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Romain Claveau

R. Claveau, B. Twamley and S. J. Connon, *Chem. Commun.*, 2018, **54**, 3231.

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Acknowledgements

After 4 years and 7 months of intensive work I still can't believe that the PhD journey has finally come to an end. It has been 5 years filled with many periods of hard time but also full of plenty enriching experiences along the way. I would like to take this chance to thank all the people that did participate one way or another in this journey and made this period an overall great experience.

First of all, I would like to thank all my family for the support and encouragements throughout this chapter of my life. I have to admit that it has been hard for me to see my 3 years younger brother getting his PhD before me but, at least, I'm pleased with the idea that from now on I'll be able to remind my dad that we both got a PhD (and that he didn't!).

I'm grateful to my supervisor Prof. Stephen Connon, who I would like to thank for the great opportunity he gave me to work within his research group during my PhD. I also would like to thank him for his constant advice throughout these five years of researches and, in particular, for the precious help he gave me during the process of publications and thesis writing.

I would like to thank all the former and current members of the Connon, and other groups, that contributed to making this PhD journey a unique experience. Thank you Emiliano, Francesco, Umar, Vikas, Francianne, Michelle, Eogahn, Claire-Louise, Ryan, Mili, Chiara, Maria-Luisa, Bruce, Aaron, Cris, Sarah, Amy, Ciara, Simon, Marie.

My gratitude is also further extended to the many people who have taken part in helping me with the proof reading/corrections/suggestions during the writing of this thesis. Thank you again Ryan, Mili, Sarah, Amy, Ciara, Bruce, Simon. A special thank you to Michelle. I am very gratefull for the time you spent on helping me with the proof reading of a big part (pretty much all of it!) of my thesis.

Finally, I would like to thank all the staff in the Chemistry department for their precious help over the past 5 years: Dr. Manuel Ruether, Dr. Brendan Twamley, Dr. Gary Hessman, Dr. Martin Feeney, Prof. Mike Southern, Prof. Eoin Scanlan, Prof. Isabel Rozas. A special thank you to Dr. John O' Brien for its time and help over the years during the elucidation of complex molecular structures by NMR analysis.

Abstract

In this thesis we explore the possibilities offered by the bifunctional properties of a series of organocatalysts derived from cinchona alkaloids for the promotion of novel asymmetric transformations. In particular, we focused our attention on the extention of the scope of enantioselective cycloaddition reactions of pronucleophilic anhydrides capable of reacting with electrophiles such as aldehydes and of yielding chiral lactones in a regio-, diastero- and enantioselective fashion.

We have shown for the first time that a series of *trans*-disubstituted aryl succinic anhydrides can participate in a unique one-pot formal cycloaddition process with aldehydes *via* dynamic kinetic resolution (DKR). The highly functionalised γ-butyrolactones products are important members of a class of compounds possessing a wide array of valuable biological properties (paraconic acid derivatives). An *ad hoc* designed squaramide organocatalyst was able to promote the reaction, at 5 mol% loading, furnishing the lactones with good to excellent stereocontrol over three chiral centres, one of which being all-carbon quaternary in nature (up to 92%, 34:1 dr, 98% *ee*). The synthetic utility of these compounds as potential building blocks for organic syntheses was demonstrated through ready manipulation of one of the products to form a stereochemically dense and complex fused lactone-lactam system in 86% *ee*.

We later extended the methodology to the more challenging kinetic resolution (KR) variant of the process and reacted α-alkylated aryl sucinnic anhydrides in a *regio*-, diastereo- and enantioselective cycloaddition with aldehydes. The first examples of the KR of these starting materials provided access to a range of chiral succinate derivatives with selectivity factors up to S* = 10.5. Densely functionalised five-membered lactones (paraconic acid derivatives, γ-butyrolactones) could be formed, in one pot, with control over three contiguous stereocentres and selectivities ranging from modest to excellent (up to 7:1 dr, 94% *ee*). This project also reports the first examples of a promising *ad hoc* designed novel class of bifunctional hydrogen-bond donor sulfamide organocatalyst capable of engaging in multiple hydrogen-bonds with the substrates.

Key-words: (dynamic) kinetic resolution, cycloaddition reaction, enolisable anhydrides, γ-butyrolactone, paraconic acid, diastereoselectivity, enantioselectivity.

Abbreviations

Å	Ångström
Ac	Acetyl
AcOH	Acetic acid
APCI	Atmospheric Pressure Chemical Ionization
Alk	Alkyl
Ar	Aryl
B	Base
BINAP	2,2'-bis(diphénylphosphino)-1,1'-binaphtyle
Boc	*tert*-Butoxycarbonyl
$(Boc)_2O$	Di-*tert*-butyl dicarbonate
cat.	Catalyst
ca.	circa (approximately)
CI	Chemical Ionisation
COD	1,5-Cyclooctadiene
conc.	Concentrated
cond.	Conditions
C or conv.	Conversion
CSP	Chiral Stationary Phase
Cy	Cyclohexyl
DIAD	Diisopropyl azodicarboxylate
DIPT	Diisopropyl tartrate
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
DFT	Density functional theory
dr	Diastereomeric ratio
DKR	Dynamic kinetic resolution
E	Electrophile
EDG	Electron donating group
ee	Enantiomeric excess
e.g.	For example
EI	Electron ionisation
equiv.	Equivalent
ESI	Electrospray ionization
EWG	Electron withdrawing group
FDA	Food and Drug Administration
HSQC	Heteronuclear Single Quantum Coherence Spectroscopy
HMBC	Heteronuclear Multiple Bond Correlation

IPA	*iso*-Propyl Alcohol
IBX	*o*-iodoxybenzoic acid
I_2	Iodine
IUPAC	International Union of Pure and Applied Chemistry
J	Coupling constant
KR	Kinetic resolution
LA	Lewis Acid
L-DOPA	L-3,4-Dihydroxyphenylalanine
MTBE	Methyl-*tert*-butyl ether
MW	Microwave
NHC	*N*-Heterocyclic Carbene
NSAID	Nonsteroidal anti-inflammatory drug
NOE	Nuclear Overhauser Effect
Nu	Nucleophile
n.d.	Not determined
Pd/C	Palladium on activated charcoal
PKR	Parallel kinetic resolution
(q)	Quaternary
(*rac*)	Racemic
RA	Resolving agent
ROESY	Rotating-frame Overhauser SpectroscoPY
R_f	Retardation factor
RT	Room Temperature
SM	Starting material
SOMO	The singly occupied molecular orbital
S	Selectivity factor
T	Temperature
TOF	Time of flight
TOCSY	Total correlated spectroscopy
t	Time
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TMS	Trimethylsilyl
$TMSN_3$	Trimethylsilyl azide
$TMSCHN_2$	Trimethylsilyl diazomethane

Introduction

1. Introduction

1.1 A general introduction: from chirality to asymmetric synthesis

In 1848, the French biologist and chemist, Louis Pasteur, discovered chiral chemistry when he manually separated a mixture of the two isomers of sodium ammonium tartrate salt as crystals.[1]

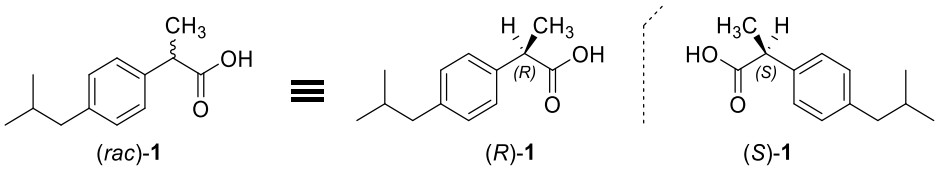
Originally, the word chiral comes from the Greek *cheir*, which means 'handedness'. Chirality is now defined by the IUPAC as follows: 'The geometric property of a rigid object (or spatial arrangement of points or atoms) of being non-superposable on its mirror image; such an object has no symmetry elements of the second kind (a mirror plane, a centre of inversion, a rotation-reflection axis). If the object is superposable on its mirror image the object is described as being achiral.'[2]

These two non-superposable mirror image forms of chiral compounds – called enantiomers – are most commonly formed when four different substituents are present on a carbon atom. However, sometimes, sulfur, phosphorus or nitrogen atoms can also lead to the formation of chiral molecules (*e.g.* the drug omeprazole which contains a chiral sulfur atom).[3] Any molecule bearing two or more chiral centres can exist as a mixture of isomers which are commonly called diastereomers. Equimolar mixtures (50:50) of enantiomers, are referred to as a racemic mixture (or as a racemate) with signs (±)-, (*rac*)- or (D,L)- and do not exhibit any optical activity.

Depending on whether they can rotate a plane-polarised light towards the left (-), or the right (+), these two enantiomers are respectively classified as levorotary or dextrorotary. With the exception of their different optical activity, enantiomers have the same physical properties in a non-chiral environment. However, the interaction of different enantiomers of the same molecule with an enantiomerically pure compound or a biological receptor may lead to completely different results.[4]

For example, in the human body, interactions with biological targets (*e.g.* receptors, enzymes, *etc*) are very often stereoselective.[4] This explains why – although they have the same chemical structure – in a chiral medium, enantiomers of the same molecule (*e.g.* racemic drugs) can exhibit different biological activities such as pharmacology,

metabolism, toxicology, *etc*. Thus, one isomer may exhibit therapeutic activity, while the other may be completely inactive or produce undesired side effects.[5]

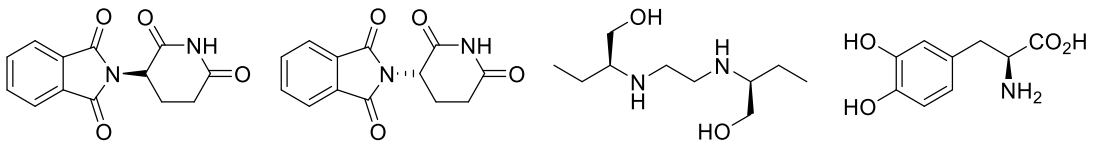


(*rac*)-**1** (*R*)-**1** (*S*)-**1**

Figure 1.1 The two enantiomers of the racemic drug ibuprofen (*rac*)-**1**.

Ibuprofen (**1**) is a nonsteroidal anti-inflammatory drug (NSAID). Both enantiomers (*i.e.* "mirror images") of this drug have an analgesic and anti-inflammatory effect as inhibitors of cyclooxygenase I, however, (*S*)-**1** is about 100 times more potent than (*R*)-**1**. Furthermore, in the body, only the (*R*)-enantiomer, can undergo chiral inversion into the active (*S*)-enantiomer by hepatic enzymes (Figure 1.1).[6]

The synthesis of the racemic version of a drug is often much simpler and less expensive than its enantiopure form, therefore, racemic drugs were often commercialised until the 80s. It was assumed that the inactive enantiomer wouldn't necessarily be toxic to the human body. The principal ingredient of Contergan, a former racemic sedative, thalidomide (**2**), was a prodrug used against morning sickness for pregnant women, which now represents a unfortunately famous example of the dramatic bankruptcy of this hypothesis. The (*R*)-**2** enantiomer was supposed to be inactive but turned out to cause foetal malformations (teratogenic activity). Nevertheless, both forms can be converted into one another *in vivo* and the teratogenic effect would not have been avoided by administering only one form (Figure 1.2).[5b,5c,5e,7]



(*R*)-**2** (*R*)-thalidomide (sleep-inducing) | (*S*)-**2** (*S*)-thalidomide (teratogenic) | **3** (*S*,*S*)-ethambutol (tuberculostatic) | **4** L-Dopa (sleep-inducing)

Figure 1.2 Example of chiral drugs.

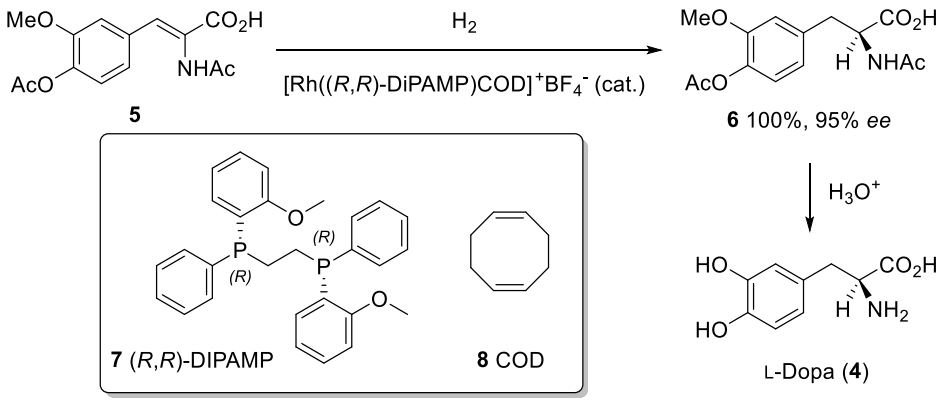
In 1992, as a result of this scandal, the drug was withdrawn from the market and other medical cases highlighting the potential danger of racemic drugs (*e.g.* tuberculostatic ethambutol (**3**), L-Dopa (**4**), *etc*)[8] led the Food and Drug Administration (FDA) to make it mandatory for pharmaceutical companies to test and evaluate separately all

stereoisomers that can be generated by the original drug before approval is given (Figure 1.2).[9]

As a direct consequence, chirality has now become subject of major importance for pharmaceutical development as well as for academic researchers. In 2006, most of the drugs approved by the FDA contained chiral centres and 75% of them were commercialised in their enantiopure form.[10] To meet the growing need to isolate enantiomerically pure compounds, over the past few decades chemists around the world started to focus their attention on the development of a new major field in organic chemistry which is now known as asymmetric synthesis.

Asymmetric synthesis is also called chiral synthesis or enantioselective synthesis and is today considered as one of the major hot topics in organic chemistry. It is defined by the IUPAC as: 'The preferential formation in a chemical reaction of one stereoisomer over another. When the stereoisomers are enantiomers, the phenomenon is called enantioselectivity and is quantitatively expressed by the enantiomer excess; when they are diastereoisomers, it is called diastereoselectivity and is quantitatively expressed by the diastereoisomer excess'.[2]

In simpler terms, asymmetric synthesis can be described as a method for preparation of chemical compounds that favour the formation of one stereoisomer (usually enantiomers) over another.



Scheme 1.1 The Monsanto synthesis of L-Dopa using catalytic asymmetric hydrogenation.[11]

A breakthrough in asymmetric synthesis came in the early sixties. At this time, it wasn't known if asymmetric hydrogenation was feasible or not. William Knowles and co-workers at the Monsanto Company discovered that highly enantioselective

hydrogenation reactions could be promoted by a cationic rhodium-based catalyst. Knowles decided to replace the original achiral triphenylphosphine ligands found in Wilkinson's catalyst with chiral phosphine-based ligands (*e.g.* **7**, Scheme 1.1).[12] He applied this enantioselective metal ion catalysis to the hydrogenation of the prochiral substrate **5**, generating the amino acid **6** (in quantitative yield and in 95% *ee*) which, after acid-catalysed hydrolysis, led to the formation of L-Dopa (**4**, Scheme 1.1). The importance of this type of research was recognised in 2001 when William S. Knowles, Ryōji Noyori and K. Barry Sharpless, pioneers in the field of metal-catalysed enantioselective synthesis, were co-awarded the Nobel Prize in Chemistry.[13]

1.2 Different approaches towards the synthesis of enantiopure compounds

The ability to select one enantiomer/diastereomer over another has become essential for academic researchers and in the pharmaceutical industry during the last few decades.

Nowadays, three main routes have been developed and are commonly used to isolate enantiopure compounds. The techniques employed are based on very different strategies and are described in Figure 1.3.[14]

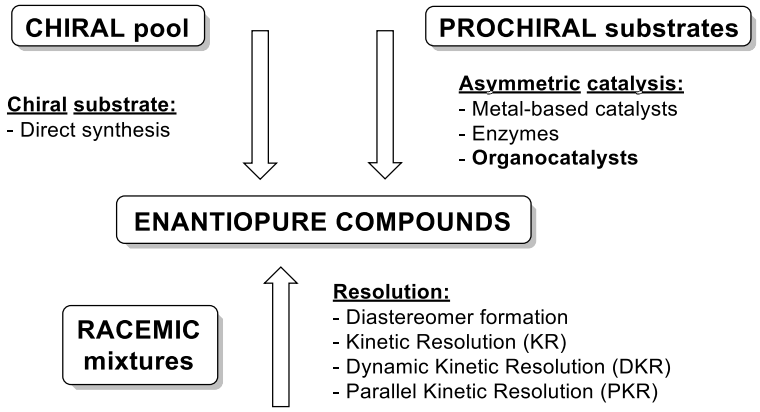
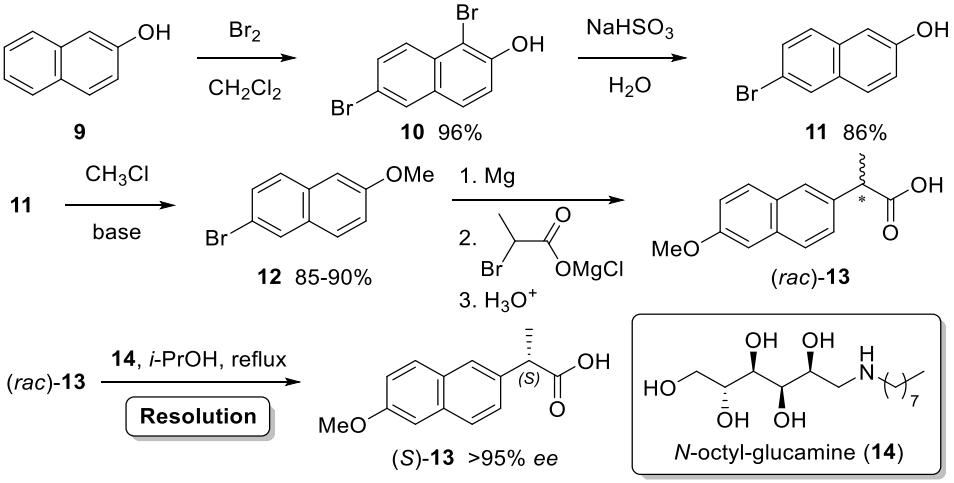


Figure 1.3 Main routes toward the synthesis of enantiomerically pure compounds.

1.2.1 The resolution of racemates

In this strategy, a single enantiomer can be isolated from a racemic mixture. This method relies on the employment of a chiral resolving agent (which must be enantiomerically pure). The enantiomers are derivatised into two diastereomers possessing physically distinct properties and thus separable (*e.g.* by crystallisation, distillation, column chromatography, *etc*).[15] The diastereomer is then transformed back into the desired enantiomer. This method is efficient if this transformation is

quantitative and if the resolving agent can be recycled afterwards (optically pure materials are potentially expensive at large scale synthesis). One of the main drawback of this methodology is that half of the material is often wasted when only one enantiomer is desired and the maximum theoretical yield of the process is only 50%.[15] This method represents the oldest method of resolution processes, nowadays other methods (*e.g.* KR and DKR) are also employed and will be described in Section 1.7.



Scheme 1.2 Resolution of (±)-naproxen developed by the Syntex company.[16]

The synthesis of the racemic naproxen (**13**) that was carried out by the Syntex company until the early 1990s is described on Scheme 1.2 is followed by its resolution process. This was achieved by the separation of the salts formed after reaction of (*rac*)-**13** with the enantiopure amine **14** that allowed the formation of (*S*)-**13** in over 95% *ee*.[16]

1.2.2 Chiral pool-based methods

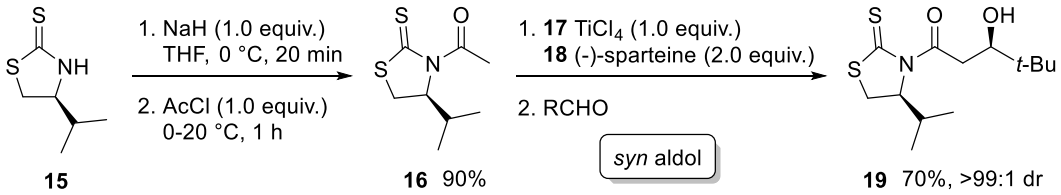
The second method is based on the bioavailability of enantiopure chiral starting materials provided in nature. This is often referred to as the "chiral pool" and relies on syntheses using enantiopure compounds as starting materials or the employment of chiral auxiliaries to induce chirality into the products.

The direct synthesis employing chiral starting materials available from nature (as single enantiomers, such as sugars, amino acids, alkaloids, *etc*) is probably the most straightforward method of obtaining enantiopure molecules.[17] This strategy relies on the conservation of the chiral information (with no racemisation) throughout the subsequent transformations. If the targeted compound has a similar structure to the chiral starting material employed this method is particularly efficient. The major drawback of this

strategy is that the cost of the starting material used can be relatively expensive in large-scale processes.[18]

In 1975, the concept of chiral auxiliaries was introduced for the first time by E. J. Corey when he used chiral 8-phenylmenthol to perform a series of asymmetric Diels-Alder reactions.[19] A typical auxiliary-guided transformation involves at least these three steps: the substrate and the chiral auxiliary are covalently coupled (*e.g.* **15→16**), then the resulting molecule undergoes a diastereoselective transformation followed in a third step by the removal of the auxiliary - under mild conditions causing no racemisation of the desired product.[19,20]

Chiral thiazolidinethiones (such as **15**) are structural variants of Evans's oxazolidinones[21] and have proven to be a highly selective and efficient chiral auxiliary for asymmetric C-C bond formation in aldol reactions.[22] Titanium tetrachloride (**17**) used in combination with the base sparteine (**18**) allows for the formation of a titanium enolate of the *N*-acylated auxiliary **16** which then reacts with aldehydes with excellent diastereocontrol (*e.g.* **16→19**, 99:1 dr, Scheme 1.3).



Scheme 1.3 An asymmetric aldol reaction mediated by a chiral auxiliary.[22]

As the products obtained are diastereomers, their separation is usually easier and they can be isolated using simple methods such as column chromatography or crystallisation. However, the cost of chiral auxiliaries (that need to be used in stochiometric amount and easily introduced/removed) makes this approach rather unattractive for large scale synthesis.

1.2.3 Asymmetric catalysis

In an achiral environment, the energy required to surmount the barrier leading to each enantiomer are the same. However, in a chiral environment, asymmetric synthesis can be achieved if the energies of the respective transition states leading to the two enantiomers can be modified in such a way that one becomes higher than the other, an enantioenriched mixture is obtained as one enantiomer is preferentially formed over the

other. The most common way to obtain asymmetric induction starting from prochiral material relies on the use of enzymes, metal ion- or organic compound-based catalysts.

In all these methods, a catalyst is involved in a number of cycles where it transfers the chiral information to the substrate. In well-designed processes only 0.1-20 mol% of catalyst is required to prepare optically pure molecules and high yield of the desired compounds can be obtained.

1.2.3.1 Enzyme mediated catalysis

In living organisms, almost all of the metabolic reactions occurring are catalysed by enzymes. Enzyme-mediated reactions involve macromolecules that are among the most efficient catalysts available and often exhibit outstanding selectivities in some chemical transformations.[23]

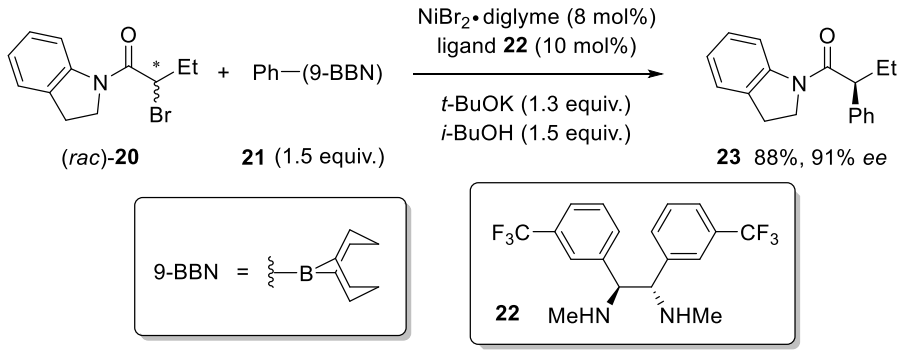
These types of processes are highly appreciated in industry due to their high selectivity as well as their ability to produce very little by-products making them environmentally friendly.[24] However, some major associated drawbacks (*e.g.* price, availability, *etc*) are responsible for the fact that they are still not widely employed. Even though the reactions are often carried out under very mild conditions, their field and scope of application is still very limited.[25]

1.2.3.2 Metal based catalysis

One of the most powerful and thoroughly explored complementary method to enzymatic transformations relies on metal(ion)-based catalysed reactions. In 2010, the importance of this field of catalysis was highlighted when Akira Suzuki, Richard F. Heck and Ei-ichi Negishi were co-awarded the Nobel Prize in Chemistry for their work on the development of new cross-coupling reactions catalysed by palladium catalysts.

Organometallic catalysts or synthetically derived catalysts have allowed the extension of the range of catalysed reactions.[26] Most of the asymmetric organometallic catalysed versions usually rely on the employment of a transition-metal (*e.g.* Ir, Rh, Pd, Ru, *etc*) working in tandem with tuneable enantiomerically pure ligands (*e.g.* **22**, Scheme 1.4).

The nature of either the ligands, the metal-ion or the counterion are virtually infinitely tuneable and allow the catalysis of a wide range of reactions.[26]



Scheme 1.4 Arylation of racemic *α*-bromoamides *via* asymmetric Suzuki Cross-Coupling of activated secondary alkyl electrophiles.[27,28]

In 2008, pioneering work carried out in G. Fu's laboratories allowed for the first example of an asymmetric stereoconvergent Suzuki type cross-coupling reaction that used a chiral nickel catalyst, racemic *α*-bromoamide starting materials (such as (*rac*)-**20**) and a series of phenyl boronic acid derivatives (*e.g.* **21**).[27] Following a single electron transfer pathway, a radical was generated on the electrophile **20**, enabling the catalyst to selectively react with only one face of the achiral intermediate leading to the formation of coupling products, such as **23**, in high yields and excellent enantioselectivities, without racemisation of the products (Scheme 1.4).

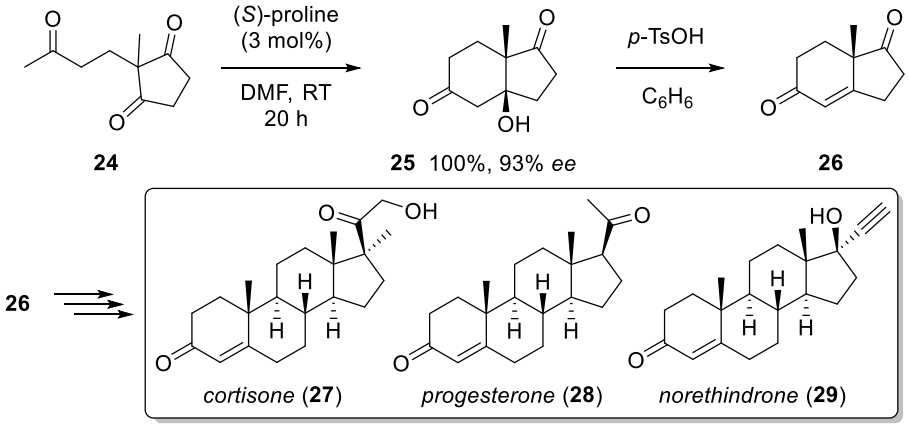
Very low catalyst loadings are frequently employed (typically 0.1-5 mol%). Unfortunately, their efficiency is also directly linked to the reaction conditions and often requires a complete oxygen-free inert atmosphere as well as anhydrous solvents. Furthermore, high prices and potential toxicity due to metal contamination are common drawbacks leading to several limitations in their use for the synthesis of regulated products in the pharmaceutical industry.[29]

1.2.3.3 Organocatalysis

Transition metal catalysts have been employed in asymmetric transformations for decades,[30] but as mentioned above, one of the major drawbacks of this class of catalysts is the high toxicity of some heavy metals (*e.g.* osmium)[31] which may leave toxic traces in the final pharmaceutical products.[30c,32] Therefore, organocatalysis, also named metal-free organic catalysis, has emerged as an appealing type of transformation for

enantioselective synthesis and is the newest subdomain in the enormous field of enantioselective (asymmetric) catalytic synthesis.[33]

Organocatalysts can enhance the rate of a reaction by the addition, in a substoichiometric ratio, of an organic compound.[33a,34] These catalysts are generally synthesised by manipulation of readily available and inexpensive compounds present in nature as a single enantiomer (*e.g.* quinine, proline).[35] In contrast to metal-based catalysis, small organic molecules are not only often less toxic and environmentally friendly but also offer many practical advantages. For example, these compounds are usually readily available,[35] easy to design and synthesise and can often be used under convenient conditions without the need of an inert atmosphere or the use of extra anhydrous solvents.



Scheme 1.5 Proline-catalysed intramolecular asymmetric aldol reaction.[36]

In the early 1970s, the first significant work in organocatalysis was reported by Hajos and Parrish at Hoffmann La Roche when they described the discovery of asymmetric enamine catalysis.[36]

They discovered that the triketone **24** could undergo an intramolecular aldol reaction catalysed by (*S*)-proline, leading to the formation of an intermediate enamine reactive species and subsequent generation of the aldol product **25**, in excellent yield and with excellent enantioselectivity (*ca.* 100%, 93% *ee*). The aldol condensation product **26**, obtained after an acid-catalysed dehydration, represents a very important intermediate in the total synthesis of several steroid compounds (*e.g.* **27**-**29**, Scheme 1.5).[36]

1.3 The emergence of organocatalysis: principal modes of action

Prior to the last two decades, the catalytic enantioselective synthesis of organic molecules was almost exclusively carried out using transition metal complexes or enzymes. A third approach has more recently emerged: asymmetric organocatalysis. Between the 1990s and 2000s, many researchers (*e.g.* Jacobsen, List, Denmark, MacMillan, among others) brought about the development of small organic molecules capable of selectively catalysing organic reactions.[37] Representatives of the main families of organocatalysts which are currently widely used are presented in Figure 1.4.

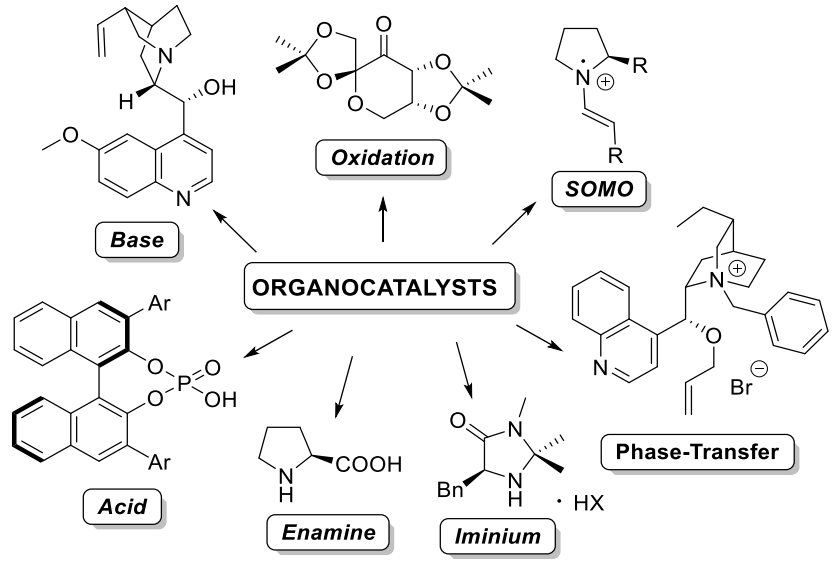


Figure 1.4 The main families of organocatatysts found in the literature.

The range of catalysed reactions involved with these families of catalyst is still growing (*e.g.* Michael additions,[38] Mannich-type reactions,[39] aza-Henry,[40] Baylis-Hillman,[41] Pictet-Spengler,[42] *etc*). These transformations often rely on different modes of activation of the starting materials (*e.g.* iminium- or enamine- catalysis,[43] phase transfer,[44] Brønsted base and nucleophilic catalysis,[44] hydrogen-bonding,[45] *etc*).

In the next two subsections, we aim to briefly introduce and describe two of the main activation modes: the amino catalysis and the hydrogen-bonding which respectively rely on covalent or non-covalent interactions with the substrates.

1.3.1 Amino catalysis: a covalent-based activation mode

Amino catalysis mainly relies on the reversible interaction between a carbonyl group and a chiral amine. Two different fundamental activation modes result from the nature

of the carbonyl employed. Isolated π systems (such as **30**) and conjugated π systems (such as **34**) can react in different fashions (Figure 1.5).

In both cases, the initial mechanism involves the formation of a covalent bond between the substrates and the chiral amine leading to the formation of an iminium ion intermediate such as **32** (or **35**).

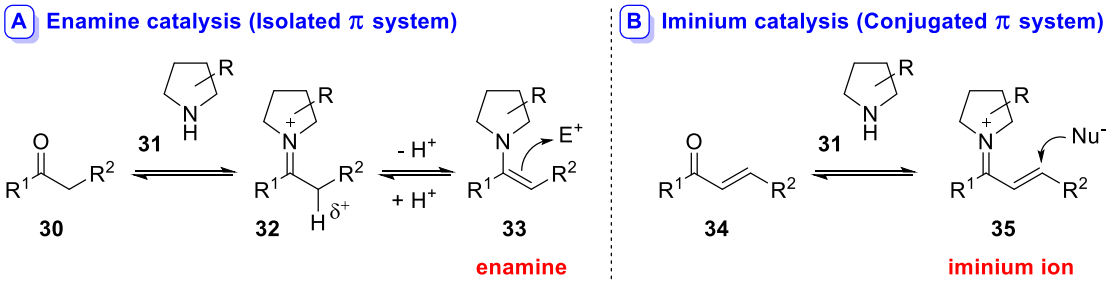
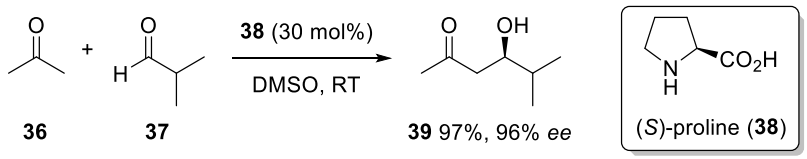


Figure 1.5 Aminocatalysis activation modes in organocatalysis.

In the particular case of isolated π systems, the acidity of the *α*-hydrogen is increased and its rapid deprotonation results in the subsequent formation of an enamine intermediate (*e.g.* **33**). The energy level of the HOMO is increased and the enamine intermediate, which can be considered as an enolate equivalent, is capable of reacting with electrophiles (Figure 1.5, A).

However, for iminium ions such as **35**, the energy level of the LUMO is lowered, which results in the activation of the system towards nucleophilic attack (Figure 1.5, B).

Proline catalysed reactions were reinvestigated for the first time nearly 30 years after the Hajos-Parrish-Eder-Sauer-Wiechert reaction was first published.



Scheme 1.6 Enantioselective intermolecular aldol reaction catalysed by proline.[46]

In 2000, B. List and co-workers reported the first example of an enantioselective intermolecular aldol reaction between acetone (**36**) and a series of aromatic and aliphatic aldehydes (*e.g.* **37**, Scheme 1.6).[46]

The same year, in parallel with List's work on asymmetric aldol reactions, MacMillan reported the first highly enantioselective Diels-Alder reactions between dienes (*e.g.* **40**) with α,β-unsaturated aldehydes (*e.g.* **41**) catalysed by amines such as the imidazolidinone hydrochloride salt **42** (Figure 1.6, A).[47]

Their initial strategy relied on the possibility of emulating the dynamic equilibrium found in Lewis acid catalysed systems (Figure 1.6, B, a) by the formation of an activated iminium ion (Figure 1.6, B, b) capable of engaging subsequently with a diene reaction partner.

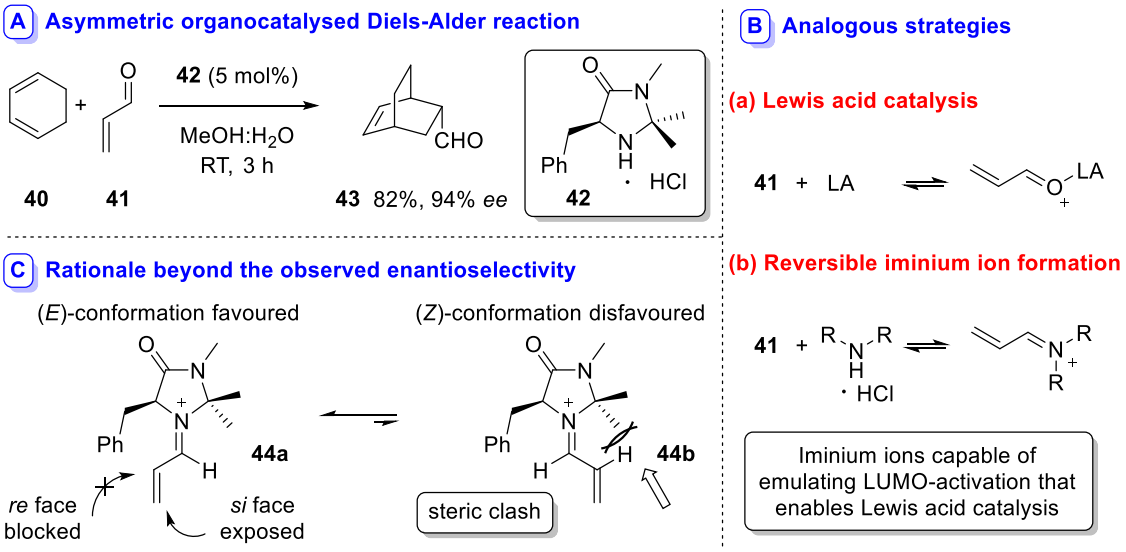


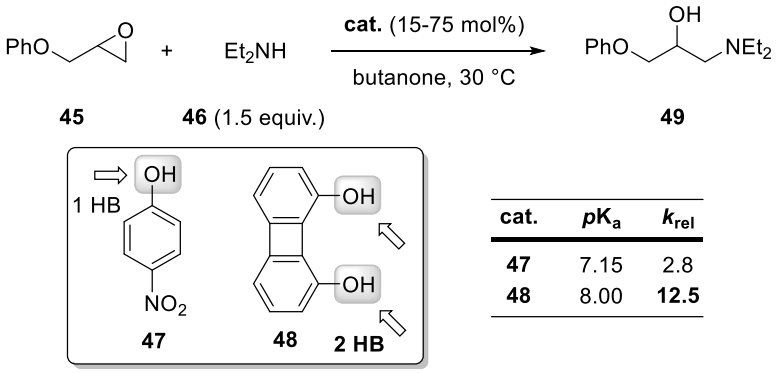
Figure 1.6 The first enantioselective organocatalytic Diels-Alder reaction.

They explained and confirmed computationally the sense of the stereoinduction observed. First, the activated iminium ion intermediate selectively adopts the (*E*)-configuration **44a** in order to avoid interactions between the geminal methyl substituents, and the substrate olefin found in the conformation **44b**. Additionally, the catalyst design, with the bulky benzyl group, shields the *re* face of the dienophile leaving the *si* face exposed to the cycloaddition reaction (Figure 1.6, C).[47]

1.3.2 Hydrogen-bonding: a non-covalent based activation mode

The two studies reported in the previous section represent two of the most important and common activation modes employed in organocatalysis. These two techniques (*i.e.* enamine- and iminium-catalysis) both rely on strong interactions with the substrates as covalent bounds are formed with the catalyst during the reaction. In contrast to this, hydrogen bonding is based on weaker non-covalent interactions with the substrate.

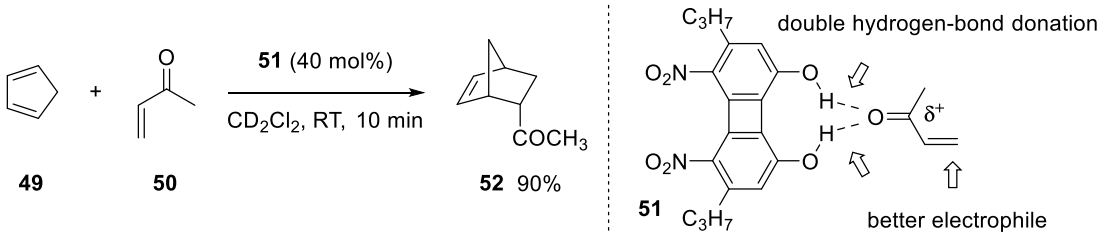
Electrophilic activation of a substrate *via* hydrogen-bonding is now a time-honoured strategy for catalysis of an organic transformation.[45] In most cases, the improvement in terms of reaction rate can be attributed to a lowering of the lowest unoccupied molecular orbital's energy upon coordination with the catalyst, or stabilisation of developing negative charge at a heteroatom in the transition state of addition reactions.[48]



cat.	pK_a	k_{rel}
47	7.15	2.8
48	8.00	**12.5**

Scheme 1.7 First example of epoxide ring-opening catalysed by hydrogen-bonding reported by Hine.[49]

The first examples of rationally-designed catalysis, mediated through hydrogen-bonding appeared in the 1980s. Hine and co-workers have shown that the biphenylenediol **48** could improve the reaction rate of epoxide aminolysis (*i.e.* **45**→**49**). They explained the enhancement observed by a double hydrogen-bond donation to **45**, lowering its LUMO and activating it toward nucleophilic attack from **46** (Scheme 1.7).[49]



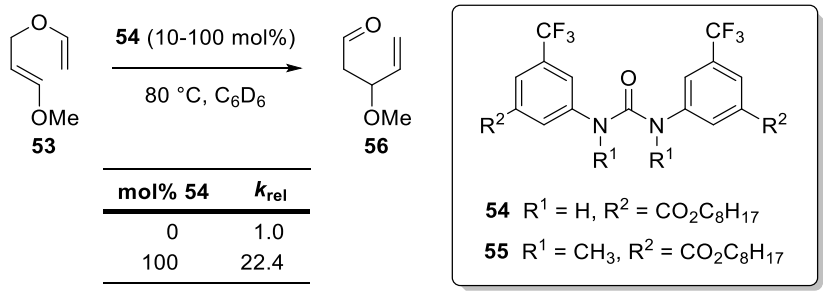
Scheme 1.8 First example of a Diels-Alder reaction catalysed by hydrogen-bonding reported by Kelly.[50]

Later in the 1990s, Kelly and co-workers[50] reported the promotion of Diels-Alder reactions between a series of dienes (*e.g.* **49**) and α,β-unsaturated aldehydes or ketones (*e.g.* **50**). They confirmed that a double hydrogen-bond donation to the dienophile **50** enhances the reaction rate and facilitates the catalysis. Although this organic catalyst (**51**) exhibited poor activity and solubility, it became one of the key milestone catalysts in hydrogen-bond donor organocatalysis (Scheme 1.8).

1.4 Development of a new class of organocatalyst containing a (thio)urea scaffold

1.4.1 The first examples of diaryl urea catalysts promoting general acid-catalysed reaction

The first examples of the utilisation of achiral (thio)ureas as organocatalysts capable of promoting general acid-catalysed reactions appeared around the 1990s. Their use in important named organic reactions represented an unprecedented advancement in the field of organocatalysis. Curran[51] found that sub-stoichiometric amounts of the diarylurea **54** could successfully be employed to accelerate the reaction rate of Claisen rearrangement reactions (*i.e.* **53**→**56**, Scheme 1.9).



Scheme 1.9 Claisen rearrangement mediated by *N*,*N*'-diaryl-urea catalyst.[51]

The original *m*-nitro groups found in the structure reported by Etter[52] were replaced by trifluoromethyl and octyl ester groups at both phenyl rings. These modifications resulted in better solubility in most organic solvents and increased reaction efficiency. The catalytic effect observed was rationalised by a *bis*-hydrogen bonded transition state model. This model proved to be relevant as the replacement of the two hydrogen bond donors with two methyl groups (*i.e.* **55**) failed in catalysing the reaction.[51]

1.4.2 Development of bifunctional (thio)ureas in asymmetric synthesis

Most of the organocatalysts currently employed rely on a dual activation mode that was initially inspired by the observation of enzymatic reactions and were meant to mimic their remarkable abilities to catalyse and control the outcome of some organic reactions.

The general concept of activating both reaction partners simultaneously is presented in Figure 1.7. Such catalysts can activate and subsequently hold both electrophile and nucleophile in a controlled chiral environment and eventually enhance the overall reactivity and stereoselectivity of a given reaction.

The exact definition of this specific type of catalysis is given by the IUPAC as follows: catalysis by a bifunctional chemical species involving a mechanism in which both functional groups are implicated in the rate-controlling step, so that the corresponding catalytic coefficient is larger than that expected for catalysis by chemical species containing only one of these functional groups. The term should not be used to describe the concerted action of two different catalysts (*e.g.* Figure 1.7).[2]

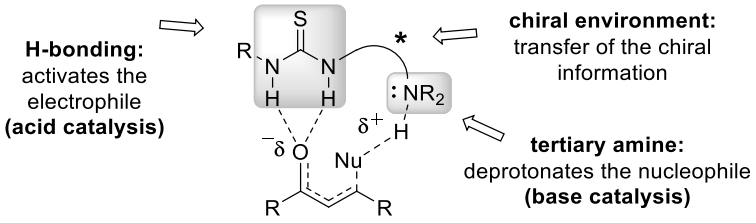
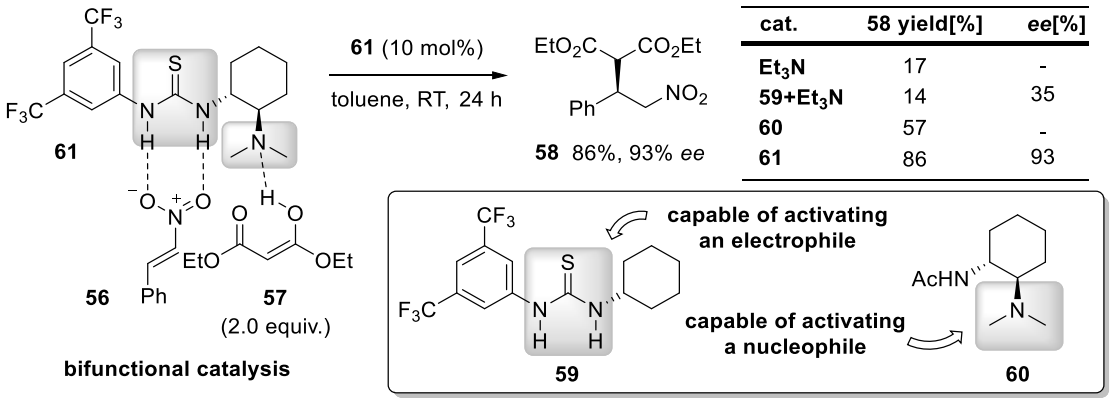


Figure 1.7 Bifunctionality: simultaneous electrophile/nucleophile activation.

To date, most of the bifunctional (thio)urea organocatalysts that have been designed rely on the combination of a tuneable *N*-aryl moiety at one of the nitrogen atoms in partnership with a Lewis base (often a tertiary chiral amine) bound *via* a tether to the other. These *N*-aryl groups often possess bulky or electron-withdrawing elements (*e.g.* CF_3 groups at the *meta*-positions) and are capable of influencing the hydrogen-bonding ability as well as improving the catalyst's rigidity (*e.g.* **61**, Scheme 1.10).



cat.	58 yield[%]	ee[%]
Et_3N	17	-
59+Et_3N	14	35
60	57	-
61	86	93

Scheme 1.10 Addition of diethylmalonate to nitroalkenes.[53]

In 2003, Takemoto and co-workers were the first to report the use of a tertiary amine bifunctional thiourea **61** to catalyse asymmetric Michael additions. They showed that **61** was capable of promoting additions of diethylmalonate esters such as **57** to *β*-nitrostyrenes (*e.g.* **56**) to provide Michael-adducts (**58**) with excellent yield and enantiocontrol (up to 93% *ee*, Scheme 1.10).[53]

The authors found that the synergistic effect of the thiourea moiety and the tertiary basic amine was required for the reaction to occur. Indeed, when the analogues of the catalyst **61**, containing a single active *motif* (*i.e.* **59** or **60**), were employed separately with or without the use of an external base as additive, the reactions didn't proceed smoothly and only poor yields and modest enantioselectivity were observed (Scheme 1.10).

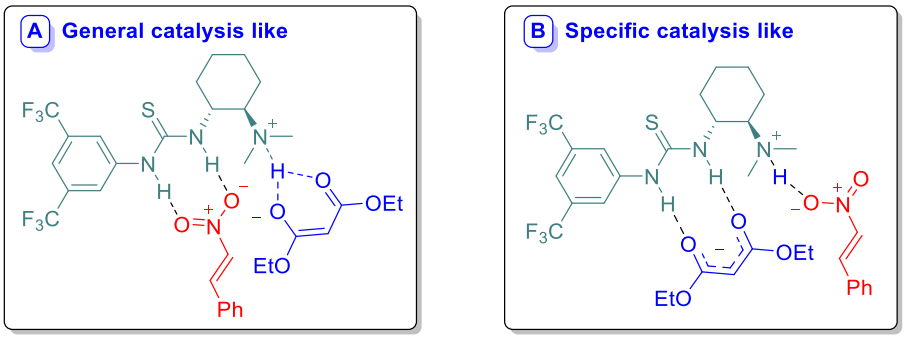


Figure 1.8 Takemoto's bifunctional mode of action of catalyst **61**.[53,54]

The general-catalysis-like mechanism was originally proposed by Takemoto (Figure 1.8, A).[53] In this model, the tertiary amine acts as a Lewis base and deprotonates, in the transition state, the pronucleophile malonate ester enol (*i.e.* **57**) while the thiourea moiety would simultaneously activate the nitro-olefin **56** by hydrogen-bonding (Figure 1.8, A). A specific-catalysis-like model, was later proposed by Soòs and co-workers as an alternative mechanism, lower in energy.[54] In this model, the key intermediate is an ionic complex formed between **61** and the deprotonated malonate ester **57** interacting by multiple hydrogen bonds. The activation of the *β*-nitrostyrene **56** occurs *via* its hydrogen-bonding interaction with the protonated tertiary amine of **61** (Figure 1.8, B).

1.5 The advent of cinchona alkaloids as bifunctional organocatalysts

1.5.1 General introduction

In the 17th century, the cinchona alkaloids were discovered in South America and identified as some of the major constituents of the bark of a tree from the genus cinchona. These natural molecules were popularised and mainly remained famous for their antimalarial properties.[55] However, for the organic chemistry community, this class of alkaloids have become exponentially famous and exploited over the last few decades for their applications in stereoselective synthesis (Figure 1.9).[56]

Over 30 different classes of alkaloids could be extracted from the bark of these cinchona trees. The most abundant members (that could be isolated in synthetically useful quantities) are presented in Figure 1.9. The two pairs of *pseudo*enantiomers, quinine (**61**) + quinidine (**62**) and cinchonidine (**63**) + cinchonine (**64**), are the main constituents of most of the derived cinchona alkaloid based organocatalysts.[57]

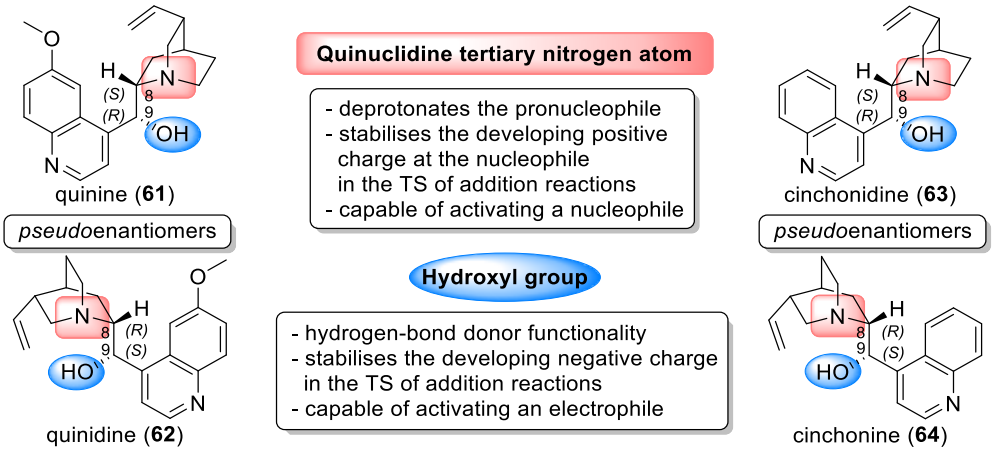
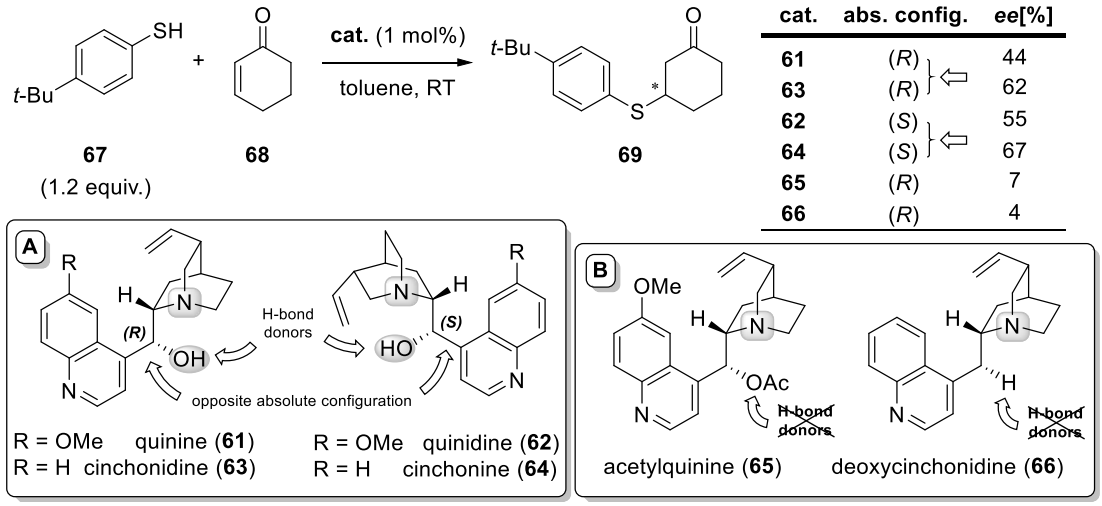


Figure 1.9 The most prominent cinchona alkaloids found in nature and their bifunctional properties.[55,56]

Their structures are now widely considered as some of the most privileged scaffolds for the design of many chiral bifunctional organocatalysts. Indeed, as described in Figure 1.9, any of these alkaloids (*i.e.* **61**-**64**) possess the two key design elements required to simultaneously activate both reactions partners of a pronucleophile-electrophile reaction. The hydrogen-bond donor functionality of the hydroxyl groups alongside the basicity of the tertiary amine quinuclidine can act synergistically to enhance the electrophilic character of the electrophile and activate a pronucleophile (by means of general base catalysis) during the transition state of addition reactions. Furthermore, these alkaloids contain a reasonably rigid chiral structure with 5 chiral centres and many positions that can easily be tuned if the process of interest requires more specific substrate-catalyst interactions (Figure 1.9).[57]

Last but not least, the commercial availability and the globally low cost of both *pseudo*enantiomeric forms of these alkaloids made them extremely attractive for asymmetric synthesis purposes and partially explains their success in the specific field of asymmetric organocatalysis.

In 1981, Wynberg *et al*.[58] reported the use of natural (*i.e.* **61**-**64**), and modified alkaloids (*i.e.* **65**-**66**), in the 1,4-Michael addition reaction of aromatic thiols (such as **67**) to cyclic ketones (such as **68**), producing thioether derivatives **69**, in quantitative yields at only 1 mol% loadings and with up to 67% *ee* (Scheme 1.11).



cat.	abs. config.	ee[%]
61	(*R*)	44
63	(*R*)	62
62	(*S*)	55
64	(*S*)	67
65	(*R*)	7
66	(*R*)	4

Scheme 1.11 First examples of Michael addition catalysed by cinchona alkaloids.[58]

From this study, the authors highlighted two fundamental outcomes:

First, they observed that the Michael adducts **69** could be formed with opposite absolute configurations when opposite absolute stereochemistry of the alkaloids (at the *C*-8/*C*-9 position) were used. Unfortunately, this observation cannot always be generalised to other processes. Indeed, as these alkaloids are not strictly enantiomers of each other, in some reactions the employment of both *pseudo*enantiomers may not always allow one to selectively choose the absolute configuration of the main enantiomer of the reaction product (Scheme 1.11, A).[58]

In addition, they also observed that the employment of the modified alkaloids **65**-**66**, where the hydrogen bonding unit had been removed, failed to promote the reaction with appreciable level of enantioselectivity (up to 7% *ee* only). Therefore, the magnitude of the stereoinduction encountered with the natural alkaloids (*i.e.* **61**-**64**) was attributed to their bifunctional mode of action (Scheme 1.11, B).[58]

1.5.2 Introduction of the (thio)urea moiety

The next step in the development of these catalysts was inspired by the studies of Takemoto and co-workers.[59] The *C*-9 position of the cinchona alkaloids is the most

frequently modified position. For example, synthetic routes make both epimers of these alkaloids accessible by transforming the alcohol into a primary amine *via* Mitsunobu reactions. It was envisaged to exploit the privileged structure of the cinchona alkaloids for their chiral basic moiety and to introduce a double hydrogen-bond *via* a (thio)urea *motif* leading to the structure presented in Figure 1.10.

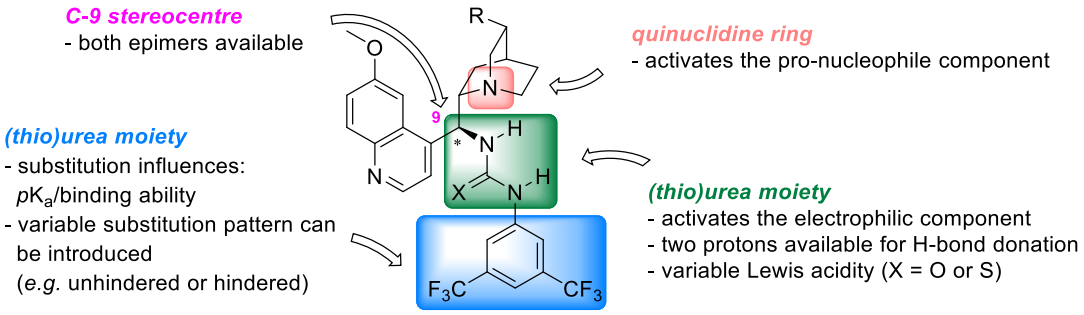


Figure 1.10 Modified cinchona (thio)urea derivatives.[59]

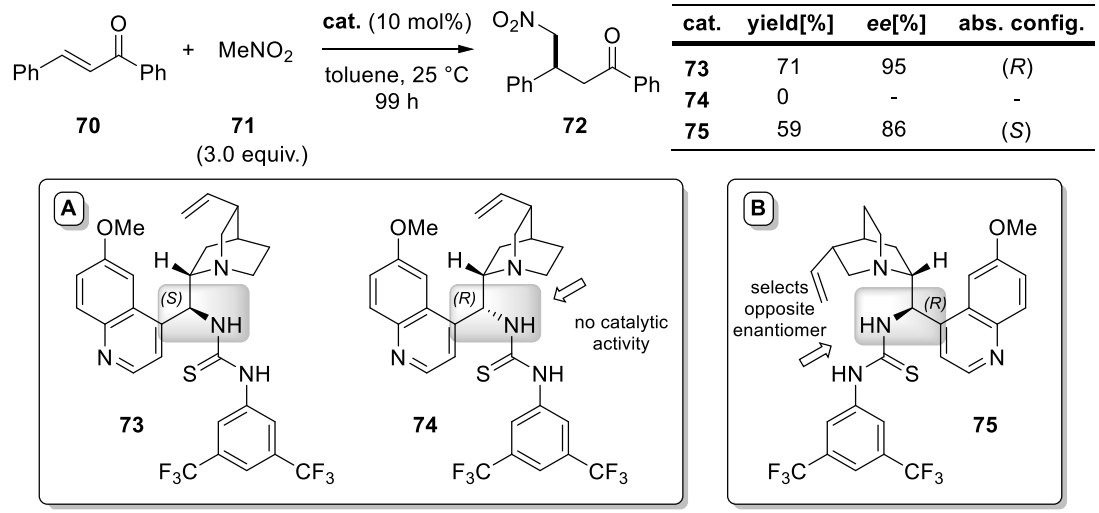
This simple transformation increased both solubility and N-H acidity and, therefore, led to the design of a new class of catalyst possessing improved hydrogen-bond donating abilities. The key design elements of (thio)urea-modified cinchona alkaloids catalysts are presented in Figure 1.10.[59]

In 2005, Soòs *et al.*,[60] reported the asymmetric Michael addition of nitromethane (**71**) to a series of (*E*)-chalcones (*e.g.* **70**) catalysed by different analogues of thiourea-substituted quinine/quinidine-derived cinchona alkaloid catalysts (**73**-**75**, Scheme 1.12).

The quinine scaffold (*i.e.* **61**), allowed for the generation of both catalysts **73** and **74** with inversion and retention of the configuration at the *C*-9 position respectively. The use of quinidine (**62**) as starting material allowed the generation of the catalyst **75**. The unexpected results they obtained are listed in the table of Scheme 1.12.

Use of catalyst **73** afforded the adduct **72** with good yield and excellent enantioselectivity (*ca.* 95% *ee*). Surprisingly, the thiourea **74** derived from the natural stereochemistry of quinine (*i.e.* the *C*-9 epimer of **73**) exhibited no catalytic activity. This result highlighted that the catalytic mode of action of this new class of catalysts most certainly operates *via* a bifunctional mode of action. Indeed, these experiments demonstrated that the catalyst efficiency strongly relies on the relative stereochemistry at *C*-8 and *C*-9 and that the relationship between the orientation of the hydrogen bonds and the tertiary quinuclidine base is fundamental (Scheme 1.12, A).[60]

Interestingly, the *pseudo*enantiomer of **73** (*i.e.* **75**) could also promote the formation of **72**, with inversion of its absolute configuration (*i.e.* (*R*)→(*S*)), also with a high level of enantiocontrol (86% *ee*, Scheme 1.12, B).[60]



cat.	yield[%]	*ee*[%]	abs. config.
73	71	95	(*R*)
74	0	-	-
75	59	86	(*S*)

Scheme 1.12 Thiourea organocatalysts **73-75** as promoters of enantioselective Michael addition reaction of nitromethane (**71**) to chalcone **70**.[60]

1.5.3 Introduction of the squaramide moiety

Since the pioneering work of Rawal, in 2008, the squaramides derived from cinchona alkaloids have emerged as a new powerful hydrogen-bonding class of organocatalyst and have quickly been established as effective alternatives to the complementary successful duo urea/thiourea.[61] Before describing an example of a reaction catalysed by a squaramide based catalyst, it is interesting to highlight some of their properties and structural differences to their analogous (thio)ureas. Indeed, their tremendous success undoubtedly relies on their rather unusual structure and particular physical properties, making them very efficient hydrogen-bond donating moieties (Figure 1.11).

Regardless of their structural properties, an additional advantage of this class of catalyst is their generally facile and straightforward mode of synthesis, making them easy to design and tune. The synthesis starts from the commercially available squaric acid (**76**) to form the reactive intermediate dimethyl squarate (**77**) in excellent yield. Subsequently, a double substitution pathway with two primary amines provides the bifunctional squaramide catalysts in only two steps (*i.e.* **76→78**). In most cases the catalyst precipitates out of the solution affording the pure product without any further purification required (Figure 1.11, A).[61]

The squaramides are capable of forming up to four hydrogen-bonds with substrates (Figure 1.11, B). In the same fashion, as is the case with the (thio)ureas, the presence of the two N-H groups provides two hydrogen-bond donors, however the presence of two carbonyls on the four-membered ring system affords two extra sources of hydrogen-bond acceptors. Squaramides and (thio)ureas also differ by the angle and distance between the two N-H groups. The distance between them is approximately one third larger in a squaramide (2.71 Å) compared with a (thio)urea (2.13 Å).[62] Furthermore, the structural scaffold of the cyclobutanedione ring tends to induce a more convergent orientation of the hydrogen bonds which influences the hydrogen-bonding abilities in a different way when compared with their (thio)urea analogues (Figure 1.11, B).[62]

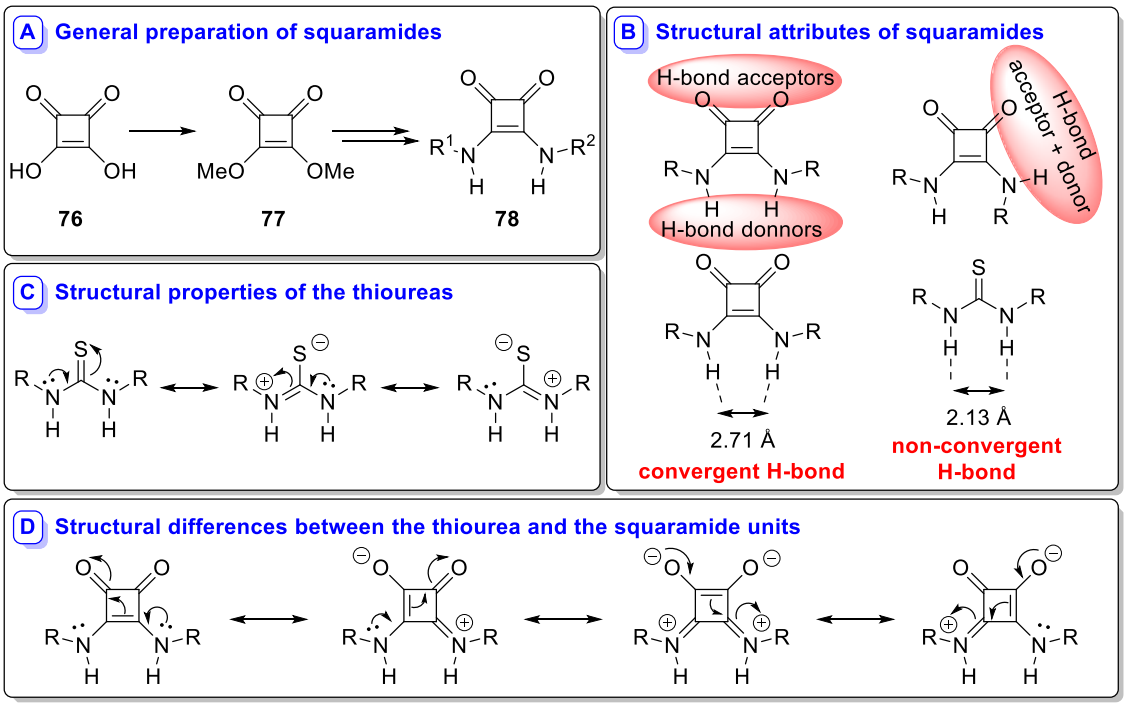
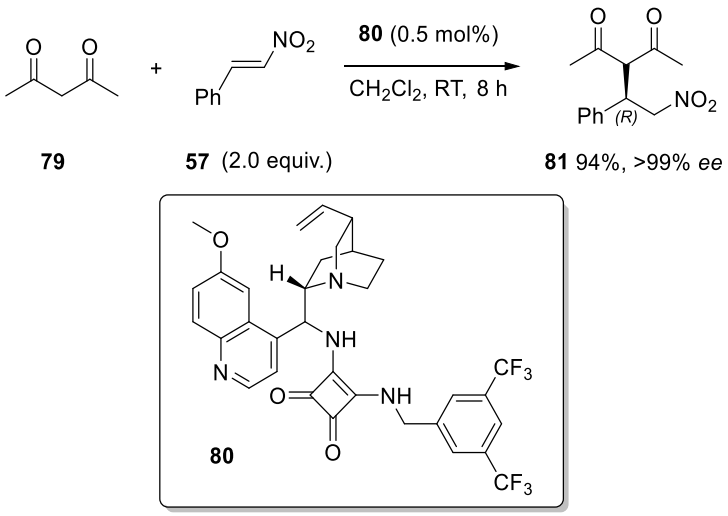


Figure 1.11 Physical properties of squaramides. Structural differences between the thiourea and the squaramide hydrogen-bond units.[61,62]

The lone pair on the nitrogen atoms is delocalised in both (thio)ureas and squaramides, thereby the rotation around the C-N bonds is restricted and conformational changes are more limited. However, for squaramides, the possibility to further delocalise the electron density, through the cyclobutenedione system, leads to two formally charged nitrogen atoms capable of forming significantly stronger hydrogen bonds. Moreover, the double bond character of the carbon-nitrogen bonds enhances the global structure rigidity and further limits the conformational changes of the catalysts (Figure 1.11, C and D).[61]

For the reasons mentioned above, Rawal and co-workers[61] decided to substitute the (thio)urea moiety of the previously successful modified alkaloids with a squaramide *motif* (*e.g.* catalyst **80**, Scheme 1.13).

The Michael addition of dicarbonyl compounds (such as **79**) to nitroolefins (such as **57**) was used as the model reaction to evaluate the catalytic abilities of the catalyst **80**. This structural modification proved to be extremely fruitful, as the Michael adducts (*e.g.* **81**) were obtained in excellent yields and with an outstanding level of enantiocontrol (up to >99% *ee*, Scheme 1.13).[61]



Scheme 1.13 Organocatalytic Michael additions revisited with the squaramide catalyst **80** as promoters of the reaction.[61]

Following this breakthrough in the design of new *motifs* for hydrogen bond donation, the insertion of squaramide units into the core of cinchona alkaloids (or other tertiary chiral amines) became more systematic and organocatalysts containing squaramide and (thio)urea analogues are now often co-evaluated during the catalyst screening of a new process development. Further examples illustrating the success encountered by this class of catalysts will be described and discussed in Section 1.6.

1.6 Formal cycloadditions involving anhydrides

1.6.1 Historical overview

The reactivity of anhydrides is generally dominated by their electrophilic nature.[63] The electrophilicity of the anhydrides units can be positioned between the less reactive ester electrophiles and the more reactive acid chlorides (Figure 1.12).

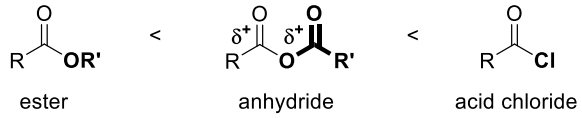
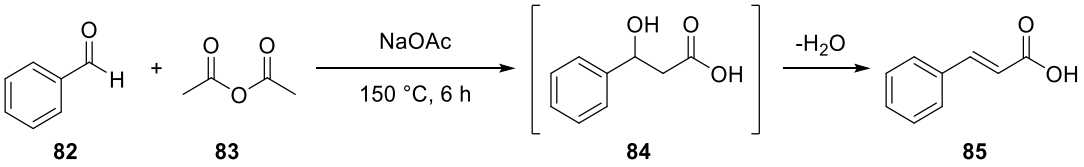


Figure 1.12 Increasing electrophilicity of carbonyl groups.

Although their reactivity is mostly dominated by their electrophilic properties, a subclass of anhydrides – enolisable anhydrides – are capable of reacting as *C*-nucleophiles in addition reactions, with a range of electrophiles such as: alkynes, alkenes, ketones/aldehydes and imines.[64]

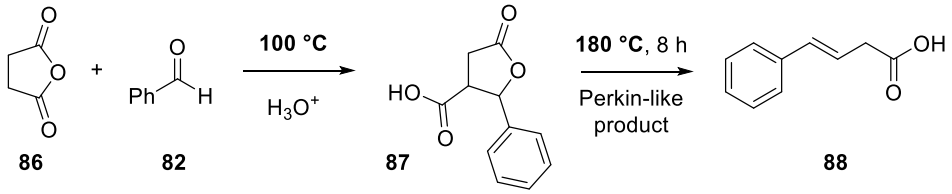
An early example of this unusual behaviour is found in the Perkin reaction.[65] In 1868, Perkin reported the first reaction between enolisable aliphatic anhydrides and aromatic aldehydes. In the presence of a weak base (*e.g.* NaOAc), anhydride **83** was able to add to aldehyde **82**, leading to intermediate **84** which was able to condense upon heating at 150 °C, to form α,β-unsaturated acid products such as **85** (Scheme 1.14).



Scheme 1.14 Perkin reaction between aromatic aldehydes and enolisable aliphatic anhydrides.

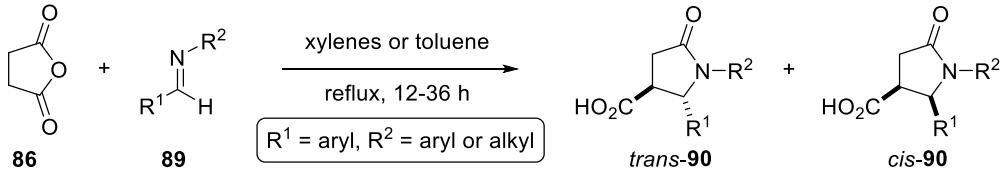
Years later, Fittig and co-workers, upon repetition of Perkin's experiments, further rationalised and clarified the mechanism of this unusual process.[66] When the reaction was conducted at a lower temperature (*i.e.* 100 °C), the major products isolated were *γ*-butyrolactones such as **87**. The overall reactivity was explained by the formation of an alkoxide intermediate, capable of attacking the second carbonyl *motif* of **86**, in an aldol-like addition process, leading to a global intramolecular lactonisation (Scheme 1.15).

The Perkin-like product **88** could also be generated upon decarboxylation of **87**, when the molecule was heated at temperatures above 150 °C (Scheme 1.15).



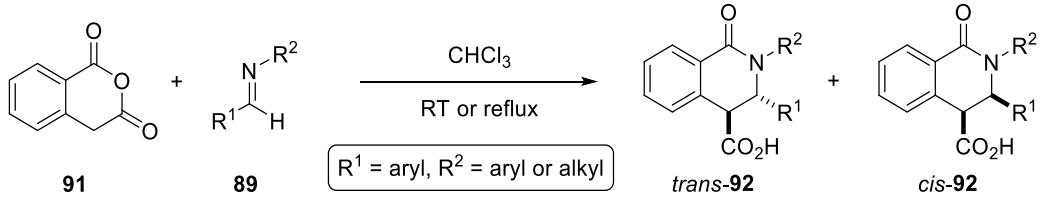
Scheme 1.15 Fittig's experiments using succinic anhydride (**86**).[66]

In 1969, Castagnoli observed for the first time that *N*-alkyl or *N*-aryl imines (*i.e.* **89**) could also react, under thermal conditions, with succinic anhydride (**86**) to produce a diastereomeric mixture of γ-lactams such as **90**. These γ-lactams were produced with good diastereoselectivity in favour of the *trans*-diastereomer (Scheme 1.16).[67]



Scheme 1.16 The first example of imines reacting with succinic anhydride (**86**) reported by Castagnoli.[67]

Castagnoli and co-workers, further expanded the scope of these cycloaddition reactions with glutaric anhydride, reacting it with a series of different imines.[68] In 1977, the substrate scope of the anhydride component was again further broadened when Cushman *et al.*[69] and Haimova[70] reported, in two separate communications, the use of a new enolisable anhydride: homophthalic anhydride (**91**), which was capable, at room temperature, of reacting with imines **89**, producing structural analogues to adducts **90** as a diastereomeric mixture of racemic lactams (**92**, Scheme 1.17).



Scheme 1.17 Reaction of imines with homophthalic anhydride (**91**) reported by Cushman and Haimova.[69,70]

Since Castagnoli's first discovery in 1969, the cycloaddition reaction involving enolisable cyclic anhydrides and imines has been widely studied.

In the next section, the aim is to discuss in detail the formal cycloaddition involving a series of enolisable cyclic anhydrides reacting with aldehydes as the electrophilic component. Indeed, the research work later presented in this thesis is related to in this particular type of transformation. However, for context, other examples focusing on the stereoselective variant of this reaction and processes and involving other types of electrophiles such as Michael acceptors,[71] nitroalkenes,[72] imines[73] or ketones[74] will also be briefly described.

1.6.2 Cycloaddition reactions of homophthalic anhydride with aldehydes

The formal cycloaddition involving cyclic anhydrides as *C*-nucleophiles, with aldehydes as electrophiles, producing lactone products, has received considerably less attention compared to the lactam-forming variant using imines as electrophiles. However, the general mechanism of the reaction mediated by general acid/base catalysis (or alternatively by a series of organocatalysts derived from the cinchona alkaloids) as well as the stereochemical outcome of the reaction has recently become clearer.[63,71,74,75,76,83,84,88]

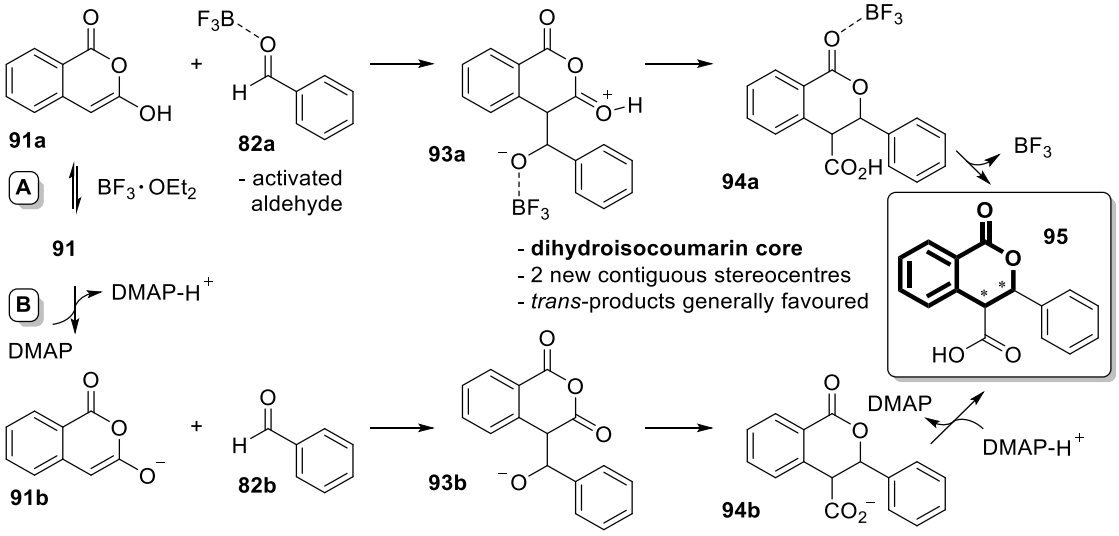
In this section, a selection of the key discoveries, related to these cycloaddition reactions involving anhydrides and aldehydes, from their discovery back in the late 19th century, up to the latest examples published in the literature will be summarised.

1.6.2.1 History and the achiral version of this transformation

In 1999, Gesquiere *et al.*[64,75] demonstrated that homophthalic anhydride (**91**) could react in the presence of a Lewis acid with aromatic aldehydes or ketones, furnishing cycloadduct products such as **95** (Scheme 1.18, A).

The first step of the proposed mechanism involves enolisation of homophthalic anhydride producing its enol form (*i.e.* **91**→**91a**, Scheme 1.18, A). It is thought that the Lewis acid employed is responsible for the activation of the aldehyde component through coordination, increasing its electrophilicity. The nucleophilic enol **91a** is now free to attack the activated aldehyde **82a**, leading to the tetrahedral alkoxide intermediate **93a**, which upon intramolecular lactonisation forms the new lactone product **95** (Scheme 1.18, A).

In 2004, Palamareva *et al.*,[76] demonstrated that stoichiometric amounts of a base (such as DMAP) could also, in a similar fashion, promote the reaction and allow for the formation of dihydroisocoumarin derivatives (**95**). The base-mediated mechanism is similar to the acid-mediated mechanism, in most respects, with the following two exceptions. Firstly, the base serves to deprotonate **91**, resulting in the formation of its enolate form instead (*i.e.* **91→91b**, Scheme 1.18, B). Then, under base catalysis, a drawback is reported by the authors. In some examples, the major product of the reaction is a Perkin-like side product (*i.e.* structural isomers to **85**, Scheme 1.14), which was previously undetected under acidic conditions but the formation of which could be supressed upon cooling the reactions to lower temperatures (Scheme 1.18, B).



Scheme 1.18 Proposed mechanism of the cycloaddition reaction involving homophthalic anhydride (**91**) with aromatic aldehydes catalysed by stoichiometric amounts of Lewis acid or base.[75,76]

Despite the potential applications and importance of the lactones synthesised in formal cycloadditions of aldehydes with anhydrides, the methodology has received considerably less attention than the variant involving the formation of lactams products. Perhaps, an element of explanation can be found in the substrate scope of the methodology. Indeed, only aromatic aldehydes and succinic or homophthalic anhydrides were employed in the vast majority of the early examples that could be found through the literature, making the scope considerably restricted, and limiting the potential applications.

1.6.2.2 The relevance of the dihydroisocoumarin unit in natural products

The dihydroisocoumarin structural unit (*i.e.* **96**) is a key element contained in a broad range of natural products (and biologically active compounds) possessing remarkable properties such as: antimicrobial,[77] antifungal,[78] antimalarial[79] and anti-inflammatory.[80]

Some examples highlighting the importance of representative members of this class of compounds are depicted in Figure 1.13.

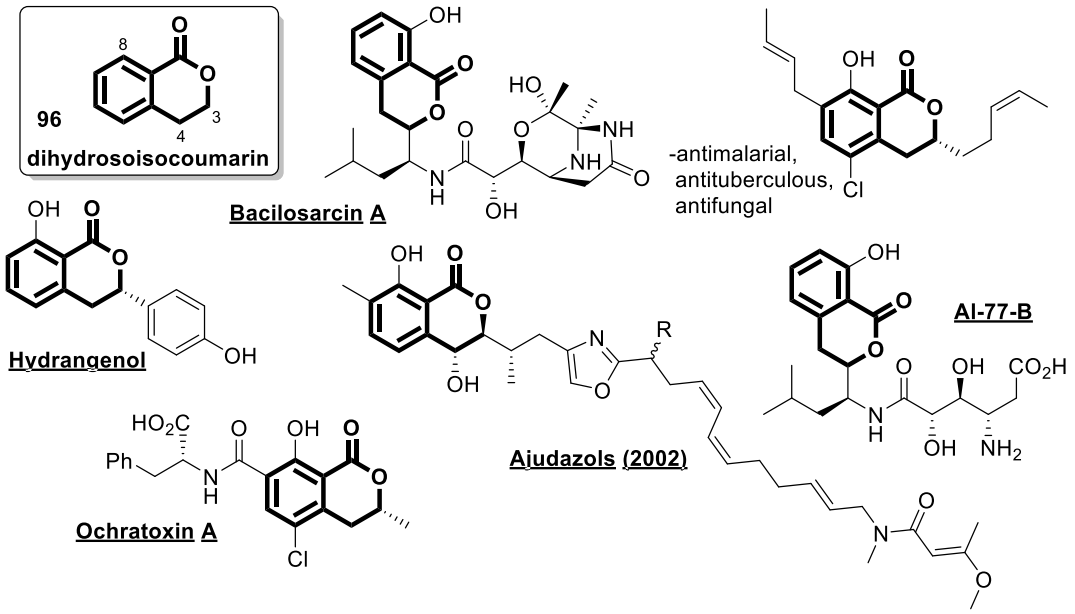


Figure 1.13 A selection of natural products or biologically active compounds containing the dihydroisocoumarin core unit.[77,78,79,80]

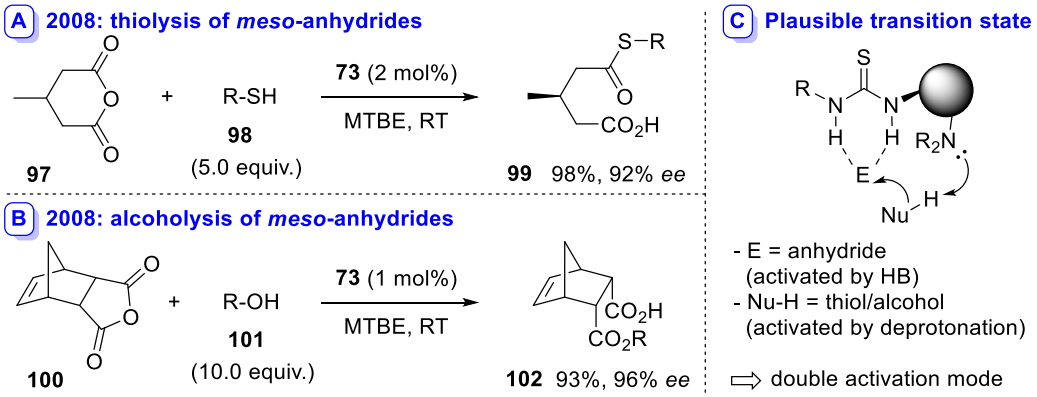
A common substitution patterns involves, a hydroxy substitution at *C*-8 and an alkyl/aryl moiety at *C*-3. This specific pattern almost always results in the presence of at least one (or more) stereogenic carbon centres on the scaffold of these compounds.

1.6.2.3 The first catalytic enantioselective cycloaddition involving enolisable anhydrides

As described in Section 1.6.2.1, the formation of racemic dihydroisocoumarin derivatives, promoted by either a Lewis acid or a base, has been known for over a decade (Figure 1.14, A and B). However, until 2012, no catalytic or asymmetric variant of this reaction had been reported in the literature. This is despite both the synthetic potential utility of these functionalised molecules and their intrinsic broad variety of biological properties (Figure 1.13).

In 2008, our group (among others), reported two highly enantioselective processes: the ring opening alcoholysis[81]/thiolysis[82] of *meso*-anhydrides (such as **97** or **100**) promoted by the bifunctional thiourea catalyst **73**. In the presence of thiourea **73**, nucleophiles **98** or **101** were enantioselectivitely added to a variety of anhydrides, producing optically active mono-thioesters (**99**) or mono-esters (**102**), in high yield and excellent selectivities (up to 96% *ee*, Scheme 1.19, A and B).

These two processes both relied on the bifunctional mode of action of the catalyst; which is capable of activating both reaction partners in the transition state. A plausible transition state involves deprotonation of the alcohol/thiol nucleophiles with simultaneous activation of the anhydride through hydrogen-bond donation (Scheme 1.19, C).



Scheme 1.19 Enantioselective alcoholysis and thiolysis of *meso*-substituted cyclic anhydrides promoted by a bifunctional thiourea catalyst.[81,82]

In a similar fashion, it was postulated that in the absence of a nucleophile in the system (such as **98** or **101**), a bifunctional organocatalyst could also be capable of simultaneously activating both an aldehyde (through hydrogen bond donation) and an anhydride pronucleophile by means of general base catalysis (*e.g.* by deprotonation of the reactive enol of the anhydride in the transition state). Both partners would also react in a controlled chiral environment thereby influencing the stereochemical outcome of the transformation (see Figure 1.14, C).

Based on a similar idea, our group rationalised a model (Figure 1.14, C) for the development of a catalytic asymmetric variant of the two racemic processes depicted in Figure 1.14 A-B.

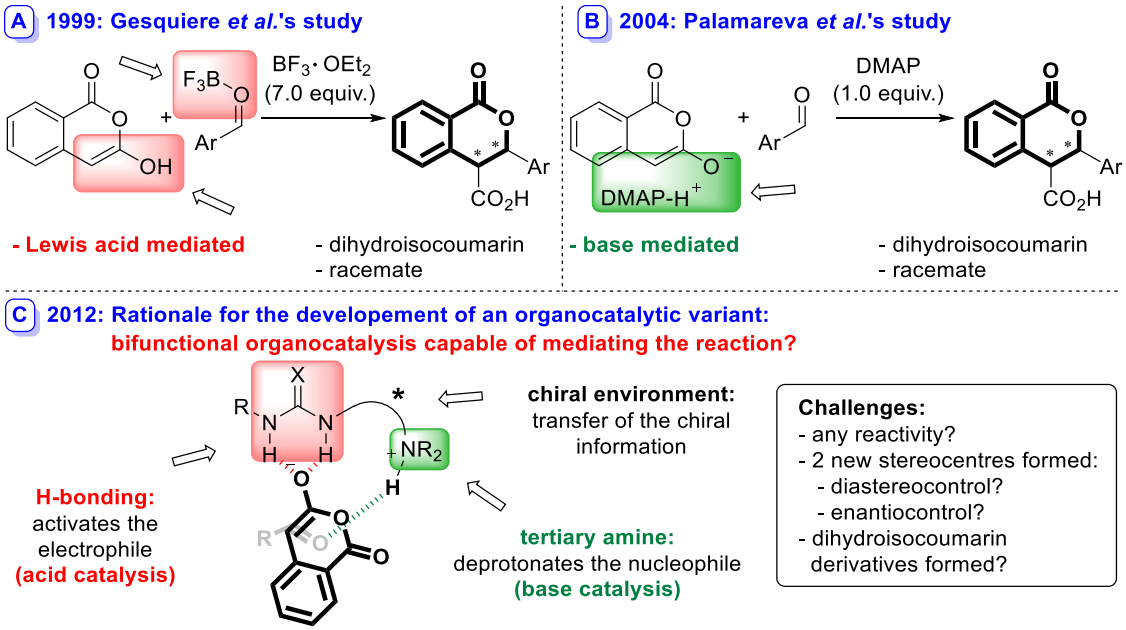


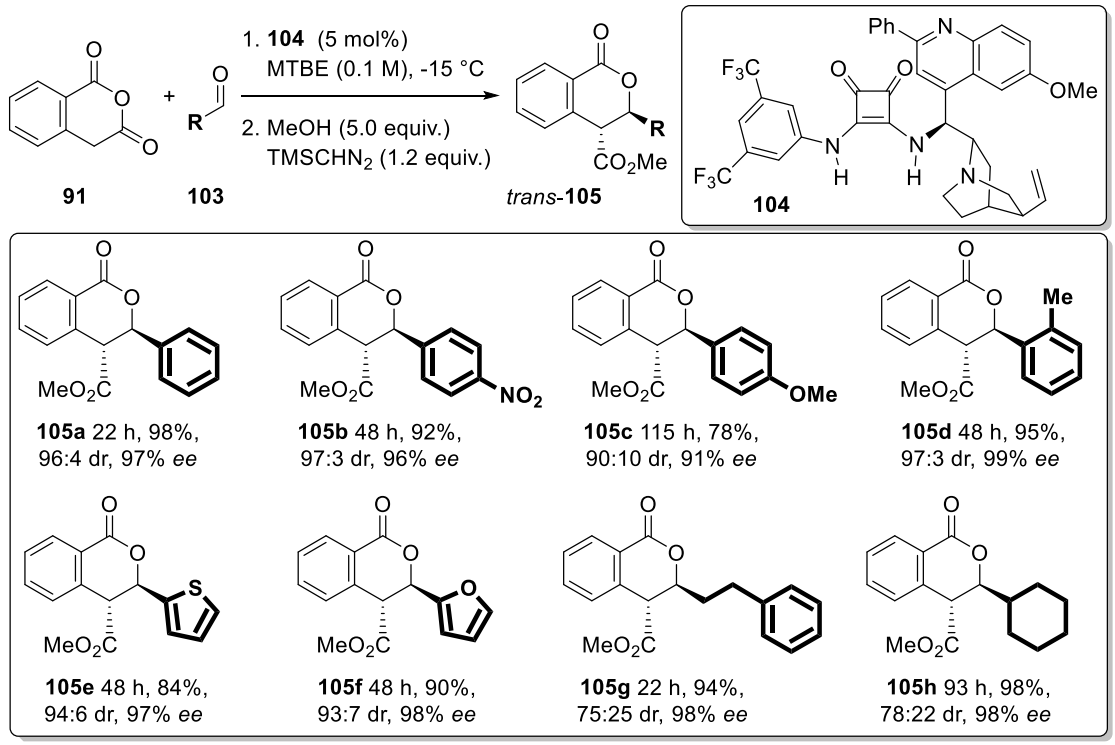
Figure 1.14 Rationale for the design of an organocatalytic cycloaddition involving homophthalic anhydride with aldehydes as electrophiles.

In 2012 our group reported the first catalytic asymmetric cycloaddition reaction between homophthalic anhydride (**91**), unusually behaving as a nucleophile, with a series of aldehydes **103** as electrophiles (Scheme 1.20).[83]

In the presence of a small amount of the novel cinchona-based squaramide organocatalyst **104**, under mild conditions, the enolisable anhydride **91** was added to a range of aromatic and aliphatic aldehydes to furnish dihydroisocoumarin (**105a-h**) derivatives in excellent yields (up to 98%, Scheme 1.20).

This methodology proved to be extremely efficient. Homophthalic anhydride (**91**) was reacted in a 1:1 ratio with various types of aldehydes bearing: electron neutral (*i.e.* **105a**), electron deficient or rich (*i.e.* **105b-c**), hindered (*i.e.* **105d**), heterocyclic aromatic (*i.e.* **105e-f**) or aliphatic (*i.e.* **105g-h**) groups, at low catalyst loadings, always furnishing the products with excellent to outstanding levels of diastereo- and enantio-selectivities (up to 96:4 dr, 97% *ee*, Scheme 1.20).

A few years later, in 2017, the group embarked on a DFT mechanistic study in order to clarify the mode of action and the plausible binding mode of the squaramide catalyst **104**.[84]



Scheme 1.20 The first catalytic enantioselective cycloaddition reaction involving homophthalic anhydride (pronucleophile) with aldehyde electrophiles.[83]

1.6.3 Cycloaddition reactions of phenyl succinic anhydride with aldehydes

The scope of the reaction described in the previous section proved to be quite broad with respect to the aldehyde. However, the substrate scope with respect to the anhydride component was restricted to substituted homophthalic anhydride derivatives, which considerably restrict the further potential applications of this transformation. Therefore, our research group became interested in the identification of different classes of anhydrides, presenting new structures that are capable of behaving as pronucleophiles (*i.e.* new enolisable anhydrides).

Since the 19th century, succinic anhydride (**86**) has been known to undergo formal cycloaddition reactions with aromatic aldehydes. The reaction conditions are often harsh: high temperatures or stoichiometric amounts of strong bases are usually required for the enolisation and initiation of the reaction.[85]

As this reaction, employing **86**, was reported in the literature only under achiral reaction conditions, **86** was chosen as a starting material for the cycloaddition process mediated by modified cinchona based organocatalysts. This choice was also influenced by the structure of the targeted products, as the reaction could potentially give access, in one-

pot, to γ-butyrolactone derivatives, a structural unit present in the core of many natural products.[86]

In particular, this reaction would generate a carboxylic acid group on the lactone core which corresponds to the general structure of a group of compounds referred to as paraconic acids (*i.e.* **106**, a subclass of γ-lactones). Many of the members of this class also possess interesting biological properties such as antibiotic, anti-tumour and anti-fungal activity.[87] Some examples highlighting the importance of certain members (*i.e.* **107**-**110**) of this class of compounds are depicted in Figure 1.15.

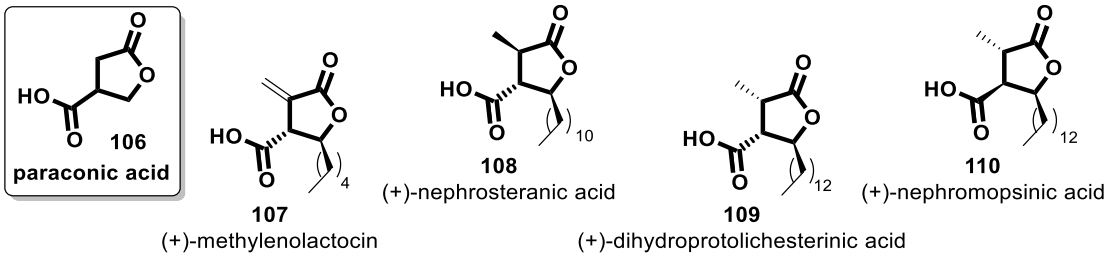
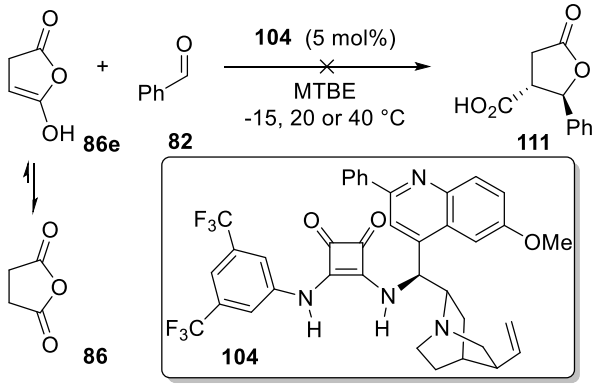


Figure 1.15 A selection of biologically active paraconic acid derivatives.[87]

Under the optimised conditions previously reported for the catalytic formal cycloaddition involving homophthalic anhydride (**91**) with aldehydes,[88] the preliminary experiment with succinic anhydride (**86**) and benzaldehyde (**82**) was a failure. In the presence of 5 mol% of **104**, **86** proved to be completely unreactive towards nucleophilic addition to **82** and the targeted cycloaddition product **111** could not be detected. Elevation of the temperature also failed to afford the product. Therefore, it was speculated that the concentration, in solution, of the enol form of the anhydride **86e**, which is capable of participating in the catalytic process, was too low (Scheme 1.21).



Scheme 1.21 First attempt at the one-pot synthesis of the paraconic acid derivative **111**.[88]

Therefore, it was rationalised that the installation of an electron withdrawing group in the scaffold of the succinic anhydride (such as an aromatic substituent) would facilitate the process by decreasing the pK_a of the acidic α-hydrogen atom while stabilising the newly formed enolate after deprotonation by the catalyst, through conjugation with the aromatic ring, therefore leading to a more substantial concentration of the reactive enol(ate) form (*i.e.* **112a→112b**, Figure 1.16).

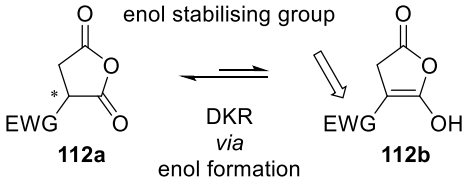
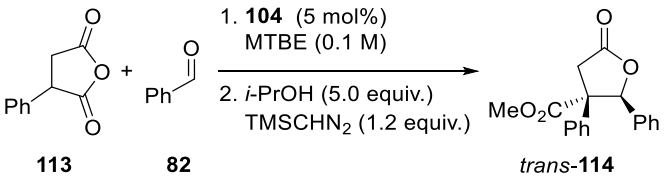


Figure 1.16 Rationale for the installation of an EWG in the anhydride scaffold.

To test this hypothesis, it was decided to evaluate the commercially available phenyl succinic anhydride (**113**). Under identical reaction conditions, at ambient temperature, lactone **114** could be formed in 44% yield, with good diastereocontrol and moderate enantioselectivity (90:10 dr, 68% *ee*). Upon cooling (*i.e.* to -15 or -30 °C), **114** could now be formed with improved diastereo- and enantioselectivity (up to >99:1 dr, 83% *ee*). Unfortunately, the yield was not synthetically useful (*ca.* 17-34%) under these conditions (Scheme 1.22).



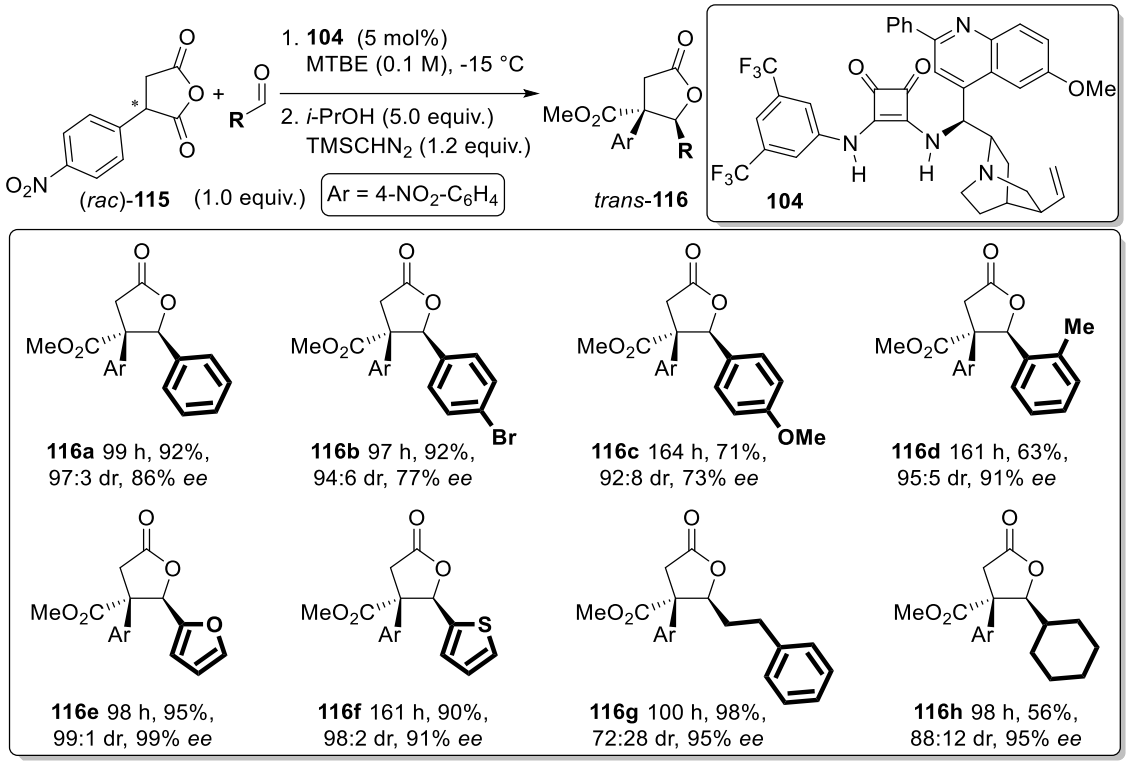
T[°C]	t[h]	yield[%]	dr (*trans*:*cis*)	ee[%]
RT	24	44	90:10	68
-15	110	34	97:3	83
-30	110	17	>99:1	83

Scheme 1.22 Evaluation of the phenylsuccinic anhydride (**113**).[88]

The replacement of the phenyl moiety with a 4-NO_2-phenyl unit resulted in an expected faster and also, gratifyingly, more efficient reaction to form the corresponding lactone **116a** (obtained in 92% yield, 97:3 dr, 86% *ee*, Scheme 1.23). Therefore, the 4-NO_2-phenyl succinic anhydride (**115**) was chosen as the optimal pronucleophile to evaluate the scope of the reaction with respect to the aldehyde component.

In 2012, the scope of these cycloaddition reactions was successfully expanded and we reported the first dynamic kinetic resolution of racemic aryl succinic anhydrides (such as (*rac*)-**115**).[88] The methodology proved to be rather efficient, (*rac*)-**115** was reacted in a 1:1 ratio with different types of aldehydes bearing: electron neutral (*i.e.* **116a**),

electron deficient or rich (*i.e.* **116b-c**), hindered (*i.e.* **116d**), heterocyclic aromatic (*i.e.* **116e-f**) or aliphatic (*i.e.* **116g-h**) groups, and underwent efficient DKR, at low catalyst loadings, furnishing the products with good to excellent level of enantiomeric excess (Scheme 1.23).

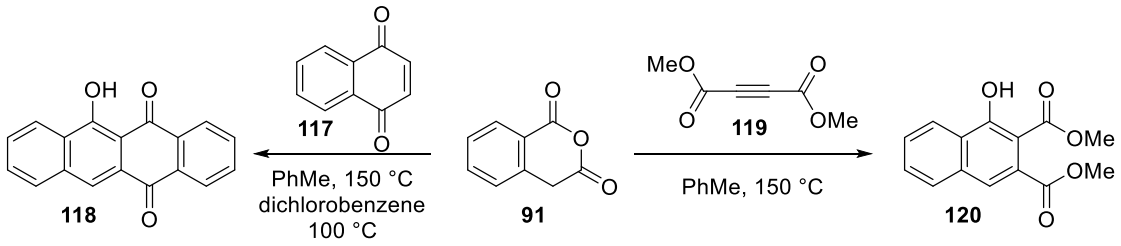


Scheme 1.23 The first catalytic enantioselective dynamic kinetic resolution of racemic aryl succinic anhydrides through their cycloaddition reaction with aldehydes.[88]

In summary, this new organocatalytic process provided access to paraconic acid derivatives (*γ*-butyrolactones) in one-pot, with excellent diastereo- and enantiocontrol (up to 99:1 dr, 99% *ee*, Scheme 1.23).

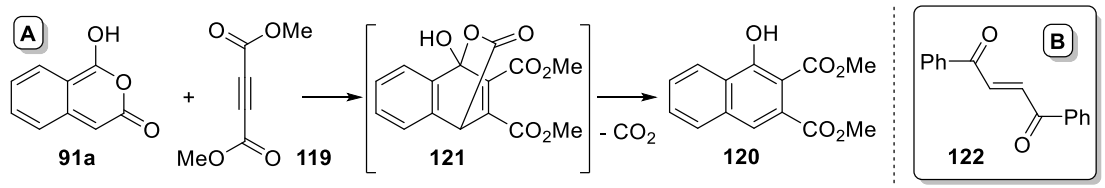
1.6.4 Cycloaddition reactions involving enolisable anhydrides with other types of electrophiles

In 1981, Tamura *et al.*[89] reported that activated alkenes (such as **117**) or alkynes (such as **119**) could react, at elevated temperatures (150 °C), with homophthalic anhydride (**91**), furnishing products such as **118** or **120** (Scheme 1.24).



Scheme 1.24 The Tamura cycloaddition reaction.[89]

The mechanism of the product formation (*i.e.* **91→118** or **91→120**) of this *C*-*C* bond-forming process still remains unclear. One possibility suggested by Tamura involves the formation of the enol **91a**, which engages next in a Diels-Alder type reaction with the dienophile **119** and subsequently releases the product **120** upon loss of a molecule of CO_2 (Scheme 1.25, A).[71] A second mechanistically conceivable pathway involves the formation of an alternative enol (*i.e.* **91b**, Scheme 1.18), which is then capable of engaging in a Michael-type addition reaction, followed by a ring closure step. This sequence would also formally lead to the same product **120**.[71]



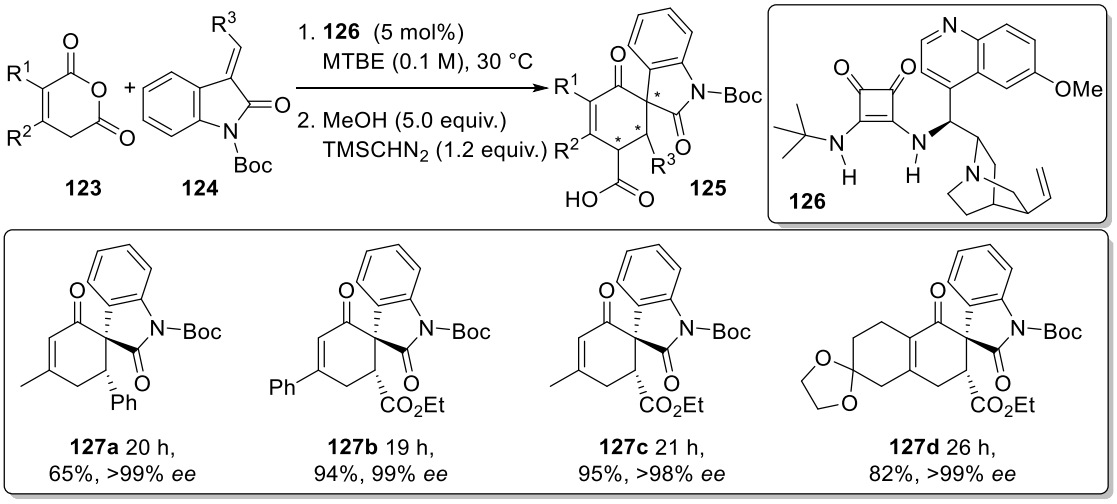
Scheme 1.25 Tamura reaction *via* a Diels-Alder mechanism.[90]

These two processes are early examples of Tamura-type cycloadditions. The processes involve a final aromatisation step (*e.g.* **121→120**) which is, unfortunately, responsible for the ablation of the newly formed stereocentres making the overall process incompatible with the development of any asymmetric catalytic variant.

However, a report involving a doubly activated Michael acceptor, such as the enedione **122** (Scheme 1.25, B), described that in the presence of a strong base (such as NaH), **91**

can react and furnish a racemic chiral cycloaddition product instead, without a loss of chirality caused by a subsequent aromatisation step.[91]

Intrigued by this scenario, it was postulated in our research group that the previously successful squaramide based organocatalyst **104** could be a suitable candidate for the organisation of the encounter between homophthalic anhydride (**91**) with a series of conjugated electrophiles in an enantioselective fashion.



Scheme 1.26 The first catalytic asymmetric Tamura cycloaddition involving enolisable anhydrides with alkylidene oxindoles.[71]

In 2014, after extensive optimisation, Connon *et al.*[71] reported the first catalytic enantioselective Tamura cycloaddition reaction between two enolisable anhydrides (homophthalic and glutaconic) with alkylidene oxindoles of general structure **124**, in a process that generates spirooxindole products bearing three contiguous stereocentres (such as **125**). In the presence of a small amount of the novel *tert*-butyl-substituted squaramide-based organocatalyst **126**, glutaconic anhydride derivatives (**123**) could be added to **124**, in one-pot, furnishing products such as **127a-d** with outstanding levels of enantiocontrol (up to 95%, >98% *ee*, Scheme 1.26).

In a more general context, over the past 5 years, our research group has been actively involved in the investigation and expansion scope of the substrates of both the anhydride components capable of acting as *C*-nucleophiles as well as their electrophilic reaction partners. Today, the substrate scope of the enolisable anhydrides, reacting under mild reaction conditions mediated by cinchona alkaloid-based organocatalysts, remains a challenge for organic chemists, as the methodology is still mainly restricted to

homophthalic (**91**), aryl succinic (*e.g.* **113** or **115**) or glutaconic anhydride derivatives (*i.e.* **123**). However, the substrate scope with respect to the electrophilic component is relatively broad. Over the past few years, many organocatalysed processes have been developed that are capable of promoting the reaction of electrophiles with **91**. This non-exhaustive overview is depicted in Figure 1.17.

To begin, rare examples of cycloaddition reactions involving enolisable anhydrides with ketones can be found in the literature.[92] These reactions were usually limited to racemic processes and the product yields were extremely poor, making the processes rather unattractive as a candidate for a catalytic asymmetric variant. It was assumed that the poor yield obtained in this type of reactions was most likely due to the relatively low electrophilicity of the ketones compared to aldehyde analogues. Therefore, it was postulated that an activated ketone (*e.g.* **128**, **130** and **132**) could react under similar conditions similar to those that we had previously developed (Figure 1.17, A, B and C).[74] In 2016, the scope of the methodology was successfully extended to activated ketones. In the presence of a novel urea-based cinchona alkaloid, diverse activated ketones such as trifluoromethyl acetophenone derivatives (*e.g.* **128**), α-ketoesters (*e.g.* **130**) or *N*-benzyl isatin (*i.e.* **132**) could be employed in the process (Figure 1.17, A, B and C). Their reaction with **91** led to highly functionalised compounds (**129**, **131** and **133**) containing two new stereocentres, with excellent yields and high level of selectivities (up to 94%, 97:3 dr, 95% *ee*).[74]

Moving forward and building on these past successes, mono-activated olefin systems such as nitrostyrene derivatives (**134**) were next targeted. Later in 2016, our research group reported the first asymmetric catalytic Tamura cycloaddition involving nitroalkenes as the new electrophilic component of the reaction (Figure 1.17, D). In the presence of the previously developed *tert*-butyl-based squaramide organocatalyst **126**, homophthalic anhydride (**91**) was added to a range of methylnitroalkenes **134** furnishing products of general structure **135** as a mixture of diastereomers with moderate to good stereoselectivities (up to 90%, 94:6 dr, 91% *ee*).[72]

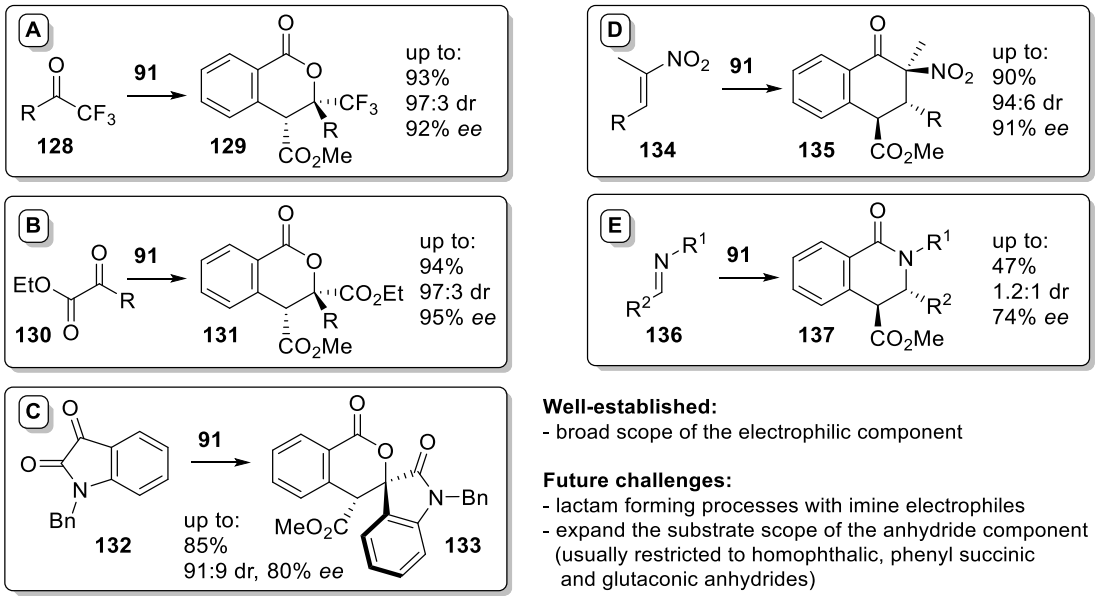


Figure 1.17 An overview of the scope of the electrophilic component in the formal cycloaddition reaction involving homophthalic anhydride (**91**).[72,73b,74]

Last but not least, we now aim to briefly introduce one of the most important branches of this powerful type of cycloaddition reaction, involving imines as the electrophilic component and producing lactam products instead of lactones (*e.g.* Figure 1.17, E).

As previously mentioned, historically this variant of the process has received considerably more attention compared to the lactone-forming variant involving aldehydes. One of the main reason for the interest in this methodology lies in its fantastic range of potential applications. Indeed, many natural products or drug molecules possessing a bewildering range of bioactivities present a chiral lactam subunit (*e.g.* the ACE inhibitor **138**).

For instance, some alkaloids, such as **138**-**141** presented in Figure 1.18 below, can directly be prepared, as racemates, from syntheses derived from this process.[64,93]

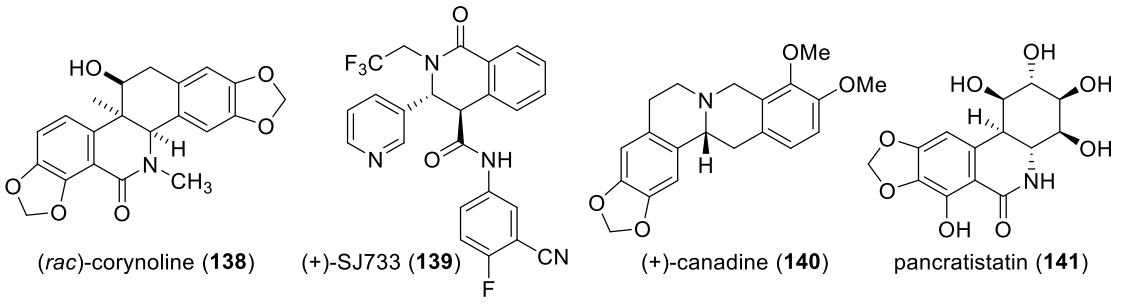


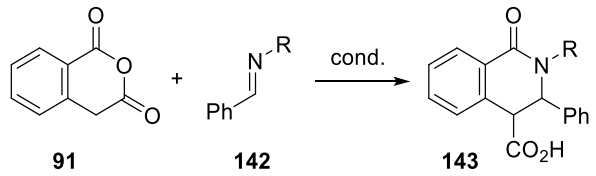
Figure 1.18 Some examples of alkaloids accessible using the process involving imines reacting with enolisable anhydrides.[93]

One of the major drawbacks of the aforementioned methodology is the lack of an asymmetric variant despite the many investigations that have been carried out to attempt to render this reaction enantioselective.[94]

In 2016, our group investigated different classes of cinchona alkaloid-based catalysts capable of promoting the reaction between *N*-alkyl or *N*-aryl imines with anhydride **91** in an enantioselective fashion. After optimisations, this new organocatalytic process provided rapid access to lactam derivatives such as **137**, in one-pot, with moderate enantioselectivity (up to 47%, 1.2:1 dr, 74% *ee*, Figure 1.17, E). [73b]

Although the actual reason for this clearly inferior stereocontrol over the process is still not entirely established, two suggestions can be made for purpose of clarification.

Firstly, a major difference between the properties of imines and aldehydes needs to be considered. An aldehyde is usually regarded as a non-nucleophilic species. However, an imine bears a lone pair of electrons capable of acting as a base/nucleophile and of activating the anhydride starting material without catalyst assistance. This difference leads, in most instances, to a considerable rate of background reaction, also referred to as uncatalysed reaction, competing with the catalysed process. In the absence of a catalyst, at low temperature (-78 °C), **91** and **142** can react on their own producing **143** in near quantitative yield after only 15 h (R = *n*-Bu, Scheme 1.27).



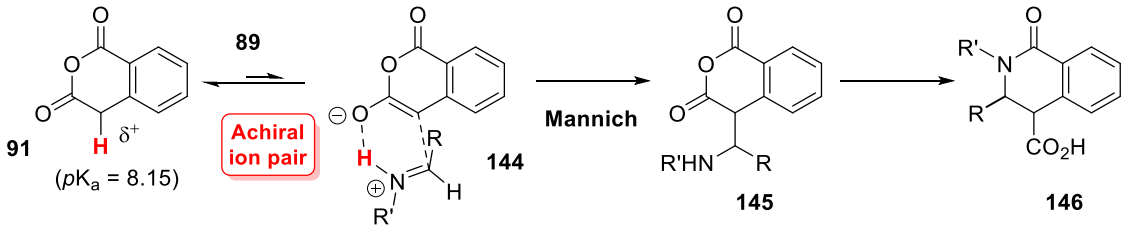
R =	solvent	T[°C]	t[h]	conv.[%]
n-Bu	THF	-78	15	>98
C_6H_5	MTBE	RT	4	39
4-NO_2-C_6H_4	MTBE	RT	24	0

Scheme 1.27 Examination of the effect of the *N*-substituent on substrate activity in the uncatalysed reaction.[73b]

The installation of electron-withdrawing groups (*i.e.* C_6H_5 or 4-NO_2-C_6H_4) respectively allows for the deactivation of the nucleophilicity of the imines and can either decrease or entirely suppress the background reaction (Table of Scheme 1.27).[73b]

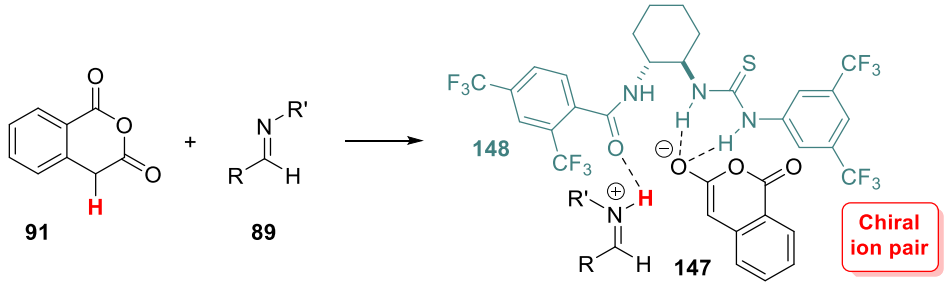
In 2017, Seidel *et al.*[73a] published a similar work and further clarified the mechanism of the reaction. Our group initially reported,[73b] that the amine nucleophilicity/basicity needed to be reduced through the installation of an EWG on the *N*-substituent of the

imine in order to suppress the background reaction occurring simultaneously in order for the catalyst to operate (Scheme 1.28).



Scheme 1.28 Background reaction proposed by Seidel.[73a]

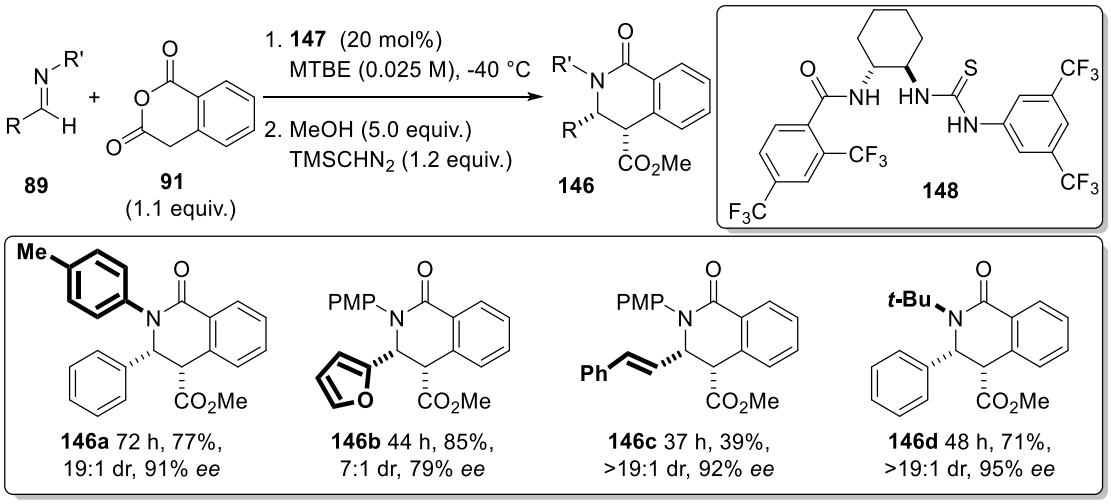
In their approach, Seidel *et al.* decided to take advantage of this background reaction using an *ad hoc* designed monofunctional organocatalyst. After initial activation of **91**, promoted by the imine **89** itself, their optimum catalyst **148** was capable of binding to the newly formed achiral ion pair **144** leading to a chiral ion pair complex (*i.e.* **147**) stabilised by multiple hydrogen-bonds to the catalyst (Scheme 1.29).



Scheme 1.29 Seidel's approach for rendering the reaction enantioselective *via* chiral ion pairing.[73a]

After optimisation of the reaction conditions, they reported the first efficient reaction involving imines as electrophiles in a highly enantioselective cycloaddition with **91**. The process was catalysed by a new catalyst capable of forming a strong chiral ion pair with both reactants, creating a chiral environment for the reaction to occur.[73a]

In the presence of 20 mol% of catalyst **148**, at low temperature (-40 °C), a wide range of substituted imines were tolerated by the process and the corresponding lactams (*e.g.* **146a-d**) were formed with high level of diastereo- and enantiocontrol (up to 71%, >19:1 dr, 95% *ee*, Scheme 1.30).[73a]



Scheme 1.30 Selected examples of lactams formed through the formal catalytic enantioselective cycloaddition of imines (**89**) with homophthalic anhydride (**91**).[73a]

1.7 Towards the development of Kinetic and Dynamic Kinetic Resolution (D)KR of new classes of enolisable anhydrides

1.7.1 Kinetic Resolution: introduction

Resolution strategies are one of the three main approaches commonly employed to access stereochemically-enriched materials (see the other two approaches in Section 1.2). These resolution strategies also break down into three subclasses: 1) The classical resolutions involving the use of stoichiometric amount of an enantiopure resolving agent. 2) Separation by chiral stationary phase column chromatography. 3) Kinetic Resolution of racemic starting materials employing chiral catalysts or reagents.[95]

The definition of a KR process is given by the IUPAC as follow: The achievement of partial or complete resolution by virtue of unequal rates of reaction of the enantiomers in a racemate with a chiral agent (reagent, catalyst, solvent, *etc*).[2]

In simpler words, KR is a method to separate one enantiomer of a racemic mixture from the other, through its selective/faster reaction with a resolving agent, promoted by a chiral catalyst. In a perfect scenario, the process allows one to access an enantiomerically pure reaction product as well as giving the possibility of recovering the enantioenriched starting material with a maximum theoretical yield of 50% for both.

If catalytic resolutions are very appealing from an academic point of view, because of the requirement of only small amounts of chiral resolving agents, the limitation to a maximum of 50% yield most certainly constitutes a major drawback for the development of high scale processes and further commercial applications.[95]

Therefore, a straightforward question which is very often encountered throughout the literature and leads to debate is: can we consider a kinetic resolution process as a practical methodology? Our answer to that question is obviously yes. In order to highlight the importance of this powerful methodology, we propose to bring elements of the response throughout this thesis, answering it in two phases. First, we will provide some representative (non-exhaustive) examples describing the scope of applications of the major processes that have been developed to date. Then, in the next chapters, we will describe in detail two distinct resolution processes that we have developed during the course of this PhD.

One of the best pieces of evidence to show that catalytic KR can actually be considered as very attractive lies in the fact that it has remained a widely used methodology with new processes appearing and being reported each year.[96]

However, for them to be considered attractive, some essential conditions must be met: 1) The racemic starting materials need to be cheap (or easy to access) and, no classical resolution of the product must already exist. 2) The catalyst employed has to be inexpensive, easy to recycle and highly selective towards one enantiomer, at low loading. 3) The starting materials, reaction products and catalysts must be easy to separate and recover. 4) In ideal KR, *both* resolved starting material and newly formed product are recovered in highly enantiomerically pure form and are valuable substrates. 5) In more specific cases, the reaction conditions offer the possibility for catalyst induced racemisation of the substrate and can lead to the theoretical transformation of 100% of the starting material to a desired enantiopure reaction product *via* dynamic kinetic resolution (DKR).[95] Such processes will be introduced in more detail in Section 1.7.6. Unlike the classical KR, this particular subclass is considered as highly efficient as it allows the circumvention of the drawbacks in terms of yield limitation.[95]

1.7.2 Theoretical considerations related to KR processes

To introduce more easily the concept and the challenges related to KR, let us consider, as an example, the resolution of a starting material (referred to as SM), presenting only one chiral centre and its two enantiomers to be resolved referred to as $SM_{(S)}$ and $SM_{(R)}$. RA stands for resolving agent while **cat*** represents a general type of chiral catalyst.

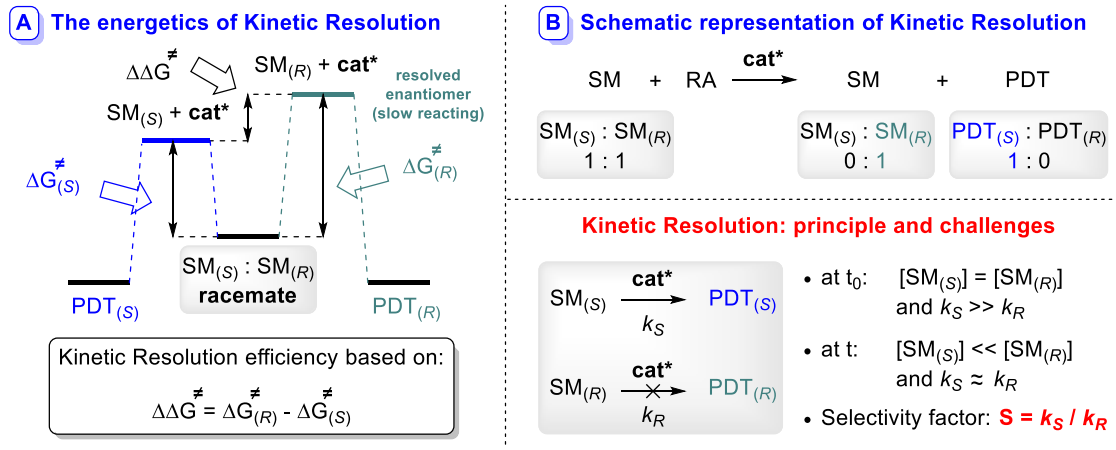


Figure 1.19 Schematic representation of the theory and the challenges behind kinetic resolution processes.[95]

In an achiral environment, the two enantiomers of a racemate are chemically equivalent as they possess the same potential energies. Therefore, their respective reaction rate with any given reaction partners are the same and they cannot be physically separated from one another (Figure 1.19, A).[95]

However, in a chiral environment, the introduction of a chiral substance such as a chiral catalyst, can force the racemate enantiomers, upon coordination to the catalyst, to formally behave, as *pseudo*diastereomers. As a result, the activation energies required for the initiation of the transformations can become different for both enantiomers. The ability and efficiency of the catalyst to discriminate between the two enantiomers depends on the size of this difference (*i.e.* $\Delta\Delta G^{\neq}$) between the relative energies of the two diastereomeric transition states and is directly linked to the overall process efficiency (Figure 1.19, A).[95]

It is noteworthy that it is particularly difficult to develop an efficient method for kinetic resolution, as a major problem encountered comes from the phenomenon itself. Initially the concentration in solution of the two enantiomers is identical, however, as the reaction proceeds, the concentration of the more reactive enantiomer decreases (*i.e.* the

one associated with the lower TS energy: $SM_{(S)}$), resulting in an increasingly competitive reaction with the less reactive-resolved enantiomer, *i.e.* the one associated with the higher TS energy: $SM_{(R)}$ (Figure 1.19, A and B).[95]

Classical enantioselective transformations usually yield products with constant enantiomeric excess (unless inhibition or coordination of the catalyst occurs due to the newly formed products). Therefore, the catalyst efficiency can directly be reflected by the magnitude of the $\Delta\Delta G^{\neq}$ created between the two enantiomers by a simple determination of the enantiomeric excesses of the products.[95]However, in the particular case of KR, because the enantiomeric excesses of both SM and products change throughout the reaction as a function of the conversion, the measurement of the enantioselectivities is usually considered as a poor indicator of the catalyst/process efficiency and a new parameter needed to be introduced.[95]

In KR, the selectivity factor (S) is usually preferred to determine the catalyst efficiency in the process. S is defined as the ratio between the rate constants for reaction of the fast reacting enantiomer divided by that of the slow reacting enantiomer and is directly linked to the gap in energy between the two diastereomeric transition states (Figure 1.20, eq.1). As an example, an S factor of 3 indicates that the faster reacting enantiomer undergoes a 3-fold acceleration in reaction rate compared to the slower reacting one, at equal concentration - regardless of the conversion. In practice, S factors can be conveniently calculated with the formulae indicated in Figure 1.20.

$$S = k_{rel} = k_{fast}/k_{slow} = e^{\Delta\Delta G/RT} \quad \text{(eq.1)}$$

$$S = \frac{\ln[(1-C)(1-ee)]}{\ln[(1-C)(1+ee)]} \quad \text{(eq.2)}$$

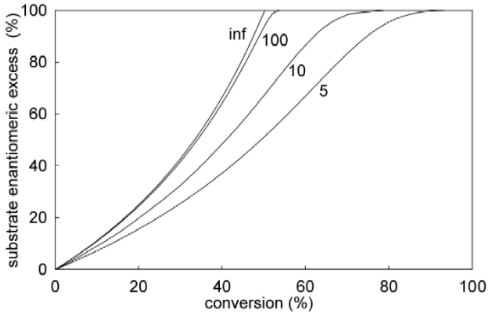
$$S = \frac{\ln[1-C(1+ee')]}{\ln[1-C(1-ee')]} \quad \text{(eq.3)}$$

- C = conversion ($0 < C < 1$)
- *ee* = enantiomeric excess of recovered SM
- *ee*' = enantiomeric excess of product
- ($0 < ee$ and $ee' < 1$)

Figure 1.20 Mathematical definition (eq.1) and convenient formulae (eq.2 and eq.3) to practically determine the selectivity factor S.[95]

With regard to developing highly efficient processes, selectivity factors higher than 10 are usually required. A selectivity factor of 10 indicates that the starting material can be recovered with 90% *ee* at >62% conversion as indicated in the table of Figure 1.21. Nevertheless, under those conditions the maximum theoretical yield of the recovered SM is only 38% (Figure 1.21).[95]

S factors as high as 50 are usually necessary to consider the KR as perfectly operational as it allows the recovery of 50% of the starting material with over 90% *ee* at only 50% conversion (Figure 1.21).[95]



S	$\Delta\Delta G^{\neq}$ (kcal/mol)	Conversion[%] required to attain: 90% *ee*	98% *ee*	>99% *ee*
1.5	0.24	99.9	99.99	99.999
2.0	0.41	97.2	99.5	99.7
5.0	0.95	74.8	84.0	86.6
10	1.35	**62.1**	**69.7**	**72.1**
50	2.31	**50.4**	54.0	54.9
100	2.72	48.9	51.8	52.4
500	3.66	47.7	50.0	50.3

Figure 1.21 Evolution of the enantiomeric excess of the recovered starting material as a function of the conversion for different values of S factors.[95]

In practice, selectivity factors over 50 are extremely challenging to attain and values as high as >200 are very often only achieved in enzyme-mediated processes (*e.g.* S=50 already corresponds to a $\Delta\Delta G$ = 2.31 kcal/mol difference in energy between the diastereomeric TS of the two enantiomers).[95]

However, perhaps one of the most attractive aspects of the KR over other classical enantioselective transformations is the fact that the SM can always be recovered in excellent enantiomeric excess (*e.g.* >99% *ee*), at the expense of a synthetically good yield, simply by pushing the conversion further than 50%. For example, a SM can be recovered with over 99% *ee* even if the S factor is as low as 10. As indicated in the table of Figure 1.21, the SM can be recovered with 90% *ee* (at C = 62%), 98% *ee* (at C = 70%) or even >99% *ee* (at C = 72%) by stopping the reaction at different conversions. In practice, it means that if the enantiopurity of a recovered substrate is the primary goal, a system affording a selectivity factor S ≈ 20 does not even require any further optimisation. Instead, the conversion should be adjusted to reach the necessary level of conversion as exemplified by the table presented in Figure 1.21.[95]

Throughout the rest of this thesis we will employ *both* selectivity factor and enantioselectivity to describe the efficiency of a process. When different catalyst efficiencies, based on the same reaction, will be compared we will prefer the comparison of their S factors. However, if two distinct processes have to be compared, yields of recovered starting material/products and enantioselectivities will also be used.

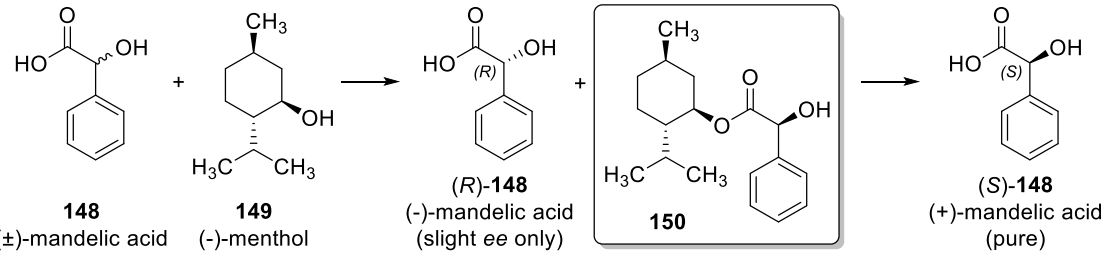
Indeed, in 2010, in a general review covering the vast subject of kinetic resolution reactions, E. N. Jacobsen reported:[95]

> "While it is certainly a simple matter to calculate S values from conversion and *ee* data using eq. 2 and 3 (Figure 1.20), it is by no means a straightforward matter to determine S values accurately. ***Indeed, it is likely that most values that are reported in the literature are in fact inaccurate***. The curves plotted in Figure 1.21 assume a first-order kinetic dependence on substrate in the reaction, but different *ee* vs. conversion curves are obtained in kinetic resolutions displaying other kinetic dependencies on substrate. In fact, the rate laws for synthetically useful kinetic resolutions are almost never determined. […] In reality, it is not at all unlikely that the kinetic dependence on substrate can change during the course of the resolution, rendering very difficult any accurate estimation of S. […] Because of the issues noted above, we will avoid description of reactions in terms of S values and present them instead in terms of recovered substrate or product yields and *ee*."

1.7.3 An historical overview: the first examples of KR

The first example of a KR mediated by synthetic means was reported in 1899. Marckwald and McKenzie discovered that the esterification reaction of mandelic acid (*i.e.* (*rac*)-**148**) with the enantiopure (-)-menthol (**149**) led to the formation of the corresponding ester (**150**) derived exclusively from the (*S*)-**148** enantiomer.[97] The composition of the unreacted carboxylic acid **148** was determined to present only a slight enantiomeric excess, however, the recovered mandelic acid **148** obtained upon saponification of the ester product resulted in the exclusive formation of (*S*)-**148** (Scheme 1.31).

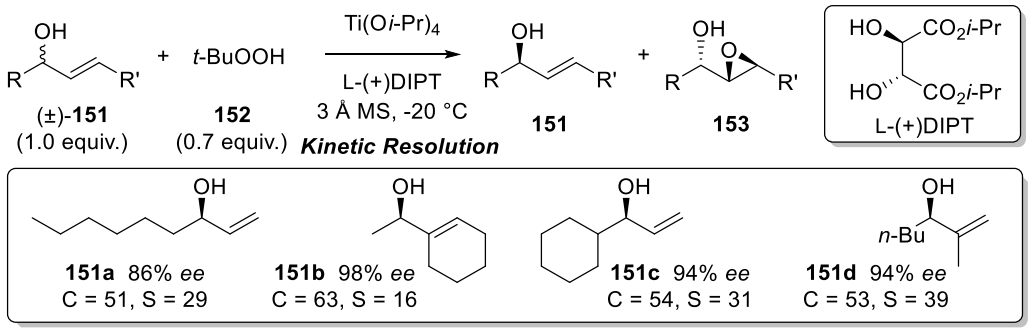
This discovery represented the first example of a KR in organic chemistry and was later followed by other similar types of KR of others chiral acids.[98]



Scheme 1.31 The first synthetic KR of a racemic carboxylic acid (**148**) by esterification with an enantiopure chiral alcohol (**149**).[97]

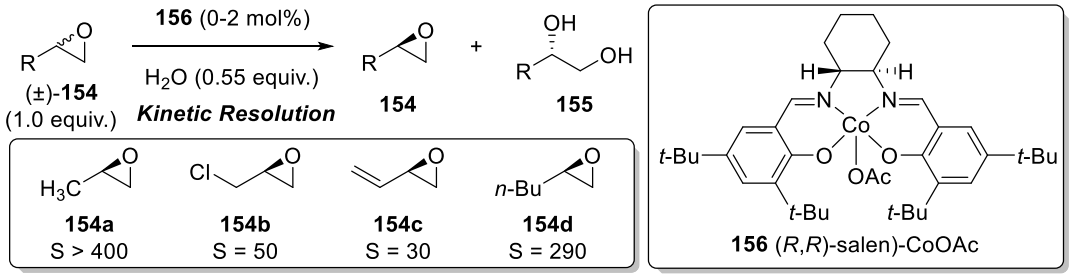
While the basics and general principles of KR had been established and were rather well understood since 1899, no significant report covering this topic appeared in the literature until almost a hundred years later.

In 1981, Barry Sharpless *et al*.[99] reported for the first time, the use of a titanium-based catalyst (at 10 mol% loading), working in tandem with an enantiomerically pure diisopropyl tartrate ligand (DIPT), in an efficient asymmetric epoxidation reaction forming optically active epoxide products such as **153**, with excellent enantioselectivity (up to >98% *ee*). These transformations were accompanied by the concomitant KR of a series of secondary allylic alcohols, of general structure (*rac*)-**151**, with excellent selectivity factors (up to S = 39). Some representative examples of resolved alcohols (**151a-d**) are depicted in Scheme 1.32.[99]



Scheme 1.32 Catalytic asymmetric epoxidation and Kinetic Resolution of secondary allylic alcohols.[99]

While we have just described a protocol allowing access to a series of chiral epoxides *via* enantioselective synthesis, a few years later, in 1997, E. N. Jacobsen proposed an alternative solution relying on a new kinetic resolution process (Scheme 1.33).[100]



Scheme 1.33 The first highly enantioselective hydrolytic Kinetic Resolution of terminal epoxides catalysed by chiral cobalt^{III} complexes.[100]

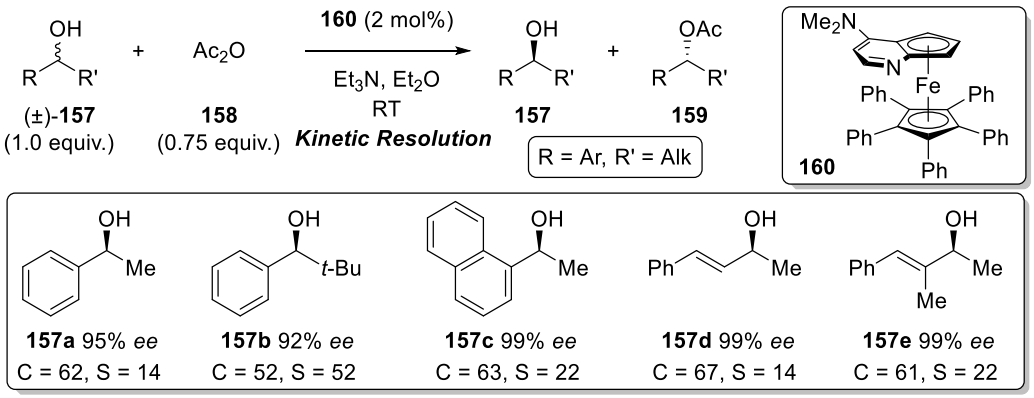
In the presence of a very low loading (0.2-2 mol%) of a chiral cobalt^{III} complex (**156**), the catalytic system mediated the asymmetric ring opening hydrolysis of racemic terminal epoxides of general structures (*rac*)-**154**. The reactions provided access to different chiral diols (such as **155**) which are synthetically useful building blocks, in high enantioselectivity (up to >99% *ee*), along with the possibility of recovering the

unreacted starting materials (*e.g.* **154a-d**) in an enantioenriched form, with excellent to outstanding selectivity factors (up to S >> 200, Scheme 1.33).[100]

1.7.4 Kinetic Resolution (KR)

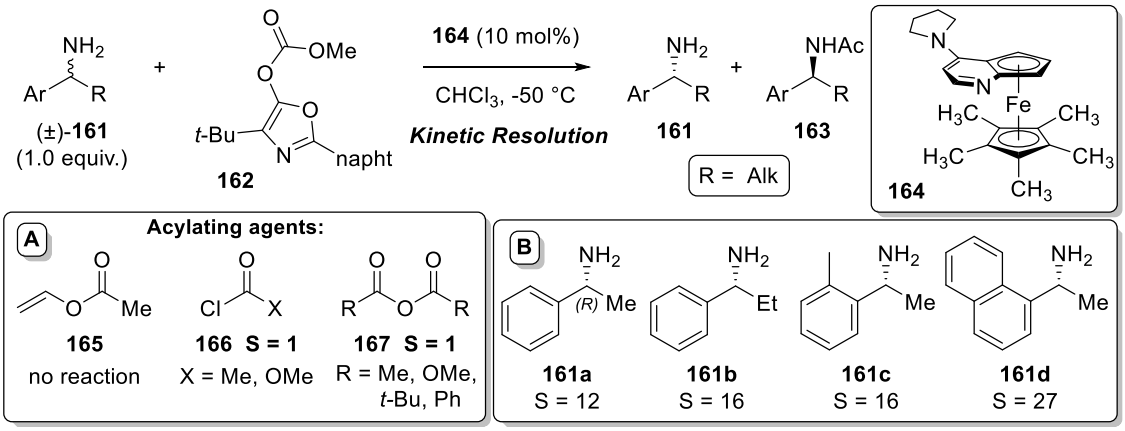
In 1997, Fu's research group developed a series of iron-complex based nucleophilic chiral-planar catalysts (such as **160**) containing a ferrocene and a 4-dimethylaminopyridine (DMAP) *motif*.[101] At only 2 mol% loading, the optimum catalyst **160** could attack the resolving agent **158**, forming, *in situ*, an activated ammonium acetate ion (*i.e.* the actual chiral acylating agent), responsible for the transfer of chiral information (Scheme 1.34).

The process proved to be (*R*)-selective towards (*rac*)-**157** and allowed for the formation of the (*R*)-enantiomer of the acylated products **159**. As a result, the (*S*)-enantiomers of the alcohols **157a-e** were recovered, with excellent selectivity (up to S = 52). Later, this methodology was further expanded to the resolution of other classes of racemic materials such as allylic and propargylic alcohols.[102] Unfortunately, one drawback associated with the process involves the relatively high price of the chiral catalyst, which needs to be recovered after completion of the reactions (Scheme 1.34).



Scheme 1.34 The first kinetic resolution of racemic secondary alcohols of general structure (*rac*)-**157** catalysed by a ferrocene derived catalyst (**160**).[101]

In 2001, moving forward and building on these successes G. Fu's research team turned their attention to the KR attempt of secondary amines of general structure (*rac*)-**161** (Scheme 1.35).[103] This type of amine can provide extremely valuable building blocks in organic synthesis if isolated in their enantiopure form. Therefore, a similar type of acylative process, as developed for alcohols, was envisaged as a viable option for the development of their catalytic KR.



Scheme 1.35 Kinetic resolution of amines *via* a non-enzymatic acylation catalyst.[103]

Under the same conditions reported in their KR publication on secondary alcohols, the first experiments did not provide access to any enantioenrichement of the starting material **161**. Indeed, if alcohols are relatively unreactive substrates towards electrophiles such as acetic anhydride (**158**), on the other hand, secondary amines such as **161** exhibited considerably superior activity and successfully competed with the catalyst **164** towards nucleophilic attack on **158**. In practice, the background reaction was faster than the actual catalysed process (*i.e.* S = 1, Scheme 1.35, A).[103]

Different sorts of common acylating agents (*e.g.* **165**-**167**) were evaluated in the catalytic process, always leading to the same unfortunate outcome (*i.e.* S = 1). In their report, Fu described the choice of the *O*-acylated azlactone **162** as their optimal acylating agent and as an unexpected consequence derived from previous research.[104] At 0 °C, the KR attempted of **161**, catalysed by **164**, in the presence of **162**, led to a low but appreciable selectivity factor of S = 3. Upon cooling (*ca.* -50 °C), good levels of enantioselectivity were obtained. Therefore, they were able to report the efficient KR of a range of secondary substituted aromatic amines **161a-d** with good selectivity (up to S=27, Scheme 1.35, B).[103]

In 2009, D. Seidel *et al.*,[105] proposed an alternative to the KR of amines first introduced by Fu. They developed a strategy relying on an elegant chiral ion pairing catalysis. Interestingly, ion pair intermediates such as ion pair **A** (which are known to be able of promoting efficient KR and desymmetrisation processes)[106] are better electrophiles than the acylating agents commonly employed to generate them (Figure 1.22, A). Practically, it means that a nucleophile should react faster with ion pair **A** rather than with the

acylating agent itself (*e.g.* such as an anhydride) and, therefore, avoid the presence of the background reaction issues previously encountered and reported by Fu.

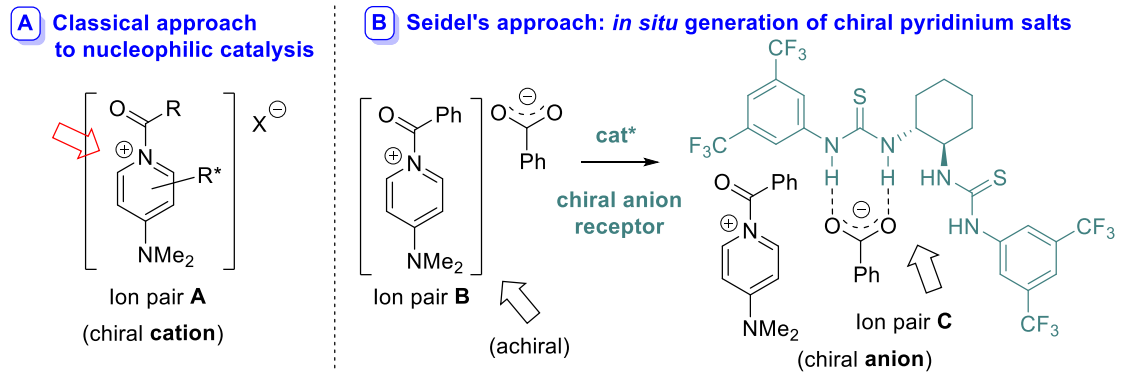
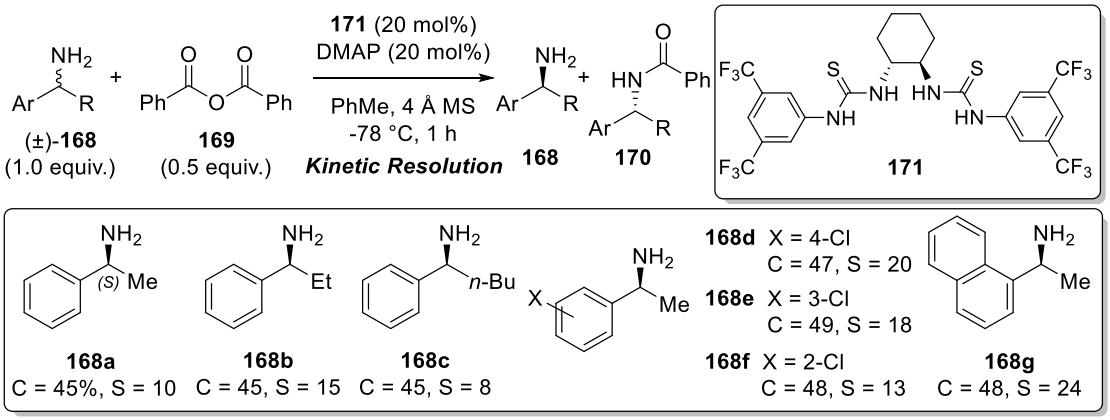


Figure 1.22 Seidel's ion pair formation strategy: nucleophilic catalysis and hydrogen bonding catalysis.[105]

Seildel's actual strategy was inspired by the model of chiral ion pairing **A** and is schematically described in Figure 1.22 (B). They explored the possibility of rendering an *achiral* acyl pyridinium ion pair salt (such as the ion pair **B**) *chiral*, by means of coordination of the carboxylate of the benzoate anion, by hydrogen bond donation from a chiral anion receptor such as the newly developed catalyst **171** (depicted in Scheme 1.36, B). Therefore, in their methodology the chiral information is not transferred to the product *via* a classical chiral acylating agent (such as the ion pair **A**) but, alternatively, from the chiral information contained in the chiral counter ion part of the generated ion pair complex **C** (Figure 1.22, B).[105]

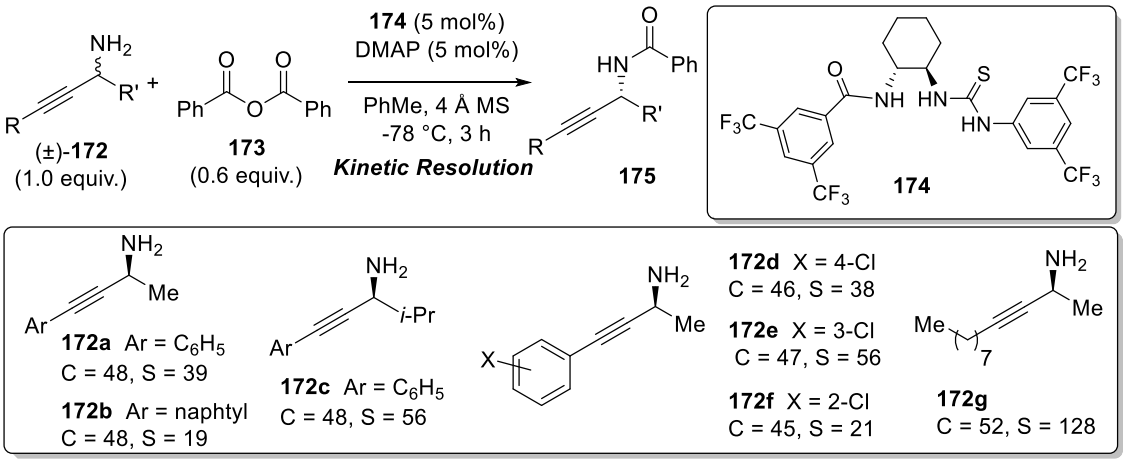
Their strategy proved to be very successful and, after a series of optimisations on the catalyst structure and reaction conditions, they were able to report the successful KR of (*rac*)-**168** mediated by the optimum chiral ion receptor **171** (Scheme 1.36).[105]



Scheme 1.36 Catalytic KR of amines *via* an anion binding approach.[105]

The substrate scope was somewhat similar to the one reported by Fu. However, in this study, the chiral catalyst is cheap and easier to synthesise (*i.e.* compared to **164**). In addition, in most instances, the selectivity factors were overall marginally higher (up to S = 24). Also, interestingly, **171** promoted the formation of the opposite enantiomer of **168**, selecting the (*R*)-enantiomer instead and thus, allowing for enantioenrichement in (*S*)-**168** (Scheme 1.36).[103,105]

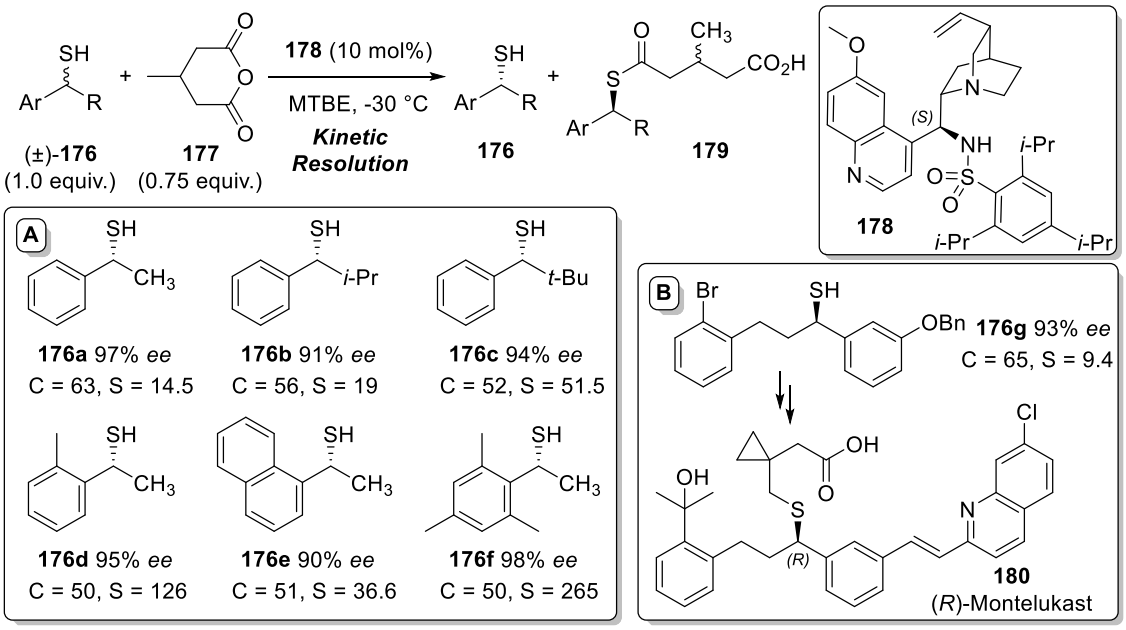
The following year, in 2010, Seidel *et al.*[107] managed to expand the scope of their ion pairing resolution methodology to propargylic amines of general structure (*rac*)-**172**. For the KR to be efficient they had to modify the scaffold of their previous catalyst and, as a result, designed the new thiourea-amide system **174**. At 5 mol% loading, **174** could promote selective acylation of a series of amines, producing enantiopure adducts products, of general structure **175**, with concomitant KR of the starting materials **172a-g**, with excellent overall selectivities (S up to 56, Scheme 1.37).



Scheme 1.37 A anion binding approach to the KR of propargylic amines (*rac*)-**172**.[107]

The next example was developed in our laboratory and is related to an important class of organosulfur precursor compounds. Thiols can be, in their enantiopure form, extremely valuable substrates in both the field of organic chemistry or biology.[108] Encouraged by previous successful reports on the KR of some of the most important families of organic compounds (*e.g.* epoxides, alcohols, amines, *etc.*), our research group became interested in the possibility of developing a similar process involving secondary racemic thiols presenting the general structure (*rac*)-**176** (Scheme 1.38).

In 2010, Connon *et al.*[109] reported, the first catalytic enantioselective KR of racemic thiols. The process was mediated by a novel bulky sulfonamide-based cinchona alkaloid catalyst (**178**) and, allowed the formation, in one-pot, of valuable enantiopure thioesters (**179**) as products of the desymmetrisation reactions between the resolving agent 3-methyl-glutaric anhydride (**177**), in a thiolysis involving a single enantiomer of (*rac*)-**176**. Simultaneously, the starting materials **176a-f** were synergistically resolved and could be recovered in their enantioenriched form with excellent to outstanding selectivity factors (S up to 265, Scheme 1.38, A).



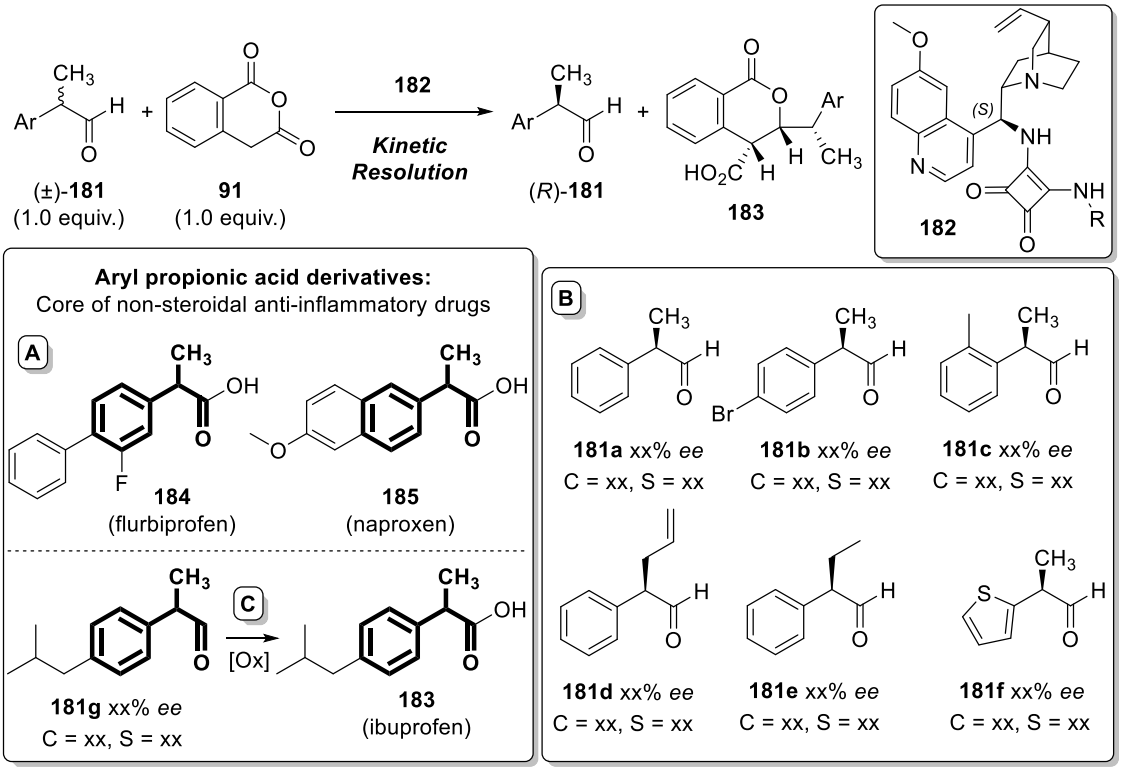
Scheme 1.38 The KR of secondary thiols (*rac*)-**176** mediated by the organocatalysed desymmetrisation ring opening thiolysis of **177**.[109]

In the same study, it was also proved that the process could be used for interesting applications with both a resolved starting material and a product thioester, through their use as building blocks in the subsequent formation of drug precursors.[109]

For example, the resolution of (*rac*)-**176g** was achieved affording a recovered starting material with a synthetically useful enantiomeric excess of 93% *ee* (at C = 65%). This starting material is one of the precursors to the leukotriene receptor antagonist (*R*)-Montelukast (**180**) and contains the key stereocentre (Scheme 1.38, B).[109]

The last example was recently developed in our laboratory and represents our latest contribution to the field of organocatalysed Kinetic Resolutions. As described through Section 1.6, different processes involving the reaction of enolisable anhydrides with a

diverse array of electrophiles and to yield optically active cycloadduct products have been developed over the past 10 years. Among all the reported examples, none of the reactants employed presented chiral centre in their scaffolds (with the exception of (*rac*)-**113** which was involved in a DKR process, Section 1.6.3).



Scheme 1.39 The first efficient KR of α-branched aldehydes (*rac*)-**181** operating *via* a cycloaddition reaction involving homophthalic anhydride (**91**).

In order to explore the full potential of those transformations it was decided to introduce some elements of chirality into both starting materials (*i.e.* the nucleophilic and electrophilic component). The challenge at hand was to determine if the process was compatible with any new kind of new resolution methodology. The purpose of this PhD thesis was the attempt at the resolution of diverse chiral anhydrides (*i.e.* the nucleophilic component, see Chapters 2 and 3), the following example, on the other hand, focused on the resolution of chiral α-branched aldehydes (*i.e.* (*rac*)-**181**, Scheme 1.39).

The decision to target the resolution of α-branched aldehydes with the structure (*rac*)-**181** was initially influenced by the further potential applications that such a process could provide. Indeed, a simple oxidation of the resolved aldehydes would potentially give access to a family of compounds known as aryl propionic acids. Among these compounds, many belong to a subclass of non-steroidal anti-inflammatory drugs

presenting interesting bioactive activities (*e.g.* flurbiprofen (**184**) and naproxen (**185**), Scheme 1.39, A).[110]

In 2017, after extensive optimisation, a squaramide-based catalyst **182** was designed and could operate, as an efficient promoter of the cycloaddition reaction assisting the resolution of a wide range of aldehydes. The selectivity factor obtained for the KR of **181a-f** ranged from good to excellent and all the aldehydes were recovered with synthetically useful enantiomeric excesses (Scheme 1.39, B).

The potential utility of the methodology described above was demonstrated through the resolution of aldehyde **181g**, which upon oxidation gives direct access, in one step, to the well-known anti-inflammatory drug ibuprofen (**183**, Scheme 1.39, C).

1.7.5 Parallel Kinetic Resolution (PKR)

Again, to introduce the concept and the challenges related to a subclass of KR known as PKR, consider, as an example, the PKR resolution strategy of a starting material (referred to as SM), presenting only one chiral centre; with its two enantiomers to be resolved referred to as $SM_{(S)}$ and $SM_{(R)}$. RA and **cat*** still respectively stands for Resolving Agent and a general chiral catalyst (Figure 1.23, A).

In a classical KR, one enantiomer would react much faster with the chiral catalyst (*e.g.* $k_R << k_S$), while the other enantiomer would be left behind, slowly reacting to form the enantiomeric side product, resulting in the global enantioenrichment of both product and starting material at the same time (Figure 1.19, A-C).[95]

In PKR, however, both enantiomers (*i.e.* $SM_{(S)}$ and $SM_{(R)}$) have similar reaction rates and their relative concentration remains almost identical throughout the entire reaction (*i.e.* $k_R \approx k_S$ and $[SM_{(S)}](t) \approx [SM_{(R)}](t)$). The resolution phenomenon occurs *via* the transformation of each enantiomer of the SM to different and *non-enantiomeric* products (*i.e.* $SM_{(S)} \rightarrow PDT_{\mathbf{A}(S)}$ and $SM_{(R)} \rightarrow PDT_{\mathbf{B}(R)}$, Figure 1.23, A and B).[95]

The main challenge associated with developing an efficient PKR strategy lies in the ability of the catalyst to discriminate between the two undesired plausible side reactions depicted in Figure 1.23 (B), resulting from the competitive reactions of each enantiomer producing the undesired *enantiomeric* products (*i.e.* $SM_{(R)} \rightarrow PDT_{\mathbf{A}(R)}$ and $SM_{(S)} \rightarrow PDT_{\mathbf{B}(S)}$).[95]

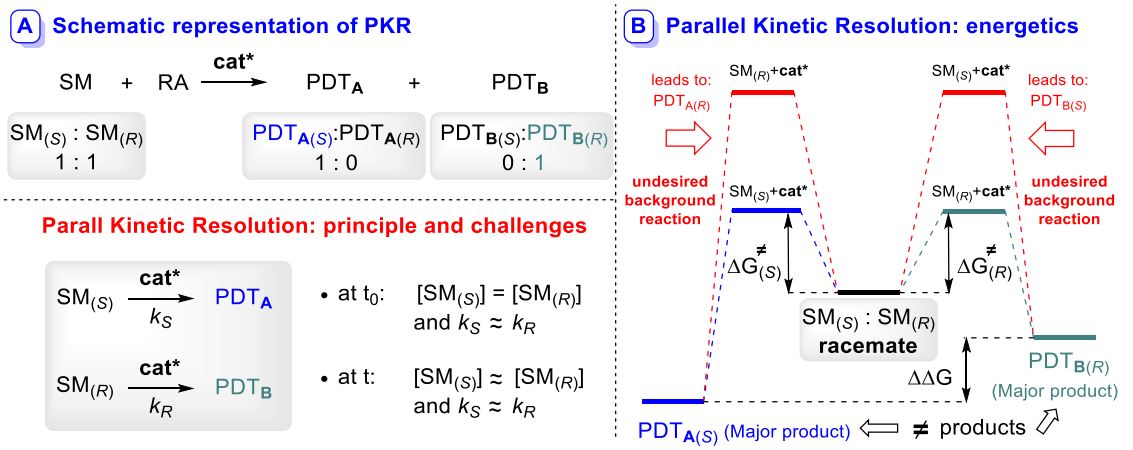
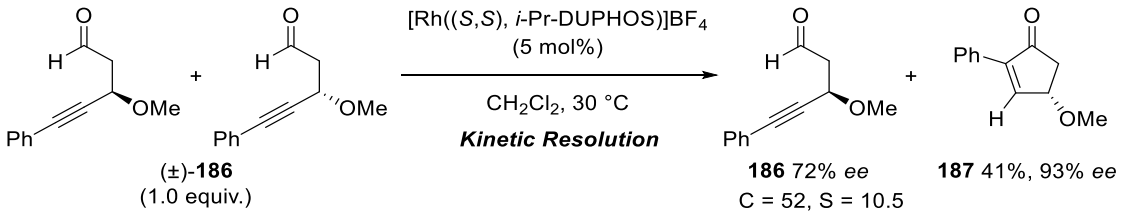


Figure 1.23 Schematic representation of the theory and the challenges behind Parallel Kinetic Resolution processes.[95]

A PKR process considered under control usually needs to meet the following conditions: 1) The reaction rate of both enantiomers of the starting material have to be similar (*i.e.* $k_R \approx k_S$). 2) Both reactions towards $PDT_{A(S)}$ and $PDT_{B(R)}$ must occur without interfering with each other. 3) The process has to afford <u>*non-enantiomeric*</u> products (*i.e.* $\Delta\Delta G \neq 0$). 4) The process also must have complementary (and opposite) enantioselectivity with respect of the SM and products. 5) It must afford products that can easily be separated from each other.[95] The schematic representation and the energetics associated with the overall process are depicted in Figure 1.23 (A and B).

Three types of situations are possible depending on the nature of the products. $PDT_{A(S)}$ and $PDT_{B(R)}$ can be: 1) Diastereomers (stereodivergent PKR). 2) Constitutional isomers (regiodivergent PKR). 3) Different compounds (chemodivergent PKR).[111]



Scheme 1.40 Fu's KR of 4-alkynals promoted by a Rhodium based catalyst.[111]

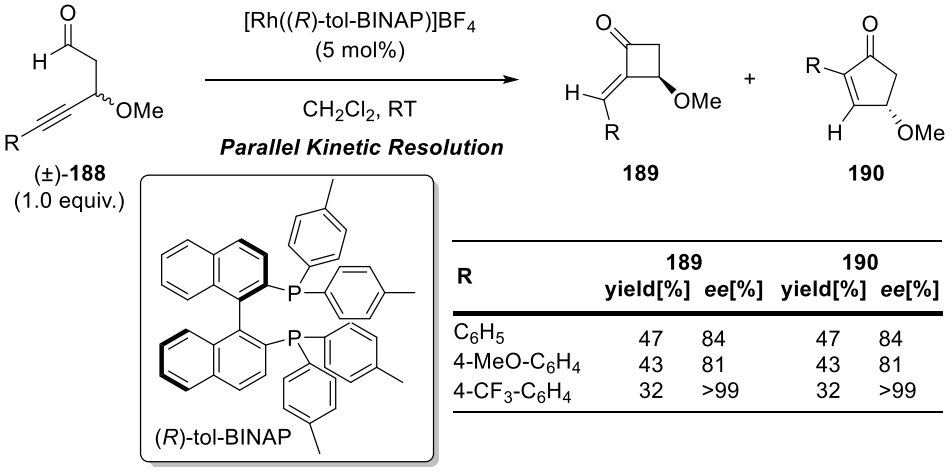
In 2002, Fu *et al.*,[111] reported the catalytic asymmetric kinetic resolution of 4-alkynals (such as **186**) promoted by a Rhodium (I) based catalyst (Scheme 1.40). Throughout their research they evaluated a poorly effective catalytic system based on the combination Rh(I)/(Tol-BINAP). This metal-ligand system yielded a complex mixture of products and, as a result, very little attention was initially paid to it. However, a

closer examination later revealed the presence of an unanticipated but valuable side product.

Upon repetition of this experiment, analysis showed the formation of a cyclobutanone product (*i.e.* **189**). Interestingly, **189** was formed in good yield along with excellent enantioselectivity (Scheme 1.41).[112]

In 2003, further investigation and optimisation allowed G. Fu's research team to report an efficient chemodivergent PKR process involving racemic 4-alkynals (*i.e.* (*rac*)-**188**) promoted by the aforementioned Rh(I)/(Tol-BINAP) catalytic system.[112]

In the presence of 5 mol% of the catalyst, a series of substituted alkynals were employed in the syntheses of two structurally different compounds **189** and **190**. In most instances, both compounds could be isolated in good yields and near optical purity (*ca.* 84-99% *ee*, Scheme 1.41).

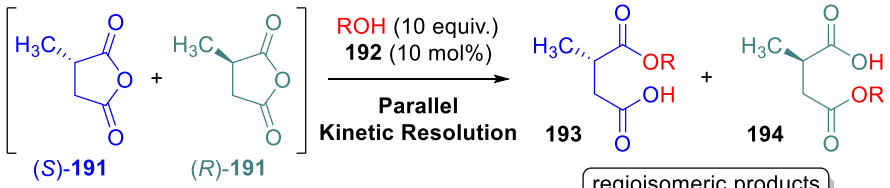


R	189 yield[%]	189 ee[%]	190 yield[%]	190 ee[%]
C_6H_5	47	84	47	84
4-MeO-C_6H_4	43	81	43	81
4-CF_3-C_6H_4	32	>99	32	>99

Scheme 1.41 Fu's PKR of 4-alkynals promoted by a Rh(I) based catalyst.[112]

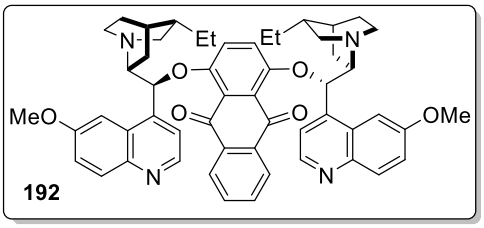
The last example that we aim to introduce belongs to the class of the regiodivergent PKR. In 2001, Deng *et al.*[113] oriented their research towards a tentative attempt at the KR of racemic monosubstituted succinic anhydrides such as (*rac*)-**191**.

Some recently developed bifunctional bis-cinchona alkaloid derivatives, such as **192**, have been shown to be capable of promoting efficient desymmetrisation reactions of prochiral substances such as *meso* anhydrides during formal ring opening methanolysis reactions.[114] In a similar fashion, they predicted that the ring opening alcoholysis of (*rac*)-**191**, promoted by **192**, could potentially enable the development of a new KR process affording optically active hemiester.



ROH	193:194	ee[%] 193:194
MeOH	39:61	74:67
EtOH	49:51	82:67
n-PrOH	45:55	81:72
CF_3CH_2OH	49:51	85:72
CF_3CH_2OH*	44:56	91:80

* Reaction performed at -25 °C



Scheme 1.42 Parallel Kinetic Resolution of monosubstituted succinic anhydride.[113]

Their first experiment, involving methanol and (*rac*)-**191**, afforded the regioisomeric products **193** and **194** in a 31:69 ratio with encouraging enantiomeric excesses (*ca*. 74 and 67% *ee* respectively). This was rationalised as PKR occurring *via* the simultaneous enantioselective and regioselective alcoholysis of the two enantiomers of **191**, leading to the formation of regioisomeric optically active hemiesters **193**-**194**. A series of alcohols were compatible with the process (up to 91% *ee*, Scheme 1.42).

1.7.6 Dynamic Kinetic Resolution (DKR)

One of the main purposes of any asymmetric transformation is to obtain enantioenriched compounds in the most efficient way possible. As presented in the previous sections, KR is a time-honoured tool for the preparation of a wide array of enantiomerically enriched materials. The main advantage of this approach lies in the fact that the starting materials can always be recovered with high enantiomeric excess, regardless of the catalyst efficiency, simply by pushing the conversions above 50%. However, synthetically useful enantiomeric excesses are often obtained at the expense of good product yields which is, in any case, limited to a theoretical maximum of 50%.

An elegant way to overcome this yield limitation can be achieved by developing dynamic variants of these processes. Dynamic kinetic resolution variations have recently emerged as powerful and attractive tools for obtaining enantioenriched compounds with the circumvention of the major drawback usually associated with the lack of atom economy related to classical resolution processes. Theoretically, it allows for the full conversion of both enantiomers of the starting materials and, a yield of 100% of a single isomer product with high optical purity.

From a theoretical point of view KR and DKR are similar. The resolution phenomenon occurs *via* the same formation of two diastereomeric transition states upon binding with a chiral catalyst and follows the same overall energetic pathway (Figure 1.24, A). The major difference encountered in DKR processes comes from the racemisation of the starting material occurring simultaneously and competitively with the resolution. In most instances, it is induced by the catalyst itself. However, in some cases a co-catalyst, referred to as racemisation catalyst, or additives, employed in catalytic or stoichiometric amounts, can be used to accelerate substrate racemisation.[95,115]

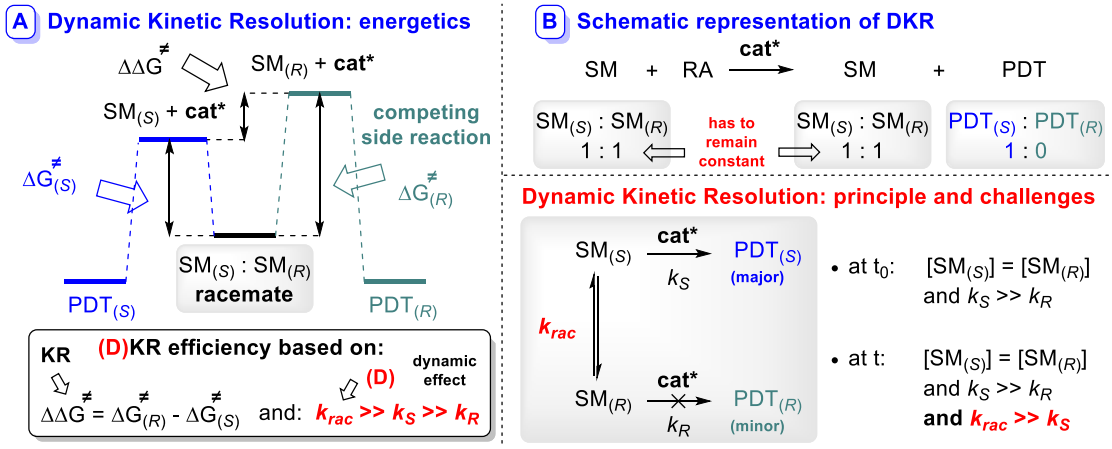


Figure 1.24 Principle of DKR and key differences with classical KR processes.[115]

The process efficiency is directly linked to both the magnitude of the ΔΔG induced between the two diastereomeric TSs and the rate of racemisation. For the resolution to occur smoothly, the rate of the racemisation must be significantly higher than the rate of the reactions occurring with any of the two enantiomers (*i.e.* $k_{rac}>>k_S>k_R$). If these two conditions are met, the concentrations of the slower and faster reacting enantiomers are almost identical throughout the reaction and the enantiomeric excess of the product

must remain close to constant as it is no longer a function of the conversion (Figure 1.24, B).[95,115]

To meet the requirement for developing an efficient DKR, the catalyst responsible for racemisation must also be compatible with the newly formed product. Indeed, if the starting material and product are structurally close, frequently, the product may also undergo racemisation or epimerisation. In order to avoid the aforementioned issue, mild racemisation conditions, which are often substrate dependent, need to be developed.[115]

Classical methods employed usually derive from one among: 1) thermal conditions, 2) acid- or base-mediated catalysis, 3) formation of a Schiff base, 4) employment of enzymes, 5) redox reactions.[115,116]

Three non-exhaustive examples, highlighting classical racemisation strategies of racemic materials such as α-branched ketones (*i.e.* **195**, A),[88] secondary amines (*i.e.* **196**, B)[117] or secondary alcohols (*i.e.* **197**, C)[118] are depicted in the Figure 1.25.

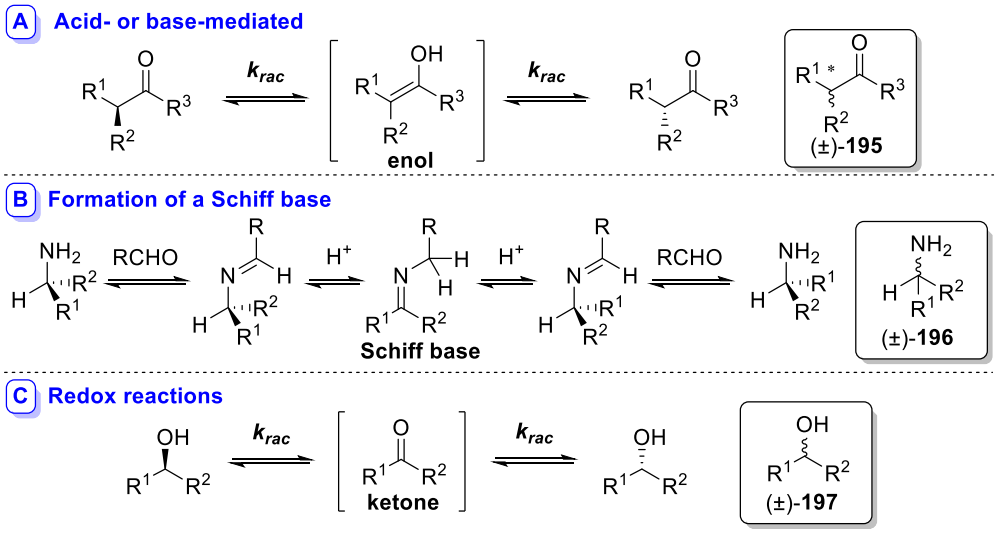
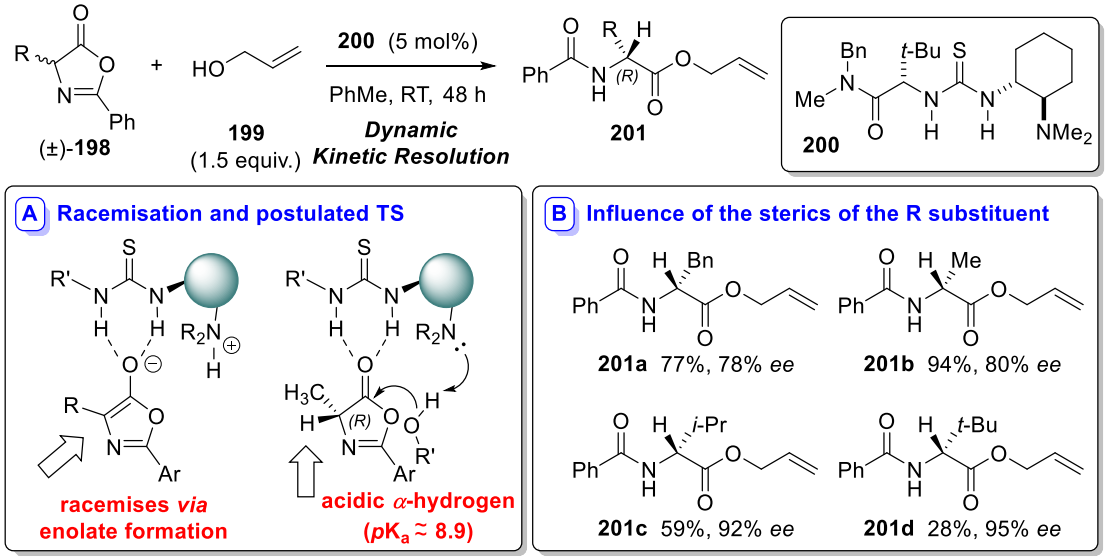


Figure 1.25 Some examples of classical racemisation strategies.[88,115,116,117,118]

The first example that we propose to describe in order to introduce these new resolution processes (*i.e.* DKR) involves a class of starting materials known as azlactones (of general structure **198**).[119] Noteworthy, is their relatively high acidity ($pK_a \approx 9$) makes them suitable candidates for racemisation catalysed by bases such as the catalyst **200**. The racemisation occurs *via* the formation of a *C=C* double bond after deprotonation promoted by **200**, during the enolate step formation (Scheme 1.43, A).[119]

In their study, Berkessel *et al.*[119] rationalised the sense of the stereoinduction *via* the activation of the electrophilic carbonyl component, of (*R*)-**198**, *via* hydrogen-bonding. As a consequence, the bulkier group (*i.e.* R) is directed downwards to avoid the steric interactions with the catalyst scaffold. Simultaneously, catalyst **200** mediates the deprotonation of the incoming nucleophile **199** and guides its approach to a single face of **198**, affording the protected amino acids **201** (Scheme 1.43, A).



Scheme 1.43 Organocatalytic DKR of Azlactones *via* ring opening alcoholysis.[119]

In the presence of 5 mol% of **200**, at ambient temperature, a series of substituted azlactones (**198**) underwent efficient DKR during a ring-opening alcoholysis involving a slight excess of allyl alcohol (**199**). The process furnished, with good selectivity, the valuable masked amino acids, as their acylated esters **201a-d**, with excellent level of selectivities (up to 95% *ee*, Scheme 1.43, B).[119]

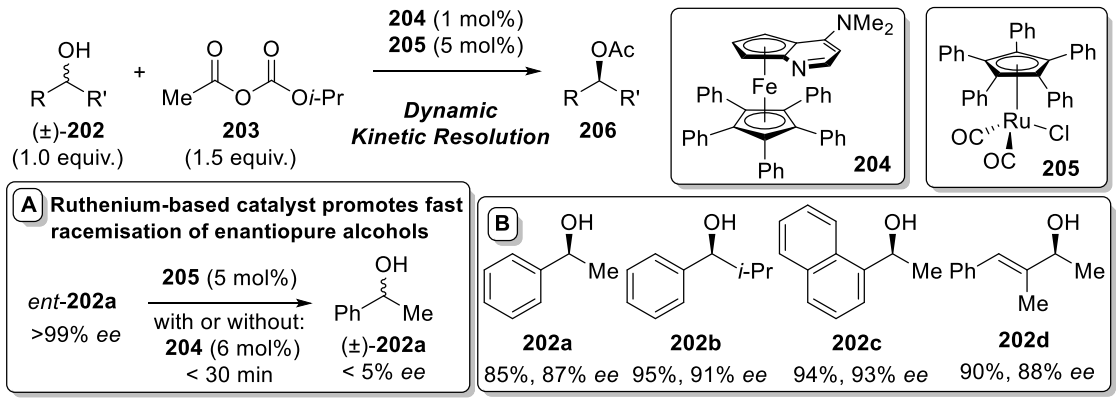
Their study also revealed a strong correlation between the steric effects of the α-substituent (*i.e.* R) and the process efficiency. Increasingly bulkier substituents led to systematically enhanced enantiomeric excesses, albeit with considerably lower reaction rates (*ca.* from 78% to 95% *ee* and 94 to 28% conversion after 48 h, Scheme 1.43, B).[119]

In 2012, Fu *et al.*[120] expanded their original work on the KR of secondary alcohols (**202**) to the more challenging DKR analogue. Originally, their first tentative attempt finds roots in a report describing the discovery of a library of ruthenium-chloride complex (Ru^{Cl}) based catalysts capable of promoting, within half an hour, fast racemisation of enantiomerically pure alcohols, (*e.g. ent*-**202a**→(±)-**202a**, Scheme 1.44,

A).[121] Their initial strategy involved the intuitive combination of the resolution catalyst **204** working in tandem with the co-catalyst **205**.

Unfortunately, under their previously developed conditions, the acylated products (**206**) were recovered in high yields but only with low enantiomeric excesses (*ca.* 38% *ee*). They discovered that the acetic anhydride (**158**), under the former conditions, can form a stable complex with the ruthenium co-catalyst which, unfortunately, proved to be completely inactive towards the racemisation of **202**, thus preventing any DKR development perspectives.[120]

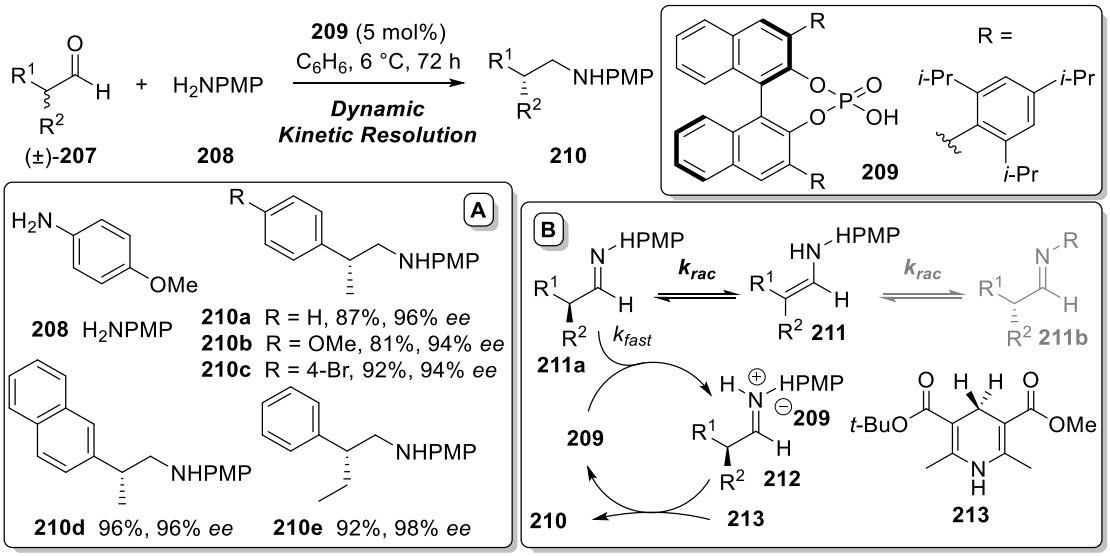
A screening of acylating agents allowed them to identify **203** as a viable source of acyl donor moiety compatible with the process and preventing catalyst inhibition. The selectivities obtained while evaluating the substrate scope proved to be rather similar to those previously reported in their KR process, however, the isolated yields of the representative examples **202a-d** were greatly enhanced (up to 94% yield, Scheme 1.44, B).[120]



Scheme 1.44 Catalytic DKR of alcohols *via* enantioselective acylation by G. Fu.[120]

In 2006, B. List *et al.*,[122] reported the highly efficient DKR of racemic α-branched aldehydes presenting the general structure (*rac*)-**207**. The resolution was mediated by an enantioselective reductive amination reaction, carried out in the presence of 5 mol% of the chiral phosphoric acid catalyst **209** (Scheme 1.45).

The DKR of a series of enolisable aldehydes (*i.e.* **207**) was achieved, employing the aromatic amine **208** as reaction coupling partner, affording chiral β-branched amines, of general structure **210**, with excellent levels of enantioselectivity (up to 96% and 96% *ee*, Scheme 1.45, A).[122]



Scheme 1.45 Dynamic Kinetic Resolution of α-branched aldehydes catalysed by chiral phosphoric acids by List.[122]

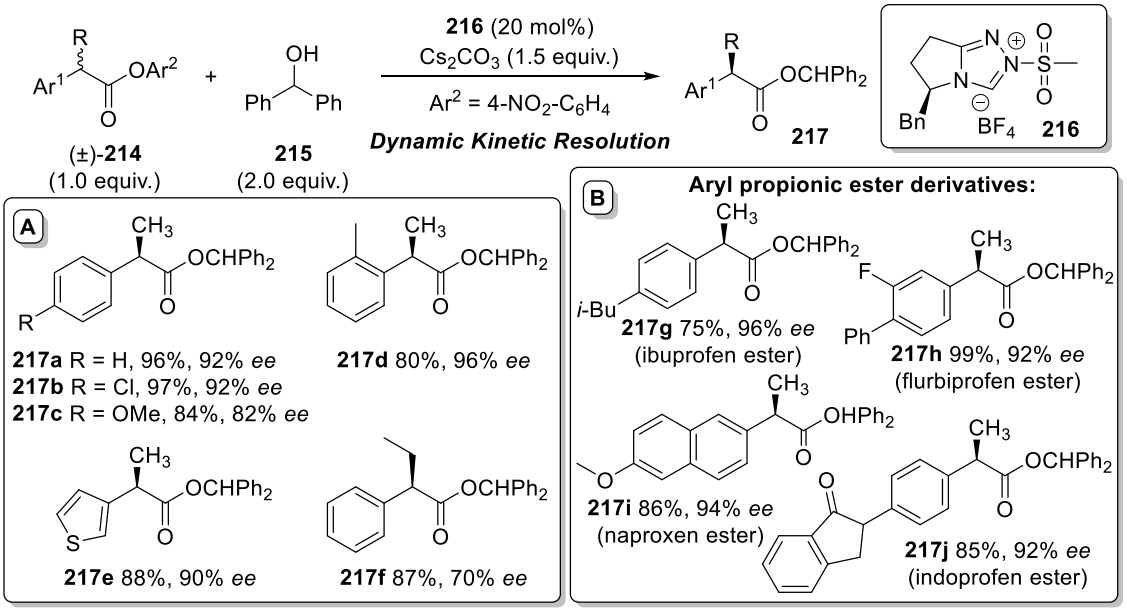
The author rationalised the racemisation of **207** *via* the formation of the *achiral* enamine intermediate **211**, generated after reaction with aniline **208** (Scheme 1.45, B). In the presence of the catalyst **209**, the fast reacting enantiomer **211a** (resulting from the imine/enamine tautomer equilibrium), undergoes rapid protonation by the catalyst and forms a tight chiral ion pair (**212**). Finally, a stoichiometric loading of the Hantzsch *bis*-esters **213**, used as a hydride source, allows the recovery of catalyst **209** and simultaneously releases optically active amines (such as **210**, Scheme 1.45, B).[122]

Two DKR examples of racemic alcohols and aldehydes, catalysed by a chiral iron or phosphorus based catalysts, have been introduced.[120,122] Recently, the DKR of α-branched carboxylic esters has also been shown to be possible for the first time (Scheme 1.46).

In 2016, Y. R. Chi and co-workers,[123] reported the first efficient DKR of esters, such as (*rac*)-**214**, *via* a new carbene-catalysed transesterification process involving alcohol **215**. After addition of the NHC catalyst (*i.e.* **216**) to **214**, the newly formed azolium ester intermediate undergoes rapid deprotonation of its acidic α-hydrogen. The base employed (Cs_2CO_3) helps to ease the enolate formation and promotes the fast racemisation of the substrate. DFT calculations determined that the transition state associated with the addition of alcohol **215** to the (*R*)-enantiomer is about 5 kcal/mol lower in energy than the one associated with the (*S*)-enantiomer.

Experimental data matched with the calculated selectivities and a series of racemic esters (**214**) were successfully resolved in the form of their transesterified products **217a-f** (up to 96% *ee*, Scheme 1.46, A).[123]

The methodology proved to be robust as, in the same study, the resolution of more densely functionalised esters provided access, in one-pot, to a series of valuable drug precursors **217g-j** in excellent yields and enantioselectivities (up to 99% yield and 92% *ee*, Scheme 1.46, B).[123]



Scheme 1.46 DKR of α-branched carboxylic esters *via* carbene catalysis.[123]

Through Section 1.7 we tried to introduce the general concepts associated with three of the main subclasses of resolution processes. These descriptions aimed to be relevant, as background, for the work that has been developed in this thesis and, which will be described in the next chapters. For each particular process (*i.e.* KR, PKR or DKR), some theoretical considerations and practical examples were discussed and highlighted.

As the scope of resolution processes is quite broad and constantly growing, only a few selected, non-exhaustive, relevant examples were discussed. More examples related to KR processes can be found in several specialised reviews.[95,115,124,125,126,127,128]

1.8 Objectives of this thesis

- Expansion of scope and identification of novel anhydrides capable of acting as *C*-nucleophiles in formal cycloaddition reactions with aldehydes as electrophiles.

- Development of the first DKR of racemic disubstituted succinic anhydrides, using bifunctional organocatalysis and of a formal cycloaddition process with aldehydes. Formation of stereochemically complex γ-butyrolactone derivatives with control over three contiguous stereocentres including one all carbon quaternary.

- Development of the first KR of racemic α-alkylated aryl succinic anhydrides using a regio-, diastereo- and enantioselective cycloaddition with aldehydes. Formation of densely functionalised five-membered paraconic acid derivatives with control over the three stereocentres (including one all carbon quaternary). Simultaneous recovery of the enantioenriched anhydride starting materials as their derivatised opened form - chiral succinates.

- Development of novel chiral cinchona based organocatalysts capable of promoting the aforementioned resolution processes in diastereo- and enantioselective fashion. In particular, development of the first examples of a novel class of sulfamide based hydrogen bond donor organocatalysts derived from cinchona alkaloids.

Results and discussion

2. The Dynamic Kinetic Resolution of di-aryl substituted anhydrides mediated *via* an enantioselective cycloaddition to aldehydes

As described in Section 1.6, several organocatalytic processes involving enolisable cyclic anhydrides, reacting in an enantioselective fashion with a diverse array of electrophiles, have been successfully developed in recent years. The substrate scope of these transformations with respect to the electrophilic component is now rather well-established.[71,72,73,74,83,84,88] However, the substrate scope with respect to the anhydride pronucleophile component is significantly narrower and remains restricted mainly to homophthalic (*i.e.* **281**), glutaconic (*i.e.* **282**) or aryl succinic (*i.e.* **283**) anhydride derivatives (Figure 2.1). This limited scope obviously represents a major drawback and significantly restrains further potential synthetic applications of the methodology.

Therefore, we became interested in the identification of new enol-stabilising candidates for broadening the scope of the anhydrides capable of engaging in reactions with aldehydes and targeted the di-aryl succinic anhydrides (**221**) depicted in Figure 2.1.

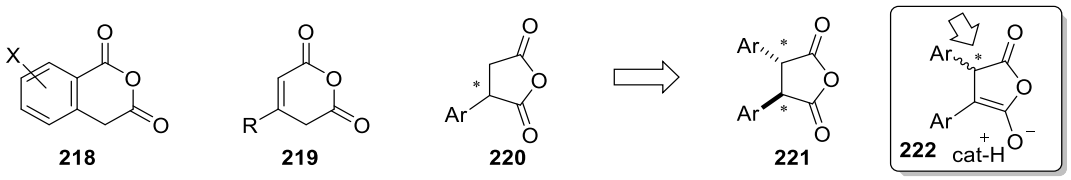


Figure 2.1 Reported pronucleophile anhydrides (**218**-**220**) and new substrate challenge: expansion of the substrate scope (**221**).

This structural modification might appear at first as trivial and of little consequence to the process. However, after closer attention, the insertion of an extra stereogenic centre into the substrate scaffold significantly increases the magnitude of the complexity of the proposed process. Previously reported pronucleophiles **218**-**219** are achiral reagents (*e.g.* **220** reacts *via* its achiral *in situ* formed enolate). However, on the other hand, for the next targeted challenge, after deprotonation of one of the acidic α-hydrogen atoms on **221**, the hypothetical newly formed enolate **222** still exists as a mixture of two enantiomeric forms due to the remaining chiral centre (Figure 2.1).

In other words, a suitable organocatalyst would have to, for the process to be under control, be capable of promoting both a stereoselective addition to the aldehyde and concomitant resolution of the two enantiomers of the starting material enolate **222**.

Such a process would theoretically afford access to highly substituted γ-butyrolactone/paraconic acid derivatives (of general structure **223**), bearing three stereocentres (two newly formed - one of which is all carbon quaternary, Figure 2.2).

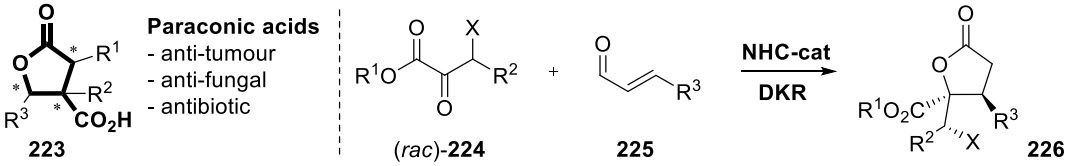


Figure 2.2 Paraconic acids and the recent utilisation of DKR in asymmetric γ-butyrolactone synthesis.[133]

Stereochemically dense γ-butyrolactones form the core of a considerable proportion (which has been estimated at *ca.* 10%) of natural products which possess remarkably diverse biological activities[129] - of which the paraconic acids[130] would be typical (Figure 2.2). The development of one-pot catalytic methods for the rapid, enantioselective construction of these privileged structural units continues to challenge synthetic chemists and the topic has very recently been reviewed.[131] A recently developed, attractive and simplifying approach involves the face-selective coupling of achiral partners with readily prepared racemic chiral materials with concomitant Dynamic Kinetic Resolution,[132] such the recent construction of lactones **226** from the racemic α-ketoesters **224** and enals **225** using homoenolate chemistry (Figure 2.2).[133]

Anhydrides have been used as acylating agents for over 100 years[134] and are often used as the electrophilic component of a Kinetic Resolution (KR) reaction[135] involving a racemic nucleophile. However, despite their enormous synthetic utility, their use as the subject of resolution processes (*i.e.* the resolution of chiral anhydrides) is entirely undeveloped.

In 2001, Deng *et al.*[113] reported the first catalytic Parallel Kinetic Resolution (PKR) of monosubstituted succinic anhydrides (*rac*)-**227** promoted by a chiral amine catalyst. The process involved the simultaneous enantioselective and regioselective alcoholysis of the two enantiomers of the starting material leading to the formation of optically active mono esters **228** and **229**. Recently, we have shown that aryl succinic anhydrides of general type (*rac*)-**230** undergo efficient DKR during a formal cycloaddition reaction with aldehydes **103** to form substituted butyrolactones **231** only if the aryl units were equipped with electron withdrawing substituents (Figure 2.3, A).[88]

To the best of our knowledge this represents the sum total of what is known concerning the catalytic resolution of monosubstituted anhydrides (Figure 2.3, A).

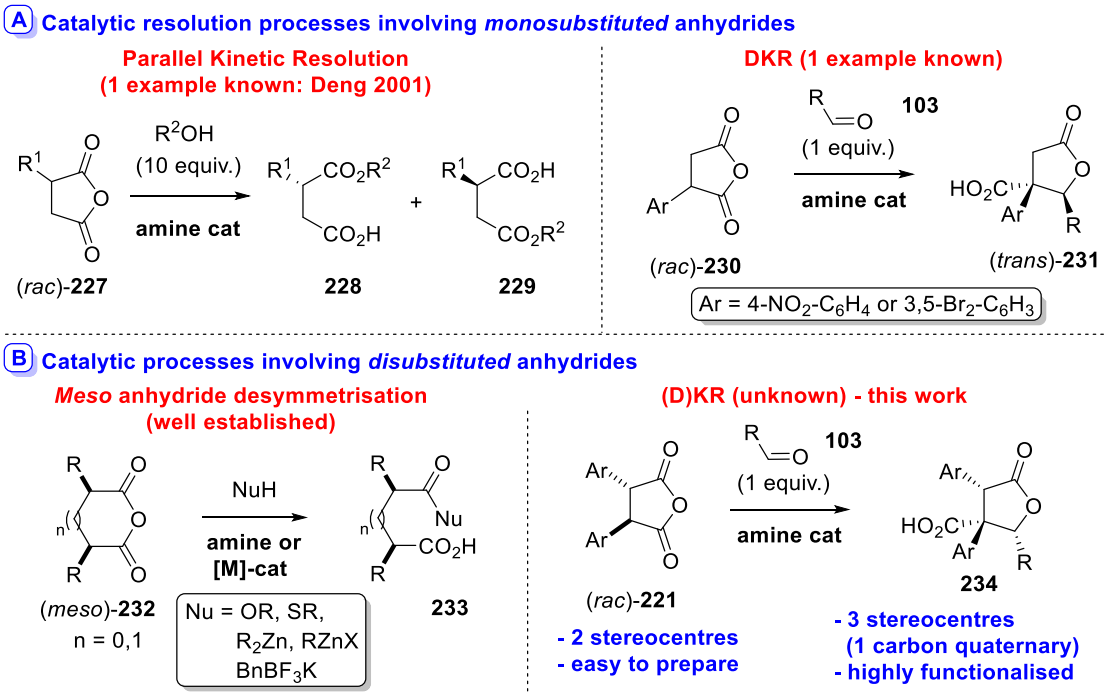


Figure 2.3 The dearth of anhydride resolution processes.[88,113,136,137]

More stereochemically complex substituted anhydrides are less studied still: the desymmetrisation of *meso*-disubstituted anhydrides (*i.e.* the conversion of (*meso*)-**232** to **233**) is a well-established process,[113,136,137] however, (D)KR processes involving racemic *trans*-anhydrides such as (*rac*)-**221** are completely unknown, despite the potential efficiencies with regard to controlling the configuration at multiple stereocentres during a single coupling operation (Figure 2.3, B).

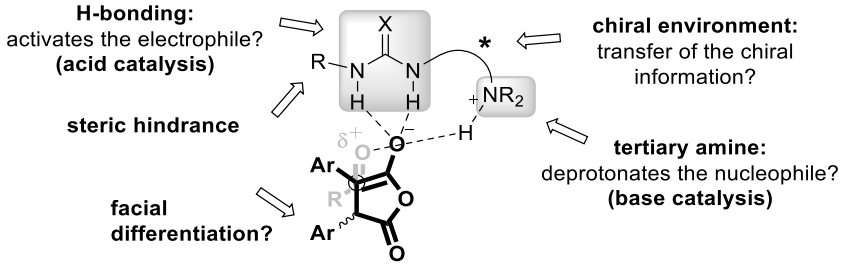


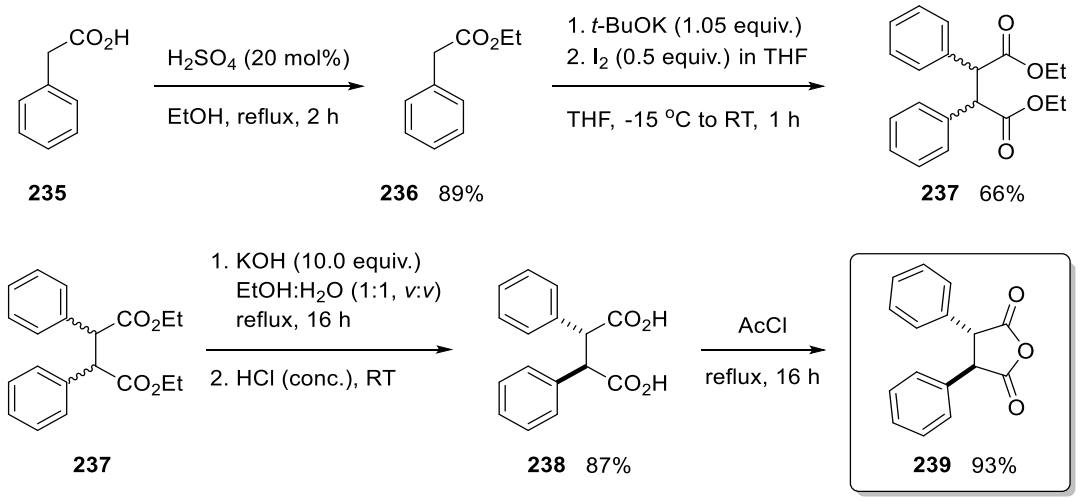
Figure 2.4 Original rationale for the development of an organocatalytic (D)KR of di-aryl succinic anhydride catalysed by bifunctional catalysis.

In this thesis we would like to report the results of our research towards the development of the first (D)KR of di-aryl succinic anhydrides **221**. The rationale at the outset of this study for the strategy of both resolution and subsequent asymmetric

induction between **221** and an aldehyde **103**, catalysed by a bifunctional catalyst is depicted in Figure 2.4.

2.1 Preliminary experiments: proof of concept

Initially, we oriented our efforts towards a tentative attempt at the KR of the simplest di-aryl succinic anhydride: 2,3-diphenyl succinic anhydride (**239**). To test our hypothesis, we synthesised (*trans*)-**239** according to a slightly modified known literature procedure (Scheme 2.1).[138]



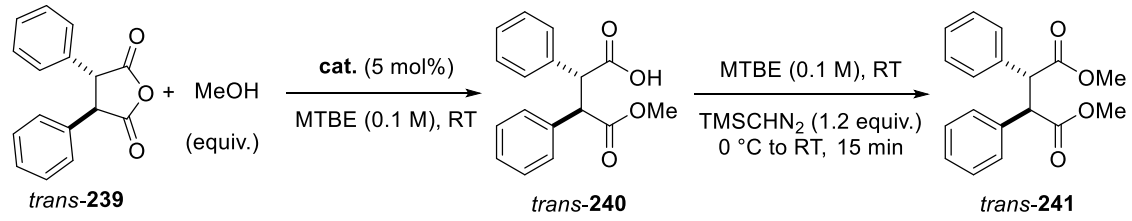
Scheme 2.1 Synthetic route towards 2,3-diphenylsuccinic anhydride (**239**).

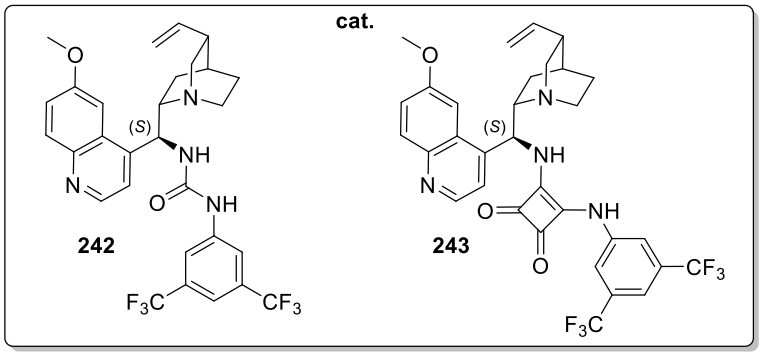
The first step involved the protection of the commercially available phenylacetic acid (**235**) as its ethyl ester **236**. *Bis*-ester **237** was synthesised *via* an iodination and *in situ* enolate alkylation sequence. Potassium *tert*-butoxide was employed to deprotonate at the acidic α-position of **236**, generating a reactive nucleophile. Subsequent addition of precisely half an equivalent of iodine allowed for the *in situ* preparation of an halogenated electrophilic intermediate, allowing for the *C-C* bond formation leading to **237**. The diastereomers of the *bis*-ester **237** (*i.e. cis*-**237** and *trans*-**237**) were isolated by column chromatography and separately subjected to saponification reaction with aim of forming both *cis*-**238** and *trans*-**238**. Under the reaction conditions outlined above, the product of the reaction was in both cases the *trans* diastereomer of **238**, highlighting the equilibration occurring during the reaction *via* epimerisation. This is a phenomenon that we had anticipated and this result led us to believe that our KR attempt of **239** could, under base-mediated conditions, lead to a dynamic kinetic resolution process instead.

Anhydride **239** was synthesised by the straightforward ring closure of *trans*-**238** mediated by reflux in acetyl chloride as solvent (Scheme 2.1).

In order to determine the enantiomeric excess of the remaining starting material **239** after catalysis (at ≈ 50% conversion), we had to develop a method allowing for the formation of a stable derivative, suitable for CSP-HPLC analysis. Indeed, anhydrides are not stable enough and could easily be subject to ring opening reactions in the presence of a vast array of nucleophiles or react with the stationary phase of the chromatography columns.

Table 2.1 Optimisation of the ring opening methanolysis protocol.





entry	cat.	time (min)	MeOH (equiv.)	conv. (%)[a]	241 *ee* (%)[b]
1	**242**	30	150	93	n.d.[c]
2	**242**	120	200	>99	<2%
3	**243**	120	200	>99	<2%

[a]Conversion of starting material **239** was determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b]Determined by CSP-HPLC after derivatisation of the carboxylic acid product to the methyl esters by *in situ* esterification with $TMSCHN_2$. [c]Not determined.

We decided to fully ring open **239** with the aid of MeOH and to convert *in situ* the resulting hemister **240** to a stable *bis*-methylester (*i.e.* **241**). To do so we needed to ensure that the methanolysis was fast enough to avoid any catalyst-mediated ring-

opening, which may have led to inaccurate results, as stereoselective ring openings of anhydrides by alcoholysis have been widely reported in the literature.[113,136,137]

In the presence of 5 mol% of **242** and 150 equivalents of MeOH, we monitored the conversion of the ring opening by ^{1}H NMR spectroscopy. After 30 min only 7% of the anhydride remained (entry 1, Table 2.1).

Therefore, we increased to 200 equivalents of MeOH and extended the reaction time to 2 h, after which time the reaction was found to have gone to completion. Esterification of **240** with trimethylsilyldiazomethane afforded **241**, which was subjected to CSP-HPLC analysis, revealing the almost total absence of asymmetric alcoholysis under the optimal conditions (<2% *ee*, entry 2). For reproducibility purposes, we repeated the process using the squaramide **243** instead, and also did not detect any enantioenrichment of the starting material (<2% *ee*, entry 3, Table 2.1).

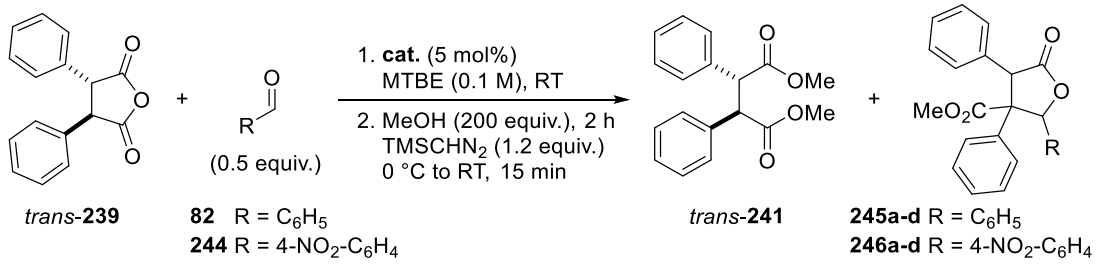
The results of our preliminary experiments into the cycloaddition of diphenyl succinic anhydride (**239**) to benzaldehyde (**82**) and 4-nitrobenzaldehyde (**244**) in MTBE catalysed by two cinchona alkaloid-based organocatalysts are presented in Table 2.2.

In the absence of either catalyst or base, no reaction occurs (entry 1). The use of Hünig's base as a catalyst to facilitate enolate formation led to the formation of the diastereomeric products **245a-d** (obtained after esterification with trimethylsilyldiazomethane in order to facilitate CSP-HPLC analysis) with a preference for diastereomer **245a** (entry 2). We were pleased to confirm that the insertion of an extra stereogenic centre into the core of the phenyl succinic scaffold (relative to monosubstituted aryl succinic anhydrides) did not destroy the reactivity due to the relatively higher steric hindrance of the starting material. The reaction occurred smoothly and no formation of side products was detected (Table 2.2).

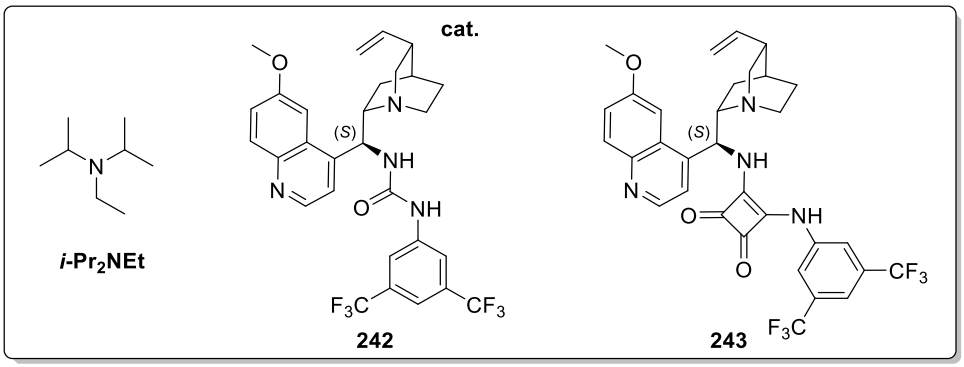
The use of either urea catalyst **242** or its squaramide analogue **243** (provided by former members of the group: Dr. F. Manoni and Dr. C. Cornaggia) allowed for the formation of lactones **245** and **246** with moderate diastereocontrol (up to 4:1 dr, entries 3-4, Table 2.2). The major diastereomers produced in the reaction (*i.e.* **245a** and **246a**) were formed with encouraging levels of enantiocontrol (*ca.* 31 and 46% *ee* respectively) along with the minor diastereomers formed with good enantiomeric excesses (*ca.* 81 and 82% *ee* respectively, entries 3-4, Table 2.2).

Given the level of enantioselectivity obtained for the products, we expected to observe some enantioenrichment of the starting material **239** at conversions close to 50%. However, CSP-HPLC analysis revealed that **239** was recovered in both cases (as its opened form **241**) as an almost racemic material (entries 3-4, Table 2.2).

Table 2.2 Proof of concept and preliminary experiments involving the cycloaddition reaction between *trans*-**239** and two aromatic aldehydes.



trans-**239** **82** R = C_6H_5; **244** R = 4-NO_2-C_6H_4 *trans*-**241** **245a-d** R = C_6H_5; **246a-d** R = 4-NO_2-C_6H_4



entry	cat.	aldehyde	product	time (h)	conv. (%)[a]	*dr*[b] a:b:c:d	241 *ee* (%)[c]	a *ee* (%)[d]	d *ee* (%)[d]
1	-	**82**	**245**	24	0	-	-	-	-
2	***i*-Pr$_2$NEt**[e]	**82**[f]	**245**	24	87	81:14:4:1	-	-	-
3	**242**	**82**	**245**	111	45	78:<2:<2:22	3	31	81
4	**243**	**82**	**245**	111	46	82:<2:<2:18	4	46	82
5	**243**	**244**	**246**	24	50	75:<2:<2:25	2	39	79

[a]Conversion of starting material **82** (or **244**) was 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 after derivatisation of the unreacted starting material 303 by ring opening alcoholysis with MeOH followed by *in situ* esterification with $TMSCHN_2$. [d]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. [e]20 mol% was used. [f]1.0 equiv. of **82** was used.

These results reinforced our belief that under base-mediated catalysis, a two-stereocentre DKR *via* a rapid epimerisation/racemisation of the anhydride starting material relative to cycloaddition to the aldehyde component would be easier to develop

than the initially targeted KR process. Again, for reproducibility purposes, a KR of **239** was attempted using the more electron deficient 4-nitrobenzaldehyde (**244**) in the presence of catalyst **243**. While the reaction was considerably faster, the enantio- and diastereocontrol associated with both starting material **241** and the main product diastereomer **246a** were in line with those expected from our preliminary experiments (*i.e.* confirmation of DKR occurring over KR, entry 5, Table 2.2).

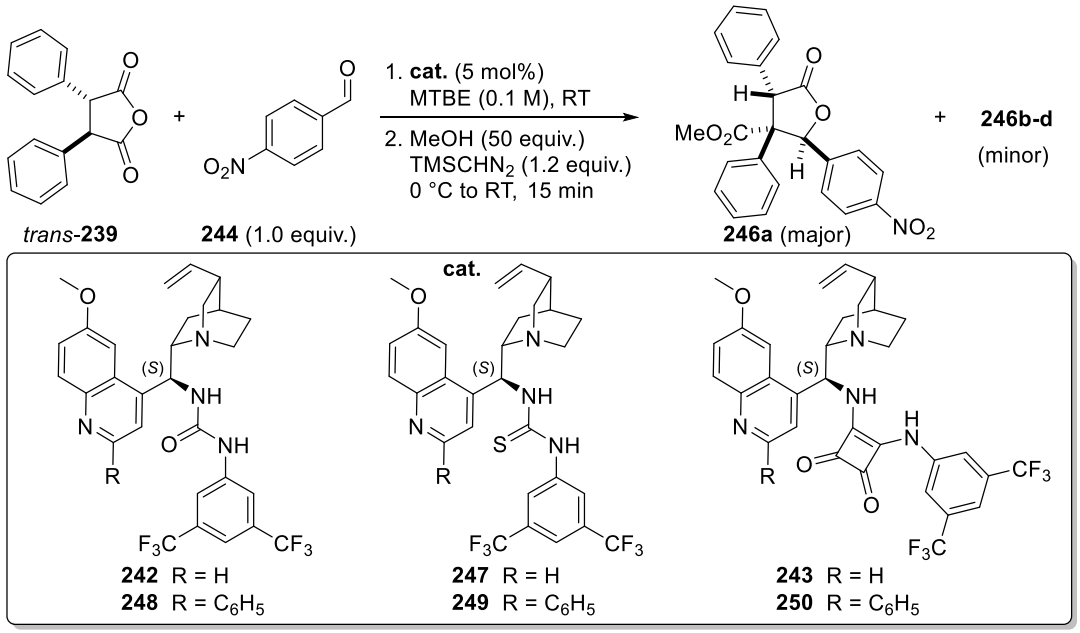
2.2 Catalyst screening for the DKR of diphenyl succinic anhydride *via* cycloaddition to 4-nitrobenzaldehyde.

Our first objective was to determine if one class of organocatalyst would emerge as significantly superior to the others for the promotion of the DKR of (*trans*)-**239**. Therefore, our attention first turned to the screening of a series of catalysts possessing a variety of electronic and steric properties belonging to three among the main families of bifunctional organocatalysts based on a cinchona alkaloid scaffold: *i.e.* ureas, thioureas and squaramides. The results of our preliminary experiments regarding the cycloaddition DKR of (*trans*)-**239** to 4-nitrobenzaldehyde (**244**) in MTBE are presented in Table 2.3.

The use of either urea-based catalyst **242** or its *C*-2 arylated analogue **248** allowed for the formation of the lactones **246a-d** with moderate diastereo- and enantiocontrol (entries 1-2, Table 2.3). The exchange of the urea functionality for the more acidic thiourea (*i.e.* **247** and **249**) led to comparable results (entries 3-4, Table 2.3).

Improvements were observed upon evaluation of squaramide analogues (*i.e.* **243** and **250**). These catalysts promoted reactions with excellent diastereoselectivity as the major lactone **246a** was formed as almost the sole product (up to 97:3 dr, entries 5-6). While these encouraging results indicated that two-stereocentre DKR of enolisable diaryl succinic anhydrides were possible – the enantioselectivity of the process remained far from synthetically useful (up to 42% *ee*, Table 2.3).

Table 2.3 Initial catalyst screening.

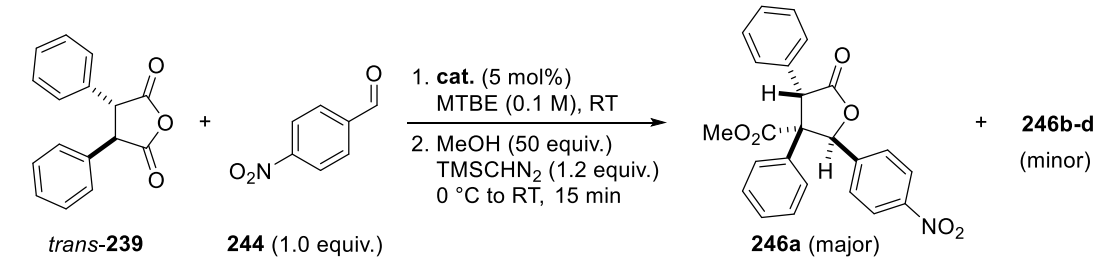


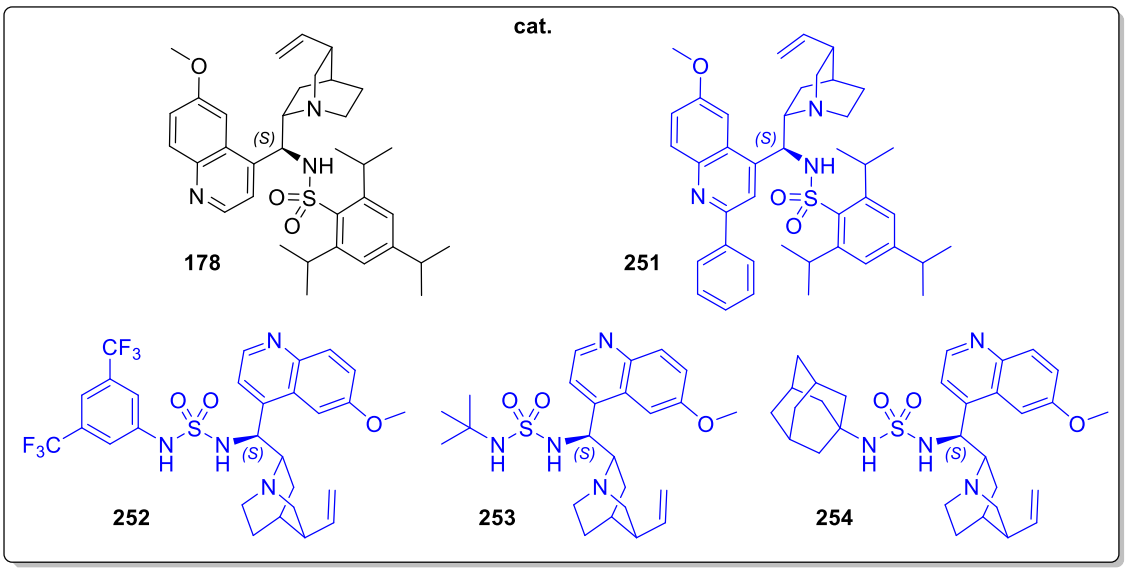
entry	cat.	time (h)	conv. (%)[a]	246 *dr*[b] a:b:c:d	246a *ee* (%)[c]
1	**242**	48	83	73:<1:<1:27	10
2	**248**	48	83	63:<1:<1:37	40
3	**247**	48	78	68:<1:<1:32	24
4	**249**	48	87	67:<1:<1:33	38
5	**243**	48	86	97:<1:<1:3	31
6	**250**	48	84	94:<1:<1:6	42

[a]Conversion of starting material **244** was determined by ^{1}H NMR spectroscopic analysis using 4-iodoanisole as an internal standard. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. [c]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$.

Given the disappointing level of enantiocontrol obtained with these three classes of catalyst, we next oriented our efforts towards the evaluation of a series of different types of hydrogen bond donor functionalities including sulfonamides (*i.e.* **178** and **251**) and sulfamides (*i.e.* **252-254**, Table 2.4).

Table 2.4 Screening of sulfonamide and sulfamide catalysts.





entry	cat.	time (h)	conv. (%)[a]	246 *dr*[b] a:b:c:d	246a *ee* (%)[c]
1	**178**	72	86	97:<2:<2:3	48
2	**251**	96	82	91:<2:<2:9	47
3	**252**	168	98	94:<2:<2:6	20
4	**253**	120	82	95:<2:<2:5	51
5	**254**	168	99	97:<2:<2:3	20

[a]Conversion of starting material **244** was 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 after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$.

Beginning with the reaction involving catalyst **178** (catalyst synthesised by former group member Dr. Aldo Peschiulli), under the reaction conditions outlined above, we obtained a good level of diastereocontrol along with marginally improved enantioselectivity (entry 1, Table 2.4). As the introduction of a *C*-2 phenyl substituent at the quinoline moiety of the catalyst had previously led to systematically improved

levels of enantioselectivity (*ca.* 10-30% *ee* improvement), we evaluated the *C*-2 phenyl arylated analogue of **178** (*i.e.* **251**, catalyst highlighted in blue and initially designed and synthesised for the purpose of developing the process described in Chapter 3. Unfortunately, this modification proved to be rather unproductive as the global stereocontrol over the reaction was similar to that obtained with **178** (entry 2, Table 2.4).

The next three catalysts employed, also highlighted in blue (*i.e.* **252**-**254**), were also synthesised with the aim of developing a completely different process which will be described in the next chapter. However, those catalysts were co-evaluated at that time in the DKR of (*rac*)-**239**. They all promoted reactions with excellent diastereoselectivity albeit with the enantioselectivity still considered to be far from synthetically useful (entries 3-5, Table 2.4).

Given the disappointing levels of enantiocontrol obtained so far, it seemed clear that a more consequential change in the catalyst structure was necessary. Therefore, we embarked in the screening and evaluation of sterically more hindered squaramide catalysts (all available in the group) with hope of obtaining better catalyst-mediated enantiodiscrimination. The results obtained are presented in Table 2.5.

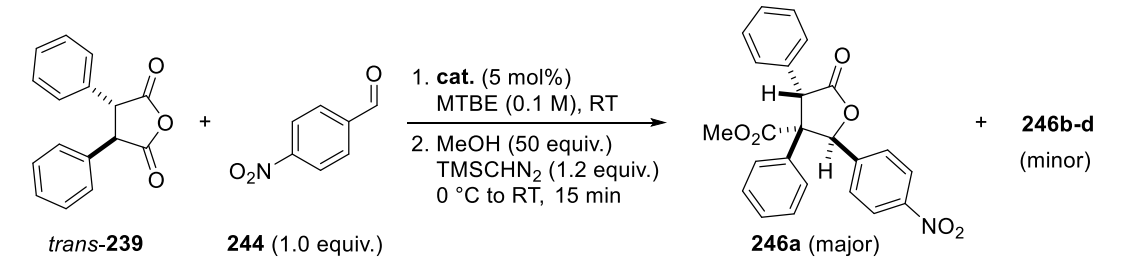
The recently developed *tert*-butyl-substituted squaramide catalysts **126** and **255** (previously successful in a catalytic Tamura cycloaddition reaction involving enolisable glutaconic anhydride with alkyldiene oxindoles[71]) proved to be rather inefficient. Interestingly, as was the case with most of the previously evaluated catalysts, the introduction of a *C*-2 phenyl substituent on the quinoline moiety of the catalyst led to improved performance (entries 1-2, Table 2.5).

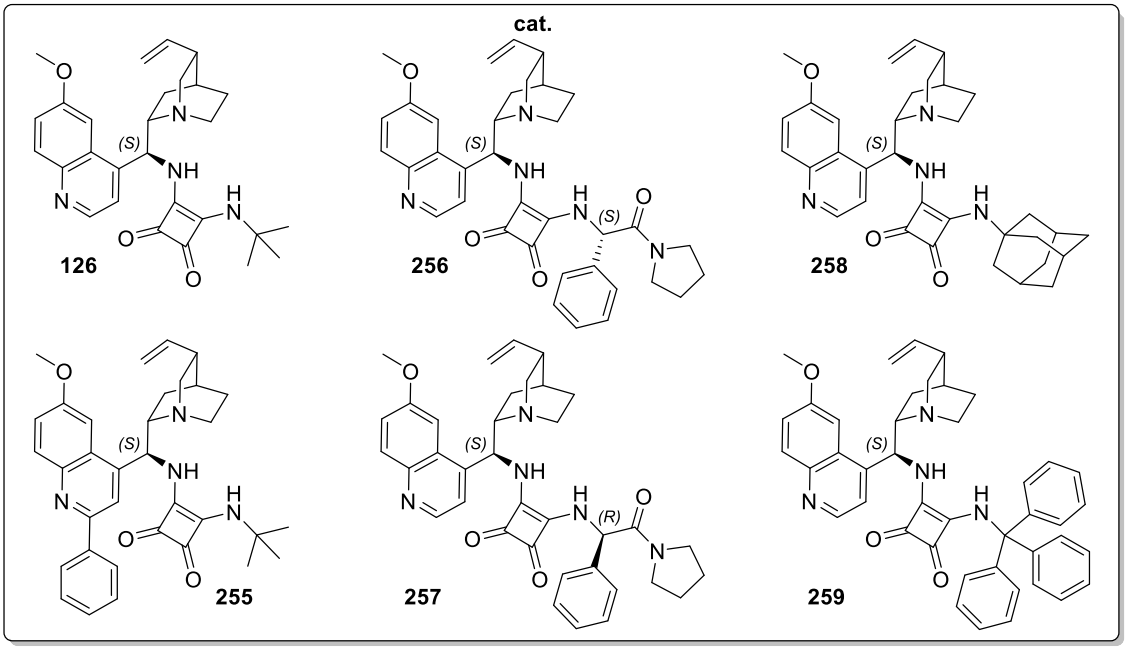
The newly-developed catalysts **256** and **257** (previously successful in a KR process of α-branched aldehydes (see Section 1.7.4) and provided by former group member Dr. U. Farid) also proved to be an unproductive structural modification in terms of catalyst performances (entries 3-4, Table 2.5).

Augmentation of the *N*-alkyl steric requirement of the substituent from a *tert*-butyl to a adamantyl and a trityl moiety (*i.e.* catalysts **258** and **259** respectively) resulted in an unexpected outcome. When **259** was employed as the promoter of the reaction, the observed diastereoselectivity was marginally diminished but reversed in favour of the

formation of the usually minor diastereomer **246d**, along with a dramatic improvement in enantioselectivity (entries 5-6, Table 2.5).

Table 2.5 Screening of different squaramide-based catalysts.





entry	cat.	time (h)	conv. (%)[a]	246 *dr*[b] a:b:c:d	246 *ee* (%)[c] a:d
1	**126**	48	84	70:<2:<2:30	8:n.d.[d]
2	**255**	48	86	84:<2:<2:16	41:n.d.[d]
3	**256**	72	76	75:<2:<2:25	34:n.d.[d]
4	**257**	72	87	74:<2:<2:26	26:n.d.[d]
5	**258**	96	85	83:<2:<2:17	18:n.d.[d]
6	**259**	144	81	35:<2:<2:65	n.d.[d]:95

[a]Conversion of starting material **244** was 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 after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. [d]Not determined.

The relative stereochemistry of lactone **246a** was assigned by a combination of ^{1}H NMR Nuclear Overhauser Effect (NOE) irradiations. NMR experiments proved that the diastereomer **246a** possesses a 1,2-*cis* and 2,3-*trans* relationship (*trans* between the two newly formed stereogenic centres).

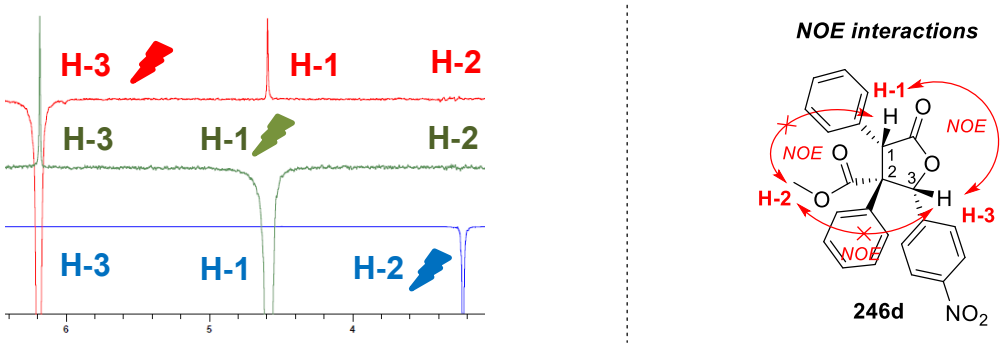


Figure 2.5 Relative stereochemistry assignment of **246d** by NOE irradiation.

Interestingly, and perhaps surprisingly, in the particular case of lactone **246d**, saturation at *H*-1, *H*-2 and *H*-3 demonstrated that both protons at *C*-1 and *C*-3 are on the same side of the molecule while no contact with the protons *H*-2 was detected. These results allowed for the assignment of an unexpected 1,2-*cis* and 2,3-*cis* relative relationship between the three aromatic substituents of diastereomer **246d** (Figure 2.5).

As part of this thesis, no computational studies were carried out to rationalise the sense of this unusual diastereoselectivity (see X-ray structures in Section 4.5 for relative stereochemistry). We hypothesised that the combination of the steric hindrance and the plausible occurrence of π stacking interactions between all the aromatic rings involved could be at the origin of the phenomenon (see Figure 2.10). While we were delighted with the enantiocontrol achieved over the process, we now faced a diastereoselectivity problem, as **246d** was formed in a low 2:1 dr (entry 6, Table 2.5).

To address this remaining challenge, we designed four new organocatalysts, all derived from the core of the successful trityl catalyst **259**. Catalysts **260** and **261** aimed to investigate the effects of the steric at the trityl and *C*-2 positions. Catalysts **262** and **263** were designed in order to investigate the influence of the electronic properties (*i.e.* modulate the acidity of N-H-bonds, Figure 2.6).

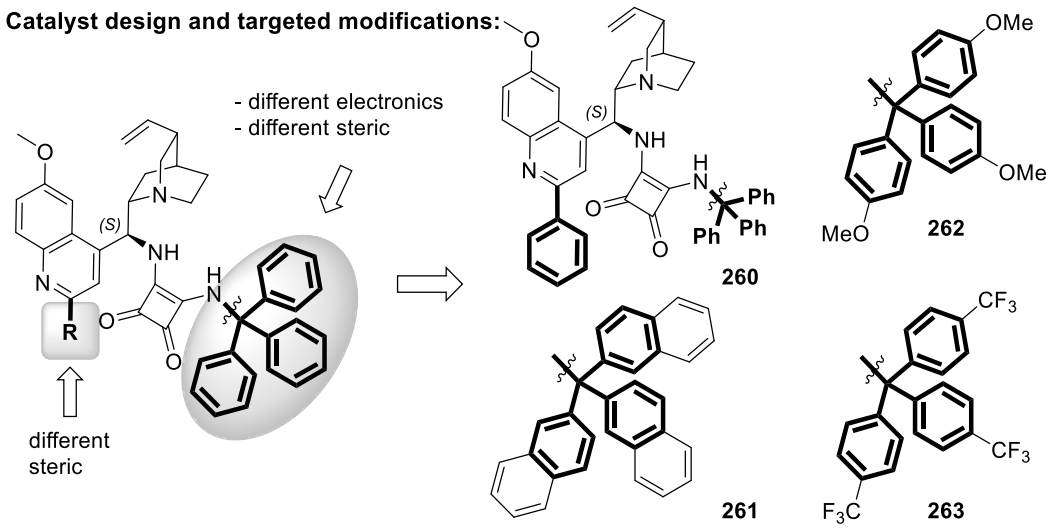
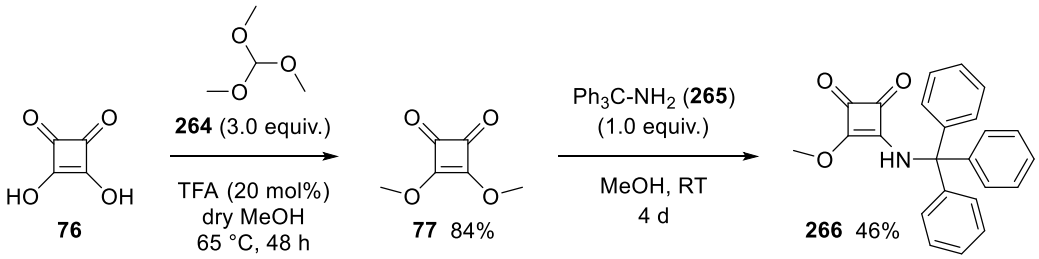


Figure 2.6 Catalyst elements of design – trityl scaffold key modifications.

2.3 Organocatalyst design: modification of the trityl moiety characteristics

The synthesis of the direct analogue to catalyst **259** (*i.e.* its *C*-2 phenyl arylated version **260**) begins with the short sequence depicted below in Scheme 2.2.



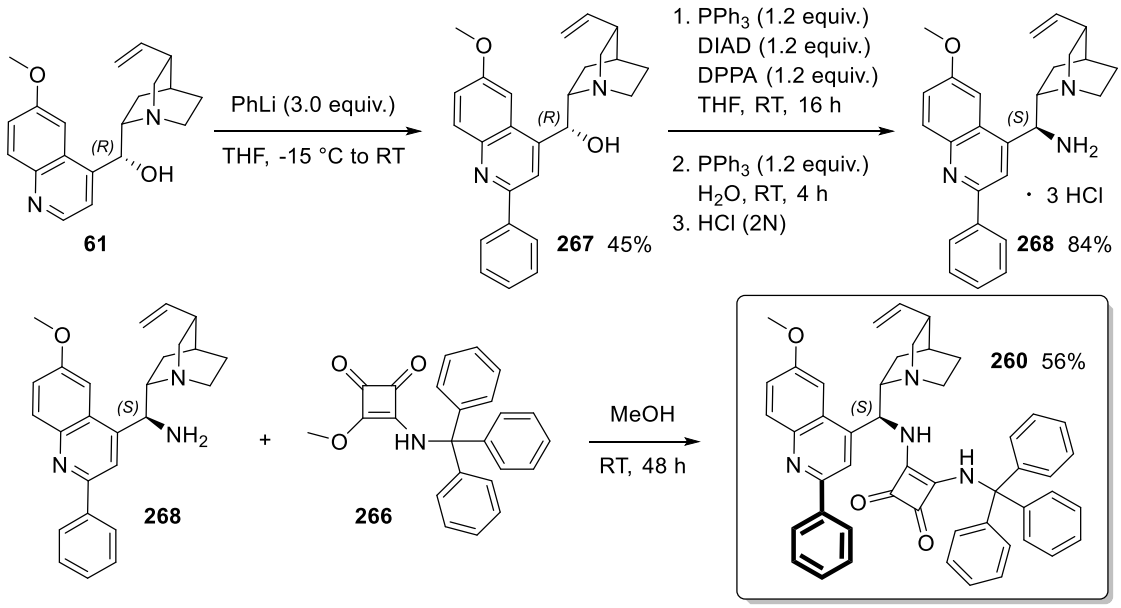
Scheme 2.2 Synthesis of catalyst precursor **266**.

Heating squaric acid **76** under reflux in anhydrous MeOH for 48 h, in the presence of trimethyl orthoformate (**264**) and a catalytic amount of trifluoroacetic acid (TFA), allows for the formation of the reactive dimethyl squarate **77**. The next step (*i.e.* **77→266**) which appears at first to be a straightforward transformation proved to be extremely concentration dependent. Dr. U. Farid developed an efficient and reproducible protocol to react **77** with trityl amine (**265**) in highly concentrated methanolic solution (see conditions in Chapter 4), furnishing **266** in 46% yield after isolation of the precipitate formed by vacuum filtration (Scheme 2.2).

The second half of the route towards **260** begins with the arylation of the *C*-2 position of the commercially available quinine (**61**). This was accomplished by following a known literature procedure,[83] the reaction involved the use of an excess of phenyl

lithium, at low temperature and furnished **337** in 45% isolated yield after column chromatography (Scheme 2.3).

The amine hydrochloride salt (*i.e.* **268**·HCl) was obtained following the one-pot multi step synthesis as follows: a Mitsunobu reaction on alcohol **267** (accompanied with inversion of the configuration at the *C*-9 position) provided an azido intermediate which was *in situ* reduced *via* a Staudinger reaction.[83] A final acidic extraction work-up allows the isolation of **268**·HCl after concentration of the aqueous layer (Scheme 2.3).

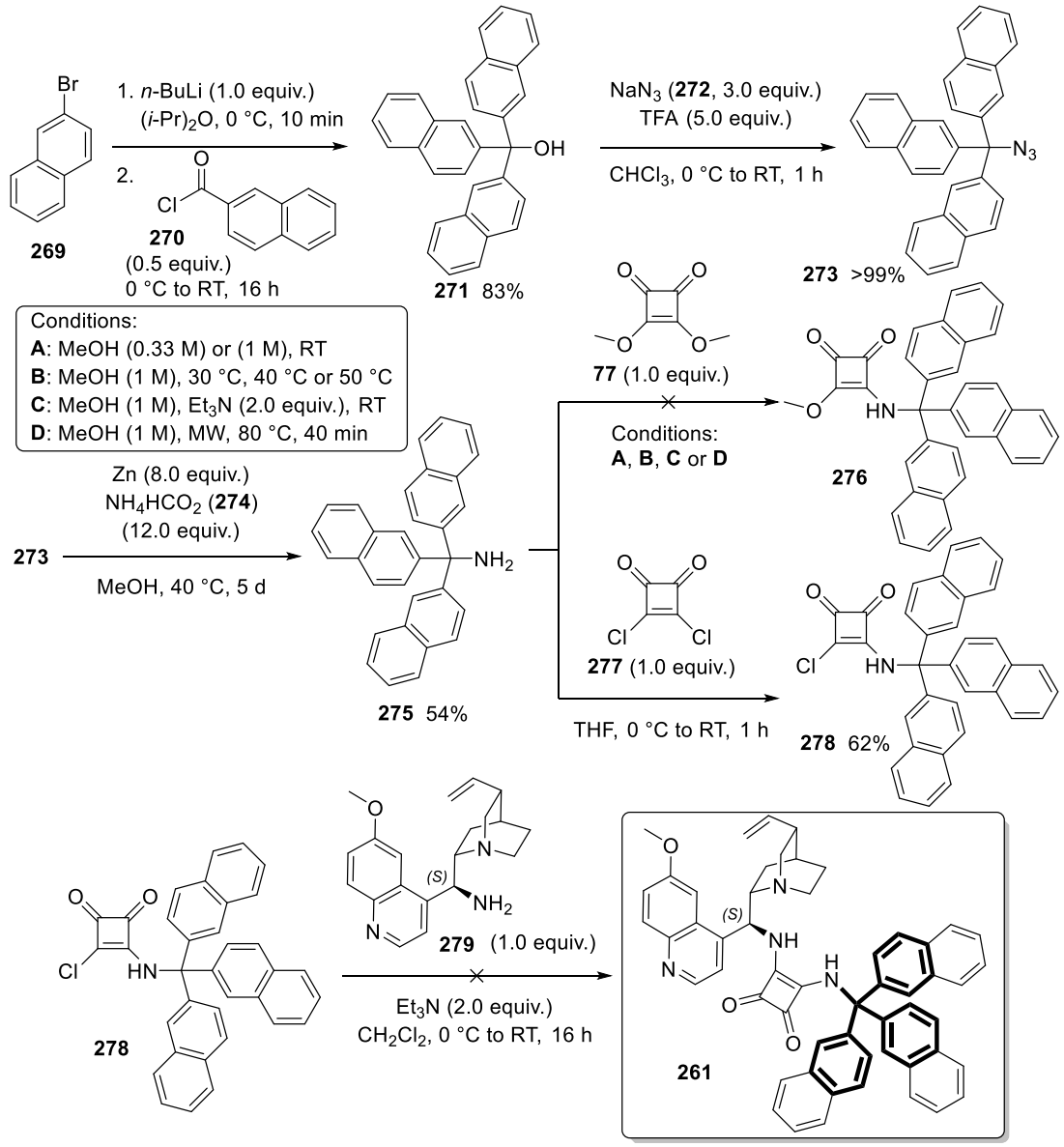


Scheme 2.3 Synthetic route towards catalyst **260**.

Treatment of the free amine of **268** and subsequent reaction with the previously synthesised coupling partner **266**, in dry methanol, afforded the catalyst **260** which was isolated as a pure material by filtration of the crude reaction mixture precipitate upon completion of the reaction (Scheme 2.3).

The targeted synthetic pathway leading to catalyst **261** is depicted in Scheme 2.4. A lithium halogen exchange on the commercially available 2-bromonaphthalene (**269**) was mediated by addition of a stoichiometric amount of *n*-butyl lithium, furnishing a lithiated nucleophilic reactive intermediate that was subsequently engaged in a double addition process with the commercially available 2-naphthoyl chloride (**270**). The reaction furnished the sterically hindered alcohol **271**, which was isolated in 83% yield after purification by column chromatography (Scheme 2.4).

A relatively stable tertiary carbocation was generated from alcohol **271** by using an excess of trifluoroacetic acid and was immediately reacted with sodium azide (**272**), in a S_N1 reaction, furnishing the azido compound **273** in near quantitative yield (Scheme 2.4). Screening of various reaction conditions for the subsequent reduction of azide **273** to the corresponding amine **275** identified the combination of zinc and ammonium formate (**274**) as an efficient system for accessing **275**, which was isolated in a modest 54% yield (Scheme 2.4).

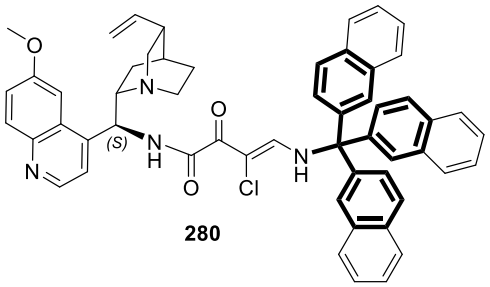


Scheme 2.4 Synthetic route towards catalyst **261**.

The next step proved to be more challenging. A series of reaction conditions were evaluated (*i.e.* **A**-**D**) and successively failed in affording the targeted substituted squaric

amide derivative **276**. Higher temperatures or base-mediated conditions did not lead to the product formation either (Scheme 2.4).

Therefore, we attempted to change the electrophilic component of the reaction to the more electrophilic dichlorosquarate (**277**) and successfully managed to isolate the squarate analogue **278** in 62% yield after column chromatography (Scheme 2.4). Unfortunately, under the conditions depicted in Scheme 2.4, the final product **261** was not formed. Instead, the reaction yielded a complex mixture of compounds containing the open squarate derivative **280** as the major side product. This compound was isolated and the structure confirmed by both mass spectrometry and a series of NMR spectroscopic analyses (Figure 2.7).



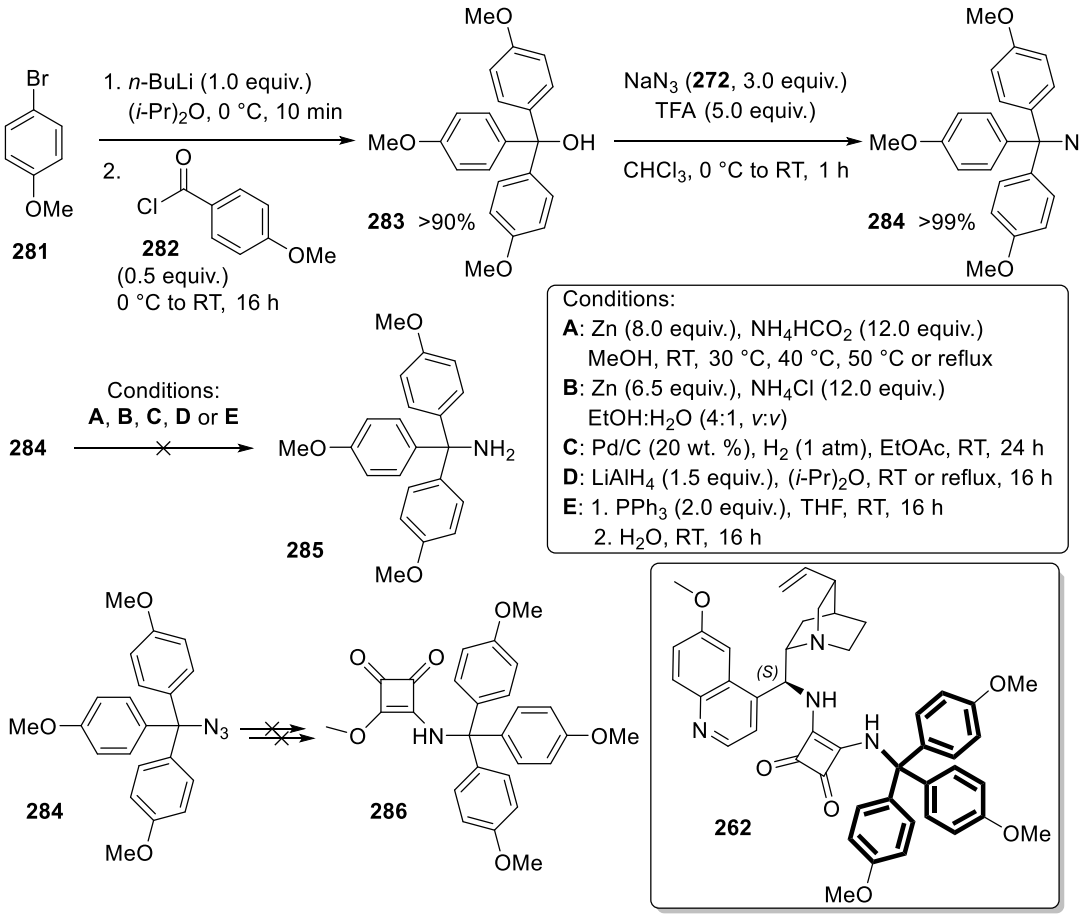
280

Figure 2.7 Main product isolated from the targeted key reaction coupling **278**→**261**.

Following a similar pathway to that used to prepare catalyst **261**, 4-methoxytrityl alcohol (**283**) was obtained in 90% yield after double addition of the *in situ* formed lithiated derivative, prepared from **281**, to the acyl chloride electrophile **282** (Scheme 2.5).

The subsequent azide formation was performed using the same conditions shown in Scheme 2.4, furnishing **284** in quantitative yield. The stability of the intermediate carbocation was greatly enhanced with this specific substitution pattern on the trityl moiety (due to the three stabilising EDG introduced) and allowed for excellent S_N1 reaction with sodium azide (**272**). However, this increased electron density proved to be rather problematic in the next step (Scheme 2.5).

Azide **284** was extremelly stable and proved completely inert towards its reduction to amine **285**. Examination of a series of reaction conditions ranging from mild to harsh were all unproductive (*i.e.* **A**-**E**). Only starting material could be recovered from the reactions, thereby, precluding access to the targeted catalyst **262** (Scheme 2.5).



Scheme 2.5 Targeted synthetic route towards catalyst **262**.

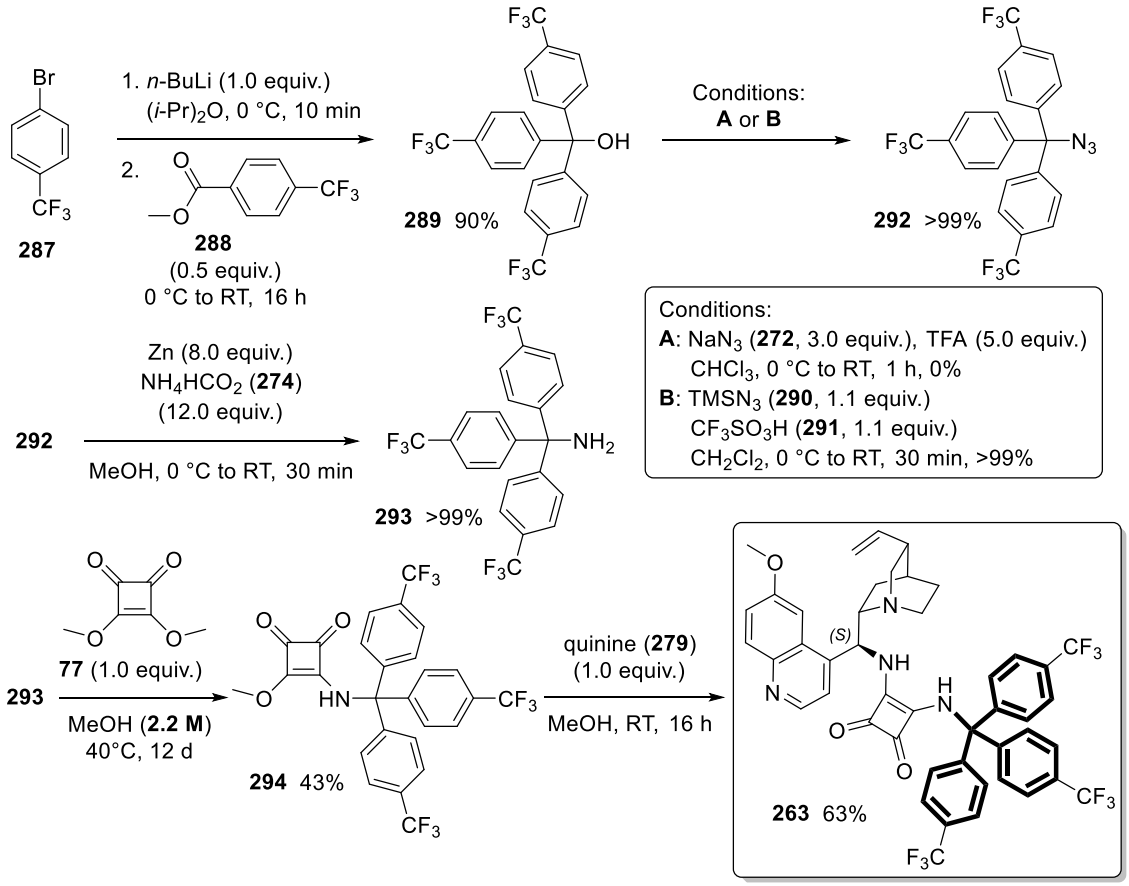
Again, following a similar route, 4-trifluoromethyltrityl alcohol (**289**) was obtained in 90% yield after attack from the *in situ* prepared lithiated derivative, prepared from **287**, to methyl ester **288** (Scheme 2.6).

It is noteworthy that the carbocations generated during the syntheses of **273** and **284** were stable and generated using the relatively mild trifluoroacetic acid (see Scheme 2.4 and Scheme 2.5). However, **289** was completely unreactive in an S_N1 reaction with sodium azide (**272**) in the presence of TFA. Significantly harsher conditions involving a combination of a slight excess of trimethyl silyl azide (**290**) and triflic acid (**291**) allowed the circumvention of the problem and led to full conversion to **292** (Scheme 2.6).

The reduction to trityl amine (**293**) was performed in the presence of a large excess of zinc and ammonium formate (**274**) which was later found totally unnecessary as the reaction went smoothly to completion, within half an hour, as monitored by TLC

analysis or by direct observation of the N_2 released out of the reaction medium (Scheme 2.6).

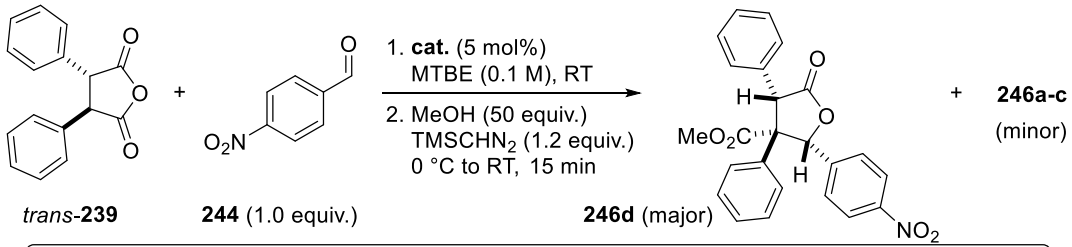
We were initially concerned that the combination of the steric hindrance and relatively weaker nucleophilicity of amine **293** compared with trityl amine **265** would most likely prevent the coupling between **77** and **293** from occuring. Gratifyingly, high concentrations in MeOH (2.2 M) and a long reaction time (12 days), at 40 °C, allowed the formation of **294**, isolated in 43% yield. A well-established literature procedure involving the reaction of the free-amine of quinine **279** with **294** allowed the formation of **263**, isolated in 63% yield after flash column chromatography (Scheme 2.6).

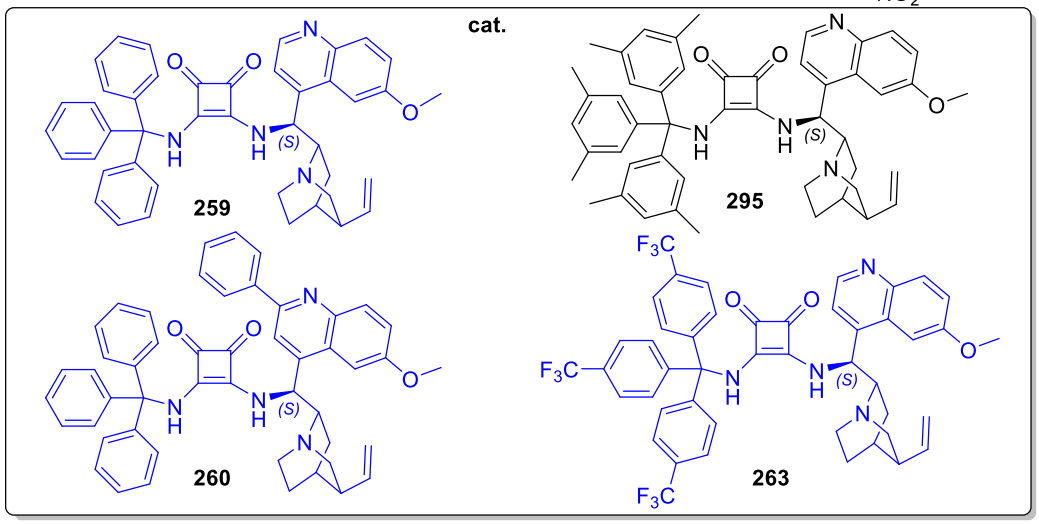


Scheme 2.6 Synthetic route towards catalyst **263**.

Despite two failed syntheses of promising catalyst structures (*i.e.* **261** and **263**) we were able to design and evaluate a total of four new catalysts based on the trityl core. These four catalysts were judged to be suitable candidates for mimicking all of the steric and electronic properties we were initially interested in. The results of their evaluation in our model reaction are summarised in Table 2.6.

Table 2.6 Influence of sterically and electronically diverse trityl-based squaramides on the DKR process.





entry	cat.	time (h)	conv. (%)[a]	246 *dr*[b] a:b:c:d	246d *ee* (%)[c]
1	**259**	144	81	35:<2:<2:65	95
2	**260**	120	68	37:<2:<2:63	85
3	**295**	96	98	37:<2:<2:63	83
4	**263**	48	98	50:<2:<2:50	90

[a]Conversion of starting material **244** was determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b]Determined by ^{1}H NMR spectroscopic analysis. [c]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$.

The first entry has been reproduced from Table 2.5 for clarity and consistency purposes. Evaluation of the *C*-2 phenyl arylated catalyst analogue of **259** (*i.e.* **260**) unfortunately resulted in slower reaction rate, lower diastereoselectivity and a reduced level of enantioseletivity (entry 2, Table 2.6).

The last two attempts to influence the stereocontrol of the process through modification of the steric and electronic characteristics of the trityl group through the evaluation of

the recently synthesised catalysts **295** (catalyst provided by Dr. U. Farid) and **263** were both unproductive (entries 3-4, Table 2.6).

2.4 Optimisation studies for the formal cycloaddition DKR of di-phenyl succinic anhydride with 4-nitrobenzaldehyde

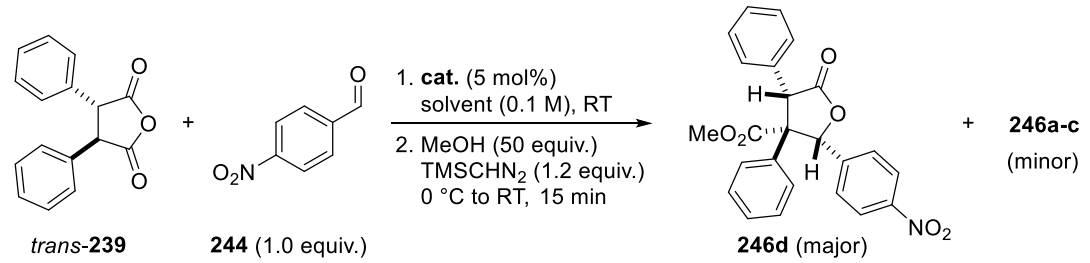
In summary, at this point of the study, we had evaluated a library of a total of 24 different organocatalysts in our model reaction (only a selection of relevant but non-exhaustive examples have been reported in Sections 2.2 and 2.3). These catalysts were all derived from the chiral quinine scaffold and presented five different types of hydrogen-bond units capable of interacting with the starting material in a specific manner (*i.e.* ureas/thioureas, sulfonamides, sulfamides and squaramides).

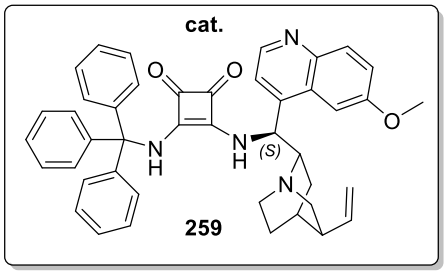
In light of the results obtained during the catalyst screening/design we decided to move forward and oriented our efforts towards the optimisation of the reaction parameters (*i.e.* solvent, temperature, solvent concentration, *etc*). We decided to focus our efforts on further improving the stereocontrol of the reaction mainly with regard to the diastereocontrol of the lactones, using as an optimal catalyst the structurally simplest, easiest to synthesise and considerably most selective squaramide organocatalyst **259**.

In the following series of optimisation experiments, the carboxylic acid lactones produced by the reaction were always esterified *in situ* with trimethylsilyldiazomethane in order to facilitate CSP-HPLC analysis and isolation of the major diastereomer *via* column chromatography. This process is now a well-established derivatisation procedure which allows for near quantitative conversion to the corresponding methyl ester, under mild reaction conditions and preventing product epimerisation.[139]

An initial screening of solvents carried out in previously reported work indicated ethereal solvents as optimal choices for the reaction.[71,83,88] At that time, this phenomenon was rationalised by the improved compatibility of sub-stoichiometric loadings of amines (*i.e.* such as the tertiary nitrogen of the quinuclidine moiety of the catalyst) with products bearing carboxylic acid functionalities due to their relatively higher pK_a in ethereal solvents and, therefore, preventing catalyst inhibition upon protonation of the quinuclidine. The influence of the solvent on the diastereoselectivity of the process cataysed by **259** is reported in Table 2.7.

Table 2.7 Influence of the choice of solvent.



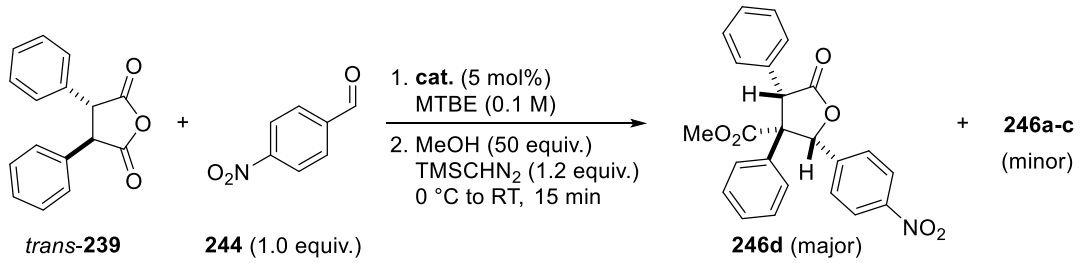


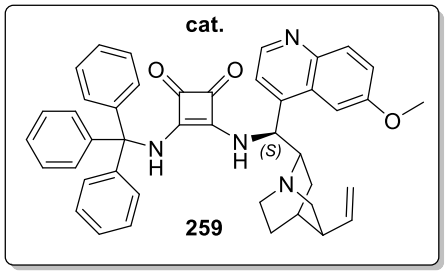
entry	time (d)	solvent	conv. (%)[a]	*dr*[b] 246d:Σothers	246d *ee* (%)[c]
1	6	THF	89	1:1	89
2	6	Et_2O	92	1.4:1	96
3[d]	20	$(i\text{-Pr})_2O$	62	1.4:1	89
4	4	2-Me-THF	86	1:1	70
5	6	MTBE:2-Me-THF (1:1, *v*:*v*)	94	1:1	93
6	4	MTBE:2-Me-THF (9:1, *v*:*v*)	81	1.4:1	91
7	6	MTBE	81	1.9:1	95

[a]Conversion of starting material **244** was determined by ^{1}H NMR spectroscopic analysis using 4-iodoanisole as an internal standard. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. Here dr = (major diastereomer):(Σ other diastereomers). [c]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. [d]Catalyst insoluble.

As we had suspected, based on previously reported work, the evaluation of a series of ethereal solvents clearly indicated MTBE as the optimal solvent choice for the reaction (Table 2.7). Indeed, most of the solvents evaluated allowed for the formation of the major diastereomer with good to excellent levels of enantioselectivity, albeit with rather poor levels of diastereoselectivity (entries 1-6). On the other hand, the choice of MTBE allows for the reaction to proceed with a slightly improved level of preference for **246d** along with an excellent and superior level of enantiocontrol (up to 1.9:1 dr, 95% *ee*, entry 7, Table 2.7).

Table 2.8 Influence of the temperature.





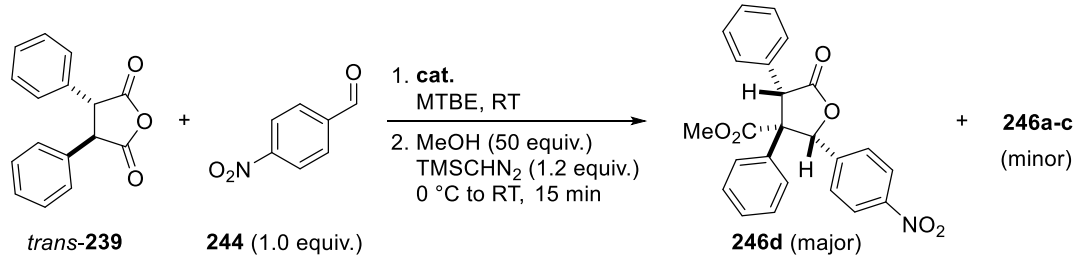
entry	time (d)	temp (°C)	conv. (%)[a]	*dr*[b] 246d:Σothers	246d *ee* (%)[c]
1[d]	17	-30	55	1:3	n.d.[e]
2	7	-15	60	1:2	n.d.[e]
3	7	0	80	1:1.4	89
4	6	RT	81	1.8:1	95
5	3	30	84	2.1:1	96
6	3	40	>99	n.d.[f]	92

[a]Conversion of starting material **244** was determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. Here dr = (major diastereomer):(Σ other diastereomers). [c]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. [d]20 mol% of the catalyst was used. [e]Not determined. [f]Not determined. Formation of 4 diastereomers. The concentration couldn't be maintained constant throughout the entire reaction.

The effect of the temperature was also studied: using catalyst **259** at -30, -15 or 0 °C respectively almost shut down the reactivity. Indeed, the conversion determined by ^{1}H NMR spectroscopy ranged from 55-80% only after 7 to 17 days of reaction (entries 1-3, Table 2.8). Furthermore, decreasing the temperature reversed the diastereoselectivity back in favour of the formation of the undesired diastereomer **246a**. This observation led us to consider the opposite approach and we evaluated the impact of the use of higher temperatures (entries 4-6, Table 2.8). At 30 °C, both diastereo- and enantiocontrol were slightly improved (up to 2.1:1 dr, 96% *ee*, entry 5, Table 2.8).

Evaluation of the performance of **259** at 40 °C resulted in a tremendously improved reaction time albeit with a diminished level of enantioselectivity (92% *ee*, entry 6, Table 2.8). These new reaction conditions initially appeared as improvements over the process control and we decided to move forward to the evaluation of the substrate scope with respect to the aldehyde component using the conditions as described in entry 5 of Table 2.8). However, while working with aldehydes less electrophilic than **244** we found it extremely challenging to maintain the solvent concentration constant for extensive periods of time. Additionally, we noticed on several occasions the formation of all four diastereomers while working at 30 °C (up to 15% of the two minors).

Table 2.9 Influence of concentration and catalyst loading.



entry	time (h)	conc. (M)	cat. loading (x mol%)	conv. (%)[a]	*dr*[b] 246d:Σothers	246d *ee* (%)[c]
1[d]	144	0.1	5	81	1.8:1	95
2	96	0.2	5	95	2.1:1	90
3	96	0.1	10	91	2.3:1	90
4	96	0.1	20	95	1.4:1	90
5[e]	20	0.1	5	90	1.6:1	90

[a]Conversion of **244** was determined by ^{1}H NMR analysis using *p*-iodoanisole as an internal standard. [b]Diastereomeric ratio determined by ^{1}H NMR analysis. Here dr = (major diastereomer):(Σ other diastereomers). [c]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters with $TMSCHN_2$. [d]Data reproduced from Table 2.6. [e]Solvent: MTBE:THF (9:1, *v*:*v*, 0.1M).

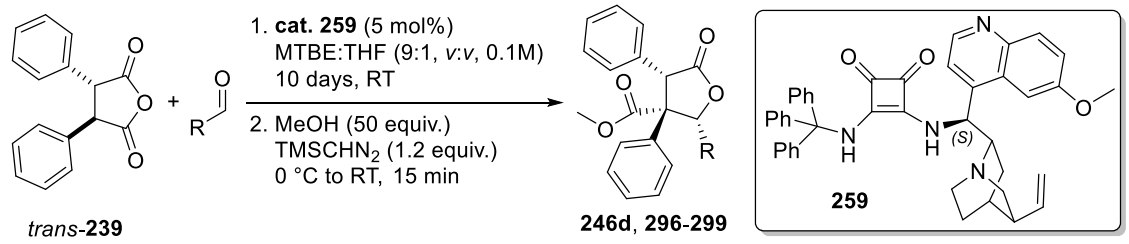
To circumvent the drawbacks associated with the use of high temperatures we decided to refine the parameters of the reaction and attempted complementary experiments aiming to increase the reaction rate. The results obtained are reported in Table 2.9.

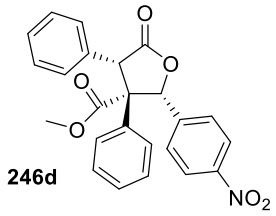
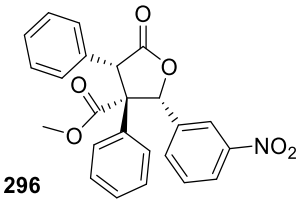
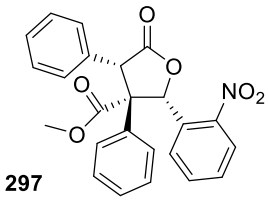
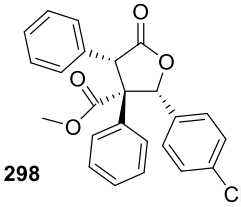
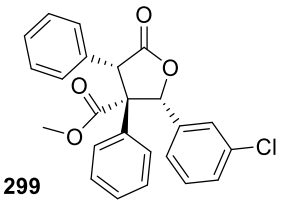
Higher molarity (0.2M, entry 2) or catalyst loadings (*e.g.* 10-20 mol%, entries 3-4) resulted in expected higher conversions after comparable reaction times. However, the levels of enantioselectivity were diminished (reduced by ≈ 5% *ee*). If MTBE proved to be the solvent of choice for several organocatalytic processes, it should be noted that a range of squaramide based organocatalysts exhibit poor solubilities in this solvent. Increasing the catalyst loading, from 10 to 20 mol%, (entries 3-4) resulted in fairly similar outcomes (*i.e.* similar conversion and reaction rate). Indeed, at room temperature, catalyst **259** forms a visible suspension in MTBE which becomes denser at higher loadings. To circumvent this remaining issue, we simply decided to use 10% of THF as co-solvent to increase the catalyst solubility in the reaction medium. Gratifyingly, this trivial modification resulted in a slightly diminished level of selectivity albeit with the tremendously improved reaction rate (90% conv after 20 h, entry 5, Table 2.9). Therefore, we decided to move forward and evaluate the substrate scope with respect to the aldehyde component with the conveniently optimised reaction conditions as follows: MTBE:THF (9:1, *v*:*v*, 0.1M) at ambient temperature, with the catalyst **326** employed at 5 mol % loading.

2.5 Evaluation of the substrate scope: the aldehyde component

With an optimal catalyst and a synthetically useful protocol in hand, our attention now turned to the important question of the substrate scope with respect to the electrophilic component. The results of this screening are reported in Table 2.10. The methodology proved to be rather robust: anhydride (*rac*)-**239** was reacted in a 1:1 ratio with various aldehydes, leading to the corresponding lactones, bearing electron-deficient (*i.e.* **246d**, **296**-**299**, **301**), electron neutral (*i.e.* **300**), rich (*i.e.* **302**), hindered (*i.e.* **303**), heterocyclic aromatic (*i.e.* **304**), and aliphatics moieties (*i.e.* **305**-**306**), in the presence of squaramide catalyst **259** (5 mol%), at ambient temperature. Substrates reacted smoothly, with the exception of 4-methoxybenzaldehyde and thiophene-2-carbaldehyde. The isolated yields of the main diastereomers produced by the reactions were in line with those expected from the conversions and the diastereoselectivities determined by ^{1}H NMR spectroscopy (Table 2.10).

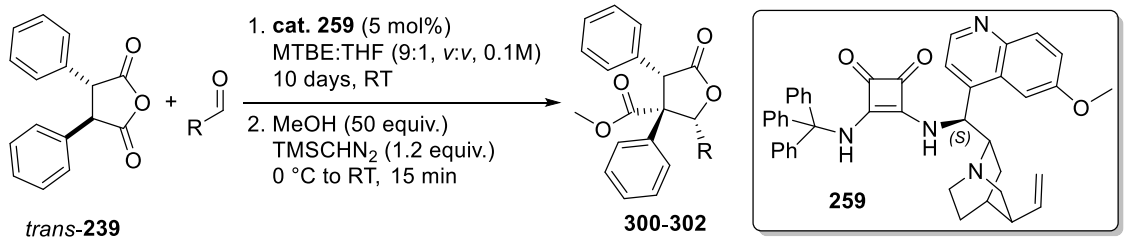
Table 2.10 Substrate scope: the electrophilic component.

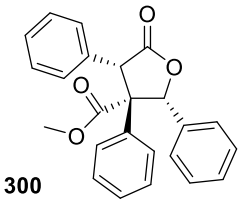
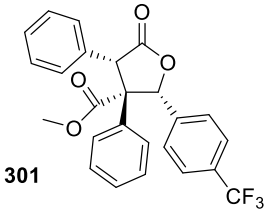
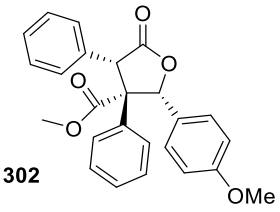


entry	product	conv. (%)[a]	yield. (%)[b]	*dr*[c]	*ee* (%)[d]
1	 **246d**	80	53	1.5:1	90
2	 **296**	83	53	2.3:1	85
3	 **297**	81	34	1:1	97
4	 **298**	91	51	2.3:1	95
5	 **299**	94	70	3.5:1	97

[a]Conversion of **239** was determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b]Isolated yield of the main diastereomer. [c]dr determined by ^{1}H NMR spectroscopic analysis. dr = (major diastereomer):(Σ other diastereomers). [d]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$.

Table 2.10 Substrate scope: the electrophilic component.

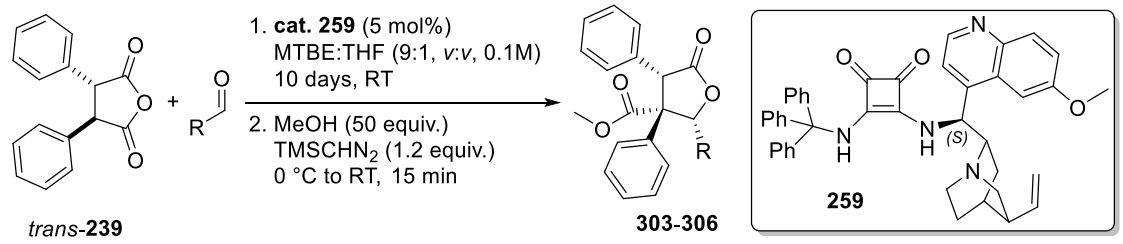


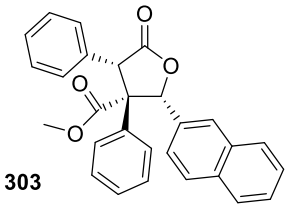
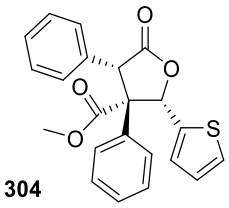
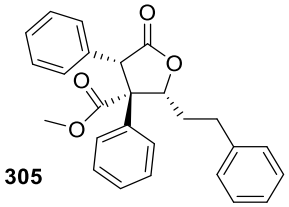
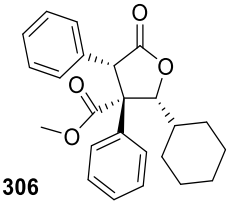
entry	product	conv. (%)[a]	yield. (%)[b]	*dr*[c]	*ee* (%)[d]
6	 **300**	89	61	3.5:1	99
7	 **301**	89	46	1.3:1	94
8[e]	 **302**	52	29	2.1:1	93

[a]Conversion of starting material **239** was determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b]Isolated yield of the main diastereomer. [c]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. Here dr = (major diastereomer):(Σ other diastereomers). [d]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. [e]10 mol% of the catalyst was used.

While diastereocontrol was variable, enantioselectiviy was generally high to excellent ranging from 85 to >99% *ee* (entries 1-12). Aliphatic aldehydes were also compatible: hydrocinnamaldehyde was demonstrated to serve as an excellent substrate, providing the corresponding lactone **305** in high yield, excellent dr and >99% *ee* (entry 11). The lactone derived from the bulkier cyclohexane carbaldehyde (*i.e.* **306**) was also formed in near optical purity and good yield albeit with diminished diastereoselectivity (entry 12, Table 2.10).

Table 2.10 Substrate scope: the electrophilic component.



entry	product	conv. (%)[a]	yield. (%)[b]	*dr*[c]	*ee* (%)[d]
9	 **303**	77	56	2.8:1	96
10	 **304**	50	37	10:1	87
11	 **305**	96	78	13:1	>99
12	 **306**	83	44	1.2:1	99

[a]Conversion of starting material **239** was determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b]Isolated yield of the main diastereomer. [c]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. Here dr = (major diastereomer):(Σ other diastereomers). [d]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. [e]10 mol% of the catalyst was used.

The relative stereochemistry of the lactones **246d**, **296**-**306** was assigned at an early stage of this study by using a combination of ^{1}H NMR Nuclear Overhauser Effect (NOE) experiments (Figure 2.5).

The absolute stereochemistry was later assigned by X-ray crystallographic analysis of a recrystallised sample of the major diastereomer formed in the reaction between **239** and benzaldehyde (*i.e.* **300**, 99% *ee*, Figure 2.8).

Figure 2.8 Absolute configuration assignment of lactone **300**.

For further confirmation and unequivocal assignment of the stereochemistry a recrystallised sample of the major diastereomer produced in the reaction between **239** and the aliphatic hydrocinnamaldehyde (*i.e.* **305**, >99% *ee*) was also subjected to X-ray crystallographic analysis (Figure 2.9).

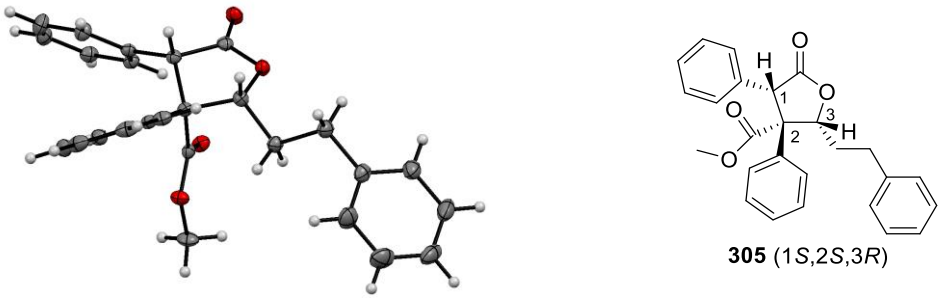


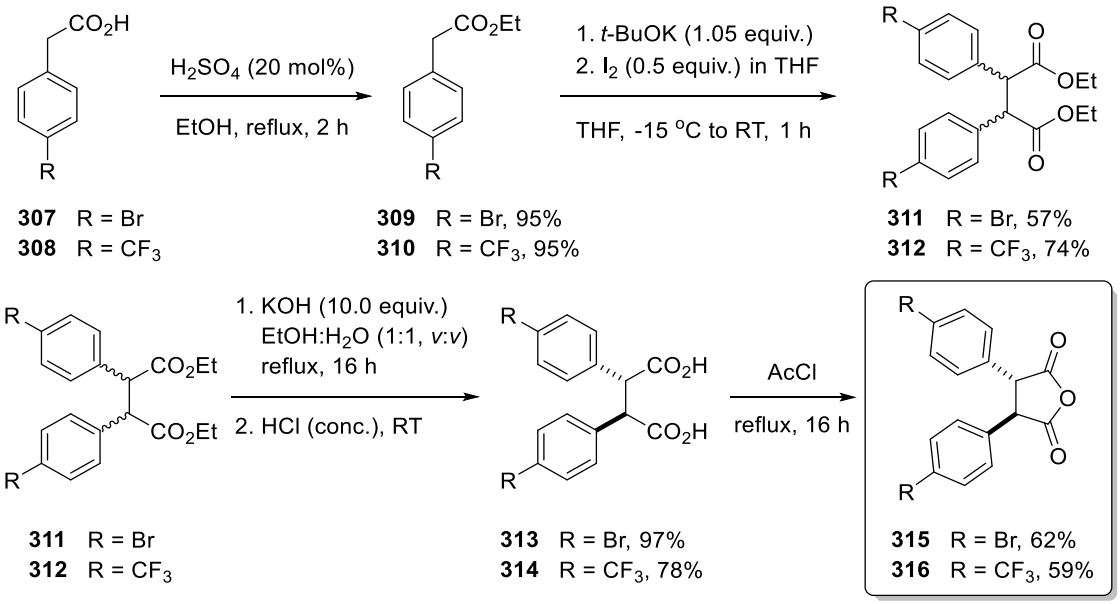
Figure 2.9 Absolute configuration assignment of lactone **305**.

Analysis of the crystals obtained by single crystal X-ray diffraction pattern analysis further confirmed the relative stereochemistry determined by NOE irradiation experiments as 1,2-*cis* and 2,3-*cis* and allowed for the assignment of the absolute stereochemistry of **300** ,and of **305**, as (1*S*,2*S*,3*R*) as depicted in Figure 2.8 and Figure 2.9 respectively. The absolute stereochemistry of all the other diastereomers produced by the reactions reported in Table 2.10 were subsequently assigned by analogy.

2.6 Evaluation of the substrate scope: the anhydride component

We had previously shown that the ease of enolate formation is key to the success of this class of process.[88] Bearing in mind that for efficient DKR to occur, enolisation at both α-carbon atoms of the anhydride must be significantly faster than the rate of reaction of the enolate derived from the slow reacting anhydride enantiomer, we supposed that the installation of electron withdrawing groups on the aryl substituents of the anhydrides could impact both activity and selectivity by i) increasing both the rate of enolate formation and the rate of racemisation relative to cycloaddition and ii) stabilising the enolate; thereby affording greater scope for catalyst-mediated enantiodiscrimination.

To test this hypothesis, we decided to prepare the modified anhydrides **315-316**, **322** equipped with bromo-, trifluromethyl- and nitro functionality respectively and to evaluate them in the cycloaddition process with various aldehydes. The effects of the installation of these electron-withdrawing groups at the *para*-positions could already be observed during the synthesis of the starting materials as different synthetic pathways were found to be required to achieve their syntheses (Scheme 2.7 and Scheme 2.8).

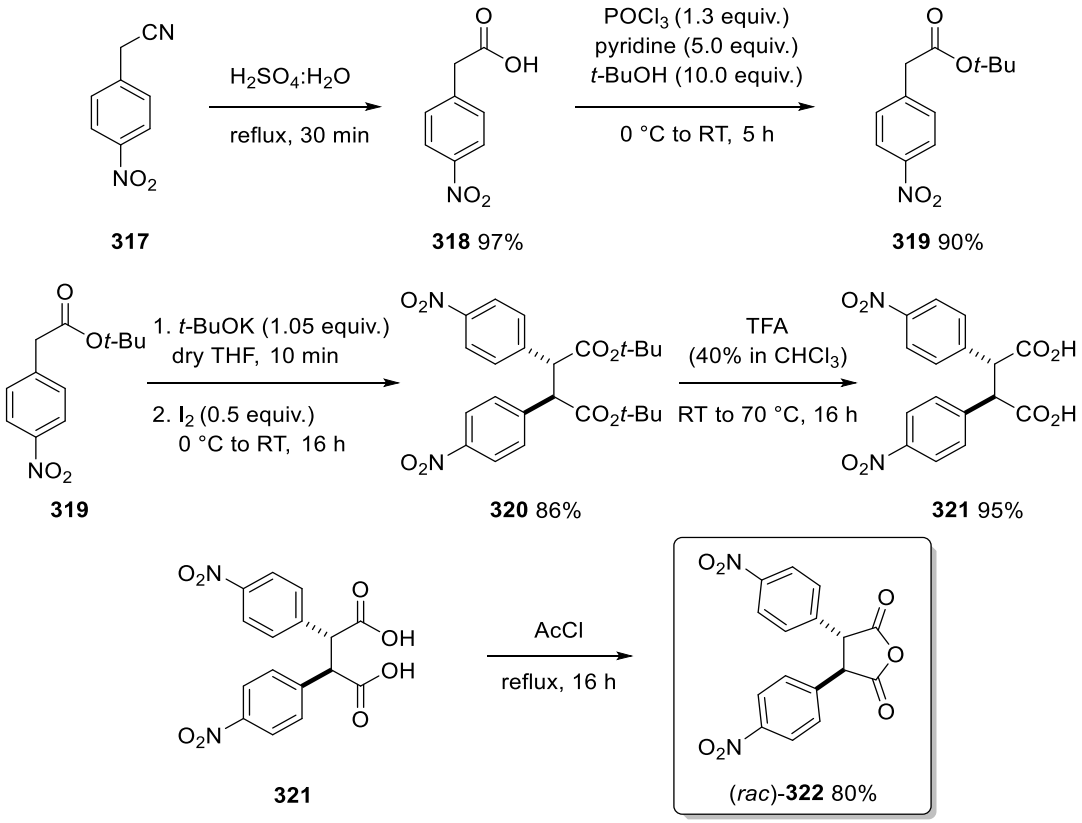


Scheme 2.7 Synthetic route towards anhydrides **315-316**.

The syntheses of anhydrides **315-316** proved to be rather straightforward as we followed an identical pathway as for the synthesis of anhydride **239** (Scheme 2.7).

Anhydrides **315**-**316** were synthesised with modest overall yields (*ca.* 32%), without any optimisation. The starting materials **307**-**308** are commercially available, inexpensive, and every step of the synthesis can easily be scaled-up (Scheme 2.7).

The synthesis of the highly reactive anhydride (*rac*)-**322** proved to be more challenging and required the design of an alternative route. The synthesis went smoothly up to the formation of the corresponding *bis*-ethyl ester derivative analogue to **311**-**312**. Initial attempts to produce the corresponding *bis*-carboxylic acid **321** under basic mediated conditions (*i.e.* KOH, reflux) resulted in complete decomposition of the *bis*-ester intermediate.

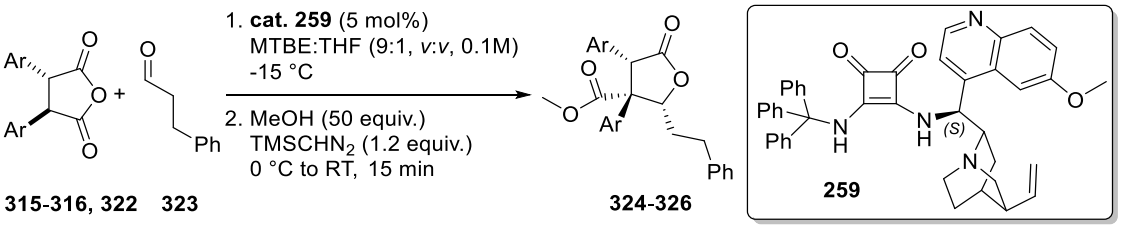


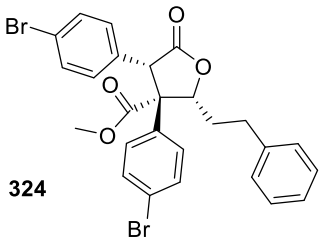
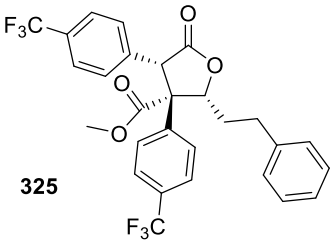
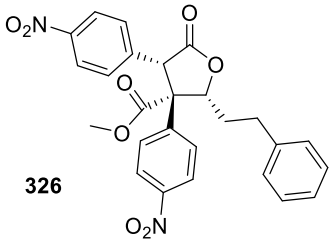
Scheme 2.8 Alternative synthetic route towards anhydride **322**.

The final synthetic route developed for accessing anhydride **322** is depicted in Scheme 2.8. A series of classic organic transformations allowed for the formation of an alternative *bis*-*tert*-butyl ester derivative **320** that underwent clean, quantitative deprotection in presence of trifluoroacetic acid. Finally, anhydride **322** was obtained by ring closure of its precursor **321**, after reflux in acetyl chloride (Scheme 2.8).

The results of the DKR of anhydrides **315**-**316**, **322** obtained are reported in Table 2.11.

Table 2.11 Substrate scope: the anhydride component.



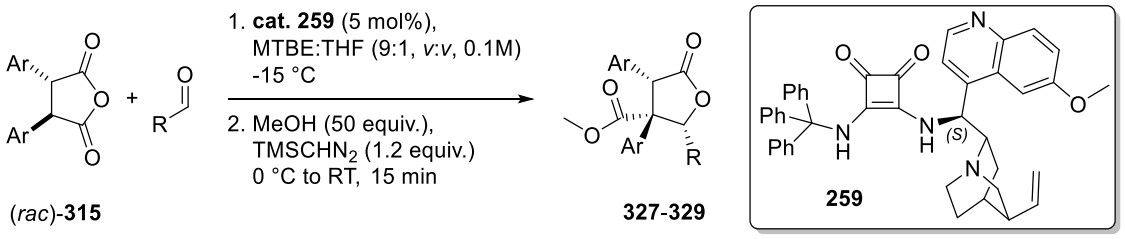
entry	product	time (d)	conv. (%)[a]	yield. (%)[b]	*dr*[c]	*ee* (%)[d]
1	 **324**	8	98	92	34:1	98
2	 **325**	5	>99	82	11:1	98
3	 **326**	3	>99	79	5:1	>99

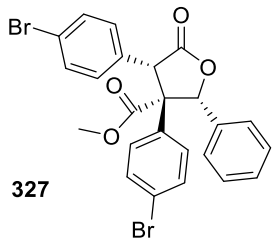
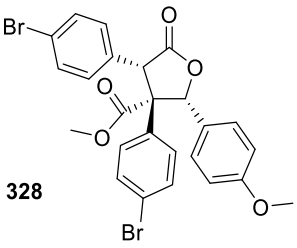
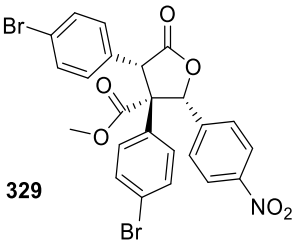
[a]Conversion of starting material **323** was determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b]Isolated yield of the main diastereomer. [c]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. Here dr = (major diastereomer):(Σ other diastereomers). [d]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$.

Initially, the performance of each newly synthesised anhydrides **315**-**316**, **323** was evaluated in their cycloaddition with the optimal hydrocinnamaldehyde (**323**), in the presence of 5 mol% of catalyst **259**, at ambient temperature. Under conditions identical to those outlined in Table 2.10, we observed some background reaction with each of the new anhydride substrates, indicating significantly faster reaction rates. Upon cooling

(*i.e.* to -15 °C), good to excellent product yields of adducts **324**-**326** could be obtained with dramatically enhanced diastereocontrol (entries 1-3, Table 2.11).

Table 2.11 Substrate scope: the electrophilic component.



entry	product	time (d)	conv. (%)[a]	yield. (%)[b]	*dr*[c]	*ee* (%)[d]
4	 **327**	7	93	69	4.4:1	97
5	 **328**	10	70	51	10:1	99
6	 **329**	6	97	66	4:1	92

[a]Conversion of starting material **315** was determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. [b]Isolated yield of the main diastereomer. [c]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. Here dr = (major diastereomer):(Σ other diastereomers). [d]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$.

While yield and selectivities of the crude acids were now considerably improved, some drawbacks were evident. Lactones **325** and **326** needed to be handled carefully in order to prevent ring opening or epimerisation during column chromatography or the occurrence of epimerisation. This epimerisation phenomenon was first detected upon

heating a sample of **324** in various mixtures of solvent while attempting to crystallise it in order to obtain its X-ray structure. If **325** or **326** proved to be more recalcitrant substrates to handle, **324** is stable when stored at room temperature in its solid state.

In order to overcome the issue associated with the instability due to the presence of the remaining acidic α-hydrogen, we decided to react the dibromo anhydride (*rac*)-**315** with representative electron neutral, electron-rich and electron-deficient aromatic aldehydes (entries 4-6, Table 2.11). Again, significant improvements in efficiency and diastereoselectivity over the process were observed (up to 10:1 dr, 99% *ee*). Since the hydro-debromination of aryl units is trivial,[140] the use of (*rac*)-**315** allows the circumvention of the drawbacks in terms of reaction rate and diastereocontrol associated with (*rac*)-**239** as its employment potentially leads back to all the substrates described in Table 2.10, with improved levels of selectivity. Additionally, the use of these aromatic aldehydes led to much more sterically congested systems, rigidifying the overall structures and preventing substrate epimerisation at the carbon containing the remaining acidic α-hydrogen.

2.7 Stereochemical outcome: rationale elements

The stereochemical outcome of the reaction was rationalised. We tried to explain the most likely mode of action of the catalyst, in particular, the way it organises the encounter between the anhydride pronucleophile and the aldehyde during the pre-transition state. ***Unfortunately, no computational calculations in order to obtain a complete energy profile of the two possible binding modes has been carried out to support the following discussion***. Therefore, any of the following discussion should be considered as purely speculative. Under the optimised reaction conditions, we have shown that the trityl squaramide-catalyst **259** can promote the cycloaddition reaction of a range of anhydride pronucleophiles to a series of aldehydes, producing as major diastereomer of the reaction the 1,2-*cis* and 2,3-*cis* isomer along with excellent-outstanding level of enantioselectivity for the (1*S*,2*S*,3*R*) enantiomer (*ca.* >95% *ee* in most examples). Two types of catalyst-substrate interactions are plausible and both can formally lead to the observed enantiomer of the product.

One possibility involves the catalyst engaging two hydrogen bonds of the squaramide moiety with the aldehyde. The anhydride enol tautomer form is activated by hydrogen

bond donation to the lone pair of the tertiary nitrogen atom of the quinuclidine ring and is being deprotonated during the transition state *via* means of general acid/base catalysis while simultaneously attacking a single face of the aldehyde. However, in a recent communication, Connon *et al.*,[84] determined for a similar organocatalytic system, this transition state as significantly higher in energy relative to the transition state associated for the specific catalysis-like mechanism ($\Delta\Delta E$ $TS_{C\text{-}C}$ = 41.0 kJ.mol^{-1}).

In light of these results and the higher barrier to *C*-*C* bond formation involved in this scenario we focused our attention to the examination of the lowest energy binding scenario specific catalysis-like mechanism. In this model, the catalyst engages two hydrogen bonds with the enolate moiety of the anhydride and simultaneously activates the aldehyde by hydrogen bond donation with the newly formed ammonium cation *via* specific acid/base catalysis. After the *C*-*C* bond formation the anhydride needs to orientate its bulky groups towards the quinuclidine in order to avoid steric interactions with the bulky trityl moiety of the catalyst, as depicted in Figure 2.10. Dr. C. Trujillo, has carried out an optimisation of the minima associated with the model for the *C*-*C* bond-forming leading to the major enantiomer by means of DFT calculations. The calculated energy minimum highlights two oxygen atoms of the anhydride interacting with the trityl-group of the catalyst as depicted in Figure 2.10. To determine the mechanism of the reaction, a full mecanistic theoretical study, involving the determination of all energy barriers would be necessary to validate the proposed model.

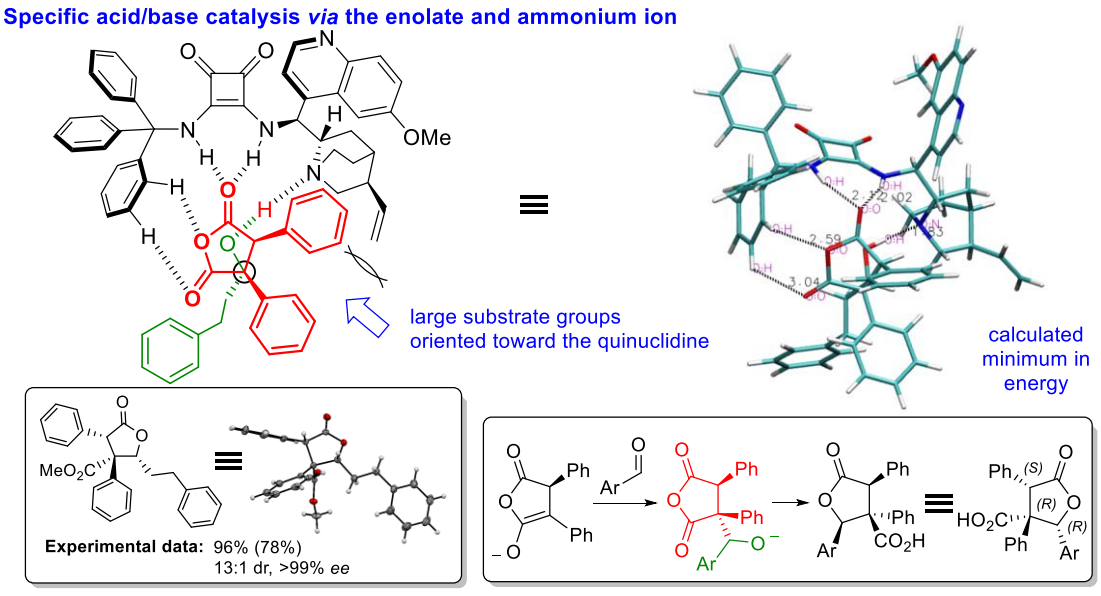
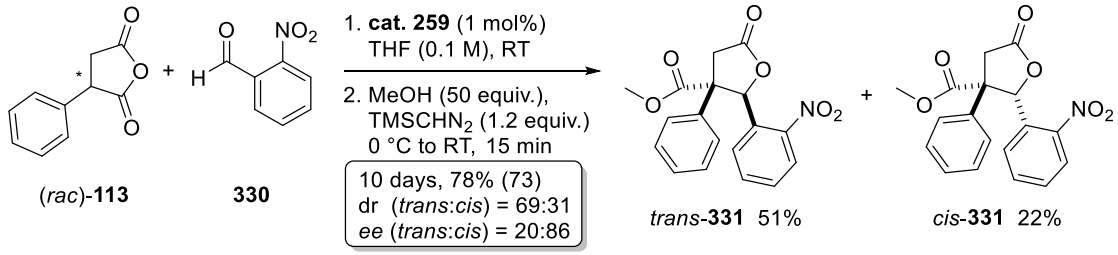


Figure 2.10 Rationale overview for the stereochemical outcome.

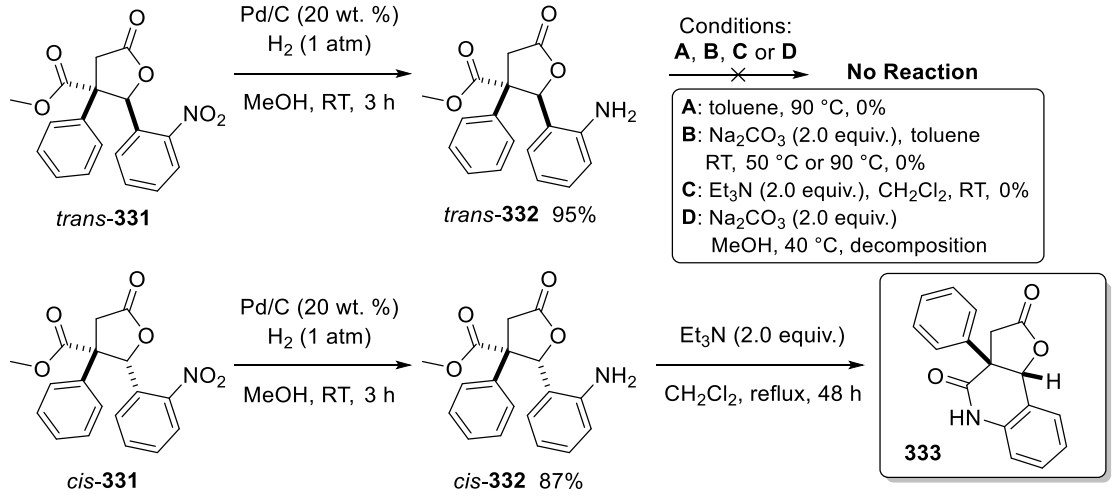
2.8 Synthetic utility and potential application of this work

Highly substituted piperidines and their precursor piperidones are very common *motifs* in both natural products/drug molecules and methods to access them *via* asymmetric synthesis have been intensively investigated.[141] To demonstrate the potential utility and malleability of the methodology outlined through this chapter, we embarked on the manipulation of two lactone products with aim of forming bicyclic systems containing both δ-lactam and γ-lactone subunits.



Scheme 2.9 Lactone synthesis using an aliphatic masked amine as electrophile.

To develop an efficient protocol for lactamisation, we first employed the commercially available phenyl succinic anhydride (**113**) which was reacted in the presence of 1 mol% of catalyst **259** with 2-nitrobenzaldehyde (**330**), at ambient temperature, affording a diastereomeric mixture of lactones **331** with a preference for the *trans* diastereomer and with good enantioselectivity associated with the formation of *cis*-**331** (Scheme 2.9). The diastereomers were separated by flash column chromatography and separately subjected to hydrogenation conditions, as described in Scheme 2.10.

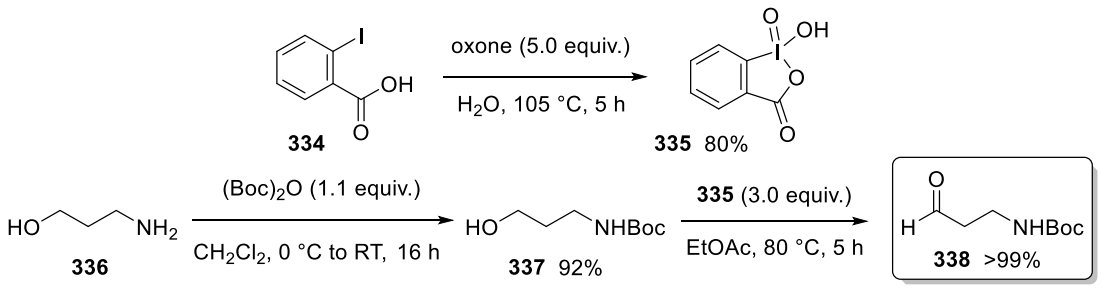


Scheme 2.10 Establishment of the regioselectivity of the lactamisation reaction.

Different reaction conditions ranging from mild to harsh were applied to the aniline derivative *trans*-**332**, all resulting with the same unsuccessful outcome, as none of the desired corresponding lactam was detected (*i.e.* **A**-**D**, Scheme 2.10).

The second attempt involving *cis*-**373** resulted in a more acceptable outcome. Reflux in dry dichloromethane, for 48 h, in the presence of triethylamine, allowed for the quantitative intramolecular amidation to lactam **333**, as depicted in Scheme 2.10.

The enantiomeric excess of lactame **333** was not determined, therefore we can not guarantee that the elaboration of *cis*-**332** was not accompanied by some level of enantioerosion. However, this 2-step lactamisation allowed us to establish with certainty the importance of the relative stereochemistry between the substituents on the ring. Close spatial proximity between the nucleophilic and electrophilic sites afforded by the *cis* configuration was crucial for obtaining the product **333** (Scheme 2.10).



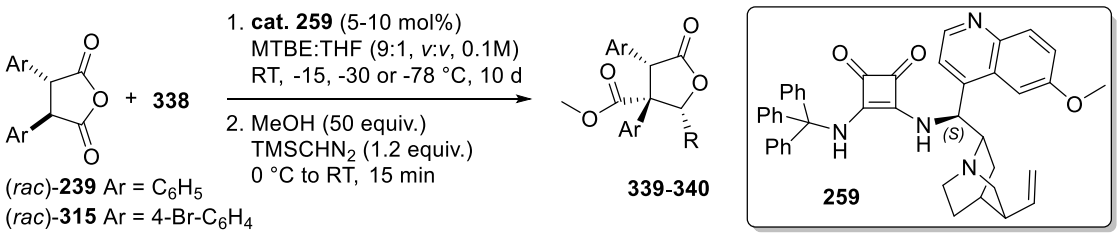
Scheme 2.11 Synthesis of aliphatic aldehyde **338** containing a protected amino group.

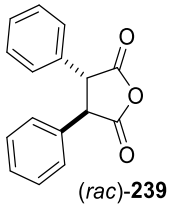
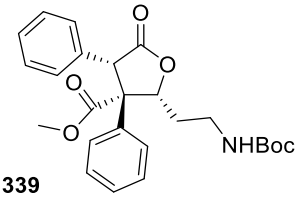
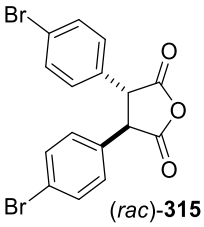
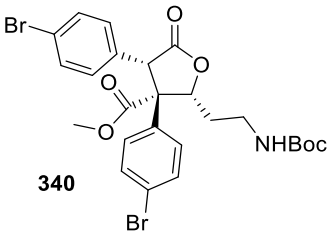
With a protocol for lactamisation already established, we moved on to the evaluation of a similar methodology, applied to one of the products obtained after catalysis between *bis*-aryl succinic anhydrides with **338**. We designed and chose to employ aldehyde **338** rather than **330** in order to provide examples with both aromatic and aliphatic aldehydes. An oxidation of the Boc-protected amino alcohol **377** was promoted by IBX as an oxidant (*i.e.* **335**), affording aldehyde **338** in quantitative yield (Scheme 2.11).

The first attempt at the DKR of (*rac*)-**239**, promoted by **259**, at 5 mol% loading, with the recently synthesised aldehyde **338** resulted in the formation of lactone **339** with excellent diastereoselectivity (>20:1 dr) albeit with low conversion (*ca.* 43%) and a disappointing level of enantioselectivity (75% *ee*, entry 1, Table 2.12). Lowering the temperature to -15 °C resulted in only 20% conversion of **239** after 10 days (entry 2, Table 2.12).

In light of these discouraging results, we decided to employ the considerably more readily enolised anhydride (*rac*)-**315** and, upon lowering the temperature to -15 °C, we were able to form the targeted lactone **340** with excellent diastereoselectivity and a slightly improved level of enantioselectivity (up to >20:1 dr, 81% *ee*, entry 3). Cooling the reaction to -30 and -78 °C allowed us to further improve the stereocontrol, as the major diastereomer **340** was finally isolated with a satisfying 58% yield and 90% *ee* when the reaction was conducted at -30 °C (entry 4, Table 2.12).

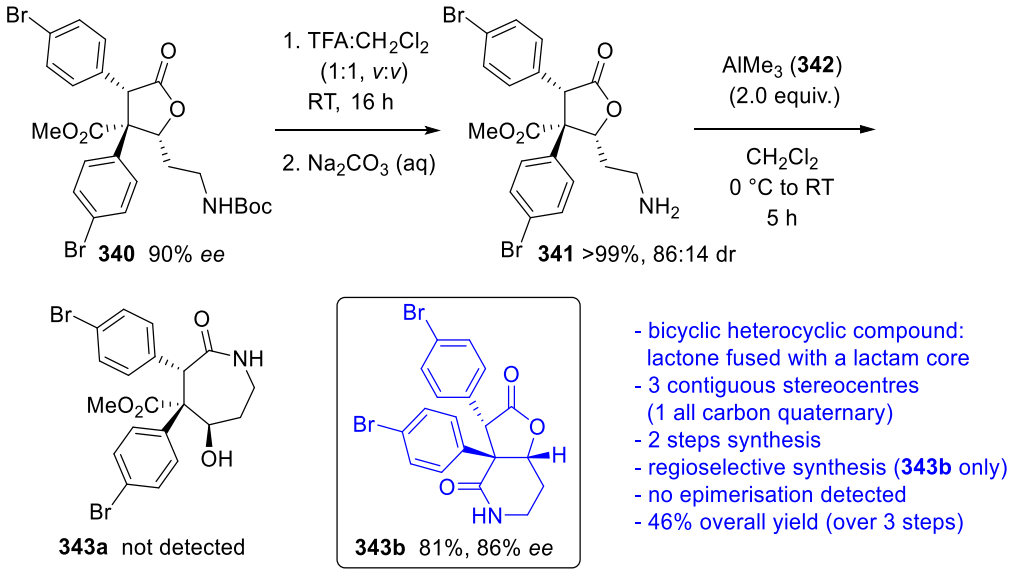
Table 2.12 Substrate scope: the electrophilic component.



entry	anhydride	product	temperature (°C)	conv. (%)[a]	yield. (%)[b]	*dr*[c]	*ee* (%)[d]
1	 (*rac*)-**239**	 **339**	RT	43	n.d.[e]	>20:1	75
2			-15	<20	n.d.[e]	n.d.[e]	n.d.[e]
3[f]	 (*rac*)-**315**	 **340**	-15	>99	n.d.[e]	>20:1	81
4[f]			-30	70	58	19:1	90
5[f]			-78	56	n.d.[e]	1.5:1	74

[a]Conversion of **338** was determined by ^{1}H using *p*-iodoanisole as an internal standard. [b]Isolated yield of the main diastereomer. [c]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. Here dr = (major diastereomer):(Σ other diastereomers). [d]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. [e]Not determined. [f]**259** (10 mol%).

Finally, the lactone **340** (19:1 dr, 90% *ee*) was deprotected with TFA to afford amine **341** in near quantitative yield. The previously developed base-mediated conditions led to extensive decomposition and were conveniently replaced by a Lewis acid to assist the ring closure reaction. In the presence of trimethylaluminium (**342**), at room temperature, amine **341** underwent an intramolecular amidation to yield the piperidonyl γ-lactone **343b** in 81% yield and 86% *ee*. Notably, the product resulting from the attack at the methyl ester was dominant, as none of the regioisomeric product **343a** resulting from cyclisation at the lactone was detected (Scheme 2.12).



Scheme 2.12 Sequential deprotection-lactamisation of a cycloaddition product.

2.9 Conclusion for Chapter 2

In summary, we have demonstrated for the first time that *trans*-disubstituted aryl succinic anhydrides can undergo efficient dynamic kinetic resolution (DKR) using an *ad hoc* designed organocatalyst and a diastereo- and enantioselective cycloaddition process with aldehydes. We demonstrated, through the modification of the anhydride scaffold, that increasing its enolisability (by incorporating EWG at the *para* positions), leads to faster, more efficient and more selective lactone formation.

The process was found to be compatible with a range of electron-rich/electron-deficient/heterocyclic aromatic and aliphatic aldehydes. The products of this one-pot formal cycloaddition are all highly functionalised γ-butyrolactones (paraconic acid derivatives) and are obtained with good to excellent control over three product stereocentres, one of which is all-carbon quaternary in nature (up to 92%, 34:1 dr, 98% *ee*).

The stereochemical configuration of the lactones was assigned using a combination of ^{1}H NMR Nuclear Overhauser Effect (NOE) experiments and crystal X-ray diffraction pattern analysis.

The synthetic utility of these compounds as potential building blocks for organic syntheses was demonstrated through the ready manipulation of one of the products to form a stereochemically dense and complex fused lactone-lactam system in 86% *ee*.

We have successfully identified 4 novel enolisable anhydrides and reacted them with various aldehydes, forming 19 novel γ-butyrolactones, in near optical purity. To do so we evaluated a library of a total of 25 organocatalysts among which 7 of them were specifically designed for the purpose of developing this work.

3. The Kinetic Resolution of racemic *α*-alkylated aryl succinic anhydrides mediated *via* an enantioselective cycloaddition to 4-nitrobenzaldehyde

As described through the first two chapters of this thesis, the scope of the anhydride pronucleophiles capable of engaging in cycloaddition type reactions with aldehydes still remains a challenge for organic chemists. Building on our experience acquired during the development of the DKR of diaryl succinic anhydrides we tried to identify another class of anhydride (bearing an enol stabilising group) susceptible of reacting in a similar fashion and, furnishing enantiomerically pure forms of valuable cycloadduct products after a catalytic transformation.

Our next substrate choice was chosen based on our previous work in which we showed that the ease of enolate formation was part of the key to the success for these reactions. For efficient DKR, enolisation had to occur at both *α*-carbon atoms and also had to be significantly faster than the rate of the reaction issued from the slowest reacting enolate enantiomer. Installation of increasingly more EWG at the *para* positions of the aryl groups of the anhydrides led to faster, more efficient DKR and more selective lactone formation, thus supporting our hypothesis (**344**, Figure 3.1, A).

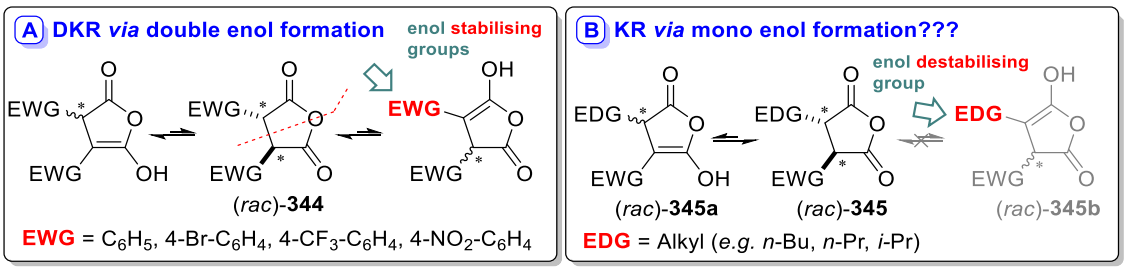


Figure 3.1 New substrate challenge (*rac*)-**345**: expansion of the substrate scope.

Our idea for the next substrate choice takes roots in desymmetrising the former diaryl substituted succinic anhydrides (*rac*)-**344** by incorporating an EDG at one side of the molecule and an EWG at the other side (*i.e.* (*rac*)-**345**, Figure 3.1, B). In other words, the initial idea was to ease enol(ate) formation at only one *α*-carbon atom (*i.e.* try to induce substrate epimerisation rather than substrate racemisation). We hoped to be able to generate a regioselective transformation by favouring nucleophilic attacks issued from (*rac*)-**345a**. To do so, we planned to influence the keto-enol equilibrium towards

(*rac*)-**345a** (*i.e.* avoid substantial amount of (*rac*)-**345b** in solution) by incorporating an enol destabilising group in the anhydride scaffold such as an alkyl chain (Figure 3.1, B).

The reaction of a single enantiomer of (*rac*)-**345**, by efficient KR, with precisely half an equivalent of an aldehyde (employed as resolving agent) would in theory provide access to a series of valuable functionalised chiral succinate building blocks after derivatisation of the resolved anhydrides **345**. This choice of the substrate, as novel enolisable anhydride, was further motivated by both the intrinsic interest of developing a completely new KR methodology and the nature of the products that could be generated after catalysis with aldehydes. Under optimised conditions, such a process would theoretically provide access to the enantiomerically enriched form of a highly valuable subclass of butyrolactones: the α-alkylated γ-butyrolactones (Figure 3.2).

Indeed, optically active γ-butyrolactones constitute a highly important *motif* in organic chemistry which can be found in the scaffold of many natural products of biological importance. This occurrence has been estimated at ~10% in all-natural products (*e.g.* the natural products from the Stemona alkaloids **346**-**348**, Figure 3.2, A).[86,129]

The γ-butyrolactone derivatives bearing a β-carboxylic acid moiety are known as paraconic acids (**349**, Figure 3.2, B).[87,130] It represents an important subclass of the family, with many members presenting remarkably diverse biological properties of interest including antiinflammatory,[142] antiallergic,[143] antimicrobial activities.[144]

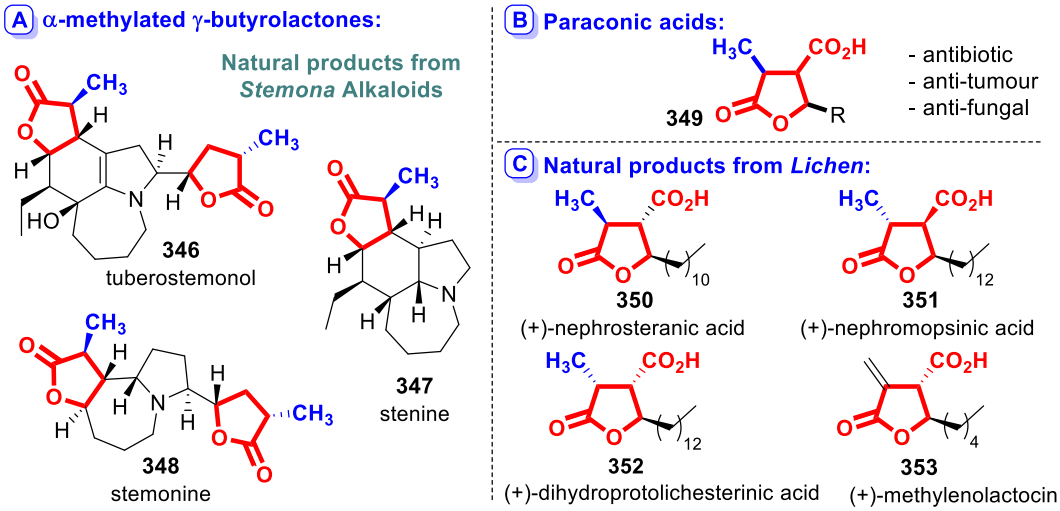
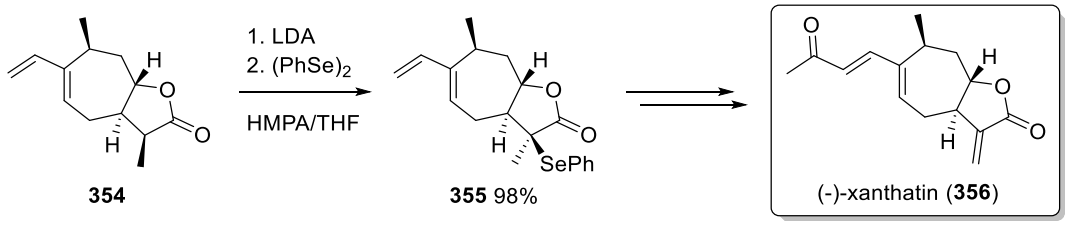


Figure 3.2 Selected bioactive molecules bearing a α-methylated paraconic acid or a α-methylated γ-butyrolactone.[86,87,129,130]

Taking the biological importance of the γ-butyrolactones into account as well as their potential as chiral building blocks in organic syntheses, asymmetric strategies have emerged as the subject of various process developments. Despite many successes in this field,[145,146,147] catalytic asymmetric methods for the regio-, diastereo- and enantioselective formation of more specific substitution patterns, such as α-methylated-γ-butyrolactones, are still lacking. Interestingly, this α-methyl substitution on butyrolactones is a frequently encountered substitution pattern. However, to the best of our knowledge, the rapid, one-pot, enantioselective construction of these privileged structures, by organocatalytic means, has never been reported despite the potential synthetic utility afforded by a such process (Figure 3.2, A and C).



Scheme 3.1 Example of utilisation of α-phenylselenide intermediate followed by regioselective β-elimination reported by Shishido and coworkers.[152]

These α-methylated-γ-butyrolactones (*e.g.* **354**) can conveniently be converted to α-phenylselenide intermediates (*e.g.* **355**), which upon a sequence of oxidation followed by a β-elimination,[148,149,150,151,152] can form α-methylene-γ-butyrolactones such as **356**, another important subclass of butyrolactones (Scheme 3.1). In 2009, the presence of this important structural unit (*i.e.* α-methylene-γ-butyrolactone) has been estimated in the core of over 14 000 compounds exhibiting a vast array of important biological activities (*e.g.* **353**, Figure 3.2).[153,154]

Processes involving alkylated-succinic anhydrides are not widely studied, still: the efficient PKR of α-methyl succinic anhydride (**191**) by regioselective/enantioselective alcoholysis has been reported (Figure 3.3, A).[113] In 2013, List *et al.*,[155] reported the enantioselective methanolytic desymmetrisation of a series of *meso* compounds including the dimethyl succinic anhydride (**357**). The process was catalysed by a novel textile-supported chiral organocatalyst and provided access to a range of optically active hemiesters (*e.g.* **358**, Figure 3.3, A).

To the best of our knowledge, only two other examples of KR processes involving racemic cyclic anhydrides have been reported to date. In 1997, Seebach *et al.*,[156] described the use of Ti-TADDOLate as the promoter for the KR of (*rac*)-**359** allowing for the recovery of the enantiomerically enriched product **360** in 94% *ee* (Figure 3.3, B). Later in 2001, Bolm and co-workers,[157] identified quinidine as the mediating agent for the KR of the bicyclic anhydride (*rac*)-**361**, furnishing access to enantioenriched *N*-protected *β*-aminoesters, such as **362**, with up to 99% *ee* (Figure 3.3, B). Although, these two processes afforded excellent levels of enantiomeric excesses (up to 99% *ee*), the resolving agents employed were used in stoichiometric amounts and the products of the KR processes were either obtained as 1:1 mixture ratio of inseparable materials or this required a subsequent four-step reaction derivatisation to allow for the isolation of the targeted structures (Figure 3.3, B).[156,157]

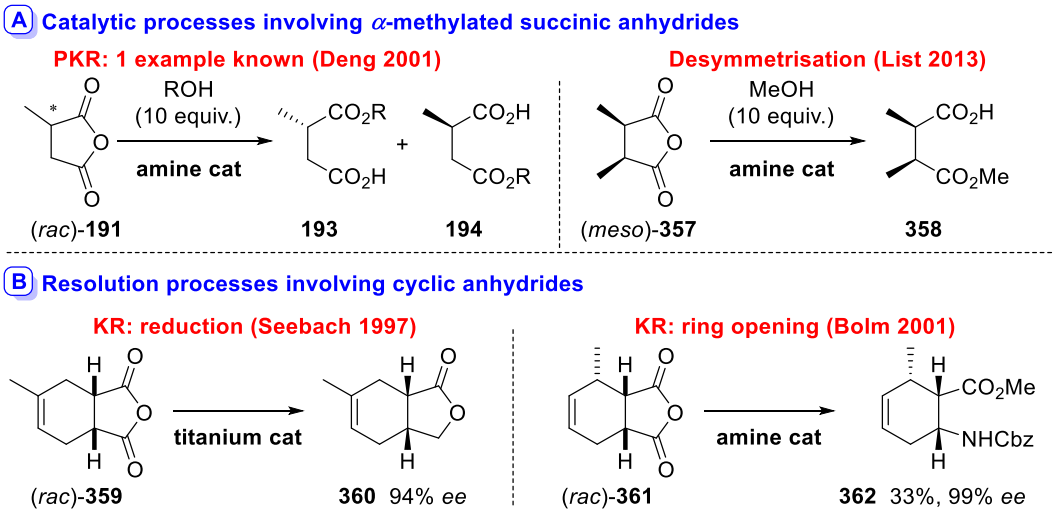


Figure 3.3 Processes involving *α*-methylated anhydrides and the dearth of anhydride KR processes.[113,155,156,157]

In this thesis, we report our results towards the first KR of *α*-alkylated succinic anhydrides of general type (*rac*)-**363** (Figure 3.4). As the starting material possesses two chiral centres it exists as a mixture of two separable diastereomers *cis*-**363** and *trans*-**363** (*i.e.* two pairs of enantiomers for each diastereomer, Figure 3.4, A). As such there were many challenges to overcome in order to tackle this complex substrate. First, the catalyst had to be capable of promoting a regioselective enolisation of **363**, affording the reactive *in situ* formed racemic enolate (*rac*)-**364e** (Figure 3.4, B). Upon binding to the catalyst, we hoped to be able to differentiate between the two enantiomeric faces of (*rac*)-**364e** (Figure 3.4, C). This differentiation would be the

result of the creation of two pseudo diastereomeric transition states presenting different relative energies (*i.e.* $\Delta\Delta G \neq 0$, Figure 3.4, D). This sequence would be followed by a nucleophilic addition of the most reactive enolate enantiomer only (*i.e.* the lowest in energy: (*S*)-**364e**), to a resolving agent chosen as an aldehyde. In total, two regioisomers of the corresponding lactones can exhist as depicted in Figure 3.4 (E).

Our final objective was to isolate, in an enantiomerically pure form, a single diastereomer between **365a-h**, with concomitant KR of **363** *via* an organocatalysed cycloaddition to an aldehyde (Figure 3.4).

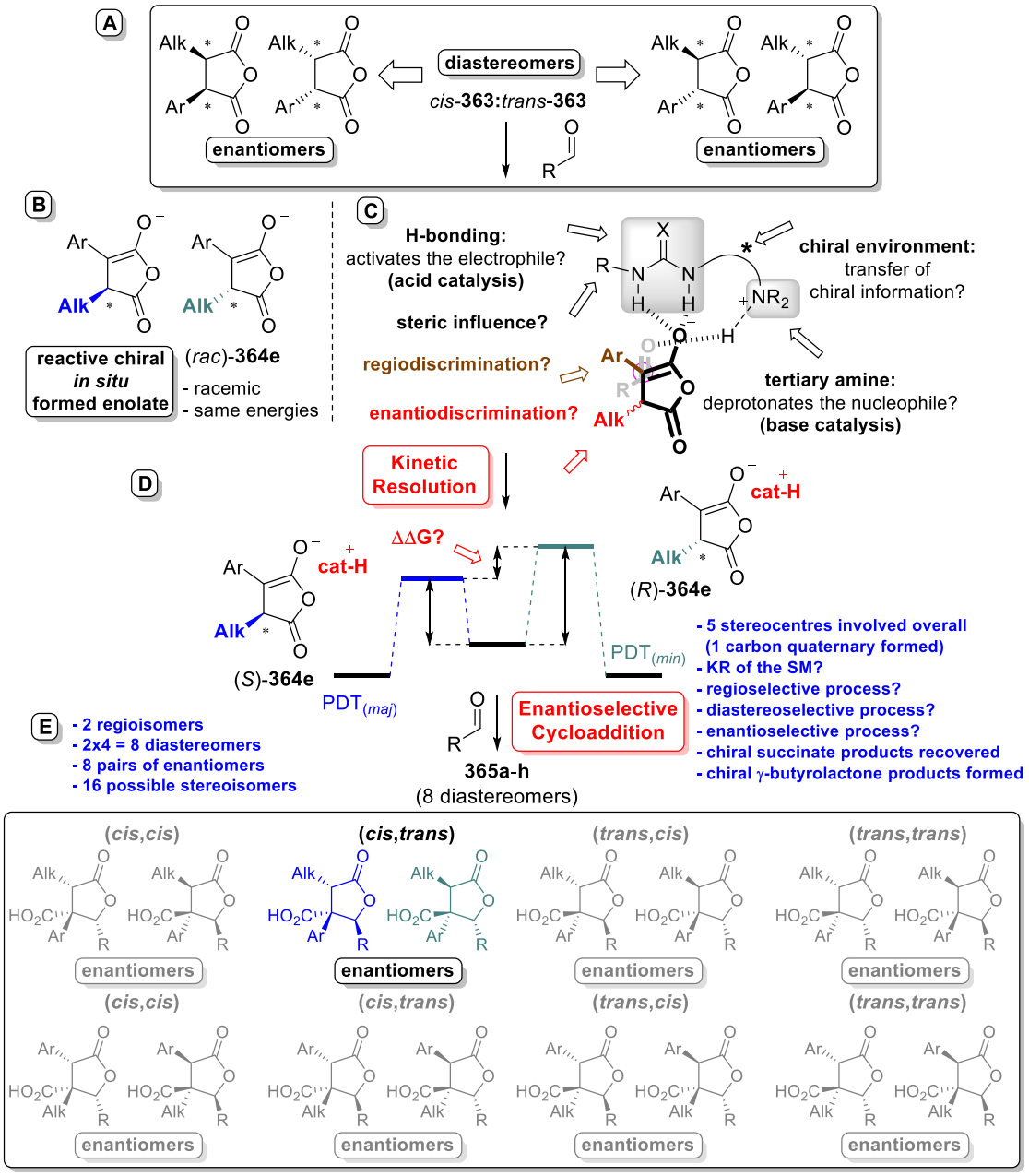


Figure 3.4 Overview of the complexity of the challenge at hand.

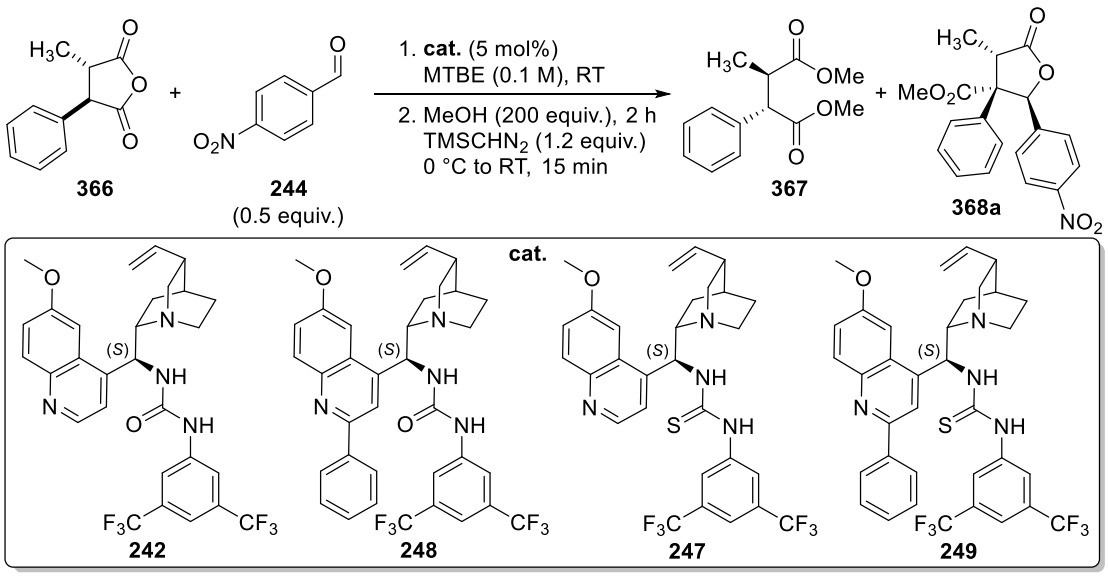
3.1 Preliminary experiments: proof of concept

In most of the KR examples previously introduced through Chapter 1, the resolved starting materials only bore a single chiral centre as did the products of the resolution processes. As a result, the measurement of the enantiomeric excesses of either the starting materials or the products, at a given conversion, was a good indicator of the overall process efficiency. On the other hand, in this process, the scenario is considerably more sophisticated. Indeed, the resolution of (*rac*)-**366** is accompanied by the formation of **368**, which involves the creation of two extra stereocentres. As a result, the measurement of the enantiomeric excess of the major diastereomer **368a**, is a better indicator of the catalyst efficiency to promote an enantioselective cycloaddition rather that its capacity to resolve the starting material enantiomers. Likewise, a poor diastereoselectivity associated with the formation of **368** can be attributed either to the poor ability of the catalyst to discriminate between the two enantiomeric forms of the starting material enolate or to the way it organises the assembly of the lactone's aryl substituents during the *C*-*C* bond forming operation. As a result, unless the lactone formation has been optimised to a completely stereoselective transformation, the measure of the enantiomeric excess of both starting material and products is required to judge of the catalyst's efficiency. The results of our preliminary experiments for the cycloaddition KR of (*rac*)-**366** to 4-nitrobenzaldehyde (**244**), in MTBE, at ambient temperature, are presented in Table 3.1.

In the absence of catalyst or base no reaction occurred (entry 1). The use of Hünig's base to facilitate enolate formation led to the formation of all the products **368a-d** (obtained after *in situ* esterification of the corresponding carboxylic acids with aid of $TMSCHN_2$ in order to facilitate CSP-HPLC) with a preference for **368a** (entry 2). Interestingly, as we had hypothesised, we observed full regioselectivity in favour of the formation of the lactone resulting from nucleophilic attack issued from the stabilised aromatic enolate only. The use of either urea catalyst **242** or its *C*-2 arylated analogue **248** allowed for the formation of lactones **368a-d** with poor levels of diastereo- and enantiocontrol (entries 3-4). At this early stage of the study the enantiomeric excess of the unreacted starting material **367** wasn't determined as the products obtained were nearly racemic. The exchange of the urea functionality for the more acidic thiourea (*i.e.* **247**, **249**) led to comparable results (entries 5-6, Table 3.1).

As a proof of concept, we determined the enantiomeric excess of the unreacted starting material **366** after derivatisation to **367**. At 33% conversion, the level of enantioenrichement was poor (*ca.* 10% *ee*) and so was the level of diastero- and enantioselectivity associated with the formation of **368** (59:41 dr, 14% *ee*, entry 5). However, this result still allowed us to establish that some level of control could be amenable *via* the designed organocatalytic process (Table 3.1).

Table 3.1 Catalyst evaluation for the reaction between **366** and **244**.



entry	cat.	time (h)	conv. (%)[a]	367 *ee* (%)[d]	S*[e]	368 *dr*[b] a:(b:c:d)	368a *ee* (%)[c]
1	-	24	-	-	-	-	-
2	**DIPEA**[f]	120	87[g]	-	-	77:(3:1.5:18.5)	-
3	**242**	72	74[g]	n.d.[h]	n.d.[h]	72:28	3
4	**248**	96	37	n.d.[h]	n.d.[h]	58:42	15
5	**247**	120	33	10	1.7	59:41	14
6	**249**	96	32	n.d.[h]	n.d.[h]	63:37	17

[a]Conversion of starting material **244** was determined by ^{1}H NMR spectroscopic analysis using 4-iodoanisole as an internal standard. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. dr = (major diastereomer):(∑other diastereomers). [c]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. Refers to the major diastereomer. [d]Determined by CSP-HPLC after derivatisation of the unreacted starting material **366** by ring opening alcoholysis with MeOH followed by *in situ* esterification with $TMSCHN_2$. [e]S* = selectivity factor calculated based on the starting material **366** after derivatisation to the product **367** by using the conversion (C) determined by ^{1}H NMR spectroscopic analysis and using the formula: $S^* = \ln[(1-C)(1-ee_{367})]:\ln[(1-C)(1+ee_{367})]$. [f]20 mol%. [g](1.0 equiv.) of **244** was used. [h]Not determined.

3.2 Catalyst screening for the KR attempt of α-methyl phenyl succinic anhydride

With a proof of concept established we decided to screen a library of organocatalysts available among the research group and possessing different hydrogen-bond units as well as different steric and/or electronic properties. Given the disappointing levels of stereocontrol obtained with the four non-bulky (thio)urea catalysts **242**, **247**-**249** evaluated in Table 3.1, we tried the significantly more sterically hindered urea-based catalysts **369**-**374** in the model reaction. The results obtained are reported in Table 3.2.

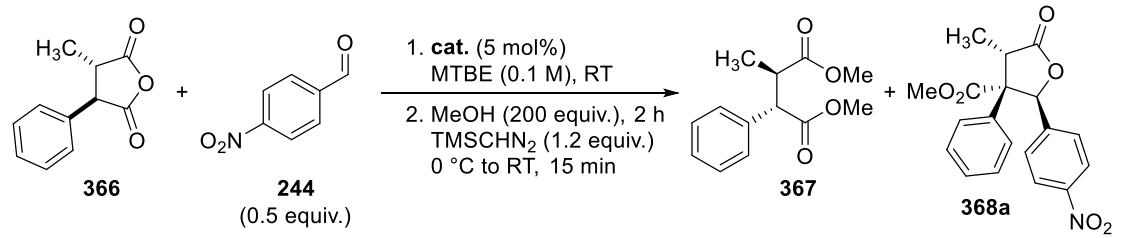
Beginning with the evaluation of the two bulky catalysts **369** and **370**, we observed the formation of **368a-d** with a really poor level of diastereoselectivity and with almost total absence of stereoinduction (entries 1-2). As we suspected based on the data obtained for lactone **368**, the derivatised unreacted starting material **367** was recovered as a close to racemic material (S^* = 1.3, entry 1, Table 3.2).

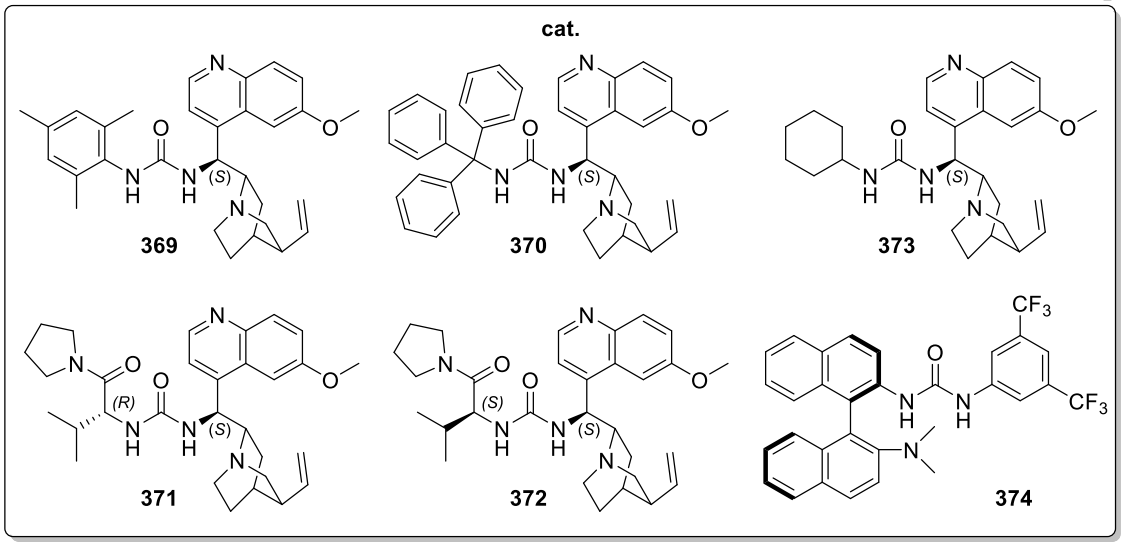
We also evaluated the performance of urea organocatalysts containing both enantiomeric forms of a chiral amino acid substituent (*i.e.* catalysts **371**-**372**), a bulky aliphatic cyclohexyl moiety (*i.e.* **373**) and a different tertiary base containing a chiral binaphthyl scaffold (*i.e.* **374**, entries 2-6). A slight improvement in S factor was observed with catalyst **372** proving that a two-sterocentre KR of (*rac*)-**366** *via* a diastereo- and enantioselective addition to **244** could indeed be achieved (S* = 2.5, entry 4, Table 3.2).

Given the poor levels of selectivity obtained with the cinchona-based urea catalysts, we decided to evaluate representative members from the squaramide family. The results of their evaluation in the model reaction, are reported in Table 3.3.

Upon evaluation of the direct analogues to catalysts **242**, **247**-**249** (*i.e.* **243** and **250**) we observed a significant improvement with regard to the diastereocontrol of the formation of lactones **368a-d** (entries 1-2, Table 3.3). Indeed, catalyst **250** promoted the formation of **368a** with excellent diastereoselectivity and clearly improved level of enantioselectivity (up to 94:6 dr, 41% *ee*, entry 2, Table 3.3). Interestingly, the unreacted recovered starting material **367** exhibited a rather low albeit improved level of enantiomeric excess corresponding to a selectivity factor S* = 3.3 (entry 2, Table 3.3).

Table 3.2 Evaluation of the performance of different urea based organocatalysts for the reaction between **366** and **244**.

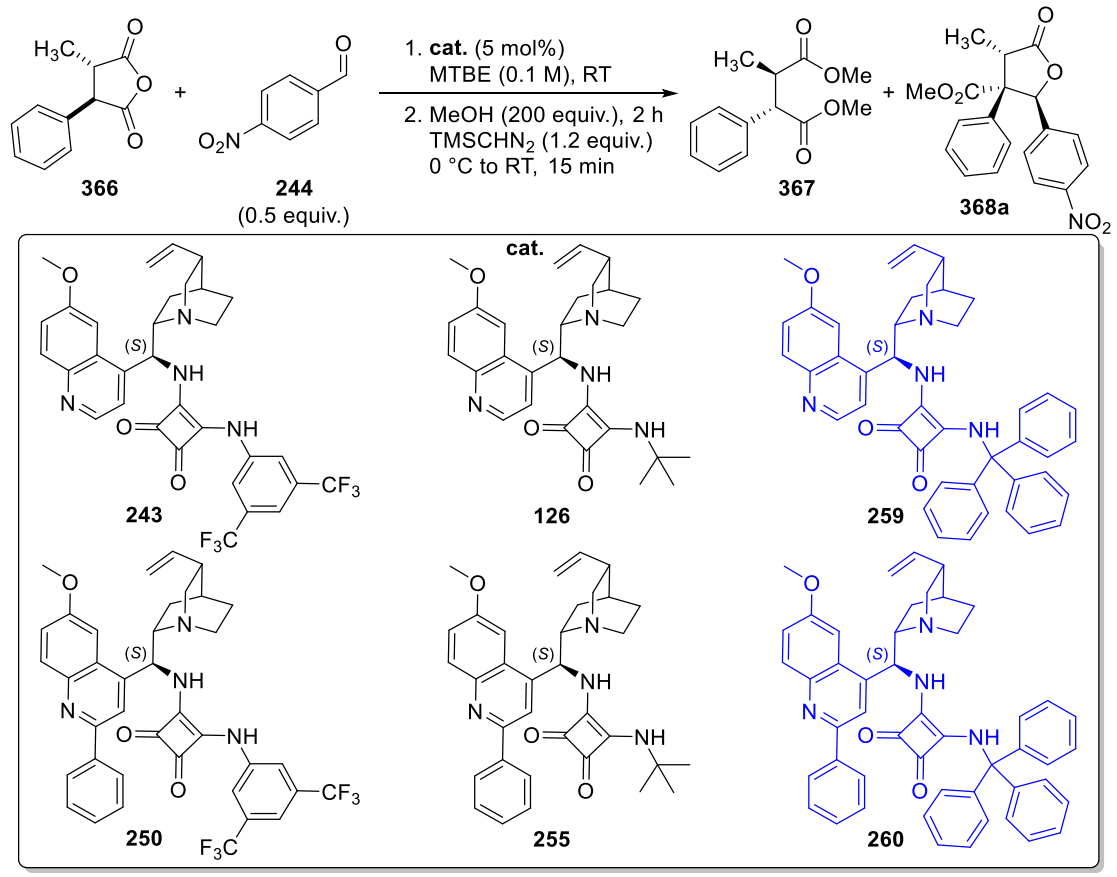




entry	cat.	time (d)	conv. (%)[a]	367 *ee* (%)[d]	S*[e]	368 *dr*[b] a:(b:c:d)	368a *ee* (%)[c]
1	**369**	7	46	9	1.3	61:39	10
2	**370**	2	43	n.d.[f]	n.d.[f]	57:43	13
3	**371**	10	35	n.d.[f]	n.d.[f]	67:33	33
4	**372**	4	46	27	2.5	69:31	29
5	**373**	13	41	n.d.[f]	n.d.[f]	73:27	23
6	**374**	2	0	-	-	-	-

[a]Conversion of **244** was determined by ^{1}H NMR using 4-iodoanisole as an internal standard. [b]Diastereomeric ratio determined by ^{1}H NMR. dr = (major diastereomer):(∑other diastereomers). [c]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. Refers to the major diastereomer. [d]Determined by CSP-HPLC after derivatisation of the unreacted starting material **366** by ring opening alcoholysis with MeOH followed by *in situ* esterification with $TMSCHN_2$. [e]S* = selectivity factor calculated based on the starting material **366** after derivatisation to the product **367** by using the conversion (C) determined by ^{1}H NMR spectroscopic analysis and using the formula: $S^* = \ln[(1-C)(1-ee_{367})]:\ln[(1-C)(1+ee_{367})]$. [f]Not determined.

Table 3.3 Evaluation of squaramide based organocatalysts.



entry	cat.	time (h)	conv. (%)[a]	367 *ee* (%)[d]	S*[e]	368 *dr*[b] a:(b:c:d)	368a *ee* (%)[c]
1	**243**	96	37	6	1.3	80:20	12
2	**250**	96	30	20	3.3	94:6	41
3	**126**	168	44	35	3.6	79:21	30
4	**255**	216	52[g]	26	2.0	90:10	36
5	**259**	168	44	40	4.5	64:36	6
6	**260**	168	42	43	5.9	65:35	10

[a]Conversion of **244** was determined by ^{1}H NMR using 4-iodoanisole as an internal standard. [b]Determined by ^{1}H NMR. [c]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. Refers to the major diastereomer. [d]Determined by CSP-HPLC after derivatisation to **367**. [e]S* = selectivity factor calculated based on the starting material **366** after derivatisation to the product **367** by using the conversion (C) determined by ^{1}H NMR spectroscopic analysis and using the formula: $S^* = \ln[(1-C)(1-ee_{367})]:\ln[(1-C)(1+ee_{367})]$. [f]Not determined.

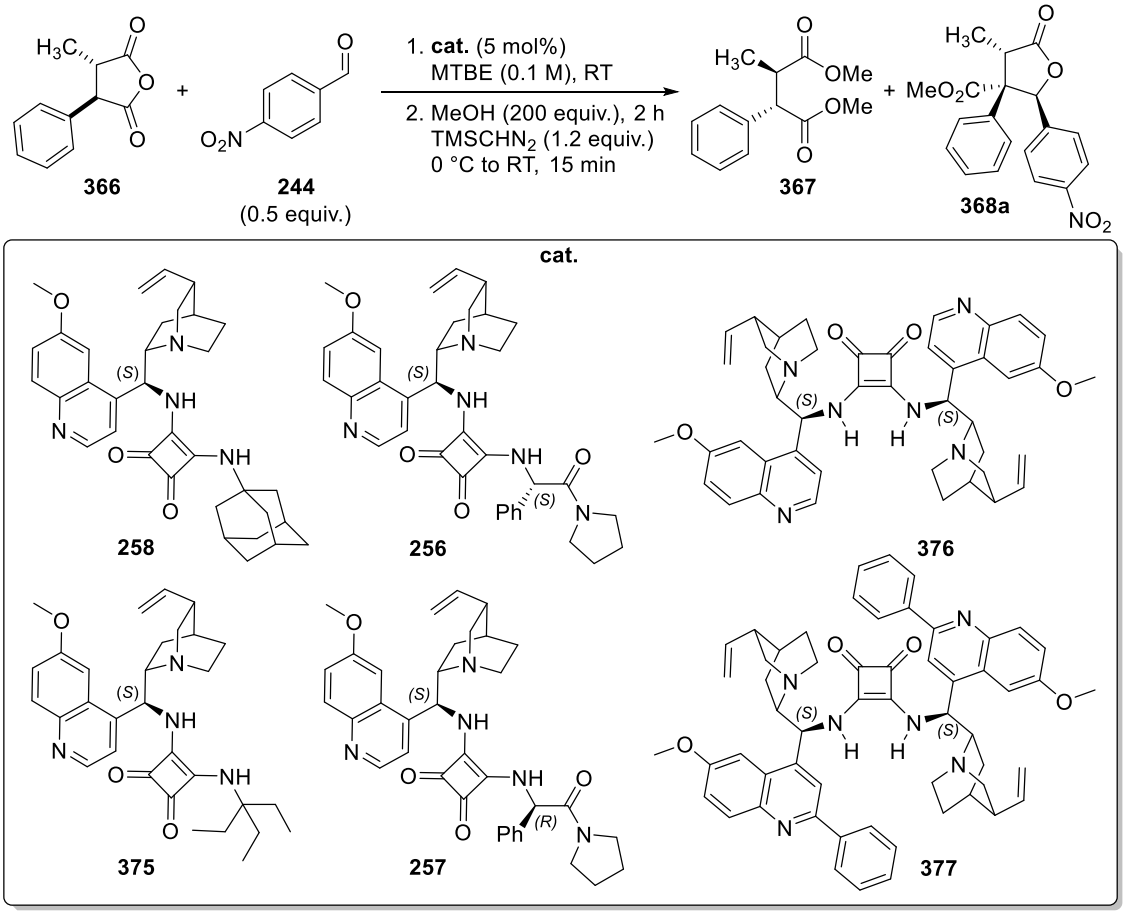
The recently developed *tert*-butyl substituted squaramides catalysts **126** and **255** proved to be rather inefficient (up to S* = 3.6, entries 3-4, Table 3.3). Some improvements were obtained upon evaluation of catalysts **259**-**260** which had previously been developed for the purpose of the DKR of diaryl succinic anhydrides (up to S* = 5.9, entries 5-6, Table 3.3). A quick series of optimisations with catalysts **259**-**260**, varying both the temperature and the solvent employed in the reaction failed to yield increased selectivity. While the minor diastereomer (*i.e.* **368d**) was always produced with excellent enantioselectivity (>90% *ee* in most instances), the enantioselectivity associated with the formation of **368a** remained far from useful (entries 5-6, Table 3.3). Following on from these results, we tried to identify other substitution patterns on the squaramide moiety that would allow the catalyst to promote increase selectivity for both the recovered starting material **367** and the major lactone diastereomer **368a**. The results obtained are reported in Table 3.4.

Beginning with the evaluation of the bulky aliphatic adamantyl- and triethylmethyl-substituted squaramides (*i.e.* catalysts **258** and **375**) no further improvements were observed (up to S* = 4.0, entries 1-2, Table 3.4). As was previously the case with the urea catalysts, the introduction of chiral information through the successive substitution of the squaric acid moiety with the two enantiomeric forms of a chiral amino acid functionality (*i.e.* **256**-**257**) proved to be rather inefficient (up to S* = 2.6, entries 3-4, Table 3.4). Evaluation of the symmetrical squaramide **376** or its *C*-2 arylated analogue **377** also resulted in comparable and unsatisfactory outcomes (up to S* = 3.6, entries 5-6, Table 3.4).

As a result of the disappointing levels of stereocontrol attained from the evaluation of a small library of squaramide catalysts, possessing different steric and electronic properties, we continued towards the evaluation of another class of hydrogen-bond donors, based on a cinchona scaffold - the sulfonamides. The results of the evaluation of five of their representatives (*i.e.* **178**, **378**-**381**) are reported in Table 3.5.

The first two examples involving electron withdrawing aryl substituents (*i.e.* **378** and **379**) were unpromising. These two-catalysts exhibited an almost total lack of selectivity towards the two enantiomers of (*rac*)-**366** and a poor level of diastereo- and enantiocontrol for the formation of lactones **368** (up to S* = 1.4, entries 1-2, Table 3.5).

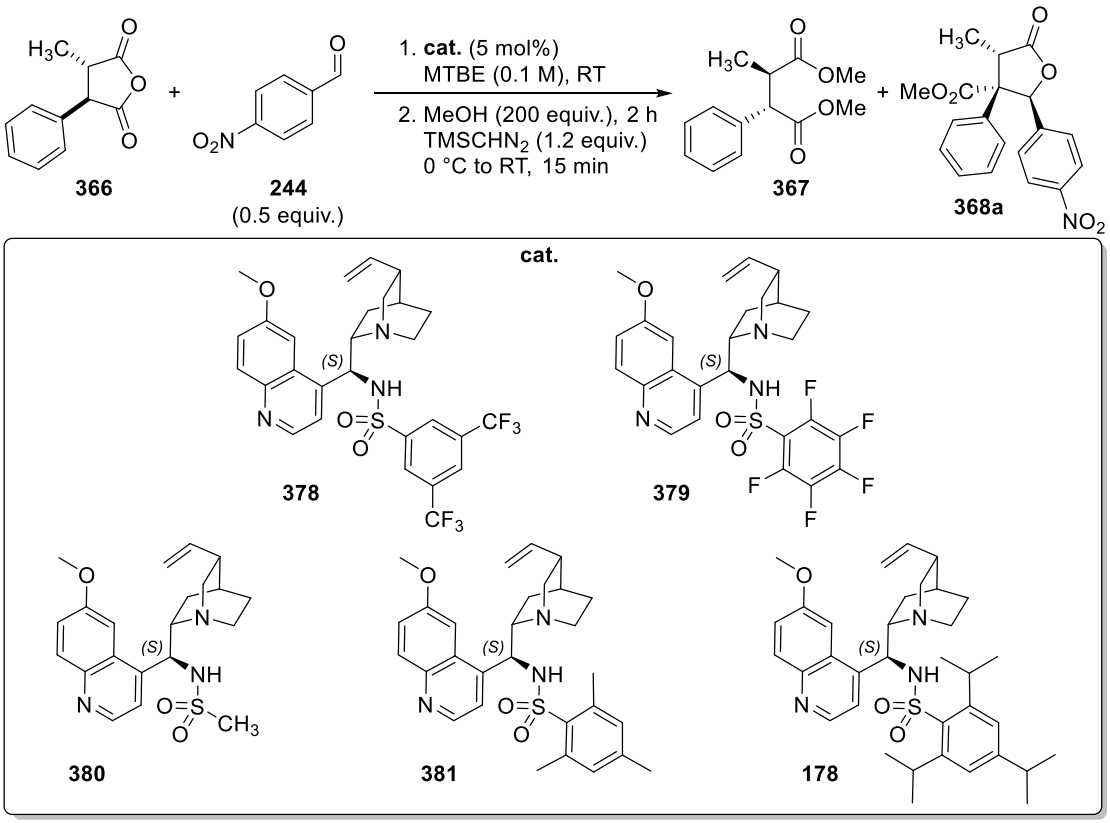
Table 3.4 Evaluation of other squaramide based organocatalysts.



entry	cat.	time (d)	conv. (%)[a]	367 *ee* (%)[d]	S*[e]	368 *dr*[b] a:(b:c:d)	368a *ee* (%)[c]
1	**258**	7	43	27	2.7	82:18	21
2	**375**	7	40	33	4.0	76:24	30
3	**256**	7	41	24	2.6	80:20	25
4	**257**	7	34	1	1.0	78:22	8
5	**376**	4	46	37	3.6	69:31	29
6	**377**	10	35	n.d.[f]	n.d.[f]	67:33	33

[a]Conversion of starting material **244** was determined by ^{1}H NMR spectroscopic analysis using 4-iodoanisole as an internal standard. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. dr = (major diastereomer):(∑other diastereomers). [c]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. Refers to the major diastereomer. [d]Determined by CSP-HPLC after derivatisation of the unreacted starting material **366** by ring opening alcoholysis with MeOH followed by *in situ* esterification with $TMSCHN_2$. [e]S* = selectivity factor calculated based on the starting material **366** after derivatisation to the product **367** by using the conversion (C) determined by ^{1}H NMR spectroscopic analysis and using the formula: $S^* = \ln[(1-C)(1-ee_{367})]:\ln[(1-C)(1+ee_{367})]$. [f]Not determined.

Table 3.5 Evaluation of sulfonamide based organocatalysts.



entry	cat.	time (d)	conv. (%)[a]	367 *ee* (%)[d]	S*[e]	368 *dr*[b] a:(b:c:d)	368a *ee* (%)[c]
1	**378**	10	35	n.d.[f]	n.d.[f]	76:24	10
2	**379**	10	31	6	1.4	75:25	35
3	**380**	6	38	n.d.[f]	n.d.[f]	77:23	30
4	**381**	6	43	n.d.[f]	n.d.[f]	81:19	57
5	**178**	7	45	50	6.7	95:5	59

[a]Conversion of starting material **244** was determined by ^{1}H NMR spectroscopic analysis using 4-iodoanisole as an internal standard. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. dr = (major diastereomer):(∑other diastereomers). [c]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. Refers to the major diastereomer. [d]Determined by CSP-HPLC after derivatisation of the unreacted starting material **366** by ring opening alcoholysis with MeOH followed by *in situ* esterification with $TMSCHN_2$. [e]S* = selectivity factor calculated based on the starting material **366** after derivatisation to the product **367** by using the conversion (C) determined by ^{1}H NMR spectroscopic analysis and using the formula: $S^* = \ln[(1-C)(1-ee_{367})]:\ln[(1-C)(1+ee_{367})]$. [f]Not determined.

Modification of the sulfonamide substituent's steric requirement from a methyl to a bulky 1,3,5-triisopropyl-phenyl group (*i.e.* catalysts **380**-**381**, **178**) resulted in an exciting outcome. When **178** was employed as promoter of the reaction (catalyst

previously successful in the KR of a series of racemic thiols)[109] **366** could be recovered, at 45% conversion, with 50% *ee* (*i.e.* S* = 6.5). It is noteworthy that the diastereoselectivity and enantioselectivity associated with the formation of **368** were also tremendously improved as the major lactone **368a** was formed as almost the sole product diastereomer (up to 95:5 dr, 59% *ee*, entries 3-5, Table 3.5).

3.3 Towards the development of the first class of cinchona based sulfamides bifunctional organocatalysts

Among the library of the 27 organocatalysts evaluated at this point of the study, the performance of **178** clearly outclassed any of the others. Moving forward, we decided to work on the scaffold of **178** and came up with the idea of designing three new organocatalysts. Catalysts **382** and **383** were designed to mimic the bulkiness of **178**, by varying the steric hindrance (*i.e.* with aim of modifying the catalyst-substrate interactions). Catalyst **251** was designed based on the knowledge that the introduction of a *C*-2 phenyl moiety tends to lend greater activity. The structures of the three targeted organocatalysts are depicted in Figure 3.5.

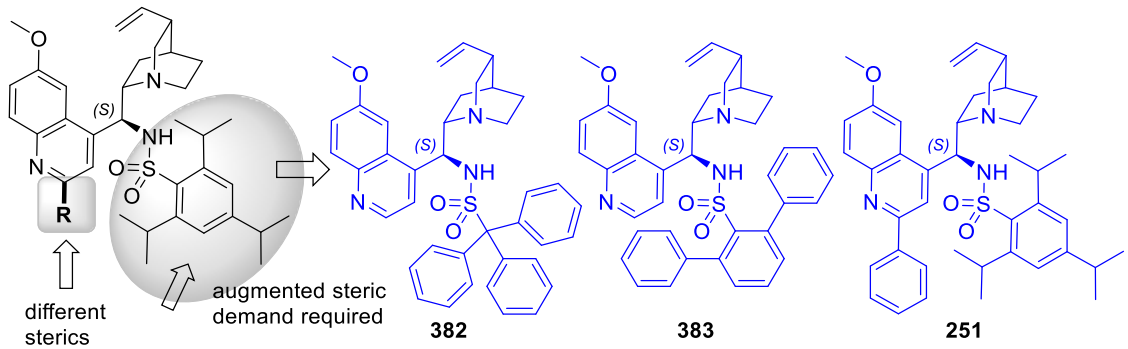
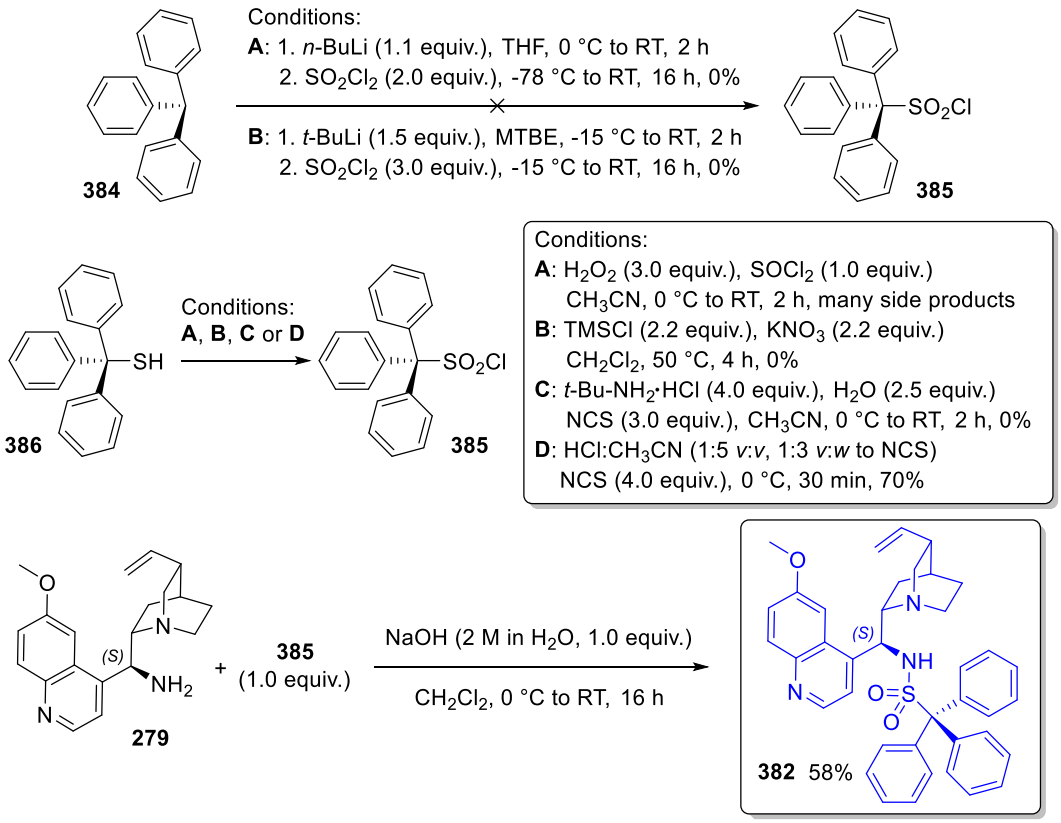


Figure 3.5 Catalyst design and targeted organocatalyst structures **382-383**, **251**.

The main intermediates for the synthesis of sulfonamide-based organocatalyst are known as sulfonyl chlorides (general formula: RSO_2Cl, *e.g.* **385**). To access catalyst **382**, we first attempted to generate an *in situ* lithiated derivative from triphenylmethane (**384**) and subsequently quench it, at low temperature, with an excess of sulfuryl chloride. Employment of the conditions **A** or **B** as described in Scheme 3.2 (*i.e.* with *n*-BuLi or *t*-BuLi as lithiating agents) failed to afford the targeted intermediate **385**. As the one-pot sequence oxidation-chlorination of aromatic thiols[158] is well-documented in the literature and as examples involving aliphatic thiols are also reported,[159] we tried a series of known literature procedures to attempt the one-pot transformation of the

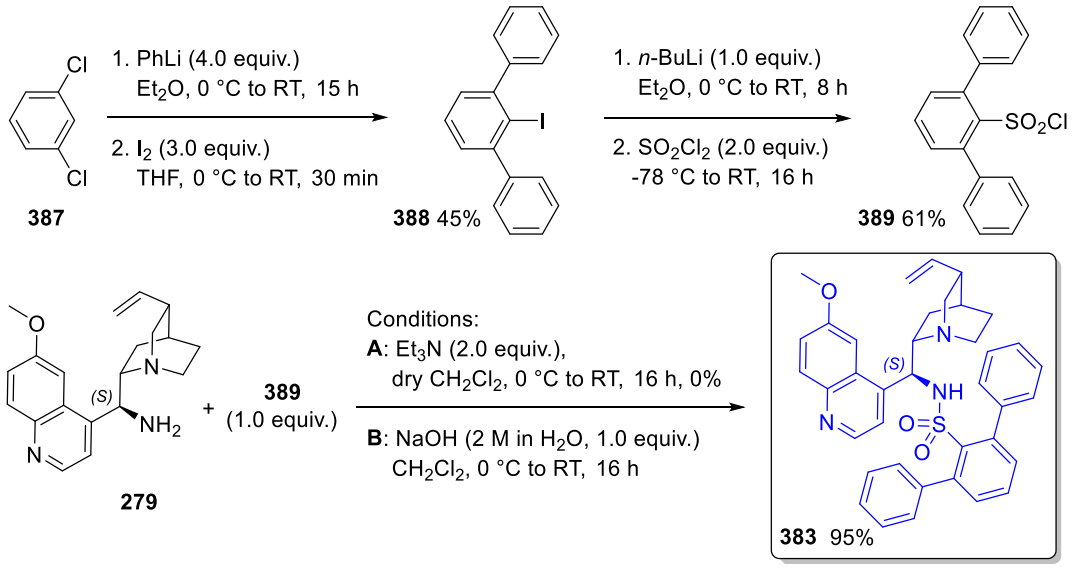
commercially available trityl thiol (**386**) to its sulfonyl chloride derivative **385**. Most of the conditions employed (*i.e.* **A-C**) led to fast and uncontrollable reactions, yielding complex mixtures of side products and/or extensive amount of decomposed material. Gratifyingly, while the conditions **D** were employed and the temperature carefully kept below 0 °C, the desired sulfonyl chloride **385** was obtained in 70% crude yield. A biphasic solvent medium and the use of 1 equivalent of sodium hydroxide allowed for the successful coupling between the free amine of quinine **279** with **385**, affording the sulfonamide **382** in 58% yield, after purification by flash column chromatography (Scheme 3.2).



Scheme 3.2 Synthetic route towards catalyst **382**.

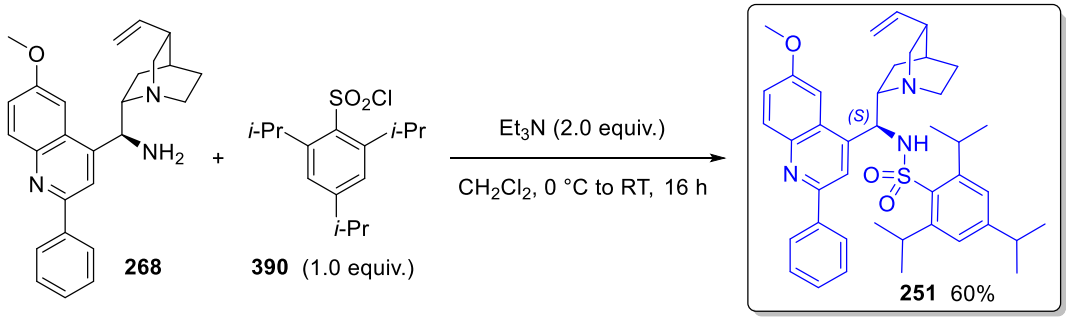
The synthesis of the sulfonyl chloride **389** begins with a double S_NAr on the commercially available 1,3-dichlorobenzene (**387**) carried out with an excess of phenyl lithium reagent. Addition of an excess of iodine to quench the reaction mixture allowed access to the iodinated intermediate **388**, isolated in 45% yield. Lithium-halogen exchange on **388** mediated by a stoichiometric amount of *n*-BuLi afforded, the *in situ* formed, a reactive lithiated nucleophilic species. This could be quenched at low temperature (-78 °C) with two equivalents of sulfuryl chloride, affording the sulfonyl

chloride **389** in 61% yield. Following a similar reaction procedure used to prepare catalyst **382** (*i.e.* employing the reaction conditions **B**), the coupling between amine **279** and sulfonyl chloride **389** allowed access to sulfonamide **383** in 95% yield after purification by flash column chromatography (Scheme 3.3).



Scheme 3.3 Synthetic route towards catalyst **383**.

The last sulfonamide of interest (*i.e.* **251**) was prepared *via* the straightforward transformation depicted in Scheme 3.4. The reaction between the *C*-2 phenyl arylated quinine derivative **268** with the commercially available 2,4,6-triisopropylbenzenesulfonyl chloride (**390**) afforded the desired organocatalyst **251**, isolated in 60% yield after purification by flash column chromatography (Scheme 3.4).

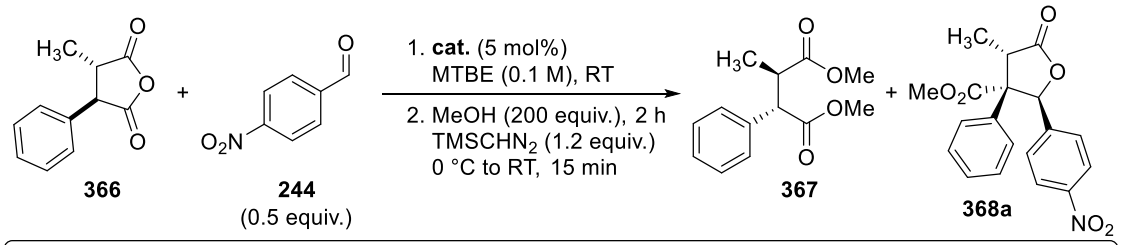


Scheme 3.4 Synthetic route towards catalyst **251**.

The results of the evaluation of these three newly designed organocatalysts **382**-**383** and **251**, in the reaction model, are reported in Table 3.6.

Beginning with the two reactions involving the bulky trityl and 2,6-diphenylbenzene-substituted sulfonamides catalysts (*i.e.* **382-383**) we observed an almost total absence of stereocontrol. Both recovered starting materials **367** or major product diastereomers **368a** were isolated as almost racemic materials (S* = 1.1, entries 1-2, Table 3.6). Unfortunately, the evaluation of the *C*-2 phenyl arylated sulfonamide **251** also resulted in a disappointing outcome. Indeed, **367** was recovered with 39% *ee*, at 46% conversion, corresponding to a low selectivity factor S* = 3.9, along with diminished levels of diastereo- and enantiocontrol associated with the formation of lactones **368a-d**, compared to the data obtained with the optimum sulfonamide **178** (94:6 dr, 56% *ee*, entry 3, Table 3.6).

Table 3.6 Evaluation of newly designed sulfonamide based organocatalysts.



entry	cat.	time (h)	conv. (%)[a]	367 *ee* (%)[d]	S*[e]	368 *dr*[b] a:(b:c:d)	368a *ee* (%)[c]
1	**382**	168	46	3	1.1	91:9	8
2	**383**	168	43	3	1.1	82:18	5
3	**251**	168	46	39	3.9	94:6	56

[a]Conversion of starting material **244** was determined by ^{1}H NMR spectroscopic analysis using 4-iodoanisole as an internal standard. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. dr = (major diastereomer):(∑other diastereomers). [c]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. Refers to the major diastereomer. [d]Determined by CSP-HPLC after derivatisation of the unreacted starting material **366** by ring opening alcoholysis with MeOH followed by *in situ* esterification with $TMSCHN_2$. [e]S* = selectivity factor calculated based on the starting material **366** after derivatisation to the product **367** by using the conversion (C) determined by ^{1}H NMR spectroscopic analysis and using the formula: $S^* = \ln[(1-C)(1-ee_{367})]:\ln[(1-C)(1+ee_{367})]$. [f]Not determined.

3.4 Development of cinchona-based sulfamides as a novel class of bifunctional organocatalysts for the KR of α-alkylated succinic anhydrides

In general, a requirement for efficient asymmetric induction is the capacity of the catalyst to organise the interaction between the reagents in a well-organised manner by means of hydrogen-bonding. Such interactions are often proportional to the acidity of the N-H bonds present in the catalyst. This general tendency can be highlighted by the number of efficient organocatalysts presenting EWG groups such as the 3,5-ditrifluoromethylphenyl unit, which is capable of enhancing the N-H acidity.

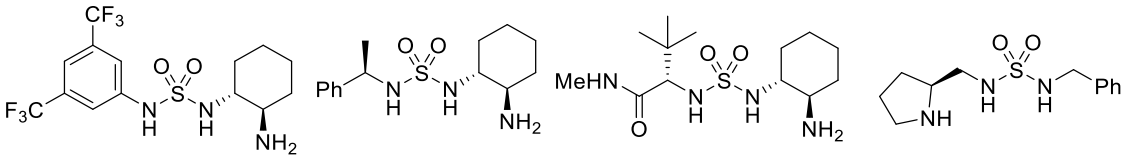


Figure 3.6 Examples of reported chiral sulfamide bifunctional catalysts.[160,161]

Recently, several research groups have orientated their efforts towards the identification of novel hydrogen-bonding *motifs* such as cyclohexyl-sulfamides[160] **391**-**393** and pyrrolidinyl-sulfamide derivatives (*e.g.* **394**),[161] for the design of new chiral bifunctional organocatalysts capable of promoting asymmetric Michael addition reactions.[160,161] Initially, the origin of these structural modifications takes root in the electronic properties of the sulfonyl group, which is considered a better EWG group compared with the corresponding (thio)ureas.[160,161] Therefore, it was targeted as a good candidate for catalyst design and elaboration due to its assumed improved ability to form stronger hydrogen-bonds with the reaction substrates (Figure 3.6).

A common feature to most of the bifunctional organocatalysts derived from the cinchona alkaloids that have been introduced throughout this thesis (*e.g.* ureas, thioureas, squaramides) is their ability to engage two or more hydrogen-bonds with the reactants. However, in the particular case of the sulfonamides, the corresponding organocatalysts can only engage in a single hydrogen bond. We reasoned that the success encountered by the best catalyst **178**, thus far, was most likely due to the steric hindrance associated with it's bulky substituent rather than its hydrogen-bonding ability.

Inspired by the successful advances reported in sulfamide design mentioned above, we became interested in attempting to introduce an extra hydrogen-bond donating unit in

the scaffold of the sulfonamide with aim of developing the first examples of a class of cinchona-based sulfamide bifunctional organocatalysts (see rationale in Figure 3.7, A).

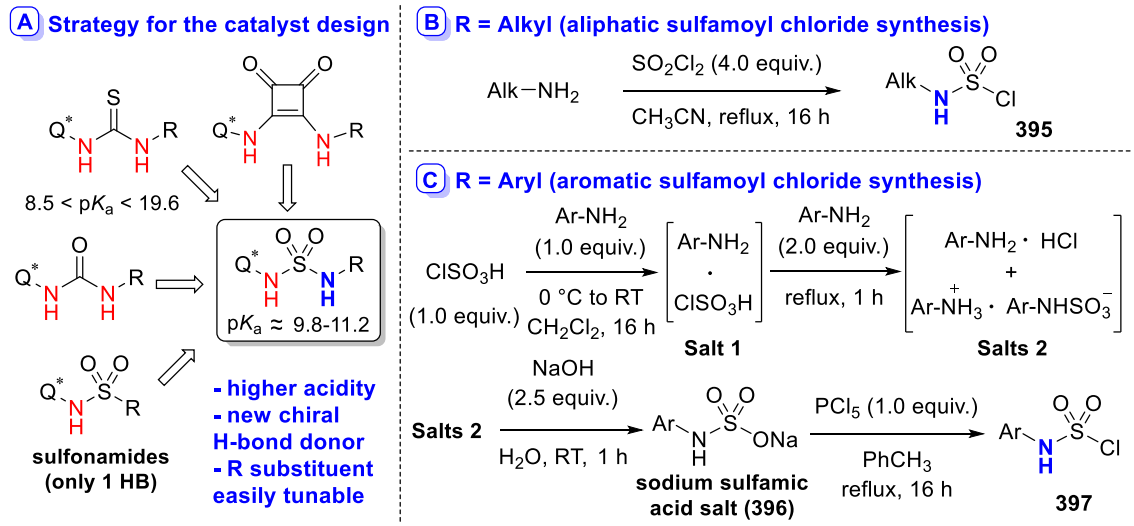


Figure 3.7 Strategy for the catalyst design and preparation of the reactive sulfamoyl chloride intermediates.[162,163,164,165]

The main intermediates commonly employed in accessing sulfonamide catalysts are known as sulfonyl chlorides (R-SO_2Cl). The synthetic equivalents to access to the corresponding sulfamides are known as sulfamoyl chlorides (R-**NH**-SO_2Cl, *e.g.* **395** and **397**).

The scientific literature to access either aliphatic or aromatic sulfamoyl chlorides is well-documented.[162,163,164,165] Probably the simplest strategy for accessing non-densely functionalised aliphatic sulfamoyl chlorides **395** consists in the direct coupling between the corresponding alkyl amine with SO_2Cl_2 (Figure 3.7, B).[163,166] The synthesis of aromatic sulfamoyl chloride is less straightforward. Indeed, sulfuryl chloride is reported as an efficient chlorinating agent that can furnish, under mild conditions, mono- or di-chlorinated ring by-products with excellent yields.[167] For this reason, the synthetic pathway usually employed relies on a different strategy (Figure 3.7, C). Addition of 1+2 (*i.e.* 3.0 equiv.) of the relevant aromatic amine relative to chlorosufonic acid ($ClSO_3H$), yields the complex mixture of **Salts 2**. These salts can be hydrolysed in presence of sodium hydroxide, releasing the excess of amine employed (*i.e.* 2 equiv.) in the organic phase while the desired sodium sulfamic acid salt **396** can be extracted and isolated after evaporation of the aqueous layer. The targeted aromatic sulfamoyl chloride **397** can be obtained by chlorination of its sodium sulfamic acid precursor **396** promoted by

reflux of a stoichiometric amount of phosphorus pentachloride in anhydrous toluene (Figure 3.7, C).

To the best of our knowledge, this sulfamide *motif* has never been introduced into the core of a cinchona alkaloid prior this study. Therefore, we initially orientated our efforts towards the identification of three simple structures that could help us to establish the feasibility of developing this new class of organocatalyst. Our initial idea was the tentative attempt at the synthesis of the simplest aliphatic **253** and aromatic **252** representatives. In parallel, **398** was also synthesised with aim of investigating if the presence of two hydrogen bond units was indeed beneficial (Figure 3.8).

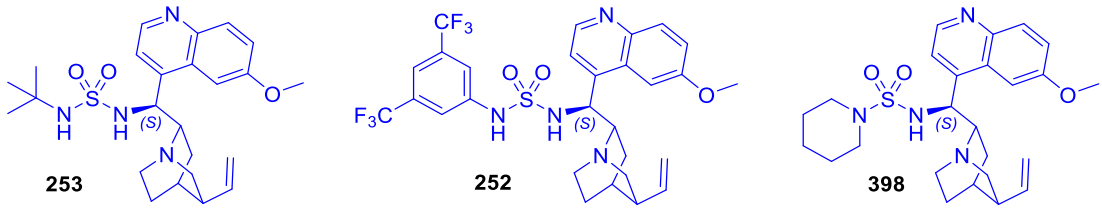
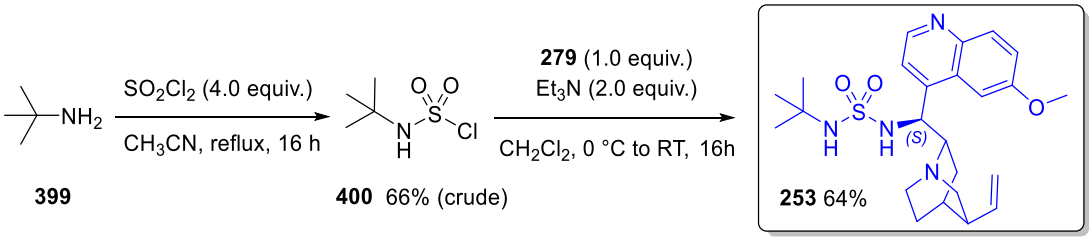


Figure 3.8 Proof of concept: structures of targeted catalysts **252-253**, **398**.

Beginning with the description of the synthesis of catalyst **253**, we began with the *N*-sulfonylation of the commercially available *tert*-butylamine (**254**) following the reported literature procedure.[163] In the next step we attempted the use of similar reaction conditions to those employed for the coupling between amines with sulfonyl chlorides. The coupling between the free amine of quinine **279** with the sulfamoyl chloride **400** occurred smoothly, furnishing sulfamide **253**, in 64% yield (Scheme 3.5).

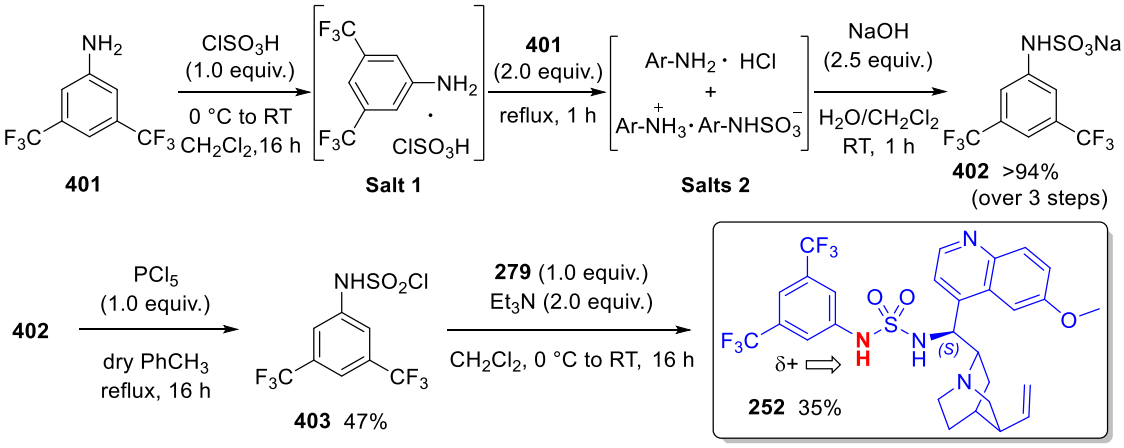


Scheme 3.5 Synthetic route towards catalyst **253**.

To the best of our knowledge, this represents the first example of a successful incorporation of a sulfamide group in a chiral cinchona-alkaloid scaffold. As is the case with most of the sulfonamide-based catalysts, after chromatography **253** was isolated as a mixture of rotamers in an 80:20 ratio (Scheme 3.5).

Gratifyingly, our next attempt towards the synthesis of the aromatic representative **252** was also successful. Starting from the commercially available 3,5-*bis*(trifluoromethyl)aniline (**401**), a two-step sequence involving the quantitative formation of the sodium sulfamic acid salt **402**, followed by its chlorination with PCl_5, afforded the sulfamoyl chloride intermediate **403** in 47% yield (Scheme 3.6).

Following the well-established coupling protocol involving quinine-derived amine **279** with sulfamoyl chloride **403**, in the presence of an excess of triethylamine, catalyst **252** was isolated after subsequent purification by flash column chromatography, in 35% yield. This catalyst also exhibited rotameric properties and was obtained as a mixture of rotamers in the ratio 69:31 (Scheme 3.6).



Scheme 3.6 Synthetic route towards catalyst **252**.

At this point of the study, we were concerned by the large proportion of the minor rotamer (*ca*. 31%). Indeed, we hypothesised that due to the high acidity of the hydrogen (highlighted in red) caused by the 3,5-*bis*(trifluoromethyl)benzene substituent and the highly EWG sulfonyl group, an intramolecular Zwitterion pair could be formed instead, after its deprotonation by the basic quinuclidine tertiary nitrogen atom (Scheme 3.6).

To confirm the presence of a rotameric species or identify a non-negligible percentage of protonated quinuclidine, we ran a series of NMR spectroscopic experiments with the aim of adressing our concerns. First, two-dimensional NOESY experiment was conducted on a Bruker Avance II 600 MHz spectrometer. This experiment revealed the presence of characteristic signals of rotameric exchanges (*i.e.* the cross-peaks on the diagonal of the spectrum, Figure 3.9).

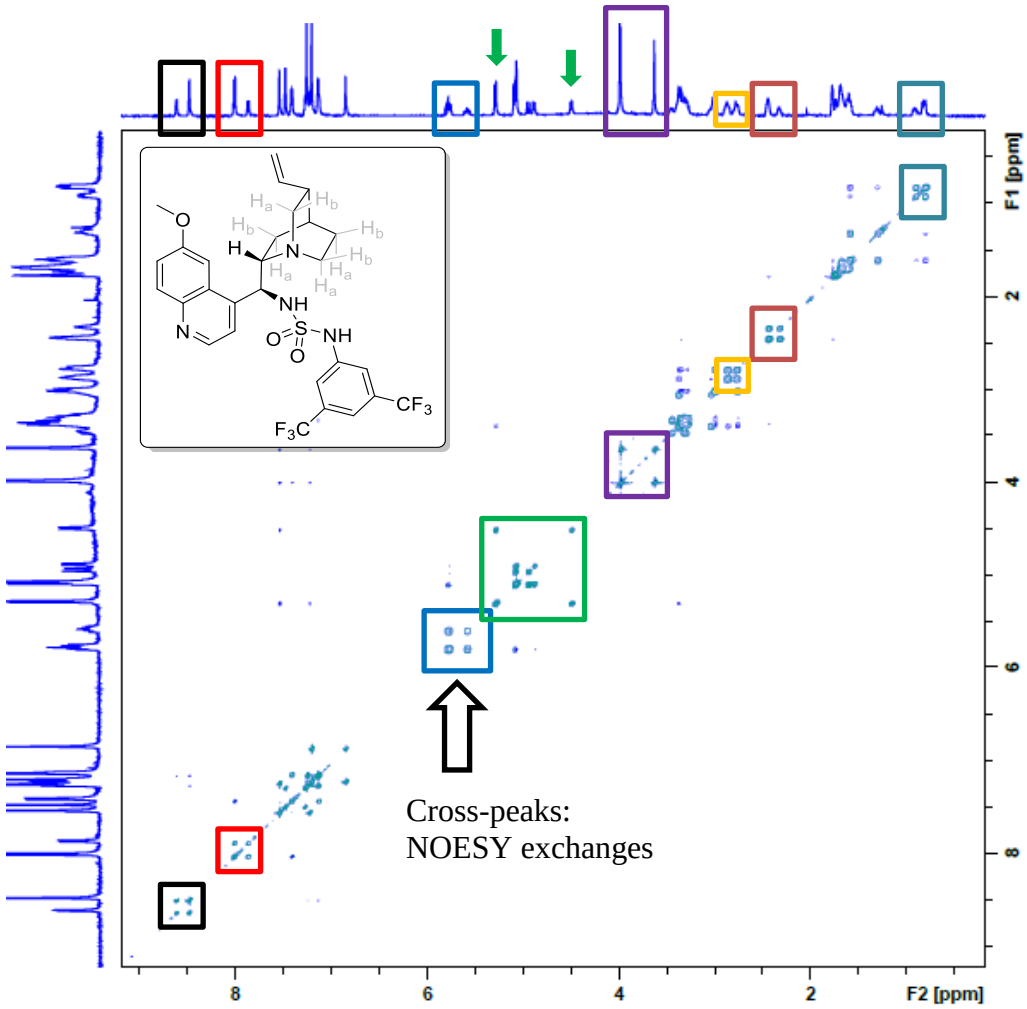


Figure 3.9 Two dimensional NOESY exchanges determined by NMR experiment on a Bruker Avance II 600 MHz spectrometer.

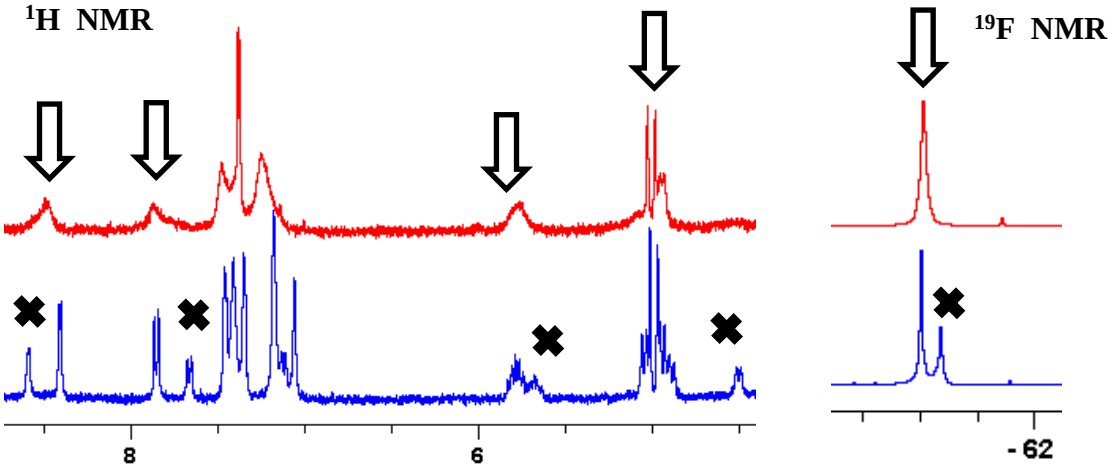


Figure 3.10 Evolution of the rotameric ratio determined by ^{1}H NMR and ^{19}F NMR experiments recorded at 25 °C (**blue**) and 60 °C (**red**) in DMSO-d_6.

We also ran a combination of one dimensional ^{1}H and ^{19}F NMR spectroscopic experiments. A pattern of split-signals can be observed that clearly corresponds to either a rotameric effect or a Zwitterion. Increasing the temperature of the NMR acquisition from 25 °C to 60 °C (*i.e.* blue and red spectra respectively, Figure 3.10) shows the complete disappearance of the minor resonances. This phenomenon is more easily observed on the ^{19}F NMR spectra. This result confirms the presence of a rotameric species. In contrast, if a Zwitterion was present, we would expect temperature elevation to favour the formation of the minor signals, as the amount of protonated quinuclidine should increase (Figure 3.10).

As an unequivocal piece of evidence, we crystallised from ethanol, a sample of **252**. Analysis of the single crystal obtained by X-ray diffraction pattern analysis confirmed our conclusions based on NMR spectroscopic experiments (Figure 3.11).

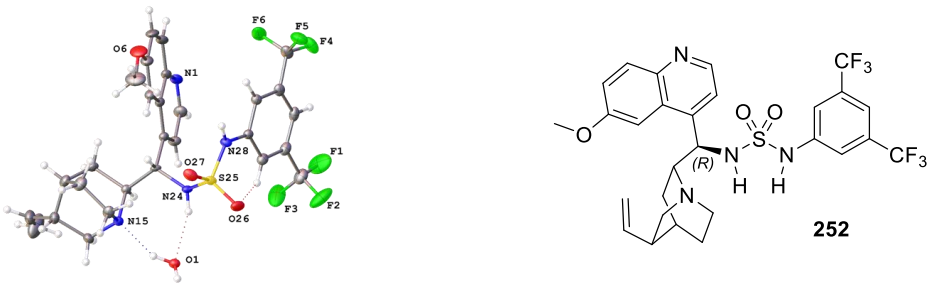
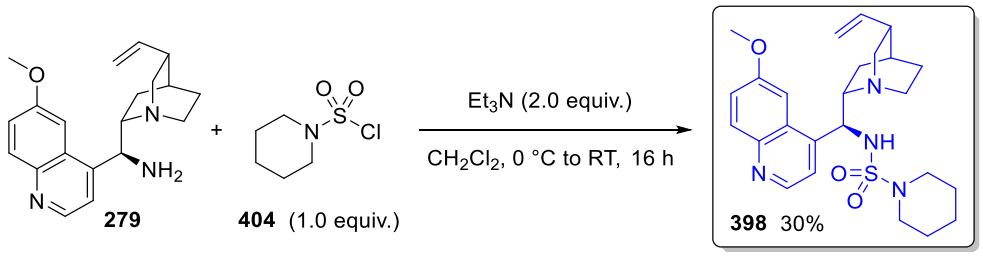


Figure 3.11 X-ray structure of sulfamide **252**.

Interestingly, during the crystallisation process a water molecule co-crystallised with **252**, as depicted in the structure presented in Figure 3.11. This crystallographic structure highlights the method by which a catalyst can activate and deliver, in an enantioselective fashion, a small nucleophile by means of bifunctional catalysis. This fortunate but totally unpredicted result, of co-crystallisation, would have been very satisfying should the X-ray structure have revealed the presence of hydrogen bonds between N(24)-H→O(1) and N(28)-H→O(1). Indeed, our primary goal was to introduce a second hydrogen-bond unit in the catalyst, to increase the strength of the catalyst-substrate interactions. Nevertheless, in solution, the catalyst most likely adopts different conformations, as confirmed by its rotameric activity, and we cannot discount the fact that it may engage in further hydrogen bonds with the substrates. Also, if this extra N(28)-H hydrogen bond unit does not participate in the activation of the

pronucleophile (unproven) we still envisaged that it could help in activating the electrophilic counterpart of the reaction (*i.e.* activate the aldehyde component).

Finally, catalyst **398** was prepared by the straightforward coupling between amine **279** with the commercially available piperidine-1-sulfonyl chloride (**404**), in the presence of triethylamine, and was isolated in 30% yield (Scheme 3.7). The results of our first experiments aiming to investigate the potential of these new sulfamide catalysts proved to be rather promising and are reported in Table 3.7.

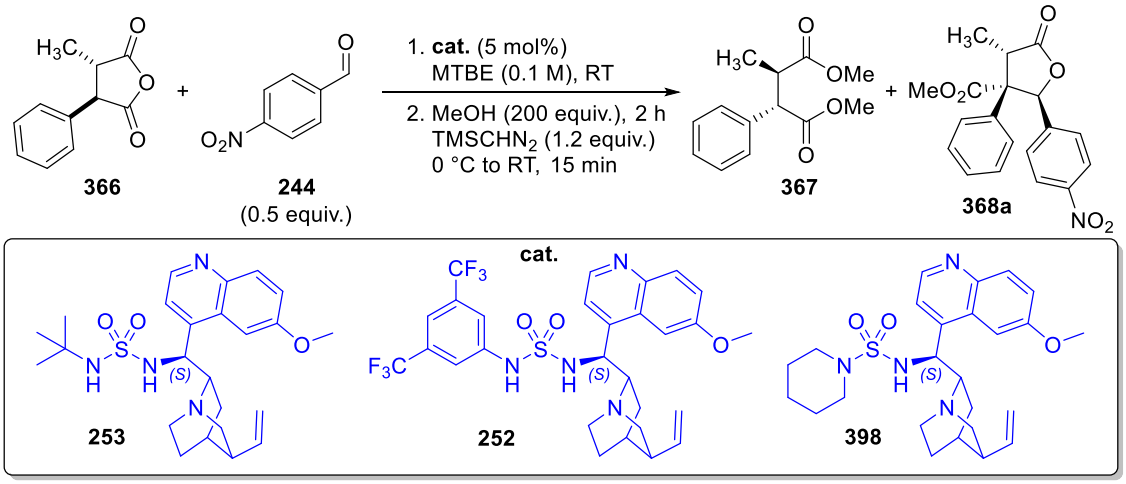


Scheme 3.7 Synthetic route towards catalyst **398**.

The selectivity factors obtained with the catalysts containing two hydrogen bond units (*i.e.* catalysts **252** and **253**) proved to be considerably superior over the mono hydrogen bond donor catalyst **398** (up to S* = 5.8 with **253** against S* = 1.9 with **398**, entries 1-3, Table 3.7). Aditionally, in both examples, lactones **368a-d** were formed with excellent diastereoselectivity in favour of **368a**; with the two catalysts containing the extra hydrogen bond unit (up to 97:3 dr, entry 2, Table 3.7).

It is worth mentioning that these two sulfamide catalysts (*i.e.* **252-253**) were initially designed as the simplest representatives of the class of catalyst. In particular, their synthesis was mainly aimed at establishing the feasibility of incorporating the sulfamide *motif* by means of simple and classical organic transformations. Interestingly, our first investigations confirmed and proved that both aliphatic- and aromatic-groups can be incorporated in the cinchona scaffold. Gratifying, one of these catalysts almost immediately matched the performance of the most selective catalyst **178** evaluated so far in this project.

Table 3.7 Evaluation of the newly designed sulfamide-based catalysts **252-253**, **398**.



entry	cat.	time (h)	conv. (%)[a]	367 *ee* (%)[d]	S*[e]	368 *dr*[b] a:(b:c:d)	368a *ee* (%)[c]
1	**253**	120	45	47	5.8	96:4	47
2	**252**	144	43	26	2.6	97:3	48
3[f]	**398**	68	60	28	1.9	92:8	40

[a]Conversion of **244** was determined by ^{1}H NMR using 4-iodoanisole as an internal standard. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. [c]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. Refers to the major diastereomer. [d]Determined by CSP-HPLC after derivatisation of the unreacted starting material **366**. [e]S* = selectivity factor calculated based on the starting material **366** after derivatisation to the product **367** by using the conversion (C) determined by ^{1}H NMR spectroscopic analysis and using the formula: estimated S* = $\ln[(1-C)(1-ee_{367})]:\ln[(1-C)(1+ee_{367})]$. [f]0.7 equiv. of **244** was used.

Following these two promising results, we thought it would be interesting to investigate the scope and possibilities offered by these new types of catalysts and decided to orientate our efforts towards the synthesis and evaluation of considerably more sterically hindered analogues, such as the catalysts depicted in Figure 3.12.

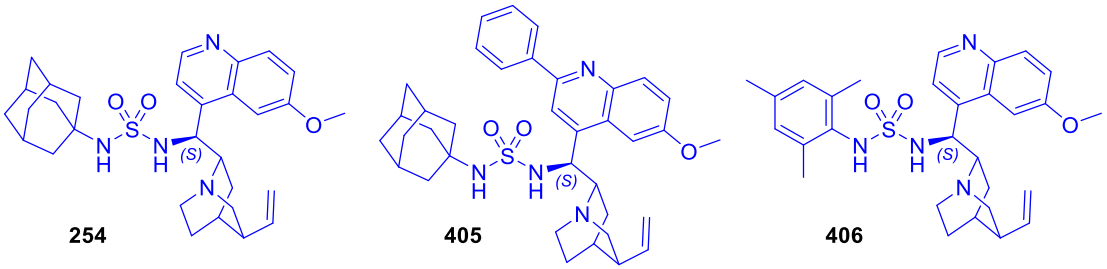
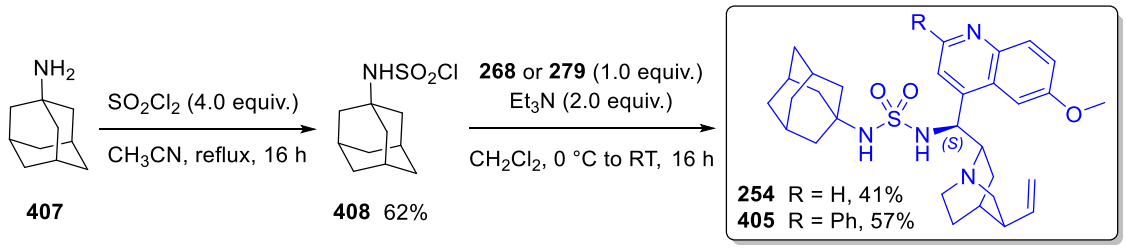


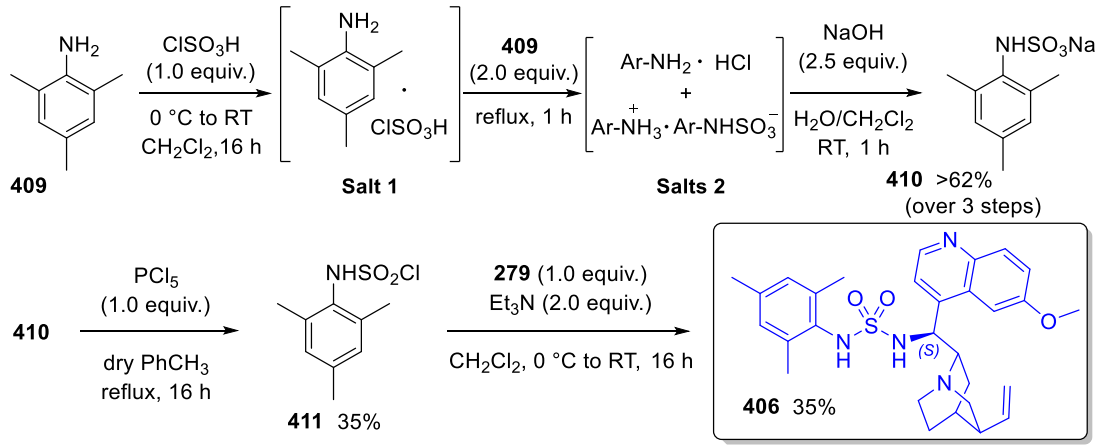
Figure 3.12 Next targets for broadening the scope of the sulfamide catalysts.

We decided to evaluate the influence of the bulkiness of the *N*-sulfonyl substituent through the incorporation of an aliphatic adamantyl (*i.e.* **254**) or aromatic 2,3,5-trimethylanilino substituent (*i.e.* **406**). We also synthesised phenyl derivative **405** in order to investigate the influence of the substitution at the *C*-2 position of the catalysts (Figure 3.12).



Scheme 3.8 Synthetic route towards catalyst **254** and **405**.

The synthesis of catalysts **254** and **405** begins with the formation of the intermediate sulfamoyl chloride **408**. After an overnight reflux in dry acetonitrile, in the presence of an excess of sulfuryl chloride, the commercially available 1-adamantylamine (**407**) was converted to adamantyl-1-sulfamoyl chloride (**408**), in 62% yield. Following a straightforward work-up procedure, intermediate **408** was utilised in the next step, without further purification due to its assumed instability. In the presence of an excess of triethylamine, reacting **408** with amines **268** and **279**, afforded catalysts **254** and **405**, which were isolated after column chromatography, in 41% and 57% yield respectively. Again, ^{1}H NMR spectroscopic analysis revealed the presence of two rotameric species with the respective ratios of 77:23 and 76:24 (Scheme 3.8).

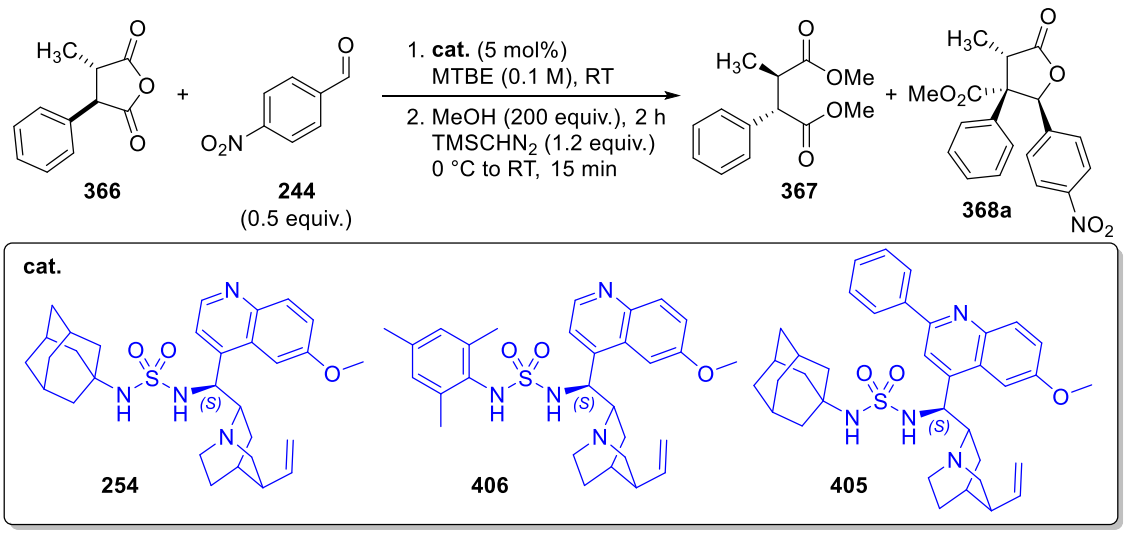


Scheme 3.9 Synthetic route towards catalyst **406**.

The synthetic route towards catalyst **406** was the same as that employed to make catalyst **252**. Commercially available 2,3,5-trimethylaniline (**409**) was converted to the sodium sulfamic acid salt **410**. Subsequent chlorination of **410** mediated by PCl_5, in toluene, yielded the corresponding sulfamoyl chloride **411**, in a 35% yield. Coupling between **279** with **411**, furnished catalyst **406** in 35% yield following column chromatography. Once again, ^{1}H NMR spectroscopic analysis revealed the presence of two rotameric species in a 98:2 ratio (Scheme 3.9).

These three newly synthesised bulky sulfamide organocatalysts (*i.e.* **254**, **405**-**406**), were subsequently evaluated in the standard reaction. The results of their performances are presented in Table 3.8 below.

Table 3.8 Evaluation of newly designed sulfamide-based organocatalysts.



entry	cat.	time (h)	conv. (%)[a]	367 *ee* (%)[d]	S*[e]	368 *dr*[b] a:(b:c:d)	368a *ee* (%)[c]
1	**254**	168	48	64	10.5	95:5	63
2	**406**	96	46	47	5.4	94:6	47
3	**405**	144	48	52	5.9	96:4	55

[a]Conversion of starting material **244** was determined by ^{1}H NMR spectroscopic analysis using 4-iodoanisole as an internal standard. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. dr = (major diastereomer):(∑other diastereomers). [c]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with $TMSCHN_2$. Refers to the major diastereomer. [d]Determined by CSP-HPLC after derivatisation of the unreacted starting material **366** by ring opening alcoholysis with MeOH followed by *in situ* esterification with $TMSCHN_2$. [e]S* = selectivity factor calculated based on the starting material **366** after derivatisation to the product **367** by using the conversion (C) determined by ^{1}H NMR spectroscopic analysis and using the formula: $S^* = \ln[(1-C)(1-ee_{367})]:\ln[(1-C)(1+ee_{367})]$. [f]Not determined.

Comparing the results obtained with the aliphatic and aromatic substituted catalysts **254** and **406**, at 48% and 46% conversion respectively, we observed with both catalysts, the formation of **368** with excellent diastereocontrol (*i.e.* >20:1 dr, entries 1-2, Table 3.8). The main diastereomer **368a** was formed with higher level of enantioselectivity when aliphatic sulfamide **254** was used as promoter of the KR process (up to 63% *ee*). As a direct consequence, the derivatised recovered starting material **367** was also recovered with a greater level of enantioenrichement when **254** catalysed the reaction (up to 64% *ee*). At these levels of conversion, **367** was recovered with selectivity factors of S* = 10.5 and S* = 5.4 respectively. This clearyl indicated **254** as considerably more selective towards one particular enantiomer of **366** rather than the other (entries 1-2, Table 3.8).

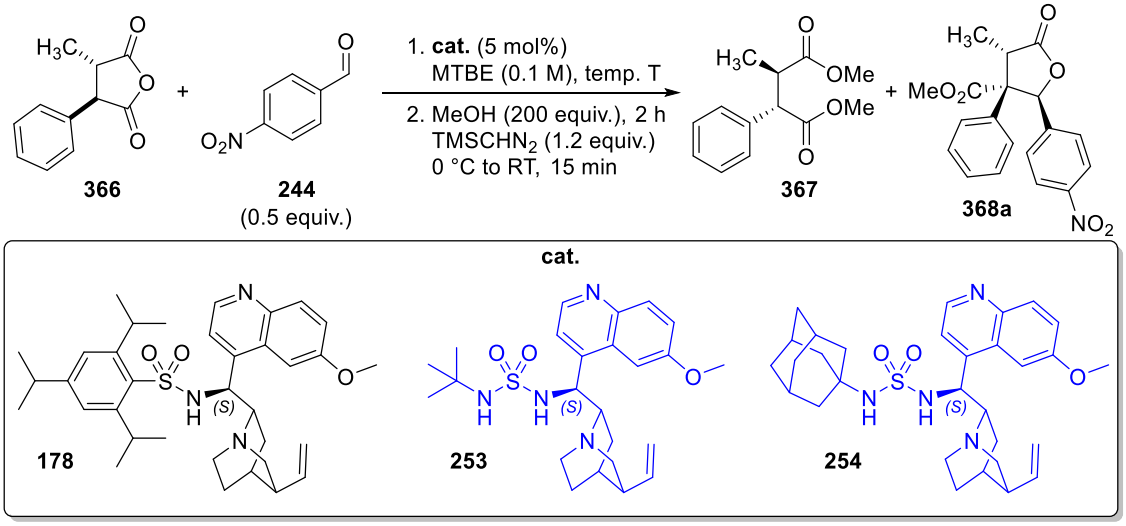
Further attempts to improve the stereocontrol through the evaluation of the *C*-2 phenyl arylated analogue of **254** (*i.e.* **405**) proved futile (entry 3). Although the selectivity factor obtained was encouraging (S* = 5.9), this remained far below the selectivity obtained with **254** (entries 1 and 3, Table 3.8). As a result, we decided to focus our attention exclusively on the non arylated version of the aliphatic sulfamide catalyst **254**.

3.5 Optimisation studies for the formal cycloaddition KR of racemic α-methyl phenyl succinic anhydride with 4-nitrobenzaldehyde

After the catalyst screening carried out for the DKR of racemic *trans* anhydrides presented in Chapter 2, a trityl based squaramide catalyst emerged as significantly more selective than the others. As a result, this catalyst was chosen as the optimal choice for evaluating the substrate scope of this novel catalytic process.

On the other hand, in this new KR challenge, after evaluating a total of thirty-two organocatalysts (including nine *ad hoc* designed for the purpose of this project), none exhibited a significant superiority in terms of reaction selectivity over the others. As a result, we selected the three catalysts promoting the most selective reactions at our disposal and decided to investigate the influence of reaction temperature. We carried out the reaction at both lower and higher temperatures than ambient (0 °C and 30 °C) with the aim of determining if one catalyst would emerge as a significantly better candidate to continue the study. The results of those experiments in which catalysts **178**, **253** and **254** were employed are reported in Table 3.9.

Table 3.9 Temperature screening for the reaction between **366** and **244**.



entry	cat.	cat. loading (mol%)	time (h)	conv. (%)[a]	temp. T (°C)	367 *ee* (%)[d]	S*[e]	368 *dr*[b] a:(b:c:d)	368a *ee* (%)[c]
1[f]	**178**	5	168	45	RT	50	6.7	95:5	59
2[g]	**253**	5	120	45	RT	47	5.8	96:4	47
3[h]	**254**	5	168	48	RT	64	10.5	95:5	63
4	**178**	5	768	36	0	n.d.[i]	n.d.[i]	64:36	19
5	**253**	20	120	48	0	28	2.4	94:6	34
6	**254**	20	120	49	0	34	2.9	93:7	52
7	**178**	5	72	43	30	46	6.4	94:6	54
8	**253**	5	68	64	30	60	3.5	92:8	47
9	**254**	5	72	46	30	47	5.4	94:6	54

[a]Conversion of **244** was determined by ^{1}H NMR using 4-iodoanisole as an internal standard. [b]Determined by ^{1}H NMR. dr = (major diastereomer):(∑other diastereomers). [c]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters with $TMSCHN_2$. Refers to the major diastereomer. [d]Determined by CSP-HPLC after derivatisation of the unreacted **366** by alcoholysis with MeOH followed by esterification with $TMSCHN_2$. [e]S* = selectivity factor calculated based on the starting material **366** after derivatisation to the product **367** by using the conversion (C) determined by ^{1}H NMR spectroscopic analysis and using the formula: $S^* = \ln[(1-C)(1-ee_{367})]:\ln[(1-C)(1+ee_{367})]$. [f]Data reproduced from Table 3.5. [g]Data reproduced from Table 3.7. [h]Data reproduced from Table 3.8. [i]Not determined.

The data obtained for the reactions initially carried out at ambient temperature, with catalysts **178**, **253**-**254**, have been reproduced to allow for comparison with the data obtained at lower and higher temperature (*i.e.* entries 1-3, Table 3.9).

A general trend was observed between the three reactions, performed at 0 °C, and employing catalysts **178**, **253** and **254** (entries 4-6). In all cases, comparable levels of conversion were achieved, however, the enantiomeric excesses associated with the major diastereomer **368a**, or with the recovered starting material **367**, was lowered by ≈ 20% *ee* compared with the data obtained with the same catalysts at room temperature (*i.e.* entries 1-3 against entries 4-6). In comparison, at 0 °C, the catalyst **254** could promote the KR of **366** with a considerably reduced level of selectivity of only S* = 2.9 (entries 3 and 6, Table 3.9).

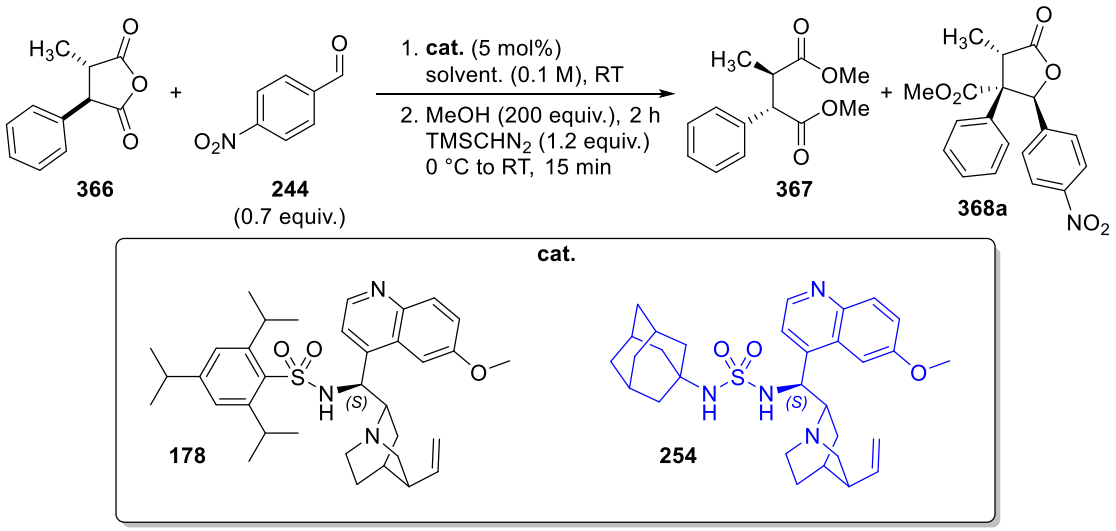
We next tried the opposite approach; evaluating the same catalysts **178**, **253**-**254**, at a higher temperature (*i.e.* at 30 °C, entries 7-9) and again, we observed a general trend. Although the reaction time to reach levels of conversion close from 50% was greatly enhanced, the selectivity factors S* remained marginally diminished compared to the selectivity factors determined at room temperature (up to S* = 6.4, entry 7, Table 3.9).

These rather unusual trends were later rationalised by the fact that compounds possessing rotameric forms such as **178**, **253** or **254**, may exist under multiple conformations depending on the reaction temperature (as exemplified in Figure 3.10) and thus, may exhibit efficiencies directly linked to the temperature and their actual distribution of conformations in solution. Considering the data reported in Table 3.9, we choose to eliminate the considerably less selective sulfamide **253**. We next carried out a solvent screen with catalysts **178** and **254**; aiming to select the optimal catalyst for the development of the process at hand. The results of the solvent screening optimisation carried out with **178** and **254** are reported in Table 3.10.

First, the performances of sulfonamide **178** were evaluated, at room temperature, in four different ethereal solvents (entries 1-4, Table 3.10). The results were consistant with previous observations, indicating methyl *tert*-butyl ether as the optimal solvent choice for the reaction. At 45% conversion, **367** was recovered with 50% *ee*, coresponding to a selectivity factor S* = 6.7 (entry 1, Table 3.10). As a result, we already knew at this stage that the newly designed sulfamide **254** could promote the reaction with better

selectivity (up to S* = 10.5 in MTBE at RT), and suspected it would be chosen as our optimised promoter of the KR process, in order to evaluate the substrate scope of the reaction with respect to the anhydride component.

Table 3.10 Solvent evaluation for the reaction between **366** and **244**.



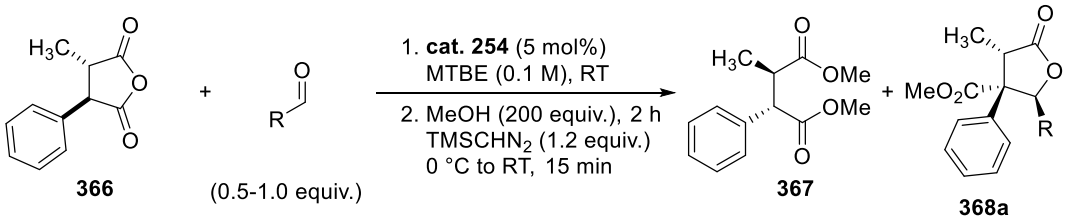
entry	cat.	cat. loading (mol%)	time (h)	conv. (%)[a]	solvent.	367 *ee* (%)[d]	S*[e]	368 *dr*[b] a:(b:c:d)	368a *ee* (%)[c]
1[f]	**178**	5	168	45	MTBE	50	6.7	95:5	59
2	**178**	5	240	39	THF	n.d.[h]	n.d.[h]	86:14	49
3	**178**	10	96	47	2-Me-THF	32	2.8	67:33	50
4	**178**	10	120	50	(*i*-Pr)$_2$O	33	2.7	88:12	47
5[g]	**254**	10	168	48	MTBE	64	10.5	95:5	63
6	**254**	10	144	53	THF	41	3.1	91:9	59
7	**254**	10	96	57	2-Me-THF	54	3.9	90:10	57
8	**254**	10	120	22	(*i*-Pr)$_2$O	n.d.[h]	n.d.[h]	94:4	n.d.[h]

[a]Conversion of starting material **244** was determined by ^{1}H NMR spectroscopic analysis using 4-iodoanisole as an internal standard. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopic analysis. dr = (major diastereomer):(∑other diastereomers). [c]Determined by CSP-HPLC after derivatisation of the carboxylic acid products to the methyl esters by *in situ* esterification with TMSCHN$_2$. Refers to the major diastereomer. [d]Determined by CSP-HPLC after derivatisation of the unreacted starting material **366** by ring opening alcoholysis with MeOH followed by *in situ* esterification with TMSCHN$_2$. [e]S* = selectivity factor calculated based on the starting material **366** after derivatisation to the product **367** by using the conversion (C) determined by ^{1}H NMR spectroscopic analysis and using the formula: S* = ln[(1-C)(1-*ee*$_{367}$)]:ln[(1-C)(1+*ee*$_{367}$)]. [f]Data reproduced from Table 1.6. [g]Data reproduced from Table 1.7. [h]Not determined.

Evaluation of the same ethereal solvents, with catalyst **254** as promoter of the reaction, under identical conditions as outlined above, resulted in similar outcomes (entries 5-8, Table 3.10). Even though the levels of stereoselectivity remained marginally higher compare to those obtained with catalyst **178**, the optimal solvent choice for the reaction remained methyl *tert*-butyl ether (S* = 10.5, entry 5, Table 3.10).

We had previously shown, that the level of stereocontrol in related cycloaddition processes is often influenced by the aldehyde electrophile employed.[83,88] 4-Nitrobenzaldehyde (**244**) was initially chosen as an activated aldehyde that reacts faster than benzaldehyde and facilitates NMR spectroscopic analysis. However, at this stage of the study, no efforts towards the choice of the electrophile had been carried out.

Table 3.11 Evaluation of aliphatic and aromatic resolving agents.



entry	aldehyde	electrophile (equiv.)	time (d)	conv. (%)[a]	367 *ee* (%)[b]	S*[c]
1	**244**	0.5	7	48	64	10.5
2	**82**	5	10	33	n.d.[d]	n.d.[d]
3	**323**	10	10	27	n.d.[d]	n.d.[d]

[a]Conversion of starting material **366** was determined by ^{1}H NMR spectroscopic analysis using 4-iodoanisole as an internal standard. [b]Determined by CSP-HPLC after derivatisation of the unreacted starting material **366** by ring opening alcoholysis with MeOH followed by *in situ* esterification with $TMSCHN_2$. [c]S* = estimated selectivity factor calculated based on the starting material **366** after derivatisation to the product **367** by using the conversion (C) determined by ^{1}H NMR spectroscopic analysis and using the formula: $S^* = \ln[(1-C)(1-ee_{367})]:\ln[(1-C)(1+ee_{367})]$. [d]Not determined.

Using the insights gained during the DKR study reported in Chapter 2, we hypothesised that either benzaldehyde (**82**) or hydrocinnamaldehyde (**323**) could be excellent coupling partners that would help catalyst **254** in promoting a diastereoselective transformation and thus, improve its catalytic abilities to kinetically resolve (*rac*)-**366** (Table 3.11).

After 7 days of reaction in MTBE, at 48% conversion, in the presence of the resolving agent **244**, the starting material **367** was recovered in 64% *ee*, corresponding to a selectivity factor S* = 10.5 (entry 1, Table 3.11).

Unfortunately, when aldehydes **82** or **323** are used as the resolving agent, in both cases, the reaction rate is significantly lowered. Indeed, even though a large excess of aldehyde was employed (0.7-1.0 equivalent, entries 2-3, Table 3.11), the conversion barely reached the unsatisfactory level of 33%, after 10 days reaction, at room temperature. The impractical reaction rate led us to temporarily reconsider the idea of optimising the structure of the resolving agent. Our choice was further motivated by the thought that the introduction of sterically more hindered alkyl chains (compared to a methyl group) would most likely result in slower reactions. Furthermore, the presence of a nitro- functionality on the lactone product resulted in, on several occasions, butyrolactone products that tends to be crystalline and can be subsequently enantioenriched by successive recrystallisation.

3.6 Evaluation of the substrate scope: the racemic nucleophilic component

With an optimised catalyst structure and a synthetically useful protocol in hand, our attention next turned to the important question of the substrate scope with respect to the anhydride pronucleophiles capable of undergoing KR.

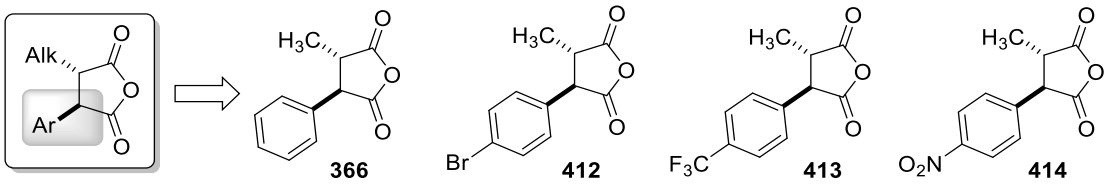


Figure 3.13 Investigation of the electronic effects at the aryl moiety of the pronucleophile component: anhydride targets **412**-**414**.

Firstly, we planned to investigate the influence of the electronic effects at the aryl moiety, by evaluating the ability of catalyst **254** to kinetically resolve the racemic

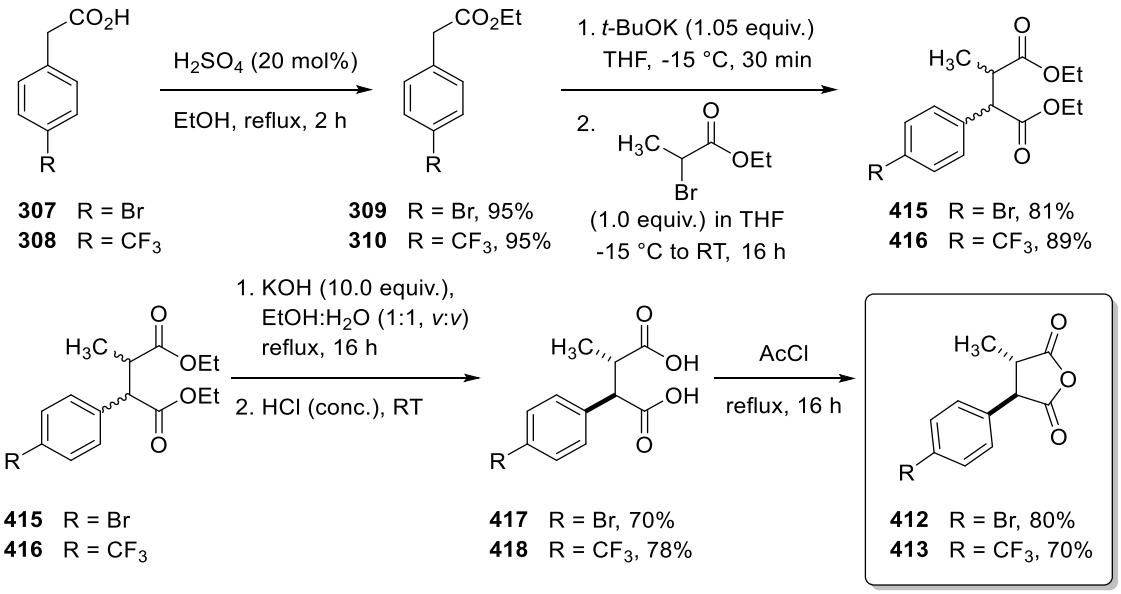
anhydrides **412-414**. Our primary objective was to identify the optimal EWG to introduce at the *para*-position of the aryl moiety in order to subsequently evaluate the scope with respect to the alkyl chain present on the anhydride scaffold (Figure 3.13).

In the second part of this study, after investigating the influence of the electronic effects on the process, we aimed to attempt the KR of anhydrides bearing larger, longer and also bulkier alkyl moieties such as *n*-Et, *n*-Pr or *i*-Pr.

As the targeted anhydrides **412-414** are not commercially available, our investigations towards their KR began with their synthesis. The facile preparation of **412-414** is depicted in Scheme 3.10 and Scheme 3.11.

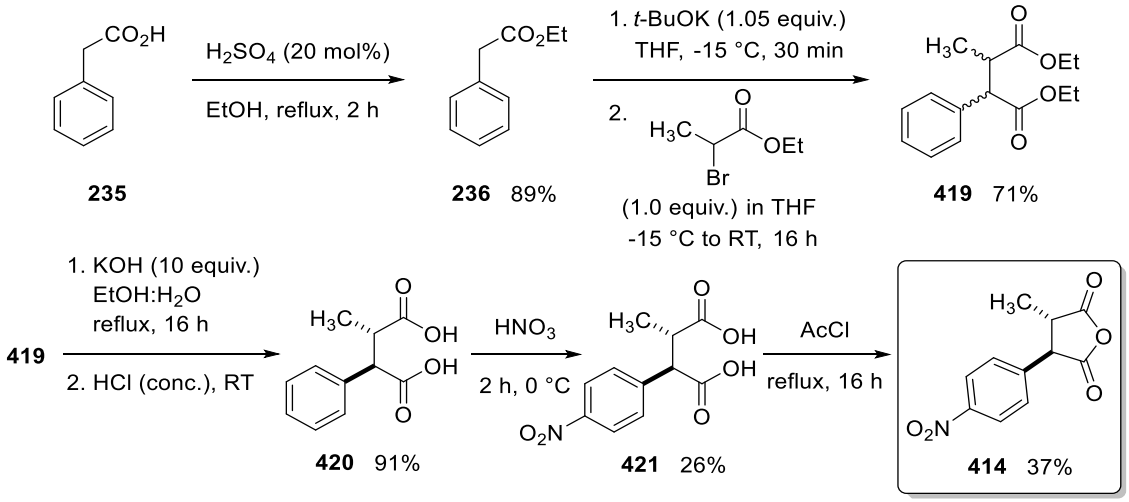
Fischer esterification of the carboxylic acids **307-308** afforded the corresponding ethyl esters **309-310** quantitatively. Then a 2-step reaction sequence beginning with the synthesis, *via* a S_N2 reaction, of the two *bis*-esters **415-416** (both isolated as a mixture of crude materials with good yields) was followed by their saponification. After work-up and upon acidification of the aqueous layer (with conc. HCl), the *trans* isomers of the *bis*-acids **417-418** precipitated and were collected by suction filtration as pure materials.

The cyclisations of *bis*-acids **417-418** leading to **412-413** were mediated by overnight reflux in acetyl chloride as solvent (Scheme 3.10).



Scheme 3.10 Synthesis of anhydrides **412** and **413**.

In order to synthesise anhydride **414**, we choose to follow an alternative route. During the previous DKR study, when we attempted the saponification reaction of the ethyl-ester derivative of a structural analogue to carboxylic acid **421**, we obtained an extensive amount of decomposition and could not isolate the targeted product *via* the synthetic pathway depicted in Scheme 3.10. Therefore, we inferred that strongly basic conditions were incompatible with manipulation of highly enolisable materials such as the 4-nitro analogue of **419**.

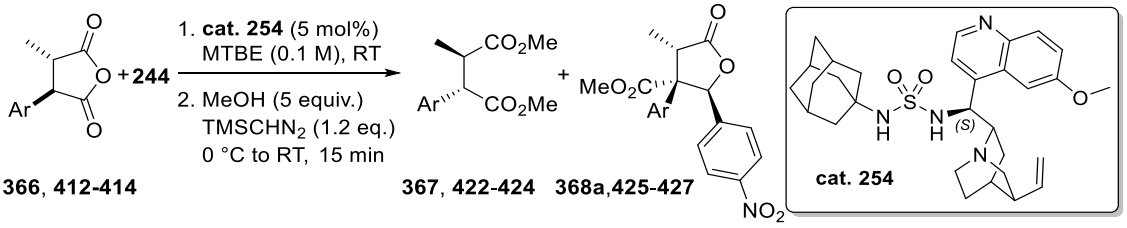


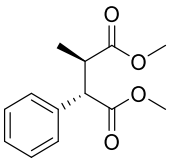
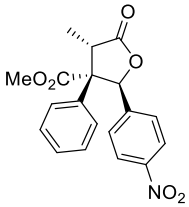
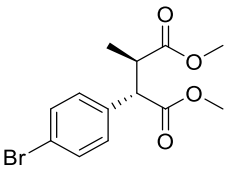
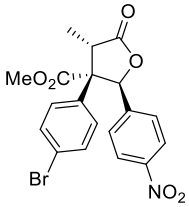
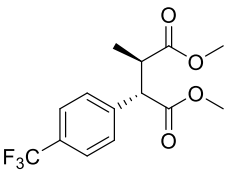
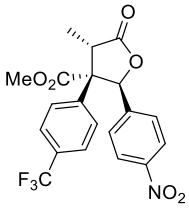
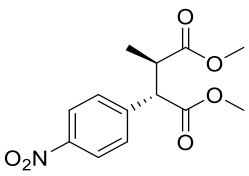
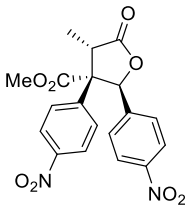
Scheme 3.11 Synthesis of anhydride **414**.

As a result, we considered safer to avoid using strong basic conditions in our synthesis. Our alternative route relied on the direct nitration of *bis*-acid **420** affording the anhydride precursor **421**, in 26% yield, after a recrystallisation from deionised water. Ring-closure of **421** led to a crude material that was purified by crystallisation, from dry diethyl ether, to afford the analytically pure product **414**, in 37% yield (Scheme 3.11).

Our attention next turned to the evaluation of the ability of the novel sulfamide catalyst **254** to kinetically resolve the anhydrides **412**-**414** *via* their cycloaddition, at ambient temperature, to 4-nitrobenzaldehyde (**244**). The results are reported in Table 3.12.

Table 3.12 Substrate scope: the anhydride pronucleophile component.



entry	succinate (367, 422-424)	lactones (368a, 425-427)	t (d)	conv. (%)[a]	S*[b]
1[c]			7	48	10.5
	367 37%, 64% *ee*	**368a** 40%, 19:1 dr, 63% *ee* (99)			
2			3	66	4.7
	422 31%, 75% *ee*	**425** 39%, 7:1 dr, 94% *ee*			
3			2	60	3.1
	423 35%, 49% *ee*	**426** 43%, 5:1 dr, 55% *ee*			
4			1	60	1.9
	424 34%, 29% *ee*	**427** 38%, 3:1 dr, 55% *ee*			

[a]Conversion of **244** was determined by ^{1}H NMR spectroscopy relative to 4-iodoanisole as an internal standard. [b]Calculated employing the same formula as in Table 3.2. [c]Reproduced from Table 3.8.

The data obtained for the reactions carried out with anhydride **366** has been reproduced from Table 3.8 to allow for comparison with the data obtained with the other three anhydrides **412**-**414** (*i.e.* entry 1, Table 3.12).

The introduction of a *p*-Br substituent in the anhydride scaffold (*i.e.* **412**) resulted in dramatically improved reaction rates. After 3 days, the reaction was quenched at 66% conversion and the starting material was recovered as its derivatised opened form **422** in 75% *ee*, corresponding to a selectivity factor S* = 4.7. As the reaction was quenched above 50% conversion, the diastereomeric ratio of the corresponding lactones **425** was necessarily diminished, however the main diastereomer was isolated with an excellent enantiomeric excess (7:1 dr, 94% *ee*, entry 2, Table 3.12).

The evaluation of other EWGs such as *p*-CF_3 or *p*-NO_2 (*i.e.* **413**-**414**) led to significantly reduced level of selectivitiy. At 60% conversion, **423**-**424** were respectively recovered with 49% *ee* and 29% *ee*, corresponding to respective selectivity factors of S* = 3.9 and S* = 1.9. We rationalised that the introduction of increasingly stronger EWGs at the *para* position resulted in faster background reactions, competing with the catalysed processes (entries 3-4, Table 3.12). We attempted two complementary experiments aiming to regain some control over the reaction by lowering the temperature to -15 °C. Unfortunately, these experiments proved unproductive and resulted in unremarkable levels of control; as nearly identical selectivity factors were obtained (*ca.* S* = 3.3 and 1.9 respectively).

The relative stereochemistry of the succinate **367** and the lactone **368a** was assigned at an early stage of this study using a combination of ^{1}H NMR Nuclear Overhauser Effect (NOE) experiments. As expected, the succinate **367** exhibited a *trans* relationship between the methyl and the 2-phenyl substituent. Analysis of the data revealed for lactone **368a** a 1,2-*cis* and 2,3-*trans* relationship as depicted in Figure 3.14.

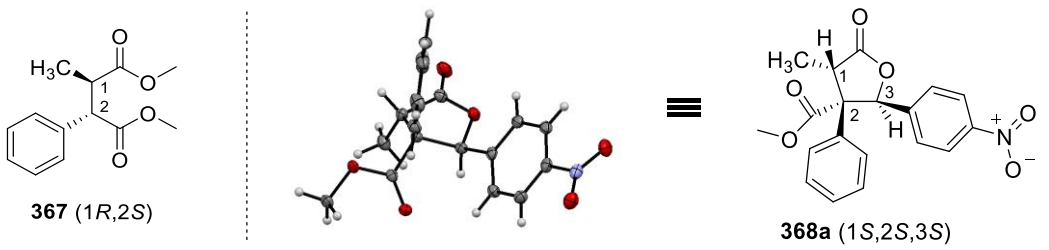


Figure 3.14 Absolute configuration assignment of succinate **367** and lactone **368a**.

The absolute stereochemistry of **368a** was later unambiguously assigned as (1*S*,2*S*,3*S*) by X-ray crystallographic analysis of a sample obtained in >99% *ee* (Figure 3.14). The stereochemical configuration of the lactones **425-427** were subsequently assigned as (*S*,*S*,*S*) by analogy to **368a**.

The absolute stereochemistry of the recovered starting materials, enantioenriched as their succinate derivatives **367**, **422-424** was subsequently assigned as (1*R*,2*S*) by comparison to the stereochemistry of **368a** and with help of a combination of ^{1}H NMR spectroscopic experiments showing a *trans* stereochemistry (Figure 3.14).

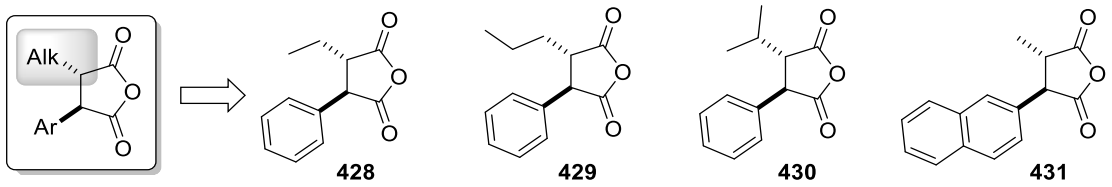
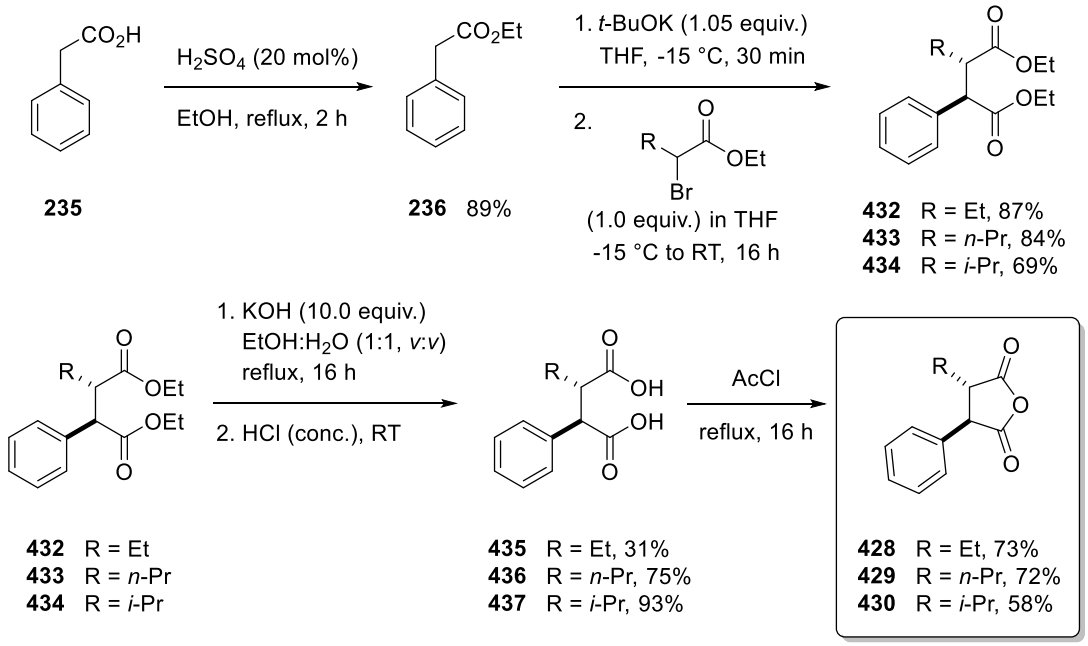


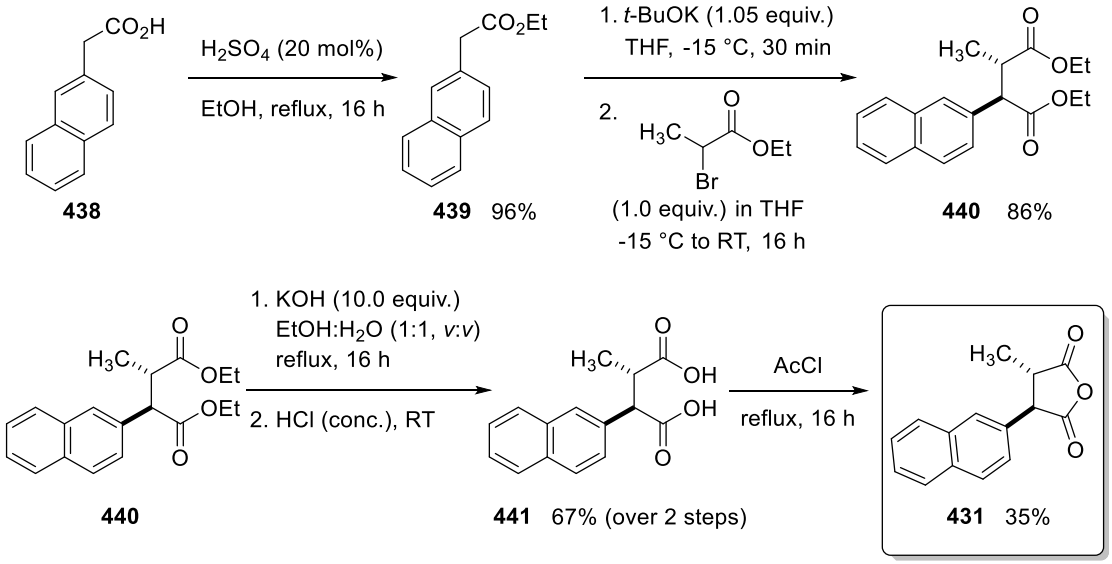
Figure 3.15 Investigation of the steric effects at the alkyl and aryl position of the pro-nucleophile component: anhydride targets **428**-**431**.

We next investigated the influence of steric hindrance at the alkyl moiety. In light of the results obtained in Table 3.12, we choose to synthesise anhydrides **428**-**431** without an EWG at the *para* position of the aryl moiety. Finally, anhydride **431** was designed in order to investigate the influence of different steric bulk using an aryl substituent (Figure 3.15).



Scheme 3.12 Synthesis of anhydrides **428** to **430**.

The synthetic pathways adopted in order to achieve the synthesis of the next 4 anhydrides of interest (*i.e.* **428**-**431**) are identical to those we previously reported for the synthesis of anhydrides **412**-**413** (Scheme 3.10). These straightforward transformations do not requiere further discussion here. The reaction conditions and yields of each individual step are provided in Scheme 3.12 and Scheme 3.13.



Scheme 3.13 Synthesis of anhydride **431**.

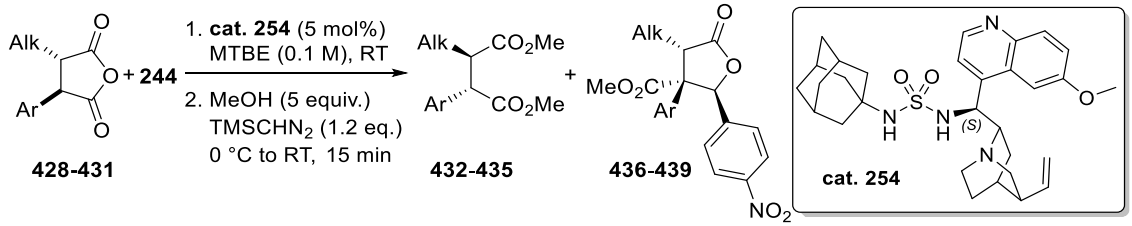
With reaction conditions optimised with the sulfamide catalyst **254**, and after identifying the optimal EWG at the *para* position of the anhydride scaffold, our attention reverted to the important question of the substrate scope with respect to the anhydrides capable to be resolved by such catalytic process. The results of the KR attempt at anhydrides **428**-**431** are reported in Table 3.13.

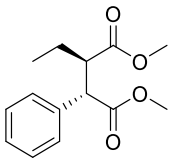
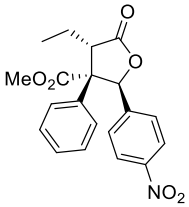
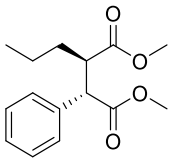
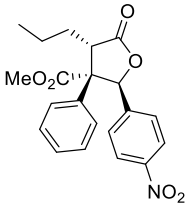
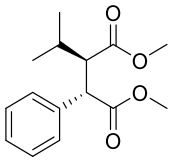
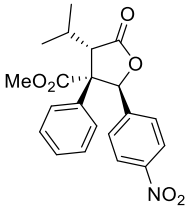
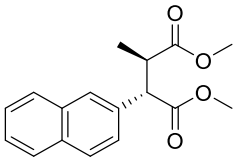
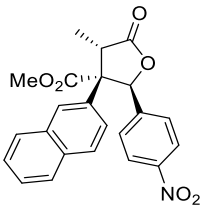
Beginning with the reaction performed with the anhydrides bearing longer alkyl chains (*i.e.* **428** and **429**, alkyl = ethyl and *n*-propyl respectively, entries 1-2) we observed similar outcomes. After 5 days, at room temperature, the reactions were quenched at 52% and 54% conversion respectively, and the starting materials were recovered as their derivatised enantioenriched form **432**-**433** with 65% *ee* and 69% *ee* respectively (*i.e.* S* = 7.6 and S* = 7.7). The similarity between the results obtained highlighted the fact that introducing longer alkyl chains on the anhydride does not seam to significantly affect the way the catalyst discriminates between the two faces of the anhydride pronucleophile component. Gratifyingly, these two processes were also accompagnied with the formation of highly functionalised lactone products **436** and **437** with good

stereocontrol. The major product diastereomers of the reactions were isolated with good diastereoselectivity and good levels of enantioselectivity (entries 1-2, Table 3.13).

The last two reactions reported aimed at investigating the influence of steric effects, by either augmenting the steric demand of the anhydrides aryl- or alkyl-substituents. Unfortunately, these two-structural modifications proved rather inefficient. Firstly, in both cases, the reactions proceeded with considerably slower reaction rates. After 6 days, the starting materials **430**-**431** were recovered as their derivatised enantioenriched form **434**-**435** with low *ee* (*i.e.* S* = 5.3 and S* = 3.3 respectively). Unsurprisingly, the lactones **438**-**439** associated to the KR processes were formed with significantly lower level of diastereo- and enantioselectivity (up to 6:1 dr, 51% *ee*, entries 3-4, Table 3.13).

Table 3.13 Substrate scope: the anhydride pronucleophile component.



entry	succinate (432-435)	lactones (436-439)	t (d)	conv. (%)[a]	S*[b]
1			5	52	7.6
	432 34%, 65% *ee*	**436** 43%, 10:1 dr, 69% *ee*			
2			5	54	7.7
	433 41%, 69% *ee*	**437** 42%, 9:1 dr, 66% *ee*			
3			6	45	5.3
	434 46%, 45% *ee*	**438** 34%, 6:1 dr, 51% *ee*			
4			6	43	3.3
	435 26%, 32% *ee*	**439** 32%, 9:1 dr, 47% *ee*			

[a]Conversion of **244** was determined by ^{1}H NMR spectroscopy relative to 4-iodoanisole as an internal standard. [b]Calculated employing the same formula as in Table 3.2.

3.7 Conclusion for Chapter 3

In summary, we have demonstrated for the first time in this work that α-alkylated aryl succinic anhydrides can undergo some kinetic resolution (KR) in an organocatalytic fashion in a regio-, diastereo- and enantioselective manner with 4-nitrobenzaldehyde.

We have demonstrated that the process is sensitive to both the steric and electronic properties of the substituents present on the anhydrides. Future work will involve the development and evaluation of novel organocatalysts/resolving agents to achieve full kinetic resolution of the racemic starting materials. At this early stage of the study we have identified two general trends. Firstly, the introduction of EWG at the *para* positions, increases the enolisability of the anhydride pronucleophiles and leads to faster reactions which were found to be more challenging to control. Secondly, longer alkyl chains do not seem to affect the KR processes while sterically more hindered substituents, dramatically affected the way the catalyst enantiodiscriminates the two faces of the starting material enolates. Under our optimised conditions, the resolved starting materials evaluated in this thesis could be recovered as their opened form - as chiral succinate derivatives - with levels of selectivity up to S* = 10.5. These processes were accompanied by the concomitant formation of densely functionalised five-membered α-alkylated lactones (paraconic acid derivatives; γ-butyrolactones) with levels of selectivity over three contiguous stereocentres ranging from moderate to excellent (up to 7:1 dr, 94% *ee*).

The stereochemical configuration of the lactones were unambiguously assigned using a combination of ^{1}H NMR Nuclear Overhauser Effect (NOE) experiments and crystal X-ray diffraction pattern analysis.

Overall, throughout this project we have identified 8 novel enolisable anhydrides and reacted them with aldehydes, forming 8 novel γ-butyrolactones and allowing for the simultaneous recovery of 8 enantioenriched chiral succinates. To do so we evaluated a library of a total of 36 organocatalysts including 9 specifically designed for the purpose of developing this work. Among these 9 novel catalysts 6 of them constituted the first examples of an *ad hoc* designed newl class of promising bifunctional hydrogen-bond donor sulfamide organocatalysts capable of engaging multiple hydrogen-bonds with the substrates.

Experimental

4. Experimental procedures and data

4.1 General

Proton Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker DPX 400 MHz and Bruker Avance II 600MHz spectrometers, using as solvent $CDCl_3$, DMSO-d_6 or D_2O and referenced relative to residual $CHCl_3$ (δ = 7.26 ppm) DMSO (δ = 2.50 ppm) or H_2O (δ = 4.79 ppm). Chemical shifts are reported in ppm and coupling constants (*J*) in Hertz. Carbon NMR spectra were recorded on the same instruments (100.6 MHz and 150.9 MHz respectively) with total proton decoupling. Fluorine NMR spectra were recorded on the Bruker DPX400 machine (376.5 MHz). HSQC, HMBC, TOCSY NOE and ROESY NMR experiments were used to aid assignment of NMR peaks when required. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. ESI mass spectra were acquired using a Waters Micromass LCT- time of flight mass spectrometer (TOF), interfaced to a Waters 2690 HPLC. The instrument was operated in positive or negative mode as required. EI mass spectra were acquired using a GCT Premier Micromass time of flight mass spectrometer (TOF). The instrument was operated in positive mode. Chemical Ionization (CI) mass spectra were determined using a GCT Premier Micromass mass spectrometer in CI mode utilising methane as the ionisation gas. APCI experiments were carried out on a Bruker microTOF-Q III spectrometer interfaced to a Dionex UltiMate 3000 LC or direct insertion probe. The instrument was operated in positive or negative mode as required. Agilent tuning mix APCI-TOF was used to calibrate the system. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualized by UV irradiation and $KMnO_4$ staining. Optical rotation measurements are quoted in units of 10^{-1} deg cm^2 g^{-1}. Toluene was distilled over calcium hydride and stored under argon. Anhydrous acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), tetrahydrofuran (THF) and diethyl ether (Et_2O) were obtained by using Pure Solv MD-4EN Solvent Purification System. Methanol (MeOH) and isopropyl alcohol (*i*-PrOH) were dried over activated 3Å molecular sieves. Commercially available anhydrous *t*-butyl methyl ether (MTBE) was used. Analytical CSP-HPLC was performed on Daicel Chiralpak, AD, AD-H, IA, or Chiralcel OD, OD-

H, OJ-H (4.6 mm x 25 cm) columns or ACQUITY UPC2 on chiral Trefoil AMY1, CEL1, CEL2 (2,5 µm, 3.0 x 150mm) columns.

4.2 Gradient tables for HPLC conditions

Table 4.1

Time (min)	FR (mL/min)	% A	% B	Curve
Initial	1.200	97.0	3.0	Initial
4.50	1.200	40.0	60.0	6
6.00	1.200	40.0	60.0	6
6.10	1.200	97.0	3.0	6

Table 4.2

Time (min)	FR (mL/min)	% A	% B	Curve
Initial	1.200	97.0	3.0	Initial
8.50	1.200	40.0	60.0	6
10.00	1.200	40.0	60.0	6
10.10	1.200	97.0	3.0	6

Table 4.3

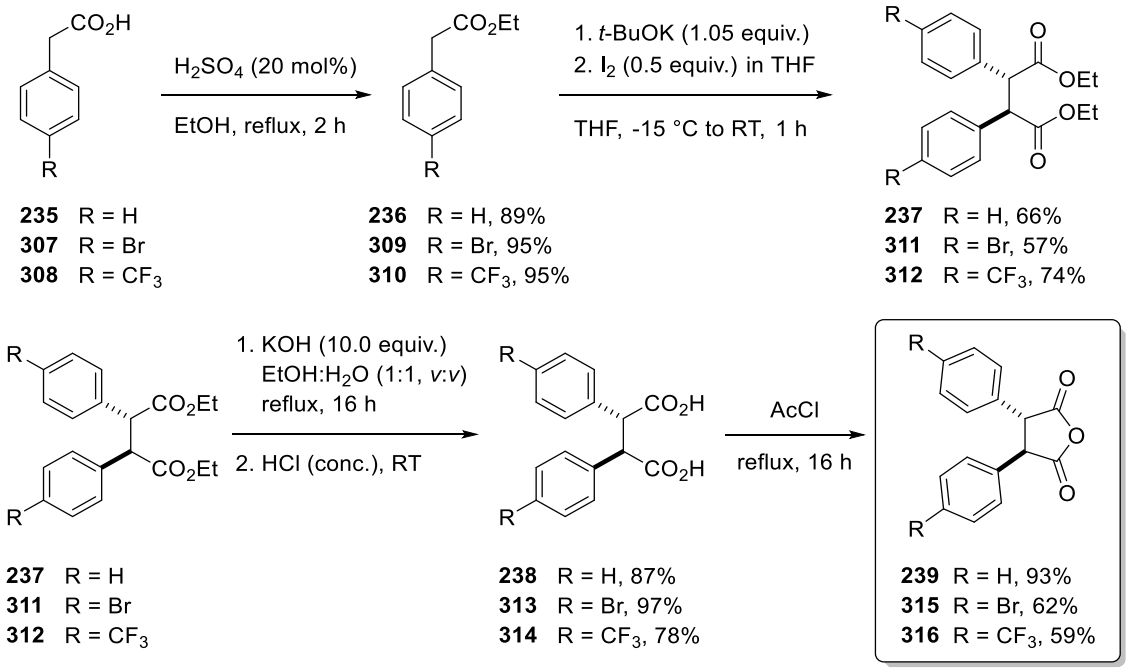
Time (min)	FR (mL/min)	% A	% B	Curve
Initial	1.200	99.0	1.0	Initial
8.50	1.200	92.0	8.0	6
10.00	1.200	40.0	60.0	6
10.10	1.200	97.0	3.0	6

Table 4.4

Time (min)	FR (mL/min)	% A	% B	Curve
Initial	1.200	99.0	1.0	Initial
4.50	1.200	40.0	60.0	6
8.10	1.200	40.0	60.0	6
8.20	1.200	97.0	3.0	6

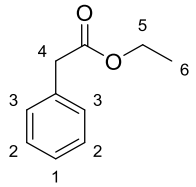
4.3 Experimental procedures for Chapter 2

4.3.1 Synthesis of anhydrides: procedures



Scheme 4.1 Synthetic route towards anhydrides **239** and **315-316**.

Ethyl 2-phenylacetate (236)



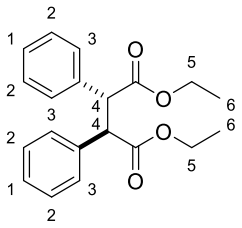
A 250 mL round-bottomed flask containing a stirring bar was charged with phenylacetic acid (**235**) (10.00 g, 73.45 mmol). EtOH (100 mL) followed by conc. H_2SO_4 (0.8 mL) were added, the flask was fitted with a condenser and the resulting mixture was stirred under reflux for 2 h. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in Et_2O (150 mL) and washed with a saturated $NaHCO_3$ solution until basic pH was reached. The mixture was extracted with Et_2O (3 x 100 mL), the combined organic fractions were washed with deionised water, dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford **236** pure as a colourless liquid (10.80 g, 65.77 mmol, 89%). TLC (hexanes:EtOAc, 4:1 *v*/*v*): R_f = 0.90.

Spectral data for this compound were consistent with those in the literature.[168]

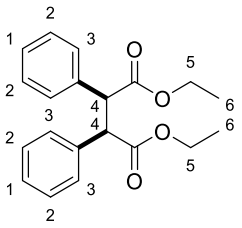
δ_H (400 MHz, $CDCl_3$): 7.36-7.25 (5 H, m, H-1, H-2 and H-3), 4.16 (2 H, q, *J* 7.1, H-5), 3.63 (2 H, s, H-4), 1.27 (3 H, t, *J* 7.1, H-6).

HRMS (*m/z* - APCI): Found: 165.0900 $(M+H)^+$ $C_{10}H_{13}O_2$ Requires: 165.0910.

Diethyl-2,3-diphenylsuccinate (*trans*-237and *cis*-237)



trans-**237**



cis-**237**

A 250 mL oven dried round-bottomed flask containing a stirring bar was charged with potassium *tert*-butoxide (*tert*-BuOK, 5.47 g, 48.77 mmol). The flask was flushed with argon, then fitted with a septum and placed under an argon atmosphere. Dry THF (80 mL) was added *via* syringe and the resulting suspension was cooled to -15 °C. To the resulting suspension, a solution of ethyl 2-phenylacetate (**236**, 7.62 g, 46.45 mmol) in dry THF (20 mL) was slowly added and the resulting mixture stirred for 30 min. Immediately after the addition, a cooled solution of iodine (5.89 g, 23.22 mmol) in dry THF (50 mL) was slowly added *via* syringe over a 10 min period (exothermic reaction). After the addition, the flask was allowed to warm up to room temperature and the reaction mixture was stirred for an additional 1 h. The mixture was treated with a saturated solution of sodium thiosulfate until the characteristic iodine colour has completely disappeared. THF was removed under reduced pressure and the remaining aqueous solution was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic extracts were washed with deionised water and dried over $MgSO_4$ and the solvent was removed *in vacuo* to allow the formation of a crude slightly yellow liquid. The crude product was purified by flash chromatography (eluting in gradient from 2% EtOAc in hexanes to 5% EtOAc in hexanes) to afford **237** (4.99 g, 15.29 mmol, 66%, combined yield for both diastereoisomers). TLC (hexanes:EtOAc, 90:10 *v*/*v*): R_f = 0.4 (*cis*-**237**) and R_f = 0.34 (*trans*-**237**).

trans-**237**:

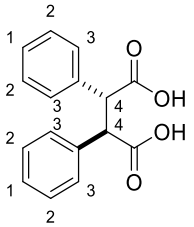
δ_H (400 MHz, $CDCl_3$): 7.14-7.01 (10 H, m, H-1, H-2 and H-3), 4.22 (2 H, s, H-4), 4.16 (4 H, q, *J* 7.1, H-5), 1.20 (6 H, t, *J* 7.1, H-6).

cis-**237**:

δ_H (400 MHz, $CDCl_3$): 7.51-7.27 (10 H, m, H-1, H-2 and H-3), 4.36 (2 H, s, H-4), 3.85 (4 H, q, *J* 7.1, H-5), 0.92 (6 H, t, *J* 7.1, H-6).

HRMS (*m/z* - ESI): Found: 327.1592 $(M+H)^+$ $C_{20}H_{23}O_4$ Requires: 327.1591.

2,3-Diphenylsuccinic acid (*trans*-238)



In a 500 mL round-bottomed flask containing a stirring bar, diester **237** (4.00 g, 12.26 mmol) was dissolved in a solution of KOH (6.88 g, 122.55 mmol) in EtOH:H_2O (200 mL, 50:50 *v*/*v*). The flask was fitted with a condenser and the solution was stirred under reflux for 16 h. The solution was allowed to cool to room temperature. EtOH was removed under reduced pressure and the remaining aqueous solution was washed several times with Et_2O. The organic layer was discarded and the aqueous layer was cooled to 0 °C. Acidification with conc. HCl (added dropwise to the aqueous layer until pH 1) resulted in the precipitation of *trans*-**238**. The solid was filtered off and washed with a little warm water, then transferred to a 250 mL round-bottomed flask followed by an addition of Et_2O (30 mL) to remove residual water. The solvent was removed *in vacuo* to afford *trans*-**238** (2.9 g, 10.73 mmol, 87%). M.p. 210-212 °C (Lit.,[169] 212- 214 °C).

Spectral data for this compound were consistent with those in the literature.[169]

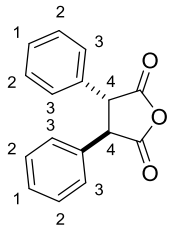
trans-**238**:

δ_H (400 MHz, $CDCl_3$): 7.16-7.10 (10 H, m, H-1, H-2 and H-3), 4.27 (2 H, s, H-4).

ν_{max} (neat)/cm^{-1}: 3031 (O-H), 1692 (C=O), 1536, 1420, 1290, 1251, 1178, 945, 731, 695.

HRMS (*m/z* - ESI): Found: 269.0814 $(M-H)^-$ $C_{16}H_{13}O_4$ Requires: 269.0814.

2,3-Diphenyl-succinic anhydride (*trans*-239)



A 50 mL oven dried two-neck round-bottomed flask containing a stirring bar was charged with *trans*-**238** (0.81 g, 6.80 mmol). The flask was then fitted with a condenser and a septum and flushed with argon. Freshly distilled acetyl chloride (10 mL) was added to the flask *via* syringe, the flask was flushed for an additional 2 min and then kept under an argon atmosphere. The reaction mixture was heated under reflux for 16 h, and then concentrated *in vacuo* to give an oil that solidified upon standing at room temperature. The crude product was purified by flash chromatography on a short plug of silica gel (eluting with 50 % EtOAc in hexanes) to afford *trans*-**239** (0.70 g, 2.78 mmol, 93%) as a pale-yellow solid. M.p. 114-116 °C (Lit.,[170] 115-117 °C); TLC (hexanes:EtOAc, 80:20 *v*/*v*): R_f = 0.46.

Spectral data for this compound were consistent with those in the literature.[170]

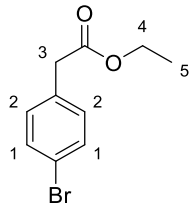
trans-**239**:

δ_H (400 MHz, $CDCl_3$): 7.3-7.07 (10 H, m, H-1, H-2 and H-3), 4.26 (2 H, s, H-4).

ν_{max} (neat)/cm^{-1}: 2906, 1862, 1772 (C=O), 1498, 1455, 1241, 1218, 1050, 937, 912, 777, 763, 741, 695, 641, 624, 610.

HRMS (*m/z* - ESI): Found: 251.0707 $(M-H)^-$ $C_{16}H_{11}O_3$ Requires: 251.0708.

Ethyl 2-(4-bromophenyl)acetate (309)



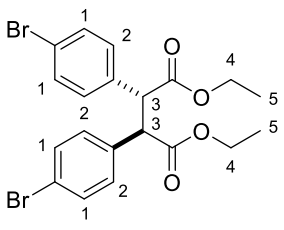
A 250 mL round-bottomed flask containing a stirring bar was charged with 4-Bromophenylacetic acid (**307**, 12.5 g, 58.13 mmol). EtOH (50 mL) followed by conc. H_2SO_4 (0.11 mL) were added, the flask was fitted with a condenser and the resulting mixture was stirred under refluxed overnight. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (150 mL), washed with a saturated $NaHCO_3$ solution until basic pH was reached. The mixture was extracted with CH_2Cl_2 (3 x 100 mL), the combined organic fractions were washed with deionised water, dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford **309** pure as a white solid (13.41 g, 55.16 mmol, 95%). M.p. 32-34 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.44.

Spectral data for this compound were consistent with those in the literature.[171]

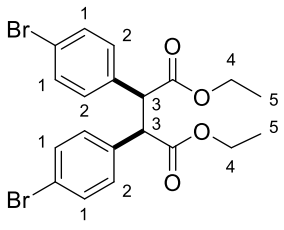
δ_H (400 MHz, $CDCl_3$): 7.43 (2 H, d, *J* 8.4, H-1), 7.15 (2 H, d, J 8.4, H-2), 4.14 (2 H, q, *J* 7.1, H-4), 3.55 (2 H, s, H-3), 1.24 (3 H, t, *J* 7.1, H-5).

HRMS (*m/z* - APCI): Found: 240.9867 $(M-H)^-$ $C_{10}H_{10}BrO_2$ Requires: 240.9869.

2,3-bis(4-Bromophenyl)succinic acid (311)



trans-**311**



cis-**311**

A 250 mL oven dried round-bottomed flask containing a stirring bar was charged with potassium *tert*-butoxide (*t*-BuOK, 2.91 g, 25.92 mmol). The flask was flushed with argon, then fitted with a septum and placed under an argon atmosphere. Dry THF (70

mL) was added *via* syringe and the resulting solution was cooled to 0 °C. To the resulting suspension, a solution of ethyl 2-(4-bromophenyl)acetate (**309**, 6.0 g, 24.68 mmol) in dry THF (30 mL) was slowly added and the resulting mixture stirred for 30 min. After 30 min, iodine (3.13 g, 12.34 mmol) was added portion wise directly as a solid. The flask was allowed to warm up to room temperature and the reaction mixture was stirred overnight. The mixture was treated with a saturated solution of sodium thiosulfate until the characteristic iodine colour has completely disappeared. THF was concentrated under reduced pressure and the remaining aqueous solution was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic extracts were washed with deionised water, dried over $MgSO_4$ and the solvent was removed *in vacuo* to allow the formation of a crude solid that was purified by recrystallisation from boiling ethanol. The recrystallised product was filtered from the mother liquor to afford **311** (3.4 g, 57%, combined yield for both diastereomers) in a 19:81 (*cis*:*trans*) ratio. M.p. 114-116 °C; TLC (hexanes:EtOAc, 90:10 *v*/*v*): R_f = 0.54 (*cis*-**311**) and R_f = 0.32 (*trans*-**311**).

trans-**311**:

δ_H (400 MHz, $CDCl_3$): 7.29 (4 H, d, *J* 8.4, H-1), 6.90 (4 H, d, *J* 8.4, H-2), 4.23-4.05 (4 H, m, H-4), 4.14 (2 H, s, H-3), 1.20 (6 H, t, *J* 7.1, H-5).

δ_C (100 MHz, $CDCl_3$): 172.3 (C=O), 134.55 (q), 131.7, 129.9, 121.6 (q), 61.4, 54.1, 13.96.

cis-**311**:

δ_H (400 MHz, $CDCl_3$): 7.47 (4 H, d, *J* 8.5, H-1), 7.35 (4 H, d, *J* 8.5, H-2), 4.26 (2 H, s, H-3), 3.94-3.81 (4 H, m, H-4), 0.97 (6 H, t, *J* 7.2, H-5).

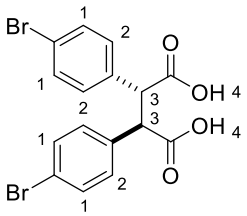
δ_C (100 MHz, $CDCl_3$): 170.8 (C=O), 135.1 (q), 131.8, 130.1, 122.1 (q), 61.1, 54.4, 13.77.

ν_{max} (neat)/cm^{-1}:* 2988, 1709, 1488, 1170, 1069, 1025, 1011, 835, 757.

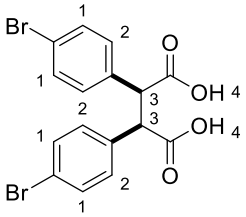
HRMS (*m/z* - APCI):* Found: 482.9797 $(M+H)^+$ $C_{20}H_{21}Br_2O_4$ Requires: 482.9801.

* Refers to mixture of *trans*-**311**:*cis*-**311** in the ratio 81:19.

2,3-bis(4-Bromophenyl)succinic acid (313)



trans-**313**



cis-**313**

In a 250 mL round-bottomed flask containing a stirring bar, **311** (3.4 g, 7.02 mmol, 19:81 (*cis*:*trans*) ratio) was dissolved in a solution of KOH (6.8 g, 121.20 mmol) in EtOH:H_2O (150 mL, 75:75 *v*/*v*). The flask was fitted with a condenser and the solution was stirred under reflux for 16 h. The solution was allowed to cool to room temperature. EtOH was concentrated under reduced pressure and the remaining aqueous solution was washed several times with Et_2O. The organic layer was discarded and the aqueous layer was cooled down to 0 °C. Acidification with conc. HCl (until pH 1) resulted in the precipitation of **313**. The solid was filtered and washed with a little warm water. The solvent was removed *in vacuo* to afford **313** (2.9 g, 97%, combined yield for both diastereomers) in a 13:87 (*cis*:*trans*) ratio. M.p. 264-266 °C.

trans-**313**:

δ_H (400 MHz, DMSO-d_6): 12.62 (2 H, bs, H-4), 7.36 (4 H, d, *J* 8.2, H-1), 7.13 (4 H, d, *J* 8.2, H-2), 4.20 (2 H, s, H-3).

δ_C (100 MHz, DMSO-d_6): 173.9 (C=O), 136.3 (q), 131.7, 131.1, 120.8 (q), 53.2.

cis-**313**:

δ_H (400 MHz, DMSO-d_6): 12.62 (2 H, bs, H-4), 7.57 (4 H, d, *J* 8.2, H-1), 7.41 (4 H, d, *J* 8.2, H-2), 4.20 (2 H, s, H-3).

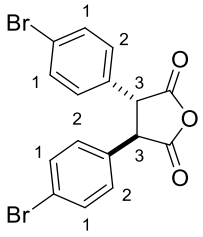
δ_C (100 MHz, DMSO-d_6): 172.4 (C=O), 137.0 (q), 131.9, 130.97, 121.4 (q), 54.1.

ν_{max} (neat)/cm^{-1}:* 2898, 2571, 1701, 1488, 1404, 1281, 1074, 1011, 921, 806.

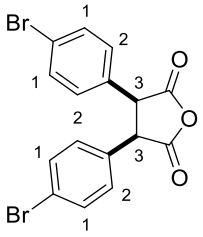
HRMS (*m/z* - ESI):* Found: 424.9026 $(M-H)^-$ $C_{16}H_{11}Br_2O_4$ Requires: 424.9029.

* Refers to mixture of *trans*-**313**:*cis*-**313** in the ratio 87:13.

3,4-bis(4-Bromophenyl)succinic anhydride (315)



trans-**315**



cis-**315**

A 50 mL oven dried two-neck round-bottomed flask containing a stirring bar was charged with **313** (1.0 g, 2.34 mmol, 13:87 (*cis*:*trans*) ratio). The flask was then fitted with a condenser and a septum and flushed with argon. Freshly distilled acetyl chloride (10 mL) was added to the flask *via* syringe, the flask was flushed for an additional 2 min and then kept under an argon atmosphere. The reaction mixture was heated under reflux for 16 h, and then concentrated *in vacuo* to give a crude solid. The crude product was purified by flash chromatography on a short plug of silica gel (eluting with 50 % EtOAc in hexanes) to afford **315** (592.0 mg, 62%, combined yield for both diastereomers) in a 36:64 (*cis*:*trans*) ratio. M.p. 180-182 °C; TLC (hexanes:EtOAc, 50:50 *v/v*): R_f = 0.88.

trans-**315**:

δ_H (400 MHz, $CDCl_3$): 7.54 (4 H, d, *J* 8.2, H-1), 7.08 (4 H, d, *J* 8.2, H-2), 4.31 (2 H, s, H-3).

δ_C (100 MHz, $CDCl_3$): 169.1 (C=O), 132.7, 131.9 (q), 129.4, 123.25 (q), 54.55.

cis-**315**:

δ_H (400 MHz, $CDCl_3$): 7.32 (4 H, d, *J* 8.2, H-1), 7.76 (4 H, d, *J* 8.2, H-2), 4.68 (2 H, s, H-3).

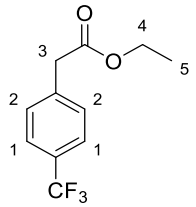
δ_C (100 MHz, $CDCl_3$): 169.7 (C=O), 132.1, 130.3, 130.0 (q), 122.80 (q), 52.2.

ν_{max} (neat)/cm^{-1}:* 1834, 1769, 1593, 1488, 1407, 1256, 1217, 1047, 1010, 935, 815, 761, 667.

HRMS (*m/z* - ESI):* Found: 406.8917 $(M-H)^-$ $C_{16}H_9Br_2O_3$ Requires: 406.8923.

* Refers to mixture of *trans*-**315**:*cis*-**315** in the ratio 64:34.

Ethyl 2-(4-(trifluoromethyl)phenyl)acetate (310)



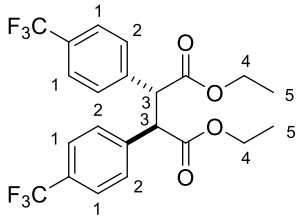
A 250 mL round-bottomed flask containing a stirring bar was charged with 4-trifluoromethylphenylacetic acid (**308**) (5.0 g, 24.49 mmol). EtOH (50 mL) followed by conc. H_2SO_4 (0.5 mL) were added, the flask was fitted with a condenser and the resulting mixture was stirred under reflux overnight. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (150 mL) and washed with a saturated $NaHCO_3$ solution until basic pH was reached. The mixture was extracted with CH_2Cl_2 (3 x 100 mL), and the combined organic fractions were washed with deionised water, and dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford ester **310** pure as a colourless oil that solidified upon standing at room temperature (5.4 g, 23.26 mmol, 95%). M.p. 34-36 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.51.

Spectral data for this compound were consistent with those in the literature.[172]

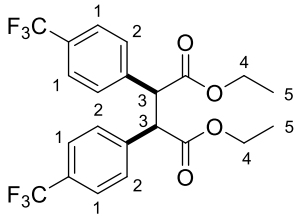
δ_H (400 MHz, $CDCl_3$): 7.58 (2 H, d, *J* 8.1, H-1), 7.40 (2 H, d, *J* 8.1, H-2), 4.16 (2 H, q, *J* 7.1, H-4), 3.67 (2 H, s, H-3), 1.26 (3 H, t, *J* 7.1, H-5).

HRMS (*m/z* - APCI): Found: 231.0646 $(M-H)^-$ $C_{11}H_{10}F_3O_2$ Requires: 231.0638.

Diethyl 2,3-bis(4-(trifluoromethyl)phenyl)succinate (312)



trans-**312**



cis-**312**

A 250 mL oven dried round-bottomed flask containing a stirring bar was charged with ethyl 2-(4-(trifluoromethyl)phenyl)acetate (**310**, 3.82 g, 16.46 mmol). The flask was

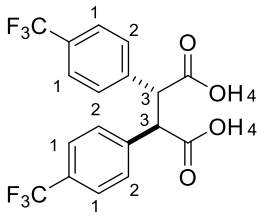
flushed with argon, then fitted with a septum and placed under an argon atmosphere. Dry THF (60 mL) was added *via* syringe and the resulting solution was cooled to 0 °C. Potassium *tert*-butoxide (*tert*-BuOK, 1.94 g, 17.28 mmol) was added portion wise directly as a solid. The solution turned red and was stired for 5 min. After 5 min, iodine (2.08 g, 8.23 mmol) was added portion wise directly as a solid, the solution was allowed to warm to room temperature and the reaction mixture was stirred overnight. The mixture was treated with a saturated solution of sodium thiosulfate until the characteristic iodine colour has completely disappeared. THF was removed under reduced pressure and the remaining aqueous solution was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic extracts were washed with deionised water, and dried over $MgSO_4$ and the solvent was removed *in vacuo* to allow the formation of a crude solid that was purified by recrystallisation from boiling ethanol. The recrystallised product was filtered off from the mother liquor to afford **312** (2.82 g, 74%, combined yield for both diastereomers) in a 1:99 (*cis*:*trans*) ratio. M.p. 134-136 °C; TLC (hexanes:EtOAc, 90:10 *v*/*v*): R_f = 0.5 (*trans*-**312**).

trans-**312**:

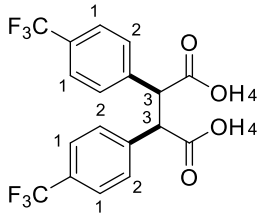
δ_H (400 MHz, $CDCl_3$):*	7.64-7.60 (8 H, m, H-1 and H-2), 4.42 (2 H, s, H-3), 3.95-3.80 (4 H, m, H-4), 0.92 (6 H, t, *J* 7.1, H-5).
δ_C (100 MHz, $CDCl_3$):*	170.4 (C=O), 139.9 (q) (q, $^5J_{C\text{-}F}$ 1.3 Hz), 130.4 (q) (q, $^2J_{C\text{-}F}$ 32.8 Hz), 128.9, 125.6 (q, $^3J_{C\text{-}F}$ 3.8 Hz), 123.9 (q) (q, $^1J_{C\text{-}F}$ 272.2 Hz), 61.3, 54.8, 13.6.
δ_F (376.5 MHz, $CDCl_3$):*	-62.76.
ν_{max} (neat)/cm^{-1}:*	2988, 1159, 1615, 1327, 1216, 1159, 1104, 1071, 1019, 832.
HRMS (*m/z* - ESI):*	Found: 461.1184 $(M\text{-}H)^-$ $C_{22}H_{19}F_6O_4$ Requires: 461.1193.

* Refers to mixture of *trans*-**312**:*cis*-**312** in the ratio 99:1.

2,3-bis(4-(Trifluoromethyl)phenyl)succinic acid (314)



trans-**314**



cis-**314**

In a 250 mL round-bottomed flask containing a stirring bar, **312** (1.5 g, 3.24 mmol, 1:99 (*cis*:*trans*) ratio) was dissolved in a solution of KOH (3.0 g, 53.47 mmol) in EtOH:H_2O (100 mL, 50:50 *v*/*v*). The flask was fitted with a condenser and the solution was stirred under reflux for 16 h. The solution was allowed to cool to room temperature. EtOH was removed under reduced pressure and the remaining aqueous solution was washed several times with Et_2O. The organic layer was discarded and the aqueous layer was cooled to 0 °C. Acidification with conc. HCl (added dropwise to the aqueous layer until pH 1) resulted in the precipitation of diacid **314**. The solid was filtered off and washed with a little warm water, then transferred to a 250 mL round-bottomed flask followed by an addition of Et_2O (30 mL) to remove residual water. The solvent was removed *in vacuo* to afford **314** (1.03 g, 78%, combined yield for both diastereomers) in a 13:87 (*cis*:*trans*) ratio. The mixture was further purified by recrystallisation from boiling water to afford analytically pure *trans*-**314**. M.p. 194-200 °C.

trans-**314**:

δ_H (400 MHz, DMSO-d_6): 12.79 (2 H, bs, H-4), 7.52 (4 H, d, *J* 8.2, H-1), 7.44 (4 H, d, *J* 8.2, H-2), 4.44 (2 H, s, H-3).

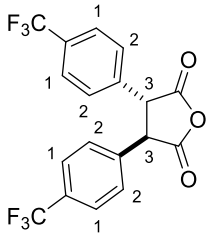
δ_C (100 MHz, DMSO-d_6): 173.6 (C=O), 141.5 (q), 129.80, 128.2 (q) (q, $^2J_{C\text{-}F}$ 31.9 Hz), 125.6 (q, $^3J_{C\text{-}F}$ 3.7 Hz), 124.5 (q) (q, $^1J_{C\text{-}F}$ 271.8 Hz), 53.5.

δ_F (376.5 MHz, DMSO-d_6): -61.1

ν_{max} (neat)/cm^{-1}: 2984, 1773, 1705, 1619, 1417, 1320, 1162, 1119, 1068, 1019, 925, 828.

HRMS (*m/z* - ESI): Found: 405.0567 $(M\text{-}H)^-$ $C_{18}H_{11}F_6O_4$ Requires: 405.0567.

2,3-bis(4-(Trifluoromethyl)phenyl)succinic anhydride (316)



trans-**316**

A 50 mL oven dried two-neck round-bottomed flask containing a stirring bar was charged with *trans*-**314** (220.0 mg, 0.54 mmol). The flask was then fitted with a condenser and a septum and flushed with argon. Freshly distilled acetyl chloride (10 mL) was added to the flask *via* syringe, the flask was flushed for an additional 2 min and then kept under an argon atmosphere. The reaction mixture was heated under reflux for 16 h, and then concentrated *in vacuo* to provide pure *trans*-**316** (124.0 mg, 59%). The product was used without further purification. M.p. 140-142 °C.

trans-**316**:

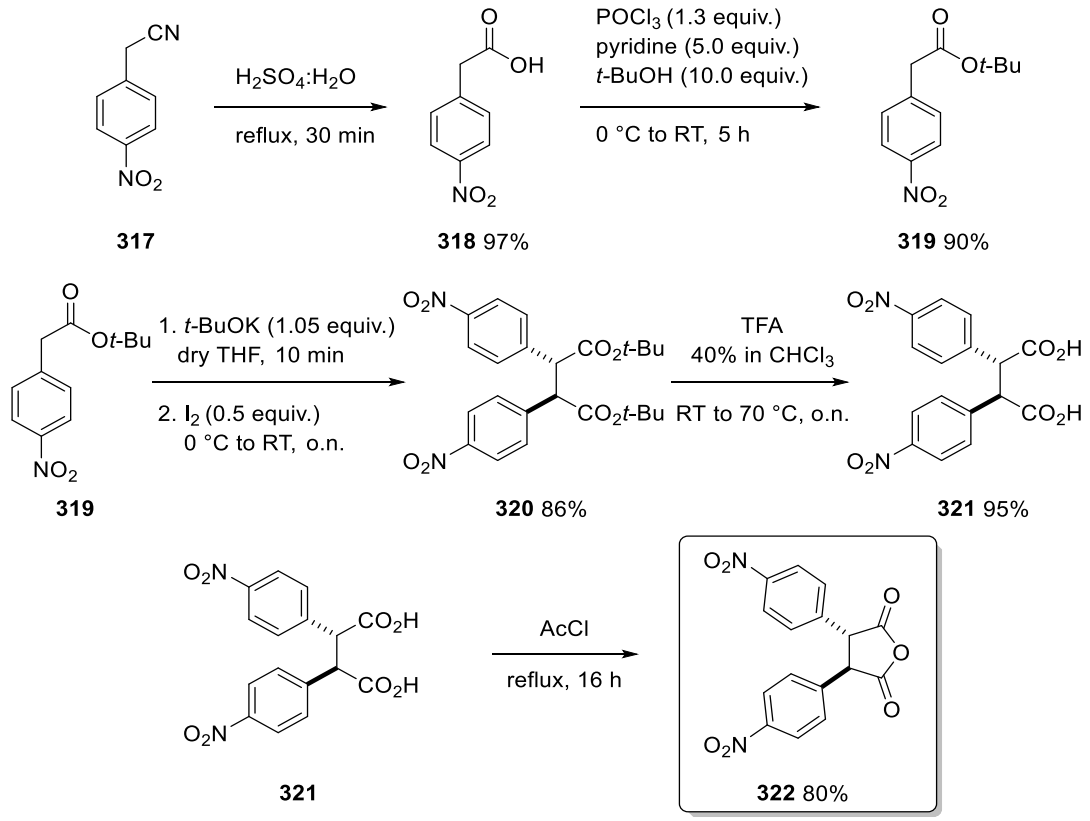
δ_H (400 MHz, $CDCl_3$): 7.69 (4 H, d, *J* 8.0, H-1), 7.36 (4 H, d, *J* 8.0, H-2), 4.49 (2 H, s, H-3).

δ_C (100 MHz, $CDCl_3$): 168.7 (C=O), 136.6 (q), 131.5 (q) (q, $^2J_{C\text{-}F}$ 33.0 Hz), 128.3, 126.6 (q, $^3J_{C\text{-}F}$ 3.7 Hz), 123.5 (q) (q, $^1J_{C\text{-}F}$ 272.5 Hz), 54.6.

δ_F (376.5 MHz, $CDCl_3$): -62.96.

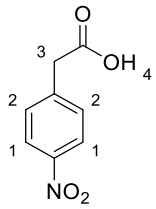
ν_{max} (neat)/cm^{-1}: 1846, 1774, 1622, 1422, 1322, 1259, 1224, 1165, 1109, 1044, 1020, 938, 832, 756, 659, 593.

HRMS (*m/z* - ESI): Found: 387.0467 $(M\text{-}H)^-$ $C_{18}H_9F_6O_3$ Requires: 387.0461.



Scheme 4.2 Synthetic route towards anhydride **322**.

2-(4-Nitrophenyl)acetic acid (318)



In a 250 mL round-bottomed flask containing a stirring bar, concentrated sulfuric acid (20 mL) was added to deionised water (20 mL) followed by 4-nitrophenylacetonitrile (**317**, 6.6 g, 40.70 mmol) added portion wise directly as a solid. The flask was fitted with a condenser and the resulting suspension was refluxed for 1 h, diluted with 20 mL of deionised water, and cooled to 0 °C when colourless crystalline solid separated. The solid was filtered off, washed with ice-cold water to remove traces of acid and dried to yield acid **318** as a light-yellow solid (7.18 g, 97%). M.p. 140-142 °C (lit.,[173] M.p. 153-155 °C).

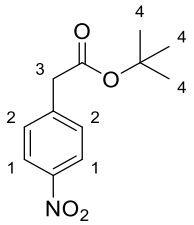
Spectral data for this compound were consistent with those in the literature.[173]

δ_H (400 MHz, DMSO-d_6): 10.06 (1 H, bs, H-4), 8.18 (2 H, d, *J* 8.7, H-1), 7.55 (2 H, d, *J* 8.7, H-2), 3.77 (2 H, s, H-3).

δ_C (100 MHz, DMSO-d_6): 172.2 (C=O), 146.8 (q), 143.5 (q), 131.2, 123.6, 40.6.

HRMS (*m/z* - ESI): Found: 180.0297 $(M-H)^-$ $C_8H_6NO_4$ Requires: 180.0302.

tert-Butyl 2-(4-nitrophenyl)acetate (319)



To a solution of acid **318** (5 g, 27.6 mmol) in $CHCl_3$ (50 mL), dry pyridine (11 mL, 138.0 mmol) and *t*-BuOH (25.9 mL, 276.0 mmol) were added followed by $POCl_3$ (3.3 mL, 36.0 mmol) dropwise over 2 min. After 5 h, the reaction mixture was poured into a solution of ice containing CH_2Cl_2 (20 mL) and of HCl solution (2.0 M, 10 mL). The aqueous solution was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic extracts were washed with brine, and deionised water, and dried over $MgSO_4$, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography, eluting in gradient from 100% hexanes to 10% EtOAc in hexanes to yield ester **319** as a yellow liquid (5.9 g, 90%). TLC (hexanes:EtOAc, 9:1 *v*/*v*): R_f = 0.38.

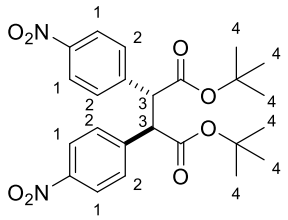
Spectral data for this compound were consistent with those in the literature.[174]

δ_H (400 MHz, $CDCl_3$): 8.18 (2 H, d, *J* 8.7, H-1), 7.44 (2 H, d, *J* 8.7, H-2), 3.63 (2 H, s, H-3), 1.44 (9 H, s, H-4).

δ_C (100 MHz, $CDCl_3$): 169.3 (C=O), 146.9 (q), 142.2 (q), 130.2, 123.4, 81.4 (q), 42.1, 27.8.

HRMS (*m/z* - ESI): Found: 236.0923 $(M-H)^-$ $C_{12}H_{14}NO_4$ Requires: 236.0928.

Di-*tert*-butyl-2,3-bis(4-nitrophenyl)succinate (*trans*-320)



trans-**320**

A 250 mL oven dried round-bottomed flask containing a stirring bar was charged with *tert*-butyl 2-(4-nitrophenyl)acetate (**319**, 3.0 g, 12.6 mmol). The flask was flushed with argon, then fitted with a septum and placed under an argon atmosphere. Dry THF (50 mL) was added *via* syringe and the resulting solution was cooled to 0 °C. Potassium *tert*-butoxide (*tert*-BuOK, 1.48 g, 13.3 mmol) was added portion wise directly as a solid. The mixture turned red and was stired for 5 min. After 5 min, iodine (1.59 g, 6.3 mmol) was added portion wise directly as a solid, the solution was allowed to warm up to room temperature and the reaction mixture was stirred overnight. The mixture was treated with a saturated solution of sodium thiosulfate until the characteristic iodine colour has completely disappeared. THF was removed under reduced pressure and the remaining aqueous solution was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic extracts were washed with deionised water, and dried over $MgSO_4$ and the solvent was removed *in vacuo* to allow the formation of a crude solid that was triturated with cold Et_2O. The solid was filtered from Et_2O to afford *trans*-**320** (2.58 g, 86%) as a single pure product diastereomer. M.p. 156-158 °C; TLC (hexanes:EtOAc, 90:10 *v/v*): R_f = 0.27 (*trans*-**320**).

trans-**320**:

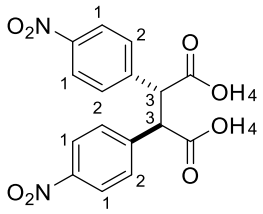
δ_H (400 MHz, $CDCl_3$): 8.03 (4 H, d, *J* 8.8, H-1), 7.21 (4 H, d, *J* 8.8, H-2), 4.22 (2 H, s, H-3), 1.40 (18 H, s, H-4).

δ_C (100 MHz, $CDCl_3$): 170.4 (C=O), 147.3 (q), 143.0 (q), 128.98, 123.9, 82.5 (q), 55.4, 27.7.

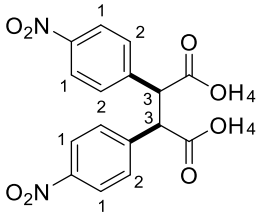
ν_{max} (neat)/cm^{-1}: 2980, 1721, 1517, 1346, 1147, 1109, 847, 785, 748, 696.

HRMS (*m/z* - ESI): Found: 471.1470 $(M-H)^-$ $C_{24}H_{27}N_2O_8$ Requires: 471.1767.

2,3-Bis(4-nitrophenyl)succinic acid (321)



trans-**321**



cis-**321**

A 250 mL round-bottomed flask containing a magnetic stirring bar was charged with diester **320** (1.39 g, 2.9 mmol). HPLC grade $CHCl_3$ (40 mL), followed by trifluoracetic acid (TFA, 26 mL) were then added *via* syringe. The flask was fitted with a condenser and the reaction mixture was heated at reflux temperature for 24 h and then cooled to room temperature. The volatiles were removed *in vacuo* to afford diacid **321** as a white solid (1.0 g, 95%) in a 19:81 (*cis*:*trans*) ratio. M.p. >200 °C (decomposition).

trans-**321**:

δ_H (400 MHz, DMSO-d_6):* 8.01 (4 H, d, *J* 8.6, H-1), 7.53 (4 H, d, *J* 8.6, H-2), 4.57 (2 H, s, H-3).

δ_C (100 MHz, DMSO-d_6): 177.9 (C=O), 152.3 (q), 151.8, 149.8 (q), 149.1, 58.0.

cis-**321**:

δ_H (400 MHz, DMSO-d_6):* 8.25 (4 H, d, *J* 8.6, H-1), 7.78 (4 H, d, *J* 8.6, H-2), 4.55 (2 H, s, H-3).

δ_C (100 MHz, DMSO-d_6): 176.4 (C=O), 135.1, 135.0 (q), 128.9 (q), 128.7, 58.96.

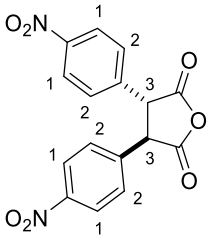
* The protic signal (H-4) is not visible in DMSO-d_6.

ν_{max} (neat)/cm^{-1}:** 2860, 1710, 1604, 1519, 1424, 1348, 1301, 1110, 903, 856, 838, 735, 706, 692.

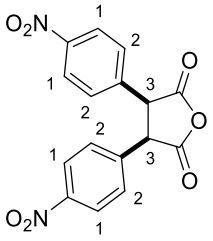
HRMS (*m/z* - ESI):** Found: 359.0519 $(M-H)^-$ $C_{16}H_{11}N_2O_8$ Requires: 359.0515.

** Refers to mixture of *trans*-**321**:*cis*-**321** in the ratio 81:19.

2,3-Bis(4-nitrophenyl)succinic anhydride (322)



trans-**322**



cis-**322**

A 25 mL oven dried two-neck round-bottomed flask containing a stirring bar was charged with diacid **321** (500.0 mg, 1.39 mmol, 19:81 *cis*:*trans* ratio). The flask was then fitted with a condenser and a septum and flushed with argon. Freshly distilled acetyl chloride (5 mL) was added to the flask *via* syringe, the flask was flushed for an additional 2 min and then kept under an argon atmosphere. The reaction mixture was heated under reflux for 16 h, and then concentrated *in vacuo*. The crude solid was triturated with dry Et_2O, filtered and dried under high vacuum to afford *trans*-anhydride **322** (381.1 mg, 80%) as a single diastereomer. M.p. 126-130 °C.

trans-**322**:

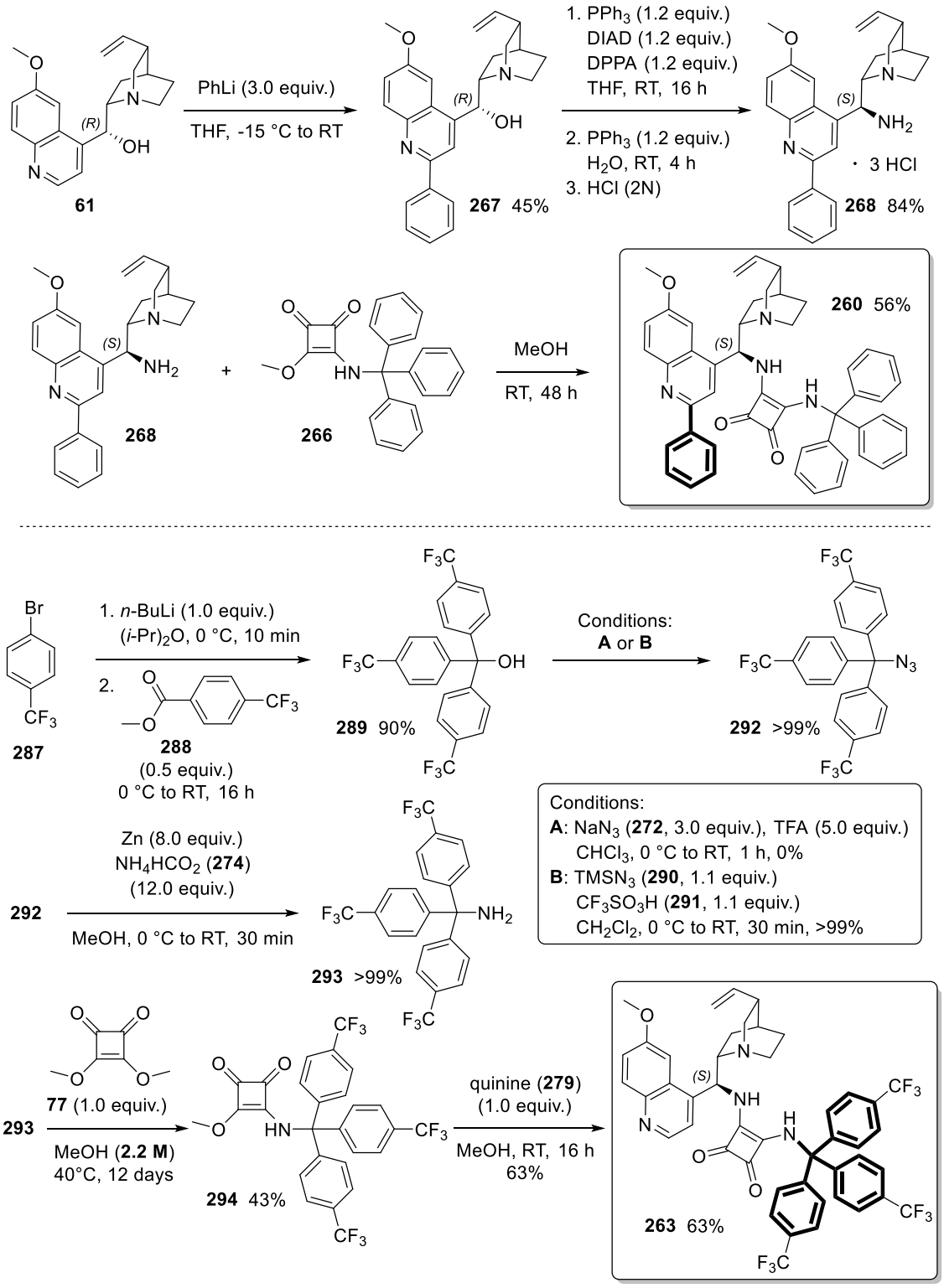
δ_H (400 MHz, $CDCl_3$): 8.27 (4 H, d, *J* 8.3, H-1), 7.45 (4 H, d, *J* 8.3, H-2), 4.61 (2 H, s, H-3).

δ_C (100 MHz, $CDCl_3$): 167.7 (C=O), 148.4 (q), 139.0 (q), 129.0, 124.8, 54.3.

ν_{max} (neat)/cm^{-1}: 1863, 1782, 1604, 1517, 1345, 1206, 1045, 932, 692, 690, 769, 841.

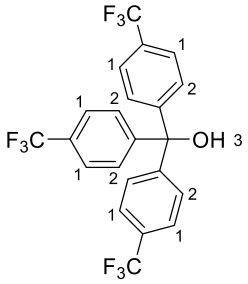
HRMS (*m/z* - ESI): Found: 341.0413 $(M-H)^-$ $C_{16}H_9N_2O_7$ Requires: 341.0410.

4.3.2 Synthesis of catalysts: procedures



Scheme 4.3 Synthesis of the catalyst precursors **260** and **263**.

Tris(4-(trifluoromethyl)phenyl)methanol (289)



A 100 mL oven dried three-neck round-bottomed flask containing a stirring bar was charged with methyl 4-bromobenzotrifluoride (**287**, 5.8 g, 25.72 mmol). Anhydrous diisopropyl ether (30 mL) was then added *via* syringe and the solution was cooled to -10 °C. A solution of *n*-butyl lithium (1.6 M in hexanes, 17.6 mL, 28.17 mmol) was added dropwise *via* syringe and the reaction was stired for 30 min. A solution of methyl 4-(trifluoromethyl)benzoate (**288**, 2.5 g, 12.25 mmol) in dry diisopropyl ether (5 mL) was added dropwise *via* syringe at -10 °C and the resulting solution was allowed to come back to room temperature and stirred for 16 h. The reaction mixture was then quenched with cold water, acidified with aqueous HCl (2.0 N), and extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a residue that was purified by flash column chromatography (hexanes:EtOAc, 95:5 *v/v*) furnishing alcohol **289** (5.34 g, 94%) as a light yellow solid. M.p. 88-90 °C (lit.,[175] M.p. 92-93 °C); TLC (hexanes:EtOAc, 95:5 *v/v*): R_f = 0.19.

Spectral data for this compound were consistent with those in the literature.[175]

δ_H (400 MHz, $CDCl_3$): 7.62 (6 H, d, *J* 8.3, H-1), 7.42 (6 H, d, *J* 8.3, H-2), 2.87 (1 H, bs, H-3).

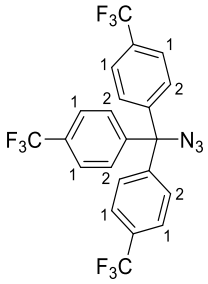
δ_C (100 MHz, $CDCl_3$): 149.1 (q), 130.3 (q) (q, $^2J_{C\text{-}F}$ 32.6 Hz), 128.1, 125.4 (q, $^3J_{C\text{-}F}$ 3.6 Hz), 123.8 (q) (q, $^1J_{C\text{-}F}$ 272.2 Hz), 81.3 (q).

δ_F (376.5 MHz, $CDCl_3$): -62.7.

ν_{max} (neat)/cm^{-1}: 3460, 2108, 1617, 1322, 1162, 1114, 1068, 1016, 832.

HRMS (*m/z* - ESI): Found: 463.0745 $(M\text{-}H)^-$ $C_{22}H_{12}OF_9$ Requires: 463.0744.

4,4',4''-(Azidomethanetriyl)tris((trifluoromethyl)benzene) (292)



A 250 mL oven dried three-neck round-bottomed flask containing a stirring bar was charged with alcohol **289** (5.08 g, 10.94 mmol). Anhydrous CH_2Cl_2 (110 mL – 0.1 M) was then added *via* syringe and the solution was cooled to -10 °C. Triflic acid (1.06 mL, 12.03 mmol) was added *via* syringe and the reaction was stired for 15 min (***Caution: triflic acid is a highly corrosive liquid and should be handled very carefully***). Trimethylsilyl azide (1.6 mL, 12.03 mmol) was added dropwise *via* syringe at -10 °C and the resulting solution was allowed to come back to room temperature and stirred for 30 min. After complete disappearance of the starting material (monitored by TLC, ≈ 30 min), the reaction mixture was poured in a large beaker containing crushed ice (≈ 200 g). The product was extracted with dichloromethane (4 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a residue that was purified by flash column chromatography eluting in gradient from 100% hexanes to 5% EtOAc in hexanes to isolate azide **292** (5.20 g, 97%) as a white solid. M.p. 70-72 °C; TLC (hexanes:EtOAc, 95:5 *v/v*): R_f = 0.89.

δ_H (400 MHz, $CDCl_3$): 7.66 (6 H, d, *J* 8.3, H-1), 7.43 (6 H, d, *J* 8.3, H-2).

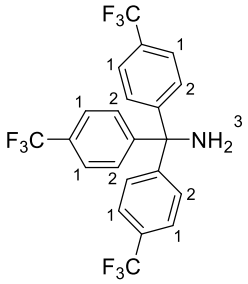
δ_C (100 MHz, $CDCl_3$): 145.4 (q), 130.6 (q) (q, $^2J_{C\text{-}F}$ 32.8 Hz), 128.6, 125.7 (q, $^3J_{C\text{-}F}$ 3.7 Hz), 123.7 (q) (q, $^1J_{C\text{-}F}$ 272.8 Hz), 75.8 (q).

δ_F (376.5 MHz, $CDCl_3$): -62.8.

ν_{max} (neat)/cm^{-1}: 2106, 1615, 1412, 1321, 1253, 1164, 1112, 1068, 829, 600.

HRMS (*m/z* - APCI): Found: 462.0898 $(M\text{-}N_2)^+$ $C_{22}H_{12}F_9N_3$ Requires: 462.0898.

Tris(4-(trifluoromethyl)phenyl)methanamine (293)



A 100 mL oven dried round-bottomed flask containing a stirring bar was charged with azide **292** (4.24 g, 8.92 mmol), activated zinc powder (2.33 g, 35.68 mmol) and ammonium formate (2.25 g, 35.68 mmol). Dry MeOH (35.7 mL - 0.25 M) was added *via* syringe and the reaction mixture was stired at room temperature (N_2 gaz was observable almost immediately), under argon until completion of the reaction (approx. 1 h, monitored by TLC). After the completion of the reaction, the reaction mixture was filtered through a Celite pad, and washed with CH_2Cl_2 and then the combined filtrates were evaporated under vacuum. The residue was taken into CH_2Cl_2, washed twice with a saturated brine solution and finally with deionised water. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a residue that was purified by flash column chromatography eluting in gradient from 100% hexanes to 30% EtOAc in hexanes to isolate **293** (3.57 g, 86%) as a white solid. M.p. 82-84 °C; TLC (hexanes:EtOAc, 70:30 *v/v*): R_f = 0.64.

δ_H (400 MHz, $CDCl_3$): 7.59 (6 H, d, *J* 8.3, H-1), 7.43 (6 H, d, *J* 8.3, H-2), 2.31 (2 H, bs, H-3).

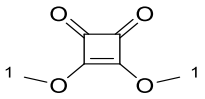
δ_C (100 MHz, $CDCl_3$): 150.9 (q), 129.6 (q) (q, $^2J_{C\text{-}F}$ 32.6 Hz), 128.2, 125.3 (q, $^3J_{C\text{-}F}$ 3.7 Hz), 123.9 (q) (q, $^1J_{C\text{-}F}$ 272.0 Hz), 66.1 (q).

δ_F (376.5 MHz, $CDCl_3$): -62.6.

ν_{max} (neat)/cm^{-1}: 1616, 1408, 1322, 1159, 1113, 1068, 1014, 844, 823, 601.

HRMS (*m/z* - ESI): Found: 462.0901 $(M\text{-}H)^-$ $C_{22}H_{13}NF_9$ Requires: 462.0904.

3,4-Dimethoxycyclobut-3-ene-1,2-dione (77)

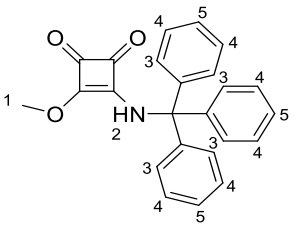


A 100 mL round-bottomed flask containing a magnetic stirring bar under argon atmosphere was charged with squaric acid (**76**, 4.00 g, 35.07 mmol). Dry MeOH (40 mL), followed by trimethyl orthoformate (**264**, 11.5 mL, 105.2 mmol) and TFA (536.8 μL, 7.01 mmol - 20 mol%), were then added *via* syringe. The flask was fitted with a condenser and the reaction mixture was heated at reflux temperature for 48 h and then cooled to room temperature. The volatiles were removed *in vacuo* and the residue obtained was purified by flash column chromatography (hexanes:EtOAc, 2:1 *v*/*v*) to give **77** as a white solid (4.1 g, 84%). M.p. 52-54 °C (lit.,[176] M.p. 52-54 °C); TLC (hexanes:EtOAc, 2:1 *v*/*v*): R_f = 0.21.

Spectral data for this compound were consistent with those in the literature.[176]

δ_H (400 MHz, $CDCl_3$): 4.36 (6 H, s, H-1).

3-Methoxy-4-(tritylamino)cyclobut-3-ene-1,2-dione (266)



A 25 mL sample vial containing a magnetic stirring bar was charged with 3,4-dimethoxycyclobut-3-ene-1,2-dione (**77**, 1.02 g, 7.2 mmol) and tritylamine (**265**, 1.87 g, 7.2 mmol). To the mixture of solids, dry MeOH (approx. 5 mL – the yield of the reaction is highly concentration dependant) was added *via* syringe. The resulting suspension was stirred at room temperature for 96 h. The reaction mixture was then cooled to 0 °C with an ice bath and the precipitate was filtered, washed with cold MeOH before being dried under high vacuum to yield **266** as a white solid (1.21 g, 46%). M.p. 196-198 °C. TLC (hexanes:EtOAc, 2:1 *v*/*v*): R_f = 0.3.

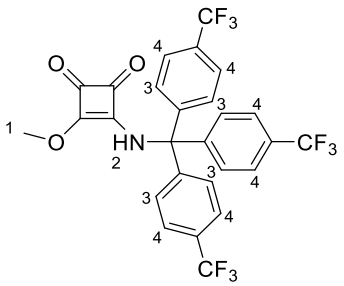
δ_H (400 MHz, $CDCl_3$): 7.35-7.31 (9 H, m, H-4 and H-5), 7.11-7.08 (6 H, m, H-3), 6.79 (1 H, bs, H-2), 3.79 (3 H, bs, H-1).

δ_C (100 MHz, $CDCl_3$): 189.2 (q), 184.5 (C=O), 178.1 (C=O), 172.4(q), ,143.7 (q), 128.7, 128.3, 127.9, 73.0 (q), 59.8.

ν_{max} (neat)/cm^{-1}: 3380, 3283, 3023, 2961, 1803, 1701, 1593, 1490, 1442, 1361, 1058, 1002, 899, 831, 752, 698.

HRMS (*m/z* - ESI): Found: 392.1267 $(M+Na)^+$ $C_{24}H_{19}NO_3Na$ Requires: 392.1263.

3-Methoxy-4-((tris(4-(trifluoromethyl)phenyl)methyl)amino)cyclobut-3-ene-1,2-dione (294)



A 25 mL sample vial containing a magnetic stirring bar was charged with 3,4-dimethoxycyclobut-3-ene-1,2-dione (**77**, 460 mg, 3.24 mmol) and amine **293** (1.50 g, 3.24 mmol). To the mixture of solids, dry MeOH (approx. 3-4 mL – the yield of the reaction is highly concentration dependant) was added *via* syringe. The resulting suspension was stirred at room temperature for 12 days. After 12 days, the solvent was removed under vacuum and the residue was purified by flash column chromatography eluting in gradient from 20% EtOAc in hexanes to 30% EtOAc in hexanes to isolate amido ester **294** (572.2 mg, 31%) as a white solid. M.p. 94-98 °C; TLC (hexanes:EtOAc, 70:30 *v/v*): R_f = 0.43.

δ_H (400 MHz, $CDCl_3$): 7.65 (6 H, d, *J* 8.3, H-4), 7.27 (6 H, d, *J* 8.3, H-3), 6.90 (1 H, bs, H-2), 3.85 (1 H, bs, H-1).

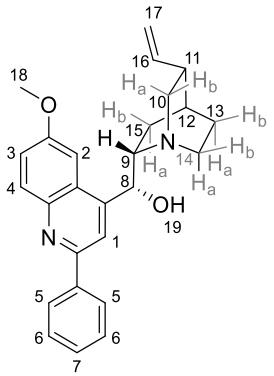
δ_C (100 MHz, $CDCl_3$): 184.4 (C=O), 178.4 (C=O), 146.2 (q), 130.9 (q) (q, $^2J_{C\text{-}F}$ 32.6 Hz), 129.0, 125.8 (q, $^3J_{C\text{-}F}$ 3.7 Hz), 123.6 (q) (q, $^1J_{C\text{-}F}$ 272.4 Hz), 72.1 (q), 60.1).

δ_F (376.5 MHz, $CDCl_3$): -62.8.

ν_{max} (neat)/cm^{-1}: 1804, 1708, 1591,1708, 1522, 1449, 1362, 1321, 1164, 1114, 1069, 1016, 834, 823, 612.

HRMS (*m/z* - ESI): Found: 572.0912 $(M\text{-}H)^-$ $C_{27}H_{15}NO_3F_9$ Requires: 572.0908.

(*R*)-(6-Methoxy-2-phenylquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanol - *C*-2 phenyl derived quinine (267)



An oven dried 500 mL round-bottomed flask containing a magnetic stirring bar was charged with quinine (**61**, 6.48 g, 20.0 mmol), fitted with a septum and placed under an argon atmosphere. Anhydrous THF (120 mL) was added *via* syringe and the resulting suspension was cooled to -15 °C. A solution of phenyllithium (1.8 M in THF, 33.3 mL, 59.9 mmol) was added *via* syringe to the vigorously stirred suspension and the reaction mixture was stired at -15 °C for 30 min then warmed to room temperature and stired for 3 h. Acetic acid (15 mL) was added dropwise *via* syringe to the reaction mixture at 0 °C, followed by water (50 mL) and EtOAc (50 mL). The reaction mixture was then warmed to room temperature and iodine was added in several portions to the stirred mixture until the appearance of a persistent deep brown colouration. A solution of sodium thiosulfate ($Na_2S_2O_3$, 3.00 g) in water (50 mL), followed by a concentrated solution of aqueous ammonia (35%, 30 mL) were added and the mixture was stired for 10 min. The organic phase was then washed with brine and the aqueous phase extracted

with dichloromethane (4 x 50 mL), the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude oily residue was purified by flash column chromatography (hexanes:EtOAc:MeOH:Et_3N, 8:1:0.5:0.5) to obtain the 2-phenyl derivative **267** (3.6 g, 45%) as a white solid. M.p. 144-146 °C (lit.,[83] M.p. 151 °C). TLC (hexanes:EtOAc:MeOH:Et_3N, 7:1:1.5:0.5): R_f = 0.35.

Spectral data for this compound were consistent with those in the literature.[83]

δ_H (400 MHz, $CDCl_3$):* 8.07 (2 H, d, *J* 7.7, H-5), 8.02 (1 H, d, *J* 8.6, H-4), 7.94 (1 H, s, H-1), 7.45 (2 H, app. t, H-6), 7.39 (1 H, app. t, H-7), 7.28 (1 H, app. d, *J* 8.6, H-3), 7.14 (1 H, app. d, H-2), 5.73-5.64 (2 H, m, H-8 and H-16), 4.96-4.89 (2 H, m, H-17), 3.84 (3 H, s, H-18), 3.66-3.55 (1 H, m, H-14a), 3.16-3.10 (2 H, m, H-9 and H-10b), 2.78-2.67 (2 H, m, H-10a and H-14b), 2.36-2.27 (1 H, m, H-11), 1.86-1.73 (3 H, m, H-12, H-13b and H-15b), 1.58-1.46 (2 H, m, H-13a and H-15a).

HRMS (*m/z* - ESI): Found: 401.2227 $(M+H)^+$ $C_{26}H_{29}N_2O_2$ Requires: 401.2229.

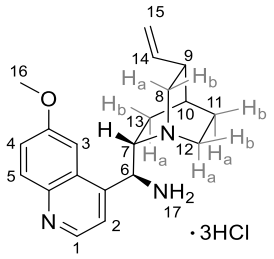
* The protic signal (H-19) is not visible in $CDCl_3$.

General procedure I: General procedure for the preparation of 9-*epi*-amine-derivatives (3.HCl salts) of quinine (279) and *C*-2 phenyl quinine (268).

A 500 mL oven-dried round bottom flask was charged with triphenylphosphine (1.2 equiv.) and the appropriate alkaloid (1 equiv.), placed under an argon atmosphere and fitted with a septum. Dry THF (150 mL) was added *via* syringe and the resulting solution was cooled to 0 °C. Diisopropyl azodicarboxylate (DIAD, 1.2 equiv.) was added dropwise *via* syringe followed by diphenylphosphoryl azide (DPPA, 1.2 equiv.) and the resulting mixture was allowed to warm up to room temperature. After stirring for 16 h, the solution was heated to 50 °C for 2 h. Triphenylphosphine (1.2 equiv.) was then added and heating was maintained for 2 h. After cooling the solution to ambient temperature, water (15 mL) was added and the mixture was stirred for 4 h. The reaction was then concentrated *in vacuo* and the residue dissolved in CH_2Cl_2 (60 mL) and HCl (2

N, 60 mL). The aqueous phase was separated and washed with CH_2Cl_2 (3 x 30 mL). The aqueous layer was then concentrated under reduced pressure and the crude product was recrystallised from EtOAc and MeOH or EtOH.

(*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanamine·3HCl (279)



Prepared according to general procedure I, using quinine (**61**, 8.16 g, 9.25 mmol). The crude product was recrystallised from EtOH to obtain **3HCl·279** (8.9 g, 82%) as a yellow solid. M.p. 216-218 °C, decomposition (lit.,[177] M.p. 220-222 °C).

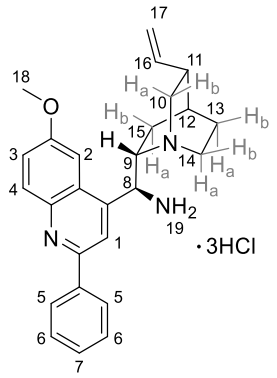
Spectral data for this compound were consistent with those in the literature.[177]

δ_H (400 MHz, D_2O):* 9.08 (1 H, d, *J* 5.8, H-1), 8.30 (1 H, d, *J* 9.4, H-5), 8.26 (1 H, d, *J* 5.8, H-2), 7.92 (1 H, dd, *J* 2.4, 9.4, H-4), 7.86 (1 H, bs, H-3), 5.88 (1 H, m, H-14), 5.8 (1 H, d, *J* 10.6, H-6), 5.28-5.20 (2 H, m, H-15), 4.50-4.41 (1 H, m, H-7), 4.12 (3 H, s, H-16), 4.08-3.97 (1 H, m, H-12a), 3.86 (1 H, dd, *J* 10.6, 13.4, H-8b), 3.65-3.48 (2 H, m, H-8a, H-12b), 2.98-2.89 (1 H, m, H-9), 2.14-2.03 (3 H, m, H-10, H-11a and H-11b), 1.91-1.85 (1 H, m, H-13b), 1.18-1.12 (1 H, m, H-13a).

HRMS (*m/z* - APCI): Found: 324.2068 $(M+H)^+$ $C_{20}H_{26}N_3O$ Requires: 324.2070.

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

(*S*)-(6-Methoxy-2-phenylquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanamine 3HCl (268)



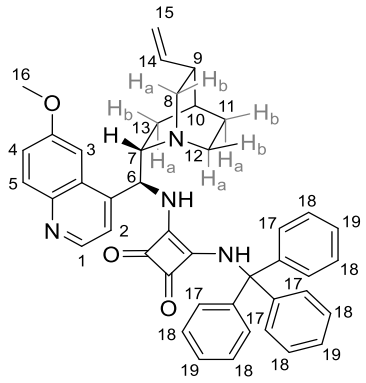
Prepared according to general procedure I, using *C*-2 phenyl quinine (**267**, 2.9 g, 7.25 mmol). The crude product was recrystallised from EtOAc and MeOH to obtain **3HCl·268** (3.1 g, 84%) as a yellow solid. M.p. 195-200 °C, decomposition.

Spectral data for this compound were consistent with those in the literature.[83]

δ_H (600 MHz, DMSO-d_6): 8.85 (1 H, s, H-1), 8.36 (2 H, d, *J* 7.3, H-5), 8.14 (1 H, d, *J* 9.1, H-4), 7.84 (1 H, d, *J* 2.4, H-3), 7.59-7.50 (4 H, m, H-4, H-6 and H-7), 5.90-5.84 (2 H, m, H-8 and H-16), 5.28 (1 H, d, *J* 17.3, H-17), 5.11 (1 H, d, *J* 10.5, H-17), 4.83-4.79 (1 H, m, H-9), 4.20-4.16 (1 H, m, H-14a), 4.01 (3 H, s, H-18), 3.76-3.72 (1 H, m, H-10b), 3.39-3.35 (2 H, m, H-10a and H-14b), 2.79-2.73 (1 H, m, H-11), 1.91-1.82 (3 H, m, H-12, H-13a and H-13b), 1.56-1.52 (1 H, m, H-15b), 0.94-0.90 (1 H, m, H-15a).

HRMS (*m/z* - ESI): Found: 400.2391 $(M+H)^+$ $C_{26}H_{30}N_3O$ Requires: 400.2389.

3-(((*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-4-(tritylamino)cyclobut-3-ene-1,2-dione (259)



A 25 mL oven dried round-bottomed flask containing a stirring bar was charged with **279** (1.10 g, 3.42 mmol) and **266** (1.26 g, 3.42 mmol). Dry MeOH (6.8 mL – 0.5 M) was added *via* syringe and the reaction mixture was placed under an argon atmosphere. The solution was stired at room temperature for 72 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (hexanes:EtOAc:MeOH:Et_3N, 70:20:5:5 *v/v*) furnishing **259** as a white solid (1.79 g, 79%). M.p. 160-162 °C. TLC (CH_2Cl_2:MeOH, 95:5 *v/v*): R_f = 0.19; $[\alpha]_D^{20}$ = +41.8 (*c* = 0.10, $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 8.62 (1 H, d, *J* 4.5, H-1), 8.01 (1 H, d, *J* 9.2, H-5), 7.57-7.49 (1 H, bs, H-3), 7.39 (1 H, dd, *J* 2.6, 9.2, H-4), 7.20-7.12 (9 H, m, H-18 and H-19), 7.03-6.98 (6 H, m, H-17), 6.56 (1 H, bs, H-2), 6.49 (1 H, bs, N-H), 5.88-5.75 (2 H, m, H-6 and H-14), 5.06-4.98 (2 H, m, H-15), 3.91 (3 H, s, H-16), 3.74 (1 H, bs, N-H), 3.31-3.17 (2 H, m, H-8b and H-12a), 2.65-2.57 (3 H, m, H-7, H-8a and H-12b), 2.28 (1 H, m, H-9), 1.67-1.61 (1 H, m, H-10), 1.56-1.42 (3 H, m, H-11a, H-11b and H-13b), 0.68-0.63 (1 H, m, H-13a).

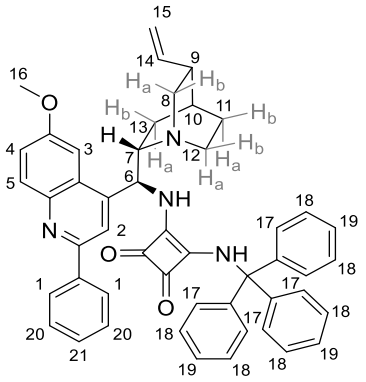
δ_C (100 MHz, $CDCl_3$)*: 183.5 (C=O), 183.0 (C=O), 167.0 (q), 158.5 (q), 146.8, 144.8 (q), 144.1 (q), 142.8 (q), 141.8, 131.4, 128.6, 128.5, 128.2, 122.7, 117.9, 114.4, 101.2, 72.1 (q), 60.1, 56.5, 56.1, 52.5, 40.8, 39.7, 27.7, 27.5, 26.5.

ν_{max} (neat)/cm^{-1}: 2934, 1792, 1668, 1624, 1509, 1576, 1433, 1228, 1031, 844, 699, 631.

HRMS (*m/z* - APCI): Found: 661.3176 $(M+H)^+$ $C_{43}H_{41}N_4O_3$ Requires: 661.3173.

* The resonance of one carbon could not be identified in the spectrum.

3-(((*S*)-(6-Methoxy-2-phenylquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-4-(tritylamino)cyclobut-3-ene-1,2-dione (260)



A 50x10 mm sample vial containing a magnetic stirring bar was charged with **268** (64.89 mg, 0.162 mmol) and **266** (60.0 mg, 0.162 mmol). To the resulting mixture, dry MeOH (0.8 mL) was added *via* syringe. The resulting suspension was stirred at room temperature for 96 h. The reaction mixture was then cooled to 0 °C with an ice bath and the precipitate was filtered, washed with cold MeOH before being dried under high vacuum to yield **260** as a white solid (67.0 mg, 56%). M.p. 152-156 °C. TLC (CH_2Cl_2:MeOH, 95:5 *v*/*v*): R_f = 0.49. $[\alpha]_D^{20}$ = -250 (*c* = 0.064, $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 8.09 (1 H, d, *J* 9.2, H-5), 8.01 (2 H, d, *J* 7.4, H-1), 7.59-7.53 (3 H, m, H-3 and H-20), 7.51-7.47 (1 H, app t, H-21), 7.40 (1 H, app. dd, *J* 2.6, 9.2, H-4), 7.14-7.05 (9 H, m, H-18 and H-19), 7.01-6.97 (6 H, m, H-17), 6.58 (1 H, bs, H-2), 5.96-5.79 (2 H, m, H-6 and H-14), 5.08-5.01 (2 H, m, H-15), 3.94 (3 H, s, H-16), 3.65 (1 H, bs, N-H), 3.38-3.20 (2 H, m, H-8b and H-12a), 2.73-2.58 (3 H, m, H-7, H-8a and H-12b), 2.30 (1 H, m, H-9), 1.60-1.46 (1 H, m, H-10 and H-13b),

1.15-0.99 (2 H, m, H-11a, H-11b), 0.76-0.68 (1 H, m, H-13a).

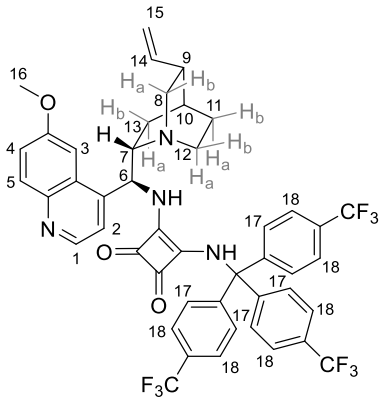
δ_C (100 MHz, $CDCl_3$)*: 183.5 (C=O), 183.0 (C=O), 166.8 (q), 158.6 (q), 154.2, 145.0 (q), 144.1 (q), 143.3 (q), 141.9 (q), 139.7 (q), 131.9, 129.2, 129.0, 128.6, 128.5, 128.3, 127.2, 123.0, 115.8, 114.4, 101.1, 72.2 (q), 63.1, 60.2, 56.6, 56.2, 52.6, 40.9, 39.8, 31.9, 29.7.

ν_{max} (neat)/cm^{-1}: 1789, 1666, 1624, 1575, 1508, 1441, 1351, 1233, 1033, 833, 767, 693, 633.

HRMS (*m/z* - ESI): Found: 737.3492 $(M+H)^+$ $C_{49}H_{45}N_4O_3$ Requires: 737.3492.

* The resonance of two carbon could not be identified in the spectrum.

3-(((*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-4-((tris(4-(trifluoromethyl)phenyl)methyl)amino)cyclobut-3-ene-1,2-dione (263)



A 5 mL oven dried round-bottomed flask containing a stirring bar was charged with **293** (290.0 mg, 0.896 mmol) and **294** (514.1 mg, 0.896 mmol). Dry MeOH (2 mL) was added *via* syringe and the reaction mixture was placed under an argon atmosphere. The solution was stired at room temperature for 48 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (CH_2Cl_2:MeOH, 95:5 *v/v*) furnishing **263** as a pale yellow solid (541 mg, 70%). M.p. 212-214 °C, decomposition.

TLC (hexanes:EtOAc:MeOH:Et_3N, 7:2:0.5:0.5): R_f = 0.25; $[\alpha]_D^{20}$ = -313 (*c* = 0.15, $CHCl_3$).

δ_H (600 MHz, $CDCl_3$): 8.56 (1 H, bs, N-H), 7.92 (1 H, d, *J* 9.0, H-5), 7.58-7.56 (7 H, m, H-1 and H-18), 7.52 (1 H, bs, H-3), 7.33 (1 H, d, *J* 9.0, H-4), 7.30-7.18 (6 H, m, H-2 and H-17), 6.43 (1 H, bs, N-H), 5.67-5.58 (2 H, m, H-6 and H-14), 4.96-4.92 (2 H, m, H-15), 3.92 (3 H, s, H-16), 3.03-2.98 (2 H, m, H-8b and H-12a), 2.45-2.42 (3 H, m, H-7, H-8a and H-12b), 2.27-2.19 (1 H, m, H-9), 1.64-1.58 (1 H, m, H-10), 1.57-1.49 (2 H, m, H-11a and H-13a), 1.29-1.23 (1 H, m, H-11b and H-13b).

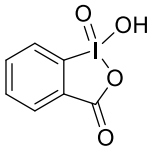
δ_C (150.9 MHz, $CDCl_3$): 167.7 (C=O), 167.3 (C=O), 158.4 (q), 147.2, 146.9 (q), 144.7 (q), 144.4 (q), 140.9, 131.6, 130.9 (q) (q, $^2J_{C\text{-}F}$ 32.4 Hz), 128.9, 127.9, 127.6, 125.9, 123.5 (q) (q, $^1J_{C\text{-}F}$ 272.5 Hz), 119.5, 117.8, 114.8, 101.5 (q), 71.3 (q), 61.7, 55.9, 55.8, 53.1, 40.7, 39.2, 27.7, 27.1, 26.9, 25.5.

δ_F (376.5 MHz, $CDCl_3$): -62.6.

ν_{max} (neat)/cm^{-1}: 2940, 1789, 1675, 1570, 1431, 1320, 1166, 1115, 1068, 1015, 919, 829.

HRMS (*m/z* - ESI): Found: 863.2664 $(M\text{-}H)^-$ $C_{46}H_{36}N_4O_3F_9$ Requires: 863.2644.

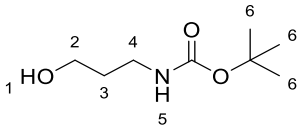
Acide 2-iodoxybenzoic (IBX, 335)



A 500 mL round-bottomed flask containing a magnetic stirring bar was charged with 2-iodobenzoic acid (**334**, 15.0 g, 60.48 mmol), oxone (46.0 g, 302.40 mmol) and 250 mL of deionised water. The flask was fitted with a condenser and the resulting suspension was heated at 105 °C for 5h and then cooled to room temperature. The suspension was

filtered, the solid washed several times with cold acetone, then allowed to dry on the bench overnight to afford IBX (**335**) as a white solid (13.62 g, 80%).

tert-Butyl (3-hydroxypropyl)carbamate (337)



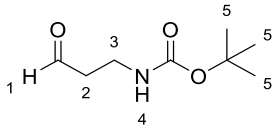
A 500 mL round-bottomed flask containing a magnetic stirring bar was charged with 3-amino-1-propanol (**336**, 10.1 g, 134.5 mmol) and anhydrous CH_2Cl_2 (70 mL). The resulting solution was placed under an argon atmosphere and cooled to 0 °C. A solution of di-*tert*-butyl dicarbonate (32.3 g, 148.0 mmol) in anhydrous CH_2Cl_2 (100 mL) was added dropwise over 30 min. The reaction mixture was then allowed to come back to room temperature and stirred overnight. The reaction was quenched with a saturated sodium hydrogen carbonate solution (100 mL). The organic layer was separated, washed with water and brine, and dried over MgSO4, the solvent was then removed *in vacuo* to allow the formation of a crude oil that was purified by flash column chromatography (hexanes:EtOAc, 1:1 *v/v*) to obtain carbamate **337** as a colorless oil (21.6 g, 92%). TLC (hexanes:EtOAc, 1:1 *v/v*): R_f = 0.31.

Spectral data for this compound were consistent with those in the literature.[178]

δ_H (400 MHz, $CDCl_3$): 5.11 (1 H, bs, H-5), 3.59-3.56 (3H, m, H-1 and H-2), 3.20-3.16 (2 H, m, H-4), 1.61-1.58 (2 H, m, H-3), 1.36 (9 H, s, H-6).

HRMS (*m/z* - ESI): Found: 198.1106 $(M+Na)^+$ $C_8H_{17}NNaO_3$ Requires: 198.1100.

tert-Butyl (3-oxopropyl)carbamate (338)



A 250 mL round-bottomed flask containing a magnetic stirring bar was charged with *tert*-butyl (3-hydroxypropyl)carbamate (**337**, 1.5 g, 8.56 mmol), IBX (**335**, 7.2 g, 25.7

mmol) and EtOAc (100 mL). The resulting suspension was stirred at 80 °C for 5 h, cooled to room temperature and filtered. The solvent was then removed *in vacuo* to afford a crude oil. The crude product was purified by flash column chromatography (hexanes:EtOAc, 2:1 *v/v*) to obtain pure aldehyde **338** as a colorless liquid (1.48 g, >99%). TLC (hexanes:EtOAc, 1:1 *v/v*): R_f = 0.5.

Spectral data for this compound were consistent with those in the literature.[179]

δ_H (400 MHz, $CDCl_3$): 9.80 (1 H, s, H-1), 4.88 (1 H, bs, H-4), 3.44-3.39 (2 H, m, H-3), 2.72-2.69 (2 H, t, *J* 5.8, H-2), 1.42 (9 H, s, H-5).

HRMS (*m/z* - ESI): Found: 196.0936 $(M+Na)^+$ $C_8H_{15}NNaO_3$ Requires: 196.0944.

4.3.3 Synthesis of racemic lactones

Racemic preparation for lactones 246d, 296-306, 324-329, 340.

An oven-dried 5 mL reaction vessel containing a magnetic stirring bar under argon atmosphere was charged with the relevant anhydride (0.1 mmol). Anhydrous MTBE or THF (1.0 mL, 0.1 M) was added *via* syringe followed by the relevant freshly distilled or recrystallized aldehyde (0.1 mmol). *N*,*N*-Diisopropylethylamine (3.6 μL, 20.0 μmol - 20 mol%) was added *via* syringe and the resulting mixture was stired for 20 to 96 h at room temperature. To the reaction mixture containing the corresponding crude carboxylic acids, anhydrous MeOH (202 μL, 5.0 mmol), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 60 μL, 0.12 mmol) were added *via* syringe and the reaction mixture was stired for 15 min at 0 °C. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash column chromatography, eluting in gradient from 100% hexanes to 30% EtOAc in hexanes to isolate all of the diastereomers combined. A sample of the purified diastereomer, isolated after column chromatography, was then re-purified by preparative TLC chromatography to produce racemic material for HPLC traces analysis.

4.3.4 Catalyst evaluation (general procedures)

Catalyst evaluation and reaction optimisation in the cycloaddition reaction between 2,3-diphenyl-succinic anhydride (239) and 4-nitrobenzaldehyde (244).

An oven-dried 5 mL reaction vessel containing a magnetic stirring bar under argon atmosphere was charged with 2,3-diphenyl-succinic anhydride (*trans*-**239**, 25.2 mg, 0.1 mmol), 4-nitrobenzaldehyde (**244**, 15.1 mg, 0.1 mmol) and the relevant catalyst (0.005 mmol - 5 mol%). Dry MTBE (1.0 mL, 0.1 M) was added *via* syringe and the reaction mixture was brought to the temperature indicated in Table 1 and Table 2. The resulting mixture was stired for the time indicated in Table 1 and Table 2. The yield and diastereomeric ratio of the products were determined by ^{1}H NMR spectroscopic analysis using *p*-iodoanisole (11.7 mg, 50.0 μmol) as an internal standard. To the reaction mixture containing the corresponding crude carboxylic acids, anhydrous MeOH (202 μL, 5.0 mmol), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 60 μL, 0.12 mmol) were added *via* syringe and the reaction was stired for 15 min at 0 °C. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash column chromatography, eluting in gradient from 100% hexanes to 15% EtOAc in hexanes to isolate both diastereomers combined.

The enantiomeric excess of the products was determined by CSP-HPLC using the conditions indicated.

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/*i*-PrOH: 90/10, 1.0 mL. min^{-1}, RT, UV detection at 254 nm, retention times: **246d** 61.3 min (major enantiomer) and 74.1 min (minor enantiomer).

General procedure II: Enantioselective preparation of lactones 246d, 296-306.

A 10 mL oven dried two-neck round-bottomed flask containing a stirring bar was charged with 2,3-diphenyl-succinic anhydride (*trans*-**239**, 100.9 mg, 0.4 mmol) and catalyst **259** (13.2 mg, 0.02 mmol - 5 mol%). The air was evacuated from the reaction vessel by placing the reaction flask under vacuum and backfilling several times with argon before being placed under an argon atmosphere (balloon). A mixture of

MTBE:THF (4.0 mL, 0.1 M, 9:1 *v*:*v*) was added *via* syringe followed by the relevant freshly distilled or recrystallised aldehyde (0.4 mmol). The resulting mixture was stired for 10 days at room temperature. To the reaction mixture containing the corresponding crude carboxylic acids, anhydrous MeOH (809 μL, 20.0 mmol), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 240 μL, 0.48 mmol) were added *via* syringe and the reaction was stired for 15 min at 0 °C. The major diastereomer produced in the reaction was then purified using a flash chromatographic purification system (Biotage SP4) using a high performance prepacked silica cartridge (Biotage SNAP 10 g), eluting the mixture in gradient of EtOAc from 100% hexanes and slightly modifying the following general method.

Flow rate: 10 $mL.min^{-1}$; Unit: CV = column volume.

Gradient: 100% hexanes for 3 CV; 100% hexanes to 20% EtOAc in hexanes over 40 CV.

The enantiomeric excess of the products was determined by CSP-HPLC using the conditions indicated for each case.

General procedure III: Enantioselective preparation of lactones 324-329, 340.

A 25 mL oven dried carousel tube containing a stirring bar was charged with the relevant anhydride (**315-316**, **322**, 0.4 mmol) and catalyst **259** (26.4 mg, 0.04 mmol - 10 mol%). The air was evacuated from the reaction vessel by flushing with a flow of argon before being placed under an argon atmosphere (balloon). A mixture of MTBE:THF (4.0 mL, 0.1 M, 9:1 *v*:*v*) was added *via* syringe and the flask was cooled to -15 °C. The relevant freshly distilled or recrystallized aldehyde (0.4 mmol) was added *via* syringe or directly as a solid. The resulting mixture was stired for the time indicated for each case and the temperature was maintained to -15 °C To the reaction mixture containing the corresponding crude carboxylic acids, anhydrous MeOH (809 μL, 20.0 mmol), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 240 μL, 0.48 mmol) were added *via* syringe and the reaction was stired for 15 min at -15 °C. The major diastereomer produced in the reaction was then purified using a flash chromatographic purification system (Biotage SP4) using a high performance prepacked silica cartridge

(Biotage SNAP 10 g), eluting the mixture in gradient of EtOAc from 100% hexanes and slightly modifying the following general method.

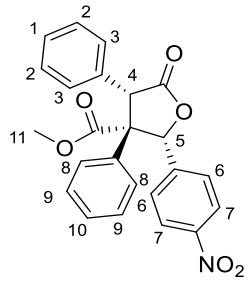
Flow rate: 10 mL.min^{-1}; Unit: CV = column volume.

Gradient: 100% hexanes for 3 CV; 100% hexanes to 20% EtOAc in hexanes over 40 CV.

The enantiomeric excess of the products was determined by CSP-HPLC using the conditions indicated for each case.

4.3.5 Experimental procedures and data for lactones 246d, 296-306, 324-329, 340.

Methyl (2*R*,3*S*,4*S*)-2-(4-nitrophenyl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (246d)



Prepared according to general procedure II, using recrystallized 4-nitrobenzaldehyde (**244**, 60.5 mg, 0.4 mmol). The reaction mixture was stired for 10 days to give a diastereomeric mixture of carboxylic acids in a 1.5:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**246d**) was isolated and purified by flash column chromatography to give a pale yellow solid (81.2 mg, 53%). M.p. 62-64 °C; TLC (hexanes:EtOAc, 8:2 *v/v*): R_f = 0.26; $[\alpha]_D^{20}$ = +50 (*c* = 0.44, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CEL1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Methanol:*i*-PrOH (1:1, *v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 254 nm, retention times: 4.78 min (minor enantiomer) and 5.23 min (major enantiomer). **90% *ee***.

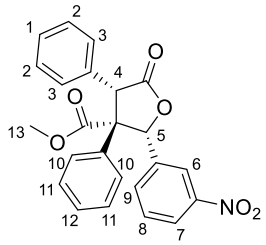
δ_H (400 MHz, $CDCl_3$): 8.14 (2 H, d, *J* 8.8, H-7), 7.48 (2 H, d, *J* 8.8, H-6), 7.46-7.41 (3 H, m, H-9 and H-10), 7.37-7.33 (2 H, m, H-8), 7.27-7.22 (3 H, m, H-1 and H-2), 7.11-7.09 (2 H, m, H-3), 6.15 (1 H, s, H-5), 4.54 (1 H, s, H-4), 3.26 (3 H, s, H-11).

δ_C (100 MHz, $CDCl_3$): 172.1 (C=O), 168.7 (C=O), 148.1 (q), 141.4 (q), 134.4 (q), 130.5 (q), 130.3, 128.8, 128.7, 128.5, 128.4, 128.2, 127.6, 123.3, 82.0, 67.2 (q), 57.2, 52.0.

ν_{max} (neat)/cm^{-1}: 3032, 2952, 1786 (C=O), 1726 (C=O), 1603, 1520 (N-O), 1497, 1448, 1434, 1347 (N-O), 1293, 1242, 1205, 1151, 1109, 1042, 1013, 863, 746, 697.

HRMS (*m/z* - APCI): Found: 418.1293 $(M+H)^+$ $C_{24}H_{20}NO_6$ Requires: 418.1285.

Methyl (2*R*,3*S*,4*S*)-2-(3-nitrophenyl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (296)



Prepared according to general procedure II, using recrystallized 3-nitrobenzaldehyde (60.5 mg, 0.4 mmol). The reaction was stired for 10 days to give a diastereomeric mixture of carboxylic acids in a 2.3:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**296**) was isolated and purified by flash column chromatography to give a pale yellow solid (84.3 mg, 53%). M.p. 174-176 °C; TLC (hexanes:EtOAc, 8:2 *v/v*): R_f = 0.23; $[\alpha]_D^{20}$ = -26 (*c* = 0.90, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CEL1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Methanol:*i*-PrOH (1:1, *v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 254 nm, retention times: 3.41 min (minor enantiomer) and 3.83 min (major enantiomer). **85% *ee***.

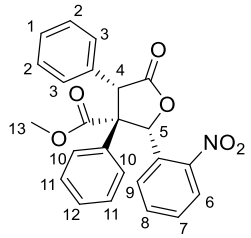
δ_H (400 MHz, $CDCl_3$): 8.22 (1 H, s, H-6), 8.20 (1 H, d, *J* 8.2, H-7), 7.62 (1 H, d, *J* 7.8, H-9), 7.51 (1 H, app. t, *J* 8.0, H-8), 7.46-7.44 (3 H, m, H-11 and H-12), 7.36-7.34 (2 H, m, H-10), 7.29-7.26 (3 H, m, H-1 and H-2), 7.19-7.16 (2 H, m, H-3), 6.0 (1 H, s, H-5), 4.62 (1 H, s, H-4), 3.33 (3 H, s, H-13).

δ_C (100 MHz, $CDCl_3$): 172.2 (C=O), 168.7 (C=O), 148.0 (q), 136.3 (q), 134.2 (q), 132.8, 130.6 (q), 130.1, 129.2, 128.8, 128.7, 128.5, 128.33, 128.27, 123.9, 121.9, 82.3, 67.0 (q), 56.4, 52.0.

ν_{max} (neat)/cm^{-1}: 3070, 1799 (C=O), 1721 (C=O), 1586, 1532 (N-O), 1493, 1445, 1433, 1352 (N-O), 1241, 1211, 1138, 1039, 957, 857.

HRMS (*m/z* - ESI): Found: 456.0848 $(M+K)^+$ $C_{24}H_{19}KNO_6$ Requires: 456.0843.

Methyl (2*R*,3*S*,4*S*)-2-(2-nitrophenyl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (297)



Prepared according to general procedure II, using recrystallized 2-nitrobenzaldehyde (60.5 mg, 0.4 mmol). The reaction was stired for 10 days to give a diastereomeric mixture of carboxylic acids in a 1:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**297**) was isolated and purified by flash column chromatography to give a pale yellow solid (54.0 mg, 34%). M.p. 54-56 °C; TLC (hexanes:EtOAc, 8:2 *v/v*): R_f = 0.19.

HPLC analysis. ACQUITY UPC^2 Trefoil CEL1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Methanol:*i*-PrOH (1:1, *v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 254 nm, retention times: 4.50 min (minor enantiomer) and 4.87 min (major enantiomer). **97% *ee***.

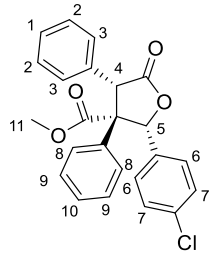
δ_H (400 MHz, $CDCl_3$): 7.88 (1 H, d, *J* 8.0, H-6), 7.82 (1 H, d, *J* 8.0, H-9), 7.65 (1 H, app. t, *J* 7.8, H-7), 7.65 (1 H, app. t, *J* 7.8, H-8), 7.38-7.32 (3 H, m, H-11 and H-12), 7.27-7.22 (5 H, m, H-1, H-2 and H-10), 7.18-7.15 (2 H, m, H-3), 6.89 (1 H, s, H-5), 4.73 (1 H, s, H-4), 3.31 (3 H, s, H-13).

δ_C (100 MHz, $CDCl_3$): 172.2 (C=O), 169.0 (C=O), 149.0 (q), 133.6 (q), 132.6, 130.9 (q), 130.0, 129.7, 129.1, 128.8, 128.7, 128.20 (q), 128.17, 128.08, 128.05, 125.0, 78.6, 67.2 (q), 55.8, 52.0.

ν_{max} (neat)/cm^{-1}: 3327, 2944, 1793 (C=O), 1719 (C=O), 1660, 1602, 1526 (N-O), 1433, 1351 (N-O), 1277, 1203, 1157, 1106, 1021, 966, 830, 743, 697.

HRMS (*m/z* - ESI): Found: 416.1129 $(M-H)^-$ $C_{24}H_{18}NO_6$ Requires: 416.1139.

Methyl (2*R*,3*S*,4*S*)-2-(4-chlorophenyl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (298)



Prepared according to general procedure II, using recrystallized 4-chlorobenzaldehyde (56.2 mg, 0.4 mmol). The reaction was stired for 10 days to give a diastereomeric mixture of carboxylic acids in a 2.3:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**298**) was isolated and purified by flash column chromatography to give a white solid (84.2 mg, 52%). M.p. 52-54 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.1; $[\alpha]_D^{20}$ = +319 (*c* = 0.27, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CEL2, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:CH_3CN (1:1, *v*:*v*) gradient as shown in Table 4.1, column temperature: 30 °C, UV detection at 254 nm, retention times: 3.11 min (major enantiomer) and 3.27 min (minor enantiomer). **95% *ee***.

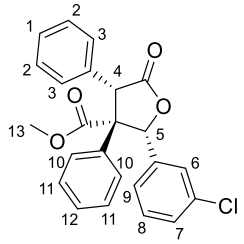
δ_H (400 MHz, $CDCl_3$): 7.42-7.40 (3 H, m, H-9 and H-10), 7.34-7.31 (4 H, m, H-7 and H-8), 7.29-7.25 (5 H, m, H-1, H-2 and H-6), 7.17-7.14 (2 H, m, H-3), 6.0 (1 H, s, H-5), 4.49 (1 H, s, H-4), 3.32 (3 H, s, H-11).

δ_C (100 MHz, $CDCl_3$): 172.6 (C=O), 169.0 (C=O), 134.9 (q), 134.7 (q), 132.6 (q), 130.8 (q), 130.3, 128.64, 128.57, 128.51, 128.47, 128.22, 128.22, 128.1, 82.5, 66.9 (q), 56.9, 52.0.

ν_{max} (neat)/cm^{-1}: 3046, 2951, 1785 (C=O), 1725 (C=O), 1599, 1493, 1448, 1433, 1240, 1202, 1153, 1091, 1013, 805, 761, 697.

HRMS (*m/z* - ESI): Found: 405.0893 $(M-H)^-$ $C_{24}H_{18}ClO_4$ Requires: 405.0899.

Methyl (2*R*,3*S*,4*S*)-2-(3-chlorophenyl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (299)



Prepared according to general procedure II, using freshly distilled 3-chlorobenzaldehyde (45.3 μL, 0.4 mmol). The reaction was stired for 10 days to give a diastereomeric mixture of carboxylic acids in a 3.5:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**299**) was isolated and purified by flash column chromatography to give a white solid (114.2 mg, 70%). M.p. 126-128 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.1; $[\alpha]_D^{20}$ = +227 (*c* = 0.1, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CEL1, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Methanol:*i*-PrOH (1:1, *v*:*v*) gradient as shown in Table 4.1, column temperature: 30 °C, UV detection at 230 nm, retention times: 3.00 min (minor enantiomer) and 3.06 min (major enantiomer). **97% *ee***.

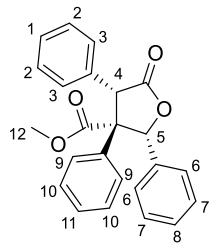
δ_H (400 MHz, $CDCl_3$): 7.42-7.40 (3 H, m, H-11 and H-12), 7.38-7.37 (1 H, m, H-7), 7.33-7.21 (7 H, m, H-1, H-2, H-6, H8 and H-10), 7.17-7.14 (3 H, m, H-3 and H-9), 6.03 (1 H, s, H-5), 4.48 (1 H, s, H-4), 3.34 (3 H, s, H-13).

δ_C (100 MHz, $CDCl_3$): 172.5 (C=O), 168.9 (C=O), 136.1 (q), 134.6 (q), 134.3 (q), 130.7 (q), 130.4, 129.4, 129.1, 128.6, 128.54, 128.47, 128.17, 128.15, 126.7, 124.9, 82.2, 66.9 (q), 56.9, 51.9.

ν_{max} (neat)/cm^{-1}: 2948, 1785, 1725, 1599, 1571, 1202, 1156, 1033, 999, 757, 696.

HRMS (*m/z* - ESI): Found: 429.0854 $(M+Na)^+$ $C_{24}H_{19}ClNaO_4$ Requires: 429.0864.

Methyl (2*R*,3*S*,4*S*)-5-oxo-2,3,4-triphenyltetrahydrofuran-3-carboxylate (300)



Prepared according to general procedure II, using freshly distilled benzaldehyde (40.8 μL, 0.4 mmol). The reaction was stired for 10 days to give a diastereomeric mixture of carboxylic acids in a 3.5:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**300**) was isolated and purified by flash column chromatography to give a white solid (90.4 mg, 61%). M.p. 158-160 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.15; $[\alpha]_D^{20}$ = +291 (*c* = 0.1, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CEL1, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Methanol:*i*-PrOH (1:1, *v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 212 nm, retention times: 3.70 min (minor enantiomer) and 3.79 min (major enantiomer). **99% *ee***.

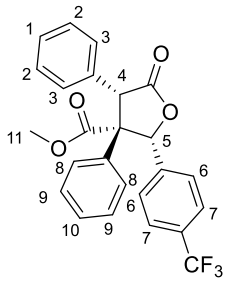
δ_H (400 MHz, $CDCl_3$): 7.34-7.08 (15 H, m, H-6, H-7, H-8, H-9, H-10 and H-11), 6.03 (1 H, s, H-5), 4.39 (1 H, H-4), 3.23 (3 H, s, H-12).

δ_C (100 MHz, $CDCl_3$): 172.8 (C=O), 169.1 (C=O), 135.0 (q), 134.0 (q), 130.9 (q), 130.4, 128.9, 128.7, 128.34, 128.32, 128.1, 128.2, 128.0, 126.5, 82.9, 66.8 (q), 57.1, 51.8.

ν_{max} (neat)/cm^{-1}: 3030, 1787 (C=O), 1714 (C=O), 1495, 1454, 1433, 1360, 1323, 1245, 1166, 1154, 1024, 1010, 965, 767, 756, 746, 692,671, 649, 592.

HRMS (*m/z* - ESI): Found: 371.1299 $(M-H)^-$ $C_{24}H_{19}O_4$ Requires: 371.1288.

Methyl (2*R*,3*S*,4*S*)-5-oxo-3,4-diphenyl-2-(4-(trifluoromethyl)phenyl) tetrahydrofuran-3-carboxylate (301)



Prepared according to general procedure II, using freshly distilled 4-CF_3-benzaldehyde (69.7 μL, 0.4 mmol). The reaction was stired for 10 days to give a diastereomeric mixture of carboxylic acids in a 1.3:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**301**) was isolated and purified by flash column chromatography to give a white solid (81.3 mg, 46%). M.p. 52-54 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.1; $[\alpha]_D^{20}$ = +310 (*c* = 0.43, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CEL1, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Methanol:*i*-PrOH (1:1, *v*:*v*) gradient as shown in Table 4.1, column temperature: 30 °C, UV detection at 212 nm, retention times: 2.91 min (minor enantiomer) and 3.06 min (major enantiomer). **94% *ee***.

δ_H (400 MHz, $CDCl_3$): 7.57 (2 H, app. d, *J* 8.2, H-7), 7.46-7.42 (5 H, m, H-6, H-9 and H-10), 7.37-7.32 (2 H, m, H-8), 7.29-7.24 (3 H, m, H-1 and H-2), 7.16-7.13 (2 H, m, H-3), 6.15 (1 H, s, H-5), 4.52 (1 H, s, H-4), 3.27 (3 H, s, H-11).

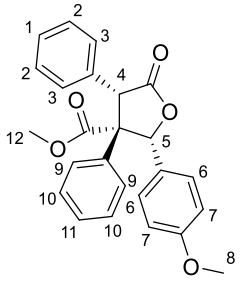
δ_C (100 MHz, $CDCl_3$): 172.5 (C=O), 168.9 (C=O), 138.2 (q), 134.6 (q), 131.0 (q) (q, $^2J_{C\text{-}F}$ 32.7 Hz), 130.7 (q), 130.4, 128.61, 128.59, 128.55, 128.25, 128.17, 126.98, 125.08 (q, $^3J_{C\text{-}F}$ 3.8 Hz), 123.81 (q) (q, $^1J_{C\text{-}F}$ 272.1 Hz), 82.2, 67.1 (q), 57.2, 51.9.

δ_F (376.5 MHz, $CDCl_3$): -62.7.

ν_{max} (neat)/cm^{-1}: 1786, 1725, 1324, 1167, 1123, 1113, 1068, 1015, 856, 758.

HRMS (*m/z* - ESI): Found: 463.1133 $(M+Na)^+$ $C_{25}H_{19}F_3NaO_4$ Requires: 463.1127.

Methyl (2*R*,3*S*,4*S*)-2-(4-methoxyphenyl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (302)



Prepared according to general procedure II, using freshly distilled 4-Methoxybenzaldehyde (48.7 μL, 0.4 mmol). The reaction was stired for 10 days to give a diastereomeric mixture of carboxylic acids in a 2.1:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**302**) was isolated and purified by flash column chromatography to give a white solid (47.0 mg, 29%). M.p. 48-50 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.14; $[\alpha]_D^{20}$ = +85 (*c* = 0.7, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil AMY1, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:CH_3CN:*i*-PrOH (1:1:1, *v*:*v*:*v*) gradient as shown in Table

4.1, column temperature: 30 °C, UV detection at 254 nm, retention times: 3.25 min (major enantiomer) and 3.34 min (minor enantiomer). **93% *ee***.

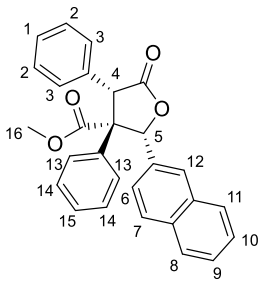
δ_H (400 MHz, $CDCl_3$): 7.42-7.40 (3 H, m, H-10 and H-11), 7.34-7.26 (7 H, m, H-1, H-2, H-6 and H-9), 7.23-7.21 (2 H, m, H-3), 6.88-6.86 (2 H, app. d, *J* 8.9, H-7), 5.99 (1 H, s, H-5), 4.52 (1 H, s, H-4), 3.82 (3 H, s, H-8), 3.39 (3 H, s, H-12).

δ_C (100 MHz, $CDCl_3$): 173.0 (C=O), 169.4 (C=O), 160.1 (q), 135.1 (q), 131.2 (q), 130.3, 128.8, 128.34, 128.30, 128.18, 128.16, 128.0, 125.7 (q), 113.6, 83.4, 66.7 (q), 56.5, 55.3, 51.97.

ν_{max} (neat)/cm^{-1}: 3031, 2952, 2926, 1784, 1741, 1724, 1612, 1514, 1451, 1299, 1250, 1204, 1154, 1025, 1009, 835, 810, 754, 697.

HRMS (*m/z* - APCI): Found: 403.1534 $(M+H)^+$ $C_{25}H_{23}O_5$ Requires: 403.1540.

Methyl (2*R*,3*S*,4*S*)-2-(naphthalen5-2-yl)-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (303)



Prepared according to general procedure II, using recrystallized 2-naphthaldehyde (62.5 mg, 0.4 mmol). The reaction was stired for 10 days to give a diastereomeric mixture of carboxylic acids in a 2.8:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**303**) was isolated and purified by flash column chromatography to give a white solid (94.7 mg, 56%). M.p. 50-52 °C; TLC (hexanes:EtOAc, 4:1 *v/v*): R_f = 0.32; $[\alpha]_D^{20}$ = +297 (*c* = 0.59, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil AMY1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:CH_3CN:*i*-PrOH (1:1:1, *v*:*v*:*v*) gradient as shown in Table

4.2, column temperature: 30 °C, UV detection at 254 nm, retention times: 5.11 min (minor enantiomer) and 5.26 min (major enantiomer). **96% *ee***.

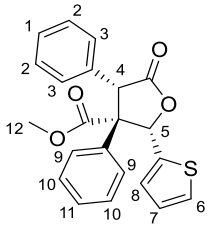
δ_H (600 MHz, $CDCl_3$): 7.86 (1 H, bs, H-12), 7.82-7.78 (2 H, m, H-8 and H-11), 7.77 (1 H, app. d, H-7), 7.51-7.47 (2 H, m, H-8 and H-9), 7.44-7.40 (3 H, m, H-14 and H-15), 7.39-7.35 (3 H, m, H-6 and H-13), 7.30-7.27 (3 H, m, H-1, H-2 and H-3), 6.22 (1 H, s, H-5), 4.55 (1 H, s, H-4), 3.24 (3 H, s, H-16).

δ_C (150.9 MHz, $CDCl_3$): 172.9 (C=O), 169.2 (C=O), 135.0 (q), 133.3 (q), 132.7 (q), 131.4 (q), 131.0 (q), 130.4, 128.8, 128.42, 128.38, 128.20, 128.1, 128.0, 127.9, 127.6, 126.6, 126.5, 126.2, 124.0, 83.3, 67.0 (q), 56.9, 51.9.

ν_{max} (neat)/cm^{-1}: 3058, 2950, 1783, 1724, 1497, 1448, 1237, 1203, 1151, 1031, 956, 811, 745, 696, 647.

HRMS (*m/z* - APCI): Found: 423.1590 $(M+H)^+$ $C_{28}H_{23}O_4$ Requires: 423.1590.

Methyl (2*S*,3*S*,4*S*)-5-oxo-3,4-diphenyl-2-(thiophen-2-yl)tetrahydrofuran-3-carboxylate (304)



Prepared according to general procedure II, using freshly distilled 2-thiophenecarboxaldehyde (37.4 μL, 0.4 mmol). The reaction was stired for 10 days to give a diastereomeric mixture of carboxylic acids in a 10:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**304**) was isolated and purified by flash column chromatography to give a white solid (49.3 mg, 37%). M.p. 165-167 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.17; $[\alpha]_D^{20}$ = +296 (*c* = 0.18, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil AMY1, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol/*i*-PrOH (1:1, *v*:*v*) gradient as shown in Table 4.1, column

temperature: 30 °C, UV detection at 254 nm, retention times: 3.40 min (minor enantiomer) and 3.57 min (major enantiomer). **87% *ee***.

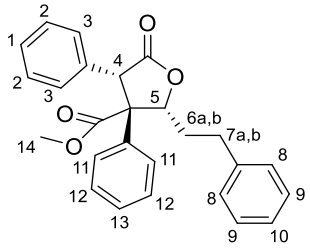
δ_H (400 MHz, $CDCl_3$): 7.39-7.34 (4 H, m, H-6, H-10 and H-11), 7.32-7.23 (7 H, m, H-1, H-2, H-3 and H-9), 7.04-7.02 (1 H, H-8), 7.03-6.97 (1 H, m, H-7), 6.11 (1 H, s, H-5), 4.52 (1 H, s, H-4), 3.50 (3 H, s, H-12).

δ_C (100 MHz, $CDCl_3$): 172.5 (C=O), 169.4 (C=O), 135.5 (q), 134.6 (q), 131.2 (q), 130.1, 128.5, 128.4, 128.32, 128.27, 128.20, 128.0, 127.0, 126.5, 80.9, 66.2 (q), 55.8, 52.3.

ν_{max} (neat)/cm^{-1}: 2951, 1783 (C=O), 1714 (C=O), 1496, 1435, 1338, 1256, 1154, 1079, 1013, 957, 816, 752, 698.

HRMS (*m/z* - ESI): Found: 377.0842 $(M-H)^-$ $C_{22}H_{17}O_4S$ Requires: 377.0853.

Methyl (2*R*,3*S*,4*S*)-5-oxo-2-phenethyl-3,4-diphenyltetrahydrofuran-3-carboxylate (305)



Prepared according to general procedure II, using freshly distilled hydrocinnamaldehyde (52.7 μL, 0.4 mmol). The reaction was stired for 10 days to give a diastereomeric mixture of carboxylic acids in a 13:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**305**) was isolated and purified by flash column chromatography to give a white solid (124.5 mg, 78%). M.p. 172-174 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.15; $[\alpha]_D^{20}$ = +307 (*c* = 1.0, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil AMY1, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:*i*-PrOH (1:1, *v*:*v*) gradient as shown in Table 4.2, column

temperature: 30 °C, UV detection at 254 nm, retention times: 3.78 min (minor enantiomer) and 4.22 min (major enantiomer). > **99% *ee***.

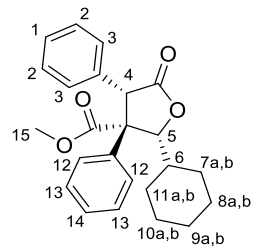
δ_H (400 MHz, $CDCl_3$): 7.37-7.23 (11 H, m, H-1, H-2, H-8, H-9, H-10, H-12 and H-13), 7.19-7.15 (2 H, m, H-3), 8.86-6.84 (2 H, m, H-11), 4.90 (1 H, dd, *J* 1.8, 10.5, H-5), 4.10 (1 H, s, H-4), 3.64 (3 H, s, H-14), 3.11 (1 H, ddd, *J* 4.4, 8.3, 13.4, H-7a), 2.87 (1 H, ddd, *J* 8.3, 8.4, 13.8, H-7b), 2.18 (1 H, dddd, *J* 1.8, 8.3, 8.4, 14.5, H-6a), 2.07 (1 H, m, H-6b).

δ_C (100 MHz, $CDCl_3$): 173.4 (C=O), 170.4 (C=O), 140.2 (q), 135.3 (q), 131.2 (q), 131.1, 128.8, 128.7, 128.3, 128.25, 128.20, 128.19, 127.8, 126.5, 80.7, 64.0 (q), 57.4, 52.2, 32.6, 31.7.

ν_{max} (neat)/cm^{-1}: 3029, 2950, 1778, 1725, 1497, 1454, 1438, 1255, 1203, 1151, 1046, 959, 696, 651.

HRMS (*m/z* - APCI): Found: 401.1744 $(M+H)^+$ $C_{26}H_{25}O_4$ Requires: 401.1747.

Methyl (2*R*,3*S*,4*S*)-2-cyclohexyl-5-oxo-3,4-diphenyltetrahydrofuran-3-carboxylate (306)



Prepared according to general procedure II, using freshly distilled cyclohexanecarboxaldehyde (48.5 μL, 0.4 mmol). The reaction was stired for 10 days to give a diastereomeric mixture of carboxylic acids in a 1.2:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**306**) was isolated and purified by flash column chromatography to give a white solid (66.0 mg, 44%). M.p. 139-141 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.19; $[\alpha]_D^{20}$ = +178 (*c* = 0.23, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil AMY1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:CH_3CN:*i*-PrOH (1:1:1, *v*:*v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 212 nm, retention times: 4.42 min (minor enantiomer) and 4.60 min (major enantiomer). **99% *ee***.

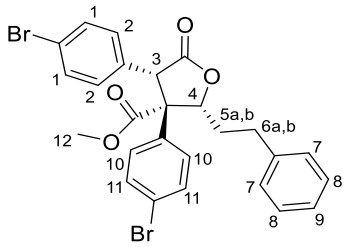
δ_H (400 MHz, $CDCl_3$): 7.27-7.26 (3 H, m, H-1 and H-2), 7.19-7.12 (5 H, m, H-3, H-13 and H-14), 6.86-6-84 (2 H, app. d, H-12), 4.94-4.91 (1 H, d, *J* 9.5, H-5), 3.90 (1 H, s, H-4), 3.66 (3 H, s, H-15), 2.16-2.14 (1 H, m, H-6), 1.73-1.71 (1 H, m, H-7a), 1.57-1.54 (1 H, m, H-11a), 1.53-1.45 (3H, m, H-7b, H-9a and H-11b), 1.23-0.93 (4 H, m, H-8a, H-8b, H-10a and H-10b), 0.82-0.74 (1 H, m, H-9b).

δ_C (100 MHz, $CDCl_3$): 172.8 (C=O), 169.9 (C=O), 136.4 (q), 131.3, 130.6 (q), 128.2, 128.1, 128.0, 127.9, 127.8, 85.2 (q), 64.8 (q), 60.1, 52.0, 41.0, 30.6, 29.8, 26.1, 25.8, 25.6.

ν_{max} (neat)/cm^{-1}: 2924, 2854, 1767, 1734, 1498, 1439, 1312, 1200, 1178, 1010, 924, 757, 695, 641.

HRMS (*m/z* - APCI): Found: 379.1896 $(M+H)^+$ $C_{24}H_{27}O_4$ Requires: 379.1903.

Methyl (2*R*,3*S*,4*S*)-3,4-bis(4-bromophenyl)-5-oxo-2-phenethyltetrahydrofuran-3-carboxylate (324)



Prepared according to general procedure III, using **315** (164.0 mg, 0.4 mmol) and freshly distilled hydrocinnamaldehyde (**323**, 52.3 µL, 0.4 mmol). The reaction was stired for 8 days to give a diastereomeric mixture of carboxylic acids in a 34:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**324**) was isolated and

purified by flash column chromatography to give a white solid (205.7 mg, 92%). M.p. 60-62 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.23; $[\alpha]_D^{20}$ = -126 (*c* = 0.31, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil AMY1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:*i*-PrOH (1:1, *v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 230 nm, retention times: 5.94 min (major enantiomer) and 6.60 min (minor enantiomer). **98% *ee***.

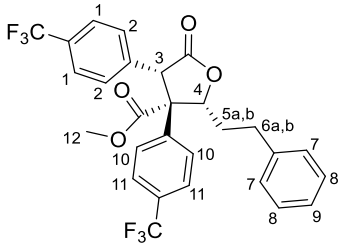
δ_H (400 MHz, $CDCl_3$): 7.34-7.32 (2 H, d, *J* 8.4, H-11), 7.28-7.26 (2 H, d, *J* 8.6, H-1), 7.28-7.13 (5 H, m, H-7, H-8 and H-9), 6.93-6.90 (2 H, d, *J* 8.4, H-10), 6.53-6.51 (2 H, d, *J* 8.6, H-2), 4.78-4.76 (1 H, app. d, H-4), 3.81 (1 H, s, H-3), 3.56 (3 H, s, H-12), 3.00-2.94 (1 H, m, H-6a), 2.78-2.70 (1 H, m, H-6b), 2.02-1.84 (2 H, m, H-5a and H-5b).

δ_C (100 MHz, $CDCl_3$): 172.4 (C=O), 169.8 (C=O), 139.9 (q), 134.0 (q), 132.9, 131.5, 131.4, 129.8 (q), 129.3, 128.79, 128.76, 126.6, 122.8 (q), 122.6 (q), 79.96, 63.5 (q), 57.0, 52.4, 32.3, 31.7.

ν_{max} (neat)/cm^{-1}: 3028, 2951, 1781, 1730, 1491, 1208, 1160, 1076, 1009, 972, 810, 797, 749, 726, 700.

HRMS (*m/z* - ESI): Found: 554.9813 $(M-H)^-$ $C_{26}H_{21}Br_2O_4$ Requires: 554.9812.

Methyl (2*R*,3*S*,4*S*)-5-oxo-2-phenethyl-3,4-bis(4-(trifluoromethyl)phenyl) tetrahydrofuran-3-carboxylate (325)



Prepared according to general procedure III, using **316** (155.3 mg, 0.4 mmol) and freshly distilled hydrocinnamaldehyde (**323**, 52.3 µL, 0.4 mmol). The reaction was stired for 5 days to give a diastereomeric mixture of carboxylic acids in a 11:1

(*major*:*others*) ratio. After esterification, the major diastereomer (**325**) was isolated as a mixture and purified by flash column chromatography to afford a white solid (176.2 mg, 82%). M.p. 78-80 °C; TLC (hexanes:EtOAc, 4:1 *v/v*): R_f = 0.47; $[\alpha]_D^{20}$ = +52 (*c* = 1.2, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CEL1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Methanol:*i*-PrOH (1:1, *v*:*v*) gradient as shown in Table 4.3, column temperature: 30 °C, UV detection at 230 nm, retention times: 5.13 min (minor enantiomer) and 6.06 min (major enantiomer). **98% *ee***.

δ_H (400 MHz, $CDCl_3$): 7.38-7.36 (2 H, d, *J* 8.2, H-11), 7.34-7.24 (9 H, m, H-1, H-7, H-8, H-9 and H-10), 6.88-6.86 (2 H, d, *J* 8.2, H-10), 6.79-6.77 (2 H, d, *J* 8.2, H-2), 5.12 (1 H, dd, *J* 2.3, 11.6, H-4), 5.04 (1 H, s, H-3), 2.44 (3 H, s, H-12), 3.12-3.05 (1 H, m, H-6a), 2.91-2.84 (1 H, m, H-6b), 2.20-2.09 (1 H, m, H-5a), 1.95-1.87 (1 H, m, H-5b).

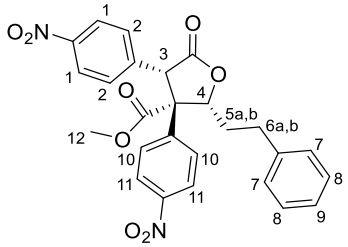
δ_C (100 MHz, $CDCl_3$): 173.3 (C=O), 170.9 (C=O), 140.0 (q), 139.8, 135.8, 131.7, 130.9, 128.8, 128.7, 128.67, 128.52, 128.1, 127.6, 126.6, 125.4, 124.7, 80.7, 64.5 (q), 50.08, 52.7, 33.2, 31.6.

δ_F (376.5 MHz, $CDCl_3$): Minor: -62.86, -62.89; Major: -62.92, -62.98.

ν_{max} (neat)/cm^{-1}: 2921, 1782, 1735, 1620, 1420, 1323, 1237, 1164, 1112, 1067, 1018, 850, 786, 749, 700.

HRMS (*m/z* - ESI): Found: 535.1340 $(M-H)^-$ $C_{28}H_{21}F_6O_4$ Requires: 535.1349.

Methyl (2*R*,3*S*,4*S*)-3,4-bis(4-nitrophenyl)-5-oxo-2-phenethyltetrahydrofuran-3-carboxylate (326)



Prepared according to general procedure III, using **322** (136.9 mg, 0.4 mmol) and freshly distilled hydrocinnamaldehyde (**323**, 52.3 μL, 0.4 mmol). The reaction was stired for 3 days to give a diastereomeric mixture of carboxylic acids in a 5:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**326**) was isolated as a mixture and purified by flash column chromatography to afford a white solid (156.5 mg, 79%). M.p. 60-62 °C; TLC (hexanes:EtOAc, 70:30 *v/v*): R_f = 0.47; $[\alpha]_D^{20}$ = -29.5 (*c* = 0.45, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil AMY1, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:CH_3CN:*i*-PrOH (1:1:1, *v*:*v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 254 nm, retention times: 3.98 min (minor enantiomer) and 4.07 min (major enantiomer). >**99% *ee***.

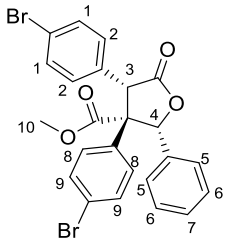
δ_H (400 MHz, $CDCl_3$): 8.01-7.99 (2 H, d, *J* 8.9, H-11), 7.96-7.94 (2 H, d, *J* 8.8, H-1), 7.39-7.22 (5 H, m, H-7, H-8 and H-9), 7.01-6.99 (2 H, d, *J* 8.9, H-10), 6.87-6.86 (2 H, d, *J* 8.8, H-2), 5.14-5.10 (1 H, dd, *J* 2.4, 8.96, H-4), 5.13 (1 H, s, H-3), 3.78 (3 H, s, H-12), 3.12-3.06 (1 H, m, H-6a), 2.92-2.84 (1 H, m, H-6b), 2.21-2.12 (1 H, m, H-5a), 1.96-1.88 (1 H, m, H-5b).

δ_C (100 MHz, $CDCl_3$): 172.4 (C=O), 170.4 (C=O), 142.8 (q), 139.5 (q), 138.7 (q), 131.5, 129.2 (q), 128.8, 128.5, 128.2, 126.7, 124.0 (q), 123.7, 123.1, 80.7, 64.6 (q), 53.4, 52.8, 33.2, 31.6.

ν_{max} (neat)/cm^{-1}: 2953, 1781, 1735, 1605, 1519, 1346, 1238, 1109, 1018, 851,736, 700.1.

HRMS (*m/z* - ESI): Found: 489.1308 $(M-H)^-$ $C_{26}H_{21}N_2O_8$ Requires: 489.1303.

Methyl (2*R*,3*S*,4*S*)-3,4-bis(4-bromophenyl)-5-oxo-2-phenyltetrahydrofuran-3-carboxylate (327)



Prepared according to general procedure III, using **315** (164.0 mg, 0.4 mmol) and freshly distilled benzaldehyde (40.8 μL, 0.4 mmol). The reaction was stired for 7 days to give a diastereomeric mixture of carboxylic acids in a 4.4:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**327**) was isolated and purified by flash column chromatography to give a white solid (145.6 mg, 69%). M.p. 78-80 °C; TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.15; $[\alpha]_D^{20}$ = +44 (*c* = 0.5, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil AMY1, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:CH_3CN:*i*-PrOH (1:1:1, *v*:*v*:*v*) gradient as shown in Table 4.1, column temperature: 30 °C, UV detection at 230 nm, retention times: 3.79 min (major enantiomer) and 4.08 min (minor enantiomer). **97% *ee***.

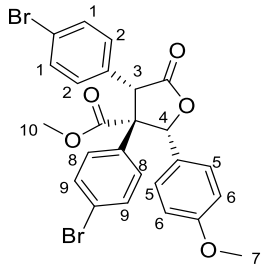
δ_H (400 MHz, $CDCl_3$): 7.55-7.53 (2 H, d, *J* 8.6, H-9), 7.42-7.40 (2 H, d, *J* 8.5, H-1), 7.34-7.27 (5 H, m, H-5, H-6 and H-7), 7.20-7.18 (2 H, d, *J* 8.6, H-8), 7.04-7.02 (2 H, d, *J* 8.5, H-2), 6.05 (1 H, s, H-4), 4.32 (1 H, s, H-3), 3.29 (3 H, s, H-10).

δ_C (100 MHz, $CDCl_3$): 171.9 (C=O), 168.6 (C=O), 133.8 (q), 133.5 (q), 132.0, 131.6, 131.4, 130.3, 129.7 (q), 129.2, 128.4, 126.3, 122.9 (q), 122.6 (q), 82.8, 66.3 (q), 56.5, 52.1.

ν_{max} (neat)/cm^{-1}: 2950, 1778, 1727, 1489, 1238, 1205, 1157, 1074, 1009, 974, 798, 753, 698, 627.

HRMS (*m/z* - ESI): Found: 526.9480 $(M-H)^-$ $C_{24}H_{17}Br_2O_4$ Requires: 526.9499.

Methyl (2*R*,3*S*,4*S*)-3,4-bis(4-bromophenyl)-2-(4-methoxyphenyl)-5-oxotetrahydrofuran-3-carboxylate (328)



Prepared according to general procedure III, using **315** (164.0 mg, 0.4 mmol) and freshly distilled 4-methoxybenzaldehyde (48.7 μL, 0.4 mmol). The reaction was stired for 10 days to give a diastereomeric mixture of carboxylic acids in a 10:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**328**) was isolated and purified by flash column chromatography to give a white solid (115.0 mg, 51%). M.p. 60-62 °C; TLC (hexanes:EtOAc, 4:1 *v/v*): R_f = 0.29; $[\alpha]_D^{20}$ = +89 (*c* = 0.08, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CEL2, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:CH_3CN (1:1, *v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 230 nm, retention times: 5.22 min (minor enantiomer) and 5.63 min (major enantiomer). **99% *ee***.

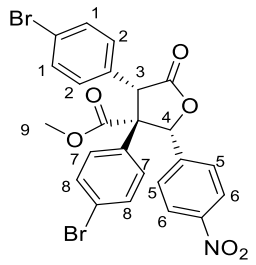
δ_H (400 MHz, $CDCl_3$): 7.54-7.52 (2 H, d, *J* 8.7, H-9), 7.43-7.41 (2 H, d, *J* 8.5, H-1), 7.21-7.19 (2 H, d, *J* 8.8, H-6), 7.17-7.15 (2 H, d, *J* 8.7, H-8), 7.07-7.05 (2 H, d, *J* 8.5, H-2), 6.87-6.84 (2 H, d, *J* 8.8, H-5), 5.90 (1 H, s, H-4), 4.35 (1 H, s, H-3), 3.80 (3 H, s, H-7), 3.59 (3 H, s, H-10).

δ_C (100 MHz, $CDCl_3$): 172.1 (C=O), 168.8 (C=O), 160.3 (q), 133.8 (q), 131.8, 131.5, 131.4, 130.3, 129.9 (q), 127.9, 125.1 (q), 122.8 (q), 122.6 (q), 113.8, 83.2, 66.1 (q), 55.8, 55.3, 52.2.

ν_{max} (neat)/cm^{-1}: 2927, 2850, 1785, 1728, 1612, 1515, 1491, 1299, 1251, 1206, 1161, 1075, 1028, 1008, 836, 809.

HRMS (*m/z* - APCI): Found: 558.9760 $(M+H)^+$ $C_{25}H_{21}Br_2O_5$ Requires: 558.9750.

Methyl (2*R*,3*S*,4*S*)-3,4-bis(4-bromophenyl)-2-(4-nitrophenyl)-5-oxotetrahydrofuran-3-carboxylate (329)



Prepared according to general procedure III, using **315** (164.0 mg, 0.4 mmol) and freshly recrystallised 4-nitrobenzaldehyde (60.4 μL, 0.4 mmol). The reaction was stired for 6 days to give a diastereomeric mixture of carboxylic acids in a 4:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**329**) was isolated and purified by flash column chromatography to give a white solid (150.7 mg, 66%). M.p. 88-90 °C; TLC (hexanes:EtOAc, 4:1 *v/v*): R_f = 0.20; $[\alpha]_D^{20}$ = +25 (*c* = 0.3, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CEL2, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:CH_3CN (1:1, *v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 230 nm, retention times: 5.47 min (minor enantiomer) and 6.43 min (major enantiomer). **92% *ee***.

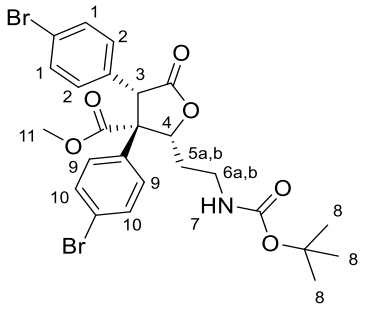
δ_H (400 MHz, $CDCl_3$): 8.20-8.18 (2 H, d, *J* 8.6, H-6), 7.61-7.59 (2 H, d, *J* 8.5, H-8), 7.49-7.47 (2 H, d, *J* 8.6, H-5), 7.43-7.41 (2 H, d, *J* 8.4, H-1), 7.24-7.22 (2 H, d, *J* 8.5, H-7), 7.00-6.98 (2 H, d, *J* 8.4, H-2), 6.14 (1 H, s, H-4), 4.37 (1 H, s, H-3), 3.27 (3 H, s, H-9).

δ_C (100 MHz, $CDCl_3$): 171.1 (C=O), 168.1 (C=O), 148.3 (q), 140.8 (q), 133.2 (q), 132.0, 131.97, 131.5, 130.0, 129.0 (q), 127.3, 123.5, 123.3 (q), 123.0 (q), 81.6, 66.6 (q), 56.8, 52.3.

ν_{max} (neat)/cm^{-1}: 2952, 1789, 1730, 1606, 1522, 1491, 1346, 1258, 1207, 1155, 1075, 1041, 1009, 799, 749, 686.

HRMS (*m/z* - APCI): Found: 571.9338 $(M-H)^-$ $C_{24}H_{16}Br_2NO_4$ Requires: 571.9349.

Methyl (2*R*,3*S*,4*S*)-3,4-bis(4-bromophenyl)-2-(2-((*tert*-butoxycarbonyl)amino) ethyl)-5-oxotetrahydrofuran-3-carboxylate (340)



Prepared according to general procedure III, using **315** (164.0 mg, 0.4 mmol) and *tert*-butyl (3-oxopropyl)carbamate (**338**, 67.9 μL, 0.4 mmol). The reaction was stired for 12 days at -30 °C, to give a diastereomeric mixture of carboxylic acids in a 19:1 (*major*:*others*) ratio. After esterification, the major diastereomer (**340**) was isolated and purified by flash column chromatography to give a white solid (139.5 mg, 58%). M.p. 62-64 °C; TLC (hexanes:EtOAc, 70:30 *v/v*): R_f = 0.34; $[\alpha]_D^{20}$ = +40.0 (*c* = 0.05, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil AMY1, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:CH_3CN:*i*-PrOH (1:1:1, *v*:*v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 230 nm, retention times: 4.61 min (minor enantiomer) and 5.14 min (major enantiomer). **90% *ee***.

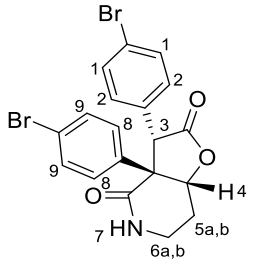
δ_H (400 MHz, $CDCl_3$): 7.46-7.42 (4 H, m (app. t), H-1 and H-10), 7.05-7.03 (2 H, d, *J* 8.5, H-9), 6.93-6.91 (2 H, d, *J* 8.6, H-2), 5.06 (1 H, app. d, H-4), 4.92 (1 H, bs, H-7 (NH)), 4.02 (1 H, s, H-3), 3.62 (3 H, s, H-11), 3.45-3.35 (2 H, m, H-6a and H-6b), 2.27-2.15 (1 H, m, H-5a), 1.75-1.66 (1 H, m, H-5b), 1.45 (9 H, s, H-8).

δ_C (100 MHz, $CDCl_3$): Mixture of diastereomers: 173.5 (C=O), 172.2 (C=O), 171.1 (C=O), 169.8 (C=O), 156.2 (C=O), 156.0 (C=O), 134.9 (q), 133.9 (q), 132.8, 132.2, 131.68, 131.66, 131.44, 131.08, 130.7 (q), 129.8 (q), 129.3, 128.8, 79.8, 79.7, 63.8 (q), 63.6 (q), 56.6, 53.0, 52.7, 52.5, 38.0 (q), 37.3 (q), 30.26, 30.20, 28.4, 28.3.

ν_{max} (neat)/cm^{-1}: 3405, 2977, 1774, 1729, 1690, 1523, 1491, 1365, 1238, 1165, 1075, 1010, 987, 835, 777, 746.

HRMS (*m/z* - APCI): Found: 594.0151 $(M-H)^-$ $C_{25}H_{26}Br_2NO_6$ Requires: 594.0132.

(2*R*,3*S*,4*S*)-3,3a-Bis(4-bromophenyl)hexahydrofuro[3,2-c]pyridine-2,4-dione (343b)



A 10 mL oven-dried round-bottomed flask containing a stirring bar was charged with the free amine of **340** (97.5 mg, 0.168 mmol, 86:14 dr) and placed under an argon atmosphere. Dry CH_2Cl_2 (1.7 mL) was added *via* syringe and the resulting solution was cooled to 0 °C. A 2M solution of trimethylaluminium in hexanes (168 μL, 0.337 mmol) was then added dropwise *via* syringe. The resulting solution was allowed to come back slowly to room temperature and stirred for 5 h. After 5 h, the reaction mixture was quenched by adding dropwise cold MeOH *via* syringe followed by cold deionised water. The resulting biphasic mixture was then diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with water, and brine, and dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford the crude product. Purification by flash column chromatography eluting in gradient from hexanes to 50% of EtOAc in hexanes furnished the desired product **343b** (74 mg, 81%). M.p. 80-82 °C; TLC (hexanes:EtOAc, 1:1 *v/v*): R_f = 0.29; $[\alpha]_D^{20}$ = +245 (*c* = 0.146, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil AMY1, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:CH_3CN:*i*-PrOH (1:1:1, *v*:*v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 254 nm, retention times: 7.11 min (major enantiomer) and 7.29 min (minor enantiomer). **86% *ee***.

δ_H (400 MHz, $CDCl_3$): 7.30-7.28 (4 H, app. bd, H-1 and H-9), 7.01 (2 H, d, *J* 8.6, H-8), 6.77 (2 H, d, *J* 8.4, H-2), 6.02 (1 H, bs, H-7 (NH)), 5.39 (1 H, dd, *J* 2.4, *J* 2.5, H-4), 4.77 (1 H, s, H-3), 3.63-3.56 (1 H, m, H-6a), 3.30-3.24 (1 H, m, H-6b), 2.45-2.38 (1 H, m, H-5a), 2.28-2.20 (1 H, m, H-5b).

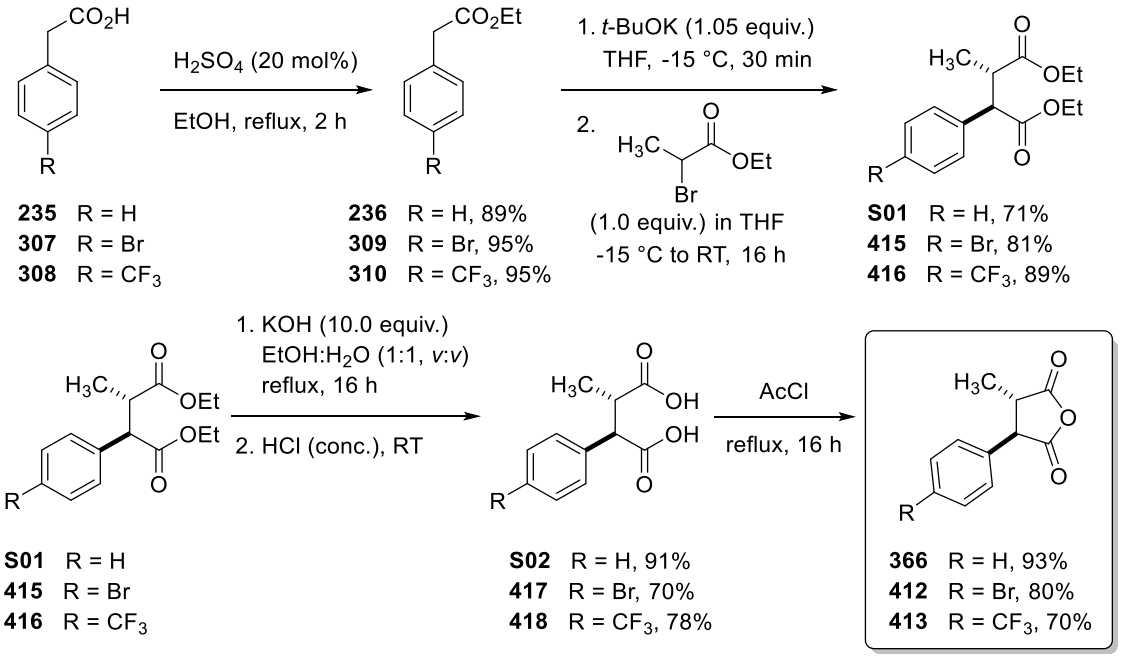
δ_C (100 MHz, $CDCl_3$): 174.2 (C=O), 170.8 (C=O), 132.4 (q), 131.78, 131.75 (q), 131.6, 130.9, 129.3, 122.5 (q), 122.2 (q), 77.9, 58.3 (q), 55.6, 37.4, 23.5.

ν_{max} (neat)/cm^{-1}: 3216, 2926, 1769, 1665, 1489, 1398, 1317, 1223, 1171, 1074, 1009, 961, 909, 812.

HRMS (*m/z* - APCI): Found: 463.9503 $(M+H)^+$ $C_{19}H_{16}Br_2NO_3$ Requires: 463.9491.

4.4 Experimental procedures for Chapter 3

4.4.1 Synthesis of anhydrides: procedures



Scheme 4.4 Synthesis of anhydrides **366**, **412** and **413**.

General procedure IV: Synthesis of anhydride precursors S02, 417-418

A 500 mL oven dried round-bottomed flask containing a stirring bar was charged with the relevant ethyl ester (**236**, **309**-**310**, 1.0 equiv.). The flask was flushed with argon, fitted with a septum and placed under an argon atmosphere. Dry THF was added *via* syringe and the resulting stirring solution was cooled to -15 °C. To the stirred solution, potassium *tert*-butoxide (1.05 equiv.) was added portion wise and the mixture was stired for 30 min. After 30 min, a cooled solution of ethyl 2-bromopropionate (1.0 equiv.) in dry THF was slowly added *via* syringe over a 10-min period. The reaction mixture was allowed to come back to room temperature and stirred for 16 h. The solvent was then removed under reduced pressure, deionised water was added to the residue and the product was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic extracts were washed with deionised water, dried over $MgSO_4$ and the solvent was removed *in vacu*o to afford a mixture of the crude esters **S01**, **415-416**. The crude products were purified with a plug of silica gel (eluting with 50% of EtOAc in hexanes) affording almost analytically pure material that was used into the next step without further purification.

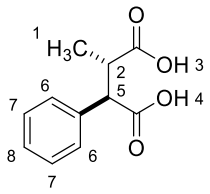
The crude mixture of diastereomers (1 equiv.) was transferred into a 500 mL round-bottomed flask containing a stirring bar and dissolved in a solution of KOH (10 equiv.) in EtOH:H_2O (50:50 *v*/*v*, 200 mL). The flask was fitted with a condenser and the solution was stirred under reflux for 16 h. The solution was allowed to cool to room temperature, the excess of EtOH was removed under reduced pressure and the remaining aqueous solution was washed several times with Et_2O. The organic layer was discarded and the aqueous solution layer was cooled to 0 °C. Acidification with conc. HCl (added dropwise until pH 1 was reached) generally resulted in the precipitation of the sole pure *trans*-isomer. The solid was then filtered and washed with a little warmed water, transferred to a 250 mL round-bottomed flask followed by an addition of Et_2O (30 mL). The solvent was removed *in vacuo* to help removing residual water to afford the pure *trans* products. When the product did not precipitate as a single diastereomer, the resulting mixture of diacids was dissolved in the minimum amount of a dilute sodium hydroxide solution and the pH of the solution was adjusted to pH 5 with dilute HCl before being stored in a freezer. The monosodium salt of the *trans* succinic acid generally crystalysed out, the solid was filtered off and the free acid was recovered by redisolving the monosodium salt in dilute sodium hydroxide until basic pH was reached

followed by acidification with conc. HCl until pH 1 was reached, resulting in the precipitation of the pure *trans* isomer. The solid was then filtered off and washed with a little warmed water before being dried under high vacuum.

General procedure V: Synthesis of anhydrides S03, 412-413

A 25 mL oven dried two-neck round-bottomed flask containing a stirring bar was charged with the appropriate succinic acid derivative **S02**, **417-418** (1.0 equiv.). The flask was then fitted with a condenser and a septum and flushed with argon. Freshly distilled acetyl chloride (≈ 15 mL/g of product) was added to the flask, the flask was flushed with argon for an additional 2 min and then kept under an argon atmosphere (balloon). The reaction mixture was heated under reflux for 16 h, and then concentrated *in vacuo*. The crude solid was triturated in dry Et_2O (≈ 10 mL/g of product) to get rid of the remaining acetyl chloride/acetic acid, cooled to 0 °C, filtered off and dried under high vacuum to yield **S03**, **412-413**.

2-Methyl-3-phenylsuccinic acid (S02)



Prepared according to general procedure IV, using potassium *tert*-butoxide (4.45 g, 39.65 mmol), ethyl 2-phenylacetate (**236**, 6.20 g, 37.76 mmol) in dry THF (80 mL) and ethyl 2-bromopropionate (6.84 g, 37.76 mmol) in dry THF (50 mL). After hydrolysis of the esters and work up as described in the general procedure I, *trans*-**S02** was obtained as a white solid (5.1 g, 64% over 2 steps). M.p. 174-175 °C (lit,[180] M.p. 192-193 °C).

Spectral data for this compound were consistent with those in the literature.[180]

trans-**S02**:

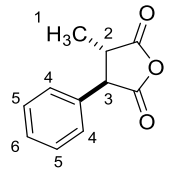
δ_H (400 MHz, DMSO-d_6): 12.3 (2 H, bs, H-3 and H-4), 7.36-7.26 (5 H, m, H-6, H-7 and H-8), 3.59 (1 H, d, *J* 11.2, H-5), 2.95-2.87 (1 H, m, H-2), 0.83 (3 H, d, *J* 7.3, H-1).

δ_C (100 MHz, DMSO-d_6): 177.1 (C=O), 174.6 (C=O), 137.6 (q), 129.1, 128.7, 127.8 (q), 54.2, 42.2, 15.7.

ν_{max} (neat)/cm^{-1}: 2985, 1690, 1421, 1313, 1275, 1253, 1204, 917, 900, 723, 698.

HRMS (*m/z* - ESI): Found: 207.0654 $(M+H)^+$ $C_{11}H_{11}O_4$ Requires: 207.0657.

3-Methyl-4-phenyldihydrofuran-2,5-dione (366)



Prepared according to general procedure V, using *trans*-**S02** (940 mg, 4.51 mmol) and freshly distilled acetyl chloride (≈ 15 mL). After work up as described in general procedure II, *trans*-**S03** was obtained as a white solid (0.804 g, 93%). M.p. 79-81 °C. TLC (hexanes:EtOAc, 4:1 *v/v*): R_f = 0.42 (*trans*-**366**).

trans-**366**:

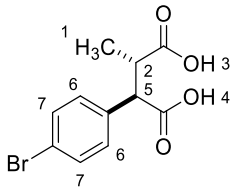
δ_H (600 MHz, $CDCl_3$): 7.60-7.49 (3 H, m, H-5 and H-6), 7.43-7.34 (2 H, m, H-4), 4.02 (1 H, d, *J* 8.4, H-3), 3.38 (1 H, m, H-2), 1.62 (3 H, d, *J* 7.1, H-1).

δ_C (100 MHz, $CDCl_3$): 172.4 (C=O), 170.6 (C=O), 133.7 (q), 129.4, 128.7, 127.7, 54.5, 44.3, 14.3.

ν_{max} (neat)/cm^{-1}: 2923, 1835, 1772, 1695, 1498, 1455, 1259, 1217, 1102, 983, 924, 763, 739, 699, 589.

HRMS (*m/z* - ESI): Found: 189.0556 $(M-H)^-$ $C_{11}H_9O_3$ Requires: 189.0552.

(4-Bromophenyl)-3-methylsuccinic acid (417)



Prepared according to general procedure IV, using potassium *tert*-butoxide (1.05 g, 9.37 mmol, 1.1 equiv.), ethyl 2-(4-bromophenyl)acetate (**309**, 2.09 g, 8.52 mmol) in dry THF (20 mL) and ethyl 2-bromopropionate (1.1 mL, 8.52 mmol) in dry THF (10 mL). After hydrolysis of the esters and work up as described in the general procedure I, *trans*-**417** was obtained as a white solid (1.4 g, 57% over 2 steps). M.p. 175-178 °C.

trans-**417**:

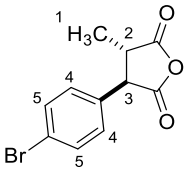
δ_H (400 MHz, DMSO-d_6): 12.37 (2 H, bs, H-3 and H-4), 7.54 (2 H, *J* 8.4, H-7), 7.25 (2 H, *J* 8.4, H-6), 3.62 (1 H, d, *J* 11.1, H-5), 2.93-2.85 (1 H, m, H-2), 0.83 (3 H, d, *J* 7.3, H-1).

δ_C (100 MHz, DMSO-d_6): 176.8 (C=O), 174.2 (C=O), 137.1 (q), 132.0, 131.0, 121.0 (q), 53.5, 42.0, 15.6.

ν_{max} (neat)/cm^{-1}: 2982, 2601, 1694, 1489, 1458, 1408, 1280, 1198, 1074, 1012, 918, 809, 750, 646, 582.

HRMS (*m/z* - APCI): Found: 284.9765 $(M-H)^-$ $C_{11}H_{10}BrO_4$ Requires: 284.9767.

(4-Bromophenyl)-4-methyldihydrofuran-2,5-dione (412)



Prepared according to general procedure V, using *trans*-**417** (500 mg, 1.74 mmol) and freshly distilled acetyl chloride (≈ 10 mL). After work up as described in general procedure II, *trans*-**412** was obtained as a white solid (372 mg, 80%). M.p. 116-118 °C.

trans-**412**:

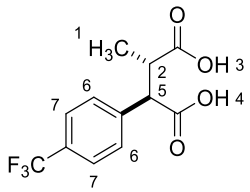
δ_H (400 MHz, $CDCl_3$): 7.56 (2 H, d, *J* 8.4, H-5), 7.14 (2 H, d, *J* 8.4, H-4), 3.86 (1 H, d, *J* 9.1, H-3), 3.24-3.16 (1 H, m, H-2), 1.49 (3 H, d, *J* 7.1, H-1).

δ_C (100 MHz, $CDCl_3$): 171.9 (C=O), 170.0 (C=O), 132.6, 132.4 (q), 129.4, 123.0 (q), 54.0, 44.1, 14.3.

ν_{max} (neat)/cm^{-1}: 2988, 2942, 2894, 1867, 1768, 1493, 1448, 1409, 1382, 1260, 1217, 1112, 1076, 1014, 978, 907, 851, 835, 804, 741, 702, 626.

HRMS (*m/z* - APCI): Found: 266.9649 $(M-H)^-$ $C_{11}H_8BrO_3$ Requires: 266.9662.

2-Methyl-3-(4-(trifluoromethyl)phenyl)succinic acid (418)



Prepared according to general procedure IV, using potassium *tert*-butoxide (0.761 g, 6.68 mmol), ethyl 2-(4-(trifluoromethyl)phenyl)acetate (**310**, 1.5 g, 6.46 mmol) in dry THF (40 m L)and ethyl 2-bromopropionate (1.17 g, 6.46 mmol) in dry THF (20 mL). After hydrolysis of the esters and work up as described in the general procedure I, *trans*-**418** was obtained as a white solid (1.26 g, 69% over 2 steps). M.p. 160-162 °C.

trans-**418**:

δ_H (400 MHz, DMSO-d_6): 12.47 (2 H, bs, H-3 and H-4), 7.70 (2 H, *J* 8.2, H-7), 7.53 (2 H, *J* 8.2, H-6), 3.77 (1 H, d, *J* 11.1, H-5), 3.01-2.93 (1 H, m, H-2), 0.84 (3 H, d, *J* 7.3, H-1).

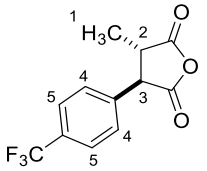
δ_C (100 MHz, DMSO-d_6): 176.8 (C=O), 174.0 (C=O), 142.4 (q), 129.7, 128.5 (q) (q, ^2J 31.8 Hz), 125.9 (q, ^3J 3.5 Hz), 124.6 (q) (q, ^1J 272.0 Hz), 54.0, 42.0, 15.5.

δ_F (376.5 MHz, DMSO-d_6):- 61.07.

ν_{max} (neat)/cm^{-1}: 3245, 2994, 2575, 1747, 1672, 1461, 1421, 1324, 1202, 1173, 1161, 1128, 1107, 1067, 1020, 915, 833, 724, 676.

HRMS (*m/z* - APCI): Found: 275.0525 $(M-H)^-$ $C_{12}H_{10}F_3O_4$ Requires: 275.0536.

3-Methyl-4-(4-(trifluoromethyl)phenyl)dihydrofuran-2,5-dione (413)



Prepared according to general procedure V, using *trans*-**418** (650 mg, 2.35 mmol) and freshly distilled acetyl chloride (≈ 10 mL). After work up as described in general procedure II, *trans*-**413** was obtained as a white solid (421.6 mg, 70%). TLC (hexanes:EtOAc, 1:1 *v/v*): R_f = 0.79 (*trans*-**413**). M.p. 80-82 °C.

trans-**413**:

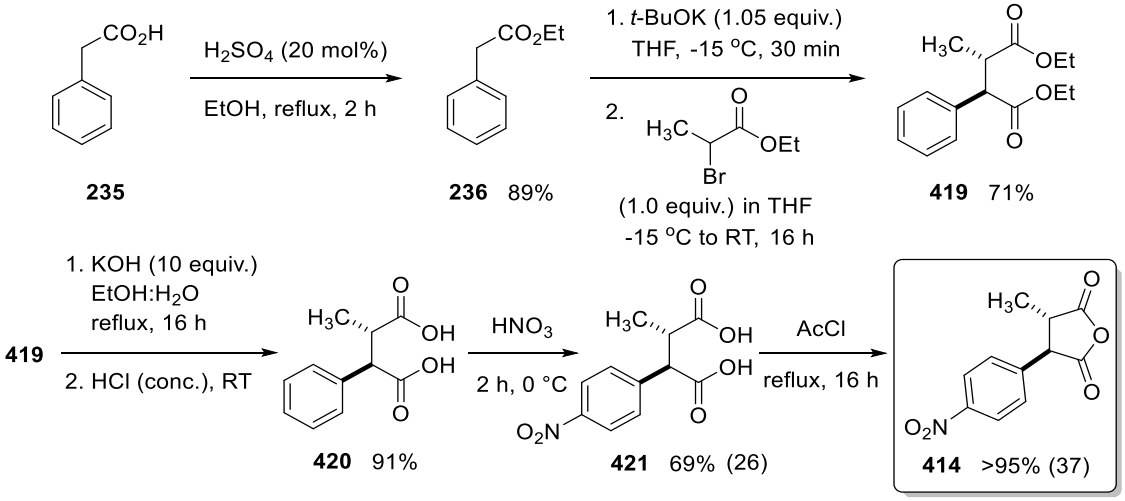
δ_H (400 MHz, $CDCl_3$): 7.70 (2 H, *J* 8.1, H-5), 7.40 (2 H, *J* 8.1, H-4), 3.96 (1 H, d, *J* 9.2, H-3), 3.29-3.22 (1 H, dq, *J* 9.2, *J* 7.1, H-2), 1.52 (3 H, d, *J* 7.1, H-1).

δ_C (100 MHz, $CDCl_3$): 171.7 (C=O), 169.8 (C=O), 137.4 (q), 131.2 (q) (q, ^2J 32.7 Hz), 128.4, 126.5 (q, ^3J 3.7 Hz), 123.7 (q) (q, ^1J 272.3 Hz), 54.2, 44.1, 14.3.

δ_F (376.5 MHz, $CDCl_3$): - 62.89.

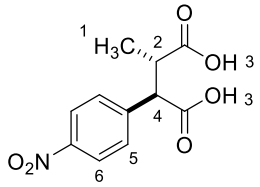
ν_{max} (neat)/cm^{-1}: 2942, 1871, 1846, 1773, 1422, 1324, 1264, 1227, 1166, 1111, 1067, 985, 926, 839, 751, 726, 628.

HRMS (*m/z* - APCI): Found: 257.0422 $(M-H)^-$ $C_{12}H_8F_3O_3$ Requires: 257.0431.



Scheme 4.5 Synthesis of anhydride **414**.

2-Methyl-3-(4-nitrophenyl)succinic acid (421)



A 25 mL oven-dried round-bottomed flask fitted with a thermometer and containing a magnetic stirring bar was charged with fuming nitric acid (≈ 4 mL) and cooled to 0 °C. 2-Methyl-3-phenylsuccinic acid (**420**, 1.0 g, 4.8 mmol) was added portion wise while keeping the temperature < 20 °C. The solution stired for 2 h, at 0 °C, then crushed ice (≈ 10 g) and water (≈ 5 mL) were added to the reaction mixture. A pale yellow solid precipitate formed. The solid was filtered off and washed with cold water. The crude product was obtained as a mixture of diastereomers in a 45:55 ratio (*cis*:*trans*) (0.840 g, 69%). The crude product was recrystallised from boiling water to obtain *trans*-**414** as a white solid (320 mg, 26%). M.p. >200 °C, decomposition.

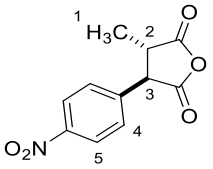
δ_H (400 MHz, DMSO-d_6): 12.34 (2 H, bs, H-3), 8.18 (2 H, *J* 8.8, H-6), 7.59 (2 H, *J* 8.8, H-5), 3.83 (1 H, d, *J* 10.2, H-4), 3.11-3.03 (1 H, dq, *J* 10.2, *J* 6.7, H-2), 1.21 (3 H, d, *J* 6.7, H-1).

δ_C (100 MHz, DMSO-d_6): 175.2 (C=O), 172.8 (C=O), 147.2 (q), 145.8 (q), 130.2, 123.9, 54.6, 43.1, 16.5.

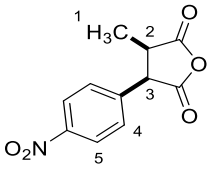
ν_{max} (neat)/cm^{-1}: 2920, 2916, 1696, 1599, 1519, 1423, 1351, 1296, 1196, 913, 836, 733, 697, 650.

HRMS (*m/z* - APCI): Found: 252.0505 $(M-H)^-$ $C_{11}H_{10}NO_6$ Requires: 252.0513.

3-Methyl-4-(4-nitrophenyl)dihydrofuran-2,5-dione (414)



trans-**414**



cis-**414**

Prepared according to general procedure V, using **421** (273.0 mg, 1.08 mmol) and freshly distilled acetyl chloride (≈ 5 mL). After work up as described in general procedure II, **414** was obtained as a brown crude residue (241.3 mg – 95% (crude)). The residue was stirred in boiling Et_2O (4 mL) and the resulting solution was separated from the insoluble remaining residue. The organic solvent was transferred to a small vial and stored in a freezer. After storage overnight, a yellow solid had formed. The solid was filtered off and dried under high vacuum to yield **414** as a mixture of pure diastereomers in the ratio 83:17 (*trans*:*cis*) (93.6 mg, 37%). M.p.* 88-90 °C.

trans-**414**:

δ_H (400 MHz, $CDCl_3$): 8.28 (2 H, *J* 8.4, H-5), 7.37 (2 H, *J* 8.4, H-4), 4.59 (1 H, *J* 10.0, H-3), 3.61-3.52 (1 H, dq, *J* 10.0, *J* 7.7, H-2), 1.02 (3 H, *J* 7.7, H-1).

δ_C (100 MHz, $CDCl_3$): 172.4 (C=O), 170.0 (C=O), 138.8 (q), 147.9 (q), 138.8 (q), 129.9, 124.4, 50.8, 40.3, 12.6.

cis-**414**:

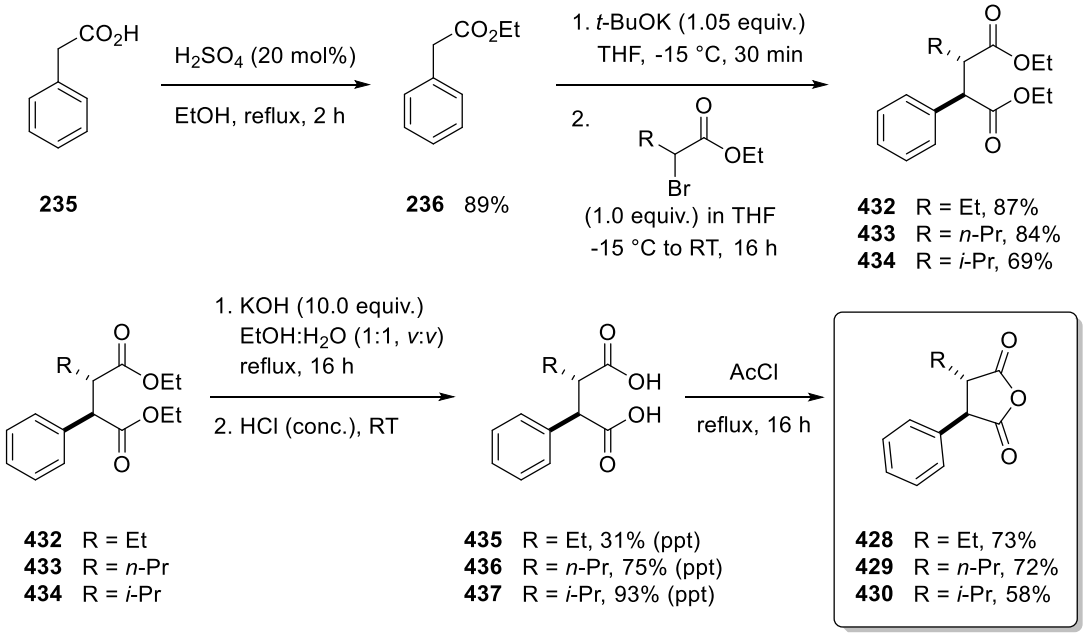
δ_H (400 MHz, $CDCl_3$): 8.30 (2 H, *J* 8.5, H-5), 7.48 (2 H, *J* 8.5, H-4), 4.05 (1 H, *J* 9.3, H-3), 3.33-3.25 (1 H, dq, *J* 9.3, *J* 7.1, H-2), 1.54 (3 H, *J* 7.1, H-1).

δ_C (100 MHz, $CDCl_3$): 171.2 (C=O), 169.3 (C=O), 142.5 (q), 140.3 (q), 128.9, 124.6, 54.0, 44.0, 14.3.

ν_{max} (neat)/cm^{-1}:* 2894, 1859, 1779, 1602, 1521, 1456, 1348, 1219, 1093, 981, 917, 853, 832, 698.

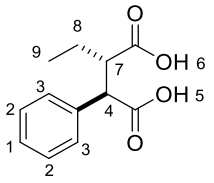
HRMS (*m/z* - APCI):* Found: 234.0419 $(M-H)^-$ $C_{11}H_8NO_5$ Requires: 234.0407.

* Refers to mixture of *trans*-**414**:*cis*-**414** in the ratio 83:17.

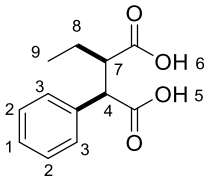


Scheme 4.6 Synthesis of anhydrides **428** to **430**.

2-Ethyl-3-phenylsuccinic acid (435)



trans-**435**



cis-**435**

Prepared according to general procedure IV, using potassium *tert*-butoxide (3.02 g, 26.92 mmol), ethyl 2-bromobutyrate (5.0 g, 25.63 mmol) in dry THF (100 mL) and ethyl 2-phenylacetate (**236**, 4.21 g, 25.63 mmol) in dry THF (50 mL). After hydrolysis of the esters and work up as described in the general procedure I, **435** was obtained as a mixture of diastereomers in a 45:55 (*cis*:*trans*) ratio as a white solid (1.54 g, 27% over 2 steps). M.p. >200 °C.*

trans-**435**:

δ_H (400 MHz, DMSO-d_6): 12.32 (2 H, bs, H-5 and H-6), 7.36-7.22 (5 H, m, H-1, H-2 and H-3), 3.68 (1 H, d, *J* 11.6, H-4), 2.92-2.86 (1 H, m, H-7), 1.67-1.52 (2 H, m, H-8), 0.72 (3 H, t, *J* 7.5, H-9).

cis-**435**:

δ_H (400 MHz, DMSO-d_6): 12.32 (2 H, bs, H-5 and H-6), 7.36-7.22 (5 H, m, H-1, H-2 and H-3), 3.58 (1 H, d, *J* 11.4, H-4), 2.92-2.86 (1 H, m, H-7), 1.37-1.28 (1 H, m, H-8), 1.16-1.08 (1 H, m, H-8), 0.90 (3 H, t, *J* 7.4, H-9).

cis-**435** + *trans*-**435**:

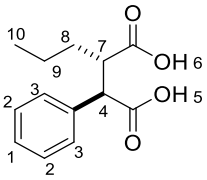
δ_C (100 MHz, DMSO-d_6):* 176.0 (C=O), 174.60 (C=O), 174.58 (C=O), 173.8 (C=O), 137.9 (q), 137.6 (q), 129.8, 129.1, 128.75, 128.7, 127.83, 127.77, 54.3, 52.3, 50.7, 48.4, 24.8, 22.2, 12.0, 10.6.

ν_{max} (neat)/cm^{-1}:* 2969, 1688, 1499, 1456, 1405, 1278, 1195, 934, 695, 633.

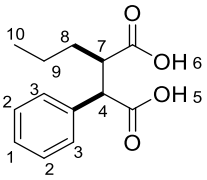
HRMS (*m/z* - ESI):* Found: 221.0810 $(M-H)^-$ $C_{12}H_{13}O_4$ Requires: 221.0819.

* Refers to mixture of *trans*-**435**:*cis*-**435** in the ratio 55:45.

2-Phenyl-3-propylsuccinic acid (436)



trans-**436**



cis-**436**

Prepared according to general procedure IV, using potassium *tert*-butoxide (2.22 g, 19.74 mmol), ethyl 2-phenylacetate (**236**, 3.09 g, 18.80 mmol) in dry THF (80 mL) and ethyl 2-bromovalerate (3.93 g, 18.80 mmol) in dry THF (50 mL). After hydrolysis of the esters and work up as described in the general procedure I, **436** was obtained as a white solid as a mixture of diastereomers in the ratio 43:57 (*cis*:*trans*) (3.2 g, 63% over 2 steps, combined yield for both diastereomers). M.p. 184-188 °C.

cis-**436** + *trans*-**436**:

δ_H (400 MHz, DMSO-*d*$_6$):* 12.31 (2 H, bs, H-5 and H-6), 7.37-7.23 (5 H, m, H-1, H-2 and H-3), 3.66 (1 H, d, *J* 11.6, H-4$_{(trans)}$), 3.57 (1 H, d, *J* 11.1, H-4$_{(cis)}$), 3.00-2.88 (1 H, m, H-7$_{(cis+trans)}$), 1.62-1.47 (1 H, m, H-8$_{(trans)}$), 1.62-1.47 (1 H, m, H-8$_{(cis)}$), 1.37-1.22 (1 H, m, H-8$_{(trans)}$), 1.20-1.04 (1 H, m, H-9$_{(cis+trans)}$), 0.89 (3 H, t, *J* 7.3, H-10$_{(cis)}$), 0.68 (3 H, t, *J* 7.0, H-10$_{(trans)}$).

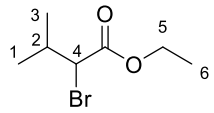
δ_C (100 MHz, DMSO-*d*$_6$):* 176.3 (C=O), 174.8 (C=O), 174.5 (C=O), 173.8 (C=O), 137.8 (q), 137.7 (q), 129.8, 129.1, 128.8, 128.75, 127.85, 127.78, 54.6, 53.0, 49.0, 47.3, 33.9, 31.7, 20.6, 19.4, 14.3, 14.2.

ν_{max} (neat)/cm^{-1}:* 2961, 1690, 1411, 1280, 1198, 934, 725, 697.

HRMS (*m/z* - ESI):* Found: 259.0950 $(M+Na)^+$ $C_{13}H_{16}NaO_4$ Requires: 259.0940.

* Refers to mixture of *trans*-**436**:*cis*-**436** in the ratio 57:43.

Ethyl 2-bromo-3-methylbutanoate (S04)



A 250 mL round-bottomed flask containing a stirring bar was charged with commercially available 2-bromo-3-methylbutyric acid (10.0 g, 55.24 mmol). MeOH (100 mL) followed by conc. H_2SO_4 (0.8 mL) were added, the flask was fitted with a condenser and the resulting mixture was stirred under reflux for 16 h. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL), washed with a saturated $NaHCO_3$ solution until basic pH was reached. The mixture was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic fractions were washed with deionised water, dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford **S04** pure as a colourless liquid (10.6 g, 50.7 mmol, 92%). TLC (hexanes:EtOAc, 9:1 *v*/*v*): R_f = 0.76.

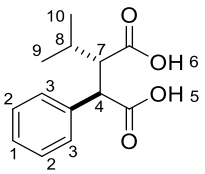
Spectral data for this compound were consistent with those in the literature.[181]

δ_H (400 MHz, $CDCl_3$): 4.23 (2 H, q, *J* 7.1, H-5), 4.03 (1 H, d, *J* 7.9, H-4), 2.27-2.19 (1 H, m, H-2), 1.29 (3 H, t, *J* 7.1, H-6), 1.09 (3 H, d, *J* 6.6, H-3), 1.03 (3 H, d, *J* 6.7, H-1).

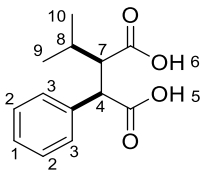
δ_C (100 MHz, $CDCl_3$): 169.5 (C=O), 61.8, 54.7, 32.3, 19.9, 19.8, 14.0.

HRMS (*m/z* - APCI): Found: 209.0171 $(M+H)^+$ C7H17BrO2 Requires: 209.0172.

2-Isopropyl-3-phenylsuccinic acid (437)



trans-**437**



cis-**437**

Prepared according to general procedure IV, using potassium *tert*-butoxide (2.15 g, 19.18 mmol), ethyl 2-bromo-3-methylbutyrate (3.82 g, 18.27 mmol) in dry THF (80 mL) and ethyl 2-phenylacetate (**236**, 3.0 g, 18.27 mmol) in dry THF (20 mL). After hydrolysis of the esters and work up as described in the general procedure I, **437** was

obtained as a mixture of diastereomers in a 22:78 (*cis*:*trans*) ratio as a white solid (0.750 g, 64% over 2 steps, combined yield for both diastereomers). M.p. >200 °C.

trans-**437**:

δ_H (400 MHz, DMSO-d_6): 12.24 (2 H, bs, H-5 and H-6), 7.36-7.22 (5 H, m, H-1, H-2 and H-3), 3.76 (1 H, d, *J* 11.8, H-4), 2.90 (1 H, dd, *J* 2.8, 11.8, H-7), 1.40-1.33 (1 H, m, H-8), 0.88 (3 H, d, *J* 6.9, H-9), 0.73 (3 H, d, *J* 6.8, H-10).

cis-**437**:

δ_H (400 MHz, DMSO-d_6): 12.24 (2 H, bs, H-5 and H-6), 7.36-7.22 (5 H, m, H-1, H-2 and H-3), 3.74 (1 H, d, *J* 11.3, H-4), 3.02 (1 H, dd, *J* 4.3, 11.3, H-7), 2.01-1.93 (1 H, m, H-8), 0.99 (3 H, d, *J* 6.9, H-9), 0.96 (3 H, d, *J* 6.8, H-10).

trans-**437** (only):

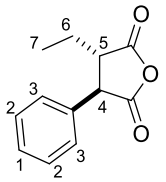
δ_C (100 MHz, DMSO-d_6): 174.70 (C=O), 174.67 (C=O), 137.8 (q), 129.2, 128.7, 127.8, 53.0, 51.7, 26.5, 22.4, 17.2.

ν_{max} (neat)/cm^{-1}:* 3216, 1699, 1418, 1070, 944, 796, 725, 698.

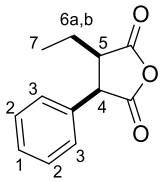
HRMS (*m/z* - ESI):* Found: 235.0967 $(M-H)^-$ $C_{13}H_{15}O_4$ Requires: 235.0975.

* Refers to mixture of *trans*-**437**:*cis*-**437** in the ratio 78:22.

2-Ethyl-3-phenylsuccinic acid anhydride (428)



trans-**428**



cis-**428**

Prepared according to general procedure V, using **435** (1.7 g, 7.64 mmol) and freshly distilled acetyl chloride (≈ 20 mL). After work up as described in general procedure II, **428** was obtained as a brown liquid. The residue was filtered through a small pad of

silica eluting with 100% EtOAc. After evaporation of the solvent the product was dried under high vacuum to yield **428** as a mixture of pure diastereomers in the ratio 52:48 (*trans*:*cis*) (1.14 g, 73%).

trans-**428**:

δ_H (400 MHz, $CDCl_3$): 7.43-7.15 (5 H, m, H-1, H-2 and H-3), 4.00 (1 H, d, *J* 7.7, H-4), 3.24-3.19 (1 H, m, H-5), 2.04-1.89 (2 H, m, H-6), 1.09 (3 H, t, *J* 7.3, H-7).

δ_C (100 MHz, $CDCl_3$): 172.7 (C=O), 172.0 (C=O), 134.6 (q), 129.5, 128.7, 127.7, 52.1, 50.3, 20.3, 10.8.

cis-**428**:

δ_H (400 MHz, $CDCl_3$): 7.43-7.15 (5 H, m, H-1, H-2 and H-3), 4.43 (1 H, d, *J* 9.5, H-4), 3.28-3.23 (1 H, m, H-5), 1.72-1.60 (1 H, m, H-6a), 1.37-1.26 (1 H, m, H-6b), 0.91 (3 H, t, *J* 7.5, H-7).

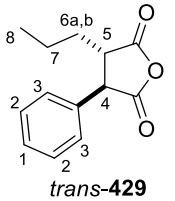
δ_C (100 MHz, $CDCl_3$): 171.04 (C=O), 171.01 (C=O), 131.6 (q), 129.2, 128.70, 128.66, 50.9, 47.3, 23.2, 11.7.

ν_{max} (neat)/cm^{-1}:* 2972, 2939, 1863, 1775, 1496, 1455, 1208, 1107, 1080, 1208, 1034, 1017, 914, 763, 698, 735.

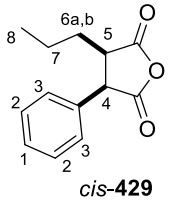
HRMS (*m/z* - APCI):* Found: 203.0707 $(M-H)^-$ $C_{12}H_{11}O_3$ Requires: 203.0713.

* Refers to mixture of *trans*-**428**:*cis*-**428** in the ratio 52:48.

2-Phenyl-3-propylsuccinic acid anhydride (429)



trans-**429**



cis-**429**

Prepared according to general procedure V, using **436** (2.3 g, 9.78 mmol) and freshly distilled acetyl chloride (≈ 20 mL). After work up as described in general procedure II,

429 was obtained as a brown liquid. The residue was filtered through a small pad of silica eluting with 100% EtOAc. After evaporation of the solvent the product was dried under high vacuum to yield **429** as a mixture of pure diastereomers in the ratio 64:36 (*trans*:*cis*) (1.52 g, 72%).

trans-**429**:

δ_H (400 MHz, $CDCl_3$): 7.43-7.14 (5 H, m, H-1, H-2 and H-3), 3.98 (1 H, d, *J* 7.5, H-4, 3.28-3.23 (1 H, m, H-5), 2.02-1.94 (1 H, m, H-6a), 1.87-1.77 (1 H, m, H-6b), 1.58-1.39 (2 H, m, H-7), 0.91 (3 H, t, *J* 7.3, H-8).

δ_C (100 MHz, $CDCl_3$): 172.3 (C=O), 171.0 (C=O), 134.6 (q), 129.5, 128.66, 127.7, 52.8, 48.8, 32.3, 19.8, 13.6.

cis-**429**:

δ_H (400 MHz, $CDCl_3$): 7.43-7.14 (5 H, m, H-1, H-2 and H-3), 4.40 (1 H, d, *J* 9.6, H-4, 3.37-3.31 (1 H, m, H-5), 1.66-1.57 (1 H, m, H-6a), 1.45-1.36 (1 H, m, H-6b), 1.28-1.17 (2 H, m, H-7), 0.79 (3 H, t, *J* 7.2, H-8).

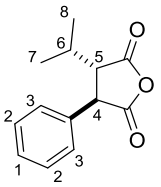
δ_C (100 MHz, $CDCl_3$): 172.9 (C=O), 171.0 (C=O), 131.7 (q), 129.2, 128.72, 128.63, 51.1, 45.5, 28.6, 20.3, 13.5.

ν_{max} (neat)/cm^{-1}:* 2963, 2935, 1862, 1776, 1498, 1455, 1208, 1051, 1038, 927, 769, 731, 698, 596.

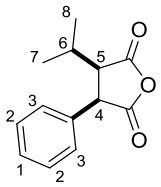
HRMS (*m/z* - APCI):* Found: 217.0861 $(M-H)^-$ $C_{13}H_{13}O_3$ Requires: 217.0870.

* Refers to mixture of *trans*-**429**:*cis*-**429** in the ratio 64:36.

2-Isopropyl-3-phenylsuccinic acid anhydride (430)



trans-**430**



cis-**430**

Prepared according to general procedure V, using **437** (0.750 g, 3.17 mmol) and freshly distilled acetyl chloride (≈ 10 mL). After work up as described in general procedure II, **430** was obtained as a brown liquid. The residue was filtered through a small pad of silica eluting with 100% EtOAc. After evaporation of the solvent the product was dried under high vacuum to yield **430** as a mixture of pure diastereomers in the ratio 86:14 (*trans*:*cis*) (0.408 g, 58%).

trans-**430**:

δ_H (400 MHz, $CDCl_3$): 7.42-7.22 (5 H, m, H-1, H-2 and H-3), 4.02 (1 H, d, *J* 6.4, H-4), 3.19-3.36 (1 H, m, H-5), 2.40-2.32 (1 H, m, H-6), 1.10 (3 H, d, *J* 6.9, H-7), 1.04 (3 H, d, *J* 6.9, H-8).

δ_C (100 MHz, $CDCl_3$): 171.7 (C=O), 171.3 (C=O), 135.5 (q), 129.5, 128.58, 127.5, 55.3, 49.7, 29.4, 19.4, 18.9.

cis-**430**:

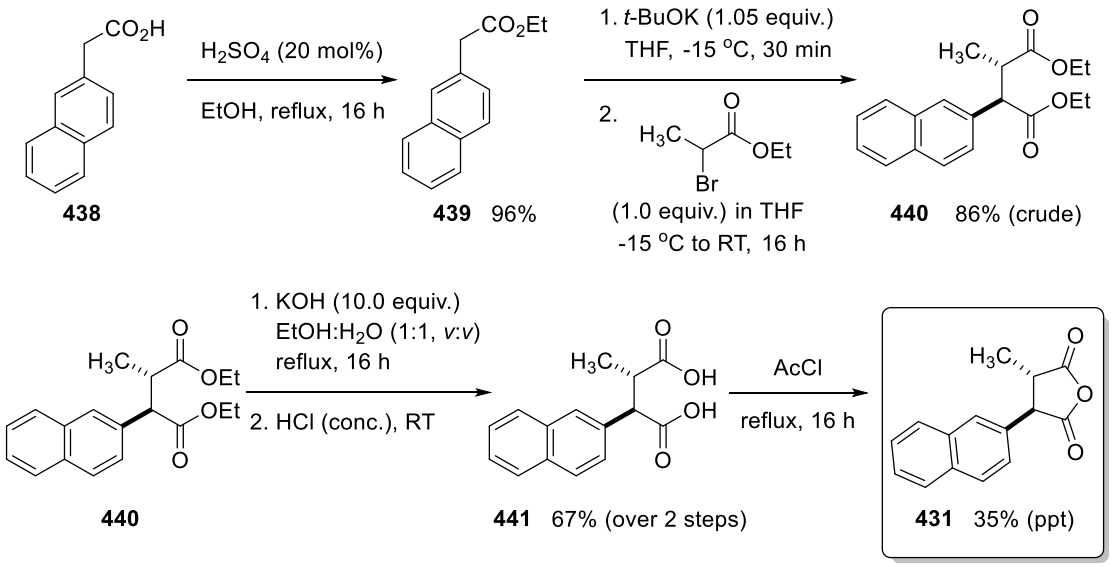
δ_H (400 MHz, $CDCl_3$): 7.42-7.22 (5 H, m, H-1, H-2 and H-3), 4.44 (1 H, d, *J* 9.4, H-4), 3.19-3.36 (1 H, m, H-5), 1.81-1.72 (1 H, m, H-6), 0.97 (3 H, d, *J* 6.7, H-7), 0.92 (3 H, d, *J* 6.8, H-8).

δ_C (100 MHz, $CDCl_3$): 171.2 (C=O), 170.5 (C=O), 131.1 (q), 129.2, 128.63, 128.57, 52.2, 50.4, 26.4, 21.3, 18.7.

ν_{max} (neat)/cm^{-1}:* 2966, 2931, 1862, 1775, 1499, 1455, 1209, 1063, 1038, 924, 771, 742, 697.

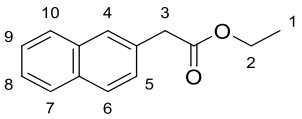
HRMS (*m/z* - APCI):* Found: 217.0878 $(M-H)^-$ $C_{13}H_{13}O_3$ Requires: 217.0870.

* Refers to mixture of *trans*-**430**:*cis*-**430** in the ratio 86:14.



Scheme 4.7 Synthesis of anhydride **431**.

Ethyl 2-(naphth-2-yl)acetate (439)



A 250 mL round-bottomed flask containing a stirring bar was charged with commercially available 2-naphthaleneacetic acid (**438**) (5.46 g, 29.32 mmol). MeOH (50 mL) followed by conc. H_2SO_4 (0.4 mL) were added, the flask was fitted with a condenser and the resulting mixture was stirred under reflux for 16 h. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL), washed with a saturated $NaHCO_3$ solution until basic pH was reached. The mixture was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic fractions were washed with deionised water, dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford **439** as a colourless liquid (6.05 g, 28.24 mmol, 96%). TLC (hexanes:EtOAc, 9:1 *v*/*v*): R_f = 0.49.

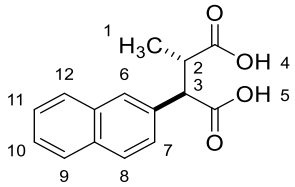
Spectral data for this compound were consistent with those in the literature.[182]

δ_H (400 MHz, $CDCl_3$): 7.84-7.80 (3 H, m, H-6, H-7 and H-10), 7.74 (1 H, bs, H-4), 7.50-7.42 (3 H, m, H-5, H-8 and H-9), 4.18 (2 H, q, *J* 7.2, H-2), 3.78 (2 H, s, H-3), 1.26 (3 H, t, *J* 7.2, H-1).

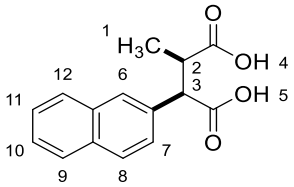
δ_C (100 MHz, $CDCl_3$): 177.7 (C=O), 133.5 (q), 132.5 (q), 131.7 (q), 128.2, 127.9, 127.71, 127.68, 127.4, 126.2, 125.8, 61.0, 41.7, 14.2.

HRMS (*m/z* - APCI): Found: 213.0922 $(M-H)^-$ $C_{14}H_{13}O_2$ Requires: 213.0921.

2-Methyl-3-(naphth-2-yl)succinic acid (441)



trans-**441**



cis-**441**

Prepared according to general procedure IV, using potassium *tert*-butoxide (3.33 g, 29.65 mmol), ethyl 2-(naphth-2-yl)acetate (**439**, 6.05 g, 28.24 mmol) in dry THF (100 mL) and ethyl 2-bromopropionate (5.11 g, 28.24 mmol) in dry THF (10 mL). After hydrolysis of the esters and work up as described in the general procedure I, **441** was obtained as a white solid as a mixture of diastereomers (*trans*:*cis*) in the ratio 63:37 (4.87 g, 67% over 2 steps, combined yield for both diastereomers). M.p. 102-104 °C.*

trans-**441**:

δ_H (400 MHz, DMSO-d_6): 12.42 (2 H, bs, H-4 and H-5), 7.91-7.87 (3 H, m, H-8, H-9 and H-12), 7.84 (1 H, bs, H-6), 7.53-7.42 (3 H, m, H-7, H-10 and H-11), 3.80 (1 H, d, *J* 11.2, H-3), 3.12-3.04 (1 H, m, *J* 7.2, 11.2, H-2), 0.88 (3 H, d, *J* 7.2, H-1).

δ_C (100 MHz, DMSO-d_6): 177.2 (C=O), 174.6 (C=O), 135.2 (q), 133.4 (q), 132.7 (q), 128.8, 128.1, 128.0, 127.8, 126.9, 126.8, 126.4, 55.1, 43.3, 16.8.

cis-**441**:

δ_H (400 MHz, DMSO-d_6): 12.42 (2 H, bs, H-4 and H-5), 7.91-7.87 (3 H, m, H-8, H-9 and H-12), 7.81 (1 H, bs, H-6), 7.53-7.42 (3 H, m, H-7, H-10 and H-11), 3.82 (1 H, d, *J* 10.8, H-3), 3.20-3.13 (1 H, m, *J* 6.9, 10.8, H-2), 1.27 (3 H, d, *J* 6.9, H-1).

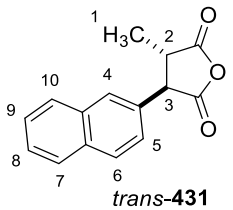
δ_C (100 MHz, DMSO-d_6): 175.6 (C=O), 173.7 (C=O), 135.8 (q), 133.2 (q), 132.7 (q), 128.3, 128.2, 127.91, 127.89, 127.5, 126.7, 126.5, 54.4, 42.2, 15.8.

ν_{max} (neat)/cm^{-1}:* 2886, 2598, 1693, 1421, 1306, 1195, 934, 818, 747.

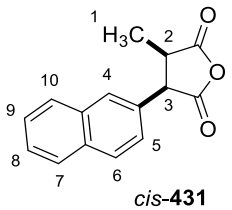
HRMS (*m/z* - ESI):* Found: 281.0787 $(M+Na)^+$ $C_{15}H_{14}NaO_4$ Requires: 281.0784.

* Refers to mixture of *trans*-**441**:*cis*-**441** in the ratio 63:37.

3-Methyl-4-(naphth-2-yl)dihydrofuran-2,5-dione (431)



trans-**431**



cis-**431**

Prepared according to general procedure V, using **441** (3.8 g, 14.71 mmol) and freshly distilled acetyl chloride (≈ 40 mL). After work up as described in general procedure II, **431** was obtained as a brown crude residue. The residue was triturated in dry Et_2O (≈ 10 mL). The remaining solid was filtered off and dried under high vacuum to yield **431** as a mixture of pure diastereomers in the ratio 81:19 (*trans*:*cis*) (1.25 g, 35%). The mother liquor containing the remaining anhydride was stored under in a vial under an argon atmosphere. M.p.* 135-137 °C.

trans-**431**:

δ_H (400 MHz, $CDCl_3$): 7.91 (1 H, d, *J* 8.6, H-6), 7.87-7.81 (2 H, m, H-7 and H-10), 7.72 (1 H, bs, H-4), 7.56-7.51 (2 H, m, H-8 and H-9), 7.31

(1 H, d, *J* 8.6, H-5), 4.05 (1 H, d, *J* 8.8, H-3), 3.38-3.31 (1 H, dq, *J* 8.8, *J* 7.2, H-2), 1.52 (3 h, d, *J* 7.2, H-1).

δ_C (100 MHz, DMSO-d_6): 172.5 (C=O), 170.7 (C=O), 133.3 (q), 133.1 (q), 130.9 (q), 129.6, 129.3, 127.9, 127.8, 127.4, 126.97, 126.88, 124.7, 54.8, 44.4, 14.4.

cis-**431**:

δ_H (400 MHz, $CDCl_3$): 7.87-7.81 (3 H, m, H-6, H-7 and H-10), 7.64 (1 H, bs, H-4), 7.56-7.51 (2 H, m, H-8 and H-9), 7.16 (1 H, d, *J* 8.4, H-5), 4.57 (1 H, d, *J* 10.2, H-3), 3.57-3.49 (1 H, dq, *J* 10.2, *J* 7.5, H-2), 1.02 (3 H, d, *J* 7.5, H-1).

δ_C (100 MHz, DMSO-d_6): 173.7 (C=O), 171.2 (C=O), 133.3 (q), 132.96 (q), 129.31 (q), 129.26, 128.2, 127.9, 127.8, 126.9, 126.89, 125.6, 51.5, 40.64, 12.0.

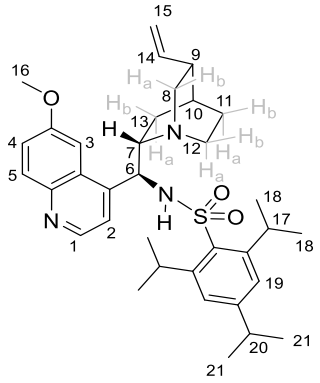
ν_{max} (neat)/cm^{-1}:* 1838, 1771, 1255, 1229, 1103, 993, 955, 925, 814, 760, 737.

HRMS (*m/z* - ESI):* Found: 263.0675 $(M+Na)^+$ $C_{15}H_{12}NaO_4$ Requires: 263.0678.

* Refers to mixture of *trans*-**431**:*cis*-**431** in the ratio 81:19.

4.4.2 Synthesis of catalysts: procedures

2,4,6-Triisopropyl-*N*-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)benzenesulfonamide (178)



A 50 mL round-bottomed flask containing a stirring bar was charged with quinine·3HCl salt (**279**, 900.0 mg, 2.08 mmol) and suspended in dry CH_2Cl_2 (20 mL). The solution was cooled to 0 °C and dry triethylamine (1.45 mL, 10.4 mmol) was added. To the resulting clear solution 2,4,6-triisopropyl-phenyl sulfonyl chloride (**390**, 629.8 mg, 2.08 mmol) was added portion wise as a solid. The reaction mixture was allowed to come back to room temperature and stirred overnight. After 16 h, the reaction was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were combined, washed successively with brine (30 mL), water (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product. The catalyst was purified by flash column chromatography eluting with 50% EtOAc in hexanes, to afford the product as a white solid (940.0 mg, 77%). M.p. 110-112 °C. TLC (hexanes:EtOAc, 50:50 *v/v*): R_f = 0.48.

Spectral data for this compound were consistent with those in the literature.[109]

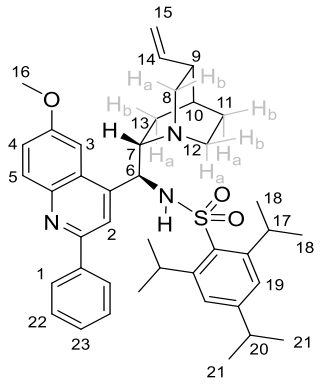
^1H and ^{13}C analysis showed the presence of two rotameric species in the ratio 78:22.

Major rotamer:

δ_H (400 MHz, DMSO-d_6): 8.51 (1 H, d, *J* 4.4, H-1), 7.90 (1 H, d, *J* 9.8, H-5), 7.49-7.41 (2 H, m, H-3 and H-4), 7.39 (1 H, d, *J* 4.4, H-2), 6.98 (2 H, s, H-19), 5.77-5.64 (1 H, m, H-14), 5.15 (1 H, d, *J* 10.5, H-6), 4.99-4.80 (2 H, m, H-15), 3.94 (3 H, s, H-16), 3.89-3.85 (3 H, m, H-9 and H-17), 3.12-3.00 (1 H, m, H-8a), 2.97-

2.74 (3 H, m, H-7, H-12a and H-20), 2.68-2.60 (1 H, m, H-8b), 2.50-2.39 (1 H, m, H-12b), 2.23-2.13 (1 H, m, H-10), 1.55-1.38 (3 H, m, H-11a, H-11b and H-13a), 1.18-1.06 (12 H, m, H-18), 0.86 (6 H, d, *J* 6.5, H-21), 0.76-0.71 (1 H, m, H-13b).

2,4,6-Triisopropyl-*N*-((*S*)-(6-methoxy-2-phenylquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)benzenesulfonamide (251)



A 50 mL round-bottomed flask containing a stirring bar was charged with *C*-2'-phenyl-9-amino-*epi*-quinine hydrochloride salt (**268**, 250.0 mg, 0.49 mmol) and suspended in dry CH_2Cl_2 (20 mL). The solution was cooled to 0 °C and dry triethylamine (0.31 mL, 2.21 mmol) was added. To the resulting clear solution 2,4,6-triisopropyl-phenyl sulfonyl chloride (**390**, 148.78 mg, 0.49 mmol) was added portion wise as a solid. The reaction was allowed to come back to room temperature and stirred overnight. After 16 h, the reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were combined, washed successively with brine (30 mL), water (30 mL), and dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product. The catalyst was purified by flash column chromatography eluting with the solvent system hexanes:EtOAc:Et_3N (80:15:5 *v*:*v*), to afford the product as a white solid (220.0 mg, 68%). M.p. 81-83 °C. TLC (hexanes:EtOAc:Et_3N, 80:18:2 *v/v*): R_f = 0.17; $[\alpha]_D^{20}$ = -10.4 (*c* = 0.5, $CHCl_3$).

^1H and ^{13}C analysis showed the presence of two rotameric species in the ratio 89:11.

Major rotamer:

δ_H (400 MHz, $CDCl_3$): 8.04 (1 H, d, *J* 9.2, H-5), 7.67 (2 H, d, *J* 6.9, H-1), 7.62 (1 H, s, H-2), 7.51 (1 H, s, H-3), 7.41-7.37 (4 H, m, H-4, H-22 and H-23), 6.87 (2 H, H-19), 5.67-5.58 (1 H, m, H-14), 5.43 (1 H, d, *J* 10.5, H-6), 4.94-4.87 (2 H, m, H-15), 4.02 (3 H, s, H-16), 3.83-3.74 (2 H, m, H-17), 3.3-3.24 (2 H, m, H-7 and H-8a), 2.85-2.72 (2 H, m, H-12a and H-20), 2.68-2.60 (2 H, m, H-9 and H-8b), 2.34-2.24 (1 H, m, H-12b), 1.71-1.61 (3 H, m, H-11a, H-11b and H-13a), 1.29-1.23 (2 H, m, H-10 and H-13b), 1.21-1.17 (4 H, m, H-18), 1.07-0.98 (8 H, m, H-18), 0.74 (6 H, d, *J* 6.6, H-21).

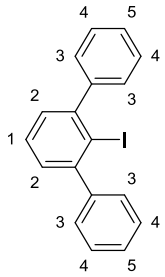
Major and minor rotamers:

δ_C (150.9 MHz, $CDCl_3$): 157.9 (q), 156.8 (q), 154.6 (q), 154.0 (q), 152.7 (q), 152.3 (q), 150.1 (q), 149.4 (q), 145.4 (q), 144.8 (q), 143.6 (q), 141.8 (q), 141.2, 141.1, 139.5 (q), 139.4 (q), 134.4 (q), 132.8 (q), 132.1, 132.0, 129.0, 128.8, 128.5, 127.5 (q), 127.3, 127.2, 126.0 (q), 123.4, 123.3, 121.5, 121.2, 120.6, 118.4, 114.7, 104.5, 101.4, 65.9, 62.5, 62.1, 56.6, 56.0, 55.9, 55.7, 55.6, 53.1, 40.4, 39.8, 39.7, 39.6, 34.0, 33.9, 29.9, 29.6, 28.0, 27.7, 27.6, 27.4, 26.9, 26.6, 25.2, 24.9, 24.7, 23.9, 23.5, 23.2, 15.3, 14.2.

ν_{max} (neat)/cm^{-1}: 2954, 2867, 1622, 1598, 1553, 1498, 1459, 1359, 1333, 1262, 1226, 1148, 1031, 882, 827, 776, 660.

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

2'-Iodo-1,1':3',1''-terphenyl (388)



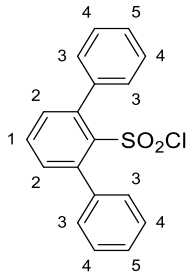
A 250 mL oven dried two-neck round-bottomed flask containing a stirring bar was placed under argon atmosphere (balloon) and charged with dry Et_2O (20 mL). To the solvent, a commercially available solution of PhLi (15.75 mL, 30 mmol: 1.9 M in Et_2O) was added carefully *via* syringe. The resulting solution was cooled to 0 °C and 1,3-dichlorobenzene (**387**, 0.85 mL, 7.5 mmol) was added dropwise to the mixture. The reaction mixture was allowed to come back to room temperature and stired for 16 h. The mixture was cooled to 0 °C (ice bath) and a solution of I_2 (5.7 g, 22.5 mmol) in dry THF (15 mL) was slowly added. The reaction mixture was allowed to come back to room temperature and an aqueous saturated solution of Na_2SO_3 was added to quench the excess of iodine until its characteristic colour disappeared. The organic phase was separated and the aqueous phase extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (15 mL), water (15 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford the crude product that was purified by recrystallisation from boiling MeOH affording the product in form of pale yellow needles (2.67 g, 45%).

Spectral data for this compound were consistent with those in the literature.[183]

δ_H (400 MHz, $CDCl_3$): 7.45-7.35 (12 H, m, H-2, H-3, H-4 and H-5), 7.25-7.24 (1 H, m, H-1).

HRMS (*m/z* - APCI): Found: 356.0061 $(M+H)^+$ $C_{18}H_{13}I$ Requires: 356.0056.

[1,1':3',1''-Terphenyl]-2'-sulfonyl chloride (389)



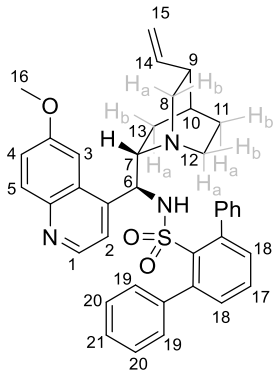
A 100 mL oven dried two-neck round-bottomed flask containing a stirring bar was charged with 2,6-diphenyliodobenzene (**388**, 0.3 g, 0.842 mmol) and dry Et_2O (10 mL). The mixture was placed under argon atmosphere (ballon), cooled to 0 °C (ice bath) and *n*-BuLi (0.53 mL, 0.842 mmol, 1.6 M in hexanes) was added dropwise. The mixture turned yellow and a white solid precipitated. After the mixture was stirred for 8 h at room temperature, the reaction mixture was cooled to -78 °C and freshly distilled sulfuryl chloride (0.136 mL, 1.68 mmol) was added slowly. The mixture was allowed to come back to room temperature and stirred overnight, cooled to 0 °C and poured into a solution of hydrochloric acid (1.5 M, ~ 20 mL). The mixture was diluted with water (20 mL) and the product extracted with Et_2O (3 x 30 mL). The organic layer was washed with brine (15 mL), water (15 mL), and dried over $MgSO_4$, filtered and the solvent was concentrate under reduced pressure to afford the crude product that was purified by recrystallisation from a mixture hexanes-$CHCl_3$ (1:1, *v*:*v*) affording the product as a pale yellow solid (0.171 g, 62%). TLC (hexanes:EtOAc, 95:5 *v/v*): R_f = 0.3.

Spectral data for this compound were consistent with those in the literature.[184]

δ_H (400 MHz, $CDCl_3$): 7.68 (1 H, app.t, H-1), 7.50-7.41 (12 H, m, H-2, H-3, H-4 and H-5).

HRMS (*m/z* - ESI): Found: 327.0249 $(M-H)^-$ $C_{18}H_{12}O_2SCl$ Requires: 327.0247.

_N_-((_S_)-(6-Methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)-[1,1':3',1''-terphenyl]-2'-sulfonamide (383)



A 25 mL round-bottomed flask containing a stirring bar was charged with quinine (190.4 mg, 0.589 mmol) and 2,6-diphenylbenzene sulfonyl chloride (**389**, 193.6 mg, 0.589 mmol) in CH_2Cl_2 (4 mL). The solution was cooled to 0 °C and 2 M NaOH (0.29 mL, 0.589 mmol) was added. The reaction mixture was allowed to come back to room temperature and stirred overnight. After 16 h, the reaction was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were combined, washed successively with brine (30 mL), water (30 mL), and dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product. The catalyst was purified by flash column chromatography, eluting in gradient from 100% hexanes to 50% EtOAc in hexanes, to afford the product as a white solid (342.3 mg, 94%). M.p. 88-90 °C. TLC (hexanes:EtOAc, 1:1 *v/v*): R_f = 0.18; $[\alpha]_D^{20}$ = -85.2 (*c* = 0.05, $CHCl_3$).

δ_H (600 MHz, $CDCl_3$): 8.41 (1 H, d, *J* 4.4, H-1), 7.98 (1 H, d, *J* 9.2, H-5), 7.39 (1 H, m, H-4), 7.39-7.19 (10 H, m, H-19, H-20 and H-21), 7.34 (1 H, t, *J* 7.8, H-17), 7.18 (1 H, bs, H-3), 7.07-7.06 (2 H, d, *J* 7.8, H-18), 6.91 (1 H, d, *J* 4.4, H-2), 5.67-5.59 (1 H, m, H-14), 4.93-4.90 (3 H, m, H-6 and H-15), 3.76 (3 H, s, H-16), 2.99-2.93 (1 H, m, H-7), 2.89-2.78 (1 H, m, H-8b), 2.52-2.32 (3 H, m, H-8a, H12a and H-12b), 2.20-2.11 (1 H, m, H-9), 1.53-1.30 (3 H, H-10, H11a and H11b), 1.18-1.12 (1 H, m, H13a), 0.59-0.54 (1 H, m, H-13b).

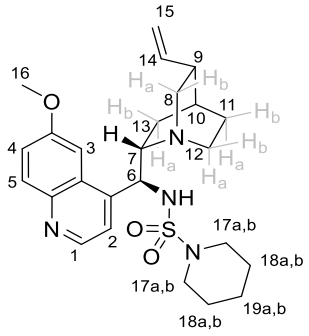
δ_C (150.9 MHz, $CDCl_3$): 157.9 (q), 146.6, 144.5 (q), 142.8 (q), 142.2 (q), 141.3, 141.0 (q), 139.4 (q), 131.4, 131.2, 130.0, 129.3 (q), 128.9

(q), 127.33, 127.27, 121.9, 119.4, 114.4, 101.6, 60.4, 55.56, 55.53, 52.9, 40.2, 39.4, 27.8, 27.2, 25.0.

ν_{max} (neat)/cm^{-1}: 2933, 1620, 1571, 1508, 1474, 1452, 1355, 1317, 1227, 1155, 1028, 909, 854, 808, 758, 748, 662, 592.

HRMS (*m/z* - ESI): Found: 616.2640 $(M+H)^+$ $C_{38}H_{38}N_3O_3S$ Requires: 616.2628.

_N_-((_S_)-(6-Methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)piperidine-1-sulfonamide (398)



A 25 mL round-bottomed flask containing a stirring bar was charged with quinine (300.0 mg, 0.927 mmol) in CH_2Cl_2 (5 mL). The solution was cooled to 0 °C and dry triethylamine (0.48 mL, 4.63 mmol) was added. To the resulting solution piperidine-1-sulfonyl chloride (**404**, 140.0 mg, 1.01 mmol) was added *via* syringe. The reaction mixture was allowed to come back to room temperature and stirred overnight. After 16 h, the reaction was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were combined, washed successively with brine (30 mL), water (30 mL), and dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product. The catalyst was purified by flash column chromatography, eluting in gradient from 2% CH_3OH in CH_2Cl_2 to 5% CH_3OH in CH_2Cl_2, to afford the product as a pale yellow solid (130.0 mg, 30%). M.p. 50-52 °C. TLC (CH_2Cl_2: CH_3OH, 95:5 *v/v*): R_f = 0.29; $[\alpha]_D^{20}$ = +36.8 (*c* = 0.05, $CHCl_3$).

^1H and ^{13}C analysis showed the presence of two rotameric species in the ratio 68:32.

Major rotamer only:

δ_H (600 MHz, $CDCl_3$): 8.81 (1 H, d, *J* 4.4, H-1), 8.05-8.02 (1 H, m, H-5), 7.57 (2 H, m, H-3 and H-4), 7.43-7.39 (1 H, m, H-2), 5.75-5.69 (1 H, m, H-14), 5.10 (1 H, d, *J* 10.8, H-6), 5.03-4.94 (2 H, m, H-15), 3.99 (3 H, s, H-16), 3.35-3.27 (1 H, m, H-9), 3.24-3.06 (1 H, m, H-8a), 2.88-2.77 (2 H, m, H-7 and H-12a), 2.71-2.60 (6 H, m, H-8b, H-12b and H-17), 2.39-2.31 (1 H, m, H-10), 1.73-1.64 (3 H, m, H-11a, H-11b and H-13a), 1.08-0.70 (6 H, m, H-18 and H-19), 0.67-0.63 (1 H, m, H-13b).

Major and minor rotamers:

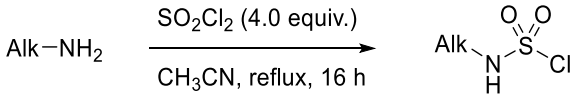
δ_C (151 MHz, $CDCl_3$): * 158.2 (q), 157.2 (q), 147.7, 147.2, 145.4 (q), 144.6 (q), 144.5 (q), 140.5 (q), 137.2, 132.1, 131.8, 129.3 (q), 127.2 (q), 123.8, 121.9, 121.7, 119.8, 115.1, 115.0, 103.2, 100.8, 63.2, 60.4, 56.1, 55.8, 55.7, 55.5, 52.9, 46.2, 46.1, 40.5, 40.0, 39.1, 27.5, 27.4, 27.3, 26.5, 25.3, 25.2, 24.4, 24.3, 23.1, 23.0.

ν_{max} (neat)/cm^{-1}: 2937, 2863, 1620, 1590, 1508, 1473, 1452, 1319, 1302, 1228, 1139, 1052, 1028, 988, 936, 854, 762, 709, 568.

HRMS (*m/z* - ESI): Found: 471.2423 $(M+H)^+$ $C_{25}H_{35}N_4O_3S$ Requires: 471.2424.

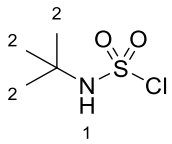
* The resonance of one carbon of the minor rotamer could not be identified in the spectrum.

General procedure VI: Synthesis of sulfamoyl chlorides for aliphatic substrates 400, 408



A 25 mL oven-dried two-neck round-bottomed flask containing a stirring bar was charged with the relevant amine (1.0 equiv.) in dry CH_3CN (10 mL per gram). To the resulting solution, sulfuryl chloride (SO_2Cl_2 ~ 4.0 equiv.) was carefully added, at 0 °C (ice bath cooled). The flask was then flushed with argon, fitted with a condenser and placed under an inert atmosphere (Ar, balloon). The reaction mixture was heated under reflux for 48 h, cooled to room temperature and, the excess of sulfuryl chloride was distilled off using a pump connected to a trap cooled with liquid nitrogen, the residue was diluted with dry CH_2Cl_2 and quickly filtered through a small plug of silica eluting with a mixture of 50% EtOAc in hexanes. The solvent was removed under reduced pressure affording the crude sulfamoyl chloride, immediately used into the next step, as a crude material, without any further purification.

***tert*-Butylsulfamoyl chloride (400)**



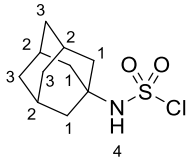
Prepared according to the general procedure VI, using *tert*-butylamine (**399**, 1.44 mL, 13.67 mmol), dry CH_3CN (4 mL) and SO_2Cl_2 (4 mL). The crude product was isolated as a yellow oil (0.941 mg, 40%). M.p. 20-22 °C (lit,[163] M.p. 23-24 °C). The product was used into the next step without further purification and stored under argon in a freezer.

Spectral data for this compound were consistent with those in the literature.[163]

δ_H (400 MHz, $CDCl_3$): 5.54 (1 H, bs, N-H, H-1), 1.47 (9 H, s, H-2).

δ_C (100 MHz, $CDCl_3$): 58.4 (q), 29.2.

(Adamantan-1-yl)sulfamoyl chloride (408)



Prepared according to the general procedure VI, using 1-adamantylamine (**407**, 1 g, 6.61 mmol), dry CH_3CN (5 mL) and SO_2Cl_2 (2.7 mL, 33.06 mmol). The crude product was isolated as a white solid (1.09 g, 66%). M.p. 100-104 °C (lit,[163] M.p. 104-106 °C). The product was used into the next step without further purification and was stored under argon in a freezer.

Spectral data for this compound were consistent with those in the literature.[163]

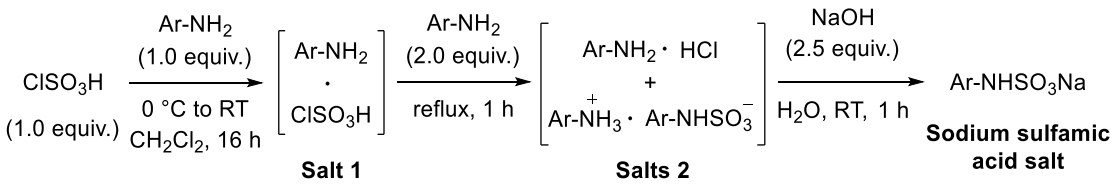
δ_H (400 MHz, $CDCl_3$): 5.45 (1 H, bs, N-H, H-4), 2.17 (3 H, app. s, H-2), 2.07 (6 H, m, H-1), 1.70 (6 H, m, H-3).

δ_C (100 MHz, $CDCl_3$): 58.9 (q), 41.9, 35.6, 29.5.

ν_{max} (neat)/cm^{-1}: 2993, 2923, 1403, 1362, 1348, 1319, 1275, 1244, 1169, 1080, 1049, 887, 617, 644, 617, 583.

HRMS (*m/z* - ESI): Found: 250.0665 $(M+H)^+$ $C_{10}H_{17}NO_2SCl$ Requires: 250.0669.

General procedure VII: Synthesis of sodium sulfamic acids 402, 410

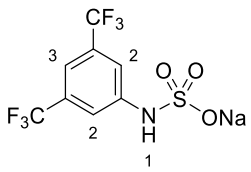


A 250 mL oven dried three-neck round-bottomed flask containing a stirring bar was carefully charged with chlorosulfonic acid (1.0 equiv.), fitted with a condenser, flushed with argon and placed under an inert atmosphere (argon, balloon). The flask was cooled to 0 °C (ice bath) and a solution of the relevant amine (1.0 equiv.), in dry CH_2Cl_2 (10 mL / 10 mmol of amine), was added dropwise *via* syringe. The mixture was allowed to come back to room temperature and stirred for 16 h. The chlorosulfonic salt (**Salt 1**) of the amine formed a suspension in the organic layer.

Over a 20-min period, a solution of the relevant amine (2.0 equiv.), in dry CH_2Cl_2 (10 mL / 10 mmol of amine), was added to the stirred suspension, at room temperature. After completion of the addition, the mixture was heated to reflux for 1 h. The **Salt 1** was converted to the mixture of **Salts 2**.

The reaction mixture xas cooled to room temperature and, an aqueous solution of sodium hydroxide (2.5 equiv.) was added. After 3 h of stirring, the sodium sulfamic acid salt was formed, the organic layer is separated from the aqueous layer and washed with water (3 x 30 mL). The water washes were added to the water layer and the combined water layers washed with CH_2Cl_2 (3 x 20 mL). The aqueous layers were concentrated under reduced pressure. The white residue was suspended in ethanol (100 mL for 30 mmol of starting material of amine), stirred at room temperature for 30 min, then refluxed for 10 min. The boiling solution was filtered and the volatiles were concentrated under reduced pressure to afford the appropriate sodium sulfamate salt that was used into the next step without further purifications.

Sodium (3,5-bis(trifluoromethyl)phenyl)sulfamate (402)

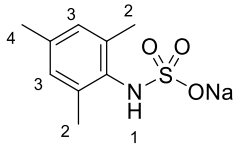


Prepared according to the general procedure VII, using 3,5-bis(trifluoromethyl)aniline (**401**, 3.3 g – 2.25 mL, 14.42 mmol, *i.e.* 3.0 equiv.), chlorosulfonic acid (0.56 g – 0.32 mL, 4.81 mmol, *i.e.* 1.0 equiv.) and sodium hydroxide (0.48 g, 12.02 mmol, *i.e.* 2.5 equiv.). The sodium sulfamic acid salt **402** was obtained as a white solid (1.5 g, 94%). M.p. > 200 °C, decomposition.

Spectral data for this compound were consistent with those in the literature.[160]

δ_H (400 MHz, DMSO-d_6): 7.59 (1 H, s, H-3), 7.25 (1 H, s, H-2), 6.99 (1 H, s, H-1).

Sodium mesitylsulfamate (410)



Prepared according to the general procedure VII, using 2,4,6-trimethylaniline (**409**, 12.2 g – 12.65 mL, 90.12 mmol, *i.e.* 3.0 equiv.), chlorosulfonic acid (3.5 g – 2.0 mL, 30.04 mmol, *i.e.* 1.0 equiv.) and sodium hydroxide (3.0 g, 75.1 mmol, *i.e.* 2.5 equiv.). When the aqueous layer was concentrated under reduced pressure, a white solid precipitated. The solid was filtered off, washed with cold water and dried under high vacuum to yield the sodium sulfamic acid salt as a white solid (4.4 g, 62%). M.p. 190-200 °C.

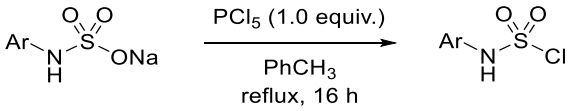
δ_H (400 MHz, DMSO-d_6): 6.70 (2 H, s, H-3), 5.85 (1 H, bs, H-1), 2.29 (6 H, s, H-2), 2.15 (3 H, s, H-4).

δ_C (100 MHz, DMSO-d_6): 137.2 (q), 136.2, 133.0 (q), 128.5, 20.8, 19.3.

ν_{max} (neat)/cm^{-1}: 3483, 3277, 1621, 1479, 1398, 1210, 1049, 880, 848, 815, 739, 689, 610.

HRMS (*m/z* - APCI): Found: 214.0534 $(M-Na)^-$ $C_9H_{12}NO_3S$ Requires: 214.0543.

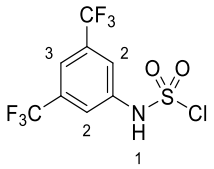
<u>General procedure VIII:</u> Synthesis of sulfamoyl chlorides for aromatic substrates 403, 411



A 25 mL oven dried round-bottomed flask containing a stirring bar was charged with the relevant sodium sulfamic acid salt (1.0 equiv.) in dry toluene (10 mL per gram). To the resulting suspension, phosphorus pentachloride (PCl_5, 1.0 equiv.) was added portion wise, at room temperature. The flask was then flushed with argon, fitted with a condenser and placed under an inert atmosphere (Ar, balloon). The reaction mixture was heated under reflux for 16 h, cooled to room temperature, filtered through a Celite pad and the filtrate was then concentrated *in vacuo* to provide almost pure material. The

sulfamoyl chlorides synthesised were immediately used in the next step, as crude material, without further purification.

(3,5-Bis(trifluoromethyl)phenyl)sulfamoyl chloride (403)

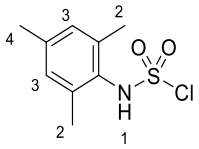


Prepared according to the general procedure VIII, using the sodium sulfamic acid salt of 3,5-bis(trifluoromethyl)aniline (**402**, 1.5 g, 4.53 mmol), phosphorus pentachloride (943 mg, 4.53 mmol) and dry toluene (15 mL). The sulfamoyl chloride was obtained as a brown residue that crystallised upon standing (701 mg, 47%).*

δ_H (400 MHz, $CDCl_3$): 8.08 (1 H, bs, H-1), 7.89 (1 H, s, H-3), 7.82 (2 H, s, H-2).

* Full analysis for this compound cannot be reported as the entire batch was immediately employed as a crude material, in the next reaction step, due to its assumed instability.

Mesitylsulfamoyl chloride (411)



Prepared according to the general procedure VIII, using the sodium sulfamic acid salt of the 2,4,6-trimethylaniline (**410**, 1.0 g, 4.21 mmol), phosphorus pentachloride (878.0 mg, 4.21 mmol) and dry toluene (10 mL). The reaction mixture was refluxed for 3 h. The sulfamoyl chloride was obtained as a crude pale-yellow residue that solidified upon standing (340 mg, 35%).*

δ_H (400 MHz, $CDCl_3$): 7.41 (1 H, bs, H-1), 6.95 (2 H, s, H-3), 2.41 (6 H, s, H-2), 2.29 (3 H, s, H-4).

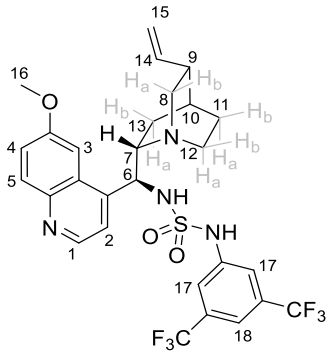
HRMS (*m/z* - APCI): Found: 232.0196 $(M-H)^-$ $C_9H_{11}ClNO_2S$ Requires: 232.0205.

* Full analysis for this compound cannot be reported as the entire batch was immediately employed as a crude material, in the next reaction step, due to its assumed instability.

General procedure IV: Synthesis of the sulfamide based catalysts 252-254, 405-406

A 25 mL oven-dried round-bottomed flask containing a stirring bar was charged with the relevant free amine of quinine (**279** or **268**, 1.0 equiv.) in dry CH_2Cl_2 (1 mL per 100 mg of quinine). The flask was flushed with argon and placed under an inert atmosphere (Ar, balloon). Freshly distilled triethylamine (2.0 equiv.) was added to the solution *via* syringe at room temperature. The solution was cooled to 0 °C and the relevant freshly synthesised crude sulfamoyl chloride (1.0 to 5.0 equiv.) was added portion wise, directly as a solid. The reaction was monitored by TLC chromatography. If required an excess of sulfamoyl chloride (up to 4 more equivalents) was added to the reaction mixture until TLC analysis indicated completed disappearance of the quinine starting material. After the reaction was judged complete, as indicated by TLC analysis, the reaction was diluted with water (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The organic extracts were combined, washed successively with brine (30 mL) and water (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product. The catalyst was purified by flash column chromatography, eluting in gradient with the conditions as indicated for each case, to afford the relevant sulfamide based catalyst.

_N_-((_S_)-(6-methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)-3,5-bis(trifluoromethyl)benzenesulfamide (252)



Prepared according to the general procedure IV, using the free amine of quinine (**279**, 306.0 mg, 0.94 mmol), Et_3N (0.26 mL, 1.9 mmol) and the sulfamoyl chloride **403** (461.0 mg, 1.41 mmol) in dry CH_2Cl_2 (4 mL). The catalyst was purified by flash column chromatography, eluting in gradient from 1% CH_3OH in CH_2Cl_2 to 5% CH_3OH in CH_2Cl_2, to afford the product as a white solid (220.3 mg, 38%). M.p. 120-122 °C. TLC (CH_2Cl_2:CH_3OH, 95:5 *v:v*): R_f = 0.18; $[\alpha]_D^{20}$ = +40.0 (*c* = 0.05, $CHCl_3$).

^1H, ^{13}C and ^{19}F analysis showed the presence of two rotameric species in the ratio 69:31.

Major rotamer:

δ_H (600 MHz, $CDCl_3$): 8.48 (1 H, d, *J* 4.3, H-1), 8.01 (1 H, d, *J* 9.2, H-5), 7.54 (1 H, s, H-3), 7.48 (1 H, s, H-18), 7.41 (1 H, d, *J* 9.2, H-4), 7.20 (1 H, s, H-17), 7.15-7.11 (1 H, m, H-2), 5.80-5.75 (1 H, m, H-14), 5.29 (1 H, d, *J* 11.5, H-6), 5.09-5.06 (2 H, m, H-15), 3.98 (3 H, s, H-16), 3.41-3.24 (2 H, m, H-7 and H-9), 2.92-2.81 (1 H, m, H-8a), 2.82-2.74 (1 H, m, H-8b), 2.47-2.39 (1 H, m, H-12a), 1.79-1.75 (1 H, m, H-12b), 1.73-1.52 (4 H, m, H-10, H-11a, H-11b and H-13a), 0.84-0.78 (1 H, m, H-13b).

Minor rotamer:

δ_H (600 MHz, $CDCl_3$): 8.61 (1 H, d, *J* 3.9, H-1), 7.86 (1 H, d, *J* 9.2, H-5), 7.27 (1 H, s, H-18), 7.26-7.24 (1 H, m, H-2), 7.22 (1 H, s, H-3),

7.16 (1 H, d, *J* 9.2, H-4), 6.84 (1 H, s, H-17), 5.61-5.55 (1 H, m, H-14), 4.49 (1 H, d, *J* 11.5, H-6), 4.95-4.87 (2 H, m, H-15), 3.63 (3 H, s, H-16), 3.38 (1 H, m, H-8a), 3.01-2.97 (2 H, m, H-7, H-8b), 2.77 (1 H, m, H-9), 2.35-2.28 (1 H, m, H-12a), 1.75-1.71 (1 H, m, H-12b), 1.34-1.22 (4 H, m, H-10, H-11a, H-11b and H-13b), 0.94-0.88 (1 H, m, H-13a).

Major and minor rotamers:

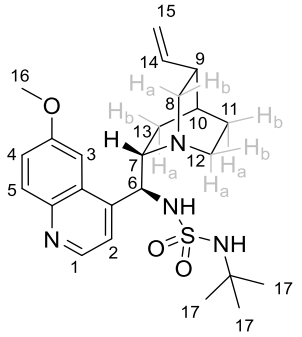
δ_C (150.9 MHz, $CDCl_3$): 158.7 (q), 156.8 (q), 147.1, 147.0, 144.8 (q), 144.6 (q), 141.1 (q), 140.8 (q), 140.1 (q), 139.5 (q), 139.1 (q), 138.4, 132.48 (q) (q, $^2J_{C\text{-}F}$ 32.6), 132.23 (q) (q, $^2J_{C\text{-}F}$ 33.3), 132.08, 131.87, 128.1, 128.09, 126.4, 125.6, 123.8, 123.78, 123.7, 122.7 (q) (q, $^1J_{C\text{-}F}$ 272.3), 122.2, 122.0, 121.0, 120.2, 119.2, 117.9, 116.6, 116.2, 115.6, 115.0, 102.9, 100.5, 63.1, 60.7, 55.9, 55.8, 55.7, 55.2, 55.1, 53.5, 40.8, 40.1, 39.3, 38.7, 27.4, 27.2, 27.1, 27.0, 26.2, 25.9.

δ_F (376.5 MHz, $CDCl_3$): -62.96 (minor), -63.08 (major).

ν_{max} (neat)/cm^{-1}: 3154, 2921, 1623, 1510, 1472, 1432, 1377, 1274, 1177, 1156, 1131, 982, 878, 693, 610.

HRMS (*m/z* - ESI): Found: 615.1876 $(M+H)^+$ $C_{28}H_{29}N_4O_3F_6S$ Requires: 315.1865.

_N_-((_S_)-(6-methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)-2-methylpropane-2-sulfamide (253)



Prepared according to the general procedure IV, using the free amine of quinine (**279**, 417.0 mg, 0.94 mmol), Et_3N (0.36 mL, 2.6 mmol) and the sulfamoyl chloride **400** (381.0 mg, 2.2 mmol) in dry CH_2Cl_2 (5 mL). The catalyst was purified by flash column chromatography, eluting in gradient from 1% CH_3OH in CH_2Cl_2 to 5% CH_3OH in CH_2Cl_2, to afford the product as a white solid (377.1 mg, 64%). M.p. 120-122 °C. TLC (CH_2Cl_2:CH_3OH, 95:5 *v:v*): R_f = 0.18; $[\alpha]_D^{20}$ = +151 (*c* = 0.05, $CHCl_3$).

^1H and ^{13}C analysis showed the presence of two rotameric species in the ratio 80:20.

Major rotamer:

δ_H (600 MHz, $CDCl_3$): 8.75 (1 H, d, *J* 4.5, H-1), 7.98 (1 H, d, *J* 9.2, H-5), 7.57 (1 H, s, H-3), 7.42-7.34 (2 H, m, H-2 and H-4), 5.77-5.71 (1 H, m, H-14), 5.17 (1 H, d, *J* 10.7, H-6), 5.04-4.96 (2 H, m, H-15), 4.72 (1 H, bs, N-H), 3.95 (3 H, s, H-16), 3.37-3.28 (1 H, m, H-7), 3.27-3.19 (1 H, m, H-8a), 3.16-3.03 (1 H, m, H-8b), 2.84-2.74 (2 H, m, H-12a and H-12b), 2.35-2.28 (1 H, m, H-9), 1.69-1.63 (1 H, m, H-10), 1.65-1.63 (2 H, m, H-11a and H-11b), 1.50-1.44 (1 H, m, H-13a), 1.00 (9 H, s, H-17), 1.01-0.94 (1 H, m, H-13b).

Minor rotamer:

δ_H (600 MHz, $CDCl_3$): 8.75 (1 H, d, *J* 4.5, H-1), 8.00 (1 H, d, *J* 9.7, H-5), 7.75 (1 H, bs, H-3), 7.42-7.34 (2 H, m, H-2 and H-4), 5.62-5.57 (1 H, m, H-14), 4.44 (1 H, d, *J* 10.9, H-6), 4.96-4.83 (2 H, m, H-15), 3.89 (3 H, s, H-16), 3.57-3.43 (1 H, m, H-7), 3.27-3.19 (1 H, m, H-8a), 3.16-3.03 (1 H, m, H-8b), 2.74-2.65 (2 H, m, H-12a and H-12b), 2.30-2.24 (1 H, m, H-9), 1.69-1.63 (1 H, m, H-10), 1.65-1.63 (2 H, m, H-11a and H-11b), 1.32-1.24 (1 H, m, H-13b), 0.84 (9 H, s, H-17), 0.78-0.72 (1 H, m, H-13a).

Major rotamer:

δ_C (150.9 MHz, $CDCl_3$): 158.3 (q), 147.3, 144.6 (q), 143.5 (q), 141.2, 131.7, 128.9 (q), 122.0, 119.6, 114.7, 101.0, 60.7, 55.9, 55.5, 53.8, 53.4, 40.5, 39.4, 29.6, 27.7, 27.3, 26.1.

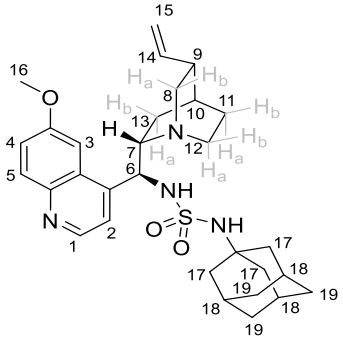
Minor rotamer:

δ_C (150.9 MHz, $CDCl_3$): 157.0 (q), 147.2, 145.2 (q), 144.5 (q), 141.3, 131.9, 127.1 (q), 123.9, 121.3, 114.6, 103.5, 63.2, 56.3, 55.9, 55.5, 54.1, 39.9, 39.7, 29.3, 27.7, 27.4, 26.5.

ν_{max} (neat)/cm^{-1}: 2941, 1618, 1475, 1435, 1299, 1239, 1227, 1083, 1057, 1016, 973, 857, 711, 660, 611.

HRMS (*m/z* - ESI): Found: 459.2430 $(M+H)^+$ $C_{24}H_{35}N_4O_3S$ Requires: 459.2430.

(3*R*,5*R*,7*R*)-*N*-((*S*)-(6-Methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)adamantane-1-sulfamide (254)



Prepared according to the general procedure IV, using the free amine of quinine (**279**, 372.0 mg, 1.15 mmol), Et_3N (0.31 mL, 2.3 mmol) and the sulfamoyl chloride **408** (574.0 mg, 2.3 mmol) in dry CH_2Cl_2 (4 mL). The catalyst was purified by flash column chromatography, eluting in gradient from 1% CH_3OH in CH_2Cl_2 to 5% CH_3OH in CH_2Cl_2, to afford the product as a white solid (252.0 mg, 41%). M.p. 118-120 °C. TLC (CH_2Cl_2:CH_3OH, 95:5 *v:v*): R_f = 0.21; $[\alpha]_D^{20}$ = +30 (*c* = 0.05, $CHCl_3$).

^1H and ^{13}C analysis showed the presence of two rotameric species in the ratio 77:23.

Major rotamer:

δ_H (600 MHz, $CDCl_3$): 8.78 (1 H, d, *J* 4.4, H-1), 8.02 (1 H, d, *J* 9.2, H-5), 7.62 (1 H, s, H-3), 7.44 (1 H, d, *J* 4.4, H-2), 7.42-7.36 (1 H, m, H-4), 5.83-5.75 (1 H, m, H-14), 5.21 (1 H, d, *J* 10.8, H-6), 5.05-5.01 (2 H, m, H-15), 3.98 (3 H, s, H-16), 3.40-3.32 (1 H, m, H-7), 3.30-3.23 (1 H, m, H-8a), 3.19-3.08 (1 H, m, H-8b), 2.87-2.77 (2 H, m, H-12a and H-12b), 2.38-2.32 (1 H, m, H-9), 1.97-1.91 (3 H, m, H-10, H-11a and H-11b), 1.74-1.22 (15 H, m, H-17, H-18 and H-19), 0.89-0.82 (1 H, m, H-13a), 0.80-0.75 (1 H, m, H-13b).

Minor rotamer:

δ_H (600 MHz, $CDCl_3$): 8.67 (1 H, d, *J* 3.6, H-1), 8.05 (1 H, d, *J* 9.3, H-5), 7.79 (1 H, s, H-3), 7.29 (1 H, d, *J* 3.6, H-2), 7.42-7.36 (1 H, m, H-4), 5.68-5.60 (1 H, m, H-14), 4.97-4.89 (2 H, m, H-15), 4.48 (1 H, d, *J* 10.9, H-6), 3.92 (3 H, s, H-16), 3.59-3.45 (1 H, m, H-7), 3.51-3.46 (1 H, m, H-8a), 3.19-3.08 (1 H, m, H-8b), 2.77-2.68 (2 H, m, H-12a and H-12b), 2.32-2.27 (1 H, m, H-9), 1.84-1.78 (3 H, m, H-10, H-11a and H-11b), 1.74-1.22 (15 H, m, H-17, H-18 and H-19), 1.57-1.50 (1 H, m, H-13a), 1.31-1.28 (1 H, m, H-13b).

Major rotamer:

δ_C (150.9 MHz, $CDCl_3$): 158.4 (q), 147.4, 144.7 (q), 141.0 (q), 131.8, 129.0 (q), 122.1, 119.8, 114.9, 101.1, 60.6, 55.8, 55.6, 54.4, 53.4, 42.6, 40.7 (q), 39.3, 35.9, 34.7, 29.7, 29.5, 27.6, 27.4, 26.1.

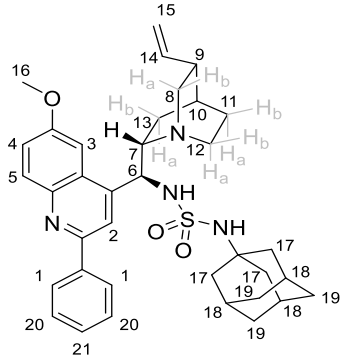
Minor rotamer:

δ_C (150.9 MHz, $CDCl_3$): 157.1 (q), 147.3, 143.5 (q), 141.3 (q), 132.1, 127.2 (q), 124.2, 121.3, 114.7, 103.9, 63.3, 56.3, 56.0, 54.6, 42.2, 40.1 (q), 39.7, 35.8, 34.5, 31.6, 29.3, 27.7, 27.5, 26.9, 26.6.

ν_{max} (neat)/cm^{-1}: 2904, 2848, 1620, 1508, 1453, 1358, 1308, 1229, 1150, 1087, 988, 911, 852, 824, 582, 569.

HRMS (*m/z* - ESI): Found: 537.2891 $(M+H)^+$ $C_{30}H_{41}N_4O_3S$ Requires: 537.2899.

(3*R*,5*R*,7*R*)-*N*-((*S*)-(6-Methoxy-2-phenylquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)adamantane-1-sulfonamide (405)



Prepared according to the general procedure IV, using the *C*-2 arylated free amine of quinine (**268**, 85.0 mg, 0.21 mmol), Et_3N (57 μL, 0.43 mmol) and the sulfamoyl chloride **408** (106.0 mg, 0.43 mmol) in dry CH_2Cl_2 (2 mL). The catalyst was purified by flash column chromatography, eluting in gradient from 1% CH_3OH in CH_2Cl_2 to 5% CH_3OH in CH_2Cl_2, to afford the product as a white solid (75.4 mg, 57%). M.p. 54-56 °C. TLC (CH_2Cl_2:CH_3OH, 95:5 *v:v*): R_f = 0.34; $[\alpha]_D^{20}$ = +280 (*c* = 0.102, $CHCl_3$).

^1H and ^{13}C analysis showed the presence of two rotameric species in the ratio 76:24.

Major rotamer:

δ_H (600 MHz, $CDCl_3$): 8.15 (2 H, d, *J* 7.8, H-1), 8.11 (1 H, d, *J* 9.3, H-5), 7.97 (1 H, s, H-3), 7.61 (1 H, bs, H-2), 7.61-7.38 (4 H, m, H-4, H-20 and H-21), 5.79-5.74 (1 H, m, H-14),5.24 (1 H, d, *J* 10.8, H-6), 5.03-4.97 (2 H, m, H-15), 4.00 (3 H, s, H-16), 3.39-3.37 (1 H, m, H-7), 3.30-3.26 (1 H, m, H-8a), 3.17-3.16 (1 H, m, H-8b), 2.83-2.78 (2 H, m, H-12a and H-12b), 2.34-2.25 (1 H, m, H-9), 1.85-1.83 (1 H, m, H-10), 1.69-0.82 (13 H, m, H-11a, H-11b, H-13a, H-13b and H-17).

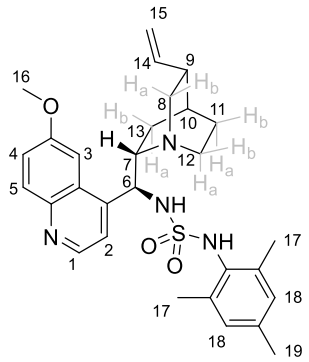
Major and minor rotamers:

δ_C (150.9 MHz, $CDCl_3$): 158.2 (q), 157.0 (q), 154.4 (q), 152.4 (q), 145.4 (q), 144.7 (q), 144.4 (q), 144.0 (q), 141.3 (q), 141.0 (q), 139.5 (q), 139.2 (q), 132.3, 132.1, 129.1, 128.9, 128.8, 128.0, 127.2, 127.1, 122.1, 122.0, 121.4, 117.9, 114.8, 114.7, 103.8, 100.9, 63.7, 60.6, 56.2, 55.9, 55.7, 55.6, 55.5, 54.5, 54.5, 53.6, 42.3, 42.1, 40.5 (q), 39.4 (q), 35.8, 35.7, 32.8, 31.9, 29.7, 29.6, 29.3, 29.3, 27.7, 27.4, 22.7, 14.1.

ν_{max} (neat)/cm^{-1}: 2919, 2848, 1622, 1600, 1497, 1450, 1358, 1308, 1229, 1149, 1084, 990, 897, 829, 693, 577, 555.

HRMS (*m/z* - ESI): Found: 613.3212 $(M+H)^+$ $C_{36}H_{45}N_4O_3S$ Requires: 613.3212.

_N_-((_S_)-(6-Methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)-2,4,6-trimethylbenzenesulfonamide (406)



Prepared according to the general procedure IV, using the free amine of quinine (**279**, 282.0 mg, 0.87 mmol), Et_3N (0.24 mL, 1.74 mmol) and the sulfamoyl chloride **411** (305.0 mg, 1.3 mmol) in dry CH_2Cl_2 (3 mL). The catalyst was purified by flash column chromatography, eluting in gradient from 1% CH_3OH in CH_2Cl_2 to 5% CH_3OH in CH_2Cl_2, to afford the product as a white solid (194.4 mg, 43%). M.p. 88-90 °C. TLC (EtOAc:CH_3OH, 95:5 *v:v*): R_f = 0.28; $[\alpha]_D^{20}$ = +16.8 (*c* = 0.05, $CHCl_3$).

^1H and ^{13}C analysis showed the presence of two rotameric species in the ratio 98:2.

Major rotamer:

δ_H (600 MHz, $CDCl_3$): 8.66 (1 H, d, *J* 4.2, H-1), 7.99 (1 H, d, *J* 9.2, H-5), 7.57 (1 H, bs, H-3), 7.37 (1 H, d, *J* 9.2, H-4), 7.25 (1 H, m, H-2), 6.75 (2 H, bs, H-18), 5.87-5.76 (1 H, m, H-14), 5.37 (1 H, d, *J* 10.8, H-6), 5.10-5.00 (2 H, m, H-15), 3.98 (3 H, s, H-16), 3.55-3.42 (1 H, m, H-7), 3.31-3.14 (2 H, m, H-8a, and H-9), 2.90-2.83 (1 H, m, H-8b), 2.40-2.31 (1 H, m, H-12a), 2.25 (6 H, s, H-17), 2.20 (3 H, s, H-19), 2.13-2.05 (1 H, m, H-12b), 1.75-1.70 (1 H, m, H-10), 1.68-1.54 (3 H, m, H-11a, H-11b and H-13a), 0.87-0.78 (1 H, m, H-13b).

Major rotamer:

δ_C (150.9 MHz, $CDCl_3$): 158.3 (q), 147.3, 144.7 (q), 142.8 (q), 141.0, 136.9 (q), 136.4, 131.6, 131.2 (q), 129.2, 128.4 (q), 122.2, 118.9, 115.0, 101.2, 61.2, 55.8, 54.3, 41.0, 39.3, 27.6, 27.3, 26.6, 20.8, 19.1, 17.6.

ν_{max} (neat)/cm^{-1}: 2919, 1620, 1508, 1474, 1310, 1227, 1143, 1029, 988, 911, 851, 828, 713, 610.

HRMS (*m/z* - APCI): Found: 519.2444 $(M-H)^-$ $C_{29}H_{35}N_4O_3S$ Requires: 519.2435.

4.4.3 Synthesis of racemic lactones

Racemic preparation of lactones 368a, 425-427, 436-439

An oven-dried 5 mL reaction vessel containing a magnetic stirring bar under argon atmosphere was charged with the relevant anhydride (0.1 mmol). Anhydrous MTBE or THF (1.0 mL, 0.1 M) was added *via* syringe followed by recrystallized 4-nitro-benzaldehyde aldehyde (**244**, 0.1 mmol). *N*,*N*-diisopropylethylamine (3.6 μL, 20.0 μmol - 20 mol%) was added *via* syringe and the resulting mixture was stired for 48 h at room temperature. To the reaction mixture containing the corresponding crude carboxylic acids, anhydrous MeOH (202.3 μL, 5.0 mmol), followed by trimethylsilyldiazomethane

(2.0 M solution in diethyl ether, 60 μL, 0.12 mmol) were added *via* syringe and the reaction mixture was stired for 15 min at 0 °C. The solvent was then removed *in vacuo* and the crude mixture of diastereomeric esters was purified by flash column chromatography, eluting in gradient from 100% hexanes to 30% EtOAc in hexanes to isolate all of the 4 diastereomers combined. A sample of the purified diastereomer, isolated after column chromatography, was then re-purified by preparative TLC chromatography to produce racemic material for HPLC traces analysis.

4.4.4 Catalyst evaluation (general procedures)

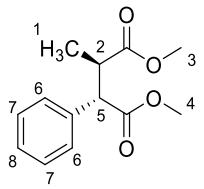
General procedure X: Evaluation of the substrate scope with respect to the anhydride component and derivatisation procedure for the determination of the enantiomeric excess of the recovered starting materials 367, 422-424, 432-435.

A 10-25 mL two-neck oven-dried round-bottomed flask containing a magnetic stirring bar was charged with the relevant anhydride (0.1 mmol), recrystallised 4-nitrobenzaldehyde (0.5-0.7 equiv.) followed by the catalyst **254** (5-10 mol%). The air was evacuated from the reaction vessel by placing the reaction flask under vacuum and backfilling several times with argon before being placed under an argon atmosphere (balloon). Methyl *tert*-butyl ether (0.1 M) was added *via* syringe to the reaction vessel. The resulting mixture was stired, at the temperature and, for the time as indicated in each specific case. The enantiomeric excesses of the unreacted starting materials were determined by CSP-HPLC after derivatisation of the anhydrides following the procedure as follow: the conversion of the reaction was determined by ^{1}H NMR spectroscopy using 4-iodoanisole (0.5-0.7 equiv.) as an internal standard and the reaction was immediately quenched by adding to the reaction mixture, *via* syringe, hplc grade MeOH (200 equiv.). The reaction was stired for 2 h, at room temperature, after which time the starting material anhydrides have been determined to be fully converted to the corresponding methyl hemiester opened form. The reaction mixture containing both hemiester and the crude mixture of carboxylic acid lactones products was cooled to 0 °C, followed by the addition *via* syringe of trimethylsilyldiazomethane (1.2 equiv., 2 M solution in Et_2O). The reaction mixture was stired for 15 min at 0 °C. The excess of

solvent was removed under reduced pressure and the crude residue was immediately subjected to flash column chromatography to isolate unreacted starting material (as its open *bis*-methyl ester derivative) and the major lactone diastereomer, eluting the mixture in gradient from 100% hexanes to 20% EtOAc in hexanes.

4.4.5 Experimental procedures and data for succinates and lactones

Dimethyl (2*R*,3*S*)-2-methyl-3-phenylsuccinate (367)



Prepared according to general procedure X, using anhydride **366** (100.0 mg, 0.525 mmol), recrystallized 4-nitrobenzaldehyde (**244**, 39.7 mg, 0.263 mmol), 4-iodoanisole (61.5 mg, 0.263 mmol) and the catalyst **254** (14.1 mg, 0.026 mmol – 5 mol%) in dry MTBE (5.25 mL – 0.1 M). The reaction was stired for 168 h, quenched with MeOH (4.25 mL, 105.1 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (315 μL, 0.631 mmol) the unreacted starting material (**367**) was isolated by flash column chromatography (as its open *bis*-methyl ester opened form) as a colourless liquid (47.4 mg, 37%). TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.31; $[\alpha]_D^{20}$ = +118.6 (*c* = 0.07, $CHCl_3$).

trans-**367**:

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/*i*-PrOH: 95/5, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: 11.71 min (minor enantiomer) and 12.72 min (major enantiomer).

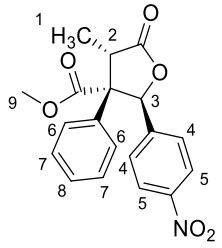
δ_H (400 MHz, $CDCl_3$): 7.34-7.24 (5 H, m, H-6, H-7 and H-8), 3.77 (1 H, d, *J* 11.3, H-5), 3.72 (3 H, s, H-3), 3.62 (3 H, s, H-4), 3.21-3.13 (1 H, dq, *J* 11.3, *J* 7.3, H-2), 0.95 (3 H, d, *J* 7.3, H-1).

δ_C (100 MHz, $CDCl_3$): 176.2 (C=O), 173.7 (C=O), 136.3 (q), 128.9, 128.4, 127.8, 54.1, 52.2, 52.0, 42.3, 15.4.

ν_{max} (neat)/cm^{-1}: 2953, 1730 (C=O), 1455, 1435, 1319, 1277, 1240, 1192, 1161, 1059, 1005, 735, 700.

HRMS (*m/z* - ESI): Found: 259.0944 $(M+Na)^+$ $C_{13}H_{16}NaO_4$ Requires: 259.0940.

Methyl (2*S*,3*S*,4*S*)-4-methyl-2-(4-nitrophenyl)-5-oxo-3-phenyltetrahydrofuran-3-carboxylate (368a)



Prepared according to general procedure X, using anhydride **S03** (100.0 mg, 0.525 mmol), recrystallized 4-nitrobenzaldehyde (**244**, 39.7 mg, 0.263 mmol), 4-iodoanisole (61.5 mg, 0.263 mmol) and the catalyst **254** (14.1 mg, 0.026 mmol – 5 mol%) in dry MTBE (5.25 mL – 0.1 M). The reaction was stired for 168 h to give a diastereomeric mixture of carboxylic acid lactones in a 95:5 (*major*:*others*) ratio, quenched with MeOH (4.25 mL, 105.1 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (125.2 μL, 0.250 mmol) the major diastereomer (**368a**) was isolated by flash column chromatography as a white solid (75.2 mg, 40%). TLC (hexanes:EtOAc, 70:30 *v/v*): R_f = 0.39; $[\alpha]_D^{20}$ = +19.2 (*c* = 0.238, $CHCl_3$).

CSP-HPLC analysis. Chiralcel ODH (4.6 mm x 25 cm), hexane/*i*-PrOH: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 19.88 min (major enantiomer) and 29.75 min (minor enantiomer).

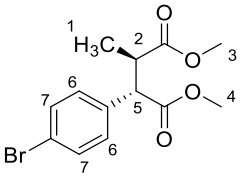
δ_H (400 MHz, $CDCl_3$): 7.90 (2 H, d, *J* 8.8, H-5), 7.20-7.07 (5 H, m, H-6, H-7 and H-8), 6.66 (2 H, d, *J* 8.8, H-4), 6.34 (1 H, s, H-3), 3.79 (3 H, s, H-9), 3.48 (1 H, q, *J* 7.6, H-2), 1.52 (3 H, d, *J* 7.6, H-1).

δ_C (100 MHz, $CDCl_3$): 176.8 (C=O), 171.8 (C=O), 147.6 (q), 141.9 (q), 135.3 (q), 128.6, 128.4, 127.7, 126.8, 122.7, 82.2, 64.0 (q), 52.8, 43.8, 13.2.

ν_{max} (neat)/cm^{-1}: 2935, 1781, 1730, 1603, 1521, 1436, 1346, 1315, 1272, 1250, 1221, 1174, 1043, 1021, 979, 861, 838, 718, 691.

HRMS (*m/z* - ESI): Found: 354.0975 $(M-H)^-$ $C_{19}H_{16}NO_6$ Requires: 354.0978.

Dimethyl (2*S*,3*R*)-2-(4-bromophenyl)-3-methylsuccinate (422)



Prepared according to general procedure X, using anhydride **412** (107.6 mg, 0.4 mmol), recrystallized 4-nitrobenzaldehyde (**244**, 42.3 mg, 0.280 mmol), 4-iodoanisole (65.5 mg, 0.280 mmol) and the catalyst **254** (10.7 mg, 0.02 mmol – 5 mol%) in dry MTBE (4.0 mL – 0.1 M). The reaction was stired for 3 days, quenched with MeOH (3.24 mL, 80.0 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (240 μL, 0.480 mmol) the unreacted starting material (*trans*-**422**) was isolated by flash column chromatography (as its open *bis*-methyl ester opened form) as a colourless liquid (38.6 mg, 31%). TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.25; $[\alpha]_D^{20}$ = +59.5 (*c* = 0.04, $CHCl_3$).

trans-**422**:

HPLC analysis. ACQUITY UPC^2 Trefoil CEL2, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:CH_3CN (1:1, *v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 230 nm, retention times: 1.46 min (minor enantiomer) and 3.15 min (major enantiomer).

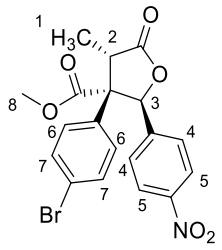
δ_H (400 MHz, $CDCl_3$): 7.46 (2 H, d, *J* 8.4, H-7), 7.14 (2 H, d, *J* 8.4, H-6), 3.74 (1 H, d, *J* 11.3, H-5), 3.72 (3 H, s, H-3), 3.62 (3 H, s, H-4), 3.17-3.09 (1 H, dq, *J* 11.3, *J* 7.3, H-2), 0.95 (3 H, d, *J* 7.3, H-1).

δ_C (100 MHz, $CDCl_3$): 175.8 (C=O), 173.2 (C=O), 135.3 (q), 132.0, 130.1, 121.8, 53.6, 52.3, 52.1, 42.2, 15.3.

ν_{max} (neat)/cm^{-1}: 2952, 1729 (C=O), 1488, 1434, 1312, 1273, 1238, 1193, 1161, 1072, 1009, 822, 769.

HRMS (*m/z* - ESI): Found: 337.0033 $(M+Na)^+$ $C_{13}H_{15}BrNaO_4$ Requires: 337.0045.

Methyl (2*S*,3*S*,4*S*)-3-(4-bromophenyl)-4-methyl-2-(4-nitrophenyl)-5-oxotetrahydrofuran-3-carboxylate (425)



Prepared according to general procedure X, using anhydride **412** (107.6 mg, 0.4 mmol), recrystallized 4-nitrobenzaldehyde (**244**, 42.3 mg, 0.280 mmol), 4-iodoanisole (65.5 mg, 0.280 mmol) and the catalyst **254** (10.7 mg, 0.02 mmol – 5 mol%) in dry MTBE (4.0 mL – 0.1 M). The reaction was stired for 3 days to give a diastereomeric mixture of carboxylic acid lactones in a 87.5:12.5 (*major*:*others*) ratio, quenched with MeOH (3.24 mL, 80.0 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (240 μL, 0.480 mmol) the major diastereomer (**425**) was isolated by flash column chromatography as a white solid (75.2 mg, 39%). TLC (hexanes:EtOAc, 70:30 *v/v*): R_f = 0.44; $[\alpha]_D^{20}$ = +21.1 (*c* = 0.189, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CEL2, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:CH_3CN (1:1, *v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 230 nm, retention times: 3.37 min (major enantiomer) and 3.60 min (minor enantiomer).

δ_H (400 MHz, $CDCl_3$): 7.98 (2 H, d, *J* 8.8, H-5), 7.26 (2 H, d, *J* 8.6, H-7), 7.22 (2 H, d, *J* 8.8, H-4), 6.54 (2 H, d, *J* 8.6, H-6), 6.33 (1 H, s, H-

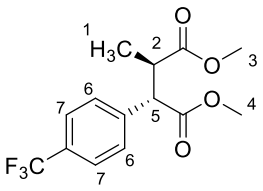
3), 3.79 (3 H, s, H-8), 3.42 (1 H, q, *J* 7.5, H-2), 1.51 (3 H, d, *J* 7.5, H-1).

δ_C (100 MHz, $CDCl_3$): 176.3 (C=O), 171.3 (C=O), 147.7 (q), 141.5 (q), 134.4 (q), 131.7, 128.5, 127.7, 122.9, 122.7 (q), 81.8, 63.7 (q), 52.9, 43.8, 13.2.

ν_{max} (neat)/cm^{-1}: 2920, 1776, 1731, 1605, 1517 1493, 1452, 1344, 1208, 1170, 1025, 1010, 857, 829, 780, 730, 695.

HRMS (*m/z* - APCI): Found: 432.0098 $(M-H)^-$ $C_{19}H_{15}BrNO_6$ Requires: 432.0088.

Dimethyl (2*R*,3*S*)-2-methyl-3-(4-(trifluoromethyl)phenyl)succinate (423)



Prepared according to general procedure X, using anhydride **413** (103.3 mg, 0.4 mmol), recrystallized 4-nitrobenzaldehyde (**244**, 42.3 mg, 0.280 mmol), 4-iodoanisole (65.5 mg, 0.280 mmol) and the catalyst **254** (10.7 mg, 0.02 mmol – 5 mol%) in dry MTBE (4.0 mL – 0.1 M). The reaction was stired for 2 days, quenched with MeOH (3.24 mL, 80.0 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (240 μL, 0.480 mmol) the unreacted starting material (*trans*-**423**) was isolated by flash column chromatography (as its open *bis*-methyl ester opened form) as a colourless liquid (42.3 mg, 35%). TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.28 (*trans*), R_f = 0.36 (*cis*); $[\alpha]_D^{20}$ = +150 (*c* = 0.05, $CHCl_3$).

trans-**423**:

CSP-HPLC analysis. Chiralpak IA (4.6 mm x 25 cm), hexane/*i*-PrOH: 95/5, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: 12.35 min (minor enantiomer) and 14.50 min (major enantiomer).

δ_H (400 MHz, $CDCl_3$): 7.60 (2 H, d, *J* 8.1, H-7), 7.39 (2 H, d, *J* 8.1, H-6), 3.86 (1 H, d, *J* 11.2, H-5), 3.73 (3 H, s, H-3), 3.64 (3 H, s, H-4), 3.23-3.15 (1 H, dq, *J* 7.3, *J* 11.3, H-2), 0.96 (3 H, d, *J* 7.3, H-1).

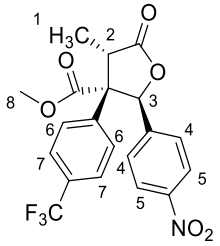
δ_C (100 MHz, $CDCl_3$): 175.7 (C=O), 173.0 (C=O), 140.3 (q), 130.1 (q) (q, ^2J 32.4 Hz), 128.9, 125.8 (q, ^3J 3.5 Hz), 123.9 (q) (q, ^1J 272.1 Hz), 53.9, 52.4, 52.1, 42.2, 15.3.

δ_F (376.5 MHz, $CDCl_3$): - 62.69.

ν_{max} (neat)/cm^{-1}: 2956, 1732 (C=O), 1619, 1459, 1436, 1421, 1322, 1278, 1244, 1161, 1122, 1066, 1018, 836, 602.

HRMS (*m/z* - APCI): Found: 305.0985 $(M+H)^+$ $C_{14}H_{16}F_3O_4$ Requires: 305.0995.

Methyl (2*S*,3*S*,4*S*)-4-methyl-2-(4-nitrophenyl)-5-oxo-3-(4-(trifluoromethyl)phenyl) tetrahydrofuran-3-carboxylate (426)



Prepared according to general procedure X, using anhydride **413** (103.3 mg, 0.4 mmol), recrystallized 4-nitrobenzaldehyde (**244**, 42.3 mg, 0.280 mmol), 4-iodoanisole (65.5 mg, 0.280 mmol) and the catalyst **254** (10.7 mg, 0.02 mmol – 5 mol%) in dry MTBE (4.0 mL – 0.1 M). The reaction was stired for 2 days to give a diastereomeric mixture of carboxylic acid lactones in a 83:17 (*major*:*others*) ratio, quenched with MeOH (3.24 mL, 80.0 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (240 μL, 0.480 mmol) the major diastereomer (**426**) was isolated by flash column chromatography as a white solid (72.5 mg, 43%). TLC (hexanes:EtOAc, 70:30 *v/v*): R_f = 0.41; $[\alpha]_D^{20}$ = +24.5 (*c* = 0.268, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CEL2, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:CH_3CN (1:1, *v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 254 nm, retention times: 2.46 min (major enantiomer) and 2.69 min (minor enantiomer).

δ_H (400 MHz, $CDCl_3$): 7.95 (2 H, d, *J* 8.8, H-5), 7.39 (2 H, d, *J* 8.4, H-7), 7.21 (2 H, d, *J* 8.8, H-4), .39 (2 H, d, *J* 8.4, H-6), 6.37 (1 H, s, H-3), 3.81 (3 H, s, H-8), 3.48 (1 H, q, *J* 7.5, H-2), 1.54 (3 H, d, *J* 7.5, H-1).

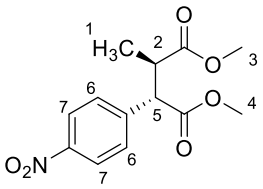
δ_C (100 MHz, $CDCl_3$): 176.1 (C=O), 171.1 (C=O), 147.8 (q), 141.3 (q), 139.4 (q), 130.7 (q) (q, ^2J 32.6 Hz), 127.6, 127.4, 125.5 (q, ^3J 3.6 Hz), 123.4 (q) (q, ^1J 272.5 Hz), 81.8, 64.0 (q), 53.1, 43.8.

δ_F (376.5 MHz, $CDCl_3$): - 62.91.

ν_{max} (neat)/cm^{-1}: 2956, 1786, 1735, 1608, 1522, 1349, 1325, 1220, 1168, 1125, 1069, 1026, 1014, 859, 751, 713.

HRMS (*m/z* - ESI): Found: 422.0872 $(M-H)^-$ $C20H15F_3NO_6$ Requires: 422.0856.

Dimethyl (2*R*,3*S*)-2-methyl-3-(4-nitrophenyl)succinate (424)



Prepared according to general procedure X, using anhydride **414** (30.5 mg, 0.129 mmol), recrystallized 4-nitrobenzaldehyde (**244**, 13.7 mg, 0.091 mmol), 4-iodoanisole (21.2 mg, 0.091 mmol) and the catalyst **254** (3.5 mg, 0.0068 mmol – 5 mol%) in dry MTBE (1.3 mL – 0.1 M). The reaction was stired for 1 day, quenched with MeOH (1.05 mL, 25.94 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (78 µL, 0.155 mmol) the unreacted starting material (*trans*-**424**) was isolated by flash column chromatography (as its open

bis-methyl ester opened form) as a colourless liquid (12.3 mg, 34%). TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.16; $[\alpha]_D^{20}$ = +52.7 (*c* = 0.03, $CHCl_3$).

trans-**424**:

CSP-HPLC analysis. Chiralcel ODH (4.6 mm x 25 cm), hexane/*i*-PrOH: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 17.21 min (minor enantiomer) and 19.36 min (major enantiomer).

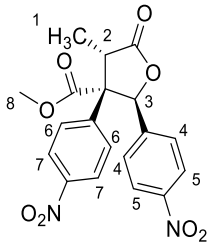
δ_H (400 MHz, $CDCl_3$): 8.16 (2 H, d, *J* 8.8, H-7), 7.52 (2 H, d, *J* 8.8, H-6), 3.93 (1 H, d, *J* 10.9, H-5), 3.69 (3 H, s, H-3), 3.45 (3 H, s, H-4), 3.31-3.23 (1 H, dq, *J* 10.9, *J* 6.9, H-2), 1.32 (3 H, d, *J* 6.9, H-1).

δ_C (100 MHz, $CDCl_3$): 173.9 (C=O), 171.6 (C=O), 143.98 (q), 130.3 (q), 129.4, 123.7, 54.4, 52.6, 51.8, 43.6, 16.5.

ν_{max} (neat)/cm^{-1}: 2967, 1727 (C=O), 1596, 1517, 1454, 1438, 1346, 1318, 1291, 1197, 1153, 1107, 1057, 1001, 973, 860, 737, 691.

HRMS (*m/z* - ESI): Found: 304.0781 $(M+H)^+$ $C_{13}H_{15}NNaO_6$ Requires: 304.0791.

Methyl (2*S*,3*S*,4*S*)-4-methyl-2,3-bis(4-nitrophenyl)-5-oxotetrahydrofuran-3-carboxylate (427)



Prepared according to general procedure X, using anhydride **414** (30.5 mg, 0.129 mmol), recrystallized 4-nitrobenzaldehyde (**244**, 13.7 mg, 0.091 mmol), 4-iodoanisole (21.2 mg, 0.091 mmol) and the catalyst **254** (3.5 mg, 0.0068 mmol – 5 mol%) in dry MTBE (1.3 mL – 0.1 M). The reaction was stired for 1 day to give a diastereomeric mixture of carboxylic acid lactones in a 87.5:12.5 (*major*:*others*) ratio, quenched with MeOH (1.05 mL, 25.94 mmol) following the derivatisation method as described in the

general procedure. After esterification with $TMSCHN_2$ (78 μL, 0.155 mmol) the major diastereomer (**427**) was isolated by flash column chromatography as a white solid (19.8 mg, 38%). TLC (hexanes:EtOAc, 70:30 *v/v*): R_f = 0.27; $[\alpha]_D^{20}$ = +21.6 (*c* = 0.05, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CEL1, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Methanol:*i*-PrOH (1:1, *v*:*v*) gradient as shown in Table 4.1, column temperature: 30 °C, UV detection at 254 nm, retention times: 3.47 min (minor enantiomer) and 3.80 min (major enantiomer).

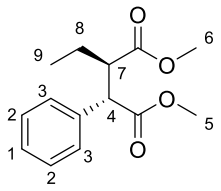
δ_H (400 MHz, $CDCl_3$): 8.00-7.96 (4 H, m, H-5 and H-7), 7.24 (2 H, d, *J* 8.6, H-6), 6.88 (2 H, d, *J* 8.8, H-4), 6.4 (1 H, d, H-3), 3.83 (3 H, s, H-8), 3.49 (1 H, q, *J* 7.5, H-2), 1.55 (3 H, d, *J* 7.5, H-1).

δ_C (151 MHz, $CDCl_3$): 175.7 (C=O), 170.7 (C=O), 147.9 (q), 147.4 (q), 142.5 (q), 141.0 (q), 128.1, 127.5, 123.6, 123.2, 81.7, 64.0 (q), 53.2, 44.0, 13.3

ν_{max} (neat)/cm^{-1}: 2921, 1785, 1734, 1606, 1517, 1348, 1221, 1171, 1026, 1012, 861, 724, 697.

HRMS (*m/z* - ESI): Found: 399.0839 $(M-H)^-$ $C_{19}H_{15}N_2O_8$ Requires: 399.0833.

Dimethyl (2*R*,3*S*)-2-ethyl-3-phenylsuccinate (432)



Prepared according to general procedure X, using anhydride **428** (98.9 mg, 0.484 mmol), recrystallized 4-nitrobenzaldehyde (**244**, 51.2 mg, 0.339 mmol), 4-iodoanisole (79.3 mg, 0.581 mmol) and the catalyst **254** (13.0 mg, 0.024 mmol – 5 mol%) in dry MTBE (4.8 mL – 0.1 M). The reaction was stired for 5 days, quenched with MeOH (3.92 mL, 96.8 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (290 μL, 0.580 mmol) the unreacted

starting material (*trans*-**432**) was isolated by flash column chromatography (as its open *bis*-methyl ester opened form) as a colourless liquid (41.2 mg, 34%). TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.46 (*cis*), R_f = 0.31 (*trans*); $[\alpha]_D^{20}$ = +243.6 (*c* = 0.123, $CHCl_3$).

trans-**432**:

HPLC analysis. ACQUITY UPC^2 Trefoil AMY1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:*i*-PrOH (1:1, *v*:*v*) gradient as shown in Table 4.4, column temperature: 30 °C, UV detection at 230 nm, retention times: 1.85 min (minor enantiomer) and 2.71 min (major enantiomer).

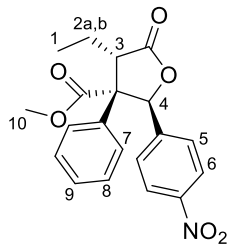
δ_H (400 MHz, $CDCl_3$): 7.28-7.19 (5 H, m, H-1, H-2 and H-3), 3.80 (1 H, d, *J* 11.4, H-4), 3.67 (3 H, s, H-6), 3.54 (3 H, s, H-5), 3.07-3.01 (1 H, m, H-7), 1.42-1.32 (1 H, m, H-8), 1.27-1.16 (1 H, m, H-8), 0.71 (3 H, t, *J* 7.5, H-9).

δ_C (100 MHz, $CDCl_3$): 175.4 (C=O), 173.7 (C=O), 136.4 (q), 128.9, 128.4, 127.7, 52.4, 52.2, 51.8, 48.8, 22.5, 10.5.

ν_{max} (neat)/cm^{-1}: 2953, 1730, 1454, 1434, 1256, 1235, 1160, 747, 734, 700.

HRMS (*m/z* - ESI): Found: 273.1091 $(M+Na)^+$ $C_{14}H_{18}NaO_4$ Requires: 273.1097.

Methyl (2*S*,3*S*,4*S*)-4-ethyl-2-(4-nitrophenyl)-5-oxo-3-phenyltetrahydrofuran-3-carboxylate (436)



Prepared according to general procedure X, using anhydride **428** (98.9 mg, 0.484 mmol), recrystallized 4-nitrobenzaldehyde (**244**, 51.2 mg, 0.339 mmol), 4-iodoanisole (79.3 mg, 0.581 mmol) and the catalyst **254** (13.0 mg, 0.024 mmol – 5 mol%) in dry

MTBE (4.8 mL – 0.1 M). The reaction was stired for 5 days to give a diastereomeric mixture of carboxylic acid lactones in a 91:9 (*major*:*others*) ratio, quenched with MeOH (3.92 mL, 96.8 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (290 μL, 0.580 mmol) the major diastereomer (**436**) was isolated by flash column chromatography as a white solid (76.6 mg, 43%). M.p. 152-154 °C. TLC (hexanes:EtOAc, 4:1 *v/v*): R_f = 0.34; $[\alpha]_D^{20}$ = +63.2 (*c* = 0.05, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CEL2, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:CH_3CN (1:1, *v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 230 nm, retention times: 2.69 min (major enantiomer) and 2.90 min (minor enantiomer).

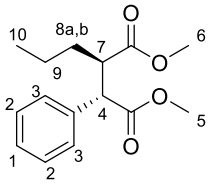
δ_H (400 MHz, $CDCl_3$): 7.91 (2 H, d, *J* 8.8, H-6), 7.18-7.15 (3 H, m, H-8 and H-9), 7.12-7.08 (2 H, m, H-7), 6.66 (2 H, d, *J* 8.8, H-5), 6.33 (1 H, s, H-4), 3.78 (1 H, s, H-3), 3.25 (1 H, dd, *J* 10.9, 4.7, H-3), 1.98-1.89 (1 H, m, H-2a), 1.87-1.77 (1 H, m, H-2b), 1.26 (3 H, t, *J* 7.4, H-1),

δ_C (100 MHz, $CDCl_3$): 175.4 (C=O), 171.8 (C=O), 147.5 (q), 142.0 (q), 135.5 (q), 128.5, 128.3, 127.7, 126.9, 122.7, 82.3, 64.5 (q), 52.7, 50.0, 21.4, 11.3.

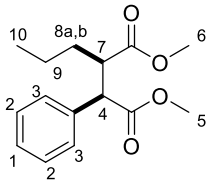
ν_{max} (neat)/cm^{-1}: 2945, 1770, 1743, 1608, 1516, 1435, 1348, 1250, 1202, 1167, 1125, 1072, 1011, 979, 875, 857, 846, 760, 715, 704, 693, 585.

HRMS (*m/z* - APCI): Found: 370.1288 $(M+H)^+$ $C_{20}H_{20}NO_6$ Requires: 370.1285.

Dimethyl 2-phenyl-3-propylsuccinate (433)



trans-**433**



cis-**433**

Prepared according to general procedure X, using anhydride **429** (148.6 mg, 0.680 mmol), recrystallized 4-nitrobenzaldehyde (**244**, 72.0 mg, 0.476 mmol), 4-iodoanisole (111.5 mg, 0.476 mmol) and the catalyst **254** (10.7 mg, 0.02 mmol – 5 mol%) in dry MTBE (4.0 mL – 0.1 M). The reaction was stired for 5 days, quenched with MeOH (5.5 mL, 136.17 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (408 μL, 0.817 mmol) the unreacted starting material (*trans*-**433**) was isolated by flash column chromatography (as its open *bis*-methyl ester opened form) as a colourless liquid (73.2 mg, 41%). TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.56 (*cis*-**433**), R_f = 0.36 (*trans*-**433**); $[\alpha]_D^{20}$ = +254.8 (*c* = 0.213, $CHCl_3$).

trans-**433**:

HPLC analysis. ACQUITY UPC^2 Trefoil AMY1, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:*i*-PrOH (1:1, *v*:*v*) gradient as shown in Table 4.4, column temperature: 30 °C, UV detection at 212 nm, retention times: 1.83 min (minor enantiomer) and 2.88 min (major enantiomer).

δ_H (400 MHz, $CDCl_3$): 7.36-7.26 (5 H, m, H-1, H-2 and H-3), 3.85 (1 H, d, *J* 11.6, H-4), 3.73 (3 H, s, H-6), 3.61 (3 H, s, H-5), 3.17-3.11 (1 H, m, H-7), 1.32-1.24 (3 H, m, H-9 and H-8a), 1.18-1.05 (1 H, m, H-8b), 0.74 (3 H, t, *J* 6.7, H-10).

δ_C (100 MHz, $CDCl_3$): 175.6 (C=O), 173.7 (C=O), 136.4 (q), 128.9, 128.4, 127.7, 53.0, 52.2, 51.8, 47.6, 31.7, 19.6, 13.8.

cis-**433**:

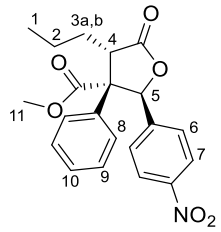
δ_H (400 MHz, $CDCl_3$): 7.32-7.23 (5 H, m, H-1, H-2 and H-3), 3.77 (1 H, d, *J* 11.2, H-4), 3.66 (3 H, s, H-6), 3.35 (3 H, s, H-5), 3.25-3.18 (1 H, m, H-7), 1.72-1.63 (1 H, m, H-8a), 1.58-1.49 (1 H, m, H-8b), 1.37-1.25 (2 H, m, H-9), 0.92 (3 H, t, *J* 7.4, H-10).

δ_C (100 MHz, $CDCl_3$): 174.0 (C=O), 172.8 (C=O), 136.4 (q), 128.5, 128.3, 127.7, 54.3, 52.2, 51.3, 49.6, 33.9, 20.7, 13.8.

ν_{max} (neat)/cm^{-1}: 2955, 1730, 1434, 1328, 1239, 1160, 1003, 782, 735, 700.

HRMS (*m/z* - ESI): Found: 287.1259 $(M+Na)^+$ $C_{15}H_{20}NaO_4$ Requires: 287.1253.

Methyl (2*S*,3*S*,4*S*)-2-(4-nitrophenyl)-5-oxo-3-phenyl-4-propyltetrahydrofuran-3-carboxylate (437)



Prepared according to general procedure X, using anhydride **429** (148.6 mg, 0.680 mmol), recrystallized 4-nitrobenzaldehyde (**244**, 72.0 mg, 0.476 mmol), 4-iodoanisole (111.5 mg, 0.476 mmol) and the catalyst **254** (10.7 mg, 0.02 mmol – 5 mol%) in dry MTBE (6.8mL – 0.1 M). The reaction was stired for 5 days to give a diastereomeric mixture of carboxylic acid lactones in a 90:10 (*major*:*others*) ratio, quenched with MeOH (5.5 mL, 136.17 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (408 μL, 0.817 mmol) the major diastereomer (**437**) was isolated by flash column chromatography as a white solid (109.4 mg, 42%). M.p. 150-152 °C. TLC (hexanes:EtOAc, 4:1 *v/v*): R_f = 0.40; $[\alpha]_D^{20}$ = +79.6 (*c* = 0.05, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil AMY1, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:*i*-PrOH (1:1, *v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 254 nm, retention times: 2.36 min (minor enantiomer) and 2.62 min (major enantiomer).

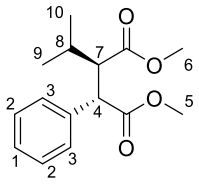
δ_H (400 MHz, $CDCl_3$): 7.90 (2 H, d, *J* 8.8, H-7), 7.19-7.15 (3 H, m, H-9 and H-10), 7.12-7.08 (2 H, m, H-8), 6.66 (2 H, d, *J* 8.8, H-6), 6.33 (1 H, s, H-5), 3.78 (3 H, s, H-11), 3.34 (1 H, dd, *J* 10.6, 4.0, H-4), 1.94-1.84 (1 H, m, H-3a), 1.84-1.74 (1 H, m, H-3b), 1.69-1.53 (2 H, m, H-2), 1.02 (3 H, t, *J* 6.9, H-1).

δ_C (100 MHz, $CDCl_3$): 175.5 (C=O), 171.8 (C=O), 147.5 (q), 142.0 (q), 135.5 (q), 128.5, 128.3, 127.7, 126.9, 122.7, 82.2, 64.5 (q), 52.7, 48.3, 29.9, 19.8, 13.8.

ν_{max} (neat)/cm^{-1}: 2947, 1771, 1744, 1664, 1595, 1518, 1458, 1434, 1349, 1204, 1167, 857, 716, 560.

HRMS (*m/z* - APCI): Found: 384.1454 $(M+H)^+$ $C_{21}H_{22}NO_6$ Requires: 384.1441.

Dimethyl (2*R*,3*S*)-2-isopropyl-3-phenylsuccinate (434)



Prepared according to general procedure X, using anhydride **430** (90.8 mg, 0.416 mmol), recrystallized 4-nitrobenzaldehyde (**244**, 44.0 mg, 0.291 mmol), 4-iodoanisole (68.2 mg, 0.291 mmol) and the catalyst **254** (11.2 mg, 0.021 mmol – 5 mol%) in dry MTBE (4.2 mL – 0.1 M). The reaction was stired for 6 days, quenched with MeOH (3.37 mL, 83.2 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (250 μL, 0.499 mmol) the unreacted starting material (*trans*-**434**) was isolated by flash column chromatography (as its open *bis*-methyl ester opened form) as a colourless liquid (50.2 mg, 46%). TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.33 (*trans*-**434**); $[\alpha]_D^{20}$ = +130 (*c* = 0.145, $CHCl_3$).

trans-**434**:

HPLC analysis. ACQUITY UPC^2 Trefoil AMY1, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:*i*-PrOH (1:1, *v*:*v*) gradient as shown in Table 4.4, column temperature: 30 °C, UV detection at 212 nm, retention times: 1.69 min (minor enantiomer) and 2.64 min (major enantiomer).

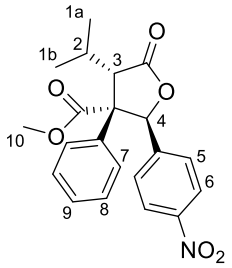
δ_H (400 MHz, $CDCl_3$): 7.35-7.27 (5 H, m, H-1, H-2 and H-3), 3.97 (1 H, d, *J* 11.9, H-4), 3.72 (3 H, s, H-6), 3.60 (3 H, s, H-5), 3.14 (1 H, dd, *J* 11.9, *J* 3.05, H-7), 1.56-1.48 (1 H, m, H-8), 0.93 (3 H, d, *J* 6.9, H-9), 0.79 (3 H, d, *J* 6.9, H-10).

δ_C (100 MHz, $CDCl_3$): 173.93 (C=O), 173.91 (C=O), 136.5 (q), 128.9, 128.4, 127.7, 53.3, 52.2, 51.6, 51.4, 26.7, 22.0, 16.8.

ν_{max} (neat)/cm^{-1}: 2958, 1729, 1454, 1435, 1286, 1259, 1235, 1158, 1006, 734, 700.

HRMS (*m/z* - ESI): Found: 287.1252 $(M+Na)^+$ $C_{15}H_{20}NaO_4$ Requires: 287.1253.

Methyl (2*S*,3*S*,4*S*)-4-isopropyl-2-(4-nitrophenyl)-5-oxo-3-phenyltetrahydrofuran-3-carboxylate (438)



Prepared according to general procedure X, using anhydride **430** (90.8 mg, 0.416 mmol), recrystallized 4-nitrobenzaldehyde (**244**, 44.0 mg, 0.291 mmol), 4-iodoanisole (68.2 mg, 0.291 mmol) and the catalyst **254** (11.2 mg, 0.021 mmol – 5 mol%) in dry MTBE (4.2 mL – 0.1 M). The reaction was stired for 6 days to give a diastereomeric mixture of carboxylic acid lactones in a 86:14 (*major*:*others*) ratio, quenched with MeOH (3.37 mL, 83.2 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (250 μL, 0.499 mmol) the major diastereomer (**438**) was isolated by flash column chromatography as a white solid (54.6 mg, 34%). TLC (hexanes:EtOAc, 4:1 *v/v*): R_f = 0.35; $[\alpha]_D^{20}$ = +38.8 (*c* = 0.05, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CEL1, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Methanol:*i*-PrOH (1:1, *v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 254 nm, retention times: 2.10 min (minor enantiomer) and 2.40 min (major enantiomer).

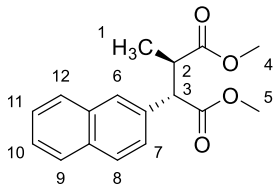
δ_H (400 MHz, $CDCl_3$): 7.89 (2 H, d, *J* 8.9, H-6), 7.18 (2 H, d, *J* 8.7, H-7), 7.13-7.05 (3 H, m, H-8 and H-9), 6.65 (2 H, d, *J* 8.9, H-5), 6.39 (1 H, s, H-4), 3.82 (3 H, s, H-10), 3.37 (1 H, d, *J* 2.8, H-3), 2.29-2.22 (1 H, m, H-2), 1.33 (1 H, d, *J* 6.8, H-1a), 1.22 (1 H, d, *J* 7.0, H-1b).

δ_C (100 MHz, $CDCl_3$): 174.8 (C=O), 172.0 (C=O), 147.4 (q), 142.4 (q), 136.8 (q), 128.4, 128.1, 127.5, 126.7, 122.6, 82.9, 64.4 (q), 55.4, 52.7, 29.0, 23.0, 18.7.

ν_{max} (neat)/cm^{-1}: 2920, 1771, 1729, 1522, 1349, 1263, 1199, 1162, 1099, 1028, 1013, 858, 848, 748, 701.

HRMS (*m/z* - ESI): Found: 406.1251 $(M+Na)^+$ $C_{21}H_{21}NNaO_6$ Requires: 406.1261.

Dimethyl (2*R*,3*S*)-2-methyl-3-(naphthalen-2-yl)succinate (435)



Prepared according to general procedure X, using anhydride **431** (96.1 mg, 0.4 mmol), recrystallized 4-nitrobenzaldehyde (**244**, 42.3 mg, 0.280 mmol), 4-iodoanisole (65.5 mg, 0.280 mmol) and the catalyst **254** (10.7 mg, 0.02 mmol – 5 mol%) in dry MTBE (4.0 mL – 0.1 M). The reaction was stired for 6 days, quenched with MeOH (3.24 mL, 80.0 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (240 μL, 0.480 mmol) the unreacted starting material (*trans*-**435**) was isolated by flash column chromatography (as its open *bis*-methyl ester opened form) as a white solid (29.6 mg, 26%). TLC (hexanes:EtOAc, 9:1 *v/v*): R_f = 0.45 (*cis*-**435**), R_f = 0.36 (*trans*-**435**); $[\alpha]_D^{20}$ = +93.4 (*c* = 0.08, $CHCl_3$).

trans-**438**:

HPLC analysis. ACQUITY UPC^2 Trefoil AMY1, 2.5µm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:CH_3CN:*i*-PrOH (1:1:1, *v*:*v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 254 nm, retention times: 2.18 min (minor enantiomer) and 3.92 min (major enantiomer).

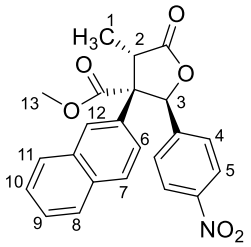
δ_H (400 MHz, $CDCl_3$): 8.83-8.81 (3 H, m, H-8, H-9 and H-12), 7.74 (1 H, bs, H-6), 7.52-7.45 (2 H, m, H-10 and H-11), 7.39-7.37 (1 H, m, H-7), 3.96 (1 H, d, *J* 11.2, H-3), 3.76 (3 H, s, H-4), 3.64 (3 H, s, H-5), 3.34-3.26 (1 H, m, *J* 7.2, 11.2, H-2), 0.99 (3 H, d, *J* 7.2, H-1).

δ_C (100 MHz, $CDCl_3$): 176.2 (C=O), 173.7 (C=O), 133.7 (q), 133.4 (q), 132.8 (q), 128.7, 127.82, 127.81, 127.7, 126.4, 126.1, 125.7, 54.3, 52.3, 52.0, 42.3, 15.5.

ν_{max} (neat)/cm^{-1}: 2955, 1728, 1454, 1433, 1375, 1316, 1281, 1233, 1170, 1154, 1063, 1007, 858, 817, 762.

HRMS (*m/z* - ESI): Found: 309.1096 $(M+Na)^+$ $C_{17}H_{18}NaO_4$ Requires: 309.1097.

Methyl (2*S*,3*S*,4*S*)-4-methyl-3-(naphthalen-2-yl)-2-(4-nitrophenyl)-5-oxotetrahydrofuran-3-carboxylate (439)



Prepared according to general procedure X, using anhydride **431** (96.1 mg, 0.4 mmol), recrystallized 4-nitrobenzaldehyde (**244**, 42.3 mg, 0.280 mmol), 4-iodoanisole (65.5 mg, 0.280 mmol) and the catalyst **254** (10.7 mg, 0.02 mmol – 5 mol%) in dry MTBE (4.0 mL – 0.1 M). The reaction was stired for 6 days to give a diastereomeric mixture of

carboxylic acid lactones in a 90:10 (*major*:*others*) ratio, quenched with MeOH (3.24 mL, 80.0 mmol) following the derivatisation method as described in the general procedure. After esterification with $TMSCHN_2$ (240 μL, 0.480 mmol) the major diastereomer (**439**) was isolated by flash column chromatography as a white solid (52.4 mg, 40%). M.p. 155-157 °C. TLC (hexanes:EtOAc, 4:1 *v/v*): R_f = 0.18; $[\alpha]_D^{20}$ = +34.8 (*c* = 0.764, $CHCl_3$).

HPLC analysis. ACQUITY UPC^2 Trefoil CEL2, 2.5μm (3.0 x 150mm). ABPR: 1500 (psi). A = CO_2 / B = Ethanol:CH_3CN (1:1, *v*:*v*) gradient as shown in Table 4.2, column temperature: 30 °C, UV detection at 254 nm, retention times: 3.46 min (major enantiomer) and 3.74 min (minor enantiomer).

δ_H (400 MHz, $CDCl_3$): 7.84 (2 H, d, *J* 8.8, H-5), 7.75-7.68 (2 H, m, H-6 and H-7), 7.51-7.41 (4 H, m, H-8, H-9, H-10 and H-11), 7.20 (2 H, d, *J* 8.8, H-4), 6.41 (1 H, s, H-3), 6.39 (1 H, app. dd, H-12), 3.80 (3 H, s, H-13), 3.65 (1 H, q, *J* 7.4, H-2), 1.57 (3 H, d, *J* 7.4, H-1).

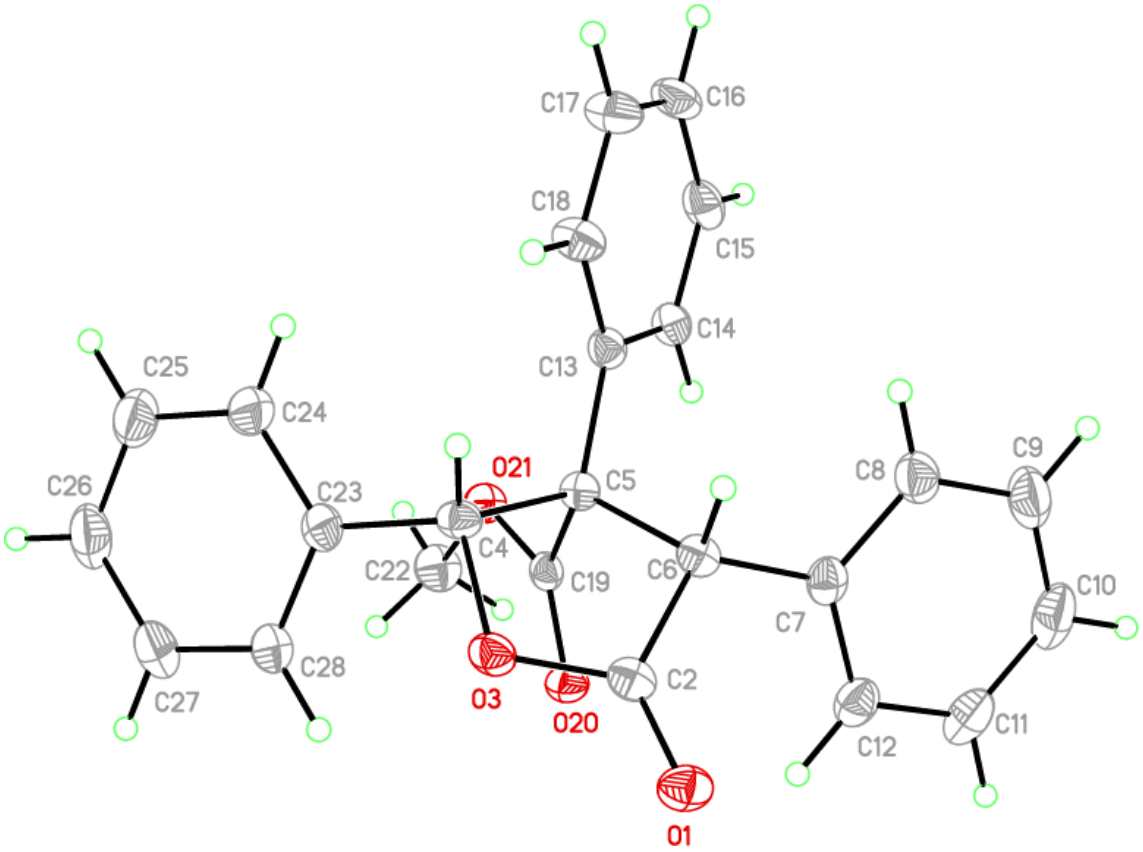
δ_C (151 MHz, $CDCl_3$): 176.8 (C=O), 171.8 (C=O), 147.6 (q), 141.7 (q), 132.65 (q), 132.62 (q), 132.3 (q), 128.08, 128.07, 127.9, 127.5, 127.1, 126.9, 125.5, 124.9, 122.8, 82.1, 64.1 (q), 52.9, 43.9, 13.3.

ν_{max} (neat)/cm^{-1}: 2950, 1784, 1721, 1607, 1518, 1463, 1437, 1351, 1253, 1200, 1162, 1013, 837, 787, 727, 745, 692.

HRMS (*m/z* - APCI): Found: 406.1292 $(M+H)^+$ $C_{23}H_{20}NO_6$ Requires: 406.1285

4.5 X-ray crystallography data

4.5.1 X-ray crystallography data for 300



A specimen of $C_{24}H_{20}O_4$, (**300**) approximate dimensions 0.010 mm x 0.250 mm x 0.450 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 100(2)K using an Oxford Cryosystems low temperature device using a MiTeGen micromount. See Table 4.6 for collection parameters and exposure time. Bruker APEX software was used to correct for Lorentz and polarization effects.

A total of 4462 frames were collected. The total exposure time was 13.63 hours. The integration of the data using an orthorhombic unit cell yielded a total of 26460 reflections to a maximum θ angle of 68.40° (0.83 Å resolution), of which 3533 were independent (average redundancy 7.489, completeness = 99.6%, R_{int} = 3.42%, R_{sig} = 1.82%) and 3525 (99.77%) were greater than $2\sigma(F^2)$. The final cell constants of a = 9.3600(4) Å, b = 10.9241(4) Å, c = 18.8533(7) Å, volume = 1927.74(13) $Å^3$, are based upon the refinement of the XYZ-centroids of reflections above 20 σ(I). Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of

minimum to maximum apparent transmission was 0.843. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.6347 and 0.7531.

The structure was solved using the Bruker APEX Software Package and refined with XL in Olex2, using the space group $P2_12_12_1$, with Z = 4 for the formula unit, $C_{24}H_{20}O_4$. The final anisotropic full-matrix least-squares refinement on F^2 with 254 variables converged at R1 = 3.10%, for the observed data and wR2 = 7.72% for all data. The goodness-of-fit was 1.080. The largest peak in the final difference electron density synthesis was 0.152 $e^-/Å^3$ and the largest hole was -0.328 $e^-/Å^3$ with an RMS deviation of 0.063 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.283 g/cm^3 and F(000), 784 e^-.

Refinement Note: Chirality assignment:

C4 = R

C5 = S

C6 = S

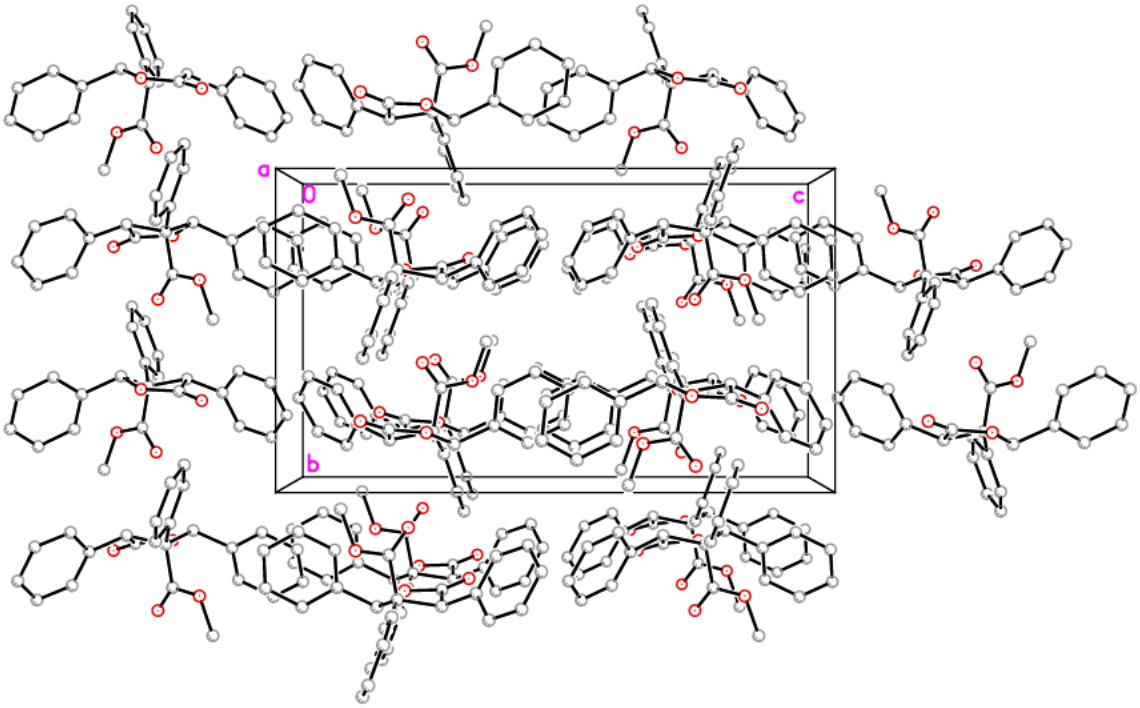


Figure 4.1 Packing of diagram of **300** viewed to the a-axis.

Table 4.5 Data collection details for **300**

Axis	dx/mm	2θ/°	ω/°	φ/°	χ/°	Width/°	Frames	Time/s	Wavelength/Å	Voltage/kV	Current/mA	Temperature/K
Omega	45.000	104.23	94.63	324.00	-54.74	0.80	157	11.00	1.54184	45	0.6	100
Omega	45.000	104.23	342.74	0.00	64.50	0.80	163	11.00	1.54184	45	0.6	100
Omega	45.000	104.23	94.63	135.00	-54.74	0.80	157	11.00	1.54184	45	0.6	100
Omega	45.000	90.14	352.61	59.39	82.71	0.80	91	11.00	1.54184	45	0.6	100
Phi	45.000	-41.42	341.01	238.61	23.00	0.80	314	11.00	1.54184	45	0.6	100
Omega	45.000	104.23	94.63	0.00	-54.74	0.80	157	11.00	1.54184	45	0.6	100
Omega	45.000	104.23	94.63	189.00	-54.74	0.80	157	11.00	1.54184	45	0.6	100
Omega	45.000	-39.23	312.62	160.00	-64.50	0.80	128	11.00	1.54184	45	0.6	100
Omega	45.000	104.23	94.63	297.00	-54.74	0.80	157	11.00	1.54184	45	0.6	100
Omega	45.000	104.23	342.74	216.00	64.50	0.80	163	11.00	1.54184	45	0.6	100
Omega	45.000	-39.23	205.13	120.00	54.74	0.80	157	11.00	1.54184	45	0.6	100
Omega	45.000	104.23	94.63	162.00	-54.74	0.80	157	11.00	1.54184	45	0.6	100
Omega	45.000	104.23	342.74	81.00	64.50	0.80	163	11.00	1.54184	45	0.6	100
Omega	45.000	104.23	342.74	270.00	64.50	0.80	163	11.00	1.54184	45	0.6	100
Omega	45.000	-39.23	312.62	0.00	-64.50	0.80	128	11.00	1.54184	45	0.6	100
Omega	45.000	104.23	94.63	54.00	-54.74	0.80	157	11.00	1.54184	45	0.6	100
Omega	45.000	104.23	342.74	135.00	64.50	0.80	163	11.00	1.54184	45	0.6	100
Omega	55.000	110.58	93.39	120.00	-54.74	0.80	179	11.00	1.54184	45	0.6	100
Omega	55.000	94.75	352.44	168.66	80.84	0.80	92	11.00	1.54184	45	0.6	100
Omega	55.000	110.58	338.50	192.00	64.50	0.80	185	11.00	1.54184	45	0.6	100
Omega	55.000	110.58	338.50	24.00	64.50	0.80	185	11.00	1.54184	45	0.6	100
Omega	55.000	110.58	93.39	96.00	-54.74	0.80	179	11.00	1.54184	45	0.6	100
Omega	55.000	110.58	93.39	168.00	-54.74	0.80	179	11.00	1.54184	45	0.6	100
Omega	55.000	-0.33	234.22	360.00	54.74	0.80	179	11.00	1.54184	45	0.6	100
Phi	55.000	-53.29	323.96	235.29	57.00	0.80	322	11.00	1.54184	45	0.6	100
Phi	55.000	110.89	0.81	292.00	23.00	0.80	230	11.00	1.54184	45	0.6	100

Table 4.6 Crystal data and structure refinement for **300**.

Identification code	tcd698	
Empirical formula	$C_{24}H_{20}O_4$	
Formula weight	372.40	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 9.3600(4) Å	α = 90°
	b = 10.9241(4) Å	β = 90°
	c = 18.8533(7) Å	γ = 90°
Volume	1927.74(13) $Å^3$	
Z	4	
Density (calculated)	1.283 Mg/m^3	
Absorption coefficient	0.703 mm^{-1}	
F(000)	784	
Crystal size	0.45 x 0.25 x 0.01 mm^3	
Theta range for data collection	4.678 to 68.398°.	
Index ranges	$-11\leq h\leq 11$, $-11\leq k\leq 12$, $-22\leq l\leq 22$	
Reflections collected	26460	
Independent reflections	3533 [R(int) = 0.0342]	
Completeness to theta = 67.679°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7531 and 0.6347	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3533 / 0 / 254	
Goodness-of-fit on F^2	1.080	
Final R indices [I>2σ(I)]	R1 = 0.0310, wR2 = 0.0772	
R indices (all data)	R1 = 0.0311, wR2 = 0.0772	
Absolute structure parameter	-0.01(3)	
Largest diff. peak and hole	0.152 and -0.328 e.$Å^{-3}$	

Table 4.7 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **300**.

U(eq) is defined as one third of the trace of the orthogonalised U_{ij} tensor.

	x	y	z	U(eq)
O(1)	6359(1)	7245(1)	8433(1)	23(1)
O(3)	6032(1)	6888(1)	7280(1)	20(1)
O(20)	3923(1)	8997(1)	7401(1)	20(1)
O(21)	2442(1)	8399(1)	6527(1)	19(1)

C(2)	5571(2)	6960(1)	7960(1)	18(1)
C(4)	4892(2)	6490(1)	6812(1)	18(1)
C(5)	3482(2)	6836(1)	7223(1)	16(1)
C(6)	4015(2)	6590(1)	7992(1)	17(1)
C(7)	3149(2)	7055(2)	8611(1)	20(1)
C(8)	1996(2)	6362(2)	8851(1)	26(1)
C(9)	1168(2)	6760(2)	9419(1)	35(1)
C(10)	1482(2)	7848(2)	9757(1)	37(1)
C(11)	2628(2)	8542(2)	9524(1)	33(1)
C(12)	3459(2)	8155(2)	8958(1)	24(1)
C(13)	2157(2)	6084(2)	7050(1)	18(1)
C(14)	806(2)	6559(2)	7206(1)	20(1)
C(15)	-418(2)	5869(2)	7103(1)	24(1)
C(16)	-319(2)	4682(2)	6846(1)	27(1)
C(17)	1010(2)	4193(2)	6702(1)	29(1)
C(18)	2240(2)	4880(2)	6808(1)	24(1)
C(19)	3291(2)	8205(2)	7082(1)	16(1)
C(22)	2349(2)	9645(2)	6274(1)	26(1)
C(23)	5100(2)	7071(2)	6093(1)	21(1)
C(24)	4497(2)	6525(2)	5499(1)	28(1)
C(25)	4606(2)	7090(2)	4840(1)	37(1)
C(26)	5326(2)	8190(2)	4770(1)	36(1)
C(27)	5941(2)	8728(2)	5358(1)	32(1)
C(28)	5838(2)	8171(2)	6019(1)	24(1)

Table 4.8 Bond lengths [Å] and angles [°] for **300**.

O(1)-C(2)	1.197(2)	C(18)-H(18)	0.9500
O(3)-C(2)	1.356(2)	C(22)-H(22A)	0.9800
O(3)-C(4)	1.4507(19)	C(22)-H(22B)	0.9800
O(20)-C(19)	1.208(2)	C(22)-H(22C)	0.9800
O(21)-C(19)	1.3310(19)	C(23)-C(24)	1.389(3)
O(21)-C(22)	1.4453(19)	C(23)-C(28)	1.393(2)
C(2)-C(6)	1.513(2)	C(24)-H(24)	0.9500
C(4)-H(4)	1.0000	C(24)-C(25)	1.390(3)
C(4)-C(5)	1.577(2)	C(25)-H(25)	0.9500
C(4)-C(23)	1.508(2)	C(25)-C(26)	1.385(3)
C(5)-C(6)	1.558(2)	C(26)-H(26)	0.9500
C(5)-C(13)	1.523(2)	C(26)-C(27)	1.381(3)
C(5)-C(19)	1.529(2)	C(27)-H(27)	0.9500
C(6)-H(6)	1.0000	C(27)-C(28)	1.390(3)
C(6)-C(7)	1.509(2)	C(28)-H(28)	0.9500

C(7)-C(8)	1.393(3)		
C(7)-C(12)	1.398(3)	C(2)-O(3)-C(4)	111.07(12)
C(8)-H(8)	0.9500	C(19)-O(21)-C(22)	116.47(13)
C(8)-C(9)	1.391(3)	O(1)-C(2)-O(3)	121.56(15)
C(9)-H(9)	0.9500	O(1)-C(2)-C(6)	129.22(15)
C(9)-C(10)	1.381(3)	O(3)-C(2)-C(6)	109.17(13)
C(10)-H(10)	0.9500	O(3)-C(4)-H(4)	108.9
C(10)-C(11)	1.385(3)	O(3)-C(4)-C(5)	104.16(12)
C(11)-H(11)	0.9500	O(3)-C(4)-C(23)	109.01(13)
C(11)-C(12)	1.387(3)	C(5)-C(4)-H(4)	108.9
C(12)-H(12)	0.9500	C(23)-C(4)-H(4)	108.9
C(13)-C(14)	1.398(2)	C(23)-C(4)-C(5)	116.65(13)
C(13)-C(18)	1.394(2)	C(6)-C(5)-C(4)	98.55(12)
C(14)-H(14)	0.9500	C(13)-C(5)-C(19)	113.29(12)
C(14)-C(15)	1.386(2)	C(13)-C(5)-C(4)	116.59(13)
C(15)-H(15)	0.9500	C(13)-C(5)-C(6)	111.49(12)
C(15)-C(16)	1.387(3)	C(19)-C(5)-C(4)	104.30(12)
C(16)-H(16)	0.9500	C(19)-C(5)-C(6)	111.59(12)
C(16)-C(17)	1.381(3)	C(2)-C(6)-C(5)	102.97(12)
C(17)-H(17)	0.9500	C(2)-C(6)-H(6)	105.3
C(17)-C(18)	1.388(2)	C(5)-C(6)-H(6)	105.3
C(7)-C(6)-C(2)	117.24(13)	C(16)-C(17)-H(17)	119.7
C(7)-C(6)-C(5)	119.37(13)	C(16)-C(17)-C(18)	120.64(16)
C(7)-C(6)-H(6)	105.3	C(18)-C(17)-H(17)	119.7
C(8)-C(7)-C(6)	118.88(15)	C(13)-C(18)-H(18)	119.6
C(8)-C(7)-C(12)	118.43(16)	C(17)-C(18)-C(13)	120.73(16)
C(12)-C(7)-C(6)	122.68(15)	C(17)-C(18)-H(18)	119.6
C(7)-C(8)-H(8)	119.6	O(20)-C(19)-O(21)	124.73(14)
C(9)-C(8)-C(7)	120.74(18)	O(20)-C(19)-C(5)	123.80(14)
C(9)-C(8)-H(8)	119.6	O(21)-C(19)-C(5)	111.23(13)
C(8)-C(9)-H(9)	119.8	O(21)-C(22)-H(22A)	109.5
C(10)-C(9)-C(8)	120.36(18)	O(21)-C(22)-H(22B)	109.5
C(10)-C(9)-H(9)	119.8	O(21)-C(22)-H(22C)	109.5
C(9)-C(10)-H(10)	120.3	H(22A)-C(22)-H(22B)	109.5
C(9)-C(10)-C(11)	119.35(18)	H(22A)-C(22)-H(22C)	109.5
C(11)-C(10)-H(10)	120.3	H(22B)-C(22)-H(22C)	109.5
C(10)-C(11)-H(11)	119.6	C(24)-C(23)-C(4)	119.47(15)
C(10)-C(11)-C(12)	120.72(19)	C(24)-C(23)-C(28)	119.38(17)
C(12)-C(11)-H(11)	119.6	C(28)-C(23)-C(4)	121.10(15)
C(7)-C(12)-H(12)	119.8	C(23)-C(24)-H(24)	120.0
C(11)-C(12)-C(7)	120.39(17)	C(23)-C(24)-C(25)	120.07(18)
C(11)-C(12)-H(12)	119.8	C(25)-C(24)-H(24)	120.0
C(14)-C(13)-C(5)	119.41(14)	C(24)-C(25)-H(25)	119.8

C(18)-C(13)-C(5)	122.27(14)	C(26)-C(25)-C(24)	120.33(18)
C(18)-C(13)-C(14)	117.99(15)	C(26)-C(25)-H(25)	119.8
C(13)-C(14)-H(14)	119.5	C(25)-C(26)-H(26)	120.1
C(15)-C(14)-C(13)	121.09(15)	C(27)-C(26)-C(25)	119.78(18)
C(15)-C(14)-H(14)	119.5	C(27)-C(26)-H(26)	120.1
C(14)-C(15)-H(15)	119.9	C(26)-C(27)-H(27)	119.8
C(14)-C(15)-C(16)	120.15(16)	C(26)-C(27)-C(28)	120.31(19)
C(16)-C(15)-H(15)	119.9	C(28)-C(27)-H(27)	119.8
C(15)-C(16)-H(16)	120.3	C(23)-C(28)-H(28)	119.9
C(17)-C(16)-C(15)	119.37(16)	C(27)-C(28)-C(23)	120.10(17)
C(17)-C(16)-H(16)	120.3	C(27)-C(28)-H(28)	119.9

Table 4.9 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **300**.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}\ U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$

	U_{11}	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
O(1)	19(1)	24(1)	26(1)	2(1)	-6(1)	0(1)
O(3)	14(1)	22(1)	23(1)	-1(1)	0(1)	-1(1)
O(20)	22(1)	16(1)	21(1)	-2(1)	-1(1)	-3(1)
O(21)	21(1)	17(1)	20(1)	3(1)	-3(1)	0(1)
C(2)	18(1)	13(1)	23(1)	2(1)	-1(1)	1(1)
C(4)	14(1)	17(1)	23(1)	-3(1)	0(1)	0(1)
C(5)	15(1)	15(1)	17(1)	-1(1)	0(1)	1(1)
C(6)	17(1)	15(1)	20(1)	3(1)	-2(1)	1(1)
C(7)	19(1)	24(1)	17(1)	4(1)	-2(1)	3(1)
C(8)	25(1)	32(1)	22(1)	5(1)	-1(1)	-2(1)
C(9)	28(1)	52(1)	26(1)	7(1)	7(1)	-3(1)
C(10)	34(1)	58(1)	19(1)	-2(1)	4(1)	7(1)
C(11)	34(1)	43(1)	22(1)	-7(1)	-4(1)	5(1)
C(12)	23(1)	30(1)	19(1)	-1(1)	-3(1)	2(1)
C(13)	17(1)	19(1)	16(1)	2(1)	-1(1)	-1(1)
C(14)	20(1)	19(1)	20(1)	2(1)	1(1)	1(1)
C(15)	16(1)	31(1)	25(1)	6(1)	2(1)	0(1)
C(16)	20(1)	29(1)	31(1)	4(1)	-3(1)	-10(1)
C(17)	29(1)	21(1)	37(1)	-3(1)	-1(1)	-6(1)
C(18)	18(1)	19(1)	33(1)	-1(1)	1(1)	0(1)
C(19)	13(1)	19(1)	15(1)	0(1)	2(1)	1(1)
C(22)	31(1)	20(1)	27(1)	7(1)	-3(1)	2(1)
C(23)	14(1)	25(1)	22(1)	-3(1)	5(1)	3(1)
C(24)	24(1)	36(1)	26(1)	-7(1)	3(1)	-4(1)
C(25)	32(1)	58(1)	21(1)	-5(1)	2(1)	-6(1)

C(26)	32(1)	55(1)	23(1)	7(1)	6(1)	-1(1)
C(27)	29(1)	37(1)	30(1)	6(1)	8(1)	-3(1)
C(28)	22(1)	28(1)	23(1)	-2(1)	5(1)	-1(1)

Table 4.10 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **300**.

	x	**y**	**z**	**U(eq)**
H(4)	4941	5580	6760	21
H(6)	4021	5679	8044	21
H(8)	1773	5610	8623	31
H(9)	382	6280	9574	42
H(10)	918	8118	10146	44
H(11)	2847	9292	9755	39
H(12)	4243	8640	8805	29
H(14)	727	7369	7386	23
H(15)	-1328	6210	7208	29
H(16)	-1157	4210	6771	32
H(17)	1084	3379	6530	35
H(18)	3147	4526	6714	28
H(22A)	1662	9688	5882	39
H(22B)	3290	9913	6107	39
H(22C)	2032	10179	6661	39
H(24)	4011	5766	5542	34
H(25)	4183	6718	4435	45
H(26)	5398	8573	4319	44
H(27)	6436	9483	5311	38
H(28)	6272	8541	6421	29

Table 4.11 Torsion angles [°] for **300**.

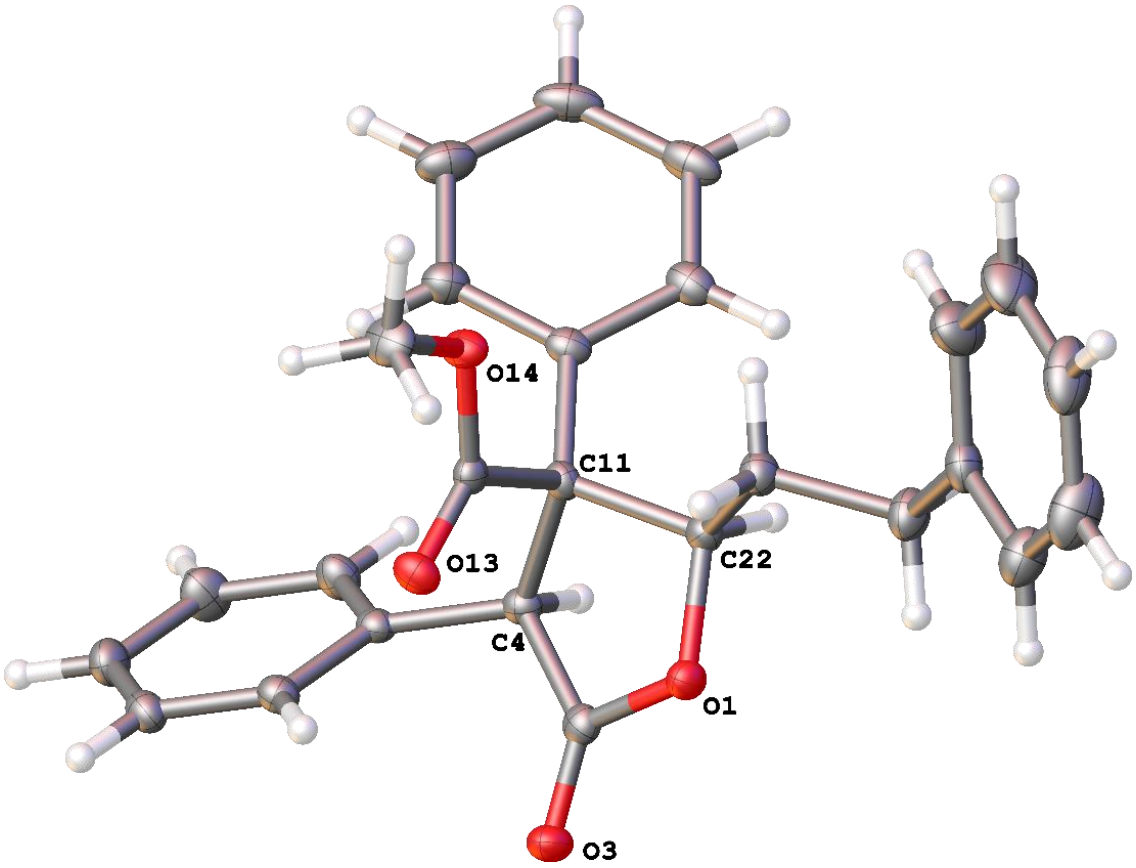
O(1)-C(2)-C(6)-C(5)	158.70(16)	C(6)-C(7)-C(8)-C(9)	-179.83(16)
O(1)-C(2)-C(6)-C(7)	25.5(2)	C(6)-C(7)-C(12)-C(11)	179.93(16)
O(3)-C(2)-C(6)-C(5)	-23.60(15)	C(7)-C(8)-C(9)-C(10)	-0.3(3)
O(3)-C(2)-C(6)-C(7)	-156.81(13)	C(8)-C(7)-C(12)-C(11)	-0.3(2)
O(3)-C(4)-C(5)-C(6)	-34.89(14)	C(8)-C(9)-C(10)-C(11)	0.2(3)
O(3)-C(4)-C(5)-C(13)	-154.19(12)	C(9)-C(10)-C(11)-C(12)	-0.1(3)
O(3)-C(4)-C(5)-C(19)	80.09(14)	C(10)-C(11)-C(12)-C(7)	0.1(3)
O(3)-C(4)-C(23)-C(24)	156.97(15)	C(12)-C(7)-C(8)-C(9)	0.4(3)
O(3)-C(4)-C(23)-C(28)	-25.6(2)	C(13)-C(5)-C(6)-C(2)	157.47(12)

C(2)-O(3)-C(4)-C(5)	22.93(16)	C(13)-C(5)-C(6)-C(7)	-70.57(17)
C(2)-O(3)-C(4)-C(23)	148.12(13)	C(13)-C(5)-C(19)-O(20)	151.58(15)
C(2)-C(6)-C(7)-C(8)	-151.32(15)	C(13)-C(5)-C(19)-O(21)	-33.83(18)
C(2)-C(6)-C(7)-C(12)	28.5(2)	C(13)-C(14)-C(15)-C(16)	0.5(2)
C(4)-O(3)-C(2)-O(1)	178.22(14)	C(14)-C(13)-C(18)-C(17)	2.1(3)
C(4)-O(3)-C(2)-C(6)	0.31(16)	C(14)-C(15)-C(16)-C(17)	0.6(3)
C(4)-C(5)-C(6)-C(2)	34.41(14)	C(15)-C(16)-C(17)-C(18)	-0.4(3)
C(4)-C(5)-C(6)-C(7)	166.37(13)	C(16)-C(17)-C(18)-C(13)	-1.0(3)
C(4)-C(5)-C(13)-C(14)	-159.49(14)	C(18)-C(13)-C(14)-C(15)	-1.9(2)
C(4)-C(5)-C(13)-C(18)	27.2(2)	C(19)-C(5)-C(6)-C(2)	-74.74(15)
C(4)-C(5)-C(19)-O(20)	-80.65(17)	C(19)-C(5)-C(6)-C(7)	57.22(18)
C(4)-C(5)-C(19)-O(21)	93.95(14)	C(19)-C(5)-C(13)-C(14)	-38.4(2)
C(4)-C(23)-C(24)-C(25)	176.05(17)	C(19)-C(5)-C(13)-C(18)	148.30(15)
C(4)-C(23)-C(28)-C(27)	-176.01(16)	C(22)-O(21)-C(19)-O(20)	3.6(2)
C(5)-C(4)-C(23)-C(24)	-85.48(19)	C(22)-O(21)-C(19)-C(5)	-170.96(13)
C(5)-C(4)-C(23)-C(28)	91.94(18)	C(23)-C(4)-C(5)-C(6)	-155.05(13)
C(5)-C(6)-C(7)-C(8)	83.27(19)	C(23)-C(4)-C(5)-C(13)	85.65(17)
C(5)-C(6)-C(7)-C(12)	-96.93(18)	C(23)-C(4)-C(5)-C(19)	-40.07(17)
C(5)-C(13)-C(14)-C(15)	-175.48(15)	C(23)-C(24)-C(25)-C(26)	0.7(3)
C(5)-C(13)-C(18)-C(17)	175.51(16)	C(24)-C(23)-C(28)-C(27)	1.4(3)
C(6)-C(5)-C(13)-C(14)	88.45(17)	C(24)-C(25)-C(26)-C(27)	0.0(3)
C(6)-C(5)-C(13)-C(18)	-84.83(18)	C(25)-C(26)-C(27)-C(28)	0.0(3)
C(6)-C(5)-C(19)-O(20)	24.8(2)	C(26)-C(27)-C(28)-C(23)	-0.7(3)
C(6)-C(5)-C(19)-O(21)	-160.64(12)	C(28)-C(23)-C(24)-C(25)	-1.4(3)

Table 4.12 Hydrogen bonds for **300** (Å^2 and °).

Symmetry transformations used to generate equivalent atoms: #1 -x+1,y-1/2,-z+3/2				
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(4)-H(4)...O(20)#1	1.00	2.57	3.2942(19)	129

4.5.2 X-ray crystallography data for 305



A clear colourless block fragment-like specimen of $C_{26}H_{24}O_4$ (**305**), approximate dimensions 0.100 mm x 0.260 mm x 0.360 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 100(2)K with an Oxford Cryosystems low temperature device using a MiTeGen micromount. See Table 4.14 for collection parameters and exposure time. Bruker APEX software was used to correct for Lorentz and polarization effects.

A total of 4075 frames were collected. The total exposure time was 14.80 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using an orthorhombic unit cell yielded a total of 24619 reflections to a maximum θ angle of 69.83° (0.82 Å resolution), of which 3890 were independent (average redundancy 6.329, completeness = 99.5%, R_{int} = 3.62%, R_{sig} = 2.01%) and 3867 (99.41%) were greater than $2\sigma(F^2)$. The final cell constants of a = 9.3111(3) Å, b = 14.0732(5) Å, c = 15.7875(6) Å, volume = 2068.75(13) $Å^3$, are based upon the refinement of the XYZ-centroids of 9982 reflections above 20 σ(I) with 6.280° < 2θ < 139.6°. Data were corrected for absorption effects using the Multi-Scan method

(SADABS). The ratio of minimum to maximum apparent transmission was 0.851. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.6413 and 0.7533.

Using Olex2, the structure was solved with the XT structure solution program using Intrinsic Phasing and refined with the XL refinement package using Least Squares minimisation, using the space group $P2_12_12_1$, with Z = 4 for the formula unit, $C_{26}H_{24}O_4$.The final anisotropic full-matrix least-squares refinement on F^2 with 272 variables converged at R1 = 3.00%, for the observed data and wR2 = 7.73% for all data. The goodness-of-fit was 1.048. The largest peak in the final difference electron density synthesis was 0.168 $e^-/Å^3$ and the largest hole was -0.225 $e^-/Å^3$ with an RMS deviation of 0.044 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.286 g/cm^3 and F(000), 848 e^-.

Refinement Note: The model has chirality at:

C4 = S

C11 = S

C22 = R

Table 4.13 Data collection details for **305**.

Axis	dx/mm	2θ/°	ω/°	φ/°	χ/°	Width/°	Frames	Time/s	Wavelength/Å	Voltage/kV	Current/mA	Temperature/K
Omega	50.043	108.90	95.00	264.00	-54.74	0.90	150	15.00	1.54184	45	0.6	100
Omega	50.043	108.90	95.00	144.00	-54.74	0.90	150	15.00	1.54184	45	0.6	100
Omega	50.043	-49.30	189.65	128.00	54.74	0.90	150	9.00	1.54184	45	0.6	100
Omega	50.043	108.90	95.00	48.00	-54.74	0.90	150	15.00	1.54184	45	0.6	100
Omega	50.043	-49.30	189.65	224.00	54.74	0.90	150	9.00	1.54184	45	0.6	100
Omega	50.043	108.90	341.90	168.00	64.50	0.90	155	15.00	1.54184	45	0.6	100
Omega	50.043	-49.30	298.92	192.00	-64.50	0.90	129	9.00	1.54184	45	0.6	100
Omega	50.043	108.90	341.90	120.00	64.50	0.90	155	15.00	1.54184	45	0.6	100
Omega	50.043	108.90	95.00	240.00	-54.74	0.90	150	15.00	1.54184	45	0.6	100
Omega	50.043	-49.30	298.92	0.00	-64.50	0.90	129	9.00	1.54184	45	0.6	100
Omega	50.043	108.90	95.00	168.00	-54.74	0.90	150	15.00	1.54184	45	0.6	100
Omega	50.043	108.90	95.00	24.00	-54.74	0.90	150	15.00	1.54184	45	0.6	100
Omega	50.043	-49.30	189.66	160.00	54.74	0.90	150	9.00	1.54184	45	0.6	100
Phi	50.043	109.30	95.73	215.75	-57.00	0.90	276	15.00	1.54184	45	0.6	100
Omega	50.043	-11.30	227.66	204.00	54.74	0.90	150	9.00	1.54184	45	0.6	100
Omega	50.043	-49.30	189.65	32.00	54.74	0.90	150	9.00	1.54184	45	0.6	100
Omega	50.043	108.90	95.00	72.00	-54.74	0.90	150	15.00	1.54184	45	0.6	100
Phi	50.043	94.30	80.73	0.00	-57.00	0.90	400	15.00	1.54184	45	0.6	100
Omega	50.043	108.90	95.00	288.00	-54.74	0.90	150	15.00	1.54184	45	0.6	100
Omega	50.043	108.90	95.00	120.00	-54.74	0.90	150	15.00	1.54184	45	0.6	100
Omega	50.043	108.90	341.90	72.00	64.50	0.90	155	15.00	1.54184	45	0.6	100
Omega	50.043	-49.30	189.65	288.00	54.74	0.90	150	9.00	1.54184	45	0.6	100
Omega	50.043	-11.30	227.66	102.00	54.74	0.90	150	9.00	1.54184	45	0.6	100
Phi	55.043	110.89	93.65	215.75	-57.00	0.90	276	15.00	1.54184	45	0.6	100

Table 4.14 Crystal data and structure refinement for **305**.

Identification code	tcd810	
Empirical formula	$C_{26}H_{24}O_4$	
Formula weight	400.45	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 9.3111(3) Å	α = 90°
	b = 14.0732(5) Å	β = 90°
	c = 15.7875(6) Å	γ = 90°
Volume	2068.75(13) $Å^3$	
Z	4	
Density (calculated)	1.286 Mg/m^3	
Absorption coefficient	0.690 mm^{-1}	
F(000)	848	
Crystal size	0.36 x 0.26 x 0.1 mm^3	
Theta range for data collection	4.208 to 69.831°.	
Index ranges	$-11 \leq h \leq 11$, $-17 \leq k \leq 16$, $-19 \leq l \leq 19$	
Reflections collected	24619	
Independent reflections	3890 [R(int) = 0.0362]	
Completeness to theta = 67.679°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7533 and 0.6413	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3890 / 0 / 272	
Goodness-of-fit on F^2	1.048	
Final R indices [I>2σ(I)]	R1 = 0.0300, wR2 = 0.0771	
R indices (all data)	R1 = 0.0301, wR2 = 0.0773	
Absolute structure parameter	-0.08(3)	
Largest diff. peak and hole	0.168 and -0.225 e.$Å^{-3}$	

Table 4.15 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **305**.

U(eq) is defined as one third of the trace of the orthogonalised U_{ij} tensor.

	x	y	z	U(eq)
O(1)	6582(1)	4392(1)	4697(1)	18(1)
O(3)	8109(1)	3205(1)	4458(1)	22(1)
O(13)	8113(1)	4397(1)	6386(1)	19(1)
O(14)	6339(1)	4961(1)	7204(1)	19(1)

C(2)	7131(2)	3522(1)	4863(1)	17(1)
C(4)	6299(2)	3063(1)	5581(1)	16(1)
C(5)	7096(2)	2294(1)	6060(1)	16(1)
C(6)	6348(2)	1490(1)	6332(1)	21(1)
C(7)	7046(2)	761(1)	6763(1)	26(1)
C(8)	8509(2)	825(1)	6922(1)	23(1)
C(9)	9266(2)	1618(1)	6651(1)	20(1)
C(10)	8571(2)	2345(1)	6220(1)	17(1)
C(11)	5676(2)	3949(1)	6055(1)	15(1)
C(12)	6860(2)	4436(1)	6567(1)	15(1)
C(15)	7415(2)	5510(1)	7652(1)	25(1)
C(16)	4339(2)	3729(1)	6573(1)	17(1)
C(17)	4489(2)	3233(1)	7336(1)	21(1)
C(18)	3301(2)	2996(1)	7821(1)	27(1)
C(19)	1939(2)	3250(1)	7552(1)	28(1)
C(20)	1772(2)	3748(1)	6800(1)	26(1)
C(21)	2961(2)	3986(1)	6316(1)	21(1)
C(22)	5396(2)	4594(1)	5270(1)	17(1)
C(23)	5330(2)	5661(1)	5419(1)	20(1)
C(24)	4797(2)	6196(1)	4632(1)	24(1)
C(25)	4832(2)	7268(1)	4736(1)	23(1)
C(26)	5538(2)	7841(1)	4153(1)	29(1)
C(27)	5548(3)	8825(1)	4242(1)	39(1)
C(28)	4873(2)	9250(1)	4921(1)	39(1)
C(29)	4163(3)	8692(1)	5503(2)	41(1)
C(30)	4142(2)	7707(1)	5412(1)	34(1)

Table 4.16 Bond lengths [Å] and angles [°] for **305**.

O(1)-C(2)	1.352(2)	C(20)-C(21)	1.387(2)
O(1)-C(22)	1.4545(18)	C(21)-H(21)	0.9500
O(3)-C(2)	1.199(2)	C(22)-H(22)	1.0000
O(13)-C(12)	1.2025(19)	C(22)-C(23)	1.521(2)
O(14)-C(12)	1.3386(19)	C(23)-H(23A)	0.9900
O(14)-C(15)	1.450(2)	C(23)-H(23B)	0.9900
C(2)-C(4)	1.518(2)	C(23)-C(24)	1.536(2)
C(4)-H(4)	1.0000	C(24)-H(24A)	0.9900
C(4)-C(5)	1.515(2)	C(24)-H(24B)	0.9900
C(4)-C(11)	1.565(2)	C(24)-C(25)	1.517(2)
C(5)-C(6)	1.396(2)	C(25)-C(26)	1.388(3)
C(5)-C(10)	1.399(2)	C(25)-C(30)	1.390(3)
C(6)-H(6)	0.9500	C(26)-H(26)	0.9500

C(6)-C(7)	1.392(2)	C(26)-C(27)	1.392(3)
C(7)-H(7)	0.9500	C(27)-H(27)	0.9500
C(7)-C(8)	1.389(2)	C(27)-C(28)	1.379(3)
C(8)-H(8)	0.9500	C(28)-H(28)	0.9500
C(8)-C(9)	1.386(2)	C(28)-C(29)	1.379(3)
C(9)-H(9)	0.9500	C(29)-H(29)	0.9500
C(9)-C(10)	1.389(2)	C(29)-C(30)	1.395(3)
C(10)-H(10)	0.9500	C(30)-H(30)	0.9500
C(11)-C(12)	1.529(2)		
C(11)-C(16)	1.521(2)	C(2)-O(1)-C(22)	110.08(12)
C(11)-C(22)	1.559(2)	C(12)-O(14)-C(15)	114.23(12)
C(15)-H(15A)	0.9800	O(1)-C(2)-C(4)	109.71(13)
C(15)-H(15B)	0.9800	O(3)-C(2)-O(1)	121.44(14)
C(15)-H(15C)	0.9800	O(3)-C(2)-C(4)	128.83(15)
C(16)-C(17)	1.399(2)	C(2)-C(4)-H(4)	105.9
C(16)-C(21)	1.393(2)	C(2)-C(4)-C(11)	101.94(12)
C(17)-H(17)	0.9500	C(5)-C(4)-C(2)	115.27(12)
C(17)-C(18)	1.386(2)	C(5)-C(4)-H(4)	105.9
C(18)-H(18)	0.9500	C(5)-C(4)-C(11)	120.82(12)
C(18)-C(19)	1.384(3)	C(11)-C(4)-H(4)	105.9
C(19)-H(19)	0.9500	C(6)-C(5)-C(4)	119.22(13)
C(19)-C(20)	1.386(3)	C(6)-C(5)-C(10)	118.43(14)
C(20)-H(20)	0.9500	C(10)-C(5)-C(4)	122.32(14)
C(5)-C(6)-H(6)	119.5	C(19)-C(18)-H(18)	120.0
C(7)-C(6)-C(5)	120.99(15)	C(18)-C(19)-H(19)	120.1
C(7)-C(6)-H(6)	119.5	C(18)-C(19)-C(20)	119.71(16)
C(6)-C(7)-H(7)	120.0	C(20)-C(19)-H(19)	120.1
C(8)-C(7)-C(6)	119.91(16)	C(19)-C(20)-H(20)	119.9
C(8)-C(7)-H(7)	120.0	C(19)-C(20)-C(21)	120.26(17)
C(7)-C(8)-H(8)	120.2	C(21)-C(20)-H(20)	119.9
C(9)-C(8)-C(7)	119.64(16)	C(16)-C(21)-H(21)	119.6
C(9)-C(8)-H(8)	120.2	C(20)-C(21)-C(16)	120.84(16)
C(8)-C(9)-H(9)	119.7	C(20)-C(21)-H(21)	119.6
C(8)-C(9)-C(10)	120.51(15)	O(1)-C(22)-C(11)	104.71(12)
C(10)-C(9)-H(9)	119.7	O(1)-C(22)-H(22)	108.6
C(5)-C(10)-H(10)	119.7	O(1)-C(22)-C(23)	108.66(12)
C(9)-C(10)-C(5)	120.51(14)	C(11)-C(22)-H(22)	108.6
C(9)-C(10)-H(10)	119.7	C(23)-C(22)-C(11)	117.31(13)
C(12)-C(11)-C(4)	110.02(12)	C(23)-C(22)-H(22)	108.6
C(12)-C(11)-C(22)	106.23(12)	C(22)-C(23)-H(23A)	109.3
C(16)-C(11)-C(4)	113.49(12)	C(22)-C(23)-H(23B)	109.3
C(16)-C(11)-C(12)	113.37(12)	C(22)-C(23)-C(24)	111.83(13)
C(16)-C(11)-C(22)	114.17(12)	H(23A)-C(23)-H(23B)	107.9

C(22)-C(11)-C(4)	98.39(11)	C(24)-C(23)-H(23A)	109.3
O(13)-C(12)-O(14)	123.67(14)	C(24)-C(23)-H(23B)	109.3
O(13)-C(12)-C(11)	123.63(14)	C(23)-C(24)-H(24A)	108.9
O(14)-C(12)-C(11)	112.54(12)	C(23)-C(24)-H(24B)	108.9
O(14)-C(15)-H(15A)	109.5	H(24A)-C(24)-H(24B)	107.8
O(14)-C(15)-H(15B)	109.5	C(25)-C(24)-C(23)	113.17(14)
O(14)-C(15)-H(15C)	109.5	C(25)-C(24)-H(24A)	108.9
H(15A)-C(15)-H(15B)	109.5	C(25)-C(24)-H(24B)	108.9
H(15A)-C(15)-H(15C)	109.5	C(26)-C(25)-C(24)	121.05(16)
H(15B)-C(15)-H(15C)	109.5	C(26)-C(25)-C(30)	118.02(16)
C(17)-C(16)-C(11)	118.86(14)	C(30)-C(25)-C(24)	120.92(16)
C(21)-C(16)-C(11)	123.00(14)	C(25)-C(26)-H(26)	119.5
C(21)-C(16)-C(17)	118.13(15)	C(25)-C(26)-C(27)	120.93(19)
C(16)-C(17)-H(17)	119.5	C(27)-C(26)-H(26)	119.5
C(18)-C(17)-C(16)	121.05(17)	C(26)-C(27)-H(27)	119.8
C(18)-C(17)-H(17)	119.5	C(28)-C(27)-C(26)	120.47(19)
C(17)-C(18)-H(18)	120.0	C(28)-C(27)-H(27)	119.8
C(19)-C(18)-C(17)	120.00(16)	C(27)-C(28)-H(28)	120.3
C(29)-C(28)-C(27)	119.34(18)	C(30)-C(29)-H(29)	119.9
C(29)-C(28)-H(28)	120.3	C(25)-C(30)-C(29)	120.96(19)
C(28)-C(29)-H(29)	119.9	C(25)-C(30)-H(30)	119.5
C(28)-C(29)-C(30)	120.3(2)	C(29)-C(30)-H(30)	119.5

Table 4.17 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **305**.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}\ U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$						
	U_{11}	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
O(1)	20(1)	18(1)	17(1)	2(1)	2(1)	2(1)
O(3)	21(1)	24(1)	20(1)	1(1)	5(1)	4(1)
O(13)	14(1)	19(1)	25(1)	-3(1)	1(1)	-1(1)
O(14)	17(1)	22(1)	18(1)	-6(1)	0(1)	-1(1)
C(2)	16(1)	18(1)	16(1)	-2(1)	-3(1)	-1(1)
C(4)	14(1)	16(1)	16(1)	-1(1)	0(1)	-1(1)
C(5)	15(1)	16(1)	15(1)	-2(1)	1(1)	2(1)
C(6)	16(1)	21(1)	26(1)	2(1)	0(1)	-1(1)
C(7)	26(1)	19(1)	33(1)	6(1)	2(1)	-3(1)
C(8)	25(1)	22(1)	23(1)	3(1)	-1(1)	5(1)
C(9)	18(1)	21(1)	21(1)	-3(1)	-2(1)	4(1)
C(10)	16(1)	16(1)	18(1)	-2(1)	1(1)	0(1)
C(11)	14(1)	14(1)	17(1)	-1(1)	-2(1)	0(1)
C(12)	16(1)	14(1)	15(1)	2(1)	-1(1)	1(1)

C(15)	23(1)	29(1)	24(1)	-9(1)	-5(1)	-4(1)
C(16)	16(1)	14(1)	21(1)	-4(1)	2(1)	-1(1)
C(17)	21(1)	19(1)	23(1)	-1(1)	3(1)	0(1)
C(18)	32(1)	23(1)	26(1)	-2(1)	10(1)	-5(1)
C(19)	24(1)	24(1)	36(1)	-10(1)	14(1)	-8(1)
C(20)	14(1)	26(1)	38(1)	-13(1)	2(1)	-3(1)
C(21)	18(1)	18(1)	26(1)	-6(1)	0(1)	-1(1)
C(22)	14(1)	19(1)	16(1)	0(1)	0(1)	1(1)
C(23)	21(1)	18(1)	20(1)	0(1)	-2(1)	2(1)
C(24)	31(1)	20(1)	23(1)	2(1)	-5(1)	2(1)
C(25)	24(1)	20(1)	25(1)	3(1)	-7(1)	3(1)
C(26)	35(1)	26(1)	25(1)	3(1)	-6(1)	-4(1)
C(27)	54(1)	26(1)	37(1)	8(1)	-12(1)	-12(1)
C(28)	56(1)	19(1)	42(1)	0(1)	-21(1)	3(1)
C(29)	52(1)	29(1)	42(1)	-5(1)	-5(1)	15(1)
C(30)	39(1)	25(1)	37(1)	4(1)	4(1)	8(1)

Table 4.18 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **305**.

	x	**y**	**z**	**U(eq)**
H(4)	5457	2742	5311	19
H(6)	5348	1440	6221	25
H(7)	6521	221	6948	31
H(8)	8990	329	7216	28
H(9)	10266	1663	6761	24
H(10)	9103	2881	6032	20
H(15A)	7968	5889	7245	38
H(15B)	8062	5079	7955	38
H(15C)	6943	5934	8058	38
H(17)	5420	3056	7525	25
H(18)	3421	2659	8337	32
H(19)	1122	3085	7881	33
H(20)	838	3926	6616	31
H(21)	2835	4329	5803	25
H(22)	4481	4388	4994	20
H(23A)	6298	5895	5573	23
H(23B)	4678	5793	5900	23
H(24A)	5402	6018	4141	29
H(24B)	3800	5996	4507	29
H(26)	6020	7557	3687	35
H(27)	6024	9206	3832	47

	x	y	z	U(eq)
H(28)	4897	9921	4986	47
H(29)	3685	8980	5969	49
H(30)	3649	7329	5817	40

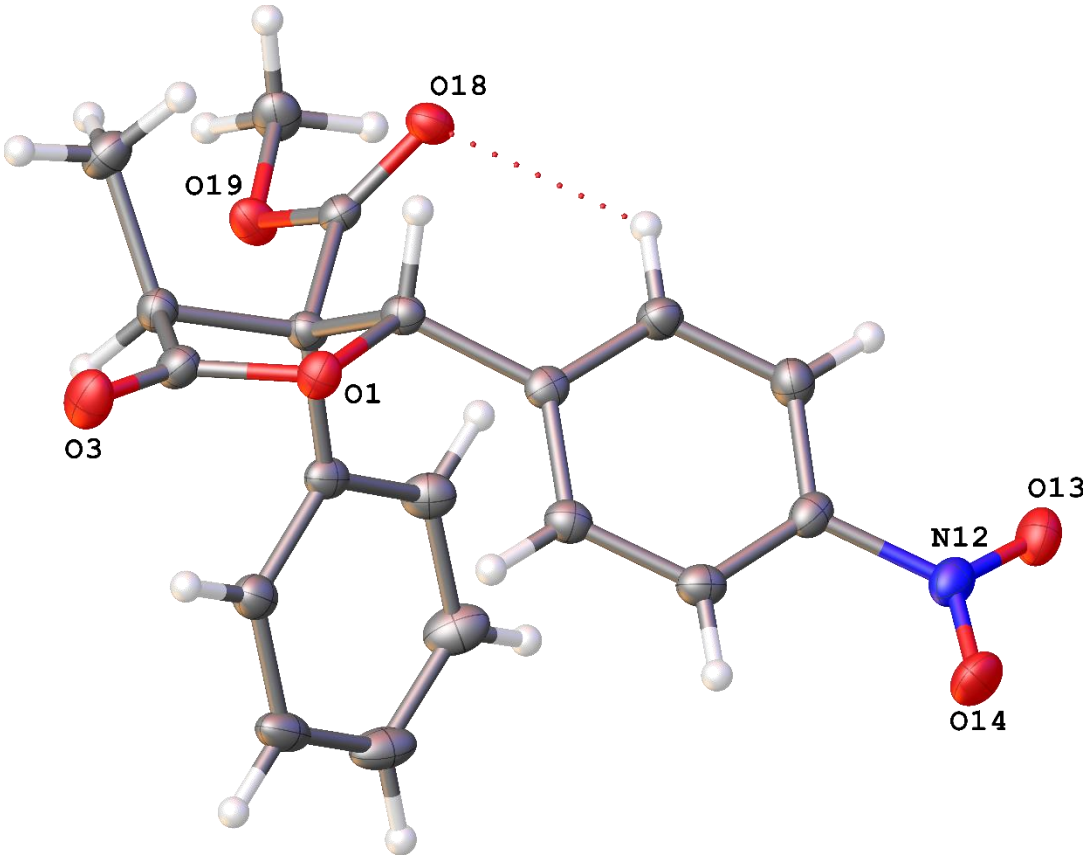
Table 4.19 Torsion angles [°] for **305**.

O(1)-C(2)-C(4)-C(5)	-157.25(12)	C(12)-C(11)-C(16)-C(17)	-52.01(18)
O(1)-C(2)-C(4)-C(11)	-24.49(15)	C(12)-C(11)-C(16)-C(21)	129.10(15)
O(1)-C(22)-C(23)-C(24)	71.37(16)	C(12)-C(11)-C(22)-O(1)	77.45(14)
O(3)-C(2)-C(4)-C(5)	24.6(2)	C(12)-C(11)-C(22)-C(23)	-43.07(17)
O(3)-C(2)-C(4)-C(11)	157.36(16)	C(15)-O(14)-C(12)-O(13)	1.6(2)
C(2)-O(1)-C(22)-C(11)	23.67(15)	C(15)-O(14)-C(12)-C(11)	-174.11(13)
C(2)-O(1)-C(22)-C(23)	149.78(12)	C(16)-C(11)-C(12)-O(13)	155.04(14)
C(2)-C(4)-C(5)-C(6)	-141.92(14)	C(16)-C(11)-C(12)-O(14)	-29.24(17)
C(2)-C(4)-C(5)-C(10)	36.2(2)	C(16)-C(11)-C(22)-O(1)	-156.86(12)
C(2)-C(4)-C(11)-C(12)	-75.19(14)	C(16)-C(11)-C(22)-C(23)	82.62(17)
C(2)-C(4)-C(11)-C(16)	156.60(13)	C(16)-C(17)-C(18)-C(19)	0.0(3)
C(2)-C(4)-C(11)-C(22)	35.57(13)	C(17)-C(16)-C(21)-C(20)	-0.6(2)
C(4)-C(5)-C(6)-C(7)	179.09(15)	C(17)-C(18)-C(19)-C(20)	-0.4(3)
C(4)-C(5)-C(10)-C(9)	-179.10(14)	C(18)-C(19)-C(20)-C(21)	0.3(2)
C(4)-C(11)-C(12)-O(13)	26.8(2)	C(19)-C(20)-C(21)-C(16)	0.2(2)
C(4)-C(11)-C(12)-O(14)	-157.52(12)	C(21)-C(16)-C(17)-C(18)	0.5(2)
C(4)-C(11)-C(16)-C(17)	74.46(18)	C(22)-O(1)-C(2)-O(3)	179.07(14)
C(4)-C(11)-C(16)-C(21)	-104.43(17)	C(22)-O(1)-C(2)-C(4)	0.76(16)
C(4)-C(11)-C(22)-O(1)	-36.34(13)	C(22)-C(11)-C(12)-O(13)	-78.78(18)
C(4)-C(11)-C(22)-C(23)	-156.85(13)	C(22)-C(11)-C(12)-O(14)	96.94(14)
C(5)-C(4)-C(11)-C(12)	54.18(17)	C(22)-C(11)-C(16)-C(17)	-173.85(13)
C(5)-C(4)-C(11)-C(16)	-74.04(17)	C(22)-C(11)-C(16)-C(21)	7.3(2)
C(5)-C(4)-C(11)-C(22)	164.93(13)	C(22)-C(23)-C(24)-C(25)	-175.37(15)
C(5)-C(6)-C(7)-C(8)	-0.5(3)	C(23)-C(24)-C(25)-C(26)	126.20(18)
C(6)-C(5)-C(10)-C(9)	-1.0(2)	C(23)-C(24)-C(25)-C(30)	-54.6(2)
C(6)-C(7)-C(8)-C(9)	0.1(3)	C(24)-C(25)-C(26)-C(27)	178.94(18)
C(7)-C(8)-C(9)-C(10)	-0.2(3)	C(24)-C(25)-C(30)-C(29)	-179.43(19)
C(8)-C(9)-C(10)-C(5)	0.6(2)	C(25)-C(26)-C(27)-C(28)	1.0(3)
C(10)-C(5)-C(6)-C(7)	0.9(2)	C(26)-C(25)-C(30)-C(29)	-0.2(3)
C(11)-C(4)-C(5)-C(6)	94.85(17)	C(26)-C(27)-C(28)-C(29)	-1.2(3)
C(11)-C(4)-C(5)-C(10)	-87.06(18)	C(27)-C(28)-C(29)-C(30)	0.7(3)
C(11)-C(16)-C(17)-C(18)	-178.42(15)	C(28)-C(29)-C(30)-C(25)	0.0(3)
C(11)-C(16)-C(21)-C(20)	178.27(14)	C(30)-C(25)-C(26)-C(27)	-0.3(3)
C(11)-C(22)-C(23)-C(24)	-170.21(13)		

Table 4.20 Hydrogen bonds for **305** (Å^2 and °).

Symmetry transformations used to generate equivalent atoms: #1 x-1/2,-y+1/2,-z+1 #2 -x+3/2,-y+1,z+1/2				
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(4)-H(4)...O(3)#1	1.00	2.59	3.4647(18)	147
C(15)-H(15C)...O(3)#2	0.98	2.52	3.413(2)	151

4.5.3 X-ray crystallography data for 368a



A clear colourless fragment-like specimen of $C_{19}H_{17}NO_6$ (**368a**), approximate dimensions 0.110 mm x 0.260 mm x 0.500 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 100(2)K on a Bruker D8 Quest ECO with an Oxford Cryostream low temperature device using a MiTeGen micromount. See Table 4.22 for collection parameters and exposure time. Bruker APEX software was used to correct for Lorentz and polarization effects.

A total of 7382 frames were collected. The total exposure time was 14.35 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a hexagonal unit cell yielded a total of 41115 reflections to a maximum θ angle of 69.94° (0.82Å resolution), of which 3197 were independent (average redundancy 12.860, completeness = 99.6%, R_{int} = 3.69%, R_{sig} = 1.49%) and 3194 (99.91%) were greater than $2\sigma(F^2)$. The final cell constants of a = 9.3038(3) Å, b = 9.3038(3) Å, c = 33.9408(13) Å, volume = 2544.33(19) $Å^3$, are based upon the refinement of the XYZ-centroids of 9971 reflections above 20 σ(I) with

$10.42° < 2\theta < 139.8°$. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.890. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.6704 and 0.7533.

The structure was solved with the XT structure solution program using Intrinsic Phasing and refined with the XL refinement package using Least Squares minimisation with Olex2, using the space group $P6_1$, with Z = 6 for the formula unit, $C_{19}H_{17}NO_6$. The final anisotropic full-matrix least-squares refinement on F^2 with 237 variables converged at R1 = 2.56%, for the observed data and wR2 = 6.61% for all data. The goodness-of-fit was 1.060. The largest peak in the final difference electron density synthesis was 0.181 $e^-/Å^3$ and the largest hole was -0.188 $e^-/Å^3$ with an RMS deviation of 0.037 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.391 g/cm^3 and F(000), 1116 e^-.

Refinement Note: Flack parameter refined. Chiral Centres:

C4 = S

C6 = S

C7 = S

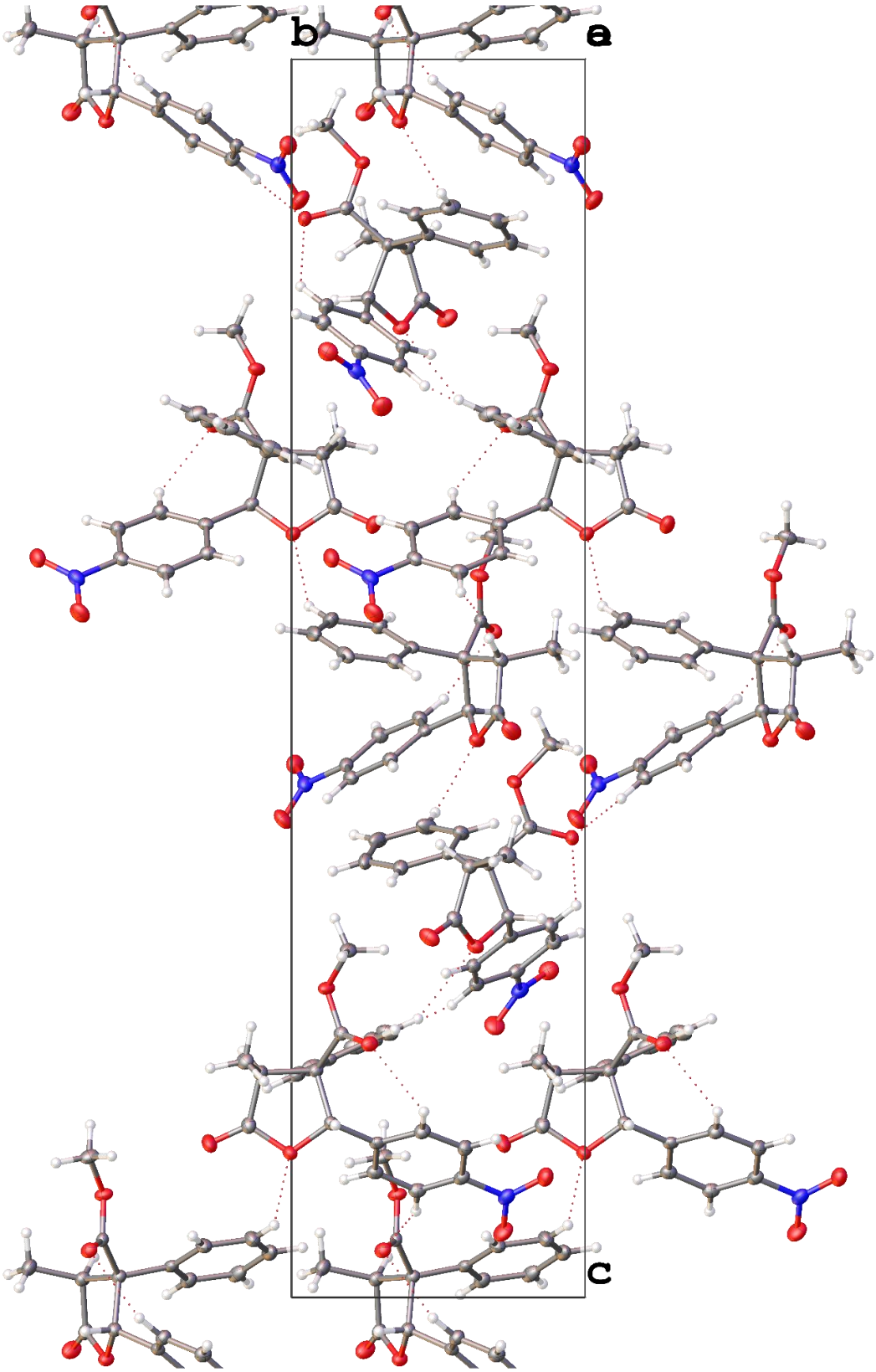


Figure 4.2 Packing diagram of **368a** viewed normal to the a-axis. Dotted lines indicate hydrogen bonds.

Table 4.21 Data collection details for **368a**.

Axis	dx/mm	2θ/°	ω/°	φ/°	χ/°	Width/°	Frames	Time/s	Wavelength/Å	Voltage/kV	Current/mA	Temperature/K
Omega	50.004	108.90	95.60	168.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	48.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Omega	50.004	-49.30	298.82	32.00	-64.50	0.70	166	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	120.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Phi	50.004	-47.74	343.92	252.00	23.00	0.70	309	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	0.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	72.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	192.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Omega	50.004	-49.30	298.82	256.00	-64.50	0.70	166	7.00	1.54184	45	0.6	100
Phi	50.004	79.30	65.73	360.00	-57.00	0.70	514	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	96.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	24.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	144.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Omega	50.004	-49.30	298.82	96.00	-64.50	0.70	166	7.00	1.54184	45	0.6	100
Phi	50.004	-7.14	24.51	296.58	23.00	0.70	284	7.00	1.54184	45	0.6	100
Phi	50.004	109.30	95.73	360.00	-57.00	0.70	514	7.00	1.54184	45	0.6	100
Phi	50.004	-49.30	73.15	0.00	-57.00	0.70	514	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	216.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Phi	50.004	94.30	80.73	360.00	-57.00	0.70	514	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	342.10	216.00	64.50	0.70	199	7.00	1.54184	45	0.6	100
Omega	50.004	108.90	95.60	264.00	-54.74	0.70	192	7.00	1.54184	45	0.6	100
Phi	50.004	-47.74	325.81	360.00	57.00	0.70	514	7.00	1.54184	45	0.6	100
Omega	55.004	-55.62	289.02	160.00	-64.50	0.70	180	7.00	1.54184	45	0.6	100
Omega	55.004	-55.62	178.62	32.00	54.74	0.70	205	7.00	1.54184	45	0.6	100
Omega	55.004	110.58	93.09	168.00	-54.74	0.70	205	7.00	1.54184	45	0.6	100
Omega	55.004	110.58	93.09	120.00	-54.74	0.70	205	7.00	1.54184	45	0.6	100
Omega	55.004	-55.62	178.62	96.00	54.74	0.70	205	7.00	1.54184	45	0.6	100
Omega	55.004	110.58	93.09	192.00	-54.74	0.70	205	7.00	1.54184	45	0.6	100
Omega	55.004	110.58	93.09	72.00	-54.74	0.70	205	7.00	1.54184	45	0.6	100

Table 4.22 Crystal data and structure refinement for **368a**.

Identification code	tcd893	
Empirical formula	$C_{19}H_{17}F_6NO_6$	
Formula weight	355.33	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Hexagonal	
Space group	$P6_1$	
Unit cell dimensions	a = 9.3038(3) Å	α = 90°
	b = 9.3038(4) Å	β = 90°
	c = 33.9408(13) Å	γ = 120°
Volume	2544.33(19) $Å^3$	
Z	6	
Density (calculated)	1.391 Mg/m^3	
Absorption coefficient	0.876 mm^{-1}	
F(000)	1116	
Crystal size	0.5 x 0.26 x 0.11 mm^3	
Theta range for data collection	5.490 to 69.943°.	
Index ranges	$-11\leq h\leq 11$, $-10\leq k\leq 11$, $-40\leq l\leq 41$	
Reflections collected	41115	
Independent reflections	3197 [R(int) = 0.0369]	
Completeness to theta = 67.679°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7533 and 0.6704	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3197 / 1 / 237	
Goodness-of-fit on F^2	1.060	
Final R indices [I>2σ(I)]	R1 = 0.0256, wR2 = 0.0661	
R indices (all data)	R1 = 0.0256, wR2 = 0.0661	
Absolute structure parameter	0.03(3)	
Largest diff. peak and hole	0.181 and -0.188 e.$Å^{-3}$	

Table 4.23 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **368a**.

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	3738(2)	3686(2)	5501(1)	19(1)
C(2)	4447(2)	2987(2)	5279(1)	20(1)
O(3)	5305(2)	2509(2)	5425(1)	28(1)
C(4)	3941(2)	2886(2)	4852(1)	19(1)

C(5)	2651(2)	1070(2)	4760(1)	24(1)
C(6)	3288(2)	4125(2)	4834(1)	16(1)
C(7)	2612(2)	3971(2)	5262(1)	17(1)
C(8)	2537(2)	5453(2)	5421(1)	17(1)
C(9)	1177(2)	5633(2)	5327(1)	20(1)
C(10)	1076(2)	6988(2)	5461(1)	22(1)
C(11)	2334(2)	8131(2)	5700(1)	20(1)
N(12)	2216(2)	9542(2)	5855(1)	23(1)
O(13)	1239(2)	9883(2)	5696(1)	28(1)
O(14)	3087(2)	10294(2)	6139(1)	31(1)
C(15)	3695(2)	7980(2)	5804(1)	20(1)
C(16)	3799(2)	6644(2)	5656(1)	19(1)
C(17)	1873(2)	3560(2)	4537(1)	16(1)
O(18)	450(2)	3105(2)	4621(1)	20(1)
O(19)	2413(2)	3603(2)	4171(1)	21(1)
C(20)	1168(2)	3110(2)	3864(1)	23(1)
C(21)	4650(2)	5906(2)	4750(1)	18(1)
C(22)	4227(2)	7015(2)	4584(1)	22(1)
C(23)	5414(3)	8668(2)	4531(1)	29(1)
C(24)	7051(3)	9246(2)	4640(1)	29(1)
C(25)	7480(2)	8157(2)	4811(1)	26(1)
C(26)	6285(2)	6494(2)	4864(1)	21(1)

Table 4.24 Bond lengths [Å] and angles [°] for **368a**.

O(1)-C(2)	1.361(2)	C(23)-H(23)	0.9500
O(1)-C(7)	1.450(2)	C(23)-C(24)	1.389(3)
C(2)-O(3)	1.198(2)	C(24)-H(24)	0.9500
C(2)-C(4)	1.511(2)	C(24)-C(25)	1.388(3)
C(4)-H(4)	1.0000	C(25)-H(25)	0.9500
C(4)-C(5)	1.538(2)	C(25)-C(26)	1.394(3)
C(4)-C(6)	1.551(2)	C(26)-H(26)	0.9500
C(5)-H(5A)	0.9800		
C(5)-H(5B)	0.9800	C(2)-O(1)-C(7)	110.18(13)
C(5)-H(5C)	0.9800	O(1)-C(2)-C(4)	110.43(14)
C(6)-C(7)	1.560(2)	O(3)-C(2)-O(1)	121.37(17)
C(6)-C(17)	1.528(2)	O(3)-C(2)-C(4)	128.17(17)
C(6)-C(21)	1.527(2)	C(2)-C(4)-H(4)	110.2
C(7)-H(7)	1.0000	C(2)-C(4)-C(5)	108.18(15)
C(7)-C(8)	1.514(2)	C(2)-C(4)-C(6)	102.59(13)
C(8)-C(9)	1.394(3)	C(5)-C(4)-H(4)	110.2
C(8)-C(16)	1.394(2)	C(5)-C(4)-C(6)	115.29(15)

C(9)-H(9)	0.9500	C(6)-C(4)-H(4)	110.2
C(9)-C(10)	1.387(3)	C(4)-C(5)-H(5A)	109.5
C(10)-H(10)	0.9500	C(4)-C(5)-H(5B)	109.5
C(10)-C(11)	1.384(3)	C(4)-C(5)-H(5C)	109.5
C(11)-N(12)	1.468(2)	H(5A)-C(5)-H(5B)	109.5
C(11)-C(15)	1.388(3)	H(5A)-C(5)-H(5C)	109.5
N(12)-O(13)	1.229(2)	H(5B)-C(5)-H(5C)	109.5
N(12)-O(14)	1.227(2)	C(4)-C(6)-C(7)	100.61(13)
C(15)-H(15)	0.9500	C(17)-C(6)-C(4)	111.18(13)
C(15)-C(16)	1.388(3)	C(17)-C(6)-C(7)	110.20(13)
C(16)-H(16)	0.9500	C(21)-C(6)-C(4)	113.13(14)
C(17)-O(18)	1.206(2)	C(21)-C(6)-C(7)	110.51(14)
C(17)-O(19)	1.331(2)	C(21)-C(6)-C(17)	110.80(14)
O(19)-C(20)	1.452(2)	O(1)-C(7)-C(6)	104.06(13)
C(20)-H(20A)	0.9800	O(1)-C(7)-H(7)	108.8
C(20)-H(20B)	0.9800	O(1)-C(7)-C(8)	109.45(13)
C(20)-H(20C)	0.9800	C(6)-C(7)-H(7)	108.8
C(21)-C(22)	1.395(3)	C(8)-C(7)-C(6)	116.64(14)
C(21)-C(26)	1.389(3)	C(8)-C(7)-H(7)	108.8
C(22)-H(22)	0.9500	C(9)-C(8)-C(7)	119.03(15)
C(22)-C(23)	1.385(3)	C(9)-C(8)-C(16)	119.35(16)
C(16)-C(8)-C(7)	121.61(16)	O(19)-C(20)-H(20B)	109.5
C(8)-C(9)-H(9)	119.6	O(19)-C(20)-H(20C)	109.5
C(10)-C(9)-C(8)	120.78(17)	H(20A)-C(20)-H(20B)	109.5
C(10)-C(9)-H(9)	119.6	H(20A)-C(20)-H(20C)	109.5
C(9)-C(10)-H(10)	120.8	H(20B)-C(20)-H(20C)	109.5
C(11)-C(10)-C(9)	118.41(17)	C(22)-C(21)-C(6)	119.34(15)
C(11)-C(10)-H(10)	120.8	C(26)-C(21)-C(6)	121.83(16)
C(10)-C(11)-N(12)	119.02(17)	C(26)-C(21)-C(22)	118.62(17)
C(10)-C(11)-C(15)	122.31(17)	C(21)-C(22)-H(22)	119.6
C(15)-C(11)-N(12)	118.67(16)	C(23)-C(22)-C(21)	120.75(18)
O(13)-N(12)-C(11)	117.96(16)	C(23)-C(22)-H(22)	119.6
O(14)-N(12)-C(11)	117.91(16)	C(22)-C(23)-H(23)	119.8
O(14)-N(12)-O(13)	124.13(16)	C(22)-C(23)-C(24)	120.41(19)
C(11)-C(15)-H(15)	120.8	C(24)-C(23)-H(23)	119.8
C(16)-C(15)-C(11)	118.37(16)	C(23)-C(24)-H(24)	120.4
C(16)-C(15)-H(15)	120.8	C(25)-C(24)-C(23)	119.29(18)
C(8)-C(16)-H(16)	119.6	C(25)-C(24)-H(24)	120.4
C(15)-C(16)-C(8)	120.72(16)	C(24)-C(25)-H(25)	119.9
C(15)-C(16)-H(16)	119.6	C(24)-C(25)-C(26)	120.21(18)
O(18)-C(17)-C(6)	124.67(15)	C(26)-C(25)-H(25)	119.9
O(18)-C(17)-O(19)	124.31(16)	C(21)-C(26)-C(25)	120.71(18)
O(19)-C(17)-C(6)	111.02(14)	C(21)-C(26)-H(26)	119.6

C(17)-O(19)-C(20)	115.55(13)	C(25)-C(26)-H(26)	119.6
O(19)-C(20)-H(20A)	109.5		

Table 4.25 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **368a**.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}\ U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	23(1)	21(1)	16(1)	-1(1)	-3(1)	13(1)
C(2)	21(1)	17(1)	22(1)	-2(1)	-2(1)	9(1)
O(3)	34(1)	32(1)	27(1)	-6(1)	-10(1)	23(1)
C(4)	19(1)	20(1)	19(1)	-2(1)	0(1)	10(1)
C(5)	28(1)	20(1)	23(1)	-4(1)	-4(1)	12(1)
C(6)	14(1)	18(1)	16(1)	-2(1)	-1(1)	7(1)
C(7)	17(1)	17(1)	17(1)	0(1)	-2(1)	8(1)
C(8)	19(1)	17(1)	13(1)	2(1)	3(1)	7(1)
C(9)	19(1)	20(1)	20(1)	-3(1)	-2(1)	8(1)
C(10)	22(1)	24(1)	21(1)	-1(1)	0(1)	13(1)
C(11)	23(1)	16(1)	18(1)	1(1)	4(1)	9(1)
N(12)	26(1)	20(1)	22(1)	0(1)	6(1)	10(1)
O(13)	33(1)	25(1)	30(1)	0(1)	3(1)	19(1)
O(14)	34(1)	27(1)	31(1)	-12(1)	-3(1)	15(1)
C(15)	19(1)	20(1)	18(1)	-1(1)	0(1)	6(1)
C(16)	18(1)	20(1)	17(1)	1(1)	1(1)	8(1)
C(17)	18(1)	13(1)	17(1)	-1(1)	-1(1)	6(1)
O(18)	16(1)	22(1)	19(1)	-2(1)	-1(1)	7(1)
O(19)	19(1)	28(1)	14(1)	-3(1)	-2(1)	12(1)
C(20)	24(1)	30(1)	18(1)	-5(1)	-6(1)	15(1)
C(21)	18(1)	19(1)	13(1)	-2(1)	2(1)	7(1)
C(22)	23(1)	22(1)	18(1)	1(1)	-3(1)	8(1)
C(23)	36(1)	22(1)	22(1)	4(1)	-2(1)	9(1)
C(24)	29(1)	21(1)	21(1)	-1(1)	4(1)	0(1)
C(25)	16(1)	28(1)	24(1)	-7(1)	1(1)	4(1)
C(26)	20(1)	23(1)	20(1)	-4(1)	1(1)	10(1)

Table 4.26 Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for **368a**.

	x	y	z	U(eq)
H(4)	4931	3269	4678	22
H(5A)	3124	359	4817	36

	x	y	z	U(eq)
H(5B)	2344	969	4481	36
H(5C)	1662	726	4923	36
H(7)	1479	2970	5277	21
H(9)	309	4817	5169	24
H(10)	166	7129	5390	26
H(15)	4535	8772	5972	25
H(16)	4740	6540	5716	23
H(20A)	1672	3143	3608	35
H(20B)	731	3875	3861	35
H(20C)	262	1980	3915	35
H(22)	3112	6633	4507	27
H(23)	5106	9410	4418	35
H(24)	7868	10375	4599	35
H(25)	8593	8546	4892	31
H(26)	6591	5756	4979	26

Table 4.27 Torsion angles [°] for **368a**.

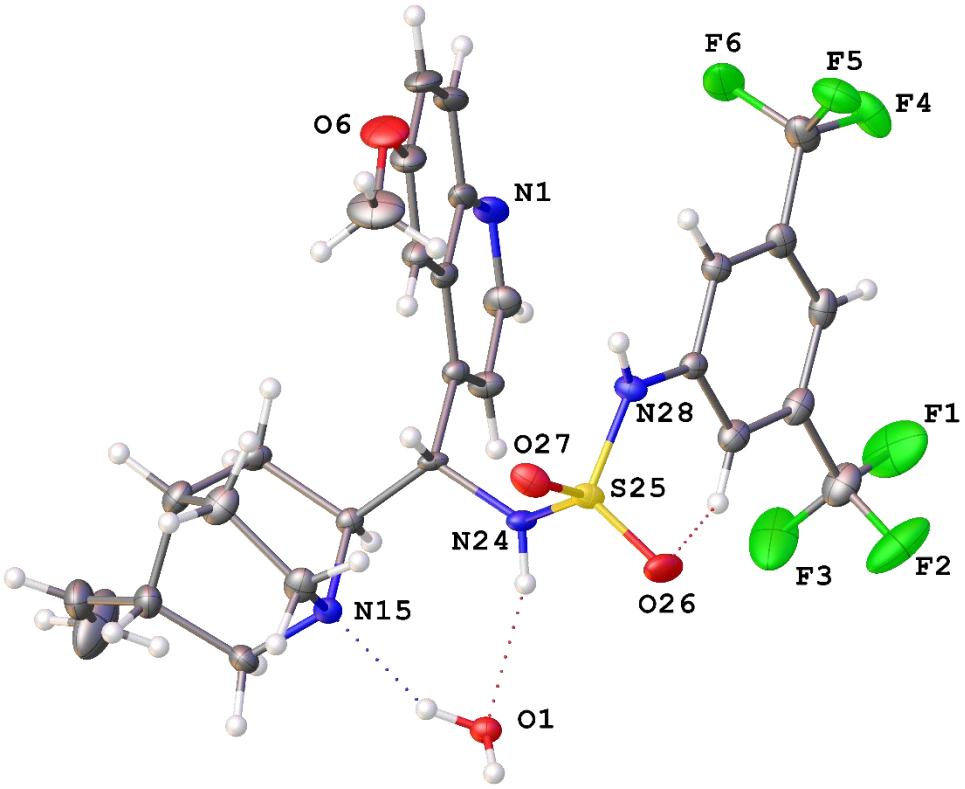
O(1)-C(2)-C(4)-C(5)	-104.99(17)	C(7)-C(6)-C(21)-C(26)	83.1(2)
O(1)-C(2)-C(4)-C(6)	17.30(18)	C(7)-C(8)-C(9)-C(10)	-178.84(16)
O(1)-C(7)-C(8)-C(9)	-159.14(15)	C(7)-C(8)-C(16)-C(15)	-179.06(16)
O(1)-C(7)-C(8)-C(16)	21.3(2)	C(8)-C(9)-C(10)-C(11)	-2.0(3)
C(2)-O(1)-C(7)-C(6)	-25.26(17)	C(9)-C(8)-C(16)-C(15)	1.4(3)
C(2)-O(1)-C(7)-C(8)	-150.62(14)	C(9)-C(10)-C(11)-N(12)	-177.99(16)
C(2)-C(4)-C(6)-C(7)	-30.33(16)	C(9)-C(10)-C(11)-C(15)	1.2(3)
C(2)-C(4)-C(6)-C(17)	-147.04(14)	C(10)-C(11)-N(12)-O(13)	-17.1(2)
C(2)-C(4)-C(6)-C(21)	87.54(17)	C(10)-C(11)-N(12)-O(14)	162.05(17)
O(3)-C(2)-C(4)-C(5)	73.2(2)	C(10)-C(11)-C(15)-C(16)	0.9(3)
O(3)-C(2)-C(4)-C(6)	-164.55(19)	C(11)-C(15)-C(16)-C(8)	-2.2(3)
C(4)-C(6)-C(7)-O(1)	33.96(15)	N(12)-C(11)-C(15)-C(16)	-179.95(15)
C(4)-C(6)-C(7)-C(8)	154.61(14)	C(15)-C(11)-N(12)-O(13)	163.69(16)
C(4)-C(6)-C(17)-O(18)	112.54(19)	C(15)-C(11)-N(12)-O(14)	-17.1(2)
C(4)-C(6)-C(17)-O(19)	-66.18(18)	C(16)-C(8)-C(9)-C(10)	0.7(3)
C(4)-C(6)-C(21)-C(22)	156.48(16)	C(17)-C(6)-C(7)-O(1)	151.39(13)
C(4)-C(6)-C(21)-C(26)	-28.8(2)	C(17)-C(6)-C(7)-C(8)	-87.97(17)
C(5)-C(4)-C(6)-C(7)	87.00(17)	C(17)-C(6)-C(21)-C(22)	30.9(2)
C(5)-C(4)-C(6)-C(17)	-29.7(2)	C(17)-C(6)-C(21)-C(26)	-154.45(16)
C(5)-C(4)-C(6)-C(21)	-155.12(15)	O(18)-C(17)-O(19)-C(20)	2.1(2)
C(6)-C(7)-C(8)-C(9)	83.1(2)	C(21)-C(6)-C(7)-O(1)	-85.82(16)
C(6)-C(7)-C(8)-C(16)	-96.42(19)	C(21)-C(6)-C(7)-C(8)	34.83(19)
C(6)-C(17)-O(19)-C(20)	-179.19(14)	C(21)-C(6)-C(17)-O(18)	-120.75(18)

C(6)-C(21)-C(22)-C(23)	175.36(18)	C(21)-C(6)-C(17)-O(19)	60.53(18)
C(6)-C(21)-C(26)-C(25)	-175.13(17)	C(21)-C(22)-C(23)-C(24)	0.3(3)
C(7)-O(1)-C(2)-O(3)	-173.23(17)	C(22)-C(21)-C(26)-C(25)	-0.4(3)
C(7)-O(1)-C(2)-C(4)	5.07(19)	C(22)-C(23)-C(24)-C(25)	-1.1(3)
C(7)-C(6)-C(17)-O(18)	1.9(2)	C(23)-C(24)-C(25)-C(26)	1.2(3)
C(7)-C(6)-C(17)-O(19)	-176.84(14)	C(24)-C(25)-C(26)-C(21)	-0.5(3)
C(7)-C(6)-C(21)-C(22)	-91.59(19)	C(26)-C(21)-C(22)-C(23)	0.5(3)

Table 4.28 Hydrogen bonds for **368a** (Å and °).

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(9)-H(9)...O(18)	0.95	2.49	3.183(2)	129

4.5.4 X-ray crystallography data for 252



A specimen of $C_{28}H_{30}F_6N_4O_4S$ (**252**), approximate dimensions 0.110 mm x 0.290 mm x 0.380 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 100(2)K on a Bruker D8 Quest ECO with an Oxford Cryostream low temperature device using a MiTeGen micromount. See Table 4.30 for collection parameters and exposure time. Bruker APEX software was used to correct for Lorentz and polarization effects.

A total of 1002 frames were collected. The total exposure time was 2.53 hours. The integration of the data using an orthorhombic unit cell yielded a total of 39589 reflections to a maximum θ angle of 28.43° (0.75 Å resolution), of which 7137 were independent (average redundancy 5.547, completeness = 99.1%, R_{int} = 5.03%, R_{sig} = 3.43%) and 6559 (91.90%) were greater than $2\sigma(F^2)$. The final cell constants of a = 10.0847(3) Å, b = 12.3157(4) Å, c = 23.0056(7) Å, volume = 2857.30(15) $Å^3$, are based upon the refinement of the XYZ-centroids of reflections above 20 σ(I). Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.879. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.6554 and 0.7457.

The structure was solved with the XT structure solution program using Intrinsic Phasing and refined with the XL refinement package using Least Squares minimisation with Olex2, using the space group $P2_12_12_1$, with Z = 4 for the formula unit, $C_{28}H_{30}F_6N_4O_4S$. The final anisotropic full-matrix least-squares refinement on F^2 with 405 variables converged at R1 = 4.58%, for the observed data and wR2 = 11.44% for all data. The goodness-of-fit was 1.103. The largest peak in the final difference electron density synthesis was 0.530 $e^-/Å^3$ and the largest hole was -0.343 $e^-/Å^3$ with an RMS deviation of 0.064 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.471 g/cm^3 and F(000), 1312 e^-.

Refinement Note: Donor hydrogen atoms (O1, N24, N28) were located and refined with restraints (DFIX). The vinyl carbons (C22, C23) were refined with restraints (SIMU). Chirality at C14, S; C18, S; C21, R.

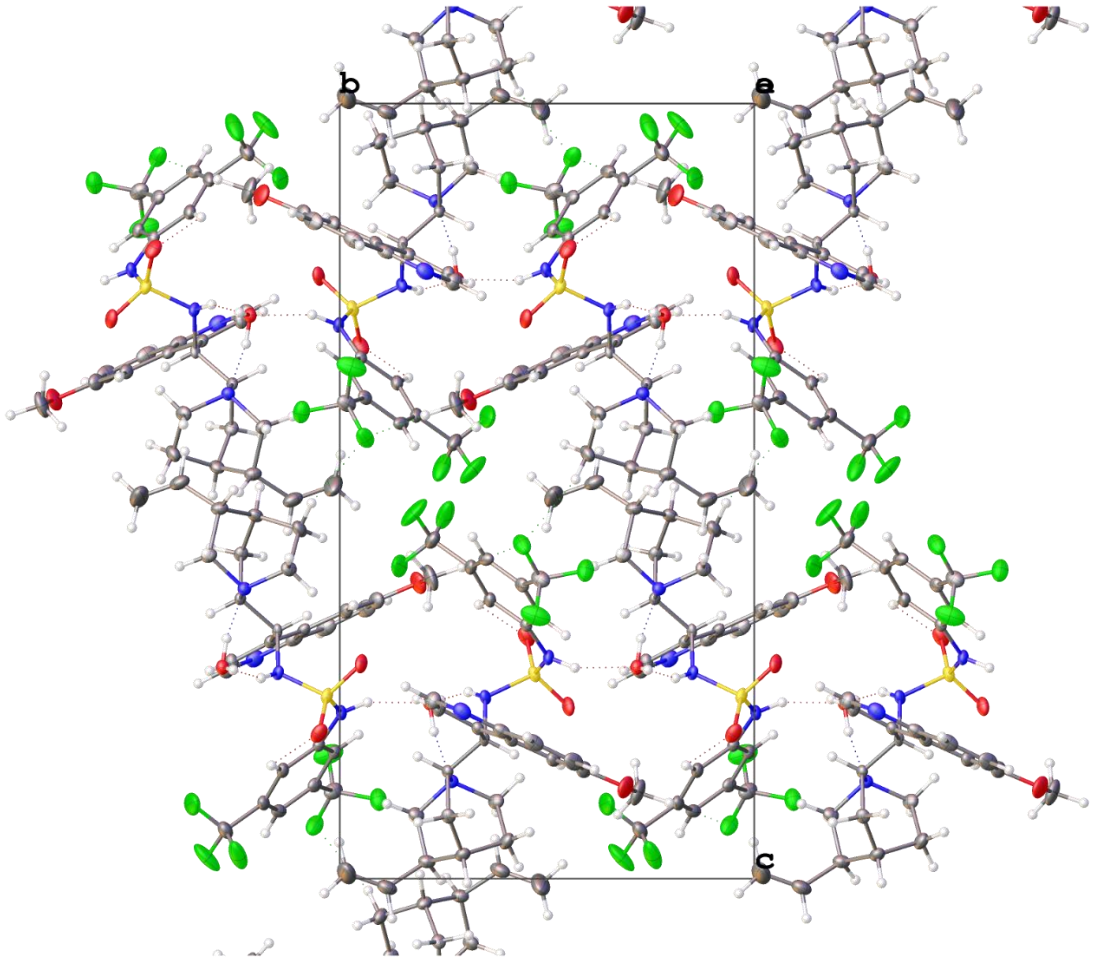


Figure 4.3 Packing diagram of **252** viewed normal to the a-axis. Dotted lines indicate hydrogen bonds.

Table 4.29 Data collection details for **252**.

Axis	dx/mm	2θ/°	ω/°	φ/°	χ/°	Width/°	Frames	Time/s	Wavelength/Å	Voltage/kV	Current/mA	Temperature/K
Phi	41.320	8.00	0.00	0.00	54.76	1.00	180	5.00	0.71073	50	20.0	100
Omega	41.320	34.33	216.97	0.00	54.76	0.80	212	10.00	0.71073	50	20.0	100
Phi	41.320	34.33	27.26	260.49	54.76	0.80	199	10.00	0.71073	50	20.0	100
Omega	41.320	-23.04	159.61	80.00	54.76	0.80	212	10.00	0.71073	50	20.0	100
Phi	41.320	34.33	216.32	172.49	54.76	0.80	199	10.00	0.71073	50	20.0	100

Crystal Data for $C_{28}H_{30}F_6N_4O_4S$ (M =632.62 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 10.0847(3) Å, b = 12.3157(4) Å, c = 23.0056(7) Å, V = 2857.30(15) Å^3, Z = 4, T = 100(2) K, μ(MoKα) = 0.195 mm^{-1}, Dcalc = 1.471 g/cm^3, 39589 reflections measured ($5.22° \leq 2\Theta \leq 56.86°$), 7137 unique ($R_{int}$ = 0.0503, R_{sigma} = 0.0343) which were used in all calculations. The final R_1 was 0.0458 ($I > 2\sigma(I)$) and wR_2 was 0.1144 (all data).

Table 4.30 Crystal data and structure refinement for **252**.

Identification code	tcd698	
Empirical formula	$C_{28}H_{30}F_6N_4O_4S$	
Formula weight	632.62	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 10.0847(3) Å	α = 90°
	b = 12.3157(4) Å	β = 90°
	c = 23.0056(7) Å	γ = 90°
Volume	2857.30(15) $Å^3$	
Z	4	
Density (calculated)	1.471 Mg/m^3	
Absorption coefficient	0.195 mm^{-1}	
F(000)	1312	
Crystal size	0.38 x 0.29 x 0.11 mm^3	
Theta range for data collection	2.610 to 28.430°.	
Index ranges	$-13\leq h\leq 13$, $-16\leq k\leq 16$, $-30\leq l\leq 30$	
Reflections collected	39589	
Independent reflections	7137 [R(int) = 0.0503]	
Completeness to theta = 25.242°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7457 and 0.6554	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7137 / 12 / 405	
Goodness-of-fit on F^2	1.103	
Final R indices [I>2σ(I)]	R1 = 0.0458, wR2 = 0.1113	
R indices (all data)	R1 = 0.0517, wR2 = 0.1144	
Absolute structure parameter	0.02(3)	
Largest diff. peak and hole	0.530 and -0.343 e.$Å^{-3}$	

Table 4.31 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **252**.

U(eq) is defined as one third of the trace of the orthogonalised U_{ij} tensor.

	x	y	z	U(eq)
F(1)	2263(3)	1790(3)	275(1)	65(1)
N(1)	-69(3)	2947(2)	2839(1)	23(1)
O(1)	7295(2)	2165(2)	2730(1)	17(1)
C(2)	338(3)	3896(3)	3091(1)	21(1)

F(2)	4163(3)	2542(2)	305(1)	58(1)
C(3)	-640(3)	4673(3)	3241(2)	27(1)
F(3)	3572(4)	1438(2)	963(1)	66(1)
C(4)	-292(4)	5635(3)	3489(2)	30(1)
F(4)	-1171(2)	4392(2)	689(1)	34(1)
F(5)	-480(2)	5925(2)	1022(1)	34(1)
C(5)	1044(4)	5884(3)	3590(2)	25(1)
O(6)	1290(3)	6892(2)	3818(1)	37(1)
F(6)	-1255(2)	4721(3)	1604(1)	46(1)
C(7)	2646(4)	7191(3)	3884(2)	42(1)
C(8)	2024(3)	5150(3)	3456(1)	21(1)
C(9)	1690(3)	4130(2)	3208(1)	16(1)
C(10)	2653(3)	3327(2)	3059(1)	15(1)
C(11)	2233(3)	2394(3)	2797(1)	20(1)
C(12)	869(3)	2242(3)	2699(2)	24(1)
C(13)	4121(3)	3489(2)	3197(1)	13(1)
C(14)	4596(3)	2597(2)	3614(1)	14(1)
N(15)	6036(2)	2696(2)	3742(1)	16(1)
C(16)	6342(3)	3770(3)	4000(1)	21(1)
C(17)	5403(4)	4025(3)	4514(2)	26(1)
C(18)	4707(3)	2964(3)	4688(1)	21(1)
C(19)	3786(3)	2617(3)	4191(1)	18(1)
C(20)	6371(3)	1842(3)	4170(1)	21(1)
C(21)	5790(3)	2097(3)	4778(1)	23(1)
C(22)	5281(4)	1134(3)	5111(2)	32(1)
N(24)	4905(2)	3511(2)	2657(1)	14(1)
S(25)	5151(1)	4687(1)	2360(1)	17(1)
O(26)	6015(2)	4497(2)	1878(1)	26(1)
O(27)	5492(2)	5512(2)	2775(1)	23(1)
N(28)	3678(2)	5034(2)	2145(1)	16(1)
C(29)	2924(3)	4493(2)	1726(1)	15(1)
C(30)	3397(3)	3621(3)	1400(1)	20(1)
C(31)	2583(3)	3158(2)	979(1)	22(1)
C(32)	3144(4)	2237(3)	629(2)	31(1)
C(33)	1304(3)	3528(3)	876(1)	22(1)
C(34)	857(3)	4392(2)	1209(1)	19(1)
C(35)	-507(3)	4841(3)	1133(2)	26(1)
C(36)	1641(3)	4867(2)	1633(1)	16(1)
C(23)	5037(7)	162(4)	4926(2)	65(2)

Table 4.32 Bond lengths [Å] and angles [°] for **252**.

F(1)-C(32)	1.324(5)	N(15)-C(16)	1.481(4)
N(1)-C(2)	1.368(5)	N(15)-C(20)	1.479(4)
N(1)-C(12)	1.323(4)	C(16)-H(16A)	0.9900
O(1)-H(1A)	0.867(14)	C(16)-H(16B)	0.9900
O(1)-H(1B)	0.874(14)	C(16)-C(17)	1.548(5)
C(2)-C(3)	1.417(4)	C(17)-H(17A)	0.9900
C(2)-C(9)	1.419(4)	C(17)-H(17B)	0.9900
F(2)-C(32)	1.323(4)	C(17)-C(18)	1.536(5)
C(3)-H(3)	0.9500	C(18)-H(18)	1.0000
C(3)-C(4)	1.361(6)	C(18)-C(19)	1.533(4)
F(3)-C(32)	1.322(5)	C(18)-C(21)	1.541(5)
C(4)-H(4)	0.9500	C(19)-H(19A)	0.9900
C(4)-C(5)	1.401(5)	C(19)-H(19B)	0.9900
F(4)-C(35)	1.340(4)	C(20)-H(20A)	0.9900
F(5)-C(35)	1.359(4)	C(20)-H(20B)	0.9900
C(5)-O(6)	1.370(4)	C(20)-C(21)	1.547(4)
C(5)-C(8)	1.376(4)	C(21)-H(21)	1.0000
O(6)-C(7)	1.424(5)	C(21)-C(22)	1.503(5)
F(6)-C(35)	1.330(4)	C(22)-H(22)	0.9500
C(7)-H(7A)	0.9800	C(22)-C(23)	1.294(7)
C(7)-H(7B)	0.9800	N(24)-H(24)	0.878(13)
C(7)-H(7C)	0.9800	N(24)-S(25)	1.622(2)
C(8)-H(8)	0.9500	S(25)-O(26)	1.428(2)
C(8)-C(9)	1.420(4)	S(25)-O(27)	1.436(2)
C(9)-C(10)	1.428(4)	S(25)-N(28)	1.623(3)
C(10)-C(11)	1.365(4)	N(28)-H(28)	0.887(13)
C(10)-C(13)	1.527(4)	N(28)-C(29)	1.396(4)
C(11)-H(11)	0.9500	C(29)-C(30)	1.394(4)
C(11)-C(12)	1.407(4)	C(29)-C(36)	1.390(4)
C(12)-H(12)	0.9500	C(30)-H(30)	0.9500
C(13)-H(13)	1.0000	C(30)-C(31)	1.392(5)
C(13)-C(14)	1.536(4)	C(31)-C(32)	1.501(5)
C(13)-N(24)	1.472(3)	C(31)-C(33)	1.388(5)
C(14)-H(14)	1.0000	C(33)-H(33)	0.9500
C(14)-N(15)	1.486(4)	C(33)-C(34)	1.387(5)
C(14)-C(19)	1.559(4)	C(34)-C(35)	1.493(5)
C(34)-C(36)	1.385(4)	N(1)-C(12)-C(11)	125.0(3)
C(36)-H(36)	0.9500	N(1)-C(12)-H(12)	117.5
C(23)-H(23A)	0.9500	C(11)-C(12)-H(12)	117.5
C(23)-H(23B)	0.9500	C(10)-C(13)-H(13)	108.2
		C(10)-C(13)-C(14)	109.8(2)
C(12)-N(1)-C(2)	116.7(3)	C(14)-C(13)-H(13)	108.2

H(1A)-O(1)-H(1B)	103(5)	N(24)-C(13)-C(10)	110.3(2)
N(1)-C(2)-C(3)	118.1(3)	N(24)-C(13)-H(13)	108.2
N(1)-C(2)-C(9)	122.8(3)	N(24)-C(13)-C(14)	111.9(2)
C(3)-C(2)-C(9)	119.1(3)	C(13)-C(14)-H(14)	108.0
C(2)-C(3)-H(3)	119.7	C(13)-C(14)-C(19)	110.9(2)
C(4)-C(3)-C(2)	120.7(3)	N(15)-C(14)-C(13)	111.7(2)
C(4)-C(3)-H(3)	119.7	N(15)-C(14)-H(14)	108.0
C(3)-C(4)-H(4)	119.7	N(15)-C(14)-C(19)	110.0(2)
C(3)-C(4)-C(5)	120.6(3)	C(19)-C(14)-H(14)	108.0
C(5)-C(4)-H(4)	119.7	C(16)-N(15)-C(14)	110.9(2)
O(6)-C(5)-C(4)	115.9(3)	C(20)-N(15)-C(14)	107.2(2)
O(6)-C(5)-C(8)	123.5(3)	C(20)-N(15)-C(16)	108.7(2)
C(8)-C(5)-C(4)	120.6(3)	N(15)-C(16)-H(16A)	109.4
C(5)-O(6)-C(7)	116.7(3)	N(15)-C(16)-H(16B)	109.4
O(6)-C(7)-H(7A)	109.5	N(15)-C(16)-C(17)	111.1(2)
O(6)-C(7)-H(7B)	109.5	H(16A)-C(16)-H(16B)	108.0
O(6)-C(7)-H(7C)	109.5	C(17)-C(16)-H(16A)	109.4
H(7A)-C(7)-H(7B)	109.5	C(17)-C(16)-H(16B)	109.4
H(7A)-C(7)-H(7C)	109.5	C(16)-C(17)-H(17A)	110.2
H(7B)-C(7)-H(7C)	109.5	C(16)-C(17)-H(17B)	110.2
C(5)-C(8)-H(8)	119.9	H(17A)-C(17)-H(17B)	108.5
C(5)-C(8)-C(9)	120.1(3)	C(18)-C(17)-C(16)	107.8(3)
C(9)-C(8)-H(8)	119.9	C(18)-C(17)-H(17A)	110.2
C(2)-C(9)-C(8)	118.9(3)	C(18)-C(17)-H(17B)	110.2
C(2)-C(9)-C(10)	117.9(3)	C(17)-C(18)-H(18)	110.3
C(8)-C(9)-C(10)	123.2(3)	C(17)-C(18)-C(21)	107.5(3)
C(9)-C(10)-C(13)	121.2(3)	C(19)-C(18)-C(17)	108.7(3)
C(11)-C(10)-C(9)	118.6(3)	C(19)-C(18)-H(18)	110.3
C(11)-C(10)-C(13)	120.2(3)	C(19)-C(18)-C(21)	109.7(3)
C(10)-C(11)-H(11)	120.5	C(21)-C(18)-H(18)	110.3
C(10)-C(11)-C(12)	119.1(3)	C(14)-C(19)-H(19A)	109.9
C(12)-C(11)-H(11)	120.5	C(14)-C(19)-H(19B)	109.9
C(18)-C(19)-C(14)	108.7(2)	C(36)-C(29)-N(28)	117.1(3)
C(18)-C(19)-H(19A)	109.9	C(36)-C(29)-C(30)	119.4(3)
C(18)-C(19)-H(19B)	109.9	C(29)-C(30)-H(30)	120.4
H(19A)-C(19)-H(19B)	108.3	C(31)-C(30)-C(29)	119.2(3)
N(15)-C(20)-H(20A)	109.3	C(31)-C(30)-H(30)	120.4
N(15)-C(20)-H(20B)	109.3	C(30)-C(31)-C(32)	117.5(3)
N(15)-C(20)-C(21)	111.7(3)	C(33)-C(31)-C(30)	122.1(3)
H(20A)-C(20)-H(20B)	107.9	C(33)-C(31)-C(32)	120.4(3)
C(21)-C(20)-H(20A)	109.3	F(1)-C(32)-C(31)	113.0(3)
C(21)-C(20)-H(20B)	109.3	F(2)-C(32)-F(1)	107.1(3)
C(18)-C(21)-C(20)	106.7(2)	F(2)-C(32)-C(31)	112.3(3)

C(18)-C(21)-H(21)	107.5	F(3)-C(32)-F(1)	105.6(3)
C(20)-C(21)-H(21)	107.5	F(3)-C(32)-F(2)	106.5(4)
C(22)-C(21)-C(18)	111.9(3)	F(3)-C(32)-C(31)	111.9(3)
C(22)-C(21)-C(20)	115.5(3)	C(31)-C(33)-H(33)	121.3
C(22)-C(21)-H(21)	107.5	C(34)-C(33)-C(31)	117.4(3)
C(21)-C(22)-H(22)	115.5	C(34)-C(33)-H(33)	121.3
C(23)-C(22)-C(21)	128.9(4)	C(33)-C(34)-C(35)	121.3(3)
C(23)-C(22)-H(22)	115.5	C(36)-C(34)-C(33)	121.8(3)
C(13)-N(24)-H(24)	124(3)	C(36)-C(34)-C(35)	116.9(3)
C(13)-N(24)-S(25)	117.05(18)	F(4)-C(35)-F(5)	105.9(3)
S(25)-N(24)-H(24)	109(3)	F(4)-C(35)-C(34)	113.4(3)
N(24)-S(25)-N(28)	102.89(12)	F(5)-C(35)-C(34)	111.6(3)
O(26)-S(25)-N(24)	105.95(13)	F(6)-C(35)-F(4)	107.0(3)
O(26)-S(25)-O(27)	119.05(14)	F(6)-C(35)-F(5)	105.8(3)
O(26)-S(25)-N(28)	111.42(14)	F(6)-C(35)-C(34)	112.7(3)
O(27)-S(25)-N(24)	112.78(13)	C(29)-C(36)-H(36)	120.0
O(27)-S(25)-N(28)	103.65(13)	C(34)-C(36)-C(29)	120.0(3)
S(25)-N(28)-H(28)	115(3)	C(34)-C(36)-H(36)	120.0
C(29)-N(28)-H(28)	119(3)	C(22)-C(23)-H(23A)	120.0
C(29)-N(28)-S(25)	125.7(2)	C(22)-C(23)-H(23B)	120.0
C(30)-C(29)-N(28)	123.5(3)	H(23A)-C(23)-H(23B)	120.0

Table 4.33 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **252**.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}\ U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$

	U_{11}	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
F(1)	62(2)	64(2)	70(2)	-50(2)	2(2)	-10(2)
N(1)	10(1)	31(1)	28(1)	5(1)	1(1)	-1(1)
O(1)	14(1)	15(1)	21(1)	-1(1)	0(1)	0(1)
C(2)	13(1)	29(2)	20(1)	7(1)	3(1)	2(1)
F(2)	69(2)	34(1)	73(2)	-21(1)	46(2)	-13(1)
C(3)	14(1)	39(2)	28(2)	10(2)	4(1)	8(1)
F(3)	124(3)	26(1)	49(2)	-3(1)	16(2)	29(2)
C(4)	24(2)	35(2)	31(2)	5(1)	9(1)	18(2)
F(4)	32(1)	31(1)	39(1)	7(1)	-18(1)	-11(1)
F(5)	26(1)	27(1)	48(1)	-3(1)	-11(1)	2(1)
C(5)	26(2)	23(2)	27(2)	0(1)	3(1)	11(1)
O(6)	39(2)	25(1)	46(2)	-11(1)	4(1)	16(1)
F(6)	14(1)	85(2)	40(1)	16(1)	2(1)	-2(1)
C(7)	41(2)	22(2)	64(3)	-18(2)	-1(2)	7(2)
C(8)	22(1)	19(2)	22(1)	1(1)	4(1)	6(1)

C(9)	15(1)	17(1)	17(1)	4(1)	4(1)	2(1)
C(10)	13(1)	15(1)	17(1)	2(1)	3(1)	0(1)
C(11)	14(1)	17(1)	27(2)	-2(1)	2(1)	0(1)
C(12)	17(1)	25(2)	29(2)	-2(1)	-2(1)	-4(1)
C(13)	8(1)	10(1)	20(1)	-1(1)	3(1)	1(1)
C(14)	13(1)	12(1)	16(1)	0(1)	2(1)	-2(1)
N(15)	12(1)	18(1)	17(1)	0(1)	-1(1)	-1(1)
C(16)	18(1)	24(2)	22(2)	-2(1)	-1(1)	-7(1)
C(17)	31(2)	20(2)	26(2)	-7(1)	5(1)	-6(1)
C(18)	22(2)	23(2)	17(1)	-4(1)	4(1)	-2(1)
C(19)	12(1)	19(1)	21(1)	2(1)	4(1)	-1(1)
C(20)	18(1)	24(2)	20(1)	4(1)	-2(1)	4(1)
C(21)	23(2)	29(2)	16(1)	1(1)	0(1)	1(1)
C(22)	38(2)	38(2)	21(2)	9(1)	2(2)	6(2)
N(24)	11(1)	12(1)	20(1)	2(1)	3(1)	3(1)
S(25)	11(1)	14(1)	25(1)	4(1)	1(1)	-2(1)
O(26)	17(1)	27(1)	34(1)	10(1)	10(1)	2(1)
O(27)	18(1)	15(1)	35(1)	3(1)	-6(1)	-6(1)
N(28)	15(1)	11(1)	22(1)	-2(1)	-2(1)	0(1)
C(29)	14(1)	14(1)	17(1)	2(1)	2(1)	-2(1)
C(30)	24(2)	14(1)	22(1)	1(1)	4(1)	-1(1)
C(31)	31(2)	14(1)	21(2)	-1(1)	6(1)	-4(1)
C(32)	41(2)	22(2)	29(2)	-8(1)	6(2)	-4(2)
C(33)	28(2)	23(2)	16(1)	0(1)	1(1)	-11(1)
C(34)	18(1)	19(2)	20(1)	3(1)	1(1)	-7(1)
C(35)	18(1)	33(2)	28(2)	5(1)	-5(1)	-7(1)
C(36)	17(1)	14(1)	19(1)	2(1)	1(1)	-2(1)
C(23)	116(5)	34(2)	46(2)	10(2)	32(3)	-5(3)

Table 4.34 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **252**.

	x	**y**	**z**	**U(eq)**
H(1A)	8090(30)	2430(50)	2700(30)	72(19)
H(1B)	7120(40)	2270(30)	3099(6)	40(13)
H(3)	-1549	4521	3168	32
H(4)	-960	6142	3594	36
H(7A)	3101	7122	3510	63
H(7B)	3068	6712	4170	63
H(7C)	2701	7944	4019	63
H(28)	3390(40)	5667(18)	2277(17)	24(10)
H(8)	2926	5325	3529	25

	x	y	z	U(eq)
H(11)	2854	1854	2682	23
H(12)	600	1583	2519	28
H(13)	4225	4206	3396	15
H(14)	4445	1879	3423	17
H(16A)	6248	4339	3699	25
H(16B)	7271	3776	4138	25
H(17A)	5915	4315	4847	31
H(17B)	4739	4575	4397	31
H(18)	4189	3070	5054	25
H(19A)	3039	3135	4157	21
H(19B)	3418	1887	4272	21
H(20A)	7347	1777	4200	25
H(20B)	6018	1137	4033	25
H(21)	6513	2435	5014	27
H(22)	5115	1256	5512	39
H(24)	5600(30)	3100(30)	2590(17)	41(13)
H(30)	4266	3347	1464	24
H(33)	757	3202	588	27
H(36)	1302	5448	1860	20
H(23A)	5180	-17	4530	78
H(23B)	4714	-374	5188	78

Table 4.35 Hydrogen bonds for **252** (Å and °).

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1A)...N(1)#1	0.867(14)	1.99(2)	2.838(3)	165(6)
O(1)-H(1B)...N(15)	0.874(14)	1.918(19)	2.732(3)	154(3)
C(7)-H(7C)...F(4)#2	0.98	2.45	3.243(4)	138
N(28)-H(28)...O(1)#3	0.887(13)	1.969(19)	2.817(3)	159(4)
C(17)-H(17A)...F(4)#4	0.99	2.52	3.422(4)	151
N(24)-H(24)...O(1)	0.878(13)	2.087(17)	2.930(3)	161(4)
C(30)-H(30)...O(26)	0.95	2.45	3.057(4)	121

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