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Asymmetric Aminocatalysis:

a modern strategy for molecules, challenges and life

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

Patrizia Galzerano, Giorgio Bencivenni, Fabio Pesciaioli, Andrea Mazzanti, Berardino Giannichi, Letizia Sambri, Giuseppe Bartoli, Paolo Melchiorre
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Targeting Structural and Stereochemical Complexity by Organocascade Catalysis: Construction of Spirocyclic Oxindoles Having Multiple Stereocenters

Giorgio Bencivenni, Dr., Li-Yuan Wu, Andrea Mazzanti, Dr., Berardino Giannichi, Fabio Pesciaioli, Mao-Ping Song, Prof. , Giuseppe Bartoli, Prof. , Paolo Melchiorre, Dr.
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Asymmetric Organocatalytic Cascade Reactions with α–Substituted α,β-Unsaturated Aldehydes

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Angew Chem Int. Ed., **2009,** *42*, 7892-7894.

Asymmetric Catalytic Aziridination of Cyclic Enones,

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Organocatalytic Asymmetric Conjugate Additions of Oxindoles and Benzofuranones to Cyclic Enones

Fabio Pesciaioli, Xu Tian, Giorgio Bencivenni, Giuseppe Bartoli and Paolo Melchiorre, **,** *Synlett* **2010**, 1704;

Organocatalytic Michael-alkylation cascade: the Enantioselective nitrocyclopropanation of oxindoles

F. Pesciaioli, P. Righi, A. Mazzanti, G. Bartoli and G. Bencivenni, *Chem. Eur. J.*, **2011**, *17*, 2842-2845.

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1. INTRODUCTION

"The best thing for being sad," replied Merlin, beginning to puff and blow, "is to learn something. That's the only thing that never fails. You may grow old and trembling in your anatomies, you may lie awake at night listening to the disorder of your veins, you may miss your only love, you may see the world about you devastated by evil lunatics, or know your honour trampled in the sewers of baser minds. There is only one thing for it then — to learn. Learn why the world wags and what wags it. That is the only thing which the mind can never exhaust, never alienate, never be tortured by, never fear or distrust, and never dream of regretting. Learning is the only thing for you. Look what a lot of things there are to learn."

T.H. White, The Once and Future King.

1.1. Asymmetric Synthesis

"*L'universe est dissymétrique*"

Louis Pasteur

With this statement the scientific environment became aware of the existence of the chirality[1] no more as philosophic concept or geometric property but as fundamental characteristic of the matter. In fact thanks to this breakthrough it was possible to understand that the chirality is a common *leitmotif* of the Nature that is able to amaze the most skeptic observer. Nature, using enzymes as catalyst, all along it was considered the uncontested master at producing chiral compounds in enantiomerically pure form. The chemist scenario itself, that has ever taken inspiration from the natural world and trying to emulate it, started to design stereoselective processes with the aim of create chemically and tridimensional unique molecules.

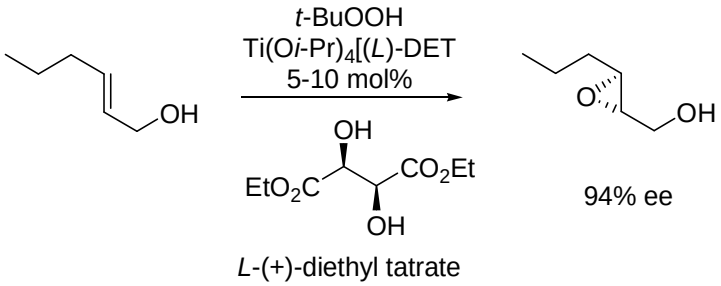
Nowadays the achievement of chiral molecules in enatiopure form is a central topic in bioscience field in particular in pharmacology and pharmaceutical industry. For the construction of chiral compound it is possible to start from chiral-pool sources with required stereocenters incorporated, or otherwise it is possible to forge them during the synthesis.[2]

The most common founts of chirality that come from nature are α-amino acids, terpenes, hydroxyl acids, and alkaloids.[3] If the target stereocenters are not present in this easy available sources they can be established through achiral synthesis and resolution protocols, the use of chiral auxiliary, or asymmetric catalysis.

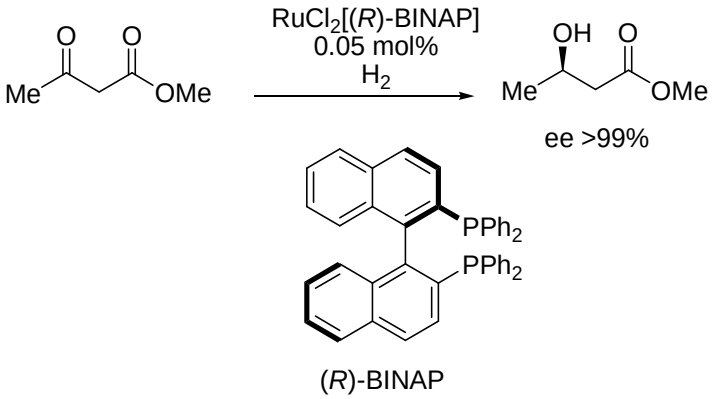
Even if the first two methods are the most applied in industry due especially for their robustness in academic research, the asymmetric catalysis has a role of primary interest and importance. The assignment of the chemistry Nobel Prize in 2001 Sharpless, Noyori and Knowels for the study and the development of Asymmetric catalytic Oxidation and Hydrogenation reactions is a proof of this (Scheme **1**).

Scheme 1: *Asymmetric Catalytic Epoxidation and Hydrogenation reactions developed by Sharpless Noyori and Knowels*

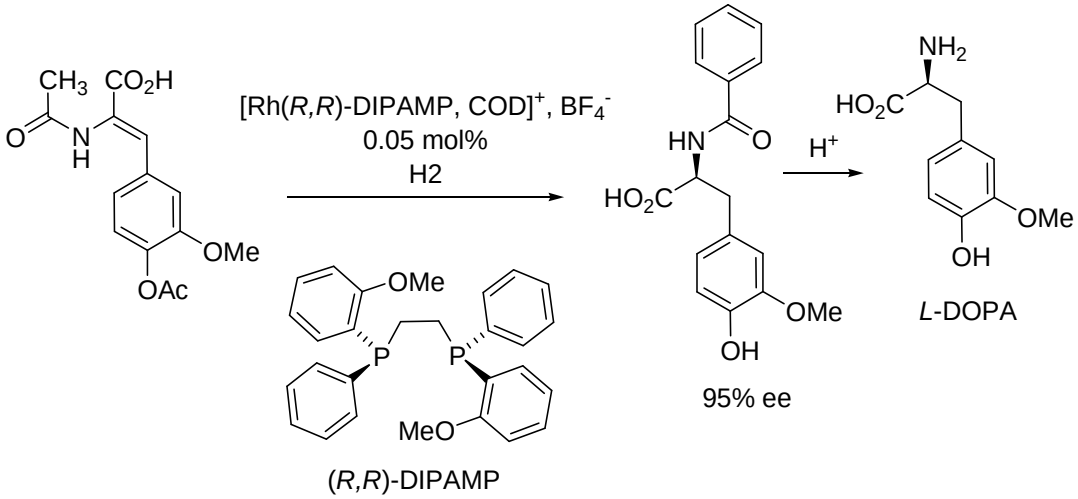
1a



1b



1c



In Scheme **1b** is reported the asymmetric epoxidation of allylic alcohols under the catalysis of Titanium diethyl-tartrate complex, also named Sharpless epoxidation.[4] Still exploiting the ability of a transition metal to dress itself with chiral ligands and drive the stereoselctivity of a process, Noyori developed the asymmetric reduction of β-ketoesthers using BINAP-Ruthenium complex[5] Scheme **1b**.Conteporany Knowles showed that this concepts could be applied to the synthesis of *L*-DOPA, a drug use to treat Parkinson's disease developed in the research laboratories of Monsanto (Scheme **1c**).[6]

This asymmetric protocols had the merit of convinced, with their elegance and atom economy, many chemical companies that asymmetric catalysis was possible on large scale.

At the end of the last century, as consequence of the excitement that was around this synthetic strategies both in academic and in industrial field, another branch of the asymmetric synthesis appeared on the stage of chemistry research.

This was no more based upon organometallic complex as catalyst for stereoselective synthesis but simple organic molecules.

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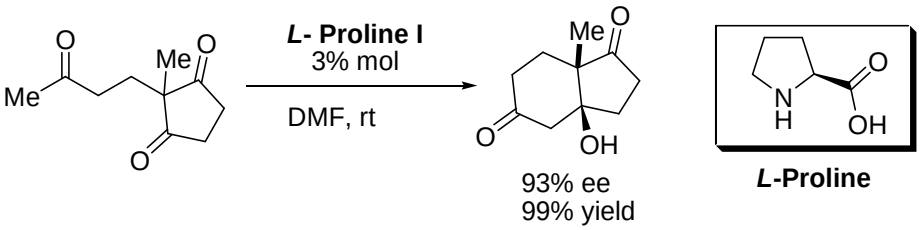
1.2. Asymmetric Organocatalysis

The miles stone of the organocatalysis was laid in 1971 when the research group of Hajos Parrish Wiechert, Eder, and Sauer published the first intramolecular aldol reaction catalyzed by *L*-Proline (Scheme **1**).[7]

Scheme 1:



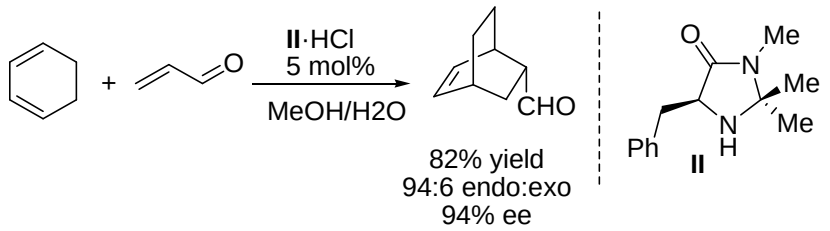
Today seems strange that, apart from few sporadic publications, it is only in 2000 that the chemical community recognized the opportunity to use chiral organic molecules as catalysts in stereoselective processes.

As mentioned in previous paragraph, following the general excitement of the scientific panorama around the asymmetric catalysis at the end of the last century, in the early 2000 two research groups published independently the organocatalytic activation of aldehydes for their α and β functionalization, mediated by chiral secondary amines (Scheme **2**).[8, 9]

Scheme 2: *Enamine and Iminium ion activation of carbonyl compounds*

a

b



List, Lerner and Barbas reported for the first time the organocatalyzed aldol reaction between acetone and a wide range of aldehydes (Scheme **2a**). The activation of this unmodified ketone occur via HOMO-raising (through the formation of an enamine) through *L*-Proline

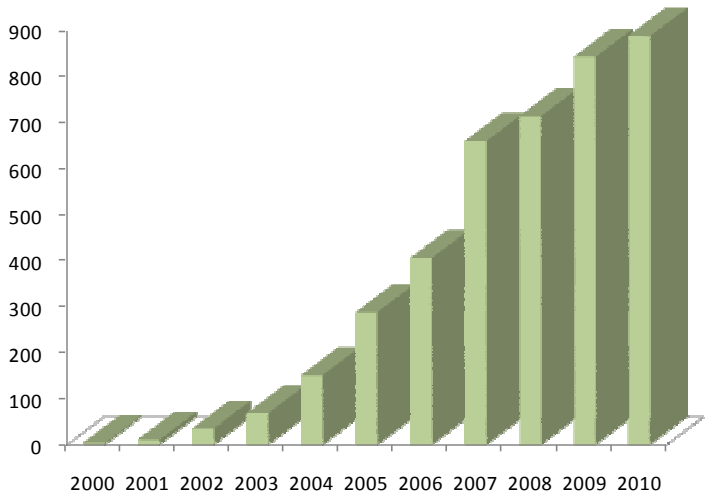
condensation. This simple amino acid also direct selectively the approach of the electrophile to only one face of the nucleophilic intermediate; the action mechanism of Proline fascinated numerous chemist, and from my point of view the most faschinating (sorry) and elegant description of it was made by Jacobsen Movassaghi that named Proline the simplest enzyme.[10]

In Scheme **2b** is described a complementary organocatalytic approach for the activation of α,β-unsaturated aldehydes via LUMO-lowering of this substrates. MacMillan Ahrendt and Borths developed the first Diels-Alder reaction of acroleins, designing *ad hoc* a new catalyst **II** easily prepared from (*L*)-Phenylalanine. This secondary amine is able to activate the substrate generating an iminium ion intermediate via condensation with the starting material.

In this way a great scientific competition, nowadays described as *"Asymmetric Aminocatalysis Gold Rush",*[11] started with the aim of expand the general scope of this two activation mode.

This challenge gave a tremendous impulse to the design of other organocatalytic kinds of activation founded upon Chiral Brønsted Base, Brønsted Acid, H-Bond donors, Phase transfer Catalyst and Carbenes Thus in this years the organocatalysis gained the attention of the scientific community (Figure **1**).

Figure 1: *Number of articles published on Organocatalysis (Source SciFinder Scolar)*



As demonstrated by this statistic (made just typing the term Organocatalysis in SciFinder Scholar) this strategy has become a complementary tool to the catalysis through Lewis acid and transition metal complex.

In the follow chapters will be described the result obtained during my Phd, in particular in the field of aminocatalysis, thus a brief introduction will be done to explain the state of art and the problems of this kind of activation.

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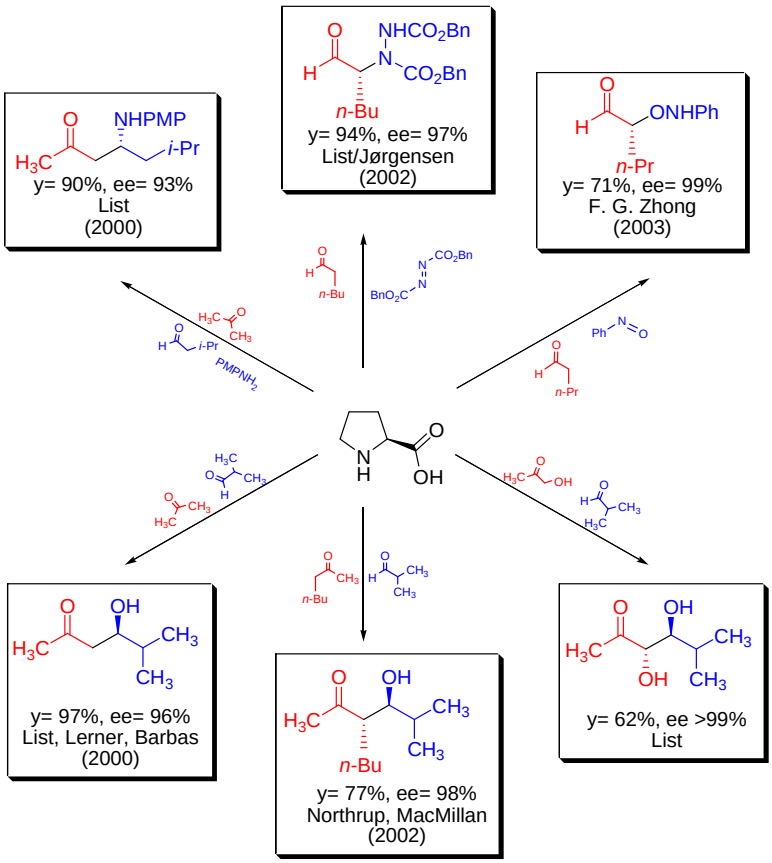
1.3. Asymmetric Aminocatalysis

The pioneristic works of List, Lerner and Barbas and MacMillan Ahrendt and Borths, besides offering asymmetric and catalytic alternative methodologies for two fundamental C-C bond forming reaction, constituted the basis for two novel organocatalytic activation modes of carbonyl compounds, pinpointing the origin of asymmetric aminocatalysis. In fact afterwards it was understood that it was possible to design an unlimited number of new reactions just using various electrophiles and nucleophiles for the functionalization of saturated ketones, aldehydes and enals. As consequence of this philosophy List reported the first, direct, catalytic and asymmetric Mannich reaction between an aldehyde, *p*-anisidine and a ketone, catalyzed by Proline.[12]

In Figure **1** it is represented a summary of the reaction catalyzed by (*L*)-Proline published in the last decades.

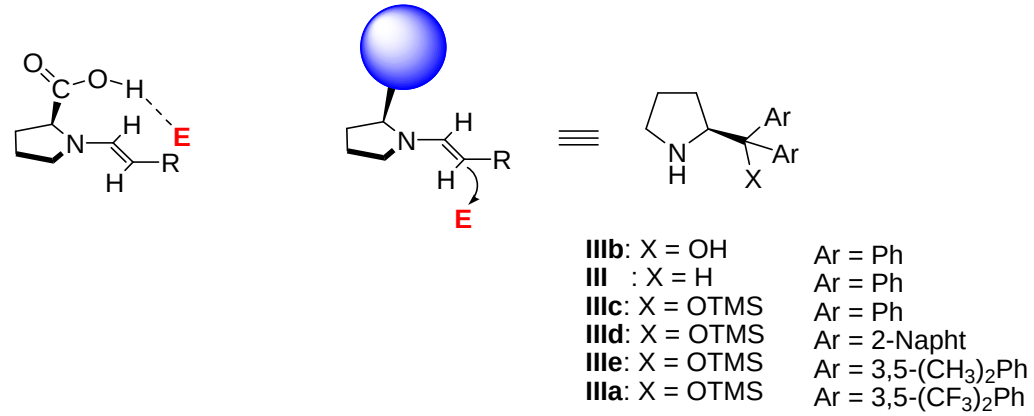


In addition to Proline several catalysts were developed with the aim of solve some problems pointed out in its employ, as poor stereoselectivity with substrates with low aptitude to form H-bonding interactions. In this context, in early 2005, Jørgensen's research group presented to the scientific community a new class of secondary amine organocatalysts, derived from

Diphenyl prolinol,[13] able to control the attack-face of the enamine through its steric hindrance (Scheme **2a**).

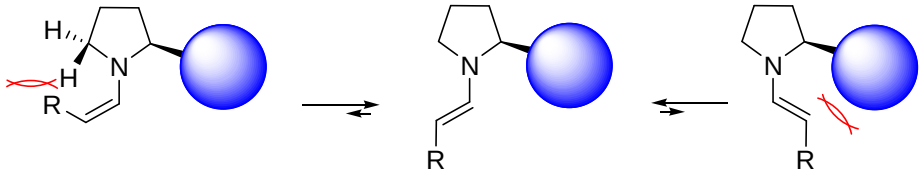
Scheme 1: Comparison between the enantioselection mechanism of *L-Proline and Jørgensen's catalyst*

a)



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

b)



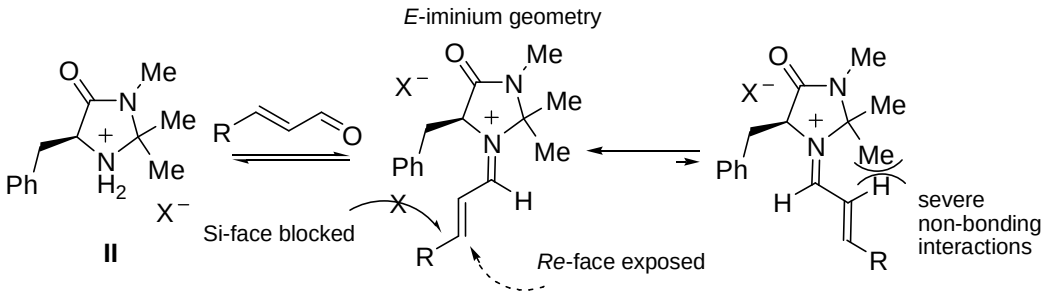
At the same time the enamine geometry is fixed as consequence of the non bonding interaction between the bulky substituent on the pirrolidine ring and the reactive carbon (E-*anti* geometry of the enamine, Scheme **1b**).[14]

It is important to notice that the mechanism of enatio-discrimination did not rely upon the structure of the electrophile. For this reason this catalyst was alredy use for the α-functionalizzation of aldehydes in several asymmetric substitution reactions and nucleophilic additions, for example conjugate additions,[2, 15] Mannich reactions,[2] C-N (α-amination[2] and oxyamination[16]), C-C[17] and C-O bond-forming reactions,[18] as well as α-halogenation, selenenylation[19] and phosphination[20] reactions.

On the other bank, also the iminim ion activation demonstrated to be a general activation not anly confined to DA or [3+2] reactions.[21]

The MacMillan's imiladazolidinone **II** controlled the stereochemical outcome of the reaction in the same way of Jørgensen's catalyst (Scheme **2**) and also in this case it was possible to extend this methodology to the most disparate nucleophile.[22]

Scheme 2: *Iminium ion geometry control and π-facial shielding by imidazolidinone catalyst* ***II***



Several catalysts based upon this strategy of stereoselection were developed by MacMillan and coworkers, making possible the activation of the α,β-unsaturated ketones too.[23]

Moreover the similitude between chiral amine **II** and **III** was easily understood in the meaning of the possibility to use Jørgensen's catalyst in iminium ion activation of aldehydes,[13-16] and MacMillan's Imidazolidinone in the α-functionalizzation of enals.[28]

The Asymmetric Aminocatalysis, as demonstrated in this chapter, have been dominated by three privileged organocatalysts: Proline, the simplest enzyme, MacMillan's Imidazolidinone and Jørgensen's catalyst.

1.3.1. ASYMMETRIC ORGANOCATALYTIC CASCADE REACTIONS

"The circle symbolizes T'ai Chi
which is formless and above duality.
Here it is manifesting itself as the progenitor of the universe.
It is divided into yin (the dark) and yang (the light)
which signify the negative and positive poles.
Pairs of opposites, passive and active,
female and male, moon and sun."

Franco Battiato
Il Ballo del Potere

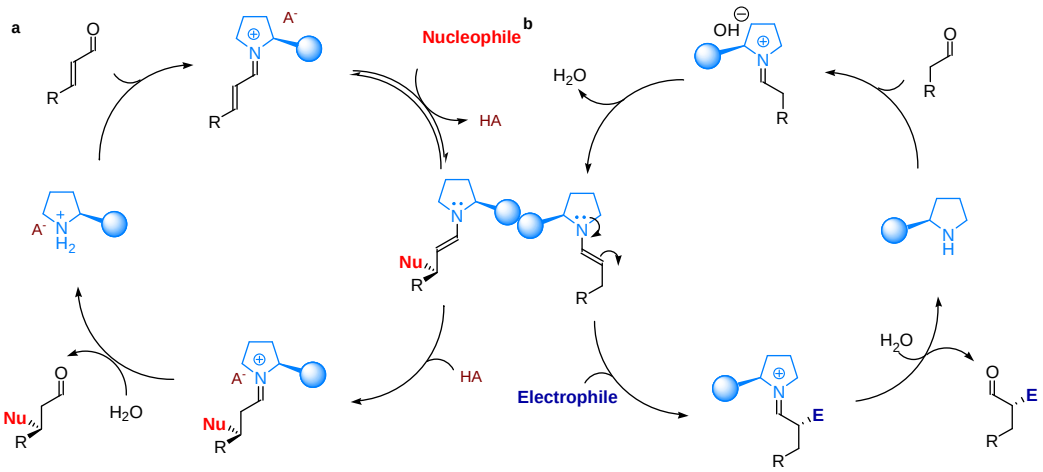
After this initial stage aminocatalisys have started to take different directions always exploiting its fundamentals concepts that can be summarized in LUMO-lowering and, more useful for further explorations, HOMO raising activations. In this chapter will be discussed the origins of the Aminocatalytic Tandem reactions and the origins of the Asymmetric Counter Anion Directed Catalysis two of the most interesting fields of amminocatalysis.

The comprehension that the face-shielding catalysts gave the possibility to activate without distinction α,β-unsaturated and saturated aldehydes and the knowledge accumulated on the mechanism of iminium ion and enamine catalysis, drove to the design of amino-catalyzed Domino Reactions. This important goal was achieved thanks also to the observation that in the two catalytic cycles there are common intermediate.

Observing the LUMO-lowering activation (Scheme **3a**) we can see that, as consequence of the addition of the nucleophile to the iminium ion, an enamine is formed. After its protonation and hydrolysis this nucleophilic intermediate furnishes the β-functionalized product.

In HOMO-raising activation (Scheme **3b**) an enamine intermediate is formed through the deprotonation of an iminium-ion. The reactive enamine generated intercepts an electrophile thus forming a functionalized iminium species which affords, after hydrolysis the α-functionalized product.

Scheme 3: *Catalytic cycles of LUMO-lowering HOMO-raising activation.*

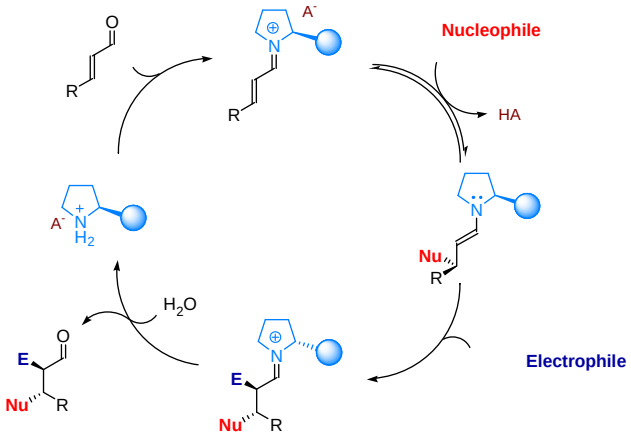


This concepts and the significance of its application are well explained in this sentence:

"Like the ying and yang, the two catalytic intermediates are opposite, yet interdependent, and they consume and support each other".[29]

As well described in this review and in two independently works appeared in **2005**, developing this idea it is possible to design a tandem organocascade sequence where an α,β-unsaturated aldehyde is activated via iminium ion for the stereoselective attack of a nucleophile leading to an enamine formation. This intermediate at this point can intercepts an electrophile (H^+ is the simplest one) present in the system and drives to the formation of the α,β-functionalized product (Scheme **4**).

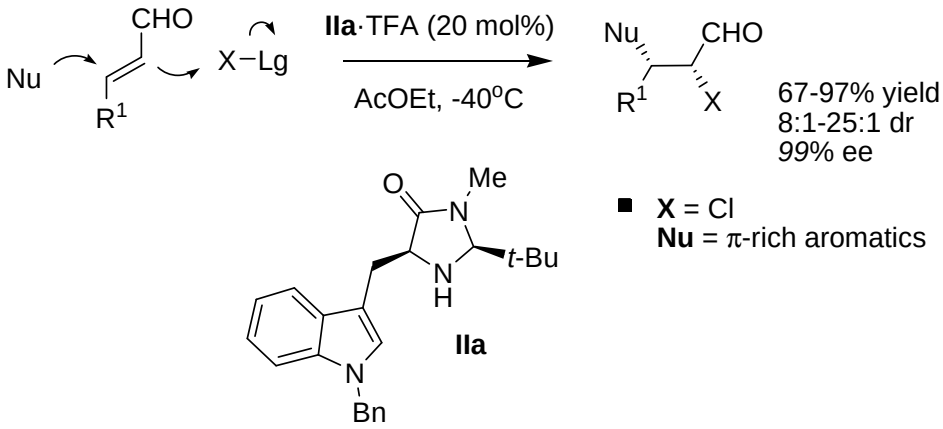
Scheme 4: *Catalytic cycle for the Tandem Organocascade reaction.*



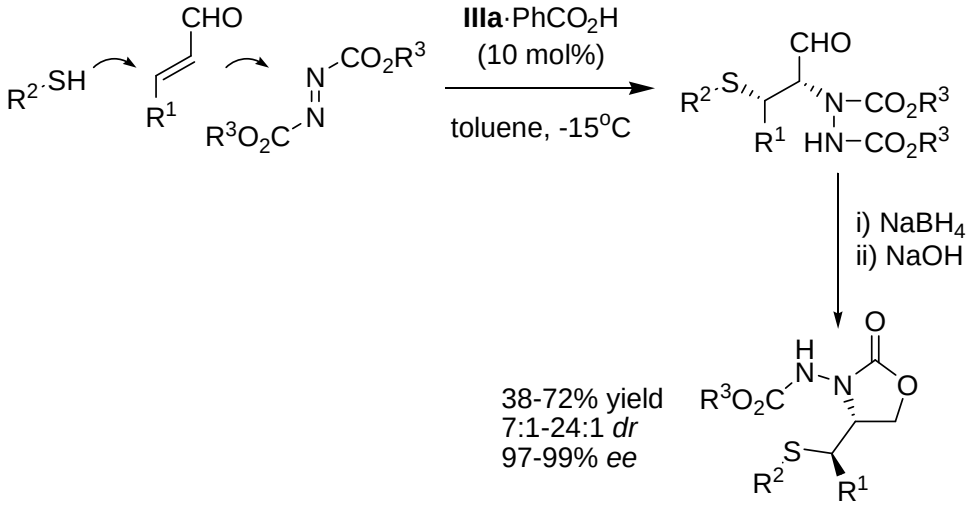
Despite some excellent intramolecular tandem reactions had been realized, for example the cyclopropanation[30] and epoxidation,[31] the complete success of this strategy was associate with the two intermolecular protocols reported in Scheme **5**.

Scheme 5: *Tandem Organocascade reactions presented by the MacMillan's and Jørgensen's groups.*

a)



b)

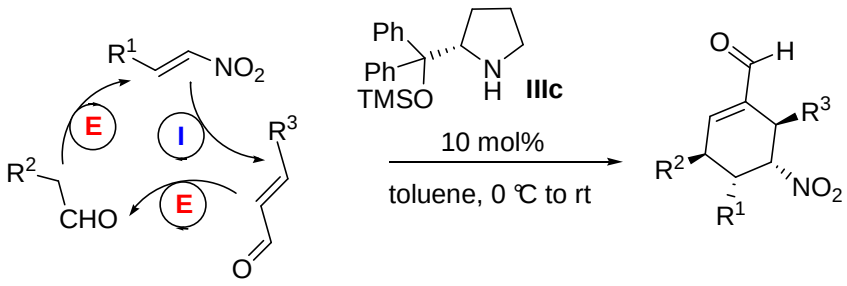


In Scheme **5a** it was reported Michael/Chlorination tandem reaction of α,β-unsaturated aldehydes developed by MacMillan *et al.* In this reaction a new kind of imidazolidinone where the face-shielding is ensured by an indolyl moiety[32]was introduced.

At the same time Jørgensen presented the first sulfa/Ammination domino strategy for the functionalization of enals, catalyzed by *O*-TMS DiArylProlinol Ether (Scheme **5b**).[33]

Since these two examples tandem reactions have been reported, 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* activation able to forge and to control completely four stereocenters in a one-pot process through a Michael/Michael/aldol condensation sequence catalyzed by O-TMS diphenyl catalyst **IIIc** (Scheme **7**).[34]



This triple organocascade was composed by three reactions that were activated time-selectively by the chiral amine catalyst. This synthetic protocol could be applied to other Michael acceptors in place of nitrostyrene.[35]

1.3.2. ASYMMETRIC COUNTER ANION DIRECTED CATALYSIS (ACDC)

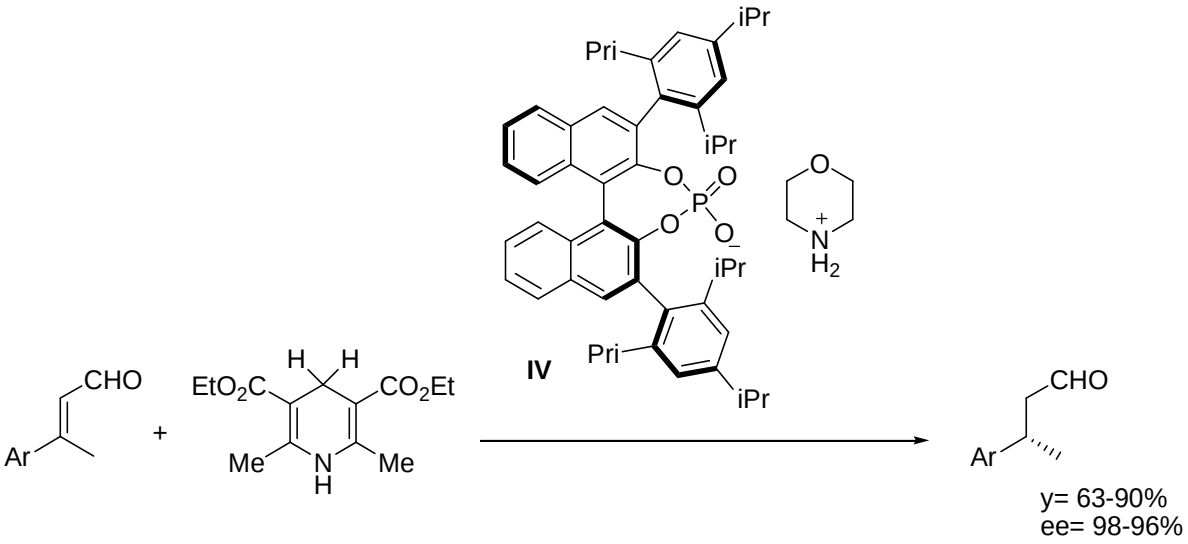
La ricerca scientifica consiste nel vedere ciò che tutti vedono,
ma nel pensare ciò che nessuno ha ancora pensato

Anonimo

In the activation of carbonyl compounds via iminium ion or enamine we can observe often the presence of catalytic amount of an acidic additive. The role of this additive has not been completely clarified and might be not the same in all the reactions. By the analysis of the empiric results it is possible to observe that acids are able to increase the rate of the overall catalytic processes by accelerating the formation and the hydrolysis of reaction intermediates.
Moreover in the LUMO-Lowering activation the characteristic of the counter anion have a direct effect on the stereoselection of the reaction; this is a consequence of the cationic nature of iminium ion, the active intermediate of the process. These concepts have been exploited for the first time by Mayer and List which reported an asymmetric transfer hydrogenation of β,β^{I}-disubstituted enals. The authors introduced for the first time the ACDC *Asymmetric Counteranion Directed Catalysis*.

The new catalytic salt designed by the authors was the combination of morpholine for the activation of the substrates through iminium ion formation and the chiral phosphoric acid **IV** for directing the stereoselction of the reaction (Scheme **7**).[36]

Scheme 7: *Asymmetric Counteranion Directed Catalysis*



The great results obtained in terms of enantiomeric excess confirmed that during the attack of the active nucleophile to the intermediate, (the stereoselction determining step), the counteranion was close to the iminium ion.

Continuing to study this phenomena List *et al.* minded to use a catalytic salt made with double chirality both in amine and in the counteranion. This strategy will be discussed in the next chapter in the context of primary amine catalysis.

1.3.3. PRIMARY AMINE CATALYSIS

"..dove la Natura finisce di produrre le sue spezie
, l'uomo quivi comincia con le cose naturali,
con l'aiutoro di essa Natura, a creare infinite spezie.."

"…where Nature finishes producing its species
, there man begins with natural things to make,
with the aid of this Nature, an infinite number of species…"

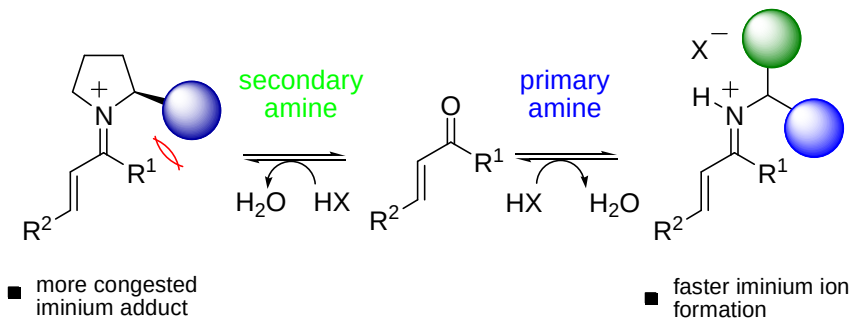
Leonardo da Vinci

The asymmetric Aminocatalysis has been developed thanks to the discover of some privileged catalysts. This chiral amine are named privileged because are general toward a wide range of nucleophiles or electrophiles. In fact several protocol for the functionalizzation of α,β-unsaturated and saturated aldehydes appear in this decade. Moreover another strong point of this catalysts is that are easily available like *L*-Proline (less than 1€/1g.), or are synthesizable from natural amino acids in few steps.

Despite the great evolution of the aminocatalysis, the activation of α,β-unsaturated ketones has remained an elusive transformation until 2006.

The reasons of the little progress in this field probably is the inherent difficulties of generating congested covalent iminium ion intermediate from ketone and privileged chiral secondary amine (Figure **2**).

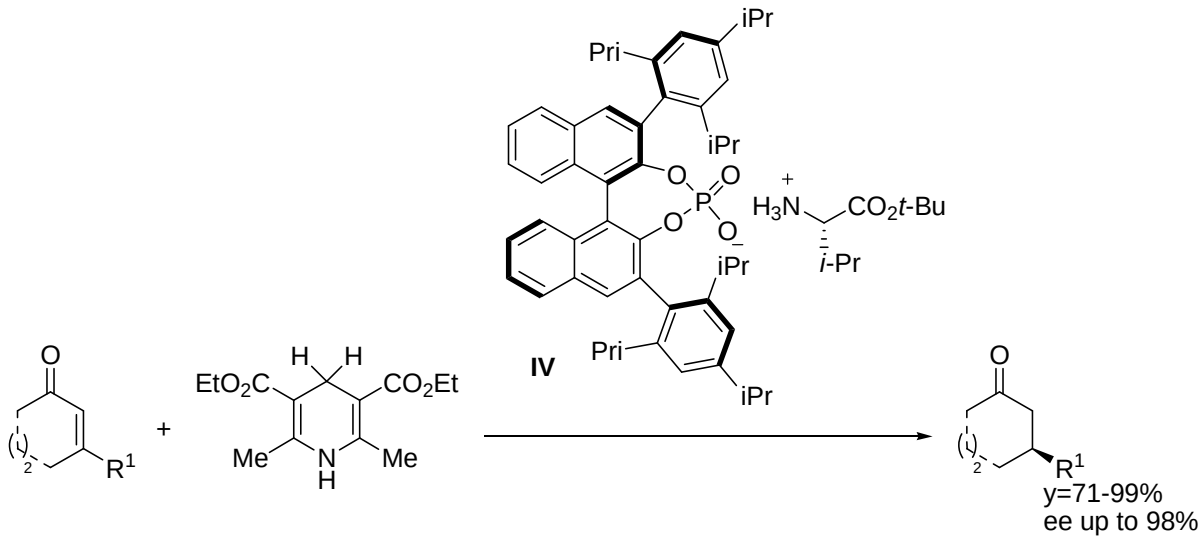
***Figure 2**: Steric factors in iminium ion activation of α,β-unsaturated ketones.*



In 2006 some reports have shown the ability of chiral primary amine derivatives to efficiently activate ketones.[37] In fact primary amine catalyst, owing to reduced steric constraints offer the unique possibility to activate more encumbered substrates overcoming the limitations of chiral secondary amines.[38]

Following some seminal reports on the Michael addition of simple ketones to nitrostyrenes via enamine intermediate, where it was described the activation of the carbonylic substrates by a primary amine thiourea catalyst, our and other few groups introduced the use of primary amines for the activation of enones (Scheme **8**).

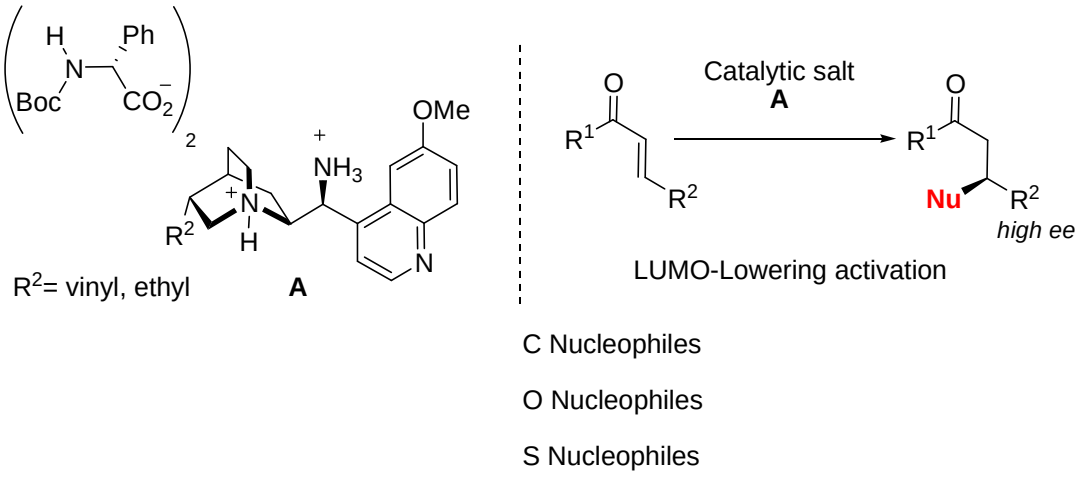
Scheme 8: *Development of the ACDC: enantioselective transfer hydrogenation of α,a-unsaturated ketones*



In the previous scheme is briefly describe the enantioselective transfer hydrogenation of α,β-unsaturated ketones activated by a catalytic salt formed by a chiarl primary α-aminoacid ester and a chiral phosphoric acid.[39] This methodology allowed to the products formation in high yield and high enatiomeric excess; it is important to notice how the combination between the two chiral entities had dramatically effect on the stereoselection of the reaction. Using *L*-Aminoacid ester and *R*-TRIP (matched pair) it is performeded the reduction of 3-Methyl Cyclohexenone with 94% of enantiomeric excess and good yield, in the other case, using *L*-Aminoacid ester and *S*-TRIP (mismatched pair), it is obtained the product in lower yield and as racemic mixture.

In this context, our group, independently from other two different research groups,[40, 41] has established a new chiral primary amines directly derived from natural cinchona alkaloids, as highly efficient catalysts for iminium ion activation of enones (Figure **3**).

Figure 3: *Primary amine based on cinchona alkaloid structure as catalyst for LUMO-lowering activation of α,β-unsaturated ketones.*



The catalytic salt reported in figure **3** were formed by 9-amino-9-deoxy-*Epi*-Quinine (or 9-amino-9-deoxy-*Epi*-HydroQuinine), synthesized in one step from Quinine or Hydro-Quinine, and a chiral *N*-Boc aminoacid. In analogy with the List's report we observed a moderate influence on the stereoselectivity due the combinations of two chiral entities.

In the following chapter will be discussed my Phd results, most of them are focused on the use of primary amine in aminocatalysis for the activation of encumbered carbonylic compounds.

During these last years the primary amine **A**, thanks to the efforts of some research groups, has become a general catalyst for the functionalization of sterically demanding substrates, thus it gained the appellative of privileged catalyst.

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2. DISCUSSION

Un uomo che coltiva il suo giardino, come voleva Voltaire.

Chi è contento che sulla terra esista la musica.

Chi scopre con piacere una etimologia.

Due impiegati che in un caffè del Sud giocano in silenzio agli scacchi.

Il ceramista che intuisce un colore e una forma.

Il tipografo che compone bene questa pagina che forse non gli piace.

Una donna e un uomo che leggono le terzine finali di un certo canto.

Chi accarezza un animale addormentato.

Chi giustifica o vuole giustificare un male che gli hanno fatto.

Chi è contento che sulla terra ci sia Stevenson.

Chi preferisce che abbiano ragione gli altri.

Tali persone, che si ignorano, stanno salvando il mondo.

"I giusti". Jorge Luis Borges

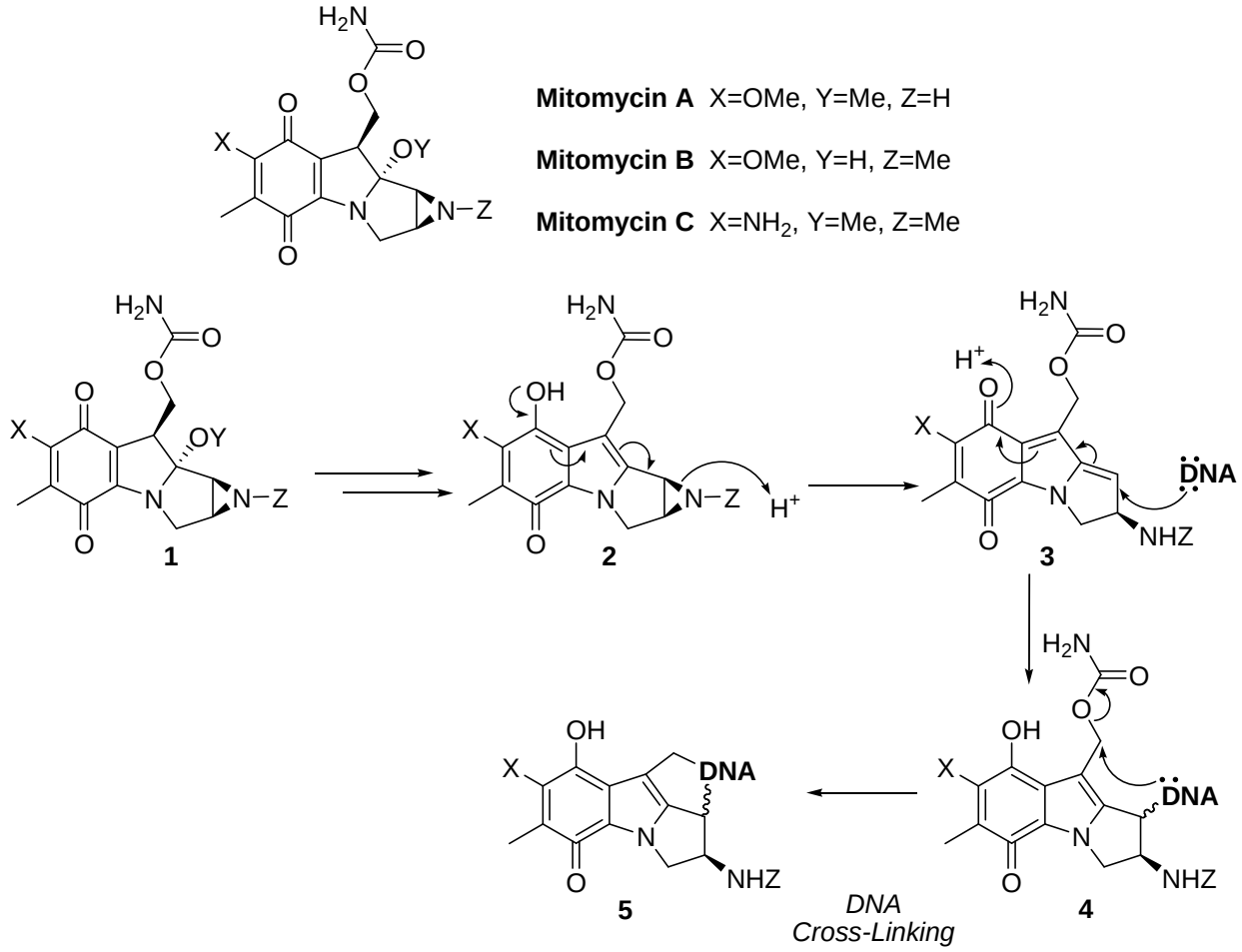
2.1 CHALLENGES

2.1.1. Asymmetric aziridination of α,β-usatured ketones

Discussion

Aziridines are three membered heterocycles containing a nitrogen atom. This class of compounds is present as a structural motif in a wide variety of strongly biological active molecules. Natural Mitomicyn A, B, and C represent an important family of antitumor and antibiotic agents. Through a structure-activity relationship is possible identify the aziridine ring as being essential for such antitumour activity (Figure **1**).[42]

Figure 1*: Family of Mitomycins and its mode of action*

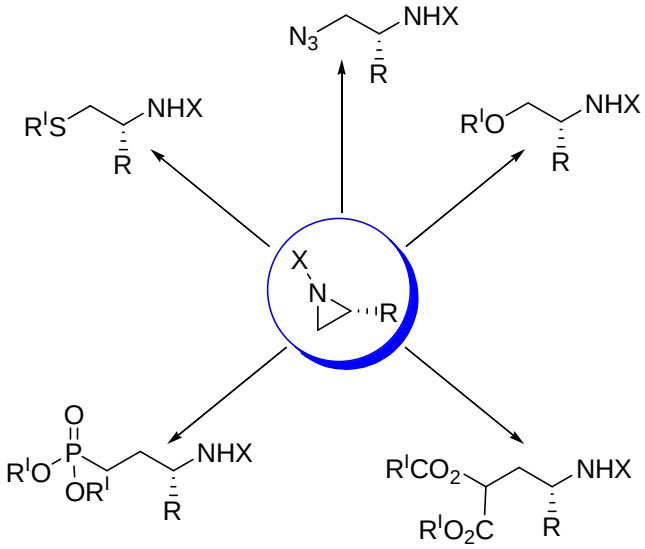


In figure **1** is represented the mode of action of Mitomicin.[43] In the first step of the postulated mechanism, the natural products are converted from native quinone form to the hydroquinone one. The DNA alkylation occurs thanks to the formation of the elettrophilic intermediate **3**, generated by mean of aziridine ring-opening process. The intramolecular

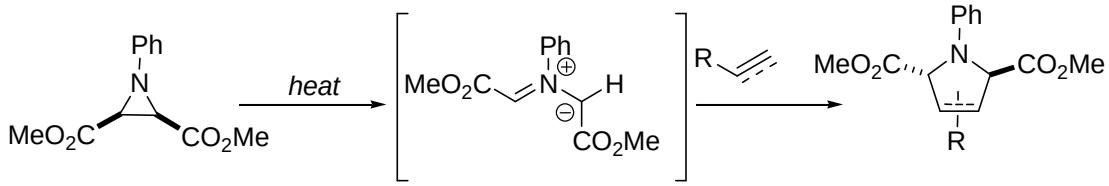
nucleophilic substitution with the elimination of the carbamate leads to DNA cross-link blocking its replication. This kind of activity is also observed in synthetic compound bearing the aziridine moiety increasing the interest in this class of heterocycles. Moreover since their discovery, aziridines have attracted the attention as starting material. Transformations of this stable but strain-loaded (27 kcal·mol^{-1}) ring allow for regio- and stereoselective installation of a wide range of functional groups in a 1,2-relationship to nitrogen (Scheme **1a**), while cicloaddition of N protected aziridines with various substrates furnish complex heteroclyclic system (Scheme **1b**).[44]

Scheme 1: *Principal reaction of aziridines*

a)



b)

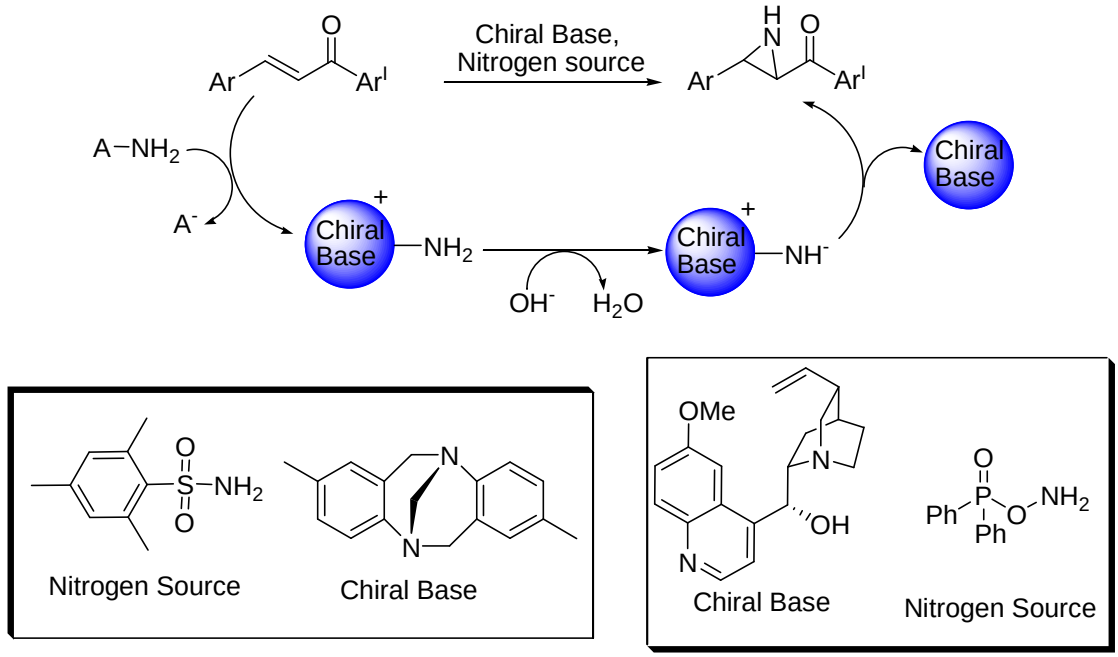


For these reasons the development of novel efficient methodologies for the stereoselective preparation of chiral aziridines is an important synthetic target.[45]

The catalytic asymmetric aziridinations of olefins provide a direct and useful access to such privileged scaffold, and great efforts and progress have been made in this field using almost exclusively transition metal complex.[46] The principal methodologies are the nitrene transfer to olefins and addition of metallocarbenes to imines, however a general and highly stereoselective aziridination of simple α,β-unsaturated enones is still lacking. In fact asymmetric aziridinations of enones have severe restrictions in scope, as only chalcones are suitable substrates: metal-based systems can provide highly enantioenriched compounds protected as N-tosyl derivatives, a protecting group that can prove difficult to remove.

Whereas two ingenious organocatalytic entries to non-protected aziridines, showing moderate enantioselectivity (up to 67% ee), were recently reported based on the use of chiral tertiary amines (Figure **2**).[47]

Figure 2: *Organocatalytic aziridination of calcones through the formation of N-N ylides*



Shi protocol *Armstrong protocol*

Both of them are based on the concept that an aminide, formed from a tertiary or secondary amine and a primary amide derived from sulfonic or phosphoric acid, can directly iminate chalcones giving aziridines, through the formation of an N-N ylide in presence of an inorganic base.

In this context we minded to apply our knowledge in the primary amine organocatalisys for address to this problem.

Recently, the spectacular advances achieved in the field of chiral secondary amine catalysis[6] have set the conditions for the development of an highly chemo- and stereoselective aziridination of α,β-unsaturated aldehydes.[48] Central to the success of this approach was the ability of the organocatalyst to integrate orthogonal activation modes (iminium ion and enamine catalysis) into a more elaborate reaction sequence,[49] thus promoting first the nucleophilic addition of a N-centered nucleophile followed by an intramolecular cyclization. On the other hand the use of a primary amine catalyst offer the unique possibility to activate efficiently enones and other classes of encumber carbonyl compounds, overcoming the inherent difficulties of chiral secondary amines.[50]

With this in mind we envisaged that the catalytic salt **A** formed from 9-*Epi*-HQ-NH_2 and the (*D) N*-Boc Phenylglycine could promoted the aziridination reaction. As previously described the primary amine might activate, thanks to its reduced steric hindrance, the α,β-unsaturated ketones, while the chiral counter anion offer the possibility to enhance the steroinduction of the reaction.[51] In the first study of this project we started to evaluate the conjugate addition of N-centered nucleophile to α,β-usatured ketones.[52] We focused on the use of the commercially available N-protected hydroxylamines **7** as the nucleophilic components, activating the α,β-usautured ketones toward a domino Michael addition-intramolecular aldol sequence.[53] This strategy leads to 5-hydroxyisoxazolidines **8**, useful chiral scaffolds,[54] 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 (Cbz to Boc or CO_2Et) 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.

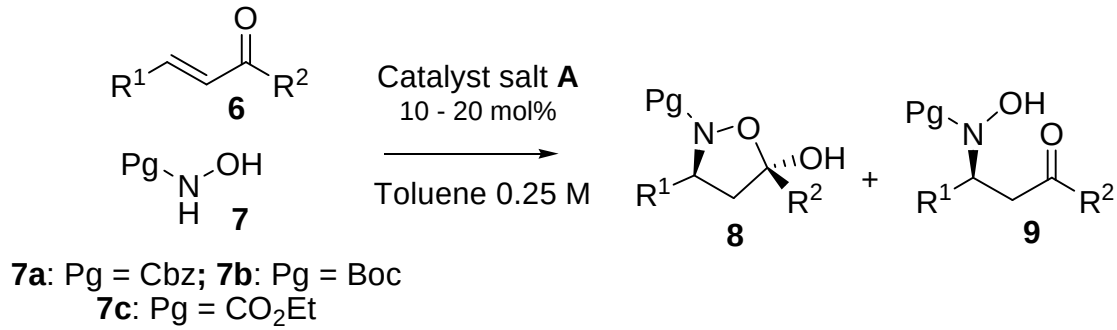


Table 1: *Scope of the enantioselective amine conjugate addition to enones.*[a]

Entry	7	R^1	R^2	T (° C), h	8:9[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_2Et	Me	30, 72	5.5:1	65	95
9	**a**	*c*-hexyl		0, 40	0:100	85	95

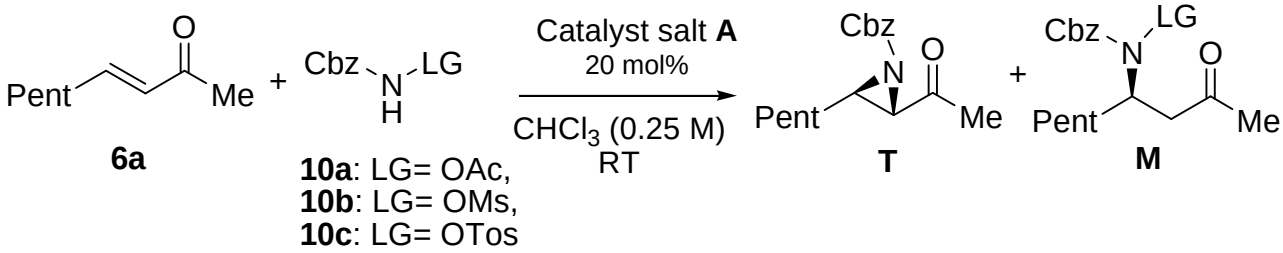
[a] Reactions carried out on a 0.2 mmol scale with 1.2 equiv of **7** and 10 mol% of the catalyst salt **A**, unless noted. [b] Determined by ^{1}H NMR analysis. [c] Overall isolated yield (sum of **8** and **9**). [d] Determined by chiral HPLC analysis. [e] 20 mol% of the catalyst

It Is important to notice that the reaction products are constituted from two forms at the equilibrium: the tandem and the conjugate addition products **8** and **9** rispectively. The relative amount of this two compounds at room temperature is strongly dependent on the electronic as well as the steric contribution of the R^2 enone substituents. Studies for the protection of the hydroxy group of **8** with the aim of *freeze* this equilibrium are currently on going.

Having demonstrated the ability of salt **A** to promote a highly enantioselective amine addition to enones, we moved toward the principal aim of our investigations, the development of a

domino conjugate-cyclization sequence, leading to chiral aziridines. From the outset, we recognized the choice of the nitrogen-atom source as the crucial parameter for developing an efficient aziridination methodology. During the reaction it should change its polarity and first act as nucleophile and attack the iminium ion in 4 position and at a later stage become electrophilic facilitating the enamine-catalyzed cyclization step. We started our investigation by reacting enone **6a** using as nitrogen source the O-Acyl N-protected hydrolamine **10a** that was successfully employed in the aziridination of enals under secondary amine catalysis by Cordova *et al*. As highlighted in Table **2** the reaction provided only the conjugate addition product (entry 1).

Table 2: *Optimization of the Nitrogen source*

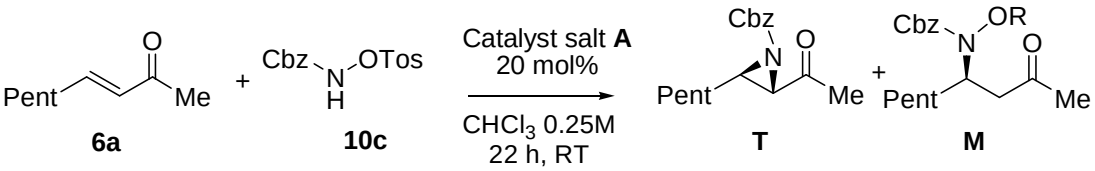


Entry	10	LG	Conv %	T:M	d.r.	ee
1	a	OAc	21	1:99	-	77
2	b	OMs	67	1.1:1	-	86
3	c	OTos	78	4.3:1	4:1	81

Gratifyingly, the installation of a better leaving group such as a tosylate (**10c**, entry 3) allowed to selectively partition the reaction manifold toward the tandem sequence, leading to the desired aziridine **T** as the major product.

Further optimization of the standard reaction parameters (Table **3)** revealed that the solvent choice (compare entries 1-4), the reagent concentration and the stoichiometric ratio of the reagents (entry 5) were important factors to improve the efficiency and generality of the catalytic system. After this studies the enantioselectivity was increased up to *ee*= 95% and d.r= 9/1 but the conversion in the aziridine adduct was yet not so high conv= 56% **T**/**M=** 9:1. Finally, we envisaged that the *p*-toluenesulfonic acid, generated during the enamine-induced ring closing step when using **10c**, may affect the activity of the catalyst. We reasoned that the presence of an inorganic base could have a beneficial effect on both the reaction rate and the selectivity of the aziridination.[55]

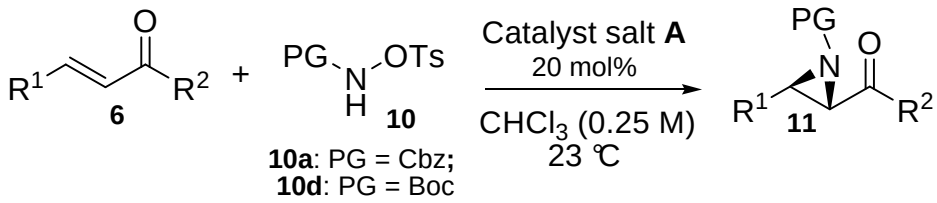
Table 3: Study of the effect of an external basic additive



Entry	solvent	additive	Conv %	T:M	d.r.	ee
1	$CHCl_3$ 0,25M	-	56	9:1	9:1	95
2	$CHCl_3$ 0,25M	K_2CO_3	<10	>99:1	-	-
3	$CHCl_3$ 0,25M	$NaHCO_{3\,(aq)}$	45	>99:1	>19:1	80
4	$CHCl_3$ 0,25M	$NaHCO_{3\,(s)}$	>95	>99:1	19:1	96

Carrying out the aziridination in $CHCl_3$ 0.25 M using 1.2 equiv of **10c** and 2 equiv of solid $NaHCO_3$ induced higher chemo-, diastereo- and enantio-selectivity (entry **4**), and these catalytic conditions were selected for further explorations in order to expand the scope of this transformation. With this condition in hands we analyzed the scope of the aziridination of α,β-unsaturated ketones.

Table 4. Asymmetric organocatalytic aziridination of enones.[a]



Entry	R^1	R^2	PG	11	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

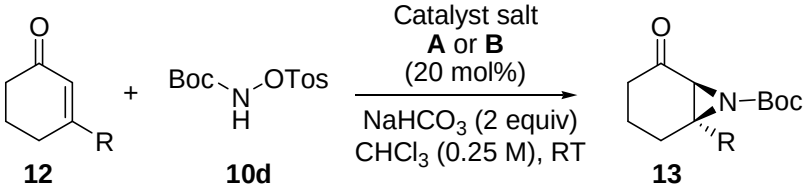
[a]The reactions were carried out on a 0.2 mmol scale with 1.2 equiv of **8** and 20 mol% of the catalyst salt combination **A** at room temperature in $CHCl_3$ 0.25 M . [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Determined by chiral HPLC analysis. [e] 5 mol% of the catalyst salt **A** was employed. [f] The absolute configuration of **8g** 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.

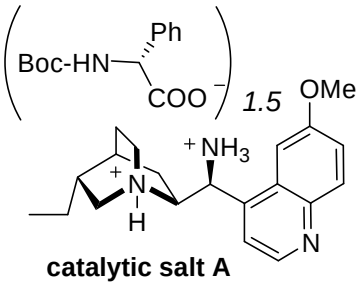
A wide range of *N*-Cbz as well as *N*-Boc ketoaziridines **11** could be obtained in good yield and with high levels of both enantio- and diastereo-selectivity. Increasing the reaction time, it was also possible to decrease the catalyst loading to 5 mol%, keeping the efficiency of the system. Importantly, different sterically and electronically substitutents on the ketonic substrates are well tolerate, enabling access to a broad variety of both aliphatic and aromatic aziridines. With further optimization was also possible extend this procedure to the functionalization of cyclic hexenones. In fact changing the hydroxylamine protecting group, form Cbz to Boc, and setting the reaction stoichiometry (1.2 equiv of ketone) we synthesized a small library of cyclic keto-aziridines obtaining both the antipodes of the products just using the pseudoenantiomeric

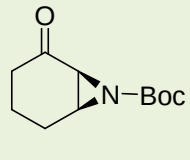
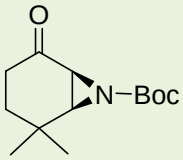
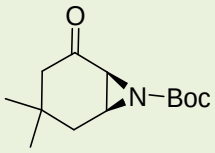
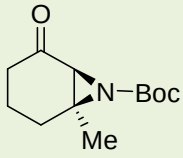
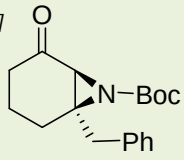
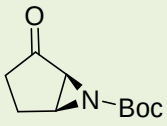
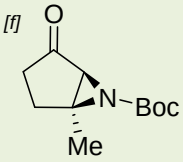
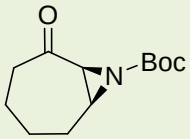
form of the catalyst salt (Table **5**). This catalyst is made from 9-*epi*-NH_2-HQD and (*L)* N-Boc Phenylglycine (catalyst salt **B**). When we used the mismatched combinations (9-*epi*-NH_2-HQ + (*L)* N-Boc Phenylglycine and 9-*epi*-NH_2-HQD and (*D)* N-Boc Phenylglycine) we observed lower reactivity and slightly decrease enantioselectivity (88% ee *vs.* 92% ee) in the reaction of 3-Methyl 2-cyclohexanone and N Boc O tosyl hydroxylamine.[56]

In table **5** is reported the scope of the aziridination of cyclic enones developed by us.

Table 5. Scope of the aziridination of cyclic enones.[a], [b], [c]





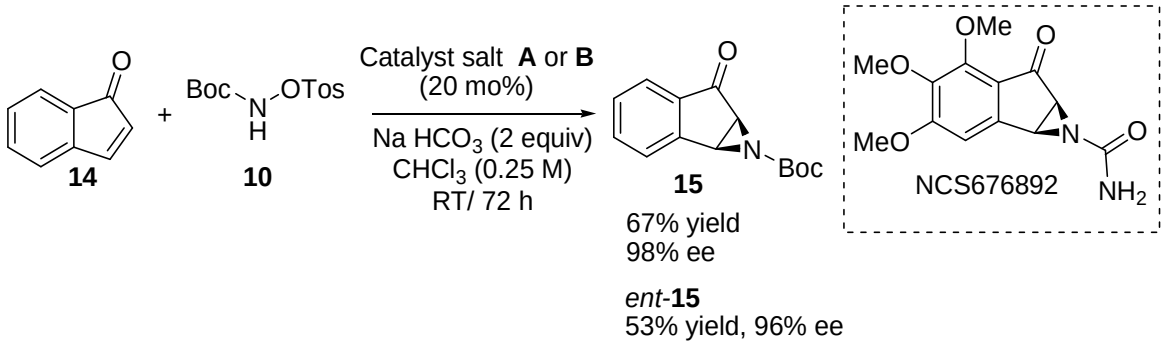
			
13	**13a**	**13b**	**13c**
y= 73% (51)[d]	y= 84%	y= 33%	y= 75%
ee= 99% (99)[d]	ee= 98%	ee= 98%	ee= 92%
***ent* 13** y= 76%	***ent* 13a** y= 84%	***ent* 13b** y= 53%	***ent* 13c** y= 88%
ee= 99%	ee= 98%	ee= 98%	ee= 86%
[e] 		[f] 	
13d	**13e**	**13f**	**13g**
y= 93%	y= 39%	y= 52%	y= 90%
ee= 95%	ee= 93%	ee= 85%	ee= 98%
***ent* 13d** y= 85%	***ent* 13e** y= 44%	***ent* 13f** y= 68%	***ent* 13g** y= 98%
ee= 93%	ee= 97%	ee= 61%	ee= 94%

[a] A single diastereoisomer has always been detected by 1H NMR spectroscopicanalysis of the crude mixture. Reactions carried out at room temperature for 24 h using 1.2 equiv of enone **12** on a 0.2 mmol scale. [b] Yield of isolated product. [c] ee of **13** 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.

In addition cyclopentanone and cyclohepanone could be converted into the correspondent *N*-Boc protected aziridines with good yield and very high stereoselectivity. Moreover it is possible to activate 3 substitued cyclic enones leading to the formation of a quaternary stereocenter adjacent a tertiary one. Notably, all this product are obtained as single distereoisomer and increasing the reaction time, it is also possible to decrease the catalyst loading up to 10%. The relative and absolute configurations of aziridines **13d**, **13e**, and **13h** were assigned by NMR NOE spectroscopic analyses and by means of time-dependent (TD) DFT calculations of the electronic circular dichroism (ECD) spectra, as described in the experimental part.

Finally, we explored the possibility of extending the aziridination method to indenone derivative **4**, a challenging compound that has never served before as a suitable substrate for iminium catalysis due to the severe steric hindrance which hampers the condensation with the catalyst. Optimizing the reaction time in order to overcome the low reactivity of this compound is possible to prepare both the antipodes of the corresponding tricyclic aziridine derivative **15** with good chemical yield and very high enantioselectivity (Scheme **2**).

Scheme 2. aziridination of 1H-inden-1-one



Extension to such a compound class opens up new opportunities to prepare in a stereoselective manner complex chiral molecules that possess an indane moiety, a framework that is found in a large number of bioactive and pharmaceutically important molecules.[57] NSC676892[14b] is only one example of the potentially bioactive tricyclic, aziridine-containing heterocycle that may be synthesized by using the present method.

In summary, in this part of my Phd thesis are described the studies on the aza-Michael reaction and on asymmetric aziridination of α,β-usatured ketones illustrating the increasing utility gained by chiral primary amine catalysis in the realm of asymmetric synthesis.

The reported protocols that use easily available reagents and catalysts establish a new platform for the aza-functionalizzation and aziridination of enones and are the starting point for further synthesis of biologiacally active compounds.

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[57] a) A. Minatti, X. Zheng, S. Buchwald, *J. Org. Chem.* **2007**, *72*, 9253 and references therein. The tricyclic aziridine **NSC676892** has been identified as a promising HIV-1 integrase inhibitor: b) H. Hong, N. Neamati, H. E. Winslow, J. L. Christensen, A. Orr, Y. Pommier, G. W. A. Milne, *Antiviral Chem. Chemother.* **1998**, *9*, 461.

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: $[\alpha]^{rt}_{D}$ (*c* in g per 100 mL, solvent). All reactions were carried out in air and using undistilled solvent, without any precautions to exclude moisture unless otherwise noted.

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

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.[3] 9-Amino(9-deoxy)*epi*-hydroquinine **VIII** was prepared from commercially available hydroquinine following the literature procedure.[4] 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.

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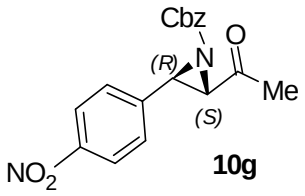
Determination of the Relative and Absolute Configurations.

Aziridination Products. The relative *trans* configuration was assigned by analysis of the *J* constants. The absolute configuration of compound **xxg** 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 **A**.[5]

DFT Calculations. Geometry optimization were carried out at the B3LYP/6-31G level by means of the Gaussian 03 series of programs:[6] 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



10g

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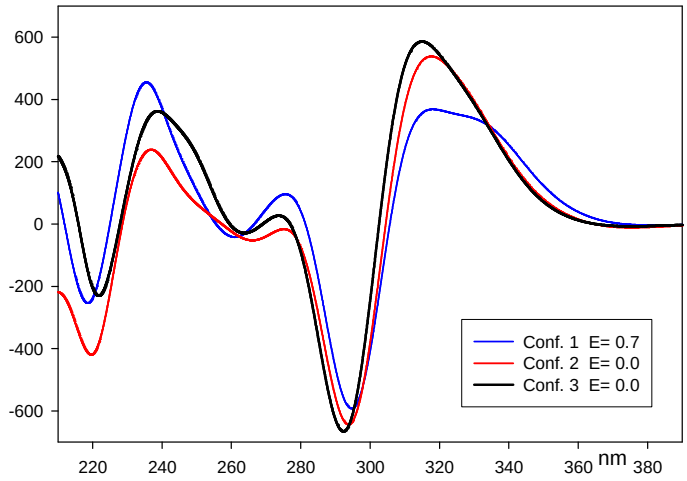
The lack of a suitable heavy atom precludes the use of the Bijovet method, based on anomalous X-ray dispersion, to unambiguously assign the absolute configuration (AC) of the single enantiomer of **10g.** Using a different approach, the Electronic Circular Dichroism (ECD) spectrum can be calculated by 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 successfully employed several times[7] 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.[8]



[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.

[8] D. Casarini, L. Lunazzi, M. Mancinelli, A. Mazzanti, P. Scafato *Chirality* **2008,** DOI: 10.1002/chir.20587

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)

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**.

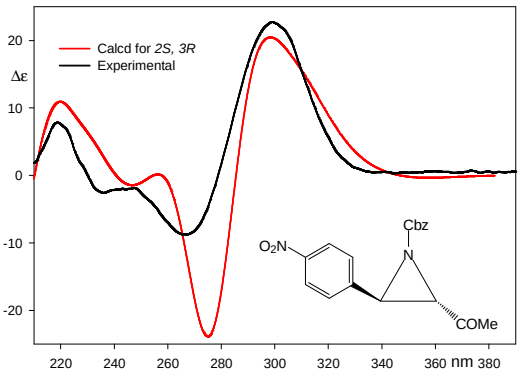
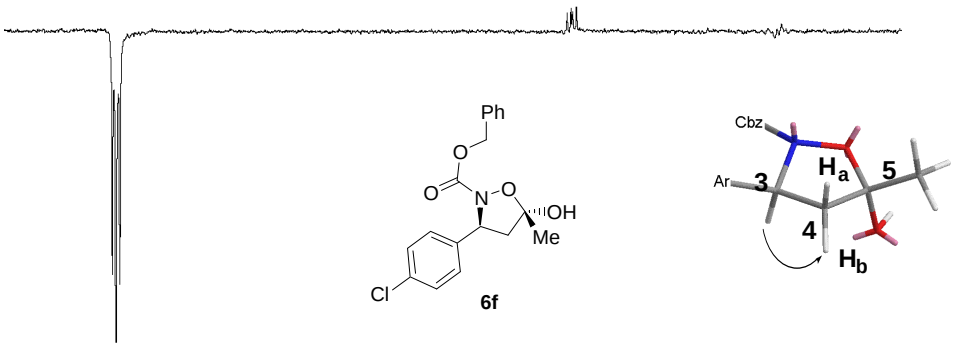


Figure S2: experimental (black trace) and calculated (red trace) ECD spectrum for compound **10g**

Relative configuration of 5-hydroxyisoxazolidines 6f: NOE studies

The relative configuration of compound 6f was assigned by extensive NOE studies.



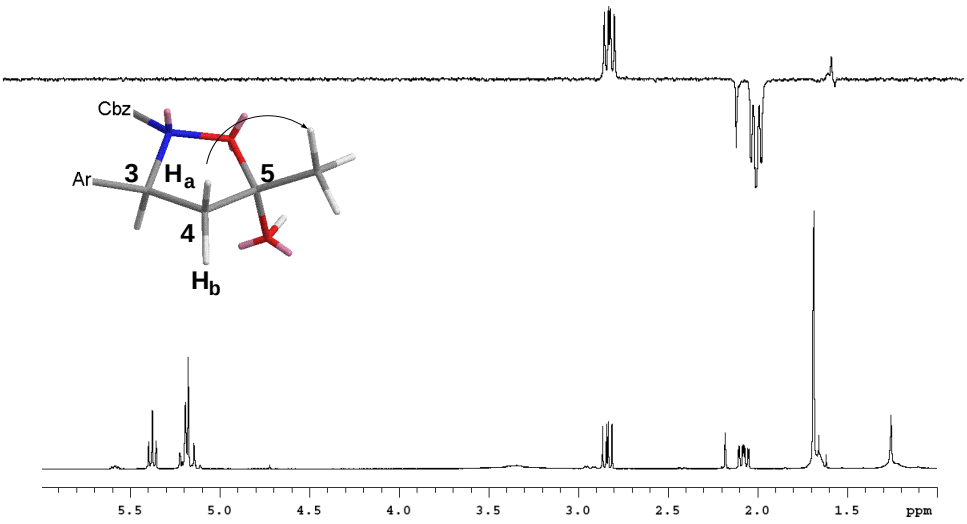
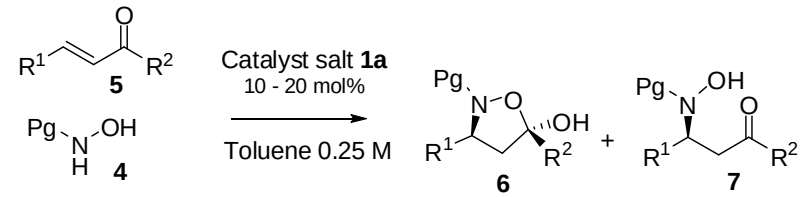


Figure S3. Bottom: part of the ^{1}H-NMR spectrum of **6f** (400 MHz, in $CDCl_3$). Middle trace: DPFGSE-NOE obtained on saturation of the H_a(4) signal, showing a NOE effect on the H_b(4) signal and on the signal of the CH_3(5), and showing no NOE effect on the CH(3) signal. Top trace: DPFGSE-NOE obtained 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

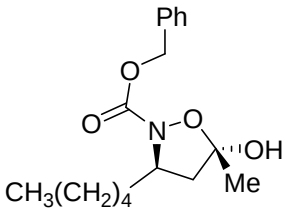
General Procedure for the Organocatalytic Asymmetric Amine Conjugate Addition to Enones.



4a: Pg = Cbz**; 4b**: Pg = Boc
4c: Pg = CO_2Et

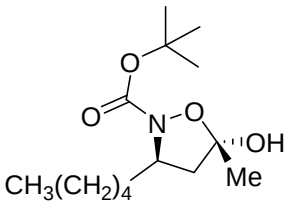
All the reactions were carried out in undistilled toluene. In an ordinary vial equipped with a Teflon-coated stir bar, 9-Amino(9-deoxy)*epi*-hydroquinine **VIII** (0.02 mmol, 6.5 mg, 10 mol%) was dissolved in 0.8 mL of toluene. After addition of D-*N*-Boc-phenylglycine **3** (0.04 mmol, 10 mg, 20 mol%), 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_2Cl_2 (1 mL) and flushed through a short plug of silica, using dichloromethane/Et_2O 1/1 as the eluent. Solvent was removed *in vacuo*, and the residue was purified by flash chromatography (FC) to yield the desired 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.



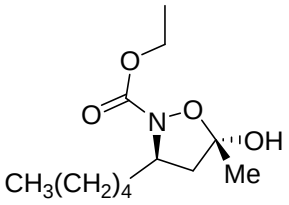
6 a

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, $CHCl_3$, 99% ee) ^{1}H 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). ^{13}C NMR: δ = 14.1 (CH_3), 22.8 (CH_2), 23.8 (CH_3), 26.0 (CH_2), 31.7 (CH_2), 36.3 (CH_2), 43.9 (CH_2), 60.5 (CH), 68.1 (CH_2), 106.5 (C), 128.4 (CH), 128.7 (CH), 136.3 (C), 160.1 (C).



6 b

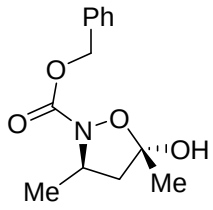
5-Hydroxy-5-methyl-3-pentyl-isoxazolidine-2-carboxylic acid tert-butyl ester 6b (Table 1, entry 2) **–** The reaction was carried out following the general procedure to furnish the crude product [**6b:7b** ratio = 9.5:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 4.16-4.28 ppm, 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. $[\alpha]_{rt}^{D}$ = -4.5 (c=1.02, $CHCl_3$, 99% ee) ^{1}H 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). ^{13}C NMR: δ = 14.2 (CH_3), 22.8 (CH_2), 23.7 (CH_3), 26.2 (CH_2), 28.4 (CH_3), 31.8 (CH_2), 36.5 (CH_2), 46.2 (CH_2), 60.4 (CH), 81.8 (C), 106.1 (C), 159.5 (C).



6 c

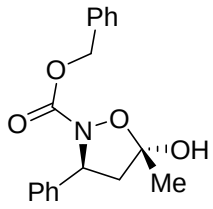
5-Hydroxy-5-methyl-3-pentyl-isoxazolidine-2-carboxylic acid ethyl ester 6c (Table 1, entry 3) **–** The reaction was carried out following the general procedure to furnish the crude product [**6c:7c** ratio = 6:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 1.65 ppm, s, δ_{minor} 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, $CHCl_3$, 99% ee) ^{1}H 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).



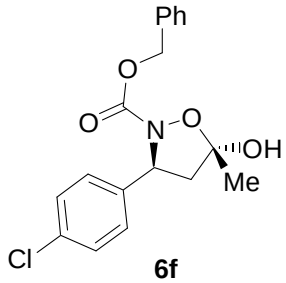
6 d

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).



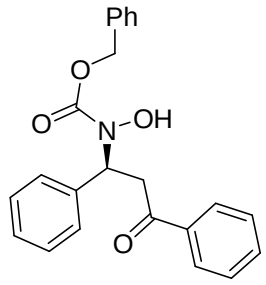
6 e

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).



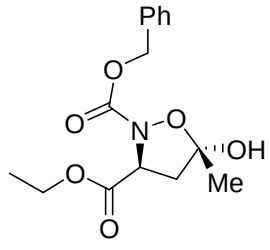
6f

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).



7g

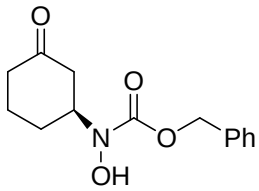
Benzyl hydroxy(3-oxo-1,3-diphenylpropyl)carbamate 7g (Table 1, entry 7) **–** The reaction was carried out following the general procedure to furnish the crude product [**6g**:**7g** ratio = 1:3, determined by integration of one set of ^{1}H NMR signal (δ_{major} 5.81 ppm, dd, δ_{minor} 5.56 ppm, t]. 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).



6 h

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

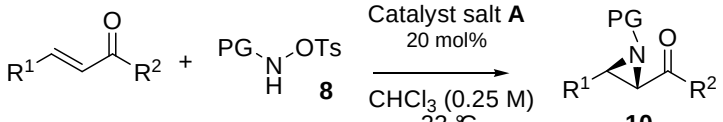
AD-H column: 80/20 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (95% ee): τ_{major} = 10.0 min, τ_{minor} = 12.1 min. $[\alpha]_{rt}^{D}$ = -15.6 (c=0.83, $CHCl_3$, 95% ee) ^{1}H NMR: δ = 1.20 (t, *J*=7.2, 3H), 1.66 (s, 3H), 2.27-2.35 (m, 1H), 2.67 (dd, *J*=9.1, *J*=12.4, 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).



7 i

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).

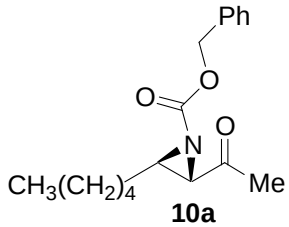
General Procedure for the Organocatalytic Asymmetric Aziridination of Enones.



8a: PG = Cbz**; 8d**: PG = Boc **10**

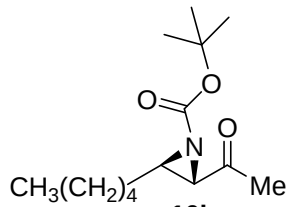
All the reactions were carried out in undistilled chloroform and using the catalytic salt combination **1b** (1.5 equiv of D-*N*-Boc-phenylglycine **3** relative to 9-Amino(9-deoxy)*epi*-hydroquinine **2**). In an ordinary vial equipped with a Teflon-coated stir bar, 9-Amino(9-deoxy)*epi*-hydroquinine **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_2Cl_2 (1 mL) and flushed through a short plug of silica, using

dichloromethane/Et_2O 1/1 as the eluent. Solvent was removed *in vacuo*, and the residue was purified by flash chromatography (FC) to yield the desired products.



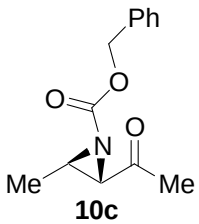
10a

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_2O = 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).



10b

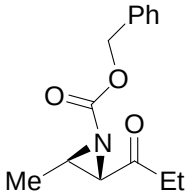
tert-Butyl 2-acetyl-3-pentylaziridine-1-carboxylate 10b (Table 3, entry 2) **–** The reaction was carried out following the general procedure to furnish the crude product [dr > 19:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 2.97 ppm, δ_{minor} 3.16 ppm - d)]. The title compound was isolated as a colourless oil by column chromatography (Hexane/Et_2O = 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).



10c

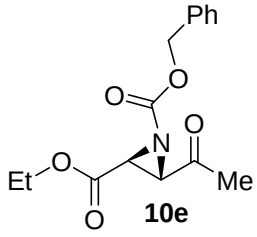
2-Acetyl-3-methyl-aziridine-1-carboxylic acid benzyl ester 10c (Table 3, entry 3) **–** The reaction was carried out following the general procedure to furnish the crude product [dr > 19:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 2.98 ppm, δ_{minor} 3.02 ppm - d)]. The title 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).



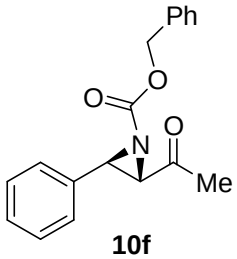
10d

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).



10e

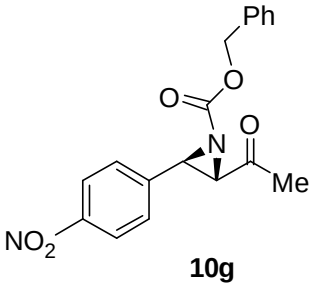
1-Benzyl 2-ethyl 3-acetylaziridine-1,2-dicarboxylate 10e (Table 3, entry 6) **–** The reaction was carried out following the general procedure to furnish the crude product [dr > 19:1, determined by integration of one set of ^{1}H NMR signal (δ_{major} 3.29 ppm, δ_{minor} 3.21 ppm - d)]. The title compound 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).



10f

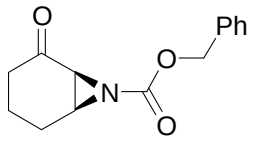
Benzyl 2-acetyl-3-phenylaziridine-1-carboxylate 10f

(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).



10g

(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).



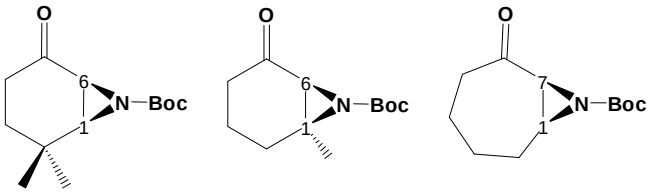
10h

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).

Determination of the Relative and Absolute Configurations



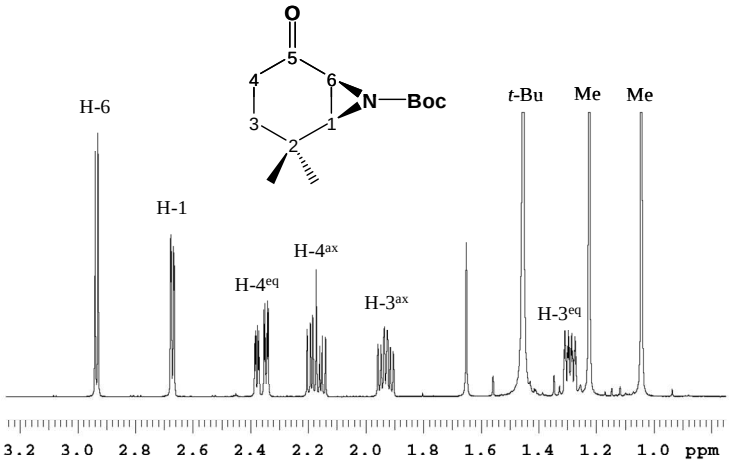
3e **3d** **3h**

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.

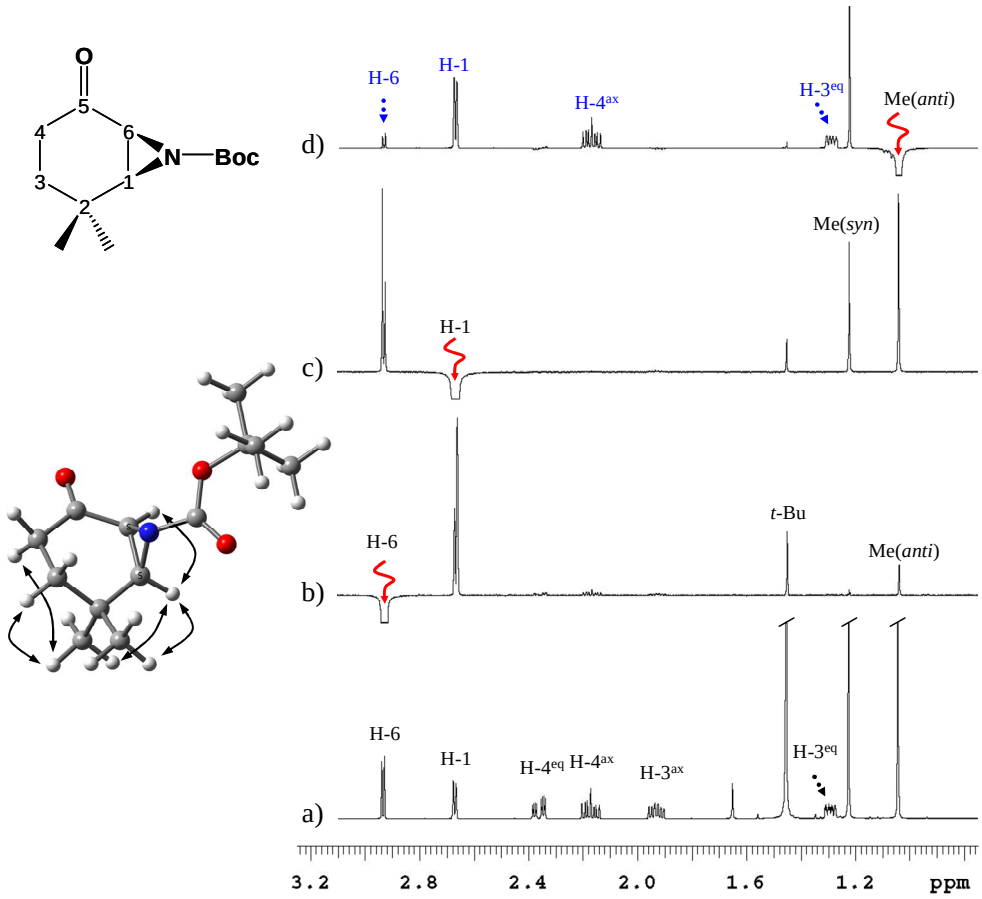
Compound xxe

Full assignment of the protons signals (and carbons as well) of compound **13e** 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 ^{4}J 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 **13e** (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 **13e**. 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[9], 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[10]. 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 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 **13e** is 1*R**, 6*R**.

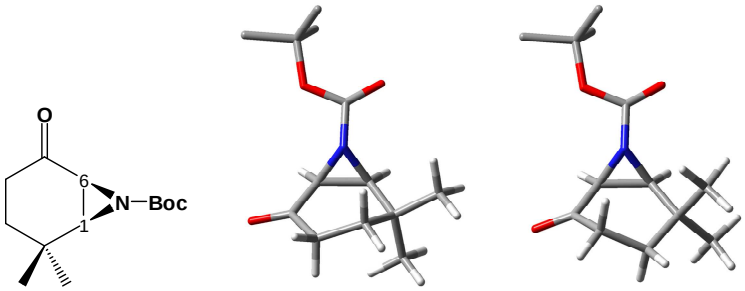
Conformational Analysis and Absolute Configuration

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

[9] (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.

[10] this is a NOE enhancement that must be observed, and it serves as a check of the reliability of the experiment.

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[11], 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)



a
E = 0.0

c
E = 1.0

Supplementary Figure 3: DFT optimized conformations **a** and **c** of compound **13e**, 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

[11] 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.

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(%)
13e	**a**	0	62
	b	0.47	28
	c	1.30	7
	d	1.90	3

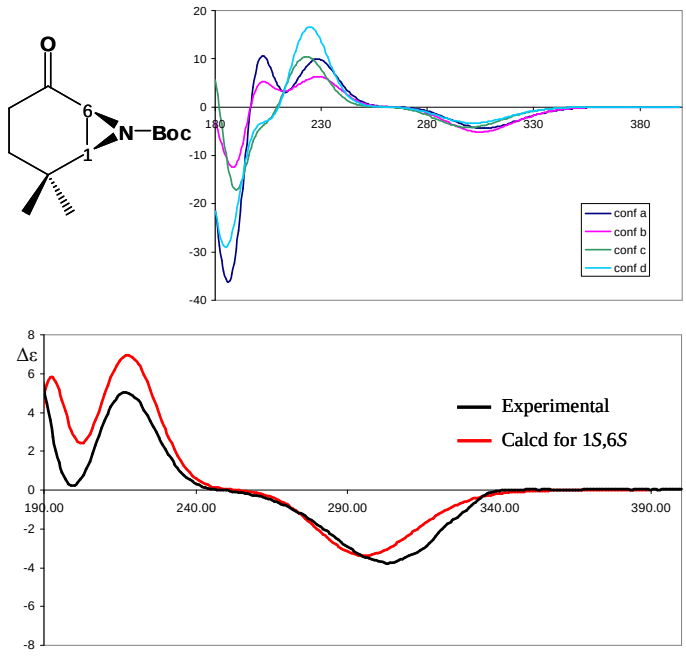
To fully confirm the geometry of the cycle, *J*-coupling calculation was carried out by DFT methods at the B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d) level[12]. (Supplementary Table 2). The values calculated for the lowest energy structure are in very good agreement with the experimental ones. This suggests 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[13]. 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.[14] 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[15] (Supplementary Figure 4). In order to cover the 170-400 nm range, 30 transition were calculated for each conformation.

[12] Calculations were performed taken into account the Fermi contact term, under the keyword "NMR(spinspin,mixed)"
[13] 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)
[14] Stephens, P.J.; McCann, D.M.; Devlin, F.J., Cheeseman, J.R.; Frisch, M.J. *J.Am.Chem.Soc.* **2004**, *126*, 7514-7521
[15] Gaussview 4.1.2, Semichem Inc., 2006

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.



Supplementary Figure 4. Top: calculated ECD spectra for the four conformations of **13e**. 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 (Δε) 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.

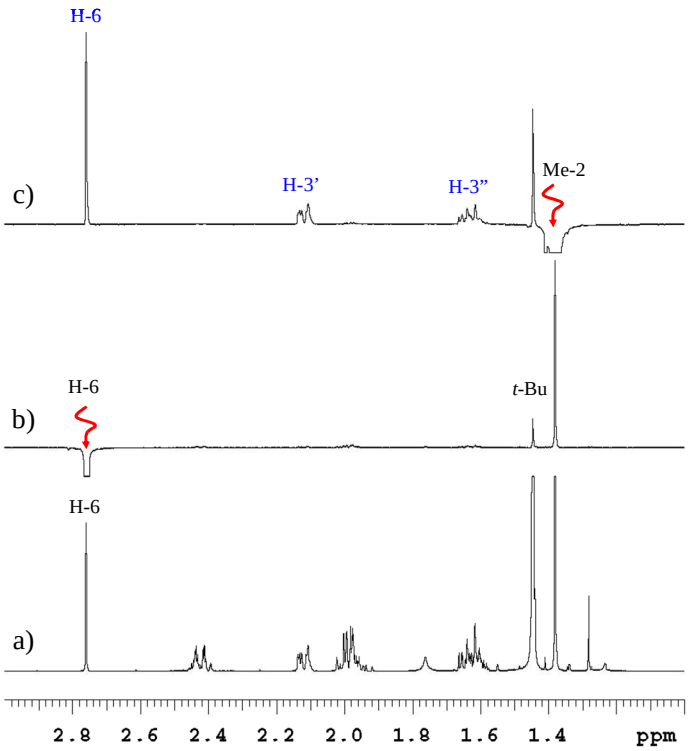
This transition is calculated to have negative chirality in all the four conformations, and the trend of the four spectra are quite similar, indicating that the resulting weighted ECD spectrum is weakly influenced by the relative population of the conformations. The final simulated ECD spectra was obtained 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 **13e**. As suggested by some authors,[2i, 16] the use of more than one chirooptic method is always desirable; in the present compound the calculation of the $[\alpha]_D$ is reasonable reliable, the experimental value being -106°. The calculated value (-61°) is negative and small, as experimentally observed. It has also to be pointed out that the well known octant rule[17], 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 13d.

Compound **13d** 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 **13e**, full assignment of the proton spectrum was obtained by bi-dimensional NMR. The proton spectrum of **13d** 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 **13e**, i.e. 1*R**, 2*R** conformation analysis of **13d** was managed in the same way of **13e**. 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 **13e**, 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

[16] (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.
[17] See Berova, N; Nakanishi, K.; Woody, R.W. "Circular Dichroism. Principles and Applications ", Wiley-VCH, Chapter 10, page 261

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).

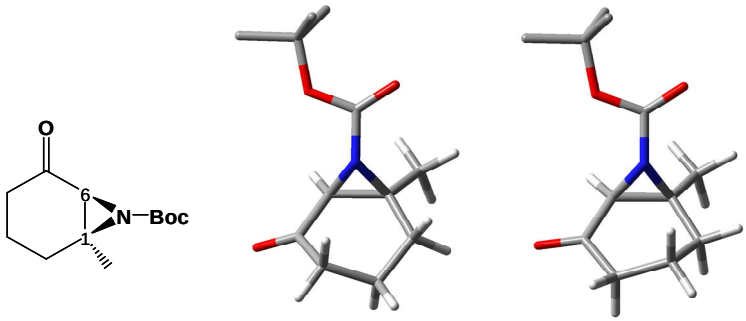


Supplementary Figure 5. DPFGSE-NOE spectra of **13d**. Trace a): control spectrum. Traces b-c: NOE spectra obtained on saturation of H-6 and Me-2.

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(%)
3d	**a**	0.00	55
	b	0.28	35
	c	1.36	6
	d	1.48	5

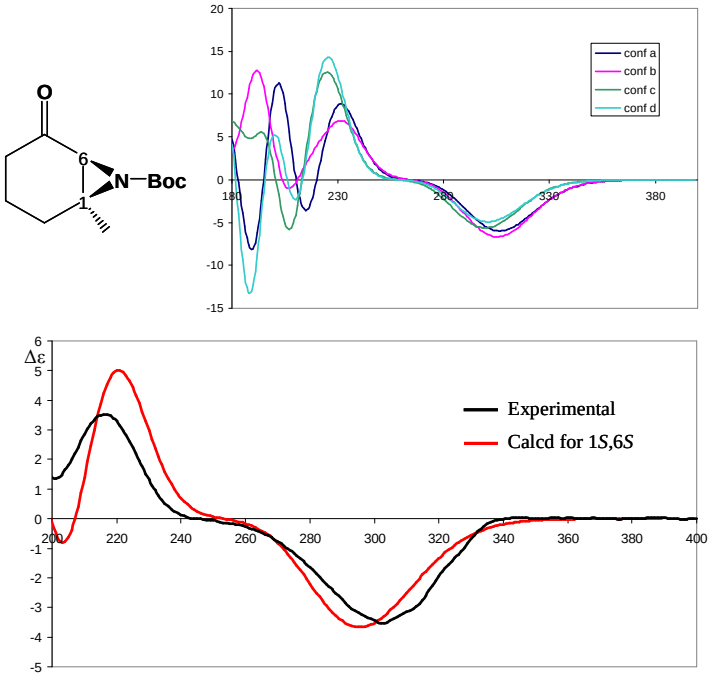
The two pairs of conformations show a different conformation of the cyclohexanone ring (Supplementary Figure 6), and both are compatible with the observed NOEs. Accordingly, in this case the conformational analysis relies only on the computed energies, that showed a good accuracy in the case of **13d**.



a
E = 0.0

c
E = 0.95

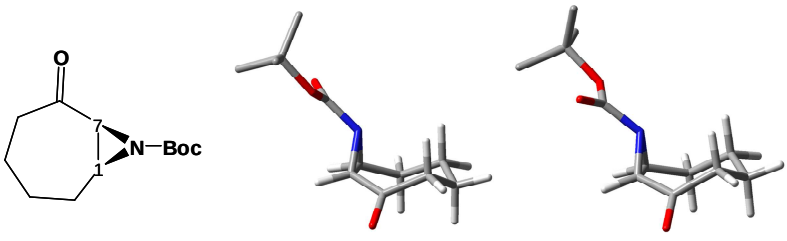
Supplementary Figure 6: DFT optimized conformations **a** and **c** of compound **13d**, showing the different conformation of the cyclohexanone ring. Conformations **b** and **d** have the Boc group rotated by 180°. Boc hydrogens are omitted for convenience. Calculation of the Electronic Circular Dichroism 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[13]. 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.[14] 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 **13d**. As in the case of **13e**, 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 **13d**. 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 (Δε) 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 13h.

The cycloheptanone ring contained in compound 1**3h** has a greater conformational freedom with respect to **13e** and **13d**. For this reason compound **13h** 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 **13e** and **13d**, a second conformation was built by 180° rotation of the Boc group and subsequently optimized. (see Supplementary Figure 8).



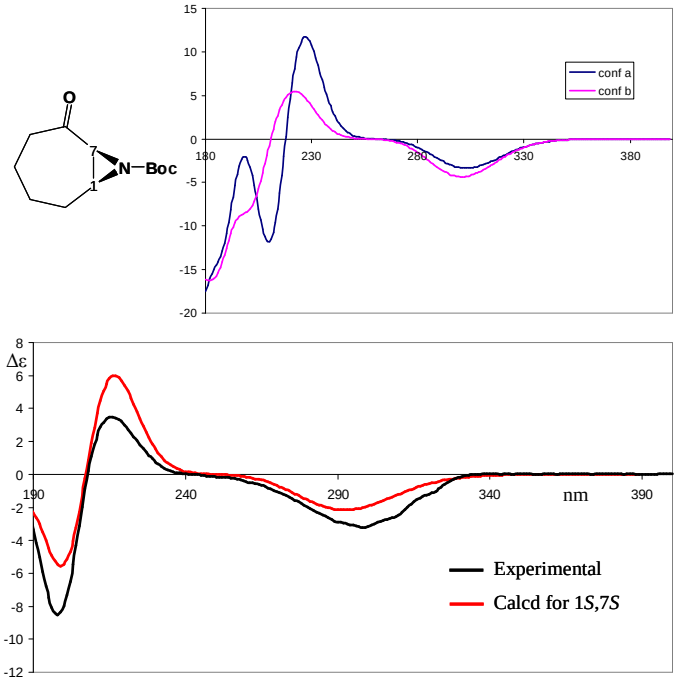
a E = 0.0 **b** E = 0.28

Supplementary Figure 8 DFT optimized conformations compound **13h,** 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 13h (in kcal/mol, B3LYP/6-31G(d) level). Populations percentages (P) are calculated assuming Boltzmann statistics at T=25°C.

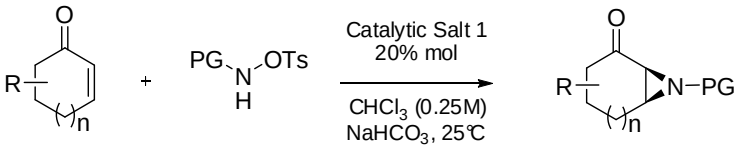
Molecule	Conf.	ΔG	P(%)
13h	**a**	0.00	75
	b	0.65	25

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 **13h**.



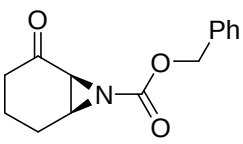
Supplementary Figure 9. Top: calculated ECD spectra for the two conformations of **13h**. Bottom: experimental (black) and calculated ECD spectra (red), weighted on the calculated free energies of the conformations and blue shifted by 10 nm. Molecular CD (Δε) is expressed in L $mol^{-1}cm^{-1}$. Solvent was acetonitrile. The vertical scale of the final simulated spectrum was scaled to obtain the best fit with the experimental trace.

General Procedure for the Organocatalytic Asymmetric Aziridination of Cyclic Enones.



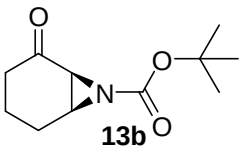
All the reactions were carried out in undistilled chloroform and using the catalytic salt combination **A** or **B** (1.5 equiv of D-*N*-Boc-phenylglycine or L-*N*-Boc-phenylglycine relative to 9-Amino(9-deoxy)*epi*-hydroquinine or 9-Amino(9-deoxy)*epi*-hydroquinidine). Both of the antipodes of the aziridine 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_2Cl_2 (1 mL) and flushed through a short plug of silica, using dichloromethane/Et_2O 1/1 as the eluent. Solvent was removed *in vacuo*, and the residue was purified by flash chromatography (FC) to yield the desired products.



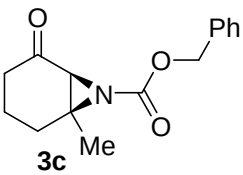
13a

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 to 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).



13b

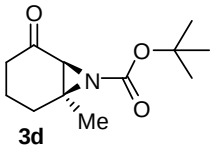
2-Oxo-7-aza-bicyclo[4.1.0]heptane-7-carboxylic acid tert-butyl ester 3b (Table 1, entry 2) – The reaction was carried out following the general procedure using catalyst salt A to furnish the crude product as a single diastereomer. The title compound was isolated as a colourless oil by column chromatography (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).



3c

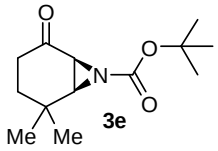
1-Methyl-5-oxo-7-aza-bicyclo[4.1.0]heptane-7-carboxylic acid benzyl ester 3c (Table 1, entry 3) – The reaction was carried out following the general procedure using catalyst salt A to furnish the crude product. The title compound was isolated as a colourless oil by column chromatography (Hexane/Acetone = 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, $CHCl_3$, 73% ee) ^{1}H 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). ^{13}C 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).



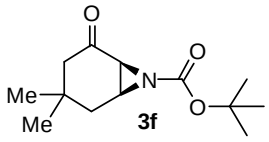
3d

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/Et_2O/$CHCl_3$ = 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. ^{1}H 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). ^{13}C 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).



3e

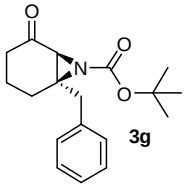
2,2-Dimethyl-5-oxo-7-aza-bicyclo[4.1.0]heptane-7-carboxylic acid tert-butyl ester 3e (Table 2, entry 2) – The reaction was carried out following the general procedure using catalyst salt A to furnish the crude product as a single diastereomer. The title compound was isolated as a white solid by column 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, $CHCl_3$, 98% ee. ESI: $[M+Na]^+$= 262, $[M+1]^+$= 240. ^{1}H 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). ^{13}C 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).



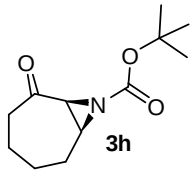
3f

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 diastereomer. 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

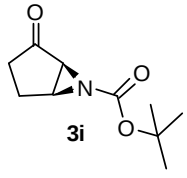
hexane/*i*-PrOH, flow rate 0.650 mL/min, λ = 214, 254 nm: τ_{minor} = 18.44 min, τ_{major}= 20.47 min. $[\alpha]_{rt}^{D}$ = +43.4 (c=0.65, $CHCl_3$, 98% ee). ESI: $[M+Na]^+$= 262, $[M+1]^+$= 240. ^{1}H NMR: δ = 0.88 (s, 3H), 1.00 (s, 3H), 1.44 (s, 9H), 1.78-1.83 (m, 2H), 1.94 (d, *J* = 14.60 Hz, 1H), 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 chromatography (Hexane/Et_2O = 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).

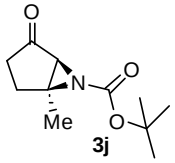


2-Oxo-8-aza-bicyclo[5.1.0]octane-8-carboxylic acid tert-butyl ester 3h (Table 2, entry 6) – The reaction was carried out following the general procedure using catalyst salt A to furnish the crude product as a single diastereomer. The title compound was isolated as a colourless oil by column chromatography (Hexane/Et_2O = 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).



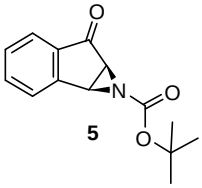
2-Oxo-6-aza-bicyclo[3.1.0]hexane-6-carboxylic acid tert-butyl ester 3i (Table 2, entry 7) – The reaction was carried out following the general procedure using catalyst salt A to furnish the crude product as a single

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).



3j

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).



5

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).

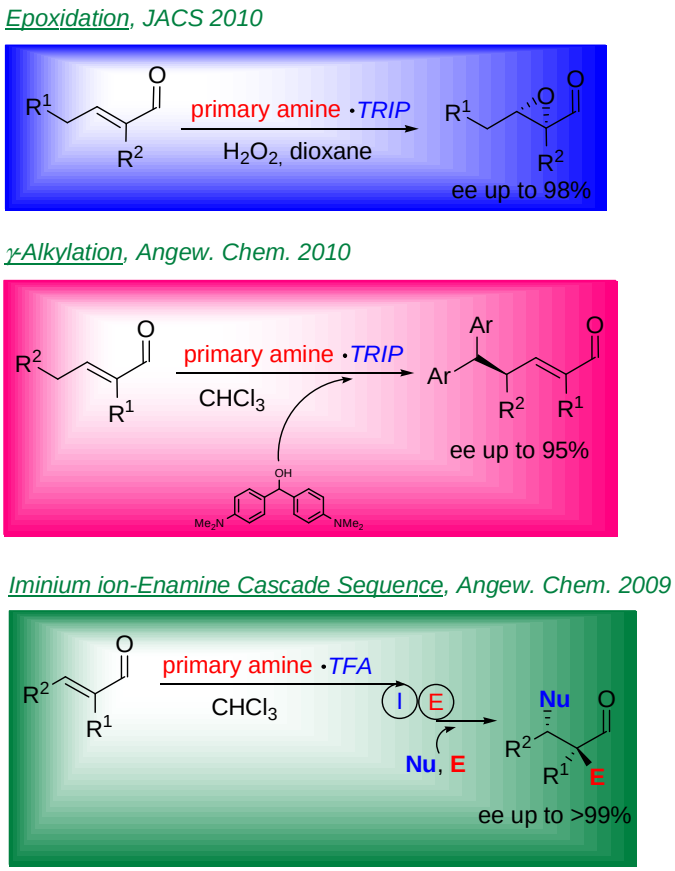
2.1.2. Asymmetric Organocatalytic Cascade Reactions with α-Substituted α,β-Unsaturated Aldehydes

Discussion

In asymmetric synthesis the activation of a new class of compounds represents the opportunity to expand both knowledge limits and the tools array in the chemist hands. In this context the development, in the past decade, of the aminocatalytic strategies offered the unique possibility to activate carbonyl compounds such as saturated aldehydes and enals, enabling previously inaccessible transformations.[58, 59] Since early 2007 it was also possible, as consequence of the simultaneous efforts of four independently groups, to activate the α,β-unsaturated ketones into an iminium ion strategy.[60]

The discover route of new activation modes in asymmetric aminocatalysis arrived at the end of 2000*s* when the activation of α,β-unsaturated α-substituted aldehydes has been realized, furnishing three different protocols for their functionalizzation (Figure **1**).

Figure 1: organocatalytic activation modes of α,β-unsaturated α-substituted aldehydes



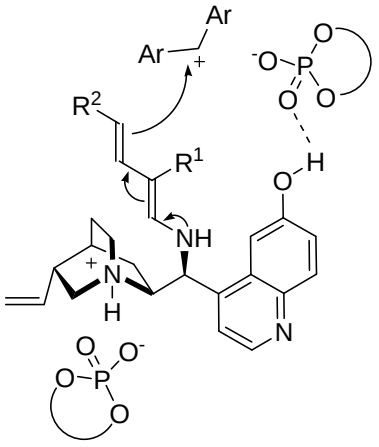
In Figure 1 are reported three different kinds of activation of α-branched aldehydes recently reported by the groups of Mechiorre *et. al.*[61] and the group of List *et. al.*[62]

In 2010 was reported the first organocatalytic epoxidation of α-branched enals. The catalytic system is based upon a double chiral catalytic salt, formed by 9-amino-9-deoxy-*epi*-Quinine and (R)-*TRIP* as chiral counter anaion.

The reaction furnished an excellent way for the epoxidation of α-branched aliphatic aldehydes with enantiomeric excess up to 98% through an intramolecular iminium ion-enamine cascade mechanism catalyzed by the primary amine catalyst. Importantly, the chiral phosphoric acid provides additional enantiodiscrimination in both steps as a chiral counterion of the iminium ion intermediate and as a Brønsted acid in the ring closure step making easy the elimination of water.

In the middle of Figure 1 is reported the γ-alkylation of α,β-unsaturated α-substituted aldehydes, through S_N1 pathway, published by Melchiorre *et al.* few months ago. In this paper these scientists activated for the first time the α-branched enals via dienamine,[63] generating a γ-nucleophilic intermediate that is able to intercept a stabilized carbocation formed in situ from bis(4-dimethylaminophenyl)methanol.[64] The activation of aldehyde was realized by a primary amine catalyst easily derived from Quinidine in two steps (Scheme **1**)

Scheme 1: Proposed mechanistic model for the Asymmetric γ-Alkilation of α-Branched Enals



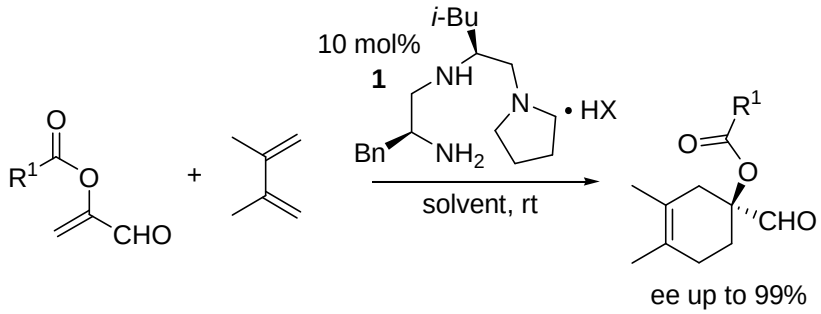
In this reaction the chiral phosphoric acid at first promote the formation of the carbocation and then act as counter anion both for the quinuclidine moiety and for the benzhydryl cation ensuring an excellent stereoselection of the process.

During my Phd we were caught by stimulating game of address the challenges in the field of the asymmetric synthesis. At the end of 2008, when it was consolidated the ability of the primary amine catalyst in the activation of enones, we started to study the activation of another class of α,β-unsaturated carbonyl compounds: the α-branched aldehydes. We showed for the first time that a primary amine catalyst was able to activate these substrates toward a

well defined iminium ion-enamine tandem sequence (Figure **1** below) building the way for their further activation.

Ispired by the pioneeristic work of Ishihara *et- al.* (Scheme **2**) we minded from the outset that a primary amine could activate the α-branched enals via iminium ion

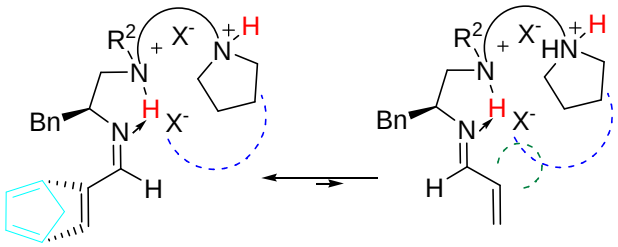
Scheme 2: Organocatalyzed Enantioselective Diels-Alder reaction with a-Acyloyacroleins



ee up to 99%

The authors reported the first Diels Alder reaction catalyzed by a primary amine with excellent enantiomeric excess. In their report Ishihara and Nakano postulated that the active form of the catalyst **1** readily derived from L-amino acid and HX induces its asymmetry to DA adducts through a five-membered cyclic *cis*-transition state (Figure **2**). The protonation of the amine groups arises to the formation of two ion pairs where, after the condensation with the aldehyde, the counter anion X^- select the geometry of the iminium ion through non bond interaction, and the benzyl group shields one of the two possible attack-face.

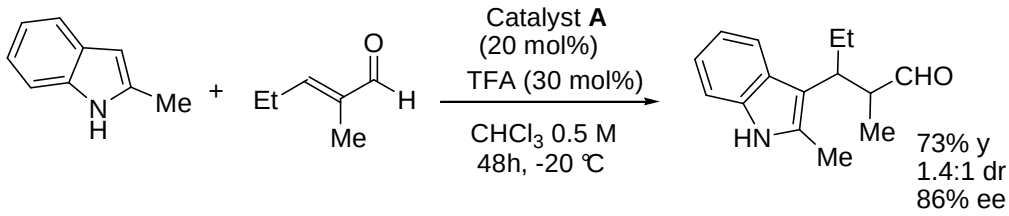
Figure 2: Proposed transition state for the DA reaction of α-acyloxy acroleins reported by Ishihara et. al.



On this ground other groups tried to solve the problem of the activation of α-branced aldehydes obtaining good results only employing acroleins,[65] thus the use of this substrates still represents an

elusive and fundamental target for asymmetric aminocatalysis.[66] This is particularly true since an alternative asymmetric metal-catalyzed strategy for the functionalization of this class of compounds is also lacking. In order to face this problem we thought to avail ourself of the primary amine **A** ability in the activation of α,β-unsaturated α-substituted aldehydes. At first we wanted design a Michael addition/protonation cascade using 2-Methyl-indole as nucleophile.

Scheme 3: Preliminary studies on the asymmetric Michael addition/protonation tandem seqience



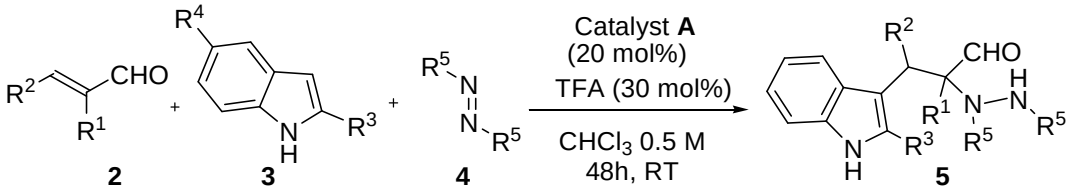
Unfortunately the catalytic system furnished a good enatioselection, but it was not able to control enamine protonation step, in fact we obtain the product as equal mixture of diastereoisomer (Scheme **3**).

Encouraged by the high stereocontrol in the Michael addition we minded to trap the enamine intermediate with another electrophile the diazocarboxylate, creating 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,[67] the combination of multiple asymmetric transformations in a cascade sequence also imparts increased enantiomeric excess to the final product when compared to the corresponding discrete transformations.[68]

Our organocascade strategy was first examined mixing three commercially available reagents, (*E*)-2-methylpent-2-enal, 2-methyl-1*H*-indole and diethyl azodicarboxylate (Table 1, entry 1). Such a reagents combination is rather challenging, due to the competitive coupling between the π-electronrich nucleophile and the electrophilic component.[69] 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 **A** (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**.

Table 1: Scope of the aryl/amination tandem sequence for the functionalization of α,β-unsaturated α-substituted aldehydes.



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

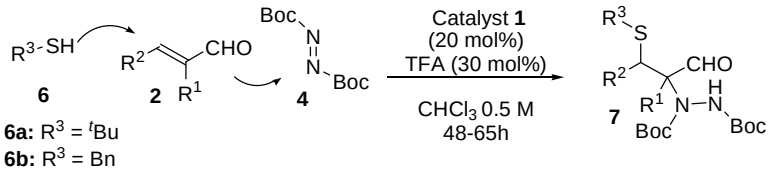
[a]Yield of isolated 5 [b] Determined by 1H NMR analysis of the crude reaction mixture. [c]Determined by HPLC analysis using chiral stationary phases. [d] Reaction conducted at - 10°C over 96 h. [e] Reaction conducted at 0°C over 65 h.

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 system efficiency, 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 (R1) 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).

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,[70] we focused on a sulfa-Michael/amination sequence, using mercaptanes having easily removable and orthogonal sulphur protecting groups (Table 2).[71]

Table 2: Organocascade catalysis with α-branched α,β-unsaturated aldehydes: sulfa-Michael/amination strategy



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.

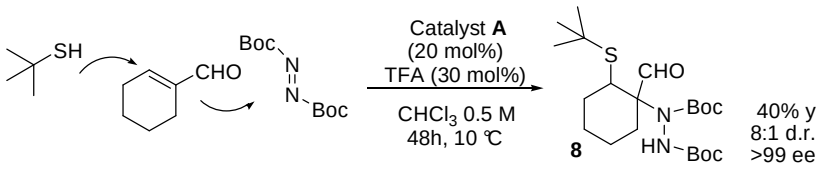
As summarized in Table 2, the reaction shows a good substrate generality: both *tert*-butyl and benzyl mercaptane are suitable nucleophiles, albeit the latter induces a less selective organocascade path (entries 1-3). There appears to be a remarkable latitude in the electronic and steric demands of the

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.[9] Satisfying, catalyst **A** proved efficient with this substrate class, leading to compound **8** with complete enantiocontrol (Scheme **4**).

Scheme 4: enantioselective sulfa-Michael/amination tandem sequence of the -cyclohexen-1-carboxaldehyde



The configuration of a derivative of compound **7** was unambiguously determined by anomalous dispersion X-ray crystallography,[72] 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.

References

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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,[73] using a mixing time of 2.00 s and "rsnob" 20 ÷ 50 Hz wide selective pulses, depending on the crowding of the spectra region. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$ and CD_3CN). Coupling constants are given in Hz. 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.[74] 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.[75] Chiral primary amine catalysts, 9-Amino(9-deoxy)epi-hydroquinine **A** and the pseudo-enantiomer 9-Amino(9-deoxy)epi-hydroquinidine **B**, were prepared from commercially available hydroquinine and hydroquinidine, respectively, following the literature procedure.[76] 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.

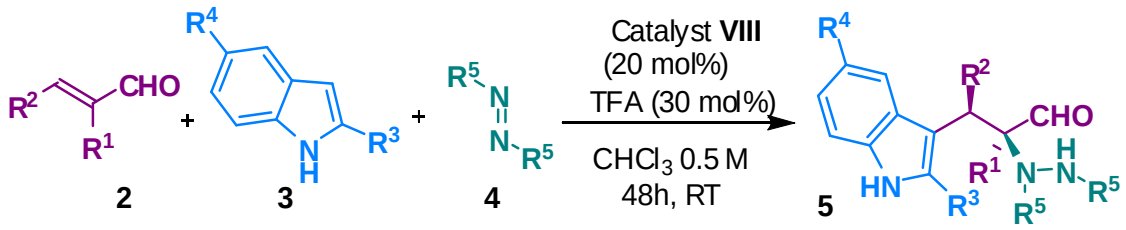
Determination of Diastereomeric Ratios. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture, and confirmed by HPLC analysis on chiral stationary phases columns.

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 **A** and its pseudoenantiomer 9-Amino(9-deoxy)epi-hydroquinidine **B**.

Calculations. MM conformational searches were performed using the MonteCarlo method implemented in Titan 1.0.5.[77] Geometry optimization were carried out at the B3LYP/6-31G(d) level by means of the Gaussian 03 series of programs.[78] 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.

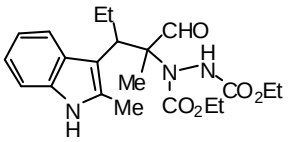
Experimental procedures

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



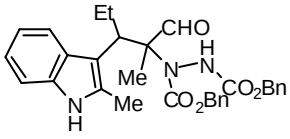
All the reactions were carried out in undistilled chloroform. In an ordinary vial equipped with a Teflon-coated stir bar, 9-Amino(9-deoxy)epi-hydroquinine **A** (0.04 mmol, 200 µL of a 0.2 M $CHCl_3$ solution, 20 mol%) was added to 200 µL of solvent. After the addition of TFA (0.06 mmol, 5 µL, 30 mol%), 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_2Cl_2 (1 mL) and flushed through a short plug of silica, using CH_2Cl_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**.



5a

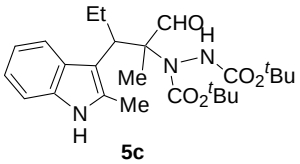
diethyl 1-(2-methyl-3-(2-methyl-1H-indol-3-yl)-1-oxopentan-2-yl)hydrazine-1,2-dicarboxylate 5a. The reaction was carried out over 48 hours in $CHCl_3$ at room temperature following the general procedure to furnish the crude product (d.r.= 8:1 was determined by integration of one set of ^{1}H-NMR signal: 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 $C_{21}H_{29}N_3O_5$: 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

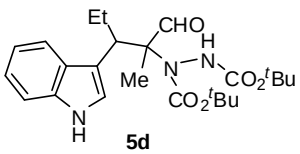
dibenzyl 1-(2-methyl-3-(2-methyl-1H-indol-3-yl)-1-oxopentan-2-yl)hydrazine-1,2-dicarboxylate 5b. The reaction was carried out over 48 hours in $CHCl_3$ at room temperature following the general procedure to furnish the crude product (d.r.= 6:1 was determined by integration of one set of ^{1}H-NMR signal: 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.



5c

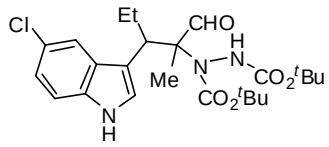
di-tert-butyl 1-(2-methyl-3-(2-methyl-1H-indol-3-yl)-1-oxopentan-2-yl)hydrazine-1,2-dicarboxylate 5c. The reaction was carried out over 24 hours in $CHCl_3$ at room temperature following the general procedure to furnish the crude product (d.r.= 11:1 was determined by integration of one set of ^{1}H-NMR 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.



5d

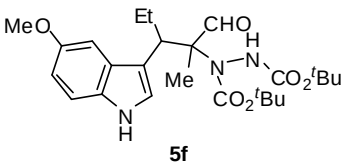
di-tert-butyl 1-(3-(1H-indol-3-yl)-2-methyl-1-oxopentan-2-yl)hydrazine-1,2-dicarboxylate 5d. The reaction was carried out over 96 hours in $CHCl_3$ at –10°C following the general procedure to furnish the crude product (d.r.= 3:1 was determined by integration of one set of ^{1}H-NMR signal: δ_{major} 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 $[\alpha]_{rt}^{D}$= -25.4 (c = 1.10, $CHCl_3$, 94% ee, dr=3:1). HRMS: (m/z) calculated for $C_{24}H_{35}N_3O_5$: 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.



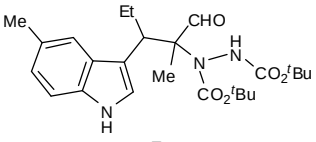
5e

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_2O, 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. $[\alpha]_{rt}^{D}$= -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

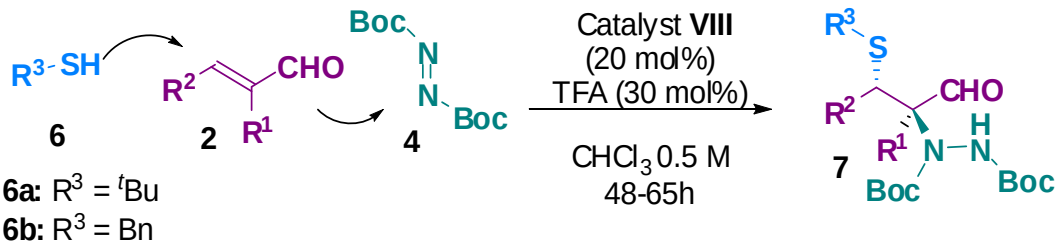
di-tert-butyl 1-(3-(5-methoxy-1H-indol-3-yl)-2-methyl-1-oxopentan-2-yl)hydrazine-1,2-dicarboxylate 5f. The reaction was carried out over 96 hours in $CHCl_3$ at -10°C following the general procedure to furnish the crude product (d.r.= 3:1 was determined by integration of one set of ^{1}H-NMR signal: δ_{major} 9.65 ppm, bs, δ_{minor} 9.61 ppm, bs). The title compound was isolated by flash column chromatography (DCM/Et_2O = 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 $C_{25}H_{37}N_3O_6$: 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.



5g

di-tert-butyl1-(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_2O = 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.

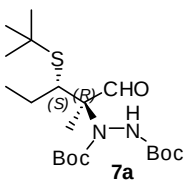
General procedure for the asymmetric organocatalytic sulpha-Michael/amination tandem sequence of α–substituted α,β–unsaturated aldehydes.



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 **A** (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 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 CH_2Cl_2 (1 mL) and flushed through a short plug of silica, using CH_2Cl_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.

General procedure for the reduction and cyclization to form oxazolidinones.

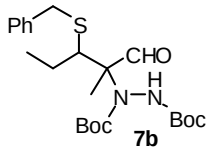
The crude reaction mixture (0.2 mmol scale referred to aldehyde) was diluted with MeOH (2 mL) and cooled to 0°C before the addition of $NaBH_4$ (0.6 mmol, 3 equiv.) After 10 minutes, 2 M solution of NaOH (2 mL) and THF (2 mL) were successively added and the crude reaction mixture was stirred for 2 hours. After standard aqueous work-up, the product was purified by flash-chromatography on silica gel.



7a

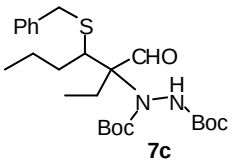
di-tert-butyl 1-((2R,3S)-3-(tert-butylthio)-2-methyl-1-oxopentan-2-yl)hydrazine-1,2-dicarboxylate 7a. The reaction was carried out over 65 hours in $CHCl_3$ at 0°C following the general procedure to furnish the crude product (d.r.= 6.5:1, determined by integration of one set of ^{1}H-NMR signals: δ_{major} 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 $C_{20}H_{38}N_2O_5S$: 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.



7b

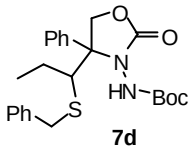
di-tert-butyl1-(3-(benzylthio)-2-methyl-1-oxopentan-2-yl)hydrazine-1,2-dicarboxylate 7b. The reaction was carried out over 65 hours in toluene at –20°C following the general procedure to furnish the crude product (d.r.= 6:1 was determined by integration of one set of ^{1}H-NMR signal: δ_{major} 9.50 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 $C_{23}H_{36}N_2O_5S$: 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.



7c

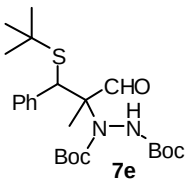
di-tert-butyl-1-(4-(benzylthio)-3-formylheptan-3-yl)hydrazine-1,2-dicarboxylate 7c. The reaction was carried out over 48 hours in $CHCl_3$ at 40°C following the general procedure to furnish the crude product (d.r.= 4:1 was determined by integration of one set of ^{1}H-NMR signal: δ_{major} 3.09 ppm. 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 $C_{25}H_{40}N_2O_5S$: 480.2658, found: 480.2658. ^{1}H NMR (400 MHz, CD_3CN 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_3CN 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.



7d

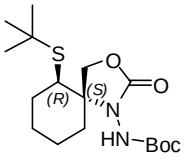
tert-butyl 4-(1-(benzylthio)propyl)-2-oxo-4-phenyloxazolidin-3-ylcarbamate 7d. The reaction was carried out over 48 hours in $CHCl_3$ at 40°C following the general procedure to furnish the crude product (d.r.= 4:1 was determined by integration of one set of ^{1}H-NMR signal: δ_{major} 10.37 ppm. bs, 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_2O = 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 $C_{24}H_{30}N_2O_4S$: 442.1925, found: 442.1926. ^{1}H NMR (400 MHz, CD_3CN 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_3CN 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.



7e

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_2O = 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 $C_{24}H_{38}N_2O_5S$: 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.

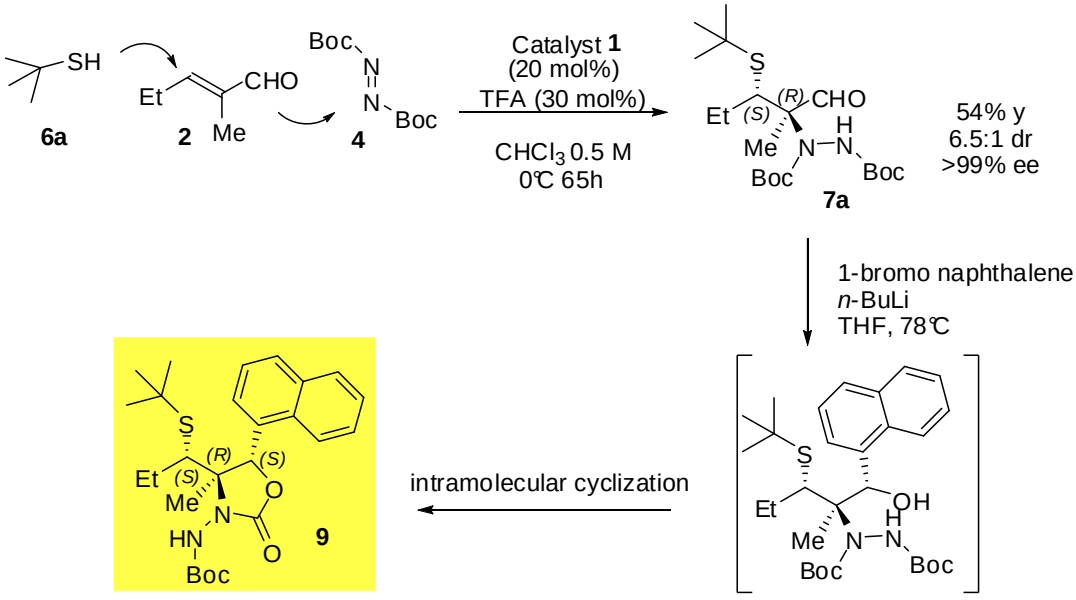


8a

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_2O = 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 $C_{17}H_{30}N_2O_4S$: 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

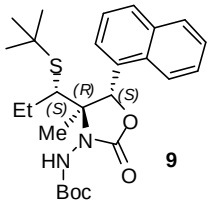
Compound 7a.



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

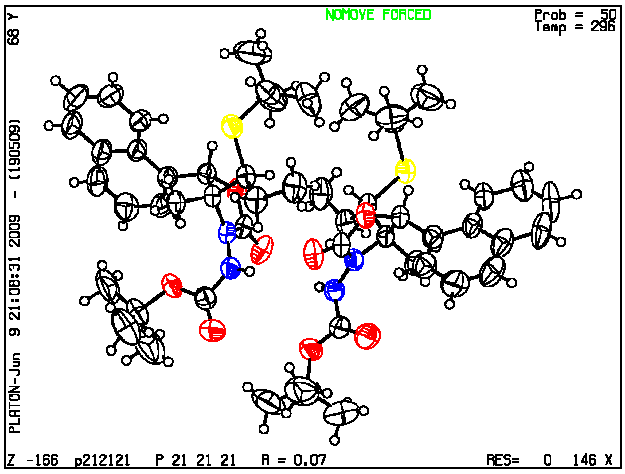
To a solution of 1-bromonaphtalene (1.5 mmol, 2 equiv. compared to compound 7a) in dry THF (4 mL), n-BuLi (1 mL, 1.6 M in Hexane) was added slowly at – 78°C. After stirring at this temperature for 15 minutes, a solution of 7a (0.75 mmol) in 1 mL of THF was added. The mixture was warmed to ambient temperature and allowed to stir for further 15 minutes. An aqueous work-up with NH_4Cl and extraction with Et_2O furnished the crude product 9a. The pure compound was isolated by flash cromatography (Hex: Et_2O = 8:2), followed by HPLC purification on a C18 Column (acetonitrile/H2O 90:10 v/v).



9

tert-butyl 4-(1-(tert-butylthio)propyl)-4-methyl-5-(naphthalen-1-yl)-2-oxooxazolidin-3-ylcarbamate 9. ^{1}H NMR (600 MHz, CD_3CN 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_3CN 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).

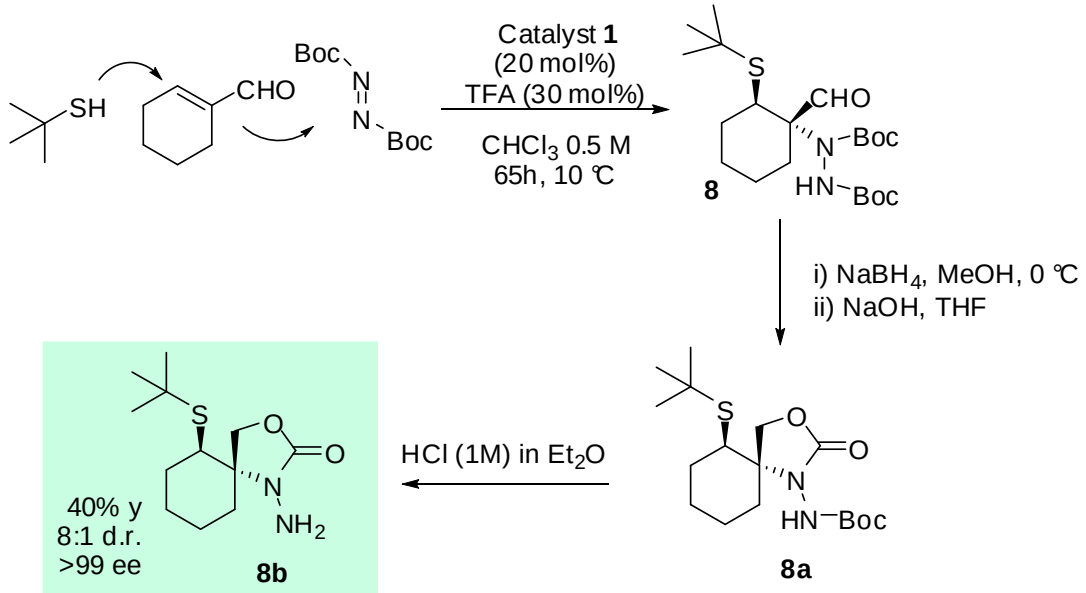
Crystal Data for compound 9



Crystals were obtained from hexane/Et_2O solution by slow evaporation. Molecular formula: $C_{26}H_{36}N_2O_4S$, M_r = 472.63, Orthorhombic, space group $P2_12_12_1$ (No. 14), a = 10.9758(9), b = 23.5089(16), c = 23.7659(19), V = 6132.3(9) Å^3, T = 298(2) °K, Z = 8, ρ_c = 1.024 g cm^{-3}, F(000) = 2032, graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å), $\mu(Mo_{K\alpha})$ = 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).

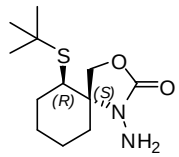
[a] Flack, H. D. Acta Cryst. 1983, A39, 876-881

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.



8b

(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.

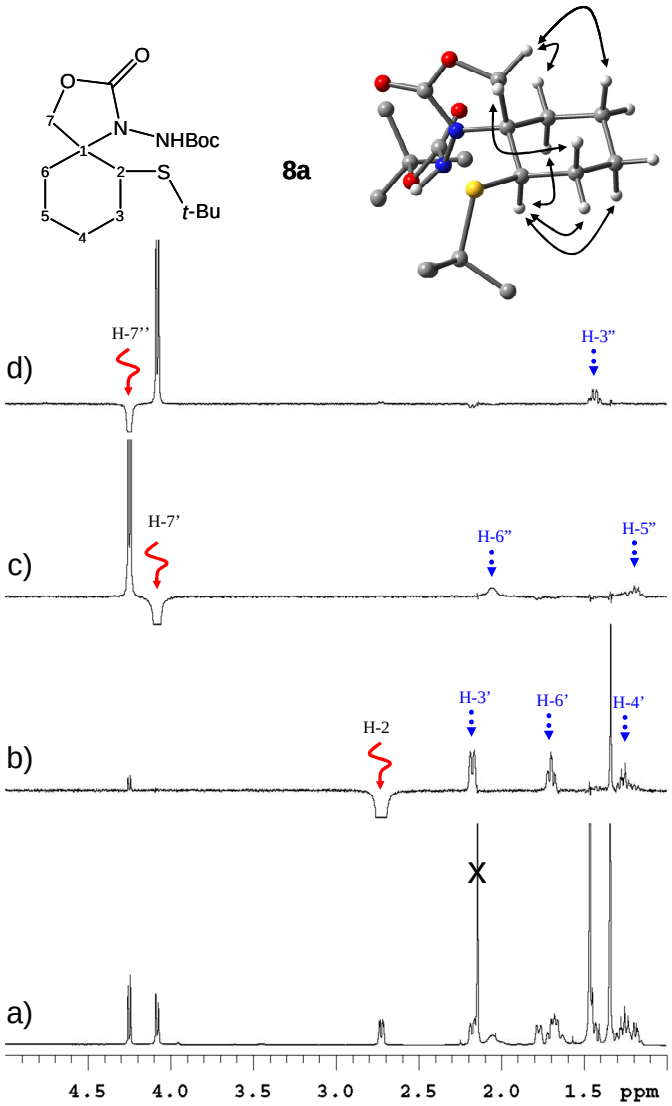


Figure S1: DPFGSE-NOE spectra obtained for 8a. trace a): control spectrum; trace b): NOE spectrum obtained on saturation of H-2; traces c) and d): NOE spectra obtained on saturation of the two diastereotopic hydrogens H7' and H7". Observed NOE (blue) are indicated as arrows in the DFT optimized structure (the hydrogen atoms of the t-butyl groups have been removed for clarity)

Full assignment of ^{1}H 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[79]. 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[80]. 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.[81] The ECD spectra was then obtained by applying a 0.25 eV Gaussian shaped line width (Figure S2).

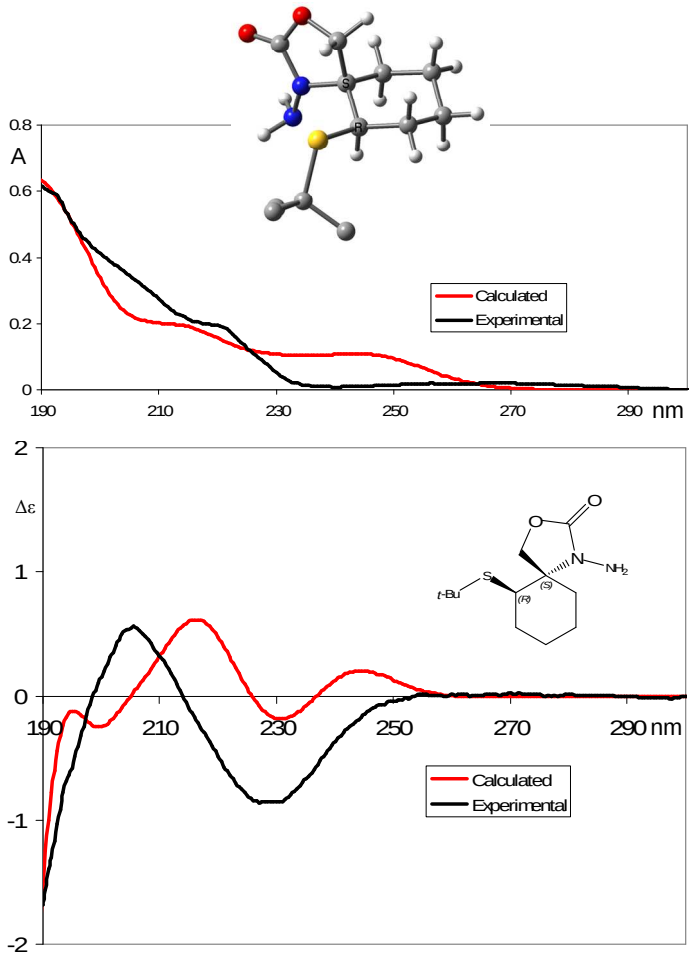


Figure S2. Top: calculated (red) and experimental (black) UV spectra of 8b. Bottom: experimental (black) and calculated ECD spectra (red), (the simulated spectrum has been red-shifted by 6 nm). Molecular CD (Δε) is expressed in L mol^{-1}cm^{-1}. Concentration in acetonitrile was 2.05·10^{-4} M, and 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[82], 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.

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[82] 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.

2.1.3. Asymmetric addition of oxindoles to α,β-unsaturated adehydes and ketones: aminocatalytic strategy for the costruction of chiral all-carbon quaternary stereocenters

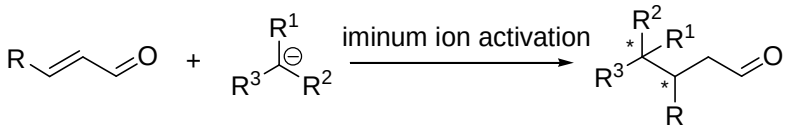
Discussion

Nowadays the art and science of total synthesis reached an incredible levels of efficiency being oftenbecouse is an important field where numerous chemists challenge each other.[83] Analysing a target molecule one of the most important point in which focus the attention is the presence of all-carbon quaternary stereocenters. This chiral motifs can be found not only in a wide range of important and useful compounds in pharmaceutical and medicinal contexts, but also in a large variety of natural products.[84] The difficult in the forging this kind of stereogenic elements arise from the steric congestion imposed by the four attached carbon and the limited number of C-C bond forming reactions that reliably assemble quaternary chiral centers. The challenge is more captivating when this motif is adjacent to a chiral tertiary stereocenter or, continuing this line of thought, to a quaternary one.

Although a number of elegant solutions have recently been devised for achieving this goal, certain types of reaction frameworks still present significant obstacles and provide platforms for novel catalyst design and innovation in synthetic methods. An important transformation that presents promising opportunities for setting quaternary stereocenters is the Michael reaction (Scheme 1). From its discover the Amminocatalisys[85] setted up the conditions for the enantioselctive Michael addition to α,β-usaturated aldehydes providing their functionalization with a wide range of nucleophile. Its development was due to the high efficiency and generality demonstrated by some "privileged" organocatalysts such as MacMillan imidazolidinones[2d] (I) and the silyl-protected diarylprolinols catalysts (II)[86] that have consolidated asymmetric aminocatalysis as a reliable and

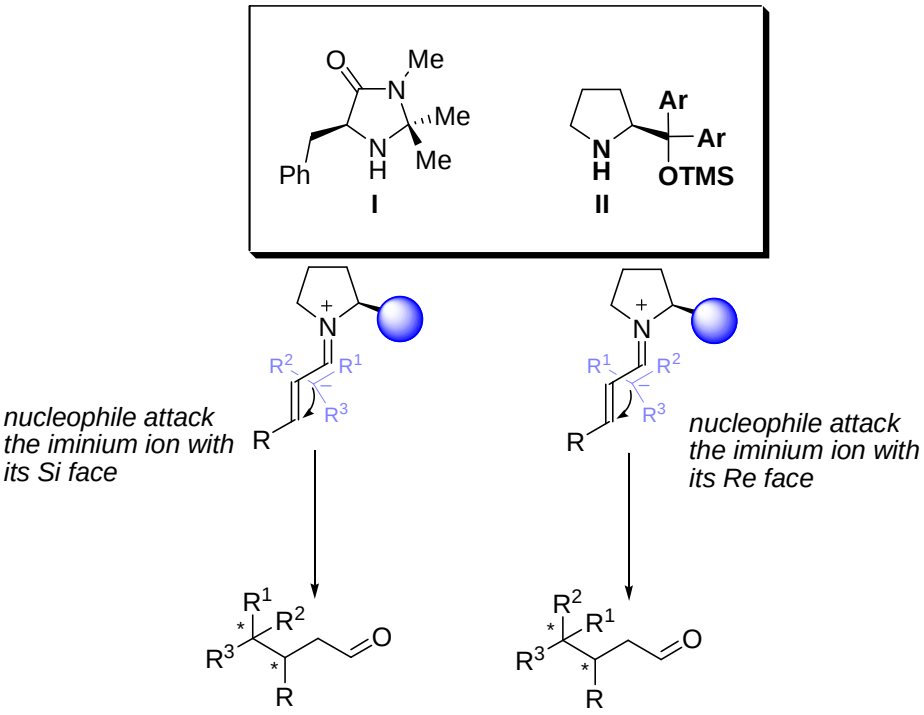
powerful synthetic tool for the chemo- and enantioselective functionalization of carbonyl compounds.

Scheme 1: Challenging task in asymmetric iminuim ion activation of carbonyl compounds



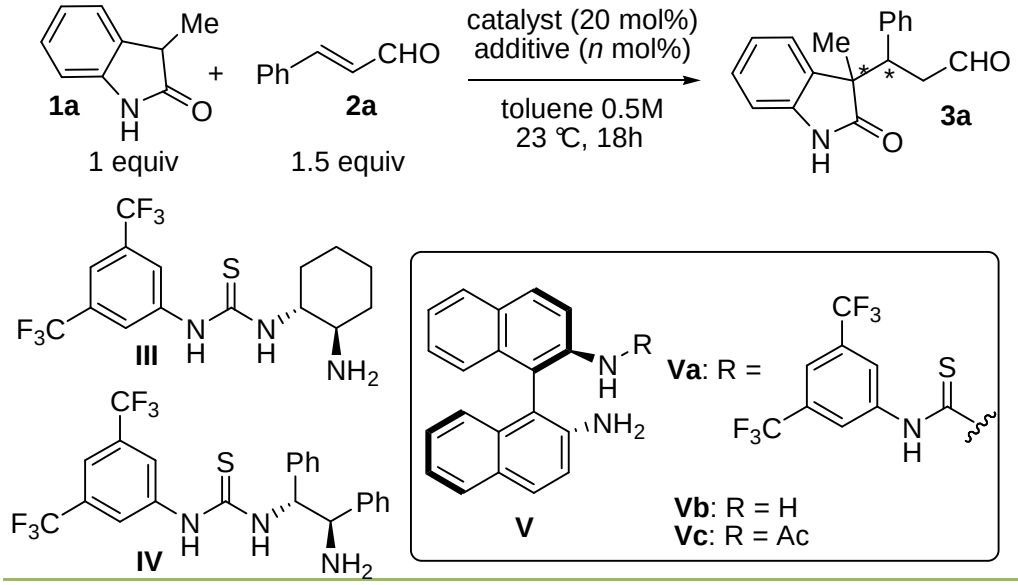
Despite their great efficiency the privileged catalyst seem not able to address the problem of the d.r. control during the addition of prochiral disustituted and, in particular, trisubstituted carbon nucleophiles to the α,β-usaturated aldehydes (Scheme 2).[87]

Scheme 2: Iminium ion activation of α,β-unsaturated aldehydes with privileged secondary amine catalyst.



This catalysts fix perfectly the attack face and the geometry of the iminium ion through non bond interactions as described in the previous chapter, but on the other hand they are not able to control the approach of the nucleophile, bearing the product with high enantioselctivity but with poor diasterocontrol. In this context, we investigated the unprecedented asymmetric conjugate addition of oxindoles to α,β-unsaturated aldehydes, which would readily give access to structurally complex oxindoles endowed with a quaternary stereogenic center at C3 adjacent a tertiary one.[88,89] Chiral 3,3-disubstituted oxindole frameworks are attractive targets in organic synthesis because of their promising biological activities[7a-b] as well as wide-ranging utility as synthetic intermediates for alkaloids, drug candidates, and clinical pharmaceutical.[7b-c] For preliminary studies (reported in Table 1), we selected the reaction between 3-methyl oxindole **1a** and cinnamaldehyde **2a**.

Table 1: Optimization studies.[a]



Entry	catalysts	additive (mol%)	[%] conv[b]	dr[b]	[%] ee[c]
1	I	DCA (20)	53	1.1:1	5
2[d]	II	pNO_2-$C_6H_4CO_2H$ (20)	>95	1.1:1	92
3	III	pNO_2-$C_6H_4CO_2H$ (20)	>95	1:1	7
4	IV	pNO_2-$C_6H_4CO_2H$ (20)	84	1:1	2
5	Va	pNO_2-$C_6H_4CO_2H$ (20)	55	4.5:1	84
6	Vb	pNO_2-$C_6H_4CO_2H$ (40)	<5	-	-
7	Vc	pNO_2-$C_6H_4CO_2H$ (20)	20	1.2:1	40
8	Va	$PhCO_2H$ (20)	51	6:1	90
9[e]	Va	$PhCO_2H$ (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.

We first test the "privileged" secondary amines **I** and **II** as iminium catalysts for this challenging reaction (entries 1-2); their employment afforded poor results, whereas the silyl protected diarylprolinol **II** provided, as expected, very high enantioselectivity, but complete absence of

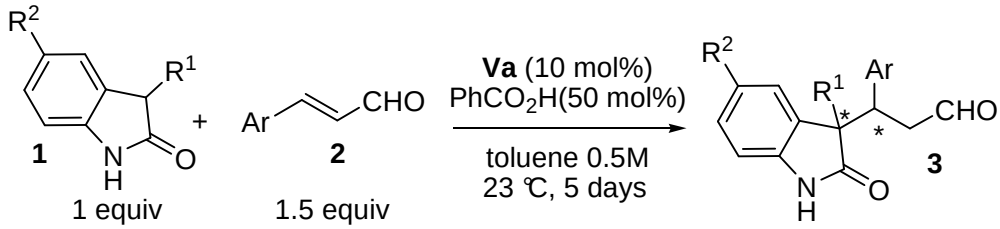
diastereocontrol, furnishing an almost 1:1 mixture of the two diastereoisomers. This evidence supports the lack of substrate-controlled stereoselectivity in the process.

Interested by the recent studies on the ability of containing thiourea moiety- catalysts of inducing high stereocontrol through a cooperative mechanism, we hypothesized 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,[90] we sought to extend the potential application of this catalyst architecture also in iminium activation[91] of simple α,β-unsaturated aldehydes.[92] We then performed an extensive screening of chiral primary amines incorporating a thiourea framework, which led to the identification of **Va** as a promising iminium catalyst.

The new catalyst **Va**, readily synthesized from commercially available compounds through a one-step procedure,[93] was able to induce high level of stereocontrol with good catalytic activity (entry 5). Moreover, the poor catalytic performance and the very low selectivity observed with **Vb** and **Vc** suggested a critical role of the thiourea moiety during the stereoselective C-C bong forming step (entries 6 and 7). Further optimization experiments 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.

By using 50 mol% of benzoic acid,[94] it was possible to reduce the catalyst loading to 10 mol%, still maintaining high diastereo- and enantio-control and significant reactivity (entry 9). The scope of the conjugate addition of oxindoles to enals under the optimized conditions, thus using as catalytic salt 10 mol% of chiral primary amine thiourea **Va** and 50% of benzoic acid in toluene 0.5M at room temperature, is 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_6H_4	e	70 (56)	7.5:1	88 (>99)
6[e]	Bn, H	pNO_2-C_6H_4	f	52 (47)	11.5:1	93
7	Bn, H	pCl-C_6H_4	g	85 (77)	5.7:1	85 (97)
8[e]	Bn, H	pCN-C_6H_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)

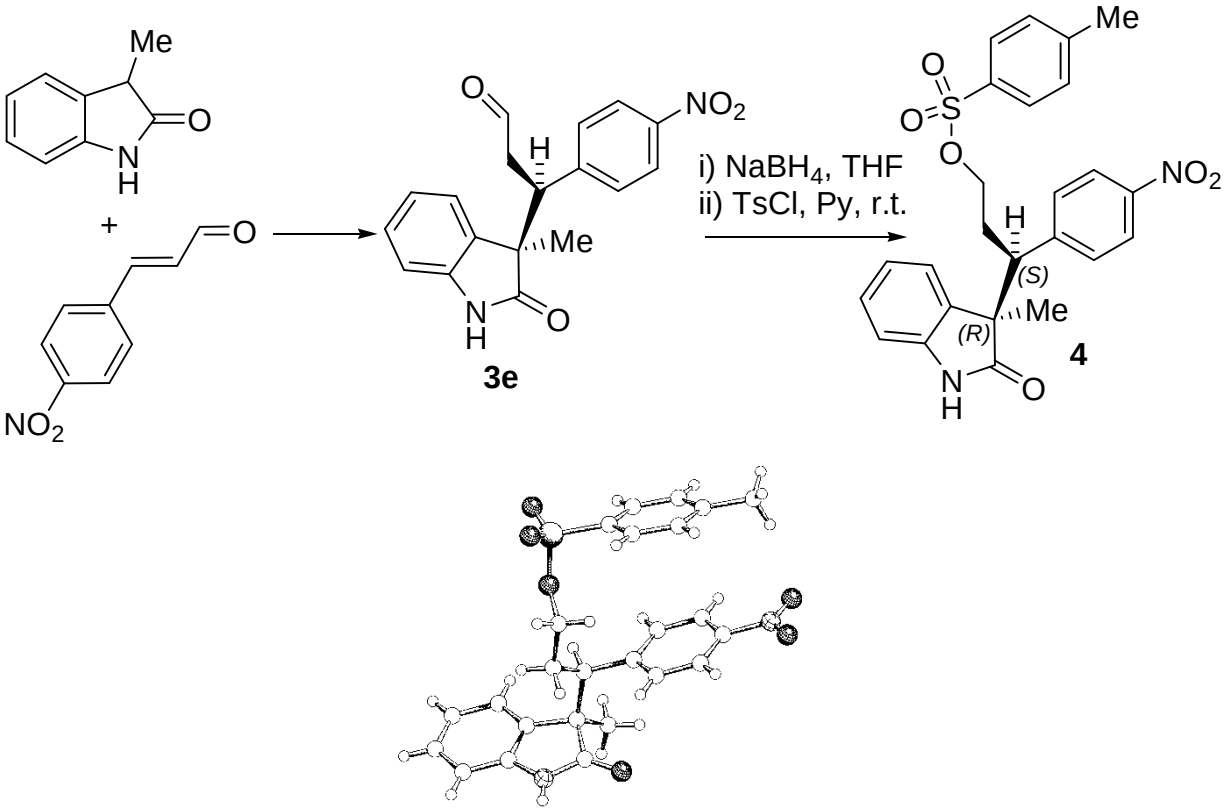
[a] Unless noted, the reactions were carried out on a 0.2 mmol scale with 1.5 equiv of 2 and $[1]_0$ = 0.5 M in toluene for 5 days in the presence of 10 mol% of VIIa and 50 mol% of $PhCO_2H$. [b] Isolated yield (sum of diastereomers). When possible, the two diastereoisomers were separated: the yield of the single major diastereomer is given in brackets. [c] Determined by ^1H 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 good diastereoselectivity.[95] 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 **II** as the iminium catalyst (see Supplementary Information for details). Importantly, by using bifunctional catalyst **Va** the main diastereoisomer 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. Unfortunately only the aromatic aldehydes undergo to the Michael addition of 3-substituted oxindoles under this reaction condition. The relative and absolute configuration of compound **3e** was determined to be (3S,3'R) by anomalous dispersion X-ray crystallography of the corresponding tosylated alcohol 4, obtained by simple aldehyde reduction (Scheme 3).[96]

Scheme 3: 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. Generally the stereoselective one-step construction of highly congested products such as 3 is dependent on the capability of the

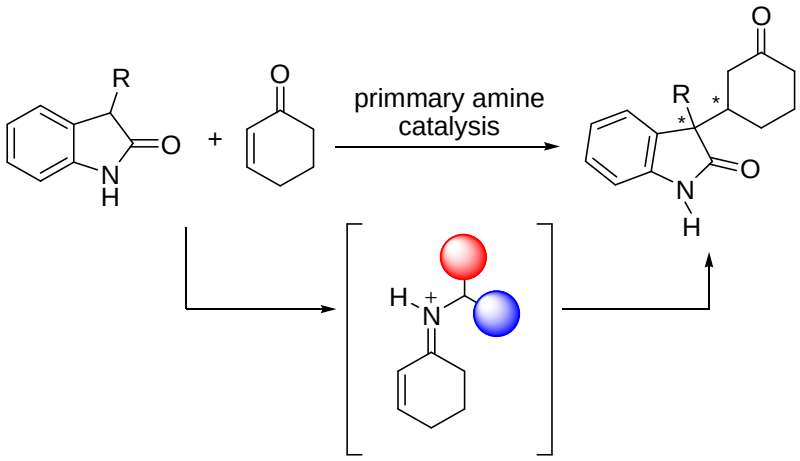
catalyst to simultaneously activate the Michael donor and the acceptor while orienting them by means of a network of H-bond interactions. Thus, we performed a series of probe experiments with the aim of confirm our hypothesis. Modifications of the catalyst scaffold revealed that the presence of the primary amine[97] 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 $PhCO_2H$, cinnamaldehyde **2a** and the N-methyl oxindole as the nucleophile.[98] 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. These experiments suggested that a plausible bifunctional activation mode of the chiral primary amine thiourea **Va** could be possible, where the thiourea moiety activates the oxindole, stabilizing its enol form, and the primary amine activates the unsaturated aldehyde via iminium ion formation.[99]

In summary, we demonstrated for the first time that a chiral primary amine thiourea catalyst, which during the last two years have been successfully applied in many enamine-based asymmetric transformations is also efficient for iminium ion activation of α,β-unsaturated aldehydes.

The use of this catalyst furnished a solution to a longstanding problem in asymmetric synthesis: the formation of framework with quaternary stereocenters. Moreover using oxindoles as 3-substitued carbon nucleophiles we synthesized a chiral quaternary stereocenter adjacent to a tertiary one, affording functionalized oxindolic structure. This motif are contained in a wide range of compounds with potential biological activity and useful intermediates for other drug candidates.

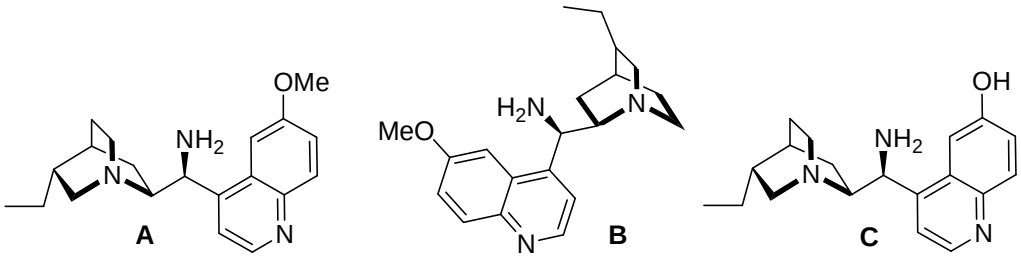
With the aim of expand our previous studies in the iminium ion activation of α,β-unsatureted ketones we envisaged that the 9-*Epi* HQ-NH_2[100] could promote efficiently the 4-addition of 3-substituted oxindoles to β-enones[101] (Scheme **4**) this transformation as described before allow to the synthesis of densely β-functionalized carbonyl compounds contain a chiral quaternary stereocenter adjacent to a tertiary one.

Scheme 4: Michael addition of oxindoles to α,β-unsaturated cyclic ketones activated by a primary amine catalyst



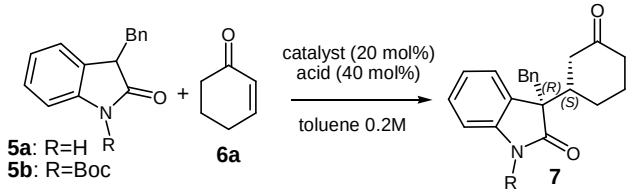
The proposed 1-4 addition of oxindoles to α,β-usaturated ketones was first evalutate using cyclohexen-2-one and a slight excess of 3-Benzil oxindoles in the presence of catalytic amount of primary amine catalyst as start point of our screening.

Figure 1: The primary amine catalysts used within this study



Initial results showed that 20 mol% of catalyst **A** in combination with an acidic co-catalyst (40 mol%) effectively promoted the reaction, furnishing the product with high enantioselectivity but moderate levels of relative stereocontrol (entry 1). All the attempts to improve the diastereoselectivity, either by lowering the reaction temperature or by using an external base to co-catalyze the process, did not reach useful synthetic standards (entries 2 and 3).

Table 3: Optimizzation studies of the Michael addition of oxindoles to cyclic ketones



5a: R=H
5b: R=Boc

6a

7

entry	amine	acid[b]	R	ºC, h	Conv (%)[c]	dr [c]	ee (%)[d]
1	A	*p*-NBA	H	rt,72	>95	2.4:1	80 (79)
2	A	*p*-NBA	H	0, 72	32	3.5:1	91 (81)
3[e]	A	*p*-NBA	H	0,72	<5	-	-
4	A	*p*-NBA	Boc	rt,24	>95	5.5:1	92 (89)
5	C	benzoic	Boc	0,48	37	2.5:1	82 (91)
6	A	NBDP	Boc	rt,24	>95	4.2:1	93 (79)
7	A	benzoic	Boc	rt,24	>95	5.6:1	97 (84)
8	A	benzoic	Boc	0,48	92	6.6:1	96 (93)
9[f]	A	benzoic	Boc	rt,24	>95	5.2:1	96 (84)

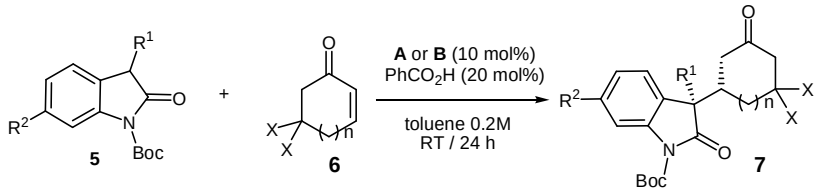
[a] The reactions were carried out on a 0.1 mmol scale with 1.2 equiv of **1** and $[\mathbf{2a}]_0$ = 0.2 M in toluene.[b] Abbreviations: *p*-NBA, 4-nitrobenzoic acid; NBDP, *N*-Boc-*D*-phenylglycine.[c] Determined by ^{1}H NMR analysis of the crude mixture.[d] Determined by HPLC analysis on chiral stationary phases. Numbers in parenthesis refer to the enantiomeric excess of the minor diastereoisomer.[e] Reaction carried out in the presence of 1.5 equiv of DABCO [f] 10 mol% of **A** and 20 mol% of benzoic acid was used

Inspired by recent studies on the Michael addition of oxindoles to nitrostyrenes[102] we focused on using *N*-Boc-protected oxindole **5b** as the nucleophilic component. Surprisigly the reaction manifold was directed toward a more diastereo- and enantioselective path (entry 4). This was probably due to steric effects. Another effect of the Boc protection was, as expected, the lowering of the pK_a of the oxindole[103] and consequently an improvement of its reactivity.

Running the reaction in the presence of multifunctional catalyst **C**, which in principle may simultaneously activate both the electrophilic and nucleophilic components, no improvements were observed (entry 5). Finally, by varying the acidic additives, we found that 10 mol% of the primary amine **A** in combination with benzoic acid (20 mol%) provided the best results,

efficiently catalyzing the process in toluene (0.2 M) at room temperature over 24 hours (5.2:1 dr, 96% ee, entry 9), and we chose this condition as the optimal for further exploration. Experiments that probe the scope of the reaction are summarized in table 2.

Table 2: Primary Amine-catalyzed Asymmetric Conjugate Addition of N-Boc Oxindoles to Cyclic Enones[a]



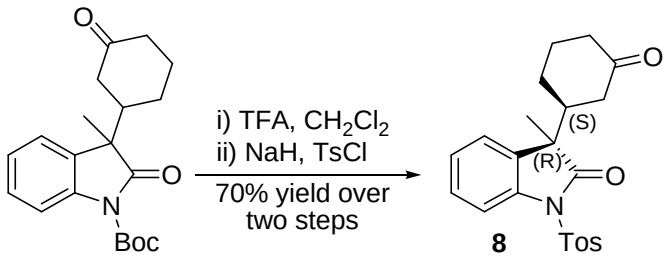
entry	R^1, R^2	Cat	n, X	3	Yield (%)[b]	dr [c]	ee (%)[d]
1	Bn, H	A	1, H	7a	80	5.2:1	96
2	Bn, H	B	1, H	7a	94	5.2:1	98 [e]
3	Bn, H	A	1, Me	7b	30	5.7:1	92
4[f,g]	Bn, H	A	0, H	7c	55	5.5:1	46
5[g]	Bn, H	A	2, H	7d	62	2.8:1	97
6	Me, H	A	1, H	7e	94	4:1	95
7	Me, H	B	1, H	7e	94	6:1	97 [e]
8[g]	Me, H	A	2, H	7f	70	2.5:1	95
9[f]	Ph, H	A	1, H	7g	95	1.6:1	98
10	3Cl-$PhCH_2$, Cl	A	1, H	7h	85	4:1	94

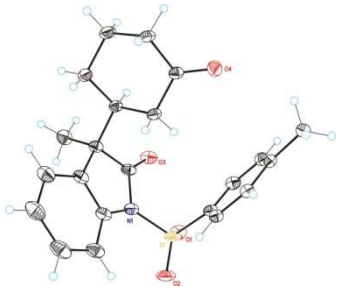
[a] The reactions were carried out at room temperature on a 0.2 mmol scale with 1.2 equiv of **5** and $[\mathbf{6}]_0$ = 0.2 M in toluene. [b] Isolated yield (sum of diastereomers). [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Determined by HPLC analysis on chiral stationary phases. [e] The opposite enantiomer of **7** has been obtained. [f] Reaction at 0 ºC. [g] Reaction carried out in the presence of 20 mol% of the catalyst over 48 hours.

Cyclohexen-2-one **6a** gave the reaction product in both the enantiomers under the catalysis of the tow chiral amine **A** and **B** (entries 1 and 2, Table 4). In addition other cyclic enones proved to be suitable substrates. The use of the cyclohexenone bearing two methyl groups at the 5-position led to the formation of product **7b** with decreased yield but high stereocontrol (entry 3). While 2-cycloheptenones afforded good results when reacted with oxindole **5b** (entry 5), 2-cyclopentenone followed a remarkably lower enantioselective path (entry 4). Oxindole with a

methyl substituent at the 3-position gave similar results in the conjugate additions (entries 6–8). Using the more reactive 3-phenyl oxindole afforded almost perfect enantiocontrol, albeit at the expense of the relative stereochemistry (entry 9).

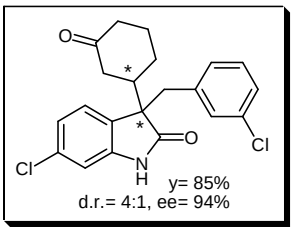
To determine the relative and absolute configuration of the reaction products the keto-oxindole **8** was deprotected and further converted to the *N*-Tos derivate **8** (Scheme 5).[104]





Interestingly, the presented organocatalytic method allowed the fast and highly stereoselective synthesis of **7h** (entry 10, see also Figure 1), a compound which has shown promising biological properties as an anticancer agent and which has been patented by Hoffmann-La Roche recently.

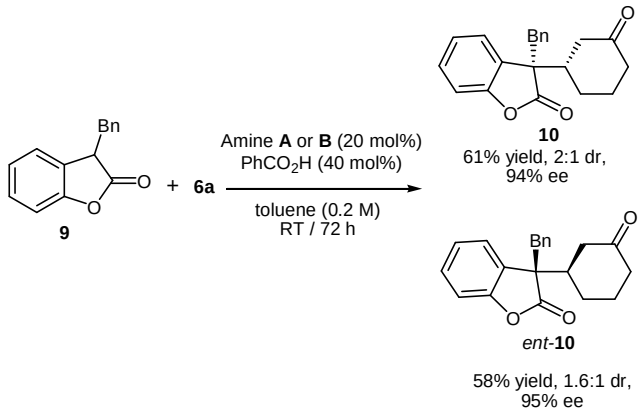
Figure 2: promising anti-cancer agent patented by Hoffmann-LaRoche[105]



Moreover we conduced also pioneering studies for the extension of this protocol to another class of heterocycle compound that had never been employed asymmetric catalytic conjugate additions.[106] We tested the reaction of 3-benzyl benzofuranone **9** with cyclohexen-2-one **6a** under the catalysis of amines **A** and **B** (Scheme 5). Notably, both the antipodes of the corresponding product **10** bearing a quaternary stereocenter were prepared with good

chemical yield and high enantioselectivity, even if the absence of the steric hinderance provided by the protecting group, has dramatic effects in the diastereocontrol of the reaction

Scheme 6: Enantioselctive fictionalization of Benzoforannones with α,β-usaturated cyclohexanone



In summary, we have presented a novel and easy way to access densely functionalized molecules that contain vicinal quaternary and tertiary stereocenters.[17] The research is based on the development of the first, highly stereoselective addition of oxindole to cyclic enones, using a readily available chiral primary amine catalyst. The utility of this reaction is related also at the synthesis in one step of a library of molecules that might exhibit biological activity. Concluding, we have extended this asymmetric organocatalytic transformation includding an unprecedented compounds class, benzofuranone derivatives.

Refereces

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[90] For recent examples on the use of chiral primary amine thiourea catalysts in enamine activation: a) D. A. Yalalov, S. B. Tsogoeva, T. E. Shubina, I. M. Martynova, T. Clark *Angew. Chem. Int. Ed.* **2008**, *47*, 6624; b) S. B. Tsogoeva, S. Wei, *Chem. Commun.* **2006**, 1451; c) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170; d) M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 6366. See also: e) S. Luo, H. Xu, J. Li. L. Zhang, J.-P. Cheng, *J. Am. Chem. Soc.* **2007**, *129*, 3074. Review: f) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713.

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[92] 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 [9]) 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.

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

[94] 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. [8b-c]

[95] 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)

[96] 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.

[97] 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.

[98] 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).

[99] The presence of the primary amine is crucial for the catalytic activity, see Ref [15]. At this point of investigations, a plausible Brønsted acid activation of unsaturated aldehydes can not be ruled out.

[100] (a) G.Bartoli, P. Melchiorre, *Synlett* **2008**, 1759. (b) Y.-C. Chen, *Synlett* **2008**, 1919 For the first demonstration that catalysts **A** or **B** can be used in iminium–enamine cascades of enones, see: (c) X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6070.

[101] For recent examples on the catalytic, asymmetric addition of oxindoles vinyl ketones, generating a single, quaternary stereocenter: (a) He, R.; Ding, C.; Maruoka, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 4559.

102 T. Bui, S. Syed and C. F. Barbas, III *J. Am. Chem. Soc.* **2009**, *131*, 8758.

[103] F. G.Bordwell, H. E. Fried *J. Org. Chem.* **1991**, *56*, 4218.

[104] Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, accession number CCDC 771490(**4**), and are available free of charge via www.ccdc.cam.ac.uk/data_request/cif.

[105] K.-C. So Lik, J. S.-S.Zhang, Z. Zhang, WO 2006/136606, **2006**.

[106] For an example of catalytic and enantioselective O-to-C rearrangements of O-acylated benzofuranone derivatives, see I. D. Hills, G. Fu *Angew. Chem. Int. Ed.* **2003**, *42*, 3921. For an early example, see: T. H. Black, S. M. Arrivo, J. S. Schumm, J. M. Knobeloch *J. Chem. Soc., Chem. Commun.* **1986**, 1524.

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.[xviii] 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.[xix] 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 **Vb**, 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene were purchased from Aldrich and used as received. Chiral primary amine catalysts, 9-Amino(9-deoxy)*epi*-hydroquinine **A**, its *pseudo*-enantiomer 9-Amino(9-deoxy)*epi*-hydroquinidine **B** and 6'-hydroxy-9-amino-9-deoxyepiquinine **C** and were prepared from commercially available hydroquinine, hydroquinidine and quinine, respectively, following the literature procedure.[xx] 2-Cyclohexen-1-one **6a**, 5,5-dimethyl-2-cyclohexen-1-one, 2-Cyclopenten-1-one, 2-Cyclohepten-1-one, 3-Methyl-2-oxindole, 6-Chloro-2-oxindole, were purchased from Aldrich or Alfa Aesar and used

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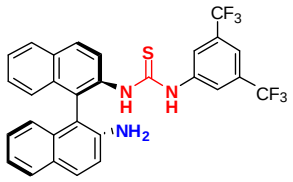
as received. *N*-Boc-Oxindole **5** derivatives[xxi] and 3-benzyl benzofuranone **8**[xxii] have been prepared according to the previously reported literature procedure.

Different substituted oxindoles were prepared following the literature procedures.[xxiii] α,β-Unsaturated aldehydes **2** were purchased from Aldrich or Lancaster and used as received or synthesized following the literature procedures.[xxiv] The "privileged" organocatalysts **I-II** were purchased from Aldrich and used as received.

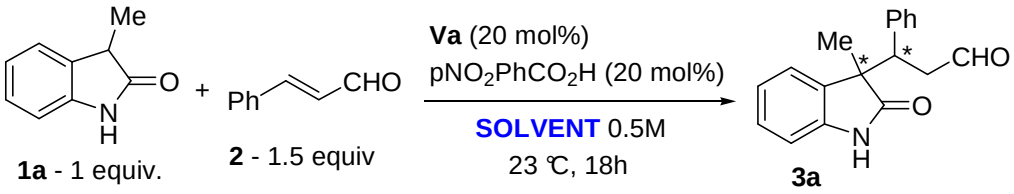
Determination of Diastereomeric Ratios. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture.

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 **IIa** as the catalyst.

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



Solvent Screen[a]



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

[xxi] (a) D. Villemin, B. Martin, *Synth. Commun.* 1998, 28, 3201-3208. (b) L. Canoira, J. G. Rodriguez, *J. Heterocyclic Chem.* 1985, 22, 1511-1518. (c) Rajeswaran, W. G.; Cohen, L. A. *Tetrahedron*, **1998**, *54*, 11375-11380; (d) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164; (e) Kato, Y.; Furutachi, M.; Chen, Z.; Mitsunuma, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9168–9169.

[xxii] M. Msaddek, M. Rammah, K. Ciamala, J. Vebrel, B. Laude, *Synthesis*, **1997**, 1495-1498.

[xxiii] (a) D. Villemin, B. Martin, Synth. Commun. **1998**, *28*, 3201-3208. (b)L. Canoira, J. G. Rodriguez, *J. Heterocyclic Chem*. **1985**, *22*, 1511-1518.

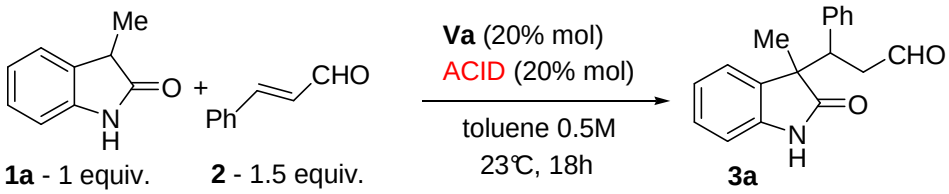
[xxiv] G. Battistuzzi, S. Cacchi, G. Fabrizi, *Org. Lett*. **2003**, 5, 777-780.

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
$CHCl_3$	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 ^{1}H NMR of the crude mixture. [c] ee of **3a** was determined by HPLC analysis (AD-H column).

Acids Screen [a]



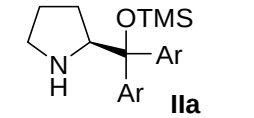
1a - 1 equiv. **2** - 1.5 equiv. **3a**

Table S2. Solvent Screen[a]

Acid	Conv (%) – 18h[b]	dr (%)[b]	ee (%)[c]
pNO_2PhCO_2H	55	4.5:1	84/31
TFA	77	1:3	<5
*o*F-$PhCO_2H$	38	5:1	86/40
$PhCO_2H$	51	6:1	90/52

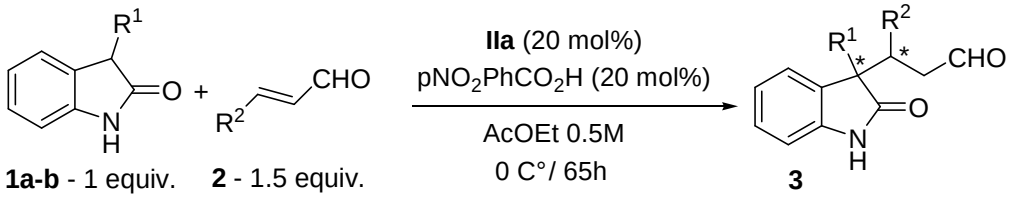
[a] Open-air reactions were carried out in undistilled solvent using a 1.5:1 ratio of **2a** to **1a**, 20 mol% of the catalyst, 20 mol% of the acid on a 0.1 mmol scale. [b] Determined by ^{1}H NMR of the crude mixture. [c] ee of **3a** was determined by HPLC analysis (AD-H column).

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



IIa

Ar = 3,5-$(CF_3)_2$-C_6H_3



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

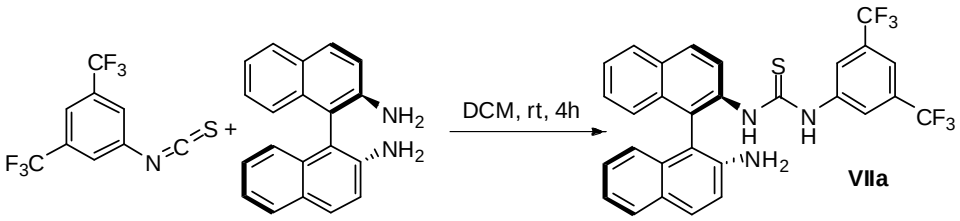
Table S3. Confronting the Privileged Catalyst IIa with Va[a]

R^1	R^2	Conv	dr[b]	IIa ee (%)		VIa	
				major	minor	dr	ee
Me	Me	80%	2.4:1	30	55	2.3:1	24
Me	p-NO_2Ph	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 **IIa**, 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

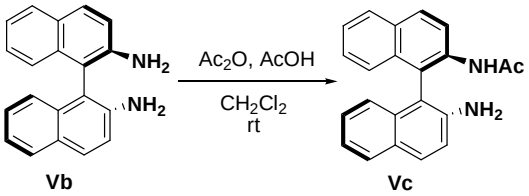
Synthesis of the Chiral Primary Amine Thiourea Catalyst VIIa. (R)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(1-(2-aminonaphthalen-1-yl)naphthalene-2-yl)thiourea.



VIIa

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)naphthalene-2-amine (2.16 mmol, 1.2 equiv., 610 mg) in dry CH_2Cl_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 **Va** 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, $CDCl_3$): δ 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 Vc



Acetic anhydride(0.5 mmol, 52 μL) is added at 0 °C to a solution of acetic acid (5 mmol, 300 μL) and **Vb** (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.[xxv]

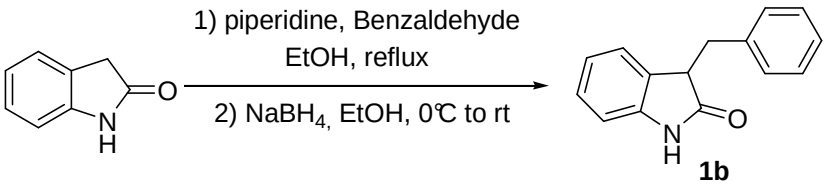
Synthesis of α,β-Unsaturated Aldehydes 2:

(*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]

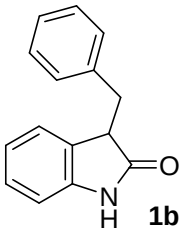
(*E*)-4-(3-oxoprop-1-enyl)benzonitrile has been obtained in a 50% yield following the literature procedure. ^{1}H-NMR and ^{13}C-NMR spectra were consistent with that previously reported.[4]

(*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

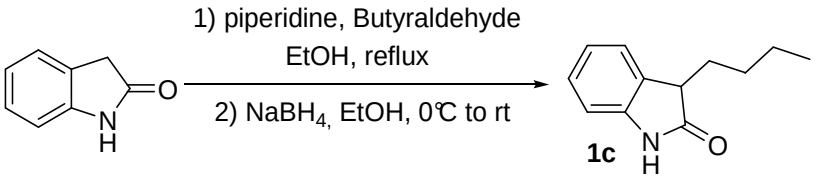


1b

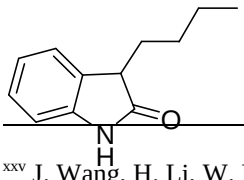


1b

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_4Cl 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]



1c

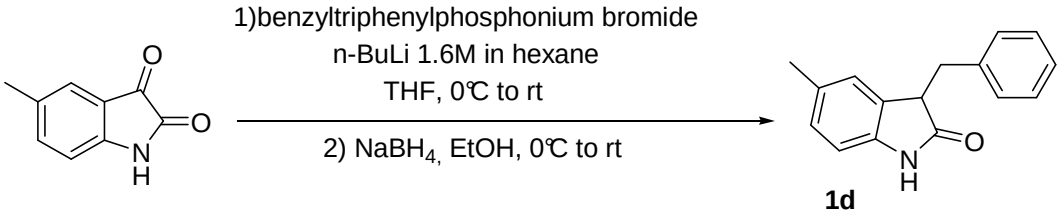


1c

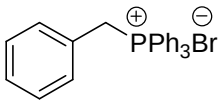
3-butylindolin-2-one 1c:In 50 ml flask containing a suspension of indolin-2-one (9 mmol, 798 mg) in absolute ethanol (9 ml)

[xxv] J. Wang, H. Li, W. Duan, L. Zu, W. Wang, *Org. Lett*. **2005,** *7*, 4713 – 4716.

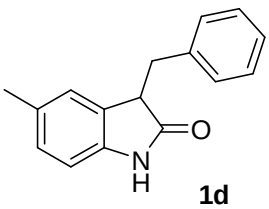
butyraldehyde (9.9 mmol, 881 µL) and piperidine (18 mmol, 1.778 ml) are added in sequence and the resulting solution is refluxed for 6 hours. Then the reaction flask is removed from the oil bath and cooled to ambient temperature and the solvent removed under reduced pressure. The crude mixture is dissolved 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_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/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, $CDCl_3$): δ13.9 (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).



1d



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.

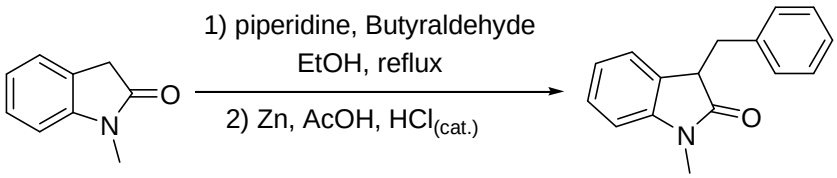


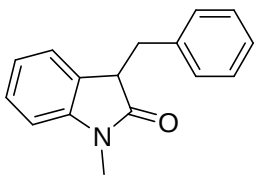
1d

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).



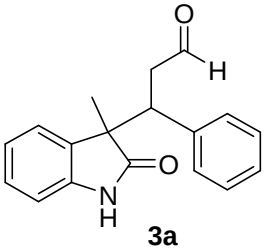


3-benzyl-1-methylindolin-2-one: In 50 ml flask containing a suspension of 1-methylindolin-2-one (2 mmol, 294.36 mg) in absolute ethanole (3 ml) benzaldehyde (2.2 mmol, 224 µL) and piperidine (4 mmol, 395 µL) are added in sequence and the resulting solution is refluxed for 4 hours. Then the reaction flask 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)naphthalene-2-yl)thiourea **Va** (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_4Cl 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.

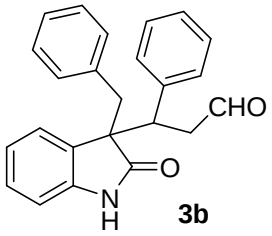


3a

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 **Va** 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

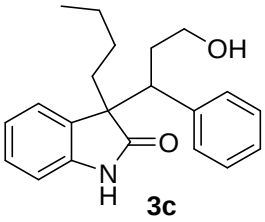
dr = 7.0:1 was determined by integration of ^{1}H-NMR signal (δ_{major} 1.45 ppm, δ_{minor} 1.34 ppm - s). The title compound was isolated by column chromatography (hexane/AcOEt = gradient from 8/2 to 7/3) as a colourless solid in 71% yield and 90% ee (major diasteroisomer). The ee was determined by 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: δ1.45 (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, $CDCl_3$): δ21.0 (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.



3b

3-(3-benzyl-2-oxoindolin-3-yl)-3-phenylpropanal – 3b (table 2 entry 2).

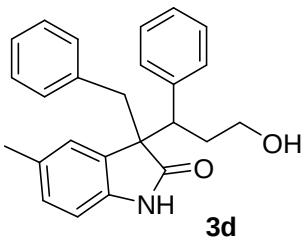
The reaction was carried out at 23 °C using 0.15 mmol (33.4 mg) of 3-benzylindolin-2-one **1b**, 0.225 mmol (28 μL) of cinnamaldehyde **2**, 0.015 mmol (10% mol, 8.3 mg) of **Va** and 0.075 mmol (50% mol, 9.1 mg) of benzoic acid in 300 μL of toluene following the general procedure. From the crude mixture 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_2Cl_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, $CDCl_3$): δ41.2 (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.



3c

3-butyl-3-(3-hydroxy-1-phenylpropyl)indolin-2-one - 3c (table 2 entry 3).

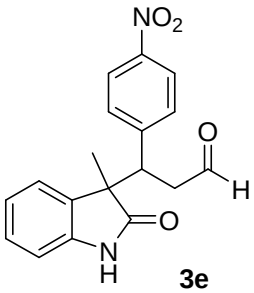
The reaction was carried out at 23 °C using 0.30 mmol (56.7 mg) of 3-butylindolin-2-one **1c**, 0.45 mmol (56.7 μL) of cinnamaldehyde **2**, 0.03 mmol (10% mol, 16.65 mg) of **VIa** and 0.15 mmol (50% mol, 18.3 mg) of benzoic acid in 600 μL of toluene following the general procedure. From the crude mixture 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_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. = 5:1 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.



3d

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.

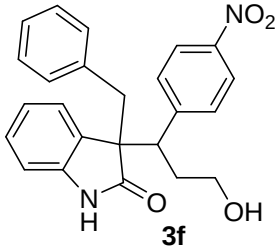


3e

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 diasteroisomer 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).

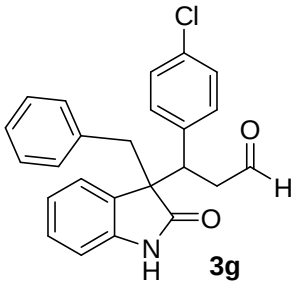
Exact mass (m/z): 338.1264, calculated: 338.1267.



3f

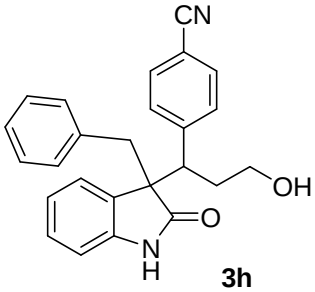
3-benzyl-3(3-hydroxy-1-(4-nitrophenyl)propyl)indolin-2-one 3f – (table 2, entry 6) The reaction was carried out at 23 °C using 0.15 mmol (33.4 mg) of 3-benzylindolin-2-one **1a**, 0.225 mmol (40 mg) of (*E*)-3-(4-nitrophenyl)acrylaldehyde **2**, 0.015 mmol (10% mol, 8.3 mg) of **VIIa** and 0.075 mmol (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 ^1H-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_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. = 11.5:1 was determined by integration of ^1H-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_2Cl_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). $[\alpha]^{rt}_D$= +37.7 (*c* = 0.910, $CHCl_3$, 92% ee). ^1H 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.



3g

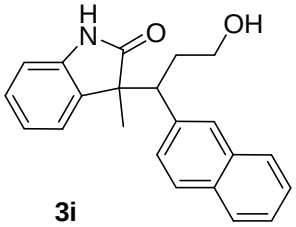
3-(3-benzyl-2-oxoindolin-3-yl)-3-(4-chlorophenyl)propanal – 3g (Table 2, entry 7). The reaction was carried out at 23 °C using 0.20 mmol (44.6 mg) of 3-benzylindolin-2-one **1b**, 0.3 mmol (49.8 mg) of (*E*)-3-(4-chlorophenyl)acrylaldehyde **2**, 0.02 mmol (10% mol, 11.1 mg) of **VIIa** and 0.10 mmol (50% mol, 12.2 mg) of benzoic acid in 400 μL 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_2Cl_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). $[\alpha]^{rt}_{D}$= -18.94 (*c* = 0.940, $CHCl_3$, 97% ee). ^{1}H NMR (400 MHz, $CDCl_3$): 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.



3h

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_4Cl was added to the solid mixture. The

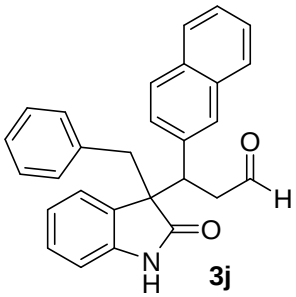
aqueous solution was extracted with dichloromethane (3 x 20 ml) and anhydrified with $MgSO_4$. NMR analysis of the crude mixture showed quantitative conversion into the corresponding alcohols as a mixture of diasteroisomers. The d.r. = 12.0:1 was determined by integration of ^{1}H-NMR signal (δ_{major} 6.45 ppm, δ_{minor} 6.52 ppm - m). The title compound was isolated as a single diastereoisomer by column chromatography (CH_2Cl_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). $[\alpha]^{rt}_D$= +22.09 (*c* = 0.825, $CHCl_3$, 83% ee).^{1}H NMR (400 MHz, $CDCl_3$): δ1.60 (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.



3i

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_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. = 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_2Cl_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} =

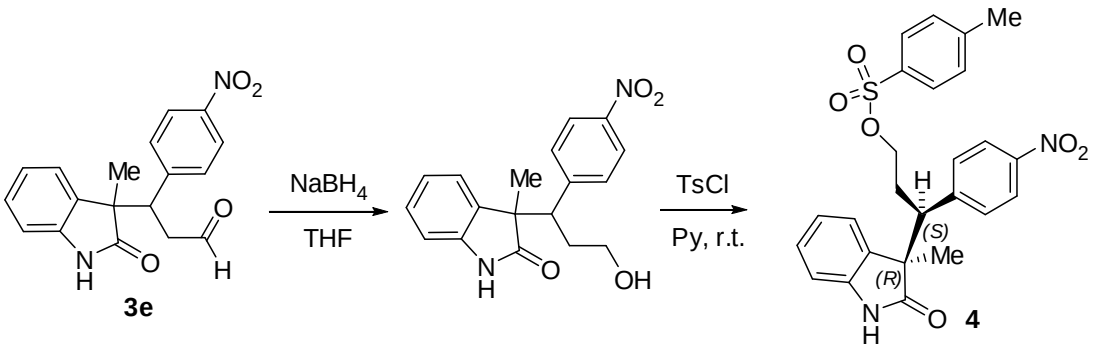
10.9 min). $[\alpha]^{rt}_D$= +67.91 (*c* = 0.925, $CHCl_3$, 80% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (s, 3H), 1.59-1.79 (brs, 1H), 2.10-2.26 (m, 1H), 2.27-2.40 (m, 1H), 3.24-3.49 (m, 3H), 6.62 (d, J = 7.7 Hz, 1H), 6.91 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.10 (dt, *J* = 1.1, 7.5 Hz, 1H), 7.20 (dt, *J* = 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.



3j

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_2Cl_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). $[\alpha]^{rt}_D$= -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.

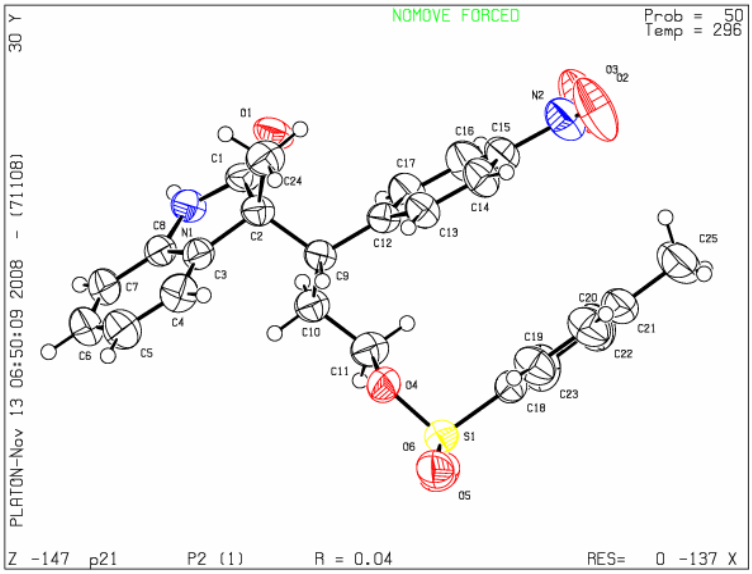
Determination of the Absolute Configuration.



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_4Cl 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_2Cl_2/AcOEt = 95/5) as a colourless solid in 50% yield. $[\alpha]^{rt}_D$= +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.

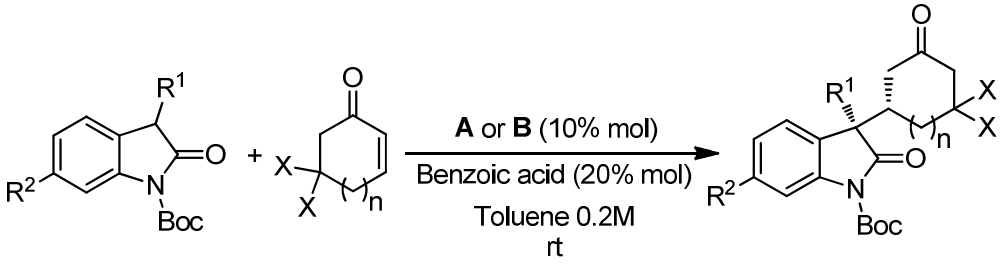
Crystal Data for compound 4



Crystals obtained from evaporation of a hexane/DCM solution, molecular formula: $C_{25}H_{24}N_2O_6S$, 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 $Mo_{K\alpha}$ radiation (λ = 0.71073 Å), $\mu(Mo_{K\alpha})$ = 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).

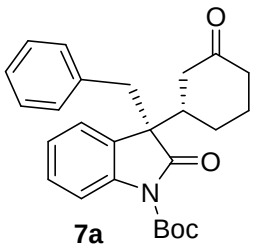
Determination of Enantiomeric Purity. HPLC analysis on chiral stationary phase was performed on an Agilent 1100-series instrumentation. Daicel Chiralpak AD-H, AS-H, IA or IC columns and Daicel Chiralcel OD-H with i-PrOH/hexane as the eluent were used. HPLC traces were compared to racemic samples prepared by carrying out the reactions in the presence of 1.5 equivalents of K_2CO_3 in THF as the solvent (RT, 48 hours reaction time).

General Procedure for the Organocatalytic Asymmetric Conjugate Additions of Oxindoles and Benzofuranones to Cyclic Enones



All the reactions were carried out with no precautions to exclude moisture in undistilled toluene. In an ordinary vial equipped with a magnetic stir bar, amine **A** or **B** (0.02 mmol, 6.5 mg, 10 mol%) and benzoic acid (0.04 mmol, 4.9 mg, 20 mol%) were dissolved in 1 mL of toluene. After stirring at r.t. for 10 minutes, the cyclic enones **2** (0.2 mmol) was added, followed by the addition of N-Boc oxindole **1** or benzofuranone **5** (0.24 mmol, 1.2 equiv). The vial was sealed, and the mixture stirred for the indicated time at r.t. The crude mixture was diluted with CH_2Cl_2 and flushed through a short plug of silica, using dichloromethane/ethyl acetate 1:1 as the eluent. Solvent was removed *in vacuo* and the Michael adduct **3** or **6** was purified by flash column chromatography (silica gel, hexane-EtOAc).

(*R*)-*tert*-butyl 3-benzyl-2-oxo-3-((*S*)-3-oxocyclohexyl)indoline-1-carboxylate (Table 4, entry 1).



7a

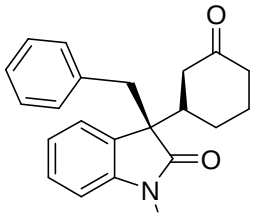
The reaction was carried out following the general procedure to furnish the crude product: (d.r. 5:1 determined by integration of ^{1}H-NMR signal: δ_{major} 3.04 ppm. d, δ_{minor} 3.05 ppm. d.).The title compound was isolated as a mixture of diastereoisomers by column chromatography (hexane/acetone = 90/10) in 80% yield 96% ee (major diastereoisomer) and 90% ee (minor diastereoisomer). HPLC analysis on a Daicel Chiralpak AD-H column: 98/2 hexane/*i*-PrOH, flow rate 0.50 mL/min, λ = 214, 254 nm: major diastereoisomer τ_{major} = 34.1 min, τ_{minor} = 41.7 min; minor diastereoisomer τ_{major} = 43.5 min,

τ_{minor} = 32.9 min; HRMS *calcd* for ($C_{26}H_{29}NO_4$): 419.2096, *found* 419.2092. $[\alpha]_{rt}^{D}$= - 17.37 (*c* = 0.98, $CHCl_3$, d.r. = 5:1, 96% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47-1.64 (m, 2H), 1.55 (s, 9H), 1.70-1.81 (m, 1H), 1.97-2.12 (m, 1H), 2.15-2.32 (m, 1H), 2.32-2.50 (m, 2H), 2.55-2.61 (m, 2H), [CH_2 A-B type spectrum (3.04, d, 1H, J_{gem}= -12.8 Hz), (3.30, d, 1H, J_{gem}= -12.8 Hz)], 6.72-6.77 (m 2H), 6.93-7.06 (m, 3H), 7.13-7.31 (m, 3H), 7.52-7.57 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 25.1 (CH_2), 26.4 (CH_2), 28.3 3X(CH_3), 41.4 (CH_2), 42.2 (CH_2), 43.0 (CH_2), 46.2 (CH), 57.4 (C), 84.3 (C), 115.0 (CH), 123.6 (CH), 124.4 (CH), 126.9 (CH), 127.9 (CH), 128.6 (CH), 129.3 (C), 130.0 (CH), 135.1 (C), 140.3 (C), 148.8 (C), 177.2 (C), 210.6 (C).

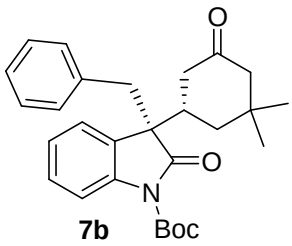
(*S*)-*tert*-butyl 3-benzyl-2-oxo-3-((*R*)-3-oxocyclohexyl)indoline-1-carboxylate (Table 4, entry 2).



ent-**7a**

The reaction was carried out following the general procedure to furnish the crude product: (d.r. 5:1 determined by integration of ^{1}H-NMR signal: δ_{major} 3.04 ppm. d, δ_{minor} 3.05 ppm. d.).The title compound was isolated as a mixture of diastereoisomers by column chromatography (hexane/acetone = 90/10) in 94% yield 96% ee (major diastereoisomer) and 90% ee (minor diastereoisomer). HPLC analysis on a Daicel Chiralpak AD-H column: 98/2 hexane/*i*-PrOH, flow rate 0.50 mL/min, λ = 214, 254 nm: major diastereoisomer τ_{major} = 41.7 min, τ_{minor} =34.1 min ; minor diastereoisomer τ_{major} = 32.9 min, τ_{minor} = 43.5 min; $[\alpha]_{rt}^{D}$= + 16.9 (*c* = 0.98, $CHCl_3$, dr = 5.2:1, 98% ee).

(*R*)-*tert*-butyl 3-benzyl-3-((*S*)-3,3-dimethyl-5-oxocyclohexyl)-2-oxoindoline-1-carboxylate (Table 4, entry 3).



7b

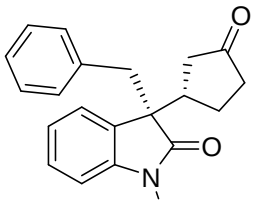
The reaction was carried out following the general procedure to furnish the crude product: (d.r. 5.7:1 determined by integration of ^{1}H-NMR signal: δ_{major} 0.86 ppm. s, δ_{minor} 0.95 ppm. s.). The title compound was isolated as a mixture of diastereoisomers by column chromatography (hexane/acetone = 90/10) in 30% yield and 92% ee, (major diastereoisomer) and 88% ee (minor diastereoisomer), d.r. 5.7:1. HPLC analysis on a Daicel Chiralpak AD-H column: 98/2 hexane/*i*-PrOH, flow rate 0.550 mL/min, λ = 214, 254 nm: major diastereoisomer τ_{major} = 17.67 min, τ_{minor} = 20.39 min; minor diastereoisomer τ_{major} = 28.40 min, τ_{minor} = 20.70 min; $[\alpha]_{rt}^{D}$= + 1.4 (*c* = 0.87, $CHCl_3$, 92% ee, d.r. = 5.7:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ0.86 (s, 3H), 1.00 (s, 3H), 1.33-1.39 (m, 1H), 1.43-1.52 (m, 2H), 1.55 (s, 9H), 2.09 (m, 1H), 2.18 (m, 2H), 2.54-2.66 (m, 3H), [CH_2 A-B type spectrum (3.01, d, 1H, J_{gem}=

-12.8 Hz), (3.30, d, 1H, J_{gem}= -12.8 Hz)], 6.71-6.76 (m, 2H), 6.94-7.00 (m, 2H), 7.01-7.05 (m, 1H), 7.17-7.24 (m, 2H), 7.25-7.28 (m, 1H), 7.51-7.56 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ25.4(CH_3), 28.0 (3 CH_3), 31.9 (CH_3), 34.3 (C), 39.3 (CH_2), 41.6 (CH_2), 41.7 (CH_2), 42.4 (CH_2), 54.2 (CH_2), 56.9 (C), 84.1 (C), 114.8 (CH), 123.0 (CH), 124.2 (CH), 126.6 (CH), 127.6 (CH), 128.3 (CH), 129.2 (C), 129.7 (CH), 134.7 (C), 140.0 (C), 148.5 (C), 177.1 (C), 210.6 (C).

(*R*)-*tert*-butyl 3-benzyl-2-oxo-3-((*S*)-3-oxocyclopentyl)indoline-1-carboxylate (Table 4, entry 4).



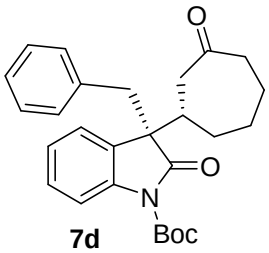
7c

The reaction was carried out following the general procedure to furnish the crude product: (d.r. 5.5:1 determined by integration of ^{1}H-NMR signal: δ_{major} 3.10 ppm. d, δ_{minor} 3.06 ppm. d.). The title compound was isolated as a mixture of diastereoisomers by column chromatography (hexane/ethyl acetate =85/15 to 70/30) in 55% yield and 46% 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: major diastereoisomer τ_{major} = 11.8 min, τ_{minor} = 14.2 min; $[\alpha]_{rt}^{D}$= - 14.1.0 (*c* = 1.00, $CHCl_3$, 46% ee).

^{1}H NMR (600 MHz, $CDCl_3$): δ 1. 54 (s, 9H), 1.57-169 (m, 1H), 1.87-1.98 (m, 1H), 2.02-2.18 (m 1H), 2.28 (dd, 1H, J^1= 19.3 Hz, J^2= 8.9 Hz), 2.42 (dd, 1H, J^1= 18.6 Hz, J^2= 7.4 Hz), 2.53 (dd, 1H, J^1=18.6 Hz, J^2= 12.0 Hz), 2.77-2.90 (m,1H), [CH_2 A-B type spectrum (3.10, d, 1H, J_{gem}= -14.1 Hz), (3.31, d, 1H, J_{gem}= -14.1 Hz)], 6.76-6.82 (m, 2H), 6.95-7.07 (m, 3H), 7.14-7.29 (m, 3H), 7.57 (d, 1H, 8.07 Hz).

^{13}C NMR (150 MHz, $CDCl_3$): δ 25.1 (CH_2), 28.3 (3 CH_3), 38.6 (CH_2), 39.9 (CH_2), 43.1 (CH_2), 45.0 (CH), 56.1 (C), 84.5 (C), 115.1 (CH), 123.8 (CH), 124.4 (CH), 127.0 (CH), 128.0 (CH), 130.0 (CH), 130.5 (C), 135.1 (C), 140.1 (C), 148.8 (C), 177.2 (C), 217.1 (C).

(*R*)-*tert*-butyl 3-benzyl-2-oxo-3-((*S*)-3-oxocycloheptyl)indoline-1-carboxylate (Table 4, entry 5).



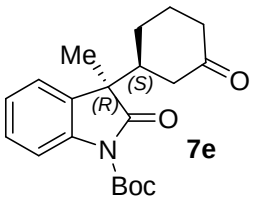
7d

The reaction was carried out following the general procedure using catalyst **A** to furnish the crude product: (d.r. 2.8:1 determined by integration of ^{1}H-NMR signal: δ_{major} 6.72-6.75 ppm. m, δ_{minor} 6.69-6.71 ppm. m). The title compound was isolated as a mixture of diastereoisomers by column chromatography (hexane/acetone =

90/10 to 85/15) in 62% yield and 98% ee. HPLC analysis on a Daicel Chiralcel OJ-H column: 98/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: major diastereoisomer τ_{major} = 23.7 min, τ_{minor} = 19.5 min; $[\alpha]_{rt}^{D}$= -29.9 (*c* = 1.10, $CHCl_3$, dr = 2.8:1, 98% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30-1.46 (m, 2H),1.53 (s, 9H), 1.64-1.82 (m, 1H), 1.83-2.09 (m, 3H), 2.43-2.66 (m, 4H), 2.66-2.76 (m, 1H), 3.04-3.35 (m, 2H), 6.67-6.75 (m, 2H), 6.93-7.07 (m, 3H), 7.09- 7.32 (m, 3H), 7.48-7.55 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9 (CH2), 28.3 (3 CH_3), 29.6 (CH_2), 31.5 (CH_2), 43.3 (CH_2), 43.4 (CH_2), 43.47 (CH), 43.7 (CH_2), 45.6 (C), 58.15 (C), 84.2 (C), 115.1 (CH), 123.7 (CH), 124.4 (CH), 126.9 (CH), 127.8 (C), 128.6, (CH), 128.8 (C), 130,0 (CH), 135.0 (C), 140.3 (C), 148.8 (C), 177.6 (C), 213.5

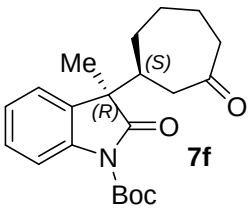


7e

(R)-tert-butyl 3-methyl-2-oxo-3-((S)-3-oxocyclohexyl)indoline-1-carboxylate (3e) (Table 4, entry 6).

The reaction was carried out at room temperature over 24 hours following the general procedure to furnish the crude product as a 4/1 mixture of diastereoisomers (d.r. 4:1 determined by HPLC and GC-MS analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 90/10) in 94% yield (as a 4:1 mixture of diastereoisomers) and 95% ee. HPLC analysis on a Daicel Chiralpak IC column: 8/2 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: Major diastereomer (95% ee): τ_{minor} = 17.7 min, τ_{major} = 25.5 min; Minor diastereomer (85% ee): τ_{major} = 11.2 min, τ_{minor}= 19.3 min. HRMS *calcd* for ($C_{20}H_{25}NO_4$+Na): 366.1681, *found* 366.1670. $[\alpha]_{rt}^{D}$= -36.9 (*c* = 0.63, $CHCl_3$, dr 4:1, 95% ee_{major}, 85% ee_{minor}).

^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers 1.5:1): δ 1.34 - 1.57 (m, 5H), 1.64 (s, 10H), 1.97 -2.04 (m, 1H), 2.13 -2.23 (m, 2H), 2.31-2.41 (m, 2H), 2.45-2.51 (m, 1H), 7.14 - 7.19 (m, 2H), 7.28 - 7.33 (m, 1H), 7.84 (d, *J* = 8.8Hz, 1H,). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 25.1, 25.9, 28.1 41.2, 42.6 46.9 51.0, 84.8 115.2 122.9, 124.8, 128.6, 132.1 (CH), 139.4 (C), 149.2, 178.2 (C), 210.8.



7f

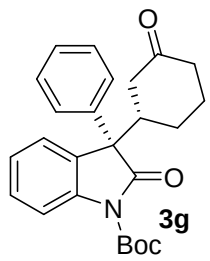
(R)-tert-butyl-3-methyl-2-oxo-3-((S)-3-oxocycloheptyl)indoline-1-carboxylate (3f) (Table 4, entry 8).

The reaction was carried out at room temperature over 48 hours following the general procedure and using 20 mol% of catalyst **A** to furnish the crude product as a 2.5/1 mixture of diastereoisomers (d.r. 2.5:1 determined by integration of ^{1}H-NMR signal: δ_{major} 1.46 s, δ_{minor} 1.44 ppm. s). The title

compound was isolated as a colorless oil by column chromatography (hexane/AcOEt = 90/10) in 70% yield (as a 2.5:1 mixture of diastereoisomers) and 95% ee. HPLC analysis on a Daicel Chiralpak IC column: 9/1 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: Major diastereomer (95% ee): τ_{minor} = 30.3 min, τ_{major} = 58.5 min; Minor diastereomer (93% ee): τ_{major} = 18.9 min, τ_{minor} = 33.9 min. HRMS *calcd* for ($C_{21}H_{27}NO_4$+Na): 380.1838, *found* 380.1833. $[\alpha]_{rt}^{D}$= -61.7 (*c* = 0.72, $CHCl_3$, dr 2.5:1, 95% ee_{major}, 93% ee_{minor}).

^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers 2.5:1): δ 1.19 - 1.35 (m, 2H), 1.44 (s,3H,minor), 1.46 (s,3H,maior), 1.48 -1.56 (m, 1H), 1.64 (s, 9H,major), 1.64 (s, 9H,minor), 1.84-1.98(m,3H), 2.16 - 2.14 (m, 1H), 2.36-2.57 (m, 4H), 7.12 - 7.18 (m, 2H), 7.27 - 7.32 (m, 1H), 7.81- 7.84(m, 1H,).

^{13}C NMR (100 MHz, $CDCl_3$): δ23.2 24.1 24.8, 28.3, 28.8, 29.4, 31.0, 32.0, 43.6, 44.1 44.3, 44.8, 45.1, 51.5, 51.8, 84.7, 115.2, 122.8, 123.1, 124.7, 128.4, 131.4, 131.8, 139.4, 149.2, 178.6, 178.8, 213.2, 213.5.



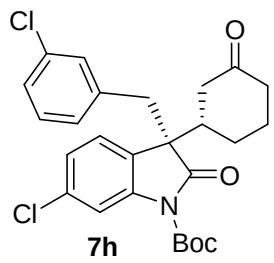
3g

(S)-tert-butyl 2-oxo-3-((S)-3-oxocyclohexyl)-3-phenylindoline-1-carboxylate (3g) (Table 4, entry 9).

The reaction was carried out at 0°C over 18 hours following the general procedure to furnish the crude product as a 1.5/1 mixture of diastereoisomers (d.r. 1.5:1 determined by integration of ^{1}H-NMR signal: δ_{major} 7.98 d, δ_{minor} 7.95 ppm. d). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 85/15) in 95% yield (as a 1.5:1 mixture of diastereoisomers) and 98% ee. HPLC analysis on a Daicel Chiralpak IC column: 8/2 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: Major diastereomer (98% ee): τ_{minor} = 9.8 min, τ_{major} = 12.5 min; Minor diastereomer (88% ee): τ_{minor} = 14.7 min, τ_{major} = 32.2 min. HRMS *calcd* for ($C_{25}H_{27}NO_4$+Na): 428.1838, *found* 428.1847. $[\alpha]_{rt}^{D}$= +26.2 (*c* = 0.65, $CHCl_3$, dr 1.5:1, 98% ee_{major}, 88% ee_{minor}).

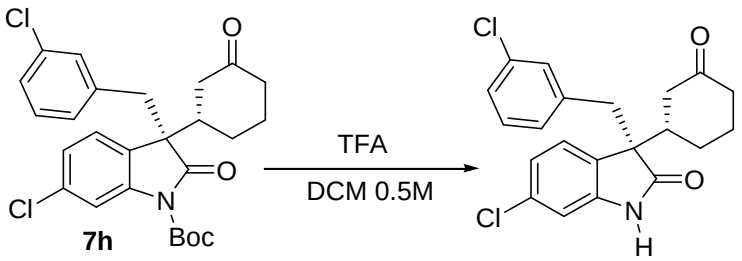
^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers 1.5:1): δ 1.61 (m, 9H), 1.54-1.76 (m, 3H), 1.92-2.05 (m, 2H), 2.09-2.20 (m, 1H), 2.25-2.39 (m, 2H), 2.95-3.05(m, 1H), 7.23-7.46 (m, 9H), 7.95 (d, *J* = 7.8, 1H, *minor*), 7.98 (d, *J* = 8.3, 1H, *major*). ^{13}C NMR (100 MHz, $CDCl_3$): δ24.5 (CH_2), 24.7 (CH_2), 25.7 (CH_2), 26.5 (CH_2), 28.0 (CH_3), 40.9 (CH_2), 41.1 (CH_2), 42.6 (CH_2), 43.1 (CH_2), 46.5 (CH), 46.6 (CH), 59.8 (C), 59.9 (C), 84.7 (CH), 115.4 (CH), 115.5 (CH), 124.2 (CH), 124.3 (CH), 125.59 (CH), 125.63 (CH), 127.3 (CH), 127.4 (CH), 127.7 (CH), 127.8 (CH), 127.91 (CH), 127.99 (CH), 128.7 (CH), 128.8 (CH), 128.9 (CH), 136.6 (C), 137.4 (C), 140.2, 148.9 (C), 149.0 (C), 175.5 (C), 175.9 (C), 209.8 (C), 209.9 (C).

(*R*)-*tert*-butyl 3-(3-chlorobenzyl)-6-chloro-2-oxo-3-((*S*)-3-oxocyclohexyl)indoline-1-carboxylate (Table 4, entry 10).



7h

The reaction was carried out following the general procedure to furnish the crude product: (d.r. 4:1 determined by integration of ^{1}H-NMR signal: δ_{major} 6.76 ppm. m, δ_{minor} 6.82 ppm. m.). The title compound was isolated as a mixture of diastereoisomers by column chromatography (hexane/acetone = 85/15) in 85% yield and 94% ee (major diastereisomer) and 94% ee (minor diastereoisomer). HPLC analysis on a Daicel Chiralcel OD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.600 mL/min, λ = 214, 254 nm: major diastereoisomer τ_{major} = 25.2 min, τ_{minor} = 40.7 min; minor diastereoisomer τ_{major} = 31.1 min, τ_{minor} = 34.7 min.

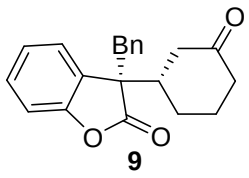


7h

Compund **7h** (0.18 mmol, 1 equiv.) was dissolved in 360 µL of dichloromethane then TFA was slowly added at room temperature. The resulting mixture was stirred at room temperature for 6 hours then it was diluited with ethyl acetate and a saturated solution of $NaHCO_3$ was added at 0°C. The organic phase was separated and water was extracted 3 times with ethyl acetate. Organic phase was anhydrified with $MgSO_4$ filtered and the solvent removed under reduced pressure. The crude mixture (d.r. 4:1 determined by integration of ^{1}H-NMR signal: δ_{major} 8.02 ppm. bs, δ_{minor} 8.12 ppm. bs.) was purified by flash column chromatography using dichloromethane/ethyl acetate 95:5 as the eluent mixture. (*R*)-3-(3-chlorobenzyl)-6-chloro-3-((*S*)-3-oxocyclohexyl)indolin-2-one was obtained as single diastereosiomers in 40% and 94% ee. HPLC analysis on a Daicel Chiralcel OD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.650 mL/min, λ = 214, 254 nm: τ_{major} = 30.4 min, τ_{minor} = 33.9 min.

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.48-1.62 (m, 2H), 1.82-1.89 (m, 1H), 2.05-2.12 (m, 1H), 2.16-2.27 (m, 1H), 2.32-2.43 (m, 3H), 2.49-2.56 (m, 1H), [CH_2 A-B type spectrum (3.04, d, 1H, J_{gem}= -12.9 Hz), (3.22, d, 1H, J_{gem}= -12.9 Hz)], 6.66-6.74 (m, 2H), 6.83 (bs, 1H), 6.96 (t, *J* = 7.9 Hz, 1H), 7.03-7.06 (m, 1H), 7.08 (dd, J_1 = 7.9 Hz, J_2 = 1.9 Hz, 1H), 7.20 (d, *J* = 8.1 Hz), 7.42 (bs, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 24.7 (CH2), 25.9 (CH_2), 40.1 (CH_2), 41.0 (CH_2), 42.5 (CH_2), 45.4 (CH), 57.2 (C), 110.4 (CH), 122.4 (CH), 125.0 (CH), 126.9 (CH), 127.9 (CH), 128.2 (C), 129.0 (CH), 129.9 (CH), 133.5 (C), 134.1 (C), 137.2 (C), 142.1 (C), 179.5 (C), 210.1 (C).



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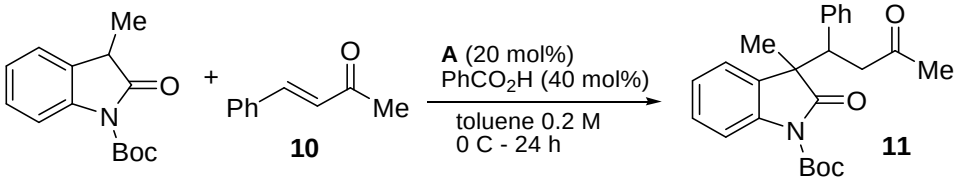
(R)-3-benzyl-3-((S)-3-oxocyclohexyl)benzofuran-2(3H)-one (6) (Scheme 2).

The reaction was carried out at room temperature over 72 hours following the general procedure to furnish the crude product as a 2/1 mixture of diastereoisomers (d.r. 2:1 determined by HPLC of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 90/10) in 61% yield (as a 2:1 mixture of diastereoisomers) and 94% ee. HPLC analysis on a Daicel Chiralpak IA column: 97/3 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: Major diastereomer (94% ee): τ_{major} = 26.1 min, τ_{minor}= 30.4 min; Minor diastereomer (95% ee): τ_{minor} = 19.34 min, τ_{major} = 24.43 min. $[\alpha]_{rt}^{D}$= 6.3 (*c* = 0.51, $CHCl_3$, dr 4:1, 95% ee_{major}, 95% ee_{minor}).

^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers 1.5:1): δ 1.45 - 1.67 (m, 3H), 2.05 - 2.11 (m, 1H), 2.17-2.33 (m, 1H), 2.37 -2.63 (m, 4H),3.13-3.17(m,1H), 3.26-3.32(m,1H),6.78 - 6.89 (m, 3H), 7.01-7.09 (m, 3H), 7.16 - 7.3 (m, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 24.6, 26.2, 41.1 42.7, 45.7, 57.2, 110.7, 124.0, 127.0, 127.5, 128.1, 129.1, 129.2, 134.5, 153.2, 177.6, 209.5.

Organocatalytic Conjugate Additions of Oxindoles to linear *trans*-4-phenyl-3-buten-2-one



The reactions was carried out with no precautions to exclude moisture in undistilled toluene. In an ordinary vial equipped with a magnetic stir bar, amine **A** (0.04 mmol, 13 mg, 20 mol%) and benzoic acid (0.08 mmol, 9.6 mg, 40 mol%) were dissolved in 0.5 mL of toluene. After stirring at 0°C for 10 minutes, the kenones **10** (0.2 mmol) was added, followed by the addition of N-Boc 3-methyl-oxindole (0.24 mmol, 1.2 equiv) in toluene (0.5 mL). The vial was sealed, and the mixture stirred for 24 hours at 0°C. The crude mixture was diluted with CH_2Cl_2 and flushed through a short plug of silica, using dichloromethane/ethyl acetate 1:1 as the eluent.

Solvent was removed *in vacuo* to furnish the crude product as a 1.4/1 mixture of diastereoisomers (d.r. 1.4:1 determined by integration of ^{1}H-NMR signal: δ_{major} 2.41 s, δ_{minor} 2.37 ppm. s). The title compound was isolated as a colorless oil by column chromatography (hexane/AcOEt = 90/10) in 72% yield (as a 1.5:1 mixture of diastereoisomers) and 95% ee. HPLC analysis on a Daicel Chiralpak IC column: 9/1 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: Major diastereomer (95% ee): τ_{major} = 11.9 min, τ_{minor} = 16.3 min; Minor diastereomer (94% ee): τ_{minor} = 14.5 min, τ_{major} = 19.0 min. HRMS *calcd* for ($C_{24}H_{27}NO_4$+Na): 416.1838, *found* 416.1829. $[\alpha]_{rt}^{D}$= +6.3 (*c* = 0.53, $CHCl_3$, dr 1.4:1, 95% ee_{major}, 94% ee_{minor}).

^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers 1.5:1): δ 1.43 (s, 3H, minor), 1.46 (s, 3H,major), 1.52(s,9H,major), 1.61(s,9H,minor), 1.97(s,3H,major), 2.02(s, 3H,minor), 3.61-3.64 (m, 4H), 3.60-3.72 (m, 2H), 6.79-6.83 (m, 2H), 6.92-6.96 (m, 2H), 7.05-7.19 (m, 10H), 7.26-7.31 (m, 1H),7.53 (d *J* = 8.8Hz 1H), 7.63 (d *J* = 7.6Hz 1H)

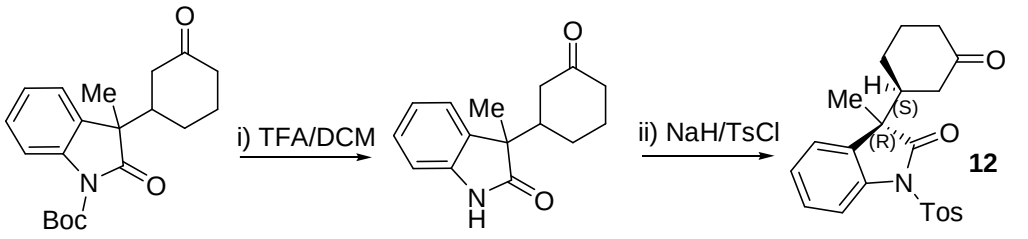
^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 22.5, 28.2 ,30.6, 43.4, 43.7, 48.9, 51.5, 51.8, 83.9, 84.2, 114.7, 114.9, 123.6, 123.7, 124.0, 124.2, 127.2, 127.4, 127.7, 127.8, 128.1 128.6, 128.8, 128.9, 130.7, 131.8, 137.9, 138.5, 138.7, 139.6, 148.7, 148.9, 178.1, 178.7, 206.4, 207.

Absolute and Relative Configuration Determination

X-Ray Structure Analysis.

The absolute and relative configurations of compound **4** (Scheme 1) were assigned by X-ray crystallographic analysis. CCDC 771490 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Synthesis of *N*-Tos derivative 4 (Scheme 1)[xxvi]



Compound **7e** (0.2 mmol) was dissolved in DCM (5 mL) and TFA (3 equiv) was added at room temperature. After 16 h, the reaction was diluted with DCM (5 mL), washed successively with

[xxvi] K. Jiang, J. Peng, H.-L. Cui, Y.-C. Chen *Chem. Comm.* **2009**, 3955-3957.

saturated Na_2CO_3 and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Then the product was purified by chromatography to yield the pure N-H free oxindole derivative as a white solid. NaH (2 equiv) was suspended in THF (3 mL), and a solution of the above compound (0.15 mmol) in THF (2 mL) was slowly added at 0 °C. Then TosCl (1.3 equiv) was added. After 6 h, the reaction was quenched with water (0.5 mL). The mixture was diluted with EtOAc (5 mL), washed with brine. The organic layer was dried (Na_2SO_4), and concentrate *in vacuo*. The crude product was purified by flash chromatography PE/EA (10:1) to afford **12** as a white solid (0.14 mmol, 70% overall yield). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers 4:1): δ 1.28 (s, 3H), 1.32-1.45 (m, 2H), 1.83-1.91 (m, 1H), 2.01-2.28 (m, 2H), 2.39 (s, 3H, minor), 2.43 (s, 3H, major), 2.02(s, 3H,minor), 7.07-7.22 (m, 2H), 7.29-7.37 (m, 4H), 7.93-7.99 (m, 4H). HPLC analysis on a Daicel Chiralpak IA column: 85/15 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: Major diastereomer (95% ee): τ_{major} = 32.4 min, τ_{minor} = 37.9 min; Minor diastereomer: τ_{minor} = 34.1 min, τ_{major} = 39.4 min. HPLC analysis on a crystal morphologically similar to the one used for X-ray ananlysis demonstrated the presence of single enantiomer of the major diasteroisomer (τ_{major} = 32.4 min, single pick).

Single Crystal X-ray Diffraction Data:

X-ray structure determinations: Crystals of compound **4** were obtained by slow evaporation in a mixture of Hexane and Diethyl-ether in a 1:1 portion at room temperature. The measured crystals were stable under atmosphere conditions; nevertheless they were prepared under inert conditions immersed in perfluoropoly-ether as protecting oil for manipulation.

Data Collection. Measurements were made on a Bruker-Nonius diffractometer equipped with an APPEX 2 4K CCD area detector, a FR591 rotating anode with $Mo_{K\alpha}$ radiation, Montel mirrors and a Kryoflex low temperature device (T = -173 °C). Full-sphere data collection was used with ω and φ scans.

Programs used: Data collection Apex2 V2009 1.0 (Bruker-Nonius 2008), data reduction Saint + Version 7.60A (Bruker AXS 2008) and absorption correction SADABS V. 2008-1 (2008).

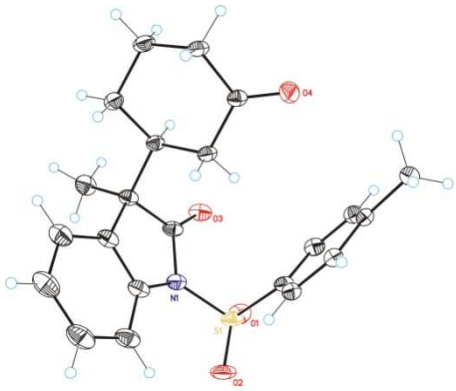
Structure Solution. SHELXTL Version 6.10 (Sheldrick, 2000) was used.[xxvii]

Structure Refinement. SHELXTL-97-UNIX VERSION.

[xxvii] G. M. Sheldrick (1998) *SHELXTL Crystallographic System Ver. 5.10*, Bruker AXS, Inc.: Madison, Wisconsin.

(1) Crystal data for **TX1** at 100 K: C_{22} H_{23} N_1 O_4 S_1 397.47 $gmol^{-1}$, orthorhombic, $P2_12_12_1$, a = 11.0798(8) Å, b = 11.7870(6) Å, c = 14.9095(7) Å, 1947.14(19) Å3, Z = 4, ρ_{calcd} = 1.356 Mg/m^3, R_1 = 0.0373 (0.0418), wR2 = 0.1039 (0.1096), for 6622 reflections with I>2σ(I) (for 7224 reflections [R_{int}: 0.0189] with a total measured of 13438 reflections), 255 parameters, goodness-of-fit on F^2 = 0.875, largest diff. peak (hole) = 0.629 (-0.214) e $Å^{-3}$. Absolute structure Flack Parameter: 0.07(4)

CCDC 771490



2.2 MOLECULES

Spiro Oriented Synthesis: Organocatalytic Asymmetric construction of Spirocyclic oxindoles

"There is excitement, adventure and challenge,
and there can be great art in organic synthesis"

R. B. Woodward[107]

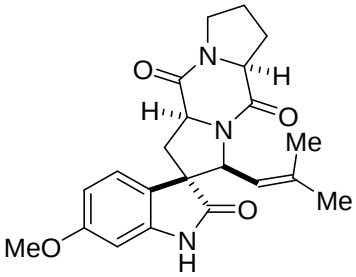
One of the goal of organic synthesis is the construction of a give organic compound from readily available starting materials and reagents in the most efficient and environmentally safe way.[108]

Nature, since millions of years, assembled her targets using this philosophy, through cascade reactions where simple raw materials are converted into complex metabolites employing numerous chemical processes in which the product of one step is the reagent for the next one. In general is possible to observe that all life is regulated through cascade reaction from the Krebs' cycle to the neurotransmission. In the field of organic chemistry the development of domino reactions represented an impressive breakthrough,[109] in fact with the introduction of this synthetic strategy was possible build intricate molecular architecture in one step avoiding time-consuming and costly protection/deprotection processes as well as the purification of intermediates.[110]

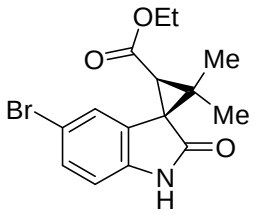
Then the design of cascades reaction to address the synthesis of molecules of considerable structural and stereochemical complexity became a significant intellectual challenge and can be one of the most impressive activities in the target oriented synthesis.

Recently spirooxindoles have attracted the attention of organic chemist for two main reasons: the first is connected to their unique structural challenge, and the second derived from their biological activity, indeed the spirooxindolic motif is the principal core of a wide range of natural products and medicinal interesting compounds (Figure **1**).[111, 112]

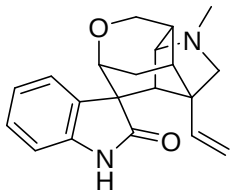
Figure 1: Some naturally occurring and bioactive spirocyclic oxindoles.



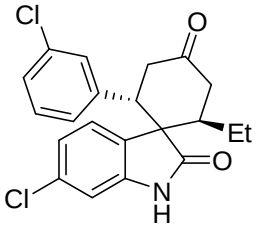
Spirotryprostatin A



NNRTIs HIV-1 inhibitor



Gelsemine



inibitor of MDM2-p53 interaction

For these reasons both the academic and the industrial world, start to evaluate small library of this class of compounds finding good drug candidates for the treatment of *e.g.* cancer,[113] tuberculosis,[114] and malaria.[115]

Despite the great interest that this class of compounds have aroused in the scientific community, their molecular and stereochemical complexity still represents a significant deterrent for their synthesis.

[116] The construction of a highly hindered, strained spirocyclic quaternary chiral centre is in fact not a trivial task, especially in an enantioselective fashion.[117]

During my Phd studies I provided to address the problem of the enantioselective synthesis of spyrooxidoles developing three asymmetric protocols, that are here discussed on the basis of the synthetic strategy employed to prepare them

Reference

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2.2.1. Aminocatalytic cascade reactions for the construction of highly densely functionalized Spirooxindoles

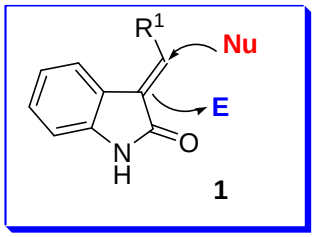
Discussion

As affirmed the design of cascade reactions to address the synthesis of molecules of considerable structural and stereochemical complexity became a significant intellectual challenge and can be considered one of the most impressive activities in the target oriented synthesis. In organocatalysis this term is undoubtedly associated with the extraordinary studies of the Jørgensen's, MacMillan's and Enders' groups.

The ability of an aminocatalyst to combine two orthogonal activation modes, as LUMO-lowering and HOMO-raising activation, allowed the design of tandem[118] and cascade[119] sequences for the functionalizzation of α,β-unsaturated aldehydes and ketones.

We applied this philosophy to the one step synthesis of complex spirooxindolic derivates. Central of our approach was the identification of a suitable compound bearing the oxindole moiety capable to change its polarity during the reaction (Figure **1**).

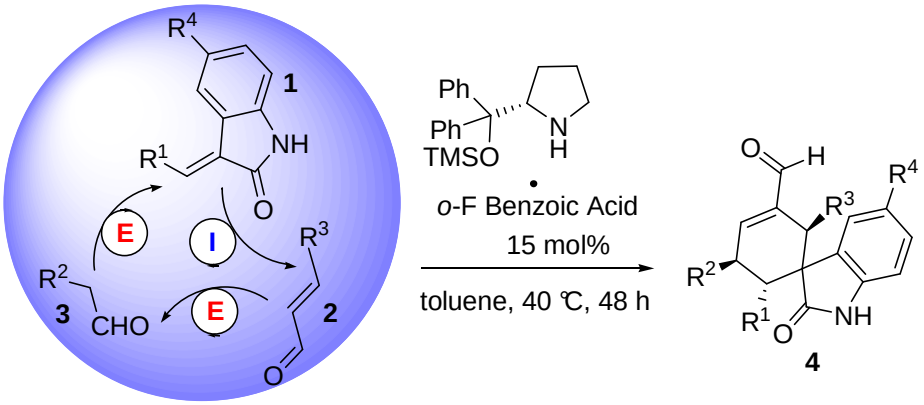
Figure 1: Suitable compound for the design of aminocatalytic cascade reaction for the synthesis of spirooxindoles.



We minded that, likewise reported in the cascade of Enders *et al.* for nitrostyrene, the substrates **1** acted as Michael acceptor and then, after the nucleophile addition, became a 3-substituted oxindole that is an electronrich compound as described in chapter 2.1.3..

We performed the tricomponent reaction between cynnamaldehyde **2**, crotonaldehydes **3** and 3-benzylidenindolin-2-one **1a** in the presence of 15 mol% of Hayashi's catalyst and 15 mol% of *ortho*-Fluoro Benzoic Acid (Table **1**, entry 1).

Table 1: Scope of the asymmetric construction of cyclohexen spirooxindoles through triple organocascade reaction.



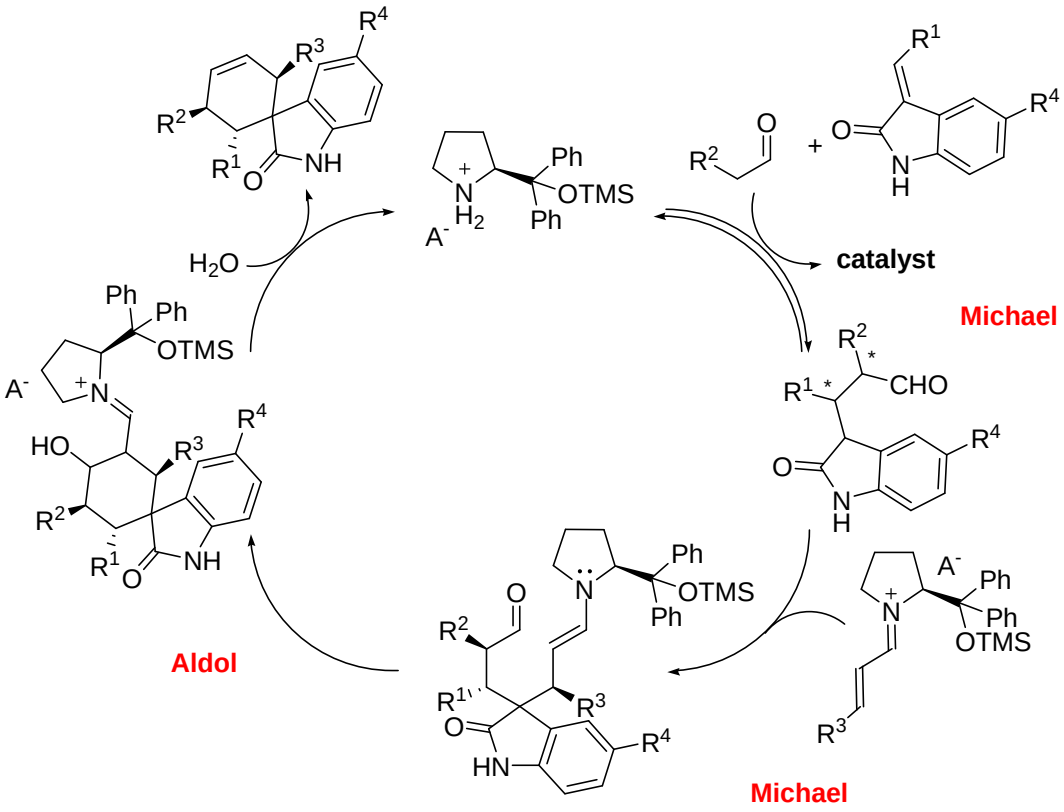
Entry	R^1	R^2	R^3	R^4	Yield (%)[a]	dr[b]	ee (%)[c]
1	Ph	Me	Ph	H	74	12:1	>99
2	Ph	Me	*p*-MeOPh	H	70	16:1	>99
3	Ph	Me	*p*-NO_2Ph	H	35	>19:1	>99
4	Ph	Me	*p*-FPh	H	50	>19:1	>99
5	Ph	Me	*o*-MePh	H	50	>19:1	98
6	Ph	Me	Ph	Cl	47	12:1	>99
7	Ph	Me	Ph	Me	40	12:1	>99
8	propyl	Me	Ph	H	40	19:1	98
9	CO_2Et	Me	Ph	H	60	12:1	>99
10	C(=O)Ph	Me	Ph	H	46	>19:1	>99
11	CO_2Et	Me	Me	H	58	>19:1	98
12	CO_2Et	n-butyl	Ph	H	65	>19:1	>99
13	CO_2Et	benzyl	Ph	H	65	19:1	>99
14	CO_2Et	allyl	Ph	H	64	19:1	>99

[a] Yield of the isolated major diastereomer. [b] The diastereomeric ratio (dr) was determined by ^{1}H NMR analysis of the crude reaction mixture. [c] The enantiomeric excess (ee) were determined by HPLC analysis on chiral stationary phases.

Surprisingly the reaction afforded smoothly almost one stereoisomer between the 16 possible,[120] in good yield. Extending this methodology to other substrates we synthesized a small library of cyclohexen spirooxidoles bearing four contiguous sterocenters whereof a quaternary one.

The high diastereoselction obtained suggests that in the first step of the reaction a retro-Michael process occurs that allowed at only one diastereoisomer (the thermodynamic) to react in the Michael/aldol step driving the reaction pathway to the final product in very high diastereoisomeric ratio (Scheme **1**).[121, 2a]

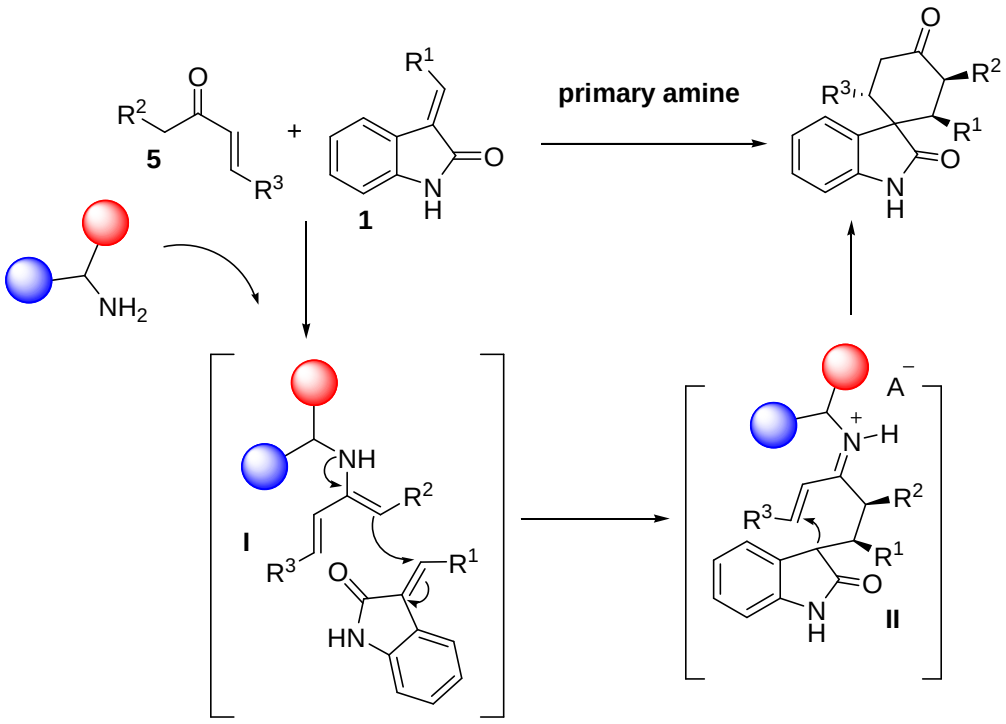
Scheme 1: Proposed mechanism of the Michael/Michael/aldol Organocascade reaction promoted by Hayashi's Catalyst



Extending our studies on the synthesis of others highly functionalized spirooxindole, we then focused on the development of a complementary organocascade strategy founded on the unique possibility that primary amine catalyst offered to activate α,β-unsaturated ketones. .

In the design plan the chiral inductor, through the condensation with the substrates, might formed a dienamine intermediate **I**. This α-nucleophilic species might attack the compound **1** and then, once formed a LUMO-lowered iminium-ion **II**, undergo the intramolecular cyclizzation (Scheme **2**).

Scheme 2: *Tandem reaction (dienamine/iminium ion) for the synthesis of spirocyclic oxindolic cyclohexanones*



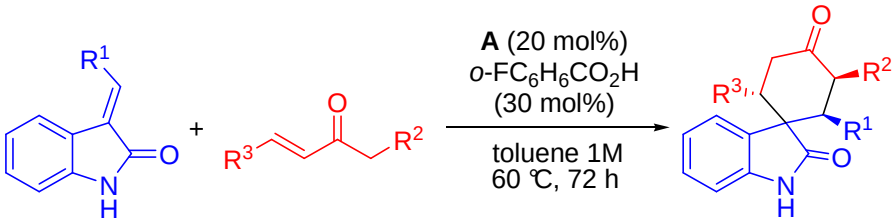
We thought the 9-amino(9-deoxy)*epi*-hydroquinidine **A**, that is used by our group for the activation of encumbered substrates, could activate efficiently the pseudo Diels-Alder reaction[122] between the 3-alkylidene oxindole **1** and the ketone **5**.

Preliminary studies showed that the 9-amino(9-deoxy)*epi*-hydroquinidine is able to activate the reaction between oxindole and α,β-unsaturated ketones.

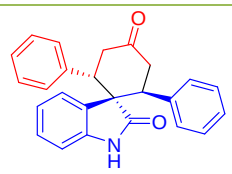
After a standard condition screening, with the aim to enhance the formation of nucleophilic dienamine intermediate **I** instead of the LUMO-lowered iminium ion, we selected a catalyst salt formed by primary amine **A** (20 mol%) and *ortho*-Fluoro Benzoic Acid (30 mol%), demonstrating that the pKa and the amount of acidic additive have a crucial role favoring the formation of one intermediate (read iminium ion) or the other (read dienamine or enamine).

With this conditions in hands we analyzed the generality of the tandem double Michael addition for the formation of spirocyclic oxindolic cyclohexanones (Scheme **3**).

***Scheme 3**: Scope of the tandem double Michael addition (enamine-iminium activation sequence)*[a], [b], [c]

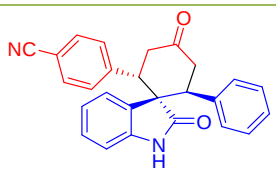


1 **5** **6**



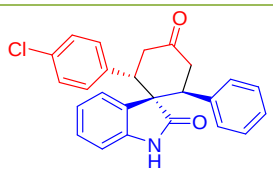
6a

59% yield,
>19:1 dr, 98% ee



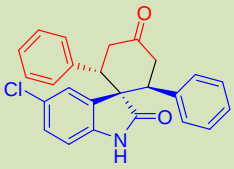
6b

76% yield,
6:1 dr, 92% ee



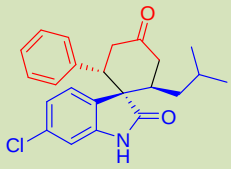
6c

65% yield,
4:1 dr, 89% ee



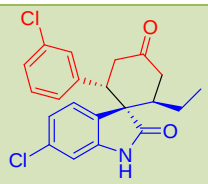
6d

82% yield,
7:1 dr, 94% ee



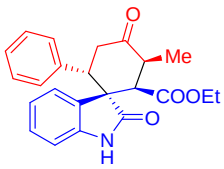
6e

80% yield,
9:1 dr, 91% ee



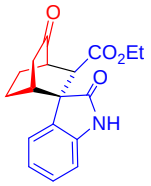
6f

70% yield
4.5:1 dr, 84% ee



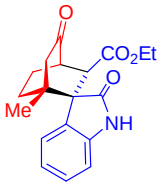
6g

63% yield,
7:1:1 dr, 97% ee



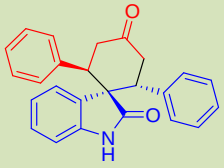
6h

28% yield,
>19:1 dr, 89% ee



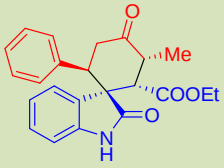
6i

24% yield,
>19:1 dr, 97% ee



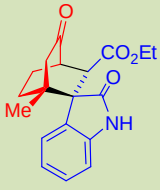
37% yield
>19:1 dr
90% ee

***ent*-6a**



56% yield
4:1:1 dr
93% ee

***ent*-6g**



20% yield
>19:1 dr
82% ee

***ent*-6i**

[a] Yield of isolated product calculated on the sum of the diastereomers. [b] The diastereomeric ratio (dr) was determined by ^{1}H NMR analysis of the crude reaction mixture. [c] The enantiomeric excess (ee) were determined by HPLC analysis on chiral stationary phases.

The reaction shows good generality toward both the substrates especially in terms of electronic contribute, bearing to the formation of highly congested chiral spiro-oxindoles with up to four stereocenters whereof a quaternary one (**6a-g**). Notably using the pseudoenatiomer of the amine catalyst **A**, prepared from hydroquinidine, it is possible to access to the antipode of the products with similar results (***ent*-6a**, ***ent*-6g**, ***ent*-6i**). Moreover, the presented organocascade furnishes good results with cyclohexenone derivatives. In fact in this project we have described the enatioselctive synthesis of bicyclo[2.2.2]octanes **6h** and **6i** bearing a spiro-oxindole moiety. In confirming of the challenge behind the synthesis of such substrates, the spiro-bicycle **6h** was a completely unknown complex scaffold with two contiguous all-carbon quaternary stereocentres.[123] As last part of the project we have applied this oganocascade to the construction of the spirooxidole **6f**, that was recently patented by Hoffmann-La Roche as new kind of anticancer agent and tested as racemic mixture.[124] The one step enantioselective synthesis of compounds having this structure-activity might enable the identification of a more selective and potent antitumor lead.

In summary we showed two complementary aminocatalytic approaches for the enantioselective synthesis of chiral spirooxindoles having a six member ring. In particular we developed a formal [2+2+2] annulation strategy in the first case, whilst in the second case a formal Diels-Alder reaction where an α,β-unsaturated ketone was activated through a dienamine/iminium ion pathway. Both this reactions describe a trivial way for the construction of a class of natural inspired molecules starting from easily available raw materials thus setting the condition for further evaluations of their biological activity.

References

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[120] The relative and absolute configurations of compound **4** were assigned by NMR NOE analyses, X-ray crystallography (for compound **4n**), and by means of TD-DFT calculations of the electronic circular

dichroism (ECD) spectra, as described in the Supporting Information. CCDC 726678 (**4n**) contain 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.

[121] Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055.

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[123] E. A. Peterson, L. E. Overman *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11943.

[124] "Spiroindolinone derivatives": J.-J. Liu, Z. Zhang (Hoffmann-La Roche AG), PCT Int. Appl. WO 2008/055812, **2008**. The other enantiomer, ent-7, is also accessible with high level of stereoselectivity (see Figure 2 in the Experimental part).

General.

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. All the ^{1}H and ^{13}C signals were assigned by means of g-COSY, g-HSQC and g-HMBC 2D-NMR sequences. NOE spectra were recorded using the DPFGSE-NOE sequence,[125] using a mixing time of 2.00 s and "rsnob" 20 ÷ 50 Hz wide selective pulses, depending on the crowding of the spectra region. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$ and CD_3CN). Coupling constants are given in Hz. When 2D-NMR were not performed, carbon types were determined from DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh) according to the method of Still.[126] 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.[127] Chiral primary amine catalysts, 9-Amino(9-deoxy)*epi*-hydroquinine **A** and the *pseudo*-enantiomer 9-Amino(9-deoxy)*epi*-hydroquinidine **C**, were prepared from commercially available hydroquinine and hydroquinidine, respectively, following the literature procedure.[128] Catalysts (*S*) and (*R*)-**B** were purchased from Aldrich and used as received.

Substituted oxindoles were prepared following the literature procedures.[129] Unsaturated ketones **2** and aldehydes **5** were purchased from Aldrich or Lancaster and used as received or synthesized following the literature procedures.[130]

Determination of Diastereomeric Ratios

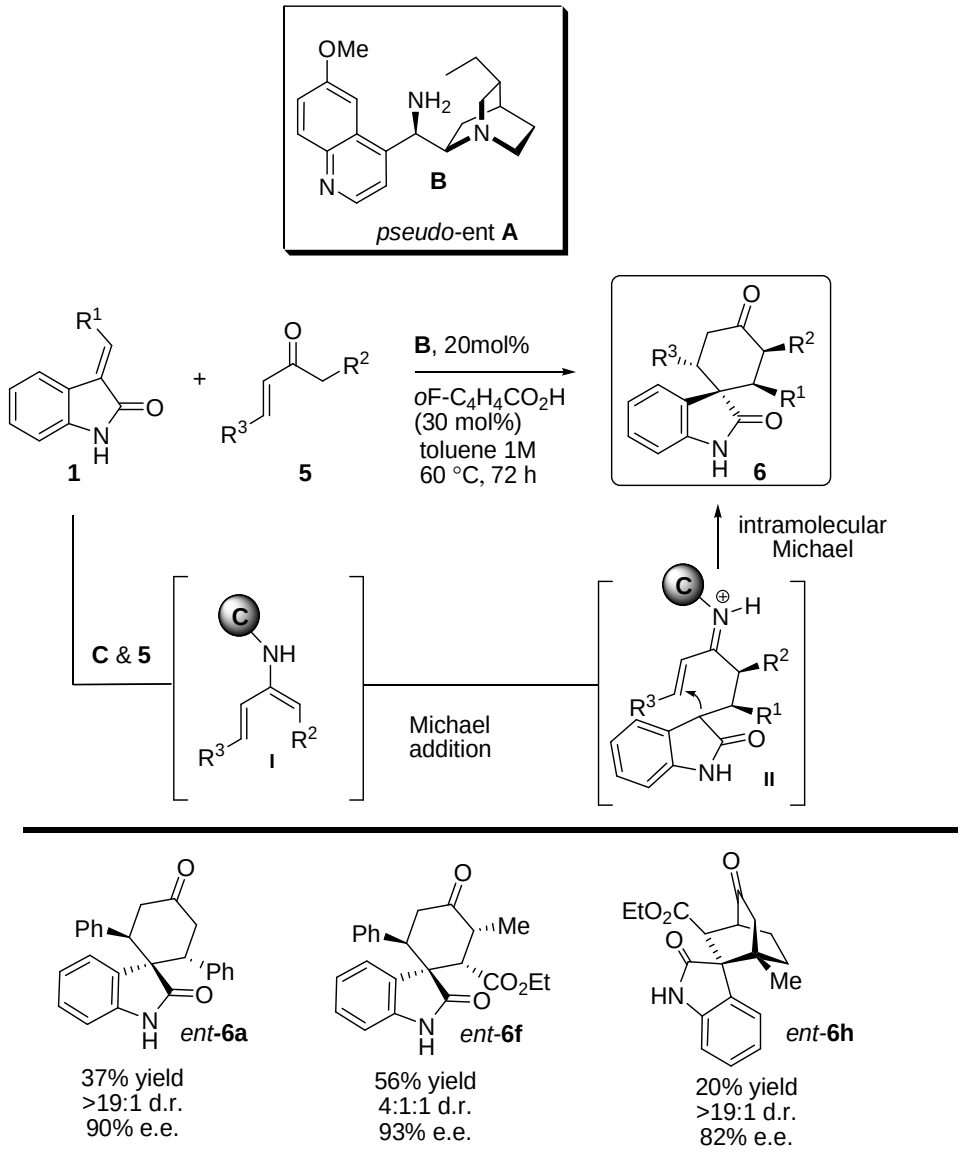
The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture.

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 performing the reactions using a 1:1 mixture of (*S*)- and (*R*)-**B** as the catalyst for the synthesis of compound **6.** Racemic mixtures for compounds **3** and **7** were obtained by mixing the two antipodes obtained performing the reaction with catalyst 9-Amino(9-deoxy)*epi*-hydroquinine **A** and the *pseudo*-enantiomer 9-Amino(9-deoxy)*epi*-hydroquinidine **C** separately.

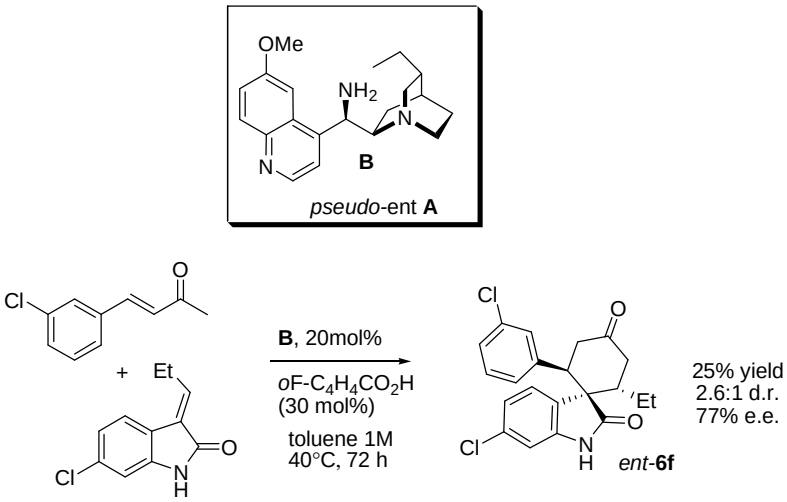
Calculations. MM conformational searches were performed using the MonteCarlo method implemented in Titan 1.0.5.[131] Geometry optimization were carried out at the B3LYP/6-31G(d) level by means of the Gaussian 03 series of programs.[132] The standard Berny algorithm in redundant internal coordinates and 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

Supplementary Figures

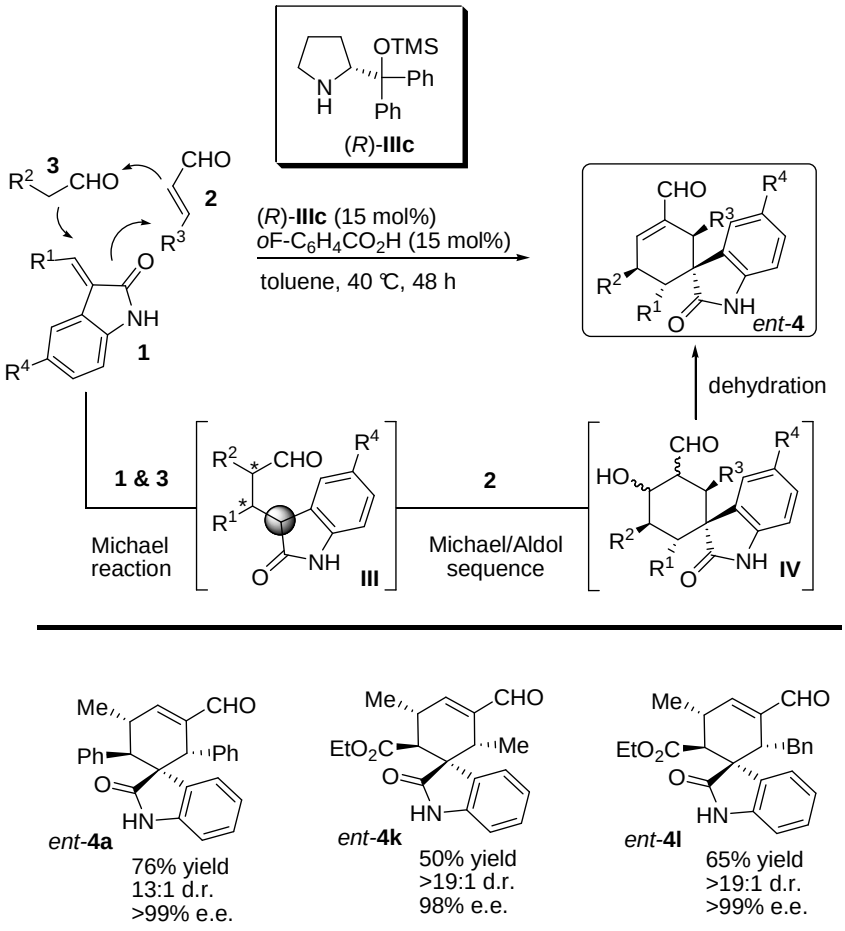
Supplementary Figure 1. Achieving both the enantiomers of the tandem double Michael additions toward spiro-oxindolic cyclohexanones **3**.



Supplementary Figure 2. Direct synthesis of antitumor agent *ent*-**7**.



Supplementary Figure 3. Triple organocascade using catalyst (*R*)-**IIIc**.



ent-**4a**
76% yield
13:1 d.r.
>99% e.e.

ent-**4k**
50% yield
>19:1 d.r.
98% e.e.

ent-**4l**
65% yield
>19:1 d.r.
>99% e.e.

Stereochemical evidence for a step-wise mechanism of the organocatalytic tandem reaction.

The domino multicomponent reaction between an α,β-unsaturated ketone **5** and the oxindole derivative **1** described in Figure 2 of the main text may proceed via two competitive reaction pathways: a concerted [4+2] cycloaddition reaction (Diels-Alder reaction) or a double Michael addition sequence following an enamine-iminium activation path. Both processes, that lead to the one step construction of spiroindolinone derivatives **6**, would first promote the formation of the dienamine intermediate **I** by catalyst **A** condensation with **5**. consideiring a stepwise mechanism, the second intramolecular conjugate addition step would be so quick that intermediate **II** could not be detected by ^{1}H-NMR spectroscopy.

It is generally accepted that the Diels-Alder reaction must follow one of two alternative paths, the first being a synchronous pericyclic process and the other a two-step or two-stage one where an zwitterionic intermediate is involved. It has been generally assumed that in the latter case the rate-determining step must be the formation of this intermediate, its collapse to product being rapid.[133]

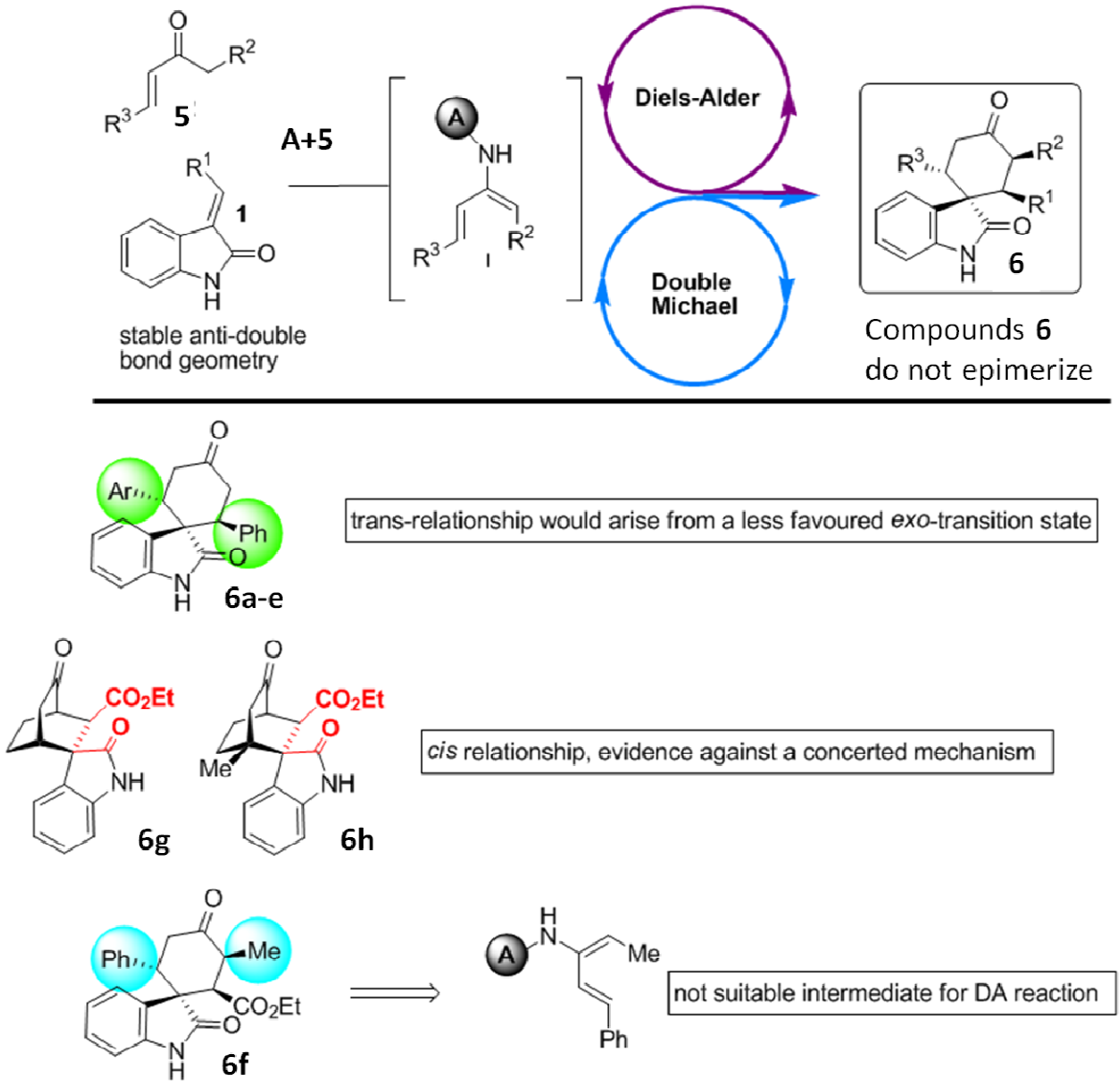
On the basis of the regio- and stereo-specific nature of the Diels-Alder reaction (always a *cis* addition) and the diastereoselectivity of the union, based on the Alder *endo* rule,[134] we can extrapolate some evidence from the relative configuration of products **6**. Our considerations are summarized as Supplementary Figure 4.

The selective formation of *trans*-spiro-oxindole cyclohexanones **6** would arise from an *exo*-transition state of a cycloaddition path. The classical *endo*-transition state in the Diels–Alder route should produce the *cis*-isomer **6**. However, the formation of this compound has never been observed under the present reaction conditions. Importantly, the obtained *anti*-compounds **6** do not epimerize under the reaction conditions, even in the presence of a base (pyrrolidine 50 mol%). At the same extent, no scrambling of the double-bond geometry in compound **1** have been observed.

The observed *trans*-relationship in compounds **6** is in sharp contrast with the study by Barbas and colleagues[135] on the organocatalytic formation of spirocyclic compounds, believed to proceed by way of a concerted pericyclic pathway, resulting in the selective formation of the *cis* isomer.

A further evidence pointing to a step-wise mechanism comes from the relative configurations of compounds **6g** and **6h**. Despite the *trans* geometry of the dienophile **1** is reflected in the relative spatial arrangement of compounds **6a-f**, compounds **6g** and **6h** show a *cis* relationship, a clear evidence for a double-Michael reaction sequence.

Supplementary Figure 4. Stepwise or concerted?



Finally, the relative *trans* relationship between the C2-C5 substituents of the cyclohexenone ring of compound **6f** should require a Diels-Alder mechanism to proceed through a relatively unstable *E-E* s-*cis* dienophile.

Structural and Absolute Configuration Determination

Introduction

The present organocascade reactions are emblematic of the recent progress by asymmetric synthesis toward the achievement of stereochemical and structural complexity. In this framework, the unambiguous determination of the relative and absolute configuration of the complex compounds yielded by the reactions is absolutely necessary.

Since many years, the anomalous dispersion X-ray crystallography (the "Bijovet method") has been the elective method[136] for the determination of absolute configuration and, thanks to the rapid development of high-resolution difractometers, it is now used routinely. The obvious limitations of the X-ray method is the need for diffraction-quality single crystals, and for the presence of an heavy atom in the molecule (i.e. Z > Si). While the second limitation is often negotiable by the organic chemists, the crystallization step is often 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 have been successfully employed in recent years to assign the AC of organic molecules[137]. The determination of the AC by chiroptical methods on newly synthesised molecules requires the knowledge of the relative configuration of the chiral centres. If the relative configuration is not known, all the relative configurations together with the related conformations must be calculated and taken into account in the final simulation of the chiroptical spectra, leading to a completely unusable and unreliable approach.

Fortunately, high resolution NMR spectroscopy, in particular the NOE experiments coupled with bi-dimensional spectra, can easily unravel the relative configuration of the chiral centres, and can also provide precious information about the molecular conformation in solution.

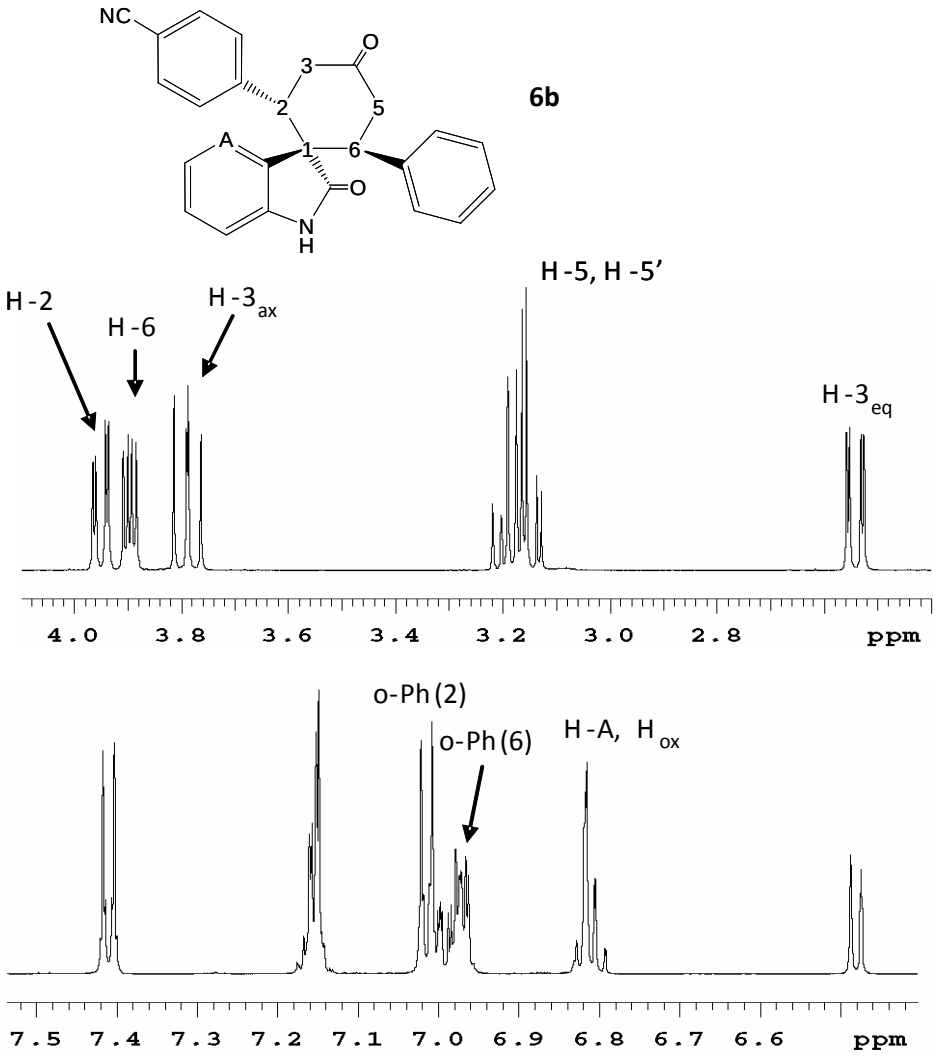
In the following analysis of the organocascade products, the AC will be determined exploiting all the mentioned techniques, i.e. anomalous dispersion X-ray diffraction when feasible, and coupled NMR/ECD/TD-DFT approach when the former cannot be applied.

Tandem double Michael addition for the synthesis of spiro-oxindolic cyclohexanones 6

Compounds **6b**, **6f** and **6h** were selected as representative samples in order to determine the relative and absolute configuration of the stereogenic centres.

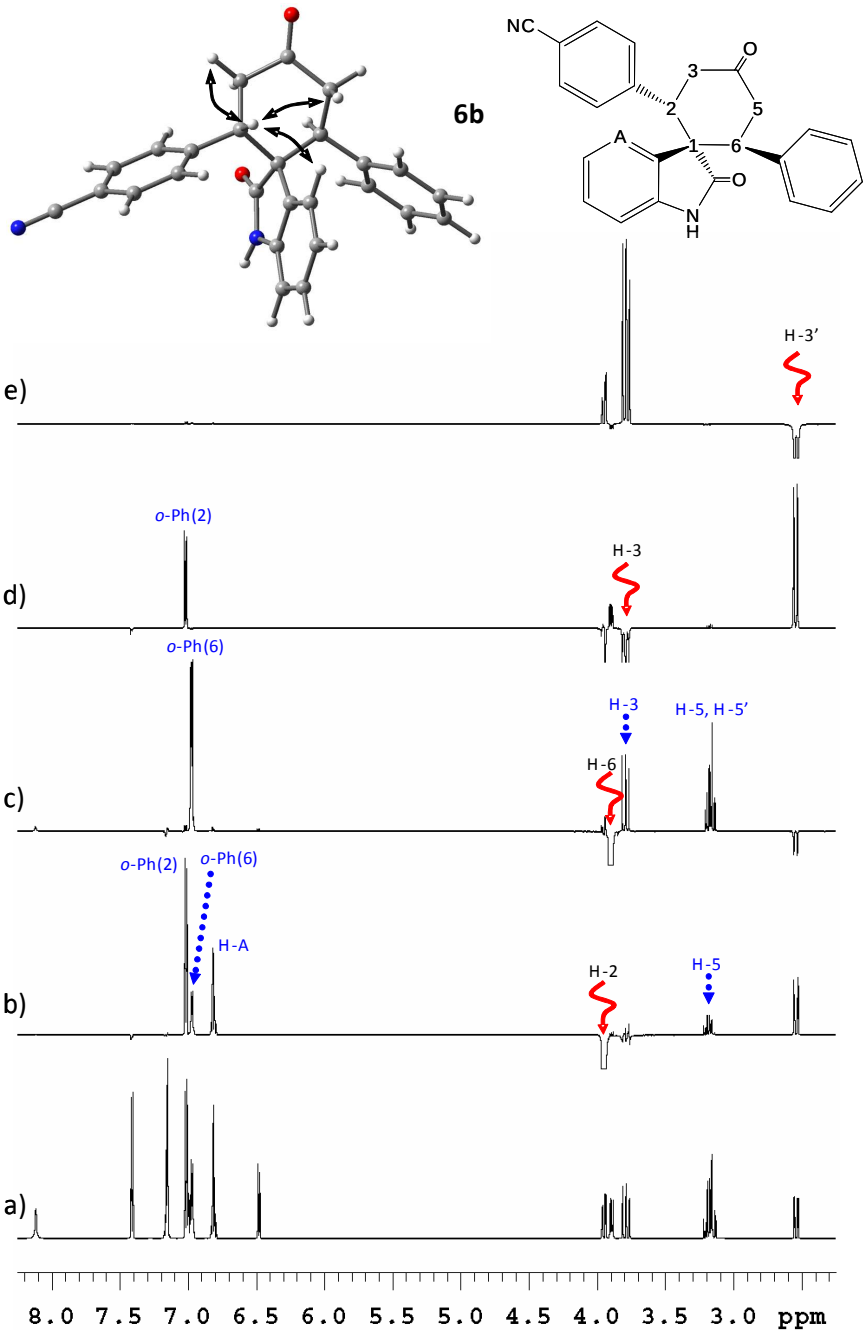
Compound 6b

Compound **6b** was selected for the NMR analysis because of its relatively simple NMR spectrum in the aromatic region. Full assignment of the protons signals (and carbons as well) was obtained by gs-HSQC, gs-HMBC and g-COSY 2D-NMR spectra. Owing to the crowding of the aromatic region of the ^{1}H spectrum, unambiguous identification of the signals of the oxindole ring and of the two aromatic rings is essential for the correct interpretation of the subsequent NOE spectra.



Supplementary Figure 5. Top: aliphatic (top) and aromatic (bottom) regions of the ^{1}H NMR spectrum of compound **6b** (600 MHz in CD_3CN solution), assigned by means of g-COSY and gs-HMBC spectrum.

Analysis of the proton spectrum in the aliphatic region (Supplementary Figure 5, top trace), show that both the signals of H-2 and H-6 have a large coupling constant with H-3 and H-5 (14.0 and 9.5 Hz, respectively), indicating a relative disposition in which the dihedral is near to 180°[138]. NOE spectra were obtained by means of the DPFGSE-NOE sequence[73], and saturating the signals corresponding to the hydrogens of the cyclohexanone, to the *ortho*-protons of the two aromatic rings, and to the hydrogen of the oxaindole *peri* to the spiranic carbon (H-A). Seleted traces are shown in Supplementary Figure 6.

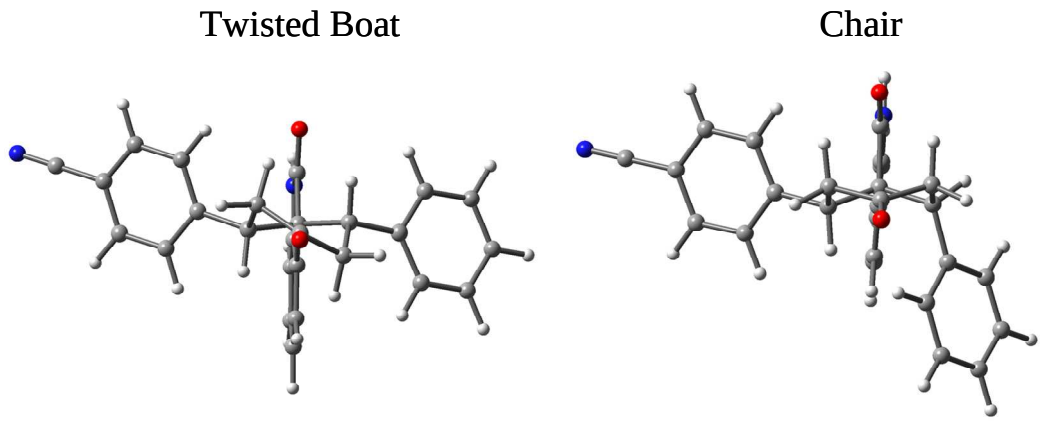


Supplementary Figure 6. DPFGSE-NOE spectra obtained for **6b** (600 MHz in CD_3CN). Trace a): control spectrum. Traces b-e: NOE spectra obtained on saturation of H-2, H-6, H-3 and H3'. Observed NOE are indicated as double arrows in the DFT-optimized structure ("control" NOE are not indicated for clarity).

The most indicative spectrum corresponds to trace b, in which the signal corresponding to H-2 is irradiated. Large NOE effects are visible on the *ortho* signals of the phenyl in position 2[139], on the *peri* signal of the oxindole (H-A in Supplementary Figure 6), and on the signal of one distereotopic hydrogen H-3. Smaller enhancements are also visible for the *ortho* hydrogens of the phenyl in position 6, and for H-5. These NOE indicate that H-2 places itself close to the

aromatic ring of oxindole, and far from H-6. The two aromatic rings are therefore in a trans relationship. Saturation of H-6 (trace c) further confirms this hypothesis: NOE enhancements are observed for the *ortho* protons of Ph(6)[10], on the second hydrogen belonging to carbon 3 (H-3'), and on the signal of H-5, while no effect was observed on the hydrogens of oxindole. There are, however, some incongruence between the observed NOEs and the results deduced from the proton spectrum. If a chair conformation of the cyclohexanone ring is taken into account and the two aromatic rings are in a trans relationship, they have to occupy axial and equatorial positions, respectively. In this case, a trans-diaxial coupling constant can play only for the proton that occupies the axial position (H-2), and not for the other hydrogen in the equatorial position (H-6). Secondly, in this conformation NOE between H-6 and H-3 cannot be observed, because of the relative 1-4 disposition on the ring. These consideration strongly indicate that the ciclohexanone ring assumes a twisted-boat conformation, in which both the aromatic rings are in a pseudo-equatorial position, probably to reduce steric hindrance.[140] Traces d) and e) of Supplementary Figure 6 fully support this hypothesis: on saturation of H-3, NOE effect is *not* observed on H-5, that would be in a 1-3 diaxial disposition in the chair conformation, and far from H-3 in the case of the twisted boat conformation. From the NOE analysis, the relative configuration of the three chiral carbons is therefore 1*R**,2*R**,6*R**.

Supplementary Scheme 1



DFT calculations (B3LYP/6-31G(d) level)[78] for both the chair and twisted-boat conformation were carried out in order to evaluate their energy difference. Both conformations corresponds to energy minima, and the chair conformation is calculated to be more stable than the twisted boat by 1.1 kcal/mol (see Supplementary Scheme 1 and Table 1). The coupling constant data and the NOE spectra suggest, however, that the twisted boat conformation has a larger population in solution (acetonitrile) with respect to that derived from the calculations (14%). In fact, the observed J-coupling of H-5 (9.5 Hz) is the weighted average between a pseudo-diaxial

coupling in the twisted boat conformation (about 14 Hz) and a equatorial-axial coupling in the chair conformation (about 6 Hz). The population of the twisted boat conformation can be calculated to be about 44% (i.e. 14·0.44 + 6·0.56 = 9.5 Hz).

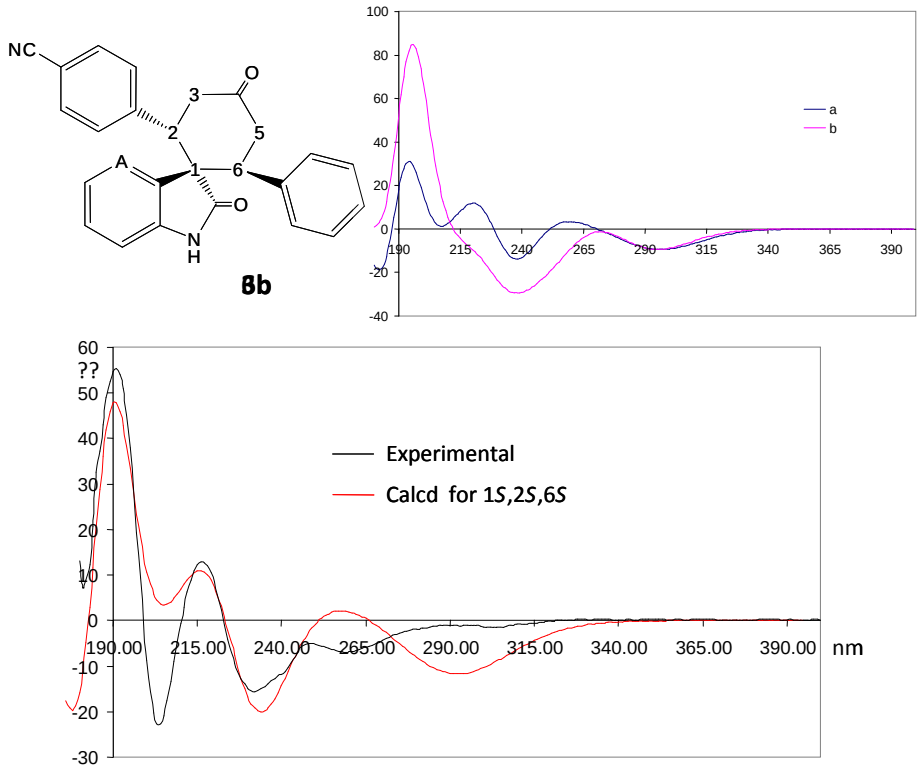
Supplementary Table 1: Calculated relative energies (ΔE) and free energies (ΔG) of the two conformations of 6b (in kcal/mol, B3LYP/6-31G(d) level). Populations percentages (P) are calculated assuming Boltzmann statistics at T=25°C.

Molecule	Conf.	ΔE	ΔG	P(%)
6b	**a (chair)**	0.00	0.00	86
	b (twisted boat)	1.74	1.07	14

Due to the absence of an "heavy" atom, the Bijovet method based on anomalous X-ray dispersion to assign the absolute configuration of **6b** is precluded. In the present case, theoretical calculation of ECD spectra 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[137]. Compound **6b** is a relatively rigid molecule, and starting from the information obtained by NOE analysis, only two conformations should be populated. In any case, 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).[77] All conformations within a 5 kcal/mol window were then optimized using DFT at the B3LYP/6-31G(d) level[78], 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 grouped into the two conformations, named **a**-**b** (see Supplementary Table 1), already deduced by NMR analysis.

Calculation of the Electronic Circular Dichroism spectrum was carried out using TD-DFT method at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) level, and assuming 1*S*, 2*S*, 6*S* absolute configuration[141]. 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.[142] Electronic excitation energies and rotational strengths have been calculated for the two conformation, and the ECD spectra were obtained by applying a 0.25 eV Gaussian shaped line width (Supplementary Figure 7). The spectra show different shapes, indicating that the relative population of the two conformations has a great influence

on the spectrum. The final simulated ECD spectrum (bottom in Supplementary Figure 7) was obtained taking into account the 76:14 population ratio determined assuming Boltzmann statistics from the calculated free energies at the B3LYP/6-31G(d) level (Supplementary Table 1). The agreement between calculated and experimental spectrum is fairly good, and the TD-DFT simulation therefore supports the conclusion that the AC of **6b** is 1*S*, 2*S*, 6*S*.



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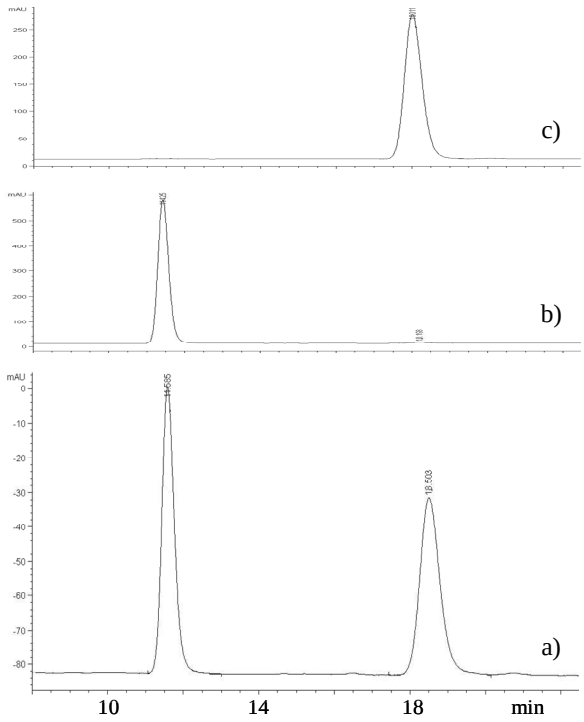
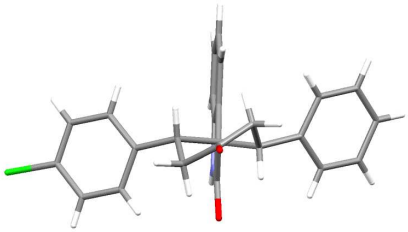
Supplementary Figure 7. Top: calculated ECD spectra for the two conformations **a-b** of **6b**. Bottom: experimental (black) and calculated ECD spectra (red), weighted on the calculated free energies of the conformations (the simulated spectrum has been blue-shifted by 4 nm). Molecular CD (Δε) is expressed in L $mol^{-1}cm^{-1}$.

Being the ECD spectrum very sensible to conformational weighting, further indications are desirable, and many attempts were carried out in order to crystallize the similar compounds **6c** or **6d**, that bears an heavy atom like chlorine, but suitable single crystals were never obtained. In a serendipitous way, some crystals were obtained on a batch of the *enantiomer* of **6c**, left (by accident) to air in a solution of hexane/Et_2O/methanol. This compound, **ent-6c**, was obtained using *pseudo*-enantiomer 9-Amino(9-deoxy)*epi*-hydroquinidine **B** in the reaction, therefore the configuration at all the stereogenic centres is opposite with respect to **6c**. When subjected to anomalous dispersion X-ray analysis, these crystals showed 1*R*, 2*R*, 6*R* stereochemistry, therefore the configuration of **6c** is 1*S*, 2*S*, 6*S*, as correctly deduced by the TD-

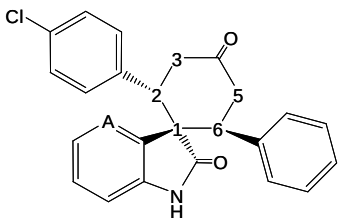
DFT simulation of **6b.** In order to avoid any error, an HPLC analysis on chiral stationary phases was performed by dissolving the very same crystal used for X-ray analysis, to confirm that the crystal used had *opposite* absolute configuration with respect to **6c** (see Supplementary Figure 8)



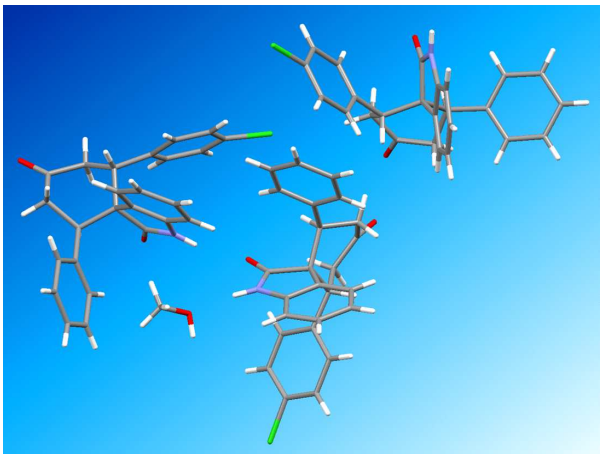
Supplementary Figure 8: a): HPLC trace on chiral stationary phase of the racemic mixture of **6c**. b): HPLC trace of the sample prepared using A catalyst. c): HPLC trace of the solution obtained by dissolving the crystal used for X-ray diffraction.



ent-8c



8c

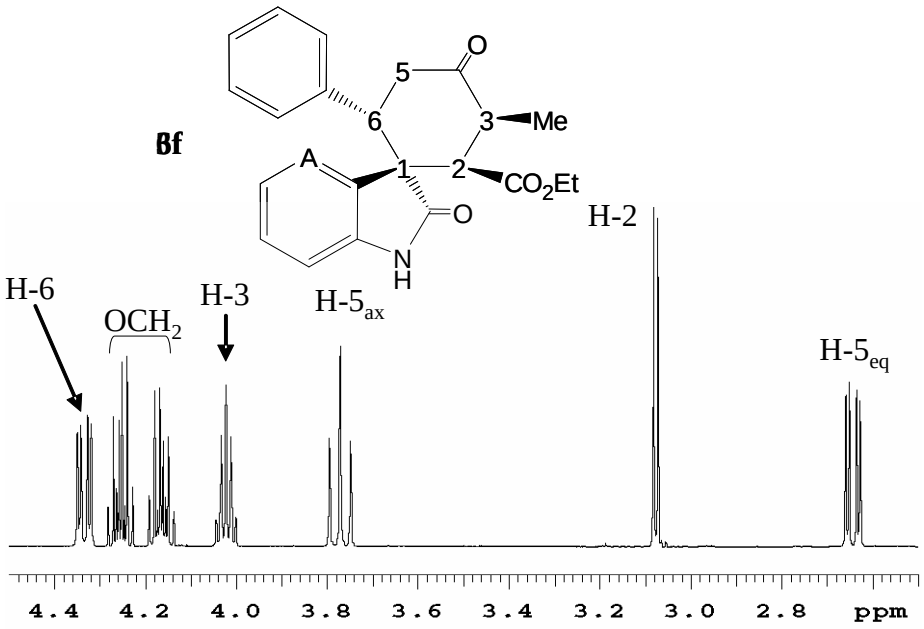


Supplementary Figure 9. Top: front view of one molecule of *ent*-**6c** extracted from the X-ray data, showing the twisted boat conformation of the cyclohexanone ring. Bottom: full view of the crystal structure, showing three independend molecules and a molecule of methanol (solvent).

The triclinic crystal cell (P1 space group) contains three independent molecules, and a molecule of methanol (Supplementary Figure 9). All the three independent molecules show a twisted boat conformation of the cyclohexanone ring, and the experimental structure is identical to that calculated by DFT calculation in the case of **6b**.

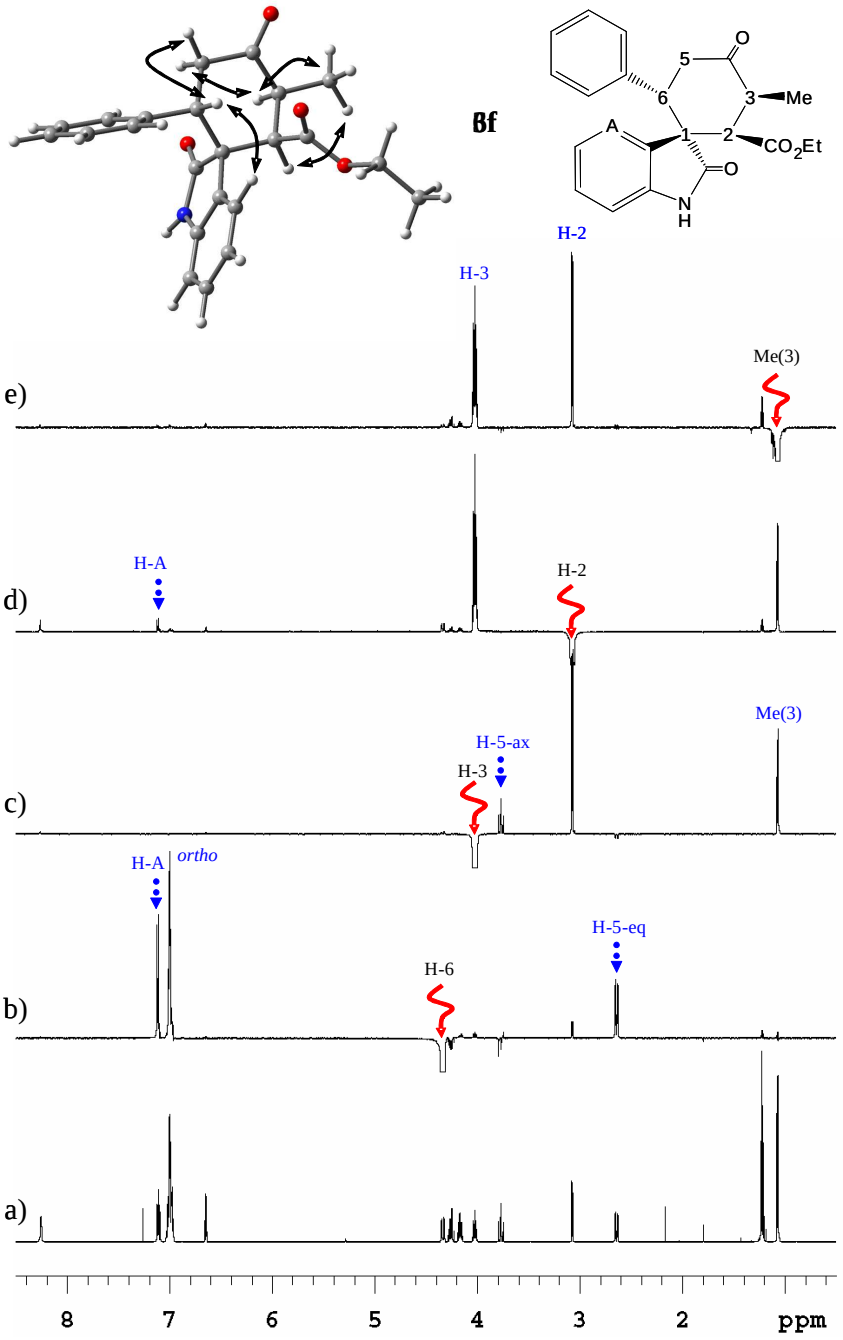
Compound 6f

Compound **6f** bears four stereogenic carbons, and it is conformationally more flexible with respect to **6b**, because of the presence of the CO_2Et group, that can assume two different orientations. All the attempts to crystallize **6f** or an analogue containing a chlorine atom were unsuccessful. As in the case of **6b**, the relative configuration was deduced from NMR analysis. All the signal in the ^{1}H and ^{13}C spectrum were routinely assigned by means of 2D-spectra (gs-HSQC, gs-HMBC and COSY), and the relative configuration deduced from NOE spectra.



Supplementary Figure 10. Aliphatic region of the ^{1}H NMR spectrum of compound **6f** (600 MHz in $CDCl_3$), assigned by means of g-COSY and gs-HMBC spectrum.

Analysis of the ^{1}H spectrum of **6f** shows that the signals of H-6 and H-2 (Supplementary Figure 10) show very different coupling constants. In the case of H-6, the coupling constants with the two hydrogens H-5 and H-5' are 13.4 and 4.8 Hz, whereas in the case of H-2 the coupling constant with H-3 is 6.0 Hz. These values suggest that H-6 occupies an axial position and it is coupled with the axial hydrogen belonging to C-5 ($H\text{-}5_{ax}$). Secondly, H-2 is probably in equatorial position and coupled with H-3 (the other possibility is that H-2 and Me(3) are both axial, therefore the 6.0 Hz J-coupling would be an axial-equatorial one). NOE spectra were acquired using the DPFGSE-NOE sequence, and saturating the signals of H-2, H-3, H-6, and Me(3) (Supplementary Figure 11).



Supplementary Figure 11. DPFGSE-NOE spectra obtained for **6f** (600 MHz in $CDCl_3$). Trace a): control spectrum. Traces b-e: NOE spectra obtained on saturation of H-6, H-3, H-2 and Me(3). Observed NOE are indicated as double arrows in the DFT-optimized structure ("control" NOEs are not indicated for clarity).

On saturation of H-6 (trace b), large NOE effects are seen on the *ortho*-hydrogens[10] of the phenyl ring, on the equatorial hydrogen H-5_{eq}, and on the signal corresponding to the *peri* hydrogen of the oxindole ring (H-A). The latter NOE indicates that H-2 is close to the aromatic ring of oxindole. The lack of a 1-3 diaxial NOE on H-2 indicates, on the other hand, that the

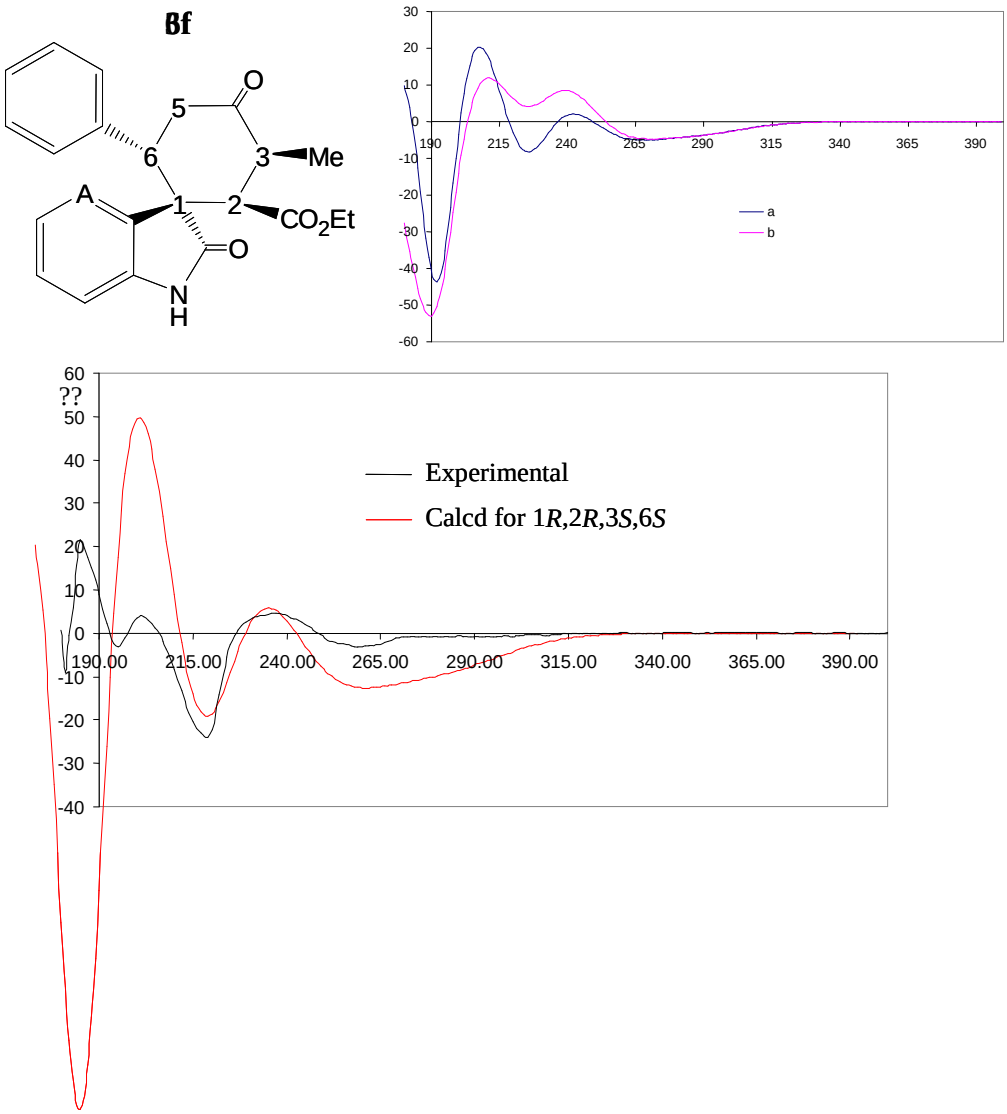
hydrogen in position 2 is in the equatorial position, and that the CO_2Et group occupies the axial position. This trans relationship between the phenyl and CO_2Et groups is confirmed when H-2 is saturated (trace c). In this case, in fact, NOE effects are observed for the signal of Me(3) and H-5_{ax}, but neither on the H-A signal of oxaindole, nor for the *ortho* signals of Ph(6). Finally, saturation of H-3 and Me(3) (traces c and e) suggest that in compound **6f** the conformation of the cyclohexanone ring is a chair, and that the Methyl group occupies the equatorial position. In fact, a 1-3 diaxial NOE is observed on H-5_{ax} when H-3 is irradiated, whereas a strong NOE is observed only on H-2 when Me(3) is saturated. NOE results therefore suggest that the relative stereochemistry of **6f** is 1*R**,2*R**,3*S**,6*S**

Compound **6f** is a molecule more flexible than **6b**, because the CO_2Et group can have different orientations due to rotation of the C(2)-CO bond. Moreover, the presence of a twisted boat conformation cannot be excluded, even if the NOE data indicate the prevalence in solution of the chair conformation. As in the case of **6b**, 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 10 kcal/mol window were then optimized using DFT at the B3LYP/6-31G(d) level[78] 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, two pairs of conformation named **a-d** (see Supplementary Table 2), were picked out. The first pair has the cyclohexane in a chair conformation, and differs from the orientation of the CO_2Et group. The two chair conformations are much more stable than the second pair, which corresponds to a twisted boat conformation of the cycle, therefore confirming the NOE results. The difference in energy is very large, and only the chair structures need to be included in the following ECD simulation.

Supplementary Table 2: Calculated relative energies (ΔE) and free energies (ΔG) of the conformations of 6f (in kcal/mol, B3LYP/6-31G(d) level). Populations percentages (P) are calculated assuming Boltzmann statistics at T=25°C.

Molecule	Conf.	ΔE	ΔG	P(%)
6f	**a (chair)**	0.00	0.00	96
	b (chair)	1.59	1.85	4
	c (twisted boat)	6.20	6.29	-
	d (twist boat)	7.25	7.63	-

As in the case of **6b**, calculation of the Electronic Circular Dichroism spectrum of **6f** was carried out using TD-DFT method at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) level, and assuming 1*R*, 2*R*, 3*S*, 6*S* absolute configuration.[80] 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.[81] Electronic excitation energies and rotational strengths have been calculated for the two conformation of **3f**, and the ECD spectra were obtained by applying a 0.25 eV Gaussian shaped line width (Supplementary Figure 12). The spectra show the same trend and differs for the intensity of the Cotton effects, indicating that the different orientation of the CO_2Et has not a great influence on the spectrum. The final simulated ECD spectrum (bottom in Supplementary Figure 12) was obtained taking into account the 96:4 population ratios determined assuming Boltzmann statistics from the calculated free energies at the B3LYP/6-31G(d) level (Supplementary Table 2). The agreement between calculated and experimental spectrum is fairly good, the trend and position of the four Cotton effects are correctly simulated. The TD-DFT simulation therefore supports the conclusion that the AC of **6f** is 1*R*, 2*R*, 3*S*, 6*S*. It is worth to note that the AC of **6f** is structurally the same obtained for **6b** and **6c**, the difference in the stereochemical descriptors being ascribable to the different numbering order of the cyclohexanone carbons, and to the different priority of the substituents in the case of the spiranic carbon. (1*R* in **6f**, 1*S* in **6b** and **6c**)

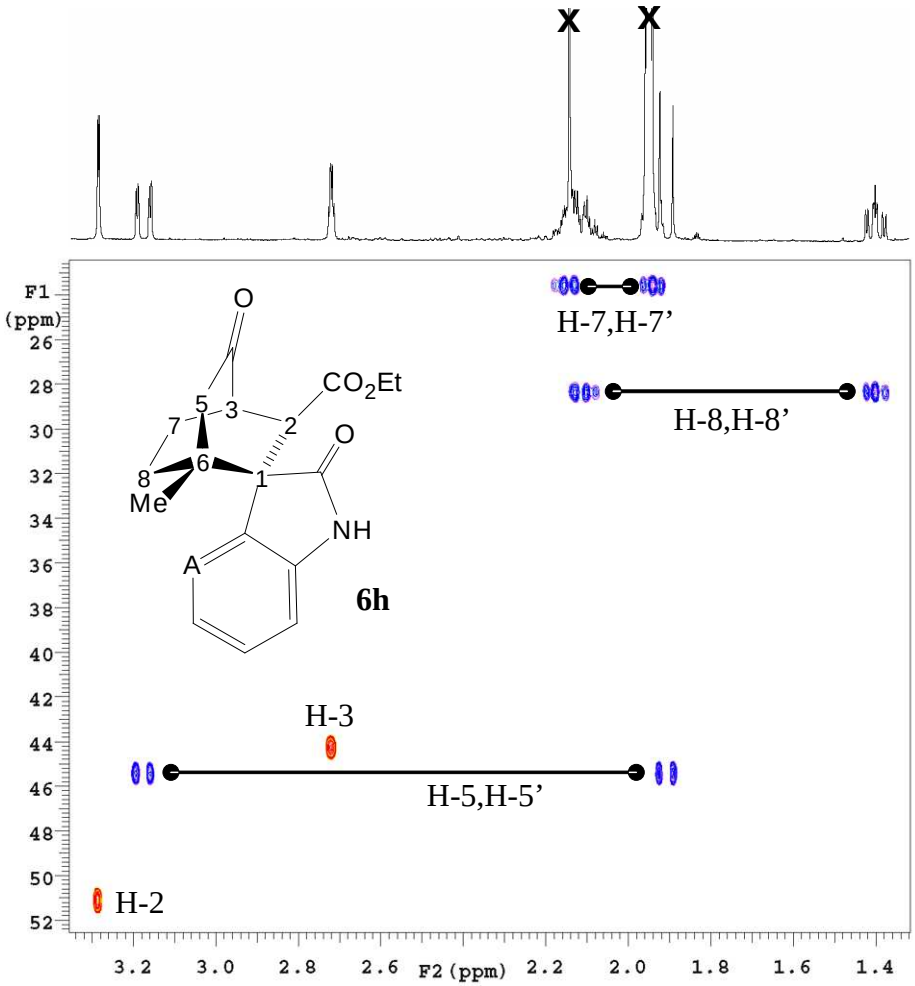


Supplementary Figure 12. Calculated ECD spectra for the two conformations **a-b** of **6f**. Bottom: experimental (black) and calculated ECD spectra (red), weighted on the calculated free energies of the conformations. Molecular CD ($\Delta\varepsilon$) is expressed in L mol^{-1}cm^{-1}.

Compound 6h

Compound **6h** is a very rigid and crowded molecule, and its stereochemical analysis has been carried out exclusively by NMR and ECD calculations. As in the previous compounds, 2D-NMR spectra helped in the assignment of the proton signals. Due the rigidity of the triciclic system, and to the presence of an aromatic ring in a spatially locked disposition, the proton spectrum of the triciclic system is spread over a very large chemical shift range, and some signals are overlapped by the solvent used for

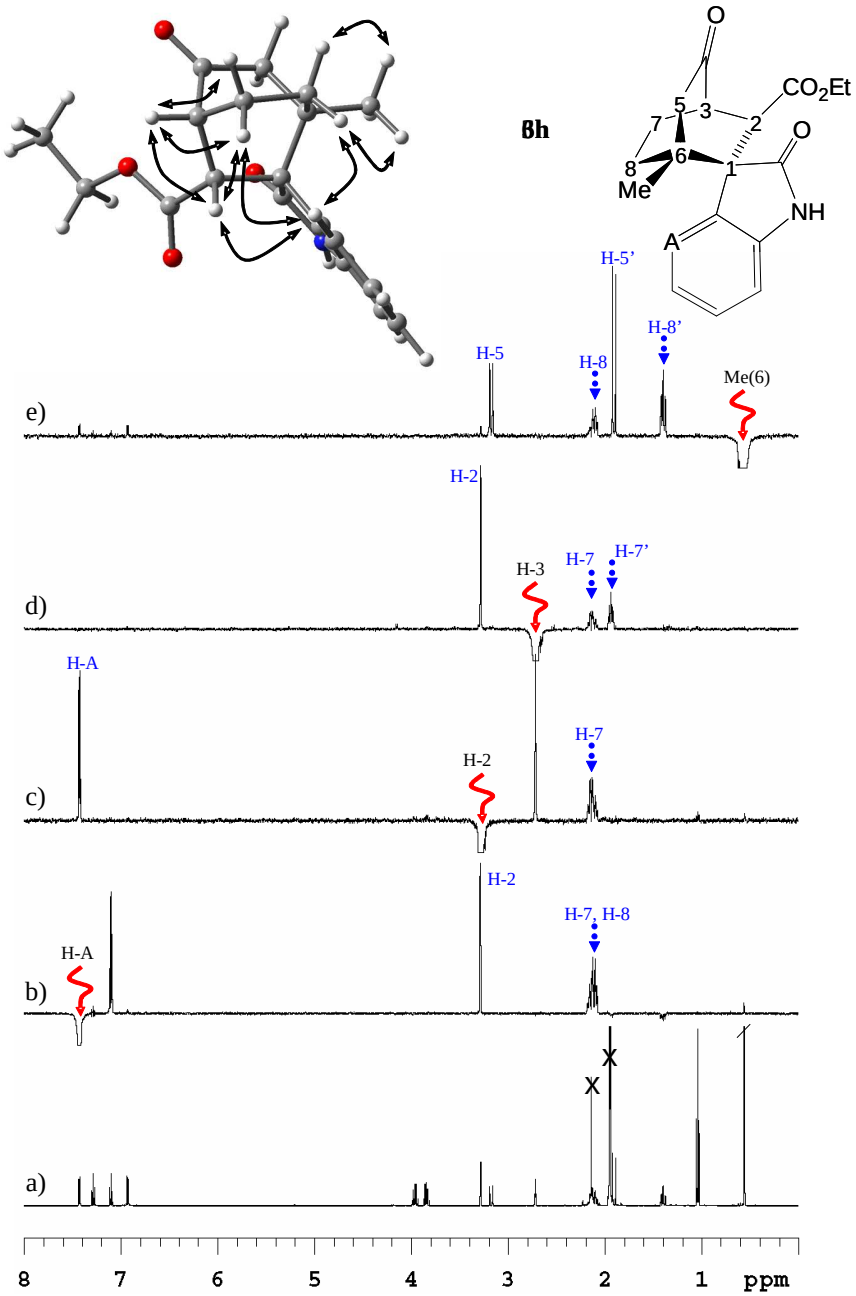
NMR (Acetonitrile-d_3) Supplementary Figure 13 shows the aliphatic region of the HSQC spectrum, and indicates the relationship of the three pair of diastereotopic hydrogens.



Supplementary Figure 13. Aliphatic region of the edited-gsHSQC spectrum of **6h** (600 MHz in CD_3CN). The blue cross peaks indicate the CH_2 signals, whereas the red cross-peaks indicate the CH signals. The signals of OCH_2 and of the two methyl groups are outside the region shown. Assignment of the signals is deduced from the gs-HMBC spectrum (not shown).

DPFGSE NOE spectra[73] were acquired to determine the orientation of the oxindole ring and the position of the CO_2Et group. (Supplementary Figure 14). Saturation of H-2 (trace b) yields large NOEs on H-3, H-7 and H-A of oxindole, indicating that the aromatic ring of oxindole is on the same side of H-2, and that H-2 places itself in the *endo* position of the triciclic system, close to H-7. Saturation of the H-A signal (trace a)

yields NOE on H-2 (a cross check), and on the two *endo* hydrogens H-7 and H-8. These NOE confirm that the aromatic system of oxindole is in the *endo* position. This disposition also implies that the two oxygens of oxindole and CO_2Et are both in *eso* position, and close to the carbonyl in position 4. The results obtained by NOE spectra conclude that the relative stereochemistry of **6h** is 1*R**,2*R**,3*R**,6*R**

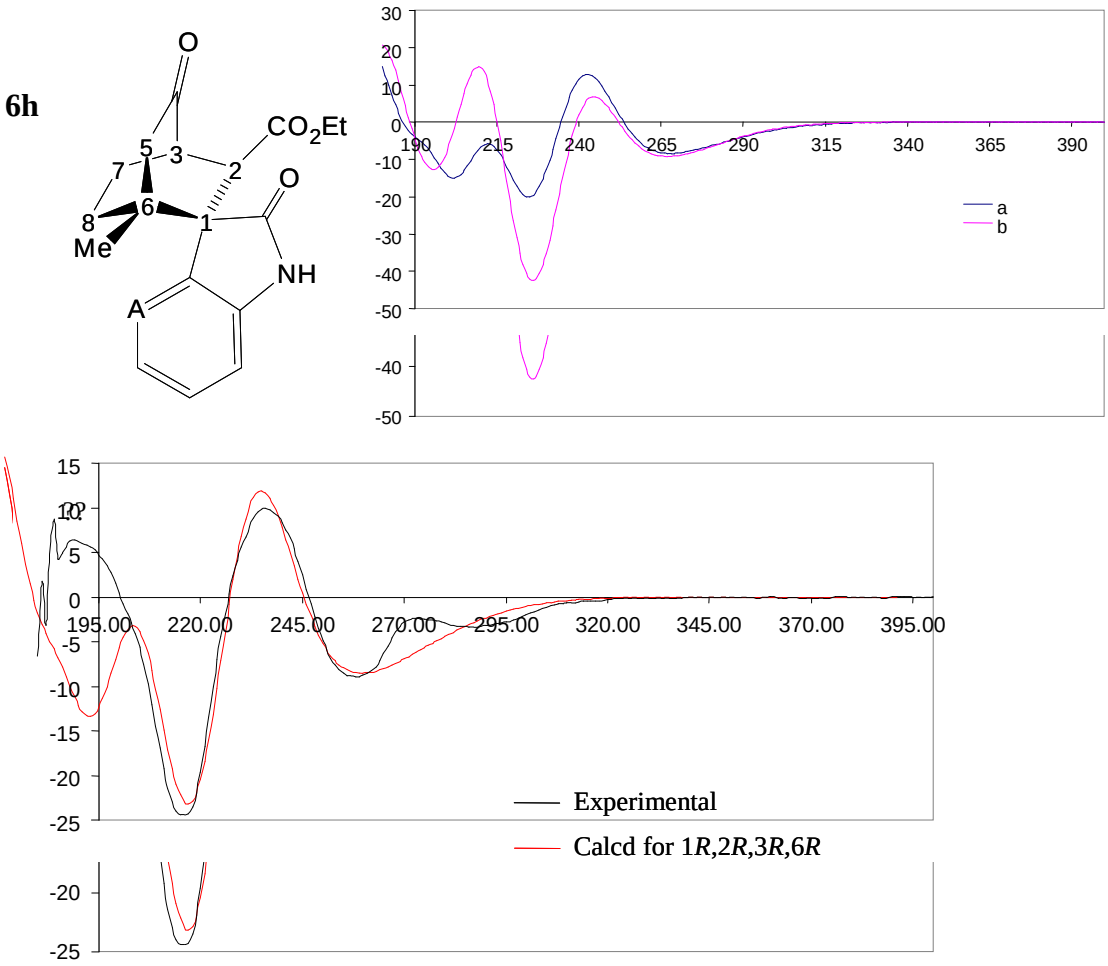


Supplementary Figure 14. DPFGSE-NOE spectra obtained for **6h** (CD_3CN solution). Trace a): control spectrum. Traces b-e: NOE spectra obtained on saturation of H-A, H-2, H-3 and Me(6). Observed NOE are indicated as double arrows in the DFT-optimized structure ("control" NOEs are not indicated for clarity).

With the exception of the CO_2Et group, compound **6h** is very rigid, and the conformational analysis by MMFF can be safely skipped, because only the two conformations in which the CO_2Et group is turned by 180° need to be considered. These were optimized using DFT at the B3LYP/6-31G(d) level,[78] and the harmonic vibrational frequencies were calculated at the same level to confirm their stability (no imaginary frequencies observed), and to evaluate the free energy of each conformation (Supplementary Table 3).

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

Molecule	Conf.	ΔE	ΔG	P(%)
6h	**a**	0.00	0.00	85
	b	0.10	1.23	15



Supplementary Figure 15. calculated ECD spectra for the two conformations **a-b** of **6h**. Bottom: experimental (black) and calculated ECD spectra (red), weighted on the calculated free energies of the conformations. Molecular CD (Δε) is expressed in L $mol^{-1}cm^{-1}$.

As in the case of **6b** and **6f**, calculation of the Electronic Circular Dichroism spectrum of **6h** was carried out using TD-DFT method at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) level, and assuming 1*R*, 2*R*, 3*R*, 6*R* absolute configuration.[80] 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.[81] Electronic excitation energies and rotational strengths have been calculated for the two conformation of **6h**, and the ECD spectra were obtained by applying a 0.25 eV Gaussian shaped line width (Supplementary Figure 15). The spectra show the same trend and differ only for the intensity of the Cotton effects, indicating that the different orientations of the CO_2Et have not a great influence on the trend of the spectrum. The final simulated ECD spectrum (bottom in Supplementary Figure 15) was obtained taking into account the 85:15 population ratio determined assuming Boltzmann

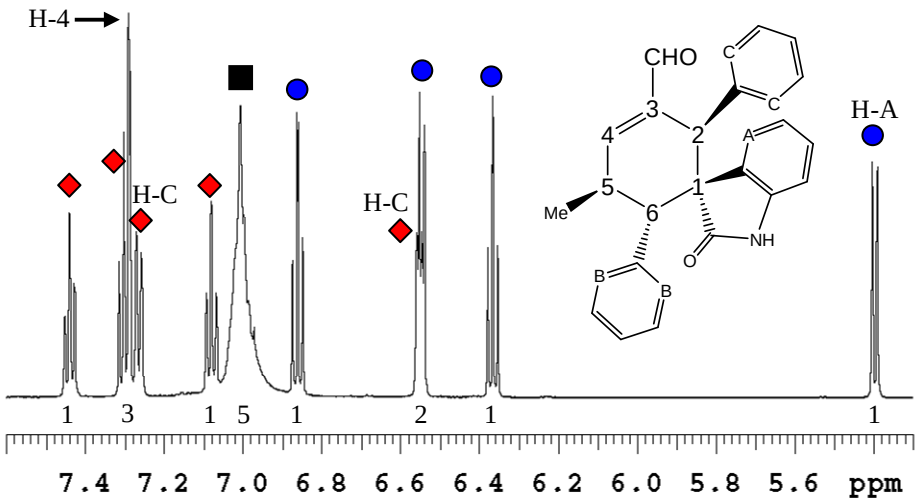
statistics from the calculated free energies at the B3LYP/6-31G(d) level (Supplementary Table 3). The agreement between calculated and experimental spectrum is very good, therefore the TD-DFT simulation assign the AC of **6b** as 1*R*, 2*R*, 3*R*, 6*R*. Except for the carbon in position 2, the AC obtained is structurally the same obtained for **6b** and **6c**, the difference in the stereochemical descriptors of carbons 1, 3 and 6 being the effect of the different numbering order, and to the different priority order of the substituents in the case of the spiranic carbon.

Triple Organocascade leading to compounds 4

Stereochemical assignment was separately done on selected examples for the two classes of compounds **4**, i.e. the ones bearing two aromatic groups in position 2 and 6 of the cyclohexene ring, and the ones bearing one aromatic substituent and a CO_2Et group in position 6 and 2, respectively.

Compound 4a

Compounds **4a-4g,** bearing two aromatic substituents in position 2 and 6 of the cyclohexene ring, did not yield crystal suitable for X-ray diffraction analysis. Accordingly, the relative stereochemistry has been determined by NMR spectroscopy, and absolute configuration determined by chiroptical methods, as in the cases of **6b, 6f, 6h**. Compound **4a,** bearing two phenyl rings, was selected to determine the stereochemistry of this series. Assignment of the NMR protons signals (and carbons as well) was obtained by gs-HSQC, gs-HMBC and g-COSY 2D-NMR spectra. Owing to the crowding of the aromatic region of the ^1H spectrum, unambiguous identification of the signals of the oxindole ring and of the two phenyl groups is essential to the correct interpretation of the subsequent NOE spectra. It is worth to note that the aromatic region of the ^1H spectrum shows, at ambient temperature, very broad signals, that sharpens on lowering the temperature. At -10°C, five separated signals are observed for the hydrogens belonging to the phenyl in position 2 (red diamonds in Supplementary Figure 16). This observation implies that the rotation of the phenyl ring around the C2-Ar axis is slow on the NMR time scale. For this reason all the NMR spectra were recorded at -10°C, in order to have well resolved signals.



Supplementary Figure 16. Aromatic region of the ^{1}H NMR spectrum of compound **4a** (600 MHz at -10°C in CD_3CN solution), assigned by means of g-COSY spectrum. Blue circles indicate the signals belonging to the oxaindole ring; red diamonds indicate the signals of Ph(2); black square indicates the signals of Ph(6); the black arrow indicates the H-4 signal. The numbers below the spectrum indicate the integrated areas.

At -10°C also the signals corresponding to the *ortho* and *meta* hydrogens of the phenyl ring in position 6 are quite broad (black square in Supplementary Figure 16), indicating that also the rotation of this ring is not completely free. A second interesting feature of the proton spectrum is the chemical shift of the oxindolic proton *peri* to the spiranic carbon C(1), that is found at 5.40 ppm. This unusual shielding is probably due to the proximity of the phenyl ring in position 2 (see below).

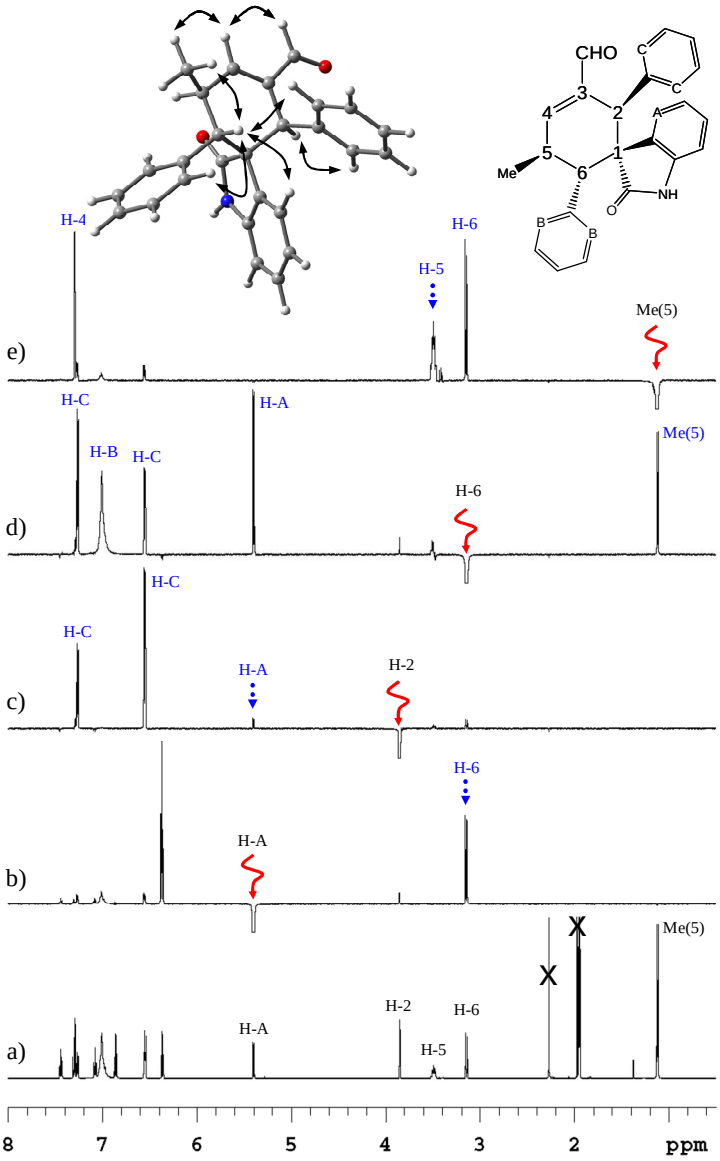
Assignment of the two pair of *ortho* hydrogens was obtained by saturation of the H-6 signal (doublet, 3.13 ppm), yielding NOE on the *ortho* hydrogens of Ph(6) at 7.00 ppm, and by saturation of the H-2 signal (singlet, 4.85 ppm), yielding NOE on the *ortho* hydrogens of Ph(2) at 6.56 ppm and 7.26 ppm (even if the rotation is slow in the NMR time scale, it can still exchange the two protons during the mixing time of the NOE sequence).

The relative configuration of the four stereogenic centres has been determined by NOE experiments, saturating the signals corresponding to H-A, H-2, H-6 and Me(5) (See Supplementary Figure 17). On selective saturation of the methyl group in position 5 (1.13 ppm, trace e), large positive NOE are observed on H-4, H-5 (these are "control" NOEs)[10] and on H-6. The latter NOE implies that the hydrogen in position 6 lies on the same side of Me(5), and Ph(6) places itself on the opposite side of the cyclohexene ring.

Small positive NOE are also detected for the two ortho hydrogen of Ph(2), indicating that Ph(2) is probably on the same side of H-6.

On saturation of H-6 (trace d), large positive NOE are observed on Me(5), on the *ortho*-hydrogens of Ph(6)[10], on the *ortho* hydroges of Ph(2) (H-C in Supplementary Figure 17), and on the oxindole hydrogen *peri* to the spiranic carbon (H-A). These effects indicate that H-6 is close to the hydrogen of the oxindole, and confirm that Ph(2) is on the same side of H-6. This latter result is further confirmed when H-2 is saturated. NOE effects are visible only on the *ortho* hydrogens of Ph(2), and no effect is observed either on H-A or H-6. Finally, saturation of H-A of the oxindole ring confirms that it is close to H-6. In conclusion, all the NOE constraints indicate that the relative configuration of **4a** is 1*R**,2*R**,5*S**,6*S**.

The hindered rotation of the phenyl in position 2, and the slow rotation of the phenyl in position 6 are symptomatic of a rigid core system, with conformational flexibility limited to the conformation of the aldehyde group. However, NOE spectrum obtained on saturation of the aldehyde signal yields NOE enhancement only on H-4, and not on H-2, showing that there is only one populated conformation, in which the H-CO hydrogen is close to H-4. Compound **4a** is therefore quite rigid, and the conformational analysis could be driven by the NOE constraints. Anyway, conformational search was performed by MM methods starting from the relative configuration obtained by NOE analysis. In the first 5 kcal/mol window, MMFF calculations find only two energy minima, corresponding to the two previously pictured structures, that differ by the 180° rotation of the CHO group. These two structures were then optimized by DFT at the B3LYP/6-31g(d) level, and the best structure fully agrees with the NOE constraints, also for the conformation of the CHO group.

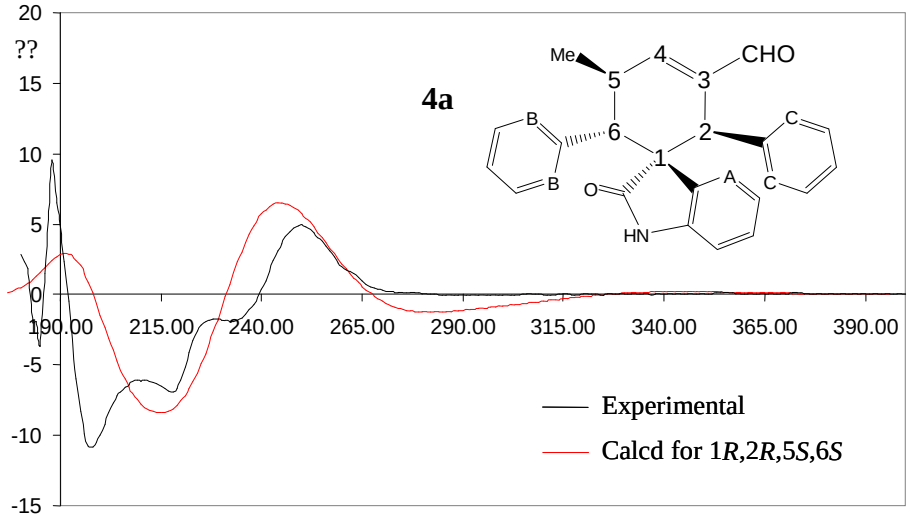


Supplementary Figure 17: DPFGSE-NOE spectra obtained for **4a** (at -10°C in CD_3CN). Trace a): control spectrum. Traces b-e: NOE spectra obtained on saturation of H-A, H-2, H-6 and Me(5). Observed NOE are indicated as arrows in the DFT-optimized structure.

The second structure has an energy higher by 2.49 kcal/mol, therefore the molecule can be considered conformationally rigid, and only one conformation has to be considered for the calculation of the ECD spectrum. Analysis of the optimized structures shows that the oxindole hydrogen H-A is located exactly in the centre of the phenyl ring in position 2, its distance from the aryl plane being about 3.2Å. This feature explains the upfield shift of this hydrogen, because of the ring currents of the aryl ring.[143]

Electronic excitation energies and rotational strengths have been calculated for the best geometry using TD-DFT at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) and assuming 1*R*, 2*R*, 5*S*,

6*S* absolute configuration (Supplementary Figure 18). Rotational strength were calculated in both length and velocity representation. The calculated values are very similar, therefore errors due to basis set incompleteness are very small. The agreement between calculated and experimental spectrum is fairly good, and correctly simulates the signs of the experimental Cotton effects. The TD-DFT simulation indicates that the AC of **4a** is 1*R*, 2*R*, 5*S*, 6*S*.

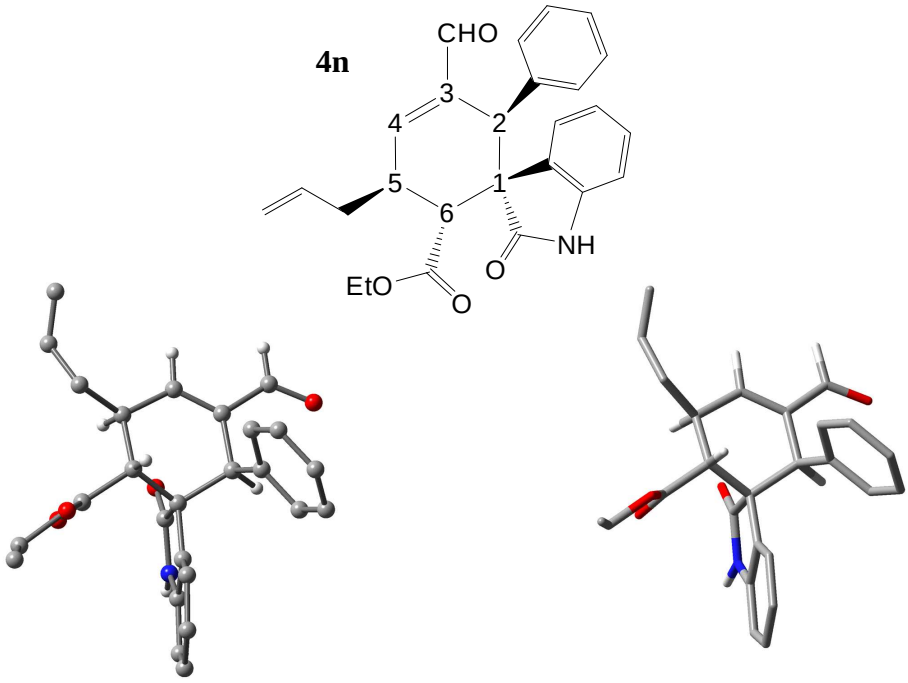


Supplementary Figure 18. Experimental (black) and calculated ECD spectra (red) for the single conformation of **4a**. Molecular CD (Δε) is expressed in L $mol^{-1}cm^{-1}$.

Compound 4n

In the case of compound 4n, crystal suitable for X-ray diffraction were obtained by slow evaporation of an hexane/dichloromethane solution. When subjected to X-ray analysis, compound 4n showed relative stereochemistry 1*R**, 2*S**, 5*R**, 6*S** (see Supplementary Figure 19). The X-ray structure shows that the allyl group in position 3 is disordered, and occupies two different crystallographic positions, each one populated at 57% and 43%, respectively. Due to the absence of an "heavy" atom, the Bijovet method based on anomalous X-ray dispersion to assign the absolute configuration is precluded. However, evaluation of the Flack parameters obtained on the two enantiomorphic structures suggests that the 1*S*, 2*R*, 5*S*, 6*R* configuration is the more probable. Starting from the two conformation observed in the X-ray diffraction, 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[78], 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 group into eight stable conformations, named a-h in Supplementary Table 4.



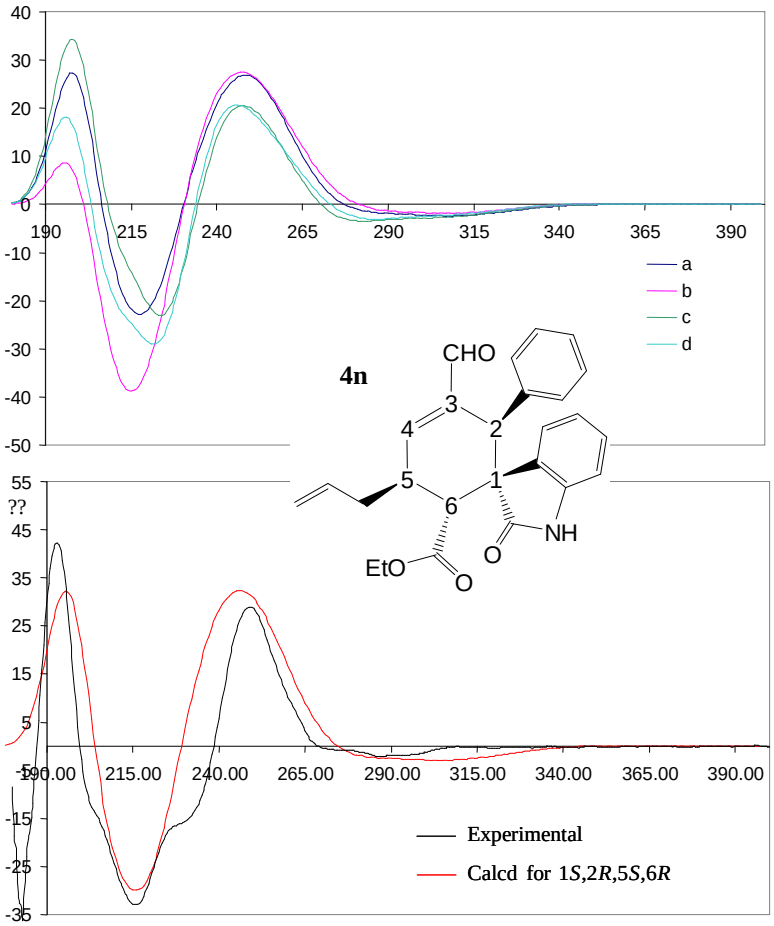
Supplementary Figure 19. Left: X-ray diffraction structure. Right: Lowest energy structure obtained by DFT calculations.

These eight conformations correspond to the combinations of the orientations of the three exocylic groups, i.e. the groups allyl, CO_2Et and CHO. Two of them are almost identical to the geometries obtained by X-ray data and the global minimum **a** comfortably corresponds to one of these two conformations.

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

Molecule	Conf.	ΔE	ΔG	P(%)
4n	**a**	0.00	0.00	72
	b	1.31	1.07	12
	c	0.82	0.98	14
	d	1.98	2.12	2
	e	2.55	2.30	-
	f	3.50	3.32	-
	g	3.38	3.20	-
	h	4.22	4.03	-

Electronic excitation energies and rotational strengths have been calculated for the first of the four conformations of **4n**, using TD-DFT at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) and assuming 1*S*, 2*R*, 5*S*, 6*R* absolute configuration, with the results shown in Supplementary Figure 20. Rotational strength were calculated in both length and velocity representation. The resulting values are very similar, therefore errors due to basis set incompleteness are very small.[81] The four ECD spectra obtained (top in Supplementary Figure 20) show similar shapes, indicating that the conformation of the exocylic groups does not exert a great influence on the spectrum. The final simulated ECD spectra was obtained taking into account the 72:12:14:2 population ratios determined assuming Boltzmann statistics from the calculated free energies at the B3LYP/6-31G(d) level (Supplementary Table 4). The agreement between calculated and experimental spectrum is very good, and correctly simulates the signs of the observed Cotton effects. The TD-DFT simulation therefore supports the conclusion that the AC of **4n** is 1*S*, 2*R*, 5*S*, 6*R*.

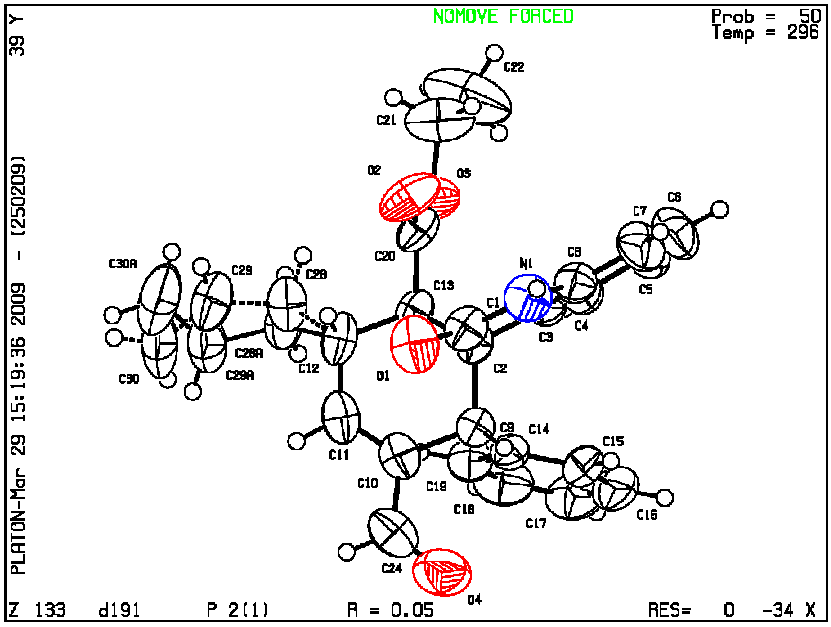


Supplementary Figure 20. Top: calculated ECD spectra for the four conformations of **4n**. Bottom: experimental (black) and calculated ECD spectra (red), weighted on the calculated free energies of the four conformations **a-d**. Molecular CD (Δε) is expressed in L $mol^{-1}cm^{-1}$.

TABLE OF RESULTS

Compd.	Relative configuration	Absolute Configuration	Method
6b	1*R**, 2*R**, 6*R**	1*S*, 2*S*, 3*S*	NMR-ECD/TD-DFT
ent-6c	-	1*R*, 2*R*,6*R*	A.D. X-Ray
6f	1*R**, 2*R**, 3*S**, 6*S**	1*R*, 2*R*, 3*S*, 6*S*	NMR-ECD/TD-DFT
6h	1*R**, 3*R**, 3*R**, 6*R**	1*R*, 2*R*, 3*R*, 6*R*,	NMR-ECD/TD-DFT
4a	1*R**, 2*R**, 5*S**, 6*S**	1*R*, 2*R*,5*S*,6*S*	X-Ray-ECD/TD-DFT
4n	1*R**, 2*S**, 5*R**, 6*S**	1*S*, 2*R*, 5*S*, 6*R*	NMR-ECD/TD-DFT

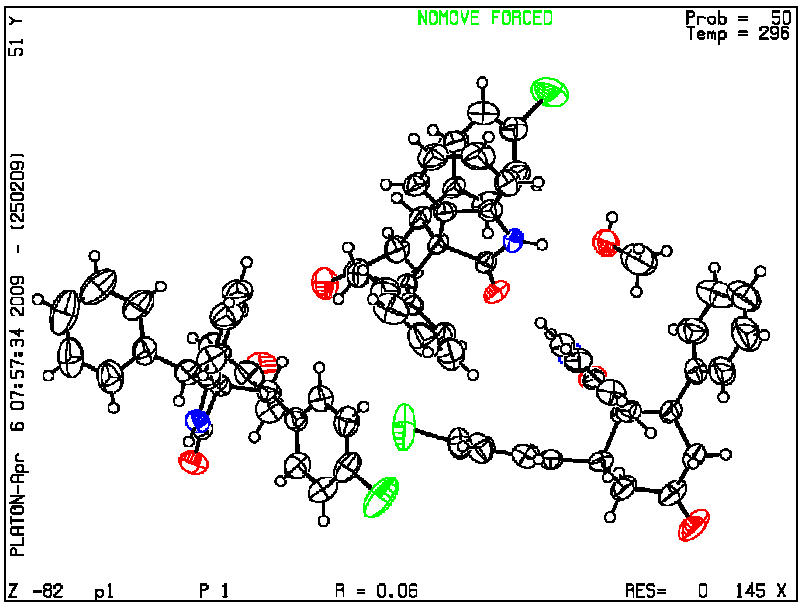
Crystal Data for 4n



Crystals obtained from hexane/dichloromethane solution, molecular formula: $C_{26}H_{25}NO_4$, M_r = 415.47, monoclinic, space group $P2_1$ (No. 3), a = 9.1003(11), b = 9.3928(12), c = 13.8607(17), β = 106,0440(10) Å, V = 1138.6(2) Å^3, T = 298(2) K, Z = 2, ρ_c = 1.212 g cm^{-3}, F(000) = 440, graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å), μ($Mo_{K\alpha}$) = 0.082 mm^{-1}, colourless plates (0.40 × 0.40 × 0.25 mm^3), empirical absorption correction with SADABS (transmission factors: 0.9681 – 0.9799), 2400 frames, exposure time 15 s, 1.53 ≤ θ ≤ 27.50, –11≤ h ≤ 11, –12 ≤ k ≤ 12, –17 ≤ l ≤ 17, 12891 reflections collected, 5172 independent reflections (R_{int} = 0.0205), 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 = 5172/ 72 / 309, $S(F^2)$ = 1.023, $R(F)$ = 0.0539 and $wR(F^2)$ = 0.1409 on all data, $R(F)$ = 0.0476 and $wR(F^2)$ = 0.1329 for 4471 reflections with I > 2σ(I), weighting scheme w = 1/[σ^2(F_o^2) + (0.0897P)^2 + 0.072400P] where P = (F_o^2 + 2F_c^2)/3, largest difference peak and hole 0.283 and –0.147 e Å^{-3}. Flack parameter[a]: -0.7(12). The allyl group is disordered over two different positions, accordingly it was split into two parts and refined (final optimized ratio 57:43). 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-726678. 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

Crystal Data for ent-6c

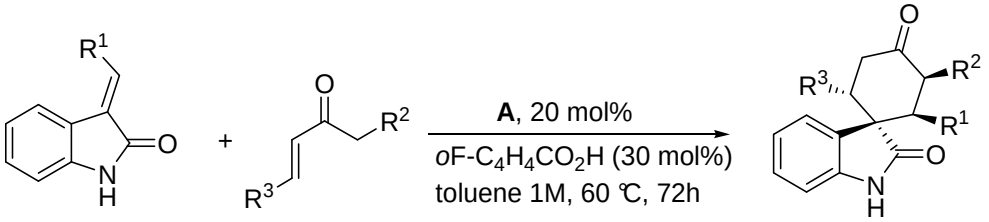


Crystals obtained from hexane/Et_2O/methanol solution, molecular formula: $C_{25}H_{21}NO_4Cl \cdot CH_4O$, M_r = 412.55, Triclinic, space group P1 (No. 1), a = 9.368(3), b = 13.827(4), c = 14.074(4), α = 116.552(4), β = 98.650(4), γ = 96.680(4), V = 1577.1(9) Å^3, T = 298(2) K, Z = 3, ρ_c = 1.303 g cm^{-3}, F(000) = 648, graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å), $\mu(Mo_{K\alpha})$ = 0.205 mm^{-1}, colourless plates (0.3 × 0.3 × 0.05 mm^3), empirical absorption correction with SADABS (transmission factors: 0.9410 – 0.9898), 2400 frames, exposure time 25 s, 1.66 ≤ θ ≤ 27.50, –12≤ h ≤ 12, –17 ≤ k ≤ 17, –18 ≤ l ≤ 18, 17596 reflections collected, 13581 independent reflections (R_{int} = 0.0232), 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 = 13581/ 3 / 804, $S(F^2)$ = 1.011, $R(F)$ = 0.1160 and $wR(F^2)$ = 0.1509 on all data, $R(F)$ = 0.0574 and $wR(F^2)$ = 0.1225 for 7776 reflections with $I > 2\sigma(I)$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0546P)^2 + 0.4625P]$ where $P = (F_o^2 + 2F_c^2)/3$, largest difference peak and hole 0.228 and –0.298 e Å^{-3}. Flack parameter[a]: 0.00(7). The unit cell contains three independent molecules and a molecule of methanol. 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-726679.

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).

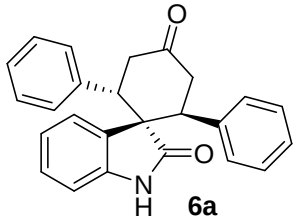
[a] Flack, H. D. Acta Cryst. **1983**, *A39*, 876-881

General procedure for Tandem double Michael addition for the synthesis of spiro-oxindolic cyclohexanone derivatives 6a-i.



1 **2** **6**

All the reaction were carried out in undistilled toluene. In an ordinary vial equipped with a Teflon-coated stir bar, 9-Amino(9-deoxy)epi-hydroquinine A (0.08 mmol., 26 mg, 20 mol%) was dissolved in 0.4 mL of toluene and 2-fluorobenzoic acid (0.12 mmol., 16.8 mg, 30 mol%) was added. The resulting solution was stirred at room temperature for 10 minutes then α,β-unsaturated ketone 2 (0.8 mmol., 2.0 equiv.) was added, followed by the addition of oxindole derivative 1 (0.4 mmol.). The vial was immerged in a oil bath at the indicated temperature and stirring continued for the indicated time. The crude mixture was flushed through a short plug of silica, using dichloromethane/diethyl ether 1:1 as the eluent (100 ml). Solvent was removed in *vacuo* and d.r was determined by ^{1}H NMR analysis. Compound 3 was isolated by flash column chromatography using hexane/diethyl ether or dichloromethane /diethyl ether as the eluent mixtures.

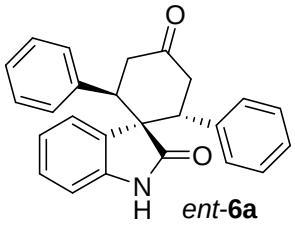


6a

(2*S*,6*S*)-2,6-diphenylspiro[cyclohexane-1,3'-indoline]-2',4-dione

(**6a**). The reaction was carried out following the general procedure using A as the catalyst to furnish the crude product (d.r. >19:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 6.18 ppm. d, δ_{minor} 6.25 ppm. d). The title compound was isolated by flash column chromatography (hexane/diethyl ether = 6/4) in 59% yield and 98% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 85:15, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 16.56 min., τ_{minor} = 24.19 min. $[\alpha]_{rt}^{D}$= -

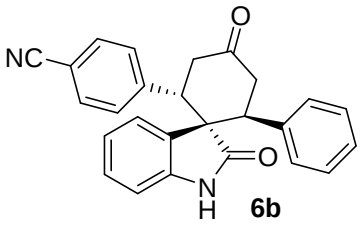
112.9 (*c* = 0.96, $CHCl_3$, 98% ee). HRMS: (*m/z*) calculated for $C_{25}H_{21}NO_2$: 367.1572, found: 367.1573. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.71 (dd, 1H, J_1 = 15.8 Hz, J_2 = 3.8 Hz), 2.98 (dd, 1H, J_1 = 16.0 Hz, J_2 = 6.0 Hz), 3.62 (dd, 1H, J_1 = 16.1 Hz, J_2 = 6.0 Hz), 3.69 (t, 1H, J = 6.0 Hz), 3.78 (dd, 1H, J_1 = 14.1 Hz, J_2 = 3.8 Hz), 3.95 (dd, 1H, J_1 = 15.7 Hz, J_2 = 14.0 Hz), 6.19 (d, 1H, J = 7.7 Hz), 6.51 (d, 1H, J = 7.7 Hz), 6.71 (dt, 1H, J_1 = 7.6 Hz, J_2 = 0.8 Hz), 6.86-6.91 (m, 2H), 6.92-6.97 (m, 2H), 6.97-7.05 (m, 4H), 7.18-7.25 (m, 3H), 7.74 (bs, 1H). ^{13}CNMR (150 MHz, $CDCl_3$): δ 41.8 (CH), 42.6 (CH), 45.5(CH_2), 46.6 (CH_2), 55.8 (C), 109.0 (CH), 121.6 (CH), 125.9 (CH), 127.1 (CH), 127.4(CH), 127.9 (CH), 127.9 (CH), 128.0 (CH), 128.2 (CH), 129.3 (CH), 130.0 (C), 137.9 (C), 139.9 (C), 180.2 (C), 211.0 (C).



ent-**6a**

(2*R*,6*R*)-2,6-diphenylspiro[cyclohexane-1,3'-indoline]-2',4-dione

(***ent*-6a**). The reaction was carried out following the general procedure using C as the catalyst to furnish the crude product (d.r. >19:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 6.18 ppm. d, δ_{minor} 6.25 ppm. d). The title compound was isolated as single diasteroisomer by flash column chromatography (hexane/diethyl ether = 6/4) in 37% yield and 90% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 85:15, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 22.56 min., τ_{minor} = 15.69 min.



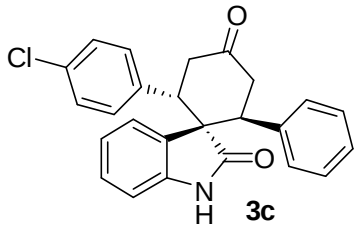
6b

4-((1*S*,2*S*,6*S*)-2',4-dioxo-2-phenylspiro[cyclohexane-1,3'-indoline]-6-yl)benzonitrile

(**3b**). The reaction was carried out following the general procedure using A as the catalyst to furnish the crude product (d.r. 6:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 2.97 ppm. dd, δ_{minor} 3.09 ppm. dd). The compound was isolated as a mixture of diasteroisomers (d.r = 4:1 determined by integration of ^{1}H-NMR signal: δ_{major} 2.97 ppm. dd, δ_{minor} 3.09 ppm. dd) by flash column chromatography (diethyl ether/hexane = 6/4) in 76% yield and 92% ee on the major diasteroisomer. After crystallization compound 3b was obtained as single diasteroisomer in 37% yield and 99% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 21.55 min., τ_{minor} = 37.02 min. $[\alpha]_{rt}^{D}$ = -174.4 (*c* = 0.75, $CHCl_3$, 99% ee). HRMS: (*m/z*) calculated for $C_{26}H_{20}N_2O_2$: 392.1525, found: 392.1525. ^{1}H NMR (600 MHz, CD_3CN): δ 2.54 (dd, 1H, J_1 = 16.2 Hz, J_2 = 3.3 Hz), 3.17 (ABX system, 2H, J_1 = 16.7 Hz, J_2 = 9.6.3 Hz, J_3 = 5.0 Hz), 3.79 (dd, 1H, J_1 = 16.2 Hz, J_2 = 14.0 Hz), 3.90 (dd, 1H, J_1 = 9.4 Hz, J_2 = 5.0 Hz), 3.95 (dd, 1H, J_1 = 14.0 Hz, J_2 = 3.3 Hz), 6.48 (d, 1H, J = 7.7 Hz),

6.78-6.84 (m, 2H), 6.94-7.04 (m, 5H), 7.23-7.18 (m, 3H), 7.41 (m, 2H), 8.12 (bs, 1H). ^{13}CNMR (150 MHz, CD_3CN): δ 41.6 (CH_2), 41.8 (CH_2), 45.8 (CH), 45.9 (CH), 56.6 (C), 109.4 (CH), 111.0 (C), 117.8 (C), 118.9 (C), 121.8 (CH), 126.0 (CH), 127.5 (CH), 128.4 (CH), 128.6 (CH), 129.3 (CH), 129.9 (CH), 130.7 (C), 131.9 (CH), 140.2 (C), 141.4 (C), 144.7 (C), 179.8 (C), 209.9 (C).

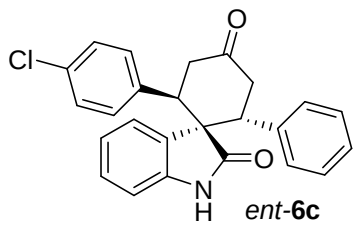
The relative and absolute configurations for 3b have been inferred by using NMR NOE analyses coupled with TD-DFT calculations of the electronic circular dichroism (ECD) spectra, see Structural Assignment section.



3c

(1*S*,2*S*,6*S*)-2-(4-chlorophenyl)-6-phenylspiro [cyclohexane-1,3'-indoline]-2',4-dione

(**6c**). The reaction was carried out following the general procedure using A as the catalyst to furnish the crude product (d.r. 4:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 6.18 ppm. d, δ_{minor} 6.38 ppm. d). The compound was isolated as a mixture of diasteroisomers (d.r = 4:1 determined by integration of ^{1}H-NMR signal: δ_{major} 2.97 ppm. dd, δ_{minor} 3.09 ppm. dd) by flash column chromatography (diethyl ether/hexane = 1.1/1) in 65% yield and 89% ee on the major diasteroisomer. After crystallization compound 3c was obtained as single diasteroisomer in 21% yield and 99% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 11.58 min., τ_{minor} = 18.57 min. $[\alpha]_{rt}^{D}$= -113.9 (*c* = 0.67, $CHCl_3$, 99% ee). MS (ESI): 424 (M^+ + Na, 100%), 440 (M^+ +K, 10%). ^{1}H NMR (600 MHz, $CDCl_3$): δ ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.67 (dd, 1H, J_1 = 15.9 Hz, J_2 = 3.7 Hz), 2.97 (dd, 1H, J_1 = 16.3 Hz, J_2 = 6.3 Hz), 3.59 (dd, 1H, J_1 = 16.2 Hz, J_2 = 5.9 Hz), 3.69 (t, 1H, *J* = 6.2 Hz), 3.75 (dd, 1H, J_1 = 14.1 Hz, J_2 = 3.7 Hz), 3.87-3.94 (m, 1H), 6.18 (d, 1H, *J* = 7.5 Hz), 6.53 (d, 1H, *J* = 7.7 Hz), 6.72 (t, 1H, *J* = 7.7 Hz), 6.81 (d, 2H, *J* = 8.6 Hz), 6.91-6.95 (m, 2H), 6.97-7.02 (m, 3H), 7.18-7.23 (m, 3H), 7.38 (bs, 1H). ^{13}CNMR (150 MHz, $CDCl_3$): δ 41. 8 (CH), 42.4 (CH), 45.0 (CH_2), 46.5 (CH_2), 55.7 (C), 109.2 (CH), 121.5 (CH), 125.8 (CH), 127.5 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 129.2 (CH), 129.6 (CH), 129.7 (C), 133.0 (C), 136.4 (C), 139.6 (C), 139.7 (C), 179.6 (C), 210.5 (C).



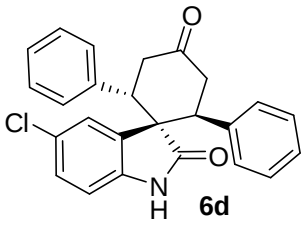
ent-**6c**

(1*R*,2*R*,6*R*)-2-(4-chlorophenyl)-6-phenylspiro [cyclohexane-1,3'-indoline]-2',4-dione

(***ent*-6c**). The reaction was carried out following the general procedure using C as the catalyst to furnish the crude product (d.r. 5:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 6.18 ppm. d, δ_{minor} 6.38 ppm. d) The compound was isolated as single diasteroisomer by

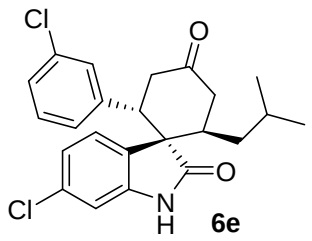
flash column chromatography (diethyl ether/hexane = 1.1/1) in 45% yield and 89% ee. After crystallization compound *ent*-3c was obtained as single diasteroisomer in 10% yield and 99% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 18.88 min., τ_{minor} = 11.73 min.

The relative and absolute configurations for *ent*-3c have been inferred by means of X-ray crystallography, see Structural Assignment section.



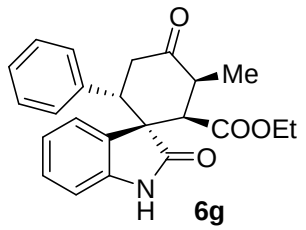
(2*S*,6*S*)-5'-chloro-2,6-diphenylspiro [cyclohexane-1,3'-indoline]-2',4-dione

(**6d**). The reaction was carried out following the general procedure using A as the catalyst to furnish the crude product (d.r. = 7:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 5.99 ppm. d, δ_{minor} 6.38 ppm. d). The title compound was isolated as single diasteroisomer by flash column chromatography (hexane/diethyl ether = 2/1) in 82% yield and 94% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 11.05 min., τ_{minor} = 16.79 min. $[\alpha]_{rt}^{D}$= -107.1 (*c* = 1.05, $CHCl_3$, 94% ee). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.72 (1H, dd, J_1 = 16.0 Hz, J_2 = 4.0 Hz), 2.95 (dd, 1H, J_1 = 18.0 Hz, J_2 = 7.4 Hz), 3.61-3.67 (m, 2H), 3.73 (dd, 1H, J_1 = 14.0 Hz, J_2 = 3.8 Hz), 3.93 (dd, 1H, J_1 = 15.7 Hz, J_2 = 14.2 Hz), 6.01 (d, 1H, *J* = 2.1 Hz), 6.48 (d, 1H, *J* = 8.2 Hz), 6.88-6.92 (m, 2H), 6.92-6.98 (m, 3H), 7.00-7.08 (m, 3H), 7.24-7.32 (m, 3H), 8.12 (bs, 1H). ^{13}CNMR (150 MHz, $CDCl_3$): δ 41.6 (CH), 42.5 (CH), 45.4 (CH_2), 46.7 (CH_2), 56.1 (C), 110.0 (CH), 126.3 (CH), 126.7 (C), 127.3 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 129.3 (CH), 131.7 (C), 137.6 (C), 138.4 (C), 139.4 (C), 180.0 (C), 210.6 (C).



(1*S*,2*S*,6*R*)-6'-chloro-2-(3-chlorophenyl)-6-isobutylspiro [cyclohexane-1,3'-indoline]-2',4-dione

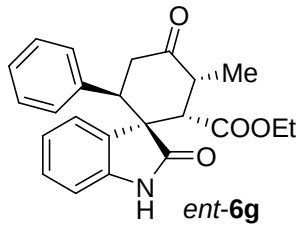
(**6e**). The reaction was carried out following the general procedure using A as the catalyst to furnish the crude product (d.r. = 12:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 3.65 ppm. m, δ_{minor} 6.05 ppm. d). The title compound was isolated as single diasteroisomer by flash column chromatography (dichloromethane/diethyl ether = 9.5/0.5) in 80% yield and 91% ee. After crystallization compound 3e was obtained as single diasteroisomer in 38% yield and 97% ee.The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 90:10, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 14.36 min., τ_{minor} = 23.11 min. $[\alpha]_{rt}^{D}$= -83.1 (*c* = 1.06, $CHCl_3$, 97% ee). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.66 (d, 3H, *J* = 6.5 Hz), 0.80 (d, 3H, *J* = 6.5 Hz), 0.90-0.97 (m, 1H), 1.14-1.20 (m, 1H), 1.42-1.51 (m, 1H), 2.46 (dd, 1H, J_1 = 15.7 Hz, J_2 = 3.3 Hz), 2.52-2.60 (m, 2H), 3.0-3.07 (m, 1H), 3.49 (dd, 1H, J_1 = 14.6 Hz, J_2 = 3.3 Hz), 3.62 (dd, 1H, J_1 = 15.4 Hz, J_2 = 14.1 Hz), 6.69 (d, 1H, *J* = 7.9 Hz), 6.72 (d, 1H, *J* =1.8 Hz), 6.83 (bs, 1H), 6.99 (t, 1H, *J* = 8.0 Hz), 7.05-7.10 (m, 2H), 7.26 (d, 1H, *J* = 8.0 Hz), 7.80 (bs, 1H). ^{13}CNMR (150 MHz, $CDCl_3$): δ 21.18 (CH_3), 23.5 (CH_3), 25.0 (CH), 37.3 CH), 40.2 (CH_2), 40.7 (CH_2), 41.7 (CH_2), 46.3 (CH), 55.8 (C), 110.5 (CH), 122.3 (CH), 125.6 (CH), 126.3 (CH), 127.6 (CH), 128.2 (CH), 129.2 (C), 129.3 (CH), 133.8 (CH), 134.1 (C), 139.6 (C), 141.6 (C), 180.1 (C), 210.1 (C).



(1*R*,2*R*,3*S*,6*S*)-ethyl 3-methyl-2',4-dioxo-6-phenylspiro [cyclohexane-1,3'-indoline]-2-carboxylate

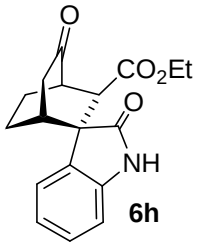
(**6g**). The reaction was carried out following the general procedure using catalyst A to furnish the crude product (d.r. = 7:1:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 6.66 ppm. d, δ_{minor} 6.61 ppm. d, δ_{minor} 6.55 ppm. d). The title compound was isolated as single diasteroisomer by flash column chromatography (dichloromethane/diethyl ether = 30/1) in 63% yield and 97% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 90:10, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 24.54 min., τ_{minor} = 27.18 min. $[\alpha]_{rt}^{D}$= -88.9 (*c* = 1.09, CH_3CN, 97% ee). HRMS: (*m/z*) calculated for $C_{23}H_{23}NO_4$: 377.1627, found: 377.1628. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.07 (d, 3H, *J* = 6.9 Hz), 1.22 (t, 3H, *J* = 7.2 Hz), 2.64 (dd, 1H, J_1 = 14.4 Hz, J_2 = 5.0 Hz), 3.08 (d, 1H, *J* = 5.7 Hz), 3.77 (t, 1H, *J* = 13.7 Hz), 4.02 (q, 1H, *J* = 6.5 Hz), 4.13-4.20 (m, 1H), 4.22-4.29 (m, 1H), 4.33 (dd, 1H, J_1 = 13.5 Hz, J_2 = 4.6 Hz), 6.65 (d, 1H, *J* = 7.7 Hz), 6.95-7.05 (m, 6H), 7.08-7.14 (m, 2H), 8.26 (s, 1H). ^{13}CNMR (150 MHz, $CDCl_3$): δ 11.5 (CH_3), 14.1 (CH_3), 40.0 (CH), 42.6 (CH_2), 45.8 (CH), 53.1 (C), 55.0 (CH), 61.0 (CH_2), 109.8 (CH), 122.2 (CH), 124.1 (CH), 127.2 (CH), 128.8 (CH), 128.5 (CH), 128.6 (CH), 129.2 (C), 138.9 (C), 139.8 (C), 171.5 (C), 179.0 (C), 209.2 (C).

The relative and absolute configurations for **6c** have been inferred by using NMR NOE analyses coupled with TD-DFT calculations of the electronic circular dichroism (ECD) spectra, see Structural Assignment section.



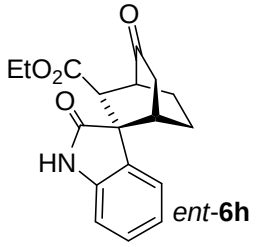
(1*S*,2*S*,3*R*,6*R*)-ethyl 3-methyl-2',4-dioxo-6-phenylspiro [cyclohexane-1,3'-indoline]-2-carboxylate

(***ent*-6g**). The reaction was carried out following the general procedure using C as the catalyst to furnish the crude product. (d.r. = 4:1:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 6.64 ppm. d, δ_{minor} 6.60 ppm. d, δ_{minor} 6.55 ppm. d). The title compound was isolated as single diasteroisomer by flash column chromatography (dichloromethane/diethyl ether = 30/1) in 56% yield and 93% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 90:10, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 26.93 min., τ_{minor} = 24.94 min.



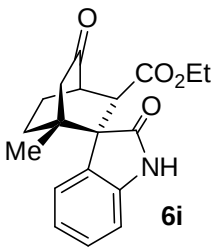
(1*R*,2*S*,3*R*)-ethyl 2',5-dioxospiro [bicyclo[2.2.2]octane-2,3'-indoline]-3-carboxylate

(**6h**). The reaction was carried out at 40 °C following the general procedure using A as the catalyst to furnish the crude product (d.r >19:1). The title compound was isolated as single diasteroisomer by flash column chromatography (dichloromethane/diethyl ether = 5/1) in 28% yield and 89% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 90:10, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 35.54 min., τ_{minor} = 16.34 min. $[\alpha]_{rt}^{D}$= -24.5 (*c* = 1.00, $CHCl_3$, 89% ee). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.10 (t, 3H, *J* = 7.2 Hz), 1.59-1.67 (m, 1H), 2.0-2.09 (m, 3H), 2.12 (dd, J_1 = 19.2 Hz, J_2 = 2.8 Hz), 2.21-2.33 (m, 1H), 2.91 (q, 1H, *J* = 2.7 Hz), 3.20 (d, 1H, *J* = 2.2 Hz), 3.46 (dt, 1H, J_1 = 19.2 Hz, J_2 = 2.7 Hz), 4.02 (q, 2H, *J* = 7.1 Hz), 6.91 (d, 1H, *J* = 7.8 Hz), 7.10 (dt, 1H, J_1 = 7.5 Hz, J_2 = 0.7 Hz), 7.27 (dt, 1H, J_1 = 7.7 Hz, J_2 = 1.2 Hz), 7.35 (d, 1H, *J* = 7.6 Hz), 7.89 (bs, 1H). ^{13}CNMR (150 MHz, $CDCl_3$): δ 13.8 (CH_3), 21.1 (CH_2), 23.2 (CH_2), 36.9 (CH), 39.4 (CH_2), 43.7 (CH), 50.1 (CH), 51.6 (C), 61.1 (CH_2), 110.0 (CH), 122.4 (CH), 124.0 (CH), 128 (CH), 133.7 (C), 140.7 (C), 170.8 (C), 179.6 (C), 211.6 (C).



(1*S*,2*R*,3*R*)-ethyl 2',5-dioxospiro [bicyclo[2.2.2]octane-2,3'-indoline]-3-carboxylate

(***ent*-6h**). The reaction was carried out at 40 °C following the general procedure using C as the catalyst to furnish the crude product (d.r >19:1). The title compound was isolated as single diasteroisomer by flash column chromatography (dichloromethane/diethyl ether = 5/1) in 18% yield and 85% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 90:10, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 16.2 min., τ_{minor} = 35.1 min.

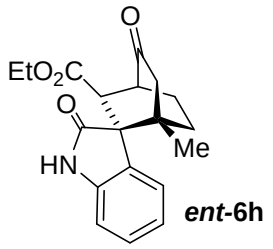


(1*R*,2*R*,3*R*,6*R*)-ethyl 1-methyl-2',5-dioxospiro [bicyclo[2.2.2]octane-2,3'-indoline]-3-carboxylate

(**6i**). The reaction was carried out at 60 °C following the general procedure using A as the catalyst to furnish the crude product (d.r >19:1). The title compound was isolated as single diasteroisomer by flash column chromatography (dichloromethane/diethyl ether = 7/3) in 24% yield and 97% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254

nm: τ_{major} = 41.45 min., τ_{minor} = 15.43 min. $[\alpha]_{rt}^{D}$= -110.6 (*c* = 0.38, $CHCl_3$, 97% ee). MS (ESI): 350 (M^+ +Na, 100%), 366 (M^+ +K, 10%), 328 (M^+ +1, 1%). ^{1}H NMR (600 MHz, CD_3CN): δ 0.56 (s, 3H), 1.04 (t, 3H, *J* = 7.2 Hz), 1.40 (m, 1H), 191 (d, 1H, *J* = 18.9 Hz), 2.07-2.19 (m, 3H), 2.72 (q, 1H, *J* = 2.7 Hz), 3.18 (dd, 1H, J_1 = 18.9 Hz, J_2 = 3.2 Hz), 3.29 (d, 1H, *J* = 2.1 Hz), 3.81-3.88 (m, 1H), 3.93-3.99 (m, 1H), 6.93 (d, 1H; *J* = 7.8 Hz), 7.10 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.1 Hz), 7.29 (dt, 1H, J_1= 7.6 Hz, J_2 = 1.2 Hz), 7.43 (d, 1H, *J* = 7.5 Hz), 8.43 (bs, 1H). ^{13}CNMR (150 MHz, CD_3CN): δ 13.4 (CH_3), 20.6 (CH_3), 23.6 (CH_2), 28.4 (CH_2), 39.5 (C), 44.2 (CH), 45.4 (CH_2), 51.1 (CH), 55.1 (C), 60.7 (CH_2), 109.6 (CH), 122.3 (CH), 124.8 (CH), 128.8 (CH), 133.4 (C), 142.5 (C), 171.4 (C), 179.3 (C), 211.9 (C).

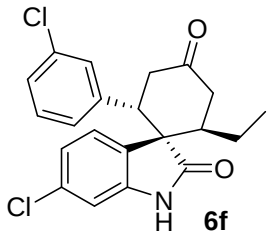
The relative and absolute configurations for **6i** have been inferred by using NMR NOE analyses coupled with TD-DFT calculations of the electronic circular dichroism (ECD) spectra, see Structural Assignment section.



***ent*-6h**

(1*S*,2*S*,3*S*,6*S*)-ethyl 1-methyl-2',5-dioxospiro [bicyclo[2.2.2]octane-2,3'-indoline]-3-carboxylate

(***ent*-6i**). The reaction was carried out at 60 °C following the general procedure using C as the catalyst to furnish the crude product (d.r >19:1). The title compound was isolated as single diasteroisomer by flash column chromatography (dichloromethane/diethyl ether = 7/3) in 20% yield and 82% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 15.64 min., τ_{minor} = 43.64 min.



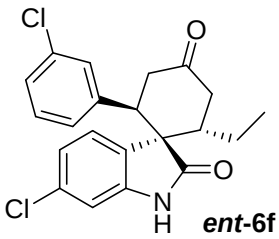
6f

(1*S*,2*S*,6*R*)-6'-chloro-2-(3-chlorophenyl)-6-ethylspiro [cyclohexane-1,3'-indoline]-2',4-dione

(**6f**). The reaction was carried out following the general procedure using A as the catalyst to furnish the crude product (d.r. = 4.5:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 3.07 ppm. dd, δ_{minor} 2.98 ppm. m). The title compound was isolated as single diasteroisomer by flash column chromatography (dichloromethane/diethyl ether = 9/1) in 70% yield and 84% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 8.12 min., τ_{minor} = 9.70 min. $[\alpha]_{rt}^{D}$= -113.5 (*c* = 0.17, $CHCl_3$, 84% ee). HRMS: (*m/z*) calculated for $C_{21}H_{19}Cl_2NO_2$: 387.0793, found: 387.0791. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.81 (t, 3H, *J* = 7.0 Hz), 1.18-1.27 (m, 1H), 1.27-1.35 (m, 1H), 2.40 (m, 1H), 2.46 (dd,

1H, J_1 = 15.7 Hz, J_2 = 3.1 Hz), 2.59 (dd, 1H, J_1 = 16.4 Hz, J_2 = 10.3 Hz), 3.06 (dd, 1H, J_1 = 16.6 Hz, J_2 = 4.1 Hz), 3.48 (dd, 1H, J_1 = 14.1 Hz, J_2 = 3.2 Hz), 3.63 (m, 1H), 6.68-6.71 (m, 2H), 6.82 (bt, 1H), 7.01 (t, 1H, J = 7.9 Hz), 7.06-7.1 (m, 2H), 7.14 (bs, 1H).

^{13}CNMR (150 MHz, $CDCl_3$): δ 11.9 (CH3), 24.2 (CH2), 40.1 (CH2), 41.5 (CH2), 41.7 (CH), 46.4 (CH), 55.8 (C), 110.3 (CH), 122.3 (CH), 125.7 (CH), 126.3 (CH), 127.7 (CH), 128.3 (CH), 129.2 (C), 129.3 (CH), 133.9 (C), 134.2 (C), 139.5 (C), 141.5 (C), 179.6 (C), 210.0 (C).

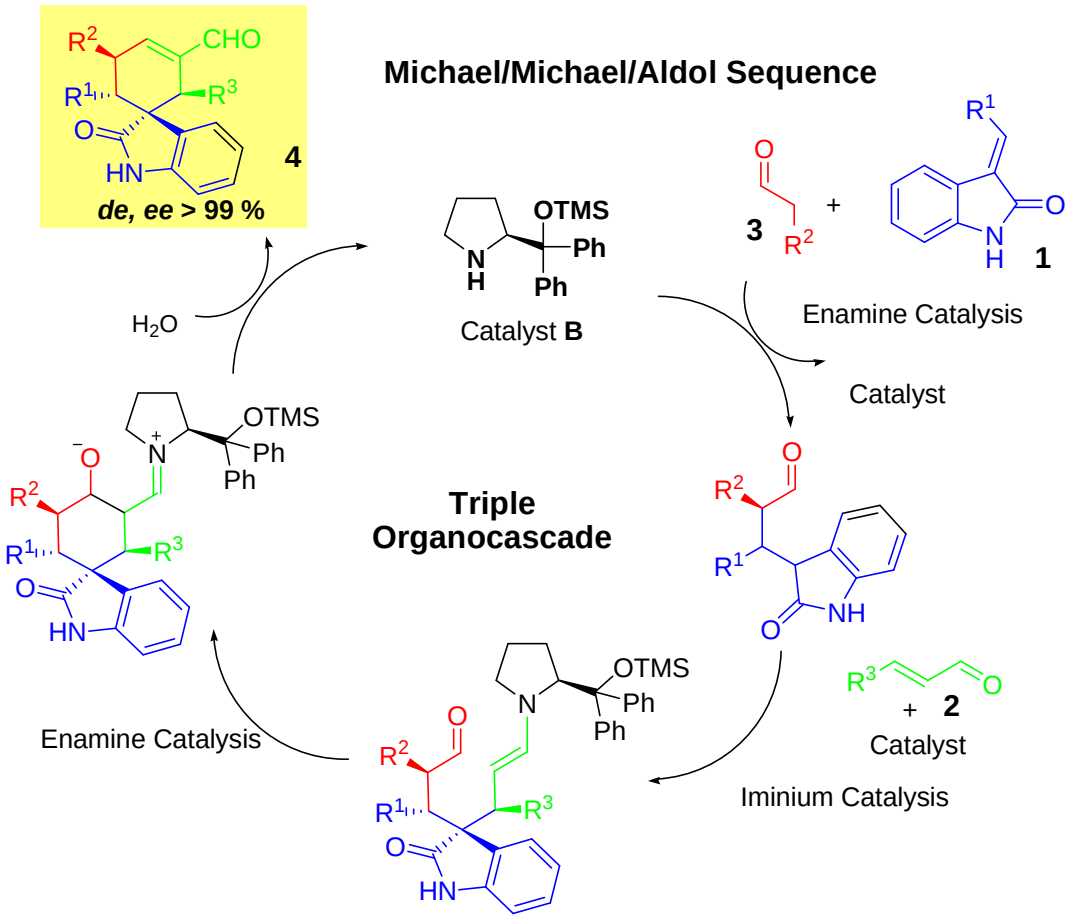


***ent*-6f**

(1*R*,2*R*,6*S*)-6'-chloro-2-(3-chlorophenyl)-6-ethylspiro [cyclohexane-1,3'-indoline]-2',4-dione

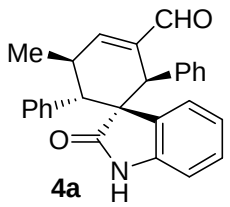
(***ent*-6f**). The reaction was carried out following the general procedure using C as the catalyst to furnish the crude product (d.r. = 2.6:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 3.07 ppm. dd, δ_{minor} 2.98 ppm. m). The title compound was isolated as single diasteroisomer by flash column chromatography (dichloromethane/diethyl ether = 9/1) in 25% yield and 77% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 9.71 min., τ_{minor} = 8.15 min.

Gneral procedures for Triple organocascade for the synthesis of spiro-oxindole derivatives **4**.



All the reactions were carried out in undistilled solvent without any precautions to exclude water and moisture. In an 10 mL flask equipped with a magnetic stirring bar, catalyst (*S*)-IIIc (19.5 mg, 0.06 mmol., 15 mol%), *ortho*-fluoro benzoic acid (8.4 mg, 0.06 mmol, 15 mol%) and aldehyde 4 (0.8 mmol, 2.0 equiv.) were dissolved in toluene (6.0 mL, 0.067 M). After 5 minutes stirring at room temperature, oxindole derivative 1 (0.6 mmol, 1.5 equiv.) and α,β–unsaturated aldehydes 5 (0.4 mmol, 1.0 equiv.) were sequentially added, and the mixture was stirred at 40 °C for 48 hours. Then the crude reaction mixture was directly charged on a chromatography column and flushed through a short plug of silica, using a 1:1 mixture of diethyl ether and dichloromethane as the eluent. After ^{1}H NMR analysis to check the distereomeric ratio, the crude residue was purified by flash column chromatography using hexane/acetone, hexane/ethyl acetate or dichloromethane/diethyl ether as the eluent mixtures, to yield the spiro-oxindolic cyclohexene carbaldehyde 6. When the separation of the two enantiomers by HPLC analysis on chiral stationary phases was not possible, in situ

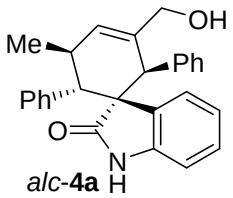
reduction ($NaBH_4$ in THF) was carried out, and the enantiomeric excess was evaluated on the corresponding alcohol.



4a

(1*R*,2*R*,5*S*,6*S*)-5-methyl-2'-oxo-2,6-diphenylspiro [cyclohex[3]ene-1,3'-indoline]-3-carbaldehyde

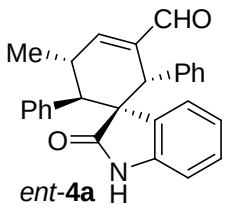
(**4a**) The reaction was carried out following the general procedure using (*S*)-IIIc as the catalyst to furnish the crude product. (d.r. 12:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 5.35 ppm. d, δ_{minor} 5.59 ppm. d). The title compound was isolated by flash column chromatography (hexane/acetone = 2/1) in 74% yield, and >99% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 10.19 min., τ_{minor} = 14.12 min. $[\alpha]_{rt}^{D}$= -75.7 (*c* = 0.80, $CHCl_3$, >99% ee). HRMS: (*m/z*) calculated for $C_{27}H_{23}NO_2$: 393.1729, found: 393.1728. ^{1}H NMR (600 MHz, CD_3CN): δ 1.11 (d, 3H, *J* = 7.1 Hz), 3.13 (d, 1H, *J* = 7.7 Hz), 3.61-3.65 (m, 1H), 3.97 (s, 1H), 5.40 (d, 1H, *J* = 7.7 Hz), 6.36 (t, 1H, *J* = 7.5 Hz), 6.53-6.56 (m, 2H), 6.86 (t, 1H, *J* = 7.5 Hz), 6.97-7.00 (m, 5H), 7.07 (t, 1H, *J* = 8.77 Hz), 7.26-7.31 (m, 3H), 7.44 (t, 1H, *J* = 6.9 Hz), 8.39 (bs, 1H), 9.48 (s, 1H). ^{13}CNMR (150 MHz, CD_3CN): δ 17.9 (CH_3), 35.4 (CH), 45.2 (CH), 49.2 (CH), 54.7 (C), 108.7 (CH), 120.2 (CH), 126.8 (CH), 126.9 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 129.7 (C), 133.4 (CH), 138.7 (C) 139.6 (C), 139.8 (C), 141.1 (C), 157.6 (CH), 179.6 (C), 193.7 (CH).



alc-**4a**

(a*lc*-4a) To a stirred solution of aldehyde 6a (82 mg, 0.2 mmol.) in THF (1.5 mL) $NaBH_4$ (24 mg, 0.6 mmol., 3 eq.) was slowly added at 0°C. Once the addition was finished the reaction was stirred for further 5 minutes then the ice bath was removed and stirring continued for 1 hour at room temperature. Solvent was removed under reduced pressure and the residual material was quenched with a saturated solution of NH_4Cl at room temperature and extracted with dichloromethane. The organic phase was dried over $MgSO_4$ then filtered and the solvent removed under reduced pressure to give the crude alcohol which was purified by flash chromatography using hexane/acetone = 2/1 as the eluent mixture. The title compound was isolated as white solid in 50% yield and >99% ee. HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 12.90 min., τ_{minor} = 13.91 min. $[\alpha]_{rt}^{D}$= -36.7 (*c* = 0.80, $CHCl_3$, >99% ee). HRMS: (*m/z*) calculated for $C_{27}H_{25}NO_2$: 395.1885, found: 395.1883. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (d, 3H, *J* = 6.2 Hz), 3.00 (d, 1H, *J* = 10.7 Hz), 3.27-3.31 (m, 1H), 3.65 (s, 1H), 3.83 (d, 1H, *J* = 12.4 Hz), 4.00 (d, 1H, *J* = 12.4 Hz), 5.40

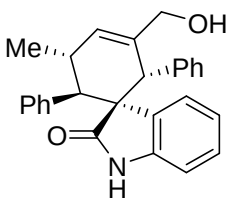
(d, 1H, *J* = 7.8 Hz), 6.17 (s, 1H), 6.41 (t, 1H, *J* = 7.0 Hz), 6.48-651 (m, 2H), 6.81-6.83 (m, 1H), 6.92 (bs, 5H), 7.07 (t, 1H, *J* = 6.6 Hz), 7.27-7.30 (m, 1H), 7.42-7.45 (m, 2H), 7.77 (bs, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 20.1 (CH_3), 33.6 (CH), 49.0 (CH), 49.8 (CH), 56.2 (C), 66.3 (CH_2), 108.7 (CH), 120.8 (CH), 126.6 (CH), 126.9 (CH), 127.4 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.3 (CH), 128.6 (CH), 130.4 (C), 132.2 (CH), 133.9 (CH), 134.2 (C), 139.4 (C), 139.7 (C), 139.8 (C), 180.7 (C).



ent-**4a**

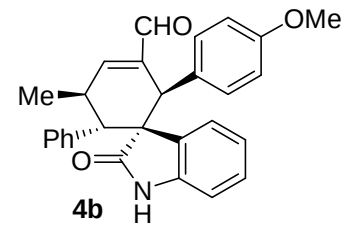
(1*S*,2*S*,5*R*,6*R*)-5-methyl-2'-oxo-2,6-diphenylspiro[cyclohex[3]ene-1,3'-indoline]-3-carbaldehyde

(***ent*-4a**) The reaction was carried out following the general procedure using (*R*)-IIIc as the catalyst to furnish the crude product (d.r. 13:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 5.42 ppm. d, δ_{minor} 5.65 ppm. d). The title compound was isolated by flash column chromatography (hexane/acetone = 2/1) in 76% yield, and >99% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 14.12 min., τ_{minor} = 10.19 min. $[\alpha]_{rt}^{D}$ = +75.0 (*c* = 0.80, $CHCl_3$, >99% ee).



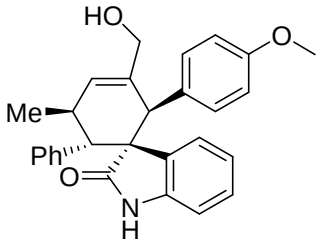
ent-alc-**4a**

(***ent-alc*-4a**) To a stirred solution of aldehyde *ent*-6a (82 mg, 0.2 mmol.) in THF (1.5 mL) $NaBH_4$ (24 mg, 0.6 mol., 3 eq.) was slowly added at 0°C. Once the addition was finished the reaction was stirred for further 5 minutes then the ice bath was removed and stirring continued for 1 hour at room temperature. Solvent was removed under reduced pressure and the residual material was quenched with a saturated solution of NH_4Cl at room temperature and extracted with dichloromethane. The organic phase was dried over $MgSO_4$ then filtered and the solvent removed under reduced pressure to give the crude alcohol which was purified by flash chromatography using hexane/acetone = 2/1 as the eluent mixture. The title compound was isolated as white solid in 50% yield and >99% ee. HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 12.90 min., τ_{minor} = 13.90 min. $[\alpha]_{rt}^{D}$ = +33.5 (*c* = 1.00, $CHCl_3$, >99% ee).



(1*R*,2*R*,5*S*,6*S*)-2-(4-methoxyphenyl)-5-methyl-2'-oxo-6-phenylspiro[cyclohex[3]ene-1,3'-indoline]-3-carbaldehyde

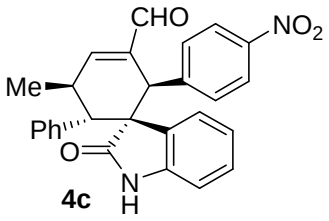
(4b) The reaction was carried out following the general procedure using (*S*)-IIIc as the catalyst to furnish the crude compound (d.r. 16:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 5.73 ppm. d, δ_{minor} 5.52 ppm. d). The title compound was isolated by flash column chromatography (hexane/acetone = 2/1) in 70% yield. The ee value was determined on the corresponding alcohol after reduction of the isolated aldehyde. $[\alpha]_{rt}^{D}$ = -54.9 (*c* = 1.00, $CHCl_3$, >99% ee). HRMS: (*m/z*) calculated for $C_{28}H_{25}NO_3$: 423.1834, found: 423.1835. ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 1.17 (d, 3H, *J* = 7.7 Hz), 3.07 (d, 1H, *J* = 10.3 Hz), 3.27-3.31 (m, 1H), 3.80 (s, 3H), 3.91 (s, 1H), 5.48 (d, 1H, *J* = 8.4 Hz), 6.46-6.49 (m, 2H), 6.54 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.5 Hz), 6.65 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.9 Hz), 6.86 (t, 1H, *J* = 7.8 Hz), 6.88-7.00 (m, 7H), 7.08-7.21 (m, 2H), 9.53 (s, 1H). ^{13}CNMR (150 MHz, $CDCl_3$): *δ* 19.0, 35.1, 44.5, 49.8, 55.2, 55.3, 108.7, 113.3, 113.4, 120.9, 125.6, 127.0, 127.3, 127.7, 128.1, 128.7, 129.5, 130.9, 133.5, 134.7, 138.7, 138.8, 139.6, 156.9, 159.0, 179.7, 193.3.



alc-**4b**

(***alc*-4b**) To a stirred solution of aldehyde 4b (0.2 mmol., 84 mg) in THF (1.5 mL) $NaBH_4$ (0.6 mmol., 24 mg, 3 eq.) was slowly added at 0°C. Once the addition was finished the reaction was stirred for further 5 minutes then the ice bath was removed and stirring continued for 1 hour at room temperature. Solvent was removed under reduced pressure and the residual material was quenched with a saturated solution of NH_4Cl at room temperature and extracted with dichloromethane. The organic phase was dried over $MgSO_4$ then filtered and the solvent removed under reduced pressure to give the crude alcohol which was purified by flash chromatography using hexane/acetone = 2/1 as the eluent mixture. The title compound was isolated as white solid in 50% yield and 99% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 7.11 min., τ_{minor} = 8.34 min. $[\alpha]_{rt}^{D}$= -113.1 (*c* = 2.00, $CHCl_3$, 99% ee). HRMS: (*m/z*) calculated for $C_{28}H_{27}NO_3$: 425.1991, found: 425.1994. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.02 (d, 3H, *J* = 7.1 Hz), 2.36 (bs, 1H), 2.99 (d, 1H, *J* = 10.8 Hz), 3.27-3.31 (m, 1H), 3.61 (s, 1H), 3.83 (s, 3H), 3.85 (bs, 1H), 3.99-4.02 (m, 1H), 5.52 (d, 1H, *J* = 7.2 Hz), 6.15 (s, 1H), 6.40-6.64 (m, 3H), 6.63 (d, 1H, *J* = 8.98 Hz), 6.83 (t, 1H, *J* = 6.3 Hz), 6.92 (s, 5H), 6.99 (d, 1H, *J* = 8.5 Hz), 7.36 (d, 1H, *J* = 8.5 Hz), 8.11 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 20.1 (CH_3), 33.7 (CH), 48.3 (CH), 49.8 (CH), 55.5 (CH_3), 56.4 (C), 66.2 (CH_2), 108.7 (CH), 113.2 (CH), 113.6 (CH), 120.8 (CH), 126.6 (CH), 127.1

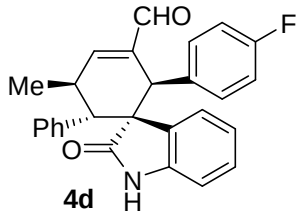
(CH), 127.4 (CH), 127.9 (CH), 129.6 (CH), 130.6 (C), 131.4 (C), 131.8 (CH), 134.6 (C), 134.8 (CH), 139.9 (C), 140.0 (C), 159.2 (C), 180.9 (C).



4c

(1*R*,2*R*,5*S*,6*S*)-5-methyl-2-(4-nitrophenyl)-2'-oxo-6-phenylspiro [cyclohex[3]ene-1,3'-indoline]-3-carbaldehyde

(4c) The reaction was carried out following the general procedure using (*S*)-IIIc as the catalyst to furnish the crude product (d.r. >19:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 5.32 ppm. d, δ_{minor} 5.51 ppm. d). The title compound was isolated by flash column chromatography (hexane/acetone = 2/1) in 35% yield and >99% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 19.09 min, τ_{minor} = 30.39 min. $[\alpha]_{rt}^{D}$ = -82.8 (*c* = 2.00, $CHCl_3$, >99% ee). HRMS: (*m/z*) calculated for $C_{27}H_{22}N_2O_4$: 438.1580; found: 438.1576. ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 1.20 (d, 3H, *J* = 8.0 Hz), 3.00 (d, 1H, *J* = 10.4 Hz), 3.66-3.68 (m, 1H), 4.05 (s, 1H), 5.42 (d, 1H, *J* = 7.5 Hz), 6.46 (t, 1H, *J* = 7.5 Hz), 6.52 (d, 1H, *J* = 7.3 Hz), 6.79 (bs, 1H), 6.88-6.98 (m, 6H), 7.22 (s, 1H), 7.30 (s, 1H), 7.35 (bs, 1H), 7.97 (bs, 1H), 8.27 (bs, 1H), 9.53 (s, 1H). ^{13}CNMR (150 MHz, $CDCl_3$): δ 18.7 (CH_3), 34.9 (CH), 45.1 (CH), 49.7 (CH), 54.5 (C), 109.2 (CH), 120.9 (CH), 123.06 (CH), 123.07 (CH), 126.3 (CH), 127.1 (CH), 128.0 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 128.9 (CH), 134.3 (C), 137.5 (C), 137.9 (C), 139.7 (C), 146.5 (C), 147.2 (C), 157.7 (CH), 179.2 (C), 192.4 (CH).

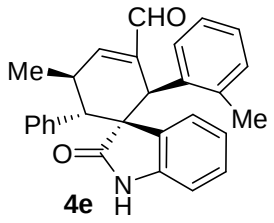


4d

(1*R*,2*R*,5*S*,6*S*)-2-(4-fluorophenyl)-5-methyl-2'-oxo-6-phenylspiro [cyclohex[3]ene-1,3'-indoline]-3-carbaldehyde

(4d) The reaction was carried out following the general procedure using (*S*)-IIIc as the catalyst to furnish the crude product. (d.r. >19:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 5.48 ppm. d, δ_{minor} 5.68 ppm. d). The title compound was isolated by flash column chromatography (dichloromethane/diethyl ether = 9/1) in 50% yield, and >99% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 10.98 min., τ_{minor} = 15.73 min. $[\alpha]_{rt}^{D}$= -44.0 (*c* = 0.40, $CHCl_3$, >99% ee). HRMS: (*m/z*) calculated for $C_{27}H_{22}FNO_2$: 411.1635, found: 411.1632. ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 1.17 (d, 3H, *J* = 7.2 Hz), 3.03 (d, 1H, *J* = 10.1 Hz), 3.59-3.63 (m, 1H), 3.94 (s, 1H), 5.45 (d, 1H, *J* = 7.2 Hz), 6.47-6.49 (m, 2H), 6.58 (bs, 1H), 6.81 (bs, 1H), 6.86 (t, 1H, *J* = 7.2 Hz), 6.93-6.98 (m, 6H), 7.06 (bs, 1H), 7.12 (bs, 1H), 7.20-7.24 (m, 1H), 9.53 (s, 1H). ^{13}CNMR (150 MHz, $CDCl_3$):*δ* 18.9 (CH_3), 31.1 (CH), 35.1

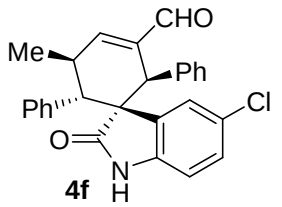
(CH), 44.8 (CH), 49.8 (CH), 55.1 (C), 108.9 (CH), 114.9 (bs, 2CH), 121.0 (CH), 127.0 (CH), 127.1 (CH), 127.9 (CH), 128.1 (bs,2CH), 128.9 (CH), 129.2 (CH), 134.8 (C), 135.2 (C), 138.5 (C), 138.6 (C), 139.7 (C), 156.9 (CH), 162.4 (d, 1CF, *J* = 244 Hz), 179.4 (CH), 179.5 (C), 192.9 (CH).



4e

(1*R*,2*R*,5*S*,6*S*)-5-methyl-2'-oxo-6-phenyl-2-*o*-tolylspiro [cyclohex[3]ene-1,3'-indoline]-3-carbaldehyde

(**4e**) The reaction was carried out following the general procedure using (*S*)-IIIc as the catalyst to furnish the crude product. (d.r. >19:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 5.42 ppm. d, δ_{minor} 5.68 ppm. d). The title compound was isolated by flash column chromatography (hexane/acetone = 2/1) in 50%. yield and 98% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 10.15 min., τ_{minor} = 12.32 min. $[\alpha]_{rt}^{D}$= -63.8 (*c* = 1.00, $CHCl_3$, 98% ee). HRMS: (*m/z*) calculated for $C_{28}H_{25}NO_2$: 407.1885, found: 407.1884. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.19 (d, 3H, *J* = 7.5 Hz), 1.54 (s, 3H), 3.17 (d, 1H, *J* = 10.1 Hz), 3.62-3.65 (m, 1H), 4.26 (s, 1H), 5.40 (d, 1H, *J* = 7.6 Hz), 6.42 (t, 1H, *J* = 7.2 Hz), 6.47 (d, 1H, *J* = 7.2 Hz), 6.86 (t, 1H, *J* = 7.2 Hz), 6.94 (bs, 6H), 7.12-7.17 (m, 2H), 7.20-7.24 (m, 2H), 7.74 (bs, 1H), 9.53 (s, 1H). ^{13}CNMR (150 MHz, $CDCl_3$):δ 17.9 (CH_3), 18.6 (CH_3), 35.1 (CH), 40.0 (CH), 49.1 (CH), 54.4 (C), 108.5 (CH), 120.4 (CH), 125.9 (CH), 125.9 (CH), 126.9 (CH), 127.3 (CH), 127.7 (CH), 128.1 (CH), 128.6 (CH), 129.6 (CH), 130.1 (CH), 138.1 (C), 139.3 (C), 139.5 (C), 139.7 (C), 14.34 (C), 157.0 (CH), 179.6 (C), 193.5 (CH).

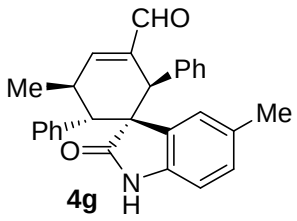


4f

(1*R*,2*R*,5*S*,6*S*)-5'-chloro-5-methyl-2'-oxo-2,6-diphenylspiro [cyclohex[3]ene-1,3'-indoline]-3-carbaldehyde

(**4f**) The reaction was carried out following the general procedure using (*S*)-IIIc as the catalyst to furnish the crude product (d.r. 12:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 5.28 ppm. d, δ_{minor} 5.51 ppm. d). The title compound was isolated by flash column chromatography (hexane/acetone = 2/1) in 47% yield, and >99% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 20.50 min., τ_{minor} = 32.00 min. $[\alpha]_{rt}^{D}$= -72.0 (*c* = 1.0, $CHCl_3$, >99% ee). HRMS: (*m/z*) calculated for $C_{27}H_{22}ClNO_2$: 427.1339, found: 427.1337. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.18 (d, 3H, *J* = 7.1 Hz), 3.06 (d, 1H, *J* = 10.0 Hz), 3.58-3.61 (m, 1H), 3.96 (s, 1H), 5.24 (d, 1H, *J* = 1.8 Hz), 6.42 (d, 1H, *J* = 7.9 Hz), 6.62 (d, 1H, *J* = 6.9 Hz), 6.83 (d, 1H, *J* = 8.9 Hz), 6.93-6.99 (m, 5H), 7.15-7.24 (m, 3H), 7.32 (t, 1H, *J* = 7.4 Hz), 7.41-7.43 (m, 1H), 7.77 (bs,

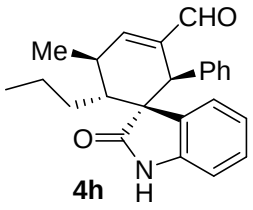
1H), 9.53 (s, 1H). ^{13}CNMR (150 MHz, $CDCl_3$): δ 18.9 (CH_3), 35.0 (CH), 45.4 (CH), 49.7 (CH), 55.7 (C) 109.8 (CH), 126.3 (CH), 127.2 (CH), 127.4 (CH), 127.5 (CH), 127.7 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 131.3 (C), 133.7 (CH), 138.3 (C), 138.3 (C), 138.4 (2C), 156.7 (CH), 179.6 (C), 192.9 (CH).



4g

(1*R*,2*R*,5*S*,6*S*)-5,5'-dimethyl-2'-oxo-2,6-diphenylspiro [cyclohex[3]ene-1,3'-indoline]-3-carbaldehyde

(**4g**) The reaction was carried out following the general procedure using (*S*)-IIIc as the catalyst to furnish the crude product (d.r. 12:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 5.12 ppm. d, δ_{minor} 5.36 ppm. d). The title compound was isolated by flash column chromatography (hexane/acetone = 2/1) in 47% yield, and >99% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 8.84 min., τ_{minor} = 11.87 min. $[\alpha]_{rt}^{D}$= -53.0 (*c* = 0.50, $CHCl_3$, >99% ee). HRMS: (*m/z*) calculated for $C_{28}H_{25}NO_2$: 407.1885, found: 407.1885. ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 1.17 (d, 3H, *J* = 8.0 Hz), 1.86 (s, 3H), 3.07 (d, 1H, *J* = 13.4 Hz), 3.57-3.63 (m, 1H), 3.93 (s, 1H), 5.09 (d, 1H, *J* = 7.5 Hz), 6.36 (d, 1H, *J* = 7.5 Hz), 6.64 (bs, 1H), 6.65 (d, 1H, *J* = 7.4 Hz), 6.94-6.97 (m, 6H), 7.14 (bs, 1H), 6.18 (bs, 1H), 7.20-7.21 (m, 1H), 7.28 (t, 1H, *J* = 7.4 Hz), 7.29 (bs, 1H), 9.53 (s, 1H). ^{13}CNMR (150 MHz, CD_3CN): *δ* 19.0 (CH_3), 21.1 (CH_3), 35.2 (CH), 45.6 (CH), 49.7 (CH), 55.2 (C), 108.2 (CH), 126.9 (CH), 127.6 (CH), 127.8 (CH), 128.0 (CH), 129.4 (CH), 130.0 (CH), 133.9 (CH), 137,1 (C), 138.6 (C), 139.0 (2C), 156.9 (CH), 179.8 (C), 193.0 (CH).

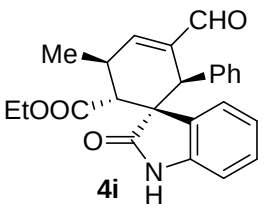


4h

(1*R*,2*R*,5*S*,6*R*)-5-methyl-2'-oxo-2-phenyl-6-propylspiro [cyclohex[3]ene-1,3'-indoline]-3-carbaldehyde

(**4h**) The reaction was carried out following the general procedure using (*S*)-IIIc as the catalyst to furnish the crude product (d.r. >19:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 5.42 ppm. d, δ_{minor} 5.63 ppm. d). The title compound was isolated by flash column chromatography (hexane/acetone = 2/1) in 40% yield and 98% ee. 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} = 12.40 min., τ_{minor} = 17.87 min. $[\alpha]_{rt}^{D}$= -48.5 (*c* = 0.50, $CHCl_3$, 98% ee). HRMS: (*m/z*) calculated for $C_{24}H_{25}NO_2$: 359.1885, found: 359.1886. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.56 (t, 3H, *J* = 7.1 Hz), 0.87-1.17 (m, 6H), 1.44 (d, 3H, *J* = 9.1 Hz), 1.96-2.00 (m, 1H), 3.06-3.09 (m, 1H), 3.79 (s, 1H), 5.41 (d, 1H, *J* = 7.4 Hz), 6.55 (t, 1H, *J* = 7.3 Hz), 6.81 (d, 1H, *J* = 7.3 Hz), 6.99-7.33 (m, 6H), 9.46 (s, 1H). ^{13}CNMR (100 MHz,$CDCl_3$): δ 14.7 (CH_3), 19.6 (CH_3), 22.1 (CH_2),

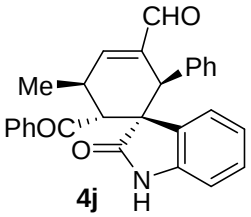
33.4 (CH_2), 35.4 (CH), 41.25 (CH), 45.4 (CH), 54.7 (C), 109.0 (CH), 110.1 (CH), 121.2 (CH), 126.7 (CH), 127.5 (m, 2 CH), 127.9 (CH), 128.1 (CH), 130.2 (C), 138.2 (C), 139.0 (C), 140.5 (C), 157.5 (CH), 179.9 (C), 193.00 (CH).



4i

(1*S*,2*R*,5*S*,6*R*)-ethyl 3-formyl-5-methyl-2'-oxo-2-phenylspiro [cyclohex[3]ene-1,3'-indoline]-6-carboxylate

(**6i**) The reaction was carried out following the general procedure using (*S*)-IIIc as the catalyst to furnish the crude product (d.r. 12:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 5.58 ppm. d, δ_{minor} 5.68 ppm. d). The title compound was isolated by flash column chromatography (hexane/acetone = 2/1) in 50%, and >99% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 19.44 min., τ_{minor} = 26.46 min. $[\alpha]_{rt}^{D}$= -86.0 (*c* = 1.00, $CHCl_3$, >99% ee). HRMS: (*m/z*) calculated for $C_{24}H_{23}NO_4$: 389.1626, found: 389.1627. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.52 (t, 3H, *J* = 7.0 Hz), 1.16 (d, 3H, *J* = 7.8 Hz), 2.75 (d, 1H, *J* = 10.5 Hz), 3.33-3.38 (m, 1H), 3.49-3.55 (m, 2H), 3.67 (s, 1H), 5.22 (d, 1H, *J* = 7.8 Hz), 6.28-6.35 (m, 2H), 6.54 (d, 1H, *J* = 8.6 Hz), 6.76-6.86 (m, 4H), 6.99-7.09 (m, 2H), 7.52 (bs, 1H), 9.25 (s, 1H). ^{13}CNMR(150 MHz, $CDCl_3$):δ 13.5 (CH_3), 18.6 (CH_3), 31.9 (CH), 44.5 (CH), 50.2 (CH), 51.3 (C), 60.7 (CH_2), 108.1 (CH), 120.9 (CH), 126.5 (CH), 127.6 (CH), 127.9 (CH), 128.1 (CH), 128.4 (CH), 133.3 (CH), 137.9 (CH), 138.3 (C), 140.5 (C), 144.8 (C), 154.9 (CH), 162.07 (C), 171.9 (C), 178.5 (C), 192.4 (CH).

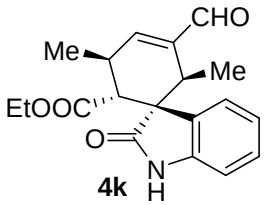


4j

(1*S*,2*R*,5*S*,6*R*)-6-benzoyl-5-methyl-2'-oxo-2-phenylspiro[cyclohex[3]ene-1,3'-indoline]-3-carbaldehyde

(4j) The reaction was carried out following the general procedure using (*S*)-IIIc as the catalyst to furnish the crude product (d.r. >19:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 5.34 ppm. d, δ_{minor} 5.53 ppm. d). The title compound was isolated by flash column chromatography (hexane/ethyl acetate = 3/1) in 46% yield, and >99% ee. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 35.17 min., τ_{minor} = 56.25 min. $[\alpha]_{rt}^{D}$= -85.0 (*c* = 1.00, $CHCl_3$, >99% ee). HRMS: (*m/z*) calculated for $C_{28}H_{23}NO_3$: 421.1678, found: 421.1678. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.27 (d, 3H, *J* = 7.6 Hz), 3.68-3.71 (m, 1H), 3.94 (s, 1H), 4.23 (d, 1H, *J* = 10.6 Hz), 5.15 (d, 1H, *J* =7.6 Hz), 6.16 (t, 1H, *J* = 7.4 Hz), 6.63 (bs, 1H), 6.68 (d, 1H, *J* = 7.8 Hz), 6.86 (t,

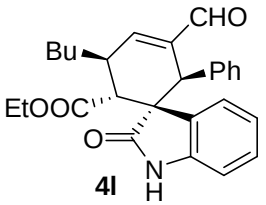
1H, *J* = 7.9 Hz) 7.10-7.29 (m, 6H), 7.39-7.51 (m, 4H), 8.00 (bs, 1H), 9.52 (s, 1H). ^{13}CNMR (150 MHz, CD_3CN): δ 19.4 (CH_3) 33.4 (CH), 45.0 (CH), 49.5 (CH), 52.0 (C), 109.4 (CH), 120.6 (CH), 126.4 (CH), 127.2 (CH), 127.5 (CH), 127.9 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 128.7 (CH), 133.4 (CH), 133.8 (CH), 138.5 (C), 138.6 (2C), 140.9 (C), 156.2 (CH), 178.9 (C), 192.7 (CH), 201.4 (C).



4k

(1*S*,2*R*,5*S*,6*R*)-ethyl 3-formyl-2,5-dimethyl-2'-oxospiro [cyclohex[3]ene-1,3'-indoline]-6-carboxylate

(4k) The reaction was carried out following the general procedure using (*S*)-IIIc as the catalyst to furnish the crude product.. (d.r. >19:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 9.49 ppm. d, δ_{minor} 9.51 ppm. d). The title compound was isolated by flash column chromatography (hexane/ethyl acetate = 2/1) in 58% yield and 98% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 25.79 min., τ_{minor} = 50.08 min. $[\alpha]_{rt}^{D}$= -78.0 (*c* = 0.10, $CHCl_3$, 98% ee). HRMS: (*m/z*) calculated for $C_{19}H_{21}NO_4$: 327.1471, found: 327.1470. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.82 (t, 3H, *J* = 14.1 Hz), 1.17 (d, 3H, *J* = 7.5 Hz), 1.24 (d, 3H, *J* = 7.5 Hz), 2.78 (q, 1H, *J* = 13.8 Hz), 2.98 (d, 1H, *J* = 9.60 Hz), 3.46-3.48 (m, 1H), 3.75-3.85 (m, 2H), 6.74 (s, 1H), 6.80 (d, 1H, *J* = 6.90 Hz), 6.96 (t, 1H, *J* = 6.9 Hz), 7.15-7.24 (m, 2H), 7.72 (bs, 1H), 9.47 (s, 1H). ^{13}CNMR (150 MHz, $CDCl_3$): δ 13.9 (CH_3), 18.1 (CH_3), 18.7 (CH_3), 32.4 (CH), 33.1 (CH), 49.9 (CH), 51.0 (C), 61.0 (CH_2), 109.8 (CH), 121.5 (CH), 126.42 (CH), 128.8 (C), 129.3 (C), 141.1 (C), 141.6 (C), 154.9 (CH), 172.2 (CH), 179.1 (C), 193.5 (CH).

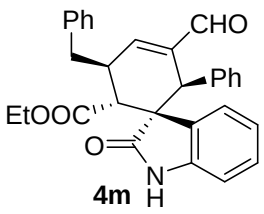


4l

(1*S*,2*R*,5*S*,6*R*)-ethyl 5-butyl-3-formyl-2'-oxo-2-phenylspiro [cyclohex[3]ene-1,3'-indoline]-6-carboxylate

(4l) The reaction was carried out following the general procedure using (*S*)-IIIc as the catalyst to furnish the crude product (d.r. >19:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 5.49 ppm. d, δ_{minor} 5.70 ppm., d). The title compound was isolated by flash column chromatography (hexane/ethyl acetate = 3/1) in 50% yield, and >99% ee. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 11.27 min., τ_{minor} = 21.84 min. $[\alpha]_{rt}^{D}$= -46.0 (*c* = 0.10, $CHCl_3$, >99% ee). HRMS: (*m/z*) calculated for $C_{27}H_{29}NO_4$: 431.2097, found: 431.2024. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.74 (t, 3H, *J* = 6.2 Hz), 0.93-0.99 (m, 3H), 1.39-2.15 (m, 6H),3.10 (d, 1H, *J* = 12.0 Hz), 3.52-3.54 (m, 1H), 3.70-3.74 (m, 2H), 3.89 (s, 1H), 5.45 (d, 1H, *J* = 7.7 Hz), 6.52-6.55

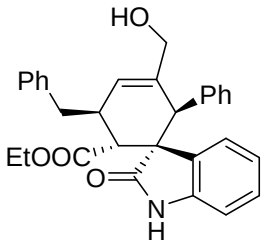
(m, 2H), 6.74 (d, 1H, *J* = 7.8 Hz), 7.00-7.07 (m, 3H), 7.09-7.24 (m, 3H), 7.56 (bs, 1H), 9.48 (s, 1H). ^{13}CNMR (150 MHz, $CDCl_3$): δ 13.8 (CH_3), 14.1 (CH_3), 23.1 (CH_2), 28.6 (CH_2), 32.5 (CH_2), 36.8 (CH), 44.8 (CH), 48.6 (CH), 51.6 (C), 60.9 (CH_2), 109.1 (CH), 121.1 (CH), 126.9 (CH), 127.8 (CH), 128.1 (CH), 128.2 (CH), 128.6 (CH), 138.3 (C), 139.0 (C), 140.7 (C), 153.8 (CH), 172.2 (C), 178.5 (C), 192.7 (CH).



4m

(1*S*,2*R*,5*S*,6*R*)-ethyl 5-benzyl-3-formyl-2'-oxo-2-phenylspiro[cyclohex[3]ene-1,3'-indoline]-6-carboxylate

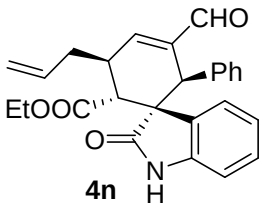
(**4m**) The reaction was carried out following the general procedure using (*S*)-IIIc as the catalyst to furnish the crude product (d.r. 19:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 5.40 ppm. d, δ_{minor} 5.52 ppm. d). The title compound was isolated by column chromatography (hexane/ethyl acetate = 3/1) in 65% yield. The ee value was determined on the corresponding alcohol after reduction of the isolated aldehyde. $[\alpha]_{rt}^{D}$= -97.0 (*c* = 0.10, $CHCl_3$, >99% ee). HRMS: (*m/z*) calculated for $C_{30}H_{27}NO_4$: 465.1940, found: 465.1942. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.78 (t, 3H, *J* = 7.6 Hz), 2.85-2.88 (m, 1H), 3.16 (d, 1H, *J* = 11.5 Hz), 3.23 (dd, 1H, J_1 = 13.6 Hz, J_2 = 4.3 Hz), 3.74-3.81 (m, 3H), 3.87-3.90 (m, 1H), 5.38 (d, 1H, *J* = 7.8 Hz), 5.98 (bs, 1H), 6.49 (bs, 1H), 6.53 (t, 1H, *J* = 7.5 Hz), 6.75 (d, 1H, *J* = 7.5 Hz), 6.94 (bs, 2H), 7.06 (t, 1H, *J* = 7.6 Hz), 7.14 (t, 1H, *J* = 7.5 Hz), 7.17 (d, 1H, *J* = 1.8 Hz), 7.35-7.42 (m, 6H), 9.42 (s, 1H). ^{13}CNMR (150 MHz, CD_3CN): δ 13.8 (CH_3), 38.3 (CH_2), 38.4 (CH), 44.5 (CH), 47.1 (CH), 51.6 (C), 61.0 (CH_2), 109.0 (CH), 121.1 (CH), 126.9 (CH), 127.2 (CH), 133.3 (C), 137.2 (C), 138.0 (C), 139.5 (C), 140.5 (C), 152.8 (CH), 172.2 (C), 178.3 (C), 192.3 (CH).



alc-**4m**

(***alc*-4m**) To a stirred solution of aldehyde 4m (0.2 mmol., 96 mg) in THF (1.5 mL) $NaBH_4$ (0.6 mmol., 24 mg, 3 eq.) was slowly added at 0°C. Once the addition was finished the reaction was stirred for further 5 minutes then the ice bath was removed and stirring continued for 1 hour at room temperature. Solvent was removed under reduced pressure and the residual material was quenched with a saturated solution of NH_4Cl at room temperature and extracted with dichloromethane. The organic phase was dried over $MgSO_4$ then filtered and the solvent removed under reduced pressure to give the crude alcohol which was purified by flash chromatography using hexane/ethyl acetate = 3/1 as the eluent mixture. The title compound was isolate as white solid in 57% yield and >99% ee. The ee was determined by HPLC analysis on a Daicel Chiralpak AD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min,

λ = 214, 254 nm: τ_{major} = 8.47 min., τ_{minor} = 18.22 min. $[\alpha]_{rt}^{D}$= -119.0 (*c* = 0.10, $CHCl_3$, >99% ee). HRMS: (*m/z*) calculated for $C_{30}H_{29}NO_4$: 467.2097, found: 467.2097. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.75 (t, 3H, *J* = 7.2 Hz), 1.19 (d, 3H, *J* = 6.2 Hz), 2.33 (bs, 1H), 2.74- 2.76 (m, 1H), 3.02-3.06 (m, 1H), 3.49 (s, 1H), 3.58 (bs, 1H), 3.69-3.74 (m, 3H), 3.87-3.89 (m, 1H), 5.38 (d, 1H, *J* = 7.5 Hz), 6.13 (s, 1H), 6.28 (d, 1H, *J* = 7.6 Hz), 6.28 (d, 1H, *J* = 7.6 Hz), 6.36 (d, 1H, *J* = 7.7 Hz), 6.50 (t, 1H, *J* = 7.7 Hz), 6.78 (d, 1H, *J* = 7.0 Hz), 6.96 (t, 1H, *J* = 7.0 Hz), 7.01-7.04 (m, 3H), 7.15 (t, 1H, *J* = 7.0 Hz), 7.29-7.35 (m, 5H), 8.26 (bs, 1H). ^{13}CNMR (150 MHz, $CDCl_3$): δ 13.8 (CH_3), 25.5 (CH), 29.5 (CH), 37.0 (CH), 39.2 (CH), 47.0 (CH), 47.8 (CH), 52.6 (C), 60.7 (CH_2), 66.0 (CH_2), 109.2 (CH), 121.0 (CH), 126.7 (2CH), 127.5 (CH), 127.7 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 129.2 (CH), 130.6 (CH), 133.5 (CH), 135.7 (C), 138.1 (C), 138.5 (C), 140.8 (C), 173.0 (C), 179.5 (C)



4n

(1*S*,2*R*,5*S*,6*R*)-ethyl 5-allyl-3-formyl-2'-oxo-2-phenylspiro[cyclohex[3]ene-1,3'-indoline]-6-carboxylate

(**4n**) The reaction was carried out following the general procedure using (*S*)-IIIc as the catalyst to furnish the crude product (d.r. 19:1 was determined by integration of ^{1}H-NMR signal: δ_{major} 5.47 ppm. d, δ_{minor} 5.58 ppm. d). The title compound was isolated by flash column chromatography (dichloromethane/diethyl ether = 4/1) in 64% yield and >99% ee. The ee was determined by HPLC analysis on a Daicel Chiralcel OD-H column: hexane/*i*-PrOH 80:20, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} = 14.47 min., τ_{minor} = 24.68 min. $[\alpha]_{rt}^{D}$= -76 (*c* = 1.00, $CHCl_3$, >99% ee). HRMS: (*m/z*) calculated for $C_{26}H_{25}NO_4$: 415.1784, found: 415.1785. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.75 (t, 3H, *J* = 6.7 Hz), 2.31-2.36 (m, 1H), 2.61-2.64 (m, 1H), 3.14 (d, 1H, *J* = 10.7 Hz), 3.66-3.68 (m, 1H), 3.73-3.91 (m, 2H), 3.91 (s, 1H), 5.28-5.31 (m, 2H), 5.47 (d, 1H, *J* = 7.59 Hz), 5.96-5.99 (m, 1H), 6.54 (t, 1H, *J* = 7.7 Hz), 6.56 (bs, 1H), 6.77 (d, 1H, *J* = 7.0 Hz), 7.07-7.10 (m, 2H), 7.19 (s, 1H), 7.19-7.27 (m, 2H),7.35 (bs, 1H), 7.45 (bs, 1H), 9.49 (s, 1H). ^{13}CNMR (150 MHz, CD_3CN): δ 13.5 (CH_3), 29.5 (CH), 36.6 (CH), 37.0 (CH_2), 44.7 (CH), 47.9 (CH), 51.7 (C), 60.9 (CH_2), 109.4 (CH), 119.4 (CH), 121.1 (CH), 126.9 (CH), 127.4 (CH), 127.8 (CH), 128.1 (CH), 128.2 (CH), 128.7 (CH), 133.5 (C), 134.2 (CH), 138.3 (C), 139.50 (C), 140.9 (C), 153.0 (CH), 172.1 (C), 179.1 (C), 192.6 (CH).

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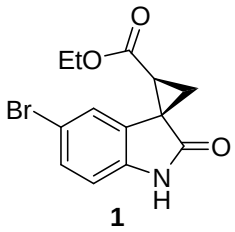
2.2.2. Organocatalytic Michael addition/Alkylation domino reaction applied to the nitrocyclopropanation of Oxindoles

Discussion

Continuing the studies on the synthesis of spirooxindoles, we then focused on the construction of strained cyclopropyl oxindoles. This class of compounds was recently evaluated in medicinal chemistry as HIV non nucleoside transcriptase inhibitor.[144]

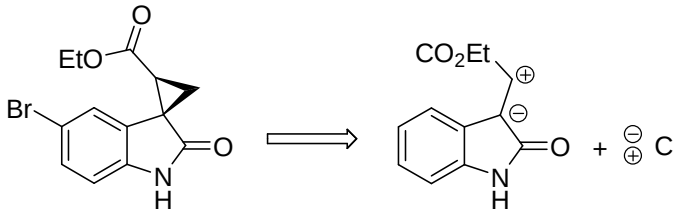
Figure 1: novel oxindole as HIV-1 non nucleoside reverse transcriptase inhibitor



1

In particular the molecule in Figure **1** was successfully docked into HIV-1 NNRTI site.[1, 145] Having established our target we minded that, for the construction of this class of compounds, a suitable retrosynthetic strategy could be the addition of C_1 *donator-acceptor* synthon to a C_2 *acceptor-donator* synthon (Scheme **1**).

Scheme 1: Retrosynthetic analysis to the synthesis of cyclopropyl spirooxindoles

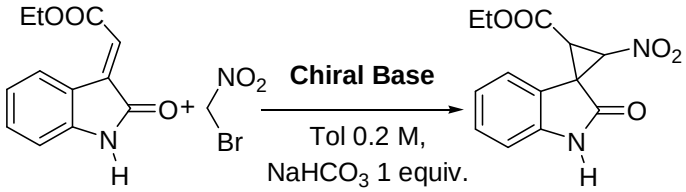


1 **2** **3**

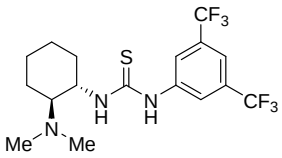
We envisaged that the synthon **2** could be rationalized by an alkyliden oxindoles, and the synthon **3** could be the idealization of Bromonitromethane or Bromomalonate. This substrates can be easily activated by chiral base and through a Michael addition/alkylation tandem sequence have been recently used for the cyclopropanation of carbonyl compounds.[146,147]

Our investigation started by reacting Bromonitromethane **4** (*E*)-ethyl 2-(2-oxoindolin-3-ylidene)acetate **5a** in presence of 40 mol% of Quinine and 1 equivalent of $NaHCO_3$ as scavenger of the HBr that is developed during the reaction (Table **1** entry 1).

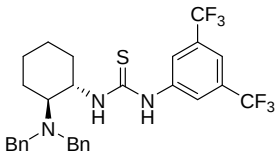
Table 1: Catalyst Screening for the cyclopropanation of 3-alkylidenoxindoles[a]



5 **4** **6**



7a



7b

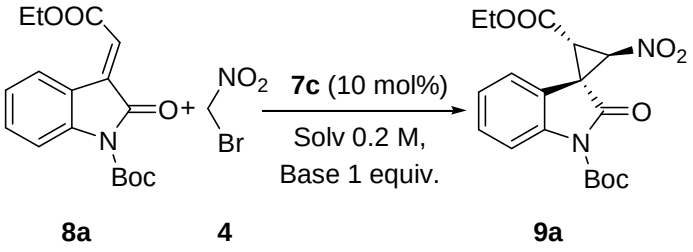
Entry	Catalyst	T (°C)	time (h)	Conv [%][b]	dr[b]	ee [%][c]
1	**Qn** (40%)	rt	65	60	3:1	41
2	**Qd** (40%)	rt	65	49	8:1:1	30
3	**$(DHQ)_2PHAL$** (10%)	rt	65	69	2.3:1	0
4	**7a** (10%)	rt	65	88	14:1	77
5	**7b** (10%)	rt	65	-	-	-
6	**HQd-TIOUREA 7c** (10%)	rt	65	81	8.8:1	79

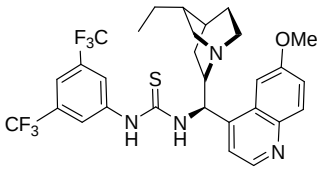
[a] The reactions were performed on a 0.2 mmol scale [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by HPLC analysis on chiral stationary phases.

Surprisingly the reaction afforded the desired product with good yield and promising stereoselectivity. After the chiral base screening, where both face-shielding and bifunctional catalyst were examinated, 9-*Epi*-HQ-tiourea has furnished the best enantioselctivity[148] (entry 6) even if this result was not yet satisfactory. Following the optimization strategy that we used for the *"Asymmetric addition of oxindoles to α,β-unsaturated ketones"* chapter **xx** we moved to the use of *N*-Boc-3Alkyliden Oxindoles, minding that the N-H protection could have a beneficial effect on both rate and stereoselctivity of the reaction.[149]

As highlighted in table 2 running the reaction with (*E*)-*tert*-butyl 3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **8a** good conversion of the substrate in the desiderated product was obtained together with excellent stereoselctivity (Table **2** entry 1).

Table 2: *Further optimization for the cyclopropanation of 3-alkylidenoxindoles*[a]





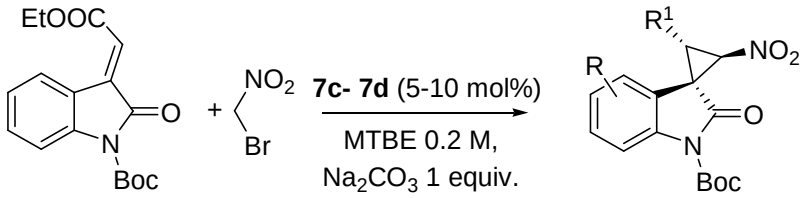
Entry	Base	Solvent	Time [h]	Conv [%].[b]	d.r.[b]	[%] ee[c]
1	$NaHCO_3$	Toluene	65	63	18:1	98
2	$NaHCO_3$	DCM	24	57	9.8:1	96
3	$NaHCO_3$	CH_3CN	24	40	9.4:1	82
4	$NaHCO_3$	THF	24	67	9.4:1	97
5	$NaHCO_3$	MTBE	24	76	16:1	98
7[d]	$NaHCO_3$	MTBE	24	47	16:1	98
8[d]	Et_3N	MTBE	24	48	5.3:1	93
9[d]	Na_2CO_3	MTBE	24	70	16:1	98
10[d],[e]	Na_2CO_3	MTBE	48	full	19:1	98

[a] Unless otherwise specified, the reactions were performed at room temperature on a 0.1 mmol scale with 10 mol% of **7c**, 1.5 equiv of **4,** 1 equiv of Base and $[\mathbf{8a}]_0$ = 0.2 M. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by HPLC analysis on chiral stationary phases. [d] Reaction performed with 5 mol% of **7c**. [e] Reaction performed at 0 °C.

Further optimization was achieved evaluating the reaction media and the nature of the external additive. In MTBE the reaction time lowed up to 24h (entries 1-7), and in presence of a stronger organic base as triethylamine the reaction has a slight decrease of performanceswhereas employing 1 equivalent of Na_2CO_3 it was observed an improvement of turnover number, leading to a good conversion in the desired product even with only 5% of catalyst (entries 7-9). Finally carrying out the reaction at 0°C in 48 hours the best conditions for this synthetic approach to cyclopropyl spirooxindoles were indentified (entry 10).

We then examined the generality of the asymmetric organocatalytic nitrocyclopropanation of *N*-Boc Alkyliden oxindoles under the optimized condition (Table **3**).

Table 3: Synthesis of nitro cyclopropyl spirooxindoles with two adjacent tertiary stereogenic centers.[a]



8a-i **4** **9a-i**

Entry	8	R	R^1	T [°C]	t [h]	Yield[b] [%]	d.r.[c]	ee[d] [%]
1	a	H	COOEt	0	48	77	19:1	98
2	b	H	COPh	0	72	52	9:1	90
3[e]	b	H	COPh	rt	72	82	>19:1	98
4	c	H	*n*-butyl	rt	72	60	3:1	93
5[f]	c	H	*n*-butyl	rt	72	75	4:1	92
6[e]	d	H	Ph	rt	72	83	7.7:1.6:1	90
7[e]	e	H	2-MePh	rt	48	80	3:1	90
8	f	5-Br	COOEt	rt	24	76	9:1	87
9[e]	f	5-Br	COOEt	0	72	74	>19:1	93
10[e]	g	5-Cl	Ph	rt	48	84	8.6:1.3:1	90
11[e]	h	6-Cl	Ph	rt	48	65	12:2:1	89
12[g]	i	5-Me	Ph	rt	72	60	7:1	91
13[h]	a	H	COOEt	rt	72	99	11:1	97

[a] Unless otherwise specified, the reactions were performed on a 0.2 mmol scale with 5 mol% of **7c**, 1.5 equiv of **4,** 1 equiv of Na_2CO_3 and $[\mathbf{8a}]_0$ = 0.2 M. [b] Sum of diastereoisomers. [c] Determined by ^1H NMR analysis of the crude mixture. [d] Determined by HPLC analysis on chiral stationary phases. [e] Reaction performed with 5 mol% of **7d**. [f] Reaction performed with 10 mol% of **7d**. [g] 99% ee after single crystallization. [h] Reaction performed with 2 mol% of **7d**.

Notably both the antipodes of the products are synthesized with high yield and high diastero- and enantioselection by appropriate selection of the catalyst (9-*Epi*-HQd-Tiourea **7c**, and9-*Epi*-HQd-Tiourea **7d**).

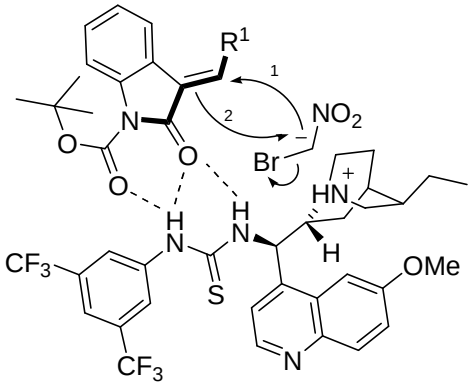
All the reactions furnished good yields in 48 or 72 hours using 5% or in one case 10% of catalyst (entry 5). Alkyliden oxindoles substituted in 3 position with electron withdrawing group underwent smoothly to the nitrocyclopropanation protocol giving impressive stereoselctivity (entries 1-3). Thanks to their great reactivity it was possible, by adjusting the reaction time, decrease the catalyst loading up to 2 mol% maintaining similar level of streoinduction.

Alkyl and aromatic substituent also proved to be suitable for the construction of the correspondent spirooxindoles in high enantiomeric excess, but with a slight decrease of the diastereoisomeric ratio (entries 4-7). Changing the electronic content, with groups in 5 and 6 position of the aromatic ring of the oxindole the reaction gave good results too (entries 8-13).

As mentioned before (Chapter xx) such level of diastereoselctivity can be justified admitting a bifunctional macchanism, considering that it is possible to obtain 8 stereoisomers divided in 4 couples of distereoisomers as outcome of the reaction.

The increasing of the diastereomeric ratio after the protection of oxindolic N-H with Boc group suggests that this moiety favors the coordination, via H-bonding interaction, between the oxindole and the tiourea part of the catalyst,[150] while the quinuclidinic basic functionality actives the Bromonitromethane (Scheme 1).

Scheme 2: Proposed transition state for the nitrocyclopropanation of Alkyliden Oxindoles

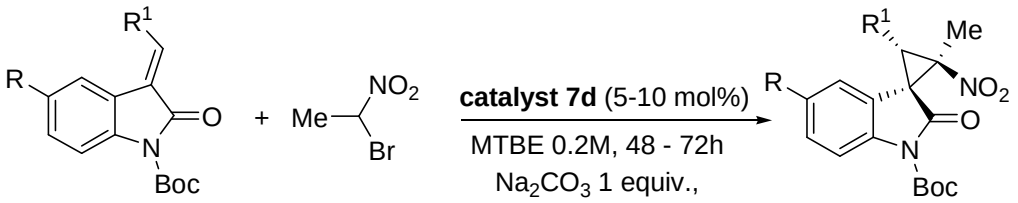


This double activation justify the stereochemical outcome of the reaction. In fact the H-bonds place the oxindole in the right spatial position to undergo the Michael addition by the nucleophile on its *Si*-face. In this way two of the three stereocenters are forged since it is plausible that the intramolecular Alkylation occurs through S_{N_2} pathway.

Encouraged by our good results we set the condition for the synthesis of cyclopropyl spirooxindoles having two adjacent quaternary stereocenters whereof one all carbon substituted.

In scheme **3** are highlighted the satisfying preliminary results obtained using 1-Bromo-1-nitromethane and *N*-Boc-3-Alkyliden Oxindoles as substrates.

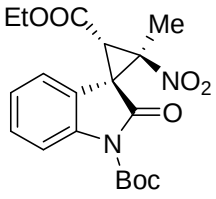
Scheme 3: Preliminary results of the synthesis of cyclopropyl spirooxindoles bearing two adjacent quaternary stereocenters.



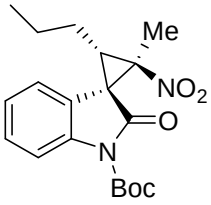
8a: R = H, R^1 = COOEt
8d: R = H, R^1 = *n*-butyl
8f: R = Br, R^1 = COOEt
8j: R = F, R^1 = COOEt

10

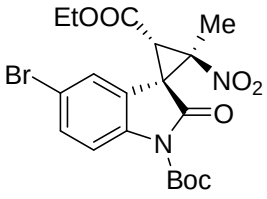
11a, d, f, j



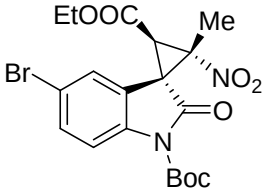
91% yield,[d] 5:1 d.r.,[e] >99% ee[f] **11a**



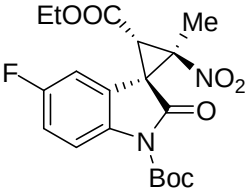
65% yield,[d] 3:1 d.r.,[e] 92% ee[f] **11b**[a]



65% yield,[d] 1.5:1 d.r.,[e] 96% ee[f] **11f**[b]



71% yield,[d] 2:1 d.r.,[e] 96.4% ee[f] ***ent*-11f**[c]



71% yield,[d] 4:1 d.r.,[e] 96% ee[f] **11j**[b]

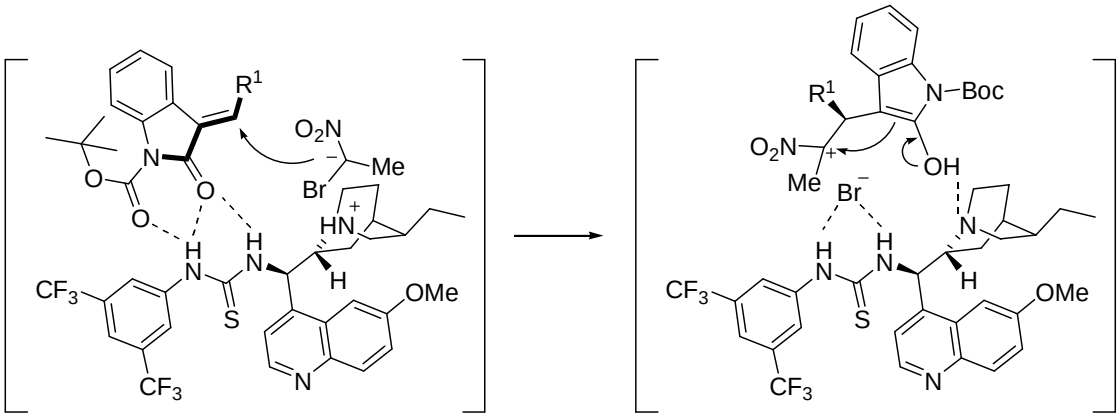
Unless otherwise specified, the reactions were performed on a 0.2 mmol scale with 5 mol% of **7d**, 1.5 equiv of **10,** 1 equiv of Na_2CO_3 and $[\mathbf{8a}]_0$ = 0.2 M. [a] Reaction performed with 20 mol% of **7d**. [b] Reaction performed with 5 mol% of **7d**. [c] Reaction performed with 10 mol% of **7c**. [d] Sum of diastereoisomers. [e] Determined by ^{1}H NMR analysis of the crude mixture. [f] Determined by HPLC analysis on chiral stationary phases.

The reaction summarized in Scheme **3** afforded the product with good yield and enantiomeric excess. Unfortunately the diastereomeric ratio seemed to be dependent on the oxindole architecture giving appreciable dr values only in two cases (products **11a** and **11j**). The relative

and absolute configuration of **9a** and **11a** were assigned by NOE-NMR analyses and through time dependent (TD) DFT calculations of the electronic circular dichroism (ECD) spectra (see experimental part for details)

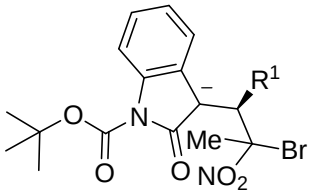
This outcome together with the inversion of the configuration of one chiral center (C3) could be explained admitting another reaction pathway (Scheme **4**).

Scheme 4: Postulated reaction pathway for the formation of cyclopropyl oxindole bearing two quateranary sterecenters: MA/intramolecular S_{N_1} tandem sequence.



In scheme **4** is reported the postulated transition state for the addition of 1-Bromo-1-NitroEthane to 3-Alkyliden Oxindoles. The observation of the experimental results promted us to hypothesize that after the MA of the BromoEthane to the oxindole, the reaction does not follow an intramolecular S_{N_2} pathway because of the high steric hindrance in proximity of the tetrasubstituted carbon bearing the bromine leaving group (Figure **2**).

Figure 2: Micheal adduct formed during the ciclopropanation of spirooxindole with 1-Bromo-1-NitroEthane



For this reason it is possible suppose that the real mechanism of the second step is an intramolecular S_{N_1} reaction where the thiourea moiety drives to the formation of a carbocation through anion binding activation and the quinuclidine stabilized the enol form of the oxindole.

Concluding we developed an unprecedented reported protocol for the synthesis of higly densely functionalized ciclopropyl oxindoles bearing three stereocenters whereof one spiranic

all carbon substituted quaternary one. This methodology was also applied to the construction of more complex cyclopropylic compounds with two adjacent quaternary stereocenters. The low catalyst loading together with the availability of the starting material, lead us to believe that this methodology is also a good start point for the stereoselective synthesis of bioactive compounds libraries.

Refereces

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General.

The ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, 400 MHz and 100 MHz, or at 600 MHz for ^{1}H and 150 MHz respectively for ^{13}C. All the ^{1}H and ^{13}C signals were assigned by means of g-COSY, g-HSQC and g-HMBC 2D-NMR sequences. NOE spectra were recorded using the DPFGSE-NOE sequence,[151] using a mixing time of 2.00 s and "rsnob" 20 ÷ 50 Hz wide selective pulses, depending on the crowding of the spectra region. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$ and CD_3CN). Coupling constants are given in Hz. When 2D-NMR were not performed, carbon types were determined from DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh) according to the method of Still.[152] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Mass spectra were obtained by electron spray ionization (ESI). All reactions were set up in the 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.[153] Chiral tiourea catalysts, 9-*epi*-9-thiourea-9-deoxy-dihydroquinidine **7c**, and its pseudoenantiomer 9-*epi*-9-thiourea-9-deoxy-dihydroquinine **7d**, were prepared from commercially available hydroquinidine, quinine and quinidine, respectively, following the literature procedure.[154]

α-bromonitromethane **4**, from Aldrich and used as received. α-bromonitroethane **10** were prepared following the literature procedures.[155] *N*-Boc protected oxindoles **8a-i** has been prepared following the literature procedures.[156]

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 phase columns.

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

compounds **9a-i, 11a, 11d, 11f and 11j** were compared to racemic samples prepared by mixing the two product antipodes obtained performing the reaction with catalyst 9-*epi*-9-thiourea-9-deoxy-dihydroquinidine **7c**, and the *pseudo*-enantiomer 9-*epi*-9-thiourea-9-deoxy-dihydroquinine **7d** separately.

Calculations. MM conformational searches were performed using the MonteCarlo method implemented in Titan 1.0.5.[157] Geometry optimization were carried out at the B3LYP/6-31G(d) level by means of the Gaussian 03 series of programs.[158] 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

Assignment of the relative and absolute configuration of compounds 9a, 6a and 7a.

Compound **9a, 11a** and **12a** were selected in order to determine the relative and absolute configuration of a prototype compound of each class. In both cases, Full assignment of ^{1}H and ^{13}C NMR signals was preliminarily determined by HSQC and HMBC bi-dimensional sequences, and NOE spectra were acquired in order to establish the relative stereochemistry.

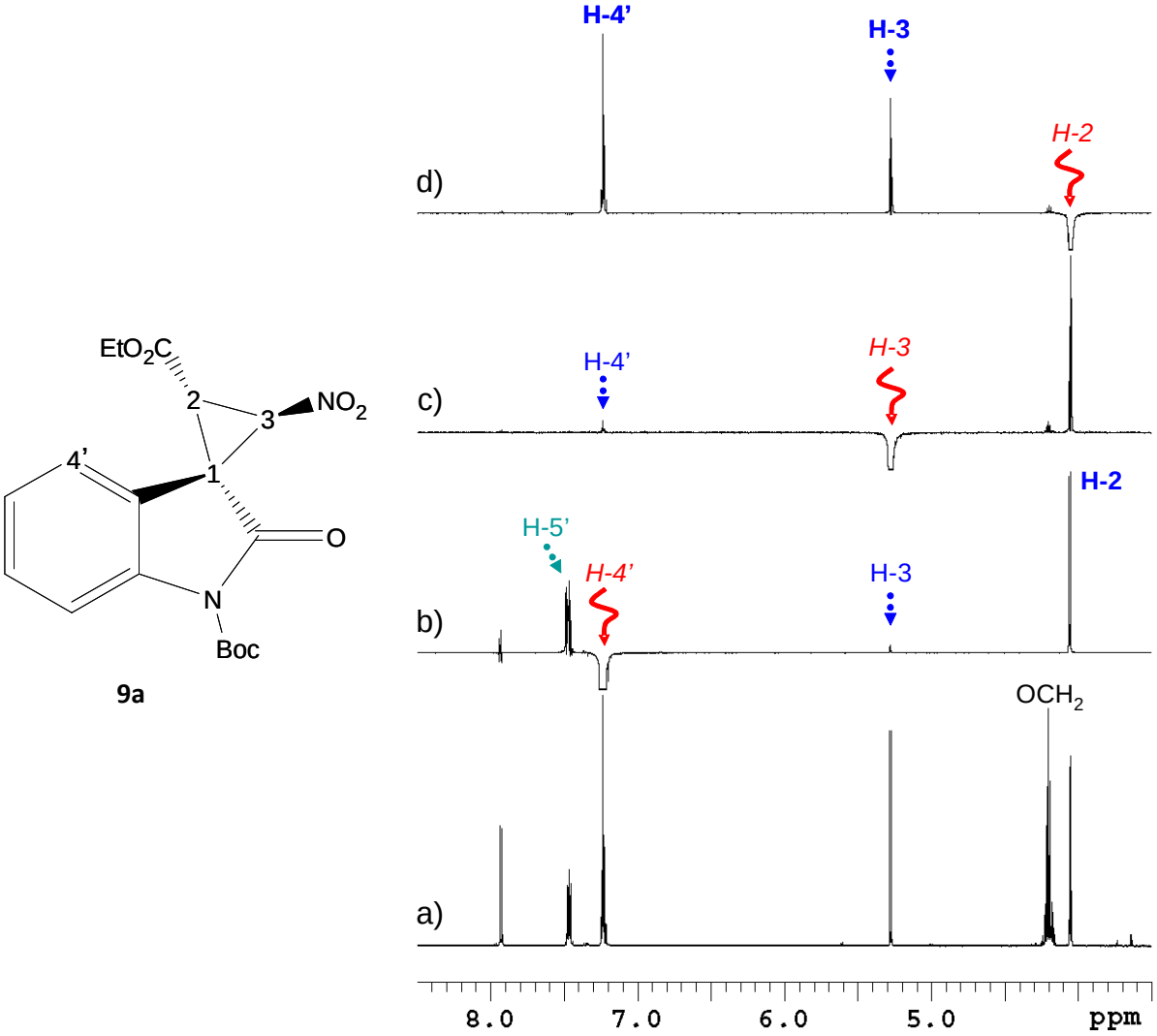


Figure S1: DPFGSE-NOE spectra obtained for **9a** (25°C, 600 MHz, CD_3CN). Trace a): control spectrum, trace b: NOE spectrum obtained on saturation of H-4'; trace c): NOE spectrum obtained on saturation of H-3; trace d): NOE spectrum obtained on saturation of H-2. Relevant NOEs are indicated in blue, "control" NOEs are in green. The spectral region displayed does not show the Boc and Methyl signals.

In the case of compound **9a**, saturation of the signal corresponding to the *peri* aromatic nitrogen H-4' (trace b in figure S1) showed a strong NOE effect on H-2 and a weak enhancement on H-3, indicating that H-2 is directed towards the aromatic ring and H-3 is on the opposite side of the three-membered ring (i.e. H-2 and H-3 are in a *trans* relationship.). This arrangement was also confirmed by the saturation of the signals of H-3 and H-2 (traces c and d, respectively). When H-3 is saturated, NOE is observed only on H-2, because of the proximity constraints imposed by the cyclopropane. On the contrary, when H-2 is saturated,

strong NOEs are observed for H-3 and H-4'. All the NOE data thus confirm that the relative stereochemistry is 1*R**,2*R**,3*S**.

The same NMR approach was used for the determination of the relative configuration of **11a** and **12a**, a derivative of compound **11a** that where the Boc group was removed (Figure S2).

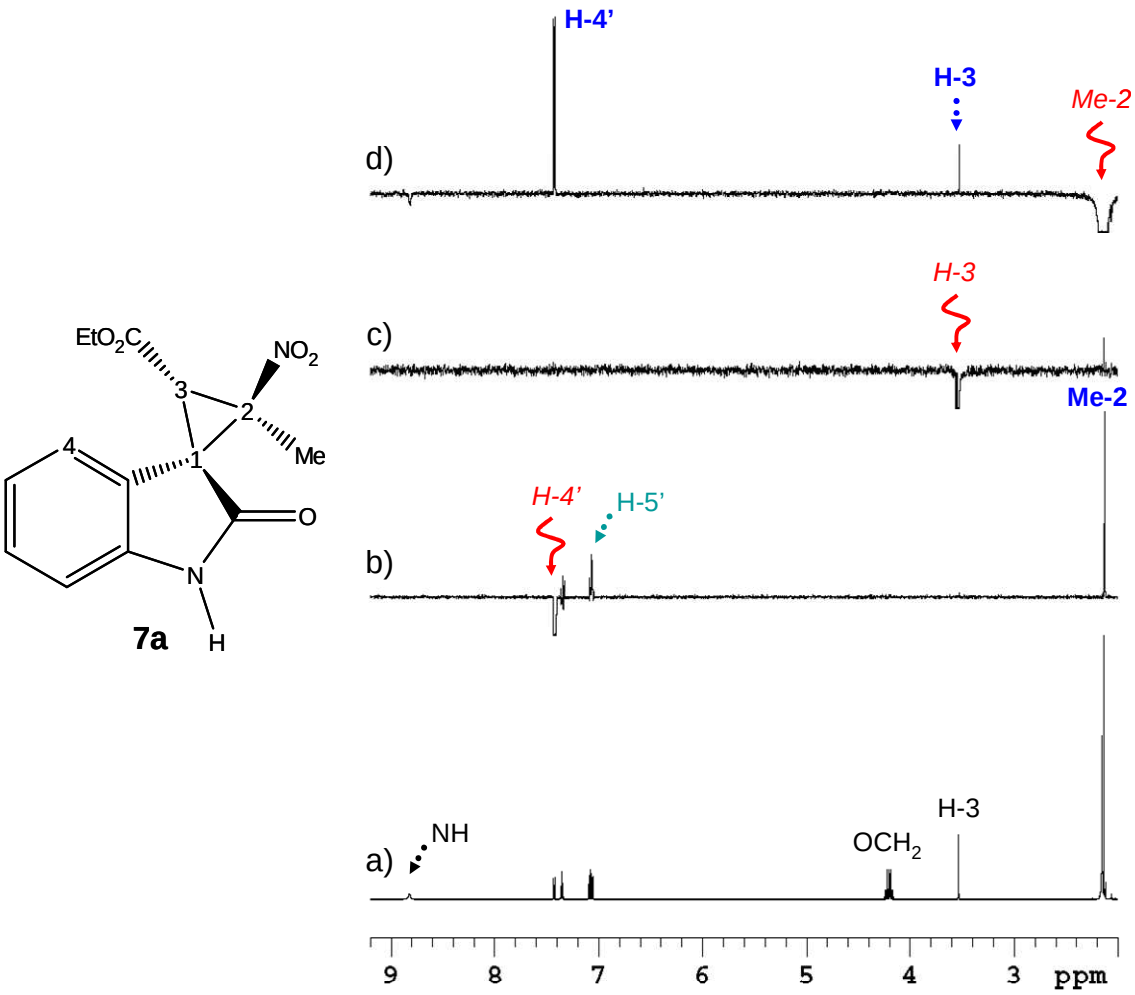


Figure S2: DPFGSE-NOE spectra obtained for compound **7a** (25°C, 600 MHz, CD_3CN). Trace a): control spectrum, trace b: NOE spectrum obtained on saturation of H-4'; trace c): NOE spectrum obtained on saturation of H-3; trace d): NOE spectrum obtained on saturation of Me-2. Relevant NOEs are indicated in blue, "control" NOEs are in green. The spectral region displayed does not show the methyl signal of the ester moiety.

In this compound the configuration at C-1 is reversed with respect to **4a**. Saturation of H-4' shows NOE effect only on the methyl group in position 2: this implies that the methyl of carbon in position 2 is directed towards the aromatic ring and the nitro group towards the oxygen of the oxaindole. The lack of NOE effect on H-3 (at 3.55 ppm) indicates that H-3 is on the opposite side of the cyclopropane, and that the COOEt moiety is on the same side of Me-2

(i.e. a *trans* relationship between the methyl and H-3). This disposition is confirmed when the methyl in position 2 is saturated. In addition to a medium NOE observed on H-3, due to the constraints imposed by the small cycle, a very strong NOE enhancement is observed on the aromatic H-4'. All the NOE data confirm that the relative stereochemistry is 1*R**,2*R**,3*S**. This relative configuration corresponds to the inversion of the spiranic quaternary center and it should be noted that the apparent identical relationship of the stereochemical descriptors with that of **4a** is due to the different priority number of the cyclopropane carbons (the carbon bearing the NO_2 group is the number 3 in **4a** and number 2 in **7a.**

Conformational analysis and absolute configuration determination

Compounds **9f-h** and **11f** possess the heavy atom required by the use of the Bijovet method, based on anomalous X-ray dispersion, to unambiguously assign the absolute configuration (AC).[159] However, despite several attempts, we were not able to grow good crystals neither of compounds **9f-h** and **11f** nor of the corresponding compounds in which the Boc protecting group was removed. For this reason the determination of the absolute configuration has been carried on by means of chiroptical techniqus. In particular, theoretical calculation of Electronic Circular Dichroism (ECD) spectra was carried out by means of the TD-DFT method, since this technique has emerged as a reliable technique to assign the AC, and it has been successfully employed many times to predict the ECD spectra of complex organic molecules.[160] It is worth to note that the relative stereochemistry has been fixed by the NOE analysis, therefore only the distribution of the molecular conformations affects the shape of the ECD spectrum.

Compound 9a

A preliminary conformational search, starting from the relative configuration derived from NOE spectra of **9a** has been carried out using Monte Carlo searching together with the MMFF94 molecular mechanics force field (as implemented in Titan 1.0.5, Wavefunction inc.). All conformations within a 5 kcal/mol window were then optimized using DFT at the B3LYP/6-31G(d) level,[161] 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 by thermochemistry corrections. After DFT minimization, four conformations were found to be true energy minima, with two of them much more stable than the other two. (Table S1 and Figure S3). The two best conformations are different because of the different orientation of the COOEt group.

Table S1: Calculated relative energies (E) and free energies (G) of the conformations of **4a** (in kcal/mol, B3LYP/6-31G(d) level). Populations percentages (Pop.) are calculated assuming using the free energies and Boltzmann statistics at T=25°C.

Molecule	Conf.	E	G	Pop (ΔG)
9a	**a**	0.00	0.00	58
	b	0.01	0.20	41
	c	2.75	2.69	0.6
	d	2.83	3.07	0.4

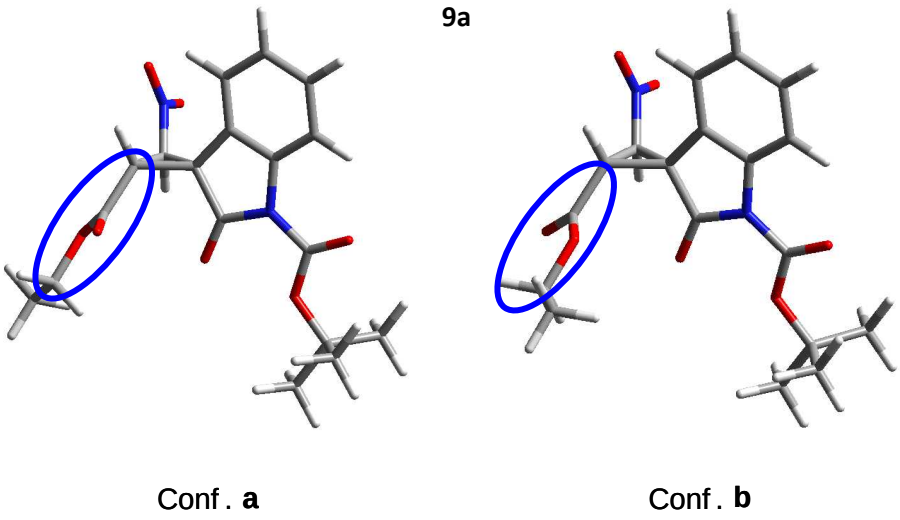


Figure S3. The two most stable conformations of **9a** obtained by DFT calculations (B3LYP/6-31G(d) level). Highlighted regions indicate the different disposition of the COOEt moiety.

Electronic excitation energies and rotational strengths have been calculated in the gas phase for the four conformations of **9a** using TD-DFT at the B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d) and supposing 1*R*, 2*R*, 3*S* Absolute Configuration, with the results shown in Figure S4 (top). Rotational strengths were calculated in both length and velocity representation, the resulting values being very similar. For this reason the errors due to basis set incompleteness should be very small, or negligible.[162] It should be noted that the ECD spectra of conformations **c** and **d** are quite different with respect to those of conformations **a** and **b**. This difference, however, has a very small effect on the final simulation because of the very small population of conformations **c** and **d**. The final simulated ECD spectra was obtained taking into account the

58:41 populations ratio determined assuming Boltzmann statistics from the calculated free energies at the B3LYP/6-31G(d) level (see Figure S5). The agreement between calculated and experimental spectra is very good, and the ECD simulations nicely support the conclusion that the absolute configuration of **9a** is 1*R*, 2*R*, 3*S*

9a

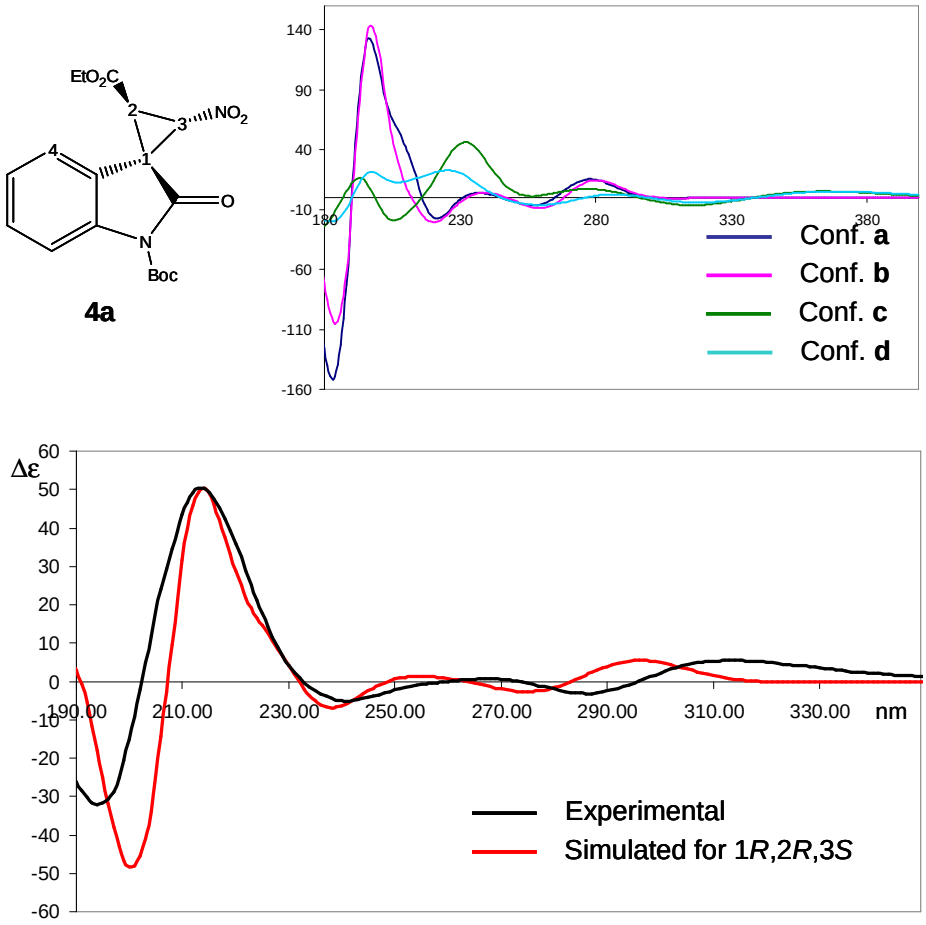


Figure S4. Top: calculated ECD spectra for the two conformation of **9a** using the geometries obtained by gas-phase calculations. TD-DFT calculations were performed at the B3LYP/6-311++G(2d,p) level. Bottom: experimental (black) and calculated ECD spectra (red) of **9a** based on calculated free energies (ΔG) and geometries calculated in the gas phase. Experimental ECD were obtained on acetonitrile solutions ($1 \cdot 10^{-4}$ M) and 0.2 cm path length. Molecular CD (Δε) are expressed in L $mol^{-1}cm^{-1}$. Simulated spectra were red-shifted by 15 nm in order to match the experimental traces.

As evenly suggested by some authors[163], the use of more than one chirooptic method is always desirable in order to enhance the reliability of the assignment. In the present case compound **11a** exhibits a value of $[\alpha]_D$ = +183°, that is well outside the "uncertainty zone" suggested by some authors[164]. For this reason the calculation of the $[\alpha]_D$ by DFT calculations can independently confirm the absolute configuration of **9a**. The optical rotation of both the lowest energy conformers of **9a** was calculated at the B3LYP/6-311++G(2d,p)/B3LYP/6-31g(d) level, yielding values of 244.1 and +215.3 for conformer **a** and **b**, respectively (see Table S2). When weighted by the Boltzmann statistic, the calculated optical rotation value is +229, in good agreement with the experimental value.[165]

Table S2: calculated and experimental $[\alpha]_D$ values.

Molecule	Conf.	$[\alpha]_D$	Pop.	$[\alpha]_D$	Exp.$[\alpha]_D$
9a	**a**	244.1	58	+229	+183.3
	b	215.3	41		
	c	-	0.6		
	d	-	0.4		
11a	**a**	-141	0.5	-95	-112.5
	b	-95.3	99.5		
	c	-	0.5		
	d	-	0.0		
12a	**a**	-57.4	99.5	-58	-121.2
	b	-155.5	0.5		

Compounds 11a and 12a

The same theoretical approach was employed for the determination of the AC of **11a** and for its derivative **12a** in which the Boc protecting group was removed for convenience (the absolute configuration is not modified during the removal of the Boc group). The conformational search is indeed facilitated in the case of **12a** because of the absence of the Boc moiety. For this compound only two conformations were localized after the MM search (see Table 2), whereas four conformation were found for **11a**, as in the case of **9a**.

The different relative configuration of **11a** and **12a** with respect to **9a**, affects the relative energies of the conformations, in that essentially one conformation is populated in both cases

(see Table S3). This implies that the most populated conformation determines the shapes of the ECD spectra.

Table S3: Calculated relative energies (E) and free energies (G) of the conformations of 6a and the derivative of **6a** and **7a** (in kcal/mol, B3LYP/6-31G(d) level). Populations percentages (Pop.) are calculated assuming using the free energies and Boltzmann statistics at T=25°C.

Molecule	Conf.	E	G	Pop (ΔG)
11a	**a**	3.4	3.3	0.5
	b	0.0	0.0	99.0
	c	3.3	3.5	0.5
	d	6.9	6.5	0.0
12a	**a**	0.0	0.0	99.5
	b	3.6	3.4	0.5

As in the case of compound **9a**, the electronic excitation energies and rotational strengths have been calculated in the gas phase for the most populated conformations of **11a** and **12a** using TD-DFT at the B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d) and supposing 1*R*,2*R*,3*S* absolute configuration, with the results shown in Figures S5. While the two experimental ECD spectra of **11a** and **12a** are similar, in both cases the calculated ECD traces do predict the correct sequence of the cotton effects, but they do not match their wavelength. Despite the use of other functionals like BH&LYP and Pw1Pw91, the calculated ECD spectra show always the same incongruence in matching the wavelength of the simulated maxima with respect to the experimental ones, while the trend is correctly simulated. Since compound **11a** is a conformationally rigid molecule having few degrees of freedom, and compound **12a** is even less flexible, a miscalculation of the ground states geometries seems unlikely because the same theoretical approach was found to be appropriate in the case of compound **9a**.

11a top, 12a bottom

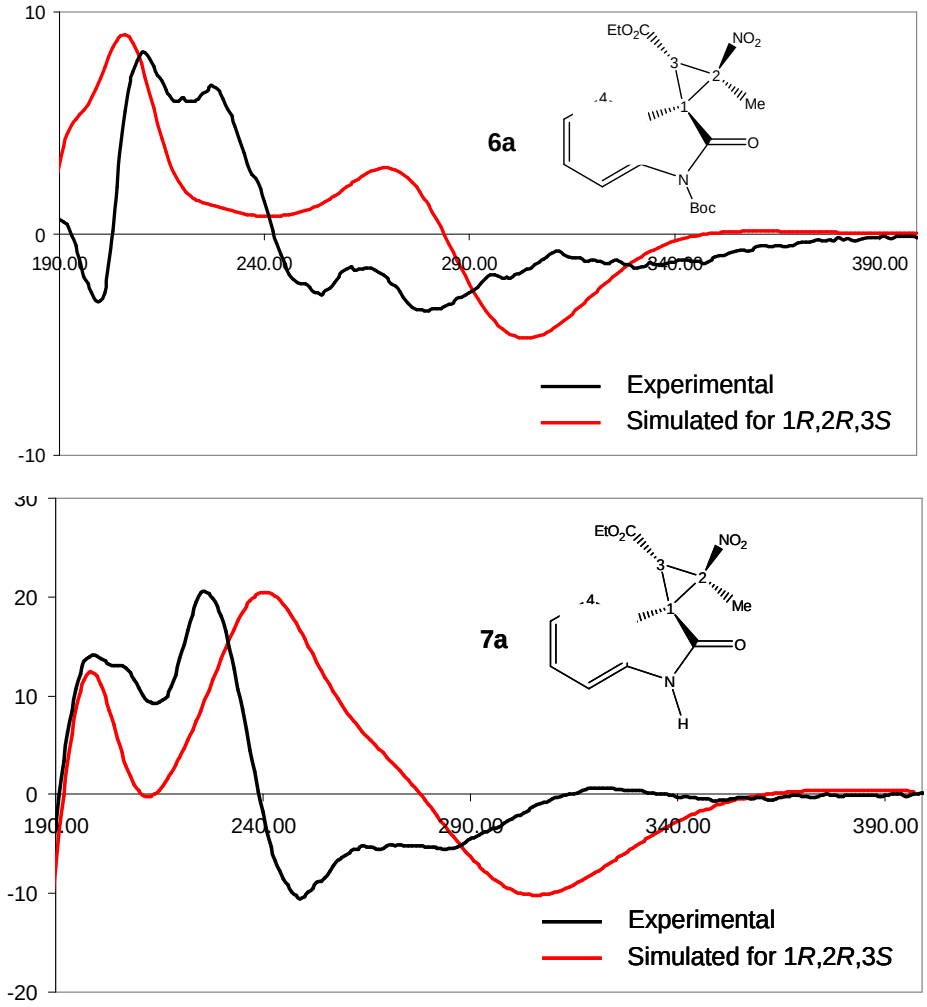
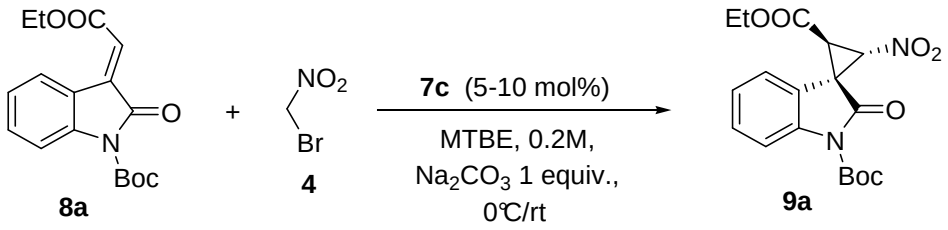


Figure S5: Top: experimental (black) and calculated ECD spectra (red) of **11a**. Bottom: experimental (black) and calculated ECD spectra (red) of **12a.** Experimental ECD were obtained on acetonitrile solutions (≈ $1 \cdot 10^{-4}$ M) and 0.2 cm path length. Molecular CD ($\Delta\varepsilon$) are expressed in L $mol^{-1}cm^{-1}$. Simulated spectra were red-shifted by 7 nm in order to match the experimental traces.

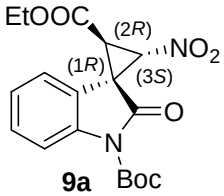
On the other hand, compounds **11a** and **12a** have $[\alpha]_D$ values of = -112.5° and -121.2°, therefore the calculation of the optical rotations could confirm the absolute configuration inferred by the ECD simulation. The optical rotations of the lowest energy conformer of **11a** and for the two conformers of **11a** were calculated at the B3LYP/6-311++G(2d,p)/B3LYP/6-31g(d) level, providing weighted values of -95° and -58° for **11a** and **12a**, respectively. Being

these value in good agreement with the experimental value, the 1*R*, 2*R*, 3*S* absolute configuration of **11a** and **12a** can be reliably assigned.[165]

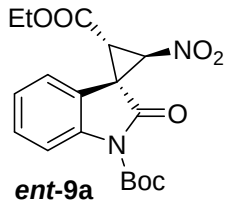
General procedure for the enantioselective nitrocyclopropanation of oxindoles



All the reactions were carried out in undistilled MTBE. In an ordinary vial equipped with a Teflon-coated stir bar, 9-*epi*-9-thiourea-9-deoxy dihydroquinidine **7c** (0.01 mmol, 5.98 mg, 5 mol%) was dissolved in 1 mL of MTBE and bromo nitromethane (0.3 mmol, 22.4 µL, 1.5 equiv.) was added. After 5 minutes *N*-Boc protected oxindole derivative (0.2 mmol, 1.0 equiv.) and Na_2CO_3 (0.2 mmol, 1 equiv.) were added. The resulting solution was stirred at the indicated temperature for 24-72 hours. The crude mixture was diluted with CH_2Cl_2 and flushed through a short plug of silica, using dichloromethane/ethyl acetate 1:1 as the eluent (100 ml). Solvent was removed in *vacuo* and the nitro cyclopropane adduct was isolated by flash column chromatography using hexane/ethyl acetate/diethyl ether as the eluent mixture.

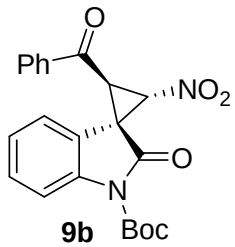


(1*R*,2*R*,3*S*)-1'-tert-butyl 2-ethyl 3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1',2-dicarboxylate (9a), (Table 3, entry 1): The reaction was carried out at 0 °C following the general procedure using **7c** (5 mol%, 5,96 mg) as the catalyst to furnish after 48 h the crude product (d.r.: 19:1 determined by integration of ^{1}H-NMR signal: δ_{major} 3.83 d., δ_{minor} 3.79 ppm. d.). The title compound was isolated as a pale yellow oil by column chromatography (hexane/Et_2O = 85/15) in 77% yield and 98% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 98/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} =19.6 min, τ_{minor} =16.4 min; ESI-MS: 399 (M^++Na), 415(M^++K); $[\alpha]_{rt}^{D}$= +183 (*c* = 0.8000, $CHCl_3$, 98% ee). ^{1}H NMR (600 MHz, CD_3CN): δ 1.05 (t, 3H, *J* = 7.2 Hz), 1.41 (s, 9H), 3.86 (d, 2H, *J* = 6.3Hz) 3.96-4.05 (m, 2H), 5.08 (d, 2H, *J* = 6.3Hz), 7.02-7.06 (m, 2H), 7.25-7.30 (m, 1H), 7.72-7.75 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.5 (CH_3), 27.4 ($C(CH_3)_3$, 36.0 (CH), 39.9 (C), 62.2 (CH_2), 70. 5 (CH), 84.9 (C), 115.6 (CH), 120.5 (C), 122.0 (CH), 124.7 (CH), 130.2 (CH), 141.3 (C), 148.5 (C), 163.0 (C), 168.4 (C).



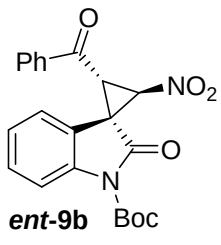
***ent*-9a**

(1*S*,2*S*,3*R*)-1'-tert-butyl 2-ethyl 3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1',2-dicarboxylate (9a), (Table 3, entry 13): The reaction was carried out at room temperature following the general procedure using **7d** (2 mol%, 2.4 mg) as the catalyst to furnish after 72 h the crude product (d.r.: 11:1 determined by integration of ^{1}H-NMR signal: δ_{major} 3.83 d., δ_{minor} 3.79 ppm. d.). The title compound was isolated as a pale yellow oil by column chromatography (hexane/Et_2O = 85/15) in 99% yield and 97% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 98/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} =16.1 min, τ_{minor} =18.9 min; $[\alpha]_{rt}^{D}$=-213 (*c* = 1.05, $CHCl_3$, 97% ee).



9b

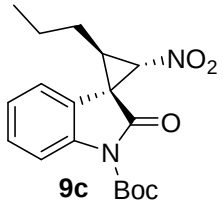
(1*R*,2*R*,3*S*)-tert-butyl 2-benzoyl-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate (9b), (Table 3, entry 2): The reaction was carried out at 0 °C following the general procedure using **7c** (5 mol%, 5,96 mg) as the catalyst to furnish after 72 h the crude product (d.r.: 19:1 determined by integration of ^{1}H-NMR signal: δ_{major} 5.51 d., δ_{minor} 5.25 ppm. d.). The title compound was isolated as a pale yellow oil by column chromatography (hexane/Ethyl Acetate = 95/5) in 52% yield and 90% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214,: τ_{major} = 20.3 min, τ_{minor} = 19.2 min; ESI-MS: 409(M^++1), 431 (M^++Na), 447 (M^++K); $[\alpha]_{rt}^{D}$= +258.5 (*c* = 1.26, $CHCl_3$, 90% ee). ^{1}H NMR (400 MHz, CH_3CN): δ 1.55 (s, 9H), 4.36 (d, 1H, *J* = 6.53Hz), 5.51 (d, 1H, *J*= 6.3 Hz), 7.28 (dd, 1H, *J* =0.96 Hz, *J* = 7.7 Hz), 7.37-7.45 (m, 3H), 7.48 (dt,1H, *J* =1.36 Hz, *J* = 7.7 Hz), 7.55-7.61 (m, 1H), 7.77-7.82 (m, 2H), 7.96-8.02 (m,1H) .^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3 ($C(CH_3)_3$, 40.2 (CH), 41.8 (C), 70.3 (CH), 85.7 (C), 116.0 (CH), 120.0 (C), 122.0 (CH), 125.4 (CH), 128.7 2x(CH), 129.4 2x(CH), 130.7 (CH), 134.7 (CH), 135.4 (C), 141.3 (C), 148.6 (C), 167.7(C), 186.8 (C).



***ent*-9b**

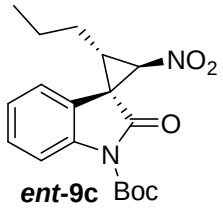
(1*S*,2*S*,3*R*)-tert-butyl 2-benzoyl-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate (*ent*-9b), (Table 3, entry 3): The reaction was carried out at room temperature following the general procedure using **7d** (5 mol%, 5,96 mg) as the catalyst to furnish after 48 h the crude product (d.r.> 19:1 determined by integration of ^{1}H-NMR signal: δ_{major} 5.51 d., δ_{minor} 5.54 ppm. d.). The title compound was isolated as a pale yellow oil by column chromatography (hexane/Ethyl Acetate = 95/5) in 82% yield and 98% ee. HPLC analysis on a

Daicel Chiralpak AD-H column: 98/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214,: τ_{major} = 35,8 min, τ_{minor} = 38.4 min; $[\alpha]_{rt}^{D}$= +258.5 (*c* = 1.26, $CHCl_3$, 98% ee).



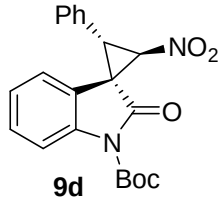
9c

(1*R*,2*R*,3*S*)-tert-butyl 2-nitro-2'-oxo-3-propylspiro[cyclopropane-1,3'-indoline]-1'-carboxylate (9c), (Table 3, entry 4): The reaction was carried out at room temperature following the general procedure using **7c** (10 mol%, 11.92 mg) as the catalyst to furnish after 48 h the crude product (d.r.: 3:1 determined by integration of ^{1}H-NMR signal: δ_{major} 7.90 m., δ_{minor} 7.99 ppm. m.). The title compound was isolated as a mixture of diastereoisomers by column chromatography (hexane/Et_2O = 95/5) in 60% yield and 93% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.550 mL/min, λ = 214, 254 nm: τ_{major} = 9.20 min, τ_{minor} = 8.00 min; ESI-MS: 347 (M^++1), 369 (M^++Na); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.92 (t, 3H, *J* = 7.4 Hz), 1.41-1.50 (m, 2H), 1.65 (s, 9H), 1.80-1.94 (m, 1H), 1.96-2.07 (m, 1H), 3.00 (m, 1H), 4.89 (d, 1H, *J* = 6.6 Hz), 7.13-7.24 (m, 2H), 7.35 (m, 1H), 7.90 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.3 (CH_3), 21.8 (CH_2), 24.6 (CH_2), 24.0 ((CH_3)$_3$), 37.5 (CH), 39.9 (C), 74.3 (CH), 85.1 (C), 122.4 (C), 140.1 (C), 148.6 (C), 169.8 (C).



***ent*-9c**

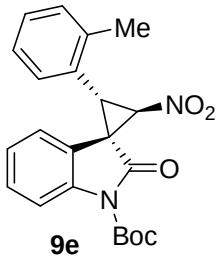
(1*S*,2*S*,3*R*)-tert-butyl 2-nitro-2'-oxo-3-propylspiro[cyclopropane-1,3'-indoline]-1'-carboxylate (*ent*-9c), (Table 3, entry 5): The reaction was carried out at room temperature following the general procedure using **7d** (5 mol%, 5.96 mg) as the catalyst to furnish after 48 h the crude product (d.r.: 4:1 determined by integration of ^{1}H-NMR signal: δ_{major} 7.90 m., δ_{minor} 7.99 ppm. m.). The title compound was isolated as a mixture of diastereoisomers by column chromatography (hexane/Et_2O = 95/5) in 75% yield and 92% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.550 mL/min, λ = 214, 254 nm: τ_{major} = 8.02 min, τ_{minor} = 9.20 min; $[\alpha]_{rt}^{D}$= - 128.2 (*c* = 1.173, $CHCl_3$, 92% ee).



9d

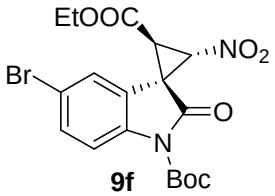
(1*S*,2*S*,3*R*)-tert-butyl 2-nitro-2'-oxo-3-phenylspiro[cyclopropane-1,3'-indoline]-1'-carboxylate (9d), (Table 3, entry 6): The reaction was carried out at room temperature following the general procedure using **7d** (5 mol%, 5.96 mg) as the catalyst to furnish after 72 h the crude product (d.r.: 7.7:1.6:1 determined by integration of ^{1}H-NMR signal: δ_{major} 4.33 d., δ_{minor} 4.45 ppm. d., δ_{minor} 3.80 ppm. d.). The title compound was isolated as a mixture of diastereoisomers by column chromatography (hexane/Et_2O =95/5 to 90/10) in

83% yield and 90% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 90/10 hexane/*i*-PrOH, flow rate 0.750 mL/min, λ = 214, 254 nm: τ_{major} = 6.88 min, τ_{minor} = 11.22 min; ESI-MS: 381 (M^++1), 403 (M^++Na), 419 (M^++K); ^{1}H NMR (400 MHz, $CDCl_3$),: δ 1.59 (9H, s), 4.33 (1H, d, *J* = 6.89 Hz), 5.49 (1H, d, *J* = 6.89 Hz), 7.19-7.25 (m, 1H), 7.28-7.43 (m, 7H), 7.91-7.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 28.2 ($(CH_3)_3$), 41.5 (CH), 42.1 (C), 73.0 (CH), 85.3 (C), 115.5 (CH), 121.8 (CH), 122.2 (C), 125.0 (CH), 128.7 (CH), 128.9 (2CH), 129.2 (2CH), 129.3 (C), 129.6 (CH), 130.3 (C), 140.8 (C), 148.8 (C), 168.1(C).



9e

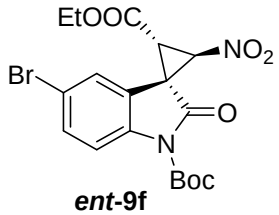
(1*S*,2*S*,3*R*)-tert-butyl 2-nitro-2'-oxo-3-o-tolylspiro[cyclopropane-1,3'-indoline]-1'-carboxylate (9e), (Table 3, entry 7): The reaction was carried out at room temperature following the general procedure using **7d** (5 mol%, 5.96 mg) as the catalyst to furnish after 65 h the crude product (d.r.: 3:1 determined by integration of ^{1}H-NMR signal: δ_{major} 4.30 d., δ_{minor} 4.20 ppm. d.). The title compound was isolated as a mixture of diastereoisomers by column chromatography (hexane/Et_2O = 90/10) in 80% and 90% ee. HPLC analysis [determined after deportection of the oxindole under standard conditions (TFA 3 equiv, DCM 0.04M, rt, 16 h)]: 80/20 hexane/*i*-PrOH, flow rate 0.750 mL/min, λ = 214, 254 nm: τ_{major} = 10.93 min, τ_{minor} = 16.50 min; ESI-MS: 395 (M^++1); ^{1}H NMR (400 MHz, $CDCl_3$), mixture of diastereoisomers: δ 1.59 (s, 9H)$_{min}$, 1.66 (s, 9H)$_{max}$, 1.89 (s, 3H)$_{max}$, 2.02 (s, 3H)$_{min}$, 4.20 (d, 1H, *J* = 7.0 Hz)$_{min}$, 4.30 (d, 1H, *J* = 6.8 Hz)$_{max}$, 5.12 (d, 1H, *J* = 6.8 Hz)$_{max}$, 5.45 (d, 1H, *J* = 7.0 Hz)$_{min}$, 5.92 (dd, 1H, *J* = 7.6 Hz, *J* = 0.9 Hz)$_{max}$, 6.82 (dd, 1H, *J* = 7.6 Hz, *J* = 0.9 Hz)$_{max}$, 7.08-7.18 (m, 2H), 7.19-7.34 (m, 8H), 7.38-7.46 (m, 2H), 7.92-7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2 (CH_3), 19.6 (CH_3), 28.0 ($(CH_3)_3$), 28.1 ($(CH_3)_3$), 39.6 (CH), 40.2 (CH), 41.5 (2C), 71.5 (CH), 72.8 (CH), 77.2 (C), 85.1 (C), 115.3 (CH), 115.3 (CH), 120.3 (CH), 121.5 (CH), 121.7 (C), 122.1 (C), 124.1 (CH), 124.9 (CH), 126.1 (CH), 126.3 (CH), 127.9 (C), 128.3 (CH), 128.5 (CH), 128.6 (CH), 129.0 (CH), 129.1 (CH), 129.4 (CH), 130.4 (CH), 130.7 (CH), 137.4 (C), 138.7 (C),140.0 (C), 140.4 (C), 148.6 (C),148.9 (C),167.8 (C), 168.2 (C).



9f

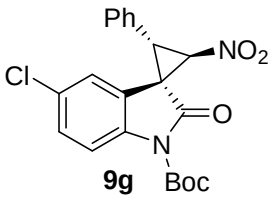
(1*R*,2*R*,3*S*)-1'-tert-butyl 2-ethyl 5'-bromo-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1',2-dicarboxylate (9f), (Table 3, entry 8): The reaction was carried out at room temperature following the general procedure using **1c** (5 mol%, 5,96 mg) as the catalyst to furnish after 24 h the crude product (d.r.: 9:1 determined by integration of ^{1}H-NMR signal: δ_{major} 5.28 d., δ_{minor} 6.25 ppm. d.). The title compound was

isolated as a pale yellow oil by column chromatography (hexane/ethyl acetate = 95/5 to 9/1) in 76% yield and 87% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 98/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} =22.9 min, τ_{minor} =14.4 min; ESI-MS [determined after deportection of the oxindole under standard conditions (TFA 3 equiv, DCM 0.04M, rt, 16 h)]: 355 (M^++1) ^{79}Br, 357 (M^++1) ^{81}Br, 377 (M^++Na) ^{79}Br, 379 (M^++Na) ^{81}Br, 393 (M^++Na) ^{79}Br, 395 (M^++1) ^{81}Br; $[\alpha]_{rt}^{D}$= +139 (*c* = 1.083, $CHCl_3$, 87% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, 3H, *J* = 7.2Hz), 1.62 (s, 9H), 3.82 (d, 1H, *J* = 6.3Hz), 4.20-4.31 (m, 2H), 5.29 (d, 1H, *J* = 6.3Hz), 7.34 (d, 1H, *J* = 2.1Hz), 7.53 (dd, 1H, *J* = 2.1Hz, *J* = 8.6Hz), 7.84 (d, 1H, *J* = 8.6Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3 (CH_3), 28.3 ($C(CH_3)_3$), 36.3 (CH), 39.7 (C), 63.1 (CH_2), 70.2 (CH), 86.1 (C), 117.4 (CH), 118.2 (C), 122.2 (C), 125.4 (CH), 133.3 (CH), , 140.2 (C), 148.4 (C), 162.7 (C), 167.6 (C).



***ent*-9f**

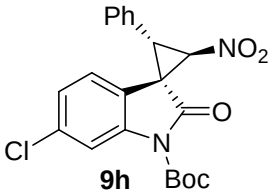
(1*S*,2*S*,3*R*)-1'-tert-butyl 2-ethyl 5'-bromo-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1',2-dicarboxylate (*ent*-9f), (Table 3, entry 9): The reaction was carried out at 0° C following the general procedure using **7d** (5 mol%, 5,96 mg) as the catalyst to furnish after 72 h the crude product (d.r.: >19:1 determined by integration of ^{1}H-NMR signal: δ_{major} 5.28 d., δ_{minor} 6.25 ppm. d.). The title compound was isolated as a pale yellow oil by column chromatography (hexane/ethyl acetate = 95/5 to 9/1) in 74% yield and 93% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 98/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} =12.2 min, τ_{minor} =20.1 min; $[\alpha]_{rt}^{D}$= -143. (*c* = 1.00, $CHCl_3$, 93% ee).



9g

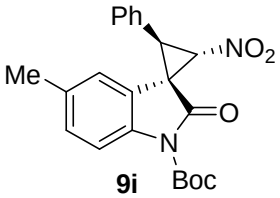
(1*S*,2*S*,3*R*)-tert-butyl 5'-chloro-2-nitro-2'-oxo-3-phenylspiro[cyclopropane-1,3'-indoline]-1'-carboxylate (9g), (Table 3, entry 10): The reaction was carried out at room temperature following the general procedure using **7d** (5 mol%, 5,96 mg) as the catalyst to furnish after 48 h the crude product (d.r.: 8.6:1.3:1 determined by integration of ^{1}H-NMR signal: δ_{major} 4.31 d., δ_{minor} 4.46 ppm. d, δ_{minor} 3.81 ppm. d.). The title compound was isolated as a pale yellow solid by column chromatography (hexane/acetone 9/1) in 84% yield and 90% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 98/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm: τ_{major} =18.3 min, τ_{minor} =12.4 min; ESI-MS: 437 (M^++Na), 453 (M^++K). $[\alpha]_{rt}^{D}$= -143. (*c* = 1.00, $CHCl_3$, 90% ee).^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (s, 9H), 4.31 (d, 1H, *J* = 7.33 Hz), 5.49 (d, 1H, *J* = 7.33 Hz), 7.27-7.39

(m, 7H), 7.87-7.91 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3 ($C(CH_3)_3$), 41.8 (C), 41.9 (CH), 72.9 (CH), 85.7 (C), 116.8 (CH), 122.3 (CH), 123.9 (C), 120.0 (CH), 129.1 (CH), , 129.6 (CH), 130.7 (C), 139.3 (C), 148.6 (C), 167.4 (C).



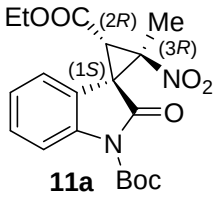
9h

(1*S*,2*S*,3*R*)-tert-butyl 6'-chloro-2-nitro-2'-oxo-3-phenylspiro[cyclopropane-1,3'-indoline]-1'-carboxylate (9h), (Table 3, entry 11): The reaction was carried out at room temperature following the general procedure using **7d** (5 mol%, 5,96 mg) as the catalyst to furnish after 48 h the crude product (d.r.: 12:2:1 determined by integration of ^{1}H-NMR signal: δ_{major} 4.31 d., δ_{minor} 4.44 ppm. d, δ_{minor} 3.79 ppm. d.) The title compound was isolated as a pale yellow solid by column chromatography (hexane/ acetone 9/1) in 84% yield and 89% 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} =6.56 min, τ_{minor} =10.79 min; ESI-MS: 437 (M^++Na), 453 (M^++K); $[\alpha]_{rt}^{D}$= -143. (*c* = 1.00, $CHCl_3$, 89% ee).^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 (s, 9H), 4.31 (d, 1H, *J* = 6.8 Hz), 5.47 (d, 1H, *J* = 6.8 Hz), 7.17-7.42 (m, 7H), 8.01 (d, 1H, *J* = 1.9 Hz).^{13}C NMR (100 MHz, $CDCl_3$): δ 28.7 ($C(CH_3)_3$), 41.6 (CH), 41.8 (C), 72.9 (CH), 85.9 (C), 116.3 (CH), 120.6 (C), 122. 8 (CH), , 125.1 (CH), 126.9 (CH), 128.7 2(CH), 128.9 2x(CH), 135.6 (C), 141. 5 (C), 148.6 (C), 167.6 (C).



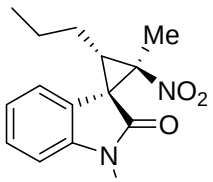
9i

(1*R*,2*R*,3*S*)-1'-tert-butyl 2-ethyl 5'-methyl-3-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1',2-dicarboxylate (9i), (Table 3, entry 12): The reaction was carried out at room temperature following the general procedure using **7c** (5 mol%, 5.96 mg) as the catalyst to furnish after 72 h the crude product (d.r.: 7:1 determined by integration of ^{1}H-NMR signal: δ_{major} 4.31 d., δ_{minor} 4.45 ppm. d.). The title compound was isolated as a mixture of diastereoisomers by column chromatography (hexane/ethyl acetate = 95/5) in 60% yield and 91% ee (99% ee after single crystallization from hexane/diethyl ether). HPLC analysis on a Daicel Chiralpak AD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.500 mL/min, λ = 214, 254 nm: τ_{major} = 19.31 min, τ_{minor} = 12.81 min; ESI-MS: 395 (M^++1), 417 (M^++Na); $[\alpha]_{rt}^{D}$= + 224.7 (*c* = 1.137, $CHCl_3$, 91% ee, dr = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 (s, 9H), 2.38 (s, 3H), 4.30 (d, 1H, *J* = 6.9 Hz), 5.47 (d, 1H, *J* = 6.9 Hz), 7.15 (m, 1H), 7.20 (m, 1H), 7.27 (m, 5H), 7.79 (d, 1H, *J* = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2 (CH_3), 28.0 ((CH_3)$_3$), 41.2 (CH), 41.9 (C), 72.7 (CH), 84.9 (C), 115.1 (CH), 121.9 (C), 122.0 (CH), 128.4 (CH), 128.6 (CH), 128.9 (CH), 129.1 (C), 129.8 (CH), 134.5 (C), 138.1 (C), 148.6 (C), 168.0 (C).



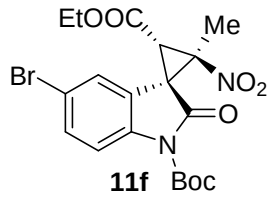
11a

(1*S*,2*R*,3*R*)-1'-tert-butyl 3-ethyl 2-methyl-2-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1',3-dicarboxylate (Scheme 3, 11a): The reaction was carried out at room temperature following the general procedure using **7d** (5 mol%, 5.96 mg) as the catalyst to furnish after 48 h the crude product (d.r.: 5:1 determined by integration of ^{1}H-NMR signal: δ_{major} 3.76 s., δ_{minor} 3.88 ppm. s.). The title compound was isolated as a mixture of diastereoisomers by column chromatography (hexane/AcOEt = 95/5) in 91% yield and >99% ee. HPLC analysis [determined after deportection of the oxindole under standard conditions (TFA 3 equiv, DCM 0.04M, rt, 16 h)] on a Daicel Chiralpak AD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.750 mL/min, λ = 214, 254 nm: τ_{major} = 14.84 min, τ_{minor} = 21.01 min; ESI-MS [determined after deportection of the oxindole under standard conditions (TFA 3 equiv, DCM 0.04M, rt, 16 h)]: 291 (M^{+}+1), 313 (M^{+}+Na), 329 (M^{+}+K); $[\alpha]_{rt}^{D}$= -112.5 (*c* = 0.820, $CHCl_3$, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, 3H, *J* = 7.1 Hz), 1.62 (s, 9H), 2.21 (s, 3H), 3.77 (s, 3H), 4.11-4.27 (m, 2H), 7.15-7.21 (m, 1H), 7.37-7.49 (m, 2H), 7.98-8.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5 (CH_3), 14.2 (CH_3), 28.2 ((CH_3)$_3$), 38.7 (CH_3), 41.8 (C), 77.4 (C), 85.5 (C), 115.7 (CH), 120.0 (C), 124.5 (CH), 124.7 (CH), 129.7 (CH), 141. 9 (C), 148.8 (C), 165.0 (C), 168.5 (C).



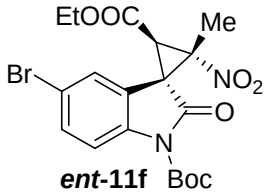
11d

(1*R*,2*R*,3*S*)-tert-butyl 2-methyl-2-nitro-2'-oxo-3-propylspiro[cyclopropane-1,3'-indoline]-1'-carboxylate (Scheme 3, 11d): The reaction was carried out at room temperature following the general procedure using **7d** (20 mol%, 23.84 mg) as the catalyst to furnish after 48 h the crude product (d.r.: 3:1 determined by integration of ^{1}H-NMR signal: δ_{major} 8.03 d., δ_{minor} 6.91 ppm. d.). The title compound was isolated as a mixture of diastereoisomers by column chromatography (hexane/AcOEt = 95/5) in 65% yield and 92% ee. HPLC analysis on a Daicel Chiralpak AS-H column: 90/10 hexane/*i*-PrOH, flow rate 0.650 mL/min, λ = 214, 254 nm: τ_{major} = 10.15 min, τ_{minor} = 9.49 min; ESI-MS: 383 (M^{+}+ Na), 399 (M^{+}+K); $[\alpha]_{rt}^{D}$= - 26.9 (*c* = 0.93, $CHCl_3$, 92% ee, d.r. = 4.5:1). ^{1}H NMR (400 MHz, $CDCl_3$), major diastereoisomer: δ 0.95 (t, 3H, *J* = 7.3 Hz), 1.32-1.56 (m, 3H), 1.61 (s, 9H), 1.72-1.82 (m, 1H), 1.92 (s, 3H), 3.0 (m, 1H), 7.02 (m, 1H), 7.17 (m, 1H), 7.39 (m, 1H), 8.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), major diatsereoisomer: δ 13.4 (CH_3), 13.6 (CH_3), 21.5 (CH_2), 24.0 (CH_2), 28.0 ((CH_3)$_3$), 39.1 (CH), 42.6 (C), 78.6 (C), 84.8 (C), 115.6 (CH), 121.5 (C), 122.6 (CH), 123.9 (CH), 128.5 (CH), 141.1 (C), 148.9 (C), 169.9 (C).



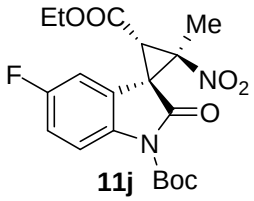
11f

(1*R*,2*R*,3*S*)-1'-tert-butyl 3-ethyl 5'-bromo-2-methyl-2-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1',3-dicarboxylate (scheme 3, 11f): The reaction was carried out at room temperature following the general procedure using **7d** (5 mol%, 5.96 mg) as the catalyst to furnish after 48 h the crude product (d.r.: 1.5:1 determined by integration of ^{1}H-NMR signal: δ_{major} 3.77 s., δ_{minor} 3.89 ppm. s.). The title compound was isolated as a mixture of diastereoisomers by column chromatography (hexane/AcOEt = 95/5) in 65% yield and 96% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.500 mL/min, λ = 214, 254 nm: τ_{major} = 11.05 min, τ_{minor} = 9.20 min; ESI-MS: 369 (M^{+}+1) ^{79}Br, 371 (M^{+}+1) ^{81}Br, 391(M^{+}+Na) ^{79}Br, 393 (M^{+}+Na) ^{81}Br, 407 (M^{+}+Na) ^{79}Br, 409 (M+1) ^{81}Br; $[\alpha]_{rt}^{D}$= - 58.1 (*c* = 1.02, $CHCl_3$, 96% ee, d.r. = 4:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.28 (t, 3H, *J* = 7.2 Hz), 1.60 (s, 9H), 2.20 (s, 3H), 3.77 (s, 1H), 4.23 (m, 2H), 7.55 (dd, 1H, *J* = 8.8 Hz, *J* = 2.0 Hz), 7.61 (d, 1H, *J* = 2.0 Hz), 7.93 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.3 (CH_3), 14.0 (CH_3), 28.0 ((CH_3)$_3$), 38.8 (CH), 41.2 (C), 62.4 (CH_2), 77.3 (C), 85.7 (C), 116.9 (CH), 117.4 (C), 121.7 (C), 127.6 (CH), 132.4 (CH), 140.3 (C), 148.4 (C), 164.5 (C), 167.6 (C).



***ent*-11f**

(1*S*,2*S*,3*R*)-1'-tert-butyl 3-ethyl 5'-bromo-2-methyl-2-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1',3-dicarboxylate (Scheme 3, *ent*-11f): The reaction was carried out at room temperature following the general procedure using **7c** (10 mol%, 11.92 mg) as the catalyst to furnish after 48 h the crude product (d.r.: 2:1 determined by integration of ^{1}H-NMR signal: δ_{major} 3.77 s., δ_{minor} 3.89 ppm. s.). The title compound was isolated as a mixture of diastereoisomers by column chromatography (hexane/AcOEt = 95/5) in 71% yield and 97% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.500 mL/min, λ = 214, 254 nm: τ_{major} = 9.48 min, τ_{minor} = 11.05 min; $[\alpha]_{rt}^{D}$= + 39.4 (*c* = 0.91, $CHCl_3$, 97% ee).



11j

(1*R*,2*R*,3*S*)-1'-tert-butyl 3-ethyl 5'-fluoro-2-methyl-2-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-1',3-dicarboxylate (Scheme 3, 11j): The reaction was carried out at room temperature following the general procedure using **7d** (5 mol%, 5.96 mg) as the catalyst to furnish after 48 h the crude product (d.r.: 4:1 determined by integration of ^{1}H-NMR signal: δ_{major} 3.78 s., δ_{minor} 3.88 ppm. s.). The title compound was isolated as a mixture of diastereoisomers by column chromatography (hexane/AcOEt = 95/5) in 71% yield and 96% ee. HPLC analysis on a Daicel Chiralpak AD-H column: 95/5 hexane/*i*-PrOH, flow rate 0.500

mL/min, λ = 214, 254 nm: τ_{major} = 9.73 min, τ_{minor} = 8.93 min; ESI-MS: 309 (M^++ 1), 331 (M^++Na), 347 (M^++K); $[\alpha]_{rt}^{D}$= - 69.5 (*c* = 0.81, $CHCl_3$, 96% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, 3H, *J* = 7.1 Hz), 1.60 (s, 9H), 2.20 (s, 3H), 3.78 (s, 1H), 4.22 (m, 2H), 7.12 (dt, 1H, *J* = 8.9 Hz, *J* = 2.8 Hz), 7.27 (dd, 1H, *J* = 8.7 Hz, *J* = 2.7 Hz), 8.02 (dd, 1H, *J* = 9.0 Hz, *J* = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.1 (CH_3), 14.0 (CH_3), 28.0 ((CH_3)$_3$), 38.7 (CH), 41.5 (C), 62.3 (CH_2), 77.2 (C), 85.5 (C), 112.6 (d, CH, *J* = 27.2 Hz), 116.0 (d, CH, *J* = 23.1 Hz), 116.6 (d, CH, *J* = 8.1 Hz), 121.3 (d, C, *J* = 9.7 Hz), 137.3 (d, C, *J* = 2.4 Hz), 148.5 (C), 158.1 (C), 160.6 (C), 164.6 (C), 167.9 (C).

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3. SUMMARY AND OUTLOOK

The studies conducted during my Phd thesis were focused on two different directions:

1. In one case we tried to face some long standing problems of the asymmetric aminocatalysis as the activation of encumbered carbonyl compounds and the control of the diastereoisomeric ratio in the diastero- and enantioselective construction of all carbon substituted quaternary stereocenters adjacent a tertiary one. In this section (Challenges) was described the asymmetric aziridination of α,β-unsaturated ketones, the activation of α,β-unsaturated α-branched aldehydes and the Michael addition of oxindoles to enals and enones.

For the activation via iminium ion formation of sterically demanding substrates, as α,β-unsaturated ketones and α,β-unsaturated α-branched aldehydes, we exploited a chiral primary amine in order to overcome the problem of the iminium ion formation between the catalyst and encumbered carbonylic componds.

For the control of diastereoisomeric ratio in the diastero- and enantioselective construction of all carbon substituted quaternary stereocenters adjacent a tertiary one we envisaged that a suitable strategy was the Michael addition to 3 substituted oxindoles to enals activated via LUMO-lowering catalysis.

In this synthetic protocol we designed a new bifunctional catalyst with an amine moiety for activate the aldehyde and a tioureidic fragment for direct the approach of the oxindole.

This part of the thesis (Challenges) could be considered pure basic research, where the solution of the synthetic problem was the goal itself of the research.

2. In the other hand (Molecules) we applied our knowledge about the carbonylic compounds activation and about cascade reaction to the synthesis of three new classes of spirooxindole in enantiopure form.

The construction of libraries of these bioactive compounds represented a scientific bridge between medicinal chemistry or biology and the asymmetric catalysis.

“Così tra questa immensità s'annega il pensier mio:
e il naufragar m'è dolce in questo mare”.
L’infinito, Giacomo Leopardi