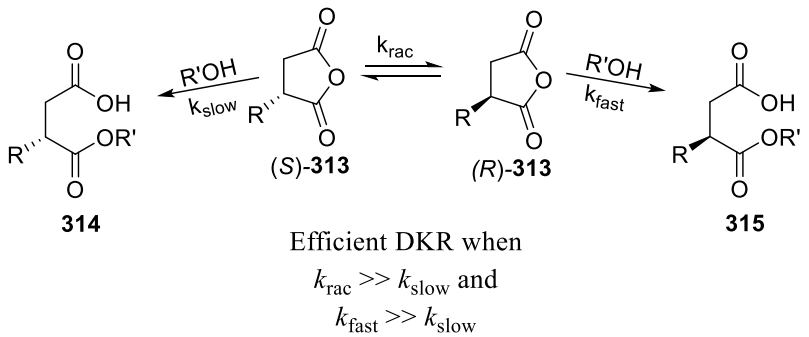
The racemisation of compounds with a stereogenic centre containing an acidic proton in the $\alpha$ position to a carbonyl group is considered an effective strategy to equilibrate the two reactive enantiomers (Scheme 3.1).[235,236]



**Scheme 3.1** Enol intermediate formation *via* racemisation.

Tang and Deng,[198] observed that in the presence of the modified cinchona alkaloid $(DHQD)_2AQN$ (**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'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[160] was recently engaged in the use of cinchona alkaloid-derived bifunctional organocatalysts to promote the enantioselective desymmetrisation of cyclic *meso* anhydrides *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 *via* general-base catalysis (Figure 3.1).

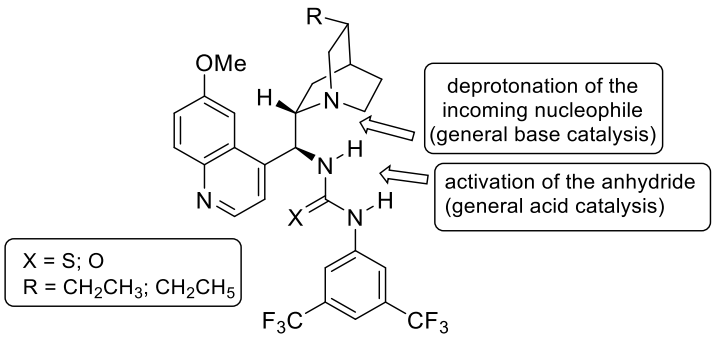
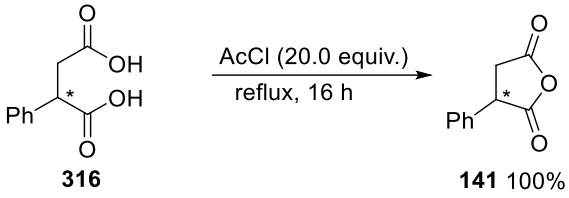



**Figure 3.1** Dual activation mode using bifunctional (thio)urea-modified cinchona alkaloids.

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.[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

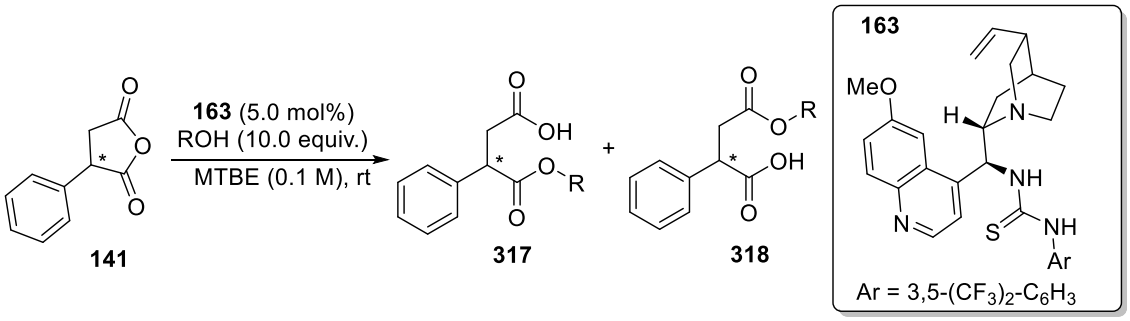
To test the hypothesis laid out in Section 3.1 we decided to evaluate the regioselectivity of the nucleophilic addition to anhydride **141**, using various alcohols (R'OH) as nucleophiles in the presence of a catalytic amount of the thiourea-based organocatalyst **163**. The anhydride **141** was easily 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 showen in Table 3.1 to furnish the corresponding hemiesters.

**Table 3.1** Alcoholysis of phenylsuccinic anhydride: preliminary experiments.



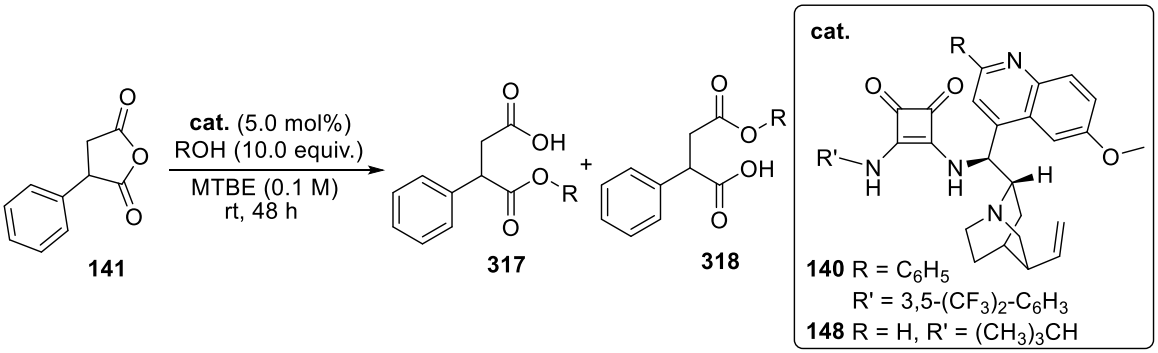

| entry | ROH | Time (h) | conv (%)[a] | ratio 317:318[a] |
|---|---|---|---|---|
| 1 | MeOH (**319**) | 24 | 98 | 49:51 |
| 2 | EtOH (**320**) | 24 | 98 | 46:54 |
| 3 | $CH_2$=$CHCH_2OH$ (**190**) | 24 | 97 | 45:55 |
| 4 | $PhCH_2OH$ (**321**) | 24 | 98 | 45:55 |
| 5 | *i*-PrOH (**322**) | 72 | 47 | 47:53 |

[a] Determined by $^1$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.



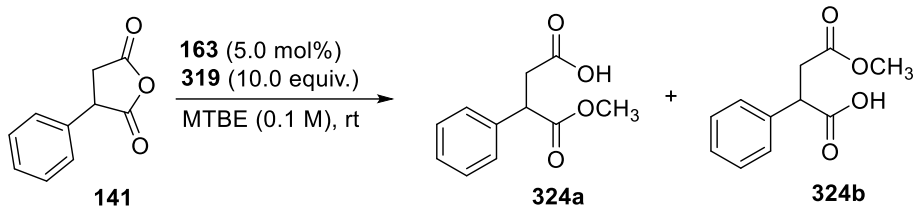

| entry | ROH | cat. | conv (%)[a] | ratio 317:318[a] |
|---|---|---|---|---|
| 1 | **319** | **140** | 98 | 50:50 |
| 2 | **319** | **148** | 98 | 50:50 |
| 3 | **190** | **140** | 97 | 50:50 |
| 4 | **190** | **148** | 97 | 50:50 |
| 5 | **321** | **140** | 98 | 45:55 |
| 6 | **321** | **148** | 98 | 45:55 |

[a] Determined by $^1$H NMR spectroscopic analysis using *p*-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.



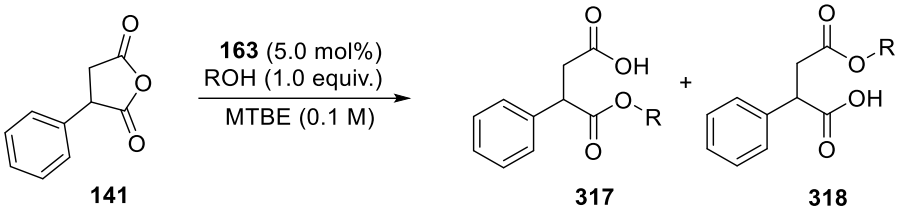

141 324a 324b

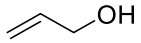
| entry | Time (h) | conv (%)[a] | ratio 323:324[a] |
|---|---|---|---|
| 1 | 1 | 72 | 49:51 |
| 2 | 2 | 86 | 49:51 |
| 3 | 19 | 98 | 49:51 |

[a]Determined by $^1$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.

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



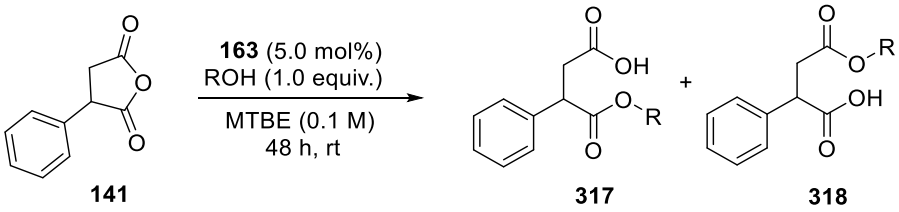

| entry | ROH | temp (°C) | conv (%)[a] | ratio 317:318[a] |
|---|---|---|---|---|
| 1 | MeOH (**319**) | -30 | 78 | 50:50 |
| 2 |  (**190**) | -30 | 45 | 45:55 |
| 3 | $PhCH_2OH$ (**321**) | -30 | 48 | 45:55 |

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

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.



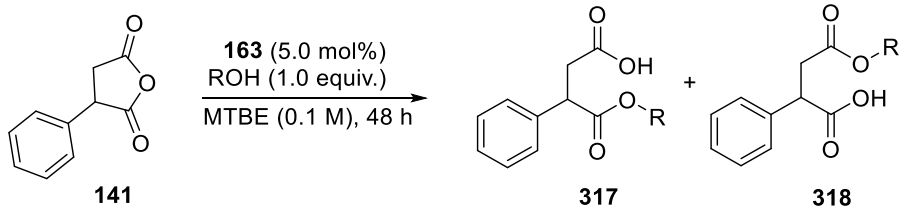

| entry | ROH | time (h) | conv (%)[a] | ratio 317:318[a] |
|---|---|---|---|---|
| 1 | $CF_3CH_2OH$ (**219**) | 48 | 98 | 38:62 |
| 2 | $CCl_3CH_2OH$ (**323**) | 48 | 96 | 32:68 |

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

Gratifingly, 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** Alcoholysis of anhydride **141** performed at 0 °C.



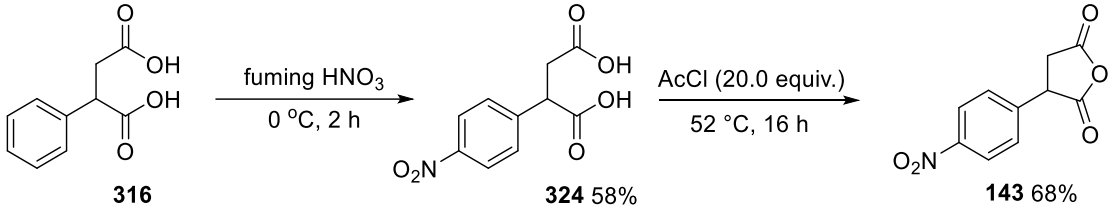

| entry | ROH | temp (°C) | conv (%)[a] | ratio 317:318[a] |
|---|---|---|---|---|
| 1 | $CF_3CH_2OH$ (**219**) | 0 | 83 | 40:60 |
| 2 | $CCl_3CH_2OH$ (**323**) | 0 | 79 | 34:66 |

[a] Determined by $^1H$ NMR spectroscopic analysis using *p*-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

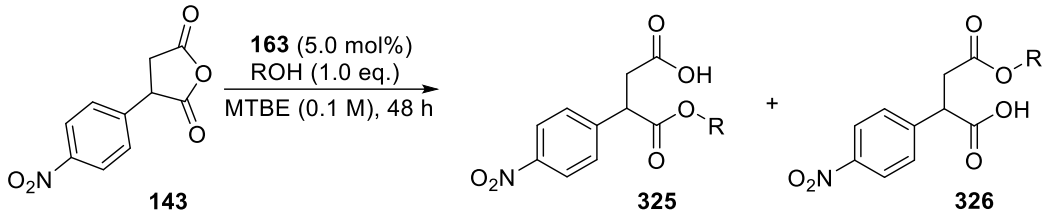
In light of the poor regioselectivities obtained, it was decided to employ anhydrides with an electron withdrawing group in order to increase the enolisation proclivity of the anhydride to allow subsequent rapid racemisation of the substrate. We decided to employ 4-nitrophenylsuccinic anhydride (**143**),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




**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.

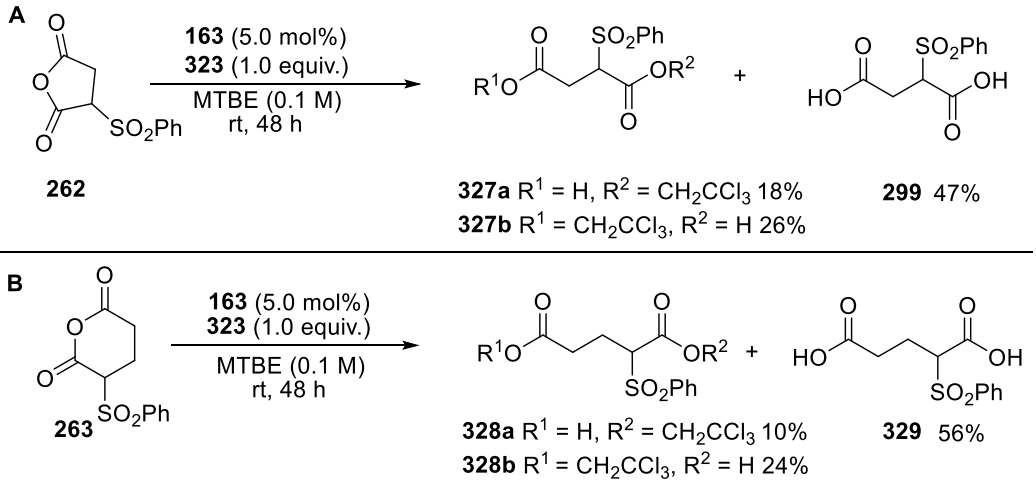



| entry | ROH | temp (°C) | conv (%)[a] | ratio 325:326[a] |
|---|---|---|---|---|
| 1 | EtOH (**320**) | 25 | 98 | 47:53 |
| 2 | $CF_3CH_2OH$ (**219**) | 25 | 98 | 42:58 |
| 3 | $CCl_3CH_2OH$ (**323**) | 25 | 98 | 38:62 |

[a]Determined by $^1$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-trifluoeoethanol (**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).

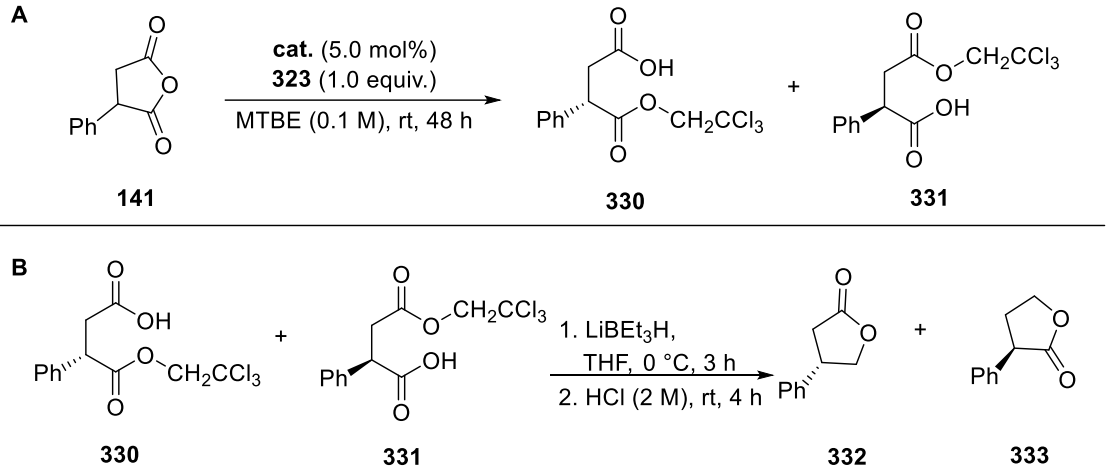



**Scheme 3.5** Alcoholysis of anhydrides **262** (A) and **263** (B).

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 athmosphere. 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

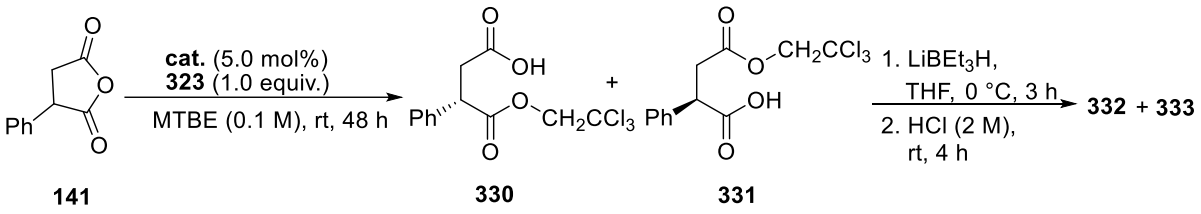
Since the preliminary investigations were directed towards the regioselectivity, our attention will now focus on the evaluation of the catalyst capability in promoting both the racemisation and the enantioselective ring-opening. Our protocol involved the reaction of equimolar amounts of **141** and alcohol **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 $\beta$- and $\alpha$-aryl-$\gamma$-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 $\beta$- and $\alpha$-aryl-$\gamma$-butyrolactones **332** and **333** which were then purified by flash column chromatography on silica gel (Scheme 3.6B).

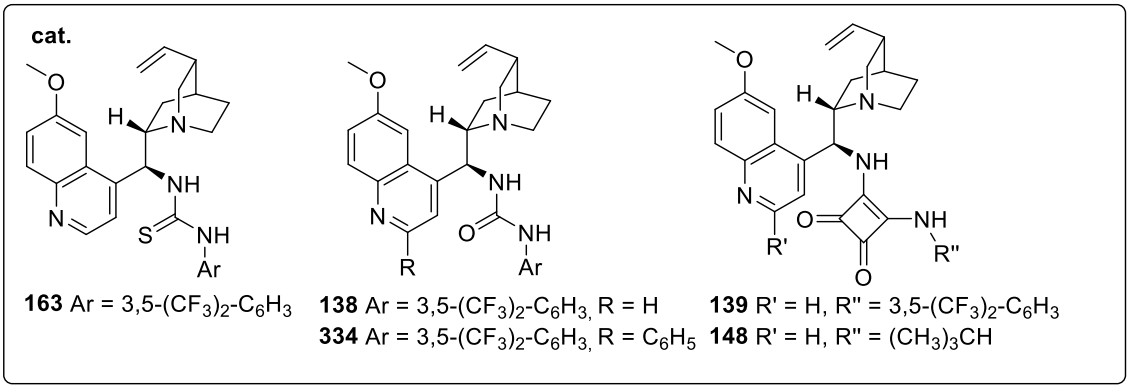



**Scheme 3.6** Conversion of the phenyl succinate products **330** and **331** to $\beta$- and $\alpha$-aryl-$\gamma$-butyrolactones **332** and **333**.

Accordingly, we decided to evaluate several cinchona-based organocatalysts which were previously made by fellow researchers in our group and were readly 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 alcoholysis of **141**.



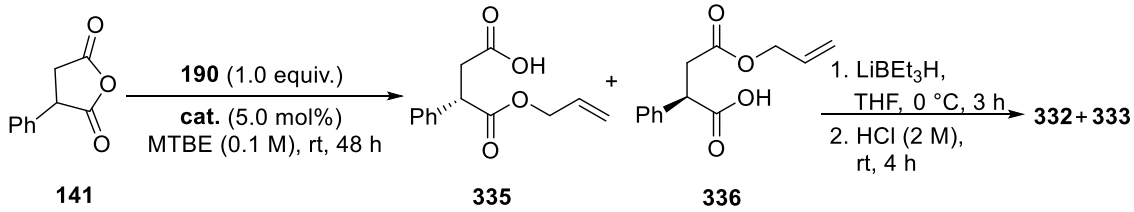

| entry | cat. | conv (%)[a] | ratio 330:331[a] | *ee* (%)[b] 332 | *ee* (%)[b] 333 | yield (%)[c] 332 | yield (%)[c] 333 |
|---|---|---|---|---|---|---|---|
| 1 | **163** | 98 | 34:66 | 88 | 81 | 26 | 46 |
| 2 | **138** | 98 | 31:69 | 85 | 68 | 26 | 44 |
| 3 | **334** | 98 | 32:68 | 84 | 63 | 25 | 42 |
| 4 | **139** | 80 | 50:50 | 90 | 77 | 42 | 31 |
| 5 | **148** | 95 | 37:63 | 90 | 72 | 31 | 45 |

[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 hemiesters 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 alcoholysis 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**.




| entry | cat. | conv (%)[a] | ratio 335:336[a] | *ee* (%)[b] 332 | *ee* (%)[b] 333 | yield (%)[c] 332 | yield (%)[c] 333 |
|---|---|---|---|---|---|---|---|
| 1 | **163** | 98 | 45:55 | 67 | 73 | 36 | 30 |
| 2 | **138** | 98 | 45:55 | 85 | 68 | 44 | 31 |
| 3 | **334** | 98 | 45:55 | 84 | 63 | 40 | 30 |
| 4 | **139** | 80 | 50:50 | 79 | 69 | 44 | 31 |
| 5 | **148** | 96 | 50:50 | 79 | 75 | 42 | 30 |

[a] Determined by $^1$H NMR spectroscopic analysis using *p*-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.

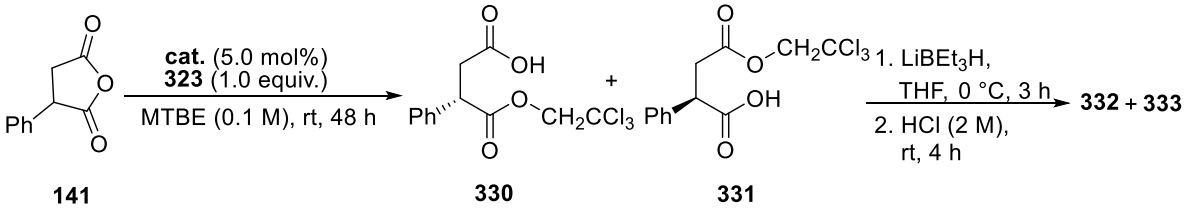
This data demonstrated the superiority of trichloroethanol (**323**) with respect to allyl alcohol (**190**) as the nucleophile in the alcoholysis of anhydride **141** promoted by (thio)urea- and squaramide-based cinchona alkaloids. Gratifingly this alcohol proved successful in giving improved hemiester product ratios with concomitant efficient

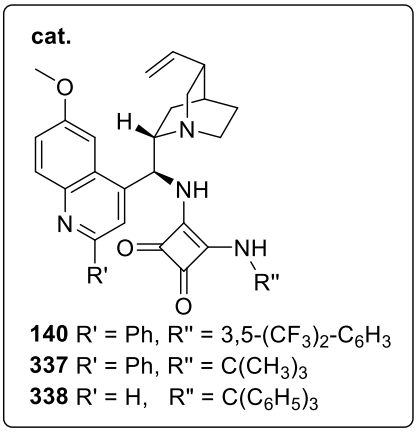
interactions with the catalysts, furnishing the mixture of lactones in considerably higher *ee*.

### 3.2.1 Squaramide-based catalyst evaluation for the regio/enantioselective alcoholysis 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 enantioseletivity; 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 alcoholysis of anhydride **141** with **323**.




| entry | cat. | conv (%)[a] | ratio 330:331[a] | *ee* (%)[b] 332 | *ee* (%)[b] 333 | yield (%)[c] 332 | yield (%)[c] 333 |
|---|---|---|---|---|---|---|---|
| 1 | **140** | 80 | 50:50 | 93 | 73 | 36 | 29 |
| 2 | **337** | 96 | 50:50 | 98 | 74 | 44 | 32 |
| 3 | **338** | 96 | 37:63 | 98 | 90 | 35 | 52 |

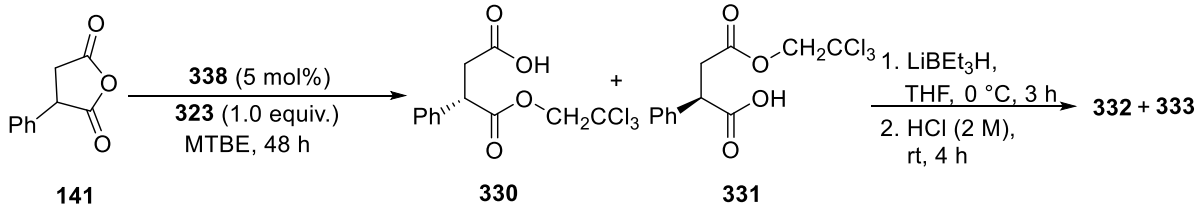
[a] Determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b] Determined by CSP-HPLC. [c] Isolated yield.

The regioselectivity of the reaction was not affected by the introduction of a phenyl substitutent 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**.




| entry | temp. (°C) | conc. [M] | 338 loading (mol %) | conv. (%)[a] | ratio[a] 330:331 | *ee* (%)[b] 332:333 | | yield (%)[c] 332:333 | |
|---|---|---|---|---|---|---|---|---|---|
| [3] previous | rt | 0.1 | 5 | 96 | 37:63 | 98 | 90 | 35 | 52 |
| 1 | -30 | 0.1 | 5 | 66 | 25:75 | 97 | 81 | 18 | 61 |
| 2 | rt | 0.05 | 5 | 90 | 28:72 | 98 | 87 | 20 | 66 |
| 3 | rt | 0.2 | 5 | 96 | 32:68 | 95 | 86 | 25 | 64 |
| 4 | rt | 0.1 | 20 | 92 | 32:68 | 94 | 82 | 17 | 50 |

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

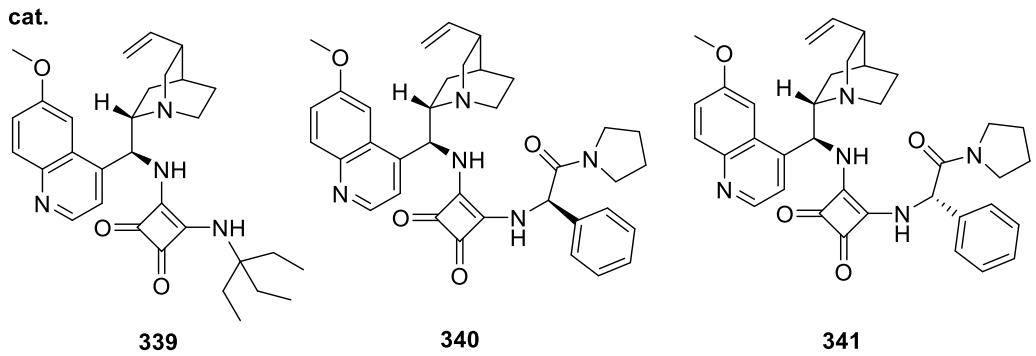
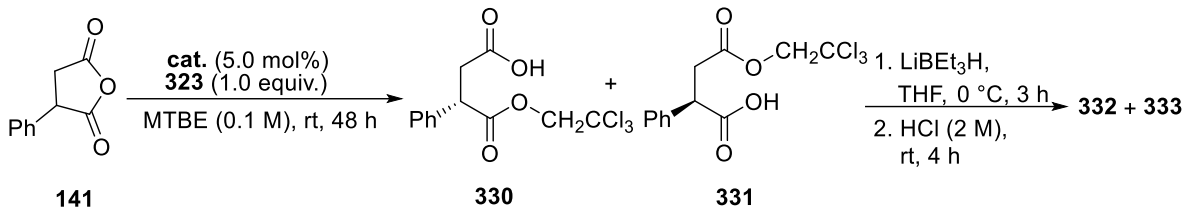



**Figure 3.2** Squaramide-substituted cinchona alkaloids evaluated as catalysts for the alcoholysis of **141** with **323**.

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**.



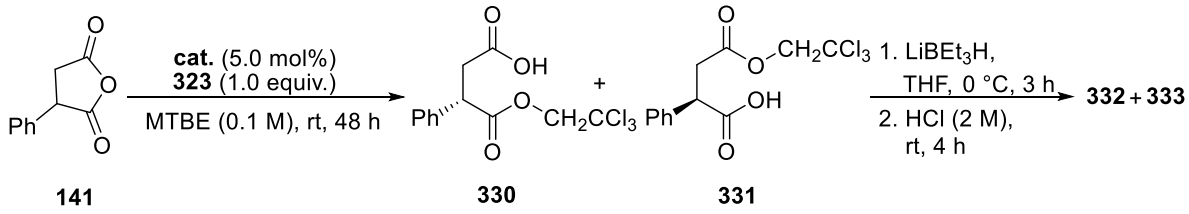

**141** **330** **331**

| entry | cat. | conv (%)[a] | ratio 330:331[a] | *ee* (%)[b] 332 | *ee* (%)[b] 333 | yield (%)[c] 332 | yield (%)[c] 333 |
|---|---|---|---|---|---|---|---|
| 1 | **339** | 96 | 35:65 | 96 | 81 | 22 | 51 |
| 2 | **340** | 87 | 36:64 | 90 | 85 | 20 | 46 |
| 3 | **341** | 84 | 23:77 | 92 | 79 | 12 | 52 |

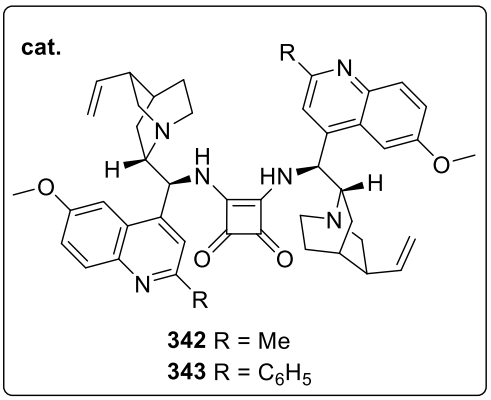
[a] Determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b] Determined by CSP-HPLC. [c] Isolated yield.

Next, we became interested in exploring the catalytic activity of $C_2$-symmetric analogues **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[238] (Table 3.13).

**Table 3.13** $C_2$-symmetric catalyst evaluation in the enantioselective alcoholysis of anhydride **141** with **323**.




**141** **330** **331**

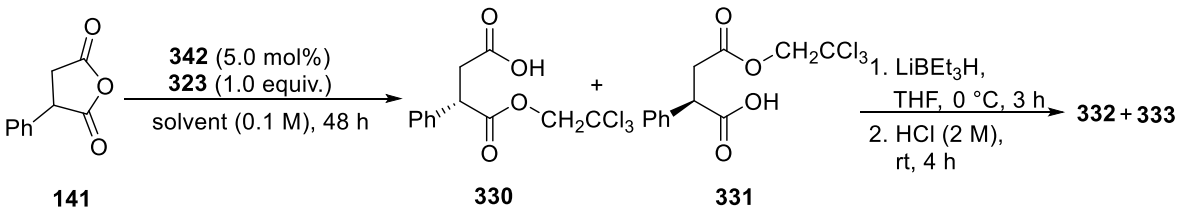


| entry | cat. | conv (%)[a] | ratio 330:331[a] | *ee* (%)[b] 332 | *ee* (%)[b] 333 | yield (%)[c] 332 | yield (%)[c] 333 |
|---|---|---|---|---|---|---|---|
| 1 | **342** | 87 | 20:80 | 68 | 66 | 13 | 66 |
| 2 | **343** | 90 | 16:84 | 87 | 67 | 11 | 69 |

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

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 alcoholysis of anhydride **141** with **323** promoted by catalyst **342**.




141 330 331

| entry | temp. (°C) | Solvent | conv (%)[a] | ratio 330:331[a] | *ee* (%)[b] 332 | *ee* (%)[b] 333 | yield (%)[c] 332 | yield (%)[c] 333 |
|---|---|---|---|---|---|---|---|---|
| 1 | -30 | MTBE | 85 | 20:80 | 54 | 62 | 9 | 66 |
| 2 | 25 | THF | 90 | 20:80 | 73 | 68 | 13 | 66 |

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

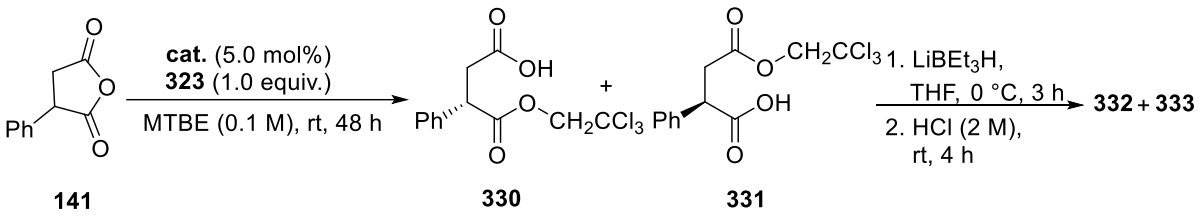
Initially, anhydride **141** was treated with alcohol **323** in the presence of catalyst **342** at

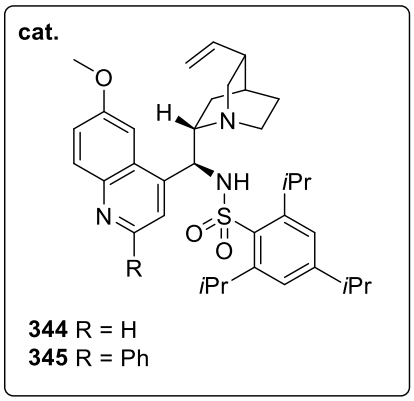
-30 °C. Unfortunately, the attempted variation of temperature did not lead to an improvement in hemiester ratio and also promoted the formation of the corresponding lactones with lower enantiomeric excess. The use of a different solvent (*i.e.* THF) at room temperature did not result in substantial improvement 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 alcoholysis 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.[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.[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 alcoholysis of anhydride **141** with **323**.




| entry | cat. | conv (%)[a] | ratio 330:331[a] | *ee* (%)[b] 332 | *ee* (%)[b] 333 | yield (%)[c] 332 | yield (%)[c] 333 |
|---|---|---|---|---|---|---|---|
| 1 | **344** | 93 | 33:67 | 92 | 91 | 25 | 51 |
| 2 | **345** | 87 | 37:63 | 95 | 87 | 24 | 44 |

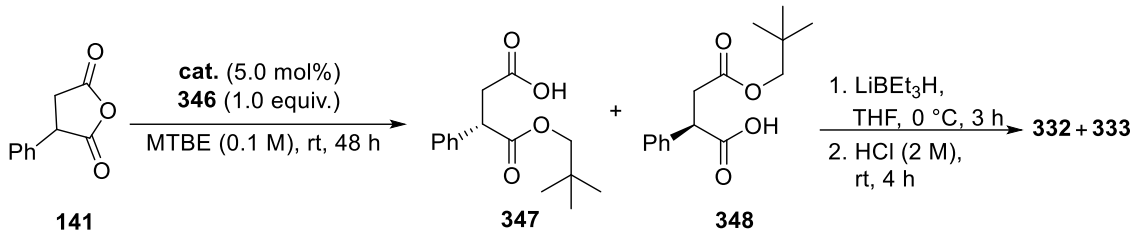
[a] Determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b] Determined by CSP-HPLC. [c] Isolated yield.

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 alcoholysis 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.



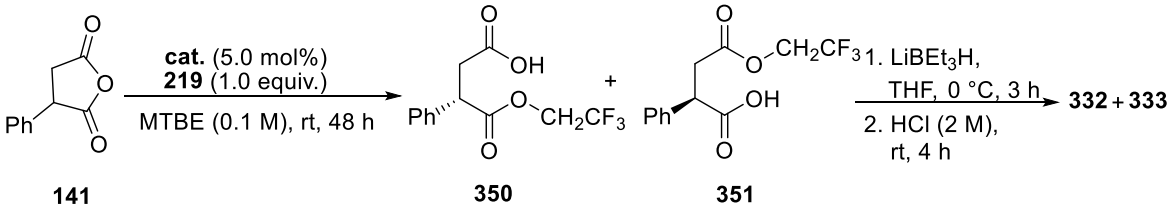

| entry | cat. | conv (%)[a] | ratio 347:348[a] | *ee* (%)[b] 332 | *ee* (%)[b] 333 | yield (%)[c] 332 | yield (%)[c] 333 |
|---|---|---|---|---|---|---|---|
| 1 | **344** | 61 | 50:50 | 64 | 57 | 41 | 30 |
| 2 | **345** | 48 | 50:50 | 66 | 51 | 42 | 32 |

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



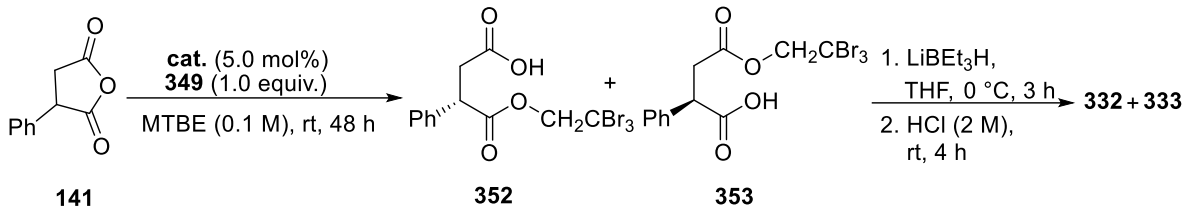

| entry | cat. | conv (%)[a] | ratio 350:351[a] | *ee* (%)[b] | | yield (%)[c] | |
|---|---|---|---|---|---|---|---|
| | | | | 332 | 333 | 332 | 333 |
| 1 | **163** | 98 | 38:62 | 88 | 69 | 22 | 48 |
| 2 | **338** | 96 | 37:63 | 94 | 88 | 24 | 47 |
| 3 | **344** | 93 | 31:69 | 90 | 84 | 22 | 53 |

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

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).

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




| entry | cat. | conv (%)[a] | ratio 352:353[a] | *ee* (%)[b] | | yield (%)[c] | |
|---|---|---|---|---|---|---|---|
| | | | | 332 | 333 | 332 | 333 |
| 1 | **163** | 88 | 34:66 | 74 | 68 | 25 | 54 |
| 2 | **338** | 96 | 30:70 | 87 | 89 | 24 | 57 |
| 3 | **344** | 96 | 39:61 | 73 | 86 | 31 | 50 |

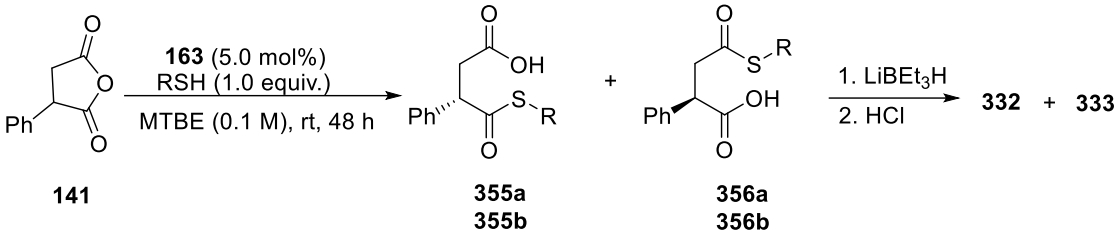
[a] Determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b] Determined by CSP-HPLC. [c] Isolated yield from **141**.

In the 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). Gratifingly, 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).

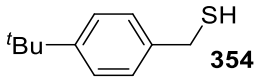
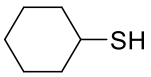
### 3.5.1 Substrate scope: thiols as nucleophiles

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 scrutinity. 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 3.19** Regio/enantioselective thiolysis of **141**.



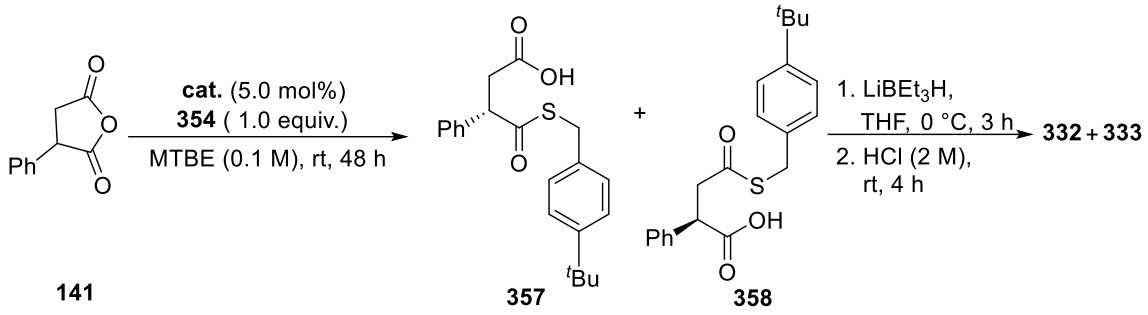

**141** **355a** **355b** **356a** **356b**

| entry | RSH | conv (%)[a] | ratio 355:356[a] | *ee* (%)[b] | | yield (%)[c] | |
|---|---|---|---|---|---|---|---|
| | | | | **332** | **333** | **332** | **333** |
| 1 |  **354** | 95 | 34:66 | 21 | 62 | 21 | 53 |
| 2 |  **210** | 52 | 35:65 | - | | - | |

[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 involving 4-*tert*-butylbenzyl 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**.




| entry | cat. | conv (%)[a] | ratio 357:358[a] | *ee* (%)[b] | | yield (%)[c] | |
|---|---|---|---|---|---|---|---|
| | | | | 332 | 333 | 332 | 333 |
| 1 | **344** | 88 | 38:62 | 2 | 63 | 22 | 46 |
| 2 | **345** | 91 | 42:58 | 48 | 60 | 36 | 31 |

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

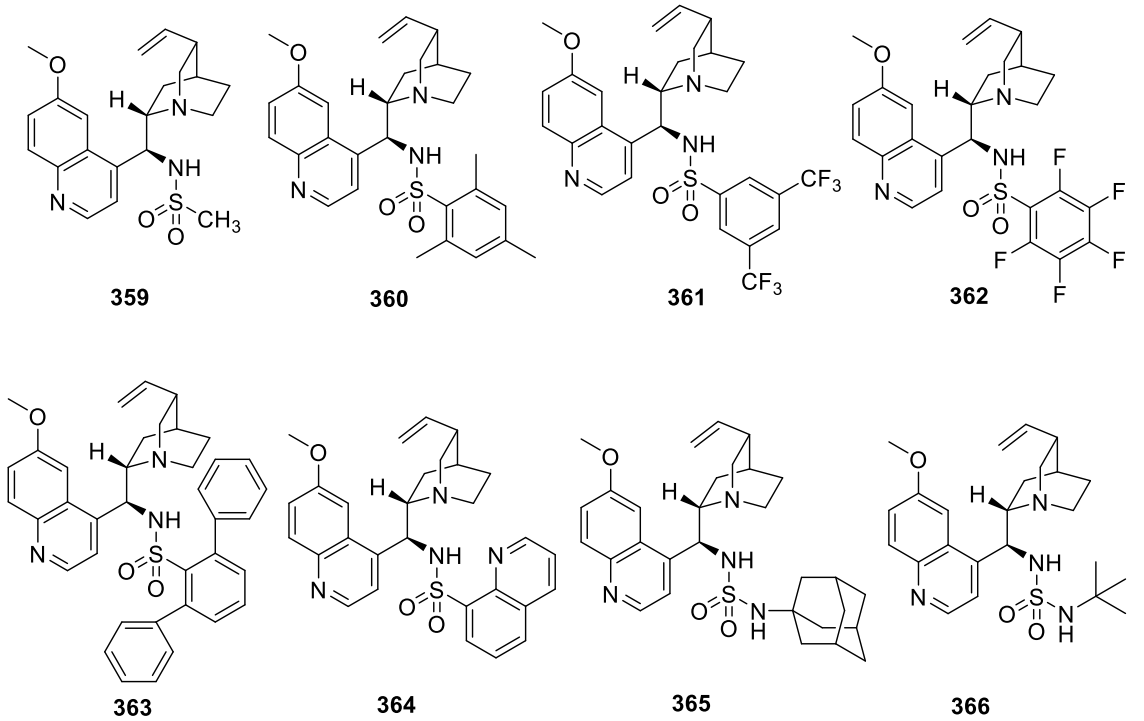
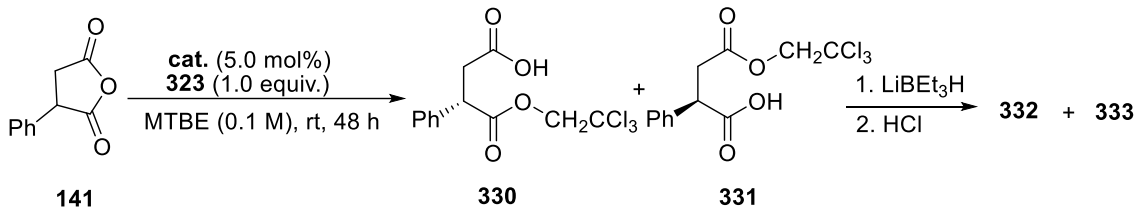



**Figure 3.3** Sulfonamide-substituted cinchona alkaloids selected at the outset of our study.

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 substitutents, 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**.



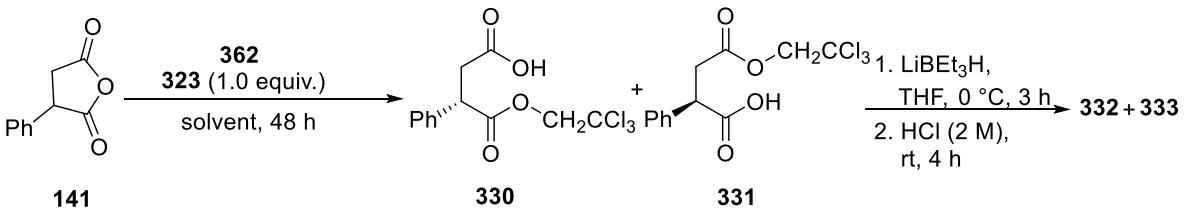

| entry | cat. | conv (%)[a] | ratio 330:331[a] | *ee* (%)[b] 332 | *ee* (%)[b] 333 | yield (%)[c] 332 | yield (%)[c] 333 |
|---|---|---|---|---|---|---|---|
| 1 | **359** | 91 | 29:71 | 90 | 90 | 20 | 62 |
| 2 | **360** | 87 | 25:75 | 93 | 89 | 17 | 66 |
| 3 | **361** | 96 | 27:73 | 97 | 89 | 19 | 68 |
| 4 | **362** | 96 | 24:76 | 97 | 92 | 17 | 69 |
| 5 | **363** | 69 | 33:67 | 81 | 73 | 21 | 53 |
| 6 | **364** | 96 | 29:71 | 77 | 57 | 17 | 58 |
| 7 | **365** | 93 | 24:76 | 88 | 89 | 15 | 61 |
| 8 | **366** | 88 | 24:76 | 84 | 84 | 15 | 66 |

[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 alcoholysis of **141**.




| entry | conc. [M] | solvent | temp. (°C) | loading 362 (%) | conv (%)[a] | ratio 330:331[a] | *ee* (%)[b] 332 | *ee* (%)[b] 333 |
|---|---|---|---|---|---|---|---|---|
| 1 | 0.05 | MTBE | 25 | 5 | 91 | 28:72 | 97 | 90 |
| 2 | 0.2 | MTBE | 25 | 5 | 96 | 32:68 | 97 | 92 |
| 3 | 0.1 | THF | 25 | 5 | 61 | 24:76 | 95 | 92 |
| 4 | 0.1 | MTBE | 30 | 5 | 97 | 24:76 | 97 | 91 |
| 5 | 0.1 | MTBE | 0 | 5 | 93 | 24:76 | 95 | 88 |
| 6 | 0.1 | MTBE | 25 | 10 | 93 | 25:75 | 97 | 90 |
| 7 | 0.1 | MTBE | 25 | 20 | 96 | 29:71 | 96 | 84 |

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

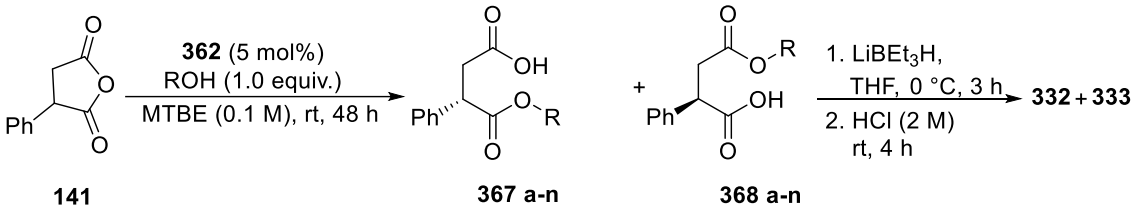
The reaction temperature was the next parameter to be evaluated. Increasing the temperature to 30 °C did not influence either the regio- or the enantioselectivity compared to that obtained at room temperature (entry 4), while the reaction performed at 0 °C provided products with slightly lower optical purity (entry 5).

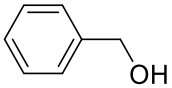
Subsequently, it was decided to increase the catalyst loading from 5 mol% to 10 and 20 mol% (entries 6 and 7 respectively). In all cases evaluated, the regioselectivity was marginally decreased, however, products were furnished in good enantiomeric excess.

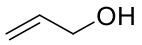
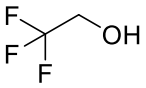
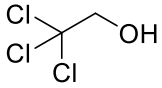
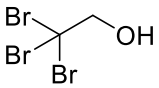
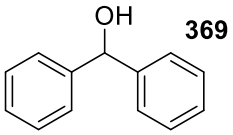
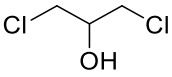
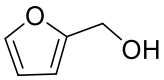
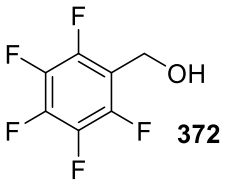
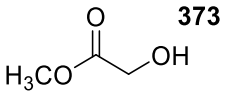
### 3.6.2 Evaluation of the substrate scope: the alcohol component

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 $pk_a$ 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 $^t$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 Es values was carried out.

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




| entry | ROH | | $pk_a$ ($H_2O$) | $E_s$[a] (log $k/k_0$) | conv (%)[b] | ratio 367a-n:368a-n[b] | *ee* (%)[c] 332 | 333 |
|---|---|---|---|---|---|---|---|---|
| 1 | MeOH | **319** | 15.7 | -1.24 | 98 | 45:55 | 72 | 63 |
| 2 | EtOH | **320** | 15.9 | -1.31 | 98 | 45:55 | 82 | 71 |
| 3 |  | **321** | 15.4 | -1.62 | 98 | 35:65 | 86 | 70 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 4 |  **190** | 15.5 | -1.55* | 97 | 33:67 | 86 | 74 |
| 5 |  **219** | 11.5 | -1.48 ($F\text{-}CH_2$) | 97 | 29:71 | 91 | 83 |
| 6 |  **323** | 12.5 | -1.48 ($Cl\text{-}CH_2$) | 96 | 24:76 | 97 | 93 |
| 7 |  **349** | 13.2 | -1.51 ($Br\text{-}CH_2$) | 96 | 24:76 | 90 | 94 |
| 8 |  **369** | 13.7 | -3.00 | 25 | 40:60 | 60 | 75 |
| 9 |  **370** | 13.6 | -- | 29 | 38:62 | 82 | 72 |
| 10 |  **371** | 14.7 | -1.58* | 97 | 35:65 | 87 | 69 |
| 11 |  **372** | 13 | -- | 94 | 29:71 | 89 | 68 |
| 12 |  **373** | 13 | -- | 96 | 29:71 | 72 | 74 |

[a] Taft $E_s$ values.[239] [b] Determined by $^1H$ NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [c] Determined by CSP-HPLC. * Revised Taft steric constant.[239]

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 enantioselectivty. 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**) mantained 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).

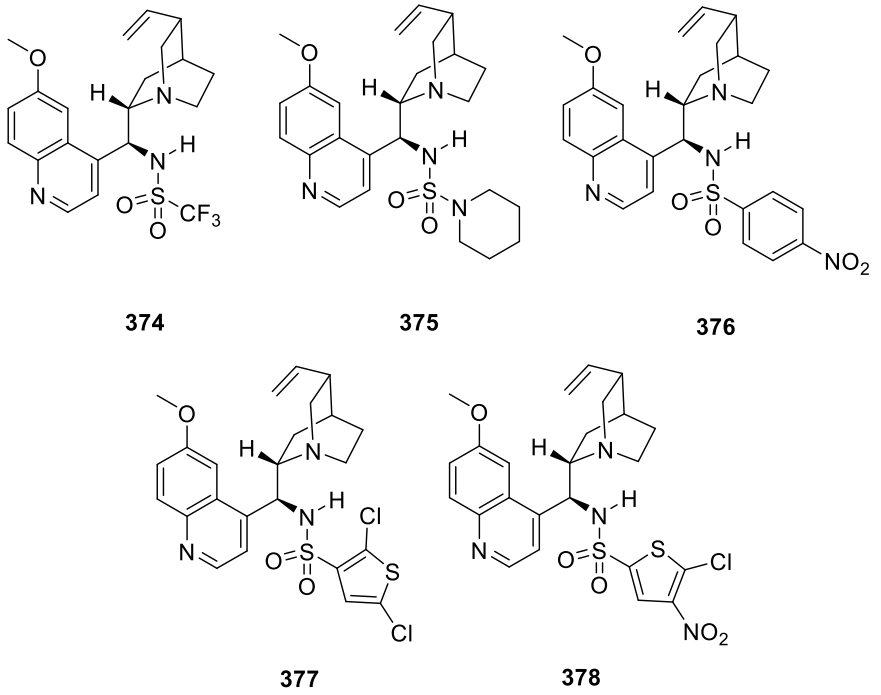
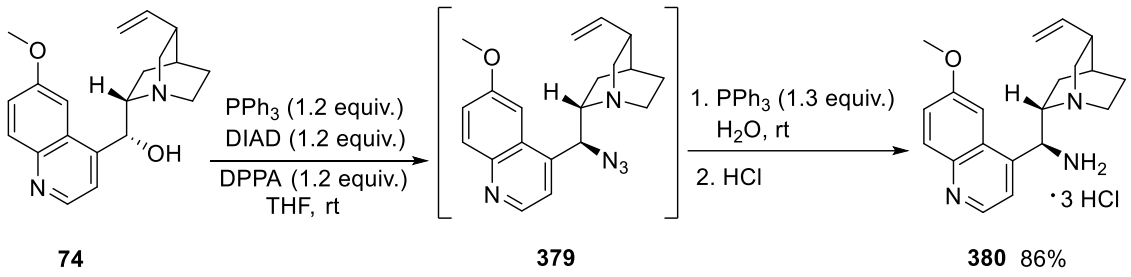


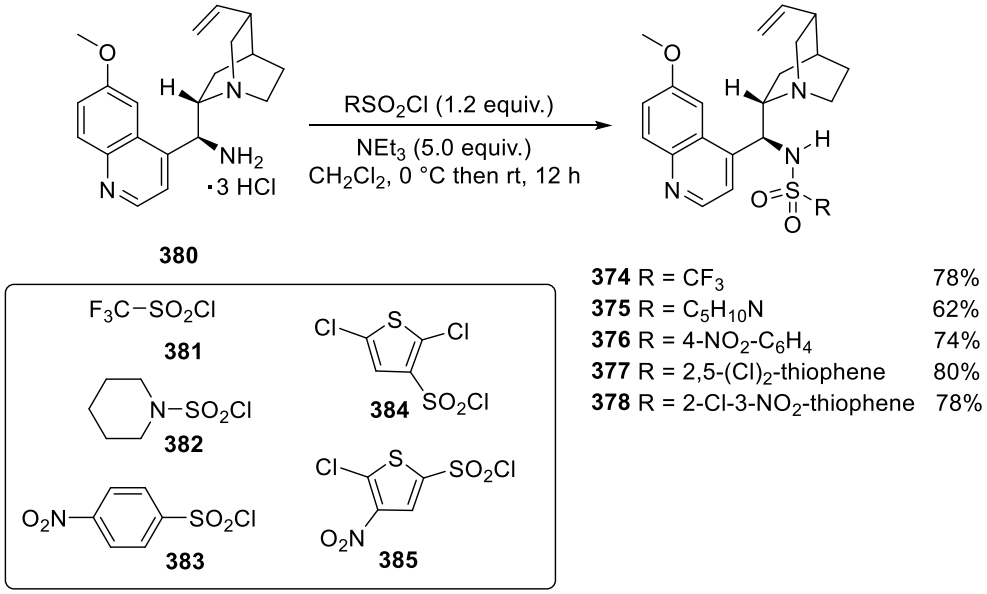

**Figure 3.4** A new generation of sulfonamide-substituted cinchona alkaloid derivatives.

According to the literature procedure,[83,240] we initially prepared the amine **380** starting from readily available quinine. The alkaloid was transformed *via* a Mitsunobu reaction into the azido intermediate with inverted configuration at *C*-9 (**379**). The following *in situ* Staudinger reduction with an excess of $PPh_3$ and acidic water furnished the hydrochloride salt **380** (Scheme 3.7).




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

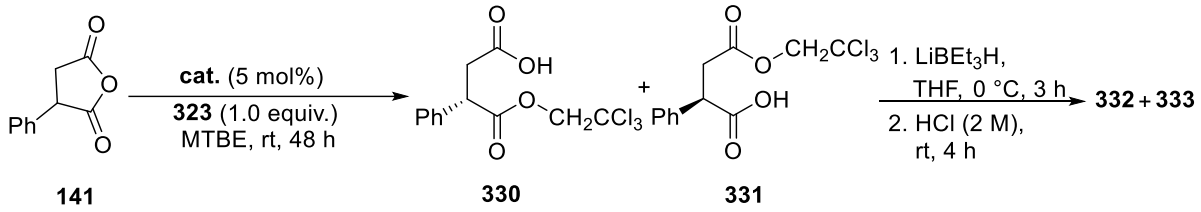
Sulfonamide-modified organocatalysts **374-378** were prepared in good yields by the reaction of 9-*epi*-quinine amine hydrochloride salt (**380**) with the relevant sulfonyl chloride (**381-385**) in the presence of a large excess of triethylamine (Scheme 3.8).




**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**.




| entry | cat. | conv (%)[a] | ratio 330:331[a] | *ee* (%)[b] 332 | *ee* (%)[b] 333 | yield (%)[c] 332 | yield (%)[c] 333 |
|---|---|---|---|---|---|---|---|
| 1 | **374** | 59 | 23:77 | 90 | 91 | 8 | 32 |
| 2 | **375** | 96 | 26:74 | 92 | 90 | 17 | 59 |
| 3 | **376** | 95 | 29:71 | 97 | 92 | 19 | 55 |
| 4 | **377** | 95 | 26:74 | 95 | 92 | 21 | 60 |
| 5 | **378** | 94 | 26:74 | 96 | 93 | 21 | 65 |

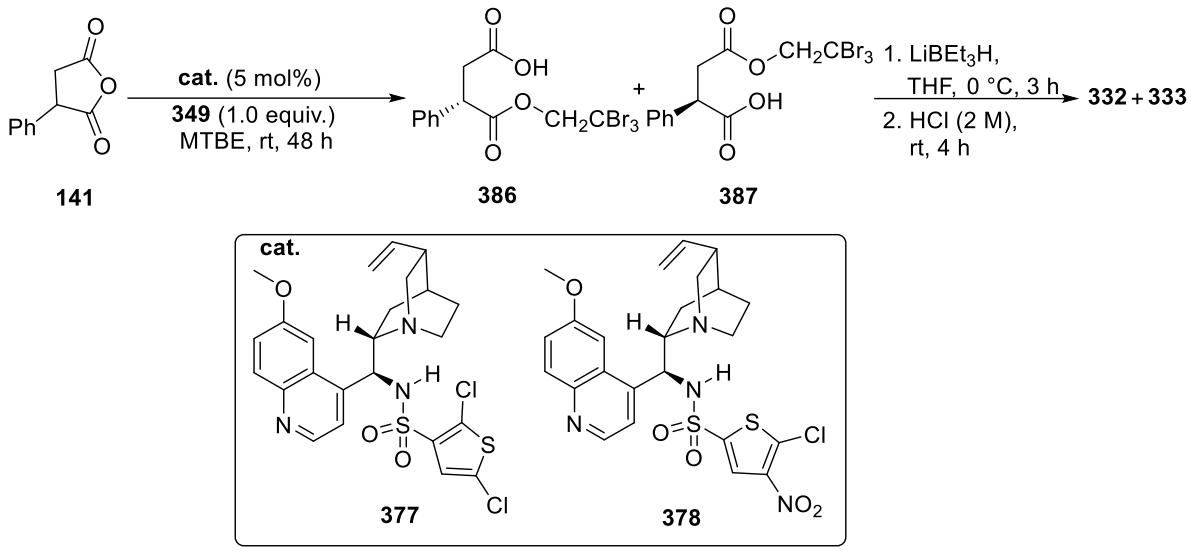
[a] Determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b]Determined by CSP-HPLC. [c] Isolated yield.

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, albieit with low conversion after 48 h. The piperidine-substituted derivative **375** was also able to promote the resolution of **141**; furnishing products with a slighlty inferior hemiester ratio, however, the enantioselectivity remained unchanged (entry 2). The introduction of a *p*-$NO_2$-phenyl substitutent 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 scrutinity, 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).

**Table 3.25** DKR of anhydride **141** with **349** promoted by thiophene-substituted sulfonamide catalysts



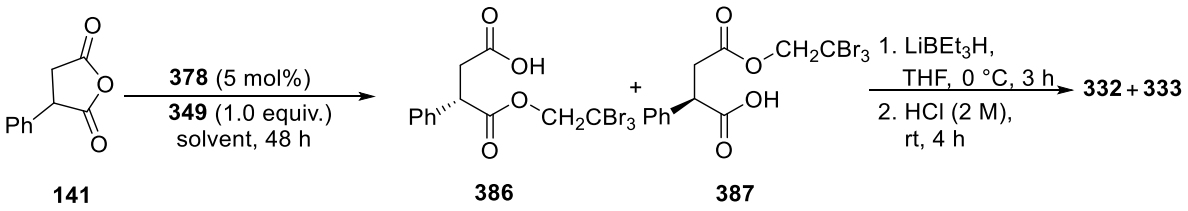

| entry | cat. | conv (%)[a] | ratio 386:387[a] | *ee* (%)[b] 332 | *ee* (%)[b] 333 | yield (%)[c] 332 | yield (%)[c] 333 |
|---|---|---|---|---|---|---|---|
| 1 | **377** | 97 | 25:75 | 87 | 93 | 17 | 66 |
| 2 | **378** | 98 | 24:76 | 94 | 94 | 21 | 68 |

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

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 alcoholysis of **141** with **349** promoted by sulfonamide catalyst **378**.




141 386 387

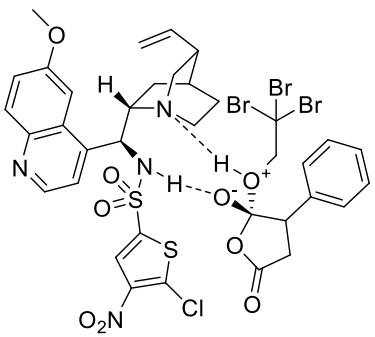
| entry | temp. (°C) | loading 378 (%) | conc. [M] | solvent | conv (%)[a] | ratio 386:387[a] | *ee* (%)[b] 332 | 333 |
|---|---|---|---|---|---|---|---|---|
| 1 | rt | 5 | 0.1 | MTBE | 98 | 24:76 | 94 | 94 |
| 2 | 0 | 5 | 0.1 | MTBE | 98 | 26:74 | 94 | 95 |
| 3 | 30 | 5 | 0.1 | MTBE | 70 | 29:71 | 96 | 94 |
| 4 | rt | 15 | 0.1 | MTBE | 98 | 26:74 | 93 | 94 |
| 5 | rt | 5 | 0.2 | MTBE | 98 | 28:72 | 88 | 96 |
| 6 | rt | 5 | 0.05 | MTBE | 98 | 24:76 | 96 | 97 |
| 7 | rt | 5 | 0.1 | THF | 35 | 28:72 | -- | |
| 8 | rt | 5 | 0.1 | Diisopropyl ether | 87 | 30:70 | 85 | 90 |

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

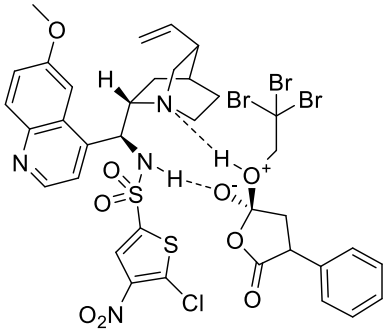
Generally, the attempted variation of temperature, catalyst loading, concentration and solvent did not improve the regioselectivity of the hemiester products (Table 3.26, entries 2-5) compared to the reaction accomplished in MTBE as the solvent at a concentration of 0.1 M with 5 mol% of catalyst **378** 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)[163] we proposed that the addition of alcohol **349** 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 **378** 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 **332** and **333** to those reported in the literature,[268] 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**



Binding mode B leading to (*R*)-**387**

**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).

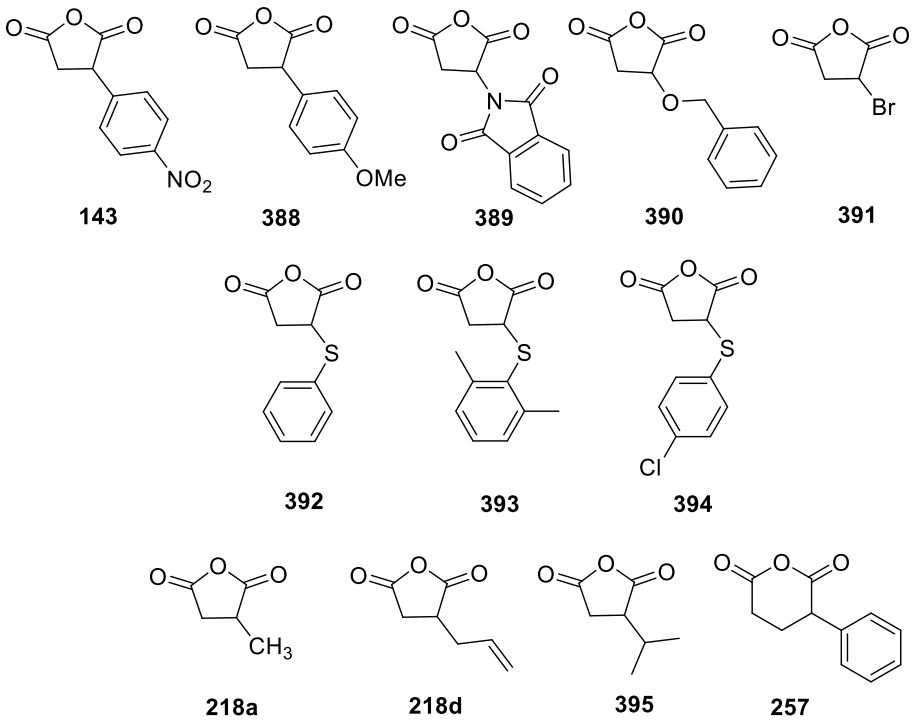
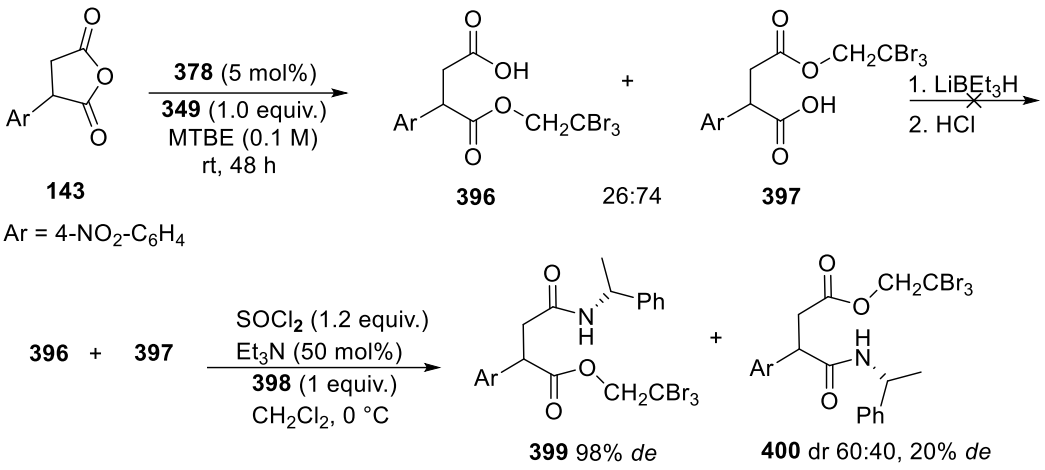



**Figure 3.6** Selection of a set of anhydrides prepared for the evaluation of substrate scope.

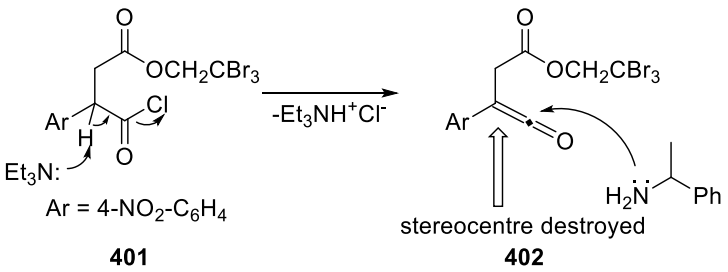
### 3.9.1 Synthesis and evaluation of alternative cyclic anhydrides as electrophiles

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).



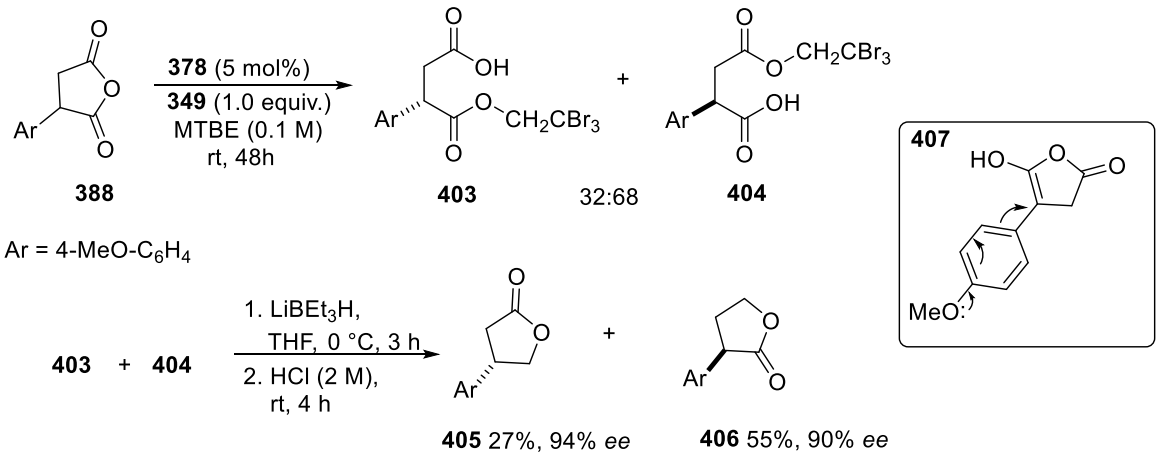

**Scheme 3.9** Enantioselective alcoholysis of anhydride **142** with **349** promoted by catalyst **378**.

Unfortunately, the alcoholysis of anydride **142** provided a hemister ratio slightly inferior to that obtained with the anhydride lacking the *p*-$NO_2$ substitutent 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.

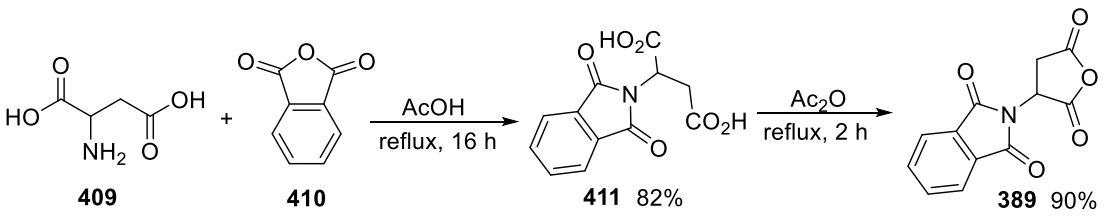
Shortly after, the substitued phenylsuccinic anhydride possessing a deactivating group (-OMe, **388**, kindly provided by fellow researcher Ms. Maria Luisa Aiello) was evaluated under the same reaction conditions (Scheme 3.11).




**Scheme 3.11** 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 $\alpha$-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 readly 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).

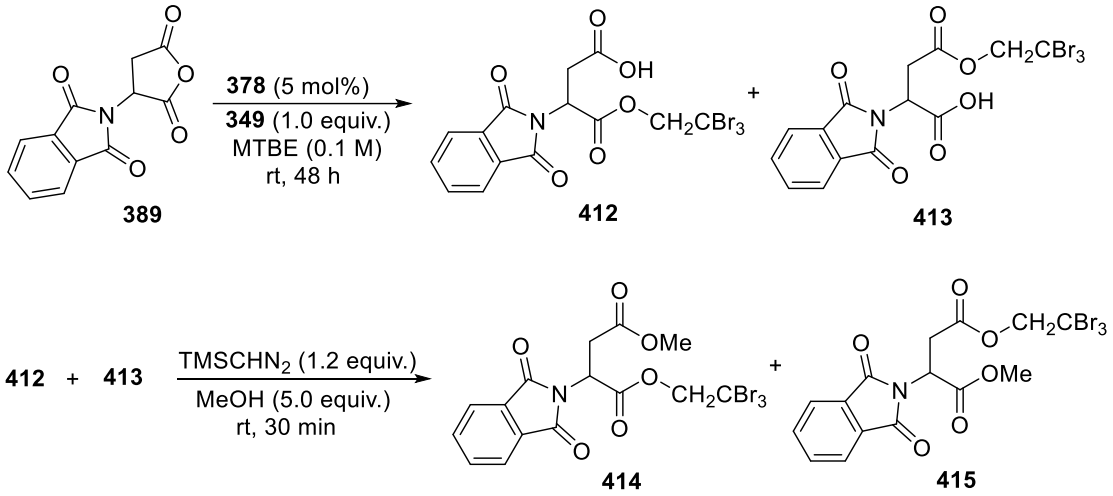



**Scheme 3.12** Synthesis of anhydride **389**.

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 $^1$H-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**.

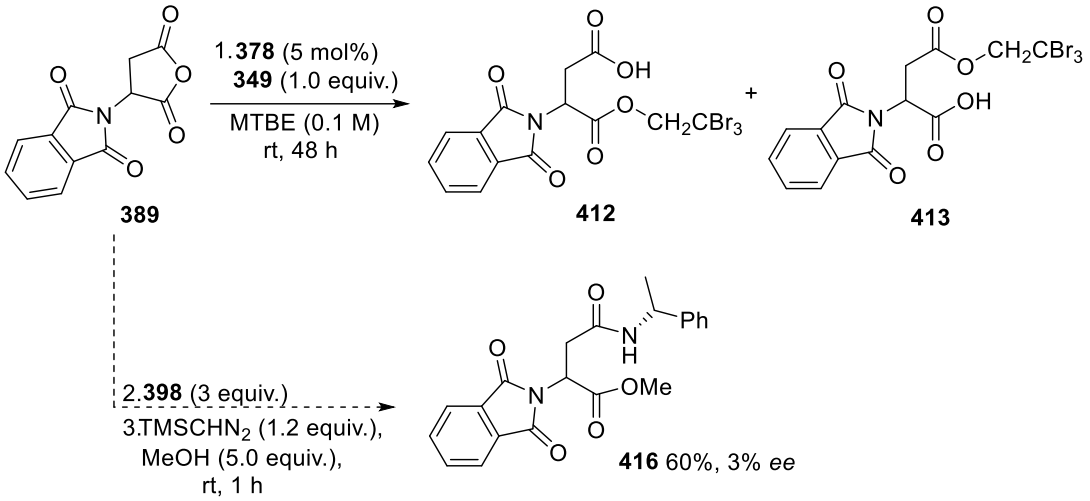



| entry | temp. (°C) | solvent | conv (%)[a] | ratio 412:413[a] | *ee* (%)[b] 414 | 415 |
|---|---|---|---|---|---|---|
| 1 | rt | MTBE | 41 | 45:55 | 79 | 76 |
| 2 | rt | THF | 0 | -- | -- | |

[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**). Subsequentially, a solution of

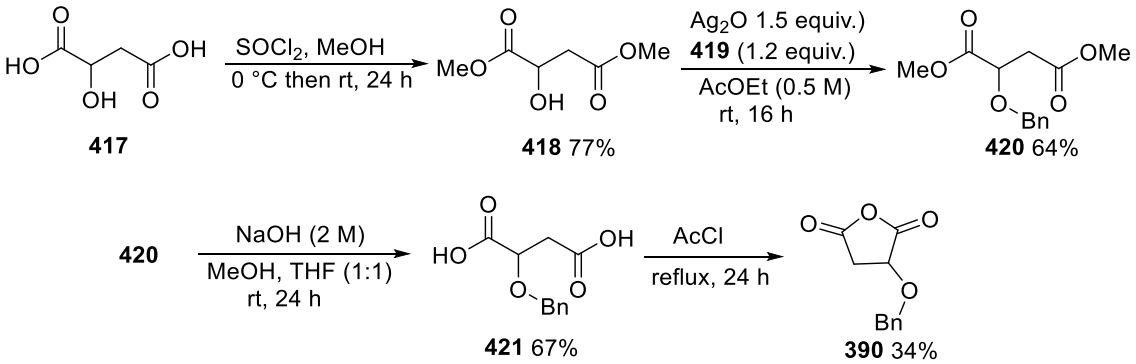
diazomethane in MeOH was added to afford, upon isolation by flash chromatography, the product **416** in only 3% *ee* (Scheme 3.13).




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

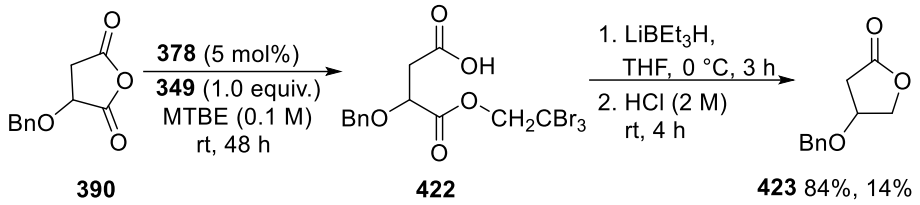
We, therefore, reasoned that no significant KR is occurring and that the solubility issue could be a plausible explanation for the low reactivity of this substrate.

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 $Ag_2O$ 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.



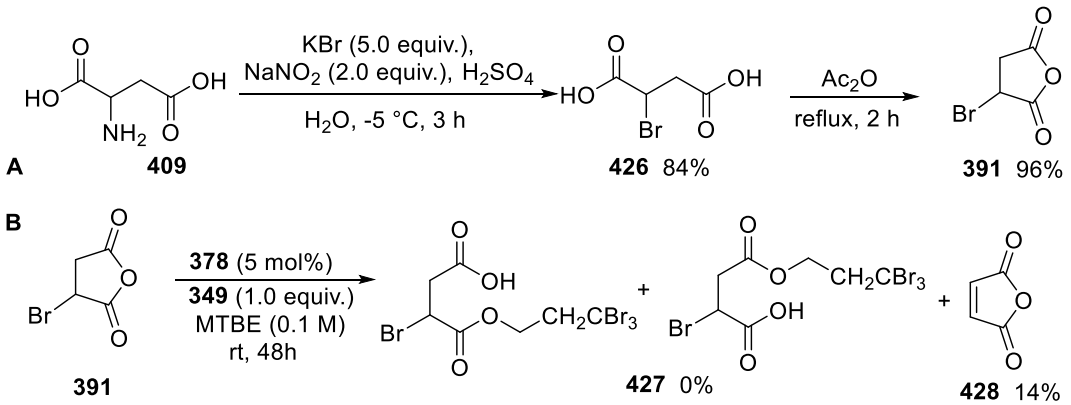

**Scheme 3.14** Synthesis of anhydride **390**.

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. Gratifingly, the alkoxyl-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 $\alpha$-carbonyl undergoing the nucleophilic attack.




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

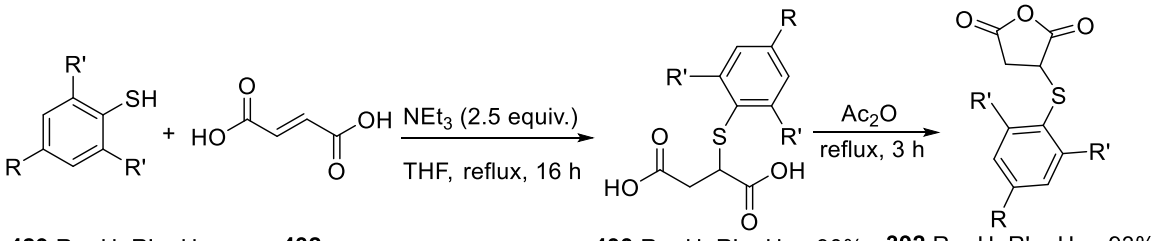
Next, we moved towards the evaluation of $\alpha$-bromosuccinic anhydride. Despite the fact that our group has recently described the lack of success of this substrate in the asymmetric annulation reaction with aldehydes due to an elimination process competing with the reaction scope, we envisaged that, 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 $\alpha$-bromo-substituted *bis*-acid **426** (*via* a Sandmeyer-type reaction[231]) 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**).

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).




**429** R = H, R' = H
**430** R = H, R' = $CH_3$
**431** R = Cl, R' = H

**432**

**433** R = H, R' = H 90%
**434** R = H, R' = $CH_3$ 88%
**435** R = Cl, R' = H 75%

**392** R = H, R' = H 93%
**393** R = H, R' = $CH_3$ 87%
**394** R = Cl, R' = H 79%

**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*.[241,242,243] 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 σ* orbital (Figure 3.7).[243]

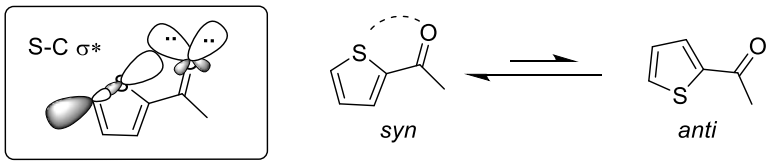
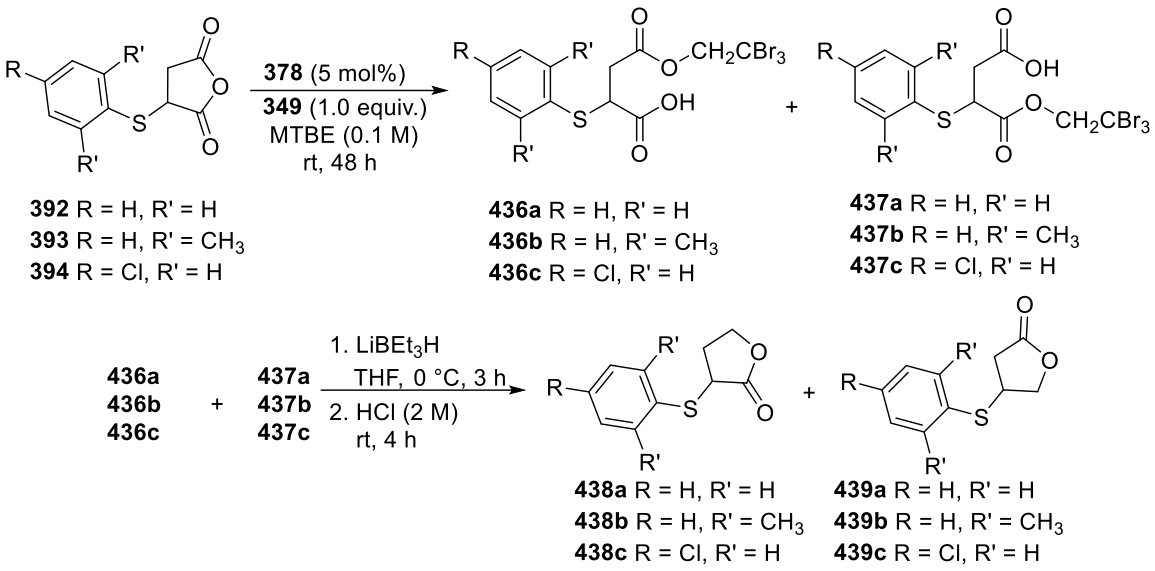



**Figure 3.7** Oxygen-sulfur orbital interactions.

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 scrutinity, we envisaged that an intramolecular delocalisation involving the lone pair of electrons of the $\alpha$-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 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**.




| entry | anhydride | conv (%)[a] | ratio | *ee* (%)[b] | | yield (%)[c] | |
|---|---|---|---|---|---|---|---|
| | | | 436:437 | 438 | 439 | 438 | 439 |
| 1 | **392** | 97 | 32:68 | 80 | 84 | 20 | 51 |
| 2 | **393** | 73 | 42:58 | 85 | 90 | 26 | 30 |
| 3 | **394** | 74 | 28:72 | 86 | 90 | 9 | 53 |

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

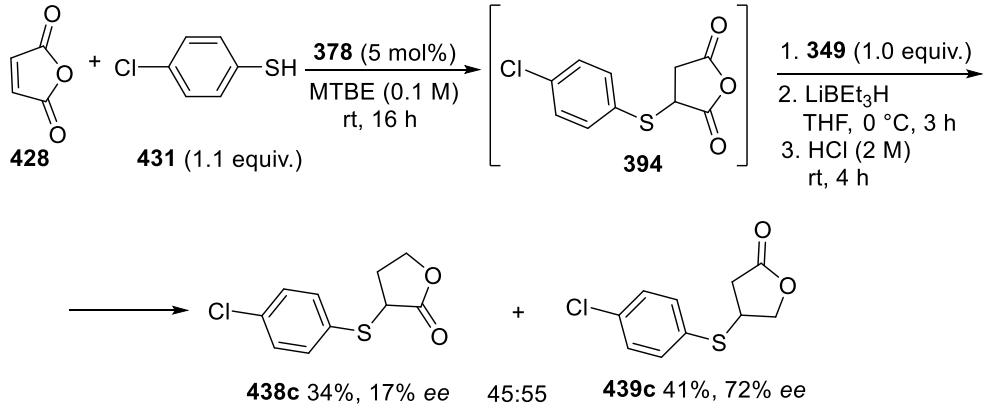
**Table 3.29** Evaluation of the effect of temperature in the enantioselective alcoholysis of thioaryl anhydrides with **349** promoted by catalyst **378**.

| entry | anhydride | temp. (°C) | conv (%)[a] | ratio 436:437 | *ee* (%)[b] 438 | 439 | yield (%)[c] 438 | 439 |
|---|---|---|---|---|---|---|---|---|
| 1 | **392** | -15 | 68 | 32:68 | 80 | 84 | 20 | 38 |
| 2 | **393** | -15 | 56 | 44:56 | 72 | 90 | 17 | 33 |
| 3 | **394** | -15 | 44 | 24:76 | 70 | 75 | 6 | 27 |

[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**.

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 diminuished 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 scrutinity 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**.

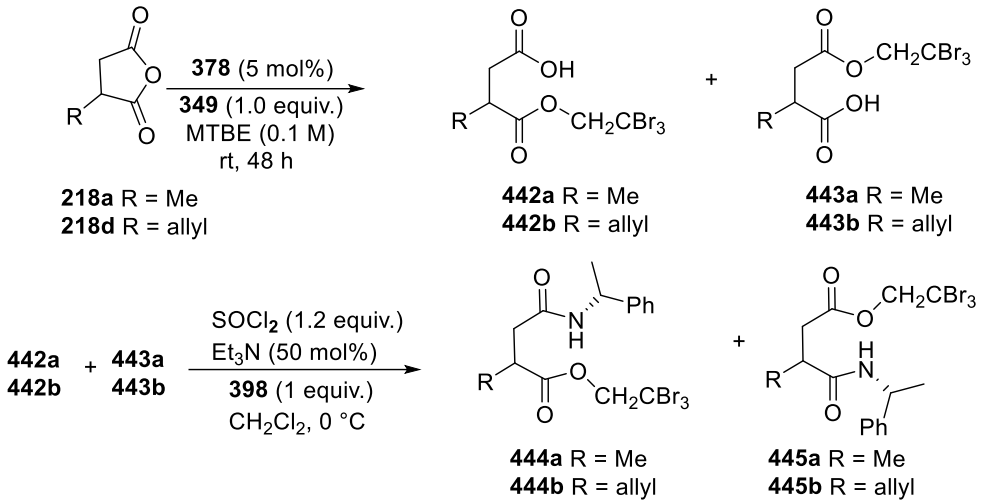
Unfortunately, the one pot alcoholysis experiment proved ineffective and was accompanied by a notable drop in regioselectivity and poor product enantiomeric excess.

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 substitutents.

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).

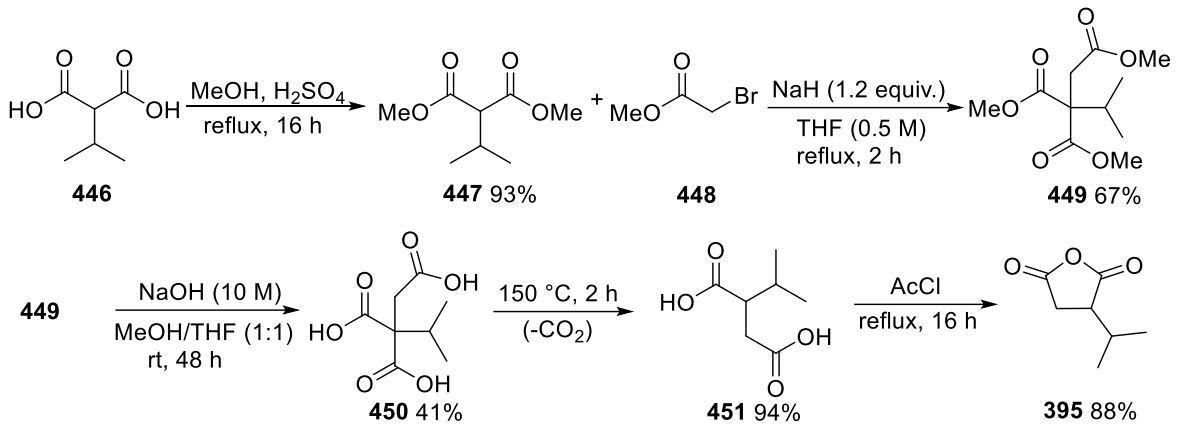
**Table 3.30** Evaluation of **218a** and **218d** in the enantioselective alcoholysis with **349** promoted by catalyst **378**.




| entry | anhydride | conv (%)[a] | ratio 442:443 | *ee* (%)[b] 444 | *ee* (%)[b] 445 | yield (%)[c] 444 | yield (%)[c] 445 |
|---|---|---|---|---|---|---|---|
| 1 | **218a** | 98 | 45:55 | 99[d] | 94[d] | 32 | 38 |
| 2 | **218d** | 98 | 46:54 | 99 | 90 | 38 | 52 |

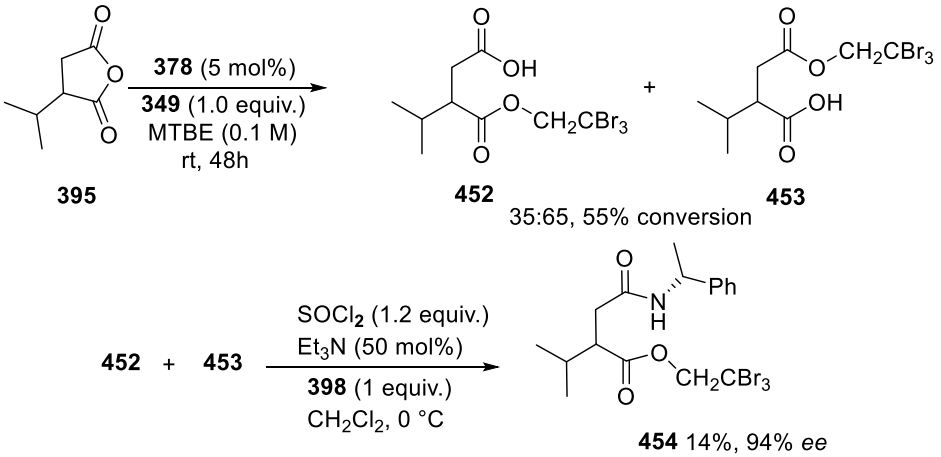
[a] Determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b] Determined by CSP-HPLC. [c] Isolated yield from **141**. [d] Determined by $^1$H NMR spectroscopic analysis.

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 substitutent. 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**.

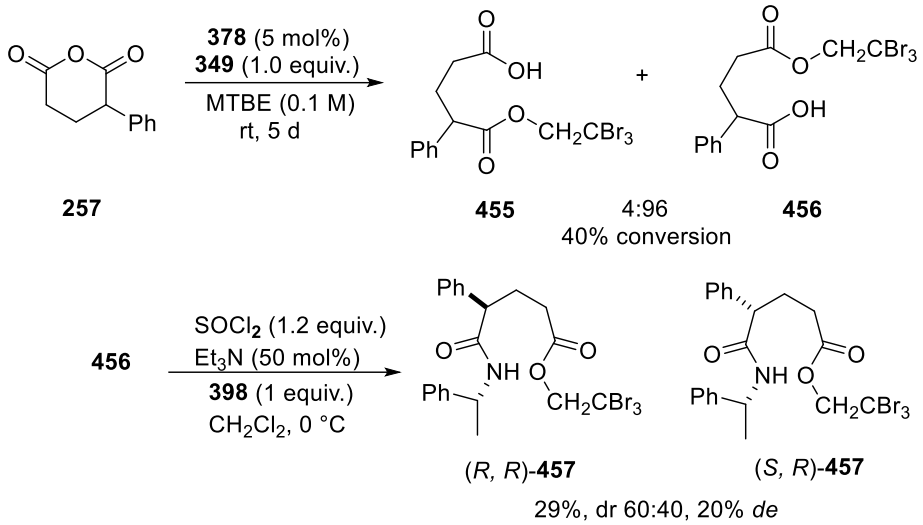
Anhydride **395** was employed in the asymmetric alcoholysis with **349** promoted by catalyst **370** at room temperature in MTBE. Pleasantly, we observed the formation of hemiesters **452** and **453** in improved ratios (35:65, Scheme 3.20) with the larger isopropyl group compared to the less hindered 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 substitutent 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 substitutent, 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).

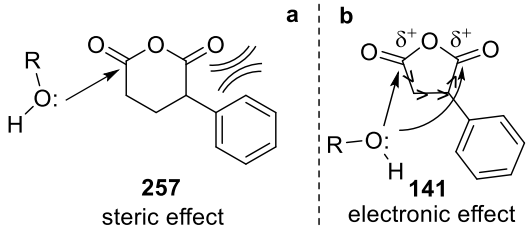


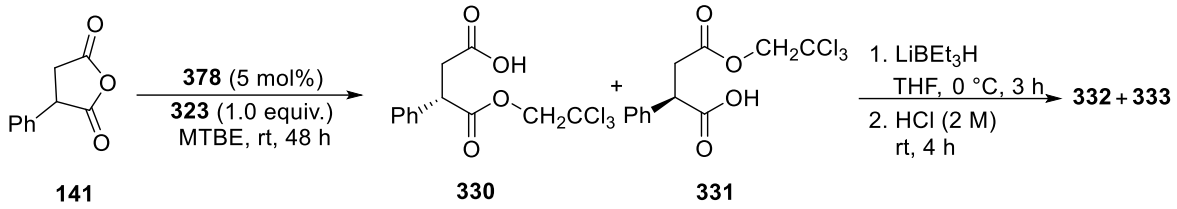

**Figure 3.8** Steric and electronic effects of anhydride **257** (**a**) and **141** (**b**).

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.




**141** **330** **331**

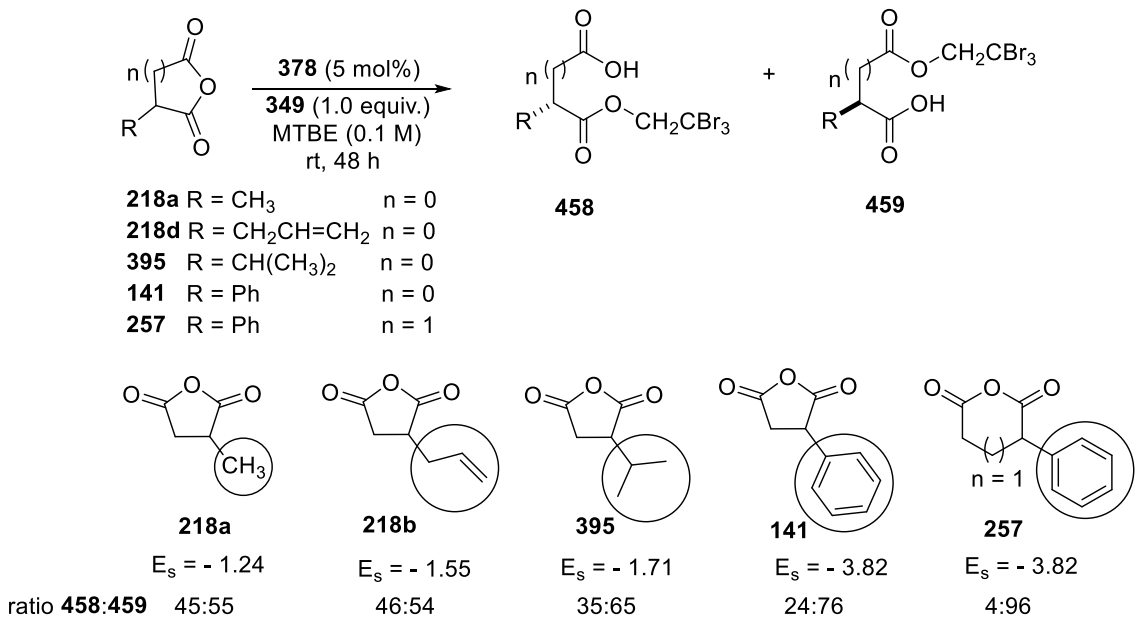
| entry | conv (%)[a] | ratio 330:331[a] | *ee* (%)[b] | | *ee* (%)[b] |
|---|---|---|---|---|---|
| | | | **332** | **333** | **141**[c] |
| 1 | 20 | 24:76 | 93 | 93 | -- |
| 2 | 50 | 24:76 | 97 | 91 | 0 |
| 3 | 80 | 24:76 | 97 | 92 | -- |

[a]Determined by $^1$H 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 scrutinity 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 $pk_a$ 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 scrutinity 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.

Interestingly, by varying the electronic properties of the anhydride (*i.e.* $\alpha$-heteroatom-substitued 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 unprecedent 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

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

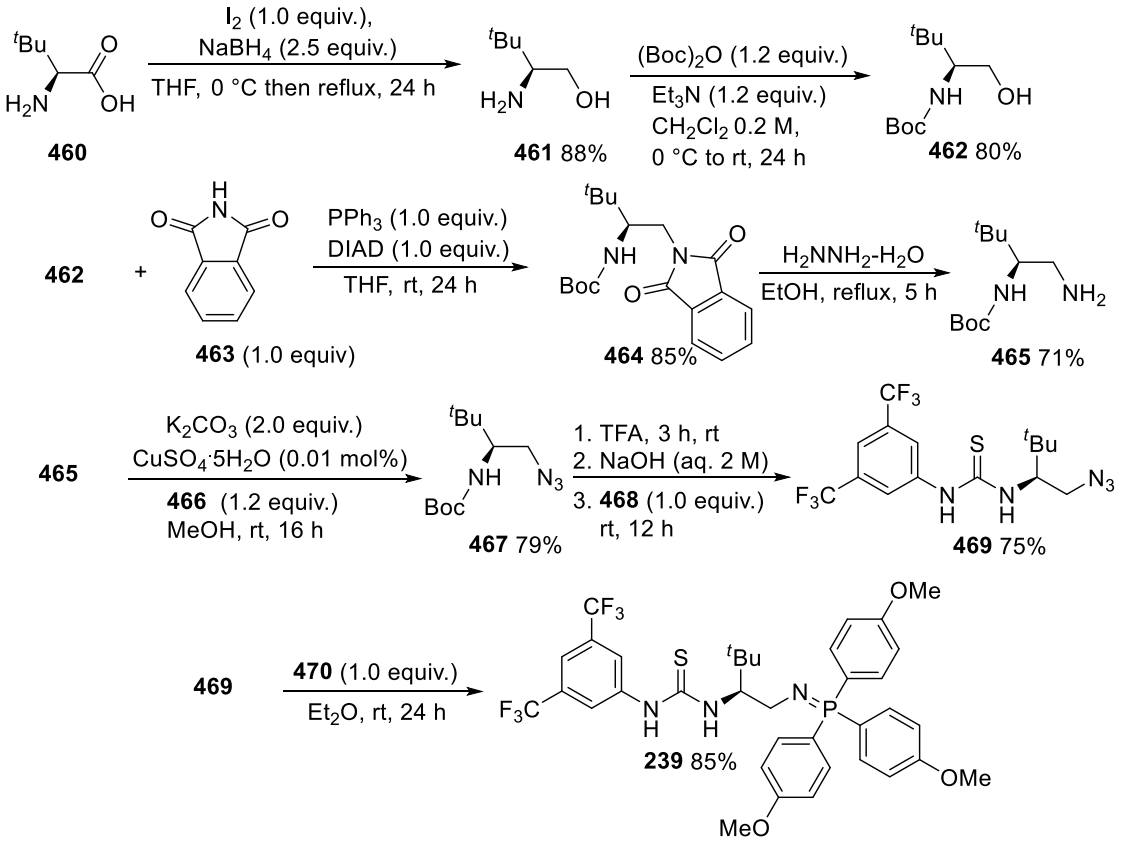
Over the years, organocatalysis has been involved in the development of organocatalysts with H-bond donating abilities capable of promoting several enantioselective chemical transformations.[211] For this reason, the investigation of catalysts with new H-bond donating moieties has become prominent in 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.[213,214,215]

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.[136,146,148] 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 **239** was synthesised following the general procedure reported by Dixon[215], as shown in Scheme 4.1. The first step of the synthesis consists of the formation of the L-*tert*-leucinol (**461**) in 88% yield by reduction of the commercially available L-*tert*-leucine (**460**) in the presence of iodine and sodium borohydride in THF according to the known literature procedure.[246] The product **461** was then protected using Boc anhydride to give **462**, which was reacted with phthalimide (**463**) 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 chromatograohy on silica gel, was reacted with an excess of hydrazine monohydrate in ethanol, furnishing the desired diamine **465**. The product **465** so obtained was then reacted with the diazotransfer reagent $N_3SO_2Im$. HCl (**466**) 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.

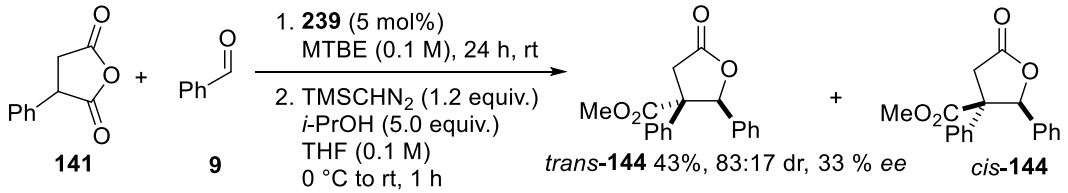



**Scheme 4.1** Synthesis of iminophosphorane catalyst **239**.

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

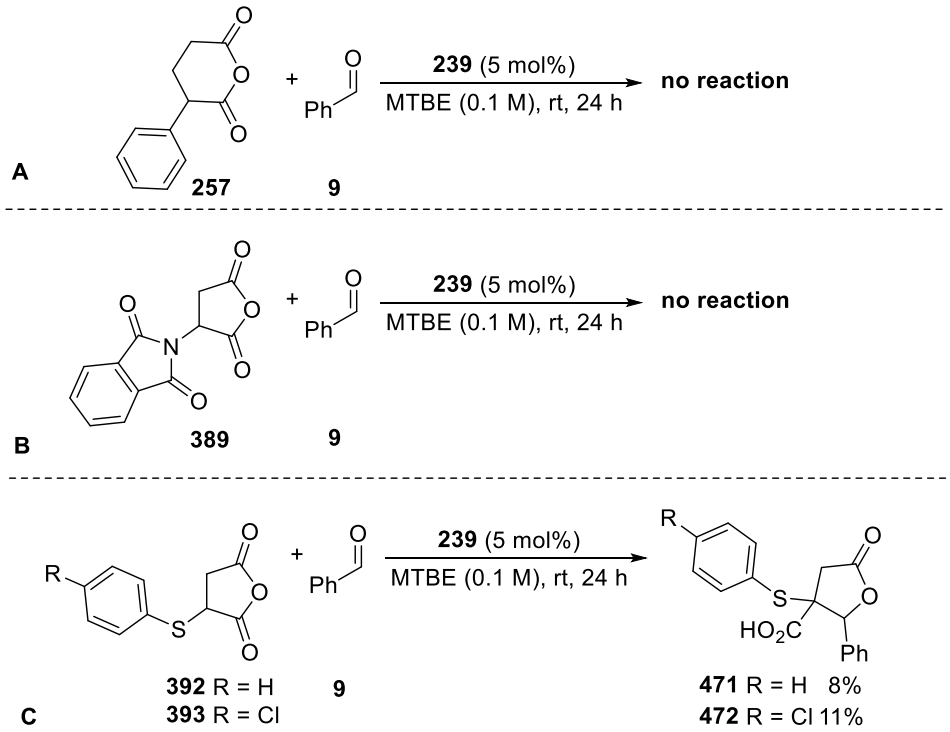
As discussed in Section 1.5.1, the asymmetric cycloaddition reaction between phenylsuccinic anhydride (**141**) and benzaldehyde (**9**) can be promoted by squaramide-based catalyst **140** in high diastereo- and enantioselectivity, however, a significant decrease in yield (44% at room temperature), 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.[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).



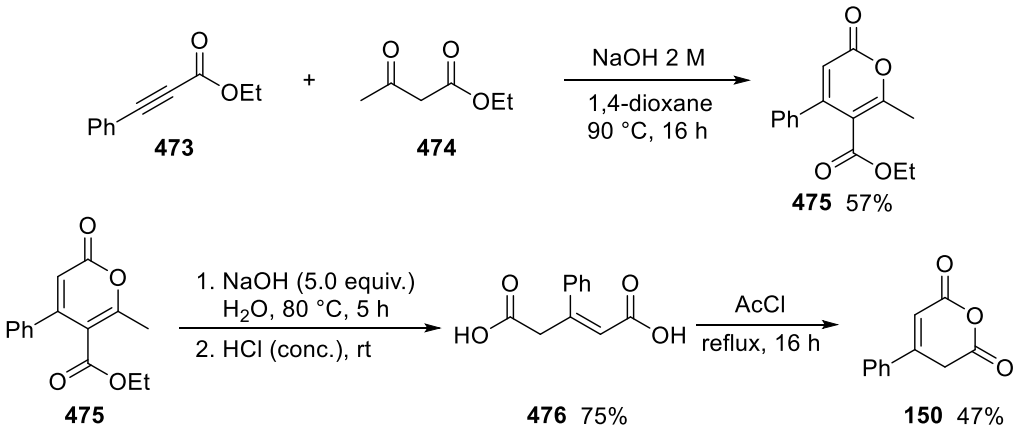

**Scheme 4.3** Evaluation of enolisable anhydrides in the asymmetric cycloaddition with **9** promoted by iminophosphorane catalyst **239**

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.

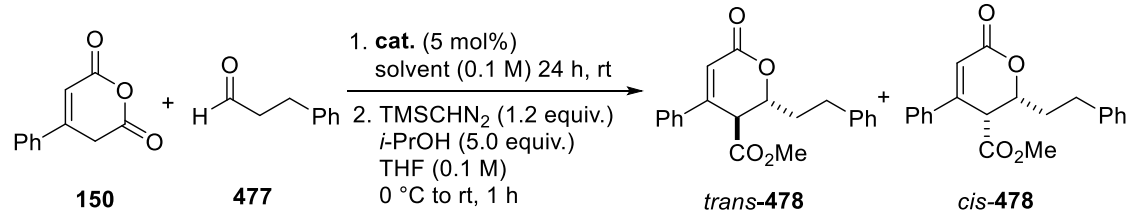
The synthesis of **150** was accomplished *via* a three step synthetic route as outlined in Scheme 4.4. The reaction between ethyl phenylpropiolate (**473**) and ethyl acetoacetate (**474**) in presence of sodium hydroxide in 1,4-dioxane furnished the lactone **475** which was then, upon purification 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.

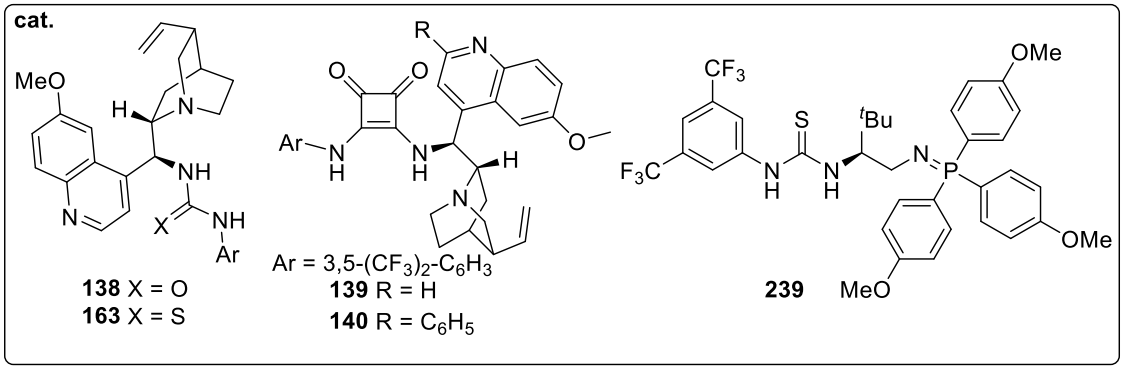



**Scheme 4.4** Synthesis of anhydride **150**.

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**.



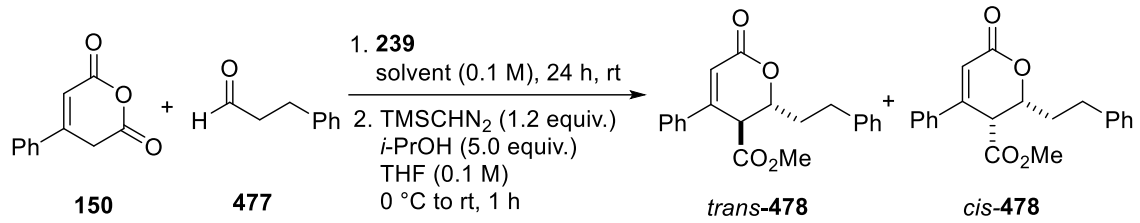

| entry | cat. | solvent | yield (%)[a] | *dr* (*trans*:*cis*)[b] | $ee_{trans}$ (%)[c] | $ee_{cis}$ (%)[c] |
|---|---|---|---|---|---|---|
| 1[d] | **138** | THF | -- | -- | -- | -- |
| 2[d] | **163** | THF | -- | --- | -- | -- |
| 3[d] | **139** | THF | 66 | 38:62 | 99 | 99 |
| 4[d] | **140** | THF | 77 | 43:57 | 95 | 93 |
| 5 | **239** | MTBE | 46 | 75:25 | 68 | 80 |

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




**150** **477** *trans*-**478** *cis*-**478**

| entry | solvent | 239 loading (mol%) | yield (%)[a] | *dr* (*trans*:*cis*)[b] | $ee_{trans}$ (%)[c] | $ee_{cis}$ (%)[c] |
|---|---|---|---|---|---|---|
| 1 | MTBE | 5 | 46 | 75:25 | 68 | 80 |
| 2 | THF | 5 | 40 | 71:29 | 73 | 80 |
| 3 | MTBE | 5+5 | 46 | 75:25 | 66 | 80 |

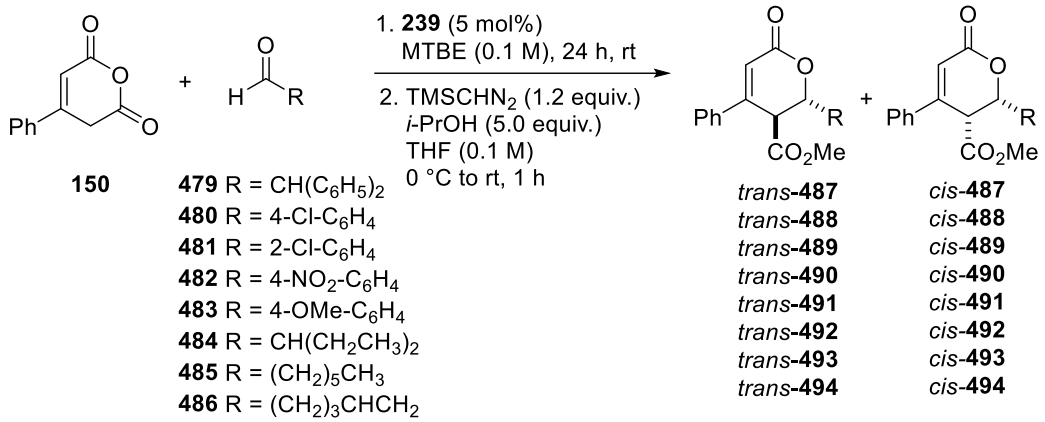
[a] Yield of combined diastereomers determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b] Diastereomeric ratio determined by $^1$H NMR spectroscopic analysis. [c] Determined by CSP-HPLC.

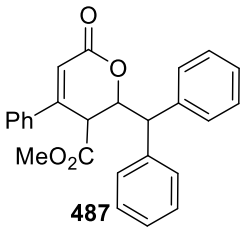
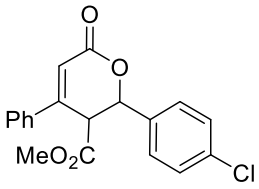
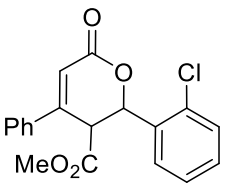
The use of THF as solvent did not prove effective in improving the yield of the reaction providing the corresponding lactone-esters in 40% yield after 24 h (entry 2) and slightly decreasing *dr*, however, the *trans* diastereomer was formed in marginally higher optical purity. Speculating on the possible 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).

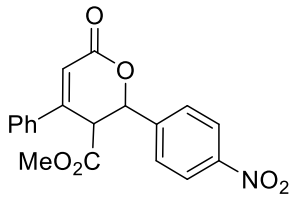
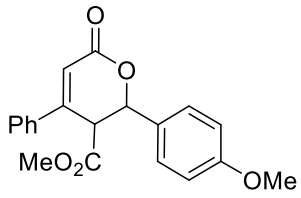
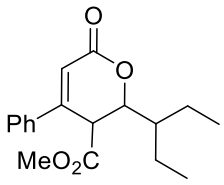
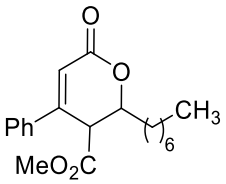
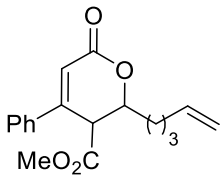
### 4.1.4.1 Evaluation of the substrate scope: the aldehyde component

The moderate diastereo- and enantiocontrol observed in the formation of the lactones using aldehyde **477** prompted the investigation into the use of different aldehydes with both aromatic and alkyl substitutents. 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**.




| entry | product | yield (%)[a] | *dr* (*trans*:*cis*)[b] | $ee_{trans}$ (%)[c] | $ee_{cis}$ (%)[c] |
|---|---|---|---|---|---|
| 1 |  **487** | 49 | 87:13 | 66 | 79 |
| 2 |  **488** | 60 | 95:5 | 31 | -- |
| 3 |  **489** | 59 | 89:11 | 16 | -- |

| | | | | | |
|---|---|---|---|---|---|
| 4 |  **490** | 60 | 90:10 | 20 | -- |
| 5 |  **491** | 49 | 99 | 42 | -- |
| 6 |  **492** | 37 | 76:24 | 94 | 99 |
| 7 |  **493** | 42 | 55:45 | 94 | 30 |
| 8 |  **494** | 36 | 70:30 | 95 | 50 |

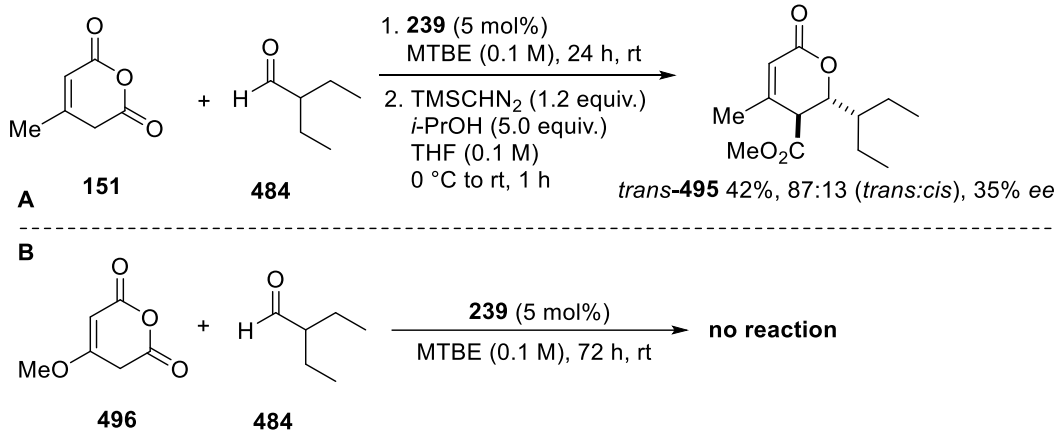
[a] Yield of combined diastereomers determined by $^1$H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b] Diastereomeric ratio determined by $^1$H NMR spectroscopic analysis. [c] Determined by CSP-HPLC.

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 substitutents 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 glutaconic 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 $CDCl_3$, DMSO-$d_6$ or $D_2O$ and referenced relative to residual $CHCl_3$ ($\delta$ = 7.26 ppm), DMSO ($\delta$ = 2.50 ppm) or $H_2O$ ($\delta$ = 4.79 ppm). Chemical shifts are reported in ppm and coupling constants (*J*) in Hertz. Carbon NMR spectra were recorded on the same instruments (100.6 MHz) 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 $60F_{254}$ slides, and visualised by UV irradiation or $KMnO_4$ staining. Optical rotation measurements were made on a Rudolph Research Analytical Autopol IV instrument, and are quoted in units of $10^{-1}$ deg $cm^2$ $g^{-1}$. Anhydrous tetrahydrofuran (THF), $CH_2Cl_2$ and $Et_2O$ 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 UPC$^2$, Trefoil CEL1, CEL2, 2.5µm (3.0 x 150 mm).

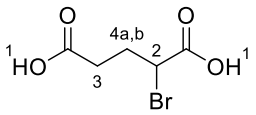
## 5.1 Experimental procedures and data for Chapter 2

### 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.

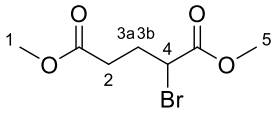
**2-Bromopentanedioic acid (265)**[247]




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 $NaNO_2$ (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 $Na_2SO_4$, filtered and the solvent was removed *in vacuo* to afford **265** as a white solid (675 mg, 12%). M.p 47 °C, (lit.,[248] m.p 40 °C).

$\delta_H$ (400 MHz, $CDCl_3$): 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)**[248]

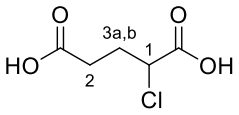



A round-bottomed flask containing a magnetic stirring bar was charged with **265** (650 mg, 2.71 mmol), sulfuric acid (1 ml) and methanol (15 mL). The reaction mixture was refluxed for 12 h, the solvent was then evaporated *in vacuo* to furnish a yellow oil, the residue was purified by column chromatography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

$\delta_H$ (400 MHz, $CDCl_3$): 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 $(M-H)^-$ $C_7H_{10}BrO_4$ Requires: 236.9896.

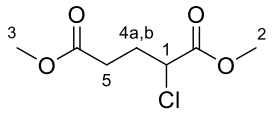
**2-Chloropentanedioic acid (269)**[249]




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 $NaNO_2$ (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 $Na_2SO_4$, filtered and the solvent was removed *in vacuo* to afford **269** as a white solid (1.0 g, 23%). M.p. 86 °C, (lit.,[249] m.p 99 °C).

$\delta_H$ (400 MHz, $CDCl_3$): 4.96 (1 H, app. t, H-1), 2.67-2.50 (3 H, m, H-2, H-3a), 2.42-2.37 (1 H, m, H-3b).

**Dimethyl 2-chloropentanedioate (270)**[249]

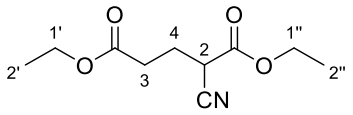



A round-bottomed flask containing a magnetic stirring bar was charged **269** (1.00 g, 6.00 mmol), sulfuric acid (1 ml) and methanol (25 mL). The reaction mixture was refluxed for 12 h, the solvent was then evaporated *in vacuo* to furnish a yellow oil, the residue was purified by column chromatography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

$\delta_H$ (400 MHz, $CDCl_3$): 4.40 (1 H, dd, *J* 5.1, 8.4, H-1), 3.77 (3-H, s, H-2), 3.67 (3 H, s, H-3), 2.52 (2 H, t, *J* 7.2, H-5), 2.40-2.31 ( 1 H, m, H-4a), 2.26-2.16 (1 H, m, H-4b).

HRMS (*m/z* – ESI): Found: 193.0380 $(M-H)^-$ $C_7H_{10}ClO_4$ Requires: 193.0389.

**Diethyl 2-cyanopentanedioate (274)**[228]

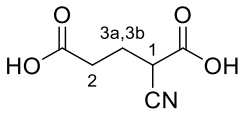



A round-bottomed flask containing a magnetic stirring bar was charged with ethyl cyanoacetate (**272**, 1 mL, 8.80 mmol) in ethanol (30 mL) and the solution was cooled at -78 °C. Sodium ethoxide (718 mg, 10.5 mmol) was added and the solution reaction mixture stirred for 10 min, after which time **273** (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 $MgSO_4$. 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 MHz, $CDCl_3$): 4.23 (2 H, q, *J* 7.1, H-1'), 4.09 (2 H, q, *J* 7.3, H-1''), 3.75 (1 H, app. t, H-2), 2.51 (2 H, t, *J* 7.2, H-3), 2.04-2.36 (2 H, m, H-4), 1.36 (3 H, t, *J* 7.1, H-2'), 1.13 (3 H, t, *J* 7.3, H-2'').

HRMS (*m/z* -ESI): Found: 212.1066. $[M-H]^-$ $C_{10}H_{14}NO_4$ Requires: 212.1066.

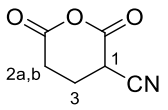
**2-Cyanopentanedioic acid** (**275**)[228]




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 hydroxyde 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 MHz, DMSO-$d_6$): 4.06 (1 H, dd, *J* 5.9, 8.1, H-1), 2.37 (2 H, t, *J* 7.4, H-2), 2.13-2.05 (1 H, m, H-3a), 2.03-1.96 ( 1H, m, H-3b).

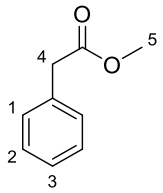
**2,6-Dioxotetrahydro-2H-pyran-3-carbonitrile (256)**[228]




A 25 mL round-bottomed flask containing a magnetic stirring bar was charged with **275** (200 mg, 1.27 mmol) and trifluorocetic 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]

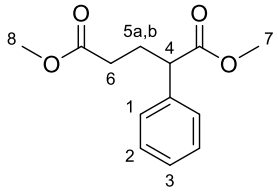



A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with 2-phenylacetic acid (**277**, 5.00 g, 36.7 mmol). Sulfuric acid (1 mL) and methanol (75 mL) were added and the reaction mixture was heated at reflux temperature for 3 h. The solvent was evaporated and the residue was dissolved in diethyl ether (30 mL) and then washed with a saturated aqueous solution of $NaHCO_3$ (3 x 15 mL) and $H_2O$ (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 $(M-H)^-$ $C_9H_9O_2$ Requires: 149.0685.

**Dimethyl-2-phenylpentanedioate (280)**[251]

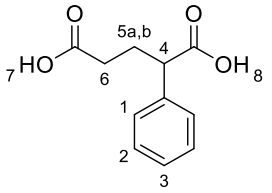



An oven dried 250 mL round-bottomed flask containing a magnetic stirring bar was charged with potassium *tert*-butoxide (586 mg, 5.2 mmol) in toluene (35 mL). A solution of methyl 2-phenylacetate **278** (3.50 g, 19.9 mmol) in toluene (35 mL) was added dropwise under an argon atmosphere at -78 °C and 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 $NH_4Cl$ (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 MHz, $CDCl_3$): 7.35-7.32 (5 H, m, H-1, H-2, H-3), 3.68 (3 H, s, H-7), 3.67 (3 H, s, H-8), 3.65 (1 H, t, *J* 8.0, H-4), 2.42-2.36 (1 H, m, H-5a), 2.29 (2 H, t, *J* 7.44, H-6), 2.18-2.11 (1 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]



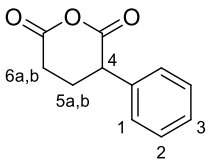

A 50 mL round-bottomed flask containing a magnetic stirring bar was charged with **280** (1.00 g, 4.2 mmol) and methanol (33 mL). A solution of NaOH in water (0.1 N) was added and the reaction mixture was refluxed for 4 h. After cooling, the PH of the solution was partially neutralised by adding a solution 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 MHz, $CDCl_3$)*: 7.35-7.27 (5 H, m, H-1, H-2 and H-3), 3.65 (1 H, t, *J* 7.14, H-4), 2.45-2.33 (3 H, m, H-5a and H-6), 2.14-2.08 (1 H, m, H-5b).

HRMS (*m/z* – ESI): Found: 207.0655 $(M-H)^-$ $C_{11}H_{11}O_4$ Requires: 207.0657

*The proton signals (H-7 and H-8) are not visible in $CDCl_3$.

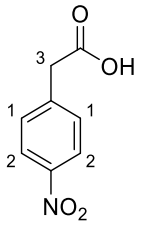
**3-Phenyldihydro-2H-pyran-2,6(3H)-dione (257)**[253]




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.,[253] m.p. 96 °C).

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

**2-(4-Nitrophenyl)acetic acid (283)**[254]

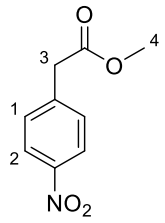



A 50 mL round-bottomed flask containing a magnetic stirring bar was charged with water (10 mL) and concentrated sulfuric acid (10 mL). 4-nitrophenylacetonitrile (**282**, 3.00 g, 18.5 mmol) was added to this mixture. The reaction mixture was refluxed for 2 h, diluted with water (150 mL) and cooled to 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 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).

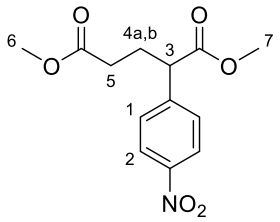
**Methyl 2-(4-nitrophenyl)acetate (284)**




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 MHz, $CDCl_3$): 8.19 (2 H, d, *J* 8.5, H-2), 7.45 (2 H, d, *J* 8.5, H-1), 3.74 (2 H, s, H-3), 3.72 (3 H, s, H-4).

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

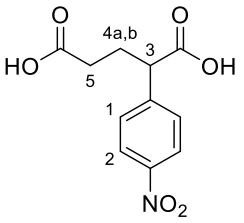



An oven dried 25 mL round-bottomed flask containing a magnetic stirring bar was charged with sodium methoxide (250 mg, 4.6 mmol) in dry methanol (5 mL). A methanolic (5 mL) solution of **285** (1.10 g, 5.60 mmol) was added dropwise under an argon atmosphere at -78 °C and stirred for 15 min. Methyl acrylate (**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 $NH_4Cl$ (25 mL), extracted with EtOAc (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) 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 $(M-H)^-$ $C_{13}H_{14}NO_6$ Requires: 280.0899.

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

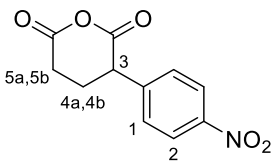



Prepared according to the hydrolysis reaction procedure described for the synthesis of **281**, using **285** (450 mg, 1.60 mmol), methanol (15 mL) and aqueous NaOH solution (15 mL). Product **286** was isolated as an oily residue (260 mg, 64%).

$\delta_H$ (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 $(M-H)^-$ $C_{11}H_{10}NO_6$ Requires: 252.0586

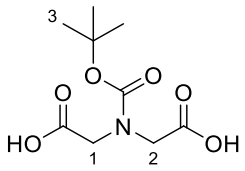
**3-(4-Nitrophenyl)dihydro-2H-pyran-2,6(3H)-dione (258)**




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).

$\delta_H$ (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]

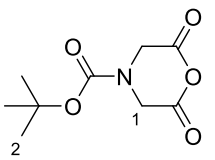



A 250 mL round-bottomed flask containing a magnetic stirring bar was charged with iminodiacetic acid (**289**, 2.55 g, 19.1 mmol) in 50% (v/v) aqueous THF (50 mL). Sodium bicarbonate (6.38 g, 76 mmol) was slowly added and the solution was stirred for 10 min. Then di-*tert*-butyl dicarbonate (5.0 g, 23 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]

$\delta_H$ (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]



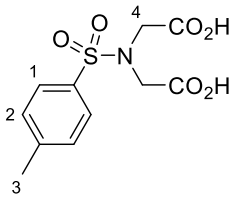

An oven dried 25 mL round-bottomed flask containing a magnetic stirring bar was charged with *N*-cyclohexylcarbodiimide, *N*'-methyl polystyrene (373 mg, 0.857 mmol). Freshly distilled $CH_2Cl_2$ (6 mL) was added and the suspension was gently stirred for 10 min. **290** (100 mg, 0.428 mmol) was added, 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.,[257] m.p. 110-111 °C).

Spectral data for this compound were consistent with those in the literature.[257]

$\delta_H$ (400 MHz, $CDCl_3$): 4.42 (4 H, s, H-1), 1.49 (9 H, s, H-2).

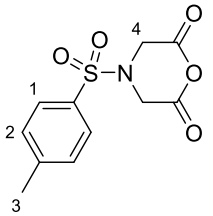
**2,2'-(Tosylazanediyl)diacetic acid (291)**




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 $Na_2SO_4$ and crystallised from water to give **291** (3.14 g, 47%). M.p. 172 °C.

$\delta_H$ (400 MHz, DMSO-$d_6$): 7.68 (2 H, d *J* 7.9, H-1), 7.35 (2 H, d, *J* 7.9, H-2), 4.12 (4 H, s, H-4), 2.37 (3 H, s, H-3).

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



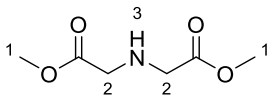

A 25 mL round-bottomed flask containing a magnetic stirring bar was charged with **291** (500 mg, 1.74 mmol). Freshly distilled acetyl chloride (7 mL) was added, the flask was fitted with a condenser and the reaction mixture was stirred at reflux under an argon atmosphere for 16 h. The acetyl chloride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

$\delta_H$ (400 MHz, $CDCl_3$): 7.68 (2 H, d, *J* 7.8, H-1), 7.40 (2 H, d, *J* 7.8, H-2), 4.22 (4 H, s, H-4), 2.46 (3 H, s, H-3).

$\delta_C$ (100 MHz, $CDCl_3$): 160.7 (C=O), 146.2 (q), 131.7 (q), 130.9, 127.7, 46.4, 21.8.

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

**Dimethyl 2,2'-azanediyldiacetate (294)**[258]

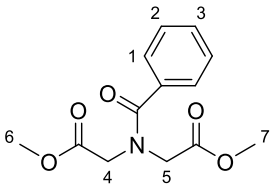



An oven dried 100 mL round-bottomed flask containing a magnetic stirring bar was charged with a solution of thionyl chloride (8.8 mL) in methanol (80 mL). **289** (3.00 g, 22.5 mmol) was added and the solution was stirred for 12 h at reflux. The solvent was then removed *in vacum* to give **294** as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

Spectral data for this compound were consistent with those in the literature.[258]

$\delta_H$ (400 MHz, $CDCl_3$): 3.72 (6 H, s, H-1), 3.46 (4 H, s, H-2), 2.04 (1 H, s, H-3).

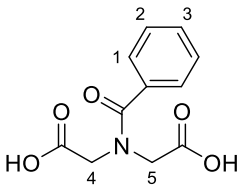
**Dimethyl 2,2'-(benzoylazanediyl)diacetate (295)**[259]




A 250 mL round-bottomed flask containing a magnetic stirring bar was charged with **294** (2.00 g, 12.4 mmol) in anhydrous $CH_2Cl_2$ (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 $CH_2Cl_2$ (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 $H_2O$ (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.,[259] m.p. 73-76 °C).

$\delta_H$ (400 MHz, $CDCl_3$): 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'-(Benzoylazanediyl)diacetic acid (296)**[260]

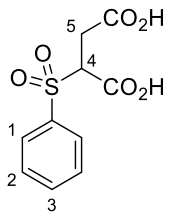



A round-bottomed flask containing a magnetic stirring bar was charged with **295** (1.00 g, 3.76 mmol) in a mixture of THF/water 3:1 (20 mL). Lithium hydroxyde monohydrate (788 mg, 18.8 mmol) was added and the solution stirred at room temperature for 3 h. The reaction mixture was acidified by adding 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.[261]

$\delta_H$ (400 MHz, $CDCl_3$): 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)**[231]

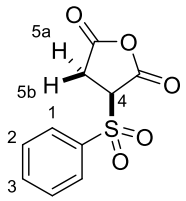



A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with benzenesulfinic sodium salt (**289**, 4.35 g, 26.5 mmol) and dissolved in water (44 mL) at 0 °C. Maleic anhydride (**298**, 2.60 g, 26.5 mmol) was added. The reaction mixture was allowed to warm slowly to room temperature 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 $MgSO_4$ and the solvent was removed *in vacuo* to yield **299** as a brown solid (5.50 g, 80%).

$\delta_H$ (400 MHz, $CDCl_3$): 7.89 (2 H, d, *J* 8.0, H-1), 7.72 (1 H, t, *J* 7.5, H-3), 7.59 (2 H, app t, H-2), 4.39 (1 H, dd, *J* 5.3, 9.8, H-4), 3.16-3.13 (2 H, m, H-5).

HRMS (*m/z* – ESI): Found: 281.0103 $(M+Na)^+$ $C_{10}H_{10}O_6NaS$ Requires: 281.0096.

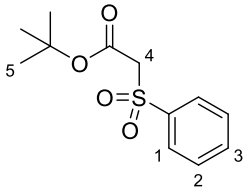
**3-(Phenylsulfonyl)dihydrofuran-2,5-dione (262)**[231]




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).

$\delta_H$ (400 MHz, $CDCl_3$): 7.96 (2 H, d, *J* 8.0, H-1), 7.80 (1 H, t, *J* 7.3, H-3), 7.66 (2 H, app. t, H-2), 4.51 (1 H, dd, *J* 4.3, 10.3, H-4), 3.67 (1 H, dd, *J* 4.31, 19.8, H-5a), 3.37 (1 H, dd, *J* 10.3, 19.8, H-5b).

***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

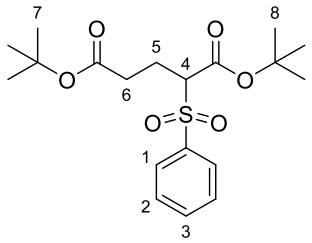
mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to yield **301** (2.60 g, 76%) as a clear oil.

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 $(M+Na)^+$ $C_{12}H_{16}O_4NaS$ Requires: 279.0667.

**Di-*tert*-butyl 2-(phenylsulfonyl)pentanedioate (303)**[231]



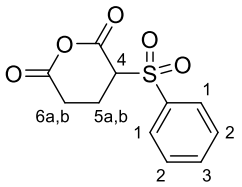

An oven dried 100 mL round-bottomed flask containing a magnetic stirring bar was charged with **301** (2.60 g, 10.1 mmol), cesium carbonate (165 mg, 0.50 mmol), *tert*-butyl acrylate (**302**, 1.49 mL, 10.1 mmol) and acetonitrile (35 mL). The reaction mixture was heated at 50 °C overnight and then diluted 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 $(M+Na)^+$ $C_{19}H_{28}O_6NaS$ Requires: 407.1504.

**3-(Phenylsulfonyl)dihydro-2H-pyran-2,6(3H)-dione (263)**[231]

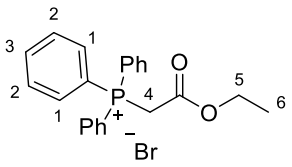



An oven dried 50 mL round bottom flask containing a magnetic stirring bar was charged with **303** (2 g, 5.2 mmol), $CH_2Cl_2$ (22 mL) and trifluoroacetic acid (22 mL). The reaction mixture was stirred for 1 h and then concentrated *in vacuo* and azeotropically distilled with $CH_2Cl_2$. Trifluoroacetic anhydride was added to the crude mixture and stirred overnight. The reaction mixture was concentrated *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.[231] m.p 122.2-122.8 °C).

Spectral data for this compound were consistent with those in the literature.[231]

$\delta_H$ (400 MHz, $CDCl_3$): 7.93 (2 H, d, *J* 7.76, H-1) 7.80 (1 H, *J* 7.49, H-3), 7.66 (2 H, t, *J* 7.92, H-2), 4.17 (1 H, app dd, H-4), 3.35-3.25 (1 H, m, H-6a), 2.91-2.84 (2 H, m, H-6b and H-5a), 2.48-2.33 (1 H, m, H-5b).

**(2-Ethoxy-2-oxoethyl)triphenylphosphonium bromide (308)**[262]

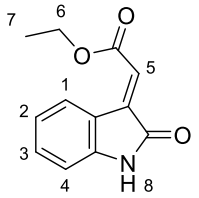



A round-bottomed flask containing a magnetic stirring bar was charged with triphenylphosphine (**307**, 6.50 g, 25.0 mmol) and toluene (65 ml). To the mixture was then added *via* syringe ethyl bromoacetate (2.75 mL, 25.0 mmol), the flask was fitted with a condenser and the reaction was heated at 90 °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 *in vacuo* to give product **308** as a white solid (9.6 g, 90%). M.p. 150-152 °C, (lit.,[261] m.p. 155-156 °C).

Spectral data for this compound were consistent with those in the literature.[262]

$\delta_H$ (400 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]

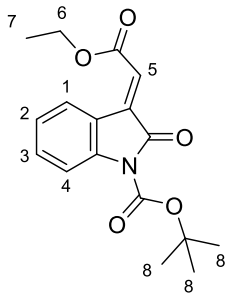



A round-bottomed flask containing a magnetic stirring bar was charged with **308** (6.0 g, 14.0 mmol) and $CH_2Cl_2$ (50 mL). To the mixture was then added an aqueous solution of NaOH (1.0 M, 50 mL) and the reaction was allowed to stir vigorously at room temperature for 15 min. The organic layer was separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *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 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)**[263]




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 $(Boc)_2O$ (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.,[263] m.p. 65-67 °C); TLC (hexanes:EtOAc, 9:1 *v/v*): $R_f = 0.50$.

Spectral data for this compound were consistent with those in the literature.[263]

$\delta_H$ (400 MHz, $CDCl_3$): 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 $LiBEt_3H$ 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

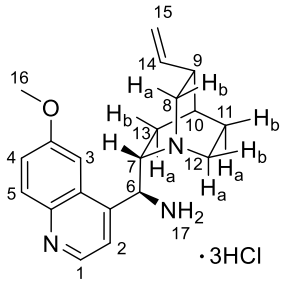
A 10 mL reaction vial containing a magnetic stirring bar was charged with the relevant anhydride (0.20 mmol) and the relevant catalyst (0.01 mmol - 5 mol%). The reaction vial was flushed with argon and fitted with a septum. MTBE (2.0 mL) was added *via* syringe followed by the appropriate alcohol (0.20 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 $MgSO_4$, and concentrated *in vacuo* to provide the desired hemiesters. A mixture of hemiesters (0.2 mmol) in anhydrous $CH_2Cl_2$ (4.0 mL) was cooled at 0 °C, a solution of thionyl chloride (17.7 μL, 0.2 mmol) in $CH_2Cl_2$ (2.0 mL) was then added and the reaction mixture was allowed to stir for 10 min under argon atmosphere. Freshly distilled $Et_3N$ (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 $NaHCO_3$ (10 mL) and saturated aqueous NaCI (10 mL). The organic layer was dried over $MgSO_4$ 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 $CH_2Cl_2$ (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)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanamine·3HCl** (**380**)[264]

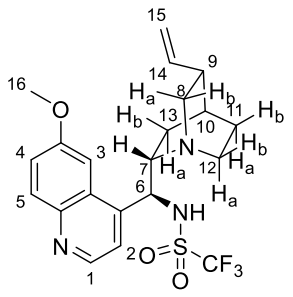


A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with quinine (**74**, 5.00 g, 15.4 mmol), triphenylphosphine (4.85 g, 2.42 mmol) and dry THF (70 mL). Diisopropyl azodicarboxylate (DIAD) (3.6 mL, 18.5 mmol) was added *via* syringe at 0 °C under an argon atmosphere and the 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 $CH_2Cl_2$ (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, $D_2O$):* 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 $D_2O$.

**1,1,1-Trifluoro-N-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-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, $[\alpha]_D^{20}$ = +25.8 (*c* = 0.86, $CHCl_3$).

$\delta_H$ (600 MHz, $CDCl_3$): 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).

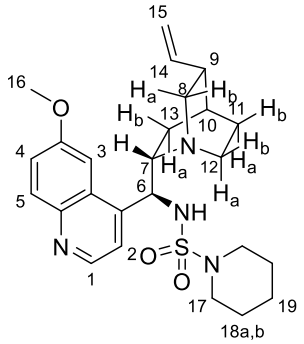
$\delta_C$ (150 MHz, $CDCl_3$): 158.2 (q, major), 157.3 (q, minor), 148.1 (major), 147.1 (minor), 145.4 (q, major), 144.4 (q, major), 144.3 (q, minor), 141.4 (q, minor), 137.4 (minor), 136.7 (major), 132.0 (major), 131.8 (minor), 127.6 (q, major), 127.3 (q, minor), 121.8 (minor), 121.4 (q, $J_{CF}$ 267, $CF_3$) 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).

$\delta_F$ (376 MHz, CDCl3): -77.5 (major), -77.7 (minor).

$\nu_{max}$ (neat)/$cm^{-1}$: 2955, 1621, 1509, 1348, 1242, 1160, 1029, 853, 606.

HRMS (*m/z* - ESI): Found: 456.1556 $(M+H)^+$ $C_{21}H_{25}F_3N_3O_3S$ Requires: 456.1567.

**N-((*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)piperidine-1-sulfonamide (375)**




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, $[\alpha]_D^{20}$ = +15 (*c* = 1.3, $CHCl_3$).

$\delta_H$ (600 MHz, $CDCl_3$): 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).

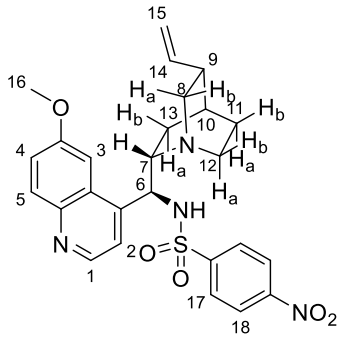
$\delta_C$ (150 MHz, $CDCl_3$): 158.2 (q), 157.2 (q), 147.7, 147.1, 145.3 (q), 144.5 (q), 144.4 (q), 144.2 (q), 141.6, 140.2, 132.0, 131.8, 129.2 (q), 127.2 (q), 123.8, 121.9, 121.7, 119.8, 116.6, 115.3, 115.1,

114.9, 103.1, 100.8, 63.1, 60.3, 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.

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

HRMS (*m/z* - ESI): Found: 471.2430 $(M+H)^+$ $C_{25}H_{35}N_4O_3S$ Requires: 471.2430.

**N-((*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-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, $CHCl_3$).

$\delta_H$ (600 MHz, $CDCl_3$): 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

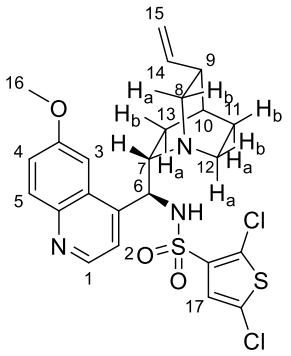
H, m, H-9), 1.80-1.68 (3 H, m, H-11a, H-11b, H-10), 1.45-1.39 (1 H, m, H-13b), 1.02 (0.5 H, dd, *J* 7.9, 13.4, H-13a), 0.91 (0.5 H, dd, *J* 7.9, 13.4, H-13b).

$\delta_C$ (150 MHz, $CDCl_3$): 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.

$\nu_{max}$ (neat)/$cm^{-1}$: 3675, 2970, 1717, 1621, 1527, 1347, 1158, 734, 571.

HRMS (*m/z* - ESI): Found: 509.1849 $(M+H)^+$ $C_{26}H_{29}N_4O_5S$ Requires: 509.1859.

**2,5-Dichloro-N-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-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, $[\alpha]_D^{20}$ = +34 (*c* = 1.1, $CHCl_3$).

$\delta_H$ (600 MHz, $CDCl_3$): 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,

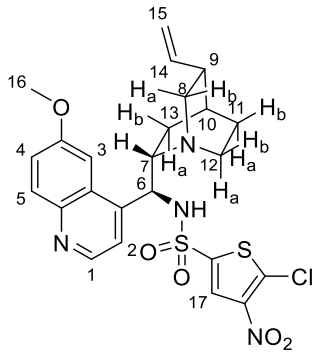
H-17), 6.21 (0.5, s, H-17), 5.76-5.61 (1 H, m, H-14), 5.12 (0.5 H, d, *J* 10.5, H-6), 5.07-4.93 (2 H, m, H-15), 4.51 (0.5 H, d, *J* 10.5, H-6), 4.03 (1.5 H, s, H-16), 3.96 (1.5 H, s, H-16), 3.55 (0.5 H, dd, *J* 9.4, 17.7, H-7), 3.44-3.19 (2 H, m, H-8b, H-12a), 3.07 (0.5 H, dd, *J* 9.4, 17.7, H-7), 2.95-2.77 (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 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.

$\nu_{max}$ (neat)/$cm^{-1}$: 2971, 1621, 1474, 1242, 1194, 1030, 879, 580.

HRMS (*m/z* - ESI): Found: 538.0797 $(M+H)^+$ $C_{24}H_{26}Cl_2N_3O_3S_2$ Requires: 538.0787.

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



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 (*c* = 1.0, $CHCl_3$).

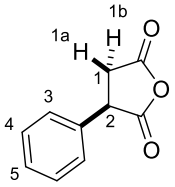
$\delta_H$ (600 MHz, $CDCl_3$): 8.75 (0.5 H, d, *J* 4.4, H-1), 8.67 (0.5 H, d, *J* 4.4, H-1), 8.04 (0.5 H, d, *J* 9.3, H-5), 77.97 (0.5 H, d, *J* 9.3, H-5), 7.47-7.42 (2 H, m, H-3, (0.5) H-4, (0.5) H-2), 7.33-7.30 (1.5 H, m, (0.5) H-3, (0.5) H-4, (0.5) H-17), 7.14 (0.5 H, s, H-17), 5.76-5.61 (1 H, m, 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 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.

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

HRMS (*m/z* - ESI): Found: 549.1031 $(M+H)^+$ $C_{24}H_{26}N_4O_5S_2Cl$ Requires: 549.1033.

**3-Phenyldihydrofuran-2,5-dione (Phenylsuccinic anhydride 141)**

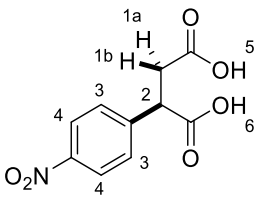



A 50 mL round-bottomed flask containing a magnetic stirring bar was charged with phenylsuccinic acid (**316**, 2.00 g, 10.3 mmol). Freshly distilled acetyl chloride (15 mL) was added, the flask was fitted with a condenser and the reaction mixture was heated at reflux temperature under an argon atmosphere 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]

$\delta_H$ (400 MHz, $CDCl_3$): 7.48-7.32 (3 H, m, H-4, H-5), 7.32-7.24 (2 H, m, H-3), 4.33 (1 H, dd, *J* 6.5, 10.3, H-2), 3.46 (1 H, dd, *J* 10.3, 19.1, H-1a), 3.12 (1 H, dd, *J* 6.5, 19.1, H-1b).

**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 $HNO_3$ (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.

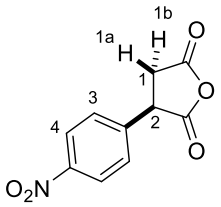
$\delta_H$ (400 MHz, DMSO-$d_6$): 12.5 (2 H, bs, H-5 and H-6), 8.20 (2 H, d, *J* 8.8, H-4), 7.61 (2 H, d, *J* 8.8, H-3), 4.08 (1 H, dd, *J* 5.6, 9.7, H-2), 3.01 (1 H, dd, *J* 9.7, 17.0, H-1b), 2.65 (1 H, dd, *J* 5.6, 17.0, H-1a).

$\delta_C$ (100 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.

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

HRMS (*m/z* - ESI): Found: 238.0353 $(M-H)^-$ $C_{10}H_8NO_6$ Requires: 238.0352.

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



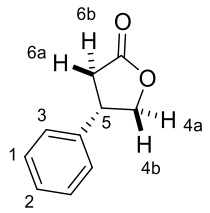

A round-bottomed flask containing a magnetic stirring bar was charged with **324** (2.00 g, 8.36 mmol). Freshly distilled acetyl chloride (15 mL) was added, the flask was fitted with a condenser and the reaction mixture was heated at reflux under an argon atmosphere for 16 h. Acetyl chloride was then removed *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 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 $(M-H)^-$ $C_{10}H_6NO_5$ Requires: 220.0246.

**(*S*)-4-Phenyldihydrofuran-2(3H)-one (332, Table 3.25, entry 2)**



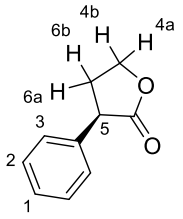

Prepared according to general procedure B using phenylsuccinic anhydride (**141**, 35.3 mg, 0.20 mmol) and the catalyst **378** (5.60 mg, 0.01 mmol). MTBE (2 mL) was added *via* syringe followed by the alcohol **349** (56.5 mg, 0.20 mmol). The mixture of hemiesters **330** and **331** (24:76 ratio, 0.2 mmol) was dissolved in THF (3.0 mL), $LiBEt_3H$ 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 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*): $R_f$ = 0.56, $[\alpha]_D^{20}$= +1.8 (*c* = 0.09, $CHCl_3$), (lit.[198] $[\alpha]_D^{20}$ = -45.9 (c = 3.3, $CHCl_3$) 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]

$\delta_H$ (400 MHz, $CDCl_3$): 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)**

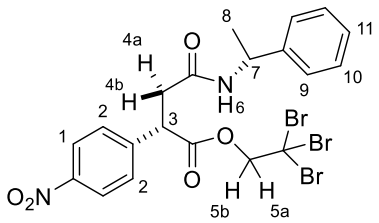



Prepared according to general procedure B using phenylsuccinic anhydride (**141**, 35.3 mg, 0.20 mmol) and the catalyst **378** (5.6 mg, 0.01 mmol). MTBE (2 mL) was added *via* syringe followed by the alcohol **349** (56.5 mg, 0.20 mmol). The mixture of hemiesters **330** and **331** (24:76 ratio, 0.2 mmol) was dissolved in THF (3.0 mL), $LiBEt_3H$ 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 **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, $[\alpha]_D^{20}$ = +1.3 (*c* = 0.12, $CHCl_3$). (lit.[197] $[\alpha]_D^{20}$ = -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).

$\delta_H$ (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)**



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 $CH_2Cl_2$ (4.0 mL), was cooled to 0 °C, a solution of thionyl chloride (17.7 μL, 0,2 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, 0.5 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*): $R_f$ = 0.32; $[\alpha]_D^{20}$ = +2.1 (*c* = 0.015, $CHCl_3$).

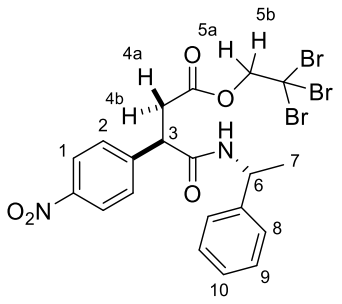
$\delta_H$ (400 MHz, $CDCl_3$): 8.23 (2 H, d, *J* 8.9 H-1), 7.58 (2 H, d, *J* 8.9, H-2), 7.38-7.35 (3 H, m, H-9, H-11), 7.31 (2 H, d, *J* 6.8, H-10), 5.75 (1 H, d, *J* 7.9, H-6), 5.15-5.11 (1 H, m, H-7), 4.96 (1 H, d, *J* 12.2, H-5a), 4.81 (1 H, d, *J* 12.2, H-5b), 4.51 (1 H, dd, *J* 5.8, 8.8, H-3), 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).

$\delta_C$ (100 MHz, $CDCl_3$): 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.

$\nu_{max}$ (neat)/$cm^{-1}$: 3665, 2297, 1754, 1540, 1413, 1245, 1070, 920, 717, 569.

HRMS (*m/z* - ESI): Found: 602.8752 $(M-H)^-$ $C_{20}H_{18}Br_3N_2O_5$ Requires: 602.8771.

**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 $CH_2Cl_2$ (4.0 mL) and 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, 0.5 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; $[\alpha]_D^{20}$ = +1.7 (*c* = 0.03, $CHCl_3$).

Major diastereomer:

$\delta_H$ (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).

$\delta_C$ (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.

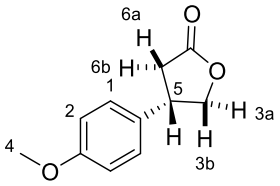
HRMS (*m/z* - ESI): Found: 602.8753 $(M-H)^-$ $C_{20}H_{18}Br_3N_2O_5$ Requires: 602.8771.

Minor diastereomer:

$\delta_H$ (400 MHz, $CDCl_3$): 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).

$\delta_C$ (100 MHz, $CDCl_3$): 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)**

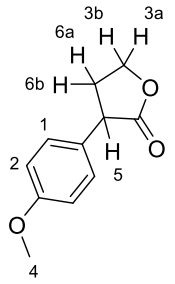



Prepared according to general procedure B using *p*-methoxy phenylsuccinic anhydride (**388**, 41.2 mg, 0.20 mmol) and the catalyst **378** (5.60 mg, 0.010 mmol). MTBE (2 mL) was added *via* syringe followed by the alcohol **349** (56.5 mg, 0.20 mmol). The mixture of hemiesters **403** and **404** (32:68 ratio, 0.2 mmol) was dissolved in THF (3.0 mL), $LiBEt_3H$ 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 **405** (obtained from hemiester **403**) was isolated as a pale yellow solid (10.0 mg, 27%). M.p. 72-74 °C, (lit.,[270] m.p 68-71 °C). TLC (diethyl ether:hexanes, 7:3 *v/v*): $R_f$ = 0.30, $[\alpha]_D^{20}$= +2.2 (*c* = 0.030, $CHCl_3$), (lit.,[268] $[\alpha]_D^{20}$ = +36.8 (c =0.60, $CHCl_3$).

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 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), $LiBEt_3H$ 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:hexane, lactone **406** (obtained from hemiester **404**) was isolated as a pale yellow solid (10.0 mg, 27%). M.p. 68-70 °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).

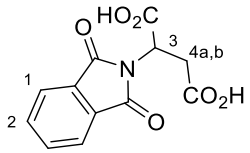
$\delta_H$ (400 MHz, $CDCl_3$): 7.28 (2 H, d, *J* 8.5, H-1), 7.01 (2 H, d, *J* 8.5 H-2), 4.52 (1 H, m, H-3a), 4.38 (1 H, ddd, *J* 6.5, 9.1, 9.1, H-3b), 3.81 (3

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.

HRMS (*m/z* - ESI): Found: 191.0886 $(M-H)^-$ $C_{11}H_{11}O_3$ Requires: 191.0885.

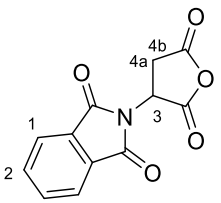
**2-(1,3-Dioxoisoindolin-2-yl)succinic acid (411)**




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 $H_2O$ to give **411** (1.62 g, 82%) as a white solid. Spectral data for this compound were consistent with those in the literature.[271] 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)**

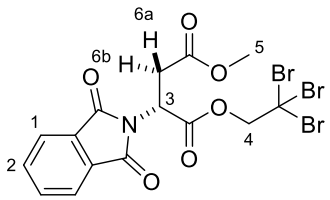



A 50 mL round-bottomed flask containing a stirring bar was charged with **411** (1.00 g, 3.80 mmol). Acetic anhydride (13 mL) was added, the flask was fitted with a condenser and the reaction mixture was heated at reflux temperature for 2 h. Acetic anhydride was

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.[272] M.p. 222-225 °C (lit.,[273] m.p. 227 °C).

$\delta_H$ (400 MHz, DMSO-$d_6$): 7.97-7.83 (4 H, m, H-1 and H-2), 5.55 (1 H, dd, *J* 6.5, 9.7, H-3), 3.49-3.31 (2 H, m, H-4a, H-4b).

**4-Methyl 1-(2,2,2-tribromoethyl)2-(1,3-dioxoisoindolin-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, $CHCl_3$).

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

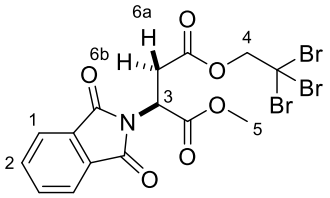
$\delta_H$ (400 MHz, $CDCl_3$): 7.91 (2 H, dd, *J* 3.1, 5.6, H-1), 7.78 (2 H, dd, *J* 3.1, 5.6, H-2), 5.61 (1 H, dd, *J* 6.1, 8.4, H-3), 4.91 (2 H, s, H-4), 3.73 (3 H, s, H-5), 3.52 (1 H, dd, *J* 6.1, 16.7, H-6a), 3.27 (1 H, dd, *J* 8.4, 16.7, H-6b).

$\delta_C$ (100 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, 226..

$\nu_{max}$ (neat)/$cm^{-1}$: 3664, 2971, 1745, 1549, 1411, 1243, 1065, 922, 718, 566.

HRMS (*m/z* - ESI): Found: 561.8229 $(M+Na)^+$ $C_{15}H_{12}Br_3NNaO_6$ Requires: 561.8225.

**1-Methyl 4-(2,2,2-tribromoethyl)2-(1,3-dioxoisoindolin-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, $CHCl_3$).

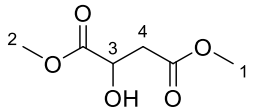
CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 70/30, 1.0 mL $min^{-1}$, rt, UV detection at 254 nm, retention times: 18.6 min (minor enantiomer) and 37.4 min (major enantiomer).

$\delta_H$ (400 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 MHz, $CDCl_3$): 170.1 (C=O), 168.4 (2 x 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 $(M+Na)^+$ $C_{15}H_{12}Br_3NNaO_6$ Requires: 561.8226.

**Dimethyl 2-hydroxysuccinate (418)**

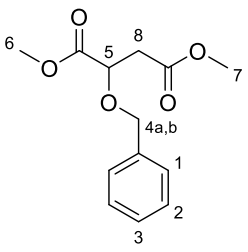



An oven dried 100 mL round-bottomed flask containing a stirring bar was fitted with a septum and then placed under an argon atmosphere (balloon). Racemic malic acid (**417**) (2.50 g, 18.6 mmol) and MeOH (15 mL) were added and the solution was cooled to 0 °C. Freshly distilled acetyl chloride (2 mL) 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 *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 *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 MHz, $CDCl_3$): 4.51 (1 H, app. t, H-3), 3.80 (3 H, s, H-2), 3.70 (3 H, s, H-1), 3.25 (1 H, bs, OH), 2.92-2.74 (2 H, m, H-4).

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



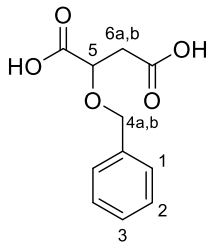

A 100 mL round-bottomed flask containing a stirring bar was charged with **418** (1.50 g, 9.26 mmol) in EtOAc (20 mL). Silver (I) oxide (3.20 g, 13.8 mmol) and benzyl bromide (1.35 mL, 11.1 mmol) were added and the reaction mixture was allowed to stir at room

temperature for 16 h. The solution was the filtered through a celite pad and the crude residue was purified by flash chromatography eluiting in gradient from 100% hexane to 10% EtOAc in hexane and isolated **420** (1.49 g, 64%) as a yellow oil.

$\delta_H$ (400 MHz, $CDCl_3$): 7.35-7.29 (5 H, m, H-1, H-2, H-3), 4.71 (H, d, *J* 11.5 H-4-a), 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 $(M-H)^-$ $C_{13}H_{15}O_5$ Requires: 251.0910.

**2-(Benzyloxy)succinic acid (421)**

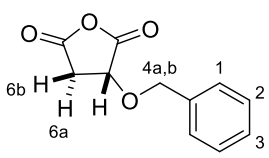



A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with **420** (1.00 g, 4.46 mmol) and THF/MeOH 1:1 (50 mL). A solution of NaOH (0.1 N) in water (50 mL) was added and the reaction mixture was refluxed for 24 h. The solution was partially neutralised with an aqueous solution of HCl (3 N). The aqueous mixture was extracted with diethyl ether (3 x 15 mL) and dried with $Na_2SO_4$ to give **421** (670 mg, 67%) as a pale yellow oil.

$\delta_H$ (400 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 $(M-H)^-$ $C_{11}H_{11}O_5$ Requires: 223.0710.

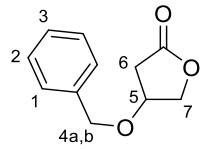
**3-(Benzyloxy)dihydrofuran-2,5-dione (390)**



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.

$\delta_H$ (400 MHz, $CDCl_3$): 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), $LiBEt_3H$ 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 **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*): $R_f$ = 0.45, $[\alpha]_D^{20}$= +8.0 (*c* = 0.20, $CHCl_3$), (lit.,[276] $[\alpha]_D^{20}$ = -28.7 (c =0.95, $CHCl_3$) for (*S*)-enantiomer).

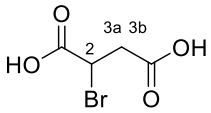
CSP-HPLC analysis. Chiralpak AS (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL $min^{-1}$, rt, UV detection at 254 nm, retention times: 60.3 min (major enantiomer) and 77.1 min (minor enantiomer).

$\delta_H$ (400 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 MHz, $CDCl_3$): 176.4 (C=O), 136.9 (q), 128.6, 128.2, 127.7, 73.8, 73.1, 71.2, 34.9.

HRMS (*m/z* - ESI): Found: 215.0675 $[M+Na]^+$ $C_{11}H_{12}NaO_3$ Requires: 215.0678.

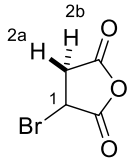
**2-Bromosuccinic acid (426)**




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 $H_2SO_4$ (100 mL) was added and the reaction mixture was cooled to -5 °C. A solution of $NaNO_2$ (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 $MgSO_4$, and concentrated *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 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).

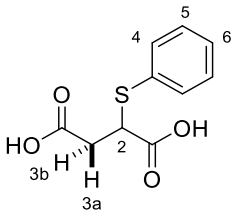
**3-Bromodihydrofuran-2,5-dione (391)**



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 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.

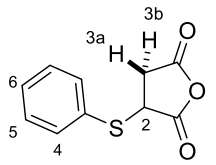
$\delta_H$ (400 MHz, DMSO-$d_6$): 12.60 (2 H, bs, COOH), 7.46 (2 H, d, *J* 7.8, H-4), 7.40-7.33 (3 H, m, H-5 and H-6), 3.90 (1 H, dd, *J* 5.3, 9.4, H-2), 2.66 (1 H, dd, *J* 9.4, 16.9, H-3a), 2.63 (1 H, dd, *J* 5.3, 16.9, H-3b).

$\delta_C$ (100 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.

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

HRMS (*m/z* -ESI): Found: 225.0218 $[M-H]^-$ $C_{10}H_9O_4S$ Requires: 225.0222.

**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.

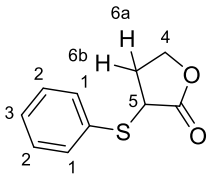
$\delta_H$ (400 MHz, DMSO-$d_6$): 7.55 (2 H, d, *J* 6.2, H-4), 7.41-7.31 (3 H, m, H-5 and H-6), 4.71 (1 H, dd, *J* 5.1, 9.8, H-2), 3.57 (1 H, dd, *J* 9.8, 18.6, H-3a), 3.03 (1 H, dd, *J* 5.1, 18.6, H-3b).

$\delta_C$ (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.

$\nu_{max}$ (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)**



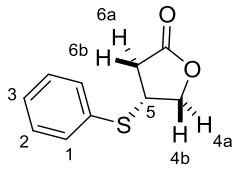

Prepared according to general procedure B using anhydride **392** (41.6 mg, 0.20 mmol) and the catalyst **378** (5.6 mg, 0.010 mmol). MTBE (2 mL) was added *via* syringe followed by the alcohol **349** (56.5 mg, 0.20 mmol). The mixture of hemiesters **436a** and **437a** (32:68 ratio) was dissolved in THF (3.0 mL) and $LiBEt_3H$ 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: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, $CHCl_3$).

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: 19.5 min (minor enantiomer) and 21.3 min (major enantiomer).

$\delta_H$ (400 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)**

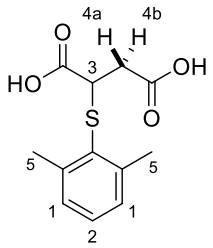



Prepared according to general procedure B using anhydride **392** (41.6 mg, 0.20 mmol) and the catalyst **378** (5.60 mg, 0.010 mmol). MTBE (2 mL) was added *via* syringe followed by the alcohol **349** (56.5 mg, 0.20 mmol). The mixture of hemiesters **436a** and **437a** (32:68 ratio) was dissolved in THF (3.0 mL), and $LiBEt_3H$ 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 **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, $CHCl_3$). (lit.[279] $[\alpha]_D^{20}$ = +36.6 (c =1.16, $CHCl_3$).

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: 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.

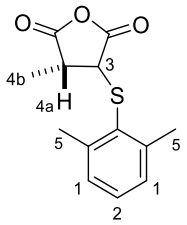
$\delta_H$ (400 MHz, DMSO-$d_6$): 7.21-7.14 (3 H, m, H-1, H-2), 4.58 (1 H, dd, *J* 4.7, 10.4, H-3), 2.74 (1 H, dd, *J* 10.4, 16.9 H-4a), 2.57 (1 H, dd *J* 4.7, 16.9, H-4 b), 2.46 (6 H, s, H-5).

$\delta_C$ (100 MHz, DMSO-$d_6$): 172.4 (C=O), 171.8 (C=O), 143.5 (q), 130.7 (q), 129.3, 128.3, 45.1, 36.2, 21.6.

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

HRMS (*m/z* -ESI): Found: 277.0515 $[M+Na]^+$ $C_{12}H_{14}O_4NaS$ Requires: 277.0505.

**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.

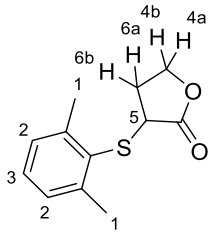
$\delta_H$ (400 MHz, DMSO-$d_6$): 7.26-7.16 (3 H, m, H-1, H-2), 4.22 (1 H, dd, *J* 5.3, 9.5, H-3), 3.50 (1 H, dd, *J* 9.5, 18.8, H-4a), 2.97 (1 H, dd, *J* 5.3, 18.8, H-4b), 2.48 (6 H, s, H-5).

$\delta_C$ (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.

$\nu_{max}$ (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 hemiester **436b**) was isolated as a white solid (11.5 mg, 26%). M.p 50-52 °C, TLC (diethyl ether:hexane, 7:3 *v/v*): $R_f$ = 0.40, $[\alpha]_D^{20}$ = +106 (*c* = 0.30, $CHCl_3$).

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: 10.1 min (major enantiomer) and 13.0 min (minor enantiomer).

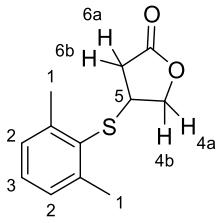
$\delta_H$ (400 MHz, $CDCl_3$): 7.11-7.19 (3 H, m, H-2, H-3), 4.34 (1 H, td, *J* 6.8, 8.8, H-4a), 4.31 (1 H, td, *J* 3.8, 8.8, H-4b), 3.69 (1 H, dd, *J* 4.3, 8.1, H-5), 2.61 (6 H, s, H-1), 2.59-2.56 (1 H, m, H-6a), 2.22-2.17 (1 H, m, H-6b).

$\delta_C$ (100 MHz, $CDCl_3$): 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.

$\nu_{max}$ (neat)/$cm^{-1}$: 2987, 1869, 1740, 1200, 1120, 1069, 910, 756, 599.

HRMS (*m/z* -ESI): Found: 245.0618 $[M+Na]^+$ $C_{12}H_{14}NaO_2S$ Requires: 245.0606.

**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 $LiBEt_3H$ in THF (1.0 mL, 1.0

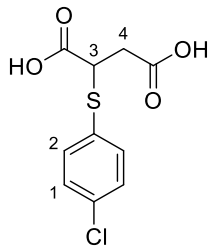
mmol) was added. The reaction mixture was allowed to stir at 0 °C for 30 min then at room temperature for additional 2.5 h under an argon atmosphere. Water (1 mL) and an aqueous solution of HCl (1 N, 2 mL) were added and the mixture was stirred for another 4 h. Upon purification by flash column chromatography eluting with 70:30 diethyl ether:hexanes, lactone **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*): $R_f$ = 0.35, $[\alpha]_D^{20}$ = +87 (*c* = 0.9, $CHCl_3$), (lit.,[277] $[\alpha]_D^{20}$ = +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).

$\delta_H$ (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).

$\delta_C$ (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)**

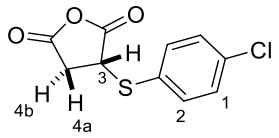



An oven dried round-bottomed flask containing a stirring bar was charged with maleic acid (1.50 g, 12.9 mmol), anhydrous THF (25 mL) and freshly distilled triethylamine (4.5 mL, 32.3 mmol). 4-Chlorothiophenol (**431**) (2.05 g, 14.21 mmol) was added *via* syringe and the reaction mixture was heated at 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.[280] m.p 165 °C).

$\delta_H$ (400 MHz, DMSO-$d_6$): 7.46 (2 H, d, *J* 7.2, H-1), 7.40 (2 H, d, *J* 7.2, H-2), 3.91 (1 H, dd, *J* 5.8, 9.2, H-3), 2.72-2.57 (2 H, m, H-4).

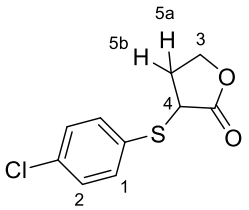
**3-((4-Chlorophenyl)thio)dihydrofuran-2,5-dione (394)**




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.,[275] m.p. 96-98 °C).

$\delta_H$ (400 MHz, DMSO-$d_6$): 7.51 (2 H, d, *J* 8.6, H-1), 7.44 (2 H, d, *J* 8.6, H-2), 4.70 (1 H, dd, *J* 5.2, 9.6, H-3), 3.52 (1 H, dd, *J* 9.6, 18.9, H-4a) 3.01 (1 H, dd, *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 $LiBEt_3H$ 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

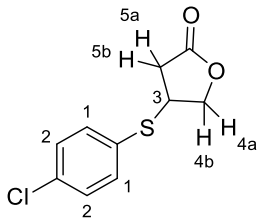
aqueous solution of HCl (1 N, 2 mL) were added and the mixture was stirred for another 4 h. Upon purification by flash column chromatography eluting with 70:30 diethyl ether:hexane, lactone **438c** (obtained from hemiester **436c**) was isolated as a white solid (4.1 mg, 9%), $[\alpha]_D^{20}$ = +116 (*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).

HRMS (*m/z* -ESI): Found: 227.0068 $[M-H]^-$ $C_{10}H_8ClO_2S$ Requires: 227.0052.

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

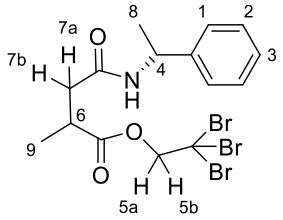



Prepared according to general procedure B using anhydride **394** (48.5 mg, 0.20 mmol) and the catalyst **378** (5.6 mg, 0.010 mmol). MTBE (2 mL) was added *via* syringe followed by the alcohol **349** (56.5 mg, 0.20 mmol). The mixture of hemiesters **436c** and **437c** (24:76 ratio) was dissolved in THF (3.0 mL), $LiBEt_3H$ 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 **439c** (obtained from hemiester **437c**) was isolated as a white solid (24.2 mg, 53%). M.p. 62-64 °C, (lit.,[281] m.p 60-61°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).

$\delta_H$ (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, $[\alpha]_D^{20}$ = +1.5 (*c* = 0.025, $CHCl_3$).

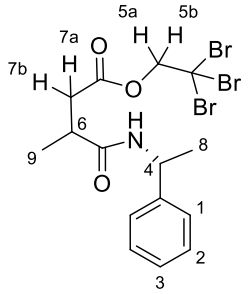
$\delta_H$ (400 MHz, $CDCl_3$): 7.38-7.31 (5 H, m, H-1, H-2, H-3), 5.83 (1 H, d, *J* 6.7, NH), 5.18-5.12 (1 H, m, H-4), 4.97 (1 H, d, *J* 11.6, H-5a), 4.82 (1 H, d, *J* 11.6, H-5b), 3.20 (1 H, m, H-6), 2.71 (1 H, dd, *J* 8.3, 15.0, H-7a), 2.37 (1 H, dd, *J* 5.9, 15.0, H-7b), 1.53 (3 H, d, *J* 6.2, H-8),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

$\delta_C$ (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.

$\nu_{max}$ (neat)/$cm^{-1}$: 3662, 2970, 1720, 1445, 1150, 1080, 880, 569.

HRMS (*m/z* -ESI): Found: 519.8730 $[M+Na]^+$ $C_{15}H_{18}Br_3NNaO_3$ 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 $CH_2Cl_2$ (4.0 mL) and the reaction 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, 0.5 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 hexane:EtOAc, amide **445a** (obtained from hemiesters **443a**) was isolated as a white solid (21.0 mg, 38%), M. p. 68-70 °C, $[\alpha]_D^{20}$ = +1.12 (*c* = 0.03, $CHCl_3$).

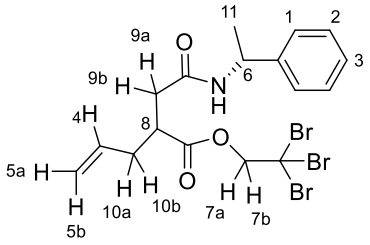
$\delta_H$ (400 MHz, $CDCl_3$): 7.39-7.32 (5 H, m, H-1, H-2, H-3), 5.90 (1 H, d, *J* 6.7, NH), 5.19-5.14 (1 H, m, H-4), 5.01 (1 H, d, *J* 12.6, H-5a), 4.92 (1 H, d, *J* 12.6, H-5b), 3.03 (1 H, dd, *J* 8.7, 17.2, H-7a), 2.79 (1 H, m, H-6), 2.59 (1 H, dd, *J* 5.9, 17.2, H-7b), 1.52 (3 H, d, *J* 6.2, H-8), 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 $[M+Na]^+$ $C_{15}H_{18}Br_3NNaO_3$ 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 $CH_2Cl_2$ (4.0 mL) and the reaction mixture was cooled to 0 °C. Thionyl chloride (17.7 μL, 0,2 mmol) in $CH_2Cl_2$ (2.0 mL) was then added and the reaction mixture was allowed to stir for 10 min under argon atmosphere. Freshly distilled $Et_3N$ (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, $[\alpha]_D^{20}$= +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*.

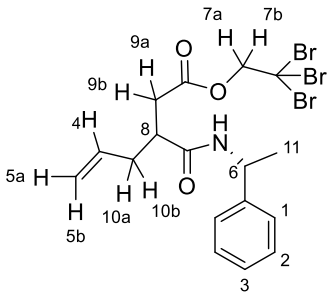
$\delta_H$ (400 MHz, $CDCl_3$): 7.38-7.30 (5 H, m, H-1, H-2, H-3), 5.86-5.75 (2 H, m, NH, H-4), 5.16-5.11 (3 H, m, H-5a, H-5b, H-6), 4.93 (1 H, d, *J* 12.0, H-7a), 4.79 (1 H, d, *J* 12.0, H-7b), 3.26 (1 H, m, H-8), 2.64 (1 H, dd, *J* 9.0, 15.1, H-9a), 2.59-2.53 (1 H, m, H-10a), 2.50-2.40 (2 H, H-9b, 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.

$\nu_{max}$ (neat)/cm$^{-1}$: 3664, 2971, 1749, 1541, 1411, 1242, 1066, 921, 716, 563.

HRMS (*m/z* -ESI): Found: 545.8878 $[M+Na]^+$ $C_{17}H_{20}Br_3NNaO_3$ 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 $CH_2Cl_2$ (4.0 mL) and the reaction mixture was cooled to 0 °C. Thionyl chloride (17.7 μL, 0,2 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, 0.5 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 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, NH), 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 H-7a), 4.90 (1 H, d, *J* 12.2, H-7b), 2.99 (1 H, dd, *J* 8.6, 16.7, H-9a), 2.75-2.62 (2 H, m, H-8,

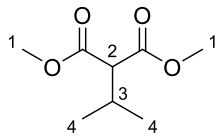
H-9b), 2.47-2.38 (1 H, m, H-10a), 2.30-2.22 (1 H, m, H-10b), 1.51 (3 H, d, *J* 7.2, H-11).

$\delta_C$ (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.

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

HRMS (*m/z* -ESI): Found: 545.8874 $[M+Na]^+$ $C_{17}H_{20}Br_3NNaO_3$ Requires: 545.8885.

**Dimethyl 2-isopropylmalonate (447)**

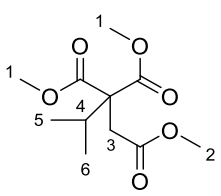



A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with 2-isopropyl acid (**277**, 5.00 g, 34.2 mmol). Concentrated sulfuric acid (1 mL) and methanol (75 mL) were added and the reaction mixture was heated at reflux temperature for 16 h. The solvent was evaporated and the residue was dissolved in diethyl ether (30 mL) and then washed with a saturated aqueous solution of $NaHCO_3$ (3 x 15 mL) and $H_2O$ (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 $(M+Na)^+$ $C_8H_{14}O_4Na$ Requires: 197.0984.

**Trimethyl 3-methylbutane-1,2,2-tricarboxylate (449)**



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%).

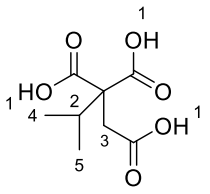
$\delta_H$ (400 MHz, $CDCl_3$): 3.71 ( 6 H, s, H-1), 3.63 (3 H, s, H-2), 2.87 (2 H, s, H-3), 2.34 (1 H, m, H-4), 0.96 (3 H, d, *J* 6.9, H-5) 0.92 (3 H, d, *J* 6.9, H-6).

$\delta_C$ (100 MHz, $CDCl_3$): 174.4 (C=O), 171.8 ( 2 x C=O), 58.1 (q), 53.4, 53.2, 51.8, 33.9, 22.8, 16.2.

$\nu_{max}$ (neat)/$cm^{-1}$: 2886, 2628, 1742, 1684, 1310, 1244, 1185, 1134, 1014, 863.

HRMS (*m/z* -ESI): Found: 269.1088 $(M+Na)^+$ $C_{11}H_{18}O_6Na$ 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 $Na_2SO_4$ to give **450** (522 mg, 41%) as a yellow oil.

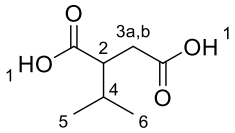
$\delta_H$ (400 MHz, $CDCl_3$): 9.44 (3 H, bs, H-1), 2.19 (1 H, m, H-2), 2.08 (2 H, s, H-3), 1.05 (3 H, d, *J* 6.9, H-4), 1.02 (3 H, d, *J* 6.9, H-5).

$\delta_C$ (100 MHz, $CDCl_3$): 177.1 (2 x C=O), 176.3 (C=O), 59.9 (q), 37.1, 22.8, 16.3.

$\nu_{max}$ (neat)/$cm^{-1}$: 2978, 1742, 1684, 1308, 1295, 1180, 1026, 904.

HRMS (*m/z* -ESI): Found: 227.0618 $(M+Na)^+$ $C_8H_{12}O_6Na$ Requires: 227.0618.

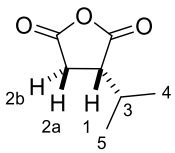
**2-isoPropylsuccinic acid (451)**




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 °C, (lit.,[283] m.p 110-111 °C)

$\delta_H$ (400 MHz, DMSO-$d_6$): 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-isoPropyldihydrofuran-2,5-dione (395)**

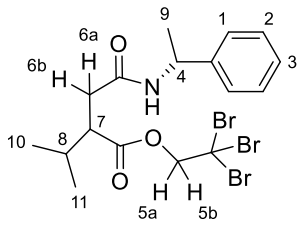



An oven dried round-bottomed flask containing a stirring bar was charged with **451** (1.00 g, 6.24 mmol) and freshly distilled acetyl chloride (15 mL), The apparatus was equipped with a condenser and a septum and kept under an argon atmosphere (balloon). The reaction mixture was heated at reflux overnight, then concentrated under reduced pressure to give anhydride **395** (781 mg, 88%) pure as a dark brown oil.

$\delta_H$ (400 MHz, DMSO-$d_6$): 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 $(M+H)^+$ $C_7H_{11}O_3$ Requires: 143.0703.

**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 $CH_2Cl_2$ (4.0 mL) and the reaction 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, 0.5 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*): $R_f$ = 0.32; $[\alpha]_D^{20}$ = +2.5 (*c* = 0.0020, $CHCl_3$), M. p. 92-94 °C.

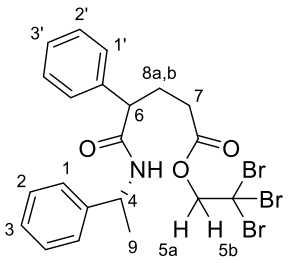
$\delta_H$ (400 MHz, $CDCl_3$): 7.37-7.33 (5 H, m, H-1, H-2, H-3), 5.86 (1 H, d, *J* 6.7, NH), 5.17-5-16 (1 H, m, H-4), 5.01 (1 H, d, *J* 12.7, H-5a), 4.88 (1 H, d, *J* 12.7, H-5b), 3.01 (1 H, dd, *J* 10.4, 17.4, H-6a), 2.65 (1 H, dd, *J* 3.3, 17.4, H-6b), 2.39, (1 H, m, H-7), 1.94 (1 H, m, H-8), 1.51 (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).

$\delta_C$ (100 MHz, $CDCl_3$): 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.

$\nu_{max}$ (neat)/$cm^{-1}$: 3663, 2971, 1716, 1446, 1153, 1078, 878, 564.

HRMS (*m/z* -ESI): Found: 547.9046 $(M+Na)^+$ $C_{17}H_{22}Br_3NNaO_3$ 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 $CH_2Cl_2$ (4.0 mL) and the reaction 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, 0.5 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*): $R_f$ = 0.39, $[\alpha]_D^{20}$ = +28.5 (*c* = 0.26, $CHCl_3$), M. p. 155-158 °C.

Major diastereomer:

$\delta_H$ (400 MHz, $CDCl_3$): 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, $CDCl_3$): 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)/$cm^{-1}$: 3660, 2968, 1724, 1445, 1149, 1065, 865, 670.

HRMS (*m/z* -ESI): Found: 595.9178 $(M+Na)^+$ $C_{21}H_{22}Br_3NNaO_3$ Requires: 595.9185.

Minor diastereomer:

$\delta_H$ (400 MHz, $CDCl_3$): 7.33-7.12 (10 H, m, H-1, H-1', H-2, H-2', H-3, H-3'), 5.62 (1 H, d, *J* 7.1, NH), 5.06-5.04 (1 H, m, H-4), 4.90 (2 H, s, H-5), 3.52 (1 H, app.t, H-6), 2.55-2.45 (3 H, m, H-7, H-8a), 2.16-2.11 (1 H, m, H-8b), 1.40 (3 H, d, *J* 6.7, H-9).

$\delta_C$ (100 MHz, $CDCl_3$): 173.6 (C=O), 171.1 (C=O), 141.7 (q), 137.4 (q), 128.8, 128.4, 127.9, 127.7, 126.9, 126.8, 79.7, 53.2, 45.9, 34.7 (q) 30.9, 24.3, 21.3 (q).

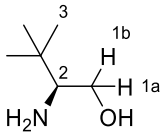
*$[\alpha]_D^{20}$ refers to a mixture of (*R*,*R*)-**457** and (*S*,*R*)-**457** (60:40).

## 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 glutaconic 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 $^1$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.

**(*S*)-2-Amino-3,3-dimethylbutan-1-ol (461)**



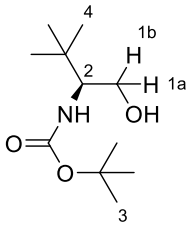

An oven-dried 100 mL reaction flask containing a magnetic stirring bar under an argon atmosphere was charged with sodium borohydride (1.38 g, 36.4 mmol) in THF (0.4 M), and L-*tert*-leucine (**460**, 2.00 g, 15.2 mmol). The reaction mixture was cooled at 0 °C and a solution of iodine (3.86 g, 15.2 mmol) 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 $CH_2Cl_2$ (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 MHz, $CDCl_3$)*: 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 $(M-H)^-$ $C_6H_{14}NO$ 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)**

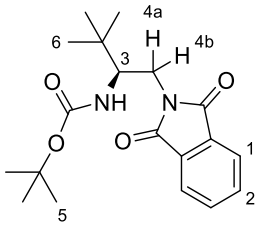



An oven-dried 100 mL reaction flask containing a magnetic stirring bar under an argon atmosphere was charged with **461** (1.50 g, 12.8 mmol) in $CH_2Cl_2$ (0.4 M), then triethylamine (2.1 mL, 15.1 mmol) was added and the reaction mixture was cooled to 0 °C using an ice bath. Boc anhydride (15.1 mmol) 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 $MgSO_4$ and volatiles were removed *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.,[285] m.p 105 °C).

$\delta_H$ (400 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).

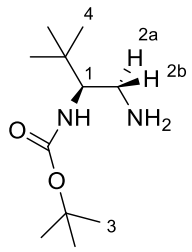
***tert*-Butyl (*S*)-(1-(1,3-dioxoisoindolin-2-yl)-3,3-dimethylbutan-2-yl)carbamate (464)**[285]




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 triphenylphosphine (2.20 g, 8.43 mmol) in THF (0.2 M). Under a $N_2$ atmosphere at room temperature DIAD (1.8 mL, 8.85 mmol) was added dropwise *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.,[285] m.p 146-147 °C).

$\delta_H$ (400 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).

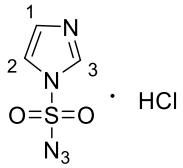
***tert*-Butyl (*S*)-(1-amino-3,3-dimethylbutan-2-yl)carbamate (465)**[285]




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 $N_2$ 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 temperatured and filtered. The precipitate was washed with $CH_2Cl_2$ (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.[285] m.p 84 °C)

$\delta_H$ (400 MHz, $CDCl_3$): 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, $NH_2$), 1.44 (9 H, s, H-3), 0.91 (9 H, s, H-4).

**1H-imidazole-1-sulfonyl azide hydrogen chloride (466)**[286]

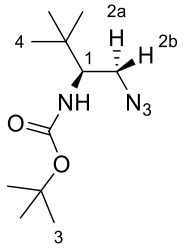



A 250 mL round bottomed flask containing a magnetic stirring bar was charged with $NaN_3$ (5.0 g, 77.0 mmol) and $CH_3CN$ (77 mL). Sulfuryl chloride (6.2 mL, 77.0 mmol) was added dropwise *via* syringe at 0° C and the reaction mixture was allowed to stir for 16 h at room temperature. Imidazole (10.0 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 $H_2O$ (2 x 150 mL) followed by a saturated aqueous solution of $NaHCO_3$ (2 x 100 mL). The combined organic phases were dried over $MgSO_4$ 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.,[287] m.p. 100-102 °C)

$\delta_H$ (400 MHz, $D_2O$): 9.11 (1 H, s, H-3), 7.86 (1 H, s, H-2), 7.42 (1 H, s, H-1).

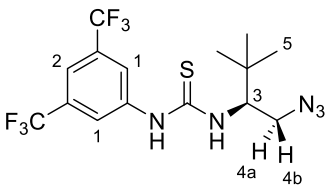
***tert*-Butyl (*S*)-(1-azido-3,3-dimethylbutan-2-yl)carbamate (467)**[213]




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), $K_2CO_3$ (1.22 g, 8.82 mmol) and $CuSO_4{\cdot}5H_2O$ (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 $Et_2O$ (20 mL). The aqueous layer was extracted with $Et_2O$ (20 mL) and the combined organics were washed with brine and dried over $MgSO_4$, 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.,[213] m.p. 58-60 °C).

$\delta_H$ (400 MHz, $CDCl_3$): 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)**[213]

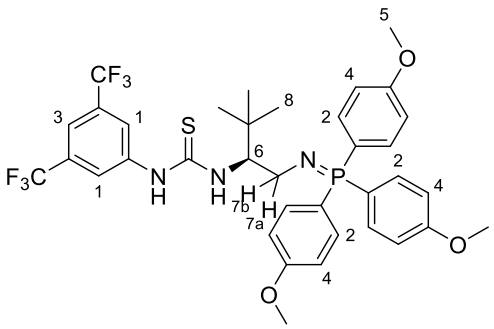


A 100 mL reaction flask containing a magnetic stirring bar under an argon atmosphere was charged with **467** (750 mg, 3.1 mmol) and cooled to 0 °C. TFA (3 mL) was added dropwise and the solution was stirred at room temperature for 3 h. TFA was evaporated under reduced pressure and the residue dissolved 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 $MgSO_4$, filtered and concentrated under a stream of $N_2$. 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).

$\delta_H$ (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-phosphaneylidene)amino)butan-2-yl)thiourea (239)**[215]

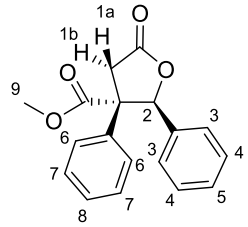


To a 25 mL round bottomed flask containing a magnetic stirring bar was added **469** (500 mg, 1.21 mmol), followed by diethyl ether (3.0 mL) and tris(4-methoxyphenyl)phosphine (426 mg, 1.21 mmol) under an argon atmosphere. The reaction mixture was allowed to stir at room temperature for 24 h, after which 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:$Et_2O$ (1:1) and dried *in vacuo* to give **239** as an off white solid (759 mg, 85%) as a colourless solid. M.p. 146-148 °C, (lit.,[215] m.p 148-150 °C ).

$\delta_H$ (400 MHz, $CDCl_3$): 7.57 (2 H, s, H-1), 7.52-7.43 (6 H, m, H-2), 7.32 (1 H, s, H-3), 7.05-6.95 (6 H, m, H-4), 3.87 (9 H, s, H-5), 4.08 (1 H, bs, H-6), 3.23 (1 H, dd, *J* 5.5, 8.7, H-7a), 2.90 (1 H, app. q, H-7b), 0.95 (9 H, s, H-8).

**(2*S*,3*S*)-Methyl 5-oxo-2,3-diphenyltetrahydrofuran-3-carboxylate (*trans*-144, Scheme 4.2)**




Prepared according to general procedure E using phenylsuccinic anhydride (**140**, 43.3 mg, 0.492 mmol), anhydrous MTBE (4.9 mL, 0.1 M), freshly distilled benzaldehyde (50 μL, 0.492 mmol) and catalyst **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 (*trans*:*cis*) ratio. After esterification, the major diastereomer (*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*): $R_f$ = 0.35, $[\alpha]_D^{20}$ = -94.2 (*c* = 0.50, $CHCl_3$).

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: 18.3 min (minor enantiomer) and 31.1 min (major enantiomer).

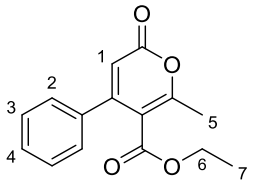
$\delta_H$ (400 MHz, $CDCl_3$): 7.20-7.01 (6 H, m, H-4, H-5, H-7 and H-8), 6.97 (2 H, d, *J* 7.3, H-3), 6.81 (2 H, d, *J* 7.3, H-6), 6.30 (1 H, s, H-2), 3.78 (3 H, s, H-9), 3.42 (1 H, d, *J* 17.6, H-1b); 3.34 (1 H, d, *J* 17.6, H-1a).

$\delta_C$ (100 MHz, $CDCl_3$): 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.

$\nu_{max}$ (neat)/$cm^{-1}$: 3039, 2954, 1782, 1731, 1499, 1435, 1235, 1178, 1008, 898, 753, 695.

HRMS (*m/z* - ESI): Found: 319.0941 $(M+Na)^+$ $C_{18}H_{16}O_4Na$ Requires: 319.0946.

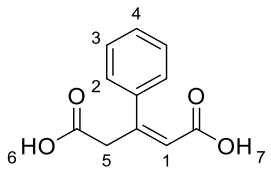
**Ethyl 6-methyl-2-oxo-4-phenyl-2*H*-pyran-5-carboxylate (475)[288]**



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). NaOH (68.8 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 EtOAc (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *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.,[289] m.p. 95-96 °C).

$\delta_H$ (400 MHz, $CDCl_3$): 7.44-7.36 (3 H, m, H-2 and H-4), 7.32-7.25 (2 H, m, H-3), 6.14 (1 H, s, H-1), 3.95 (2 H, q, *J* 7.1, H-6), 2.45 (3 H, s, H-5), 0.86 (3 H, t, *J* 7.1, H-7).

***(E)*-3-Phenylpent-2-enedioic acid (476)[148]**

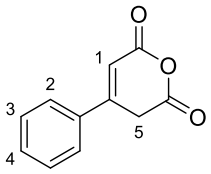


A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with **475** (1.0 g, 3.8 mmol), water (15 mL) and NaOH (760 mg, 19.0 mmol). The flask was fitted with a condenser and the reaction mixture was heated at 80 °C for 5 h. The mixture was then cooled to room temperature and diluted 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 $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to afford a residue that was triturated with $Et_2O$ (5 mL) to give **476** as a white solid (587 mg, 75%). M.p. 136-138 °C, (lit.[289] m.p. 128-130 °C).

$\delta_H$ (400 MHz, DMSO-$d_6$): 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).

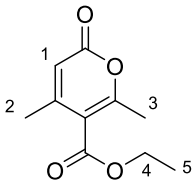
**Phenyl-2*H*-pyran-2,6(3*H*)-dione (150)[290]**




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).

$\delta_H$ (400 MHz, DMSO-$d_6$): 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-2*H*-pyran-5-carboxylate (497)[292]**



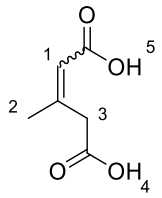

A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with $H_2SO_4$ conc. (20 mL) and the reaction was cooled to 10 °C. Ethyl 3-oxobutanoate (**473**, 26.0 mL, 204 mmol) was added dropwise *via* syringe while keeping the reaction temperature below 15 °C. The resultant mixture was allowed to stir at room temperature

for 72 h after which time the reaction was poured into ice (60 g) and extracted with $Et_2O$ (3 x 100 mL). The combined organic layers were washed with a 10% aqueous solution of $Na_2CO_3$ (1 x 100 mL), dried over $MgSO_4$, 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%).

$\delta_H$ (400 MHz, $CDCl_3$): 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).

HRMS (*m/z* -APCI): Found: 195.0805 $[M+H]^+$ $C_{10}H_{13}O_4$ Requires: 197.0808.

**3-Methylpent-2-enedioic acid (498)**[289]




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 $Et_2O$ (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 $MgSO_4$, filtered and the solvent removed under reduced pressure to furnish a residue that was triturated with $Et_2O$ (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).

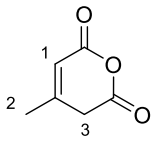
(*E*)-**498**:

$\delta_H$ (400 MHz, DMSO-$d_6$): 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**:

$\delta_H$ (400 MHz, DMSO-$d_6$): 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).

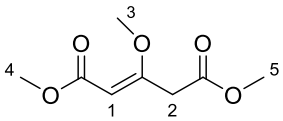
**4-Methyl-2*H*-pyran-2,6(3*H*)-dione (151)**[289]




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)**[233]

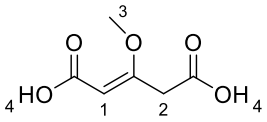



A 100 mL round-bottomed flask containing a magneting stirring bar was charged with dimethyl-1,3-acetonedicarboxylate (3.20 g, 22.9 mmol) in MeOH (50.0 mL). Trimethyl orthoformate (5.0 mL, 45.9 mmol) and *p*-toluenesulfonic acid (196 mg, 1.14 mmol) were then added. The flask was fitted with a condenser 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): Found: 211.0581 $[M+Na]^+$ $C_8H_{12}O_5Na$ Requires: 211.0582.

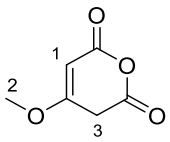
**(*Z*)-3-Methoxypent-2-enedioic acid (500)**[291]



A 100 mL round-bottomed flask containing a magneting 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 $Et_2O$ (3 x 30 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resultant residue was triturated with $Et_2O$ (5 mL) to give **500** as an off white solid (614 mg, 50%). M.p. 175-177 °C, (lit.,[291] 180 °C).

$\delta_H$ (400 MHz, DMSO-$d_6$): 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).

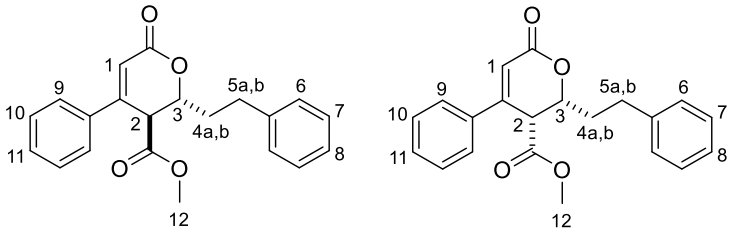
**4-Methoxy-2H-pyran-2,6(3H)-dione (496)**[293]



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.,[294] 85-87 °C)

$\delta_H$ (400 MHz,DMSO-$d_6$): 5.55 (1 H, s, H-1), 3.78 (3 H, s, H-2), 3.72 (2 H, s, H-3).

**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, $CHCl_3$).*

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: *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 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 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.

$\nu_{max}$ (neat)/$cm^{-1}$: 2927, 2855, 1725, 1457, 1261, 1237, 1158, 1110, 1086, 1030, 993, 709, 645.

HRMS (*m/z* - ESI): Found: 337.1443 $[M+H]^+$ $C_{21}H_{21}O_4$ Requires: 337.1434.

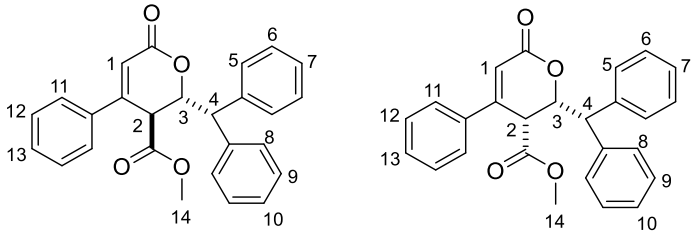
*cis*-**478**:

$\delta_H$ (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).

$\delta_C$ (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 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 the diastereomeric mixture was purified by flash columm 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 *v/v*): $R_f$ 0.67, $[\alpha]_D^{20}$ = - 23.0 (*c* = 0.05, $CHCl_3$)*.

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: *trans*-**487** 2.98 min (major enantiomer) and 3.5 min (minor enantiomer), *cis*-**487** 3.2 min (major enantiomer), 3.9 min (minor enantiomer).

*trans*-**487**:

$\delta_H$ (400 MHz, $CDCl_3$): 7.49-7.45 (2 H, m, H-11), 7.44-7.39 (5 H, m, H-5, H-12 and H-13),7.38-7.35 (4 H, m, H-8 and H-9), 7.35-7.29 (3 H, m, H-6 and H-10), 7.21-7.19 (1 H, m, H-7), 6.53 (1 H, s, H-1), 5.83 (1 H, dd, *J* 2.9, 10.4, H-3), 4.34 (1 H, d, *J* 10.4, H-4), 3.83 (1 H, d, *J* 2.9, H-2), 3.67 (3 H, s, H-14).

$\delta_C$ (100 MHz, $CDCl_3$): 169.7 (C=O), 162.4 (C=O), 150.3 (q), 140.6 (q), 139.5 (q), 135.7 (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.

$\nu_{max}$ (neat)/$cm^{-1}$: 3088, 2971, 2923, 1660, 1592, 1506, 1472, 1311, 1217, 1072, 998, 768, 642.

HRMS (m/z -ESI): Found: 421.1407 $[M+Na]^+$ $C_{26}H_{22}O_4Na$ Requires: 421.1410.

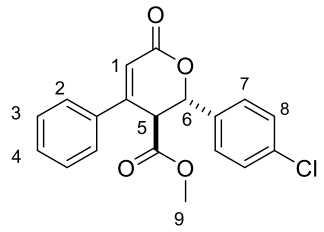
*cis*-**487**:

$\delta_H$ (400 MHz, $CDCl_3$): 7.49-7.45 (2 H, m, H-11), 7.44-7.39 (5 H, m, H-5, H-12 and H-13),7.38-7.35 (4 H, m, H-8 and H-9), 7.35-7.29 (3 H, m, H-6 and H-10), 7.21- 7.19 (1 H, m, H-7) ,6.55 (1 H, s, H-1), 5.37 (1 H, dd, *J* 1.4, 10.6, H-3), 4.33 (1 H, d, *J* 10.6, H-4), 3.82 (1 H, d, *J* 1.4, H-2), 3.67 (3 H, s, H-14).

$\delta_C$ (100 MHz, $CDCl_3$): 168.1 (C=O), 164.4 (C=O), 152.3 (q), 140.2 (q), 139.9 (q), 134.6 (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.

* $[\alpha]_D^{20}$ refers to a mixture of *trans*-**487**: *cis*-**487** (87:13)

**Methyl 2-(4-chlorophenyl)-6-oxo-4-phenyl-3,6-dihydro-2H-pyran-3-carboxylate (*trans*-488, Table 4.3, entry 2)**




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 (*trans:cis*). After esterification by flash column chromatography eluting with 75:25 hexane:EtOAc, *trans*-**487** was isolated as a pale yellow oil (50.6 mg, 60%). TLC (hexane/EtOAc, 8:2 *v/v*): $R_f$ 0.6, $[\alpha]_D^{20}$ = - 17 (*c* = 0.03, $CHCl_3$).

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).

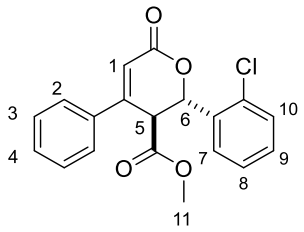
$\delta_H$ (400 MHz, $CDCl_3$): 7.46 (5 H, m, H-2, H-3, H-4), 7.39-7.29 (4 H, m, H-7, H-8), 6.44 (1 H, s, H-1), 5.97 (1 H, d, *J* 5.4, H-6), 4.23 (1 H, d, *J* 5.4, H-5), 3.65 (3 H, s, H-9).

$\delta_C$ (100 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.

$\nu_{max}$ (neat)/$cm^{-1}$: 2952, 2925, 2861, 1735, 1708, 1601, 1458, 1260, 1002, 825, 741.

HRMS (m/z -ESI): Found: 365.0547 $[M+Na]^+$ $C_{19}H_{15}ClNaO_4$ Requires: 365.0551.

**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*): $R_f$ 0.6, $[\alpha]_D^{20}$ = - 4.0 (*c* = 0.01, $CHCl_3$).

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).

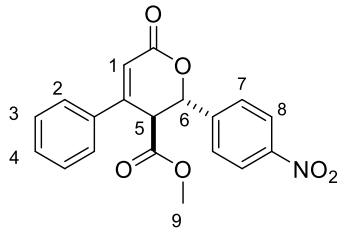
$\delta_H$ (400 MHz, $CDCl_3$): 7.48-7.43 (5 H, m, H-2, H-3, H-4), 7.36-7.30 (4 H, m, H-7, H-8, H-9, H-10), 6.45 (1 H, s, H-1), 4.45 (1 H, d, *J* 5.5, H-6), 3.77 (1 H, d, *J* 5.5, H-5), 3.75 (3 H, s, H-11).

$\delta_C$ (100 MHz, $CDCl_3$): 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.

$\nu_{max}$ (neat)/$cm^{-1}$: 2952, 2925, 2861, 1732, 1708, 1601, 1458, 1268, 1002, 825, 744.

HRMS (m/z -ESI): Found: 365.0558 $[M+Na]^+$ $C_{19}H_{15}ClNaO_4$ Requires: 365.0551.

**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), recristallysed 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*): $R_f$ 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).

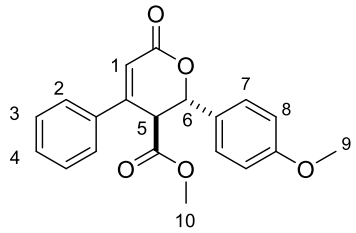
$\delta_H$ (400 MHz, $CDCl_3$): 8.27 (2 H, d, *J* 8.8, H-8), 7.58 (2 H, d, *J* 8.8, H-7), 7.47-7.42 (5 H, m, H-2, H-3, H-4), 6.46 (1 H, s, H-1), 6.11 (1 H, d, *J* 5.1, H-6), 4.26 (1 H, d, *J* 5.1, H-5), 3.68 (3 H, s, H-9).

$\delta_C$ (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.

$\nu_{max}$ (neat)/$cm^{-1}$: 2968, 1715, 1601, 1453, 1420, 1287,1253, 1119, 1002, 862, 824, 731, 720.

HRMS (m/z -ESI): Found: 376.0787 $[M+Na]^+$ $C_{19}H_{15}NNaO_6$ Requires: 376.0791.

**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*): $R_f$ 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).

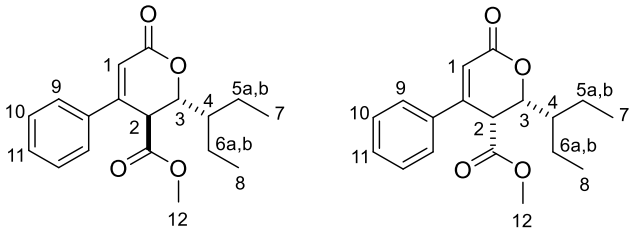
$\delta_H$ (400 MHz, $CDCl_3$): 7.46-7.43 (5 H, m, H-2, H-3, H-4), 7.30 (2 H, d, *J*, 8.6, H-7), 6.90 (2 H, d, *J*, 8.6, H-8), 6.43 (1 H, s, H-1), 5.94 (1 H, d, *J* 5.3, H-6), 4.27 (1 H, d, *J* 5.3, H-5), 3.81 (3 H, s, H-9), 3.62 (3 H, s, H-10).

$\delta_C$ (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*): $R_f$ 0.59, . $[\alpha]_D^{20}$ = - 36.0 (*c* = 0.04, $CHCl_3$)*.

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**:

$\delta_H$ (400 MHz, $CDCl_3$): 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).

δc (100 MHz, $CDCl_3$): 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.

$\nu_{max}$ (neat)/$cm^{-1}$: 3086, 2965, 2877, 1721, 1696, 1624, 1446, 1353, 1269, 1245, 1086, 1012, 990, 893, 777, 689, 602, 576.

HRMS (*m/z* -APCI): Found: 303.1598 $[M+H]^+$ $C_{18}H_{23}O_4$ Requires: 303.1590.

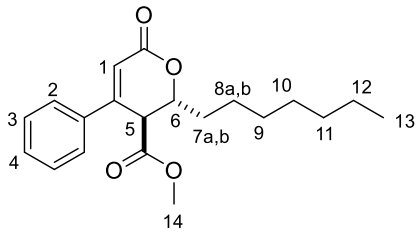
*cis*-**492**:

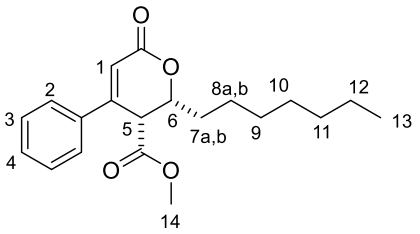
$\delta_H$ (400 MHz, $CDCl_3$): 7.63-7.54 (2 H, m, H-10), 7.48-7.44 (3 H, m, H-9 and H-11), 6.55 (1 H, s, H-1), 4.44 (1 H, dd, *J* 3.1, 9.1, H-3), 3.93 (1 H, d, *J* 3.1, H-2), 3.73 (3 H, s, H-12), 1.84-1.69 (3 H, m, H-4, H-5a, H-6a), 1.70-1.62 (1 H, m, H-5b), 1.53-1.44 (1 H, m, H-6b), 0.98-0.94 (6 H, m, H-7 and H-8).

δc (100 MHz, $CDCl_3$): 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.

* $[\alpha]_D^{20}$ 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)**




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**:

$\delta_H$ (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).

$\delta_C$ (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.

$\nu_{max}$ (neat)/$cm^{-1}$: 2927, 2856, 1712, 1624, 1447, 1350, 1242, 1161, 1020, 875, 772, 726, 686.

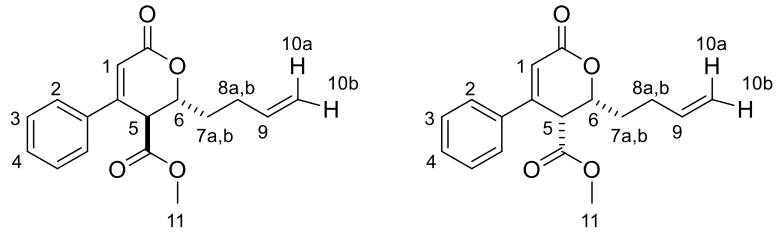
HRMS (*m/z* - APCI): Found: 331.1913 $[M+H]^+$ $C_{20}H_{27}O_4$ Requires: 331.1903.

*cis*-**493**:

$\delta_H$ (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).

$\delta_C$ (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)**




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*): $R_f$ 0.72, $[\alpha]_D^{20}$ = - 45.0 (*c* = 0.01, $CHCl_3$)*.

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: *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**:

$\delta_H$ (600 MHz, $CDCl_3$): 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).

$\delta_C$ (100 MHz, $CDCl_3$): 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.

$\nu_{max}$ (neat)/$cm^{-1}$: 2952, 1710, 1641, 1447, 1352, 1255, 1118, 1055, 973, 909, 878, 774, 683, 603.

HRMS (*m/z* - APCI): Found: 287.1277 $[M+H]^+$ $C_{17}H_{19}O_4$ Requires: 287.1277.

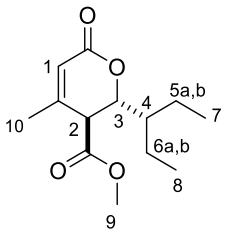
*cis*-**494**:

$\delta_H$ (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* 3.4, 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*): $R_f$ 0.7, $[\alpha]_D^{20}$ = - 23.3 (*c* = 0.02, $CHCl_3$).

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 MHz, $CDCl_3$): 5.93 (1 H, s, H-1), 4.73 (1 H, dd, *J* 4.5, 8.4, H-3), 3.49 (1 H, d, *J* 8.4, H-2), 3.81 (3 H, s, H-9), 2.01 (3 H, s, H-10), 1.78-1.61 (3 H, m, H-4, H-5a, H-6a), 1.56-1.41 (2 H, H-5b, H-6b), 0.97-0.91 (6 H, m, H-7, H-8).

$\delta_C$ (100 MHz, $CDCl_3$): 172.9 (C=O), 164.2 (C=O), 161.3 (q), 116.4, 78.3, 52.3, 45.5, 44.8, 23.7, 22.6, 20.2, 11.4, 10.9.

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

# Chapter 6

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