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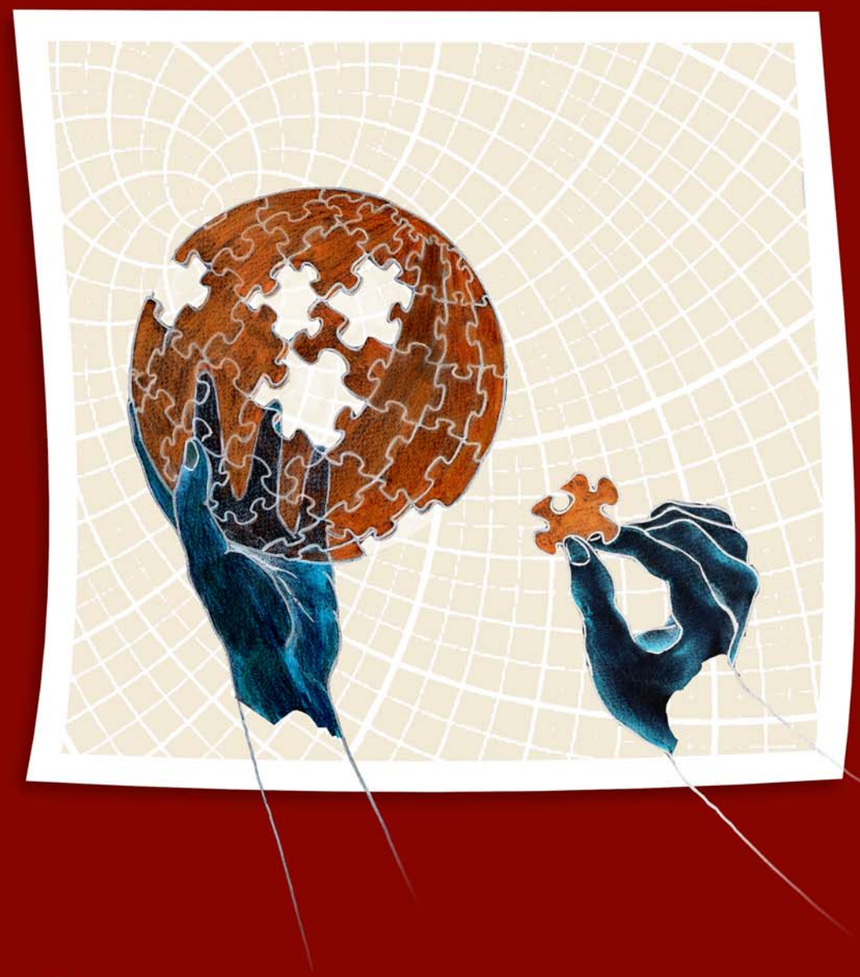

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Preface

The work presented in this PhD thesis has been mainly carried out at the Department of Organic Chemistry "A. Mangini", Alma Mater Studiorum – Università di Bologna (Italy), under the direction of Prof. Giuseppe Bartoli and the supervision of Paolo Melchiorre, PhD. Nearly a third of the PhD research was performed at the Center for Catalysis, Kemisk Institute, Aarhus Universitet (Denmark), under the supervision of Prof. Karl Anker Jørgensen.

The whole PhD was devoted to the Enantioselective Aminocatalysis, a fairly wide branch in the very young yet fastly expanding field of asymmetric organocatalysis.

The thesis is organized in 2 main sections made up of 7 chapters. A brief introduction presents the concept of chirality to the reader and shows the high need for asymmetric catalysis nowadays. Soon after, asymmetric organocatalysis (Chap 2) is presented along with the main activations exploited during the PhD. Although "aminocatalysis" usually refers to the particular reactivity of secondary amines to give rise either to enamine or iminium intermediates, I preferred to simplify the classification by incorporating the Brønsted base activation mediated by tertiary amines such as *Cinchona* alkaloids. For a smoother and more relaxing reading the references are given at the end and the numbering is reset at every chapter.

Section I deals with Chiral Brønsted Base Catalysis; an enantioselective chlorination of β-ketoesters (Chap 3) is followed by a Michael addition to maleimides giving insights to a bifunctional activation mode (Chap 4).

Section II shifts the focus to the activation of carbonyl compounds via enamine or iminium activation. The Chapters are organized into *main objectives* grouping different, but related, research works. Each of these individual reactions is presented separately, along with its relevant references and Experimental Part, with the aim to give a quick snapshot on the advancement.

A journey around the periodic table (Chap 5) brings the reader to the β- and α-functionalization of aldehydes with phosphorous and selenium derivatives, respectively.

A step forward in the iminium ion activation is presented in Chap 6 where the identification of a new chiral catalyst salt allows the addition of carbon, oxygen and sulphur nucleophiles to α,β-unsaturated ketones .

Access to complex structures either in a single or a one-pot operation is one of the main goals of organic chemists. This is addressed in Chap 7 where a one-pot access to chiral cyclohexenones and two domino reactions providing complex structures with up to 4 stereocenters are presented.

Eventually a short overview of the progress will provide a platform for perspectives.

"Thunder is good, thunder is impressive," wrote Mark Twain "But it is the lightning that does the work." Often it's some people's thunder, which holds the credit and the attention; but it is also other people's lightning one of the main factors in group success. And, indeed, the research presented was possible thanks to a lot of people I shared time and work with.

Prof. Giuseppe Bartoli welcomed me in his research group for my PhD. His informal way of communicating opinions and discussing things has been a warm companion of my daily life in the group. No need to be "dressed up" made me enjoy every minute, and the autonomy I had helped me in relieving the stress that sometimes comes with research. His direction has been invaluable to pursue everyday and longterm results.

Paolo Melchiorre, PhD, has been a great mentor in every moment of this adventure. The enthusiasm and the great curiosity he has, inspired and fuelled me; passion for research can indeed be contagious. Research is not just a mere collection of data, it's also about plot composition and story-telling; it is mainly thanks to him and our discussions that I am now aware of this facet. A good mentor does not only supervise and guide research, they are also mates to exchange opinions with and seek for advice; in this view I can dare to say he has been an excellent mentor.

I enjoyed working everyday next to Manuela Locatelli, PhD; it took a couple of years to finally work on the same project.

Paolo Ricci and Fabio Pesciaioli gave me the opportunity to learn the pain and satisfaction to be a supervisor; probably the pain was more on their side and the satisfaction on mine.

Oriol Penon was an indefatigable Erasmus student; his nights out had an incredible effect as he was every morning full of energy.

Other members of the group also need to be mentioned; Prof Marcella Bosco and Letizia Sambri, PhD, Patrizia Galzerano and Roberto Giri. Their help, nice talks and opinions have been friendly accompanying.

Prof. Karl Anker Jørgensen gave me the opportunity to spend one of the most fruitful, interesting and greatest periods in his group. A great group leader and professor, he made me feel at home and relaxed every day of my stay. His great advices and his being keen on listening to people and guiding them towards their goals are incredibly valuable qualities.

Mauro Marigo, PhD, has been a great labmate and he introduced me to the secondary amine catalysis with a lot of small secrets and hints; he shared with me a new perspective on research and a lot of interesting talks on politics and society.

Aitor Landa, PhD, was one of the funniest people I met. Despite his extravagant look he taught me the precision and order in daily research.

Søren Bertelsen, happy and joyful labmate, besides interesting discussions, he enjoyed building up with me a set for photos and giving advice on the post-process for one of my graphical abstracts.

The collaboration of Silvia Cabrera, PhD, and Chris North was very valuable in two projects; that is beside the good kitchen and the English tea I could often taste.

I would also like to remember other people from the group for the interesting and valuable chemistry discussions: José Alemán, PhD, Sebastian Brandes, PhD, Mark Bell, PhD, Eddy Maerten, PhD and Luca Bernardi, PhD. Everyone there was contributing to make my stay great and, therefore, I would also like to mention Lise Schmelling Ravn-Petersen, Peter Dinér, PhD, Barbara Niess, Thomas Poulsen, PhD, Kim Frisch, PhD, Sara Kobbelgaard, Martin Nielsen, Sven Brandau, PhD.

A special acknowledgement for the cover; Stefano Barbaresco for providing me with the drawing and to Valerio Varrone for his help with the layout.

Bologna, March 2008

Armando Carlone

1. CHIRALITY AND ASYMMETRIC SYNTHESIS

The concept of *chirality* and the adjective *chiral* interest and inspire scientists worldwide. The subject generated speculations and interpretations long time ago,[1] much before the concept itself was incorporated in the scientific disciplines.

Immanuel Kant, the famous Prussian philosopher, was captivated by what he dubbed incongruent counterparts to describe the existence of two non-superimposable mirror-image objects: "*What can more resemble my hand or my ear, and be more equal in all points, than its image in the mirror? And yet I cannot put such a hand as is seen in the mirror in the place of its original …*".[2] This Kantian analysis certainly fits in with our perception of identical and non-identical objects, and that incongruent forms, exactly alike in all geometrical properties, are clearly not the same.[3] Many other philosophers, writers and artists were fascinated by chirality; the ideas they put forward were surely useful to the development of the relevant consciousness in scientists.

Still nowadays, fortunately, there's a subtle opinion among eminent researchers that humanists should take part in scientific conferences and discussions and viceversa; this is a powerful means to enrich each other and boost the progress by a useful interpenetration of ideas and perspectives. In fact, looking at our everyday life through different glasses is often indispensable to see things we might overlook.

We could argue whether Pasteur was influence by philosophers in his crystallographic studies; surely his speculations on the concept of hemihedric faces observed in crystals applied to the realm of molecules in solution gave interesting insights: "*I consider as extremely probable that the mysterious, unknown disposition of physical molecules in a whole and finite quartz crystal is found in (optically) active bodies, but, this time, in each molecule taken in particular*".[4]

Eventually, Kelvin defined chirality: "*I call any geometrical figure or group of points, chiral, and say that it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself. Two equal and similar right hands are homochirally similar. Equal and similar right and left hands are heterochirally similar or allochirally similar (but heterochirally is better). These are also called enantiomorphs, after a usage introduced, I believe, by German writers. Any chiral object and its image in a plane mirror are heterochirally similar*".[5]

Nowadays the idea of chirality is widespread in chemistry and related disciplines. We can refer to chirality with 'modern' words and concepts. Chirality, the 'left-handed' or 'right-handed' property of objects that are mirror images of each other, is ubiquitous in the observable world -shoes, conch shells, wood screws and umbilical cords, for instance. This property extends to objects in the nanoscale

dimension; nearly all molecules in nature (such as amino acids, sugars, alkaloids and terpenes) and legions of synthetic compounds are chiral. For chemists who wish to prepare purpose-built compounds with specific attributes -for example, medicinal, mechanical, physical- the ability to imbue molecules with the appropriate chirality is paramount. Chirality is fundamental to the structure, properties and function of molecules. How such molecules interact with one another in recognition, binding and chemical reaction is crucially dependent on their chirality.

Almost two decades ago the pharmaceutical industry experienced a shift of research focus away from already established and crowded therapeutic areas into new, unproven biological areas with subsequent need for new reactions and methodologies. In parallel, the FDA's 1992 policy statement on stereoisomers has triggered a move away from the development of racemates to the development of single-enantiomer drugs.

Awareness of the stereoselectivity of drug action has intensified since the thalidomide tragedies of the 1960s as differences in the pharmacology and pharmacokinetics of enantiomers have become better understood. By the mid-1980s, people really hit on the idea that we would do better with single enantiomers than with racemates.[6] Since 1990, the proportion of single-enantiomer drugs among approved new chemical entities worldwide has been consistently greater than that of racemates.[7] Clearly, the additional cost of producing a single enantiomers is almost always lower than the development work which is needed to elucidate the toxicological and pharmaco-kinetic profile of the unwanted enantiomer (distomer) as well. In this view, the pharmaceutical industry has started to subscribe to an alternative economic philosophy based on the assumption that wasted resources equates to decreased productivity and thus reduced profits. Such thoughts have clearly been inspired by the desire to drive down costs, but also by environmental and ethical considerations.[8] As of 2001, racemic mixtures are virtually no longer registered.[9]

It is not surprising, therefore, that discovery of truly efficient methods of obtaining chiral substances is a substantial challenge for synthetic chemists. Today, there are a variety of methods, but until the early of 1970's, the classical resolution of racemates was the primary method used to obtain optically active compounds. Other methods involve transformation or derivatization of readily available natural chiral compounds. In the early days, practical access to enantiomerically pure compounds from prochiral precursors was considered possible only by using biochemical or biological methods. Such methods, which use enzymes, cell cultures, or whole microorganisms, are powerful when used to produce chiral substances, particularly those that occur in nature; however, the scope of such reactions is limited because many biological production systems exhibit single-handed, lock-and-key specificity. Organic synthesis, on the other hand, is characterized by generality and flexibility. Synthetic chemists have discovered a variety of versatile stereoselective reactions that complement biological processes.

However, much of the chirality contained in marketed drugs is derived from the chiral pool;[9] it is, then, evident that use of asymmetric synthesis has been the exception rather than the rule. Companies prefer the chiral pool strategy not so much for its intrinsic power, which is limited, but rather for the commercial availability of such building blocks to the discovery chemists; they often tend to use just what is available and process chemists -because of market, short-term profits and process- usually have little incentive to totally redesign a discovery synthesis. In fact, newer methods, being less established, are perceived as requiring more time to be fully developed and turned into robust chemistry.

Nevertheless innovation is acknowledged as essential in development and companies are exploring new fields, sometimes outsourcing their research. This important trend is what has brought asymmetric synthesis[10] to the forefront as a theme in drug discovery and development.

Asymmetric catalysis is an ideal method for synthesizing optically active compounds.[11] The chemical approach, which uses a small amount of a chiral often man-made catalyst, produces naturally occurring and non-naturally occurring chiral materials in large quantities. The efficiency of chirality multiplication can be almost infinite for asymmetric catalysis. Recent advances in this area are turning chemists' dreams into reality at both academic and industrial levels.

Asymmetric catalysis is four-dimensional chemistry. Simple stereochemical scrutiny of the substrate or reagent is not enough. The high efficiency that these reactions provide can only be achieved through a combination of both an ideal three-dimensional structure and suitable kinetics. To achieve maximum chiral multiplication, chemists must create efficient catalytic systems that permit precise discrimination among enantiotopic atoms, groups, or faces in achiral molecules. While high efficiency has been achieved with chiral metal complexes, this is not completely true in each branch of asymmetric catalysis.

For example, asymmetric organocatalysis (catalysis mediated by small organic molecules) has reached impressive levels of enantiodiscrimination and it has expanded its field of application beyond what could have been imagined at the beginning. However, the very high levels of efficiency in terms of turnover exhibited by metal complexes are one of the next goals to be met. Asymmetric organocatalysis is a very young field and therefore we can expect chemists to go beyond the limits that, at the state of the art, can be criticized.

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2. ENANTIOSELECTIVE ORGANOCATALYSIS

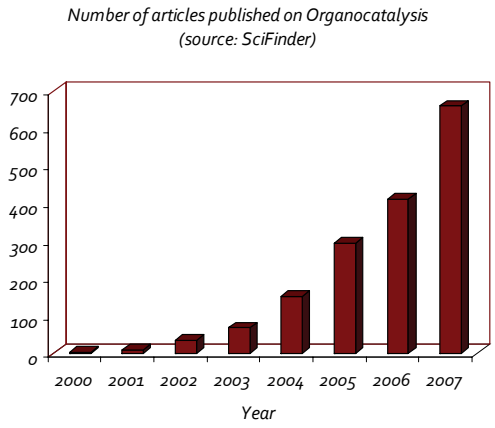
Using enzymes as catalysts, Nature is the uncontested master at producing chiral compounds in enantiomerically pure form. Chemists, as aforementioned, have to rely on different approaches to render their reaction enantioselective, although their inspiration may still come from nature. Early efforts emulated metal-containing enzymes, and many metal catalysts have been developed that induce one particular chirality in a wide range of chemical transformations.[1] But half of all known enzymes are metal-free, and it is these that organic chemists seek to mimic. Organocatalysis has now emerged as a promising strategy that avoids using protein catalysts or potentially toxic and expensive metals. Not only does it complement established methods, but it sometimes also overcomes their limitations, so that many unprecedented transformations can be realized.

Given the historically deep roots of this type of catalysis,[2] it is striking that decades had to pass before the landmark works[3] were unveiled and exploited. Culture and the actual chemical mechanisms are probably elements that hampered the development of this type of catalysis.[4] The compartmentalization of ideas in the cultures of organic chemistry and biochemistry often inhibited the flow of information between the organic chemist and the biochemist and vice versa. Historically, cross-referencing between these two cultures tended to be rare. To date, the emergence of the new field of chemical biology (also called bioorganic chemistry) has merged the fields of organic chemistry and biochemistry and hopefully it might serve as a bridge between disciplines.

As already mentioned, it was known for a long time that chiral small organic molecules were able to promote different transformations in a stereoselective fashion; unfortunately we had to wait until two seminal reports on chiral secondary amine catalysis by List, Lerner, and Barbas,[5] and MacMillan and co-workers,[6] before the chemical community realized the potential of this approach. Following these publications, there was an explosion in competition and high quality research on catalysis using chiral secondary amines (asymmetric aminocatalysis)[7] that would shortly extend to different organocatalytic activation concepts.[8,9,10] Nowadays, asymmetric organocatalysis is recognized as an efficient and reliable strategy for the stereoselective preparation of valuable chiral compounds.[11] The use of purely organic molecules as chiral catalysts complements the traditional organometallic and biological approaches to asymmetric catalysis, enabling synthetic chemists to move closer to being able to build any chiral scaffold in an efficient, rapid, and stereoselective manner. Asymmetric organocatalysis enriches chemistry with novel modes of substrate activation, which can deliver unique, orthogonal, or complementary selectivities in comparison to metal-catalyzed processes. In addition, it offers some attractive benefits. The metal-free organic catalysts are generally non-

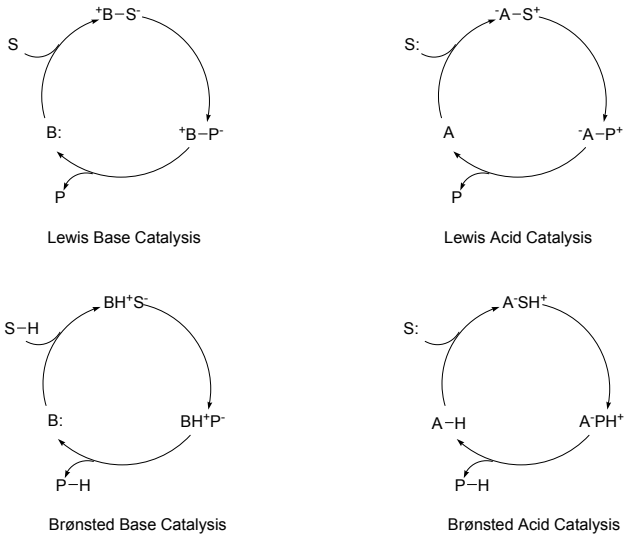
toxic, readily available, and stable. This allows most reactions to be performed in wet solvent and under an aerobic atmosphere, with beneficial consequences for the reproducibility and operational simplicity. Asymmetric organocatalysis is impressive because of its synthetic utility and because it gained its prominent role in such a short period of time: from 2000 to now!

In fact, as illustrated by the statistics, it is obvious that organocatalysis has grown quite dramatically in recent years. Yet, the field should certainly not be considered "mature", maybe not even "adolescent". Several areas are yet completely unexplored, and new concepts will surely arise within the more established ones. Also, there are already a number of organocatalytic reactions being used in the pharmaceutical and chemical industries.[12] Yet, the area is clearly not as "mainstream" in industry as it already is in academia.



At this stage we can surely assert that modern asymmetric catalysis is built on three rather than two pillars, namely biocatalysis, metal catalysis, *and* organocatalysis.

Most but not all organocatalysts can be broadly classified as Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids (Scheme 1).[11g]



Scheme 1: Organocatalytic cycles.

Accordingly, Lewis base catalysts (B:) initiate the catalytic cycle *via* nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and then releases the product (P) and the catalyst for further turnover. Lewis acid catalysts (A) activate nucleophilic substrates (S:) in a similar manner. Brønsted base and acid catalytic cycles are initiated *via* a (partial) deprotonation or protonation, respectively.

Among the mentioned catalytic activations we will shortly describe two kinds of organocatalysts in order to introduce the research described in the following chapters.

2.1 Cinchona Alkaloids (Brønsted base catalysis)

Cinchona alkaloids are recognized as a privileged class of chiral catalysts.[13] The four main *Cinchona* alkaloids are depicted in Figure 1. All these compounds have four chiral carbon and one chirally bridgehead nitrogen. The quinuclidine nitrogen is the most basic one (pK_b= 5.48 for quinine) and can be readily alkylated with alkyl iodides at room temperature; the hydroxyl and methoxy groups are also among the most often derivatized groups in the scaffolds.

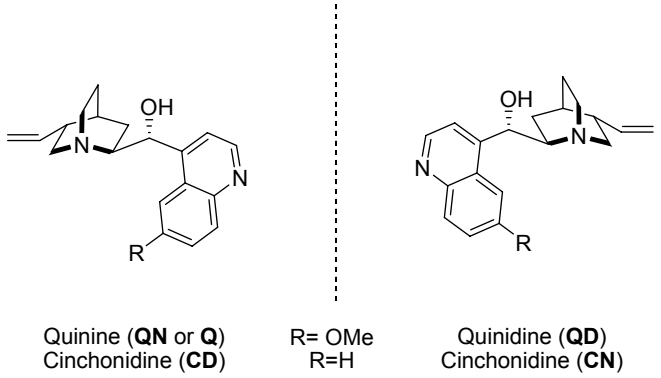
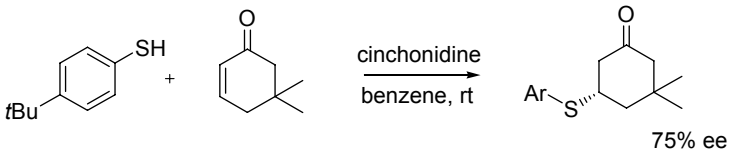


Figure 1: Structure of *Cinchona* alkaloids.

The absolute configuration at C_3 and C_4 is identical in all *Cinchona*. On the other hand, the other chiral centers (N_1, C_8, C_9) have opposite absolute configuration in **QD** and **QN** (and in **CN**/**CD**); since these three chiral centers are considered responsible for asymmetric induction in organocatalysis, *Cinchona* alkaloids are usually described as pairs of *pseudoenantiomers*.[14] As a result, when a quinine derivative is used as a chiral organocatalysts, employment of the corresponding quinidine derivative usually gives the opposite enantiomers of the same product with comparable selectivity. This feature makes *Cinchona* alkaloids attractive scaffolds for the development of asymmetric catalysts because, unlike other chiral bases such as (-)-sparteine, both pseudoenantiomers are commercially available in bulk amounts at a relatively low price.

Far before the explosion of asymmetric catalysis Cinchona alkaloids were already shown to be outstanding catalysts for enantioselective reactions. The first report on asymmetric organocatalysis involving the hydrocyanation of aldehydes catalyzed by cinchonidine dates back to 1912.[15] The group of Hans Wynberg gave an impulse to organocatalysis during the 1970's-1980's with the development of several highly enantioselective Cinchona catalyzed reactions.[16] As an example, the asymmetric addition of aromatic thiols to enones was investigated in detail (Scheme 1).[17]



Scheme 2: The enantioselective Michael addition of a thiophenol.

In order to gain insights into their mode of action, the conformational behaviour of the alkaloids has been investigated by means of NMR and computational techniques, resulting in the identification of four low-energy *Cinchona* conformers.[18]

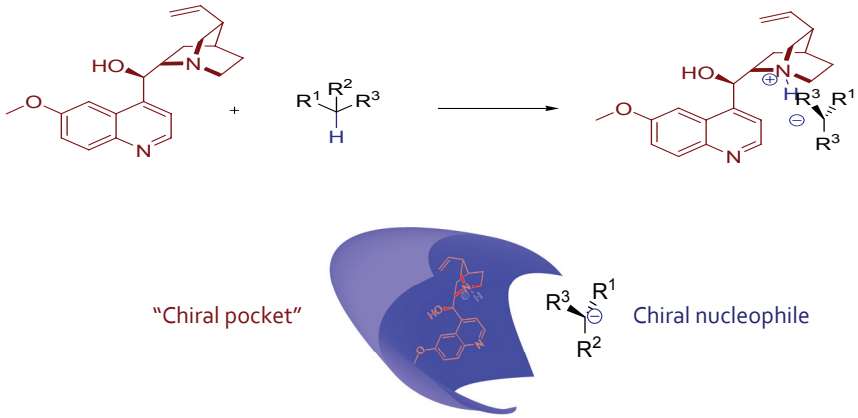


Figure 2: Enantioselective activation mediated by *Cinchona* alkaloid.

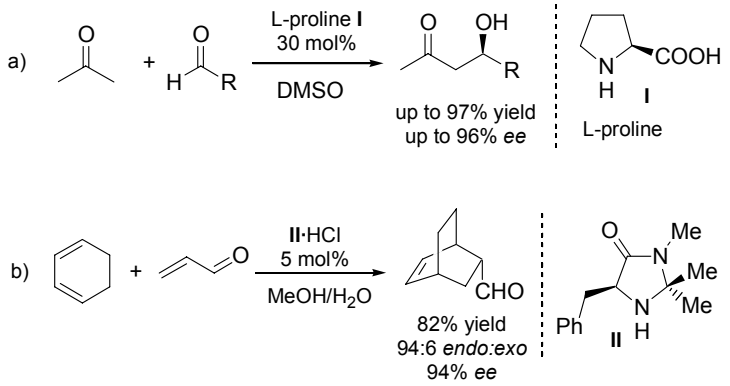
The concept governing the use of *Cinchona* as chiral Brønsted bases can be generalized as outlined in Figure 2 with quinine as the chiral catalyst. Quinine reacts as a base with the substrate having an acidic hydrogen atom. The reaction between the chiral base and the substrate generates a chiral nucleophile in a "chiral pocket".[10] However, besides the extended studies, it is clear that many factors are responsible for the complex behaviour of *Cinchona* alkaloids in solution and, therefore, it is highly difficult to predict the outcomes of the reaction.

Since there is no "perfect" rationale behind the mode of action of *Cinchona* and therefore a screening on several derivatives is usually needed; of course speculations on the activations and shielding of the substrates can often narrow the number of derivatives to be screened. As a result, at this stage, there is no *Cinchona* alkaloid

derivative that can be regarded as a *general* catalyst as it is, on the other hand, the case for secondary amine catalysts.

2.2 Secondary Amine Catalysis (Lewis base catalysis)[19]

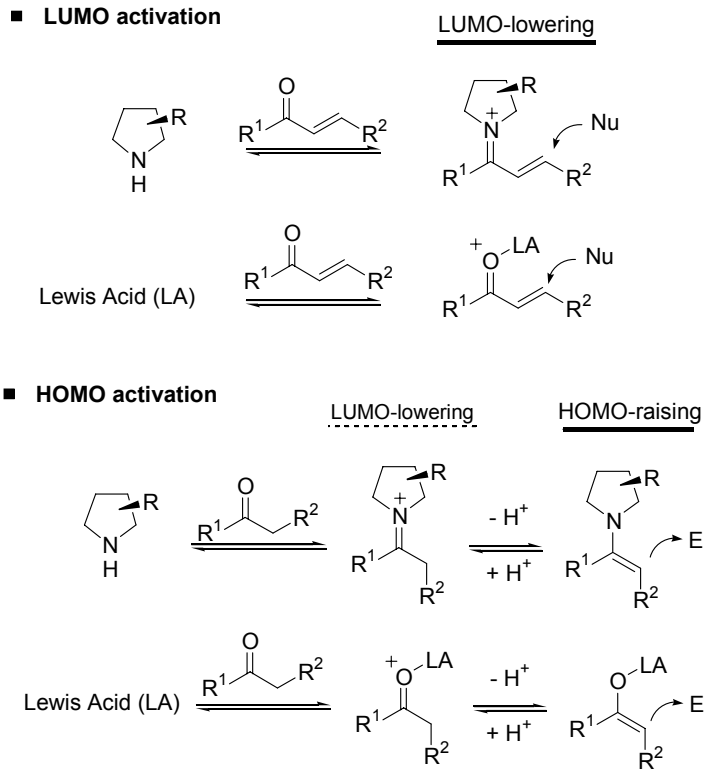
In 2000, two seminal reports established the possibility of employing simple, chiral cyclic secondary amines to efficiently catalyze the asymmetric functionalization of carbonyl compounds. List, Lerner, and Barbas reported that a catalytic amount of a molecule as simple as the proteinogenic aminoacid L-proline (**I**) was able to promote the enantioselective direct aldol reaction between an unmodified ketone, such as acetone, and a variety of aldehydes (Scheme 3a).[5] Soon after this publication, MacMillan described the development of the first asymmetric amine-catalyzed Diels-Alder reaction, demonstrating the effectiveness of the newly designed imidazolidinone catalyst (**II**) in the activation of α,β-unsaturated aldehydes (Scheme 3b).[6]



Scheme 3: a) Proline-catalyzed intermolecular aldol reaction between acetone (donor) and aldehydes (acceptors). b) Imidazolidinone II catalyzed asymmetric Diels-Alder reaction.

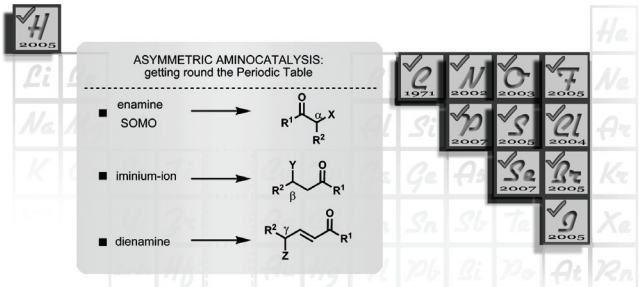
Besides offering alternative asymmetric and catalytic methodologies for two fundamental C-C bond forming reactions in chemistry, these researches constituted the basis for two novel organocatalytic activation modes of carbonyl compounds, pinpointing the origin of asymmetric aminocatalysis. Both were based on covalent active intermediates generated by condensation of chiral cyclic amines with a carbonyl group. The aminocatalytic activation platform emulates the mechanism of Lewis acids activation of carbonyl compounds. This is a well-established strategy for enantioselective catalysis, in which rate acceleration occurs via the reversible binding of the Lewis acid to isolated or conjugated π-systems, resulting in an electronic redistribution toward the positive metal center (Scheme 4). The reversible condensation of a chiral secondary amine with carbonyl compounds to form positively charged iminium ion intermediates mimics the π-orbital electronics inherent to Lewis acid catalysis, effectively lowering the lowest unoccupied

molecular orbital (LUMO) energy of the system. For conjugated π-systems, the electronic redistribution induced by iminium intermediates facilitates nucleophilic additions, including conjugate additions and pericyclic reactions (LUMO activation). In the case of isolated π-systems, the LUMO-lowering increases the α-proton acidity. This induces a fast deprotonation, which leads to the generation of the enamine, a nucleophilic enolate equivalent (HOMO activation). Here too, aminocatalysis emulates the HOMO-raising (HOMO = highest occupied molecular orbital) activation of carbonyls used by Lewis acids to generate activated nucleophiles.



Scheme 4: Comparing carbonyl compounds activation by Lewis acids and by aminocatalysis; E = electrophiles, Nu = nucleophiles.

Exploiting the HOMO-raising activation path (*enamine catalysis*),[20] a vast number of α-functionalizations of aldehydes and ketones with carbon- and heteroatom-based electrophilic reagents has been accomplished,[21] whereas the LUMO-lowering approach (*iminium*



ion catalysis)[20] allowed the asymmetric introduction of several nucleophiles to the β position of unsaturated aldehydes and ketones.[22] Recently, two new methods for the enantioselective functionalization of carbonyl compounds have been described: *Dienamine catalysis* accounts for the γ-functionalization of α,β-unsaturated aldehydes proceeding by reaction of the electron-rich dienamine intermediate with electrophilic dienophiles.[23] A fourth aminocatalytic pathway uses a single unpaired electron in the activated enamine intermediate (*SOMO catalysis*).[24] At present, aminocatalysis is considered a well-established and reliable tool in asymmetric synthesis.

We already mentioned imidazolidinone **II** in Scheme 3; its success as a stereoselective iminium activators relies on its ability to effectively and reversibly form a reactive iminium ion intermediate with high levels of both geometry control and π-facial discrimination (Figure 3). The catalyst-activated iminium intermediate predominantly exists in the (*E*)-conformation to avoid severe non-bonding interactions between the substrate double bond and *gem*-dimethyl groups on the catalyst scaffold. Selective π-facial coverage by the benzyl group of the imidazolidinone framework leaves the iminium ion *Re*-face exposed for the nucleophilic attack, resulting in highly enantioselective bond formation.

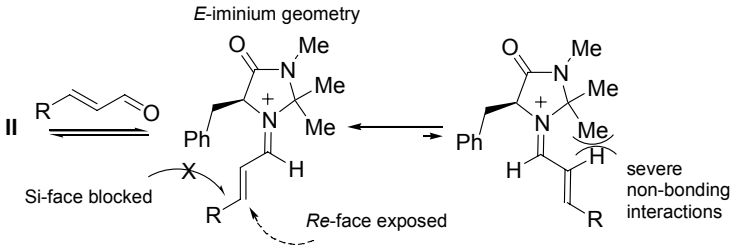
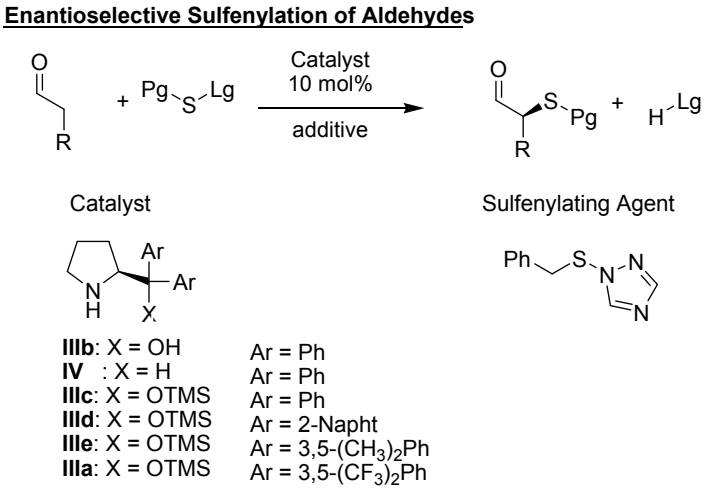


Figure 3: Iminium geometry control and π-facial shielding by imidazolidinone catalyst II.

While MacMillan's imidazolidinones were developed and used for iminium ion activation, a new type of organocatalysts based on chiral secondary amines was about to be presented to the scientific community. This new class of organocatalysts was presented in a new organocatalytic electrophilic α-sulfenylation reaction of aldehydes by Jørgensen's group (Scheme 5).[25] In addition to the value of this transformation,[25c] the highlight of this paper is without doubt the synthesis of a new class of organocatalysts. Simple trimethylsilyl (TMS) *O*-protection of the inactive diphenyl prolinol **IIIb** produced the catalyst **IIIc**, excellent in terms of both yield (90%) and enantioselectivity (77% *ee*).



Scheme 5: The amino catalyzed sulfenylation of aldehydes; Lg = leaving group; Pg= protecting group.

From this groundbreaking result, a small structure optimization of the aromatic moieties of the catalyst led to the (*S*)-2-[bis-(3,5-bis-trifluoromethyl-phenyl)-trimethylsilanyloxy-methyl]-pyrrolidine **IIIa** (Jørgensen catalyst), which catalyzes the formation of sulfenylated products in high yield with *ee* consistently over 95%.[25a]

Diphenyl prolinol **IIIb** is an amino alcohol which was first synthesized in the thirties of the last century[26a] and used by Enders and co-workers[26b] as a chiral auxiliary and by Corey as a ligand in Lewis acid reactions.[26c] The compound rarely demonstrated useful catalytic activity when used as an enamine activator, although in some transformations it could induce high stereocontrol.[27] The poor yields obtained with this catalyst were explained by the larger size of the substituents relative to catalyst **IV**, which, in contrast, often showed good activity and low levels of stereocontrol.[26a,b] Jørgensen and co-workers, however, suggested that the reason for the disappointing behaviour of **IIIb** in enamine catalyzed reactions relied on the formation of unreactive hemiaminal species (Figure 4).[28] It was not the size but the chemical reactivity of the free hydroxyl group that needed to be addressed. Consequently, a simple protection of this functionality restored the high activity.

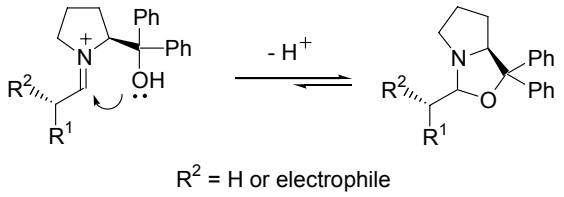
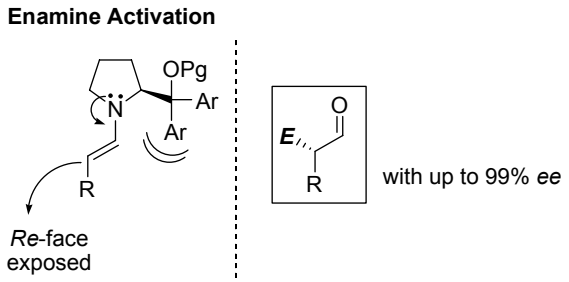


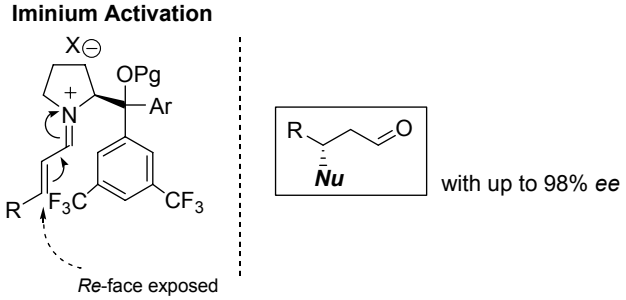
Figure 5: Hemiaminal equilibrium.

Outstanding enantiomeric excesses and a consistent absolute configuration were observed for these diarylprolinol silylether-catalyzed transformations. This is in agreement with a transition state that minimizes the steric interactions between the bulky substituents on the pyrrolidine ring and the reactive carbon (*E-anti* geometry of the enamine).[29] At the same time, the catalyst architecture guarantees an excellent shielding of the *Si*-face of the enamine and the overall result is an almost complete stereocontrol of the reaction (Scheme 6). Furthermore, the sterically encumbered chiral amine seems to prevent racemization of the optically active products. Notably, the proposed model, which explains the activity and the asymmetric induction, does not rely upon the structure of the electrophile.



Scheme 6: Enantioselectivity in the diarylprolinol ethers-catalyzed reactions via enamine activation.

MacMillan catalysts had been designed for iminium ion catalysis, however they turned out to be effective in enamine-catalyzed reactions. In a similary manner the silyl ether diarylprolinols (designed for application in enamine-catalyzed reactions) found application in iminium ion catalysis (Scheme 7). Here too, the excellent stereoselectivities reported are closely connected to the size of the catalyst substituents. In the transition state, the geometry of the iminium ion is such that steric repulsions are minimized. The chiral fragment extends enough to provide efficient face-shielding to the more distant β-carbon. Catalytic amounts of organic acid are usually beneficial for the rate of this kind of transformation. There is most likely a relationship between the energy of the LUMO of the iminium ion and the nature of its counteranion. However, the role of these additives has not been completely clarified and might be not the same in all situations. It is commonly accepted that acids are able to increase the rate of the overall catalytic process by accelerating enamine formation and/or hydrolysis.



Scheme 7: Enantioselectivity in the diarylprolinol ethers-catalyzed reactions via iminium ion activation.

In both models (Scheme 6 and 7), the efficiency of the *O*-protected diarylprolinols seems related only to the size of the catalyst substituents and not to their chemical nature. The first consequence is that fine-tuning of the catalytic activity can be easily achieved by subtle modifications of the aryl structure. It has been demonstrated how the smaller[28,30] (and often, therefore, more reactive) catalyst with the phenyl substituents **IIIc** could be applied in some transformations, maintaining outstanding levels of selectivity.

There are two further properties of *O*-protected diarylprolinols that need to be mentioned. First, they are poor catalysts for the homo-aldol reaction of aldehydes under the mild conditions in which they are usually applied. This is very important since the formation of such by-products often forces the use of a large excess of aldehyde when other chiral amines are used as organocatalysts. Secondly, the catalysts are compatible with different reaction media. Successful applications have been reported in a variety of solvents ranging from the apolar and aprotic hexane and toluene to polar and protic solvents such as ethanol or water.

The catalytic cycles in Figure 6 operate in enamine and iminium ion catalysis. Condensation of the secondary amine with an unsaturated aldehyde (Figure 6, left) gives rise to the iminium ion intermediate **A** that can react with an appropriate nucleophile to generate the enamine intermediate **B**; this, upon release of the catalyst, provides the β–functionalized aldehyde **C** (iminium ion catalysis). On the other hand, in presence of a saturated aldehyde, a secondary amine can give rise to an enamine intermediate **D** (Figure 6, right) prone to react with an electrophile; in this case the α-functionalized aldehyde **E** is the product of the reaction.

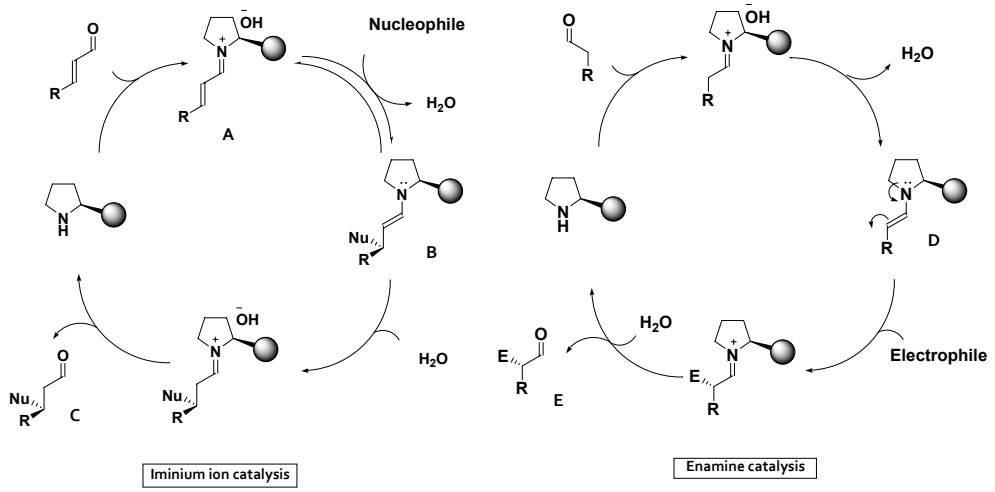
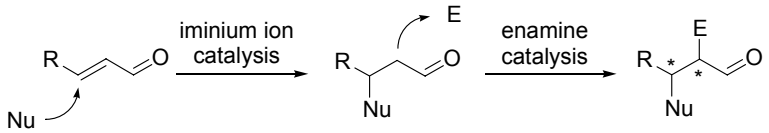


Figure 6: Iminium ion and enamine catalytic cycles

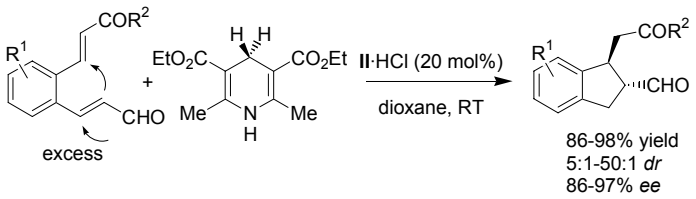
Interestingly, common intermediates are present in the two catalytic cycles; indeed, iminium ion and enamine are two opposite catalytic intermediates, yet interdependent, and they consume and support each other during the catalysis. The observation of this feature -named Ying and Yang of Asymmetric Aminocatalysis[7b]- gave impulse to a great advancement in the field.

The conjugate addition of a nucleophile to α,β-unsaturated aldehydes provides a functionalized saturated aldehyde; this can form a reactive enamine intermediate ready to undergo to further functionalization (Scheme 8). In this well-defined sequence, the catalyst has an active role in both steps, initially forming the activated iminium ion species and later the electron-rich enamine intermediate.



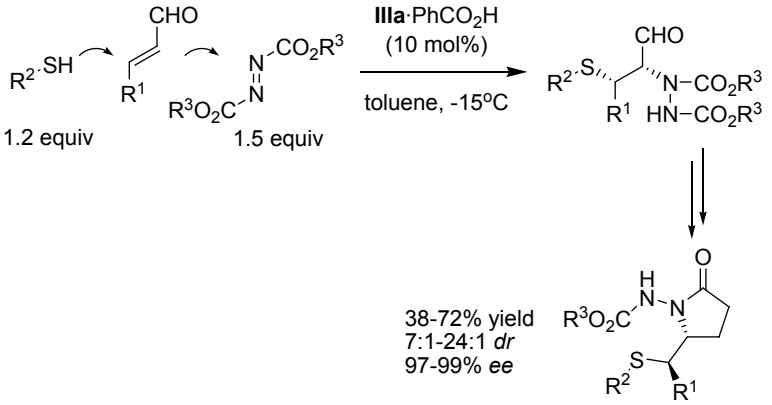
Scheme 8: Domino iminium ion – enamine catalyzed reaction; Nu= nucleophiles, E= electrophiles.

Fundamental developments for the application of the iminium ion – enamine activation strategy were independently and simultaneously reported by the groups of List, Jørgensen, and MacMillan. List and co-workers disclosed a domino organocatalytic hydrogenation-Michael cyclization using the HCl salt of the MacMillan catalyst **II**, affording excellent yields and levels of stereocontrol under very mild reaction conditions (Scheme 9).[31]



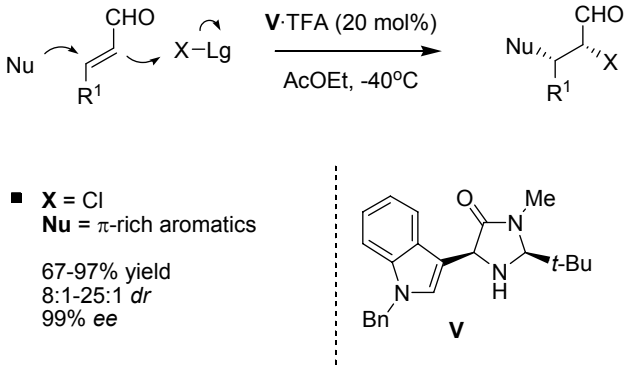
Scheme 9: Organocatalytic hydrogenation-Michael cyclization.

The groups of Jørgensen[32] and MacMillan[33] went one step further by applying the iminium ion – enamine activation strategy to develop a series of new multicomponent reactions in which the two stereoselective steps are *inter*molecular reactions. Jørgensen and co-workers combined the first highly enantioselective organocatalytic addition of thiols to α,β-unsaturated aldehydes with the α-amination reaction (Scheme 10).[32a] The products were further reduced and cyclizated in a one-pot process to afford the final product in good yields with excellent diastereomeric ratios and enantiomeric excess.



Scheme 10: Aminocatalytic sulfa-Michael addition-amination.

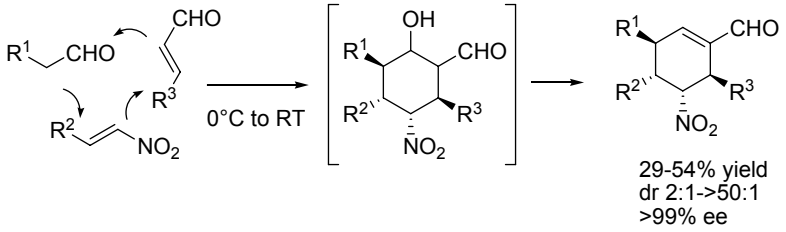
The group of MacMillan applied a variation of their chiral imidazolidinones (catalyst **V**) to combine the enantioselective conjugate additions of a large number of diverse carbon-based nucleophiles with the α-chlorination (Scheme 11).[33]



Scheme 11: Aminocatalytic conjugate addition-halogenation; Lg= leaving group.

An extremely appealing feature of these domino sequences, observed both by Jørgensen and MacMillan's groups, is that the interaction between the chiral catalyst and the chiral intermediate, resulting from the first conjugate addition, induces a remarkable enantioenrichment in the final enamine step, affording rapid access to products with enantiomeric excess generally over 99% for the *syn*-diastereoisomer.

Enders and co-workers found success in the even more ambitious synthetic task of controlling four stereocenters in a triple domino reaction based on an outstanding enamine-iminium-enamine sequential activation by the aminocatalyst (Scheme 12).[34]



Scheme 12: Aminocatalytic enamine – iminium ion – enamine catalyzed domino reaction.

The *O*-TMS diphenyl prolinol catalyst **IIIc** first controls a Michael addition of aliphatic aldehydes to nitrostyrene derivatives (Figure 7). In the second step the chiral amine catalyzes the conjugate addition of the nitroalkane intermediate to α,β–unsaturated aldehydes. The last step is an aldol reaction, where the less hindered aldehyde acts as a nucleophile, followed by elimination of water. The highly functionalized products are obtained in essentially enantiopure form in a simple single operation.[34a]

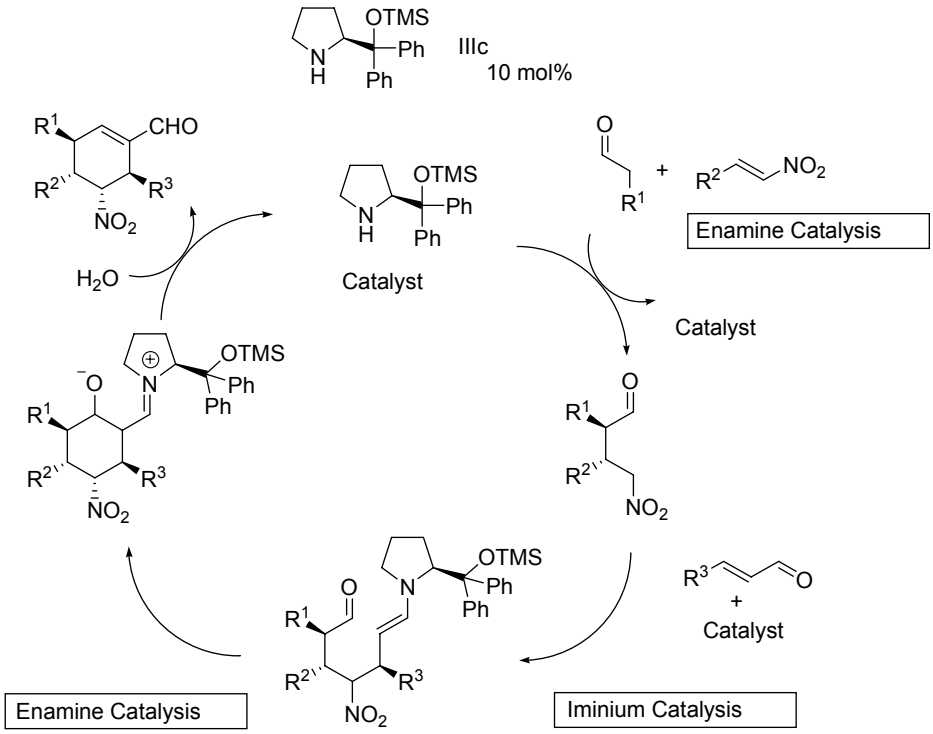


Figure 7: Aminocatalytic enamine – iminium ion – enamine catalytic cycle.

In the cycle, the nitrostyrene derivatives need to intercept enamine faster than the unsaturated aldehyde (or the relative iminium) does; moreover the resulting nitroalkane adduct is a latent nucleophile that requires iminium activation of the unsaturated aldehyde to react. These are very important features for the success of the strategic plan.

2.3 Summary

After this small introduction on organocatalysis it should be obvious to the reader that both *Cinchona* alkaloids and secondary amine catalysis offer a unique platform for the development of new reactions and methodologies.

Cinchona alkaloids give the possibility to functionalize compounds with an acidic hydrogen by means of Brønsted Base catalysis; the catalyst forms a chiral pocket around the nucleophile and brings it in contact with the electrophile. *Cinchona* can be easily derivatized to fine-tune their characteristics in order to better shield and modulate the activation of the reagents. This gives a very broad range of possible catalyst to screen among; however their shielding is not rationalized yet and therefore a large survey is needed although speculation on activation of the shielding can help. Moreover, at the forefront of Brønsted base catalysis research there is the

engineering and synthesis of bifunctional chiral catalysts, able to simultaneously bind and activate two reacting partners.

On the other hand, secondary amines give easy access to the functionalization of aldehydes with several activation modes. Chiral secondary amine catalysis provides a bunch of small molecules that can be regarded as general organocatalysts. Their mode of action and mechanism is far better understood compared to *Cinchona* alkaloids. Therefore a shorter screening is needed and the outcomes can be more predictable; additionally different and orthogonal activations allow to plan sequential, tandem and domino reactions that are at the forefront of nowadays research. However, the same results have not been achieved with ketones; this is a kind of improvement that is highly desirable.

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SECTION I

CHIRAL BRØNSTED BASE CATALYSIS MEDIATED BY *CINCHONA* ALKALOIDS

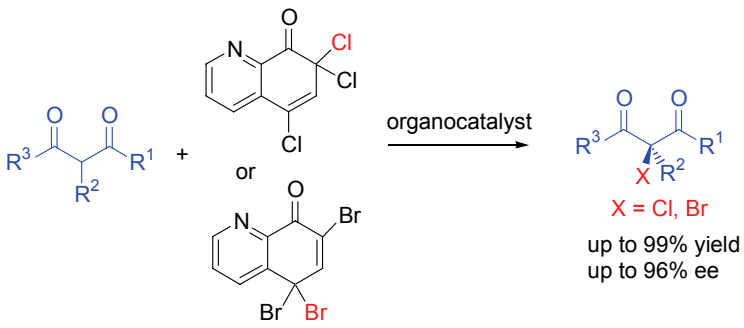
Brønsted Base catalysis has been exploited to introduce halogens in β-ketoesters and for a Michael addition on maleimides, with high diastereo- and enantioselectivities and in good yields.

In the first paper, investigating the halogenation with N-chlorosuccinimide in presence of *Cinchona* derivatives, a first glance at the data suggested that the OH group in quinine needed to be protected; a subsequent screening on different substituents showed that an acyl group was essential to impart high stereocontrol. At this stage, however, the optimization was not over since, even at low temperatures, the non-catalyzed reaction was of a rate comparable to the catalyzed one; this has been one of the main challenges in the project. A screening on chlorinating agents brought to the synthesis and first use of quinolinones as halogenating agents in high enantioselective reactions. With these conditions in hand, the chlorination on less reactive substrates was somehow slow and a speculation on the catalytic cycle prompt us to include the use of $NaHCO_3$ in the reaction; this way the reaction times were indeed shortened. Moreover the use of such an additive was an excellent example that an inorganic base could coexist with a chiral organic base such as a *Cinchona* alkaloid derivative without detrimental effects on enantioselectivity.

Following, the research presented is a Michael addition on maleimides. The peculiarity of this reaction is a one-step construction of two adjacent stereogenic centers. Therefore, beside enantioselectivity, the additional challenge is to control the diastereoselectivity; in other words the approach of the electrophile has to be properly directed in order to achieve optimal stereocontrol. A free OH group on the *Cinchona* derivative soon proves essential for the success of the protocol; speculations on the mechanism by means of results and computational studies being carried out at the moment, suggest that a hydrogen bond properly orientates the approach of the maleimides, thus providing very high sterecontrol.

In the case of the Michael addition to maleimides, a bifunctional catalysis seems to take place; on the other hand, halogenation of β-ketoesters does seem to be controlled by a simpler appropriate shielding of the catalyst.

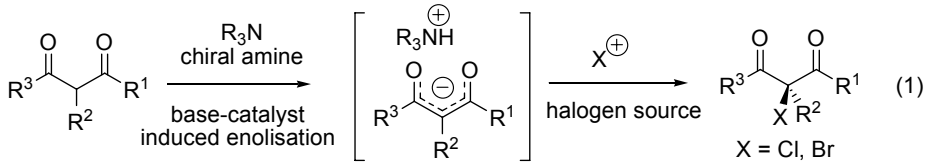
3. Organocatalytic Asymmetric α-Halogenation of 1,3-Dicarbonyl Compounds



No metal required: A protocol for the enantioselective organocatalytic chlorination of cyclic and acyclic β-keto esters and cyclic β-diketones has been developed which is also effective for the asymmetric bromination of β-keto esters. The methodology employs an inexpensive organocatalysts and polyhalogenated quinolinones as the source of the halogen.

The enantioselective construction of carbon-halogen stereogenicity belongs to the topical area of current asymmetric catalysis[1] by virtue of the fact that halogen atoms attached to a chiral stereocenter can serve as linchpin for further stereospecific manipulations.[2] Moreover, optically active halogen-containing compounds are increasingly important targets in drug discovery and material sciences.[3] Notwithstanding this, only in the last few years different efficient catalytic asymmetric halogenation strategies have been developed.[1a,b] To date, the most notable advances have been made in the α-halogenation of carbonyl compounds by using mild and stable sources of electrophilic halogen. All the reported asymmetric catalytic methodologies, starting from the first Lewis acid asymmetric α-fluorination of β-keto esters reported by Togni,[4] to several highly practical metal-free

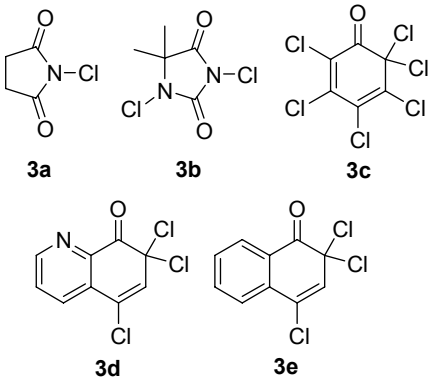
(organocatalytic)[5] approaches, involve the transient formation of an enolate (enol) that can be halogenated to generate the desired product. The crucial enolisation process can be efficiently promoted through i) coordination of chiral Lewis acids with 1,3-dicarbonyl compounds;[6] ii) formation of an enamine intermediate derived from the reaction between a secondary chiral amine and enolisable aldehydes and ketones;[7] iii) attack of a chiral nucleophile on a ketene intermediate to generate a zwitterionic enolate;[8] iv) ionic association of a phase-transfer catalyst with the enolate.[9]



(1)

Recently, chiral tertiary amines have been successfully applied in various organocatalytic transformations acting as chiral-base catalysts.[10] However, this concept has not yet been applied to the asymmetric halogen-carbon bond forming reactions. Thus a new effective approach that uses a cinchona alkaloid derivative as a chiral base for promoting the enolisation of 1,3-dicarbonyl compounds and the subsequent highly enantioselective electrophilic α-chlorination and α-bromination [Eq.(1)] is of high interest.

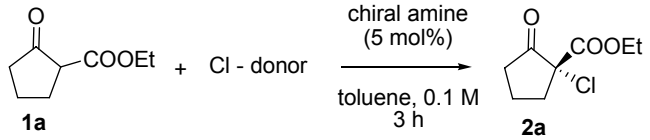
Despite the considerable recent advances, the development of a novel halogenation system of 1,3-dicarbonyl compounds affording satisfactory selectivity as well as generality is still in high demand as the reported Lewis acids-catalysed asymmetric chlorination and bromination of β-keto esters are efficient only with selected substrates.[6a-c] The presented organocatalytic halogenation is effective with both cyclic and acyclic β-keto esters and with cyclic β-diketones, affording highly optically enriched α-halogenated compounds (up to 96% *ee*) in good yields using inexpensive benzoylquinidine (BQd) as the catalyst and easy-to-prepare polyhalogenated quinolinones as new halogen sources.



To verify the feasibility of such organocatalytic asymmetric halogenation strategy, we examined the reaction of ethyl 2-oxo-cyclopentanecarboxylate **1a** with N-chlorosuccinimide (NCS, **3a**) as the halogen source in the presence of some cinchona alkaloid derivatives as the chiral-base catalyst; representative results of the extensive screen of reaction conditions are listed in Table 3.1. Several solvents have been

investigated, and toluene was selected as the solvent of choice, although ethereal solvents afforded analogous results (see Experimental Part for details).

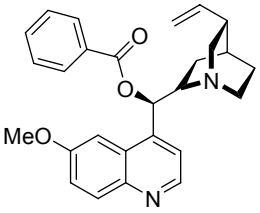
Table 3.1: Some screening results for the organocatalytic asymmetric chlorination.[a]



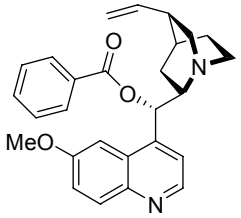
Entry	Cat.[b]	Cl-donor	t[h]	*T*[°C]	Conv.[c]	*ee*[%][d]
1	$(DHQ)_2PYR$	**3a**	2	RT	>95%	21 (*R*)
2	$(DHQD)_2PHAL$	**3a**	2	RT	>95%	33 (*S*)
3	$(DHQ)_2AQN$	**3a**	2	RT	>95%	46 (*R*)
4	cinchonidine	**3a**	2	RT	>95%	10 (*R*)
5	quinine	**3a**	2	RT	>95%	18 (*R*)
6	**4a** - BQ	**3a**	2	RT	>95%	60 (*R*)
7	**4a** - BQ	**3a**	3	-78	>95%	58 (*R*)
8	**4a** - BQ	**3b**	3	RT	>95	36 (*R*)
9	**4a** - BQ	**3c**	3	RT	>95	57 (*R*)
10	**4a** - BQ	**3d**	3	RT	>95 (98)[e]	79 (*R*)
11	**4a** - BQ	**3e**	3	RT	58	78 (*R*)
12	**4a** - BQ	**3d**	24	-78	70	95 (*R*)
13[f]	**4a** - BQ	**3d**	24	-78	74	95 (*R*)
14[g]	**4b** - BQ	**3d**	24	-78	80 (68)[e]	95 (*R*)
15[g]	**4b** - BQd	**3d**	3	RT	>95 (96)[e]	85 (*S*)
16[g]	**4b** - BQd	**3d**	24	-40	>95 (98)[e]	95 (*S*)

[a] Experimental conditions (0.4 mmol scale): open-air reactions run in undistilled solvent (0.1 M) using a 1:1.2 ratio of **1a** to **3** and 5 mol% of the catalyst. [b] Catalyst structures available in Experimental Part. [c] Conversion determined by ^{1}H NMR spectroscopy of the crude mixture. [d] Determined by GC analyses on commercially available chiral stationary phases. The absolute configuration reported in parenthesis was determined by comparison of optical rotation values with those reported in the literature. [e] Number in parenthesis indicates yield of the isolated product **2a**. [f] Reaction carried out with 1 equiv on $NaHCO_3$. [g] Reaction carried out with 1 equiv on $NaHCO_3$ in toluene 0.25 M.

In the initial studies, benzoylquinine (BQ, **4a**) proved to be the most promising catalyst among the chiral amines tested, affording the (*R*)-chloro derivative **2a** in moderate enantiomeric excess (60% *ee*, entry 6, Table 1). However, a slight decrease in enantioselectivity was observed performing the BQ-catalysed reaction at –78 °C (entry 7). We speculated that, under these reaction conditions, the uncatalysed



4a - BQ
benzoylquinine



4b - BQd
benzoylquinidine

background reaction of the enol form effectively competes with the stereoselective pathway, even at low temperature. Thus, the primary goal was to employ a less reactive, finely tuned chlorinating agent possessing minimal background rate with the substrate **1a**.

Along those lines, a series of electrophilic halogens was screened employing BQ **4a** as the catalyst (entries 8-11). The use of the trichloroquinolinone **3d**, easily prepared from 8-hydroxyquinoline and 3 equiv of *tert*-butylhypochlorite, gave the best result, as the product **2a** was obtained in 79% *ee*. The structurally related chlorinating agent **3e** provided the same stereochemical outcome with a significant decrease in reactivity. Performing the reaction at –78 °C in the presence of **3d** afforded a dramatic increase in enantioselectivity, albeit at the expense of reactivity (95% *ee*, entry 12), indicating that, under these conditions, the discrimination between the background reaction and the asymmetric catalysed chlorination was maximised.[11] It is important to note that the capacity of the trichloroquinolinone **3d** to function in highly enantioselective enolate halogenations has been disclosed here for the first time.[12]

Halogen transfers involving quinolinone **3d** are expected to release stabilised aromatic phenolate anion **5** in a thermodynamically favourable process (Figure 3.1). We envisaged that the plausible tight ionic association of **5** with the protonated chiral amine catalyst might affect the efficiency of the system. We reasoned that an

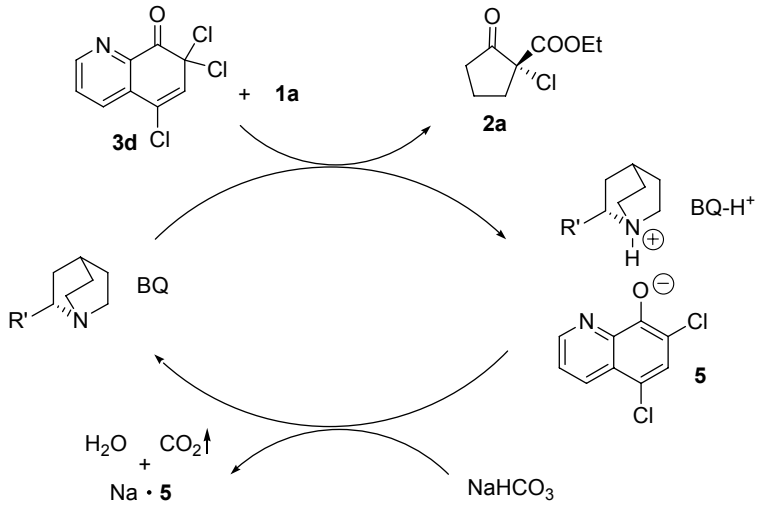


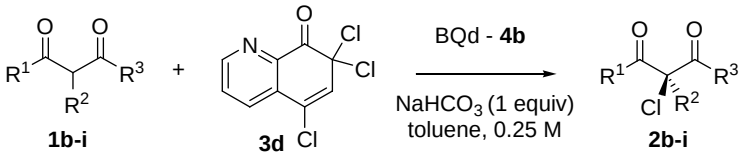
Figure 3.1: Halogen transfer from quinolinone **3d** to **1a** catalyzed by BQ (**4a**)

inorganic base able to facilitate the proton transfer from the protonated chiral amine (BQ-H$^+$), thus regenerating the active catalyst, without promoting a racemic chlorination path could have a beneficial effect on the reaction rate.[13] With this consideration in mind, a survey of reaction conditions was accomplished, revealing that the BQ-catalysed asymmetric chlorination of **1a** was accelerated by using 1

equiv of $NaHCO_3$ in a more concentrated solution (toluene, 0.25 M, entries 13-14, Table 3.1).[14] Noteworthy, when the "pseudoenantiomeric" benzoylquinidine BQd **4b** was used as catalyst the opposite enantiomer (*S*)-**2a** was obtained in significantly higher *ee* (entry 15). Such a selectivity allowed to perform the reaction at higher temperature without affecting the optical purity of the product, that was isolated in quantitative yield (*ee* = 95%, entry 16).

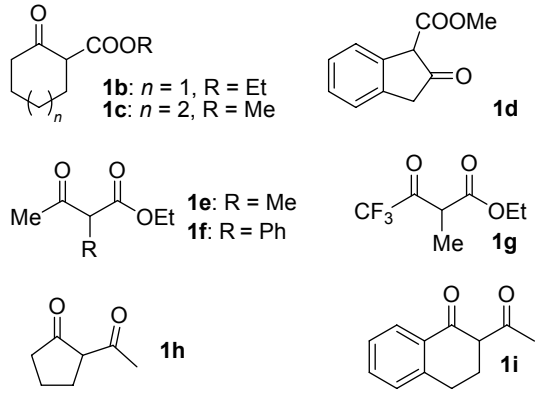
The superior levels of induction and efficiency exhibited by BQd **4b** in the presence of $NaHCO_3$ (1 equiv) and toluene (0.25 M), prompted us to select these conditions to examine the scope of the 1,3-dicarbonyl substrates in this asymmetric chlorination protocol. As highlighted in Table 3.2, cyclic β-ketoesters were all converted to the corresponding chloro derivatives in fairly good yields and excellent optical purity (entries 1-3). The asymmetric chlorination of different substituted acyclic β-ketoesters also afforded the desired product in good enantioselectivity, although a decreased reactivity was observed (entries 4-6). In the presence of a more reactive substrate such as **1g**, the possibility to perform the reaction at low temperature allowed the generation of the chlorinated adduct **2g** in high optical purity (*ee* = 89%, entry 6).[15]

Table 3.2: Organocatalytic asymmetric chlorination of β-keto esters and β-diketones.[a]



Entry	Product	BQd [mol%]	T[°C]	t[h]	Yield [%][b]	ee [%][c]
1	**2b**	15	-40	40	83	96
2	**2c**	15	-40	52	48[d]	90
3	**2d**	5	-78	36	80 (75)	93 (91)
4	**2e**	20	RT	48	75	76 (69)
5	**2f**	15	-10	36	99	80
6[e]	**2g**	15	-78	52	44[f]	89
7[g]	**2h**	5	-78	30	90 (87)	51 (56)
8[g]	**2i**	15	-40	48	74 (78)	59 (58)

[a] Experimental conditions (0.4 mmol scale): open-air reactions run in undistilled toluene (0.25 M) using a 1:1.2 ratio of **1** to **3d**, 1 equiv of $NaHCO_3$ and benzoylquinidine BQd **4b** as the catalyst. Results in parenthesis were obtained by using BQ **4a** as the catalyst to give the opposite enantiomer. [b] Yield of isolated products **2**. [c] The *ee* values of **2** were determined by HPLC or by GC analyses on commercially available chiral stationary phases, see Experimental Part for details. [d] 65% conversion. [e] Reaction carried out in *tert*-butyl methyl ether (TBME). [f] 80% conversion, lower yield due to the volatility of **2g**. [g] Performed without $NaHCO_3$.



We next investigated the efficiency of the method with β-diketones, a particularly challenging class of substrates as, to our knowledge, just one example of low enantioselective chlorination has been reported.[6b] Reactions of cyclic diketones **1h-i** proceeded smoothly to give the expected products in moderate enantioselectivity (entries 7-8).

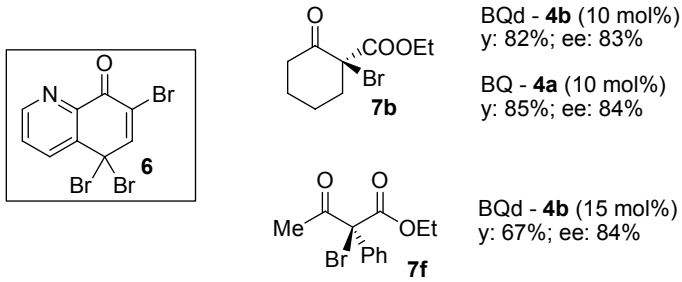


Figure 3.2: Results for the organocatalytic asymmetric bromination of β-keto esters in the presence of 1.2 equiv of **6** as the halogen source; toluene (0.25 M),–78 °C, 30 h.

Last, the extension of the presented organocatalytic protocol to the asymmetric bromination was evaluated. We presumed that the newly synthesised tribromoquinolinone **6** (Figure 2), structurally related to the chlorinating agent **3d**, might have been a useful bromo source for the organocatalytic enantioselective α-bromination. Proof-of-principle was provided through BQd-catalysed reactions of β-ketoesters **1b** and **1f**: the corresponding bromo derivatives were obtained in good yields and interesting enantioselectivity (up to 84% *ee*, Figure 2).[16] Further studies to improve the efficiency and the applicability of the organocatalytic enantioselective bromination are ongoing in our laboratories.

In summary, we have developed the first organocatalytic asymmetric α-chlorination and α-bromination of 1,3-dicarbonyl compounds by using an inexpensive chiral amine as the catalyst and a mild, operationally simple protocol that allows direct access to highly enantioenriched halogen-containing compounds. It was established that the use of the polihalogenated quinolinones as new halogen sources was essential to achieve high enantioselectivity.

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[11] The uncatalysed background chlorination of **1a** was demonstrated to proceed to different extent depending on the chlorinating agent, *i.e.* (ratio **1a**/**3** : 1/1, 3 h, toluene, RT): **3a** conversion = 100%; **3c** conversion = 58%; **3d** conversion = 12%.

[12] It was reported that the use of trichloroquinolinone **3d** in the asymmetric catalytic α-chlorination of acid halides resulted in poor chemical and optical yields; see Ref 8b.

[13] For a similar system in which the proton-transfer from the protonated benzoylquinine to $NaHCO_3$ represents a key step of catalysis, see the α-chlorination of acid halides, Ref 8b.

[14] The beneficial effect of $NaHCO_3$ on reactivity is more appreciable with less reactive substrates such as linear β-ketoesters. The effects of various bases on the asymmetric halogenation were evaluated, see Experimental Part.

[15] The absolute configurations of **2a**-**b** and **2e** were determined to be (*S*) by comparison of the specific optical rotations with the literature values. All other absolute configurations were assigned by analogy. Although it is premature to provide a detailed mechanistic explanation at this level, the sense of stereochemical induction suggests the formation of a BQd-enolate ionic complex in which the *Re*-face is effectively shielded by the chiral organocatalyst.

[16] The use of different brominating agents such as *N*-bromosuccinimide and 2,4,4,6-tetrabromo-2,5-cyclohexadione resulted in very low enantioselectivity.

3.EP Experimental Part

Contents

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$). Coupling constants are given in Hz. Carbon types were determined from DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh) according to the method of Still.[1] Optical rotations are reported as follows: $[\alpha]^{rt}_{D}$ (*c* in g per 100 mL, solvent).

Materials. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[2]

β-keto esters **1a-g** and β-diketones **1h-i** were purchased from Aldrich or Lancaster and used as received.

Cinchona alkaloids derivatives such as Cinchonidine, Quinine, $(DHQD)_2PHAL$, $(DHQ)_2PYR$ and $(DHQ)_2AQN$ were purchased from Aldrich and used as received. Benzoylquinine (BQ) **4a** and Benzoylquinidine (BQd) **4b** were prepared according to standard literature procedures (Quinine or Quinidine / Et_3N / benzoylchloride / DCM / overnight,RT).

N-chlorosuccinimide (NCS) **3a**, 1,3-dichloro-5,5-dimethylhydantoin **3b** and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one **3c** were purchased from Acros Organics and used as received.

5,7,7-trichloro-7*H*-quinolin-8-one **3d** and 2,2,4-trichloro-2*H*-naphthalen-1-one **3e** were prepared starting from 8-hydroxyquinoline and 1-naphthol, respectively, following the literature procedure (*t*-butylhypochlorite/DCM/RT, 3h).[3]

Determination of Enantiomeric Purity. Chiral HPLC analysis was performed on an Agilent 1100-series instrumentation. Daicel Chiralpak AD-H or AS-H columns with i-PrOH/hexane as the eluent were used.

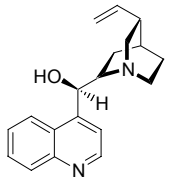
Chiral GC analysis was performed on a Hewlett-Packard 5890 gas chromatography using a RT-BetaDEX-sm chiral column.

The enantiomeric excess (ee) of the products was determined by GC analysis for chloro compounds **2a-c, 2e** and **2g-h** and by HPLC analysis for chloro compounds **2d, 2f, 2i** and for bromo compounds **7b** and **7f**. HPLC and GC traces were compared to racemic samples prepared with Et_3N as the catalyst.

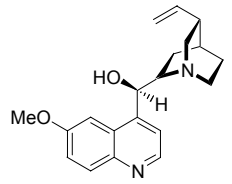
Determination of Absolute Configuration. The absolute configurations of the optically active chloro compounds **2a-b**[4] and **2e**[4] were determined on the basis of the measured optical rotations that were compared with literature values. All other absolute configurations were assigned by analogy.

Structure of the Catalysts.

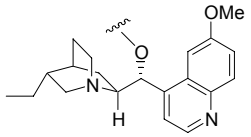
Cinchona alkaloids derivatives tested in Table 1.



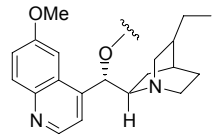
cinchonidine



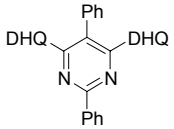
quinine



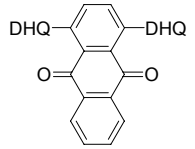
DHQ



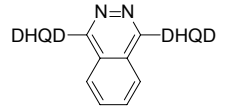
DHQD



$(DHQ)_2PYR$

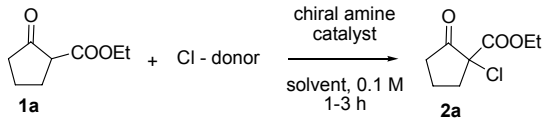


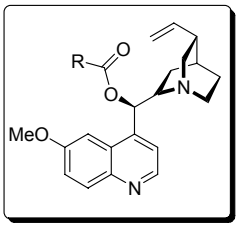
$(DHQ)_2AQN$

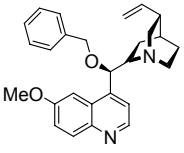


$(DHQD)_2PHAL$

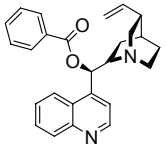
Table S1. Screening results for the organocatalytic asymmetric chlorination of **1a** (not reported in Table 1).







F



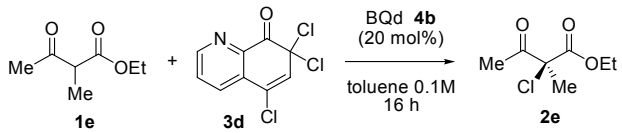
G
O-benzoyl cinchonidine

R = Ph **4a** (BQ)
R = *t*-Butyl **A**
R = *p*-NO_2Ph **B**
R = o-MeOPh **C**
R = 1-Naphthyl **D**
R = $C(O)CH_3$ **E**

Catalyst	Cl - donor	T [°C]	solvent	ee [%]
4a (BQ)	**NCS**	RT	toluene	60
A	NCS	RT	toluene	59
B	NCS	RT	toluene	60
C	NCS	RT	toluene	44
E	NCS	RT	toluene	46
F	NCS	RT	toluene	31
G	NCS	RT	toluene	40
4a (BQ)	3d	RT	toluene	79
4a (BQ)	3d	-78	toluene	95 (70)[a]
A	3d	RT	toluene	66
B	3d	-78	toluene	91
D	3d	-78	toluene	95
4a (BQ)	3d	-78	THF	91 (66)[a]
4a (BQ)	3d	-78	DCM	62 (25)[a]
4a (BQ)	3d	-78	TBME	95 (68)[a]

[a] Reaction time 24 h: number in parenthesis indicates conversion as determined by ^{1}H NMR spectroscopy of the crude mixture.

Table S2. Screening results for the organocatalytic asymmetric chlorination of **1e** in the presence of additives.[a]



Additive [x equiv]	Conversion	ee [%]
None	22%	78
$NaHCO_3$ (1)	45%	77
$NaHCO_3$ (5)	46%	77
K_2CO_3 (1)	15%	76
$KHPO_4$ (1)	28%	75
8-hydroxyquinoline (1)	20%	76
HFIP (1)	23%	69
Proton sponge (1)	No reaction	-
$NaHCO_3$ (1)[b]	63%	76

[a] Experimental conditions: open-air reactions run in undistilled toluene (0.1 M) for 16 h using a 1:1.2 ratio of **1e** to **3d** and 20 mol% of BQd **4b** as catalyst. [b] Reaction carried out in toluene 0.25 M.

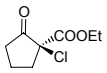
Experimental Procedures.

Synthesis of 5,7,7-trichloro-7*H*-quinolin-8-one (3d)[3]: To a solution of 8-hydroxyquinoline (725 mg, 5 mmol, 1 equiv) in CH_2Cl_2 (15 mL) was slowly added *t*-butylhypochlorite (2.3 mL, 3.6 equiv) at 0°C. The reaction was stirred at room temperature for 3 hours. After removal of the solvent under reduced pressure, 5 mL of Et_2O was added to the crude residue. The solid was collected by vacuum filtration and washed with 5 mL of cold hexane to afford product **3d** as a pale solid in 85% yield. ^{1}H NMR ($CDCl_3$): δ = 6.81 (s, 1H), 7.68 (dd, 1H, J = 4.8, 8.0), 8.10 (dd, 1H, J = 1.6, 8.0), 8.83 (dd, 1H, J = 1.6, 4.8); ^{13}C NMR ($CDCl_3$): δ = 77.3 (C), 128.7 (CH), 129.4 (C), 130.9 (CH), 131.3 (C), 134.2 (CH), 143.7 (C), 151.7 (CH), 182.0 (C). Structure of compound **3d** was further confirmed by HMBC and HSQC experiments.

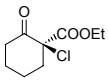
Synthesis of 5,5,7-tribromo-5*H*-quinolin-8-one (6): A 9/1 glacial acetic acid/distilled water solution (40 mL) was added to 8-hydroxyquinoline (290 mg, 2 mmol, 1 equiv). The yellow solution was cooled to 0°C in an ice bath and bromine (1.056 g, 6.6 mmol, 3.3 equiv) was added dropwise over 10 minutes. After 1 hour stirring, ice was added to the reaction causing the formation of a precipitate. The solution was carefully extracted with DCM (3 x 30 mL) and the organic layer was washed with a saturated solution of $NaHCO_3$ (4 x 30 mL), brine (1 x 30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield product **6** as a pale yellow solid. ^{1}H NMR ($CDCl_3$): δ = 7.69 (dd, 1H, J = 4.4, 8.4), 7.99 (s, 1H), 8.49 (dd, 1H, J = 1.6, 8.4), 8.87 (dd, 1H, J = 1.6, 4.4); ^{13}C NMR ($CDCl_3$): δ = 46.9 (C), 121.8 (C), 128.1 (CH), 139.5 (C), 139.8 (CH), 141.6 (C), 147.4 (CH), 152.4 (CH), 174.7 (C). Structure of compound **6** was further confirmed by HMBC and HSQC experiments.

General Procedure for the Organocatalytic Asymmetric α-Halogenation of 1,3-Dicarbonyl Compounds. All the reactions were carried out in undistilled solvent without any precautions to exclude water. In an ordinary test tube equipped with a magnetic stirring bar, benzoylquinine BQ **4a** or benzoylquinidine BQd **4b** (0.02 mmol) was dissolved in 1.6 mL of toluene. After addition of the 1,3-dicarbonyl compound (0.4 mmol), the tube was closed with a rubber stopper and the mixture was stirred at the indicated temperature for 10 minutes. Then the freshly prepared halogenating agent **3d** or **6** (0.48 mmol) and $NaHCO_3$ (0.4 mmol) were added and stirring was continued until GC and TLC analysis showed disappearance of the 1,3-dicarbonyl compound. Then the crude reaction mixture was diluted with hexane (5 mL) and filtered by suction. The organic phase was concentrated under reduced pressure and then flushed through a plug of silica, using hexane/Et_2O 9/1 as the eluent. Solvent was removed in

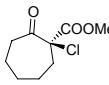
vacuo, and the residue was dissolved in an hexane/Et_2O solution. After precipitation, the solid was filtered away and the organic phase concentrated to yield the pure halogenated product.



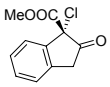
(*S*)-1-Chloro-2-oxo-cyclopentanecarboxylic acid ethyl ester (2a)[4] **–** The reaction was carried out at –40 °C for 24 h using 5 mol% of benzoylquinidine (BQd) **4b** following the general procedure. The title compound was isolated as a colourless oil in 98% yield. The ee was determined by GC analysis using a RT-BetaDEX-sm chiral column (T_1 = 50 °C; T_2 = 210 °C, rate = 4 °C/min.; τ_R = 27.4 min, τ_S = 27.6 min). $[\alpha]^{rt}_D$= -9.3 (*c* = 0.9, $CHCl_3$, 95% ee), lit.[4] $[\alpha]^{rt}_D$= -15.6, (*S*)-**2a** (*c* = 1.2, $CHCl_3$, 72% ee). ESI-MS *m/z* 191 $[M+H]^+$, 213 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ = 1.30 (t, *J* = 7.1, 3H), 2.13 (m, 2H), 2.40 (m, 2H), 2.56 (m, 1H), 2.75 (m, 1H), 4.27 (q, *J* = 7.1, 2H); ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3), 19.1 (CH_2), 35.3 (CH_2), 38.4 (CH_2), 63.1 (CH_2), 69.6 (C), 167.2 (C), 206.1 (C).



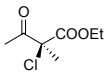
(*S*)-1-Chloro-2-oxo-cyclohexanecarboxylic acid ethyl ester (2b)[4] **–** The reaction was carried out at –40 °C for 40 h using 15 mol% of benzoylquinidine (BQd) **4b** following the general procedure. The title compound was isolated as a colourless oil in 83% yield. The ee was determined by GC analysis using a RT-BetaDEX-sm chiral column (isotherm 115 °C; τ_R = 36.4 min, τ_S = 37.1 min). $[\alpha]^{rt}_D$= -22.8 (*c* = 2.0, $CHCl_3$, 96% ee), lit.[4] $[\alpha]^{rt}_D$= -10.9, (*S*)-**2b** (*c* = 1.2, $CHCl_3$, 76% ee). ESI-MS *m/z* 205 $[M+H]^+$, 227 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, *J* = 7.1, 3H), 1.74 (m, 2H), 1.91 (m, 2H), 2.14 (m, 1H), 2.43 (m, 1H), 2.83 (m, 2H), 4.30 (q, *J* = 7.1, 2H); ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_3), 22.1 (CH_2), 26.7 (CH_2), 38.8 (CH_2), 39.6 (CH_2), 62.9 (CH_2), 73.5 (C), 167.2 (C), 199.6 (C).



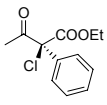
(S)-1-Chloro-2-oxo-cycloheptanecarboxylic acid methyl ester (2c) – The reaction was carried out following the general procedure at –40 °C for 52 h using 15 mol% of benzoylquinidine (BQd) **4b**. The title compound was isolated after filtration and flash chromatography (hexane - hexane/Et_2O 9/1) as a colourless oil in 48% yield. The ee was determined by GC analysis using a RT-BetaDEX-sm chiral column (isotherm 130 °C; τ_R = 24.6 min, τ_S = 25.2 min). $[\alpha]^{rt}_D$= -13.2 (*c* = 1.1, $CHCl_3$, 90% ee). ESI-MS *m/z* 205 $[M+H]^+$, 227 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): 1.47-1.90 (m, 6H), 2.26-2.34 (m, 1H), 2.41-2.49 (m, 1H), 2.62-2.70 (m, 1H), 2.80-2.87 (m, 1H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 24.6 (CH_2), 25.2 (CH_2), 28.9 (CH_2), 37.6 (CH_2), 40.5 (CH_2), 53.5 (CH_3), 75.9 (C), 168.5 (C), 202.3 (C).



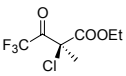
(S)-methyl 1-chloro-2-oxo-2,3-dihydro-1H-indene-1-carboxylate (2d) – The reaction was carried out at –78 °C for 36 h using 5 mol% of benzoylquinidine (BQd) **4b** following the general procedure. The title compound was isolated as a pale yellow oil in 80% yield. The ee was determined by HPLC analysis using a Chiralpak AS-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 230 nm; τ_R = 9.5 min; τ_S = 10.2 min). $[\alpha]^{rt}_D$= +12.0 (*c* = 0.25, $CHCl_3$, 93% ee). ESI-MS *m/z* 225 $[M+H]^+$, 247 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ = 3.74 (d, AB system, *J* = 22.4, 1H), 3.77 (s, 3H), 3.87 (d, AB system, *J* = 22.4, 1H), 7.35-7.47 (m, 3H), 7.50-7.55 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 41.1 (CH_2), 54.0 (CH_3), 70.3 (C), 125.2 (CH), 125.5 (CH), 128.8 (CH), 130.7 (CH), 136.5 (C), 138.6 (C), 166.5 (C), 203.1 (C).



(*S*)-2-Chloro-2-methyl-3-oxo-butyric acid ethyl ester (2e)[4] **–** The reaction was carried out following the general procedure at room temperature for 48 h using 20 mol% of benzoylquinidine (BQd) **4b**. The title compound was isolated after filtration and flash chromatography (hexane - hexane/Et_2O 9/1) as a colourless oil in 75% yield. The ee was determined by GC analysis using a RT-BetaDEX-sm chiral column (isotherm 75 °C; τ_S = 22.4 min; τ_R = 22.7 min). $[\alpha]^{rt}_D$= +8.9 (*c* = 1.2, $CHCl_3$, 76% ee), lit.[4] $[\alpha]^{rt}_D$= +3.6, (*S*)-**2e** (*c* = 1.0, $CHCl_3$, 77% ee). ESI-MS *m/z* 179 $[M+H]^+$, 201 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, *J* = 7.2, 3H), 1.81 (s, 3H), 2.36 (s, 3H), 4.27 (q, *J* = 7.2, 2H); ^{13}C NMR ($CDCl_3$): δ = 13.8 (CH_3), 24.2 (CH_3) 25.2 (CH_3), 63.0 (CH_2), 70.7 (C), 168.0 (C), 198.8 (C).



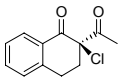
(S)-2-Chloro-3-oxo-2-phenyl-butyric acid ethyl ester (2f) – The reaction was carried out following the general procedure at -10 °C for 36 h using 15 mol% of benzoylquinidine (BQd) **4b**. The title compound was isolated as a pale yellow oil in 99% yield. The ee was determined by HPLC analysis using a Chiralpak AD-H column (98/2 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 254 nm; τ_R = 8.6 min; τ_S = 8.9 min). $[\alpha]^{rt}_D$= +21.4° (*c* = 1.0, $CHCl_3$, 80% ee). ESI-MS *m/z* 241 $[M+H]^+$, 263 $[M+Na]^+$. ^{1}H NMR (600 MHz; $CDCl_3$): δ = 1.30 (t, *J* = 7.2, 3H), 2.33 (s, 3H), 4.31 (q, *J* = 7.2, 2H), 7.35-7.42 (m, 3H), 7.48-7.53 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.8 (CH_3), 25.8 (CH_3), 63.3 (CH_2), 77.3 (C), 127.7 (CH, 2C), 128.4 (CH, 2C), 129.1 (CH), 133.9 (C), 170.0 (C), 197.5 (C).



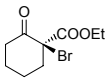
(*S*)-2-Chloro-4,4,4-trifluoro-2-methyl-3-oxo-butyric acid ethyl ester (2g) – The reaction was carried out in TBME as the solvent at –78 °C for 52 h using 15 mol% of

benzoylquinidine (BQd) **4b**. The title compound was isolated after filtration using pentane as solvent and flash chromatography (pentane - pentane/Et_2O 9/1) as a colourless oil in 44% yield (be careful, the product is volatile). The ee was determined by GC analysis using a RT-BetaDEX-sm chiral column (T_1 = 50 °C; T_2 = 210 °C, rate = 4 °C/min.; τ_S = 9.7 min; τ_R = 9.8 min). $[\alpha]^{rt}_D$= +9.8 (*c* = 1.47, $CHCl_3$, 89% ee). ESI-MS *m/z* 233 $[M+H]^+$, 255 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ = 1.30 (t, *J* = 7.2, 3H), 1.93 (s, 3H), 4.33 (q, *J* = 7.2, 2H); ^{13}C NMR ($CDCl_3$): δ = 13.6 (CH_3), 23.8 (CH_3), 64.0 (CH_2), 65.8 (C), 118.9 (q, CF, *J* = 290 Hz), 165.9 (C).

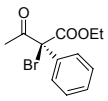
(*R*)-2-Acetyl-2-chloro-cyclopentanone (2h) – The reaction was carried out at –78 °C for 30 h using 5 mol% of benzoylquinidine (BQd) **4b** without $NaHCO_3$; the use of $NaHCO_3$ was avoided because no beneficial effect was observed under those conditions. The title compound was isolated as a colourless oil in 90% yield. The ee was determined by GC analysis using a RT-BetaDEX-sm chiral column (T_1 = 50 °C; T_2 = 210 °C, rate = 4 °C/min.; τ_S = 20.4 min; τ_R = 21.0 min). $[\alpha]^{rt}_D$= +5.6 (*c* = 0.25, $CHCl_3$, 51% ee). ESI-MS *m/z* 161 $[M+H]^+$, 183 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ = 2.02-2.15 (m, 2H), 2.17-2.27 (m, 1H), 2.30-2.38 (m, 1H), 2.48 (s, 3H), 2.48-2.58 (m, 1H), 2.78-2.86 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 18.5 (CH_2), 27.1 (CH_3), 35.9 (CH_2), 36.3 (CH_2), 73.8 (C), 201.6 (C), 207.8 (C).



(*R*)-2-Acetyl-2-chloro-3,4-dihydro-2*H*-naphthalen-1-one (2i) – The reaction was carried out at –40 °C for 48 h using 15 mol% of benzoylquinidine (BQd) **4b**; the use of $NaHCO_3$ was avoided because a lower enantiomeric excess was observed under those conditions. The title compound was isolated as a colourless oil in 74% yield. The ee was determined by HPLC analysis using a Chiralpak AS-H column (9/1hexane/*i*-PrOH; flow rate 0.75 mL/min; λ=254 nm; τ_R = 8.7 min; τ_S = 9.2 min). $[\alpha]^{rt}_D$ = +29.9° (*c* = 0.65, $CHCl_3$, 59% ee). ESI-MS *m/z* 223 $[M+H]^+$, 245 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ = 2.37-2.44 (m, 1H), 2.52 (s, 3H), 2.87-2.95 (m, 1H), 3.00-3.08 (m, 1H), 3.22-3.32 (m, 1H), 7.25-7.29 (m, 1H), 7.33-7.38 (m, 1H), 7.50-7.56 (m, 1H), 8.04-8.08 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 25.5 (CH_2), 27.6 (CH_3), 33.4 (CH_2), 73.7 (C), 127.2 (CH), 128.7 (CH), 128.8 (CH), 130.0 (C), 134.5 (CH), 142.8 (C), 189.8 (C), 201.8 (C).



(*S*)-1-Bromo-2-oxo-cyclohexanecarboxylic acid ethyl ester (7b)[4] **–** The reaction was carried out at –78 °C for 30 h using 10 mol% of benzoylquinidine (BQd) **4b** and freshly prepared brominating agent **6**, without using $NaHCO_3$. The title compound was isolated after careful filtration and flash chromatography (hexane - hexane/Et_2O 9/1) as a colourless oil in 82% yield. The ee was determined by HPLC analysis using a Chiralpak AD-H column (95/5 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ=214 nm; τ_S = 7.3 min; τ_R = 7.6 min). $[\alpha]^{rt}_D$ = -50.2 (*c* = 0.87, $CHCl_3$, 83% ee). ESI-MS *m/z* 249 $[M+H]^+$, 271 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ = 1.30 (t, *J* = 7.2, 3H), 1.69-1.97 (m, 4H), 2.18-2.26 (m, 1H), 2.42-2.50 (m, 1H), 2.83-2.95 (m, 2H), 4.29 (q, *J* = 7.2, 2H); ^{13}C NMR ($CDCl_3$): δ = 13.8 (CH_3), 23.1 (CH_2), 26.7 (CH_2), 38.8 (CH_2), 40.5 (CH_2), 62.9 (CH_2), 67.5 (C), 167.5 (C), 199.1 (C).



(S)-2-Bromo-3-oxo-2-phenyl-butyric acid ethyl ester (7f) – The reaction was carried out at –78 °C for 30 h using 15 mol% of benzoylquinidine (BQd) **4b** and freshly prepared brominating agent **6**, without using $NaHCO_3$. The title compound was isolated after careful filtration and flash chromatography (hexane - hexane/Et_2O 95/5) as a colourless oil in 67% yield. The ee was determined by HPLC analysis using a Chiralpak AS-H column (99/1 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ= 254 nm; τ_S = 9.8 min; τ_R = 10.3 min). $[\alpha]^{rt}_D$= -11.6 (*c* = 1.12, $CHCl_3$, 84% ee). ESI-MS *m/z* 285 $[M+H]^+$, 307 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, *J* = 7.2, 3H), 2.40 (s, 3H), 4.33 (q, *J* = 7.2, 2H), 7.36-7.40 (m, 3H), 7.48-7.53 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 13.8 (CH_3), 26.4 (CH_3), 63.4 (CH_2), 71.2 (C), 128.4 (CH,2C), 128.7 (CH,2C), 129.1 (CH), 134.2 (C), 167.3 (C), 196.7 (C).

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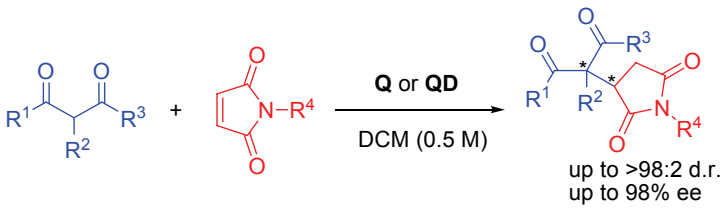
4. Organocatalytic Asymmetric Conjugate Addition of 1,3-Dicarbonyl Compounds to Maleimides

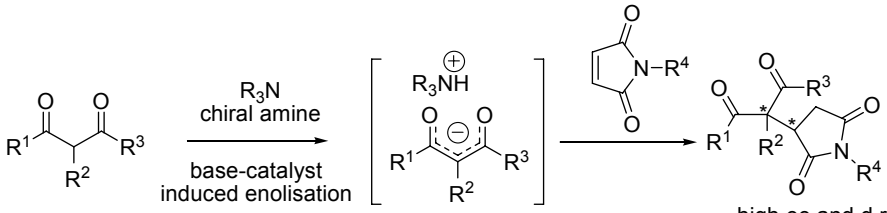


Nature, our teacher! Natural cinchona alkaloids (quinine **Q** and quinidine **QD**) serve as efficient bifunctional organocatalysts for the first asymmetric conjugate addition of 1,3-dicarbonyl compounds to maleimides with very high selectivity (up to >98:2 d.r.; up to 98% ee). The asymmetric one-step construction of highly functionalized products with two adjacent stereogenic carbon atoms, one of which is quaternary by all-carbon substitution, is achieved from commercially available precursors and with a simple protocol.

The enantioselective construction of all-carbon quaternary stereogenic centers by efficient asymmetric methods represents a great synthetic challenge as creation of such complex fragments is complicated by steric factors.[1] Currently, despite the substantial progress achieved in the last few years, only a few catalytic asymmetric C-C bond forming strategies have proven to be useful to forge quaternary carbons.[2] Among them, the catalytic conjugate addition[3] of prochiral trisubstituted carbon nucleophiles to β-substituted Michael acceptors constitutes an effective approach for the asymmetric construction of highly functionalized products having adjacent quaternary and tertiary carbon atoms. The stereocontrolled, one-step synthesis of such important congested motifs from simple precursors represents a formidable synthetic challenge as the catalyst must provide high levels of stereoselectivity in a sterically demanding C-C bond forming process.[4] To date, the acceptors employed in

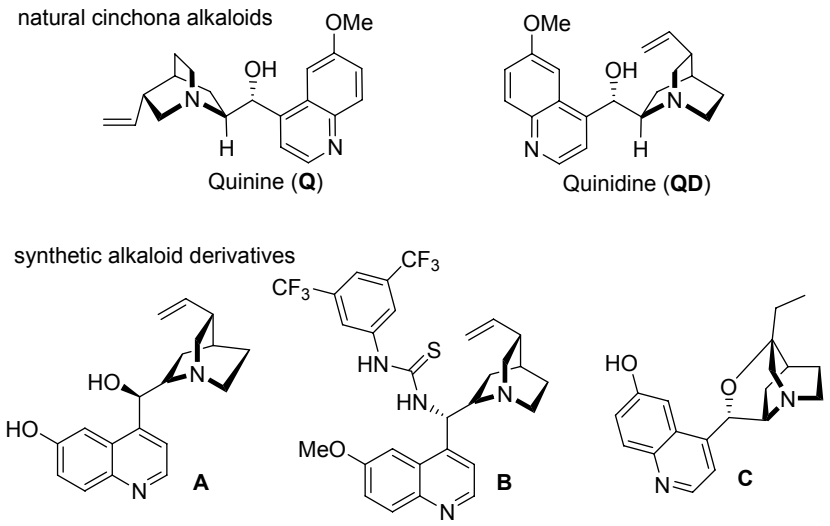
this type of powerful tactic have been restricted to enones,[5] nitroalkenes[6] and unsaturated imides.[7] Expanding the scope of such an efficient strategy to other classes of Michael acceptors would represent an useful and challenging objective.

We present the development of the first asymmetric direct conjugate addition of 1,3-dicarbonyl compounds to maleimides promoted by natural cinchona alkaloids acting as chiral base-catalysts,[8] which affords highly functionalized products with two consecutive stereogenic carbon atoms, one of which is quaternary by all-carbon substitution [Eq. (1)]. This organocatalytic[9] approach affords high levels of both enantio- (up to 98% ee) and diastereo-selectivity (d.r. up to >98:2) with both cyclic and acyclic β-keto esters and with cyclic β-diketones. Furthermore, the strategy is based on an operationally trivial procedure that employs unmodified, cheap and commercially available starting materials and catalysts.



(1)

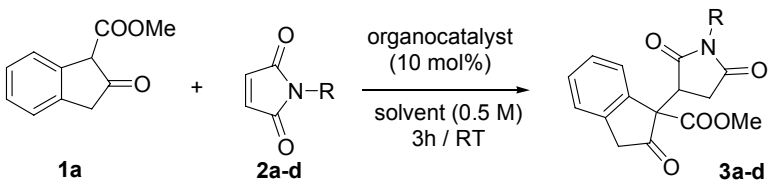
Asymmetric conjugate additions of carbon nucleophiles to maleimides provide a practical access to synthetically and biologically important chiral α-substituted succinimides.[10] Thus, it is surprising that, to our knowledge, just one effective asymmetric strategy has been described to date.[11] The feasibility of our organocatalytic asymmetric approach was first tested by mixing methyl-2-oxo-1-indanecarboxylate **1a** and maleimide **2a** in dichloromethane as the solvent (DCM, 0.5 M) in the presence of a catalytic amount (10 mol%) of some cinchona alkaloid derivatives (Figure 1); representative results of the extensive screen of reaction conditions are listed in Table 1. Natural cinchona alkaloid quinine **Q** proved to be the most promising catalyst, affording the 1,4-adduct with interesting diastereo- and enantioselectivity (entry 2). Synthetic cinchona alkaloids derivatives **A** and **B**, that have proven to be broadly effective bifunctional organocatalysts for several asymmetric C-C bond forming reactions,[12] afforded poor results (entries 3 and 4). The rigid phenolic quinidine derivative β-isocupreidine **C**[13] was able to promote the conjugate addition with satisfactory selectivity (entry 5), but the results obtained by performing the reaction at –20°C indicated a significant difference between **Q** and **C** in terms of catalytic activity (entries 6-9).



Scheme 1: Alkaloid catalysts and 1,3-dicarbonyl compounds **1b–1i** used in this study.

Next, we identified the nature of the maleimidic *N*-substituent as a critical parameter for the stereochemical outcome of the process (entries 8-11). The presence of a benzyl substituent had a dramatic impact on enantioselectivity and, more importantly, on diastereoselectivity: performing the quinine-catalyzed reaction at -20°C in DCM, the product was isolated after 24 h in quantitative yield, with considerable preference for one of the two possible diastereomers (d.r. 94/6) and with high enantioselectivity (92% ee, entry 11). Importantly, the use of the "pseudoenantiomeric" quinidine **QD** allowed access to the opposite antipode of the 1,4-adduct with similar selectivity (entry 12). Further optimization of the reaction conditions revealed that apolar solvents engendered optimal stereocontrol (entries 11-14); DCM was selected as the solvent of choice for its ability to impart higher reactivity. Employing hydrogen-bond-accepting solvents led to a drastic decrease in stereoselectivity (entries 15-16). Noteworthy, the result obtained by using benzoylquinine as the catalyst (**BQ**, entry 17) clearly demonstrated that the presence of the free hydroxyl group on **Q** is essential for imparting high levels of reactivity and selectivity. This experimental evidence, together with preliminary kinetic studies establishing a first-order dependence on the catalyst, the nucleophile and the electrophile for the conjugate addition (see Experimental Part for details), is consistent with an acid-base bifunctional catalysis mode of quinine. Importantly, although the double activation ability of natural cinchona alkaloids was established 25 years ago by the seminal studies of Wynberg and Hiemstra,[14] their capability to catalyze stereoselective conjugate additions with very high fidelity (ee > 90%) has been disclosed here for the first time.[15]

Table 1: Screening of reaction conditions for the organocatalytic asymmetric conjugate addition of **1a** to maleimides **2**.[a]



1a **2a-d** **3a-d**

Entry	Cat.	R	Solv.	Conv.[b]	**3**	d.r.[b]	*ee* [%][c]
1	-	H (**2a**)	DCM	0	**a**	-	-
2	**Q**	H (**2a**)	DCM	>95%	**a**	74:26	69/28
3	**A**	H (**2a**)	DCM	30%	**a**	77:23	14/17
4	**B**	H (**2a**)	DCM	65%	**a**	75:25	33/34[d]
5	**C**	H (**2a**)	DCM	75%	**a**	65:35	62/45
6	**Q**[e]	H (**2a**)	DCM	75%	**a**	82:18	81/70
7	**C**[e]	H (**2a**)	DCM	25%	**a**	75:25	74/-
8	**Q**[e]	Ph (**2b**)	DCM	>95%	**b**	87:13	63/40
9	**C**[e]	Ph (**2b**)	DCM	13%	**b**	70:30	-/-
10	**Q**[e]	*t*Bu(**2c**)	DCM	15%	**c**	95:5	-/-
11	**Q**[e]	Bn (**2d**)	DCM	>95% (97)[f]	**d**	94:6	92/5
12	**QD**[e]	Bn (**2d**)	DCM	>95% (95)[f]	**d**	94:6	87/4[d]
13	**Q**[e]	Bn (**2d**)	Toluene	80%	**d**	95:5	92/6
14	**Q**[e]	Bn (**2d**)	THF	56%	**d**	95:5	90/5
15	**Q**[g]	Bn (**2d**)	CH_3CN	>95%	**d**	85:15	66/0
16	**Q**[g]	Bn (**2d**)	MeOH	>95%	**d**	44:56	24/0
17	**BQ**[h]	Bn (**2d**)	DCM	45%	**d**	81:19	5/12

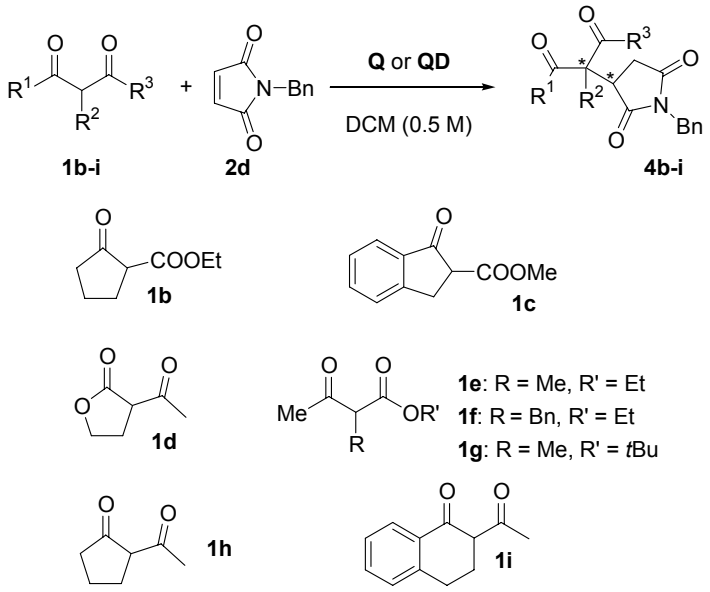
[a] Experimental conditions (0.2 mmol scale): open-air reactions run in undistilled solvent (0.5 M) at room temperature using a 1:1.2 ratio of **1a** to **2** and 10 mol% of the catalyst. [b] Conversion and d.r. determined by ^{1}H NMR spectroscopy of the crude mixture. [c] Determined by HPLC analyses on commercially available chiral stationary phases; values for both diastereomers given. [d] The opposite enantiomer was obtained. [e] 24 h reaction time, -20°C reaction temperature. [f] Number in parenthesis indicates yield of the isolated product **3d**. [g] 16 h reaction time, -20°C reaction temperature. [h] **BQ** = benzoylquinine.

We then examined the generality of this new organocatalytic asymmetric strategy under the optimized reaction conditions: experiments probing the scope of the 1,3-dicarbonyl substrates are summarized in Table 2. Importantly, both enantiomers of the 1,4-adducts were efficiently synthesized with high yield and selectivity by appropriate selection of the catalysts (**Q** or **QD**). Cyclic β-ketoesters **1b-d** were all converted into the corresponding 1,4-adducts in good yields and with very high levels of both diastereo- and enantioselectivity (entries 1-6). The protocol also proved to be effective for acyclic β-ketoesters, affording the expected products with high selectivity, although a decreased reactivity was observed (entries 7-8). Interestingly, we found a significant effect of the size of the ester group on the

stereoselctivity: reaction of acyclic *tert*-butyl ketoester **1g** occurred in a highly enantio- and diasteroselective fashion even at room temperature (92% ee, 92/8 d.r., entry 9).[16] Outstanding results were achieved with β-diketones (entries 9-12), a particularly challenging class of substrates for which, to our knowledge, just two examples of effective asymmetric organocatalytic conjugate addition have been reported.[17]

It is noteworthy that, being the conjugate addition products **4** generally solid substances, it is possible to obtain a single stereoisomer in essentially enantiopure form after a single crystallization, as demonstrated for adducts **4c** and **4d** (entries 4 and 6).

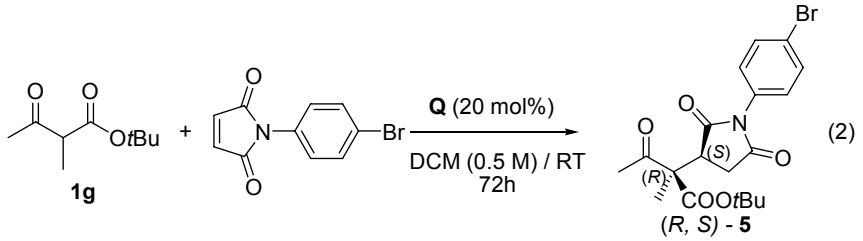
Table 2: Highly stereoselective conjugate addition of 1,3-dicarbonyl compounds catalyzed by natural cinchona alkaloids.[a]



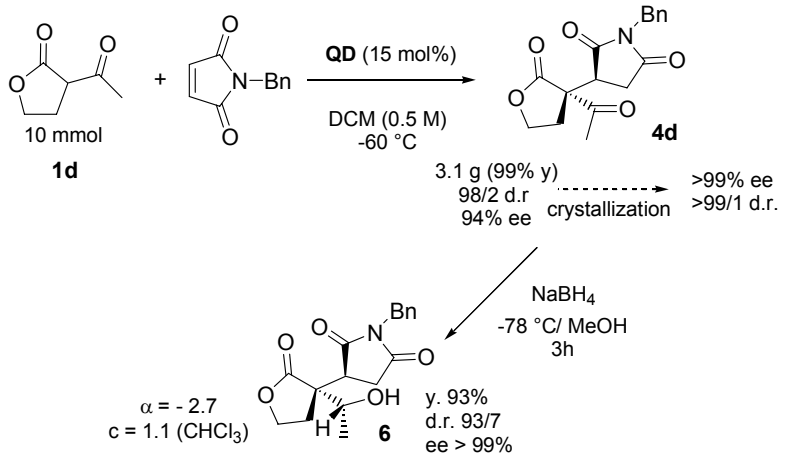
Entry	**4**	Cat.[mol%][b]	*T*[°C]	t[h]	Yield [%][c]	d.r.[d]	*ee* [%][e]
1	**b**	**Q** (10)	-30	24	99	84:16	94
2	**b**	**QD** (10)	-60	40	99	87:13	98
3	**c**	**Q** (10)	-60	38	98	91:9	94
4	**c**	**QD** (10)	-60	38	99	90:10	95 (>99)[g]
5	**d**	**Q** (15)	-60	40	99	>98:2	89
6	**d**	**QD** (15)	-60	40	91	>98:2	93 (>99)[g]
7	**e**	**QD** (20)	-15	50	52(55)[f]	93:7	85
8	**f**	**QD** (20)	-15	88	63(65)[f]	77:23	85
9	**g**	**Q** (20)	RT	72	75(78)[f]	92:8	92
10	**h**	**Q** (15)	-30	24	72(80)[f]	92:8	82
11	**h**	**QD** (15)	-60	40	99	92:8	91
12	**i**	**Q** (20)	-15	48	55(58)[f]	95:5	82
13	**i**	**QD** (20)	-30	66	72 (75)[f]	95:5	84

[a] Experimental conditions (0.2 mmol scale): open-air reactions run in undistilled DCM (0.5 M) using a 1:1.2 ratio of **1** to **2d**. [b] Quinine **Q** and quinidine **QD** were used as the catalyst, affording the opposite antipodes of the same diastereomer. [c] Yield of isolated products **4**. [d] Determined by ^{1}H NMR spectroscopy of the crude mixture. [e] Determined by HPLC analyses on commercially available chiral stationary phases; values for the major diastereomer given. For the ee's of minor diastereomers, see Experimental Part. [f] Number in parenthesis indicates reaction conversion, as determined by ^{1}H NMR analysis. [g] After a single crystallization.

The absolute configuration of compound **5**, generated by quinine-catalyzed addition of **1g** to *N*-4-bromo-phenyl maleimide [Eq. (2)], was assigned by X-ray crystallographic analysis.[18] The relative configuration of **4d** was unequivocally determined by X-ray crystallographic analysis[19] whereas the relative configurations of **4b** and **4h** were assigned by extensive NMR NOE analysis (see Experimental Part for details).



The synthetic utility of the presented organocatalytic approach was evaluated by a gram-scale experiment (10 mmol), leading to the preparation of **4d** in quantitative yield (Scheme 1). Single crystallization from a mixture of EtOH/Et_2O afforded the optically pure product. Subsequent highly stereo- and chemoselective reduction of the keto moiety allowed access to compound (-)-**6** having three consecutive stereogenic centers with defined absolute stereochemistry.[20]



Scheme 1: Stereo- and chemoselective reduction of **4d.**

In summary, we have developed an operationally simple protocol that employs unmodified and commercially available materials and catalysts for the first asymmetric organocatalytic conjugate addition of 1,3-dicarbonyl compounds to maleimides with the highest enantioselectivity reported to date in this class of Michael acceptors. Natural cinchona alkaloids proved to be highly efficient catalysts affording the one-step construction of functionalized products with two adjacent stereogenic carbon atoms with very high diastereo- and enantioselectivity.

Dr. Andrea Mazzanti is gratefully acknowledged for useful discussion and for extensive NMR studies on the compounds.

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[16] For a similar effect of the size of the ester group on the selectivity of organocatalytic asymmetric transformations, see Ref. 2a and 8a.

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[18] Compound **5**, obtained in 65% yield, 85% ee and 96/4 d.r., was slowly crystallized from a mixture of hexane/Et_2O to give fine colourless needles of a single diastereomer, with the configuration as shown in [Eq. (2)]. The very same crystal used for X-ray crystallography was analyzed by chiral HPLC confirming the presence of the major enantiomer. CCDC-296418 contains the crystallographic data for **5**.

[19] CCDC-605040 contains the supplementary crystallographic data for compound **4d**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif .

[20] The relative configuration of **6** was assigned by extensive NMR NOE analysis, see Experimental Part for details.

4.EP Experimental Part

Contents

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. NMR NOE experiments were recorded at 600 MHz. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$). Coupling constants are given in Hz. Carbon types were determined from DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh) according to the method of Still.[1] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Mass spectra were obtained from the Department of Organic Chemistry *"A. Mangini"* Mass Spectroscopy facility. X-ray structure analysis was carried out at the Department of Organic Chemistry *"A. Mangini"* X-ray Crystallography facility. Optical rotations are reported as follows: $[\alpha]^{rt}_{D}$ (*c* in g per 100 mL, solvent).

Materials. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[2]

β-keto esters **1a-b** and **1d-f** and β-diketones **1h-i** were purchased from Aldrich or Lancaster and used as received. β-keto esters **1c**[3] and **1g**[4] were prepared following the literature procedures.

Maleimides **2a-d** were purchased from Aldrich and used as received.

Natural cinchona alkaloids quinine **Q** and quinidine **QD** were purchased from Aldrich and used as received. Benzoylquinine (**BQ**) was prepared according to standard literature procedures (quinine / Et_3N / benzoylchloride /DCM/ overnight, RT).[5] Bifunctional organocatalysts **A**,[6] **B**[7] and **C**[8] were prepared following the literature procedures.

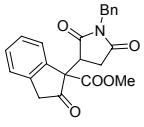
Determination of Enantiomeric Purity. Chiral HPLC analysis was performed on an Agilent 1100-series instrumentation. Daicel Chiralpak AD-H or AS-H columns and Chiralcel OD-H with i-PrOH/hexane as the eluent were used.

HPLC traces were compared to racemic samples prepared with equimolar amount of quinine and quinidine or by using Et_3N as the catalyst.

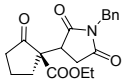
Experimental Procedures.

General Procedure for the Natural Cinchona Alkaloids-catalyzed Asymmetric Conjugate Addition of 1,3-Dicarbonyl Compounds to *N*-Benzylmaleimide. All the reactions were carried out in undistilled solvent without any precautions to exclude water. In an ordinary test tube equipped with a magnetic stirring bar, quinine **Q** or quinidine **QD** (0.02 mmol) was dissolved in 0.4 mL of DCM. After addition of the 1,3-dicarbonyl compound (0.2 mmol), the tube was closed with a rubber stopper and the mixture

was stirred at the indicated temperature for 10 minutes. Then *N*-benzylmaleimide **2d** (0.24 mmol) was added in one portion and stirring was continued until GC and TLC analysis showed disappearance of the 1,3-dicarbonyl compound. Then the crude reaction mixture was diluted with hexane (2 mL) and flushed through a plug of silica, using hexane/Et_2O 1/1 as the eluent. Solvent was removed *in vacuo*, and the residue was purified by flash chromatography (FC) to yield the desired 1,4-adduct.

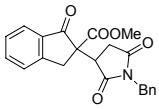


3d – The reaction was carried out at –20°C for 24 h using 10 mol% of **Q** to furnish the crude product [dr = 94:6, determined by integration of one set of ^{1}H NMR signal (δ_{major} 2.63 ppm, δ_{minor} 2.66 ppm - dd)]. The title compound was isolated by column chromatography (hexane/AcOEt = 75/25) as a white solid (melting point: 57-62 °C) in 97% yield (dr = 95:5, confirmed by relative areas of HPLC analysis) and 92% ee (major diastereomer) [HPLC analysis on a Chiralpak AD-H column: 75/25 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (92% ee): τ_{major} = 15.6 min, τ_{minor} = 18.2 min; minor diastereomer (5% ee): τ_{major} = 22.5 min, τ_{minor} = 24.6 min;]. $[\alpha]^{rt}_D$= - 9.6 (*c* = 1.0, $CHCl_3$, 92% ee). HRMS: *m/z* calcd for $C_{22}H_{19}NO_5$: 377.12632; found: 377.12601. ^{1}H NMR ($CDCl_3$): δ = 2.54 (dd, *J* = 6.0, 18.0, 1H), 2.92 (dd, *J* = 9.2, 18.0, 1H), 3.59 (AB, *J* = 22.8, 2H), 3.73 (s, 3H), 3.98 (dd, *J* = 6.0, 9.2, 1H), 4.59 (AB, *J* = 14.0, 2H), 7.08-7.38 (m, 9H); ^{13}C NMR ($CDCl_3$): δ = 32.1 (CH_2), 42.5 (CH_2), 43.1 (CH_2), 44.6(CH), 53.4 (CH_3), 64.8 (C), 124.5 (CH), 125.1 (CH), 127.9 (CH), 128.3 (CH), 128.6 (CH, 2C), 128.7 (CH, 2C), 129.3 (CH), 135.3 (C), 137.1 (C), 137.5 (C), 168.3 (C), 174.7 (C), 175.9 (C), 209.6 (C).

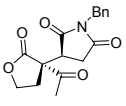


4b – The reaction was carried out at –60°C for 40 h using 10 mol% of **QD** to furnish the crude product [dr = 87:13, determined by integration of one set of ^{1}H NMR signal (δ_{major} 4.20-4.25 ppm, δ_{minor} 4.10-4.14 ppm)]. The title compound was isolated by column chromatography (hexane/AcOEt = 8/2) as a colourless foam in 99% yield (dr = 87:13, confirmed by relative areas of HPLC analysis) and 98% ee (major diastereomer) [HPLC analysis on a Chiralpak AD-H column: 85/15 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214; (R*,S*)-major diastereomer (98% ee): τ_{minor} = 14.4 min, τ_{major} = 16.2 min; (R*,R*)-minor diastereomer (24% ee): τ_{minor} = 18.0 min, τ_{major} = 19.1 min]. $[\alpha]^{rt}_D$= - 11.8 (*c* = 1.04, $CHCl_3$, 98% ee). HRMS: *m/z* calcd for $C_{19}H_{21}NO_5$: 343.14197; found 343.14184. ^{1}H NMR ($CDCl_3$): δ = 1.27 (t, *J* = 7.2, 3H), 1.97-2.07 (m, 2H), 2.14-2.24 (m, 1H), 2.38-2.56 (m, 3H), 2.68 (dd, *J* = 6.0, 18.0, 1H), 2.87 (dd, *J* = 9.2, 18.0, 1H), 3.50 (dd, *J* = 6.0, 9.2, 1H), 4.22 (q, *J* = 7.2, 2H), 4.62 (AB, *J* = 14.2, 2H), 7.24-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_3), 19.1 (CH_2), 31.6 (CH_2), 32.6 (CH_2), 37.9 (CH_2), 42.1 (CH), 42.2 (CH_2), 60.6 (C), 62.0 (CH_2), 127.7 (CH), 128.3 (CH, 2C), 128.5 (CH, 2C), 135.4 (C), 169.5 (C), 175.0 (C), 177.0 (C), 213.5 (C).

The relative configuration (R*, S*) of the major diastereomer of (-)-4b was determined by extensive NMR NOE studies.



4c – The reaction was carried out at –60°C for 38 h using 10 mol% of **Q** to furnish the crude product [dr = 91:9, determined by integration of one set of ^{1}H NMR signal (δ_{major} 3.75 ppm, δ_{minor} 3.57 ppm - s)]. The title compound was isolated by column chromatography (hexane/AcOEt = 7/3) as a white solid (melting point: 57-60 °C) in 98% yield (dr = 91:9, confirmed by relative areas of HPLC analysis) and 94% ee (major diastereomer) [HPLC analysis on a Chiralpak AD-H column: 75/25 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254; major diastereomer (94% ee): τ_{major} = 19.9 min, τ_{minor} = 31.0 min; minor diastereomer (27% ee): τ_{major} = 23.2 min, τ_{minor} = 28.3 min]. $[\alpha]^{rt}_D$= - 47.1 (*c* = 1.87, $CHCl_3$, 94% ee). HRMS: *m/z* calcd for $C_{19}H_{21}NO_5$: 377.12632; found: 377.12659. ^{1}H NMR ($CDCl_3$): δ = 2.38 (dd, *J* = 6.0, 18.4, 1H), 2.88 (dd, *J* = 9.2, 18.4, 1H), 3.43 (AB, *J* = 17.6, 2H), 3.75 (s, 3H), 4.06 (dd, *J* = 6.0, 9.2, 1H), 4.60 (AB, *J* = 14.4, 2H), 7.25-7.30 (m, 5H), 7.37-7.41 (m, 1H), 7.45-7.48 (m, 1H), 7.61-7.66 (m, 1H), 7.69-7.72 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 31.4 (CH_2), 34.0 (CH_2), 42.5 (CH_2), 43.1 (CH), 53.4 (CH_3), 60.5 (C), 124.9 (CH), 126.4 (CH), 127.9 (CH), 128.1 (CH), 128.6 (CH, 4C), 134.8 (C), 135.4 (C), 136.1 (CH), 152.8 (C), 169.2 (C), 174.8 (C), 176.6 (C), 199.5 (C).

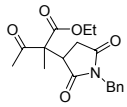


4d – The reaction was carried out at –60°C for 40 h using 15 mol% of **QD** to furnish the crude product [dr = >98:2, determined by integration of one set of ^{1}H NMR signal (δ_{major} 2.80-2.90 ppm, δ_{minor} 2.98-3.08 ppm)]. The title compound was isolated by column chromatography (DCM/AcOEt = 95/5) as a white solid (melting point: 120-124 °C) in 91% yield (dr = >98:2, confirmed by relative areas of HPLC analysis) and 93% ee (major diastereomer) [HPLC analysis on a Chiralpak AD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254; major diastereomer (93% ee): τ_{major} = 26.4 min, τ_{minor} = 29.6 min; minor diastereomer (54% ee): τ_{minor} = 19.3 min, τ_{major} = 23.4 min]. $[\alpha]^{rt}_D$= - 19.1 (*c* = 0.98, $CHCl_3$, 93% ee). HRMS: *m/z* calcd for $C_{17}H_{17}NO_5$: 315.11067; found: 315.11064. ^{1}H NMR ($CDCl_3$): δ = 2.30 (s, 3H), 2.43-2.51 (m, 1H), 2.53 (dd, *J* = 6.4, 18.4, 1H), 2.73-2.78 (m, 1H), 2.83 (dd, *J* = 9.2, 18.4, 1H), 3.39 (dd, *J* = 6.4, 9.2, 1H), 4.32-4.38 (m, 2H),

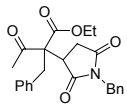
4.68 (AB, *J* = 14.4, 2H), 7.27-7.34 (m, 3H), 7.37-7.40 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 25.9 (CH_3), 28.7 (CH_2), 31.7 (CH_2), 42.1 (CH), 42.6 (CH_2), 61.6 (C), 65.9 (CH_2), 127.9 (CH), 128.5 (CH, 2C), 128.6 (CH, 2C), 135.3 (C), 173.6 (C), 174.4 (C), 176.1 (C), 200.7 (C).

Single crystallization from a mixture of EtOH/Et_2O afforded the optically pure product as a single steroisomer.

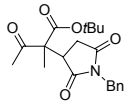
The relative configuration (R*, S*) of the major diastereomer of 4d was determined by X-ray crystallographic analysis of (-)-4d.



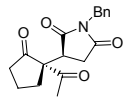
4e – The reaction was carried out at –15°C for 50 h using 20 mol% of **QD** to furnish the crude product [dr = 93/7, determined by integration of two sets of ^{1}H NMR signal (δ_{major} 2.24 ppm, δ_{minor} 2.27 ppm - singlet; δ_{major} 3.37 ppm, δ_{minor} 3.43 ppm - dd)]. The title compound was isolated by column chromatography (hexane/AcOEt = 8/2) as a white foam in 52% yield (dr = 93:7, confirmed by relative areas of HPLC analysis) and 85% ee (major diastereomer) [HPLC analysis on a Chiralpak AS-H column: 75/25 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254; major diastereomer (85% ee): τ_{major} = 20.3 min, τ_{minor} = 27.3 min; minor diastereomer (11% ee): τ_{major} = 30.0 min, τ_{minor} = 41.2 min]. $[\alpha]^{rt}_D$= - 21.2 (*c* = 0.98, $CHCl_3$, 85% ee). HRMS: *m/z* calcd for $C_{18}H_{21}NO_5$: 331.14197; found: 331.14175. ^{1}H NMR ($CDCl_3$): δ = 1.22 (t, *J* = 7.2, 3H), 1.50 (s, 3H), 2.24 (s, 3H), 2.44 (dd, *J* = 6.0, 18.4, 1H), 2.85 (dd, *J* = 9.2, 18.4, 1H), 3.37 (dd, *J* = 6.0, 9.2, 1H), 4.18 (q, *J* = 7.2, 2H), 4.64 (AB, *J* = 14.0, 2H), 7.23-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_3), 18.9 (CH_3), 26.8 (CH_3), 32.4 (CH_2), 42.4 (CH_2), 44.9(CH), 61.2 (C), 62.2 (CH_2), 127.8 (CH), 128.5 (CH, 2C), 128.7 (CH, 2C), 135.6 (C), 170.7 (C), 175.2 (C), 177.0 (C), 204.2 (C).



4f – The reaction was carried out at –15°C for 88 h using 20 mol% of **QD** to furnish the crude product [dr = 77/23, determined by integration of one set of ^{1}H NMR signal (δ_{major} 2.64 ppm, δ_{minor} 2.82 ppm - dd)]. The title compound was isolated by column chromatography (DCM/AcOEt = 99/1) as a white foam in 63% yield (dr = 78:22, confirmed by relative areas of HPLC analysis) and 85% ee (major diastereomer) [HPLC analysis on a Chiralcel OD-H column: 85/15 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254; major diastereomer (85% ee): τ_{major} = 25.7 min, τ_{minor} = 50.4 min; minor diastereomer (24% ee): τ_{major} = 44.7 min, τ_{minor} = 32.2 min]. $[\alpha]^{rt}_D$= - 16.2 (*c* = 1.0, $CHCl_3$, 85% ee). HRMS: *m/z* calcd for $C_{24}H_{25}NO_5$: 407.17327; found: 407.17361. ^{1}H NMR (600MHz, $CDCl_3$): major diastereomer: δ = 1.16 (t, *J* = 7.2, 3H), 2.27 (dd, *J* = 6.6, 18.6, 1H), 2.33 (s, 3H), 2.64 (dd, *J* = 9.6, 18.6, 1H), 3.33 (dd, *J* = 6.6, 9.6, 1H), 3.49 (s, 2H), 4.14 (q, *J* = 7.2, 2H), 4.60 (AB, *J* = 14.4, 2H), 7.18-7.38 (m, 10H); ^{13}C NMR ($CDCl_3$): δ = 13.8 (CH_3), 28.5 (CH_3), 33.8 (CH_2), 39.9 (CH_2), 42.3 (CH_2), 42.5 (CH), 62.0 (CH_2), 66.9 (C), 127.6 (CH), 127.7 (CH), 128.5 (CH, 2C), 128.6 (CH, 2C), 128.7 (CH, 2C), 130.3 (CH, 2C), 135.0 (C), 135.6 (C), 169.9 (C), 175.6 (C), 177.6 (C), 204.5 (C); minor diastereomer (selected signals): δ = 1.07 (t, *J* = 7.2, 3H), 2.29 (s, 3H), 2.42 (dd, *J* = 5.4, 18.6, 1H), 2.82 (dd, *J* = 6.4, 18.6, 1H), 3.37 (d, *J* = 13.8, 1H), 3.83 (d, *J* = 13.8, 1H), 3.90 (m, 1H), 4.04 (m, 1H).



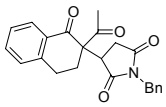
4g – The reaction was carried out at RT for 72 h using 20 mol% of **Q** to furnish the crude product [dr = 92:8, determined by integration of two sets of ^{1}H NMR signal (δ_{major} 1.47 ppm, δ_{minor} 1.48 ppm – s; δ_{major} 2.24 ppm, δ_{minor} 2.26 ppm – s)]. The title compound was isolated by column chromatography (hexane/AcOEt = 75/25) as a white foam in 75% yield (dr = 92:8, confirmed by relative areas of HPLC analysis) and 92% ee (major diastereomer) [HPLC analysis on a Chiralpak AS-H column: 9/1 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254; major diastereomer (92% ee): τ_{major} = 30.4 min, τ_{minor} = 22.0 min; minor diastereomer (9% ee): τ_{major} = 42.0 min, τ_{minor} = 33.5 min]. $[\alpha]^{rt}_D$= + 26.8 (*c* = 1.0, $CHCl_3$, 92% ee). HRMS: *m/z* calcd for $C_{20}H_{25}NO_5$: 359,17327; found: 359.17341. ^{1}H NMR ($CDCl_3$): δ = 1.47 (s, 9H), 1.51 (s, 3H), 2.26 (s, 3H), 2.49 (dd, *J* = 6.4, 18.4, 1H), 2.84 (dd, *J* = 9.2, 18.4, 1H), 3.29 (dd, *J* = 6.4, 9.2, 1H), 4.65 (AB, *J* = 14.4, 2H), 7.27-7.33 (m, 3H), 7.35-7.38 (m, 2H); δ = 19.2 (CH_3), 26.9 (CH_3), 27.7 (CH_3, 3C), 32.6 (CH_2), 42.3 (CH_2), 45.0 (CH), 61.8 (C), 83.4 (C), 127.8 (CH), 128.5 (CH, 2C), 128.6 (CH, 2C), 135.6 (C), 169.7 (C), 175.4 (C), 177.1 (C), 204.6 (C).



4h – The reaction was carried out at –60°C for 40 h using 15 mol% of **QD** to furnish the crude product [dr = 92:8, determined by integration of one set of ^{1}H NMR signal (δ_{major} 2.74 ppm, δ_{minor} 2.85 ppm - dd)]. The title compound was isolated by column chromatography (hexane/AcOEt = 75/25) as a white foam in 99% yield (dr = 92:8, confirmed by relative areas of HPLC analysis) and 91% ee (major diastereomer) [HPLC analysis on a Chiralpak AD-H column: 75/25 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254; major diastereomer (91% ee): τ_{major} = 14.5 min, τ_{minor} = 14.9 min; minor diastereomer (88% ee): τ_{major} = 13.2 min, τ_{minor} = 13.5 min]. $[\alpha]^{rt}_D$= + 24.5 (*c* = 1.0, $CHCl_3$, 91% ee). HRMS: *m/z* calcd for $C_{18}H_{19}NO_4$: 313.13141; found: 313.13133. ^{1}H NMR ($CDCl_3$): δ = 1.80-2.00 (m, 3H), 2.17 (s, 3H), 2.34 (dd, *J* = 6.4, 18.4, 1H), 2.40-2.56 (m, 3H), 2.74

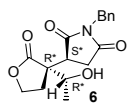
(dd, *J* = 9.2, 18.4, 1H), 3.54 (dd, *J* = 6.4, 9.2, 1H), 4.63 (AB, *J* = 14.0, 2H), 7.24-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 19.4 (CH_2), 26.2 (CH_3), 28.8 (CH_2), 31.8 (CH_2), 38.4 (CH_2), 42.5 (CH_2), 43.6 (CH), 68.7 (C), 128.0 (CH), 128.6 (CH, 2C), 128.7 (CH, 2C), 135.4 (C), 174.7 (C), 176.5 (C), 202.0 (C), 213.4 (C).

The relative configuration (S*, S*) of the major diastereomer of (+)-4h was determined by extensive NMR NOE studies.



4i – The reaction was carried out at –30°C for 66 h using 20 mol% of **QD** to furnish the crude product [dr = 95:5, determined by integration of one set of ^{1}H NMR signal (δ_{major} 3.30 ppm, δ_{minor} 3.37 ppm - dd)]. The title compound was isolated by column chromatography (hexane/AcOEt = 75/25) as a solid (melting point = 184-189 °C) in 75% yield (dr = 95:5, confirmed by relative areas of HPLC analysis) and 84% ee (major diastereomer) [HPLC analysis on a Chiralpak AD-H column: 75/25 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254; major diastereomer (84% ee): τ_{major} = 22.7 min, τ_{minor} = 19.8 min; minor diastereomer (26% ee): τ_{major} = 23.9 min, τ_{minor} = 19.0 min]. $[\alpha]^{rt}_D$= + 44.4 (*c* = 0.99, $CHCl_3$, 84% ee). HRMS: *m/z* calcd for $C_{23}H_{21}NO_4$: 375.14706; found: 375.14641. ^{1}H NMR ($CDCl_3$, T = 50 °C): δ = 2.19 (s, 3H), 2.40-2.56 (m, 3H), 2.65 (dd, *J* = 6.0, 18.4, 1H), 2.98-3.03 (m, 2H), 3.30 (dd, *J* = 6.0, 9.2, 1H), 4.73 (AB, *J* = 14.4, 2H), 7.23-7.38 (m, 5H), 7.39-7.45 (m, 2H), 7.53 (t, *J* = 7.6, 9.2, 1H), 8.07 (d, *J* = 7.6, 9.2, 1H); ^{13}C NMR ($CDCl_3$, T = 50 °C): δ = 25.6 (CH_2), 29.1 (CH_3), 31.1 (CH_2), 31.9 (CH_2), 42.6 (CH_2), 44.2 (CH), 65.5 (C), 127.4 (CH), 127.7 (CH), 128.1 (CH), 128.5 (CH, 2C), 128.6 (CH, 2C), 129.0 (CH), 132.1 (CH), 134.4 (C), 135.9 (C), 142.9 (C), 175.0 (C), 177.1 (C), 196.1 (C), 205.6 (C).

Gram-scale experiment and synthesis of (-)-6.



6

In an ordinary 50mL round-bottom flask equipped with a magnetic stirring bar, quinidine **QD** (1.5 mmol, 486 mg) was dissolved in 20 mL of DCM. After addition of the 1,3-dicarbonyl compound (10 mmol, 1.08 mL), the flask was closed with a rubber stopper and the mixture was stirred at –60 °C for 10 minutes. Then *N*-benzylmaleimide **2d** (11 mmol, 2.057 g) was added in one portion and stirring was continued for 48h. Then the crude reaction mixture was concentrated to 3 mL and directly charged on the chromatography column and purified on silica, using DCM/AcOEt 95/5 as the eluent. **4d** was isolated as a white solid in quantitative yield (3.12 g) and dr = >98:2 (confirmed by relative areas of HPLC analysis) and 94% ee (major diastereomer). Single crystallization from a mixture of EtOH/Et_2O afforded the optically pure product as a single steroisomer.

Enantiomerically pure (-)-**4d** (2 mmol, 630 mg) was dissolved in MeOH (20 mL) and stirred at –78 °C for 5 minutes. Then, $NaBH_4$ (1.5 equiv., 3 mmol) was added in one portion and stirring continued for 3 hours, at which time the reaction mixture was quenched with brine, extracted with AcOEt (3 times) and dried over anhydrous $MgSO_4$. NMR analysis of the crude mixture showed that the reduction proceeded with complete chemoselectivity and high stereocontrol (d.r. 93/7, determined by integration of two sets of ^{1}H NMR signal (δ_{major} 2.98 ppm, δ_{minor} 2.89 ppm – dd / δ_{major} 3.63 ppm, δ_{minor} 3.32 ppm – dd). The title compound **6** was isolated by column chromatography (DCM/AcOEt = 75/25) as a white foam in 93% yield (dr = 93:7, confirmed by relative areas of HPLC analysis) and >99% ee (major diastereomer) [HPLC analysis on a Chiralpak AD-H column: 75/25 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254; major diastereomer (>99% ee): τ_{major} = 16.9 min, τ_{minor} = 14.4 min; minor diastereomer (>99% ee): τ_{major} = 11.5 min, τ_{minor} = 10.7 min]. $[\alpha]^{rt}_D$= -2.7 (*c* = 1.1, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{17}H_{19}NO_5$: 317.12632; found: 317.12665. ^{1}H NMR ($CDCl_3$): δ = 1.26 (d, *J* = 6.4, 3H), 1.80-1.88 (m, 1H), 2.02-2.08 (m, 1H), 2.49 (dd, *J* = 6.4, 18.4, 1H), 2.50 (br s, 1H), 2.98 (dd, *J* = 9.6, 18.4, 1H), 3.63 (dd, *J* = 6.4, 9.6, 1H), 3.82-3.89 (m, 1H), 4.17-4.28 (m, 2H), 4.65 (s, 2H), 7.27-7.32 (m, 3H), 7.35-7.38 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 18.5 (CH_3), 26.8 (CH_2), 31.6 (CH_2), 42.6 (CH_2), 43.9 (CH), 52.3 (C), 65.7 (CH_2), 70.0 (CH), 128.1 (CH), 128.7 (CH, 2C), 128.8 (CH, 2C), 135.5 (C), 174.9 (C), 177.3 (C), 178.7 (C).

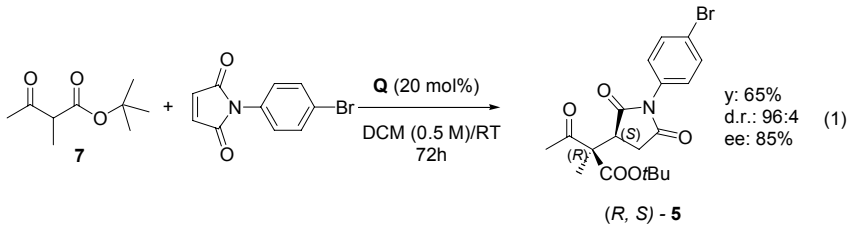
The relative configuration (R*, R*, S*) of the major diastereomer of (-)-6 was determined by extensive NMR NOE studies.

X-Ray Structure Analysis.

Determination of Absolute and Relative Configurations of 5.

The absolute and relative configurations of compound **5** (Eq. 1) were assigned by X-ray crystallographic analysis. CCDC-296418 contains the supplementary crystallographic data for this compound. These data

can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif .



Compound **5** was prepared following the general procedure by mixing **1g** (1 equiv) and *N*-4-bromophenylmaleimide (1.2 equiv) in DCM (0.5 M) at RT in the presence of quinine **Q** (20 mol%) as the catalyst. The title compound was isolated after 72h by column chromatography (hexane/AcOEt = 80/20) as a white solid (melting point: 135-140°C) in 65% yield (dr = 96:4, determined by integration of one set of ^{1}H NMR signal: δ_{major} 2.28 ppm, δ_{minor} 2.30 ppm - s) and 85% ee (major diastereomer) [HPLC analysis on a Chiralpak AD-H column: 75/25 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (85% ee): τ_{major} = 18.0 min, τ_{minor} = 20.5 min]. $[\alpha]^{rt}_D$= + 13.7 (*c* = 1.1, $CHCl_3$, 85% ee). HRMS: *m/z* calcd for $C_{19}H_{22}NO_5Br$: 423.06813; found: 423.06824. ^{1}H NMR ($CDCl_3$): δ = 1.50 (s, 9H), 1.65 (s, 3H), 2.28 (s, 3H), 2.66 (dd, *J* = 6.4, 18.4, 1H), 2.98 (dd, *J* = 9.2, 18.4, 1H), 3.39 (dd, *J* = 6.4, 9.2, 1H), 7.21 (d, *J* = 8.8, 2H), 7.59 (d, *J* = 8.8, 2H); δ = 19.9 (CH_3), 27.2 (CH_3), 27.8 (CH_3, 3C), 32.9 (CH_2), 45.1 (CH), 62.5 (C), 83.7 (C), 122.5 (C), 128.1 (CH, 2C), 130.9 (C), 132.3 (CH, 2C), 169.8 (C), 174.5 (C), 176.4 (C), 205.1 (C).

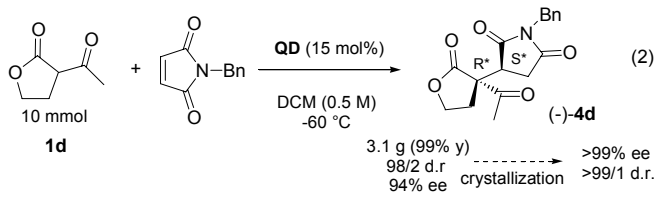
Crystallization from a mixture of hexane/Et_2O afforded a single enantiopure stereoisomer (confirmed by HPLC analysis of the very same crystal used for X-ray analysis) as fine colourless needles suitable for X-ray diffraction measurements with the configuration as shown in Equation 1.

Molecular formula: $C_{19}H_{22}BrNO_5$, orthorhombic, space group $P2_12_12_1$ (No. 19), *a* = 6.486(1), *b* = 15.479(2), *c* = 19.892(3) Å, *V* = 1997.1(5) Å^3, T = 298(2) K, *Z* = 4, ρ_c = 1.411 g cm^{-3}, *F*(000) = 872, graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å), μ($Mo_{K\alpha}$) = 2.086 mm^{-1}, colourless needle (0.50 × 0.15 × 0.10 mm^3), empirical absorption correction with SADABS (transmission factors: 0.6804 – 0.2862), 2400 frames, exposure time 20 s, 1.67 ≤ θ ≤ 28.70, –8 ≤ *h* ≤ 8, –20 ≤ *k* ≤ 20, –26 ≤ *l* ≤ 26, 22454 reflections collected, 4834 independent reflections (R_{int} = 0.0548), 3195 reflections with $I > 2\sigma(I)$ (R_σ = 0.0482), solution by direct methods (SHELXS) and subsequent Fourier syntheses, full-matrix least-squares on F_o^2 (XSHELL), hydrogen atoms refined with a riding model, data / parameters = 4834 / 241, $S(F^2)$ = 1.008, $R(F)$ = 0.0800 and $wR(F^2)$ = 0.1251 on all data, $R(F)$ = 0.0440 and $wR(F^2)$ = 0.1096 for reflections with $I > 2\sigma(I)$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0603P)^2 + 0.000P]$ where $P = (F_o^2 + 2F_c^2)/3$, largest difference between peak and hole 0.692 and –0.409 e Å^{-3}, Flack parameter[9] 0.000(12). The absolute structure has been also confirmed by comparison of the structural refinements of the two enantiomorphs. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-296418. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Determination of Relative Configuration of (-)-4d.

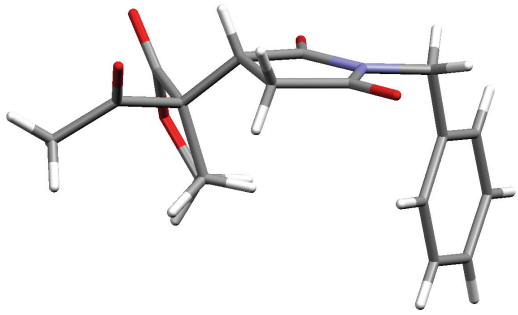
The relative configuration of compound (-)-**4d** was assigned by X-ray crystallographic analysis. CCDC-605040 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif .

Crystallization from a mixture of EtOH/Et_2O afforded a single enantiopure stereoisomer (confirmed by HPLC analysis) as fine colourless needles suitable for X-ray diffraction measurements with the relative configuration as shown in Equation 2.



Compound **4d** lacks of a sufficiently heavy atom to allow the determination of the absolute configuration.

Figure 1: X-ray data for compound (R*, S*)-(-)-**4d**



NMR NOE Analysis.

The relative configurations of compounds **4b**, **4h** and **6** were deduced from extensive NMR NOE analysis of both the major and the minor diastereomers. Diasteroisomeric separation was achieved by means of semipreparative HPLC (Waters Novapak, silica 6 um, 8x300 mm, hexane/iPrOH) for compounds **4b** and **6**, and by flash chromatography on silica gel for compound **4h**.

All the ^{1}H and ^{13}C NMR signals of the two diastereomers were recorded at 600 MHz and previously assigned by means of g-COSY, g-HSQC and g-HMBC 2D-NMR sequences. NOE spectra were obtained using the DPFGSE-NOE sequence,[10] with a mixing time of 1.00-2.00 s and two "rsnob" 30-50 Hz wide selective pulses. Zero-Quantum Coherence effects were reduced according to the method proposed by Keeler.[11] As an example of the method, the NOE spectrum of **6**, obtained on irradiation of the carbinolic CH, is shown in Figure 2.

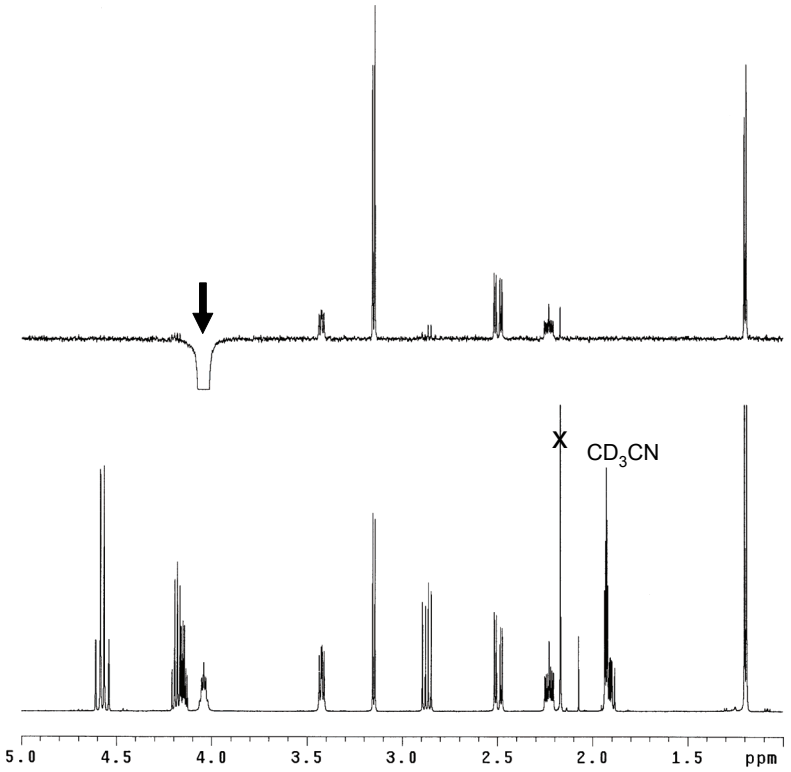
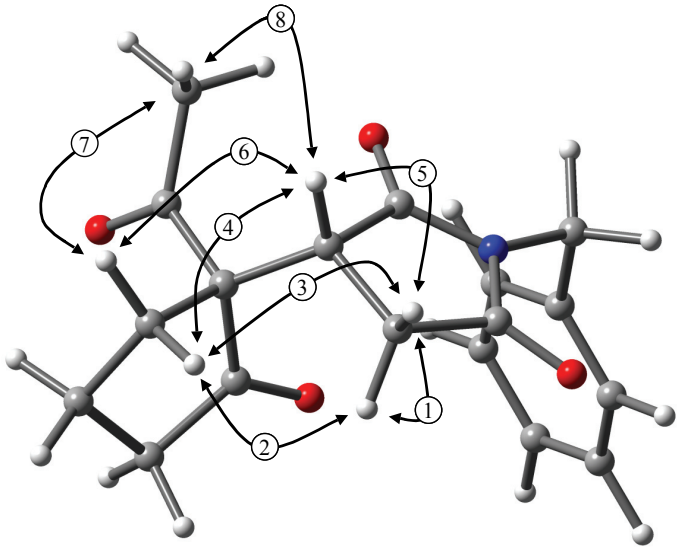


Figure 2. Bottom: ^{1}H-NMR spectrum (600 MHz in CD_3CN) of the major diastereoisomer of compound **6**. Top: DPFGSE-NOE spectrum obtained on saturation of the carbinolic CH (indicated by the arrow).

Determination of the Relative Configuration of (+)-**4h.**

The two diastereomers of compound **4h**, obtained by the **QD**-catalyzed reaction (92/8 d.r. 91% ee major diastereomer), were previously isolated by flash chromatography on silica gel (hexane/AcOEt 75/25; R_f^{minor} = 0.3 - R_f^{major} = 0.2).

In the case of the minor isomer of **4h**, selective saturation of the CH signal shows positive NOEs on the syn hydrogen of the maleimmide moiety, (Figure 3, NOE n° 5), on the COMe signal (NOE n° 8), and on both the diastereotopic hydrogens of the CH_2 near to the quaternary carbon of the cyclic ketone (NOE n° 4 and n° 6). Selective saturation of the hydrogen of maleimmide syn to the CH shows positive NOEs on the CH (NOE n° 5), on the hydrogen anti to the CH (NOE n° 1) and solely one hydrogen of the CH_2 near to the quaternary carbon of the cyclic ketone (NOE n° 3).



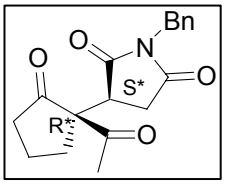


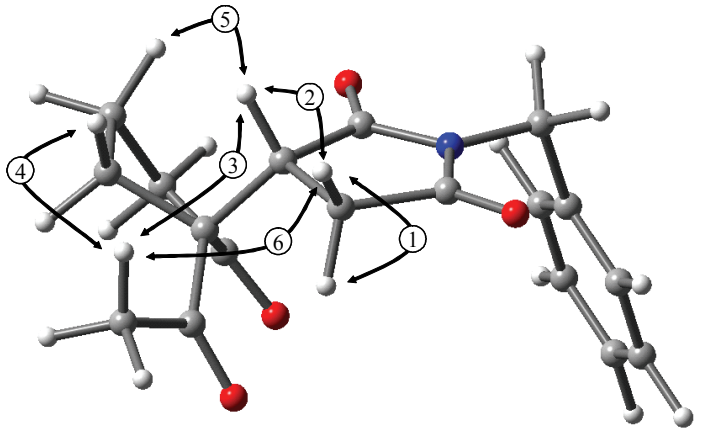
Figure 3: minor diastereoisomer of **4h** (8%, R*S* configuration)

Selective saturation of the hydrogen of maleimmide anti to the CH shows positive NOE on the other portion of the AB system (NOE n° 1) and on the same hydrogen of the alfa-quaternary CH_2 mentioned before (NOE n° 2). Finally, saturation of the COMe signal yields a very strong effect on the CH (NOE n° 8), on one of the hydrogens of the CH_2 near to the quaternary carbon of the cyclic ketone (NOE n° 7) and a very weak effect on the hydrogen syn to the CH. (not shown in Figure 3).

All the constrains agree very well with the structure in which the two chiral centers have opposite descriptors (so R*S*).

In the case of the major isomer of **4h** (Figure 4), selective saturation of the maleimidic CH signal shows positive NOEs on the syn hydrogen of the maleimmidic CH_2 (NOE n° 2), on the COMe signal (NOE n°3) and on one of the hydrogens in β-CO position of the cyclic ketone (NOE n° 5).

Selective saturation of the maleimmidic hydrogen syn to the CH shows positive NOEs on the CH (NOE n° 2), on the other diastereotopic hydrogen (NOE n° 1) and on the COMe signal (NOE n° 6). Selective saturation of the hydrogen of maleimmide anti to the CH shows positive NOE only on the other diastereotopic hydrogen of the AB system (NOE n° 1). Finally, saturation of the COMe signal yields a very strong positive NOE on the CH (NOE n° 3), on one of the hydrogens near to the quaternary carbon of the cyclic ketone (NOE n° 4) and a weak effect on the hydrogen syn to the CH (NOE n° 6). In this case all the constrains agree very well with the structure in which the two chiral centres have the same descriptor (so R*R*).



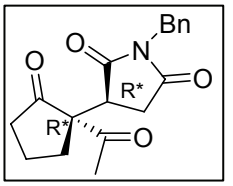


Figure 4 - major diastereoisomer of **4h** (92%, R*R* configuration).

Thus, in the mayor diastereoisomer of **4h**, the main differences lie in the absence of any NOE between the maleimmidic hydrogens and the hydrogens of the cyclopentanone ring. In both isomers relevant NOE effects are visible between the methyl group and the maleimmidic CH.

Compound **4b**

The two diastereomers of compound **4b**, obtained by the **QD**-catalyzed reaction (87/13 d.r. 98% ee major diastereomer), were previously isolated by semi preparative HPLC (Waters Novapak, silica, 6 μm, 7.8x300 mm, hexane/*i*PrOH 98/2).

In the case of **4b**, NOE spectra show the same trend of **4h**. In Figures 5 and 6 are reported the structure derived. In this case the NOE spectra assign the R*S* configuration to the major diastereoisomer, and the R*R* configuration to the minor. It is important to note that the change in the configuration is due to the different priority of the COOEt substituent with respect to the COMe group. In other words, the two major diastereoisomers of **4b** and **4h** have the same structure, but one of the two chiral centres has changed its descriptor.

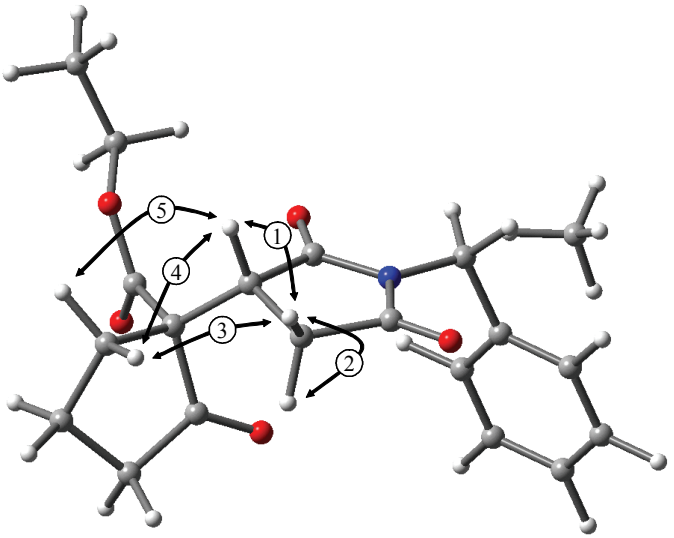


Figure 5 - minor diastereoisomer of **4b** (13%, R*R* configuration)

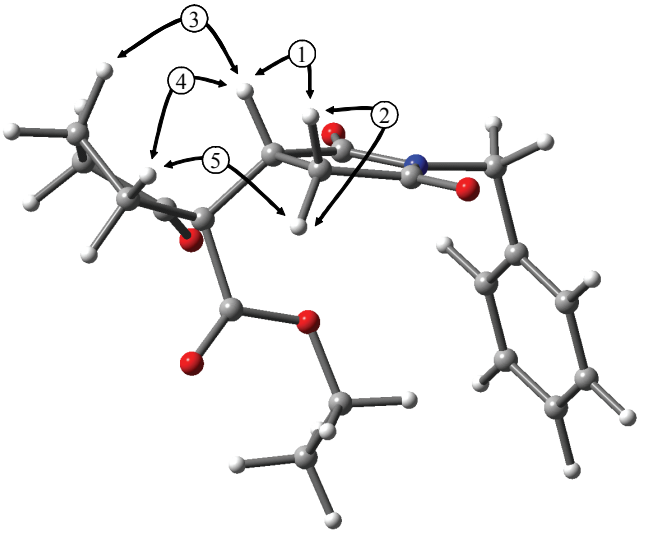
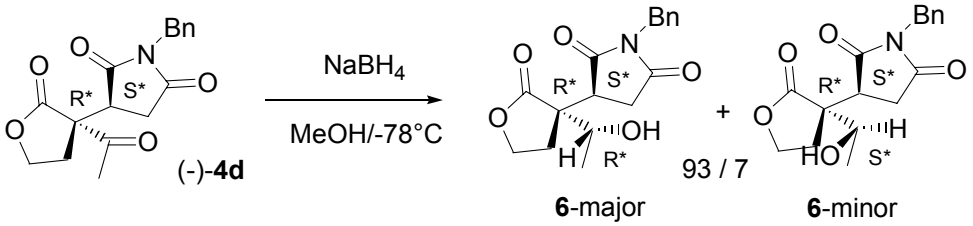


Figure 6 - major diastereoisomer of **4b** (87%, R*S* configuration).

Determination of the Relative Configuration of (-)-**6.**

A mixture 60/40 of compound **6** was prepared by reduction of **4d** at – 30 °C in DCM as the solvent, using BH_3.THF as the reducing agent in the presence of a stoichiometric amount of $TiCl_4$. The two diastereomers were separated by HPLC (Waters Novapak, silica, 6 µm, 7.8x300 mm, hexane/*i*PrOH 80/20).



All the ^1H and ^{13}C NMR signals of the two diastereomers were previously assigned as reported above. NOE spectra were obtained using the DPFGSE-NOE sequence,[10] with a mixing time of 1.50-2.00 s and two "rsnob" 30-50 Hz wide selective pulses. Zero-Quantum Coherence effects were reduced according to the method proposed by Keeler.[11]

The X-ray structural analysis of the precursor of **6** (i.e. **4d**) was available (see Figure 1, X-ray section), so the relative R*S* stereochemistry of two out of the three chiral centres of **6** was known (compound **4d** lacks of a sufficiently heavy atom to allow the determination of the absolute configuration).

In this case the NOE analysis is complicated by the presence of the two identical chiral centres that make the NOE constraints between the hydrogens of the two cycles almost indistinguishable (NOE constraints from 1 to 8 in Figures 7 and 8). Thus the NOE analysis has to be focused on the effects revealed when the methyl group and the carbinolic CH are saturated. In both diastereoisomers, selective saturation of the CH shows NOE effects on the three maleimmidic CH (NOE n° 6, 7, 9) and on one hydrogen of the lactone (NOE n° 4). These results indicate that in both cases the CH is located more or less in the same position (see Figure 2 for the NOE spectrum of the major diastereoisomer).

On the other hand, in the case of the major stereoisomer, selective saturation of the methyl group yields two strong NOE effects on two hydrogens of the lactone (NOE n° 11 and 12 in Figure 7), while in the case of the minor stereoisomer the saturation of the methyl group shows NOE effect on the maleimmidic CH (NOE n°11 of Figure 8), whereas NOE effects are not observed on the hydrogen of the lactone. Finally, although a NOE effect obtained on saturation of an hydroxyl group is never completely sound, the NOE effect is observable on the maleimmidic CH in the case of the major diastereoisomer, while in the minor diastereoisomer NOE is observed on one hydrogen of the lactone. These convergent results show that the predominant stereoisomer of **6** has the R*S*S* configuration, while the minor has the R*S*R* configuration.

It has also to be noted that the major isomer is a viscous and soluble liquid, while the minor is a almost insoluble powder in apolar solvents like chloroform. This unusual behaviour can be explained by inspection of the two structures of **6**: in the case of the major isomer the OH is involved in a intra-molecular hydrogen bond (indicated by the dotted line in Figure 7) with the carbonyl of the lactone. In the other stereoisomer, on the contrary, the hydroxyl group is free for an inter-molecular hydrogen bond, thus accounting for the solid appearance of the compound.

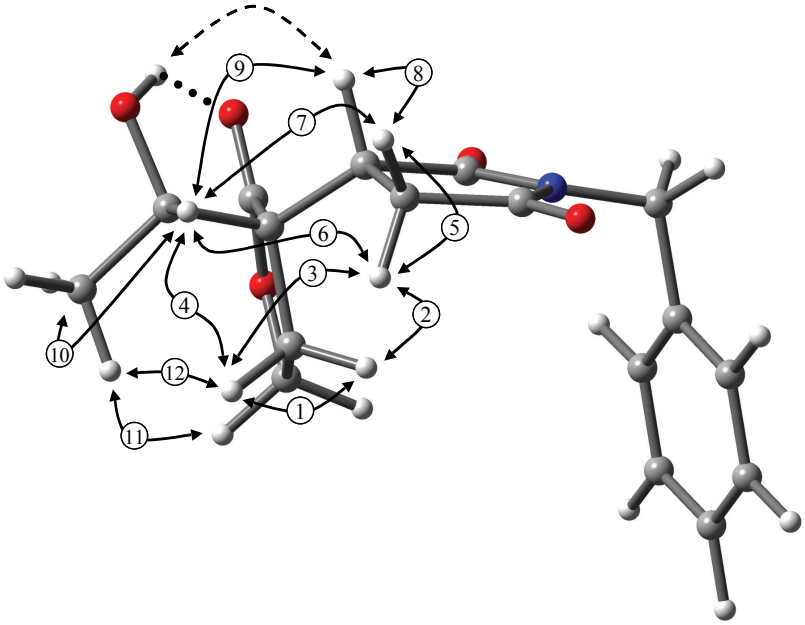


Figure 7 – major reaction product (93%, R*S*S* configuration) of compound **6**

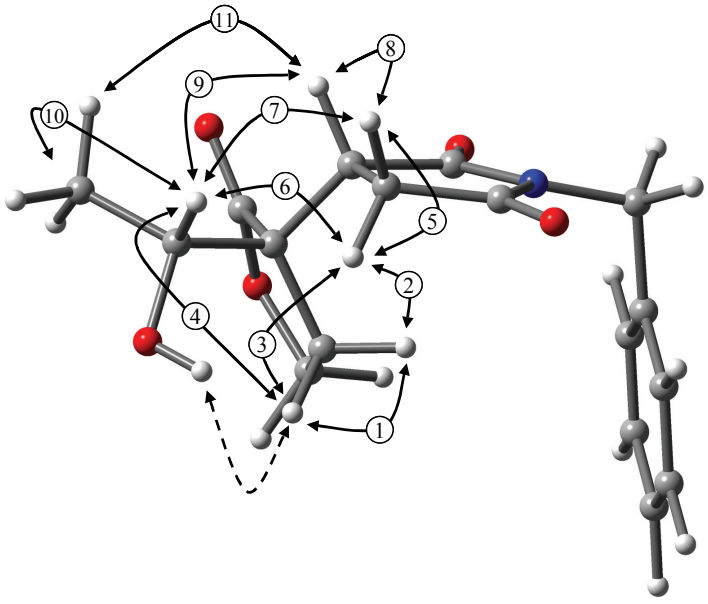
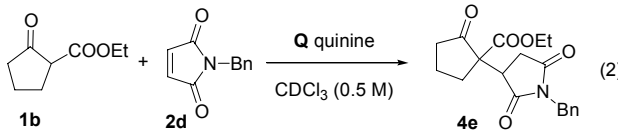


Figure 8 – minor reaction product (7%, R*S*R* configuration) of compound **6**

Kinetic Studies.

The kinetic parameters of the reaction depicted in Eq. 2 were determined by *in situ* monitoring of the consumption of ethyl 2-oxocyclopentane carboxylate **1b** (triplet at 3.14 ppm) and *N*-benzylmaleimide **2d** (singlet at 6.71 ppm) by using ^{1}H NMR spectroscopy.



(2)

Order in ethyl 2-oxocyclopentane carboxylate **1b** was established by using a large excess of *N*-benzylmaleimide **2d** (5 equiv) and 10 mol% **Q**. Plotting in ln[**1b**] versus time gave a straight line (R^2 = 0.9993, Figure 8), thus establishing a first-order dependence on **1b**.

Order in *N*-benzylmaleimide **2d** was established by using a large excess of ethyl 2-oxocyclopentane carboxylate **1b** (5 equiv) and 10 mol% quinine as the catalyst. Plotting in ln[**2d**] versus time gave a straight line (R^2 = 0.9987, Figure 10), thus establishing a first-order dependence on maleimide (**2d**).

The reaction order in catalyst was established by determining the kinetic rate constants at various catalyst concentrations (equimolar amounts of *N*-benzylmaleimide **2d** and ethyl 2-oxocyclopentane carboxylate **1b**). A plot of the rate constants k_{obs} vs the catalyst concentration gave a straight line for quinine (R^2 = 0.9808, Figure 12). The reaction displays first-order dependence on catalyst.

General procedure for kinetic studies.

In an ordinary NMR tube, *N*-benzylmaleimide **2d** (65.5 mg, 0.35 mmol) and quinine (11.3 mg, 0.035 mmol) were dissolved in 0.7 mL of $CDCl_3$ (0.5 M solution in nucleophile). Then in a period as short as possible ethyl 2-oxocyclopentane carboxylate **1b** (52 µL, 0.35 mmol) was introduced in one portion via a syringe and the resulting mixture was shaken well. The first ^{1}H NMR acquisition was collected after 3 minutes, and the resulting reaction mixture was monitored every 60 seconds for 20-40 minutes.

Figure 8. Determination of the order of the ketoester **1b**: the linear relationship between ln[**1b**] and time indicates that the reaction is first order on **1b**.

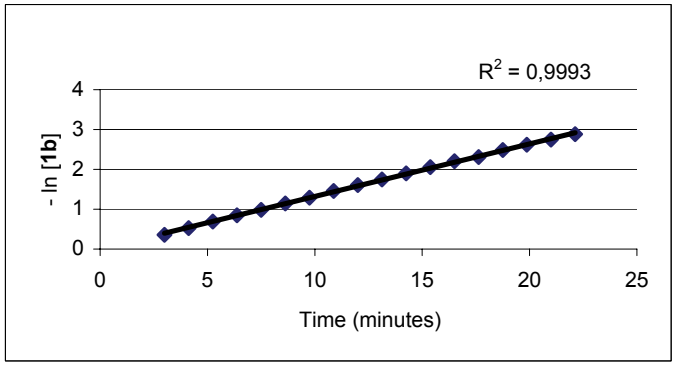


Figure 9. Determination of the order of the ketoester **1b**: the non-linear relationship between 1/[**1b**] and time clearly indicates that the reaction is not second order on **1b**.

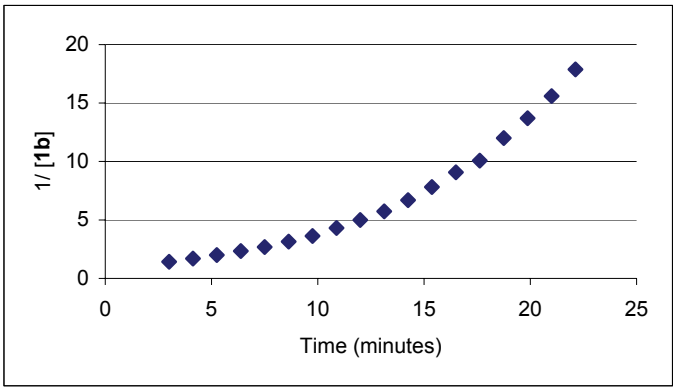


Figure 10. Determination of the order of the maleimide **2d**: the linear relationship between ln[**2d**] and time indicates that the reaction is first order on **2d**.

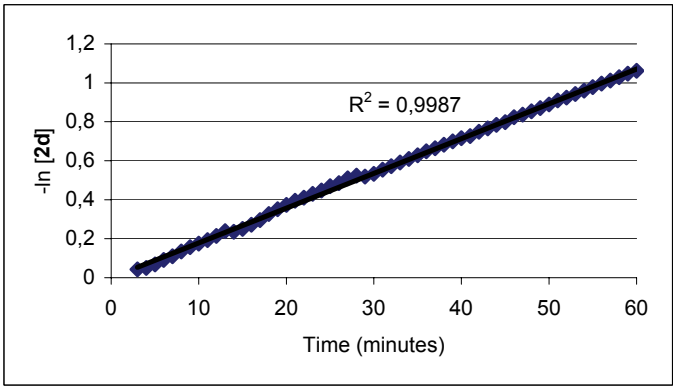
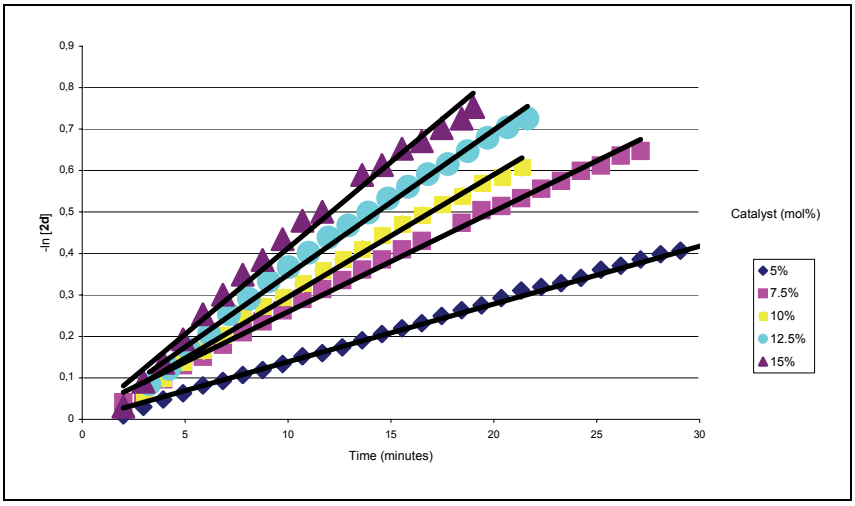
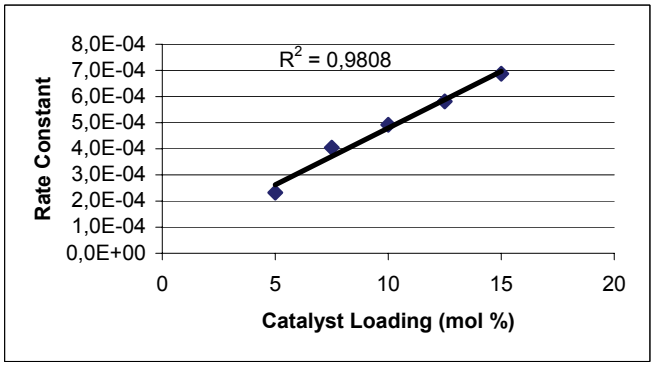


Figure 11. kinetic profiles for the catalyst quinine **Q**



Catalyst [mol%]	k_{obs}	R^2
5	2,322 E-04	0.9980
7.5	4,044 E-04	0.9946
10	4,919 E-04	0.9935
12.5	5,816 E-04	0.9932
15	6,870 E-04	0.9846

Figure 12. Kinetic rate constant (k_{obs}) at different concentration of quinine **Q**



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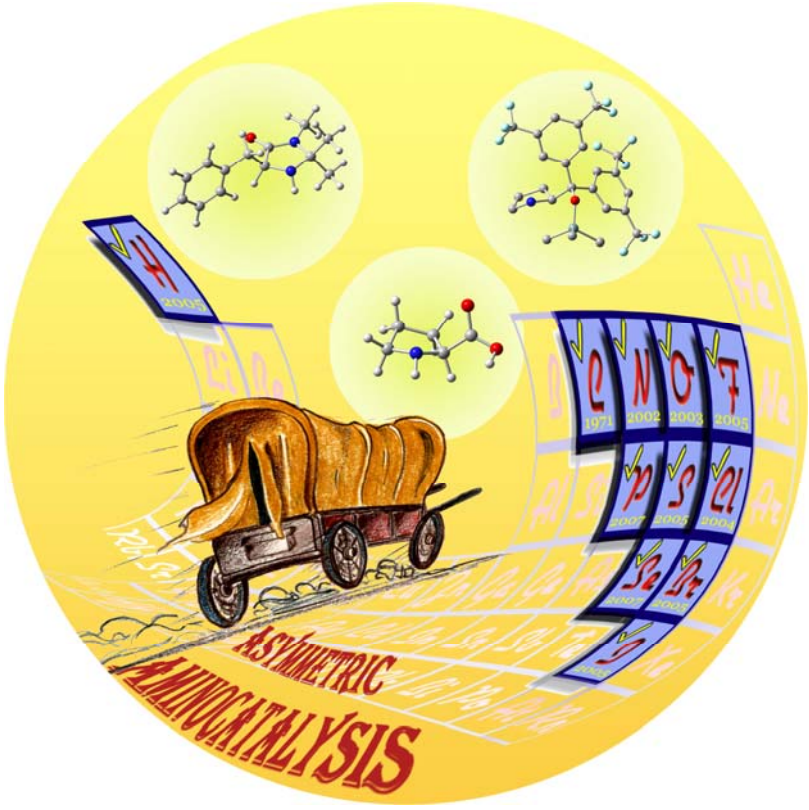
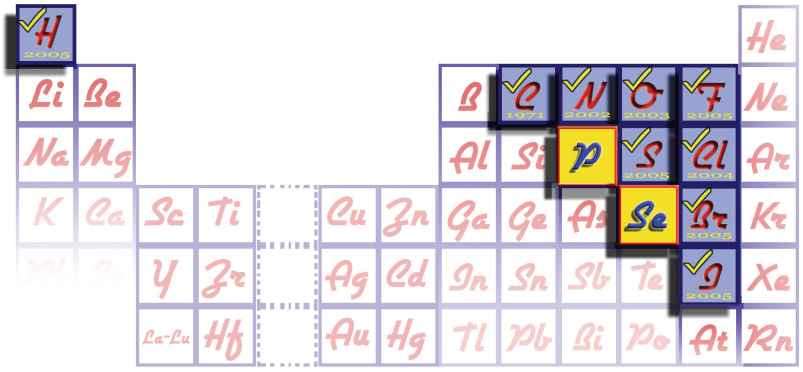
SECTION II



CHIRAL LEWIS BASE CATALYSIS MEDIATED BY CHIRAL AMINES

5. A JOURNEY AROUND THE PERIODIC TABLE

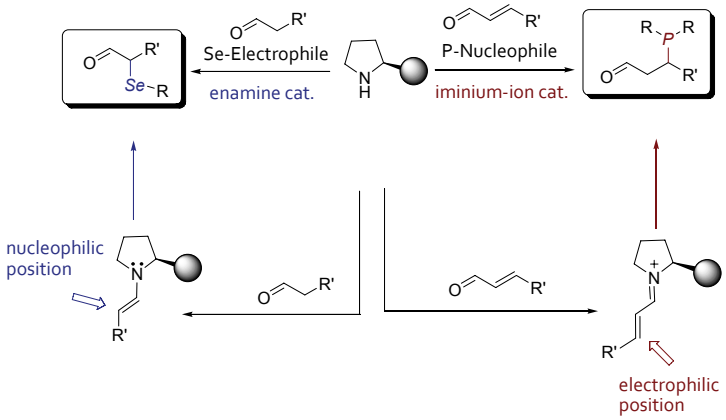


Over the past few years, Asymmetric Aminocatalysis proved to be a reliable tool for the enantioselective functionalization of aldehydes in a broad range of reactions. Thus, researchers worldwide used chiral secondary amines to efficiently activate substrates, sometimes mimicking metal catalysis, sometimes discovering new reactivities; all in all, the elegance and efficiency consistently demonstrated was stunning.

At this stage, we could ideally start compiling an encyclopedia. A list of the reactions and activations would prove useful for researchers. However, it could be interesting to approach it from a different point of view; the Periodic Table.

While reactions are important, it is also useful to be able to enantioselectively functionalize the molecule of interest with the desired element. Looking at the Periodic Table it was clearly popping out that among the non-inert elements classified as "non-metals" Phosphorous- and Selenium-based compounds had not yet been stereoselectivily incorporated into carbonyls compounds using organocatalysis.

In the following pages we will see that, exploiting iminium ion and enamine catalysis with chiral secondary amines, aldehydes have been enantioselectively functionalized with Phosphorous- and Selenium-based compounds. In both examples, as usual in organocatalysis, unmodified and commercially available starting materials and catalysts were employed under mild reaction conditions.



In the beginning, a highly enantioselective Asymmetric Hydrophosphination of α,β-unsaturated aldehydes will be presented. Given the background for the asymmetric addition of diphenylphosphine to nitroolefins in the group, it was almost spontaneous to use a similar strategy for the functionalization of aldehydes and therefore we set for. Due to the extremely high importance of chiral phosphorous compounds this was a very interesting goal. One of the main difficulties, quite probably because of the non-catalyzed reaction, was to optimize the reaction for both aromatic and aliphatic aldehydes as they showed a very different behaviour. Once the best conditions were found the protocol proved general, providing the desired products in high yields and selectivities, for this kind of reaction.

On the other hand, the asymmetric α-selenenylation of aldehydes proved easier with regards to the optimization of the conditions; the main challenge was to lower the catalyst loading and show the importance of selenium-functionalized compounds.

The extreme competition and challenge in this field of organocatalysis has been striking shown in this case as another group published the same P-addition in a back-to-back paper following ours.[1] Surprisingly, also the Se-functionalization was published on a different journal some months after our publication.[2]

[1] I. Ibrahem, R. Rios, J. Vesely, P. Hammar, L. Eriksson, F. Himo, A. Córdova, *Angew. Chem.* **2007**, *119*, 4591; *Angew. Chem. Int. Ed.* **2007**, *46*, 4507.

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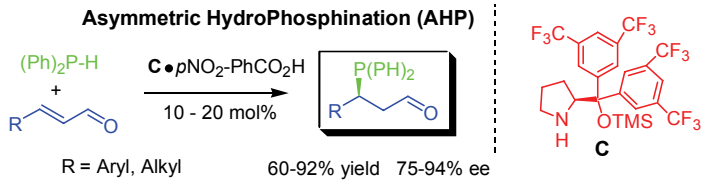
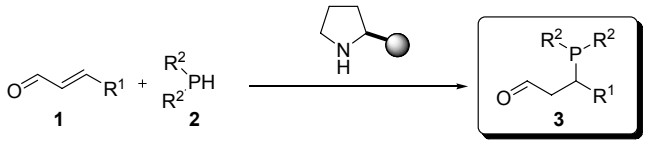
5.1 Organocatalytic Asymmetric Hydrophosphination of α,β-Unsaturated Aldehydes



Getting round the (Periodic) Table –Volume II-: A highly chemo- and enantioselective conjugate addition of diphenylphosphine to α,β-unsaturated aldehydes in the presence of a chiral secondary amine **C** provides a direct route to chiral β-phosphino aldehyde intermediates . The synthetic utility of the strategy was exemplified in a rapid one-pot (two-step) synthesis of highly enantioenriched 1,3-aminophosphines.

Optically active aldehydes constitute an important class of versatile precursors for the synthesis of chiral molecules. Not surprisingly, therefore, the rapidly expanding field of asymmetric organocatalysis[1] has focused great attention on their preparation either by enamine[2] or by iminium-ion[3] activation *via* chiral secondary amine catalysis.[4] Over the past few years, enormous progress has been achieved in the asymmetric functionalization of aldehydes with a wide range of electrophiles and nucleophiles. Thus, the organocatalytic enantioselective introduction of C-,[5] O-,[6] S-,[7] H-,[8] N-[9] and halogen-centered[10] reagents has been efficiently developed. However, looking at the periodic table, it is intriguing to note that not all the non-inert elements classified as "non-metals" have been stereoselectivily incorporated into aldehydes; surprisingly, the asymmetric introduction of P-based compounds has not been reported, in spite of the high synthetic potential of the phosphorus-adducts and the merits of an organocatalytic approach that, compared to a metal-catalyzed process, prevents product inhibition arising from the coordination ability of the phosphorus atom.

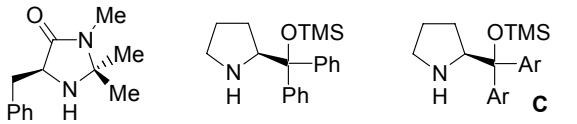
We document the successful exploitation of the iminium-ion activation strategy for the direct enantioselective addition of secondary phosphines to α,β-unsaturated aldehydes catalyzed by an easily available chiral secondary amine. To our knowledge, this study represents the first example of asymmetric hydrophosphination (AHP) of aldehydes, affording a direct access to highly enantioenriched β-phosphine aldehydes **3** [Eq. (1)] which, after simple manipulations, can provide potentially useful bidentate P-ligands.



Chiral phosphines, valuable ligands for metal-catalyzed enantioselective transformations, are generally prepared by resolution or by using a stoichiometric amount of chiral auxiliaries.[11] Thus, the development of more efficient catalytic methods for the enantioselective synthesis of optically active phosphines is of pressing current importance.[12] In this context, an organocatalytic AHP of α,β-unsaturated aldehydes is obviously highly desirable.

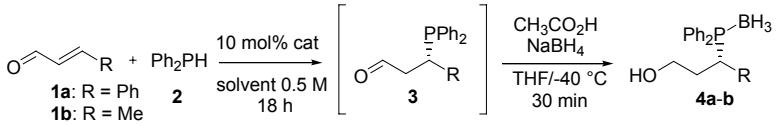
Recently, we have demonstrated the capability of a chiral tertiary amine to act as a base catalyst for the asymmetric addition of diphenyl phosphine to nitroolefins.[13] Given the known capability of the LUMO-lowering iminium catalysis to impart high chemo- and enantio-selectivity in conjugate additions,[3a] we considered this tactic as more suitable to accomplish the desired hydrophosphination of α,β-unsaturated aldehydes.

To assess the feasibility of such an organocatalytic hydrophosphination strategy, we focused upon the use of chiral secondary amines to catalyze the addition of diphenylphosphine **2** to cinnamaldehyde **1a** in toluene (Table 1). The sequential one-pot formation of the air-stable phosphine-borane alcohol derivative **4a**, generated *in situ* by employing a trivial procedure,[14] facilitates the purification process, rendering the adduct bench stable for a long time.



The reaction was screened with some of the most widely employed chiral secondary amines; in the presence of catalyst **B**·$PhCO_2H$, the desired product could be obtained in 52% ee (entry 2). To our delight, better enantiocontrol was achieved with catalyst **C**·$PhCO_2H$[15] (entry 3, 75% ee); a survey of the reaction media revealed that Et_2O induced better selectivity (entry 6, 87% ee).

Table 1: Selected screening results for the AHP of aldehydes.

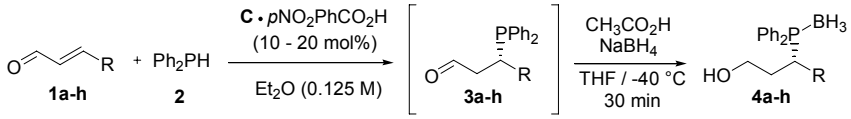


Entry	R	Catalyst	Solvent	T [C°]	[%] conv.[a]	[%] ee[b]
1	Ph	**A**·TFA	Toluene	RT	76	0
2	Ph	**B**·$PhCO_2H$	Toluene	RT	>95	52
3	Ph	**C**·$PhCO_2H$	Toluene	RT	>95	75
4	Ph	**C**·$PhCO_2H$	MeOH	RT	<5	-
5	Ph	**C**·$PhCO_2H$	CH_2Cl_2	RT	>95	32
6	Ph	**C**·$PhCO_2H$	Et_2O	RT	>95 (88)	87
7	Me	**C**·$PhCO_2H$	Et_2O	RT	>95	19
8	Me	**C**·$PhCO_2H$	Et_2O	-30	>95	30
9[c]	Me	**C**·*p*NO_2PhCO_2H	Et_2O	-30	85 (60)	84
10[c]	Ph	**C**·*p*NO_2PhCO_2H	Et_2O	-10	>95 (72)	94

[a] Conversion determined by ^{1}H NMR analysis; isolated yield is indicated between brackets. [b] Determined by chiral HPLC analysis. [c] $[\mathbf{2}]_0$ = 0.125 M.

Unfortunately, under the same reaction conditions exposure of crotonaldehyde **1b** to **2** did not provide the desired adduct **4b** in satisfactory enantiopurity, even at low temperature (entries 7 and 8). Further optimization of the standard reaction parameters revealed the nature of the acidic additive and reagent concentration as the crucial factors to improve the efficiency and generality of the catalytic system with both aromatic and aliphatic aldehydes. Carrying out the reaction in the presence of **C**·*p*NO_2PhCO_2H, at lower concentration ($[\mathbf{2}]_0$ = 0.125 M), both adducts **4a** and **4b** were obtained in high enantiomeric excess (entries 9 and 10). Thus, the superior level of induction and reaction efficiency exhibited by this system prompted us to select these conditions in order to explore the scope of the presented organocatalytic AHP of aldehydes.[16]

Table 2: Scope of the AHP of α,β-unsaturated aldehydes.[a]

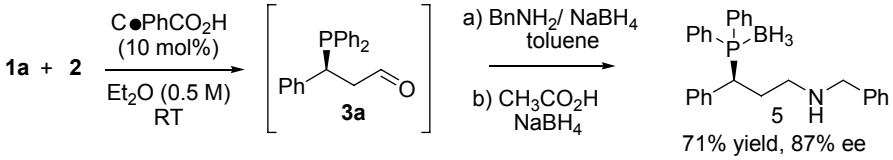


Entry	R	T [C°]	Time [h]	[%] yield[b]	[%]ee[c]
1	Ph, **1a**	-10	24	**4a** - 72	94
2	Ph, **1a**	-10	24	**4a** - 75	-94[d]
3	Me, **1b**	-30	36	**4b** - 60	84[e]
4	2-Furyl, **1c**	-30	48	**4c** - 64	90
5	*p*MeO-C_6H_4, **1d**	-30	24	**4d** - 67	93
6	*o*Cl-C_6H_4, **1e**	-30	44	**4e** - 62	81
7	Et, **1f**	-30	44	**4f** - 82	80
8	*i*Pr, **1g**	0	24	**4g** - 92	79
9	CH_3CH=CH, **1h**	0	36	**4h** - 68	75

[a] Reactions performed on a 0.2 mmol scale with 1.5 equiv of enal **1**. [b] Isolated yield. [c] Determined by HPLC analysis. [d] (*R*)-**C** was used as the catalyst. [e] Absolute configuration determined to be (*R*) by comparison of the specific optical rotation with the value reported in the literature.[17]

As highlighted in Table 2, the method proved successful for a wide range of enal substituents, including aryl, heteroaryl, alkyl and alkenyl groups, the desired products **4** being isolated in high to excellent enantiomeric excess (ee ranging from 75% to 94%) and good yields.

The sense of asymmetric induction, based on the (*R*) absolute configuration of compound **4b**,[17] is consistent with a "steric control approach"[15a] in which the efficient shielding of the chiral fragment in **C** determines the selective engagement of **2** with the *Re* face of the iminium intermediate.[18]



Scheme 1: Asymmetric One-Pot Synthesis of 1,3-Amino-Phosphines

A demonstration of the utility of this novel organocatalytic AHP is presented in the one-pot (two-step) conversion of simple aldehydes to enantioenriched 1,3-amino-phosphine derivatives; the AHP of **1a** under our catalytic conditions, followed by *in situ* reductive amination, provided the product **5** in 71% overall yield without erosion of the enantiomeric excess (Scheme 1). The easy swap from potentially useful chiral P-O ligands to P-N ligands,[19] by means of a simple and short manipulation, demonstrates the high synthetic potential of this transformation. In a broader sense, the organocatalytic AHP could provide a bridge between the two

complementary areas of asymmetric catalysis; organo- and metal-catalyzed transformations.

In summary, we have disclosed the first organocatalytic asymmetric β-functionalization of aldehydes with a P-centered nucleophile; the presented AHP constitutes an easy and efficient method for the direct preparation of highly enantioenriched phosphines.[20]

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[2] a) B. List, *Chem. Commun.* **2006**, 819; b) M. Marigo, K. A. Jørgensen, *Chem. Commun.* **2006**, 2001 and references therein. For a recent disclosure by dienamine catalysis, see: c) S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973.

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[4] For domino multicomponent reactions combining enamine-iminium activations, see: a) D. Enders, C. Grondal, R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570. For selected examples, see: b) J. W. Yang, M. T. Hechavarria Fonseca, B. List, *J. Am. Chem. Soc.* **2005**, *127*, 15036; c) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051; d) M. Marigo, T. Schulte, J. Franzen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 15710; e) D. Enders, C. Grondal, R. M. Hüttl, *Nature*, **2006**, *441*, 861; f) A. Carlone, S. Cabrera, M. Marigo, K. A Jørgensen, *Angew. Chem.* **2007**, *119*, 1119; *Angew. Chem. Int. Ed.* **2007**, *46*, 1101.

[5] For pioneering studies, see: a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395; b) W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874.

[6] For selected publications, see: a) G. F. Zhong, *Angew. Chem.* **2003**, *115*, 4379; *Angew. Chem. Int. Ed.* **2003**, *42*, 4247; b) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808; c) A. Bøgevig, H. Sunden, A. Córdova, *Angew. Chem.* **2004**, *116*, 1129; *Angew. Chem. Int. Ed.* **2004**, *43*, 1109; d) M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964; e) T. Govender, L. Hojabri, F. M. Moghaddam, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2006**, *17*, 1763; f) S. Bertelsen, P. Diner, R. L. Johansen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 1529.

[7] a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804; *Angew. Chem. Int. Ed.* **2005**, *44*, 794; b) W. Wang, H. Li, J. Wang, L. Zu, *J. Am. Chem. Soc.* **2006**, *128*, 10354. See also Ref 4d.

[8] a) J. W. Yang, M. T. Hechavarria Fonseca, N. Vignola, B. List, *Angew. Chem.* **2005**, *117*, 110; *Angew. Chem. Int. Ed.* **2005**, *44*, 108; b) S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 32.

[9] a) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656; b) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem.* **2002**, *114*, 1868; *Angew. Chem. Int. Ed.* **2002**, *41*, 1790; c) Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 9328; d) J. Vesely, I. Ibrahem, G.-L. Zhao, R. Rios, A. Córdova, *Angew. Chem.* **2007**, *119*, 792; *Angew. Chem. Int. Ed.*

2007, *46*, 778; e) P. Dinér, M. Nielsen, M. Marigo, K. A. *Angew. Chem.* **2007,** *119*, 2029; *Angew. Chem. Int. Ed.* **2007,** *46*, 1983.

[10] *α-Chlorination:* a) M. P. Brochu, S. P. Brown, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2004,** *126*, 4108; b) N. Halland, A. Braunton, S. Bachmann, M. Marigo, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004,** *126*, 4790. Review on *α-Fluorination:* c) P. M. Pihko, *Angew. Chem.* **2006,** *118*, 558; *Angew. Chem. Int. Ed.* **2006,** *45*, 544 and references therein; *α-Bromination and Iodination:* d) S. Bertelsen, N. Halland, S. Bachmann, M. Marigo, A. Braunton, Jørgensen, K. A. *Chem. Commun.* **2005**, 4821.

[11] a) H.-U. Blaser, E. Schmidt, Eds. *Asymmetric Catalysis on Industrial Scale. Challenges, Approaches, and Solutions*; Wiley-WCH: Weinheim, Germany, 2004; b) K. V. L. Crépy, T. Imamoto, *Top. Curr. Chem.* **2003,** *229*, 1; c) W. Tang, X. Zhang, *Chem. Rev.* **2003,** *103*, 3029.

[12] To our knowledge, just one highly effective metal-catalyzed AHP of methacrylonitrile has been recently reported: a) A. D. Sadow, I. Haller, L. Fadini, A. Togni, *J. Am. Chem. Soc.* **2004,** *126*, 14704; b) A. D. Sadow, A. Togni, *J. Am. Chem. Soc.* **2005,** *127*, 17012. For a review on phospha-Michael additions, see: c) D. Enders, A. Saint-Dizier, M.-I. Lannou, A. Lenzen, *Eur. J. Org. Chem.* **2006**, 29.

[13] G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, A. Mazzanti, L. Sambri, P. Melchiorre, *Chem. Commun.* **2007**, 722.

[14] a) J. McNulty, Y. Zhou, *Tetrahedron Lett.* **2004,** *45*, 407. Phosphine-borane deprotection can be easily accomplished under mild conditions, see: b) H. Brisset, Y. Gourdel, P. Pellon, M. Le Corre, *Tetrahedron Lett.* **1993,** *34*, 4523.

[15] a) C. Palomo, A. Mielgo, *Angew. Chem.* **2006,** *118*, 8042; *Angew. Chem. Int. Ed* **2006,** *45*, 7876 and references therein; b) J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjarsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005,** *127*, 18296.

[16] Other nucleophilic phosphorus reagents examined under the optimal conditions included di-*t*-butyl phosphine (no reaction after 24 h at RT), Ph_2PH-borane complex (0% ee) and diphenyl phosphine oxide (1,2 addition product).

[17] N. Boyer, M. Léautey, P. Jubault, X. Pannecoucke, J.-C. Quiron, *Tetrahedron: Asymmetry* **2005,** *16*, 2455.

[18] It should be noted that different substituents at the β-carbon of the iminium-ion intermediate could change the priority of the prochiral centre, switching the nomenclature of the considered enantiotopic face. Thus, the efficient shielding of the catalyst takes place at the *Si*-face or *Re*-face when the β-substituent of the iminium-ion intermediate is a methyl or an aryl group, respectively.

[19] For reviews on the utility of bidentate P-ligands, see: a) P. Braunstein, F. Naud, *Angew. Chem.* **2001,** *113*, 702; *Angew. Chem. Int. Ed.* **2001,** *40*, 680; b) P. J. Guiry, C. P. Saunders, *Adv. Synth. Catal.* **2004,** *346*, 497.

[20] After acceptance of the manuscript, we received a request from the Editor for a back-to-back publication with a similar manuscript by Cordova *et al.* which was submitted few days after ours. See: *Angew. Chem.* **2007,** *119*, 4591; *Angew. Chem. Int. Ed.* **2007,** *46*, 4507.

5.1.EP Experimental Part

Contents

General Methods. The ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded in $CDCl_3$ at 400 MHz, 100 MHz and 162 MHz, respectively. The chemical shifts (δ) are referenced to internal standard TMS (^{1}H NMR), to residual signals of the solvents ($CHCl_3$ - 77.0 ppm for ^{13}C NMR) and to external standard 85% H_3PO_4 (^{31}P NMR). Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh) according to the method of Still.[1] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Mass spectra were obtained from the Department of Organic Chemistry *"A. Mangini"* Mass Spectroscopy facility. Optical rotations are reported as follows: $[\alpha]^{rt}_{D}$ (*c* in g per 100 mL, solvent). All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted.

Materials. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[2]

α,β-unsaturated aldehyde **1e** was prepared following the procedure described in the literature.[3] Catalyst **C** was prepared according to literature procedure.[4]

Diphenyl phosphine **2** was purchased from Fluka and used as received. CAUTION: Phosphines are highly oxidizable and potentially toxic molecules. All reactions should be carried out in a well-ventilated hood.

Determination of Enantiomeric Purity. Chiral HPLC analysis was performed on an Agilent 1100-series instrumentation. Daicel Chiralpak AD-H or AS-H columns and Daicel Chiralcel OD-H column with *i*-PrOH/hexane as the eluent were used. HPLC traces were compared to racemic samples prepared by carrying out the reactions with racemic catalyst.

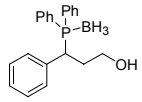
Determination of Absolute Configuration.

The absolute configuration of the optically active compounds **4b** was determined on the basis of the measured optical rotation that was compared with literature value.[5] All other absolute configurations were assigned by analogy based on an uniform reaction mechanism and the uniform elution order observed in the HPLC chromatograms.

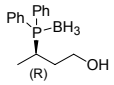
Experimental Procedures

General Procedure for the Organocatalytic AHP of Aldehydes. All hydrophosphination reactions were conducted under an atmosphere of argon in flame-dried round bottomed flasks fitted with rubber septa. Stainless steel syringes were used to transfer air and moisture sensitive liquids. Catalyst **C** (0.02

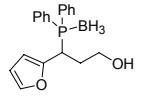
mmol, 12.0 mg) and *p*NO_2PhCO_2H (0.02 mmol, 3.3 mg) were placed in a 10 mL vial equipped with a Teflon-coated stir bar. Anhydrous Et_2O (1.6 mL) was added followed by the addition of the α,β-unsaturated aldehyde **1** (0.3 mmol, 1.5 equiv). The vial was capped and the resulting mixture was stirred at RT for 5 minutes and then cooled to the indicated temperature. After 10 minutes diphenyl phosphine **2** (0.2 mmol, 1 equiv, 34 µL) was added and stirring was continued. Upon completion of the reaction, the mixture was cooled to - 40 °C and diluted with 1.6 mL of anhydrous THF; solid $NaBH_4$ (0.7 mmol, 3.5 equiv, 26 mg) was added in one portion followed, after 20 minutes, by a solution of glacial acetic acid (0.6 mmol, 3 equiv, 34 µL) in THF (400 µL). Frothing occurs but is readily controllable through magnetic stirring of the solution. After 10 minutes the mixture was quenched with few drops of water. Brine (5 mL) was added and the resulting mixture extracted with AcOEt (3 × 5 mL). The combined organics were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (FC) to yield the desired air-stable phosphine-borane alcohol derivatives **4**.



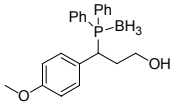
4a (Table 2, entries 1 and 2) **–** The reaction was carried out at –10 °C for 24 h using 10 mol% of catalyst **C**·*p*NO_2PhCO_2H following the general procedure. The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 70/30) in 72% yield and 94% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 7.9 min; τ_{major} = 8.7 min). $[\alpha]^{rt}_D$= - 151.1 (*c* = 0.91, $CHCl_3$, 94% ee). HRMS: *m/z* calcd for $C_{21}H_{24}BOP$: 334.16578; found: 334.1658. ^{31}P NMR: δ = + 24.3 (m); ^{1}H NMR: δ = 8.08-7.88 (m, 2H), 7.58-7.46 (m, 3H), 7.36-7.11 (m, 10H), 4.03 (ddd, *J* = 3.0, 12.3, 16.0 Hz, 1H), 3.63-3.56 (m, 1H), 3.38-3.32 (m, 1H), 2.39-2.24 (m, 1H), 2.18-2.04 (m, 1H), 1.09 (br q, 3H); ^{13}C NMR: δ = 135.0 (d, $J_{C\text{-}P}$ = 1.0 Hz), 133.1 (d, $J_{C\text{-}P}$ = 8.3 Hz), 132.6 (d, $J_{C\text{-}P}$ = 8.5 Hz), 131.4 (d, $J_{C\text{-}P}$ = 2.3 Hz), 130.7 (d, $J_{C\text{-}P}$ = 2.4 Hz), 130.0 (d, $J_{C\text{-}P}$ = 4.7 Hz), 128.9 (d, $J_{C\text{-}P}$ = 9.5 Hz), 128.3, 128.1, 128.0, 127.5, 127.2 (d, $J_{C\text{-}P}$ = 2.7 Hz), 59.8 (d, $J_{C\text{-}P}$ = 12.8 Hz), 38.9 (d, $J_{C\text{-}P}$ = 32.5 Hz), 32.8 (d, $J_{C\text{-}P}$ = 4.3 Hz).



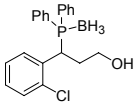
(*R*)-**4b** (Table 2, entry 3)[5] **–** The reaction was carried out at –30 °C for 36 h using 20 mol% of catalyst **C**·*p*NO_2PhCO_2H following the general procedure. The title compound was isolated as a white foam by column chromatography (DCM/AcOEt = 95/5) in 60% yield and 84% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (90/10 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 12.6 min; τ_{minor} = 13.3 min). $[\alpha]^{rt}_D$= - 3.4 (*c* = 0.73, $CHCl_3$, 84% ee). Lit.[5] $[\alpha]^{20}_D$= + 5.0, (*S*)-**4b**, (*c* = 1.1, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{16}H_{22}BOP$: 272.15013; found: 272.1499. ^{31}P NMR: δ = + 25.1 (m); ^{1}H NMR: δ = 7.86-7.69 (m, 4H), 7.52-7.39 (m, 6H), 3.90-3.51 (m, 2H), 3.01-2.80 (m, 1H), 1.92-1.75 (m, 1H), 1.71-1.51 (m, 2H), 1.15 (dd, *J* = 7.2, 16.8 Hz, 3H), 0.95 (br q, 3H); ^{13}C NMR: δ = 132.7, 132.6, 132.5, 128.9, 128.7, 128.6, 128.4, 128.3, 59.8 (d, $J_{C\text{-}P}$ = 12.6 Hz), 33.2 (d, $J_{C\text{-}P}$ = 3.1 Hz), 24.5 (d, $J_{C\text{-}P}$ = 9.9 Hz), 13.3 (d, $J_{C\text{-}P}$ = 8.6 Hz)



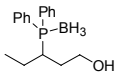
4c (Table 2, entry 4)**–** The reaction was carried out at –30 °C for 48 h using 10 mol% of catalyst **C**·*p*NO_2PhCO_2H following the general procedure. The title compound was isolated as a white solid by column chromatography (DCM/Et_2O = 98/2) in 64% yield and 90% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 7.8 min; τ_{major} = 9.5 min). $[\alpha]^{rt}_D$= - 21.7 (*c* = 1.13, $CHCl_3$, 90% ee). HRMS: *m/z* calcd for $C_{19}H_{22}BO_2P$: 324.14505; found: 324.1453. ^{31}P NMR: δ = + 24.9 (m); ^{1}H NMR: δ = 7.91-7.76 (m, 2H), 7.59-7.29 (m, 8H), 7.23-7.15 (m, 1H), 6.24-6.20 (m, 1H), 6.12-6.09 (m, 1H), 4.21 (ddd, *J* = 3.0, 11.9, 14.9 Hz, 1H), 3.72-3.63 (m, 1H), 3.51-3.40 (m, 1H), 2.27-2.15 (m, 1H), 2.13-2.00 (m, 1H), 1.05 (br q, 3H); ^{13}C NMR: δ = 149.5 (d, $J_{C\text{-}P}$ = 3.0 Hz), 141.7 (d, $J_{C\text{-}P}$ = 2.7 Hz), 141.7 (d, $J_{C\text{-}P}$ = 2.9 Hz), 132.8 (d, $J_{C\text{-}P}$ = 8.5 Hz), 131.3 (d, $J_{C\text{-}P}$ = 28.2 Hz), 128.8 (d, $J_{C\text{-}P}$ = 9.4 Hz), 128.3 (d, $J_{C\text{-}P}$ = 11.7 Hz), 128.1, 127.7, 127.6, 110.7 (d, $J_{C\text{-}P}$ = 11.4 Hz), 109.4 (d, $J_{C\text{-}P}$ = 10.4 Hz), 60.1 (d, $J_{C\text{-}P}$ = 12.0 Hz), 33.3 (d, $J_{C\text{-}P}$ = 3.0 Hz), 32.1 (d, $J_{C\text{-}P}$ = 4.8 Hz).



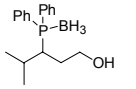
4d (Table 2, entry 5) – The reaction was carried out at –30 °C for 24 h using 20 mol% of catalyst **C**·*p*NO_2PhCO_2H following the general procedure. The title compound was isolated as a white solid by column chromatography (DCM/AcOEt = 97/3) in 67% yield and 93% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 11.0 min; τ_{major} = 12.0 min). $[\alpha]^{rt}_D$= - 104.6 (*c* = 1.04, $CHCl_3$, 93% ee). HRMS: *m/z* calcd for $C_{22}H_{26}BO_2P$: 364.17635; found: 364.1763. ^{31}P NMR: δ = + 23.8 (m); ^{1}H NMR: δ = 8.00-7.89 (m, 2H), 7.58-7.47 (m, 3H), 7.40-7.29 (m, 3H), 7.26-7.18 (m, 2H), 7.08-7.01 (m, 2H), 6.75-6.65 (m, 2H), 3.97 (ddd, *J* = 3.2, 12.4, 16.1 Hz, 1H), 3.74 (s, 3H), 3.65-3.55 (m, 1H), 3.36 (dt, *J* = 4.3, 10.2, 10.3, Hz, 1H), 2.32-2.18 (m, 1H), 2.13-2.01 (m, 1H), 1.05 (br q, 3H); ^{13}C NMR: δ = 158.7 (d, $J_{C\text{-}P}$ = 2.6 Hz), 133.1, 133.0, 132.6 (d, $J_{C\text{-}P}$ = 6.8 Hz), 131.1 (d, $J_{C\text{-}P}$ = 34.5 Hz), 131.0 (d, $J_{C\text{-}P}$ = 28.2 Hz), 128.8 (d, $J_{C\text{-}P}$ = 9.4 Hz), 128.4, 128.0 (d, $J_{C\text{-}P}$ = 12.0 Hz), 127.7, 126.7, 113.4 (d, $J_{C\text{-}P}$ = 1.8 Hz), 59.8 (d, $J_{C\text{-}P}$ = 12.8 Hz), 55.1 (d, $J_{C\text{-}P}$ = 8.2 Hz), 38.1 (d, $J_{C\text{-}P}$ = 35.6 Hz), 32.8 (d, $J_{C\text{-}P}$ = 4.4 Hz).



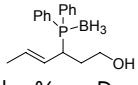
4e (Table 2, entry 6) – The reaction was carried out at –30 °C for 44 h using 20 mol% of catalyst **C**·*p*NO_2PhCO_2H following the general procedure. The title compound was isolated as a white solid by column chromatography (DCM/Et_2O = 98/2) in 62% yield and 81% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 8.2 min; τ_{major} = 10.7 min). $[\alpha]^{rt}_D$= - 60.7 (*c* = 1.0, $CHCl_3$, 81% ee). HRMS: *m/z* calcd for $C_{21}H_{23}BClOP$: 368.12681; found: 368.1263. ^{31}P NMR: δ = +23.5 (m); ^{1}H NMR: δ = 8.10-8.00 (m, 2H), 7.81-7.77 (m, 1H), 7.60-7.53 (m, 3H), 7.32-7.21 (m, 4H), 7.18-7.08 (m, 4H), 4.83 (ddd, *J* = 2.9, 11.8, 15.4 Hz, 1H), 3.61-3.50 (m, 1H), 3.38-3.27 (m, 1H), 2.39-2.21 (m, 1H), 2.17-2.06 (m, 1H), 1.05 (br q, 3H); ^{13}C NMR: δ = 171.1, 135.3 (d, $J_{C\text{-}P}$ = 6.0 Hz), 133.9, 133.2 (d, $J_{C\text{-}P}$ = 8.4 Hz), 132.5 (d, $J_{C\text{-}P}$ = 8.6 Hz), 131.6 (d, $J_{C\text{-}P}$ = 1.2 Hz), 130.7 (d, $J_{C\text{-}P}$ = 1.5 Hz), 130.5 (d, $J_{C\text{-}P}$ = 2.9 Hz), 129.1, 129.0 (d, $J_{C\text{-}P}$ = 9.6 Hz), 128.5 (d, $J_{C\text{-}P}$ = 1.6 Hz), 127.8 (d, $J_{C\text{-}P}$ = 9.9 Hz), 127.7, 127.0, 59.9 (d, $J_{C\text{-}P}$ = 12.7 Hz), 33.8 (d, $J_{C\text{-}P}$ = 4.7 Hz), 33.58 (d, $J_{C\text{-}P}$ = 33.4 Hz).



4f (Table 2, entry 7) – The reaction was carried out at –30 °C for 44 h using 20 mol% of catalyst **C**·*p*NO_2PhCO_2H following the general procedure. The title compound was isolated as a white foam by column chromatography (DCM/Et_2O = 98/2) in 82% yield and 80% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 11.6 min; τ_{major} = 14.5 min). $[\alpha]^{rt}_D$= + 2.1 (*c* = 0.97, $CHCl_3$, 80% ee). HRMS: *m/z* calcd for $C_{17}H_{24}BOP$: 286.16578; found: 286.1649. ^{31}P NMR: δ = + 21.7 (m); ^{1}H NMR: δ = 7.88-7.73 (m, 4H), 7.52-7.38 (m, 6H), 3.64-3.47 (m, 2H), 2.72-2.53 (m, 1H), 2.00-1.62 (m, 3H), 1.61-1.48 (m, 1H), 0.95 (br q, 3H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR: δ = 132.6, 132.6, 132.5, 131.1, 129.4, 129.2, 128.9, 128.8, 60.8 (d, $J_{C\text{-}P}$ = 9.5 Hz), 32.3 (d, $J_{C\text{-}P}$ = 3.1 Hz), 31.3 (d, $J_{C\text{-}P}$ = 10.7 Hz), 30.9 (d, $J_{C\text{-}P}$ = 10.6 Hz), 22.91 (d, $J_{C\text{-}P}$ = 2.1 Hz).



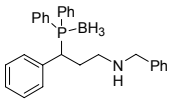
4g (Table 2, entry 8) – The reaction was carried out at 0 °C for 24 h using 20 mol% of catalyst **C**·*p*NO_2PhCO_2H following the general procedure. The title compound was isolated as a white foam by column chromatography (DCM/Et_2O = 97/3) in 92% yield and 79% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 6.6 min; τ_{major} = 7.0. min). $[\alpha]^{rt}_D$= + 4.1 (*c* = 1.04, $CHCl_3$, 79% ee). HRMS: *m/z* calcd for $C_{18}H_{26}BOP$: 300.18143; found: 300.1815. ^{31}P NMR: δ = + 23.1 (m); ^{1}H NMR: δ = 7.94-7.75 (m, 4H), 7.55-7.36 (m, 6H), 3.46-3.34 (m, 2H), 2.80-2.64 (m, 1H), 2.13-1.75 (m, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.89 (br q, 3H); ^{13}C NMR: δ = 132.6, 132.5, 132.4, 131.0, 130.1, 129.6, 129.1, 128.7, 61.7 (d, $J_{C\text{-}P}$ = 8.8 Hz), 35.0 (d, $J_{C\text{-}P}$ = 4.6 Hz), 34.7 (d, $J_{C\text{-}P}$ = 4.9 Hz), 28.1 (d, $J_{C\text{-}P}$ = 3.9 Hz), 27.6, 24.4 (d, $J_{C\text{-}P}$ = 11.6 Hz).



4h (Table 2, entry 9) – The reaction was carried out at 0 °C for 36 h using 20 mol% of catalyst **C**·*p*NO_2PhCO_2H following the general procedure. The title compound was isolated as a white foam by column chromatography (DCM/Et_2O = 99/1) in 68% yield and 75% ee. Due to the presence of the inseparable E/Z isomers in the aldehyde **1h** the title compound was obtained with a 10% of the Z product. The ee was determined by HPLC analysis using a Chiralpak AD-H column (90/10 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 10.9 min; τ_{major} = 12.7 min). $[\alpha]^{rt}_D$= - 26.7 (*c* = 1.2, $CHCl_3$, 75% ee). HRMS: *m/z* calcd for $C_{21}H_{24}BOP$: 298.16578; found: 298.166. ^{31}P NMR: δ = + 22.4 (m); ^{1}H NMR: δ = 7.87-7.78 (m, 1H), 7.71-7.62 (m, 1H), 7.55-7.31 (m, 8H), 5.38-5.28 (m, 2H), 3.76-3.66 (m, 1H), 3.65-3.52 (m, 1H), 3.45-3.32 (m, 1H), 1.88-1.70 (m, 2H), 1.57-1.53 (m, 3H), 1.05 (br q, 3H); ^{13}C NMR: δ = 132.8 (d, $J_{C\text{-}P}$ = 8.5 Hz), 132.7 (d, $J_{C\text{-}P}$ = 8.3 Hz), 131.4 (d, $J_{C\text{-}P}$ = 11.2 Hz), 131.2, 131.0 (d,

$J_{C\text{-}P}$ = 40.0 Hz), 129.5 (d, $J_{C\text{-}P}$ = 11.2 Hz), 128.8, 128.7 (d, $J_{C\text{-}P}$ = 9.4 Hz), 128.2 (d, $J_{C\text{-}P}$ = 9.7 Hz), 125.3, 60.1 (d, $J_{C\text{-}P}$ = 13.0 Hz), 36.1 (d, $J_{C\text{-}P}$ = 36.0 Hz), 31.7 (d, $J_{C\text{-}P}$ = 2.0 Hz), 17.9.

One-Pot (two-step) Direct Synthesis of Enantioenriched 1,3-Amino-Phosphine 5



5 – Catalyst **C** (0.02 mmol, 12.0 mg) and $PhCO_2H$ (0.02 mmol, 2.4 mg) were placed in a 10 mL vial equipped with a Teflon-coated stir bar. Anhydrous Et_2O (0.4 mL) was added under argon, followed by the addition of the cinnamaldehyde **1a** (0.3 mmol, 1.5 equiv). The vial was capped and the resulting mixture was stirred at RT for 5 minutes. Diphenyl phosphine **2** (0.2 mmol, 1 equiv, 34 µL) was added and stirring was continued at RT. Upon completion of the reaction (2 h), the mixture was diluted with 1.0 mL of anhydrous toluene, and benzylamine (0.6 mmol, 3.0 equiv., 65 µL) and $MgSO_4$ (50 mg) were added. After 1h vigorous stirring, solid $NaBH_4$ (0.8 mmol, 4.0 equiv, 30 mg) was added and the reaction stirred overnight. The mixture was then cooled to –40 °C and diluted with 1.6 mL of anhydrous THF, solid $NaBH_4$ (0.3 mmol, 1.5 equiv, 11 mg) was added in one portion followed by a solution of glacial acetic acid (0.6 mmol, 3 equiv, 34 µL) in THF (400 µL). Frothing occurs but is readily controllable through magnetic stirring of the solution. After 10 minutes the mixture was quenched with few drops of water. Brine (5 mL) was added and the resulting mixture extracted with AcOEt (3 × 5 mL). The combined organics were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (CH_2Cl_2/Et_2O = 85/15) to yield the desired 1,3-amino-phosphine-borane complex **5** in 71% overall yield and 87% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (90/10 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 9.8 min; τ_{minor} = 10.3 min). $[\alpha]^{rt}_D$= - 40.1 (*c* = 1.14, $CHCl_3$, 87% ee). HRMS: *m/z* calcd for $C_{28}H_{31}BNP$: 423.22871; found: 423.2282. ^{31}P NMR: δ = + 24.3 (m); ^{1}H NMR: δ = 8.02-7.91 (m, 2H), 7.58-7.46 (m, 3H), 7.40-7.09 (m, 15H), 4.00 (ddd, *J* = 2.78, 11.92, 15.69 Hz, 1H), 3.66 (d, AB, *J* = 13.34 Hz, 1H), 3.57 (d, AB, *J* = 13.34 Hz, 1H), 2.63-2.53 (m, 1H), 2.48-2.38 (m, 1H), 2.35-2.22 (m, 1H), 2.11-1.95 (m, 1H), 1.05 (br q, 3H); ^{13}C NMR: δ = 140.2 (d, $J_{C\text{-}P}$ = 3.6 Hz), 135.6 (d, $J_{C\text{-}P}$ = 0.9 Hz), 133.2 (d, $J_{C\text{-}P}$ = 8.2 Hz), 132.6 (d, $J_{C\text{-}P}$ = 8.4 Hz), 131.3 (d, $J_{C\text{-}P}$ = 2.3 Hz), 130.7 (d, $J_{C\text{-}P}$ = 2.4 Hz), 129.9 (d, $J_{C\text{-}P}$ = 4.7 Hz), 128.8 (d, $J_{C\text{-}P}$ = 9.5 Hz), 128.3 (d, $J_{C\text{-}P}$ = 6.5 Hz), 128.1, 128.0, 127.9 (d, $J_{C\text{-}P}$ = 2.1 Hz), 127.8, 127.7, 127.1 (d, $J_{C\text{-}P}$ = 2.7 Hz), 126.9 (d, $J_{C\text{-}P}$ = 7.1 Hz), 53.3 (d, $J_{C\text{-}P}$ = 30.2 Hz), 46.6 (d, $J_{C\text{-}P}$ = 12.6 Hz), 40.5 (d, $J_{C\text{-}P}$ = 31.9 Hz), 30.3 (d, $J_{C\text{-}P}$ = 4.3 Hz).

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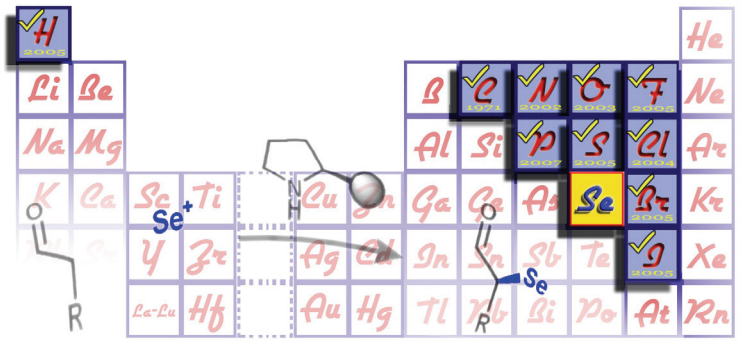
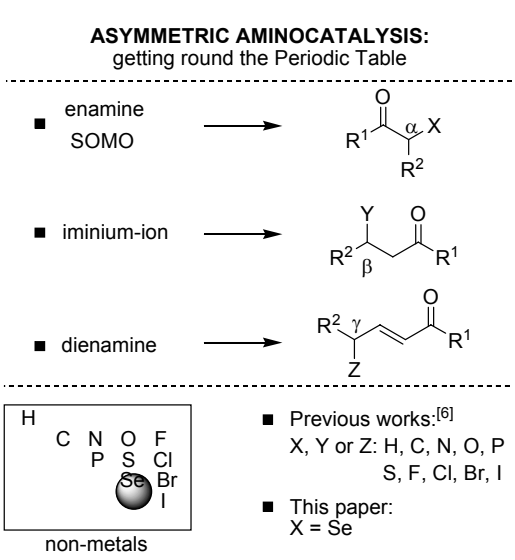
5.2 Organocatalytic Asymmetric α-Selenenylation of Aldehydes



Getting round the (Periodic) Table –Volume II-: The enamine activation concept has been extended to the asymmetric addition of selenium-based compounds to aldehydes in an organocatalytic transformation that provides high reaction efficiency and stereocontrol (ee values ranging from 95 to 99%) with readily available chiral secondary amines. The chiral α-seleno aldehydes thus formed can be used as versatile intermediates.

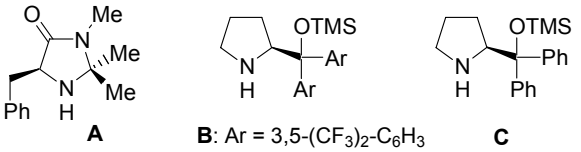
Asymmetric organocatalysis has become a field of central importance for the stereoselective preparation of chiral enantioenriched molecules.[1] In particular, chiral secondary amine catalysis has proven to be a powerful procedure for the enantioselective transformations of carbonyl compounds. By exploiting distinct catalytic activation modes such as enamine,[2] SOMO,[3] iminium-ion,[4] and dienamine[5] activation, aminocatalysis has enabled the asymmetric α-, β-, and γ-functionalization of aldehydes and ketones with a wide range of electrophiles and nucleophiles. Within the realm of the non-inert elements classified as "non-metals" in the Periodic Table, just Selenium-based compounds have not yet been stereoselectivily incorporated into carbonyls compounds using organocatalysis.[6]

We document the successful exploitation of the enamine activation strategy for the first highly enantioselective α-selenenylation of aldehydes catalyzed by an easily available chiral secondary amine.[7] This process provides access to highly attractive α-seleno aldehydes in high yield and excellent enantiomeric excess (ranging from 95 to 99%) from commercially available starting materials under mild and simple reaction conditions. The synthetic utility of such intermediates[8] was demonstrated by easy and rapid conversions to valuable chiral building blocks.



To date, the only access to chiral α-seleno aldehydes relies on the "chiral pool" approach that involves multistep procedures[9] and, to our knowledge, no catalytic enantioselective processes are available for the preparation of these useful optically active building blocks. On these grounds, and considering our recent efforts to expand the scope of asymmetric aminocatalysis,[10] we questioned whether the enamine activation concept might be successfully extended to the highly enantioselective introduction of Selenium-based compounds into aldehydes.

To assess the feasibility of such an asymmetric organocatalytic α-selenenylation strategy, we focused on the use of the bench-stable, commercially available *N*-(phenylseleno)phthalimide (**2**) as the electrophilic selenium source.[11] Exposure of propanal (**1a**) to **2** in the presence of 10 mol% of L-proline in CH_2Cl_2 (0.5 M) resulted in a clean but poorly selective aldehyde selenenylation (Table 1, entry 1). We then turned our attention on the use of imidazolidinone **A**[12] and the diarylprolinol silyl ethers **B** and **C** (TMS = trimethylsilyl),[13] which have emerged recently as potentially general enamine organocatalysts suitable for a broad range of highly selective α-functionalization of aldehydes.

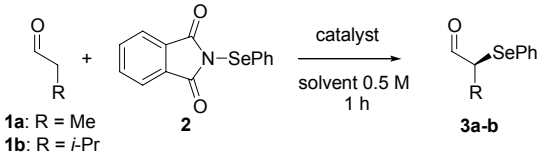


As reported in Table 1, preliminary studies indicated that both catalyst **B** and the TFA salt of catalyst **A** were able to promote the reaction with interesting levels of enantioselectivity (entries 2-5). Extensive evaluation of a variety of catalyst salts (entries 7-12) revealed that imidazolidinone **A**·DCA and **B**·*p*$NO_2C_6H_4COOH$ exhibited superior selectivity and, notably, much higher catalytic activity (entries 9 and 12, respectively). Significantly, these findings allowed us to reduce the loading of the

organocatalysts to 0.5 mol% without compromising the chemical and the optical yields (entries 13 and 14).[14]

Both the employed organocatalysts afforded the α-seleno aldehyde **3a** with (*S*) absolute configuration, as determined by comparison of the specific optical rotation with the value reported in the literature.[9] The sense of asymmetric induction is consistent with previously reported selectivity models in which the *Re*-face of the *E*-configured enamine intermediate is effectively shielded by the chiral fragments.[6e,12b,13b]

Table 1: Selected screening results for the α-Selenenylation of aldehydes. [a]



1a: R = Me
1b: R = *i*-Pr
2
3a-b

Entry	**1**	catalyst	mol%	Solvent	T [C°]	% conv.[b]	%ee[c]
1[d]	**a**	L-proline	10	CH_2Cl_2	RT	82	18
2	**a**	**A**·TFA	10	CH_2Cl_2	RT	>95	85
3	**a**	**B**	10	CH_2Cl_2	RT	>95	84
4	**a**	**A**·TFA	10	CH_2Cl_2	-20	44	90
5	**a**	**B**	10	CH_2Cl_2	-20	15	86
6	**a**	**C**	10	CH_2Cl_2	-20	83	78
7	**a**	**A**·*p*NO_2PhCO_2H	10	CH_2Cl_2	-20	53	87
8	**a**	**A**·TCA	10	CH_2Cl_2	-20	64	93
9	**a**	**A**·DCA	10	CH_2Cl_2	-20	>95	94
10	**a**	**B**·$PhCO_2H$	10	CH_2Cl_2	-20	47	88
11	**a**	**B**·*o*NO_2PhCO_2H	10	CH_2Cl_2	-20	54	91
12	**a**	**B**·*p*NO_2PhCO_2H	10	CH_2Cl_2	-20	65	91
13[e]	**a**	**A**·DCA	0.5	CH_2Cl_2	0	>95 (96)	92
14[f]	**a**	**B**·*p*NO_2PhCO_2H	0.5	CH_2Cl_2	0	>95 (95)	90
15[f]	**a**	**B**·*p*NO_2PhCO_2H	5	Toluene	0	>95 (99)	95
16[f]	**b**	**A**·DCA	5	CH_2Cl_2	-20	91	82
17[f]	**b**	**B**·*p*NO_2PhCO_2H	5	Toluene	0	95 (89)	99

[a] Reactions carried out on a 0.2 mmol scale with 1.5 equiv of aldehyde **1**; TFA: trifluorocetic acid; TCA: trichloroacetic acid; DCA: dichloroacetic acid; the absolute configuration of **3a** obtained with catalysts **A**-**C** was determined to be (*S*) by comparison of the specific optical rotation with the value reported in the literature.[9] [b] Conversion determined by ^{1}H NMR analysis; isolated yield is indicated between brackets. [c] ee values were determined by chiral HPLC analysis of the crude mixture and confirmed after reduction of **3a**-**b** to the corresponding alcohols. [d] The opposite (*R*) enantiomer of **3a** was obtained. [e] 40 h reaction time, 0.4 mmol scale. [f] 16 h reaction time, 0.4 mmol scale.

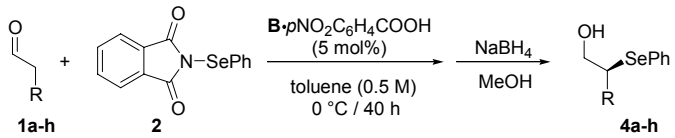
Finally, further optimization of the standard reaction parameters[15] revealed that carrying out the reaction in toluene 0.5 M in presence of catalyst **B**·*p*$NO_2C_6H_4CO_2H$ (5 mol%) induced higher stereocontrol (95% ee, entry 15), albeit at the expense of reactivity. On this basis, and considering the results obtained in the organocatalytic α-selenenylation of isovaleraldehyde (**1b**, entries 16 and 17), these

catalytic conditions were identified as the more consistent and general and thus selected for further explorations.

We next examined the scope of the aldehyde component in this enantioselective α-selenenylation strategy. To facilitate work-up, the reaction products were isolated as the alcohols **4** after in situ reduction of the aldehyde moiety with $NaBH_4$.[16] The reduction of the α-seleno aldehyde **3a** to **4a** demonstrated that this process occurs without loss of optical purity (entry 1, Table 2).

As highlighted in Table 2, the method proved successful for a wide range of aldehyde substituents, including alkyl, alkenyl, and hetero-substituted groups, the desired products **4** being isolated in excellent enantiomeric excess (ee ranging from 95% to 99%) and high yields. Similarly, the sterically encumbered aldehyde **1h** was transformed smoothly into the corresponding chiral alcohol **4h** with excellent chemical and optical yields (entry 9).[17] Notably, under these reaction conditions no side products such as aldol dimerization or the formation of α,α-diseleno aldehydes were observed.

Table 2: Asymmetric α-selenenylation: substrate scope.[a]

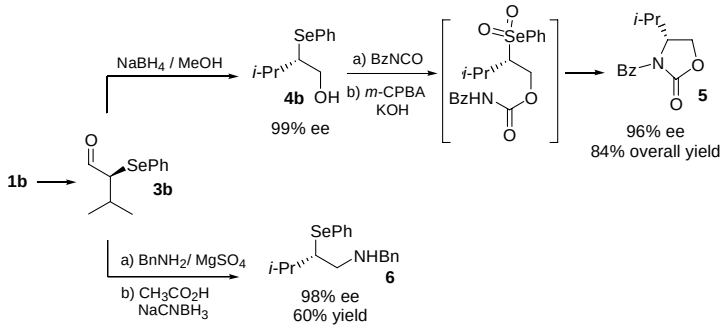


Entry	R	[%] yield[b]	[%] ee[c]
1	Me, **1a**	99 (**4a**)	95
2	*i*-Pr, **1b**	89 (**4b**)	99
3	*i*-Pr, **1b**	94 (*ent*-**4b**)	99[d]
4	Et, **1c**	84 (**4c**)	97
5	Bu, **1d**	99 (**4d**)	98
6	$PhCH_2$, **1e**	81 (**4e**)	97
7	allyl, **1f**	91 (**4f**)	98
8	CH_2SCH_3, **1g**	94 (**4g**)	98
9	*t*-Bu, **1h**	99 (**4h**)	99

[a] Reactions performed on a 0.4 mmol scale with 1.5 equiv of aldehyde **1**. [b] Isolated yield. [c] Determined by HPLC analysis. [d] (*R*)-**B** was used as the catalyst, affording the (*R*) enantiomer of compound **4b**.

This organocatalytic enantioselective α-selenenylation reaction of aldehydes provides highly versatile chiral building blocks for different synthetic transformations leading to valuable optically active compounds. Scheme 1 outlines some examples. The β-phenylseleno alcohol **4b**, generated from direct reduction of the aldehyde **3b**, was converted into the corresponding carbamate and then oxidized *in situ* in order to generate a selenonyl group. The stereospecific intramolecular nucleophilic substitution of this excellent leaving group by the nitrogen atom of the carbamate gave rise to the ring closure reaction, affording the highly enantioenriched 4-substituted 1,3-oxazolidinone **5**.[18] The (*R*) absolute configuration of **5**, determined by

comparison of the specific optical rotation with the value reported in the literature,[19] indicates that the substitution occurs with inversion of configuration. α-Selenenylated aldehydes can also undergo *in situ* reductive amination by treatment with benzylamine and $NaCNBH_3$ without loss in enantiomeric purity.[20] Interestingly, the phenylseleno amine **6**, generated in good yield and high enantioselectivity, constitutes a useful intermediate for the preparation of several compounds.[8]



Scheme 1: Synthetic transformations of α–seleno aldehydes.

In summary, we have disclosed an organocatalytic asymmetric α-selenenylation of aldehydes that employs unmodified and commercially available starting materials and catalysts under mild reaction conditions. Besides expanding the scope of asymmetric aminocatalysis, this transformation constitutes the first catalytic access to highly enantioenriched (ee's ranging from 95 to 99%) α-seleno aldehydes, versatile chiral intermediates for different synthetic transformations leading to valuable, optically active compounds.

5.2.R References

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[5] S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973.

[6] For selected publications, see: *Carbon*-based compounds: a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395; b) W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874. *Oxygen*-based compounds: c) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808; d) S. Bertelsen, P. Dinér, R. L. Johansen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 1536. *Sulphur*-based compounds: e) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804; *Angew. Chem. Int. Ed.* **2005**, *44*, 794; f) W. Wang, H. Li, J. Wang, L. Zu, *J. Am. Chem. Soc.* **2006**, *128*, 10354. *Hydride* transfer: g) J. W. Yang, M. T. Hechavarria Fonseca, N. Vignola, B. List, *Angew. Chem.* **2005**, *117*, 110; *Angew. Chem. Int. Ed.* **2005**, *44*, 108; h) S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 32. *Nitrogen*-based compounds: i) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656; j) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem.* **2002**, *114*, 1868; *Angew. Chem. Int. Ed.* **2002**, *41*, 1790; k) Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 9328; l) J. Vesely, I. Ibrahem, G.-L. Zhao, R. Rios, A. Córdova, *Angew. Chem.* **2007**, *119*, 792; *Angew. Chem. Int. Ed.* **2007**, *46*, 778; m) P. Dinér, M. Nielsen, M. Marigo, K. A. *Angew. Chem.* **2007**, *119*, 2029; *Angew. Chem. Int. Ed.* **2007**, *46*, 1983. *Halogen*-centered reagents: for a review see, n) P. M. Pihko, *Angew. Chem.* **2006**, *118*, 558; *Angew. Chem. Int. Ed.* **2006**, *45*, 544 and references therein; o) N. Halland, A. Braunton, S. Bachmann, M. Marigo, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 4790. *Phosphorus*-based compounds see ref [10a]; see also: p) I. Ibrahem, R. Rios, J. Vesely, P. Hammar, L. Eriksson, F. Himo, A. Córdova, *Angew. Chem.* **2007**, *119*, 4591; *Angew. Chem. Int. Ed.* **2007**, *46*, 4507.

[7] For a direct preparation of racemic α-seleno carbonyl compounds promoted by secondary amines via enamine catalysis, see: a) W. Wang, J. Wang, H. Lao, *Org. Lett.* **2004**, *6*, 2817; b) J. Wang, H. Li, Y. Mei, B. Lou, D. Xu, D. Xie, H. Guo, W. Wang, *J. Org. Chem.* **2005**, *70*, 5678. In these reports, initial attempts to perform an asymmetric catalytic version using the (*S*)-pyrrolidine tosyl sulfonamide and the MacMillan second generation imidazolidinone afforded poor selectivity (60% and 40% ee, respectively). See also, c) F. Giacalone, M. Gruttadauria, A. Mossuto Marculescu, R. Noto, *Tetrahedron Lett.* **2007**, *48*, 255.

[8] a) *Top. Curr. Chem.,* (Ed. T. Wirth), Springer-Verlag Berlin, **2000**; b) *Organoselenium Chemistry-A Practical Approach*. (Ed. T. G. Back), Oxford University Press Inc., New York, **2000**; c) C. Miniejew, F. Outurquin, X. Pannecoucke *Org. Biomol. Chem*., **2004**, *2*, 1575.

[9] a) J. N. Fitzner, R. G. Shea, J. E. Fankhauser, P. B. Hopkins, *J. Org. Chem.* **1985**, *50*, 417; b) R. G. Shea, J. N. Fitzner, J. E. Fankhauser, A. Spaltenstein, P. A. Carpino, R. M. Peevey, D. V. Pratt, B. J. Tenge, P. B. Hopkins, *J. Org. Chem.* **1986**, *51*, 5243.

[10] a) A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Melchiorre, *Angew. Chem.* **2007**, *119*, 4588; *Angew. Chem. Int. Ed.* **2007**, *46*, 4504; b) G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403.

[11] The use of a different electrophilic selenium source such as PhSeCl in the selenenylation of **1a** in the presence of catalysts **A** or **B** resulted in sluggish reaction with low conversion and poor enantioselectivity (lower than 10% ee)

[12] For selected examples, see: a) M. P. Brochu, S. P. Brown, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2004**, *126*, 4108; b) I. K. Mangion, A. B. Northrup, D. W. C. MacMillan, *Angew. Chem.* **2004**, *116*, 6890; *Angew. Chem. Int. Ed* **2004**, *43*, 6722; c) T. D. Beeson, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 8826; d) T. J. Peelen, Y. Chi, S. H. Gellman, *J. Am. Chem. Soc.* **2005**, *127*, 11598.

[13] For the use of catalyst B and C in enamine catalysis, see: a) C. Palomo, A. Mielgo, *Angew. Chem.* **2006**, *118*, 8042; *Angew. Chem. Int. Ed.* **2006**, *45*, 7876 and references therein; b) J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjarsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296; c) M. Marigo, D. Fielenbach, A. Braunton, A. Kjærsgaard, K. A.

Jørgensen, *Angew. Chem.* **2005**, *117*, 3769; *Angew. Chem. Int. Ed.* **2005**, *44*, 3703. See also Ref 6e.

[14] This condition responds to the actual trend of reducing the loading of catalyst, that until recently has been a longstanding limitation and source of criticism of asymmetric organocatalysis, see: a) S. Borman, *Chem. Eng. News* **2006**, *84* (46), 13; for recent examples of asymmetric organocatalytic transformations with catalyst loadings lower than 1 mol%, see: b) M. He, G. J. Uc, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 15088; c) F. Wu, R. Hong, J. Khan, X. Liu, L. Deng, *Angew. Chem.* **2006**, *118*, 4407; *Angew. Chem. Int. Ed.* **2006**, *45*, 4301.

[15] Solvent study for α-selenenylation of **3a** (10 mol% of the catalyst, -20 °C, 1 h reaction time) - catalyst **A**·DCA: CH_2Cl_2: >95% conversion, 94% ee; toluene: 47% conversion, 90% ee; THF: 50% conversion, 70% ee; acetone: 85% conversion, 87% ee. Catalyst **B**·*p*$NO_2C_6H_4COOH$: CH_2Cl_2: 65% conversion, 91% ee; toluene: 20% conversion, 95% ee; AcOEt: 15% conversion, 90% ee; Et_2O: 23% conversion, 94% ee; acetone: 29% conversion, 80% ee; EtOH: no reaction; $CHCl_3$: 17% conversion, 90% ee.

[16] The optically active α-seleno aldehyde **3a** slowly racemizes during column chromatography on silica gel; see Experimental Part for details.

[17] α,α-disubstituted aldehydes, such as 2-phenyl propanal, reacted smoothly under our α-selenation conditions to form quaternary stereocenters, albeit with low enantioselectivity: -20 °C, 10 mol% catalyst **B**·*p*$NO_2C_6H_4COOH$, 24 h, >95% conversion, 34% ee.

[18] M. Tiecco, L. Testaferri, A. Temperini, L. Bagnoli, F. Marini, C. Santi *Chem. Eur. J.* **2004**, *10*, 1752.

[19] M. Feroci, A. Inesi, L. Palombi, L. Rossi, G. Sotgiu *J. Org. Chem.* **2001**, *66*, 6185.

[20] The α-selenenylation step was carried out in CH_2Cl_2 at -10°C in presence of 10 mol% of **B**•*p*$NO_2C_6H_4COOH$ as the catalyst, affording the aldehyde intermediate **3b** in 98% ee.

5.2.EP Experimental Part

Contents

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 MHz and 100 MHz, respectively. The chemical shifts (δ) are referenced to internal standard TMS (^{1}H NMR) and to residual signals of the solvents ($CHCl_3$ - 77.0 ppm for ^{13}C NMR). Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; sept, septet; m, multiplet; br, broad signal. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh) according to the method of Still.[1] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Mass spectra were obtained from the Department of Organic Chemistry *"A. Mangini"* Mass Spectroscopy facility. Optical rotations are reported as follows: $[\alpha]^{rt}_{D}$ (*c* in g per 100 mL, solvent). All reactions were carried out in air and using undistilled solvent, without any precautions to exclude moisture unless otherwise noted.

Materials. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[2] Aldehyde **1a-h** were purchased from Aldrich or Alfa Aesar and used as received. Catalysts **A**,[3] **B**,[4] and **C**[5] were prepared according to literature procedure.

N-(Phenylseleno)-phthalimide **2** was purchased from Aldrich and used as received. Note that **2** is provided in 77% of purity (Technical grade) and the stoichiometry of the reaction was adjusted accordingly.

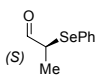
Determination of Enantiomeric Purity. Chiral HPLC analysis was performed on an Agilent 1100-series instrumentation. Daicel Chiralpak AD-H column and Daicel Chiralcel OD-H column with i-PrOH/hexane as the eluent were used.

HPLC traces were compared to racemic samples prepared by carrying out the reactions with racemic Proline as the catalyst.

Determination of Absolute Configuration.

The absolute configuration of the optically active α-seleno aldehyde **3a** was determined to be (*S*) on the basis of the measured optical rotation that was compared with the literature value.[6] All other absolute configurations were assigned by analogy based on an uniform reaction mechanism.

The absolute configuration of the optically active 1,3-oxazolidinone **5** was determined to be (*R*) on the basis of the measured optical rotation that was compared with the literature value.[7]

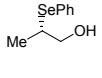


(*S*)-**3a** (Table 1, entry 9)[6,8] **–** The reaction was carried out at –20 °C for 1 h using 10 mol% of (*S*)-5-benzyl-2,2,3,-trimethylimidazolidin-4-one dichloroacetic acid salt (**A·DCA**, 13.9 mg, 0.04 mmol) as the catalyst. To an ordinary vial equipped with a Teflon-coated stir bar and charged with catalyst **A·DCA**, 0.8 mL of CH_2Cl_2 was added. After addition of 0.6 mmol (1.5 equiv., 43 μL) of propanal **1a**, the solution was stirred for 5 minutes at –20 °C. Then *N*-(Phenylseleno)-phthalimide **2**

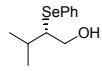
(0.4 mmol, 157 mg) was added in one portion, the vial was capped with a rubber stopper and stirring was continued for 1 h, after which the reaction mixture was directly charged on column chromatography. The ee of the crude reaction mixture was determined by HPLC analysis to be 94%. The title compound was isolated as a yellowish oil in 99% yield (84 mg) after column chromatography (hexane/AcOEt = 92/8) with a slight racemization (80% ee).[8] The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_R = 6.2 min; τ_S = 6.7 min). $[\alpha]^{rt}_D$= - 205.6 (*c* = 1.02, CH_2Cl_2, 80% ee. Lit.[6] $[\alpha]^{20}_D$= + 265-290, (*R*)-**3a**, (*c* = 1.8, CH_2Cl_2, 95% ee). HRMS: *m/z* calcd for $C_9H_{10}OSe$: 213.98969; found: 213.9897. ^{1}H NMR: δ = 1.47 (d, *J* = 6.8, 3H), 3.72 (dq, *J* = 2.8, 6.8 Hz, 1H), 7.26–7.38 (m, 3H), 7.50-7.55 (m, 2H), 9.45 (d, *J* = 2.8, 1H); ^{13}C NMR: δ = 13.4 (CH_3), 45.6 (CH), 125.7 (C), 128.9 (CH), 129.3 (CH), 136.1 (C), 193.5 (C).

Experimental Procedures

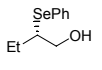
General Procedure for the Organocatalytic Asymmetric α-Selenenylation of Aldehydes. All the reactions were carried out in undistilled solvents without any precautions to exclude water. In an ordinary vial equipped with a Teflon-coated stir bar, catalyst **B** (0.02 mmol, 12.0 mg, 5 mol%) and *p*$NO_2C_4H_4CO_2H$ (0.02 mmol, 3.3 mg, 5 mol%) were dissolved in 0.8 mL of toluene (0.5 M). After addition of 0.6 mmol (1.5 equiv.) of the aldehyde **1**, the solution was stirred for 10 minutes at the indicated temperature (generally 0 °C). Then *N*-(Phenylseleno)-phthalimide **2** (0.4 mmol, 77% purity, 157 mg) was added in one portion, the vial was capped with a rubber stopper and stirring was continued for the indicated time (generally 40 h). Upon completion of the reaction, the mixture was cooled to 0 °C and diluted with 1.6 mL of MeOH; solid $NaBH_4$ (0.7 mmol, 1.75 equiv) was added in one portion. Frothing occurs but is readily controllable through magnetic stirring of the solution. After 30 minutes the mixture was quenched with few drops of water. Brine (5 mL) was added and the resulting mixture extracted with AcOEt (3 × 10 mL). The combined organics were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (FC) to yield the desired α-seleno alcohol derivatives **4**.



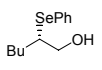
(*S*)-**4a** (Table 2, entry 1) – The reaction was carried out at 0 °C for 40 h using 5 mol% of catalyst **B**·*p*NO_2PhCO_2H following the general procedure. The title compound was isolated as a colourless oil by column chromatography (DCM/Et_2O = 95/5) in 99% yield and 95% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (90/10 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_S = 9.6 min; τ_R = 11.2 min). $[\alpha]^{rt}_D$= + 4.2 (*c* = 1.1, $CHCl_3$, 95% ee). HRMS: *m/z* calcd for $C_9H_{12}OSe$: 216.00534; found: 216.0053. ^{1}H NMR: δ = 1.41 (d, *J* = 7.2, 3H), 2.12 (br, OH), 3.33-3.41 (m, 1H), 3.48-3.63 (m, 2H), 7.26–7.32 (m, 3H), 7.55-7.59 (m, 2H); ^{13}C NMR: δ = 18.1 (CH_3), 43.1 (CH), 60.0 (CH_2), 127.2 (C), 128.0(CH), 129.1 (CH), 135.5 (C).



(*S*)-**4b** (Table 2, entry 2)– The reaction was carried out at 0 °C for 40 h using 5 mol% of catalyst **B**·*p*NO_2PhCO_2H following the general procedure. The title compound was isolated as a colourless oil by column chromatography (DCM/Et_2O = 97/3) in 89% yield and 99% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (90/10 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 7.5 min; τ_{major} = 8.5 min). $[\alpha]^{rt}_D$= - 11.6 (*c* = 1.5, $CHCl_3$, 98.5% ee). HRMS: *m/z* calcd for $C_{11}H_{16}OSe$: 244.03664; found: 244.0366. ^{1}H NMR: δ = 1.06 (d, *J* = 6.8, 3H), 1.08 (d, *J* = 6.8, 3H), 1.98-2.09 (m, 1H), 2.25 (br, OH), 3.14-3.20 (m, 1H), 3.63-3.71 (m, 1H), 3.71-3.78 (m, 1H), 7.25–7.28 (m, 3H), 7.56-7.59 (m, 2H); ^{13}C NMR: δ = 20.5 (CH_3), 21.1 (CH_3), 29.9 (CH), 60.0 (CH), 63.3 (CH_2), 127.5 (CH), 129.1 (CH), 134.5 (C).

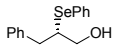


(*S*)-**4c** (Table 2, entry 4)– The reaction was carried out at 0 °C for 40 h using 5 mol% of catalyst **B**·*p*NO_2PhCO_2H following the general procedure. The title compound was isolated as a colourless oil by column chromatography (DCM/Et_2O = 97/3) in 84% yield and 97% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (90/10 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_S = 8.9 min; τ_R = 9.4 min). $[\alpha]^{rt}_D$= - 23.5 (*c* = 1.04, $CHCl_3$, 97% ee). HRMS: *m/z* calcd for $C_{10}H_{14}OSe$: 230.02099; found: 230.0211. ^{1}H NMR: δ = 1.09 (t, *J* = 7.2, 3H), 1.56-1.78 (m, 2H), 2.17 (dd, *J* = 5.6, 7.6, OH), 3.14-3.20 (m, 1H), 3.51-3.58 (m, 1H), 3.61-3.68 (m, 1H), 7.25–7.32 (m, 3H), 7.55-7.59 (m, 2H); ^{13}C NMR: δ = 12.5 (CH_3), 24.8 (CH_2), 52.4 (CH), 64.0 (CH_2), 127.4 (C), 127.9 (CH), 129.1 (CH), 135.4 (C).

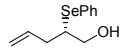


(*S*)-**4d** (Table 2, entry 5)– The reaction was carried out at 0 °C for 40 h using 5 mol% of catalyst **B**·*p*NO_2PhCO_2H following the general procedure. The title compound was isolated as a colourless oil by column chromatography (DCM/Et_2O = 97/3) in 99% yield and 98% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (90/10 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_S = 7.5 min; τ_R = 7.9 min). $[\alpha]^{rt}_D$= - 24.5 (*c* = 1.1, $CHCl_3$, 98% ee). HRMS: *m/z* calcd for $C_{12}H_{18}OSe$: 258.05228; found: 258.0523. ^{1}H NMR: δ = 0.90 (t, *J* = 7.2, 3H),

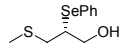
1.25-1.70 (m, 6H), 2.21 (br, OH), 3.20-3.26 (m, 1H), 3.49-3.56 (m, 1H), 3.59-3.65 (m, 1H), 7.25–7.31 (m, 3H), 7.55-7.58 (m, 2H); ^{13}C NMR: δ = 13.9 (CH_3), 22.5 (CH_2), 29.9 (CH_2), 31.4(CH_2), 50.6 (CH), 64.3 (CH_2), 127.4 (C), 127.4 (C), 127.9 (CH), 129.1 (CH), 135.4 (C).



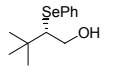
(*S*)-**4e** (Table 2, entry 6)**–** The reaction was carried out at 0 °C for 40 h using 5 mol% of catalyst **B**·*p*NO_2PhCO_2H following the general procedure. The title compound was isolated as a colourless oil by column chromatography (DCM/Et_2O = 97/3) in 81% yield and 97.2% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (90/10 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_R = 11.3 min; τ_S = 12.5 min). $[\alpha]^{rt}_D$= - 14.9 (*c* = 1.4, $CHCl_3$, 97% ee). HRMS: *m/z* calcd for $C_{15}H_{16}OSe$: 292.03664; found: 292.0365. ^{1}H NMR: δ = 2.14 (br, OH), 2.96-3.06 (m, 2H), 3.47-3.65 (m, 3H), 7.19–7.33 (m, 8H), 7.52-7.55 (m, 2H); ^{13}C NMR: δ = 38.2 (CH_2), 50.6 (CH), 63.1 (CH_2), 126.6 (CH), 127.7 (C), 128.0 (CH), 128.5 (CH), 129.1 (CH), 129.15 (CH), 135.2 (CH), 139.0 (C).



(*S*)-**4f** (Table 2, entry 7)**–** The reaction was carried out at 0 °C for 40 h using 5 mol% of catalyst **B**·*p*NO_2PhCO_2H following the general procedure. The title compound was isolated as a colourless oil by column chromatography (DCM/Et_2O = 97/3) in 91% yield and 98% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (90/10 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_R = 8.9 min; τ_S = 9.4 min). $[\alpha]^{rt}_D$= - 17.3 (*c* = 1.2, $CHCl_3$, 98% ee). HRMS: *m/z* calcd for $C_{11}H_{14}OSe$: 242.02099; found: 242.0209. ^{1}H NMR: δ = 2.11 (br, OH), 2.44-2.48 (m, 2H), 3.27-3.34 (m, 1H), 3.58 (dd, *J* = 6.0, 11.6 Hz, 1H), 3.66 (dd, *J* = 5.6, 11.6 Hz, 1H), 5.09–5.16 (m, 2H), 5.83-5.94 (m, 1H), 7.25–7.32 (m, 3H), 7.56-7.59 (m, 2H); ^{13}C NMR: δ = 36.3 (CH_2), 48.7 (CH), 63.9 (CH_2), 117.4 (CH), 127.3 (C), 128.0 (CH), 129.1 (CH), 135.4 (CH), 135.5 (C).

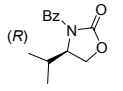


(*R*)-**4g** (Table 2, entry 8)**–** The reaction was carried out at 0 °C for 40 h using 5 mol% of catalyst **B**·*p*NO_2PhCO_2H following the general procedure. The title compound was isolated as a colourless oil by column chromatography (DCM/Et_2O = 97/3) in 94% yield and 98% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (90/10 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_S = 9.6 min; τ_R = 11.0 min). $[\alpha]^{rt}_D$= + 0.7 (*c* = 2.1, $CHCl_3$, 98% ee). HRMS: *m/z* calcd for $C_{10}H_{14}OSSe$: 261.99306; found: 261.9933. ^{1}H NMR: δ = 2.12 (s, 3H), 2.29 (t, *J* = 6.4, OH), 2.81 (dd, *J* = 9.6, 13.6 Hz, 1H), 2.94 (dd, *J* = 9.6, 13.6 Hz, 1H), 3.41-3.47 (m, 1H), 3.74–3.88 (m, 2H), 7.27–7.33 (m, 3H), 7.58-7.62 (m, 2H); ^{13}C NMR: δ = 16.1 (CH_3), 36.9 (CH_2), 47.4 (CH), 63.5 (CH_2), 127.1 (C), 128.3 (CH), 129.3 (CH), 135.5 (CH).



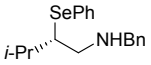
(*S*)-**4h** (Table 2, entry 9)**–** The reaction was carried out at 0 °C for 40 h using 5 mol% of catalyst **B**·*p*NO_2PhCO_2H following the general procedure. The title compound was isolated as a colourless oil by column chromatography (DCM/Et_2O = 97/3) in 99% yield and 99% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_R = 5.7 min; τ_S = 6.4 min). $[\alpha]^{rt}_D$= + 3.7 (*c* = 1.0, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{12}H_{18}OSe$: 258.05228; found: 258.0523. ^{1}H NMR: δ = 1.09 (s, 9H), 2.42 (br, OH), 3.13 (dd, *J* = 4.4, 8.8 Hz, 1H), 3.65 (dd, *J* = 8.8, 12.0 Hz, 1H), 3.83-3.92 (m, 1H), 7.23–7.28 (m, 3H), 7.58-7.62 (m, 2H); ^{13}C NMR: δ = 28.8 (CH_3), 34.9 (C), 61.1 (CH_2), 67.6 (CH), 127.4 (CH), 129.2 (CH), 134.1 (CH).

Synthesis of the 1,3-oxazolidinone 5



(*R*)-**5** (Scheme 1)[7] **–** In a 10 mL vial equipped with a Teflon-coated stir bar compound **4b** (0.4 mmol, 98 mg) was dissolved in CH_2Cl_2 (2 mL) and treated with benzoyl isocyanate (90% of purity, 0.44 mmol, 72 mg). The vial was capped with a rubber septum and the reaction was stirred under nitrogen at room temperature overnight. Then, the mixture was diluted with 5.0 mL of CH_2Cl_2 and K_2HPO_4 (2 mmol, 0.35 g) and MCPBA, (77% of purity, 1.6 mmol, 0.36 g) were added. After 15 minutes KOH (2.8 mmol, 0.16 g) was added and the mixture was stirred for 2 h, then quenched with water (10 mL) and extracted with diethyl ether (3 x 10 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (light petroleum/Et_2O = 60/40) to yield the (4*R*)-3-benzoyl-4-isopropyl-1,3-oxazolidin-2-one **5** in 84% yield and 96% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (85/15 hexane/*i*-PrOH; flow rate 0.8 mL/min; λ = 230 nm; τ_S = 14.3 min; τ_R = 15.6 min). $[\alpha]^{rt}_D$= - 105.0 (*c* = 0.3, AcOEt, 96% ee). Lit.[7] $[\alpha]^{20}_D$= + 155, (*S*)-**5**, (*c* = 1.0, AcOEt, 99% ee). ^{1}H NMR: δ = 1.0 (d, *J* = 6.9, 3H), 1.01 (d, *J* = 6.9, 3H), 2.51 (dsept, *J* = 4.4, 7.0, 1H), 4.28 (dd, *J* = 5.5, 9.0, 1H), 4.42 (t, *J* = 9.0, 1H), 4.71 (ddd, *J* = 4.4, 5.5, 9.0, 1H),7.43-7.49 (m, 2H), 7.54-7.59 (m, 1H), 7.71-7.66 (m, 2H); ^{13}C NMR: δ = 15.1 (CH_3), 17.9 (CH_3), 28.3 (CH), 58.6 (CH), 63.4 (CH_2), 127.9 (CH), 129.1 (CH), 132.4 (CH), 133 2 (C), 153.8 (C), 169.8 (C).

Synthesis of the N-benzyl seleno amine 6



(*S*)-**6** (Scheme 1) **–** In a 10 mL vial equipped with a Teflon-coated stir bar catalyst **B** (0.04 mmol, 24.0 mg) and *p*NO_2PhCO_2H (0.04 mmol, 6.7 mg) were dissolved in 0.8 mL of CH_2Cl_2. After addition of the aldehyde **1b** (0.6 mmol, 64.4 μL), the solution was stirred for 5 minutes at -10 °C. Then, N-(Phenylseleno)-phthalimide **2** (0.4 mmol, 157 mg) was added and the vial was capped with a rubber stopper. Stirring was continued for 2.5 h then the reaction was diluted with CH_2Cl_2 (3 mL) and $MgSO_4$ (0.24 g) was added.

The ee of the aldehyde intermediate **3b** was determined to be 98% by HPLC analysis of the crude reaction mixture (Chiralpak AS-H column, 85/15 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 230 nm; τ_{minor} = 6.2 min; τ_{major} = 6.7 min). The mixture was stirred for ten minutes and benzylamine (1 mmol, 109.0 μL) was added. After 4h vigorous stirring at room temperature EtOH (5 mL), $NaCNBH_3$ (0.25 mmol, 16 mg) and acetic acid (0.4 mmol, 23 μL) were added successively at -78 °C under nitrogen. The temperature was allowed to rise to room temperature in one hour and then the reaction was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (light petroleum/Et_2O = 80/20) to yield **6**[9] in 60% overall yield and 98% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (99.3/0.7 hexane/*i*-PrOH; flow rate 1.0 mL/min; λ = 230 nm; τ_S = 6.7 min; τ_R = 7.5 min). $[\alpha]^{rt}_D$= - 18.0 (*c* = 3.2, $CHCl_3$, 98% ee), ^{1}H NMR: δ = 1.03 (d, *J* = 6.8, 3H), 1.07 (d, *J* = 6.8, 3H), 1.82 (br s, 1H), 1.99-2.09 (m, 1H), 2.83 (dd, *J* = 8.5, 12.6, 1H), 2.92 (dd, *J* = *5.1*, 12.6, 1H), 3.29 (dt, *J* = 5.1, 8.5, 1H), 3.77 (d, *J* = *13.3*, 1H), 3.82 (d, *J* = 13.3, 1H), 7.25-7.38 (m, 8H), 7.50-7.55 (m, 2H); ^{13}C NMR: δ = 20.1 (CH_3), 21.0 (CH_3), 31.3 (CH), 51.7 (CH_2), 53.6 (CH_2), 56.7 (CH), 126.9 (CH), 127.2 (CH), 128.0 (CH), 128.4 (CH), 129.0 (CH), 130.1 (C), 134 4 (CH), 140.2 (C).

[1] W. C. Still, M. Kahn, A. J. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

[2] W. L. F. Armarengo, D. D. Perrin, In *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, 1996.

[3] a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am Chem Soc.* **2000**, *122*, 4243. b) W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am Chem Soc.* **2000**, *122*, 9874.

[4] M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794.

[5] The catalyst **C** can be easily prepared by protection of the commercial available α,α -diphenylprolinol with TMSOTf. See: J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen *J. Am. Chem. Soc.* **200**5, *127*, 18296.

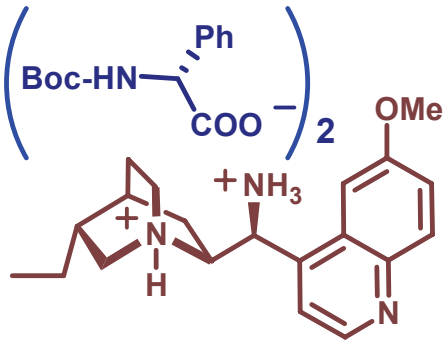
[6] a) R. G. Shea, J. N. Fitzner, J. E. Fankhauser, A. Spaltenstein, P. A. Carpino, R. M. Peevey, D. V. Pratt, B. J. Tenge, P. B. Hopkins, *J. Org. Chem*. **1986**, *51*, 5243; b) W. Wang, J. Wang, H. Lao, *Org. Lett.* **2004**, *6*, 2817.

[7] M. Feroci, A. Inesi, L. Palombi, L. Rossi, G. Sotgiu *J. Org. Chem*., **2001**, *66*, 6185.

[8] The authors in reference 6 stated that the α-seleno aldehyde **3a** was prone to racemization and all the attempts to isolate the title compound following standard procedures resulted in a slight racemization.

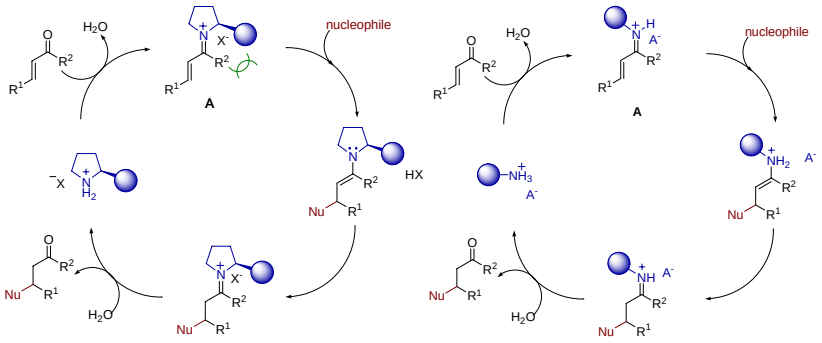
[9] C. Miniejew, F. Outurquin, X. Pannecoucke *Tetrahedron*, **2005**, *61*, 447.

6. A Novel Organocatalytic System for Iminium-Ion Activation of Ketones



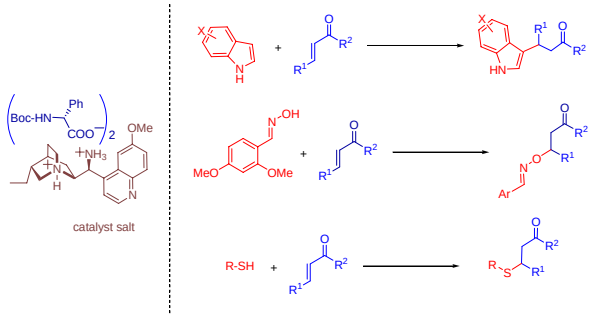
Over the past years chiral secondary amine catalysis has demonstrated great potentiality to induce high enantioselectivities in aldehydes within a vast number of reactions and reagents. Nevertheless it cannot exhibit a similar behaviour with ketones. Due to the importance of this class of compounds and their asymmetric functionalization, it is of demanding interest to develop a catalytic system for their activation. Moreover, similar to secondary amine catalysis, a general catalyst would be desirable.

The high interest in the enantioselective functionalization of ketones, prompted us to exploit our experience and to investigate their activation via iminium ion catalysis. However, the activation of ketones by secondary amines is difficult; this can be easily understood by looking at the catalytic cycle.



In the catalytic cycle of secondary amines, steric constraints hamper the formation of the active iminium ion species **A** and it is, therefore this issue that needs to be addressed. A primary amine would certainly display a lower steric hindrance and, upon protonation, activate α,β–unsaturated ketones towards β-addition.

In the following pages we will see our efforts toward the development of a general catalyst for iminium ion activation of α,β-unsaturated ketones. The potential benefit of using a less hindered chiral primary amine was our speculation; incidentally we already had the amine in figure in our lab, as we synthesized it as a precursor for another project.[1] This two elements combined together triggered our research; this is a vivid example that the mingling of knowledge coming from different research areas is of high importance.

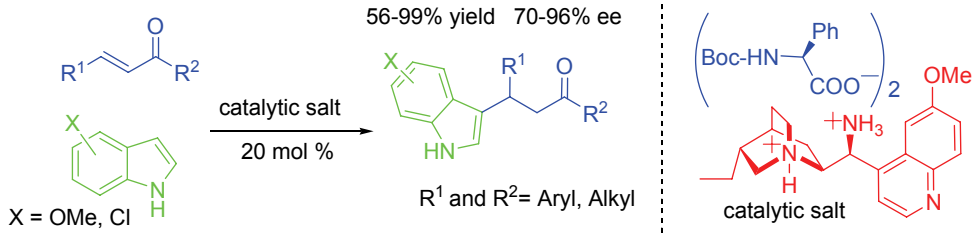


The results obtained with indoles, O- and S-nucleophiles render the system developed a reliable catalyst for broader application in the β-addition to unsaturated ketones.[2]

[1] G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, A. Mazzanti, L. Sambri, P. Melchiorre, *Chem. Commun.* **2007**, 722.

[2] For an upcoming account on the catalyst salt developed, see: G. Bartoli, P. Melchiorre, *submitted*.

6.1 Organocatalytic Asymmetric Friedel-Crafts Alkylation of Indoles with Simple α,β-Unsaturated Ketones



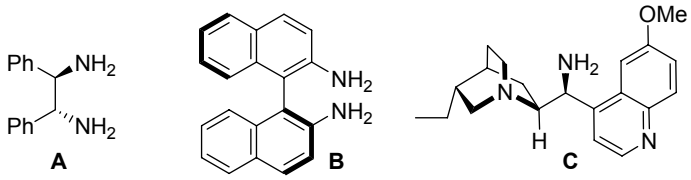
The first general and highly enantioselective organocatalytic Friedel-Crafts alkylation of indoles with simple α,β-unsaturated ketones has been accomplished. Central to these studies has been the identification of a new catalyst amine salt, in which both the cation and the anion are chiral, that exhibits high reactivity and selectivity for iminium ion catalysis.

The indole framework represents a privileged structural motif of established value in medicinal chemistry and complex target synthesis.[1] In this regard, the development of effective asymmetric entries to indole architecture constitutes an important research field. Over the past few years, the catalytic enantioselective additions of indoles to unsaturated carbonyl compounds, namely known as Friedel-Crafts (F-C)-type alkylation, have been the topic of particularly intensive investigations.[2] A number of highly selective metal-catalyzed asymmetric F-C reactions of bidentate chelating carbonyls have been developed,[3] whereas in 2002 MacMillan and co-workers[4] first demonstrated the feasibility of organocatalytic strategies based on LUMO-lowering activation of α,β-unsaturated aldehydes via the reversible formation of iminium-ion with chiral imidazolidinones.[5,6] Despite these recent advances, just one efficient metal-catalyzed asymmetric addition of indoles to mono-chelating ketones has been reported recently by the group of Bandini and Umani-Ronchi, affording the indolyl derivatives in moderate to good optical purity

but with important restrictions in substrate scope.[7,8] Thus, the use of simple α,β-unsaturated ketones still remains an important challenge for the asymmetric F-C alkylations of indoles.

We document the first efficient asymmetric organocatalytic addition of indoles to simple enones,[8] a general and operationally trivial protocol that allows rapid access to a broad range of highly enantioenriched β-indolyl derivatives (up to 96% ee). In particular, the successful application of the iminium-ion activation strategy to enone substrates was achieved by developing a new catalyst amine salt, in which both the cation and the anion are chiral.[9]

The proposed organocatalytic F-C alkylation strategy was first examined by reacting indole **1** with *trans*-4-phenyl-3-buten-2-one **2a** in the presence of a series of chiral amine salts as the catalysts (Table 1). Interestingly, secondary amines such as L-Proline (entry 1) and the MacMillan second generation imidazolidinone catalyst, which has previously enabled highly enantioselective nucleophilic addition to α,β-unsaturated ketones via iminum-ion catalysis,[10] afforded poor results.[8a] Considering the inherent problems of forming congested iminium ions from ketones, we questioned whether primary amines, owing to their reduced steric requirements, might be suitable for enone activation.[11-13]

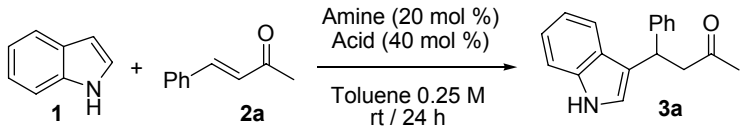


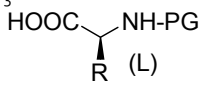
Preliminary studies confirmed that TFA salts of primary amines **A**-**B** were able to promote the reaction with good catalytic efficiency but with low levels of enantioselectivity (entries 2-3). Notably, the use of TFA salts of the easily available 9-amino(9-deoxy)*epi*-hydroquinine **C**, which was very recently described as an effective catalyst for enones activation,[12,13] afforded promising stereoinduction, albeit not yet satisfactory. We speculated that the nature of the counter-anion is the crucial factor for the optimization of the catalyst efficiency. With this consideration in mind, a survey of various salts of the chiral primary amine **C** was performed.

An extensive screen of the acidic additives, besides establishing the beneficial effect of a 1:2 ratio of amine **C** to co-catalyst (entries 4-5), revealed that the use of N-Boc glycine as an achiral counter-anion gave the product 3a with high enantiomeric excess (85% ee, entry 8) albeit at the expense of reactivity. Considering that asymmetric counterion directed catalysis (ACDC)[9] has recently been recognized as an efficient strategy for enantioselective transformations, we evaluated the efficiency of catalytic salts derived from the combination of C with a series of N-protected L-aminoacids. The absence of a protecting group in the amino acid had a deleterious effect on the catalytic activity (entry 9) whereas the variation of the chiral architecture had a substantial impact on reactivity but minimal impact on

stereoselectivity (entries 10-14). Surprisingly, employing the racemic or the opposite enantiomeric counterion, the same enantiomeric product **3a** was formed with very similar selectivity although with slightly different reactivity (entries 14-16).[14] On the basis of these studies, *D*-N-Boc phenylglycine was chosen for further investigations as it proved to be superior with regard to enantioselectivity and catalytic efficiency. Interestingly, the ee remained very high even at 70 °C, at which temperature the reaction reached completion after 24 h (entry 17).

Table 1: Selected Screening Results.[a]



entry	amine	acidic additive	convn (%)[b]	ee (%)[c]
1	L-Proline	-	0	-
2	**A**	TFA	85	-16
3	**B**	TFA	73	29
4	**C**	TFA	44	65
5	**C**	TFA[d]	23	61
6	**C**	*p*TSA	20	59
7	**C**	CF_3SO_3H	18	31
				
8	**C**	R: H PG: Boc	<5	85
9	**C**	R: Ph PG: H	0	-
10	**C**	R: *t*-Bu PG: Boc	7	89
11	**C**	R: Bn PG: Boc	8	90
12	**C**	R: Bn PG: Cbz	10	85
13	**C**	R: Bn PG: Fmoc	<5	86
14	**C**	R: Ph PG: Boc	16	90
15[e]	**C**	R: Ph PG: Boc	18	92
16[f]	**C**	R: Ph PG: Boc	21	93
17[f],[g]	**C**	R: Ph PG: Boc	>95	87

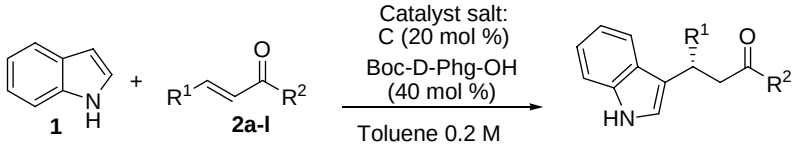
[a] For additional studied catalysts, additives and conditions, see the Experimental Part. [b] Determined by ^{1}H NMR of the crude mixture. [c] ee of **3a** was determined by HPLC analysis. [d] 20 mol % of TFA. [e] Racemic *N*-Boc phenylglycine (Boc-Phg-OH) was used. [f] (D)-Boc-Phg-OH was used. [g] 70 °C reaction temperature.

After optimizing the standard reaction parameters, the scope of this new organocatalytic F-C indole alkylation was explored using the condition reported in Table 2: there appears to be significant tolerance toward steric and electronic demands of the β-olefin substituent to enable access to a broad variety of highly enantioenriched β-indolyl ketones (entries 1-10).

Importantly, it is possible to decrease the catalyst loading to 10 mol % without affecting the efficiency of the system (entries 2 and 7); the products were isolated in high yield and enantioselectivity, increasing accordingly the reaction time.

Variation in the steric contribution of the R^2 ketone substituents (entries 11 and 13) reveals that the more encumbered ethyl group engenders higher selectivity, albeit with slightly lower reactivity.[14] Notably, our organocatalytic protocol is also effective with aromatic ketones (R^2 = Ph, entries 12 and 14), a class of substrates which, to our knowledge, has not yet been recognized as suitable for iminium-ion activation.

Table 2: Organocatalytic Alkylation of Indole **1** with Simple Enones.

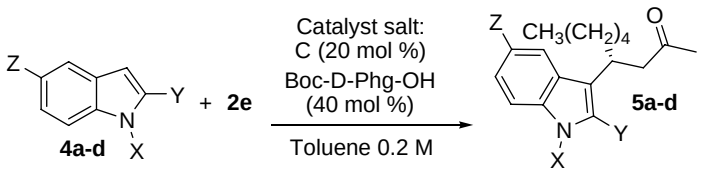


entry	R^1	R^2	temp (°C)	time (h)	% yield[a]	% ee[b]
1	Ph	Me, **2a**	70	24	**3a** - 90	88
2[c]	Ph	Me, **2a**	70	60	**3a** - 76	88
3	*p*-ClC_6H_4	Me, **2b**	70	24	**3b** - 92	89
4	2-thienyl	Me, **2c**	70	48	**3c** - 92	84
5	Me	Me, **2d**	40	70	**3d** - 98	87[d]
6	$CH_3(CH_2)_4$	Me, **2e**	rt	96	**3e** - 91	93
7[c]	$CH_3(CH_2)_4$	Me, **2e**	40	90	**3e** - 87	92
8	$Ph(CH_2)_2$	Me, **2f**	rt	96	**3f** - 67	93[d]
9	COOEt	Me, **2g**	50	66	**3g** - 99	95
10	$(CH_2)_3$, **2h**		40	70	**3h** - 65	78
11	Ph	Et, **2i**	70	72	**3i** - 56	95
12	Ph	Ph, **2j**	70	96	**3j** - 78	82
13	Me	Et, **2k**	50	72	**3k** - 76	96
14	Me	Ph, **2l**	70	90	**3l** - 94	70[d]

[a] Isolated yield. [b]Determined by HPLC analysis. [c] 10 mol % of **C** and 20 mol % of Boc-D-Phg-OH were employed. [d] Absolute configuration determined by comparison of the specific optical rotations with those reported in the literature.

The presented organocatalytic tactic is also general with respect to indole architecture, as electronic modification of the aromatic ring can be accomplished without affecting the efficiency of the system (Table 3, ee ranging from 92% to 94%).

Table 3: Organocatalytic Alkylation of Substituted Indoles with **2e**.



entry	indole substituents X	Y	Z	temp (°C)	time (h)	% yield[a]		% ee[b]
1	H		H	H, **1**	rt	96	**3e** - 91	93
2	H		CH_3	H, **4a**	rt	24	**5a** - 87	94
3[c]	H		CH_3	H, **4a**	rt	72	**5a** - 84	94
4	H		H	Cl, **4b**	40	96	**5b** - 74	92
5	H		H	MeO, **4c**	rt	40	**5c** - 76	93
6	CH_3		H	H, **4d**	70	48	**5d** - <5	62

[a] Isolated yield. [b] Determined by HPLC analysis. [c] 10 mol % of **C** and 20 mol % of Boc-D-Phg-OH were employed.

As a limitation of the approach, it is worth noting that substitution on the indolic nitrogen had a detrimental effect on both reactivity and selectivity (entry 6). This feature has already been observed in other organocatalytic F-C alkylation of indoles believed to proceed via a dual activation mechanism.[6a,b]

In summary, we have disclosed the first general and highly enantioselective organocatalytic Friedel-Crafts alkylation of indoles with simple α,β-unsaturated ketones. Central to these studies has been the identification of a new catalyst amine salt, in which both the cation and the anion are chiral, that exhibits high reactivity and selectivity for iminium ion catalysis.

6.1.R References

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[4] (a) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172-1173. (b) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482-5487. See also: (c) King, H. D.; Meng, Z.; Denhart, D.; Mattson, R.; Kimura, R.; Wu, D.; Gao, Q.; Macor, J. E. *Org. Lett.* **2005**, *7*, 3437-3440.

[5] For an excellent review on iminium-ion activation, see: Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79-87.

[6] For some leading examples that rely on different organocatalytic strategies, see: a) Török, B.; Abid , M.; London, G.; Esquibel, J.; Török, M. S.; Mhadgut, C.; Yan, P.; Prakash, G. K. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3086-3089. (b) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. E*d. **2005**, *44*, 6576-6579. (c) Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156-8157.

[7] (a) Bandini, M.; Fagioli, M.; Melchiorre, P.; Umani-Ronchi, A. *Tetrahedron Lett.* **2003**, *44*, 5846-5849. (b) Bandini, M.; Fagioli, M.; Garavelli, M.; Melloni, A.; Trigari, V.; Umani-Ronchi, A. *J. Org. Chem.* **2004**, *69*, 7511-7518.

[8] For an organocatalytic indole alkylation with enones promoted by an achiral amine, see: (a) Li, D.-P.; Guo, Y.-C.; Ding, Y.; Xiao, W.-J. *Chem. Commun.* **2006**, 799-801. In this report, an initial attempt to perform an asymmetric version using the MacMillan second generation imidazolidinone afforded poor selectivity (28% ee). Recently, a low selective (up to 29 % ee) addition of indole to chalcone promoted by *D*-camphorsulfonic acid was reported, see: (b) Zhou, W.; Xu, L.-W.; Li, L.; Yang, L.; Xia, C.-G. *Eur. J. Org. Chem.* **2006**, 5225-5227. See also ref. 13.

[9] During our studies, the successful application of a similar ACDC tactic for the enantioselective hydrogenation of simple enones was described, see: (a) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368-13369. See also: (b) Mayer, S.; List, B. *Angew. Chem., Int. E*d. **2006**, *45*, 4193-4195.

[10] (a) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458-2460. (b) Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662-12663. For selected examples using other secondary chiral amines, see: (c) Halland, N.; Hansen, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955-4957. (d) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272-1276. (e) Hanessian, S.; Shao, Z.; Warrier, J. S. *Org. Lett.* **2006**, *8*, 4787-4790.

[11] For recent use of primary amine salts in asymmetric iminium catalysis with unsaturated ketones, see: Kim, H.; Yen, C.; Preston, P.; Chin, J. *Org. Lett.* **2006**, *8*, 5239-5242. See also ref. 9a.

[12] During our studies, the TFA salt of 9-amino(9-deoxy)*epi*-quinine was reported to be an excellent catalyst for the asymmetric conjugate addition of carbon-centered nucleophiles to α,β-unsaturated ketones: (a) Xie, J.-W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem. Int. Ed.* **2007**, *46*, 389-392. (b) J.-W. Xie, L. Yue, W. Chen, W. Du, J. Zhu, J.-G. Deng, Y.-C. Chen, *Org. Lett.* **2007**, *9*, 413-415.

[13] After our original submission, the asymmetric alkylation of indoles with unsaturated ketones catalyzed by 30 mol% of the CF_3SO_3H salt of 9-amino(9-deoxy)*epi*-quinine was reported, affording moderate to good level of enantioselectivity (ee ranging from 47% to 89%), see: (a) Chen, W.; Du, W.; Yue, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2007**, *5*, 816.

[14] The use of a more encumbered R^2 group resulted in lower reactivity; R^2 = *c*-hexyl: 23% yield, 81% ee after 96 h at 70 °C.

6.1.EP Experimental Part

Contents

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts (δ) are referenced to residual signals of the solvents ($CHCl_3$ – 7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR). Coupling constants are given in Hz. Carbon types were determined by DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh) according to the method of Still.[1] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Mass spectra were obtained from the Department of Organic Chemistry *"A. Mangini"* Mass Spectroscopy facility. Optical rotations are reported as follows: $[\alpha]^{rt}_{D}$ (*c* in g per 100 mL, solvent). All reactions were carried out in air and using undistilled solvent, without any precautions to exclude moisture unless otherwise noted.

Materials. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[2] Indoles **1** and **4a-d** were purchased from Aldrich and used as received. α,β-Unsaturated ketones **2a-e**, **2h** and **2j-k** were purchased from Aldrich or Lancaster and used as received. Enones **2f** and **2g** were prepared by Wittig reaction between commercially available acetylmethylene-triphenylphosphorane and hydrocinnamaldehyde or ethyl glyoxalate, respectively, (DCM/48 h/RT). Enones **2i**[3] and **2l**[4] were synthesized following the literature procedures. *N*-protected amino acids were purchased from Aldrich or Fluka and used as received. Chiral primary amines **A** and **B** were purchased from Aldrich and used as received.

9-Amino(9-deoxy)*epi*-hydroquinine **C** was prepared from commercially available hydroquinine following the literature procedure.[5]

Determination of Enantiomeric Purity. Chiral HPLC analysis was performed on an Agilent 1100-series instrumentation. Daicel Chiralpak AD-H or AS-H columns and Daicel Chiralcel OD-H with i-PrOH/hexane as the eluent were used. HPLC traces were compared to racemic samples prepared by $InBr_3$-catalyzed F-C reaction.[6]

Determination of Absolute Configuration. The absolute configurations of the optically active compounds **3d**[7], **3f**[8] and **3l**[9] were determined on the basis of the measured optical rotations that were compared with literature values. All other absolute configurations were assigned by analogy based on an uniform reaction mechanism and the uniform elution order observed in the HPLC chromatograms.

Organocatalytic Asymmetric Addition of Indole to *E*-Benzylidenaceton 2a

Catalyst Screen.

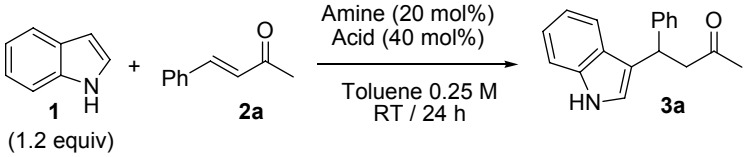
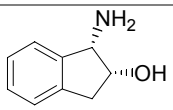
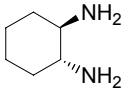
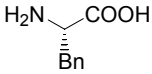
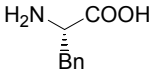
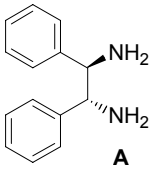
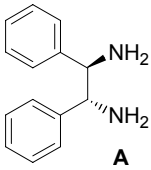
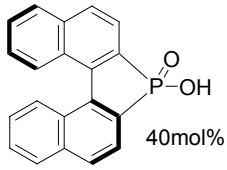
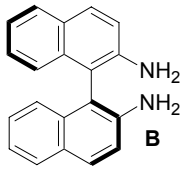
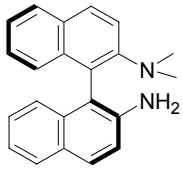
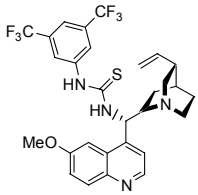
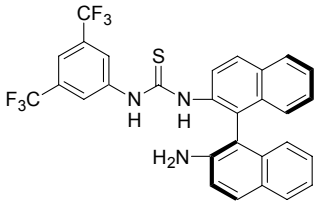
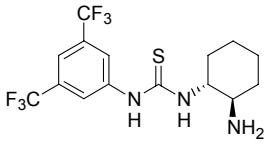
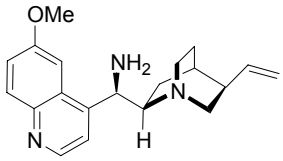
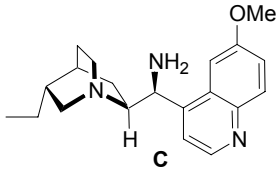
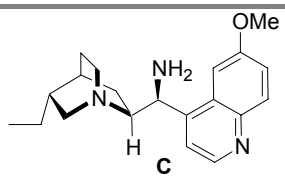


Table S1. Catalyst screen.[a]

Amine	Acid	Conversion (%)[b]	ee (%)[c]
	TFA	18	0
	TFA	90	0
L-Proline	-	0	-
	-	0	-
	TFA (20 mol%)	<5%	<5%
 **A**	TFA	85	-16
 **A**	 40mol%	0	-

 **B**	TFA	73	29
	TFA	18	5
	-	0	-
	TFA (20 mol%)	80	6
	TFA (20 mol%)	0	-
 **9-*Epi*-QD-NH$_2$**	TFA (40 mol%)	22	53
 **C** **9-*Epi*-HQ-NH$_2$**	TFA (20 mol%)	23	61

 **9-*Epi*-HQ-NH$_2$**	TFA (40 mol%)	44	65

[a] Open-air reactions were carried out in undistilled toluene using a 1.2:1 ratio of **1** to **2a**, 20 mol% of the catalyst, 40 mol% of the acid on a 0.2 mmol scale. [b] Determined by ^{1}H NMR of the crude mixture. [c] ee of **3a** was determined by HPLC analysis on a Daicel Chiralpak AD-H column.

Acidic Additives Screen.[a]

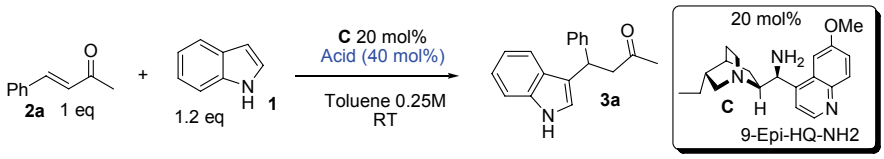
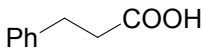
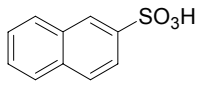
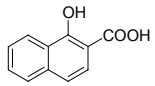
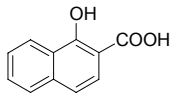
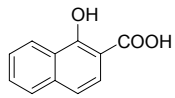
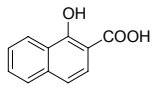


Table S2. Acidic Additives Screen.a

Acid	Conv (%) – 24h[b]	ee (%)[c]
TFA (20 mol%)	23	61
TFA	44	65
CF_3SO_3H	18	31
p-NO_2-Benzoic acid	7	80
o-NO_2-Benzoic acid	24	79
	No reaction	-
	No reaction	-
p-TSA	20	59
	25	82
	THF / 2	88
	AcOEt / 5	78
	$CHCl_3$ / 23	82

[a] Open-air reactions were carried out in undistilled solvent using a 1.2:1 ratio of **1** to **2a,** 20 mol% of the catalyst, 40 mol% of the acid on a 0.2 mmol scale. [b] Determined by ^{1}H NMR of the crude mixture. [c] ee of **3a** was determined by HPLC analysis (AD-H column).

Amino acids Screen.[a]

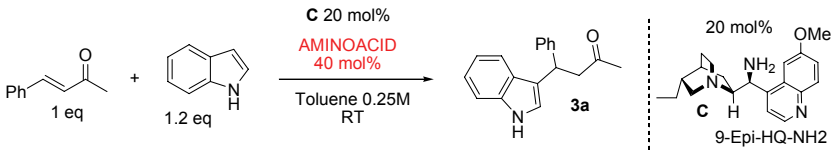
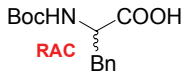
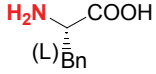
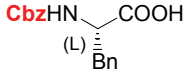
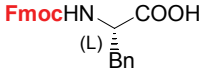
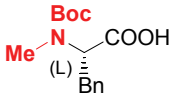
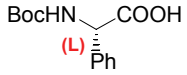
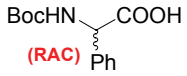
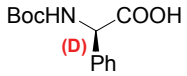
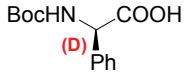
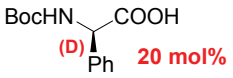


Table S3: Amino acids Screen.a

Aminoacid	Conv (%) – 24h[b]	*ee (%)*[c]
-	No reaction	
BocHN COOH	<5	85
BocHN COOH (L) *t*-Bu	7 20 (5days)	89
BocHN COOH (L) *t*-Bu 10 mol% + TFA 10 mol%	12	76
BocHN COOH (L) OH	No reaction	-
BocHN COOH (L) NH	6	78
BocHN COOH (L)	6	89
BocHN COOH (L)	5	90
BocHN COOH (D) Bn	9	89
BocHN COOH (L) Bn	8	90

	9	89
	No reaction	-
	10	85
	<5	86
	<5 (48h)	84
	16	90
	18	92
	21	93
	>95	87[d]
	62	87[d]

[a] Open-air reactions were carried out in undistilled toluene using a 1.2:1 ratio of 1 to 2a, 20 mol% of the catalyst, 40 mol% of the acid on a 0.2 mmol scale. [b] Determined by ^{1}H NMR of the crude mixture. [c] ee of 3a was determined by HPLC analysis (AD-H column). [d] 70 °C reaction temperature.

Optimisation of the Standard Reaction Parameters.

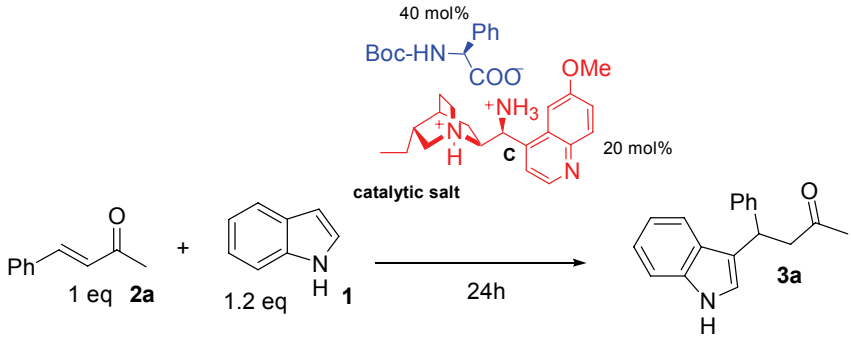


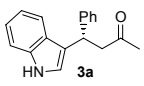
Table S3. Standard Reaction Parameters.

solvent	[**2a**]$_0$	*T* (°C)	Conversion (%)[b]	ee (%)[c]
toluene	0.25 M	70	>95	87
toluene: 9 *i*-PrOH : 1	0.25 M	70	90	85
H_2O: 9 THF: 1	0.25 M	70	>95	36
CH_3Cl	0.25 M	70	>95	80
THF	0.25 M	70	14	56
(*n*-Bu)$_2$O	0.25 M	70	42	87
toluene	0.1 M	70	50	90
toluene	0.5 M	70	>95	84
toluene	1 M	50	>95	78
EtOH	1 M	50	84	62
toluene	**0.2 M**	**70**	**>95 (90)[d]**	**88**

[a] Open-air reactions were carried out in undistilled solvent using a 1.2:1 ratio of **1** to **2a**, 20 mol% of the catalyst, 40 mol% of the acid on a 0.2 mmol scale. [b] Determined by ^{1}H NMR of the crude mixture. [c] ee of **3a** was determined by HPLC analysis (AD-H column). [d] Isolated yield is reported in parenthesis.

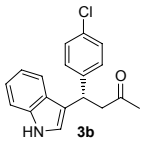
Experimental Procedures

General Procedure for the Organocatalytic Asymmetric Friedel-Crafts Alkylation of Indoles with Simple α,β-Unsaturated Ketones. All the reactions were carried out in undistilled toluene without any precautions to exclude water. In an ordinary test tube equipped with a magnetic stirring bar, 9-Amino(9-deoxy)*epi*-hydroquinine **C** (0.04 mmol, 13.0 mg) was dissolved in 1 mL of toluene. After addition of 0.08 mmol (20 mg) of D-*N*-Boc-phenylglycine, the solution was stirred for 5 minutes at room temperature. After addition of α,β-unsaturated ketones (0.2 mmol), the mixture was stirred at the indicated temperature for 10 minutes. Then indole derivatives (0.24 mmol) was added in one portion, the tube was closed with a rubber stopper and stirring was continued for the indicated time (24-96 h). Then the crude reaction mixture was diluted with hexane (2 mL) and flushed through a plug of silica, using hexane/Et_2O 1/1 as the eluent. Solvent was removed *in vacuo*, and the residue was purified by flash chromatography to yield the desired F-C-adduct.



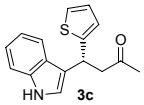
3a

(S)-4-(1*H*-Indol-3-yl)-4-phenyl-butan-2-one[10,11] **- 3a** (Table 2, entries 1-2). The reaction was carried out at 70 °C for 24 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 85/15) as a white foam in 90% yield and 88% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 10.2 min; τ_{major} = 10.8 min). $[\alpha]^{rt}_D$= + 20.3 (*c* = 0.95, $CHCl_3$, 88% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 3.16 (dd, *J* = 7.6, 16.0 Hz, 1H), 3.25 (dd, *J* = 7.6, 16.0 Hz, 1H), 4.84 (t, *J* = 7.6 Hz, 1H), 6.96-6.99 (m, 1H), 7.00-7.05 (m, 1H), 7.12-7.20 (m, 2H), 7.23-7.33 (m, 5H), 7.42 (d, *J* = 8 Hz, 1H), 8.02 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 30.3 (CH_3), 38.4 (CH), 50.3 (CH_2), 111.1 (CH), 118.8 (C), 119.39 (CH), 119.41 (CH), 121.3 (CH), 122.1 (CH), 126.4 (CH), 126.5 (C), 127.7 (CH), 128.5 (CH), 136.6 (C), 143.9 (C), 207.6 (C).



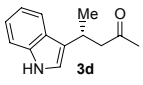
3b

(S)-4-(4-Chloro-phenyl)-4-(1*H*-indol-3-yl)-butan-2-one – 3b (Table 2, entry 3). The reaction was carried out at 70 °C for 24 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 7/3) as a white foam in 92% yield and 89% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 9.6 min; τ_{major} = 11.5 min). $[\alpha]^{rt}_D$= + 10.9 (*c* = 1.04, $CHCl_3$, 89% ee). HRMS: *m/z* calcd for $C_{18}H_{16}NOCl$: 297.092043; found: 297.09175. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12 (s, 3H), 3.16 (dd, *J* = 8.0, 16.0 Hz, 1H), 3.27 (dd, *J* = 7.2, 16.0 Hz, 1H), 4.85 (t, *J* = 7.2 Hz, 1H), 6.97-7.00 (m, 1H), 7.04-7.09 (m, 1H), 7.17-7.22 (m, 1H), 7.24-7.30 (m, 4H), 7.33-7.36 (m 1H), 7.40-7.44 (m 1H), 8.11 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 30.4 (CH_3), 37.6 (CH), 50.0 (CH_2), 111.2 (CH), 118.3 (C), 119.2 (CH), 119.5 (CH), 121.2 (CH), 122.2 (CH), 126.3 (C), 128.5 (CH), 129.1 (CH), 131.9 (C), 136.6 (C), 142.5 (C), 207.2 (C).



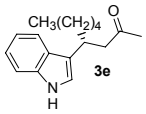
3c

(R)-4-(1*H*-Indol-3-yl)-4-thiophen-2-yl-butan-2-one – 3c (Table 2, entry 4). The reaction was carried out at 70 °C for 48 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 75/25) as a yellowish oil in 92% yield and 84% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 10.4 min; τ_{major} = 12.1 min). $[\alpha]^{rt}_D$= + 2.88 (*c* = 0.47, $CHCl_3$, 84% ee). HRMS: *m/z* calcd for $C_{16}H_{15}NOS$: 269.08743; found: 269.087. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11 (s, 3H), 3.24-3.34 (m, 2H), 5.14 (t, *J* = 7.6 Hz, 1H), 6.88-6.92 (m, 2H), 7.03-7.13 (m, 3H), 7.16-7.20 (m, 1H), 7.33-7.36 (m 1H), 7.52-7.56 (m 1H), 8.07 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 30.5 (CH_3), 33.5 (CH), 50.9 (CH_2), 111.3 (CH), 118.5 (C), 119.3 (CH), 119.5 (CH), 121.6 (CH), 122.2 (CH), 123.5 (CH), 124.1 (CH), 126.1 (C), 126.5 (CH), 136.5 (C), 148.5 (C), 207.0 (C).

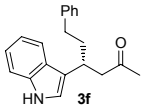


3d

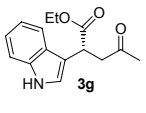
(R)-4-(1*H*-Indol-3-yl)-pentan-2-one[7,11] **– 3d** (Table 2, entry 5). The reaction was carried out at 40°C for 70 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/ Et_2O = 6/4) as a colourless oil in 98% yield and 87% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 12.5 min; τ_{minor} = 14.6 min). $[\alpha]^{rt}_D$= - 5.1 (*c* = 0.96, $CHCl_3$, 87% ee; Lit.[7] $[\alpha]^{rt}_D$= - 3.6, (R)-**3d**, (*c* = 0.55, $CHCl_3$, 30% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.8, 3H), 2.10 (s, 3H), 2.71 (dd, *J* = 8.4, 16.0 Hz, 1H), 2.94 (dd, *J* = 6.0, 16.0 Hz, 1H), 3.60-3.70 (m, 1H), 6.96-6.98 (m, 1H), 7.10-7.15 (m, 1H), 7.18-7.22 (m, 1H), 7.35-7.38 (m, 1H), 7.63-7.67 (m, 1H), 7.96 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.2 (CH_3), 27.0 (CH), 30.4 (CH_3), 51.5 (CH_2), 111.2 (CH), 119.1 (CH), 119.3 (CH), 120.1 (CH), 121.1 (C), 122.1 (CH), 126.3 (C), 136.5 (C), 208.6 (C).



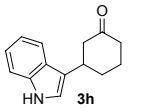
(R)-4-(1*H*-Indol-3-yl)-nonan-2-one – 3e (Table 2, entries 6-7). The reaction was carried out at RT for 96 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/Et_2O = 7/3) as a colourless oil in 91% yield and 93% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (95/5 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 24.1 min; τ_{minor} = 25.5 min). $[\alpha]^{rt}_D$= - 35.7 (*c* = 1.01, $CHCl_3$, 93% ee). HRMS: *m/z* calcd for $C_{17}H_{23}NO$: 257.17796; found: 257.1777. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80-0.84 (m, 3H), 1.19-1.29 (m, 6H), 1.64-1.80 (m, 2H), 2.02 (s, 3H), 2.80 (dd, *J* = 6.8, 16.0 Hz, 1H), 2.89 (dd, *J* = 7.2, 16.0 Hz, 1H), 3.43-3.53 (m, 1H), 6.96-6.98 (m, 1H), 7.08-7.13 (m, 1H), 7.16-7.22 (m, 1H), 7.35 (d, *J* = 8.4, 1H), 7.65 (d, *J* = 8.4, 1H), 7.99 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.5 (CH_2), 27.2 (CH_2), 30.4 (CH_3), 31.7 (CH_2), 32.9 (CH), 35.8 (CH_2), 50.2 (CH_2), 111.3 (CH), 118.9 (C), 119.1 (CH), 119.2 (CH), 121.2 (CH), 121.8 (CH), 126.5 (C), 136.5 (C), 209.2 (C).



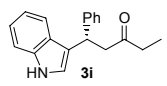
(R)-4-(1*H*-Indol-3-yl)-6-phenyl-hexan-2-one[8] **– 3f** (Table 2, entry 8). The reaction was carried out at RT for 96 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 75/25) as a colourless viscous oil in 67% yield and 93% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 11.5 min, τ_{minor} = 12.6 min). $[\alpha]^{rt}_D$= - 9.2 (*c* = 0.85, CH_2Cl_2, 93% ee; Lit.[8] $[\alpha]^{rt}_D$= + 12.6, (S)-**3f**, (*c* = 1.0, CH_2Cl_2, 94.6% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.00 (s, 3H), 2.01-2.18 (m, 2H), 2.52-2.62 (m, 2H), 2.84 (dd, *J* = 7.2, 16.0 Hz, 1H), 2.93 (dd, *J* = 7.6, 16.0 Hz, 1H), 3.48-3.56 (m, 1H), 7.01 (d, *J* = 2.4, 1H), 7.09-7.28 (m, 6H), 7.26-7.40 (m, 1H), 7.37 (d, *J* = 8.0, 1H), 7.65 (d, *J* = 8.0, 1H), 8.04 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 30.4 (CH_3), 32.6 (CH), 33.9 (CH_2), 37.4 (CH_2), 50.2 (CH_2), 111.3 (CH), 118.4 (C), 119.3 (CH), 121.5 (CH), 122.0 (CH), 125.7 (CH), 126.4 (C), 128.2 (CH), 128.4 (CH), 136.6 (C), 142.3 (C), 211.3 (C).



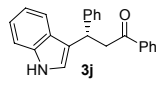
(R)-2-(1*H*-Indol-3-yl)-4-oxo-hexanoic acid ethyl ester – 3g (Table 2, entry 9). The reaction was carried out at 50 °C for 66 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 65/35) as a white solid in 99% yield and 95% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (75/25 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 10.9 min, τ_{minor} = 16.2 min). $[\alpha]^{rt}_D$= - 106.4 (*c* = 1.04, $CHCl_3$, 95% ee). HRMS: *m/z* calcd for $C_{15}H_{17}NO_3$: 259.12084; found: 259.1210. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.2 Hz, 3H), 2.18 (s, 3H), 2.85 (dd, *J* = 4.8, 18.0 Hz, 1H), 3.51 (dd, *J* = 10.4, 18.0 Hz, 1H), 4.08 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.18 (dq, *J* = 7.2, 10.8 Hz, 1H), 4.40 (dd, *J*= 4.8, 10.4 Hz, 1H), 7.06 (d, *J*= 2.4 Hz, 1H), 7.12-7.23 (m, 2H), 7.35 (dt, *J*= 0.8, 8.0 Hz, 1H), 7.71-7.73 (d, *J*= 8.4 Hz, 1H), 8.25 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.0 (CH_3), 29.9 (CH_3), 37.8 (CH), 46.2 (CH_2), 61.0 (CH_2), 111.3 (CH), 112.8 (C), 119.2 (CH), 119.7 (CH), 122.1 (CH), 122.3 (CH), 126.1 (C), 136.2 (C), 173.8 (C), 206.9 (C).



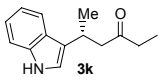
3-(1*H*-Indol-3-yl)-cyclohexanone[10,12] **– 3h** (Table 2, entry 10). The reaction was carried out at 40 °C for 70 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 75/25) as a colourless oil in 65% yield and 78% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 9.3 min, τ_{minor} = 10.9 min). $[\alpha]^{rt}_D$= + 11.1 (*c* = 0.51, $CHCl_3$, 78% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.80-2.10 (m, 3H), 2.24-2.50 (m, 3H), 2.60-2.68 (m, 1H), 2.78-2.85 (m, 1H), 3.42-3.49 (m, 1H), 6.97-7.00 (m, 1H), 7.10-7.15 (m, 1H), 7.19-7.23 (m, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 8.09 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 24.9 (CH_2), 31.7 (CH_2), 35.9 (CH), 41.5 (CH_2), 48.1 (CH_2), 111.3 (CH), 119.0 (CH), 119.3 (CH), 119.7 (C), 120.3 (CH), 122.2 (CH), 126.1 (C), 136.4 (C), 211.8 (C).



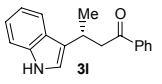
(S)-1-(1*H*-Indol-3-yl)-1-phenyl-pentan-3-one – 3i (Table 2, entry 11). The reaction was carried out at 70 °C for 72 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 8/2) as a white solid in 56% yield and 95% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 9.4 min; τ_{major} = 10.1 min). $[\alpha]^{rt}_D$= + 38.2 (*c* = 0.77, $CHCl_3$, 95% ee). HRMS: *m/z* calcd for $C_{19}H_{19}NO$: 277.14666; found: 277.146. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.2, 3H), 2.25-2.44 (m, 2H), 3.15 (dd, *J* = 8.0, 16.0 Hz, 1H), 3.24 (dd, *J* = 7.2, 16.0 Hz, 1H), 4.86 (t, *J* = 7.2 Hz, 1H), 6.98-7.00 (m, 1H), 7.01-7.05 (m, 1H), 7.13-7.20 (m, 2H), 7.24-7.34 (m, 5H), 7.42-7.46 (m, 1H), 8.01 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 7.55 (CH_3), 36.4 (CH_2), 38.3 (CH), 49.1 (CH_2), 111.1 (CH), 119.0 (C), 119.39 (CH), 119.47 (CH), 121.3 (CH), 122.1 (CH), 126.3 (CH), 126.5 (C), 127.7 (CH), 128.4 (CH), 136.6 (C), 144.0 (C), 210.2 (C).



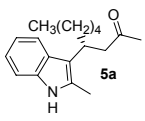
(S)-1-(1*H*-Indol-3-yl)-1,3-diphenyl-propan-1-one[6] **– 3j** (Table 2, entry 12). The reaction was carried out at 70 °C for 96 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 85/15 to 6/4) as a white solid in 78% yield and 82% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 16.9 min; τ_{major} = 18.9 min). $[\alpha]^{rt}_D$= + 23.3 (*c* = 0.82, $CHCl_3$, 82% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.73 (dd, *J* = 7.6, 16.8 Hz, 1H), 3.83 (dd, *J* = 7.2, 16.8 Hz, 1H), 5.08 (t, *J* = 7.2 Hz, 1H), 6.98-7.00 (m, 1H), 7.00-7.05 (m, 1H), 7.13-7.20 (m, 2H), 7.24-7.38 (m, 5H), 7.41-7.46 (m, 3H), 7.52-7.56 (m, 1H), 7.92-7.95 (m, 2H), 7.98 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 38.2 (CH), 45.2 (CH_2), 111.1 (CH), 119.28 (C), 119.38 (CH), 119.52 (CH), 121.4 (CH), 122.1 (CH), 126.3 (CH), 126.6 (C), 127.8 (CH), 128.1 (CH), 128.4 (CH), 128.5 (CH), 132.9 (CH), 136.6 (C), 137.1 (C), 144.2 (C), 198.6 (C).



(R)-5-(1*H*-Indol-3-yl)-hexan-3-one – 3k[13] (Table 2, entry 13). The reaction was carried out at 50 °C for 72 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/ Et_2O = 7/3) as a colourless oil in 76% yield and 96% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 7.3 min; τ_{major} = 7.7 min). $[\alpha]^{rt}_D$= - 8.5 (*c* = 0.93, $CHCl_3$, 96% ee). HRMS: *m/z* calcd for $C_{14}H_{17}NO$: 215.13101; found: 215.130. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.2, 3H), 1.39 (d, *J* = 7.2, 3H), 2.37 (q, *J* = 7.2, 2H), 2.69 (dd, *J* = 8.4, 16.0 Hz, 1H), 2.92 (dd, *J* = 5.6, 16.0 Hz, 1H), 3.62-3.72 (m, 1H), 6.96-6.98 (m, 1H), 7.10-7.15 (m, 1H), 7.18-7.22 (m, 1H), 7.34-7.37 (m, 1H), 7.64-7.68 (m, 1H), 8.00 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 7.7 (CH_3), 21.2 (CH_3), 27.1 (CH), 36.4 (CH_2), 50.2 (CH_2), 111.2 (CH), 119.15 (CH), 119.19 (CH), 120.1 (CH), 121.2 (C), 122.0 (CH), 126.2 (C), 136.5 (C), 211.3 (C).

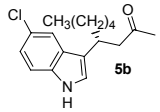


(R)-5-(1*H*-Indol-3-yl)-1-phenyl-butan-1-one – 3l[6] (Table 2, entry 14). The reaction was carried out at 70 °C for 90 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/ AcOEt = 85/15) as a white solid in 94% yield and 70% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 11.3 min; τ_{major} = 12.5 min). $[\alpha]^{rt}_D$= + 14.2 (*c* = 1.22, $CHCl_3$, 70% ee; Lit.[9] $[\alpha]^{rt}_D$= + 7.4, (R)-**3l**, (*c* = 1.0, $CHCl_3$, 64% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (d, *J* = 6.8, 3H), 3.26 (dd, *J* = 8.8, 16.4 Hz, 1H), 3.49 (dd, *J* = 4.8, 16.4 Hz, 1H), 3.81-3.91 (m, 1H), 7.00-7.04 (m, 1H), 7.14 (t, *J* = 6.8 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 7.2 Hz, 2H), 8.00 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.0 (CH_3), 27.1 (CH), 46.4 (CH_2), 111.3 (CH), 119.19 (CH), 119.21 (CH), 120.1 (CH), 121.5 (C), 122.0 (CH), 126.3 (C), 128.1 (CH), 128.5 (CH), 132.9 (CH), 136.5 (C), 137.3 (C), 199.8 (C).

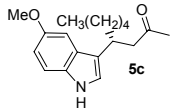


(R)-4-(2-Methyl-1*H*-indol-3-yl)-nonan-2-one – 5a (Table 3, entries 2 and 3). The reaction was carried out at RT for 24 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/Et_2O = 7/3) as a yellowish oil in 87% yield and 94% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 7.2 min, τ_{minor} = 8.3 min). $[\alpha]^{rt}_D$= - 32.3 (*c* = 0.98, $CHCl_3$, 94% ee). HRMS: *m/z* calcd for $C_{18}H_{25}NO$: 271.19361; found: 271.1942. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79-0.84 (m, 3H), 1.08-1.28 (m, 6H), 1.65-1.75 (m, 1H), 1.80-1.90 (m, 1H), 1.95 (s, 3H), 2.38 (s, 3H), 2.81 (dd, *J* = 6.0, 16.0 Hz, 1H), 3.05 (dd, *J* = 4.4, 16.0 Hz, 1H), 3.33-3.40 (m, 1H), 7.02-7.12 (m, 2H), 7.24-7.28 (m, 1H), 7.69 (d, *J* = 7.6, 1H), 7.75 (br s, 1H); ^{13}C NMR (150

MHz, $CDCl_3$): δ = 12.0 (CH_3), 14.0 (CH_3), 22.6 (CH_2), 27.6 (CH_2), 30.7 (CH_3), 31.7 (CH_2), 32.6 (CH), 35.1 (CH_2), 49.3 (CH_2), 110.4 (CH), 113.3 (C), 118.8 (CH), 118.9 (CH), 120.6 (CH), 127.1 (C), 131.4 (C), 135.6 (C), 209.0 (C).



(R)-4-(5-Chloro-1*H*-indol-3-yl)-nonan-2-one – 5b (Table 3, entry 4). The reaction was carried out at 40 °C for 96 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/Et_2O = 7/3) as a yellowish oil in 74% yield and 92% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (95/5 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 22.5 min, τ_{minor} = 23.8 min). $[\alpha]^{rt}_D$= - 16.9 (*c* = 0.92, $CHCl_3$, 92% ee). HRMS: *m/z* calcd for $C_{17}H_{22}NOCl$: 291.13899; found: 291.1390. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80-0.86 (m, 3H), 1.18-1.26 (m, 6H), 1.62-1.76 (m, 2H), 2.03 (s, 3H), 2.78 (dd, *J* = 6.8, 16.0 Hz, 1H), 2.85 (dd, *J* = 7.6, 16.0 Hz, 1H), 3.37-3.44 (m, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 7.12 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.60 (d, *J* = 2.4, 1H), 8.13 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.5 (CH_2), 27.2 (CH_2), 30.4 (CH_3), 31.7 (CH_2), 32.7 (CH), 35.7 (CH_2), 50.0 (CH_2), 112.3 (CH), 118.7 (CH), 118.9 (C), 122.1 (CH), 122.7 (CH), 124.9 (C), 127.6 (C), 134.8 (C), 208.7 (C).



(R)-4-(5-Methoxy-1*H*-indol-3-yl)-nonan-2-one – 5c (Table 3, entry 5). The reaction was carried out at RT for 40 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/Et_2O = 6/4) as a colourless oil in 76% yield and 93% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (85/15 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 8.7 min; τ_{major} = 9.2 min). $[\alpha]^{rt}_D$= - 16.8 (*c* = 1.0, $CHCl_3$, 93% ee). HRMS: *m/z* calcd for $C_{18}H_{25}NO_2$: 287.18853; found: 287.1884. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82-0.86 (m, 3H), 1.22-1.27 (m, 6H), 1.64-1.78 (m, 2H), 2.03 (s, 3H), 2.78 (dd, *J* = 6.8, 16.0 Hz, 1H), 2.86 (dd, *J* = 7.2, 16.0 Hz, 1H), 3.39-3.46 (m, 1H), 3.88 (s, 3H), 6.85 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 7.22 (dd, *J* = 0.4, 8.8 Hz, 1H), 7.99 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.5 (CH_2), 27.2 (CH_2), 30.4 (CH_3), 31.8 (CH_2), 32.7 (CH), 35.7 (CH_2), 50.1 (CH_2), 55.9 (CH_3), 101.4 (CH), 111.7 (CH), 111.8 (CH), 118.7 (C), 121.9 (CH), 126.9 (C), 131.6 (C), 153.6 (C), 209.0 (C).

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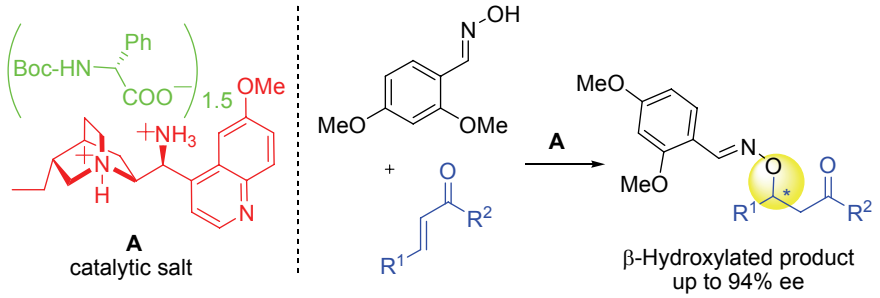
6.2 Organocatalytic Asymmetric β-Hydroxylation of α,β-Unsaturated Ketones

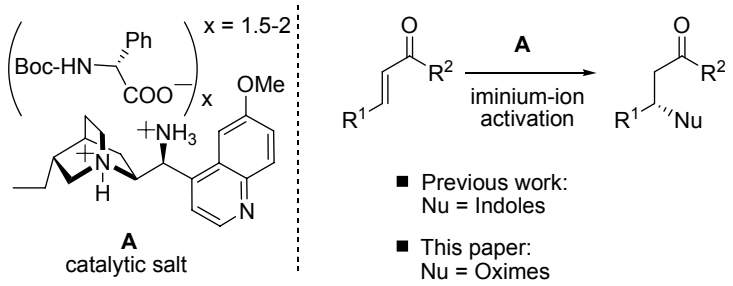


The highly enantioselective organocatalytic β-hydroxylation of α,β-unsaturated ketones has been accomplished using oximes as the oxygen-centered nucleophile. Optically active products are obtained with enantioselectivity up to 94%. Central to these studies has been the use of the catalytic primary amine salt **A**, in which both the cation and the anion are chiral, that exhibits high reactivity and selectivity for iminium-ion catalysis with enones. The potential interest of this novel transformation has been demonstrated with the easy conversion of the Michael adducts in enantioenriched *anti* and *syn* 1,2-diols without erosion of the optical purity.

In recent years asymmetric organocatalysis has become a field of central importance for the stereoselective preparation of chiral interesting compounds.[1] Novel modes of substrate activation have been achieved that can deliver unique, orthogonal or complementary selectivities in comparison to metal-catalysed processes. In particular, chiral secondary amine catalysis has proven to be a powerful procedure for the enantioselective transformations of carbonyl compounds. By exploiting distinct catalytic activation modes such as enamine,[2] SOMO,[3] iminium-ion,[4] and dienamine[5] activation, aminocatalysis has enabled the asymmetric α-, β-, and γ-functionalization of aldehydes with a wide range of electrophiles and nucleophiles.[6] In comparison, little progress has been achieved in the corresponding asymmetric functionalization of ketones, probably due to the inherent difficulties of

generating congested covalent intermediates from ketones and chiral secondary amines.

Recently, some reports have demonstrated the ability of chiral primary amine derivatives to efficiently activate ketones, owing to reduced steric constraints.[7] Meanwhile, List and co-workers have introduced asymmetric counterion directed catalysis (ACDC)[8] as an efficient strategy for enantioselective transformations that proceed via cationic species, including iminium-ion intermediates. In this vein, we have developed a new catalyst primary amine salt, in which both the cation and the anion are chiral, that exhibits high reactivity and selectivity for iminium ion catalysis with α,β-unsaturated ketones.[9] In particular we have shown that salt **A**, made by combining the easily available 9-amino(9-deoxy)*epi*-hydroquinine[10] with D-*N*-Boc phenylglycine as the chiral counter-anion, can function as highly efficient catalyst for the asymmetric conjugated addition of indoles to simple enones;[9] the efficient activation relies on the proven ability of primary amines to form iminium-ion intermediates from ketones combined synergistically with the benefits of asymmetric counterion directed catalysis.



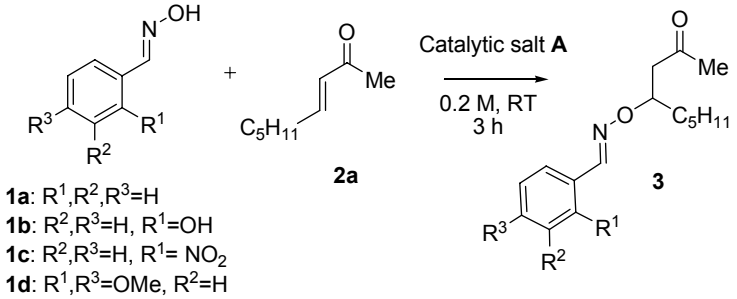
We report the first highly chemo- and enantioselective oxygen-centered addition of oximes to α,β-unsaturated ketones catalysed by the chiral salt **A**, demonstrating the generality and efficiency of this catalytic system as iminium-ion activator of simple enones.

β-Hydroxy ketones and the corresponding alkoxy analogues constitute highly valuable chiral building blocks in organic synthesis and structural recurring motifs in a variety of natural products. They are generally synthesised either via aldol chemistry or sequential epoxidation and reduction of enones.[11] In contrast, the direct asymmetric conjugate addition of *O*-centered nucleophiles to α,β-unsaturated ketones has proven a challenging task[12] mainly as a consequence of the relative weakness of such nucleophiles coupled with problems associated with reaction reversibility.

Recently, oximes have been identified as suitable nucleophile for a range of highly enantioselective catalytic *oxa*-Michael addition to electron deficient olefins.[13] Moreover, the oxime ethers resulting from this type of conjugate addition contain a labile *N*-*O* bond, enabling a reductive cleavage to afford formal hydration products.

With this in mind, a series of commercially available oximes **1** was screened in the addition to *trans*-3-nonen-2-one **2a** in the presence of catalytic salt **A** (1:2 ratio of amine to acid); the results of this survey are reported in Table 1. Despite (*E*)-benzaldehyde oxime **1a** afforded the desired product with high enantioselectivity, the commercially available 2,4-dimethoxybenzaldoxime **1d** reacted with **2a** within 3 h in toluene to yield β-addition product with superior chemical and optical yield (89% ee, entry 4).

Table 1: Screening results for the organocatalytic addition of aromatic oximes to enone 2a.[a]



1a: R^1,R^2,R^3=H
1b: R^2,R^3=H, R^1=OH
1c: R^2,R^3=H, R^1= NO_2
1d: R^1,R^3=OMe, R^2=H

Entry	Oxime	Solvent	Catalytic Salt **A**		yield (%)[b]	ee (%)[c]
			% amine	% acid		
1	**1a**	Toluene	20	40	22	86
2	**1b**	Toluene	20	40	75	32
3	**1c**	Toluene	20	40	31	66
4	**1d**	Toluene	20	40	55	89
5[d]	**1d**	Toluene	20	40	50	50
6[e]	**1d**	Toluene	20	40	49	80
7[f]	**1d**	Toluene	20	40	48	82
8[g]	**1d**	Toluene	20	40	56	81
9	**1d**	CH_2Cl_2	20	40	52	76
10	**1d**	AcOEt	20	40	46	86
11	**1d**	Hexane	20	40	42	72
12	**1d**	Et_2O	20	40	52	90
13[g]	**1d**	Et_2O	20	40	53	90
14[h]	**1d**	Et_2O	10	20	55	90
15[i]	**1d**	Et_2O	20	40	49	91
16[j]	**1d**	Et_2O	10	20	49	80
17[k]	**1d**	Et_2O	10	10	31	90
18[k]	**1d**	Et_2O	10	15	52	90

[a] Reactions were carried out at room temperature using 3 equiv. of oxime on a 0.1 mmol scale. [b] Yield of isolated product. [c] ee of **3** was determined by HPLC analysis. [d] TFA was used as counteranion. [e] L-*N*-Boc phenylalanine was used as chiral counteranion. [f] L-*N*-Boc phenylglycine was used as chiral counteranion. [g] 24 h reaction time. [h] 18 h reaction time. [i] Reaction carried out at 0 °C for 18 h. [j] Reaction carried out at reflux for 18 h. [k] 40 h reaction time.

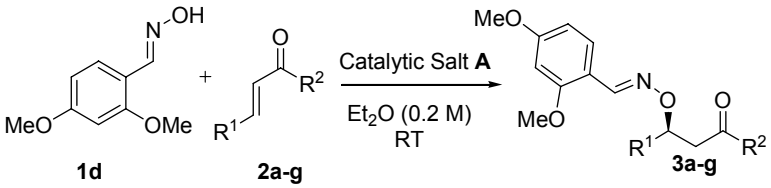
The results obtained with different counteranions (e.g.: trifluoroacetic acid, L-*N*-Boc phenylalanine, entries 5 and 6) did not bring any appreciable improvement.[14] Remarkably, as previously observed,[9] employing the opposite enantiomeric counteranion (L-*N*-Boc phenylglycine) afforded the same enantiomeric product **3** with lower reactivity and selectivity (entry 7), illustrating a marked case of a matched/mismatched catalyst-ion pair combination. On the basis of these studies, the catalytic salt **A** was chosen as the best system and used for further optimisations.

Interestingly, prolonging the reaction time did not allow to improve the conversion, probably as a consequence of the reversibility of the process. Moreover, the products formed in toluene slowly racemized after reaching the thermodynamic equilibrium (entry 8). In order to circumvent this problem, an extensive study of the standard reaction parameters was performed, indicating solvent choice, catalyst loading and catalytic salt composition as the crucial factors. Evaluation of the reaction media (entries 9-12) led to the observation that carrying out the reaction in Et_2O provided comparable results in terms of both yield and enantioselectivity respect to toluene (compare entries 4 and 12) but, more importantly, without erosion of the enantiomeric purity during time (entry 13). This condition allowed to reduce the catalyst loading to 10 mol% (1:2 ratio of amine to acid) without affecting the efficiency of the system (entry 14). In addition, variation of the reaction temperature with the aim of improving the levels of yield and enantiopurity did not provide useful results (entries 15 and 16).

Importantly, a survey of the catalytic salt composition revealed that, whereas a 1:1 ratio of 9-amino(9-deoxy)*epi*-hydroquinine to D-*N*-Boc phenylglycine had a detrimental impact on reactivity, a 1:1.5 ratio represents the best compromise between catalyst loading and catalytic efficiency (entries 17 and 18).

After optimisation of the catalytic system, the scope of this novel organocatalytic β-hydroxylation was explored using the conditions reported in Table 2. Different linear α,β-unsaturated ketones reacted smoothly to afford the optically active oxime addition products **3** in moderate to good yield and high enantioselectivity (up to 94% ee). Notably, the mild reaction conditions adopted are tolerant of silyl ether functionality (entry 7).

Table 2: Scope of the organocatalytic asymmetric β-hydroxylation of α,β-unsaturated ketones using oxime 1d.[a]

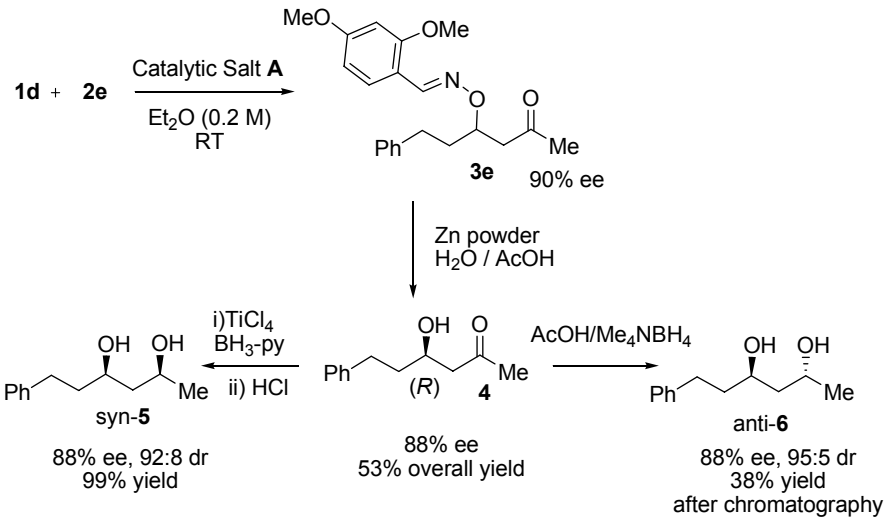


Entry	R^1	R^2	Catalytic Salt **A** % amine	% acid	*t* (h)	yield (%)[b]	ee (%)[c]
1	Pentyl	Me, **2a**	10	15	40	**3a** - 52	90
2	Pentyl	Et, **2b**	20	30	48	**3b** - 56	94
3	Me	Me, **2c**	10	15	40	**3c** - 53	80
4	Me	Et, **2d**	20	30	60	**3d** - 46	88
5	$PhCH_2CH_2$	Me, **2e**	10	15	40	**3e** - 55	90
6	Propyl	Et, **2f**	20	30	55	**3f** - 55	92
7[d]	CH_2OTIPS	Et, **2g**	20	30	60	**3g** - 35	80

[a] Reactions were carried out at room temperature using 3 equiv. of **1d** on a 0.2 mmol scale. [b] Yield of isolated product. [c] ee of **3** was determined by HPLC analysis. [d] TIPS: triisopropylsilyl.

Variation in the steric contribution of the R^2 ketone substituents reveals that the more encumbered ethyl group engenders higher stereoselectivity, albeit with slightly lower reactivity (entries 1-2 and 3-4). Practical limitations of the method include prohibitively slow reaction rates with enones bearing aromatic or highly hindered β-substituents.

A demonstration of the synthetic utility of this novel organocatalytic reaction is presented in the stereoselective preparation of optically active *syn*- or *anti*-configured 1,3-diols (Scheme 1), highly valuable chiral structural motifs present in many poliketide-derived natural products of proven biological activity.[15] The asymmetric oxime addition to **2e** under our catalytic conditions, followed by simple reductive cleavage, provided the formal hydration product **4** with a minimal erosion of the optical purity (88% ee). This process enabled the verification of the absolute configuration of the β-hydroxy ketone **4** by comparison of the measured optical rotation with the value reported in the literature.[16,17] The stereoselective *syn* or *anti* reduction[18] of **4** furnished the corresponding 1,3-diols **5** and **6**, respectively, with preserved optical purity (88% ee) and the desired relative stereochemistry.



Scheme 1: Stereoselective route to optically active *syn*- or *anti*-configured 1,3-diols

In summary, we have disclosed the first catalytic and highly enantioselective β-hydroxylation of α,β-unsaturated ketones using aromatic oximes as the *O*-centered nucleophiles, catalysed by primary amine salt **A**, in which both the cation and the anion are chiral. Besides establishing the generality and the efficiency of this new catalytic system as iminium-ion activator of simple enones, this novel organocatalytic transformation shows potential applicability to the synthesis of poliketide-derived natural products.

6.2.R References

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6.2.EP Experimental Part

Contents

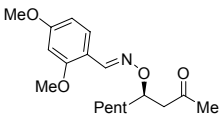
General Methods. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts (δ) are referenced to residual signals of the solvents ($CHCl_3$ – 7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR). Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh). Optical rotations are reported as follows: $[\alpha]_{rt}^{D}$ (c in g per 100 mL, solvent). Mass spectra were obtained from the Department of Organic Chemistry "A. Mangini" Mass Spectroscopy facility. Chiral HPLC analysis was performed on an Agilent 1100-series instrumentation. Daicel Chiralpak AD-H or AS-H columns and Daicel Chiralcel OD-H with i-PrOH/hexane as the eluent were used. HPLC traces were compared to racemic samples prepared by benzylamine·TFA-catalyzed reaction. All reactions were carried out in air and using undistilled solvent, without any precautions to exclude moisture.

Materials. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended. Oximes **1** were purchased from AlfaAesar and used as received. α,β-unsaturated ketones were purchased and used as received, prepared by Wittig reaction with commercially available acetylmethylene-triphenylphosphorane (R^2= Me), or by addition of ethyl Grignard on the corresponding unsatured aldehyde followed by oxidation with MnO_2 (R^2= Et). 9-Amino(9-deoxy)epi-hydroquinine was prepared from commercially available hydroquinine following the literature procedure.[1]

Determination of the Absolute Configuration. The absolute configuration of the optically active compound (R)-**3e** was determined by reductive cleavage to afford (R)-**4** and subsequent comparison of the measured optical rotation of (R)-**4** with literature value.[2] All other absolute configurations were assigned by analogy based on an uniform reaction mechanism.

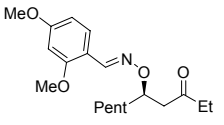
General Procedure for the Organocatalytic β-Hydroxylation of α,β-Unsaturated Ketones

All the reactions were carried out in undistilled Et_2O without any precautions to exclude water. In an ordinary test tube equipped with a magnetic stirring bar, catalytic salt **A**, prepared by mixing 9-amino(9-deoxy)epi-hydroquinine (10 or 20 mol%) with D-N-Boc phenylglycine (15 or 30 mol%) as the chiral counter-anion, was dissolved in 1 mL of Et_2O. After addition of α,β-unsaturated ketones (0.2 mmol), the mixture was stirred at room temperature for 10 minutes. Then oxime (0.6 mmol, 3 equiv.) was added in one portion, the tube was closed with a rubber stopper and stirring was continued for the indicated time. The crude reaction mixture was diluted with hexane (2 mL) and flushed through a plug of silica, using hexane/Et_2O 1/1 as the eluent. Solvent was removed in vacuo, and the residue was purified by flash chromatography to yield the desired product.

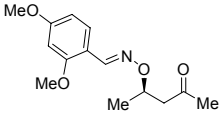


2,4-Dimethoxy-benzaldehyde O-[1-(2-oxo-propyl)-hexyl]-oxime - 3a (Table 2, entry 1). The reaction w as carried out at RT for 40 h following the general procedure. The title compound was isolated by column chromatography (hexane/acetone = 95/5) in 52% yield and 90% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (80/20 hexane/i-PrOH; flow rate

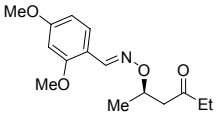
0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 6.2 min; τ_{major} = 6.5 min). $[\alpha]_{rt}^{D}$ = + 2.8 (c = 1.2, $CHCl_3$, 90% ee). HRMS: m/z calcd for $C_{18}H_{27}NO_4$: 321,1940; found: 321.1943. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3H), 1.21-1.50 (m, 6H), 1.52-1.75 (m, 2H), 2.20 (s, 3H), 2.56 (dd, J = 7.4, 15.6 Hz, 1H), 2.86 (dd, J = 4.8, 15.6 Hz, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 4.55-4.61 (m, 1H), 6.41 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 2.4, 8.8 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 22.5, 25.0, 30.9, 31.7, 34.0, 48.6, 55.4, 55.5, 79.4, 98.1, 105.4, 113.9, 127.2, 144.2, 158.7, 162.3, 207.7.



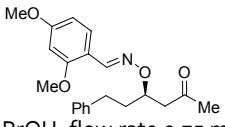
2,4-Dimethoxy-benzaldehyde O-[1-(2-oxo-butyl)-hexyl]-oxime – **3b** (Table 2, entry 2). The reaction was carried out at RT for 48 h following the general procedure. The title compound was isolated by column chromatography (hexane/acetone = 95/5) in 56% yield and 94% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (90/10 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 6.6 min; τ_{major} = 7.1 min). $[\alpha]_{rt}^{D}$ = - 8.1 (c = 1.5, $CHCl_3$, 94% ee). HRMS: m/z calcd for $C_{19}H_{29}NO_4$: 335.2097; found: 335.2095. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3H), 1.04 (t, J = 7.2 Hz, 3H), 1.25-1.47 (m, 6H), 1.52-1.75 (m, 2H), 3.74 (q, J = 7.2 Hz, 2H), 2.54 (dd, J = 5.2, 15.2 Hz, 1H), 2.56 (dd, J = 7.2, 15.2 Hz, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 4.55-4.61 (m, 1H), 6.41 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 2.4, 8.8 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.6, 14.0, 22.5, 25.1, 31.7, 34.0, 36.8, 47.3, 55.4, 55.5, 79.4, 98.1, 105.4, 114.0, 127.2, 144.1, 158.7, 162.3, 210.2.



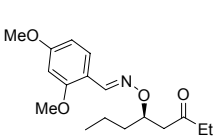
2,4-Dimethoxy-benzaldehyde O-(1-methyl-3-oxo-butyl)-oxime – **3c** (Table 2, entry 3). The reaction was carried out at RT for 40 h following the general procedure. The title compound was isolated by column chromatography (hexane/acetone = 95/5) in 53% yield and 80% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (90/10 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 9.9 min; τ_{major} = 10.4 min). $[\alpha]_{rt}^{D}$ = + 4.9 (c = 0.8, $CHCl_3$, 80% ee). HRMS: m/z calcd for $C_{14}H_{19}NO_4$: 265.13140; found: 265.1314. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (d, J = 6.4 Hz, 3H), 2.20 (s, 3H), 2.56 (dd, J = 5.6, 15.6 Hz, 1H), 2.90 (dd, J = 7.2, 15.6 Hz, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 4.68-4.75 (m, 1H), 6.42 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 2.4, 8.8 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 30.8, 50.0, 55.4, 55.5, 75.4, 98.2, 105.4, 113.9, 127.3, 144.5, 158.8, 162.3, 207.3.



2,4-Dimethoxy-benzaldehyde O-(1-methyl-3-oxo-pentyl)-oxime – **3d** (Table 2, entry 4). The reaction was carried out at RT for 60 h following the general procedure. The title compound was isolated by column chromatography (hexane/acetone = 95/5) in 46% yield and 88% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (95/5 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 11.7 min; τ_{major} = 12.4 min). $[\alpha]_{rt}^{D}$ = - 4.8 (c = 1.2, $CHCl_3$, 88% ee). HRMS: m/z calcd for $C_{15}H_{21}NO_4$: 279.14705; found: 279.1472. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t, J = 7.2 Hz, 3H), 1.32 (d, J = 6.4 Hz, 3H), 2.49 (q, J = 7.2 Hz, 2H), 2.52 (dd, J = 5.6, 15.6 Hz, 1H), 2.90 (dd, J = 6.8, 15.6 Hz, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 4.68-4.75 (m, 1H), 6.42 (d, J = 2.4 Hz, 1H), 6.48 (dd, , J = 2.4, 8.8 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 8.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.6, 19.9, 36.8, 48.8, 55.4, 55.5, 75.5, 98.2, 105.4, 113.9, 127.3, 144.4, 158.8, 162.3, 209.8.

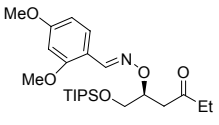


(R)-2,4-Dimethoxy-benzaldehyde O-(3-oxo-1-phenethyl-butyl)-oxime – **3e** (Table 2, entry 5). The reaction was carried out at RT for 40 h following the general procedure. The title compound was isolated by column chromatography (hexane/acetone = 95/5) in 55% yield and 90% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (90/10 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 18.6 min; τ_{major} = 20.4 min). $[\alpha]_{rt}^{D}$ = +10.4 (c = 1.0, $CHCl_3$, 90% ee). HRMS: m/z calcd for $C_{21}H_{25}NO_4$: 355,1784; found: 355,1780. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.87-1.93 (m, 1H), 1.99-2.06 (m, 1H), 2.17 (s, 3H), 2.58 (dd, J = 5.4, 15.6 Hz, 1H), 2.68-2.73 (m, 1H), 2.78-2.83 (m, 1H), 2.91 (dd, J = 7.2, 15.6 Hz, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 4.60-4.64 (m, 1H), 6.42 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 2.4, 9.0 Hz, 1H), 7.15-7.27 (m, 5H), 2.78-2.83 (m, 1H), 7.68 (d, J = 9.0 Hz, 1H), 8.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.8, 31.7, 35.8, 48.5, 55.4, 55.5, 78.5, 98.1, 105.4, 113.8, 125.8, 127.3, 128.3, 128.4, 141.9, 144.5, 158.8, 162.4, 207.4.

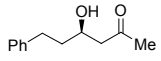


2,4-Dimethoxy-benzaldehyde O-(3-oxo-1-propyl-pentyl)-oxime – **3f** (Table 2, entry 6). The reaction was carried out at RT for 55 h following the general procedure. The title compound was isolated by column chromatography (hexane/acetone = 95/5) in 55% yield and 92% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (90/10 hexane/i-PrOH; flow rate

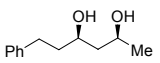
0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 6.9 min; τ_{major} = 7.4 min). $[\alpha]_{rt}^{D}$= - 12.6 (c = 1.1, $CHCl_3$, 92% ee). HRMS: m/z calcd for $C_{17}H_{25}NO_4$: 307.17835; found: 307.1783. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91-0.96 (m, 3H), 1.00-1.06 (m, 3H), 1.38-1.80 (m, 4H), 2.43-2.62 (m, 3H), 2.84-2.93 (m, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 4.57-4.62 (m, 1H), 6.42 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 2.4, 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 8.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.6, 14.0, 18.7, 36.1, 36.9, 47.4, 55.4, 55.6, 79.2, 98.1, 105.4, 113.9, 127.2, 144.1, 158.7, 162.3, 210.2.



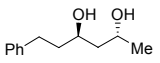
2,4-Dimethoxy-benzaldehyde O-(3-oxo-1-triisopropylsilanyloxymethyl-pentyl)-oxime – **3g** (Table 2, entry 7). The reaction was carried out at RT for 60 h following the general procedure. The title compound was isolated by column chromatography (hexane/acetone = 95/5) in 35% yield and 80% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (95/5 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 5.4 min; τ_{minor} = 6.7 min). $[\alpha]_{rt}^{D}$= - 19.2 (c = 0.5, $CHCl_3$, 80% ee). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.89-1.07 (m, 24H), 2.43-2.47 (m, 2H), 2.74-2.76 (m, 2H), 3.69-3.89 (m, 2H), 3.73 (s, 3H), 3.75 (s, 3H), 4.57-4.62 (m, 1H), 6.34 (d, J = 2.4 Hz, 1H), 6.41 (dd, J = 2.4, 9.0 Hz, 1H), 7.60 (d, J = 9.0 Hz, 1H), 8.26 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 7.6, 11.9, 18.0, 36.7, 43.6, 55.4, 55.5, 64.2, 79.8, 98.2, 105.4, 113.9, 127.3, 144.6, 158.8, 162.3, 209.9.



(R)-4-Hydroxy-6-phenyl-hexan-2-one – **4** (Scheme 4). To a suspension of oxime ether **3e** (0.15 M) in AcOH/H2O (1:1 v/v) was added Zn powder (40 equiv) under argon atmosphere.[13b] After being stirred for 24 h the reaction mixture was diluted with Et_2O, filtered and the aqueous phase extracted with Et_2O. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The title compound was isolated by column chromatography (hexane/AcOEt = 80/20) in 96% yield and 88% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (90/10 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 10.3 min; τ_{major} = 11.4 min). $[\alpha]_{rt}^{D}$= - 12.0 (c = 1.1, $CHCl_3$, 88% ee); (S)-**4**:[16] $[\alpha]_{rt}^{19}$= + 20.6 (c = 1.0, $CHCl_3$, 90% ee);. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.63-1.73 (m, 1H), 1.78-1.87 (m, 1H), 2.16 (s, 3H), 2.58-2.61 (m, 2H), 2.65-2.86 (m, 2H), 3.10 (bs, 1H), 4.02-4.08 (m, 1H), 7.15-7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.7, 31.7, 37.9, 49.9, 66.7, 125.8, 128.3, 128.4, 147.8, 209.8.



(2S,4R)-6-Phenyl-hexane-2,4-diol – syn-**5** (Scheme 1). The syn reduction was carried out following the literature procedure[18a] yielding the crude compound syn-**5** in a 9/1 diastereomeric ratio. The title compound was isolated by column chromatography (CH_2Cl_2/acetone = 90/10) in 99% yield, 9/1 dr and 88% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (90/10 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 9.4 min; τ_{minor} = 9.8 min). $[\alpha]_{rt}^{D}$= + 11.7 (c = 0.6, $CHCl_3$, 88% ee). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.19 (d, J = 6.6 Hz, 3H), 1.50-1.59 (m, 2H), 1.71-1.80 (m, 2H), 2.63-2.77 (m, 2H), 3.29 (bs, 1H), 3.43 (bs, 1H), 3.86-3.90 (m, 1H), 4.00-4.05 (m, 1H), 7.17-7.29 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 24.2, 31.6, 39.7, 44.6, 69.1, 72.2, 125.8, 128.3, 128.4, 141.9.



(2R,4R)-6-Phenyl-hexane-2,4-diol – anti-**6** (Scheme 1). To a solution of **4** (0.1 M) in AcOH was added Me_4NBH_4 (2 equiv), at RT under argon atmosphere. After being stirred for 4 h the reaction mixture was diluted with Et_2O, quenched with H_2O, and extracted with Et_2O.[18b] The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure yielding the crude compound anti-**5** in a 2.5/1 diastereomeric ratio. The title compound was isolated by column chromatography (gradient CH_2Cl_2/acetone from 99/1 to 9/1) in 38% yield, 95/5 dr and 88% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (90/10 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 10.0 min; τ_{major} = 10.6 min). $[\alpha]_{rt}^{D}$= + 2.7 (c = 0.6, $CHCl_3$, 88% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (d, J = 9.6 Hz, 3H), 1.62-1.89 (m, 4H), 2.65-2.84 (m, 2H), 3.95-4.00 (m, 1H), 4.14-4.20 (m, 1H), 7.17-7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.6, 32.2, 39.0, 44.0, 65.5, 68.8, 125.8, 128.3, 128.4, 141.9.

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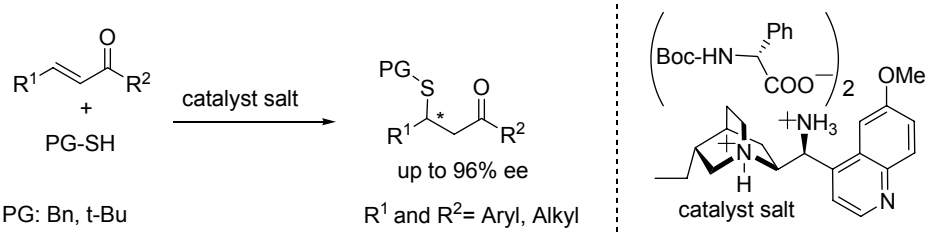
6.3 Organocatalytic Asymmetric Sulfa-Michael Addition to α,β-Unsaturated Ketones



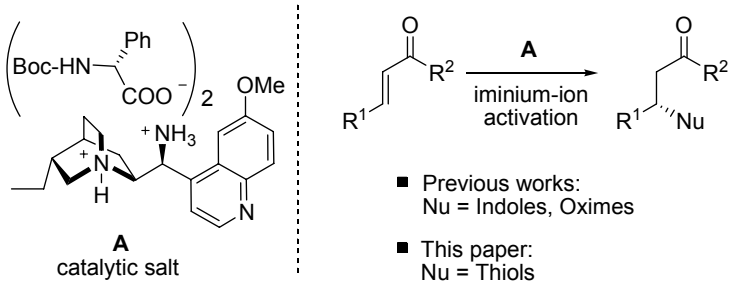
The highly enantioselective organocatalytic sulfa-Michael addition to α,β-unsaturated ketones has been accomplished using benzyl and *tert*-butyl mercaptans as the sulfur-centered nucleophiles. Optically active products are obtained in high yields and good to excellent stereocontrol (up to 96% ee) from a large variety of enones. Central to these studies has been the use of the catalytic primary amine salt **A**, derived from 9-amino(9-deoxy)*epi*-hydroquinine and D-*N*-Boc phenylglycine, in which both the cation and the anion are chiral, that exhibits high reactivity and selectivity for iminium-ion catalysis with enones.

The enantioselective construction of carbon-sulfur stereogenicity represents an important objective in organic and pharmaceutical synthesis.[1] Among the existing methods for the preparation of chiral sulfur-containing molecules the asymmetric sulfa-Michael addition (SMA), the reaction of sulfur-centered nucleophiles with electron deficient olefins, is of prime importance.[2] While the use of stoichiometric chiral auxiliaries and reagents has been established as an effective strategy for C-S bond construction,[3] the corresponding catalytic variants have been far less developed.[4]

Highly enantioselective sulfa-Michael additions promoted by both metal- or organo-catalysts have been limited to unsaturated imides,[5] cyclic enones[6] and, more recently, unsaturated aldehydes.[7] On the contrary, just two organocatalytic

asymmetric SMA to simple enones have been reported recently, affording the β-functionalized carbonyl derivatives in moderate optical purity and with important restrictions in substrate scope.[8] Thus, the use of simple α,β-unsaturated ketones still remains an important challenge for the asymmetric SMA strategy. Additionally, the range of sulfur-centered nucleophiles well suited for both catalytic and stoichiometric methodologies is generally restricted to aromatic thiols.[9]

In the previous chapters, we saw the development of a new catalyst primary amine salt, in which both the cation and the anion are chiral, that exhibits high reactivity and selectivity for iminium ion catalysis with α,β-unsaturated ketones.[10] In particular we have shown that salt **A**, made by combining the easily available 9-amino(9-deoxy)*epi*-hydroquinine[11] with D-*N*-Boc phenylglycine as the chiral counter-anion, can function as highly efficient catalyst for the asymmetric conjugated addition of indoles[10a] and oximes[10b] to simple enones; the efficient activation relies on the proven ability of primary amines to form iminium-ion intermediates from ketones, owing to reduced steric constraints,[12] combined synergistically with the benefits of asymmetric counterion directed catalysis (ACDC), an efficient strategy for enantioselective transformations that proceed via cationic species.[13]

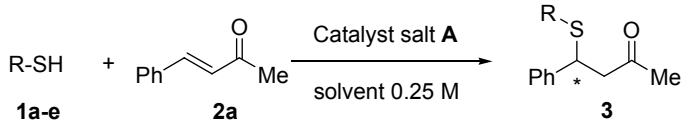


Herein, we further advance this organocatalytic activation strategy to document an operationally trivial procedure for the highly chemo- and enantioselective sulfa-Michael addition of benzyl and *tert*-butyl mercaptans to α,β-unsaturated ketones catalysed by the chiral salt **A**. The high efficiency obtained in terms of both yield and enantioselectivity (up to 96% ee) for a large variety of Michael acceptors highlights the applicability and utility of this catalytic system as iminium ion activator of simple enones.

To assess the feasibility of such an asymmetric organocatalytic sulfa-Michael addition to α,β-unsaturated ketones, we screened various *S*-centered nucleophiles in the addition to *trans*-4-phenyl-3-buten-2-one **2a** in the presence of catalytic salt **A**;[14] the results of this survey are reported in Table 1. Aromatic thiols did not furnish the desired product in good enantioselectivity. Thiophenol **1a** provided the Michael adduct in 45% ee after 18 h at room temperature (entry 1) and lowering the reaction temperature to -10°C did not improve the enantioselectivity to a satisfactory level

(55% ee, entry 2).[15] The employment of a more encumbered aromatic thiol brought to a dramatic loss in stereocontrol (entry 3).

Table 1: Screening results for the organocatalytic addition of different thiols (**1**) to enone (**2a**).[a]



entry	R	**A** [mol%]	solvent	T [°C]	time [h]	conv. [%][b]	ee [%][c]
1	Ph, **1a**	20	toluene	RT	18	>95	45
2	Ph, **1a**	20	toluene	-10	30	75	55
3	Naphthyl, **1b**	20	toluene	RT	3	>95	0
4	Bn, **1c**	20	toluene	RT	18	>95	56
5	Bn, **1c**	10	toluene	RT	18	>95	40
6	Bn, **1c**	10	toluene	-30	24	40	86
7[d]	Bn, **1c**	20	toluene	RT	18	30	- 8
8[e]	Bn, **1c**	20	toluene	-30	24	26	76
9	Bn, **1c**	10	CH_2Cl_2	-30	24	37	70
10	Bn, **1c**	10	Et_2O	-30	24	70	79
11[f]	Bn, **1c**	10	toluene	-30	24	60	83
12	Bn, **1c**	5	toluene	-30	24	20	85
13	Bn, **1c**	15	toluene	-20	66	90 (81)	85
14	*t*-Bu, **1d**	20	toluene	RT	116	72 (59)	95

[a] Reactions were carried out in undistilled solvents without any precaution to exclude air, using 1.2 equiv. of thiols **1** on a 0.2 mmol scale. [b] Determined by ^{1}H NMR of the crude mixture; isolated yield is indicated between brackets. [c] ee of **3** was determined by HPLC analysis on chiral support. [d] 9-amino(9-deoxy)*epi*-hydroquinine without any acidic counterion was used as the catalysts. [e] (L)-*N*-Boc-phenylglycine was used as the counterion. [f] $[\mathbf{2a}]_0$ = 0.5 M.

Interestingly, the use of benzyl mercaptan **1c** provided the desired product with improved steroselectivity (56% ee, entry 4) and this prompted us to further screen such a nucleophile. Lowering the catalyst loading showed the occurrence of a decrease in enantioselectivity (40% ee, entry 5); nevertheless carrying out the reaction at lower temperature in the presence of 10 mol% of **A**, the stereoselectivity reached satisfactory levels, albeit at the expenses of reactivity (40% conv and 86% ee, entry 6).

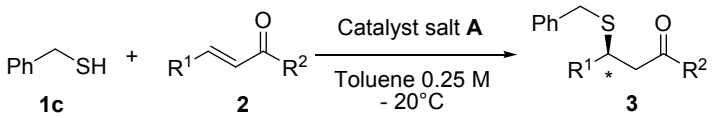
Noteworthy, in the absence of an acidic counteranion (entry 7), the diamine 9-amino(9-deoxy)*epi*-hydroquinine is still able to promote the sulfa-Michael addition, albeit with lower reactivity, by activating the nucleophilic component **1c** through Brønsted-base catalysis.[16] However, the observed low optical purity (8% ee) together with reversal in the stereochemistry supports an iminium-ion activation mode of catalysis when the chiral salt **A** is employed. Remarkably, consistently with previous observations,[10] using the opposite enantiomeric counteranion (L-*N*-Boc phenylglycine) afforded the same enantiomeric product **3** with lower reactivity and

selectivity (entry 8), illustrating a marked case of a matched/mismatched catalyst-ion pair combination.[17]

Evaluation of usual reaction media led to the identification of toluene as the best solvent (entries 6 and 9-10). Further optimisation of standard parameters revealed that carrying out the reaction at -20 °C in the presence of 15 mol% of the catalytic salt **A** represents the best compromise between reactivity and enantioselectivity (81% isolated yield and 85% ee after 66 h, entry 13). Finally *tert*-butyl mercaptan **1d**, albeit less reactive, proved to be a promising alternative *S*-nucleophile for the present SMA strategy, as the corresponding product was isolated in satisfactory yield and very high enantiomeric excess (59% yield and 95% ee, entry 14). Besides these interesting results, the use of benzyl and *tert*-butyl mercaptan represents an important feature from a synthetical standpoint, providing orthogonal sets of removable *S*-protecting groups.[18]

Having identified **1c** and **1d** as two suitable nucleophiles, we set out to investigate the scope of the organocatalysed SMA reaction with respect to various α,β-unsaturated ketones. The addition of benzyl mercaptan **1c** proved to be efficiently activated by the catalytic salt **A**, providing the desired adduct in good yields and high ee (Table 2). There appears to be significant tolerance towards steric and electronic demands of the β-olefin substituent as highly enantioenriched adducts could be obtained using aromatic, heteroaromatic and alkyl groups.

Table 2: Organocatalytic asymmetric sulfa-Michael addition of benzyl mercaptan (**1c**) to enones (**2**).[a]



entry	R^1	R^2	**A** [mol%]	time [h]	yield [%][b]	ee [%][c]
1	Ph	Me, **2a**	15	66	**3a** - 81	85
2	*p*-ClC_6H_4	Me, **2b**	15	46	**3b** - 78	84
3	2-thienyl	Me, **2c**	15	66	**3c** - 84	84
4	Pent	Me, **2d**	20	96	**3d** - 81	89
5	Pent	Et, **2e**	20	96	**3e** - 75	96
6	Me	Et, **2f**	20	96	**3f** - 55	94
7[d]	Ph	Ph, **2g**	20	40	**3g** - 75	54[e]

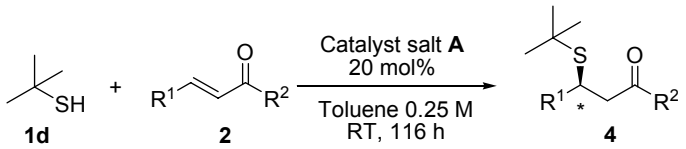
[a] Reactions carried out using 1.2 equiv. of **1c** on a 0.2 mmol scale. [b] Isolated yield. [c] Determined by HPLC analysis on chiral support. [d] Reaction carried out at RT. [d] The absolute configuration of the product **3g** was assigned to be (*S*) by comparison of the measured optical rotation with the value reported in the literature.[8a]

Variation in the steric contribution of R^2 ketone substituents (compare entries 4 and 5) revealed that the more encumbered ethyl group engenders higher selectivity, albeit at the expenses of the reactivity; the sulfa-Michael adducts could be isolated in good yields and very high optical purity (ee values ranging from 94% to 96%) by adjusting the catalyst loading and the reaction time (entries 5-6).[19]

In our previous studies[10a] we observed that the chiral salt **A** was an effective catalyst also for aromatic ketones (R^2= Ph), a class of substrates which is not generally suitable for iminium-ion activation. Notably, our organocatalytic protocol confirms its efficiency in activating aromatic ketones such as *trans*-chalcone **2g** providing the desired product **3g,** albeit with moderate stereocontrol (entry 7). The absolute configuration of the product **3g** was assigned to be (*S*) by comparison of the measured optical rotation with the value reported in the literature.[8a] The sense of the stereochemical induction is in agreement with the observation made in the previously reported Michael additions catalyzed by the catalytic salt **A**.[10]

We next examined whether the presented organocatalytic SMA protocol could be extended to an alternative thiol having a different removable protecting group. Indeed, the catalytic salt **A** efficiently catalysed the sulfa-Michael addition of *tert*-butyl mercaptan **1d** to a large variety of simple enones. Albeit the low reactivity of **1d** required the use of 20 mol% of the catalyst and prolonged reaction time, impressive levels of stereocontrol was achieved even at room temperature (Table 3).

Table 3: Organocatalytic asymmetric sulfa-Michael addition of *tert*-butyl mercaptan (**1d**) to enones (**2**).[a]



entry	R^1	R^2	yield [%][b]	ee [%][c]
1	Ph	Me, **2a**	**4a** – 59	95
2	*p*-ClC_6H_4	Me, **2b**	**4b** – 70	94
3	*p*-$NO_2C_6H_4$	Me, **2i**	**4c** – 98	91
4	*p*-CNC_6H_4	Me, **2j**	**4d** – 96	94
5	2-thienyl	Me, **2c**	**4e** – 65	92
6	Pent	Me, **2d**	**4f** – 76	91
7	Me	Me, **2k**	**4g** - 71	82
8	*i*Pr	Me, **2l**	**4h** – 46	88
9	$PhCH_2CH_2$	Me, **2m**	**4i** – 49	87
10[d]		$(CH_2)_3$, **2n**	**4j** – 96	87
11	Ph	Ph, **2h**	**4k** – 44	95

[a] Reactions carried out using 1.2 equiv. of **1d** on a 0.2 mmol scale. [b] Isolated yield. [c] Determined by HPLC analysis on chiral support. [d] Reaction carried out over 5h.

In the presence of aromatic substituents at the β-position of the Michael acceptor, enantioselectivities ranging from 91% to 95% were obtained with great tolerance for heteroaromatic and variously substituted functional groups (entries 1-5). The protocol was also efficient for aliphatic enones providing the expected products in high optical purity and good yields (entries 6-9).

Interestingly, the presented organocatalytic SMA proceeds efficiently also with cyclic enones, the product derived from 2-cycloexen-1-one being isolated in high yield and enantioselectivity (96% yield, 87% ee, entry 10). This result, in conjunction with the observation that reaction with *trans*-chalcone provided product **4k** with excellent enantiomeric excess (95% ee, entry 11), adds significant importance to the present organocatalytic SMA protocol demonstrating that **A** is able to activate efficiently and in a high stereoselective fashion different classes of α,β-unsaturated ketones.[20]

In summary, we have disclosed an organocatalytic asymmetric protocol for the highly enantioselective sulfa-Michael addition that is effective for a large variety of α,β-unsaturated ketones. The high chemical yields and enantioselectivities obtained consolidate the catalytic salt **A** as a general iminium-ion activator of simple enones. From a synthetic perspective, the simplicity of the procedure that employs easily available starting materials and catalyst in combination with the use of *S*-centered nucleophiles having different removable protecting groups, renders the method potentially useful to the chemical community.

6.3.R References

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[9] For examples of sulfur-centered nucleophiles used in asymmetric SMA that can be easily removed to afford versatile SH functionality, see Ref. 7a and Ref. 8b.

[10] a) G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403; b) A. Carlone, G. Bartoli, M. Bosco, F. Pesciaioli, P. Ricci, L. Sambri, P. Melchiorre, *Euro J. Org. Chem.* **2007**, *33*, 5492.

[11] Recently, 9-amino(9-deoxy)*epi*-cinchona alkaloids in combination with achiral acids was reported to be an effective catalyst for the asymmetric conjugate addition of carbon-centered nucleophiles to simple enones via iminium-ion catalysis: a) J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y.-C. Chen, Y. Wu, J. Zhu, J.-G. Deng, *Angew. Chem.* **2007**, *119*, 393; *Angew. Chem. Int. Ed.* **2007**, *46*, 389; b) J.-W. Xie, L. Yue, W. Chen, W. Du, J. Zhu, J.-G. Deng, Y.-C. Chen, *Org. Lett.* **2007**, *9*, 413; c) W. Chen, W. Du, L. Yue, R. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Org. Biomol. Chem.* **2007**, *5*, 816; for a recent ACDC approach with a multifunctional primary amine, see: d) W. Chen, W. Du, Y.-Z. Duan, Y. Wu, S.-Y. Yang, Y.-C. Chen, *Angew. Chem.* **2007**, *119*, 7811; *Angew. Chem. Int. Ed.* **2007**, *46*, 7667. For the use in asymmetric enamine catalysis with ketones, see: (e) S. H. McCooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599; f) T.-Y. Liu, H.-L. Cui, Y. Zhang, K. Jiang, W. Du, Z.-Q. He, Y.-C. Chen, *Org. Lett.* **2007**, *9*, 3671; g) B.-L. Zheng, Q.-Z. Liu, C.-S. Guo, X.-L. Wang, L. He, *Org. Biomol. Chem.* **2007**, *5*, 2913.

[12] For recent use of primary amines in the activation of ketones via enamine catalysis, see: a) S. B. Tsogoeva, S. Wei, *Chem. Commun*. **2006**, 1451; b) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170; for the use of primary amine salts in asymmetric iminium-ion catalysis with enones, see: c) H. Kim, C. Yen, P. Preston, J. Chin, *Org. Lett.* **2006**, *8*, 5239. See also Ref. 11.

[13] a) S. Mayer, B. List, *Angew. Chem.* **2006**, *118*, 4299; *Angew. Chem. Int. Ed*. **2006**, *45*, 4193; b) N. J. A. Martin, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13368.

[14] The results obtained by using 9-amino(9-deoxy)*epi*-hydroquinine in combination with different counterions (TFA, *p*-TSA, L-*N*-Boc phenylalanine) in the organocatalyzed SMA did not bring any appreciable improvement in term of enantioselectivity, confirming the superior efficiency of the catalytic salt **A**.

[15] Considering the relative high acidity of phenyl thiol **1a**, its Michael addition to **2a** could be easily promoted by weak bases, see Ref. 16. Since the catalyst amine component 9-amino(9-deoxy)*epi*-hydroquinine has three basic nitrogen atoms, a Brønsted base-catalyzed background reaction, affecting the stereoselectivity of the process, could be envisaged. As interestingly suggested by one reviewer, the use of 3 equiv. of D-*N*-Boc phenylalanine as the acidic additive to avoid this parasitic reaction has been investigated, resulting in only a slight

enhancement of enantioselectivity: T = -10 °C, 30h reaction time, 80% conversion, 62% ee (compare to entry 2, Table 1).

[16] The potentiality of *Cinchona* alkaloids to act as bases to deprotonate substrates with relatively acidic protons such as thiols, thus forming contact ion-pair between the resulting anion and the protonated quinuclidine moiety, is well established, see Ref. 4b and 6b.

[17] For a similar behavior in ACDC activation strategy, see Ref. 13b.

[18] T. W. Greene, P. G. M Wuts, *Protective Groups in Organic Synthesis (Third Edition)*; Wiley-VCH, New York, **1999**, chapter 6, pp 454.

[19] α,β-unsaturated ketone with R^1= Ph and R^2= Et gave a sluggish reaction rate (27% conversion after 42 h), albeit the product was formed in 90% ee at -30 °C in the presence of 20 mol% of catalytic salt **A**.

[20] Achieving high levels of generality and selectivity in asymmetric SMA under catalytic conditions is rather challenging, as methods that provide regularly high enantioselectivity (ee's above 90%) are scarce; see Ref. 6b and Ref. 7a-c.

6.3.EP Experimental Part

Contents

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts (δ) are referenced to residual signals of the solvents ($CHCl_3$ – 7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR). Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Mass spectra were obtained from the Department of Organic Chemistry "A. Mangini" Mass Spectroscopy facility. Optical rotations are reported as follows: $[\alpha]^{D}_{rt}$ (c in g per 100 mL, solvent). All reactions were carried out in air and using undistilled solvent without any precautions to exclude moisture, unless otherwise noted.

Materials. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[1]

Thiols **1** were purchased from Aldrich and Fluka. α,β-unsaturated ketones **2** were purchased and used as received, prepared by Wittig reaction with commercially available acetylmethylene-triphenylphosphorane (when R^2= Me), or by addition of ethyl Grignard to the corresponding unsatured aldehyde followed by oxidation with MnO_2 (when R^2= Et).

N-protected amino acids were purchased from Aldrich or Fluka and used as received.

9-Amino(9-deoxy)*epi*-hydroquinine was prepared from commercially available hydroquinine following the literature procedure.[2]

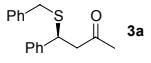
Determination of Enantiomeric Purity. Chiral HPLC analysis was performed on an Agilent 1100-series instrumentation. Daicel Chiralpak AD-H or AS-H columns and Daicel Chiralcel OD-H with i-PrOH/hexane as the eluent were used. HPLC traces were compared to racemic samples prepared by $FeCl_3$-catalyzed reaction.[3]

Determination of Absolute Configuration. The absolute configuration of the optically active compound **3g** was assigned to be (*S*) by comparison of the measured optical rotation with the value reported in the literature.[4] All other absolute configurations were assigned by analogy based on an uniform reaction mechanism.

Experimental Procedures

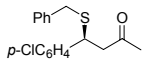
General Procedure for the Organocatalytic Sulfa-Michael Addition to α,β-Unsaturated Ketones. All the reactions were carried out in undistilled toluene without any precautions to exclude water. In an ordinary test tube equipped with a magnetic stirring bar, 9-amino(9-deoxy)epi-hydroquinine (10-20 mol%) and D-*N*-Boc phenylglycine (20-40 mol%) as the chiral counter-anion were dissolved in 0.8 mL of toluene. The solution was stirred for 20 minutes at room temperature to allow the formation of the

catalytic salt **A**. After addition of α,β-unsaturated ketones **2** (0.2 mmol), the mixture was stirred at the appropriate temperature for 10 minutes. Then thiol **1** (0.24 mmol, 1.2 equiv) was added in one portion, the tube was closed with a rubber stopper and stirring was continued for the indicated time. Then the crude reaction mixture was diluted with hexane (2 mL) and flushed through a short plug of silica, using hexane/Et2O 1/1 as the eluent. Solvent was removed *in vacuo*, and the residue was purified by flash chromatography to yield the desired product.



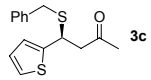
3a

3a (Table 2, entry 1). The reaction was carried out at -20 °C for 66 h using 15 mol% of catalytic salt **A** following the general procedure. The title compound was isolated by column chromatography (hexane/ Et_2O = 85/15) in 81% yield and 85% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (90/10 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 10.4 min; τ_{minor} = 11.9 min). $[\alpha]^{D}_{rt}$= - 162.5 (c = 1.0, $CHCl_3$, 85% ee). HRMS: m/z calcd for $C_{17}H_{18}OS$: 270.1078; found: 270.1076. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.02 (s, 3H), 2.92-2.95 (m, 2H), 3.50 (AB system, *J* = 13.3 Hz, 2H), 4.22 (t, *J* = 7.2 Hz, 1H), 7.20-7.34 (m, 10H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 30.4, 35.7, 43.9, 49.9, 127.0, 127.4, 127.9, 128.4, 128.5, 128.9, 137.8, 141.5, 205.2.



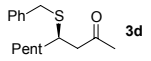
3b

3b (Table 2, entry 2). The reaction was carried out at -20 °C for 46 h using 15 mol% of catalytic salt **A** following the general procedure. The title compound was isolated by column chromatography (hexane/ Et_2O = 85/15) in 78% yield and 84% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (95/5 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 11.6 min; τ_{major} = 12.3 min). $[\alpha]^{D}_{rt}$= - 200.7 (c = 1.0, $CHCl_3$, 84% ee). HRMS: m/z calcd for $C_{17}H_{17}ClOS$: 304.0689; found: 304.0689. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.02 (s, 3H), 2.90 (brd, *J* = 7.2 Hz, 2H), 3.49 (AB system, *J* = 13.3 Hz, 2H), 4.17 (t, *J* = 7.2 Hz, 1H), 7.18-7.30 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 30.5, 35.7, 43.1, 49.9, 127.1, 128.5, 128.7, 128.9, 129.3, 132.9, 137.5, 140.2, 204.8.



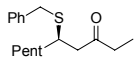
3c

3c (Table 2, entry 3). The reaction was carried out at -20 °C for 66 h using 15 mol% of catalytic salt **A** following the general procedure. The title compound was isolated by column chromatography (hexane/ Et_2O = 85/15) in 84% yield and 84% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 8.4 min; τ_{minor} = 9.5 min). $[\alpha]^{D}_{rt}$= - 202.6 (c = 1.0, $CHCl_3$, 84% ee). HRMS: m/z calcd for $C_{15}H_{16}OS_2$: 276.0643; found: 276.0640. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.05 (s, 3H), 2.91-3.04 (m, 2H), 3.62 (AB system, *J* = 13.3 Hz, 2H), 4.52 (t, *J* = 7.4 Hz, 1H), 6.90-6.93 (m, 3H), 7.22-7.32 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 30.5, 36.0, 39.1, 50.8, 124.8, 125.8, 126.4, 127.1, 128.5, 128.9, 137.6, 146.3, 204.8.



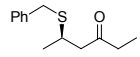
3d

3d (Table 2, entry 4). The reaction was carried out at -20 °C for 96 h using 20 mol% of catalytic salt **A** following the general procedure. The title compound was isolated by column chromatography (hexane/ Et_2O = 90/10) in 81% yield and 89% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (98/2 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 10.3 min; τ_{minor} = 10.8 min). $[\alpha]^{D}_{rt}$= + 0.4 (c = 1.0, $CHCl_3$, 89% ee). HRMS: m/z calcd for $C_{16}H_{24}OS$: 264.1548; found: 264.1545. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.0 Hz, 3H), 1.16-1.52 (m, 8H), 2.08 (s, 3H), 2.56-2.69 (m, 2H), 3.03-3.09 (m, 1H), 3.73 (AB system, *J* = 13.2 Hz, 2H), 7.20-7.34 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.0, 22.5, 26.3, 30.5, 31.5, 35.1, 35.7, 40.4, 49.6, 126.9, 128.4, 128.9, 138.5, 206.9.



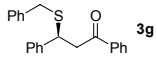
3e

3e (Table 2, entry 5). The reaction was carried out at -20 °C for 96 h using 20 mol% of catalytic salt **A** following the general procedure. The title compound was isolated by column chromatography (hexane/ Et_2O = 85/15) in 75% yield and 96% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (99/1 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 7.8 min; τ_{minor} = 8.5 min). $[\alpha]^{D}_{rt}$= + 8.2 (c = 1.0, $CHCl_3$, 96% ee). HRMS: m/z calcd for $C_{17}H_{26}OS$: 278.1704; found: 278.1702. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 7.2 Hz, 3H), 1.14-1.51 (m, 8H), 2.36 (q, *J* = 7.2 Hz, 2H), 2.54-2.68 (m, 2H), 3.03-3.10 (m, 1H), 3.72 (AB system, *J* = 13.2 Hz, 2H), 7.20-7.31 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 7.6, 14.0, 22.5, 26.3, 31.5, 35.2, 35.9, 36.7, 40.6, 48.5, 126.9, 128.4, 128.9, 138.6, 209.6.



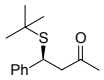
3f

3f (Table 2, entry 6). The reaction was carried out at -20 °C for 96 h using 20 mol% of catalytic salt **A** following the general procedure. The title compound was isolated by column chromatography (hexane/ Et_2O = 95/5) in 55% yield and 94% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (98/2 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 9.9 min; τ_{major} = 10.2 min). $[\alpha]^{D}_{rt}$= - 6.9 (c = 1.0, $CHCl_3$, 94% ee). HRMS: m/z calcd for $C_{13}H_{18}OS$: 222.1078; found: 222.1077. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 7.6 Hz, 3H), 1.26 (d, *J* = 6.8 Hz, 3H), 2.32-2.39 (m, 2H), 2.58 (AB system, *J* = 6.0, 16.4 Hz, 2H), 3.15-3.23 (m, 1H) 3.75 (AB system, *J* = 13.2, 2H), 7.21-7.33 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 7.6, 21.5, 35.1, 35.6, 36.6, 49.6, 127.0, 128.5, 128.8, 138.3, 209.2.



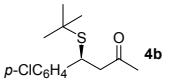
3g

(*S*)-**3g** (Table 2, entry 7). The reaction was carried out at RT for 40 h using 20 mol% of catalytic salt **A** following the general procedure. The title compound was isolated by column chromatography (hexane/Et_2O = 95/5) in 75% yield and 54% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (90/10 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 9.2 min; τ_{major} = 11.1 min). $[\alpha]^{D}_{rt}$= - 67.5 (c = 1.0, CH_2Cl_2, 54% ee); lit.[4] $[\alpha]^{D}_{rt}$= + 136, (*R*)-**3g** (c = 1.02, CH_2Cl_2, >95% ee) . ESI: m/z calcd for $C_{22}H_{20}OS+H^+$: 332; found: 333. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.46-3.60 (m, 4H), 4.47-4.50 (m, 1H), 7.22-7.68 (m, 15H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 35.8, 44.1, 45.2, 126.9, 127.2, 128.0, 128.1, 128.4, 128.5, 128.6, 128.9, 133.1, 136.7, 137.8, 141.7, 196.7.



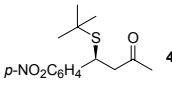
4a

4a (Table 3, entry 1). The reaction was carried out at RT for 116 h using 20 mol% of catalytic salt **A** following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 92/8) in 59% yield and 95% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (80/20 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 5.8 min; τ_{minor} = 6.3 min). $[\alpha]^{D}_{rt}$= -124.8 (c = 1.0, $CHCl_3$, 95% ee). HRMS: m/z calcd for $C_{14}H_{20}OS$: 236.1235; found: 236.1236. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (s, 9H), 2.05 (s, 3H), 2.83-2.96 (m, 2H), 4.41 (t, *J* = 7.6 Hz, 1H), 7.16-7.40 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 30.9, 31.2, 42.5, 44.2, 52.1, 126.8, 127.6, 128.4, 144.5, 205.5.



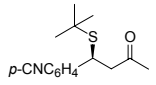
4b

4b (Table 3, entry 2). The reaction was carried out at RT for 116 h using 20 mol% of catalytic salt **A** following the general procedure. The title compound was isolated by column chromatography (hexane/ Et_2O = 85/15) in 70% yield and 94% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (90/10 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 5.2 min; τ_{minor} = 5.5 min). $[\alpha]^{D}_{rt}$= -137.5 (c = 1.0, $CHCl_3$, 94% ee). HRMS: m/z calcd for $C_{14}H_{19}ClOS$: 270.0845; found: 270.0842. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (s, 9H), 2.05 (s, 3H), 2.78-2.94 (m, 2H), 4.38 (t, *J* = 6.9 Hz, 1H), 7.21-7.34 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 30.9, 31.2, 41.7, 44.4, 51.9, 128.5, 129.0, 132.4, 143.2, 205.1.



4c

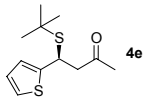
4c (Table 3, entry 3). The reaction was carried out at RT for 116 h using 20 mol% of catalytic salt **A** following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 85/15) in 98% yield and 91% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (80/20 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 9.2 min; τ_{major} = 9.9 min). $[\alpha]^{D}_{rt}$= -181.5 (c = 1.0, $CHCl_3$, 91% ee). HRMS: m/z calcd for $C_{14}H_{19}NO_3S$: 281.10856; found: 281.1085. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (s, 9H), 2.07 (s, 3H), 2.92 (AB system, *J* = 6.4, 17.2 Hz, 2H), 4.48 (t, *J* = 7.2 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 8.13 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 30.7, 31.2, 41.5, 44.7, 51.6, 123.7, 128.7, 146.7, 152.6, 204.5.



4d

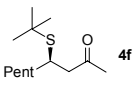
4d (Table 3, entry 4). The reaction was carried out at RT for 116 h using 20 mol% of catalytic salt **A** following the general procedure. The title compound was isolated by column chromatography (hexane/ Et_2O = 70/30) in 96% yield and 94% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 5.2 min; τ_{minor} = 5.5 min). $[\alpha]^{D}_{rt}$= - 188.0

(c = 1.0, $CHCl_3$, 94% ee). HRMS: m/z calcd for $C_{15}H_{19}NOS$: 261.1187; found: 261.1185. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.18 (s, 9H), 2.07 (s, 3H), 2.89 (AB system, *J* = 7.6, 17.2 Hz, 2H), 4.43 (t, *J* = 7.2 Hz, 1H), 7.50-7.58 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 30.7, 31.1, 41.8, 44.7, 51.6, 110.6, 118.7, 128.6, 132.2, 150.5, 205.6.



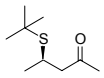
4e

4e (Table 3, entry 5). The reaction was carried out at RT for 116 h using 20 mol% of catalytic salt **A** following the general procedure. The title compound was isolated by column chromatography (hexane/ Et_2O = 80/20) in 65% yield and 92% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (80/20 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 6.8 min; τ_{minor} = 7.2 min). $[\alpha]^D_{rt}$ = - 143.4 (c = 1.0, $CHCl_3$, 92% ee). HRMS: m/z calcd for $C_{12}H_{18}OS_2$: 242.0799; found: 242.0798. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 9H), 2.10 (s, 3H), 2.91-3.03 (m, 2H), 4.70 (t, *J* = 7.2 Hz, 1H), 6.85-6.88 (m, 1H), 6.94-6.97 (m, 1H), 7.14-7.17 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 30.9, 31.0, 37.4, 44.7, 53.0, 124.1, 124.4, 126.5, 149.7, 205.1.



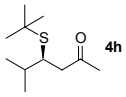
4f

4f (Table 3, entry 6). The reaction was carried out at RT for 116 h using 20 mol% of catalytic salt **A** following the general procedure. The title compound was isolated by column chromatography (hexane/Et_2O = 95/5) in 76% yield and 91% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (95/5 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 4.6 min; τ_{major} = 4.9 min). $[\alpha]^D_{rt}$= - 7.1 (c = 1.0, $CHCl_3$, 91% ee). HRMS: m/z calcd for $C_{13}H_{26}OS$: 230.1704; found: 230.1703. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.8 Hz, 3H), 1.29 (s, 9H), 1.20-1.53 (m, 8H), 2.14 (s, 3H), 2.63-2.75 (m, 2H), 3.04-3.11 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.0, 22.5, 26.5, 31.1, 31.4, 31.7, 37.3, 37.8, 43.4, 51.4, 207.2.



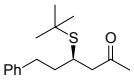
4g

4g (Table 3, entry 7). The reaction was carried out at RT for 116 h using 20 mol% of catalytic salt **A** following the general procedure. The title compound was isolated by column chromatography (hexane/ Et_2O = 95/5) in 71% yield and 82% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (90/10 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 5.0 min; τ_{major} = 5.4 min). $[\alpha]^D_{rt}$= - 6.9 (c = 1.0, $CHCl_3$, 82% ee). HRMS: m/z calcd for $C_9H_{18}OS$: 174.1078; found: 174.1077. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26-1.29 (m, 12H), 2.11 (s, 3H), 2.62 (AB system, *J* = 6.4, 17.2 Hz, 2H), 3.15-3.25 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 24.5, 30.9, 31.3, 32.8, 43.5, 52.6, 206.7.



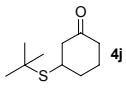
4h

4h (Table 3, entry 8). The reaction was carried out at RT for 116 h using 20 mol% of catalytic salt **A** following the general procedure. The title compound was isolated by column chromatography (hexane/ Et_2O = 95/5) in 46% yield and 88% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (95/5 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 4.6 min; τ_{major} = 5.0 min). $[\alpha]^D_{rt}$= - 4.1 (c = 1.0, $CHCl_3$, 88% ee). HRMS: m/z calcd for $C_{11}H_{22}OS$: 202.1391; found: 202.1395. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.8 Hz, 1H), 0.95 (d, *J* = 6.8 Hz, 1H), 1.28 (s, 9H), 1.83-1.91 (m, 1H), 2.15 (s, 3H), 2.62-2.75 (m, 2H), 3.05-3.10 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 18.8, 19.2, 31.2, 31.4, 33.1, 43.0, 43.8, 48.2, 207.4.



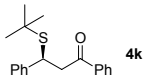
4i

4i (Table 3, entry 9). The reaction was carried out at RT for 116 h using 20 mol% of catalytic salt **A** following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 90/10) in 49% yield and 87% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (80/20 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 5.0 min; τ_{major} = 5.2 min). $[\alpha]^D_{rt}$= - 10.5 (c = 1.0, $CHCl_3$, 87% ee). HRMS: m/z calcd for $C_{16}H_{24}OS$: 264.1548; found: 264.1548. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 9H), 1.74-1.84 (m, 1H), 1.88-1.95 (m, 1H), 2.14 (s, 3H), 2.68-2.84 (m, 4H), 3.13-3.20 (m, 1H), 7.15-7.30 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 31.0, 31.4, 33.2, 37.6, 38.8, 43.6, 51.5, 125.8, 128.3, 128.4, 141.8, 206.9.



4j

4j (Table 3, entry 10). The reaction was carried out at RT for 5 h using 20 mol% of catalytic salt A following the general procedure. The title compound was isolated by column chromatography (hexane/Et_2O = 85/15) in 96% yield and 87% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (95/5 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 6.2 min; τ_{minor} = 6.5 min). $[\alpha]^D_{rt}$= - 98.7 (c = 2.0, $CHCl_3$, 87% ee). HRMS: m/z calcd for $C_{10}H_{18}OS$: 186.1078; found: 186.1076. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 9H), 1.67-1.76 (m, 2H), 2.05-2.41 (m, 5H), 2.68-2.74 (m, 1H), 2.94-3.02 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 24.7, 31.4, 34.4, 40.6, 40.7, 43.7, 50.9, 209.3.



4k

4k (Table 3, entry 11). The reaction was carried out at RT for 116 h using 20 mol% of catalytic salt **A** following the general procedure. The title compound was isolated by column chromatography (hexane/Et_2O = 90/10) in 44% yield and 95% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (90/10 hexane/i-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 5.5 min; τ_{major} = 5.7 min). $[\alpha]^{D}_{rt}$= -37.0 (c = 1.0, $CHCl_3$, 82% ee). HRMS: m/z calcd for $C_{19}H_{22}OS$: 298.1391; found: 298.1392. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (s, 9H), 3.41-3.55 (m, 2H), 4.67 (t, *J* = 7.2 Hz, 1H), 6.85-6.88 (m, 1H), 7.15-7.30 (m, 3H), 7.40-7.55 (m, 5H), 7.88-7.90 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 31.2, 42.5, 44.3, 47.5, 126.8, 127.7, 128.0, 128.4, 128.5, 133.0, 136.9, 144.7, 196.9.

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7. Domino Reactions: a Facile Access to Complex and Important Scaffolds

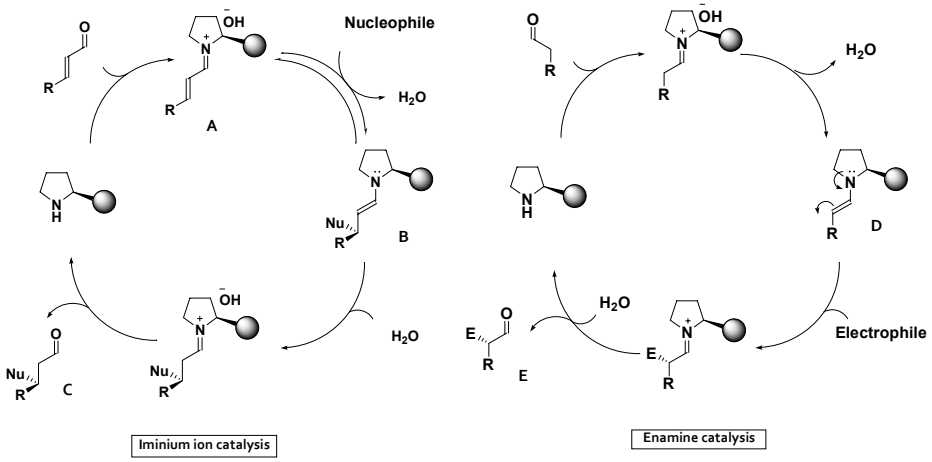
At the hearth of the research there is the discovery of new single reactions. It is, however, of increasingly interest the development of methodologies that could combine different reactions in a one-pot sequence. This allows the minimization of waste and purification, along with rendering the whole process a lot easier. Additionally, a higher molecular complexity is achieved, giving facile access to structurally elaborated molecules.

Chiral secondary amines usually used in organocatalysis are robust molecules that display orthogonal reactivities depending on the substrates. It is obvious, therefore, that they fulfil the requirements for domino reactions.

It is straightforward that domino reactions are at the forefront of nowadays research in Asymmetric Aminocatalysis.

There is an extreme increasingly interest, nowadays, to design new catalytic processes, that could be easily incorporated into the synthesis of complex chiral structures in one simple, safe, environmentally acceptable, and resource-effective operation that proceeds quickly and in high yield.

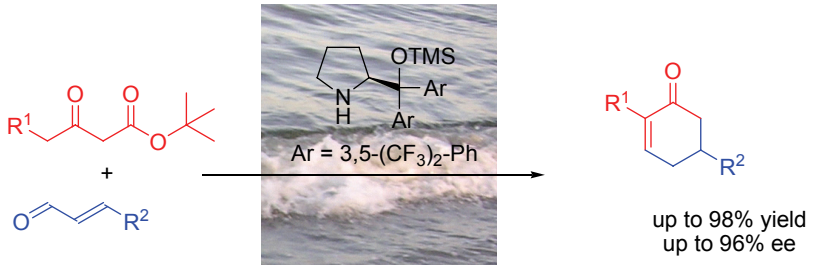
As already mentioned (Chap 2), Asymmetric Aminocatalysis provides several modes of action and, among all, iminium ion and enamine catalysis show orthogonal activations that can be exploited to combine the two catalytic principles in tandem sequences.



Herein we describe the exploitation of an iminium ion activation for the first enantioselective addition of β-ketoesters on aldehydes and subsequent reactions in a one-pot process. This way, optically active 2,5-disubstituted-cyclohexen-2-one derivatives have been prepared in a one-pot process consisting of five reaction steps; thus, simple but very important products can be obtained with very easy handling shortening all the separation and purification steps. It is striking that from small and simple starting materials, versatile building blocks for the synthesis of a large number of natural occurring products and other important compounds for the life science industry can be easily obtained. Moreover, the use of aqueous solutions or the absence of solvent for the first step are also appealing conditions for the development of the protocol as they allow the use of any other solvent in the subsequent steps.

Following, a domino multicomponent reaction is presented. A sequential iminium–iminium–enamine catalysis allows the consecutive formation of three new carbon–carbon bonds and provides enantiopure products through reaction of α,β-unsaturated aldehydes with activated methylene compounds. Moreover, the research presented allowed the synthesis of complex and congested products with quaternary stereocenters. A noteworthy feature is the use of a tertiary amine (DABCO) –in place of an acidic additivie- to speed up the reaction. It shines the spot on the fact that a tertiary and a chiral secondary amine can coexist; this obviously allows the fantasy of researchers to span an even broader range of reactions.

7.1 A simple asymmetric organocatalytic approach to optically active cyclohexenones

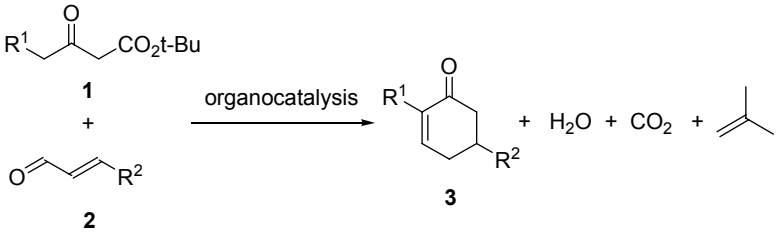


Optically active 2,5-disubstituted-cyclohexen-2-one derivatives have been prepared in a one-pot process consisting of five reaction steps: an organocatalytic asymmetric conjugated addition of β-ketoesters to α,β-unsaturated aldehydes that proceeds in aqueous solutions or under solvent-free conditions has been implemented in a multi-step process.

Organocatalysis[1] has in the last few years gained considerable attention in chemistry, because the use of metal-free catalysts rather than organometallic complexes for the formation of optically active molecules has several potential advantages. For instance, the organocatalytic approach might become valuable in the preparation of life-science products such as pharmaceutical compounds which do not tolerate metal contamination. Furthermore, organocatalysis is often associated with mild and simple reaction conditions that are appealing because of the easy handling, cost and safety issues. Unfortunately, the advantages have sometimes been tempered by the use of large excesses of solvent and/or reagent and catalyst, and by long reaction times. To overcome these limitations, recently serious efforts have been dedicated, not only to develop new organocatalytic transformations, but also to select more appealing reaction conditions. For example, the use of water/aqueous solutions[2] as an environmentally friendly solvent has naturally received special attention.[3]

We report a new series of asymmetric organocatalytic transformations that focus on the preparation of important optically active molecules and on the green chemistry principles.[4] We thought it would be important to design a new catalytic process, that could be easily incorporated into the synthesis of complex chiral structures in "one simple, safe, environmentally acceptable, and resource-effective operation that proceeds quickly and in high yield".[5]

In this context, we have developed a one-pot (5 step) asymmetric synthesis of the important optically active cyclohex-2-enone derivatives, based on organocatalysis and which gives H_2O and CO_2 as major by-products, along with isobutene (Scheme 1).



Scheme 1: One-pot organocatalytic asymmetric synthesis of cyclohex-2-enone derivatives.

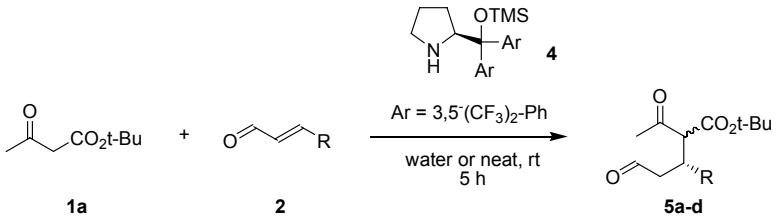
Chiral cyclohex-2-enones are versatile building blocks for the synthesis of a large number of natural occurring products and other important compounds for the life-science industry.[6] They can be prepared by kinetic resolution,[7] or by more articulated multi-step synthesis,[8] but a well exploited approach is based on the functionalization of readily available chiral pools, such as carvone, pulegone or piperitone. Optical purity and low cost starting materials are advantages of the latter strategy; however, this has as the obvious limitation, the lack of flexibility deriving from the necessity of planning the synthesis of any desired product using only a limited number of different starting materials.

Our goal is to develop a practical, efficient and flexible method to access a broad range of optically active cyclohex-2-enone derivatives. The optimization of our synthesis started with the extension of the asymmetric Michael reactions of α,β-unsaturated aldehydes to different β-ketoesters as nucleophiles[9,10] but focusing the screening process only on environmentally friendly reaction conditions (Table 1).

The *tert*-butyl-3-oxo-butyric ester **1a** reacted smoothly with cinnamaldehyde **2a** in distilled H_2O using 2-[bis(3,5-bistrifluoromethyl-phenyl)trimethylsilanyl-oxymethyl]pyrrolidine **4** as the catalyst[3d,9a-b,9d,11] (Table 1, entry 1). In solvents, such as AcOH(aq), sea water and beer (ca. 5% EtOH) (entries 2, 4, 5) high yields and enantioselectivities were also obtained, while somewhat surprisingly, the reaction gave low yield when performed using a basic water solution (entry 3). This iminium-ion catalyzed Michael reaction is very effective and good yields (71-97%) and enantioselectivities, 84-94% ee of the Michael adducts **5a-d** can generally be obtained using H_2O as solvent at room temperature (entries 1, 7-9). It is important to

highlight that the use of H_2O as solvent in processes catalyzed by secondary amines often imposes the use of a large excess of the organic reagents to force the reaction to completion[3a] but in this transformation, using **4** as the catalyst, only a slight excess of cinnamaldehyde **2a** is required to achieve very high yields. A closer look at the reaction reveals that the chosen reagents and the catalyst "cluster together" in H_2O and the reaction probably occurs in the organic phase constituted by the α,β-unsaturated aldehyde, the β-ketoester and the newly formed product.[3b-c] In fact, under solvent-free conditions product **5a** was also obtained with 90% yield and 94% ee (Table 1, entry 6). The same results can also obtained with 5 mol% of catalyst.

Table 1: Organocatalytic Michael addition of *tert*-butyl-3-oxo-butyric ester **1a** with α,β-unsaturated aldehydes **2**.[a]

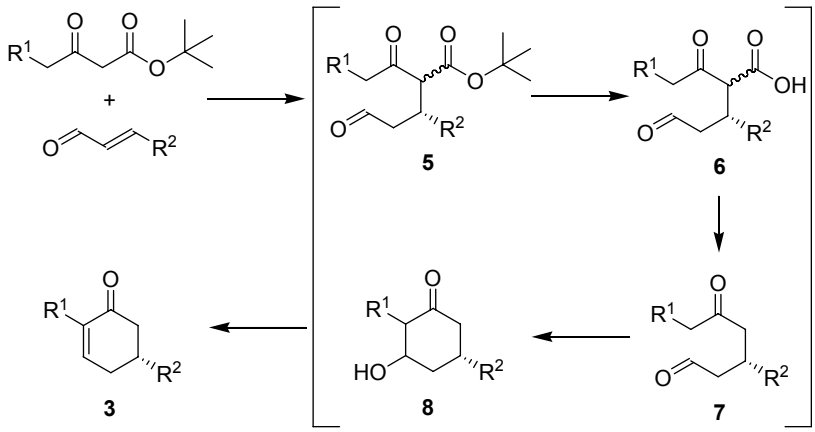


1a **2** **5a-d**

entry	solvent	R	yield (%)[b],[c]	ee (%)[d]
1	H_2O	Ph – **5a**	97	94
2[e]	AcOH (0.5 M)	Ph – **5a**	89	95
3[e]	$NaHCO_3$ (0.5 M)	Ph – **5a**	<10	68
4	sea water (aq. NaCl)	Ph – **5a**	88	93
5	beer (5% EtOH)[f]	Ph – **5a**	98	96
6	-[g]	Ph – **5a**	90	94
7	H_2O	Me – **5b**	82	84
8	H_2O	Et – **5c**	95	90
9	H_2O	*n*-Bu – **5d**	71	93

[a] All reactions were performed on a 0.25 mmol scale using 0.5 mL of solvent. [b] Product isolated by flash chromatography. [c] 1:1-6:1 dr were obtained. [d] Determined by chiral HPLC or GC after derivatization (see Experimental Part). [e] Reaction time: 16 h. [f] Carlsberg Hof. [g] Neat reaction conditions.

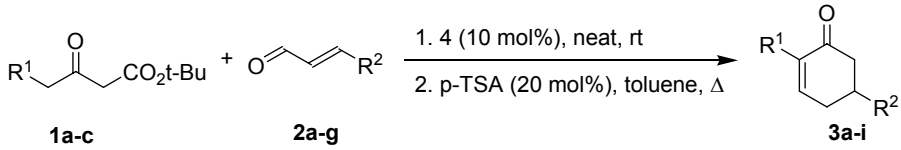
The *tert*-butyl ester group was essential for the integration of the Michael reaction into our synthetic strategy. Under the chosen conditions, the addition of *p*-TSA[12] as the second organocatalyst leads directly to the formation of the chiral cyclohex-2-enones **3**. The Brønsted acid is capable of catalyzing the hydrolysis of the *tert*-butyl ester, the decarboxylation of the newly formed β-ketoacid **6**, and finally *p*-TSA catalyzes also the aldol reaction of **7**, and the elimination reaction of **8**. The combination of organocatalysts 2-[bis(3,5-bistrifluoromethyl-phenyl)trimethylsilanyloxymethyl]pyr-rolidine **4** and *p*-TSA constitutes a catalytic system which leads to the one-pot five reaction step synthesis of the optically active cyclohex-2-enones **3** (Scheme 2).



Scheme 2: Mechanism of the one-pot organocatalytic asymmetric synthesis of optically active cyclohex-2-enone derivatives.[13]

The carefully designed five step and one-pot reaction for the formation of the optically active cyclohex-2-enones derivatives proceed in excellent yield and with remarkable enantioselectivities (Table 2).

Table 2: One-pot organocatalytic asymmetric synthesis of **3a-i.**[a]



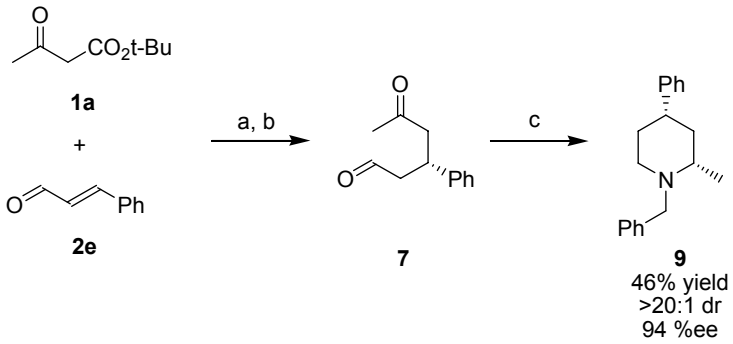
entry	R^1	R^2	product	yield (%)[b]	ee (%)[c]
1	H	Me	**3a**	93	80
2	H	Et	**3b**	98	94
3	H	*i*-Pr	**3c**	56	96
4	H	*n*-Bu	**3d**	69	92
5	H	Ph	**3e**	63 (81)[d]	94
6	H	*p*-F-Ph	**3f**	65	95
7	H	*m*-Me-Ph	**3g**	72	94
8	Me	Et	**3h**	82	91
9	Et	Et	**3i**	(74)[d]	89

[a]The β-ketoester **1** (0.25 mmol) was added to a mixture of catalyst **4** (0.025 mmol, 10 mol%) and α,β-unsaturated aldehyde **2** (0.37 mmol) and after 5-16 h toluene (1 mL) and *p*-TSA (0.05 mmol, 20 mol%) were added. The product was isolated after 16 h at 80 °C. [b] Product isolated by flash chromatography. [c] Determined by chiral HPLC or GC. [d] The yield in brackets refers to the two-pot process involving the isolation of the Michael adduct.

Our model substrate *tert*-butyl-3-oxo-butyric ester **1a** works perfectly well with different β-alkyl substituted α,β-unsaturated aldehydes, and with the exception of 2-butenal, the enantioselectivity of the products are in the range of 92-96% ee (Table 2, entries 1-4). It should be noted that the reaction works well for α,β-unsaturated aldehydes having aromatic substituents and both electronic withdrawing and

donating groups are tolerated leading to products with excellent stereoselectivity (entries 5-7). The one-pot organocatalytic asymmetric reaction can also be used for the formation of more complex products by modifying the structure of the β-ketoester. The very interesting 2,5-disubstituted cyclohex-2-enones **3h,i** were synthesized in 74-82% yield and 89-91% ee with the same simple procedure (entries 8, 9).

The optically active products obtained from this solvent-free Michael reaction are also excellent starting materials for the preparation of other biologically active compounds such as optically active piperidines (Scheme 4).[14]



Scheme 4: Synthesis of (2*S*,4*S*)-1-benzyl-2-methyl-4-phenylpiperi-dine. Reagents: a) **4** (10 mol%), neat, rt; b) 50% TFA in CH_2Cl_2, rt, 1 h; c) benzyl amine (1.5 equiv.), $NaBH_3CN$, MeOH, rt, 20 h.

The five step synthesis of the benzyl protected piperidine **9** was achieved with a limited number of manual operations. In this case, the Michael addition between *tert*-butyl-3-oxo-butyric ester and cinnamaldehyde was followed by the addition of TFA and CH_2Cl_2. The crude mixture of **7**, obtained after aqueous workup, was directly subjected to double reductive amination and the *cis*-2-methyl-4-phenyl-piperidine[15] derivative **9** was isolated as one diastereomer with 94% ee and in 46% overall yield.

In summary, we reported the first organocatalytic asymmetric conjugated addition of β-ketoesters to α,β-unsaturated aldehydes that proceeds in aqueous solutions or under solvent-free conditions. The potentiality of this reaction has been demonstrated by its easy and efficient incorporation in the synthesis of important optically active molecules and by the great substrate generality. In particular, the preparation of optically active 2,5-disubstituted-cyclohex-2-enone derivatives was achieved in very high yield and enantiomeric excess, in a simple one-pot procedure. The value of this "green" process is further enhanced by having isobutene, H_2O and CO_2 as the sole by-products.

7.1.R References

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[4] a) P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, **1998**; b) J. H. Clark, *Green Chemistry* **1999**, *1*, 1.

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[10] For organocatalyzed addition of β-ketoesters to enones see: a) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2003**, *42*, 661; b) C. E. T. Mitchell, S. E. Brenner, J. Garcia-Fortanet, S. V. Ley, *Org. Biomol. Chem.* **2006**, *4*, 2039 and references therein.

[11] For application of **4** in enamine catalyzed reaction, see: a) J. Fránzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296; b) M. Marigo, D. Fielenbach, A. Braunton, A. Kjærsgaard, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 3703; c) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794; see also: d) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; h) Y. Chi, S. H. Gellman, *J. Am. Chem. Soc.* **2006**, *128*, 6804.

[12] *p*-TSA: *p*-toluensulfonic acid.

[13] Our studies revealed that the overall transformation can also proceed through the alternative aldol-elimination-hydrolysis-decarboxylation sequence.

[14] a) A. D. Elbein, R. Molyneux in *Alkaloids; Chemical and Biological Perspectives;* S. W. Pelletier, Ed. John Wiley & Sons: New York, **1987,** *57*, 1. For the synthesis of *cis*-2,4-disubstituted piperidines, see *e.g.*: b) M. S. Taylor, D. W. Zalatan, A. M. Lerchner, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 1313; c) M. P. Dwyer, J. E. Lamar, A. I. Meyers, *Tetrahedron Lett.*, **1999**, *40*, 8965.

[15] For the determination of relative configuration see Experimental Part.

7.1.EP Experimental Part

Contents

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$). Coupling constants (J) are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Chromatography was carried out by flash chromatography (FC) using Merck silica gel 60 (230-400 mesh) according to the method of Still *et al.*[1] Optical rotations were measured on a Perkin-Elmer 241 polarimeter and they are reported as follows: $[\alpha]^{rt}_{D}$ (*c* in g per 100 mL, solvent).

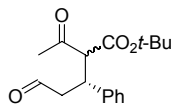
Materials. Commercial grade reagents and aldehydes were used without further purification; catalyst **4** was prepared according to literature procedure.[2]

Determination of Absolute Configuration. The absolute configurations of the optically active compounds **3a**,**d**,**e** and **9** were determined on the basis of the measured optical rotations that were compared with literature values. All other absolute configurations were assigned by analogy.

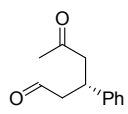
Experimental Procedures and Characterizations

General Procedure for the Organocatalytic Asymmetric Michael Reaction. In an ordinary vial equipped with a magnetic stirring bar, β-ketoester **1** (0.25 mmol) was added to a mixture of catalyst **4** (0.025 mmol, 10 mol%) and α,β-unsatured aldehyde **2** (0.37 mmol) in the aqueous solution (0.5 mL). The stirring was maintained at room temperature until complete consumption of the β-ketoester. The crude reaction mixture was directly charged on silica gel and subjected to FC.

General Procedure for the Organocatalytic Asymmetric Synthesis of Cyclohexenones 3a-i. In an ordinary vial equipped with a magnetic stirring bar, β-ketoester **1** (0.25 mmol) was added to a mixture of catalyst **4** (0.025 mmol, 10 mol%), α,β-unsatured aldehyde **2** (0.37 mmol). The stirring was maintained at room temperature until complete consumption of the β-ketoester. After addition of toluene (1 mL) and *p*-TSA (0.05 mmol, 20 mol%), the reaction was stirred at 80 °C for 16 h. The crude reaction mixture was directly charged on silica gel and subjected to FC.

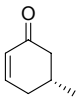


(*R*)-*tert*-Butyl-2-acetyl-5-oxo-3-phenylpentanoate 5a. The title compound was isolated after FC (CH_2Cl_2/Et_2O: 99/1). The ee was determined on the relative compound **7**. HRMS: $C_{18}H_{26}NaO_5$ – $[M+Na^+$+MeOH] calcd.: 345.1678, found: 345.1665. δ_H (400 MHz; $CDCl_3$) (dr 6/1, major diasteromer) 1.13 (s, 9H), 2.26 (s, 3H), 2.72 (m, 2H), 3.81 (d, J = 10.8, 1H), 3.95 (ddd, J = 10.8, 9.08, 4.66, 1H), 7.41-7.13 (m, 5H), 9.58 (t, J = 1.65, 1H); δ_C (100 MHz; $CDCl_3$) 27.3, 29.5, 38.9, 48.2, 66.4, 82.2, 127.3, 128.4, 128.6, 140.2, 166.6, 200.5, 202.1.

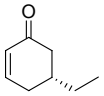


(*R*)-5-Oxo-3-phenylhexanal 7. The title compound was isolated after treatment of **5a** (0.25 mmol) with 50% TFA in CH_2Cl_2 (0.5 mL). After 1 h reaction time the crude mixture was quenched with H_2O and extracted with CH_2Cl_2. Filtration on a silica pad afforded the pure product. The ee was determined by GC analysis on a Astec G-TA chiral

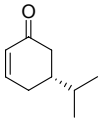
stationary phase (T_1 = 70 °C; T_2 = 165 °C, rate = 10 °C/min; T_3 = 165 °C; τ_R = 16.5 min, τ_S = 16.6 min). $[\alpha]^{rt}_D$ = -12.9 (c = 1.0, CH_2Cl_2, 94% ee). Spectroscopic data are in accordance with literature values.[3]



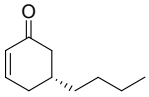
(*R*)-5-Methyl-cyclohex-2-enone 3a. The title compound was obtained following the general procedure and isolated after FC (CH_2Cl_2/Et_2O: 99/1) in 93% yield and 80% ee. $[\alpha]^{rt}_D$ = -74.6 (c = 0.5, $CHCl_3$, 80% ee), lit.[4] $[\alpha]^{rt}_D$ = -91.0 (c = 0.8, $CHCl_3$). The ee was determined by GC analysis on an Astec G-TA chiral stationary phase (T_1 = 60 °C; T_2 = 70 °C, rate = 2 °C/min; T_3 = 90 °C, rate = 1 °C/min; τ_R = 20.7 min, τ_S = 21.6 min). Spectroscopic data are in accordance with literature values.[5]



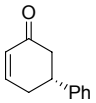
(*R*)-5-Ethyl-cyclohex-2-enone 3b. The title compound was obtained following the general procedure and isolated after FC (CH_2Cl_2/Et_2O: 99/1) in 98% yield and 94% ee. $[\alpha]^{rt}_D$ = -43.1 (c = 0.1, $CHCl_3$, 94% ee). The ee was determined by GC analysis on a Chromopak CP-Chirasil Dex CB-column (T_1 = 70 °C; T_2 = 200 °C, rate = 10 °C/min; τ_R = 6.8 min, τ_S = 6.9 min). Spectroscopic data are in accordance with literature values.[6]



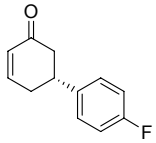
(*R*)-5-*iso*-Propyl-cyclohex-2-enone 3c. The title compound was obtained following the general procedure and isolated after FC (CH_2Cl_2/Et_2O: 99/1) in 56% yield and 96% ee. $[\alpha]^{rt}_D$ = -33.0 (c = 0.1, $CHCl_3$, 96% ee). The ee was determined by GC analysis on a Chromopak CP-Chirasil Dex CB-column (T_1 = 70 °C; T_2 = 200 °C, rate = 10 °C/min; τ_R = 7.8 min, τ_S = 7.9 min). δ_H (400 MHz; $CDCl_3$) 0.92 (d, *J* = 2.0, 3H), 0.94 (d, *J* = 2.0, 3H), 1.60 (m, 1H), 1.94-1.84 (m, 1H), 2.08-2.20 (m, 2H), 2.44-2.36 (m, 1H), 2.49-2,53 (m, 1H), 6.02 (m, 1H), 7.00 (ddd, *J* = 10.0, 6.0, 2.4, 1H); δ_C (100 MHz; $CDCl_3$) 19.4, 19.5, 29.6, 32.0, 41.5, 41.9, 129.5, 150.5, 200.7.



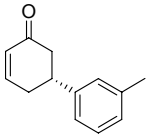
(*R*)-5-Butyl-cyclohex-2-enone 3d. The title compound was obtained following the general procedure and isolated after FC (CH_2Cl_2/Et_2O: 99/1) in 69% yield and 92% ee. $[\alpha]^{rt}_D$ = -44.9 (c = 0.5, $CHCl_3$, 92% ee), lit.[7] $[\alpha]^{rt}_D$ = -51.2 (c = 1.4, $CHCl_3$). The ee was determined by GC analysis on a Chromopak CP-Chirasil Dex CB-column (T_1 = 70 °C; T_2 = 120 °C, rate = 5 °C/min; T_3 = 136 °C, rate = 2 °C/min; τ_R = 15.8 min, τ_S = 15.9 min). Spectroscopic data are in accordance with literature values.[8]



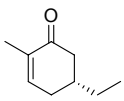
(*R*)-5-Phenylcyclohex-2-enone 3e. The title compound was obtained following the general procedure and isolated after FC (hexane/Et_2O: 80/20) in 63% yield and 94% ee. The ee was determined on the parent compound **7**. $[\alpha]^{rt}_D$ = -39.5 (c = 1.0, $CHCl_3$, 94% ee), lit.[9] $[\alpha]^{rt}_D$ = -43.0 (c = 1.25, $CHCl_3$).[10] Spectroscopic data are in accordance with literature values.



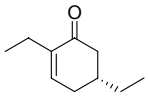
(*R*)-5-(4-Fluorophenyl)cyclohex-2-enone 3f. The title compound was obtained following the general procedure and isolated after FC (hexane/AcOEt: 85/15) in 65% yield and 95% ee. The ee was determined by HPLC analysis on 2 Daicel Chiralpak AD columns in a row (hexane/*i*-PrOH: 95/5, flow 0.8 mL/min; τ_S = 24.1 min, τ_R = 25.0 min). $[\alpha]^{rt}_D$ = -29.1 (c = 1.0, $CHCl_3$, 95% ee). HRMS: $C_{12}H_{11}FNaO$ - $[M+Na^+]$ calcd.: 213.0692, found: 213.0680. δ_H (400 MHz; $CDCl_3$) 2.40-2.75 (m, 4H), 3.27-3.39 (m, 1H), 6.12 (dd, *J* = 10.1, 2.75, 1H), 7.15-7.23 (m, 2H), 6.97-7.07 (m, 3H); δ_C (100 MHz; $CDCl_3$) 33.7, 40.2, 44.9, 115.5 (d, *J* = 21.3), 128.1 (d, *J* = 8.3), 129.8, 138.8 149.3, 161.6 (d, *J* = 246.9), 198.9.



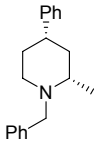
(*R*)-5-*m*-Tolylcyclohex-2-enone 3g. The title compound was obtained following the general procedure and isolated after FC (hexane/AcOEt: 90/10) in 72% yield and 94% ee. The ee was determined by HPLC analysis on 2 Daicel Chiralpak AD columns in a row (hexane/*i*-PrOH: 98/2, flow 0.5 mL/min; τ_R = 29.7 min, τ_S = 30.7 min). $[\alpha]^{rt}_D$ = -34.2 (c = 0.5, CH_2Cl_2, 94% ee). HRMS: $C_{13}H_{14}NaO$ - $[M+Na^+]$ calcd.: 209.0942, found: 209.0947. δ_H (400 MHz; $CDCl_3$) 2.36 (s, 3H), 2.46-2.82 (m, 4H), 3.26-3.37 (m, 1H), 6.05-6.24 (m, 1H), 7.00-7.13 (m, 4H), 7.24 (t, *J* = 7.07, 1H); δ_C (100 MHz; $CDCl_3$) 21.4, 33.7, 40.9, 44.9, 123.6, 127.4, 127.7, 128.6, 129.7, 138.3, 143.1, 149.6, 199.3.



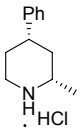
(*R*)-5-Ethyl-2-methyl-cyclohex-2-enone 3h. The title compound was obtained following the general procedure and isolated after FC (hexane/Et_2O: 80/20) in 82% yield and 91% ee. $[\alpha]^{rt}_D$ = -66.0 (c = 0.1, $CHCl_3$). The ee was determined by HPLC analysis on a Daicel Chiralpak AD column at 0 °C (hexane/*i*-PrOH: 99/1, flow 0.5 mL/min; τ_R = 14.5 min, τ_S = 16.3 min). δ_H (400 MHz; $CDCl_3$) 0.91 (t, *J* = 7.2, 3H), 1.37 (m, 2H), 1.70 (s, 3H), 1.77-2.14 (m, 3H), 2.24-2.32 (m, 1H), 2.56 (m, 1H), 6.71 (dd, *J* = 2.6, 1.4 Hz, 1H); δ_C (100 MHz; $CDCl_3$) 11.0, 15.8, 28.5, 32.2, 37.3, 44.3, 135.5, 145.0, 200.42.



(*R*)-2,5-Diethylcyclohex-2-enone 3i. The title compound was obtained following the general procedure isolating the intermediate Michael adduct; the title compound was purified by FC (Et_2O/pentane: 1/10) in 74% overall yield and 89% ee. The ee was determined by GC analysis on an Astec G-TA chiral stationary phase (T_1 = 70 °C; T_2 = 100 °C, rate = 10 °C/min; T_3 = 100 °C, time = 8 min; T_4 = 180 °C, rate = 10 °C/min; τ_R = 14.2 min, τ_S = 14.4 min). $[\alpha]^{rt}_D$ = -10.1 (c = 1.0, $CHCl_3$, 89% ee). HRMS: $C_{10}H_{16}NaO$ - $[M+Na^+]$ calcd.: 175.1099, found: 175.1093. δ_H (400 MHz; $CDCl_3$) 0.91 (t, *J* = 7.46, 3H), 1.00 (t, *J* = 7.46, 3H), 1.33-1.47 (m, 2H), 1.88-2.15 (m, 3H), 2.14-2.27 (m, 2H), 2.37-2.48 (m, 1H), 2.49-2.59 (m, 1H), 6.62-6.72 (m, 1H); δ_C (100 MHz; $CDCl_3$) 11.1, 12.8, 22.2, 28.6, 32.2, 37.2, 44.6, 140.9, 143.3, 199.9.



Synthesis of (*2S,4S*)-1-benzyl-2-methyl-4-phenylpiperidine 9. In an ordinary vial equipped with a magnetic stirring bar, β-ketoester **1a** (0.25 mmol) was added to a mixture of catalyst **4** (0.025 mmol, 10 mol%) and α,β-unsatured aldehyde **2** (0.37 mmol). After 5 h CH_2Cl_2 (0.5 mL) and TFA (0.5 mL) were added and the stirring was maintained for 1 h. The reaction was quenched with $NaHCO_3$, extracted with AcOEt, dried over $MgSO_4$ and evaporated. The crude reaction mixture was transferred to an ordinary vial equipped with a magnetic stirring bar and MeOH, $NaBH_3CN$ (0.75 mmol, 3 equiv.) and benzylamine (1M in MeOH, pH ≈6-7; 0.37 mmol, 1.5 equiv.) were added. After 5 min $NaBH_3CN$ (0.125 mmol, 0.5 equiv.) was added and the stirring was maintained for 20 h until GC/MS showed the reaction to be complete. The reaction was quenched with NH_4Cl, extracted with AcOEt, dried over $MgSO_4$ and evaporated. The title compound was purified by FC (hexane/AcOEt: 90/10) in 46% overall yield, dr >20:1 and 94% ee. The ee was determined on the parent compound **7**. $[\alpha]^{rt}_D$ = -57.2 (c = 1.0, CH_2Cl_2, 94% ee). HRMS: $C_{19}H_{24}N$ - $[M+H^+]$ calcd.: 266.1909, found: 266.1919. δ_H (400 MHz; $CDCl_3$) 1.29 (d, *J* = 6.1, 3H), 1.52-1.91 (m, 4H), 2.08 (dt, *J* = 11.6, 3.4, 1H), 2.31-2.46 (m, 1H), 2.51-2.68 (m, 1H), 2.95 (td, *J* = 11.6, 3.4, 1H), 3.21 (d, *J* = 13.3, 1H), 4.18 (d, *J* = 13.3, 1H), 7.45-7.14 (m, 10H); δ_C (100 MHz; $CDCl_3$) 21.4, 33.3, 42.9, 43.0, 53.2, 57.1, 58.1, 126.0, 126.7, 126.8, 128.1, 128.3, 129.2, 139.1, 146.4.



Determination of relative configuration of the compound 9. (*2S,4S*)-1-benzyl-2-methyl-4-phenylpiperidine **9** (0.12 mmol) was subjected to hydrogenation on 10% Pd/C, in *i*-PrOH (2 mL) and catalytic amount of AcOH under an atmosphere of 70 psi H_2, for 30 h. The reaction was filtered, washed with K_2CO_3 (aq.), dried over $MgSO_4$ and evaporated. Toluene (0.8 mL) and HCl (37% aq, 0.18 mmol, 1.5 equiv.) were added. The stirring was maintained at rt for 0.5 h and then the solution was kept at 5 °C for 6 h without stirring. The precipitate was filtered off and washed with cold toluene. Comparison of the spectroscopic data with literature values[11] gave the *cis*-relative configuration.

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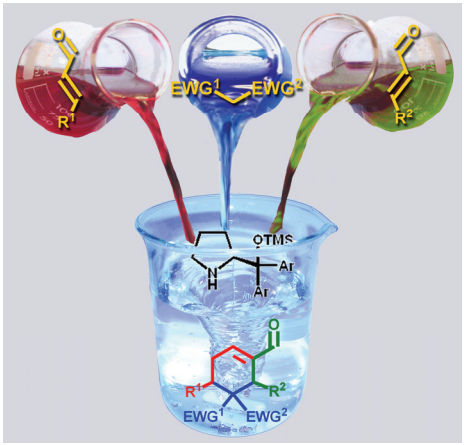
7.2 A New Approach for an Organocatalytic Multicomponent-Domino Asymmetric Reaction



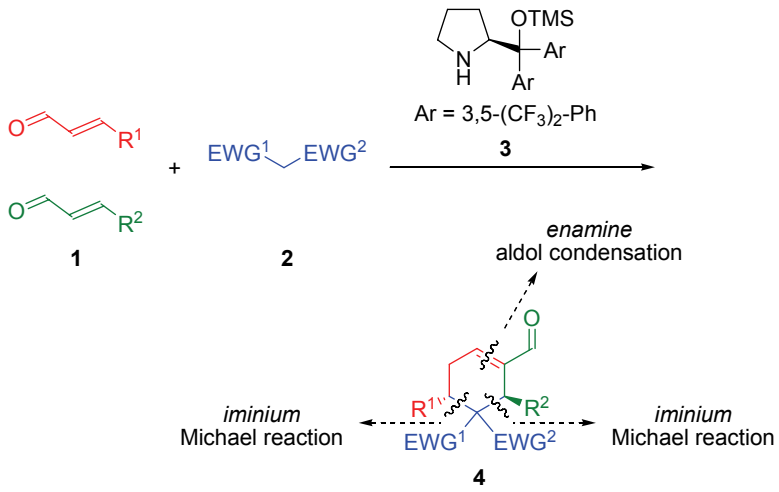
As easy as pouring! Three new C-C bonds, up to three new stereocentres and *ee*'s >97% are created via a new organocatalyzed multicomponent domino reaction. Very high enantioselectivity, control of the substituents, easy handling and user-friendly reaction conditions are key features of this transformation.

The scene of asymmetric catalysis has recently been complemented with organocatalysis – a rapidly expanding and new important field in organic chemistry.[1] A central role in organocatalysis is played by chiral secondary amines which can activate carbonyl compounds, either by enamine- or iminium-intermediates.[1,2,3] These types of activation have been exploited to functionalize aldehydes and ketones, and α,β-unsaturated compounds, with electrophiles and nucleophiles, respectively.[1-3]

One of the challenges in organocatalysis is to implement various activation concepts in a domino-, multicomponent reaction in order to achieve multi-bond formation in one operation. This strategy is atom economical, avoids the need of

protecting groups and isolation of intermediates and as the goal resembles nature in its highly selective sequential transformations.[4] Recently, combinations of enamine-iminium-ion activations in asymmetric organocatalytic domino- and multicomponent reactions have been developed in order to achieve the enantioselective consecutive formation of two bonds in a stereoselective fashion.[5] This paved the way for the sequential creation of three bonds that has been recently reported by Enders *et al.*; they described a highly enantioselective combination of enamine-iminium-enamine catalysis for a triple cascade reaction by reacting aldehydes, α,β-unsaturated aldehydes and nitroalkenes to afford cyclohexene derivatives.[6]

We present a new approach for an enantioselective concurrent multicomponent-domino organocatalytic reaction: a sequential iminium-iminium-enamine catalysis enables the consecutive formation of three new carbon-carbon bonds, providing for a large number of reagents enantiopure products by reacting α,β-unsaturated aldehydes **1** with activated methylene compounds **2** using (*S*)-2-[bis(3,5-bistrifluoromethyl-phenyl)trimethylsilanyl-oxymethyl]pyr-rolidine **3** as the catalyst[2b-f,3c,d,h] (Scheme 1). The high stereoselectivities obtained in this multicomponent-domino organocatalytic reaction rely on the sequential activation of α,β-unsaturated aldehydes **1** by catalyst **3** leading to iminium-enamine intermediates in which the efficient shielding of the chiral fragment in **3** provides the high diastereo- and enantioselectivity.



Scheme 1: Multicomponent-domino organocatalytic asymmetric reaction.

The stereoselective multicomponent-domino organocatalytic formation of the cyclohex-1-ene-carbaldehyde derivatives **4** can be explained by an iminium-iminium-enamine sequential activation of the α,β-unsaturated aldehydes by the catalyst **3** as outlined in Figure 1. In the first step (Cycle I), the aldehyde **1** reacts with catalyst **3** giving the iminium-ion intermediate. The malononitrile, or another active methylene compound (vide infra) **2**, reacts as a nucleophile with this intermediate leading to **A**, followed by hydrolysis of the resulting enamine yielding to the formation of

compound **B** and regeneration of the catalyst. Then, catalyst **3** re-enters the second cycle (Cycle II) forming an iminium-intermediate **C** that subsequently reacts with **B** to generate an additional stereocenter (if $EWG^1 = EWG^2$) in intermediate **D**. At this stage the final product, the cyclohex-1-ene-carbaldehyde derivative **4**, having up to three stereocenters (if $EWG^1 \neq EWG^2$), is formed from the enamine intermediate mediating the ring-closure reaction by an intramolecular aldol reaction, followed by elimination of water.

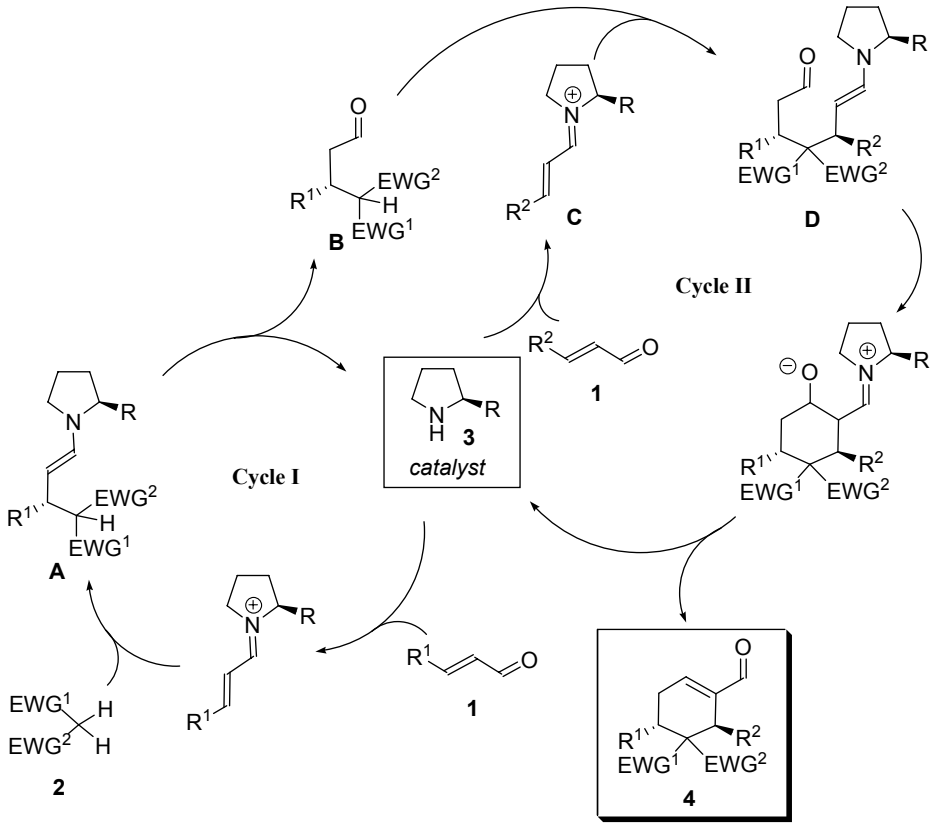
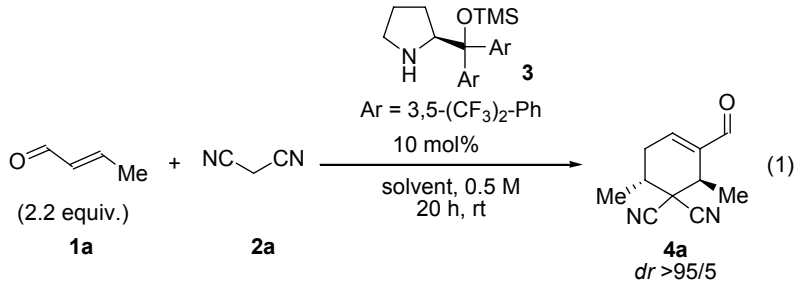


Figure 1: Proposed mechanism for the organocatalyzed asymmetric multicomponent-domino reaction.

We started our investigations by reacting crotonaldehyde **1a** with malononitrile **2a** in presence of the catalyst **3** (10 mol%) (eq. 1 and Table 1). To our delight, performing the reaction in CH_2Cl_2 as the solvent, we were able to isolate the desired product **4a** in 50% yield as a single diastereoisomer and in enantiopure form (Table 1, entry 1). In attempts to improve the yield, we screened several solvents and reaction conditions; whereas in some solvents such as alcohols, H_2O, Et_2O and acetone no product was formed, we were pleased to find that, with respect to CH_2Cl_2, toluene and $CHCl_3$ led to higher yields, maintaining the optimal stereocontrol of the reaction course (entries 7-11). As expected, the opposite enantiomer of the catalyst furnished the desired product with the same enantioselectivity and opposite

configuration (entry 12). It should also be noted that the reaction can be performed with only 5 mol% of catalyst **3** providing product **4a** in 90% isolated yield, without affecting the enantioselectivity (entry 13).

Table 1: Representative screening results for the reaction of crotonaldehyde **1a** with malononitrile **2a** using **3** as the catalyst.[a]



Entry	Solvent	Conversion [%]	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	>98	50	>99
2	EtOH	-	-	-
3	H_2O	-	-	-
4	Et_2O	-	-	-
5	Acetone	-	-	-
6	AcOEt	95	57	>99
7	Toluene	>98	72	>99
8	$CHCl_3$	>98	74	>99
9[d]	Toluene	>98	78	>99
10[d]	$CHCl_3$	>98	67	>99
11[d],[e]	Toluene	>98	89	>99
12[d],[e],[f]	Toluene	>98	90	>99[g]
13[d],[e],[h]	Toluene	>98	90	>99

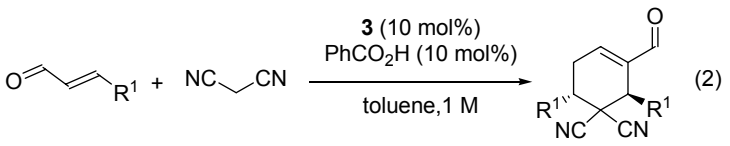
[a] Reactions performed on a 0.3 mmol scale with $PhCO_2H$ (10 mol%) as additive. In all cases only one diastereoisomer was identified (via GC and ^1H NMR analysis of the crude reaction). [b] Product isolated by flash chromatography. [c] Determined by chiral HPLC (see Experimental Part). [d] 0.3 mL of solvent was used. [e] 3 equiv. of the α,β-unsaturated aldehyde **1a** were used. [f] The *R* enantiomer of the catalyst **3** was used. [g] The opposite enantiomer was obtained. [h] 5 mol% of catalyst **3** was used.

We then set up to investigate the present reaction with respect to other α,β-unsaturated aldehydes **1b**-**h** ($R^1 = R^2$ in Scheme 1) as electrophiles with malononitrile **2a** catalyzed by **3** (10 mol%) and in the presence of benzoic acid as additive (10 mol%) (eq. 2, Table 2).

As shown in Table 2, the domino reaction proceeds well for both aliphatic and aromatic aldehydes leading to almost enantiopure products. For the alkyl α,β-unsaturated aldehydes **1b**-**d** having both unbranched-, branched and unsaturated substituents, the yields of **4b**-**d** are in the range 68-89% and only one diastereoisomer was obtained having 97- >99% *ee* (entries 1-3). In terms of diastereo- and enantioselectivity, aromatic and heteroaromatic substituents gave also only one diastereomer with enantioselectivities in the range 97->99% *ee*; however, the yield of

the products **4e**-**h** are slightly lower (entries 4-7) compared to the aliphatic α,β-unsaturated aldehydes.

Table 2: Reaction of various α,β-unsaturated aldehydes **1b-g** with malononitrile **2a**.[a]



1b-g **2a** **4b-h** *dr* >95/5

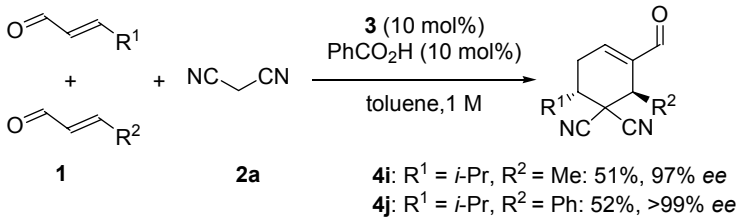
Entry	R^1	Yield [%][b]	*ee* [%][c]
1	Et – **1b**	**4b** – 89	98
2	*i*-Pr – **1c**	**4c** – 68	>99
3	CH_3CH=CH – **1d**	**4d** – 80	97
4	Ph – **1e**	**4e** – 77	>99
5	*p*-Cl-C_6H_4 – **1f**	**4f** – 54 (65[d])	>99 (>99[d])
6	2-Furyl – **1g**	**4g** – 57	98
7	2-Thiophene – **1h**	**4h** – 66	97

[a] Reactions performed on a 0.3 mmol scale. In all cases only one diastereoisomer was identified (via GC and ^{1}H NMR analysis of the crude reaction). [b] Product isolated by flash chromatography. [c] Determined by chiral HPLC (see Experimental Part). [d] 20 mol% of **3** and $PhCO_2H$ were used.

Based on the mechanism outlined in Figure 1 we decided to further investigate the reaction: ^{1}H NMR spectroscopic studies showed the formation of the monoadduct **A** and the subsequent formation of the product **4** without being able to see any of the other intermediates. This indicates that the enamine-mediate ring-closure probably takes place when the catalyst is still attached on the adduct **D** (i.e.: no hydrolysis of the intermediate **D** occurs).

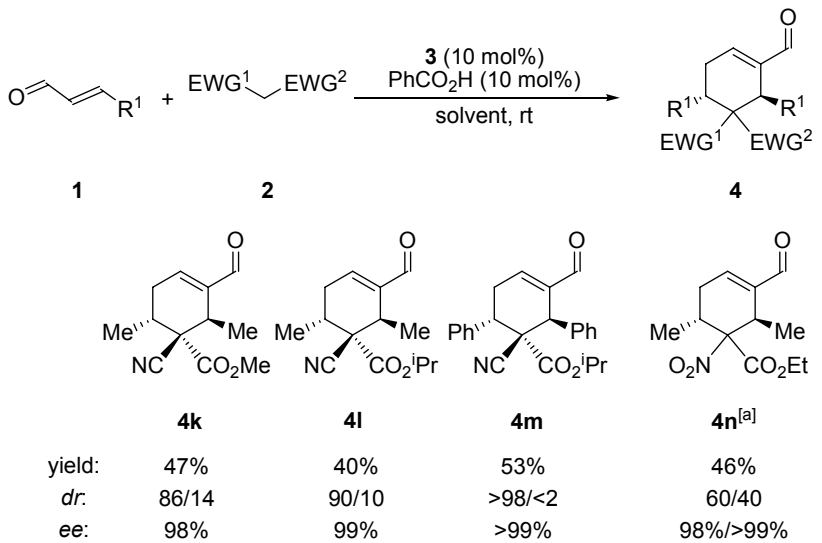
We therefore questioned whether it could be possible to generate **4** having two different R groups (i.e.: letting two different α,β-unsaturated aldehydes to react). In order to accomplish this task, we reasoned that the first α,β-unsaturated aldehyde **1** leading to **B**, needed to be enough unreactive in the Cycle II, for the Cycle I to be completed prior to the beginning of the formation of adduct **D**. This way, the second α,β-unsaturated aldehyde can be subsequently added and then enters Cycle II together with **B**. The products obtained will thus be different substituted (R^1 and R^2) cyclohex-1-ene-carbaldehyde derivatives **4**.

This reasoning was then applied as proof-of-principle and the results support our blueprint. It was shown that it is possible to control the reaction sequence with regard to the α,β-unsaturated aldehydes. Interestingly, the sequence can be applied to both aliphatic and aromatic aldehydes providing **4i** and **4j**, respectively, as exclusively one regioisomer and one diastereoisomer formed with excellent enantiomeric excess (Scheme 2).



Scheme 2: Organocatalytic multicomponent-domino reactions with two different α,β-unsaturated aldehydes.

We then questioned whether it would be possible to extend the presented multicomponent-domino transformation to other activated methylene compounds. In particular, nucleophiles having two different electron-withdrawing groups might be interesting, as a quaternary stereocenter would be generated.[7]



Scheme 3: Reaction of α,β-unsaturated aldehydes **1a** or **1e** with activated methylene compounds.

As outlined in Scheme 3, the approach proved fruitful using cyanoacetates as nucleophiles providing the products **4k**-**m** in excellent enantiomeric excess and good to very good diasteromeric ratio. The results show, that a better diasterocontrol is obtained with increasing the size of the ester group (compare **4k** and **4l**).[8] Thus, reacting isopropyl cyanoacetate with crotonaldehyde **1a**, product **4l** was obtained in

99% *ee* and 90/10 *dr,* while cinnamic aldehyde **1e** showed to work better in terms of yield and diasterocontrol, leading to the product **4m** with >99% *ee*, >98/<2 *dr* and 53% yield.

Interestingly, these compounds could give access to both of the two isomers at the full-substituted carbon atom of quaternary α-amino acid derivatives[9] by choosing the appropriate sequence of reactions.[10]

Another way of accessing potential precursors of α-amino acids is by reacting nitromalonates; the reaction between **1a** and ethyl nitroacetate proved to be successful and the expected product **4n** was obtained in excellent enantiomeric excess. Even though the diasterocontrol is moderate, the possibility of separating the two diasteroisomers by flash chromatography renders the approach appealing as it gives access - once again - to the two isomers of quaternary α-amino acids. The major isomer of **4n** is the one having the nitro group and the methyl substituent in the 6-position *syn*. It is interesting to note that in this case, although Cycle II being sluggish, it was possible to improve the reactivity of the system by changing the additive: swapping from the usual acidic additive to a basic one (DABCO: 1,4-diazabicyclo[2.2.2]octane)[11] the reaction was smooth without erosion of neither the enantioselectivity nor of the diastereoselectivity. It is noteworthy, the outcome that a chiral secondary amine and a tertiary amine could successfully cooperate without interfering with each other.

The absolute configuration of the addition product was assigned by a single-crystal X-ray analysis of 3-formyl-2,6-di-2-thienylcyclohex-3-ene-1,1-dicarbonitrile **4h** as shown in Figure 2.[12] The structure led to an assignment of the chiral centres formed as (2*S*,6*R*) indicating that the addition takes place from below – the *Re*-face[13]– in the two intermediates in the Cycle I and II in Figure 1.

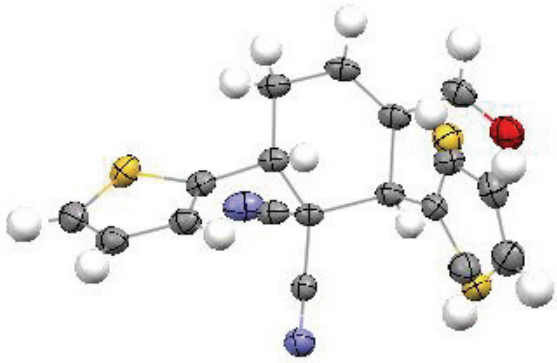


Figure 2: X-ray structure of 3-formyl-2,6-di-2-thienylcyclohex-3-ene-1,1-dicarbonitrile **4h**.

In conclusion, we have developed a new multicomponent-domino asymmetric approach which applies an iminium-iminium-enamine sequence by reacting α,β-

unsaturated aldehydes with activated methylene compounds. The reaction proceeds in good to high yields for the malononitrile and only one nearly enantiopure diastereomer is formed. The concept has also been employed for combination of different aldehydes and for other activated methylene compounds such as cyanoacetates and nitro esters.

7.2.R References

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[6] a) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861. For a pioneer work on asymmetric organocatalytic multicomponent three-bond forming reaction, see: b) D. B. Ramachary, C. F. Barbas III, *Chem. Eur. J.* **2004**, *10*, 5323; c) N. S. Chowdari, D. B. Ramachary, A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 9591.

[7] For reviews on the catalytic asymmetric construction of quaternary stereocenters, see e.g.: a) C. J. Douglas, L. E. Overman, *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5363; b) J. Christoffers, A. Baro, *Angew. Chem. Int. Ed.* **2003**, *42*, 1688; c) E. J. Corey, A. Guzman-Perez, *Angew. Chem. Int. Ed.* **1998**, *37*, 388.

[8] The reaction with the *t*Bu ester proved to be sluggish.

[9] a) M. Lasa, C. Cativiela, *Synlett* **2006**, *16*, 2517; b) T. Satoh, M. Hirano, A. Kuroiwa, *Tetrahedron Lett.* **2005**, *46*, 2659; c) C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry*, **2000**, *11*, 645; c) C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry*, **1998**, *9*, 3517.

[10] C. Cativiela, A. Avenoza, M. París, J. M. Peregrina, *J. Org. Chem.* **1994**, *59*, 774.

[11] Other conditions and additives (e.g.: *o*-NO_2PhCO_2H, *m*-NO_2PhCO_2H, Et_3N, Hünig's base) were tested but all gave inferior results.

[12] CCDC 627399 contains the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk].

[13] Please note that the assignment of the face change for the alkyl substituted α,β-unsaturated compounds.

7.2.EP Experimental Part

Contents

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$). Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Chromatography was carried out by flash chromatography (FC) using Merck silica gel 60 (230-400 mesh). Optical rotations were measured on a Perkin-Elmer 241 polarimeter and they are reported as follows: $[\alpha]_D^{20}$ (*c* in g per 100 mL, solvent).

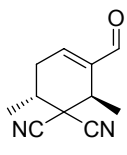
The absolute configuration of the cyclohex-1-ene-carbaldehydes **4a**-**h** was established by single-crystal X-ray analysis of **4h**. The same approach of the nucleophile to the corresponding α,β-unsaturated aldehyde was assumed for assigning the absolute configuration of the rest of the compounds. In addition, the stereochemical assignment of the quaternary stereocenter of compounds **4k**-**n** was determined by NOE experiments.

Materials. Commercial grade reagents and aldehydes were used without further purification. α,β-Unsaturated aldehyde **1f** was prepared following the procedure described in the literature.[1] Catalyst **3** was prepared according to literature procedure.[2]

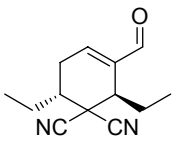
Experimental procedures and characterizations.

General Procedure. In an ordinary vial equipped with a magnetic stirring bar, 2 (0.3 mmol) was added to a mixture of catalyst 3 (0.03 mmol, 10 mol%), benzoic acid (0.03 mmol, 10 mol%) and α,β-unsatured aldehyde 1 (0.9 mmol) in toluene (0.3 mL). The stirring was maintaned at room temperature until completion of the reaction. The crude reaction mixture was directly charged on silica gel and subjected to flash chromatography.

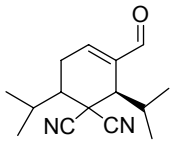
Modified General Procedure. In an ordinary vial equipped with a magnetic stirring bar, malononitrile **2a** (20 mg, 0.3 mmol) was added to a mixture of catalyst **3** (0.03 mmol, 10 mol%), benzoic acid (0.03 mmol, 10 mol%) and α,β-unsatured aldehyde **1c** (0.3 mmol) in toluene (0.3 mL). After 17h α,β-unsatured aldehyde **1a** or **1e** (0.3 mmol) was added. The stirring was maintaned at room temperature until completion of the reaction. The crude reaction mixture was directly charged on silica gel and subjected to flash chromatography.



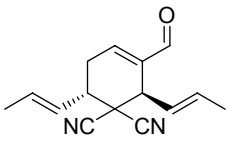
(2S,*6R*)-3-Formyl-2,6-dimethyl-cyclohex-3-ene-1,1-dicarbonitrile (4a) - Following the general procedure **4a** was isolated after 1 h by flash chromatography (CH_2Cl_2/Et_2O : 98/2) in 89% yield. $[\alpha]^{20}_D$ = -78 (*c* = 1.0, CH_2Cl_2, >99% *ee*). The *ee* was determined by HPLC analysis on Daicel Chiralcel OJ column: Hex/*i*-PrOH: 90/10, flow rate = 1.0 mL/min, τ= 18.8 min (minor) and τ= 26.8 min (major). GC/MS: 188 (m/z). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.44 (s, 1H), 6.82 (dd, *J* = 4.7, 2.5 Hz, 1H), 3.39 (q, *J* = 7.2 Hz, 1H), 2.71 (m, 1H), 2.46-2.26 (m, 2H), 1.41 (d, *J* = 6.4 Hz, 3H), 1.34 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.2, 147.2, 140.2, 114.1, 113.6, 41.9, 34.8, 31.3, 30.3, 17.6, 16.6.



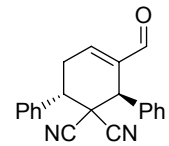
(2S,*6R*)-2,6-Diethyl-3-formyl-cyclohex-3-ene-1,1-dicarbonitrile (4b) - Following the general procedure **4b** was isolated after 4 h by flash chromatography (pentane/AcOEt : 85/15) in 89% yield as a yellow oil. $[\alpha]_D^{20}$ = -100 (*c* = 0.27, CH_2Cl_2), 98% *ee*. The *ee* was determined by HPLC analysis on Daicel Chiralcel AS, Hex/*i*-PrOH 90/10, flow rate = 1.0 mL/min, *τ*= 9.2 min (minor) and *τ*= 12.3 min (major), 230 nm. GC/MS: 216 (m/z). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 9.49 (s, 1H), 6.87-6.86 (m, 1H), 3.29 (dd, *J* = 7.6, 4.8 Hz, 1H), 2.87-2.78 (m, 1H), 2.29-2.17 (m, 1H), 2.13-2.07 (m, 1H), 1.98-1.90 (m, 1H), 1.60-1.41 (m, 2H), 1.09 (t, *J* = 7.6 Hz, 3H), 1.02 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 191.3, 147.7, 139.9, 114.6, 113.8, 41.4, 40.4, 36.9, 28.9, 26.2, 25.7, 12.7, 10.8.



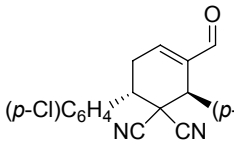
(2S,*6R*)-3-Formyl-2,6-di(isopropyl)-cyclohex-3-ene-1,1-dicarbonitrile (4c) - Following the general procedure **4c** was isolated after 40 h by flash chromatography (pentane/AcOEt: 70/30) in 68% yield. $[\alpha]^{20}_D$ = -72 (*c* = 1.0, CH_2Cl_2, >99% *ee*). The *ee* was determined by HPLC analysis on Daicel Chiralcel OJ column: Hex/*i*-PrOH: 95/5, flow rate = 1.0 mL/min, τ= 10.7 min (minor) and τ= 12.7 min (major). GC/MS: 244 (m/z). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 9.51 (s, 1H), 6.97 (t, *J* = 3.7 Hz, 1H), 3.24 (d, *J* = 3.0 Hz, 1H), 2.58-2.49 (m, 1H), 2.47-2.36 (m, 1H), 2.21-2.13 (m, 2H), 1.96-1.87 (m, 1H), 1.33 (d, *J* = 6.8 Hz, 3H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 192.1, 148.7, 139.2, 114.9, 114.4, 46.9, 40.1, 40.0, 30.9, 29.3, 24.8, 23.9, 21.6, 21.0, 15.8.



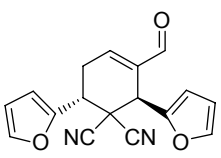
(2S,*6S*)-3-Formyl-2,6-bis-((*E*)-propenyl)-cyclohex-3-ene-1,1-dicarbonitrile (4d) - Following the general procedure **4d** was isolated after 20 h by flash chromatography (pentane/AcOEt: 70/30) in 80% yield. Due to the presence of the inseparable E/Z isomers in the starting material the title compound was obtained with a 10% of the mixed E/Z product. $[\alpha]^{20}_D$ = -131 (*c* = 1.0, CH_2Cl_2, 97% *ee*). The *ee* was determined by GC analysis on a Chromopak CP-Chirasil Dex CB-column: T_1 = 70 °C; T_2 = 180 °C, rate = 10 °C/min, τ= 15.5 min (major) and τ= 15.7 min (minor). GC/MS: 239 (m/z). ^{1}H NMR (400 MHz, $CDCl_3$): *δ*= 9.46 (s, 1H), 6.98-6.92 (m, 1H), 5.93-5.84 (m, 1H), 5.73-5.62 (m, 1H), 5.54-5.42 (m, 2H), 3.96 (d, *J* = 7.0 Hz, 1H), 2.84-2.63 (m, 2H), 2.59-2.47 (m, 1H), 1.80 (dd, *J* = 6.6, 1.7 Hz, 3H), 1.75 (ddd, *J* = 6.6, 1.7, 0.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ*= 190.4, 147.6, 137.4, 135.1, 133.2, 126.0, 123.8, 113.7, 113.6, 41.9, 41.3, 38.9, 29.7, 18.0, 17.9.



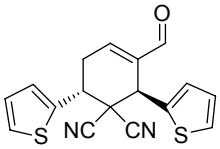
(2S,*6S*)-3-Formyl-2,6-diphenyl-cyclohex-3-ene-1,1-dicarbonitrile (4e) - Following the general procedure **4e** was isolated after 24 h by flash chromatography (pentane/AcOEt: 70/30) in 77% yield. $[\alpha]^{20}_D$ = -124 (*c* = 1.0, CH_2Cl_2, >99% *ee*). The *ee* was determined by HPLC analysis on Daicel Chiralcel OD column: Hex/*i*-PrOH: 80/20, flow rate = 1.0 mL/min, τ= 22.8 min (major) and τ= 44.9 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): *δ*= 9.54 (s, 1H), 7.55-7.21 (m, 11H), 4.67 (s, 1H), 3.42 (dd, *J* = 11.4, 5.7 Hz, 1H), 3.20 (dddd, *J* = 20.9, 11.4, 2.7, 1.7 Hz, 1H), 3.04 (dt, *J* = 20.9, 5.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ*= 190.2, 148.4, 137.6, 135.5, 133.6, 129.9, 129.5, 129.4, 129.2, 128.9, 128.3, 114.3, 112.9, 46.6, 43.4, 40.9, 30.3.



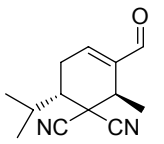
(2S,*6S*)-2,6-(*p*-Chlorophenyl)-3-formyl-cyclohex-3-ene-1,1-dicarbonitrile (4f) - Following the general procedure **4f** was isolated after 48 h (using 20 mol% of **3** and benzoic acid) by flash chromatography (pentane/AcOEt: 80/20) in 65% yield as a white solid. Mp = 123-125 °C. $[\alpha]_D^{20}$ = -207 (*c* = 0.12, CH_2Cl_2), >99% *ee*. The *ee* was determined by HPLC analysis on Daicel Chiralcel OD, Hex/*i*-PrOH: 80/20, flow rate = 1.0 mL/min, *τ*= 16.1 min (major) and *τ*= 32.7 min (minor), 220 nm. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 9.55 (s, 1H), 7.43-7.37 (m, 4H), 7.33-7.24 (m, 5H), 4.63 (s, 1H), 3.33 (dd, *J* = 11.2, 5.6 Hz, 1H), 3.21-3.12 (m, 1H), 3.04 (dt, *J* = 20.8, 5.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 190.0, 148.1, 137.3, 135.8, 135.6, 133.6, 132.0, 131.1, 129.7, 129.5, 129.3, 113.8, 112.6, 45.9, 43.2, 40.4, 30.2.



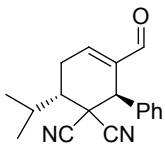
(2S,6*R*)-3-Formyl-2,6-(2-furyl)cyclohex-3-ene-1,1-dicarbonitrile (4g) - Following the general procedure **4g** was isolated after 24 h by flash chromatography (pentane/AcOEt: 80/20) in 57% yield as a beige solid. Mp = 148-150 °C. $[\alpha]_D^{20}$ = -205 (*c* = 0.21, CH_2Cl_2), 98% *ee*. The *ee* was determined by HPLC analysis on Daicel Chiralcel OD, Hex/*i*-PrOH: 80/20, flow rate = 1.0 mL/min, *τ*= 17.6 min (minor) and *τ*= 27.4 min (major), 220 nm. GC/MS: 292 (m/z).^{1}H NMR (400 MHz, $CDCl_3$): δ= 9.51 (s, 1H), 7.47-7.44 (m, 2H), 7.16-7.14 (m, 1H), 6.47 (t, *J* = 4.0 Hz, 2H), 6.42-6.41 (m, 2H), 4.77 (s, 1H), 3.86 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.14 (dddd, *J* = 20.8, 10.8, 2.8, 1.6 Hz, 1H), 3.05 (ddd, *J* = 20.8, 6.0, 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 189.8, 149.1, 147.7, 146.7, 144.1, 143.6, 135.4, 113.0, 112.7, 112.4, 111.2, 110.8, 109.6, 41.2, 40.3, 36.7, 28.7.



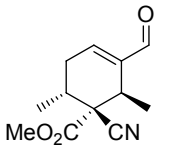
(2S,6*R*)-3-Formyl-2,6-di-(2-thienyl)cyclohex-3-ene-1,1-dicarbonitrile (4h). Following the general procedure **4h** was isolated after 24 h by FC (pentane/AcOEt: 70/30) in 66% yield as a white solid. Mp = 170-172 °C. $[\alpha]^D_{20}$ = -149 (*c* = 0.46, CH_2Cl_2), 97% *ee*. The *ee* was determined by HPLC analysis on Daicel Chiralcel AS, Hex/*i*-PrOH: 80/20, flow rate = 1.0 mL/min, *t* = 19.5 min (minor) and *t*= 23.7 min (major), 220 nm. ^{1}H NMR (400 MHz, $CDCl_3$) d 9.55 (s, 1H), 7.38-7.34 (m, 2H), 7.21 (d, *J* = 3.6 Hz, 1H), 7.16 (d, *J* = 3.6 Hz, 2H), 7.10 (dd, *J* = 5.2, 3.6 Hz, 1H), 7.05 (dd, *J* = 5.2, 3.6 Hz, 1H), 4.98 (s, 1H), 3.95 (dd, *J* = 11.4, 6.0 Hz, 1H), 3.24-3.06 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) d 189.8, 147.0, 138.1, 137.9, 136.0, 130.2, 128.1, 127.7, 127.4, 127.3, 126.3, 113.4, 113.0, 44.8, 41.6, 37.6, 32.1.



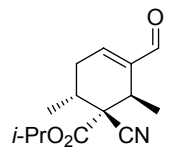
(2S,6*R*)-3-Formyl-6-isopropyl-2-methyl-cyclohex-3-ene-1,1-dicarbonitrile (4i) - Following the modified general procedure **4i** was isolated by flash chromatography (pentane/AcOEt: 70/30) in 51% yield. $[\alpha]^{20}_D$ = -36 (*c* = 1.0, CH_2Cl_2, 97% *ee*). The *ee* was determined by HPLC analysis on Daicel Chiracel OJ column: Hex/*i*-PrOH: 90/10, flow rate = 1.0 mL/min, τ= 13.6 min (minor) and τ= 21.0 min (major). GC/MS: 201 (m/z). ^{1}H NMR (400 MHz, $CDCl_3$): *δ*= 9.46 (s, 1H), 6.93-6.89 (m, 1H), 3.42 (q, *J* = 6.9 Hz, 1H), 2.59-2.53 (m, 1H), 2.53-2.51 (m, 1H), 2.43-2.37 (m, 1H), 2.23-2.15 (m, 1H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.12 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ*= 191.2, 148.1, 140.4, 114.8, 113.9, 39.8, 39.4, 37.2, 29.2, 23.7, 21.8, 16.5, 15.9.



(2S,6*R*)-3-Formyl-6-isopropyl-2-phenyl-cyclohex-3-ene-1,1-dicarbonitrile (4j) - Following the modified general procedure **4j** was isolated by flash chromatography (Pentane/AcOEt: 70/30) in 52% yield. $[\alpha]^{20}_D$ = -139 (*c* = 1.0, CH_2Cl_2, >99% *ee*). The *ee* was determined by HPLC analysis on Daicel Chiralcel OD column: Hex/*i*-PrOH: 80/20, flow rate = 1.0 mL/min, τ= 9.4 min (major) and τ= 13.2 min (minor). GC/MS: 278 (m/z). ^{1}H NMR (400 MHz, $CDCl_3$): *δ*= 9.48 (s, 1H), 7.39-7.36 (m, 5H), 7.26-7.22 (m, 1H), 4.57 (s, 1H), 2.74 (dt, *J* = 20.6, 5.1 Hz, 1H), 2.64 (dddd, *J* = 20.6, 11.2, 2.7, 1.7 Hz, 1H), 2.27-2.15 (m, 2H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.02 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ*= 190.3, 149.0, 137.8, 133.5, 130.0, 129.3, 128.7, 115.0, 113.3, 47.2, 40.8, 39.0, 28.9, 23.6, 21.6, 15.8.

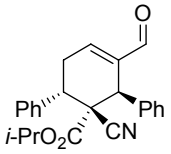


(1*R*,2*R*,6*R*)-Methyl 1-cyano-3-formyl-2,6-dimethylcyclohex-3-ene-1-carboxylate (4k) - Following the general procedure **4k** was obtained, using EtOH as solvent, after 24 h by flash chromatography (pentane/Et_2O: 75/25) in 47% yield as a mixture of diasteroisomers (*dr* = 86/14). $[\alpha]_D^{20}$ = -87 (*c* = 0.13, CH_2Cl_2), 98% *ee*. The *ee* was determined by HPLC analysis on Daicel Chiralcel AS, Hex/*i*-PrOH: 90/10, flow rate = 1.0 mL/min, *τ*= 11.8 min (major) and *τ*= 16.8 min (minor), 220 nm. GC/MS: 221 (m/z). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 9.44 (s, 1H), 6.82 (dd, *J* = 4.4, 2.8 Hz, 1H), 3.86 (s, 3H), 3.35 (qd, *J* = 6.8, 1.3 Hz, 1H), 2.66 (dt, *J* = 20.4, 5.2 Hz, 1H), 2.53-2.44 (m, 1H), 2.28 (dddd, *J* = 20.8, 10.8, 2.8, 1.6 Hz, 1H), 1.20 (d, *J* = 6.4 Hz, 3H), 0.98 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 192.0, 167.0, 148.6, 141.7, 117.3, 53.4, 51.7, 35.0, 32.3, 27.5, 17.5, 16.3.

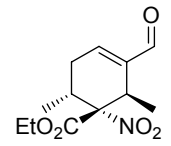


(1*R*,2*R*,6*R*)-Isopropyl 1-cyano-3-formyl-2,6-dimethylcyclohex-3-ene-1-carboxylate (4l) - Following the general procedure **4l** was obtained, using EtOH as solvent, after 24 h by flash chromatography (pentane/Et_2O: 75/25) in 40% yield as a mixture of diasteroisomers (*dr* = 90/10). $[\alpha]_D^{20}$ = -84 (*c* = 0.22, CH_2Cl_2), 99% *ee*. The *ee* was determined by GC analysis on a Chromopak CP-Chirasil Dex CB-column: T_1 = 70 °C; T_2 = 180 °C, rate = 10 °C/min, τ= 13.1 min (major) and τ= 13.2 min (minor). GC/MS: 249 (m/z). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 9.44 (s, 1H), 6.81 (dd, *J* = 4.4, 2.9 Hz, 1H), 5.13 (sept, *J* = 6.4 Hz, 1H), 3.34 (q, *J* = 6.8 Hz, 1H), 2.65 (dt, *J* = 20.8, 5.2 Hz, 1H),

2.51-2.40 (m, 1H), 2.27 (dddd, *J* = 20.4, 10.8, 2.8, 1.6 Hz, 1H), 1.35-1.32 (m, 6H), 1.20 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 191.1, 166.0, 148.8, 141.9, 117.5, 70.9, 51.8, 34.8, 32.4, 27.3, 21.6, 21.5, 17.5, 16.1.



(1*R*,2*R*,6*S*)-Isopropyl 1-cyano-3-formyl-2,6-diphenylcyclohex-3-ene-1-carboxilate (4m) - Following the general procedure **4m** was obtained after 48 h by flash chromatography (pentane/Et_2O: 75/25) in 53% yield as a white solid. Mp = 137-138 °C. $[\alpha]_D^{20}$ = -128 (*c* = 0.38, CH_2Cl_2), >99% *ee*. The *ee* was determined by HPLC analysis on Daicel Chiralcel OD, Hex/*i*-PrOH: 90/10, flow rate = 1.0 mL/min, *τ*= 15.4 min (major) and *τ*= 19.6 min (minor), 220 nm. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 9.51 (s, 1H), 7.43 (d, *J* = 6.8 Hz, 2H), 7.33-7.23 (m, 7H), 7.17-7.14 (m, 2H), 4.65 (s, 1H), 4.48 (sept, *J* = 6.4 Hz, 1H), 3.58 (t, *J* = 8.4 Hz, 1H), 3.01 (dd, *J* = 8.4, 3.6 Hz, 2H), 0.80 (d, *J* = 6.4 Hz, 3H), 0.62 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 191.1, 164.8, 149.1, 139.2, 135.7, 129.2, 128.6, 128.5, 128.4, 127.7, 118.7, 70.7, 53.2, 47.8, 38.8, 33.2, 20.8, 20.7.



(1*R*,2*R*,6*R*)-Ethyl 3-Formyl-2,6-dimethyl-1-nitro-cyclohex-3-ene-1-carboxylate (4n) - Following the general procedure **4n** was isolated after 18 h by flash chromatography (pentane/AcOEt: 80/20) in 46% overall yield (*dr* = 60/40).

Major isomer: $[\alpha]^{20}_D$ = -137 (*c* = 1.0, CH_2Cl_2, 98% *ee*). The *ee* was determined by GC analysis on a Chromopak CP-Chirasil Dex CB-column: T_1 = 70 °C, 4 min; T_2 = 180 °C, rate = 4 °C/min, τ= 31.2 min (major) and τ= 31.4 min (minor). GC/MS(-NO_2): 209 (m/z). ^{1}H NMR (400 MHz, $CDCl_3$): *δ*= 9.44 (s, 1H), 6.72-6.67 (m, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.61 (q, *J* = 6.9 Hz, 1H), 2.74-2.63 (m, 1H), 2.63-2.58 (m, 1H), 2.01-1.89 (m, 1H), 1.33-1.28 (m, 6H), 1.04 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ*= 192.1, 165.2, 146.8, 142.6, 97.2, 62.6, 33.6, 32.0, 29.8, 17.1, 16.5, 13.8.

Minor isomer: $[\alpha]^{20}_D$ = -167 (*c* = 1.0, CH_2Cl_2, >99% *ee*). The *ee* was determined by HPLC analysis on Daicel Chiralcel OD column: Hex/*i*-PrOH: 90/10, flow rate = 1.0 mL/min, τ= 8.1 min (major) and τ= 10.2 min (minor). GC/MS(-NO_2): 209 (m/z). ^{1}H NMR (400 MHz, $CDCl_3$): *δ*= 9.44 (s, 1H), 6.66-6.62 (m, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.67 (q, *J* = 6.9 Hz, 1H), 2.89-2.68 (m, 2H), 2.08-1.98 (m, 1H), 1.31-1.23 (m, 6H), 0.99 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ*= 191.6, 165.0, 146.3, 143.7, 97.6, 62.6, 34.8, 33.7, 29.2, 16.5, 15.9, 13.8.

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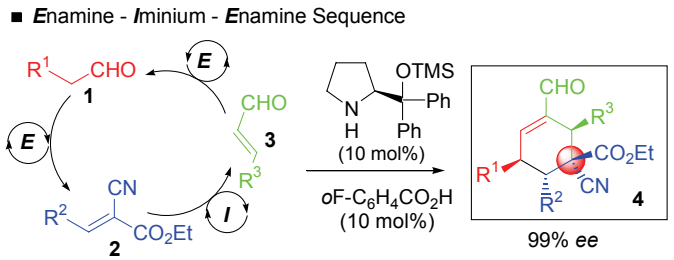
7.3 Quaternary Stereogenic Carbons in Complex Molecules by an Asymmetric Organocatalytic Triple-Cascade Reaction



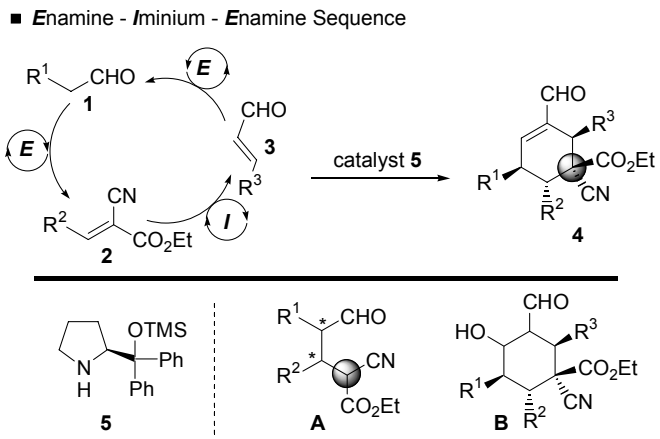
Triple (Super) Attack. The use of 2-cyanoacrylate derivatives **2** – the main component of one of the most used superglue solution – in an asymmetric triple organocascade allows the direct synthesis of *tri*- and *tetra*-substituted cyclohexene carbaldehydes **4** having three or four stereogenic carbon atoms, one of which is quaternary by all-carbon substitution, with complete enantioselectivity (>99% ee).

The stereoselective construction of all-carbon quaternary sterogenic centers in complex organic molecules is an ongoing synthetic challenge.[1] This is due to the growing number of biologically active natural products and pharmaceutical agents which possess quaternary stereogenic carbons. However, creating these complex fragments rapidly and selectively is a difficult task because of the inherent steric bias encountered in the C-C bond-forming event. In this field, enantioselective cascade catalysis has been recognized as a new synthetic solution to the stereoselective construction of molecular complexity.[2] This bio-inspired strategy is based upon the combination of multiple asymmetric transformations in a cascade sequence, providing rapid access to complex molecules containing multiple stereocenters from simple precursors and in a single operation.

We present the development of an organocatalytic[3] triple cascade reaction that allows the direct, one-pot synthesis of *tri*- and *tetra*-substituted cyclohexene

carbaldehydes **4** having three or four stereogenic carbon atoms, one of which is quaternary by all-carbon substitution (Scheme 1). This three-component domino strategy is based on an operationally trivial procedure that employs unmodified, cheap and commercially available starting materials and catalyst while achieving exquisite levels of stereocontrol (up to 20:1 *dr* and complete enantioselectivity). Notably, the development of the first asymmetric conjugate addition of aldehydes **1** to cyanoacrylates **2**, a new class of suitable Michael acceptors for enantioselective aminocatalysis, is at the heart of the presented triple organocascade.

Recently, the use of simple chiral organic molecules to catalyze asymmetric domino reactions has represented an additional step forward to the identification of a powerful and reliable strategy for the stereoselective synthesis of complex molecules.[4] In this approach, the synthetic benefits inherent to cascade sequences – that avoids time consuming and costly protection/deprotection as well as isolation procedures of intermediates – is combined with the use of environmentally friendly, robust and nontoxic organocatalysts. Inparticular, chiral secondary amines have been successfully used in cascade catalysis because of the possibility to integrate orthogonal activation modes of carbonyl compounds (enamine and iminium ion catalysis)[5] into more elaborate reaction sequences.[6,7]



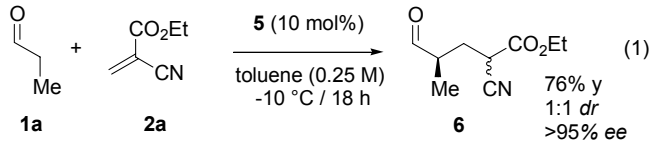
Scheme 1: Quaternary stereocenters via triple organocascade.

Despite the impressive recent achievements in the field, a general and efficient organocatalytic cascade reaction that allows the direct preparation of complex fragments, containing all-carbon quaternary stereocenters, is still lacking.[8] Toward this ambitious goal, we were inspired by the spectacular example of an enantioselective triple organo-cascade reaction recently reported by Enders and colleagues.[6] Exploiting the catalytic behaviour of the chiral secondary amine **5**,[9] they realized an outstanding enamine-iminium-enamine sequential activation of aldehydes **1**, nitroalkenes, and α,β-unsaturated aldehydes **3**, affording cyclohexene aldehydes with four stereocenters in essentially enantiopure form.[6a] We speculated that an adequate combination of the reaction components, still including the

aldehydic partners **1** and **3** to preserve the catalytic machinery of this efficient triple organo-cascade sequence, might provide a rapid and highly selective creation of quaternary stereocenters in complex molecules.

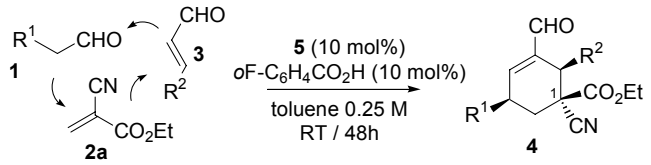
Central to the implementation of this strategy was the individuation of a suitable Michael acceptor **2** that must address some specific issues. Initially, such reagent must intercept the enamine intermediate, generated by catalyst condensation with aldehyde **1**, much faster than the unsaturated carbonyl compounds do (aldehyde **3** or the corresponding activated iminium intermediate). The resulting conjugate adduct **A** (Scheme 1) should constitute a prochiral carbon nucleophile that can selectively engage in the iminium catalyzed conjugate addition to **3**. The last step is an enamine-promoted aldol reaction, where the less hindered aldehyde acts as a nucleophile affording the intermediate **B** and, after dehydration, the desired cyclohexene carbaldehydes **4**. Along these lines, we envisaged cyanoacrylate derivatives **2** as a potential candidate to address these concerns.

To assess the feasibility of such an asymmetric organocatalytic triple cascade strategy, we focused on the use of ethyl 2-cyanoacrylate (**2a**),[10] probing its ability to act as a suitable Michael acceptor for enamine-catalyzed enantioselective, direct conjugate addition of aldehydes. Exposure of propanal (**1a**) to **2a** in the presence of diphenylprolinol silyl ether **5** (10 mol%) in toluene (0.25 M) resulted in a fast, clean and highly selective (>95% ee, determined by ^{1}H NMR analysis in chiral medium, see Experimental Part) conjugate addition [Eq. (1)].



These results, besides broadening the scope of enamine catalysis, set conditions for the realization of the cascade sequence. Extensive optimization experiments revealed that the presence of an acidic additive and the relative ratios of the reagents were the crucial parameters to obtain high levels of stereocontrol and reaction efficiency:[11] mixing aldehyde **1** (2 equiv), cyanoacrylate **2a** (1.2 equiv), and unsaturated aldehyde **3** at room temperature in the presence of the catalytic salt **5**·*o*F-$C_6H_4CO_2H$ (10 mol%) in toluene, the desired cyclohexene carbaldehyde **4** was obtained in good diastereoselectivity and complete enantiocontrol after 48 hours. Importantly, the main diastereomer can be easily isolated (*de* and *ee* up to 99%) by column chromatography.

Table 1: Organocatalytic triple-cascade: a route toward quaternary stereocenters.[a]



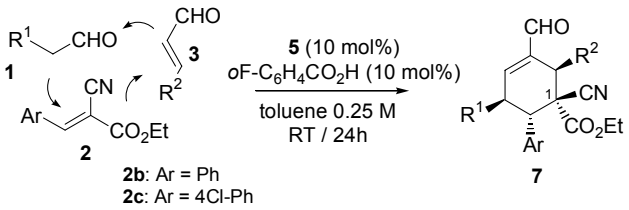
Entry	R^1	R^2	**4**	[%] yield [b]	dr[c]	[%] *ee*[d]	*de*,
1	Me	Ph	**a**	42	5.5:1	>99	
2[e]	Me	Ph	**a**	40	5.4:1	>99	
3	Et	Ph	**b**	35	3.5:1	>99	
4	allyl	Ph	**c**	40	3:1	>99	
5	Me	*p*NO_2-C_6H_4	**d**	34	3.8:1	98	
6	Me	Me	**e**	42	2.5:1	>99	

[a] Reactions performed on a 0.4 mmol scale using 2 equiv of aldehyde **1**, 1.2 equiv of **2a** and 1 equiv of enal **3**. [b] Yield of the isolated main diastereomer. [c] Determined by ^{1}H NMR analysis of the crude mixture. The minor diastereomer was identified as the 1-epimer of **4**. [d] The diastereomeric and enantiomeric excesses were determined by HPLC analysis of the isolated products **4**. [e] (*R*)-**5** was used as the catalyst, affording the opposite enantiomer of compound *ent*-**4a**.

As summarized in Table 1, the triple organocascade proved successful for a range of aldehyde substituents, providing a facile and flexible access to highly functionalized *tri*-substituted cyclohexenals **4a**-**e**, having a quaternary stereocenter, in almost enantiomerically pure form.

This three component domino strategy can also be successfully extended to the highly chemo-, diastereo-, and enantioselective synthesis of *tetra*-substituted cyclohexene carbaldehydes **7** (Table 2). The use of *trans*-alpha-cyanocinnamates **2b**-**c**[12] determines a fast and efficient triple organocascade, leading to the desired products after 24 hours reaction time. Interestingly, aliphatic β-substituted enals induce an higher stereocontrol, with diastereomeric ratio up to 20:1.

Table 2: Control of four stereocenters via an organocatalytic triple-cascade.[a]

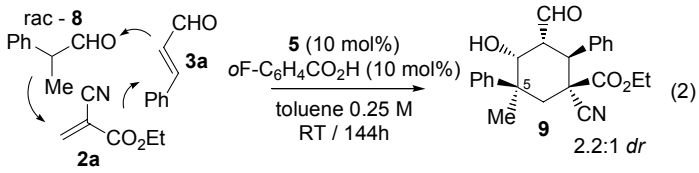


Entry	**2**	R^1	R^2	**7**	[%] yield [b]	dr[c]	[%] *de*, *ee*[d]
1	**b**	Me	Ph	**a**	52	2.6:1	>99
2[e]	**b**	Me	Ph	**a**	45	2.2:1	>99
3	**b**	Et	Ph	**b**	40	2.3:1	>99
4	**c**	Me	Ph	**c**	32	2:1	>99
5	**b**	Me	Me	**d**	48	>20:1	98

6	**b**	Et	Me	**e**	39	>20:1	98
7	**b**	allyl	Me	**f**	40	>20:1	99
8	**c**	Me	Me	**g**	38	7.6:1	99

[a] Reactions performed on a 0.4 mmol scale using 2 equiv of aldehyde **1**, 1.2 equiv of **2** and 1 equiv of enal **3**. [b] Yield of the isolated main diastereomer. [c] Determined by ^{1}H NMR analysis of the crude mixture. The minor diastereomer was identified as the 1-epimer of **7**. [d] The diastereomeric and enantiomeric excess was determined by HPLC analysis of the isolated products **7**. [e] Reaction carried out using 5 mol% of the catalyst **5**.

The efficiency of the presented organocatalytic strategy prompted us toward a more ambitious goal, the formation of a complex structure having *two* all-carbon quaternary stereocenters. Employing an α,α-disubstituted aldehyde, such as 2-phenyl propanal (**8**), as a component of the triple organocascade led to the unexpected formation of cyclohexane **9**, an highly functionalized molecule with five stereocenters [Eq. (2)]. Noteworthy, this reaction allows the highly enantioselective synthesis of just two diastereomers, out of the 16 possible, – compound **9** and its 5-epimer (epi-**9**) – that can be separated by chromatography.[13]



9: 36% isolated yield, 96% *ee*
epi-**9**: 19% isolated yield, 91% *ee*

The relative configuration of the *tri-* and *tetra*-substituted cyclohexene carbaldehydes **4a** and **7a** and the cyclohexanes **9** and epi-**9** was determined by NMR NOE analysis and X-ray crystallography (see Experimental Part). Interestingly, **4a** and **7a** have an opposite configuration at the C(1) quaternary center, while the other stereogenic carbons, directly forged by the catalyst stereo-induction, have the same configuration. The absolute configuration was assigned by means of TD-DFT calculations of the Electronic Circular Dichroism (ECD) spectra.[14] As shown in Figure 1, the experimental ECD spectra match with the theoretical ones. The relative and absolute configurations are in agreement with related aminocatalytic conjugate additions promoted by catalyst **5**.[6,9]

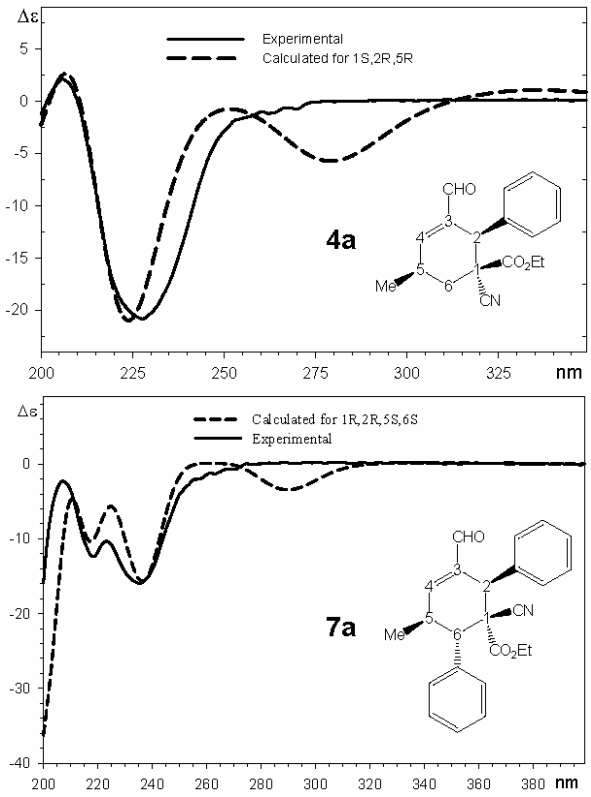


Figure 1: Experimental (full trace) and calculated ECD spectra (dotted trace) of the *tri-* and *tetra*-substituted cyclohexene carbaldehydes **4a** (top) and **7a** (bottom).

In summary, we presented a novel organocatalytic triple cascade that allows the stereoselective construction of all-carbon quaternary sterogenic centers in complex organic molecules. The method provides a flexible and direct access to cyclohexene carbaldehydes having three or four stereogenic carbon atoms with high diastereo- and complete enantio-control, and can be extended to the preparation of enantiopure cyclohexanes with five chiral centers and two quaternary carbons.[13]

Dr. Andrea Mazzanti is gratefully acknowledged for useful discussion, extensive NMR studies on the compounds and on TD-DFT calculations of the Electronic Circular Dichroism (ECD) spectra and experimental ECD spectra.

7.3.R References

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[10] It is impressive how, despite being the main component of one of the most used superglue solution (Loctite® Super Attak - Henkel), ethyl 2-cyanoacrylate **2a** is compatible with organocatalytic reaction conditions. This underscores, once again, the reliability and the synthetic potential of asymmetric aminocatalysis.

[11] The use of different acidic additives (*e.g.* $p$$NO_2$-$C_6H_4CO_2H$) and base additives (*e.g.* DABCO) resulted in considerably lower reaction rate and worse diastereoselectivity.

[12] Efforts to use aliphatic cyanoacrylate derivatives in the triple organocascade resulted in very poor conversion.

[13] Further studies toward the asymmetric preparation of enantiopure cyclohexanes having six stereocenters are underway.

[14] For recent examples of this method to assign the absolute configurations of organic molecules, see: a) C. Diedrich, S. Grimme, *J. Phys. Chem. A* **2003**, *107*, 2524; b) D. Casarini, L. Lunazzi, M. Mancinelli, A. Mazzanti, C. Rosini, *J. Org. Chem.* **2007**, *72*, 7667; c) A. Goel, F.V.

Singh, V. Kumar, M. Reichert, T.A.M. Goulder, G. Bringmann, G. *J. Org. Chem.* **2007**, *72*, 7765; d) P. J. Stephens, D. M. McCann, F. J. Devlin, J. R. Cheeseman, M. J. Frisch, *J. Am. Chem. Soc.* **2004**, *126*, 7514. For a review: e) N. Berova, L. Di Bari, G. Pescitelli, *Chem. Soc. Rev*. **2007**, *36*, 914.

7.3.EP Experimental Part

Contents

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. ^{1}H and ^{13}C NMR spectra of compounds **4a, 7a** and **9** were recorded at 600 MHz for ^{1}H and 150.8 for ^{13}C. All the ^{1}H and ^{13}C signals were assigned by means of g-COSY, g-HSQC and g-HMBC 2D-NMR sequences. NOE spectra were recorded using the DPFGSE-NOE sequence,[3] using a mixing time of 2.00 s and "rsnob" 20 ÷ 50 Hz wide selective pulses, depending on the crowding of the spectra region. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$ and CD_3CN). Coupling constants are given in Hz. When 2D-NMR were not performed, carbon types were determined from DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh) according to the method of Still.[4] Analytically pure stereoisomers were obtained by crystallization (hexane/*i*-PrOH 9:1) for compound **7a**, and by means of semipreparative HPLC for compounds **4a** (Waters Novapak, silica 6 μm, 8x300 mm, hexane/iPrOH 97:3) and **9** (two jointed Phenomenex Luna C18(2), 10x250 mm, ACN/H_2O 90:10). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. High

[3] a) J. Stonehouse, P. Adell, J. Keeler, A. J. Shaka, *J .Am. Chem. Soc.* **1994**, *116*, 6037; b) K. Stott, J. Stonehouse, J. Keeler, T. L. Hwang, A. J. Shaka, *J. Am. Chem. Soc.* **1995**, *117*, 4199; c) K. Stott, J. Keeler, Q. N. Van, A. J. Shaka, *J. Magn. Reson.* **1997**, *125*, 302.

[4] W. C. Still, M. Kahn, A. J. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

Resolution Mass spectra were obtained from the Department of Organic Chemistry *"A. Mangini"* Mass Spectroscopy facility. X-ray data were acquired at the Department of Physical and Inorganic Chemistry X-ray Crystallography facility, on a Bruker APEX-2 difractometer. Optical rotations are reported as follows: $[\alpha]^{rt}_{D}$ (*c* in g per 100 mL, solvent). All reactions were carried out in air and using undistilled solvent, without any precautions to exclude moisture unless otherwise noted.

Determination of Enantiomeric Purity. Chiral HPLC analysis was performed on an Agilent 1100-series instrumentation. Daicel Chiralpak AD-H or AS-H columns and Daicel Chiralcel OD-H column with *i*-PrOH/hexane as the eluent were used.

HPLC traces were compared to racemic samples prepared by carrying out the reactions with racemic **5** as the catalyst.

ECD spectra. UV absorption spectra were recorded at 25 °C in acetonitrile in the 200-400 nm spectral region. The cell path length was 0.1 cm, concentration was $1.43 \cdot 10^{-4}$ mol L^{-1}. CD spectra were recorded at 25°C in acetonitrile, with the same path lengths of 0.1 cm, in the range 200-400 nm; reported Δε values are expressed as L $mol^{-1}cm^{-1}$.

DFT Calculations. Geometry optimization were carried out at the B3LYP/6-31G(d) level by means of the Gaussian 03 series of programs[5] : the standard Berny algorithm in redundant internal coordinates and default criteria of convergence were employed. The reported energy values are not ZPE corrected. Harmonic vibrational frequencies were calculated for all the stationary points. For each optimized ground state the frequency analysis showed the absence of imaginary frequencies, whereas each transition state showed a single imaginary frequency. Visual inspection of the corresponding normal mode was used to confirm that the correct transition state had been found. NMR chemical shift calculations were obtained with the GIAO method at the B3LYP/6-311++G(2df,p)//B3LYP/6-31G(d) level. TMS, calculated at the same level of theory, was used as reference to scale the absolute shielding value. *J*-coupling calculations were obtained at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) level using the program[5] option that includes the Fermi contact contribution. TD-DFT calculations were obtained at the B3LYP/6-311++G(2df,p)//B3LYP/6-31G(d) level. In order to cover the whole 190-400 nm range, 40 to 50 transition were calculated. The CD spectrum was then obtained applying a 0.3 eV Gaussian bandshape.

Materials. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[6] Aldehydes **1**, **3** and **8** were purchased from

[5] Gaussian 03, Revision D.01 and E.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

[6] W. L. F. Armarengo, D. D. Perrin, In *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, 1996.

Aldrich or Alfa Aesar and used as received. Catalyst **5** was prepared according to literature procedure.[7] Ethyl *trans*-alpha-cyanocinnamate **2b** and methyl 2-chloro-alpha-cyanocinnamate **2c** were purchased from Aldrich and used as received.

CAUTION: Ethyl 2-cyanoacrylate **2a** was purchased from Aldrich; due to its high tendency to polymerization and its sensibility to light, it was diluted in toluene (1M solution) and stored in the dark at 0°C under an argon atmosphere.

Structural assignment of compounds 4a,7a and 9

NOE analysis of 7a

In the whole class of compounds 7, the 4 stereogenic centres created during the reaction can generate up to 16 stereoisomers, but only two of them were isolated in the reaction products.

In the case of the major diastereoisomer (2° eluted from the silica column), the proton spectrum of Figure 1 shows that H-6 is coupled with H-5 with quite a large coupling constant (11.3 Hz); according to the Karplus equation, this large value should correspond to an anti-periplanar disposition of H-5 and H-6, thus the Methyl in position 5 and the phenyl ring in position 6 should be both in a pseudo-equatorial position. The coupling constant can be also calculated by DFT methods (see below), that predict a J coupling of 10.7 Hz, in fairly good agreement with the experimental value.

Owing to the crowding of the aromatic region, unambiguous identification of the proton signals of the two phenyl groups is essential to the correct interpretation of the subsequent NOE spectra. Assignment of the two pair of ortho hydrogens was obtained by saturation of the H-6 signal (3.0 ppm), yielding NOE on the ortho hydrogens of Ph(6) at 7.17 ppm, and by saturation of the H-2 signal (4.4 ppm), yielding NOE on the ortho hydrogens of Ph(2) at 7.38 ppm. (spectra not shown in Figure 1)

On selective saturation of the methyl group in position 5 (1.15 ppm), positive NOE are observed on both the o-Ph(2) and o-Ph(6) signals, being the first more intense. On the contrary, no enhancement was observed on the H-2 signal. These results imply that the phenyl group in position 2 lies on the same side of Me(5). Further data that supports this hypothesis are obtained when the H-6 signal is saturated (trace c), showing large NOE for the o-Ph(2) and for the Me(5), indicating that both these signals are very close to H-6. Using the "control" NOE on the o-Ph(6) hydrogens as a distance reference, a distance ratio of 1.24 between Me(5) and o-Ph(2) was derived, to be compared with the 1.22 ratio calculated on the lowest energy DFT calculated structure (see below). These data also confirm the anti relationship between H-6 and H-5, already inferred from the J-coupling analysis.

[7] The catalyst **5** can be easily prepared by protection of the commercial available α,α -diphenylprolinol with TMSOTf. See: J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen *J. Am. Chem. Soc.* **2005**, *127*, 18296.

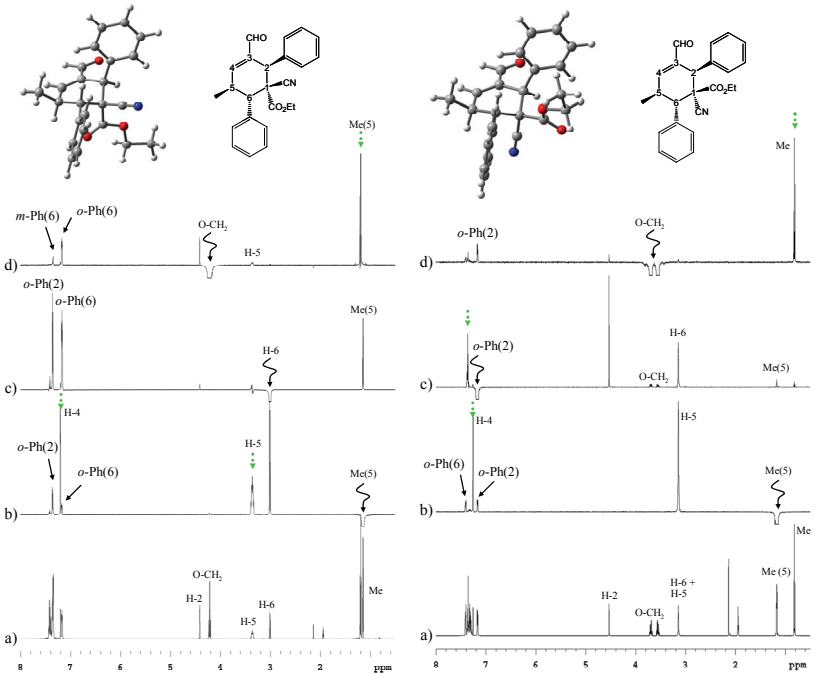


Figure 1-left. a) ^{1}H-NMR spectrum (600 MHz in CD_3CN) of the major diastereoisomer of compound **7a**. Trace b)DPFGSE-NOE spectrum obtained on saturation of the Methyl group in position 5. Trace c) DPFGSE-NOE spectrum obtained on saturation of the hydrogen in position 6. Trace d) DPFGSE-NOE spectrum obtained on saturation of the O-CH_2 signal. Green arrows indicate the "control" NOEs for each trace (i.e. enhancements that must be in any case observed due to the relative position with the saturated signal).

Figure 2-right. a) ^{1}H-NMR spectrum (600 MHz in $CDCl_3$) of the minor diastereoisomer of compound **7a**. Trace b)DPFGSE-NOE spectrum obtained on saturation of the Methyl group in position 5. Trace c) DPFGSE-NOE spectrum obtained on saturation of the ortho hydrogens of the phenyl in position 2. Trace d) DPFGSE-NOE spectrum obtained on saturation of the O-CH_2 signal. Green arrows indicate the "control" NOEs for each trace (i.e. enhancements that must be observed due to the relative position of the saturated signal).

Assignment of the relative configuration of the quaternary stereogenic centre on C(1) was deduced from selective saturation of the O-CH_2 signal: Positive NOE are observed on the o-Ph(6) signals at 7.17 ppm, on the m-Ph(6) signals (at 7.40 ppm, assigned by 2D-COSY) and on the H-5 signal; the OCH_2 group is thus syn to the phenyl in position 6, and anti to the phenyl in position 2. A small signal is visible also for H-2, due to its relatively short distance from the OCH_2. All the NOE data thus satisfactorily converge to assign the 1R*,2R*,5S*,6S* relative configuration to the major isomer of **7a**.

The NOE spectra recorded for the minor diastereoisomer of **7a** (Figure 2) show the same behaviour in the cases of the three stereogenic centres on C(2), C(5) and C(6) (trace b and c). In this isomer the signals of H5 and H6 are superimposed, thus selective saturation of the H-6 signal was unfeasible. Instead, saturation of the o-Ph(2) signal at 7.18 ppm (trace c) shows a large positive effect on H-6 (H-5 is too far to yield NOE), and a negligible enhancement of Me(5), thus confirming the same relative configuration at C(2), C(5) and C(6) already observed in the major isomer. It should be noted that the preliminary NOE spectra obtained on irradiation of H-2 and H-6 show that in the case of the minor stereoisomer of **7a**, the chemical shift of the ortho hydrogens of the two phenyl ring are reversed, thus the signal at 7.18 ppm corresponds to the pair of ortho hydrogens belonging to the phenyl in position 2, while the doublet at 7.41 ppm corresponds to the ortho hydrogens belonging to the phenyl in position 6.

On saturation of the o-Ph(2) signal (trace c), a positive NOE is also observed on the OCH_2 signal, indicating the change in the configuration of the quaternary C(1) carbon. Saturation of the OCH_2 confirms the NOE on the o-Ph(2) hydrogens, while no effect is visible on H-5 (the small effect at 3.05 ppm should be assigned to a positive NOE on the superimposed H-6), thus the 1S*,2R*,5S*,6S* relative configuration can be satisfactorily assigned. Again, a NOE effect is visible on H-2, being its intensity lower with respect to the same NOE observed in the case of the major stereoisomer.

Large variation of chemical shift is observable in the proton spectra of the two isomers of **7a**, particularly in the case of the OCH_2 that is moved upfield by 0.6 ppm (from 4.20 to 3.62 ppm) in the minor isomer, and in the case of the H-5 signal, that is moved downfield in the case of the major isomer with respect to the minor.

The upfield shift of the OCH_2 could be explained by the effect of the aromatic ring currents, since in the minor isomer the group lies above the plane of the phenyl ring in position 2.[8]

The trend of the chemical shift can be also evaluated by computational method: DFT calculation of the chemical shifts (isolated molecule, at the B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d) level) predicts an upfield shift of 0.35 ppm of the OCH_2 signal of the minor isomer with respect to the same signal of the major isomer, in good agreement with the observed trend. The same calculations also indicate that the H-5 signal of the major isomer is moved downfield by 0.75 ppm with respect to the same signal of the minor isomer, again in agreement with the experimental data. Finally, as a proof of the reliability of the calculation, a very small chemical shift difference (0.08 ppm) is calculated for the H-2 signal of the two isomers, to be compared with the experimental 0.06 ppm difference.

This peculiar behaviour of the chemical shift of the OCH_2 and H-5 signals can thus be used as an indicator to assign the stereochemistry of the quaternary centre at C(1) in the whole class of compounds.

X-RAY analysis

In the case of the minor diastereoisomer of compound **7a**, crystals suitable for X-ray diffraction were obtained by slow evaporation of an Hexane/iPrOH solution. The experimentally observed structure in the solid state fully confirms the relative stereochemistry already determined by NOE spectra; the crystal structure is almost identical to the one obtained by DFT calculation in the gas phase and used for the evaluation of the NOE spectra, the only difference being the orientation of the methyl group of the COOEt Moiety (Figure 3).

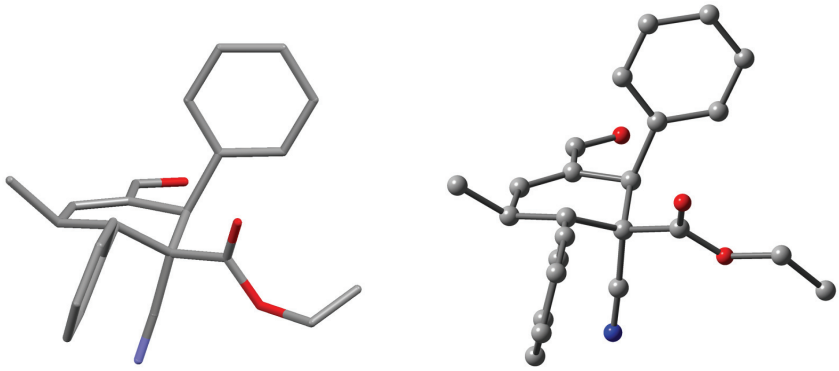
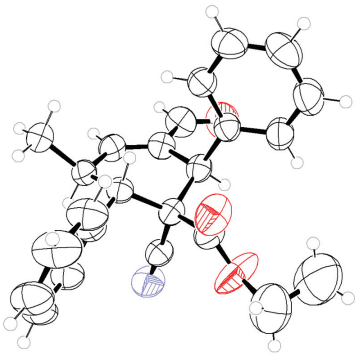


Figure 3. Left: X-ray structure of the minor isomer of **7a**
Right: Best DFT calculated structure

[8] a) L. M. Jackman, S. Sternhell, *Applications of NMR Spectroscopy in Organic Chemistry*, 2nd edition; Pergamon Press: Oxford, 1969; p 95; b) W. B. Jennings, B. M. Farrell, J. F. Malone, *Acc. Chem. Res*. **2001**, *34*, 885; c) K. Wüthrich, *Angew. Chem. Int. Ed*. **2003**, *42*, 3340.)

Crystal Data for 7a, minor isomer



Crystals obtained from hexane/iPrOH, molecular formula: $C_{26}H_{20}$, M_r = 373.43, monoclinic, space group $P2_1$ (No. 4), a = 8.4878(9), b = 9.9976(10), c = 12.5499(13) Å, β = 103.3610(10), V = 1036.13(19) Å^3, T = 298(2) K, Z = 2, ρ_c = 1.197 g cm^{-3}, F(000) = 396, graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å), $\mu(Mo_{K\alpha})$ = 0.079 mm^{-1}, colourless needle (0.6 × 0.2 × 0.2 mm^3), empirical absorption correction with SADABS (transmission factors: 0.9543 – 0.9844), 2400 frames, exposure time 15 s, 1.67 ≤ θ ≤ 26.00, –10≤ h ≤ 10, –12 ≤ k ≤ 12, –15 ≤ l ≤ 15, 10729 reflections collected, 4074 independent reflections (R_{int} = 0.0183), solution by direct methods (SHELXS) and subsequent Fourier syntheses, full-matrix least-squares on F_o^2 (SHELXL), hydrogen atoms refined with a riding model, data / restraints / parameters = 4074/ 1 / 256, $S(F^2)$ = 1.079, $R(F)$ = 0.0476 and $wR(F^2)$ = 0.1150 on all data, $R(F)$ = 0.0433 and $wR(F^2)$ = 0.1112 for 3726 reflections with $I > 2\sigma(I)$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0495P)^2 + 0.1949P]$ where $P = (F_o^2 + 2F_c^2)/3$, largest difference peak and hole 0.228 and –0.268 e Å^{-3}. Flack Parameter 0.4 (15). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-678444. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

ECD spectra and Absolute Configuration of 7a

The lack of a suitable heavy atom precludes the use of the Bijovet method, based on anomalous X-ray dispersion, to unambiguously assign the absolute configuration (AC) of the minor diastereomer of **7a**, even if the Flack parameter[9] value obtained at the end of the structure refinement indicates the 1S,2R,5S,6S configuration as the more probable.

Using a different approach, the Electronic Circular Dichroism (ECD) spectrum could be calculated by theoretical methods and its shape (and intensity) compared with that of the experimental spectrum. If they match, the AC assumed in the calculations should then be assigned to the enantiomer whose experimental spectrum has been recorded. Theoretical calculation was carried out by means of TD-DFT method, since such a technique has been successfully employed several times[10] to predict ECD spectra and to assign the AC of organic molecules.

[9] H. D. Flack *Acta Cryst.* **1983**, *A39*, 876

[10] See ref. 14 in the main text.

A preliminary conformational search, starting from the relative configuration derived from NOE spectra and X-ray data, was obtained for the minor diastereoisomers of compound **7a,** using Molecular Mechanics (MMFF force field, TITAN 1.0.4, Montecarlo algorithm).

The analysis of the output structures revealed that, up to 2 kcal/mol with respect to the lowest energy structure, they differ only for the position of the methyl group of the COOEt moiety. The three best structures were then optimized at the B3LYP/6-31G(d) level, and for each of the optimized structures, the ECD spectrum was calculated in the 200-400 nm region at the same level (Figure 4) The three CD spectra obtained are almost super imposable, a result quite obvious when considering the very small influence of the position of the methyl group with respect to the chromophoric groups that generate the ECD spectrum.

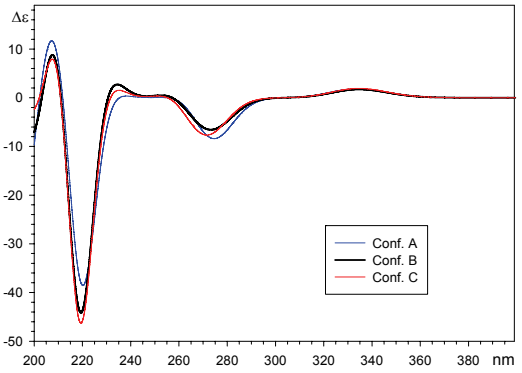


Figure 4. Calculated ECD spectra for the best three conformers of the minor isomer of **7a**

The final CD spectrum to be compared with the experimental one was then calculated only for the lowest energy structure (Figure 3, right) at the B3LYP/6-311++G(2df,p)//B3LYP/6-31G(d) level. As shown in Figure 4, the CD spectrum calculated assuming the 1S,2R,5S,6S configuration shows a shape and relative intensities analogous to that of the experimental spectrum, with a strong negative Cotton effect at lower wavelengths (≈ 220 nm), as well as a small positive effect at higher wavelengths (≈ 340 nm).

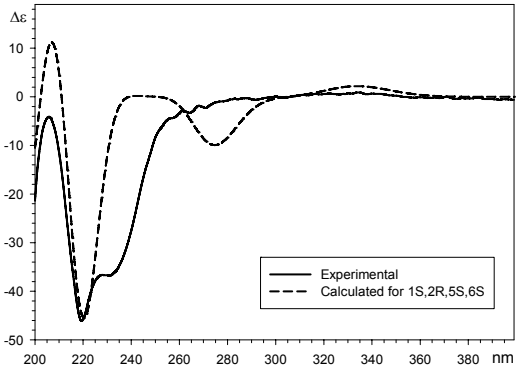


Figure 5: experimental (full trace) and calculated (dotted trace) ECD spectrum for the minor isomer of **7a**.

Accordingly, the 1S,2R,5S,6S configuration should be assigned to the minor diastereoisomer, and, as a consequence, the 1R,2R,5S,6S configuration should be assigned to the major diastereoisomer of **7a**. As a final validation, the ECD spectrum was calculated at the highest level of theory also for the major stereoisomer, following the same theoretical approach and assuming the **1R,2R,5S,6S** configuration. In this case, the calculated trace is even in a better agreement with the experimental spectrum (see Figure 1 in the main text).

Determination of the Configuration of the two diastereoisomers of **4a**

In the case of the mayor isomer of **4a**, selective saturation of the Methyl signal in position 5 shows positive NOEs on the ortho hydrogens of the phenyl ring, (Figure 5, trace a), on both the diastereotopic hydrogens of the CH_2(6) and a very strong effect on the vinilic CH in position 4 of the six-membered ring. This very strong effect can be used as a distance reference to calculate the others distances. From these data the syn relationship between the Me(5) and the phenyl group can be satisfactorily assigned. Saturation of the ortho hydrogens of the phenyl group (Figure 5, trace b) confirms the relative syn relationship with the Me(5) group.

The relative stereochemistry of the quaternary centre in position 1 of the ring can be obtained from the selective saturation of the O-CH_2 signal (trace c). When this signal is irradiated, NOE effect is observed on both the ortho and meta signals of the phenyl group. These signals can be observed only if the COOEt group and the phenyl group lie on the same side of the six-membered ring. *Vice versa*, the complementary effect can be seen as NOE enhancement of the OCH_2 when the ortho hydrogens of the phenyl group are saturated (Figure 5, trace b).

It should be noted that a NOE signal is visible also for the CH in position 2. The distance of this hydrogen can be evaluated using the strong NOE effect on the ester methyl group as a distance reference, and it is consistent with the distances obtained from the DFT calculated structure.

The relative distance of the ortho hydrogens and of the H-2 from the OCH_2 can be evaluated by their NOE ratio (1.32). From the calculated structure, a very similar ratio (1.37) was obtained only in the case of a syn relationship between the COOEt and the phenyl group.

These data satisfactorily assign the 1S*,2R*,5R* relative stereochemistry to the major diastereoisomer. Further data supporting this assignment can be obtained by the NOE spectra recorded on the minor diastereoisomer (Figure 6).

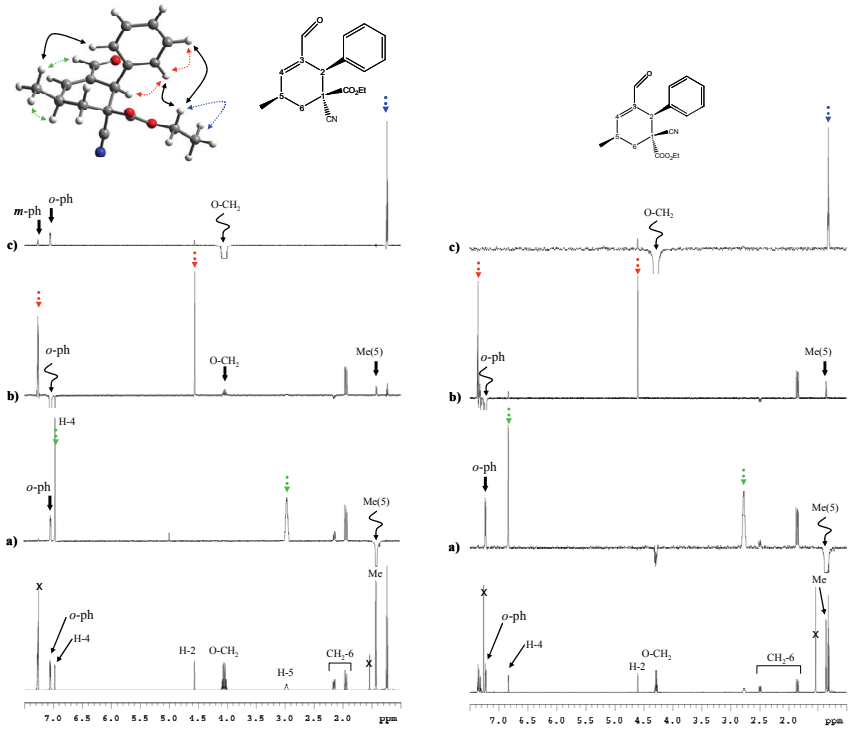


Figure 5-left. Bottom: ^{1}H-NMR spectrum (600 MHz in $CDCl_3$) of the major diastereoisomer of compound **4a**. Trace a):DPFGSE-NOE spectrum obtained on saturation of the Methyl group in position 5. Trace b) DPFGSE-NOE spectrum obtained on saturation of the ortho hydrogens of the phenyl group. Trace c) DPFGSE-NOE spectrum obtained on saturation of the O-CH_2 signal. Coloured arrows indicate the "control" NOE for each trace (i.e. enhancements that must be in any case observed due to the relative position with the saturated signal).

Figure 6-right. Bottom: ^{1}H-NMR spectrum (600 MHz in $CDCl_3$) of the minor diastereoisomer of compound **4a**. Trace a):DPFGSE-NOE spectrum obtained on saturation of the Methyl group in position 5. Trace b) DPFGSE-NOE spectrum obtained on saturation of the ortho hydrogens signal. Trace c) DPFGSE-NOE spectrum obtained on saturation of the O-CH_2 signal. Coloured arrows indicate the "control" NOEs for each trace (i.e. enhancements that must be observed due to the relative position of the saturated signal).

On saturation of the Methyl group, NOE effect is observed on the ortho phenyl hydrogens, thus confirming the same syn relationship between phenyl and Me(5) already observed in the major diastereoisomer. Reversely, irradiation of the ortho hydrogens shows NOE effect on the Me(5) signal, but not on the OCH_2 group (Figure 6, trace b). Finally, saturation of the OCH_2 signal does not show any enhancement in the aromatic region, thus confirming the anti relationship between the phenyl and the COOEt group. As already underlined for the major isomer, a small effect is visible also in this case on the CH in position 2, that has the same distance from the OCH_2 in both the two diastereoisomers.

Absolute Configuration of the major isomer of 4a

The same TD-DFT theoretical approach already used in the case of **7a** was applied in order to assign the Absolute Configuration of the major isomer of **4a**. A preliminary conformational search, starting from the relative configuration derived from NOE spectra was obtained using Molecular Mechanics (MMFF force field, TITAN 1.0.4, Montecarlo algorithm).

Also in this case the analysis of the output structures revealed that the lowest energy structures differ only for the position of the methyl group of the COOEt moiety. Thus, the ECD spectrum to be compared with the experimental one was then calculated only for the lowest energy structure at the B3LYP/6-311++G(2df,p)//B3LYP/6-31G(d) level. As shown in Figure 1 of the main text, the CD spectrum calculated assuming the 1S,2R,5R configuration has a shape and relative intensities analogous to that of the experimental spectrum, with a strong negative Cotton effect at low wavelengths (≈ 220 nm). Consequently, the ***1R,2R,5R*** configuration has to be assigned to the minor isomer.

Relative configuration of 9 and epi-9

In the case of compounds 9 and its isomer epi-9, the presence of a cyclohexane motif helps in determining the relative configuration of some stereocenters, because of the stereospecific and well known J-coupling relationship generated in this kind of systems.

From the analysis of the ^{1}H-NMR spectra of the three H-2, H-3 and H-4 hydrogens (assigned by HSQC and HMBC spectra) it is evident, in both the major **9** and minor **epi-9** stereoisomer, the presence of a trans-diaxial J-coupling between H-2 and H-3 (J = 12.8 Hz), and a equatorial-axial J-coupling between H-3 and H-4 (J = 1.8 Hz for **9** and 2.0 for **epi-9**).

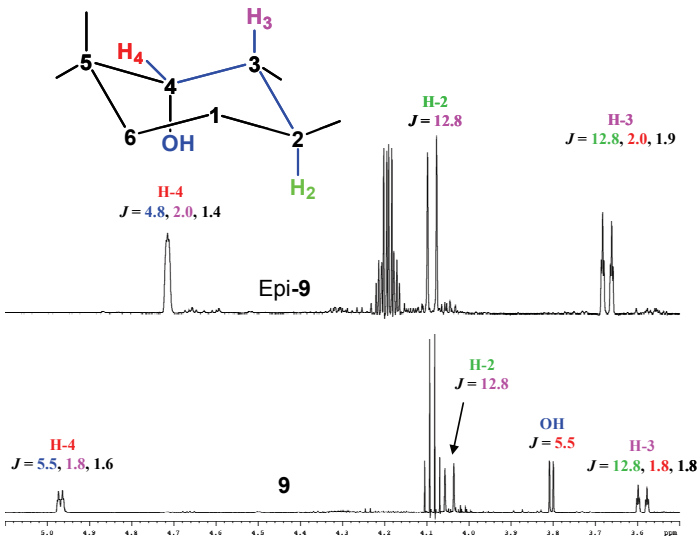


Figure 7: Part of the ^{1}H-NMR spectrum (600 MHz in CD_3CN) of compound **9** and **epi-9**. The colours indicate the relationship between the J-couplings.

These values well agree with the theoretical J-coupling obtained by DFT calculation (isolated molecule, at the B3LYP/6-31+G(d,p) //B3LYP/6-31G(d) level, and including the Fermi contact contribution), yielding

values of 13.7 and 3.1 Hz for **9** (13.7 and 3.6 for epi-**9**). The relative configuration at C(2), C(3) and C(4) is thus easily assigned as shown in Figure 7.

To solve the relative configuration of the two quaternary centres, NOE spectra were acquired on saturating the Methyl group on C(5), the OCH_2, and the H-3 signal. The main difference between the NOE spectra is observed on saturation of Me(5) and of H-3: in the case of the major isomer, NOE effect on the o-Ph(5) hydrogens was observed when H-3 was saturated (figure 8, trace b), while no NOE effect was observed on the Me(5). On the contrary when the H-3 signal of the minor isomer was saturated (figure 9, trace a), a strong NOE was visible on Me(5), and no effect was observed on the o-Ph(5) hydrogens.

Thus, in the case of **9** and **epi-9,** the two isomer obtained from the reaction clearly differ in the configuration of the C(5) centre. NOE spectra obtained on saturation of the OCH_2 group show the same NOEs on the o-Ph(2) hydrogens, confirming the same configuration at the C(1) centre in both the stereoisomers. The configuration of the C(1) centre is the same already determined for the major isomer of compound **4a**. The resulting configuration is thus 1S*,2S*,3R*,4R*,5S* for the major isomer **9,** and 1S*,2S*,3R*,4R*,5R* for the minor one, **epi-9**.

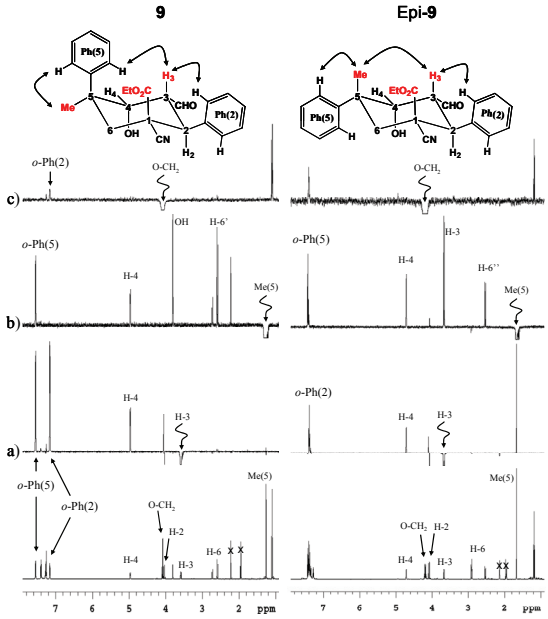
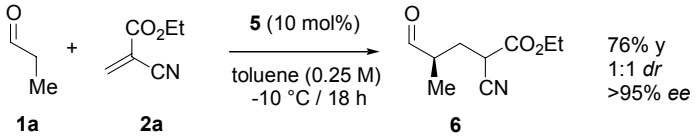


Figure 8-left. Bottom: ^{1}H-NMR spectrum (600 MHz in CD_3CN) of the major diastereoisomer of compound **9**. Trace a):DPFGSE-NOE spectrum obtained on saturation of the H-3 signal. Trace b) DPFGSE-NOE spectrum obtained on saturation of the Me(5). Trace c) DPFGSE-NOE spectrum obtained on saturation of the O-CH_2 signal.

Figure 9-right. Bottom: ^{1}H-NMR spectrum (600 MHz in CD_3CN) of the minor diastereoisomer of compound **epi-9**. Trace a):DPFGSE-NOE spectrum obtained on saturation of the H-3 signal. Trace b) DPFGSE-NOE spectrum obtained on saturation of the Me(5).. Trace c) DPFGSE-NOE spectrum obtained on saturation of the O-CH_2 signal.

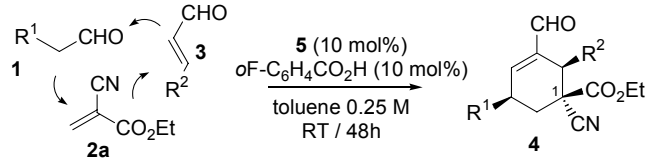
Experimental Procedures

Direct Aminocatalytic and Enantioselective Conjugate Addition of Aldehydes to Ethyl 2-cyanoacrylate.

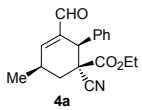


In an ordinary vial equipped with a Teflon-coated stir bar, catalyst **5** (0.03 mmol, 9.8 mg, 10 mol%) was dissolved in 0.9 mL of toluene. After addition of 0.45 mmol (1.5 equiv) of propanal **1a**, the solution was stirred for 10 minutes at -10 °C. Then ethyl 2-cyanoacrylate **2a** (1 equiv, 1M in toluene, 0.3 mL) was added and the solution was stirred for 18 hours at -10 °C. The crude reaction mixture was directly charged on silica gel and purified by flash chromatography (FC: Hexanes/AcOEt = 80/20). The compound was isolated as an inseparable 1:1 mixture of two diastereoisomers (due to the fast epimerization of one stereocenter) as a colourless oil in 76% yield and >95% ee, determined by H-NMR analysis in chiral medium (Pirkle's alcohol, R-(-)-2,2,2-trifluoroanthrylethanol). $[\alpha]^{rt}_{D}$ = + 19.1 (c = 1.0, $CHCl_3$, >95%ee, 1:1 mixture of two diastereoisomers). ^{1}H NMR (1:1 mixture of the two diastereoisomers): δ = 1.24 (d, *J* = 7.2, 3H), 1.26 (d, *J* = 7.6, 3H), 1.33 (d, J = 7.2, 6H), 1.83-1.99 (m, 2H), 2.35-2.43 (m, 2H), 2.65-2.75 (m, 2H), 3.63 (dd, *J* = 6.8, 1H), 3.79 (dd, *J* = 6.0, 1H), 4.24-4.30 (m, 4H), 9.65 (bs, 1H), 9.66 (bs, 1H); ^{13}C NMR: δ = 13.2, 13.9, 14.0, 14.1, 29.9 (2C), 35.1, 35.4, 43.4, 43.5, 63.0, 63.1, 115.9, 116.2, 165.6, 165.7, 201.9, 202.4.

General Procedure for the Organocatalytic Asymmetric Synthesis of Cyclohexene Carbaldehydes 4.



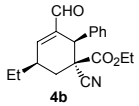
All the reactions were carried out in undistilled toluene without any precautions to exclude air. In an ordinary vial equipped with a Teflon-coated stir bar, catalyst **5** (0.04 mmol, 13.0 mg, 10 mol%) and 2-fluorobenzoic acid (0.04 mmol, 5.6 mg, 10 mol%) were dissolved in 1.12 mL of toluene. After addition of 0.8 mmol (2 equiv) of the aldehyde **1**, the solution was stirred for 10 minutes at room temperature. Then ethyl 2-cyanoacrylate **2a** (0.48 mmol, 1.2 equiv, 0.48 mL of a 1M solution in toluene) and 0.4 mmol of α,β-unsaturated aldehyde **3** (1 equiv) were sequentially added. After 48 hours stirring, the crude reaction mixture was diluted with DCM (2 mL) and flushed through a short plug of silica, using DCM/Et_2O 2/1 as the eluent. Solvent was removed *in vacuo*, and the residue was purified by flash chromatography (FC) to yield the desired product **4**.



(1R,2R,5R)-1-Cyano-3-formyl-5-methyl-2-phenyl-cyclohex 3-enecarboxylic acid ethyl ester 4a (Table 1, entry 1) **–** The reaction was carried out following the general procedure to furnish the crude product [dr = 5.5:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.44 ppm, δ_{minor} 9.39 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a colourless oil by column chromatography (hexane/AcOEt = gradient from 9/1 to 8/2 – R_F^{major}: 0.35, R_F^{minor}: 0.3 in hexane/AcOEt 7/3) in 42% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and >99% ee). HPLC analysis on a Chiralpak AD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 7.6 min, τ_{major} = 8.7 min; $[\alpha]^{rt}_{D}$= - 171.3 (*c* = 1.05, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{18}H_{19}NO_3$: 297.13649; found: 297.1366. **Major isomer**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.2, 3H), 1.43 (d, *J* = 7.3, 3H, Me(5)), 1.95 (dd, *J* = 14.5 and 11.4, 1H, H6′), 2.15 (dddd, *J* = 14.5 and 6.3, 1.7 and 1.2, 1H, H6″), 2.98 (m, 1H, H-5), 4.05 (ABX_3 system, J=10.8 and 7.2, 2H, OCH_2), 4.56(s, 1H H-2), 6.98(m, 1H, H-4), 7.06(m, 2H, orto-Ph), 7.25-7.30 (m, 3H, Ph), 9.45(s, 1H, CHO); ^{13}C NMR 150.8 MHz, $CDCl_3$): δ = 12.8 (CH_3), 18.5(CH_3), 28.7 (CH), 29.6 (CH_2), 43.8 (CH),46.3 (C), 61.8 (OCH_2), 117.8 (CN), 127.5 (CH), 127.55(CH), 128.2 (CH), 134.2 (C), 137.2 (C), 153.4(CH), 165.2 (CO), 190.5(CHO).

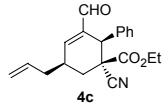
Minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.2, 3H), 1.36 (d, *J* = 7.3, 3H, Me(5)), 1.85 (dd, *J* = 14.0 and 10.8, 1H, H6'), 2.49 (dddd, *J* = 14.0 and 6.5, 1.6 and 1.1, 1H, H6"), 2.77 (m, 1H, H-5), 4.29 (ABX_3 system, 2H, OCH_2), 4.60(s, 1H H-2), 6.83(d, *J* = 2.7, 1H, H-4), 7.23(m, 2H, orto-Ph), 7.30-7.38 (m, 3H, Ph), 9.40(s, 1H, CHO); ^{13}C NMR 150.8 MHz, $CDCl_3$): δ = 13.9 (CH_3), 19.6(CH_3), 29.0 (CH), 32.8 (CH_2), 41.8 (CH),47.8 (C), 63.3 (OCH_2), 117.9 (CN), 128.3 (CH), 128.5(CH), 129.6 (CH), 136.2 (C), 138.5 (C), 153.4(CH), 166.7 (CO), 191.3(CHO).

The *relative configuration* of both the major and the minor diastereomers were determined by extensive NMR NOE studies (see page S13). The minor diastereomer was determined as the 1-epimer of **4a**. The *absolute configuration* of compound **4a** (major diastereomer) was assigned by CD spectrum (see page S15).



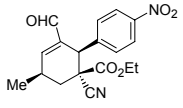
4b

4b (Table 1, entry 3) – The reaction was carried out following the general procedure to furnish the crude product [dr = 3.5:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.46 ppm, δ_{minor} 9.44 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a colourless oil by column chromatography (DCM/Et_2O = 98/2) in 35% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and >99% ee). HPLC analysis on a Chiralcel OD-H: 95/5 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 18.3 min, τ_{minor} = 19.8 min; $[\alpha]^{rt}_D$= - 329.6 (*c* = 0.76, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{19}H_{21}NO_3$: 311.15214; found: 311.1521. ^{1}H NMR (400 MHz): δ = 1.18 (t, *J* = 7.2, 3H), 1.24 (t, *J* = 7.2, 3H), 1.70-1.88 (m, 2H), 1.95 (dd, *J* = 11.2, *J* = 14.4, 1H), 2.15 (dd, *J* = 6.4, *J* = 14.4, 1H), 2.74-2.84 (m, 1H), 3.99-4.12 (m, 2H), 4.57 (s, 1H), 7.03–7.08 (m, 3H), 7.25-7.28 (m, 3H), 9.46 (s, 1H); ^{13}C NMR: δ = 11.4 (CH_3), 13.8 (CH_3), 27.3 (CH_2), 28.5 (CH_2), 36.1 (CH), 45.1 (CH), 47.3 (C), 62.8 (CH_2), 118.9 (C), 128.50 (CH), 128.53 (CH), 129.1 (CH), 135.2 (C), 138.6 (C), 153.5 (CH), 166.3 (C), 191.6 (CH).



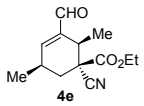
4c

4c (Table 1, entry 4) – The reaction was carried out following the general procedure to furnish the crude product [dr = 3:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.44 ppm, δ_{minor} 9.45 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a colourless oil by column chromatography (hexane/AcOEt = 9/1) in 40% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and >99% ee). HPLC analysis on a Chiralpak AD-H: 9/1 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 10.8 min, τ_{major} = 11.6 min; $[\alpha]^{rt}_D$= - 265.9 (*c* = 0.7, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{20}H_{21}NO_3$: 323.15214; found: 323.1522. ^{1}H NMR: δ = 1.24 (t, *J* = 7.2, 3H), 1.99 (dd, *J* = 11.2, *J* = 14.4, 1H), 2.11-2.17 (m, 1H), 2.42-2.56 (m, 2H), 2.91-3.01 (m, 1H), 3.98-4.12 (m, 2H), 4.56 (s, 1H), 5.24-5.30 (m, 2H), 5.87-5.99 (m, 1H), 7.03-7.08 (m, 3H), 7.25-7.28 (m, 3H), 9.44 (s, 1H); ^{13}C NMR: δ = 13.7 (CH_3), 28.6 (CH_2), 31.6 (C), 34.5 (CH), 38.2 (CH_2), 45.0 (CH), 47.3 (C), 62.8 (CH_2), 118.8 (C), 118.9 (CH_2), 128.5 (CH), 129.1 (CH), 134.0 (CH), 135.2 (C), 139.0 (C), 152.4 (CH), 166.1 (C), 191.4 (CH).



4d

4d (Table 1, entry 5) – The reaction was carried out following the general procedure to furnish the crude product [dr = 3.8:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.46 ppm, δ_{minor} 9.42 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a white solid by column chromatography (hexane/AcOEt = gradient from 9/1 to 8/2) in 34% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and 98% ee). HPLC analysis on a Chiralpak AD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 12.9 min, τ_{major} = 17.5 min; $[\alpha]^{rt}_D$= - 249.6 (*c* = 0.575, $CHCl_3$, 98% ee). HRMS: *m/z* calcd for $C_{18}H_{18}N_2O_5$: 342.12157; found: 342.1212. ^{1}H NMR (400 MHz): δ = 1.27 (t, *J* = 7.2, 3H), 1.45 (d, *J* = 7.2, 3H), 1.86 (dd, *J* = 11.2, *J* = 14.4, 1H), 2.22 (dd, *J* = 6.4, *J* = 14.4, 1H), 2.98-3.07 (m, 1H), 4.02-4.16 (m, 2H), 4.62 (s, 1H), 7.07 (s, 1H), 7.24 (d, *J* = 8.8, 2H), 8.14 (d, *J* = 8.8, 2H), 9.46 (s, 1H); ^{13}C NMR: δ = 13.8 (CH_3), 19.4 (CH_3), 29.7 (CH), 30.7 (CH_2), 44.3 (CH), 47.1 (C), 63.3 (CH_2), 118.1 (C), 123.7 (CH), 130.1 (CH), 137.5 (C), 142.7 (C), 147.9 (C), 155.3 (CH), 165.7 (C), 191.2 (CH).

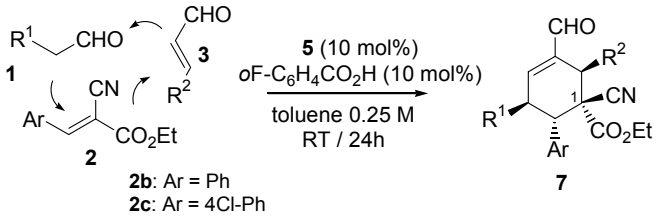


4e

4e (Table 1, entry 6) – The reaction was carried out following the general procedure to furnish the crude product [dr = 2.5:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.44 ppm, δ_{minor} 9.38 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a colourless oil by column chromatography (hexane/AcOEt = gradient from 95/5 to 85/15 – R_F^{minor}: 0.35, R_F^{major}: 0.3 in hexane/AcOEt 8/2) in 42% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and >99% ee). HPLC analysis on a Chiralpak AD-H column: 98/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 13.3 min, τ_{minor} = 13.7 min; $[\alpha]^{rt}_D$= - 25.8 (*c* = 0.875, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{13}H_{17}NO_3$: 235.12084; found: 235.1206. ^{1}H NMR: δ = 1.21 (d, *J* = 7.2, 3H), 1.27 (t, *J* = 7.2, 3H), 1.30 (d, *J* = 7.2, 3H), 1.83

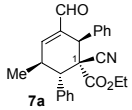
(dd, *J* = 10.4, *J* = 13.6, 1H), 2.51-2.68 (m, 2H), 3.36-3.46 (m, 1H), 4.21 (q, *J* = 7.2, 2H), 6.50 (d, *J* = 2.4, 1H), 9.38 (s, 1H); ^{13}C NMR: δ = 13.8 (CH_3), 17.7 (CH_3), 19.7 (CH_3), 29.1 (CH), 30.6 (CH), 33.1 (CH_2), 46.7 (C), 63.0 (CH_2), 118.5 (C), 141.7 (C), 152.8 (CH), 166.8 (C), 192.2 (CH).

General Procedure for the Organocatalytic Asymmetric Synthesis of Cyclohexene Carbaldehydes 7 Having Four Stereogenic Centers.



2b: Ar = Ph
2c: Ar = 4Cl-Ph

All the reactions were carried out in undistilled toluene without any precautions to exclude air. In an ordinary vial equipped with a Teflon-coated stir bar, catalyst **5** (0.04 mmol, 13.0 mg, 10 mol%) and 2-fluorobenzoic acid (0.04 mmol, 5.6 mg, 10 mol%) were dissolved in 1.6 mL of toluene. After addition of 0.8 mmol (2 equiv) of the aldehyde **1**, the solution was stirred for 10 minutes at room temperature. Then cyanoacrylate **2b** or **2c** (0.48 mmol, 1.2 equiv) and 0.4 mmol of α,β-unsaturated aldehyde **3** (1 equiv) were sequentially added. After 24 hours stirring, the crude reaction mixture was diluted with DCM (2 mL) and flushed through a short plug of silica, using DCM/Et_2O 2/1 as the eluent. Solvent was removed *in vacuo*, and the residue was purified by flash chromatography (FC) to yield the desired product **7**.

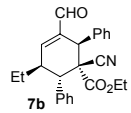


7a

(1R,2R,5S,6S)-1-Cyano-3-formyl-5-methyl-2,6-diphenyl-cyclohex-3-enecarboxylic acid ethyl ester 7a (Table 2, entry 1) **–** The reaction was carried out following the general procedure to furnish the crude product [dr = 2.6:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.48 ppm, δ_{minor} 9.52 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a white solid by column chromatography (hexane/AcOEt = gradient from 9/1 to 8/2 – R_F^{minor}: 0.35, R_F^{major}: 0.3 in hexane/AcOEt 7/3) in 52% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and >99% ee). HPLC analysis on a Chiralpak AD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 8.1 min, τ_{major} = 9.1 min; $[\alpha]^{rt}_D$= - 15.2 (*c* = 0.87, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{24}H_{23}NO_3$: 373.16779; found: 373.1678. ^{1}H NMR (600 MHz, CD_3CN): δ = 1.15 (d, *J* = 7.0, 3H, Me(5)),1.20 (t, *J* = 7.2, 3H), 3.01 (d, *J* = 10.8, 1H, H6), 3.36 (m, 1H, H-5), 4.22 (q, *J* = 7.2, 2H, OCH_2), 4.41 (s, 1H, H-2), 7.17(dd, *J* = 7.2 and 3.7, 2H, orto-Ph), 7.20(m, 1H, H-4), 7.33-7.45 (m, 8H, Ph), 9.45(s, 1H, CHO); ^{13}C NMR 150.8 MHz, CD_3CN): δ = 13.2 (CH_3), 17.6(CH_3), 34.4 (CH), 44.7 (CH), 49.0 (CH), 54.8 (C), 63.0 (OCH_2), 117.6 (CN), 128.3 (CH), 128.4(CH), 128.5 (CH), 128.6(CH), 129.6 (CH), 130.3 (CH), 137.1 (C), 137.4 (C), 137.8 (C), 155.7(CH), 166.8 (CO), 192.4(CHO).

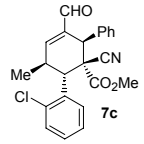
The minor diastereomer was also isolated as a single stereoisomer and as a white solid by column chromatography in 20% yield. (dr > 99:1, confirmed by relative areas of HPLC analysis, and >99% ee). HPLC analysis on a Chiralcel OD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 19.8 min, τ_{minor} = 23.9 min. $[\alpha]^{rt}_D$= - 152.4 (*c* = 0.79, $CHCl_3$, 99% ee). Crystal suitable for X-ray diffraction studies were obtained by slow evaporation of a hexane/iPrOH 9:1 v/v solution. ^{1}H NMR (600 MHz, CD_3CN): δ = 0.82 (t, *J* = 7.0, 3H), 1.15 (m, 3H, Me(5)), 3.14 (m, 2H, H6+H5), 3.56 (dq, J=10.7, 7.0, 1H, OCH_2), 3.69 (dq, J=10.7, 7.0, 1H, OCH_2), 4.53 (s, 1H, H-2), 7.17(m, 2H, orto-Ph), 7.26(bs, 1H, H-4), 7.28-7.39 (m, 6H, Ph), 7.40-7.47 (m, 2H, Ph), 9.51(s, 1H, CHO); ^{13}C NMR 150.8 MHz, CD_3CN): δ = 12.7 (CH_3), 17.0(CH_3), 36.9 (CH), 45.9 (CH), 48.0 (CH), 54.5 (C), 62.3 (OCH_2), 119.2 (CN), 128.0 (CH), 128.4(CH), 128.45 (CH), 128.7(CH), 129.3 (CH), 129.5 (CH), 133.3 (C), 137.4 (C), 138.4 (C), 155.6(CH), 165.6 (CO), 192.3(CHO).

The *relative configuration* of both the major and the minor diastereomers were determined by extensive NMR NOE studies (see page S5) and X-ray analysis (minor isomer, see page S8). The minor diastereomer was determined as the 1-epimer of **7a**. *The absolute configuration* of compound **7a** (major diastereomer) was assigned by CD spectrum (see page S10).



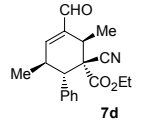
7b

7b (Table 2, entry 3) – The reaction was carried out following the general procedure to furnish the crude product [dr = 2.3:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.50 ppm, δ_{minor} 9.53 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a white solid by column chromatography (hexane/AcOEt = gradient from 9/1 to 85/15 – R_F^{minor}: 0.35, R_F^{major}: 0.3 in hexane/AcOEt 7/3) in 40% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and >99% ee). HPLC analysis on a Chiralcel OD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 16.2 min, τ_{minor} = 25.4 min; $[\alpha]^{rt}_D$= - 77.3 (*c* = 0.97, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{25}H_{25}NO_3$: 387.18344; found: 387.1832. ^{1}H NMR: δ = 1.07 (t, *J* = 7.2, 3H), 1.23 (t, *J* = 7.2, 3H), 1.39-1.50 (m, 1H), 1.66-1.76 (m, 1H), 3.08 (d, *J* = 10.8, 1H), 3.36-3.44 (m, 1H), 4.16-4.24 (m, 2H), 4.41 (s, 1H), 7.16-7.21 (m, 2H), 7.25-7.33 (m, 6H), 7.36-7.42 (m, 3H), 9.50 (s, 1H); ^{13}C NMR: δ = 11.1 (CH_3), 13.8 (CH_3), 25.3 (CH_2), 40.5 (CH), 45.3 (CH), 46.7 (CH), 54.6 (C), 62.9 (CH_2), 117.0 (C), 128.4 (CH), 128.56 (CH), 128.61 (CH), 129.47 (CH), 129.85 (CH), 136.5 (C), 137.9 (C), 153.5 (CH), 166.8 (C), 191.6 (CH).



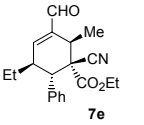
7c

7c (Table 2, entry 4) – The reaction was carried out following the general procedure to furnish the crude product [dr = 2.0:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.54 ppm, δ_{minor} 9.50 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a white solid by column chromatography (hexane/AcOEt = gradient from 9/1 to 85/15 – R_F^{major}: 0.3, R_F^{minor}: 0.25 in hexane/AcOEt 7/3) in 32% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and >99% ee). HPLC analysis on a Chiralcel OD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 10.5 min, τ_{major} = 11.7 min; $[\alpha]^{rt}_D$= - 84.1 (*c* = 0.875, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{23}H_{20}NO_3Cl$: 393.11317; found: 393.1133. ^{1}H NMR: δ = 1.23 (d, *J* = 7.2, 3H), 3.01-3.11 (m, 1H), 3.29 (s, 3H), 4.08 (d, *J* = 10.8, 1H), 4.66 (s, 1H), 7.10-7.20 (m, 4H), 7.25-7.30 (m, 1H), 7.37-7.41 (m, 4H), 7.86 (dd, *J* = 1.6, *J* = 8.0, 1H), 9.54 (s, 1H); ^{13}C NMR: δ = 17.1 (CH_3), 38.3 (CH), 39.7 (CH), 48.7 (CH), 52.7 (C), 53.8 (CH_3), 118.9 (C), 126.7 (CH), 127.6 (CH), 128.68 (CH), 128.71 (CH), 128.81 (CH), 128.96 (CH), 129.5 (CH), 135.0 (C), 136.5 (C), 136.8 (C), 137.9 (C), 154.4 (CH), 165.5 (C), 191.2 (CH).



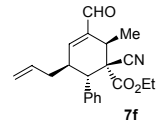
7d

7d (Table 2, entry 5) – The reaction was carried out following the general procedure to furnish the crude product [dr = >20:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.48 ppm, δ_{minor} 9.52 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a colourless liquid by column chromatography (hexane/AcOEt = gradient from 9/1 to 8/2) in 48% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and 98% ee). HPLC analysis on a Chiralcel OD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 7.7 min, τ_{minor} = 11.4 min; $[\alpha]^{rt}_D$= + 116.6 (*c* = 1.14, $CHCl_3$, 98% ee). HRMS: *m/z* calcd for $C_{19}H_{21}NO_3$: 311.15214; found: 311.1522. ^{1}H NMR: δ = 1.06 (d, *J* = 7.2, 3H), 1.17 (t, *J* = 7.2, 3H), 1.46 (d, *J* = 7.2, 3H), 2.89 (d, *J* = 10.4, 1H), 3.23-3.30 (m, 1H), 3.36-3.44 (m, 1H), 4.10-4.16 (m, 2H), 6.79 (d, *J* = 2.8, 1H), 7.29-7.37 (m, 5H), 9.48 (s, 1H); ^{13}C NMR: δ = 13.7 (CH_3), 18.67 (CH_3), 18.71 (CH_3), 38.1 (CH), 34.7 (CH), 49.2 (CH), 53.6 (C), 62.6 (CH_2), 117.6 (C), 128.4 (CH), 128.7 (CH), 129.3 (CH), 136.8 (C), 140.1 (C), 154.8 (CH), 166.8 (C), 192.4 (CH).



7e

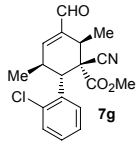
7e (Table 2, entry 6) – The reaction was carried out following the general procedure to furnish the crude product [dr = >20:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.49 ppm, δ_{minor} 9.53 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a colourless liquid by column chromatography (hexane/Et_2O = gradient from 85/15 to 75/25) in 39% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and 98% ee). HPLC analysis on a Chiralcel OD-H column: 9/1 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 8.0 min, τ_{minor} = 12.9 min; $[\alpha]^{rt}_D$= + 187.4 (*c* = 0.975, $CHCl_3$, 98% ee). HRMS: *m/z* calcd for $C_{24}H_{23}NO_3$: 373.16779; found: 373.1678. ^{1}H NMR: δ = 0.92 (t, *J* = 6.8, 3H), 1.17 (t, *J* = 6.8, 3H), 1.25-1.35 (m, 1H), 1.45 (d, *J* = 6.8, 3H), 1.56-1.66 (m, 1H), 3.05 (d, *J* = 10.4, 1H), 3.24-3.34 (m, 2H), 4.08-4.15 (m, 2H), 6.90 (d, *J* = 2.4, 1H), 7.29-7.37 (m, 5H), 9.49 (s, 1H); ^{13}C NMR: δ = 10.3 (CH_3), 13.7 (CH_3), 18.6 (CH_3), 24.8 (CH_2), 33.9 (CH), 40.6 (CH), 46.3 (CH), 53.6 (C), 62.6 (CH_2), 117.7 (C), 128.4 (CH), 128.7 (CH), 129.3 (CH), 136.8 (C), 141.0 (C), 153.1 (CH), 166.9 (C), 192.3 (CH).



7f

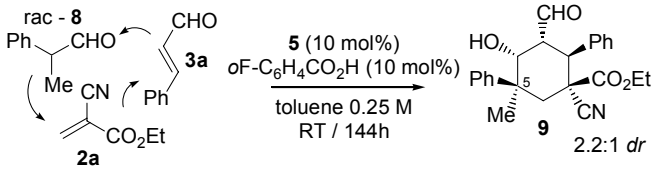
7f (Table 2, entry 7) – The reaction was carried out following the general procedure to furnish the crude product [dr = >20:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.48 ppm, δ_{minor} 9.52 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a colourless liquid by column chromatography (hexane/Et_2O = gradient from 85/15 to 75/25) in 40% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and >99% ee). HPLC analysis on a Chiralpak AD-

H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 5.9 min, τ_{major} = 6.4 min; $[\alpha]^{rt}_D$= + 166.2 (*c* = 1.04, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{21}H_{23}NO_3$: 337.16779; found: 337.1679. ^{1}H NMR: δ = 1.17 (t, *J* = 7.2, 3H), 1.44 (d, *J* = 7.2, 3H), 1.91-2.01 (m, 1H), 2.33-2.40 (m, 1H), 3.07 (d, *J* = 10.8, 1H), 3.23-3.28 (m, 1H), 3.42-3.49 (m, 1H), 4.09-4.15 (m, 2H), 4.99-5.07 (m, 1H), 5.12-5.16 (m, 1H), 5.59-5.71 (m, 1H), 6.89 (d, *J* = 2.8, 1H), 7.29-7.38 (m, 5H), 9.48 (s, 1H); ^{13}C NMR: δ = 13.7 (CH_3), 18.6 (CH_3), 34.0 (CH), 35.9 (CH_2), 39.2 (CH), 45.9 (CH), 53.5 (C), 62.6 (CH_2), 117.6 (C), 119.1 (CH_2), 128.5 (CH), 128.8 (CH), 129.4 (CH), 133.6 (CH), 136.5 (C), 144.1 (CH), 152.6 (CH), 166.9 (C), 192.2 (CH).



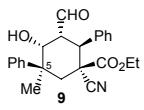
7g (Table 2, entry 8) **–** The reaction was carried out following the general procedure to furnish the crude product [dr = 7.6:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.48 ppm, δ_{minor} 9.53 ppm - s)]. The title compound (major diastereomer) was isolated as a single stereoisomer and as a colourless liquid by column chromatography (hexane/Et_2O = 8/2) in 38% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and 99% ee). HPLC analysis on a Chiralcel OD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 9.6 min, τ_{minor} = 15.0 min; $[\alpha]^{rt}_D$= + 272.1 (*c* = 0.92, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{18}H_{18}NO_3Cl$: 331.09752; found: 331.0976. ^{1}H NMR: δ = 1.04 (d, *J* = 7.2, 3H), 1.52 (d, *J* = 7.2, 3H), 3.25-3.37 (m, 2H), 3.72 (s, 3H), 3.95 (d, *J* = 10.8, 1H), 6.79 (d, *J* = 2.8, 1H), 7.26-7.34 (m, 3H), 7.47-7.50 (m, 1H), 9.48 (s, 1H); ^{13}C NMR: δ = 18.1 (CH_3), 18.4 (CH_3), 34.8 (CH), 35.5 (CH), 43.3 (CH), 52.3 (C), 53.3 (CH), 116.8 (C), 127.4 (CH), 127.9 (CH), 129.4 (CH), 130.2 (CH), 135.1 (C), 136.5 (C), 140.1 (C), 154.6 (CH), 167.5 (C), 192.3 (CH).

Organocatalytic Asymmetric Synthesis of Cyclohexane 9 Having Five Stereocenters - Two of which Quaternary by all-Carbon Substitution.



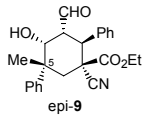
9: 36% isolated yield, 96% *ee*
epi-**9**: 19% isolated yield, 91% *ee*

In an ordinary vial equipped with a Teflon-coated stir bar, catalyst **5** (0.04 mmol, 13.0 mg, 10 mol%) and 2-fluorobenzoic acid (0.04 mmol, 5.6 mg, 10 mol%) were dissolved in 1.12 mL of toluene. After addition of 0.8 mmol (2 equiv, 106 μL) of rac-2-phenyl propanal **8**, the solution was stirred for 10 minutes at room temperature. Then ethyl 2-cyanoacrylate **2a** (0.48 mmol, 1.2 equiv, 0.48 mL of a 1M solution in toluene) and 0.4 mmol cinnamaldehyde **3a** (1 equiv, 50.2 μL) were sequentially added. After 48 hours stirring, the crude reaction mixture was diluted with DCM (2 mL) and flushed through a short plug of silica, using DCM/Et_2O 2/1 as the eluent. Solvent was removed *in vacuo* to furnish the crude product [dr = 2.2:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.47 ppm, δ_{minor} 9.44 ppm – d, in $CDCl_3$)]. Both the diastereomers were isolated as white solids by column chromatography (hexane/Et_2O = gradient from 85/15 to 6/4 – R_F^{minor}: 0.3, R_F^{major}: 0.2 in hexane/Et_2O 1/1) and subsequently further purified by semipreparative HPLC using a Luna C18(2) column (5 μm, 10x250 mm, 5 ml/min, ACN/H_2O 90:10 v/v, UV detector at 220 nm). *The relative configuration of both the diastereomers **9** was determined by extensive NMR NOE studies* (see page S16), whereas the absolute configuration was assumed in analogy with compounds **4a** and **7a**, considering an uniform reaction mechanism. In particular, the C(2) stereocenter should have the same absolute configuration as it is directly forged by the efficient shielding of the chiral fragment of the catalyst, which determines a selective engagement with the *Re* face of the iminium intermediate formed with cinnamaldehyde.



9 – The major diastereomer **9** was isolated in 36% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and 96% ee). HPLC analysis on a Chiralpak AD-H: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 7.9 min, τ_{minor} = 11.4 min; $[\alpha]^{rt}_D$= - 7.9 (*c* = 0.9, $CHCl_3$, 96% ee). HRMS: *m/z* calcd for $C_{24}H_{25}NO_4$: 391.17835; found: 391.1786. ^{1}H NMR (600 MHz, CD_3CN): δ = 1.10 (t, *J* = 7.2, 3H), 1.26 (s, 3H, Me(5)), 2.59 (d, *J* = 14.4, 1H, H-6'), 2.73 (dd, *J* = 14.4 and 1.4, 1H, H-6''), 3.59 (ddd, J= 12.8, 1.8 and 1.8, 1H, H-3), 3.80 (d, J = 5.5, 1H, OH), 4.05 (d, J=12.8, 1H, H-2), 4.09 (q, *J* = 7.2, 2H, OCH_2), 4.97 (ddd, J= 5.5, 1.8 and 1.6, 1H, H-4), 7.16(m,

2H, orto-Ph-2), 7.24-7.29 (m, 4H, Ph), 7.55 (m, 2H, Ph), 7.55 (m, 2H, ortho-Ph-5), 9.50(d, J = 1.8, 1H, CHO); ^{13}C NMR 150.8 MHz, CD_3CN): δ = 13.4 (CH_3), 30.8(CH_3), 37.5 (CH), 41.9 (CH), 42.2 (C), 51.2 (CH), 51.7 (C), 63.1 (OCH_2), 69.0 (CH), 116.6 (CN), 126.6 (CH), 126.8(CH), 128.2 (CH), 128.6 (CH), 128.8 (CH), 129.2 (CH), 136.9 (C), 144.1 (C), 168.7 7(CO), 202.5(CHO).



epi-**9**

epi-9 (5 epimer) – The minor diastereomer epi-**9** was isolated in 19% yield (dr > 99:1, confirmed by relative areas of HPLC analysis, and 91% ee). HPLC analysis on a Chiralcel OD-H: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 17.1 min, τ_{major} = 27.4 min; $[\alpha]^{rt}_D$= + 2.1 (*c* = 0.83, $CHCl_3$, 91% ee). ^{1}H NMR (600 MHz, CD_3CN): δ = 1.18 (t, *J* = 7.3, 3H), 1.67 (s, 3H, Me(5)), 2.53 (dd, *J* = 13.7 and 1.5, 1H, H-6″), 2.90 (d, J = 4.4, 1H, OH), 2.92 (d, *J* = 13.7, 1H, H-6′), 3.67 (ddd, J= 12.8, 2.0 and 1.9, 1H, H-3), 4.09 (d, J=12.8, 1H, H-2), 4.19 (m, 2H, OCH_2), 4.71 (ddd, J = 4.8, 2.0 and 1.4, 1H, H-4), 7.28(m, 2H, Ph), 7.33-7.45 (m, 8H, Ph), 9.45(d, J = 1.9, 1H, CHO); ^{13}C NMR 150.8 MHz, CD_3CN): δ = 13.4 (CH_3), 26.1(CH_3), 36.8 (CH), 41.0 (CH), 42.7 (C), 50.9 (CH), 51.6 (C), 63.4 (OCH_2), 72.0 (CH), 119.5 (CN), 125.7 (CH), 126.7(CH), 128.4 (CH), 128.7 (CH), 128.9 (CH), 129.4 (CH), 137.3 (C), 147.0 (C), 169.0 (CO), 202.1(CHO).

Summary and Outlook

The discovery of truly efficient methods of obtaining chiral compounds is a substantial challenge for synthetic chemists. Despite the importance and flexibility of asymmetric synthesis, companies prefer the chiral pool strategy because newer methods, being less established, are perceived as requiring more time to be fully developed and turned into robust chemistry.

Organocatalysis is acknowledged as fairly robust chemistry; it does not require distilled solvents nor inert atmosphere, the catalyst are generally non toxic and easily available and, recently, scale-up and low catalyst loading are being studied and developed. Nevertheless, the trend imposed by companies has confined research on organocatalysis –and asymmetric synthesis in general– to the basic research developed in Academia. Hopefully new and exciting results will provide good reasons for using organocatalysis in industry, beside the few processes already carried out.

We have seen, in the past chapters, how aldehydes and β-ketoesters can be easily functionalized giving new insights. Then, speculations on the mechanism provided clues to develop a general catalyst salt for the activation of unsaturated ketones. Eventually, the combination of various activation concepts allowed the synthesis of important and complex products.

This research demonstrates the versatility and potentiality of aminocatalysis. Obviously, it is just a small piece in the jigsaw puzzle of Science; hopefully, once it will be more complete, we will have a more definite and general view and nowadays research will explicitly unveil its impact on society.

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