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**Enantioselective Reactions Promoted by Organocatalytic
Species From The Natural Chiral Pool**

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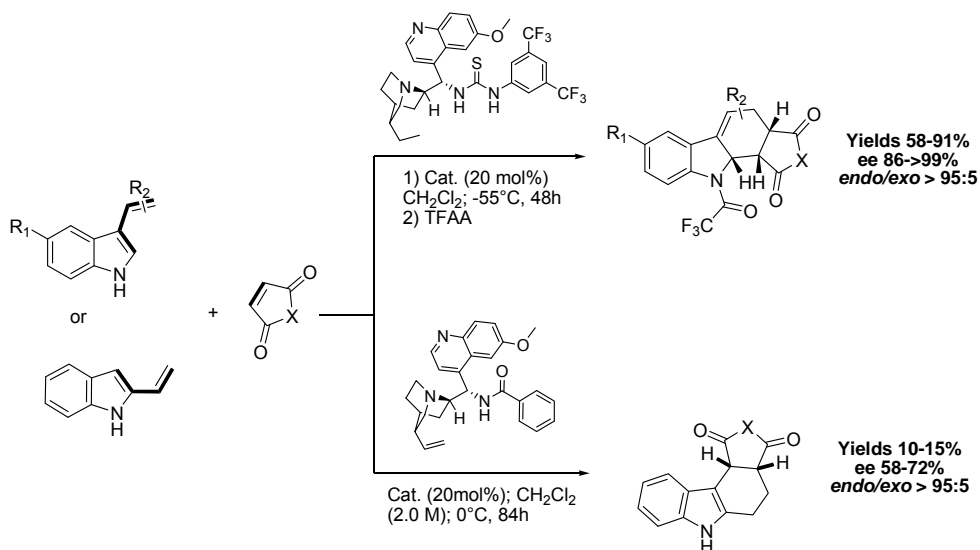
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Preface

During the course of my Ph.D. in the laboratories directed by Prof. Alfredo Ricci at the Department of Organic Chemistry “A. Mangini” of the University of Bologna, I have been involved in a project lying in the field of asymmetric organocatalysis. Since this field has been explosively growing during the last decade, both the study of new reaction pathways and the discovery of novel organocatalytic species represent nowadays challenging and hot research topics. As outlined in the following chapters my own contribution has been directed towards the study and the application of a number of organocatalytic systems, all coming from the natural chiral pool. In this journey in the world of organocatalysis the natural products engaged in asymmetric catalytic protocols ranged from simple polyfunctionalized alkaloids to oligomeric species based on essential aminoacids, till marine derived biopolymers. Their efficacy in promoting asymmetric catalysis has been highlighted not only in homogeneous but also in heterogeneous organocatalysis an emerging field of relevant interest for practical applications.

In Chapter 1 a short overview on the general aspects of organocatalysis is presented, outlining the milestones from the first experimental attempts to the most recent insights. The main organocatalytic pathways are also introduced, describing the most recurring catalytic species from the natural chiral pool and their modes of action.

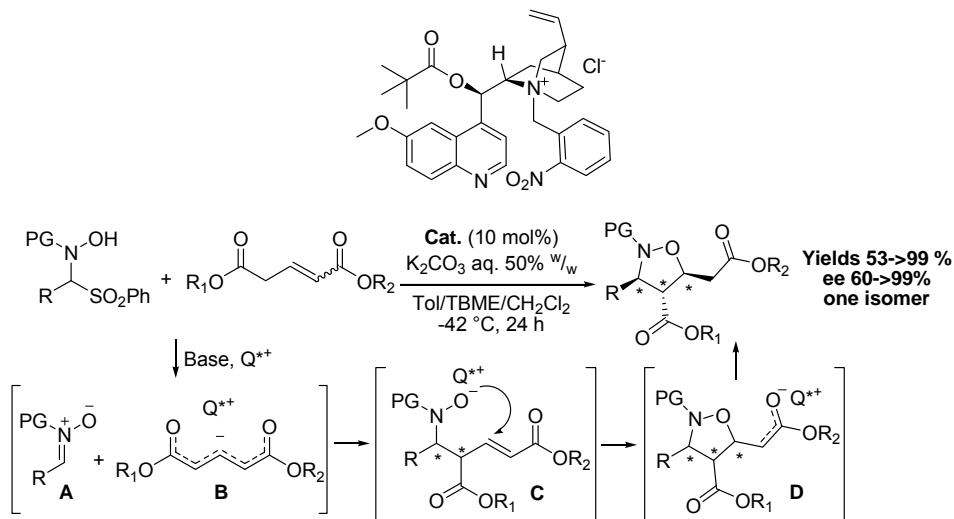
Chapter 2 is devoted to new homogeneous organocatalytic reactions promoted by *Cinchona* alkaloid-based organocatalytic species. A thiourea/quinine hybrid was found (Scheme I) to be a very effective catalyst for Diels-Alder reactions involving 3-vinylindoles.



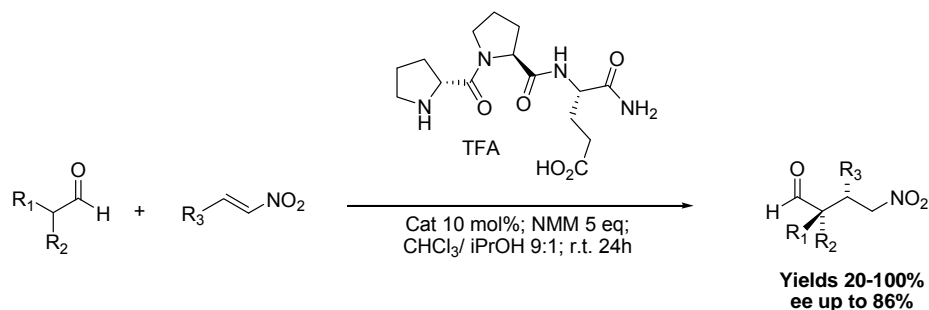
Scheme I

Excellent results in terms of yields and enantioselectivities were achieved, outlining the operational mode of the organocatalytic species mimicking enzymatic catalysis. However, the

same reaction with 2-vinylindoles, involving an amide-derived quinine as the catalyst, showed a completely different behaviour resulting in an unusual resolution-type process. The asymmetric formal [3+2] cycloaddition with *in situ* generated N-carbamoyl nitrones using *Cinchona*-derived quaternary ammonium salts as versatile catalysts under phase transfer conditions, outlines another application in organocatalysis of this class of alkaloids. The formation in high yields and excellent enantioselectivities (Scheme II) of isoxazolidines via a Mannich reaction followed by an intramolecular oxa-Michael addition, supports the potential in enantioselective catalysis of these simple derivatives of a natural product.

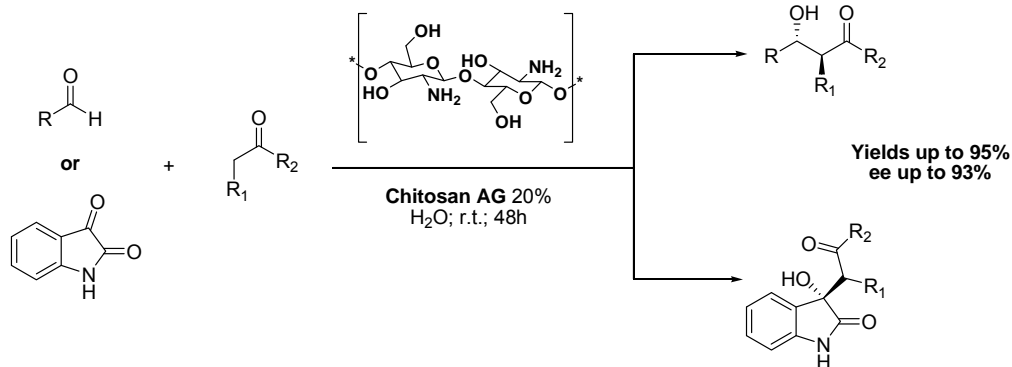


Chapter 3 describes the use of oligopeptides in homogeneous organocatalysis. This part of the work, based on more complex organocatalytic species, refers to the seven months stage in the Prof. Helma Wennemers' group at the Department of Chemistry of the University of Basel (Switzerland). These oligomeric molecules, derived from natural and non-natural α -amino acids, present unique features such as the large number of exploitable functionalities, the easy modulation of the main structure and the possibility of using combinatorial strategies. My work in this field focused on the 1,4-addition reaction of aldehydes to nitroolefins. A preliminary kinetic study of a reaction involving a very low catalysts loading, was followed by the optimization of the Michael reaction using branched aldehydes (Scheme III)



Scheme III

In the work performed at the Department of Organic Chemistry “A. Mangini” of the University of Bologna, in collaboration with the ‘Institut Charles Gerhardt-Montpellier, Matériaux Avancés pour la Catalyse et la Santé’ of Montpellier (France), reported in Chapter 4, the possibility of performing for the first time heterogeneous organocatalysis by using a natural polysaccharide biopolymer as the source of chirality was disclosed. With chitosan derived from deacetylation of chitin, a marine derived polysaccharide, a highly enantioselective heterogeneous organocatalytic aldol reaction could be performed (Scheme IV).



Scheme IV

The use of an eco-friendly medium such as water, the recyclability of the catalytic specie and the renewable nature of the polysaccharide are assets of this new approach in organocatalysis and open interesting new perspectives for the use of other natural biopolymers of marine origin such as the alginic acid which is now under investigation.

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Chapter 1

1.1 Asymmetric Organocatalysis

Asymmetric organocatalysis is an important field in the stereoselective synthesis of chiral compounds; essentially it concerns the catalytic behaviour of small enantiopure organic molecules where an inorganic element is not part of the active principle.¹

This relatively new concept, developed mainly in the last decade, nowadays is a highly dynamic area in chemical research, and has become one of the main branches of enantioselective synthesis along with the more known enzymatic and transition metal complex catalysis. Each of these three important fields actually presents different features concerning the mode of action and the conditions of application, resulting mutually complementary.²

Metal complex catalysis is based on a transition metal as the catalytic center. The main advantages are related to the possibility of using different transition metals, to optimize the structure of the ligand in order to obtain high yields and the desired stereoisomer, and to the usually very low catalyst loadings (up to 1000000/1 in S/C). The problems are essentially the cost of the metal, the instability of several metal catalysts toward moisture or oxygen, and some concerns in the purification process, as the products for pharmaceuticals tolerate only small traces of metal contaminants.³

Enzymatic catalysis is based on the catalytic activity of enzymes, antibodies and microorganisms. They often present very high values of enantioselection due to their protein structure and, obviously, they have no toxicity. Negative features of enzymatic catalysis are the narrow conditions of applicability; parameters like the presence of organic solvents, temperature and concentration of the substrates may, in fact, inhibit or denaturize the enzyme. Furthermore in this case the synthesis of both enantiomers is difficult, and the substrate scope is generally very limited.

Finally, organocatalysts compared to metallorganic and bio-catalysts, usually presents some advantageous features such as simpler reaction conditions, higher tolerability towards air and moisture, combined with the absence of heavy metals. However rather high catalyst loading (typically under 100/1 in S/C) are usually required.

Despite the development of this field has occurred only in the last ten years, historically organocatalysis precedes metallorganic catalysis. However, because of poor generality of the

¹a) *Asymmetric Organocatalysis*, A. Berkessel, H. Gröger, Eds.; Wiley-VCH, Weinheim, **2005**; b) *Enantioselective Organocatalysis*, P. I. Dalko, Ed.; Wiley-VCH, Weinheim, **2007**; c) P. I. Dalko, L. Moisan *Angew. Chem. Int. Ed.*, **2001**, *40*, 3726; d) P. I. Dalko, L. Moisan *Angew. Chem. Int. Ed.*, **2004**, *43*, 5138; e) *Organocatalysis*, B. List, Ed. *Chem. Rev.*, **2007**, *107*, Nr 12; f) *Asymmetric Organocatalysis* K. N. Houk and B. List, Eds. *Acc. Chem. Res.*, **2004**, *37*, Nr 8. g) D. W. C. MacMillan *Nature*, **2008**, *455*, 304.

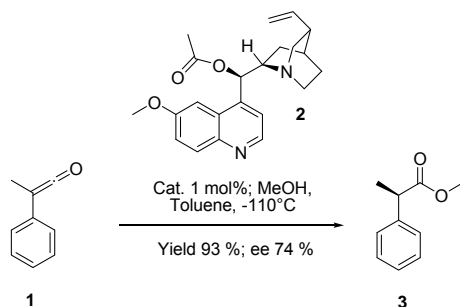
² *Asymmetric Organocatalysis*, A. Berkessel, H. Gröger, Eds.; Wiley-VCH, Weinheim, **2005**, xi-xiv, 1-8.

³ The European Agency for Evaluation of Medicinal Products (EMA) sets the Oral Concentration Limit in active components for Pt, Pd, Ru, Rh, Ir and Os as 5 ppm: *Note for Guidance on Specification Limits for Residues of Metal Catalysts*, CPMP/SWP/QWP/4446/00, London, **2002**.

reactions, and the lack of a generalised approach, it was at first mainly used as mechanistic/biomimetic branch of enzymatic catalysis with scarce synthetic applications.

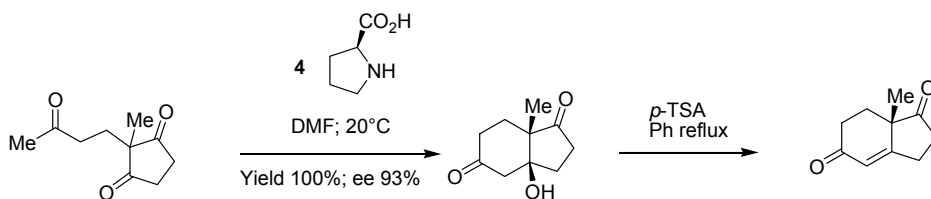
In the first half of 1900s, in fact, a small number of examples were reported and all of them were with low enantiomeric excess (less than 20%).⁴

A change occurred in the second half of 1900s, when two pioneering works with different kinds of catalysts appeared. First, Pracejus et al. in 1960 reported that Cinchona alkaloid derivative **2** catalyzed the addition of methanol to phenylmethylketene **1**, affording the (-)- α -phenyl methylpropionate **3** with 74 % ee (Scheme 1).⁵



Scheme 1

The second milestone in the history of organocatalysis was the L-proline **4** mediated highly enantioselective Robinson annulation reported by Eder, Sauer, Wiechert and Hajos, Parrish, in the 1970s (Scheme 2).⁶ The results were very impressive, and the products obtained in up to 93% ee, have been used as important key intermediates in the synthesis of some natural products.⁷



Scheme 2

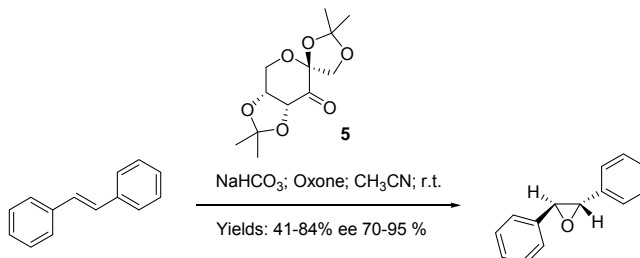
⁴ For a detailed discussion about organocatalytic examples reported before 1960 see: *Enantioselective Organocatalysis*, P. I. Dalko, Ed.; Wiley-VCH, Weinheim, **2007**, 2-6.

⁵ a) H. Pracejus *Justus Liebigs Ann. Chem.*, **1960**, 634, 9. b) H. Pracejus, H. Mätje *J. Prakt. Chem.*, **1964**, 24, 195.

⁶ a) U. Eder, G. Sauer, R. Wiechert *Angew. Chem. Int. Ed.*, **1971**, 10, 496. b) Z. G. Hajos, D. R. Parrish *J. Org. Chem.*, **1974**, 39, 1615.

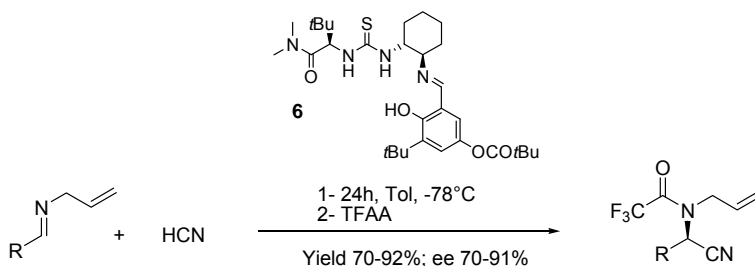
⁷ For recent examples see: a) S. Yamashita, K. Iso, K. Kitajima, M. Himuro, M. Hiramata, *J. Org. Chem.*, **2011**, 76, 2408; b) Y. Murata, D. Yamashita, K. Kitahara, Y. Minamoto, A. Nakazaki, S. Kobayashi, *Angew. Chem. Int. Ed.*, **2009**, 48, 1400; c) T. P. Brady, S. H. Kim, K. Wen, E. A. Theodorakis, *Angew. Chem. Int. Ed.*, **2004**, 43, 739.

Albeit these remarkable results, organocatalysis remained relatively unexplored for twenty years, since the 1990s, when Shi,⁸ Denmark⁹ and Yang¹⁰, and their co-workers, demonstrated that enantiomerically pure ketones, such as **5**, could catalyze the enantioselective epoxidation of alkenes (Scheme 3).



Scheme 3

Shortly afterwards, Lipton,¹¹ Jacobsen,¹² Corey,¹³ and their co-workers, introduced the first examples of hydrogen-bonding catalysis in asymmetric Strecker reactions. Although these works could not conceptualize organocatalysis as a field of research, they let to realize, for the first time, the importance of small organocatalysts in the synthesis of valuable chiral compounds. Particularly relevant to the subsequent development of the field has been the work of Jacobsen, who demonstrated for the first time that enantiopure thioureas such as **6** (Scheme 4), could be used as hydrogen bond donor catalysts in highly enantioselective transformations.



Scheme 4

It was not until 2000, however, that the field of organocatalysis was effectively launched simultaneously by Barbas, Lerner and List¹⁴ introducing enamine catalysis for intermolecular aldol reactions and by MacMillan introducing iminium catalysis for a Diels-Alder cycloaddition.¹⁵ In particular, the work of MacMillan for the first time defined the use of small organic molecules as a new field in asymmetric catalysis, coining the word “organocatalysis”

⁸ Y. Tu, Z. X. Wang, Y. Shi, *J. Am. Chem. Soc.*, **1996**, *118*, 9806.

⁹ S. E. Denmark, Z. Wu, C. M. Crudden, H. Matsuhashi, *J. Org. Chem.*, **1997**, *62*, 8288

¹⁰ D. Yang, Y. C. Yip, M. W. Tang, M. K. Wong, J. H. K. K. Cheung, *J. Am. Chem. Soc.*, **1996**, *118*, 491.

¹¹ M. S. Iyer, K. M. Gigstad, N. D. Namdev, M. Lipton, *J. Am. Chem. Soc.*, **1996**, *118*, 4910.

¹² M. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.*, **1998**, *120*, 4901.

¹³ E. J. Corey, M. J. Grogan, *Org. Lett.*, **1999**, *1*, 157.

¹⁴ B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.*, **2000**, *122*, 2395.

¹⁵ K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2000**, *122*, 4243.

and describing the different advantages related to this branch of research (i.e. the avoidance of inert atmosphere, absence of metals etc.). Furthermore, the same work anticipated that this new mode of substrate activation, induction and reactivity (iminium ion activation) could be generalised to a great deal of transformations. On the other hand, the intermolecular aldol reaction reported by List Barbas III and Lerner, followed shortly afterwards by the corresponding Mannich reaction,¹⁶ established the usefulness of even exceedingly simple natural compounds, such as proline, in promoting asymmetric reactions. The similar behaviour of a low molecular weight organic compound like proline to macromolecular catalytic antibodies was also a remarkable feature in these reports.¹⁷ Together with the work of Miller, who demonstrated that short oligopeptides sequences are able to efficiently catalyse reactions following the same mechanistic principles of enzymes,¹⁸ this analogy has served as a linchpin in the development of organic catalysts and reactions inspired from the biological world.

After these works there was, in fact, a fast development of this field and the number of publications increased dramatically in less than ten years.

¹⁶ B. List, *J. Am. Chem. Soc.*, **2000**, *122*, 9336.

¹⁷ B. List, *Tetrahedron*, **2002**, *58*, 5573.

¹⁸ S. J. Miller, G. T. Copeland, N. Papaioannou, T. E. Horstmann, E. M. Ruel, *J. Am. Chem. Soc.*, **1998**, *120*, 1629.

1.2 The Pool of Catalysts

The enormous efforts of many international groups during the last decade produced a large number of publications outlining the general modes of substrate activation, induction and reactivity. These generic activation modes describe how the catalysts are able to interact with the reagents and how they are able to transfer the chiral information. Herein a short overview is reported describing the principal catalytic systems developed, and the general modes of activation discovered in the last decade.

The first important area in organocatalysis involves catalysts able to activate the reagents through the formation of a covalent bond; this field encompasses enamine, iminium ion and nucleophilic catalysis.

1.2.1 Enamine Catalysis

Both enamine and iminium ion catalysis are based on the presence of a primary or secondary amine able to react with the reagent (a ketone or an aldehyde).¹⁹ In 2000 Barbas III, List and Lerner¹⁴ used enamine catalysis to functionalize carbonyl-containing compounds at the α -carbon. Based on the analogies with intermolecular aldol reactions catalysed by antibodies, wherein a lysine residue is essential for catalysis through the formation of an enamine intermediate with the aldol donor, they hypothesized that the amine containing catalyst, proline **4** in Table 1, could interact with a carbonyl substrate to form an enamine intermediate. Simultaneously, an electrophilic partner is activated through hydrogen bond of the acid. Because of the evident broad applicability of this mode a tremendous amount of research has been directed towards identifying new types of chiral enamine catalysts.²⁰

1.2.2 Iminium ion Catalysis

This kind of catalysis is based on the capacity of chiral amines to activate substrates in transformations usually catalyzed by Lewis acids. This concept is based on the hypothesis that the formation of iminium ions from α,β -unsaturated aldehydes and chiral amines, such as catalyst **7** in Table 1, could activate the α,β double bond toward nucleophilic attack.²¹

¹⁹ For a recent reviews see: P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem. Int. Ed.*, **2008**, *47*, 6238.


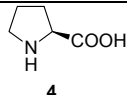
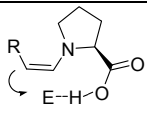
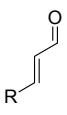
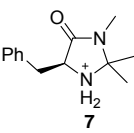
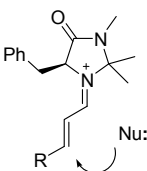

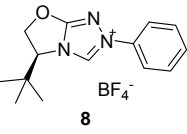
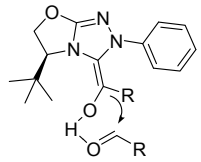
²⁰ S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.*, **2007**, *107*, 5471.

²¹ G. Lelais, D. W. C. MacMillan, *Aldrichim. Acta*, **2006**, *39*, 79; A. Erkkila, I. Majander, P. M. Pihko, *Chem. Rev.*, **2007**, *107*, 5416.

1.2.3 Nucleophilic Catalysis

Nucleophilic catalysis can involve a highly nucleophilic nitrogen, oxygen, phosphorous, sulfur or carbon atom for the formation of a covalent bond with a substrate. Although many examples involving nucleophilic heteroatoms are reported in literature,²² one of the most interesting branch is represented by carbene based molecules, which are again based on the enzymatic blueprints (thiamine containing enzymes).²³ The carbene compound is formed in situ by deprotonation of his triazole precursor **8** (Table 1); the resulting active species couple with an aldehyde molecule to generate an active adduct that subsequently reacts as nucleophile (umpolung reactivity). The reaction with an electrophilic specie, such as a second aldehyde molecule or an electron poor double bond, leads to the desired product and restores the catalytic cycle after catalyst release.

Table 1. Different typologies of covalent activation modes.

Catalysis	Substrates	Catalyst: example	Activation Mode
Enamin		 4	
Iminium		 7	
Nucleophilic		 8	

²² For examples see: a) S. E. Denmark, S. Ghosh, *Angew. Chem. Int. Ed.*, **2001**, *40*, 4759; b) G. C. Fu *Acc. Chem. Res.*, **2000**, *33*, 412; c) Y. Iwabuchi, M. Nakatami, N. Yokoyama, S. Hatakeyama *J. Am. Chem. Soc.*, **1999**, *121*, 10219; d) C. D. Papageorgiou, M. A. Cubillo de Dios, S. V. Ley, M. J. Gaunt *Angew. Chem. Int. Ed.*, **2004**, *43*, 4641; e) N. Bremeyer, S. C. Smith, S. V. Ley, M. J. Gaunt *Angew. Chem. Int. Ed.*, **2004**, *43*, 2681;

²³ D. Enders, T. Balensiefer, *Acc. Chem. Res.*, **2004**, *37*, 534

The second important area in organocatalysis involves weak interactions between the catalyst and the substrates. These interactions can be summarized in: hydrogen bond catalysis, Brønsted acid catalysis, Brønsted base catalysis and phase transfer catalysis.

1.2.4 Hydrogen Bond Catalysis

This kind of catalysis is based on well defined hydrogen-bonding interactions able to stabilize the transition state of the reactions.²⁴ As already mentioned for the first time in 1998, Jacobsen and Sigman introduced the thiourea **6** (Scheme 4) in a Strecker reaction obtaining the first highly enantioselective transformation based on a H-bond activation given by a thiourea H-bond donor.¹² Moreover, four years later, Jacobsen showed that the thiourea catalysts could be used for other synthetic reactions²⁵ launching this large and dynamic area. As represented in Table 2, catalyst **9** is able to enhance the electrophilicity of the substrate while the nucleophile is activated through a different hydrogen bond. The enantioselection is given in the transition state by this high ordered wire of directed weak interactions. Bifunctionality in the catalyst structure is thus essential for the generation of a highly ordered and geometrically defined transition state complex involving the catalyst coordinating both reagents (vide infra).

1.2.5 Brønsted Acid Catalysis²⁶

A more recently developed class of organocatalysts uses a phosphoric acid moiety combined with chiral binaphthyl systems to mediate organic reactions (Table 2). These catalysts, developed by Terada and Akiyama,²⁷ are strong acids ($pK_a < 1$) and very efficient activators of imines through protonation. For example Terada used catalyst **10** in the asymmetric addition of 2-methoxyfuran to *N*-Boc imines with good results in terms of yields and enantioselections.²⁸ Although coordination/activation is given by the strong pair between the acid catalyst and the basic substrate, also in this case coordination of both partners results essential for enantioselectivity.

²⁴ R. R. Knowles, E. N. Jacobsen, *Proc. Natl. Acad. Sci.*, **2010**, *107*, 20678; Z. Zhang, P. Schreiner, *Chem. Soc. Rev.*, **2009**, *38*, 1187; M. S. Taylor, E. N. Jacobsen, *Angew. Chem.*, **2006**, *118*, 1550; *Angew. Chem. Int. Ed.*, **2006**, *45*, 1520


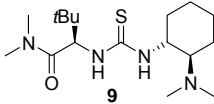
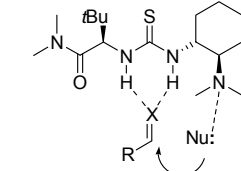

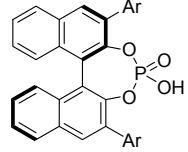
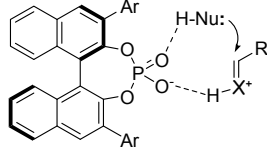

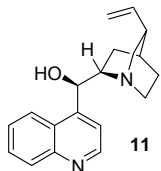
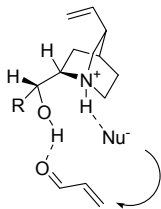
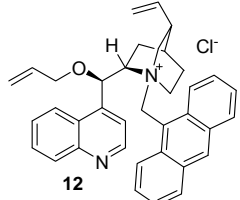
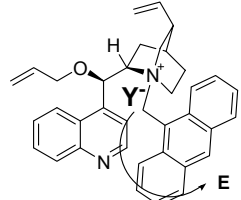
²⁵ A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.*, **2002**, *124*, 12964.

²⁶ For a recent review about chiral Brønsted catalysis see: T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.*, **2006**, *348*, 999

²⁷ D. Uraguchi, M. Terada *J. Am. Chem. Soc.*, **2004**, *126*, 5356-5357 T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe *Angew. Chem.*, **2004**, *116*, 1592-1594; *Angew. Chem. Int. Ed.*, **2004**, *43*, 1566-1568

²⁸ D. Uraguchi, K. Sorimachi, Terada, M. *J. Am. Chem. Soc.*, **2004**, *126*, 11804.

Table 2. Different typologies of activation modes involving weak interactions.

Catalysis	Substrates	Catalyst: example	Activation Mode
Hydrogen Bond	 X = O, NR ₁	 9	
Brønsted Acid	 X = O, NR ₁	 Ar = 3,5-dimesitylphenyl 10	
Brønsted Base		 11	
Phase Transfer	$\text{HY} \xrightarrow{\text{Base}} \text{Y}^-$	 12	

1.2.6 Brønsted Base Catalysis

Chiral bases are another very useful class of organocatalysts and *Cinchona* alkaloids are certainly the most representative members of this class.²⁹ A pioneering example was reported by Wynberg and Hiemstra in 1981; they used cinchonidine **11** in the addition of some thiophenol derivatives to cyclic α,β unsaturated ketones.³⁰ As shown in Table 2 the nucleophile is created in situ by deprotonation of his precursor. As previously reported in Brønsted acid catalysis, also in this kind of activation, the enantioselection is due to the strong ionic interaction between the catalyst and the substrate.

²⁹ For reviews, see: C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.*, **2009**, 38, 632; T. Marcelli, H. Hiemstra, *Synthesis*, **2010**, 1229

³⁰ H. Hiemstra, H. Wynberg *J. Am. Chem. Soc.*, **1981**, 103, 417.

1.2.7 Phase-Transfer Catalysis

The phase-transfer catalysis is a powerful method based on ion pair interactions between a nucleophilic anion and a positively charged catalyst, often an ammonium salt.³¹ One of the most important catalysts is the cinchonidine derived phase transfer catalyst **12**, independently developed by Corey and by Lygo and used for several transformations.³² As represented in Table 2, the substrate is deprotonated by an inorganic base, for example in aqueous phase; this ion can pair with the catalyst salt through an ion exchange and can be transported in the other phase (the organic phase) to find the reaction partner and react. The higher separation of charge between the catalyst and the substrate and its reduced hydration affect positively the reactivity of the system. The enantioselection is achieved with the steric control of the chiral catalyst on the subsequent reaction.

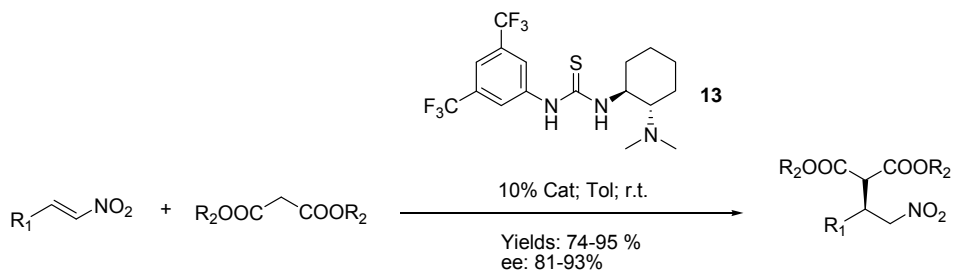
During the development of the different areas previously illustrated, emerged the important concept of the *bifunctional catalysis*.³³ This concept regards the capability of many catalysts in using different kinds of activation in a cooperative way, in order to achieve a highly ordered transition state in the reaction. For example, the structure of proline **4** (Table 1) combines a secondary amine moiety (enamine catalysis) with an acidic group (Brønsted acid catalysis). The phosphoric acid **10** (Table 2) can also be considered a bifunctional catalyst; it can, in fact, activate a carbonyl group or an imine with the Brønsted acid moiety, while the phosphoryl oxygen can coordinate/activate the nucleophile acting as a Lewis base and assisting proton-transfer processes through a relay mechanism. Albeit many catalysts can be considered bifunctional, the thiourea moiety, associated with different groups, resulted one of the most common and versatile motifs developed in this field. For example Takemoto and co-workers developed catalyst **13** for the addition of malonates to nitroolefins (Scheme 5).³⁴

³¹ For reviews, see: (a) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.*, **2007**, *46*, 4222. (b) Maruoka, K. *Org. Proc. Res. Dev.*, **2008**, *12*, 679.

³² (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.*, **1997**, *38*, 8595. (b) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.*, **1997**, *119*, 12414.

³³ L. Bernardi, F. Fini, M. Fochi, A. Ricci *Chimia*, **2007**, *61*, 224.

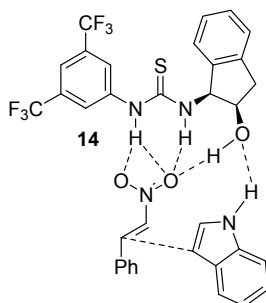
³⁴ T. Okino, Y. Hoashi, Y. Takemoto *J. Am. Chem. Soc.*, **2003**, *125*, 12672.



Scheme 5

In this case the thiourea **13** can deprotonate the malonate with the tertiary amine and activate the nitro group with the thiourea favouring the nucleophilic attack on the nitroolefin.

Another remarkable example of bifunctional catalysis was introduced by Ricci and co-workers when they developed the Friedel-Crafts alkylation of indoles and nitroalkenes with catalyst **14**.³⁵ Scheme 6 represent the proposed the transition state of the reaction in which the catalyst can direct the reaction path with the cooperative interaction of the two active site.



Scheme 6

³⁵ R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci *Angew. Chem. Int. Ed.*, **2005**, *44*, 6576.

1.3 The Natural Chiral Pool in Organocatalysis

A huge number of different structures has been investigated in order to obtain new catalytic systems. The achievement of molecules able to transfer their chirality, obtained through synthetic procedures, laid the basis for many enantioselective procedures and for the development of an important branch of both metallorganic and organic catalysis. The possibility to synthesize both the enantiomers and the high modularity of these structures outline the most important advantages. However, several synthetic steps are often necessary in order to obtain the catalytic structure. Furthermore, chiral resolving agents have to be used for the resolution of racemic mixtures.

For these reasons one of the main route developed for the design of structures presenting enantioselective catalytic activity involves molecules from the natural chiral pool. Nature, in fact, provided the chemists with a large number of different structures rich of functional groups, in enantiopure form. Among this pool of structures, three main classes have been found to be particularly suitable in catalysis, for their ready availability and low cost: *cinchona* alkaloids, aminoacids and sugars.

1.3.1 Cinchona Alkaloids³⁶

Cinchona alkaloids are a large class of compounds extracted from the bark of *Cinchona ledgeriana*. This tree is cultivated above 1400 m in equatorial climatic zones, between Africa, Latin America and Indonesia (isle of Java). In Figure 1 are represented the most common structures: quinine (QN), quinidine (QD), cinchonidine (CD), cinchonine (CN).

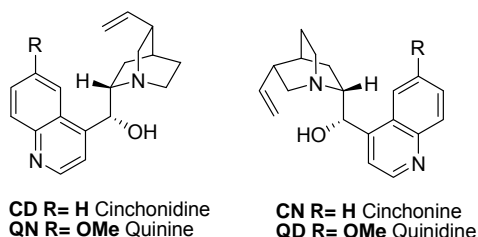


Figure 1

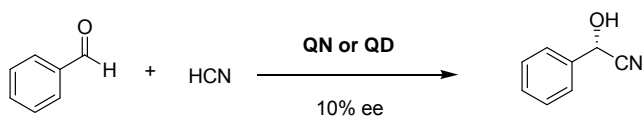
Approximately 700 tons of cinchona alkaloids are extracted annually and nearly half of it is used in the food and beverages industry as a bitter additive.³⁷ The other major use of these alkaloids, especially quinine and quinidine, deals with medicine since they are respectively an anti malarial drug and a cardiac depressant.

³⁶ Cinchona Alkaloids in Synthesis and Catalysis, Ligands, Immobilization and Organocatalysis, C. E. Song, WILEY-VCH, Weinheim, 2009.

³⁷ a) D. C. McHale *The Biologist* **1986**, 33, 45; b) F. Eiden *Pharmazie in unserer Zeit*, **1998**, 27, 257; c) P. M. Dewick *Medicinal Natural Products*, John Wiley & Sons, Chichester, New York, **1997**, 335; d) J. Herrmann *Pharm. Ztg.*, **2001**, 146, 1486.

For the first time Pasteur in 1853 identified the important role of these alkaloids in organic chemistry with the discovery of their potential as resolving agents in the resolution of racemates through crystallization of diastereomeric salts.³⁸ Today many processes involve *Cinchona* alkaloids as resolving agents.³⁹

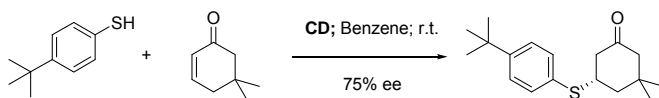
The most interesting application of these alkaloids in organic chemistry derives from their role in many enantioselective organocatalytic transformations. The first example in asymmetric catalysis was published by Breiding and Fiske⁴⁰ in 1912. They demonstrated that pseudoenantiomeric quinine and quinidine could catalyze the hydrocyanation of aldehydes (Scheme 7). The products obtained were optically active with opposite chirality but the enantiomeric excess were poor (<10%) yet reproducible.



Scheme 7

Another milestone in *Cinchona* alkaloid catalyzed reactions is the *O*-Acetyl quinine catalysed methanolysis of phenylmethylketene **1** to (–)- α -phenyl methylpropionate **3** with 74 % ee, disclosed by Pracejus et al and described in Scheme 1 in the first part of this introduction.⁵

In the late 1970s and 1980s Wynberg enlarged the range of applicability of *Cinchona* alkaloids in organocatalysis demonstrating that this class of catalysts could be highly versatile for a broad spectrum of reactions. A remarkable example was the addition of thiophenols on cyclohexenones, as reported in Scheme 8.³⁰



Scheme 8

Another important advance in this field was given in the 1990s when *Cinchona* alkaloids derivatives were used in a phase transfer alkylation of glycine derivatives,⁴¹ and in the Sharpless asymmetric dihydroxylation.⁴²

Since the development of the concept of organocatalysis in 2000, a great development of highly stereoselective reactions involving catalysts derived from cinchona alkaloids

³⁸ (a) L. Pasteur, *Acad. Sci.*, **1853**, 37, 162; (b) L. Pasteur, *Liebigs Ann. Chem.*, **1853**, 88, 209.

³⁹ (a) P. Newman, *Optical Resolution Procedures for Chemical Compounds: Acids*, vol. 2, *Optical Resolution Information Center*, Manhattan College, Riverdale, NY, **1981**, 7; (b) J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates and Resolutions*, John Wiley & Sons, Inc., New York, **1981**, 254; (c) D. Kozma, *Handbook of Optical Resolutions via Diastereomeric Salts*, CRC Press, Boca Raton, FL, **2002**.

⁴⁰ G. Breiding, P. S. Fiske *Biochem. Z.*, **1912**, 46, 7.

⁴¹ For a review, see: M. J. O'Donnell *Acc. Chem. Res.*, **2004**, 37, 506.

⁴² For a review, see: H.C. Kolb, M. S. Van Nieuwenhze, K. B. Sharpless *Chem. Rev.*, **1994**, 94, 2483.

occurred.^{29,36} For these remarkable results *Cinchona* alkaloids are nowadays recognised as a privileged class of chiral catalyst.⁴³

The key for their successful use in organocatalysis derives from the easy derivatization of the main structure and the presence of different functional groups. The structure of the four *Cinchona* alkaloids can be divided into three different parts: the quinoline ring, the 1,2 amino alcohol subunit and the quinuclidine moiety (Figure.2)

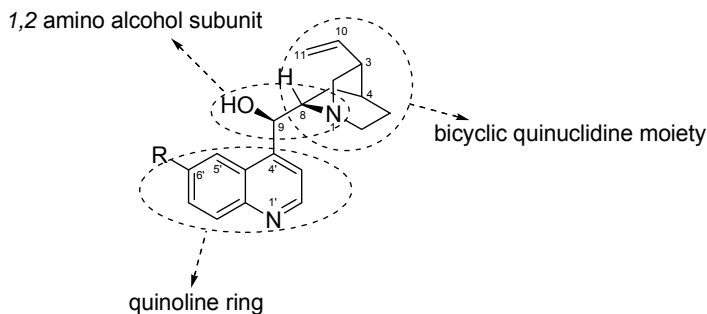


Figure 2

The structure contains five stereogenic centers presenting also a chiral nitrogen group; since the 1,2-amino-alcohol subunit is usually responsible for the catalytic activity, the enantioselection of the products depends on the configuration of these chiral centers. Quinine and quinidine as well cinchonidine and cinchonine present opposite absolute configuration at these centres (see Figure 1); for this reason often these pairs of diastereoisomers act as enantiomers and are named pseudoenantiomers (or quasienantiomers). Furthermore, the structure reported in Figure 2 presents two different active sites: the tertiary amino group, responsible for base/nucleophilic activation, and the secondary alcoholic group, capable of acid/hydrogen-bond activation.

Concerning the functionalization, the structure presents different sites for simple selective transformations as represented in Figure 3.

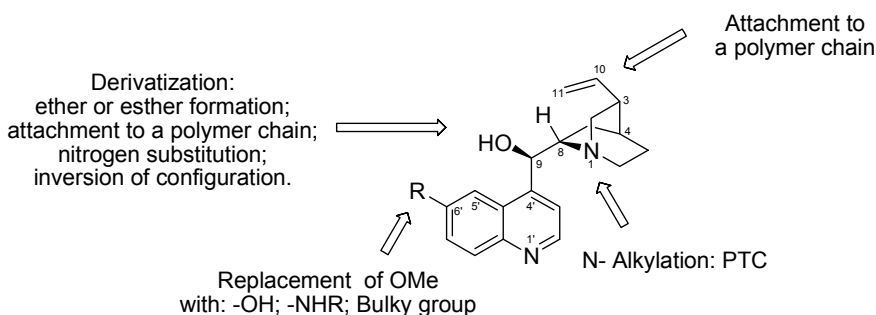


Figure 3

⁴³ T. P. Yoon, E. N. Jacobsen *Science*, **2003**, 299, 1691.

The secondary 9-hydroxy group can be easily derivatized or replaced by different groups, delivering at this position ethers, esters, ureas, amides, free amino group moieties and so on. Some of these transformations are concomitant with the inversion of configuration of the stereocenter. Also the 6¹-methoxy group can be readily manipulated giving a free phenolic OH group, or even substituted with a nitrogen functionality such as (thio)urea moieties.

Even more important is the possibility to alkylate the tertiary nitrogen in order to obtain a quaternary chiral ammonium salt, valuable in phase-transfer catalysis. Moreover, some sites such as the quinuclidinic double bond or the 9-hydroxy group, are suitable for the anchoring of the catalyst on a solid support in order to obtain an heterogeneous catalyst.

1.3.2 Amino Acids:

In living organisms natural amino acids constitute the building blocks of protein and enzymes. Their application in human activities is extremely various and comprehensive, ranging from animal feed additives, flavour enhancers and active principles in medical treatments. The three current general approaches for the production of the twenty natural amino acids are direct chemical synthesis, fermentation and bioconversion. The choice between the possible processes depends on available technology, cost of raw material, market prices and sizes, cost of running fermentation versus synthesis, and the environmental impact of the process itself. Table 3 illustrates the estimated global production of natural amino acids in 1996.⁴⁴ The synthetic processes have not changed very much since then, but the amounts increased at a rate of about 2-5% per year.

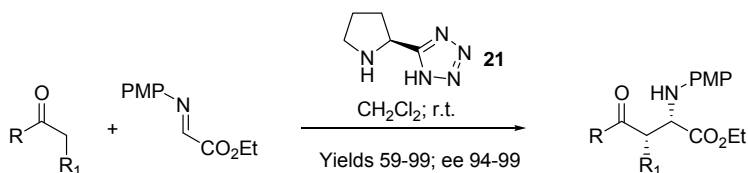
Table 3. Estimated global production of amino acids in 1996

Amino Acid	Amount (ton/y)	Amino Acid	Amount (ton/y)
<i>L-Glutamate</i>	1000000	<i>L-Arginine</i>	1200
<i>D, L Methionine</i>	350000	<i>L-Tryptophane</i>	500
<i>L-Lysine</i>	250000	<i>L-Valine</i>	500
<i>Glycine</i>	22000	<i>L-Leucine</i>	500
<i>L-Phenylalanine</i>	8000	<i>L-Isoleucine</i>	400
<i>L-Aspartic Acid</i>	7000	<i>L-Histidine</i>	400
<i>L-Threonine</i>	4000	<i>L-Proline</i>	350
<i>L-Cysteine</i>	1500	<i>L-Serine</i>	200
<i>D,L-Alanine</i>	1500	<i>L-Tyrosine</i>	120
<i>L-Glutamine</i>	1300	<i>Tot.</i>	1649470

⁴⁴ M. Ikeda, *Adv. Biochem. Eng. Biotech.*, **2003**, 79, 1

Because of their ready availability, these compounds have been used as valuable chiral building blocks in synthetic transformations. The catalytic activity of natural amino acids as well their semi-synthetic derivatives have been tested in many important reactions such as aldol and Mannich reactions, Michael additions, cycloadditions etc. leading to the formation of a wide field of research.

Concerning metal-free approaches, the main role in this field is played by proline **4** and its derivatives. The pyrrolidine ring, in fact, confers conformational rigidity to the structure while the carboxylic moiety can be exploited as a secondary catalytic centre for bifunctional catalysis or can be easily modified for the formation of a large number of catalysts. Among the derivatives of proline the most remarkable examples are the proline tetrazole **21** derivative introduced by Ley⁴⁵ and silyl prolinol derivatives such **22** introduced by Jørgensen and Hayashi.⁴⁶ Catalyst **21** was applied in a Mannich reaction as a version of proline more soluble in organic solvents (Scheme 9).

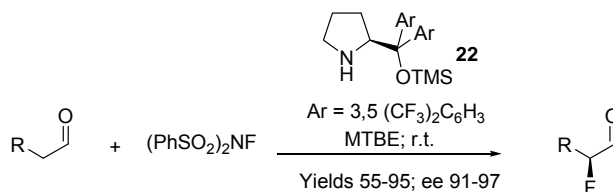


Scheme 9

As represented in Scheme 10, Jørgensen developed catalyst **22** for the enantioselective formation of stereogenic carbon-fluorine centers. In this case, the secondary amine drove the reaction through enamine catalysis while the excellent values of enantioselection were obtained due to the highly hindered moiety. The high value of catalyst **21** and **22** had been subsequently confirmed by a huge number of publications involving these catalysts in different kind of organocatalytic transformations providing usually excellent results in terms of yield and enantioselection.

⁴⁵ a) A. J. A. Cobb, D. M. Shaw, S. V. Ley *Synlett*, **2004**, 558. b) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley *Org. Biomol. Chem.*, **2005**, *3*, 84. c) K. Knudsen, C. E. T. Mitchell, S. V. Ley *Chem. Commun.*, **2005**, 66. d) S. Kumarn, D. M. Shaw, S. V. Ley *Chem. Commun.*, **2006**, 3211

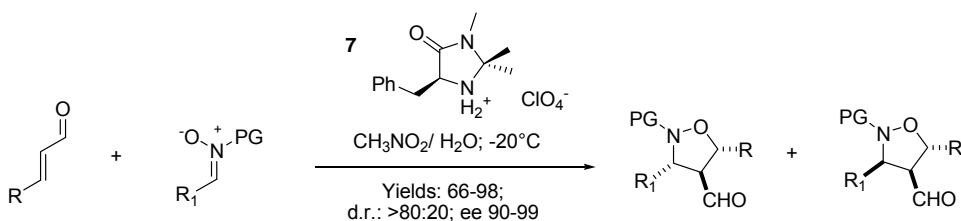
⁴⁶ a) M. Marigo, D. Fielenbach, A. Braunton, A. Kjærsgaard, K. A. Jørgensen *Angew. Chem. Int. Ed.*, **2005**, *44*, 3703. b) J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen *J. Am. Chem. Soc.*, **2005**, *127*, 18296 and references cited therein. c) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.*, **2005**, *44*, 4212.



Scheme 10

Other amino acids, such as alanine, valine, aspartate, isoleucine and serine, have been applied in direct asymmetric aldol and Mannich reactions for the formation of products in high yields and up to 99% ee.⁴⁷ The main advantage of using primary amino acids over proline was observed in all the reactions involving bulky substrates. In these cases, in fact, a less hindered primary amino acid could be more effective in comparison with proline.

The most representative catalyst derived from a primary amino acid is the imidazolidinone **7** developed by MacMillan.^{15a} This molecule, obtained from L-phenylalanine, was introduced in the asymmetric 1,3 dipolar cycloaddition between α,β unsaturated aldehydes and nitrones (Scheme 11).



Scheme 11

As previously reported, this catalyst is able to lower the LUMO of the double bond by forming an intermediate iminium ion, promoting the dipolar cycloaddition reaction in high yields and excellent enantioselection. For this reason catalyst **7** is nowadays broadly applied in many iminium-ion involving reactions.

Another important class of catalysts derived from natural amino acids is constituted by peptides.⁴⁸ The innovation introduced with this field consists in the possibility to have a large structural and functional diversity achieved by connecting amino acids with different residues while conserving the advantages of a small molecule catalyst. I will describe, in Session 3, the use of peptides as valuable catalysts for C-C bond formation reactions. In particular, I will report the application of small tri-peptides in Michael addition reactions of aldehydes to nitroolefins.

⁴⁷ a) A. Cordova, W. Zou, I. Ibrahim, E. Reyes, M. Engqvist, W.-W. Liao, *Chem. Commun.*, **2005**, 3586; b) A. Cordova, W. Zou, P. Dziedzic, I. Ibrahim, E. Reyes, Y. Xu, *Chem.-Eur. J.*, **2006**, *12*, 5383; c) A. Bassan, W. Zou, E. Reyes, F. Himo, A. Cordova, *Angew. Chem. Int. Ed.*, **2005**, *44*, 7028; d) I. Ibrahim, W. Zou, M. Engqvist, Y. Xu, A. Cordova, *Chem. Eur. J.*, **2005**, *11*, 7024.

⁴⁸ S. J. Miller, *Acc. Chem. Res.*, **2004**, *37*, 601; H. Wennemers, *Chem. Commun.*, **2011**, *47*, 12036.

1.3.3 Sugars⁴⁹

Carbohydrates constitute the large renewable part of biomass produced by living organisms: for this reason they are readily available, abundant and very cheap substances. In chemistry they have been widely used as chiral templates in many synthetic processes for high valuable products. The presence of different hydroxy groups, potentially able to coordinate metals and/or to undergo different synthetic manipulations, together with the chiral scaffold made this class of molecules suitable as chiral ligands. Many metals such as Zn, Ti, Ga, Rh, etc were complexed with different carbohydrate derived ligands and applied for numerous asymmetric reaction like Reformatsky, hydrogenation process and alkylation of aldehydes.⁵⁰

Concerning the application of carbohydrates in organocatalysis the first example were the fructose based ketones (Figure 4) introduced by Shi and Denmark for the organocatalytic enantioselective epoxidation of alkenes (Scheme 3).⁸

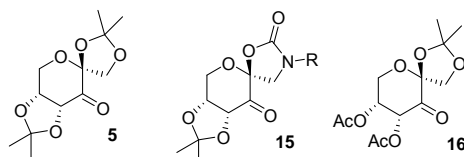


Figure 4

Catalyst **5** gave excellent results in the epoxidation of *trans*-disubstituted and trisubstituted olefins, including hydroxyalkenes, dienes, enynes and enolethers. Replacing the spiro dioxolane with a spiro oxazolidinone moiety (Catalyst **15**), Shi and co-workers could expand the scope to a wide number of *cis*-olefins. Furthermore, the simple modification of the protecting groups (Catalyst **16**), provided excellent results with the less reactive double bond of α,β -unsaturated carbonyl compounds.⁵¹

Another important application of sugar derived scaffolds in organocatalysis derives from coupling a sugar-derived moiety with different chiral or non chiral residues. In Figure 5 some examples of catalysts constituted by a sugar scaffold coupled with different thioureas are reported.

⁴⁹ T. Lehnert, G. Ozuduru, H. Grugel, F. Albrecht, S. M. Telligmann, M. M. K. Boysen, *Synthesis*, **2011**, 17, 2685.

⁵⁰ For representative examples see: (a) D. P. G. Emmerson, W. P. Hems, B. G. Davis, *Tetrahedron Asymmetry*, **2005**, 16, 213; (b) R. Selke, M. Ohff, A. Riepe, *Tetrahedron*, **1996**, 52, 15079; (c) D. P. G. Emmerson, R. Villard, C. Mugnaini, A. Batsanov, J. A. K. Howard, W. P. Hems, R. P. Tooze, B. G. Davis, *Org. Biomol. Chem.*, **2003**, 1, 3826.

⁵¹ For a review, see: O. A. Wong, Y. Shi, *Chem. Rev.*, **2008**, 108, 3958.

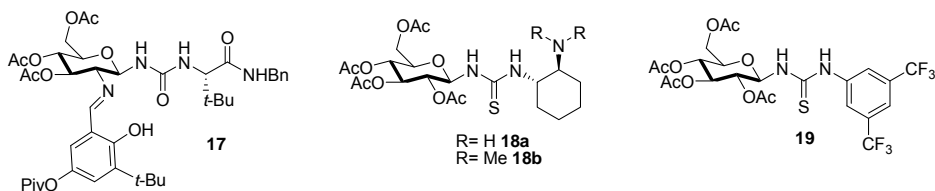
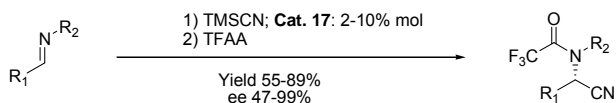


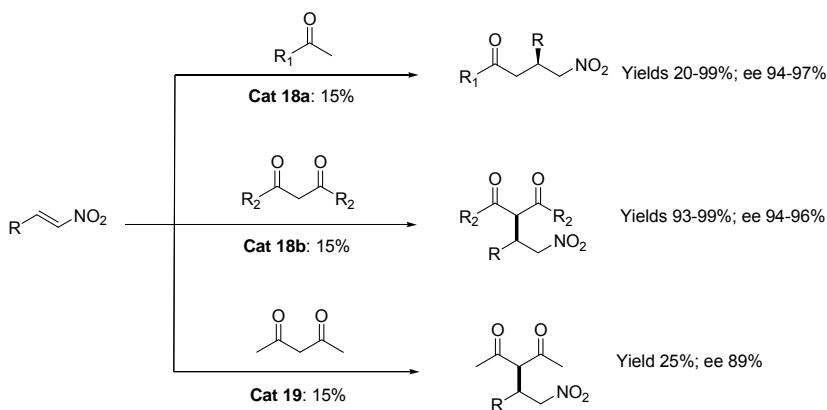
Figure 5

Kunz and co-workers, for example, introduced Catalyst **17** in a Strecker reaction (Scheme 12).⁵² The products obtained show valuable results in terms of yields and enantioselections. This promising result demonstrated the effective validity of a cooperation between these two residues and constituted the groundwork for the development of subsequent catalysts.



Scheme 12

Ma and co-workers developed the thiourea **18a**⁵³ and **18b**⁵⁴ for the asymmetric 1,4 additions of carbon nucleophiles on Michael acceptors. They introduced a 1,2-diaminocyclohexane moiety as an additional chiral element. While catalyst **18a** promoted the reaction through an enamine catalytic cycle, catalyst **18b** employs the tertiary amine group for base catalysis (Scheme 13).



Scheme 13

In both cases Ma and co-workers reported that the sense of stereoselection was exclusively determined by the configuration of the chiral diamine. Albeit the catalytic activity of the molecule looked like to be centered in the thiourea/dienamine cooperation, Benaglia⁵⁵ demonstrated the role of the sugar scaffold performing the 1,4-addition reaction with thiourea

⁵² C. Becker, C. Hoben, H. Kunz, *Adv. Synth. Catal.*, **2007**, *349*, 417.

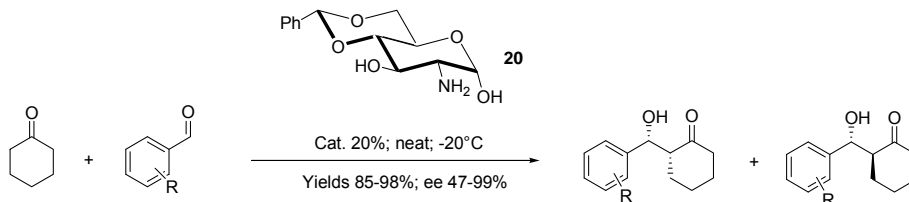
⁵³ K. Liu, H.-F. Cui, J. Nie, K.-Y. Dong, X.-J. Li, J.-A. Ma, *Org. Lett.*, **2007**, *9*, 923.

⁵⁴ X.-J. Li, K. Liu, H. Ma, J. Nie, J.-A. Ma, *Synlett*, **2008**, *20*, 3242.

⁵⁵ A. Puglisi, M. Benaglia, L. Raimondi, *Org. Biomol. Chem.*, **2011**, *9*, 3295.

19. In this case, in fact, catalyst **19**, without any other chiral groups, gave the product with 89% ee. Yields were however only modest. This result demonstrated the essential role of the carbohydrate unit in the enantioselection.

Another important improvement in carbohydrates derived organocatalysis concerns the development of glucosamine based catalysts for the direct asymmetric aldol reaction between ketones and aryl aldehydes.⁵⁶ The interest for this molecule regards the presence of a chiral primary amine moiety, responsible for enamine catalysis, associated with different hydroxyl groups easy to manipulate.



Scheme 14

The remarkable result showed in Scheme 14 is another example of the possibility for carbohydrates-derived organocatalysts to promote a highly enantioselective reaction without any contribution of other chiral components.

All the examples previously reported demonstrated the potential of carbohydrates-derived molecules in catalysis. The limitations of this approach are related to the necessity to obtain stable catalytic structures avoiding the equilibrium between open and closed forms, and the many functional groups (hydroxyl moieties) which can interact with the substrates through H-bonds, giving several possible transition state intermediates. The solution adopted in all the cases reported is the appropriate selective protection of sensible groups and the stabilization of the closed form.

The use of polymeric heterogeneous carbohydrates constitute a different approach, which avoids the necessity of difficult protecting steps in the achieving of the catalytic species. In Chapter 4 a detailed investigation concerning the use of chitosan in organocatalysis is described; the reported results demonstrate the effectiveness of this completely natural polymer in highly enantioselective reactions.

⁵⁶ J. Agarwal, R. K. Peddinti, *J. Org. Chem.*, **2011**, 76, 3502.

Chapter 2

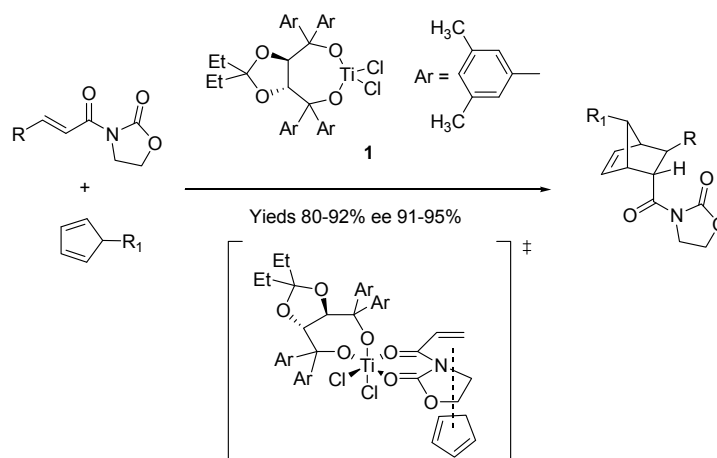
Homogeneous Catalysis Promoted by *Cinchona* alkaloid derivatives

2.1 Asymmetric Diels-Alder Reaction of Vinylindoles¹

2.1.1 Introduction

The Diels-Alder reaction constitutes one of the most important transformations in organic chemistry for the formation of cyclic and polycyclic structures. It occurs between a conjugated diene and a double bond, named dienophile, to form a substituted cyclohexene system. Since the Diels-Alder reaction not only leads to an increase in molecular complexity but also produces synthetically versatile structures prone to additional manipulations giving increasing complexity, catalytic asymmetric variants of these [4+2] cycloadditions have been reported to be valuable strategies for the total synthesis of bioactive natural products.²

A traditional approach to this kind of reaction involves its promotion by Lewis acids. The theoretical interpretation resides in a donor-acceptor interaction between the dienophile and the catalyst in order to lower the energy of the frontier orbitals (LUMO) of the former. The direct consequence is the decrease of the separation between the HOMO of the diene and the LUMO of the dienophile with the stabilization of the transition state of the reaction. In Scheme 1 is reported a representative example in which the Lewis acid **1** is able to perform the reaction through a bidentate activation of the dienophile while no apparent coordination involves the diene.³



Scheme 1

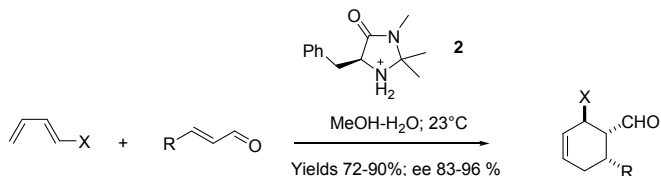
Albeit the efficient catalytic action provided by metallorganic molecules, it was also demonstrated that Diels-Alder cycloaddition reactions can also be performed under metal-free

¹ (a) C. Gioia, A. Hauville, L. Bernardi, F. Fini, A. Ricci, *Angew. Chem. Int. Ed.*, **2008**, *47*, 9236; (b) C. Gioia, L. Bernardi, A. Ricci, *Synthesis*, **2010**, *1*, 161.

² For recent reviews, see: K. C. Nicolau, S. A. Snyder, T. Montagnon, G. Vasilikogiannakis, *Angew. Chem. Int. Ed.*, **2002**, *41*, 1668; E. J. Corey, *Angew. Chem. Int. Ed.*, **2002**, *41*, 1650; K. -I. Takao, R. Munsaka, K. -I. Tadano, *Chem. Rev.*, **2005**, *105*, 4779.

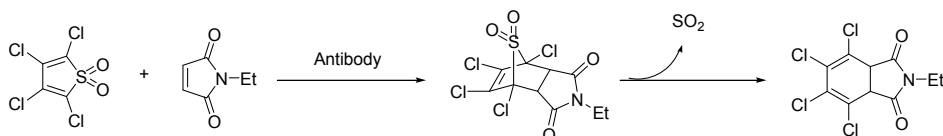
³ E. J. Corey, Y. Matsumura, *Tetrahedron Lett.*, **1991**, *32*, 6289.

catalysis. In the last decade, the enantioselective Diels-Alder reaction promoted by organocatalysts has in fact attracted great attention. Many important organocatalytic reactions involve ammonium salts of secondary amine action through an iminium-ion mode of action. As previously reported in Section 1, MacMillan demonstrated that catalyst **2** could perform a highly enantioselective organocatalytic Diels-Alder reaction activating the dienophile through an iminium-ion interaction (Scheme 2).⁴



Scheme 2

Some recent studies of various secondary metabolites suggested the possibility also for Nature to make use of Diels-Alder reaction via enzymatic catalysis.⁵ Even if the discovery of a Diels-Alderase remained elusive until very recently,⁶ many cycloaddition reactions have been performed by biomolecules such as enzymes,⁷ rybozymes,⁸ and deoxyribozymes.⁹ For the first time in 1989, Hilvert reported the non-asymmetric catalysis of a Diels-Alder cycloaddition promoted by an antibody (Scheme 3).¹⁰



Scheme 3

The catalytic action provided by biological molecules concerns the stabilization of the transition state of the Diels-Alder reaction through directed interactions of the catalyst with either the diene and the dienophile. Since the structure of the products resembles the transition state of the reaction, a strong product inhibition of the catalysis is expected. In their work Hilvert and co-workers overcame this problem with the degradation of the product of cycloaddition and the subsequent loss of SO₂. As the final product does not resemble the transition state, the product inhibition resulted minimized.

⁴ K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2000**, *122*, 4243.

⁵ W. L. Kelly, *Org. Biomol. Chem.*, **2008**, *6*, 4483.

⁶ H. J. Kim, M. W. Ruzsyczky, S.-h. Choi, Y.-n. Liu and H.-w. Liu, *Nature*, **2011**, *473*, 109.

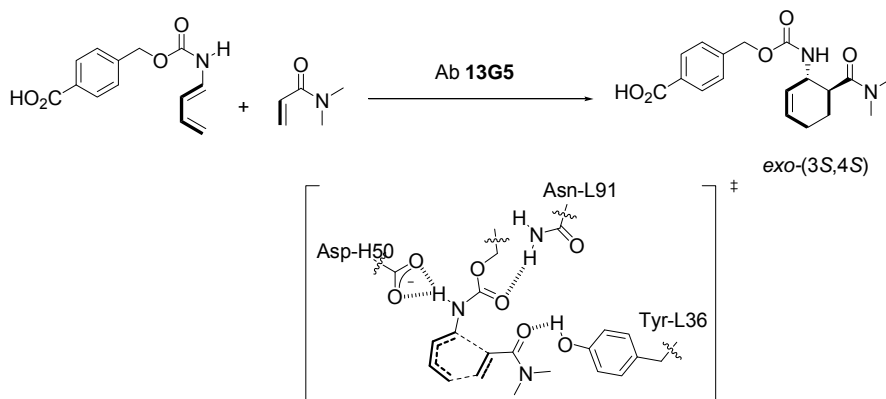
⁷ R. M. Williams, E. M. Stocking, *Angew. Chem. Int. Ed.*, **2003**, *42*, 3078

⁸ (a) T. M. Tarasow, S. L. Tarasow, B. E. Eaton, *Nature*, **1997**, *389*, 54; (b) B. Seelig, A. Jaschke, *Chem. Biol.*, **1999**, *6*, 167.

⁹ M. Chandra, S. K. Silverman, *J. Am. Chem. Soc.*, **2008**, *130*, 2936.

¹⁰ D. Hilvert, K. W. Hill, K. D. Nared, M. -T. Auditor, *J. Am. Chem. Soc.*, **1989**, *111*, 9261.

Another remarkable example demonstrated how the hydrogen bond interactions performed by antibody **13G5** in the Diels-Alder reaction between *N*-carbamoyl-1-azadienes and *N,N*-dimethylacrylamide are essential for the catalytic activity. (Scheme 4)¹¹



Scheme 4

As exemplified in Scheme 4, in the transition state, the Brønsted acidic phenol of **TyrL36** residue stabilizes the negative charge at the acrylamide, while the carboxylate of **AspH50** binds the positively charged carbamate proton. This example elucidate how antibodies can catalyse Diels-Alder reactions by simultaneously raising the HOMO of the diene and lowering the LUMO of the dienophile through a bifunctional acid-base mechanism. This binding is particularly relevant in the transition state, wherein charges are much more pronounced and thus interactions are strengthened.

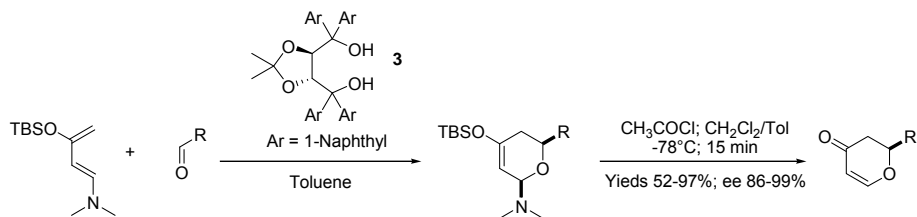
Often unconsciously, the same concept has been used in the past few years in several organocatalytic asymmetric Diels-Alder reactions.¹² In 2003 Schreiner could demonstrate that achiral thiourea derivatives could activate α , β -unsaturated compounds in [4+2] cycloadditions.¹³ Shortly after Rawal reported the first successful development of enantioselective hydrogen-bonding catalyzed cycloaddition reactions employing TADDOL (catalyst **3**) in hetero-Diels-Alder reactions (Scheme 5)¹⁴

¹¹ (a) J. T. Yli-Kauhala, J. A. Ashley, C.-H. Lo, L. Tucker, M. M. Wolfe and K. D. Janda, *J. Am. Chem. Soc.*, **1995**, *117*, 7041; (b) V. F. Gouverneur, B. de Pasqual-Teresa, B. Beno, K. D. Janda and R. A. Lerner, *Science*, **1993**, *262*, 204.

¹² (a) A. Moyano and R. Rios, *Chem. Rev.*, **2011**, *111*, 4703; (b) P. Merino, E. Marqués-López, T. Tejero and R. P. Herrera, *Synthesis*, **2010**, 1; For a review on bioinspired organocatalytic asymmetric reactions see: A. Ricci, L. Bernardi, M. Fochi, M. Franchini, *Org. Biomol. Chem.*, **2012**, DOI: 10.1039/c2ob07037e

¹³ P. R. Schreiner, A. Wittkopp, *Org. Lett.*, **2002**, *4*, 217; P. R. Schreiner, A. Wittkopp, *Chem. Eur. J.*, **2003**, *9*, 407.

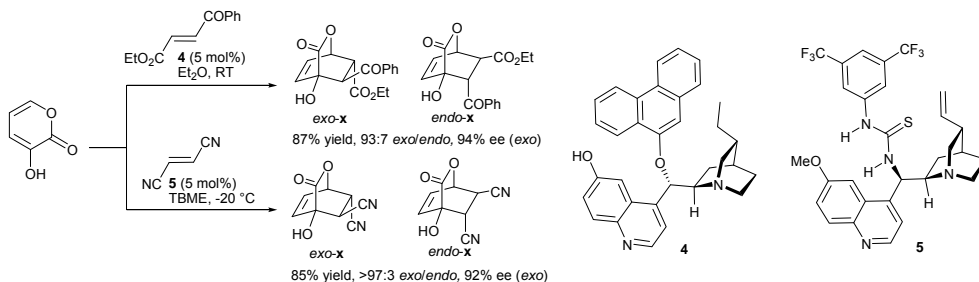
¹⁴ Y. Huang, A.K. Unni, A.N. Thadani, V. H. Rawal, *Nature*, **2003**, *424*, 146; A. Unni, N. Takenaka, H. Yamamoto, V. H. Rawal, *J. Am. Chem. Soc.*, **2005**, *127*, 1336.



Scheme 5

This achievement demonstrated, for the first time, the possibility for hydrogen bond organocatalysts to offer interesting perspectives in the developments of previously unknown cycloaddition reactions.

Subsequently one of the most synthetically useful enantioselective protocols appeared in literature was introduced by Deng and co-workers for the Diels-Alder reaction of 3-hydroxy-2-pyrones catalyzed by *Cinchona* alkaloids derivatives (Scheme 6).¹⁵



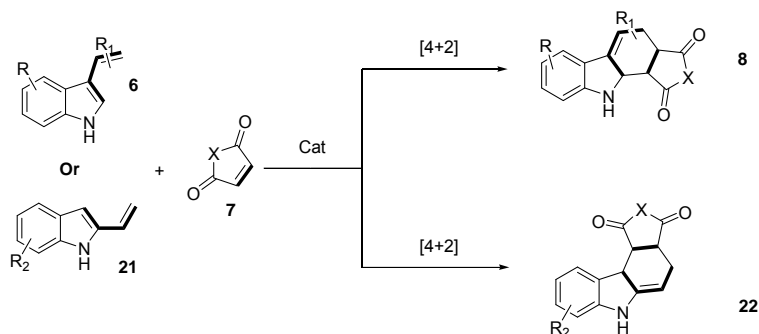
Scheme 6

The reported protocol is effective for several diene-dienophile combinations, encompassing different ketones and nitrile activated double bonds although the catalytic structure needs to be tuned depending on the class of substrate used. The enormous potential associated with this kind of activation led us to become interested in the development of new synthetic transformations involving Diels-Alder reaction promoted by hydrogen-bonding bifunctional organic catalysts.

In this chapter is reported the development of a catalytic asymmetric Diels-Alder reaction involving 2- and 3-vinylindoles **21** and **6** with various representative dienophiles **7** (Scheme 7), highlighting also the different behaviour occurring between these systems under hydrogen-bond-driven organocatalysis. It has long been recognized, in fact, that vinylindoles can participate in Diels-Alder reactions with the HOMO of their electron-rich diene system.¹⁶ However, no catalytic asymmetric variants of these transformations were reported before our work.

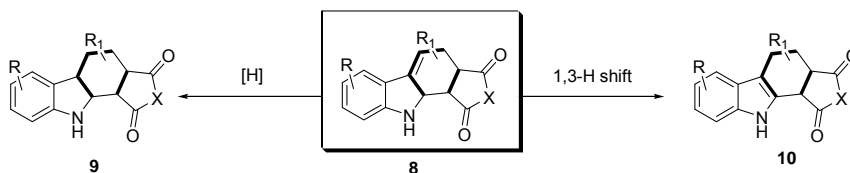
¹⁵ Y. Wang, H. Li, Y.-Q. Wang, Y. Liu, B. M. Foxman and L. Deng, *J. Am. Chem. Soc.*, 2007, **129**, 6364.

¹⁶ For reviews, see: a) U. Pindur, *Heterocycles*, **1998**, 27, 1253; b) R. J. Sundberg, in *Indoles*, Academic Press, London, **1996**, p. 156. Recent examples: c) M. Bleile, H.-H. Otto, *Monatsh. Chem.*, **2005**, 136, 1799; d) M. Bleile, T. Wagner, H.-H. Otto, *Helv. Chim. Acta*, **2005**, 88, 2879; e) W. E. Noland, G.-M. Xia, K. R. Gee, M. J. Konkel, M. J. Wahlstrom, J. J. Condoluci, D. L. Rieger, *Tetrahedron*, **1996**, 52, 4555.



Scheme 7

This study was also motivated by the synthetic versatility of the [b]annellation of indole nucleus for the construction of azapolyheterocycles (**8** and **22**). The synthetic value of these polycyclic compounds is given by their straightforward modifications giving access to a wide class of cycloadducts such as tricyclic indolines **9** and tetrahydrocarbazoles **10**, which are common scaffolds in a variety of natural and/or biologically active alkaloids (Scheme 8).¹⁷



Scheme 8

¹⁷ a) M. Hesse, *Alkaloids, Nature Curse or Blessing?*, Wiley-VCH, New York, **2002**; b) J. E. Saxton, *Nat. Prod. Rep.* **1997**, *14*, 559; c) J. Bonjoch, D. Sol, *Chem. Rev.*, **2000**, *100*, 3455; d) G. Abbiati, V. Canevari, D. Facoetti, E. Rossi, *Eur. J. Org. Chem.*, **2007**, 517, and references therein.

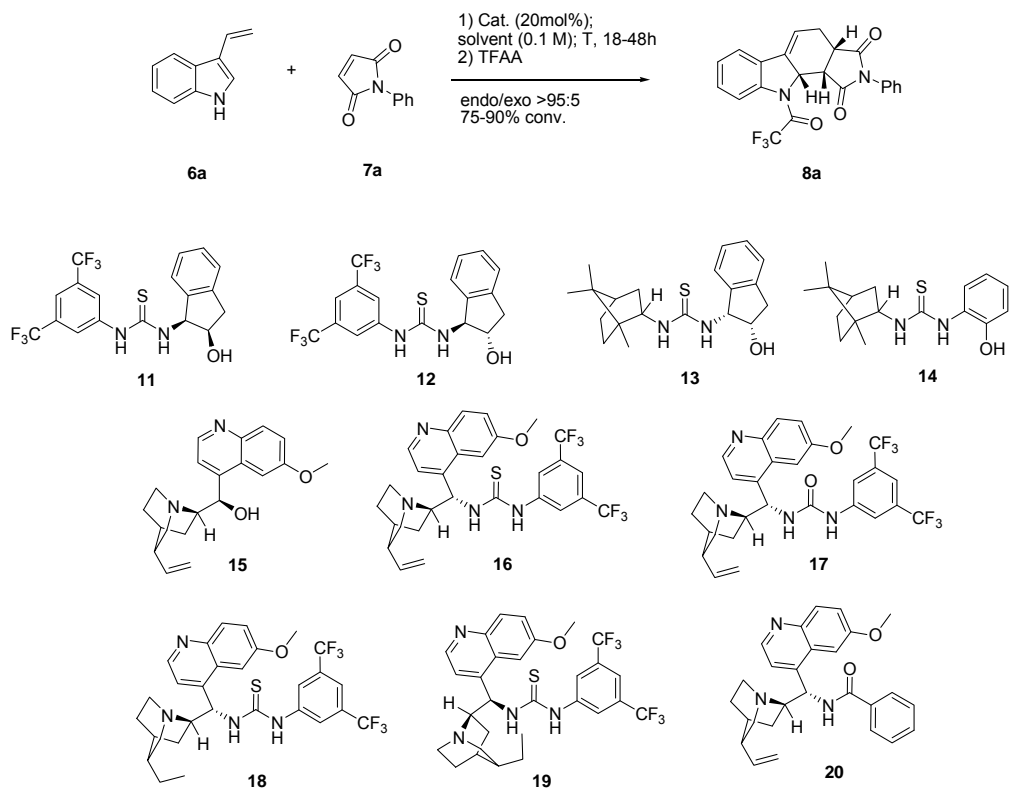
2.1.2 Results and discussions

3-Vinylindoles

Initial investigations focused on the catalytic reaction between 3-vinylindole **6a** and N-phenylmaleimide **7a**. In order to find a suitable catalytic system for this reaction, we envisioned a scenario where the catalyst might simultaneously raise the energy of the HOMO of the diene and lower the energy of the LUMO of the dienophile while orienting the two reactants to exert stereochemistry control. Guided by this hypothesis we considered the series of bifunctional organic catalysts reported in Scheme 9. Except for catalysts **11** and **12**, the structures represented are derived from natural compounds associated with a (thio)urea or amide motifs. The mild acidic nature of the screened catalysts was dictated by the rather acid-sensitive nature of 3-vinylindole. Preliminary experiments indicated the necessity of operating at low temperatures, in order to overcome a significant background reaction occurring at room temperature.

Furthermore, although under the mild reaction conditions employed the cycloaddition reaction furnished smoothly the product bearing the double bond at the 3,4-position, stabilized by conjugation with the aromatic nucleus. This compound proved to be rather difficult to isolate in a pure form by chromatography on silica gel, presumably for its tendency to undergo a formal 1,3-hydrogen shift to the rearomatized compound under acidic conditions. As this shift proceeds through protonation of the double bond,¹⁸ we reasoned that decreasing its electron density could prevent the rearomatization process. Indeed, it was found that derivatization with trifluoroacetic anhydride of the indoline nitrogen atom after completion of the reaction rendered the 3,4-unsaturated cycloadducts **8a** sufficiently stable to be isolated by chromatography and subsequently analyzed by chiral stationary phase HPLC.

¹⁸ W. E. Noland, G. -M. Xia, K. R. Gee, M. J. Konkel, M. J. Wahlstrom, J. J. Condoluci, D. L. Rieger, *Tetrahedron*, **1996**, 52, 4555.



Scheme 9

We, thus, screened catalysts and reaction conditions (Table 1). Performing the reaction at -25 °C gave **8a** with significant, though still unsatisfactory enantioselectivity with catalyst **11**, previously reported in the introduction for the Friedel–Crafts alkylation of indole, and with slightly modified catalysts **12** and **13** (entries 1–7). Replacement of the structurally rigid aminoindanol motif in **14** with other amino alcohol moieties or the use of the natural *Cinchona* alkaloid quinine **15** resulted in no enantioselection (entries 8, 9). The use of catalysts **16**–**18**, obtained by combining the (thio)urea and quinine moieties,¹⁹ proved to be of critical importance for the catalytic efficiency in the asymmetric Diels–Alder reaction (entries 10–18). In contrast, the corresponding amide **20** gave very low enantioselectivity, even at -55 °C (entry 16). After briefly screening the reaction medium with the most efficient catalysts (entries 1–5, 10–12), dichloromethane was identified as the solvent of choice for this transformation, and excellent selectivity (98% ee) was finally reached by performing the reaction at -55 °C using catalyst **18** derived from hydroquinine (entry 17). A decrease in the catalyst loading to 10 mol% was found to be detrimental to the enantioselectivity of the product **8a** (entry 18). Background reactivity can be considered responsible for this decrease, as a control

¹⁹ (a) B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.*, **2005**, *7*, 1967. (b) S. J. Connon, *Chem. Commun.*, **2008**, 2499.

experiment in dichloromethane without catalyst showed a significant non-catalyzed cycloaddition reaction between **6a** and **7a** even at $-55\text{ }^{\circ}\text{C}$ (33% conversion after 48 h).

It is worthy of note that a single diastereoisomer was formed in all cases, derived from an *endo* approach as determined by ^1H NMR NOE experiments on the 1-tosyl derivative **8l**, obtained simply quenching the reaction mixture with 4-toluenesulfonic anhydride instead of trifluoroacetic anhydride (Figure 1).

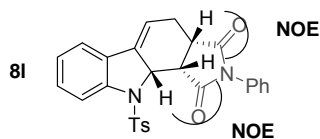


Figure 1

The use of the tosyl derivative was found to be necessary as in the ^1H NMR spectrum of the trifluoroacetate **8a** some of the protons showed multiple resonances, due to the presence of slowly interconverting rotamers.

Table 1 Catalyst and solvent screening and temperature effect on the cycloaddition reaction of 3-Vinyl-1*H*-indole (**6a**) with *N*-Phenylmaleimide (**7a**)^a

Entry	Catalyst	Solvent	Temp. ($^{\circ}\text{C}$)	Ee (%) ^b
1	11	CH_2Cl_2	-25	63
2	11	Toluene	-25	66
3	11	<i>n</i> -hexane	-25	17
4	11	MTBE	-25	10
5	11	MeCN	-25	5
6	12	CH_2Cl_2	-25	52
7	13	CH_2Cl_2	-25	22
8	14	CH_2Cl_2	-25	0
9	15	CH_2Cl_2	-25	0
10	16	CH_2Cl_2	-25	91
11	16	CHCl_3	-25	88
12	16	Toluene	-25	87
13	16	CH_2Cl_2	-55	96
14	17	CH_2Cl_2	-25	91
15	18	CH_2Cl_2	-25	93
16	20	CH_2Cl_2	-55	10
17	18	CH_2Cl_2	-55	98
18 ^c	18	CH_2Cl_2	-55	93

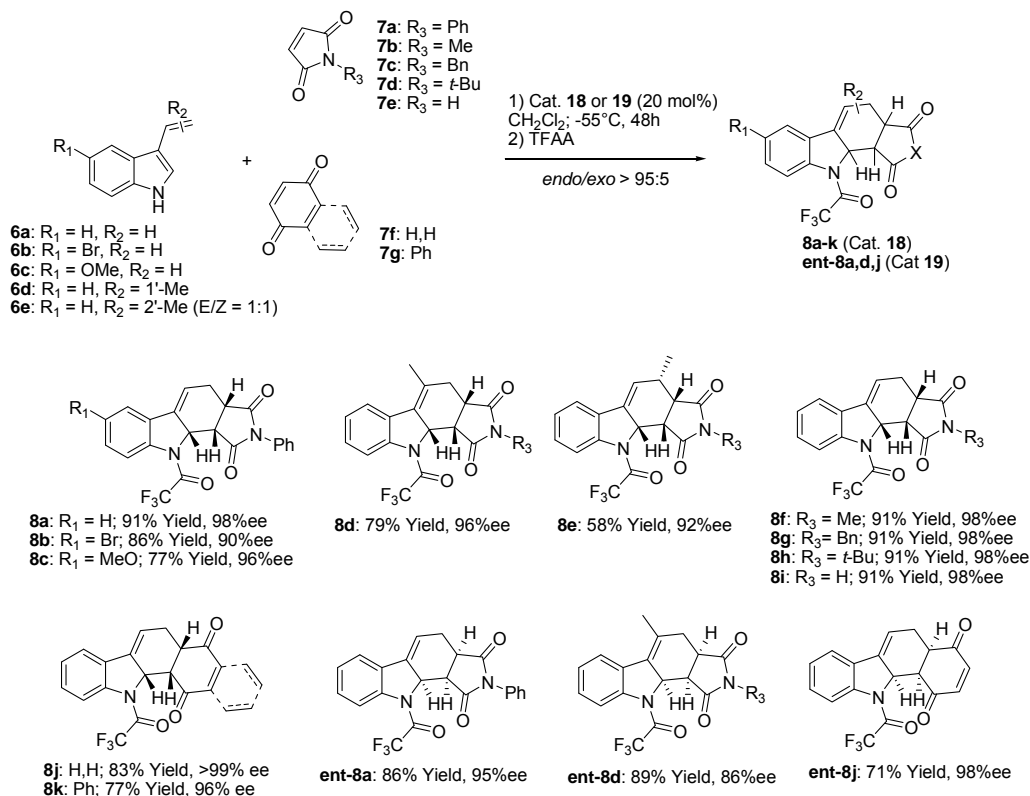
^a Conditions: (i) **6a** (0.10 mmol), catalyst (0.02 mmol), **7a** (0.12 mmol), solvent (1.0 mL), 18–48 h, (ii) TFAA (0.50 mmol). Conversion 75–90% (^1H NMR). A single *endo*-diastereoisomer (^1H NMR) was observed in all cases; ^b Determined by chiral HPLC analysis; ^c With 0.01 mmol catalyst (10.0 mol%).

This exceptional *endo* diastereoselectivity is however not attributable to catalyst activity, as it is a common feature of all the reported Diels–Alder cycloadditions of 3-vinylindoles,²⁰ and is normally ascribed to secondary orbital interactions.

The scope of the reaction investigated by using catalyst **18** was found to tolerate a significant degree of alterations in both diene and dienophile partners (Scheme 10). Both electron-withdrawing or donating groups at the 5-position of the indole nucleus were tolerated as well as a methyl substituent at the exocyclic double bond (cycloadducts **8a–e**). Using the unsubstituted 3-vinylindole **6a** variation in the dienophile counterpart was also examined. Maleimides **7a–e**, differently substituted at nitrogen, afforded the cycloadducts **8f–i** in generally very good yields and excellent enantioselectivities; the only serious decrease in enantioselectivity (52% ee) was noticed in the case of the N-unprotected maleimide **7e**.

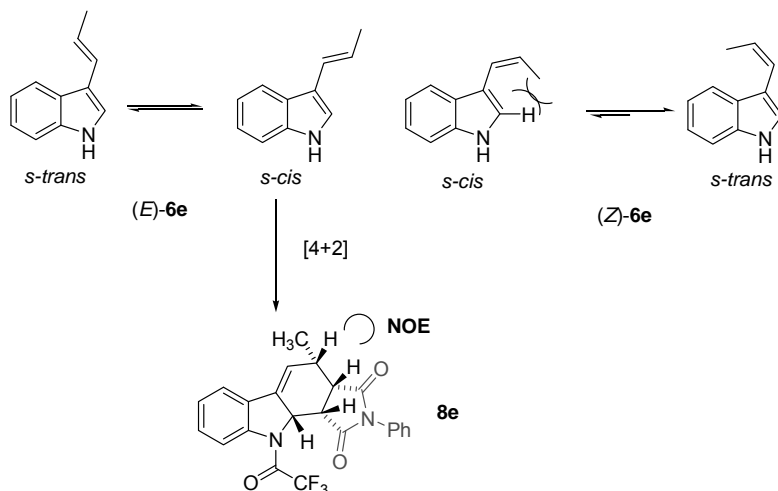
Compound **6a** reacted stereoselectively also with 1,4-benzoquinone (**7f**) and 1,4-naphthoquinone (**7g**), another useful class of dienophiles for Diels–Alder cycloadditions, to furnish **8j,k**, respectively, in very good yields and excellent enantioselectivities. Using the pseudoenantiomeric catalyst **19** derived from dihydroquinidine (Scheme 9) led to the expected cycloadducts *ent*-**8a,d,j** in comparable yields, but with a slight decrease in enantioselectivity (Scheme 9).

²⁰ For recent examples see: (a) M. Bleile, H. -H. Otto, *Monatsh. Chem.*, **2005**, *136*, 1799. (b) M. Bleile, T. Wagner, H. -H. Otto, *Helv. Chim. Acta*, **2005**, *88*, 2879.



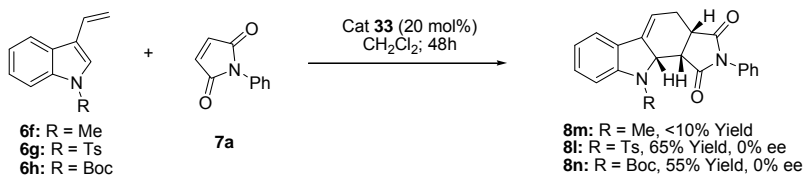
Scheme 10 Generality of the catalytic asymmetric Diels–Alder reaction of 3-vinylindoles **6**. *Reagents and conditions:* (1) **7** (0.15 mmol), catalyst **18** for **8a–k**, or catalyst **19** for **ent-8a,d,j** (0.030 mmol), **6a,d** (0.18 mmol) or **6b,c,e** (0.30 mmol), solvent (1.5 mL), –55 °C, 48 h, (2) TFAA (0.75 mmol), (3) chromatography (silica gel).

The stereospecific Diels–Alder reactions leading to products **8a–k** are indicative of a concerted mechanism and a stepwise tandem Michael–aldol-type reaction can be ruled out. A zwitterionic intermediate with a long lifetime that could neither be detected nor captured in these reactions can be discounted since such an intermediate would lead to a stereomeric mixture of products. Furthermore looking at the reactivity of 3-vinylindole **6e** with a methyl group on the exocyclic double bond, although this diene was employed as an *E/Z* mixture (1:1), the *E*-isomer exclusively underwent the cycloaddition reaction, giving the expected product **8e** as a single diastereoisomer (Scheme 11).



Scheme 11

This reaction outcome closely recalls the preferential reactivity of (*E*)-2'-methoxy-substituted 3-vinylindole over its (*Z*)-counterpart previously described by Pindur et al.²¹ in the uncatalyzed cycloaddition of some carbo- and azadienophiles, which has been rationalized by the greater stability of the *s-cis-E-endo*-transition state towards the *s-cis-Z-endo* analogue due to the presence in the former of more favourable stereoelectronic (n/σ^*) interactions and of lower steric requirements. The preferential reactivity of (*E*)-**6e** towards (*Z*)-**6e** can be justified along the same lines and strongly points in favour of an easier accessibility to the *s-cis*-conformation, which is, on the other hand, the key structural feature for the cycloaddition to occur (Scheme 11). Replacement of 1-H in the indole with methyl, tosyl, or Boc moieties in **6f–h** was detrimental in the reaction with **7a** (Scheme 12). Whereas the use of 1-methyl-3-vinyl-1*H*indole (**6f**) resulted in extensive decomposition at different temperatures, probably due to its increased acid sensitivity, 1-tosyl and 1-Boc derivatives **6g** and **6h** smoothly afforded the expected products **8l,n** as single diastereoisomers, at $-4\text{ }^\circ\text{C}$ and $-25\text{ }^\circ\text{C}$, respectively, though in racemic form in both cases (Scheme 12).



Scheme 12

These latter results support the crucial role played by the indole N–H as a suitable moiety for recognition of the indole nucleus by the Brønsted basic site of the organocatalytic species, giving a highly organized hydrogen bond network, as previously described for the hydrogen bonding catalysis in the introductory chapter.

²¹ U. Pindur, M. -H Kim, M. Rogge, W. Massa, M. Molinier, *J. Org. Chem.*, **1992**, *57*, 910.

The acceptors reported in Figure 2 were investigated as other potential dienophiles for the Diels-Alder reaction but, because of their lower reactivity associated with the tendency of 3-vinylindoles **6** to undergo to degradation, no products could be isolated.

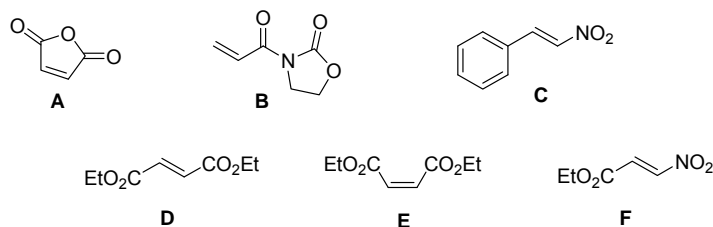


Figure 2

The results collected were tentatively taken in order to propose the working model of the reaction transition state reported in Figure 3.

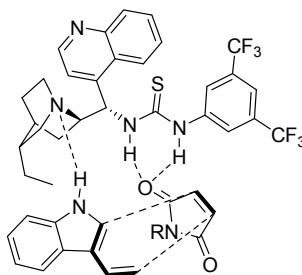
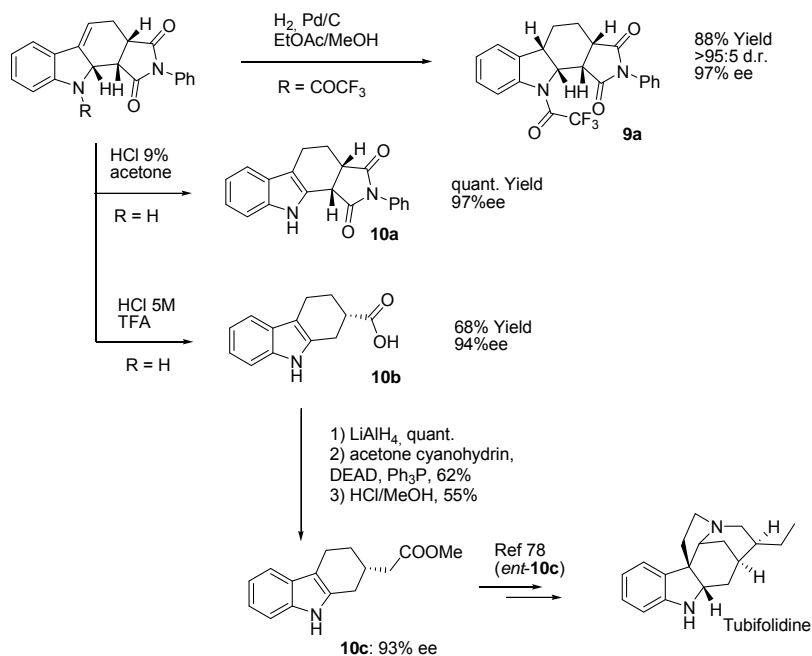


Figure 3

Furthermore a reasonable assumption for the rather low enantioselectivity observed when using **7e** as the dienophile (Scheme 10), could be accounted by the possibility that the imide hydrogen might interfere with the organization of this hydrogen bond system.

With the optimized conditions in hands, and after the demonstration of the wide generality of the reaction we studied the possibility to modify product **8**. The reduction of the cycloadduct **8a** to the indoline **9a** was straightforward, as was the synthesis of the tetrahydrocarbazoles **10a** through a 1,3-H shift, by treatment of the cycloadduct (before TFAC derivatization) with dilute aqueous HCl (Scheme 13). Use of harsher conditions gave, besides the 1,3-H shift, hydrolysis of the imide and regioselective decarboxylation²² at the 1-position (Scheme 13).

²² W. E. Noland, G.-M. Xia, K. R. Gee, M. J. Konkel, M. J. Wahlstrom, J. J. Condoluci, D. L. Rieger, *Tetrahedron*, **1996**, *52*, 4555.



Scheme 13

Reduction of the carboxylic acid of **10b**, followed by homologation with a Mitsunobu reaction,²³ and methanolysis of the cyano group, afforded **10c**, the enantiomer of a synthetic intermediate used in the asymmetric synthesis of tubifolidine,²⁴ a Strychnos alkaloid, highlighting the synthetic potential of this catalytic transformation and allowing the assignment of the absolute configuration of the products.

2-Vinylindoles

With these encouraging results for the cycloaddition of 3-vinylindoles **6** in hand, we turned our attention to the corresponding reaction employing the isomeric 2-vinyl-1*H*indole (**21**). The olefin moiety of this diene is considerably less electron rich with respect to the 3-vinylindole **6**, rendering this compound more stable towards acidic conditions.

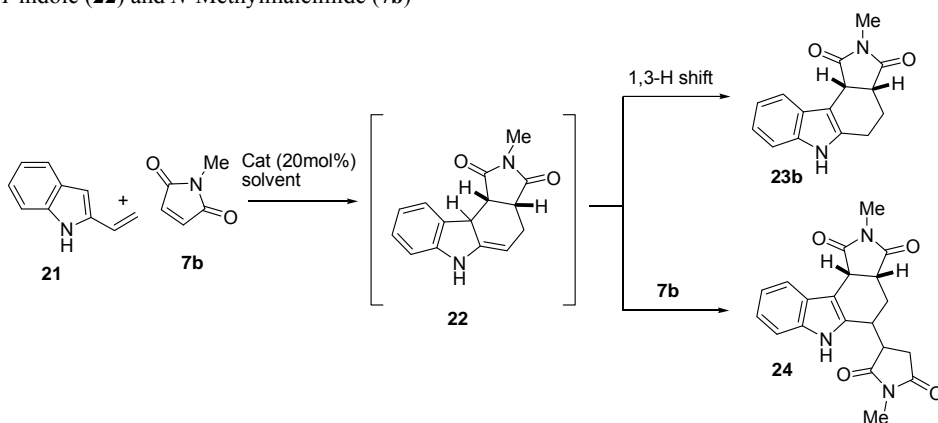
Considering the lower reactivity of 2-vinylindole **21** as a diene, we examined the cycloaddition reaction of **21** at room temperature using *N*-methylmaleimide (**7b**) (Table 2) and employing some of the catalysts (Scheme 9) that afforded the most promising results with the 3-vinylindoles **6**. As the double bond in the [4+2] cycloadducts **22** derived from the cycloaddition reaction is not stabilized by conjugation as it was in the cycloadducts **8** from 3-vinylindoles **6**, a fast formal 1,3-hydrogen shift occurred in cycloadduct **22** providing the tetrahydrocarbazole **23b**. This aromatic compound was sufficiently stable to be isolated by chromatography on silica

²³ T. Tsunoda, K. Uemoto, C. Nagino, M. Kawamura, H. Kaku, S. Ito, *Tetrahedron Lett.*, **1999**, 40, 7355.

²⁴ S. Shimizu, K. Ohori, T. Arai, H. Sasai, M. Shibasaki, *J. Org. Chem.*, **1998**, 63, 7547.

gel and analyzed by chiral stationary phase HPLC without requiring trifluoroacetic anhydride derivatization.

Table 2 Screening of Catalysts and Reaction Conditions in the Diels–Alder Reaction between 2-Vinyl-1*H*-indole (**21**) and *N*-Methylmaleimide (**7b**)^a



Entry	Catalyst	Solvent(M)	Temp. (°C)	Time (h)	Conv ^b (%)	Ee ^c (%) of 38b	Ratio ^b 38b/39
1	11	CH ₂ Cl ₂ (0.2)	25	48	35	3	>95:5
2	12	CH ₂ Cl ₂ (0.2)	25	47	29	2	>95:5
3	11	CH ₂ Cl ₂ (0.2)	25	120	46	23	52:48
4	16	CH ₂ Cl ₂ (0.2)	25	120	40	3	90:10
5	17	CH ₂ Cl ₂ (0.2)	25	120	45	4	58:42
6	20	CH ₂ Cl ₂ (0.2)	25	47	21	15 ^d	71:29
7	20	Toluene (0.25)	25	72	69	15	58:42
8	20	CH ₂ Cl ₂ /MTBE 7/3 (0.2)	25	72	78	14	63:37
9	-	CH ₂ Cl ₂ (0.2)	25	47	19	-	>95:5
10	20	CH ₂ Cl ₂ (1.0)	0	65	39	67	22:78
11	20	CH ₂ Cl ₂ (1.5)	0	47	39	67	23:77
12	20	CH ₂ Cl ₂ (2)	0	47	47	74 ^e	19:81
13	15	CH ₂ Cl ₂ (1.0)	0	60	55	- ^f	<5:95
14	-	CH ₂ Cl ₂ (1.0)	0	48	30	-	90:10

^a Conditions: **7b** (0.05 mmol), catalyst (0.01 mmol), **21** (0.056 mmol), solvent. ^b Determined by ¹H NMR spectroscopy. ^c Determined by chiral stationary phase HPLC. ^d **24**: 5% ee. ^e **24**: 5% ee. ^f **24**: 1% ee.

To our disappointment, however, all catalysts tested in dichloromethane as a solvent gave very low enantiomeric excesses in this reaction, accompanied by an incomplete conversion of starting materials **21** and **7b** (entries 1–6). Also changing the reaction medium did not seem to

give any improvement (entries 7, 8). Furthermore, a control experiment in the absence of catalyst (entry 9) indicated the absence of a significant acceleration of the Diels–Alder cycloaddition by the catalysts employed. In a last attempt several reactions were carried out at 0 °C, under more concentrated conditions in order to reach a reasonable conversion, using the ‘best’ catalysts quinine **15** and amide **20** found in the first set of experiments (entries 10–13). To our surprise, the cycloadducts **23b** obtained with catalyst **20** using these conditions showed a great enhancement in its enantiomeric excess (entries 10–12, up to 74% ee), compared to the same reactions carried out at room temperature.

A closer inspection of these reaction mixtures revealed the presence of the diastereomerically pure tandem Diels–Alder–Michael adduct **24** as the major component (entries 10–12), and as the only observable product when quinine **15** was employed (entry 13). This product derives from the reaction of the intermediate [4+2] cycloadduct **22** with a second molecule of *N*-methylmaleimide (**7b**) through an ene-type reaction, before rearomatization occurred. This tandem process, favoured by the enamine functionality, has been already reported for thermal cycloadditions of 2-vinylindoles.²⁵ In our reactions carried out at room temperature in dichloromethane under more diluted conditions (entries 1–6), in all cases the 1,3-hydrogen shift predominated over the tandem product **24**.

A second control experiment carried out at 0 °C (entry 14) further confirmed the inability of the catalysts employed to catalyze the Diels–Alder cycloaddition. From these data, it, thus, seems clear that the enantioselectivity observed in the cycloadduct **23b** does not originate from the organocatalyzed Diels–Alder cycloaddition reaction of **21** with **7b**. On the other hand, the participation of the catalyst in the following Michael reaction was proven by the almost complete absence of **24** when the reactions were carried out without catalyst (entries 9, 14). In particular, the basic moiety of the catalysts employed seems to play a crucial role in the formation of **24**, as witnessed by the apparent correlation between the amount of **24** and the basicity of the catalyst in the reactions carried out at room temperature, wherein catalysts **15**, **16**, **17** and **20** bearing a basic tertiary amino moiety furnished substantially higher amounts of **24** compared to **11** and **12**.

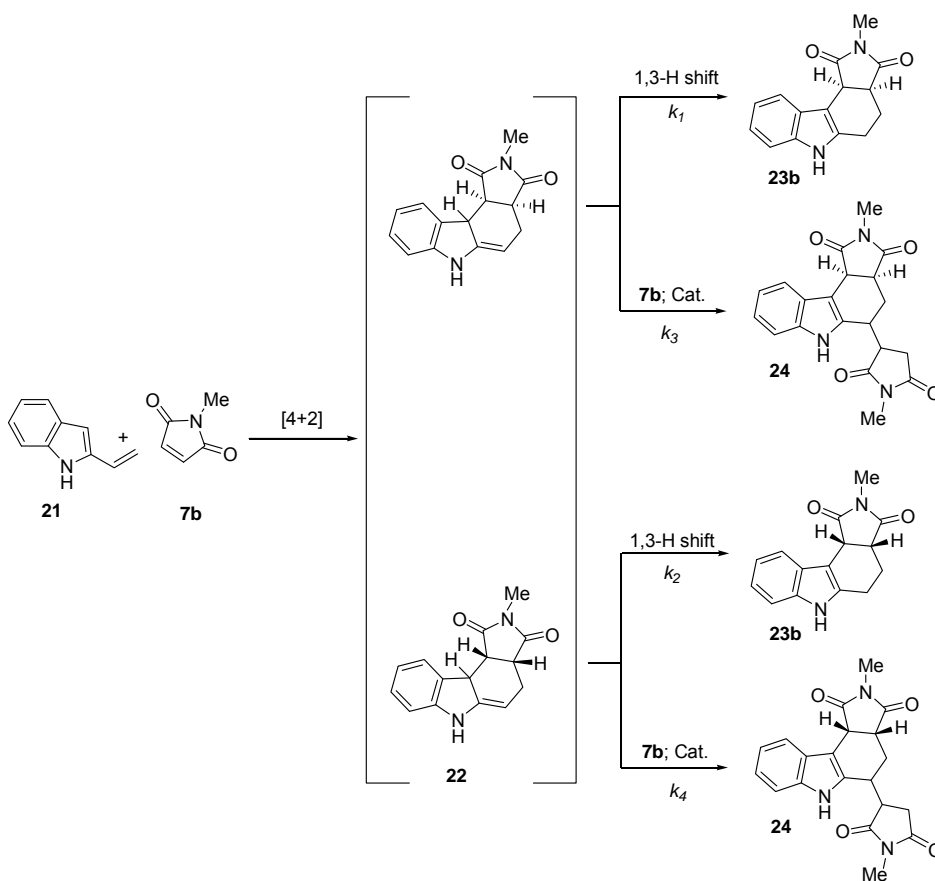
The role of the catalyst in the process leading to enantioenriched **23b** seems, thus, rather connected with the second Michael addition step leading to **24**, presumably with a hydrogen bond interaction between the basic moiety of the catalysts and the N–H of the enamine, which results thus activated for the Michael addition. However, the tandem adduct **24** was obtained with low enantioselectivity, even when the cycloadducts **23b** showed an appreciable enantioenrichment (entries 6, 12).

Our current interpretation, which accounts for the observed results, considers that the enantioselectivity of **23b** originates mainly from a kinetic resolution of the transient

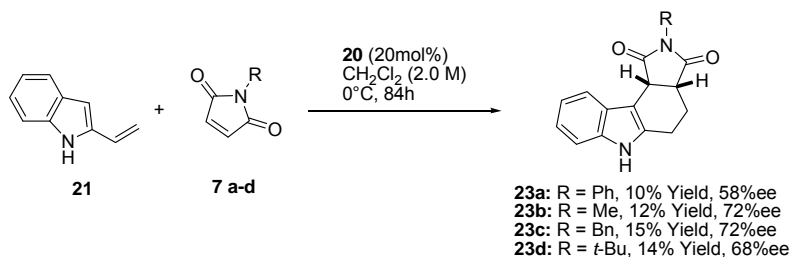
²⁵ (a) M. Eitel, U. H. Pindur, *Synthesis*, **1989**, 364. (b) M. Eitel, U. H. Pindur, *J. Org. Chem.*, **1990**, *55*, 5368.

intermediate **22** (Scheme 14). Our hypothesis involves the formation of the intermediate **22** in low enantiomeric excess, promoted only marginally by the catalyst. This intermediate can then undergo a presumably non-catalyzed 1,3-hydrogen shift (i.e., $k_1 = k_2$), giving the tetrahydrocarbazoles **23b**. Under more diluted conditions (0.2 M, entries 1– 6), this hydrogen shift is considerably faster than the Michael addition involving also a second molecule of maleimide **7b** and the catalyst, and the tetrahydrocarbazoles **23b** is obtained as the major product with understandably low enantioselectivity. However, if the concentration of catalyst and maleimide **7b** is sufficiently high, the trimolecular Michael addition can compete with the mono- or bimolecular 1,3-hydrogen shift. If the catalyst is able to discriminate between the two enantiomers of **22** (i.e., $k_3 \neq k_4$), giving possibly some enantioenrichment in the remaining unreacted **22**, the 1,3-hydrogen shift then affords the tetrahydrocarbazole **23b** with appreciable enantiomeric excess. This scheme does not fall into the general categories of kinetic resolution processes,²⁶ as we consider the catalyst influencing only marginally, if at all, the 1,3-hydrogen shift, in contrast with what would be a parallel kinetic resolution. It is instead a kinetic resolution involving a transient intermediate, wherein the resolution step needs to compete with the transformation of this transient intermediate to be proficient. The collected data indicate that in our case the catalysts are operating with low efficiency, as **24** was obtained with low enantiomeric excess in all cases (entries 6, 12, 13). However, in a classical kinetic resolution even with a low selective catalyst the starting material can be recovered with significant enantioenrichment when the conversion is high. According to our scheme it should be possible to raise the enantioselectivity of the tetrahydrocarbazole **23b**, at the expense of its yield, increasing the ratio between the rate of formation of the tandem product and the 1,3-hydrogen shift. Indeed, we observed, in our case, considerable enantioselectivity in the cycloadduct **23b** only when most of the intermediate **22** to be resolved is consumed to give the tandem adduct **24** (Table 2, entries 10–12). Although as mentioned the selectivity of the catalyst **20** in this particular resolution process is rather low, it should be considered that the tetrahydrocarbazole **23b** is very easily separated by column chromatography both from starting materials and from the tandem adduct **24**.

²⁶ (a) J. M. Keith, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.*, **2001**, *343*, 5. (b) H. B. Kagan, J. C. Fiaud, *Top. Stereochem.*, **1988**, *18*, 249. Recent examples of enantioenrichment of catalytic products through organocatalysis: (c) D. Enders, A. A. Narine, F. Toulgoat, T. Bisschops, *Angew. Chem. Int. Ed.*, **2008**, *47*, 5661. (d) T. Akiyama, T. Katoh, K. Mori, *Angew. Chem. Int. Ed.*, **2009**, *48*, 4226. (e) K. Frisch, K. A. Jørgensen, *Org. Biomol. Chem.*, **2007**, *5*, 2966.



Hence, this protocol, despite its inherent limitation in terms of yield, gives an unprecedented entry to the cycloadducts deriving from 2-vinylindole **21** with reasonable enantioselectivity. The possibility of using different maleimides was then tested (Scheme 15), showing that despite the expected low yields, the corresponding Diels–Alder cycloadducts **23a–d** could be isolated with moderate enantioselectivity.



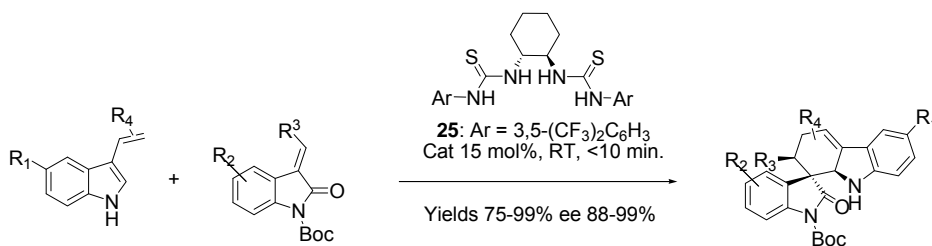
2.1.3 Conclusions

We have described the first application of asymmetric organocatalysis to the [4+2]-cycloaddition reaction of vinylindoles **6** and **21**. With 3-vinylindoles **6** the reactions proceed under mild operational conditions to give a wide range of optically active tetrahydrocarbazoles **8** in synthetically useful yields and excellent enantioselectivities. The operational mode of the catalysis could be established according to a HOMO and LUMO activation respectively by the Brønsted basic and acidic sites of the organocatalytic species.

As compared to the 3-vinylindoles **6**, its 2-vinyl counterpart **21** under similar reaction conditions exhibited poor reactivity and the expected cycloadducts were obtained in low yields, though with substantial enantioselectivity together with variable amounts of tandem Michael-type adducts, derived from attack of the enamine of the intermediate cycloadduct to the dienophile.

Evidence in favour of the intervention of the catalyst mainly in the Michael step of the reaction suggested an unusual resolution-type process accounting for the observed enantioselectivity.

Furthermore, motivated by the strategic formation of important intermediates in the synthesis of natural compounds, other studies involved vinylindoles as partner for different cycloaddition reactions. Barbas III and co-workers, for example, demonstrated that even a catalyst at first sight lacking a basic moiety, such as the bithiourea, is able to promote very efficiently Diels-Alder reactions of 3-vinylindoles (Scheme 16).²⁷



Scheme 16

In particular, cycloadditions with methyleneindolinones furnished biologically interesting spirocyclic oxindoles with excellent enantioselectivities.

Further studies, performed in our group, regarded the use of vinylindoles in different kind of reactions such as Povarov reaction²⁸ and oxa-Diels Alder.²⁹ These studies investigated the

²⁷ B. Tan, G. Hernández-Torres and C. F. Barbas III, *J. Am. Chem. Soc.*, 2011, **133**, 12354

²⁸ G. Bergonzini, L. Gramigna, A. Mazzanti, M. Fochi, L. Bernardi, A. Ricci, *Chem Commun*, **2010**, 46, 327.

²⁹ L. Bernardi, M. Comes-Franchini, M. Fochi, V. Leo, A. Mazzanti, A. Ricci, *Adv. Synth. Catal.*, **2010**, 352, 3399.

catalytic activity of more acidic catalysts, such as phosphoric acid derivatives, in Brønsted acid catalytic cycle, obtaining excellent values in yields and enantioselections.

2.1.4 Experimental Section

General Methods. ^1H , ^{13}C , ^{19}F NMR spectra were recorded on a Varian AS 300, 400 or 600 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for ^1H and ^{13}C NMR (^1H NMR: 7.26 ppm for CDCl_3 , 7.16 ppm for C_6D_6 , 2.50 ppm for $\text{DMSO}-d_6$, 2.05 ppm for acetone- d_6 ; ^{13}C NMR: 77.0 ppm for CDCl_3 , 128.0 ppm for C_6D_6 , 39.5 ppm for $\text{DMSO}-d_6$, 29.8 ppm for acetone- d_6), or using an external reference for ^{19}F NMR (C_6F_6 , -163.0 ppm). ^{13}C NMR and ^{19}F NMR spectra were acquired on a broad band decoupled mode. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES) ionization techniques. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (*ee*) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD-H or Daicel Chiralcel OJ-H columns), using a UV detector operating at 254 nm. Melting points were measured on a Büchi smp-20 apparatus and are uncorrected.

Materials. Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated. CH_2Cl_2 was passed through basic alumina before use. THF was distilled from Na before use. Et_2O was distilled twice from P_2O_5 before use. Chromatographic purifications were performed using 70-230 mesh silica. Catalysts **18** and **19** were prepared in two steps from hydroquinine and hydroquinidine, respectively, following literature procedures.³⁰ 3-Vinylindoles **6a-c** and **6e** were prepared by a Wittig reaction from the corresponding aldehydes, following a literature procedure as outlined below,³¹ and were stored at -30°C . Vinylindoles **6a,b,d** were found to be stable at this temperature for months, whereas **6c** and **6e** had to be used within a few days after their preparation. Racemic samples were prepared using 1,2-bis(3,5-bis(trifluoromethyl)phenyl)thiourea³² as a catalyst at -30°C overnight.

General procedure for the preparation of 3-vinylindoles through a Wittig reaction.³⁰ To a stirred suspension of methyltriphenylphosphonium bromide (8.21 g, 23.0 mmol) in THF (60 mL), cooled to -50°C , *n*-BuLi (12.5 mL, 1.6 M in hexanes, 20.0 mmol) was slowly added. The resulting yellow suspension was stirred and allowed to warm to 0°C in approximately 45 minutes. After cooling to -30°C , a pre-mixed solution of an indole 3-carboxaldehyde (20.0 mmol) and LiHMDS (20 mL, 1.0 M in THF, 20 mmol), in THF (24 mL) was added. The resulting suspension was then stirred at room temperature for 1h, then poured onto H_2O and extracted with EtOAc (2x). The combined organic phases were dried (Na_2SO_4), filtered and evaporated. The crude residue was then purified by a short chromatography on silica gel (petroleum ether/ Et_2O 7:3).

3-Vinyl-1H-indole (6a). Following the general procedure, the title compound was obtained as a white solid in 85% yield. Mp = $80-81^\circ\text{C}$; ^1H NMR (C_6D_6 , 400 MHz) δ 7.98-7.94 (m, 1H), 7.22-7.16 (m, 2H), 7.00-6.96 (m, 1H), 6.92 (dd, $J = 17.7, 11.1$ Hz, 1H), 6.61-6.48 (br s, 1H), 6.55 (d, $J = 2.4$ Hz, 1H), 5.79 (dd, $J = 17.8, 1.5$ Hz, 1H), 5.21 (dd, $J = 11.6, 1.6$ Hz, 1H); ^{13}C NMR (C_6D_6 , 100 MHz) δ 130.1, 126.2, 123.6, 122.6, 120.6, 120.5, 119.1, 116.0, 111.4, 110.5; ESI-MS: 143 [M⁺].

³⁰ a) 9-Amino-9-deoxyhydroquinine and 9-amino-9-deoxyhydroquinidine: S. H. McCooey, S. J. Connon, *Org. Lett.*, **2007**, *9*, 599; b) catalysts **33** and **34**: B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.*, **2005**, *7*, 1967.

³¹ M. S. Scott, A. C. Lucas, C. A. Luckhurst, J. C. Prodder, D. J. Dixon, *Org. Biomol. Chem.*, **2006**, *4*, 1313.

³² P. R. Schreiner, A. Wittkopp, *Org. Lett.*, **2002**, *4*, 217.

5-Bromo-3-vinyl-1H-indole (6b). Following the general procedure, the title compound was obtained as a white solid in 79% yield. M.p. = 82-84 °C; ¹H NMR (C₆D₆, 400 MHz) δ 8.14 (d, *J* = 2.0 Hz, 1H), 7.30 (dd, *J* = 8.5, 1.9 Hz, 1H), 6.67 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.60 (d, *J* = 8.6 Hz, 1H), 6.50-6.39 (br s, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 5.55 (dd, *J* = 17.8, 1.5 Hz, 1H), 5.09 (dd, *J* = 11.2, 1.4 Hz, 1H); ¹³C NMR (C₆D₆, 100 MHz) δ 135.4, 129.0, 125.4, 124.3, 123.1, 115.6, 114.0, 112.9, 111.3; ESI-MS: 221-223 [M⁺].

5-Methoxy-3-vinyl-1H-indole (6c). Following the general procedure, the title compound was obtained as an orange waxy solid in 82% yield. ¹H NMR (acetone-*d*₆, 300 MHz) δ 10.22 (br s, 1H), 7.46-7.31 (m, 3H), 6.93 (ddd, *J* = 18.0, 11.3, 0.6 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.65 (dd, 17.9, 1.8 Hz, 1H), 5.08 (dd, *J* = 11.3, 1.7 Hz, 1H), 3.85 (s, 3H); ¹³C NMR (acetone-*d*₆, 75 MHz) δ 155.2, 133.0, 130.9, 126.8, 126.0, 115.4, 112.9, 112.6, 109.0, 102.4, 55.8; ESI-MS: 173.

(E)-3-(Prop-1-enyl)-1H-indole and (Z)-3-(prop-1-enyl)-1H-indole (6e). Following the general procedure and using ethyltriphenylphosphonium bromide, the title compound was obtained as a pale yellow solid in 55% yield and as a 1:1 *E/Z* mixture. ¹H NMR (C₆D₆, 400 MHz) δ [signals of both *E* and *Z* isomer] 7.98-7.89 (m, 1H), 7.77-7.71 (m, 1H), 7.26-7.15 (m, 4H), 7.04-6.98 (m, 2H), 6.79 (ddq, *J*_d = 11.2, 0.6 Hz, *J*_q = 1.7 Hz, 1H), 6.82-6.70 (br s, 1H), 6.71 (d, *J* = 2.4 Hz, 1H), 6.63 (dq, *J*_d = 15.9 Hz, *J*_q = 1.7 Hz, 1H), 6.61-6.52 (br s, 1H), 6.56 (d, *J* = 2.1 Hz, 1H), 6.21 (dq, *J*_d = 15.8 Hz, *J*_q = 6.5 Hz, 1H), 5.75 (dq, *J*_d = 11.3 Hz, *J*_q = 7.0 Hz, 1H), 1.85 (d, *J* = 1.8 Hz, 3H), 1.83 (dd, *J* = 1.7, 0.7 Hz, 3H); ¹³C NMR (C₆D₆, 100 MHz) δ [signals of both *E* and *Z* isomer] 137.0, 135.8, 126.3, 124.3, 123.1, 122.8, 122.5, 122.4, 122.2, 121.4, 120.5, 120.2, 120.1, 119.4, 115.9, 114.0, 111.4, 111.2, 19.0, 15.6; ESI-MS 157 [M⁺].

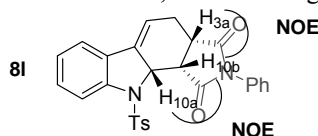
3-(Prop-1-en-2-yl)-1H-indole (6d). To a stirred suspension of methyltriphenylphosphonium bromide (5.34 g, 15.0 mmol) in THF (25 mL), cooled to 0 °C, *n*-BuLi (8.4 mL, 1.6 M in hexanes, 13.5 mmol) was slowly added. The resulting yellow suspension was stirred for 2 h at the same temperature, then 3-acetyl-1H-indole (1.59 g, 10.0 mmol) was added in one portion. The mixture was refluxed overnight with vigorous stirring, then poured onto H₂O and extracted with EtOAc (2x). The combined organic extracts were dried (Na₂SO₄), filtered, evaporated, and the residue purified by a short chromatography on silica gel (petroleum ether/Et₂O 7:3), affording the title compound in 26% yield as a white solid. M.p. = 89-90 °C; ¹H NMR (C₆D₆, 400 MHz) δ 8.12-8.06 (m, 1H), 7.26-7.17 (m, 2H), 7.03-7.00 (m, 1H), 6.98-6.55 (br s, 1H), 6.59 (d, *J* = 2.5 Hz, 1H), 5.69 (br s, 1H), 5.16 (quint, *J* = 1.4 Hz, 1H), 2.10 (dd, *J* = 1.5, 0.8 Hz, 3H); ¹³C NMR (C₆D₆, 100 MHz) δ 138.1, 126.0, 122.5, 122.3, 121.4, 120.6, 118.8, 111.4, 110.0, 23.3; ESI-MS 157 [M⁺].

General procedure for the organocatalytic, enantioselective Diels-Alder reaction. To a test tube equipped with a magnetic stirring bar were sequentially added the dienophile **7** (0.15 mmol), CH₂Cl₂ (1.0 mL) and catalyst **18** (17.8 mg, 0.030 mmol). After cooling to -55 °C, a pre-cooled solution of 3-vinylindole **6** (0.18 mmol) in CH₂Cl₂ (0.50 mL), was added via a syringe. The mixture was then stirred at the same temperature, with no precautions to exclude moisture or air. After 48 h, a solution of trifluoroacetic anhydride (104 μL, 0.75 mmol) in CH₂Cl₂ (1.5 mL) was added and the mixture allowed to warm to room temperature over 1 h. Sat. NaHCO₃ was then added slowly, and the product was extracted with CH₂Cl₂ (3x5 mL). The combined organic phases were dried (Na₂SO₄), filtered and evaporated, and the residue analyzed by ¹H

NMR spectroscopy. In all cases, exclusively the *endo* cycloadduct was observed. Finally, the product **8** was obtained after chromatographic purification on silica gel (CH₂Cl₂/Et₂O mixtures).

(3a*S*,10a*S*,10b*S*)-2-Phenyl-10-(2,2,2-trifluoroacetyl)-3a,4,10,10-tetrahydropyrrolo [3,4-*a*]carbazole-1,3(2*H*,10b*H*)-dione (8a**).** Following the general procedure, the title compound was obtained in 91% yield as a pale yellow solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.75 mL/min, *t*_{major} = 20.2 min, *t*_{minor} = 35.5 min, 98% *ee*). [α]_D₂₀ = +292 (*c* = 0.50 in CH₂Cl₂); mp = 85-87 °C; ¹H NMR (CDCl₃, 400 MHz) [some signals show multiple resonances for the presence of different rotamers due to restricted rotation around the trifluoroacetamide C-N bond] δ 8.39 (bd, *J* = 8.2 Hz, 0.5H), 7.50 (m, 1H), 7.37-7.27 (m, 4.5H), 7.18 (m, 1H), 6.95 (m, 2H), 6.35 (m, 1H), 5.13 (bs, 0.5H), 5.06 (bs, 0.5H), 4.52 (bt, *J* = 8.5 Hz, 0.5H), 4.02 (bt, *J* = 7.7 Hz, 0.5H), 3.41 (ddd, *J* = 8.8, 7.0, 1.9 Hz, 1H), 3.2 (dd, *J* = 15.8 Hz, *J* = 7.9 Hz, 1H), 2.36 (m, 1H); ¹³C NMR (CDCl₃, 150 MHz) the spectrum is reported but not described because most carbons show multiple resonances for the presence of different rotamers and coupling with ¹⁹F. ¹⁹F NMR (CDCl₃, 376 MHz) [the spectrum shows two distinct resonances for the presence of different rotamers] δ -71.4, -71.3. ESI-MS: 412 [M⁺ + Na]. The relative configuration of compound **8a** was determined by means of NMR NOE experiments on the corresponding 10-tosyl derivative, obtained as outlined below, whose ¹H NMR spectrum did not show multiple resonances and was therefore more easily interpreted.

(3a*S*,10a*S*,10b*S*)-2-Phenyl-10-tosyl-3a,4,10,10a-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,10b*H*)-dione (8l**)** Following the general procedure and quenching the catalytic reaction with solid (Ts)₂O (163 mg, 0.50 mmol) instead of trifluoroacetic anhydride, the title compound was obtained as a white solid. [α]_D₂₀ = +215 (*c* = 0.30 in AcOEt); mp = 80-90°C; ¹H NMR (DMSO-*d*₆, 400 MHz) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.42-7.32 (m, 5H), 7.26 (dt, *J*₁ = 8.3 Hz, *J*_d = 1.1 Hz, 1H), 7.01 (dt, *J*₁ = 7.6 Hz, *J*_d = 0.7 Hz, 1H), 6.94 (br d, *J* = 7.2 Hz, 2H), 6.34 (dt, *J*_d = 7.2 Hz, *J*_t = 3.7 Hz, 1H), 4.89 (dt, *J*_d = 7.2 Hz, *J*_t = 2.8 Hz, 1H), 4.12 (dd, *J* = 8.9, 7.3 Hz, 1H), 3.45 (br t, *J* = 8.3 Hz, 1H), 2.82 (ddd, *J* = 15.5, 7.6, 1.4 Hz, 1H), 2.45-2.42 (m, 1H), 2.32 (s, 3H); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ 178.3, 173.8, 144.5, 143.8, 136.5, 133.5, 132.1, 129.9, 129.8, 128.8, 128.3, 127.3, 126.7, 126.6, 123.9, 121.2, 114.6, 114.3, 61.5, 43.8, 37.4, 25.2, 21.0; ESI-MS: 493 [M⁺ + Na]. The relative configuration of the title compound was tentatively assigned by means of NMR NOE experiments. The signals of the ¹H NMR spectrum were assigned by means of gCOSY, ghsqc NMR experiments and in analogy with literature data.⁴ Irradiation at 3.45 ppm (H_{3a}) gives a signal at 4.12 ppm (H_{10b}). Irradiation at 4.12 ppm (H_{10b}) gives signals at 3.45 ppm (H_{3a}) and 4.89 ppm (H_{10a}). Therefore, a 3a,10b-*cis* and 10a,10b-*cis* configuration can be assumed.



(3a*R*,10a*R*,10b*R*)-2-Phenyl-10-(2,2,2-trifluoroacetyl)-3a,4,10,10a-tetrahydropyrrolo [3,4-*a*]carbazole-1,3(2*H*,10b*H*)-dione (*ent*-8a**).** Following the general procedure and using catalyst **34** derived from hydroquinidine, the title compound was obtained in 86% yield as a pale yellow solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/ *i*PrOH 80:20, flow rate 0.75 mL/min, *t*_{major} 35.5 min, *t*_{minor} 20.2 min, 95% *ee*). [α]_D₂₀ = -240 (*c* = 0.19 in CH₂Cl₂). Spectral data were identical to compound **8a**.

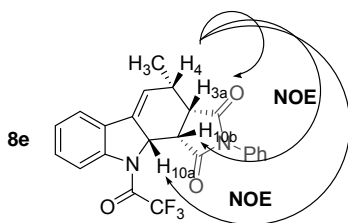
(3aS,10aS,10bS)-7-Bromo-2-phenyl-10-(2,2,2-trifluoroacetyl)-3a,4,10,10a-tetrahydro pyrrolo [3,4-*a*]carbazole- 1,3(2*H*,10*bH*)-dione (8b). Following the general procedure, and using 2 equivalents of diene 6b, the title compound was obtained in 86% yield as a pale yellow solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.75 mL/min, $t_{\text{maj}} = 29.6$ min, $t_{\text{min}} = 42.9$ min, 90% *ee*). $[\alpha]_{\text{D } 30} = +147$ ($c = 0.49$ in CH_2Cl_2); mp = 117-121 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) [some signals show multiple resonances for the presence of different rotamers due to restricted rotation around the trifluoroacetamide C-N bond] δ 8.27 (br d, $J = 8.9$ Hz, 0.5H), 7.63-7.58 (m, 1H), 7.45 (br d, $J = 10.0$ Hz, 0.5H), 7.39-7.28 (m, 5H), 6.98 (brt, $J = 6.2$ Hz, 2H), 5.12 (br s, 0.5H), 5.05 (br s, 0.5H), 4.52 (br t, $J = 8.0$ Hz, 0.5H), 4.03 (br t, $J = 8.0$ Hz, 0.5H), 3.43 (ddd, $J = 9.2, 7.3, 2.0$ Hz, 1H), 3.22 (dd, $J = 15.8, 7.6$ Hz, 1H), 2.42-2.30 (m, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 150 MHz) the spectrum is reported but not described because most carbons show multiple resonances for the presence of different rotamers and coupling with ^{19}F . $^{19}\text{F NMR}$ (376 MHz, CDCl_3) [the spectrum shows two distinct resonances for the presence of different rotamers] δ -71.7, -72.7; ESI-MS: 513 [$\text{M}^+ + \text{Na}$].

(3aS,10aS,10bS)-7-Methoxy-2-phenyl-10-(2,2,2-trifluoroacetyl)-3a,4,10,10a-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,10*bH*)-dione (8c). Following the general procedure, and using 2 equivalents of diene 23c, the title compound was obtained in 77% yield as a pale yellow solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.75 mL/min, $t_{\text{maj}} = 24.0$ min, $t_{\text{min}} = 32.4$ min, 96% *ee*). $[\alpha]_{\text{D } 30} = +212$ ($c = 0.24$ in CH_2Cl_2); mp = 90-93 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) [some signals show multiple resonances for the presence of different rotamers due to restricted rotation around the trifluoroacetamide C-N bond] δ 8.33 (d, $J = 9.3$ Hz, 0.5 H), 7.42 (d, $J = 9.3$ Hz, 0.5 H), 7.37-7.26 (m, 3H), 7.00-6.93 (m, 3H), 6.93-6.84 (m, 1H), 6.36-6.29 (m, 1H), 5.15-5.11 (m, 0.5 H), 5.07-5.03 (m, 0.5 H), 4.53 (dd, $J = 8.9, 7.4$ Hz, 0.5 H), 4.02 (dd, $J = 9.0, 7.0$ Hz, 0.5 H), 3.81 (s, 3H), 3.42 (ddd, $J = 8.7, 7.0, 1.6$ Hz, 1H), 3.20 (ddt, $J_{\text{d}} = 15.6, 7.4$ Hz, $J_{\text{t}} = 1.7$ Hz, 1H), 2.42-2.32 (m, 1H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) the spectrum is reported but not described because most carbons show multiple resonances for the presence of different rotamers and coupling with ^{19}F ; $^{19}\text{F NMR}$ (376 MHz, CDCl_3) [the spectrum shows two distinct resonances for the presence of different rotamers] δ -71.5, -72.7; ESI-MS: 465 [$\text{M}^+ + \text{Na}$].

(3aS,10aS,10bS)-5-Methyl-2-phenyl-10-(2,2,2-trifluoroacetyl)-3a,4,10,10a-tetrahydro pyrrolo[3,4-*a*]carbazole-1,3(2*H*,10*bH*)-dione (8d). Following the general procedure the title compound was obtained in 79% yield as a pale yellow solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.75 mL/min, $t_{\text{maj}} = 21.4$ min, $t_{\text{min}} = 33.1$ min, 96% *ee*). $[\alpha]_{\text{D } 20} = +265$ ($c = 0.50$ in CH_2Cl_2); mp = 90-94 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) [some signals show multiple resonances for the presence of different rotamers due to restricted rotation around the trifluoroacetamide C-N bond] δ 8.43 (m, 0.5H), 7.61 (m, 1H), 7.50 (m, 0.5H), 7.33-7.25 (m, 4H), 7.22-7.15 (m, 1H), 6.89-6.83 (m, 2H), 5.08 (br s, 0.5H), 5.00 (br s, 0.5H), 4.44 (brt, $J = 7.8$ Hz, 0.5H), 3.92 (br t, $J = 7.3$ Hz, 0.5H), 3.38 (ddd, $J = 8.4, 6.2, 2.0$ Hz, 1H), 2.98 (dd, $J = 15.4, 2.2$ Hz, 1H), 2.55-2.45 (m, 1H), 2.23 (br s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 150 MHz) the spectrum is reported but not described because most carbons show multiple resonances for the presence of different rotamers and coupling with ^{19}F . $^{19}\text{F NMR}$ (376 MHz, CDCl_3) [The spectrum shows two distinct resonances for the presence of different rotamers] δ -71.2, -72.1; ESI-MS: 449 [$\text{M}^+ + \text{Na}$].

(3aR,10aR,10bR)-5-Methyl-2-phenyl-10-(2,2,2-trifluoroacetyl)-3a,4,10,10a-tetrahydro pyrrolo[3,4-a]carbazole-1,3(2H,10bH)-dione (ent-8d). Following the general procedure and using catalyst 19 derived from hydroquinidine, the title compound was obtained in 89% yield as a pale yellow solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.75 mL/min, $t_{\text{maj}} = 33.1$ min, $t_{\text{min}} = 21.4$ min, 86% *ee*). $[\alpha]_{\text{D}}^{20} = -246$ ($c = 0.50$ in CH_2Cl_2). Spectral data were identical to compound 8d.

(3aS,4S,10aS,10bS)-4-Methyl-2-phenyl-10-(2,2,2-trifluoroacetyl)-3a,4,10,10a-tetrahydropyrrolo[3,4-a]carbazole-1,3(2H,10bH)-dione (8e). Following the general procedure and using 2 equivalents of diene 6e the title compound was obtained in 58% yield as a pale yellow solid. A single diastereoisomer was observed by ^1H NMR in the crude reaction mixture. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.75 mL/min, $t_{\text{maj}} = 16.9$ min, $t_{\text{min}} = 20.7$ min, 92% *ee*). $[\alpha]_{\text{D}}^{20} = +221$ ($c = 0.50$ in CH_2Cl_2); mp = 68-69 °C; ^1H NMR (CDCl_3 , 400 MHz) [some signals show multiple resonances for the presence of different rotamers due to restricted rotation around the trifluoroacetamide C-N bond] δ 8.39 (m, 0.5H), 7.52-7.48 (m, 1H), 7.37 (m, 0.5H), 7.34-7.27 (m, 4H), 7.22-7.15 (m, 1H), 6.90-6.84 (m, 2H), 6.17-6.12 (m, 1H), 5.16 (br d, $J = 6.2$ Hz, 0.5H), 5.07 (br d, $J = 6.5$ Hz, 0.5H), 4.48 (br t, $J = 8.4$ Hz, 0.5H), 3.99 (br t, $J = 8.1$ Hz, 0.5H), 3.29 (dd, $J = 8.8, 6.2$ Hz, 1H), 2.72-2.60 (m, 1H), 1.68 (d, $J = 6.9$, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) the spectrum is reported but not described because most carbons show multiple resonances for the presence of different rotamers and coupling with ^{19}F . ^{19}F NMR (376 MHz, CDCl_3) [the spectrum shows two distinct resonances for the presence of different rotamers] δ -71.3, -72.3; ESI-MS: 449 [$\text{M}^+ + \text{Na}$]. The relative configuration between C4 and C3a was tentatively assigned by means of NMR NOE experiments. The signals of the ^1H NMR spectrum were assigned by means of gCOSY NMR experiments. Irradiation at 3.29 ppm ($\text{H}_{3\text{a}}$) gives signals at 3.99 and 4.48 ppm ($\text{H}_{10\text{b}}$) and at 2.67 ppm (H_4). Irradiation at 2.67 ppm (H_4) gives signals at 3.29 ppm ($\text{H}_{3\text{a}}$), 3.99 and 4.48 ppm ($\text{H}_{10\text{b}}$) and 5.07 and 5.16 ppm ($\text{H}_{10\text{a}}$). Irradiation at 1.68 ppm (C_4CH_3) does not give any significant signal at 3.29 ppm ($\text{H}_{3\text{a}}$). Therefore, a 3a,4-*cis* configuration can be assumed.



(3aS,10aS,10bS)-2-Methyl-10-(2,2,2-trifluoroacetyl)-3a,4,10,10a-tetrahydropyrrolo[3,4-a]carbazole-1,3(2H,10bH)-dione(8f). Following the general procedure the title compound was obtained in 89% yield as a pale yellow solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.75 mL/min, $t_{\text{maj}} = 13.7$ min, $t_{\text{min}} = 16.2$ min, 98% *ee*). $[\alpha]_{\text{D}}^{20} = +306$ ($c = 0.50$ in CH_2Cl_2); mp = 74-80 °C; ^1H NMR (CDCl_3 , 400 MHz) [some signals show multiple resonances for the presence of different rotamers due to restricted rotation around the trifluoroacetamide C-N bond] δ 8.38 (bd, $J = 8.5$ Hz, 0.5H), 7.49-7.41 (m, 1.5H), 7.37-7.27 (m, 1H), 7.20-7.10 (m, 1H), 6.28-6.19 (m, 1H), 5.06 (br s, 0.5H), 4.99 (br s, 0.5H), 4.36 (t, $J = 8.3$ Hz, 0.5H), 3.83 (t, $J = 8.1$ Hz, 0.5H), 3.25 (br t, $J = 8.3$ Hz, 1H), 3.09 (dd, $J = 15.4, 7.7$ Hz, 1H), 2.77 (s, 3H), 2.34-2.21 (m, 1H); ^{13}C NMR (CDCl_3 , 150 MHz) the spectrum is reported but not described because most carbons show multiple resonances for the presence of different rotamers and coupling with ^{19}F . ^{19}F NMR

(CDCl₃, 376 MHz,) [the spectrum shows two distinct resonances for the presence of different rotamers] δ - 71.4, - 72.4; ESI-MS: 373 [M+ + Na].

(3aS,10aS,10bS)-2-Benzyl-10-(2,2,2-trifluoroacetyl)-3a,4,10,10-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,10*bH*)-dione(8g). Following the general procedure the title compound was obtained in 89% yield as a pale yellow solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.75 mL/min, t_{maj} = 14.2 min, t_{min} = 17.5 min, 96% *ee*). $[\alpha]_{\text{D}}^{20}$ = +284 (c = 0.5 in CH₂Cl₂); mp = 68-72 °C; ¹H NMR (CDCl₃, 400 MHz) [some signals show multiple resonances for the presence of different rotamers due to restricted rotation around the trifluoroacetamide C-N bond] δ 8.38 (bd, J = 8.6 Hz, 0.5H), 7.49 (bd, J = 8.6 Hz, 0.5H), 7.37-7.28 (m, 2H), 7.18-7.04 (m, 4H), 6.92 (br d, J = 7.6 Hz, 2H), 6.18-6.06 (m, 1H), 5.08-5.04 (m, 0.5H), 5.02-4.95 (m, 0.5H), 4.48 (d, J = 14.8 Hz, 1H), 4.42-4.32 (m, 1.5H), 3.86 (br t, J = 7.9 Hz, 0.5H), 3.23 (ddd, J = 8.6, 6.8, 1.6 Hz, 1H), 3.14-3.01 (m, 1H), 2.32-2.20 (m, 1H); ¹³C NMR (CDCl₃, 150 MHz) the spectrum is reported but not described because most carbons show multiple resonances for the presence of different rotamers and coupling with ¹⁹F; ¹⁹F NMR (CDCl₃, 376 MHz) [the spectrum shows two distinct resonances for the presence of different rotamers] δ -71.7, -72.6; ESIMS: 449 [M+ + Na].

(3aS,10aS,10bS)-2-*tert*-Butyl-10-(2,2,2-trifluoroacetyl)-3a,4,10,10-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,10*bH*)-dione(8h). Following the general procedure and performing the reaction at -30 °C for 72 h, the title compound was obtained in 81% yield as a pale yellow solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 95:5, flow rate 0.75 mL/min, t_{maj} = 12.7 min, t_{min} = 11.9 min, 88% *ee*). $[\alpha]_{\text{D}}^{20}$ = +210 (c = 0.25 in CH₂Cl₂); mp = 52-55 °C; ¹H NMR (CDCl₃, 400 MHz) [some signals show multiple resonances for the presence of different rotamers due to restricted rotation around the trifluoroacetamide C-N bond] δ 8.38 (d, J = 8.8 Hz, 0.6H) 7.52-7.42 (m, 1.4H), 7.36-7.27 (m, 1H), 7.19-7.12 (m, 1H), 6.30-6.24 (m, 1H), 5.03- 4.99 (m, 0.6H), 4.96-4.90 (m, 0.4H), 4.14 (t, J = 8.1 Hz, 0.4H), 3.68 (t, J = 8.1 Hz, 0.6H), 3.11-3.03 (m, 2H), 2.27-2.16 (m, 1H), 1.27 (s, 3.6H), 1.25 (s, 5.4H); ¹³C NMR (CDCl₃, 150 MHz) the spectrum is reported but not described because most carbons show multiple resonances for the presence of different rotamers and coupling with ¹⁹F; ¹⁹F NMR (CDCl₃, 376 MHz) [the spectrum shows two distinct resonances for the presence of different rotamers] δ -71.7, -72.6; ESIMS: 415 [M+ + Na].

(3aS,10aS,10bS)-10-(2,2,2-trifluoroacetyl)-3a,4,10,10-tetrahydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,10*bH*)-dione(8i). Following the general procedure the title compound was obtained in 72% yield as a pale yellow solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.75 mL/min, t_{maj} = 14.0 min, t_{min} = 17.4 min, 52% *ee*). $[\alpha]_{\text{D}}^{30}$ = +148 (c = 0.19 in EtOAc); mp = 208-210 °C; ¹H NMR (acetone-*d*₆, 600 MHz) [some signals show multiple resonances for the presence of different rotamers due to restricted rotation around the trifluoroacetamide C-N bond] δ 10.01 (br s, 1H), 8.32 (d, J = 8.1 Hz, 0.7H), 7.67-7.61 (m, 1H), 7.45 (br s, 0.3H), 7.34 (br t, J = 7.7 Hz, 1H), 7.20 (br t, J = 7.7 Hz, 1H), 6.48-6.45 (m, 1H), 5.32 (br s, 0.7H), 5.10 (br s, 0.3H), 4.34 (t, J = 7.6 Hz, 0.3H), 4.02 (t, J = 7.6 Hz, 0.7H), 3.46-3.36 (m, 1H), 2.92 (dd, J = 15.4, 7.4 Hz, 1H), 2.46- 2.34 (m, 1H); ¹³C NMR (acetone-*d*₆, 150 MHz) the spectrum is reported but not described because most carbons show multiple resonances for the presence of different rotamers and coupling with ¹⁹F; ¹⁹F NMR (acetone-*d*₆, 376 MHz) [the spectrum shows two distinct resonances for the presence of different rotamers] δ -71.6, -72.5; ESIMS: 359 [M+ +Na].

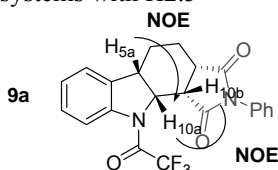
(4aS,11aS,11bS)-11-(2,2,2-trifluoroacetyl)-4a,5,11,11a-tetrahydro-11bH-benzo[a]carbazole-1,4-dione (8j). Following the general procedure the title compound was obtained in 83% yield as a red solid. The *ee* of the product was determined by HPLC using a Chiralcel OJ-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.75 mL/min, $t_{\text{maj}} = 70.9$ min; $t_{\text{min}} = 64.9$ min, >99% *ee*). $[\alpha]_{\text{D}_{30}} = +423$ ($c = 0.13$ in CH_2Cl_2); mp = 158-161 °C; ^1H NMR (acetone- d_6 , 400 MHz) [some signals show multiple resonances for the presence of different rotamers due to restricted rotation around the trifluoroacetamide C-N bond] δ 8.37 (br s, 0.5H), 7.60 (d, $J = 7.4$ Hz, 1H), 7.53 (br s, 0.5 H), 7.37 (dt, $J_{\text{t}} = 7.8$ Hz, $J_{\text{d}} = 1.1$ Hz, 1H), 7.23 (dt, $J_{\text{t}} = 7.4$, $J_{\text{d}} = 1.0$ Hz, 1H), 6.71 (d, $J = 10.3$ Hz, 1H), 6.58 (d, $J = 10.3$ Hz, 1H), 6.14 (dt, $J_{\text{d}} = 5.0$ Hz, $J_{\text{t}} = 3.2$ Hz, 1H), 5.19 (br s, 1H), 4.65 (br s, 0.5H), 4.39 (br s, 0.5H), 3.63-3.52 (m, 1H), 2.83- 2.69 (m, 1H), 2.47-2.36 (m, 1H); ^{13}C NMR (150 MHz, CDCl_3) the spectrum is reported but not described because most carbons show multiple resonances for the presence of different rotamers and coupling with ^{19}F ; ^{19}F NMR (376 MHz, CDCl_3) δ -71.8; ESIMS: 370 [M+ + Na].

(4aR,11aR,11bR)-11-(2,2,2-trifluoroacetyl)-4a,5,11,11a-tetrahydro-11bH-benzo[a]carbazole-1,4-dione (ent-8j). Following the general procedure and using catalyst **19** derived from hydroquinidine, the title compound was obtained in 71% yield as a red solid. The *ee* of the product was determined by HPLC using a Chiralcel OJ-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.75 mL/min, $t_{\text{maj}} = 64.9$ min; $t_{\text{min}} = 70.9$ min, 98% *ee*). $[\alpha]_{\text{D}_{30}} = -411$ ($c = 0.26$ in CH_2Cl_2). Spectral data were identical to compound **8j**.

(5aS,12aS,12bS)-12-(2,2,2-trifluoroacetyl)-5a,6,12,12a-tetrahydro-12bH-naphtho[2,3-a]carbazole-5,13-dione (8k). Following the general procedure the title compound was obtained in 77% yield as a pale yellow solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*hexane/ *i*PrOH 80:20, flow rate 0.75 mL/min, $t_{\text{maj}} = 15.8$ min, $t_{\text{min}} = 14.0$ min, 96% *ee*). $[\alpha]_{\text{D}_{30}} = +386$ ($c = 0.39$ in CH_2Cl_2); mp = 173-174 °C; ^1H NMR (acetone- d_6 , 400 MHz) [some signals show multiple resonances for the presence of different rotamers due to restricted rotation around the trifluoroacetamide C-N bond] δ 8.41 (br s, 0.5H), 8.06 (dt, $J_{\text{d}} = 7.4$ Hz, $J_{\text{t}} = 1.2$ Hz, 1H), 7.90-7.80 (m, 3H), 7.60 (d, $J = 7.6$ Hz, 1H), 7.58 (br s, 0.5 H), 7.40 (dt, $J_{\text{t}} = 7.7$, $J_{\text{d}} = 1.2$ Hz, 1H), 7.24 (dt, $J_{\text{t}} = 7.6$ Hz, $J_{\text{d}} = 1.0$ Hz, 1H), 6.09 (dt, $J_{\text{d}} = 4.1$ Hz, $J_{\text{t}} = 3.5$ Hz, 1H), 5.33 (br s, 1H), 4.87 (br s, 0.5H), 4.64 (br s, 0.5H), 3.77 (br s, 1H), 2.86-2.75 (m, 1H), 2.37-2.26 (m, 1H); ^{13}C NMR (150 MHz, CDCl_3) the spectrum is reported but not described because most carbons show multiple resonances for the presence of different rotamers and coupling with ^{19}F ; ^{19}F NMR (376 MHz, CDCl_3) δ -71.8; ESIMS: 420 [M+ + Na].

(3aS,5aS,10aR,10bS)-2-Phenyl-10-(2,2,2-trifluoroacetyl)-3a,4,5,5a,10,10a-hexahydro pyrrolo [3,4-a]carbazole-1,3(2H,10bH)-dione (9a). To a solution of compound **8a** (39 mg, 0.10 mmol) in a EtOAc/MeOH mixture (1:1, 2 mL), Pd/C 10% (25 mg) was added. The suspension was stirred at room temperature overnight under a H_2 atmosphere (1 atm, balloon), then filtered through a plug of celite, the plug washed with EtOAc, and the solvents evaporated. ^1H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The title compound was then obtained after chromatographic purification on silica gel (CH_2Cl_2) in 88% yield as a white solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.75 mL/min, $t_{\text{maj}} = 25.4$ min, $t_{\text{min}} = 29.4$ min, 97% *ee*) and was found to be consistent with the *ee* of the starting compound **3a** (98% *ee*). $[\alpha]_{\text{D}_{30}} = +201$ ($c = 0.27$ in CH_2Cl_2); mp = 85-88 °C; ^1H NMR (CDCl_3 , 400 MHz) [some signals show multiple resonances for the presence of different rotamers due to restricted rotation around the trifluoroacetamide C-N bond] δ 8.15 (d, $J = 6.0$ Hz, 0.6H), 7.41 (br s, 0.4H), 7.36-7.24 (m, 4H), 7.22-7.14 (m, 2H), 6.89-6.71 (m, 2H), 5.20-5.02 (m, 1H), 4.01-3.87 (m, 1H), 3.82 (t, $J = 8.6$ Hz,

0.4H), 3.55 (t, $J = 8.6$ Hz, 0.6H), 3.33 (t, $J = 6.7$ Hz, 1H), 2.53-2.43 (m, 1H), 2.34-2.23 (m, 1H), 2.04-1.87 (m, 1H), 1.68- 1.52 (m, 1H); ^{13}C NMR (150 MHz, CDCl_3) the spectrum is reported but not described because most carbons show multiple resonances for the presence of different rotamers and coupling with ^{19}F ; ^{19}F NMR (376 MHz, CDCl_3) [the spectrum shows two distinct resonances for the presence of different rotamers] δ -71.7, -71.9; ESIMS: 437 [$\text{M}^+ + \text{Na}$]. The relative configuration between C_{5a} and C_{10a} was tentatively assigned by means of NMR NOE experiments. The signals of the ^1H NMR spectrum were assigned by means of gCOSY NMR experiments. Irradiation at 5.10 ppm (H_{10a}) gives signals at 4.01-3.87 ppm (H_{5a}) and at 3.82 and 3.55 ppm (H_{10b}). Therefore, a 5a,10a-*cis* configuration can be assumed, deriving from hydrogenation occurring at the least hindered side of the double bond, in line with previous reports on the reduction of similar systems with H_2 .



(3a*S*,10b*S*)-2-Phenyl-4,5-dihydropyrrolo[3,4-*a*]carbazole-1,3(2*H*,3*aH*,10*H*,10b*H*)-dione (10a). To a test tube equipped with a magnetic stirring bar were sequentially added *N*-phenylmaleimide **7a** (26.0 mg, 0.15 mmol), CH_2Cl_2 (1.0 mL) and catalyst **18** (17.8 mg, 0.030 mmol). After cooling to -55°C , a pre-cooled solution of 3-vinylindole **6a** (25.7 mg, 0.18 mmol) in CH_2Cl_2 (0.50 mL), was added via a syringe. The mixture was then stirred at the same temperature, with no precautions to exclude moisture or air. After 48 h, acetone (2.4 mL) and a 9% w/w HCl solution (90 μL) were sequentially added and the mixture allowed to warm to room temperature. After 2 h stirring, sat. NaHCO_3 was then added slowly, and the product was extracted with CH_2Cl_2 (3x5 mL). The combined organic phases were dried (Na_2SO_4), filtered and evaporated. The title compound was then obtained after chromatographic purification on silica gel (CH_2Cl_2) as a white solid in quantitative yield. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.75 mL/min, $t_{\text{maj}} = 27.9$ min, $t_{\text{min}} = 22.7$ min, 97% *ee*). $[\alpha]_{\text{D}30} = +33$ ($c = 0.36$ in CH_2Cl_2); mp = 136-139 $^\circ\text{C}$; ^1H NMR (CDCl_3 , 400 MHz) δ 8.60 (br s, 1H), 7.53 (br d, $J = 7.7$ Hz, 1H), 7.47-7.35 (m, 3H), 7.30 (dt, $J_{\text{d}} = 8.1$ Hz, $J_{\text{t}} = 0.9$ Hz, 1H), 7.25-7.22 (m, 2H), 7.20 (dt, $J_{\text{t}} = 7.1$ Hz, $J_{\text{d}} = 1.4$ Hz, 1H), 7.14 (dt, $J_{\text{t}} = 7.1$ Hz, $J_{\text{d}} = 1.4$ Hz, 1H), 4.28 (dt, $J_{\text{d}} = 8.5$ Hz, $J_{\text{t}} = 1.3$ Hz, 1H), 3.56 (dt, $J_{\text{d}} = 8.3$ Hz, $J_{\text{t}} = 5.5$ Hz, 1H), 2.88 (ddt, $J_{\text{d}} = 16.2$, 1.5 Hz, $J_{\text{t}} = 5.5$ Hz, 1H), 2.77 (dddd, $J = 15.7$, 9.2, 5.0, 1.6 Hz, 1H), 2.48 (dq, $J_{\text{d}} = 13.5$ Hz, $J_{\text{q}} = 5.1$ Hz, 1H), 2.21-2.11 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 177.6, 175.3, 136.6, 131.6, 129.1, 128.7, 126.5, 126.4, 125.8, 122.5, 119.6, 118.4, 112.1, 111.2, 40.6, 40.0, 22.6, 17.8; ESI-MS: 339 [$\text{M}^+ + \text{Na}$].

Catalytic Reactions between 2-Vinylindole **21** and Maleimides **7a-d**; General Procedure.

In a test tube the maleimide **7a-d** (0.20 mmol) and catalyst **20** (17.2 mg, 0.04 mmol) were dissolved in CH_2Cl_2 (0.10 mL). The mixture was cooled to 0°C and 2-vinylindole **21** (34.3 mg, 0.24 mmol) was added. The reaction was left at this temperature for 84 h then directly purified by chromatography (silica gel, CH_2Cl_2 , then CH_2Cl_2 - Et_2O , 97:3).

(3a*R,10c*R**)-2-Phenyl-4,5,6,10c-tetrahydropyrrolo[3,4-*c*]carbazole-1,3(2*H*,3*aH*)-dione (23a).** Pale-yellow solid; yield: 10%; 58% *ee* [chiral HPLC (Daicel Chiralpak AD-H, *n*-hexane-*i*-PrOH, 80:20, flow rate 0.75 mL/min): $t_{\text{maj}} = 24.3$, $t_{\text{min}} = 28.1$ min. $[\alpha]_{\text{D}30} +129$ (c 0.25, CDCl_3). ^1H NMR (400 MHz, $\text{DMSO-}d_6$): $\delta = 11.01$ (s, 1 H), 7.73 (d, $J = 7.8$ Hz, 1 H), 7.42-7.38 (m, 2 H), 7.35-7.32 (m, 1 H), 7.27 (d, $J = 7.5$ Hz, 1 H), 7.18-7.15 (m, 2 H), 7.02 (t, $J = 6.9$ Hz, 1 H), 6.97 (t, $J = 6.9$ Hz, 1 H), 4.39 (d, $J = 7.9$ Hz, 1 H), 3.65 (dt, $J_{\text{d}} = 8.3$ Hz, $J_{\text{t}} = 4.8$ Hz, 1

H), 2.76 (dt, $J_d = 15.9$ Hz, $J_t = 4.9$ Hz, 1 H), 2.64 (ddd, $J_1 = 16.3$ Hz, $J_2 = 11.0$ Hz, $J_3 = 5.3$ Hz, 1 H), 2.41–2.35 (m, 1 H), 1.96–1.89 (m, 1 H). ^{13}C NMR (100 MHz, DMSO- d_6): $\delta = 178.8, 176.9, 136.4, 136.1, 133.1, 129.5, 128.8, 127.5, 127.3, 121.5, 119.9, 119.4, 111.5, 102.9, 60.4, 55.5, 21.4, 20.2$. MS (ESI+): $m/z = 339$ [M + Na+].

(3aR*,10cR*)-2-Methyl-4,5,6,10c-tetrahydropyrrolo[3,4-c]carbazole-1,3(2H,3aH)-dione (23b). Pale-yellow solid; yield: 12%; 72% ee [chiral HPLC (Daicel Chiralcel OD, *n*-hexane-*i*-PrOH, 80:20, flow rate 1.0 mL/min): $t_{\text{maj}} = 21.1$ min, $t_{\text{min}} = 14.8$ min. [a] $D_{30} +146$ (c 0.25, CDCl $_3$). ^1H NMR (600 MHz, CDCl $_3$): $\delta = 8.00\text{--}7.93$ (m, 2 H), 7.26–7.22 (m, 1 H), 7.17–7.13 (m, 2 H), 4.28 (d, $J = 7.9$ Hz, 1 H), 3.38–3.34 (m, 1 H), 2.91 (s, 3 H), 2.72–2.61 (m, 2 H), 2.60–2.54 (m, 1 H), 1.99–1.92 (m, 1 H). ^{13}C NMR (150 MHz, CDCl $_3$): $\delta = 179.0, 177.3, 135.5, 134.2, 126.7, 122.0, 120.2, 119.7, 110.5, 103.6, 40.1, 39.5, 24.7, 21.3, 19.8$. MS (ESI+): $m/z = 277$ [M + Na+].

(3aR*,10cR*)-2-Benzyl-4,5,6,10c-tetrahydropyrrolo[3,4-c]carbazole-1,3(2H,3aH)-dione (23c). Pale-yellow solid; yield: 15%; 72% ee [chiral HPLC (Daicel Chiralpak AD-H, *n*-hexane-*i*-PrOH, 80:20, flow rate 0.75 mL/min): $t_{\text{maj}} = 21.0$ min, $t_{\text{min}} = 17.1$ min. [a] $D_{30} +142$ (c 0.45, CDCl $_3$). ^1H NMR (400 MHz, DMSO- d_6): $\delta = 10.97$ (s, 1 H), 7.72 (d, $J = 8.2$ Hz, 1 H), 7.27–7.16 (m, 4 H), 7.12–7.07 (m, 2 H), 7.06–6.94 (m, 2 H), 4.51 (d, $J = 15.4$ Hz, 1 H), 4.48 (d, $J = 15.4$ Hz, 1 H), 4.31 (d, $J = 7.7$ Hz, 1 H), 3.54 (dt, $J_d = 7.8$ Hz, $J_t = 4.9$ Hz, 1 H), 2.73 (dt, $J_d = 16.3$ Hz, $J_t = 4.5$ Hz, 1 H), 2.55–2.54 (m, 1 H), 2.32–2.22 (m, 1 H), 1.94–1.83 (m, 1 H). ^{13}C NMR (100 MHz, DMSO- d_6): $\delta = 179.6, 177.7, 136.9, 136.3, 135.8, 129.1, 128.0, 127.8, 127.3, 121.5, 119.9, 119.4, 111.5, 103.1, 55.6, 41.8, 22.4, 20.3$. MS (ESI+): $m/z = 353$ [M + Na+].

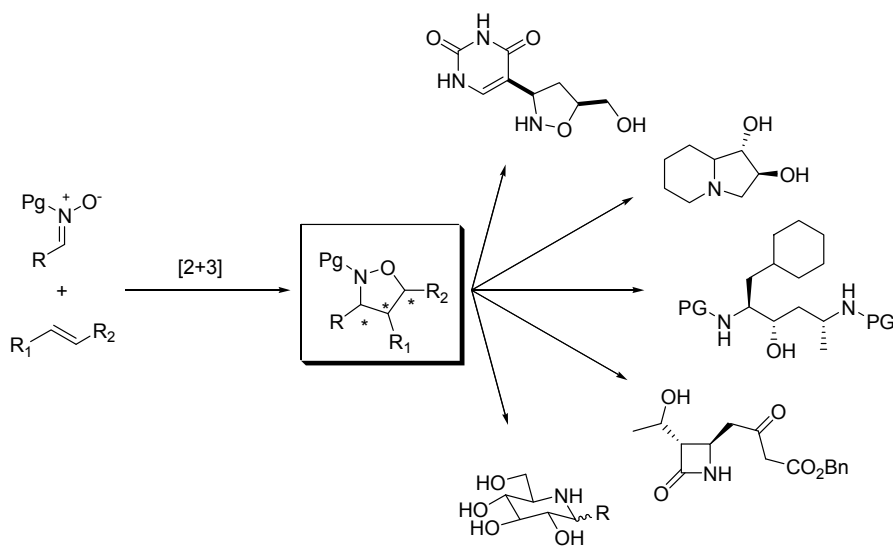
(3aR*,10cR*)-2-tert-Butyl-4,5,6,10c-tetrahydropyrrolo[3,4-c]carbazole-1,3(2H,3aH)-dione (23d). Pale-yellow solid; yield: 14%; 68% ee [chiral HPLC (Daicel Chiralpak AD-H, *n*-hexane-*i*-PrOH, 80:20, flow rate 0.75 mL/min): $t_{\text{maj}} = 7.6$ min, $t_{\text{min}} = 9.0$ min. [a] $D_{30} +177$ (c 0.35, CDCl $_3$). ^1H NMR (400 MHz, CDCl $_3$): $\delta = 7.96\text{--}7.91$ (m, 2 H), 7.30–7.25 (m, 1 H), 7.18–7.13 (m, 2 H), 4.14 (d, $J = 8.2$ Hz, 1 H), 3.21 (dt, $J_d = 8.2$ Hz, $J_t = 4.9$ Hz, 1 H), 2.69 (dd, $J_1 = 7.2$ Hz, $J_2 = 4.4$ Hz, 1 H), 2.50–2.41 (m, 1 H), 1.99–1.89 (m, 2 H), 1.51 (s, 9 H). ^{13}C NMR (400 MHz, CDCl $_3$): $\delta = 180.3, 178.5, 135.8, 134.5, 127.3, 122.1, 120.4, 120.1, 110.7, 104.3, 58.5, 40.3, 40.2, 28.6, 22.1, 20.1$. MS (ESI+): $m/z = 219$ [M + Na+].

(3aR*,10cR*)-2-Methyl-5-(1-methyl-2,5-dioxopyrrolidin-3-yl)-4,5,6,10c-tetrahydropyrrolo [3,4-c]carbazole-1,3(2H,3aH)-dione (24). White solid; 15% ee [chiral HPLC (Daicel Chiralpak AD-H, *n*-hexane-*i*-PrOH, 80:20, flow rate 0.75 mL/min): $t_{\text{min}} = 21.3$ (minor), $t_{\text{maj}} = 53.4$ min (major)]. ^1H NMR (400 MHz, DMSO- d_6): $\delta = 11.03$ (s, 1 H), 7.75 (d, $J = 8.0$ Hz, 1 H), 7.29 (d, $J = 8.0$ Hz, 1 H), 7.06 (t, $J = 7.6$ Hz, 1 H), 7.00 (t, $J = 6.8$ Hz, 1 H), 4.22 (dd, $J_1 = 7.9$ Hz, $J_2 = 1.6$ Hz, 1 H), 3.78 (quint, $J = 4.3$ Hz, 1 H), 3.57–3.49 (m, 1 H), 3.35–3.25 (m, 1 H), 2.89 (s, 3 H), 2.73 (s, 3 H), 2.66 (dd, $J_1 = 18.1$ Hz, $J_2 = 9.3$ Hz, 1 H), 2.18 (dd, $J_1 = 18.2$ Hz, $J_2 = 4.4$ Hz, 1 H), 2.08 (dddd, $J_1 = 13.2$ Hz, $J_2 = 7.6$ Hz, $J_3 = 4.7$ Hz, $J_4 = 2.8$ Hz, 1 H), 1.53 (dt, $J_t = 12.6$ Hz, $J_d = 5.5$ Hz, 1 H). ^{13}C NMR (100 MHz, DMSO- d_6): $\delta = 179.3, 178.8, 177.7, 177.0, 136.7, 135.3, 127.0, 122.0, 120.3, 119.6, 111.7, 105.6, 55.6, 41.6, 30.9, 30.7, 25.2, 25.0, 21.7$. MS (ESI+): $m/z = 388$ [M + Na+].

2.2 Asymmetric Formal [3+2] Cycloaddition with in Situ Generated N-Carbamoyl Nitrones¹

2.2.1 Introduction

The [3+2] cycloaddition between nitrones and alkenes is an extremely powerful synthetic method for the creation of complex heterocyclic structures.² It offers the possibility to generate isoxazolidines, five membered heterocycles containing adjacent nitrogen oxygen atoms, with up to three new contiguous stereocenters. As a result of the labile nature of the N-O bond under mildly reducing conditions, isoxazolidines have long been regarded as important synthetic intermediate and have been extensively utilized as 1,3-aminoalcohol equivalents for the synthesis of a wide variety of natural products such as alkaloids, amino acids, lactams and amino sugars (Scheme 1).³ Besides, isoxazolidines bear considerable interest themselves as nucleoside analogues.⁴



Scheme 1

Usually regarded as a concerted but asynchronous suprafacial process, electron-deficient alkenes are often involved in reactions with nitrones (direct electron demand 1,3 dipolar

¹ C. Gioia, F. Fini, A. Mazzanti, L. Bernardi, A. Ricci, *J. Am. Chem. Soc.*, **2009**, *131*, 9614.

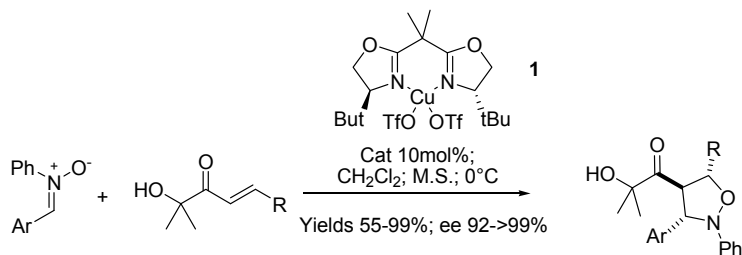
² For a recent review see: P. Merino In *Science of Synthesis*, Vol. 27; A. Padwa, Ed.; Thieme: Stuttgart, **2004**, 511.

³ M. Fredrickson, *Tetrahedron*, **1997**, *53*, 403.

⁴ (a) U. Chiacchio, E. Balestrieri, B. Macchi, D. Iannazzo, A. Piperno, A. Rescifina, R. Romeo, M. Saglimbeni, M. T. Sciortino, V. Valveri, A. Mastino, G. Romeo, *J. Med. Chem.*, **2005**, *48*, 1389. (b) S. P. Rowe, R. J. Casey, B. B. Brennan, S. J. Buhrlage, A. K. Mapp, *J. Am. Chem. Soc.*, **2007**, *129*, 10654.

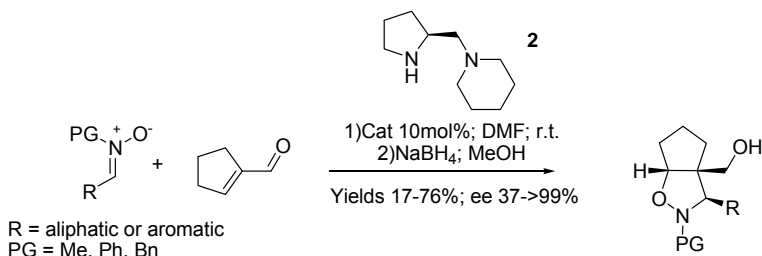
cycloaddition), with the interaction between the LUMO of the alkene and the HOMO of the nitron being the determinant for the relative orientation of the reactants.

The high synthetic value of this cycloaddition led to the development of several asymmetric catalytic methods. A remarkable example was introduced by Palomo and co-workers in the asymmetric [3+2] cycloaddition of phenyl-nitrones with α -hydroxy enones promoted by chiral Lewis acids (Scheme 2).⁵ Catalyst **1** demonstrated to produce the cycloadducts with very high combined levels of regio- and stereoselectivity.



Scheme 2

As previously reported in Scheme 11 (Chapter 1), MacMillan and co-workers developed the first enantioselective organocatalytic 1,3-dipolar cycloaddition promoted through an iminium-ion activation.⁶ In this case *N*-benzyl, *N*-methyl and *N*-allyl nitrones could react with α,β unsaturated aldehydes for the formation of optically active isoxazolidines in high yields and high values of enantioselectivity. With the same activation path, few years later, Karlsson and co-workers reported their studies on the catalytic performance of the chiral pyrrolidine **2** in the 1,3-dipolar cycloaddition reaction of the 1-cycloalkene-1-carboxaldehydes with different kind of nitrones (Scheme3).⁷



Scheme 3

A different approach was introduced by Yamamoto and co-workers (Scheme 4). For the first time, they reported a remarkable example of 1,3 dipolar cycloaddition involving ethyl vinyl ether and diaryl nitrones activated by means of the chiral Brønsted acid **3**.⁸ Innovative features reside in a rarely studied direct dipolar cycloaddition involving electron-rich dienophiles, with

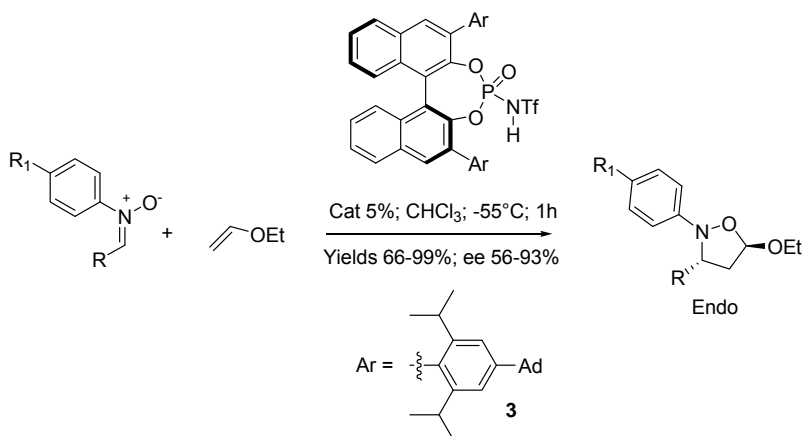
⁵ C. Palomo, M. Oiarbide, E. Arceo, J. M. Garcia, R. Lopez, A. Gonzalez, A. Linden, *Angew. Chem. Int. Ed.*, **2005**, *44*, 6187.

⁶ K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2000**, *122*, 4243.

⁷ S. Karlsson, H. E. Hogberg, *Eur. J. Org. Chem.*, **2003**, 2782.

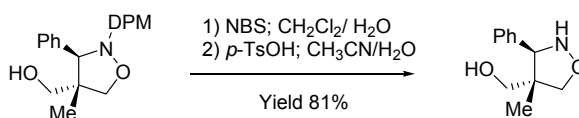
⁸ P. Jiao, D. Nakashima, H. Yamamoto, *Angew. Chem., Int. Ed.*, **2008**, *47*, 2411.

an auxiliary Brønsted acid catalyst able to increase the electrophilic character of the nitrones. Furthermore, in contrast with the results obtained under Lewis acid activation,⁹ a marked endo diastereoselectivity was reported.



Scheme 4

These and several other catalytic asymmetric 1,3 dipolar cycloaddition reactions of nitrones, involving either metallorganic and organic catalysts,¹⁰ invariably involved *N*-benzyl- and *N*-aryl-substituted nitrones. The reason for the diffuse use of these nitrones resides in their stability, easy preparation and storage, but gives isoxazolidines bearing nitrogen protecting groups that are very difficult to remove without cleavage of the N-O bond. The unfeasibility of the preparation of unprotected isoxazolidines for further elaborations is a significant limitation of these otherwise exceptional methods, given the mentioned biological interest in these heterocycles as nucleoside analogues.⁴ One exception, wherein oxidatively removable diphenylmethyl protecting groups were used, has been reported.¹¹ However, rather harsh oxidative conditions (NBS) had to be used to remove this particular protecting group (Scheme 5).



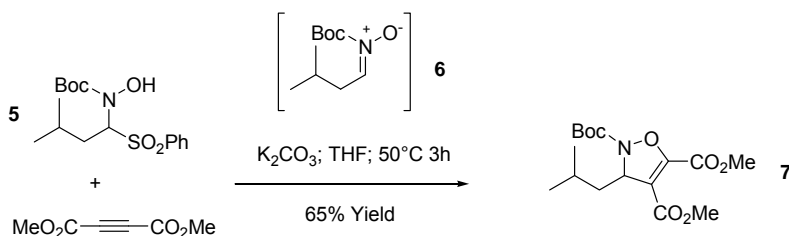
Scheme 5

⁹ K. B. Simonsen, P. Bayon, R. G. Hazell, K. V. Gothelf, K. A. Jørgensen, *J. Am. Chem. Soc.*, **1999**, *121*, 3845.

¹⁰ For a review, see: (a) K. V. Gothelf, K. A. Jørgensen, *Chem. Commun.*, **2000**, 1449. For recent examples, see: (b) D. A. Evans, H. -J Song, K. R. Fandrick, *Org. Lett.*, **2006**, *8*, 3351. (c) M. P. Sibi, Z. Ma, C. P. Jasperse, *J. Am. Chem. Soc.*, **2004**, *126*, 718. (d) T. Kano, T. Hashimoto, K. Maruoka, *J. Am. Chem. Soc.*, **2005**, *127*, 11926.

¹¹ For an oxidatively removable *N*-diphenylmethyl group, see: (a) T. Hashimoto, M. Omote, T. Kano, K. Maruoka, *Org. Lett.*, **2007**, *9*, 4805. For carbohydrate derivatives as hydrolytically removable chiral auxiliaries, see: (b) A. Vasella, *Helv. Chim. Acta*, **1977**, *60*, 1273.

Obviously, readily removable protecting groups at nitrogen, such as carbamoyl, in the isoxazolidine products would be highly desirable. However, just few contributions in the literature have reported nitrones bearing electron-withdrawing groups at nitrogen for use in 1,3-cycloadditions¹² due to their high reactivity and instability. Furthermore, all examples deal with non-asymmetric processes. In this context, Denis and co-workers developed *tert*-butyl (phenylsulfonyl)alkyl-*N*-hydroxycarbamates as *N*-(Boc)-protected nitrones precursors (Scheme 6), overcoming the instability of *N*-carbamoyl nitrones by their formation in situ.¹³



Scheme 6

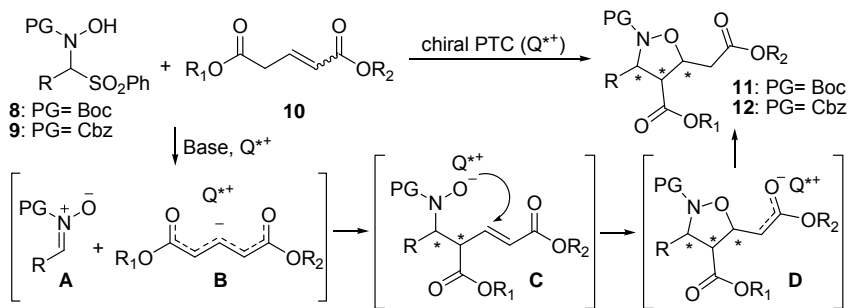
The formation of product **7** proved undoubtedly that sulfone **5** could suffer a base-assisted elimination of the phenylsulfonyl group, to provide the unstable *N*-(Boc) nitrone **6**, trapped by the reaction with an acetylenedicarboxylate in the reaction mixture. The advantages deriving from this kind of approach concern the presence of easily removable nitrogen protecting groups, the easy synthetic procedures and affordable storage conditions of the nitrone precursors.

On this basis and in view of the knowledge recently developed in our group for the in situ generation of *N*-carbamoyl imines by means of phase-transfer catalysis (PTC),¹⁴ we decided to develop a novel asymmetric formal [3+2] nitrone cycloaddition reaction using *N*-Boc- and *N*-Cbz-protected *N*-hydroxy-*R*-amido sulfones (**8** and **9**, respectively) as nitrone precursors (Scheme 7). However, to proceed under phase-transfer catalyzed conditions, a suitable anionic dipolarophile, able to interact with the cationic chiral catalyst had to be identified. This proved to be a considerable challenge, as all electron rich dienophiles used in inverse-electron-demand 1,3-dipolar cycloaddition reactions with nitrones are neutral electron rich compounds such as vinyl ethers. Glutaconates **10** were finally selected as potentially suitable reaction partners for the formation of formal anionic dipolarophiles.

¹² (a) S. A. Hussain, A. H. Sharma, M. J. Perkins, D. Griller, *J. Chem. Soc., Chem. Commun.*, **1979**, 289. (b) K. M. Partridge, M. E. Anzovino, T. P. Yoon, *J. Am. Chem. Soc.*, **2008**, *130*, 2920. (c) X. Guinchard, Y. Vallee, J. -N. Denis, *Org. Lett.*, **2005**, *7*, 5147.

¹³ X. Guinchard, Y. Vallee, J. -N. Denis, *Org. Lett.*, **2005**, *7*, 5147.

¹⁴ F. Fini, V. Sgarzani, D. Pettersen, R. P. Herrera, L. Bernardi, A. Ricci, *Angew. Chem., Int. Ed.*, **2005**, *44*, 7975. For an example of generation of imines under PTC conditions see: C. Palomo, M. Oiarbide, A. Laso, R. Lopez, *J. Am. Chem. Soc.*, **2005**, *127*, 17622.



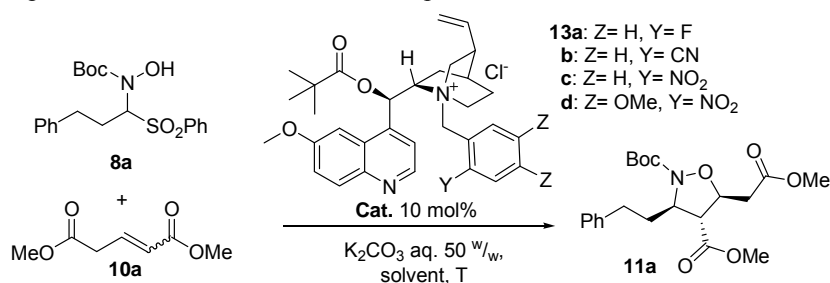
Scheme 7

In fact, using these particular multifunctional compounds, we expected that after highly reactive *N*-carbamoyl nitrones **A** were formed in situ, these dipoles could undergo an enantioselective Mannich addition by the deprotonated glutaconate coordinated by electrostatic interactions to the chiral quaternary ammonium enolate **B**. The resulting anionic adducts **C** should then directly cyclize intramolecularly to the cycloadducts **D**, possibly diastereoselectively, affording isoxazolidines **11** and **12**.

2.2.2 Results and discussions

Preliminary experiments on the reaction between sulfone **8a** and dimethyl glutaconate **10a** using *Cinchona* alkaloid-derived ammonium salts revealed that alkylation or acylation at the alcoholic moiety of the catalyst had a very positive effect on the observed asymmetric induction. In particular, useful enantioselectivities could be obtained by using Quinine-derived catalysts such as **13a-d** (Table 3), which bear an ortho-substituted benzyl group at the quinuclidinic nitrogen¹⁵ and the hindered pivaloyl ester at C9.¹⁶ Remarkably, the cycloadduct **11a** was always obtained as a single diastereoisomer. As shown in Table 3, when the reaction was performed in 10:1 toluene/CH₂Cl₂ at -30 °C with aqueous K₂CO₃ as the base, catalyst **13c** was identified as the best one, giving the cycloadduct **11a** with modest enantioselectivity (entries 1-4). A beneficial effect on the asymmetric induction was obtained by increasing the amount of CH₂Cl₂ and adding TBME (entries 5 and 6). Whereas the larger amount of CH₂Cl₂ markedly increased the solubility of catalyst **13c**, TBME facilitated solubilization of sulfone **8a** in the mixture. Finally, lowering the temperature to -42 °C and diluting the reaction led to a further improvement in the enantioselectivity (entry 7).

Table 1 Optimization of reaction conditions: representative results.^a



Entry	Cat.	Solvent	T (°C)	Conv. (%) ^b	Ee (%) ^c
1	13a	Tol/CH ₂ Cl ₂ 10/1	-30	90	70
2	13b	Tol/CH ₂ Cl ₂ 10/1	-30	90	75
3	13c	Tol/CH ₂ Cl ₂ 10/1	-30	90	76
4	13d	Tol/CH ₂ Cl ₂ 10/1	-30	90	70
5	13c	Tol/CH ₂ Cl ₂ 7/3	-30	65	82
6	13c	Tol/TBME/CH ₂ Cl ₂ 3.5/3.5/3	-30	>95	83
7 ^d	13c	Tol/TBME/CH ₂ Cl ₂ 3.5/3.5/3	-42	>95	91

^a Reactions performed on 0.10 mmol scale using 2 equiv of **10a**, 10 mol% of **13** and 5 equiv of K₂CO₃ aq. 50% w/w in the solvent (1.0 mL) for 21-24 h. ^b Determined by ¹H NMR analysis. ^c Determined by chiral HPLC analysis after Boc deprotection and Cbz derivatization. ^d 2 mL of solvent.

With these conditions in hand, we evaluated the scope of the formal [3+2] cycloaddition (Table 2); in every case a single diastereoisomer was observed by ¹H NMR analysis of the

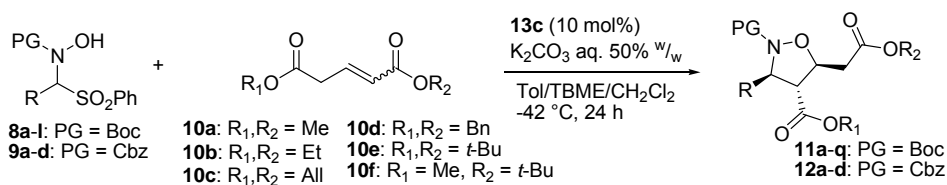
¹⁵ M. -S Yoo, B. -S. Jeong, J. -H. Lee, H. -G. Park, S. -S. Jew, *Org. Lett.*, **2005**, 7, 1129

¹⁶ T. B. Poulsen, L. Bernardi, M. Bell, K. A. Jørgensen, *Angew. Chem., Int. Ed.*, **2006**, 45, 6551.

crude mixture. Several *N*-Boc sulfones **8a-j** derived from aliphatic aldehydes reacted well with glutaconate **10a** to give the cycloadducts **11a-j** with good results (entries 1-10), even on a preparative scale (entries 1 and 9). Because of the low efficiency of the available preparations of *N*-hydroxy- α -amido sulfones from aromatic aldehydes, only the two sulfones **8k** and **8l** were tested, giving the corresponding products **11k** and **11l** with moderate enantioselectivities (entries 11 and 12). Variation of the dipolarophile using glutaconates **10b-f** in combination with sulfone **8a** showed a considerable sensitivity of the reaction to the sterics of the diester used. In particular, while a simple increase in reaction time was sufficient for obtaining the cycloadducts **11m-o** with good results (entries 13-15), the more hindered di-*tert*-butyl derivative **10e** did not react with sulfone **8a**, even at 0 °C (entry 16). To differentiate the two ester groups in the cycloadducts through a regioselective, sterically controlled Mannich reaction, *tert*-butyl methyl glutaconate **10f** was reacted with **8a**, but this gave **11q** in poor yield, only at 0 °C, and with a surprising lack of regioselectivity (entry 17). This result seems to suggest that the two ester groups are not as independent as assumed in the simplified two-step pathway depicted in Scheme 6, although ¹H NMR analysis of the crude products **11b-e** revealed the presence of small amounts (<7 mol %) of the linear non-cyclized products (adduct **C** in Scheme 7).

Finally this methodology was tested with Cbz as the protecting group, affording **12a-d** with good results (entries 18-21).

The quasi-enantiomeric quinidine catalyst **QD-13c** gave access to the opposite enantiomer of the products, though with lower selectivities (values in parentheses in entries 1, 6, 7, and 9).

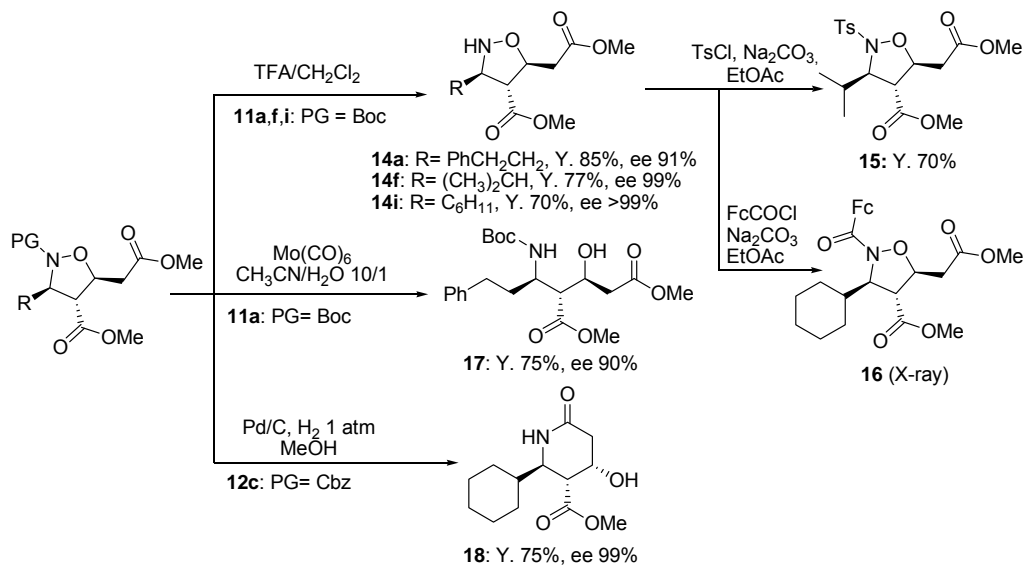
Table 2: Scope of the catalytic reaction^a

Entry	8,9	R	10	11,12	Yield (%) ^b	ee (%) ^c
1 ^d	8a	PhCH ₂ CH ₂	10a	11a	86 (86)	91 (60) ^e
2 ^f	8b	CH ₃	10a	11b	53	60 ^e
3	8c	CH ₃ CH ₂	10a	11c	80	88 ^e
4	8d	CH ₃ (CH ₂) ₃	10a	11d	70	92 ^e
5	8e	CH ₃ (CH ₂) ₅	10a	11e	72	94 ^e
6	8f	(CH ₃) ₂ CH	10a	11f	93 (87)	99 (80) ^e
7	8g	(CH ₃) ₂ CHCH ₂	10a	11g	97 (83)	98 (57) ^e
8	8h	<i>c</i> -C ₅ H ₉	10a	11h	97	99 ^e
9 ^g	8i	<i>c</i> -C ₆ H ₁₁	10a	11i	>99 (98)	>99 (83) ^e
10	8j	PhCH ₂	10a	11j	81	95 ^e
11 ^h	8k	Ph	10a	11k	>99	67
12	8l	4-BrC ₆ H ₄	10a	11l	63	60
13 ⁱ	8a	PhCH ₂ CH ₂	10b	11m	60	91
14 ⁱ	8a	PhCH ₂ CH ₂	10c	11n	76	94
15 ⁱ	8a	PhCH ₂ CH ₂	10d	11o	73	95
16 ^{ij}	8a	PhCH ₂ CH ₂	10e	11p	<10	-
17 ^{ij}	8a	PhCH ₂ CH ₂	10f	11q	25 ^k	73 ^l
18	9a	(CH ₃) ₂ CHCH ₂	10a	12a	60	75
19	9b	(CH ₃) ₂ CH	10a	12b	72	80
20	9c	<i>c</i> -C ₆ H ₁₁	10a	12c	>99	94
21	9d	<i>c</i> -C ₅ H ₉	10a	12d	68	85

^a Reactions performed with 0.10 mmol of **8a-l**, **9a-d**, 0.20 mmol of **10a-f**, 0.01 mmol of **13c** in Tol/TBME/CH₂Cl₂ 3.5/3.5/3 (0.05 M) and 0.50 mmol of K₂CO₃ aq. 50% w/w for 24 h. Results in parentheses refer to the opposite enantiomer, obtained using **QD-13c** as the catalyst. ^b Isolated yields. ^c Determined by chiral HPLC analysis. ^d 1.0 mmol scale. ^e Determined after Boc deprotection and Cbz derivatization. ^f Tol/TBME/CH₂Cl₂ 4.5/4.5/1 (0.10 M), 48 h. ^g 5.0 mmol scale. ^h Tol/CH₂Cl₂ 10/1. ⁱ 96 h. ^j 0 °C. ^k Regioisomeric ratio: 60:40 (¹H NMR analysis). ^l ee of the major regioisomer.

The synthetic utility of the obtained isoxazolidines was first demonstrated by chemoselectively performing Boc deprotection and N-O cleavage. In fact, it was possible to isolate the non-*N*-protected isoxazolidines **14a**, **14f**, and **14i** in good yields by treatment with trifluoroacetic acid (TFA) in CH₂Cl₂ (Scheme 8, top) and the *N*-Boc protected 1,3-aminoalcohol

17 using $\text{Mo}(\text{CO})_6$ as the reducing agent¹⁷ (Scheme 8, middle). The highly substituted δ -lactam **18** could instead be obtained by hydrogenolysis of **12c**, giving simultaneous *N*-Cbz deprotection and *N*-O cleavage, followed by a spontaneous lactamization (Scheme 8, bottom).



Scheme 8

The relative and absolute configurations of the cycloadducts were determined by nuclear Overhauser effect NMR experiments and by theoretical calculations of the ECD spectra and $[\text{R}]_D$ values using time dependent density functional theory performed on the tosyl derivative **15**. Finally, in order to confirm the correctness of this assignment, deprotected compound **14i** was subsequently functionalized with ferrocenoyl chloride (derivative **16**)¹⁸ in order to have a solid compound containing the heavy atom required for the X-ray analysis. Some good crystals of adduct **16** were obtained by slow evaporation of a wet hexane/ Et_2O solution. The absolute configuration deduced from X-ray diffraction confirms the assignment made by the TD-DFT approach (*3R,4R,5S*). The unit cell demonstrated to contain molecules bonded together by an hydrogen bond with a molecule of co-crystallized water (Figure 1).¹⁹

¹⁷ T. Kudoh, T. Ishikawa, Y. Shimizu, S. Saito, *Org. Lett.*, **2003**, *5*, 3875.

¹⁸ Aguilar-Aguilar, A.; Allen, A.D.; Peña Cabrera, E.; Fedorov, A. Fu, N.; Henry-Riyad, H. Leuninger, J. Schmid, U.; Tidwell, T. T.; Verma, R. *J. Org. Chem.*, **2005**, *70*, 9556.

¹⁹ Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-735613.

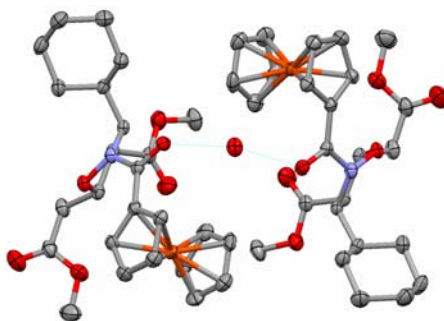


Figure 1

2.2.3 Conclusions

In summary, we have developed a novel organocatalytic process that uses simple reaction conditions and an inexpensive, readily available natural origin catalyst. This powerful synthetic strategy gave access to *N*-Boc- and *N*-Cbz-protected isoxazolidines in remarkable yields and enantioselectivities. The cycloadducts obtained demonstrated high versatility toward deprotection or selective cleavage of the N-O bond in high yields and retention of configuration.

2.2.4 Experimental section

^1H NMR and ^{13}C NMR were recorded on a Varian Mercury 400 or Inova 600 MHz spectrometer, in CDCl_3 , CD_3OD , CD_3CN as solvents. Chemical shifts are reported in the δ scale relative to residual CHCl_3 (7.26 ppm), CHD_2OD (3.34 ppm), CHD_2CN (1.96 ppm) for ^1H NMR and to the central line of CDCl_3 (77.0 ppm) CD_3OD (49.86 ppm), CD_3CN (1.79 ppm) for ^{13}C NMR. ^{13}C NMR were recorded with ^1H broadband decoupling. Unless otherwise noted all the NMR spectra were performed in CDCl_3 . Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES+) ionization techniques. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC. Melting points were measured on a Buchi smp-20 apparatus and are uncorrected. ECD spectra were recorded on a Jasco J- 810 dichrograph at 25°C in acetonitrile solutions, using path lengths of 1.0 cm, in the range 190-400 nm; reported $\Delta\epsilon$ values are expressed as $\text{L mol}^{-1}\text{cm}^{-1}$. Unless otherwise noted all commercially available solvents and reagents were used as received. *N*-carbamoyl- *N*-hydroxy- α -amido sulfones **8a-j**, **9a-d** were obtained following literature procedures.²⁰ Racemic samples were obtained using tetrabutylammonium bromide as the catalyst.

General procedure for the catalytic reactions. In a test tube equipped with a magnetic stirring bar were added in sequence the *N*-carbamoyl-*N*-hydroxy- α -amido sulfones **8a-j** or **9a-d** (0.10 mmol), catalyst **13c** (5.8 mg, 0.01 mmol) a toluene/MTBE/ CH_2Cl_2 mixture (2.0 mL, 3.5:3.5:3) and dimethyl glutaconate **10** (28 μL , 0.20 mmol). The reaction was cooled to -42°C , then K_2CO_3 50% w/w (0.10 mL, 5.0 mmol) was added. The reaction was vigorously stirred at the same temperature for 24 h, then Na_2CO_3 10% w/w (2 mL) was added and the mixture was allowed to warm to room temperature. The crude product was extracted with AcOEt (3x2 mL), the combined organic phases were filtered on a plug of silica to remove the catalyst, dried in vacuo and analyzed by means of ^1H NMR spectroscopy, which always showed the presence of a single diastereoisomer. The crude mixtures of compounds **11b-e** showed the presence of linear not-cyclized compound not exceeding 7%. The product was finally obtained after column chromatography on silica gel (*n*-hexane/AcOEt 90:10 then 80:20). Due to their very low UV absorbance which prevented the direct determination of their ee by HPLC-UV, the *N*-Boc protected cycloadducts **11a-j** were converted as follows to the corresponding *N*-Cbz derivatives. Pure compounds **11a-j** were dissolved in CH_2Cl_2 (0.5 mL), cooled to 0°C and treated with TFA (0.2 mL, 25 equiv.) After 5 h stirring at room temperature, Na_2CO_3 10% w/w (2 mL) was added, followed by EtOAc (2 mL) and CbzCl (0.1 mL, 7 equiv.). The reaction was vigorously stirred at room temperature overnight. The organic phase was extracted with AcOEt (3x2 mL) and filtered on a plug of silica. The solvents were evaporated and the pure *N*-Cbz product was obtained after chromatography on silica gel (*n*-hexane/AcOEt 90:10 then 80:20).

(3*R*,4*R*,5*S*)-2-(*tert*-Butyl 4-methyl 5-(2-methoxy-2-oxoethyl)-3-phenethylisoxazolidine-2,4-dicarboxylate (11a). Following the general procedure and performing the reaction at a 1.0 mmol, scale, compound **11a** was obtained as a colourless oil in 86% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 19.8 min, τ_{min} = 24.1 min); ^1H NMR (400 MHz) δ 7.30-7.25 (m, 2H), 7.22-7.15

²⁰ (a) X. Guinchard, Y. Vallée, J. -N Denis, *Org. Lett.*, **2005**, 7, 5147. (b) X. Guinchard, J. -N Denis, *J. Org. Chem.*, **2008**, 73, 2028.

(m, 3H), 4.55-4.43 (m, 2H), 3.72 (s, 3H), 3.69 (s, 3H), 2.89 (dd, $J_1 = 8.3$ Hz, $J_2 = 3.9$ Hz, 1H), 2.85-2.65 (m, 4H), 2.02-1.83 (m, 2H), 1.51 (s, 9H); ^{13}C NMR δ 171.7, 169.8, 157.9, 141.2, 128.4, 128.3, 125.9, 82.5, 80.0, 65.0, 58.4, 52.5, 52.0, 37.6, 36.9, 32.7, 28.2; ESIMS m/z 430 $[\text{M} + \text{Na}^+]$; $[\alpha]_{\text{D}}^{20} - 13.0$ ($c = 0.6$, CHCl_3), 91% ee.

(3R,4R,5S)-2-(tert-Butyl 4-methyl 5-(2-methoxy-2-oxoethyl)-3-phenethylisoxazolidine-2,4-dicarboxylate (ent-11a). Following the general procedure and using cat **QD-13c** compound **ent-47a** was obtained as a colourless oil in 86% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, $\tau_{\text{maj}} = 24.1$ min, $\tau_{\text{min}} = 19.8$ min); spectral data were identical to compound **47a**; $[\alpha]_{\text{D}}^{20} + 8$ ($c = 0.6$, CHCl_3), 60% ee.

(3R,4R,5S)-2-tert-Butyl 4-methyl 5-(2-methoxy-2-oxoethyl)-3-methylisoxazolidine-2,4-dicarboxylate (11b). Following the general procedure, but performing the reaction in a toluene/MTBE/ CH_2Cl_2 mixture (2.0 mL, 4.5:4.5:1.0), at -40 °C for 48 h compound **11b** was obtained as a colourless oil in 53% yield. The ee of the product was determined on the corresponding Cbz derivative obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, $\tau_{\text{maj}} = 14.0$ min, $\tau_{\text{min}} = 17.0$ min); ^1H NMR (400 MHz) δ 4.55-4.48 (m, 2H), 3.73 (s, 3H), 3.69 (s, 3H), 2.88-2.83 (m, 2H), 2.73 (dd, $J_1 = 16.3$ Hz, $J_2 = 6.9$ Hz, 1H), 1.50 (s, 9H), 1.38 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR δ 171.4, 169.8, 157.4, 82.4, 79.7, 60.7, 59.6, 52.4, 52.0, 37.0, 28.0, 21.7; ESIMS m/z 340 $[\text{M} + \text{Na}^+]$; $[\alpha]_{\text{D}}^{20} - 31$ ($c = 0.5$, CHCl_3), 60% ee.

(3R,4R,5S)-2-tert-Butyl 4-methyl 3-ethyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (11c). Following the general procedure, compound **11c** was obtained as a colourless oil in 80% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, $\tau_{\text{maj}} = 13.0$ min, $\tau_{\text{min}} = 16.0$ min); ^1H NMR (400 MHz) δ 4.49 (dt, $J_{\text{d}} = 8.5$ Hz, $J_{\text{t}} = 6.5$ Hz, 1H), 4.30 (dd, $J_1 = 7.9$ Hz, $J_2 = 4.3$ Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.88-2.81 (m, 2H), 2.72 (dd, $J_1 = 16.1$ Hz, $J_2 = 6.8$ Hz, 1H), 1.72-1.57 (m, 2H), 1.50 (s, 9H), 0.96 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR δ 171.8, 169.8, 158.0, 82.3, 79.9, 66.7, 58.1, 52.4, 52.0, 36.9, 28.8, 28.0, 10.7; ESIMS m/z 354 $[\text{M} + \text{Na}^+]$; $[\alpha]_{\text{D}}^{20} - 43$ ($c = 0.6$, CHCl_3), 88% ee.

(3R,4R,5S)-2-tert-Butyl 4-methyl 3-butyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (11d). Following the general procedure, compound **11d** was obtained as a colourless oil in 70% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, $\tau_{\text{maj}} = 12.0$ min, $\tau_{\text{min}} = 14.0$ min); ^1H NMR (400 MHz) δ 4.49 (dt, $J_{\text{d}} = 8.3$ Hz, $J_{\text{t}} = 6.8$ Hz, 1H), 4.15 (dd, $J_1 = 7.9$ Hz, $J_2 = 4.3$ Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.88-2.82 (m, 2H), 2.72 (dd, $J_1 = 16.1$ Hz, $J_2 = 6.8$ Hz, 1H), 1.68-1.29 (m, 6H), 1.50 (s, 9H), 0.90 (bt, $J = 6.9$ Hz, 3H); ^{13}C NMR δ 171.8, 169.8, 157.9, 82.3, 79.9, 65.3, 58.5, 52.4, 52.0, 37.0, 35.5, 28.4, 28.1, 22.1, 13.9; ESIMS m/z 382 $[\text{M} + \text{Na}^+]$; $[\alpha]_{\text{D}}^{20} - 37$ ($c = 0.6$, CHCl_3), 92% ee.

(3R,4R,5S)-2-tert-Butyl 4-methyl 3-hexyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (11e). Following the general procedure, compound **11e** was obtained as a colourless oil in 72% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-

hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 11.5 min, τ_{min} = 13.0 min); ^1H NMR (400 MHz) δ 4.49 (dt, J_{d} = 8.3 Hz, J_{t} = 6.2 Hz, 1H), 4.38 (dd, J_1 = 9.0 Hz, J_2 = 4.0 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.88-2.82 (m, 2H), 2.71 (dd, J_1 = 15.9 Hz, J_2 = 6.6 Hz, 1H), 1.70-1.23 (m, 10H), 1.50 (s, 9H), 0.87 (bt, J = 6.8 Hz, 3H); ^{13}C NMR δ 171.8, 169.8, 157.9, 82.3, 79.9, 65.3, 58.5, 52.4, 52.0, 37.0, 35.8, 31.7, 28.7, 28.1, 26.2, 22.5, 14.0; ESIMS m/z 410 [M + Na⁺]; $[\alpha]_{\text{D}}^{20}$ -25 (c = 0.6, CHCl₃), 94% ee.

(3R,4R,5S)-2-tert-Butyl 4-methyl 3-isopropyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (11f). Following the general procedure, compound **11f** was obtained as a colourless oil in 93% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 11.5 min, τ_{min} = 14.5 min); ^1H NMR (400 MHz) δ 4.46 (dt, J_{d} = 9.2 Hz, J_{t} = 6.1 Hz, 1H), 4.15 (dd, J_1 = 7.9 Hz, J_2 = 4.3 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.96 (dd, J_1 = 8.8 Hz, J_2 = 5.2 Hz, 1H), 2.84 (dd, J_1 = 16.1 Hz, J_2 = 6.1 Hz, 1H), 2.71 (dd, J_1 = 15.7 Hz, J_2 = 6.0 Hz, 1H), 1.80 (oct, J = 7.5 Hz, 1H), 1.50 (s, 9H), 0.96 (d, J = 6.8 Hz, 6H); ^{13}C NMR δ 172.0, 169.8, 158.2, 82.3, 80.5, 71.1, 56.3, 52.5, 52.0, 36.6, 32.8, 28.1, 19.0, 18.9; ESIMS m/z 368 [M + Na⁺]; $[\alpha]_{\text{D}}^{20}$ -37 (c = 0.6, CHCl₃), 99% ee.

(3S,4S,5R)-2-tert-Butyl 4-methyl 3-isopropyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (ent-11f). Following the general procedure and using cat **QD-13c** compound **ent-11f** was obtained as a colourless oil in 87% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 14.5 min, τ_{min} = 11.5 min); spectral data were identical to compound **11f**; $[\alpha]_{\text{D}}^{20}$ +35 (c = 0.5, CHCl₃), 80% ee.

(3R,4R,5S)-2-tert-Butyl 4-methyl 3-isobutyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (11g). Following the general procedure, compound **11g** was obtained as a colourless oil in 97% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 11.0 min, τ_{min} = 12.5 min); ^1H NMR (400 MHz) δ 4.49 (m, 2H), 3.72 (s, 3H), 3.68 (s, 3H), 2.85 (dd, J_1 = 16.4 Hz, J_2 = 6.1 Hz, 1H), 2.80 (dd, J_1 = 8.1 Hz, J_2 = 3.7 Hz, 1H), 2.70 (dd, J_1 = 16.0 Hz, J_2 = 7.2 Hz, 1H), 1.70 (oct, J = 6.9 Hz, 1H), 1.65-1.58 (m, 1H), 1.50 (s, 9H), 1.32-1.24 (m, 1H), 0.95 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H); ^{13}C NMR δ 172.2, 170.0, 158.1, 82.6, 80.2, 64.1, 59.1, 52.6, 52.2, 45.2, 37.3, 28.3, 25.5, 23.1, 21.8; ESIMS m/z 382 [M + Na⁺]; $[\alpha]_{\text{D}}^{20}$ -22 (c = 0.6, CHCl₃), 98% ee.

(3S,4S,5R)-2-tert-Butyl 4-methyl 3-isobutyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (ent-11g). Following the general procedure and using cat **QD-13c** compound **ent-11g** was obtained as a colourless oil in 83% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 12.5 min, τ_{min} = 11.0 min); spectral data were identical to compound **11g**; $[\alpha]_{\text{D}}^{20}$ +10 (c = 0.5, CHCl₃), 57% ee.

(3R,4R,5S)-2-tert-Butyl 4-methyl 3-cyclopentyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (11h). Following the general procedure, compound **11h** was obtained as a colourless oil in 97% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 12.7 min, τ_{min} = 18.2 min); ^1H NMR (400

MHz) δ 4.48 (dt, $J_d = 8.3$ Hz, $J_t = 6.2$ Hz, 1H), 4.26 (dd, $J_1 = 8.8$ Hz, $J_2 = 4.0$ Hz, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 2.94 (dd, $J_1 = 8.5$ Hz, $J_2 = 4.1$ Hz, 1H), 2.85 (dd, $J_1 = 15.9$ Hz, $J_2 = 6.1$ Hz, 1H), 2.70 (dd, $J_1 = 16.1$ Hz, $J_2 = 6.9$ Hz, 1H), 2.08 (sext, $J = 8.4$ Hz, 1H), 1.77-1.24 (m, 8H), 1.50 (s, 9H); ^{13}C NMR δ 172.0, 169.8, 158.2, 82.3, 80.4, 69.4, 57.7, 52.4, 52.0, 44.8, 36.9, 29.6, 29.0, 28.1, 25.3, 25.0; ESIMS m/z 394 [M + Na⁺]; $[\alpha]_D^{20}$ -27 (c = 0.6, CHCl₃), 99% ee.

(3R,4R,5S)-2-tert-Butyl 4-methyl 3-cyclohexyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (11i). Following the general procedure and performing the reaction on a 5.0 mmol scale, compound **11i** was obtained as a colourless oil in quantitative yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, $\tau_{\text{maj}} = 12.8$ min, $\tau_{\text{min}} = 17.5$ min); ^1H NMR (400 MHz) δ 4.45 (dt, $J_d = 8.4$ Hz, $J_t = 6.6$ Hz, 1H), 4.16 (dd, $J_1 = 7.8$ Hz, $J_2 = 4.3$ Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 2.97 (dd, $J_1 = 8.5$ Hz, $J_2 = 4.4$ Hz, 1H), 2.83 (dd, $J_1 = 16.2$ Hz, $J_2 = 6.3$ Hz, 1H), 2.70 (dd, $J_1 = 16.2$ Hz, $J_2 = 6.8$ Hz, 1H), 1.86-0.96 (m, 11H), 1.50 (s, 9H); ^{13}C NMR δ 172.1, 169.8, 158.3, 82.2, 80.4, 70.3, 56.2, 52.4, 52.0, 42.2, 36.7, 29.5, 29.4, 28.1, 26.2, 25.9, 25.7; ESIMS m/z 408 [M + Na⁺]; $[\alpha]_D^{20}$ -34 (c = 0.6, CHCl₃), >99% ee.

(3S,4S,5R)-2-tert-Butyl 4-methyl 3-cyclohexyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (ent-11i). Following the general procedure and using cat **QD-13c** compound **ent-11i** was obtained as a colourless oil in 98% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, $\tau_{\text{maj}} = 17.5$ min, $\tau_{\text{min}} = 12.8$ min); spectral data were identical to compound **11i**; $[\alpha]_D^{20}$ +17 (c = 0.5, CHCl₃), 83% ee.

(3R,4R,5S)-2-tert-Butyl 4-methyl 3-benzyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (11j). Following the general procedure, compound **11j** was obtained as a colourless oil in 81% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, $\tau_{\text{maj}} = 19.5$ min, $\tau_{\text{min}} = 22.0$ min); ^1H NMR (400 MHz) δ 7.30-7.20 (m, 5H), 4.70 (dt, $J_d = 4.7$ Hz, $J_t = 6.9$ Hz, 1H), 4.48 (dt, $J_d = 8.3$ Hz, $J_t = 6.6$ Hz, 1H), 3.68 (s, 3H), 3.62 (s, 3H), 3.05 (dd, $J_1 = 13.7$ Hz, $J_2 = 7.8$ Hz, 1H), 2.98 (dd, $J_1 = 8.4$ Hz, $J_2 = 4.6$ Hz, 1H), 2.87 (dd, $J_1 = 13.7$ Hz, $J_2 = 6.8$ Hz, 1H), 2.80 (dd, $J_1 = 16.1$ Hz, $J_2 = 6.0$ Hz, 1H), 2.66 (dd, $J_1 = 15.9$ Hz, $J_2 = 6.6$ Hz, 1H), 1.42 (s, 9H); ^{13}C NMR δ 171.4, 169.7, 157.2, 137.1, 129.6, 128.4, 126.7, 82.4, 80.1, 65.7, 57.5, 52.4, 52.0, 41.2, 36.6, 28.0; ESIMS m/z 416 [M + Na⁺]; $[\alpha]_D^{20}$ -10 (c = 0.6, CHCl₃), 95% ee.

(3S,4R,5S)-2-tert-Butyl 4-methyl 5-(2-methoxy-2-oxoethyl)-3-phenylisoxazolidine-2,4-dicarboxylate (11k). Following the general procedure and using a toluene/CH₂Cl₂ 10/1 mixture as the solvent, compound **11k** was obtained as a colourless oil in quantitative yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, $\tau_{\text{maj}} = 12.0$ min, $\tau_{\text{min}} = 13.1$ min); ^1H NMR (600 MHz) δ 7.38-7.35 (m, 2H), 7.34-7.31 (m, 2H), 7.27-7.24 (m, 1H), 5.55 (d, $J = 4.8$ Hz, 1H), 4.62 (dt, $J_d = 8.3$ Hz, $J_t = 6.4$ Hz, 1H), 3.77 (s, 3H), 3.65 (s, 3H), 3.26 (dd, $J_1 = 8.6$ Hz, $J_2 = 5.0$ Hz, 1H), 2.83 (dd, $J_1 = 16.3$ Hz, $J_2 = 6.4$ Hz, 1H), 2.71 (dd, $J_1 = 16.1$ Hz, $J_2 = 6.0$ Hz, 1H), 1.47 (s, 9H); ^{13}C NMR δ 171.3, 169.9, 157.4, 141.1, 128.9, 127.8, 126.1, 83.0, 80.3, 67.4, 61.8, 52.9, 52.2, 37.0, 28.3; ESIMS m/z 402 [M + Na⁺]; $[\alpha]_D^{20}$ -7 (c = 0.5, CH₃OH), 67% ee.

(3*S*,4*R*,5*S*)-2-*tert*-Butyl 4-methyl 3-(4-bromophenyl)-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (11i). Following the general procedure, compound **47i** was obtained as a colourless oil in 63% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column cooled to 0° C (*n*-hexane/*i*-PrOH = 95:5, flow rate 0.75 mL/min, $\tau_{\text{maj}} = 42.6$ min, $\tau_{\text{min}} = 46.3$ min); ¹H NMR (400 MHz) δ 7.49-7.45 (m, 2H), 7.28-7.24 (m, 2H), 5.51 (d, $J = 5.1$ Hz, 1H), 4.61 (dt, $J_{\text{d}} = 8.3$ Hz, $J_{\text{t}} = 6.4$ Hz, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 3.23 (dd, $J_1 = 8.6$ Hz, $J_2 = 5.1$ Hz, 1H), 2.82 (dd, $J_1 = 16.2$ Hz, $J_2 = 6.1$ Hz, 1H), 2.72 (dd, $J_1 = 16.5$ Hz, $J_2 = 6.5$ Hz, 1H), 1.49 (s, 9H); ¹³C NMR δ 171.0, 169.8, 157.3, 140.2, 132.1, 127.9, 121.8, 83.3, 80.3, 66.8, 61.6, 53.0, 52.2, 36.8, 28.3; ESIMS *m/z* 480-482 [*M* + Na⁺]; [α]_D²⁰ +2 (c = 0.5, CHCl₃), 60% ee.

(3*R*,4*R*,5*S*)-2-*tert*-Butyl 4-ethyl 5-(2-ethoxy-2-oxoethyl)-3-phenethylisoxazolidine-2,4-dicarboxylate (11m). Following the general procedure (96 h reaction time), compound **11m** was obtained as a colourless oil in 60% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 95:5, flow rate 0.75 mL/min, $\tau_{\text{maj}} = 11.4$ min, $\tau_{\text{min}} = 12.1$ min); ¹H NMR (600 MHz) δ 7.28-7.24 (m, 2H), 7.20-7.15 (m, 3H), 4.52 (dd, $J_1 = 14.2$ Hz, $J_2 = 6.7$ Hz, 1H), 4.44 (quint, $J_1 = 4.6$ Hz, 1H), 4.20-4.11 (m, 4H), 2.86 (dd, $J_1 = 8.1$ Hz, $J_2 = 3.9$ Hz, 1H), 2.82 (dd, $J_1 = 15.9$ Hz, $J_2 = 5.8$ Hz, 1H), 2.79-2.74 (m, 1H), 2.72-2.66 (m, 2H), 2.01-1.93 (m, 1H), 1.90-1.84 (m, 1H), 1.49 (s, 9H), 1.24 (t, $J = 7.7$ Hz, 6H); ¹³C NMR δ 171.4, 169.6, 158.1, 141.5, 128.7, 128.6, 126.2, 82.7, 80.3, 65.2, 61.6, 61.2, 58.8, 37.8, 37.5, 32.9, 28.3, 14.4, 14.3; ESIMS *m/z* 458 [*M* + Na⁺]; [α]_D²⁰ -11 (c = 0.5, CHCl₃), 91% ee.

(3*R*,4*R*,5*S*)-4-Allyl 2-*tert*-butyl 5-(2-(allyloxy)-2-oxoethyl)-3-phenethylisoxazolidine-2,4-dicarboxylate (12n). Following the general procedure (96 h reaction time), compound **12n** was obtained as a colourless oil in 76% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 90:10, flow rate 0.75 mL/min, $\tau_{\text{maj}} = 7.0$ min, $\tau_{\text{min}} = 6.7$ min); ¹H NMR (600 MHz) δ 7.28-7.24 (m, 2H), 7.21-7.15 (m, 3H), 5.91-5.83 (m, 2H), 5.32-5.26 (m, 2H), 5.23 (dd, $J_1 = 10.0$ Hz, $J_2 = 7.4$ Hz, 2H), 4.63-4.52 (m, 5H), 4.46 (quint, $J = 4.8$ Hz, 1H), 2.91 (dd, $J_1 = 8.3$ Hz, $J_2 = 4.0$ Hz, 1H), 2.87 (dd, $J_1 = 15.9$ Hz, $J_2 = 5.8$ Hz, 1H), 2.80-2.65 (m, 3H), 2.03-1.94 (m, 1H), 1.91-1.84 (m, 1H), 1.50 (s, 9H); ¹³C NMR δ 171.1, 169.2, 158.1, 141.4, 131.9, 131.7, 128.7, 128.6, 126.2, 119.1, 118.9, 82.8, 80.2, 66.2, 65.9, 65.2, 58.7, 37.8, 37.3, 32.9, 28.3; ESIMS *m/z* 482 [*M* + Na⁺]; [α]_D²⁰ -10 (c = 0.5, CHCl₃), 94% ee.

(3*R*,4*R*,5*S*)-4-Benzyl 2-*tert*-butyl 5-(2-(benzyloxy)-2-oxoethyl)-3-phenethylisoxazolidine-2,4-dicarboxylate (11o). Following the general procedure (96 h reaction time), compound **11o** was obtained as a colourless oil in 73% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 95:5, flow rate 0.75 mL/min, $\tau_{\text{maj}} = 30.1$ min, $\tau_{\text{min}} = 28.8$ min); ¹H NMR (600 MHz) δ 7.36-7.24 (m, 12H), 7.19-7.15 (m, 3H), 5.14-5.05 (m, 4H), 4.58 (dd, $J_1 = 13.8$ Hz, $J_2 = 7.0$ Hz, 1H), 4.46 (quint, $J = 4.8$ Hz, 1H), 2.95 (dd, $J_1 = 8.3$ Hz, $J_2 = 4.1$ Hz, 1H), 2.90 (dd, $J_1 = 16.3$ Hz, $J_2 = 6.0$ Hz, 1H), 2.78-2.72 (m, 2H), 2.71-2.64 (m, 1H), 2.00-1.92 (m, 1H), 1.90-1.82 (m, 1H), 1.45 (s, 9H); ¹³C NMR δ 171.0, 169.1, 157.8, 141.1, 135.4, 135.3, 128.6, 128.5, 128.4, 128.3, 128.2, 125.9, 82.5, 80.0, 67.2, 66.7, 65.0, 58.5, 37.4, 37.0, 32.6, 28.0; ESIMS *m/z* 582 [*M* + Na⁺]; [α]_D²⁰ -9 (c = 0.5, CHCl₃), 95% ee.

(3*R*,4*R*,5*S*)-2-*tert*-Butyl 4-methyl 5-(2-*tert*-butoxy-2-oxoethyl)-3-phenethylisoxazolidine-2,4-dicarboxylate and (3*R*,4*R*,5*S*)-di-*tert*-butyl 5-(2-methoxy-2-oxoethyl)-3-phenethylisoxazolidine-2,4-dicarboxylate (11q). Following the general procedure (96 h reaction time, 0 °C), compounds **11q** were obtained as a colourless oil in 25% yield and as a

regioisomeric mixture (60:40 favouring the 4-methyl carboxylate isomer) as determined by ^1H NMR analysis from the integration of the signals relative to the methyl ester protons. The ee of the major regioisomer was determined by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 95:5, flow rate 0.75 mL/min, τ_{maj} = 10.5 min, τ_{min} = 13.1 min; minor regioisomer, τ = 9.5 min, not separated); ^1H NMR (400 MHz) δ 7.30-7.16 (m, 5H_{maj}, 5H_{min}), 4.54-4.40 (m, 2H_{maj}, 2H_{min}), 3.71 (s, 3H_{maj}), 3.69 (s, 3H_{min}), 2.89-2.56 (m, 5H_{maj}, 5H_{min}), 2.04-1.81 (m, 2H_{maj}, 2H_{min}), 1.51 (s, 9H_{maj}), 1.50 (s, 9H_{min}), 1.44 (s, 9H_{maj}), 1.43 (s, 9H_{min}); ^{13}C NMR δ [signals of both isomers] 172.0, 170.3, 170.0, 168.8, 158.1, 141.6, 141.5, 128.7, 128.6, 126.2, 82.7, 82.6, 82.2, 81.8, 80.7, 80.0, 65.3, 65.0, 59.6, 58.6, 52.6, 52.2, 38.7, 37.8, 37.7, 37.3, 33.0, 32.9, 28.3, 28.2, 28.1; ESIMS *m/z* 472 [*M* + Na⁺], 73% ee (major regioisomer).

Small amounts of the two compounds as single regioisomers were obtained by extensive column chromatography on silica gel (petroleum ether/Et₂O/CH₂Cl₂ 8/1.5/0.5), and were used for the determination of their structure by means of NMR experiments as follows:

Major regioisomer: *R_f* 0.14 (petroleum ether/Et₂O/CH₂Cl₂ 8.0/1.5/0.5); ^1H NMR (CD₃CN, 600 MHz) δ 7.36-7.12 (m, 5H), 4.44-4.40 (m, 1H), 4.39-4.36 (m, 1H), 3.67 (s, 3H), 2.93 (dd, *J* = 7.7, 3.6 Hz, 1H), 2.73-2.68 (m, 2H), 2.68 (dd, *J* = 15.7, 9.4 Hz, 1H), 2.64 (dd, *J* = 15.7, 6.7 Hz, 1H), 1.93-1.82 (m, 2H), 1.46 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (CD₃CN) δ [deduced from the gHSQC and gHMBC experiments, Boc carbonyl missing] 172.3, 169.0, 141.7, 128.7, 128.6, 126.1, 82.1, 81.0, 80.8, 65.3, 58.0, 52.2, 38.4, 37.3, 32.5, 27.5, 27.4.

A gHMBC NMR experiment showed a relation between the ^1H signal at 3.67 ppm (OCH₃) and the ^{13}C signal at 172.3 ppm, which could thus be assigned to the carbonyl carbon of the methyl ester. The same experiment showed a relation between the ^1H signal at 4.44-4.40 ppm and the ^{13}C signals of both carbonyl groups at 172.3 and 169.0 ppm, thus allowing the assignment of this ^1H signal to the C⁵H of the isoxazolidine cycle (CHO), and consequently of the ^1H signal at 4.39-4.36 ppm to the C²H of the isoxazolidine (CHN). As the gHMBC spectrum presented a relation between this latter ^1H signal and the ^{13}C signal at 172.3 ppm, the quaternary carbon of the methyl ester, it was possible to conclude that in this isomer the methyl ester moiety is at the C⁴ position of the isoxazolidine ring.

Minor regioisomer: *R_f* 0.13 (petroleum ether/Et₂O/CH₂Cl₂ 8/1.5/0.5); ^1H NMR (CD₃CN, 600 MHz) δ 7.32-7.28 (m, 2H), 7.27-7.24 (m, 2H), 7.22-7.18 (m, 1H), 4.43-4.38 (m, 1H), 4.38-4.33 (m, 1H), 3.66 (s, 3H), 2.85-2.82 (m, 1H), 2.78-2.73 (m, 2H), 2.73-2.68 (m, 2H), 1.93-1.81 (m, 2H), 1.45 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (CD₃CN) δ [signals deduced from a gHMBC experiment, Boc carbonyl missing] 170.6, 170.3, 155.0, 141.8, 128.7, 128.6, 126.1, 82.1, 81.7, 80.1, 65.0, 59.0, 52.5, 38.2, 37.1, 32.3, 27.6, 27.3.

A gHMBC NMR experiment showed a relation between the ^1H signal at 3.66 ppm (OCH₃) and the ^{13}C signal at 170.3 ppm, which could therefore be assigned to the carbonyl carbon of the methyl ester. The remaining ^{13}C carbonyl signal at 170.6 ppm could thus be assigned to the carbonyl of the *tert*-butyl ester. As the gHMBC spectrum presented relations between both ^1H signals at 4.43-4.38 and 4.38-4.33 ppm (C²H and C⁴H of the isoxazolidine cycle) and the ^{13}C signal at 170.6 ppm, the carbonyl carbon of the *tert*-butyl ester, it was possible to conclude that in this isomer the *tert*-butyl ester moiety is at the C⁴ position of the isoxazolidine ring.

(3*R*,4*R*,5*S*)-2-Benzyl 4-methyl 3-isobutyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (12a). Following the general procedure, compound **12a** was obtained as a colourless oil in 60% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 11.0 min; τ_{min} = 12.5 min); ^1H NMR (600 MHz) δ 7.40-7.29 (m, 5H), 5.25 (d, *J* = 12.3 Hz, 1H), 5.18 (d, *J* = 12.3 Hz, 1H), 4.58-4.49 (m, 2H), 3.67 (s, 6H), 2.90-2.84 (m, 2H), 2.73 (dd, *J*₁ = 16.5 Hz, *J*₂ = 7.0 Hz, 1H), 1.78-1.68 (m, 1H), 1.66-1.60 (m, 1H), 1.34-1.29 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H),

0.91 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR δ 171.8, 169.9, 158.0, 135.9, 128.7, 128.5, 128.3, 80.6, 68.5, 63.8, 58.8, 52.7, 52.2, 45.0, 37.2, 25.5, 23.1, 21.8; ESIMS m/z 416 [$\text{M} + \text{Na}^+$]; $[\alpha]_{\text{D}}^{20}$ -25 ($c = 0.5$, CHCl_3), 75% ee.

(3R,4R,5S)-2-Benzyl 4-methyl 3-isopropyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (12b). Following the general procedure, compound **12b** was obtained as a colourless oil in 72% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (n -hexane/ i -PrOH = 80:20, flow rate 0.75 mL/min, $\tau_{\text{maj}} = 11.5$ min, $\tau_{\text{min}} = 14.5$ min); ^1H NMR (600 MHz) δ 7.38-7.29 (m, 5H), 5.28-5.15 (m, 2H), 4.47 (dt, $J_{\text{d}} = 8.6$ Hz, $J_{\text{t}} = 6.5$ Hz, 1H), 4.23 (dd, $J_1 = 7.7$ Hz, $J_2 = 4.5$ Hz, 1H), 3.67 (s, 3H), 3.65 (s, 3H), 3.01 (dd, $J_1 = 8.6$ Hz, $J_2 = 4.9$ Hz, 1H), 2.84 (dd, $J_1 = 16.6$ Hz, $J_2 = 5.9$ Hz, 1H), 2.72 (dd, $J_1 = 16.2$ Hz, $J_2 = 6.8$ Hz, 1H), 1.83 (oct, $J = 6.8$ Hz, 1H), 0.97 (bd, $J = 6.8$ Hz, 3H), 0.95 (bd, $J = 6.8$ Hz, 3H); ^{13}C NMR δ 171.9, 169.9, 159.1, 136.0, 128.7, 128.4, 128.2, 81.1, 71.0, 68.4, 56.2, 52.7, 52.2, 36.7, 32.9, 19.1, 18.9; ESIMS m/z 402 [$\text{M} + \text{Na}^+$]; $[\alpha]_{\text{D}}^{20}$ -37 ($c = 0.25$, CHCl_3), 80% ee.

(3R,4R,5S)-2-Benzyl 4-methyl 3-cyclohexyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (12c). Following the general procedure, compound **12c** was obtained as a colourless oil in quantitative yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (n -hexane/ i -PrOH = 80:20, flow rate 0.75 mL/min, $\tau_{\text{maj}} = 12.8$ min, $\tau_{\text{min}} = 17.5$ min); ^1H NMR (600 MHz) δ 7.38-7.29 (m, 5H), 5.23 (d, $J = 12.9$ Hz, 1H), 5.18 (d, $J = 12.6$ Hz, 1H), 4.46 (dt, $J_{\text{d}} = 9.0$ Hz, $J_{\text{t}} = 5.7$ Hz, 1H), 4.24 (dd, $J_1 = 8.5$ Hz, $J_2 = 4.5$ Hz, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 3.02 (dd, $J_1 = 8.9$ Hz, $J_2 = 4.3$ Hz, 1H), 2.84 (dd, $J_1 = 15.7$ Hz, $J_2 = 5.9$ Hz, 1H), 2.71 (dd, $J_1 = 16.0$ Hz, $J_2 = 6.8$ Hz, 1H), 1.82-0.97 (m, 11H); ^{13}C NMR δ 171.9, 169.9, 159.2, 136.0, 128.7, 128.4, 128.2, 81.0, 70.2, 68.4, 56.2, 52.7, 52.2, 42.3, 36.8, 29.6, 29.5, 26.4, 26.0, 25.9; ESIMS m/z 442 [$\text{M} + \text{Na}^+$]; $[\alpha]_{\text{D}}^{20}$ -39 ($c = 0.5$, CHCl_3), 94% ee.

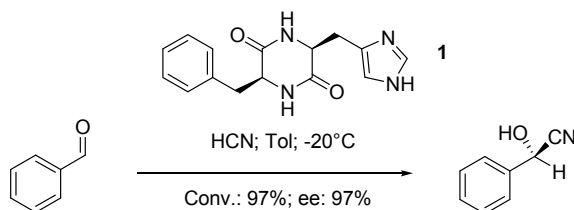
(3R,4R,5S)-2-Benzyl 4-methyl 3-cyclopentyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (12d). Following the general procedure, compound **12d** was obtained as a colourless oil in 68% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (n -hexane/ i -PrOH = 80:20, flow rate 0.75 mL/min, $\tau_{\text{maj}} = 12.7$ min; $\tau_{\text{min}} = 18.2$ min); ^1H NMR (400 MHz) δ 7.40-7.29 (m, 5H), 5.25 (d, $J = 12.7$ Hz, 1H), 5.18 (d, $J = 12.7$ Hz, 1H), 4.50 (dt, $J_{\text{d}} = 7.9$ Hz, $J_{\text{t}} = 6.8$ Hz, 1H), 4.36 (dd, $J_1 = 9.1$ Hz, $J_2 = 4.0$ Hz, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.01 (dd, $J_1 = 8.9$ Hz, $J_2 = 4.0$ Hz, 1H), 2.87 (dd, $J_1 = 16.4$ Hz, $J_2 = 6.3$ Hz, 1H), 2.73 (dd, $J_1 = 16.1$ Hz, $J_2 = 6.8$ Hz, 1H), 2.11 (sext, $J = 7.5$ Hz, 1H), 1.79-1.19 (m, 8H); ^{13}C NMR δ 171.9, 169.9, 159.1, 136.0, 128.7, 128.4, 128.2, 81.0, 69.4, 68.5, 57.7, 52.7, 52.2, 45.0, 37.0, 29.8, 29.2, 25.5, 25.3; ESIMS m/z 428 [$\text{M} + \text{Na}^+$]; $[\alpha]_{\text{D}}^{20}$ -34 ($c = 0.5$, CHCl_3), 85% ee.

Chapter 3

Peptide Catalyzed Michael Reactions of Aldehydes with Nitroolefins

3.1 Introduction

Deriving from natural and non-natural amino acids, peptides nowadays are becoming an interesting and dynamic field in organocatalysis. Many different research groups recently demonstrated that these molecules can promote a range of different reactions such as nucleophilic additions, oxidations, brominations and hydrolytic reactions.¹ Among these important transformations, stereoselective C–C bond forming reactions are indeed the most useful and challenging reactions, playing a relevant role in organic synthesis. A pioneering study in this field dates back to 1979, when Inoue and Oku demonstrated for the first time that cyclic di-peptides are valuable catalysts for hydrocyanations of aldehydes (Scheme 1).²



Scheme 1

Remarkable yields and enantioselections were achieved in the presence of catalyst **1** consisting of phenylalanine and histidine residues. Since this study, peptides have been involved in a large number of asymmetric transformations including Morita–Baylis–Hillman reactions, Stetter reactions, nitroalkane addition reactions, Friedel–Crafts alkylations, aldol and Michael reactions.³

The development of such synthetically relevant transformations led the chemists to consider peptidic catalysis as an highly innovative branch in organocatalysis, justified by its strictly connection with bio-catalysis. As a matter of fact, peptidic catalysis established itself as an important area at the interface of asymmetric catalysis, peptide chemistry and enzyme research. Aside from the value for providing important chiral compounds, the research showed that peptidic catalysts have often unique features compared to other small synthetic catalysts and enzymes. The reason for their wide applicability resides in a large structural and functional diversity easily accessible by linking amino acids with different functional groups in their side chains to construct a myriad of peptidic structures.

Because of the common structure of small peptides and enzymes, bio-catalytic activation pathways were taken as inspiration for investigating peptides as new catalytic systems. Aldolases, for example, are a specific group of lyases that catalyze the stereoselective addition of a ketone donor to an aldehyde acceptor.⁴ As represented in Figure 1, the mechanism of **Type**

¹ S. J. Miller, *Acc. Chem. Res.* **2004**, *37*, 601; H. Wennemers, *Chem. Commun.* **2011**, *47*, 12036.

² J. I. Oku, S. Inoue, *Makromol. Chem.* **1979**, *180*, 1089; J. I. Oku, S. Inoue, *Chem. Commun.*, **1981**, 299.

³ E. A. C. Davie, S. M. Mennen, Y. Xu and S. J. Miller, *Chem. Rev.*, **2007**, *107*, 5759.

⁴ T. D. Machajewski, C. -H. Wong, *Angew. Chem. Int. Ed.* **2000**, *39*, 1352

1 Aldolases involves the formation of an enamine intermediate with the ketone donor, followed by a subsequent reaction with the aldehyde acceptor.

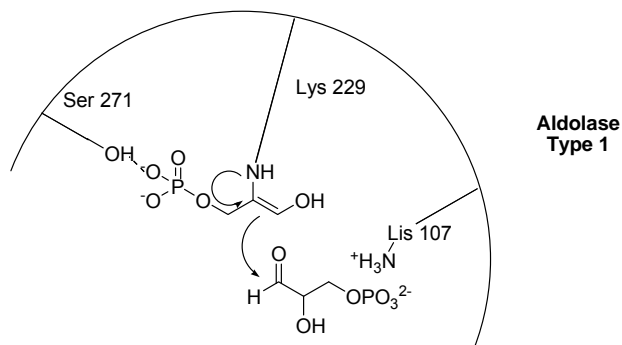
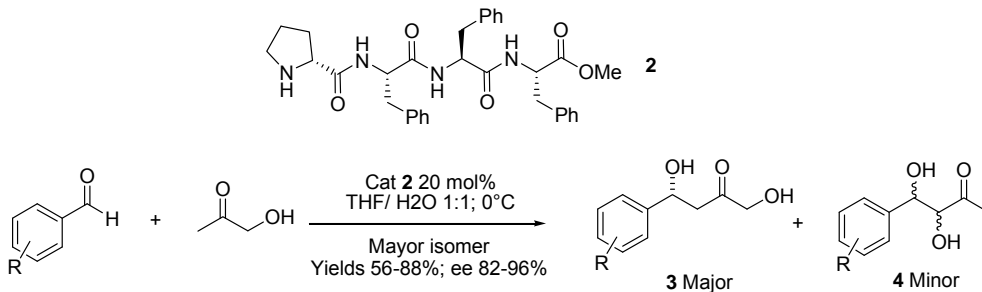


Figure 1

Inspired by these natural aldolases several research groups evaluated peptides bearing *N*-terminal prolyl residues as catalysts for enamine or iminium-ion catalysis. Gong and co-workers, for example, developed peptide **2** for the stereoselective aldol reaction between hydroxyacetone and aromatic aldehydes (Scheme 2).⁵



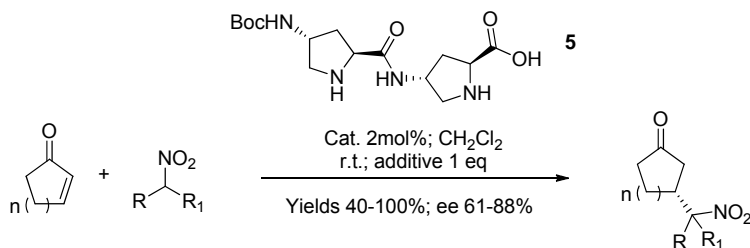
Scheme 2

Peptide **2** not only promoted the reaction with good results in yields and enantioselectivities, but could also direct the regioselectivity toward the regiosomer **3**. In fact, whereas product **4** is typically obtained in many organocatalytic systems, the 1,4-diol **3** is formed preferentially in the presence of peptides.

Another example was reported by Tsogoeva et al.: they demonstrated the potential of peptidic catalysts for nitroalkane addition reactions to cyclic α,β -unsaturated carbonyl compounds through an iminium-ion reaction pathway (Scheme 3).⁶

⁵ Z. Tang, Z.-H. Yang, L.-F. Cun, L.-Z. Gong, A.-Q. Mi and Y.-Z. Jiang, *Org. Lett.*, **2004**, *6*, 2285.

⁶ S. B. Tsogoeva, S. B. Jagtap and Z. A. Ardemasova, *Tetrahedron: Asymmetry*, **2006**, *17*, 989.

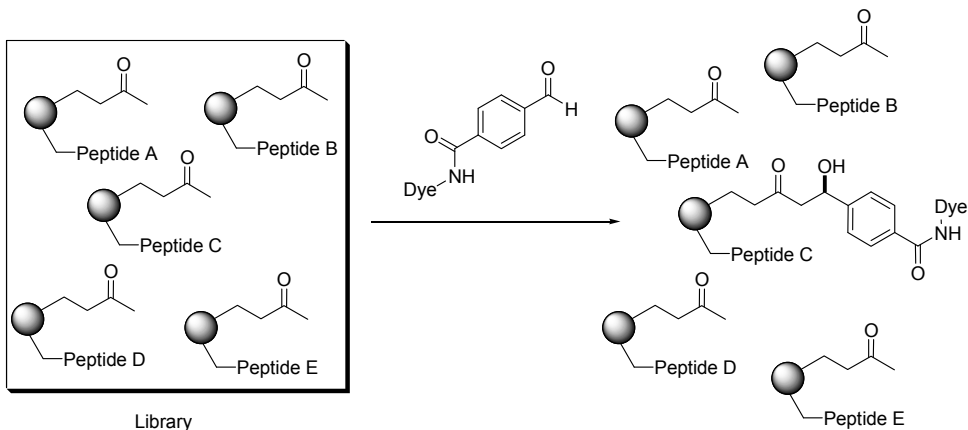


Scheme 3

Among the different peptides considered, the dimer of γ -amino proline linked via the γ -amino group **5** provided the products with the best yields and enantioselectivities.

One of the major challenges in the development of peptidic catalysts consists in their rational design. Due to our limited understanding of their catalytic activity, combined with the difficulty of predicting the conformation of even a simple di- or tri-peptide, the rational design of peptides results difficult. Since the formation of peptides libraries allows the easy obtainment of a huge number of random structures in a short time and with little synthetic effort, combinatorial chemistry can overcome the rational design and is thus a powerful tool for the identification of several effective peptidic catalysts.⁷

Wennemers and co-workers, for example, adopted the method of ‘catalyst–substrate co-immobilization’ to identify catalytically active peptides in a one-bead–one-compound library (Scheme 4).

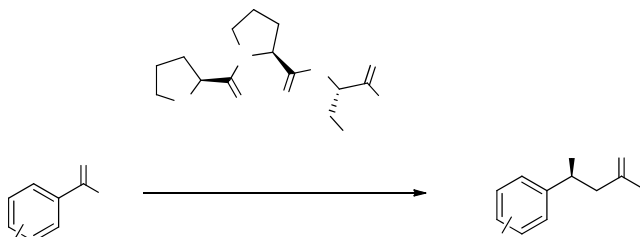


Scheme 4

This screening technique consisted in the co-immobilization of one of the reaction partners together with each library member on the same heterogeneous bead. Incubation of the library with a dye-labelled reaction partner leads to its covalent attachment, and thus the labelling, of only those beads carrying compounds that mediate a reaction between the supported reagent

⁷ J. D. Revell, H. Wennemers, *Top. Curr. Chem.*, **2007**, 277, 251; J. D. Revell, H. Wennemers, *Current Opinion in Chemical Biology*, **2007**, 11, 269

and the labelled one. Active compounds are therefore easily identified by visual inspection of the library under a low-power microscope. To identify catalytically active peptides, a one-bead-one-compound library 3375 different tri-peptides was tested. This screening method led to the identification of peptide **6** as particularly effective for the aldol reaction between acetone and aromatic aldehydes (Scheme 5).⁸



Scheme 5

Peptide **6** demonstrated remarkable stereoselective properties and excellent reactivity allowing the formation of the product with 1 mol% catalyst loading when usually other organocatalytic systems need 10-30 mol%. Conformational studies demonstrated that the secondary amine at the N terminus, the carboxylic acid in the side chain of the aspartic acid (Asp) residue, and a well-defined turn conformation are crucial for the high catalytic activity and selectivity of **6**.

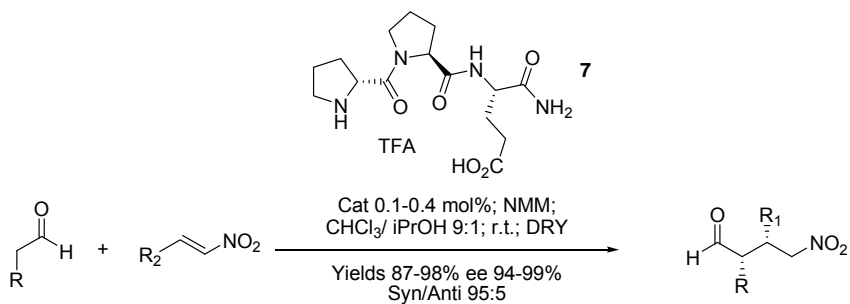
Based on these studies, the Wennemers' group could discover the strictly related peptide **7** as an excellent catalyst for conjugate addition reactions between aldehydes and nitroolefins.⁹ Further optimization studies on the kinetic of the system provided insight into the rate determining steps of this reaction. They demonstrated that both the reaction of the enamine with the electrophile and hydrolysis of the resulting imine are rate limiting. These findings allowed for reducing the catalyst loading by a factor of 10 to as little as 0.1 mol% for a broad range of substrates. This impressive result represent to date the lowest catalyst loading achieved in enamine based catalysis (Scheme 6).¹⁰

R

⁸ P. Krattiger, R. Kovasy, J. D. Revell, S. Ivan, H. Wennemers, *Org. Lett.*, **2005**, 7, 1101.

⁹ M. Wiesner, M. Neuburger and H. Wennemers, *Chem.-Eur. J.*, **2009**, 15, 10103; M. Wiesner, J. D. Revell and H. Wennemers, *Angew. Chem., Int. Ed.*, **2008**, 47, 1871; M. Wiesner and H. Wennemers, *Synthesis*, **2010**, 1568

¹⁰ M. Wiesner, G. Upert, G. Angelici and H. Wennemers, *J. Am. Chem. Soc.*, **2010**, 132, 6;

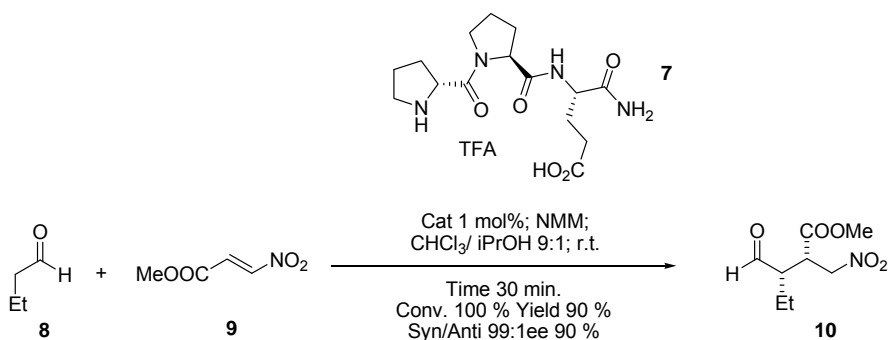


Scheme 6

3.2 Results and Discussions

The aim of the project was the study of peptidic catalysts in Michael addition reaction of aldehydes to different nitroolefins.

Preliminary kinetic investigation involving catalyst **5** in the Michael reaction of *n*-butanal **6** to methyl 3-nitroacrilate **7** (Scheme 7) was performed. A particular focus was set towards the behaviour of this catalyst for the study of this highly reactive systems under very low catalyst loading.



Scheme 7

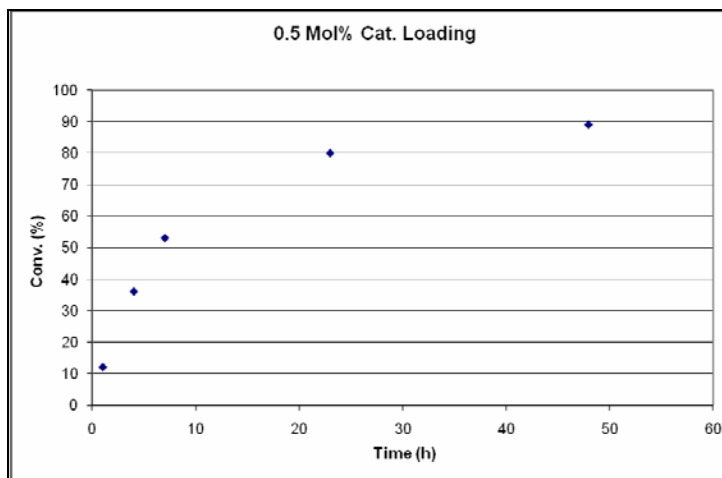
Preliminary tests were performed with 1 mol% of catalyst loading (Table 1 entry 1). The reaction worked surprisingly well leading to product **8** in only thirty minutes with complete conversion, formation of only one diastereoisomer and excellent enantioselectivity. However, the high reactivity demonstrated by this nitroolefin was competitive with a fast degradation of methyl 3-nitroacrilate **7** promoted probably by the amount of the added base (N-methyl morpholine); for this reason compound **7** was used in excess (1.5 eq.).

Table 1 Screening of reaction conditions in the conjugate addition reaction of butanal (**8**) and methyl 3-nitroacrilate (**9**)

Entry	Cat (%)	NMM (%)	Molarity (M)	Time (h)	Conv. ^a (%) ^b	Ee ^b (%) ^c
1	1 ^a	1	0.225	0.5	100	90
2	0.5	0.5	0.225	48	89	85
3 ^c	0.1	0.1	0.225	96	50	82
4 ^c	0.05	0.05	0.225	240	26	80
5	0.5	0.5	0.45	24	93	87
6	0.5	1	0.225	3	90	92

^a Determined by ¹H NMR spectroscopy. ^b Determined by chiral stationary phase HPLC. ^c dry conditions: molecular sieves.

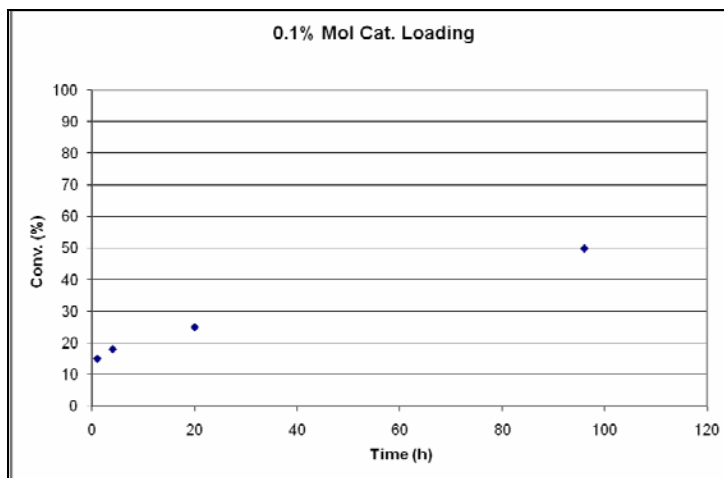
Graph 1 represents the conversion at different reaction times of the same reaction performed with a catalyst loading of 0.5% (table 1, entry 2). The reaction shows a drop in reactivity and, even if enantioselectivity is marginally affected, the conversion is 89% only after 48 h.



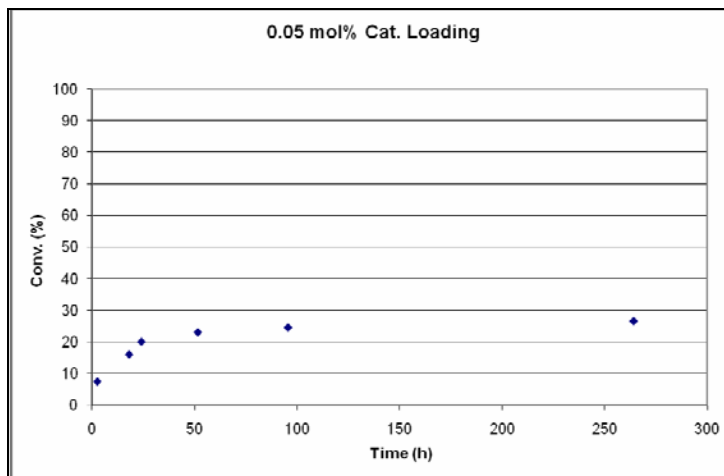
Graph 1

A further decreasing of the catalyst loading was performed under dry conditions. It was previously found that dry conditions could positively affect the kinetics of a similar transformation.¹⁰ Surprisingly, with 0.1 mol% of catalyst loading, the reaction could exceed 50% conversion, even after 96 hours (entry 3) while catalyst **7** in 0.05 mol% loading resulted poorly effective with 26% conversion after 240 hours (entry 4). As shown in Graph 2 and Graph 3 respectively, the kinetics of catalyst **7** resulted extremely slow compared with the encouraging results observed with 0.5 and 1 mol% loading. A possible interpretation of these results is the experimental difficulty of performing the reaction under strictly dry conditions, as the nitroolefin **9** is highly hygroscopic. Since water affects negatively the kinetics of the reaction,¹⁰ the presence of traces of moisture, introduced with **9**, could have dramatic effects when such small amounts of catalyst are used. Besides, **9** could involve catalyst **7** in some processes of deactivation.

Subsequent analysis of the reaction conditions demonstrated, as expected, that the concentration of the reagents positively affected the kinetics of the reaction; as reported in entry 5 a higher concentration produced product **10** in good yield in only 24 hours, even at 0.5 mol% catalyst loading. A more unusual role was envisaged in the amount of the basic additive. Doubling the amount of base (entry 6), in fact, 0.5 mol% of catalyst **7** produced excellent results with a conversion of 90% in just 3 hours. Further insights into the role played by the nature and the amount of the basic additive will be necessary for future optimizations.



Graph 2



Graph 3

The second part of the project focused on the investigation and optimization of the conjugate addition reaction of α,α disubstituted aldehydes to nitroolefins. Although Michael reaction of aldehydes with nitroolefins represent a versatile method for obtaining γ -nitroaldehydes, valuable synthetic intermediates,¹¹ only few examples involve α,α di-substituted aldehydes as reaction partners due to their steric hindrance and lower reactivity.¹²

The reaction between *iso*-butyraldehyde **17a** and nitrostyrene **18a** was considered as reference reaction for the optimization of the conditions (Table 2). In order to test the feasibility of the reaction, we considered the catalytic activity of different peptides (Figure 2).

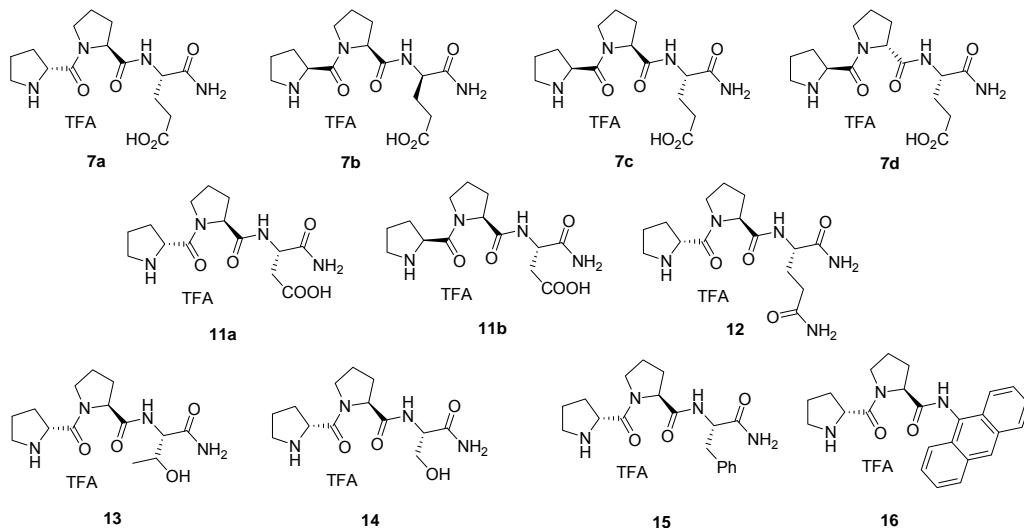


Figure 2

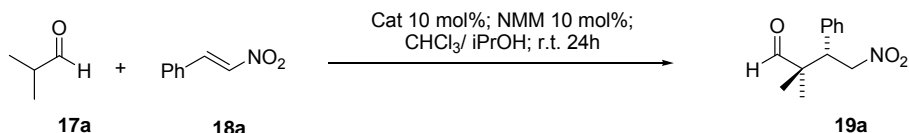
All the different catalysts considered consist in tri-peptides presenting a rigid and well defined structure provided by the two prolines, associated with a third amino acid bearing different groups on the side chain. This initial screening demonstrated that a carboxylic acid on the side chain of the third amino acid residue is crucial for high activity and selectivity (Table 2). Glutamic acid and aspartic acid (entry 1-2) demonstrated to be more effective compared with peptide **10** presenting an amide functionality (entry 3). Peptides **13** and **14**, presenting neutral alcoholic functions (entry 4,5), gave inferior results; this behaviour confirms the necessity of a carboxylic acid in the catalyst for activity and enantioselectivity. Peptides **15** and

¹¹ For recent reviews on 1,4 addition reactions see: a) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701; b) S. Sulzer-MossI, A. Alexakis, *Chem. Commun.* **2007**, 3123; c) J. L. Vicario, D. BadKa, L. Carrillo, *Synthesis* **2007**, 2065; d) D. Almasi, D. A. Alonso, C. NLjera, *Tetrahedron: Asymmetry* **2007**, 18, 299.

¹² For representative example of Michael reaction of di-substituted aldehydes see: a) Y. F. Ting, C. Chang, R. J. Reddy, D. R. Magar, K. Chen, *Chem. Eur., J.* **2010**, 16, 7030; b) W. Wang, J. Wang, H. Li, *Angew. Chem. Int. Ed.*, **2005**, 44, 1369; c) C. Chang, S.H. Li, R. J. Reddy, K. Chen, *Adv. Synth. Catal.*, **2009**, 351, 1273; d) N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.*, **2004**, 6, 2527; e) M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem. Int. Ed.*, **2006**, 45, 6366; f) S. H. McCooley, S. J. Connon, *Org. Lett.*, **2007**, 9, 599.

16 demonstrated that sterics can be sufficient to provide moderate enantioselection, but results in very poor activity (entries 6,7).

Table 2 Screening of different catalysts in the 1,4 addition reaction between isobutyraldehyde (**17a**) and nitrostyrene (**18a**).^a



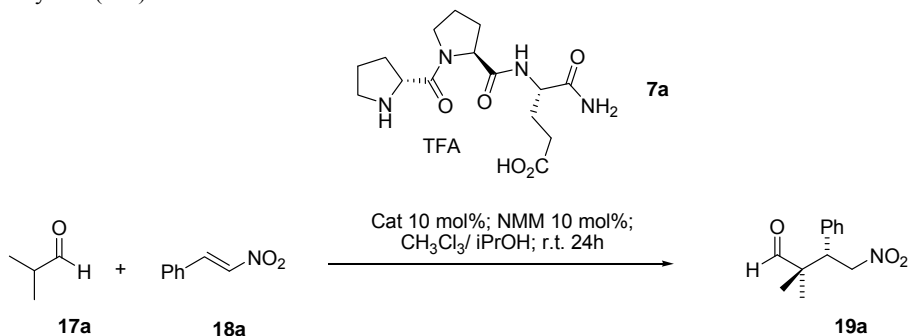
Entry	Cat.	Conv % ^b	Ee % ^c
1	7a	70	75
2	11a	57	67
3	12	44	62
4	13	4	n.r.
5	14	26	59
6	15	17	64
7	16	26	50
8	7b	40	-55
9	7c	56	-62
10	7d	71	-55
11	11b	50	-55

^a Conditions: **17a** (0.22 mmol), catalyst (0.022 mmol), NMM (0.022 mmol) **18a** (0.33 mmol), CHCl₃/*i*PrOH 7/3 (1 ml). ^b Determined by ¹H NMR spectroscopy. ^c Determined by chiral stationary phase HPLC.

Further efforts were centred on the optimization of the correct absolute configuration of the different units of most active catalysts **7** and **11** (entry 1, 2, 8-11). As evidenced in Table 2, the absolute configuration of the first proline residue controls the enantioselection of the reaction (compare entry 1 and entry 9). Peptide **7a** was used for further optimizations, being the most effective catalyst able to give high conversion and promising enantioselectivity.

Different conditions were then investigated for the optimization of the 1,4 addition reaction of *iso*-butyraldehyde and nitrostyrene promoted by **7a**. The right choice of the reaction solvent represents a particularly important issue for these peptidic systems: in non polar solvents, like toluene, hexane and even chloroform, these peptidic salts are poorly soluble while more polar solvents, like DMF or DMSO, interfere with the weak interactions between catalyst and substrates dramatically affecting the enantioselection. As previously reported,¹⁰ the binary chloroform/*iso*-propanol mixture resulted to be the most effective with this kind of catalytic systems. Different ratio between these two solvents, under slightly different reaction conditions, were thus investigated (Table 3).

Table 3 Screening of different conditions for the 1,4 addition reaction between isobutyraldehyde (**17a**) and nitrostyrene (**18a**).^a



Entry	$\text{CHCl}_3/\text{iPrOH}$	NMM (eq.)	T (°C)	Conv. (%) ^b	Ee (%) ^c
1	9:1	1	25	20	80
2	7:3	1	25	70	75
3	5:5	1	25	90	70
4	3:7	1	25	90	66
5	7:3	2	25	90	80
6	7:3	5	25	98	83
7	7:3	10	25	100	83
8	7:3	5	10 ^d	75	88
9	7:3	5	0 ^d	50	91
10	9:1	5	25	85	84

^a Conditions: **17a** (0.22 mmol), catalyst **7a** (0.022 mmol), NMM, **18a** (0.33 mmol), $\text{CHCl}_3/\text{iPrOH}$. ^b Determined by ¹H NMR spectroscopy. ^c Determined by chiral stationary phase HPLC. ^d Time 48h.

From these experiments it is possible to state that *iso*-propanol positively affects the activity of peptide **7**, contributing to its optimal dissolution, while chloroform has a beneficial effect on the stereoselectivity of the reaction (entry 1-4). Although a problem of reproducibility associated to the difficult dissolution of catalyst **7c** and nitrostyrene **18a** was observed, from this initial screening we considered chloroform-*iso*-propanol 7:3 as the optimal compromise between activity and enantioselectivity (entry 2). An attempt to avoid the reproducibility problem using more diluted conditions resulted in a drop of catalytic activity.

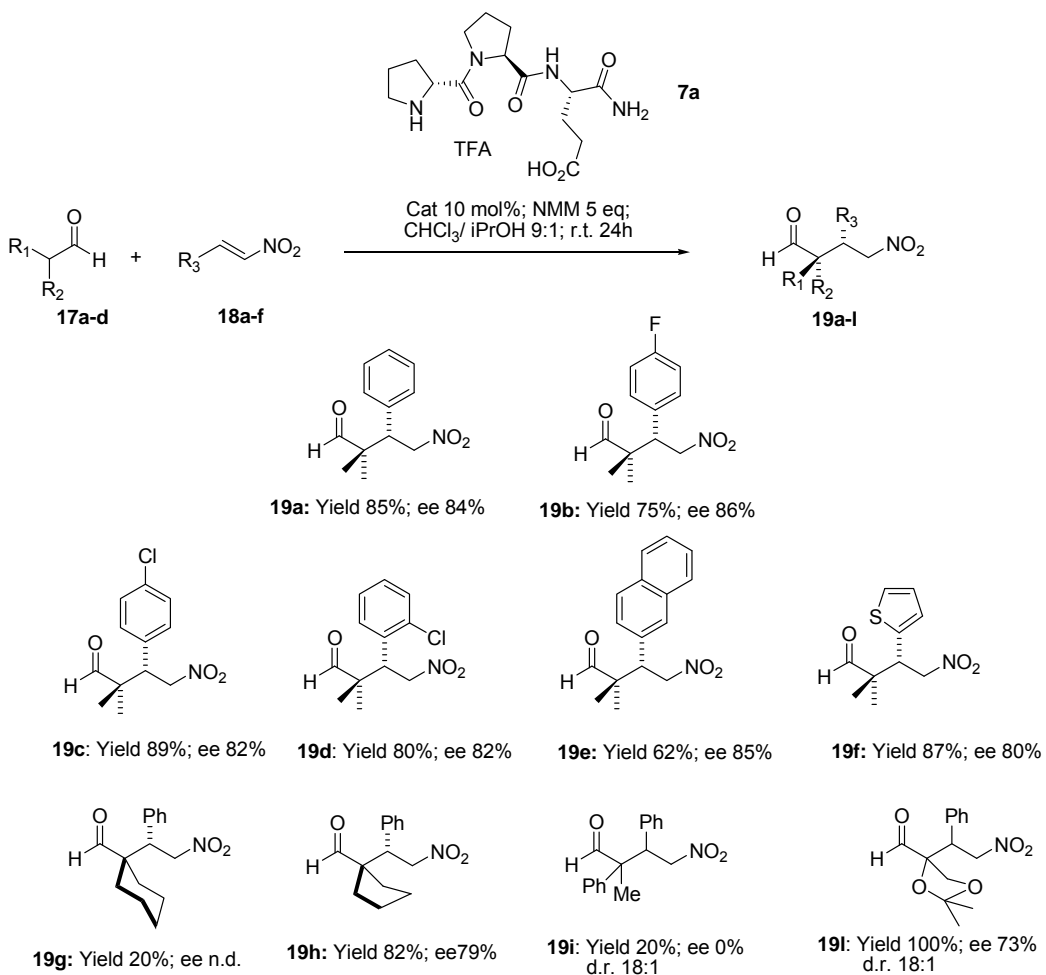
The amount of basic additive demonstrated to be particularly influential on the reaction. When an higher amount of base was used in the reaction, both activity of the catalyst and enantioselectivity increased (compare entries 2,5,6,7). Five equivalents of N-methylmorpholine compared to the catalyst led to product **19a** in quantitative yield and 83% enantiomeric excess. This excess of base probably favoured a better dissolution of the catalytic system in the reaction medium (entry 6).

Performing the reaction at lower temperatures (entries 8,9) gave **19a** in higher enantiomeric excess (up to 91% at 0 °C). However, to our disappointment, the reaction required considerable

longer reaction times, giving low yields, due to the reduced solubility of nitrostyrene in the medium.

In order to avoid long reaction times and the problem of solubility of nitrostyrene, room temperature and an increased ratio of chloroform up to 9:1 were chosen (entry 10). In this case, the higher amount of chloroform dissolved properly both the reagents, while five equivalents of base avoided the precipitation of the catalyst. Under these optimal conditions, the Michael reaction could be promoted by catalyst **7a** at 10 mol% loading, furnishing the adduct **19a** in high yield and ee.

With these conditions the scope of the reaction was evaluated (Scheme 8).



Scheme 8

The reaction was initially tested with different nitroolefins. Various aromatic residues were tolerated in this substrate, as halogen atoms on the aromatic ring do not affect the reactivity of the system; both products **19b** and **19c**, bearing in the *para* position of the aromatic ring respectively a fluoride and a chloride atom, were obtained in good yields and ee's. Also product

19d, with a chloride at the *ortho* position, was obtained with similar results. Substituting the phenyl group with a more hindered naphthalene moiety led to product **19e** in lower yields, probably due to the steric hindrance, but with remarkable values of enantioselection. Thiophenyl nitroolefin **18f** is also well tolerated by catalyst **7a** providing product **19f** in good results.

The behaviour of other di-substituted aldehydes was found to be more variable regarding the nature of the substituents. For example, a striking difference in reactivity was observed between cyclohexane carboxaldehyde **17b** and cyclopentane carboxaldehyde **17c**. While product **19h** was isolated in good yields and good enantiomeric excess, product **19g** was afforded in only 20% yield. Particularly disappointing results were obtained with 2-phenylpropanal **17d**, as product **19i** was obtained in low yields and as a racemic mixture. This low reactivity can be explained considering the less nucleophilic nature of the benzylic enamine intermediate respect to aliphatic enamines previously employed. The lack of enantioselection can be instead be ascribed to the steric crowding between this planar hindered substrate with catalyst **7a**. Protected glyceraldehyde **17e**, led to product **19l** with remarkable results: a good value of enantioselectivity, in fact, was obtained with an excellent yield combined with a remarkable value of diastereomeric excess. Product **19l** is of particular interest, as it presents a quaternary chiral center bearing a protected alcoholic function.

3.3 Conclusions

In conclusion, in this section two different aspects of the involvement of peptidic molecules in catalysis were investigated: the first part consisted in a kinetic evaluation of a highly reactive substrate, in order to study the behaviour of peptide catalyst **7a** under a low catalyst loading. The second part was centred on the optimization of the reaction conditions for the Michael addition of branched aldehydes, usually considered difficult substrates, to nitroolefins.

In both cases the reported results must be considered as a preliminary platform for the achievement of a more comprehensive understanding of these fascinating catalytic systems. Further studies will be carried out in order to overcome the observed limitations.

3.4 Experimental Section

Materials and reagents were of the highest commercially available grade and used without further purification. Reactions were monitored by thin layer chromatography using Merck silica gel 60 F₂₅₄ plates. Compounds were visualized by UV and KMnO₄. Flash chromatography was performed using Merck silica gel 60, particle size 40 - 63 μm . ¹H and ¹³C NMR spectra were recorded on a Bruker DPX 400 spectrometer. Chemical shifts are reported in ppm using TMS or the residual solvent peak as a reference. HPLC analyses were performed on an analytical HPLC with a diode array detector from Shimadzu. For automated peptide synthesis, a Syro I Peptide Synthesizer (MultiSynTech GmbH, Witten, Germany) was employed.

Synthesis of peptidic catalysts: general protocols for solid phase synthesis

Peptides **7**, **11-16** were prepared on solid phase (Rink Amid resin) following the general protocol for Fmoc/tBu peptide synthesis.

Synthesis of TFA•H-D-Pro-Pro-Glu-NH₂ 7a: *i*-Pr₂NEt (9 eq as a 3 M solution in N-methylpyrrolidone) was added to a solution of Fmoc-Glu(OtBu)-OH (3 eq) and HCTU (3 eq) in DMF. The activated amino acid was added to the amino-functionalized Rink Amide AM resin (0.62 g/mol, 5 g, 3.1 mmol) and the mixture was agitated for 1.5 h before washing with DMF and CH₂Cl₂ (5x each). 20% v/v piperidine in DMF was added to the resin (pre-swollen in DMF) and the reaction mixture was agitated for 5 min, drained and the piperidine treatment repeated for 10 min. The resin was then washed with DMF and CH₂Cl₂ (5x each). The coupling- and Fmoc deprotection-cycles were repeated with Fmoc-Pro-OH (3 eq) and then with Boc-D-Pro-OH (3 eq). All couplings and deprotections were monitored by TNBS,¹³ qualitative Kaiser,¹⁴ and chloranil tests (secondary amines).¹⁵ The immobilized peptide was cleaved into solution by agitating the resin in a mixture of TFA/CH₂Cl₂ 2:1 v/v for 1 h, filtration and then repeating the acid treatment for a further 30 minutes. Pooling of filtrates and removal of volatiles under vacuum followed by precipitation and thorough washing with Et₂O afforded the peptides as their trifluoroacetate salts that were dried under high vacuum and used without further purification. ¹H NMR (400 MHz, D₂O, 25°C) δ = 4.51 (dd, *J* = 7.1 Hz, 8.8 Hz, 1H), 4.34 (dd, *J* = 3.6 Hz, 9.0 Hz, 1H), 4.23 (dd, *J* = 5.2 Hz, 9.5 Hz, 1H), 3.60 (m, 1H), 3.49 (m, 1H), 3.29 (m, 2H), 2.40 (m, 3H), 2.19 (m, 1H), 2.08-1.80 (m, 8H); ¹³C NMR (100 MHz, D₂O, 25°C) δ = 177.4, 176.2, 174.5, 168.6, 61.2, 59.6, 53.2, 48.0, 47.0, 30.3, 29.8, 28.5, 26.4, 24.7, 24.3; HRMS (ESI) *m/z*: calc. for C₁₅H₂₅N₄O₅ [M+H]⁺ 341.1824; found, 341.1821.

General procedure for the 1,4 addition reaction between butanal (**8**) and methyl 3-nitroacrylate (**9**).

-Catalyst loading 1%:

In a 5 ml flask, equipped with a stirring bar, add 2 mg of catalyst (0.0044 mmol), 39.7 μl of butanal (0.44 mmol, 1 eq), 1.9 ml of solvent mixture (9/1 Chloroform/isopropanol), 100 μl of a stock solution of NMM in the solvent mixture (0.0044 mmol; stock solution: 24.2 μl of NMM in 5 ml of solvent mixture) and 86.5 mg of nitroolefin (0.66mmol, 1.5 eq). The reaction is stopped after 1h, dried in vacuum and purified after chromatography (mixture of pentane and ethyl acetate 9/1-8/2).

¹³ W. S. Hancock, J. E. Battersby, D. R. K. Harding, *Anal. Biochem.*, **1975**, *69*, 497.

¹⁴ E. Kaiser, R. L. Colescot, C. D. Bossinge, P. I. Cook, *Anal. Biochem.*, **1970**, *34*, 595.

¹⁵ T. Vojkovsky, *Pept. Res.*, **1995**, *8*, 236.

-Catalyst loading 0.5%

In a 5 ml flask, equipped with a stirring bar, add 1 mg of catalyst (0.0022 mmol), 39.7 μ l of butanal (0.44 mmol, 1 eq), 1.9 ml of solvent mixture (9/1 Chloroform/isopropanol), 100 μ l of a stock solution of NMM in the solvent mixture (0.0044 mmol; stock solution: 12.1 μ l of NMM in 5 ml of solvent mixture) and 86.5 mg of nitroolefin (0.66mmol, 1.5 eq).

-Catalyst loading 0.1%

In a 10 ml flask, equipped with a stirring bar, dried with the heat gun under a nitrogen flux, add 1 mg of catalyst (0.0022 mmol), 198.3 μ l of butanal stocked on molecular sieves (2.2 mmol, 1 eq), 3.8 ml of dry solvent mixture (9/1 Chloroform/isopropanol) and 50 μ l of a dry stock solution of NMM in the solvent mixture (0.0044 mmol; stock solution: 96.8 μ l of NMM in 20 ml of dry solvent mixture).

-Catalyst loading 0.05% (0.5%NMM)

In a 5 ml flask, equipped with a stirring bar, add 1 mg of catalyst (0.0022 mmol), 394 μ l of butanal (4.4 mmol, 1 eq), 1 ml of solvent mixture (9/1 Chloroform/isopropanol), 100 μ l of a stock solution of NMM in the solvent mixture (0.0044 mmol; stock solution: 12.1 μ l of NMM in 5 ml of solvent mixture) and 865 mg of nitroolefin (6.6mmol, 1.5 eq).

General procedure for the catalytic 1,4 addition reaction of α,α disubstituted aldehydes **17 and nitroolefins **18**.**

In a 1 ml flask, were added catalyst **7a** (0.022 mmol), the aldehyde **17** (0.22 mmol, 1 eq), 250 μ l of stock solution of NMM in the solvent mixture (0.11 mmol of NMM in *n*-hexane/ *i*PrOH 9/1; stock solution) and the corresponding nitroolefin (1.5 eq). The reaction was interrupted after 24h of stirring with a shaker, dried under reduced pressure and purified on silica gel flash chromatography (mixture of pentane and ethyl acetate).

Spectroscopic analysis and characterisation of products **19a-19i** was performed by comparison with literature.

Methyl 3-formyl-2-(nitromethyl)pentanoate (10): the product is obtained as colourless oil in 90% yield and 80% ee [HPLC AD-H, *n*-hexane- *i*-PrOH, 90-10, flow rate 0.5 ml/min, T= 10°C, t₁= 26.1 min, t₂= 25 min (major diastereoisomer), t₁= 27.4 min, t₂= 24 min (minor diastereoisomer)]. ¹H-NMR (400 Mhz CDCl₃): 9.70 (s, 1H, minor diast.); 9.62 (s, 1H); 4.89 (dd, 1H, J₁= 37 Hz, J₂= 24 Hz); 4.77 (dd, 1H, J₁= 37 Hz, J₂= 24 Hz, minor diaste.); 4.50 (dd, 1H, J₁= 37 Hz, J₂= 10 Hz, minor diast.); 4.39 (dd, 1H, J₁= 37 Hz, J₂= 10 Hz); 3.72 (s, 3H); 3.63 (ddd, 1H, J₁= 24 Hz, J₂= 15 Hz, J₃= 10 Hz); 2.78 (dd, 1H, J₁= 33 Hz, J₂= 15 Hz); 1.81 (sept, 1H, J= 18 Hz); 1.53 (sept, 1H, J= 18 Hz); 1.05 (t, 3H, J= 18 Hz); ¹³C-NMR (400 Mhz CDCl₃): 201.4; 171.5; 73.2; 53.1; 52.6; 41.9; 19.9; 11.9.

2,2-dimethyl-4-(2-nitro-1-phenylethyl)-1,3-dioxolane-4-carbaldehyde (19l): the product is obtained as a colorless oil in quantitative yield, d.r. =18:1 and 73% ee. HPLC OD-H, *n*-hexane-*i*-PrOH, 80-20, flow rate 0.8 ml/min, T= 25°C, t= 21 min, 16 min (major diastereoisomer), t= 13. min, minor diastereoisomer probably not separated in these conditions). ¹H-NMR (400 Mhz CDCl₃): 9.75 (s, 1H); 9.43 (s, 1H, minor diast.); 7.35-7.25 (m, 5H); 4.91 (dd, 1H, J₁= 34 Hz, J₂= 27 Hz); 4.71 (dd, 1H, J₁= 34 Hz, J₂= 12 Hz); 4.11 (d, 1H, J_d= 24 Hz);); 4.03 (dd, 1H, J₁= 27 Hz, J₂= 12 Hz); 3.70 (d, 1H, J_d= 24 Hz); 1.54 (s, 3H, minor diast.); 1.42 (s, 3H); 1.38 (s, 3H, minor diast.); 1.31 (s, 3H); ¹³C-NMR (400 Mhz CDCl₃): 202.7; 134.0; 129.6; 129.3; 129.2; 112.6; 88.0; 68.5; 45.9; 27.1; 26.3.

Chapter 4

Heterogeneous Catalysis Promoted by Chitosan.

4.1 Heterogeneous Organocatalysis

The principal features of processes based on heterogeneous catalysts are certainly the simple product purification, catalyst recovering and recycling. For this reason all fields involving homogeneous catalysts developed heterogeneous versions of the same processes in order to achieve these valuable advantages. Metal transition catalysis, for example, developed ligands covalently bound to heterogeneous matrixes in order to immobilize the metal complexes. The main problem of this methodology concerns the leaching of the metal into the solution, giving product contamination, the lowering of catalyst efficiency after recycling, and the often unpredictable effect of the solid support on catalyst activity/selectivity. Analogously, the grafting of enzymes to a solid support or their immobilization into a matrix can have a deep impact on their structure.¹ However, in many cases this has proved to be a highly valuable tool for improving enzyme stability and activity.

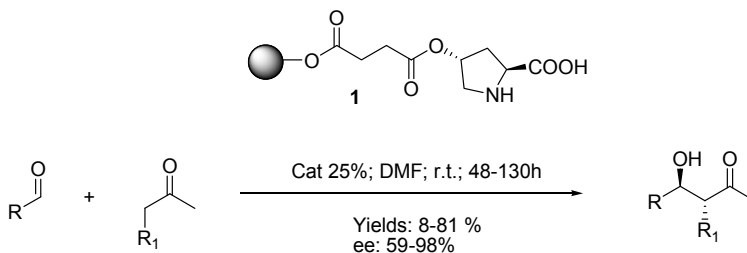
The heterogeneization of organocatalysis and the subsequently recycling of the catalyst may provide a potential solution for the high catalyst loading usually required in this field.² In this regard, the principal strategy to obtain heterogeneous organocatalysts, in similarity to metallorganic heterogeneous catalysis, is the covalent attachment to a solid support. Albeit some heterogeneous organocatalytic systems produced remarkable results, the main problems of this particular approach are essentially the less effectiveness of the supported catalysts in comparison to their homogeneous counterparts and the multiple synthetic manipulations required to achieve the immobilization.

One of the first examples of enantioselective heterogeneous organocatalysis was developed by Cozzi and co-workers. They introduced a PEG supported 4-hydroxyproline by means of a succinate spacer (catalyst 1). The supported catalyst was used in a heterogeneous enantioselective aldol reaction (Scheme 1).³

¹ a) G.F. Bickerstaff, *Immobilization of Enzyme and Cells*, Humana Press, Totowa, NJ, **1999**; b) S. Pedersen, M. W. Christensen, *Immobilized Biocatalysts*. In *Applied Biocatalysis*, 2nd Edition; A. J. J. Straathof, P. Adler-creutz, Amsterdam, **2000**, 213

² For comprehensive reviews, see: a) M. Benaglia, A. Pugliesi, F. Cozzi, *Chem Rev.*, **2003**, *103*, 3401; b) M. Benaglia, *New J. Chem.* **2006**, *30*, 1525; c) F. Cozzi, *Adv. Synth. Catal.*, **2006**, *348*, 1367.

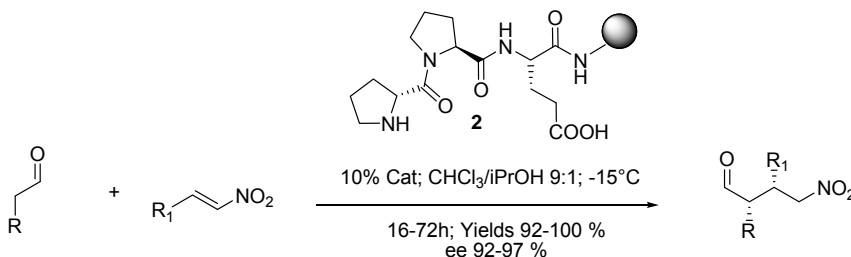
³ M. Benaglia, G. Celentano, F. Cozzi, *Adv. Synth. Catal.*, **2001**, *343*, 171.



Scheme 1

This work demonstrated the feasibility of a heterogeneous enantioselective approach in organocatalysis, albeit high reaction times and high catalytic loadings were required.

A more recent example was introduced by Wennemers and co-workers. They could immobilize the peptide catalyst **2** on different kind of polymeric supports (Polystyrene, PEGA, Tentagel) in order to perform a heterogeneous version of the conjugate addition between different aldehydes and nitroolefins, previously described in Chapter 3.⁴



Scheme 2

The results reported in Scheme 2, demonstrated the validity of this approach, which gave quantitative yields, very high enantioselections and high recycling features (up to 30 times catalyst recycling).

Another route toward heterogeneous organocatalytic systems involves non covalent immobilization; the main advantages of this strategy are related to the minimal catalyst modification, the easier assembly of the catalytic system and the possibility of fine tuning the support structure. The main strategies developed through non covalent immobilization are biphasic technology,⁵ physical adsorption⁶ and acid-base interaction.⁷

Biphasic technology consists of a liquid/liquid strategy in which the catalyst resides only in one phase. Ionic liquids are often used as organic medium for amino acidic catalysts. Yang⁸ and

⁴ Y. Arakawa, M. Wiesner, H. Wennemers, *Adv. Synth. Catal.*, **2011**, 353, 1201.

⁵ For recent example see: a) H. M. Guo, H. Y. Niu, M. X. Xue, Q. X. Guo, L. F. Cun, A. Q. Mi, Y. Z. Jiang, J. J. Wang, *Green Chem.*, **2006**, 8, 682; b) L. Zu, J. Wang, H. Li, W. Wang, *Org. Lett.*, **2006**, 8, 3077; c) L. Zu, H. Li, J. Wang, X. Yu, W. Wang, *Tetrahedron Lett.*, **2006**, 47, 5131.

⁶ For recent examples see: a) M. Gruttadauria, S. RIELA, P. L. Meo, F. D'Anna, R. Noto, *Adv. Synth. Catal.*, **2006**, 348, 82; b) Z. An, W. H. Zang, H. M. Shi, J. He, *J. Catal.*, **2006**, 241, 319.

⁷ S. Luo, J. Li, L. Zhang, H. Xu, J. Chen, *Chem. Eur. J.*, **2008**, 14, 1273.

⁸ T-P. Loh, L-C. Feng, H-Y. Yang, J-Y. Yang, *Tetrahedron Letters*, **2002**, 42, 8741

co-workers, for the first time, demonstrated that proline could perform the asymmetric aldol reaction with good results in ionic liquids, with the benefit of the easy recovery of both catalyst and organic solvent for several times. A more recent version of this approach consisted in simple modifications of some catalysts in order to increase their affinity towards one phase. In Figure 1 are reported two different kind of organocatalysts anchored to ionic liquids. 4-Hydroxyproline derivative **3** was developed for an aldol reaction⁹ while catalyst **4** was designed for a Michael addition reaction of carbonyl compounds and nitroolefins;¹⁰ in both cases good results were obtained in terms of both yields and enantioselection, and the possibility to recycle the catalyst several times was demonstrated.

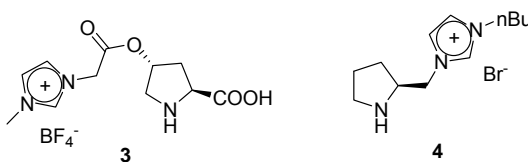


Figure 1

Another strategy consists in the adsorption of an organocatalyst on a solid support. Since some examples involving proline adsorbed on silica gel gave poor reactivity and enantioselection, Gruttadauria¹¹ and co-workers developed a ionic liquid monolayer covalently bonded to silica gel, in which proline could be adsorbed. Also in this case, the supported catalyst was tested in the direct aldol reaction, demonstrating that the monolayer could act as a reaction phase, giving also an easy recovery of the catalytic system for up to three catalytic recyclings with good results. The advantage of this strategy is that the expensive ionic liquid is used in limited amounts. A similar concept was used recently by Hagiwara et al¹² in the enantioselective Diels-Alder cycloaddition reaction. In this case the catalyst was adsorbed on silica gel, with the aid of a non-covalently functionalized ionic liquid.

A third method of non covalent immobilization concerns electrostatic interactions between the catalyst and the solid support. As shown in Figure 2, Cheng and co-workers investigated several chiral diamines and solid acids, such as polystyrene sulfonic acid, for the aldol reaction (catalyst **5**) and Michael addition (catalyst **6**). The advantage of this route is the possibility to mix catalyst and support without any permanent modification.⁷

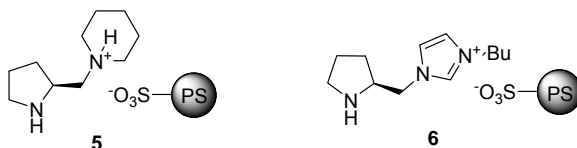


Figure 2

⁹ W. Miao, T. H. Chan, *Adv. Synth. Catal.*, **2006**, *348*, 1711

¹⁰ S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J.-P. Cheng, *Angew. Chem. Int. Ed.*, **2006**, *45*, 3093

¹¹ M. Gruttadauria, S. Riela, P. L. Meo, F. D'Anna, R. Noto, *Tetrahedron Letters*, **2004**, *45*, 6113.

¹² H. Hagiwara, T. Kuroda, T. Hoshi, T. Suzuki, *Adv. Synth. Catal.*, **2010**, *352*, 909.

In this section we developed a conceptually new approach towards the achievement of heterogeneous organocatalysis; all the previously reported examples were based on an homogeneous catalyst supported on an heterogeneous matrix through covalent or non-covalent interactions. For the first time we developed an asymmetric reaction catalyzed by chitosan, a chiral heterogeneous natural polymer, without using any chemical functionalization.

4.2 Chitosan Aerogel: a Recyclable, Heterogeneous Organocatalyst for the Asymmetric Direct Aldol Reaction in Water

4.2.1 Introduction

The advantages of using biopolymers in chemistry are connected with the shift from petrochemical-based feedstock to biological materials. Indeed, polysaccharides represent a valuable option in chemistry as they are available in enormous quantity, they contain many exploitable functionalities, are stable yet biodegradable, and chiral.

Chitosan is a linear polysaccharide composed by randomly distributed β -(1-4) linked D glucosamine and N-acetyl glucosamine; it derives by extensive deacetylation of chitin, the most abundant biopolymer in Nature after cellulose. As a matter of fact, it can be considered as a natural polyamine (Figure 3).

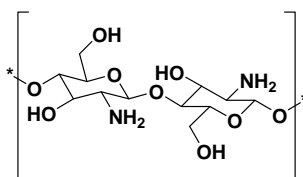


Figure 3

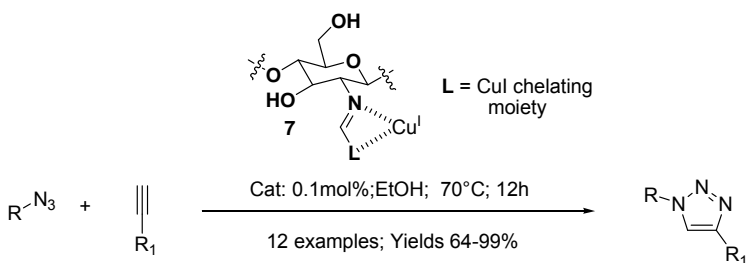
The flexibility of this material, its insolubility in the vast majority of solvents along with its tendency to act as an absorbent of metals, make chitosan an excellent candidate for building heterogeneous catalysts.¹³ Quignard and co-worker¹⁴ centered their recent attention toward polysaccharides, in particular on their use as polymeric supports for catalysis. Their studies on chitosan gel led to the development of different physical forms of this polysaccharide (*hydrogel*, *alcogel*, *aerogel*). Usually, commercially available chitosan is initially purified in order to remove traces of biological impurities. This material is then reprecipitated in aqueous solution in the form of *hydrogel*. If this material is treated extensively with ethanol, the *alcogel* is obtained. The subsequent exchange of ethanol with CO₂ in supercritical conditions leads to chitosan *aerogel* as white solid spheres. Chitosan aerogel can be properly characterized. Features relevant to heterogeneous catalysis regard the surface area (over 100 m²g⁻¹) and the number of accessible amine functions (5 mmolg⁻¹).

Quignard and co-workers employed chitosan aerogel as a polymeric support able to strongly chelate copper salts in the azide-alkyne Huisgen [3+2] cycloaddition reaction (Scheme 3). In

¹³ a) E. Guibal, *Progr. Polym. Sci.*, **2005**, 30, 71; (b) D. J. Macquerrie and J. J. Hardy, *Ind. Eng. Chem. Res.*, **2005**, 44, 8499;

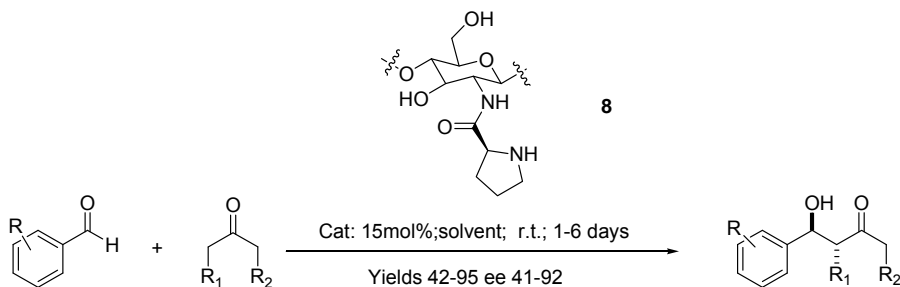
¹⁴ M. Chtchigrovsky, A. Primo, P. Gonzalez, K. Molvinger, M. Robitzer, F. Quignard and R. Taran, *Angew. Chem. Int. Ed.*, **2009**, 48, 5916.

this remarkable work they used chitosan for the synthesis of a recyclable hybrid catalyst **7** which combines the catalytic power of transition metal complexes with the architecture of polysaccharides.



Scheme 3

Furthermore, chitosan was used as heterogeneous support for a chiral organic framework such as L-proline.¹⁵ Cui's group prepared a chitosan-proline hybrid **8** in a four step sequence. This heterogeneous catalyst was used in the asymmetric direct aldol reaction in various organic solvents and water (Scheme 4).



Scheme 4

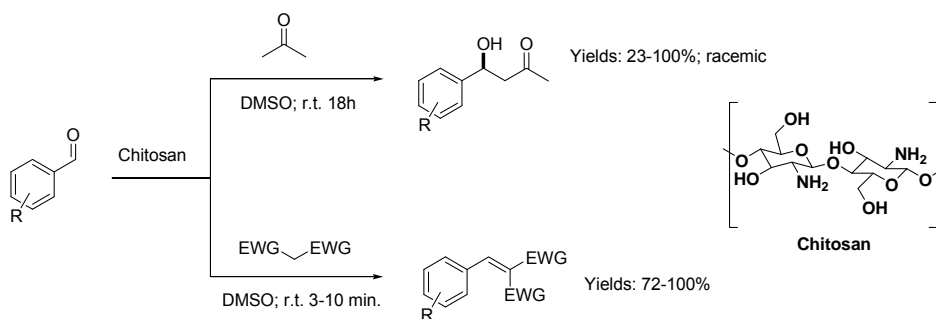
The effect of different additives on the activity and selectivity of catalyst **8** was thoroughly investigated. Interestingly, this system could interact with surfactant agents in aqueous conditions. While the presence of water mainly affected the swelling of the catalyst, the surfactant additive could act as a hydrophobic pocket allowing the reactants to be dissolved and the reaction to proceed.

Chitosan is a chiral natural polyamine. It thus possesses useful functionalities for many organocatalytic manifolds, wherein amines play a key role. However, its direct use in heterogeneous organocatalysis has been poorly explored. Chitosan hydrogel was used as a green and recyclable catalyst for the achiral cyclopropanation of olefins,¹⁶ in the synthesis of monoglyceride by fatty acid addition to glycidol¹⁷ and for aldol and Knoevenagel reactions.¹⁸ In particular, this last example was introduced by Reddy's group (Scheme 5).

¹⁵ H. Zhang, W. Zhao, J. Zou, Y. Liu, R. Li and Y. Cui, *Chirality*, **2009**, *21*, 492.

¹⁶ W. Sun, C.-G. Xia and H.-W. Wang, *New J. Chem.*, **2002**, *26*, 755.

¹⁷ (a) R. Valentin, K. Molvinger, F. Quignard and D. Brunel, *New J. Chem.*, **2003**, *27*, 1690; (b) K. Molvinger, F. Quignard, D. Brunel, M. Boissière and J.-M. Devoisselle, *Chem. Mat.*, **2004**, *16*, 3367.



Scheme 5

Although chitosan demonstrated good results in conversion and selectivity, no significant induction of stereoselectivity by the backbone chirality of the polymer was observed in any of these reactions. The explanation reported for these results indicated that in these conditions the catalysts was not involved through an enamine activation pathway, but simply as a Brønsted base. Albeit the absence of enantioselection, it is worth noting that in these examples this natural polymer was involved in heterogeneous catalysis without any kind of chemical modification or group protection.

The lack of literature reports dealing with the heterogeneous asymmetric organocatalysis displayed by polysaccharides prompted us to undertake a detailed study on the evaluation of the chitosan potential in this new frontier area of organocatalytic reactions. To this purpose, and considering the polyamino structure of this renewable natural material, we focused on the field of primary amine organocatalysis,¹⁹ emerged in the past few years.

¹⁸ K. R. Reddy, K. Rajgopal, C. U. Maheswari and M. L. Kantam, *New. J. Chem.*, **2006**, *30*, 1549.

¹⁹ S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.*, **2007**, *107*, 5471; P. Melchiorre, M. Marigo, A. Carlone G. Bartoli, *Angew. Chem., Int. Ed.*, **2008**, *47*, 6138; S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.*, **2009**, *38*, 2178; D. W. C. MacMillan, *Nature*, **2008**, *455*, 304.

4.2.2 Results and discussions²⁰

To evaluate the putative chitosan catalytic activity, the direct aldol reaction,²¹ one of the most important carbon–carbon bond forming reactions,²² was investigated in the presence of water²³ without any organic co-solvent, by using supercritical CO₂ dried chitosan (*aerogel*) as the catalyst (Table 1). Initial tests were performed in the prototype reaction between *p*-nitrobenzaldehyde **9a** and cyclohexanone **10a** as the pronucleophile, and were aimed at establishing the optimized reaction conditions (Table 1). For this purpose, a catalytic loading of 22 mol%, referred to the estimated amount of the free amino group functions, was considered. Several organic solvents such as DMSO and THF were screened but very little or no aldol product was detected (entries 1,2). The same disappointing outcome was observed (entry 3) when the reaction was performed in neat cyclohexanone. The aqueous medium demonstrated to be necessary for the reaction leading to product **11a** with acceptable reaction rates and in high yields. No substantial variations were noticed on varying the amount of water (compare entries 4–6). We were delighted to see that high enantiomeric excess up to 84% ee for the major diastereoisomer and up to 60% for the minor were obtained (entry 5) with an *anti/syn* ratio in the range of 3 : 1.

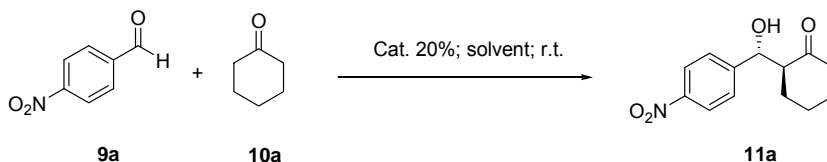
²⁰ A. Ricci, L. Bernardi, C. Gioia, S. Vierucci, M. Robitzer, F. Quignard, *Chem. Commun.*, **2010**, 46, 6288.

²¹ A. Cordova, W. Zou, I. Ibrahim, E. Reyes, M. Engqvist, W.-W. Liao, *Chem. Commun.*, **2005**, 3586; A. Cordova, W. Zou, P. Dziedzic, I. Ibrahim, E. Reyes and Y. Xu, *Chem.–Eur. J.*, **2006**, *12*, 5383; L.-W. Xu, J. Luo and Y. Lu, *Chem. Commun.*, **2009**, 1807.

²² Modern Aldol Reactions, ed. R. Mahrwald, Wiley-VCH, Weinheim, **2004**, vol. 1 and 2.

²³ E. A. C. Davie, S.M.Mennen, Y. Miller, S. J. Xu, *Chem. Rev.*, **2007**, *107*, 5759; A. P. Brogan, T. J. Dickerson and K. D. Janda, *Angew. Chem., Int. Ed.*, **2006**, *45*, 100; (c) Y. Hayashi, *Angew. Chem., Int. Ed.*, **2006**, *45*, 8103; J. Paradowska, M. Stodulski and J. Mlynarski, *Angew. Chem., Int. Ed.*, **2009**, *48*, 4288.

Table 1 Direct aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde: screening of catalyst system and reaction medium.^a

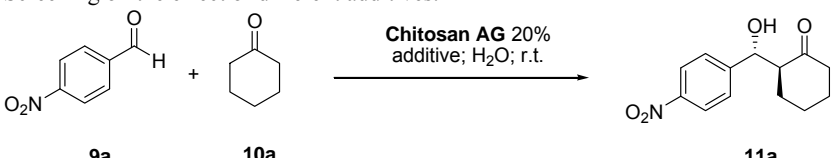


Entry	Solvent (ml)	Catalyst	Yield (%) ^b	Anti/Syn ^c	Ee (%) ^d
1	THF 0.3	Chit. AG	traces	n.d.	n.d.
2	DMSO 0.3	Chit. AG	traces	n.d.	n.d.
3	Neat	Chit. AG	traces	n.d.	n.d.
4	H ₂ O 0.3	Chit. AG	75	70/30	80 (50)
5	H ₂ O 0.5	Chit. AG	85	70/30	84 (60)
6	H ₂ O 1	Chit. AG	80	69/31	85 (50)
7	H ₂ O 0.5	Chit. HG^e	75	68/32	80 (53)
8	H ₂ O 0.5	Gluc.Amine	38	58/42	50 (28)

^a Conditions: chitosan 4.5 mg (corresponding to 22 mol% free amino units with respect to aldehyde), *p*-nitrobenzaldehyde (0.10 mmol), cyclohexanone (2.0 mmol), H₂O. ^b Isolated yield after chromatography on silica gel. ^c Determined by ¹H NMR spectroscopy on the crude mixture. ^d Determined by chiral-phase HPLC analyses, results in parentheses refer to the minor diastereomer. ^e This figure does not take into account the amount of H₂O in the hydrogel beads employed, evaluated in ca. 0.05 mL.

This is to the best of our knowledge the first report on the capability of chitosan to act as an asymmetric organocatalyst. A lower catalyst loading caused a substantial drop of the conversion without affecting however the enantioselectivity. Moreover, replacing chitosan **aerogel** with **hydrogel** the reaction led to slightly diminished yields and to some erosion of the enantioselectivity (entry 7). Finally, comparison with the monomeric **glucosamine** (entry 8) highlighted the superiority of the polymeric bio-material as catalyst with respect to the monomeric aminosugar.

We then turned our attention to the effect of different type of additives (Table 2). In the direct aldol reaction, the amine-catalyzed version usually proceeds via an enamine intermediate^{Errore. Il segnalibro non è definito.} whose formation is catalysed by acids matching the basicity of the amine. In line with these assumptions, when the reaction between cyclohexanone **9a** and *p*-nitrobenzaldehyde **10a** was performed in the presence of 20 mol% of 2,4-dinitrophenol (DNP, pK_a = 4.11), a substantial increase of the enantiomeric excess to 92% was observed that however diminished in the presence of 10 mol% of the additive (entries 7–8). This improvement was not observed when a weaker acid such as *p*-nitrophenol (pK_a = 7.2) was employed.

Table 2. Screening on the effect of different additives.


Entry	Additive (mol %)	Time (h)	Yield (%)	Anti/Syn	Ee (%)
1	None	48	85	70/30	84 (60)
2	DNP (10)	24	78	74/26	86 (55)
3	DNP (20)	24	85	76/24	92 (75)
4	SDS (20)	48	90	70/30	90 (80)
5	PEG (20)	48	92	66/44	85 (57)
6	Acetic acid (20)	48	90	70/30	84 (60)
7	Linoleic acid (20)	48	95	70/30	87 (50)
8	Stearic acid (20)	48	88	69/31	93 (54)

Surfactants such as PEG and SDS are frequently employed in order to perform reactions in aqueous media and this strategy has also been attempted in organocatalysis.²⁴ Moreover, chitosan is known to be a lipid binder as demonstrated for example by its use in pharmaceutical chemistry as an antilipidemic.²⁵ These considerations prompted us to consider that fatty acids might result beneficial for catalysis in pure water, since they would simultaneously act as efficient acidic co-catalysts and at the same time assist in solubilising the organic substrates with their lipophilic tail. It is also conceivable that the proved affinity of saturated and unsaturated fatty acids versus chitosan²⁶ might provide an additional asset favouring the recognition of the reagents by the catalyst. As shown in Table 2, a general modest improvement of the yields and enantiomeric excess can be observed in the presence of both anionic (SDS) (entry 4) and neutral (PEG) (entry 5) surfactants and of acidic additives (fatty acids, acetic acid). The beneficial effect of the latter does not seem in all cases related only to their pKa values as suggested by comparison between the reaction outcome induced by DNP (pKa = 4.11) (entry 3), acetic acid (pKa = 4.76) (entry 6), linoleic acid (pKa = 9,24) (entry 7) and stearic acid (pKa = 10.15) (entry 8). Presumably, both the acidity and the chain lipophilicity of the additives affect the catalytic processes, even though the efficacy of lipophilicity under the conditions employed might be depressed by the presence of the conspicuous amount of organic phase coming from the excess (20:1) of the donor system.

²⁴ A. Cordova, W. Notz, C. F. Barbas III, *Chem. Commun.*, **2002**, 3024; Y.-Y. Peng, Q.-P. Ding, Z. Li, P. G. Wang, J.-P. Cheng, *Tetrahedron Lett.*, **2003**, *44*, 3871; D.-S. Deng, J. Cai, *Helv. Chim. Acta*, **2007**, *90*, 114; (d) X.-L. Liu, X.-M. Zhang, W.-C. Yuan, *Tetrahedron Lett.*, **2011**, *52*, 903.

²⁵ K. M. Shields, *Am. J. Health-Syst. Pharm.*, **2003**, *60*, 1310.

²⁶ P. Wydro and B. Krajewska, K. Hac-Wydro, *Biomacro-molecules*, **2007**, *8*, 2611.

Although the mechanism through which fatty acids improve yields and stereoselectivity is presumably complex, the possibility exists that the liquid organic donor and the acceptor form an emulsion with the fatty acid in water²⁷ and because of this aggregation the organic molecules could be favourably driven towards the intermediate enamine formation.

With the optimised set of conditions in hand, the scope of the direct aldol reaction was inspected using several ketone donors and a range of acceptors (Scheme 6). In most cases, reactions afforded the aldol products **11** with good diastereoselectivities and in fairly high yields and enantioselectivities for the major anti diastereomer. As shown in Scheme 6, not only aromatic and heteroaromatic aldehydes (compounds **9a,b,c**) but also differently structured acceptor systems (compounds **9e,f,g**) afforded the aldol products in fairly high yields moderate diastereoselectivities and significant e.e.s. Only in the case of the water miscible formaldehyde **9d**, the reaction failed, a behaviour predictable from previous literature reports²⁸ and attributed to the fact that this acceptor system in bulk water is strongly hydrated²⁹ which results in a low concentration of the reactive form.

Using isatin **9h** as the acceptor system allowed the formation in very high yields and good enantioselectivity of the oxindole **11h** having a structural moiety of high interest in medicinal chemistry.³⁰

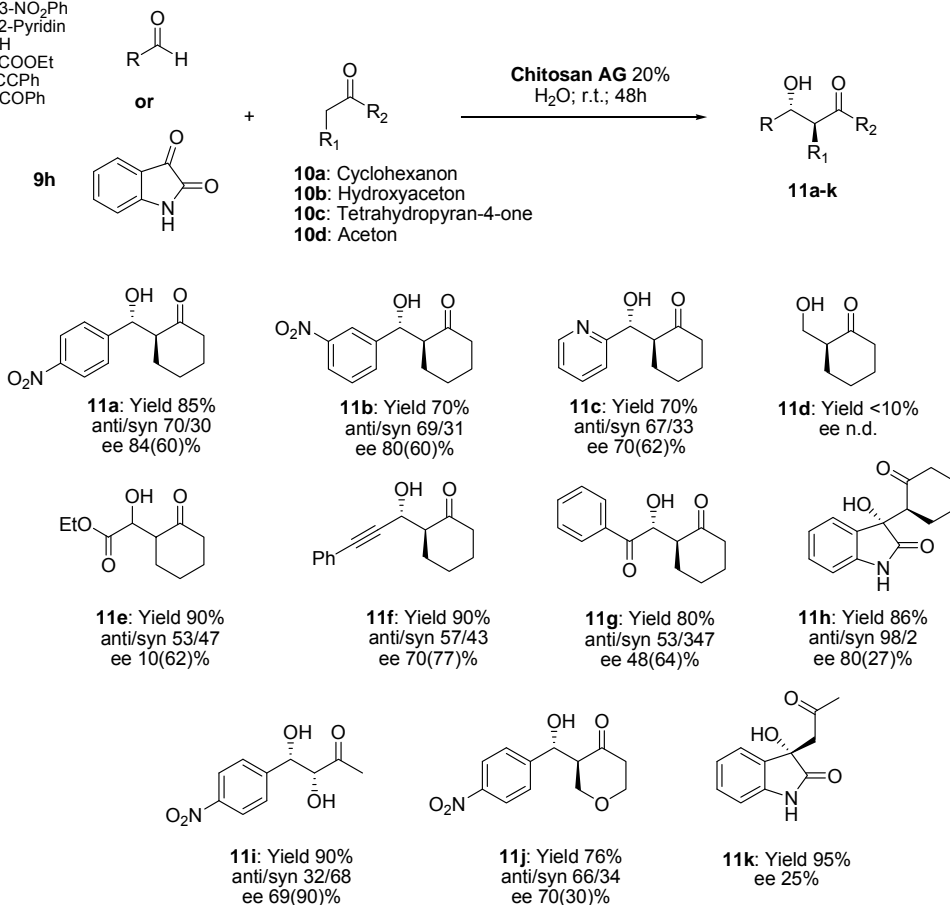
²⁷ N. Mase, N. Noshiro, A. Moyuka and K. Takabe, *Adv. Synth. Catal.*, **2009**, 351, 2791.

²⁸ M. Pasternak, J. Paradowska, M. Rogozinska, and J. Mlynarski, *Tetrahedron Lett.*, **2010**, 51, 4088.

²⁹ J. G. M. Winkelman, O. K. Voorwinde, M. Ottens, A.A.C. M. Beenackers and L. P. B. Janssen, *Chem. Eng. Sci.*, **2002**, 57, 4067.

³⁰ M. Raj, N. Veerasamy and V. K. Singh, *Tetrahedron Lett.*, **2010**, 51, 2157.

9a: R = 4-NO₂Ph
9b: R = 3-NO₂Ph
9c: R = 2-Pyridin
9d: R = H
9e: R = COOEt
9f: R = CCPH
9g: R = COPh



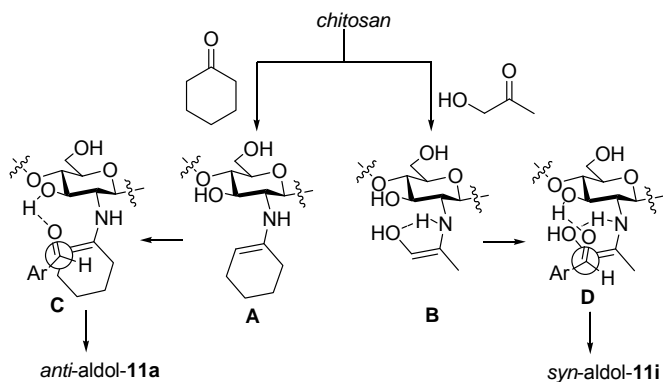
Scheme 6

Besides cyclohexanone **10a** other donors like hydroxyacetone **10b**, tetrahydro-4H-pyran-4-one **10c** and acetone **10d** were used in these reactions. Although in most of the cases good results were obtained, the reaction of isatin **9h** with water miscible acetone **10d** yielded the product **11k** in good yields but not in synthetically useful enantioselectivities, a result which parallels previous literature reports.³¹

The contrasting diastereoselectivity observed when cyclohexanone **10a** and hydroxyacetone **10b** were used as donors can be rationalised with the models shown in Scheme 7. Following the generally accepted mechanistic picture,^{19,32} cyclohexanone condenses with chitosan primary amine to give E-enamine A, whereas hydroxyacetone results predominantly in Z-enamine B stabilised by an intramolecular hydrogen bond.

³¹ N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka and C. F. Barbas III, *J. Am. Chem. Soc.*, **2006**, *128*, 734.

³² S. S. V. Ramasastry, H. Zhang, F. Tanaka and C. F. Barbas III, *J. Am. Chem. Soc.*, **2007**, *129*, 288.

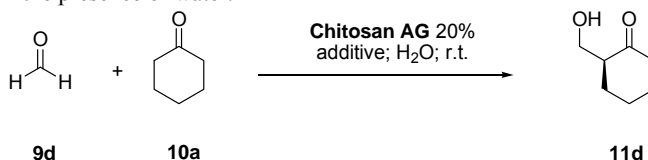


Scheme 7

These enamines then react with the incoming aldehyde, likely activated by a hydrogen-bond with the 4-hydroxy group in intermediates C and D, affording as the major products the corresponding anti and syn-aldol adducts, respectively. However, the possibility of additional hydrogen-bond interactions between substrates and other hydroxyl moieties (of the same or adjacent saccharide units) cannot be ruled out.

Compared to the advantages induced by the additive in the prototype reaction, a more sizeable beneficial effect was detected (Table 3) when the reaction with formaldehyde as the acceptor system was studied. The corresponding aldol product was obtained in moderate yield and with a substantial improvement, though still not satisfactory, in enantioselectivities. The benefits of additives such as SDS when using formaldehyde in the presence of water, have on the other hand very recently highlighted in the aminomethylation of oxindoles via three-component Mannich reaction.^{24c}

Table 3: effect of additives on the asymmetric direct aldol reaction between formaldehyde **9d** and cyclohexanone **10a** in the presence of water.



Entry	Additive	Yield (%)	Ee (%) ^a
1	SDS	40	57
2	PEG	15	46
3	Stearic Acid	35	44
4	Linoleic Acid	30	48

^a After benzoylation

Attempts at improving the reaction outcome performing the reaction in the presence of strongly reduced amounts of water (300 mol %) resulted however unsuccessful probably due to the inefficacy of chitosan aerogel to act as a catalytic specie under these conditions.

Despite the great variety of aldol acceptors used in the direct aldol reaction in the presence of water, the range of donors remains quite narrow. Moreover whereas the prototype reaction is good for establishing the potential usefulness of the new catalysts it leads to products lacking the functional group diversity typical of drug-like building blocks. Recently several highly stereoselective aldol reactions of heterocyclic ketones such as 4-thianone **10e** and 4-Boc-piperidinone **10f** have been reported in organic media³³ under solvent free conditions³⁴ and in the presence of water (Figure 4).³⁵

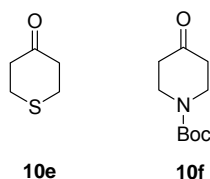


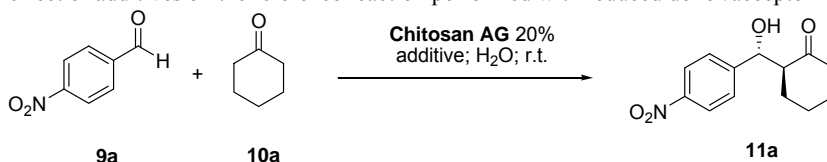
Figure 4

Since both these donors as well as the acceptor 4-nitro-benzaldehyde and the catalyst are water insoluble solids which in our case would make the operational mode difficult, and also given the fact that these donors are not the cheapest ones the use of large excess of ketone to push the reactions should be avoided. To this aim we examined the effect of lowering the ketone/aldehyde ratio to 2:1 firstly for the aldol addition of cyclohexanone to 4-nitro-benzaldehyde using aerogel chitosan as the organocatalyst.

³³ J.-R. Chen, X.-Y. Li, X.-N. Xing, W.-J. Xiao, *J. Org. Chem.*, **2006**, *71*, 8198.

³⁴ D. Almasi, D. A. Alonso, C. Nájera, *Adv. Synth. Catal.*, **2008**, *350*, 2467.

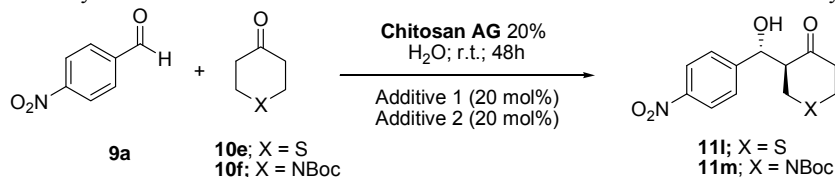
³⁵ (a) D. A. Ward and V. Jheengut, *Tetrahedron Lett.*, **2004**, *45*, 8347; (b) T. Nugent, M. N. Umar and A. Bibi, *Org. & Biomol. Chem.*, **2010**, *8*, 4085 and references therein

Table 4: effect of additives on the reference reaction performed with reduced donor/acceptor ratio.

Entry	Additive 1	Additive 2	Yield (%)	Anti/Syn	Ee (%)
1	None	None	45	66/34	70 (60)
2	Linoleic Acid	None	65	65/35	77 (63)
3	Stearic Acid	None	63	67/33	80 (66)
4	None	SDS	75	70/30	87 (82)
5	Linoleic Acid	SDS	85	63/37	74 (35)
6	DNP	SDS	90	71/29	90 (77)

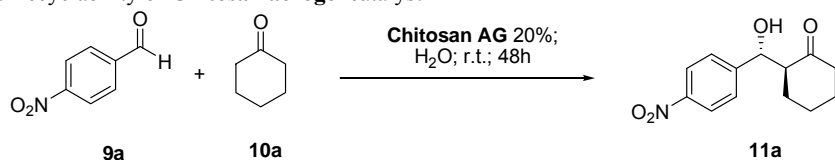
The reaction run for 48 h takes place (Table 4) with satisfactory albeit to some extent reduced yields but still with remarkably good enantiomeric excess. Worth noting the significant quantities of the aldol elimination product formed in the absence of additives (entry 1) or in the presence of lipophilic acids (entries 2,3) were almost completely suppressed (entries 4-6) in the presence of SDS.

Having established the feasibility of the benchmark direct aldol reaction with cyclohexanone under these new conditions, the extension to the heterocyclic donors was carried out (Table 5). In the colloidal dispersions formed in water by the presence of SDS the reaction of tetrahydro-4H-thiopyran-4-one (**10e**) and 1-Boc-4-piperidone (**10f**) occurred however with poor yields and negligible enantioselectivities (entries 1,4). The susceptibility to syn/anti isomerisation via enolization^{35a} and the occurrence of a retro-aldol reaction of **11l** in the presence of bases and the marked tendency of **11m** to racemize,³⁴ account for the poor results obtained in the presence of an anionic surfactant. On the other hand, the heterocyclic donors smoothly reacted with 4-nitrobenzaldehyde in the presence of both SDS and acid co-catalysts leading (entries 2,3,5,6) the aldol products **11l** and **11m** respectively in generally good yields with low diastereoselectivity and fairly high enantioselectivity, thus confirming for the reactions performed in bulk water the beneficial effect of combining an anionic surfactant with an acidic additive.^{35b}

Table 5: heterocyclic ketones **10e** and **10f** as donor in the aldol reaction with 4-nitrobenzaldehyde.

Entry	X	Additive 1	Additive 2	Product	Yield (%)	Anti/Syn	Ee (%)
1	S	None	SDS	11i	10	60/40	15 (n.d)
2	S	Lin. Acid	SDS	11i	55	73/27	50 (50)
3	S	DNP	SDS	11i	45	87/13	67 (8)
4	N-Boc	none	SDS	11m	25	82/18	33 (10)
5	N-Boc	Lin. Acid	SDS	11m	70	61/39	60 (5)
6	N-Boc	DNP	SDS	11m	83	75/25	85 (60)

The efficacy of chitosan aerogel in terms of its reusability as an organocatalyst in the aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde was finally tested. After completion of the reaction and decantation of the organic/aqueous layer the aerogel did not seem macroscopically affected and could be reused for at least 3 more additional runs displaying the same efficiency and stereoselectivity (Table 6).

Table 6: Recyclability of Chitosan aerogel catalyst

Cycle	Yield (%)	Anti/Syn	Ee (%)
1	85	70/30	84
2	80	67/33	82
3	82	69/31	80
4	87	65/35	83

4.2.3 Conclusions

In summary, we have developed the first direct asymmetric aldol reaction that can be performed in the presence of water using chitosan as a heterogeneous organocatalyst. The ability of this renewable feedstock material has been successfully applied to a range of acceptor and donor systems. The effect of additives of different nature has been studied in order to improve the reaction outcomes and investigate the reactivity of this natural compound. A beneficial effect can be noticed by using surfactants and acid co-catalysts and their combination has proven particularly useful in the case of heterocyclic ketone donors. The simple and environmentally friendly experimental procedure and the recycling of the catalytic system highlight good assets of this catalytic protocol.

4.2.4 Experimental Section

General Methods and Materials. ^1H , ^{13}C NMR spectra were recorded on a Varian AS 400 or 600 spectrometer. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD-H, Chiralcel OJ-H), using a UV detector operating at 254 nm. Analytical grade solvents and commercially available reagents were used as received. Chromatographic purifications were performed using 70-230 mesh (chromatography) or 230-400 mesh silica gel (flash chromatography). Racemic samples were prepared using *rac*-proline as the catalyst. Chitosan from Aldrich, extracted from the crab shell, was characterized by an acetylation degree of 8% determined by infrared and ^1H NMR and a molecular weight of $700000\text{ g}\cdot\text{mol}^{-1}$ determined by viscosimetry. The chitosan was purified before use according to the following procedure. It was dissolved at 1% (w/v) during 15 hours, in an aqueous solution containing a stoichiometric amount of acetic acid with respect to the number of amine functions in the chitosan. The solution was filtered over Millipore nitrocellulose filters of $3\ \mu\text{m}$; $1.2\ \mu\text{m}$; $0.8\ \mu\text{m}$; $0.45\ \mu\text{m}$ and $0.2\ \mu\text{m}$. Then, a 50% ammoniac solution is introduced until pH 9. Then, precipitated chitosan was washed with distilled water by centrifugation until the conductivity of the solution was the same as the distilled water ($6\text{-}9\ \mu\text{Siemens}$). Chitosan was dried by lyophilisation. Chitosan aerogel microspheres ($0.90 \pm 0.05\ \text{mg}$, $350\ \text{m}^2\cdot\text{g}^{-1}$, $5.2\ \text{mmol}\cdot\text{g}^{-1}$ accessible NH_2 groups) were prepared as described previously.³⁶

General procedure for the aldol reaction. In a vial equipped with a magnetic stirring bar were sequentially added chitosan aerogel microspheres (15 beads, 13.5 mg, corresponding to 22 mol % free amino units respect to the acceptor), the aldol acceptor (0.30 mmol), eventually the additive (20 mol %), H_2O (1.5 mL) and the ketone donor (6.0 mmol). The mixture was gently stirred at r.t. for the stated time. EtOAc/ Et_2O were then added, and the phases separated. The aqueous phase, containing the chitosan beads, was then extracted with EtOAc/ Et_2O (2 x). The combined organic phases were evaporated, and the crude product analysed by ^1H NMR spectroscopy, to determine the diastereomeric ratio. The aldol adducts **11** were finally obtained by chromatographic purification or as outlined below.

2-(Hydroxy(4-nitrophenyl)methyl)cyclohexanone (11a). Following the general procedure and performing the reaction without additives (48 h reaction time), the title compound was obtained in 85 % yield as a white solid and as a mixture of diastereoisomers, after chromatography on silica gel (*n*-hexane/EtOAc from 85:15 to 75:25). The diastereomeric ratio, as determined by ^1H NMR analysis of the crude mixture, was found to be 70/30, favouring the *anti* isomer. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralpak ADH column, flow $0.75\ \text{mL}\cdot\text{min}^{-1}$, *n*-hexane/*i*-PrOH 90:10: *anti* isomer: t_{maj} 43.9 min, t_{min} 33.1 min, 84 % ee; *syn* isomer: t_{maj} 29.5 min, t_{min} 26.1 min, 60 % ee). ^1H NMR (CDCl_3 , 400 MHz) δ : 8.23-8.17 (m, 2H_{anti} , 2H_{syn}), 7.54-7.45(m, 2H_{anti} , 2H_{syn}), 5.48 (br t, $J = 2.6\ \text{Hz}$, 1H_{syn}), 4.90 (dd, $J = 8.5, 3.1\ \text{Hz}$, 1H_{anti}), 4.07 (d, $J = 3.1\ \text{Hz}$, 1H_{anti}), 3.18 (d, $J = 3.1\ \text{Hz}$, 1H_{syn}), 2.69-2.27 (m, 2H_{anti} , 2H_{syn}), 2.19-2.05 (m, 1H_{anti} , 1H_{syn}), 1.92-1.23 (m, 6H_{anti} , 6H_{syn}). HRMS: calculated for $\text{C}_{13}\text{H}_{15}\text{NNaO}_4$ [$\text{M} + \text{Na}^+$]: 272.0899; found: 272.0989. Spectral and analytical data are consistent with literature values.³⁷

The same reaction, performed using DNP as additive (24 h reaction time), gave the title compound in 85 % yield, 76/24 *anti/syn* ratio (determined by ^1H NMR on the crude mixture),

³⁶ F. Quignard, R. Valentin, F. Di Renzo, *New J. Chem.*, **2008**, 32, 1300.

³⁷ A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.*, **2005**, 3, 84.

92 % ee in the *anti* isomer, and 75 % ee in the *syn* isomer (determined by HPLC). The same reaction, performed using stearic acid as additive (48 h reaction time), gave the title compound in 88 % yield, 69/31 *anti/syn* ratio (determined by ^1H NMR on the crude mixture), 93 % ee in the *anti* isomer, and 54 % ee in the *syn* isomer (determined by HPLC). The relative configuration of the two diastereomers was determined by comparison of their ^1H NMR spectra with literature data,³⁷ giving an *anti* relative configuration in the major diastereoisomer. The absolute configuration of the major *anti* diastereoisomer was assigned as 2*S*,1'*R*, by comparison of the HPLC retention times of its two enantiomers with literature values.³⁸

For catalyst recycling, at the end of the reaction, both aqueous and organic phase were transferred to a separatory funnel, leaving chitosan beads in the vial, by means of a Pasteur pipette. Chitosan beads were washed twice with H_2O , and these aqueous phases added to the funnel as well for the above described work up and product purification. The washed chitosan beads were then used directly in the next run.

3-Hydroxy-3-(2-oxocyclohexyl)indolin-2-one (11h). Following the general procedure and performing the reaction without additives (48 h reaction time), the title compound was obtained in 86 % yield as a pale yellow solid and as a mixture of diastereoisomers, purifying the crude solid mixture with *n*-hexane/ CH_2Cl_2 washings. The diastereomeric ratio was found to be 98/2 (determined by HPLC analysis). The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralcel OJH column, flow 0.75 mL.min⁻¹, *n*-hexane/*i*-PrOH 80:20: major diastereoisomer: t_{maj} 14.8 min, t_{min} 18.3 min, 80 % ee; minor diastereoisomer: t_{maj} 12.0 min, t_{min} 13.5 min, 27 % ee). ^1H NMR (DMSO-*d*₆, 400 MHz) δ : 10.16 (s, 1H), 7.24-7.10 (m, 2H), 6.87-6.71 (m, 2H), 5.79 (s, 1H), 3.06 (dd, $J = 13.0, 5.0$ Hz, 1H), 2.61-2.53 (m, 1H), 2.36-2.53 (m, 1H), 2.36-2.21 (m, 1H), 2.08-1.58 (m, 5H), 1.53-1.34 (m, 1H); ^{13}C NMR (DMSO-*d*₆, 100 MHz) δ : 209.8, 179.4, 144.1, 131.5, 129.3, 125.5, 121.5, 110.1, 74.6, 58.1, 42.1, 27.4, 27.3, 25.1; HRMS: calculated for $\text{C}_{14}\text{H}_{15}\text{NNaO}_3$ [$\text{M} + \text{Na}^+$]: 268.0950; found: 268.0925. The same reaction, performed using DNP as additive (24 h reaction time), gave the title compound in 89 % yield, 97/3 diastereomeric ratio, 77 % ee in the major diastereoisomer, and 30 % ee in the minor diastereoisomer (determined by HPLC).

3,4-Dihydroxy-4-(4-nitrophenyl)butan-2-one (11i). Following the general procedure and performing the reaction without additives (48 h reaction time), the title compound was obtained in 90 % yield as a white solid and as a mixture of diastereoisomers, after flash chromatography on silica gel (*n*-hexane/EtOAc 85:15-75:25). The diastereomeric ratio, as determined by ^1H NMR analysis of the crude mixture, was found to be 68/32, favouring the *syn* isomer. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralpak ADH column, flow 0.75 mL.min⁻¹, *n*-hexane/*i*-PrOH 90:10: *anti* isomer: t_{maj} 23.3 min, t_{min} 27.6 min, 90 % ee; *syn* isomer: t_{maj} 44.4 min, t_{min} 32.8 min, 69 % ee). ^1H NMR (CDCl_3 , 400 MHz) δ : 8.26-8.20 (m, 2H_{anti}, 2H_{syn}), 7.64-7.57 (m, 2H_{anti}, 2H_{syn}), 5.22 (dd, $J = 7.8, 2.0$ Hz, 1H_{syn}), 5.08 (t, $J = 4.6$ Hz, 1H_{anti}), 4.48 (t, $J = 4.8$ Hz, 1H_{anti}), 4.42 (dd, $J = 4.5, 2.1$ Hz, 1H_{syn}), 3.74 (d, $J = 4.6$ Hz, 1H_{syn}), 3.68 (d, $J = 5.0$ Hz, 1H_{anti}), 2.96 (d, $J = 4.6$ Hz, 1H_{anti}), 2.78 (d, $J = 7.8$ Hz, 1H_{syn}), 2.36 (s, 3H_{syn}), 2.02 (s, 3H_{anti}). HRMS: calculated for $\text{C}_{10}\text{H}_{11}\text{NNaO}_5$ [$\text{M} + \text{Na}^+$]: 248.0535; found: 248.0501. Spectral and analytical data were consistent with literature values.³⁹

The same reaction, performed using DNP as additive (24 h reaction time), gave the title compound in 90 % yield, 36/64 *anti/syn* ratio (determined by ^1H NMR on the crude mixture), 90 % ee in the *anti* isomer, and 68 % ee in the *syn* isomer (determined by HPLC). The same

³⁸ S. Doherty, J. G. Knight, A. McRae, R. W. Harrington, W. Clegg, *Eur. J. Org. Chem.*, **2008**, 1759.

³⁹ Q. G., X.-F. Wang, L. Wang, X.-Y. Wu, Q.-L. Zhou, *Tetrahedron: Asymmetry*, **2006**, 17, 1537.

reaction, performed using stearic acid as additive (48 h reaction time), gave the title compound in 83 % yield, 33/67 *anti/syn* ratio (determined by ^1H NMR on the crude mixture), 83 % ee in the *anti* isomer, and 65 % ee in the *syn* isomer (determined by HPLC). The relative configuration of the two diastereomers was determined by comparison of their ^1H NMR spectra with literature data,³⁹ giving a *syn* relative configuration in the major diastereoisomer. The absolute configuration of the major *syn* diastereoisomer was assigned as 3R,4S, by comparison of the HPLC retention times of its two enantiomers with literature values.⁴⁰

3-(Hydroxy(4-nitrophenyl)methyl)dihydro-2H-pyran-4(3H)-one (11j). Following the general procedure and performing the reaction without additives (48 h reaction time), the title compound was obtained in 76 % yield as a white solid and as a mixture of diastereoisomers, after flash chromatography on silica gel (*n*-hexane/EtOAc 80:20-70:30). The diastereomeric ratio, as determined by ^1H NMR analysis of the crude mixture, was found to be 66/34, favouring the *anti* isomer. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralpak ADH column, flow 0.75 mL.min⁻¹, *n*-hexane/*i*-PrOH 90:10: *anti* isomer: t_{maj} 30.6 min, t_{min} 26.3 min, 70 % ee; *syn* isomer: t_{maj} 21.4 min, t_{min} 17.8 min, 30 % ee). ^1H NMR (CDCl₃, 400 MHz) δ : 8.26-8.20 (m, 2H_{anti}, 2H_{syn}), 7.54-7.48 (m, 2H_{anti}, 2H_{syn}), 5.54 (br s, 1H_{syn}), 4.98 (d, $J = 8.5$ Hz, 1H_{anti}), 4.28-4.18 (m, 1H_{anti}, 1H_{syn}), 3.88- 3.67 (m, 3H_{anti}, 4H_{syn}), 3.46 (dd, $J = 11.4, 10.1$ Hz, 1H_{anti}), 2.99-2.83 (m, 1H_{anti}, 1H_{syn}), 2.78-2.62 (m, 1H_{anti}, 1H_{syn}); 2.58-2.42 (m, 1H_{anti}, 1H_{syn}). HRMS: calculated for C₁₂H₁₃NNaO₅ [M + Na⁺]: 274.0691; found: 274.0685. Spectral and analytical data were consistent with literature values.⁴¹

The same reaction, performed using DNP as additive (24 h reaction time), gave the title compound in 78 % yield, 70/30 *anti/syn* ratio (determined by ^1H NMR on the crude mixture), 72 % ee in the *anti* isomer, and 24 % ee in the *syn* isomer (determined by HPLC). The relative configuration of the two diastereomers was determined by comparison of their ^1H NMR spectra with literature data,⁴¹ giving an *anti* relative configuration in the major diastereoisomer. The absolute configuration of the major *anti* diastereoisomer was assigned as S at the cyclohexanone chiral center, and R at the hydroxy substituted center, by analogy with the reaction performed using cyclohexanone.

(S)-3-Hydroxy-3-(2-oxopropyl)indolin-2-one (11k). Following the general procedure, but using 12.0 mmol of acetone donor and performing the reaction without additives (48 h reaction time), the title compound was obtained in 95 % yield as a pale yellow solid, purifying the crude solid mixture with *n*-hexane/CH₂Cl₂ washings. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralcel OJH column, flow 0.75 mL.min⁻¹, *n*-hexane/*i*-PrOH 80:20: t_{maj} 22.2 min, t_{min} 19.1 min, 25 % ee). ^1H NMR (DMSO-*d*₆, 400 MHz) δ : 10.18 (br s, 1H), 7.22 (br d, $J = 7.2$ Hz, 1H), 7.15 (dt, $J_t = 7.6$ Hz, $J_d = 1.3$ Hz, 1H), 6.88 (dt, $J_t = 7.6$ Hz, $J_d = 1.0$ Hz, 1H), 6.75 (br d, $J = 7.6$ Hz, 1H), 5.94 (s, 1H), 3.24 (d, $J = 16.8$ Hz, 1H), 2.97 (d, $J = 16.8$ Hz, 1H), 1.98 (s, 3H); HRMS: calculated for C₁₁H₁₁NNaO₃ [M + Na⁺]: 228.0637; found: 228.0660. Spectral and analytical data were consistent with literature values.⁴² The same reaction, performed using DNP as additive (48 h reaction time), gave the title compound in 97 % yield and 5 % ee (determined by HPLC). The same reaction, performed using DNP as additive (48 h reaction time), gave the title compound in 97 % conversion (determined by ^1H NMR) and 5 % ee (determined by HPLC). The same reaction, performed using stearic acid as additive (48 h reaction time), gave the title compound in 97 % conversion (determined by ^1H

⁴⁰ S. S. V. Ramasastry, H. Zhang, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.*, **2007**, *129*, 288.

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NMR) and 25 % ee (determined by HPLC). The absolute configuration of the title compound was assigned as S, by comparison of the HPLC retention times of its two enantiomers with literature values.⁴²