Alma Mater Studiorum – Università di Bologna

NEW ORGANOCATALYTIC ASYMMETRIC STRATEGIES:

SIMPLE CATALYSTS FOR COMPLEX MOLECULES

DOTTORATO DI RICERCA IN Scienze Chimiche
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Art is never finished, only abandoned.

Leonardo Da Vinci

Contents

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, under the direction of Prof. Giuseppe Bartoli and the supervision of Dott. Paolo Melchiorre, PhD. A fruitful part of the PhD research was performed at the Max-Planck Institut für kohlenforschung, Mülheim an der Ruhr (Germany), under the supervision of Prof. Benjamin List.

In the following pages, an overview of *Enantioselective Aminocatalysis*, the main topic of my PhD research, will be presented. Starting from the historical background in which asymmetric aminocatalysis developed, we will try to give an idea of the features that make it so appealing for synthetic organic chemists, of its enormous potentiality and its applicability in a vast range of chemical transformations.

The thesis, after a brief introduction to the concept of *chirality* and to the state of art of asymmetric aminocatalysis, presents three main sections.
In particular, we will show our efforts in the extension and potentiality of aminocatalysis, reporting our contribution to the synthetically useful *Mannich reaction* (Chapter 3). The second part will be the individuation of a *new primary amine bifunctional catalyst*, to solve the challenging problem of generate adjacent quaternary and tertiary stereogenic centers with high stereocontrol (Chapter 4). Finally, we will have a look in the recently developed *organocascade reactions*, an useful tool for achieving, through simple catalysts, molecular complexity in a one-pot operation (Chapter 5).

1

CHIRALITY AND ASYMMETRIC SYNTHESIS

The interconnection between several scientific disciplines, as well as their application and expression in everyday life, is nowadays unmistakable. The concept of *chirality* belongs to this constructive interpenetration of ideas and perspectives. First of all, it is easily perceived in the observable world – conch shells, shoes, gloves; moreover, it is a common concept not only between different disciplinary scientific communities but also among philosophic and humanist culture.

In extremely simple terms, *chirality* is the 'left-handed' or 'right-handed' property of objects that are mirror imagines of each other. The word derives from the Greek *kheir* that means 'hand', so *chirality* means 'handedness' and was apparently coined by Lord Kelvin in 1904, during a lecture in which he stated: "*I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself.*"[1]

Chiral molecules were first discovered in 1848 by Louis Pasteur during his crystallographic studies when he realized that a crystalline deposit formed on wine casks during fermentation contain equal amounts of left- and right-handed crystals of sodium ammonium tartrate. After separating them, he showed the two forms polarized light differently (one to the left and the other to the right).[2]

Starting from a geometrical and spatial concept of chirality, this idea is currently well-known in mathematics, physics and chemistry. Concerning this last discipline the notion of chirality has a fundamental role both in natural compound scaffolds and in the man-made ones. The chemistry of life selects for specific versions of chiral compounds, choosing to use only left-handed forms of amino acids and right-handed forms of sugars, a phenomenon called homochirality.[3] At the same time, chemists' efforts are devoted to synthesize chiral molecules, being the appropriate three dimensional structure a fundamental feature for the properties and functions of a molecule, especially in the perspective of creating synthetic fragments with specific properties, for example medicinal or physical ones.

Chiral molecules are already exploited by pharmaceutical companies, but despite the explosive growth in the field of asymmetric synthesis -and, in particular of asymmetric catalysis- approximately 50% of the drugs launched contain no stereochemical elements, whereas the remaining 50% have at least one element of chirality.[4] However, during the last years there is a new tendency towards the development of synthetic strategies directly leading to a single enantiomer rather than to the isolation of the therapeutically more active form of a drug from the existing racemic drug mixture. Clearly, the additional cost of producing a single enantiomer is almost always lower than the development work which is needed to elucidate the toxicological and pharmacokinetic profile of the unwanted enantiomer (distomer) as well.[4] Considering the importance of chiral compounds is evident that the organic chemists community is moving towards the development of new strategies devoted to the achievement of enantiopure molecules. The only method to purchase this goal had been for long time the resolution of racemates; today there is a variety of methods based on transformations or derivation of prochiral precursors essentially by using biochemical or biological techniques, like enzymes, cell cultures, microorganisms. The efficiency of such methods is

very high but quite limited in terms of scope; on the other hand the enormous versatility of organic synthesis led to a wide range of stereoselective transformations that enable a multiplicity of chiral compounds. However, the most used mode of achieving enantiopure molecules for the pharmaceutical industry derives from the functionalization of chiral pool, using nature as source of synthons. The commercial availability of such building blocks is the major reason for the success of the chiral pool strategy, much more than its intrinsic power, which is quite limited.

Over the past few decades asymmetric synthesis, the ability of controlling the three dimensional structure of the molecular architectures, has revolutionized chemistry. The chiral auxiliary-controlled asymmetric reactions have been extensively studied and have reached a high level of sophistication.[5] The cleavage of the chiral auxiliary from the reaction product is just as important as the asymmetric reaction itself and, therefore, should always be considered during the synthetic design. In this perspective it is not surprising that in the last years the panorama of asymmetric synthesis is dominated by asymmetric catalysis. The control of a chemical transformation by a small amount of chiral synthetic catalyst is considered as the most attractive, permitting to yield both naturally occurring and non-naturally occurring chiral products with high efficiency, in an economically more appealing and environmentally friendlier way.[6]

The extraordinary knowledge accumulated in the field of asymmetric catalysis, and the consequent development of new concepts and methods make this discipline a powerful strategy for the creation of enantiomerically enriched products. Its actual maturity is undoubtedly related to the enormous progresses made in the field of metal-catalyzed transformations; nevertheless the outstanding growth of the "adolescent" organocatalysis – the use of small organic molecules to accelerate chemical transformations- in the past decade

greatly contributed to the affirmation of asymmetric catalysis as the most appealing strategy to achieve enantiopure compounds.

1.R References

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[2] L. Pasteur, *La dissymétrie moléculaire*, Œuvres de Pasteur, Vol. 1, Masson, Paris, **1922**, 21.

[3] *Chirality & Bioactivity I.: Pharmacology*, Leffingwell Reports, Vol. 3 (N. 1), **2003**.

[4] V. Farina, J. T. Reeves, C. H. Senanayake, J. J. Song, *Chem. Rev.* **2006**, *1*, 753.

[5] J. Seyden-Penne, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis* J. Wiley: New York, **1995**.

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2

ASYMMETRIC ORGANOCATALYSIS

*"You might ask: what's in a name? But consider the success of the terms nanotechnology and diversity-oriented synthesis at globally shifting the visibility and perception of areas of research. The term **organocatalysis** provided a strong identity and helped to unify a fledgling field, as well as attracting the attention of the broader chemical synthesis community."* [1]

With this statement, D.W.C. MacMillan, a leading light in the field, furnished one the reasons –together with its intrinsic potential and applicability and its clearly identifiable advantages- of the incredible explosion in the number of publications and in the research groups working on organocatalysis in the past decade. It is, in fact, a relatively new discipline, although today is widely accepted that organocatalysis is one of the main branches of enantioselective catalysis (together with the previously established enzymatic and organometallic catalysis) and it is considered as a powerful and reliable tool for organic chemists.

The first evidences of an organocatalyzed-reaction date back to early 1970s when the pioneering research by Hajos, Parrish, Eder, Sauer and Wiechert, showed the ability of a simple amino acid – proline - to act as enantioselective catalyst for the intramolecular aldol cyclization of a triketone.[2] Considering that, it is today surprising to notice how long organocatalysis was unveiled and unexploited, indeed - apart from few sporadic publications- it is only in 2000 with two landmark reports on chiral secondary amine catalysis,

one by List, Lerner and Barbas[3] and the other by MacMillan and co-workers,[4] that the chemical community hails the naissance of a new concept and field of exploration.

This time the researchers immediately realized the enormous advantages of the new catalytic approach: the metal-free organocatalysts are non-toxic and usually less expensive when compared to the organometallic ones. Moreover, their purely organic nature make them generally insensitive to oxygen and moisture in the atmosphere, overcoming the need for special reaction vessels, storage containers and dry reagents and solvents. The primary beneficial consequence of these characteristics is translated into the great operational simplicity of organocatalysis and in its high reproducibility. Withal, being a wide variety of organic fragments –such as amino acids and carbohydrates –available from biological sources as single enantiomers, simple organocatalysts are usually cheap and easily to prepare in large quantities. Moreover, often both enantiomers of catalyst are available. After a short period of time, following the two seminal reports of 2000, the explosion of interest in organocatalysis, the increased knowledge of the area and the big competition between several research groups worldwide developed the field in such an exceptional way that only after a decade, organocatalysis has reached incredible levels of sophistication, playing nowadays a central role in the scenario of enantioselective catalysis,[5-8] delivering new generic modes of activation and induction of substrates, both complementary and opposite to the metal and biological approaches. We can surely affirm that the advent of organocatalysis brought the prospect of a new mode of catalysis, with the potential for saving in cost, time and energy, an easier experimental procedure and reductions in chemical waste.[1]

Lots of explorations, studies, discussions are - of course- still needed for this "young" discipline, not only from the critics' point of view that see in the low turnover numbers of the organocatalysts the major weak point for the industrial application of organocatalysis, but also in the discovery of new

reactivities and in the development of computation models that can help in the design of new organocatalysts.

Despite these considerations we can assert that not only the modern asymmetric catalysis considers catalysis mediated by organic molecules as one of its most powerful devices, but also the modern organic synthesis directed to the design of enantiopure complex molecules, numbers organocatalysis as a convenient strategy among its toolbox.[9]

Most of the organocatalysts – but not all- can be broadly classified as Lewis bases, Lewis acids, Brønsted bases and Brønsted acids (Scheme 1).[8,10]

Lewis Base Catalysis   Lewis Acid Catalysis

Brønsted Base Catalysis   Brønsted Acid Catalysis
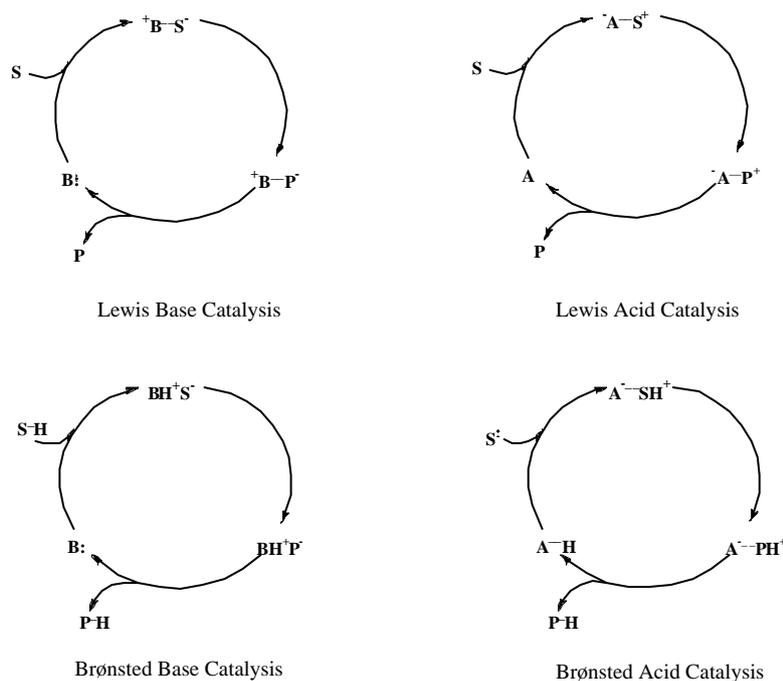
Scheme 1. Organocatalytic cycles

In view of that, Lewis base catalysis uses a nucleophilic addition of the catalyst (B:) to the substrate (S) to initiate the cycle, leading to a resulting complex that undergoes a reaction, delivering the product (P) and the catalyst for further turnovers.

A similar pathway of activation is shown by Lewis acid catalysts (A) towards a nucleophilic substrate (S:). On the other hand, Brønsted base and acid catalytic cycles are initiated via a (partial) deprotonation or protonation, respectively.

In the following chapters our attention will be focused on Lewis base catalysis, in particular on **aminocatalysis**, based on the use of chiral amines for asymmetric enantioselective transformations.

## 2.1 Secondary Amine Catalysis (Lewis base catalysis)

2.1.1 Enamine & Iminium Ion Strategies

As mentioned afore, the conventional date of birth of organocatalysis is related to the appearance in 2000 of two papers in which two new modes of activation of carbonyl compounds are reported. The first, by List, Lerner and Barbas, reporting the asymmetric intermolecular aldol reaction between ketones and unmodified aldehydes catalyzed by proline **I**, provided the basis for the development of *enamine*-based asymmetric *catalysis* (Scheme 2).[3]
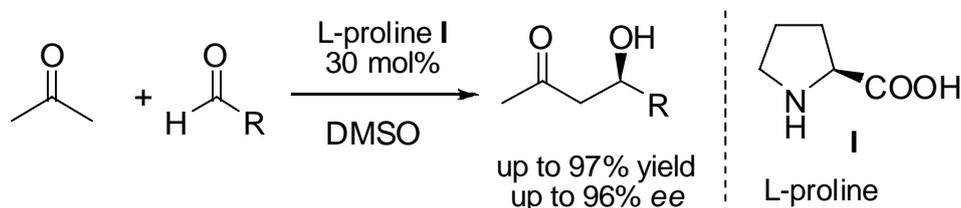
Scheme 2. Proline-catalyzed *inter*molecular aldol reaction between acetone (donor) and aldehydes (acceptors)

Undoubtedly, their discovery tapped into two different yet related areas of chemistry: organic and biochemistry.[4] We already said that the Hajos-Parrish-Eder-Sauer-Wiechert reaction, an intramolecular cyclization aldolation catalyzed by proline, remained unexplored for 30 years. At that time the authors interpreted their result as *" a simplified model of a biological system in which (S)-proline plays the role of an enzyme"* [2d] (Scheme 3).
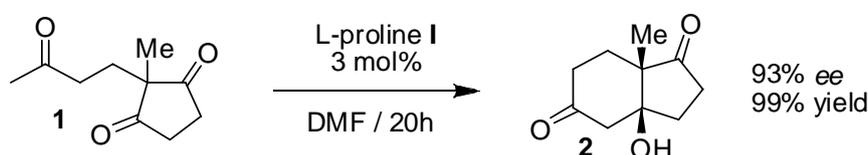

Scheme 3. The Hajos-Parrish-Eder-Sauer-Wiechert reaction

In one of the two proposed mechanisms, they hypothesized – already 40 years ago! - the formation of an enamine intermediate as the nucleophilic substrate.[11] The other useful study for this finding dates to 1990s, when the research group of Lerner and Barbas, during their explorations in the aldolase enzymes, discovered that the aldolase antibobody 38C2 was able to catalyse aldol cyclodehydration reactions, included the Hajos-Parrish-Eder-Sauer-Wiechert reaction.[12] The mechanistic analogy between proline- and enzyme-catalyzed aldol reactions, based on a common enamine intermediate, was suddenly clear, confirming the role of Nature as great source of inspiration for men.

Soon after enamine catalysis' paper, MacMillan presented the first asymmetric amine-catalyzed Diels-Alder reaction, demonstrating the possibility of using a designed imidazolidinone catalyst **II** in the activation of α,β-

unsaturated aldehydes through a covalent intermediate based on an iminium ion (Scheme 4).[4]
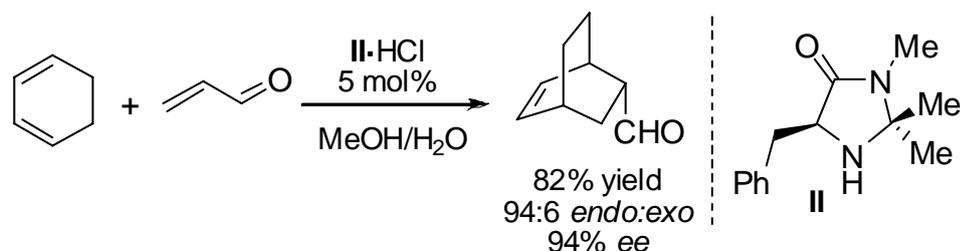
Scheme 4. Imidazolidinone **II-** catalyzed asymmetric Diels-Alder reaction

With this report, introducing a totally new activation concept - *iminium ion catalysis*- the foundation for the development of a wide range of asymmetric transformations of unsaturated carbonyl compounds was laid.

Both activation modes show a covalent active intermediate generated by the reversible condensation of the catalyst (a chiral cyclic amine) and a carbonyl group. Mechanistically, they mimic the activation of carbonyl compounds by Lewis acids, in which the reversible binding of the Lewis acid to isolated or conjugated π systems results in a redistribution of the electronic density towards the positively charged metal center, accountable for the rate acceleration of the process. The formation of a positively charged iminium ion covalent intermediate, with a resulting redistribution of electrons in π orbitals (similar to Lewis acid activation), has as consequence a lowering in the energy of the lowest unoccupied molecular orbital (LUMO). For conjugated π systems this is translated in an enhancement of the electrophilicity of β-carbon that facilitate nucleophilic additions, including Michael additions and pericyclic reactions (Scheme 5a).
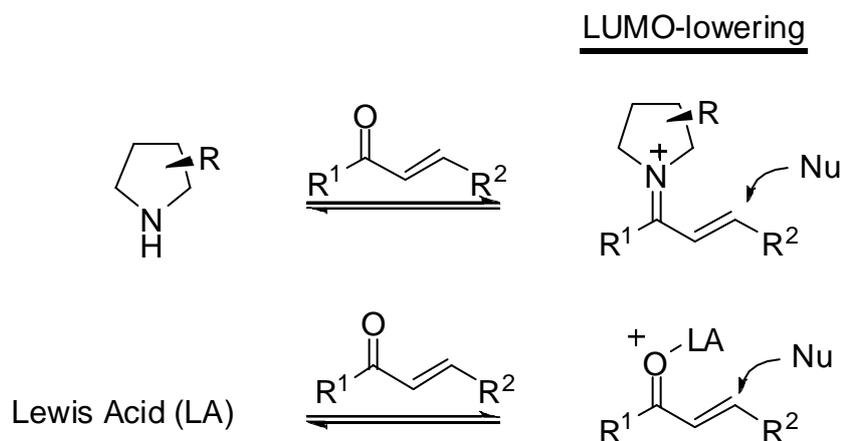
LUMO-lowering

Scheme 5a. Comparing carbonyl compounds activation by Lewis acids and by aminocatalysis; Nu= nucleophiles

For isolated π systems, the lowering of the LUMO energy increases the α-proton acidity, inducing a fast deprotonation which leads to the generation of an enamine intermediate, a nucleophilic enolate equivalent. As consequence of the electronic rearrangement, a raising of the energy of the highest occupied molecular orbital (HOMO) occurs, with the activation of the starting carbonyl compound towards electrophiles (Scheme 5b).

LUMO-lowering   HOMO-raising
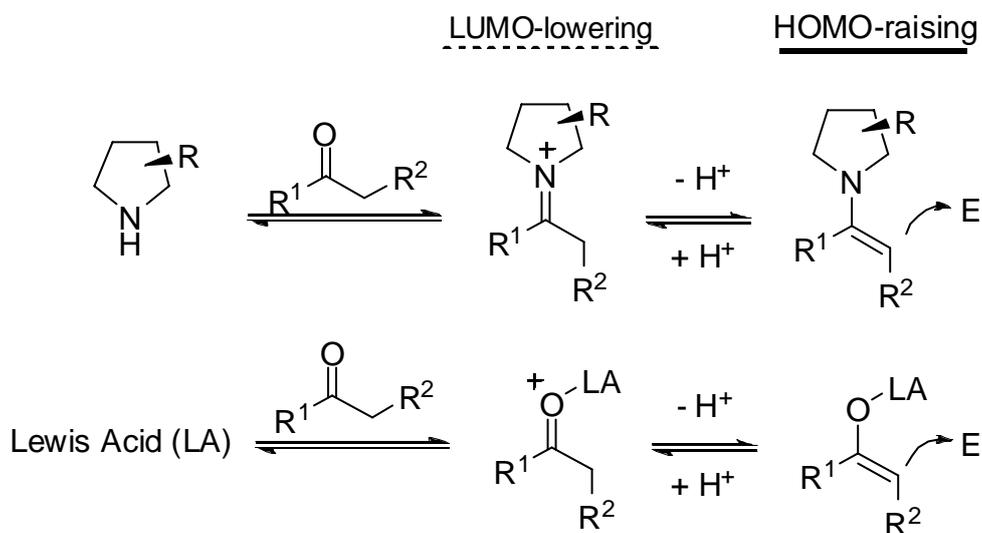
Scheme 5b. Comparing carbonyl compounds activation by Lewis acids and by aminocatalysis; E = electrophiles

The described activation pathways still dominate the scene of asymmetric aminocatalysis; after the first reports of 2000, lots of papers appeared reporting a vast number of α-functionalizations of aldehydes and ketones *via* HOMO-raising activation path (*enamine catalysis*) and of several β-functionalisations of unsaturated carbonyl compounds trough *iminium ion catalysis*.

A second publication by List in 2000, had undoubtedly a big impact on the development of the enamine catalysis strategy. In this paper List reported the first, direct, catalytic and asymmetric Mannich reaction between an aldehyde, *p*-anisidine and a ketone, catalyzed by proline.[13] The proved efficiency of the organocatalytic strategy of using electrophiles other than aldehydes, represents a cornestore in the area of *proline catalysis*. As it is easily to observe, the aminocatalysis panorama was at first dominated by this naturally available catalyst but soon several new proline-based catalysts were designed in order to improve its efficiency. In early 2005, Jørgensen's research group published the organocatalytic electrophilic α-sulfenylation reaction of aldehydes,[14] presenting to the scientific community a new class of secondary amine organocatalysts (Scheme 6). Diphenyl prolinol **IIIb** was already used by Enders and co-workers[15] as chiral auxiliary and by Corey as a ligand in Lewis acid reactions.[16] As catalyst, it often showed high stereocontrol[17] although achieving poor yields; the larger size of its substituents compared with **III**, which often showed good activity but low levels of stereocontrol,[15-16] was considered the reason for its low efficiency.
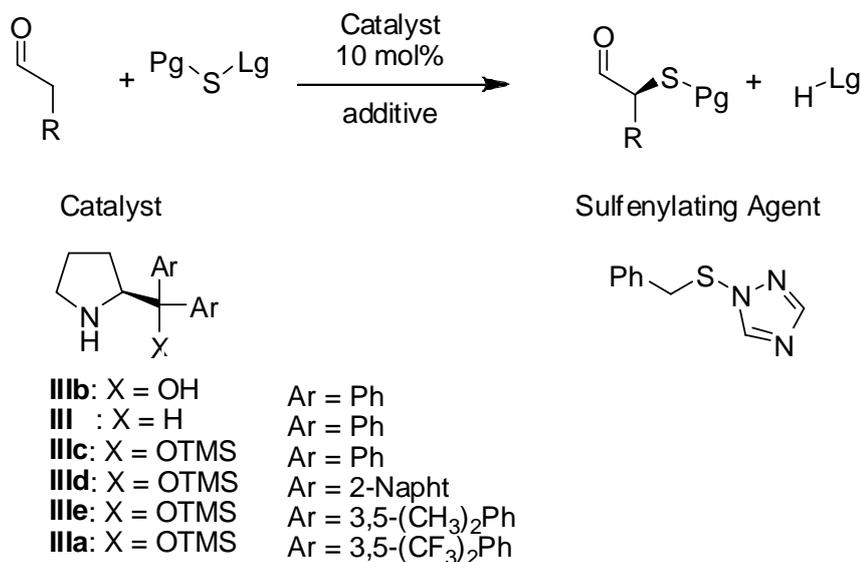
Scheme 6. The amino catalyzed sulfenylation of aldehydes; Lg = leaving group; Pg= protecting group

However, a new explanation for the insufficient activity of **IIIb** was furnished by Jørgensen and co-workers: the presence of the free hydroxyl group, through the formation of the unreactive hemiaminal specie (Figure 1).[17]
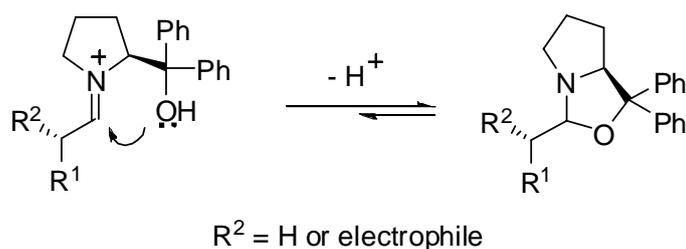

R^2 = H or electrophile

Figure 1. Hemiaminal equilibrium

A simple trimethylsilyl (TMS) *O*-protection of the inactive prolinol **IIIb** produced the catalyst **IIIc** and, after a small optimization of the aromatic moiety - with the introduction of 3,5-bis-trifluoromethyl substituents- the catalyst **IIIa**. The silyl protected diarylprolinols catalysts immediately took their place among the "privileged" organocatalysts , together with proline and - as we will discuss later- with MacMillan's imidazolidones.

The employment of the new catalysts for enantioselective transformations led to outstanding enantiomeric excesses and to a consistent absolute configuration in different reactions. The structures of the enamine intermediate have been intensively studied to establish the origin of the stereoinduction observed. It is generally accepted that the *E-anti* enamine intermediate is the most stable conformer, in agreement with a transition state which minimizes the steric interactions between the bulky substituents on the pyrrolidine catalyst and the reactive carbon atom.[18]
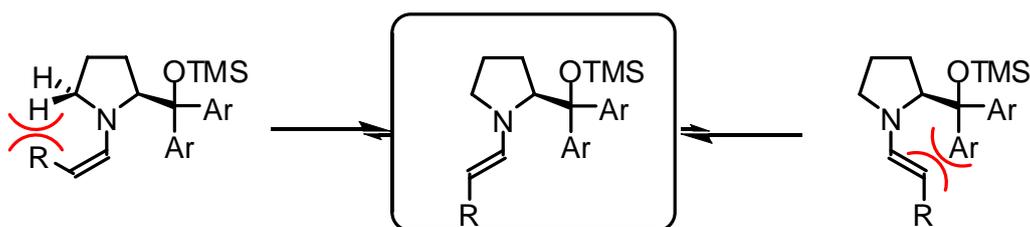

Figure 2. Possible enamine intermediates

The highly asymmetric induction achieved is explained by the excellent shielding of the *Si* face of the enamine, directing – through a steric control- the electrophile approach from below, on the *Re*-exposed face. Remarkably, the proposed model does not rely upon the structure of the electrophile,

opening the way for the potential employment of these catalysts in reactions other than the α-sulfenylation transformation.[19] This suggestion immediately found his realization in several asymmetric substitution reactions and nucleophilic additions, for example conjugate additions,[20] Mannich reactions,[20a] C-N (α-amination[20a] and oxyamination[21]), C-C [22] and C-O bond-forming reactions,[23] as well α-halogenation and selenenylation reactions[24] (Figure 3).
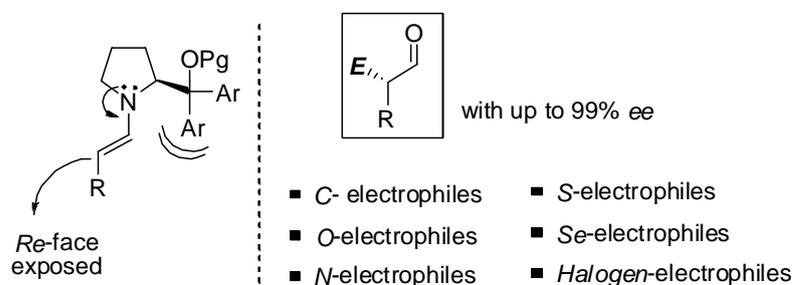

Figure 3. Enantioselectivity in the diarylprolinol ethers-catalyzed reactions via enamine activation.ossible enamine intermediates

It is interesting to note that the '*steric shielding directing approach*', responsible for the high stereocontrol achieved by using this class of catalysts, is also accountable for the inversion of the absolute configuration of the products obtained in presence of proline - and its hydrogen bond-containing catalyst derivatives- having the same absolute stereochemistry. Extensive mechanistic investigations of proline-catalyzed reactions showed in fact, that a specific hydrogen-bonding interaction between the carboxylic acid moiety and the electrophile, not only stabilizes the transition state of the reaction and provides electrophilic activation, but determines the stereoselectivity of the process by directing the electrophile approach from the upper face of the enamine intermediate (Figure 4).
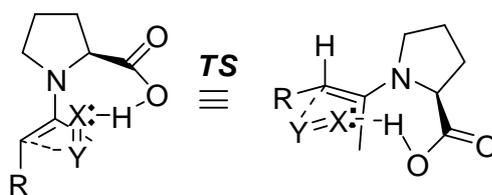
Figure 4. Bifunctional mode of proline catalysis (Y=X: electrophilic component, X: heteroatom)

This bifunctional activation mode of proline catalysis is effective with electrophilic substrates with lone pairs of electrons and can be extended also to other proline-based catalysts, specifically designed for improving the solubility or enhancing the acidity of the directing acid proton.

The affirmation of diaryl prolinol silyl ethers as general catalysts for the functionalization of carbonyl compounds is further highlighted by the finding that they turned out to be effective also in iminium ion catalysis. Several kind of asymmetric conjugated additions, based on C-,[25] N-,[26] O-,[27] S-,[28] and P-based nucleophiles to α,β- unsaturated aldehydes were reported, achieving high enantiomeric excesses (Figure 5).
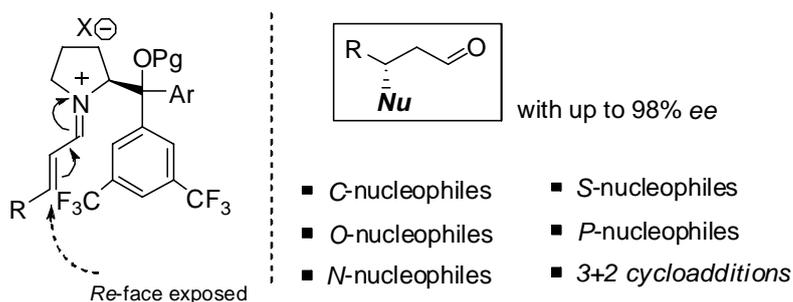

Figure 5. Enantioselectivity in the diarylprolinol ethers-catalyzed reactions via iminium ion activation

As mentioned before, the first example of *iminium ion activation* was reported by MacMillan's group as an enantioselective Diels-Alder reaction between dienes and α,β-unsaturated aldehydes as dienophiles. MacMillan and co-workers, after preliminary experimental findings and computational studies, *designed* the imidazolidinone-based catalyst **II**. As indicated from computational models, the catalyst-activated iminium ion intermediate predominantly exists in the (*E*)-conformation, to minimize non-bonding interactions between the substrate double bond and the *gem*-dimethyl substituents of the catalyst. This leads to high levels of iminium geometry control, while the benzyl group of the imidazolidinone framework effectively shield the iminium ion *Si*-face, achieving a high selective π-facial discrimination required for an excellent stereocontrol (Figure 6).
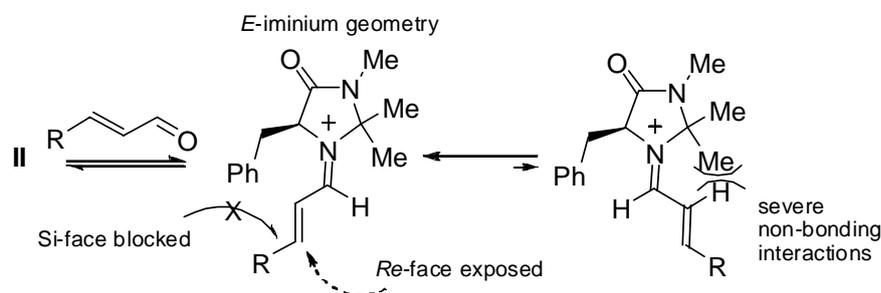
Figure 6. Iminium geometry control and π-facial shielding by imidazolidinone catalyst **II**

After its first employment in the Diels-Alder reaction e in [3+2] cycloaddition,[29] catalyst **II** and derivatives were successfully used for organocatalytic addition of pyrroles,[30] indole and furan derivatives[31] to unsaturated aldehydes and for iminium ion activation of unsaturated ketones.[32] Notably, the efficiency of imidazolidinone family catalysts was further expanded with their fruitfully use in enamine catalysis, with an elegant enantioselective chlorination of aldehydes[33] (almost simultaneous with that reported by Jørgensen and co-

workers),[34] an asymmetric enamine-aldol reaction,[35] followed by the highly challenging fluorination reaction.[36,37]

At the end of 2004, thanks, above all, to contributions from MacMillan's imidazolidinones and later, from the research of Jørgensen's group, iminium ion catalysis became an established and powerful method for the β-functionalization of unsaturated carbonyl compounds.

2.1.2 Organocascade strategy

With the fundamental functionalizations of carbonyl compounds and the asymmetric incorporation of most non-metallic elements outlined above, organocatalysis started moving in several directions: from one side the continue work on known transformations, searching for better selectivity, more efficient designed catalysts and theoretical mechanicistic studies; on the other hand new topics and challenging tasks started to attract the attention of organocatalytic chemistry's world. This represents the theoretical context in which the suitable conditions for the merging of enamine and iminium ion catalysis were set, with associated outstanding synthetic advantages.

Iminium ion and *enamine catalysis* were for long time considered two divergent and separate amino-catalytic pathways, which allowed discrete types of transformations. The awareness of the enormous potentiality and applicability of organocatalysis motivated several researchers worldwide to the study and the development of this fascinating research field, with consequent increased competition and extraordinary growth of the area. As every new field, it took some time to really understand the intrinsic power of this toolbox.

Anyway gradually the scientific community of the field started to carefully analyze the two catalytic cycles operating in these two activation pathways, foreseeing a possibility of taking advantage of them at the same time. As matter of fact, considering the catalytic cycles depicted in Figure 7, we can immediately realize that common intermediates are present.
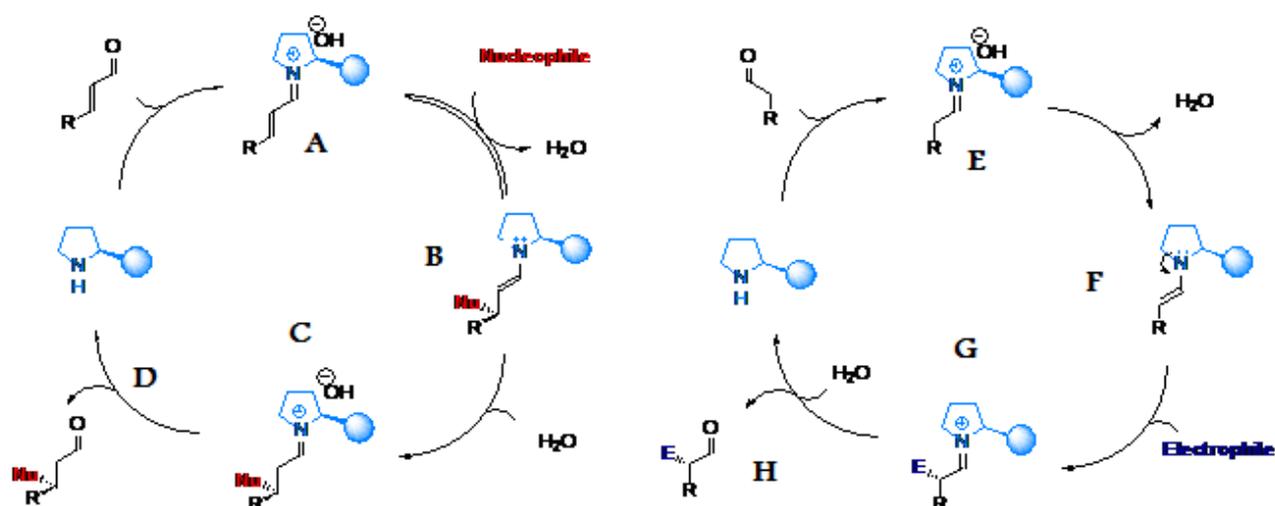

Figure 7. Iminium ion and enamine catalytic cycles

In the iminium catalysis (left), the condensation of the catalyst with an unsaturated aldehyde gives rise to the iminium ion intermediate **A** which generates an enamine intermediate **B** after reaction with a nucleophile. After its conversion to the iminium structure **C** and upon the release of the catalyst, the β-functionalized aldehyde **D** is provided. On the other hand, (Figure 7, right), the enamine intermediate **F** derives from the fast deprotonation of the previous intermediate **E**, which is formed between the condensation of the chiral amine and a saturated aldehyde. The electron rich intermediate **F** is able to react with an electrophile, generating a new iminium ion intermediate (**G**) that, after hydrolysis, furnishes the α-functionalized aldehyde **H**. At this point

two considerations needed to be highlight: as discussed before, the same catalyst is effective in the two different catalytic cycles and common intermediates are formed during the catalytic pathways. Indeed, iminium ion and enamine are opposite catalytic structures, in the sense that they provide a different reactivity, but they are yet interdependent and they consume and support each other during the catalysis. This feature led List to define them as the *Yin and Yang* of Asymmetric Aminocatalysis.[5b]

The major application of this new strategy, outlining in 2005, is an elaborate reaction sequence involving the conjugate addition of a nucleophile to α,β-unsaturated aldehydes *via* iminium ion catalysis, that furnishes a β-functionalized saturated aldehyde. This intermediate is then further activate by the catalyst evolving to an electron-rich enamine intermediate, which reacts with an electrophile with consequent simultaneously α- and β-functionalization of the starting aldehyde.

Iminium - Enamine Activation Sequence
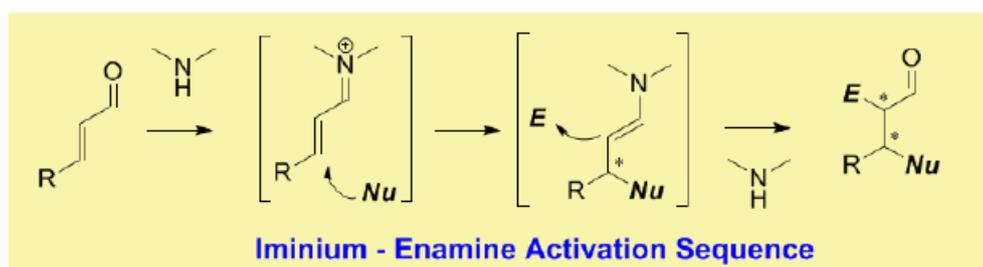
The idea of using chiral organic molecules to catalyze asymmetric domino reactions and integrating orthogonal activation modes of carbonyl compounds into more elaborate reaction sequences, led to an additional step forward to the identification of powerful and reliable strategy for the stereoselective synthesis of complex molecules[38-39] and to the development of a new concept: *Asymmetric Organocascade*. In this approach, environmentally friendly and

robust organocatalysts are used to promote domino reactions by which structurally diverse complex scaffolds are forged with high stereoselectivity in an optimal atom-economical process, starting from simple precursors and in a single operation.[38] This strategy, besides the synthetic benefits inherent to cascade reactions, as avoid time consuming and costly protection/deprotection and isolation of intermediates, has a remarkable benefit in the mathematical requirement for enantioenrichment in the second cycle, following Horeau's principle.[40]

The first examples of amino catalyzed *domino reactions* have usually been Michael additions to unsaturated carbonyl compounds followed by an *intramolecular* step, as the asymmetric Robinson annulation reported by Barbas.[41] Other fundamental contributions and extension in applicability, involving an iminium ion- enamine activation sequence, were independently reported by the groups of List, Jørgensen and MacMillan. In the following section we will discuss this kind of cascade reactions, presenting the first asymmetric organocatalyzed aziridination of enones. The following step was to extend this strategy to multicomponent reactions that involve two *intermolecular* stereoselective steps.

In 2005, almost simultaneously Jørgensen and MacMillan's groups achieved this challenging task. The former disclosed the first highly enantioselective addition of thiols to enals, combined with a α-amination reaction (Scheme 7).[28] The highly valuable products, containing two adjacent S-C and N-C stereocenters, were reduced and ciclyzated *in situ* to afford the final products in good yields with excellent diastereo- and enantioselectivities.
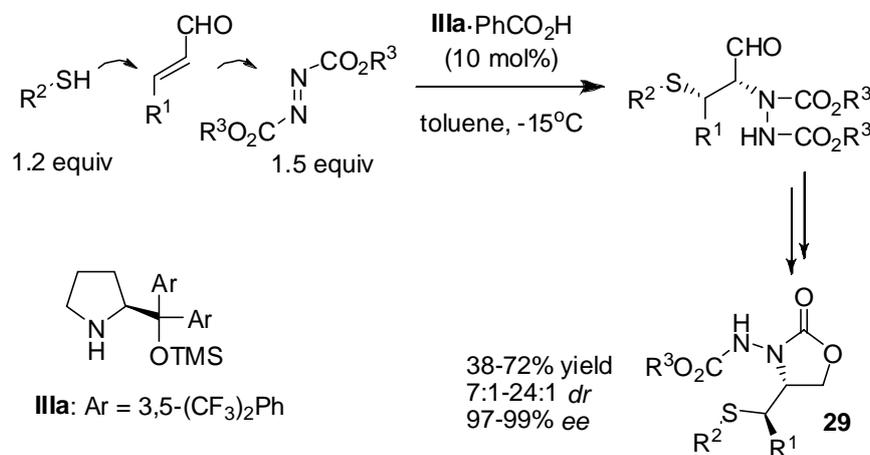
Scheme 7. Aminocatalytic sulfa-Michael addition-amination

MacMillan and co-workers applied this strategy to an enantioselective conjugate addition of different carbon-based nucleophiles, in combination with the α-chlorination (Scheme 8), by using a modified imidazolidinone **IIa**.[42]
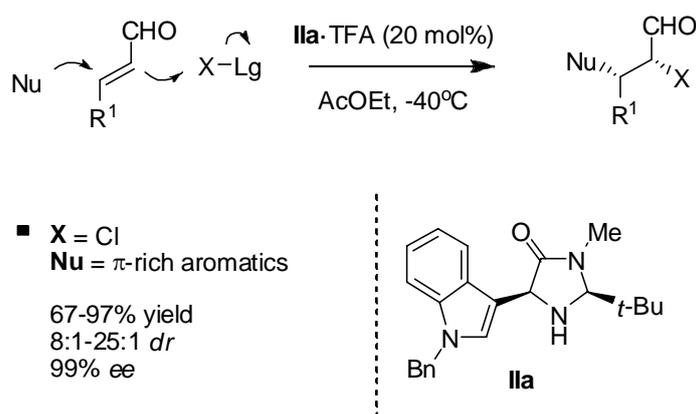
Scheme 8. Aminocatalytic conjugate addition-halogenation; Lg= leaving group

From these two examples the enormous potentiality of this approach appeared clear and multiple efforts have been made by chemists to further expand the applicability and the reliability of this strategy. In 2006 Enders and co-workers reported a triple domino reaction based on an *enamime-iminium-enamine*

sequential activation, through a Michael/Michael/aldol condensation catalyzed by O-TMS diphenyl catalyst **IIIc,** able to forge and completely control four stereocenters in a one-pot process. (Scheme 9).[43]
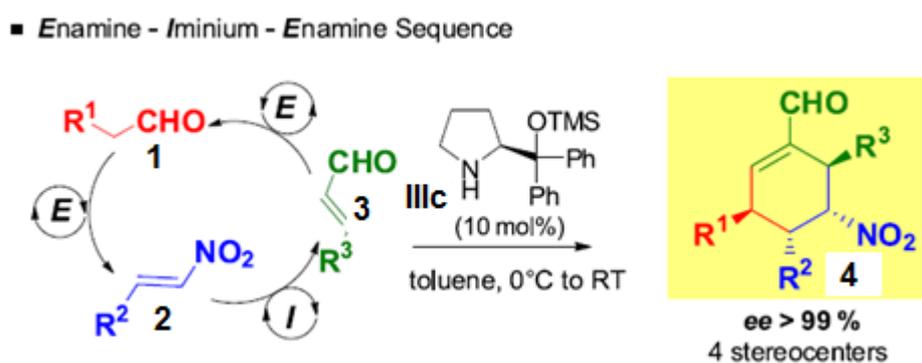
Scheme 9. Triple Organocascade

The catalytic cycle initiates with the Michael addition of the saturated aldehyde to nitroalkene, giving rise to intermediate **B**; to address this point the nitrostyrene derivatives need to intercept enamine faster than the unsaturated aldehyde does. The resulting nucleophilic intermediate, activated trough iminium ion formation, reacts with the electrophilic unsaturated aldehyde, forming an other saturated aldehydic intermediate, which is further activate by the catalyst via enamine catalysis towards an intramolecular aldol reaction affording the intermediate **C** and, after dehydration, the desired cyclohene carbaldehydes **4** with complete enantioselectivity (Scheme 10).
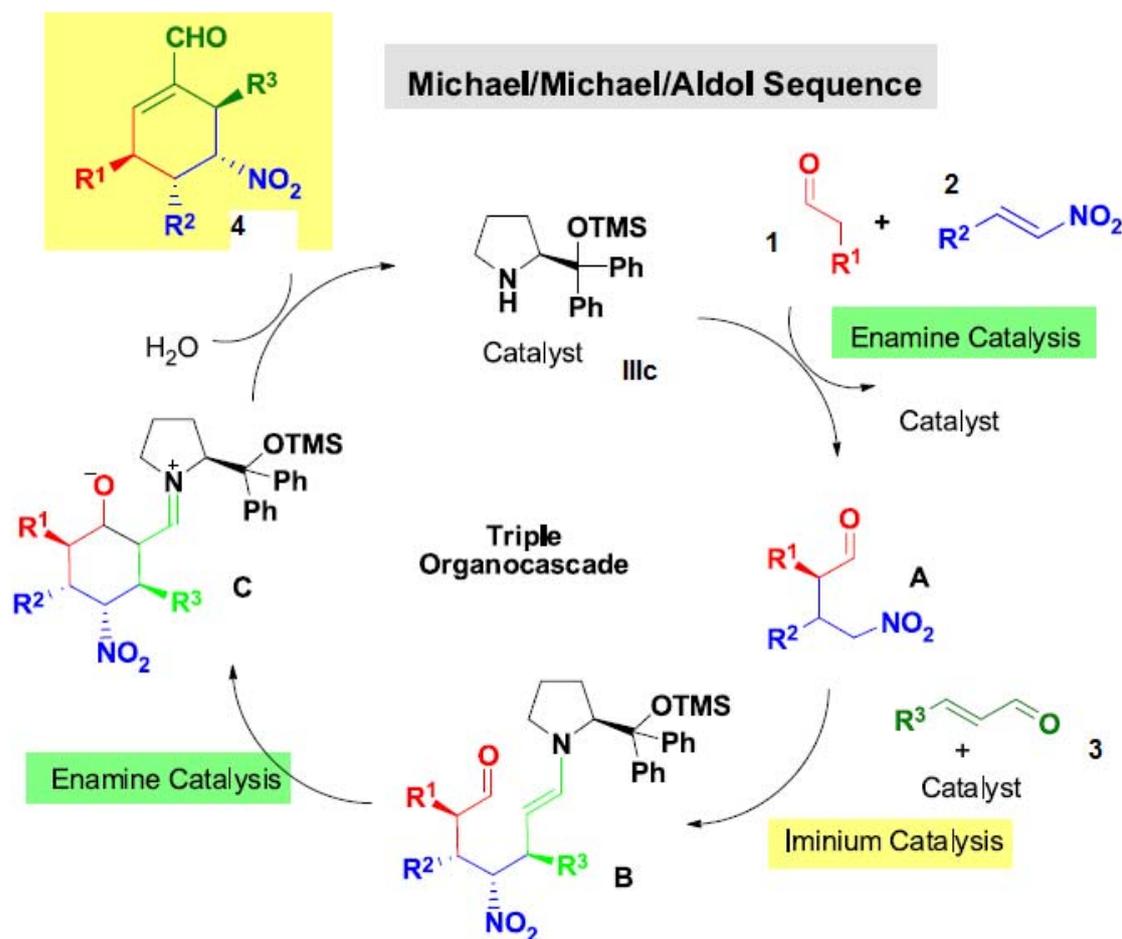
Scheme 10. The catalytic machinery of the Triple Organocascade

As shown, the sequencing of multiple catalytic transformations of a substrate provides a powerful – and nowadays- established strategy for the rapid construction of molecular complexity with incredible levels of diastereocontrol.[39] Starting from this concept several organocascade strategies have been developed and recently applied also to the synthesis of natural and pharmaceutical compounds.

2.1.3 New activation modes and strategies

The enormous interest and competition aroused by Asymmetric Organocatalysis into the scientific community and the consequent increased knowledge of the area allowed its rapid affirmation as reliable tool in synthetic chemistry and stimulated chemists' creativity to solve synthetic problems by designing new catalysts, new activation sequences, improving established asymmetric reactions and to investigate new reactivities, also by merging organocatalysis with concepts derived from other chemical contexts.

This frenetic and intense study led to the broadening of the two initially known activation modes – iminium and enamine catalysis- and to the exploration, as we will discuss later, of the use of chiral primary amines, complementing the nearly exclusive use of secondary amines in asymmetric aminocatalysis.

During the NMR spectroscopic investigations of the intermediate involved in the organocatalytic β-functionalization of α,β-unsaturated aldehydes, Jørgensen and co-workers realized that under the usual conditions used, the concentration of the expected iminium ion is so low that it could not be detected and the most abundant species in solution is the dienamine **2** (scheme 11).

Iminium ion   Dienamine
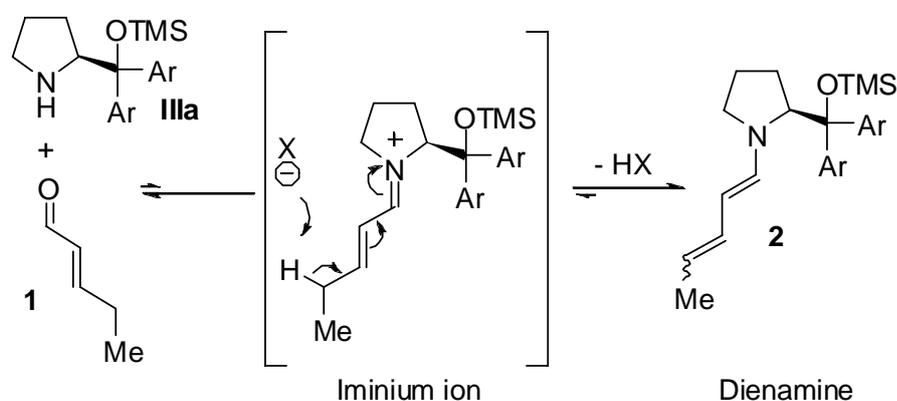
Scheme 11. HOMO activation of α,β-unsaturated aldehydes - dienamine formation.

The formation of this intermediate derived from the deprotonation in the -position of the iminium ion by the negatively charged counterion and leads to an electron-rich dienamine that can be easily functionalyzed with electrophiles. Following up on this discovery, Jørgensen's group investigated the reactivity of this new intermediate, developing the first -amination of enals and opening up a new activation pathway in asymmetric aminocatalysis.[44]
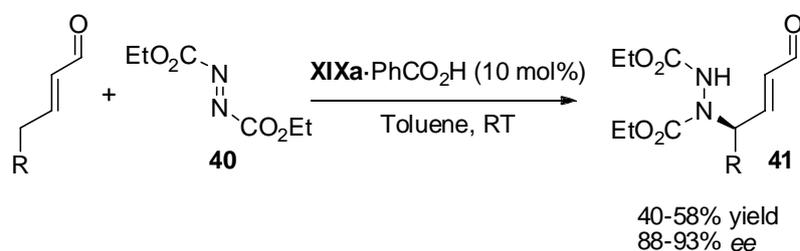
Scheme 12. Dienamine catalyzed γ-amination of α,β-unsaturated aldehydes

At this point, only few years after the first seminal reports, the "*state of art*" of Asymmetric Aminocatalysis appears as a huge matrix of different activation modes with a wide range of functionalization possibilities, although still (also nowadays) limited to carbonyl compounds. This multi-dimensional matrix was further extended with the introduction by MacMillan and Sibi of the *SOMO*-catalysis (singly occupied molecular orbital) in which organocatalysis and radical chemistry were linked. The key-step of this new activation mode is the susceptibility of an enamine intermediate to undergo selective oxidation relative to other reaction components, generating a radical cation with three π-electrons and a singly occupied molecular orbital which is activated towards nucleophilic reagents (Scheme 13).
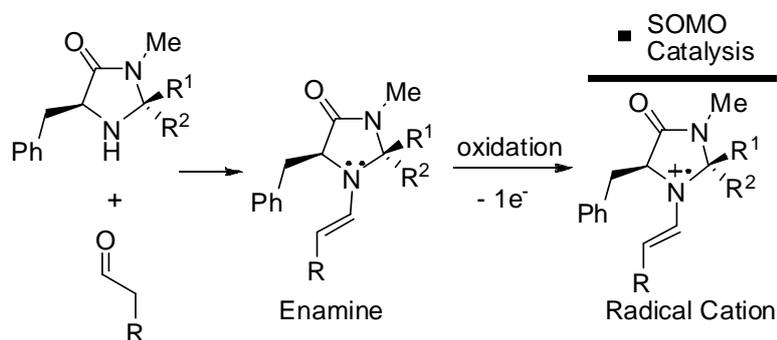
Scheme 13. The principle of SOMO catalysis

It is remarkable to note that in this case the polar reactivity of the α-carbon atom is reversed compared to classical enamine catalysis and this leads to complete different possibilities of transformations. *SOMO*-catalysis has been applied to asymmetric α-allylation, α-enolation and α-arylation of aldehydes.[45] Recently, several efforts have been made towards the elusive stereoselective α-alkylation of aldehydes and ketones.[46] The intermolecular version of this useful transformation by using traditional asymmetric organocatalytic methods have been hampered by N-alkylation of the catalyst. To address this problem, a different approach - employing photochemically generated radical reagents in contrast to the generation of the chiral radical enamine- was recently reported. The photochemically-generated radical species reacts with the classical enamine intermediate, generated by the condensation of the chiral catalyst and the aldehyde, leading to an electron-rich α-amino radical that is oxidized to an iminium ion, while the photoredox co-catalyst is regenerated. Finally, hydrolysis of the iminium ion furnishes the final α-alkylated product and regenerates the organocatalyst (Scheme 14).
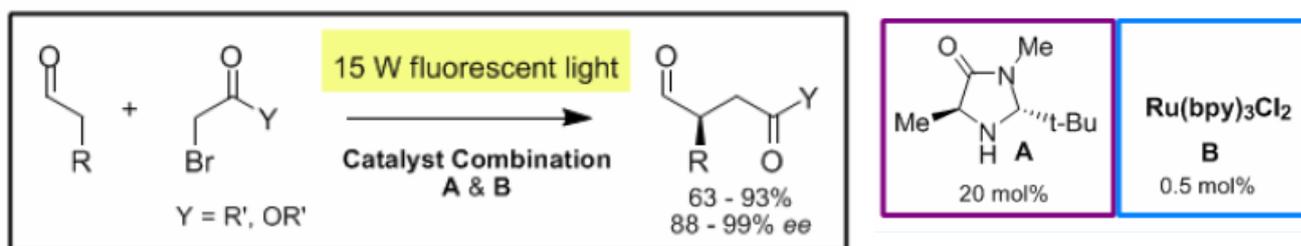
Scheme 14. Combination of photoredox and enamine catalysis for the α-alkylation reaction of aldehydes.

Considering the high complexity of the system, both the chemo- and the stereo-control of the reaction, are outstanding. Moreover, this study further illustrates the new tendency of the 'mature' organocatalysis: tapping into different chemical areas to solve more and more challenging synthetic tasks.

2.2 Summary

With this brief introduction on Asymmetric Organocatalysis a rapid 'journey' focused on the field of Aminocatalysis was accomplished, starting from the first milestones on enamine and iminium ion activation pathway, having a look into the principal α- and β-functionalizations of carbonyl compounds by the 'privileged' organocatalysts, until the design and the development of new catalysts. We will go into more depth in chapter 4, showing a new bifunctional catalyst to face problems that the 'privileged' catalyst failed to solve. Following the theoretical background developed in the years of the 'Aminocatalysis Gold Rush', we have discussed about the need of the field to further expand its power and applicability, to try to face always more difficult problematics. The intensive studies and efforts of the scientific community led to the introduction of new strategies and reactivities, like *dienamine* and *SOMO*-catalysis and to the incorporation of several

aminocatalytic sequences in a single process, giving rise to several organocascade approaches; we will see more in details some examples in the next pages. Although the rapid development of the area (only ten years!) thanks to its multiple advantages over the other catalytic methods, organocatalysis is actually considered one of the most powerful tool in the synthetic paradigm that organic chemists can use to forge new chemical structures. Obviously, lot of work and studies are still needed and while some challenges have been only recently overcame – for example efficient activation of encumbered substrates like ketones[47] and α-substituted aldehydes- it is in no doubt that the continue curiosity of scientific community will submit organocatalysis always to new matches.
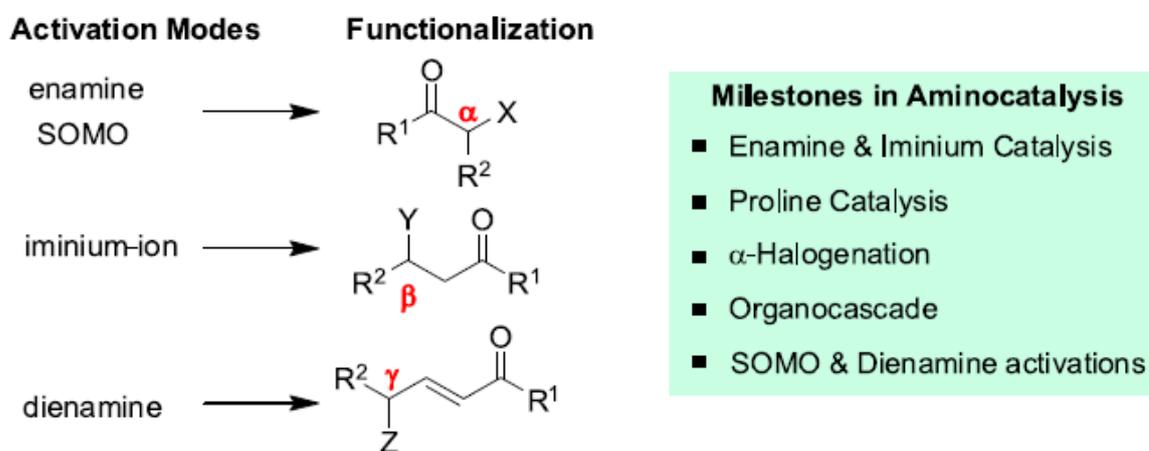

Figure 8. State of art and milestone concept in Asymmetric Amminocatalysis.

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ASYMMETRIC CHIRAL SECONDARY AMINE-CATALYZED MANNICH REACTION:

- Proline-catalyzed Mannich Reaction of Acetaldehyde and N-Boc Imines
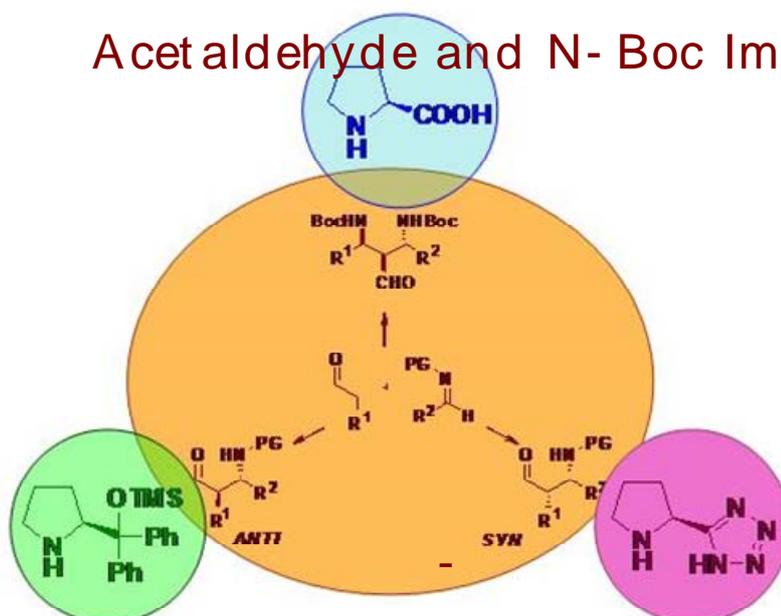
- Controlling Stereoselectivity in the Aminocatalytic Enantioselective Mannich Reaction of Aldehydes with *In Situ* Generated *N*-Boc and *N*-Cbz Imines

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EXPANDING THE SCOPE OF THE ASYMMETRIC SECONDARY AMINE-CATALYZED MANNICH REACTION

In the following pages we will introduce the progresses made by our group in the asymmetric Mannich reaction between unmodified aldehydes and *N*-protected imines, catalyzed by chiral secondary amines. The Mannich reaction, one of the most powerful tool for the creation of stereogenic carbon-nitrogen bond, is considered as a benchmark reaction for testing the advancement of asymmetric aminocatalysis.

In the beginning, an organocatalytic sequence for the Mannich reaction of aldehydes and *N*-protected imines will be reported. A very efficient protocol for the *in situ* generation of imines, highly reactive and unstable substrates will be discussed, leading to a simple procedure for achieving chiral *N*-containing molecules. Moreover, we will see that the judicious choice of the catalyst permits to direct the reaction towards the formation of the desired diastereoisomer in high optical purity.

On the other hand, a double Mannich reaction of acetaldehyde with *N*-Boc imines will be presented. The reaction, catalyzed by proline, represents a nice example of an *in situ double activation enamine pathway* of acetaldehyde, highly challenging substrate in organocatalysis. Once the best conditions were set, the methodology proved to be general, affording the desired final products - precursors of di-amino acids- in high yields and with total stereocontrol.

3.1 Controlling Stereoselectivity in the Aminocatalytic Enantioselective Mannich Reaction of Aldehydes with In Situ Generated N-Boc and N-Cbz Imines
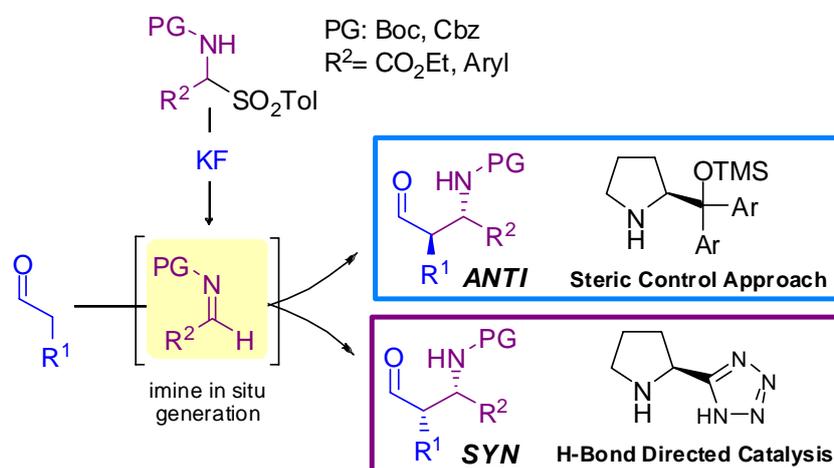
Simple Mannich: in situ generation of highly reactive *N*-carbamate-protected imines from stable and easily handling α-amido sulfones accounts for the design of a very simple and highly efficient aminocatalytic Mannich strategy. The judicious selection of commercially available chiral amine catalysts allows to fully control the stereochemistry of the Mannich process, either the *syn* or *anti*-β-amino aldehydes being accessible with very high stereocontrol.

The rapid affirmation of organocatalysis as a reliable tool for the synthesis of chiral compounds[1] has been warranted by its efficiency, cost-effectiveness, low environmental impact and operational simplicity. The continuous development of new organocatalysts and new activation strategies opened new synthetic opportunities that were considered inaccessible only a few years ago,[2] leading synthetic chemists to produce a wide range of useful and complex chiral molecules, often with the possibility of selectively achieving all possible enantio- and diastereoisomers. Moreover, the remarkable scientific competition of the field also contributed to the development of new and valuable synthetic methodologies. Among them, the catalytic asymmetric Mannich reaction – a reliable route for the synthesis of chiral β-amino carbonyl compounds – has been considered as a point of reference for measuring the progress of aminocatalysis.[3] In this context, the discovery that chiral secondary amines, such as proline and its derivatives, are able to catalyze the direct addition of unmodified carbonyl compounds to *N*-PMP (p-methoxyphenyl) imines with very high stereoselectivity[4] has greatly contributed to the development of new atom-economy based Mannich strategies.[5] Besides, recently List and co-workers introduced preformed *N*-Boc (tert-butyloxycarbonyl) imines to the proline-catalyzed *syn*-Mannich reaction of aldehydes,[6] bringing in important synthetic benefits connected to the easier removal of *N*-protecting group necessary for the delivery of the corresponding unfunctionalized chiral amines. Considering the synthetic merit of the Mannich transformations, several highly enantioselective and *syn*-diastereoselective methodologies have been developed, while the challenging synthetic problem of an efficient *anti*-Mannich protocol has been only partially solved by the specific design of new chiral catalysts, that often requires several synthetic steps.[7]

During our studies on aminocatalysis, we were interested in extending the synthetic potential of the aminocatalytic Mannich reaction, moving on two

concomitant directions. First, as highlighted before, being an efficient *anti*-selective version of the Mannich reaction still lacking, we put our efforts in the development of highly stereoselective enamine-catalyzed additions of unmodified aldehydes to *N*-carbamoyl imines. However, the formation of versatile *N*-Boc or *N*-Cbz (*Cbz = benzyloxycarbonyl*) protected adducts has as main drawback the employment of unstable substrates, since the *N*-carbamoyl imines present an higher reactivity compared to the corresponding *N*-PMP imines that makes them rather sensitive to moisture and air and renders their preparation and storage disadvantageous. At the same time, in this perspective, to simplify the procedure and make it useful and applicable for the scientific community, we sought to introduce the use of stable α-amido sulfones **1** as imine precursors. Recently, the benefit of using stable α-amido sulfones **1** as imine surrogate[8] has been exploited in phase-transfer catalyzed Mannich-type reactions[8b-c] and, later, extended to chiral base catalysis,[8d] with important procedural simplification.

Inspired by these studies, we would like to describe our contribution to the progress of the aminocatalytic Mannich transformation by reporting a simple protocol for the first *anti*- and highly enantioselective addition of aldehydes to *N*-Cbz and *N*-Boc protected α-imino esters catalyzed by the commercially available TMS-diaryl prolinol derived catalysts **IIIa** and **IIIc**.[9-10] Herein, we also show the application of our approach to the hitherto difficult *anti*-Mannich reaction of *N*-carbamoyl aromatic imines. Moreover, once proved the compatibility between the chiral secondary amine and an inorganic base necessary for the *in situ* generation of *N*-carbamoyl imines from the starting sulfones **1**, we found that the commercially available proline-derived tetrazole catalyst **IV** is able to promote the high enantioselective *syn*-Mannich additions[11] to *in situ* generated aromatic *N*-carbamoyl imines. In this way, extending our methodology to the *syn*-Mannich version, a selective access to all the four stereoisomers of the valuable β-amino aldehydes is allowed by

simply selecting the appropriate organocatalyst and using a very simple protocol which avoids the requirement of preparing and isolating the unstable imines (Scheme 1).
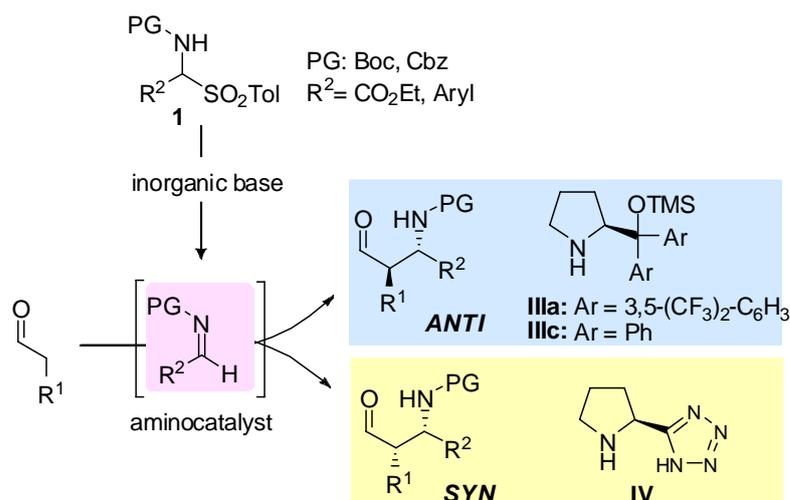
Scheme 1. *Design plan for the aminocatalytic anti- and syn-Mannich reaction of aldehydes with in situ generated N-carbamoyl imines*

3.1.1 Aminocatalytic *anti*-selective Mannich reaction of *in situ* generated *N*-carbamoyl α-imino ethyl glyoxylate:[9]

Being the asymmetric Mannich reaction one of the most powerful synthetic route for achieving enantio-enriched *N*-containing molecules, it has been extensively studied. In particular, after the discovery of proline's efficiency to catalyze highly enantioselective addition of carbonyl compounds to *N*-PMP imines,[4,5] several asymmetric catalytic methodologies have been developed.[3]

Following studies have been devoted to the identification of new efficient strategies to achieve high level of absolute and relative stereocontrol, in order to selectively achieve *syn* or *anti* β-amino carbonyl compounds, as well as the introduction of easily removable *N*-protective groups. From this last point of view, a great contribution has been given by Enders and co-workers and, almost simultaneously by List et al., which introduced *N*-Boc-protected imines as electrophilic substrates in the Mannich reaction of aldehydes and ketones catalyzed by proline.[6] However, despite several *syn*-directed aminocatalytic routes for the Mannich reaction, only few *anti*-selective asymmetric Mannich reactions using *N*-PMP-protected imines have been recently reported, catalyzed by carefully engineered catalysts.[7,9,10]

Considering the "state of art" of the amino-catalytic Mannich transformation, very recently we focused our attention upon the - at that time[9,10] - unprecedented *anti*-selective direct addition of aldehydes to *N*-Cbz and *N*-Boc protected imines, a method that would allow an easy access to unfunctionalized chiral amines owing to the easy removal of the *N*-protecting group. However, the preparation and the use of *N*-carbamoyl imines requires particular reaction conditions: their high reactivity makes them unstable substrates, sensitive to moisture and air, with a series of consequent practical disadvantages during their preparation and storage. Toward the aim of suggesting an easier procedural methodology, we sought to develop a simple protocol for the aminocatalytic *anti*-Mannich reaction of aldehydes using stable α-amido sulfones **1** as imine precursors. This approach would introduce important synthetic advantages, avoiding the requirement of preparing and isolating the unstable imines.

For exploratory studies, we selected the reaction between hydrocinnamaldehyde **2a** and the bench stable α-amido sulfone **1a** catalyzed by the commercially available TMS-diaryl prolinol derived catalysts **IIIa** and **IIIc** (Table 1).[12] It is known in fact, the ability of these catalysts to impart

high *anti*-selectivity in the direct addition of aldehydes to preformed *N*-PMP imines[5b] exploiting a "steric control approach".[12] As shown in Figure 1, the bulky chiral fragment of the catalyst efficiently shields the *Re*-face of the enamine intermediate, which selectively engage the imine *Si*-face with an *unlike* topicity that forges an *anti* relative configuration in the β–aminoaldehyde product.
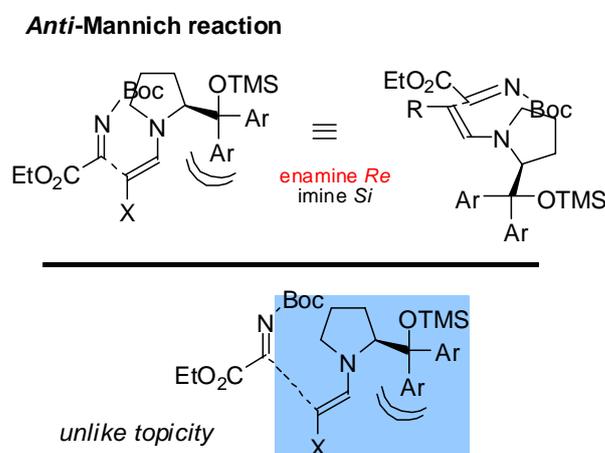
Anti-Mannich reaction

Figure 1. *Origin of the stereoselectivity in the anti-Mannich reaction catalyzed by TMS-diaryl prolinol derived catalysts*

The employment of *N*-carbamate-protected α-imino esters in organic synthesis has been rather limited because of their high instability, since they must be used immediately after their preparation.[13] Despite the drawbacks associated with their utilization, *N*-carbamoyl-protected α-imino esters are much-sought substrates since they would directly lead to synthetically useful amino acid derivatives. The α-amido sulfone **1a** was selected as the precursor of the highly challenging substrate *N*-Boc protected α-imino ethyl glyoxylate. The in situ preparation method seems a suitable route to overcome the limitations described above.

Optimisation studies (Table 1) highlighted the ability of a range of bases, either as a solid or as an aqueous solution (entries 1-5), to generate in situ the *N*-Boc imino ester. Both the catalyst **IIIa** and the 'smaller' catalyst **IIIc** were tested: the first one proved to impart very high stereocontrol even at room temperature, albeit the *anti* adduct **3a** was isolated with moderate yield.

Table 1. Optimization studies.[a]
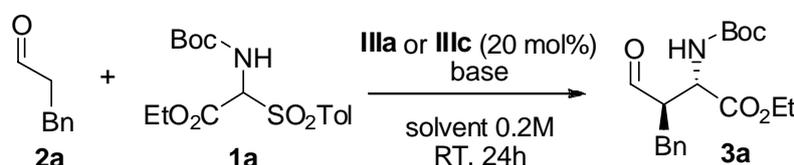
Entry	Catalyst	Base (equiv)	Solvent	Time (h)	Yield [%][b]	dr[c]	ee [%][d]
1	**IIIa**	K₃PO₄ (1)	Toluene	36	32	13:1	92
2	**IIIa**	K₂CO₃ (1)	Toluene	36	53	13:1	92
3	**IIIc**	K₂CO₃ (1)	Toluene	24	65	5.3:1	85
4	**IIIa**	K₂CO₃(aq) (1)	Toluene	36	24	8:1	91
5	**IIIa**	KF (3)	Toluene	36	31	19:1	95
6	**IIIa**	KF (3)	CHCl₃	24	95	16:1	96
7[f]	**IIIa**	KF (3)	CHCl₃	24	65	16:1	95
8[f]	**IIIa**	KF (5)	CHCl₃	24	87	16:1	96

[a]Reactions carried out on a 0.1 mmol scale, using 2 equiv of 2a. [b] Isolated yield after chromatography. [c] Determined by ¹H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis on chiral stationary phases. [e] 0.1 M solution of K₂CO₃. [f] Reaction carried out with 10 mol% of the catalyst **IIIa**.

By employing the α,α-diphenyl prolinol silyl ether **IIIc** slightly lower selectivity was achieved, albeit with improved reactivity (entry 3). This evidence prompted us to select **IIIa** for further explorations and optimization of the standard reaction parameters. The nature and the amount of the inorganic base and the solvent[14] turned out to be crucial for achieving high reaction efficiency. Using 5 equiv of KF in chloroform, the catalyst loading could be reduced to 10 mol% while affording **3a** with high diastereo- and enantio-control and in high yield (entry 8). These catalytic conditions were selected for further explorations aimed at expanding the scope of this transformation.

As shown in Table 2, different aliphatic aldehydes were suitable substrates for the Mannich reaction leading to product **3** in high yields and with very high optical purity and *anti* diastereoselectivity. The catalyst **IIIa** proved active also with the more encumbered isovaleraldehyde, furnishing product **3c** with good yield and without affecting the efficiency of the system (Table 2, entry 4). Using the same conditions the method was extended to the *N*-Cbz-protected α-amido sulfone **1b**, affording the expected *anti*-β-amino aldehydes **3d-g** in good yield and high stereocontrol. The employment of different carbamates for the *anti*-Mannich procedure represents an important feature from a synthetical standpoint, providing orthogonal sets of easily removable *N*-protecting groups.[15] As expected, it is possible to access both of the antipodes of the *anti* products **3** simply selecting the appropriate catalyst enantiomer, still maintaining a very high level of selectivity (entries 2 & 9).

Table 2. *anti*-Mannich reaction with in situ generated aromatic *N*-carbamoyl imines.[a]
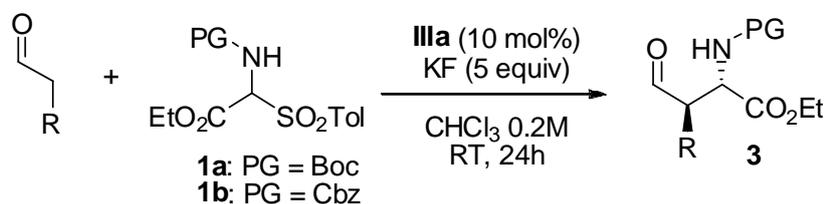
Entry	R	PG	3	Yield [%][b]	dr[c]	ee [%][d]
1	Bn	Boc	**a**	87	16:1	96
2	Bn	Boc	**a**	82	13:1	-96[e]
3	Me	Boc	**b**	92	10:1	94[f]
4[g]	*i*Pr	Boc	**c**	65	>19:1	95
5	Et	Cbz	**d**	95	13:1	96
6	Bn	Cbz	**e**	95	10:1	92
7	nBu	Cbz	**f**	96	11.5:1	98
8	*i*Pr	Cbz	**g**	85	13:1	95
9	*i*Pr	Cbz	**g**	87	13:1	-95[e]

[a] Reactions carried out on a 0.2 mmol scale, using 2 equiv of aldehydes. [b] Isolated yield after chromatography. [c] Determined by 1H NMR of the crude mixture. [d] Determined by HPLC analysis on chiral stationary phases. [e] Reaction carried out using the (D) enantiomer of the catalyst **IIIa**, leading to the opposite antipode of anti products **3**. [f] ee determined by HPLC analysis of the corresponding oxime prepared with O-benzylhydroxylamine. [g] Reaction on a 1.2 mmol scale.

As anticipated before, the Mannich adducts **3** represent versatile intermediates for accessing valuable chiral building blocks. Scheme 2 illustrates a concise synthetic route, starting from **3c** and based on an oxidation-esterification step and subsequent cyclization of the aspartic acid

derivative **4**, leading to the *trans*-β-lactam **6** . Therefore, treatment of *anti*-**3c** with NaClO$_2$ followed by the addition of TMSCHN$_2$ led to the formation of the corresponding methyl ester **4** (83% yield over two steps). Subsequent Boc deprotection and cyclization step, based on a known procedure,[16] gave β-lactam **5**. Finally, a saponification-methylation sequence affords the *N*-Boc protected compound **6**. This substrate was used to clarify the absolute configuration of the *anti*-Mannich adducts, being the *trans* configuration confirmed by the ^{1}H-NMR coupling constant (J$_{2-3}$=3.2 Hz) observed. HPLC analysis using chiral stationary phase confirmed that the whole synthetic sequence did not affect the enantiopurity of the compound **6** and its absolute configuration was determined to be (2*S*,3*R*) by comparison of the specific optical rotation with the value reported in the literature.[17]
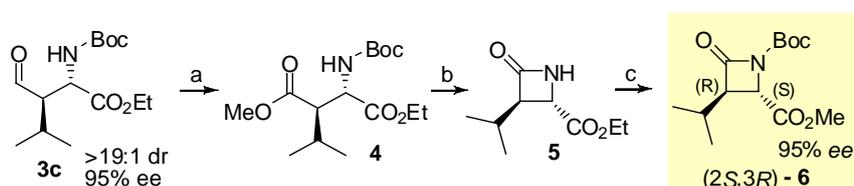
Scheme 2. *Assignment of the absolute configuration of anti-3c: Conditions: a) i) NaClO$_2$, NaH$_2$PO$_4$, 2-methyl-2-butene, t-BuOH, H2O; ii) TMSCHN$_2$; b) i) TFA; ii) Et$_3$N, TMSCl; iii) tBuMgCl; c) i) NaOH; ii) TMSCHN$_2$; iii) Boc$_2$O, DMAP. Et$_3$N.*

Therefore, catalyst **IIIa** promotes the asymmetric formation of (2*S*,3*R*)-amino acid derivatives **3**. The stereochemical outcome of the Mannich reaction can be rationalized on the basis of the proposed transition state depicted in Figure 1. As highlighted before, the stereoinduction of the reaction is explained through a 'steric control' operated by the bulky catalyst **IIIa**. The high level of diastereo-selectivity is based on the efficient coverage of the *Si* face of the chiral enamine intermediate that leaves the *Re* face available for the imine approach. The steric hindrance of the catalyst also determines the electrophile-enantiofaciality, enforcing an *unlike* topicity for the Mannich reaction.

3.1.2 Aminocatalytic *anti*-selective Mannich reaction of in situ generated *N*-carbamoyl aromatic imines:

In the previous pages we have seen how the recent discovery that proline can enforce incredible level of enantio- and *syn*-diastereo-selectivity also in the addition of aldehydes to *N*-Boc protected aromatic imines has broadly expanded the applicability of this asymmetric system.[6]

The substitution of the *N*-PMP protective group, which requires drastic oxidative conditions involving harmful reagents for its removal from nitrogen, and its substitution with the facile and easier removable *N*-carbamoyl group, has represented a crucial improvement to the promotion of the aminocatalytic Mannich reaction as a practical synthetic tool for organic chemists. However, a general and highly efficient version for obtaining *anti*-β-amino-β-aryl aldehydes still represents a difficult target, being only few and limited examples available. Very recently, during our investigations, Maruoka and co-workers reported an amino sulphonamide-catalyzed *anti*-Mannich reaction of aldehydes and preformed aromatic *N*-Boc imines, a procedure that affords a wide range of adducts with high level of stereocontrol.[10]

We have previously shown our aminocatalytic strategy for selectively achieving *anti*-β-amino aldehydes; in addition to the high stereoselectivity reached, the main novelty of our approach is the in situ generation of *N*-protected imines starting from stable α-amido sulfones. Convinced of the synthetic utility of our strategy, that avoids the need of preparing and isolating unstable imines, we turned our attention to the addition of aldehydes to in situ generated *N*-carbamoyl aromatic imines starting from the corresponding aromatic α-amido sulfones (Scheme 1).

Specifically, we investigated the reaction between propanal and aromatic sulfones, using the same catalytic conditions developed for the *anti*-Mannich reaction of in situ generated *N*-carbamoyl α-imino ethyl glyoxylate. As reported in Scheme 3, catalyst **IIIa** proved efficient to promote the Mannich reaction with both in situ generated *N*-Cbz and *N*-Boc phenyl imines with high level of efficiency, the *anti*-adducts **7** being obtained in good yield and high stereoselectivity. However, the lower reactivity of aromatic imines compared to imino glyoxylate derivatives requires longer and impractical reaction time, thus lowering the synthetic utility of the method.

7a: PG= Boc
87% y, 11.5:1 dr, 98% ee

7b: PG= Cbz
94% y, 6.2:1 dr, 94% ee
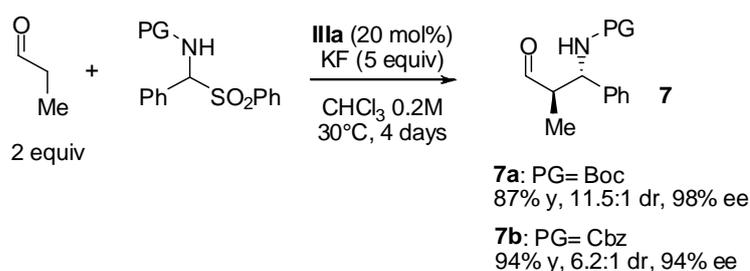
Scheme 3. *anti-Mannich addition of propanal to in situ generated N-Cbz and N-Boc-protected phenyl imines catalyzed by TMS-diaryl prolinol derived catalyst **IIIa***

From the point of view of the catalytic system development, we considered these results quite encouraging, since they clearly demonstrate that the *N*-carbamoyl aromatic imines can be also formed in situ in the presence of KF, an inorganic base that seems to be highly compatible with the catalytic efficiency of chiral secondary amines. On this ground, being known that the less encumbered catalyst **IIIc** - bearing simple phenyl ring on the crucial bulky chiral fragment of the pyrrolidine ring - usually presents an higher reactivity compared to **IIIa**, albeit at the expense of the lower geometry control and face discrimination, we wondered whether it may be useful to speed up the Mannich reaction of aromatic imines while maintaining high levels

of *anti*-diastereoselectivity and enantiocontrol. To our delight we found that by using only 10 mol% of catalyst **IIIc** the addition of propanal to in situ generated *N*-Boc phenyl imine occurs with useful levels of enantio- and *anti*-diastereoselectivity and in excellent yield (Table 3, entry 1). Moreover, since the reaction reaches completion after 24 hours, the aim of identifying a simple yet practical *anti*-Mannich protocol has been addressed.

As portrayed in Table 3, the catalytic system allows a wide scope in terms of the nucleophilic component: aldehydes bearing a long alkyl chain, a benzylic moiety and a more encumbered chain all worked well in the *anti*-Mannich protocol, leading to products **7c-e** in high yields and good to very high stereo-control (entries 2-4). Interestingly, under the reported reaction conditions, acetaldehyde - the simplest among the aldehydic donors, only recently introduced in the aminocatalytic scenario[18] - proved a suitable nucleophilic partner, delivering highly important synthetic intermediate **7f**[18a] in good yield, although with moderate enantioselectivity (entry 5). The use of the catalyst **IIIa** enforced higher enantioselectivity in this transformation (77% ee, entry 6), but with poor chemical yield.

We next examined the generality of the reaction, performing a series of experiments to determine the scope of the imine component in this aminocatalytic *anti*-Mannich protocol. Given the higher level of stereo-induction achieved when using isovaleraldehyde (R=*i*Pr, entry 4), we further investigated its employment as Mannich donor with several in situ generated aromatic imines, using 20% mol of catalyst **IIIc**. A wide latitude in the steric and electronic demand of the aromatic ring substituent can be accommodated without loss in stereochemical control. Both electron releasing and electron withdrawing groups were well tolerated, leading to the formation of variously substituted aromatic, *N*-Boc protected *anti*-β-amino aldehydes **7g-i** (entries 7-

9). A hetero-aromatic substituent also proved a suitable substrate for the Mannich reaction, affording product **7j** with good stereocontrol (entry 10). In addition, the corresponding in situ generated *N*-Cbz aromatic imines were also tested. The high reactivity and stereoselectivity observed further highlight the generality of our approach, since Mannich products with orthogonal *N*-protecting group can be easily accessed (entries 11-12). The stereochemical outcome of the *anti*-Mannich reaction of aromatic imines is in agreement with that observed in the *anti*-selective reaction of in situ generated *N*-carbamoyl α-imino ethyl glyoxylate.

Table 3. Scope of the *anti*-Mannich reaction with in situ generated *N*-carbamoyl aromatic imines.[a]
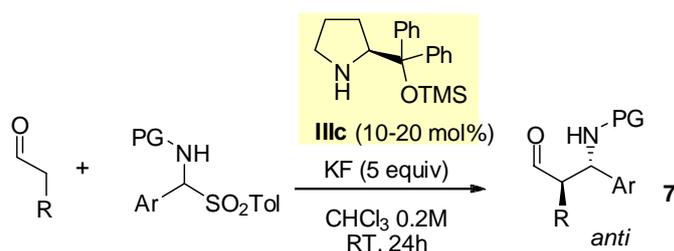
Entry	R	Ar	PG	7	Yield [%][b]	dr[c]	ee [%][d]
1	Me	Ph	Boc	**a**	95	5.2:1	94
2	Bu	Ph	Boc	**c**	90	5:1	96
3	Bn	Ph	Boc	**d**	70	5.2:1	76
4[e]	*i*Pr	Ph	Boc	**e**	94	9.2:1	98
5[f]	H	Ph	Boc	**f**	64	-	64[g]
6[e,f,h]	H	Ph	Boc	**f**	31	-	77[g]
7[e]	*i*Pr	4-MeC$_6$H$_4$	Boc	**g**	74	6:1	84[g]

8[e]	*i*Pr	4-MeOC$_6$H$_4$	Boc	**h**	95	7:1	91
9[e]	*i*Pr	4-ClC$_6$H$_4$	Boc	**i**	73	10:1	94
10[e]	*i*Pr	2-thiophenyl	Boc	**j**	73	8:1	96
11[e]	*i*Pr	4-MeC$_6$H$_4$	Cbz	**k**	74	8:1	93[g]
12[e]	*i*Pr	4-MeOC$_6$H$_4$	Cbz	**l**	82	9:1	99

[a] Reactions carried out at room temperature on a 0.2 mmol scale, using 2 equiv of aldehydes and 10 mol% of the catalyst **IIIc**. [b] Isolated yield after chromatography. [c] Determined by ^{1}H NMR of the crude mixture. [d] Determined by HPLC analysis on chiral stationary phases. [e] Reaction carried out using **IIIc** over 65 h. [f] Reaction carried out using 5 equiv of acetaldehyde and 20 mol% of the catalyst; the absolute configuration of **7f** was determined to be (*S*) by comparison of the specific optical rotation with the value reported in the literature, see Ref [10a]. [g] Determined by HPLC analysis after reduction of the isolated aldehydic product. [h] Reaction carried out in the presence of 20 mol% of catalyst **IIIa**.

3.1.3 Aminocatalytic *syn*-selective Mannich reaction of in situ generated *N*-carbamoyl aromatic imines

Achieving the full matrix of all possible stereoisomeric products during the preparation of molecules having multiple stereocenters is a challenging yet important synthetic target. This is particularly true when we approach medicinally relevant chemical structures, in order to have a complete stereochemistry based structure/activity relationships (SARs).[19]

It is then intuitive - being the Mannich adducts versatile building blocks with potentially pharmaceutical properties- how exceedingly significant is to develop highly efficient, catalytic methodologies to fully control the stereochemistry of this reaction. Incited by these considerations, we sought to apply our simple protocol to the asymmetric, aminocatalytic *syn*-selective Mannich reaction.

The identification of a suitable amine catalyst that may coexist with the inorganic base necessary to in situ generate the reactive imines, while imparting high *syn*-diastereo- and enantio-selectivity to the Mannich process, is the crucial point for the success of the strategy. We focused on the use of the commercially available proline-derived tetrazole catalyst **IV**. This catalyst belongs to a family of proline-derived catalysts originally designed and synthesized with the intention of overcoming some of the drawbacks associated with the use of proline, such as the poor solubility in conventional organic solvents, yet preserving the dual activation ability of the catalyst.[11] Due to the similarity in pK_a between the proline carboxylic acid and the tetrazole moiety, catalyst **IV** can effectively mimic the bifunctional activation mode of proline catalysis.[20] Tetrazole-catalyst **IV** has been used by Lay and colleagues in the Mannich reaction between ketones and preformed *N*-PMP-protected α-imino ethyl glyoxylate, proving to impart high *syn* diastereoselectivity.[11] On this basis, we decided to investigate the potential of **IV** to catalyze the *syn*-selective addition of aldehydes to in situ generated imines. Using the same reaction protocol developed for the *anti*-version, we found that the tetrazole catalyst preserves its efficiency in the presence of KF, catalyzing the highly stereoselective Mannich reaction directly leading to highly enantioenriched *syn*-β-aminoaldehydes (Table 4). The desired *syn*-stereochemical outcome of the reaction can be explained by a transition state conforming to the classical catalysis model of proline[21]. In figure 2 we can easily observe the specific hydrogen-bonding interaction[22] between the carboxylic moiety and the nitrogen lone pair, accountable for the stereoselectivity of the process, by directing the electrophile approach (with its *Si*-face) from the upper *Si*-face of the enamine (*like* topicity).
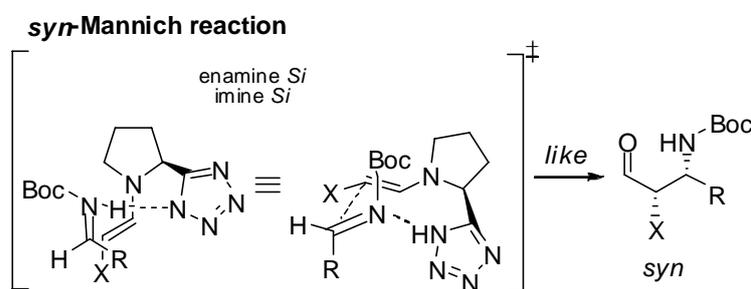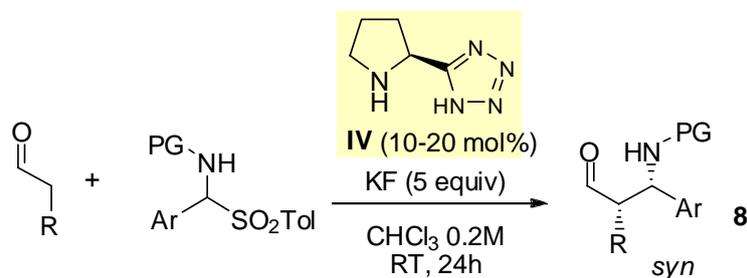
syn-Mannich reaction

Figure 2. Origin of the *syn*-stereoselectivity in the Mannich reaction catalyzed by **IV.**

The employment of tetrazole catalyst **IV** gave excellent results for the *syn*-Mannich reaction of aldehydes and in situ generated *N*-carbamate aromatic imines, both in terms of chemical yields and stereocontrol, as shown in Table 4. The method proved successful for a wide range of aliphatic aldehyde substituents, leading to β-amino aldehydes **8a-d** in high yields, with high diastereocontrol and almost perfect enantioselectivity. Interestingly, the *syn*-Mannich products **8** can be easily isolated in good yields by a simple trituration of the crude mixture with cool hexane, thus avoiding time- and cost-expensive chromatography. To prove that the remarkably high stereoselectivity achieved did not arise from an enantio-enrichment during the purification process but it is only ascribable to the catalyst efficiency, the enantiomeric purity of product **8b** (Table 4, entry 2) has been also measured after isolation by column chromatography on silica gel, and it turned out to be the same obtained via the trituration method (99% ee). The small nucleophilic acetaldehyde in the presence of **IV** gave rise to the highly important synthetic intermediate **7f** with interesting enantioselectivity (84% ee, entry 5).

Table 4. *Scope of the syn-Mannich reaction with in situ generated N-carbamoyl imines.*[a]

Entry	R	Ar	PG	8	Yield [%][b]	dr[c]	ee [%][d]
1	Me	Ph	Boc	a	77	16:1	99
2	Bu	Ph	Boc	b	70	10:1	99
3	Bn	Ph	Boc	c	89	10:1	>99
4[e]	iPr	Ph	Boc	d	80	11.2:1	>99
5[e,f]	H	Ph	Boc	7f	43	-	84[g]
6[e]	iPr	4-MeC$_6$H$_4$	Boc	e	76	11:1	>99[g]
7[e]	iPr	4-MeOC$_6$H$_4$	Boc	f	85	7:1	99
8[e]	iPr	4-ClC$_6$H$_4$	Boc	g	73	3:1	>99
9[e]	iPr	2-thiophenyl	Boc	h	86	9:1	99
10[e]	iPr	4-MeC$_6$H$_4$	Cbz	i	70	3.2:1	98[g]
11[e]	iPr	4-MeOC$_6$H$_4$	Cbz	j	70	5:1	>99

[a] Reactions carried out at room temperature on a 0.2 mmol scale, using 2 equiv of aldehydes and 10 mol% of the catalyst **IV**. [b] Isolated yield after chromatography. [c] Determined by ^{1}H NMR of the crude mixture. [d] Determined by HPLC analysis on chiral stationary phases. [e] Reaction carried out using the 20 mol% of the catalyst **IV** over 65 h. [f] Reaction carried out using 5 equiv of acetaldehyde for 36h; the absolute configuration of **7f** was determined to be (*S*) by comparison of the specific optical rotation with the value reported in the literature, see Ref [10a]. [g] Determined by HPLC analysis after reduction of the isolated aldehydic products.

Noteworthy, both TMS-diaryl prolinol and tetrazole catalyst catalyzed the Mannich reaction of acetaldehyde enforcing the same stereoinduction, the related β-amino aldehyde **7f** being formed with the (*S*) absolute configuration.[10,18a,b] This observation is in line with the proposed transition states for the Mannich reactions shown in Figure 1 & 2, where the electrophile-enantiofaciality is common to both transformations. In fact, the opposite *syn* or *anti* relative stereochemistry observed when using linear aldehydes, leading to α,β–branched β-amino aldehydes, arises from an opposite enamine-enantiofaciality imparted by the two catalyst types.

Examining the generality of the reaction, we then used isovaleraldehyde (R=*i*-Pr) as nucleophilic donor and different aromatic *N*-Boc and *N*-Cbz sulfones as imine precursors. The catalyst **IV** proved largely efficient, affording products **8e-j**, bearing a range of different aromatic substituents, with high level of diastereocontrol and with almost total enantio-purity (entries 6-11).

The absolute configuration of the *syn*-Mannich product **8a** was determined to be (1*S*,2*S*) by comparison of the specific optical rotation with the value reported in the literature.[6b] This supports a bifunctional mode of catalysis of **IV**, as depicted in Figure 2, which is able to activate both the reaction partners leading to a well organized transition state, thus mimicking the accepted mechanism of the proline-catalyed Mannich reaction.[21]

3.1.4 Conclusion

In summary, we have developed a high efficient system for the asymmetric aminocatalytic Mannich reaction of unmodified aldehydes with in situ generated *N*-carbamoyl imines. The main feature of this method lies on the operational simplicity, since it is avoided the preparation and isolation of

the highly reactive *N*-carbamate-protected imines, which are now directly generated in situ from stable and easily handling α-amido sulfones. The judicious selection of the commercially available chiral amine catalysts **IIIa**, **IIIc** and **IV** allows to fully controlling the stereochemical matrix of the Mannich process, either the *syn* or *anti*-β-amino aldehydes being accessible with very high stereocontrol. From a synthetic standpoint, the presented method is a rare example of highly *anti*-selective Mannich reaction with *N*-carbamoyl aromatic imines. We believe that our approach provides a simple and convenient protocol that may be useful to the synthetic community.

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3.1 Supplementary Information

Contents

General Methods

Materials

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Experimental Procedures

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded at 400 or 600 MHz and 100 or 150 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] 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, without any precautions to exclude moisture unless otherwise noted. To avoid the formation of *N,O*-aminals,[2] arising from the addition of adventitious methanol within $CHCl_3$ to the in situ generated imines, the Mannich reactions have been performed in anhydrous chloroform stabilized with amilene.

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Materials. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[3] Aldehydes were purchased from Aldrich and used as received. Catalysts **IIIa**, **IIIc** and **IV** are commercially available. α-Amido sulfones **1a-1b**[4] and aromatic α-amido sulfones[5] were prepared according to literature procedures.

Determination of Diastereomeric Ratios

The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. The Mannich products are prone to epimerization during silica gel chromatography, which decreases the diastereomeric ratio of the isolated compounds. To obtain excellent dr, flash chromatography was performed quickly.

Determination of Enantiomeric Purity.

Chiral HPLC analysis was performed on an Agilent 1100-series instrumentation. Daicel Chiralpak AD-H column and OD-H Chiralcel 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 **IIIa** or **IIIc** as the catalyst.

Experimental procedures

General procedure for the *anti*-Mannich reaction of aldehydes with in situ generated *N*-Cbz and *N*-Boc aromatic imines from α-amido sulfones.

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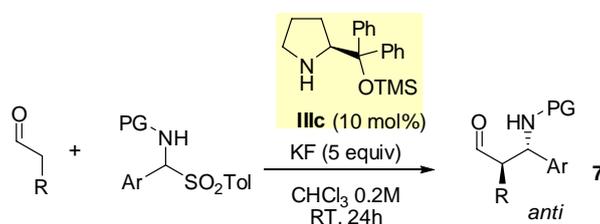
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To a solution of the catalyst **IIIc** (0.02 mmol or 0.04 mmol, 0.1 equiv. or 0.2 equiv.) in CHCl$_3$ (1.0 mL) the corresponding aldehyde (0.4 mmol, 2 equiv.) was added at room temperature. After 5 min stirring, aromatic α-amido sulfone (0.2 mmol, 1 equiv.) and KF (58.1 mg, 1.0 mmol, 5 equiv.) were successively added. The reaction mixture was stirred at room temperature for 24-65 hours. Then the crude reaction mixture was diluted with CH$_2$Cl$_2$ (2 mL) and flushed through a plug of silica, using CH$_2$Cl$_2$/Et$_2$O 1/1 as the eluent and the solvent was removed *in vacuo* or extracted with H$_2$O/CH$_2$Cl$_2$ and the combined organic layers were dried over MgSO$_4$ and concentrated. In both cases the residue was purified by flash column chromatography using mixtures of ethyl acetate/hexane as the eluent.

General procedure for the reduction of products 7f, 7g, 7k, 8e, 8i to the corresponding alcohols.

To a solution of the β-amino aldehyde in THF (0.1 M) were added 3 equivalents of NaBH$_4$ at 0 °C. After 2 h of stirring at room temperature, the reaction mixture was quenched with water and extracted with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated.

Characterization of compounds 3a-3g
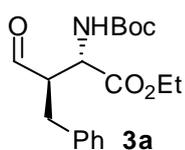
(2S,3R)-ethyl 3-benzyl-2-(tert-butoxycarbonylamino)-4-oxobutanoate (3a)

The reaction was carried out following the general procedure to furnish the crude product [dr = 94:6, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.65 ppm, δ_{minor} 9.74 ppm - s)]. The title compound was isolated as a colourless oil by column chromatography (hexane/AcOEt = 75/25) in 87% yield and 96% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 13.5 min, τ_{minor} = 15.9 min; HRMS: *m/z* calcd for C$_{18}$H$_{25}$NO$_5$: 335.17327; found: 335.1733. $[\alpha]_{rt}^D$= + 52.8 (*c* = 0.9, CHCl$_3$, 96% ee). ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.24 (t, 3H, *J*=7.2 Hz), 1.47 (s, 9H), 2.80 (dd, 1H, *J*=8.2 Hz, *J*=14.3 Hz), 3.09 (dd, 1H, *J*=7.5 Hz, *J*=14.3 Hz), 3.45 (dt, 1H, *J*=7.5 Hz, *J*=3.8 Hz), 4.12-4.15 (m, 2H), 4.55 (dd, 1H, *J*=3.8 Hz, *J*=9.8 Hz), 5.28 (d, *J*=9.8 Hz), 7.15-7.35 (m, 5H), 9.65 (s, 1H). ^{13}C NMR (150 MHz, CDCl$_3$): δ 14.0 (CH$_3$), 28.2 (CH$_3$), 31.6 (CH$_2$), 52.5 (CH), 55.5 (CH), 61.8 (CH$_2$), 80.1 (C), 126.8 (CH), 128.8 (CH), 129.0 (CH), 137.9 (C), 155.8 (C), 170.9 (C), 201.9 (C).
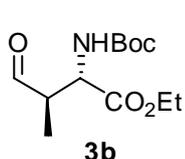
**(2S,3R)-Ethyl 2-(tert-butoxycarbonylamino)-3-methyl-4-oxobutanoate (3b)** (Table 1, entry 2) – The reaction was carried out following the general procedure to furnish the crude product [dr = 91:9, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.63 ppm, δ_{minor} 9.73 ppm - s)]. The title compound was isolated as a colourless oil by column chromatography (hexane/AcOEt = 8/2) in 92% yield. HRMS: m/z calcd for $C_{12}H_{21}NO_5$: 259.14197; found: 259.1418. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.15 (d, 3H, J=7.3 Hz), 1.23 (t, 3H, J=7.2 Hz), 1.43 (s, 9H), 3.07-3.15 (m, 1H), 4.12-4.25 (m, 2H), 4.63 (dd, 1H, J=3.8 Hz, J=8.8 Hz), 5.29 (d, 1H, J=8.8 Hz), 9.64 (s, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 9.3 (CH$_3$), 14.0 (CH$_3$), 28.2 (CH$_3$), 48.8 (CH), 53.6 (CH), 61.8 (CH$_2$), 80.2 (C), 155.6 (C), 170.5 (C), 201.6 (CH). The enantiomeric excess of **3b** was determined by HPLC analysis of the corresponding oxime prepared with *O*-benzylhydroxylamine:

(2*S*, 3*R*)-Ethyl 4-(benzyloxyimino)-2-(tert-butoxycarbonylamino)-3-methylbutanoate
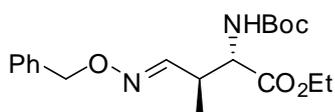
To the crude aldehyde **3a** (0.1 mmol) prepared according to the general procedure and dissolved in CH$_2$Cl$_2$ (2 mL), *O*-benzylhydroxylamine hydrochloride (0.26 equiv, 0.26 mmol) and pyridine (0.1 mL) were added.[6] The mixture was stirred for 4 h at room temperature, filtered through celite, and concentrated in vacuo. The title compound was isolated as a colourless oil by column chromatography (hexane/AcOEt = 85/15) in 90% yield, dr = 91:9, determined by integration of one set of ^{1}H NMR signal (δ_{major} 5.00 ppm, δ_{minor} 5.03 ppm - s) and 94% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 90/10 hexane/i-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 13.1 min, τ_{major} = 15.9 min. $[\alpha]_{rt}^{D}$= + 14.0 (c = 0.1, CHCl$_3$, 94% ee). ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.14 (d, 3H, J=7.2 Hz), 1.22 (t, 3H, J=7.0 Hz), 1.45 (s, 9H), 3.00-3.10 (m, 1H), 4.11 (q, 2H, J=7.2 Hz), 4.38 (dd, 1H, J=4.4 Hz, J=9.0 Hz), 5.02 (s, 2H), 5.18 (d, J=9.0 Hz), 7.28-7.38 (m, 6H). ^{13}C NMR (150 MHz, CDCl$_3$): δ 14.1 (CH$_3$), 14.7 (CH$_3$), 28.3 (CH$_3$), 37.2 (CH), 56.0 (CH), 61.4 (CH$_2$), 75.9 (CH$_2$), 79.9 (C), 127.9 (CH), 128.3 (CH), 128.4 (CH), 137.5 (C), 151.0 (CH), 155.8 (C), 171.1 (C).

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[6] S. Mitsumori, H. Zhang, P. Ha-Yeon Cheong, K. N. Houk, F. Tanaka, C. F. Barbas, III *J. Am. Chem. Soc.* **2006;** *128*, 1040-1041

(2S,3R)-ethyl 2-(tert-butoxycarbonylamino)-3-formyl-4-methylpentanoate (3c)
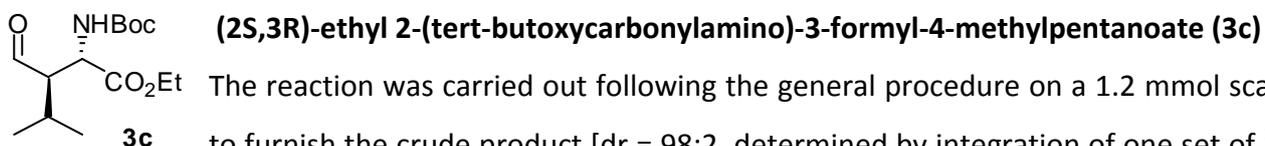
The reaction was carried out following the general procedure on a 1.2 mmol scale to furnish the crude product [dr = 98:2, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.80 ppm-t, δ_{minor} 9.74 ppm -d)]. The title compound was isolated as a colourless oil by column chromatography (hexane/AcOEt = 75/25) in 65% yield (0.224 g). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.09 (d, 3H, *J*=6.9 Hz), 1.17 (d, 3H, *J*=6.9 Hz), 1.26 (t, 3H, *J*=7.3 Hz), 1.45 (s, 9H), 2.08-2.16 (m, 1H), 2.93 (dd, 1H, *J*=4.5 Hz, *J*=8.7 Hz), 4.12-4.22 (m, 2H), 4.61 (dd, 1H, *J*=4.5 Hz, *J*=10.2 Hz), 4.61 (d, 1H, *J*=10.2 Hz), 9.89 (t, 1H, *J*=1.1 Hz). ^{13}C NMR (100 MHz, CDCl$_3$): δ 14.2 (CH$_3$), 20.6 (CH$_3$), 21.5 (CH$_3$), 27.6 (CH), 28.5 (CH$_3$), 52.0 (CH), 59.3 (CH), 61.9 (CH$_2$), 80.2 (C), 156.1 (C), 172.0 (C), 204.9 (CH).
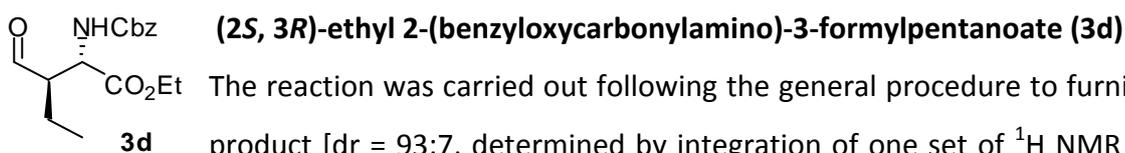
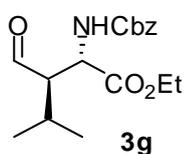**(2S, 3R)-ethyl 2-(benzyloxycarbonylamino)-3-formylpentanoate (3d)**

The reaction was carried out following the general procedure to furnish the crude product [dr = 93:7, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.62 ppm, δ_{minor} 9.70 ppm - s)]. The title compound was isolated as a yellow oil by column chromatography (hexane/AcOEt = 76/24) in 95% yield and 96% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 80/20 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 11.8 min; τ_{minor} = 18.3 min. HRMS: *m/z* calcd for C$_{16}$H$_{21}$NO$_5$: 307.14197; found: 307.1418. [α]$_{rt}^{D}$= + 48.3 (*c* = 0.85, CHCl$_3$, 96% ee). ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.13 (t, 3H, *J*=7.2 Hz), 1.24 (t, 3H, *J*=7.2 Hz), 1.45-1.58 (m, 1H), 1.75-1.90 (m, 1H), 3.02-3.08 (m, 1H), 4.18 (q, 2H, *J*=7.2 Hz), 4.66 (dd, 1H, *J*=3.7 Hz, *J*=9.6 Hz), 5.11 (d, 1H, *J*=12.1 Hz), 5.16 (d, 1H, *J*=12.1 Hz), 5.53 (d, 1H, *J*=9.6 Hz), 7.25-7.40 (m, 5H), 9.62 (s, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 12.1 (CH$_3$), 14.0 (CH$_3$), 18.5 (CH$_2$), 52.3 (CH), 55.4 (CH), 61.9 (CH$_2$), 67.1 (CH$_2$), 128.0 (CH), 128.2 (CH), 128.5 (CH), 136.1 (C), 156.5 (C), 170.9 (C), 202.3 (CH).
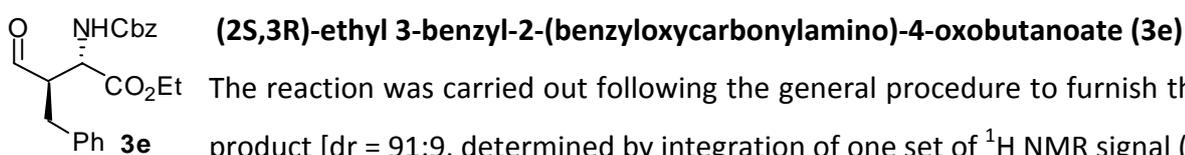
(2S,3R)-ethyl 3-benzyl-2-(benzyloxycarbonylamino)-4-oxobutanoate (3e)

The reaction was carried out following the general procedure to furnish the crude product [dr = 91:9, determined by integration of one set of ^{1}H NMR signal (δ_{major}

9.65 ppm, δ_{minor} 9.76 ppm - s)]. The title compound was isolated as a colourless oil by column chromatography (hexane/AcOEt = 77/23) in 95% yield and 92% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 90/10 hexane/i-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm, τ_{major} = 34.8 min; τ_{minor} = 46.2 min. HRMS: m/z calcd for $C_{21}H_{23}NO_5$: 369.15762; found: 369.1578. $[\alpha]_{rt}^D$ = + 27.9 (c = 0.85, CHCl$_3$, 92% ee). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.23 (t, 3H, J=7.2 Hz), 2.80 (dd, 1H, J=8.4 Hz, J=14.1 Hz), 3.10 (dd, 1H, J=7.0 Hz, J=14.1 Hz), 3.46-3.53 (m, 1H), 4.17 (q, 2H, J=7.2 Hz), 4.61 (dd, 1H, J=3.5 Hz, J=9.7 Hz), 5.16 (s, 2H), 5.58 (d, J=9.7 Hz), 7.15-7.40 (m, 10H), 9.65 (s, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 14.0 (CH$_3$), 31.6 (CH$_2$), 52.8 (CH), 55.4 (CH), 62.0 (CH$_2$), 67.2 (CH$_2$), 126.9 (CH), 128.0 (CH), 128.2 (CH), 128.5 (CH), 128.8 (CH), 129.0 (CH), 136.2 (C), 137.6 (C), 156.4 (C), 170.6 (C), 201.8 (C).
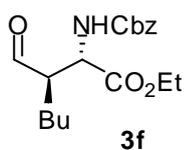
(2S,3R)-ethyl 2-(benzyloxycarbonylamino)-3-formylheptanoate (3f)

The reaction was carried out following the general procedure to furnish the crude product [dr = 92:8, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.60 ppm, δ_{minor} 9.68 ppm - s)]. The title compound was isolated as a yellow oil by column chromatography (hexane/AcOEt = 77/23) in 96% yield and 98% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 80/20 hexane/i-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 10.1 min; τ_{minor} = 141 min. HRMS: m/z calcd for $C_{18}H_{25}NO_5$: 335.17327; found: 335.1732. $[\alpha]_{rt}^D$ = + 65.3 (c = 0.83, CHCl$_3$, 98% ee). ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.91 (t, 3H, J=7.2 Hz), 1.23 (t, 3H, J=7.3 Hz), 1.25-1.55 (m, 5H), 1.69-1.89 (m, 1H), 3.08-3.15 (m, 1H), 4.18 (q, 2H, J=7.3 Hz), 4.63 (dd, 1H, J=3.6 Hz, J=9.5 Hz), 5.13 (s, 2H), 5.55 (d, 1H, J=9.5 Hz), 7.28-7.38 (m, 5H), 9.60 (s, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 13.6 (CH$_3$), 14.0 (CH$_3$), 22.4 (CH$_2$), 24.7 (CH$_2$), 29.4 (CH$_2$), 52.5 (CH), 53.6 (CH), 61.9 (CH$_2$), 67.1 (CH$_2$), 127.9 (CH), 128.1 (CH), 128.5 (CH), 136.2 (C), 156.5 (C), 170.9 (C), 202.4 (CH).
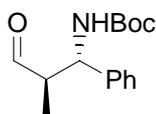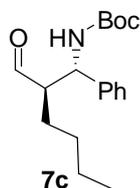
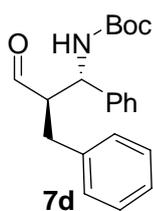**(2*S*, 3*R*)-Ethyl 2-(benzyloxycarbonylamino)-3-formyl-4-methylpentanoate (3g)**

The reaction was carried out following the general procedure to furnish the crude product [dr = 92:8, determined by integration of one set of ^{1}H NMR signal (δ_{minor} 9.75 ppm-d, δ_{major} 9.80 ppm- s)]. The title compound was isolated as a colourless oil by column

chromatography (hexane/AcOEt = 77/23) in 85% yield and 95% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 80/20 hexane/i-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 11.2 min, τ_{major} = 15.5 min; HRMS: *m/z* calcd for $C_{17}H_{23}NO_5$: 321.1576; found: 3215.1579. $[\alpha]_{rt}^D$= + 30.5 (*c* = 0.88, CHCl$_3$, 95% ee). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.10 (d, 3H, *J*=6.9 Hz), 1.18 (d, 3H, *J*=6.9 Hz),1.23 (t, 3H, *J*=7.1 Hz), 2.05-2.15 (m, 1H), 2.98 (dd, 1H, *J*=3.7 Hz, *J*=8.3 Hz), 4.12-4.21 (m, 2H), 4.68 (dd, 1H, *J*=3.7 Hz, *J*=10.1 Hz), 5.11 (d, 1H, *J*=12.2 Hz), 5.17 (d, 1H, *J*=12.2 Hz), 5.64(d, 1H, *J*=10.1 Hz), 7.28-7.38 (m, 5H), 9.80 (bs, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 14.0 (CH$_3$), 20.5 (CH$_3$), 21.4 (CH$_3$), 27.5 (CH), 52.3 (CH), 59.0 (CH), 61.9 (CH$_2$), 67.1 (CH$_2$), 127.9 (CH), 128.2 (CH), 128.5 (CH), 136.3 (C), 156.6 (C), 171.4 (C), 204.7 (CH).

Characterization of compounds 7a-7l

tert-Butyl (1*S*, 2*R*)-2-methyl-3-oxo-1-phenylpropylcarbamate (7a)

The reaction was carried out following the general procedure to furnish the crude product [dr = 5.2:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.65 ppm - d, δ_{minor} 9.72 ppm - s)]. The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 77/23) in 95% yield and 94% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 90/10 hexane/i-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: *anti* diastereoisomer τ_{major} = 12.3 min, τ_{minor} = 13.8 min; *syn* diastereoisomer τ_{major} = 17.7 min, τ_{minor} = 13.0 min. HRMS: *m/z* calcd for $C_{16}H_{21}NO_5$: 263.15214; found: 263.1522. $[\alpha]_{rt}^D$= − 14.6 (*c* = 1.1, CHCl$_3$, 94% ee). ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.03 (d, 3H, *J*=7.0 Hz), 1.40 (s, 9H), 2.75-2.82 (m, 1H), 4.80-4.93 (m, 1H), 5.10-5.25 (m, 1H), 7.24-7.38 (m, 5H), 9.64 (d, 1H, *J*=3.0 Hz). ^{13}C NMR (150 MHz, CDCl$_3$): δ 11.9 (CH$_3$), 28.3 (**C**(CH$_3$)$_3$), 52.2 (CH), 55.8 (CH), 80.0 (C), 126.8 (CH), 127.7 (CH), 128.8 (CH), 139.9 (C), 155.1 (C), 203.4 (C).

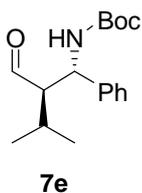**tert-butyl (1S,2R)-2-formyl-1-phenylhexylcarbamate (7c)**

The reaction was carried out following the general procedure to furnish the crude product [dr = 5:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.60

ppm - d, δ_{minor} 9.58 ppm - s)]. The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 85/15) in 90% yield and 96% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 80/20 hexane/*i*-PrOH, flow rate 0.50 mL/min, λ = 214, 254 nm: *anti* diastereoisomer τ_{major} = 11.7 min, τ_{minor} = 10.9 min; *syn* diastereoisomer τ_{major} = 12.9 min, τ_{minor} = 10.1 min . ESI-MS[M+Na]$^+$= 328; [α]$_{rt}^D$= + 1.9 (*c* = 1.0, CHCl$_3$, 96% ee). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.83 (t, 3H, *J*=6.3 Hz), 1.22-1.31 (m, 5H), 1.39 (s, 9H), 1.61 (bs, 1H), 2.66-2.77 (m, 1H), 4.91 (bs, 1H), 5.26 (d, 1H, *J*=5.6 Hz), 7.22-7.37 (m, 5H), 9.61 (d, 1H, *J*=3.7 Hz). ^{13}C NMR (150 MHz, CDCl$_3$): δ 13.6 (CH$_3$), 22.5 (CH$_2$), 26.9 (CH$_2$), 28.18 (**C**(CH$_3$)$_3$), 29.2 (CH$_2$), 54.4 (CH), 57.8 (CH), 79.9 (C), 126.8 (CH), 127.7 (CH), 128.8 (CH), 140.3 (C), 155.2 (C), 203.4 (C).

tert-butyl (1S,2R)-2-benzyl-3-oxo-1-phenylpropylcarbamate (7d)

The reaction was carried out following the general procedure to furnish the crude product [dr = 5.2:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.65 ppm - d, δ_{minor} 9.63 ppm - s)]. The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 87/13) in 70% yield and 76% ee. HPLC analysis on a Daicel Chiralcel OD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: *anti* diastereoisomer τ_{major} = 26.5 min, τ_{minor} = 22.9 min; *syn* diastereoisomer τ_{major} = 33.3 min, τ_{minor} = 29.1 min. ESI-MS [M+Na]$^+$=362; ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.44 (s, 9H), 2.74 (dd, 1H, *J*= 8.7 Hz, *J*= 13.7 Hz,), 3.00 (m, 1H dd, 1H, *J*= 8.7 Hz, *J*= 13.7 Hz), 4.98 (bs, 1H), 5.45 (d, 1 H, *J*= 7.2 Hz), 7.10-7.38 (m, 10H), 9.65 (d, 1H, *J*=2.6 Hz). ^{13}C NMR (150 MHz, CDCl$_3$): δ 28.3 (**C**(CH$_3$)$_3$), 33.4 (CH$_2$), 54.3 (CH), 59.1 (CH), 79.9 (C), 126.6 (CH), 126.7 (CH), 127.7 (CH), 128.7 (CH), 128.8 (CH), 128.9 (CH), 137.9 (C), 140.2 (C), 155.1 (C), 203.5 (C).
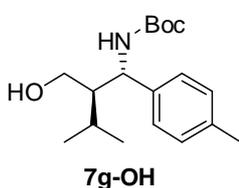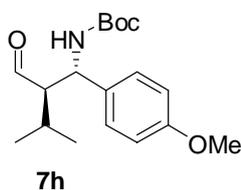
tert-butyl (1S,2R)-2-formyl-3-methyl-1-phenylbutylcarbamate (7e)

The reaction was carried out following the general procedure using 20% mol of **B** and ran for 65h at room temperature to furnish the crude product [dr = 9.2:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.75 ppm - d, δ_{minor} 9.49 ppm - d)]. The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 85/15) in 94% yield and 98% ee. HPLC analysis on a Daicel Chiralcel OD-H column: 98/2 hexane/*i*-

PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: *anti* diastereoisomer τ_{major} = 8.9 min, τ_{minor} = 10.2 min; *syn* diastereoisomer τ_{major} = 12.7 min, τ_{minor} = 11.3 min. ESI-MS [M+Na]$^+$=314; [α]$_{rt}^D$= − 13.1 (c = 1.3, CHCl$_3$, 98% ee). ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.01 (d, 3H, J= 7.0 Hz), 1.06 (d, 3H, J= 7.0 Hz), 1.39 (s, 9H), 1.81-1.92 (m, 1H), 2.62 (bs, 1H), 5.12 (bs, 1H), 5.42 (d, 1H, J=9.6 Hz), 7.21-7.38 (m, 5H), 9.75 (d, 1H, J=3.6 Hz). ^{13}C NMR (150 MHz, CDCl$_3$): δ 18.9 (CH$_3$), 21.3 (CH$_3$), 28.3 (**C**(CH$_3$)$_3$), 29.7 (CH), 53.1 (CH), 62.9 (CH), 79.8 (C), 126.6 (CH), 127.5 (CH), 128.7 (CH), 140.8 (C), 155.1 (C), 206.1 (C).

(S)-tert-butyl 3-oxo-1-phenylpropylcarbamate (7f)
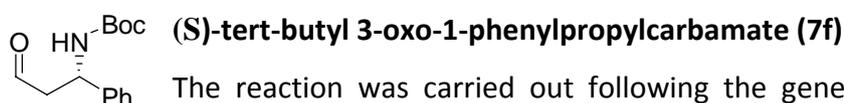
The reaction was carried out following the general procedure, using 20% mol of catalyst **B** and 5 equivalents of freshly distilled acetaldehyde to furnish the crude product. The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 80/20) in 64% yield and 64% ee (determined after reduction of the isolated product to the corresponding alcohol). HPLC analysis on a Daicel Chiralpak AD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 15.0 min, τ_{minor} = 23.2 min. ESI-MS: [M+H]$^+$= 250, [M+Na]$^+$=272. [α]$_{rt}^D$= − 33.4 (c = 1.1, CHCl$_3$, 64% ee); Lit[7] (S)-**7f**, [α]$_{rt}^D$= − 59.6 (c = 1.0, CHCl$_3$, 99% ee);. ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.43 (s, 9H), 2.88-2.97 (m, 1H), 5.08 (bs, 1H), 5.19 (bs, 1H), 7.27-7.36 (m, 5H), 9.74 (t, 1H, J=1.8 Hz). ^{13}C NMR (150 MHz, CDCl$_3$): δ 28.3 (**C**(CH$_3$)$_3$), 49.9 (CH), 30.9 (CH), 80.0 (C), 126.3 (CH), 127.8 (CH), 128.9 (CH), 140.2 (C), 155.0 (C), 200.0 (C).

tert-butyl (1S,2R)-2-(hydroxymethyl)-3-methyl-1-p-tolylbutylcarbamate (7g). The reaction was carried out following the general procedure to furnish the crude product [dr = 6:1, determined by integration of one set of ^{1}H NMR signal (δ$_{major}$ 9.87 ppm - d, δ$_{minor}$ 9.60 ppm - d)]. The β-amino aldehyde **7g** was isolated as a white solid by column chromatography (hexane/AcOEt = 85/15) in 74% yield. ESI-MS (aldehyde)= [M+Na]$^+$= 328

Then, pure **7g** was reduced to the corresponding alcohol **7g-OH** to measure the enantiomeric purity (84% ee). HPLC analysis on a Daicel Chiralpak AD-H column: 98/2 hexane/*i*-PrOH, flow rate

[7] T. Kano, Y. Yamaguchi, K. Maruoka, *Angew. Chem. Int. Ed.* **2009**, *48*, 1838.

0.75 mL/min, λ = 214, 254 nm: *anti* diastereoisomer τ_{major} = 42.8 min, τ_{minor} = 52.1 min.; *syn* diastereoisomer τ_{major} = 57.3 min, τ_{minor} = 44.6 min; $[\alpha]_{rt}^{D}$= − 27.4 (*c* = 1.0, CHCl$_3$, 84% ee).

^{1}H NMR **7g-OH** (600 MHz, CDCl$_3$): δ 0.83 (t, 3H, J= 7.6Hz), 0.96 (t, 3H, J= 7.6Hz), 1.40 (s, 9H), 1.81 (bs, 1H), 2.31 (s, 3H), 3.45-2.51 (m, 1H), 3.58-3.68 (m, 1H), 3.71-3.76 (m, 1H), 4.90-4.98 (m, 1H), 5.48 (d, 1H, *J*= 9.6 Hz), 5.86 (bs, 1H), 7.10-7.19 (m, 4H). ^{13}C NMR (150 MHz, CDCl$_3$): δ 21.0 (CH$_3$), 21.4 (CH$_3$), 26.1 (CH), 28.8 (**C**(CH$_3$)$_3$), 51.4 (CH), 59.9 (CH$_2$), 60.9 (CH); 79.9 (C), 126.2 (CH), 126.7 (CH), 129.2 (CH), 136.7 (C), 140.2 (C), 155.6 (C).

tert-butyl (1S,2R)-2-formyl-1-(4-methoxyphenyl)-3-methylbutylcarbamate (7h). The reaction was carried out following the general procedure using 20% mol of **B** and ran fo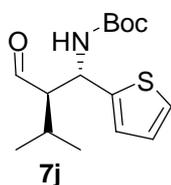r 65h at room temperature to furnish the crude product [dr = 7:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.74 ppm - d, δ_{minor} 9.47 ppm - d)]. The title compound was isolated as a white solid by column chromatography (hexane/acetone = 9/1) in 95% yield and 91% ee. HPLC analysis on a Daicel Chiralcel OD-H column: 98/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: *anti* diastereoisomer τ_{major} = 11.3, τ_{minor} = 14.4min; *syn* diastereoisomer τ_{major} = 17.6 min, τ_{minor} = 19.4 min. ESI-MS: [M+Na]$^+$=344. $[\alpha]_{rt}^{D}$= − 37.5 (*c* = 0.98, CHCl$_3$, 91% ee). ^{1}H NMR (600 MHz, CDCl$_3$): δ 0.97 (d, 3H, *J*= 7.1 Hz), 1.03 (d, 3H, *J*= 7.1 Hz), 1.36 (s, 9H), 1.79-1.83 (m, 1H), 2.54 (bs, 1H), 3.77 (s, 3H), 5.04 (bs, 1H), 5.27 (d, 1H, *J*=9.2 Hz), 6.84-76.86 (m, 2H), 7.14-7.17 (m, 2H), 9.74 (d, 1H, *J*=3.8 Hz). ^{13}C NMR (150 MHz, CDCl$_3$): δ 18.6 (CH$_3$), 21.1 (CH), 21.3 (CH$_3$), 28.3 (**C**(CH$_3$)$_3$), 52.5 (CH), 55.2 (CH$_3$), 63.1 (CH), 79.7 (C), 114.1 (CH), 127.7 (CH), 132.8 (C), 155.0 (C), 158.9 (C), 206.1 (C).
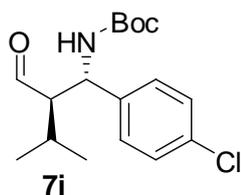
tert-butyl (1S,2R)-1-(4-chlorophenyl)-2-formyl-3-methylbutylcarbamate (7i). The reaction was carried out following the general procedure using 20% mol of **IIIc** and ran for 65h at room temperature to furnish the crude product [dr = 10:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.73 ppm - d, δ_{minor} 9.49 ppm - d)]. The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 85/15) in 73% yield and 94% ee. HPLC analysis on a Daicel Chiralpack AD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: *anti*

diastereoisomer τ_{major} = 11.0, τ_{minor} = 7.7 min; *syn* diastereoisomer τ_{major} = 9.7min, τ_{minor} = 8.6 min. ESI-MS: [M+Na]$^+$=348, 350 $[\alpha]_{rt}^D$= − 32.6 (*c* = 1.0, CHCl$_3$, 94% ee). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.03 (d, 3H, *J*= 6.9 Hz), 1.07 (d, 3H, *J*= 6.9 Hz), 1.39 (s, 9H), 1.85-1.95 (m, 1H), 2.60 (bs, 1H), 5.08 (bs, 1H), 5.47 (bs, 1H), 7.18-7.31 (m, 4H), 9.73 (d, 1H, *J*=3.8 Hz). ^{13}C NMR (150 MHz, CDCl$_3$): δ 21.2 (CH$_3$), 21.4 (CH$_3$), 28.5 (**C**(CH$_3$)$_3$), 52.3 (CH), 58.0 (CH), 62.7 (CH), 80.0 (C), 127.3 (CH), 128.8 (CH), 128.7 (CH), 139.6 (C), 155.3 (C), 205.9 (C).

7j

tert-butyl (1S,2R)-2-formyl-3-methyl-1-(thiophen-2-yl)butylcarbamate (7j)

The reaction was carried out following the general procedure using 20% mol of **IIIc** and ran for 65h at room temperature to furnish the crude product [dr = 8:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.79 ppm - d, δ_{minor} 9.64 ppm - s)]. The title compound was isolated as a yellow solid by column chromatography (hexane/Et$_2$O = 85/15) in 73% yield and 96% ee. HPLC analysis on a Daicel Chiralcel OD-H column: 99/1 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: *anti* diastereoisomer τ_{major} = 11.3, τ_{minor} = 12.3 min; *syn* diastereoisomer τ_{major} = 16.9 min, τ_{minor} = 13.6 min. ESI-MS: [M+Na]$^+$= 320. $[\alpha]_{rt}^D$= − 26.8 (*c* = 0.90, CHCl$_3$, 96% ee). ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.03 (d, 3H, *J*= 7.0 Hz), 1.07 (d, 3H, *J*= 7.0 Hz), 1.41 (s, 9H), 1.97-1.99 (m, 1H), 2.69 (bs, 1H), 5.41 (bs, 2H), 6.89-6.94 (m, 2H), 7.15-7.19 (m, 1H), 9.79 (d, 1H, *J*= 4.1 Hz). ^{13}C NMR (150 MHz, CDCl$_3$): δ 19.9 (CH$_3$), 21.4 (CH$_3$), 28.3 (**C**(CH$_3$)$_3$), 49.1 (CH), 62.0 (CH), 80.0 (C), 124.4 (CH), 125.0 (CH), 126.9 (CH), 145.1(C), 155.0 (C), 205.6 (C).


7k-OH
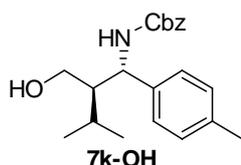
benzyl (1S,2R)-2-(hydroxymethyl)-3-methyl-1-p-tolylbutylcarbamate (7k)

The reaction was carried out following the general procedure using 20% mol of **IIIc** and ran for 65h at room temperature to furnish the crude product [dr = 8:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.77 ppm - d, δ_{minor} 9.57 ppm - d)]. The β-amino aldehyde **7k** was isolated as a white solid by column chromatography (hexane/AcOEt = 85/15) in 74% yield. Then, pure **7k** was reduced to the corresponding alcohol **7k-OH** to measure the enantiomeric purity (93% ee). HPLC analysis on a Daicel Chiralpack AD-H

column: 95/5 hexane/*i*-PrOH, flow rate 0.50 mL/min, λ = 214, 254 nm: τ_{major} = 97.7, τ_{minor} = 85.7 min. $[\alpha]_{rt}^D$= − 27.1 (*c* = 0.76, CHCl$_3$, 93% ee). ^{1}H NMR (600 MHz, CDCl$_3$): δ 0.96 (d, 3H, *J*= 6.9 Hz), 1.05 (d, 3H, *J*= 6.9 Hz), 1.38 (bs, 1H), 1.61 (bs, 1H), 1.62-1.79 (m, 1H), 2.33 (s, 3H), 3.59 (d, 1H, *J*=11.1 Hz), 3.73(d, 1H, *J*= 11.1 Hz), 4.98-5.11 (m, 3H), 6.37 (bs, 1H), 7.10-7.16 (m, 4H), 7.31-7.35 (m, 4H). ^{13}C NMR (150 MHz, CDCl$_3$): δ 19.9 (CH$_3$), 21.1 (CH$_3$), 21.4 (CH$_3$), 25.7 (CH), 51.3 (CH), 55.9 (CH), 60.1 (CH$_2$), 66.6 (CH$_2$), 126.2 (CH), 127.9 (CH), 128.0 (CH), 128.4 (CH), 129.1 (CH), 136.7 (C), 139.4 (C), 156.3 (C).

7l
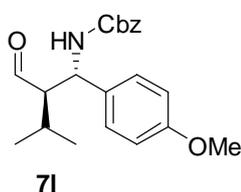
benzyl (1S,2R)-2-formyl-1-(4-methoxyphenyl)-3-methylbutylcarbamate (7l)

The reaction was carried out following the general procedure using 20% mol of **IIIc** and ran for 65h at room temperature to furnish the crude product [dr = 9:1, determined by integration of one set of ^{1}H NMR signal (δ$_{major}$ 9.75 ppm - d, δ$_{minor}$ 9.48 ppm - s)]. The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 85/15) in 82% yield and 99% ee. HPLC analysis on a Daicel Chiralcel OD-H column: 85/15 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: *anti* diastereoisomer τ_{major} = 10.6, τ_{minor} = 13.4 min; *syn* diastereoisomer τ_{major} = 12.0 min, τ_{minor} = 15.4 min. ESI-MS: [M+Na]$^+$= 278. $[\alpha]_{rt}^D$= − 12.4 (*c* = 1.0, CHCl$_3$, 99% ee). ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.03 (d, 3H, *J*= 7.2 Hz), 1.10 (d, 3H, *J*= 7.2 Hz), 1.80-1.88 (m, 1H), 2.61 (bs, 1H), 3.77 (s, 3H), 4.99-5.49 (m, 3H), 5.68 (bs, 1H), 6.82-6.86 (m, 2H), 7.13-7.34 (m, 6H), 9.75 (d, 1H, *J*= 2.6 Hz). ^{13}C NMR (150 MHz, CDCl$_3$): δ 18.7 (CH$_3$), 21.1 (CH), 21.3 (CH$_3$), 53.0 (CH), 55.2 (CH$_3$), 62.6 (CH), 68.9 (CH$_2$), 114.1 (CH), 127.7 (CH), 128.0 (CH), 128.4 (CH), 132.5 (C), 136.3 (C), 155.6(C), 158.9 (C), 206.1 (C).

Determination of Relative and Absolute Configuration

Compound **3c** was converted in the *trans* β-lactam **6** by the following simple synthetic steps. The *trans* configuration was confirmed by the ^{1}H-NMR coupling constant ($J_{2,3}$=3.2 Hz) observed. The absolute configuration was determined by comparison of the specific optical rotation with the value reported in the literature.[8]

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[8] C. Palomo, J. M. Aizpurua, J. J. Gracenea, S. Garcìa-Granda, P. Pertierra *Eur. J. Org. Chem.* **1998**, 2201-2207.
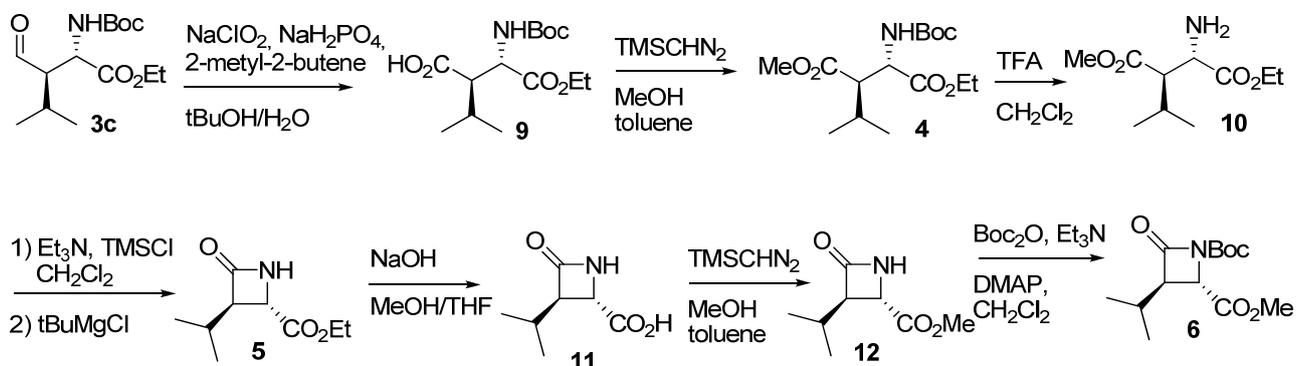
Compound 9
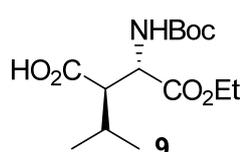
To a magnetically stirred solution of **3c** (220 mg, 0.77 mmol) in *tert*-butyl alcohol/water (5:1, 11.5 mL) NaH_2PO_4 (158 mg, 1.3 mmol, 1.7 equiv.), 2-methyl-2-butene (2.65 mL, 2 M solution in THF, 5.3 mmol, 4.8 equiv.), and $NaClO_2$ (239 mg, 2.7 mmol, 3.45 equiv.) were added successively.[9] The resulting mixture was stirred for 1.5 h until the yellow solution turned colorless. The solvent was removed under reduced pressure, and the residue was extracted with ethyl acetate, washed with water, and dried over $MgSO_4$. The combined organic layers were concentrated to give the crude acid **9** (265 mg).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (d, 3H, *J*=6.7 Hz), 1.05 (d, 3H, *J*=6.7 Hz), 1.26 (t, 3H, *J*=7.3 Hz), 1.45 (s, 9H), 2.00-2.15 (m, 1H), 2.77 (dd, 1H, *J*=3.7 Hz, *J*=9.0 Hz), 4.08-4.26 (m, 2H), 4.62 (dd, 1H, *J*=3.9 Hz, *J*=10.3 Hz), 5.62 (d, 1H, *J*=9.8 Hz), 6.8 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (CH_3), 20.0 (CH_3), 21.0 (CH_3), 27.8 (CH), 28.3 (CH_3), 52.9 (CH), 54.2 (CH), 61.7 (CH_2), 79.7 (C), 156.0 (C), 173.5 (C), 179.5 (C).

(2*S*, 3*R*)-1-Ethyl 4-methyl 2-(tert-butoxycarbonylamino)-3-isopropylsuccinate
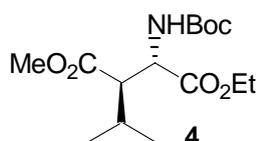
To a solution of **9** (265 mg) in toluene (4.6 mL)-MeOH (11.5 mL), $TMSCHN_2$ (2M solution in diethyl ether) was added dropwise at 0 °C until the yellow

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[9] A. Córdova, W. Notz, C. F. Barbas III *J. Org. Chem.* **2002,** *67,* 301-303.

color persisted.[10] The solution was stirred for additional 20 min and quenched with a drop of acetic acid. The solvents were removed *in vacuo* to give the crude methyl ester **4** (264 mg). ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.93 (d, 3H, *J*=6.9 Hz), 1.00 (d, 3H, *J*=6.9 Hz), 1.23 (t, 3H, *J*=7.1 Hz), 1.43 (s, 9H), 1.97-2.10 (m, 1H), 2.67 (dd, 1H, *J*=4.0 Hz, *J*=9.7 Hz), 3.65 (s, 3H), 4.08-4.24 (m, 2H), 4.55 (dd, 1H, *J*=4.0 Hz, *J*=10.0 Hz), 5.66 (d, 1H, *J*=10.0 Hz). ^{13}C NMR (100 MHz, CDCl$_3$): δ 14.0 (CH$_3$), 20.1 (CH$_3$), 20.8 (CH$_3$), 27.9 (CH), 28.3 (CH$_3$), 51.7 (CH$_3$), 52.8 (CH), 53.1 (CH), 61.5 (CH$_2$), 79.8 (C), 155.8 (C), 171.7 (C), 174.2 (C).

(2*S*, 3*R*)-1-Ethyl 4-methyl 2-amino-3-isopropylsuccinate
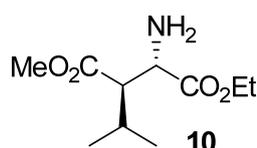
The crude product **4** (264 mg) was dissolved in dry CH$_2$Cl$_2$ (140 mL). The solution was cooled to 0°C and TFA (1.48 mL, 15.4 mmol, 20 eq.) was added.[11] The reaction mixture was stirred at room temperature for 2 h. Then, the mixture was cooled to 0°C and a solution of sat. NaHCO3 (250 mL) was added. The aqueous layer was extracted twice with CH$_2$Cl$_2$ (10 mL) and the combined organic layers were washed with water (20 mL), dried over MgSO$_4$, filtered and concentrated under reduced pressure, affording compound **10** (175 mg). ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.96 (d, 3H, *J*=6.7 Hz), 1.01 (d, 3H, *J*=6.7 Hz), 1.27 (t, 3H, *J*=7.2 Hz), 2.00-2.14 (m, 1H), 2.61 (dd, 1H, *J*=5.4 Hz, *J*=9.2 Hz), 2.76 (bs, 2H), 3.67 (s, 3H), 3.78 (d, 1H, *J*=5.4 Hz), 4.13-4.28 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 14.1 (CH$_3$), 20.3 (2CH$_3$), 27.4 (CH), 51.4 (CH$_3$), 54.3 (CH), 55.1 (CH), 61.4 (CH$_2$), 173.5 (C), 174.5 (C).

(2*S*, 3*R*)-Ethyl 3-isopropyl-4-oxoazetidine-2-carboxylate 5
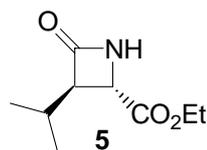
A cooled (0°C) solution of the crude amino-succinate **10** (175 mg) in dry CH$_2$Cl$_2$ (4 ml) was treated with triethylamine (0.85 mmol) and trimethylchlorosilane (0.85 mmol).[12] The resulting solution was stirred at the same temperature for 30 min, then *tert*-butylmagnesium chloride (1 M in diethyl ether, 5.1 mmol) was added and stirring was

[10] H. Zhang, S. Mitsumori, N. Utsumi, M. Imai, N. Garcia-Delgado, M. Mifsud, K. Albertshofer, F. Tanaka, C. F. Barbas, III *J. Am. Chem. Soc.* **2008**, *130*, 875-886.
[11] J.-A. Richard, L. Jean, A. Romieu, M. Massonneau, P. Noack-Fraissignes, P.-Y. Renard *Org. Lett.* **2007**, *9*, 4853–4855.
[12] C. De Risi, G. P. Pollini, A. C. Veronese, V. Bertolasi, Tetrahedron **2001**, *57*, 10155.

continued at room temperature overnight. Water (10 ml) was added and the precipitated magnesium salts were filtered through celite. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3×10 ml) and the combined organic extracts were dried and evaporated to give crude oxoazetidine-2-carboxylate **5** (166mg). ^{1}H NMR (600 MHz, CDCl₃): δ 1.04 (d, 3H, J=6.7 Hz), 1.09 (d, 3H, J=6.7 Hz), 1.28 (t, 3H, J=7.2 Hz), 2.05-2.14 (m, 1H), 3.05 (dd, 1H, J=2.7 Hz, J=7.9 Hz), 3.90 (d, 1H, J=2.7 Hz), 4.18-4.28 (m, 2H), 6.2 (bs, 1H). ^{13}C NMR (150 MHz, CDCl₃): δ 14.1 (CH₃), 19.8 (CH₃), 20.0 (CH₃), 27.9 (CH), 51.7 (CH), 61.6 (CH₂), 64.4 (CH), 169.1 (C), 171.3 (C).

(2*S*, 3*R*)-3-Isopropyl-4-oxoazetidine-2-carboxylic acid 11
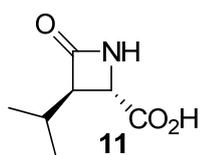
Crude compound **5** (166mg) was dissolved in a mixture of MeOH (2 mL) and toluene (5.4 mL) and 0.78 mL of aqueous NaOH 1M were added. The mixture was left to stir at room temperature for 2 h, and then was acidified with aqueous HCl 1M. After evaporation of the methanol under reduced pressure, the residue was extracted with ethyl acetate to give crude oxoazetidine-2-carboxylic acid **11** (166mg). ^{1}H NMR (400 MHz, CDCl₃): 1.05 (d, 3H, J=6.7 Hz), 1.10 (d, 3H, J=6.7 Hz), 2.05-2.14 (m, 1H), 3.15 (bd, 1H, J=8.2), 3.95 (d, 1H, J=2.3 Hz), 6.2 (bs, 1H), 6.6 (bs, 1H). ^{13}C NMR (100 MHz, CDCl₃):   19.6 (CH₃), 19.8.0 (CH₃), 27.8 (CH), 51.7 (CH), 63.8 (CH), 171.0 (C), 174.5 (C).

## (2*S*, 3*R*)-Methyl 3-isopropyl-4-oxoazetidine-2-carboxylate 12
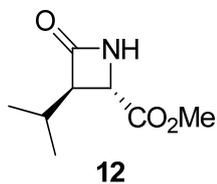
To a solution of crude **11** (166 mg) in toluene (4.6 mL)-MeOH (11.5 mL), TMSCHN₂ (2M solution in diethyl ether) was added by dropwise at 0 °C until the yellow color persisted. The solution was stirred for additional 20 min and quenched with a drop of acetic acid. The solvents were removed *in vacuo* to give the crude methyl ester **11** (145 mg). ^{1}H NMR (400 MHz, CDCl₃): δ 1.05 (d, 3H, J=6.7 Hz), 1.10 (d, 3H, J=6.7 Hz), 2.05-2.14 (m, 1H), 3.10 (dt, 1H, J=2.6 Hz, J=8.1 Hz), 3.78 (s, 3H), 3.93 (d, 1H, J=2.6 Hz), 6.2 (bs, 1H). ^{13}C NMR (100 MHz, CDCl₃): 19.6 (CH₃), 19.9 (CH₃), 27.8 (CH), 51.6 (CH), 52.5 (CH₃), 64.2 (CH), 171.8 (C), 175.5 (C).

(2*S*, 3*R*)-1-tert-Butyl 2-methyl 3-isopropyl-4-oxoazetidine-1,2-dicarboxylate 6
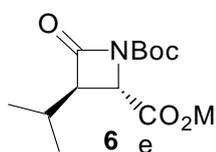
To a CH_2Cl_2 (2mL) solution of crude compound **12** (145 mg) Et_3N (0.106mL), Boc_2O (0.353 mL) and DMAP (94 mg) were added at 0°C. Then the mixture was left to stir overnight at room temperature. The reaction was acidified with aqueous HCl 1M, the phases were separated and the aqueous phase was extracted twice with CH_2Cl_2 (5 mL). The combined organic extracts were dried and evaporated. The residue was purified by flash column chromatography (hexane/EtOAc= 9/1) to afford (2*S*, 3*R*)-**6** (238 mg, 54% yields from **3c**, dr=95/5, ee%=95) as a colorless oil. HPLC analysis on a Daicel Chiralpak AD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: $τ_{minor}$ = 7.9 min, $τ_{major}$ = 12.7 min; HRMS : m/z calcd for $C_{13}H_{21}NO_5$: 271.1419, found: 271.1414. $[α]^{rt}_D$ = −31.4 (*c*=1.0, CH_2Cl_2), lit.[8]: (2*R*,3*S*)-**6** $[α]^{25}_D$ = +51.3 (*c*=1.0, CH_2Cl_2, dr>99:1, ee>99%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.01 (d, 3H, *J*=6.7 Hz), 1.08 (d, 3H, *J*=6.7 Hz), 1.48 (s, 9H), 2.00-2.14 (m, 1H), 2.97 (dd, 1H, $J_{2,3}$=3.2 Hz, *J*=8.4 Hz), 3.80 (s, 3H), 4.13 (d, 1H, $J_{2,3}$=3.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 19.7 (CH_3), 20.0 (CH_3), 27.9 (CH_3), 28.0 (CH), 52.6 (CH_3), 53.9 (CH), 61.9 (CH), 83.8 (C), 147.1 (C), 164.9 (C), 169.8 (C).

The *trans* configuration was confirmed by the ^1H-NMR coupling constant $J_{2,3}$=3.2 Hz observed. The corresponding coupling constant of the minor *syn*-diastereoisomer was $J_{2,3}$=6.6 Hz.

General procedure for the *syn*-Mannich reaction of aldehydes with in situ generated *N*-carbamoyl aromatic imines. The reactions were carried out using 10-20 mol% of the proline-derived tetrazole catalyst **IV**, following the same experimental procedure described above. The only difference concerns the isolation of the *syn*-adducts **8**, which can be easily obtained in good yields after a simple trituration of the crude mixture with cool hexane.
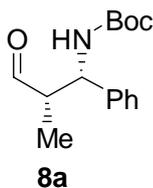
tert-butyl (1S,2S)-2-methyl-3-oxo-1-phenylpropylcarbamate (8a)
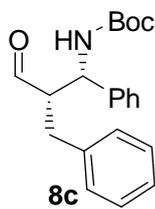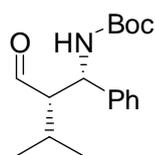
The reaction was carried out following the general procedure to furnish the crude product [dr = 15:1, determined by integration of one set of ^1H NMR signal ($δ_{major}$ 9.72 ppm - s, $δ_{minor}$ 9.65 ppm - d)]. The title compound was isolated as a white solid by trituration with cool hexane of the crude mixture in 77% yield and 99% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: *syn*

diastereoisomer τ_{major} = 17.7 min, τ_{minor} = 13.0 min; *anti* diastereoisomer τ_{major} = 12.3 min, τ_{minor} = 13.8 min; $[\alpha]_{rt}^{D}$= +4.1 (*c* = 1.1, CHCl$_3$, 99% ee). ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.09 (d, 3H, *J*= 6.9 Hz), 1.44 (s, 9H), 2.89 (bs, 1H), 5.15 (bs, 1H), 5.21 (bs, 1H), 7.25-7.39 (m, 5H), 9.74 (bs, 1H). ^{13}C NMR (150 MHz, CDCl$_3$): δ 9.2 (CH$_3$), 28.3 (**C**(CH$_3$)$_3$), 51.5 (CH), 54.7 (CH), 80.0 (C), 126.6 (CH), 127.6 (CH), 128.7 (CH), 139.5 (C), 155.1 (C), 202.9 (C).
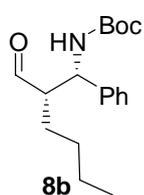
tert-butyl (1S,2S)-2-formyl-1-phenylhexylcarbamate (8b)

The reaction was carried out following the general procedure to furnish the crude product [dr = 5:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.58 ppm - s, δ_{minor} 9.60 ppm - d)]. The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 85/15) in 70% yield and 99% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 80/20 hexane/*i*-PrOH, flow rate 0.50 mL/min, λ = 214, 254 nm: *syn* diastereoisomer τ_{major} = 12.9 min, τ_{minor} = 10.1 min, *anti* diastereoisomer τ_{major} = 11.7 min, τ_{minor} = 10.9 min; $[\alpha]_{rt}^{D}$= − 17.6 (*c* = 0.90, CHCl$_3$, 99% ee). ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.85 (t, 3H, *J*=6.8Hz), 1.18-1.32 (m, 5H), 1.41 (s, 9H), 1.63 (bs, 1H), 2.69 (bs, 1H), 5.05 (bs, 1H), 5.15 (bs, 1H), 7.21-7.37 (m, 5H), 9.58 (bs, 1H). ^{13}C NMR (150 MHz, CDCl$_3$): δ 13.7 (CH$_3$), 22.6 (CH$_2$), 25.3 (CH$_2$), 28.3 (**C**(CH$_3$)$_3$), 29.6 (CH$_2$), 54.6 (CH), 56.7 (CH), 79.9 (C), 126.8 (CH), 127.7 (CH), 128.7 (CH), 139.6 (C), 155.0 (C), 203.7 (C).
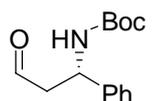
tert-butyl (1S,2S)-2-benzyl-3-oxo-1-phenylpropylcarbamate (8c)

The reaction was carried out following the general procedure to furnish the crude product [dr = 10:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.63 ppm - s, δ_{minor} 9.65 ppm - s)]. The title compound was isolated as a white solid by trituration of the crude mixture with cool hexane in 89% yield and >99% ee. HPLC analysis on a Daicel Chiralcel OD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: *syn* diastereoisomer τ_{major} = 33.3 min, τ_{minor} = 29.1 min, *anti* diastereoisomer τ_{major} = 26.5 min, τ_{minor} = 22.9 min. ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.43 (s, 9H), 2.79 (bs, 1H), 3.02 (t, 1H, *J*= 11.9 Hz), 3.19 (bs, 1H), 5.14 (bs, 1H), 5.23 (bs, 1 H), 7.09-7.38 (m, 10 H), 9.63 (bs, 1H). ^{13}C NMR (150 MHz, CDCl$_3$):

δ 28.3 (**C**(CH$_3$)$_3$), 31.6 (CH$_2$), 54.7 (CH), 58.1 (CH), 80.1 (C), 126.5 (CH), 126.9 (CH), 127.9 (CH), 128.3 (CH), 128.6 (CH), 128.9 (CH), 138.4 (C), 139.2 (C), 155.0 (C), 202.8 (C).

tert-butyl (1S,2S)-2-formyl-3-methyl-1-phenylbutylcarbamate (8d)

The reaction was carried out following the general procedure using 20% mol of **IV** and ran for 65h at room temperature to furnish the crude product [dr = 11.2:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.49 ppm - d, δ_{minor} 9.75 ppm - d)]. The title compound was isolated as a white solid by trituration of the crude mixture with cool hexane in 80% yield and >99% ee. HPLC analysis on a Daicel Chiralcel OD-H column: 98/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: *syn* diastereoisomer τ_{major} = 12.7 min, τ_{minor} = 11.3 min, *anti* diastereoisomer τ_{major} = 8.9 min, τ_{minor} = 10.2 min. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.02 (d, 3H, *J*= 7.1 Hz), 1.13 (d, 3H, *J*= 7.1 Hz), 1.40 (s, 9H), 2.12 (bs, 1H), 2.49 (bs, 1H), 5.12 (bs, 2H), 7.21-7.35 (m, 5H), 9.49 (d, 1H, *J*=3.9 Hz). ^{13}C NMR (150 MHz, CDCl$_3$): δ 21.2 (CH$_3$), 21.6 (CH$_3$), 26.9 (CH), 27.9 (CH), 28.3 (**C**(CH$_3$)$_3$), 53.4 (CH), 61.9 (CH), 79.9 (C), 126.5 (CH), 127.8 (CH), 129.6 (CH), 139.6 (C), 154.9 (C), 294.9 (C).

(S)-tert-butyl 3-oxo-1-phenylpropylcarbamate (7f)

The reaction was carried out for 65h following the general procedure, using 20% mol of catalyst **IV** and 5 equivalents of freshly distilled acetaldehyde to furnish the crude product. The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 80/20) in 43% yield and 84% ee (determined after reduction of the isolated product to the corresponding alcohol). HPLC analysis on a Daicel Chiralpak AD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 15.0 min, τ_{minor} = 23.2 min. ESI-MS: [M+H]$^+$= 250, [M+Na]$^+$=272. $[\alpha]_{rt}^D$= − 33.5 (*c* = 1.0, CHCl$_3$, 84% ee); Lit[7] (*S*)-**7f**, $[\alpha]_{rt}^D$= − 59.6 (*c* = 1.0, CHCl$_3$, 99% ee).

8e-OH
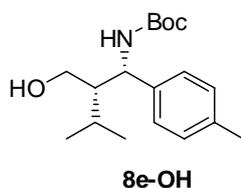
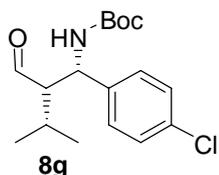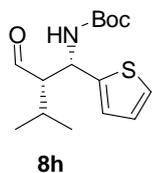**tert-butyl (1S,2S)-2-(hydroxymethyl)-3-methyl-1-p-tolylbutylcarbamate (8e).** The reaction was carried out following the general procedure using 20% mol of **IV** and ran for 65h at room temperature to furnish the crude product [dr = 11:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.60 ppm - d, δ_{minor} 9.87 ppm - d)]. The β-amino aldehyde **8e** was isolated as a white solid by trituration of the crude with cold hexane in 76% yield. Then, pure **8e** was reduced to the corresponding alcohol **8e-OH** to measure the enantiomeric purity (>99% ee). HPLC analysis on a Daicel Chiralcel OD-H column: 98/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: *syn* diastereoisomer τ_{major} = 17.6 min, τ_{minor} = 19.4 min, *anti* diastereoisomer τ_{major} = 11.3, τ_{minor} = 14.4min. $[\alpha]_{rt}^D$ = − 33.5 (*c* = 0.99, CHCl$_3$, >99% ee). ^{1}H NMR (600 MHz, CDCl$_3$): δ 0.82 (d, 3H, *J*= 6.9 Hz), 0.98 (d, 3H, *J*= 6.9 Hz), 1.40 (s, 9H), 1.71 (bs, 1H), 1.81 (bs, 1H), 2.16 (bs, 1H), 2.31 (s, 3H), 3.41 (t, 3H, *J*= 11.2 Hz), 3.63 (bs, 1H), 4.98 (bs, 1H), 5.50 (d, 1H, *J*= 8.8 Hz), 7.11-7.21 (m, 4H). ^{13}C NMR (150 MHz, CDCl$_3$): δ 18.9 (CH$_3$), 21.0(CH$_3$), 22.5 (CH$_3$), 26.3 (CH), 28.4 (**C**(CH$_3$)$_3$), 51.4 (CH), 54.4(CH), 60.9 (CH$_2$), 79.5 (C), 126.7 (CH), 129.1 (CH), 136.6 (C), 155.7 (C).

8f
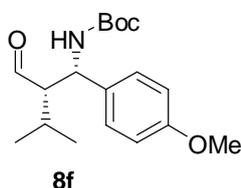
tert-butyl(1S,2S)-2-formyl-1-(4-methoxyphenyl)-3-methylbutylcarbamate (8f). The reaction was carried out following the general procedure using 20% mol of **IV** and ran for 65h at room temperature to furnish the crude product [dr = 7:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.47 ppm - d, δ_{minor} 9.70 ppm - s)]. The title compound was isolated as a white solid by trituration of the crude mixture with cool hexane in 85% yield and 99% ee. HPLC analysis on a Daicel Chiralcel OD-H column: 85/15 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: *syn* diastereoisomer τ_{major} = 12.0 min, τ_{minor} = 15.4 min *anti* diastereoisomer τ_{major} = 10.6, τ_{minor} = 13.4 min. $[\alpha]_{rt}^D$ = − 98.5 (*c* = 1.11, CHCl$_3$, 99% ee). ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.01 (d, 3H, *J*= 7.1 Hz), 1.09 (d, 3H, *J*= 7.1 Hz), 2.04-2.13 (m, 1H), 2.51 (bs, 1H), 3.76 (s, 3H), 4.99-5.12 (m, 3H), 5.34 (bs, 1H), 7.69-7.84 (m, 2H), 7.14-7.17 (m, 2H), 7.27-7.34 (m, 5H), 9.48 (bs, 1H). ^{13}C NMR (150 MHz, CDCl$_3$): δ 18.9 (CH), 21.3 (CH$_3$), 27.1 (CH$_3$), 28.3 (**C**(CH$_3$)$_3$), 55.2 (CH$_3$), 62.1 (CH), 68.1 (CH), 79.7 (C), 114.1 (CH), 128.3 (CH), 130.8 (C), 154.8 (C), 159.0 (C), 205.0 (C).
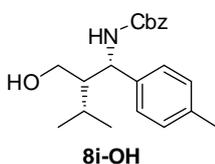
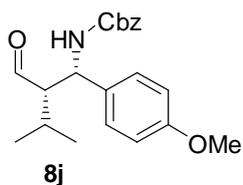**tert-butyl (1S,2S)-1-(4-chlorophenyl)-2-formyl-3-methylbutylcarbamate 8g.**

The reaction was carried out following the general procedure using 20% mol of **IV** and ran for 65h at room temperature to furnish the crude product [dr = 3:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.73 ppm - d, δ_{minor} 9.49 ppm - d)]. The title compound was isolated as a white solid by trituration of the crude mixture with cool hexane in 73% yield and >99% ee. HPLC analysis on a Daicel Chiralpack AD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: *anti* diastereoisomer τ_{major} = 11.0, τ_{minor} = 7.7 min; *syn* diastereoisomer τ_{major} = 9.7min, τ_{minor} = 8.6 min. $[\alpha]_{rt}^{D}$= − 51.3 (*c* = 1.1, CHCl₃, >99% ee). ^{1}H NMR (400 MHz, CDCl₃): δ 1.00 (d, 3H, *J*= 6.9 Hz), 1.12 (d, 3H, *J*= 6.9 Hz), 1.39 (s, 9H), 2.09 (bs, 1H), 2.48 (bs, 1H), 5.05 (bs, 1H), 5.12 (bs, 1H), 7.18-7.33 (m, 4H), 9.49 (d, 1H, *J*=3.6 Hz). ^{13}C NMR (150 MHz, CDCl₃): δ 19.1 (CH₃), 21.2 (CH₃), 26.9 (CH), 28.2 (**C**(CH₃)₃), 52.8 (CH), 61.7 (CH), 80.0 (C), 127.9 (CH), 128.6 (CH), 128.9 (CH), 133.6 (C), 154.8 (C), 204.6 (C).

tert-butyl (1S,2S)-2-formyl-3-methyl-1-(thiophen-2-yl)butylcarbamate 8h.

The reaction was carried out following the general procedure using 20% mol of **IV** and ran for 65h at room temperature to furnish the crude product [dr = 9:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.64 ppm - s, δ_{minor} 9.79 ppm - d)]. The title compound was isolated as a white solid by trituration of the crude mixture with cool hexane in 86% yield and 99% ee. HPLC analysis on a Daicel Chiralcel OD-H column: 99/1 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: *syn* diastereoisomer τ_{major} = 16.9 min, τ_{minor} = 13.6 min, *anti* diastereoisomer τ_{major} = 11.3, τ_{minor} = 12.3 min. $[\alpha]_{rt}^{D}$= − 88.7 (*c* = 1.00, CHCl₃, 99% ee). ^{1}H NMR (600 MHz, CDCl₃): δ 1.03 (d, 3H, *J*= 6.5 Hz), 1.11 (d, 3H, *J*= 6.5 Hz), 1.42 (s, 9H), 2.14 (bs, 1H), 2.53 (bs, 1H), 5.14 (bs, 1H), 5.37 (bs, 1H), 6.90-6.94 (m, 2H), 7.20-7.22 (m, 1H), 9.64 (bs, 1H). ^{13}C NMR (150 MHz, CDCl₃): δ 19.1 (CH₃), 21.2 (CH₃), 26.9 (CH), 28.3 (**C**(CH₃)₃), 52.7 (CH), 61.7 (CH), 80.0 (C), 127.9 (CH), 128.6 (CH), 128.9 (CH), 133.6(C), 154.8 (C), 204.6 (C).

benzyl (1S,2S)-2-(hydroxymethyl)-3-methyl-1-p-tolylbutylcarbamate (8i)

The reaction was carried out following the general procedure using 20% mol of **IV** and ran for 65h at room temperature to furnish the crude product [dr = 3.2:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 9.57 ppm - d, δ_{minor} 9.77 ppm - d)].

The β-amino aldehyde **8i** was isolated as a white solid by trituration of the crude with cold hexane in 70% yield. Then, pure **8i** was reduced to the corresponding alcohol **8i-OH** to measure the enantiomeric purity (98% ee). HPLC analysis on a Daicel Chiralpack AD-H column: 9/1 hexane/*i*-PrOH, flow rate 0.60 mL/min, λ = 214, 254 nm: τ_{major} = 47.1, τ_{minor} = 29.5 min. $[\alpha]_{rt}^{D}$ = − 8.6 (*c* = 0.73, CHCl₃, 98% ee). ¹H NMR **8i-OH** (600 MHz, CDCl₃): δ 0.94 (d, 3H, *J*= 6.9 Hz), 1.15 (d, 3H, *J*= 6.9 Hz), 1.80-2.02 (bs, 2H), 2.45 (s, 3H), 3.52-3.67 (m, 1H), 3.68-3.92 (m, 1H), 5.04-5.23 (m, 3H), 6.04 (d, 1H, *J*= 11.0 Hz), 7.20-7.45 (m, 9H), 7.31. ¹³C NMR (150 MHz, CDCl₃): δ 18.7 (CH₃), 21.0 (CH₃), 22.3 (CH₃), 26.5 (CH), 51.3 (CH), 55.6 (CH), 61.1 (CH₂), 66.7 (CH₂), 127.0 (CH), 128.1 (CH), 128.4 (CH), 129.2 (CH), 136.5 (C), 136.9 (C), 136.6 (C), 159.3 (C).

benzyl (1S,2S)-2-formyl-1-(4-methoxyphenyl)-3-methylbutylcarbamate 8j

The reaction was carried out following the general procedure using 20% mol of **IV** and ran for 65h at room temperature to furnish the crude product [dr = 5:1, determined by integration of one set of ¹H NMR signal (δ_{major} 9.48 ppm - d, δ_{minor} 9.75 ppm - d)]. The title compound was isolated as a white solid by trituration of the crude mixture with cool hexane 70% yield and > 99% ee. HPLC analysis on a Daicel Chiralcel OD-H column: 85/15 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: *syn* diastereoisomer τ_{major} = 12.0 min, τ_{minor} = 15.4 min *anti* diastereoisomer τ_{major} = 10.6, τ_{minor} = 13.4 min; $[\alpha]_{rt}^{D}$ = − 59.0 (*c* = 0.97, CHCl₃, > 99% ee). ¹H NMR (600 MHz, CDCl₃): δ 1.01 (d, 3H, *J*= 7.0 Hz), 1.09 (d, 3H, *J*= 7.0 Hz), 2.04-2.13 (bs, 1H), 2.46-2.52 (bs, 1H), 3.76 (s, 3H), 4.99-5.12 (m, 3H), 5.35 (bs, 1H), 6.69-7.84 (m, 2H), 7.14-34 (m, 6H), 9.48 (bs, 1 H). ¹³C NMR (150 MHz, CDCl₃): δ 18.8 (CH), 21.1 (CH₃), 27.1 (CH₃), 53.3 (CH), 55.2 (CH₃), 61.7 (CH), 66.9 (CH₂), 114.2 (CH), 128.1 (CH), 128.5 (CH), 131.5 (C), 136.2 (C), 155.5 (C), 159.2 (C), 204.7 (C).

3.2 The Proline-catalyzed Double Mannich Reaction of Acetaldehyde with N-Boc Imines

meso

99% yield, *dr* > 99:1
er = 9905 (99.98% ee)
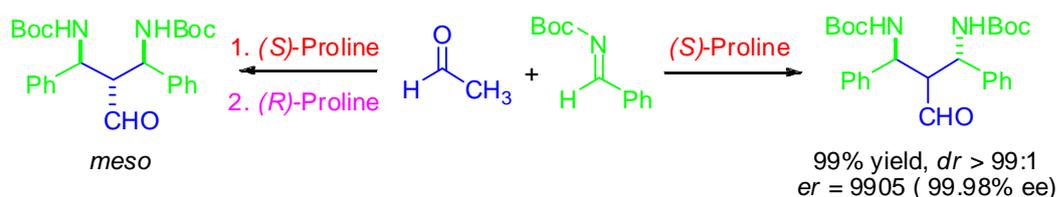
Double cross: Proline catalyzes the double Mannich reaction of acetaldehyde with *N*-Boc imines in excellent yields (up to 99%) and close to perfect diastereo- and enantioselectivities. Depending on the choice of catalysts, both the chiral, pseudo C_2-symmetric diastereomer as well as the corresponding meso-compound can be prepared. In addition, cross double Mannich reactions of acetaldehyde with two different imines are also demonstrated.

As anticipated before, remarkably, despite attempts[1,2] it is only very recently that acetaldehyde - the simplest of all enolizable carbonyl compounds - could be used as nucleophile with success. This issue has been addressed by the research group of List, which has developed a proline-catalyzed Mannich reaction of acetaldehyde with preformed *N*-Boc imines that gives rise to α-unbranched β-aminoaldehydes with outstanding level of enantiocontrol (Scheme 1).[3]


1   5-10 equiv.
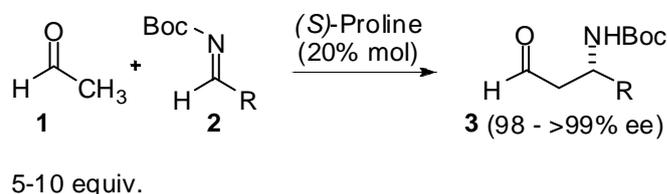
Scheme 1. *Mannich reaction of acetaldehyde with imine 2*

Acetaldehyde's employment has been hampered in organocatalysis because of its high reactivity; it rapidly reacts with itself via aldol condensation, forming coloured oligomers and polymers in presence of proline. It would be quite surprising then, if organocatalysis would not already accustom us so often to the simultaneous solution of problems, that in few months this challenging nucleophile, never used before, proved suitable also for the cross-aldol reaction[4] and in the related Michael reactions with nitroalkenes.[5]

Despite the synthetic value of compounds derived from the Mannich[6] reaction of acetaldehyde as precursors of β^3 – amino acids, recently pioneered by Gellman and co-workers[7] and by Seebach and collaborators[8] in investigations of so called β-peptides and pharmaceuticals, the main benefit of employing acetaldehyde is that it gives access to α-unbranched aldehydes. Interestingly, these substrates are not sterically encumbered and they should be in principle suitable substrates for a further enamine activation, with the possibility of undergoing a double in situ enamine activation sequence with two

electrophiles, delivering highly functionalyzed carbonyl compounds (Scheme 2).
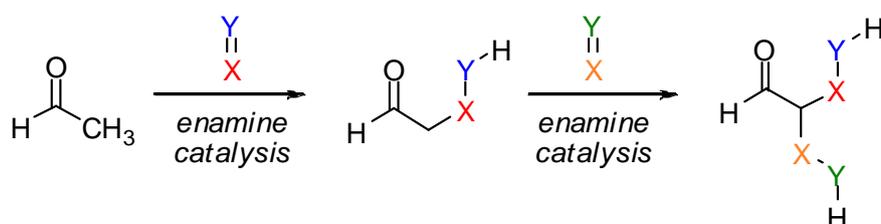
Scheme 2. *Concept: enamine catalysis in situ sequences of acetaldehyde with two electrophiles.*

Here we document the first successful exploitation of this concept with a double Mannich reaction of acetaldehyde with either a single or two different *N*-Boc imines, catalyzed by proline. During the initial study of the Mannich reaction of acetaldehyde, it was found that product **3** - deriving from a first enamine activation of acetaldehyde- reacts with an additional equivalent of imine **2a**, leading to the formation of the bis-addition product **4a** in traces.
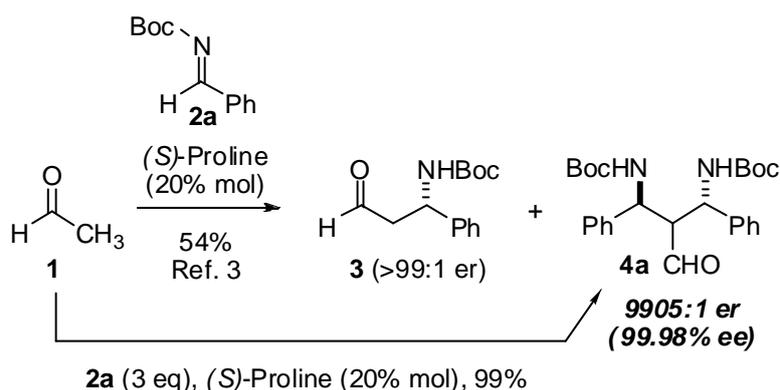
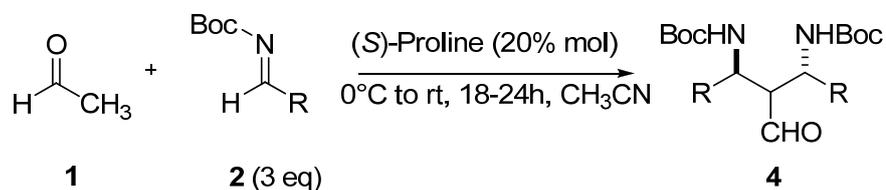**Scheme 3.** *Double Mannich reaction of acetaldehyde with imine 2a.*

Having undergone two cycles of enamine activation during the course of the reaction, this pseudo C$_2$-symmetric compound contains a chirotopic non

stereogenic center embedded between two new stereogenic centers. We were interested in the enantiomeric ratio of the product **4a**, as it was expected to be high, due to the occurrence of two concomitant highly enantioselective transformations for its formation. Indeed, careful HPLC analysis, including determination of the detection limit of the enantiomers, revealed an er of 9905:1 corresponding to an ee of 99.98% for the double-addition product. This finding led us to the further investigation of the reaction, as this transformation- unique to the Mannich reaction with acetaldehyde- furnishes highly valuable molecular structures, for instance, precursors of β,β'-di amino acids.

We sought to optimize the reaction conditions to give consistently high yields for the double-adduct product. By varying parameters such as the equivalents of acetaldehyde, time, rate of addition and dilution, we found that if one equivalent of acetaldehyde was treated with three equivalent of imine **2a**, compound **4a** was obtained in essentially quantitative yield.

Encouraged by this exciting result, we performed the reaction employing our optimized conditions with a variety of *N*-Boc imines to evaluate the scope of the double Mannich reaction. As highlighted in Table 1, the method proved successful for a wide range of imines; the aromatic ring substitution is well tolerated and imines with differing electronic properties (entries 1-5) provided products in high yields (76-99%) and with exceptionally high diastereo- and enantioselectivities (> 99:1 dr, > 300:1 er).

A heteroaromatic imine also participated in the reaction furnishing product **4f** in 93% yield with similar stereoselectivity (entry 6). Even the highly challenging aliphatic isovaleraldehyde-derived *N*-Boc imine gave the double Mannich adduct highly enantioselectively (>300:1 er) albeit in moderate yield (30%) due to the instability of this imine (entry 7); aliphatic *N*-Boc imines must be in fact handled quickly and used immediately for the reaction upon formation from correspond sulfone.[9]

Table 1. Double Mannich Reactions of Acetaldehyde.[a]

Entry	Product	Yield [%][b]	d.r.[c]	e.r. (ee%)[d]
1[e]	4a	99	> 99:1	9905 (99.98)
2	4b	86	> 99:1	> 300 (> 99)
3	4c	90	> 99:1	> 300 (> 99)
4	4d	85	> 99:1	> 300 (> 99)
5	4e	76	> 99:1	> 300 (> 99)
6[e]	4f	93	> 99:1	> 300 (> 99)
7[f]	4g	30	> 99:1	> 300 (> 99)

[a] Unless otherwise noted, reactions were run with imine **2** (0.75 mmol) and acetaldehyde (0.25 mmol) in CH_3CN at 0°C for 2 h and then allowed to warm to r.t. for 18-22h. [b] Isolated yield. [c] Determined by NMR of the crude mixture. [d] Determined by HPLC analysis of the corresponding alcohol. [e] Reaction run at 0°C for 24 h. [f] To a solution of *(S)*-proline (0.2 equiv) in CH_3CN at 0°C was added a solution of the *N*-Boc imine (0.31mmol, 1 equiv.) in CH_3CN and acetaldehyde (1.5 equiv). The solution was allowed to stir for 2h at 0°C before a second addition of freshly prepared *N*-Boc imine (1.5 equiv.) was added.

The following step was to extend the methodology to a cross-double addition product by sequencing the addition of two different aromatic *N*-Boc imines, trying to develop a high desirable one-pot protocol for the setting of three new stereogenic centers. Unfortunately, several attempts under a variety of conditions[10] led to the corresponding desired cross-Mannich products in low yields, being the major products both the homocoupling compounds. We decided then to turn towards a step by step procedure, isolating the initial mono-addition products and then perform a second reaction with the second imine. Indeed, treating isolated Mannich products **3** (> 99:1 e.r.) with a different aromatic imine in the presence of either (*S*)- or (*R*)-proline gave the corresponding cross-Mannich products in reasonably good yields and with high diastereoselectivities, and, as anticipated, with enantiomeric ratios greater than 99:1. The results are reported in Table 2.

Table 2. *Mannich Reactions of compound **3** with different imines **2**.*
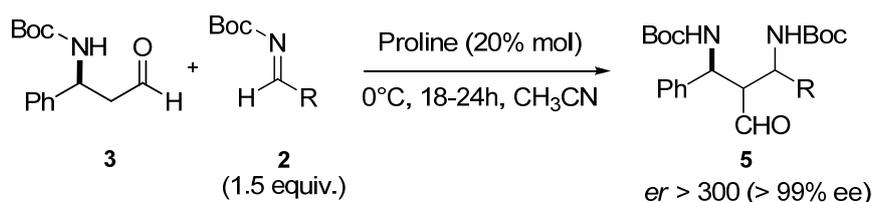
Entry	Product	Yield [%][a]	Dr[b]
1[c]	**5a**	61	45:2:1:0
2[d]	**5b**	59	70:2:1:0

3[c,e]	**5c**	58	>20:1:1:1
4[d,e]	**5d**	60	>20:1:1:1
5[d]	**5e**	53	>20:1:1:1

[a] Isolated yield of the corresponding alcohol after in situ reduction. [b] The d.r. refers to the ratio of the four possible diastereomers and was determined by HPLC analysis of the corresponding crude alcohol mixture after in situ reduction (entries 1,2) or follwoing column chromatography (entries 3-5). [c] Using *(S)*-proline. [d] Using *(R)*-proline. [e] Reaction performed with 1.3 equiv. of imine **2**.

Interestingly, by the judicious selection of the absolute configuration of the catalyst it is possible to selectively achieve a single well-defined diastereoisomer. Judging from the excellent diastereocontrol of the reaction either using (*S*)- or (*R*)-proline, in both cases these reactions are completely catalyst-controlled. Using (*S*)-proline, the reaction leads to products **5a** and **5c** (entries 1 and 3), resulting from the inherent *syn*-diastereoselectivity and imine *Si*-facial enantioselectivity of the (*S*)-proline-catalyzed Mannich reaction. In contrast, when we used (*R*)-proline as the catalyst, diastereisomers **5b** and **5d** were obtained. In these cases, the two new stereogenic centers are formed with the opposite configuration (entries 2 and 4).

The strategy of sequencing first (*S*)-proline and then (*R*)-proline in subsequent acetaldehyde Mannich reactions with the same imine (**2a**) can be used to create the corresponding *meso*-product **5e** highly diastereoselectively (entry 5). In this rather sophisticated symmetrisation process, two highly enantioselective catalytic reactions are sequenced to create an achiral molecule.

Finally, since the Mannich adducts **4**-**5** represent versatile intermediates for accessing valuable chiral building blocks, we readily converted aldehyde **4b** into the corresponding diamino acid **6** via a straightforward two-step oxidation-deprotection sequence in 73% overall yield (Eq. 1). [11]
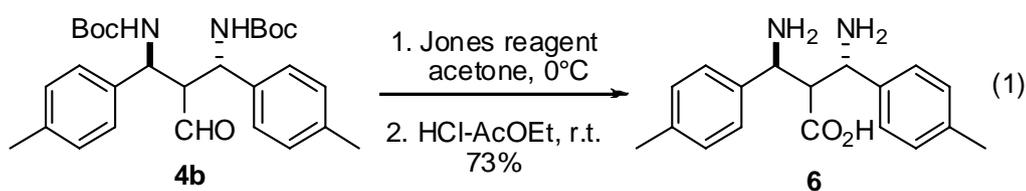
In summary, the first realization of a double enamine catalysis sequence using acetaldehyde as the nucleophile has been developed. Our methodology provided a simple access to pseudo C_2-symmetric β,β'-diamino aldehydes with extremely high stereoselectivities starting from acetaldehyde and both aromatic and aliphatic *N*-Boc imines, through an efficient one-pot catalytic asymmetric protocol. The synthetic procedure has been extended to cross-Mannich reactions furnishing β,β'-diamino aldehydes **5** containing stereotriads. The general strategy should be of use for alternative double enamine catalysis sequences using different reactions and even triple enamine catalysis sequences of acetaldehyde can be envisioned.

3.2 R References

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[9] Unfortunately, despite attempts, our previous described methodology of in situ generation of N-Boc imines from sulfones, failed for aliphatic imine substrates.

[10] A representative *in-situ* attempt for the synthesis of cross double Mannich products is as follows: A standard Mannich reaction mixture of (*S*)-proline (20% mol), imine **2a** (1 equiv), and acetaldehyde (1.5 equiv.) was stirred for three hours. N-Boc imine **2b** (1.5 equiv.) was added and a complex mixture of the two first Mannich adducts of type **3**, the two homo double Mannich products **4a** and **4b**, and the desired cross Mannich product of type **5** resulted. The ratio **4b**:**5** was close to 1:1 and could be slightly improved to 0.6: 1 by slowly adding imine **4b** under dilute conditions.

[11] For a multistep synthesis of similar *β,β'*-diamino acid derivatives, see: A. A. Taubinger, D. Fenske, J. Podlech, *Tetrahedron* **2008**, *64*, 8659-8667.

3.2 Supplementary Information

Contents

General Methods

Materials

Determination of Diastereomeric Ratios

Determination of Enantiomeric Purity

Experimental Procedures

General Methods: Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Reactions were monitored by thin layer chromatography on silica gel precoated glass plates (0.25 mm, 60F-254, E. Merck) using fluorescence quenching with UV light at 254 nm; anisaldehyde or ninhydrin stains were used to visualize the course of the reactions. Flash column chromatography was performed using E. Merck silica gel (60, particle size 0.040-0.063 mm). Chemical yields refer to pure isolated substances. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300, AV-400 or AV-500 spectrometer. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard (CDCl$_3$, δ 7.26 ppm, (CD$_3$)$_2$CO, δ 2.05 ppm and (CD$_3$)$_2$SO, δ 2.50 ppm). The following abbreviations were used to designate chemical shift multiplicities: s=singlet, d=doublet, q=quartet, m=multiplet, br=broad. Mass spectra were obtained on a Finnigan MAT 8200 (70 eV), accurate mass determinations were done on a Bruker APEX III FT-MS (7 T magnet).

Materials

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All solvents employed in the reactions were distilled from appropriate drying agents prior to use.

Determination of Diastereomeric Ratios

The diastereomeric ratios of homo double Mannich products **4a-g** were determined by NMR analysis of the crude mixtures (other diastereomers were never observed in these mixtures).

Determination of Enantiomeric Purity. The optical purities (er, ee) of homo double Mannich compounds 4a-g and cross double Mannich compounds **5a-b** were determined by HPLC analysis specified in the individual experiments. Comparisons with the racemic samples obtained by mixing the products from individual reactions with (*S*)-proline and (*R*)-proline were made.

Experimental procedures

Preparation of *N*-Boc imines

N-Boc imines **2a-f** were prepared from the corresponding *N*-(tert-butoxycarbonyl)-α-(phenylsulfonyl)amines following modified literature procedures.[13-2] All physical data were in agreement with the literature.

General Procedure for the Catalytic Enantioselective Double Mannich Reaction of Acetaldehyde with *N*-Boc Arylimines.

N-Boc imine 2 (0.75 mmol, 3 equiv.) was dissolved in anhydrous acetonitrile (3.75 mL) and stirred under an atmosphere of argon. The solution was cooled to 0°C and freshly distilled acetaldehyde

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[13] For the synthesis of *N*-(tert-butoxycarbonyl)-α-(phenylsulfonyl)amines , see: T. Mecozzi and M. Petrini, *J. Org. Chem.* **1999,** *64,* 8970-8972.

[2] For the synthesis of aromatic *N*-Boc imines **2a-f**, see A. G. Wenzel and E. N. Jacobsen *J. Am. Chem. Soc.* **2002**, 124, 2964-12965 and for the aliphatic *N*-Boc imine **2g**, see, J. Song, Y. Wang, L. Deng *J. Am. Chem. Soc.* **2006**, *128*, 6048-6049.

(0.25 mmol, 1 equiv.) and (S)-proline (0.05 mmol, 0.2 equiv.) were added. The reaction was allowed to stir for 2 h at 0°C and then warmed to room temperature. After stirring for 18-22h, the reaction mixture was extracted with CH_2Cl_2 (15 mL x 3) and the combined organic phases were washed with brine, dried over $MgSO_4$, and filtered. Evaporation of the solvents furnished the crude products, which were subjected to silica gel column chromatography using hexane/ethyl acetate as eluent to afford pure products 4a-f as white solids. Determination of optical purity was carried out upon reduction of aldehydes 4a-f to the corresponding alcohols with $NaBH_4$ (3 equiv.) in $THF:H_2O$ (4:1 v/v).
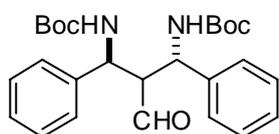
tert-butyl-(1S,3S)-2-formyl-1,3-diphenylpropane-1,3-diyldicarbamate 4a. The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 90:10) in 99% yield. ^1H NMR ($CDCl_3$, 500 MHz) δ 9.58 (brs, 1H), 7.33-7.09 (m, 8H), 7.01 (brm, 2H), 5.83 (brd, J = 8.0 Hz, 1H), 5.76 (brd, J = 9.8 Hz, 1H), 5.27 (brs, 1H), 4.94 (brs, 1H), 3.22 (brs, 1H), 1.36 (s, 9H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.1, 155.3, 141.1, 139.2, 128.9, 128.7, 127.9, 127.5, 126.7, 126.4, 80.1, 80.0, 61.6, 53.7, 51.1, 28.4, 28.2; HRMS (ESI) calculated for ($C_{26}H_{34}N_2NaO_5Na^+$), 477.2360; found 477.2355; MS (EI) m/z 454 (M^+). The enantiomeric ratio was determined to be 9905 (99.98 % ee) by HPLC analysis after reduction to the corresponding alcohol using a Chiracel OD-R column, mobile phase: $MeOH/H_2O$ = 70:30 (v/v), flow: 0.5 mL/min, UV detector: 210 nm. Major enantiomer: t_R = 32.34 min, minor enantiomer: t_R = 27.53 min.
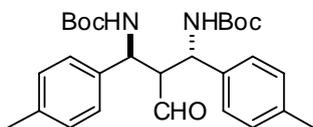
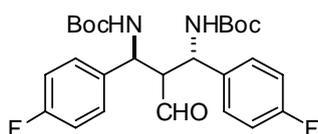**tert-butyl-(1S,3S)-2-formyl-1,3-dip-tolylpropane-1,3-diyldicarbamate 4b.** The title compound was isolated as a white solid by column chromatography (hexane/AcOEt= 90:10) in 86% yield. ^1H NMR ($CDCl_3$, 500 MHz) δ 9.67 (brs, 1H), 7.18-7.14 (m, 4H), 7.11-7.09 (m, 2H), 7.00-7.02 (m, 2H), 5.72 (brs, 1H), 5.63 (brd, J= 8.4 Hz, 1H), 5.21 (brs, 1H), 4.95 (brs, 1H), 3.26 (brs, 1H), 2.34 (s, 3H), 2.30 (s, 3H), 1.42 (s, 9H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.4 ,155.2, 155.0, 137.9, 137.5, 137.2, 135.9, 129.6, 129.4, 126.6, 126.4, 80.0, 79.8, 61.3, 53.5, 51.1, 28.3, 28.2 , 21.0, 20.9; HRMS (ESI) calculated for ($C_{28}H_{38}N_2O_5Na^+$), 505.267602; found 505.267289; MS (EI) m/z 482 (M^+). The enantiomeric ratio was determined to be > 300 (> 99% ee) by HPLC analysis after reduction to the corresponding alcohol using a Chiracel OD-R column; mobile phase:

CH$_3$CN/H$_2$O = 60:40 (v/v), flow: 0.5 mL/min, UV detector: 220 nm. Major enantiomer: t$_R$ = 18.97 min, minor enantiomer: t$_R$ = 17.46 min.
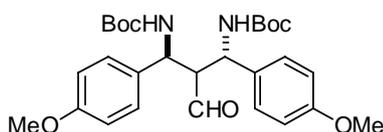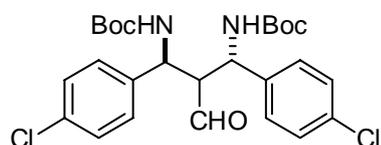

tert-butyl-(1S,3S)-2-formyl-1,3-bis(4-methoxyphenyl)propane-1,3-diyldicarbamate 4c. The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 90:10) in 90% yield. ^{1}H NMR (CDCl$_3$, 500 MHz) δ 9.66 (brs, 1H), 7.18 -7.16 (m, 2H), 7.07-7.05 (m, 2H), 6.89-6.87 (m, 2H), 6.82-6.81 (m, 2H), 5.71 (brs, 1H), 5.61 (brd, J= 9.7 Hz, 1H), 5.15 (brs, 1H), 4.94 (brs, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.24 (s, 1H), 1.45 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 203.7, 159.0, 158.8, 155.2, 155.0, 132.8, 131.0, 128.0, 127.6, 114.1, 114.0, 79.8, 79.7, 61.0, 55.1, 53.2, 50.9, 28.2, 28.1; HRMS (ESI) calculated for (C$_{28}$H$_{38}$N$_2$O$_7$Na$^+$), 537.257515; found 537.257118; MS (EI) m/z 514 (M$^+$). The enantiomeric ratio was determined to be > 300 (> 99% ee) by HPLC analysis after reduction to the corresponding alcohol using a Kromasil Cellucoat RP column; mobile phase: CH$_3$CN/H$_2$O = 60:40 (v/v), flow: 0.5 mL/min, UV detector: 220 nm. Major enantiomer: t$_R$ = 7.48 min, minor enantiomer: t$_R$ = 6.81 min.
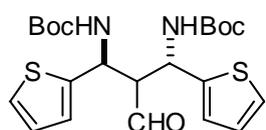

tert-butyl-(1S,3S)-1,3-bis(4-fluorophenyl)-2-formylpropane-1,3-diyldicarbamate 4d. The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 90:10) in 85% yield. ^{1}H NMR (CDCl$_3$, 500 MHz) δ 9.68 (brs, 1H), 7.30 -7.26 (m, 2H), 7.10-7.09 (m, 4H), 6.98-6.96 (m, 2H), 5.79-5.73 (m, 2H), 5.31 (brs, 1H), 4.95 (brs, 1H), 3.24 (brs, 1H), 1.44 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 202.8, 163.2, 163.0, 161.2, 161.0, 155.3, 155.1, 136.7, 135.0, 128.5, 128.4, 128.1, 128.0, 116.4, 116.3, 116.0, 115.8, 115.7, 115.6, 115,4, 115.2, 80.4, 80.2, 61.3, 53.2, 50.6, 28.3, 28.2; HRMS (ESI) calculated for (C$_{26}$H$_{32}$F$_2$N$_2$O$_5$Na$^+$), 513.216885; found 513.217152; MS (EI) m/z 490 (M$^+$). The enantiomeric ratio was determined to be > 300 (> 99% ee) by HPLC analysis after reduction to the corresponding alcohol using a Chiralcel OD-R column; mobile phase: CH$_3$CN/H$_2$O = 60:40 (v/v), flow: 0.5 mL/min, UV detector: 220 nm. Major enantiomer: t$_R$ = 13.62 min, minor enantiomer: t$_R$ = 11.95 min.

tert-butyl-(1S,3S)-1,3-bis(4-chlorophenyl)-2-formylpropane-1,3-diyldicarbamate 4e. The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 90:10) in 76% yield. ^{1}H NMR (CDCl$_3$, 500 MHz) δ 9.65 (m, 1H), 7.39-7.34 (m, 2H), 7.28-7.22 (m, 4H),7.01 (brm, 2H), 5.74 (brd, J = 9.0 Hz, 2H), 5.30 (brs, 1H), 4.92 (brs, 1H), 3.23 (brs, 1H), 1.43 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 202.6, 155.1, 139.3, 133.8, 133.4, 129.2, 128.9, 128.1, 127.7, 80.5, 61.0, 60.4, 28.3, 28.2; HRMS (ESI) calculated for (C$_{26}$H$_{32}$N$_2$NaO$_5$Cl$_2$Na$^+$), 545.158045; found 545.158159; MS (EI) m/z 466 (M$^+$). The enantiomeric ratio was determined to be > 300 (> 99% ee) by HPLC analysis after reduction to the corresponding alcohol using a Chiralcel OD-R column; mobile phase: MeOH/H$_2$O = 65:35 (v/v), flow: 0.5 mL/min, UV detector: 220 nm. Major enantiomer: t$_R$ = 16.13 min, minor enantiomer: t$_R$ = 13.83 min.
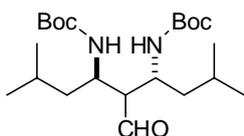

tert-butyl-(1S,3S)-2-formyl-1,3-di(thiophen-2-yl)propane-1,3-diyldicarbamate 4f. The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 90:10) in 93% yield. ^{1}H NMR (CDCl$_3$, 500 MHz) δ 9.77 (s, 1H), 7.26-7.23 (m, 1H), 7.20 (d, 1H), 7.03-6.95 (m, 2H), 6.95-6.86 (m, 2H), 5.54-5.80 (m, 2H), 5.36 (brs, 1H), 3.47 (s, 1H), 1.43 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 201.9, 155.2, 154.9, 144.6, 142.4, 127.3, 127.0, 125.5, 125.3, 124.8, 124.7, 80.4, 80.3, 61.5, 49.9, 47.7, 28.4, 28.3; HRMS (ESI) calculated for (C$_{22}$H$_{30}$N$_2$S$_2$O$_5$Na$^+$), 489.148840; found 489.148764; MS (EI) m/z 466 (M$^+$). The enantiomeric ratio was determined to be > 300 (> 99% ee) by HPLC analysis after reduction to the corresponding alcohol using Kromasil-3-CelluCoat RP column; mobile phase: CH$_3$CN/H$_2$O = 45:55 (v/v), flow: 0.5 mL/min, UV detector: 220 nm. Major enantiomer, t$_R$ = 21.83 min, minor enantiomer, t$_R$ = 23.94 min.

Procedure for the Catalytic Enantioselective Double Mannich Reaction of Acetaldehyde with isovaleraldehyde-derived *N*-Boc imine.

To a solution of (S)-proline (0.062 mmol, 0.2 equiv.) in CH$_3$CN (250 μL) at 0°C was added a solution of the N-Boc imine (0.31 mmol, 1 equiv.) in CH$_3$CN (1.3 mL). Freshly distilled acetaldehyde (0.465 mmol, 1.5 equiv.) was immediately added and the resulting solution was allowed to stir for 2 h at

0°C. At this time a second solution of freshly prepared N-Boc imine (0.465 mmol, 1.5 equiv.) in CH$_3$CN (1 mL) was added and the mixture was allowed to stir an additional 3 h at 0°C. The reaction mixture was extracted with CH$_2$Cl$_2$ (15 mL x 3) and the combined organic phases were washed with brine, dried over MgSO$_4$ and filtered. Evaporation of the solvents furnished the crude product, which was subjected to silica gel column chromatography using hexane/ethyl acetate 95:5 as eluent to afford pure product **4g** as a white solid. Determination of optical purity was carried out upon reduction of aldehyde **4g** to the corresponding alcohol with NaBH$_4$ (3 equiv.) in THF: H$_2$O (4:1 v/v).

tert-butyl-(4R,6R)-5-formyl-2,8-dimethylnonane-4,6-diyldicarbamate 4g. The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 95:5) in 30% yield. ^{1}H NMR (CDCl$_3$, 500 MHz) δ 9.73 (m, 1H), 5.15-5.07 (m, 2H), 4.29 (brm, 1H), 3.97 (brm, 1H), 2.40 (m, 1H), 1.75-1.60 (m, 4H), 1.43 (s, 9H), 1.38 (s, 9H), 0.96 (d, J= 6.5 Hz, 6H), 0.91 (d, J= 6.5 Hz, 3 H), 0.90 (d, J= 6.5 Hz, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 203.9, 156.1, 155.7, 79.5, 79.3, 59.4, 47.7, 45.2, 44.9, 42.0, 28.5, 28.3, 25.1, 24.9, 23.0, 22.9, 22.1, 21.7; HRMS (ESI) calculated for (C$_{22}$H$_{42}$N$_2$O$_5$Na$^+$), 437.298435; found 437.298588; MS (EI) m/z 414 (M$^+$). The enantiomeric ratio was determined to be > 300 (> 99% ee) by HPLC analysis after reduction to the corresponding alcohol using a Chiralcel OD-R column; mobile phase: n-Heptane/i-PrOH = 98:02 (v/v), flow: 0.5 mL/min, detector: RI. Major enantiomer: t$_R$ = 11.33 min, minor enantiomer: t$_R$ = 10.00 min.

General Procedure for the Catalytic Enantioselective Mannich Reaction of aldehyde 3 with *N*-Boc Arylimines.

To a solution of aldehyde 3 (0.14 mmol, 1 equiv.) and (S)-proline[3] (0.028 mmol, 0.2 equiv.) in CH$_3$CN (280 μL) at 0°C, was added the N-Boc imine (0.21 mmol, 1.5 equiv.[4]). The resulting solution was allowed to stir for 18-24 h at 0°C before adding a solution of 4:1 (v/v) THF: H$_2$O and NaBH$_4$ (3 equiv). The reaction mixture was allowed to stir an additional hour at 0°C and then extracted with CH$_2$Cl$_2$ (10 mL x 3). The combined organic phases were washed with brine, dried over MgSO$_4$ and

filtered. Evaporation of the solvents furnished the crude products which were subjected to silica gel column chromatography using hexane/ethyl acetate as eluent. Products **5a-e** were isolated as white solids.
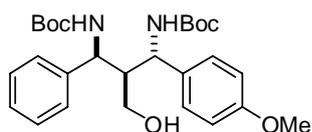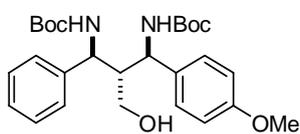

tert-butyl-(1S,2S,3S)-2-formyl-1-(4-methoxyphenyl)-3-phenylpropane-1,3-diyldicarbamate 5a. The title compound was isolated as a white solid by column chromatography (hexane/AcOEt =80:20) in 61% yield. ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.30-7.26 (m, 4H), 7.20-7.18 (m, 1H), 7.06 (brs, 2H), 6.90-6.85 (m, 2H), 5.76 (brs, 2H), 5.09 (brs, 1H), 4.98 (brs, 1H), 3.80 (s, 3H), 3.62 (brs, 1H), 3.55 (brs, 1H), 2.23 (brs, 1H), 1.46 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 158.7, 156.1, 155.8, 142.6, 133.1, 128.6, 128.0, 127.0, 126.0, 114.1, 79.7, 60.3, 55.3, 53.0, 52.5, 51.1, 28.5, 28.4; HRMS (ESI) calculated for (C$_{27}$H$_{38}$N$_2$O$_6$Na$^+$), 509.262722; found 509.262203; MS (EI) m/z 486 (M$^+$). The diastereomeric ratio of the crude mixture was determined to be: 1: 1.7: 44.5 by HPLC analysis using an achiral Zorbax XDB- C18, USWDY 06874 column, mobile phase: MeOH/H$_2$O=70:30 (v/v), flow: 1 ml/min, UV detector: 220 nm. Major diastereosomer (5a) t$_R$ = 3.35 min, second diastereosomer t$_R$ = 3.58, third diastereosomer (5b) t$_R$ = 3.79. The diastereomeric ratio of the isolated product after column chromatography was determined to be > 95:5 by HPLC analysis using an achiral YMC Pack ODS-A column; mobile phase: CH$_3$CN/H$_2$O = 55:45 (v/v), flow: 0.8 mL/min, UV detector: 220 nm. Major diastereomer: t$_R$ = 15.66 min. The enantiomeric ratio was determined to be > 300 (> 99% ee) using a Chiralcel OD-R column, mobile phase: CH$_3$CN/H$_2$O = 50:50 (v/v), flow: 0.5 mL/min, UV detector: 220 nm. Major enantiomer: t$_R$ = 27.43 min, minor enantiomer: t$_R$ = 23.93 min.

[3] For the synthesis of compounds 5b, 5d and 5e (R)-proline was used with the same procedure.
[4] For the synthesis of compounds 5c and 5d 1.3 equiv. of the corresponding imine was used.

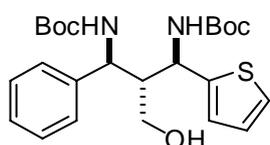**tert-butyl-(1R,2R,3S)-2-formyl-1-(4-methoxyphenyl)-3-phenylpropane 1,3-diyldicarbamate 5b.** The title compound was isolated as a white solid by column chromatography (hexane/AcOEt =80:20) in 59% yield. ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.32-7.18 (m, 8H), 6.87-6.86 (m, 2H), 5.63 (brd, 1H), 5.24 (brd, 1H), 4.98 (brs, 1H), 4.81 (brs, 1H), 3.79 (s, 3H), 3.25- 3.24 (m, 2 H), 2.72 (brs, 1H), 1.42 (brs, 9H), 1.38 (s, 9H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 158.7, 156.2, 155.8, 141.4, 133.1, 128.7, 127.4, 127.0, 126.1, 114.1, 80.0, 79.9, 61.9, 55.6, 55.3, 52.5, 50.5, 28.4. The diastereomeric ratio of the crude mixture was determined to be: 70.2 : 2.4: 1 by HPLC analysis using an achiral Zorbax XDB-C18, USWDY 06874 column; mobile phase: MeOH/H$_2$O=70:30 (v/v), flow: 1 ml/min, UV detector: 220 nm. Major diastereosomer (5b) t$_R$ = 3.79, second diastereosomer t$_R$ = 3.58, third diastereosomer (5a) t$_R$ = 3.35 min. The diastereomeric ratio of the isolated product after column chromatography was determined to be > 95:5 by HPLC analysis using an achiral YMC Pack ODS-A column, mobile phase: CH$_3$CN/H$_2$O = 55:45 (v/v), flow: 0.8 mL/min, UV detector: 220 nm. Major diastereomer: t$_R$ = 16.23 min. The enantiomeric ratio was determined to be > 300 (> 99% ee) using a Kromasil CelluCoat RP, mobile phase: CH$_3$CN/H$_2$O = 50:50 (v/v), flow: 1 mL/min, UV detector: 220 nm. Major enantiomer: t$_R$ = 6.11 min, minor enantiomer: t$_R$ = 6.48 min.
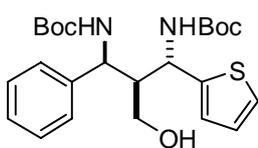
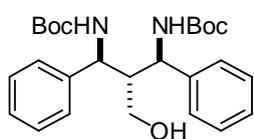**tert-butyl-(1S,2S,3S)-2-formyl-1-phenyl-3-(thiophen-2-yl)propane-1,3-diyldicarbamate 5c.** The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 90:10) in 58% yield. ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.34-7.26 (m, 2H), 7.24-7.19 (m, 2H), 7.19-7.12 (m, 2H), 7.04 (brs, 1H), 6.97 (t, J = 4.1 Hz, 1H), 5.81 (brs, 1H), 5.69 (brs, 1H), 5.37 (brs, 1H), 5.02 (brd, J = 7.3 Hz, 1H),3.66 (brs, 2H), 2.38 (brs, 1H), 1.43 (brs, 18H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 155.7, 144.7, 128.6, 127.1, 127.0, 126.0, 125.0, 124.4, 80.1, 79.8, 60.2, 52.8, 51.1, 28.4, 28.3, 28.2; HRMS (ESI) calculated for (C$_{24}$H$_{34}$N$_2$SO$_5$Na$^+$), 485.208065; found 485.208309; MS (EI) m/z 462 (M$^+$). The diastereomeric ratio of the isolated product after column chromatography was determined to be 90.83: 3.85 by HPLC analysis using an achiral YMC Pack ODS-A column; mobile phase: CH$_3$CN/H$_2$O = 65:35 (v/v), flow: 0.5 mL/min, UV detector: 220 nm. Major diastereomer t$_R$ = 19.51 min., minor diastereomer t$_R$ = 21.83 min.

**tert-butyl-(1S,2R,3R)-2-formyl-1-phenyl-3-(thiophen-2-yl)propane-1,3-diyldicarbamate 5d.** The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 90:10) in 60% yield. ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.38-7.30 (m, 2H), 7.29-7.23 (m, 2H), 7.21 (t, J = 3.2 Hz, 1H), 6.95 (d, J = 3.6 Hz, 2H), 5.87 (brd, J = 9.2 Hz, 1H), 5.36 (dd, J = 9.2, J = 4.0 Hz, 1H), 5.10 (brd, J = 9.6 Hz, 1H), 4.77 (t, J = 8.4 Hz, 1H), 3.39-3.21 (m, 2H), 2.73 (brs, 1H), 1.44 (s, 9H), 1.35 (s, 9H). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 128.9, 127.1, 127.5, 127.0, 126.4, 123.9, 123.6, 80.2, 79.9, 61.8, 53.0, 51.6, 49.2, 28.4, 28.4, 28.3; The diastereomeric ratio of the isolated product after column chromatography was determined to be 94.28: 1.94 by HPLC analysis using an achiral Zorbax Eclipse XDB-C16 column; mobile phase: CH$_3$OH/H$_2$O = 70:30 (v/v), flow: 1 mL/min, UV detector: 220 nm. Major diastereomer t$_R$ = 3.62 min. minor diastereomer t$_R$ = 3.75 min.

**tert-butyl-(1R,2r,3S)2-formyl-1,3-diphenylpropane-1,3-diyldicarbamate 5e.** The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 80:20) in 53% yield. ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.36-7.24 (m, 10H), 5.42 (brd, J = 8.0 Hz, 2H), 4.94 (brs, 2H), 3.25 (brd, J = 6.8 Hz, 2H), 2.79 (brs, 1H), 1.40 (s, 18H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 156.1, 141.3, 128.8, 127.1, 126.2, 80.0, 62.0, 52.6, 50.6, 28.4; HRMS (ESI) calculated for (C$_{26}$H$_{36}$N$_2$O$_5$Na$^+$), 479.251904; found 479.251645; MS (EI) m/z 456 (M$^+$).

Conversion of *N*-Boc aldehyde 4b to β,β'-diamino acid 6
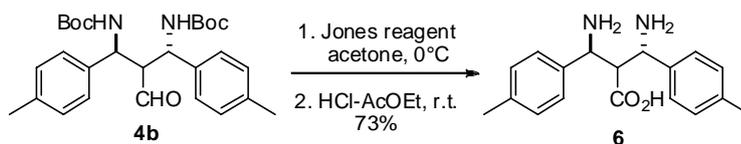
1. Oxidation: To a stirred solution of aldehyde 4b (0.1 mmol, 1 equiv.) at 0°C in acetone (1M) was added dropwise Jones reagent (CrO$_3$/H$_2$SO$_4$ = 1 mmol/4mL, 0.025 mol, 0.25 equiv). The solution was allowed to stir for 30 min and quenched with ^{i}PrOH. The reaction mixture was then allowed

to stir 15 min while warming to room temperature. The mixture was poured into a separatory funnel containing H_2O (30 mL) and extracted with EtOAc (20 mL x 3). The combined organic fractions were dried over $MgSO_4$, filtered and the solvent was removed in vacuo.
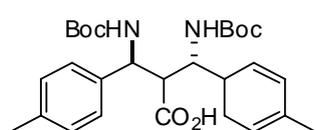
**(S)-3-(tert-butoxycarbonylamino)-2-((S)-(tert-butoxycarbonylamino)(p-tolyl)methyl)-3-p-tolylpropanoic acid.** The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 70:30) in 79% yield. ^{1}H NMR ((CD_3)$_2$CO, 500 MHz) δ 7.16 (d, J= 7.8 Hz, 2H), 7.08 (d, J= 7.8 Hz, 2H), 6.97 (t, 1H), 6.74 (brd, J= 10.3 Hz), 6.35 (brs, 1H), 5.18 (brd, J = 10.3 Hz, 1H), 4.95-4.91 (m, 1H), 3.30 (brs, 1H), 2.13 (s, 6H), 1.31 (s, 9H), 1.23 (s, 9H); ^{13}C NMR ((CD_3)$_2$CO, 125 MHz): δ 174.3, 155.6, 139.9, 139.6, 137.7, 137.1, 129.8, 129.7, 128.3, 126.7, 79.1, 79.0, 57.1, 54.8, 52.7, 28.8, 21.1, 21.0; HRMS (ESI) calculated for ($C_{28}H_{38}N_2O_6Na^+$), 521.262547; found 521.262204; MS (EI) m/z 498 (M^+).

2. Deprotection: To a stirred solution of the bis-protected amine (0.1 mmol) at room temperature were added 5 mL of EtOAc and a solution of HCl-EtOAc (3M, 5 mL). The solution was allowed to stir for 2 h and the solvent was concentrated in vacuo to furnish β,β'-diamino acid 6 as the HCl salt in 92% yield.
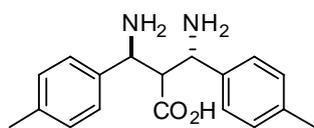
(S)-3-amino-2-((S)-amino(p-tolyl)methyl)-3-p-tolylpropanoic acid 6. The title compound was isolated as a white solid in 92% yield. ^{1}H NMR ((CD_3)$_2$SO, 500 MHz) δ 8.99 (brs, 2H), 8.54 (brs, 2H), 7.34 (d, J= 7.9 Hz, 2H), 7.20 (d, J= 7.9 Hz, 2H), 7.17-7.13 (m, 4H), 4.59 (brs, 1H), 4.43 (brs, 1H), 3.56 (brs, 1H), 2.25 (s, 3H), 2.22 (s, 3H); ^{13}C NMR ((CD_3)$_2$SO, 125 MHz): δ 170.9, 138.6, 138.2, 132.1, 131.9, 129.2, 128.1, 127.4, 52.4, 52.1, 20.7; HRMS (ESI) calculated for ($C_{18}H_{23}N_2O_2Na^+$), 299.175432; found 299.175401; MS (EI) m/z 299 (M^+ + H).
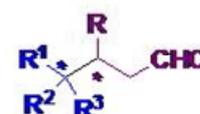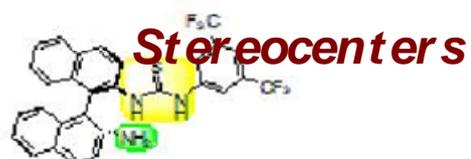
IMINIUM ION CATALYSIS WITH A NOVEL

BIFUNCTIONAL PRIMARY AMINE THIOUREA:

Controlling Adjacent Quaternary and Tertiary

Stereocenters

4

# CONTROLLING ADJACENT QUATERNARY AND TERTIARY STEREOCENTERS
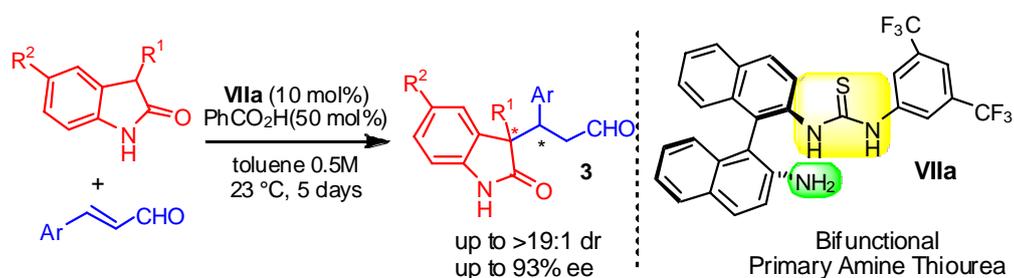
Chiral primary amine thiourea catalyzes the stereoselective addition of oxindoles to α,β-unsaturated aldehydes, generating valuable chiral scaffolds with contiguous quaternary and tertiary stereocenters For the first time a chiral primary amine thiourea catalyst has been applied successfully for iminium ion activation.

4.1 Asymmetric Iminium Ion Catalysis with a Novel Bifunctional Primary Amine Thiourea: Controlling Adjacent Quaternary and Tertiary Stereocenters

As shown in the previous chapters, nowadays the stereoselective preparation of chiral enantio-enriched molecules can exploit not only the long-time established strategies of asymmetric metal-catalysis and bio-organic approaches, but also the recently developed activation modes of organocatalysis.[1] In particular, chiral secondary amine catalysis has proven to be a powerful synthetic tool for the enantioselective transformations of carbonyl compounds, by exploiting distinct catalytic activation modes, such as enamine,[2] iminium ion,[3] SOMO[4] and dienamine,[5] enabling the asymmetric α-, β-, and γ-functionalization of aldehydes and ketones with a wide range of electrophiles and nucleophiles. Although often asymmetric catalysis utilizes the same principles with enzymes and small organic molecules,[6] some striking and rather surprising differences have been noted. It would be reasonable to expect the man-made systems to have a highly specific activity, just like enzymes' specific affinity between substrate and ligand. Surprisingly, some organocatalysts such as proline[7a] **I** or the synthetic MacMillan imidazolidinones1[1d] **II** and the silyl protected diarylprolinols catalysts[7b] **III** have shown an incredible high efficiency and generality, proved useful for a range of applications, demonstrating excellent levels of enantioselectivity for a wide range of substrates. This is very important to synthetic chemists, who must rely on the predictable behavior of catalysts when planning new syntheses. Such catalysts may be called "privileged structures" , in much the same manner that the term has been applied in pharmaceutical research to compound classes that are active against a number of different biological targets.

Privileged chiral catalysts offer an unprecedented effective asymmetric environments for new investigations and mechanistically unrelated reactions. The "privileged" organocatalysts, easily available, represent an important starting point for the investigations of new asymmetric processes as they often avoid large screening of catalysts when setting the optimal reaction conditions. However, after an initial period of validations, in which asymmetric organocatalysis has explored a wide range of important model reactions that constitute the essential tool for organic synthesis, aminocatalysis is going to face problems of increasing complexity and diversity, highlighting that the privileged catalysts might not be always the best candidate to solve some specific and challenging tasks. The stereocontrolled conjugate addition of prochiral trisubstituted carbon nucleophiles to α,β-unsaturated aldehydes via iminium activation, for example, still represents a daunting synthetic challenge,[8] as the privileged catalysts generally allow the formation of products with high enantioselectivity but with poor diastereocontrol.[9]

■ **Priviliged Organocatalysts**

Challenging Task

Creating Adjacent Stereocenters by Iminium Ion Catalysis
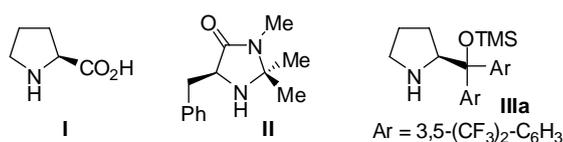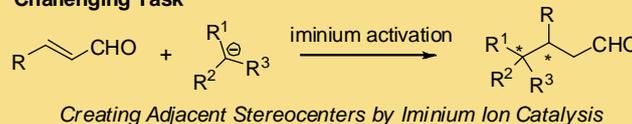
In this context, we investigated the unprecedented asymmetric conjugate addition of oxindoles to enals, which would readily give access to structurally complex oxindoles endowed with a quaternary stereogenic center at C3.[10,11] Chiral 3,3-disubstituted oxindole frameworks are attractive targets in organic synthesis because of their promising biological activities[11a-b] as well
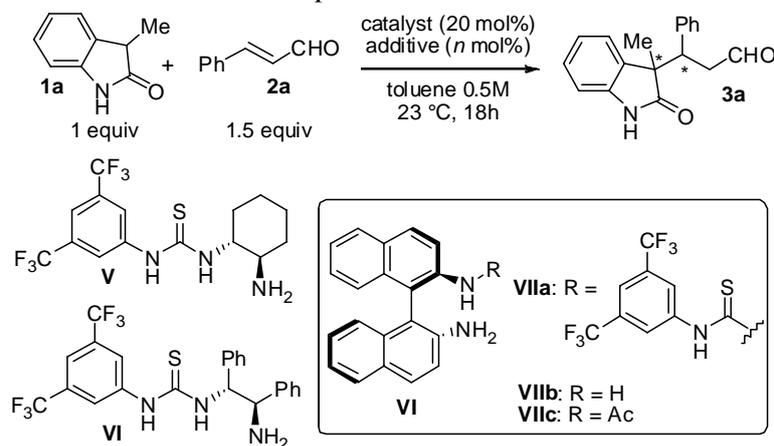
as wide-ranging utility as synthetic intermediates for alkaloids, drug candidates, and clinical pharmaceutical.[11b-c] For exploratory studies (reported in Table 1), we selected the reaction between 3-methyl oxindole **1a** and cinnamaldehyde **2a**, a combination of simple and readily available starting materials. We first test the "privileged" secondary amines **I** and **II** as iminium catalysts for this challenging reaction (entries 1-3); anyway their employment afforded poor results, whereas the silyl protected diarylprolinol **IIIa** provided – as expected - very high enantioselectivity, but complete absence of diastereocontrol, furnishing an almost 1:1 mixture of the two diastereoisomers. This evidence supports the lack of substrate-controlled stereoselectivity in the process.

Inspired by the recent studies on the ability of containing thiourea moiety-catalysts of inducing high stereocontrol through a cooperative mechanism, we speculated that the crucial factor to achieve a good diastereocontrol, while maintaining high level of enantioselectivity, might be the use of a bifunctional catalyst capable to synergistically arrange and activate both the reagents, enforcing high diastereocontrol during the C-C bond forming event. Encouraged by the proved ability of primary amine thiourea catalysts in a variety of enamine-based transformations,[12] we sought to extend the potential application of this catalyst architecture also in iminium activation,[13] even of simple α,β-unsaturated aldehydes.[14] We then performed an extensive screening of chiral primary amines incorporating a thiourea framework, which led to the identification of **VIIa** as a promising iminium catalyst.

The new catalyst **VIIa**, readily synthesized from commercially available compounds through a one-step procedure,[15] demonstrated able to induce high level of stereocontrol with good catalytic activity (entry 6). Moreover, the poor catalytic performance and the very low selectivity observed with **VIIb** and **VIIc** suggested a critical role of the thiourea moiety during the stereoselective C-C bong forming step (entries 7 and 8). Further optimization experiments

(see Supplementary Information for details) revealed that both the nature and the amount of the acidic additive were the crucial parameters to obtain high levels of stereoselectivity and reaction efficiency.
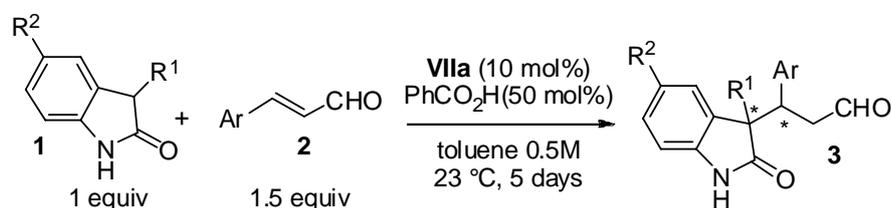
***Table 1.** Optimization studies.[a]*

Entry	catalysts	additive (mol%)	conv[b] [%]	dr[b]	ee[c] [%]
1	**I**	none	<5	-	-
2	**II**	DCA (20)	53	1.1:1	5
3[d]	**III**	pNO$_2$-C$_6$H$_4$CO$_2$H (20)	>95	1.1:1	92
4	**V**	pNO$_2$-C$_6$H$_4$CO$_2$H (20)	>95	1:1	7
5	**VI**	pNO$_2$-C$_6$H$_4$CO$_2$H (20)	84	1:1	2
6	**VIIa**	pNO$_2$-C$_6$H$_4$CO$_2$H (20)	55	4.5:1	84
7	**VIIb**	pNO$_2$-C$_6$H$_4$CO$_2$H (40)	<5	-	-
8	**VIIc**	pNO$_2$-C$_6$H$_4$CO$_2$H (20)	20	1.2:1	40
9	**VIIa**	PhCO$_2$H (20)	51	6:1	90
10[e]	**VIIa**	PhCO$_2$H (50)	35	7:1	90

[a] For additional studied additives and conditions, see the Supporting Information. DCA: dichloroacetic acid. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by chiral HPLC analysis. [d] Reaction carried out at −10 °C in AcOEt as the solvent for 66 h. [e] 10 mol% of **VIIa** was employed.

By using 50 mol% of benzoic acid,[16] it was possible to reduce the catalyst loading to 10 mol%, still maintaining high diastereo- and enantio-control and significant reactivity (entry 10). The scope of the conjugate addition of oxindoles to enals under the optimized conditions using 10 mol% of chiral primary amine thiourea **VIIa**, demonstrated to be broad, as summarized in Table 2.

Table 2. *Diastereo- and enantio-selective conjugate addition of oxindoles to enals catalyzed by* **VIIa**.[a]

Entry	R^1, R^2	Ar	3	[%] yield[b]	dr[c]	[%] ee[d]
1	Me, H	Ph	**a**	71	7:1	90
2	Bn, H	Ph	**b**	80 (73)	7:1	92 (>99)
3[e]	Butyl, H	Ph	**c**	65	5:1	73
4	Bn, Me	Ph	**d**	55	5:1	81
5	Me, H	pNO$_2$-C$_6$H$_4$	**e**	70 (56)	7.5:1	88 (>99)
6[e]	Bn, H	pNO$_2$-C$_6$H$_4$	**f**	52 (47)	11.5:1	93
7	Bn, H	pCl-C$_6$H$_4$	**g**	85 (77)	5.7:1	85 (97)
8[e]	Bn, H	pCN-C$_6$H$_4$	**h**	56	12:1	83
9[e]	Me, H	Naphthyl	**i**	71	13.2:1	80
10[e]	Bn, H	Naphthyl	**j**	55 (49)	>19:1	89 (>99)

[a] Unless noted, the reactions were carried out on a 0.2 mmol scale with 1.5 equiv of **2** and [**1**]$_0$ = 0.5 M in toluene for 5 days in the presence of 10 mol% of **VIIa** and 50 mol% of PhCO$_2$H. [b] Isolated yield (sum of diastereomers). When possible, the two diastereoisomers were separated: the yield of the single major diastereomer is given in brackets. [c] Determined by ^{1}H NMR of the crude mixture. [d] Determined by chiral HPLC analysis. In brackets are reported the ee obtained after a single crystallization. [e] ee determined on the corresponding alcohols after reduction with NaBH$_4$.

As shown, different combinations of substituted oxindoles and a variety of aldehydes are suitable substrates for the reaction, affording high enantioselectivity and useful levels of diastereoselectivity.[17] These results are in sharp contrast with the very low diastereocontrol (dr's from 1:1 to 2:1) obtained in the same process by using **IIIa** as the iminium catalyst (see Supplementary Information for details). Importantly, by using bifunctional catalyst **VIIa** the main diastereomer can be isolated by column chromatography in many cases (entries 2, 5-7 and 10). This observation, taken together with the possibility to obtain a single diastereomer in almost enantiopure form after a single crystallization (entries 2, 5, 7 and 10), renders this novel catalytic system a useful synthetic route to valuable chiral scaffolds with contiguous quaternary and tertiary stereocenters.

The best combination of substrates for the transformation, in terms of diastereocontrol, was observed for enals bearing a naphthyl β-substituent (up to 19:1 dr, entries 9 and 10) and by using oxindole having a benzyl substituent. The relative and absolute configuration of compound **3e** was determined to be (3*S*,3′*R*) by anomalous dispersion X-ray crystallography of the corresponding tosylated alcohol **4**, obtained by simple aldehyde reduction (Figure 1).[18]
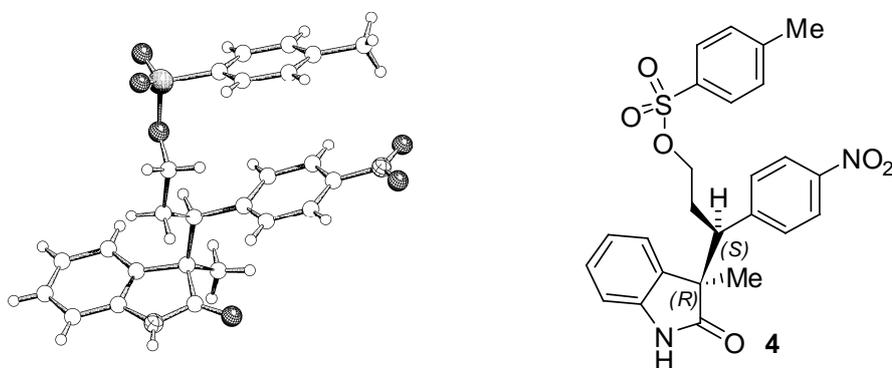

Figure 1. *X-ray structure of toluene-4-sulfonic acid (S)-3-((R)-3-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-3-(4-nitro-phenyl)-propyl ester **4**.*

As previously discussed, we suggested a simultaneously activation of both reagents partners by the bifunctional catalyst to explain the improved stereoselectivity of the reaction compared to the "privileged" chiral amines-catalyzed reaction. Moreover, being generally the stereoselective one-step construction of highly congested products such as **3**, dependent not only on the capability of the catalyst to simultaneously activate the Michael donor and the acceptor, but also to orient them by means of a network of H-bond interactions, we performed a series of experiments to prove our suggested mechanism. Modifications of the catalyst scaffold revealed that the presence of the primary amine[19] as well as the thiourea group play an active role during the catalysis (compare entries 6-8 in Table 1). To gain some insight into the substrate-catalyst interactions, we run the reaction using catalyst **VIIa** in combination with 50 mol% of PhCO$_2$H, cinnamaldehyde **2a** and the *N*-methyl oxindole as the nucleophile.[20] The very poor reactivity and selectivity observed (less than 10% conversion after 5 days, 1.4:1 dr) strongly suggest a direct interactions of the amidic nitrogen in the nucleophilic component with the catalyst. On these grounds, a plausible bifuntional activation mode of the chiral primary amine thiourea **VIIa** can be envisaged, where the thiourea moiety activates the oxindole, stabilizing its enol form, and the primary amine activates the unsaturated aldehyde via iminium ion formation.[21]

In summary, we demonstrated for the first time that chiral primary amine thiourea catalysts, which during the last two years have been successfully applied in many enamine-based asymmetric transformations are also efficient catalysts for iminium ion activation of α,β-unsaturated aldehydes. Besides expanding the applicability of this class of bifunctional catalysts, the main merit of the presented study is to provide, through the high levels of both enantio- as well as diastereo-selectivity achieved, a solution to the challenging

problem of generating valuable chiral scaffolds with contiguous quaternary and tertiary stereocenters.

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[14] To our knowledge, chiral primary amines have not yet been used for the iminium activation of α,β-unsaturated aldehydes. They proved effective for the iminium activation of enones (see Ref [13]) as well as of α-substituted acroleins, see: a) K. Ishihara, K. Nakano, J. Am. Chem. Soc. 2005, 127, 10504; b) A. Sakakura, K. Suzuki, K. Nakano, K. Ishihara, Org. Lett. 2006, 8, 2229; c) K. Ishihara, K. Nakano, J. Am. Chem. Soc. 2007, 129, 8930.

[15] Both enantiomers of **VIa** are easily accessible from a single-step synthesis, see Supplementary Information.

[16] The acid likely serves to facilitate catalyst turnover by promoting iminium formation - imine hydrolysis. For similar effects with primary amine thiourea catalysts in enamine catalysis, see Ref. [12b-c].

[17] Enals with alkyl β–substituents afforded poor results; e.g. crotonaldehyde, 2.3:1 dr, 24% ee. The presence of a chlorine on the oxindole scaffold (R^2= Cl) led to a decreased stereoselectivity in the reaction with cinnamaldehyde (dr 1.5:1, 11% ee)

[18] CCDC-710802 (compound **4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] Replacement of the primary amine moiety with a tertiary one (NMe_2) in the catalyst scaffold led to a completely loss of catalytic activity. This evidence ruled out a possible activation of the nucleophile via chiral Brønsted base catalysis.

[20] Also the employment of the N-Boc protected oxindole, under the best reaction condition, afforded low stereocontrol, albeit with improved reactivity (18 h, >95% conversion, 2:1 dr, 67% ee).

[21] The presence of the primary amine is crucial for the catalytic activity, see Ref [19]. At this point of investigations, a plausible Brønsted acid activation of unsaturated aldehydes can not be ruled out.

4.1 Supplementary Information

Contents

General Methods

Materials

Determination of Diastereomeric Ratios

Determination of Enantiomeric Purity

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Organocatalytic Asymmetric Addition of Oxindole 1a,b to α,β-Unsaturated Aldehydes 2 Catalyzed by IIIa

Experimental Procedures

Determination of the Absolute Configuration.

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: [α]$^{rt}_D$ (*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.

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Materials. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[2] 3-methylindolin-2-one **1a**, cinnamaldehyde **2a** (*E*)-3-(4-nitrophenyl)acrylaldehyde, buthyllithium (1.6 M in hexane), indolin-2-one, benzylbromide, 5-methylindolin-2,3-dione, piperidine, 4-iodobenzonitrile, 1-chloro-4-iodobenzene, 2-bromonaphthalene, (*R*)-(+)-1-(2-aminonaphthalen-1-yl)naphthalene-2-amine **VIIb**, 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene were purchased from Aldrich and used as received. Different substituted oxindoles were prepared following the literature procedures.[3] α,β-Unsaturated aldehydes 2 were purchased from Aldrich or Lancaster and used as received or synthesized following the literature procedures.[4] The "privileged" organocatalysts **I-III** were purchased from Aldrich and used as received.

Determination of Diastereomeric Ratios. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture.

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 carrying out the reactions with racemic **IIIa** as the catalyst.

Organocatalytic Asymmetric Addition of Methyl Oxindole 1a to Cinnamaldehyde 2 Catalyzed by VIIa

Solvent Screen[a]

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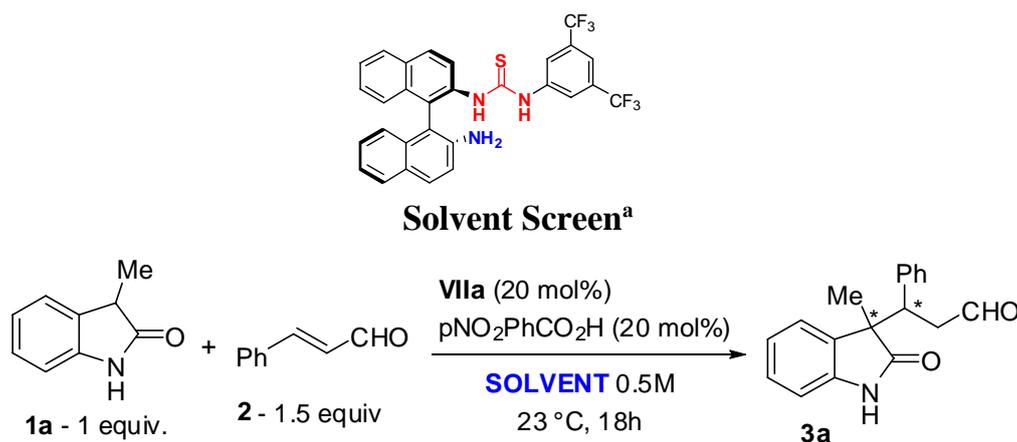
[2] W. L. F. Armarengo, D. D. Perrin, In *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, 1996.

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Table S1. Solvent Screen [a]

Solvent	Conv (%) – 18h[b]	dr (%)[b]	ee (%)[c]
Toluene	55	4.5:1	84/31
DCM	52	2:1	67/38
CHCl₃	38	3:1	73/40
Acetone	53	1.1:1	31/6
THF	27	2:1	47/36

[a] Open-air reactions were carried out in undistilled solvent using a 1.5:1 ratio of **2a** to **1a**, 20 mol% of the catalyst, 20 mol% of the acid on a 0.1 mmol scale. [b] Determined by ¹H NMR of the crude mixture. [c] ee of **3a** was determined by HPLC analysis (AD-H column).

Acids Screen [a]

1a - 1 equiv.   **2** - 1.5 equiv.   **3a**

VIIa (20% mol)
ACID (20% mol)
toluene 0.5M
23°C, 18h
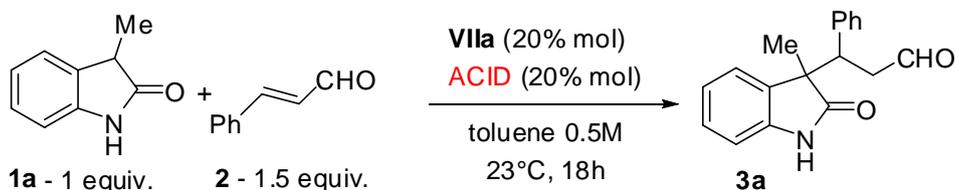
Table S2. Solvent Screen[a]

Acid	Conv (%) – 18h[b]	dr (%)[b]	ee (%)[c]
*p*NO₂PhCO₂H	55	4.5:1	84/31
TFA	77	1:3	<5
*o*F-PhCO₂H	38	5:1	86/40
PhCO₂H	51	6:1	90/52

[a] Open-air reactions were carried out in undistilled solvent using a 1.5:1 ratio of **2a** to **1a**, 20 mol% of the catalyst, 20 mol% of the acid on a 0.1 mmol scale. [b] Determined by ¹H NMR of the crude mixture. [c] ee of **3a** was determined by HPLC analysis (AD-H column).

Organocatalytic Asymmetric Addition of Oxindole 1a,b to α,β-Unsaturated Aldehydes 2 Catalyzed by IIIa

Ar = 3,5-(CF₃)₂-C₆H₃
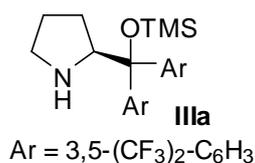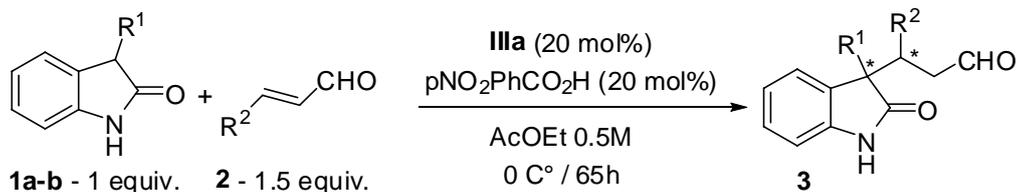
Table S3. Confronting the Privileged Catalyst IIIa with VIIa[a]

| R[1] | R[2] | Conv | dr[b] | ee (%) | | VIa | |
				major	minor	dr	ee
Me	Me	80%	2.4:1	30	55	2.3:1	24
Me	p-NO2Ph	80%	1.1:1	89	90	7.5:1	88
Me	Ph	>95%	1:1	93	89	7:1	90
Bn	Ph	>95%	1.1:1	96	91	7:1	92

[a] Open-air reactions were carried out in undistilled solvent using a 1.5:1 ratio of **2** to **1**, 20 mol% of the catalyst **IIIa**, 20 mol% of the acid on a 0.1 mmol scale. [b] Determined by ^{1}H NMR of the crude mixture. [c] ee of **3** was determined by HPLC analysis (AD-H column). [d] ee of **3** was determined by HPLC analysis (OD-H column).

Experimental procedures

Synthesis of the Chiral Primary Amine Thiourea Catalyst VIIa. (R)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(1-(2-aminonaphthalen-1-yl)naphthalen-2-yl)thiourea.
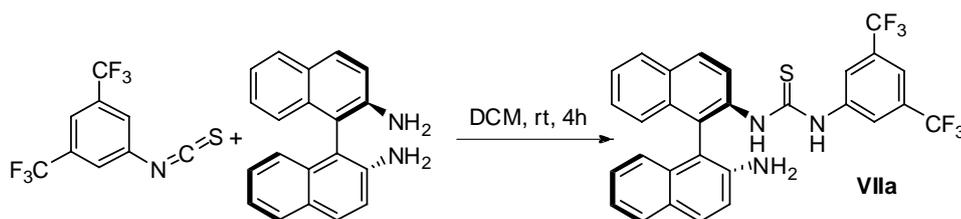
Under argon atmosphere, 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (1.8 mmol, 329 μL) is added dropwise to a solution of (*R*)-(+)-1-(2-aminonaphthalen-1-yl)naphthalen-2-amine (2.16 mmol, 1.2 equiv., 610 mg) in dry CH$_2$Cl$_2$ (9 ml) and the reaction is stirred for 4 hours at room temperature. Dichloromethane is evaporated under reduced pressure and the crude mixture is purified by flash chromatography (hexane/ethyl acetate 9:1). Catalyst **VIIa** is obtained in 70% yield as a pale yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.57 (br s, 2H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 7.04-7.20 (m, 2H), 7.28-7.39 (m, 2H), 7.45 (s, 2H), 7.49-7.58 (m, 1H), 7.60 (br s, 1H),

7.67-7.78 (m, 2H), 7.90-8.12 (m, 5H). ^{13}C NMR (150 MHz, CDCl$_3$):   111.9 (C), 118.1 (CH), 119.7 (CH), 121.4 (C), 122.8 (CH), 123.0 (CH), 124.1 (C), 124.9 (CH), 126.0 (CH), 126.8 (CH), 127.4 (CH), 127.5 (CH), 128.2 (C), 128.4 (CH), 128.5 (CH), 128.9 (C), 129.5 (C), 129.6 (CH), 130.4 (CH), 131.6 (C), 131.9 (C), 132.3 (C), 132.7 (C), 132.8 (C), 133.1 (C), 133.8 (C), 138.5 (C), 141.8.

Synthesis of (*R*)-*N*-(1-(2-aminonaphthalen-1-yl)naphthalene-2-yl)acetamide VIIc
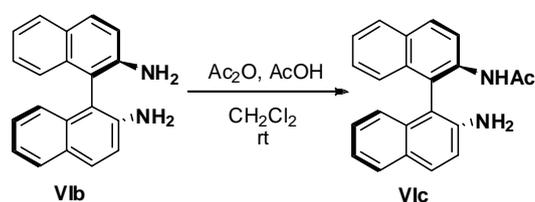
Acetic anhydride(0.5 mmol, 52 μL) is added at 0 °C to a solution of acetic acid (5 mmol, 300 μL) and **VIIb** (0.5 mmol, 142 mg) in anhydrous dichloromethane (5 ml) under argon atmosphere. The reaction is stirred overnight at room temperature, then a 2N NaOH solution is added and the resulting mixture is extracted with dichloromethane. Flash chromatography over silica gel (Hexane/ethyl acetate 1:2) furnished the desired compound in 75% yield. ^{1}H-NMR and ^{13}C-NMR spectra were consistent with that previously reported.[5]

## Synthesis of α,β-Unsaturated Aldehydes 2:

(*E*)-3-(4-chlorophenyl)acrylaldehyde has been obtained in a 80% yield following the literature procedure. ^{1}H-NMR and ^{13}C-NMR spectra were consistent with that previously reported.[4]

(*E*)-4-(3-oxoprop-1-enyl)benzonitrile has been obtained in a 50% yield following the literature procedure. ^{1}H-NMR and ^{13}C-NMR spectra were consistent with that previously reported.[4]

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(*E*)-3-(naphthalen-2-yl)acrylaldehyde has been obtained in a 75% yield following the literature procedure. ^{1}H-NMR and ^{13}C-NMR spectra were consistent with that previously reported.[4]

Synthesis of Oxindoles Derivatives
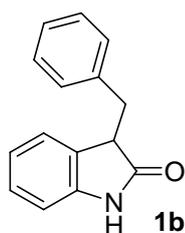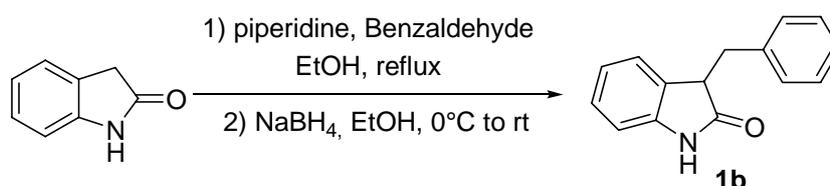
3-benzylindolin-2-one 1b: In 50 ml flask containing a suspension of indolin-2-one (6 mmol, 798 mg) in absolute ethanol (6 ml) benzaldehyde (6.6 mmol, 660 μL) and piperidine (12 mmol, 1.18 ml) are added in sequence and the resulting solution is refluxed for 3 hours. Then the reaction flask is removed from the oil bath and cooled to ambient temperature and the solvent removed under reduced pressure. The crude mixture is dissolved again in 20 ml of ethanol and added dropwise to a previously prepared suspension of NaBH$_4$ (6.6 mmol, 249.74 mg) in 10 ml of absolute ethanol at 0 °C. Once the addition is complete the resulting mixture is vigorously stirred for 3 hours at room temperature. The reaction is quenched by addition of 20 ml of a saturated solution of NH$_4$Cl and the extracted with ethyl acetate (3 x 20 ml). The organic phase is anhydrified with MgSO$_4$, filtered and the solvent evaporated under reduced pressure. Flash chromatography over silica gel (eluent mixture hexane/diethyl ether 1:1) furnished the desired compound as a pale yellow solid in 87% yield. The NMR spectra is consistent with the one previously reported.[3]
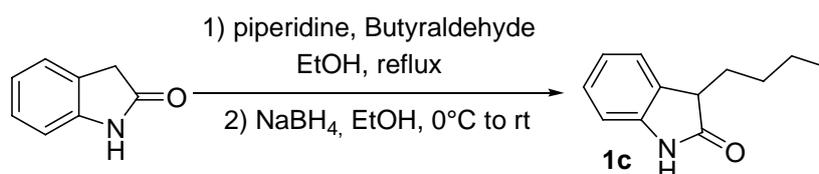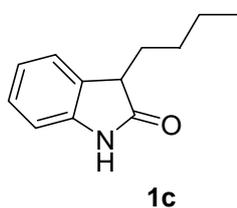
3-butylindolin-2-one 1c:In 50 ml flask containing a suspension of indolin-2-one (9 mmol, 798 mg) in absolute ethanol (9 ml) butyraldehyde (9.9 mmol, 881 μL) and piperidine (18 mmol, 1.778 ml) are added in sequence and the resulting solution is refluxed for 6 hours. Then the reaction flask is removed from the oil bath and cooled to ambient temperature and the solvent removed under reduced pressure. The crude mixture is dissolved again in 30 ml of ethanol and added dropwise to a previously prepared suspension of NaBH$_4$ (9.9 mmol, 376.62 mg) in 25 ml of absolute ethanol at 0 °C. Once the addition is complete the resulting mixture is vigorously stirred at room temperature overnight. The reaction is quenched by addition of 20 ml of a saturated solution of NH$_4$Cl and the extracted with ethyl acetate (3 x 30 ml). The organic phase is anhydrified with MgSO$_4$, filtered and the solvent evaporated under reduced pressure. Flash chromatography over silica gel (eluent mixture hexane/diethyl ether 1:1) furnished the desired compound as a pale orange oil in 60% yield. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 0.87 (t, J = 7.1 Hz, 3H), 1.20-1.47 (m, 4H), 1.83-2.09 (m, 2H), 3.47 (t, J = 6.1 Hz, 1H), 6.94 (d, J = 7.7 Hz, 1H), 6.97-7.05 (m, 1H), 7.14-7.25 (m, 2H), 9.72 (br s, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 13.9 (CH$_3$), 22.7 (CH$_2$), 27.9 (CH$_2$), 30.2 (CH$_2$), 46.2 (CH), 109.8 (CH), 122.0 (CH) 123.8 (CH), 127.6 (CH), 129.8 (C), 141.7 (C), 181.2 (C).
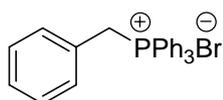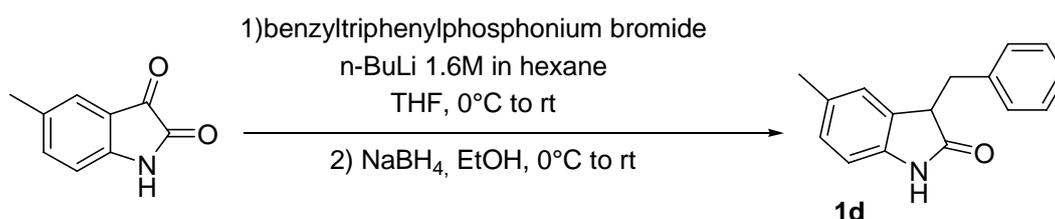
Benzyltriphenylphosphonium bromide: Triphenylphosphine (17.5 mmol, 4.6 g) is added to a solution of benzylbromide (17.5 mmol, 3g) in benzene and the resulting mixture is refluxed for 12 hours. The white solid is filtered and washed with diethyl ether (3 x 20 ml) and hexane (3 x 20 ml) and then is dried under high vacuum for 3 hours. The titled compound has been obtained in 95% yield.
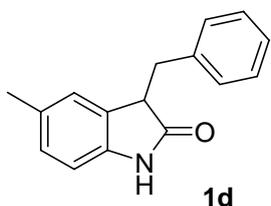
3-benzylidene-5-methylindolin-2-one: Benzyltriphenylphosphonium bromide (1 mmol, 432.06 mg) is placed in a flame dried three nacked 50 ml flask under argon atmosphere and anhydrous THF (10 ml) is added. To the resulting suspension buthyllithium (1.6 M in hexane, 1 mmol., 0.625 ml) is added dropwise at 0 °C and the deep red mixture is stirred for 1 hour at that temperature. After that a solution of 5-methylindolin-2,3-dione (1 mmol., 161.16 mg) in anhydrous THF (15 ml) is added in 30 minutes at 0 °C and the resulting solution is stirred for 6 hours. The reaction is poured in a saturated solution of NH_4Cl at 0 °C and then extracted with DCM (3 x 20 ml). The organic phase is dried over magnesium sulphate, filtered and the solvent removed under reduced pressure. The crude mixture is dissolved in 10 ml of ethanol and added dropwise to a previously prepared suspension of $NaBH_4$ (2.0 mmol, 75.68 mg) in 5 ml of absolute ethanol at 0 °C. Once the addition is complete the resulting mixture is vigorously stirred at room temperature overnight. The reaction is quenched by addition of 20 ml of a saturated solution of NH_4Cl and the extracted with ethyl acetate (3 x 30 ml). The organic phase is anhydrified with $MgSO_4$, filtered and the solvent evaporated under reduced pressure. Flash chromatography over silica gel (eluent mixture hexane/ethyl acetate 8:2) furnished the desired compound as a pale orange solid in 82% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.23 (s, 3H), 2.94 (dd, J = 13.7, 9.1 Hz, 1H), 3.48 (dd, J = 13.7, 4.5 Hz, 1H), 3.71 (dd, J = 9.1, 4.5 Hz, 1H), 6.57 (s, 1H), 6.75 (d, J = 7.9 Hz, 1H), 6.93-7.00 (m, 1H), 7.14-7.31 (m, 5H), 8.70 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.1 (CH_3), 36.6 (CH_2), 47.6 (CH), 109.4 (CH), 125.4(CH) 126.5 (CH), 128.0 (CH), 128.1 (CH), 129.0 (C), 129.3 (CH), 131.2 (C), 137.8 (C), 138.9 (C), 179.7 (C).
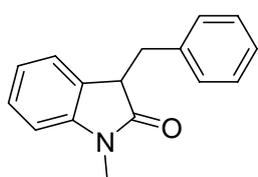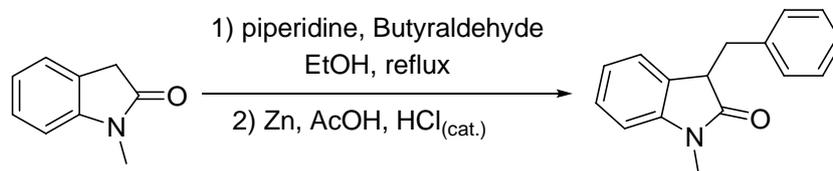
3-benzyl-1-methylindolin-2-one: In 50 ml flask containing a suspension of 1-methylindolin-2-one (2 mmol, 294.36 mg) in absolute ethanole (3 ml) benzaldehyde (2.2 mmol, 224 μL) and piperidine (4 mmol, 395 μL) are added in sequence and the resulting solution is refluxed for 4 hours. Then the reaction flask is removed from the oil bath and cooled to ambient temperature and the solvent

removed under reduced pressure. The crude mixture is dissolved in acetic acid (3 ml) then zinc powder (11.9 mmol, 780 mg) and HCl (50 μL) are added and the resulting solution is stirred for 24 hours at room temperature. The reaction mixture is then filtered over a pad of celite which is washed with ethyl acetate (20 ml) three times. The collected organic phase is placed in a separatory funnel and washed with a saturated solution of $NaHCO_3$ (3 x 20 ml) and with a saturated solution of NaCl (2 x 20 ml) and then dried over $MgSO_4$. After removal of the solvent under reduced pressure the crude mixture is purified by flash chromatography to give the titled compound in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.88 (dd, J = 13.7, 9.4 Hz, 1H), 3.15 (s, 3H), 3.50 (dd, J = 13.7, 4.5, 1H), 3.71 (dd, J = 9.4, 4.5 Hz, 1H), 6.74 (d, J = 8.1 Hz, 2H), 6.88-6.95 (m, 1H), 7.13-7.30 (m, 6H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 26.0 (CH_3), 36.7 (CH_2), 46.9 (CH), 107.8 (CH), 122.0 (CH), 124.4 (CH), 126.5 (CH), 127.8 (CH), 128.1 (CH), 128.3 (C), 129.3 (CH), 137.8 (C), 144.1 (C), 176.9 (C).

General Procedure for the Organocatalytic Asymmetric Conjugate Addition of Oxindoles to Enals. 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, catalyst (R)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(1-(2-aminonaphthalen-1-yl)naphthalen-2-yl)thiourea **VIIa** (0.02 mmol, 11.1 mg) was dissolved in 400 μL of toluene. After addition of 0.1 mmol (12.2 mg) of benzoic acid, the solution was stirred for 5 minutes at room temperature. After addition of α,β-unsaturated aldehyde (0.3 mmol), the mixture was stirred for 10 minutes. Then the oxindole derivative (0.20 mmol) was added in one portion and the tube was closed with a rubber stopper and stirring was continued for the indicated time (5 days). Then the crude reaction mixture was diluted with 1:1 mixture of dichloromethane and ethyl acetate (1 mL) and flushed through a plug of silica gel, using the same mixture as the eluent. Solvent was removed *in vacuo*, and the residue was purified by flash chromatography to yield the desired compound. When the separation of the two diastereoisomers by Chiral HPLC analysis was not possible, the compounds were reduced to the corresponding alcohols. The crude mixture was dissolved in THF (2 ml) and $NaBH_4$ (2 eq. based on the starting oxindole) was added at 0 °C. Once the addition was complete the reaction was stirred for further 5 minutes at that temperature then the ice bath was removed and the vigorous

stirring continued for 1 hour at room temperature. Once the reaction was finished, THF was removed under reduced pressure and the residual material was quenched with a saturated solution of NH$_4$Cl at room temperature and then extracted with DCM. MgSO$_4$ was added to the organic phase then filtered and the solvent removed under reduced pressure to give a mixture of alcohols which can be easily separated by flash chromatography using mixtures of DCM and ethyl acetate.
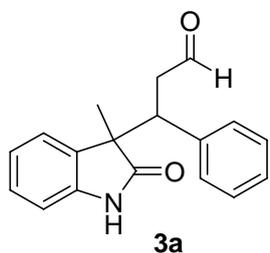
**3-(3-methyl-2-oxoindolin-3-yl)-3-phenylpropanal – 3a (table 2 entry 1).**

The reaction was carried out at 23 °C using 0.2 mmol (29.4 mg) of 3-methylindolin-2-one **1a** 0.3 mmol (38 µL) of cinnamaldehyde **2**, 0.010 mmol (10% mol, 11.1 mg) of **VIIa** and 0.1 mmol (50% mol, 12.2 mg) of benzoic acid in 400 µL of toluene following the general procedure. From the crude mixture the dr = 7.0:1 was determined by integration of ^{1}H-NMR signal (δ_{major} 1.45 ppm, δ_{minor} 1.34 ppm - s). The title compound was isolated by column chromatography (hexane/AcOEt = gradient from 8/2 to 7/3) as a colourless solid in 71% yield and 90% ee (major diasteroisomer). The ee was determined by HPLC analysis on a Diacel Chiralpak AD-H column: 9/1 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: major diastero τ_{minor} = 19.5min, τ_{major} = 17.7 min, $[\alpha]^{rt}_{D}$= +1.55 (*c* = 0.916, CHCl$_3$, dr = 84:16) ^{1}H NMR (400 MHz, CDCl$_3$), dr: = 4.17:1: δ 1.45 (s, 3H), 2.92-3.31 (m, 4H), 3.82-3.93 (dd *J* = 10.3, 4.9 Hz, 1H), 6.46 (d, *J* = 7.4 Hz, 1H), 6.78-6.88 (m, 2H), 6.93-7.05 (m, 5H), 7.06-7.20 (m, 5H), 7.38 (d, *J* = 7.1 Hz, 1H), 9.53 (m, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 21.0 (CH3), 44.0 (CH2), 46.6 (CH), 51.8 (C), 109.7 (CH), 122.2 (CH), 124.1 (CH), 127.4 (CH), 127.9 (CH), 128.4 (CH), 129.0 (CH), 132.2 (C), 130.0 (CH), 138.1 (C), 140.5 (C), 181.1 (C), 200.6 (CH).Exact mass (m/z): 279.1256, calculated: 279.1259.
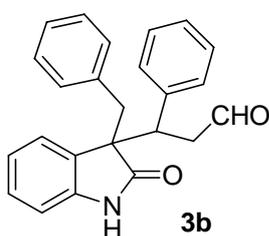
3-(3-benzyl-2-oxoindolin-3-yl)-3-phenylpropanal – 3b (table 2 entry 2).

The reaction was carried out at 23 °C using 0.15 mmol (33.4 mg) of 3-benzylindolin-2-one **1b**, 0.225 mmol (28 µL) of cinnamaldehyde **2**, 0.015 mmol (10% mol, 8.3 mg) of **VIa** and 0.075 mmol (50% mol, 9.1
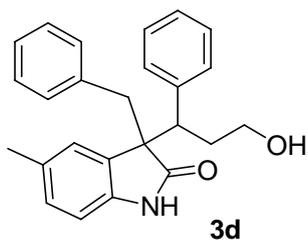
mg) of benzoic acid in 300 μL of toluene following the general procedure. From the crude mixture the dr = 7.0:1 was determined by integration of ^{1}H-NMR signal (δ_{major} 9.53 ppm, δ_{minor} 9.49 ppm - m). The title compound was isolated as a single diastereoisomer by column chromatography (CH$_2$Cl$_2$/AcOEt = gradient from 98/2 to 95/5) as a colourless solid in 73% yield and 92% ee (major diasteroisomer) R$_f$ (0.35). After single recrystallization of the major diasteroisomer from DCM and hexane a colourless solid was obtained in 55% yield and 99% ee. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: 8/2 hexane/i-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: major diastero τ_{minor} = 10.3 min, τ_{major} = 13.8 min, $[\alpha]^{rt}_D$= - 47.27 (c = 0.760, CHCl$_3$, >99% ee) ^{1}H NMR (400 MHz, CDCl$_3$):   2.92-3.31 (m, 4H), 3.82-3.93 (dd, J = 10.3, 4.9 Hz, 1H), 6.46 (d, J = 7.4 Hz, 1H), 6.78-6.88 (m, 2H), 6.93-7.05 (m, 5H), 7.06-7.20 (m, 5H), 7.38 (d, J = 7.1 Hz, 1H), 9.53 (m, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 41.2 (CH$_2$), 44.4 (CH$_2$), 46.9 (CH), 58.2 (C), 109.4 (CH), 122 (CH), 124.7 (CH), 126.5 (CH), 127.4 (CH), 127.6 (CH), 128.0 (CH), 128.5 (CH), 129.4 (CH), 129.7 (C), 130.0 (CH), 135.4 (C), 138.0 (C), 141.0 (C), 178.7 (C), 200.6 (CH). Exact mass (m/z): 355.1570, calculated: 355.1572.
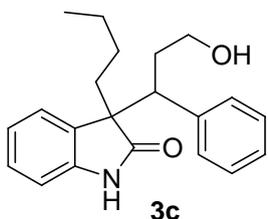
3-butyl-3-(3-hydroxy-1-phenylpropyl)indolin-2-one - 3c (table 2 entry 3).
The reaction was carried out at 23 °C using 0.30 mmol (56.7 mg) of 3-butylindolin-2-one **1c**, 0.45 mmol (56.7 μL) of cinnamaldehyde **2**, 0.03 mmol (10% mol, 16.65 mg) of **VIa** and 0.15 mmol (50% mol, 18.3 mg) of benzoic acid in 600 μL of toluene following the general procedure. From the crude mixture the dr = 5:1 was determined by integration of ^{1}H-NMR signal (δ_{major} 3.70 ppm, δ_{minor} 3.76 ppm – m) and the conversion based on the starting oxindole derivative was 80%. The crude mixture of two diastereoisomers was tranferred in a 25 ml two necked flask and dissolved under argon with 2 ml of anhydrous THF then NaBH$_4$, 0.60 mmol (22.70 mg) was added at 0 °C. After 1 hour under vigorous stirring at room temperature, the solvent was evaporated and a solution of saturated NH$_4$Cl was added to the solid mixture. The aqueous solution was extracted with dichloromethane (3 x 20 ml) and dried over MgSO$_4$. NMR analysis of the crude mixture showed quantitative conversion into the corresponding alcohols as a mixture of diasteroisomers. The d.r. = 5:1 was determined by integration of ^{1}H-NMR signal (δ_{major} 6.80 ppm, δ_{minor} 6.83 ppm – br d). The title

compound as a single diastereoisomer was isolated by column chromatography (CH_2Cl_2/AcOEt = 4:1) as a colourless solid in 36.5% yield and 73% ee (major diasteroisomer) R_f (0.30). The ee was determined by HPLC analysis on a Diacel Chiralpak AD-H column (80/20 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: major diastero τ_{minor} = 8.9 min, τ_{major} = 12.3 min). $[\alpha]^{rt}_D$= +29.59 (*c* = 1.025, $CHCl_3$, 73% ee).^{1}H NMR (400 MHz, $CDCl_3$): δ 0.75 (t, *J* = 7.3 Hz, 3H), 0.93-1.42 (m, 5H), 1.85-195 (m, 1H), 1.97-2.14 (m, 2H), 2.24-2.35 (m, 2H), 3.20 (dd, *J* = 12.51, 2.71, 1H), 3.26-3.37 (m, 1H), 3.38-3.48 (m, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.75-6.83 (m, 2H), 6.98-7.11 (m, 4h), 7.20 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.28-7.32 (m, 1H), 7.62 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.8 (CH_3), 22.9 (CH_2), 26.6 (CH_2), 32.5 (CH_2), 35.3 (CH_2), 49.3 (CH_2), 57.4 (C), 61.0 (CH_2), 109.3 (CH), 122.0 (CH), 124.1 (CH), 126.9 (CH), 127.7 (CH), 127.9 (CH), 128.9 (C), 131.3 (C), 139.0 (C), 141.5 (C), 181.1 (C). Exact mass (m/z): 323.1882, calculated: 323.1885.

3-benzyl-3-(3-hydroxy-1-phenylpropyl)-5-methylindolin-2-one – 3d (Table 2, entry 4). The reaction was carried out at 23 °C using 0.273 mmol (36.8 mg) of 3-benzyl-5-methylindolin-2-one **1d**, 0.4095 mmol (39.1 μL) of cinnamaldehyde **2**, 0.0273 mmol (10% mol, 15.15 mg) of **VIa** and 0.1365 mmol (50% mol, 16.65 mg) of benzoic acid in 546 μL of toluene following the general procedure. From the crude mixture the dr = 5.0:1 was determined by integration of ^{1}H-NMR signal (δ_{major} 3.87 ppm, δ_{minor} 3.97 ppm - dd) and the conversion based on the starting oxindole was 80%. The crude mixture of two diastereoisomer was tranferred in a 25 ml two necked flask and dissolved under argon with 2 ml of anhydrous THF then $NaBH_4$, 0.546 mmol (20.66 mg) was added at 0 °C. After 1 hour under vigorous stirring at room temperature, the solvent was evaporated and a solution of saturated NH_4Cl was added to the solid mixture. The aqueous solution was extracted with dichloromethane (3 x 20 ml) and dried over $MgSO_4$. NMR analysis of the crude mixture showed quantitative conversion into the corresponding alcohols as a mixture of diasteroisomers. The d.r. = 5.0:1 was determined by integration of ^{1}H-NMR signal (δ_{major} 3.14 ppm, δ_{minor} 2.69 ppm - d). The title compound was isolated as a single diastereoisomer by column chromatography (CH_2Cl_2/AcOEt = 4/1) as a colourless solid in 48% yield and 81% ee (major diasteroisomer) R_f (0.30). The ee was determined by HPLC analysis on a Diacel Chiralpak AD-H column (80/20 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: major diastero τ_{minor} = 17.4

min, τ_{major} = 8.4 min). $[\alpha]^{rt}_D$= -22.37 (*c* = 0.9125, CHCl$_3$, 81% ee). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.68 (br s, 1H), 2.20 (tdd, *J* = 12.7, 6.2, 4.6 Hz, 1H), 2.50 (m, 4H), 3.14 (d, *J* = 12.7 Hz, 1H), 3.31 (d, *J* = 12.7 Hz, 1H), 3.34-3.43 (m, 2H), 3.44-3.55 (m, 1H), 6.31 (d, *J* = 7.8 Hz, 1H), 6.76-6.85 (m, 2H), 6.86-7.03 (m, 6H), 7.04-7.17 (m, 4H), 7.31 (s, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 21.4 (CH$_3$), 32.9 (CH$_2$), 41.7 (CH$_2$), 49.5 (CH), 58.9 (C), 61.0 (CH$_2$), 109.0 (CH), 125.5 (CH), 126.2 (CH), 127.0 (CH), 127.5 (CH), 127.8 (CH), 128.5 (CH), 129.2 (CH), 130.0 (CH), 130.4 (C), 131.1 (C), 136.1 (C), 138.8 (C), 139.1 (C), 179.5 (C). Exact mass (m/z): 371.1884, calculated: 371.1885.
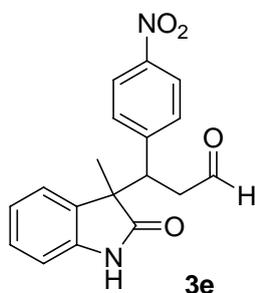
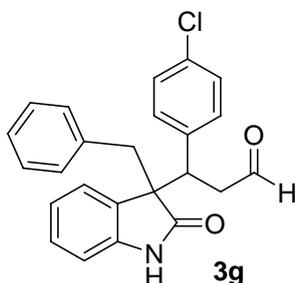**3-(3-methyl-2-oxoindolin-3-yl)-3-(4-nitrophenyl)propanal 3e (table 2 entry 5).** The reaction was carried out at 23 °C using 0.2 mmol (29.4 mg) of 3-methylindolin-2-one **1a**, 0.3 mmol (53 mg) of (*E*)-3-(4-nitrophenyl)acrylaldehyde **2**, 0.010 mmol (10% mol, 11.1 mg) of **VIIa** and 0.1 mmol (50% mol, 12.2 mg) of benzoic acid in 400 µL of toluene following the general procedure. From the crude mixture the dr = 7.5:1 was determined by integration of ^{1}H-NMR signal (δ_{major} 9.58 ppm, δ_{minor} 9.63 ppm - m). The product was isolated as a mixture of diastereoisomers in 70% yield and 88% ee of the major disteroisomer (d.r. = 86:14). After single recrystallization from DCM and hexane the first diastereoisomer was isolated as colourless solid in 56% yield and >99% ee. The ee was determined by HPLC analysis on a Diacel Chiralpak AD-H column: 85/15 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: major diastero τ_{minor} = 24.3 min, τ_{major} = 25.46 min, minor diastero τ_{minor} = 20.5 min, τ_{major} = 19.10 min. $[\alpha]^{rt}_D$= -28.54 (*c* = 0.825, CHCl$_3$, >99% ee) ^{1}H NMR (400 MHz, CDCl$_3$) mixture of diastroisomer dr = 9:1: δ 1.44 (s, 3H), 3.07-3.13 (m, 2H), 3.80-3.86 (m, 1H), 6.72-6.80 (m, 1H), 7.09-7.16 (m, 3H), 7.20-7.31 (m, 3H), 7.74 (br s, 1H), 7.94-7.99 (m, 2H), 9.57 (t, *J* = 1.2 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 21.3 (CH$_3$), 44.0 (CH$_2$), 45.9 (CH), 51.5 (C), 110.1 (CH), 122.7 (CH), 123.0 (CH), 123.8 (CH), 128.4 (C), 128.9 (CH), 129.9 (CH), 130.0 (C), 140.3 (C), 146.1 (C), 180.7 (C), 199,1 (CH). Exact mass (m/z): 338.1264, calculated: 338.1267.
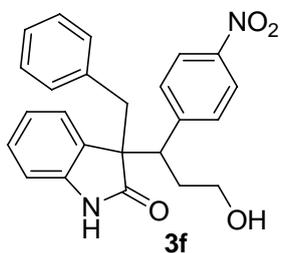
3-benzyl-3(3-hydroxy-1-(4-nitrophenyl)propyl)indolin-2-one 3f – (table 2, entry 6) The reaction was carried out at 23 °C using 0.15 mmol (33.4 mg) of 3-benzylindolin-2-one **1a**, 0.225 mmol (40 mg) of (*E*)-3-(4-nitrophenyl)acrylaldehyde **2**, 0.015 mmol (10% mol, 8.3 mg) of **VIIa** and 0.075 mmol (50% mol, 9.1 mg) of benzoic acid in 300 μL of toluene following the general procedure. From the crude mixture the dr = 11.5:1 was determined by integration of ^{1}H-NMR signal (δ_{major} 9.60 ppm, δ_{minor} 9.65 ppm – br s) and the conversion based on the starting oxindole derivative was 57%. The crude mixture of two diastereoisomer was tranferred in a 25 ml two necked flask and dissolved under argon with 2 ml of anhydrous THF then NaBH$_4$, 0.30 mmol (11.35 mg) was added at 0 °C. After 1 hour under vigorous stirring at room temperature, the solvent was evaporated and a solution of saturated NH$_4$Cl was added to the solid mixture. The aqueous solution was extracted with dichloromethane (3 x 20 ml) and dried over MgSO$_4$. NMR analysis of the crude mixture showed quantitative conversion into the corresponding alcohols as a mixture of diasteroisomers. The d.r. = 11.5:1 was determined by integration of ^{1}H-NMR signal (δ_{major} 3.14 ppm, δ_{minor} 2.77 ppm - d). The title compound was isolated as a single diastereoisomer by column chromatography (CH$_2$Cl$_2$/AcOEt = 4/1) as a colourless solid in 47% yield and 93% ee (major diasteroisomer) R$_f$ (0.57). The ee was determined by HPLC analysis on a Diacel Chiralpak AD-H column (75/25 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: major diastero τ_{minor} = 37.15 min, τ_{major} = 10.6 min). [α]$^{rt}_D$= +37.7 (*c* = 0.910, CHCl$_3$, 92% ee). ^{1}H NMR (400 MHz, CDCl$_3$): 1.41 (br s, 1H), 2.17-2.29 (m, 1H), 2.40-2.53 (m, 1H), 3.17 (d, *J* = 12.9 Hz, 1H), 3.26-3.40 (m, 2H), 3.49-3.57 (m, 1H), 3.47-3.57 (m, 1H), 3.65 (dd, *J* = 12.5, 2.37 Hz, 1H), 6.40-6.49 (m, 1H), 6.78-6.84 (m, 2H), 6.95-7.06 (m, 3H), 7.07-7.12 (m, 2H), 7.13-7.19 (m, 2H), 7.53-7.60 (m, 1H), 7.91-7.97 (m, 2H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 32.6 (CH$_2$), 41.7 (CH$_2$), 48.9 (CH), 58.7 (C), 60.3 (CH$_2$), 109.6 (CH), 122.2 (CH), 122.9 (CH), 124.8 (CH), 126.6 (CH), 127.7 (CH), 128.7 (CH), 129.3 (C), 130.0 (CH), 130.1 (CH), 135.3 (C), 141.0 (C), 146.9 (C), 147.0 (C), 178.7 (C). Exact mass (m/z): 402.1577, calculated: 402.1580.

3-(3-benzyl-2-oxoindolin-3-yl)-3-(4-chlorophenyl)propanal – 3g (Table 2, entry 7). The reaction was carried out at 23 °C using 0.20 mmol (44.6 mg) of 3-benzylindolin-2-one **1b**, 0.3 mmol (49.8 mg) of (*E*)-3-(4-chlorophenyl)acrylaldehyde **2**, 0.02 mmol (10% mol, 11.1 mg) of **VIIa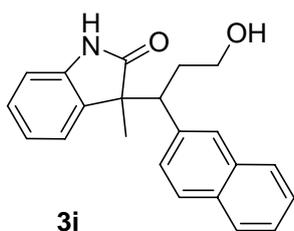** and 0.10 mmol (50% mol, 12.2 mg) of benzoic acid in 400 L of toluene following the general procedure. From the crude mixture the dr = 5.7:1 was determined by integration of ^{1}H-NMR signal (δ_{major} 3.87 ppm, δ_{minor} 3.93 ppm - dd). The title compound was isolated by column chromatography (CH$_2$Cl$_2$/AcOEt = 19/1) as a colourless solid in 85% yield and 85% ee (major diasteroisomer) R$_f$ (0.56). After single recrystallization of the major diasteroisomer from DCM and hexane a colourless solid was obtained in 77% yield and 97% ee. The ee was determined by HPLC analysis on a Diacel Chiralpak AD-H column (80/20 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: major diastero τ_{minor} = 18.14 min, τ_{major} = 15.47 min). [α]$^{rt}_D$= -18.94 (*c* = 0.940, CHCl$_3$, 97% ee). ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.05-3.13 (m, 2H), 3.18 (s, 2H), 3.87 (dd, *J* = 9, 6.3 Hz, 1H), 6.44-6.50 (m, 1H), 6.71-6.85 (m, 2H), 6.90-7.04 (m, 6H), 7.06-7.17 (m, 4H), 7.37-7.44 (m, 1H), 9.55 (t, *J* = 1.7 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): 41.3 (CH$_2$), 44.4 (CH$_2$), 46.0 (CH), 58.1 (C), 109.6 (CH), 122.1 (CH), 124.6 (CH), 126.5 (CH), 127.7 (CH), 128.2 (CH), 128.7 (CH), 129.3 (C), 130.0 (CH), 130.7 (CH), 133.3 , 135.3 (C), 136.7 (C), 141,0 (C), 178.5 (C) 199.9 (CH). Exact mass (m/z): 389.1182, calculated: 389.1183.
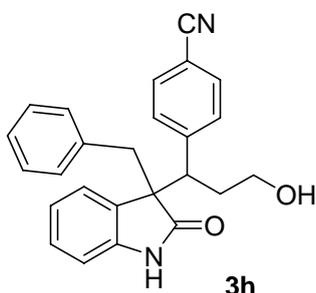
4-(1-(3-benzyl-2-oxoindolin-3-yl)-3-hydroxypropyl)benzonitrile 3h (table 2 entry 8). The reaction was carried out at 23 °C using 0.20 mmol (44.6 mg) of 3-benzylindolin-2-one **1a**, 0.3 mmol (49.8 mg) of (*E*)-4-(3-oxoprop-1-enyl)benzonitrile **2**, 0.02 mmol (10% mol, 11.1 mg) of **VIIa** and 0.10 mmol (50% mol, 12.2 mg) of benzoic acid in 400 μL of toluene following the general procedure. From the crude mixture the dr = 12:1 was determined by integration of ^{1}H-NMR signal (δ_{major} 9.58 ppm, δ_{minor} 9.63 ppm – br s) and the conversion based on the starting oxindole derivative was 89%. The crude mixture of two diastereoisomers was tranferred in a 25 ml two necked flask and dissolved under argon with 2 ml of anhydrous THF then NaBH$_4$, 0.40 mmol (15.136 mg) was added at 0 °C. After 1 hour under

vigorous stirring at room temperature, the solvent was evaporated and a solution of saturated NH$_4$Cl was added to the solid mixture. The aqueous solution was extracted with dichloromethane (3 x 20 ml) and anhydrified with MgSO$_4$. NMR analysis of the crude mixture showed quantitative conversion into the corresponding alcohols as a mixture of diasteroisomers. The d.r. = 12.0:1 was determined by integration of ^{1}H-NMR signal (δ_{major} 6.45 ppm, δ_{minor} 6.52 ppm - m). The title compound was isolated as a single diastereoisomer by column chromatography (CH$_2$Cl$_2$/AcOEt = 4:1) as a colourless solid in 52% yield and 83% ee (major diasteroisomer) R$_f$ (0.25). The ee was determined by HPLC analysis on a Diacel Chiralpak AD-H column (90/10 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: major diastero τ_{minor} = 41.70 min, τ_{major} = 12.80 min). [α]$^{rt}_D$= +22.09 (*c* = 0.825, CHCl$_3$, 83% ee).^{1}H NMR (400 MHz, CDCl$_3$): δ 1.60 (br s, 1H), 2.10-2,23 (m, 1H), 2.36-2.49 (m, 1H), 3.13 (d, *J* = 12.9 Hz, 1H), 3.24-3.38 (m, 2H), 3.46-3.59 (m, 2H), 6.43-6.49 (m, 1H), 6.76-6.83 (m, 2H), 6.93-7.06 (m, 5H), 7.08-7.17 (m, 2H), 7.17-7.22 (br s, 1H), 7.31-7.41 (m, 2H), 7.50-7.59 (m, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 32.5 (CH$_2$), 41.7 (CH$_2$), 49.1 (CH), 58.8 (C), 60.3 (CH$_2$), 109.6 (CH), 110.9 (C), 118.7 (C), 122.2 (CH), 124.8 (CH), 126.5 (CH), 127.6 (CH), 128.6 (CH), 129.5 (C), 129.9 (CH), 130.0 (CH), 131.5 (CH), 135.3 (C), 141.0 (C), 144.8 (C), 179.0 (C). Exact mass (m/z): 382.1683, calculated: 382.1681.

3-(3-hydroxy-1-(naphthalen-2-yl)propyl)-3-methylindolin-2-one – 3i (Table 2, entry 9). The reaction was carried out at 23 °C using 0.25 mmol (36.8 mg) of 3-methylindolin-2-one **1a**, 0.375 mmol (68.25 mg) of (*E*)-3-(naphthalen-2-yl)acrylaldehyde **2**, 0.025 mmol (10% mol, 13.87 mg) of **VIa** and 0.125 mmol (50% mol, 15.25 mg) of benzoic acid in 500 μL of toluene following the general procedure. From the crude mixture the dr = 13.3:1 was determined by integration of ^{1}H-NMR signal (δ_{major} 1.49 ppm, δ_{minor} 1.38 ppm - s) and the conversion based on the starting oxindole derivative was 85%. The crude mixture of two diastereoisomer was tranferred in a 25 ml two necked flask and dissolved under argon with 2 ml of anhydrous THF then NaBH$_4$, 0.5mmol (18.92 mg) was added at 0 °C. After 1 hour under vigorous stirring at room temperature, the solvent was evaporated and a solution of saturated NH$_4$Cl was added to the solid mixture. The aqueous solution was extracted with dichloromethane (3 x 20 ml) and dried over MgSO$_4$. NMR analysis of the crude mixture showed quantitative conversion into the corresponding alcohols as a mixture of

diasteroisomers. The d.r. = 13.0:1 was determined by integration of ^{1}H-NMR signal (δ_{major} 1.47 ppm, δ_{minor} 1.33 ppm - s). The title compound was isolated as a single diastereoisomer by column chromatography (CH$_2$Cl$_2$/AcOEt = 3/2) as a colourless solid in 53% yield and 80% ee (major diasteroisomer) R$_f$ (0.25). The ee was determined by HPLC analysis on a Diacel Chiralpak AD-H column (80/20 hexane/i-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: major diastero τ_{minor} = 10.0 min, τ_{major} = 10.9 min). [α]$^{rt}_{D}$= +67.91 (c = 0.925, CHCl$_3$, 80% ee). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.47 (s, 3H), 1.59-1.79 (brs, 1H), 2.10-2.26 (m, 1H), 2.27-2.40 (m, 1H), 3.24-3.49 (m, 3H), 6.62 (d, J = 7.7 Hz, 1H), 6.91 (dd, J = 8.5, 1.4 Hz, 1H), 7.10 (dt, J = 1.1, 7.5 Hz, 1H), 7.20 (dt, J = 1.3, 7.7 Hz, 1H), 7.28-7.41 (m, 4H), 7.43-7.54 (m, 2H), 7.55-7.63 (m, 1H), 7.64-7.77 (m, 1H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 21.5 (CH$_3$), 32.3 (CH$_2$), 49.2 (CH), 52.5 (C), 60.8 (CH$_2$), 109.6 (CH), 122.1 (CH), 124.1 (CH), 125.5 (CH), 126.6 (CH), 127.1 (CH), 127.3 (CH), 127.9 (CH), 128.0 (CH), 128.2 (CH), 132.5 (C), 132.7 (C), 132.9 (C), 136.7 (C), 140.7 (C), 181.7 (C). Exact mass (m/z): 331.1571, calculated: 331.1572.
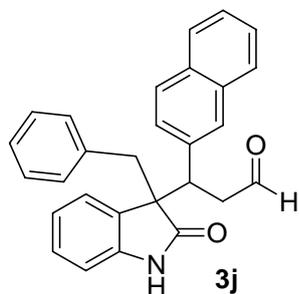

3-(3-benzyl-2-oxoindolin-3-yl)-3-(naphthalen-2-yl)propanal – 3j (Table 2, entry 10). The reaction was carried out at 23 °C using 0.32 mmol (71.2 mg) of 3-benzylindolin-2-one xx, 0.48 mmol (87.36 mg) of (*E*)-3-(naphthalen-2-yl)acrylaldehyde **2**, 0.032 mmol (10% mol, 17.76 mg) of **VIIa** and 0.16 mmol (50% mol, 19.52 mg) of benzoic acid in 640 μL of toluene following the general procedure. From the crude mixture the dr = 20:1 was determined by integration of ^{1}H-NMR signal (δ_{major} 9.54 ppm, δ_{minor} 9.48 ppm - m). The title compound was isolated as a single diastereoisomer by column chromatography (CH$_2$Cl$_2$/AcOEt = 9/1) as a colourless solid in 55% yield and 89% ee (major diasteroisomer) R$_f$ (0.52). After single recrystallization of the major diasteroisomer from CDCl$_3$ and hexane a colourless solid was obtained in 49% yield and >99% ee. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column (80/20 hexane/i-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: single diastero τ = 19.6 min). [α]$^{rt}_{D}$= -1.64 (c = 0.800, CHCl$_3$, 99% ee). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.15 (ddd, J = 16.4, 4.1, 1.4 Hz, 1H), 3.20-3.31 (m, 3H), 4.05 (dd, J = 11.2, 4.2 Hz, 1H), 6.37-6.43 (m, 1H), 6.81-6.86 (m, 2H), 6.93-7.03 (m, 4H), 7.08-7.18 (m, 3H), 7.36-7.43 (m, 2H), 7.44-7.50 (m, 2H), 7.57-7.62 (d, J = 8.7 Hz, 1H), 7.63-7.68 (m, 1H), 7.69-7.75 (m, 1H), 9.53-9.56 (dd, J = 2.4 Hz, 1.5, 1H); ^{13}C NMR (150

MHz, CDCl$_3$): δ = 41.3 (CH$_2$), 44.5 (CH$_2$), 46.9 (CH), 58.4 (C), 109.6 (CH), 122.0 (CH), 124.7 (CH), 125.9 (CH), 125.9 (CH), 126.4 (CH), 127.0 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 127.9 (CH), 128.5 (CH), 128.6 (CH), 129.7 (C), 130.0 (CH), 132.6 (C), 132.9 (C), 135.3 (C), 135.6 (C), 141.1 (C), 179.0 (C), 200.5 (CH). Exact mass (m/z): 405.1725, calculated: 405.1728.

Determination of the Absolute Configuration.
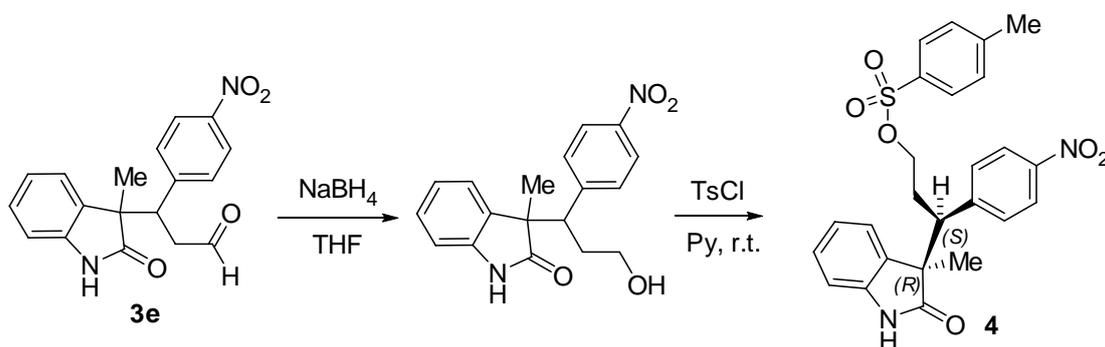
The absolute configuration of compound **3e** was assigned to be (3*S*,3'*R*) by X-ray crystallographic analysis of the corresponding protected alcohol toluene-4-sulfonic acid (S)-3-((R)-3-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-3-(4-nitro-phenyl)-propyl ester **4**. All the other relative and absolute configurations for compounds **3** were assigned by analogy, considering an uniform mechanistic pathway. The single diasteroisomer of **3e** 0.112 mmol (36.4 mg) was dissolved under argon in 2 ml of anhydrous THF and then NaBH$_4$, 0.224 mmol (8.5 mg) was added at 0 °C. After 1 hour under vigorous stirring at room temperature, the solvent was evaporated and a solution of saturated NH$_4$Cl was added to the solid mixture. The aqueous solution was extracted with dichloromethane (3 x 10 ml) and dried over MgSO$_4$. NMR analysis of the crude mixture showed quantitative conversion into the corresponding alcohol which was used for the next step without further purification. The crude alcohol 0.112 mmol. was dissolved in 4 ml of pyridine and *p*-tosyl chloride 0.448 mmol. (85.41 mg) was added at room temperature. After 18 hours of vigorous stirring at room temperature water was added (15 ml) and the crude mixture was extracted with diethyl ether (3 x 10 ml). The combined organic phases were washed with 1M HCl solution (3 x 10 ml) and then dried over MgSO$_4$. The title compound was purified as by column chromatography (CH$_2$Cl$_2$/AcOEt = 95/5) as a colourless solid in 50% yield. [α]$^{rt}_D$= +32.7 (*c* = 0. 5, CHCl$_3$, >99% ee).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.43 (s, 3H), 2.07-2.19 (m, 1H), 2.43 (s, 3H), 2.44-2.53 (m, 1H), 3.29 (dd, *J* = 12.7, 2.8 Hz, 1H), 3.52 (m, 1H), 3.93 (m, 1H), 7.75 (m, 2H), 6.84 (m, 2H), 7.10 (dt, *J* = 7.5, 1.0 Hz), 7.21-7.30 (m, 3H), 7.60 (m, 2H), 7.82 (m, 2H); ^{13}C NMR (150 MHz, CDCl$_3$): δ = 21.56 (CH), 21.60 (CH$_3$), 28.8 (CH$_2$), 48.4 (CH$_3$), 51.9 (C), 67.4 (CH$_2$), 109.9 (CH), 122.6 (CH), 124.0 (CH), 127.8 (CH), 128.8 (CH), 129.7 (CH), 129.8 (CH), 131.3 (C), 132.5 (C), 140.3 (C), 145.1 (C), 145.4 (C), 147.0 (C), 180.2 (C).

Single crystals suitable for X-ray crystallographic analysis were obtained by means of slow crystallization from a mixture of DCM-hexane.

Crystal Data for compound 4
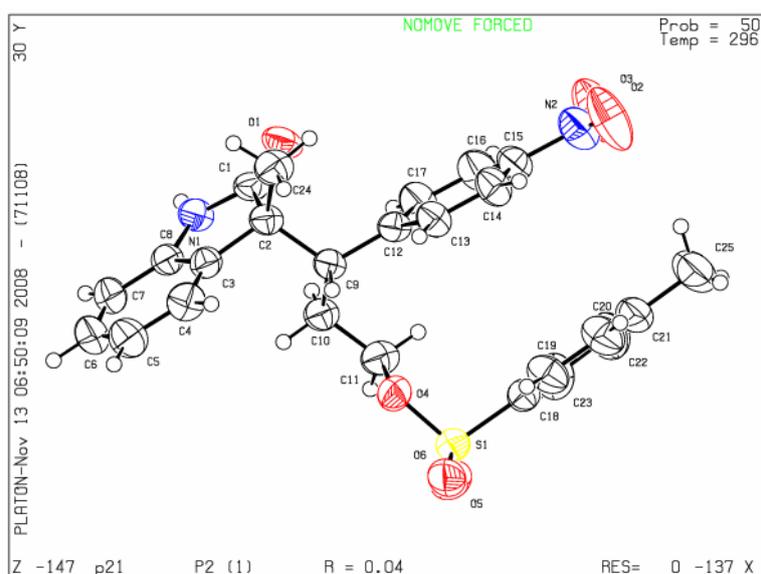
Crystals obtained from evaporation of a hexane/DCM solution, molecular formula: C$_{25}$H$_{24}$N$_2$O$_6$S, M_r = 480.32, monoclinic, space group P2$_1$ (No. 4), *a* = 11.2607(12), *b* = 8.5360(9), *c* = 13.1993(14) Å, β =110.6240(10), *V* = 1186.6(2) Å^3, T = 296(2)°K, *Z* = 2, ρ_c = 1.345 g cm^{-3}, *F*(000) = 504, graphite-monochromated Mo$_K$ radiation (λ = 0.71073 Å), μ(Mo$_K$) = 0.180 mm^{-1}, colourless needle (0.40 × 0.1 × 0.1 mm^3), empirical absorption correction with SADABS (transmission factors: 0.9314 – 0.9822), 2400 frames, exposure time 25 s, 1.65 ≤ θ ≤ 28.56, −15≤ *h* ≤ 14, −11 ≤ *k* ≤ 11, −17 ≤ *l* ≤ 17, 13702 reflections collected, 5514 independent reflections (R_{int} = 0.0200), solution by direct methods (SHELXS97[a]) and subsequent Fourier syntheses, full-matrix least-squares on F_o^2 (SHELX97), hydrogen atoms refined with a riding model except for the N-H hydrogen, that was

experimentally localized and isotropically refined. Data / restraints / parameters ratio was 5514 / 1 / 312, $S(F^2)$ = 1.039, $R(F)$ = 0.0438 and $wR(F^2)$ = 0.0961 on all data, $R(F)$ = 0.0373 and $wR(F^2)$ = 0.922 for 4800 reflections with $I > 2\sigma(I)$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0440P)^2 + 0.1070P]$ where $P = (F_o^2 + 2F_c^2)/3$, largest difference peak and hole 0.156 and –0.225 e Å^{-3}. Absolute structure Flack parameter: 0.03(6). 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-710802. 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).

ORGANOCASCADES REACTIONS MEDIATED BY CINCHONA ALKALOIDS-BASED PRIMARY AMINES:

- Organocatalytic Asymmetric Aziridination of Enones

- Asymmetric Organocatalytic Cascade Reactions with α- Substituted α,β- Unsaturated Aldehydes

5

ORGANOCASCADES REACTIONS MEDIATED BY *CINCHONA* ALKALOIDS-BASED PRIMARY AMINES: SIMPLE CATALYSTS FOR COMPLEX MOLECULES

In the following chapter the recently established strategy of *Asymmetric Organocascade* will be presented. The great potentiality of this approach is nowadays fully recognized by the organic chemical community working on asymmetric catalysis and this innovative methodology is finding more and more supporters also between chemists involved in the pharmaceutical and therapeutic field.

Initially, the first organocatalytic asymmetric aziridination of enones, both linear and cyclic compounds, mediated by quinine-based amine, will be presented. The reported domino sequence is based on an initial iminium activation followed by an enamine intramolecular cyclization step. The main novelty of this work relies on the high level of efficiency and stereo-induction obtained for the ketoaziridines, being α,β-unsaturated ketones challenging substrates in organocatalysis. Indeed, minor progresses have been achieved in organocatalyzed-functionalizations of ketones, compared to their aldehydic counterpart.

In the second part, a highly efficient cascade reaction following an iminium-intermolecular enamine activations sequence will be reported, achieving high molecular complexity with the formation of structurally elaborated and highly valuable molecules. We will see that, through a simple one-pot protocol, two adjacent quaternary and tertiary stereogenic centers can be forged in high optical purity. Moreover the present work shows how chiral

primary amines derived from *Chincona* alkaloids proved efficient towards the activation of α-branched enals, longstanding challenging substrates in asymmetric catalysis because of their low reactivity, mainly due to the difficult formation of the catalytically active, covalent intermediate.

As anticipated, the leitmotif of the following section is the organocascade strategy applied in two different Michael processes followed by enamine activation. In addition, the two reported transformations have an other common feature: the employment of chiral primary amine derived from *Chincona* alkaloyds. Indeed the two types of substrates employed, enones and α,β-substituted enals, are as attractive scaffolds as they are highly challenging compounds. Let's go to see the reasons of their importance and of their quite limited explorations in asymmetric catalysis.

As we have discussed in the previous sections, chiral secondary amine catalysis has demonstrated great potentiality to induce high stereocontrol in the functionalization of aldehydes with a wide range of reagents and by exploiting different reactivities. Nevertheless it has turned out to be not efficient with ketones. Thus, identifying a general catalysts for the highly desirable asymmetric functionalizations of these substrates, has represented a challenging issue.

The use of unsaturated ketones in aminocatalysis have been quite limited because of the sluggish reaction rates observed under secondary amine catalysis, along with the issue associated with the difficult control of the iminium ion geometry. Due to the steric constraints, the iminium ions derived from ketones and secondary amines are highly congested, with a consequent low efficiency of the catalytic system. A similar behaviour is also common to the steric encumbered α,β-disubstituted α,β-unsaturated aldehydes, demonstrating the low efficiency of chiral secondary amines to activate sterically demanding partners.

5.1 Cinchona Alkaloids-derived Primary Amines as efficient catalysts for sterically demanding substrates

Recently, some reports have shown the ability of chiral primary amine derivatives to efficiently activate ketones.[1] Probably because of the notion of the unfavourable imine-enamine equilibria by using primary amines, little attention had been devoted to the development of these catalysts in asymmetric aminocatalysis. Few years ago, following the appearance of some reports showing the ability of simple natural and unnatural amino acids derivatives to efficiently promote aldol[2] and Michael[3] reactions by exploiting enamine activation strategy, primary amine catalysis started to arouse interest between chemists involved in the field of asymmetric aminocatalysis. Owing to reduced steric constraints these primary amine-based catalysts offer the unique possibility of participating in processes between sterically demanding
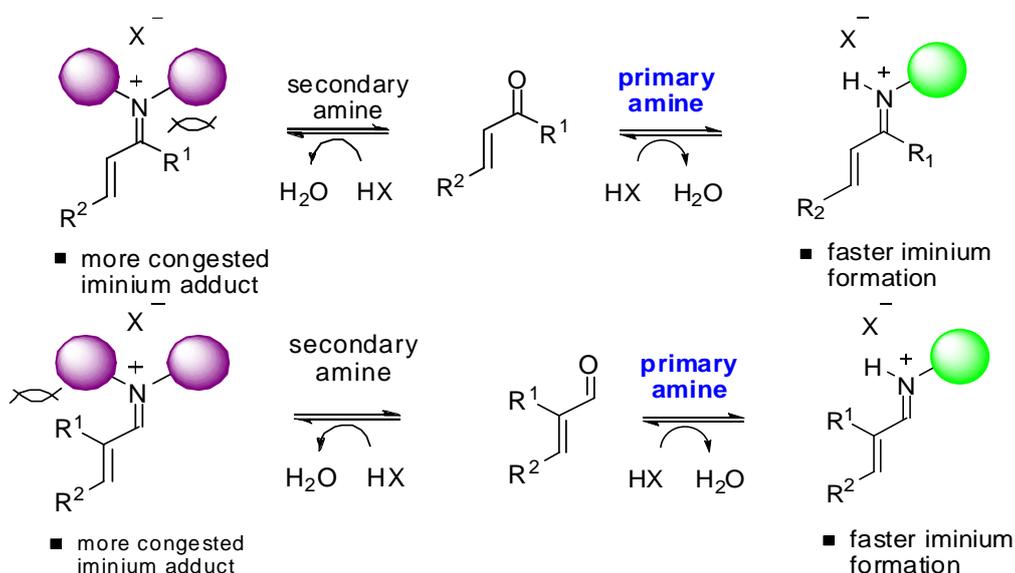

Figure 1. *Steric factors in iminium ion activation*

partners, overcoming the limitations of chiral secondary amines.

In this context, our group, and independently and almost simultaneously a different research group,[4,5] has established chiral primary amines directly derived from natural *cinchona* alkaloids as highly efficient catalysts for iminium ion activation of enones. In particular, we have shown the ability of primary amine **VIII**, readily available in a single synthetic step, from hydroquinine through a Mitsunobu reaction, as a powerful and general catalyst for the efficient and highly enantioselective β-functionalization of enones with C-, S-, and O- nucleophiles.
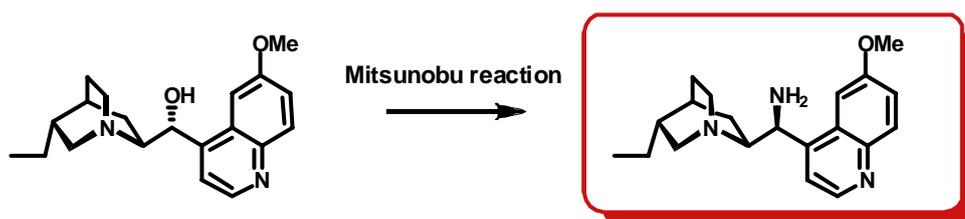
Figure 2. *Synthesis of catalyst VIII*

As shown, this class of catalyst is easily obtainable from the *Chincona* alkaloid family. Being the subject of the current section, a brief introduction to this high valuable natural compounds needs to be provided. We previously mentioned that these chiral primary amines derive directly from C*inchona* alkaloids, which have been themselves employed as organocatalysts in Chiral Brønsted Base Catalysis.[6]

Figure 3 reports the main primary amines derived from this family of catalysts. They have as the most basic fragment a quinuclidine nitrogen that can be easily alkylated with alkyl iodides at room temperature while the most common derivatization are performed at the R^1 and R^2 substituents.

R^1 = H, OMe, OH
R^2= vinyl, ethyl

R^1 = H, OMe, OH
R^2 = vinyl, ethyl

QUININE- and CINCHONINE-derivatives   **QUINIDINE- and CINCHONIDINE derivatives**
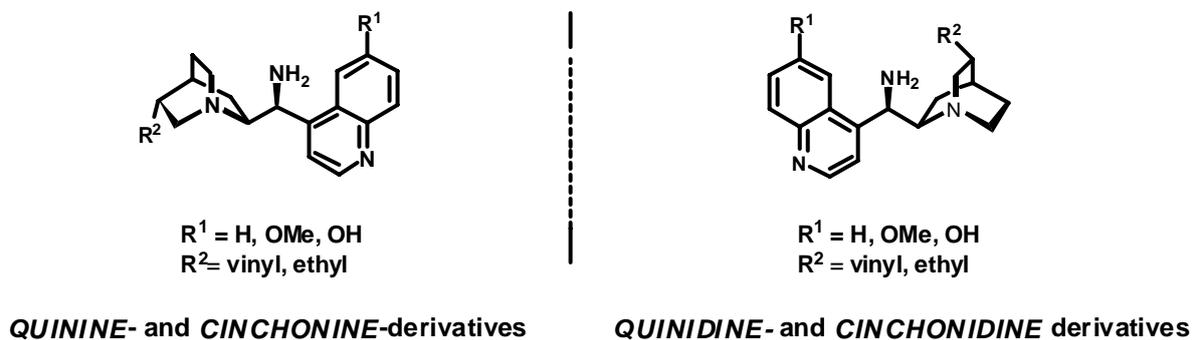
Figure 3. *Structure of Cinchona alkaloid-derived amines.*

All these substrates have four chiral carbon and one chirally bridgehead nitrogen. They present the same absolute configuration at C3 and C4 while the other chiral centers (N1, C8, C9) have opposite absolute configuration in Quinine- and Quinidine-derivatives. Being the asymmetric induction directed by these three chiral centers, *Cinchona* alkaloids-derivatives are usually described as pairs of *pseudoenantiomers*. In simple words, this means that we can access both of the enantiomers of a chiral compounds by judiciously selecting the appropriate quinine or quinidine-based catalysts. This feature makes this kind of catalysts very appealing since both enantiomers are commercially available at a relatively low price. The potentiality and the effectiveness of this class of catalysts will be show in the next pages.

5.1 R References

[1] For recent review on chiral primary amine catalysis, see: a) G. Bartoli, P. Melchiorre, *Synlett* **2008**, 1759 b) F. Peng, Z. Shao, *J. Mol. Cat. A: Chem.* **2008**, *285*, 1; c) L.-W. Xu, J. Luo, Y. Lu, *Chem. Comm.* **2009, *14*,** 1807-1821.

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5.2 **Organocatalytic Asymmetric Aziridination of α,β-unsaturated ketones**
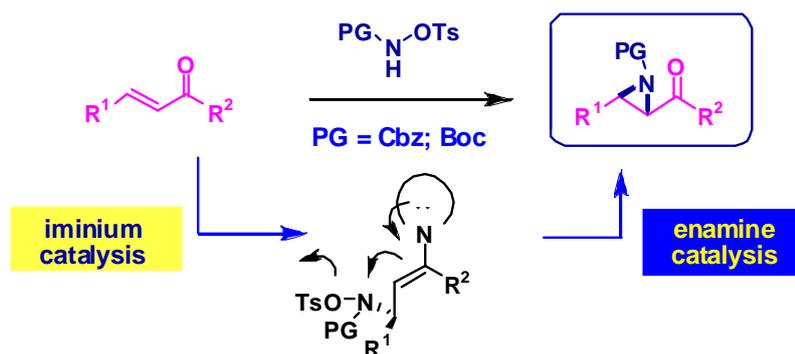
A primary amine derived from *cinchona* alkaloids as a salt with D-*N*-Boc phenylglycine (Boc=tert-butoxycarbonyl) is an efficient catalyst for the aziridination of α,β-unsaturated ketones. This highly effective method, leads to chiral aziridines in high yield, with complete diastereoselectivity, and with very high enantioselectivity (Cbz=benzyloxycarbonyl).

The stereoselective Michael addition to α,β-unsaturated ketones represents an important goal in asymmetric catalysis. The metal-catalyzed asymmetric approach does not generally permit high stereocontrol in the conjugate addition because of the steric and electronic similarity of the two carbonyl substituents that does not allow high levels of discrimination in the metal-association step. In this context, the iminium ion activation strategy would be a suitable alternative strategy since it overcomes the necessity of a specific lone-pair coordination. However, the use of unsaturated ketones in aminocatalysis have been quite limited by some problems due to their sluggish reaction rates observed under secondary amine catalysis. Due to the steric constraints, the iminium ions derived from ketones and secondary amines are highly congested, with a consequent low efficiency of the catalysis. We recently introduce the catalyst primary amine salt **1a**,[1] which is made by combining the easily available 9-amino(9-deoxy)*epi*-hydroquinine **VIII** with D-*N*-Boc phenylglycine. Its employment in the asymmetric conjugate additions of carbon-, oxygen- and sulphur-centered nucleophiles to α,β-unsaturated ketones gave excellent results both in terms of catalytic efficiency and in enantioselectivity.
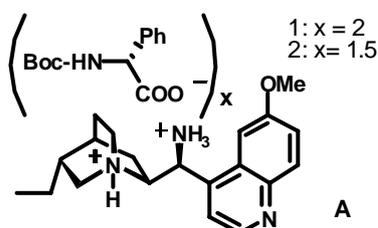

Figure 1. *Catalytic salt* **A**.

To consolidate catalytic salt **1a** as a general and selective catalyst for the activation of enones through iminium ion intermediate, we thought to test its

efficiency in an enantioselective amine conjugate addition, an useful strategy for the chiral C-N bond construction.[2] Inspired by a recently reported chemo- and stereo-selective aziridination of enals,[3] we sought to extend this organocatalyzed strategy to α,β-unsaturated ketones, also prompted by the recent applications of primary amine salts as enones activators.[4]

Moreover, since aziridines constitute important structural motif in several classes of natural compounds and they are versatile building blocks for further synthetically useful transformations,[5] the development of novel and efficient catalytic methodologies for the stereoselective preparation of such a valuable scaffolds, represents an important synthetic target.[6] In addition, to our knowledge, a general and highly stereoselective aziridination of simple enones is still lacking,[7,8] since the previously reported asymmetric protocols were efficient only using chalcones as substrates, while the metal-catalyzed approach, furnishing the *N*-tosyl protected aziridines, although in high enantioselectivity, does not represent a general methodology because of the difficulty to achieve the correspondent unprotected aziridines.[7]

As anticipated, we utilized the catalytic salt for an initial investigation of the asymmetric aza-Michael transformation, focusing on the employment of the commercially available *N*-protected hydroxylamines **4** as nucleophilic components (Table 1). In analogy with the recently reported aza-Michael addition to α,β-unsaturated aldehydes catalyzed by a chiral secondary amine, the reaction with enones in presence of the salt **1a** occurs through a domino Michael addition-intramolecular aldol sequence, leading to 5-hydroxyisoxazolidines **6**, useful chiral scaffolds,[9] in high yield and with ee values ranging from 93 to 99%. As shown in Table 1, a wide range of orthogonal carbamate protecting group can be used without affecting the enantioselectivity of the system (entries 1-3). A broad scope is also achieved

in the ketone component and even the highly challenge chalcone could be used successfully, leading in all cases to products with high optical purity.

Table *Scope of the enantioselective amine conjugate addition to enones.*[a]

4a: Pg = Cbz; 4b: Pg = Boc
4c: Pg = CO$_2$Et
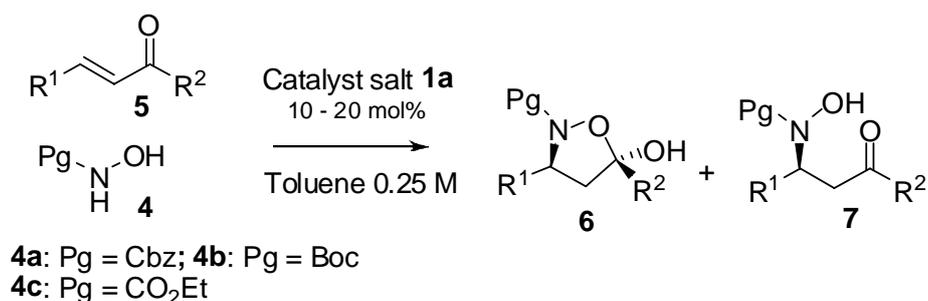
Entry	4	R^1	R^2	C°, h	6 :7[b]	[%] yield[c]	[%] ee[d]
1	a	Pent	Me	RT, 72	9:1	85	99
2	b	Pent	Me	RT, 72	9:1	77	99
3	c	Pent	Me	RT, 72	9:1	43	99
4	a	Me	Me	RT, 72	8:1	63	95
5[e]	a	Ph	Me	30, 72	5:1	78	94
6[e]	a	*p*-Cl Ph	Me	30, 72	5:1	68	93
7[e]	a	Ph	Ph	50, 96	1:3	51	95
8[e]	a	CO$_2$Et	Me	30, 72	5.5:1	65	95
9	a	*c*-hexyl		0, 40	0:100	85	95

[a] Reactions carried out on a 0.2 mmol scale with 1.2 equiv of **4** and 10 mol% of the catalyst salt **1a**, unless noted. [b] Determined by ^{1}H NMR analysis. [c] Overall isolated yield (sum of **6** and **7**). [d] Determined by chiral HPLC analysis. [e] 20 mol% of the catalyst **1a**.

Once proved the ability of our catalytic system to activate enones towards an efficient aza-Michael reaction, we turned our attention to the principal aim of our investigations, the development of a domino sequence in which the iminium activation would be followed by a cyclization step, leading to chiral aziridines. The central issue of our planned strategy has been the choice of the

nitrogen-atom source as the crucial parameter for an efficient aziridination methodology. Indeed, this compound should first act as an efficient nucleophile engaged in the iminium ion activation by catalyst, and then, once the enamine intermediate containing the heteroatom substrate is formed, it should became electrophilic to facilitate the cyclization step under enamine catalysis conditions. We started our investigations examining the reaction of enone **9** with different nitrogen-based reagents **8**, in presence of the catalyst salt combination **1b** (1.5 equivalents of **3** relative to **2**). Table 2 shows the obtained results; the employment of the acylated hydroxycarbamate **8a**, previously used in the aziridination of enals[3] led to the exclusive formation of the conjugate product **11** (Table 2, entry 1). However, the substitution of the leaving group with a better one, such as a tosyl moiety, gave better results, directing the reaction towards the formation of the desired aziridine **10** as main product. Other reaction parameters such the solvent, the reagent concentration and the stoichiometry were explored in order to individuate the best reaction conditions. Finally, because of the not excellent conversion, we investigated if *p*-toluenesulfonic acid, generated during the enamine-induced ring-closing step when using **8c**, may affect the activity of the catalyst. Satisfyingly, we found that the employment of an inorganic base, such as solid NaHCO$_3$, neutralising the formed acid, had a beneficial effect both on the conversion and the selectivity of the process. The selected reaction conditions (using CHCl$_3$ as solvent with $[\mathbf{9}]_0 = 0.25$ M, 1.2 equivalents of **8c** and 2 equivalent of solid NaHCO$_3$) were then employed to examine the scope of our aziridination strategy.
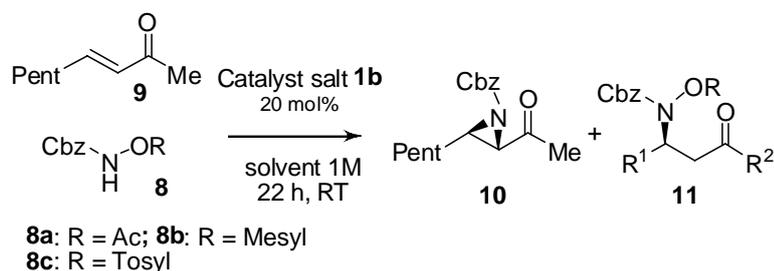
8a: R = Ac; **8b**: R = Mesyl
8c: R = Tosyl

Table 2. Selected screening results for the aziridination of enones.[a]

Entry	8	solvent	Additive (2 equiv)	conv[b]	10:11[b]	dr[b]	[%] ee[c]
1	**a**	toluene	-	21	1:99	-	77[d]
2	**b**	toluene	-	67	1.1:1	-	86
3	**c**	toluene	-	78	4.3:1	4:1	81
4	**c**	H_2O	-	57	4:1	7:3	79
5	**c**	THF	-	58	2:1	5.6:1	82
6	**c**	$CHCl_3$	-	65	7.3:1	7.5:1	89
7[e]	**c**	$CHCl_3$	-	56	9:1	9:1	95
8[e]	**c**	$CHCl_3$	$K_2CO_{3\,(s)}$	<10	>99:1	-	-
9[e]	**c**	$CHCl_3$	$NaHCO_{3\,(aq)}$	45	>99:1	>19:1	80
10[e]	**c**	$CHCl_3$	$NaHCO_{3\,(s)}$	>95	>99:1	19:1	96

[a] Unless noted, the reactions were carried out on a 0.1 mmol scale with 2 equiv of **9** and $[8]_0$ = 1 M for 22 h in the presence of 20 mol% of the catalyst salt combination **1b** (30 mol% of **3** and 20 mol% of **2**). [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by chiral HPLC analysis. [d] ee of compound **11**. [e] $[9]_0$ = 0.25 M and 1.2 equiv of **8c** were employed.

As highlighted in Table 3, a wide range of *N*-Cbz as well as *N*-Boc ketoaziridines **10** could be obtained in good yield and with high levels of both enantio- and diastereo-selectivity. By adjusting the reaction time, it was also possible to decrease the catalyst loading to 5 mol%, keeping the efficiency of the system. Importantly, different sterically and electronically substitutents on the ketonic substrates are well tolerate, enabling access to a broad variety of both aliphatic and aromatic aziridines.

Table 3. Asymmetric organocatalytic aziridination of enones.[a]

8a: PG = Cbz; **8d**: PG = Boc
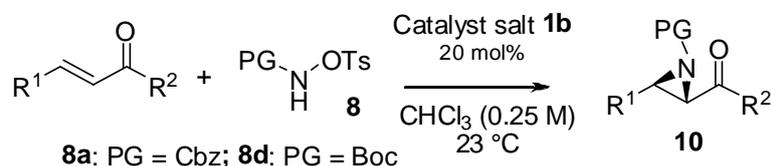
Entry	R^1	R^2	PG	10	Time [h]	yield[b]	dr[c]	[%] ee[d]
1	Pent	Me	Cbz	a	24	93	19:1	96
2	Pent	Me	Boc	b	24	82	>19:1	99
3	Me	Me	Cbz	c	16	96	>19:1	93
4[e]	Me	Me	Cbz	c	72	79	>19:1	93
5	Me	Et	Cbz	d	48	94	19:1	98
6	CO_2Et	Me	Cbz	e	48	74	>19:1	95
7	Ph	Me	Cbz	f	72	85	>19:1	73
8	*p*-NO$_2$ Ph	Me	Cbz	g	72	92	>19:1	99[f]
9	*c*-hexyl		Cbz	h	20	86	>19:1	98

[a] The reactions were carried out on a 0.2 mmol scale with 1.2 equiv of **8** and 20 mol% of the catalyst salt combination **1b** at room temperature in CHCl$_3$ 0.25 M . [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Determined by chiral HPLC analysis. [e] 5 mol% of the catalyst salt **1b** was employed. [f] The absolute configuration of **10g** was determined to be (2*S*, 3*R*) by means of TD-DFT calculations of the electronic circular dichroism (ECD) spectra, see Supporting Information for details.

Moreover, the presented protocol is also effective with cyclohexenone, affording the desired cyclic aziridine **10h** with high optical purity. Along this line, we investigated the aziridination of β-substituted cyclohexenone **12** (Eq 1), leading to the valuable compound **13**, having a quaternary stereogenic center embedded in a cycle, albeit in modest optical purity.[10]

$$\text{(1)}$$
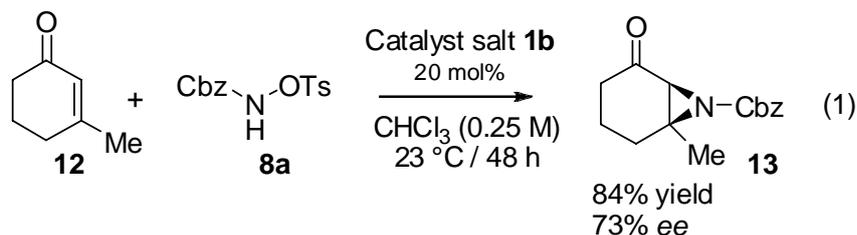
This result highlighted the need of extending the organocatalytic aziridination strategy to cyclic enones, enhancing the level of enantioselectivity of the reaction with a further optimization of the system, as we will report in the next chapter. In summary, we have reported an asymmetric amine conjugated addition to enones that provides a suitable platform for developing an unprecedented example of highly chemo- and stereoselective aziridination of α,β-unsaturated ketones, confirming the ability of catalytic salt **1a** as efficient promoter of iminium-enamine intramolecular sequence leading to the highly valuable *N*-Cbz and *N*-Boc aziridines with almost perfect diastereoselectivity and very high enantioselectivity.

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5.2 Supplementary Information

Contents

General Methods

Materials

Determination of Diastereomeric Ratios

Determination of Enantiomeric Purity

Determination of the Relative and Absolute Configurations.

Experimental Procedures

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.[i] 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.[ii] α,β-unsaturate ketones were

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[i] W. C. Still, M. Kahn, A. J. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.
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purchased from Aldrich or Lancaster and used as received, or prepared by Wittig reaction between commercially available acetylmethylene-triphenylphosphorane and the corresponding aldehydes (i. e. ethyl glyoxalate, and p-nitro benzaldehyde in DCM for 48 h at RT). N-Protected hydroxylamines **4a**-**c** were purchased from Aldrich (**4b**-**c**) or Alfa Aesar (**4a**) and used as received. Compounds **8a**-**d** were prepared following the literature procedures.[iii] 9-Amino(9-deoxy)*epi*-hydroquinine **VIII** was prepared from commercially available hydroquinine following the literature procedure.[iv] D-N-Boc-Phenyl glycine was purchased from Fluka and used as received.

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 or OB-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 stoichiometric amount of benzylamine or pyrrolidine as the catalyst in the presence of 0.5 equiv of benzoic acid.

Determination of the Relative and Absolute Configurations.

Aziridination Products. The relative *trans* configuration was assigned by analysis of the *J* constants. The absolute configuration of compound **10g** was assigned by means of TD-DFT calculations of the Electronic Circular Dichroism (ECD) spectra. The experimental ECD spectra match with the theoretical ones. Other absolute configurations were assigned by analogy considering an uniform mechanistic path. The absolute configurations are in agreement with related aminocatalytic conjugate additions promoted by catalyst **1**.[v]

ECD spectra. UV absorption spectra were recorded at 25 °C in the 210-400 nm spectral region in acetonitrile. The cell path length was 0.1 cm, concentration was $9.8 \cdot 10^{-5}$ mol L^{-1}. CD spectra were

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recorded at 25°C in acetonitrile, with the same path lengths of 0.1 cm, in the range 210-400 nm; reported Δε values are expressed as L mol^{-1}cm^{-1}.

DFT Calculations. Geometry optimization were carried out at the B3LYP/6-31G level by means of the Gaussian 03 series of programs:[vi] 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. TD-DFT calculations were obtained at the B3LYP/6-31+G(d,p)//B3LYP/6-31G level. In order to cover the whole 200-400 nm range, 60 transition were calculated. The CD spectrum was then obtained applying a 0.3 eV Gaussian bandshape.

ECD spectra and Absolute Configuration of compound 10g
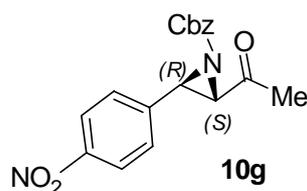
The lack of a suitable heavy atom precludes the use of the Bijovet method, based on anomalous X-ray dispersion, to unambiguously assign the absolute configuration (AC) of the single enantiomer of **10g.** Using a different approach, the Electronic Circular Dichroism (ECD) spectrum can be calculated by 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

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[vi] Gaussian 03, Revision 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.

successfully employed several times[vii] to predict ECD spectra and to assign the AC of organic molecules. A preliminary conformational search, starting from the relative configuration derived from NMR spectra, was performed using Molecular Mechanics (MMFF force field, Montecarlo algorithm implemented in TITAN 1.0.4). The analysis of the output structures revealed that the three best structures differ only for the position of the benzyl group with respect to the carboxamide moiety. These structures were further optimized at the B3LYP/6-31G level, and for each of the optimized structures, the ECD spectrum was calculated in the 200-400 nm region at the B3LYP/6-31+G(d,p) level. As shown in Figure S1 the three calculated spectra are very similar, and this result reduces the possibility of errors in the final comparison of the calculated spectrum. In fact, in the case of flexible molecules, geometrically different conformations might give substantially different contributions to the ECD spectra.[viii]
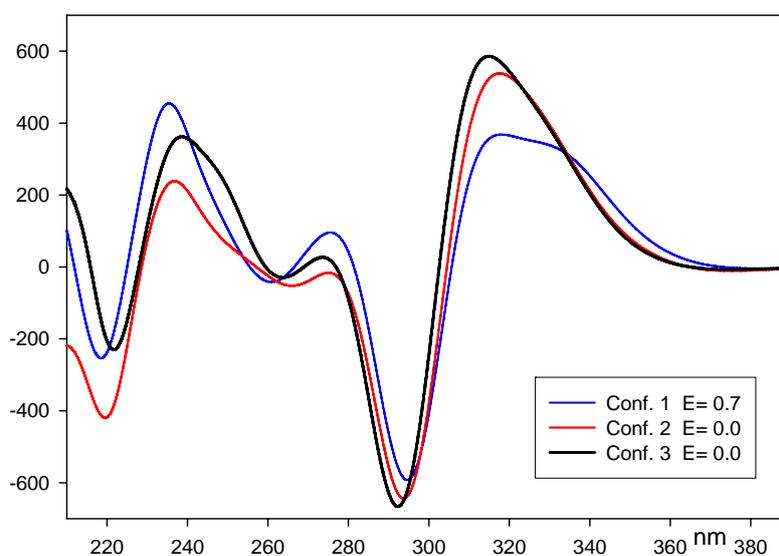
Figure S1. Calculated ECD spectra (B3LYP/6-31+G(d,p)//B3LYP/6-31G) for the best three conformers of **10g** (energies are in kcal/mol)

[vii] 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; e) O. Penon, A. Carlone, A. Mazzanti, M. Locatelli, L. Sambri, G. Bartoli, P. Melchiorre, *Chem. Eur. J.* **2008**, *14*, 4788-4791. For a review: f) N. Berova, L. Di Bari, G. Pescitelli, *Chem. Soc. Rev.* **2007**, *36,* 914.

The final ECD spectrum to be compared with the experimental one was calculated taking into account the relative population of the three conformations at +25°C (14%, 43%, and 43%, respectively), and weighting the calculated spectra in the same ratio. As shown in Figure S2, the ECD spectrum calculated assuming the 2S,3R configuration shows a shape and relative intensities that match that of the experimental spectrum, with a strong positive Cotton effect at 300 nm, followed by a negative band at 265 nm. Accordingly, the 2S,3R configuration should be assigned to the single enantiomer obtained for compound **10g**.
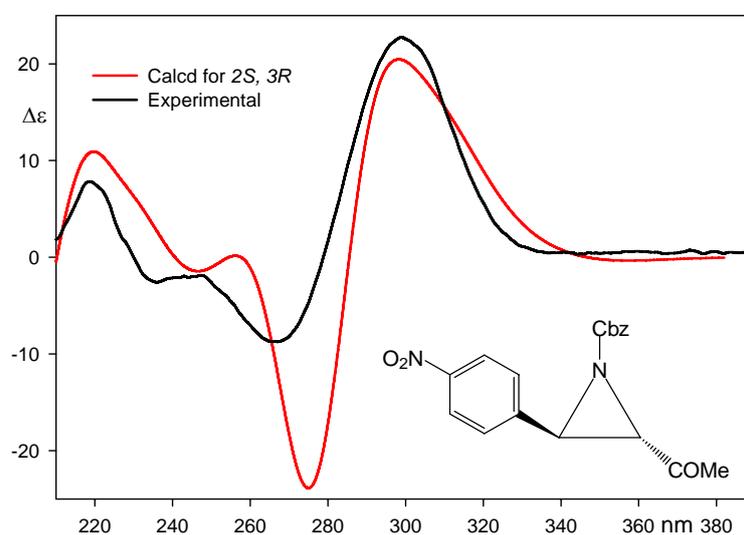
Figure S2: experimental (black trace) and calculated (red trace) ECD spectrum for compound **10g**.

Relative configuration of 5-hydroxyisoxazolidines 6f: NOE studies

The relative configuration of compound 6f was assigned by extensive NOE studies.
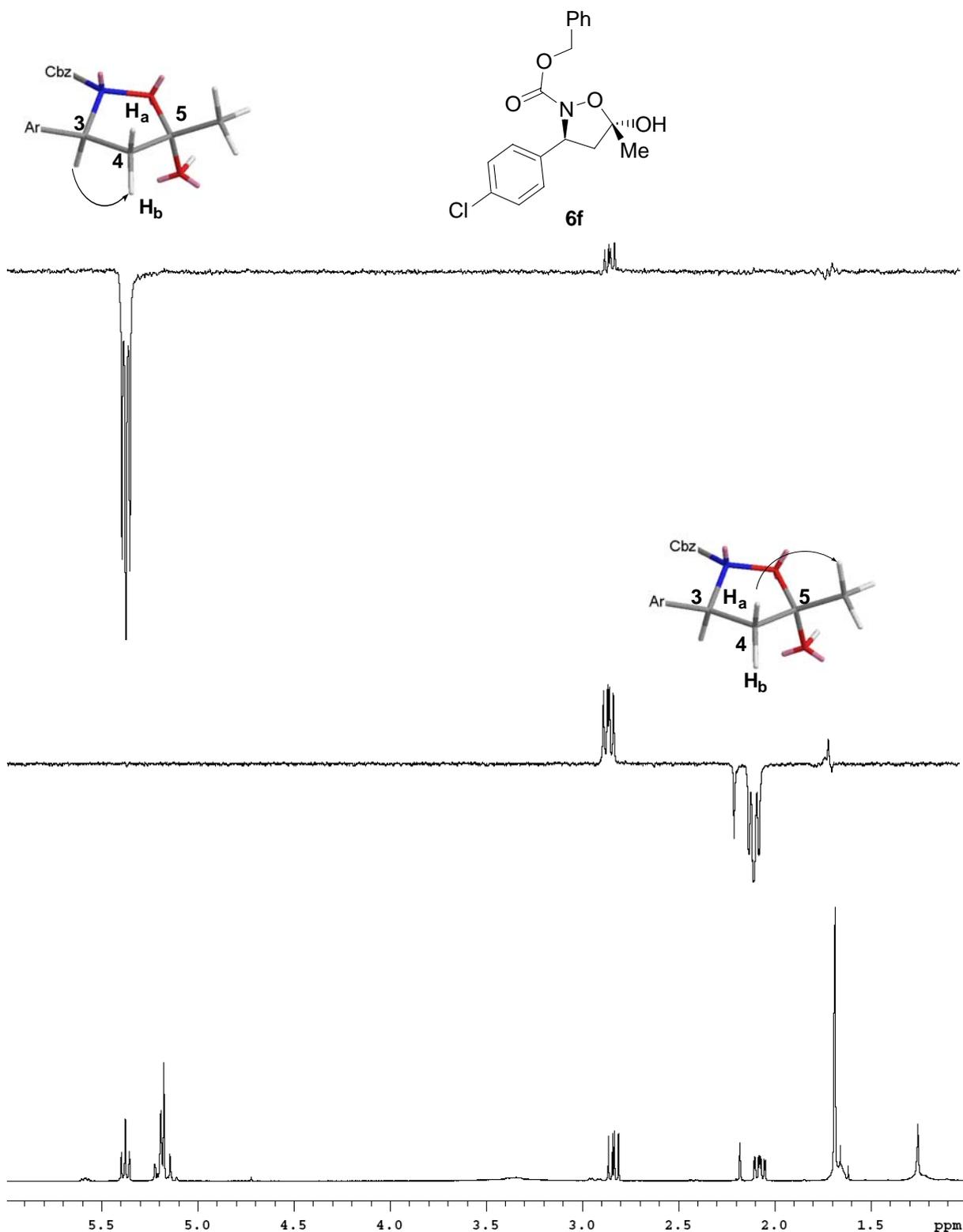
Figure S3. Bottom: part of the ^{1}H-NMR spectrum of **6f** (400 MHz, in CDCl$_3$). Middle trace: DPFGSE-NOE obtained on saturation of the H$_a$(4) signal, showing a NOE effect on the H$_b$(4) signal and on the signal of the CH$_3$(5), and showing no NOE effect on the CH(3) signal. Top trace: DPFGSE-NOE obtained on saturation of the CH(3) signal, showing NOE effect on the H$_b$(4) signal. Except for those relevant to the NOE spectra, all the hydrogens are omitted for clarity.

Experimental Procedures

General Procedure for the Organocatalytic Asymmetric Amine Conjugate Addition to Enones.

4a: Pg = Cbz; **4b**: Pg = Boc
4c: Pg = CO$_2$Et
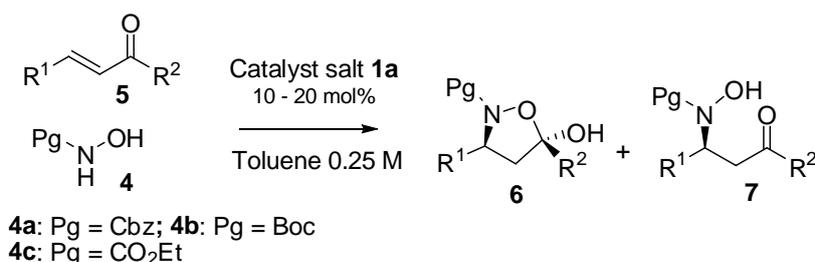
All the reactions were carried out in undistilled toluene. In an ordinary vial equipped with a Teflon-coated stir bar, 9-Amino(9-deoxy)*epi*-hydroquinine **VIII** (0.02 mmol, 6.5 mg, 10 mol%) was dissolved in 0.8 mL of toluene. After addition of D-*N*-Boc-phenylglycine **3** (0.04 mmol, 10 mg, 20 mol%), the solution was stirred for 10 minutes at room temperature. After addition of α,β-unsaturated ketones **5** (0.2 mmol), the mixture was stirred at the indicated temperature for 10 minutes. Then N-Protected hydroxylamines **4a**-**c** (0.24 mmol, 1.2 equiv) was added and stirring was continued for the indicated time. Upon completion of the reaction, the crude reaction mixture was diluted with CH$_2$Cl$_2$ (1 mL) and flushed through a short plug of silica, using dichloromethane/Et$_2$O 1/1 as the eluent. Solvent was removed *in vacuo*, and the residue was purified by flash chromatography (FC) to yield the desired products. The ratio between the tandem or the conjugate addition products **6** and **7**, respectively, was determined by ^{1}H NMR analysis of the crude mixture. 5-hydroxyisoxazolidines **6** were formed in diasteromerically pure form. Unfortunately, the two compounds **6** and **7** can not be separated by means of flash chromatography.
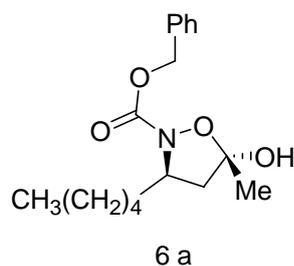
5-Hydroxy-5-methyl-3-pentyl-isoxazolidine-2-carboxylic acid benzyl ester 6a (Table 1, entry 1) – The reaction was carried out following the general procedure to furnish the crude product [**6a:7a** ratio = 8:1, determined by integration of one set of ^{1}H NMR signal (δ$_{major}$ 4.28-4.38 ppm, m, δ$_{minor}$ 4.45-4.54 ppm, m]. The title compound was isolated as a
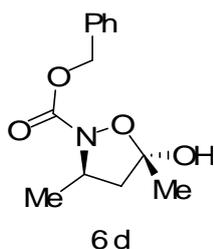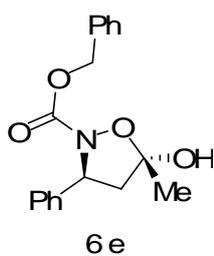
colourless oil by column chromatography (Hexane/Ethyl Acetate = 7/3) in 85% yield and 99% ee. HPLC analysis on a Chiralcel AD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (99% ee): τ_{major} = 16.7 min, τ_{minor} = 17.3 min. $[\alpha]_{rt}^{D}$ = -5.8 (c=1.04, CHCl₃, 99% ee) ¹H NMR: δ = 0.81-0.93 (m, 3H), 1.16-1.36 (m, 8H), 1.63 (s, 3H), 1.73 (dd, *J*=12.5, *J*=7.3, 1H), 2.48 (dd, *J*=12.2,J=8.2, 1H), 3.60 (bs, 1H), 4.29-4.37(m, 1H), 5.18 (dd, J=39.10,J=12.5, 2H), 7.30-7.39 (m, 5H). ¹³C NMR: δ = 14.1 (CH₃), 22.8 (CH₂), 23.8 (CH₃), 26.0 (CH₂), 31.7 (CH₂), 36.3 (CH₂), 43.9 (CH₂), 60.5 (CH), 68.1 (CH₂), 106.5 (C), 128.4 (CH), 128.7 (CH), 136.3 (C), 160.1 (C).
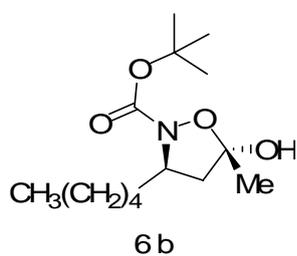
5-Hydroxy-5-methyl-3-pentyl-isoxazolidine-2-carboxylic acid tert-butyl ester 6b (Table 1, entry 2) – The reaction was carried out following the general procedure to furnish the crude product [**6b:7b** ratio = 9.5:1, determined by integration of one set of ¹H NMR signal (δ$_{major}$ 4.16-4.28 ppm, m, δ$_{minor}$ 4.39-4.49 ppm, m]. The title compound was isolated as a colourless oil by column chromatography (Hexane/Ethyl Acetate = 8/2) in 77% yield and 99% ee. HPLC analysis on a Chiralcel AD-H column: 98/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (99% ee): τ_{major} = 11.3 min, τ_{minor} = 11.77 min. $[]_{rt}^{D}$ = -4.5 (c=1.02, CHCl₃, 99% ee) ¹H NMR: δ = 0.81-0.94 (m, 3H), 1.19-1.38 (m, 8H), 1.46 (s, 9H), 1.63 (s, 3H), 1.67 (dd, *J*=12.2,J=7.4, 1H), 2.44 (dd,J=12.1,*J=8.0,* 1H), 4.02 (bs, 1H), 4.17-4.26 (m, 1H). ¹³C NMR: δ = 14.2 (CH₃), 22.8 (CH₂), 23.7 (CH₃), 26.2 (CH₂), 28.4 (CH₃), 31.8 (CH₂), 36.5 (CH₂), 46.2 (CH₂), 60.4 (CH), 81.8 (C), 106.1 (C), 159.5 (C).
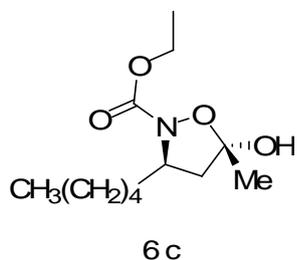
5-Hydroxy-5-methyl-3-pentyl-isoxazolidine-2-carboxylic acid ethyl ester 6c (Table 1, entry 3) – The reaction was carried out following the general procedure to furnish the crude product [**6c:7c** ratio = 6:1, determined by integration of one set of ¹H NMR signal (δ$_{major}$ 1.65 ppm, s, δ$_{minor}$ 2.18 ppm, s]. The title compound was isolated as a colourless oil by column chromatography (Hexane/Ethyl Acetate = 8/2) in 43% yield and 99% ee. HPLC analysis on a Chiralcel AD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (99% ee): τ_{major} = 10.7 min, τ_{minor} = 11.1 min. $[\alpha]_{rt}^{D}$ = -2.4 (c=1.04, CHCl₃, 99% ee) ¹H NMR: δ = 0.82-0.97 (m, 3H), 1.2-1.40 (m, 11H), 1.64 (s, 3H), 1.70-1.76 (m, 1H), 2.48 (dd,

J=8.2,J=12.4, 1H), 3.29 (ds, 1H), 4.14-4.25 (m, 2H), 4.26-4.34 (m, 1H). ^{13}C NMR: δ = 14.2 (CH$_3$), 14.7 (CH$_3$), 22.8 (CH$_2$), 23.9 (CH$_3$), 26.0 (CH$_2$), 31.7 (CH$_2$), 36.3 (CH$_2$), 45.9 (CH$_2$), 60.3 (CH), 62.5 (CH$_2$), 106.4 (C), 157.9 (C).
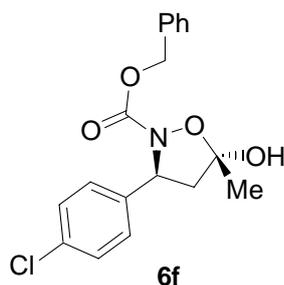
5-Hydroxy-3,5-dimethyl-isoxazolidine-2-carboxylic acid benzyl ester 6 d (Table 1, entry 4) – The reaction was carried out following the general procedure to furnish the crude product [**6d:7d** ratio = 3:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 4.39-4.49 ppm, m, δ_{minor} 4.59-4.65 ppm, m]. The title compound was isolated as a colourless oil by column chromatography (DCM/Acetone = 7/3) in 63% yield and 95% ee. HPLC analysis on a Chiralcel OD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (95% ee): τ_{major} = 10.5 min, τ_{minor} = 11.4 min. $[\alpha]_{rt}^D$ = -11.0 (c=0.83, CHCl$_3$, 95% ee) ^{1}H NMR: δ = 1.32 (d, J=6.44, 3H), 1.65 (s, 3H), 1.70-1.78 (m, 1H), 2.51 (dd, J=7.9,J=12.2, 1H), 4.38-4.50 (m, 1H), 5.13-5.25 (m, 2H), 7.27-7.42 (m, 5H). ^{13}C NMR: δ = 21.8 (CH$_3$) , 23.7 (CH$_3$), 47.6 (CH$_2$), 56.3 (CH), 68 (CH$_2$), 106.3 (C), 128.1 (CH), 128.4 (CH), 128.8 (CH) , 136.3 (C), 159.6 (C).

5-Hydroxy-5-methyl-3-phenyl-isoxazolidine-2-carboxylic acid benzyl ester 6 e (Table 1, entry 5) – The reaction was carried out following the general procedure to furnish the crude product [**6e:7e** ratio = 7.5:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 5.42 ppm, t, δ_{minor} 5.67 ppm, dd]. The title compound was isolated as a colourless oil by column chromatography (Hexane/Ethyl Acetate = 8/2) in 78% yield and 94% ee. HPLC analysis on a Chiralcel OD-H column: 80/20 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (94% ee): τ_{major} = 6.7 min, τ_{minor} = 7.7 min. $[]_{rt}^D$ = -31.4 (c=0.958, CHCl$_3$, 94% ee) ^{1}H NMR: δ = 1.73 (s, 3H), 2.14 (dd, J=12.3,J=8.3, 1H), 2.86 (dd, J=12.4,J=8.3, 1H), 5.14-5.22 (m, 2H), 5.42 (t, J=8.3, 1H), 7.19-7.40 (m, 10H). ^{13}C NMR: δ = 23.3 (CH$_3$), 49.6 (CH$_2$), 63.5 (CH$_2$), 68.1 (CH$_2$), 106.5 (C), 126.3 (CH), 127.7 (CH), 128.0 (CH), 128.3 (CH), 128.7 (CH), 128.9 (CH), 136.1 (C), 141.9 (C), 159.5 (C).
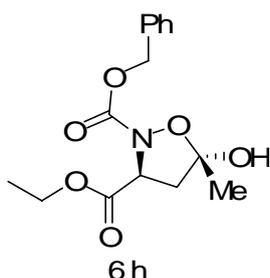
3-(4-Chloro-phenyl)-5-hydroxy-5-methyl-isoxazolidine-2-carboxylic acid benzyl ester 6f (Table 1, entry 6) **–** The reaction was carried out following the general procedure to furnish the crude product [**6f:7f** ratio = 5.5:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 5.38 ppm, t, δ_{minor} 5.55-5-61 ppm, m]. The title compound was isolated as a white solid by column chromatography (Hexane/Ethyl Acetate = 7/3) in 68% yield and 93% ee. HPLC analysis on a Chiralcel AD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (93% ee): τ_{major} = 11.3 min, τ_{minor} = 10.5 min. $[\alpha]_{rt}^{D}$ = -46.6 (c=0.88, CHCl$_3$, 93% ee) ^{1}H NMR: δ = 1.69 (s, 3H), 2.04-2.12 (m, 1H), 2.84 (dd, J=8.5,J=12.4, 1H), 3.36 (ds, 1H), 5.13-5.24 (m, 2H), 5.38 (t, J=8.36, 1H), 7.22-7.35 (m, 9H). ^{13}C NMR: δ = 23.4 (CH3), 49.5 (CH2), 63.0 (CH), 68.3 (CH2), 106.5 (C), 127.7 (CH), 128.0 (CH), 128.4 (CH), 128.7 (CH), 129.0 (CH), 133.5 (C), 136.0 (C), 140.4 (C), 159.5 (C).
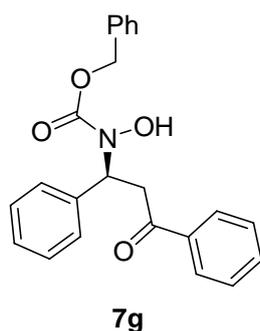
Benzyl hydroxy(3-oxo-1,3-diphenylpropyl)carbamate 7g (Table 1, entry 7) **–** The reaction was carried out following the general procedure to furnish the crude product [**6g:7g** ratio = 1:3, determined by integration of one set of ^{1}H NMR signal (δ_{major} 5.81 ppm, dd, δ_{minor} 5.56 ppm, t]. The title compound was isolated as a white solid by column chromatography (Hexane/Ethyl Acetate = 8/2) in 51% yield and 95% ee. HPLC analysis on a Chiralcel AD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (95% ee): τ_{major} = 23.8 min, τ_{minor} = 26.6 min. $[\alpha]_{rt}^{D}$ = -29.5 (c=0.95, CHCl$_3$, 95% ee) ^{1}H NMR: δ = 1.66 (bs, 1H), 3.50-3.60 (m, 1H), 3.78-3.89 (m, 1H), 5.07 (d, *J*=12.2, 1H), 5.12 (d, *J*=12.2, 1H), 5.81 (dd, *J*=5.5, *J*=9.0, 1H), 7.19-7.64 (m, 14H), 7.95-8.01 (m, 1H). ^{13}C NMR: δ = 40.7 (CH$_2$), 59.1 (CH), 68.4 (CH$_2$), 127.6 (CH), 128.14 (CH), 128.2 (CH), 128.55 (CH), 128.7 (CH), 128.72 (CH), 128.83 (CH), 129.0 (CH), 133.77 (CH), 136.1 (C), 136.8 (C), 139.4 (C), 157.33 (C), 197.9 (C).

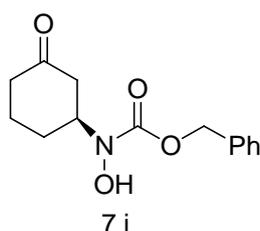**5-Hydroxy-5-methyl-isoxazolidine-2,3-dicarboxylic acid 2-benzyl ester 3-ethyl ester 6h**(Table 1, entry 8) **–** The reaction was carried out following the general procedure to furnish the crude product [**6h:7h** ratio = 9:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 4.90-4.97, m, δ_{minor} 4.63-4.67 ppm, m]. The title compound was isolated as a colourless oil by column chromatography (DCM/Acetone = 97/3) in 65% yield and 95% ee. HPLC analysis on a

Chiralcel AD-H column: 80/20 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (95% ee): τ_{major} = 10.0 min, τ_{minor} = 12.1 min. $[\alpha]_{rt}^D$ = -15.6 (c=0.83, CHCl$_3$, 95% ee) ^{1}H NMR: *δ* = 1.20 (t, *J*=7.2, 3H), 1.66 (s, 3H), 2.27-2.35 (m, 1H), 2.67 (dd, *J*=9.1, *J*=12.4, 1H), 4.11-4.19 (m, 2H), 4.90-4.97 (m, 1H), 5.13-5.30 (m, 2H), 7.28-7.42 (m, 5H). ^{13}C NMR: *δ* = 14.2, 14.3, 30.5, 42.3, 58.6, 68.6, 106.3 (C), 128.4 (CH), 128.6 (CH), 128.8 (CH), 135.9 (C), 149.9 (C), 170.6 (C).

Benzyl hydroxy(3-oxocyclohexyl)carbamate 7i (Table 1, entry 9) − The reaction was carried out following the general procedure to furnish the crude product [**6i:7i** ratio = 0:100, no signal detected for the hydroxyisoxazolidine **6i**]The title compound was isolated as a colourless oil by column chromatography (DCM/Acetone = 95/5) in 85% yield and 95% ee. HPLC analysis on a Chiralcel OD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (95% ee): τ_{major} = 40.0 min, τ_{minor} = 38.0 min. $[\alpha]_{rt}^D$ = -5.1 (c=0.89, CHCl$_3$, 95% ee) ^{1}H NMR: *δ* = 1.51-1.64 (m, 1H), 1.84-1.94 (m, 1H), 1.94-2.13 (m, 2H), 2.18-2.39 (m, 2H), 2.47 (dd, J=14.3,J=5.2, 1H), 2.76 (dd, J=14.2,J=11.2, 1H), 4.25-4.36 (m, 1H), 5.11-5.21 (m, 2H), 7.28-7.38 (m, 5H), 7.72 (bs, 1H). ^{13}C NMR: *δ* = 21.7 (CH$_2$), 27.7 (CH$_2$), 40.4 (CH$_2$), 44.4 (CH$_2$), 57.2 (CH), 68.2 (CH$_2$), 128.1 (CH), 128.4 (CH), 128.6 (CH), 135.6 (C), 156.9 (C), 209.8 (C).

General Procedure for the Organocatalytic Asymmetric Aziridination of Enones.
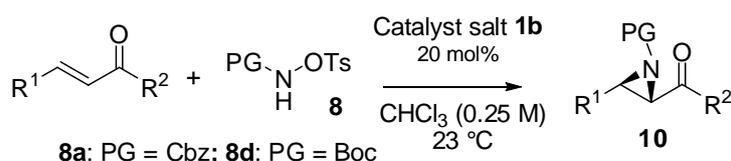

8a: PG = Cbz; **8d**: PG = Boc

All the reactions were carried out in undistilled chloroform and using the catalytic salt combination **1b** (1.5 equiv of D-*N*-Boc-phenylglycine **3** relative to 9-Amino(9-deoxy)*epi*-hydroquinine **2**). In an ordinary vial equipped with a Teflon-coated stir bar, 9-Amino(9-deoxy)*epi*-hydroquinine **2** (0.04 mmol, 13 mg, 20 mol%) was dissolved in 0.8 mL of CHCl$_3$. After addition of D-*N*-Boc-phenylglycine **3** (0.06 mmol, 15 mg, 30 mol%), the solution was stirred for 10 minutes at room temperature. After addition of α,β-unsaturated ketones (0.2 mmol), the mixture was stirred at room temperature for 10 minutes. Then nucleophile **8** (0.24 mmol, 1.2 equiv) was added followed , after 5 minutes stirring, by the addition of NaHCO$_3$ (0.4 mmol, 32 mg, 2 equiv) in one portion.

Stirring was continued for the indicated time, then the crude reaction mixture was diluted with CH$_2$Cl$_2$ (1 mL) and flushed through a short plug of silica, using dichloromethane/Et$_2$O 1/1 as the eluent. Solvent was removed *in vacuo*, and the residue was purified by flash chromatography (FC) to yield the desired products.
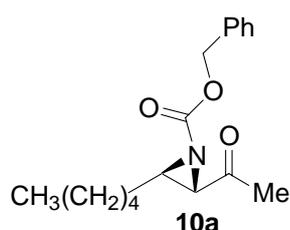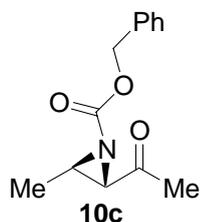
Benzyl 2-acetyl-3-phenylaziridine-1-carboxylate 10a

(Table 3, entry 1) – The reaction was carried out following the general procedure to furnish the crude product [dr = 19:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 3.04 ppm, δ_{minor} 3.10 ppm - d)]. The title compound was isolated as a colourless oil by column chromatography (Hexane/Et$_2$O = 85/15) in 93% yield and 96% ee. HPLC analysis on a Chiralpak AD-H column: 9/1 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (96% ee): τ_{major} = 10.84 min, τ_{minor} = 13.13 min; HRMS: *m/z* calcd for C$_{18}$H$_{17}$NO$_3$: 289.1678; found: 233.1053. $[\alpha]_{rt}^D$ = +12.7 (c=0.96, CHCl$_3$, 96% ee) ^{1}H NMR: δ = 0.80-0.93 (m, 3H), 1.20-1.35 (m, 3H), 2.25 (s, 3H), 2.65-2.70 (m, 1H), 3.04 (d, *J*=2.72, 1H), 5.08 (d, *J*=12.1, 1H), 5.17 (d, *J*=12.1, 1H), 7.28-7.36 (m, 5H). ^{13}C NMR: δ = 13.9 (CH$_3$), 22.3 (CH$_2$), 26.3 (CH$_2$), 29.0 (CH$_3$), 31.38 (CH$_2$), 31.40 (CH$_2$), 45.9 (CH$_2$), 46.6 (CH$_2$), 68.2 (CH$_2$), 128.2 (CH), 128.3 (CH), 128.4 (CH), 135.5 (C), 160.3(C), 202.3 (C).
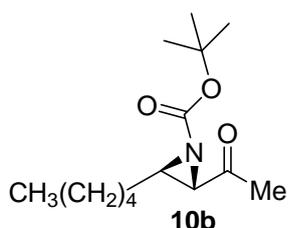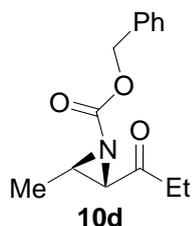
tert-Butyl 2-acetyl-3-pentylaziridine-1-carboxylate

10b (Table 3, entry 2) – The reaction was carried out following the general procedure to furnish the crude product [dr > 19:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 2.97 ppm, δ_{minor} 3.16 ppm - d)]. The title compound was isolated as a colourless oil by column chromatography (Hexane/Et$_2$O = 8/2) in 82% yield and 99% ee. HPLC analysis on a Chiralpak AS-H column: 95/5 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (99% ee): τ_{major} = 5.8 min, τ_{minor} = 6.0 min; HRMS: *m/z* calcd for C$_{14}$H$_{25}$NO$_3$: 255.1834; found: 233.1053. $[\alpha]_{rt}^D$ = +7.0 (c=1.04, CHCl$_3$, 99% ee) ^{1}H NMR: δ = 0.83-0.93 (m, 3H), 1.20-1.35 (m, 8H), 1.45 (s, 9H), 2.26 (s, 3H), 2.62-2.66 (m, 1H), 2.97 (d, *J*=2.8, 1H). ^{13}C NMR: δ = 14.2 (CH$_3$), 22.7 (CH$_3$), 26.7 (CH$_2$), 28.16 (CH$_3$), 29.3 (CH$_3$), 31.46 (CH$_2$), 31.49 (CH$_2$), 45.8 (CH), 46.9 (CH), 81.9 (C), 159.4(C), 202.9(C).
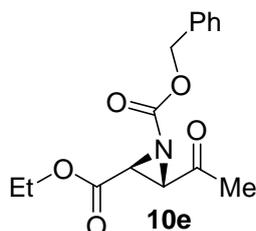
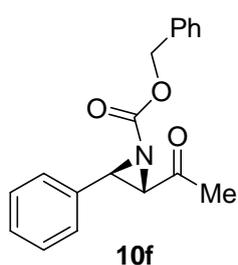**2-Acetyl-3-methyl-aziridine-1-carboxylic acid benzyl ester 10c** (Table 3, entry 3) – The reaction was carried out following the general procedure to furnish the crude product [dr > 19:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 2.98 ppm, δ_{minor} 3.02 ppm - d)]. The title compound was isolated as a colourless oil by column chromatography (Hexane/Acetone = 95/5) in 96% yield and 93% ee. HPLC analysis on a Chiralcel OD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (93% ee): τ_{major} = 16.7 min, τ_{minor} = 17.9 min; HRMS: *m/z* calcd for $C_{13}H_{15}NO_3$: 233.1052; found: 233.1053. $[\alpha]_{rt}^D$ = +5.2 (c=0.89, CHCl$_3$, 93% ee) ^{1}H NMR: δ = 1.33 (d, *J*=5.4, 3H), 2.23 (s, 3H), 2.73-2.80 (m, 1H), 3.00 (d, *J*=2.5, 1H) 5.09 (d, *J*=12.1, 1H), 5.19 (d, *J*=12.1, 1H), 7.29-7.40 (m, 5H). ^{13}C NMR: δ = 17.0 (CH$_3$), 28.8 (CH$_3$), 41.4 (CH), 68.6 (CH$_2$), 128.6 (CH), 128.7 (CH), 128.8 (CH), 135.8 (C), 160.5 (C), 202.9 (C).

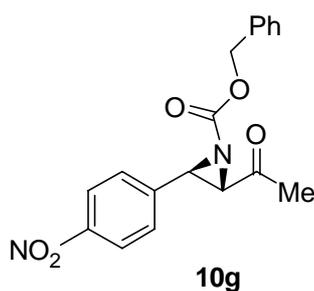**2-Methyl-3-propionyl-aziridine-1-carboxylic acid benzyl ester 10d** (Table 3, entry 5) – The reaction was carried out following the general procedure to furnish the crude product [dr = 19:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 1.33 ppm, δ_{minor} 1.75 ppm - d)]. The title compound was isolated as a colourless oil by column chromatography (Hexane/Ethyl Acetate = 9/1) in 94% yield and 98% ee. HPLC analysis on a Chiralcel OB-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (98% ee): τ_{major} = 18.1 min, τ_{minor} = 21.1 min; HRMS: *m/z* calcd for $C_{14}H_{17}NO_3$: 247.1208; found: 247.1207. $[\alpha]_{rt}^D$ = +12.3 (c=0.77, CHCl$_3$, 98% ee) ^{1}H NMR: δ = 1.06 (t, *J*=7.9, 3H), 1.33 (d, *J*=5.6, 3H), 2.51-2.65 (m, 2H), 2.76 (dq, *J*=5.6, *J*=2.8, 1H), 3.00 (d, *J*=2.8, 1H), 5.10 (d, *J*=12.1, 1H), 5.16 (d, *J*=12.1, 1H), 7.29-7.39 (m, 5H). ^{13}C NMR: δ = 7.4 (CH$_3$), 16.9 (CH$_3$), 35.6 (CH$_2$), 41.33 (CH), 47.1 (CH), 68.5 (CH$_2$), 128.5 (CH), 128.66 (CH), 128.7 (CH), 135.9 (C), 160.7 (C), 205.3 (C).
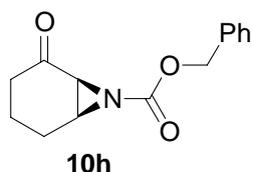
1-Benzyl 2-ethyl 3-acetylaziridine-1,2-dicarboxylate 10e (Table 3, entry 6) – The reaction was carried out following the general procedure to furnish the crude product [dr > 19:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 3.29 ppm, δ_{minor} 3.21 ppm - d)]. The title compound was isolated as a colourless oil by column chromatography (Hexane/Acetone = 95/5) in 74% yield and 95% ee. HPLC analysis on a Chiralpak AD-H column: 9/1 hexane/*i*-PrOH,

flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (95% ee): τ_{minor} = 21.5 min, τ_{major} = 23.6 min; HRMS: *m/z* calcd for $C_{15}H_{17}NO_5$: 291.1107; found: 291.1107. $[\alpha]_{rt}^D$ = +22.6 (c=1.005, CHCl$_3$, 95% ee) ^{1}H NMR: δ = 1.26 (t, *J*=7.3, 3H), 2.33 (s, 3H), 3.29 (d, *J*=2.4, 1H), 3.50 (d, *J*=2.4, 1H), 4.14-4.23 (m, 2H), 5.11 (d, *J*=11.9, 1H), 5.20 (d, *J*=11.9, 1H), 7.30-7.39 (m, 5H). ^{13}C NMR: δ = 14.2 (CH$_3$), 27.7(CH$_3$), 40.8(CH), 46.0(CH), 62.7(CH$_2$), 69.2 (CH$_2$), 128.8 (3CH), 135.3 (C), 158.6 (C), 166.6 (C), 201.0 (C).

**Benzyl 2-acetyl-3-phenylaziridine-1-carboxylate 10f**

(Table 3, entry 7) – The reaction was carried out following the general procedure to furnish the crude product [dr > 19:1, determined by integration of one set of ^{1}H NMR signal (δ$_{major}$ 3.75 ppm, δ$_{minor}$ 3.87 ppm - d)]. The title compound was isolated as a white solid by column chromatography (Hexane/Ethyl Acetate = 9/1) in 85% yield and 73% ee. HPLC analysis on a Chiralpak AD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (73% ee): τ_{major} = 12.40 min, τ_{minor} = 15.79 min; HRMS: *m/z* calcd for $C_{18}H_{17}NO_3$: 295.1208; found: 295.1207. $[\alpha]_{rt}^D$ = +15.2 (c=0.89, CHCl$_3$, 73% ee) ^{1}H NMR: δ = 2.36 (s, 3H), 3.36 (d, *J*=2.3, 1H), 3.75 (d, *J*=2.3, 1H), 5.11 (d, *J*=12.1, 1H), 5.25 (d, *J*=12.1, 1H), 7.28-7.40 (m, 10H). ^{13}C NMR: δ = 30.4 (CH$_3$), 47.2 (CH), 50.0 (CH), 68.8 (CH$_2$), 126.6 (CH), 128.6 (CH), 128.7 (2CH), 128.8 (CH), 128.9 (CH), 135.5 (C), 135.7 (C), 160.2 (C), 201.1(C).

(2S,3R)-2-Acetyl-3-(4-nitro-phenyl)-aziridine-1-carboxylic acid benzyl ester 10g (Table 3, entry 8) – The reaction was carried out following the general procedure to furnish the crude product [dr > 19:1, determined by integration of one set of ^{1}H NMR signal (δ$_{major}$ 3.34 ppm, δ$_{minor}$ 3.12 ppm - d)]. The title compound was isolated as a yellow solid by column chromatography (Hexane/Ethyl Acetate = 9/1) in 92% yield 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; major diastereomer (99% ee): τ_{major} = 33.5 min, τ_{minor} = 42.0 min; HRMS: *m/z* calcd for $C_{13}H_{15}NO_3$: 340.1059; found: 340.1056. $[\alpha]_{rt}^D$ = +94.0 (c=0.75, CHCl$_3$, 99% ee) ^{1}H NMR: δ = 2.37 (s, 3H), 3.35 (d, *J*=2.3, 1H), 3.83 (d, *J*=2.3, 1H), 5.11 (d, *J*=12.1, 1H), 5.24 (d, *J*=12.1, 1H), 7.29-7.42 (m, 5H), 7.44-7.50 (m, 2H), 8.15-8.21 (m, 2H). ^{13}C NMR: δ = 30.7 (CH$_3$), 45.8 (CH), 50.0 (CH), 69.1 (CH$_2$), 124.1 (CH), 127.5 (CH), 128.77 (CH), 128.80 (CH), 128.81 (CH), 135.4 (C), 142.8 (C), 148.2 (C), 159.6 (C), 200.3 (C).

2-Oxo-7-aza-bicyclo[4.1.0]heptane-7-carboxylic acid benzyl ester 10h

(Table 3, entry 9) **–** The reaction was carried out following the general procedure to furnish the crude product [dr = 9:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 2.99 ppm, δ_{minor} 2.85 ppm - d)]. The title compound was isolated as a colourless oil by column chromatography (Hexane/Ethyl Acetate = 9/1) in 86% yield 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; major diastereomer (98% ee): τ_{major} = 9.8 min, τ_{minor} = 12.2 min; HRMS: m/z calcd for $C_{15}H_{17}NO_3$: 245.1052; found: 245.1053. $[\alpha]_{rt}^D$ = - 7.3 (c=0.87, CHCl$_3$, 98% ee). ^{1}H NMR: δ = 1.59-1.70 (m, 1H), 1.73-1.85 (m, 1H), 1.89-2.12 (m, 2H), 2.21-2.31 (m, 1H), 2.45-2.54 (m, 1H), 2.99 (d, J=5.9, 1H), 3.12-3.17 (m, 1H), 5.14 (s, 2H), 7.30-7.38 (m, 5H). ^{13}C NMR: δ = 17.3 (CH$_2$), 22.8 (CH$_2$), 37.1 (CH$_2$), 40.8 (CH), 43.2 (CH), 68.9 (CH$_2$), 128.6 (CH), 128.8 (CH), 128.9 (CH), 135.5 (C), 161.8(C), 204 (C).

5.3 The First Enantioselective Catalytic Aziridination of Cyclic Enones
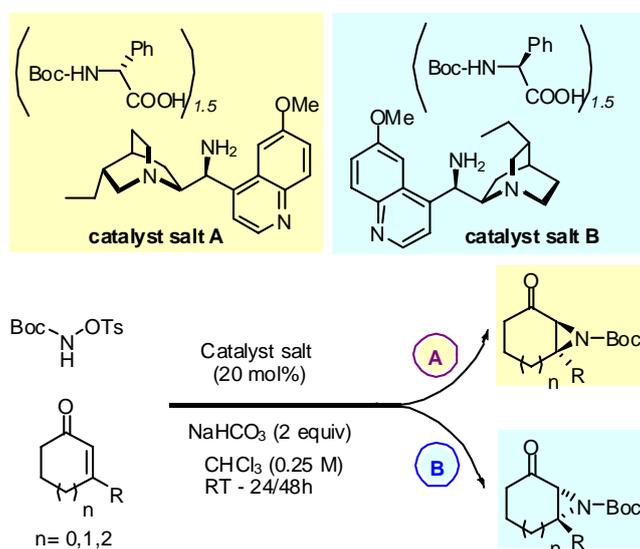
Cyclic Enones: The first catalytic method for the asymmetric aziridination of cyclic enones is described. The presented organocatalytic strategy is effective for a wide variety of substrates providing a fast access to both of the antipodes of the aziridines with very high enantiomeric purity.

We have previously discussed the importance of achieving enantiomerically pure aziridines in organic synthesis. Besides the intrinsic biological activity of such compounds, they represent important chiral synthons which can be stereoselectively converted to useful amine derivatives.[1] In this context, it is undoubtedly the significance of a reliable methodology for their asymmetric synthesis from nonchiral precursors.[2] We presented above our recent success in the asymmetric organo-catalyzed aziridination of linear enones, together with a modest efficiency of our catalytic system when extended to cyclic substrates. On this ground, being a highly enantioselective aziridination of cyclic enones still lacking, we sought to expand the scope of our method, turning our attention to cyclic α,β-unsaturated ketones.

The pioneering works of Pellacani, Tardella and co-workers, in which they highlighted the potential of a conjugate addition–cyclization strategy to directly access aziridines from electron-deficient olefins,[3] inspired our approach. Indeed, this sequential strategy, based on the use of a suitable compound which should first act as a N-centered nucleophile and then become electrophilic to facilitate an intramolecular cyclization step, can be in principle viewed as a powerful platform for developing asymmetric catalytic aziridinations. The employment of a chiral catalyst able to promote the first aza-Michael step while enforcing high level of stereocontrol would lead to the one-step preparation of highly enantioenriched chiral aziridines. However, previously described asymmetric variants - based on phase transfer catalysis[3d,4a] or chiral tertiary amines[6b,c] - often lack scope, reactivity, and selectivity.[4]

The starting point for our investigations has been our recently exploitation of chiral primary amine 9-amino(9-deoxy)epi-hydroquinine **VIII** (**9-*epi*-NH₂-HQ**) in a well defined iminium-enamine tandem sequence of linear α,β-unsaturated ketones, delivering enantiopure *N*-Cbz and *N*-Boc protected *trans*-aziridines. Initially, we exploited the use of primary amine salt **A** (made

by combining the easily available **9-*epi*-NH₂-HQ** with D-*N*-Boc phenylglycine) in the aziridination of cyclohexanone **1a**. After extensive screening of the standard reaction parameters,[5] we found that treating 1.2 equivalents of **1a** with tosylated hydroxycarbamate **2a-b** in the presence of 2 equivalents of NaHCO₃[6] and catalyst salt **A** (20 mol%) in chloroform for 24 h directly resulted in the formation of *N*-Cbz or *N*-Boc bicyclic adducts **3a** and **3b**, respectively, in high yield and almost perfect stereoselectivity (dr and er ≥99:1, entries 1 & 2, Table 1). The method proved efficient also with the challenging substrate β-methyl cyclohexenone **1b**, leading to a heterocyclic adduct with a quaternary stereocenter, albeit the corresponding *N*-Cbz aziridine **3c** was obtained with moderate enantioselectivity (entry 3).[5]

Table 1. Catalyst investigations for the aziridination of cyclic enone. [a]
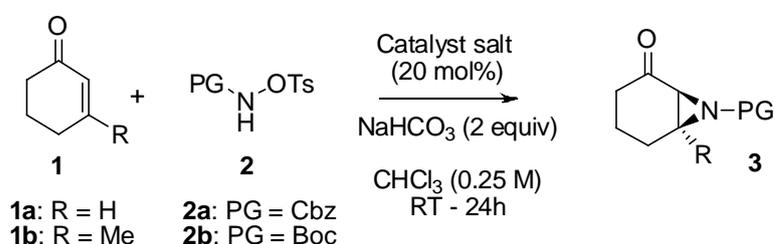
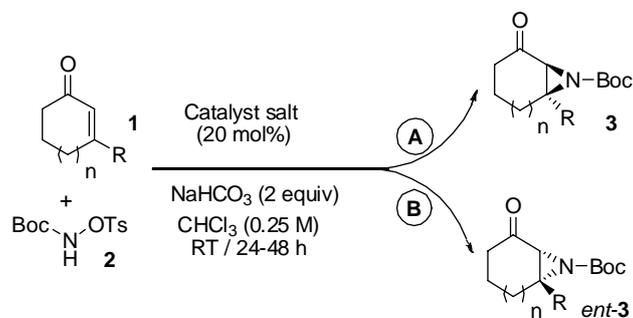| Entry	1	2	Catalyst Salt		3	yield	er[c]
			amine	acid		(%)[b]	
1	a	a	Catalyst salt **A**		a	86	99:1
2	a	b	Catalyst salt **A**		b	73	99.5:0.5
3	b	a	Catalyst salt **A**		c	84	86:14
4	b	b	Catalyst salt **A**		d	75	96:4
5	a	a	Catalyst salt **B**		a	98	0.5:99.5
6	a	b	Catalyst salt **B**		b	76	0.5:99.5
7	b	b	Catalyst salt **B**		d	88	7:93
8	b	b	9-*epi*-NH₂-HQD	(*D*)-PhgOH	d	56	9:91
9	b	b	9-*epi*-NH₂-HQ	(*L*)-PhgOH	d	54	94:6

[a] Ts = Tosyl. PhgOH: N-Boc phenylglycine. A single diastereoisomer has been always detected by 1H NMR analysis of the crude mixture. Reactions carried out on a 0.2 mmol scale at room temperature for 24 h using 1.2 equiv. of enone 1 and 20 mol% of the catalyst salt (1:1.5 amine to acid ratio). [b] Isolated yield after chromatography. [c] Enantiomeric ratio determined by HPLC analysis on chiral stationary phases.

Fortunately, using the *N*-Boc-protected nucleophile **2b** we found that the aziridination proceeds with greatly improved selectivity, delivering the compound **3d** in 92% ee (entry 4). As described above, the employed catalyst salt **A** is composed by two distinct chiral entities, one derived from *Cinchona* alkaloid and the other from a *N*-Boc protected amino acid; obviously, it is possible that both the chiral moieties can influence the reactivity, as well as the stereochemistry of the process. With the aim of selectively access both the antipodes of the products with high enantiomeric purity, we decided to further explore the exact influence of the two chiral components of the catalytic salt. Notably, the combination of the pseudo-enantiomer **9-*epi*-NH₂-HQD IX**, derived from hydroquinidine, with L-*N*-Boc phenylglycine in a 1:1.5 ratio (catalyst salt **B**) and its use in the aziridination of both **1a** and **1b** affords the corresponding aziridines **3** with opposite absolute configuration while maintaining a very high level of selectivity (entries 5-7). These studies can place in the recently conceptualized ACDC (Asymmetric Counterion-Directed Catalysis), exploited by List and co-workers. This strategy is funded upon the fact that most chemical transformations proceed via charged transition states or intermediates and high stereocontrol can be induced by chiral catalysts able to form chiral ion pairs (as iminium ion and its counteranion, in our case).[7] In this context, to gain more insights on the role played by the two chiral entities of the catalyst salts **A** & **B** within the present chemistry, we used the miss-matched combinations to promote the reaction of **1b** with **2b** (entries 8 & 9). The observed lower reactivity and slightly decreased stereoselectivity (88% against 92% ee) and the sense of asymmetric induction clearly indicate that, albeit the chiral primary amine is mainly responsible of directing the process toward a stereoselective path, the chiral co-catalyst is important to improve the general efficiency of the aziridination.

Further investigations on the scope of the asymmetric aziridination of cyclic enones were done, using **2b** as the nucleophile and both catalyst salts **A** & **B** in order to access the two enantiomeric aziridines **3** (Table 2).

The catalytic system proved efficient with various substituted cyclic enones, converted into *N*-Boc protected aziridines with excellent results (entries 2 & 3).

**Table 2.** Scope of the aziridination of cyclic enones. [a]

Entry	Aziridine	Catalyst salt	yield (%)[b]	ee (%)[c]
1	3b	A	73 (51)[d]	99 (99)[d]
		B	76	99
2	3e	A	84	98
		B	84	98
3	3f	A	33	98
		B	53	98
4	3d	A	75	92
		B	88	86
5[e]	3g	A	93	95
		B	85	93
6	3h	A	90	98
		B	98	94
7	3i	A	39	93
		B	44	97
8[f]	3j	A	52	85
		B	68	61

[a] A single diastereoisomer has been always detected by ^{1}H NMR analysis of the crude mixture. Reactions carried out at room temperature for 24 h using 1.2 equiv. of enone **1** on a 0.2 mmol scale. [b] Yield of isolated product. [c] ee of **3** was determined by HPLC analysis. [d] Number in parenthesis refers to reaction carried out using 10 mol% of catalyst salt **A**. [e] 48 h reaction time. [f] Using 2 equiv. of enone, 72 h reaction time.

The process allows forging quaternary stereogenic centres with high fidelity when employing β-substituted cyclohexanones (entries 4 & 5).

Both 2-cycloheptenone and 2-cyclopentenone turned out to be excellent substrates, albeit the latter shows a reduced reactivity (entries 6 & 7). Also β-methyl 2-cyclopentenone reacts under the reported conditions, albeit the corresponding aziridine **3j** is formed with moderate enantioselectivity (entry 8), whereas α-substituted cyclic enones proved to be unreactive. The relative and absolute configurations of aziridines **3d**, **3e**, and **3h** were assigned by NMR NOE analyses and by means of TD-DFT calculations of the electronic circular dichroism (ECD) spectra, as described in Supplementary Information.

As anticipated, chiral aziridines represent a valuable class of bioactive and pharmaceutically important molecules. For example, the tricyclic, aziridine-containing indane moiety is largely present in molecules with these properties; NSC676892,[8] reported below, is only one example of them.

NSC676892
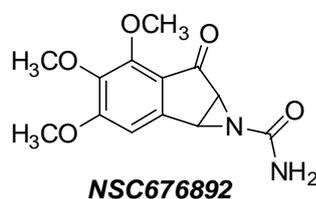
We therefore explored the possibility of extending the aziridination method to indenone derivative **4**, a challenging compound for iminium catalysis, due to the severe steric hindrance hampering the condensation with the catalyst. Notably, both the antipodes of the corresponding tricyclic aziridine derivative **5** can be prepared with good chemical yield and very high enantioselectivity (Scheme 1).
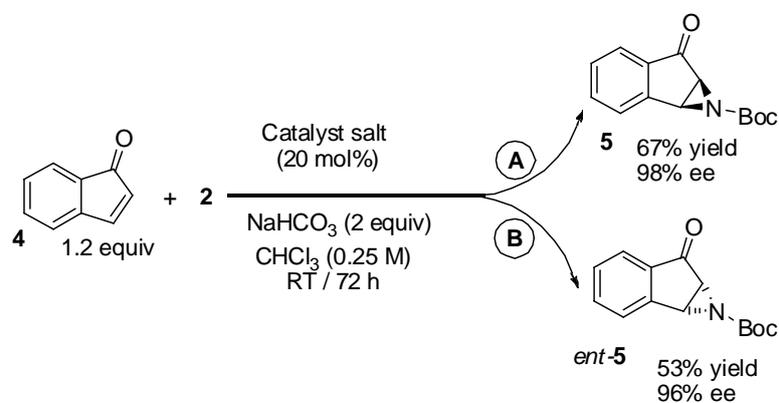
Scheme 1. *Aziridination of 1H-inden-1-one.*

In summary, reporting the first catalytic and highly enantioselective aziridination of cyclic α,β-unsaturated ketones, we further illustrated the increasing role gained by chiral primary amine catalysis in the realm of asymmetric synthesis. Moreover, the method uses easily available reagents and catalysts and provides a reliable and highly stereoselective access to a wide variety of *N*-Boc protected aziridines.

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[4] a) S. Minakata, Y. Murakami, R. Tsuruoka, S. Kitanaka, M. Komatsu *Chem. Commun.* **2008**, 6363 and references therein; b) Y.-M. Shen, M.-X. Zhao, J. Xu, Y. Shi, *Angew. Chem.* **2006**, *118*, 8173; *Angew. Chem. Int. Ed* **2006**, *45*, 8005; c) A. Armstrong, C. A. Baxter, S. G. Lamont, A. R. Pape, R. Wincewicz, *Org. Lett.* **2007**, *9*, 351. For a highly enantioselective aziridination of α,β-unsaturated aldehydes catalyzed by chiral secondary amines, see: 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) H. Arai, N. Sugaya, N. Sasaki, K. Makino, S. Lectard, Y. Hamada, *Tetrahedron Lett.* **2009**, *50*, 3329.

[5] The choice of the solvent, the stoichiometry of the reaction and the nature of the acidic co-catalyst turned out to be crucial parameters for the method optimization. Selected results for reactions between **1b** & **2a**, leading to **3c**, to be compared with entry 3, table 1: *Solvent screening*: CHCl$_3$, 90% conv., 72% ee; toluene, 60% conv., 67% ee; dioxane, 23% conv., 79% ee. *Acidic co-catalyst* (using **9-*epi*-NH$_2$-HQ** in CHCl$_3$ as the solvent): D-*N*-Boc phenylglycine, 90% conv., 72% ee; N-Boc glycine, 93% conv., 65% ee; 2-F benzoic acid, 22% conv., 71% ee; no acidic co-catalyst, less than 5% conversion.

[6] The presence of an inorganic base has a beneficial effect on both the reaction rate and the selectivity of the aziridination. The role of NaHCO$_3$ is likely to neutralize the *p*-toluenesulfonic acid generated during the enamine-induced intramolecular ring closing step, which otherwise might affect the activity of the catalyst. Other inorganic bases tested (e. g. K$_2$CO$_3$, KF) afforded much worse results.

[7] The use of chiral, cationic catalysts in asymmetric reactions involving anionic achiral intermediates is at the heart of phase-transfer catalysis , for reviews on asymmetric phase-transfer catalysis: a) T. Ooi, K. Maruoka, *Angew. Chem.* **2007**, *119*, 4300–4345; *Angew. Chem. Int. Ed.* **2007**, *46*, 4222–4266; b) M. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506–517; c) B. Lygo, B. I.

Andrews, *Acc. Chem. Res.* **2004**, *37*, 518–525; d) K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013–3028.

[8] H. Hong, N. Neamati, H. E. Winslow, J. L. Christensen, A. Orr, Y. Pommier, G. W. A. Milne, *Antiviral Chemistry Chemotherapy* **1998**, *9*, 461.

5.3 Supplementary Information

Contents

General Methods

Materials

Determination of Diastereomeric Ratios

Determination of Enantiomeric Purity

Determination of the Relative and Absolute Configurations

Experimental Procedures

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded at 600 MHz and 150 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] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. ESI spectra were obtained from the Department of Organic Chemistry *"A. Mangini"*. Optical rotations are reported as follows: [α]$^{rt}_D$ (*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] Cyclic enones were purchased from Aldrich or Alfa Aesar and used as received, whereas enones **1f**,[3] **1g**,[4] **4**[5] were prepared according to literature procedures. Compounds **2a-b** were prepared following the literature procedures[6]. 9-Amino(9-deoxy)*epi*-hydroquinine (**9-*epi*-NH₂-HQ**) and 9-Amino(9-deoxy)*epi*-hydroquinidine (**9-*epi*-NH₂-HQD**) were prepared from commercially available hydroquinine and hydroquinidine, respectively, following the literature procedure.[7] D-N-Boc-Phenylglycine and L-N-Boc-Phenylglycine were purchased from Fluka and used as received.

Determination of Diastereomeric Ratios

The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture, and confirmed by HPLC analysis on chiral stationary phases columns.

Determination of Enantiomeric Purity

Chiral HPLC analysis was performed on an Agilent 1100-series instrumentation. Daicel Chiralpak AD-H column with *i*-PrOH/hexane as the eluent proved to be effective for all the aziridines synthesised.

HPLC traces were compared with racemic samples obtained by carefully mixing the two product antipodes obtained performing the individual reactions with 9-Amino(9-deoxy)*epi*-hydroquinine (catalyst salt **A**) and its pseudoenantiomer 9-Amino(9-deoxy)*epi*hydroquinidine (catalyst salt **B**) separately.

Determination of the Relative and Absolute Configurations

Introduction

The present reaction is emblematic of the recent rapid progress in asymmetric synthesis, yielding complex compounds containing more than one stereogenic carbon. In this framework, the

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[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) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368-13369; b) Bergma, R.; Magnusson, G. *J. Org. Chem.* **1986**, *51*, 212-217

[4] X. Wang, C. Reisinger, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6070-6071

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[6] a) T. J. Donohoe, C. J. R. Bataille, W. Gattrell, J. Kloesges, E. Rossignol, *Org. Lett.* **2007**, *9*, 1725 ; b) J. A. Stafford, S. S. Gonzales, D.   G. barrett, E. M. Suh, P. L. Feldmanm, *J. Org. Chem.* **1998**, *63*, 10040.

unambiguous determination of the relative and absolute configuration of the chiral carbons is strictly necessary, in order to understand the reaction mechanism.

Since many years the elective method for the determination of absolute configuration has been the anomalous dispersion X-ray crystallography (the "Bijovet method")[8], that has become simpler thanks to rapid development of high-resolution single-crystal difractometers. The obvious limitations of the X-ray method is the need for diffraction-quality single crystals, and for the presence of a "heavy" atom in the molecule (i.e. Z > Si). While the second limitation is often negotiable by the organic chemists, quite often the crystallization step is unconquerable.

Recently, the determination of the absolute configuration (AC) of chiral molecules by means of the chiroptical techniques of optical rotation (OR), electronic circular dichroism (ECD), and vibrational circular dichroism (VCD) has been revolutionized by the development of density functional theory (DFT) methods for the prediction of these properties. Theoretical calculation of ECD and VCD has been successfully employed in recent years to assign the AC of known organic molecules[9]. The determination of the AC by chiroptical methods on newly synthesized molecules requires the knowledge of the relative configuration of the chiral centres. If the relative configuration is not known, all the relative configurations and all the populated conformation of each relative configuration should be calculated and taken into account in the final simulation of chiroptical spectra, leading to a completely unusable and unreliable approach.

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[7] B. Vakulya, Sz. Varga, A. Csámpai, T. Soos, *Org. Lett.* **2005**, *7*, 1967.

[8] Bijvoet J.M., Peerdeman A.F., van Bommel A.J. Determination of the absolute configuration of optically active compounds by means of X-rays. *Nature* **1951**, *168*, 271.

[9] For recent examples of this method to assign the absolute configurations of organic molecules, see: (a) Diedrich, C.; Grimme, S. *J. Phys. Chem. A* **2003**, *107*, 2524; (b) Casarini, D.; Lunazzi, L.; Mancinelli, M.; Mazzanti, A.; Rosini, C. *J. Org. Chem.* **2007**, *72*, 7667; (c) Goel, A.; Singh, F. V.; Kumar, V.; Reichert, M.; Goulder, T. A. M.; Bringmann, G. *J. Org. Chem.* **2007**, *72*, 7765. (d) Stephens, P. J.; Pan, J. J.; Devlin, F. J.; Cheeseman, J. R. *J. Nat. Prod.* **2008**, *71*, 285.(e) Penon, O.; Carlone, A.; Mazzanti, A.; Locatelli, M.; Sambri, L; Bartoli, G.; Melchiorre, P. *Chem. Eur. J.* **2008**, *14*, 4788; (f) Pesciaioli, F.; De Vincentiis, F.; Galzerano, P.; Bencivenni, G.; Bartoli, G.; Mazzanti, A.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 8703. (g) Shaikh, R.R.; Mazzanti, A.; Petrini, M.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 8707. (h) Gioia, C.; Fini, F.; Mazzanti, A.; Bernardi, L.; Ricci, A. *J. Am. Chem. Soc.* **2009**, *131*, 9614. (i) Taniguchi, T.; Martin, C.L.; Monde, K.;Nakanishi, K.;Berova, N.; Overman, L.E. *J. Nat. Prod.* **2009**, *72*, 430-432 (j) Polavarapu, P.L.; Petrovic, A.G.; Vick, S.E.; Wulff, W.D; Ren, H.; Ding, Z.; Staples, R.J. *J. Org. Chem.*, **2009**, *74*, 5451-5457. For reviews: (k) Berova, N.; Di Bari, L.; Pescitelli, G. *Chem. Soc. Rev.* **2007**, *36*, 914. (l) Bringmann, G.; Bruhn, T.; Maksimenka, K.; Hemberger, Y. *Eur. J. Org. Chem.* **2009**, 2717.

3e   **3d**   **3h**
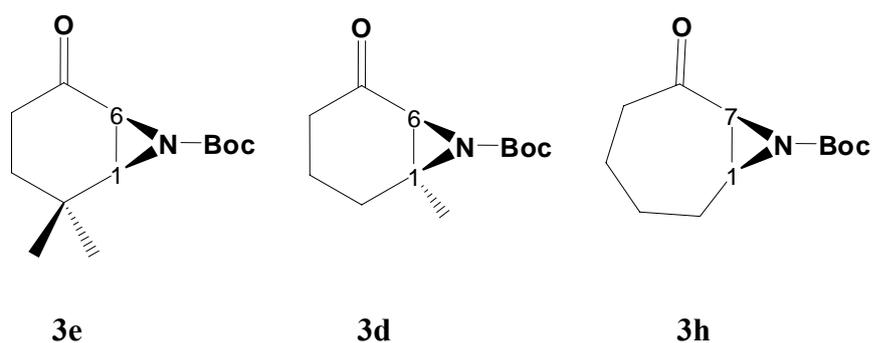
Scheme 1

Fortunately, high resolution NOE-NMR experiments coupled with bi-dimensional spectra, can reliably determine the relative configuration of the stereogenic centres, and can also give precious hints about the molecular conformations populated in solution.

Compounds **3d**, **3e**, **3h** were selected as representative samples in order to determine the relative and absolute configuration.

Compound 3e

Full assignment of the protons signals (and carbons as well) of compound **3e** was preliminary determined by gs-HSQC, gs-HMBC and g-COSY bi-dimensional NMR spectra. The analysis of the proton spectrum (see Supplementary Figure 1) reveals some diagnostic features. The signal of H-1 at 2.67 ppm shows a relatively large coupling constant with H-6 (6.0 Hz), whereas the signal of H-6 at 4.01 ppm exibits an additional small ^4J coupling with one of the two diastereotopic hydrogens H-3^{eq} (1.6 Hz). This coupling constant has a significative value because of a "W" relationship of H-1 and H-3^{eq}.
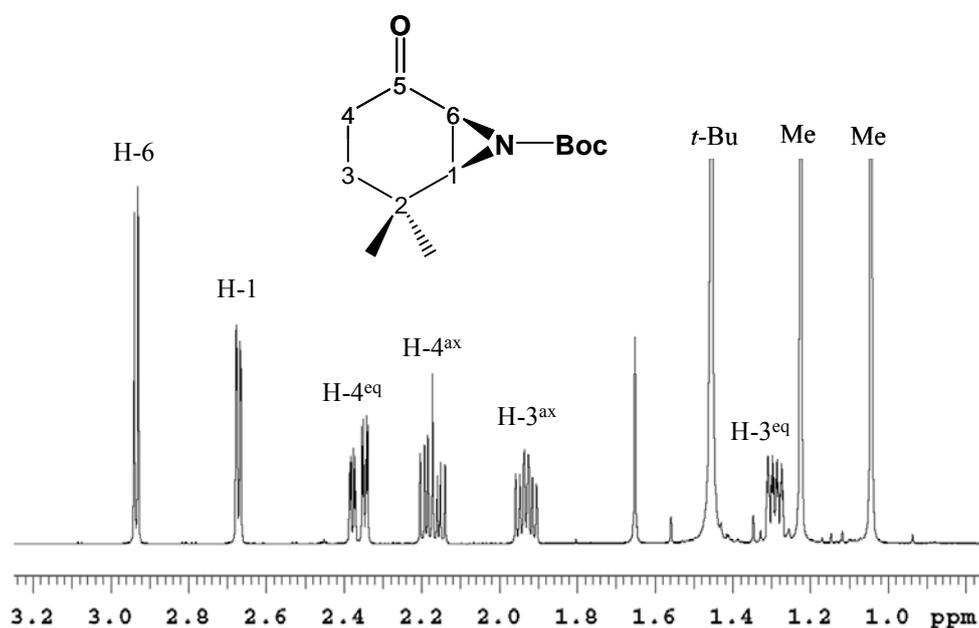
Supplementary Figure 1. ^{1}H NMR spectrum of compound **3e** (600 MHz, CDCl$_3$ solution, +25°C). Proton assignments were deduced by HSQC, HMBC and COSY spectra.

Two of the signals belonging to hydrogens in position 3 (1.94 ppm) and 4 (2.17 ppm) show a large vicinal coupling (12.2 Hz), indicating a trans-diaxial relationship (therefore they are indicated as H-3^{ax} and H-4^{ax}). The two remaining signals at 2.36 ppm and 1.29 ppm correspond to the two hydrogens H-4^{eq} and H-3^{eq} that lie in the equatorial positions.
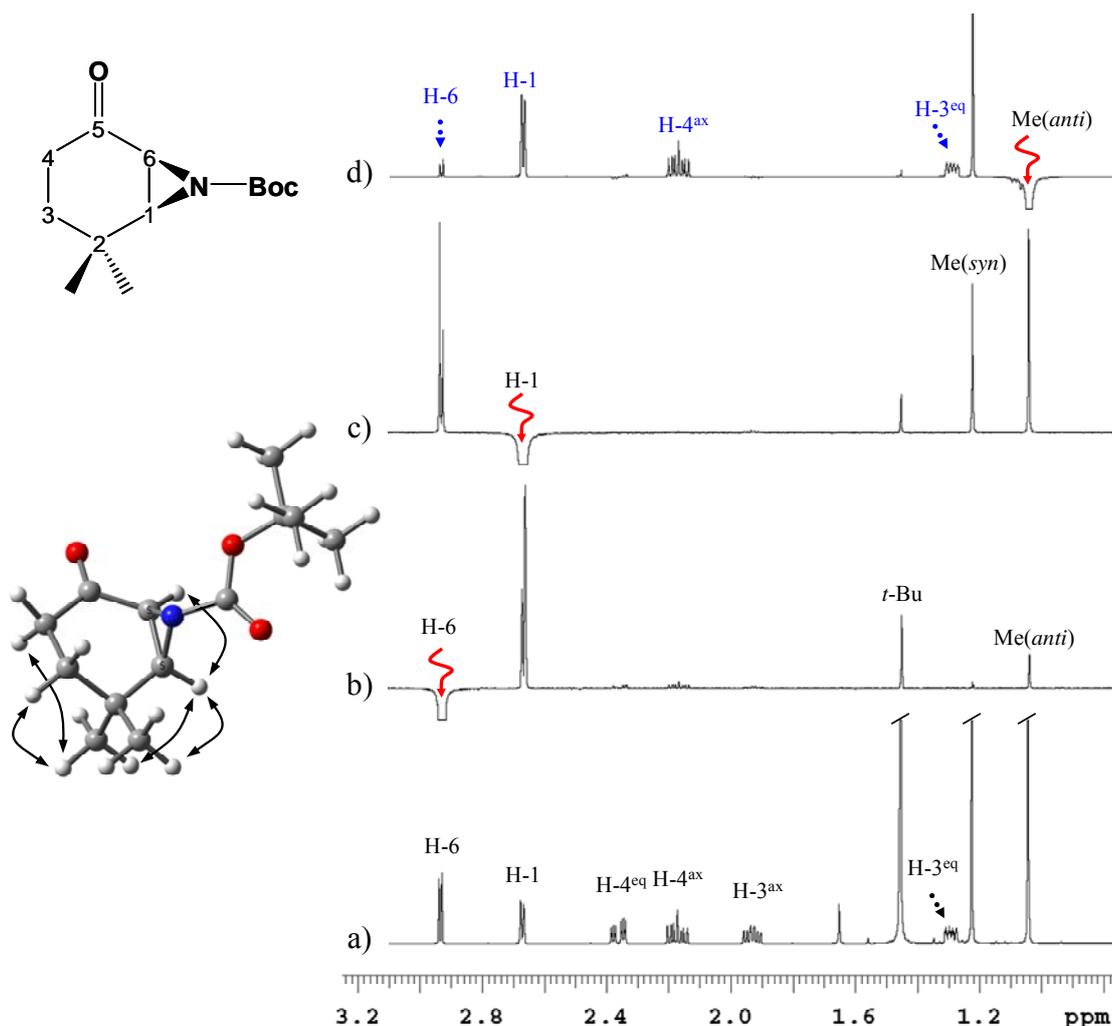
Supplementary Figure 2. DPFGSE-NOE spectra of **3e**. Trace a): control spectrum. Traces b-d: NOE spectra obtained on saturation of H-6, H-1, and the methyl *anti* to the nitrogen atom. Observed NOE are indicated as double arrows in the DFT-optimized structure

In order to determine the relative configuration of carbons C-1 and C-6, NOE spectra were obtained by means of the DPFGSE-NOE sequence[10], and saturating the signals corresponding to the two CH of the aziridine, and to the signal of the two diastereotopic methyls in position 2. Selected traces are shown in Supplementary Figure 2. The most indicative spectrum corresponds to trace c), in which the signal corresponding to H-1 is irradiated. Large NOE effects are visible on H-6 and on the signals of the two diastereotopic methyls in position 2[11]. On saturation of the Methyl signal at 1.04 ppm, large NOEs are observed for the other methyl group, for H-1, for H-4^{ax} and for H-3^{eq}. A small but meaningful enhancement is also observable on H-6. These NOE constraints suggest that the two CHs of the aziridine ring are in a cis relationship (this is also confirmed by the *J*-coupling

[10] (a) Stott, K.; Stonehouse, J.; Keeler, J.; Hwand, T.-L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199. (b) Stott, K.; Keeler, J.; Van, Q. N.; Shaka, A. J. *J. Magn. Resonance* **1997**, *125*, 302. (c) Van, Q. N.; Smith, E. M.; Shaka, A. J. *J. Magn. Resonance* **1999**, *141*, 191. (d) See also: Claridge, T.D.W. *High Resolution NMR Techniques in Organic Chemistry*; Pergamon: Amsterdam, 1999.
[11] this is a NOE enhancement that must be observed, and it serves as a check of the reliability of the experiment.

of 6.0 Hz, that correspond to a dihedral of nearly 0°), and that the Methyl at 1.04 ppm corresponds to the methyl *anti* to the nitrogen atom. In fact, only this methyl group can generate a NOE effect on H-6, being the cis one too far to induce NOE on the same hydrogen (about 4.95 Å in the DFT optimized structure). The enhancements observed on H-4[ax] and H-3[eq] indicate that the methyl *anti* to the nitrogen occupies the axial position of C-2. Consequently, the NOE on H-4[ax] is due to a 1-3 diaxial relationship with the Methyl. This precious information about the conformation of the cyclohexanone ring will help in the following conformational analysis (*vide infra*). Finally, when H-6 is saturated (trace b), the absence of any NOE except for the "control" enhancement on H-1 indicates that H-6 occupies the equatorial position. From the NOE data the relative configuration of the two chiral carbons of **3e** is 1*R**, 6*R**.

Conformational Analysis and Absolute Configuration

In the present case, the absolute configuration determination was carried out by means of TD-DFT method. Since the acting chromophors of the molecule are the two carbonyl groups, a very accurate determination of the conformation of the molecule in solution is crucial for the calculation of the ECD spectrum.

Starting from the relative configuration obtained by NMR analysis, a conformational search has been carried out using Monte Carlo searching together with the MMFF94 molecular mechanics force field (as implemented in Titan 1.0.5). All conformations within a 5 kcal/mol window were then optimized using DFT at the B3LYP/6-31G(d) level[12], and the harmonic vibrational frequencies of each conformation were calculated at the same level to confirm their stability (no imaginary frequencies observed), and to evaluate the free energy of each conformation. After DFT minimization, the MMFF structures clustered into two conformations (**a** and **c**), that are different because of the different shape of the cyclohexanone. In both the optimized structures, the dihedral angle C6-N-C=O is close to -120° (Supplementary Figure 3)

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[12] Gaussian 03, Revision 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.

Supplementary Figure 3: DFT optimized conformations **a** and **c** of compound **3e**, showing the different conformation of carbons 3 and 4 of the cyclohexanone moiety. Conformations **b** and **d** have the Boc group rotated by 180°. BOC hydrogens are omitted for convenience.

It seemed strange to us that conformations with the same dihedral close to 60° (i.e. corresponding to a 180° rotation of the Boc group), were not identified by MM search. Visual inspection of the MM optimized geometries revealed that the Boc group was wrongly calculated to be perpendicular to the aziridine plane, and not nearly coplanar, as in the DFT minimized structures (this is a known problem of the MM force fields that does not account for the partial double bond character of the CO-N bond in amides).

For this reason two more conformations were built starting from the former by 180° rotation of the Boc group around the C6-N-C=O dihedral. When subjected to DFT minimization, two new energy minima were located (**b** and **d**), with energies close to the first two conformations. In summary, four stable conformations enclosed in a 2 kcal/mol range were located by DFT calculation. Comfortably, the lowest energy minimum is fully compatible with the NOE constraints, in particular for the axial position of the methyl *anti* to the nitrogen, and for its position with respect to H4^{ax}. (see Supplementary Figure 3).

Supplementary Table 1: Calculated relative free energies (ΔG) of the conformations of 3e (in kcal/mol, B3LYP/6-31G(d) level). Populations percentages (P) are calculated assuming Boltzmann statistics at T=25°C.

Molecule	Conf.	ΔG	P(%)
	a	0	62
3e	b	0.47	28
	c	1.30	7
	d	1.90	3

To fully confirm the geometry of the cycle, *J*-coupling calculation was carried out by DFT methods at the B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d) level[13]. (Supplementary Table 2). The values calculated for the lowest energy structure are in very good agreement with the experimental ones. This suggests that this conformation of the cycle is the most populated in solution, together with the structure with the Boc rotated by 180° (conformation **b**). Also the calculated free energies of the four conformation agree with this experimentally deduced situation.

Calculation of the Electronic Circular Dichroism spectrum was carried out using the TD-DFT method at the B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d) level, and assuming 1*S*, 6*S* absolute configuration[14]. Rotational strength were calculated in both length and velocity representation. The resulting values are very similar, therefore the errors due to basis set incompleteness are very small.[15] Electronic excitation energies and rotational strengths have been calculated for the four conformation, and the ECD spectra were obtained by applying a 0.4 eV Gaussian shaped line width[16] (Supplementary Figure 4). In order to cover the 170-400 nm range, 30 transition were calculated for each conformation.

Supplementary Table 2: experimental and calculated coupling constant for conformations a and c. Values are expressed in Hz.

Coupled spins	Exp. *J*	Calcd *J*. conf. **a**	Calcd *J*. Conf. **c**
H1-H6	6.0	6.4	6.5
H1-H3^{eq}	1.6	1.6	-0.4
H3^{eq}-H3^{ax}	-13.7	-14.7	-15.0
H3^{eq}-H4^{eq}	2.3	1.5	0.4
H3^{eq}-H4^{ax}	7.2	7.8	4.8
H3^{ax}-H4^{eq}	6.4	6.6	3.6
H3^{ax}-H4^{ax}	12.2	14.3	16.4
H4^{eq}-H4^{ax}	-19.1	-22.7	-14.5

The most important feature of the simulated spectra is the transition centred at about 290 nm, corresponding to the n-π* transition of the carbonyl group of cyclohexanone.

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[13] Calculations were performed taken into account the Fermi contact term, under the keyword "NMR(spinspin,mixed)"

[14] The use of a moderate basis set is dictated by the molecular size, and by the need of limiting the computational time (about 20-24 hours on a 8-core Xeon X7355 server)

[15] Stephens, P.J.; McCann, D.M.; Devlin, F.J., Cheeseman, J.R.; Frisch, M.J. *J.Am.Chem.Soc.* **2004**, *126*, 7514-7521

[16] Gaussview 4.1.2, Semichem Inc., 2006
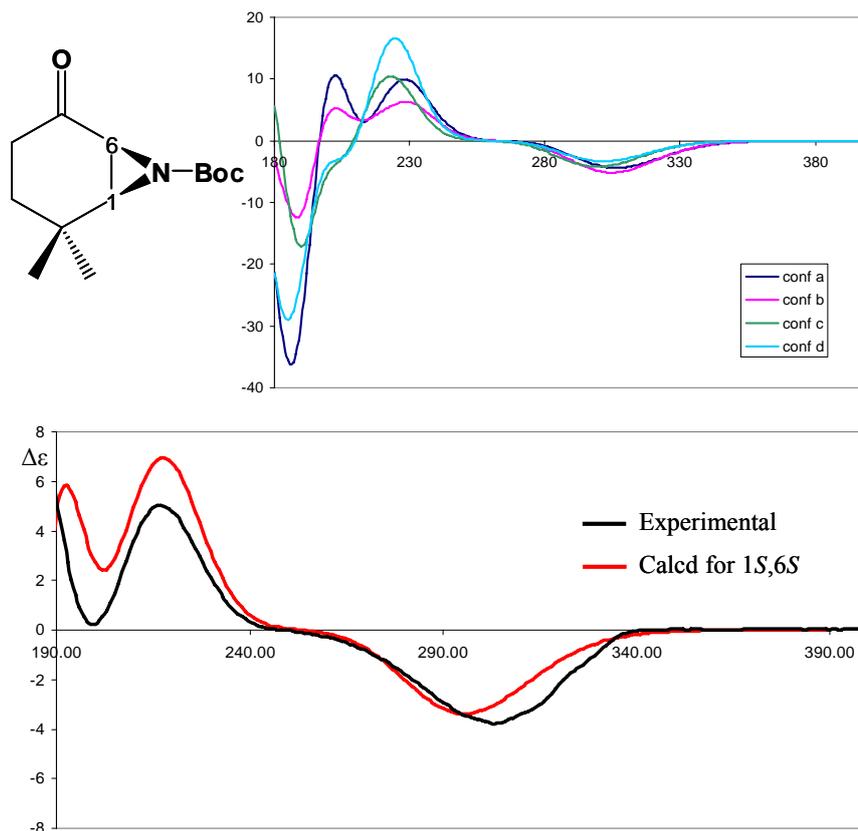
Supplementary Figure 4. Top: calculated ECD spectra for the four conformations of **3e**. Bottom: experimental (black) and calculated ECD spectra (red), weighted on the calculated free energies of the conformations, and blue shifted by 12 nm. Molecular CD ($\Delta\varepsilon$) is expressed in L mol^{-1}cm^{-1}. Solvent was acetonitrile. The vertical scale of the final simulated spectrum was scaled to obtain the best fit with the experimental trace.

This transition is calculated to have negative chirality in all the four conformations, and the trend of the four spectra are quite similar, indicating that the resulting weighted ECD spectrum is weakly influenced by the relative population of the conformations. The final simulated ECD spectra was obtained taking into account the 62:28:7:3 population ratios determined starting from the calculated free energies at the B3LYP/6-31G(d) level, and assuming Boltzmann statistics. Despite the small intensities of the experimental Cotton effects, the simulated spectrum is in very good agreement with the experimental one, and the 1S, 6S configuration can be reliably assigned to compound **3e**.

As suggested by some authors,[2i],[17] the use of more than one chirooptic method is always desirable; in the present compound the calculation of the [α]$_D$ is reasonable reliable, the experimental value being -106°. The calculated value (-61°) is negative and small, as experimentally observed. It has

[17] (a) Polavarapu, P. L. *Chirality*, **2008**, *20*, 664; (b) Stephens, P. J.; Pan, J. J.; Devlin, F. J.; Krohn, K.; Kurtn, T. *J. Org. Chem* **2007**, *72*, 3521.

also to be pointed out that the well known octant rule[18], when applied to the present case, assigned the opposite configuration, probably because of the presence of the second carbonyl group of the Boc moiety.

Compound 3d.

Compound **3d** bears a quaternary carbon in position 1. In order to confirm the reaction path, the absolute configuration has to be checked again. As in the case of **3e**, full assignment of the proton spectrum was obtained by bi-dimensional NMR. The proton spectrum of **3d** is quite complicated because of superimpositions of some hydrogens belonging to C-2 and C-3. Consequently, a full analysis of the coupling constants is not feasible. NOE spectra obtained on saturation of H-6 and Me-2 (See Supplementary Figure 5) confirm that the aziridine ring has again the methyl and the CH *cis* to each other. Saturation of the methyl also shows NOE effects on both the diastereotopic hydrogens of C-3 (assigned by HSQC). The relative configuration is therefore the same for **3e**, i.e. 1*R**, 2*R**

Conformation analysis of **3d** was managed in the same way of **3e**. MM conformational search was preliminary performed, and the minima included in a 5 kcal/mol windows were subsequently minimized by DFT at the B3LYP/6-31G(d) level, that clustered them in two conformation. As in the case of **3e**, the MMFF force field failed to determine the correct geometry of the Boc moiety. For this reason, starting from the two DFT optimized structure, a second pair of conformations was build by 180° rotation of the Boc group, and minimized again. In summary, four conformations were found to exist into a 2 kcal/mol range (**a-d** in Supplementary Table 3).

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[18] See Berova, N; Nakanishi, K.; Woody, R.W. "Circular Dichroism. Principles and Applications ", Wiley-VCH, Chapter 10, page 261
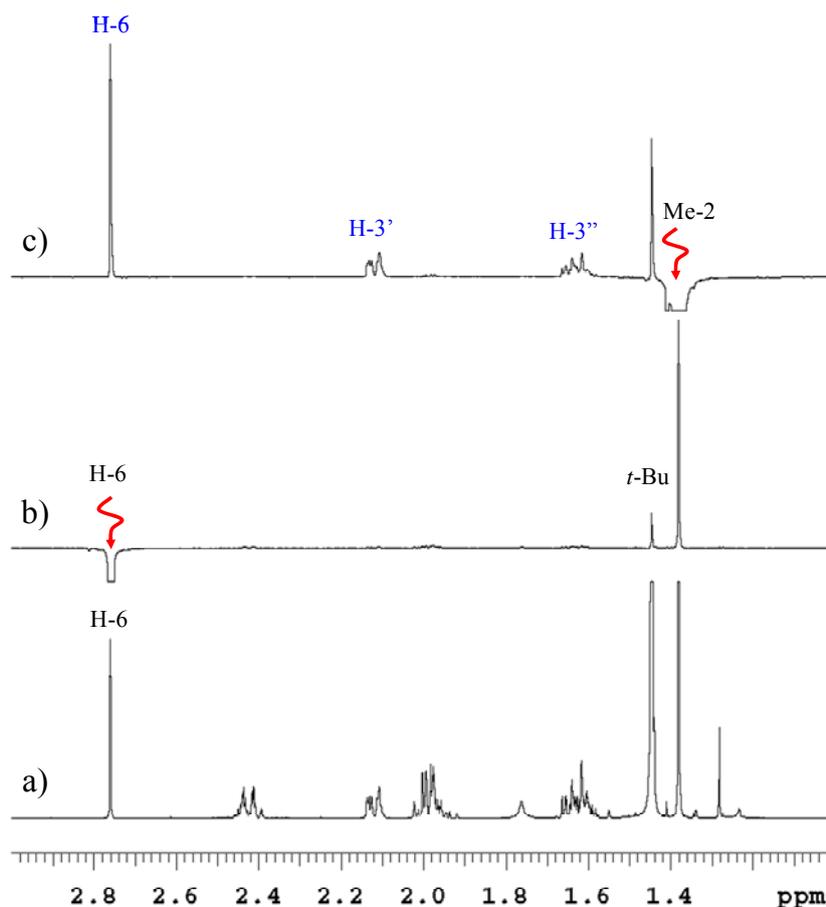
Supplementary Figure 5. DPFGSE-NOE spectra of **3d**. Trace a): control spectrum. Traces b-c: NOE spectra obtained on saturation of H-6 and Me-2.

Supplementary Table 3: Calculated free energies (ΔG) of the conformations of 3d (in kcal/mol, B3LYP/6-31G(d) level). Populations percentages (P) are calculated assuming Boltzmann statistics at T=25°C.

Molecule	Conf.	ΔG	P(%)
	a	0.00	55
3d	**b**	0.28	35
	c	1.36	6
	d	1.48	5

The two pairs of conformations show a different conformation of the cyclohexanone ring (Supplementary Figure 6), and both are compatible with the observed NOEs. Accordingly, in this case the conformational analysis relies only on the computed energies, that showed a good accuracy in the case of **3d**.
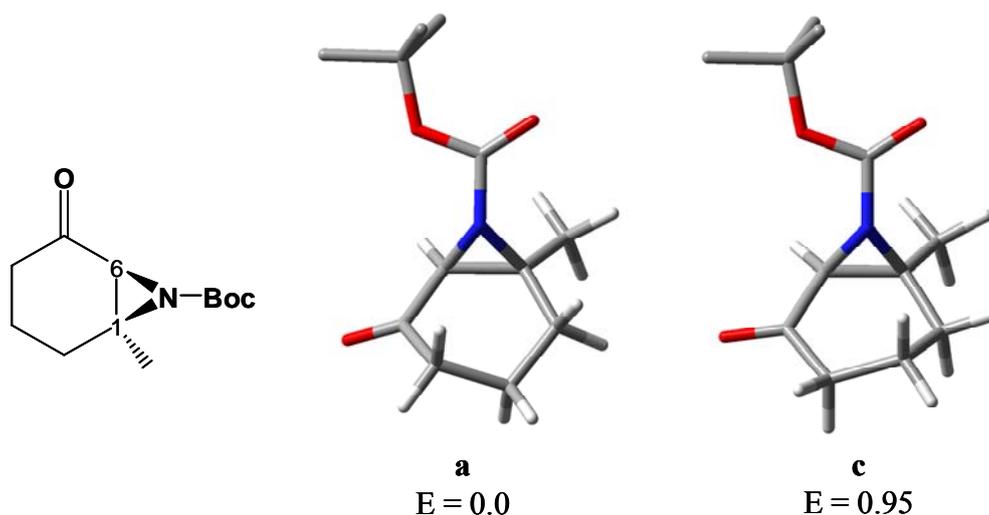
Supplementary Figure 6: DFT optimized conformations **a** and **c** of compound **3d**, showing the different conformation of the cyclohexanone ring. Conformations **b** and **d** have the Boc group rotated by 180°. Boc hydrogens are omitted for convenience.

Calculation of the Electronic Circular Dichroism spectrum was carried out using the TD-DFT method at the B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d) level, and assuming 1*S*, 6*S* absolute configuration[14]. Rotational strength were calculated in both length and velocity representation. The resulting values are very similar, therefore the errors due to basis set incompleteness are very small.[15] Electronic excitation energies and rotational strengths have been calculated for the four conformation, and the ECD spectra were obtained by applying a 0.4 eV Gaussian shaped line width (Supplementary Figure 7). In order to cover the 170-400 nm range, 30 transition were calculated for each conformation. From 400 to 200 nm, the four resulting spectra are quite similar, indicating that the trend of the resulting weighted ECD spectrum will not be largely influenced by the relative population of the conformations. The final simulated ECD spectra was obtained taking into account the 55:35:6:5 population ratios determined by Boltzmann statistics from the calculated free energies at the B3LYP/6-31G(d) level (Supplementary Table 3). To compensate the solvent effect, the simulated trace had to be blue shifted by 10 nm, in order to match the experimental wavelengths. Being the agreement with the experimental spectrum very good, the 1*S*, 6*S* absolute configuration can be assigned to compound **3d**. As in the case of **3e**, the low-energy n-π* transition is negative, indicating that the sign of this transition is not influenced by the substitution of the cycle.
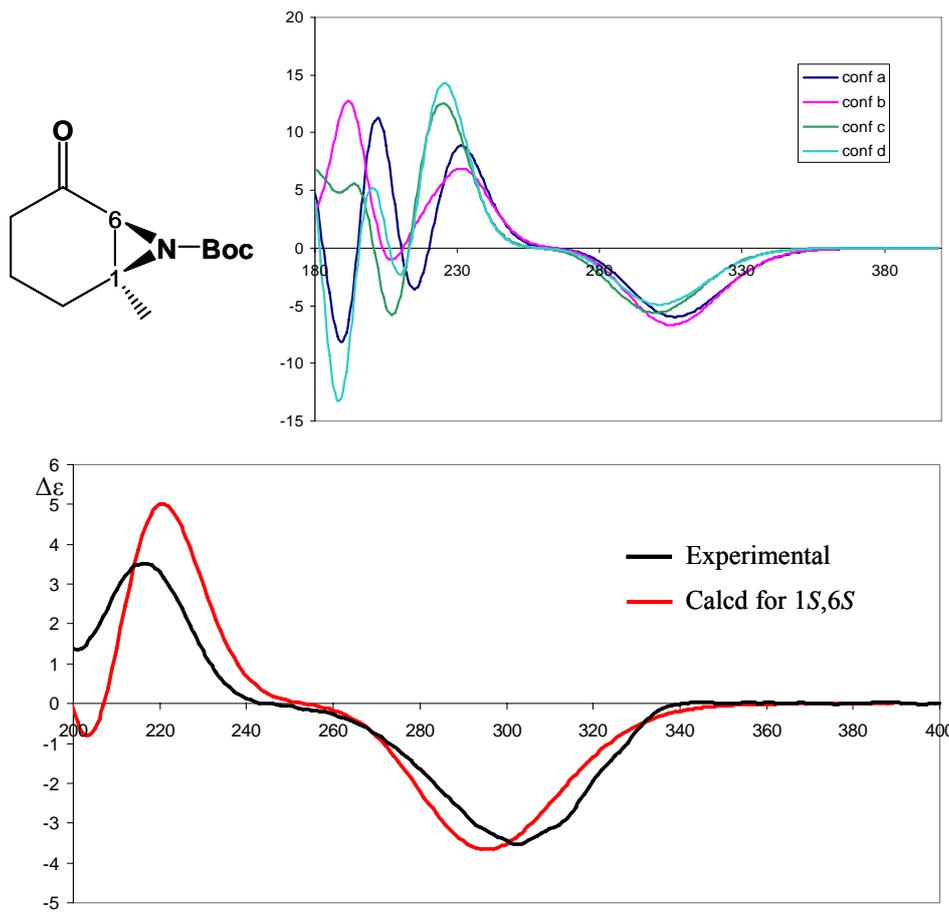
Supplementary Figure 7. Top: calculated ECD spectra for the four conformations of **3d**. Bottom: experimental (black) and calculated ECD spectra (red), weighted on the calculated free energies of the four conformations and blue shifted by 10 nm. Molecular CD ($\Delta\varepsilon$) is expressed in L mol^{-1}cm^{-1}. Solvent was acetonitrile. The vertical scale of the final simulated spectrum was scaled to obtain the best fit with the experimental trace.

Compound 3h.

The cycloheptanone ring contained in compound **3h** has a greater conformational freedom with respect to **3e** and **3d**. For this reason compound **3h** was chosen as model of a more flexible system. NMR spectra show that also in this case the two CH of the aziridine ring are in a cis relationship. MM conformational search was performed also in this case to localize all the energy minima. Quite surprisingly, one structure was found to be much more stable than the others. DFT minimization of the energy minima found by MM in a 5 kcal/mol window confirmed this trend. As in the case of **3e** and **3d**, a second conformation was built by 180° rotation of the Boc group and subsequently optimized. (see Supplementary Figure 8).

a
E = 0.0

b
E = 0.28
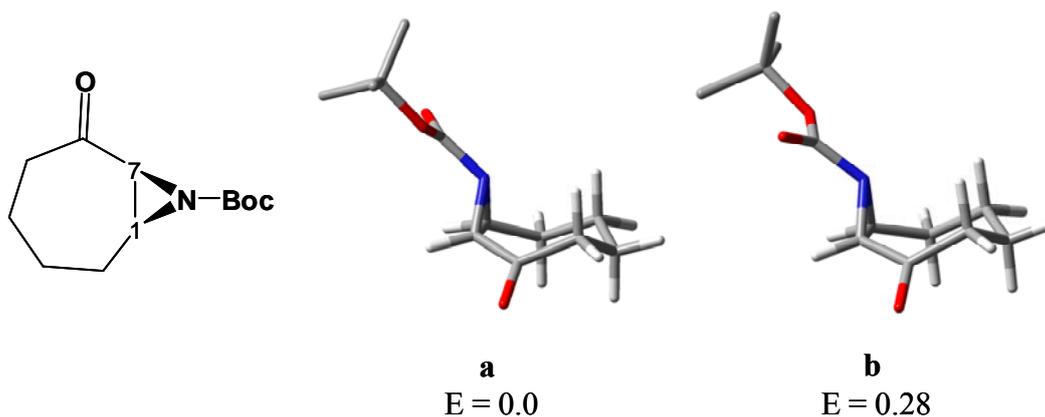
Supplementary Figure 8 DFT optimized conformations compound **3h,** showing the different conformation of the Boc group and the chair-like conformation of the cycloheptanone ring. Boc hydrogens are omitted for convenience.

Supplementary Table 4: Calculated free energies (ΔG) of the conformations of 3h (in kcal/mol, B3LYP/6-31G(d) level). Populations percentages (P) are calculated assuming Boltzmann statistics at T=25°C.

Molecule	Conf.	ΔG	P(%)
3h	**a**	0.00	75
	b	0.65	25

The cycloheptanone ring, due to the geometry requirements imposed by the three-membered ring, exibits a chair-like conformation, in which the carbonyl moiety occupies a pseudo-axial position. The structure in which the carbonyl is pseudo-equatorial is higher in energy by 3.8 kcal/mol, and represents the second conformation in the energy scale.

Calculation of the ECD spectrum was carried out only for the two conformation of Supplementary Figure 8 using the TD-DFT method at the B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d) level. Electronic excitation energies and rotational strengths have been calculated for both conformation, and the ECD spectra were obtained by applying a 0.4 eV Gaussian shaped line width (Supplementary Figure 9). The two simulated spectra have different shapes below 240 nm, and both show negative chirality at the n-π* transition. When weighted by Boltzmann statistics from the calculated free energies at the B3LYP/6-31G(d) level (Supplementary Table 4), the resulting spectrum is in very good agreement with the experimental. To compensate the solvent effect, the simulated trace had to be shifted by 10 nm, in order to match the experimental wavelengths. Being the agreement with the experimental spectrum very good, the 1*S*, 7*S* absolute configuration can be assigned to compound **3h**.
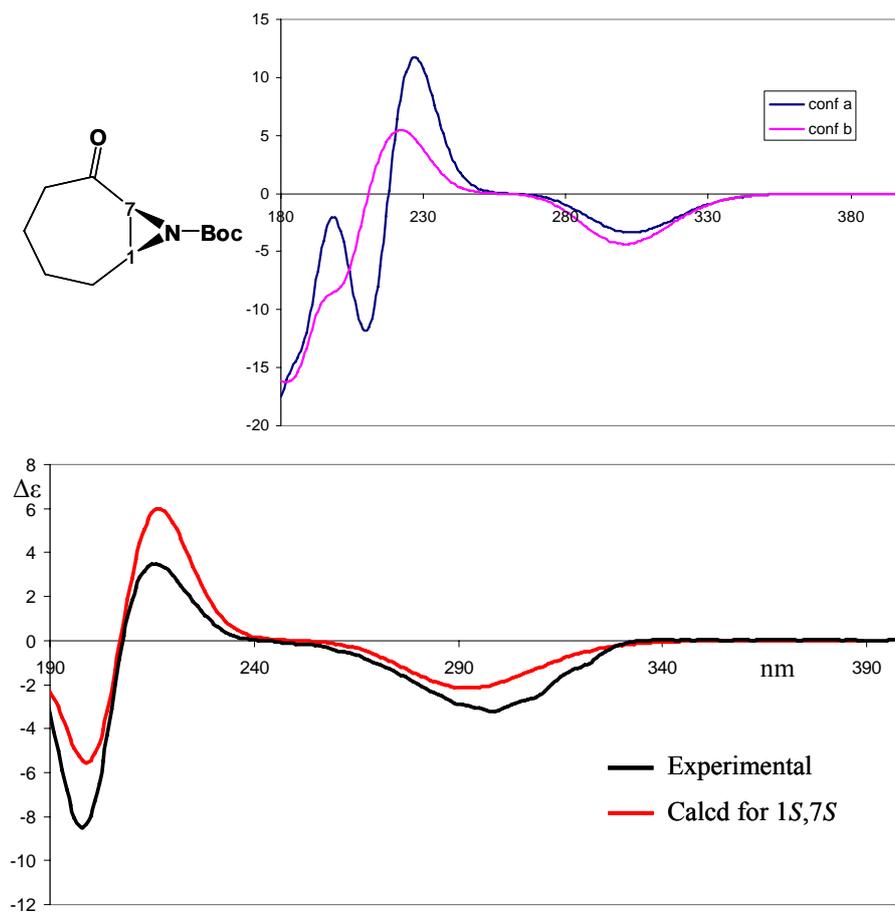
Supplementary Figure 9. Top: calculated ECD spectra for the two conformations of **3h**. Bottom: experimental (black) and calculated ECD spectra (red), weighted on the calculated free energies of the conformations and blue shifted by 10 nm. Molecular CD ($\Delta\varepsilon$) is expressed in L mol^{-1}cm^{-1}. Solvent was acetonitrile. The vertical scale of the final simulated spectrum was scaled to obtain the best fit with the experimental trace.

NMR Details

The spectra were recorded at 600 MHz for ^{1}H and 150.8 MHz for ^{13}C on a Varian Inova spectrometer. The assignments of the ^{1}H and ^{13}C signals were obtained by bi-dimensional experiments (edited-gsHSQC[19] and gsHMBC[20]). The NOE experiments were obtained by means of the DPFGSE-NOE[10] sequence. To selectively irradiate the desired signal, a 50 Hz wide shaped pulse was calculated with a refocusing-SNOB shape[21] and a pulse width of 37 ms. Mixing time was set to 1.5s.

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[20] R. E. Hurd, R.E. John, B.K. *J. Magn. Reson.* **1991**, *91*, 648.

Calculations Details

All calculations were performed using the Gaussian 03 suite of programs were run on servers based on Intel XEON® quad-core processors, The operating system was the Scientific Linux 5.2 X86_64[22]. The standard geometry optimization algorithm included in Gaussian 03 was used.[23] All the calculations employed the B3LYP hybrid HF-DFT functional[24] and the 6-31G(d) basis set. Harmonic vibrational frequencies were calculated for all stationary points. As revealed by the frequency analysis, imaginary frequencies were absent in all ground states. Free energies to be used for the evaluation of the conformers populations were calculated by frequency analysis.

General Procedure for the Organocatalytic Asymmetric Aziridination of Cyclic Enones.
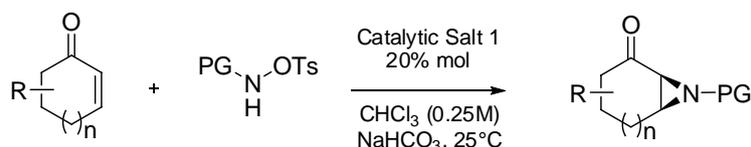
All the reactions were carried out in undistilled chloroform and using the catalytic salt combination **A** or **B** (1.5 equiv of D-*N*-Boc-phenylglycine or L-*N*-Boc-phenylglycine relative to 9-Amino(9-deoxy)*epi*-hydroquinine or 9-Amino(9-deoxy)*epi*-hydroquinidine).

Both of the antipodes of the aziridine products can be accessed simply selecting the appropriate catalyst enantiomer.

In an ordinary vial equipped with a Teflon-coated stir bar, 9-Amino(9-deoxy)*epi*-hydroquinine or 9-Amino(9-deoxy)*epi*-hydroquinidine (0.04 mmol, 13 mg, 20 mol%) was dissolved in 0.8 mL of CHCl$_3$. After addition of D-*N*-Boc-phenylglycine or L-*N*-Boc-phenylglycine (0.06 mmol, 15 mg, 30 mol%), the solution was stirred for 10 minutes at room temperature. After addition of α,β-unsaturated ketones (0.24 mmol, 1.2 equiv), the mixture was stirred at room temperature for 10 minutes. Then nucleophile **2** (0.2 mmol) was added followed, after 5 minutes stirring, by the addition of NaHCO$_3$ (0.4 mmol, 32 mg, 2 equiv) in one portion. Stirring was continued for the indicated time, then the crude reaction mixture was diluted with CH$_2$Cl$_2$ (1 mL) and flushed through

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[24] (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652. (b) Lee, C. ; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785-789. (c) Vosko, S. H.; Wilk, L. ; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200-1211. (d) Stephens, P. J.; Devlin, F. J. ; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623-11627.

a short plug of silica, using dichloromethane/Et$_2$O 1/1 as the eluent. Solvent was removed *in vacuo*, and the residue was purified by flash chromatography (FC) to yield the desired products.
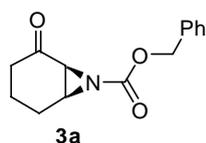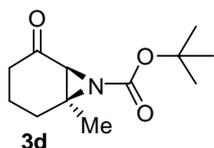
2-Oxo-7-aza-bicyclo[4.1.0]heptane-7-carboxylic acid benzyl ester 3a (Table 1, entry 1) – The reaction was carried out following the general procedure and using catalyst salt A t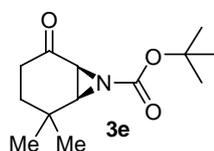o furnish the crude product as a single diastereomer. The title compound was isolated as a colourless oil by column chromatography (Hexane/Ethyl Acetate = 9/1) in 86% yield and 98% ee. HPLC analysis on a Chiralpak AD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (98% ee): τ_{major} = 9.8 min, τ_{minor} = 12.2 min; HRMS: *m/z* calcd for C$_{15}$H$_{17}$NO$_3$: 245.1052; found: 245.1053. $[\alpha]_{rt}^D$ = - 7.3 (c = 0.87, CHCl$_3$, 98% ee). ^{1}H NMR: δ = 1.59-1.70 (m, 1H), 1.73-1.85 (m, 1H), 1.89-2.12 (m, 2H), 2.21-2.31 (m, 1H), 2.45-2.54 (m, 1H), 2.99 (d, *J* = 5.9 Hz, 1H), 3.12-3.17 (m, 1H), 5.14 (s, 2H), 7.30-7.38 (m, 5H). ^{13}C NMR: δ = 17.3 (CH$_2$), 22.8 (CH$_2$), 37.1 (CH$_2$), 40.8 (CH), 43.2 (CH), 68.9 (CH$_2$), 128.6 (CH), 128.8 (CH), 128.9 (CH), 135.5 (C), 161.8(C), 204 (C).
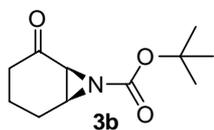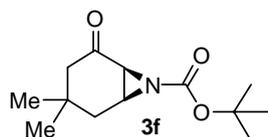
2-Oxo-7-aza-bicyclo[4.1.0]heptane-7-carboxylic acid tert-butyl ester 3b (Table 1, entry 2) – The reaction was carried out following the general procedure using catalyst salt A to furnish the crude product as a single diastereomer. The title compound was isolated as a colourless oil by column chromatography (Hexane/Acetone = 8/2) in 73% yield and 99% ee. The ee was determined by HPLC analysis on a Chiralcel AD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 7.6 min, τ_{minor} = 8.2 min. $[\alpha]_{rt}^D$ = - 95.5 (c = 0.74, CHCl$_3$, 99% ee). ESI: [M+Na]$^+$= 234, [M+1]$^+$= 212. ^{1}H NMR: δ = 1.45 (s, 9H), 1.63-1.68 (m, 1H) 1.74-1.82 (m, 1H), 1.92-1.08 (m, 2H), 2.20-2.27 (m, 1H), 2.47-2.52 (m, 1H), 2.88 (d, *J* = 5.89 Hz, 1H), 3.05-3.09 (m, 1H). ^{13}C NMR: δ = 17.5 (CH$_2$), 22.8 (CH$_2$), 28.0 (CH$_3$), 37.1 (CH$_2$), 40.6 (CH), 43.4 (CH), 82.5 (C), 160.8 (C), 204.5 (C).
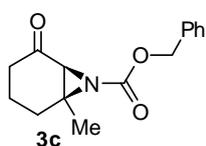
1-Methyl-5-oxo-7-aza-bicyclo[4.1.0]heptane-7-carboxylic acid benzyl ester 3c (Table 1, entry 3) – The reaction was carried out following the general procedure using catalyst salt A to furnish the crude product. The title

compound was isolated as a colourless oil by column chromatography (Hexane/Acetone = 9/1) in 84% yield and 73% ee. HPLC analysis on a Chiralpak AD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (75% ee): τ_{major} = 15.79 min, τ_{minor} = 16.32 min; HRMS: *m/z* calcd for $C_{15}H_{17}NO_3$: 259.1208; found: 259.1208 $[\alpha]_{rt}^D$ = -15.6 (c = 0.797, CHCl₃, 73% ee) ¹H NMR: δ = 1.36 (s, 3H), 1.62-1.72 (m, 2H), 1.90-2.08 (m, 2H), 2.11-2.20 (m, 1H), 2.38-2.50 (m, 1H), 2.86 (s, 1H), 5.12-5.19 (m, 2H), 7.30-7.40 (m, 5H). ¹³C NMR: δ = 17.5 (CH_2) , 20.6 (CH_3), 29.3 (CH_2), 36.3 (CH_2), 48.2 (C), 49.8 (CH), 68.7 (CH_2), 128.7 (2CH), 128.8 (CH), 135.8 (C), 160.2 (C), 205.1 (C).

1-Methyl-5-oxo-7-aza-bicyclo[4.1.0]heptane-7-carboxylic acid tert-butyl ester 3d (Table 1, entry 4) – The reaction was carried out following the general procedure using catalyst salt A to furnish the crude product as a single diastereomer. The title compound was isolated as a white solid by column chromatography (Hexane/Et₂O/CHCl₃ = 50/33/17) in 75% yield and 92% ee. The ee was determined by HPLC analysis on a Chiralcel AD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 8.20 min τ_{major} = 10.38 min. ESI: $[M+Na]^+$= 248, $[M+1]^+$= 226. ¹H NMR: δ = 1.44 (s, 3H), 1.51 (s, 9H), 1.64-1.75 (m, 2H), 2.01-2.10 (m, 2H), 2.14-2.22 (m, 1H), 2.44-2.52 (m, 1H), 2.83 (s, 1H). ¹³C NMR: δ = 17.4 (CH), 20.2 (CH_3), 27.9 (CH_3), 29.1 (CH), 36.0 (CH), 47.4 (C), 49.5 (CH), 81.9 (C), 158.9 (C), 205.4 (C).

2,2-Dimethyl-5-oxo-7-aza-bicyclo[4.1.0]heptane-7-carboxylic acid tert-butyl ester 3e (Table 2, entry 2) – The reaction was carried out following the general procedure using catalyst salt A to furnish the crude product as a single diastereomer. The title compound was isolated as a white solid by column chromatography (Hexane/Acetone = 8/2) in 84% yield and 98% ee. HPLC analysis on a Chiralcel AD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 5.98 min, τ_{major} = 6.86 min. $[\alpha]_{rt}^D$ = -106.7 (c = 0.98, CHCl₃, 98% ee. ESI: $[M+Na]^+$= 262, $[M+1]^+$= 240. ¹H NMR: δ = 1.03 (s, 3H), 1.21 (s, 3H), 1.26-1.38 (m, 1H), 1.44 (s, 9H), 1.88-1.95 (m, 1H), 2.12-2.20 (m, 1H), 2.35 (ddd, *J* = 19.23 Hz, *J* = 8.93 Hz, *J* = 19.11 Hz, 1H), 2.64-2.67 (dd, *J* = 5.89 Hz, *J* = 1.47 Hz, 1H), 2.92 (d, *J* = 5.91 Hz, 1H). ¹³C

NMR: δ = 23.4 (CH$_3$), 27.8 (CH$_3$), 28.0 (CH$_3$), 30.42 (CH$_2$), 33.82 (CH$_2$), 44.25 (CH), 50.2 (CH), 82.3 (C), 160.5 (C), 204.8 (C).

4,4-Dimethyl-2-oxo-7-aza-bicyclo[4.1.0]heptane-7-carboxylic acid tert-butyl ester 3f (Table 2, entry 3) – The reaction was carried out following the general procedure using catalyst salt A to furnish the crude product as a single diastere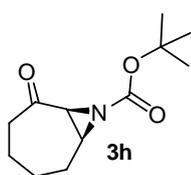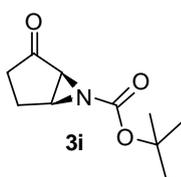omer. The title compound was isolated as a colourless oil by column chromatography (Hexane/Etyl Acetate = 8/2) in 33% yield and 98% ee. The ee was determined by HPLC analysis on a Chiralcel AD-H column: 99/1 hexane/i-PrOH, flow rate 0.650 mL/min, λ = 214, 254 nm: τ_{minor} = 18.44 min, τ_{major}= 20.47 min. $[\alpha]_{rt}^D$ = +43.4 (c=0.65, CHCl$_3$, 98% ee). ESI: [M+Na]$^+$= 262, [M+1]$^+$= 240. ^{1}H NMR: δ = 0.88 (s, 3H), 1.00 (s, 3H), 1.44 (s, 9H), 1.78-1.83 (m, 2H), 1.94 (d, J = 14.60 Hz, 1H), 2.58 (d, J = 14.00 Hz, 1H), 2.87 (d, J = 6.46 Hz, 1H), 2.97 (t, J = 6.18 Hz, 1H). ^{13}C NMR: δ = 27.4 (CH$_3$), 27.8 (CH$_3$), 30.8 (CH$_3$), 36.8 (CH$_2$), 37.7 (C), 41.0 (CH), 42.8 (CH), 48.8 (CH$_2$), 82.3 (C), 160.3 (C), 206.0 (C).
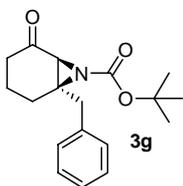
1-Benzyl-5-oxo-7-aza-bicyclo[4.1.0]heptane-7-carboxylic acid tert-butyl ester 3g (Table 2, entry 5) – The reaction was carried out following the general procedure using catalyst salt A to furnish the crude product as a single diastereomer. The title compound was isolated as a colourless oil by column chroma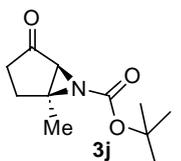tography (Hexane/Et$_2$O = 7/3) in 93% yield and 95% ee. The ee was determined by HPLC analysis on a Chiralcel AD-H column: 95/5 hexane/i-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{minor} = 12.52 min, τ_{major} = 15.15 min. $[\alpha]_{rt}^D$ = -59.7 (c = 0.73, CHCl$_3$, 95% ee). ESI: [M+Na]$^+$= 324. ^{1}H NMR: δ = 1.48 (s, 9H), 1.51-1.59 (m, 2H), 1.86-1.98 (m, 2H), 2.01-2.07 (m, 1H), 2.35-2.41 (m, 1H), 2.46 (d, J = 14.45 Hz, 1H), 3.05 (s, 1H), 3.23 (d, J = 14.53 Hz, 1H), 7.20 (d, J = 7.79 Hz, 2H), 7.23-7.27 (m, 1H), 7.28-7.32 (m, 2H). ^{13}C NMR: δ = 1.2 (CH$_3$), 17.6 (CH$_2$), 26.3 (CH$_2$), 28.2 (CH), 36.3 (CH$_2$), 41.5 (CH$_2$), 48.9 (CH), 51.3 (C), 82.4 (C), 127.4 (CH), 128.9 (CH), 129.6 (CH), 136.5 (C), 205.2 (C).

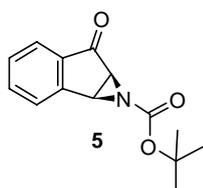**2-Oxo-8-aza-bicyclo[5.1.0]octane-8-carboxylic acid tert-butyl ester 3h (Table 2, entry 6) –** The reaction was carried out following the general procedure using catalyst salt A to furnish the crude product as a single diastereomer. The title compound was isolated as a colourless oil by column chromatography (Hexane/Et$_2$O = 7/3) in 90%

yield and 98% ee. The ee was determined by HPLC analysis on a Chiralcel AD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 8.07 min, τ_{minor} = 8.88 min. $[\alpha]_{rt}^D$ = -103.2 (c = 0.8, CHCl$_3$, 98% ee). ESI: $[M+Na]^+$ = 248, $[M+1]^+$ = 226. ^{1}H NMR: δ = 0.92-1.01 (m, 1H), 1.44 (s, 9H), 1.60-1.67 (m, 1H), 1.67-1.68 (m, 2H), 1.79-1.85 (m, 1H), 2.23-2.30 (m, 1H), 2.39-2.46 (m, 1H), 2.72-2.78 (m, 1H), 2.84-2.88 (m, 1H), 3.00-3.02 (dd, J = 1.61 Hz, J = 7.22 Hz, 1H).^{13}C NMR: δ = 23.67 (CH$_2$), 23.85 (CH$_2$), 28 (CH$_2$), 28.08 (CH$_3$), 40.57 (CH$_2$), 40.99 (CH), 47.57 (CH), 82.20 (C), 161.11 (C), 209.50 (C).

2-Oxo-6-aza-bicyclo[3.1.0]hexane-6-carboxylic acid tert-butyl ester 3i (Table 2, entry 7) – The reaction was carried out following the general procedure using catalyst salt A to furnish the crude product as a single diastereomer. The title compound was isolated as a pale yellow oil by column chromatography (Hexane/Etyl Acetate = 8/2) in 39% yield and 93% ee. The ee was determined by HPLC analysis on a Chiralcel AD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.750 mL/min, λ = 214, 254 nm: τ_{minor} = 10.66 min, τ_{major}= 11.42 min. $[\alpha]_{rt}^D$ = +43.4 (c = 0.72, CHCl$_3$, 93% ee). ESI: $[M+Na]^+$= 220, $[M+1]^+$= 198. ^{1}H NMR: δ = 1.46 (s, 9H), 1.93-2.03 (m, 1H), 2.07-2.22 (m, 2H), 2.47-2.51 (m, 1H), 3.01 (d, J= 3.09 Hz, 1H), 3.38 (t, J= 3.11 Hz, 1H). ^{13}C NMR: δ = 21.5 (CH$_2$), 28.1 (CH$_3$), 31.7 (CH2), 44.1 (CH), 44.3 (CH), 129.9 (C).

1-Methyl-4-oxo-6-aza-bicyclo[3.1.0]hexane-6-carboxylic acid tert-butyl ester 3j (Table 2, entry 8) – The reaction was carried out following the general procedure to furnish the crude product as a single diastereomer. The title compound was isolated as a colourless oil by column chromatography (Hexane/Acetone = 8/2) in 52% yield and 85% ee. The ee was determined by HPLC analysis on a Chiralcel AD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.750 mL/min, λ = 214, 254 nm: τ_{minor} = 6.83 min, τ_{major}= 12.54 min. $[\alpha]_{rt}^D$ = +39.9 (c = 0.90, CHCl$_3$, 85% ee). ESI: $[M+Na]^+$= 234, $[M+1]^+$= 212. ^{1}H NMR: δ = 1.45 (s, 9H), 1.51 (s, 3H), 1.94-2.04 (m, 2H), 2.19-2.28 (m, 1H), 2.46-2.54 (m, 1H), 2.83 (s, 1H). ^{13}C NMR: δ = 19.5 (CH$_3$), 26.3 (CH$_2$), 28.1 (CH$_3$), 33.6 (CH$_2$), 50.3 (CH), 52.6 (C), 82.4 (C), 158.1 (C), 207.9 (C).

6-Oxo-6,6a-dihydro-1aH-1-aza-cyclopropa[a]indene-1-carboxylic acid tert-butyl ester 5 (Scheme 1) – The reaction was carried out following the general procedure using catalyst salt A to furnish the crude product as a single diastereomer. The title compound was isolated as a red solid by column chromatography (Hexane/Acetone = 85/15) in 67% yield and 98% ee. The ee was determined by HPLC analysis on a Chiralcel AD-H column: 95/50 hexane/i-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 15.71 min, τ_{minor} = 16.39 min. $[\alpha]_{rt}^{D}$ = +24.5 (c = 0.86, CHCl$_3$, 98% ee). ESI: $[M+Na]^{+}$= 268. ^{1}H NMR: δ = 1.12 (s, 9H), 3.53 (d, J = 2.87 Hz, 1H), 4.09 (d, J = 2.77 Hz, 1H), 7.41 (td, J = 1.16 Hz, J = 7.46 Hz, 1H), 7.58 (dt, J = 1.26 Hz, J = 7.40 Hz, 1H), 7.62 (dt, J = 1.09 Hz, J = 7.60 Hz, 1H), 7.70 (dt, J = 0.59 Hz, J = 7.59 Hz, 1H). ^{13}C NMR: δ = 27.6 (CH$_3$), 42.4 (CH), 43.1 (CH), 82.6 (C), 125.4 (CH), 127.1 (CH), 129.6 (CH), 133.1 (C), 134.5 (CH), 146.6 (C), 157.8 (C), 195.3 (C).

5.4 Asymmetric Organocatalytic Cascade Reactions with α-Substituted α,β-Unsaturated Aldehydes
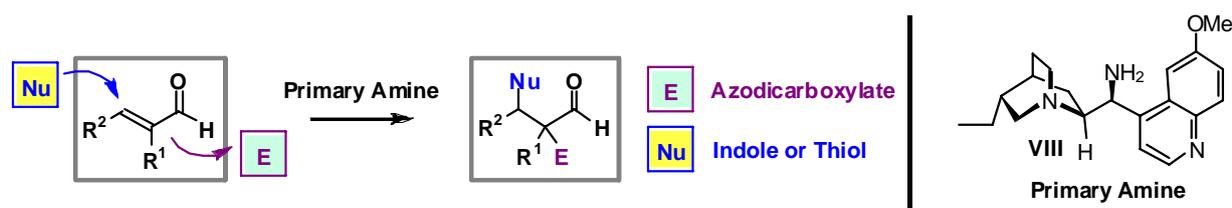
Time to α-branch out! The first highly enantioselective aminocatalytic activation of α-substituted α,β-unsaturated aldehydes is presented. The chiral primary amine **VIII** selectively activates α–branched enals toward a well-defined iminium ion/enamine reaction sequence for both Friedel-Crafts/amination and Sulfa-Michael/amination cascades. The valuable multifunctional compounds, having two contiguous sterocenters, are isolated in high enantiomeric purity.

In the previous chapters, we described the extraordinary rapidity of development and affirmation of organocatalysis as reliable toolbox for the creation of variegated matrix of chemical structures. From a small collection of exotic and underdeveloped transformations not completely mechanistically understood, the field became one of the three main areas of asymmetric catalysis, delivering unique, orthogonal or complementary delectivity compared to bio- and metal-catalysis approaches. In particular our attention focused on asymmetric aminocatalysis that, indeed, in few years has achieved amazing progresses.[1] Commonly, the naissance of aminocatalysis is located in 2000, being correlated to the first reports on two main activation modes: *enamine* and *iminium ion* pathways.[2] In agreement with this opinion, we can assert that although it is a young discipline, (being only 'tenth years old'!),[3] asymmetric aminocatalysis boasts of features - like reliability, generality, reproducibility and efficiency- that make it a powerful platform from which new synthetic strategies can get off the ground. We have already shown the prominent role that chiral secondary amines had in the highly efficient functionalyzation of aldehydes and the recently affirmation of primary amines in the activation of the sterically encumbered ketones. In addition, chiral primary amine-based catalysts have been also successfully employed for the enamine activation of other challenging substrates, like α,α-disubstituted aldehydes.[4] In 2005, Ishihara and Nakano further extended the potential of these catalysts to the iminium ion activation of α-acyloxy-acroleins toward a stereoselective Diels-Alder process.[5,6] Along these lines, since the use of the even more challenging α,β-disubstituted unsaturated aldehydes is still elusive for asymmetric aminocatalysis and an alternative asymmetric metal-catalyzed strategy for their functionalization is also lacking,[7] we sought to provide an efficient solution to this longstanding issue. Our idea was triggered by the

demonstrated ability of catalyst **VIII** to promote the intramolecular tandem reaction with α,β-unsaturated ketones[8] reported in the previous chapter. On these grounds, we hypothesized whether the unique ability of catalyst **VIII** to engage in iminium ion formation with encumbered enones while enforcing high geometry control and face discrimination, might be translated to the α-substituted α,β–unsaturated aldehydes.

For our preliminary investigations we tested the Friedel-Crafts alkylation of 2-methyl-1H-indole with (*E*)-2-methylpent-2-enal in presence of the TFA salt of **VIII**. Satisfactory, the reaction proceeded, leading to the desired product in high enantioselectivity, indicating that a selective π-facial shielding of the iminium intermediate is effective (Eq 1). The poor diastereocontrol, however, clearly demonstrates that the following enamine-based protonation step escapes catalyst control.

$$\text{(1)}$$
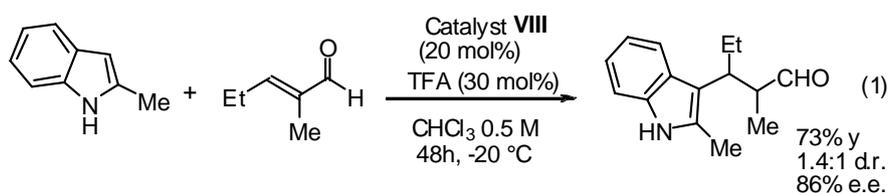
Nevertheless, the ability of **VIII** to impart high stereocontrol in the iminium activation of α-branched enals prompted us toward a more intriguing target: to activate α,β-disubstituted enals toward a well defined *iminium-enamine tandem sequence* in order to create multifunctional compounds with two contiguous stereocenters in a one-step process. Besides the benefit to generate complex scaffolds in a rapid and atom-economical way, the combination of multiple asymmetric transformations in a cascade sequence[9]

also imparts increased enantiomeric excess to the final product when compared to the corresponding discrete transformations.[10] Specifically, our plan was that of developing an organocascade reactions that combine two intermolecular and stereoselective steps, following a Michael addition-amination pathway. If this strategy would be successfully we could afford a straightforward access to valuable precursors of α–amino acids having two adjacent stereogenic centers -one of which quaternary- through an olefin aryl-amination and a thio-amination processes (Figure 1).
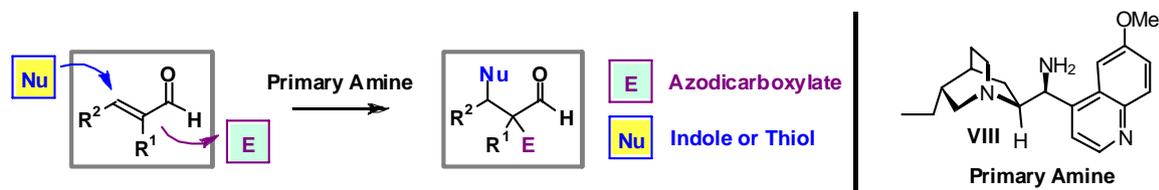
Figure 1. *Designed Organocascade Plan*

Our organocascade strategy was first examined mixing three commercially available reagents, (*E*)-2-methylpent-2-enal, 2-methyl-1H-indole and diethyl azodicarboxylate (Table 1, entry 1). Such a reagents combination is rather challenging, due to the competitive coupling between the π-rich nucleophile and the electrophilic component.[11] A survey of the reaction conditions revealed that using a 1:1.2:1.5 ratio of enal **2**, nucleophile **3** and electrophile **4**, respectively, in the presence of the catalytic salt - made by combining **VIII** (20 mol%) and TFA (30 mol%) in CHCl$_3$ (0.5M) as solvent - provides product **5a** with excellent levels of stereoinduction and in good yield, thus minimizing deleterious side reactions. The scope of the reaction is examined in Table 1.

Different azodicarboxylates having orthogonal protecting groups are suitable as electrophilic component for the process (Entries 1-3). On basis of the superior diastereomeric ratio and isolated yield, tert-butyl azodicarboxylate was selected for further explorations. A wide scope of the different substituents

on the indole core can be achieved, since electronic modification of the aromatic ring can be accomplished without affecting the efficiency of the system, leading to valuable tryptophane derivatives **5** in good yields and very high diastereo- and enantio-selectivity (entries 3-7). As expected, a more encumbered ethyl group (R^1) at the α-position of aldehyde, decreases the overall reaction rates (entry 8) while the necessity to perform the reaction at room temperature leads to a slightly lower level of stereocontrol in the formation of **5h** (83% ee).

Table 1. Organocascade catalysis with α,β-disubstituted enals: indoles and azodicarboxylates combination
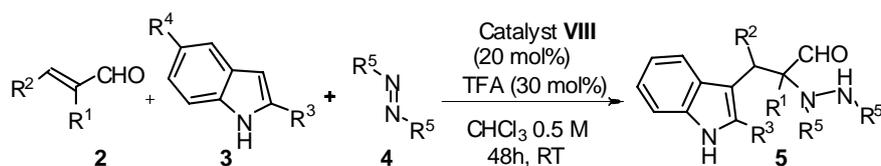
Entry	R^1	R^2	R^3	R^4	R^5	Yield [%][a]	d.r.[b]	ee[%][c]
1	Me	Et	Me	H	CO_2Et	57 (**5a**)	8:1	99
2	Me	Et	Me	H	CO_2Bn	49 (**5b**)	6:1	99
3	Me	Et	Me	H	CO_2t-Bu	80 (**5c**)	11:1	98
4[d]	Me	Et	H	H	CO_2t-Bu	51 (**5d**)	3:1	94
5[e]	Me	Et	H	Cl	CO_2t-Bu	43 (**5e**)	4:1	91
6[d]	Me	Et	H	OMe	CO_2t-Bu	54 (**5f**)	3:1	96
7[d]	Me	Et	H	H	CO_2t-Bu	47 (**5g**)	3:1	91
8	Et	$CH_3(CH_2)_2$	H	H	CO_2t-Bu	31 (**5h**)	3:1	83

[a]Yield of isolated **5** [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Determined by HPLC analysis using chiral stationary phases. [d] Reaction conducted at - 10°C over 96 h. [e] Reaction conducted at 0°C over 65 h.

To probe the scope of the nucleophilic component and further expand the synthetic utility of this organocascade methodology, by forging a quaternary stereocenter contiguous to a C-S tertiary one with the tandem sequence,[12] we focused on a sulfa-Michael/amination sequence, using mercaptanes having easily removable and orthogonal sulphur protecting groups (Table 2).[13]

**Table 2.** Organocascade catalysis with α-branched α,β-unsaturated aldehydes: sulfa-Michael/amination strategy[a]

6a: R^3 = ^{t}Bu
6b: R^3 = Bn
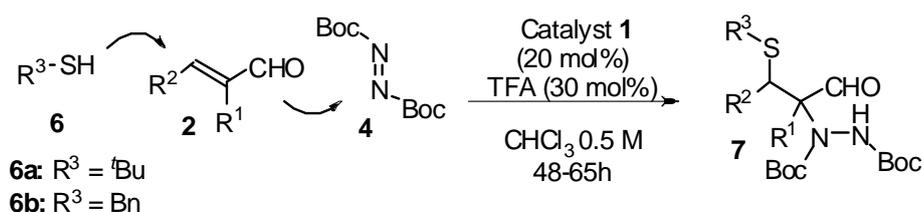
Entry	R^1	R^2	Thiol	t [°C]	Yield [%][b]	d.r.[c]	ee[%][d]
1	Me	Et	**6a**	0	54 (**7a**)	6.5:1	> 99
2[e]	Me	Et	**6b**	0	**57 (7b)**	5:1	72
3[e]	Me	Et	**6b**	-20	27 (**7b**)	6:1	89
4[f]	Et	CH$_3$(CH$_2$)$_2$	**6b**	40	45 (**7c**)[g]	4:1	92
5[h]	Ph	Et	**6b**	40	47 (**7d**)	4:1	92
6	Me	Ph	**6a**	40	40 (**7e**)	20:1	99

[a] Reactions conditions: **2** (1 equiv), **6** (1.2 equiv), and **4** (1.5 equiv). [b] Yield of the isolated, single, major diastereoisomer. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis using chiral stationary phases. [e] Reaction carried out in toluene. [f] The *ee* value was dermined after reduction and cyclization to form oxazolidinone. [g] Sum of diastereoisomers (4.5:1 ratio). [h] Yield and *ee* value were determined after in situ reduction and cyclization.

As summarized in Table 2, the reaction shows a good substrate generality: both *tert*-butyl and benzyl mercaptane are suitable nucleophiles, albeit the

latter induces a less selective organocascade path (entries 1-3). There appears to be a remarkable latitude in the electronic and steric demands of the aldehydic component. Different aliphatic substituents and even a phenyl group in both the α- and β- position of the enals are well tolerated (entries 4-6), enabling access to a broad variety of multifunctional complex molecules having adjacent stereocenters with high stereoselectivity. For example, when α-substituted cinnamic aldehyde is involved in the organocascade, the corresponding product **7e** is obtained almost as a single stereoisomer (entry 6, >20:1 dr, 99% ee). Notably, in most of the cases, compounds **7** are isolated as single diastereoisomer by standard chromatography.

To further increase the complexity of our organo-cascade generated products, we finally explored the possibility to extend the organocascade to 1-cycloalkene-1-carboxaldehyde, to access complex products having a quaternary stereogenic center embedded in a cycle. Satisfying, catalyst **VIII** proved efficient with this substrate class, leading to compound 8 with complete enantiocontrol (Eq. 2).
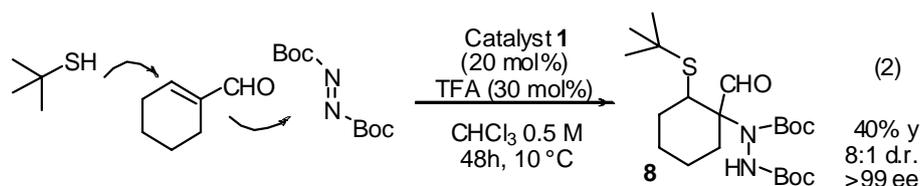
The configuration of a derivative of compound **7** was unambiguously determined by anomalous dispersion X-ray crystallography,[14] whereas the relative and absolute configurations of a derivative of compound **8** were assigned by NMR NOE analyses and by means of TD-DFT calculations of the electronic circular dichroism (ECD) spectra, as described in the Supplementary Information.

In summary, reporting two organocascade reactions as the olefin aryl-amination and thio-amination processes, we introduced α,β-disubstituted enals to the asymmetric amino-catalytic panorama, providing an efficient solution to their highly challenging activation. Specifically, our described strategy affords a straightforward access to valuable precursors of α-amino acids having two adjacent stereogenic centers, one of which quaternary, with very high optical purity. Importantly, we confirmed the applicability of primary amine *Chincona* alkaloids-derivatives as general catalysts for highly encumbered substrates, giving our contribution to an envisaged affirmation of them as '*privileged*' catalysts for the activation of sterically demanding partners.

5.4 R References

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[5]   (a) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504. For a more recent example, see: (b) Kano, T.; Tanaka, Y.; Osawa, K.; Yurino, T.; Maruoka, K. *Chem. Commun.* **2009**, 1956. In this report, a single, low enantioselective example of Diels-Alder reaction using 2-methyl but-2-enal has been described.

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[7]   Chiral Lewis acid-mediated activation of α-branched unsaturated compounds is generally founded upon the use of bidentate chelating carbonyls. See for example: (a) Sibi, M. P.; Coulomb, J.; Stanley, L. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 9913, and references therein. For a metal-catalyzed activation of α-substituted enones, see: (b) Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. *Angew. Chem., Int. Ed.* **2008**, *47*, 10133.

[8]   (a) Pesciaioli, F.; De Vincentiis, F.; Galzerano, P.; Bencivenni, G.; Bartoli, G.; Mazzanti, A.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8703. See also: (b) Wang, X.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6070.

[9]   (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.

[10] Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055. For example, if two catalytic cycles, each 86% ee selective, were combined, the resulting cascade would furnish a 7:1 mixture of diastereomers, with the major diastereoisomer being formed in 99% ee.

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5.4 Supplementary Information

Contents

General Methods

Materials

Determination of Diastereomeric Ratios

Determination of Enantiomeric Purity

Determination of the Relative and Absolute Configurations.

Experimental Procedures

General methods.

The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, or at 600 MHz for ^{1}H and 150 MHz for ^{13}C. NOE spectra were recorded using the DPFGSE-NOE sequence,[i] 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$_3$CN). 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.[ii] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. High 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.

Materials. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[iii] Chiral primary amine catalysts, 9-Amino(9-deoxy)epi-hydroquinine **VIII** and the pseudo-enantiomer 9-Amino(9-deoxy)epi-hydroquinidine **IX**, were prepared from commercially available hydroquinine and hydroquinidine, respectively, following the literature procedure.[iv] 2-Ethyl-Hex-2-enal (Table 1, entry 8 and Table 2, entry 4) was prepared through a self-condensation reaction treating butyraldehyde with 1M solution of NaOH at RT overnight. All other aldehydes employed are commercially available. Indole derivatives **3**, azodicarboxylates **4**, and thiols **6a** and **6b** were purchased from Aldrich or Lancaster and used as received.

Determination of Diastereomeric Ratios. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture, and confirmed by HPLC analysis on chiral stationary phases columns.

Determination of Enantiomeric Purity. HPLC analysis of the optical purity of the compounds 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 with racemic samples obtained by mixing the products from individual reactions with 9-Amino(9-deoxy)epi-hydroquinine **VIII** and its pseudoenantiomer 9-Amino(9-deoxy)epi-hydroquinidine **IX**.

Calculations. MM conformational searches were performed using the MonteCarlo method implemented in Titan 1.0.5.[v] Geometry optimization were carried out at the B3LYP/6-31G(d) level by means of the Gaussian 03 series of programs.[vi] The standard Berny algorithm in redundant internal coordinates and default criteria of convergence were employed. Harmonic vibrational frequencies were calculated for all the stationary points. For each optimized ground state the frequency analysis showed the absence of imaginary frequencies. Standard thermochemistry analysis was used to calculate the free energies. TD-DFT calculations were obtained at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) level. In order to cover the whole 180-400 nm range, 60 to 75 transition were calculated. The CD spectra was then obtained applying a 0.25 eV Gaussian bandshape.

Experimental procedures

General procedure for the asymmetric organocatalytic Friedel-Crafts/amination tandem sequence of α-substituted α,β−unsaturated aldehydes.
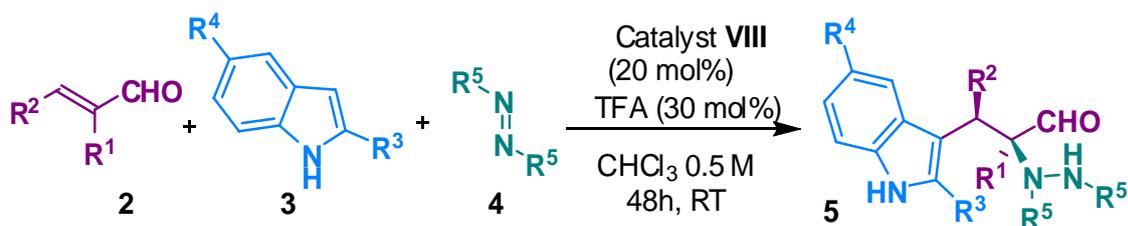

All the reactions were carried out in undistilled chloroform. In an ordinary vial equipped with a Teflon-coated stir bar, 9-Amino(9-deoxy)epi-hydroquinine **VIII** (0.04 mmol, 200 μL of a 0.2 M CHCl$_3$ solution, 20 mol%) was added to 200 μL of solvent. After the addition of TFA (0.06 mmol, 5 μL, 30 mol%), the solution was stirred for 5 minutes at room temperature before adding the α-substituted enal 2 (0.2 mmol). The mixture was then allowed to stir for further 5 minutes at room temperature before the addition of indole derivative 3 (0.24 mmol, 1.2 equiv.). After 5 minutes, azodicarboxylate (0.3 mmol, 1.5 equiv.) was added and stirring continued at the indicated temperature and for the indicated time. The crude reaction mixture was diluted with CH$_2$Cl$_2$ (1 mL) and flushed through a short plug of silica, using CH$_2$Cl$_2$/ AcOEt 1/1 as the eluent. Solvent was removed in vacuo and the residue was purified by flash chromatography to yield the desired product **5**.
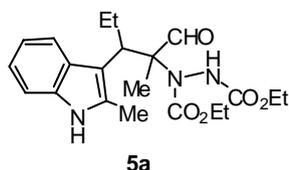
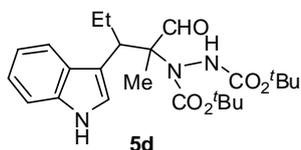**diethyl 1-(2-methyl-3-(2-methyl-1H-indol-3-yl)-1-oxopentan-2-yl)hydrazine-1,2-dicarboxylate 5a.** The reaction was carried out over 48 hours in CHCl$_3$ at room temperature following the general procedure to furnish the crude product (d.r.= 8:1 was determined by integration of one set of ^{1}H-NMR signal: δ$_{major}$ 5.84 ppm bs, δ$_{minor}$ 5.18 ppm bs). The title compound was isolated by flash column chromatography (hexane/acetone = 8/2) in 57% yield as mixture of diastereoisomers in 6:1 ratio and 99% ee (major diastereoisomer). The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/i-PrOH 9:1, flow rate 0.75 mL/min, λ = 214, 254 nm: τ$_{major}$ = 13.8 min., τ$_{minor}$

= 19.9 min. $[\alpha]_{rt}^{D}$= - 55.4 (c = 0.73, CHCl$_3$, 99% ee, dr=6:1). HRMS: (m/z) calculated for C$_{21}$H$_{29}$N$_3$O$_5$: 403.2107, found: 403.2107. ^{1}H NMR (400 MHz, CDCl$_3$ 25°C): Major diastereoisomer, major rotamer: δ 0.61 (t, 3H, J = 7.19 Hz), 1.12 (s, 3H), 1.22-1.38 (m, 6H), 1.87-2.01 (m, 1H), 2.04-2.15 (m, 1H) 2.37 (s, 3H), 3.32 (dd, 1H, J$_1$= 12.4 Hz, J$_2$=3.2 Hz), 3.94-4.40 (m, 4H), 5.82 (bs, 1H), 7.02-7.18 (m, 2H), 7.29-7.43 (m, 2H), 7.94 (bs, 1H), 9.74 (s, 1H). ^{13}CNMR (100 MHz, CDCl$_3$ 25°C): δ 12.6 (CH$_3$), 13.2 (CH$_3$), 14.3 (CH$_3$), 14.4 (CH$_3$), 19.97 (C), 22.03 (CH$_3$), 45.62 (CH), 62.3 (CH$_2$), 63.4 (CH$_2$), 64.4 (CH$_2$), 108.8 (C), 111.5 (CH), 118.1 (CH), 120.5 (CH), 121.2 (CH), 127.2 (C), 134.5 (C), 136.1 (C), 156.2 (C), 156.7 (C), 197.9 (C). Additional peaks and line broadenings are observed due to rotameric species.

5b
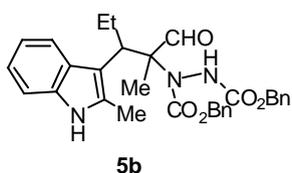
dibenzyl 1-(2-methyl-3-(2-methyl-1H-indol-3-yl)-1-oxopentan-2-yl)hydrazine-1,2-dicarboxylate 5b. The reaction was carried out over 48 hours in CHCl$_3$ at room temperature following the general procedure to furnish the crude product (d.r.= 6:1 was determined by integration of one set of ^{1}H-NMR signal: δ$_{major}$ 0.57 ppm t, δ$_{minor}$ 0.68 ppm t). The title compound was isolated by flash column chromatography (hexane/acetone = 8/2) in 49% yield as mixture of diastereoisomers in 7.5:1 ratio and 99% ee (major diastereoisomer). The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/i-PrOH 85:15, flow rate 0.75 mL/min, λ = 214, 254 nm: τ$_{major}$ = 17.64 min., τ$_{minor}$ = 23.24 min. $[\alpha]_{rt}^{D}$= - 21.3 (c = 1.50, CHCl$_3$, 99% ee, 7.5:1 dr). ^{1}H NMR (400 MHz, CDCl$_3$ 25°C): Major diastereoisomer, major rotamer δ 0.57 (t, 3H, J = 7.18 Hz), 1.31 (s, 9H), 1.14 (s, 3H), 1.81-1.93 (m, 1H), 2.04-2.15 (m, 1H), 2.34 (s, 3H), 3.30 (dd, 1H, J$_1$= 11.9 Hz, J$_2$=3.2 Hz), 4.96-5.40 (m, 5H), 5.94 (bs, 1H), 6.90 (m, 1H), 7.06-7.39 (m, 15H), 7.91 (bs, 1H), 9.78 (bs, 1H). ^{13}C NMR (150 MHz, CDCl$_3$ 25°C): δ 12.6 (CH$_3$), 13.2 (CH$_3$), 19.9 (CH$_3$), 22.03 (CH$_2$), 45.62 (CH), 67.8 (CH$_2$), 68.1 (CH$_2$), 73.18 (C), 108.8 (C), 111.4 (CH), 118.0 (CH), 120.4 (CH), 120.7 (CH), 121.3 (CH), 121.5 (CH), 127.0 (C), 128.2 (CH), 128.4 (C), 128.6 (CH), 128.7 (CH), 128.8 (CH), 134.4 (C), 135.7 (C), 136.0 (C), 156.5 (C), 156.7 (C), 197.7 (C). Additional peaks and line broadenings are observed due to rotameric species.
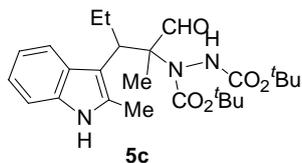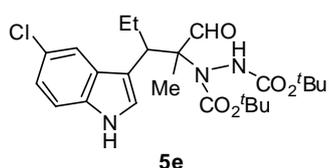
di-tert-butyl 1-(2-methyl-3-(2-methyl-1H-indol-3-yl)-1-oxopentan-2-yl)hydrazine-1,2-dicarboxylate 5c. The reaction was carried out over 24 hours in $CHCl_3$ at room temperature following the general procedure to furnish the crude product (d.r.= 11:1 was determined by integration of one set of ^{1}H-NMR signal: δ_{major} 9.73 ppm, bs, δ_{minor} 9.58 ppm, bs). The title compound was isolated by flash column chromatography (DCM/Et_2O = 98/2) in 80% yield as mixture of diastereoisomers in 7.3:1 ratio and 98% ee (major diastereoisomer). The ee was determined by HPLC analysis Daicel Chiralcel OD-H column: hexane/i-PrOH 95:5, flow rate 0.60 mL/min, λ = 214, 254 nm: τ_{major} = 14.63 min., τ_{minor} = 16.32 min. $[\alpha]_{rt}^D$= -41.3 (c = 2.00, $CHCl_3$, 98% ee, dr=7.3:1). HRMS: (m/z) calculated for $C_{25}H_{37}N_3O_5$: 459.2733, found: 459.2734. ^{1}H NMR (600 MHz, $CHCl_3$ -30°C): sum of rotamer (a+b) δ 0.54 (m, 6H, J= 7.2 Hz) (a+b), 1.31 (bs, 9H) (a), 1.41 (s, 9H) (b), 1.51 (s, 9H) (a), 1.56 (s, 9H) (b), 1.85-2.13 (m, 4H) (a+b), 2.29 (s, 3H) (a), 2.31 (s, 3H) (b), 3.18-3.24 (m, 2H,) (a+b), 5.22 (bs, 1H) (a), 5.35 (bs, 1H) (b), 6.98-7.15 (m, 4H) (a+b), 7.25-7.39 (m, 4H) (a+b), 8.30 (bs, 1H) (a), 8.36 (bs, 1 H) (b), 9.62 (bs, 1H) (a), 9.75 (bs, 1H) (b) ^{13}CNMR (150 MHz, $CHCl_3$ -30°C): δ 12.7 (CH_3) (a+b), 13.4 (CH_3) (a), 13.5 (CH_3) (b), 20.1 (CH_3) (a), 20.5 (CH_3) (b), 22.1 (CH_2) (a), 22.2 (CH_2) (b), 28.3 (C (CH_3)$_3$) (a), 28.4 (C (CH_3)$_3$) (a), 28.4 (C (CH_3)$_3$) (b), 28.5 (C (CH_3)$_3$) (b), 45.7 (CH) (a), 45.9 (CH) (b), 71.8 (C) (a), 71.9 (C) (b), 81.7 (C) (a), 81.12 (C) (b), 82.7 (C) (a), 82.7 (C) (a), 108.2 (C) (a), 108.7 (C) (b), 111.6 (CH) (a), 111.7 (CH) (b), 117.8 (CH) (a), 118.2 (CH) (b), 120.0 (CH) (a), 120.1 (CH) (b), 120.9 (CH) (a), 121.3 (CH) (b), 126.8 (C) (a), 127.1 (C) (b), 134. 6 (CH) (a), 134.7 (CH) (b), 135.9 (C) (a), 136 (C) (b), 155.3 (C) (a), 155.8 (C) (b), 155.9 (C) (a), 156.2 (C) (b), 198.3 (C) (a), 198.9 (C) (b). Additional peaks and line broadenings are observed due to rotameric species.

di-tert-butyl 1-(3-(1H-indol-3-yl)-2-methyl-1-oxopentan-2-yl)hydrazine-1,2-dicarboxylate 5d. The reaction was carried out over 96 hours in $CHCl_3$ at −10°C following the general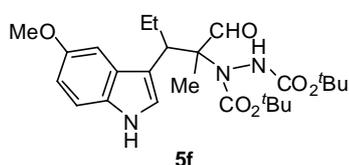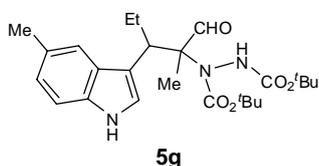 procedure to furnish the crude product (d.r.= 3:1 was determined by integration of one set of ^{1}H-NMR signal: δ_{major} 9.57 ppm bs, δ_{minor} 9.60 ppm bs). The title compound was isolated by flash column chromatography (DCM/Ethyl Acetate, gradient from 98/2 to 95/5) in 51% yield as mixture of diastereosimers in 3:1 ratio. Major diastereoisomer ee = 94%; minor diastereoisomer ee= 99%. The ee was determined by HPLC analysis on Daicel Chiralpak AD-H column: hexane/i-PrOH 9:1, flow rate 0.75 mL/min, λ = 214, 254

nm: Major diastereoisomer τ$_{major}$ = 30. 62 min., τ$_{minor}$ = 16.34 min; minor diastereoisomer τ$_{major}$ = 20. 37 min., τ$_{minor}$ = 10.03 min [α]$_{rt}^D$= -25.4 (c = 1.10, CHCl$_3$, 94% ee, dr=3:1). HRMS: (m/z) calculated for C$_{24}$H$_{35}$N$_3$O$_5$: 445.2577, found: 445.2577. ^{1}H NMR (400 MHz, CHCl$_3$ 25°C): δ 0.62-0.69 (m, 3H), 1.34 (bs, 3H), 1.42 (bs, 9H), 1.43 (bs, 9H), 1.54-1.76 (m, 1 H), 1.97-2.13 (m, 1H), 3.34 (dd, 1H, J$_1$= 12.8 Hz, J$_2$=2.8 Hz), 5.92 (bs, 1H), 6.98 (bs, 1H), 7.00-7.24 (m, 2H), 7.29-7.45 (m, 1H), 7.50-7.66 (m, 1H) 8.37 (bd, J=13.7), 9.68 (bs, 1H). ^{13}CNMR (100 MHz, CHCl$_3$ 25°C): δ 12.9 (CH$_3$), 19.9 (CH$_3$), 24.4 (C), 28.3 (C (CH$_3$)$_3$), 28.4 (C (CH$_3$)$_3$), 31.1 (CH$_2$), 45.0 (CH), 72.2 (C), 81.4 (C), 111.8 (CH), 114.8 (C), 119.3 (CH), 120.0 (CH), 122.3 (CH), 122.4 (CH), 123.6 (C), 136.5 (C), 155.6, 198.6. Additional peaks and line broadenings are observed due to rotameric species.

5e

di-tert-butyl 1-(3-(5-chloro-1H-indol-3-yl)-2-methyl-1-oxopentan-2-yl)hydrazine-1,2-dicarboxylate 5e. The reaction was carried out over 65 hours in CHCl$_3$ at 0°C following the general procedure to furnish the crude product (d.r.= 4:1 was determined by integration of one set of ^{1}H-NMR signal: δ$_{major}$ 9.65 ppm bs, δ$_{minor}$ 9.60 ppm bs). The title compound was isolated by flash column chromatography (DCM/Et$_2$O, gradient from 98/2 to 95/5) in 43% yield as mixture of diastereoisomers in 3:1 ratio and 91% ee (major diastereoismer). The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/i-PrOH 95:5, flow rate 0.3 mL/min, λ = 214, 254 nm: τ$_{major}$ = 41.84 min., τ$_{minor}$ = 37.9 min. [α]$_{rt}^D$= -15.1 (c = 0.6, CHCl$_3$, 91% ee, dr=3:1). ^{1}H NMR (400 MHz, CHCl$_3$ 25°C): Major diastereoisomer, major rotamer δ 0.64 (t, 3H, J=7.3 Hz), 1.44-1.45 (19H), 2.00-2.15 (m, 1H), 3.25 (d, 1H, J=11.4 Hz), 5.81 (bs, 1H), 7.01 (bs, 1H), 7.15-7.19 (m, 2H), 7.30-7.34 (m, 1H), 7.54 (bs, 1H), 8.24 (bs, 1H), 9.66 (bs, 1H). ^{13}CNMR (125 MHz, CHCl$_3$ -20°C): sum of diastereoisomer and rotamers: δ 13.0, 13.4, 19.8, 25.5, 28.2, 28.3, 28.4, 30.1, 30.5, 31.6, 81.8, 82.3, 82.9, 83.1, 113.0, 118.5, 118.8, 122.6, 122.8, 123.11, 125.6, 125.8, 125.9, 126.1, 155.2, 155.6, 155.8, 155.9, 197.8, 198.2, 198.9, 199.1.


5f

di-tert-butyl 1-(3-(5-methoxy-1H-indol-3-yl)-2-methyl-1-oxopentan-2-yl)hydrazine-1,2-dicarboxylate 5f. The reaction was carried out over 96 hours in CHCl$_3$ at -10°C following the general procedure to furnish the crude product (d.r.= 3:1 was determined by integration of

one set of ^{1}H-NMR signal: δ_{major} 9.65 ppm, bs, δ_{minor} 9.61 ppm, bs). The title compound was isolated by flash column chromatography (DCM/Et$_2$O = 98/2) in 54% yield as mixture of diastereoisomers in 3:1 ratio. Major diastereoisomer ee=96% ; minor diastereoisomer ee= 99%. The ee was determined by HPLC analysis on a Daicel Chiralpack AD-H column: hexane/i-PrOH 9:1, flow rate 0.75 mL/min, λ = 214, 254 nm: Major diastereoisomer τ_{major} = 38.96 min., τ_{minor} = 19.43 min. $[\alpha]_{rt}^D$= -15.5 (c = 1.02, CHCl$_3$, 96% ee, dr= 3:1). HRMS: (m/z) calculated for C$_{25}$H$_{37}$N$_3$O$_6$: 475.2682, found: 475.2682. Major diastereoisomer, major rotamer ^{1}H NMR (600 MHz, CHCl$_3$ -30°C): δ 0.64 (m, 3H), 1.40-1.52 (m, 21H), 2.01-2.14 (m, 2 H), 3.29 (d, 1H, J= 11.3 Hz), 3.91 (s, 3H), 6.44 (bs, 1H), 6.84-7.01 (m, 3H), 7.25-7.36 (m, 1H), 7.50-7.66 (m, 1H) 8.64 (bs, 1H), 9.69 (bs, 1H). ^{13}CNMR (125 MHz, CHCl$_3$ -30°C): δ 12.7 (CH$_3$), 19.2 (CH$_3$), 25.5 (CH$_2$), 27.9 (C (CH$_3$)$_3$), 28.1 (C (CH$_3$)$_3$), 31.1 (CH$_2$), 44.8 (CH), 55.9 (CH$_3$), 71.8 (C), 81.7 (C), 82.4 (C), 100.7 (CH), 112.0 (CH), 112.3 (CH), 114.1 (CH), 124.1 (CH), 128.2 (C), 131.4 (CH), 131.7 (CH), 154.3 (C), 155.3 (C), 155.7 (C), 198.6 (C). Additional peaks and line broadenings are observed due to rotameric species.

di-tert-butyl 1-(2-methyl-3-(5-methyl-1H-indol-3-yl)-1-oxopentan-2-yl)hydrazine-1,2-dicarboxylate 5g. The reaction was carried out over 96 hours in CHCl$_3$ at -10°C following the general procedure to furnish the crude product (d.r.= 3:1 was determined by integration of one set of ^{1}H-NMR signal: δ_{major} 9.67 ppm, bs, δ_{minor} 9.65 ppm, bs). The title compound was isolated by flash column chromatography (DCM/Et$_2$O = 98/2) in 47% yield as mixture of diastereoisomers in 3:1 ratio. Major diastereoisomer ee=91% ; minor diastereoisomer ee= 99%. The ee was determined by HPLC analysis on a Daicel Chiralpack AD-H column: hexane/i-PrOH 9:1, flow rate 0.75 mL/min, λ = 214, 254 nm: Major diastereoisomer τ_{major} = 20.62 min., τ_{minor} = 12.36 min. $[\alpha]_{rt}^D$= -18.3 (c = 1.02, CHCl$_3$, 91% ee, dr= 3:1). Major diastereoisomer, major rotamer ^{1}H NMR (600 MHz, CHCl$_3$ 25°C): δ 0.68 (m, 3H), 1.38-1.52 (m, 22H), 2.02-2.17 (m, 1 H), 2.51 (s, 3H), 3.32 (d, 1H, J$_1$= 12.1 Hz), 5.99 (bs, 1H), 6.95 (bs, 1H), 7.01-7.09 (m, 1H), 7.28-7.41 (m, 2H), 8.30 (bs, 1H), 9.71 (bs, 1H). ^{13}CNMR (125 MHz, CHCl$_3$ 25°C): δ 12.9 (CH$_3$), 19.9 (CH$_3$), 24.5 (CH$_2$), 28.3 (C (CH$_3$)$_3$), 45.0 (CH), 72.0 (C), 81.3 (C),82.3 (C), 111.3 (CH), 111.7 (CH), 118.7 (C), 119.0 (C), 123.7 (CH), 123.9 (CH), 129.2 (C), 134.8 (C), 155.5 (C), 198.7 (C). Additional peaks and line broadenings are observed due to rotameric species.

General procedure for the asymmetric organocatalytic sulpha-Michael/amination tandem sequence of α−substituted α,β−unsaturated aldehydes.

6a: R³ = ᵗBu
6b: R³ = Bn
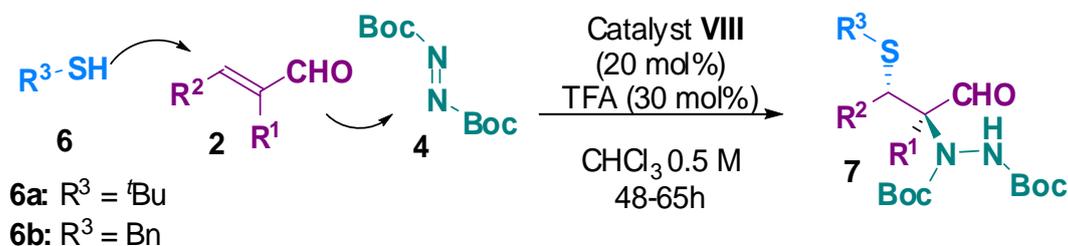
All the reactions were carried out in undistilled chloroform or toluene. In an ordinary vial equipped with a Teflon-coated stir bar, 9-Amino(9-deoxy)epi-hydroquinine **VIII** (0.04 mmol, 200 µL of a 0.2 M CHCl₃ solution, 20 mol%) was added to 200 µL of solvent. After the addition of TFA (0.06 mmol, 5 µL, 30 mol%), the solution was stirred for 5 minutes at room temperature before adding the α-substituted enal 2 (0.2 mmol). The mixture was then allowed to stir for further 5 minutes at room temperature before the addition of thiol (0.24 mmol, 1.2 equiv.) and then stirred at the indicated temperature. After 5 minutes, azodicarboxylate (0.3 mmol, 1.5 equiv.) was added and stirring continued for the indicated time. The crude reaction mixture was diluted with CH₂Cl₂ (1 mL) and flushed through a short plug of silica, using CH₂Cl₂/AcOEt 1/1 as the eluent. Solvent was removed in vacuo and the residue was purified by flash chromatography to yield the desired product.

General procedure for the reduction and cyclization to form oxazolidinones.

The crude reaction mixture (0.2 mmol scale referred to aldehyde) was diluted with MeOH (2 mL) and cooled to 0°C before the addition of NaBH₄ (0.6 mmol, 3 equiv.) After 10 minutes, 2 M solution of NaOH (2 mL) and THF (2 mL) were successively added and the crude reaction mixture was stirred for 2 hours. After standard aqueous work-up, the product was purified by flash-chromatography on silica gel.
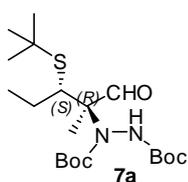
di-tert-butyl 1-((2R,3S)-3-(tert-butylthio)-2-methyl-1-oxopentan-2-yl)hydrazine-1,2-dicarboxylate 7a. The reaction was carried out over 65 hours in CHCl₃ at 0°C following the general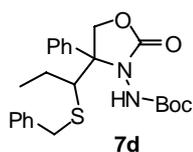 procedure to furnish the crude product (d.r.= 6.5:1, determined by integration of one set of ¹H-NMR signals: δ_major 3.03 ppm d, δ_minor

3.29 ppm d). The title compound was isolated by flash column chromatography (hexane/diethyl ether = 9/1) in 54% yield as single diastereoisomer and > 99% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/i-PrOH 98:2, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 19.74 min., τ_{minor} = 14.95 min. $[\alpha]_{rt}^D$ = + 5.3 (c = 1.16, CHCl$_3$, > 99% ee). HRMS: (m/z) calculated for C$_{20}$H$_{38}$N$_2$O$_5$S: 418.2501, found: 418.2502. ^{1}H NMR (600 MHz, CDCl$_3$ -20°C): Major rotamer δ 1.02 (t, 3H, J = 6.65 Hz), 1.31 (s, 9H), 1.40-1.42 (9H), 1.44 (bs, 3H), 1.46 (s, 9H+1H), 2.03 (bs, 1H), 2.95 (d, 1H, J = 8.4 Hz), 6.42 (s, 1H), 9.65 (s, 1H). ^{13}CNMR (150 MHz, CDCl$_3$ -20°C): δ 13.1 (CH$_3$), 19.8 (CH$_3$), 26.5 (CH$_2$), 28.2 (C(CH$_3$)$_3$), 28.5 (C(CH$_3$)$_3$), 32.5 (C (CH$_3$)$_3$), 44.2 (CH), 51.8 (C), 72.2 (C), 81.7 (C), 82.7 (C), 155.4 (C), 155.6 (C), 197.9 (C). Additional peaks and line broadenings are observed due to rotameric species.
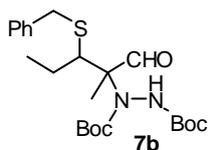
di-tert-butyl1-(3-(benzylthio)-2-methyl-1-oxopentan-2-yl)hydrazine-1,2-dicarboxylate 7b. The reaction was carried out over 65 hours in toluene at – 20°C following the general procedure to furnish the crude product (d.r.= 6:1 was determined by integration of one set of ^{1}H-NMR signal: δ_{major} 9.50 ppm bs, δ_{minor} 9.73 ppm bs). The title compound was isolated by flash column chromatography (hexane/acetone = 97/3) in 27% yield as single diastereoisomer and 89% ee. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/i-PrOH 98:2, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 10.09 min., τ_{minor} = 8.46 min. $[\alpha]_{rt}^D$ = - 3.2 (c = 1.16, CHCl$_3$, 89% ee). HRMS: (m/z) calculated for C$_{23}$H$_{36}$N$_2$O$_5$S: 452.2346, found: 452.2345. ^{1}H NMR (600 MHz, CDCl$_3$ -30°C): Major rotamer δ 0.93 (t, 3H, J = 7.30 Hz), 1.29 (s, 3H), 1.39 (s, 9H), 1.44 (bs, 9H+1H), 1.87 (bs, 1H), 2.69 (d, 1H, J = 9.9 Hz), 3.67-3.74 (m, 2H), 6.1 (bs, 1H), 7.26-7.32 (m, 5 H), 9.50 (bs, 1 H). ^{13}CNMR (150 MHz, CDCl$_3$ -30°C): δ 12.9 (CH$_3$), 19.1 (CH$_3$), 25.4 (CH$_2$), 28.3 (C(CH$_3$)$_3$), 28.4 (C(CH$_3$)$_3$), 38.7 (CH$_2$), 53.8 (CH), 72.3 (C), 81.8 (C), 83.0 (C), 127.7 (CH), 129.0 (CH), 138.2 (C), 155.5 (C), 155.6(C), 196.3 (C). Additional peaks and line broadenings are observed due to rotameric species.
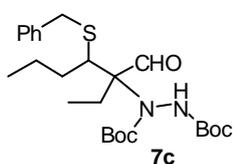
di-tert-butyl-1-(4-(benzylthio)-3-formylheptan-3-yl)hydrazine-1,2-dicarboxylate 7c. The reaction was carried out over 48 hours in CHCl$_3$ at 40°C following the gen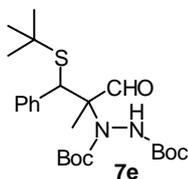eral procedure to furnish the crude product (d.r.= 4:1 was determined by integration of one set of ^{1}H-NMR signal: δ_{major} 3.09 ppm. d, δ_{minor} 3.41 ppm. d). The

title compound was isolated by flash column chromatography (hexane/acetone = 95/5) in 45% yield as mixture of diastereoisomers in 4.5:1 ratio and 92% ee (major diastereoisomer). The ee was determined after reduction and cyclization to form oxazolidinone by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/i-PrOH 9:1, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 11.23 min., τ_{minor} = 8.37 min. $[\alpha]_{rt}^{D}$= + 1.5 (c = 1.02, CHCl$_3$, 92% ee). HRMS: (m/z) calculated for C$_{25}$H$_{40}$N$_2$O$_5$S: 480.2658, found: 480.2658. ^{1}H NMR (400 MHz, CD$_3$CN 60°C): Sum of rotamers (a+b) δ 0.80-0.98 (m, 6H), 1.29-1.38 (bs, 2H), 1.46 (s, 9H), 1.50 (s, 9H), 1.59-1.91 (bs, 3H), 2.08-2.27 (bs, 2H), 3.14 (d, 1H, J = 7.86 Hz), 3.74-3.88 (m, 2H), 7.27-7.36 (m, 5H), 9.47-9.56 (2 bs, 1H) ^{13}CNMR (100 MHz, CD$_3$CN 60°C): δ 13.2, 13.4, 20.1, 24.8, 27.6, 27.8, 35.0, 38.7, 50.9, 75.1, 82.4, 127.3, 128.7, 129.2, 138.9, 155.8, 195.2. Additional peaks and line broadenings are observed due to rotameric species.

tert-butyl 4-(1-(benzylthio)propyl)-2-oxo-4-phenyloxazolidin-3-ylcarbamate 7d. The reaction was carried out over 48 hours in CHCl$_3$ at 40°C following the general procedure to furnish the crude product (d.r.= 4:1 was determined by integration of one set of ^{1}H-NMR signal: δ_{major} 10.37 ppm. bs, δ_{minor} 10.02 ppm. bs). The crude reaction mixture was reduced and cyclized to form oxazolidinone 7d. The title compound was isolated by flash column chromatography (DCM/Et$_2$O = 97/3) in 47% yield as single diastereoisomer and 92% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/i-PrOH 9:1, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 13.82 min., τ_{minor} = 12.73 min. $[\alpha]_{rt}^{D}$= + 88.0 (c = 1.10, CHCl$_3$, 92% ee, dr=4.5:1). HRMS: (m/z) calculated for C$_{24}$H$_{30}$N$_2$O$_4$S: 442.1925, found: 442.1926. ^{1}H NMR (400 MHz, CD$_3$CN 60°C): δ 0.96 (t, 3H, J= 7.16), 1.3 (bs, 9H + 1H), 1.57 (bs, 1H), 3.39 (dd, 1H, J$_1$= 9.85 Hz, J$_2$=2.8 Hz), 3.87 (d$_{A-B}$, 1H, J=12.8), 3.92 (d$_{A-B}$, 1H J=12.8), 4.53 (d, 1H, J=10.0), 4.81 (d, 1H, J =10.0 Hz), 6.43 (bs, 1H), 7.32-7.47 (m, 10H) ^{13}CNMR (100 MHz, CD$_3$CN 60°C): δ 12.5, 26.9, 28.5, 39.1, 55.3, 69.8, 71.4, 82.3, 127.6, 128.7, 129.4, 129.8, 130.0, 130.4, 139.7, 140.0, 155.5, 156.6.

di-tert-butyl-1-(1-(tert-butylthio)-2-methyl-3-oxo-1-phenylpropan-2-yl)hydrazine-1,2-dicarboxylate 7e. The reaction was carried out over 48 hours in CHCl$_3$ at 40°C following the general procedure to furnish the crude product (d.r.=

20:1 was determined by integration of one set of ^{1}H-NMR signal: δ_{major} 9.81 ppm. bs, δ_{minor} 9.59 ppm). The title compound was isolated by flash column chromatography (DCM/Et$_2$O = 98/2) in 40% yield as a single diastereoisomer and 99% ee. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/i-PrOH 98:2, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 6.06 min., τ_{minor} = 5.50 min. $[\alpha]_{rt}^D$= + 38.9 (c = 1.10, CHCl$_3$, 99% ee). HRMS: (m/z) calculated for C$_{24}$H$_{38}$N$_2$O$_5$S: 466.2502, found: 466.2501. ^{1}H NMR (600 MHz, CDCl$_3$ -20°C): Major diastereoisomer, sum of rotamers (a+b) δ 1.16 (a)-1.17 (b) (s, 9H), 1.22 (a)-1.26 (b) (s, 3H), 1.40 (s, 9H) (a),1.44 (s, 9H) (b), 4.39 (a)- 4.94 (b) (bs, 1 H), 4.67 (a)- 4.70 (b) (bs,1 H), 7.26-7.37 (m, 5 H), 9.79 (a)- 9.81 (b) (bs, 1H). ^{13}CNMR (100 MHz, CDCl$_3$ -20°C): δ 16.2 (a)-16.5 (b) (CH$_3$), 28.2 (C(CH$_3$)$_3$), 28.3 (C(CH$_3$)$_3$), 31.4 (a)-31.5 (b) (C(CH$_3$)$_3$), 45.0 (a)-45.1 (b) (C), 48.2 (a)- 48.8 (b) (CH), 69.7 (a)-70.2 (b) (C), 81.6 (a)-81.9 (b) (C), 82.7 (a)-82.8 (b) (C), 127.8-128.2 (CH), 128.6- 128.8 (CH), 129.5-129.7 (CH), 140.4 (a)-140.6 (b) (C), 154.8 (a)-154.9 (b) (C), 155.0 (a)- 155.3 (b) (C), 197.0 (a)-197.1(b) (C). Additional peaks and line broadenings are observed due to rotameric species.
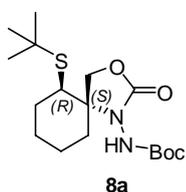
tert-butyl (5S,6R)-6-(tert-butylthio)-2-oxo-3-oxa-1-azaspiro[4.5]decan-1-ylcarbamate 8a. The reaction was carried out over 65 hours in CHCl$_3$ at 10°C following the general procedure to furnish the crude product. The crude reaction mixture was reduced and cyclized to form oxazolidinone 8a (d.r.= 8:1 was determined by integration of one set of ^{1}H-NMR signal: δ_{major} 1.35 ppm s, δ_{minor} 1.31 ppm s). The title compound was isolated by flash column chromatography (DCM/Et$_2$O = 95/5) in 40% yield as single diastereoisomer and > 99% ee. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/i-PrOH 98:2, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 21.13 min., τ_{minor} = 31.87 min. $[\alpha]_{rt}^D$= + 20.3 (c = 0.98, CHCl$_3$, > 99% ee). HRMS: (m/z) calculated for C$_{17}$H$_{30}$N$_2$O$_4$S: 358.1925, found: 358.1926. ^{1}H NMR (400 MHz, CDCl$_3$ 25°C): δ 1.18-1.31 (m, 3H), 1.36 (s, 9H), 1.49 (s, 9H), 1.65-1.83 (m, 3H), 1.98-2.09 (m, 1 H), 2.15-2.23 (m, 1H), 2.75 (dd, 1H, J$_1$ =12.4 Hz, J$_2$ =3.7 Hz), 4.10 (d$_{A-B}$, 1H, J=9.07 Hz), 4.27 (d$_{A-B}$, 1H, J=9.07 Hz), 6.02 (bs, 1H) ^{13}CNMR (100 MHz, CDCl$_3$ 20°C): δ 22.5 (CH$_2$), 25.9 (CH$_2$), 28.3 (C(CH$_3$)$_3$), 32.2 (C(CH$_3$)$_3$), 34.9 (CH$_2$), 36.8 (CH$_2$), 44.4 (C), 46.0 (CH), 64.2 (C), 69.4 (CH$_2$), 82.7 (C), 155.6 (C), 156.8 (C).

**Determination of the Relative and Absolute Configuration**

Compound 7a.
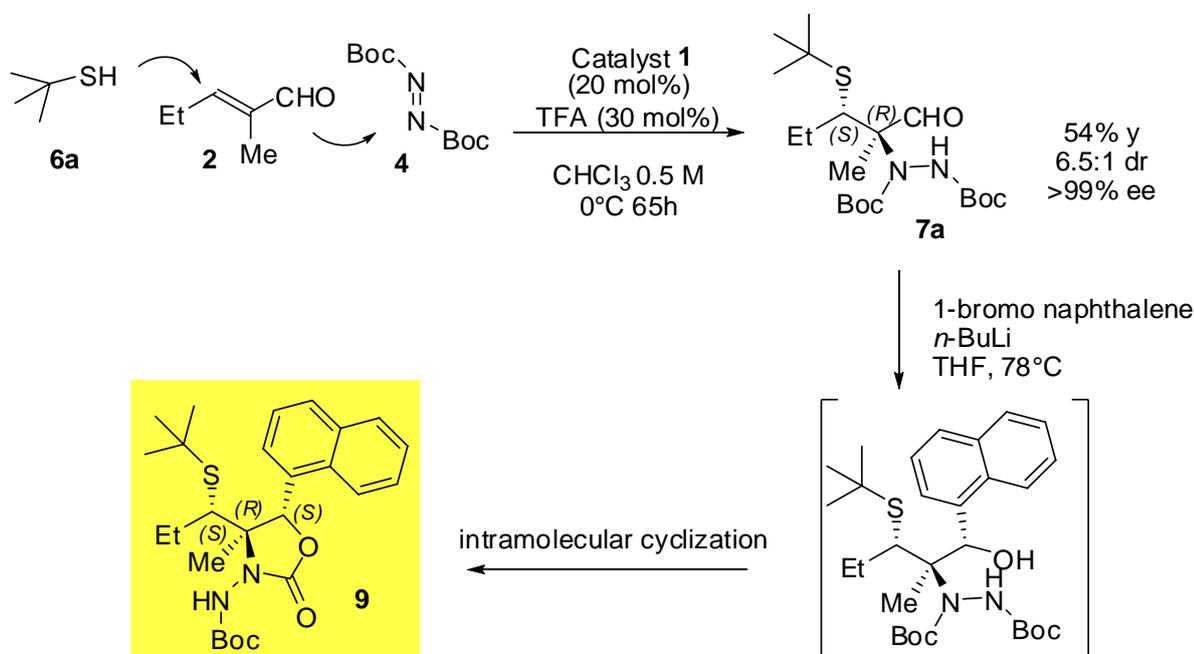
The absolute configuration of compound **7a** was assigned to be (2S,3R) by anomalous dispersion X-ray crystallographic analysis of the corresponding oxazolidinone derivative **9**. All the other relative and absolute configurations for both compound classes **5** and **7** were assigned by analogy, considering an uniform mechanistic pathway.

General procedure for formation of compound 9

To a solution of 1-bromonaphtalene (1.5 mmol, 2 equiv. compared to compound 7a) in dry THF (4 mL), n-BuLi (1 mL, 1.6 M in Hexane) was added slowly at − 78°C. After stirring at this temperature for 15 minutes, a solution of 7a (0.75 mmol) in 1 mL of THF was added. The mixture was warmed to ambient temperature and allowed to stir for further 15 minutes. An aqueous work-up with NH$_4$Cl and extraction with Et$_2$O furnished the crude product 9a. The pure compound was isolated by flash cromatography (Hex: Et$_2$O = 8:2), followed by HPLC purification on a C18 Column (acetonitrile/H2O 90:10 v/v).
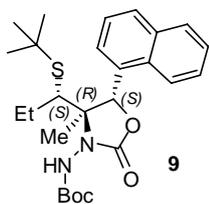
tert-butyl 4-(1-(tert-butylthio)propyl)-4-methyl-5-(naphthalen-1-yl)-2-oxooxazolidin-3-ylcarbamate 9. ^{1}H NMR (600 MHz, CD$_3$CN 50°C): δ 0.84 (s, 3H), 1.25 (t, 3H, J= 7.2 Hz), 1.41 (s, 9H), 1.45 (s, 9H), 1.58-1.67 (bs, 1 H), 2.10-2.17 (bs, 1H), 3.01 (dd, 1H, J$_1$ = 6.07 Hz, J$_2$ = 2.7 Hz), 6.57 (bs, 1H), 7.56-7.65 (m, 4H), 7.94-7.99 (m, 2H), 8.43 (bs, 1H). ^{13}CNMR (125 MHz, CD$_3$CN 50°C): δ 0.8 (CH$_3$), 12.6 (CH$_3$, bs), 25.7 (CH$_2$), 27.6 (C(CH$_3$)$_3$), 31.7 (C(CH$_3$)$_3$), 44.4 (C), 54.6 (CH), 68.6 (C), 80.0 (C), 81.6 (C bs), 123.6 (CH), 125.3 (CH), 125.5 (CH), 126.2 (CH), 126.7 (CH), 129.2 (CH), 129.3 (CH), 131.3 (C), 133.1 (C), 133.8 (C), 155.2 (C), 155.7 (C).

Crystal Data for compound 9
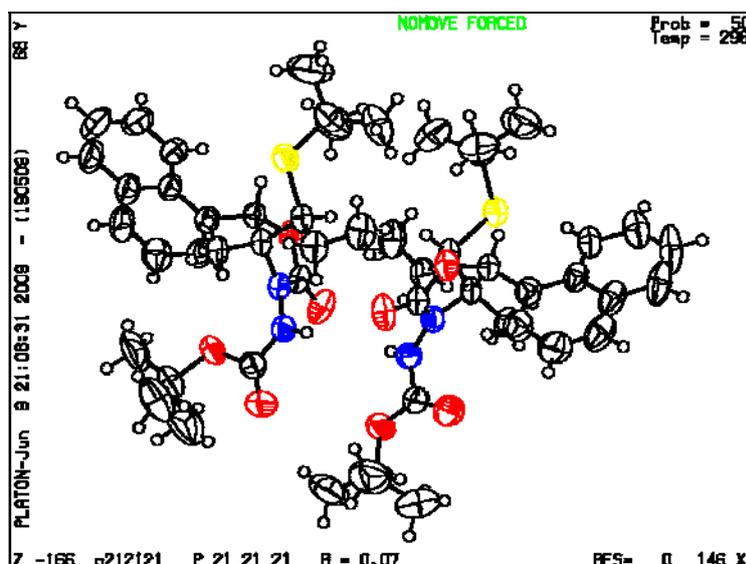
Crystals were obtained from hexane/Et$_2$O solution by slow evaporation. Molecular formula: C$_{26}$H$_{36}$N$_2$O$_4$S, M$_r$ = 472.63, Orthorhombic, space group P2$_1$2$_1$2$_1$ (No. 14), a = 10.9758(9), b = 23.5089(16), c = 23.7659(19) Å^3, V = 6132.3(9) Å^3, T = 298(2) °K, Z = 8, ρ$_c$ = 1.024 g cm^{-3}, F(000) = 2032, graphite-monochromated Mo$_{Kα}$ radiation (λ = 0.71073 Å), μ(Mo$_{Kα}$) = 0.133 mm^{-1}, colourless brick (0.4 × 0.2 × 0.2 mm^3), empirical absorption correction with SADABS (transmission factors: 0.9738 – 0.9486), 2400 frames, exposure time 20 s, 2.04 ≤ θ ≤ 26.00, −13≤ h ≤ 13, −29 ≤ k ≤ 29, −29 ≤ l ≤ 29, 46587 reflections collected, 9815 independent reflections (R$_{int}$ = 0.0466), solution by direct methods (SHELXS97) and subsequent Fourier syntheses, full-matrix least-squares on F$_o^2$ (SHELX97), hydrogen atoms refined with a riding model, data / restraints / parameters = 9815/ 0 / 608, S(F^2) = 1.041, R(F) = 0.0862 and wR(F^2) = 0.1771 on all data, R(F) = 0.0676 and wR(F^2) = 0.1639

for 7349 reflections with $F_0 > 4\sigma(F_0)$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.1132P)^2 + 0.000P]$ where $P = (F_o^2 + 2F_c^2)/3$, largest difference peak and hole 0.499 and −0.297 e Å^{-3}. Flack parameter[a]: 0.05(8). The asymmetric unit contains two independent molecules. 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-XXXXXX. 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).

[a] Flack, H. D. Acta Cryst. 1983, A39, 876-881

Compound 8.
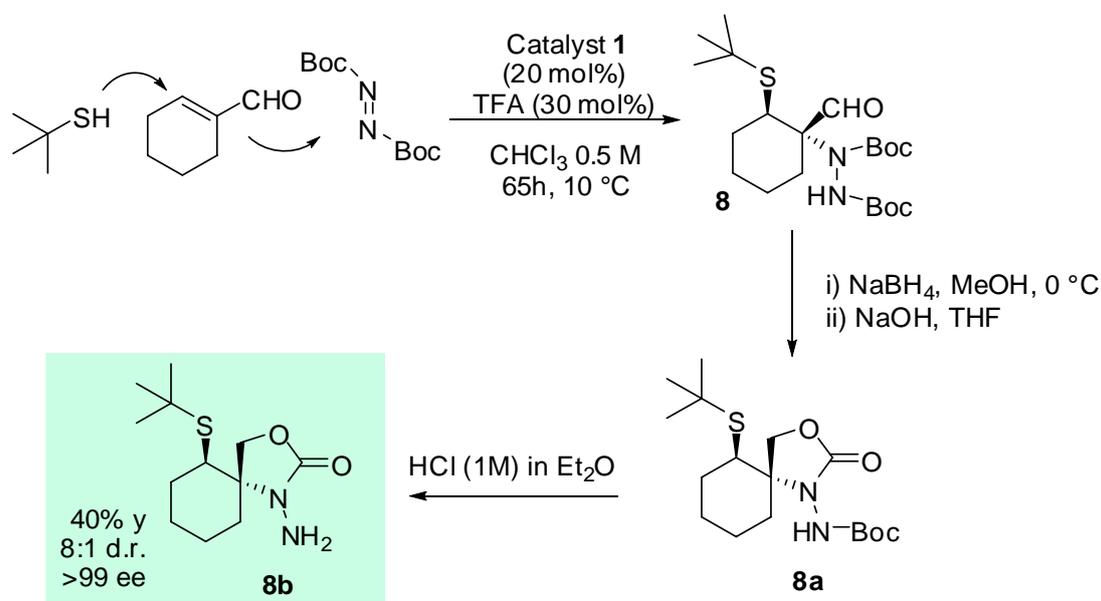
General procedure for N-Boc deprotection of compound 8a

The Boc-oxazolidinone **8a** (20 mg, 0.056 mmol) was dissolved in a solution of 1 M HCl in diethyl ether (4 mL) and stirred at room temperature for 3 h. The reaction was concentrated under a stream of N$_2$. The residue was dissolved in EtOAc and washed with saturated aqueous NaHCO$_3$ (2x) and brine, dried over MgSO$_4$ and concentrated to give a pale yellow solid. The resulted crude mixture was then purified by flash cromatography (hexane/ EtOAc 6/4) to give compound **8b** as a white solid.

(5S,6R)-1-amino-6-(tert-butylthio)-3-oxa-1-azaspiro[4.5]decan-2-one 8b.
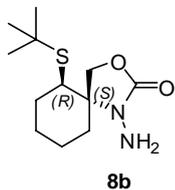
ESI: [M+Na]$^+$ 281. ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.97-1.31 (m, 2H), 1.34 (s, 9H), 1.36-1.45 (m, 1H), 1.65-1.80 (m, 3H), 1.88-1.97 (m, 1H), 2.15-2.20 (bs, 1H), 2.91 (dd,1 H, J$_1$=12.7 Hz, J$_2$= 4.2 Hz), 3.67 (bs, 2 H), 3.96 (d$_{A-B}$, 1H, J=9.1 Hz), 4.19 (d$_{A-B}$, 1H, J=9.1 Hz). ^{13}CNMR (100 MHz, CDCl$_3$): δ 22.6 (CH$_2$), 26.1 (CH$_2$), 32.2 (C(CH$_3$)$_3$), 35.2 (CH$_2$), 35.9 (CH$_2$), 44.2 (C), 45.6 (CH), 64.1 (C), 68.9 (CH$_2$), 159.0 (C).

Relative Configuration Absolute Configuration of 8a and 8b

In the case of compound **7**, a different stereochemical outcome for the organocascade might be envisaged, due to the use of a cyclic aldehyde. The steric interactions in the active iminium ion (formed with catalyst 1) might determine a different face shielding. Thus, an independent determination of the relative and absolute configuration is required. Unfortunately, despite several attempts, in this case we did not obtain suitable crystals. However, due to the low conformational freedom, the absolute configuration of compound **8a** (derived by reduction-cyclization sequence directly from 7) and its derivative 8b can be assigned by means of a combined use of NMR spectroscopy, chiroptical methods and quantum-mechanical calculations.
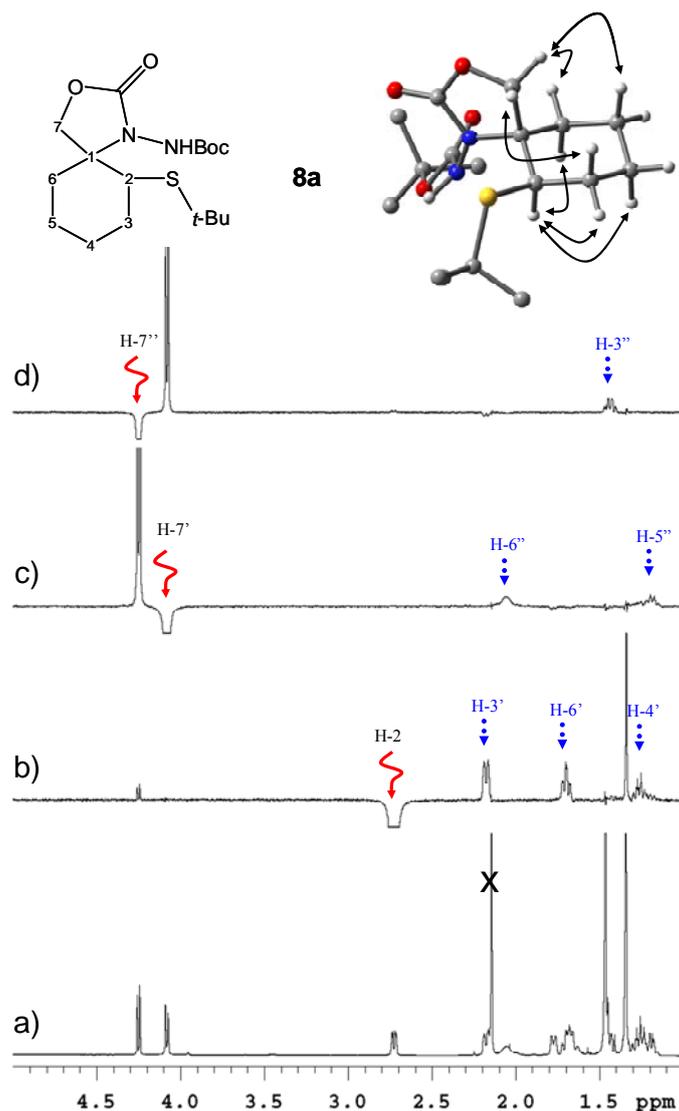
Figure S1: DPFGSE-NOE spectra obtained for 8a. trace a): control spectrum; trace b): NOE spectrum obtained on saturation of H-2; traces c) and d): NOE spectra obtained on saturation of the two diastereotopic hydrogens H7' and H7". Observed NOE (blue) are indicated as arrows in the DFT optimized structure (the hydrogen atoms of the t-butyl groups have been removed for clarity)

Full assignment of ^1H and ^{13}C NMR signals of 8a was obtained by HSQC and HMBC bi-dimensional sequences. For **8a**, NOE spectra were acquired in order to establish the relative stereochemistry of the two stereogenic centres (Figure S1).

In particular, saturation of the H-2 signal(trace b) showed nearly equivalent NOE effects on the H-3', H-6', H-4' hydrogens, and on the t-butyl signal. These NOE constraints imply that H-2 is in the axial position of the cyclohexane ring, and that H-3 lies on the opposite sides of the ring with respect to the CH_2 in position 7. This relationship is confirmed when the signals of the two diastereotopic protons belonging to C-7 are saturated (traces c and d). On saturation of H-7' NOE

effects are observed on H-6" and H-5", whereas on saturation of H-7" a significant enhancement is observed only for the signal of H3", being the equatorial position of C-2 occupied by the sulphur atom. The relative stereochemistry is therefore trans (i.e. 1R*2S*), and the DFT calculated structure[6] matches very well the experimental NOE ratios. It is worth mentioning that the relative stereochemistry is the same determined by X-ray analysis for compound 7a.

Conformational analysis and absolute configuration determination.

Compounds **8a** and **8b** are viscous oils, therefore the use of the Bijovet method, based on anomalous X-ray dispersion, to unambiguously assign the absolute configuration (AC) is precluded. Recently, the determination of the absolute configurations (ACs) of chiral molecules using the chiroptical techniques of optical rotation (OR), electronic circular dichroism (ECD), and vibrational circular dichroism (VCD) has been revolutionized by the development of density functional theory (DFT) methods for the prediction of these properties. In the present case, theoretical calculation of ECD spectra and optical rotation was carried out by means of TD-DFT method, since this technique has been successfully employed several times to predict ECD spectra and to assign the AC of organic molecules[vii]. It is worth to note that the relative stereochemistry has been already fixed by the NOE analysis, therefore only the conformation of the molecule can modify the shape of the ECD spectrum.

Compound **8b**, in which the Boc protecting group was removed, was considered more suitable for the following analysis because the presence of the protecting group in 8a increases the conformational freedom of the compound, thus complicating the conformational analysis. A preliminary conformational search, starting from the relative configuration derived from NOE spectra, has been carried out using Monte Carlo searching together with the MMFF94 molecular mechanics force field (as implemented in Titan 1.0.5). Due to the rigidity of the two fused rings, the conformational freedom is very low, and limited to the position of the t-butyl group.

All the conformations yielded by MM within a 5 kcal/mol window were then optimized using DFT at the B3LYP/6-31G(d) level, and the harmonic vibrational frequencies of each conformation were calculated at the same level to confirm their stability (no imaginary frequencies observed), and to evaluate the free energy of each conformation. After DFT minimization, only one stable conformation was found. This structure is fully compatible with the experimental NOE data, in particular for the conformation of the exocyclic S-Bu^t moiety. Calculation of the Electronic Circular Dichroism spectrum was carried out using TD-DFT method at the B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d) level, and assuming 1S, 2R, absolute configuration[viii]. Rotational strength were calculated in both length and velocity representation. Since the resulting values are very similar, errors due to basis set incompleteness are very small.[ix] The ECD spectra was then obtained by applying a 0.25 eV Gaussian shaped line width (Figure S2).
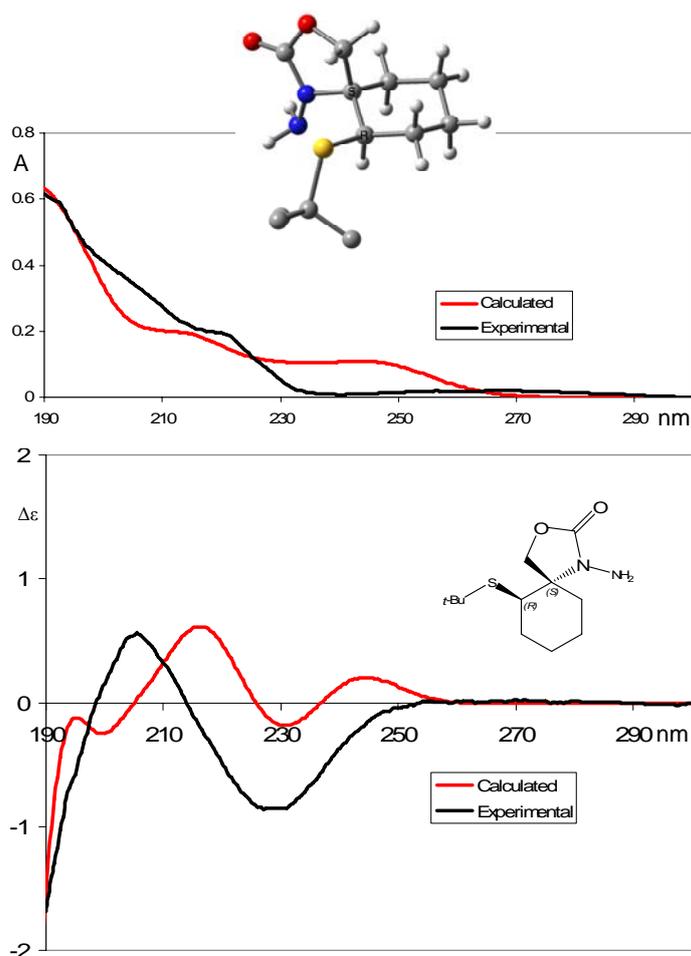
Figure S2. Top: calculated (red) and experimental (black) UV spectra of 8b. Bottom: experimental (black) and calculated ECD spectra (red), (the simulated spectrum has been red-shifted by 6 nm). Molecular CD (Δε) is expressed in L mol^{-1}cm^{-1}. Concentration in acetonitrile was 2.05·10^{-4} M, and a 1 cm cell was used.

The agreement between calculated and experimental spectra is whatever fairly good, over the relatively limited spectral range of the experimental CD spectrum[x], therefore the TD-DFT simulation supports the conclusion that the AC of 8b is 1S, 2R. This configuration is opposite to that obtained for **7a** by X-ray analysis.

[i] (a) Stott, K.; Stonehouse, J.; Keeler, J.; Hwand, T.-L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199. (b) Stott, K.; Keeler, J.; Van, Q. N.; Shaka, A. J. *J. Magn. Resonance* **1997**, *125*, 302. (c) Van, Q. N.; Smith, E. M.; Shaka, A. J. *J. Magn. Resonance* **1999**, *141*, 191. (d) See also: Claridge, T.D.W. *High Resolution NMR Techniques in Organic Chemistry*; Pergamon: Amsterdam, 1999.

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[v] Montecarlo algorithm (version 1.0.3), MMFF force field, as implemented in Titan 1.0.5, Wavefunction Inc., Irvine, CA.

[vi] Program Gaussian 03, Revision 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.

[vii] (a) Diedrich, C.; Grimme, S. *J. Phys. Chem. A* **2003**, *107*, 2524; (b) Casarini, D.; Lunazzi, L.; Mancinelli, M.; Mazzanti, A.; Rosini, C. *J. Org. Chem.* **2007**, *72*, 7667; (c) Goel, A.; Singh, F.V; Kumar, V.; Reichert, M.; Goulder, T. A. M; Bringmann, G. *J. Org. Chem.* **2007**, *72*, 7765; (d) Stephens, P. J.; Pan, J. J.; Devlin, F. J.; Cheeseman, J. R. *J. Nat. Prod.* **2008**, *71*, 285; (e) Penon, O.; Carlone, A.; Mazzanti, A.; Locatelli, M.; Sambri, L; Bartoli, G.;. Melchiorre, P. *Chem. Eur. J.* **2008**, *14*, 4788-4791; (f) Pesciaioli, F.; De Vincentiis, F.; Galzerano, P.; Bencivenni, G.; Bartoli, G.; Mazzanti, A.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 8703-8706; (g) Shaikh, R.R.; Mazzanti, A.; Petrini, M.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 8707-8710; (h) Lunazzi, L.; Mancinelli, M. Mazzanti, A. *J. Org. Chem.* **2009**, *74*, 1345; (i) Casarini, D.; Lunazzi, L.; Mancinelli, M.; Mazzanti, A.; Scafato, P. *Chirality* **2009**, *21*, 16-23; (j) Galzerano, P.; Bencivenni, G.; Pesciaioli, F.; Mazzanti, A.; Giannichi, B.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem. Eur. J.* **2009**, *15*, DOI 10.1002/chem.200802466. For two reviews: (k) Berova, N.; Di Bari, L.; Pescitelli, G. *Chem. Soc. Rev.* **2007**, *36*, 914; (l) Bringmann, G.; Bruhn, T.; Maksimenka, K.; Hemberger, Y. *Eur. J. Org. Chem.* **2009**, *22*, DOI 10.1002/ejoc.200801121

[viii] The use of a moderate basis set is dictated by the dimension of the molecules, and by the need of keeping the computational time into reasonable times (about 24 hours on a 8-core Xeon X7355 server).

[ix] Stephens, P.J.; McCann, D.M.; Devlin, F.J., Cheeseman, J.R.; Frisch, M.J. *J.Am.Chem.Soc.* **2004**, *126*, 7514-7521

[x] It is worth to note that the first cotton effect in the simulated spectra (at 244 nm) is not present in the experimental spectrum. However, also the UV simulated spectra does not correctly simulate the intensity of the experimental one in the same region. This mismatch is probably the result of errors in the calculation of the intensities of the lowest energy transitions.

6

SUMMARY AND OUTLOOK

It is undoubted that *Science* taps its inspiration on *Nature* since hundred of years, with a continuous effort on understanding Its Mechanisms and to reproduce Its efficiency. Most biological molecules are chiral and are synthesized in living cells by exploiting the extraordinary molecular machinery of enzymes, using asymmetric catalysis. The synthesis of complex chiral molecules is an important, as well as challenging, target in organic chemistry, so the development of new highly stereoselective reactions plays a fundamental role in the modern synthetic strategies, especially when considering that the optical purity is a rigorous requirement for new drugs and biologically-active compounds.

To a small extent, chemists use enzymes to achieve chiral compounds; in particular, *biological catalysis* is increasingly used on an industrial scale with hydrolytic reactions. In addition, a *bio-inorganic approach*, exploiting *metal* complexes with organic ligands, is also highly used for the achievement of chiral compounds. Moreover, the continuous demands for cheaper and more environmentally friendly catalytic processes, has guided the scientific community towards the development and the rapid affirmation of *organocatalysis* as a leading asymmetric catalytic strategy for the rapid access to enantiopure molecules.

We have seen in the previous chapters the advantages, the historical background and the enormous versatility of *asymmetric aminocatalysis*, trying to give a rapid yet complete overview of its progresses since its discovery.

In particular, we have shown our efforts on to the extension and potentiality of aminocatalysis, reporting our contribution in the synthetically useful *Mannich reaction* (Chapter 3), in the individuation of a *new primary amine bifunctional catalyst* (Chapter 4) and in the development of new, highly challenging *organocascade reactions* (Chapter 5).

We named the 'discovery' of aminocatalysis, it is probably more appropriate to refer to its *'rediscovery'*, as the scientist who coined the terms *enamine and imiunium ion catalysis*, Benjamin List, recently reported in his fascinating essay on the roots of Aminocatalysis, linking the modern asymmetric Aminocatalysis back to the pioneering contribution of Emil Knoevenagel over 100 years ago.[1]

Naturally, we are not at the end of the story: organocatalysis continue to be a highly lively, competitive and fruitful research field. Hopefully, new and exciting results will be achieved and optimistically, thanks to its features, it will be soon applied on an industrial scale. In fact, reporting List's words:[2]

'There is little doubt that organocatalysis is here to stay'

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[1] B. List *Angew. Chem.* **2010,** DOI: 10.1002/anie.200906900

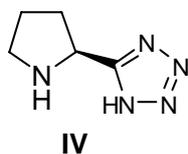[2] B. List, J. W. Yang, *Science*, 313.
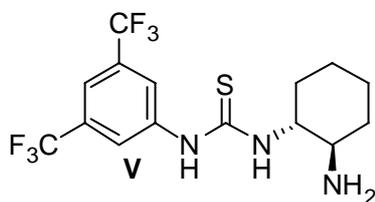
-*Appendix*-

Catalysts
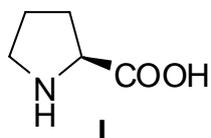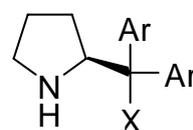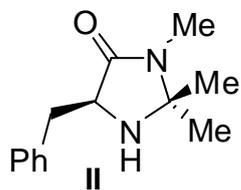
I

L-proline

II

IIIb: X = OH   Ar = Ph
III : X = H   Ar = Ph
IIIc: X = OTMS   Ar = Ph
IIId: X = OTMS   Ar = 2-Napht
IIIe: X = OTMS   Ar = 3,5-(CH$_3$)$_2$Ph
IIIa: X = OTMS   Ar = 3,5-(CF$_3$)$_2$Ph
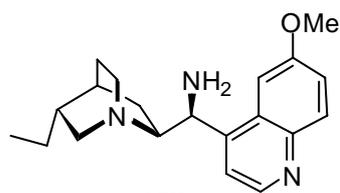
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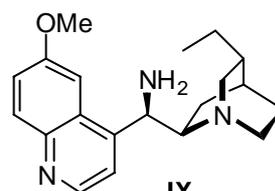
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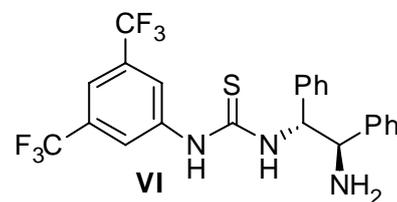
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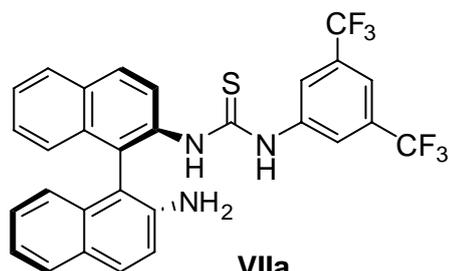
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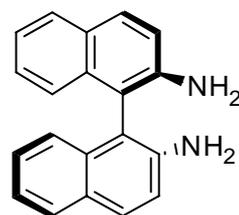
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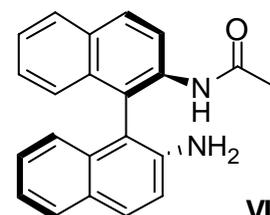
VIIc

VIII

IX

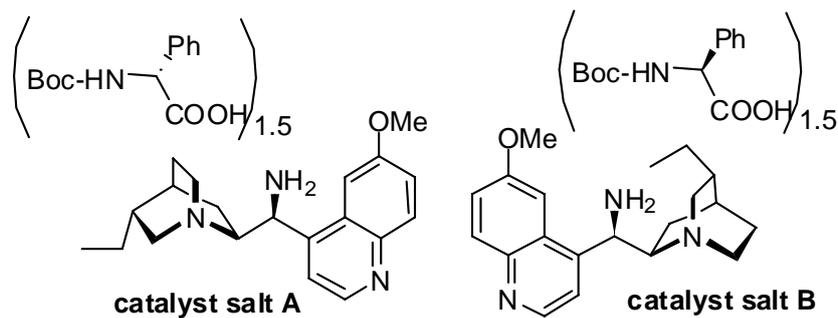**catalyst salt A**

catalyst salt B

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