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Ph. D. Thesis in Chemistry

CHIRAL ORGANOCATALYSTS MEDIATED ASYMMETRIC OXYFUNCTIONALIZATION AND TANDEM REACTIONS

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To my wonderful family

"Credo di poter affermare che nella ricerca scientifica né il grado di intelligenza né la capacità di eseguire e portare a termine il compito intrapreso siano fattori essenziali per la riuscita e per la soddisfazione personale. Nell'uno e nell'altro contano maggiormente la totale dedizione e il chiudere gli occhi davanti alle difficoltà: in tal modo possiamo affrontare i problemi che altri, più critici e più acuti, non affronterebbero".

[Rita Levi Montalcini]

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ABSTRACT

Asymmetric organocatalysis is a new rapidly growing field whose huge potential is becoming more and more evident. This PhD project has been conceived and developed in the context of non-covalent organocatalysis.

The aim of this work has been to design, plan and develop new organocatalytic methodologies for the synthesis of optically active, densely functionalized, organic molecules whose functional groups are susceptible to further manipulation. The target molecules represent important motifs present in many biologically active natural and non-natural substances.

The catalysts used are small chiral organic molecules, in particular the attention has been focused on bifunctional organocatalysts. The main features of the catalysts are their non-toxicity, stability to air and moisture and the ability to work under mild conditions that make them convenient tools in organic chemistry. These promoters are able to synergistically activate both the electrophile and the nucleophile through multiple hydrogen-bonding interactions provided by their acid and basic groups with the reactive groups of the reagents. The best-performing chiral scaffold of the bifunctional organocatalysts, employed in the methodologies herein developed, has been selected screening the activity of previously reported promoters such as ureas, thioureas, squaramides, amino alcohols. However, the design and synthesis of new optically pure bifunctional organocatalysts, modifying the chiral backbone and by tuning their stereoelectronic features has been one of the objectives of this doctoral project. The

stereoselective construction of a quaternary stereocentre, especially when it is an all-carbon quaternary stereocentre, is one of the most difficult goals in organic synthesis due to the steric congestion imposed by the four attached substituents. In this project, the synthesis of challenging molecules, bearing quaternary stereocentres in their structure, has been accomplished.

The methodologies developed aimed to the stereocontrolled construction of carbon-carbon and carbon-heteroatom bonds to give access to new and important cyclic compounds of different nature and size (such as epoxides, tetrahydrothiophenes, γ-butyrolactones) and non-cyclic compounds, such as α-hydroxy β-ketoamides.

In order to access the cyclic compounds, the one-pot tandem organocatalytic methodologies developed, such as Michael/Michael, aldol/lactonization, allowed us to obtain the densely functionalized molecules with a minimum number of synthetic operations. Unquestionably, these processes are becoming of considerable synthetic interest in terms of sustainability and advantageous in terms of time, costs saving issues and minimal manual operations.

In this doctoral work, the first stereoselective cascade sulfa-Michael/Michael reaction for the synthesis of tetrahydrothiophenes from *trans*-α-carbonyl-β-substituted acrylonitriles has been developed, by using a novel readily available secondary amine thiourea. Highly functionalized tetrahydrothiophenes, bearing three contiguous stereocentres, one of them quaternary, were formed by means of a highly stereoselective cascade transformation. This work represents an unprecedented case in which the stereochemical

outcome of an asymmetric synthesis of tetrahydrothiophenes has been controlled exclusively by a dinamic kinetic resolution process.

The first straighforward approach to enantioenriched β,β-disubstituted γ-butyrolactones has been achieved through a cascade aldol/lactonization process. From simple starting materials and working under mild reaction conditions, highly challenging γ-butyrolactones, bearing an all-carbon quaternary stereocentre at the remote β-position were obtained. Remarkably, this work represents the first example of an enantioselective hydroxymethylation reaction of 2-substituted-1,3-dicarbonyl compounds catalyzed by an organocatalyst.

Moreover, we demonstrated that these products can be elaborated to prepare valuable hydroxy γ-butyrolactones, bearing contiguous tertiary and quaternary stereocentres, so far inaccessible via alternative methods.

Another important goal of this project concerned the development of a first approach to enantiomerically enriched aromatic α-nitroepoxides. An aminolytic kinetic resolution of racemic aromatic α-nitroepoxides with aniline, catalyzed by an easily accessible cinchona alkaloid-derived thiourea, was devised as a successful strategy. The first demonstration of synthetic utility of the chiral epoxides obtained has been reported: they have been transformed into highly valuable *anti*-1,2-amino alcohols through an one-pot stereoselective ring-opening reaction followed by reduction.

Finally, the first enantioselective α-hydroxylation reaction of α-substituted β-ketoamides, organocatalyzed by a commercially

available HQN/TBHP system, has been realized in this PhD project. This protocol enables a facile access to functionalized tertiary alcohols bearing a quaternary stereocentre, substituted with both ketone and amido groups, amenable to chemoselective manipulation.

LIST OF ABBREVIATIONS

Ad	adamantyl
Ac	acetyl
ACDC	Asymmetric Counteranion-Directed Catalysis
AcOH	Acetic acid
AKR	aminolytic kinetic resolution
Alk	alkyl
aq.	aqueous
Ar	aryl
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1’-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
cat.	catalyst(s)
Cbz	carbobenzyloxy
CHP	cumene hydroperoxide
CD	cinchonidine
CN	cinchonine
C	Concentration
c	cyclic
d	days
d	doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
dd	double doublet
ddd	doublet of double doublets
DCE	1,2-dichloroethane

DCM	dichloromethane
de	diastereoisomeric excess
DHQD	dihydroquinidine
diast.	diastereomer
DIBAL-H	diisobutylaluminum hydride
DIC	diisopropylcarbodiimide
DMAP	4-(Dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereoisomeric ratio
DSIs	disulfonimides
ee	enantiomeric excess
El	electrophile
eq.	equivalent(s)
eCDT	9-Amino-(9-deoxy)epi-cinchonidine thiourea
eCNT	9-Amino-(9-deoxy)epi-cinchonine thiourea
eHQNT	9-Amino-(9-deoxy)epi-hydroquinine thiourea
eQDT	9-Amino-(9-deoxy)epi-quinidine thiourea
eQNT	9-Amino-(9-deoxy)epi-quinine thiourea
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
G	Gibbs energy
h	hour(s)
Het	heteroaromatic
hex	hexyl
HOMO	Higher Occupied Molecular Orbital
HPLC	high performance liquid chromatography

Hz	Herz
i	iso
IUPAC	International Union of Pure and Applied Chemistry
KHMDS	hexamethyldisilazane potassium salt
LDA	lithium diisopropylamide
LUMO	Lower Unoccupied Molecular Orbital
M	molar (concentration)
m	*meta*
m	multiplet
*m*CPBA	*meta*-chloroperbenzoic acid
Me	Methyl
min	minutes
mp	melting point
MS	mass spectrometry
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
m/z	atomic mass units per charge
Nap	naphthyl
nd	not determined
NMP	N-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance spectroscopy
Nu	nucleophile
o	*ortho*
p	*para*
P	protecting group
PCC	pyridinium chlorochromate
Ph	phenyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl

Pr	propyl
PTC	Phase Transfer Catalysis
PTSA	*p*-toluenesulfonic acid
q	quartet
QN	quinine
QD	quinidine
r.t.	room temperature
s	singlet
s	*sec*
S_N	nucleophilic substitution
t	*tert*
t	time
t	triplet
T	Temperature
TADDOL	α,α,α',α'-tetraaryl-1,3-dioxolan-4,5-dimethanol
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBME	*tert*-butylmethyl ether
Tf	triflate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	tetramethylsilyl
Tol.	toluene
tol	*p*-tolyl
TPP	tetraphenylporphyrin
t_R	retention time

TS	transition state
TSA	*p*-toluenesulfonic acid
TSOH	*p*-toluenesulfonic acid
UHP	urea hydrogen peroxide

1. INTRODUCTION: ASYMMETRIC ORGANOCATALYSIS

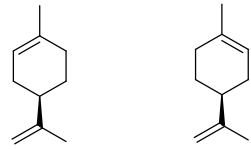
1.1 Asymmetric Synthesis

IUPAC defines Asymmetric Synthesis as: "*a chemical reaction (or reaction sequence) in which one or more new elements of chirality are formed in a substrate molecule and which produces the stereoisomeric (enantiomeric or diastereoisomeric) products in unequal amounts*".[1]

More enantiopure is a compound, more is "valuable". In fact, it should be kept in mind that life is strictly connected with chirality. Many building blocks of the biological systems are chiral, such as sugars and amino acids, and the chirality is often the basis of the interactions receptor-substrate. Frequently, only one enantiomer is recognized by its receptor and the opposite is inactive, less active or, in some cases, it is even a poison. This concept is very important in the field of pharmaceutical industry. For example, an α-amino acid metabolite of penicillin, the D-penicillamine, sold under the trade names Cupreimine and Depen, is active in treatment of rheumatoid arthritis and used as chelating agent in the treatment of several diseases such as the Wilson's desease. The enantiomer L-penicillamine, on the contrary, is toxic because inhibits the action of the B vitamin pyridoxine.

The opposite chirality of the enantiomers leads, in hundreds of known compounds, also to differences in flavor and in the aroma.[2] Is the case, for example, of cyclic terpene limonene, shown in

Figure 1.1: the (*R*)-limonene has a strong smell of oranges while the (*S*)-isomer of turpentine.



(*R*)-(+)-limonene (*S*)-(-)-limonene

Figure 1.1 (*R*)- and (*S*)-limonene.

Other classical examples of enantiomers showing different odour and/or taste properties are amino-acids - L-amino acids usually are bitter while D-amino acids are sweet - carvone, menthol, β-cintronellol and linalool.

The enantioselective synthesis is difficult to achieve because enantiomers have identical enthalpies and entropies. In achiral reactions they are produced in equal amounts, as racemic mixture, because transition states that lead to enantiomers are also enantiomeric, having equal energy. The only way to perform a reaction in a stereoselective manner is to use a chiral "component" that produces diastereomeric transition states with different energy leading the formation of one enantiomer over another (Figure 1.2).[3]

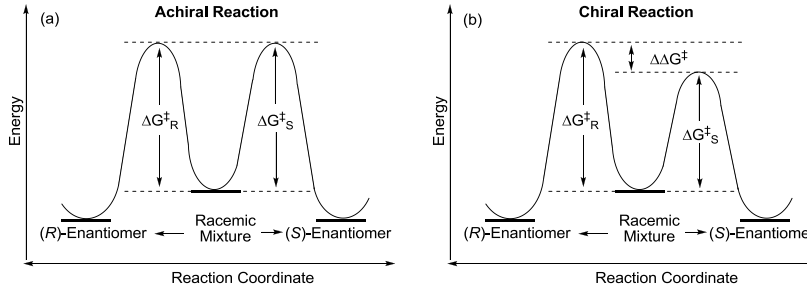


Figure 1.2 Gibbs free energy plots of (a) an achiral and (b) a chiral reaction.

An approach to asymmetric synthesis involves the use of molecules from the chiral pool: chiral non racemic starting materials are manipulated through successive reactions, often using achiral reagents, to obtain the desired enantiopure molecule. However, this approach is not cheap because a stoichiometric amount of a chiral reagent is required, the synthetic routs may be not very easy and, unfortunately, the range of enantiopure compounds provided by Nature is limited with respect to structure and stereochemistry. It is possible to use chiral auxiliaries, chiral solvents or chiral catalysts in order to make the activation energy needed to form an enantiomer lower than needed for the opposite enantiomer.

In a reaction that occurs in solution, components are solvated, therefore, if the solvent is chiral, it is possible to have an asymmetric synthesis because transition states become diastereomeric. Nevertheless, chiral solvents are seldom utilized because the level of stereoselectivity is often low and not predictable and a large amount of chiral substance is required. Chiral auxiliaries, hooked to the prochiral substrate before the reaction, are used in stoichiometric amounts and this strategy

requires additional synthetic steps to append and remove the auxiliary. However, the reactions usually give predictable and reproducible results, the auxiliary can be recycled and purification is usually easy because the products are diastereomeric. In some cases, this is the only available stereoselective methodology to access enantiomerically pure products.

An alternative approach to perform an asymmetric synthesis is the kinetic resolution: in the presence of an enantiomerically pure reagent or a catalyst, the two enantiomers of a racemate can have different reaction rates. If the rate difference is very large (the ideal cases are enzymes) one enantiomer is inert and the other one reacts quickly and the product can be separated from the unreacted enantiomer.

The asymmetric synthesis performed employing chiral catalysts provides the best "atom economy", because the amount of chiral substance used in the transformation is minimized.

Until recently, the catalytic enantioselective synthesis of chiral organic compounds such as agrochemicals, synthetic intermediates and pharmaceuticals was based on metal and enzymatic catalysis.[4]

The organometallic catalysis is the field that received more emphasis in asymmetric synthesis over the years. The chiral organometallic catalysts can be modulated and tailored to many kinds of organic reactions. Several transformations in asymmetric catalysis are promoted by organometallic complexes and there are many well-established metal-based methodologies in this field.[5] At the beginning of the new century, the field of biocatalysis has made great progress thanks to the discovery that is possible to prepare

useful enzymes from novel organisms and optimize the enzyme performance by evolutionary methods and selective mutation.[6]

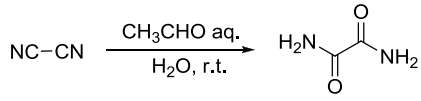
Nevertheless, in the last ten years, this picture is changing: between these two pillars the organocatalysis has emerged.[7] As metal complexes and enzymes, even small organic molecules may promote chemical reactions. Organic molecules, without metal element, used in a substoichiometric amount, are useful means to accelerate chemical transformations.

Organocatalysis offers several advantages over transition metal- and bio-catalysis: reactions can be performed under an aerobic atmosphere, with not perfectly anhydrous solvents, indeed, in some cases, the presence of water has proven to be beneficial to the rate and selectivity of the reaction. Organocatalysts are usually readily available, less toxic and cheaper than metal complexes. They are more stable and robust than metal complexes and enzymes. The risk of metal leakage is avoided and no expensive waste treatment is required. Thanks to the sustainability of the catalysts, environmentally friendliness and green features, organocatalysis has found applications in several industrial asymmetric syntheses.[8] Moreover, these organic catalysts are particularly efficient in promoting tandem stereoselective multistep and multicomponent reactions, thus offering the opportunity to increase the structural complexity of the products.

1.2 Historical Background

The organocatalysis has a very ancient story: there are evidences that such catalysis has played a key role in the beginning of life on Earth. It is thought that such catalysis has been responsible for the formation of probiotic key building-blocks such as sugars, leading to the birth of homochirality in living systems.[9] Pizzarello and Weber demonstrated that L-isovaline, found in the Murchison meteorite, promotes the self- aldol reaction of glycolaldehyde in water, generating sugar aldol products such as L-threose and D-erythrose with up to 10.7 ± 1.2% and 4.8 ± 0.9% *ee*, respectively.9 This means that enantiomerically enriched amino acids such as L-alanine and L-isovaline, which may be present in up to 15% *ee* in carbonaceous meteorites, probably were able to catalyze aldol reactions of glycolaldehyde and formaldehyde producing sugar derivatives. After the formation of sugars, more complex carbohydrates and complex molecules such as DNA and RNA were formed. Most likely, prebiotic RNA had a key role in basic biochemical transformations necessary for life, in which sugars were the chiral templates.[10] For example, it is believed, that, as the first step of protein synthesis is the asymmetric aminoacylation, the homochirality of RNA determined homochirality of amino acids in proteins and hence the selectivity of the amino acids (L or D) derived.[11]

Accidentally, von Liebig, in the 1800s, discovered the first organocatalytic reaction, developed in an aqueous solution of acetaldehyde and dicyan leading to the oxalamide (Scheme 1.1).

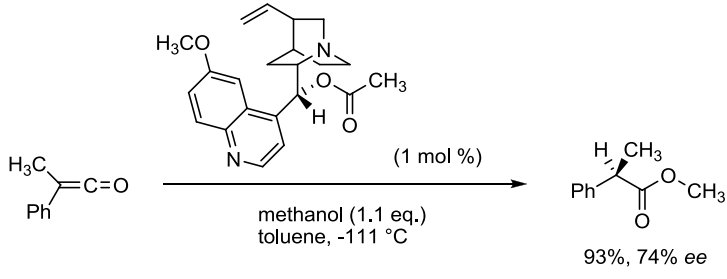


Scheme 1.1 von Liebig's oxamide synthesis.

Later, this reaction has been the basis of the industrial Degussa oxamide synthesis.

The organocatalysis was born when chemists began to use little organic molecules in an attempt to understand and to mimic the catalytic activity and selectivity displayed by enzymes.

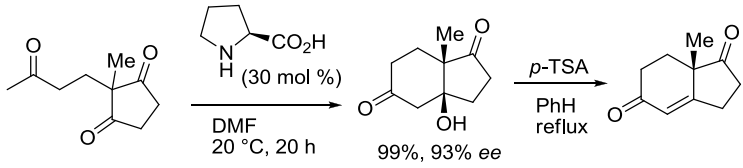
In 1912, Bredig and Friske discovered that quinine and quinidine accelerate the addition of HCN to benzaldehyde giving chiral cyanohydrins of opposite chirality, albeit with low *ee* (≤ 10%).[12] Subsequently, Pracejus et al., in 1960, obtained the product of addition of methanol to phenylmethylketene in 74% *ee* using 1 mol % O-acetylquinine as the catalyst (Scheme 1.2).[13]



Scheme 1.2 Pracejus' reaction.

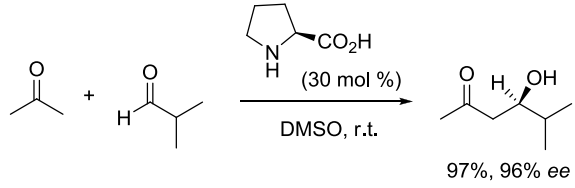
Further milestones in the organocatalysis field were laid in the 1970s and 1980s. In 1971, Hajos-Parrish-Eder-Sauer-Wiechert reported the synthesis of an important intermediate in steroid synthesis, the Wieland-Miescher ketone, exploiting a proline-

catalyzed enantioselective intramolecular aldol reaction (Scheme 1.3).[14]



Scheme 1.3 The L-proline catalyzed Robinson annulation.

The real growth of organocatalysis has taken place, however, in the early 2000s when List, Barbas et al. disclosed that acetone can react with a number of aldehydes in the presence of L-proline, obtaining the corresponding aldols in high yield and excellent enantiomeric excess. For example, with *iso*-butyraldehyde the product was isolated in 97% yield and 96% *ee* (Scheme 1.4).[15]

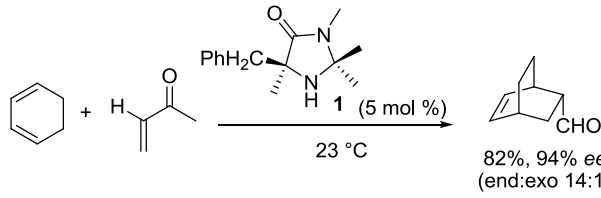


Scheme 1.4 Intermolecular aldol reaction catalyzed by L-proline.

List and Barbas' pioneering work has given rise to an intense study by several research groups on the catalytic activity of L-proline in many organic reactions such as Michael, Mannich, aldol and so on.

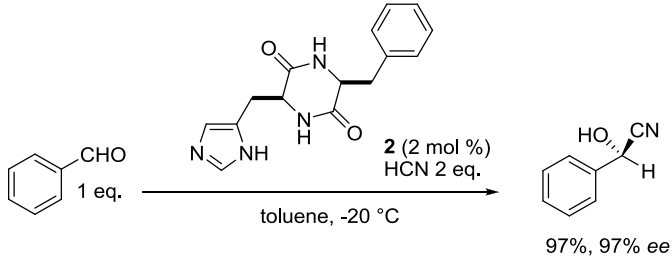
Another catalyst widely adopted in several reactions, after its discovery in the same year of List and Barbas' work, was the phenylalanine-derived secondary amine **1** (Scheme 1.5). MacMillan demontrated that the Diels-Alder reaction of α,β-unsaturated

aldehydes is effectively catalyzed in terms of yield and enantioselective by compound **1** (Scheme 1.5).[16]



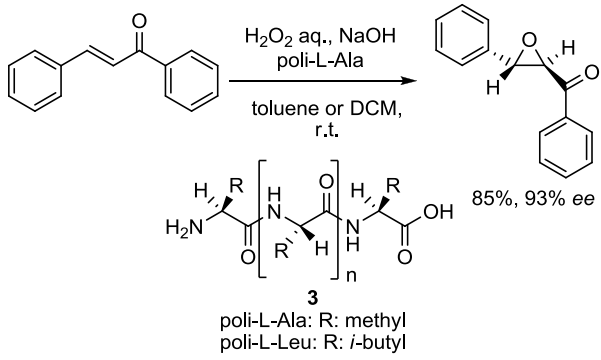
Scheme 1.5 Diels-Alder reaction promoted by MacMillan's catalyst.

A massive research activity in the field of peptide-catalyzed reactions started after the Inoue's work in 1981. The cyclic dipeptide **2** derived from L-histidine and L-phenylalanine catalyzes the reaction between HCN and benzaldehyde giving the product with 90% *ee* (Scheme 1.6).[17]



Scheme 1.6 The dipeptide catalyst by Inoue.

In the same period, Juliá, Colonna et al. reported the highly enantioselective epoxidation of chalcones with hydrogen peroxide promoted by catalyst **3** (Scheme 1.7).[18]



Scheme 1.7 Enantioselective Juliá-Colonna epoxidation.

In summary, although the first catalytic reactions date back to the early 1900s, organocatalysis had a very slow growth until the early 2000s, when an exponential growth of organocatalysis led off with the groundbreaking works of List, Barbas, MacMillan and others.

Every year, new methodologies promoted by new organocatalysts are published and the studies are becoming more sophisticated, complex and in-depth thanks to the advancement of analytical techniques and the support of theoretical and computational chemistry.

1.3 Mechanistic Aspects

Generally, the organocatalytic reactions can be grouped into two categories depending on whether the structure of the transition state between catalyst and substrate/s is "tight" or "loose". The former category is defined covalent catalysis and includes reactions in which covalent bonds between the catalyst and reagent/s are formed with energies higher than 15 kcal mol^{-1}. The latter set involves reactions in which complexes maintained by non-covalent bonds, between the catalyst and the substrate, are formed. These non-covalent interactions are weaker – ion pairing, neutral host-guest interactions, acid-base associations, H-bonding – with energies that usually don't exceed 4 kcal mol^{-1}.

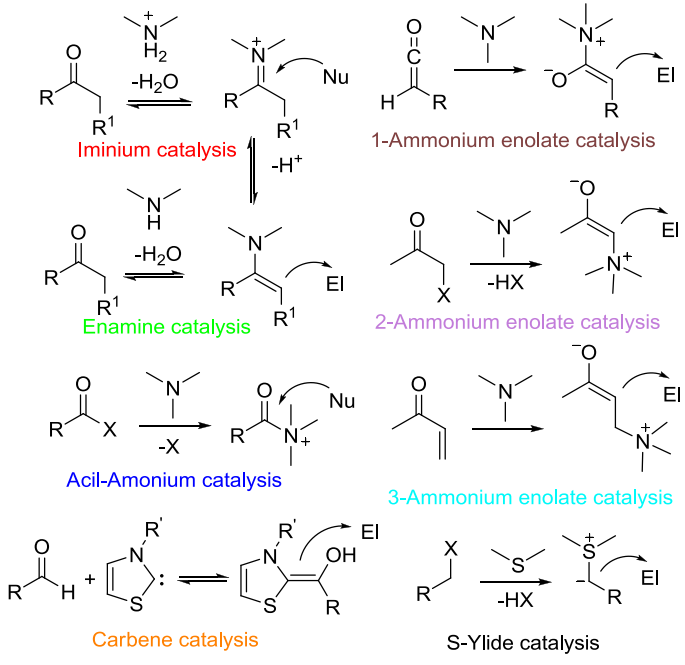
The bonds formed in the transition state are determined by the activation strategy of the substrates by the catalyst and by its chemical nature. Most but not all organocatalysts can be grouped in four typologies: Lewis base, Lewis acid, Brønsted base or Brønsted acid.[19]

1.3.1 Lewis base catalysis

Unlike metal catalysts, which act as Lewis acids, organocatalysts form especially Lewis bases. The Lewis base can be centred on N-, C-, O-, P-, and S- but the N- and P-based catalysts are the most used and studied. The amine catalysts are more easily available than phosphorus ones and these latter catalysts have to be synthesized. Since the phosphorus atom is less basic than amine nitrogen, the phosphorus Lewis basic catalysts are chosen when it's necessary to

avoid side reactions promoted by the base.

There are various activation mechanisms depending on the Lewis base and several are the intermediates that are formed. The intermediates are nucleophiles or electrophiles, more reactive than the starting reagents. Some of them are shown in Scheme 1.8.[19]

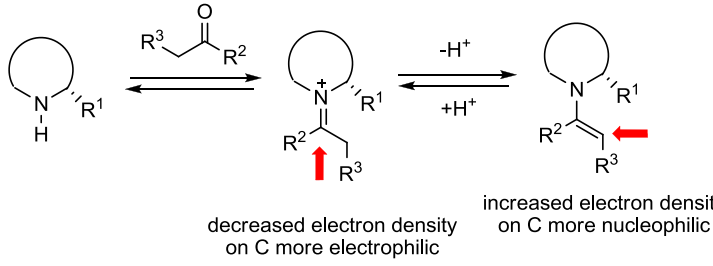


Scheme 1.8 Intermediates formed in Lewis base organocatalysis.

All the examples of Lewis base organocatalysis are examples of covalent catalysis and an important subcategory widely used is the so-called *aminocatalysis*.[4,19,20]

As we can see in the first two examples in the upper left in Scheme 1.8, the amine catalysts may activate the substrates forming imminium ions and enamines as intermediates.[21]

By the formation of the iminium ion the carbonyl carbon is made more electrophilic and the α-position more acidic (Scheme 1.9). This facilitates reactions such as Knoevenagel-type condensations, cleavage of σ-bonds adjacent to the α-carbon and cyclo- and nucleophilic additions. The formation of the enamine increases the electron density on the α-carbon, thus becoming more nucleophilic (Scheme 1.9).[7] Enamines react with different electrophiles giving aldol, Michael and Mannich reactions, α-functionalization of aldehydes and ketones or undergo pericyclic reactions. The enamine is generated by deprotonation of an ion iminium and the equilibrium between the two species (acid and basic form) is a protonation-deprotonation equilibrium which makes more active the reagents and also makes more kinetically labile the chiral catalyst.



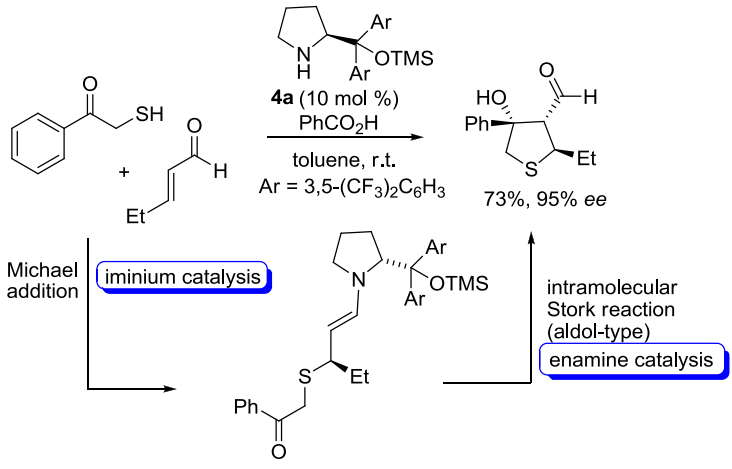
Scheme 1.9

In the reaction mixture both species are formed and are in equilibrium with each other, so the same centre can behave both as a Lewis base and acid. The relative amount of the two species depends on the reaction conditions, therefore a chemical reaction can also have different mechanistic pathways giving different products. Morover, thanks to the fact that the same catalyst can

adopt both methods of activation, aminocatalysis is widely exploited in cascade reactions, especially with secondary amine catalysts.[22]

Primary amine organocatalysts have been less exploited than secondary amines and their use is more recent because the equilibrium between the iminium ion and enamine is unfavorable, almost completely shifted to the left toward the iminium ion. Recently, primary amines have been used to activate more congested substrates that did not react with secondary amines.[23]

α,α-Diarilprolinol ethers, such as **4a** illustrated in Scheme 1.10 have been and are widely used in many α-functionalizations of carbonyl compounds and more recently in domino enantioselective reactions.[24] For example, Jørgensen et al. reported a tandem synthesis of tetrahydrothiophenes in which the catalyst **4a** catalyzes first a thia-Michael addition via iminium catalysis, and then an intramolecular aldol cyclization, via enamine catalysis, in the same reaction pot (Scheme 1.10).[25]



Scheme 1.10 Tandem reaction catalyzed by prolinol catalyst.

1.3.2 Lewis acid catalysis

Lewis acid catalyst initiates the catalytic cycle activating the nucleophilic substrate accepting its electron pair. Brønsted acid catalysis is the major research field in acid organocatalysis.[26] Until today, the Lewis acid organocatalysis was the field less explored, as it has proven the most challenging.[19,27]

The phase transfer catalysts are an important class of organocatalysts and they can be considered as Lewis acids. The reactions promoted by PTCs fall into the non-covalent catalysis category because the interactions between catalyst and substrate/s are ion pairing-type. In these reactions, anionic intermediates are formed and their countercation, formed by the catalyst, is chiral. If the ion pairing association is sufficiently strong, chirality in the product is induced.

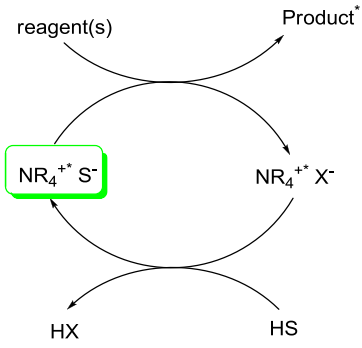
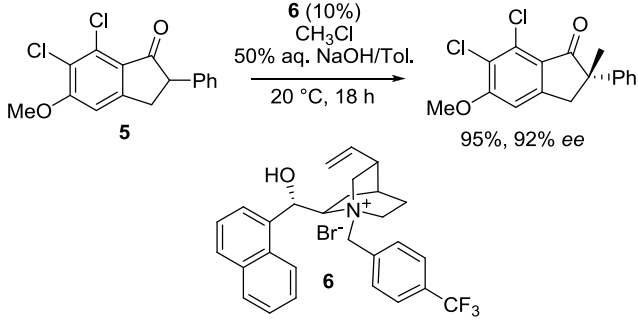


Figure 1.3 Phase-tranfer catalysis with chiral countercations (PTC). S = substrate, X^- = anion, NR_4^{+*} = cationic chiral catalyst.

The first efficient phase transfer catalyst has been discovered by a group at Merk, who used it for the enantioselective α-methylation of indanone **5**.[28] It is a *N*-benzyl cinchonidinium salt **6** that promoted the reaction giving the product in 95% yield and 92% *ee* (Scheme 1.11).



Scheme 1.11 First example of a PTC catalyzed reaction.

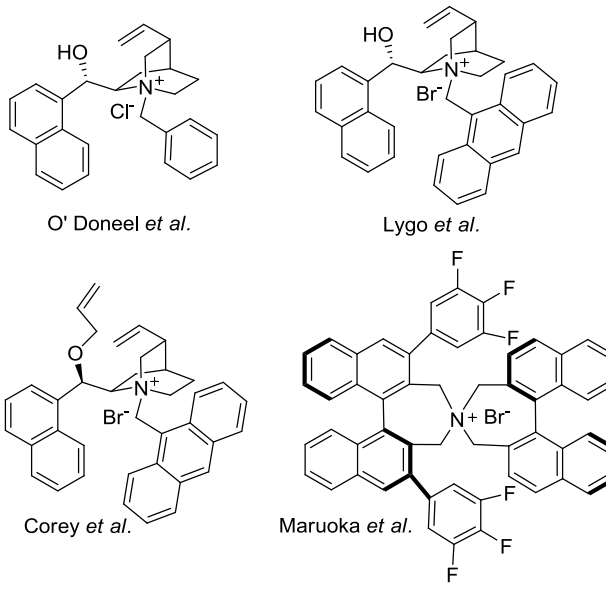


Figure 1.4 PTC catalysts.

Since then, the phase-transfer catalysis has made enormous progress and many other PTC catalysts have been developed.[29] In Figure1.4 are shown some examples.

In 2006, the concept of ACDC, *asimmetric counteranion-directed catalysis* was introduced (Figure 1.5).[30] This type of catalysis is conceptually the opposite of the phase-transfer catalysis. List defines it as: "*the induction of enantioselectivity in a reaction proceeding through a cationic intermediate by means of ion pairing with a chiral, enantiomerically pure anion provided by the catalyst*".[31]

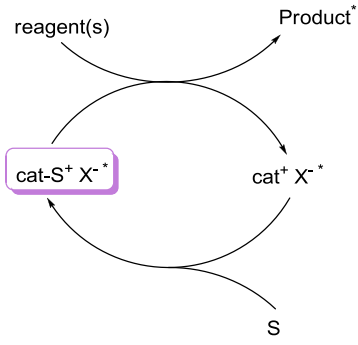


Figure 1.5 Asymmetric counteranion-directed catalysis (ACDC). S = substrate, X^- = anion.

The concept can be expanded to all types of enantioselective catalytic reactions whose mechanism involves cationic intermediates in the stereodetermining step.

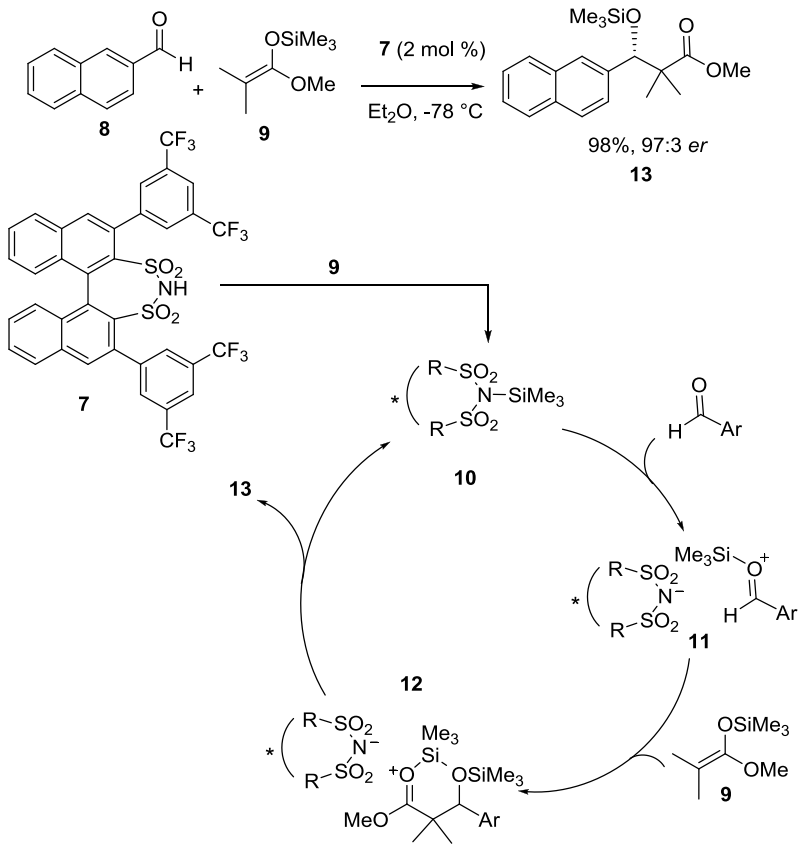
In the mechanism of this type of catalysis ion pairs are involved. An ion pair was defined by Anslyn and Dougherty: "*An ion pair is defined to exist when a cation and anion are close enough in space that the energy associated with their electrostatic attraction is larger than the thermal energy (RT) available to separate them.*"[32]

This definition, however, must not be used in a narrow sense because the ion pairs are stabilized by Coulomb attraction forces but different additional stabilizing interactions, such as hydrogen bonding, could be implicated. Inter alia, hydrogen bonds can be thought as a kind of ion pairing between an acceptor atom and the dipole of a donor bond and frequently, we cannot determine if a "real" ion pair is involved. So, the ion pair definition used, when we talk about ACDC, is a "broader" definition and the presence of different stabilizing interactions is allowed. In particular, List defines ACDC reactions as: "*all those reactions in which a*

considerable anion character can be attributed to the component responsible for the asymmetric induction".[31]

As an example, the enantioselective Brønsted acid catalysis is a specific case of ACDC when, even if the ion pairs are stabilized by further stabilizing interactions (such as hydrogen bonds, in addition to Coulomb attraction), the ionic character of the intermediate is not negligible. Brønsted acid catalysts, which will be discussed in the following paragraph, can be divided into neutral hydrogen-bonding catalysts (such as TADDOLs and thioureas/ureas) and stonger Brønsted acid catalysts (such as binol-derived phosphoric acids) whose activation mode has an ion pair character.[19]

The ACDC concept can be applied to transition-metal catalysis and to organocatalytic Bronsted acid catalysis and Lewis acid catalysis. The following example (Scheme 1.12) shows an application of the ACDC concept to Lewis acid organocatalysis, a field that has been unexplored until a few years ago.[27]



Scheme 1.12 ACDC of Mukaiama-aldol reaction.

Lewis acid catalysts are more "powerful" than Brønsted acid catalysts, in fact they are able to activate much less reactive substrates, such as ketones and aldehydes, on which the Brønsted acid catalysis doesn't work.[33]

In order to activate the aldehydes, the List's research group has designed and developed chiral disulfonimides (DSIs), as **7** in Scheme 1.12, that are Lewis acid catalyst precursors.[34] The DSIs are Brønsted acids,[35] but, in the presence of a silicon nucleophile, a

protodesilylation takes place and they are transformed into Lewis acids.[36] The Lewis acid catalyst is thus formed in situ and doesn't need to be pre-formed, unlike the first reported silicon-based Lewis acid catalysts.[37] List explored the activity of **7** in Mukaiyama-aldol reaction by using the ACDC strategy (Scheme 1.12).

First, the disulfonimide **7** is silylated by silyl ketene acetal **9**, thus forming the active Lewis acid **10**. Then, **10** activates the aldehyde affording ion pair **11** which reacts with nucleophile **9** giving intermediate **12**. In the last step of the catalytic cycle, the product **13** is liberated and the catalyst is regenerated. Although Yamamoto reported another possible interpretation of the mechanism, via pentavalent silicon intermediates instead of ion-pairs, the ACDC mechanism involving a chiral counteranion is believed to be the most plausible.[37]

1.3.3 Brønsted acid catalysis

Chiral metal-based Lewis acids are well-known catalysts in asymmetric synthesis employed to activate electrophiles.[38] In this strategy electron-poor metal sites interact with electron-rich sites (Lewis bases), typically heteroatom-centred (O, N, S, Halogen) or multiple bonds establishing a dative bond that accelerates the nucleophilic attack by lowering the LUMO (lowest unoccupied molecular orbital) energy of the electrophile.

The same effect is carried out by the formation of iminium ions between secondary amines and carbonyl compounds in covalent catalysis, as illustrated above in paragraph 1.3.1. The third way to electrophilic activation is the formation of hydrogen bonds between

a Brønsted acid catalyst and the substrate (Figure 1.6).[39]

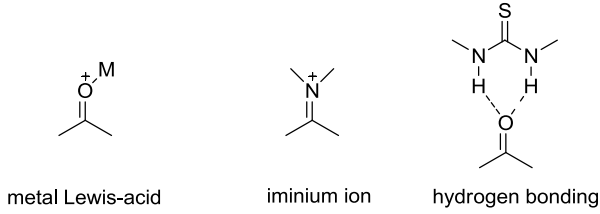
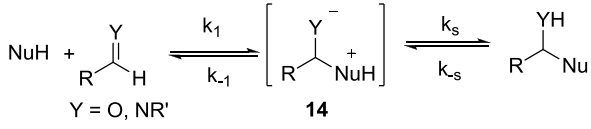


Figure 1.6 Electrophilic activation of the carbonyl group by hydrogen bonding, coordination to metal Lewis-acid and iminium ion formation.

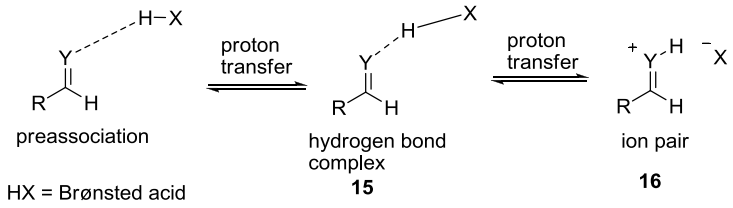
Also in this third case, the electrophile LUMO energy is lowered, thereby accelerating the reaction. In fact, when a weak nucleophile reacts with a rather stable electrophile, the intermediate conversion rate to the reactants is faster than the product formation by abstracting a proton ($k_{-1} > k_s$) (Scheme 1.13).[39a]



Scheme 1.13 Nucleophilic addition to a carbonyl compound.

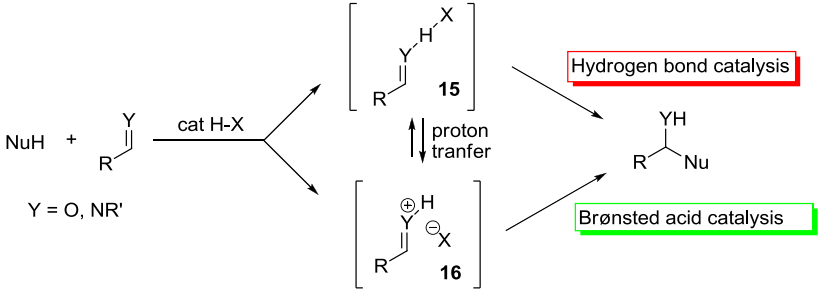
In the presence of an acid catalyst, the tetrahedral negatively charged intermediate, which has an accumulation of electron density on oxygen or nitrogen atom, and the transition state leading to it, are stabilized by hydrogen bonding thus increasing the reaction rate.

As shown in Scheme 1.14,[39a] first the carbonyl compound associates with the acid catalyst, then a partial proton transfer occurs leading to the formation of the hydrogen-bond complex **15** and then a proton transfer forms an ion pair **16**.



Scheme 1.14

Nucleophilic attack to provide addition product can take place by **15** or by **16**, it depends on the nature of the catalyst. If the catalyst forms a hydrogen-bond complex **15** and the nucleophilic attack takes place on it, the reaction is called hydrogen-bond catalyzed reaction. Instead, if the catalyst forms ion pair **16** and this species undergoes the nucleophilic addition, the reaction is termed as Brønsted-acid-catalyzed reaction (Scheme 1.15).[39]



Scheme 1.15 Hydrogen-bond and Brønsted-acid catalysis.

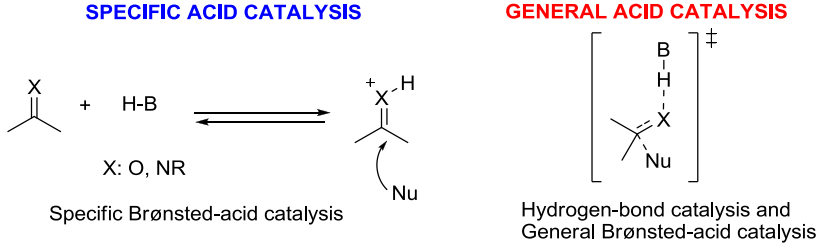
In analogy with enzymatic catalysis, the term *general acid catalysis* is used when:

i) the transition state of the rate-determining step is stabilized by pure hydrogen bonding, without full proton transfer (*hydrogen bond catalysis*) or ii) the reactions are initiated by hydrogen bonding but

the proton is fully transferred in the transition state of the rate-determining step (*General Brønsted-acid catalysis*).[19,39,40]

The term *specific acid catalysis* is used when:

the proton transfer takes place on the electrophilic substrate in its ground state in a pre-equilibrium step and successively the nucleophilic attack occurs in the rate-determining step (*Specific Brønsted-acid catalysis*) (Scheme 1.16).[19,39]



Scheme 1.16

Given that between the hydrogen-bond complex **15** and ion pair **16** there is an equilibrium and the formation of a hydrogen bond always precedes the proton transfer, it is often difficult to distinguish if hydrogen-bond or Brønsted acid catalysis is involved. In general, compounds able to furnish H-bonding catalysis may be classified into: neutral Brønsted acids and stronger Brønsted acids (Figure 1.7).[26c, 41]

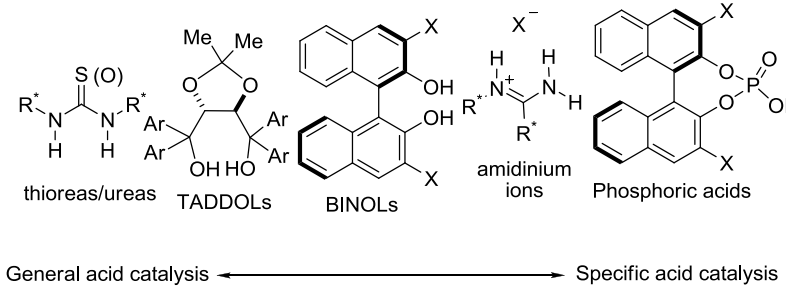
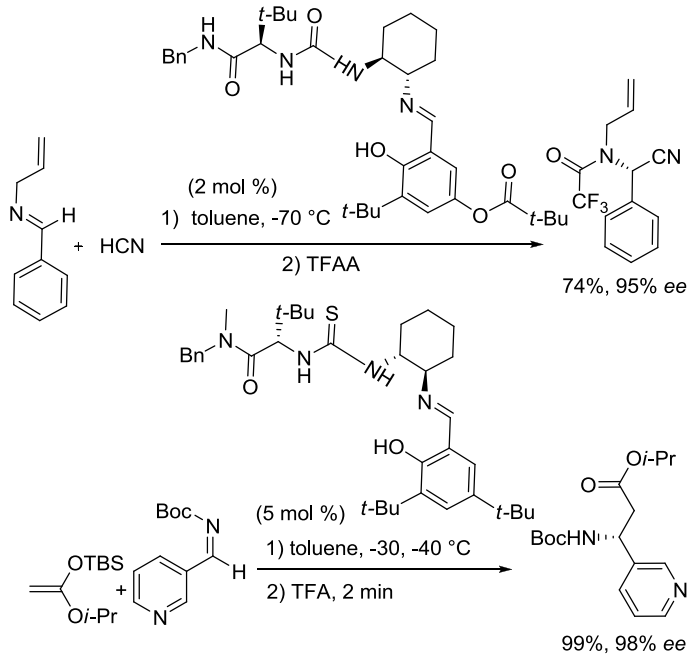


Figure 1.7 Neutral and stronger Brønsted acids.

Species such as ureas, thioureas, diols, BINOL derivatives are defined neutral Brønsted acids and usually named hydrogen-bonding catalysts. Stronger Brønsted acids, instead, such as phosphoric acids, guanidinium and amidinium ions, have more acidic sites. The latter ones are more reactive general acid catalysts and they can provide also specific acid catalysis. For example, phosphoric acids are considered able to give both general and specific acid catalysis.[42]

The hydrogen bonds can stabilize the charge of transition states and intermediates, can activate the reagents by polarization, and can pre-organize their spatial arrangement if the hydrogen donor-acceptor sites are connected onto a chiral scaffold affording chiral products. For example, Jacobsen *et. al*. performed enantioselective Strecker and Mannich reactions of imines catalyzed by chiral ureas and thioureas (Scheme 1.17).[43]



Scheme 1.17

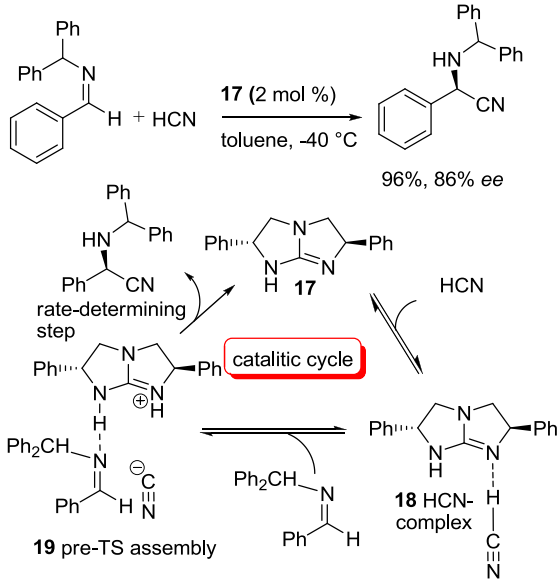
It is believed that in these reactions the catalyst activates the imine by means of hydrogen-bridge bonds between the urea/thiourea and the nitrogen of the imine forming an organized transition state responsible for the asymmetric induction.

1.3.4 Brønsted base catalysis

In analogy to Brønsted acid catalysis, Brønsted base catalysis mechanisms can be distinguished in: i) *specific base catalysis* when reactants are fully deprotonated prior to rate-determining step; ii) *general base catalysis* when proton transfer from reactants to base occurs during the rate-determining step or the proton is partially transferred to base in the transition state of the slow step. Generally,

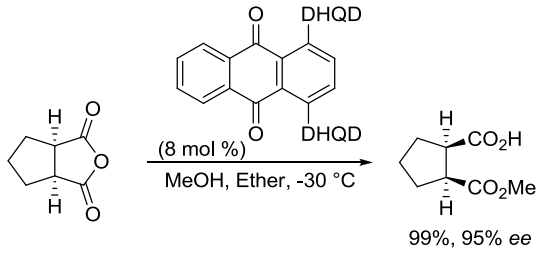
the former type of catalysis requires strong bases while the latter needs a weak base. Basically, how the Brønsted acid catalysts, shown in the previous paragraph, help making the substrates more electrophilic, Brønsted base catalysts help making reactants more nucleophilic.

For example, the addition reaction of HCN to aldehydes for the synthesis of chiral cyanohydrins reported by Inoue, shown in Scheme 1.6 in paragraph 1.2, is an example of Brønsted base catalysis.[17] Another classical example of Brønsted base catalyzed reaction is the Strecker reaction. Corey and Grogan reported that this process is catalyzed by a C_2-symmetric guanidine compound **17** (Scheme 1.18).[44] The authors suggested that in the first step of the catalytic cycle a hydrogen bond between HCN and the catalyst is created, generating a guanidinium cyanide complex **18**. Then, binding of aldimine to this complex via hydrogen bond takes place forming the pre-transition-state termolecular assembly **19**. Finally, cyanide ion attacks the hydrogen-bond-activated aldimine in the ion pair affording the Strecker product. They suggested that the rate-determinig step is the last step of the catalytic cycle.



Scheme 1.18 Strecker reaction catalyzed by a chiral bicyclic guanidine.

This kind of catalysis has been applied to many different asymmetric reactions such as, among others, Michael reactions,[45] or desymmetrization of cyclic *meso*-anhydrides. In particular, the last mentioned reaction (Scheme 1.19), reported by Deng,[46] is an example of general base catalysis: the alcohol is activated by a cinchona alkaloid-derived catalyst towards nucleophilic attack via hydrogen bonding.

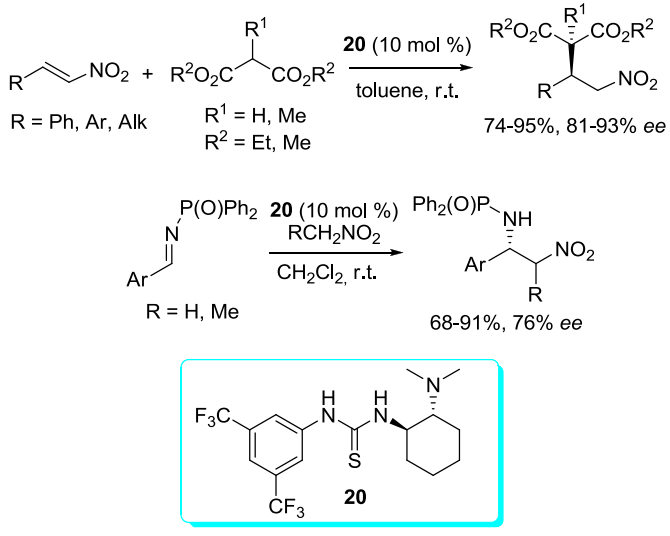


Scheme 1.19 Desymmetrization of cyclic anhydrides with modified cinchona alkaloids.

1.4 Bifunctional Organocatalysts

As the organocatalysis progresses, the design and the synthesis of a steadily growing number of organic catalysts is developed. Most of the nowadays used efficient organocatalysts have more than one active centre and most of them are bifunctional organocatalysts. They usually have a Brønsted acid and Lewis base centre by means of which they can activate simultaneously both the donor and the acceptor. In this way the reaction is accelerated thanks to the spatial approaching of the reactants (that react in a more restricted reaction space) and becomes more stereoselective because the transition state is geometrically well-organized and rigid. The hydrogen bonds are the forces that most frequently stabilize the intermediates and the transition state by forming definite geometries and increasing the reaction rate. A typical example of this kind of catalyst is the Takemoto's thiourea **20** (Scheme 1.20). This catalyst has a tertiary amino group close to the thiourea H-bonding donor site. Takemoto firstly demonstrated its effeciency in the pivotal examples of enantioselective Michael[47] and aza-Henry[48] catalyzed reactions

(Scheme 1.20). Since then catalyst **20** has been used in several different reactions and it has become commercially available.



Scheme 1.20 Michael and aza-Henry reaction catalyzed by Takemoto's thiourea.

The authors proposed that the thiourea interacts with the nitro group via hydrogen-bonding, enhancing the electrophilicity of the nitroalkene, while, simultaneously, the neighboring dimethylamino group activates the pronucleophile. In this way, nucleophile and electrophile will approach stereoselectively in an organized transition state and the nucleophile will preferential attack one face of the olefin affording an enantioenriched product (Figure 1.8).[49]

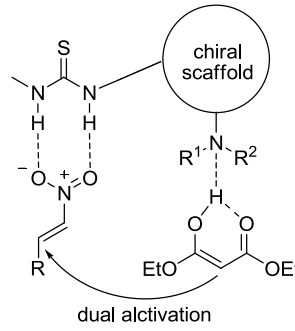


Figure 1.8 Activation mode of a bifunctional thiourea.

The cinchona alkaloids such as quinine and quinidine, cinchonine and cinchonidine, are bifunctional organocatalysts and are among the most efficient catalysts.[50] In their structure, tertiary quinuclidine basic nitrogen (Lewis base) and a proximal hydroxyl group, which is a H-bonding group, are contained (Figure 1.9). A very large number of their derivatives have been applied in a wide diversity of asymmetric reactions.

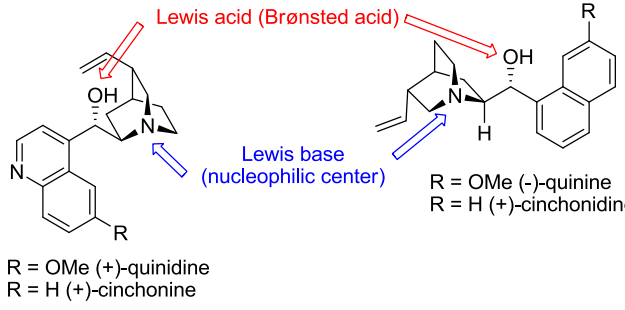


Figure 1.9 Cinchona alkaloids catalysts.

Another class of efficient bifunctional organocatalysts are the readily available α,α-L-diaryl prolinols. They can provide non-covalent general acid/base catalysis, in a similar way to cinchona alkaloids, as they have Lewis/Brønsted basic secondary amine

functionality and the hydroxyl H-bonding donating group (Figure 1.10). Unlike cinchona alkaloids, thanks to the secondary amine moiety, they can also provide covalent catalysis by forming enamine or iminium ion with carbonyl compounds, in the same way of α,α-L-diaryl prolinols ethers developed by Jørgensen's[51] and Hayashi's[52] groups. In the field of covalent catalysis, α,α-L-diaryl prolinols have been investigated in Michael type additions, aldol reactions, cycloaddition reactions and carbon–carbon and carbon–heteroatom bond forming reactions.[53,24a,b] They can also promote asymmetric epoxidation and peroxidation of electron-poor olefins, Michael type additions, cyclopropanation, sulfenylation and desymmetrization reactions under non-covalent activation of the reagents.[53]

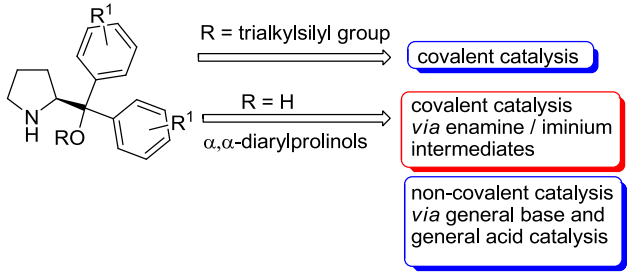


Figure 1.10

The two types of catalysis provided by these compounds can be thought as two sides of the same coin (Figure 1.11) and they are a rare example of organic catalysts able to exploit two alternative mechanistic pathways.

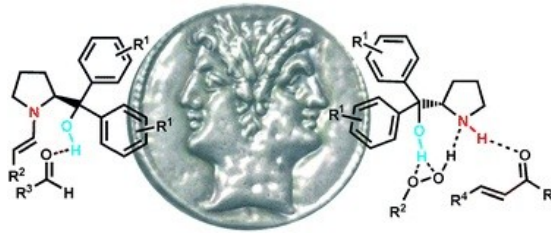
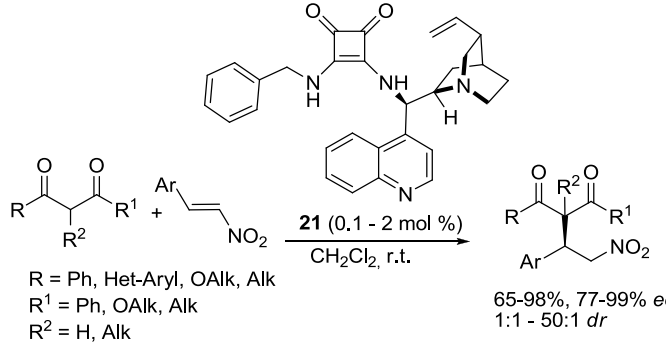


Figure 1.11

Squaramides are among the youngest organocatalysts reported, originally born as anion receptors and only recently exploited as bifunctional organocatalysts.[54] The first example of squaramides as bifunctional organocatalysts was reported by Rawal in 2008, who used a low loading of a cinchona alkaloid derived compound **21** to catalyze the enantioselective Michael addition of dicarbonyl compounds to nitroalkenes with high stereocontrol (Scheme 1.21).[55]



Scheme 1.21

Ureas and thioureas, likewise squaramides, show strong anion-binding affinities, but their ability to recognize cations is much more limited. Squaramides, instead, can recognize both anions and cations (Figure 1.12).

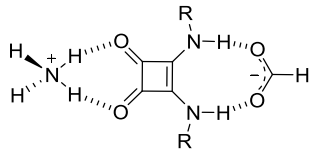


Figure 1.12 Squaramide recognition of cations and anions.

Moreover, it has been demonstrated that they form 1-2 orders of magnitude more stable complexes with carboxylates and nitrates than ureas.[56] They are nitrogenated derivatives of squaric acid so they have a conformationally rigid square-shaped structure. The ureas and thioureas are (thio)amides but squaramides are considered as vinylogous amides. In both (thio)ureas and squaramides the rotation of the C-N bond is restricted because the nitrogen lone pair is delocalized through the carbon-oxygen double bond (Figure 1.13). The cyclobutenedione system, however, is partially aromatic (n = 0, Hückel's rule) so other resonance structures with two positive charges in the ring are possible giving further delocalization. It is believed that the ability to recognize cations is due to the "increase of aromatic character" in the cyclobutenic ring after complexation.[57] They are bifunctional H-bond donor and acceptor and, due to higher conformational restriction compared to ureas and thioreas, the carbonyl and the amine groups are coplanar[58] (Figure 1.13).[54] It was calculated that the distance between the two N-H groups is bigger in squaramides (2.7 Å) than in thioureas (2.1 Å) and the two N-H bonds have a convergent orientation being bent of 6°.[55,59]

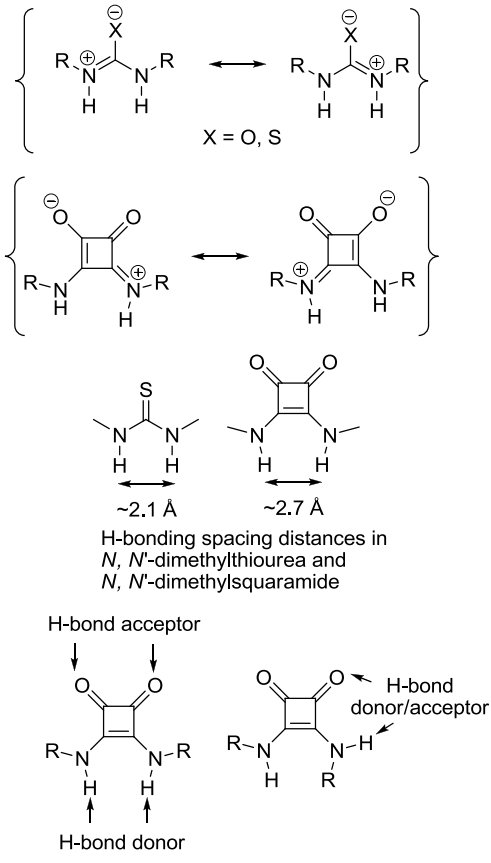


Figure 1.13 Squaramide properties and comparison with urea/thiourea.

This offers the possibility to form different hydrogen bonds compared to ureas and thioureas and squaramides can be able to bind substrates of different size and shape. Finally, the two different functionalities have also different pK_a values. For the sake of comparison, pK_a values of H_2CO_3 (pK_{a1}: 3.62, pK_{a2}: 10.3) and squaric acid (pK_{a1}: 1.5, pK_{a2}: 3.4) can be considered, so the squaramides are more acidic than ureas. Therefore, being more acidic and more conformationally rigid, squaramides are generally

more effective in the activation of substrates at a lower catalyst loading (0.1 – 5 mol %) with respect to ureas and thioureas. The only drawback of these catalysts is their self-association tendency, so the use of more polar solvents is often required. Although their discovery came quite late compared to ureas and thioureas, the development of structural changes for the improvement of their catalytic ability has been fast and many squaramides, bearing different chiral scaffolds, have been synthesized and exploited in a variety of reactions.[54]

Bifunctional organocatalysts having a much stronger Brønsted acid group are BINOL-derived phosphoric acids (Figure 1.14). They have a single acidic proton (pK_a: 1.39 for diethylphosphate), implicated in the electrophile activation, and a close Lewis base phosphoryl moiety that can simultaneously activate a nucleophile. This scaffold can be derived from either (*R*)- or (*S*)-BINOL introducing substituents at the 3,3'-positions to modulate the chiral induction.

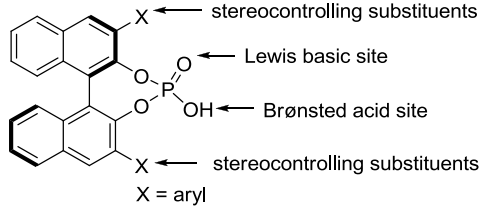
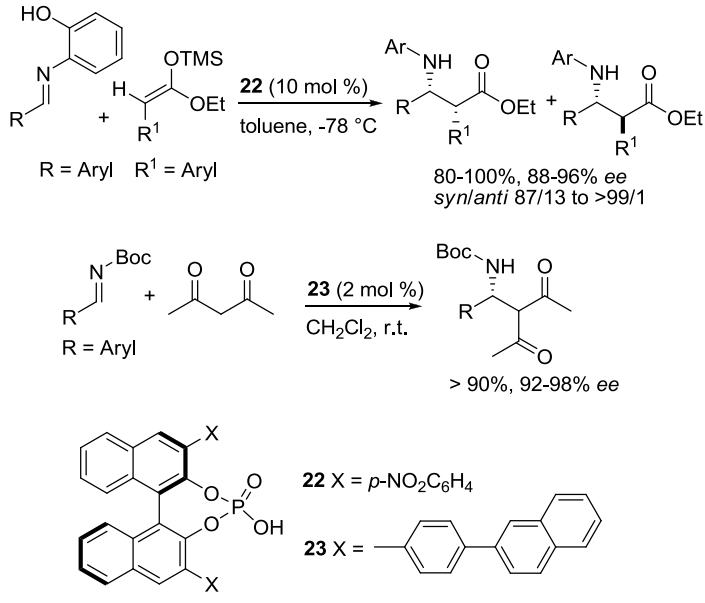


Figure 1.14 BINOL-derived phosphoric acids.

Akiyama's[42a] and Terada's[42b] groups, independently, firstly reported the application of these compounds in organocatalysis. In particular, they used chiral phosphoric acids **22** and **23** in enantioselective Mannich reactions of *N*-aryl and *N*-Boc substituted

imines with silyl ketene acetals and acetyl acetone, respectively (Scheme 1.22).



Scheme 1.22 Stereoselective Mannich reactions catalyzed by phosphoric acids.

Akiyama proposed a cyclic nine-membered zwitterionic transition state. Differently, Terada proposed a transition state structure in which the catalyst activates the imine via H-bonding with the acidic proton and, simultaneously, forms another hydrogen bond between the Brønsted basic phosphoryl oxygen and the hydroxylic proton of the enol form of acetyl acetone (Figure 1.15). These examples show how catalysis exploited by phosphoric acids is halfway between specific and general Brønsted acid catalysis, as mentioned above.

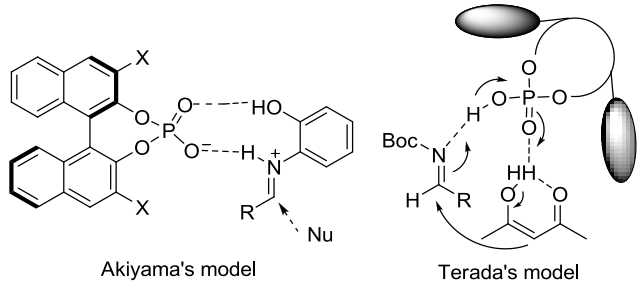

X
O
P
O
O
O
HO
H
N
R
Nu
X
Akiyama's model
O
O
P
O
H
O
Boc
N
H
R
HH
O
O
Terada's model

Figure 1.15

2. ASYMMETRIC SYNTHESIS OF TETRAHYDROTHIOPHENES BEARING A QUATERNARY STEREOCENTRE

2.1 Tandem Reactions

In general, one-pot, domino, tandem, multi-component reactions are processes that allow us to perform two or more transformations of an organic substrate in a single reactor carrying out a single work-up step. In these processes, the isolation and purification of intermediate products are avoided saving time, cost, purification solvents and reducing the amount of waste.

Tietze defined a *domino reaction* as:" *process involving two or more bond-forming transformations (usually C-C bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step".*[60]

A reaction in which several functionalities of a substrate undergo individually a transformation in just one reactor is not a domino reaction.

Tandem reaction, *cascade reaction* and *sequential reaction* are terms generally used as synonyms.

However, as regards their catalytic variants there is a distinction between *domino catalysis* or *tandem catalysis* and *sequential* reactions. In both domino and tandem catalysis, all catalytic species are present from the outset. On the contrary, in the *sequential one-*

pot reactions an organic reagent is modified via successive chemical reactions in a single reactor (without purification or separation steps) but reagents and catalysts necessary in each transformation are added only after the previous transformation is complete. The reaction intermediates in a one-pot reaction are, in general, isolable and stable.[61] A *multicomponent reaction* (MCR) is defined as a chemical transformation in which three or more organic molecules react in the same reaction pot, furnishing a product that includes in its structure considerable portions of all the reactants.[62] In general, the chemical community uses the term multi-component in a more general sense, i.e. including both domino (reactions in which all the reagents are added at the beginning of the reaction) and one-pot reactions (in which the reagents are added one after the other).

2.1.1 Domino catalysis

Figure 2.1 is a representation of a catalytic domino reaction (domino catalysis): reagents **A** and **B** can react intra- or intermolecularly giving intermediate **I**. Then **I** reacts with another reagent **R** (or with another reactive portion in **I** itself, intramolecularly) affording product **C**.[61]

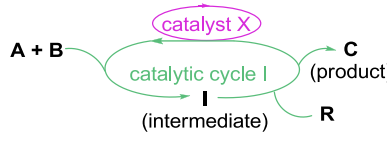


Figure 2.1 Catalytic domino reaction.

Takemoto and Takasu explained that in domino catalysis, substrates **A** and/or **B** are activated by the catalyst **X** only at the beginning of the process and, for the second reaction to give product **C**, additional activation of intermediate **I** by **X** is not necessary. They make clear also that the diversity and complexity of product **C** is determined in the first catalytic reaction step and the intermediate **I** is, in general, transient and not isolable.[61]

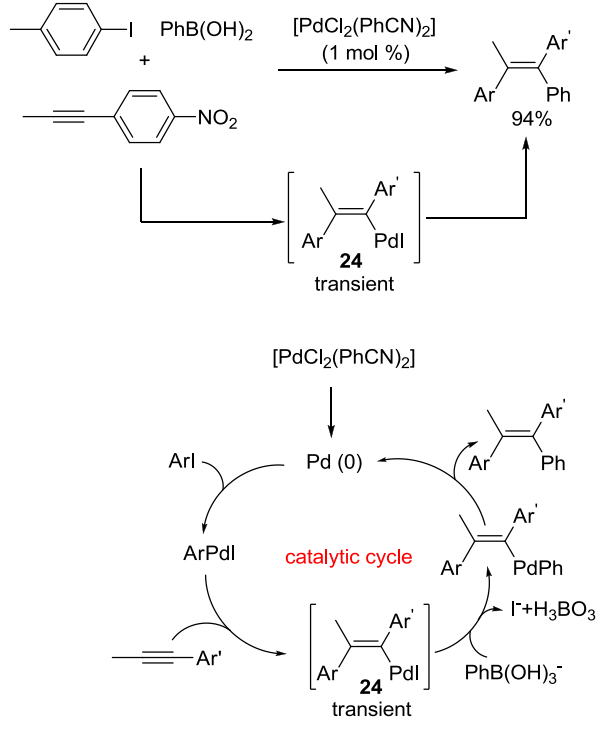
Besides, Faber defined that in domino catalysis: "*the starting material undergoes a transformation via two (or more) reactions one after another in an inseparable fashion*" and "*both individual reactions belong tightly together and are rather difficult to perform in a stepwise (independent) fashion. As a consequence, the intermediate between both steps is likely to be unstable and (often) eludes isolation and characterization*".[63] Later, Fogg and dos Santos added that in domino catalysis, in contrast with tandem catalysis, multiple transformations are effected via a *single* catalytic mechanism.[64] The catalyst must be essential to both of the bond-forming transformations.[65]

This precise definition excludes from domino catalysis definition the reactions that consist of a single catalytic transformation followed by a stoichiometric modification. This process is classified as a domino reaction but does not constitute tandem or domino catalysis because the catalyst does not participate in the second transformation. In other words, a single catalytic transformation took place.

The terms domino and tandem catalysis refer only to sequential elaborations of an organic substrate via multiple catalytic

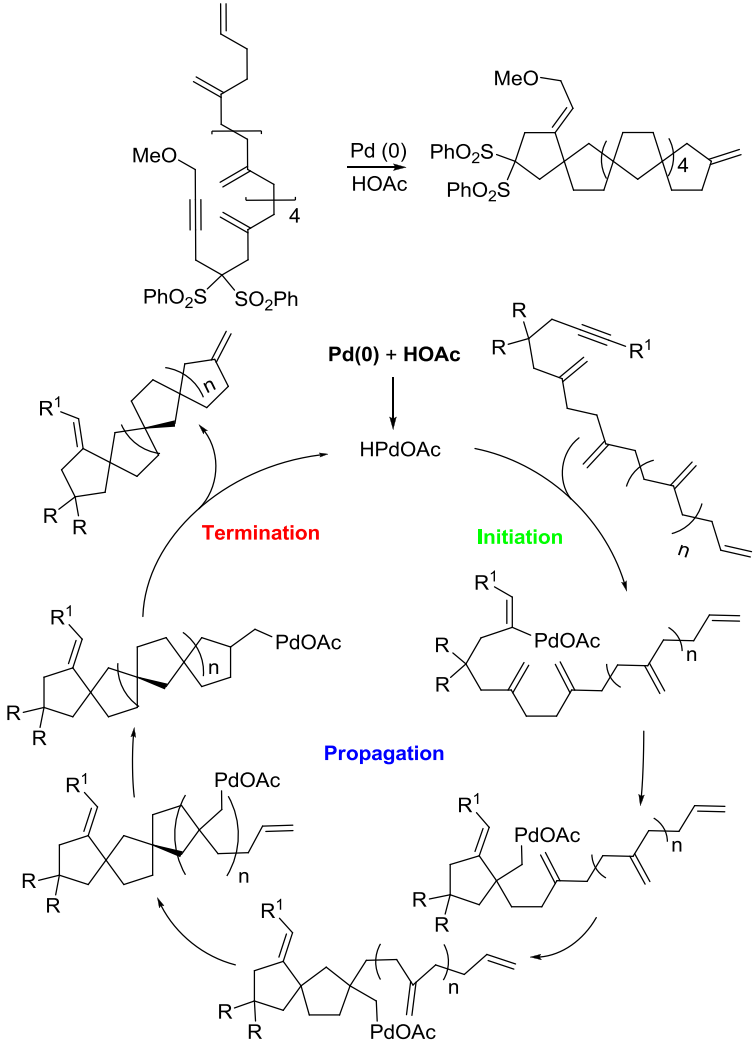
transformations (transformations in which the catalyst is involved).[64]

In Scheme 2.1 is shown a typical example of a catalytic domino intermolecular reaction.[66] In the reaction sequence, first the Pd(0) catalyst formation occurs followed by oxidative addition of the aryl iodide to Pd(0) and regioselettive *cis*-carbopalladation of the internal alkyne to generate a vinyl palladium intermediate **24**. Then Suzuki type transmetalation with phenyl boronic acid and reductive elimination produce the tetrasubstituted olefin, regenerating the Pd(0) catalyst.



Scheme 2.1 Example of intermolecular domino catalytic reaction.

In this reaction, the catalytic activation event takes place only once and intermediate **24** is a transient species that cannot be isolated as a stable species. Likewise, sequential transformations may occur in intramolecular processes. In Scheme 2.2 is reported an example of intramolecular domino cascade reaction.[67]



Scheme 2.2 Example of intramolecular domino catalysis.

2.1.2 Tandem catalysis

Fogg and dos Santos defined *tandem catalysis* as: "*coupled catalyses in which sequential transformation of the substrate occurs through two or more mechanistically distinct processes*".[64] Previously, Faber stated that: "*tandem reactions are considered to be two-step reactions that proceed in a consecutive fashion where each of the steps can be performed separately. Thus the intermediate species will be a rather stable compound*".[63]

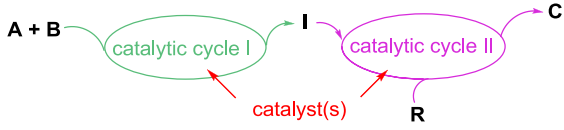


Figure 2.2 Tandem catalysis in domino reactions.

In Figure 2.2 is reported a conceptual diagram of tandem catalysis.[61]

In this type of catalysis, intermediate **I** is isolable and both the conversion of **A** and **B** into **I** and the consecutive transformation of **I** into final product **C** are promoted by catalyst(s). How explained by Takemoto and Takasu, the two (or more) involved catalytic cycles are independent and different from a mechanistic point of view. The domino reaction involves two or more catalyst-controlled processes: in the reaction pathway the catalyst(s) interacts with the substrates and the intermediate. The diversity and complexity of product **C** is affected by the catalyst(s) and both the substrates. [61]

Fogg and dos Santos proposed three subcategories of tandem catalysis: *orthogonal*-, *assisted*-, and *auto-tandem* catalysis.[64]

In orthogonal-tandem catalysis two (or more) sequential and indipendent catalytic cycles operate simultaneously catalyzed by two (or more) noninterfering catalysts or precatalysts. Starting materials **A** and **B** undergo preferential reaction with catalyst **X** forming **I**, which in turn is the substrate for catalyst **Y**.

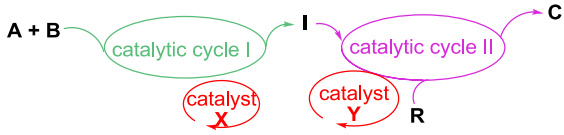


Figure 2.3 Orthogonal-tandem catalysis.

In assisted-tandem catalysis only one catalyst is used. Catalyst **X** catalyzes the first transformation and, after the first process is completed, catalyst **X** is transformed into catalyst **X'** by addition of chemical triggers and the second catalytic cycle starts. Clearly, in this process, in contrast with orthogonal-tandem catalysis, the two catalytic cycles are not coexistent.

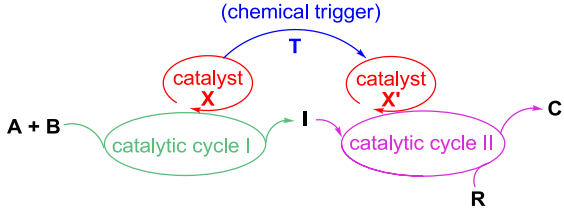


Figure 2.4 Assisted-tandem catalysis.

In auto-tandem catalysis the reaction sequence that consists of two (or more) mechanistically distinct catalytic cycles, is promoted by only one catalyst and no chemical triggers are needed. Both cycles take place concurrently and spontaneously.

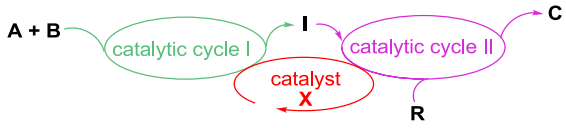
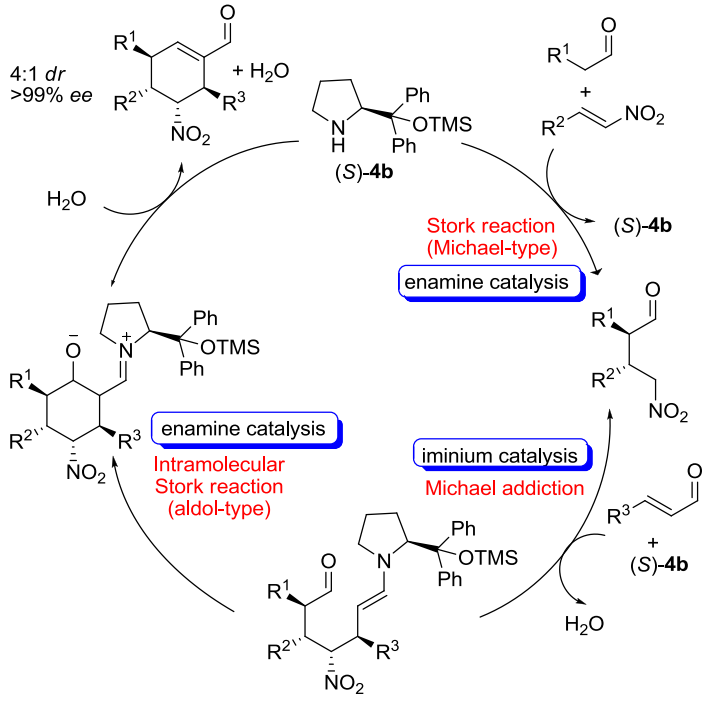


Figure 2.5 Auto-tandem catalysis.

Each of the three types of catalysis has its advantages and disadvantages, but the auto-tandem catalysis is the less complex in terms of manual operations and takes full advantage of the catalyst.

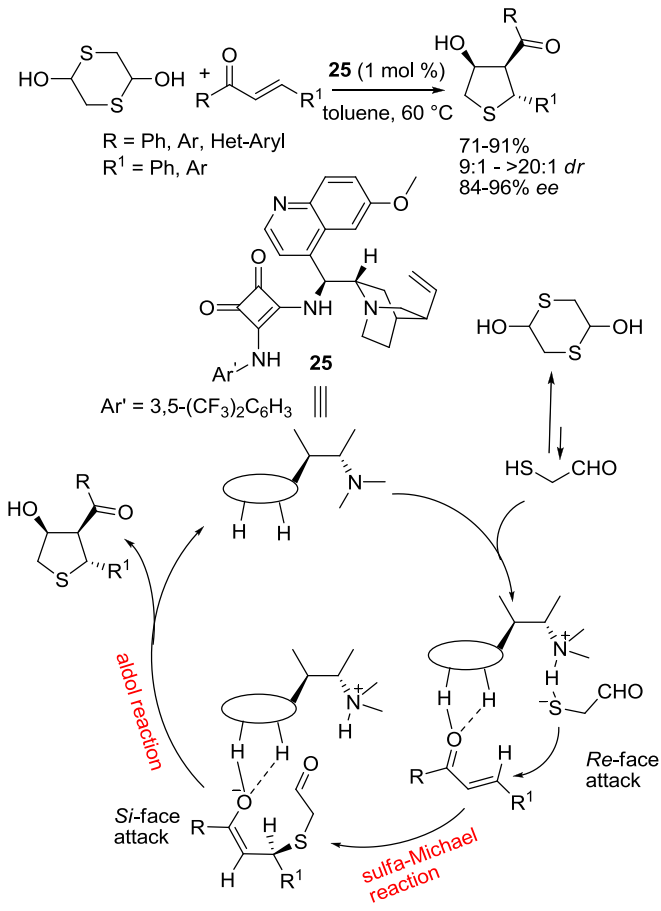
There are a lot of asymmetric organocatalytic domino reactions performed in organocatalysis.[61,65,68] Many of these are performed with secondary amino catalysts and there are several examples of auto-tandem catalysis.[69]

The reaction illustrated in Scheme 2.3 is an example of auto tandem-catalysis.[70] The amine catalyst **4b** catalyzes three different reactions determining the stereoselective formation of four stereocentres.



Scheme 2.3 Example of auto-tandem catalysis prolinol derivative-catalyzed.

Unlike covalent catalysis, non-covalent organocatalysis has been much less exploited in cascade processes, but this field is growing fast and the number of examples in the literature is increasing tremendously.[71] In Scheme 2.4 is reported a sulfa-Michael/aldol cascade reaction between 1,4-dithiane-2,5-diol and various chalcones, catalyzed by a bifunctional squaramide.[72] This is an example of H-bond-mediated cascade reaction in which the catalyst effectively controls the stereoselectivity of three contiguous stereocentres. Although the authors did not specify, it represents an example of auto-tandem catalysis.



Scheme 2.4 Hydrogen-bond-mediated auto-tandem catalysis.

Figure 2.6 shows a diagram that summarizes the classification of one-pot processes involving sequential elaboration of an organic substrate via multiple catalytic transformations.[64]

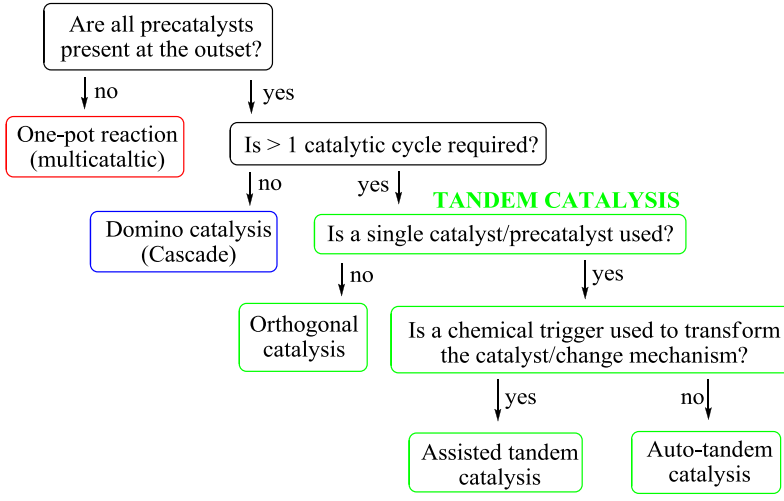

Are all precatalysts present at the outset?
no
yes
One-pot reaction (multicataltic)
Is > 1 catalytic cycle required?
no
yes
TANDEM CATALYSIS
Domino catalysis (Cascade)
Is a single catalyst/precatalyst used?
no
yes
Orthogonal catalysis
Is a chemical trigger used to transform the catalyst/change mechanism?
yes
no
Assisted tandem catalysis
Auto-tandem catalysis

Figure 2.6

2.2 Background

Organic sulfur compounds are widely present in Nature and in disparate biological systems. Among the organosulfur compounds, dihydro- but especially tetrahydrothiophenes are particularly important because the tetrahydrothiophene moiety is found in a lot of natural and non-natural bioactive compounds. Some examples are: α-glucosidase inhibitors **26-29** (salacinol, kotalanol, salaprinol, ponkoranol),[73] coenzyme biotin **30**, which is a water-soluble vitamin involved in gluconeogenesis, fatty acid production/metabolism and amino acid metabolism,[74] brain-type cholecystokinin (CCK) receptor antagonist tetronothiodin **31**,[75] oral hypocholesterolemic agents, such as breynin A-B and epibreynin B,[76] agonists/antagonists form the human A_3 adenosine receptor, such as 4'-thioadenosine derivative **32**,[77] **33** active against HSV-1 and HSV-2[78] and potential inhibitors of HIV[79] **34-36** (Figure 2.7).

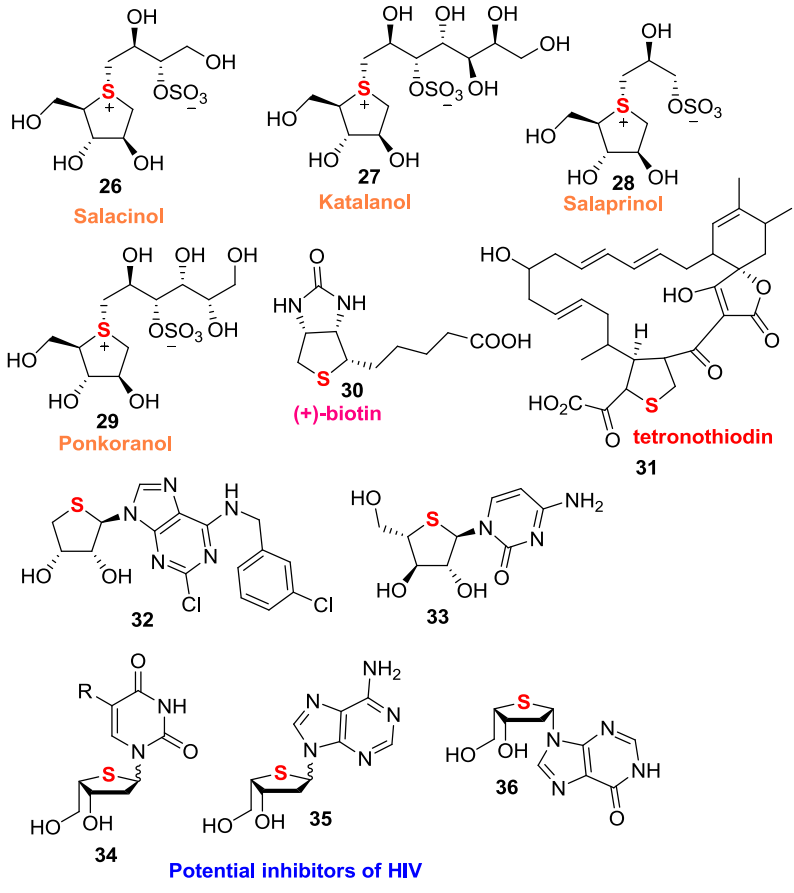


Figure 2.7 Valuable biologically active tetrahydrothiophenes.

Tetrahydrothiofenes have also proven to be useful chiral ligands for several enantioselective reactions including asymmetric hydrogenation,[80] enantioselective epoxidations,[81] aziridinations[82] and cyclopropanations[83] (Figure 2.8). They have also been used as ligands in gold complexes.[84]

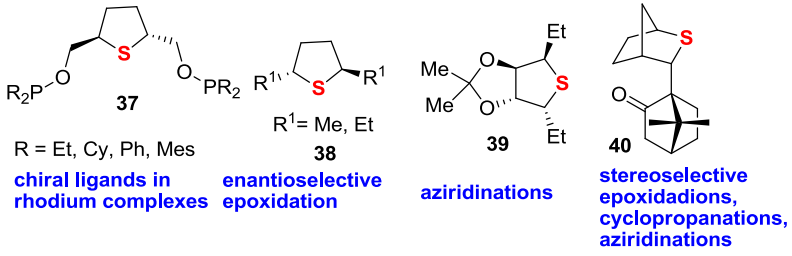
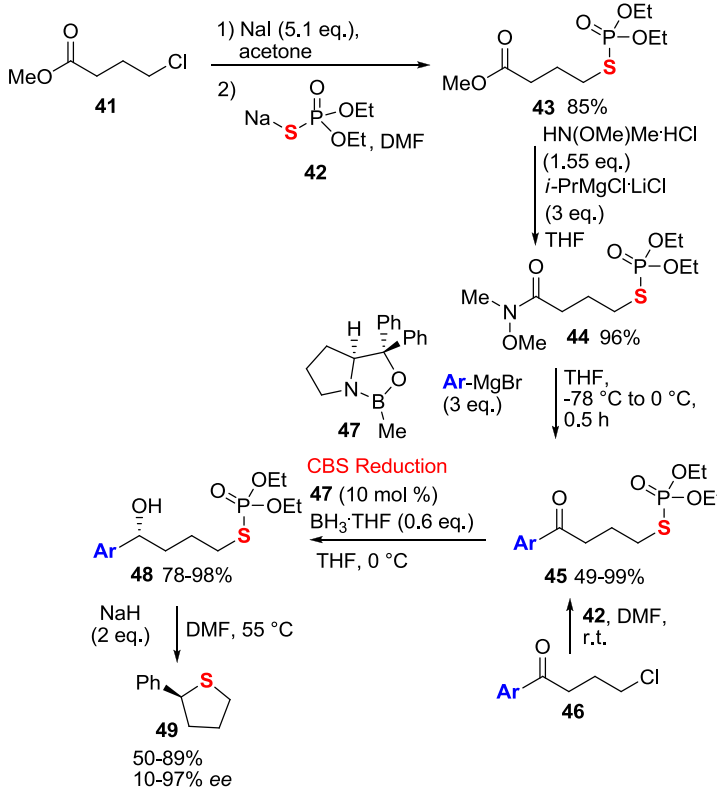


Figure 2.8 Representative tetrahydrothiophenes used as chiral ligands.

Despite their importance, few methods have been reported for the stereoselective synthesis of tetrahydrothiophenes.[85]

Recently, Wu et al. have developed an efficient stereospecific synthesis of enantioenriched tetrahydrothiophenes, which utilizes phosphorothioic acids and related compounds as H_2S surrogates (Scheme 2.5).[86]



Scheme 2.5 Chiral tetrahydrothiophenes formation via phosphorothioic acids.

In this methodology, the ketophosphorothioate esters **45** can be obtained from chloroketones **46**, by reacting them with sodium diethylphosphorothioate **42**, or treating the Weinreb amide **44** (synthesized with the two pot procedure reported in Scheme 2.5 starting from commercially available chloroester **41** and sodium diethylphosphorothioate **42**) with various organomagnesium reagents. In particular, the latter strategy makes more flexible and general the methodology since it is possible to access to a wide assortment of ketones **45** from a single common intermediate.

The ketophosphorothioate esters **45** are converted with high enantioselectivity into the chiral alcohols **48** through the Corey−Bakshi−Shibata (CBS) asymmetric reduction, using the chiral oxazaborolidine catalyst **47**. Treatment of chiral alcohols **48** with NaH in DMF at 55 °C leads to efficient ring closure, without loss of enantiopurity in the carbon-sulfur bond formation. With respect to the mechanism of tetrahydrothiophene formation, the authors believe that the chiral alcohol is first deprotonated by NaH to generate a transient alkoxide. Then, in a second step, the transfer of the phosphate group onto the oxygen (driven by the relatively strong phosphorus−oxygen bond that is formed) occurs. The resultant highly nucleophilic thiolate displaces phosphate via a S_N2 pathway to furnish the desired 5-membered ring with high enantiopurity. This approach although flexible enabled the formation of enantioenriched tetrahydrotiophenes bearing only one stereocentre.

Chiral tetrahydrothiophenes have been synthesized using various strategies: employing chiral auxiliaries, manipulating synthons from the chiral pool, exploiting desymmetrization processes or more recently, and perhaps more usefully, exploiting organocatalytic transformations.[85b]

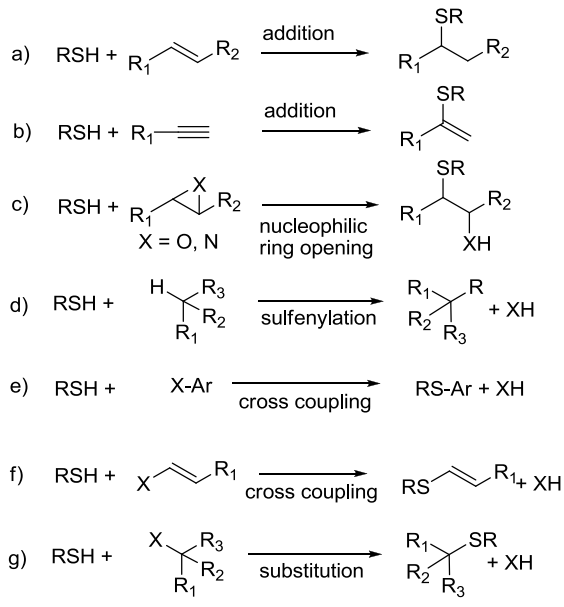
Using chiral auxiliaries, such as carbohydrates, camphorsultams, menthyl derivatives and 1-phenylethylamine, chiral dihydro- and tetrahydrothiophenes have been prepared. In this field, the 1,3-dipolar cycloaddition reaction between achiral sulfur 1,3-dipoles and dipolarophiles containing the chiral auxiliary (camphorsultams

or carbohydrates) has proven to be very useful to obtain enantioenriched dihydro- and tetrahydrothiophenes.

Chiral tetrahydrothiophenes have been synthesized also starting from enantiopure molecules available from the chiral pool, such as α-amino acids, sugars, α-hydroxy acid esters, glycidols, and terpenes or exploiting desymmetrization processes on *meso* and prochiral compounds performed by either enzymatic or synthetic catalysts. In recent years, several organocatalytic cascade methodologies for the synthesis of these heterocyclic compounds have been developed. These cascade reactions, promoted by small readily available chiral molecules, have proven to be straightforward and convenient processes that allow us to obtain multifunctionalized chiral tetrahydrothiophene scaffolds, often with different stereogenic centres.

2.2.1 Enantioselective organocatalytic sulfa-Michael additions

Let's take a wider look at the formation of C-S bonds. The general strategies used to generate C-S bonds are those shown in Scheme 2.6.[85a]



Scheme 2.6 General approaches for the construction of C-S bonds.

These C-S bond formation reactions can be promoted by transition-metal-based catalysts, and in this respect a rich literature exists,[87] but recently organocatalysis is offering an increasing number of examples. Some organocatalytic methodologies for the creation of C-S bonds are antecedent to 2000s, but the majority has been reported in the last ten years.

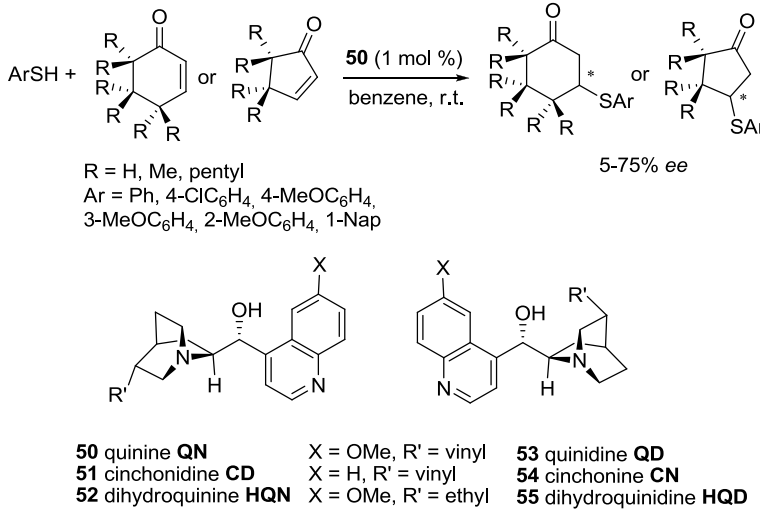
The utility of organocatalysts lies in the fact that, besides being able to catalyze the single C-C and C-heteroatom bond formations, they promote multistep domino more complex reactions and, with respect to the synthesis of chiral tetrahydrothiophenes, cascade organocatalytic Michael-Michael and Michael-aldol reactions are among the best-performing methods. The first step of all these

cascade methods is a sulfa-Michael addition (SMA), i.e. 1,4-addition of sulfur nucleophiles to unsaturated acceptors.

Secondary and primary amine catalysts, via covalent catalysis, and Lewis bases but especially bifunctional Lewis base – Brønsted acid catalysts, via non-covalent catalysis, were found to be effective in the asymmetric sulfa-Michael additions.

With regard to non-covalent catalysis, organocatalysts derived from either natural compounds, such as amino acids or cinchona alkaloids, or non-natural chiral amines have been used to promote sulfa-Michael additions to α,β-unsaturated carbonyl compounds, nitroalkenes, maleimides, sulfones, and sulfonates.

One of the earliest successes in this area was reported by Wynberg in 1977, who developed the enantioselctive SMA of aromatic thiols to cyclic enones catalyzed by cinchona alkaloids (Scheme 2.7).[88]

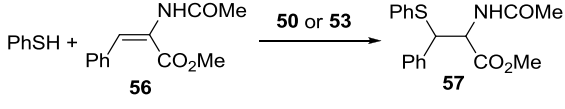


Scheme 2.7 Enantioselctive SMA of aromatic thiols to cyclic enones.

Quinine **50** was the most efficient catalyst and the reaction proceeded efficiently working at low catalysts loading, affording the desired products with low to good enantioselectivities (up to 75% *ee*). The authors demonstrated the bifunctional character of quinine in the activation of the substrates by means of NOESY experiments, kinetic and computational studies. They proposed that, in the transition state, the catalyst forms a ternary complex with thiol, deprotonated by the tertiary amine of quinuclidine moiety, and the enone, bound to quinine hydroxyl group via H-bonding. Wynberg's studies were among the first to highlight the bifunctional character of this catalyst.

In the same year, Pracejus reported the first SMA of a thiol to an α,β-unsaturated ester: the enantioselective sulfa-Michael addition of benzylthiol to α-phthalimidomethacrylate, followed by protonation.[89] After screening of several chiral amines (cinchona alkaloids, strychnine, brucine, *N*-methylephedrine, *N*,*N*-dimethylphenylethylamine) cinchona alkaloids proved to be the most efficient in terms of enantioselectivity.

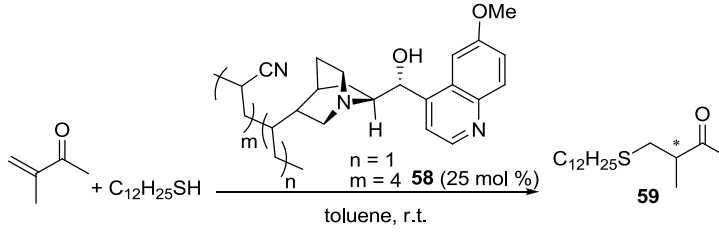
In 1986, Keniya showed that quinidine **53** and quinine **50** were also effective for the sulfa-Michael addition of thiophenol to **56**, affording the product **57** in 40% *ee* (Scheme 2.8).[90]



Scheme 2.8 Enantioselective SMA of thiophenol to **56**.

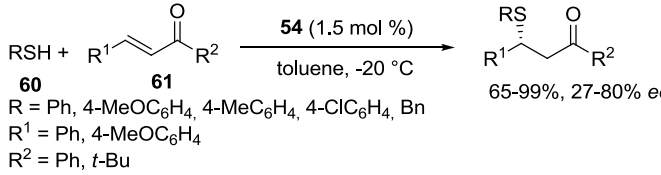
Furthermore, in 1977, Pracejus published an enantioselective SMA of benzyl and *tert*-butylthiol to β-nitrostyrenes catalyzed by brucine, which afforded the product in 27% *ee*.[89]

In 1978, Kobayashi and Iwai described the first sulfa-Michael addition of a thiol to acyclic α,β-unsaturated ketone: SMA/protonation of dodecanethiol with 3-methylbut-3-en-2-one organocatalyzed by a quinine-acrylonitrile (1:4) copolymer **58**. With this catalyst, after 7 days, product **59** was obtained in 76% yield and 57% *ee* (Scheme 2.9).[91]



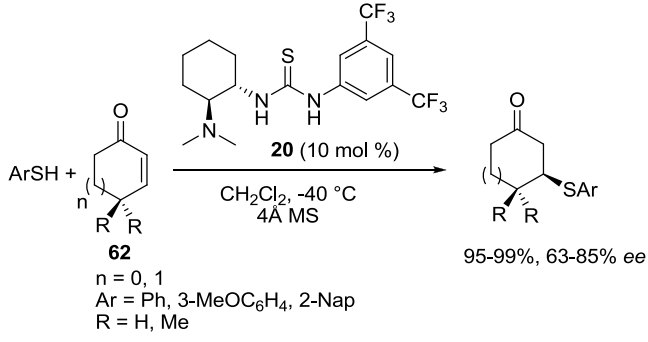
Scheme 2.9 SMA of dodecanethiol to 3-methyl-butenone catalyzed by quinine-acrylonitrile copolymer.

Another example of SMA on acyclic α,β-unsaturated ketones was published in 2001 by Sharżewski. A cinchonine-catalyzed sulfa-Michael addition of thiol **60** to acyclic α,β-unsaturated ketone **61** afforded the products in good yields and enantioselectivities ranging from 27% to 80% *ee,* increased in some cases up to 95% recrystallizing the enantioenriched product (Scheme 2.10).[92]



Scheme 2.10 SMA of acyclic enones to thiols catalyzed by cinchonine.

A thiourea catalyst, in particular Takemoto's catalyst **20**, was used for the first time in an asymmetric SMA of thiols to α,β-unsaturated carbonyl compounds in 2005 by Chen (Scheme 2.11).[93] In particular, in Chen's reaction, various thiophenols were reacted with cyclic enones **62** at -40 °C in the presence of 10 mol % of **20** to give the sulfa-Michael adducts in high yields (95-99%) and moderate to good enantioselectivity (63-85%).



Scheme 2.11 Takemoto's thiourea catalyzed SMA of thiols to cyclic enones.

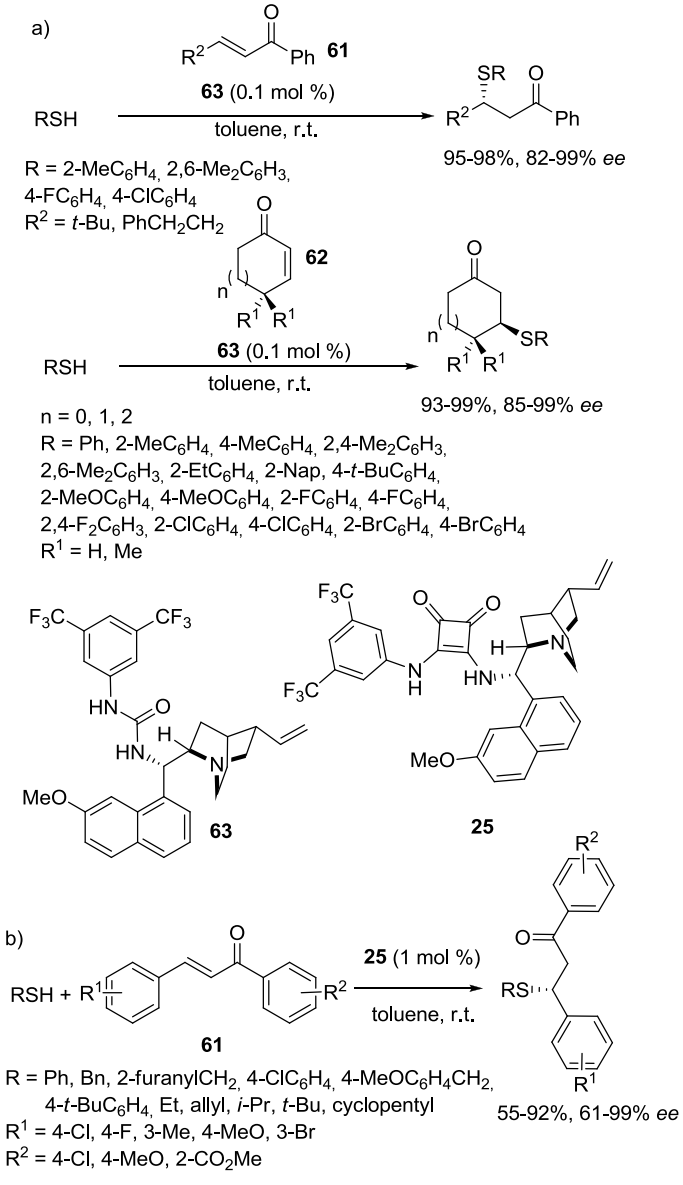
Later, in 2006, Wang used Takemoto's thiourea **20** in SMA of thiocarboxylic acids to chalcones[94] and SMA of thioacetic acid with nitroolefines[95], isolating the products with low to moderate enantioselectivities (up to 65% *ee* for chalcones and up to 70% *ee* for nitroalkenes).

Between 2006 and 2007, the catalytic activity of L-proline in SMA of thiophenol to chalcones was investigated but a low level of enantioselectivity was achieved (up to 45% *ee*).[96]

After the initial examples shown, the last decade has witnessed great strides in the area of organocatalytic sulfa-Michael additions.[85a]

Among the numerous organocatalytic examples of sulfa-Michael addition on α,β-unsaturated ketones, esters and nitroalkenes, subsequently reported by several research groups, amino acids and cinchona alkaloids and their derivatives, polymer supported cinchona alkaloids, supported thiourea catalysts, ureas and thioureas with various chiral scaffolds, amine-thiourea-sulfonamide catalysts and squaramides have been investigated.[85a]

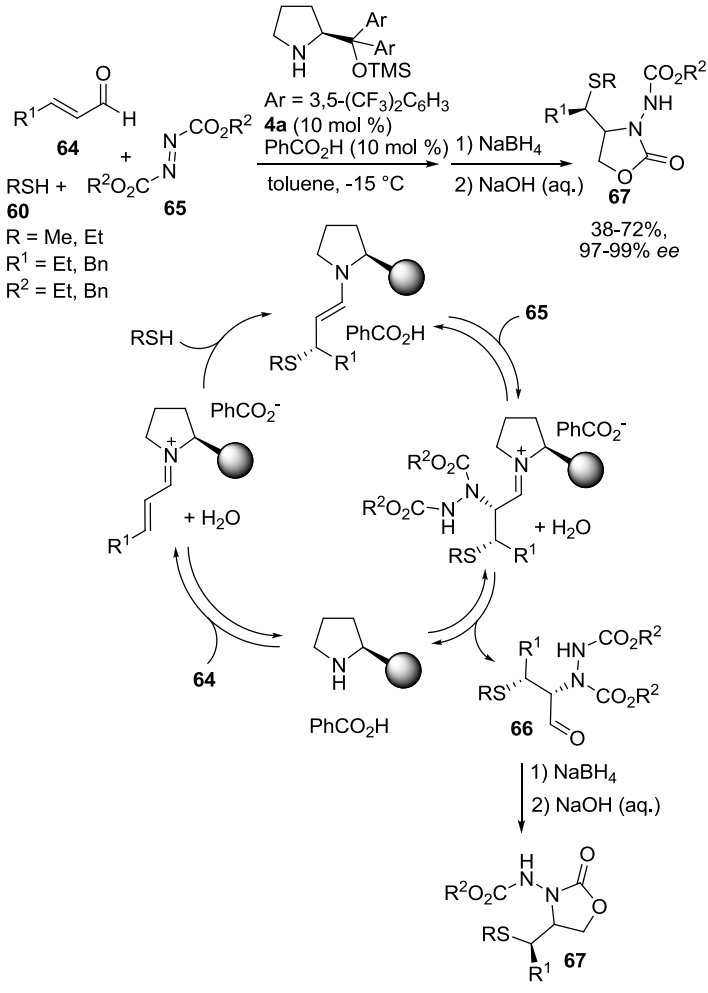
For example, in 2010 Singh reported a SMA of thiols with cyclic **62** and acyclic enones **61**, effectively promoted by a cinchona-derived amine-urea **63**,[97] and Chen discovered that a bifunctional cinchona alkaloid squaramide **25** was able to catalyze the enantioselective SMA of thiols to chalcones **61**[98]. Both research groups obtained the products with good to excellent enantioselectivities (up to 99% *ee*) (Scheme 2.12).



Scheme 2.12 SMA of thiols to cyclic and acyclic enones and chalcones.

During the past ten years, sulfa-Michael additions of thiols to unsaturated amides, imides, sulfonates and sulfones promoted by thioureas catalysts have been reported.[85a]

With regard to covalent amino catalysis, the first application of a chiral secondary amine organocatalyst in asymmetric sulfa-Michael addition was described by Jørgensen's group in 2005.[99] They devised a multicomponent domino sulfa-Michael/amination reaction, starting from enals **64**, azodicarboxylates **65** and alkyl thiols **60**, catalyzed by α,α-L-diaryl prolinols ether **4a**, to obtain highly functionalized oxazolidinones **67**, after reduction of aldehyde product **66** and base-catalyzed cyclization (Scheme 2.13). The products were isolated in acceptable yields (38-72%) and high enantioselectivities (97-99% *ee*).



Scheme 2.13 Domino Sulfa-Michael/Amination reaction.

In the proposed mechanism of domino reaction, the amino organocatalyst forms an iminium ion intermediate with enal **64** which undergoes the stereoselective addition by thiol, forming an enamine which, in turn, reacts with the azo-dicarboxylate **65** forming an iminium ion subsequently hydrolyzed to aldehyde **66**.

Later, the amino catalysis, using chiral secondary amines, has been exploited in many domino cascade reactions, expecially sulfa-Michael/aldol reactions for the synthesis of sulfur containing heterocyclic compounds (some examples are reported below).[85]

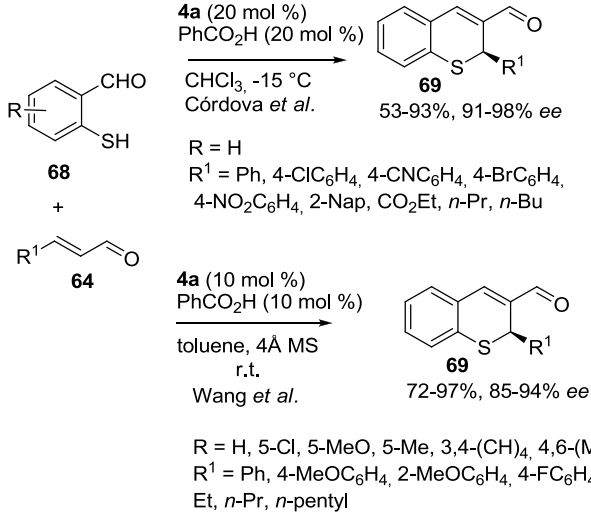
Contrary, primary amine organocatalysts have been much less applied in asymmetric sulfa-Michael additions. The first reaction was developed by Melchiorre in 2008: the SMA of benzyl and *tert*-butyl mercaptans to various enones, catalyzed by a salt derived from amino-(9-deoxy)-*epi*-hydroquinine and D-*N*-Boc-phenylglycine.[100]

Subsequently, this group reported a domino sulfa-Michael/amination reaction on enals and a domino sulfa-Michael/protonation on α-substituted α,β-unsaturated ketones, both catalyzed by cinchona alkaloids-derived primary amines.[101] However, there are no examples of heterocyclic product formation via primary amine catalysis.

2.2.1.2 Organocatalytic cascade Michael/aldol and Michael/Michael processes for asymmetric synthesis of tetrahydrothiophenes

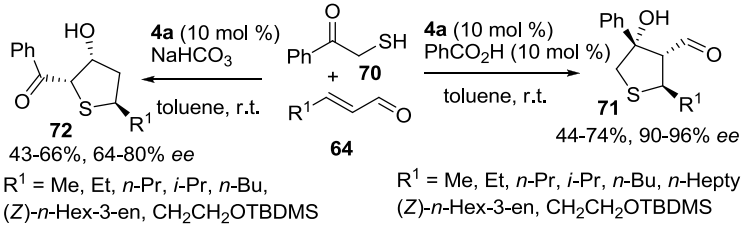
In 2006, Wang[102] and Córdova[103], independently, disclosed an asymmetric domino sulfa-Michael/aldol reaction between 2-mercaptobenzaldehydes **68** and α,β-unsaturated aldehydes **64**, promoted by α,α-L-diaryl prolinols ether **4a**. In both transformations, benzothiopyrans **69** were obtained in good to high yields and high enantioselectivities (Scheme 2.14). In the reaction sequence of these domino sulfa-Michael/aldol reactions, amine **4a**

activates enal **64** via iminium ion for the SMA of mercaptobenzaldehyde **68** and the subsequent intramolecular aldol reaction via enamine. Finally, the dehydration of aldol product affords benzothiopyrans **69**.



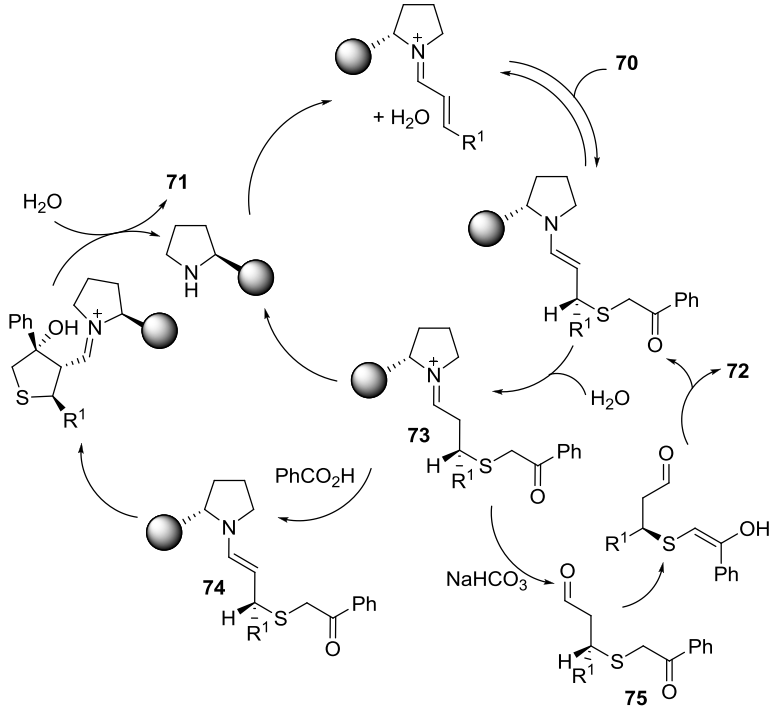
Scheme 2.14 Domino sulfa-Michael/aldol reaction promoted by a secondary amine organocatalyst for the synthesis of thiochromanes.

In the same year, the Jørgensen's group developed an asymmetric synthesis of functionalized tetrahydrothiophenes having three stereogenic centres via a similar organocatalytic Michael/aldol domino transformation, catalyzed by TMS-protected proline derivative (*S*)-**4a** (Scheme 2.15 and 1.10).[25]



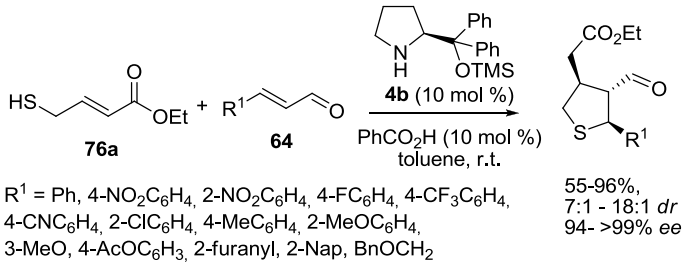
Scheme 2.15 Domino sulfa-Michael/aldol reaction promoted by a secondary amine organocatalyst for synthesis of tetrahydrothiophenes.

Starting from ketothiols **70** and enals **64**, in the presence of benzoic acid as an additive, tetrahydrothiophenes carbaldehydes **71**, bearing a quaternary stereocentre, were obtained in 44-74% yields and 90-96% *ee*. When using a base as an additive, isomeric tetrahydrothiophenes **72** were recovered in 43-66% yields and 60-80% *ee*. The mechanism of domino sequence follows the known pathway of related domino Michael/aldol transformations, shown above. Nevertheless, under acid conditions, the iminium ion **73** is converted to enamine **74** which gives rise to **71** via intramolecular aldol-type reaction followed by hydrolysis. Under basic conditions, **73** undergoes hydrolysis giving the free catalyst and thioether **75** which forms **72** through an aldol reaction (Scheme 2.16).



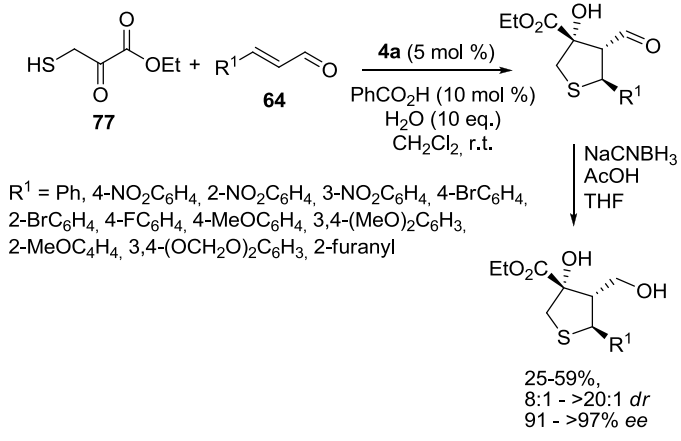
Schema 2.16 Catalytic cycle of Jørgensen's domino Michael/aldol reaction.

Similar organocatalytic cascade reactions have been devised by Wang for the synthesis of tetrahydrothiophenes. In 2007, his research group developed an enantioselective domino sulfa-Michael/Michael reaction, organocatalyzed by α,α-L-diphenyl prolinol ether **4b**, for the synthesis of tetrahydrothiophenes, starting from various α,β-unsaturated aldehydes **64** and 4-mercapto-2-butenoate **76a** (Scheme 2.17).[104]



Scheme 2.17 Domino sulfa-Michael/Michael addition reaction.

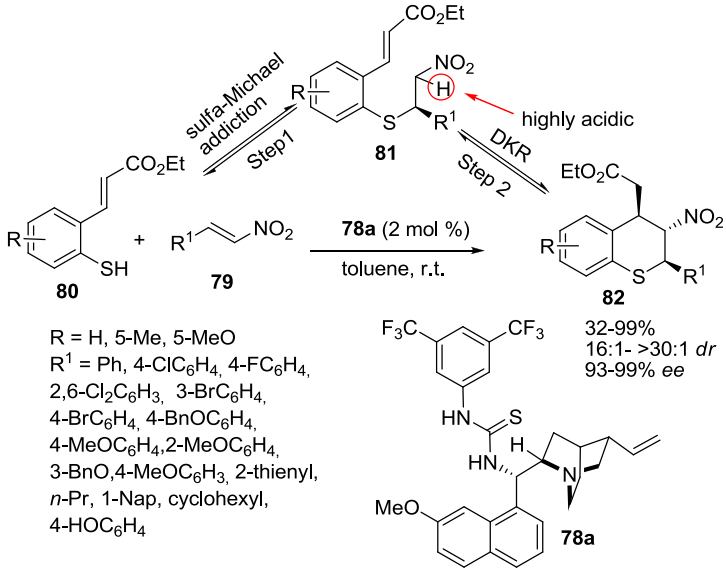
In 2009, the same research group published a domino sulfa-Michael/aldol reaction between α,β-unsaturated aldehydes **64** and ethyl 3-mercapto-2-oxopropanoate **77**, promoted by 5 mol % of **4a** in the presence of water and benzoic acid as an additive (Scheme 2.18).[105] In this case, the tetrahydrothiophenes products have a quaternary stereocentre.



Scheme 2.18 Domino sulfa-Michael/aldol reaction.

In the context of non-covalent organocatalysis, worthy of note are the Wang's methodologies for thiochromanes and tetrahydrothiophenes synthesis.

In 2008, Wang reported a highly stereoselective hydrogen-bond-mediated Michael/Michael cascade process, catalyzed by a cinchona alkaloid thiourea **78a** (Scheme 2.19).[106]



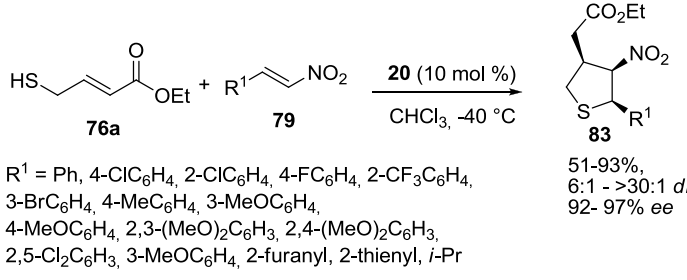
Scheme 2.19 Domino sulfa-Michael/Michael reaction.

This example is particularly important because, for the first time, a novel activation mode by the chiral amine thiourea, which involves a dynamic kinetic resolution (DKR, see paragraph 2.3), has been disclosed. The domino transformation between various nitrostyrenes **79** and 3-(2-mercaptophenyl)-2-propenoic acid ethyl esters **80**, catalyzed by only 2 mol % of cinchona-derived thiourea **78a**, afforded thiochromanes **82** in notably high stereoselectivity (93-99% *ee*). The authors proved the DKR mechanism isolating the racemic Michael adduct **81** and reacting it with the catalyst **78a** under the standard conditions optimized for the cascade process.

Product **82** was obtained in 94% yield, 95% *ee*, *dr* > 30:1 and with

the same absolute configuration of the product isolated from **79** and **80** in the direct domino process. They rationalized that the first Michael adduct **81** undergoes a DKR process because it has a highly acidic nitroalkane proton which is deprotonated by amine thiourea catalyst, leading to a reversible stereoselective retro-Michael/Michael/Michael process. Moreover, as a further confirmation, the enantioselectivity of adduct **81** isolated from the single conjugate addition reaction of thiophenol to *trans*-β-nitrostyrene in the presence of the catalyst **78a** was very low (12% *ee*).

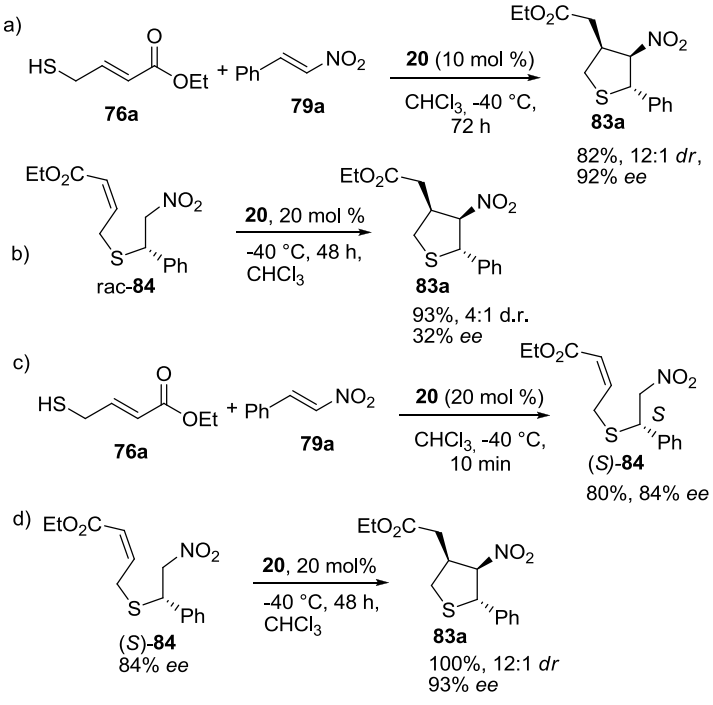
Another Michael/Michael cascade catalyzed by chiral bifunctional tertiary amine-thiourea **20** was developed by Wang in 2011.[107] In this reaction **76a** reacts with *trans*-β-nitroolefins **79** in $CHCl_3$ at -40 °C in the presence of 20 mol % of **20** producing 3-nitro-tetrahydrothiophenes **83**, bearing three contiguous tertiary stereocentres, with good yields (51-93%), high diasteroselectivities (6:1-30:1 *dr*) and excellent enantioselectivities (92-99% *ee*) (Scheme 2.20).



Scheme 2.20 Domino sulfa-Michael/Michael reaction of nitroolefins.

Unlike the precedent cascade Michael/Michael reaction for the

synthesis of thiochromanes, in this case the authors demonstrated that cooperative direct stereocontrol and dynamic kinetic resolution are involved in the reaction mechanism. To verify the mechanistic hypothesis, the authors carried out several studies (Scheme 2.21).

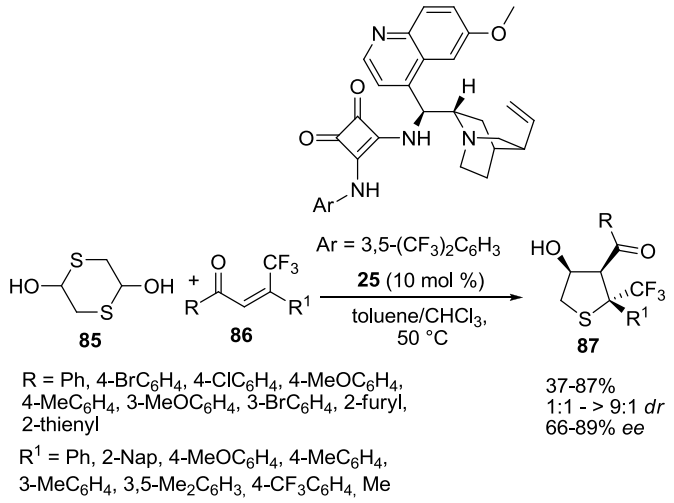


Scheme 2.21 Mechanistic studies of domino Michael/Michael reaction reported by Wang.

Performing the same experiment reported for the synthesis of thiochromanes described above, the authors isolated the racemic adduct of the first Michael addition **84** and left it to react with 20 mol % of **20**, under the same reaction conditions of the cascade Michael/Michael reaction. However, in this case they obtained the

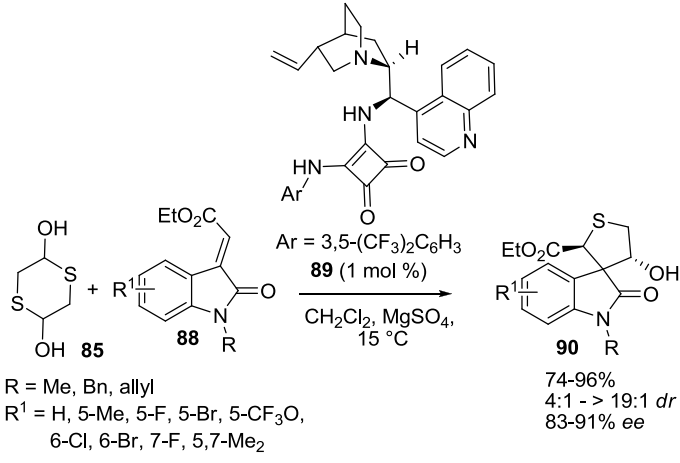
product in 93% yield, 4:1 *dr* and 32% *ee* (Scheme 2.21b), whereas the results achieved performing the cascade reaction were 12:1 *dr* and 93% *ee* (Scheme 2.21a). These results indicated that a DKR is involved in the domino reaction but this is not the only mechanism implicated. The stereoselectivity of the cascade process is governed both by DKR and direct stereocontrol by the catalyst. In fact, the enantioselectivity of the adduct **84**, isolated from the single conjugate addition reaction of **76a** to *trans*-β-nitrostyrene **79a** in the presence of catalyst **20**, was 84% *ee* (Scheme 2.21c). Besides, when the adduct **84** with 84% *ee* was treated with the catalyst at -40 °C, the tetrahydrothiophene **83a** with 93% *ee,* in quantitative yield, was obtained, finding the same result of the direct cascade reaction (Scheme 2.21d vs 2.21a).

In addition to Wang's methodologies, Xu reported a sulfa-Michael/aldol cascade reaction between 1,4-dithiane-2,5-diol **85** and various chalcones catalyzed by a bifunctional squaramide, as shown above in Scheme 2.4.[72] More recently, the same research group applied this methodology also to β-aryl-β-trifluoromethylated enones **86** (Scheme 2.22).[108]



Scheme 2.22 Domino sulfa-Michael/aldol reaction.

In 2012, Xiao developed a similar sulfa-Michael/aldol cascade reaction of 3-ylideneoxindoles **88** with 1,4-dithiane-2,5-diol **85** for the synthesis of spirocyclic oxindole derivative, fused with tetrahydrothiphene ring, **90**. Even in this case, the process is promoted by an amino-squaramide **89** (Scheme 2.23).[109]



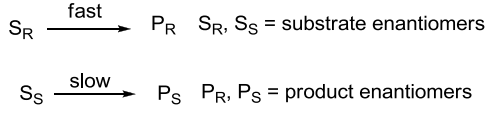
Scheme 2.23 Domino sulfa-Michael/aldol reaction of 3-ylideneoxindoles.

2.3 Kinetic Resolution and Dynamic Kinetic Resolution

The kinetic resolution allows the preparation of enantiomerically enriched molecules starting from a stereoisomeric mixture by exploiting the difference in reactivity of the substrate stereoisomers. The simplest scenario is when enantiomeric substrates form stereospecifically the corresponding chiral products.

In standard kinetic resolution two enantiomers of a racemate are transformed under chiral conditions (using chiral reagents or catalysts, for example enzymes or non-enzymatic chiral catalysts) into products at different rates (Scheme 2.24).[110] Noyori stated that, in a kinetic resolution: "*Each enantiomer is transformed to a single or plural, chiral or achiral compound, depending on the reaction system*".[111]

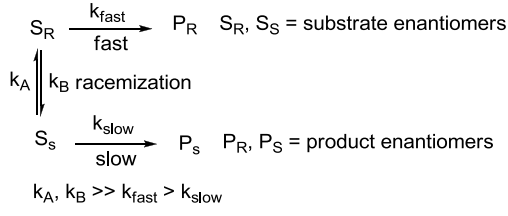
When the kinetic resolution is effective, we can recover the unreacted enantiomer and the highly enantiomerically enriched product of the other enantiomer. The major limitation of this technique is that the theoretical yields for such process may not exceed the maximum theoretical of 50%, due to the consumption of only one enantiomer. This is a strong disadvantage especially for practical applications at an industrial scale.



Scheme 2.24 Classical kinetic resolution.

Other inherent drawbacks are the following: *i*) separation of the product from the unreacted substrate is always needed and this step may be not easy; *ii*) only one product could be desired and not both; *iii*) how explained below, the *ee* of the substrate and/or product decreases around 50% conversion which is, from a preparative point of view, the most convenient point to stop the reaction.[112]

The drawbacks of classical kinetic resolution are overcome in the *Dynamic Kinetic Resolution* (DKR). In a DKR process, a kinetic resolution step is combined with an in situ equilibration or racemization of the chirally labile substrate (Scheme 2.25). If the rate of substrate epimerization is greater than the rate of substrate transformation, the enantioenriched product can theoretically be isolated in 100% yield.[110,111,112,113]



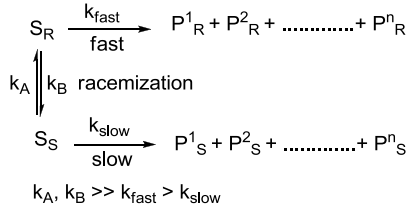
Scheme 2.25 Dinamic kinetic resolution.

Contrary to standard kinetic resolution, where the reaction can reach a maximum of 50% conversion when the fast reacting enantiomer is consumed, the in situ fast racemization ensures the formation of other fast reacting enantiomer from the slow reacting counterpart while the reaction proceeds, so all of the racemic starting material can be transformed into the desired stereoisomer.[112] The dynamic adjective before kinetic resolution indicates exactly the non-static feature of the process.

In such process two competitive reactions are closely interrelated by the steroinversion of the substrates and the effectiveness of the resolution is dictated by the kinetic parameters of the parallel reactions and racemization.[112]

Racemization of the substrate can be induced either chemically, biocatalytically or can occur even spontaneously but the racemization of the product must be avoided.

With a DKR process not only a selective synthesis of an enantiomer can be accomplished, but, if in the reaction a new stereocentre is created, an enantioselective synthesis of a diastereomer is also possible (Scheme 2.26).[114]



Scheme 2.26 Formation of diastereomeric products in DKR.

Noyori has given a very good description of this process: "*This reaction system is characterized not only by the presence of the substrate stereoinversion* $S_R \rightleftarrows S_S$ *but also by formation of diastereomeric products, where both enantioselection and diastereoselection are exhibited. Thus, under appropriate conditions, this kinetic resolution method can convert a racemic compound to one stereoisomer among many*."[115]

In classical kinetic resolution, for evaluating the efficiency of the resolution, S or $k_{rel} = k_{fast}/k_{slow}$ is used. This value is dictated by the magnitude of $\Delta\Delta G^{\ddagger}$ i.e. the difference in energies between the

diastereomeric transition states in the selectivity-determining step of the catalytic reaction (Figure 2.9).[110]

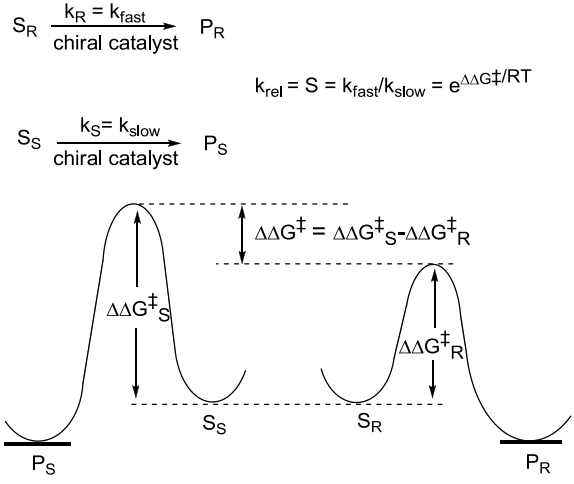


Figure 2.9 Relative rate constants in kinetic resolutions.

As studied by Kagan, Sharpless, and others, k_{rel} or S is correlated to the extent of substrate conversion (*conv*) and the enantiomeric excess of the recovered substrate and product, ee_s and ee_p, respectively.[110,115]

$$k_{rel} = \frac{k_{fast}}{k_{slow}} = \frac{\ln[(1-conv)(1-ee_S)]}{\ln[(1-conv)(1+ee_S)]} = \frac{\ln[1-conv(1+ee_P)]}{\ln[1-conv(1-ee_P)]}$$

This means that the *ee* of the product and recovered starting material in a kinetic resolution changes as a function of conversion.

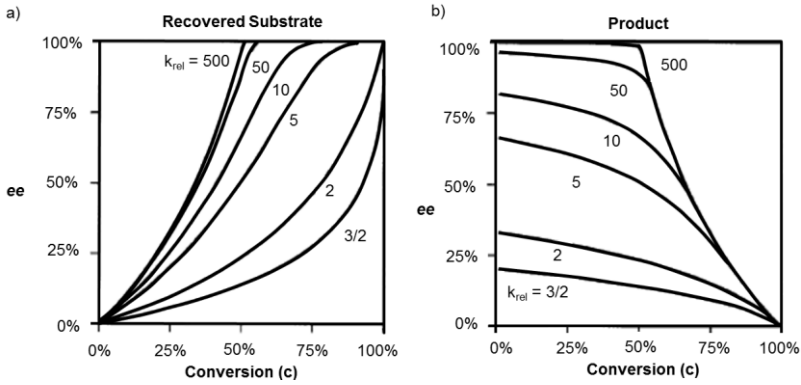


Figure 2.10 Plots of *ee* vs. conversion (c) as a function of k_{rel} for a) recovered substrate and b) product.

As we can see from the plots in Figure 2.10, in a kinetic resolution the unreacted substrate is recovered in high *ee* even if k_{rel} is not very high, quenching the reaction at a relatively high conversion. On the other hand, in order to isolate a product with high *ee* and acceptable yield, $k_{rel} > 50$ is generally required.[110,i]

The plots in Figure 2.10 show that the *ee* of the product (ee_p) is maximum at the outset of the reaction and begins to decrease as the reaction proceeds, as the faster reacting enantiomer is consumed from the reaction mixture. In particular, the *ee* of the product drops around 50% of conversion.

In DKR process, the racemization of the substrate is faster than its transformation to product (Scheme 2.25) so the catalyst is always facing a racemic starting material. Therefore, the ee_p of the product is determined only by the k_{rel} value and is not a function of

[i] Generally, a first-order kinetic in substrate is assumed in kinetic resolutions. So, as reported by Jacobsen,[110] a first order kinetic was assumed for calculation of plots in Figure 2.10 and for stereoselectivity factors k_{rel}.

the conversion, but remains constant throughout the reaction (Figure 2.11).[112]

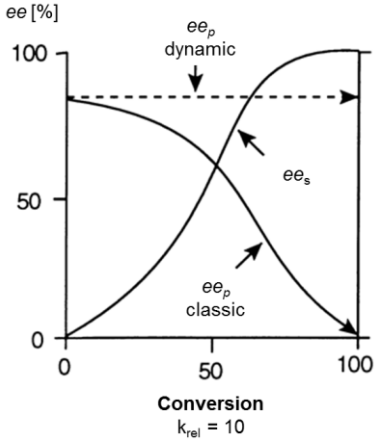


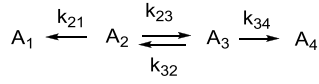
Figure 2.11 Comparison of plots of *ee* vs. conversion for classical and dynamic kinetic resolution calculated for k_{rel}=10.

The mathematical treatment of DKR has been realized by Noyori (see Ref. 111 and 115). In order to obtain products with high optical purity, certain requirements have to be respected: *i*) the resolution step should be irreversible; *ii*) k_{rel} should be at least 20; *iii*) the rate constant k_{rac} for the racemization should be faster or at least equal than the rate constant of the resolution step k_{fast}; *iv*) if the selectivities are moderate, k_{rac} should be higher than k_{fast} by a factor of ~10; *v*) the formed products have to be configurationally stable under the reaction conditions (otherwise we have a thermodynamically derived product distribution) and the racemization of the product must not occur.

The dynamics of DKR processes can be explained with the Curtin-Hammet principle.[116] As described by Seeman : "*The simplest situation which examines the relationship between a*

molecule's conformations and its chemical reactivity is illustrated by Scheme II which is the basic Curtin-Hammett (C-H)/ Winstein-Holness (WH) kinetic system. It reflects the reactivity of a molecule which exists in two interconverting forms, each of which gives a different product. Scheme II is also valid for any two molecules, A_2 and A_3, not solely for conformational isomers of a single compound".[116b]

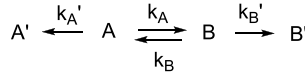
Scheme II



The definition of Curtin-Hammett principle proposed by the I.U.P.A.C. Commission on Physical Organic Chemistry is:[117] "*In a chemical reaction that yields one product from one conformational isomer and a different product from another conformational isomer (and provided these two isomers are rapidly interconvertible relative to the rate of product formation, whereas the products do not interconvert), the product composition is not solely dependent on the relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies of the respective transition states. (It is also true that the product composition is related to the relative concentrations of the conformational isomers -i.e., the conformational equilibrium constant- and the respective rate constants of their reactions: these parameters are generally -though not invariably- unknown.)*".[116b]

The Curtin-Hammett principle may be extended to rapidly interconvertible diastereomers, enantiomers or constitutional isomers as well.

Therefore, for a reaction in which two rapidly interconverting reactants are each transformed irreversibly in a different product, the product composition will not necessarily reflect the distribution of the reactants A/B at the equilibrium, but it will be controlled on the difference in energy between the two reactants (or conformers) and on the free energy of the transition state going to each product.

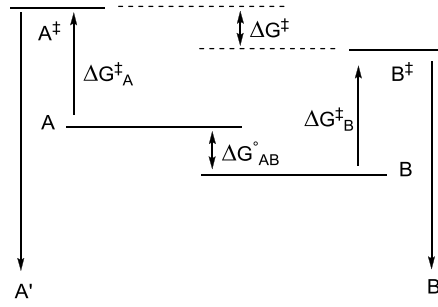


$k_A, k_B >> k_B' > k_A' ; k_A/k_B = K_{AB}$

Scheme 2.27 DKR.

Indeed, Caddick and Jenkins showed that, using Winstein-Holness and Curtin-Hammett kinetics, the product distribution can be expressed as [B']/[A'] = k_B' K_{AB}/k_A' were k_A', k_B' are the transformation rates and K_{AB} is the equilibrium constant.[113c]

From this expression, equation in Scheme 2.28 can be obtained through expansion with Gibbs free energy and activation free energy parameters.



$$[B']/[A'] = \exp\left[\frac{-\Delta G^{\circ}_{AB} + \Delta G^{\ddagger}_{A} - \Delta G^{\ddagger}_{B}}{RT}\right]$$

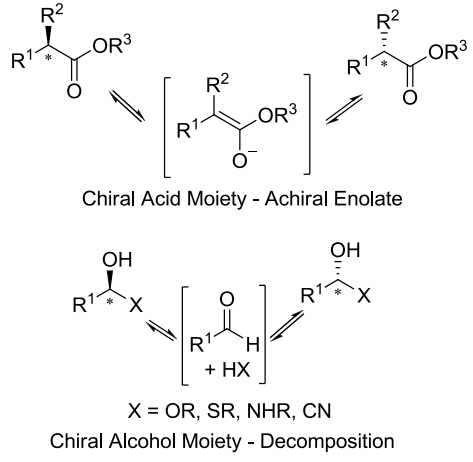
(first order/pseudo first-order reactions)

Scheme 2.28

Caddick and Jenkis explained that: "*Where the substrate stereoisomers are related as enantiomers, chiral discrimination must occur via a chiral catalyst/promoter or by using a chiral reagent. Since* ΔG°_{AB} *=0, the relative transition state energies* ($\Delta\Delta G^{\ddagger}$) *solely determines the kinetic preference. If the substrate stereoisomers are related as diastereoisomers, the stereoselection arises as a function of the transition state energies* ($A^{\ddagger}$, $B^{\ddagger}$) *relative to the ground state energies (A,B) of the substrate isomers".*[113c]

There are several strategies to perform the in-situ racemization and only racemization proceeding under mild reaction conditions, compatible with the subsequent resolution step, are suitable for DKR. Many DKR processes involve thermal racemization, base- or acid- catalyzed racemization, racemization via redox reaction, enzymatic racemization and formation of stereolabile intermediates such as organolithium or transition metal complexes.[118]

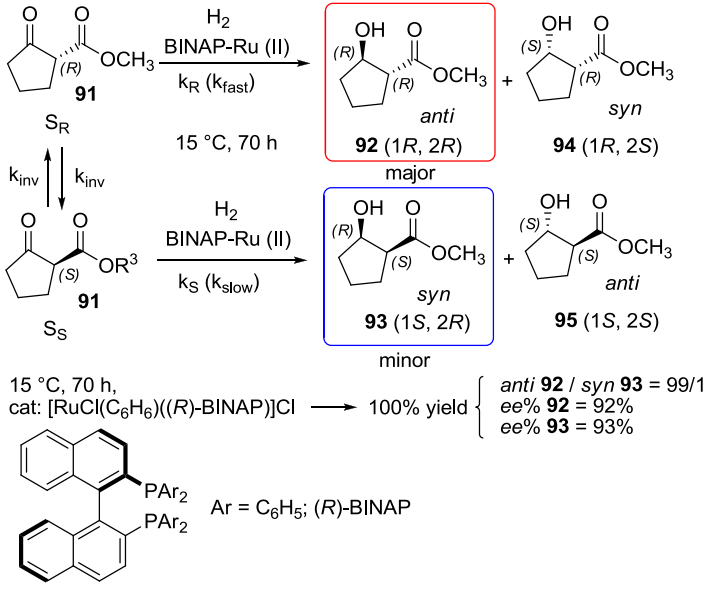
For example, when the compounds have a stereogenic centre bearing an acidic proton (for example a proton in the α-position to a carbonyl group), the racemization is promoted by a base that can deprotonate the compound forming an achiral enolate. When there is not this acidic proton, racemization is performed via a decomposition reaction, such as the cleavage of hemi(thio)acetals and cyanohydrins (Scheme 2.29).[112]



Scheme 2.29 In situ racemization of substrate in DKR process.

The DKR concept has been applied to both enzymatic and nonenzymatic reactions.[114,119]

The first example of DKR was reported in 1989: the stereoselective hydrogenation of racemic 2-substituted 3-oxo carboxylic esters catalyzed by BINAPRu(II) complexes (Scheme 2.30).[120]



Scheme 2.30 Stereoselective hydrogenation via DKR.

Until recently, enzymes have been almost exclusively used for DKR of racemic substrates[121] but, in recent years non-enzymatic chiral catalysts and organocatalysts are gaining a widespread application in DKR processes.[122]

2.4 Results and Discussion

Despite the fact that the non-covalent activation methods have been widely used in single step asymmetric transformations, their potential application in cascade catalysis is still poorly investigated.

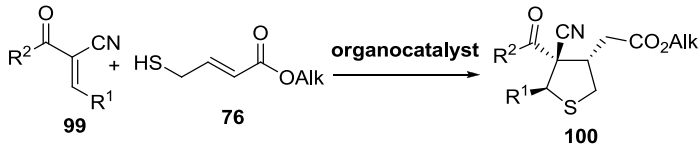
One of the aims of this PhD project has been the development of organocatalytic tandem processes for the construction of heterocyclic compounds bearing different stereocentres. Our plan has been focused on the investigation of different optically pure bifunctional organocatalysts, which may synergistically activate both the electrophile and the nucleophile via general acid-base catalysis provided by their acid and basic groups.

In this context, an organocatalyzed tandem Michael-Michael process for the synthesis of chiral tetrahydrothiophenes was envisaged (Scheme 2.31).[123]

Our investigation focused on *trans*-α-carbonyl-β-substitued acrylonitriles **99** as starting Michael acceptors, where both the issue of diastereo- and enantioselectivity should have been addressed.

As described in the previous paragraph, up to now the organocatalytic tandem methodologies have been restricted to the use of α,β-unsaturated aldehydes, nitroalkenes and, to a lesser extent, esters as the Michael acceptors. We were interested in introducing a cyano group in the alkene given its potential usefulness, as a synthetic group susceptible of further transformation, and by considering that an ever-increasing number of important pharmaceuticals and natural products are nitrile-containing compounds.[124] Indeed, the expected

tetrahydrothiophenes **100** (Scheme 2.31) contain three different functional groups amenable of selective manipulations.

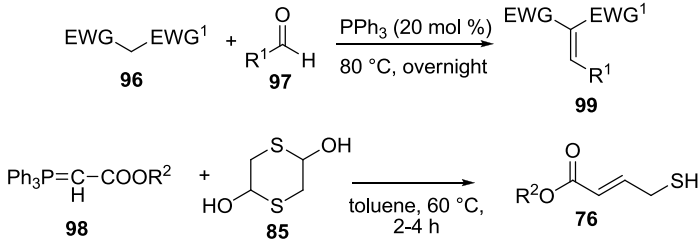


99 **76** **100**

Scheme 2.31

Furthermore, the tetrahydrothiophenes so far synthesized bear carbon tertiary stereocentres and there are a few examples in which quaternary stereogenic centres have been installed in the chiral scaffold, a target which is particularly challenging in asymmetric synthesis.[125]

The electron-poor olefins **99** have been easily synthesized via Knoevenagel reactions as reported in the literature,[126] while the 4-mercapto-2-butenoates **76** were obtained by a Wittig reaction of the mercaptoacetaldehyde dimer **85** and stabilized phosphonates[127](Scheme 2.32).



96 **97** **99** **98** **85** **76**

Scheme 2.32

A first screening of the catalysts has been carried out in toluene at room temperature on the model substrate **99a** with **76a** (Figure

2.12, Table 2.1). $(DHQ)_2PHAL$ **101** and catalysts bearing a single hydrogen bond donor site such as α,α-diarylprolinols **4b**, **4a**, **4c**, quinine **50**, indole derivatives catalysts having a tertiary amino group **102a**, **102b** and sulfonamide **103** allowed us to obtain the product with modest to good yields and in some cases with good diasteroselectivity but poor enantioselectivity (Table 2.1, entries 1-9).

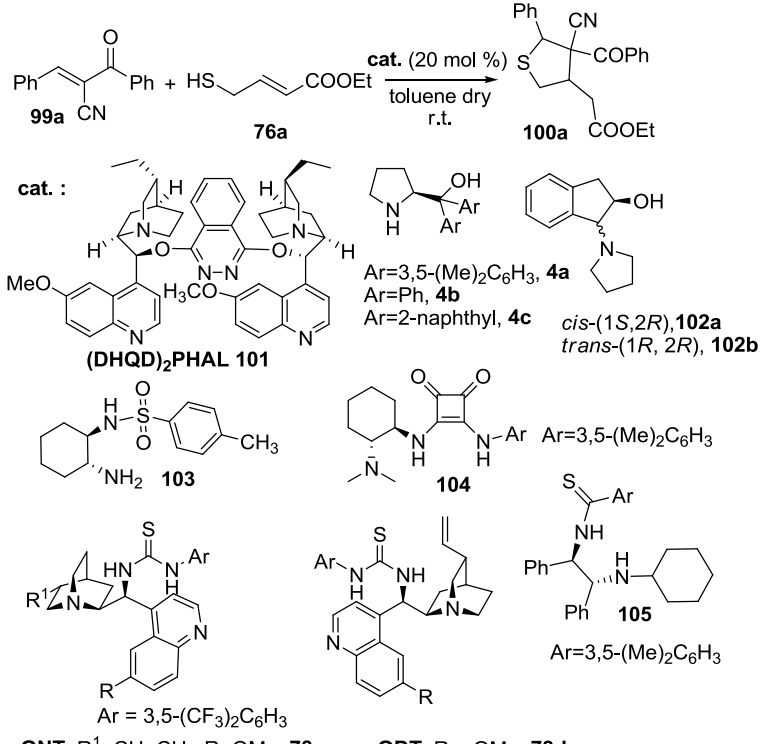
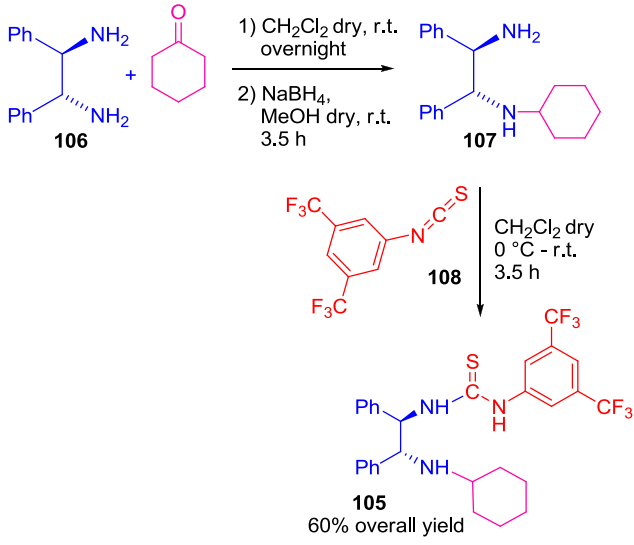


Figure 2.12 Catalysts screened in the model reaction between **99a** and **76a**.

However, it should be noted that in all cases, only two diastereoisomers were formed with respect to the four potentially obtainable, considering that three stereocentres are formed. The enantioselectivity of the reaction considerably improved by using catalysts having two hydrogen bond donor sites as the squaramide **104** (entry 10) and more markedly with thioureas.

The cinchona alkaloid derived thioureas **78b**, **78c**, **78d**, **78e** (entries 12-15) were found to be the best catalysts in this series affording good yields (up to 80%) and encouraging levels of enantio- (up to 83% *ee*) and diastereoselectivity (up to 3:1). Takemoto's thiourea **20** was also an effective promoter, leading to the product with good yield (85%) enantio- (75% *ee*) and diastereoselectivity (3:1) (entry 11). Given the ability of thioureas to catalyze the reaction, we decided to synthesize a thiourea having a different chiral scaffold and bearing a secondary rather than a tertiary amino group **105** via a simple two-step protocol (Scheme 2.33). Starting from commercially available (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine **106**, the sterically demanding secondary amine portion was inserted via reductive amination with cyclohexanone. Diamine **107** was then reacted with isothiocyanate **108** to afford the final organocatalyst **105** in good overall yield.



Scheme 2.33 Synthesis of catalyst **105**.

With our great delight, we observed a marked improvement of the enantioselectivity in the tandem reaction when using catalyst **105** (Table 2.1, entry 16). The product was isolated in good yield, diastereoselectivity (1:4) and excellent enantioselectivity (98% *ee*).

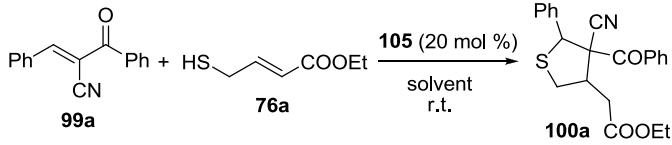
Table 2.1 Catalyst screening.[a]

entry	cat.	t (h)	yield (%)[c]	*dr*[d]	*ee*% (major)[e]
1[b]	**$(DHQ)_2PHAL$**	90	89	1:1	32
2	**4b**	70	76	3:1	19
4	**4a**	70	68	5:1	-11
5	**4c**	70	41	3:1	-9
6	**50**	69	56	2:1	rac
7	**102a**	41	50	1:1	4
8	**102b**	42	46	1:1	17
9	**103**	72	42	2:1	3
10	**104**	70	65	3:1	-39
11	**20**	89	85	3:1	-75
12	**78b**	68	78	2:1	74
13	**78c**	70	63	3:1	-80
14	**78d**	70	54	3:1	-80
15	**78e**	70	80	3:1	-83
16	**105**	48	80	1:4	98

[a]Reaction conditions: **99a** (0.1 mmol), **76a** (1.2 eq.), anhydrous toluene (1 mL).[b]The reaction was carried out with 30 mol % catalyst loading. [c]Yields of isolated product. [d] Determined by ^{1}H NMR spectra of crude reaction. [e]Determined by chiral HPLC analysis.

Amino thiourea **105** was then selected as the catalyst to optimize the reaction parameters, in order to improve the process (Table 2.2). It is known that in non-covalent catalysis, nonpolar solvents are generally the most suitable media, since they do not interfere with the hydrogen bonding interactions established between the organocatalyst and the reactants. Among the aromatic solvents tested, toluene was found to be the most effective (Table 2.2, entry 1).

Table 2.2 Solvent screening for the cascade thia-Michael–Michael reaction.[a]

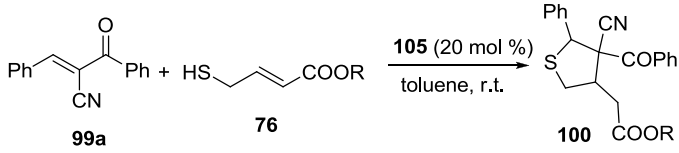


entry	solvent	t(h)	yield (%)[b]	*dr*[c]	*ee*% (major)[d]
1	toluene	48	80	1:4	98
2	$CHCl_3$	74	69	1:4	98
3	Et_2O	74	76	1:4	94
4	*m*-xylene	71	67	1:3	97
5	ClC_6H_5	72	74	1:3	97
6	$CF_3C_6H_5$	70	74	1:3	94

[a]Reaction conditions: **99a** (0.1 mmol), **76a** (1.2 eq.), anhydrous solvent (1 mL). [c]Yields of isolated product. [c]Determined by ^1H NMR spectra of crude reaction. [d]Determined by chiral HPLC analysis.

Subsequently, different 4-mercapto-2-butenoates **76** were employed with model compound **99a** (Table 2.3). The steric hindrance of the ester group proved to positively affect the diastereoselectivity, and an excellent level of enantioselectivity was mantained (Table 2.3, entry 1). The catalyst loading could be decreased to 10 mol %, without affecting the process (entry 4).

Table 2.3 Screening of different 4-mercapto-2-butenoates **76** and reaction conditions for the tandem thia-Michael-Michael reaction.[a]

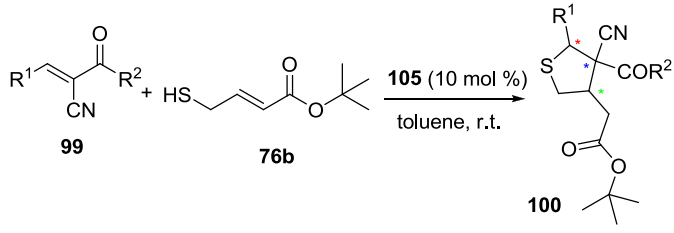


entry	**76** (-R)	t(h)	yield(%)[b]	*dr*[c]	*ee*% (major)[d]
1	**76b** –*t*-Bu	71	84	1:9	99
2[e]	**76c** -Me	93	90	1:4	98
3[f,g]	**76b** –*t*-Bu	90	96	1:9	99
4[g,h]	**76b** –*t*-Bu	91	96	1:9	99

[a]Reaction conditions: **99a** (0.1 mmol), **76** (1.2 eq.), anhydrous toluene (1 mL). [b]Isolated yield after flash chromatography. [c]Determined by ^{1}H NMR analysis of crude reaction mixture. [d]Determined by chiral HPLC analysis. [e]The reaction was carried out with 1.5 eq. of **76c.** [f]The reaction was carried out in 1.25 mL of toluene. [g]The reaction was carried out with 1.3 eq. of **76b**. [h]The reaction was carried out with 10 mol % catalyst loading.

Under the optimized conditions, several *trans*-α-carbonyl-β-substitued acrylonitriles **99** were investigated to explore the substrate scope of the process. In all cases, the tetrahydrothiophenes **100** were formed in high to excellent yields, good diastereoisomeric ratio and high to complete enantiocontrol for the major diastereomer, with both electron-rich and electron-poor phenyl substituted derivatives and also with compounds bearing heteroaromatic residues (Table 2.4, entries 1-9). Alkenes bearing electron-withdrawing groups on the aromatic R^1 residue reacted faster than other compounds although the level of enantioselectivity was constantly maintained in all examples.

Table 2.4 Substrate scope of the tandem process.[a]



en.	R^1	R^2	**100**	t(h)	yield (%)[b]	*dr*[c]	*ee*% (major)[d]
1	Ph	Ph	**100b**	50	94	9:1	99
2	4-$MeOC_6H_4$	Ph	**100d**	120	70	12:1	99
3[e]	4-*t*-BuC_6H_4	Ph	**100e**	150	70	7:1	99
4	4-BrC_6H_4	Ph	**100f**	88	97	12:1	99
5	3-BrC_6H_4	Ph	**100g**	93	99	9:1	99
6	4-CNC_6H_4	Ph	**100h**	65	98	9:1	99
7	4-$NO_2C_6H_4$	Ph	**100i**	40	98	9:1	>99
8	2-naphthyl	Ph	**100j**	180	85	9:1	>99
9[f]	3-furyl	Ph	**100k**	160	72	9:1	99
10	Ph	3-ClC_6H_4	**100l**	70	96	5:1	98
11	Ph	4-$MeOC_6H_4$	**100m**	78	98	9:1	99
12	cyclohexyl	Ph	**100n**	69	98	1:1	>99(87)
13	Ph	$(CH_2)_2Ph$	**100o**	96	79	3:1	89

[a]Reaction conditions: **99** (0.1 mmol), **76b** (1.3 eq.), anhydrous toluene (1 mL). [b]Isolated yield after flash chromatography. [c] Determined by ^1H NMR spectra of crude reaction. [d]Determined by chiral HPLC analysis. [e]The reaction was carried out with 20 mol % catalyst loading. [f]The reaction was carried out with 1.5 eq. of **76b**. In parentheses the enantiomeric excess of the other diastereoisomer.

Both electron-withdrawing and electron-donating groups on the aroyl moiety R^2 of alkene **99** did not affect the yield and stereoselectivity (entries 10 and 11). The diasteroselectivity of the reaction drastically drop to 1:1 ratio of diastereomers when an alkyl group was installed at the β-position of enone **99**, but the product

100n was obtained in excellent yield and enantioselectivities (entry 12).

Starting from an alkene bearing an alkyl group at the keto-position, **99o,** it was possible to isolate the tetrahydrothiophene **110o**, albeit with slightly reduced diastero- (3:1 *dr*) and enantioselectivity (89% *ee*) for the major diastereoisomer (entry 13).

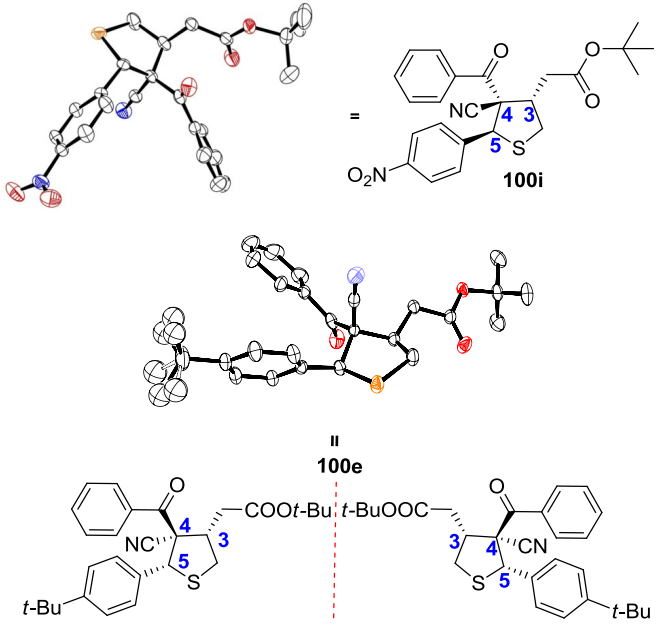


Figure 2.13 Crystallografic structure of enantioenriched tetrahydrothiophene **100i** and racemic **100e** determined by X-ray analysis. **ORTEP plot** with 30% probability ellipsoids (disordered part is represented with dotted bond; for seek of brevity H atoms are not shown).

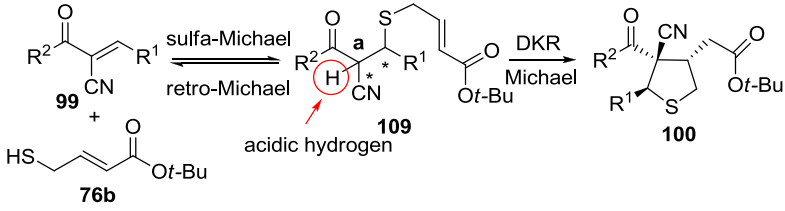
X-ray analysis, performed on a single crystal of the major diastereomer of nitro-derivative **100i**, allowed the determination of the absolute configuration as (3*S*,4*R*,5*S*) (Figure 2.13). The absolute configuration for all other compounds **100** was assigned by

analogy.[ii] Since we observed that the diastereoisomeric ratios obtained with catalyst **105** are inverted compared to those obtained when using the DABCO, we determined also the relative configuration of the minor racemic diastereomer of the *tert*-butyl derivative **100e**, that proved to be (3*S**,4*S**,5*R**) from X-ray analysis (Figure 2.13).

As reported by Wang and described in Scheme 2.19, in cascade asymmetric organocatalytic thia-Michael/Michael reaction to thiochromanes starting from nitroalkenes, a dynamic kinetic resolution (DKR) was found to govern the stereochemical result. This DKR process was encouraged by the highly acidic nitroalkane proton which was deprotonated by amine thiourea catalyst leading to a reversible stereoselective retro-Michael/Michael/Michael process.

In our cascade process, the intermediate adduct **109** has an acidic α-proton, which could be deprotonated by the amine moiety of the organocatalyst promoting a retro-sulfa Michael reaction (Scheme 2.34). Therefore, we hypothesized that the mechanism of our tandem reaction could involve a DKR process through a retro-sulfa Michael reaction followed by a highly stereoselective double Michael process, organocatalyzed by **105** (Scheme 2.34).

[ii] See the Experimental Section for details.



Scheme 2.34 Suggested cascade patway involving DKR.

To gain isight into the mechanism of the process, first we monitored the model reaction of **99a** and **76b**, catalyzed by **105**, by ^{1}H NMR spectroscopy, to examine the transformation of Michael adduct **109** over the time (Figure 2.14).

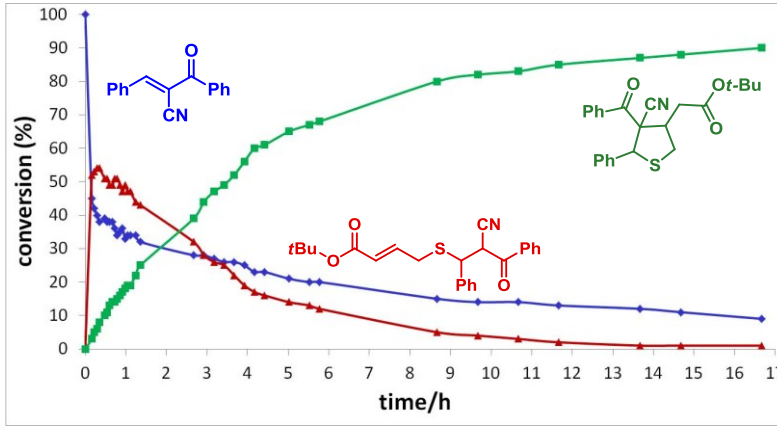
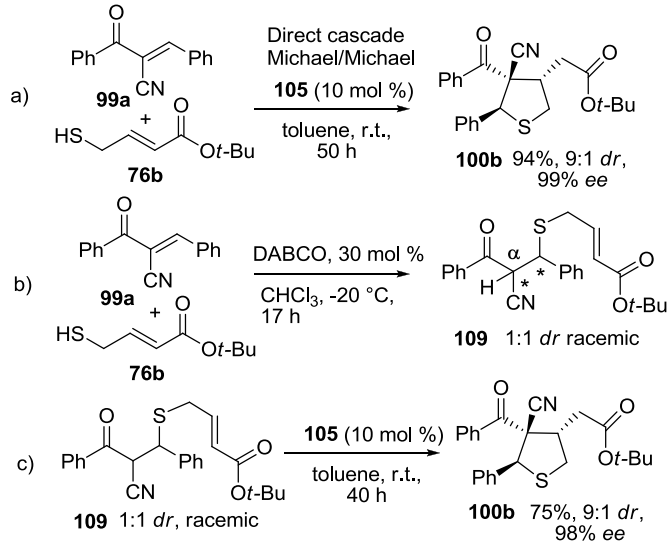


Figure 2.14 Reaction progress profile (entry 1 of Table 2.4) monitored by ^{1}H-NMR in deuterated toluene.

The reaction progress profile in Figure 2.14, shows that the adduct **109** is quickly produced and consumed. Nevertheless, we are able to isolate the racemic mixture of diastereoisomers **109** working under more controlled conditions using DABCO (in $CHCl_3$ at -20

°C for 17 hours, Scheme 2.35b).[iii] To confirm the mechanistic hypothesis, showed in Scheme 2.34, we carried out the intramolecular Michael addition of racemic adduct **109** under the optimized reaction conditions reported in Table 2.4 for the cascade double Michael reaction (Scheme 2.35c).



Scheme 2.35 Mechanistic studies of tandem double Michael reaction.

We were pleased to observe that, starting from the racemic mixture of diastereoisomers of the adduct **109**, the organocatalyst was able to generate the chiral tetrahydrothiophene **100b** in 75% yield, 9:1 diastereoisomeric ratio, and 98% *ee* for the major diastereoisomer (Scheme 2.35c). In other words, the organocatalyst provided the tetrahydrothiophene product with the same result, in terms of yield and stereocontrol, achieved when reacting enone **99a** and thiol **76b** directly (entry1, Table 2.4 and Scheme 2.35a), thus validating our

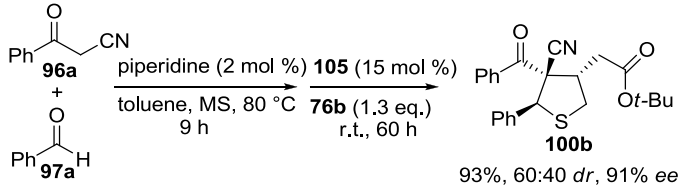
[iii] See the Experimental Section for details.

hypothesis. This means that an efficient process of dynamic kinetic resolution is involved in our cascade double Michael reaction for the synthesis of highly functionalized tetrahydrothiophenes.

It is important to underline that this represents the first case in which the stereoselectivity of an asymmetric synthesis of tetrahydrothiophenes is completely governed by dynamic kinetic resolution.

Currently, tandem multicomponent reactions are getting more and more attention, as highlighted in the paragraph 2.1, thanks to their several advantages over traditional syntheses. These processes are becoming more and more popular in asymmetric synthesis and medicinal chemistry, since they allow the formation of complex scaffolds,[128] bearing several stereogenic centres, starting from commercially available reagents, with a minimum number of synthetic operations.

Prompted by these considerations, we evaluated the feasibility of a one-pot sequential synthesis of tetrahydrothiophenes (Scheme 2.36).



Scheme 2.36 Stereoselective one-pot sequential Knoevenagel/double Michael approach to tetrahydrothiophenes **100**.

Benzaldehyde **97a** and benzoyl acetonitrile **96a** were treated under typical Knoevenagel conditions to generate **99a** and, when the

formation of the enone was completed (monitored by TLC), catalyst **105** and thiol **76b** were added at room temperature. The Knoevenagel reaction conditions were found to be compatible with the cascade double Michael reaction herein developed. In fact, although the process has not been optimized, we were able to isolate product **100b** in 93% yield, with 60:40 diastereoisomeric ratio and 91% *ee* for the major diastereoisomer.

CONCLUSIONS

The first stereoselective cascade sulfa-Michael/Michael reaction for the synthesis of tetrahydrothiophenes from *trans*-α-carbonyl-β-substituted acrylonitriles has been developed, by using a novel readily available secondary amine thiourea as an organocatalyst.

Highly functionalized tetrahydrothiophenes, bearing three contiguous stereocentres, one of them quaternary, were effectively achieved by means of a highly stereoselective cascade transformation. The products were isolated in high yield, good diastereoselectivity and excellent enantiocontrol. This work represents an unprecedented case in which the stereochemical outcome was controlled exclusively by a dinamic kinetic resolution process.

Finally, a highly convenient one-pot Knoevenagel/double Michael process, starting directly from commercially available reagents and involving a minimal number of operations has been demonstrated applicable to obtain the tetrahydrothiophenes in comparable stereoselectivity.

3. ENANTIOSELECTIVE SYNTHESIS OF γ-BUTYROLACTONES BEARING AN ALL-CARBON β-QUATERNARY STEREOCENTRE

3.1 Background

γ-Butyrolactone scaffold is a common naturally-occurring motif, present in about 10% of all natural products.[129] It is an important framework present in a wide variety of compounds possessing biological activities. Mono-, di- and trisubstituted monocyclic γ–butyrolactones and mainly bicyclic and tricyclic ring systems show a wide range of biological activities, spanning from strong antibiotic, antihelmitic, antifungal, antitumor to antiviral and anti-inflammatory (Figure 3.1).[130]

Sesquiterpene lactones, characteristic constituents of exceedingly large and widespread family of "*Compositae*" plants, represent an important class of natural compounds that exhibit interesting biological properties.[131] These molecules are especially present in the leaf tissue, where they can constitute up to 5% of the dry weight and are colorless, lipophilic and often bitter-tasting.[129a]

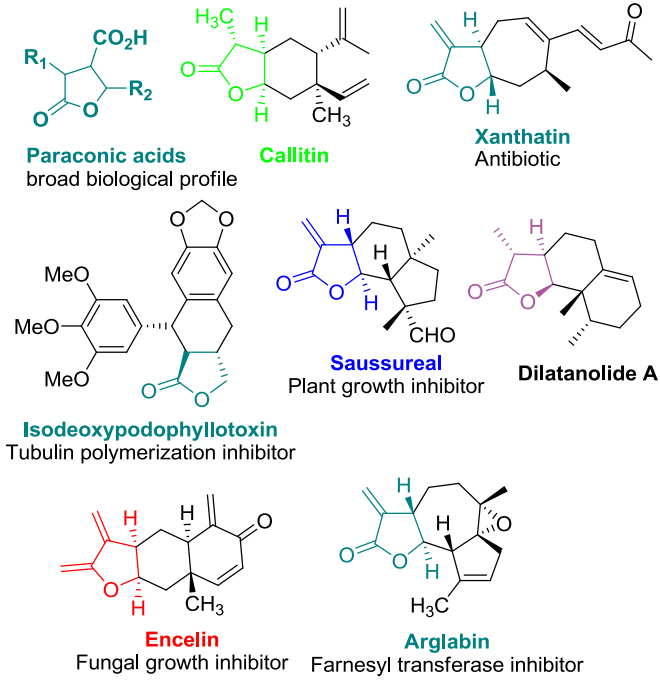


Figure 3.1 Examples of γ-butyrolactone natural products.

They show in their structure an α-methylene-γ-butyrolactone ring, which is the core of their activity. In fact, these compounds have two reactive functionalities: the double bond, that is able to undergo Michael addition with nucleophilic sites of biomolecules, such as L-cysteine or thiol-containing enzymes, and the lactone unit that is a possible target for nucleophilic and electrophilic centres of the biomolecules. For example, these sesquiterpene lactones can act as inhibitors of cellular steroids, blockers of tumor necrosis factor production, DNA polymerase inhibitors or apoptosis inducers.[132] Some of them, sometimes present in the pollen, cause an allergenic

contact dermatitis. Others are used in the regulation of plant growth.[129a]

A lot of active sesquiterpene lactones, such as vernolepin, aromaticin and elephantopin, estracted from plants, display tumor inhibiting activity (Figure 3.2) but many others have bactericidal, fungicidal and anthelminthic activity.[133,129a]

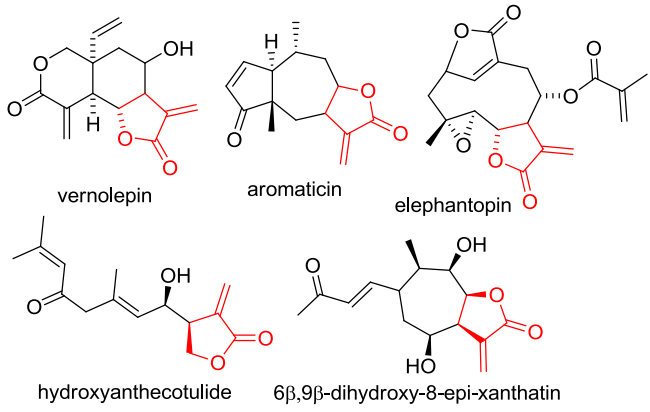
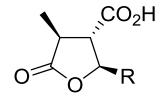


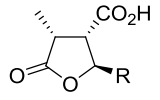
Figure 3.2

Given the biological importance of these compounds, many methods to access α-methylene-γ-butyrolactones, for use in targeted synthesis and for testing as potential drug candidates, have been developed.[134]

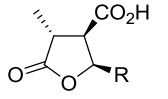
γ-Butyrolactones bearing a carboxylic acid function at the β-position to the carbonyl group, named paraconic acids, (Figure 3.3) are another important group of naturally occurring γ-butyrolactones, endowed with a variety of biological and pharmacologically activities such as antibiotic and antitumor properties.[135]



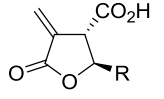
R = *n*-$C_{13}H_{27}$: (+)-Roccellaric acid
R = *n*-$C_{11}H_{23}$: (+)-Nephrosteranic acid
R = $(CH_2)_{13}CH(OH)CH_3$: (+)-Neodihydromurolic acid



R = *n*-$C_{13}H_{27}$: (+)-Dihydroprotolichesterinic acid
R = $(CH_2)_{13}COCH_3$: (+)-Dihydropertusaric acid



R = *n*-C_5H_{11}: (+)-Phaseolinic acid
R = $C_{13}H_{27}$: (+)-Nephromopsinic acid
R = $(CH_2)_{13}COCH_3$: (+)-Pertusarinic acid



R = *n*-$C_{12}H_{24}CO_2H$: (+)-Protopraesorediosic acid
R = *n*-$C_{13}H_{27}$: (+)-Protolichesterinic acid
R = *n*-C_5H_{11}: (+)-Methylenolactocin

Figure 3.3 Most notable paraconic acids.

Lichens are the natural source of paraconic acids, but, given their important properties, several synthetic routes towards these natural compounds have been devised using starting materials from the chiral pool, chiral auxiliaries or by using chiral catalysts.[136]

Hydroxy-γ-butyrolactones bearing a hydroxyl-methyl group at β-position of lactonic ring, constitute another important class of natural products. For example, they are implicated in the production of secondary metabolites such as antibiotics. In Figure 3.4 are shown some of these compounds useful in the synthesis of different antibiotics of which A-factor is the best known compound.[137]

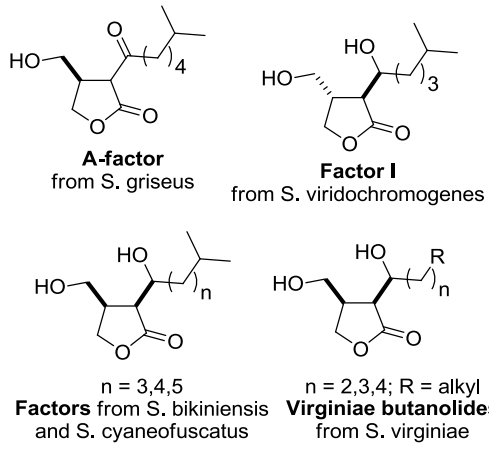


Figure 3.4 Factors from Streptomyces.

Generally, the biological activity of γ-lactones is strictly related to the nature and position of the substituents in the heterocycle. It is known that substituted γ-butyrolactones are potent antagonists or agonists – depending upon the substitution pattern – of the γ-aminobutiric acid (GABA) receptor, the principal inhibitory neurotransmitter receptor in the mammalian central nervous system. For example, the β-substituted γ-butyrolactones in Figure 3.5, bearing quaternary and tertiary stereocentres have antagonist activity.[138]

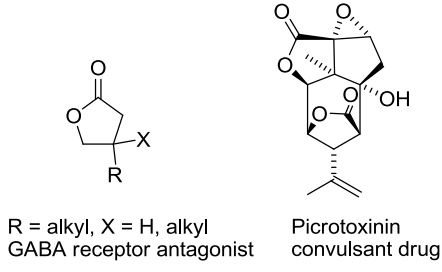


Figure 3.5

Many other natural and bioactive unnatural γ-butyrolactones have a quaternary stereocentre in their structure, such as the highly neurotrophic compounds jiadifenin and tricholomalide A and the anticancer compound maoecrystal V (Figure 3.6).[139]

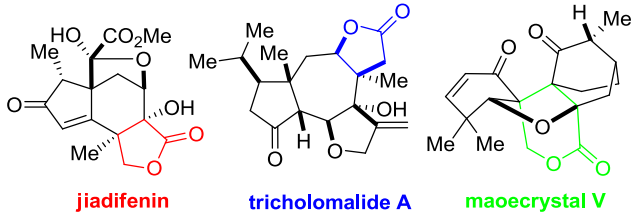


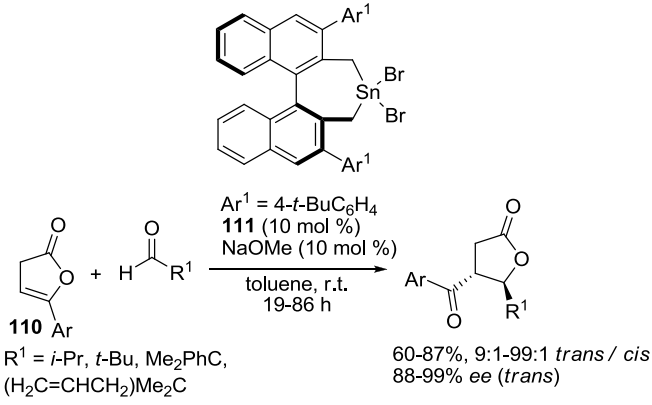
Figure 3.6 Selected natural products containing a lactone subunit bearing a quaternary stereocentre.

Chiral γ-butyrolactones have been used as valuable building blocks in the synthesis of several types of natural products or synthetic drugs: alkaloids, macrocyclic antibiotics, lignan lactones, pheromones, antileukemics and flavor components.[129b,138,140]

Various methods for the stereoselective synthesis of such useful synthons have been developed. Some of these employ simple natural products such as amino acids, tartaric acid, ascorbic acids, carbohydrates or chiral sulfoxides, epoxides or substituted acetylenic acids as starting materials.[137]

The enantioselective synthesis of chiral γ-butyrolactones has been performed by using chiral catalysts. In this context, examples of hydrogenations, C-H insertions, allylic alkylation, Baeyer-Villiger oxidations, 1,4-additions, kinetic resolutions, 1,4-hydrosilylation and aldol reaction/cyclization have been reported.[141]

In particular, the first catalytic synthesis of chiral γ-butyrolactones via aldol reaction was illustrated by Yanagisawa in 2011 (Scheme 3.1).[141,142]



Scheme 3.1 Tandem tin-catalyzed asymmetric aldol reaction/cyclization.

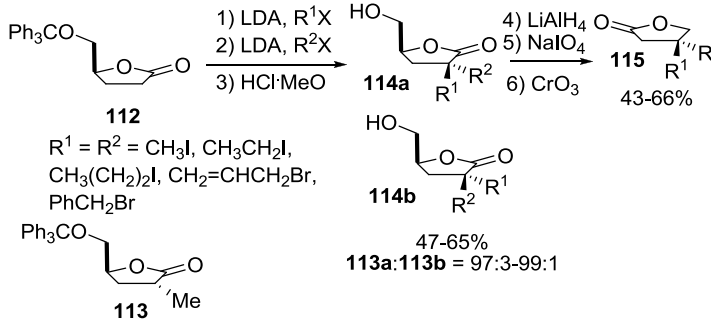
In this methodology, the starting material γ-substituted β,γ-didehydro-γ-butyrolactone **110** reacts with various aldehydes (aliphatic aldehydes give the best results in terms of enantioselectivity) via enantioselective aldol reaction, followed by subsequent lactonization of a tin alkoxide of aldol adduct intermediate, affording the β,γ-disubstituted γ-butyrolactones bearing two tertiary contiguous stereocentres. The catalytically active species is a chiral tin bromide methoxide formed from chiral tin dibromide **111** and sodium methoxide.

However, among the stereoselective approaches to these important molecules, only a few methodologies to access enantioenriched γ-butyrolactones, possessing an all-carbon quaternary stereocentre at the β-position, were reported.

The synthesis of these challenging frameworks is made particularly

difficult because (*i*) the stereoselective construction of all-carbon quaternary centres is a difficult target in a chemical synthesis due to the steric congestion imposed by the four attached carbons[125] and (*ii*) the remote β-position of the stereocentre is a less "controllable" position respect to the α- and γ-positions. Multi-step approaches have been essentially developed.

For example Koga, in the 1980s, reported the synthesis of optically active β,β-disubstituted γ-butyrolactones starting from the chiral synthon **112** prepared from L-glutamic acid (Scheme 3.2).[143]

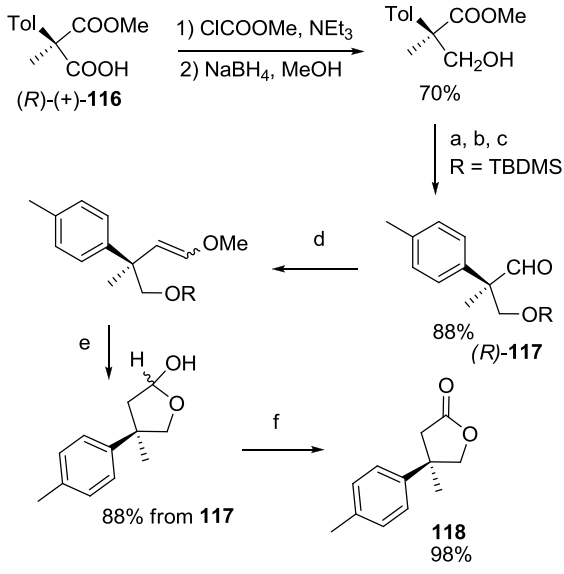


Scheme 3.2 Synthesis of chiral β,β-disubstituted γ-butyrolactones via sequential dialkylation of **112**.

In this reaction, the chiral synthon **112** may be methylated (treating with LDA-THF and then with R^1X= MeI) affording product **113** (in 73% yield) which may in turn be alkylated with another alkyl halide (treating with LDA/(HMPA)-THF and then R^2X). Otherwise, the sequential dialkylations can be performed with two different alkyl halides in one operation (performing both the sequential dialkylations using LDA in the presence of HMPA and alkylating the corresponding enolate in THF at -78 °C). The crude dialkylation

products are then detritylated with HCl in methanol, affording product **114** in high diastereomeric excess. Finally, removal of the hydroxymethyl stereocentre gives product **115** bearing one quaternary stereocentre. Inverting the introduction order of electrophiles leads to the opposite enantiomer of **115**.

In 1992, Fadel described a series of syntheses of efficient precursors of some natural products containing a cyclopentane ring with a quaternary stereocentre (the enantiomers of α- and β-cuparenones), starting from monomethyl 2-methyl-2-*p*-tolylmalonic acid ester (*R*)-**116**. In one of these syntheses, a γ-butyrolactone, bearing a quaternary all-carbon stereocentre, **118** was obtained as shown in Scheme 3.3.[144]



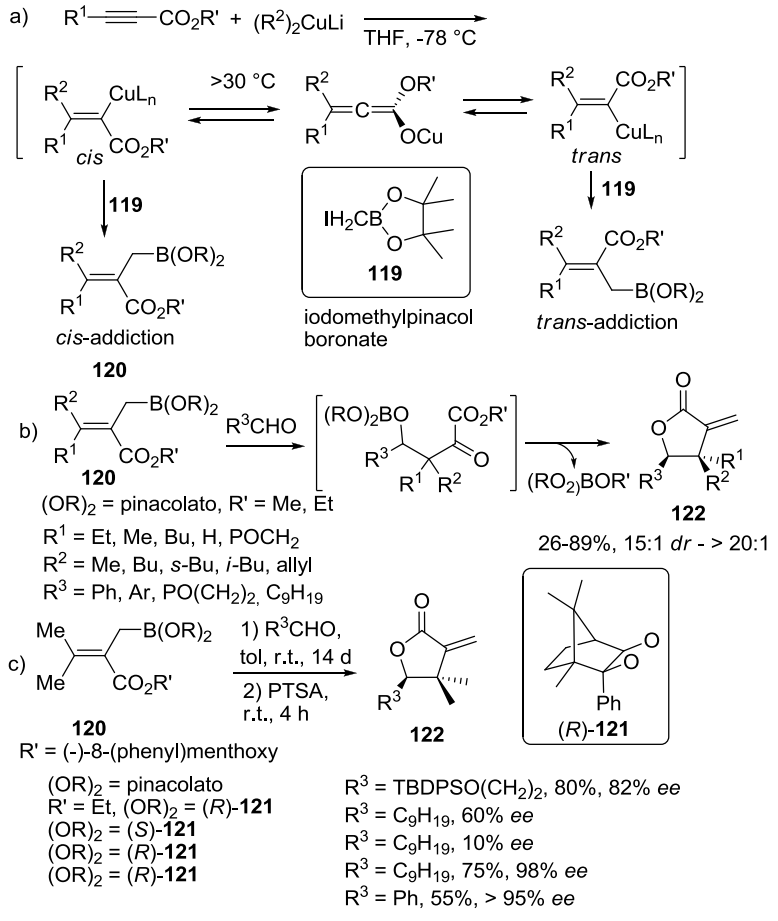
(a) TBDMSCl, imidazole, DMF, 40 °C, 10 min;
(b) DIBAL-H, 2 eq., CH_2Cl_2, -78 °C;
(c) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -60 °C;
(d) *n*-BuLi, 2.5 eq., $(Ph)_3MeOCH_2P^+$ Cl^- 3 eq., THF, -15 °C, 0.5 h, then 0 °C, 3 h;
(e) 2 N HCl, THF, 30 °C, 2 h;
(f) 2 eq., PCC, Celite, 1 eq. of NaOAc, CH_2Cl_2, 20 °C, 10 h.

Scheme 3.3 Asymmetric construction of a quaternary carbon centre from a chiral malonate.

In 2002, Hall's research group reported a stereocontrolled synthesis of α-exomethylene γ-lactones **122** with a stereogenic quaternary carbon centre starting from isomerically pure tetrasubstituted allylboronates **120** (Scheme 3.4).[145]

They were able to obtain tetrasubstituted 2-alkoxycarbonyl allylboronates **120** as pure isomers in a single operation by tandem carbocupration of alkynoate esters followed by electrophilic trapping with iodomethyl boronates **119** (Scheme 3.4a). Using chiral 3,3-dialkyl allylboronates in the subsequent addition onto

aldehydes, they isolated α-methylene γ-lactones **122** as aldol-like adducts, bearing a quaternary stereocentre in high diasteroselectivity (Scheme 3.4b).

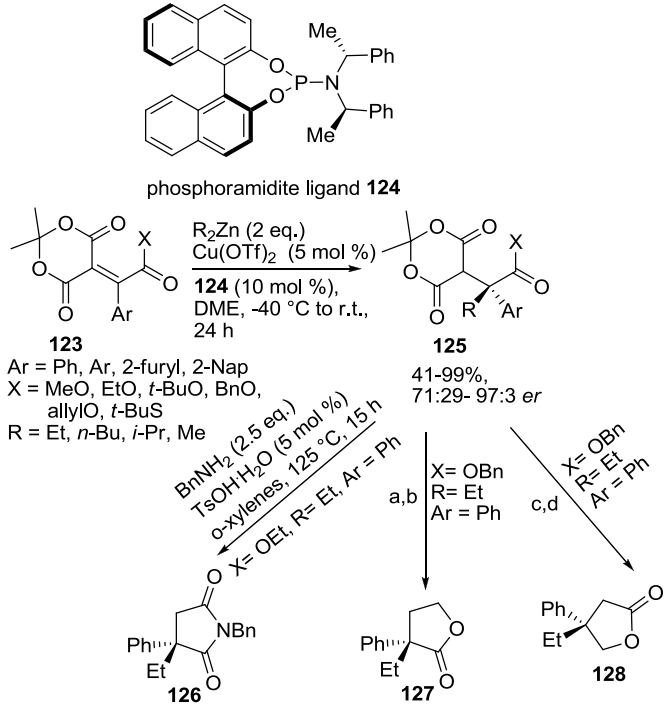


Scheme 3.4 Synthesis of γ-lactones from tetrasubstituted allylboronates.

Using 3,3-dimethyl allylboronates having chiral auxiliaries on the alcohol and on the boronate, they obtained lactones **122** with up to 98% *ee,* when a matched combination of the chiral inducers was

found (Scheme 3.4c).

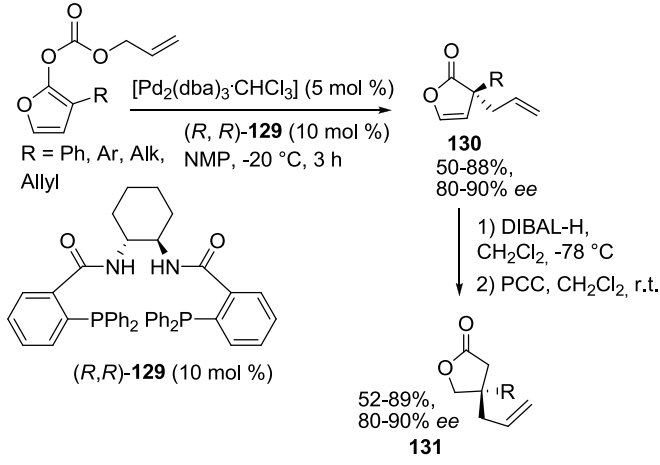
More recently, Fillion reported the synthesis of carboxylic acid derivatives **125,** bearing an all-carbon quaternary stereocentre, and demonstrated their usefulness in the preparation of chiral succinimides **126** and γ-butyrolactones **127** and **128** (Scheme 3.5).[146] The chiral starting compounds **125** were prepared via copper-catalyzed 1,4-addition of dialkyl reagents to aryl acetate derivatives **123** in the presence of phosphoramidite ligand **124**.



(a) pyridine:MeOH (10:1), Cu (20 mol %), 100 °C, 3 h, 88% yield
(b) 1) $BH_3{\cdot}SMe_2$ (5 eq.), r.t., 4 h; 2) HBr (aq.), reflux, 1.5 h, 77% yield
(c) 10% Pd/C, H_2 (1 atm), EtOAc, r.t., 16 h then SiO_2, 73% yield
(d) $NaBH_4$ (2 eq.), MeOH, 0 °C, 2 h, 93% yield

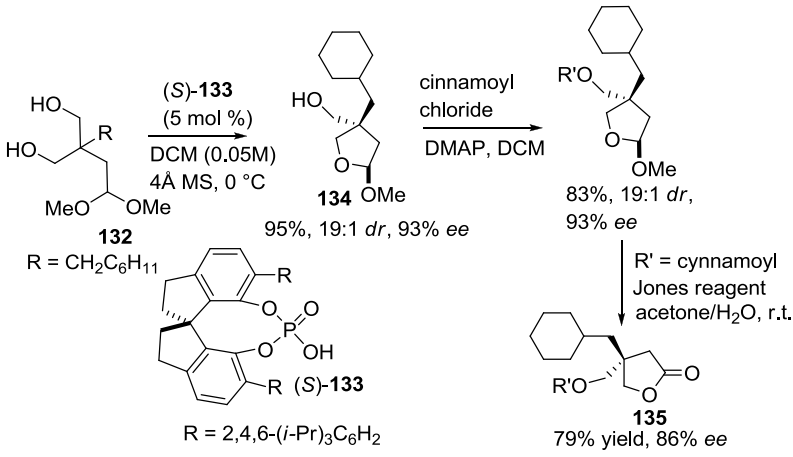
Scheme 3.5 Preparation of succinimides and γ-butyrolactones from chiral carboxylic acid derivatives.

Recently, Cossy and Arseniyadis described a palladium-catalyzed allylic alkylation of cyclic dienol carbonates to enantioenriched γ-butenolides **130**. These compounds were then transformed, in two steps (reduction and oxidation), into β,β-disubstituted γ-butyrolactones **131**, bearing an all-carbon quaternary stereocentre in fairly good enantioselectivity (Scheme 3.6).[147]



Scheme 3.6 Synthesis of β-quaternary butyrolactones from enantioenriched γ-butenolides.

In the same year, Sun et al. developed a chiral phosphoric acid catalyzed desymmetrization of prochiral 1,3-diol tethered to an acetal **132**, to give five-membered cyclic acetals **134**, that are useful starting material to obtain, via oxidation, enantioenriched β,β-disubstituted γ-butyrolactones **135** (Scheme 3.7).[139]

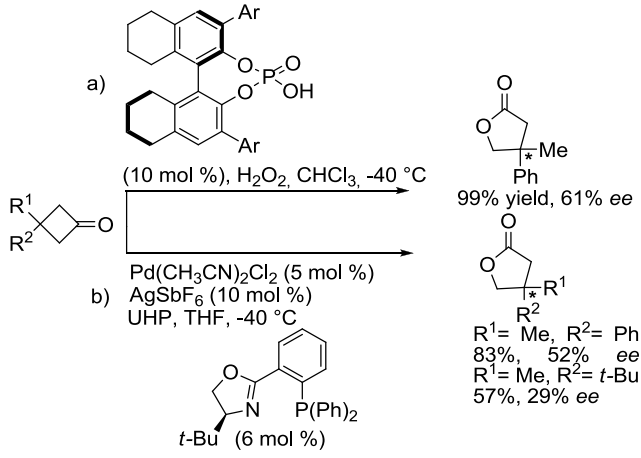


Scheme 3.7 Synthesis of five-membered cyclic acetals and their oxidation to lactones.

In both these methodologies, enantioenriched γ-butyrolactones were synthesized starting from chiral reagents through multiple synthetic steps with very good level of enantioselectivity (80-90% *ee*).

It would be highly convenient to have a direct method for the synthesis of these compounds.

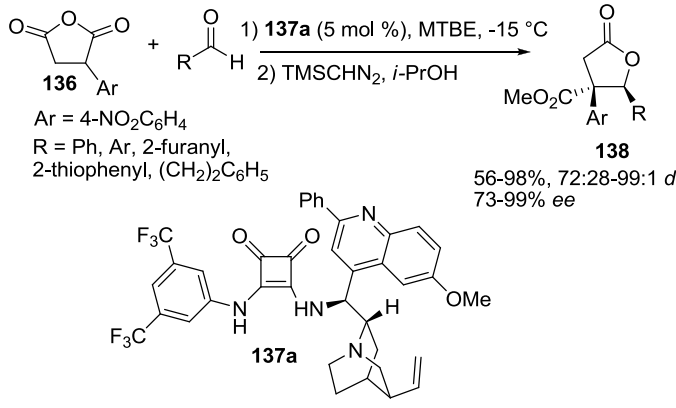
With regard to direct methodologies, only the asymmetric Baeyer-Villiger reaction on 3-disubstituted cyclobutanones has been reported. The groups of Ding[148] and Stoltz[149] were able to isolate β,β-disubstituted γ-butyrolactones exploiting the Bayer-Villiger reaction performed either under organocatalytic (Scheme 3.8a) or metal-catalyzed conditions (Scheme 3.8b), respectively. However, only in the few examples reported until now, a modest level of enantioselectivity was achieved.



Scheme 3.8 Asymmetric Baeyer-Villiger reaction on 3-disubstituted cyclobutanones.

A recent example on the asymmetric synthesis of paraconic acid derivatives bearing quaternary and tertiary stereocentre has been reported by Connon's group.[150] They illustrated a higly enantio- and diasteroselective organocatalytic one-pot process which provides a facile access to γ-butyrolactones paraconic acid derivatives **138** from aryl succinic anhydrides **136** and aldehydes (Scheme 3.9). The proposed mechanism of the reaction involves initial enolization of the anhydride, followed by its addition to the electrophilic aldehyde to produce a tetrahedral intermediate which subsequently lactonizes forming the product. However, simple succinic anhydride does not react with benzaldehyde. The authors suggested that this is due to scarse enolizability of succinic anhydride in the presence of the organocatalyst. So, an appropriately substituted aryl succinic anhydride was chosen (having an electron withdrawing group, such as *p*-nitro substituted anhydride **136**), which on the one hand

facilitated the keto-enol equilibrium, and, on the other hand, allowed the formation of aryl paraconic acid derivatives, having two stereocentres, one of which quaternary, in good to excellent diastero and enantioselectivity.



Scheme 3.9 Organocatalytic stereoselective one-pot synthesis of paraconic acid derivatives.

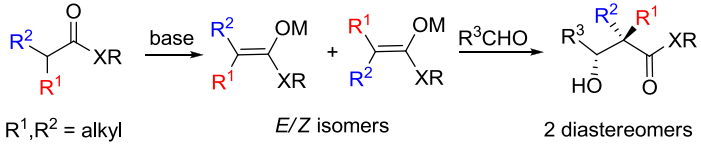
This reaction is promoted by a bifunctional organocatalyst squaramide via non-covalent catalysis.

As described in the numerous mechanistically different organocatalytic reactions promoted by bifunctional organocatalysts, such as chiral amine-thioureas, amine-squaramides or β-amino alcohols, it is recognized in the chemical community that these promoters are able to activate synergistically pronucleophiles via general base catalysis and electrophiles via general acid catalysis. In the next paragraph, it will be illustrated our methodology for the asymmetric synthesis of γ-butyrolactones bearing an all-carbon β-quaternary stereocentre. For this purpose, we conceived a simple

aldol/lactonization organocatalytic cascade sequence starting from acylated succinic esters and formaldehyde, exploiting non-covalent activation of the reagents by a bifunctional organocatalyst.

As underlined above, the stereoselective construction of all-carbon quaternary centres is a difficult target. In fact, few general methods for realizing this task in a highly diastereo- and enantiocontrolled fashion have been reported.[125]

The preparation of an all-carbon quaternary stereocentre at the α-position of a carbonyl group via aldol reaction represents one of the most challenging synthetic transformations. Ideed, the aldol-based methodologies are generally not applicable to the construction of chiral quaternary centre due to the absence of *E/Z* selectivity in the enolization of α,α-disubstituted (especially unfunctionalized) carbonyl compounds (Scheme 3.10).[151]



Scheme 3.10

Therefore, strategies leading to complete control of the geometry of fully substituted enolates are highly desirable.[152]

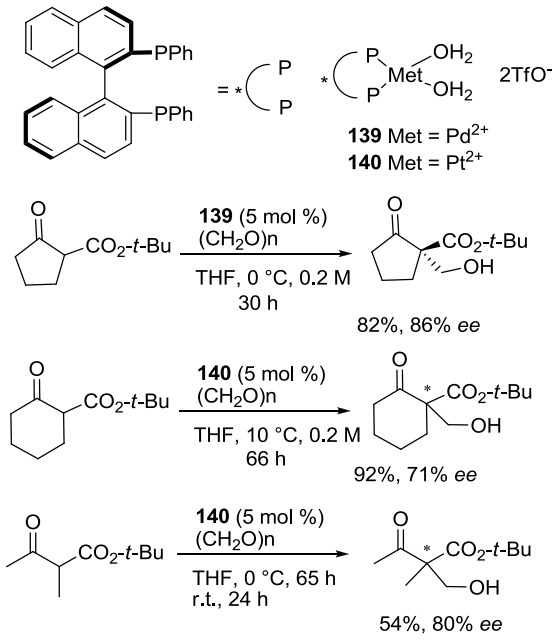
For monosubstituted ester and ketone enolates, the proper choice of solvent, base and temperature can often influence the stereochemistry[153] and for monosubstituted tertiary amide enolates, minimization of A-1,3 (1,3-allylic strain) interactions generally promotes Z-enolate formation.[154] For disubstituted enolates is more difficult to control the stereochemistry. Usually, a highest

stereocontrol is achieved with cyclic frameworks, including metal chelate, whereas control based on differential steric environments is more complicated.[155]

After the Shibasaki's pioneering work on the intermolecular direct catalytic asymmetric aldol reaction,[156] considerable efforts have been made to perform in situ activation of carbonyl compounds as nucleophiles with disparate systems including chiral metal complexes and organocatalysts.[157]

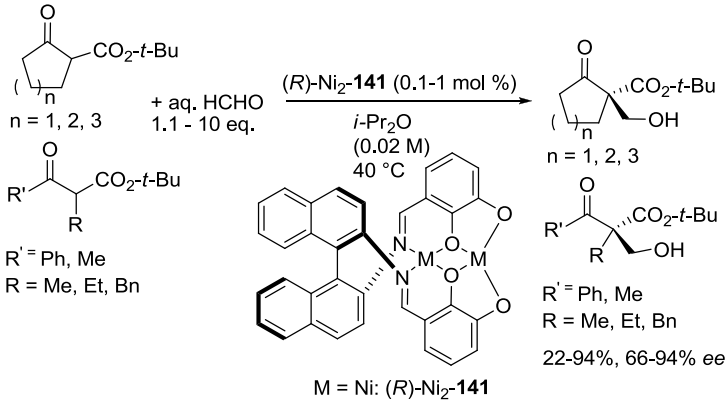
However, the high reactivity of formaldehyde and glyoxylate likely has limited their use as C1 and C2 units. Consequently, the asymmetric hydroxymethylation reaction of 2-substituted-1,3-dicarbonyl compounds has been a scarcely investigated process and modest success has been achieved. Remarkably, only transition-metal based systems have been reported to catalyze this reaction reaching moderate to high enantioselectivity.

In 2009, the Sodeoka's group reported a catalytic hydroxymethylation of β-keto esters with formaldehyde, using Pd and Pt BINAP-complexes (Scheme 3.11).[158]



Scheme 3.11 Hydroxymethylation of β-keto ester catalyzed by Pd and Pt BINAP-complexes.

Subsequently, Shibasaki et al. developed a direct catalytic asymmetric aldol reaction of β-keto esters with formaldehyde catalyzed by a dinuclear Ni_2-Schiff base complex (Scheme 3.12).[159]



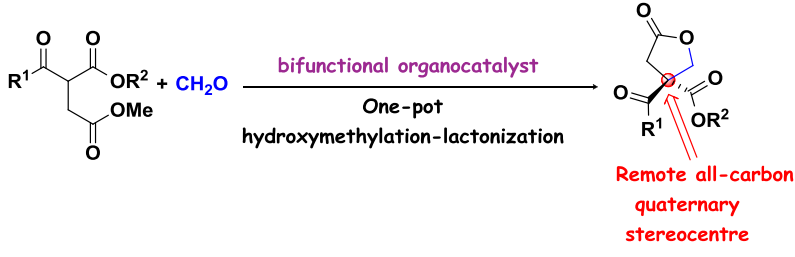
Scheme 3.12 Asymmetric aldol reaction of β-keto esters with formaldehyde catalyzed by a dinuclear Ni_2-Schiff base complex.

Reaction conditions needed to be optimized according to the structure of the β-keto ester used.

3.2 Results and Discussion

As described in the previous paragraph, β-substituted-γ-butyrolactones are common motives in a wide range of natural products and pharmaceuticals. Many efforts have been made to develop stereoselective syntheses of these molecules. Enantioenriched γ-butyrolactones, bearing one carbon quaternary stereocentre at the β-position**,** are the most challenging targets due to the enantioselective construction of an all-carbon quaternary stereocentre at the remote β-position, far from relatively more easy to manipulate α- and γ-positions.

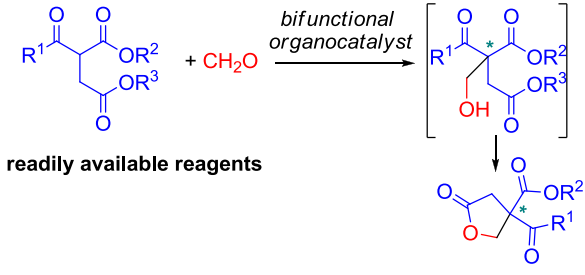
For this purpose, we devised and developed a simple aldol/lactonization organocatalytic cascade sequence to β,β-disubstituted γ-butyrolactones, starting from acylated succinic esters and formaldehyde, exploiting non-covalent activation of the reagents provided by a bifunctional organocatalyst (Scheme 3.13).[160]



Scheme 3.13 Organocatalytic approach to β,β-disubstituted γ-butyrolactones.

We hypothesized that the cascade reaction could involve the formation of a prochiral enolate of acylated succinic esters,

generated by the bifunctional organocatalyst, which then would react in a chiral environment with formaldehyde to afford an enantioenriched aldol product. Next, assistance by the organocatalyst in the lactonization step of the aldol intermediate would lead to the desired γ-butyrolactone. (Scheme 3.14).



Scheme 3.14 Tandem aldol/lactonization sequence.

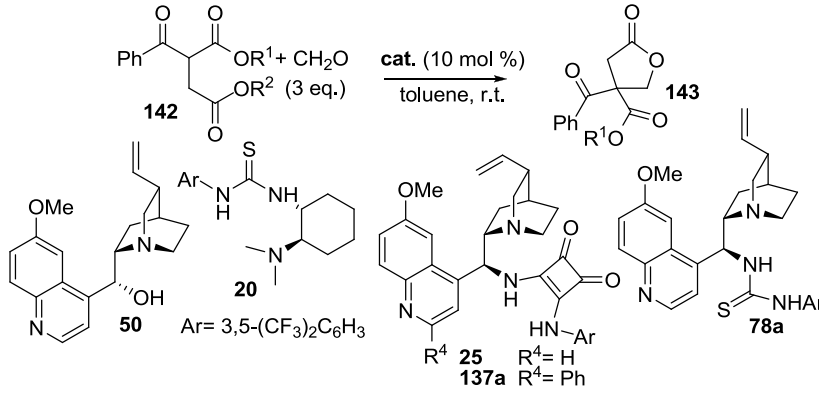
We demonstrated that this straightforward enantioselective route to β,β-disubstituted γ-butyrolactones is efficiently catalyzed by *Cinchona* alkaloids derived squaramides.

The products obtained are paraconic acid derivatives, bearing a quaternary stereocentre, and they can be transformed into diversely functionalized hydroxy-γ-butyrolactone derivatives, that belong to another important class of γ-butyrolactones. Remarkably, preliminary results showed that the designed organocatalytic aldol/lactonization strategy can be applied for the synthesis of enantioenriched δ-valerolactones with an all-carbon γ-quaternary stereocentre.

To evaluate the feasibility of the organocatalytic sequence reported in Scheme 3.14, we began our study by reacting the

diethyl 2-benzoyl succinate **142a** and paraformaldehyde in toluene at room temperature with 10 mol % of quinine **50** (Table 3.1). We were pleased to observe that γ-butyrolactone **143a** was formed, although in low yield and without enantiocontrol (entry 1). By using Takemoto's thiourea **20** (entry 2) and *epi*-quinine derived thiourea **78a** (entry 3), which are known to be better H-bond donating organocatalysts, the yield considerably improved but the enantioselectivity was still low. We thought that a better enantiocontrol would be achievable by placing two sterically different ester groups in the starting material **142**. In fact, compound **142b**, bearing the *t*-butyl and methyl ester groups, in the presence of amine-thioureas **20** and **78a** reacted with formaldehyde giving the product **143b** in a good conversion and with a significant increase of the enantioselectivity (entries 4 and 5). Interestingly, the reaction catalyzed by 5 mol % of *epi*-quinine derived squaramide **25**, in $CHCl_3$ as solvent, afforded the product with 50% *ee* (entry 6), revealing that amine-squaramides are suitable organocatalysts to promote our process. The presence of sterically demanding cyclohexyl, 2-adamanthyl or 1-carbonaphthyl ester groups in reagents **142c-e** consistently demonstrated catalyst **25** to be more effective than amine-thiourea **20** (entries 7-12).

Table 3.1 Optimization of the one-pot sequence: bifunctional organocatalysts and benzoyl succinate substrate structure.[a]



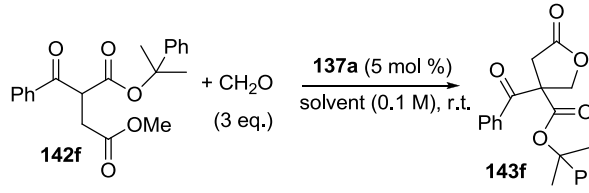
entry	R^1	R^2	cat.	t (h)	yield (%)[b]	*ee* (%)[c]	**143**
1	Et	Et	**50**	123	28	2	**143a**
2	Et	Et	**20**	122	80	7	**143a**
3	Et	Et	**78a**	86	88	-7	**143a**
4	*t*-Bu	Me	**20**	60	78	51	**143b**
5	*t*-Bu	Me	**78a**	20	64	-35	**143b**
6[d,e,f]	*t*-Bu	Me	**25**	21	31	-50	**143b**
7	C_6H_{11}	Me	**20**	63	57	35	**143c**
8[d,e,f]	C_6H_{11}	Me	**25**	66	83	-42	**143c**
9[f]	2-adamanthyl	Me	**20**	23	92	-36	**143d**
10[d,e,f]	2-adamanthyl	Me	**25**	24	74	40	**143d**
11[f]	1-carbonaphthyl	Me	**20**	44	78	20	**143e**
12[d,e,f]	1-carbonaphthyl	Me	**25**	44	95	-42	**143e**
13[f]	cumyl	Me	**20**	42	58	11	**143f**
14[f]	cumyl	Me	**78a**	21	73	-32	**143f**
15[d,e,f]	cumyl	Me	**25**	43	47	-59	**143f**
16[d,e,f]	cumyl	Me	**137a**	66	74	-65	**143f**

[a]Reaction carried out at C = 0.05 M of **142** on 0.1 mmol scale. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]In chloroform as solvent. [e]5mol % of catalyst was used. [f]Reaction carried out at C 0.1M of **142**.

Finally, reactions carried out on compound **143f**, bearing a cumyl group as the R^1 residue, confirmed catalyst **25** as the most enantioselective (entry 15) when compared to amine-thioureas **20** and **78a** (entries 13-14). With our delight, we found that more sterically demanding amine-squaramide **137a**, bearing a phenyl group at 2'-position of the quinoline residue, provided the γ-butyrolactone **143f** in good yield and 65% *ee* (entry 16).

A solvent screening conducted with organocatalyst **137a**, showed that in aromatic solvents, such as toluene, clorobenzene and ethereal solvent, such as methyl *tert*-butyl ether, poor conversions (30-36%) and moderate enantioselectivities (50-62%) were achieved (Table 3.2, entries 2, 4-5). In hexafluorobenzene the yield improved, althogh not the enantioselectivity, and in α,α,α-trifluorotoluene the product was isolated in 72% *ee*, but in moderate conversion (49%) (entries 6-7). Dibromomethane, 1,1,1-trichloroethane and especially 1,2-dichloroethane proved to be the most suitable solvents for the reaction in terms of conversion and enantioselectivity (entries 1, 3, 8).

Table 3.2 Solvent screening.[a]



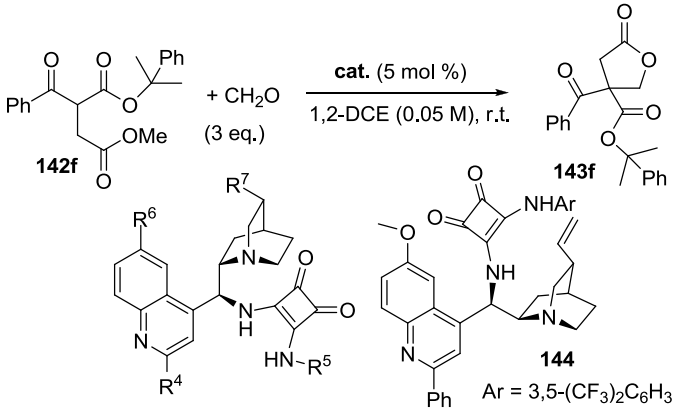
entry	t (h)	solvent	yield (%)[b]	*ee* (%)[c]
1	23	CH_2Br_2	53	71
2	45	ClC_6H_5	36	62
3	63	CCl_3CH_3	57	64
4	67	*t*-$BuOCH_3$	31	50
5	64	toluene	30	60
6	64	$CF_3C_6H_5$	49	72
7	158	hexafluorobenzene	70	62
8	23	$Cl(CH_2)_2Cl$	70	73
9[d]	18	$Cl(CH_2)_2Cl$	72	74

[a]Reactions conditions: **142f** (0.10 mmol) and **137a** (0.005 mmol) solvent (1 mL). [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]Reaction carried out at C = 0.05 M of **142f**.

Product **143f** was isolated in 72% yield and 74% *ee*, working in 1,2-dichloroethane at concentration of 0.05M of **142f** (entry 9).

Differently 2'-substituted *epi*-quinine, *epi*-quinidine or *epi*-cinchonidine derived squaramides were then employed under these conditions (Table 3.3).

Table 3.3 Screening of 2'-substituted *epi*-cinchona amines derived squaramides.[a]



137a R^4= Ph, R^5= 3,5-$(CF_3)_2C_6H_3$, R^6= OMe, R^7= vinyl
137b R^4= *n*-Bu, R^5= 3,5-$(CF_3)_2C_6H_3$, R^6= OMe, R^7= vinyl
137c R^4= *t*-Bu, R^5= 3,5-$(CF_3)_2C_6H_3$, R^6= OMe, R^7= vinyl
137d R^4= 1-Nap, R^5= 3,5-$(CF_3)_2C_6H_3$, R^6= H, R^7= vinyl
137e R^4= Ph, R^5= 3,5-$(CF_3)_2C_6H_3CH_2$, R^6= OMe, R^7= vinyl
137f R^4= Ph, R^5= 3,5-$(CF_3)_2C_6H_3$, R^6= OMe, R^7= ethyl

entry	cat.	t (h)	yield (%)[b]	*ee* (%)[c]
1	**137a**	18	72	-74
2	**137b**	23	65	-69
3	**137c**	24	75	-69
4	**137d**	19	71	-68
5	**137e**	29	48	-70
6	**144**	19	64	68
7	**137f**	15	79	-78

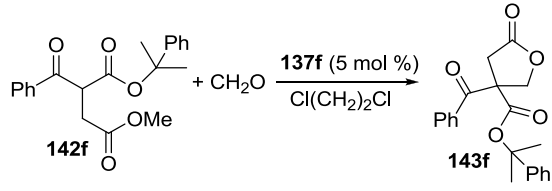
[a]Reaction carried out at C = 0.05 M of **142** on 0.1 mmol scale. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

Alkyl groups at the 2'-position of the *epi*-quinine (entries 2-3) or a sterically demanding 1-naphthyl group at 2'-position of *epi*-cinchonidine (entry 4) were detrimental to catalyst efficiency. The presence of a benzylic squaramide moiety as in catalyst **137e** was unfavourable (entry 5). Catalyst **144**, the

pseudo-enantiomer of catalyst **137a**, gave the opposite enantiomer of product **143f** but proved to be slightly less effective than compound **137a** (entry 6). Finally, *epi*-hydroquinine derived squaramide **137f** was found to be the best catalyst as product **143f** was isolated in 79% yield and 78% *ee* (entry 7).

To further improve the yield and the enantioselectivity, nature of formaldehyde, additives and reaction temperature were examined (Table 3.4).

Table 3.4 Optimization of the reaction conditions.[a]



entry	Additive	T (°C)	t (h)	yield[b] (%)	*ee*[c] (%)
1	-	r.t.	16	77	73
2	Na_2SO_4	r.t.	15	83	75
3[d,e]	-	0	40	35	82
4[e]	-	0	17	94	80
5[e]	-	-20	67	70	84
6[e]	3Å MS	-20	65	80	83
7[e]	3Å MS	-30	60	58	79

[a]Reaction carried out at C = 0.05 M of **142f** on 0.1 mmol scale with 2 eq. of formalin. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Paraformaldehyde was used. [e]Performed at C = 0.1 M of **142f**.

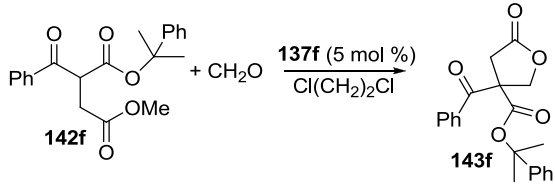
We obtained a similar result using two equivalents of 37% water solution of formaldehyde (entry 1, Table 3.4) to that obtained when using 3 equivalents of paraformaldehyde (entry 7, Table 3.3). The

addition of a drying agent such as Na_2SO_4 slightly improved the reaction outcome (entry 2). Formalin proved to be a better reagent than paraformaldehyde (entry 3) when decreasing the reaction temperature to 0 or -20 °C. (entries 4 and 5). Higher conversion was observed at -20 °C in the presence of molecular sieves, with the product recovered in 83% *ee* (entry 6). However, lowering the reaction temperature at -30 °C had a detrimental effect both on conversion and enantiocontrol (entry 7).

The effect of acidic additives was also investigated (Table 3.5).[161] In the presence of different loading of benzoic acid, an improvement of the *ee* up to 84% was observed working at 0 °C (entries 1 and 2). Slightly less acidic 4-methoxybenzoic acid proved to be less efficient than benzoic acid (entry 3).

Less acidic additives, such as *p*-substituted phenols, can be also used as useful additives (entries 4 and 5) and, in particular, the addition of 4-nitrophenol significantly enhanced the reactivity of the system either at 0 °C or -20 °C and the product was isolated in high yield and up to 86% *ee* (entries 6 and 7). Importantly, the catalyst loading can be reduced to 3 mol % (entries 8 and 9), affording the product in 95% yield and 87% *ee* (entry 9).

Table 3.5 Effect of additive, temperature and catalyst loading on model compound **142f**.[a]



entry	**137f** (mol %)	Additive	T (°C)	t (h)	yield[b] (%)	*ee*[c] (%)
1[d]	5	$PhCO_2H$ (2.5 mol %)	0	16	80	84
2[d]	5	$PhCO_2H$ (5 mol %)	0	27	52	83
3[d]	5	4-Methoxybenzoic Acid (2.5 mol %)	0	20	70	80
4[d]	5	$4\text{-}MeOC_6H_4OH$ (2.5 mol %)	0	18	84	81
5[d]	5	$4\text{-}NO_2C_6H_4OH$ (2.5 mol %)	0	17	88	84
6[d]	5	$4\text{-}NO_2C_6H_4OH$ (5 mol %)	0	14	98	84
7[d]	5	$4\text{-}NO_2C_6H_4OH$ (5 mol %)	-20	20	90	86
8[d]	2	$4\text{-}NO_2C_6H_4OH$ (5 mol %)	-20	30	81	84
9[d]	3	$4\text{-}NO_2C_6H_4OH$ (5 mol %)	-20	46	95	87

[a]Reaction carried out at C = 0.1 M of **142f** on 0.1 mmol scale with 2 eq. of formalin. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]3Å MS (≈17 mg) were added.

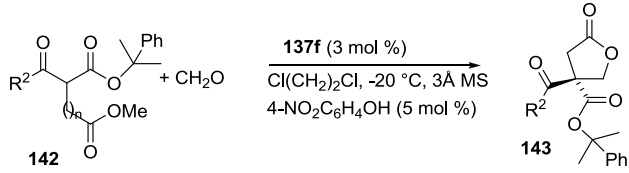
The presence of an acidic additive significantly improved the activity of the bifunctional organocatalyst and to a lesser extent the enantiocontrol. It is plausible to suppose that the

additive might help to decrease catalyst self-aggregation leading to more active monomeric forms.[162]

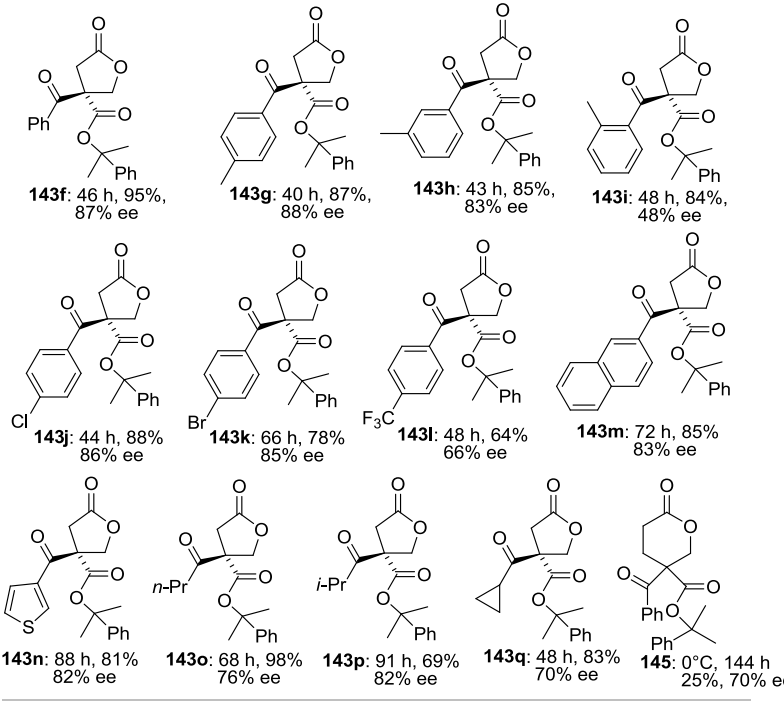
Under optimized reaction conditions, the reactivity of different acylated succinic esters **142** was investigated to study the scope of the cascade reaction to γ-butyrolactones **143** (Table 3.6).

The scope of the reaction was found to be quite general for various functionalized succinic esters. Either electron-donating or electron-withdrawing groups can be introduced on the phenyl ring of the aroyl residue affording the products in high yields and very good *ee* (up to 88%). (**143f-l**). Only substitution at the *orto*-position affects negatively the enantioselectivity (**143i**). The 2-naphthyl and heteroaromatic substituted reagents **142m**,**n** showed to be good substrates for the process (**143m**,**n**). Remarkably, compounds **142o-q**, bearing either linear or sterically demanding alkyl groups, were also checked in the process and the products (**143o-q**) were recovered in very good yield and the enantioselectivity was only slightly affected.

Table 3.6 Substrate scope of the asymmetric cascade aldol/lactonization sequence.[a]



142f, R^2= Ph, n= 1; **142g**, R^2= 4-MeC_6H_4, n= 1; **142h**, R^2= 3-MeC_6H_4, n= 1;
142i, R^2= 2-MeC_6H_4, n= 1; **142j**, R^2= 4-ClC_6H_4, n= 1; **142k**, R^2= 4-BrC_6H_4, n= 1;
142l, R^2= 4-$CF_3C_6H_4$, n= 1; **142m**, R^2= 2-Naphthyl, n= 1;
142n, R^2= 3-Thiophenyl, n=1; **142o**, R^2= n-Propyl, n= 1; **142p**, R^2= *i*-Propyl, n= 1;
142q, R^2= Cyclopropyl, n= 1; **142r**, R^2= Ph, n= 2

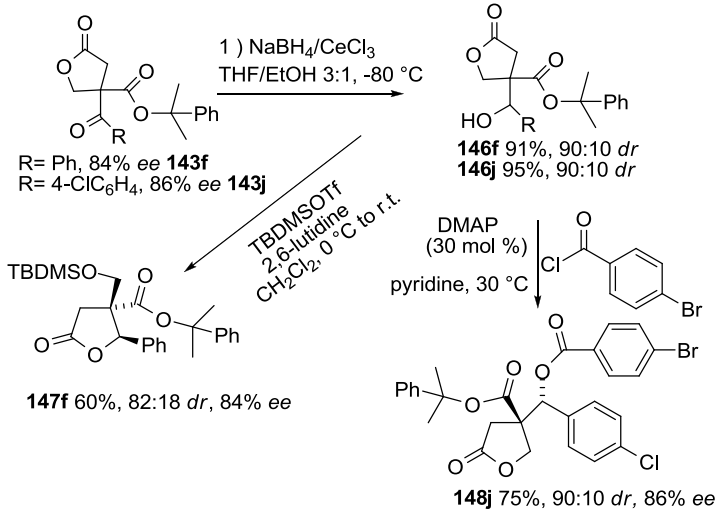


[a]Reaction carried out at C = 0.1 M of **142** on 0.1 mmol scale with 2 eq. of formalin and 3Å MS (≈17 mg). *ee* values determined by chiral HPLC analysis. Yields values refer to isolated products.

Finally, a preliminary investigation on the applicability of the process for the synthesis of enantioeriched γ,γ-disubstituted-δ-valerolactones was undertaken. 1-Cumyl-5-methyl-2-benzoylpentanedioate **142r** was reacted under optimal conditions, but at 0 °C, and the corresponding δ-valeroactone **145** was formed, after predictably longer reaction time, in 25% yield, but with an encouraging 70% *ee*.

Additionally, we demonstrated that the paraconic acid derivatives **143** can be transformed into diversely functionalized hydroxy-γ-butyrolactone derivatives, important motives in natural products and synthetically useful building blocks.[163]

γ-Butyrolactones **143** were stereoselectively converted into β-(hydroxyalkyl)-γ-butyrolactones **146** and **147** bearing contiguous quaternary and tertiary stereocentres (Scheme 3.15). Treatment of enantioenriched compounds **143f-j** with $NaBH_4/CeCl_3$ at -80 °C afforded β-(hydroxyalkyl)-γ-butyrolactones **146f-j** in high yield and 90:10 *dr*. Benzoylation of alcohol **146j** led to product **148j** in 75% yield.



Scheme 3.15 Elaboration of lactones **143** to β-(hydroxyalkyl)-γ-butyrolactones.

By means of benzoylation of alcohol **146j** we succeeded to obtain a single crystal of product **148j**, whose X-ray analysis on major diastereoisomer, enabled us to assign relative and absolute configuration of the stereocentres as (*R*,*R*). So, we could assign, by analogy, the (*R*)-absolute configuration to γ-butyrolactones **143** (Figure 3.7).

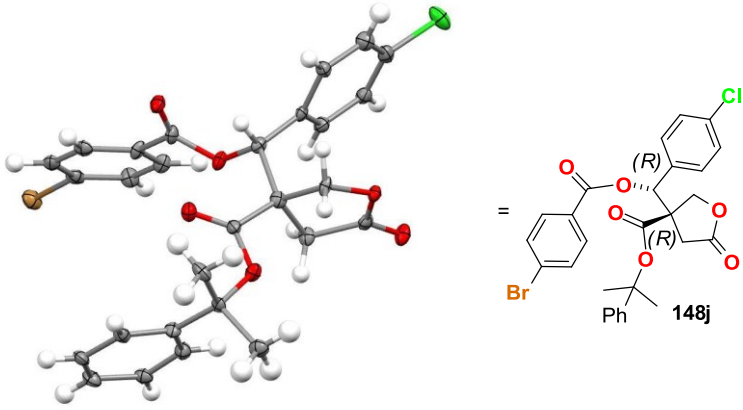
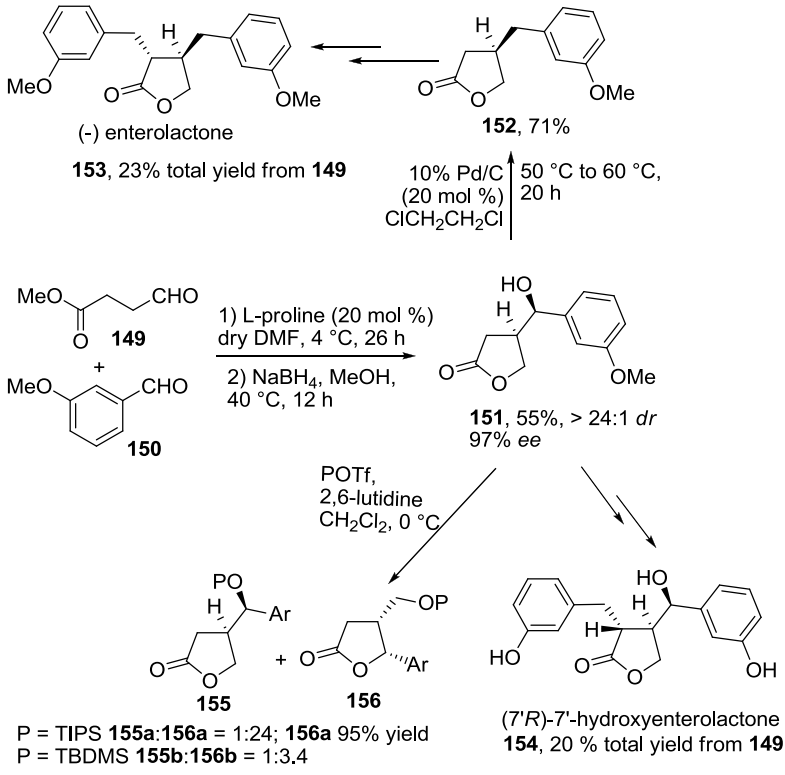


Figure 3.7 Crystallografic structure of **148j** by X-ray analysis. **ORTEP plot** with 30% probability ellipsoids.

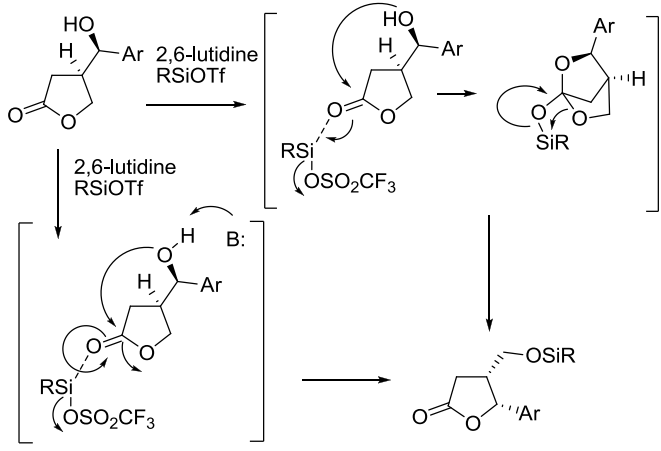
Hydroxy-γ-butyrolactones are challenging targets to be synthesized: only a small number of stereoselective methodologies have been reported and the β-(hydroxyalkyl)-γ-butyrolactones obtained have only two contiguous tertiary stereocentres.[137,164]

For example, in 2009 the Hajra's group, reported a short synthesis of (-)-enterolactone **153** and (7'*R*)-7'-hydroxyenterolactone **154**, achieved by means of an organocatalyzed asymmetric cross-aldol reaction of aldehydes **149** and **150** and a base-mediated alkylation of lactones **151** and **152** (Scheme 3.16).[164b] Enterolactone **153**, found in human and animal urine, is involved in the metabolism of plant lignans and displays antiestrogenic and anticarcinogenic activities among other biological properties.[165] (7'*R*)-7'-hydroxyenterolactone **154** was detected in human urine and is also derived from the plant lignan 7'-hydroxymetairesinol.[166]



Scheme 3.16 Asymmetric synthesis of β-(hydroxyalkyl)-γ-butyrolactones bearing tertiary stereocentres.

During the synthesis of **154**, the authors attempted to protect the hydroxyl group of **151** with silylating reagents and they observed the formation of a rearranged lactone **156**. No epimerization was observed during the rearrangement. They proposed that activation of the carbonyl oxygen with RSiOTf promotes the translactonization via either stepwise or a concerted mechanism (Scheme 3.17).



Scheme 3.17 Proposed pathways for translactonization.

In a similar way, our diastereoisomeric mixture of enantioenriched compound **146f** (90:10 *dr*) was treated with TBDMSOTf and 2,6-lutidine in CH_2Cl_2[116b,167] and the rearranged *O*-protected-β,γ-substitued-γ-butyrolactone **147f** was isolated in 60% yield and 82:18 *dr* (Scheme 3.15). No erosion of the enantioselectivity over the two-step sequence, occurred as verified by chiral HPLC analysis on major diastereomer **147f**, whose relative configuration was established by NOESY experiment to be (3*R*,4*R*)-**147f**.[iv]

[iv] See Experimental Section.

CONCLUSIONS

In summary, we developed the first straighforward approach to enantioenriched β,β-disubstituted γ-butyrolactones through a cascade aldol/lactonization process. A variety of acylated succinic esters have been reacted with aqueous formaldehyde in the presence of 3 mol % loading of cinchona alkaloid derived squaramide and 4-nitrophenol as additive. Exploiting simple starting materials and working under mild reaction conditions we were able to obtain highly challenging γ-butyrolactones, bearing an all-carbon quaternary stereocentre at the remote β-position. This methodology allows the preparation of functionalized paraconic acid derivatives, in high yields and fairly good level of enantioselectivity (up to 88% *ee*).

The methodology proved to be suitable to access γ,γ-disubstitued-δ-valerolactones. Interestingly, this work represents the first example of enantioselective hydroxymethylation reaction of 2-substituted-1,3-dicarbonyl compounds catalyzed by an organocatalyst.

Finally, we demonstrated that these products can be elaborated to prepare valuable hydroxy γ-butyrolactones, bearing contiguous tertiary and quaternary stereocentres, until now not accessible by alternative methods.

4. ORGANOCATALYTIC ENANTIOSELECTIVE SYNTHESIS OF α-NITROEPOXIDES VIA KINETIC RESOLUTION

4.1 Background

A large number of natural and biologically active molecules exhibit chiral oxiranes in their structure and their activity often lies in the epoxy functional group.

For example fumagillin and epoximicin in Figure 4.1 bind covalently proteases, trapping them by means of their reactive epoxide.[168] Fumagillin inhibits the methionine aminopeptidase type 2, thus repressing the angiogenesis[169] (the formation of new blood vessels). For this property fumagillin and its derivatives are thought to have anti-cancer activity. Epoxomicin is able to inhibit the degradation of proteins by the proteasome.[170]

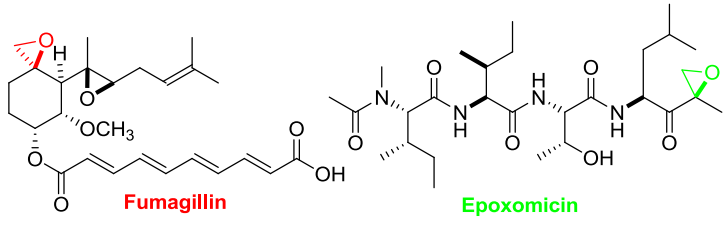


Figure 4.1

Torreyanic acid, isolated from fungal species *P. microspora*, causes cell death by apoptosis in human cancer cells and the monomeric jesterone, isolated from *P. jester,* is active against the oomycetous

fungi, which are some of the most pathogenic fungi (Figure 4.2).[171,172]

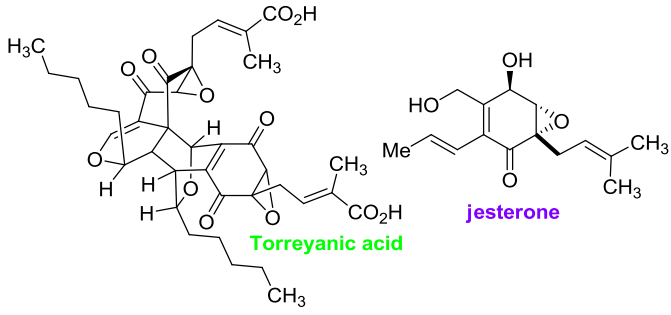


Figure 4.2

Manumycin antibiotics are a subset of widely distributed natural compounds having an epoxyquinone structure endowed with interesting biological properties such as, among others, antitumor, antibacterial, antifungal and enzyme-inhibition.[172, 173]

Manumycin antibiotics (Figure 4.3) are characterized by having in their structure the active epoxyaminocyclohexanone central core. The most known member of this large family of natural compounds, isolated from *Streptomyces* species,[174] is manumycin A (Figure 4.3). Generally, manumycins have biological activities such as antibacterial, especially against Gram-positive bacteria, antifungal, cytotoxic, elastase and Ras farnesyltransferase[175] inhibitory effects.

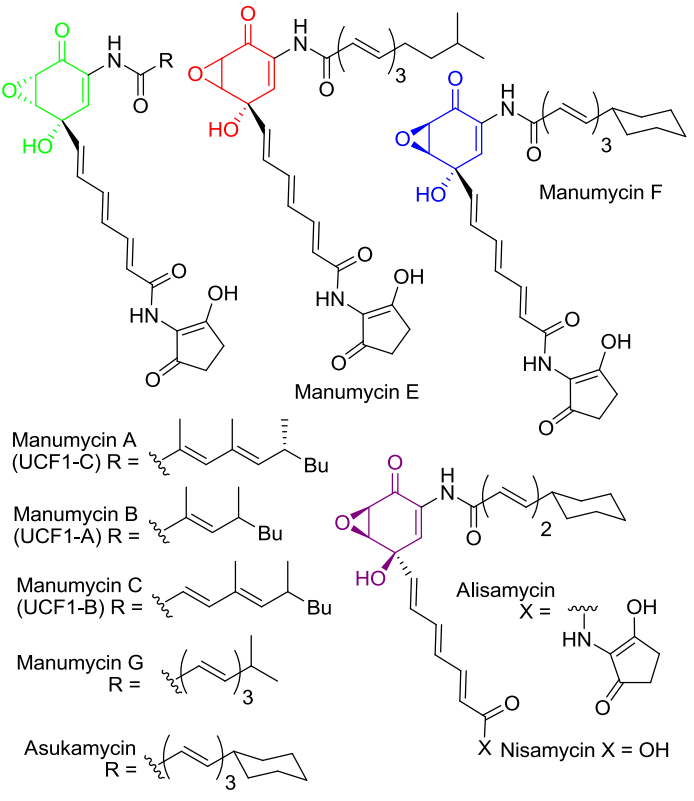


Figure 4.3 Manumycins.

The triptolide is another example of strongly biologically active compound (Figure 4.4). It is a diterpenoid triepoxide whose three epoxy groups have been recognized to determine its biological activities.[176] Triptolide is the principal bioactive constituent of *Tripterygium wilfordii* Hook F and is a potent antitumoral, showing in vivo and in vitro activities against mouse models of polycystic kidney disease[177] and pancreatic cancer[178]. It exhibits also anti-inflammatory, immunosuppressive, anti-fertility and anti-cystogenesis effects. Unfortunately, its toxicological properties

towards multiple tissues and organs limit its therapeutic potential and many efforts to overcome its toxicity by chemical modifications are being made.[176]

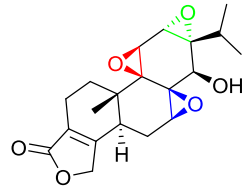


Figure 4.4 Triptolide.

All the examples illustrate just some of the diverse natural substances whose biological activity can be ascribed to chiral epoxy units. Optically active epoxides are also highly useful intermediates exploited in total syntheses.[172,173,176] In fact, they are able to undergo regio- and stereoselective ring opening by nucleophiles giving access to a wide variety of differently functionalized products.[179]

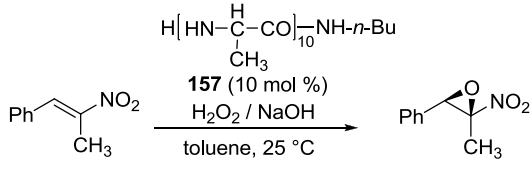
4.1.1 Epoxidation of nitroalkenes

Generally, the epoxides can be synthesized by different methods: olefin peroxidation, intramolecular S_N2 substitution (including the Darzens reaction), the Corey-Chaykovsky reaction (sulfur ylides with carbonyl compounds) and nucleophilic epoxidation. With eletron-rich olefins, alkene acts as the nucleophile and peroxide as the electrophile and the reaction proceeds via the so-called concerted "butterfly mechanism". When an alkoxide ion can intramolecularly displace a leaving group in the molecule, a S_N2 substitution occurs leading to the formation of an oxirane ring. In order to epoxidize electron-poor olefins, such as enones, enals or

acrylate derivatives, nucleophilic epoxidation conditions are required. A nucleophilic peroxide species, generated from an alkyl hydroperoxide under basic conditions, attacks in a conjugate fashion the electron-poor alkene. Then ring closure occurs in a non-concerted pathway. Asymmetric epoxidation of alkenes is the most exploited methodology to synthesize chiral epoxides.[7,180] In the context of asymmetric nucleophilic epoxidation reactions, in recent years, a great variety of methods for the epoxidation of simple and functionalized enones[181] and enals[182] have been developed.

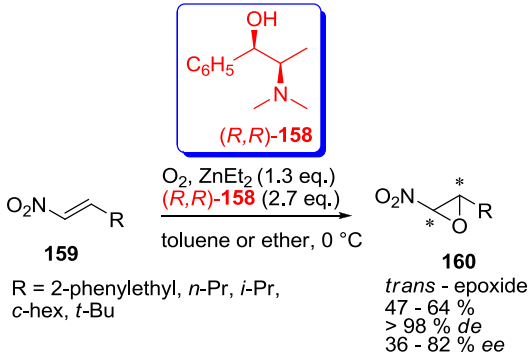
On the contrary, the asymmetric epoxidation of nitroalkenes has proven to be a challenging transformation and, indeed, only a few diasteroselective methods have been reported.[183] Nitroolefins are one of the most attractive Michael acceptors, thanks to the synthetic usefulness of nitro group, which can be readily transformed into a variety of functional groups such as ketone, carboxylic acid, amine, nitrile oxide, hydrogen, and so on.[184]

In the 1980s, a pioneering attempt at an enantioselective epoxidation was published by Juliá and Colonna, who illustrated the epoxidation of nitroalkenes catalyzed by polyaminoacids in the presence of $NaOH/H_2O_2$. This process afforded the epoxide in nearly racemic form (7% *ee*) (Scheme 4.1).[18a,185]



Scheme 4.1 Juliá-Colonna epoxidation of *trans*-β-methyl-β-nitro-styrene.

Until today, only one example of epoxidation of nitro-olefins with modest success has been reported. In 1998, Enders developed a zinc-mediated enantioselective epoxidation of aliphatic *trans*-disubstituted nitroalkenes with molecular oxygen (Scheme 4.2).[186]



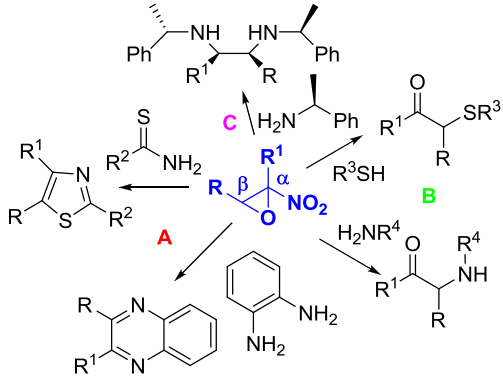
Scheme 4.2 Enantioselective synthesis of aliphatic *trans*-2-nitro-oxiranes.

The epoxidation was performed by using O_2 in the presence of diethylzinc and an over-stoichiometric amount of the chiral reagent *N*-methyl pseudo-ephedrine **158**.

4.1.2 Ring-opening of α-nitroepoxides

Racemic α-nitroepoxides are useful synthons in organic synthesis thank to the regioselective ring-opening reactions that they can undergo at the β-position in the presence of nucleophiles (Scheme 4.3). The preparation of racemic α-nitroepoxides is easily achieved reacting nitro-olefins and hydrogen peroxide under basic conditions. The first studies on the reactivity of nitroepoxides with several nucleophiles dates back as early as 1970.[187] Racemic α-nitroepoxides can be transformed into heterocycles such as 1,3-thiazoles and quinoxalines (Scheme 4.3A),[187,188] functionalized α-

aminoacids[189] and carbonyl compounds (Scheme 4.3B)[187,190]. Recently, González reported the stereoselective synthesis of vicinal diamines starting from racemic α-nitroepoxides through a dynamic kinetic asymmetric ring-opening / reductive amination sequence. The α-nitroepoxides were treated with chiral primary amines affording diastereomeric mixtures of aminoimines followed by stereoselective imine reduction in a one-pot manner (Scheme 4.3C).[191]



Scheme 4.3 Synthetic elaborations of α-nitroepoxides.

It is interesting to note that the chemical behaviour of α-nitroepoxides towards nucleophiles could be, virtually, considered as that of α-keto carbocation (Figure 4.5).[190]

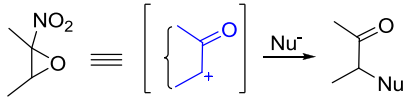
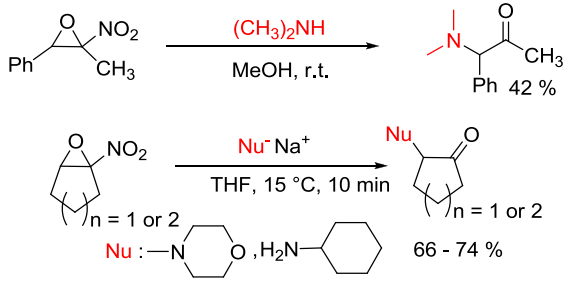


Figure 4.5

In particular, the regioselective ring-opening of nitro-oxiranes at the β-position by amines has been reported by Newman and Angier[187] in 1970 and Vankar[190] in 1991 (Scheme 4.4).



Scheme 4.4 First examples of ring opening of α-nitroepoxides by amines.

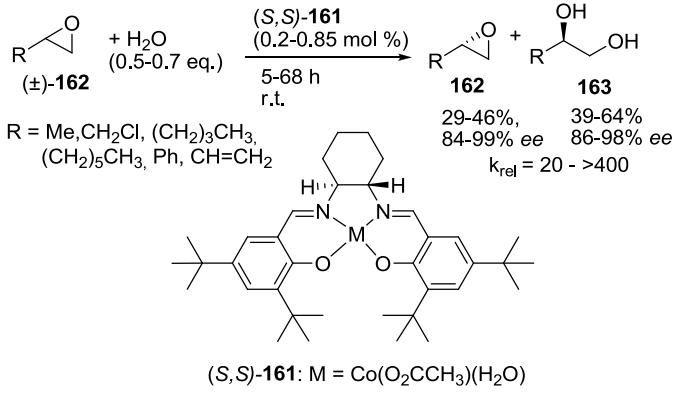
These reports and the paucity of asymmetric epoxidation reactions performed on nitroalkenes inspired us to develop a methodology for the asymmetric epoxidation of nitroalkenes. Having previously disclosed that bifunctional organocatalysts, such as prolinols and tertiary amine thioureas, are able to promote the asymmetric epoxidation of *trans*-chalcones and electron-poor terminal alkenes, we attempted, without success, the enantioselective epoxidation of *trans*-β-methyl-β-nitro-styrene.[192] Consequently, we decided to achieve our target exploiting, as an alternative process, the aminolitic kinetic resolution of racemic α-nitroepoxides.

4.1.3 Kinetic resolution of racemic epoxides

The kinetic resolution of racemic compounds (see paragraph 2.3) represents a highly valuable and sometimes unique strategy to synthesize chiral products.

The first pioneering example of kinetic resolution, performed on terminal racemic epoxides, has been reported by Jacobsen in 1997.[193] In this elegant work, he developed an efficient asymmetric

hydrolytic kinetic resolution of racemic terminal epoxides **162** using water as the only reagent, without solvents and low loading (0.5 mol %) of a recyclable chiral cobalt-based salen complex catalyst **161** (Scheme 4.5). Highly valuable enantioenriched terminal epoxides and 1,2-diols, **163** were thus obtained. Due to the high values of k_{rel} of this process (> 400 for propylene oxide, 290 and 260 for 1-hexene and 1-octene oxide, respectively) both recovered epoxides and chiral 1,2-diols were isolated in high yields (close to the theoretical maximum) and excellent enantioselectivity (84-99% *ee*).

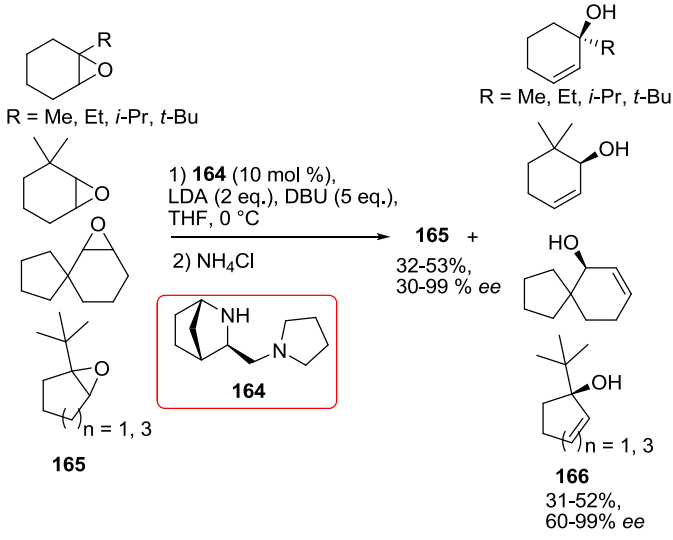


Scheme 4.5 Hydrolytic kinetic resolution of terminal epoxides.

This class of racemic epoxides is inexpensive and easily available, the reaction proceeds with water under solvent-free conditions. These appealing features, together with the high efficiency of the process, made it applicable at an industrial scale.[110,194]

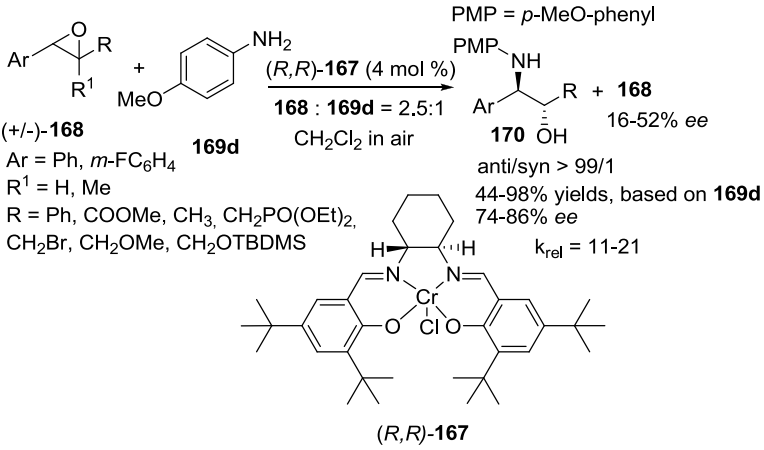
Another example of kinetic resolution of racemic epoxides was reported by Andersson et al. in the 2000s (Scheme 4.6).[195] They reported the kinetic resolution of cyclic epoxides via catalytic

enantioselective rearrangement to allylic alcohols using the Li-salt of (1*S*,3*R*,4*R*)-3-(pyrrolidinyl)methyl-2-azabicyclo [2.2.1] heptane **164**, an excess of DBU and LDA as the stoichiometric base. Unreacted epoxides and allylic alcohols were obtained in moderate to high *ee*s.



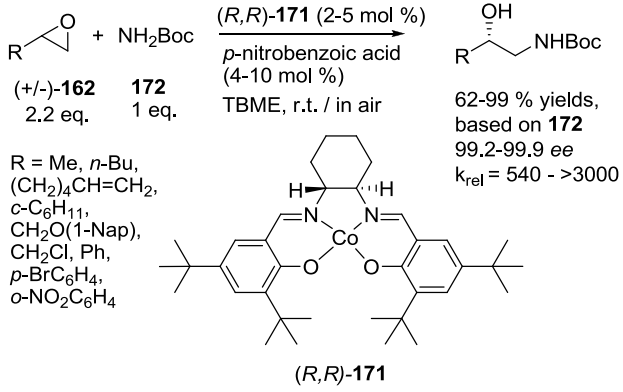
Scheme 4.6 Kinetic resolution of cyclic epoxides to allylic alcohols.

In 2004, Melchiorre and Bartoli reported the first asymmetric aminolysis of *trans*-aromatic epoxides with anilines. The process was catalyzed by a commercially available [Cr(Salen)Cl] Lewis acid **167** and afforded *anti*-β-amino alcohols **170** in up to 99% *ee* with complete regio- and diasteroselectivity (Scheme 4.7).[196]



Scheme 4.7 Aminolytic kinetic resolution (AKR) of aromatic *trans*-epoxides.

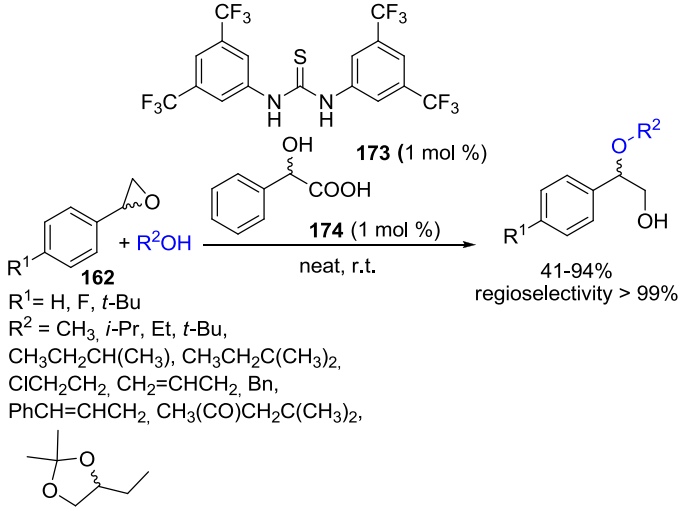
The same research group developed the asymmetric catalytic kinetic resolution of racemic terminal epoxides for the synthesis of aliphatic and aromatic *N*-Boc and *N*-Cbz-protected 1,2-amino alcohols. The reaction was catalyzed by the (salen)Co^{III} complexes **171** using for the first time carbamates as nucleophiles. The levels of selectivity observed were exceptionally high (k_{rel} up to >3000) (Scheme 4.8). [197]



Scheme 4.8 AKR of terminal epoxides with *tert*-butyl carbamate.

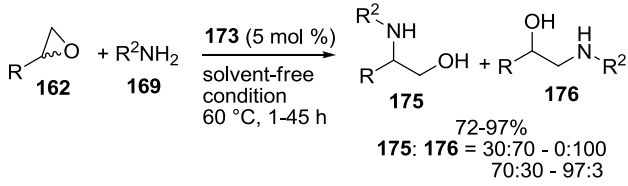
In the field of organocatalysis, it has been reported that hydrogen-bonding donors such as hexafluoro-2-propanol,[198] achiral ureas[199] and thioureas[200] are able to assist the regioselective ring-opening reaction of epoxide affording differently substituted alcohols.

For example, Schreiner in 2008 reported the regioselctive alcoholysis of styrene oxides using an organocatalytic system composed of two Brønsted acids, mandelic acid **174** and *N*,*N*-bis-[3,5-bis-(trifluoromethyl)phenyl]-thiourea **173** (Scheme 4.9).[200a]



Scheme 4.9 Alcoholysis of styrene oxides promoted by cooperative Brønsted acid-type organocatalysis.

In 2010, Chimni illustrated a thiourea catalyzed aminolysis of epoxides under solvent-free conditions (Scheme 4.10).[200b] The authors proved by ^{13}C NMR data and DFT calculations that the regioselectivity of the reaction is controlled by the electronic nature of the substituent on the styrene oxide.

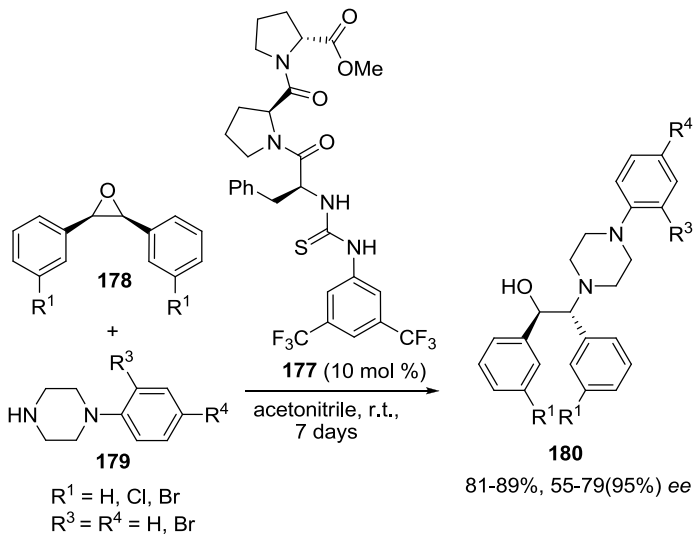


R = Ph, *p*-$OMeC_6H_4$, *p*-FC_6H_4, *p*-ClC_6H_4,
p-MeC_6H_4, *p*-$NO_2C_6H_4$, *m*-$NO_2C_6H_4$, $PhOCH_2$,
o-$MeC_4H_4OCH_2$, *m*-$MeC_4H_4OCH_2$, *p*-$MeC_4H_4OCH_2$,
p-$ClC_4H_4OCH_2$, $CH_2=CHCH_2OCH_2$, $CH_3(CH_2)_8CH_2$

R^2 = Ph, *p*-$OMeC_6H_4$, *o*-$OMeC_6H_4$, *p*-ClC_6H_4,
m-ClC_6H_4, *p*-FC_6H_4,o-$NH_2C_6H_4$, *o,m*-$NH_2CH_3C_6H_3$,
Nap, hexyl, butyl, pyperidine, pyrrolidine

Scheme 4.10 Thiourea catalyzed aminolysis of epoxides.

Very recently, a few examples on the desymmetrization of *meso*-epoxides promoted by chiral organocatalysts, such as sulfinamides[201] and phosphoric acids,[202] have been developed. In 2014, Chimni et al. developed an enantioselective ring opening of *meso*-stilbene oxides **178** with *N*-phenylpiperazines **179** catalyzed by a peptidyl thiourea derivative **177**. β-Amino alcohols **180** were obtained with up to 95% *ee* after crystallization (Scheme 4.11).[203]



Scheme 4.11 Desymmetrization of *meso*-stilbene oxides organocatalyzed by a peptidyl thiourea derivative.

The authors reasoned that the catalyst, bearing a thiourea unit, would activate the epoxide ring through double hydrogen-bonding and the peptide, chosen intentionally with a β-turn scaffold, would anchor the nucleophile in a chiral environment (Figure 4.6).

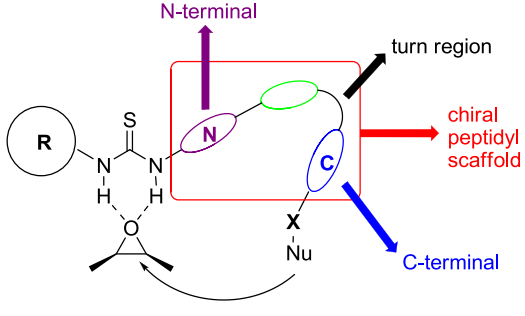
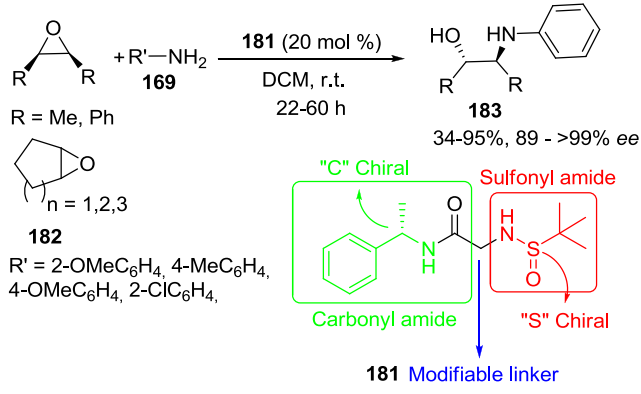


Figure 4.6 Proposed activation model of the reagents by a peptidyl thiourea organocatalyst.

At the same time, independently, Kureshy reported the asymmetric ring-opening reaction of *meso*-epoxides **182** with aniline catalyzed by a chiral sulfinamide **181** as the organocatalyst. They obtained chiral β-amino alcohols **183** in high yield (up to 95%) and excellent enantioselectivity (up to 99% *ee*) (Scheme 4.12).[201]



Scheme 4.12 Desymmetrization of *meso*-epoxides with anilines catalyzed by chiral sulfinamide.

A series of ^{1}H- and ^{13}C-NMR experiments was performed in $CDCl_3$ in order to investigate the interactions among the catalyst and the two reagents and a mechanism for the activation has been proposed (Figure 4.7).

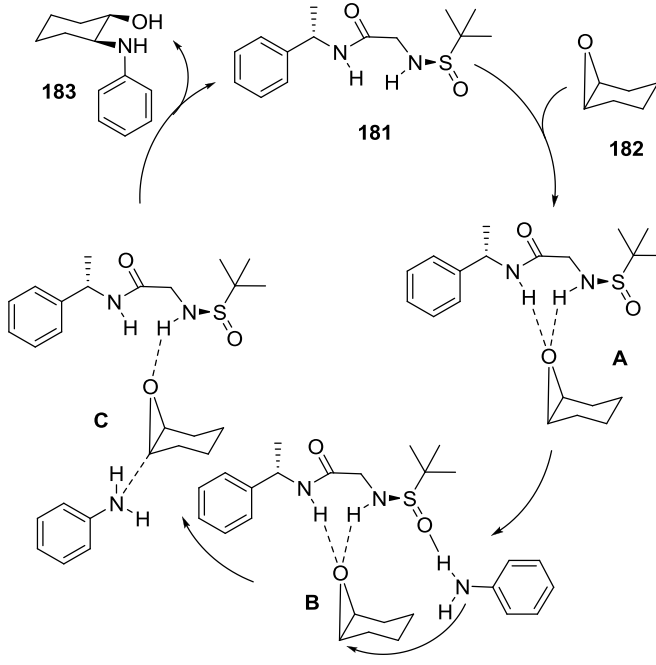
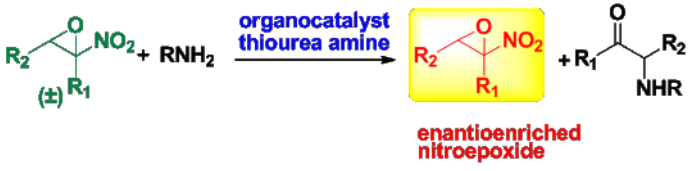


Figure 4.7 Proposed catalytic cycle.

4.2 Results and Discussion

Given the lack in literature of a methodology for the synthesis of enantioenriched β-substituted α-nitroepoxides, we decided to embark upon this study. As anticipated in the previous paragraph, at the outset of our study, we tried to epoxidize β-methyl-β-nitrostyrene with different bifunctional organocatalysts without success.[192] However, we succeeded to achieve our target exploiting an aminolytic kinetic resolution of racemic α-nitroepoxides. The kinetic resolution proceeds through a completely regioselective ring-opening reaction by aniline, organocatalyzed by a bifunctional cinchona-alkaloid derived thiourea (Scheme 4.13).



Scheme 4.13 Aminolytic kinetic resolution of racemic α-nitroepoxides promoted by a bifunctional thiourea.

We reasoned that a bifunctional organocatalyst would activate simultaneously the epoxide and the aniline via general acid-base catalysis in a chiral environment, thus leading to the preferential regioselective opening of one enantiomer of the α-nitroepoxide (Figure 4.8).

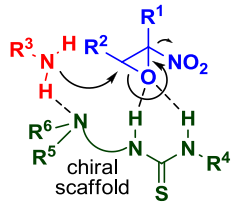


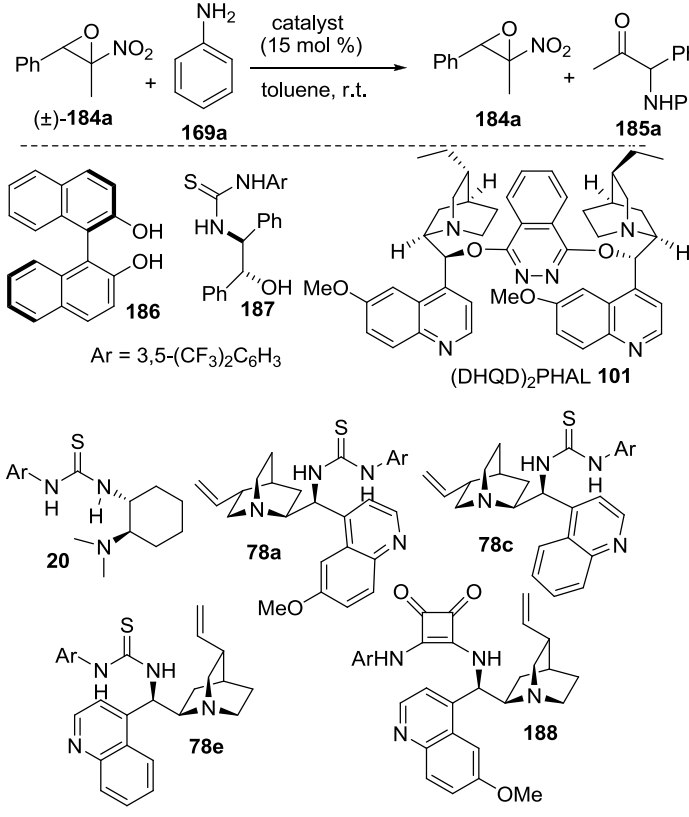
Figure 4.8 Proposed activation model of reagents by organocatalyst in the AKR.

trans-β-Methyl-β-nitrostyrene was epoxidized with the well-known H_2O_2/NaOH system.[187] Racemic *trans*-2-methyl-2-nitro-3-phenyloxirane **184a** was treated with aniline **169a** in the presence of 15 mol % of (*R*)-BINOL **186** at room temperature in toluene (entry 1, Table 4.1). At first, a catalyst bearing only H-bonding donating groups was employed to observe if it could be active enough for the ring-opening of epoxide. An excess of aniline **169a** with respect to the epoxide **184a** was added to neutralize nitrous acid formed as a deleterious by-product. In the presence of this organocatalyst, conversion of the epoxide to the expected ketone **185** was very low after 48 h (entry 1). When using a similar organocatalyst, the amino alcohol derived thiourea **187**, the conversion to the ketone slightly improved (entry 2), but the epoxide was isolated with 2% *ee* value. A Brønsted base catalyst $(DHQD)_2PHAL$ **101** provided a similar result, in terms of conversion and enantioselectivity (entry 3). A significant improvement was observed when a bifunctional organocatalyst, bearing both H-bonding and Brønsted base groups in its structure, was used. Indeed, Takemoto's thiourea **20** afforded unreacted epoxide in 50% yield and an enacouraging 23% *ee* (entry 4). This

result demonstrated that a synergistic activation of both epoxide and aniline by the bifunctional organocatalyst, as proposed in Figure 4.8, is needed to develop an efficient process of kinetic resolution.

Next, the catalytic activity of other bifunctional readily available promoters was investigated. Cinchona derived thiourea **78a** afforded a similar result in term of yield but the enantioselectivity of the process was lower (entry 5). The *epi*-cinchonidine derived thiourea **78c** performed more effectively, allowing the isolation of the unreacted epoxide in 63% yield and 30% *ee* (entry 6). Its *pseudo*-enantiomer **78e** proved to be a less efficient catalyst (entry 7). The *epi*-quinidine derived squaramide **188**, was also examined in the process. It catalyzed the AKR leading to the same result achieved with *pseudo*-enantiomeric amine thiourea **78a** (entry 8).

Table 4.1 Screening of catalysts in the model aminolytic kinetic resolution of (±)-**184a** with aniline.[a]

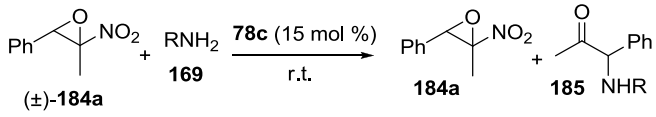


entry	cat.	t (h)	**185**[b]	yield **184a** (%)[c]	*ee* **184a** (%)[d]
1	**186**	48	12	nd	nd
2	**187**	48	24	68	2
3	**101**	48	21	74	6
4	**20**	65	40	50	-23
5	**78a**	69	37	51	-11
6	**78c**	48	33	63	-30
7	**78e**	48	40	47	28
8	**188**	48	35	59	6

[a]All reactions were carried out using (±)-**184a** (0.15 mmol), **169a** (0.18 mmol), catalyst (15 mol %) in toluene (1.5 mL). [b]Determined by ^{1}H NMR analysis. [c]Isolated yield. [d]Determined by chiral HPLC analysis.

Having identified the best-perfoming catalyst **78c**, the aminolytic kinetic resolution of the model racemic epoxide **184a** was further optimized (Table 4.2). Aromatic amines of different steric demand, 1- and 2-naphthyl amines **169b** and **169c**, did not improve the process (entries 1 and 2).

Table 4.2 Optimization of reaction conditions.[a]



entry	R	solvent	t (h)	**185** (%)[b]	yield **184a** (%)[c]	*ee* **184a** (%)[d]
1	1-naphthyl	toluene	63	34(**b**)	64	24
2	2-naphthyl	toluene	25	32(**c**)	61	20
3	4-$MeOC_6H_4$	toluene	65	38(**d**)	47	40
4	Benzyl	toluene	46	nd	34	6
5	Ph	$CHCl_3$	44	30(**a**)	65	18
6	Ph	*t*BuOMe	46	52(**a**)	43	22
7	Ph	*p*-xylene	48	36(**a**)	59	30
8[e]	Ph	toluene	113	65(**a**)	28	59
9[f]	Ph	toluene	113	55(**a**)	38	50
10[g]	Ph	toluene	96	70(**a**)	28	72
11[h]	Ph	toluene	96	35(**a**)	62	-

[a]All reactions were carried out using (±)-**184a** (0.15 mmol), **169** (0.18 mmol), **78c** (15 mol %) solvent (1.5 mL). [b]Determined by ^{1}H NMR analysis. [c]Isolated yield. [d]Determined by chiral HPLC analysis. [e]Reaction carried out with 20 mol % of **78c**, 1.5 eq. of aniline at $C_{\mathbf{184a}}$ (0.2 M). [f]Reaction carried out with 20 mol % of **78c**, 3.0 eq. of aniline at $C_{\mathbf{184a}}$ (0.05 M). [g]Reaction carried out with 20 mol % of **78c**, 3.0 eq. of aniline at $C_{\mathbf{184a}}$ (0.1 M). [h]Reaction carried out without catalyst, with 3.0 eq. of aniline at $C_{\mathbf{184a}}$ (0.1 M).

Slightly more basic *p*-anisidine gave inferior results compared to aniline (entry 3). More nucleophilic amines, such as benzyl amine

provided the unreacted epoxide with lower *ee* and the formation of other unidentified by-products was observed (entry 4).

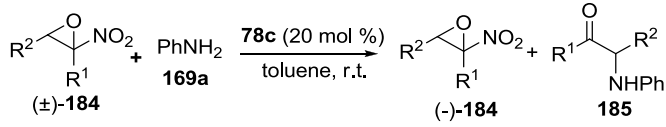
Nonpolar aromatic solvents proved to be the most suitable media for the reaction (entries 5-7), according to what usually observed in non-covalent catalysis. Among the aromatic solvents tested for the reaction between (±)-**184a** and aniline **169a**, toluene was found to be the most effective (Table 4.1, entry 6).

The reaction was further optimized in toluene varying the reagents ratio and the concentration. The catalyst loading and the equivalents of aniline were increased to accelerate the reaction. The AKR were carried out with 20 mol % of catalyst loading and 3 equivalents of aniline at different concentrations in toluene (entries 8-10). The best result was observed working at C = 0.1 M of epoxide **184a**. Under these conditions enantioenriched epoxide **184a** was recovered in 28% yield and 72% *ee* (entry 10).

Finally, a control experiment was performed under the same conditions without the catalyst (entry 11). Unfortunately, the epoxide ring-opening proved to be not a negligible process, thus partially contributing to affect the efficiency of the kinetic resolution.

Under the optimum reaction conditions illustrated in Table 4.2, entry 10, the scope of the aminolytic kinetic resolution was extended to various α-nitroepoxides (Table 4.3).

Table 4.3 Scope of the AKR of α-nitroepoxides with aniline organocatalyzed by *epi*-cinchonidine derived thiourea.[a]



entry	R^2	R^1	t (h)	yield **185** (%)[b]	yield **184** (%)[b]	*ee* **184** (%)[c]	k_{rel}[d]
1	Ph	Me	96	65	28 (**a**)	72	3.5
2	4-MeC_6H_4	Me	86	79	17 (**e**)	84	3.1
3	4-ClC_6H_4	Me	91	67	29 (**f**)	86	5.9
4	4-$CF_3C_6H_4$	Me	158	48	36 (**g**)	77	5.5
5	2-naphthyl	Me	84	72	26 (**h**)	95	5.8
6	Ph	Et	91	59	21 (**i**)	92	4.5
7	3-MeC_6H_4	Et	89	66	31 (**j**)	92	7.1
8	4-BrC_6H_4	Et	86	64	33 (**k**)	90	7.3
9	3,4-$Cl_2C_6H_3$	Et	86	47	35 (**l**)	61	3.6
10	$Ph(CH_2)_2$	Me	115	28	35 (**m**)	16	-

[a]All reactions were carried out using (±)-**184** (0.2 mmol), **169a** (0.6 mmol), **78c** (20 mol %), toluene (2 mL). [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]The values for k_{rel} were calculated using the equation k_{rel} = ln [(1-*c*)(1-*ee*)]/ ln [(1-*c*)(1+*ee*)], where *ee* is the enantiomeric excess and (1-*c*) is the yield/100 of recovered epoxide.

The aminolytic kinetic resolution of different α-nitroepoxides has shown that both electron-donating and withdrawing groups in the aromatic ring of the α-methyl or α-ethyl nitroepoxide (entries 1-4, 6-9) and 2-naphthyl group (entry 5) are well-tolerated in the process. The unreacted epoxides were isolated in acceptable yield and good to high enantioselectivity (up to 95% *ee*). Finally, we investigated the applicability of this protocol to an aliphatic α-

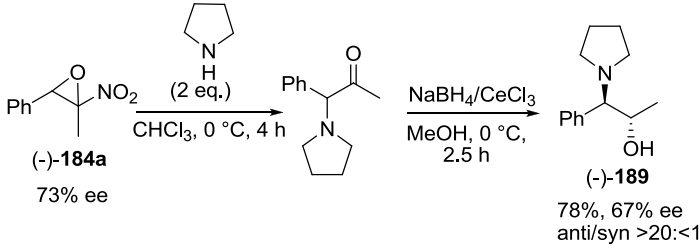
nitroepoxide **184m**. However, the AKR proved to be a poorly efficient process (entry 10), as the epoxide was recovered in 35% yield and 16% *ee*. The *ee* values of the α-amino ketones **185** were not calculated because low values have to be expected. This assumption is based on the following considerations: *i*) the estimated stereoselectivity factors of the AKR,[v] shown in Table 4.3, are modest ($3 < k_{rel} < 7$) and, how explained in paragraph 2.3, low *ee* values for the α-amino ketone products are expected; *ii*) it has been shown that enantiomerically enriched α-amino ketones are susceptible of partial racemization under basic conditions.[204] Indeed, as an example, the amino ketone **185a**, reported in entry 1 of Table 4.3, was recovered with 16% *ee*. It is important to note that, k_{rel} values are underestimated due to the contribution of the background ring-opening reaction by aniline.

We have also demonstrated, for the first time, that enantiomerically enriched α-nitro epoxides can be useful intermediates in asymmetric synthesis. Indeed, they have been transformed into chiral *anti*-1,2-amino alcohols through a diasteroselective one-pot ring-opening reaction with pyrrolidine followed by reduction of the ketone intermediate (Scheme 4.14).

In this context, the Jackson's[183a,b] and Aggarwal's[205] groups illustrated a variety of ring-opening reactions of diastereoisomerically pure arylthionitroepoxides or spirocyclic bis-sulfinyl oxiranes with amines, affording enantioenriched α-amino

[v] First order kinetics was assumed for the calculation of the stereoselectivity factors. See paragraph 2.3.

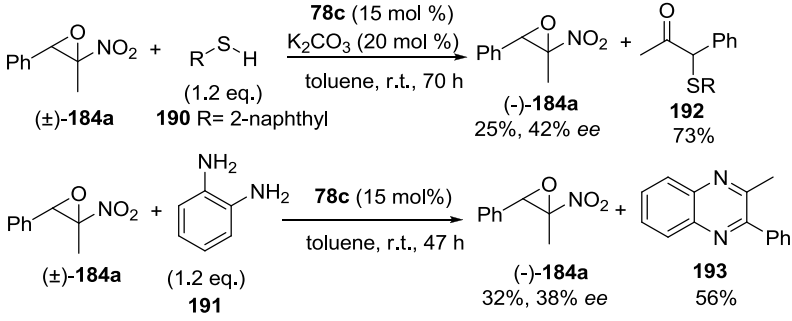
thioesters and amides, respectively. As expected these transformations occurred with inversion of configuration, thus demonstrating to be stereospecific.



Scheme 4.14 Stereoselective one-pot ring-opening/reduction sequence to *anti*-1,2-amino alcohol **189**.

Enantiomerically enriched (-)-**184a** was reacted with pyrrolidine at 0 °C to give the corresponding α-amino ketone, which was in situ reduced, after the addition of MeOH followed by $CeCl_3/NaBH_4$, in fairly good overall yield and highly diastereoselective manner to the *anti*-1,2-amino alcohol.[206] It is important to highlight that a slightly erosion of the enantioselectivity occurs over the two steps of the one-pot procedure. By comparing the optical rotation of **189** with the value reported in literature,[207] we were able to assign the absolute configuration of the amino-alcohol as (1*R*, 2*S*). From the absolute configuration of the amino alcohol we could determine the absolute configuration of 2-methyl-2-nitro-3-phenyloxirane **184a** as (2*R*, 3*S*). Finally, we proved that the kinetic resolution of α-nitro epoxide can be performed using different nucleophiles such as a thiols and 1,2-diamines, as demonstrated by the preliminary results

showed in Scheme 4.15.



Scheme 4.15 Kinetic resolution of racemic epoxide **184a** with naphthyl thiol and *o*-phenylenediamine.

When using *o*-phenylenediamine **191** as the nucleophile, besides the enantioenriched nitroepoxide, the pharmaceutically important quinoxaline **193**[208] was isolated in satisfactory yield.

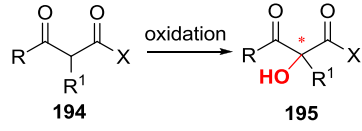
CONCLUSIONS

We have developed the first enantioselective synthesis of aromatic α-nitroepoxides exploiting an aminolytic kinetic resolution with aniline, catalyzed by an easily accessible cinchona alkaloid-derived thiourea. The unreacted epoxides were isolated in acceptable yield and good to high enantioselectivity. We also demonstrated that enantioenriched α-nitroepoxides can be used as synthetically useful intermediates: a convenient one-pot stereoselective approach to highly valuable *anti*-1,2-amino alcohols has been described. Despite this AKR process needs yet to be improved, in terms of efficiency, to be of practical value, this work is conceptually interesting in showing that bifunctional organocatalysts are able to catalyze the ring-opening reaction of epoxides. Improvements of this process are likely to be envisaged in the next future by checking novel multifunctional organocatalysts.

5. ENANTIOSELECTIVE α- HYDROXYLATION OF β-KETOAMIDES

5.1 Background

The α-hydroxy-β-dicarbonyl moiety is an important structural motif present in bioactive compounds of natural and synthetic origin.[209] The most convenient and direct approach to synthesize these scaffolds is the α-hydroxylation reaction of 1,3-dicarbonyl compounds, which allows to transform a carbon-hydrogen bond in a carbon-oxygen bond. In particular, the asymmetric α-hydroxylation of α-substituted 1,3-dicarbonyl compounds constitutes an efficient route to directly access enantiomerically enriched compounds bearing a quaternary stereocentre (Scheme 5.1).[210]



Scheme 5.1 α-Hydroxylation of α-substituted 1,3-dicarbonyl compounds.

This class of densely functionalized alcohols **195**, with a quaternary stereocentre, includes useful synthetic intermediates and this scaffold is an integral feature of a variety of natural products and pharmaceuticals (Figure 5.1). For example, α-acetolactate and α-acetohydroxybutyrate are the biosynthetic precursors of valine and

isoleucine,[211] Indoxacarb is an insecticide produced by Dupont,[212] kjellmanianone, hamigeran A and doxycycline are antibiotics.[213]

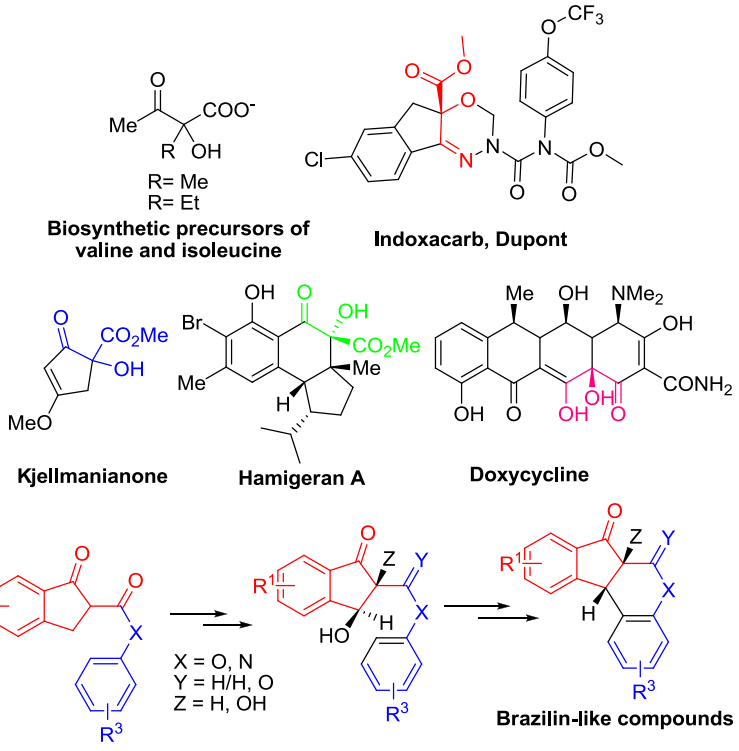


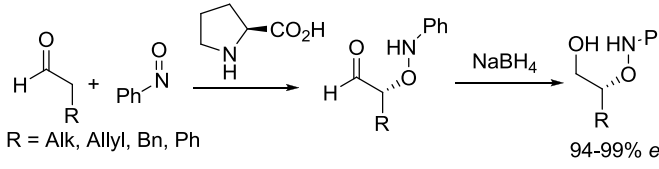
Figure 5.1 Examples of biologically active compounds bearing α-hydroxy-β-dicarbonyl moiety.

This functional unit appears in key-intermediates in several multi-step reaction sequences, for example in the synthesis of brazilin-like compounds.[214] Brazilin is a tetracyclic homoisoflavanoid, the major component present in the heartwood of *Caesalpinia sappan* L. (Leguminosae), used for a long time in traditional Chinese medicine. Biological studies demonstrated that brazilin improved rheological abnormalities in diabetes, had antiplatelet and anti-inflammatory activity and modulated immune function. Recent

studies have shown that brazilin possesses anticancer activity.[214]

5.1.1 α-Hydroxylation of aldehydes and ketones

The first source of electrophilic oxygen introduced for the α-oxidation of aldehydes was the nitroso benzene, in the asymmetric metal-catalyzed α-oxidation of tin-enolates.[215] Subsequently, three different research groups used the nitrosobenzene in the functionalization of aldehydes using L-proline as a catalyst. Zhong,[216] MacMillan[217] and Hayashi,[218] independently, showed the regio- and enantiocontrol of L-proline in different solvents and reaction conditions (Scheme 5.2).

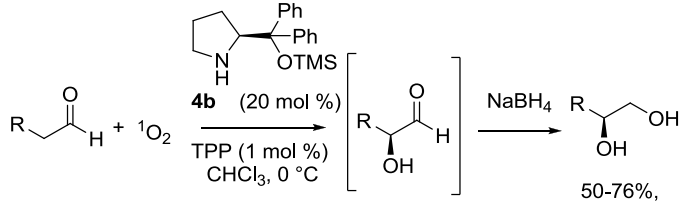


Scheme 5.2 α-Hydroxylation of aldehydes using nitrosobenzene, catalyzed by L-proline.

The oxygen-nitrogen bond can be cleaved using $CuSO_4$ or with Adam's catalyst.[219]

The same functionalization can be extended to ketones. Their use, however, is hampered by the fact that the addition on both two enolizable carbons and poor regioselectivity can occur and, usually, low yield and reaction rate are observed. Hayashi[220] and Córdova[221] were able to circumvent the problem by using a large excess of ketone and performing slow addition of nitrosobenene. In this way, good yields (44-91%) and high enantioselectivity (96-99% *ee*) were achieved.

In 2004, the Córdova's group reported the α-oxidation of aldehydes catalyzed by α-methylproline but, subsequently, they demonstrated that α,α-L-diphenyl prolinol ether **4b** is a more effective catalyst (Scheme 5.3).[222] The oxidizing agent is molecular singlet oxygen, generated from atmospheric oxygen in the presence of a catalytic amount of tetraphenyl porphyrin (TPP). The α-hydroxyaldehyde intermediate was reduced in situ with $NaBH_4$ to the corresponding diol with good yields (50-76%) (Scheme 5.3).

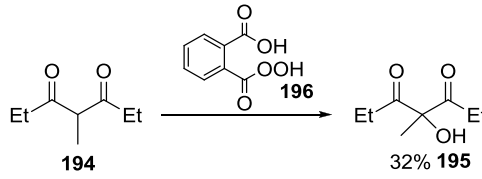


Scheme 5.3 α-Hydroxylation of aldehydes with molecular singlet oxygen catalyzed by α,α-L-diphenyl prolinol ether **4b**.

5.1.2 α-Hydroxylation of 1,3-dicarbonyl compounds

Oxidations of β-dicarbonyl compounds **194** can be performed with different oxidants.[209]

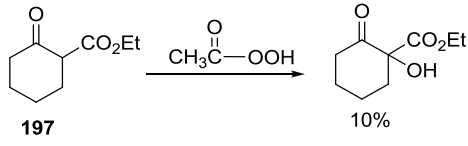
In the context of oxidation with peracids, the first α-hydroxylation to the α-hydroxy-β-diketone **195** was reported in 1958, using the monoperphthalic acid **196** as the oxidant (Scheme 5.4).[223]



Scheme 5.4 Oxidation of β-diketone **194**.

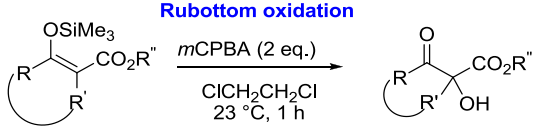
However, performing analogous reactions between other diketones and peracids, only small amounts of the α-hydroxylated product was obtained together with other decomposition products.

The first α-hydroxylation of a β-ketoester was reported in 1968 using peracetic acid, but the yield was very low (Scheme 5.5).[224]



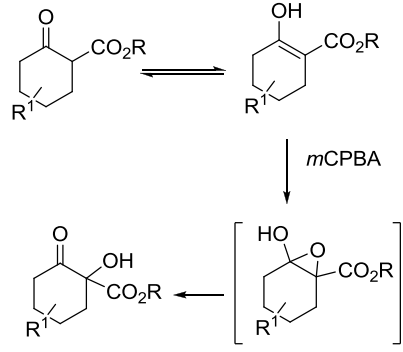
Scheme 5.5 Oxidation of β-ketoester **197**.

The Rubottom oxidation is a well-established method for the hydroxylation of cyclic β-dicarbonyl compounds with *m*CPBA. This is a three-step sequence, consisting of deprotonation, silyl enol ether formation and epoxidation, followed by acidic hydrolysis. This method, however, does not work on acyclic substrates (Scheme 5.6).[225]



Scheme 5.6 Rubottom oxidation of cyclic silyl enol ethers.

In a few cases, when the the enol form of the six-membered ring β-oxo ester in the tautomeric keto-enol equilibrium is predominant, the direct hydroxylation with *m*CPBA can be performed. This is a different version of the Rubottom oxidation, whose mechanism is showed in Scheme 5.7.[226]



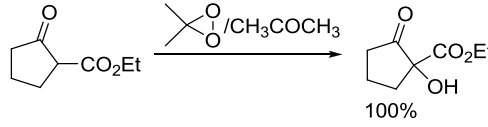
Scheme 5.7 Generally accepted mechanism of α-hydroxylation with *m*CPBA.

The Rubottom oxidation is a well-established method and easily reliable on the laboratory scale, but it requires three steps and stoichiometric amounts of peracid, base and trialkylsilyl halide.

Therefore, more convenient oxidation methods have been devised, as those using dimethyldioxirane or atmospheric oxygen as the oxidants. The main advantage of these procedures is less amount of waste products formed during the reaction.

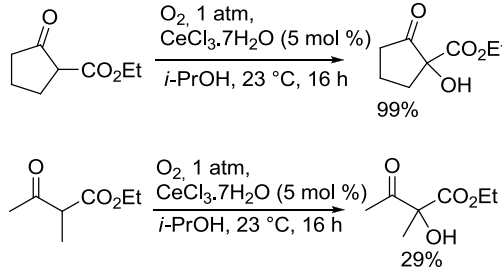
Dimethyldioxirane (DMD) is prepared from acetone and hydrogen peroxide or persulfates and it is used for the epoxidation of olefins. However, several dicarbonyl compounds have been hydroxylated with this reagent, sometimes with the addition of fluoride in order to shift the keto-enol equilibrium in favour of the enol form. One

example is shown in Scheme 5.8.[227]



Scheme 5.8 Oxidation with DMD.

From an economic and ecological point of view, the oxidations with atmospheric oxygen in the presence of Mn, Co or Ce salts are the best methodologies.[209] In particular, the cerium salt $CeCl_3 \cdot 7H_2O$ is the optimal catalyst since it is non-toxic and inexpensive. Just two examples are reported in Scheme 5.9.[228] Unfortunately, this methodology is restricted to certain substrates such as carbo- and heterocyclic compounds.

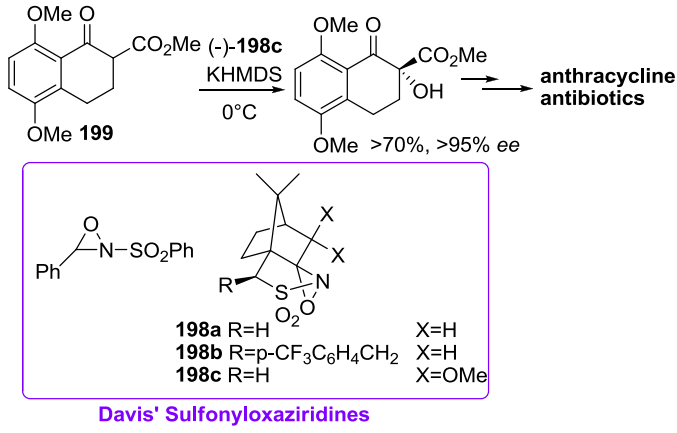


Scheme 5.9 Oxidations with molecular oxygen.

By means of the methodologies shown above, only racemic products can be obtained.

Asymmetric α-hydroxylations can be performed using an optically active oxaziridine (Davis' reagent).[229]

In Scheme 5.10 is reported one example in which the hydroxylation of **199** proceeded with high enantioselectivity using the (-)-**198c** camphor-derived sulfonyloxaziridine.[230]



Scheme 5.10 α-Hydroxylations with Davis' oxaziridine.

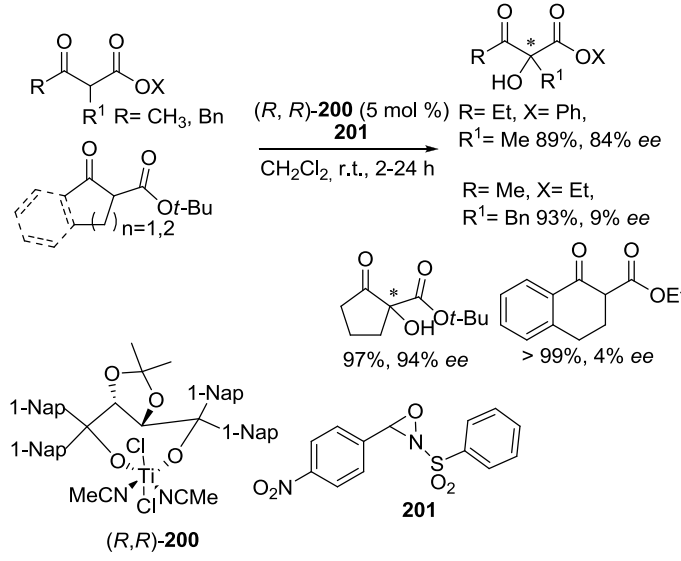
However, even if highly reliable in most cases, the α-hydroxylation with oxaziridines needs stoichiometric deprotonation before oxidation and an optimization of the chiral reagent is often required. A limited number of direct enantioselective α-hydroxylations have been developed and the majority is focused on β-ketoesters.

Transition metal-chiral ligand complexes[210a] with different oxidants on the one hand, and organocatalysis,[210b] mediated by bifunctional, phase transfer catalysts and chiral phosphoric acids, on the other hand have been reported.

The inherent acidity of β-ketoesters allows their reaction with electrophiles and the formation of metal enolates is not needed.

Togni, Mezzetti et al. used a catalyst previously exploited by the same group in the asymmetric α-fluorination reaction of β-ketoesters. The Ti(TADDOLato)complex **200** was found to catalyze the enantioselective α-hydroxylation of β-ketoesters, in the

presence of racemic 2-(phenylsulfonyl)-3-(4-nitrophenyl)oxaziridine **201** as the oxidant, obtaining the products with up to 94% *ee* (Scheme 5.11).[231] However, the enantioselectivity of the reaction was strongly dependent on the substrate structure.



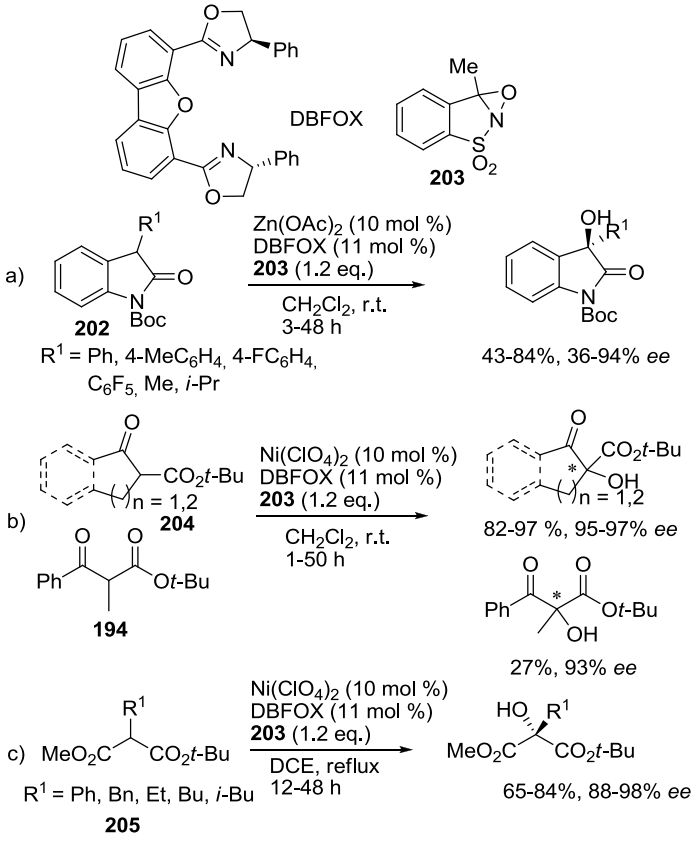
Scheme 5.11 Asymmetric α-hydroxylation of β-ketoesters catalyzed by a Ti-chiral ligand complex.

A ruthenium salt was also employed in the same study for the α-hydroxylation of the β-ketoesters with H_2O_2, but the products were isolated in low yields and modest *ee*s (up to 36%).[231]

In 2006, Toru, Shibata and co-workers described the first example of a catalytic enantioselective hydroxylation reaction of 2-oxindoles **202**, using DBFOX ligand in combination with a Zn salt as Lewis acid, and oxaziridine **203** as the oxidant (Scheme 5.12a).[232]

In an extension of the above investigations, the enantioselective

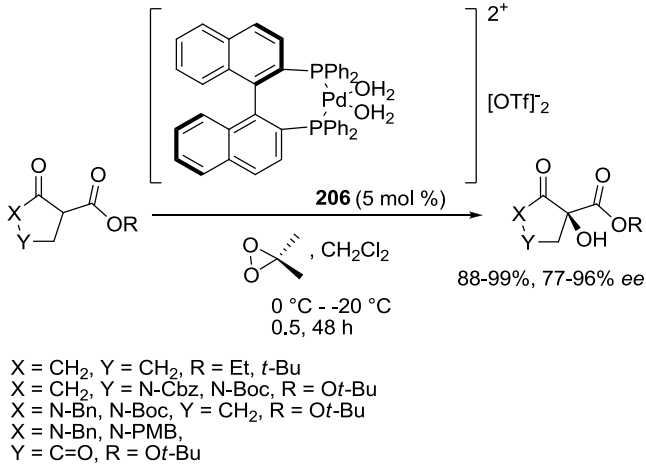
hydroxylation reaction of a linear β-ketoesters **194** catalyzed by a DBFOX/Ni(II) salt, was reported (Scheme 5.12b). In 2009, the same group successfully applied the Ni-catalyzed procedure to unsymmetrical *tert*-butyl malonates **205** (Scheme 5.12c).[233]



Scheme 5.12 Hydroxylation reactions catalyzed by Lewis acid using DBFOX as chiral ligand.

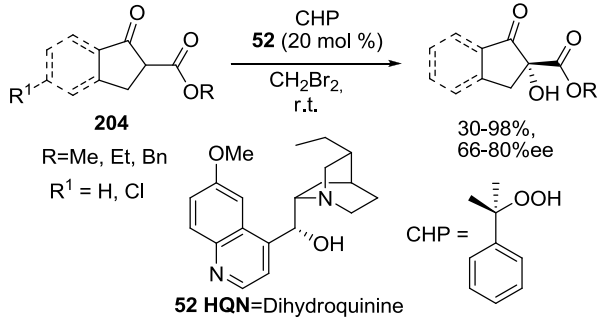
In 2009, Hii documented the ability of a dicationic Pd(II)-BINAP catalyst **206**·OTf, air- and moisture-stable, to catalyze the α-hydroxylation of β-ketoesters, using dimethyldioxirane as the

oxidant. The methodology proved to be effective with cyclic substrates (Scheme 5.13), but unsuccessful with less reactive acyclic substrates, obtaining lower *ee*s.[234]



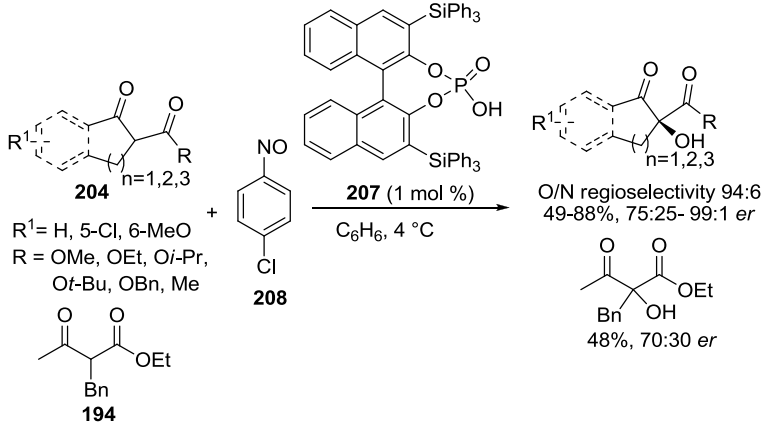
Scheme 5.13 Pd(II)-catalyzed α-hydroxylation of the β-ketoesters.

In 2004, the Jørgensen's group demonstrated the ability of Cinchona alkaloids to organocatalyze the enantioselective hydroxylation of β-ketoesters (Scheme 5.14).[235] After optimization of the reaction conditions, commercially available hydroquinine **52** was found to be the best-performing catalyst, with cumyl hydroperoxide as the oxidant in CH_2Br_2 as the solvent. Under these conditions, optically active products were obtained in up to 80% *ee*.



Scheme 5.14 Organocatalytic enantioselective hydroxylation of β-ketoesters.

In 2009, Zhong and co-workers illustrated the use of chiral phosphoric acids, at only 1 mol % loading, in the α-hydroxylation reaction of β-dicarbonyl compounds with nitroso benzene as the oxidizing agent. The reaction directly led to the enantioenriched α-hydroxy-β-dicarbonyl products with high regio- and enantiocontrol (Scheme 5.15).[236]



Scheme 5.15 Enantioselective α-hydroxylation of β-dicarbonyl compounds catalyzed by a chiral Brønsted acid.

The protonation of the basic nitrogen atom of **208** occurs followed

by a tandem aminoxylation of β-dicarbonyl compounds and subsequent heterolysis of the N-O bond. The selective protonation of the nitrogen atom instead of oxygen atom in the transition state is the crucial point of this type of catalysis (Figure 5.2).

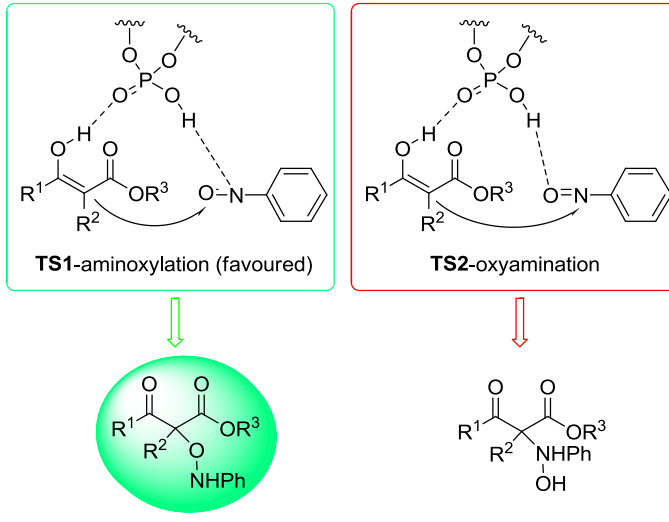
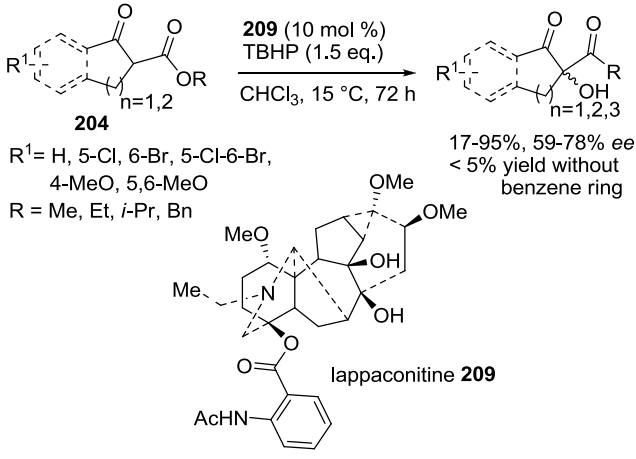


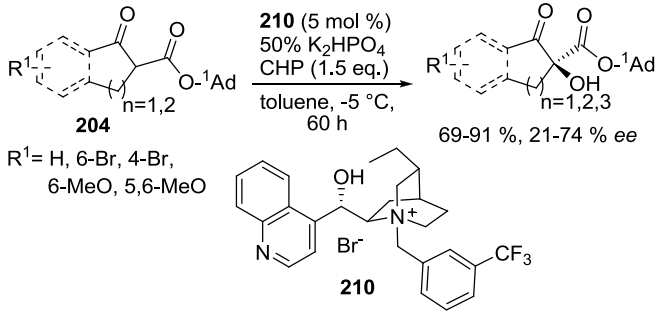
Figure 5.2

Gao and co-authors illustrated the first application of the diterpenoid alkaloid lappaconitine **209** as a chiral Brønsted base in the α-hydroxylation of β-ketoesters using *tert*-butyl hydroperoxide (TBHP) as the oxidant, achieving moderate enantioselectivity (Scheme 5.16). The *ee* values could be improved to >99% by single recrystallization.[237]



Scheme 5.16 α-Hydroxylation of β-ketoesters catalyzed by a terpenoid alkaloid.

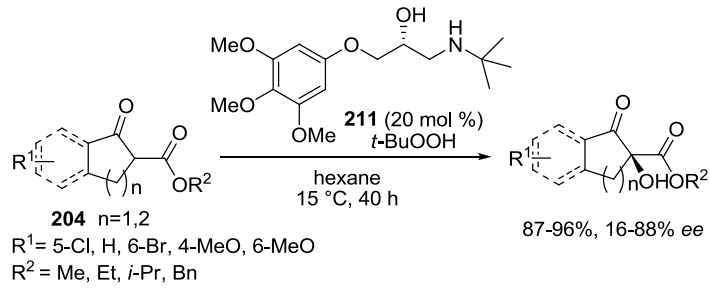
In 2010, the first PTC catalyzed oxidation of 1-adamantyl (1-Ad) β-ketoesters with cinchonine-derived ammonium salt **210** in the presence of CHP as the oxidant was developed (Scheme 5.17).[238] However, this methodology is restricted to indanone based β-ketoesters, whose products have been isolated with up to 74% *ee*.



Scheme 5.17 PTC catalyzed α-hydroxylation of β-ketoesters.

In 2012, Meng showed the enantioselective α-hydroxylation of β-ketoesters catalyzed by a chiral *S*-timolol derivative **211** (Scheme

5.18).[239] Again, the methodology is applicable only to indanone based β-ketoesters.



Scheme 5.18 Enantioselective α-hydroxylation of β-ketoesters catalyzed by *S*-timolol derivative **211**.

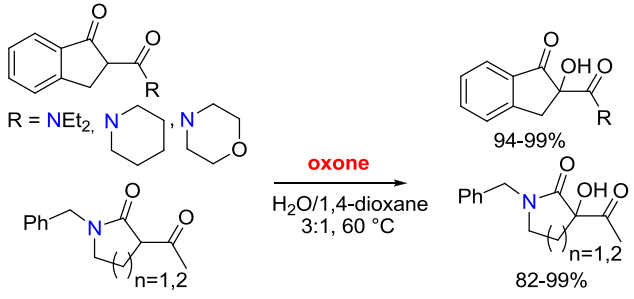
5.1.2.1 α-Hydroxylation of β-ketoamides

Unlike β-ketoesters, the enantioselective α-hydroxylation of β-ketoamides has been a scarcely investigated transformation. The lack of enantioselective methodologies to install a hydroxyl group at the α-position of β-ketoamides is likely due to the higher pK_a of their α-hydrogen, which determines the necessity of more basic reaction conditions to form the reactive enolate. The amido group is a versatile functionality in organic synthesis owing to the further tranformations it can undergo.[240]Hence, the development of enantioselective processes for the α-hydroxylation of β-ketoamides is highly desirable. These procedures would directly allow the generation of tertiary alcohols, bearing an enantioenriched tetrasubstituted carbon with both ketone and amido functionalities, amenable to chemoselective manipulations.

Very few examples of α-hydroxylation of β-ketoamides have been

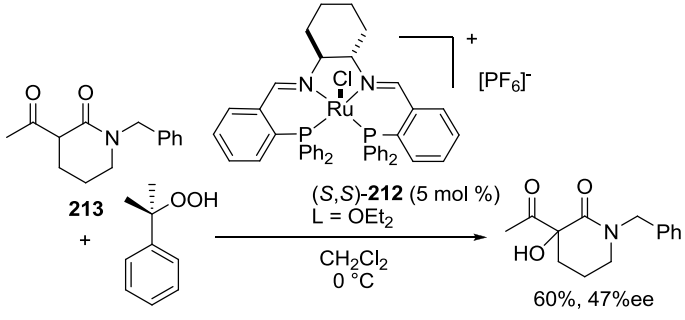
reported.

In 2012, Zhang developed a method for the racemic α-hydroxylation of β-dicarbonyl compounds.[241] Under a homogeneous solvent mixture of water and 1,4-dioxane at 60 °C, without the aid of a catalyst, a variety of cyclic β-dicarbonyl compounds, including β-keto esters, β-diketones and β-ketoamides were reacted using oxone as the stoichiometric oxidant. The examples on β-ketoamides are reported in Scheme 5.19.



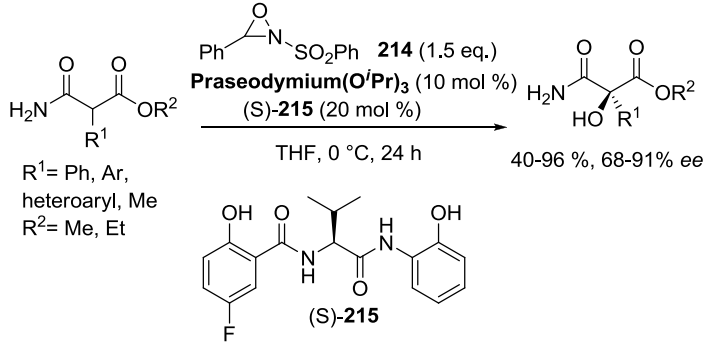
Scheme 5.19 Racemic α-hydroxylation of β-ketoamides with oxone.

A single example of enantioselective α-hydroxylation of a β-ketoamide was reported in 2004 exploiting a ruthenium-based chiral catalyst **212** and CHP as an oxidant (Scheme 5.20).[231]



Scheme 5.20 Enantioselective ruthenium catalyzed hydroxylation of β-ketoamide **213**.

Recently, a more successful protocol has been developed by Kumagai and Shibasaki who reported the first asymmetric hydroxylation of *N*-unsubstituted α-alkoxycarbonyl amides, using a catalytic system consisting of a rare earth metal alkoxide and a chiral amide-based ligand **215** (Scheme 5.21).[242] Davis's oxaziridine **214** was used as the oxidizing reagent.



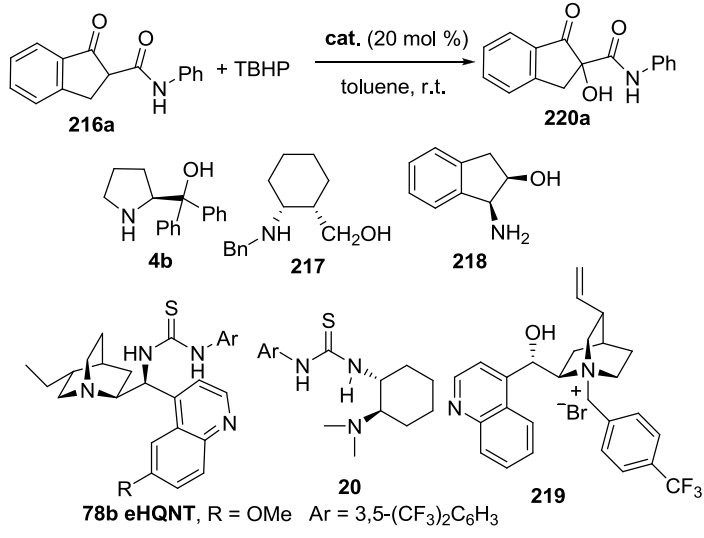
Scheme 5.21 Asymmetric hydroxylation of α-alkoxycarbonyl amides promoted by $Pr(O^iPr)_3$/amide-based ligand catalyst.

The optically active tertiary alcohols were isolated in moderate to good yields and good to high enantioselectivity. The authors suggested that metal coordination and hydrogen bonding of chiral ligand worked cooperatively to determine the stereochemical outcome of the reaction.

Given the paucity of protocols for the enantioselective α-hydroxylation of a β-ketoamides, we decided to embark on this study in order to develop a simple organocatalytic oxidative system.

5.2 Results and Discussion

We set up the first organocatalytic enantioselective α-hydroxylation reaction of α-substituted β-ketoamides. On the basis of literature precedents,[235] we assumed that a bifunctional organocatalyst would have been suitable to promote the process. Hence, we commenced our screening investigating the reaction of model β-ketoamide **216a** with TBHP as the oxidant, in the presence of 20 mol % loading of a variety of readily available bifunctional organocatalysts (Scheme 5.22), in toluene at room temperature (Table 5.1).



Scheme 5.22 Organocatalysts screened in the α-hydroxylation of β-ketoamide **216a**.

α,α-L-diphenyl prolinol **4b**, bearing a secondary amine group, was able to promote the α-hydroxylation reaction of β-ketoamide **216a**.

Table 5.1 Screening of the reaction conditions.[a]

entry	cat.	t (h)	yield (%)[b]	*ee* (%)[c]
1	**4b**	69	51	18
2	**217**	51	38	2
3	**218**	40	62	rac
4	**20**	65	22	4
5[d]	**78b**	70	13	4
6[e]	**219**	42	90	-30
7	**QN 50**	43	79	50
8	**QD 53**	72	57	-44
9	**HQN 52**	65	99	54
10	**HQD 55**	70	92	-50
11[f]	**HQN 52**	48	81	45
12[g]	**HQN 52**	8	88	14

[a]Reaction conditions: **216a** (0.1 mmol), cat. (20 mol %), TBHP (1.2 eq.), solvent (0.5 mL) at r.t. [b]Isolated yield after silica gel chromatography. [c]Determined by chiral HPLC analysis. Negative values indicate the preferential formation of the opposite enantiomer. [d]10 mol % of catalyst was used. [e]Reaction conditions: **216a** (0.1 mmol), **219** (5 mol %), CHP (1.5 eq.), K_2HPO_3 (50%) (0.5 mL), toluene (1 mL) at 0 °C. [f]Cumyl hydroperoxide was used. [g]Reaction conditions: **216a** (0.1 mmol), **HQN** (20 mol %), H_2O_2 (50%) (1.2 eq.), $MgSO_4$ (45 mg), toluene (0.5 mL).

Indeed, the expected tertiary alcohol was obtained in 51% yield, although with 18% *ee* (entry 1). Other β-aminol alcohols, such as the *cis*- derivative **217** and *cis*-(1*R*,2*S*)-amino indanol **218** afforded the almost racemic product (entries 2 and 3). Bifunctional tertiary amine-thioureas, such as *epi*-hydroquinine derived thiourea **78b** and Takemoto's thiourea **20**, were not suitable catalysts for the process. Indeed, product **220a** was recovered in low yield and in racemic form in both cases (entries 4 and 5). A PTC catalyst, the *N*-[4-(trifluoromethyl)benzyl]- cinchoninium bromide **219** was checked using CHP as the oxidant at 0 °C (entry 6). The alcohol **220a** was recovered in high yield and 30% *ee*. Common cinchona alkaloids were then tested and we were pleased to observe that they exhibited

fairly good catalytic activity and stereocontrol in the model α-hydroxylation reaction (entries 7-10). In particular, hydroquinine proved to be the most efficient promoter, affording the product in quantitative yield and 54% *ee* (entry 9). The effect of different oxygen sources was then examinated, although CHP and hydrogen peroxide gave inferior results (entries 11 and 12).

Based on these data, hydroquinine was selected as the catalyst and TBHP as the oxidant for further optimization of the reaction conditions (Table 5.2).

Table 5.2 Solvent and reaction conditions screening.[a]

entry	solvent	t (h)	yield (%)[b]	*ee* (%)[c]
1	CH_2Cl_2	12	90	52
2	CH_2Br_2	16	82	52
3	$ClCH_2CH_2Cl$	16	94	49
4	C_6H_5Cl	21	89	50
5	$CHCl_3$	18	97	56
6	$CHCl_3$	22	10[d]	-
7[e]	$CHCl_3$	118	83	76

[a]Reaction conditions: **216a** (0.1 mmol), **HQN** (20 mol %), TBHP (1.2 eq.), solvent (0.5 mL) at r.t. [b]Isolated yield after silica gel chromatography. [c]Determined by chiral HPLC analysis. [d]Conversion of **220a** determined by ^1H NMR analysis in absence of the catalyst. [e]$CHCl_3$ (2 mL) at -20 °C.

By a solvent screening, product *ee* could be improved working in halogenated solvents (entries 1-5). Chloroform proved to be the most suitable as the product was isolated in 97% yield and with an encouraging level of enantioselectivity (56% *ee*) (entry 5). We checked if the racemic oxidative pathway was a negligible process in absence of the catalyst (entry 6). After 22 h the conversion to product **220a** was only 10%. Finally, the highest *ee* value of 76%

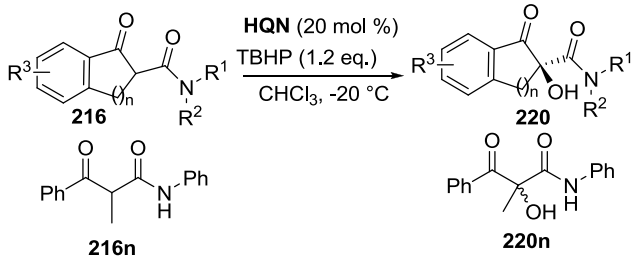
was achieved when the α-hydroxylation reaction was conducted at -20 °C, under more diluted conditions (entry 7).

Once the reaction conditions were optimized, we investigated the substrate scope of the reaction and the results are collected in Table 5.3. According to the data in Table 5.3, the electronic nature of the substituent on the phenyl ring of the indane scaffold has no effect on both the yield and enantioselectivity. Higher yield (84-88%) and enantioselectivity (up to 83%) were observed for the products bearing either halogen atoms or electron-donating groups on the aromatic ring of the indane moiety compared to model product **220a** (entries 2-5).

On the contrary, the substitution pattern at the secondary amido moiety affected the outcome of the reaction. The 1-naphthyl substituted compound **216f** and substrate **216i**, bearing an electron-donating substituent, were converted into the product in almost the same manner as the model compound **216a** (entries 6 and 9). Products **220g-h**, bearing electron-withdrawing groups, were isolated with slightly lower *ee* values (entries 7 and 8). Substitution of the aromatic with an aliphatic group on the amide, as in substrates **216j-k**, affected the reaction rate significantly and the products were recovered in modest yields and *ee* (entries 10 and 11).

Finally, the presence of the secondary amido functionality in the starting reagent was found to be essential for the reaction to proceed.

Table 5.3 Substrate scope of the organocatalytic enantioselective α-hydroxylation of β-ketoamides.[a]



entry	R^1, R^2, R^3, n	t (h)	yield (%)[b]	*ee* (%)[c]
1	Ph, H, H, 1, **a**	118	83 (66)	76 (87)
2	Ph, H, 4-Br, 1, **b**	115	88 (66)	83 (96)
3	Ph, H, 5-Cl, 1, **c**	92	85	79
4	Ph, H, 5-Br, 1, **d**	117	87	78
5	Ph, H, 6-OMe, 1, **e**	117	84 (60)	81 (98)
6	1-Naphthyl, H, H, 1, **f**	64	82	74
7	2-ClC_6H_4, H, H, 1, **g**	111	76 (48)	67 (99)
8	3-$CF_3C_6H_4$, H, H, 1, **h**	93	88	56
9	4-O(*n*-pentyl)C_6H_4, H, H, 1, **i**	139	89	76
10[d]	Cyclohexyl, H, H, 1, **j**	144	37	40
11[d]	Bn, H, H, 1, **k**	142	50	29
12[d]	Bn, Me, H, 1, **l**	142	-	-
13[d]	Ph, H, H, 2, **m**	164	-	-
14[d]	**216n**	160	-	-

[a]Reaction conditions: **216a** (0.1 mmol), **HQN** (20 mol %), TBHP (1.2 eq.), $CHCl_3$ (2 mL). [b]Isolated yield after silica gel chromatography. In parenthesis yield after crystallization. [c]Determined by chiral HPLC analysis. In parenthesis *ee* after crystallization. [d]Reaction performed at r.t.

When substrate **216l**, bearing a tertiary amide moiety, was reacted under standard conditions, unreacted starting material was observed (entry 12). Unfortunately, less reactive tetralone derived **216m** and acyclic **216n** β-ketoamides did not react under optimized conditions at room temperature (entries 13 and 14).

Pleasingly, the *ee* values could be improved by single crystallization up to 99% *ee* (entries 1, 2, 5 and 7). The absolute configuration of the quaternary stereocentre for the tertiary alcohols products **220** was assigned to be (2*S*) in analogy to that determined on compound **220b** by single-crystal X-ray analysis (Figure 5.3).

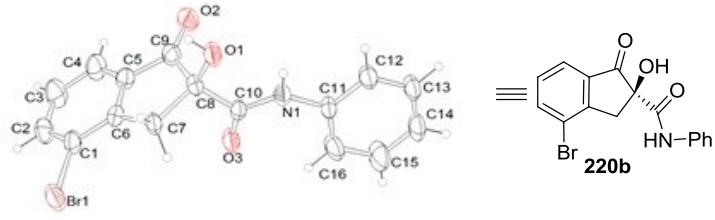
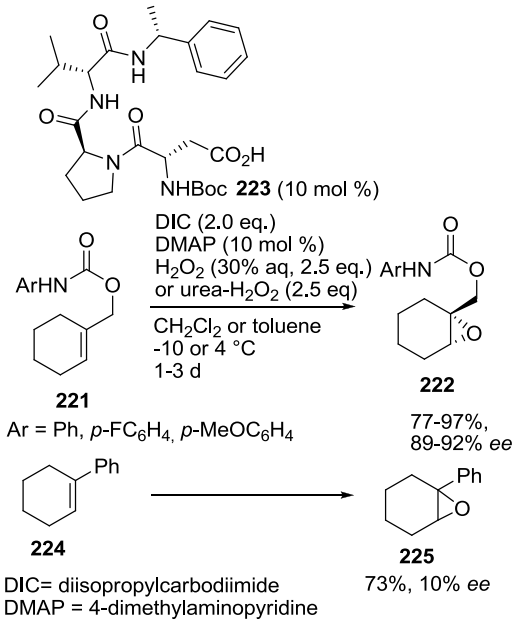


Figure 5.3 Absolute configuration of (*S*)-**220b** by X-ray analysis. Ellipsoids set at 30% probability level.

As shown in entry 12 of Table 5.3, the secondary amido group is indispensable for the reactivity. Hence, we anticipated that the amidic NH- could be involved in the organization of the transition state via H-bonding.

Miller has previously illustrated the importance of secondary amido groups in the asymmetric epoxidation of functionalized alkenes promoted by peptide-based catalysts (Scheme 5.23).[243]



Scheme 5.23 Asymmetric catalytic epoxidation with peptide **223**.

The asymmetric epoxidation is based on an electrophilic mechanism, orthogonal to the well-known peptide-catalyzed[18,244] nucleophilic epoxidation. The authors suggested that a substrate-catalyst hydrogen bonding complex might contribute to organize the transition state. Indeed, a confirmation of a plausible H-bonding interaction has been observed when reacting phenylcyclohexene **224**, which was epoxidized without enantiocontrol (10% *ee*). They performed several elegant experiments to study the mode of action of catalyst **223** and suggested the hypothetical transition state models illustrated in Figure 5.4.

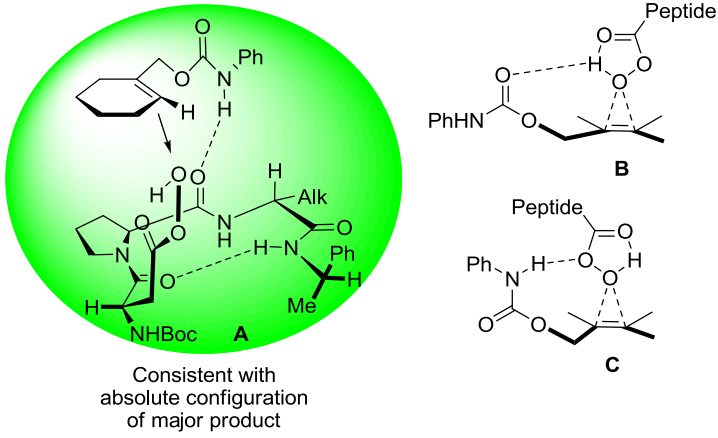


Figure 5.4 Hypothetical transition structures indicating potential catalyst-substrate contacts.

In the attempt to identify potential binding sites of interactions between hydroquinine **52** and the β-ketoamide **216a**, we recorded ^{1}H NMR spectra of HQN at room temperature in $CDCl_3$ adding different amounts of compound **216a** (up to 3 eq.) (Figure 5.5).

Signals of the α-hydrogens to the quinuclidine nitrogen (*) appear to be broader, increasing the amount of reagent **216a**. This result would be in agreement with the hypothesis that the quinuclidine nitrogen would be protonated by reagent **216a**.[245] A confirmation of nitrogen protonation would come from the significant line broadening of the β-ketoamide protons between 3.4-4.0 ppm.

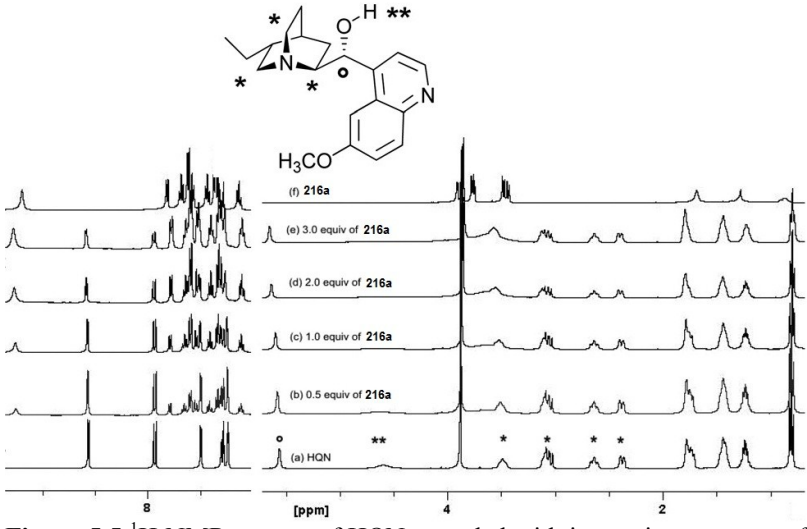
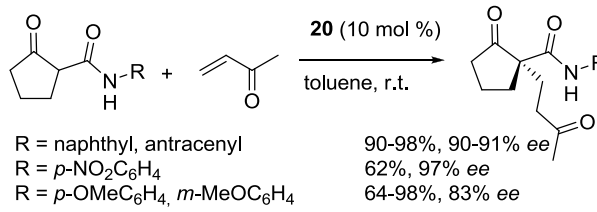


Figure 5.5 ^{1}H-NMR spectra of HQN recorded with increasing amounts of compound **216a** in $CDCl_3$ (C 0.1 M) at room temperature. The HQN protons which were significantly shifted or broadened are marked with symbols.

The carbinolic proton of the hydroquinine was found slightly downshifted (○) and the peak of hydroxyl group of the catalyst (**) gradually decreased, until it almost disappeared, increasing the amount of **216a**. This observation would suggested that the OH group of the catalyst is likely involved in H-bonding interaction with the enolate of compound **216a**. Rather surprisingly, we did not observe a significant shift of the CONH proton in **216a** (signal at 9.3 ppm).

In 2011, Rodriguez and Constantieux documented a cooperative participation of the amido group in the organocatalytic Michael addition of α-substituted β-ketoamides to α,β-unsaturated ketones (Scheme 5.24).[246]



Scheme 5.24 Michael addition of β-ketoamides to methylvinylketone.

In particular, they observed that there was a correlation between the acidity of the amide proton and the *ee* value. Substrates with polyaromatic substituents or bearing an electron-withdrawing substituent on the aromatic ring of the amide led to high *ee*s. Amides bearing an electron-donating group on the aromatic ring proved to be the poorest substrates. Theoretical calculations confirmed that the *ee* increased with the acidity of the amide proton. The authors highlighted the crucial role of the amide proton in the activation of the substrate and proposed that the imidic acidic form of the β-ketoamide, in the presence of the bifunctional organocatalyst, would aid the deprotonation of the methine proton generating a reactive enolate intermediate, stabilized by the thiourea moiety (Figure 5.6).

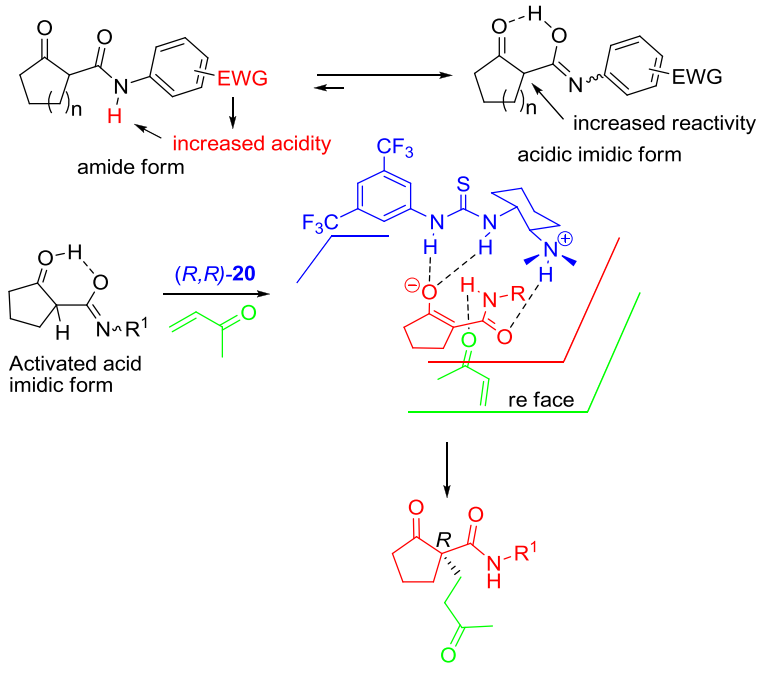


Figure 5.6 Amide and acidic imide forms of β-ketoamides and transition-state model for the Michael addition of β-ketoamides.

In our case, it appears that a comparable correlation between the acidity of the amide proton and the enantioselectivity does not hold. Indeed substrate **216i**, bearing an electron-donating substituent on the amidic phenyl ring, was converted into the product similarly to model substrate **216a** (entries 1 and 9, Table 5.3). Moreover, products **220g-h,** bearing electron-withdrawing groups, have been isolated with slightly lower *ee* values (entries 7 and 8, Table 5.3).

CONCLUSIONS

In summary, we developed a first enantioselective α-hydroxylation reaction of α-substituted β-ketoamides organocatalyzed by a bifunctional organocatalyst. The key features of this methodology are *i*) the use of commercially available HQN/TBHP system, which makes it very convenient and easy to reproduce; *ii*) this protocol enables a facile access to functionalized tertiary alcohols bearing a quaternary stereocentre in good to high yield and up to 83% *ee*. Moreover, the *ee* values can be improved by a single crystallization up to 99% *ee*. The isolated products bear on the quaternary stereocentre both ketone and amido groups, amenable to chemoselective manipulation.

SUMMARY

In this PhD work the design, plan and development of new organocatalytic methodologies for the synthesis of optically active, densely functionalized, organic molecules has been accomplished. The molecules obtained are important motifs present in many biologically active natural and non-natural substances.

Non-covalent activation mode by means of bifunctional organocatalysts has been exploited. The design and synthesis of new bifunctional promoters has been reported and their catalytic ability documented.

Another challenging target of this doctoral work has been the synthesis of molecules bearing quaternary stereocentres. The stereoselective construction of a quaternary stereocentre, especially when it is an all-carbon quaternary stereocentre, represents one of the most difficult transformations in organic synthesis.

The methodologies developed in this PhD work allowed the stereocontrolled construction of carbon-carbon and carbon-heteroatom bonds to give access to new and important cyclic and non-cyclic compounds, such as epoxides, tetrahydrothiophenes, γ-butyrolactones and α-hydroxylate β-ketoamides.

A significant part of the PhD work was spent to develop tandem organocatalytic methodologies such as Michael/Michael and aldol/lactonization process, which allowed the synthesis of chiral densely functionalized molecules with a minimum number of synthetic operations.

The contributions given by this PhD work to the field of organocatalysis have been the following:

The first stereoselective cascade sulfa-Michael/Michael reaction to access tetrahydrothiophenes from *trans*-α-carbonyl-β-substituted acrylonitriles has been developed. A novel readily available secondary amine thiourea proved to be the catalyst of choice. The products, bearing three contiguous stereocentres, one of them quaternary, were isolated in high yield, good diastereoselectivity and excellent enantiocontrol. This work represents an unprecedented case where the stereochemical outcome of an asymmetric synthesis of tetrahydrothiophenes has been controlled exclusively by a dinamic kinetic resolution process. Finally, a highly convenient one-pot Knoevenagel/double Michael process, starting directly from commercially available reagents and involving a minimal number of operations has been demonstrated applicable to obtain the tetrahydrothiophenes in comparable stereoselectivity.

A cascade aldol/lactonization process has been devised for the synthesis of enantioenriched β,β-disubstituted γ-butyrolactones. This represents the first direct approach to these highly challenging products. A variety of acylated succinic esters have been reacted with aqueous formaldehyde in the presence of 3 mol % loading of cinchona alkaloid derived squaramide and 4-nitrophenol as additive. We were able to obtain the γ-butyrolactones, bearing an all-carbon quaternary stereocentre at the remote β-position, in high yields and fairly good level of enantioselectivity (up to 88% *ee*).

The methodology proved to be suitable to access γ,γ-disubstitued-δ-

valerolactones. Moreover, we demonstrated that these products can be elaborated to prepare valuable hydroxy γ-butyrolactones, bearing contiguous tertiary and quaternary stereocentres, until now not accessible by alternative methods.

The first enantioselective synthesis of aromatic α-nitroepoxides, exploiting an aminolytic kinetic resolution of racemic aromatic α-nitroepoxides with aniline catalyzed by an easily accessible cinchona alkaloid-derived thiourea, has been set up. The epoxides can be recovered in acceptable yield and good to high enantioselectivity. We also demonstrated for the first time that enantioenriched α-nitroepoxides can be used as synthetically useful intermediates: a convenient one-pot stereoselective approach to highly valuable *anti*-1,2-amino alcohols has been described.
This work highlights the great potential and conceptual novelty on the employment of bifunctional organocatalysts in epoxides ring-opening reactions and it would pave the way for future achievements in this underdeveloped area.

Finally, the first enantioselective α-hydroxylation reaction of α-substituted β-ketoamides has been accomplished. This goal has been successfully achieved using the commercially available HQN/TBHP system, which makes it very convenient and easy to reproduce. The functionalized tertiary alcohols bearing a quaternary stereocentre were obtained in good to high yield and up to 83% *ee*. Interestingly, the *ee* values can be eventually improved by a single crystallization up to 99% *ee*.

6. EXPERIMENTAL SECTION

6.1 General experimental conditions

General methods and material

All reactions requiring dry or inert conditions were conducted in flame dried glassware under a positive pressure of nitrogen. THF and DCM were freshly distilled prior to use respectively over $LiAlH_4$ and calcium hydride and stored under nitrogen, chloroform was dried over molecular sieves. Molecular sieves (Aldrich Molecular Sieves 3 Å, 1.6 mm pellets) were activated under vacuum at 200 °C overnight. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel plates (0.25 mm) and visualised by UV light and, when necessary, by ninhydrin spray test, anisaldehyde or phosphomolybdic acid/ethanol spray test. Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance-400 spectrometer, Bruker Avance-300 spectrometer, Bruker Avance-250 or Bruker Avance III HD 600 spectrometer in $CDCl_3$, methanol-d_4 or DMSO-d_6 as solvent. Where the temperature has not been specified, the spectra were recorded at room temperature. Chemical shifts are reported using residual solvent protons (^{1}H NMR: δ = 7.26 ppm for $CDCl_3$, δH = 3.33 ppm for Methanol-d_4, δ = 2.50 ppm for DMSO-d_6) as internal standard. Carbon spectra were referenced to the shift of the ^{13}C signal of $CDCl_3$ (δ= 77.0 ppm) or CD_3OD (δ = 49.0 ppm), DMSO-d_6 (δ = 39.5 ppm). Optical rotation of compounds was

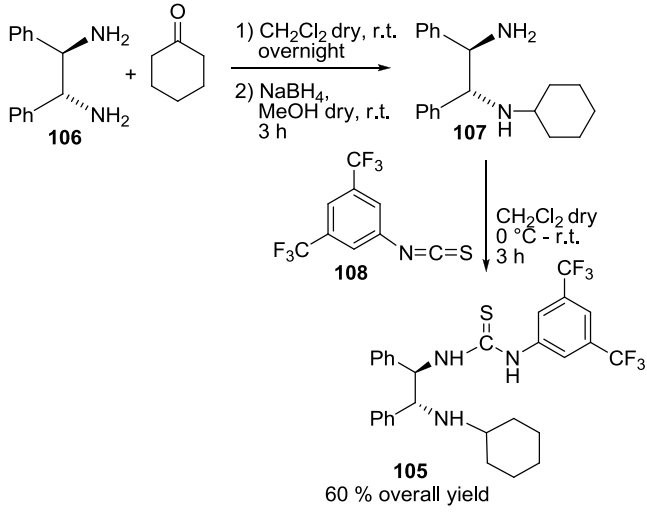
performed on a Jasco Dip-1000 digital polarimeter using the Na lamp (582 nm). FTIR spectra were recorded as thin films on KBr plates using Bruker Tensor 27 or Bruker Vertex 70 spectrometer and absorption maxima are reported in wavenumber (cm-1). ESI-MS was performed using a Bio-Q triple quadrupole mass spectrometer (Micromass, Manchester, UK) equipped with an electrospray ion source. Elemental analyses were carried out by using Flash EA 1112 (Thermo Electron Corporation) analyzer. Melting points were measured with a Stuart Model SMP 30 melting point apparatus or a digital Electrothermal 9100 apparatus. Petrol ether (PE) refers to light petroleum ether (boiling point 40-60 °C). Anhydrous toluene, 1,2-dichloroethane, methanol and all starting materials (unless otherwise noted) were purchased from Aldrich and used as received. Catalysts **104**, **78**, **102** were synthesized according to literature procedure.[247] Cinchona alkaloids **50-55** were purchased from Aldrich and used as received. Catalysts **4a, 4b, 4c, 103, 186, $(DHQD)_2PHAL$ 101, 218**, **219, 217** were purchased from Aldrich and **20** from Strem Chemicals and used as received. Enantiomeric excess of tetrahydrothiophenes **100a-o**, γ-butyrolactones **143a-q, 145** and compounds **148j** and **147f**, α-nitroepoxides **184a**, **184e-m**, **185a** and 1,2-amino alcohol **189**, compounds **220** was determined by HPLC (Waters-Breeze 2487, UV dual λ absorbance detector and 1525 Binary HPLC Pump) using Daicel chiral columns.

6.2 Asymmetric synthesis of tetrahydrothiophenes bearing a quaternary stereocentre

Experimental procedures and compounds characterization

Alkenes **99** were synthesized via Knoevenagel reactions as reported in the literature.[248] Compounds **76** were prepared using general procedures reported in the literature.[249]

Synthesis of catalyst 105

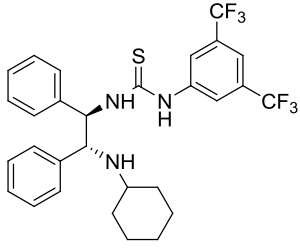


Under a positive pressure of nitrogen, a flamed two necked round bottom flask was charged with anhydrous DCM (20 mL), (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine **106** (425 mg, 2 mmol), and cyclohexanone (622 μL, 6 mmol). Molecular sieves were then added (≈ 50 mg) and the mixture was stirred overnight at room temperature (TLC eluent $CHCl_3$/ MeOH 9:1). Then, the solvent was removed under reduced pressure, anhydrous MeOH was added (40 mL) followed by addition of $NaBH_4$ (309 mg, 8 mmol) portionwise under nitrogen atmosphere. The mixture was stirred until

completion at room temperature (TLC eluent $CHCl_3$/ MeOH 9:1). The solvent was removed under reduced pressure and the residue was diluted with ethyl acetate (30 mL) and washed with water (3 x 40 mL). The organic layer was dried over anhydrous Na_2SO_4 and then the solvent was removed under vacuum. The product was isolated by flash chromatography (eluent: PE/ ethyl acetate 8:2, then $CHCl_3$ to $CHCl_3$/ MeOH 9:1) to give (1*R*,2*R*)-N^1-cyclohexyl-1,2-diphenylethane-1,2-diamine **107** as a viscous pale yellow oil (489 mg, 83%). Spectral data for this compound were consistent with those reported in the literature.[250]

(1*R*,2*R*)-N^1-cyclohexyl-1,2-diphenylethane-1,2-diamine (489 mg, 1.7 mmol) **107** was dissolved in anhydrous DCM (9 mL) in a flamed two necked round bottom flask under a positive pressure of nitrogen. The solution was cooled to 0 °C and 3,5-bis(trifluoromethyl)phenyl isothiocyanate **108** (310 μL, 1.7 mmol) was added *via* syringe dropwised in 15 minutes. The reaction mixture was stirred at room temperature for 3 hours and after completion, monitored by TLC (eluent PE/ diethyl ether 8:2), the solvent was removed under reduced pressure. The product was purified by flash chromatography (PE/ ethyl acetate 8:2, then $CHCl_3$) to give catalyst **105** (679 mg, 60% overall yield).

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*R*,2*R*)-2-(cyclohexylamino)-1,2-diphenylethyl)thiourea 105



Pale yellow solid, **mp** 57.3-60.7 °C. $[\alpha]_D^{21}$ = +8.7 (*c* 0.7, $CHCl_3$). **FTIR** ν_{max} (KBr)/cm^{-1} 2930, 2855, 1496, 1473, 1384, 1278, 1219, 1177, 1135, 773. **^{1}H NMR** (CD_3OD, 400 MHz): δ 8.21 (s, 2H), 7.64 (s, 1H), 7.45-7.21 (m, 11H), 5.66 (bs, 1H), 4.33 (d, 1H, *J*= 6.5 Hz), 2.30-2.25 (m, 1H), 1.91-1.53 (m, 6H), 1.17-0.89 (m, 6H). **^{13}C NMR** (CD_3OD, 100 MHz): δ 182.8, 143.2, 141.7, 141.0, 132.6 (q, $^2J_{CF}$= 33.1 Hz), 129.32, 129.27, 129.2, 128.4, 128.3, 124.7 (q, $^1J_{CF}$= 270.3 Hz, CF_3), 123.5, 117.8, 65.1, 64.7, 54.6, 35.2, 33.0, 27.1, 26.1, 25.7. **MS** (ESI *m/z*) 566.19 [MH+, 100%].

General procedure for the synthesis of racemic tetrahydrothiophenes 100

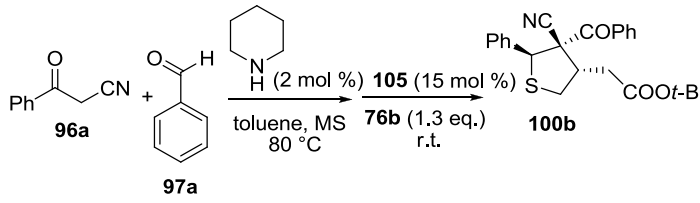
A sample vial was charged with the appropriate (*E*)-alkyl 4-mercaptobut-2-enoate **76** (0.13 mmol) and compound **99** (0.10 mmol) in anhydrous toluene (1.0 mL) under a nitrogen atmosphere. 1,4- Diazabicyclo[2.2.2]octane (5.6 mg, 0.05 mmol) was added and the solution was stirred at room temperature until completion (22-113 hours), monitored by TLC (eluent PE/ ethyl acetate 90:10). The diastereoisomeric ratio was determined by ^{1}H-NMR analysis of the crude reaction mixture. The product was isolated by flash chromatography (eluting in gradient from PE/ ethyl acetate 98:2 to 90:10).

General procedure for the asymmetric synthesis of tetrahydrothiophenes 100

Under a nitrogen atmosphere, a sample vial was charged with the appropriate (*E*)-alkyl 4- mercaptobut-2-enoate **76** (0.13 mmol) and compound **99** (0.10 mmol) in anhydrous toluene (1.0 mL).

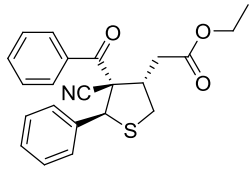
Catalyst **105** (5.7 mg, 0.01 mmol) was added and the reaction mixture was stirred at room temperature until completion, monitored by TLC (eluent PE/ ethyl acetate 90:10). The diastereoisomeric ratio was determined by ^{1}H-NMR analysis of the crude reaction mixture. The crude mixture of compound **100** was purified by flash chromatography (eluting from PE/ ethyl acetate 98:2 to 90:10) to isolate the major and minor diastereomers or their mixture. The diastereoisomeric ratios obtained with catalyst **105** are inverted compared to those obtained when using the DABCO. The absolute configuration of the major diastereoisomers of compounds **100a-m** was assigned to be (3*S*,4*R*,5*S*) by analogy to the structure determined by single-crystal X-ray analysis performed on the major diastereoisomer of compound **100i** (see the X-ray analysis section). The relative configuration of racemic minor diastereomer of compounds **100a-m** was assigned to be (3*S**,4*S**,5*R**) by analogy to the structure determined by single-crystal X-ray analysis performed on the minor diastereomer of compound **100e** (see the X-ray analysis section).

Asymmetric one-pot sequential synthesis of tetrahydrothiophene 100b



In a two necked round bottom flask containing anhydrous toluene (4 mL) and molecular sieves (≈ 20 mg), benzoylacetonitrile **96a** (73 mg, 0.50 mmol), benzaldehyde **97a** (51 μL, 0.50 mmol) and piperidine (1 μL, 2 mol %) were added. The reaction was stirred at 80 °C for 9 hours monitored by TLC till the formation of alkene **99a** was complete (eluent PE/ ethyl acetate 8:2). The reaction mixture was allowed to cool up to room temperature, then (*E*)-*tert*-butyl 4-mercaptobut-2-enoate **76b** (113 mg, 0.65 mmol), dissolved in 1 mL of anhydrous toluene, was added to the reaction mixture together with catalyst **105** (42.4 mg, 0.075 mmol). The reaction mixture was stirred at room temperature until completion as monitored by TLC (eluent PE/ ethyl acetate 9:1). The reaction mixture was purified by flash chromatography (eluent PE/ ethyl acetate 95:5) to give product **100b** in 93% yield (190 mg, *dr* 60:40).

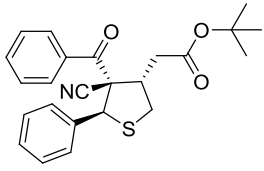
Ethyl 2-((3*S*,4*R*,5*S*)-4-benzoyl-4-cyano-5-phenyltetrahydrothiophen-3-yl)acetate 100a



White wax, 30.3 mg, 80% yield. The diastereoisomeric ratio was found to be 4:1 by ^{1}H-NMR analysis. **FTIR** ν_{max} (KBr)/cm^{-1} 2932, 2237, 1734, 1684, 1597, 1447, 1378, 1278, 1235, 1135, 1024, 699. **MS** (ESI *m/z*) 380.12 [MH+, 15%], 402.10 [MNa+, 100%], 418.16 [MK+, 20%]. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.08 (d, 2H, *J*= 7.6 Hz), 7.71 (d, 2H, *J*= 7.6 Hz), 7.61 (t, 1H, *J*= 7.5 Hz) [minor diast.: 7.56 (d, 0.27H, *J*= 7.2 Hz)], 7.50-7.46 (m, 2H), 7.37-7.29 (m, 3H) [minor diast.: 7.23-7.18 (m, 0.44H)], 5.39 (s, 1H) [minor diast.: 5.02 (s, 0.22H), 4.22 (q, 0.42H, *J*= 7.0 Hz), 4.15- 4.12 (m, 0.22H)], 4.08 (q, 2H, *J*= 7.1 Hz), 3.94 (dd, 1H, J_1= 11.0, J_2= 5.8 Hz), 3.82-3.77 (m, 1H) [minor diast.: 3.53 (dd, 0.22H, J_1= 11.0 Hz, *J*2= 7.7 Hz), 3.20 (t, 0.22H, *J*= 11.0 Hz], 3.08 (dd, 1H, J_1= 11.4, J_2= 2.0 Hz), 2.83 (dd, 1H, J_1= 16.9, J_2= 10.0 Hz) [minor diast.: 2.62 (dd, 0.22H, J_1= 15.6 Hz, J_2= 9.7 Hz), 2.52 (dd, 0.23H, J_1= 15.3 Hz, J_2= 4.6 Hz)], 2.42 (dd, 1H, J_1= 16.9, J_2= 2.8 Hz) [minor diast.: 1.31 (t, 0.67H, *J*= 7.5 Hz)], 1.21 (t, 3H, *J*= 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 190.5, 170.8 [minor diast.: 170.2], 135.4, 134.4, 134.3 [minor diast.: 133.8, 133.5], 129.8 [minor diast.: 129.6], 129.2 [minor diast.: 129.1, 128.9], 128.8, 128.7, 128.3 [minor diast.: 128.1], 118.2, 64.8 [minor diast.: 67.3], 61.11 [minor diast.: 61.06, 60.0], 53.8, 48.8 [minor diast.: 49.8], 35.8 [minor diast.: 35.7, 33.8], 33.6, 14.0 [minor diast.: 14.2].

HPLC analysis with Chiralpak IC column, 90:10 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; **major diast**.: minor enantiomer t_R = 7.0 min, major enantiomer t_R = 7.6 min, *ee* = 98%.

***tert*-Butyl 2-((3*S*,4*R*,5*S*)-4-benzoyl-4-cyano-5-phenyltetrahydrothiophen-3-yl)acetate 100b**



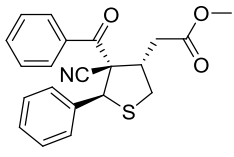
Yellow wax, 38.3 mg, 94% yield. The diastereoisomeric ratio was found to be 9:1 by ^{1}H-NMR analysis. **FTIR** ν_{max} (KBr)/cm^{-1} 2977, 2931, 2237, 1728, 1680, 1597, 1447, 1368, 1236, 1157, 698. **MS** (ESI *m/z*) 408.06 [MH$^+$, 5%], 430.20 [MNa$^+$, 95%], 446.08 [MK$^+$, 27%].

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (d, 2H, *J*= 7.7 Hz), 7.72 (d, 2H, *J*= 7.4 Hz), 7.60 (t, 1H, *J*= 7.3 Hz) [minor diast.: 7.56 (d, 0.22H, *J*= 7.6 Hz)], 7.49-7.46 (m, 2H), 7.37-7.30 (m, 3H) [minor diast.: 7.23-7.21 (m, 0.22H)], 5.40 (s, 1H) [minor diast.: 5.03 (s, 0.11H)], 3.93 (dd, 1H, J_1= 11.2, J_2= 5.9 Hz), 3.81-3.76 (m, 1H) [minor diast.: 3.73-3.69 (m, 0.12H), 3.51 (dd, 0.12H, J_1= 10.8 Hz, J_2= 7.4 Hz), 3.19 (t, 0.11H, *J*= 10.9 Hz)], 3.05 (dd, 1H, J_1= 11.2, J_2= 2.8 Hz), 2.72 (dd, 1H, J_1= 16.7, J_2= 9.9 Hz) [minor diast.: 2.53 (dd, 0.12H, J_1= 15.9, J_2= 10.3 Hz), 2.44 (dd, 0.12H, J_1= 15.9, J_2= 3.8 Hz)], 2.35 (dd, 1H, J_1= 16.8, J_2= 3.5 Hz) [minor diast.: 1.44 (s, 1.07H)], 1.38 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 190.6 [minor diast.: 193.7], 170.0 [minor diast.: 169.3, 136.0], 135.4, 134.5, 134.2 [minor diast.: 133.9], 129.8 [minor diast.: 129.5], 129.2 [minor diast.: 129.1, 128.9], 128.8, 128.7, 128.3 [minor diast.: 128.0], 118.4 [minor diast.: 117.1], 81.7 [minor diast.: 81.5, 67.5],

64.9 [minor diast.: 60.0], 53.9 [minor diast.: 50.1], 49.0, 35.8 [minor diast.: 36.9], 34.8 [minor diast.: 33.7], 27.9.

HPLC analysis with Chiralpak IC column, 98:2 *n*-hexane:2-propanol, 0.7 mL/min, detection at 254 nm; **major diast**.: minor enantiomer t_R = 13.6 min, major enantiomer t_R = 15.8 min, *ee* = 99%.

Methyl 2-((3*S*,4*R*,5*S*)-4-benzoyl-4-cyano-5-phenyltetrahydrothiophen-3-yl)acetate 100c

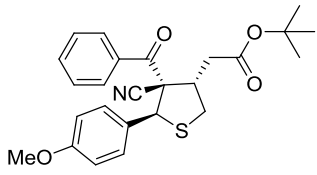


Pale yellow wax, 32.9 mg, 90% yield. The diastereoisomeric ratio was found to be 4:1 by ^{1}H-NMR analysis. **FTIR** ν_{max} (KBr)/cm^{-1} 2927, 2237, 1738, 1679, 1597, 1447, 1378, 1235, 1199, 1022, 698. **MS** (ESI *m/z*) 352.14 [M-CH_3+2H$^+$, 40%].

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (d, 2H, *J*= 7.3 Hz), 7.71 (d, 2H, *J*= 6.8 Hz), 7.61 (t, 1H, *J*= 7.3 Hz) [minor diast.: 7.56 (d, 0.46H, *J*= 7.0 Hz)], 7.50-7.46 (m, 2H), 7.36-7.31 (m, 3H), 5.39 (s, 1H) [minor diast.: 5.01 (s, 0.23H)], 3.93 (dd, 1H, J_1= 10.7, J_2= 5.2 Hz), 3.82-3.79 (m, 1H) [minor diast.: 3.73-3.71 (m, 0.20H), 3.68 (s, 0.62H)], 3.63 (s, 3H) [minor diast.: 3.54-3.50 (m, 0.23H), 3.20 (t, 0.22H, *J*= 11.0 Hz)], 3.07 (d, 1H, *J*= 9.8 Hz), 2.86 (dd, 1H, J_1= 16.9, J_2= 9.6 Hz) [minor diast.: 2.66-2.55 (m, 0.46H)], 2.44 (d, 1H, J_1= 16.6 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 190.5 [minor diast.: 193.5], 171.3 [minor diast.: 170.6, 135.8], 135.4, 134.3 [minor diast.: 133.8], 129.8 [minor diast.: 129.6], 129.2 [minor diast.: 129.1, 128.9], 128.8, 128.7, 128.3 [minor diast.: 128.1], 118.2

[minor diast.: 117.0, 67.2], 64.7 [minor diast.: 60.0], 53.8, 52.1 [minor diast.: 51.7, 49.7], 48.7, 35.8 [minor diast.: 35.4, 33.8], 33.3. HPLC analysis with Chiralpak IC column, 90:10 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; **major diast**.: minor enantiomer t_R = 8.0 min, major enantiomer t_R = 8.5 min, *ee* = 98%.

***tert*-Butyl 2-((3*S*,4*R*,5*S*)-4-benzoyl-4-cyano-5-(4-methoxyphenyl)tetrahydrothiophen-3-yl)acetate 100d**



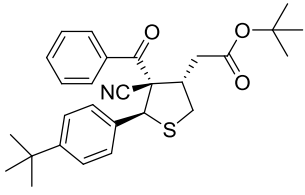
Pale yellow wax, 30.6 mg, 70% yield. The diastereoisomeric ratio was found to be 12:1 by ^{1}H-NMR analysis. **FTIR** ν_{max} (KBr)/cm^{-1} 2926, 2235, 1728, 1680, 1610, 1512, 1447, 1368, 1252, 1158, 1033, 836, 772, 694. **MS** (ESI *m/z*) 438.21 [MH$^+$, 7%], 460.21 [MNa$^+$, 100%], 476.18 [MK$^+$, 18%].

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, 2H, *J*= 7.4 Hz), 7.64 (d, 2H, *J*= 8.8 Hz), 7.60 (t, 1H, *J*= 7.4 Hz), 7.49-7.45 (m, 2H) [minor diast.: 7.30-7.28 (m, 0.10H), 7.25-7.22 (m, 0.09H)], 6.86 (d, 2H, *J*= 8.8 Hz) [minor diast.: 6.83 (d, 0.18H *J*= 8.9 Hz)], 5.37 (s, 1H) [minor diast.: 5.01 (s, 0.09H)], 3.91 (dd, 1H, J_1= 11.2, J_2= 5.9 Hz), 3.79-3.75 (m, 4H) [minor diast.: 3.71-3.68 (m, 0.09H), 3.48 (dd, 0.09H, J_1= 10.8, J_2= 7.1 Hz), 3.17 (t, 0.09H, *J*= 11.0 Hz)], 3.02 (dd, 1H, J_1= 11.2, J_2= 2.9 Hz), 2.70 (dd, 1H, J_1= 16.8, J_2= 10.0 Hz) [minor diast.: 2.53 (dd, 0.09H, J_1= 15.7, J_2= 10.1 Hz), 2.44 (dd, 0.09H, J_1= 15.7, J_2= 4.4 Hz)], 2.33 (dd, 1H, J_1= 16.8, J_2= 3.5 Hz), 1.38 (s, 9H) [minor diast.: 1.44 (s, 0.82H)]. **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 190.7 [minor diast.: 194.0], 170.0 [minor diast.: 169.4,

160.4], 159.9 [minor diast.: 136.1], 134.6, 134.2 [minor diast.: 133.4], 131.0 [minor diast.: 130.3], 129.2 [minor diast.: 128.9], 128.7 [minor diast.: 128.1], 127.0 [minor diast.: 125.6], 118.5 [minor diast.: 117.3, 114.1], 113.6, 81.7 [minor diast.: 81.6, 67.6], 65.0 [minor diast.: 59.5, 55.3], 55.2, 53.4 [minor diast.: 50.0], 48.9 [minor diast.: 37.0], 35.8, 34.8 [minor diast.: 33.7, 29.7], 28.0.

HPLC analysis with Chiralpak ADH column, 90:10 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; **major diast**.: minor enantiomer t_R = 11.5 min, major enantiomer t_R = 8.1 min, *ee* = 99%.

tert-Butyl 2-((3*S*,4*R*,5*S*)-4-benzoyl-5-(4-_tert_-butylphenyl)-4-cyanotetrahydrothiophen-3-yl)acetate 100e



32.4 mg, 70% yield. The diastereoisomeric ratio was found to be 7:1 by ^{1}H-NMR analysis. **FTIR** ν_{max} (KBr)/cm^{-1} 2967, 2869, 2237, 1727, 1681, 1646, 1448, 1368, 1235, 1152, 760, 699, 660. **MS** (ESI *m/z*) 486.50 [MNa$^+$, 30%], 502.15 [MK$^+$, 20%].

Major diast.: waxy pale yellow solid. $[\alpha]_D^{22}$ = -78.9 (*c* 0.6, $CHCl_3$), *ee* = 99%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (d, 2H, *J*= 8.0 Hz), 7.63 (d, 2H, *J*= 8.4 Hz), 7.62-7.58 (m, 1H), 7.49-7.45 (m, 2H), 7.35 (d, 2H, *J*= 8.4 Hz), 5.36 (s, 1H), 3.92 (dd, 1H, J_1= 11.1, J_2= 6.2 Hz), 3.81-3.76 (m, 1H), 3.03 (dd, 1H, J_1= 11.1, J_2= 3.0 Hz), 2.72 (dd, 1H, J_1= 16.7, J_2= 10.2 Hz), 2.33 (dd, 1H, J_1= 16.7, J_2= 3.5 Hz), 1.38 (s, 9H), 1.29 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 190.4, 170.0, 151.7,

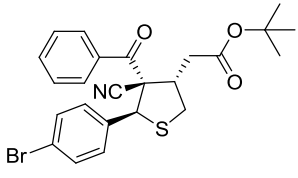
134.4, 134.2, 132.2, 129.5, 129.3, 128.6, 125.2, 118.5, 81.6, 64.8, 53.5, 48.9, 35.7, 34.8, 34.5, 31.2, 27.9.

HPLC analysis with Chiralpak ADH column, 95:5 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; **major diast**.: minor enantiomer t_R = 5.1 min, major enantiomer t_R = 5.7 min, *ee* = 99%.

Minor diast.: white solid, **mp** 114.9-115.7 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (d, 2H, J= 8.4 Hz), 7.43-7.39 (m, 1H), 7.32 (d, 2H, J= 8.4 Hz), 7.17-7.16 (m, 4H), 4.97 (s, 1H), 3.79-3.70 (m, 1H), 3.50 (dd, 1H, J_1= 10.7, J_2= 7.2 Hz), 3.18 (t, 1H, J= 11.0 Hz), 2.52 (dd, 1H, J_1= 15.6, J_2= 10.0 Hz), 2.44 (dd, 1H, J_1= 15.6, J_2= 4.4 Hz), 1.44 (s, 9H), 1.29 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 193.7, 169.4, 153.0, 135.9, 133.3, 130.8, 129.0, 128.8, 127.9, 125.7, 117.3, 81.5, 67.6, 59.7, 49.7, 37.0, 34.7, 33.6, 31.2, 28.0.

***tert*-Butyl 2-((3*S*,4*R*,5*S*)-4-benzoyl-5-(4-bromophenyl)-4-cyanotetrahydrothiophen-3-yl)acetate 100f**



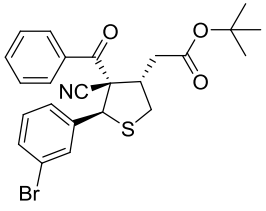
Colourless wax, 47.2 mg, 97% yield. The diastereoisomeric ratio was found to be 10:1 by ^{1}H-NMR analysis. **FTIR** ν_{max} (KBr)/cm^{-1} 2931, 2237, 1729, 1680, 1488, 1447, 1368, 1239, 1158, 1075, 1011, 759, 653. **MS** (ESI *m/z*) 429.77 [M-C$(CH_3)_3$+2H$^+$, 57%], 507.85 [MNa$^+$, 72%].

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, 2H, J= 7.6 Hz), 7.62-7.60 (m, 3H), 7.50-7.43 (m, 4H), 5.37 (s, 1H) [minor diast.: 5.02 (s, 0.09H)], 3.94 (dd, 1H, J_1= 10.7, J_2= 5.7 Hz), 3.84-3.78 (m, 1H) [minor diast.: 3.53-3.48 (m, 0.08H), 3.38 (d, 0.10H, J= 8.2 Hz),

3.22-3.16 (m, 0.09H)], 3.04 (dd, 1H, J_1= 11.3, J_2= 2.4 Hz), 2.66 (dd, 1H, J_1= 16.6, J_2= 9.9 Hz) [minor diast.: 2.54-2.47 (m, 0.20H)], 2.35-2.26 (m, 1H) [minor diast.: 1.43 (s, 0.85H)], 1.37 (s, 9H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 190.3, 169.8, 134.4 [minor diast.: 133.7, 131.9], 131.6, 131.4 [minor diast.: 130.7], 129.2 [minor diast.: 128.9], 128.7 [minor diast.: 128.2], 122.9, 118.2, 81.8, 65.0 [minor diast.: 67.2, 59.1], 53.0 [minor diast.: 50.2], 49.1, 36.0 [minor diast.: 36.9], 34.7 [minor diast.: 33.9], 27.9.

HPLC analysis with Chiralpak ADH column, 90:10 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; **major diast**.: minor enantiomer t_R = 6.4 min, major enantiomer t_R = 6.8 min, *ee* = 99%.

tert-Butyl 2-((3*S*,4*R*,5*S*)-4-benzoyl-5-(3-bromophenyl)-4-cyanotetrahydrothiophen-3-yl)acetate 100g

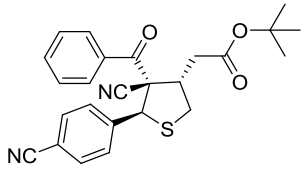


Colourless wax, 47.7 mg, 98% yield. The diastereoisomeric ratio was found to be 10:1 by ^{1}H-NMR analysis. **FTIR** ν_{max} (KBr)/cm^{-1} 2929, 1728, 1678, 1635, 1447, 1368, 1237, 1156, 1074, 757, 695. **MS** (ESI *m/z*) 508.15 [MNa^+, 40%].

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (d, 2H, *J*= 7.4 Hz), 7.86 (t, 1H, *J*= 1.6 Hz), 7.68 (d, 1H, *J*= 7.9 Hz), 7.61 (t, 1H, *J*= 7.4 Hz), 7.51-7.47 (m, 2H), 7.44-7.42 (m, 1H) [minor diast.: 7.38 (d, 0.10H, *J*= 7.2 Hz), 7.29 (d, 0.20H, *J*= 8.2 Hz)], 7.21 (t, 1H, *J*= 7.9 Hz), 5.37 (s, 1H) [minor diast.: 5.00 (s, 0.10H)], 3.95 (dd, 1H, J_1= 11.2, J_2= 5.7 Hz), 3.85-3.80 (m, 1H) [minor diast.: 3.75-3.66 (m, 0.10H), 3.51 (dd, 0.10H, J_1= 10.7, J_2= 6.9 Hz), 3.19 (t, 0.11H, *J*= 11.0 Hz)],

3.04 (dd, 1H, J_1= 11.3, J_2= 2.3 Hz), 2.66 (dd, 1H, J_1= 16.8, J_2= 9.9 Hz) [minor diast.: 2.56 (dd, 0.10H, J_1= 15.8, J_2= 10.0 Hz), 2.47 (dd, 0.11 H, J_1= 15.7, J_2= 4.5 Hz)], 2.28 (dd, 1H, J_1= 16.8, J_2= 3.8 Hz) [minor diast.: 1.44 (s, 0.91H)], 1.37 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 190.2, 169.8, 137.7, 134.4, 134.3, 133.0 [minor diast.: 133.7, 132.6, 132.2], 131.9 [minor diast.: 130.2], 129.8, 129.3 [minor diast.: 128.9], 128.7, 128.6 [minor diast.: 128.3, 127.8], 122.2, 118.1, 81.8, 65.0 [minor diast.: 59.0], 53.0 [minor diast.: 50.2], 49.2, 36.0 [minor diast.: 36.9], 34.7 [minor diast.: 33.9], 27.9. HPLC analysis with Chiralpak ADH column, 90:10 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; **major diast**.: minor enantiomer t_R = 6.6 min, major enantiomer t_R = 6.0 min, *ee* = 99%.

***tert*-Butyl 2-((3*S*,4*R*,5*S*)-4-benzoyl-4-cyano-5-(4-cyanophenyl)tetrahydrothiophen-3-yl)acetate 100h**



42.4 mg, 98% yield. The diastereoisomeric ratio was found to be 9:1 by ^{1}H-NMR analysis. **FTIR** ν_{max} (KBr)/cm^{-1} 2927, 2230, 1728, 1681, 1597, 1447, 1368, 1236, 1157, 839, 759, 694, 657. **MS** (ESI *m/z*) 454.64 [MNa^+, 50%], 470.99 [MK^+, 40%].

Major diast.: white solid, **mp** 130.8-132.7 °C. **$[\alpha]_D^{24}$** = -78.5 (*c* 0.5, $CHCl_3$), *ee* = 99%.

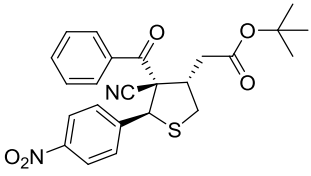
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.10-8.07 (m, 2H), 7.87 (d, 2H, *J*= 8.5 Hz), 7.66-7.61 (m, 3H), 7.52-7.47 (m, 2H), 5.47 (s, 1H), 3.99 (dd, 1H, J_1= 11.3, J_2= 5.5 Hz), 3.91-3.86 (m, 1H), 3.07 (dd, 1H, J_1= 11.3, J_2= 1.8 Hz), 2.65 (dd, 1H, J_1= 16.8, J_2= 9.9 Hz), 2.24 (dd, 1H,

J_1= 16.8, J_2= 3.9 Hz), 1.37 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 189.9, 169.6, 140.8, 134.7, 134.1, 132.0, 130.9, 129.3, 128.9, 118.4, 117.9, 112.7, 82.0, 65.2, 53.0, 49.4, 36.2, 34.6, 27.9.

HPLC analysis with Chiralpak ADH column, 90:10 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; **major diast**.: minor enantiomer t_R = 17.3 min, major enantiomer t_R = 12.6 min, *ee* = 99%.

Minor diast.: waxy white solid. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.66 (d, 2H, *J*= 8.3 Hz), 7.59 (d, 2H, *J*= 8.3 Hz), 7.50 (t, 1H, *J*= 7.4 Hz), 7.39-7.38 (m, 2H), 7.30-7.28 (m, 2H), 5.11 (s, 1H), 3.73-3.68 (m, 1H), 3.53 (dd, 1H, J_1= 10.8, J_2= 7.0 Hz), 3.22 (t, 1H, *J*= 11.0 Hz), 2.56 (dd, 1H, J_1= 15.8, J_2= 9.8 Hz), 2.48 (dd, 1H, J_1= 15.8, J_2= 4.6 Hz), 1.42 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 192.8, 169.1, 139.6, 135.7, 134.0, 132.4, 130.0, 128.8, 128.4, 118.1, 116.7, 113.2, 81.8, 66.9, 59.0, 50.4, 36.8, 34.1, 27.9.

***tert*-Butyl 2-((3*S*,4*R*,5*S*)-4-benzoyl-4-cyano-5-(4-nitrophenyl)tetrahydrothiophen-3-yl)acetate 100i**



44.3 mg, 98% yield. The diastereoisomeric ratio was found to be 9:1 by ^{1}H-NMR analysis. **FTIR** ν_{max} (KBr)/cm^{-1} 2937, 1727, 1677, 1636, 1525, 1447, 1368, 1349, 1236, 1156, 756, 697. **MS** (ESI *m/z*) 475.13 [MNa^+, 42%], 491.33 [MK^+, 15%].

Major diast.: white solid, **mp** 122.0-125.0 °C. **$[\alpha]_D^{22}$** = -92.3 (*c* 0.8, $CHCl_3$), *ee* >99%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19 (d, 2H, *J*= 8.8 Hz), 8.09 (d,

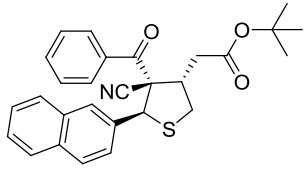
2H, *J*= 7.5 Hz), 7.94 (d, 2H, *J*= 8.8 Hz), 7.63 (t, 1H, *J*= 7.5 Hz), 7.51-7.47 (m, 2H), 5.53 (s, 1H), 4.02 (dd, 1H, J_1= 11.4, J_2= 5.6 Hz), 3.92-3.89 (m, 1H), 3.08 (d, 1H, *J*= 11.4 Hz), 2.66 (dd, 1H, J_1= 16.8, J_2= 10.0 Hz), 2.25 (dd, 1H, J_1= 16.8, J_2= 3.7 Hz), 1.37 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.8, 169.5, 148.0, 142.7, 134.7, 134.0, 131.2, 129.3, 128.8, 123.3, 117.8, 82.0, 65.2, 52.7, 49.4, 36.3, 34.5, 27.9.

HPLC analysis with Chiralpak ADH column, 98:2 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; **major diast**.: major enantiomer t_R = 34.4 min, *ee* >99%.

Minor diast.: colourless waxy solid. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.16 (d, 2H, *J*= 8.8 Hz), 7.73 (d, 2H, *J*= 8.8 Hz), 7.52-7.43 (m, 3H), 7.31-7.29 (m, 2H), 5.19 (s, 1H), 3.76-3.67 (m, 1H), 3.55 (dd, 1H, J_1= 10.8, J_2= 7.0 Hz), 3.24 (t, 1H, *J*= 11.0 Hz), 2.59 (dd, 1H, J_1= 15.9, J_2= 9.8 Hz), 2.50 (dd, 1H, J_1= 15.9, J_2= 4.6 Hz), 1.43 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 192.8, 169.1, 148.4, 141.6, 135.8, 134.1, 130.3, 128.8, 128.5, 123.8, 116.7, 81.9, 66.9, 58.7, 50.6, 36.8, 34.2, 28.0.

***tert*-Butyl 2-((3*S*,4*R*,5*S*)-4-benzoyl-4-cyano-5-(naphthalen-2-yl)tetrahydrothiophen-3-yl)acetate 100j**



38.9 mg, 85% yield. The diastereoisomeric ratio was found to be 9:1 by ^{1}H-NMR analysis. **FTIR** ν_{max} (KBr)/cm^{-1} 2930, 2237, 1728, 1678, 1597, 1447, 1368, 1238, 1156, 755, 694. **MS** (ESI *m/z*) 480.19 [MNa^+, 28%], 496.19 [MK^+, 28%].

Major diast.: yellow solid, **mp** 63.5-65.7 °C. $[\alpha]_D^{21}$ = -53.9 (*c* 0.7, $CHCl_3$), *ee* >99%.

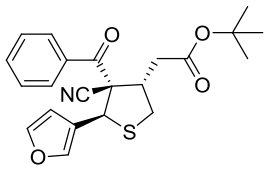
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (s, 1H), 8.07 (d, 2H, *J*= 7.8 Hz), 7.88-7.79 (m, 4H), 7.58 (t, 1H, *J*= 7.5 Hz), 7.48-7.44 (m, 4H), 5.58 (s, 1H), 4.00 (dd, 1H, J_1= 11.0, J_2= 6.0 Hz), 3.88-3.82 (m, 1H), 3.10 (dd, 1H, J_1= 11.1, J_2= 3.0 Hz), 2.76 (dd, 1H, J_1= 16.8, J_2= 9.9 Hz), 2.39 (dd, 1H, J_1= 16.9, J_2= 3.7 Hz), 1.39 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 190.7, 170.0, 134.5, 134.2, 133.4, 132.9, 132.7, 129.5, 129.2, 128.6, 128.2, 127.9, 127.5, 127.1, 126.5, 126.2, 118.5, 81.7, 65.0, 54.0, 49.2, 36.0, 34.8, 28.0.

HPLC analysis with Chiralpak IC column, 98:2 *n*-hexane:2-propanol, 0.7 mL/min, detection at 254 nm; **major diast**.: major enantiomer t_R = 21.6 min, *ee* > 99%.

Minor diast.: pale yellow solid, **mp** 143.7-144.7 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (s, 1H), 7.82-7.75 (m, 3H), 7.68 (dd, 1H, J_1= 8.5, J_2= 1.8 Hz), 7.51-7.44 (m, 2H), 7.36-7.32 (m, 1H), 7.28-7.27 (m, 1H), 7.26-7.25 (m, 1H), 7.11-7.07 (m, 2H), 5.24 (s, 1H), 3.83-3.75 (m, 1H), 3.56 (dd, 1H, J_1= 10.8, J_2= 7.0 Hz), 3.25 (t, 1H, *J*= 11.0 Hz), 2.57 (dd, 1H, J_1= 15.7, J_2= 10.2 Hz), 2.48 (dd, 1H, J_1= 15.7, J_2= 4.4 Hz), 1.45 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 193.9, 169.4, 136.0, 133.7, 133.4, 133.0, 131.3, 128.8, 128.6, 128.2, 128.1, 127.6, 126.7, 126.5, 126.2, 117.2, 81.6, 67.5, 60.1, 50.4, 36.9, 33.9, 28.0.

***tert*-Butyl 2-((3*S*,4*R*,5*S*)-4-benzoyl-4-cyano-5-(furan-3-yl)tetrahydrothiophen-3-yl)acetate 100k**



28.6 mg, 72% yield. The diastereoisomeric ratio was found to be 9:1 by ^{1}H-NMR analysis. **FTIR** ν_{max} (KBr)/cm^{-1} 2931, 2237, 1728, 1677, 1598, 1447, 1368, 1239, 1159, 1023, 874, 695. **MS** (ESI *m/z*) 420.20 [MNa^{+}, 100%].

Major diast.: white solid, **mp** 109.0-110.4 °C. **[α]$_D^{22}$** = -82.8 (*c* 0.6, $CHCl_3$), *ee* = 99%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (d, 2H, *J*= 7.7 Hz), 7.65-7.61 (m, 2H), 7.52-7.48 (m, 2H), 7.35 (bs, 1H), 6.62 (bs, 1H), 5.31 (s, 1H), 3.89 (dd, 1H, J_1= 11.2, J_2= 5.8 Hz), 3.82-3.78 (m, 1H), 2.98 (dd, 1H, J_1= 11.2, J_2= 1.6 Hz), 2.59 (dd, 1H, J_1= 16.7, J_2= 10.0 Hz), 2.21 (dd, 1H, J_1= 16.7, J_2= 3.6 Hz), 1.36 (s, 9H).

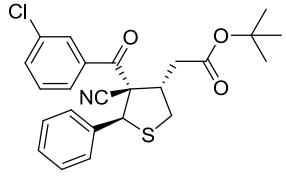
^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.3, 169.8, 143.1, 142.5, 134.5, 134.3, 129.3, 128.8, 120.7, 118.3, 110.9, 81.8, 64.5, 48.5, 45.3, 35.5, 34.7, 27.9. HPLC analysis with Chiralpak ADH column, 90:10 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; **major diast**.: minor enantiomer t_R = 7.1 min, major enantiomer t_R = 6.3 min, *ee* = 99%.

Minor diast.: pale yellow solid, **mp** 81.2-83.7 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64-7.61 (m, 2H), 7.56-7.52 (m, 1H), 7.44-7.35 (m, 4H), 6.66 (d, 1H, *J*= 1.2 Hz), 4.98 (s, 1H), 3.68-3.60 (m, 1H), 3.46 (dd, 1H, J_1= 10.7, J_2= 7.2 Hz), 3.13 (t, 1H, 11.0 Hz), 2.54 (dd, 1H, J_1= 15.8, J_2= 9.7 Hz), 2.47 (dd, 1H, J_1= 15.8, J_2= 4.8 Hz), 1.42 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 193.6, 169.3, 143.8, 142.0, 136.1, 133.7, 129.0, 128.3, 119.7, 117.3, 110.4, 81.6,

66.7, 50.7, 49.8, 37.0, 33.7, 28.0.

***tert*-Butyl 2-((3*S*,4*R*,5*S*)-4-(3-chlorobenzoyl)-4-cyano-5-phenyltetrahydrothiophen-3-yl)acetate 100l**



42.4 mg, 96% yield. The diastereoisomeric ratio was found to be 5:1 by ^{1}H-NMR analysis. **FTIR** ν_{max} (KBr)/cm^{-1} 2932, 2236, 1729, 1683, 1645, 1455, 1368, 1233, 1159, 759, 700. **MS** (ESI *m/z*) 441.89 [MH$^+$, 15%], 464.26 [MNa$^+$, 52%].

Major diast.: pale yellow wax. $[\alpha]_D^{21}$ = -86.2 (*c* 1.0, $CHCl_3$), *ee* = 98%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98 (d, 1H, *J*= 8.1 Hz), 7.94 (s, 1H), 7.69 (d, 2H, *J*= 7.4 Hz), 7.56 (d, 1H, *J*= 8.3 Hz), 7.42 (t, 1H, *J*= 8.0 Hz), 7.38-7.30 (m, 3H), 5.35 (s, 1H), 3.92 (dd, 1H, J_1= 11.4, J_2= 5.8 Hz), 3.78-3.72 (m, 1H), 3.04 (dd, 1H, J_1= 11.2, J_2= 3.0 Hz), 2.71 (dd, 1H, J_1= 17.0, J_2= 9.5 Hz), 2.38 (dd, 1H, J_1= 17.0, J_2= 4.5 Hz), 1.39 (s, 9H).

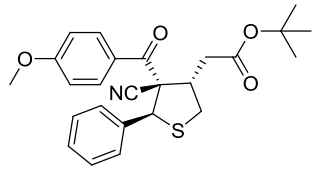
^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.9, 169.8, 136.1, 135.1, 134.0, 129.8, 129.7, 129.2, 128.9, 128.4, 127.0, 118.1, 81.7, 65.0, 54.0, 48.9, 35.9, 34.9, 27.9.

HPLC analysis with Chiralpak ADH column, 90:10 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; **major diast**.: minor enantiomer t_R = 5.9 min, major enantiomer t_R = 5.4 min, *ee* = 98%.

Minor diast.: Colourless wax. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.56-7.54 (m, 2H), 7.40-7.32 (m, 4H), 7.21 (t, 1H, *J*= 1.6 Hz), 7.11 (t, 1H, *J*= 7.9 Hz), 7.00-6.99 (m, 1H), 4.98 (s, 1H), 3.78-3.70 (m,

1H), 3.51 (dd, 1H, J_1= 10.8, J_2= 7.2 Hz), 3.18 (t, 1H, J= 11.0 Hz), 2.53 (dd, 1H, J_1= 15.8, J_2= 9.8 Hz), 2.43 (dd, 1H, J_1= 15.8, J_2= 4.7 Hz), 1.44 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 192.7, 169.3, 137.3, 134.5, 133.6, 133.3, 129.8, 129.2, 129.1, 129.0, 128.9, 126.9, 116.9, 81.7, 67.6, 60.2, 49.9, 36.9, 33.8, 28.0.

***tert*-Butyl 2-((3*S*,4*R*,5*S*)-4-cyano-4-(4-methoxybenzoyl)-5-phenyltetrahydrothiophen-3-yl)acetate 100m**



42.9 mg, 98% yield. The diastereoisomeric ratio was found to be 9:1 by ^{1}H-NMR analysis. **FTIR** ν_{max} (KBr)/cm^{-1} 2977, 2934, 1729, 1671, 1600, 1574, 1455, 1369, 1251, 1174, 1134, 1023, 844, 772, 705. **MS** (ESI *m/z*) 438.21 [MH^+, 3%], 460.14 [MNa^+, 35%], 476.14 [MK^+, 5%].

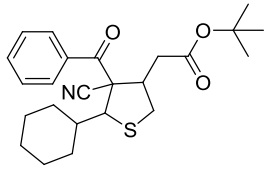
Major diast.: white wax. **$[\alpha]_D^{18}$** = -79.8 (*c* 0.7, $CHCl_3$), *ee* = 99%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (d, 2H, J= 8.8 Hz), 7.73 (d, 2H, J= 7.6 Hz), 7.36-7.29 (m, 3H), 6.93 (d, 2H, J= 8.8 Hz), 5.42 (s, 1H), 3.92 (dd, 1H, J_1= 11.2, J_2= 5.7 Hz), 3.87 (s, 3H), 3.78-3.73 (m, 1H), 3.04 (dd, 1H, J_1= 11.2, J_2= 2.4 Hz), 2.70 (dd, 1H, J_1= 16.7, J_2= 10.4 Hz), 2.27 (dd, 1H, J_1= 16.7, J_2= 3.3 Hz), 1.38 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 188.1, 170.1, 164.4, 135.6, 132.0, 129.9, 128.7, 128.2, 127.0, 118.7, 113.9, 81.6, 64.5, 55.6, 53.6, 49.1, 35.7, 34.6, 27.9.

HPLC analysis with Chiralpak ADH column, 80:20 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; **major diast**.: minor enantiomer t_R = 12.2 min, major enantiomer t_R = 7.2 min, *ee* = 99%.

Minor diast.: pale yellow wax. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.55-7.53 (m, 2H), 7.33-7.28 (m, 5H), 6.66 (d, 2H, J= 9.0 Hz), 4.96 (s, 1H), 3.80-3.70 (m, 4H), 3.50 (dd, 1H, J_1= 10.6, J_2= 7.0 Hz), 3.19 (t, 1H, J= 11.0 Hz), 2.51 (dd, 1H, J_1= 15.6, J_2= 10.2 Hz), 2.44 (dd, 1H, J_1= 15.6, J_2= 4.3 Hz), 1.44 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 191.0, 169.5, 163.8, 134.2, 131.9, 129.4, 129.2, 128.7, 128.6, 117.6, 113.3, 81.5, 66.8, 59.6, 55.5, 49.8, 36.9, 33.6, 28.0.

***tert*-Butyl 2-(4-benzoyl-4-cyano-5-cyclohexyltetrahydrothiophen-3-yl)acetate 100n**



40.5 mg, 98% yield. The diastereoisomeric ratio was found to be 1:1 by ^{1}H-NMR analysis. **FTIR** ν_{max} (KBr)/cm^{-1} 2928, 2853, 2236, 1732, 1679, 1597, 1447, 1368, 1236, 1159, 1136, 1022, 845, 759, 695, 653. **MS** (ESI *m/z*) 414.21 [MH^+, 15%], 436.20 [MNa^+, 100%], 452.14 [MK^+, 18%].

First diast.: Colourless wax. **$[\alpha]_D^{22}$** = -73.3 (*c* 0.5, $CHCl_3$), *ee* >99%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (d, 2H, J= 7.7 Hz), 7.65-7.62 (m, 1H), 7.53-7.50 (m, 2H), 4.10 (d, 1H, J= 10.1 Hz), 3.74-3.67 (m, 2H), 2.89 (d, 1H, J= 10.5 Hz), 2.52 (dd, 1H, J_1= 16.9, J_2= 8.5 Hz), 2.29-2.23 (m, 1H), 2.01-1.61 (m, 6H), 1.33 (s, 9H), 1.19-1.05 (m, 3H), 0.96-0.83 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.9, 170.1, 135.0, 134.0, 129.2, 128.6, 118.8, 81.5, 61.4, 56.8, 49.7, 43.6, 35.7, 34.9, 33.6, 33.4, 27.9, 26.1, 26.0, 25.8.

HPLC analysis with Chiralpak IC column, 98:2 *n*-hexane:2-

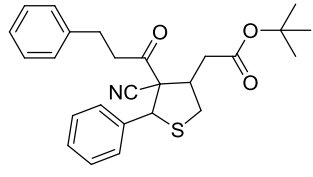
propanol, 0.7 mL/min, detection at 254 nm; **first diast**.: major enantiomer t_R = 9.8 min, *ee* >99%.

Second diast.: white solid, **mp** 101.7-104.5 °C. $[\alpha]_D^{22}$ = +12.0 (*c* 0.9, $CHCl_3$), *ee* = 87%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, 2H, *J*= 7.9 Hz), 7.65-7.61 (m, 1H), 7.54-7.50 (m, 2H), 4.15 (d, 1H, *J*= 10.5 Hz), 3.33-3.25 (m, 2H), 2.98-2.92 (m, 1H), 2.63 (dd, 1H, J_1= 15.6, J_2= 9.8 Hz), 2.54 (dd, 1H, J_1= 15.6, J_2= 4.2 Hz), 1.85-1.60 (m, 4H), 1.45-1.42 (m, 2H), 1.36 (s, 9H), 1.25-0.99 (m, 3H), 0.89-0.75 (m, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 194.0, 169.1, 136.0, 133.8, 129.2, 128.7, 117.1, 81.7, 63.6, 62.0, 52.0, 42.6, 36.9, 33.2, 33.0, 32.9, 27.9, 25.8, 25.69, 25.66.

HPLC analysis with Chiralpak IC column, 98:2 *n*-hexane:2-propanol, 0.7 mL/min, detection at 254 nm; **second diast**.: minor enantiomer t_R = 14.5 min, major enantiomer t_R = 17.4 min, *ee* = 87%.

***tert*-Butyl 2-(4-cyano-5-phenyl-4-(3-phenylpropanoyl)tetrahydrothiophen-3-yl)acetate 100o**



Pale yellow wax, 35.3 mg, 79% yield. The diastereoisomeric ratio was found to be 3:1 by ^{1}H-NMR analysis. **FTIR** ν_{max} (KBr)/cm^{-1} 2978, 2932, 1726, 1652, 1497, 1454, 1393, 1368, 1154, 843, 751, 700. **MS** (ESI *m/z*) 458.18 [MNa^+, 100%], 474.25 [MK^+, 55%].

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54-7.51 (m, 2H) [minor diast.: 7.41-7.39 (m, 0.66H)], 7.34-7.27 (m, 4H), 7.25-7.11 (m, 4H) [minor

diast.: 7.03-7.01 (m, 0.67H)], 5.11 (s, 1H) [minor diast.: 4.81 (s, 0.33H)], 3.79 (dd, 1H, J_1= 11.4, J_2= 5.8 Hz), 3.50-3.44 (m, 1H) [minor diast.: 3.43-3.36 (m, 0.66H)], 3.18-3.10 (m, 1H) [minor diast.: 3.05 (t, 0.33H, J= 13.4 Hz)], 3.00-2.90 (m, 1H), 2.86 (dd, 1H, J_1= 11.4, J_2= 2.5 Hz), 2.81 (t, 2H, J= 7.2 Hz) [minor diast.: 2.78-2.71 (m, 0.66H), 2.53-2.47 (m, 0.33H], 2.42 (dd, 1H, J_1= 17.5, J_2= 7.2 Hz), 2.36 (dd, 1H, J_1= 17.5, J_2= 6.6 Hz) [partially overlapped with minor diast.: 2.35-2.24 (m, 0.66H)], 1.46 (s, 9H) [minor diast.: 1.44 (s, 2.96H)]. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 200.3 [minor diast.: 201.3], 170.2 [minor diast.: 169.4], 139.9 [minor diast.: 139.8], 134.7 [minor diast.: 133.5, 129.4], 129.3 [minor diast.: 128.9, 128.8, 128.6], 128.51, 128.48, 128.4, 126.36 [minor diast.: 126.30], 118.5, 81.7 [minor diast.: 68.9], 67.4 [minor diast.: 59.5], 53.6, 48.9 [minor diast.: 48.2, 45.6], 44.4, 37.0, 35.1 [minor diast.: 34.1, 29.7], 29.1 [minor diast.: 28.8], 28.1 [minor diast.: 28.0].

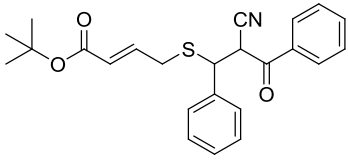
HPLC analysis with Chiralpak IA-3 column, 100:1 *n*-hexane: ethanol, 1 mL/min, detection at 210 nm; **major diast**.: major enantiomer t_R = 8.6 min, minor enantiomer t_R = 9.5 min, *ee* = 89%.

Michael reaction to racemic product 109

A sample vial was charged with (*E*)-*tert*-butyl 4-mercaptobut-2-enoate **76b** (22.6 mg, 0.13 mmol) and compound **99a** (23.3 mg, 0.10 mmol) in chloroform (1.0 mL) under nitrogen atmosphere. 1,4-Diazabicyclo[2.2.2]octane (3.3 mg, 0.03 mmol) was added and the solution was stirred at -20 °C for 17 hours. Michael adduct **109** was recovered by flash chromatography (eluent PE/ ethyl acetate 98:2 to

95:5) as mixture of diastereoisomers (dr 1:1) and residual **99a** (23.2 mg, 70% purity) as these compounds have the same Rf (TLC eluent PE/ ethyl acetate 90:10). Attempts to remove **99a** by crystallization failed.

(*E*)-*tert*-Butyl 4-(2-cyano-3-oxo-1,3-diphenylpropylthio)but-2-enoate 109



23.2 mg, 70% purity. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ [**99a**: 8.06-8.02 (m, 2.57H)], 7.95 (d, 2H, *J*= 7.7 Hz) [**99a**: 7.90 (d, 1.70H, *J*= 7.4 Hz)], 7.81 (d, 2H, *J*= 7.6 Hz), 7.69-7.51 (m, 6H overlapped with **99a**: m, 5.10 H), 7.47-7.28 (m, 9H), 7.24-7.20 (m, 1H), 6.68-6.56 (m, 2H), 5.66 (d, 1H, *J*= 15.4 Hz) partially overlapped with 5.65 (d, 1H, *J*= 15.4 Hz), 4.822 (d, 1H, *J*= 8.4 Hz) partially overlapped with 4.82 (d, 1H, *J*= 8.7 Hz), 4.51 (d, 1H, *J*= 8.4 Hz), 4.46 (d, 1H, *J*= 8.7 Hz), 3.25 (dd, 1H, J_1= 14.2, J_2= 6.8 Hz), 3.16-2.99 (m, 3H), 1.47 (s, 18H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ [**99a**: 188.96] 188.63, 188,60, 164.92, 164.89 [**99a**: 155.56], 140.98, 140.79, 137.55, 136.68 [**99a**: 135.74], 134.70, 134.66, 134.57, 134.12 [**99a**: 133.42, 133.39, 131.75, 131.09, 129.31, 129.30], 129.16, 129.02, 128.99, 128.91, 128.88, 128.83 [**99a**: 128.67], 128.58, 128.45, 128.00, 125.72 [**99a**: 116.84], 115.39, 115.04 [**99a**: 110.11], 80.70, 80.63, 48.09, 47.72, 46.37, 45.86, 33.08, 32.88, 28.06.

Michael reaction of adduct 109

Compound **109** (23.2 mg, 70% purity) was dissolved in anhydrous toluene (460 μL), then catalyst **105** was added (2.6 mg, 0.0046 mmol) and the reaction mixture was stirred at room temperature monitored by TLC (eluent PE/ ethyl acetate 90:10). The crude mixture was purified by flash chromatography (eluting from PE/ ethyl acetate 98:2 to 90:10) to give **100b** (13.7 mg, 75% yield). The diastereoisomeric ratio was found to be 9:1 by ^{1}H-NMR analysis of crude reaction mixture.

X-Ray data for the absolute configuration assignment of compound 100i

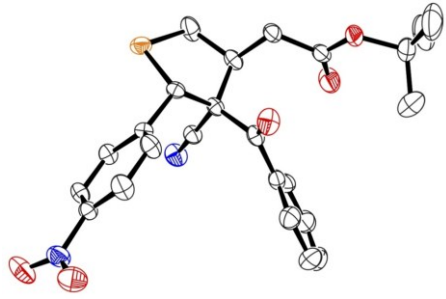
Single crystals of major diastereoisomer of compound **100i** were obtained by slow evaporation of a *n*-hexane / ethanol solvent mixture at room temperature.

Single crystal diffraction data were collected on a Oxford Xcalibur CCD area detector diffractometer, using graphite monochromatic Mo Kα (λ = 0.71069Å) radiation. Data reduction and absorption correction were performed using CrysAlisPRO 171.34.44 (Oxford Diffraction). The structure was solved by direct methods using SIR2011[251] and refined by full-matrix least squares using SHELX-97[252]. Hydrogen atoms were generated in calculated position using SHELX-97. The absolute structure of the title compound was determined on the basis of the Flack x parameter[253].

CCDC 937229 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Details of data collections and refinements are given in table below.

ORTEP plot with 30% probability ellipsoids (for seek of brevity H atoms are not shown).



Crystal data

Empirical formula	$C_{24}\ H_{24}\ N_2\ O_5\ S_1$
Formula weight	452.51
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 21
Unit cell dimensions	a = 10.107(1) Å
	b = 6.848(9) Å
	c = 16.925(2) Å
Volume	1171.49(14) $Å^3$
Z	2
Density (calculated)	1.283 Mg/m^3
Absorption coefficient	0.18 mm^{-1}
F(000)	476
Crystal size	068 x 0.4 x 0.2
mm^3	

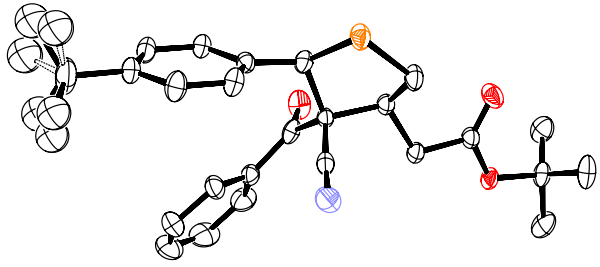
Theta range for data collection	4.1 to 28.2°.
Index ranges	-13<=h<=13, -9<=k<=8, -22<=l<=22
Reflections collected	48340
Independent reflections	5483 [R(int) = 0.1]
Completeness to theta = 25.0°	98.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.978
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4481 / 1 / 249
Goodness-of-fit on F^2	1.046
Final R indices [I>2sigma(I)]	R1 = 0.051, wR2 = 0.103
R indices (all data)	R1 = 0.1119, wR2 = 0.0865
Largest diff. peak and hole	0.15and -0.18 $e.V.^{-3}$

X-Ray data for the relative configuration assignment of the minor diastereoisomer of compound 100e

Single crystals of minor diastereoisomer of compound **100e** were obtained by slow evaporation of ethanol at room temperature.

Single crystal diffraction data were collected on an Oxford Xcalibur CCD area detector diffractometer, using graphite monochromatic Mo Kα (λ = 0.71069Å) radiation. Data reduction and absorption correction were performed using CrysAlisPRO 171.34.44 (Oxford Diffraction). The structure was solved by direct methods using SIR2011[251] and refined by full-matrix least squares using SHELX-97[252]. The *tert*-butyl disordered part of the model was restrained with the SADI and EADP SHELX-97 instructions. Hydrogen atoms were generated in calculated position using SHELX-97. CCDC 937228 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Details of data collections and refinements are given in table below.

ORTEP plot with 30% probability ellipsoids (disordered part is represented with dotted bond; for seek of brevity H atoms are not shown).



Crystal data

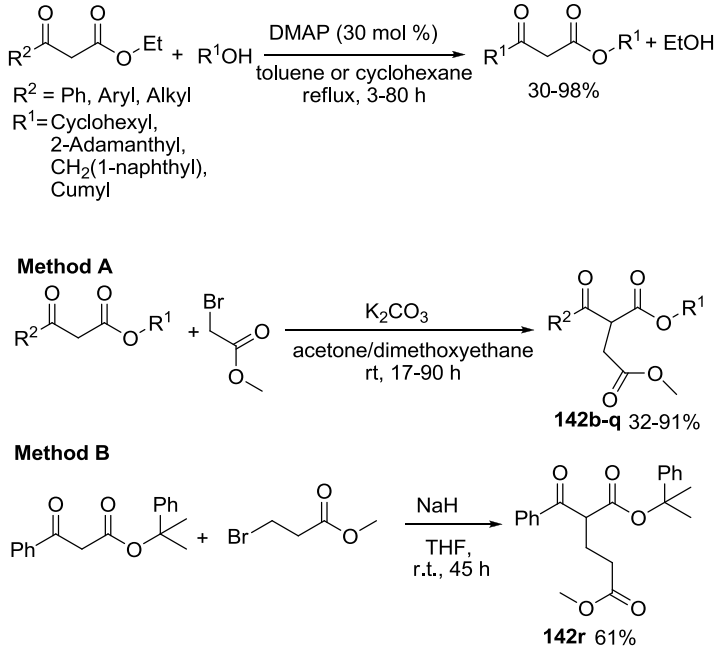
Empirical formula	$C_{28}\ H_{33}\ N\ O_3\ S$
Formula weight	463.61
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 11.835(5) Å
	b = 11.975(5) Å
	c = 12.118(5) Å
Volume	1334.0(10) $Å^3$
Z	2
Density (calculated)	1.154 Mg/m^3
Absorption coefficient	0.149 mm^{-1}
F(000)	496
Crystal size	0.5 x 0.5 x 0.4 mm^3
Theta range for data collection	4.17 to 30.48°.

Index ranges	-15<=h<=15, -16<=k<=17, -16<=l<=17
Reflections collected	19077
Independent reflections	6365 [R(int) = 0.1110]
Completeness to theta = 25.0°	89.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.96940
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6365 / 30 / 293
Goodness-of-fit on F^2	1.069
Final R indices [I>2sigma(I)]	R1 = 0.1269, wR2 = 0.2229
R indices (all data)	R1 = 0.2377, wR2 = 0.2724
Largest diff. peak and hole	0.493 and -0.359 e.V.$^{-3}$

6.3 Enantioselective synthesis of γ-butyrolactones bearing an all-carbon β-quaternary stereocentre

Experimental procedures and compounds characterization

General procedure for synthesis of compounds 142a-r



tert-Butyl 3-oxo-3-phenylpropanoate was synthesized according to the literature.[254]

β-Keto esters were synthesized according to a slightly modified literature procedure.[255] To a flask equipped with a Dean-Stark trap and reflux condenser was added β-keto ethyl ester (1 mmol), corresponding alcohol (2 mmol),[vi] DMAP (36.7 mg, 0.3 mmol) in

[vi] For the synthesis of cyclohexyl 3-oxo-3-phenylpropanoate and 2-phenylpropan 2-yl 3- (naphthalen-2-yl)-3-oxopropanoate 3 mmol and 4 mmol of alchohol were respectively added.

toluene (20 mL). For the synthesis of 2-phenylpropan-2-yl 3-(naphthalen-2-yl)-3-oxopropanoate cyclohexane was used as solvent. The mixture was heated to reflux, distilling the ethanol formed during the reaction. After completion, monitored by ^{1}H NMR spectroscopy, the reaction mixture was directly loaded onto silica gel and purified by flash chromatography (eluting in gradient from PE/ ethyl acetate 98:2 to 95:5) to give the β-keto esters. Compound **142a** was synthesized according to literature procedure.[256]

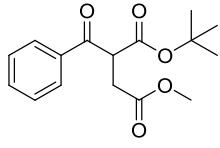
Compounds **142b-q** were synthesized as described here:[256b]

METHOD A: In a screw capped vial containing acetone (3 mL) and dimethoxyethane (2 mL) the appropiate β-keto ester (1 mmol) and K_2CO_3 (152 mg, 1.1 mmol) were added. Methyl bromoacetate (99 μL, 1.05 mmol) was then added and the mixture stirred until completion (17-90 h), monitored by TLC (eluent PE/ ethyl acetate 90:10, visualized by UV and, when necessary, by anisaldehyde staining solution). The crude mixture was diluted with ethyl acetate and water was added, followed by HCl 1N to adjust at pH ~ 7. The organic layer was washed with water two times and then dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by flash chromatography (eluting with a gradient PE/ diethyl ether 95:5 to 80:20) to give compounds **142b-q**.

Compound **142r** was synthesized according to **METHOD B**:[257] NaH (60% w/w dispersion in mineral oil, 36 mg, 0.89 mmol) was suspended in dry THF (600 μL) under nitrogen atmosphere and the suspension was cooled to 0 °C. A solution of 2-phenylpropan-2-yl

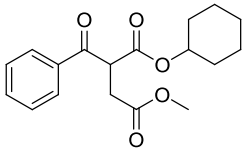
3-oxo-3-phenylpropanoate (250 mg, 0.89 mmol), in dry THF (200 μL) was added dropwise over 30 minutes to the suspension of NaH. The mixture was stirred at room temperature for 15 min and then a solution of methyl 3-bromopropanoate (97 μL, 0.89 mmol), in dry THF (400 μL) was added dropwise over 20 minutes. The reaction was stirred at room temperature for 45 hours, monitored by TLC (eluent PE/ ethyl acetate 8:2). After cooling, the reaction mixture was quenched with water and extracted with diethyl ether. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash chromatography (eluting with a gradient PE/ diethyl ether 90:10 to 70:30) to give the product **142r** (201 mg, 61% yield).

1-*tert*-Butyl 4-methyl 2-benzoylsuccinate (142b)



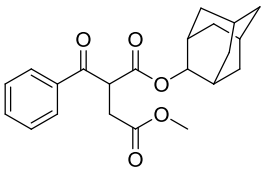
Colourless oil, 150.3 mg, 68% yield. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 8.07-7.98 (m, 2H), 7.63-7.53 (m, 1H), 7.52-7.40 (m, 2H), 4.80-4.72 (m, 1H), 3.67 (s, 3H), 3.06 (dd, 1H, J = 17.3, 7.7 Hz), 2.96 (dd, 1H, J = 17.3, 6.7 Hz), 1.32 (s, 9H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 194.5, 171.9, 167.6, 136.2, 133.4, 128.8, 128.5, 82.5, 52.0, 50.8, 32.8, 27.6. **MS** (ESI *m/z*) 315.6 [MNa^+, 16%]. Elemental analysis calcd (%) for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90; found: C, 66.00; H, 6.81.

1-Cyclohexyl 4-methyl 2-benzoylsuccinate (142c)



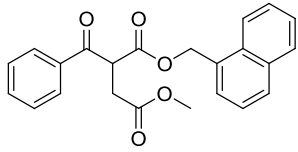
White wax, 332 mg, 85% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.04 (d, 2H, J= 7.6 Hz), 7.62-7.55 (m, 1H), 7.51-7.45 (m, 2H), 4.87-4.82 (m, 1H), 4.81-4.73 (m, 1H), 3.68 (s, 3H), 3.11 (dd, 1H, J = 17.3, 7.9 Hz), 3.02 (dd, 1H, J = 17.3, 6.4 Hz), 1.74-1.62 (m, 2H), 1.46-1.16 (m, 8H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 194.2, 171.8, 168.0, 136.0, 133.5, 128.8, 128.6, 74.0, 52.0, 49.9, 32.8, 31.0, 30.9, 25.1, 23.1, 23.0. **MS** (ESI *m/z*) 340.9 [MNa^+, 100%], 356.8 [MK^+, 7%]. Elemental analysis calcd (%) for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97; found C, 67.70; H, 7.09.

2-Adamantyl 4-methyl 2-benzoylsuccinate (142d)



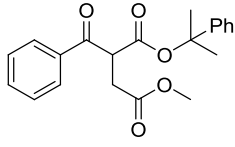
White solid, 371 mg, 82% yield. **mp** 66.9-69.8 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.09-8.04 (m, 2H), 7.62-7.55 (m, 1H), 7.52-7.44 (m, 2H), 4.92 (dd, 2H, J = 8.1, 6.4 Hz), 3.68 (s, 3H), 3.15 (dd, 1H, J = 17.4, 8.1 Hz), 3.05 (dd, 1H, J = 17.4, 6.3 Hz), 1.89-1.82 (m, 2H), 1.81-1.72 (m, 3H), 1.71-1.54 (m, 7H), 1.43-1.34 (m, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 194.3, 171.9, 167.9, 136.2, 133.5, 128.9, 128.6, 78.8, 52.0, 49.7, 37.2, 36.15, 36.10, 32.9, 31.7, 31.5, 31.38, 31.35, 26.9, 26.8. **MS** (ESI *m/z*) 371.1 [MH^+, 2%], 392.9 [MNa^+, 100%], 409.0 [MK^+, 11%]. Elemental analysis calcd (%) for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07; found C, 71.04; H, 6.83

4-Methyl 1-naphthalen-1-ylmethyl 2-benzoylsuccinate (142e)



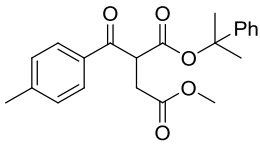
Yellow oil, 573 mg, 91% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.95-7.89 (m, 2H), 7.86-7.79 (m, 2H), 7.78-7.75 (m, 1H), 7.53-7.30 (m, 7H), 5.57 (s, 2H), 4.92-4.85 (m, 1H), 3.62 (s, 3H), 3.12 (dd, 1H, J = 17.4, 7.8 Hz), 3.03 (dd, 1H, J = 17.4, 6.6 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 193.7, 171.5, 168.5, 135.6, 133.5, 131.3, 130.4, 129.4, 128.7, 128.5, 127.6, 126.5, 125.8, 125.0, 123.2, 65.8, 52.0, 49.5, 32.8. **MS** (ESI *m/z*) 399.3 [MNa^+, 100%]. Elemental analysis calcd (%) for $C_{23}H_{20}O_5$: C, 73.39; H, 5.36; found C, 73.10; H, 5.20.

4-Methyl 1-(2-phenylpropan-2-yl) 2-benzoylsuccinate (142f)



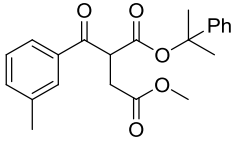
Colourless oil, 339 mg, 87% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.07-8.04 (m, 2H), 7.64-7.60 (m, 1H), 7.52-7.48 (m, 2H), 7.24-7.19 (m, 3H), 7.13-7.11 (m, 2H), 4.84 (dd, 1H, J_1= 7.8 Hz, J_2= 6.5 Hz), 3.67 (s, 3H), 3.09 (dd, 1H, J = 17.3, 8.0 Hz), 2.97 (dd, 1H, J = 17.3, 6.4 Hz), 1.64 (s, 3H), 1.63 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 194.2, 171.8, 166.8, 144.7, 136.2, 133.6, 128.9, 128.7, 128.2, 127.1, 124.1, 83.6, 52.0, 50.6, 32.7, 28.1, 28.0. **MS** (ESI *m/z*) 355.4 [MH^+, 13%]. Elemental analysis calcd (%) for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26; found C, 71.39; H, 6.41.

4-Methyl 1-(2-phenylpropan-2-yl) 2-(4-methylbenzoyl)succinate (142g)



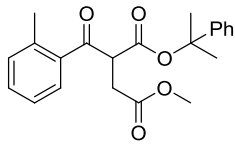
Yellow oil, 97 mg, 88% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.96 (d, 2H, *J*= 8.2 Hz), 7.29 (d, 2H, *J*= 8.0 Hz), 7.24-7.17 (m, 3H), 7.15-7.11 (m, 2H), 4.81 (dd, 1H, *J* = 7.6, 6.7 Hz), 3.66 (s, 3H), 3.06 (dd, 1H, *J* = 17.3, 7.8 Hz), 2.97 (dd, 1H, *J* = 17.3, 6.6 Hz), 2.44 (s, 3H), 1.65 (s, 3H), 1.64 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 193.8, 171.8, 167.0, 144.8, 144.5, 133.6, 129.3, 129.1, 128.2, 127.1, 124.1, 83.5, 52.0, 50.5, 32.8, 28.2, 28.05, 21.7. **MS** (ESI *m/z*) 369.4 [MH^+, 43%], 391.4 [MNa^+, 100%]. Elemental analysis calcd (%) for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57; found C, 71.51; H, 6.69.

4-Methyl 1-(2-phenylpropan-2-yl) 2-(3-methylbenzoyl)succinate (142h)



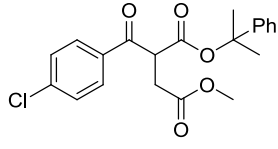
Colourless oil, 147 mg, 65% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.90-7.79 (m, 2H), 7.47-7.33 (m, 2H), 7.25-7.17 (m, 3H), 7.16-7.09 (m, 2H), 4.86-4.79 (m, 1H), 3.67 (s, 3H), 3.07 (dd, 1H, *J* = 17.3, 7.8 Hz), 2.97 (dd, 1H, *J* = 17.3, 6.6 Hz), 2.42 (s, 3H), 1.65 (s, 6H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 194.4, 171.8, 166.9, 144.7, 138.5, 136.2, 134.4, 129.4, 128.6, 128.2, 127.1, 126.2, 124.1, 83.5, 52.0, 50.7, 32.8, 28.2, 28.0, 21.3. **MS** (ESI *m/z*) 369.3 [MH^+, 55%], 391.3 [MNa^+, 38%]. Elemental analysis calcd (%) for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57; found C, 71.93; H, 6.44.

4-Methyl 1-(2-phenylpropan-2-yl) 2-(2-methylbenzoyl)succinate (142i)



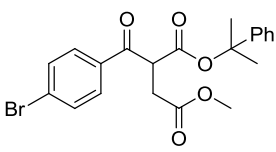
Pale yellow oil, 202 mg, 48% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.83 (d, 1H, J= 7.7 Hz), 7.46-7.36 (m, 1H), 7.35-7.27 (m, 2H), 7.24-7.16 (m, 3H), 7.09-7.03 (m, 2H), 4.74 (dd, 1H, J = 7.9, 6.3 Hz), 3.68 (s, 3H), 3.09 (dd, 1H, J = 17.3, 8.2 Hz), 2.90 (dd, 1H, J = 17.3, 6.2 Hz), 2.47 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 197.1, 171.7, 166.7, 144.6, 138.7, 136.9, 131.8, 131.7, 128.9, 128.1, 127.0, 125.6, 123.9, 83.3, 53.1, 51.9, 32.5, 28.1, 27.7, 20.9. **MS** (ESI *m/z*) 369.4 [MH^+, 2%], 391.3 [MNa^+, 100%], 407.3 [MK^+, 10%]. Elemental analysis calcd (%) for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57; found C, 71.47; H, 6.72.

4-Methyl 1-(2-phenylpropan-2-yl) 2-(4-chlorobenzoyl)succinate (142j)



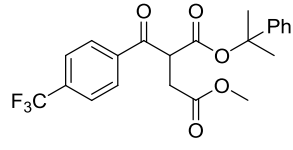
Colourless wax, 64 mg, 55% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.00 (d, 2H, J= 8.6 Hz), 7.47 (d, 2H, J= 8.6 Hz), 7.25-7.19 (m, 3H), 7.15-7.10 (m, 2H), 4.77 (dd, 1H, J = 8.3, 6.0 Hz), 3.67 (s, 3H), 3.11 (dd, 1H, J = 17.4, 8.3 Hz), 2.97 (dd, 1H, J = 17.4, 6.0 Hz), 1.65 (s, 6H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 193.1, 171.8, 166.5, 144.5, 140.1, 134.6, 130.3, 129.0, 128.2, 127.3, 124.1, 83.8, 52.1, 50.6, 32.7, 28.2, 28.0. **MS** (ESI *m/z*) 411.6 [MNa^+, 6%]. Elemental analysis calcd (%) for $C_{21}H_{21}ClO_5$: C, 64.87; H, 5.44; found C, 64.50; H, 5.58.

4-Methyl 1-(2-phenylpropan-2-yl) 2-(4-bromobenzoyl)succinate (142k)



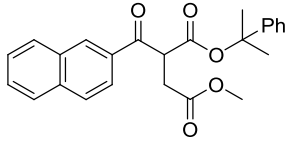
Pale yellow oil, 261 mg, 76% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.92 (d, 2H, *J*= 8.6 Hz), 7.64 (d, 2H, *J*= 8.6 Hz), 7.25-7.19 (m, 3H), 7.14-7.10 (m, 2H), 4.76 (dd, 1H, *J* = 8.3, 6.0 Hz), 3.67 (s, 3H), 3.11 (dd, 1H, *J* = 17.4, 8.3 Hz), 2.96 (dd, 1H, *J* = 17.4, 6.0 Hz), 1.66 (s, 3H), 1.65 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 193.3, 171.7, 166.4, 144.4, 134.9, 131.9, 130.4, 128.8, 128.2, 127.2, 124.0, 83.8, 52.0, 50.5, 32.7, 28.1, 28.0. **MS** (ESI *m/z*) 457.6 [MNa^+, 78%], 473.6 [MK^+, 18%]. Elemental analysis calcd (%) for $C_{21}H_{21}BrO_5$: C, 58.21; H, 4.89; found C, 57.91; H, 5.00.

4-Methyl 1-(2-phenylpropan-2-yl) 2-(4 -(trifluoromethyl)benzoyl)succinate (142l)



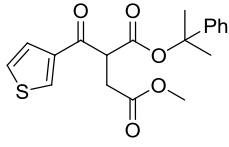
Colourless oil, 247 mg, 45% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.15 (d, 2H, *J*= 8.4 Hz), 7.76 (d, 2H, *J*= 8.3 Hz), 7.25-7.17 (m, 3H), 7.14-7.08 (m, 2H), 4.82 (dd, 1H, *J* = 8.7, 5.6 Hz), 3.67 (s, 3H), 3.16 (dd, 1H, *J* = 17.4, 8.7 Hz), 2.98 (dd, 1H, *J* = 17.4, 5.6 Hz), 1.65 (s, 6H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 193.7, 171.7, 166.3, 144.3, 139.1, 134.7 (q, $^2J_{C\text{-}F}$= 32.5 Hz), 129.2, 128.2, 127.4, 125.74, 125.70, 124.1, 123.5 (q, $^1J_{C\text{-}F}$= 271.2 Hz), 84.1, 52.1, 50.8, 32.7, 28.1, 28.0. **MS** (ESI *m/z*) 445.2 [MNa^+, 49%]. Elemental analysis calcd (%) for $C_{22}H_{21}F_3O_5$: C, 62.56; H, 5.01; found C, 62.74; H, 5.03.

4-Methyl 1-(2-phenylpropan-2-yl) 2-(2-naphthoyl)succinate (142m)



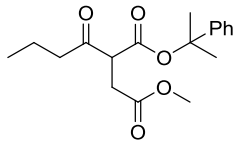
Pale yellow wax, 93 mg, 60% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.62 (s, 1H), 8.09 (dd, 1H, J_1= 8.7 Hz, J_2= 1.8 Hz), 8.02-7.87 (m, 4H), 7.66-7.62 (m, 1H), 7.61-7.55 (m, 1H), 7.16-7.07 (m, 4H), 5.00 (dd, 1H, J = 7.8, 6.6 Hz), 3.68 (s, 3H), 3.15 (dd, 1H, J = 17.3, 7.9 Hz), 3.04 (dd, 1H, J = 17.3, 6.5 Hz), 1.64 (s, 6H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 194.1, 171.9, 166.9, 144.6, 135.8, 133.5, 132.4, 131.0, 129.8, 128.8, 128.6, 128.1, 127.8, 127.1, 126.9, 124.3, 124.1, 83.7, 52.0, 50.8, 32.9, 28.2, 28.0. **MS** (ESI *m/z*) 427.4 [MNa^+, 100%], 443.7 [MK^+, 39%]. Elemental analysis calcd (%) for $C_{25}H_{24}O_5$: C, 74.24; H, 5.98; found C 73.95; H, 6.17.

4-Methyl 1-(2-phenylpropan-2-yl) 2-(thiophene-3-carbonyl)succinate (142n)



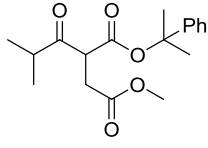
Colourless oil, 124 mg, 82% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.26-8.23 (m, 1H), 7.63 (d, 1H, J= 5.1 Hz), 7.36 (dd, 1H, J = 5.1, 2.8 Hz), 7.25-7.19 (m, 3H), 7.17-7.13 (m, 2H), 4.66-4.60 (m, 1H), 3.67 (s, 3H), 3.06 (dd, 1H, J = 17.4, 10.2 Hz), 2.97 (dd, 1H, J = 17.4, 6.7 Hz), 1.68 (s, 6H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 187.7, 171.8, 166.7, 144.7, 141.1, 133.9, 128.2, 127.4, 127.2, 126.5, 124.1, 83.6, 52.5, 52.0, 32.5, 28.3, 28.0. **MS** (ESI *m/z*) 383.2 [MNa^+, 34%], 399.6 [MK^+, 19%]. Elemental analysis calcd (%) for $C_{19}H_{20}O_5S$: C, 63.32; H, 5.59; S, 8.90; found C, 63.59; H, 5.73; S, 9.08.

4-Methyl 1-(2-phenylpropan-2-yl) 2-butyrylsuccinate (142o)



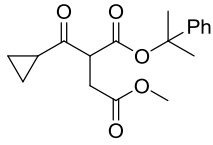
Colourless oil, 133 mg, 35% yield. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.38-7.29 (m, 3H), 7.28-7.21 (m, 2H), 3.96 (dd, 1H, J = 8.4, 6.4 Hz), 3.66 (s, 3H), 2.94 (dd, 1H, J = 17.5, 8.4 Hz), 2.79 (dd, 1H, J = 17.5, 6.3 Hz), 2.71-2.60 (m, 2H), 1.77 (s, 6H), 1.65 (sextet, 2H, J= 7.4 Hz), 0.92 (t, 3H, J= 7.4 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 204.1, 171.9, 166.7, 144.7, 128.3, 127.3, 124.1, 83.5, 54.8, 51.9, 44.8, 32.1, 28.4, 28.1, 16.8, 13.5. **MS** (ESI *m/z*) 358.5 [MK^+, 26%]. Elemental analysis calcd (%) for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55; found C, 67.27; H, 7.70.

4-Methyl 1-(2-phenylpropan-2-yl) 2-isobutyrylsuccinate (142p)



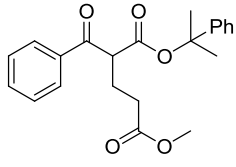
Colourless oil, 118 mg, 32% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.37-7.29 (m, 5H), 4.15 (dd, 1H, J = 8.1, 6.1 Hz), 3.66 (s, 3H), 3.01-2.87 (m, 2H), 2.80 (dd, 1H, J = 17.3, 6.2 Hz), 1.76 (s, 6H), 1.18 (d, 3H, J= 7.0 Hz), 1.14 (d, 3H, J= 7.0 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 208.0, 171.7, 166.7, 144.7, 128.3, 127.2, 124.1, 83.5, 53.0, 51.9, 40.8, 32.2, 28.4, 28.1, 18.6, 17.7. **MS** (ESI *m/z*) 343.5 [MNa^+, 47%]. Elemental analysis calcd (%) for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55; found C, 67.79; H, 7.76.

4-Methyl 1-(2-phenylpropan-2-yl) 2-(cyclopropanecarbonyl)succinate (142q)



Colourless oil, 99 mg, 43% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.36-7.29 (m, 3H), 7.28-7.21 (m, 2H), 4.18-4.13 (m, 1H), 3.67 (s, 3H), 2.91 (dd, 1H, J = 17.4, 7.4 Hz), 2.83 (dd, 1H, J = 17.4, 7.2 Hz), 2.27-2.18 (m, 1H), 1.79 (s, 3H), 1.78 (s, 3H), 1.17-1.10 (m, 2H), 1.01-0.93 (m, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 203.9, 171.8, 166.7, 144.9, 128.3, 127.2, 124.2, 83.5, 56.1, 51.9, 32.0, 28.5, 28.2, 20.6, 12.2, 12.1. **MS** (ESI *m/z*) 319.4 [MH^+, 11%], 341.5 [MNa^+, 100%], 357.3 [MK^+, 6%]. Elemental analysis calcd (%) for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97; found C, 67.66; H, 7.14.

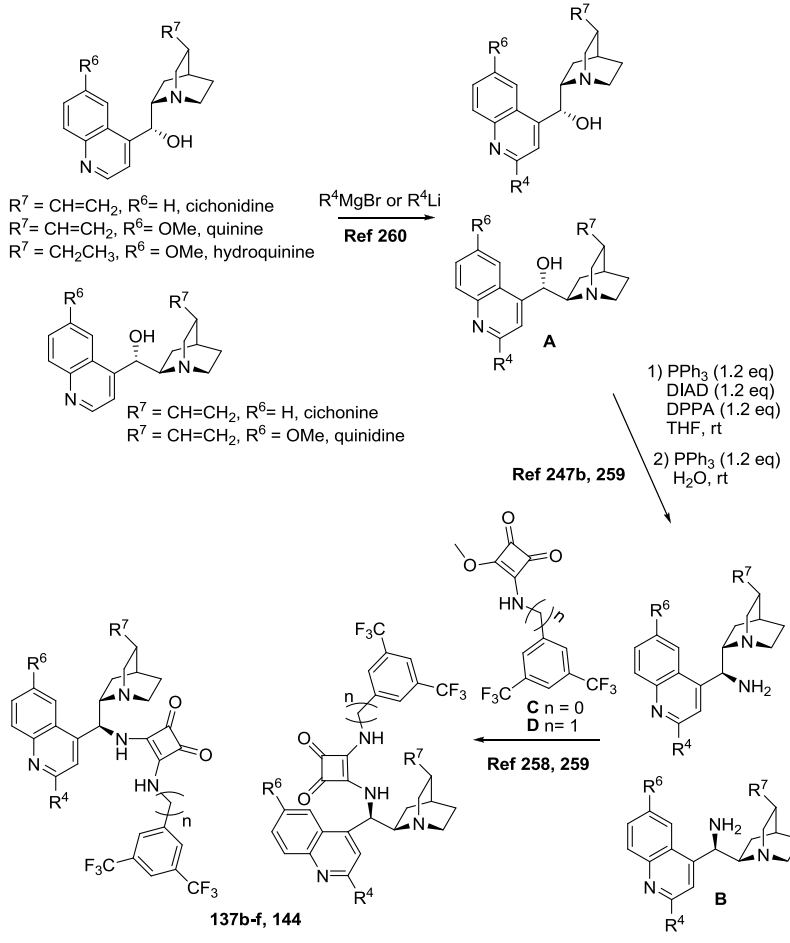
5-Methyl 1-(2-phenylpropan-2-yl) 2-benzoylpentanedioate (142r)



Colourless oil, 201 mg, 61% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.05-8.00 (m, 2H), 7.64-7.56 (m, 1H), 7.53-7.46 (m, 2H), 7.25-7.19 (m, 3H), 7.18-7.13 (m, 2H), 4.54-4.39 (m, 1H), 3.67 (s, 3H), 2.46-2.39 (m, 2H), 2.34-2.22 (m, 2H), 1.68 (s, 3H), 1.65 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 194.8, 173.2, 167.8, 144.9, 136.3, 133.5, 128.7, 128.1, 127.1, 124.1, 83.2, 53.8, 51.6, 31.2, 28.4, 27.8, 23.6. **MS** (ESI *m/z*) 391.1 [MNa^+, 22%]. Elemental analysis calcd (%) for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57; found C, 71.50; H, 6.75.

Synthesis of catalysts

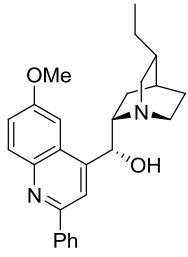
Catalysts **25a**[258] and **137a**[259] are known compounds, they were prepared according to the published procedure.



Compounds **A**,[260] **B**,[247b,259] **C**,[247a] **D**,[55] and **137b-f, 144**[259] were synthesized according to procedures described in the literature. The spectral data for compounds 2'-phenyl-quinine,[260] 2'-*n*-buthyl-quinine,[260] 2'-(1-naphthyl)-cinchonidine,[260] 9-amino-(9-deoxy)-*epi*-

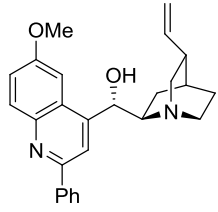
(2'-phenyl-quinine),[261] 9-amino-(9-deoxy)-*epi*-(2'-*n*-buthyl-quinine)[261] and 9-amino-(9-deoxy)-*epi*-(2'-*tert*-buthyl-quinine),[261] were consistent with those in the literature.

2'-Phenyl-hydroquinine (A1)



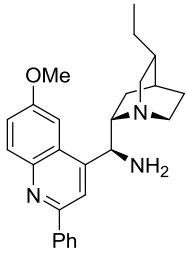
Prepared from hydroquinine (1.17 g, 3.58 mmol) and PhLi (1.8 M in Bu_2O; 6 mL, 10.75 mmol) according to ref. 260. The raw mixture was purified by flash chromatography (Ethyl acetate/MeOH = 100:5 to 70:30) to give the product. Pale yellow solid, 770 mg, 53% yield. **mp** 74.8-78.6 °C. $[\alpha]_D^{23}$ = -25.7 (*c* 0.63, $CHCl_3$). **FTIR** ν_{max} (KBr)/cm^{-1} 3454, 2931, 2871, 1622, 1598, 1499, 1352, 1231, 1031, 832, 755, 697. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.05-8.02 (m, 3H), 7.91 (s, 1H), 7.45-7.38 (m, 3H), 7.30 (dd, 1H, *J* = 9.2, 2.6 Hz), 7.13 (d, 1H, *J* = 2.5 Hz), 5.51 (d, 1H, *J* = 3.2 Hz), 3.85 (s, 3H), 3.51-3.46 (m, 1H), 3.08-3.02 (m, 2H), 2.66-2.60 (m, 1H), 2.38-2.35 (m, 1H), 1.75-1.70 (m, 3H), 1.44-1.40 (m, 3H), 1.26-1.17 (m, 2H), 0.78 (t, 3H, *J* = 7.3 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 157.6, 154.5, 148.2, 144.3, 139.7, 131.8, 128.9, 128.7, 127.2, 125.5, 121.5, 116.2, 101.3, 72.1, 59.8, 58.6, 55.6, 43.4, 37.5, 28.2, 27.6, 25.5, 21.2, 12.0. **MS** (ESI *m/z*) 403.3 [MH^+, 100%], 441.2 [MK^+, 8%]. Elemental analysis calcd (%) for $C_{26}H_{30}N_2O_2$: C, 77.58; H, 7.51; N, 6.96; found C, 77.84, H, 7.38, N, 7.15.

2'-Phenyl-quinidine (A2)



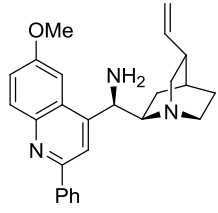
Prepared from quinidine (1.61 g, 5 mmol) and PhLi (1.8 M in Bu_2O; 8.4 mL, 15 mmol) according to ref. 260. The raw mixture was purified by flash chromatography (Ethyl acetate/MeOH = 100:5 to 70:30) to give the product. Yellow solid, 1.073g, 54% yield. **mp** 182.6-185.7 °C. $[\alpha]_D^{31}$ = +133.4 (*c* 0.63, $CHCl_3$). **FTIR** ν_{max} (KBr)/cm^{-1} 3418, 2940, 2878, 1622, 1556, 1500, 1353, 1231, 1031, 834, 757, 697. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.08-8.04 (m, 3H), 7.95 (s, 1H), 7.50-7.31 (m, 4H), 7.14-7.13 (m, 1H), 6.02 (ddd, 1H vinyl, J = 16.7, 10.7, 7.6 Hz), 5.63 (d, 1H, J= 3.2 Hz), 5.06-5.02 (m, 2H), 3.87 (s, 3H), 3.37-3-32 (m, 1H), 3.12-3.07 (m, 1H), 2.97-2.89 (m, 2H), 2.83-2.75 (m, 1H), 2.27-2.21 (m, 1H), 2.08-2.03 (m, 1H), 1.77 (m, 1H), 1.58-1.47 (m, 2H), 1.27-1.16 (m, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 157.5, 154.5, 147.9, 144.2, 140.4, 139.6, 131.8, 128.9, 128.7, 127.2, 125.5, 121.6, 116.1, 114.7, 101.2, 71.9, 59.8, 55.6, 50.1, 49.5, 39.9, 28.2, 26.2, 21.0. **MS** (ESI *m/z*) 401.3 [MH^+, 19%]. Elemental analysis calcd (%) for $C_{26}H_{28}N_2O_2$: C, 77.97; H, 7.05; N, 6.99; found C, 78.20; H 7.01; N, 6.76.

(*S*)-((2*S*,4*S*,8*R*)-8-ethylquinuclidin-2-yl)(6-methoxy-2-phenylquinolin-4-yl)methanamine (B1)



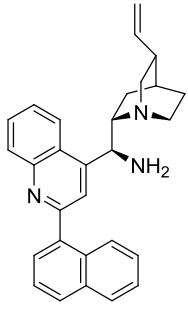
Prepared from **A1** (719 mg, 1.79 mmol) according to the procedure reported in references 247b,259. The residue was purified by flash chromatography (eluent: EtOAc to EtOAc /MeOH 9:1 and then to EtOAc/MeOH/aq. NH_4OH = 80/20/5). Yellow solid, 339 mg, 47% yield. **mp** 60.0-63.8 °C. $[\alpha]_D^{22}$ = +17.6 (*c* 0.52, $CHCl_3$). **FTIR** ν_{max} (KBr)/cm^{-1} 2933, 2864, 1622, 1597, 1498, 1452, 1354, 1264, 1229, 1031, 831, 755, 697. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.17-8.10 (m, 3H), 8.00 (br s, 1H), 7.70-7.57 (m, 1H), 7.54-7.50 (m, 2H), 7.46-7.38 (m, 2H), 4.67 (br s, 1H), 3.98 (s, 3H), 3.30-3.11 (m, 3H), 2.84-2.77 (m, 1H), 2.56-2.52 (m, 1H), 2.30 (br s, 2H), 1.59-1.24 (m, 7H), 0.81 (t, 3H, *J* = 7.3 Hz) overlapped with 0.85-0.79 (m, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 157.4, 154.8, 147.9, 144.8, 139.8, 132.1, 128.9, 128.7, 127.6, 127.3, 121.3, 117.9 (br s), 102.1(br s), 62.2 (br s), 57.9, 55.5, 41.1, 37.4, 28.8, 27.6, 25.7, 25.2, 12.0. **MS** (ESI *m/z*) 403.3 [MH^+, 18%], 420.4 [$M+H_3O^+$, 100%]. Elemental analysis calcd (%) for $C_{26}H_{31}N_3O$: C, 77.77; H, 7.78; N, 10.46; found C, 77.52; H, 7.90; N, 10.31.

(*R*)-(6-methoxy-2-phenylquinolin-4-yl)((2*R*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methanamine (B2)



Prepared from **A2** (400 mg, 1 mmol) according to the procedure reported in references 247b,259. The residue was purified by flash chromatography (eluent: EtOAc to EtOAc /MeOH 9:1 and then to EtOAc/MeOH/aq. NH_4OH = 90/10/5). Yellow solid, 116 mg, 29% yield. **mp** 57.3-60.0 °C. $[\alpha]_D^{30}$ = +66.5 (*c* 0.54, $CHCl_3$). **FTIR** ν_{max} (KBr)/cm^{-1} 2931, 2866, 1621, 1596, 1554, 1498, 1453, 1353, 1227, 1030, 831, 758, 696. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 8.18-8.09 (m, 3H), 8.06 (br s, 1H), 7.70-7.61 (m, 1H), 7.54-7.37 (m, 4H), 5.91 (ddd, 1H vinyl, *J* = 16.8, 10.9, 6.5 Hz), 5.12-5.06 (m, 2H), 4.76 (d, 1H, *J* = 9.8 Hz), 3.98 (s, 3H), 3.14-2.93 (m, 5H), 2.32-2.27 (m, 1H), 2.16-2.01 (m, 2H), 1.64-1.54 (m, 3H), 1.26-1.18 (m, 1H), 1.04-0.95 (m, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 157.6, 154.8, 148.1, 144.8, 140.7, 139.8, 132.0, 128.9, 128.7, 127.6, 127.3, 121.7, 117.7 (br s), 114.5, 101.4 (br s), 62.7 (br s), 55.4, 49.5, 47.4, 39.4, 27.6, 26.6, 24.9. **MS** (ESI *m/z*) 400.3 [MH^+, 100%]. Elemental analysis calcd (%) for $C_{26}H_{29}N_3O$: C, 78.16; H, 7.32; N, 10.52; found C, 78.44; H, 7.48; N, 10.35.

(*S*)-(2-(naphthalen-1-yl)quinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methanamine (B3)

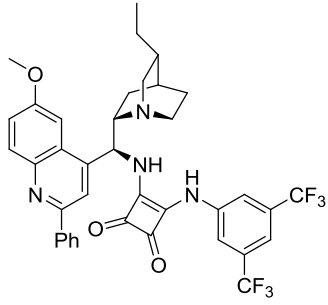


Prepared from 2'-(1-naphthyl)-cinchonidine[260] (150 mg, 0.36 mmol) according to procedure reported in references 247b,259. The residue was purified by flash chromatography (eluent: EtOAc to EtOAc /MeOH 9:1 and then to EtOAc/MeOH/aq. NH_4OH = 90/10/5). Pale yellow solid, 68 mg, 45% yield. **mp** 91.4-94.4 °C. $[\alpha]_D^{29}$ = +28.9 (*c* 0.55, $CHCl_3$). **FTIR** ν_{max} (KBr)/cm^{-1} 2930, 2864, 1594, 1552, 1508, 1455, 1346, 913, 803, 759. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.47-8.45 (m, 1H), 8.26 (d, 1H, *J* = 8.4 Hz), 8.10 (d, 1H, *J* = 8.2 Hz), 7.97-7.93 (m, 2H), 7.82-7.73 (m, 3H), 7.67-7.59 (m, 2H), 7.54-7.45 (m, 2H), 5.80 (ddd, 1H, *J* = 17.1, 10.3, 7.7 Hz), 5.02-4.94 (m, 2H), 4.78 (br d, 1H), 3.30-3.14 (m, 3H), 2.85-2.78 (m, 2H), 2.29 (br s, 3H), 1.67-1.57 (m, 3H), 1.28-1.24 (m, 1H), 0.90-0.85 (m, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 159.2, 148.6, 148.4, 141.3,138.6, 134.0, 131.2, 130.7, 129.4, 129.1, 128.4, 127.8, 126.6, 126.5, 126.4, 125.9, 125.6, 125.4, 123.2, 121.7, 114.6, 61.9, 56.0, 40.9, 39.5, 27.7, 27.5, 26.1. **MS** (ESI *m/z*) 420.3 [MH^+, 100%]. Elemental analysis calcd (%) for $C_{26}H_{29}N_3$: C, 83.02; H, 6.97; N, 10.02; found C, 82.80; H, 6.87; N, 10.25.

General procedure for the synthesis of squaramide catalysts

To a stirred solution of **B1** (150 mg, 0.37 mmol) under nitrogen atmosphere in dry methanol (1 mL) a solution of **C** (123 mg, 0.36 mmol) in dry methanol (1 mL) was added *via* syringe. The mixture was stirred at room temperature for 70 h. The solvent was removed under reduced pressure and product **137f** was isolated by flash chromatography (eluent: $CHCl_3$ to $CHCl_3$/MeOH 95:5).

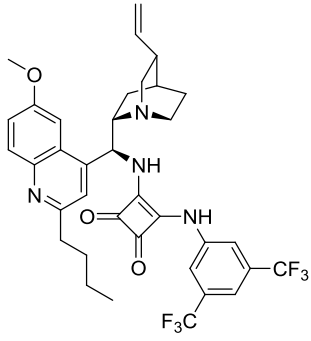
3-(3,5-Bis(trifluoromethyl)phenylamino)-4-((*S*)-((2*S*,4*S*,8*R*)-8-ethylquinuclidin-2-yl)(6 methoxy-2-phenylquinolin-4-yl)methylamino)cyclobut-3-ene-1,2-dione (137f)



Yellow solid, 210 mg, 82% yield. **mp** 193 °C (Decomp.). $[\alpha]_D^{20}$ = +112.7 (*c* 0.55, MeOH). **FTIR** ν_{max} (KBr)/cm^{-1} 3064, 2930, 2864, 1718, 1637, 1593, 1552, 1508, 1455, 1418, 1346, 1216, 913, 803, 777, 759. **^{1}H NMR** (DMSO-d$_6$, 300 MHz, 100 °C): δ 8.27-8.24 (m, 2H), 8.16 (s, 1H), 8.05 (d, 1H, J = 9.2 Hz), 7.99 (s, 2H), 7.78 (d, 1H, J = 2.5 Hz), 7.60-7.46 (m, 5H), 6.08 (d, 1H, J = 9.9 Hz), 4.02 (s, 3H), 3.78-3.68 (m, 1H), 3.42-3.32 (m, 2H), 2.80-2.65 (m, 2H), 1.68-1.28 (m, 7H), 0.89-0.83 (m, 4H). **^{13}C NMR** (DMSO-d$_6$, 100 MHz): δ 184.6, 179.9, 168.6, 163.1, 157.8, 153.7, 144.3, 144.1, 141.0, 138.6, 131.7, 131.2 (q, $^2J_{C\text{-}F}$ = 32.8 Hz), 129.2, 128.7, 127.0, 126.2, 123.0 (q, $^1J_{C\text{-}F}$ = 271.1 Hz), 122.2, 118.1, 116.9, 114.7, 101.4, 59.1, 56.7, 55.6, 53.2, 40.7, 36.4, 28.4, 26.4, 25.1, 24.8, 11.7. **MS** (ESI *m/z*) 710.0 [MH$^+$, 100%], 731.2 [MNa$^+$, 11%]. Elemental analysis calcd (%)

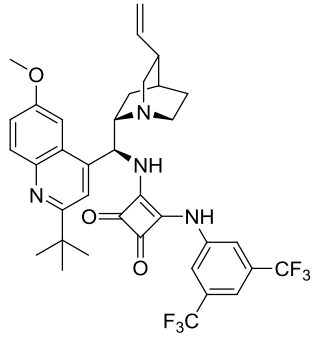
for $C_{38}H_{34}F_6N_4O_3$: C, 64.40; H, 4.84; N, 7.91; found C, 64.68; H, 4.70; N, 7.77.

3-(3,5-Bis(trifluoromethyl)phenylamino)-4-((*S*)-(2-butyl-6-methoxyquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methylamino)cyclobut-3-ene-1,2-dione (137b)



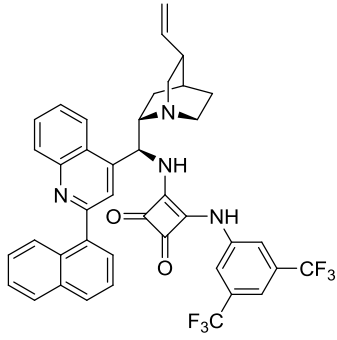
Yellow solid, 242 mg, 62 % yield. **mp** 145 °C (Decomp.). $[\alpha]_D^{30}$ = -17.2 (*c* 0.54, MeOH). **FTIR** ν_{max} (KBr)/cm^{-1} 3271, 3094, 2957, 2933, 2864, 1794, 1689, 1624, 1601, 1558, 1476, 1440, 1381, 1279, 1182, 1134, 1035, 932, 881, 835, 757, 680. **^{1}H NMR** (DMSO-d_6, 300 MHz, 100 °C): δ 8.00 (s, 2H), 7.90 (d, 1H, J = 9.2 Hz), 7.71 (d, 1H, J = 2.3 Hz), 7.53 (s, 1H), 7.49 (s, 1H), 7.41-7.37 (m, 1H), 6.01-5.88 (m, 2H), 5.12-5.02 (m, 2H), 3.97 (s, 3H), 3.64 (m, 1H), 3.47-3-30 (m, 2H), 2.95-2.77 (m, 4H), 2.47-2.38 (m, 1H), 1.83-1.50 (m, 6H), 1.40 (sextet, 2H, J = 7.2 Hz), 0.94 (t, 3H, J = 7.2 Hz), 0.86-0.80 (m, 1H). **^{13}C NMR** (DMSO-d_6, 75 MHz): δ 184.6, 179.9, 168.5, 162.9, 159.6, 157.3, 143.9, 141.8, 140.9, 131.2 (q, $^2J_{C\text{-}F}$= 32.8 Hz), 131.0, 125.7, 123.1 (q, $^1J_{C\text{-}F}$ = 271.1 Hz), 121.5, 118.1, 117.0, 114.9, 101.4, 58.9, 55.6, 55.4, 53.0, 37.6, 31.2, 27.0, 25.6, 21.9, 13.8. **MS** (ESI *m/z*) 687.2 [MH$^+$, 32%], 709.7 [MNa$^+$, 37%]. Elemental analysis calcd (%) for $C_{36}H_{36}F_6N_4O_3$: C, 62.97; H, 5.28; N, 8.16; found C, 62.67; H, 5.12; N, 8.34.

3-(3,5-Bis(trifluoromethyl)phenylamino)-4-((*S*)-(2-*tert*-butyl-6-methoxyquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methylamino)cyclobut-3-ene-1,2-dione (137c)



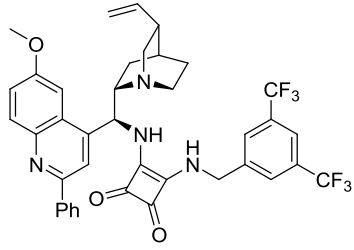
Ochre solid, 130 mg, 50% yield. **mp** 174 °C (Decomp.). $[\alpha]_D^{31}$ = -22.5 (*c* 0.53, MeOH). **FTIR** ν_{max} (KBr)/cm^{-1} 3502, 3257, 2952, 1794, 1690, 1600, 1556, 1474, 1450, 1381, 1279, 1182, 1134, 1035, 932, 881, 834, 757, 700. **^{1}H NMR** (DMSO-d$_6$, 300 MHz, 100 °C): δ 8.03-7.96 (m, 2H), 7.91 (d, 1H, J = 9.2 Hz), 7.70 (d, 1H, J = 2.7 Hz), 7.66 (s, 1H), 7.60-7.52 (m, 1H), 7.39 (dd, 1H, J = 9.2, 2.7 Hz), 6.00-5.85 (m, 2H), 5.18-5.00 (m, 2H), 3.96 (s, 3H), 3.72-3.54 (m, 1H), 3.46-3.25 (m, 2H), 3.00-2.87 (m, 1H), 2.85-2.72 (m, 1H), 2.47-2.33 (m, 1H), 1.78-1.55 (m, 4H), 1.45 (s, 9H), 0.86 (m, 1H). **^{13}C NMR** (DMSO-d$_6$, 100 MHz): δ 184.7, 180.0, 168.7, 165.8, 162.7, 157.4, 144.7, 143.1, 142.1, 140.8, 131.4, 131.2 (q, $^2J_{C\text{-}F}$= 32.4 Hz), 127.3, 123.1 (q, $^1J_{C\text{-}F}$ = 271.3 Hz), 121.4, 118.2, 117.0, 114.8, 114.1, 101.3, 58.5, 55.6, 55.3, 54.8, 37.7, 31.2, 29.9, 27.2, 26.2. **MS** (ESI *m/z*) 687.0 [MH$^+$, 5%]. Elemental analysis calcd (%) for $C_{36}H_{36}F_6N_4O_3$: C, 62.97; H, 5.28; N, 8.16; found C, 62.70; H, 5.43; N, 7.90.

3-(3,5-Bis(trifluoromethyl)phenylamino)-4-((*S*)-(2-(naphthalen-1-yl)quinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methylamino)cyclobut-3-ene-1,2-dione (137d)



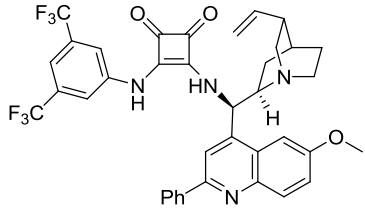
Yellow solid, 44 mg, 66% yield. **mp** 170 °C (Decomp.). $[\alpha]_D^{28}$ = +59.4 (*c* 0.51, MeOH). **FTIR** ν_{max} (KBr)/cm^{-1} 2953, 2869, 1794, 1655, 1626, 1596, 1560, 1475, 1449, 1382, 1278, 1180, 1133, 932, 881, 756. **^{1}H NMR** (DMSO-d$_6$, 300 MHz, 100 °C): δ 8.54 (d, 1H, J = 8.2 Hz), 8.17-8.03 (m, 3H), 7.97 (s, 2H), 7.91 (s, 1H), 7.88-7.66 (m, 5H), 7.59-7.46 (m, 3H), 6.09 (d, 1H, J = 11.0 Hz), 5.90 (ddd, 1H, J = 17.1, 10.4 Hz, 6.9 Hz), 5.07-4.97 (m, 2H), 3.55-3.43 (m, 1H), 3.40-3.22 (m, 2H), 2.87-2.71 (m, 2H), 2.36 (br s, 1H), 1.72-1.49 (m, 4H), 1.02-0.96 (m, 1H). **^{13}C NMR** (DMSO-d$_6$, 75 MHz): δ 184.5, 180.3, 168.9, 162.9, 158.3, 148.0, 145.7, 142.0, 140.9, 137.8, 133.5, 131.2 (q, $^2J_{C\text{-}F}$= 33.5 Hz), 130.5, 130.1, 129.9, 129.1, 128.5, 128.0, 127.3, 126.6, 126.1, 125.4, 125.2, 123.4, 123.1 (q, $^1J_{C\text{-}F}$ = 271.8 Hz), 118.2, 114.8, 114.3, 59.5, 55.2, 53.4, 27.1, 25.5. **MS** (ESI *m/z*) 727.3 [MH$^+$, 100%]. Elemental analysis calcd (%) for $C_{41}H_{32}F_6N_4O_3$: C, 67.76; H, 4.44; N, 7.71; found C, 68.07; H, 4.61; N, 7.93.

3-(3,5-Bis(trifluoromethyl)benzylamino)-4-((*S*)-(6-methoxy-2-phenylquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methylamino)cyclobut-3-ene-1,2-dione (137e)



White solid, 20 mg, 28% yield. Decomposition before melting at 230 °C. $[\alpha]_D^{31}$ = +52.4 (*c* 0.53, $CHCl_3$). **FTIR** ν_{max} (KBr)/cm^{-1} 3174, 2937, 2871, 1798, 1643, 1622, 1572, 1557, 1474, 1456, 1381, 1347, 1279, 1231, 1176, 1131, 1034, 837, 751, 702, 682. **^{1}H NMR** (DMSO-d_6, 300 MHz, 100 °C): δ 8.18 (d, 2H, J = 6.7 Hz), 8.06 (s, 1H), 8.02 (d, 1H, J = 9.4 Hz), 7.97 (s, 1H), 7.90-7.80 (m, 2H), 7.67-7.44 (m, 5H), 6.01-5.86 (m, 2H), 5.06-4.96 (m, 2H), 4.88 (br d, 2H, J = 5.3 Hz), 3.98 (s, 3H), 3.53-3.46 (m, 1H), 3.36-3.19 (m, 2H), 2.81-2.63 (m, 2H), 2.33 (m, 1H), 1.64-1.48 (m, 4H), 0.88-0.78 (m, 1H). **^{13}C NMR** (DMSO-d_6, 75 MHz): δ 182.7, 181.9, 167.2, 167.0, 157.6, 153.4, 145.0, 144.0, 142.11, 142.06, 138.6, 131.5, 130.3 (q, $^2J_{C\text{-}F}$= 32.5 Hz), 129.1, 128.6, 128.5, 126.8, 126.3, 123.1 (q, $^1J_{C\text{-}F}$ = 271.5 Hz), 122.0, 121.0, 114.0, 101.6, 58.6, 55.5, 55.4, 53.8, 45.7, 27.3, 27.1, 25.8. **MS** (ESI *m/z*) 721.5 [MH^+, 8%]. Elemental analysis calcd (%) for $C_{39}H_{34}F_6N_4O_3$: C, 64.99; H, 4.76; N, 7.77; found C, 64.75; H, 4.93; N, 7.94.

3-(3,5-Bis(trifluoromethyl)phenylamino)-4-((*R*)-(6-methoxy-2-phenylquinolin-4-yl)((2*R*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methylamino)cyclobut-3-ene-1,2-dione (144)



Yellow solid, 89 mg, 53% yield. **mp** 180 °C (Decomp.). $[\alpha]_D^{30}$ = -92.3 (*c* 0.53, MeOH). **FTIR** ν_{max} (KBr)/cm^{-1} 2926, 2854, 1791, 1682, 1623, 1598, 1556, 1473, 1437, 1381, 1277, 1229, 1180, 1133, 1030, 931, 832, 770, 697. **^{1}H NMR** (DMSO-d$_6$, 300 MHz, 100 °C): δ 8.28-8.25 (m, 2H), 8.16 (s, 1H), 8.05 (d, 1H, J = 9.2 Hz), 7.99 (s, 2H), 7.71 (d, 1H, J = 2.5 Hz), 7.60-7.45 (m, 5H), 6.17 (d, 1H, J = 10.7 Hz), 5.94 (ddd, 1H, J = 17.4, 10.6, 6.1 Hz), 5.25-5.12 (m, 2H), 4.02 (s, 3H), 3.65 (m, 1H), 3.22-2.73 (m, 4H), 2.38 (bs, 1H), 1.69-1.62 (m, 3H), 1.22-1.10 (m, 2H). **^{13}C NMR** (DMSO-d$_6$, 100 MHz): δ 184.8, 179.9, 168.7, 162.6, 157.8, 153.6, 144.4, 144.0, 140.9, 140.8, 138.6, 131.6, 131.1 (q, $^2J_{C\text{-}F}$ = 32.1 Hz), 129.2, 128.6, 127.0, 126.3, 123.0 (q, $^1J_{C\text{-}F}$ = 270.8 Hz), 122.3, 118.1, 116.8, 114.6, 114.4, 101.1, 58.8, 55.5, 52.5, 48.8, 45.6, 27.1, 25.9, 24.8. **MS** (ESI *m/z*) 709.1 [MH$^+$, 100%]. Elemental analysis calcd (%) for $C_{38}H_{32}F_6N_4O_3$: C, 64.59; H, 4.56; N, 7.93; found C, 64.87; H, 4.71; N, 7.75.

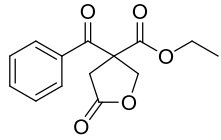
General procedure for the synthesis of racemic γ-butyrolactones 143a-q, 145

A sample vial was charged with compound **142** (0.10 mmol), paraformaldehyde (9.0 mg, 0.30 mmol) and 1,4-diazabicyclo[2.2.2]octane (5.6 mg, 0.05 mmol) in anhydrous toluene (0.5 mL). The reaction was stirred at room temperature until **1** disappeared (20-90 h), monitored by TLC (eluent PE/ ethyl acetate 9:1 or 8:2). The product was isolated (63-98% yield) by flash chromatography (eluting from PE/ ethyl acetate 98:2 to 90:10).

General procedure for the asymmetric synthesis of γ-butyrolactones 143f-q, 145

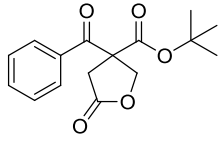
A sample vial was charged with compound **142** (0.10 mmol) and catalyst **137f** (2.1 mg, 0.003 mmol) in anhydrous 1,2-dicholoethane (1.0 mL). 4-Nitrophenol (solution 0.25 M in dry 1,2-dichloroethane, 20 μL, 0.005 mmol), formaldehyde (solution 37 wt% in H_2O, 15 μL, 0.20 mmol) and 3Å molecular sieves (≈ 17 mg) were added. The solution was stirred at -20 °C until completion, monitored by TLC (eluent PE/ ethyl acetate 9:1 or 8:2). Purification of the crude mixture by flash chromatography (eluting from PE/ ethyl acetate 98:2 to 90:10 and PE/ ethyl acetate 95:5 to 8:2 for the compound **145**) gave γ-butyrolactones **143f-q**, **145**. Absolute configuration of γ-butyrolactones **143f-q** was assumed to be (*R*) in analogy to that indirectly determined on compound **143j** (see the X-ray analysis section).

Ethyl 3-benzoyl-5-oxotetrahydrofuran-3-carboxylate (143a)



Data for this compound were consistent with those reported in the literature.[262] Colourless oil, 21 mg, 80% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.83-7.77 (m, 2H), 7.65-7.58 (m, 1H), 7.52-7.45 (m, 2H), 4.93 and 4.79 (AX, 2H, J= 9.8 Hz), 4.18 (q, 2H, J= 7.1 Hz), 3.30 (A_2, 2H), 1.06 (t, 3H, J= 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 191.0, 173.3, 170.3, 134.2, 133.4, 129.1, 128.7, 70.9, 63.1, 59.8, 35.3, 13.6. Elemental analysis calcd (%) for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38; found C, 64.38, H, 5.50. HPLC analysis with Chiralpak AD column, 95:5 *n*-hexane:2-propanol, 1.0 mL/min, 254 nm; minor enantiomer t_R = 20.8 min, major enantiomer t_R = 22.3 min, *ee* 7%.

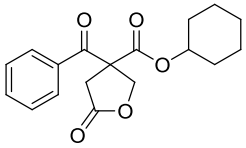
***tert*-Butyl 3-benzoyl-5-oxotetrahydrofuran-3-carboxylate (143b)**



White solid, 19.7 mg, 68% yield. **mp** 70.3-72.1 °C. **$[\alpha]_D^{20}$** = -20.8 (c 0.50, $CHCl_3$), *ee* 47%. **FTIR** ν_{max} (KBr)/cm^{-1} 2980, 2932, 1791, 1732, 1688, 1598, 1449, 1371, 1293, 1261, 1180, 1153, 1078, 1037, 839, 709. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.81 (d, 2H, J= 7.6 Hz), 7.66-7.58 (m, 1H), 7.55-7.45 (m, 2H), 4.92 and 4.73 (AX, 2H, J= 9.7 Hz), 3.30 and 3.22 (ABq, 2H, J= 18.0 Hz), 1.28 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 191.4, 173.5, 169.1, 134.0, 133.6, 129.0, 128.6, 84.3, 70.9, 60.5, 35.2, 27.4. **MS** (ESI *m/z*) 291.7 [MH^+, 12%], 313.4 [MNa^+, 48%]. Elemental analysis calcd (%) for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25; found C, 66.49, H, 6.39. HPLC analysis with Chiralpak AD-H column, 95:5 *n*-hexane:2-propanol,

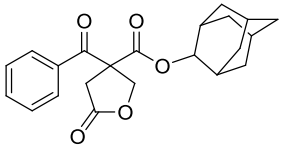
0.8 mL/min, 254 nm; minor enantiomer t_R = 16.7 min, major enantiomer t_R = 15.9 min.

Cyclohexyl 3-benzoyl-5-oxotetrahydrofuran-3-carboxylate (143c)



White solid, 26.2 mg, 83% yield. **mp** 75.3-78.1 °C. $[\alpha]_D^{22}$ = +11.0 (*c* 0.56, $CHCl_3$), *ee* 45%. **FTIR** ν_{max} (KBr)/cm^{-1} 2937, 2860, 1791, 1733, 1687, 1598, 1449, 1289, 1260, 1215, 1179, 1077, 1037, 903, 691. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.83-7.79 (m, 2H), 7.65-7.58 (m, 1H), 7.52-7.45 (m, 2H), 4.93 and 4.77 (AX, 2H, J = 9.8 Hz), 4.87-4.80 (m, 1H), 3.30 (A_2, 2H), 1.51-1.38 (m, 4H), 1.33-1.12 (m, 6H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 191.2, 173.3, 169.7, 134.1, 133.4, 129.0, 128.6, 75.5, 70.9, 59.9, 35.3, 30.7, 30.6, 24.9, 23.0. **MS** (ESI *m/z*) 339.4 [MNa^+, 21%]. Elemental analysis calcd (%) for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37; found C, 68.60; H, 6.20. HPLC analysis with Chiralpak AS-H column, 70:30 *n*-hexane:2-propanol, 0.9 mL/min, 254 nm; minor enantiomer t_R = 21.4 min, major enantiomer t_R = 24.4 min.

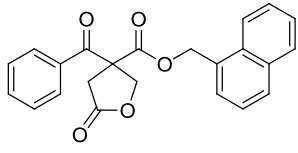
2-Adamantyl 3-benzoyl-5-oxotetrahydrofuran-3-carboxylate (143d)



White solid, 27.4 mg, 74% yield. **mp** 84.5-88.1 °C. $[\alpha]_D^{26}$ = +11.4 (*c* 0.29, MeOH), *ee* 40%. **FTIR** ν_{max} (KBr)/cm^{-1} 2908, 2856, 1792, 1735, 1687, 1598, 1450, 1287, 1261, 1211, 1179, 1074, 1038, 974, 916, 755, 691. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ

7.85-7.81 (m, 2H), 7.64-7.58 (m, 1H), 7.51-7.44 (m, 2H), 5.01-4.99 (m, 1H), 4.97 and 4.80 (AX, 2H, *J*= 9.7 Hz), 3.34 and 3.29 (ABq, 2H, *J*= 18.2 Hz), 1.80-1.71 (m, 4H), 1.70-1.56 (m, 6H), 1.51-1.23 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 191.2, 173.3, 169.7, 134.2, 133.5, 129.1, 128.7, 80.1, 71.0, 60.0, 36.9, 36.1, 36.0, 35.3, 31.62, 31.57, 31.3, 31.2, 26.7, 26.6. **MS** (ESI *m/z*) 369.4 [MH^+, 48%], 390.6 [MNa^+, 13%]. Elemental analysis calcd (%) for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57; found C, 71.46; H, 6.72. HPLC analysis with Chiralpak AS-H column, 70:30 *n*-hexane:2-propanol, 0.9 mL/min, 254 nm; minor enantiomer t_R = 18.3 min, major enantiomer t_R = 14.7 min.

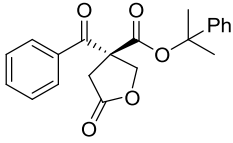
Naphthalen-1-ylmethyl 3-benzoyl-5-oxotetrahydrofuran-3-carboxylate (143e)



White solid, 35.6 mg, 95% yield. **mp** 87.9-91.0 °C. **$[\alpha]_D^{24}$** = +3.7 (*c* 0.57, $CHCl_3$), *ee* 36%. **FTIR** ν_{max} (KBr)/cm^{-1} 2925, 2853, 1789, 1739, 1687, 1598, 1449, 1286, 1258, 1177, 1075, 1037, 941, 801, 777, 690. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.82-7.76 (m, 2H), 7.58-7.51 (m, 3H), 7.45-7.34 (m, 4H), 7.33-7.27 (m, 1H), 7.17-7.11 (m, 2H), 5.59 (s, 2H), 4.87 and 4.76 (ABq, 2H, *J*= 9.8 Hz), 3.26 (A_2, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 190.6, 173.1, 170.2, 133.9, 132.9, 130.0, 129.3, 128.7, 128.6, 128.4, 126.7, 125.9, 124.9, 122.9, 70.8, 67.1, 59.7, 35.2. **MS** (ESI *m/z*) 397.8 [MNa^+, 100%]. Elemental analysis calcd (%) for $C_{23}H_{18}O_5$: C, 73.79; H, 4.85; found C, 73.52; H, 5.00. HPLC analysis with Chiralpak IC column, 70:30 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor

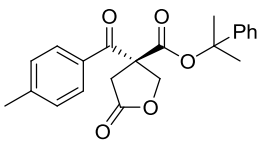
enantiomer t_R = 33.1 min, major enantiomer t_R = 26.3 min.

(*R*)-2-phenylpropan-2-yl 3-benzoyl-5-oxotetrahydrofuran-3-carboxylate (143f)



White wax, 33.5 mg, 95% yield. $[\alpha]_D^{21}$ = +22.8 (*c* 0.78, $CHCl_3$), *ee* 87%. **FTIR** ν_{max} (KBr)/cm^{-1} 2984, 2935, 1790, 1737, 1687, 1598, 1449, 1368, 1260, 1218, 1181, 1134, 1102, 1075, 1037, 762, 701. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.80-7.78 (m, 2H), 7.65 (t, 1H, *J* = 7.4 Hz), 7.50-7.46 (m, 2H), 7.24-7.19 (m, 3H), 7.05-7.03 (m, 2H), 4.96 and 4.72 (AX, 2H, *J* = 9.8 Hz), 3.26 (A_2, 2H), 1.64 (s, 3H), 1.62 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 191.1, 173.3, 168.2, 143.6, 134.2, 133.4, 129.1, 129.0, 128.3, 127.7, 124.1, 85.1, 70.7, 60.4, 35.0, 27.8, 27.5. **MS** (ESI *m/z*) 353.1[MH^+, 3%], 375.2 [MNa^+, 100%], 391.1 [MK^+, 18%]. Elemental analysis calcd (%) for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72; found C, 71.86; H, 5.91. HPLC analysis with Chiralpak IC column, 70:30 *n*-hexane:2-propanol, 1.0 mL/min, 254 nm; minor enantiomer t_R = 27.4 min, major enantiomer t_R = 18.2 min.

(*R*)-2-phenylpropan-2-yl 3-(4-methylbenzoyl)-5-oxotetrahydrofuran-3-carboxylate (143g)



White solid, 31.9 mg, 87% yield. **mp** 107.7-110.0 °C. $[\alpha]_D^{21}$ = +17.3 (*c* 0.76, $CHCl_3$), *ee* 88%. **FTIR** ν_{max} (KBr)/cm^{-1} 2924, 2854, 1791, 1737, 1684, 1606, 1450, 1369, 1261, 1182, 1133, 1102, 1075, 1036, 835, 763, 700. **^{1}H NMR**

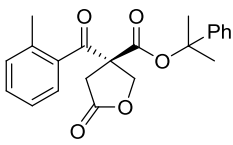
($CDCl_3$, 400 MHz): δ 7.69 (d, 2H, *J*= 8.2 Hz), 7.30-7.26 (m, 2H), 7.25-7.18 (m, 3H), 7.10-7.04 (m, 2H), 4.94 and 4.72 (AX, 2H, *J*= 9.7 Hz), 3.27 and 3.23 (ABq, 2H, *J*= 18.1 Hz), 2.45 (s, 3H), 1.65 (s, 3H), 1.63 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 190.6, 173.4, 168.4, 145.3, 143.7, 130.9, 129.8, 129.1, 128.3, 127.6, 124.2, 85.0, 70.7, 60.4, 35.1, 27.8, 27.5, 21.7. **MS** (ESI *m/z*) 367.4 [MH^+, 11%]. Elemental analysis calcd (%) for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05; found C, 71.90; H, 6.18. HPLC analysis with Chiralpak IC column, 70:30 *n*-hexane:2-propanol, 1.0 mL/min, 254 nm; minor enantiomer t_R = 32.5 min, major enantiomer t_R = 21.3 min.

(*R*)-2-phenylpropan-2-yl 3-(3-methylbenzoyl)-5-oxotetrahydrofuran-3-carboxylate (143h)

Colourless waxy solid, 30.4 mg, 85% yield. **$[\alpha]_D^{18}$** = +19.8 (*c* 0.50, $CHCl_3$), *ee* 83%. **FTIR** ν_{max} (KBr)/cm^{-1} 2922, 2852, 1789, 1737, 1686, 1449, 1385, 1369, 1265, 1236, 1176, 1134, 1101, 1076, 1037, 762, 700. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.61 (s, 1H), 7.55 (d, 1H, *J*= 7.5 Hz), 7.45 (d, 1H, *J*= 7.5 Hz), 7.35 (t, 1H, *J*= 7.6 Hz), 7.25-7.18 (m, 3H), 7.06-7.03 (m, 2H), 4.94 and 4.72 (AX, 2H, *J* = 9.8 Hz), 3.27 and 3.24 (ABq, 2H, *J*= 18.2 Hz), 2.38 (s, 3H), 1.65 (s, 3H), 1.62 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ.191.2, 173.4, 168.3, 143.6, 139.1, 134.9, 133.5, 129.5, 128.9, 128.3, 127.6, 126.1, 124.1, 85.0, 70.7, 60.4, 35.1, 27.8, 27.5, 21.4. **MS** (ESI *m/z*) 367.4 [MH^+, 11%], 389.3 [MNa^+, 26%]. Elemental analysis calcd (%) for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05; found C, 72.34; H, 6.23. HPLC analysis with Chiralpak IC column, 70:30 *n*-hexane:2-propanol, 1.0

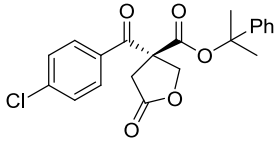
mL/min, 254 nm; minor enantiomer t_R = 22.1 min, major enantiomer t_R = 18.3 min.

(*R*)-2-phenylpropan-2-yl 3-(2-methylbenzoyl)-5-oxotetrahydrofuran-3-carboxylate (143i)



White solid, 30.8 mg, 84% yield. **mp** 70.9-72.6 °C. $[\alpha]_D^{23}$ = +13.7 (*c* 0.66, $CHCl_3$), *ee* 48%. **FTIR** ν_{max} (KBr)/cm^{-1} 2927, 2852, 1790, 1740, 1692, 1451, 1385, 1369, 1252, 1180, 1132, 1100, 1073, 1034, 764, 700. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.49-7.42 (m, 1H), 7.36 (d, 1H, *J*= 7.6 Hz), 7.25-7.18 (m, 5H), 7.06-6.99 (m, 2H), 4.87 and 4.75 (AX, 2H, *J*= 9.7 Hz), 3.27 and 3.22 (ABq, 2H, *J*= 18.2 Hz), 2.52 (s, 3H), 1.56 (s, 3H), 1.55 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 194.8, 173.4, 168.2, 143.7, 140.2, 134.2, 132.7, 132.4, 128.3, 127.6, 127.4, 125.9, 124.0, 84.8, 71.3, 61.8, 35.7, 27.5, 27.3, 21.5. **MS** (ESI *m/z*) 388.8 [MNa^+, 16%], 404.5 [MK^+, 14%]. Elemental analysis calcd (%) for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05; found C, 72.39; H, 5.84. HPLC analysis with Chiralpak IC column, 80:20 *n*-hexane:2-propanol, 1.0 mL/min, 254 nm; minor enantiomer t_R = 23.0 min, major enantiomer t_R = 21.0 min.

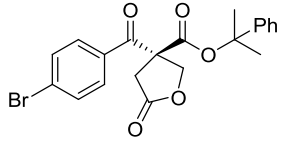
(*R*)-2-phenylpropan-2-yl 3-(4-chlorobenzoyl)-5-oxotetrahydrofuran-3-carboxylate (143j)



Colourless wax, 34.0 mg, 88% yield. $[\alpha]_D^{22}$ = +29.7 (*c* 0.56, $CHCl_3$), *ee* 86%. **FTIR** ν_{max} (KBr)/cm^{-1} 2924, 2852, 1791, 1737, 1688, 1589, 1489, 1402, 1369, 1259, 1179, 1133, 1094, 1037,

846, 763, 700. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.72 (d, 2H, J = 8.6 Hz), 7.44 (d, 2H, J = 8.6 Hz), 7.28-7.20 (m, 3H), 7.06-7.04 (m, 2H), 4.94 and 4.70 (AX, 2H, J = 9.8 Hz), 3.25 and 3.22 (ABq, 2H, J = 18.1 Hz), 1.67 (s, 3H), 1.64 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 190.0, 173.0, 168.1, 143.3, 140.9, 131.7, 130.3, 129.5, 128.4, 127.8, 124.2, 85.3, 70.5, 60.5, 34.9, 27.8, 27.5. **MS** (ESI *m/z*) 386.5 [MH^+, 63%]. Elemental analysis calcd (%) for $C_{21}H_{19}ClO_5$: C, 65.20; H, 4.95; found C, 65.49; H, 4.82. HPLC analysis with Chiralpak IC column, 70:30 *n*-hexane:2-propanol, 1.0 mL/min, 254 nm; minor enantiomer t_R = 28.3 min, major enantiomer t_R = 18.4 min.

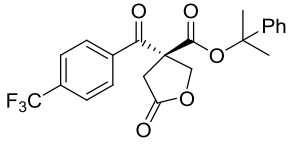
(*R*)-2-phenylpropan-2-yl 3-(4-bromobenzoyl)-5-oxotetrahydrofuran-3-carboxylate (143k)



White wax, 33.6 mg, 78% yield. **$[\alpha]_D^{19}$** = +21.6 (*c* 0.55, $CHCl_3$), *ee* 85%. **FTIR** ν_{max} (KBr)/cm^{-1} 2924, 2851, 1790, 1737, 1688, 1585, 1398, 1259, 1180, 1133, 1101, 1075, 1037, 1010, 844, 763, 700. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.65-7.59 (m, 3H), 7.25-7.19 (m, 4H), 7.09-7.02 (m, 2H), 4.93 and 4.69 (AX, 2H, J= 9.8 Hz), 3.27 and 3.19 (ABq, 2H, J= 18.2 Hz), 1.66 (s, 3H), 1.64 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 190.2, 173.0, 168.0, 143.3, 132.5, 132.1, 130.4, 129.7, 128.3, 127.8, 124.2, 85.4, 70.5, 60.5, 34.9, 27.8, 27.5. **MS** (ESI *m/z*) 431.3 [MH^+, 5%]. Elemental analysis calcd (%) for $C_{21}H_{19}BrO_5$: C, 58.48; H, 4.44; found C, 58.20; H, 4.59. HPLC analysis with Chiralpak IC column, 70:30 *n*-hexane:2-propanol, 1.0 mL/min, 254 nm; minor enantiomer t_R =

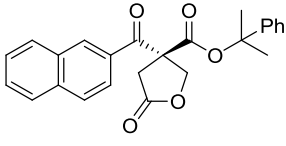
28.0 min, major enantiomer t_R = 17.1 min.

(*R*)-2-phenylpropan-2-yl 5-oxo-3-(4 (trifluoromethyl)benzoyl)tetrahydrofuran-3-carboxylate (143l)



Pale yellow wax, 26.9 mg, 64% yield. $[\alpha]_D^{19}$ = +17.1 (*c* 0.50, $CHCl_3$), *ee* 66%. **FTIR** ν_{max} (KBr)/cm^{-1} 2925, 2853, 1792, 1740, 1695, 1410, 1328, 1259, 1173, 1133, 1069, 1039, 858, 764, 700. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.88 (d, 2H, *J*= 8.2 Hz), 7.73 (d, 2H, *J*= 8.2 Hz), 7.25-7.16 (m, 3H), 7.03 (d, 2H, *J*= 7.2 Hz), 4.95 and 4.71 (AX, 2H, *J*= 9.8 Hz), 3.28 and 3.21 (ABq, 2H, *J*= 18.1 Hz), 1.67 (s, 3H), 1.64 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 190.3, 172.8, 167.8, 143.0, 136.1, 135.4 (q, $^2J_{C\text{-}F}$= 32.9 Hz), 129.3, 128.3, 127.9, 126.2, 126.1, 124.2, 123.2 (q, $^1J_{C\text{-}F}$= 271.4 Hz), 85.5, 70.4, 60.6, 34.8, 27.8, 27.4. **MS** (ESI *m/z*) 443.3 [MNa^+, 30%], 459.5 [MK^+, 8%]. Elemental analysis calcd (%) for $C_{22}H_{19}F_3O_5$: C, 62.86; H, 4.56; found C, 63.09; H, 4.79. HPLC analysis with Chiralpak IC column, 80:20 *n*-hexane:2-propanol, 1.0 mL/min, 254 nm; minor enantiomer t_R = 21.9 min, major enantiomer t_R = 14.7 min.

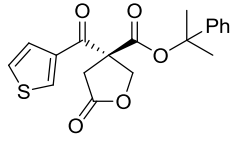
(*R*)-2-phenylpropan-2-yl 3-(2-naphthoyl)-5 oxotetrahydrofuran-3-carboxylate (143m)



White solid, 34.2 mg, 85% yield. **mp** 111.9-114.2 °C. $[\alpha]_D^{24}$ = +23.4 (*c* 0.55, $CHCl_3$), *ee* 83%. **FTIR** ν_{max} (KBr)/cm^{-1} 2926, 2852, 1789, 1736, 1684, 1627, 1466, 1369, 1273, 1241, 1178,

1133, 1100, 1074, 1036, 762, 700. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.18 (s, 1H), 7.98-7.90 (m, 3H), 7.84 (d, 1H, *J*= 8.0 Hz), 7.72-7.65 (m, 1H), 7.63-7.56 (m, 1H), 7.17-7.09 (m, 1H), 7.05-6.95 (m, 4H), 5.02 and 4.80 (AX, 2H, *J*= 9.8 Hz), 3.34 (A_2, 2H), 1.63 (s, 3H), 1.60 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 191.0, 173.4, 168.4, 143.4, 135.8, 132.2, 130.9, 130.7, 129.9, 129.4, 129.2, 128.2, 127.8, 127.6, 127.3, 124.2, 124.1, 85.1, 70.8, 60.5, 35.2, 27.8, 27.5. **MS** (ESI *m/z*) 403.1 [MH^+, 10%]. Elemental analysis calcd (%) for $C_{25}H_{22}O_5$: C, 74.61; H, 5.51; found C, 74.35; H, 5.40. HPLC analysis with Chiralpak IC column, 70:30 *n*-hexane:2-propanol, 1.0 mL/min, 254 nm; minor enantiomer t_R = 34.6 min, major enantiomer t_R = 22.2 min.

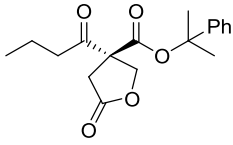
(*R*)-2-phenylpropan-2-yl 5-oxo-3-(thiophene-2 carbonyl)tetrahydrofuran-3-carboxylate (143n)



White solid, 29.0 mg, 81% yield. **mp** 85.7-88.9 °C. **$[\alpha]_D^{22}$** = +18.8 (*c* 0.54, $CHCl_3$), *ee* 82%. **FTIR** ν_{max} (KBr)/cm^{-1} 2923, 2851, 1788, 1736, 1677, 1509, 1413, 1259, 1177, 1133, 1076, 1034, 828, 763, 700. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.93-7.91 (m, 1H), 7.52-7.49 (m, 1H), 7.40-7.37 (m, 1H), 7.25-7.19 (m, 3H), 7.10-7.05 (m, 2H), 4.95 and 4.70 (AX, 2H, *J*= 9.8 Hz), 3.25 (A_2, 2H), 1.68 (s, 3H), 1.66 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 184.8, 173.4, 168.0, 143.5, 137.8, 134.0, 128.3, 127.7, 127.4, 127.1, 124.1, 85.1, 70.3, 61.1, 34.6, 27.9, 27.6. **MS** (ESI *m/z*) 358.6 [MH^+, 17%], 381.4 [MNa^+, 11%], 397.2 [MK^+, 22%]. Elemental analysis calcd (%) for $C_{19}H_{18}O_5S$: C, 63.67; H, 5.06; S, 8.95; found C, 63.51; H, 5.00; S,

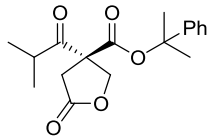
8.76. HPLC analysis with Chiralpak IC column, 70:30 *n*-hexane:2-propanol, 1.0 mL/min, 254 nm; minor enantiomer t_R = 38.5 min, major enantiomer t_R = 20.1 min.

(*R*)-2-phenylpropan-2-yl 3-butyryl-5-oxotetrahydrofuran-3-carboxylate (143o)



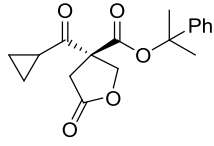
Colourless oil, 31.2 mg, 98% yield. $[\alpha]_D^{24}$ = +13.2 (*c* 0.57, $CHCl_3$), *ee* 76%. **FTIR** ν_{max} (KBr)/cm^{-1} 2924, 2852, 1790, 1716, 1519, 1497, 1464, 1450, 1369, 1338, 1274, 1242, 1175, 1135, 1098, 1031, 896, 825, 765, 700, 556. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.39-7.29 (m, 5H), 4.62 and 4.58 (ABq, 2H, *J* = 9.8 Hz), 3.04 and 2.98 (ABq, 2H, *J* = 17.9 Hz), 2.45-2.39 (m, 2H), 1.82 (s, 6H), 1.66 (sextet, 2H, *J* = 7.3 Hz), 0.91 (t, 3H, *J* = 7.3 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 201.2, 173.3, 167.3, 143.7, 128.5, 127.9, 124.2, 85.1, 70.0, 63.1, 40.8, 33.8, 27.95, 27.91, 17.0, 13.5. **MS** (ESI *m/z*) 341.4 [MNa^+, 100%], 357.4 [MK^+, 47%]. Elemental analysis calcd (%) for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97; found C, 67.70; H, 6.78. HPLC analysis with Chiralpak IC column, 80:20 *n*-hexane:2-propanol, 1.0 mL/min, 220 nm; minor enantiomer t_R = 23.3 min, major enantiomer t_R = 18.2 min.

(*R*)-2-phenylpropan-2-yl 3-isobutyryl-5-oxotetrahydrofuran-3-carboxylate (143p)



Yellow oil, 22.0 mg, 69% yield. $[\alpha]_D^{25}$ = +14.6 (*c* 0.87, $CHCl_3$), *ee* 82%. **FTIR** ν_{max} (KBr)/cm^{-1} 2978, 2937, 1790, 1739, 1715, 1469, 1368, 1274, 1238, 1171, 1136, 1100, 1030, 764, 700. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.41-7.28 (m, 5H), 4.66 and 4.58 (ABq, 2H, *J*= 9.7 Hz), 3.04 (A_2, 2H), 2.84 (sept, 1H, *J*= 7.0 Hz), 1.82 (s, 6H), 1.14 (d, 3H, *J*= 7.0 Hz), 1.13 (d, 3H, *J*= 7.0 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 206.2, 173.3, 167.3, 143.6, 128.6, 127.9, 124.2, 85.3, 70.3, 63.3, 38.1, 34.1, 28.0, 27.9, 20.0, 19.8. **MS** (ESI *m/z*) 341.4 [MNa^+, 100%], 357.4 [MK^+, 40%]. Elemental analysis calcd (%) for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97; found C, 68.19; H, 7.16. HPLC analysis with Chiralpak IC column, 70:30 *n*-hexane:2-propanol, 1.0 mL/min, 220 nm; minor enantiomer t_R = 15.9 min, major enantiomer t_R = 14.0 min.

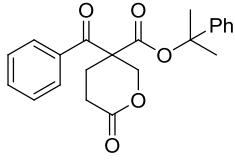
(*R*)-2-phenylpropan-2-yl 3-(cyclopropanecarbonyl)-5-oxotetrahydrofuran-3-carboxylate (143q)



White solid, 26.3 mg, 83% yield. **mp** 66.3-67.9 °C. $[\alpha]_D^{21}$ = +4.6 (*c* 0.58, $CHCl_3$), *ee* 69%. **FTIR** ν_{max} (KBr)/cm^{-1} 2984, 2926, 2853, 1789, 1739, 1705, 1449, 1386, 1275, 1244, 1178, 1138, 1102, 1076, 1031, 765, 700. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.37-7.29 (m, 5H), 4.77 and 4.62 (AX, 2H, *J* = 9.8 Hz), 3.11 (A_2, 2H), 1.88-1-83 (m, 1H), 1.81 (s, 6H), 1.24-1.20 (m, 2H), 1.08-1.03 (m, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 201.4, 173.5, 167.2, 143.9, 128.5, 127.8,

124.2, 84.9, 69.7, 63.2, 33.5, 28.05, 28.00, 18.1, 13.2, 13.1. **MS** (ESI *m/z*) 339.4 [MNa^+, 100%]. %]. Elemental analysis calcd (%) for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37; found C, 68.60; H, 6.21. HPLC analysis with Chiralpak AD-H column, 90:10 *n*-hexane:2-propanol, 1.0 mL/min, 254 nm; minor enantiomer t_R = 9.7 min, major enantiomer t_R = 10.7 min.

2-Phenylpropan-2-yl 3-benzoyl-6-oxotetrahydro-2H-pyran-3-carboxylate (145)

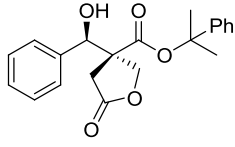


White wax, 9.2 mg, 25% yield. $[\alpha]_D^{24}$ = +58.6 (*c* 0.46, $CHCl_3$), *ee* 70%. **FTIR** ν_{max} (KBr)/cm^{-1} 2982, 2931, 2854, 1762, 1741, 1679, 1598, 1448, 1369, 1271, 1236, 1215, 1131, 1100, 1056, 767, 699. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.86-7.77 (m, 2H), 7.66-7.57 (m, 1H), 7.50-7.39 (m, 2H), 7.25-7.15 (m, 3H), 7.12-7.04 (m, 2H), 4.84 and 4.75 (ABq, 2H, *J*= 11.9 Hz), 2.93-2.80 (m, 1H), 2.75-2.51 (m, 2H), 2.35-2.23 (m, 1H), 1.70 (s, 3H), 1.62 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 193.8, 171.1, 168.7, 143.9, 134.0, 133.8, 129.0, 128.9, 128.3, 127.5, 124.2, 84.8, 70.4, 56.9, 28.2, 27.3, 27.1, 25.4. **MS** (ESI *m/z*) 389.4 [MNa^+, 11%]. Elemental analysis calcd (%) for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05; found C, 72.40; H, 6.20. HPLC analysis with Chiralpak AD-H column, 95:5 *n*-hexane:2-propanol, 1.0 mL/min, 254 nm; minor enantiomer t_R = 28.1 min, major enantiomer t_R = 33.9 min.

Reduction of γ-butyrolactones 143f and 143j

Reduction of γ-butyrolactones **143f** and **143j** was performed by using a modified protocol reported in the literature.[263] Finely ground $CeCl_3 \bullet 7H_2O$ was dried by heating at 100 °C under vacuum overnight. γ-Butyrolactone **143f** or **143j** (0.45 mmol) was dissolved in THF/EtOH= 3/1 (2.25 mL/750 μL) in a dried round-bottomed flask under nitrogen atmosphere and dry $CeCl_3$ (73 mg, 0.30 mmol) was added. The reaction mixture was cooled at -80 °C and stirred for 10 min at this temperature. After 10 min, $NaBH_4$ (10.2 mg, 0.27 mmol) was added and the reaction mixture was left under stirring at -80 °C for 10 h and 16 h, respectively (TLC eluent PE/ ethyl acetate 7:3). The reaction was quenched diluting with brine (50 mL) and extracted with ethyl acetate (3x50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography was not necessary and compounds **146f** (91% yield) and **146j** (95% yield) were obtained as an inseparable mixture of diastereomers (90:10 *dr*), as white solids. The diastereisomeric ratio was determined by ^{1}H NMR analysis.

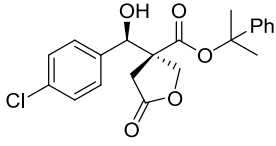
(*R*)-2-phenylpropan-2-yl 3-((*R*)-hydroxy(phenyl)methyl)-5-oxotetrahydrofuran-3-carboxylate (146f)



White solid, 90.2 mg, 91% yield. **FTIR** ν_{max} (KBr)/cm^{-1} 3418, 2925, 2854, 1783, 1732, 1455, 1221, 1137, 1027, 770, 701. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.38-7.26 (m, 8H), 7.26-7.20 (m, 2H), 5.04 (s, 1H) [minor 5.10 (s, 0.11H)], 4.47 (A_2, 2H) [minor 4.62 and 4.53

(AX, 0.22H, *J*= 9.6 Hz)], 3.05 (br s, OH), 2.93 and 2.87 (ABq, 2H, *J*= 17.8 Hz) [partially overlapped with minor 2.90 and 2.84 (ABq, 0.22H, *J*= 18.0 Hz)], 1.75 (s, 3H), 1.74 (s, 3H) [minor 1.72 (s, 0.33H), 1.70 (s, 0.33H)]. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 174.9 [minor 175.1], 171.0 [minor 170.7], 144.2, 138.6 [minor 138.7], 128.8, 128.6, 128.4, 127.5 [minor 127.7], 126.7 [minor 127.1], 124.1 [minor 126.4, 124.3], 84.5 [minor 84.3], 75.6 [minor 74.1], 71.1 [minor 71.6], 56.4 [minor 56.7], 34.3 [minor 32.7], 28.1 [minor 29.6], 27.8 [minor 27.7]. **MS** (ESI *m/z*) 377.6 [MNa^+, 100%]. Elemental analysis calcd (%) for $C_{21}H_{22}O_5$: C, 71.19; H, 6.26; found C, 70.90; H, 6.45.

(*R*)-2-phenylpropan-2-yl 3-((*R*)-(4-chlorophenyl)(hydroxy)methyl)-5-oxotetrahydrofuran-3-carboxylate (146j)



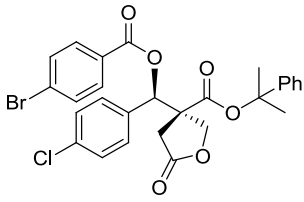
White solid, 165.8 mg, 95% yield. **FTIR** ν_{max} (KBr)/cm^{-1} 3435, 2928, 1779, 1732, 1494, 1449, 1414, 1368, 1273, 1234, 1195, 1136, 1028, 843, 764, 700. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.39-7.26 (m, 5H), 7.26-7.18 (m, 4H), 5.00 (d, 1H, *J*= 6.0 Hz) [minor 5.07 (d, 0.11H, *J*= 3.0 Hz)], 4.46 and 4.44 (ABq, 2H, *J*= 9.7 Hz) [minor 4.58 and 4.49 (ABq, 0.22H, *J*= 9.6 Hz)], 3.16 (br d, OH, *J*= 6.0 Hz), 2.91 and 2.82 (ABq, 2H, *J*= 17.6 Hz) [overlapped with minor 2.90 and 2.78 (m, 0.22H)], 1.75 (s, 6H) [minor 1.722 (s, 0.33H), 1.718 (s, 0.33H)]. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 174.8 [minor 175.1], 170.8 [minor 170.5], 143.96 [minor 144.0], 137.3 [minor 137.4], 134.5, 128.7, 128.4, 128.1, 127.6 [minor 127.5],

124.1 [minor 124.3], 84.7 [minor 84.4], 74.8 [minor 73.2], 70.9 [minor 71.7], 56.3 [minor 56.8], 34.5 [minor 32.2], 28.1, 27.9 [minor 27.8]. **MS** (ESI *m/z*) 411.5 [MNa^+, 49%], 427.5 [MK^+, 23%]. %]. Elemental analysis calcd (%) for $C_{21}H_{21}ClO_5$: C, 64.87; H, 5.44; found C, 64.62; H, 5.58.

Synthesis of compound 148j

To the diastereoisomeric mixture of alcohol **146j** (100 mg, 0.26 mmol) in dry pyridine (1.3 mL) was added DMAP (9.5 mg, 0.078 mmol) and then 4-bromobenzoyl chloride (282 mg, 1.29 mmol) at 0 °C. The resulting mixture was stirred for 4 hours at 30 °C. The reaction was quenched by addition of saturated $NaHCO_3$ (TLC eluent: PE/ethyl acetate 8:2). The organic materials were extracted three times with $CHCl_3$, the combined organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The diastereoisomeric ratio was determined by ^1H NMR analysis of the crude reaction mixture (90:10 dr). Purification by flash chromatography eluting with mixtures of PE/ethyl acetate 95/5 to 9/1, afforded compound **148j** in 75% yield (111.5 mg; major diast.: 90 mg).

(*R*)-2'-phenylpropan-2'-yl 3-[(*R*)-(4'-bromobenzoyloxy)(4'-chlorophenyl)methyl)]-5 oxotetrahydrofuran-3-carboxylate (148j)

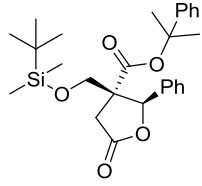


Major diast.: White solid, 90 mg. **mp** 125.0-126.3 °C. $[\alpha]_D^{21}$ = +45.4 (*c* 0.56, $CHCl_3$), *ee* 86%. The *ee* was improved up to 99% by a single crystallization performed by slow evaporation of a *n*-hexane / ethanol solvent mixture at room temperature. **FTIR** ν_{max} (KBr)/cm^{-1} 2927, 1791, 1733, 1590, 1493, 1399, 1265, 1174, 1136, 1094, 1032, 1011, 837, 756, 699. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.84 (d, 2H, J = 8.1 Hz), 7.61 (d, 2H, J = 8.1 Hz), 7.34 and 7.28 (ABq, 4H, J = 8.3 Hz), 7.24-7.20 (m, 5H), 6.37 (s, 1H), 4.54 and 4.47 (ABq, 2H, J = 10.0 Hz), 3.10 and 2.86 (AX, 2H, J = 17.9 Hz), 1.77 (s, 3H), 1.73 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 173.6, 168.5, 164.0, 143.7, 135.5, 133.2, 132.1, 131.2, 129.24, 129.18, 128.4, 128.3, 127.7, 127.6, 124.2, 84.6, 76.4, 69.8, 55.5, 34.0, 28.2, 27.7. **MS** (ESI *m/z*) 571.4 [MH^+, 4%], 595.0 [MNa^+, 10%], 610.2 [MK^+, 6%]. Elemental analysis calcd (%) for $C_{28}H_{24}BrClO_6$: C, 58.81; H, 4.23; found C, 59.08; H, 4.02. HPLC analysis with Chiralpak IC column, 90:10 *n*-hexane:2-propanol, 1.0 mL/min, 254 nm, major diastereoisomer: minor enantiomer t_R = 27.5 min, major enantiomer t_R = 30.5 min.

Synthesis of compound 147f

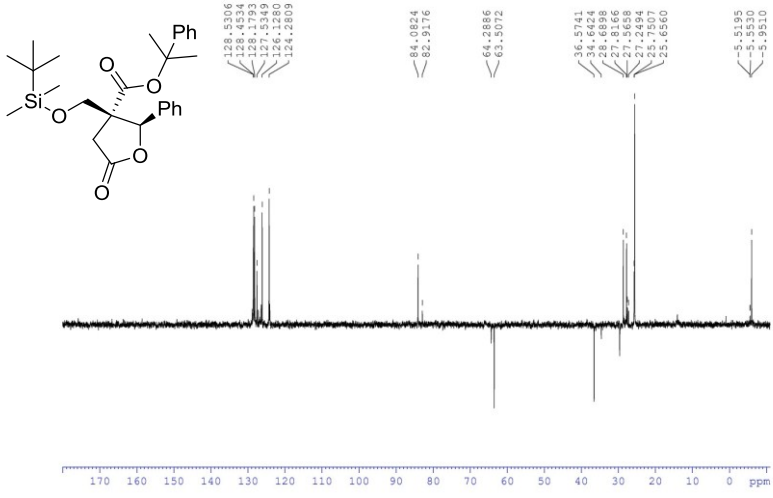
The title compound was synthesized according to the literature.[164b] Alcohol **146f** was obtained after reduction of enantioenriched compound **143f** (90:10 *dr*, 84% *ee*). Under a positive pressure of nitrogen, a flamed round bottom two necked flask was charged with anhydrous DCM (600 μL), alcohol **146f** (42.2 mg, 0.12 mmol) and 2,6-lutidine (28 μL, 0.24 mmol). The solution was cooled at 0 °C and *tert*-butyldimethylsilyl trifluoromethanesulfonate TBDMSOTf (41 μL, 0.18 mmol) was added. The reaction mixture was allowed to slowly warm up to room temperature under stirring, until the complete consumption of the starting material (19 h, TLC eluent: PE/ethyl acetate 8:2). The reaction mixture was then diluted with DCM and sat. aq. $NaHCO_3$ solution was added. The organic solution was separated, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with mixtures of PE/ethyl acetate 100/1 to 95/5) to give colourless gummy compound **147f** in 60% yield (33.7 mg) as an inseparable mixture of diastereomers (85:15 *dr*). The diastereisomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture.

(*2R,3R*)-2'-phenylpropan-2'-yl 3-[(tert butyldimethylsilyloxy)methyl]-5-oxo-2-phenyltetrahydrofuran-3-carboxylate (147f)

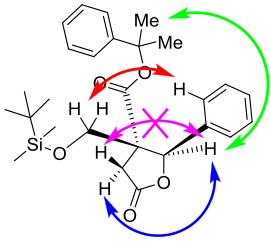


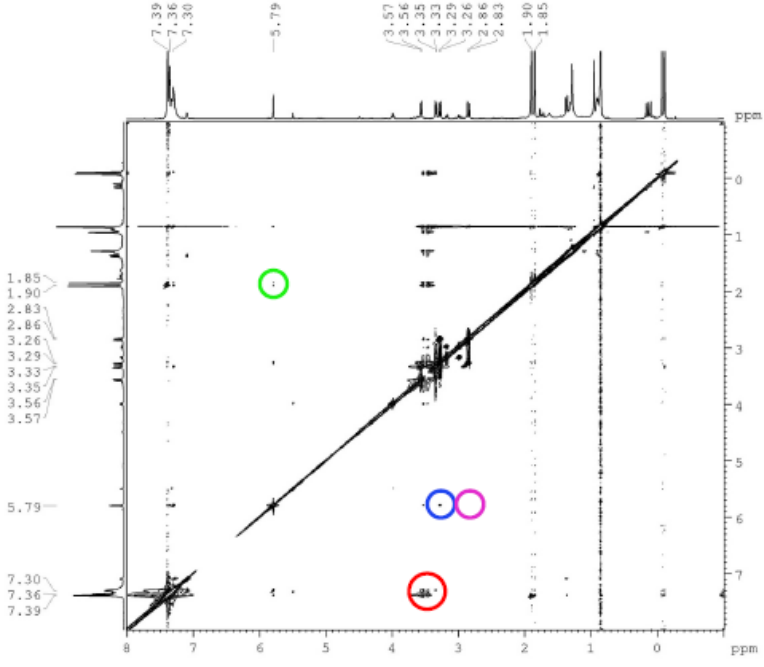
Colourless liquid gum, 33.7 mg, 60% yield. **FTIR** ν_{max} (KBr)/cm^{-1} 2927, 2856, 1796, 1734, 1497, 1464, 1385, 1366, 1255, 1179, 1137, 1105, 1023, 839, 764, 699. **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.42-7.22 (m, 10H), 5.79 (s, 1H) [minor 5.49 (s, 0.20H)], 3.56 and 3.34 (AX, 2H, J = 10.0 Hz) [minor 4.00 and 3.98 (ABq, 0.40H, J= 10.0 Hz)], 3.28 and 2.85 (AX, 2H, J= 17.3 Hz) [minor 3.17 and 2.98 (AX, 0.40H, J= 17.5 Hz)], 1.90 (s, 3H), 1.85 (s, 3H), 0.85 (s, 9H), -0.07 (s, 3H), -0.11 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 174.4 [minor 174.9], 169.8 [minor 168.3], 144.4 [minor 144.7], 134.3 [minor 135.6], 128.5, 128.4, 128.2, 127.5, 126.1, 124.3, 84.1 [minor 82.9], 83.9 [minor 83.7], 63.5 [minor 64.3], 56.4 [minor 57.9], 36.6 [minor 34.6], 28.7, 27.8 [minor 27.6, 27.2], 25.7 [minor 25.8], 18.1 [minor 22.7], -6.0 [minor -5.5, -5.6]. **MS** (ESI *m/z*) 491.7 [MNa^+, 62%], 507.8 [MK^+, 100%]. Elemental analysis calcd (%) for $C_{27}H_{36}O_5Si$: C, 69.20; H, 7.74; found C, 69.38; H, 7.64. HPLC analysis with Chiralpak AD-H column, 100:1 *n*-hexane : ethanol, 1.0 mL/min, 220 nm, major diastereoisomer: minor enantiomer t_R = 10.2 min, major enantiomer t_R = 8.1 min, *ee* 84%.

DEPT-135 of compound 147f
(100MHz, $CDCl_3$)



Confirmation of the relative configuration of compound 147f by NOESY
(600 MHz, $CDCl_3$)





X-ray data for the relative and absolute configuration assignment of compound 148j

X-ray diffraction quality single crystals of major diastereoisomer of compound **148j** were obtained by slow evaporation of a solution of **148j** in *n*-hexane / ethanol solvent mixture at room temperature.

A suitable crystal of **148j** was selected and mounted on a cryo-loop with Paratone oil and measured at 100 K room temperature with a Rigaku AFC7S diffractometer equipped with a Mercury2 CCD detector using Mo$K\alpha$ radiation. Data reduction was performed with the crystallographic package CrystalClear.[264] Data have been corrected for Lorentz, polarization and absorption. The structures were solved by direct methods using the program SIR2011[265] and refined by means of full matrix least-squares based on F^2 using the program SHELXL97.[266]

All non-hydrogen atoms were refined anisotropically, hydrogen atoms were positioned geometrically and included in structure factors calculations but not refined.

A total of 325 refinable parameters were finally considered, final disagreement indices are $R1$= 0.0608 (3058 reflections $F^2>2\sigma F^2$), $_wR2$= 0.1902 (all 6047 independent. reflections).

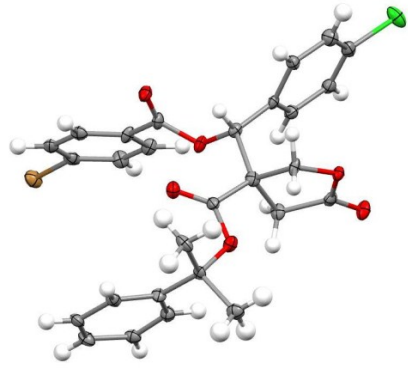
Flack parameter is -0.010(14).

ORTEP plot is obtained by means of the program Mercury.[267]

Crystal data:

$C_{28}H_{24}BrClO_6$, FW= 571.83, monoclinic, space group $P2_1$, Z= 2, a= 14.053(2) Å, b= 6.2308(9) Å, c=14.438(2) Å, β = 95.626(3) °,

V=1258.1(3) Å^3, D_x = 1.509 gcm^{-3}, μ_{calc}= 1.782 mm^{-1}.



Molecular structure of **148j**. Thermal ellipsoids are drawn at 30% probability level.

6.4 Organocatalytic enantioselective synthesis of α-nitroepoxides via kinetic resolution

Experimental procedures and compounds characterization

Catalyst **187** was prepared according to the literature.[268]

General procedure for the epoxidation of nitroalkenes

The (*E*)-α,β- disubstituted nitroalkenes were synthesized according to the literature.[269]

α-Nitroepoxides were prepared according to published procedures.[187,188c,191] To a stirred ice-bath cold suspension of (*E*)-α,β-disubstituted nitroalkene (6 mmol) in methanol (12 mL) and hydrogen peroxide 50% aqueous solution (450 μL, 7.8 mmol), aqueous NaOH 2M (1.5 mL, 3 mmol) was added rapidly (ca. 5 minutes) with stirring. The reaction was stirred at 0 ºC for 1 h (5 h for compound **184h)**. Then, water was added (30 mL), extracted with diethyl ether (3 x 30 mL) and the combined ethereal extracts were washed with brine (40 mL), dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (PE/ diethyl ether 100:5) to give compounds **184a**, **184e-m** (13-72% yields).

General procedure for the aminolytic kinetic resolution (AKR) of racemic α-nitro epoxides

A sample vial was charged with nitroepoxide **184** (0.20 mmol) and catalyst **78c** (22.5 mg, 0.04 mmol) in anhydrous toluene (2 mL). Aniline (55 μL, 0.60 mmol) was added and the reaction stirred at room temperature for 84-115 h, monitored by TLC (eluent PE/

diethyl ether 95:5 or 90:10 and PE/ ethyl acetate 90:10 only for compounds **184**, **185g** and **184**, **185k**). The enantioenriched α-nitroepoxides **184a**, **184e-m** and products **185a**-**185e-m** were isolated by flash chromatography (eluting from PE/ diethyl ether 100:2 to 100:5 and to 80:20 only for compound **185m**. In particular, aniline and α-amino ketone **185m** have the same polarity. To remove aniline from the mixture of the two products, recovered after silica gel chromatography, the mixture was diluted with Et_2O and washed with water.

General procedure for the kinetic resolution of 184a with thiol 190

A sample vial was charged with nitroepoxide **184a-(±)** (17.9 mg, 0.10 mmol), K_2CO_3 (2.8 mg, 0.02 mmol) and catalyst **783c** (8.5 mg, 0.015 mmol) in anhydrous toluene (1 mL). Then, 2-naphthalenethiol (19.2 mg, 0.12 mmol) was added and the reaction stirred at room temperature for 70 h, monitored by TLC (eluent PE/ diethyl ether 95:5).

The enantioenriched α-nitroepoxide **184a** (4.5 mg, 25% yield) and product **192 (**21.3 mg, 73% yield) were isolated by flash chromatography (eluting from PE/ diethyl ether 100:1 to 80:20).

General procedure for the kinetic resolution of 184a with diamine 191

A sample vial was charged with nitroepoxide **184a-(±)** (26.9 mg, 0.15 mmol) and catalyst **78c** (12.7 mg, 0.022 mmol) in anhydrous toluene (1.5 mL). Then *o*-phenylenediamine **191** (19.5 mg, 0.18

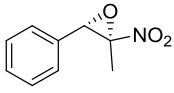
mmol) was added and the reaction was stirred at room temperature for 47 h, monitored by TLC (eluent PE/ diethyl ether 95:5). The enantioenriched α-nitroepoxide **184a** (8.6 mg, 32% yield) and product **193 (**18.5 mg, 56% yield) were isolated by flash chromatography (eluting from PE/ diethyl ether 100:2 to 90:10).

General procedure for one-pot stereoselective ring-opening/reduction sequence to amino alcohol 189

To a solution of nitroepoxide **184a-(±)** (22.6 mg, 0.126 mmol) in dry $CHCl_3$ (315 μL), pyrrolidine (21 μL, 0.252 mmol) was added at 0 °C. The resulting mixture was stirred for 6 hours at 0 °C (TLC eluent PE/ diethyl ether 95:5). After completion, dry MeOH (105 μL) was added at 0 °C, followed by dry $CeCl_3$ (31.1 mg, 0.126 mmol, finely ground $CeCl_3 \bullet 7H_2O$ dried at 100 °C under vacuum overnight). The reaction mixture was stirred for 10 min at the same temperature and then $NaBH_4$ (4.8 mg, 0.126 mmol) was added. After stirring at 0 °C for 2.5 h, a second portion of $NaBH_4$ (4.8 mg, 0.126 mmol) and $CeCl_3$ (31.1 mg, 0.126 mmol) was added, and stirring continued for additional 3 h. After complete conversion of the ketone to the alcohol (TLC eluent ethyl acetate/ MeOH 10 mL : 1 mL with 6 drops of NH_4OH, stained with permanganate) the reaction was quenched by diluting with brine (20 mL) and extracting with ethyl acetate (3x20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography eluting with CH_2Cl_2 and then with diethyl ether afforded *anti*-1,2-amino alcohol **189** in 78% yield (20.2 mg).

Absolute configuration of (1*R*,2*S*)-1-phenyl-1-(pyrrolidin-1-yl)propan-2-ol **189** was determined by comparison of optical rotation with the literature.[207] The absolute configuration of α-nitroepoxide **184a** was assigned to be (2*R*,3*S*) and the absolute configuration of α-nitroepoxides **184** was assigned to be (2*R*,3*S*) by analogy.

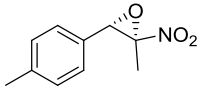
(*2R*, *3S*)-2-Methyl-2-nitro-3-phenyloxirane (184a)



Data for this compound were consistent with those reported in the literature.[188c]

Yellow oil, 10 mg, 28 % yield. $[\alpha]_D^{17}$ = -36.7 (*c* 0.48, $CHCl_3$), *ee* 72%. **FTIR** ν_{max} (KBr)/cm^{-1} 3066, 3035, 2947, 1558, 1451, 1357, 1159, 1107, 901, 770, 754, 703, 602. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.46-7.40 (m, 3H), 7.32-7.29 (m, 2H), 4.54 (s, 1H), 1.80 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 130.9, 129.4, 128.7, 126.4, 88.9, 62.6, 12.4. HPLC analysis with Chiralpak AS-H column, 95:5 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 6.1 min, major enantiomer t_R = 6.8 min.

(*2R*, *3S*)-2-Methyl-2-nitro-3-p-tolyloxirane (184e)

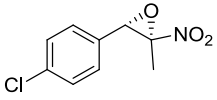


Data for this compound were consistent with those reported in the literature.[188c]

Yellow oil, 6.6 mg, 17% yield. $[\alpha]_D^{24}$ = -33.5 (*c* 0.50, $CHCl_3$), *ee* 84%. **FTIR** ν_{max} (KBr)/cm^{-1} 3028, 2925, 1559, 1452, 1346, 1159, 1106, 903, 848, 817, 772. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.25-7.16 (m, 4H), 4.50 (s, 1H), 2.38 (s, 3H), 1.80 (d, 3H, *J*= 1.3 Hz).

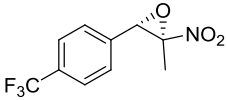
^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.5, 129.4, 127.9, 126.3, 89.0, 62.8, 21.3, 12.4. MS (ESI *m/z*) 216.5 [MNa^+, 12%]. HPLC analysis with Chiralpak IE-3 column, 98:2 *n*-hexane:2-propanol, 0.7 mL/min, 220 nm; minor enantiomer t_R = 16.2 min, major enantiomer t_R = 14.2 min.

(*2R*, *3S*)-3-(4-Chlorophenyl)-2-methyl-2-nitrooxirane (184f)



White solid, 12.4 mg, 29% yield. **mp** 55.9-57.9 °C. **$[\alpha]_D^{22}$** = -53.8 (*c* 0.65, $CHCl_3$), *ee* 86%. **FTIR** ν_{max} (KBr)/cm^{-1} 1561, 1495, 1436, 1352, 1159, 1091, 1015, 900, 763. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.41 (d, 2H, *J*= 8.2 Hz), 7.25 (d, 2H, *J*= 8.2 Hz), 4.52 (s, 1H), 1.79 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 135.6, 129.4, 129.1, 127.8, 88.6, 62.0, 12.4. Elemental analysis calcd (%) for $C_9H_8ClNO_3$: C, 50.60; H, 3.77; N, 6.56; found C, 50.89; H, 3.97; N, 6.60. HPLC analysis with Chiralpak AS-H column, 90:10 *n*-hexane:2-propanol, 1 mL/min, 220 nm; minor enantiomer t_R = 6.9 min, major enantiomer t_R = 7.5 min.

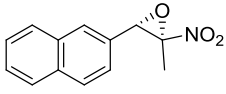
(*2R*, *3S*)-2-Methyl-2-nitro-3-(4-(trifluoromethyl)phenyl)oxirane (184g)



Yellow solid, 18 mg, 36% yield. **mp** 58.2-62.6 °C. **$[\alpha]_D^{23}$** = -30.9 (*c* 0.53, $CHCl_3$), *ee* 77%. **FTIR** ν_{max} (KBr)/cm^{-1} 1561, 1325, 1167, 1127, 1067, 1019, 857, 832. **^{1}H NMR** ($CDCl_3$, 250 MHz): δ 7.69 (d, 2H, *J*= 8.1 Hz), 7.45 (d, 2H, *J*= 8.1 Hz), 4.61 (s, 1H), 1.78 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 134.9, 131.7 (q, $^2J_{(C\text{-}C\text{-}F)}$=

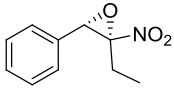
32.8 Hz), 126.9, 125.9, 125.8, 123.6 (q, $^1J_{(C\text{-}F)}$= 271.0 Hz), 88.5, 61.8, 12.4. **MS** (ESI *m/z*) 285.6 [MK^+, 20%]. Elemental analysis calcd (%) for $C_{10}H_8F_3NO_3$: C, 48.59; H, 3.26; N, 5.67; found C, 48.94; H, 3.48; N, 5.40. HPLC analysis with Chiralpak IE-3 column, 98:2 *n*-hexane:2-propanol, 0.7 mL/min, 220 nm; minor enantiomer t_R = 18.4 min, major enantiomer t_R = 13.2 min.

(*2R*, *3S*)-2-Methyl-3-(naphthalen-2-yl)-2-nitrooxirane (184h)



Pale yellow solid, 11.9 mg, 26% yield. **mp** 63.8-65.7 °C. **$[\alpha]_D^{20}$** = -72.2 (*c* 0.67, $CHCl_3$), *ee* 95%. **FTIR** ν_{max} (KBr)/cm^{-1} 3057, 2925, 1559, 1343, 1105, 893, 861, 821, 756. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.92-7.85 (m, 3H), 7.79 (s, 1H), 7.58-7.53 (m, 2H), 7.39 (dd, 1H, J_1= 8.4 Hz, J_2= 1.5 Hz), 4.71 (s, 1H), 1.83 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 133.6, 132.8, 128.8, 128.3, 128.0, 127.9, 126.9, 126.1, 123.2, 80.0, 62.9, 12.5. **MS** (ESI *m/z*) 230.0 [MH^+, 6%], 248.6 [$M+H_3O^+$, 38%]. Elemental analysis calcd (%) for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11; found C, 68.44; H, 5.10; N, 6.24. HPLC analysis with Chiralpak IE-3 column, 98:2 *n*-hexane:2-propanol, 0.7 mL/min, 254 nm; minor enantiomer t_R = 24.7 min, major enantiomer t_R = 20.3 min.

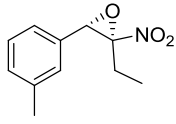
(*2R*, *3S*)-2-Ethyl-2-nitro-3-phenyloxirane (184i)



Yellow oil, 8 mg, 21% yield. **$[\alpha]_D^{22}$** = -25.1 (*c* 0.67, $CHCl_3$), *ee* 92%. **FTIR** ν_{max} (KBr)/cm^{-1} 2918, 1557, 1458, 1435, 1351, 938, 813, 768. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.44-7.38 (m, 3H), 7.33-7.29 (m, 2H), 4.52 (s, 1H),

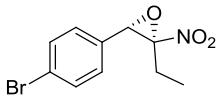
2.55-2.41 (m, 1H), 1.69 (dq, 1H, J_1= 15.1 Hz, J_2= 7.3 Hz), 1.07 (t, 3H, J_1= 7.4 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 131.1, 129.4, 128.7, 126.3, 92.5, 63.2, 19.5, 7.6. **MS** (ESI *m/z*) 193.8 [MH^+, 7%], 216.5 [MNa^+, 15%]. Elemental analysis calcd (%) for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25; found C, 62.46; H, 5.50; N, 7.48. HPLC analysis with Chiralpak IE-3 column, 98:2 *n*-hexane:2-propanol, 0.7 mL/min, 220 nm; minor enantiomer t_R = 13.7 min, major enantiomer t_R = 11.9 min.

(*2R*, *3S*)-2-Ethyl-2-nitro-3-m-tolyloxirane (184j)



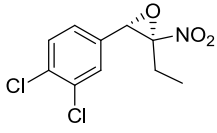
Yellow oil, 12.8 mg, 31% yield. **$[\alpha]_D^{23}$** = -30.6 (*c* 0.57, $CHCl_3$), *ee* 92%. **FTIR** ν_{max} (KBr)/cm^{-1} 2984, 2945, 1559, 1462, 1435, 1351, 1152, 1083, 969, 815, 790. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.30 (t, 1H, *J*= 7.5 Hz), 7.23-7.18 (m, 1H), 7.12-7.07 (m, 2H), 4.47 (s, 1H), 2.48 (dq, 1H, J_1= 15.1 Hz, J_2= 7.4 Hz), 2.38 (s, 3H), 1.69 (dq, 1H, J_1= 15.1 Hz, J_2= 7.4 Hz), 1.08 (t, 3H, *J*= 7.4 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 138.6, 131.0, 130.1, 128.6, 126.9, 123.3, 92.6, 63.3, 21.4, 19.5, 7.6. **MS** (ESI *m/z*) 207.9 [MH^+, 8%], 230.5 [MNa^+, 10%]. Elemental analysis calcd (%) for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76; found C, 64.07; H, 6.53; N, 6.63. HPLC analysis with Chiralpak IE-3 column, 98:2 *n*-hexane:2-propanol, 0.7 mL/min, 254 nm; minor enantiomer t_R = 13.4 min, major enantiomer t_R = 11.6 min.

(*2R*, *3S*)-3-(4-Bromophenyl)-2-ethyl-2-nitrooxirane (184k)



White solid, 18.2 mg, 33% yield. Mp 59.6-60.3 °C. $[\alpha]_D^{21}$ = -29.0 (*c* 0.53, $CHCl_3$), *ee* 90%. **FTIR** ν_{max} (KBr)/cm^{-1} 2984, 1557, 1489, 1463, 1434, 1346, 1071, 1011, 936, 808. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.56 (d, 2H, *J*= 8.4 Hz), 7.19 (d, 2H, *J*= 8.4 Hz), 4.48 (s, 1H), 2.46 (dq, 1H, J_1= 15.1 Hz, J_2= 7.4 Hz), 1.66 (dq, 1H, J_1= 15.1 Hz, J_2= 7.4 Hz), 1.07 (t, 3H, *J*= 7.4 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 132.0, 130.1, 127.9, 123.7, 92.2, 62.6, 19.5, 7.6. **MS** (ESI *m/z*) 225.8 [M^+-NO_2, 5%], 261.7 [M^+-NO_2+$2H_2O$, 20%]. Elemental analysis calcd (%) for $C_{10}H_{10}BrNO_3$: C, 44.14; H, 3.70; N, 5.15; found C, 43.87; H, 3.88; N, 5.37. HPLC analysis with Chiralpak IE-3 column, 98:2 *n*-hexane:2-propanol, 0.7 mL/min, 220 nm; minor enantiomer t_R = 17.4 min, major enantiomer t_R = 14.6 min.

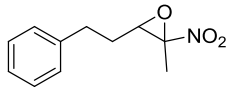
(2R, 3S)-3-(3,4-Dichlorophenyl)-2-ethyl-2-nitrooxirane (184l)



Yellow oil, 18.1 mg, 35% yield. $[\alpha]_D^{25}$ = -18.3 (*c* 0.76, $CHCl_3$), *ee* 61%. **FTIR** ν_{max} (KBr)/cm^{-1} 2984, 2944, 1561, 1474, 1435, 1350, 1133, 1033, 944, 811. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.51 (d, 1H, *J*= 8.3 Hz), 7.40 (d, 1H, *J*= 1.9 Hz), 7.16 (dd, 1H, J_1= 8.3 Hz, J_2= 1.9 Hz), 4.48 (s, 1H), 2.46 (dq, 1H, J_1= 15.1 Hz, J_2= 7.4 Hz), 1.65 (dq, 1H, J_1= 15.1 Hz, J_2= 7.4 Hz), 1.09 (t, 3H, *J*= 7.4 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 133.8, 133.3, 131.3, 130.9, 128.2, 125.6, 92.0, 61.8, 19.5, 7.6. **MS** (ESI *m/z*) 251.6 [M^+-NO_2+$2H_2O$, 100%]. Elemental analysis calcd (%) for $C_{10}H_9Cl_2NO_3$: C, 45.83; H, 3.46; N, 5.34; found C, 46.16; H, 3.24; N, 5.55. HPLC analysis with

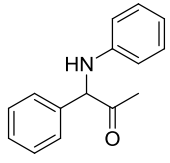
Chiralpak IE-3 column, 98:2 *n*-hexane:2-propanol, 0.7 mL/min, 254 nm; minor enantiomer t_R = 17.3 min, major enantiomer t_R = 13.5 min.

2-Methyl-2-nitro-3-phenethyloxirane (184m)



Yellow oil, 14.5 mg, 35% yield. $[\alpha]_D^{25}$ = -4.6 (*c* 0.88, $CHCl_3$), *ee* 16%. **FTIR** ν_{max} (KBr)/cm^{-1} 3027, 2924, 1557, 1496, 1455, 1388, 1357, 1112, 1083, 751, 699. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.35-7.24 (m, 3H), 7.21-7.16 (m, 2H), 3.48 (t, 1H, *J*= 6.3 Hz), 2.95-2.87 (m, 1H), 2.83-2.74 (m, 1H), 2.06-1.95 (m, 1H), 1.93-1.83 (m, 1H), 1.74 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 139.6, 128.8, 128.3, 126.7, 62.4, 31.9, 29.8, 13.5. Elemental analysis calcd (%) for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76; found C, 64.11; H, 6.58; N, 6.65. HPLC analysis with Chiralpak AS-H column, 99:1 *n*-hexane:2-propanol, 0.8 mL/min, 220 nm; minor enantiomer t_R = 12.7 min, major enantiomer t_R = 11.5 min.

1-Phenyl-1-(phenylamino)propan-2-one (185a)

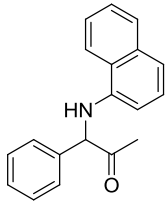


Data for this compound were consistent with those reported in the literature.[270]

Wax, 29.3 mg, 65% yield. $[\alpha]_D^{27}$ = +27.9 (*c* 0.50, $CHCl_3$), *ee* 16%. **FTIR** ν_{max} (KBr)/cm^{-1} 3393, 2863, 1714, 1600, 1505, 1312, 1230, 1165, 745, 692. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.55-7.32 (m, 5H), 7.13-7.06 (m, 2H), 6.73-6.66 (m, 1H), 6.63-6.57 (m, 2H), 5.01 (brd, 1H), 2.14 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 203.8, 145.4, 137.6, 129.7, 129.2, 129.1,

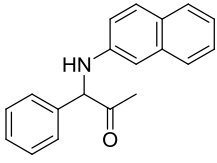
128.8, 127.8, 118.0, 113.7, 68.4, 26.7. **MS** (ESI *m/z*) 248.5 [MNa^+, 10%]. HPLC analysis with Chiralpak IE-3 column, 95:5 *n*-hexane:2-propanol, 0.7 mL/min, 254 nm; minor enantiomer t_R = 18.8 min, major enantiomer t_R = 15.6 min.

1-(naphthalen-1-ylamino)-1-phenylpropan-2-one (185b)



Red solid, 12.4 mg, 30% yield. **mp** 81 °C (Decomp.). **FTIR** ν_{max} (KBr)/cm^{-1} 3415, 3064, 1715, 1625, 1582, 1526, 1476, 1165, 769, 701. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.09 (d, 1H, *J*= 8.2 Hz), 7.76 (d, 1H, *J*= 8.0 Hz), 7.58-7.44 (m, 3H), 7.41-7.29 (m, 3H), 7.20-7.13 (m, 2H), 6.36-6.30 (m, 2H), 5.15 (d, 1H, *J*= 2.7 Hz), 2.20 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 204.0, 140.9, 137.8, 134.3, 129.3, 128.6, 128.5, 127.8, 126.3, 125.8, 124.9, 123.4, 120.2, 117.6, 105.3, 68.2, 26.6. MS (ESI *m/z*) 276.7 [MH^+, 28%], 298.6 [MNa^+, 100%]. Elemental analysis calcd (%) for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09; found C, 83.25; H, 6.47; N, 4.94.

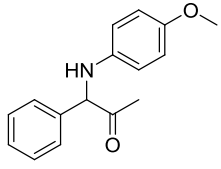
1-(naphthalen-2-ylamino)-1-phenylpropan-2-one (185c)



Red solid, 12.8 mg, 31% yield. **mp** 83 °C (Decomp.). **FTIR** ν_{max} (KBr)/cm^{-1} 3398, 3057, 1714, 1629, 1519, 1482, 1358, 1190, 827, 748, 701. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.64-7.58 (m, 2H), 7.54-7.45 (m, 3H), 7.42-7.37 (m, 2H), 7.34-7.28 (m, 1H), 7.18-7.13 (m, 1H), 6.96 (dd, 1H, J_1= 8.8 Hz, J_2= 2.5 Hz), 6.63-6.60 (m, 2H), 5.61 (brs, 1H), 5.13 (d, 1H, *J*= 4.3 Hz), 2.18 (s, 3H). **^{13}C**

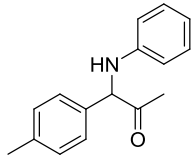
NMR ($CDCl_3$, 100 MHz): δ 203.9, 143.5, 137.8, 134.8, 129.3, 129.0, 128.5, 127.8, 127.6, 126.2, 125.9, 122.1, 118.1, 105.4, 68.1, 26.7. **MS** (ESI *m/z*) 276.7 [MH^+, 26%], 298.6 [MNa^+, 100%]. Elemental analysis calcd (%) for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09; found C, 83.22; H, 6.50; N, 4.84.

1-(4-methoxyphenylamino)-1-phenylpropan-2-one (185d)



Ochre wax, 14.6 mg, 38% yield. **FTIR** ν_{max} (KBr)/cm^{-1} 3404, 1719, 1654, 1513, 1239, 1178, 1035, 820, 762, 701. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.48-7.30 (m, 5H), 6.69 (d, 2H, *J*= 8.8 Hz), 6.50 (d, 2H, *J*= 8.8 Hz), 5.15 (brs, 1H), 4.93 (s, 1H), 3.68 (s, 3H), 2.12 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 204.4, 152.1, 140.3, 138.3, 129.2, 128.3, 127.8, 114.8, 114.5, 69.1, 55.7, 26.7. MS (ESI *m/z*) 255.7 [MH^+, 13%], 278.0 [MNa^+, 16%]. Elemental analysis calcd (%) for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49; found C, 75.58; H, 7.00; N, 5.72.

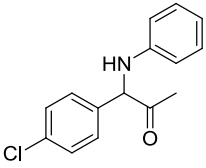
1-(phenylamino)-1-p-tolylpropan-2-one (185e)



Red wax, 37.8 mg, 79% yield. FTIR ν_{max} (KBr)/cm^{-1} 3422, 2921, 1707, 1668, 1601, 1496, 1444, 1314, 1159, 1113, 1030, 901, 823, 744. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.32 (d, 2H, *J*= 7.7 Hz), 7.17 (d, 2H, *J*= 7.7 Hz), 7.13-7.06 (m, 2H), 6.72-6.66 (m, 1H), 6.64-6.58 (m, 2H), 4.99 (brs, 1H), 2.33 (s, 3H), 2.13 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 204.2, 145.8, 138.2, 134.8, 130.4, 129.9, 129.5, 129.1, 127.6, 117.6, 113.3, 67.8, 26.6, 21.1. MS (ESI *m/z*)

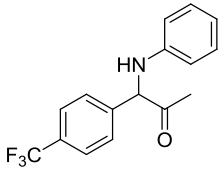
240.8 [MH^+, 10%], 262.8 [MNa^+, 14%]. Elemental analysis calcd (%) for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85; found C, 79.98; H, 7.41; N, 6.06.

1-(4-chlorophenyl)-1-(phenylamino)propan-2-one (185f)



Red wax, 34.9 mg, 67% yield. **FTIR** ν_{max} (KBr)/cm^{-1} 3449, 1715, 1670, 1601, 1542, 1500, 1489, 1441, 1315, 1162, 1091, 836, 752, 693. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.46-7.33 (m, 4H), 7.14-7.07 (m, 2H), 6.70-6.66 (m, 1H), 6.55-6.50 (m, 2H), 4.98 (brs, 1H), 2.14 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 203.2, 145.5, 136.6, 131.7, 129.4, 129.2, 129.1, 117.9, 113.3, 67.4, 26.6. **MS** (ESI *m/z*) 260.5 [MH^+, 37%], 282.5 [MNa^+, 10%]. Elemental analysis calcd (%) for $C_{15}H_{14}ClNO$: C, 69.36; H, 5.43; N, 5.39; found C, 69.70; H, 5.60; N, 5.21.

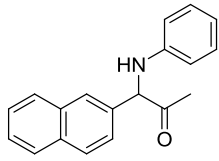
1-(phenylamino)-1-(4-(trifluoromethyl)phenyl)propan-2-one (185g)



Yellow wax, 28.1 mg, 48% yield. **FTIR** ν_{max} (KBr)/cm^{-1} 3392, 3052, 2926, 1721, 1603, 1505, 1417, 1325, 1279, 1166, 1125, 1066, 1017, 845, 751, 692. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.67-7.58 (m, 4H), 7.12-7.07(m, 2H), 6.70-6.66 (m, 1H), 6.53-6.48 (m, 2H), 5.47 (brs, 1H), 5.06 (brs, 1H), 2.16 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 202.7, 145.5, 142.3, 130.7 (q, $^2J_{(C\text{-}C\text{-}F)}$ = 32.3 Hz), 129.3, 128.2, 126.2 (q, $^3J_{(C\text{-}C\text{-}C\text{-}F)}$ = 3.6 Hz), 123.9 (q, $^1J_{(C\text{-}F)}$ = 270.5 Hz), 118.1, 113.3., 67.8, 26.8. **MS** (ESI *m/z*) 293.6 [MH^+,

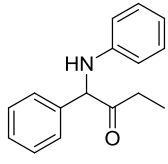
17%], 316.7 [MNa^+, 21%]. Elemental analysis calcd (%) for $C_{16}H_{14}F_3NO$: C, 65.52; H, 4.81; N, 4.78; found C,65.79; H, 4.97; N, 4.63.

1-(naphthalen-2-yl)-1-(phenylamino)propan-2-one (185h)



Red wax, 39.6 mg, 72% yield. **FTIR** ν_{max} (KBr)/cm^{-1} 3056, 1711, 1667, 1598, 1544, 1496, 1444, 1313, 1232, 1155, 1028, 821, 753, 693. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.99 (s, 1H), 7.93-7.80 (m, 2H), 7.58-7.35 (m, 5H), 7.17-7.05 (m, 2H), 6.70-6.58 (m, 2H), 5.17 (s, 1H), 2.16 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 203.9, 145.9, 135.5, 133.4, 133.2, 129.2, 129.1, 128.3, 127.8, 127.7, 127.3, 126.5, 126.3, 124.9, 117.7, 113.3, 68.3, 26.8. **MS** (ESI *m/z*) 276.6 [MH^+, 39%], 298.6 [MNa^+, 77%]. Elemental analysis calcd (%) for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09; found C, 82.58; H, 6.38; N, 5.37.

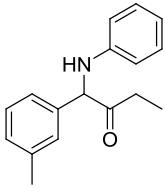
1-phenyl-1-(phenylamino)butan-2-one (185i)



Ochre solid, 28.2 mg, 59% yield. **mp** 84.2-86.7 °C. **FTIR** ν_{max} (KBr)/cm^{-1} 3395, 2923, 1716, 1603, 1504, 1454, 1428, 1317, 1260, 1111, 1034, 749. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.47-7.42 (m, 2H), 7.39-7.34 (m, 3H), 7.30 (d, 1H, *J*= 7.2 Hz), 7.12-7.05 (m, 2H), 6.65 (t, 1H, *J*= 7.3 Hz), 6.57-6.53 (m, 2H), 5.50 (brs, 1H), 5.00 (s, 1H), 2.53-2.40 (m, 2H), 0.99 (t, 3H, *J*= 7.3 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 206.9, 146.0, 138.3, 129.14, 129.12, 128.3, 127.8, 117.6, 113.3., 67.4, 32.5, 7.86. **MS** (ESI *m/z*) 240.7 [MH^+, 18%], 262.6 [MNa^+, 43%]. Elemental analysis calcd (%) for $C_{16}H_{17}NO$: C,

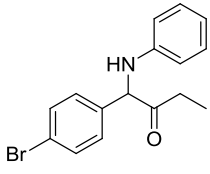
80.30; H, 7.16; N, 5.85; found C, 80.57; H, 7.41; N, 6.12.

1-(phenylamino)-1-m-tolylbutan-2-one (185j)



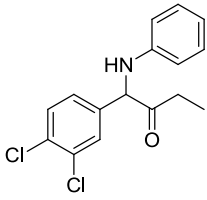
Orange wax, 33.4 mg, 66% yield. **FTIR** ν_{max} (KBr)/cm^{-1} 3386, 1716, 1603, 1505, 1428, 1321, 1111, 1035, 749, 692. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.31-7.23 (m, 3H), 7.16-7.08 (m, 3H), 6.68 (t, 1H, *J*= 7.3 Hz), 6.61-6.56 (m, 2H), 5.48 (brs, 1H), 4.98 (s, 1H), 2.48 (q, 2H, *J*= 7.3 Hz), 2.36 (s, 3H), 1.01 (t, 3H, *J*= 7.3 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 207.1, 146.2, 138.9, 138.3, 129.13, 129.09, 128.95, 128.21, 125.0, 117.5, 113.3, 67.4, 32.4, 21.4, 7.9. **MS** (ESI *m/z*) 276.5 [MNa^+, 100%]. Elemental analysis calcd (%) for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53; found C, 80.28; H, 7.81; N, 5.80.

1-(4-Bromophenyl)-1-(phenylamino)butan-2-one (185k)



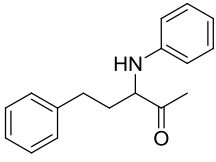
Red wax, 40.7 mg, 64% yield. **FTIR** ν_{max} (KBr)/cm^{-1} 3066, 1719, 1602, 1505, 1428, 1404, 1316, 1140, 1111, 1071, 1010, 833, 750, 692. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.50 (d, 2H, *J*= 8.3 Hz), 7.34 (d, 2H, *J*= 8.3 Hz), 7.13-7.05 (m, 2H), 6.67 (t, 1H, *J*= 7.2 Hz), 6.54-6.49 (m, 2H), 4.96 (s, 1H), 2.50-2.40 (m, 2H), 1.00 (t, 3H, *J*= 7.3 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 206.1, 145.6, 137.4, 132.3, 129.3, 129.1, 122.2, 117.8, 113.3, 66.7, 32.4, 7.8. **MS** (ESI *m/z*) 318.5 [MH^+, 45%]. Elemental analysis calcd (%) for $C_{16}H_{16}BrNO$: C, 60.39; H, 5.07; N, 4.40; found C, 60.13; H, 5.28; N, 4.63.

1-(3,4-Dichlorophenyl)-1-(phenylamino)butan-2-one (185l)



Red wax, 29 mg, 47% yield. **FTIR** ν_{max} (KBr)/cm^{-1} 3390, 1720, 1604, 1505, 1467, 1429, 1394, 1318, 1135, 1031, 752, 740, 692. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.56 (s, 1H), 7.48-7.42 (m, 1H), 7.35-7.28 (m, 1H), 7.16-7.07 (m, 2H), 6.70 (t, 1H, *J*= 7.3 Hz), 6.55-6.48 (m, 2H), 5.55 (brs, 1H), 4.95 (s, 1H), 2.53-2.41 (m, 2H), 1.02 (t, 3H, *J*= 7.3 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 205.5, 145.4, 138.9, 133.4, 132.5, 131.1, 129.5, 129.2, 127.0, 118.1, 113.3, 66.4, 32.6, 7.7. **MS** (ESI *m/z*) 307.7 [MH^+, 19%], 331.4 [MNa^+, 12%]. Elemental analysis calcd (%) for $C_{16}H_{15}Cl_2NO$: C, 62.35; H, 4.91; N, 4.54; found C, 62.57; H, 5.07; N, 4.37.

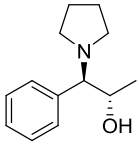
5-Phenyl-3-(phenylamino)pentan-2-one (185m)



Yellow oil, 14.2 mg, 28% yield. Aniline and α-amino ketone **185m** have the same polarity. To remove aniline from the mixture of the two products, recovered after silica gel chromatography, the mixture was diluted with Et_2O and washed with water. **FTIR** ν_{max} (KBr)/cm^{-1} 3441, 2918, 2850, 1705, 1635, 1602, 1506, 1454, 1260, 1093, 799, 748, 693. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.33-7.15 (m, 7H), 6.77-6.72 (m, 1H), 6.59-6.52 (m, 2H), 4.32 (brs, 1H), 4.07-4.02 (m, 1H), 2.94-2.84 (m, 1H), 2.80-2.65 (m, 2H), 2.19 (s, 3H), 2.03-1.93 (m, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 210.0, 146.8, 140.8, 129.4, 128.5, 128.4, 126.2, 118.1, 113.2, 62.8, 33.4, 31.5, 26.4. Elemental analysis calcd (%) for

$C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53; found C, 82.32; H, 7.72; N, 5.70.

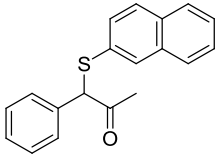
(1*R*,2*S*)-1-phenyl-1-(pyrrolidin-1-yl)propan-2-ol (189)



Data for this compound were consistent with those reported in the literature.[271]

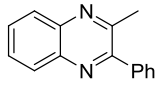
White solid, 20.2 mg, 78% yield. $[\alpha]_D^{24}$ = -53.0 (c 0.82, CH_2Cl_2), ee 67%. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.32-7.27 (m, 5H), 4.27-4.21 (m, 1H), 2.99 (d, 1H, *J*= 3.3 Hz), 2.69-2.60 (m, 2H), 2.47-2.40 (m, 2H), 1.79-1.74 (m, 4H), 0.83 (d, 3H, *J*= 6.4 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 138.4, 129.4, 127.8, 127.4, 75.7, 66.9, 52.8, 23.3, 19.1. HPLC analysis with Chiralcel OD-H column, 99:1 *n*-hexane: ethanol, 1 mL/min, 220 nm; minor enantiomer t_R = 7.5 min, major enantiomer t_R = 8.4 min, *ee* 67 %.

1-(Naphthalen-2-ylthio)-1-phenylpropan-2-one (192)



Pink solid, 21.3 mg, 73% yield. **mp** 70.8-74.3 °C. **FTIR** ν_{max} (KBr)/cm^{-1} 2923, 1712, 1585, 1493, 1454, 1355, 1067, 815, 744, 699, 569. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.81-7.68 (m, 4H), 7.48-7.44 (m, 2H), 7.41-7.31 (m, 6H), 5.10 (s, 1H), 2.21 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 203.1, 135.4, 133.5, 132.5, 131.3, 131.0, 129.3, 128.9, 128.6, 128.5, 128.3, 127.6, 127.5, 126.5, 126.4, 64.4, 27.3. **MS** (ESI *m/z*) 293.4 [MH^+, 14%]. Elemental analysis calcd (%) for $C_{19}H_{16}OS$: C, 78.05; H, 5.52; S, 10.97; found C, 78.27; H, 5.34; S, 11.12.

2-methyl-3-phenylquinoxaline (193)



Data for this compound were consistent with those reported in the literature.[188b]

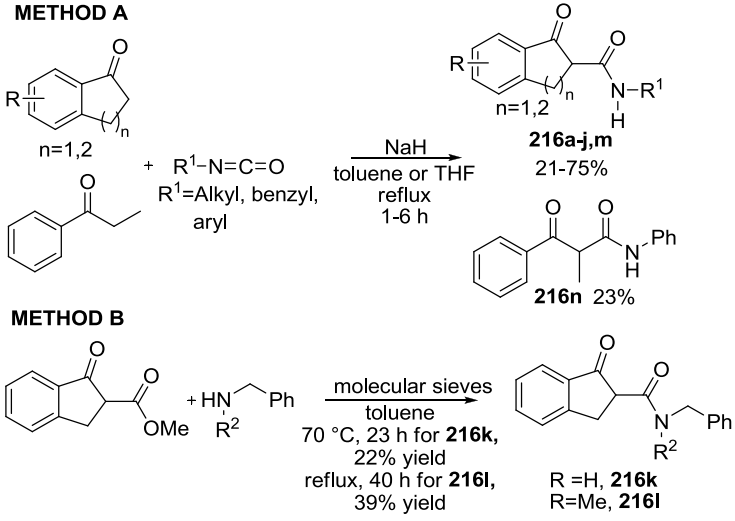
White wax, 18.5 mg, 56% yield. **FTIR** ν_{max} (KBr)/cm^{-1} 3060, 2924, 1562, 1483, 1445, 1396, 1374, 1343, 1191, 1132, 1006, 996, 766, 699. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.13-8.10 (m, 1H), 8.07-8.05 (m, 1H), 7.76-7.68 (m, 2H), 7.68-7.63 (m, 2H), 7.56-7.47 (m, 3H), 2.77 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 154.9, 152.5, 141.1, 140.9, 138.9, 129.7, 129.21, 129.17, 129.0, 128.9, 128.5, 128.2, 24.3.

6.5 Enantioselective α-hydroxylation of β-ketoamides

Experimental procedures and compounds characterization

General procedure for the synthesis of β-ketoamides

1-Isocyanato-4-(pentyloxy)benzene was synthesized according to procedures reported in the literature.[272]



METHOD A: β-ketoamides **216a-j**, **m** were prepared following a general procedure reported in the literature.[273]

In a two necked round bottom flask under a positive pressure of nitrogen, NaH (60% w/w dispersion in mineral oil, 10 mmol) was suspended in dry THF (10 mL) for 10 minutes under stirring. The suspension was allowed to settle and after removal of the supernatant, fresh THF (10 mL) was added. A solution of the appropriate indanone or α-tetralone (4 mmol) and isocyanate (4.8 mmol) in dry THF (1.5 mL) was added dropwise over 10 minutes to the refluxing suspension. After completion, monitored by TLC (eluent: PE/ AcOEt 8:2) the mixture was cooled to 0 °C and 1 N

HCl was added cautiously until the solid completely dissolved (≈ 15 mL). The solution was extracted with ethyl acetate (2 x 20 mL) and the organic phase was washed with saturated $NaHCO_3$ (20 mL), brine (20 mL), dried (Na_2SO_4) and concentrated. The residue was triturated with Et_2O to give the desired compound as yellow/white solid.

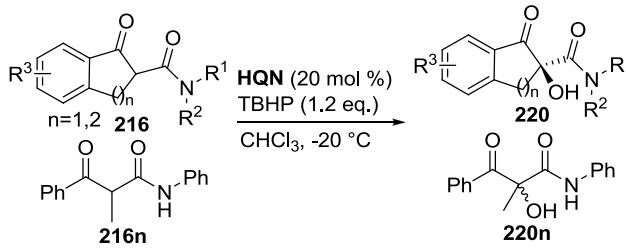
METHOD B: β-ketoamides **216k** and **216l** were prepared by using a general procedure reported in the literature.[274]

The β-ketoester (4 mmol) and appropriate benzylamine (8 mmol) in dry toluene (40 mL) were heated to reflux or to 70 °C under nitrogen over molecular sieves for the necessary time (monitoring by TLC, PE/AcOEt 8:2 as eluent). Then molecular sieves were filtered off, and the mixture was purified by flash chromatography, using PE/AcOEt 9:1 to 7:3 as eluent, to give compounds **216k**, **216l**.

General procedure for the racemic hydroxylation of compounds 216

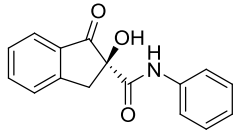
In a sample vial, the appropriate β-ketoamide **216** (0.10 mmol), TBHP (0.12 mmol), and 2-piperidinemethanol (3.5 mg, 0.03 mmol) were dissolved in dry $CHCl_3$ or anhydrous toluene (0.5 mL). The reaction was stirred at room temperature for 17-41 h until completion, monitored by TLC (PE/AcOEt 8:2 or 7:3). After removing the solvent under vacuum, the mixture was directly purified by flash chromatography (PE/AcOEt 9:1 to 7:3) to give products **220** in 34-97%.

General procedure for the asymmetric hydroxylation of compounds 216a-n



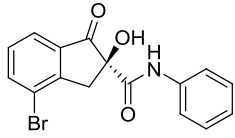
To a sample vial charged with the appropriate β-ketoamide **216** (0.10 mmol) and the hydroquinine (6.5 mg, 0.02 mmol) in anhydrous chloroform (2.0 mL), TBHP (0.12 mmol) was added and the reaction was stirred at –20 °C for 64-144 h until completion (monitored by TLC, PE/AcOEt 8:2 or 7:3). The solvent was removed under vacuum and the product **220** was isolated by flash chromatography (PE/AcOEt 9:1 to 7:3). The absolute configuration of compounds **220** was assigned to be (*S*) by analogy to the structure determined by single-crystal X-ray analysis performed on compound **220b** (see the X-ray analysis section). Crystallization using *n*-hexane/$CHCl_3$ or *n*-pentane/$CHCl_3$ mixtures performed at room temperature gave needle-shaped crystals in an enantioenriched form.

(*S*)-2-hydroxy-1-oxo-*N*-phenyl-2,3-dihydro-1*H*-indene-2-carboxamide (220a)



White solid (83% yield, 66% after crystallization), **mp** 149.9-151.3 °C. $[\alpha]_D^{25}$ = +6.4 (*c* 0.6, $CHCl_3$), *ee* 87%. **FTIR** ν_{max} (KBr)/cm^{-1} 3342, 1719, 1654, 1599, 1533, 1445, 750 . **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.83 (bs, 1H), 7.77 (d, 1H, *J*= 7.7 Hz), 7.67 (t, 1H, *J*= 7.2 Hz), 7.52-7.50 (m, 3H), 7.42 (t, 1H, *J*= 7.2 Hz), 7.29 (t, 2H, *J*= 7.5 Hz), 7.11 (t, 1H, *J*= 7.1 Hz), 4.36 (bs, 1H), 3.87 (d, 1H, *J*= 16.8 Hz), 3.18 (d, 1H, *J*= 16.8 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 203.2, 168.4, 153.1, 136.9, 136.5, 133.7, 129.0, 128.1, 126.4, 125.2, 124.7, 119.7, 82.6, 40.8. **MS** (ESI *m/z*) 268.10 [MH^+, 100%], 290.09 [MNa^+, 85%]. HPLC analysis with Chiralcel ODH column, 70:30 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 9.1 min, major enantiomer t_R = 6.4 min.

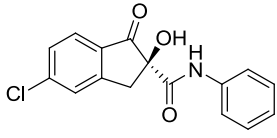
(*S*)-4-bromo-2-hydroxy-1-oxo-*N*-phenyl-2,3-dihydro-1*H*-indene-2-carboxamide (220b)



White solid (88% yield, 66% after crystallization), **mp** 171.9-173.6 °C. $[\alpha]_D^{25}$ = +50.0 (*c* 0.6, $CHCl_3$), *ee* 96%. **FTIR** ν_{max} (KBr)/cm^{-1} 3339, 1728, 1657, 1598, 1533, 1445, 1267, 1120, 943, 753, 692. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.70 (bs, 1H), 7.84 (d, 1H, *J*= 7.8 Hz), 7.76 (d, 1H, *J*= 7.6 Hz), 7.53 (d, 2H, J = 8.4 Hz), 7.36-7.29 (m, 3H), 7.15-7.11 (m, 1H), 3.84 (d, 1H, *J*= 17.3 Hz), 3.72 (bs, 1H), 3.12 (d, 1H, *J*= 17.3 Hz) **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 202.6, 168.0, 152.7, 139.1, 136.7, 135.7, 129.8, 129.0,

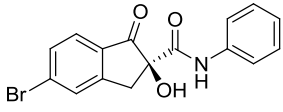
124.9, 123.9, 121.7, 119.7, 82.2, 41.9. **MS** (ESI *m/z*) 346.00 [MH^+, 100%], 368.05 [MNa^+, 25%]. HPLC analysis with Chiralcel ODH column, 80:20 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 8.5 min, major enantiomer t_R = 9.4 min.

(*S*)-5-chloro-2-hydroxy-1-oxo-*N*-phenyl-2,3-dihydro-1*H*-indene-2-carboxamide (220c)



Pale yellow solid (85% yield), **mp** 182.7-183.1 °C. $[\alpha]_D^{23}$ = +48.9 (*c* 0.6, $CHCl_3$), *ee* 79%. **FTIR** ν_{max} (KBr)/cm^{-1} 3307, 1732, 1646, 1449, 1081, 759. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.70 (bs, 1H), 7.73 (d, 1H, *J*= 8.2 Hz), 7.53-7.51 (m, 3H), 7.41 (d, 1H, *J*= 7.9 Hz), 7.33-7.29 (m, 2H), 7.13 (t, 1H, *J*= 7.4 Hz), 3.84 (d, 1H, *J*= 16.9 Hz), 3.80 (bs, 1H), 3.17 (d, 1H, *J*= 16.9 Hz) **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 201.6, 167.8, 154.3, 143.3, 136.7, 132.1, 129.1, 126.7, 126.2, 124.9, 119.7, 82.8, 40.6. **MS** (ESI *m/z*) 301.97 [MH^+, 8%], 324.02 [MNa^+, 100%]. HPLC analysis with Chiralcel ODH column, 70:30 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 9.6 min, major enantiomer t_R = 7.0 min.

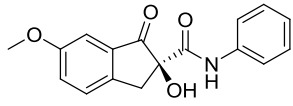
(*S*)-5-bromo-2-hydroxy-1-oxo-*N*-phenyl-2,3-dihydro-1*H*-indene-2-carboxamide (220d)



White solid (87% yield), **mp** 187.1-188.3 °C. $[\alpha]_D^{26}$=+45.1 (*c* 0.9, $CHCl_3$), *ee* 78%. **FTIR** ν_{max} (KBr)/cm^{-1} 3355, 1723, 1659, 1595, 1532, 1445, 1219, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.70

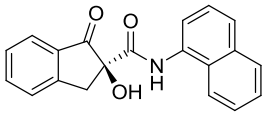
(bs, 1H), 7.71 (s, 1H), 7.66 (d, 1H, *J*= 8.2 Hz), 7.58 (d, 1H, *J*= 8.0 Hz), 7.52 (d, 2H, *J*= 8.6 Hz), 7.33-7.30 (m, 2H), 7.15-7.11 (m, 1H), 3.84 (d, 1 H, *J*= 17.1 Hz), 3.75 (bs, 1H), 3.18 (d, 1H, *J*= 17.1 Hz) **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 201.8, 167.8, 154.3, 136.8, 132.5, 132.2, 131.9, 129.7, 129.1, 126.2, 124.9, 119.7, 82.8, 40.5 **MS** (ESI *m/z*) 367.91 [MNa^+, 100%]. HPLC analysis with Chiralcel ODH column, 70:30 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; minor enantiomer t_R =10.0 min, major enantiomer t_R =7.8 min.

(*S*)-2-hydroxy-6-methoxy-1-oxo-*N*-phenyl-2,3-dihydro-1*H*-indene-2-carboxamide (220e)



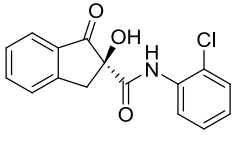
White solid (84% yield, 60% after crystallization), **mp** 146.0-147.2 °C. **$[\alpha]_D^{20}$**= -31.3 (*c* 0.9, $CHCl_3$), *ee* 98%. **FTIR** ν_{max} (KBr)/cm^{-1} 3343, 1717, 1661, 1600, 1532, 1494, 1445, 1281, 1241, 1026, 754. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.79 (bs, 1H), 7.48 (d, 2H, *J*= 7.7 Hz), 7.36 (d, 1H, *J*= 8.4 Hz), 7.29-7.27 (m, 1H), 7.25-7.23 (m, 2H) 7.15 (d, 1H, *J*= 2.5 Hz), 7.09 (t, 1H, *J*= 7.4 Hz), 4.40 (bs, 1H), 3.80 (s, 3H), 3.75 (d, 1H, *J*= 16.6 Hz), 3.08 (d, 1H, *J*= 16.5 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 203.1, 168.5, 159.7, 146.1, 136.9, 134.8, 128.9, 127.1, 125.9, 124.7, 119.7, 106.1, 83.2, 55.6, 40.2, **MS** (ESI *m/z*) 297.95 [MH^+, 17%], 320.07 [MNa^+, 100%], 336.07 [MK^+, 8%]. HPLC analysis with Chiralcel ODH column, 70:30 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 10.9 min, major enantiomer t_R = 7.5 min.

(*S*)-2-hydroxy-*N*-(naphthalen-1-yl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxamide (220f)



Pale yellow solid (82% yield), **mp** 166.2-167.5 °C. $[\alpha]_D^{21}$=+28.9 (*c* 0.6, $CHCl_3$), *ee* 74%. **FTIR** ν_{max} (KBr)/cm^{-1} 3368, 1722, 1661, 1538, 1532, 1500, 1219, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 9.23 (bs, 1H), 7.98 (d, 1H, *J*= 7.5 Hz), 7.89-7.81 (m, 3H), 7.68-7.66 (m, 2H), 7.57-7.48 (m, 3H), 7.44-7.40 (m, 2H), 4.09 (bs, 1H), 3.94 (d, 1H, *J*= 16.7 Hz), 3.26 (d, 1H, *J*= 16.7 Hz) **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 203.0, 168.6, 153.0, 136.5, 134.0, 133.7, 131.3, 128.7, 128.2, 126.53, 126.48, 126.42, 126.0, 125.8, 125.6, 125.3, 120.2, 119.6, 83.1, 40.8 **MS** (ESI *m/z*) 318.10 [MH^+, 40%], 340.09 [MNa^+, 100%], 355.90 [MK^+, 25%]. HPLC analysis with Chiralpak ASH column, 70:30 *n*-hexane:2-propanol, 0.8 mL/min, detection at 254 nm; minor enantiomer t_R = 12.4 min, major enantiomer t_R =16.4 min.

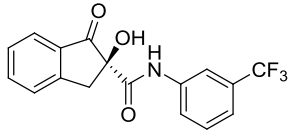
(*S*)-*N*-(2-chlorophenyl)-2-hydroxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxamide (220g)



White solid (76% yield, 48% after crystallization), **mp** 90.3-93.0 °C. $[\alpha]_D^{21}$ = +22.8 (*c* 0.6, $CHCl_3$), *ee* 99%. **FTIR** ν_{max} (KBr)/cm^{-1} 3352, 1723, 1685, 1594, 1529, 1443, 1304, 1214, 751. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 9.31 (bs, 1H), 8.31 (dd, 1H, J_1= 8.2, J_2=1.3 Hz), 7.84 (d, 1H, *J*= 7.8 Hz), 7.73-7.69 (m, 1H), 7.54 (d, 1H, *J*= 7.8 Hz), 7.48-7.44 (m, 1H), 7.38 (dd, 1H, J_1= 8.1, J_2=1.3 Hz), 7.23-7.21 (m, 1H), 7.08-7.03 (m, 1H), 3.86 (d, 1H, *J*= 16.8 Hz),

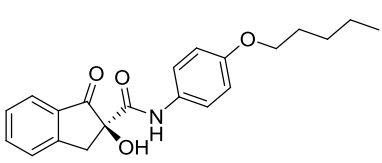
3.78 (bs, 1H), 3.27 (d, 1H, *J*= 16.8 Hz) **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 202.6, 168.6, 152.7, 136.5, 133.7, 129.1, 128.2, 127.7, 126.4, 125.3, 125.1, 123.2, 121.0, 82.9, 40.8 **MS** (ESI *m/z*) 302.10 [MH^+, 13%], 324.02 [MNa^+, 100%], 340.03 [MK^+, 5%]. HPLC analysis with Chiralcel ODH column, 80:20 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 6.4 min, major enantiomer t_R = 7.4 min.

(*S*)-2-hydroxy-1-oxo-*N*-(3-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-indene-2-carboxamide (220h)



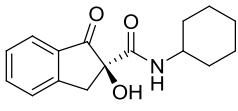
Pale yellow solid (88% yield), **mp** 138.4-139.8 °C. **$[\alpha]_D^{26}$**=+9.7 (*c* 0.5, $CHCl_3$), *ee* 56%. **FTIR** ν_{max} (KBr)/cm^{-1} 3333, 1719, 1682, 1603, 1542, 1449, 1333, 1167, 1125, 772, 698. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.93 (bs, 1H), 7.93 (s, 1H), 7.80 (d, 1H, *J*= 7.7 Hz), 7.72-7.68 (m, 1H), 7.64 (d, 1H, *J*= 7.9 Hz), 7.52 (d, 1H, *J*= 7.7 Hz), 7.46-7.41 (m, 1H), 7.39-7.35 (m, 2H), 3.95 (bs, 1H), 3.88 (d, 1H, *J*= 16.7 Hz), 3.21 (d, 1H, *J*= 16.7 Hz) **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 202.8, 168.6, 152.9, 137.4, 136.7, 133.5, 131.5 (q, *J*=32 Hz), 129.5, 128.3, 126.4, 125.3, 122.6, 121.3 (d, *J*=36 Hz), 116.5 (d, *J*=36 Hz), 82.9, 40.8 **MS** (ESI *m/z*) 336.06 [MH^+, 5%], 358.04 [MNa^+, 100%]. HPLC analysis with Chiralpak ASH column, 70:30 *n*-hexane:2-propanol, 0.8 mL/min, detection at 254 nm; minor enantiomer t_R = 6.5 min, major enantiomer t_R = 8.1 min.

(*S*)-2-hydroxy-1-oxo-*N*-(4-(pentyloxy)phenyl)-2,3-dihydro-1*H*-indene-2-carboxamide (220i)



White solid (89% yield), **mp** 125.6-127.0 °C. $[\alpha]_D^{23}$=+2.8 (*c* 0.6, $CHCl_3$), *ee* 76%. **FTIR** ν_{max} (KBr)/cm^{-1} 3325, 2930, 1721, 1645, 1512, 1220, 828, 772. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.70 (bs, 1H), 7.74 (d, 1H, *J*= 7.7 Hz), 7.66-7.62 (m, 1H), 7.46 (d, 1H, *J*= 7.7 Hz), 7.40-7.35 (m, 3H), 6.77 (d, 2H, J= 9.0 Hz), 4.35 (bs, 1H), 3.88 (t, 2H, *J*= 6.6 Hz), 3.82 (d, 1H, *J*= 16.8 Hz), 3.13 (d, 1H, *J*= 16.8 Hz), 1.79-1.73 (m, 2H), 1.44-1.34 (m, 4H), 0.92 (t, 3H, *J*= 7.0 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 203.4, 168.1, 156.2, 153.2, 136.4, 133.7, 129.9, 128.0, 126.4, 125.1, 121.3, 114.7, 82.5, 68.2, 40.8, 28.9, 28.1, 22.4, 14.0. **MS** (ESI *m/z*) 354.24 [MH^+, 100%], 376.17 [MNa^+, 10%]. HPLC analysis with Chiralcel ODH column, 70:30 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 7.3 min, major enantiomer t_R = 8.7 min.

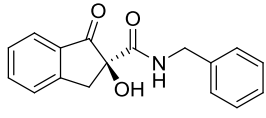
(S)-*N*-cyclohexyl-2-hydroxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxamide (220j)



White wax (37% yield). $[\alpha]_D^{30}$= -7.2 (*c* 0.7, $CHCl_3$), *ee* 40%. **FTIR** ν_{max} (KBr)/cm^{-1} 3353, 2930, 2855, 1723, 1646, 1530, 1465, 1215, 752. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.76 (d, 1H, *J*= 7.7 Hz), 7.64 (t, 1H, *J*= 7.0 Hz), 7.47 (d, 1H, *J*= 7.7 Hz), 7.40 (t, 1H, *J*= 7.5 Hz), 6.69 (d, 1H, *J*= 6.6 Hz), 3.79 (bs, 1H), 3.72 (d, 1H, *J*= 16.8 Hz), 3.68-3.63 (m, 1H), 3.10 (d, 1H, *J*= 16.8 Hz), 1.89-1.86 (m, 2H),

1.70-1.57 (m, 4H), 1.36-1.14 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 203.4, 169.2, 152.9, 136.2, 133.9, 128.0, 126.3, 125.1, 82.1, 48.4, 40.7, 32.83, 32.77, 29.7, 25.4, 24.7. **MS** (ESI *m/z*) 274.13 [MH^+, 97%], 296.06 [MNa^+, 100%]. HPLC analysis with Chiralcel ODH column, 80:20 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 5.3 min, major enantiomer t_R = 6.2 min.

(*S*)-*N*-benzyl-2-hydroxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxamide (220k)



Yellow wax (50% yield). **$[\alpha]_D^{23}$**= -4.1 (*c* 0.6, $CHCl_3$), *ee* 29%. **FTIR** ν_{max} (KBr)/cm^{-1} 3394, 2924, 1722, 1653, 1608, 1528, 1455, 1218, 928, 772, 699. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.77 (d, 1H, *J*= 7.6 Hz), 7.65 (t, 1H, *J*= 7.5 Hz), 7.47 (d, 1H, *J*= 7.6 Hz), 7.40 (t, 1H, *J*= 7.5 Hz), 7.35-7.29 (m, 2H), 7.27-7.25 (m, 3H), 7.18 (bs, 1H), 4.41 (d, 2H, *J*= 5.9Hz), 3.83 (bs, 1H), 3.77 (d, 1H, *J*= 16.8 Hz), 3.13 (d, 1H, *J*= 16.8 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 203.2, 170.3, 153.0, 137.6, 136.3, 133.8, 128.7, 128.1, 127.7, 127.6, 126.4, 125.2, 82.2, 43.4, 40.7 **MS** (ESI *m/z*) 282.00 [MH^+, 10%], 304.05 [MNa^+, 100%]. HPLC analysis with Chiralcel ODH column, 80:20 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 10.1 min, major enantiomer t_R = 12.1 min.

X-Ray Data for the Absolute Configuration Assignment of Compound 220b

X-ray diffraction quality single crystals of **220b** were obtained by slow evaporation of a solution of **220b** in *n*-pentane/$CHCl_3$ mixture performed at room temperature.

A suitable crystal of **220b** was selected and glued on a glass fiber and measured at room temperature with a Rigaku AFC7S diffractometer equipped with a Mercury CCD detector using Mo$K\alpha$ radiation. Data reduction was performed with the crystallographic package CrystalClear.[264] Data have been corrected for Lorentz, polarization and absorption. The structures were solved by direct methods using the program SIR2002[275] and refined by means of full matrix least-squares based on F^2 using the program SHELXL97.[266]

All non-hydrogen atoms were refined anisotropically, hydrogen atoms were positioned geometrically and included in structure factors calculations but not refined.

A total of 190 refinable parameters were finally considered, final disagreement indices are R = 0.079 (2339 reflections $F^2>2\sigma F^2$), $_wR2$= 0.199 (all 3466 independent. reflections).

Flack parameter is 0.018(19).

ORTEP plot is obtained by means of the program ORTEP32.[276]

Crystal data:

$C_{16}H_{12}BrNO_3$, orthorhombic, space group $P2_12_12_1$, Z= 4, a = 9.801(3)Å, b = 10.969(3) Å, c = 14.070(4) Å, V=1512.6(8)Å^3, D_x = 1.520 g cm^{-3}, μ_{calc} = 2.73 mm^{-1}.

The work contained within this thesis is partially described in the following publications:

"*Asymmetric Synthesis of Trisubstiuted Tetrahydrothiophenes Bearing a Quaternary Stereocentre via Double Michael Reaction Involving Dynamic Kinetic Resolution*"
S. Meninno, G. Croce, A. Lattanzi, *Org. Lett*. **2013**, *15*, 3436.

"*Straighforward Enantioselective Access to γ-Butyrolactones Bearing an All-Carbon β-Quaternary Stereocentre*"
S. Meninno, T. Fuoco, C. Tedesco, A. Lattanzi, *Org. Lett*. **2014**, *16*, 4746.

"Catalytic Enantioselective Synthesis of α-Nitroepoxides via Aminolytic Kinetic Resolution"
S. Meninno, L. Napolitano, A. Lattanzi, *Catal. Sci. Technol*. **2015**, *5*, 124.

"Enantioselective α-Hydroxylation of β-ketoamides"
C. De Fusco, S. Meninno, C. Tedesco, A. Lattanzi, *Org. Biomol. Chem*. **2013**, *11*, 896.

"Asymmetric Organocatalysis Mediated by α,α-L-diaryl prolinols: recent advances"
S. Meninno, A. Lattanzi, *Chem. Comm.* **2013**, *49*, 3821.

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