UNIVERSITAT ROVIRA I VIRGILI

AMINOCATALYTIC FUNCTIONALIZATION OF CARBONYL COMPOUNDS: A POWERFUL STRATEGY FOR ENANTIOSELECTIVE REACTION DEVELOPMENT

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Carlo Cassani

Aminocatalytic Functionalization of Carbonyl Compounds: a Powerful Strategy for Enantioselective Reaction Development

Doctoral Thesis

Supervised by Prof. Paolo Melchiorre

ICIQ - Institut Català d'Investigació Química

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I STATE that the present study, entitled "Aminocatalytic Functionalization of Carbonyl Compounds: a Powerful Strategy for Enantioselective Reaction Development", presented by CARLO CASSANI to receive the degree of Doctor, has been carried out under my supervision at the Institut Català d'Investigació Química (ICIQ).

Tarragona, October the 18th 2013

Doctoral Thesis Supervisor

Prof. Paolo Melchiorre

To my family and Giulia

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List of Publications

The results presented in this thesis have been published:

- "Multiple approaches to enantiopure spirocyclic benzofuranones using organocatalytic cascade reactions"
C. Cassani, X. Tian, E.C. Escudero-Adán, P. Melchiorre.
Chem.Commun., **2011**, *47*, 233-235.

- "Diastereodivergent asymmetric sulfa-Michael additions of α-branched enones using a single chiral organic catalyst"
X. Tian, C. Cassani, L. Yankai, A. Moran, A. Urakawa, P. Galzerano, E. Arceo., P. Melchiorre
J. Am. Chem. Soc., **2011**, *133*, 17934-17941.
This article was highlighted in *Science* by JSY (**2011**, 334, 570) and in Synfacts by B. List and J. H. Kim (**2012**, 2, 213).

- "Direct catalytic enantioselective vinylogous aldol reaction of α-branched enals with isatins"
C. Cassani, P. Melchiorre.
Org. Lett., **2012**, *14*, 5590-5593.

- "Secondary amine-catalyzed asymmetric γ-alkylation of α-branched enals via dienamine activation"
M. Silvi, C. Cassani, A. Moran, P. Melchiorre.
Helv. Chim. Acta, **2012**, *95*, 1985-2006.

- "Synthesis of 9-amino(9-deoxy)*epi* cinchona alkaloids, general chiral organocatalysts for the stereoselective functionalization of carbonyl compounds"
C. Cassani, R. Martín-Rapún, E. Arceo, F. Bravo, P. Melchiorre.
Nat. Protoc., **2013**, *8*, 325-344.

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Chapter I

Introduction

1.1 Organocatalysis

The use of chiral organic small molecules to promote enantioselective chemical transformations has been known in the literature since the first pioneering report of Bredig and Fiske, dated 1913. In this report, it was shown that cinchona alkaloids could accelerate the addition of HCN to benzaldehyde.[1] The use of organic molecules as catalysts is now recognized as an independent area of chemical research, distinct to asymmetric metal catalysis and enzymatic catalysis.[2] The advantage of using organocatalysts is mainly related to the mild reaction conditions generally required. Moreover, organocatalysts can hold a variety of practical advantages relative to macromolecular or precious metal catalysts, including air and water stability, low cost, and availability from renewable resources. In addition, their general lower levels of toxicity confer a direct benefit in the production of pharmaceutical intermediates when compared with some transition metal catalysts.

Over the past 13 years, hardly any other field has impacted the art and science of chemical synthesis more profoundly than asymmetric organocatalysis. The organocatalysts can activate the substrates using different operating modes. They can be easily classified on the basis of their interaction with the substrate, either being covalent or non-covalent.[3]

In covalent activation, the catalyst forms a temporary bond with the substrate generating the active species directly involved in the transition-state. Carbenes and primary or secondary amines are the catalysts most frequently used in covalent activation of the substrates.

In non-covalent activation, the interaction between catalysts and substrates can be *via* hydrogen-bonding (*e.g.* thioureas, squaramides and weaker Brønsted acids), or through ionic interaction (*e.g.* phase-transfer catalysts, chiral Brønsted bases).[4,5]

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[1] G. Bredig, P. S. Fiske. Asymmetric Syntheses Caused by Catalyzers. *Biochem. Z.,* **1913**, *46,* 7.

[2] D. W. C. MacMillan. The Advent and Development of Organocatalysis. *Nature*, **2008**, *455*, 304.

[3] E. N. Jacobsen, D. W. C. MacMillan. Organocatalysis. *Proc. Natl. Acad. Sci. USA,* **2010**, *107*, 20618.

[4] M. Mahlau, B. List. Asymmetric Counteranion-Direct Catalysis: Concept, Definition, and Application. *Angew. Chem. Int. Ed.*, **2013**, *52*, 518.

[5] K. Brak, E. N. Jacobsen. Asymmetric Ion-Pairing Catalysis. *Angew. Chem. Int. Ed.*, **2013**, *52*, 534.

1.2 Aminocatalysis

The use of primary and secondary chiral amines to catalyze the direct asymmetric functionalization of carbonyl compounds defines the field of aminocatalysis. During the renowned "Gold Rush" of organocatalysis,[6] the progress has been mainly dictated by the development achieved in asymmetric aminocatalysis.[7] Even though the roots of this catalysis can be traced back to the beginning of the last century,[8] the first milestone of the modern aminocatalysis was independently developed by research groups from Hoffman-La Roche and Schering AG in the early 1970s: the intramolecular aldol reaction catalyzed by proline. This transformation, also known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction (Scheme 1a),[9] allowed the preparation of intermediates for the synthesis of steroids and other enantiomerically pure molecules. The report provided the first example of a highly enantioselective aminocatalytic process, although neither its mechanism was clearly understood nor its potential was realized. These considerations, together with the fact that the scientific trends of the time were mainly focusing on the development of metal-catalyzed asymmetric processes, explain why the field of aminocatalysis has remained dormant for almost 30 years.

It was only after the publications of List, Lerner and Barbas III on the proline catalyzed asymmetric aldol reaction and MacMillan on the first aminocatalytic asymmetric Diels-Alder reaction, both in the year 2000 (Scheme 1b and 1c),[10,11] that aminocatalysis was brought to the forefront of the scientific community and became an appealing and competitive field of research.

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[6] P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli. Asymmetric Aminocatalysis-Gold Rush in Organic Chemistry. *Angew. Chem. Int. Ed.*, **2008**, *47*, 6138.

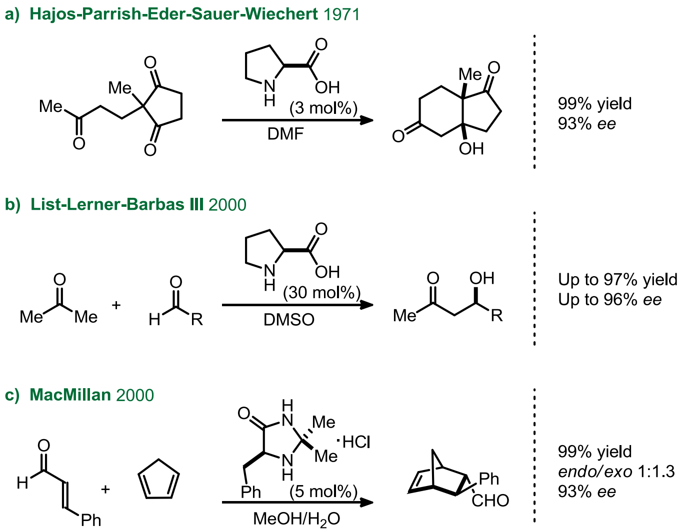
[7] S. Bertelsen, K. A. Jørgensen. Organocatalysis-After the Gold Rush. *Chem. Soc. Rev.*, **2009**, *38*, 2178.

[8] Insightful perspectives have recently addressed the historical origins of aminocatalysis mediated by secondary amines, see: a) C. F. Barbas III. Organocatalysis Lost: Modern Chemistry, Ancient Chemistry, and an Unseen Biosynthetic Apparatus. *Angew. Chem. Int. Ed.*, **2008**, *47*, 42. b) B. List. Emil Knoevenagel and the Roots of Aminocatalysis. *Angew. Chem. Int. Ed.* **2010**, *49*, 1730.

[9] a)U. Eder, G. Sauer, R. Wiechert. New Type of Asymmetric Cyclization to Optically Active Steroid CD Partial Structures. *Angew. Chem. Int. Ed. Engl.*, **1971**, *10*, 496. b) Z. G Hajos, D. R. Parrish. Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry. *J. Org. Chem.*, **1974**, *39*, 1615.

[10] B. List, R. A. Lerner, C. F. Barbas III. Proline-Catalyzed Direct Asymmetric Aldol Reactions. *J. Am. Chem. Soc.*, **2000**, *122*, 2395.

[11] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan. New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels-Alder Reaction. *J. Am. Chem. Soc.*, **2000**, *122*, 4243.



Scheme 1. Milestones in Asymmetric Aminocatalysis.[9,10,11]

The two pioneering works published in 2000 (Scheme 1b and 1c) introduced the concepts of enamine activation and iminium ion activation, respectively.[10,11] These aminocatalytic activation modes are based on the ability of chiral secondary amines to reversibly condense with carbonyl compounds and α,β-unsaturated carbonyl compounds to form a covalent reactive intermediate. These activation modes have provided reliable synthetic platforms for generating stereogenic centers at both the α- and β-position of unmodified carbonyls with very high fidelity.

The application of aminocatalysis has led to the development of new and interesting methodologies for the activation of carbonyl compounds. On the wave of these discoveries, aminocatalysis began to grow at an extraordinary pace from a small collection of unique reactions to a thriving area of generally applicable concepts, reactivities, and highly enantioselective and regioselective reactions. In addition, novel modes of substrate activation were discovered that can provide unique, orthogonal, or complementary selectivity in comparison to many established metal-catalyzed transformations.[6]

1.2.1 Enamine Activation

The term enamine activation describes the reactions promoted by an *in situ* generated enamine, which plays the role of transient nucleophilic intermediate (Scheme 2).[12]

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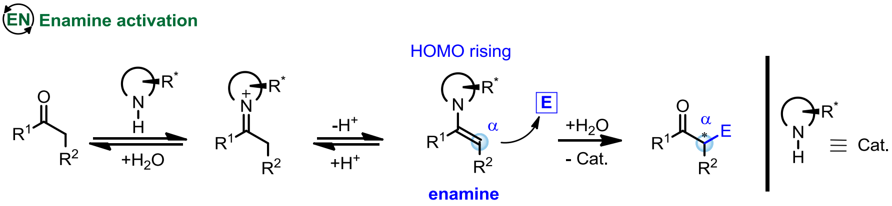
[12] S. Makherjee, J. W. Yang, S. Hoffmann, B. List. Asymmetric Enamine Catalysis. *Chem. Rev.,* **2007**, *107*, 5471.



Scheme 2. Enamine Activation Mode. E = electrophile.

The reversible condensation of a catalytic amount of a secondary amine with an enolizable carbonyl compound leads to a positively charged intermediate (an iminium ion) that induces an increase of the acidity at the α-proton. This drives a fast deprotonation, which leads to the generation of the enamine, a nucleophilic enolate equivalent. The enamine intermediate is indeed characterized by a higher energy level of the highest occupied molecular orbital (HOMO) with respect to the parent enol form, which leads to the activation of the α-carbon toward nucleophilic addition.

Enamine activation allows a number of different electrophiles to be stereoselectively incorporated at the α-carbon of unmodified carbonyl compounds by means of highly enantioselective nucleophilic addition or substitution reactions. After the first aldol reaction reported by List, Lerner and Barbas III,[10] a great variety of addition reactions have been developed. The direct, catalytic and asymmetric Mannich reaction, one of the most useful organic transformation for the synthesis of chiral nitrogen-containing molecules, was developed using both preformed imines or in a one-pot, three-component fashion.[13] Many Michael acceptors were also successfully employed in enantioselective transformations as well as molecules containing electrophilic halogens-, nitrogen-, oxygen-, sulfur- and selenium-centered electrophilic substrates.[12,14,15]

1.2.2 Iminium Ion Activation

Developed in parallel to enamine activation, iminium ion activation is based on the use of chiral amines to function as enantioselective catalyst mainly for the direct β-functionalization of α,β-unsaturated carbonyl compounds (Scheme 3).[16]

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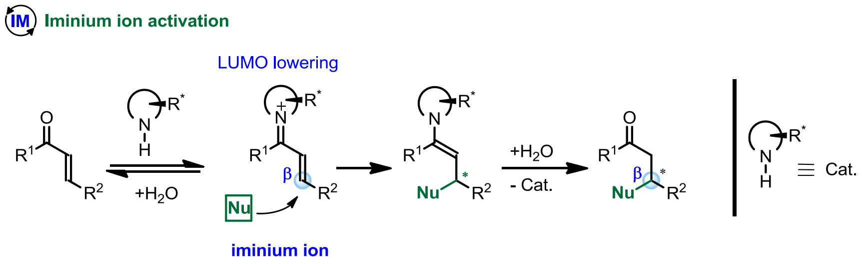
[13] B. List. The Direct Asymmetric Three-Component Mannich Reaction. *J. Am. Chem. Soc.*, **2000**, *122*, 9336.

[14] K. L. Jensen, G. Dickmeiss, H. Jiang, Ł. Albrecht., K. A. Jørgensen. The Diarylprolinol Silyl Ether System: A General Organocatalyst. *Acc. Chem. Res.*, **2012**, *45,* 248.

[15] S. Bertelsen, K. A. Jørgensen. Organocatalysis – After the Gold Rush. *Chem. Soc. Rev.*, **2009**, *38*, 2178.

[16] G. Lelais, D. W. C. MacMillan. Modern Strategies in Organic Catalysis: The Advent and Development of Iminium Activation. *Aldrichimica Acta*, **2006**, *39*, 79.



Scheme 3. Iminium Ion Activation Mode. Nu = nucleophile.

Initial condensation between the amine catalyst and the α,β-unsaturated carbonyl compound forms the positively charged iminium ion intermediate. Thus, the energy of the lowest unoccupied molecular orbital (LUMO) of the system is effectively lowered in comparison with the starting carbonyl substrate. For conjugated π-systems, the electronic redistribution induced by the iminium ion intermediates facilitates nucleophilic additions, including conjugate additions and pericyclic reactions.

Utilizing the iminium ion platform, a large number of transformations have been designed. The addition of a variety of carbon-, nitrogen-, oxygen-, sulfur-, phosphorus-, and boron-centered nucleophiles have been reported with high levels of enantioselectivity. Many different cycloaddition reactions were also successfully developed on the basis of this activation mode.[17]

1.2.3 Cascade Reactions

A non-obvious consequence of the condition tolerance and flexibility of the aminocatalytic processes relies on the possibility of integrating mechanistically distinct modes of catalysis in a single sequence (cascade reactions).[18] To fully harness the synthetic power of aminocatalysis, it was crucial to identify the iminium ion/enamine activation sequence as an approach toward highly efficient asymmetric cascade transformations. The strategy is based on the conjugate addition of a nucleophile to an α,β-unsaturated aldehyde or ketone followed by the α-functionalization of the resulting saturated carbonyl (Scheme 4). In this well-defined sequence, the chiral amine catalyst has an active role in both steps, initially forming the activated iminium ion species and later the electron-rich enamine intermediate.

The iminium ion/enamine approach is currently the most applied strategy to develop new asymmetric organocatalytic cascade reactions.[19] This approach is based on the unique ability of

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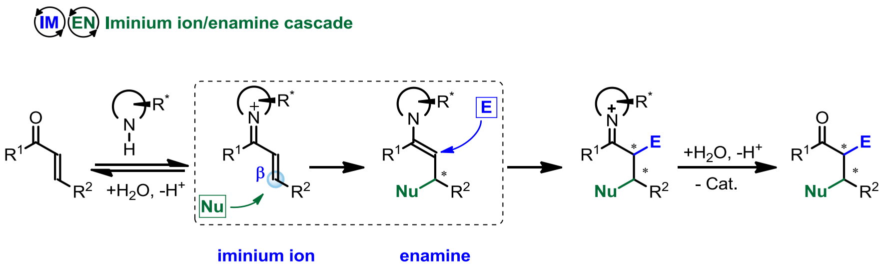
[17] A. Erkkilä, I. Majander, P. M. Pihko. Iminium Catalysis. *Chem. Rev.*, **2007**, *107*, 5416.

[18] L. F. Tietze, U. Beifuss. Sequential Transformations in Organic Chemistry: A Synthetic Strategy with a Future. *Angew. Chem. Int. Ed.*, **1993**, *32,* 131.

[19] D. Enders, C. Grondal, M. R. M. Hüttl. Asymmetric Organocatalytic Cascade Reactions. *Angew. Chem. Int. Ed.*, **2007**, *52*, 1570.

certain amine catalysts to promote orthogonal asymmetric functionalizations on unsaturated carbonyl compounds in a sequential manner, so to achieve the enantioselective β- and α-functionalization of carbonyl compounds in a single operation procedure (Scheme 4).



Scheme 4. Iminium Ion/Enamine Cascade.

Cascade reactions are considered an important tool for the generation of elaborate scaffolds in a single operational step.[19] This approach, which maximizes the cost/effect of the synthesis, has become an attractive alternative to stepwise procedures and allows access to complex molecules with high stereocontrol in an efficient and atom-economical manner.[20]
Asymmetric aminocatalytic reactions will be further discussed in chapter **II**.

1.2.4 Vinylogous Reactivity

Recently, chemists have become interested in using aminocatalysis to target stereocenters remote from the catalyst's point of interacion. This can be achieved by exploiting the ability of the aminocatalyst to propagate the electronic effects inherent to aminocatalytic reactivity modes through the conjugated π-system of the poly-unsaturated carbonyl while transmitting the stereochemical information at distant positions.[21]

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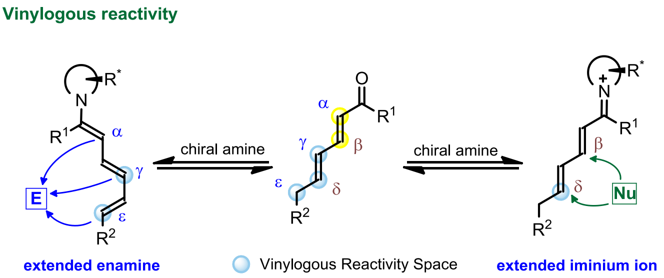
[20] C. Grondal, M. Jeanty, D. Enders. Organocatalytic Cascade Reactions as a New Tool in Total Synthesis. *Nature Chem.*, **2010**, *2*,167.

[21] I. D. Jurberg, I. Chatterjee, R. Tannert, P. Melchiorre. When Asymmetric Aminocatalysis Meets Vinylogy Principle. *Chemm. Commun.*, **2013**, *49*, 4869.



Scheme 5. Vinylogous Reactivity Space. E = electrophile; Nu = nucleophile.

This approach has resulted in the development of dienamine, trienamine, and vinylogous iminium ion activations as novel strategies for the asymmetric functionalization of unmodified carbonyl compounds at their γ, δ, and ε positions, respectively (Scheme 5).[22]

The concept of dienamine activation was defined by Jørgensen in 2006.[23] Among the different aminocatalytic intermediates, dienamines significantly expanded the arsenal of stereoselective functionalization strategies offered by aminocatalysis. The principle of vinylogous reactivity in aminocatalysis has been successfully applied to many different transformations of poly-unsaturated carbonyl compounds. Therefore it became a reliable platform for the remote generation of stereogenic centers and a tool for the synthesis of natural compounds.[24,25]

1.2.5 The Tools of Aminocatalysis

Secondary Amine Catalysts

From the outset, modern asymmetric aminocatalysis has been based on the use of secondary amine catalysts to induce asymmetric transformations. Proline and the MacMillan's imidazolidinones have emerged as fairly general and efficient organocatalysts.[26,27] In addition,

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[22] H. Jiang, Ł. Albrecht., K. A. Jørgensen. Aminocatalysis Remote Functionalization Strategies. *Chem. Sci.*, **2013**, *4*, 2287.

[23] S. Bertelsen, M. Marigo, K. A. Jørgensen. Dienamine Catalysis: Organocatalytic Asymmetric γ-Amination of α,β-Unsaturated Aldehydes. *J. Am. Chem. Soc.*, **2006**, *128*, 12973.

[24] H. Jiang, D. Cruz Cruz, Y. Li, V. H. Lauridsen, K. A. Jørgensen. Asymmetric Organocatalytic Thio-Diels-Alder Reaction *via* Trienamine Catalysis. *J. Am. Chem. Soc.*, **2013**, *135*, 5200.

[25] K. Liu, A. Chougnet, W.-D. Woggon. A Short Route to α-Tocopherol. *Angew. Chem. Int. Ed.*, **2008**, *47*, 5827.

[26] B. List. Proline-catalyzed Asymmetric Reactions. *Tetrahedron* **2002**, *58*, 5573.

[27] S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan. The Direct and Enantioselective Organocatalytic α-Oxidation of Aldehydes. *J. Am. Chem. Soc.*, **2006**, *128*, 12973.

protected prolinol derivatives, particularly α,α-diarylprolinol silyl ethers,[28] have also shown high catalytic performance in promoting asymmetric transformations with very high levels of reactivity and enantio-induction (Figure 1).[14]

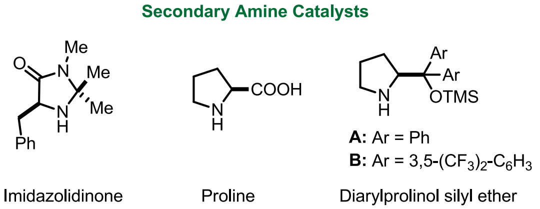

Figure 1. Secondary Amine Catalysts - Privileged Aminocatalysts.[29]

Very high enantiomeric excess and a consistent absolute configuration were observed for the transformations catalyzed by diarylprolinol silyl ethers, both in enamine and in iminium ion activation. Mechanistic studies to rationalize the excellent stereocontrol ability of the catalyst showed the importance of the bulky chiral fragment on the pyrrolidine ring.[30,31] This group, acting as a steric control element, is crucial to induce a single geometry of the covalent intermediate in the transition state while selectively shielding one of the prochiral faces of the enamine or iminium ion intermediate (*Steric Control Approach*, Figure 2).[32]

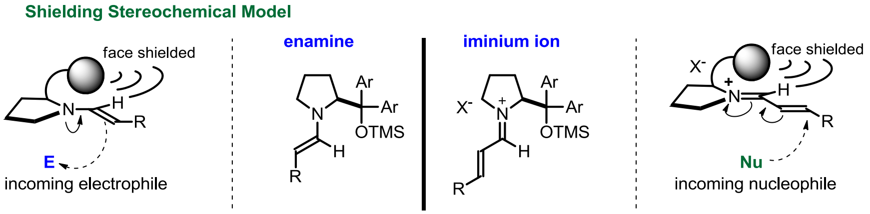

Figure 2. Steric Control Model for Diarylprolinol Silyl Ethers.

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[28] a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen. Enantioselective Organocatalyzed a Sulfenylation of Aldehydes. *Angew. Chem. Int. Ed.*, **2005**, *44,* 794. b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji. Diphenylprolinol Silyl Ethers as Efficient Organocatalysts for the Asymmetric Michael Reaction of Aldehydes and Nitroalkenes. *Angew. Chem. Int. Ed.*, **2005**, *44,* 4212.

[29] To make it easier to read the manuscript, catalysts **A** and **B** will maintain the same numbering throughout the entire thesis.

[30] M. B. Schmid, K. Zeitler, R. M. Gschwind. Distinct conformational preferences of prolinol and prolinol ether enamines in solution revealed by NMR. *Chem. Sci.*, **2011**, *2*, 1793.

[31] U. Grošelj, D. Seebach, D. M. Badine, W. B. Schweizer, A. K. Beck, I. Krossing, P. Klose, Y. Hayashi, T. Uchimaru. Structures of the Reactive Intermediates in Organocatalysis with Diarylprolinol Ethers. *Helv. Chim. Acta*, **2009**, *92*, 1225.

[32] M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen. Mechanisms in Aminocatalysis. *Chem. Commun.*, **2011**, *47*, 632.

An important consideration that can be extrapolated from the stereochemical model is that the asymmetric induction is completely independent of the structure of the incoming electrophile or nucleophile, but it is an intrinsic feature of the chiral transiently generated active intermediate. This explains why a single catalyst could promote mechanistically unrelated reactions with high efficiency, a merit that made diarylprolinol silyl ether the "workhorse" of aminocatalysis.[33]

Primary Amine Catalysts

Recently, many researchers, and in particular our research group, have recognized that chiral primary amines offer new opportunities for expanding the applicability and synthetic potential of aminocatalysis.[34] In comparison to cyclic secondary amines, primary amines suffer reduced nucleophilicity and an unfavorable imine/enamine equilibrium. Generally, primary and secondary enamines rearrange spontaneously to the more stable imine.[35] However, primary amines are characterized by a superior ability to effectively functionalize sterically biased carbonyls (*e.g.* simple ketones as well as α-branched substituted aldehydes and ketones, and their α,β-unsaturated counterparts) because they are less influenced by the structural features of the substrates. Primary amines thus offer the unique possibility of extending the scope of aminocatalysis to include sterically demanding carbonyl compounds (Figure 3).

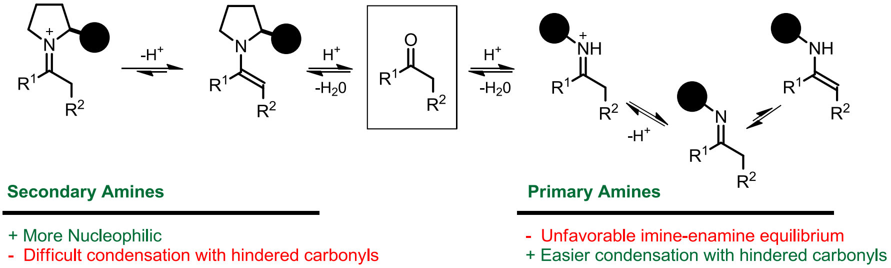

Figure 3. Secondary *vs* Primary Amines in the Condensation with non-Hindered Carbonyls.

In particular, 9-amino(9-deoxy)-*epi* cinchona alkaloids, primary amines easily derived from natural sources, have enabled the stereoselective functionalization of a variety of sterically

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[33] D. Seebach, U. Grošelj, D. M. Badine, W. B Schweizer, A K. Beck. Isolation and X-Ray Structures of Reactive Intermediates of Organocatalysis with Diphenylprolinol Ethers and with Imidazolidinones A Survey and Comparison with Computed Structures and with 1-Acylimidazolidinones: The 1,5-Repulsion and the Geminal-Diaryl Effect at Work. *Helv. Chim. Acta,* **2008**, *91*, 1999.

[34] P. Melchiorre. Cinchona-based Primary Amine Catalysis in the Asymmetric Functionalization of Carbonyl Compounds. *Angew. Chem. Int. Ed.*, **2012**, *51*, 9748.

[35] R. A. Clark, D. C. Parker. Imine-Enamine Tautomerism. I. 2-(*N*-Cyclohexylimino)-1,3-diphenylpropane. *J. Am. Chem. Soc.*, **1971**, *93*, 7257.

hindered carbonyl compounds, which cannot be functionalized using secondary amines and which are often unsuccessful substrates for metal-based approaches too (Figure 4).

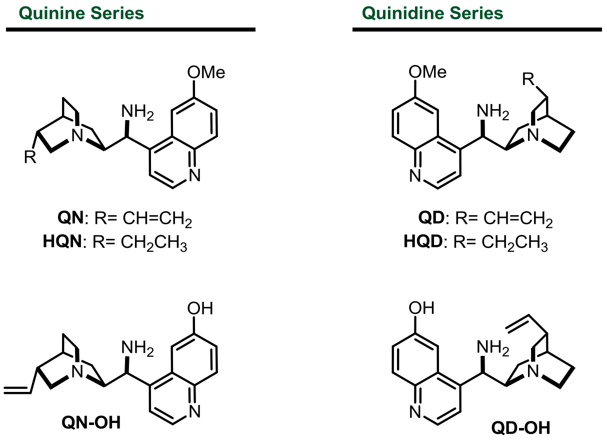

Figure 4. Cinchona Primary Amines Derivatives.[36]

It is remarkable how this single catalyst class can activate carbonyl compounds characterized by completely different structural features and steric bias while exploiting the different aminocatalytic activation modes (iminium ion, enamine, dienamine, vinylogous iminium ion and trienamine activations). The consistently high level of stereocontrol inferred by these natural aminocatalysts testifies to their impressive versatility and reliability.[37,38]

The unique ability of the cinchona primary amines to perform as aminocatalyst derives from particular features (Figure 5):

(i) the flexibility of the cinchona scaffold: cinchona alkaloid derivatives are characterized by a high degree of conformational flexibility in solution, where they exist in a mixture of conformers. Three-dimensional structural modifications can be induced by different chemical stimuli, such as a solvent change or protonation of the N-quinuclidine moiety.[39,40]

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[36] Quinine and quinidine constitute a pseudo-enantiomeric pair (formally they are diastereoisomeres), allowing access to both antipodes of the chiral product of the reaction. To make it easier to read the manuscript, the numbering used in Figure 4 to identify the cinchona primary amine catalysts will be maintained throughout the entire thesis.

[37] A. Moran, A. Hamilton, C. Bo, P. Melchiorre. A Mechanistic Rationale for the 9-Amino(9-deoxy)*epi* Cinchona Alkaloids Catalyzed Asymmetric Reactions *via* Iminium Ion Activation of Enones. *J. Am. Chem. Soc.*, **2013**, *135*, 9091.

[38] O. Lifchits, M. Mahlau, C. M. Reisinger, A. Lee, C. Farès, I. Polyak, G. Gopakumar, W. Thiel, B. List. The Cinchona Primary Amine-Catalyzed Asymmetric Epoxidation and Hydroperoxidation of α,β-Unsaturated Carbonyl Compounds with Hydrogen Peroxide. *J. Am. Chem. Soc.*, **2013**, *135*, 6677.

[39] T. Bürgi, A. Baiker. Conformational Behavior of Cinchonidine in Different Solvents: A Combined NMR and *ab Initio* Investigation. *J. Am. Chem. Soc.*, **1998**, *120*, 12920.

(ii) The multifunctional nature of the cinchona scaffold, adorned with the presence of additional elements (*e.g.* the substituent on the quinoline ring) which can be used to modify the catalytic activity.

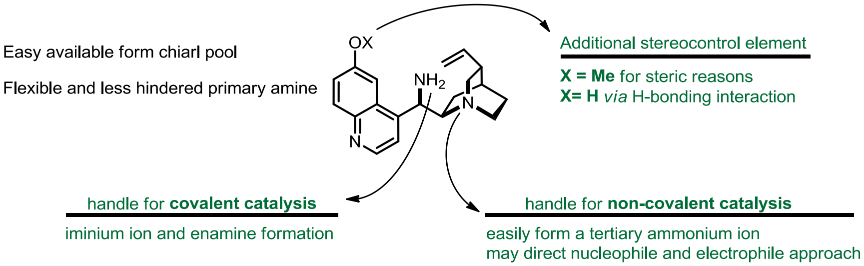

Figure 5. The Multifunctional Nature of 9-Amino(9-deoxy)-*epi* Cinchona Alkaloids.

In the cinchona-based diamine catalysts, the key role is played by the primary amino moiety, which provides the necessary chemical handle for the covalent activation of carbonyl compounds. Still, the presence of the basic bridgehead nitrogen in the quinuclidine core can greatly contribute to the catalysis while altering the electronic nature of the primary amine. Generally an acid co-catalyst is needed to power the catalytic functions of these amines. This is because condensation with carbonyls is greatly accelerated under acidic conditions: otherwise, the carbonyl compounds remain almost inactive toward the aminocatalytic transformations.[41]

For the enamine activation of enolizable carbonyls, an equimolar amount of the acid with respect to the aminocatalyst is often used. A two fold excess is generally used for the iminium ion-promoted transformations of unsaturated carbonyls. This ratio determines a selective protonation of the more basic tertiary amine and the resulting formation of a monoprotonated diamine (intermediate **I** in Figure 6), which represents the active catalyst governing the formation of the covalent intermediate. The charged catalytic species **I** may strongly influence the rate of imine formation through internal acid catalysis, since the tertiary ammonium ion may favor the dehydration of the intermediate hemiaminal by proton transfer.[42] To the same extent, the positively charged protonated tertiary amine in **I** can greatly alter the electronic nature of the vicinal primary amine. Such electrostatic perturbation may decreases the basicity (or the

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[40] R. A. Olsen, D. Borchardt, L. Mink, A. Agarwal, L. J. Mueller, F. Zaera. Effect of Protonation on the Conformation of Cinchonidine. *J. Am. Chem. Soc.*, **2006**, *128*, 15594.

[41] G. J. S. Evans, K. White, J. A. Platts, N. C. O. Tomkinson. Computational Study of Iminium Ion Formation: Effects of Amine Structure. *Org. Biomol. Chem.*, **2006**, *4*, 2616.

[42] This possibility finds support upon previous investigations by Jack Hine, who demonstrated the superior ability of a primary-tertiary diamine, with respect to a simple primary amine, to condense with carbonyl compounds under acidic conditions, see: J. Hine. Bifunctional Catalysis of α-Hydrogen Exchange of Aldehydes and Ketones. *Acc. Chem. Res.*, **1978**, *1*, 1.

proton affinity) of the primary amino moiety, lowering its propensity of getting protonated, thus facilitating its nucleophilic attack to the carbonyl compound under acidic conditions.[43]

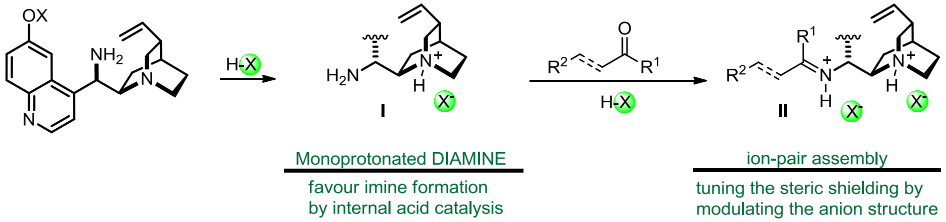

Figure 6. Role of the Acid.[34]

A distinct feature of the iminium ion assembly (intermediate **II** in Figure 6) formed by condensation of the cinchona-based primary amine with a carbonyl compound is that its stereocontrolling ability can be fine-tuned by structurally modifying the counteranion. The presence of a tight ion-pair between an anion derived from the acid and the active intermediate offers a further handle to control the chiral space around the reactive site. The modular nature of the ion pair assembly, which can be modified using different acids or solvents, can be used to enhance the catalytic performance of the cinchona primary amine derivative.

1.3 Objectives of the Thesis Research

The following chapters show how some aminocatalytic tools have been refined and further developed to solve different synthetic problems.

In chapter **II,** three enantioselective aminocatalytic cascade reactions leading to the formation of a complex, stereochemically dense, natural scaffold is discussed. Spirocyclic benzofuranones have been synthesized in an enantiopure form following three distinct approaches, which are based on three different catalytic pathways. To access this goal, we exploited the ability of both primary and secondary aminocatalysts to orthogonally activate ketones and aldehydes in an elaborate cascade sequences (Scheme 6).

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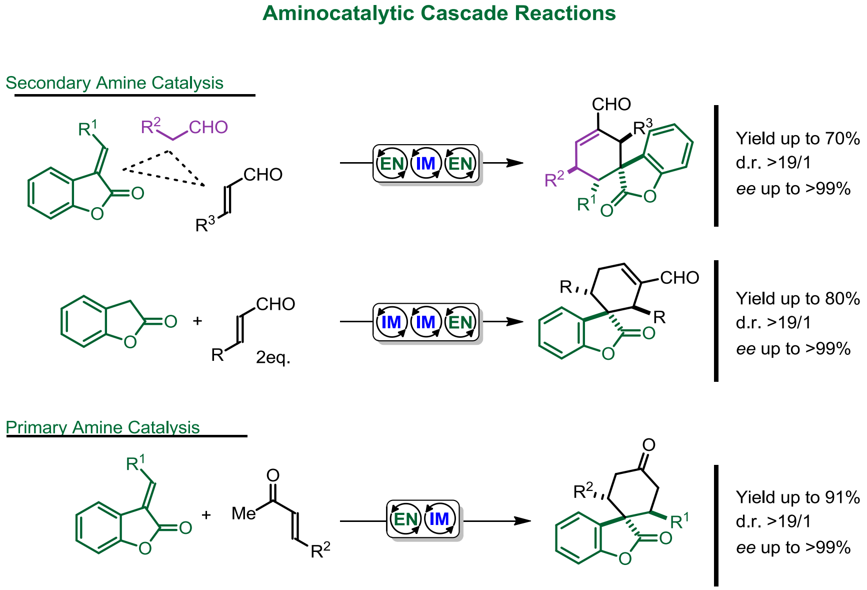
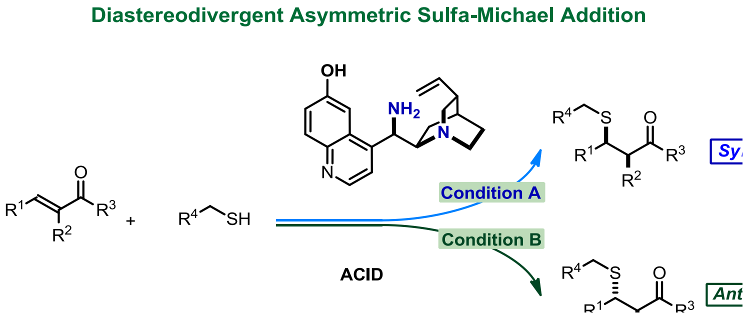
[43] This electrostatic mechanism closely resembles the microenvironment effect that is operative in many enzymes (operating *via* enamine intermediates) to lower the p*Ka* of the catalytically active lysine residue, as originally proposed by Frank H. Westheimer more than 45 years ago, see: a) S. Warren, B. Zerner, F. H. Westheimer. Acetoacetate Decarboxylase. Identification of Lysine at the Active Site. *Biochemistry*, **1966**, *5*, 817; b) F. H. Westheimer. Coincidences, Decarboxylation, and Electrostatic Effects. *Tetrahedron*, **1995**, *51*, 3.



Scheme 6. Aminocatalyzed Synthesis of Enantiopure Spirocyclic-Benzofuranones.

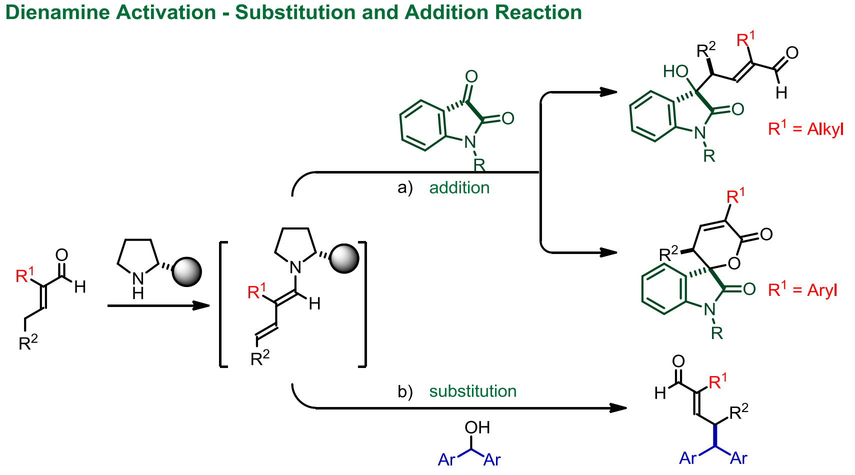
Chapter **III** discusses the aminocatalytic activation of α,β-disubstituted unsaturated ketones, a class of carbonyls which has never before succumbed to a catalytic approach. The unique versatility of the cinchona-based primary amines to functionalize hindered carbonyls has served for developing an asymmetric sulfa-Michael addition (SMA) with alkylthiols. In addition, and probably more importantly, a difficult problem in asymmetric catalytic synthesis has been solved: the modulation of the enforced sense of diastereoselectivity of an asymmetric reaction using a single chiral catalyst (Scheme 7).



Scheme 7. Diastereodivergent SMA of α-Branched Enones using a Single Chiral Catlayst.

In Chapter **IV,** the successful use of a chiral secondary amine to promote the dienamine activation of α-branched enals is discussed. The catalytic system has been used to realize two enantioselective transformations, a nucleophilic addition and a substitution reaction, with high control over the remotely forged stereocenter. In a first example, a direct vinylogous aldol reaction with isatins is reported. Preliminary mechanistic studies suggest that, depending on the nature of the α-branched enal substituents, two divergent reaction mechanisms can be operating, leading to different products and stereochemical outcomes. Specifically, when α-aryl substituted enals have been used, a hetero-Diels-Alder pathway was observed (Scheme 8a). In the second case, the dienamine intermediate has been employed to trap a long-lived, *in situ* generated carbocation, thus leading to a net S_N1-type substitution reaction (Scheme 8b).

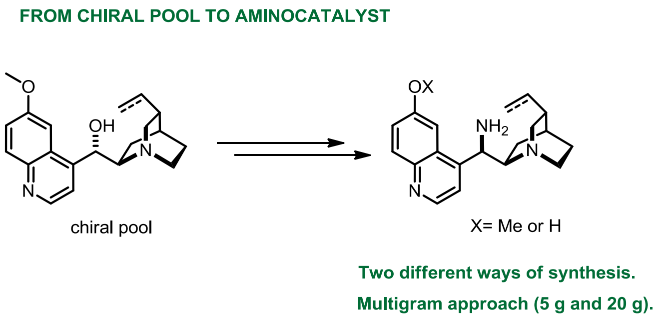
Moreover the active intermediate has been studied and its geometry in solution has been assigned by NMR spectroscopy.



Scheme 8. Dienamine Activation in Vinylogous Nucleophilic Substitution and Addition Reactions.

The strategy enabled the chirality transfer, from the catalyst to the γ-carbon, located five bonds away from the stereo-defining element within the aminocatalyst, with a high degree of stereo-induction.

Chapter **V** discusses the optimized synthesis of the most commonly used cinchona primary amine catalysts *via* two distinct approaches: a laboratory oriented synthesis and a more scalable industrial method of preparation. Both routes will be discussed and the key points highlighted (Scheme 9).



Scheme 9. Cinchona-Based Primary Amines Synthesis.

Chapter II

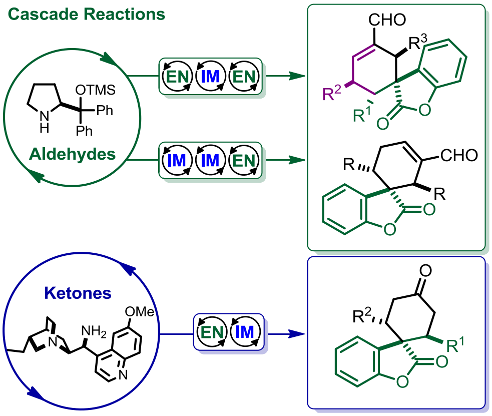
Multiple Approaches to Enantiopure Spirocyclic Benzofuranones Using Organocatalytic Cascade Reactions

Target

Identify distinct synthetic procedures to effectively reproduce, in a rapid way, the structural and stereochemical complexity of naturally-inspired compounds containg the spirocyclic benzofuranone moiety.

Tool

The potential of aminocatalytic cascade reactions to generate high degrees of architectural and stereochemical complexity in a single transformation.[1]



2.1 Background

Finding cost-effective and sustainable synthetic pathways to reproduce the rich structural diversity and complexity found in natural molecules has always captured the attention of chemists, especially in relation to biologically active compounds.[2] In this context, cascade processes represent a flourishing area in organic chemistry with characteristic advantages over more classical stepwise synthesis. Cascade reactions are sequences of chemical transformations which take place under the same reaction conditions. Thus, all the reagents and catalysts are added at (or nearly at) the outset of the process to undergo a chemical transformation whose product becomes the substrate for the next step, whose product again becomes the substrate

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[1] The work discussed in this chapter has been published, see: C. Cassani, X. Tian, E. Escudero-Adán, P. Melchiorre. Multiple Approaches to Enantiopure Spirocyclic Benzofuranones Using Organocatalytic Cascade Reactions. *Chem. Commun.*, **2011**, *47*, 233. Experimental part developed together with X. Tian.

[2] J. T. Mohr, M. R. Krout, B. M. Stoltz. Natural Products as Inspiration for the Development of Asymmetric Catalysis. *Nature*, **2008**, *455*, 323.

for the next step, and so on, until a product stable to the reaction conditions is reached.[3] Cascade reactions avoid time-consuming and costly protection/deprotection processes as well as the purification of intermediates. In addition, this experimentally simple synthetic strategy offers the potential for rapidly increasing structural and stereochemical complexity. In a single synthetic step, simple starting materials are converted into complex molecular systems containing multiple stereocenters. One of the main issues related to these transformations is the compatibility of the transiently formed intermediates with the substrates, which should not undergo alternative irreversible reactions to form by-products.

A major topic of current research is the design of asymmetric catalytic cascade reactions mediated by a single chiral catalyst capable of promoting each single step. Organocatalysts are particularly favorable when used in this context because they allow for distinct modes of substrate activation to be easily combined. The emerging field of asymmetric aminocatalytic cascade reactions has recently provided a means of achieving stereochemical and molecular complexity while addressing the requirements for both atom and step economy, and protecting-group-free synthesis.[4] To fully harness the synthetic power of aminocatalytic cascade processes, it was crucial to identify the iminium ion/enamine activation sequence as an enabling approach to highly efficient cascade reactions. This strategy, nowadays the most used in aminocatalytic cascade reactions, is based on the conjugate addition of a nucleophile to an α,β-unsaturated aldehyde or ketone followed by the α-functionalization of the resulting saturated carbonyl (Figure 1). In this cascade, the ability of chiral amino catalysts to impart orthogonal activation modes is exploited to initially form the activated iminium ion species and then the electron-rich enamine intermediate.

The main reactivity issue to be addressed lies in identifying a nucleophilic and an electrophilic substrate that can coexist under the reaction conditions without interacting with each other through competitive reactions.

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[3] a) L. F. Tietze, U. Beifuss. Sequential Transformations in Organic Chemistry: A Synthetic Strategy with a Future. *Angew. Chem. Int. Ed.*, **1993**, *32,* 131. b) L. F. Tietze. Domino Reactions in Organic Synthesis. *Chem. Rev.*, **1996**, *96*, 115; c) L. F. Tietze, G. Brasche, K. Gericke, Domino Reactions in Organic Synthesis, Wiley-VCH, Weinheim (**2006**).

[4] D. Enders, C. Grondal, M. R. M. Hüttl. Asymmetric Organocatalytic Cascade Reactions. *Angew. Chem. Int. Ed.*, **2007**, *52*, 1570.

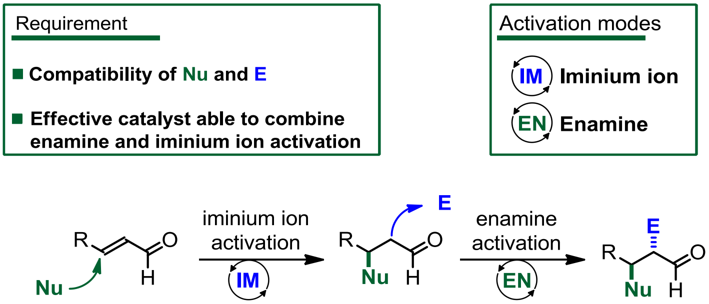
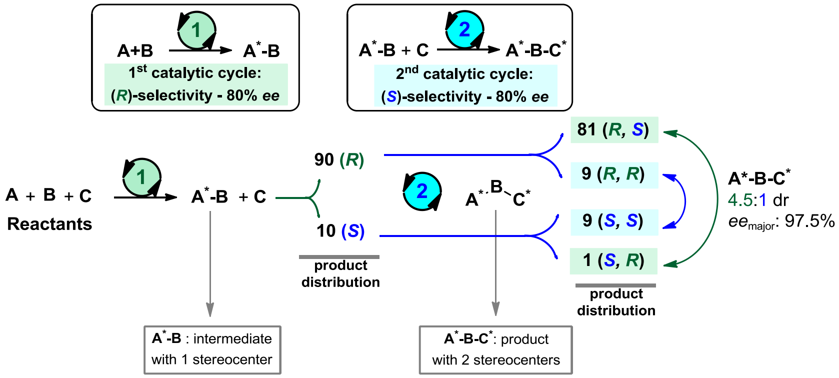


Figure 1. The Iminium Ion/Enamine Activation Sequence for Designing Organocascade Reactions; Compatibility between the Nucleophile (Nu) and the Electrophile (E) is Required.

Another appealing feature of cascade reactions is that the combination of multiple asymmetric, catalytic transformations in a domino sequence imparts increased enantiomeric excess to the final product when compared to the corresponding discrete transformations. The *Horeau* principle provides the mathematical foundation for the rationalization of the enantioenrichment observed in successive catalytic cycles typical of asymmetric cascade reactions.[5]

The simple calculations in Scheme 1 reveal that this strategy can provide the major diastereoisomer of a chiral product which has two stereogenic centers with exquisite levels of enantiocontrol. This is despite combining two consecutive catalytic processes which might be only moderately selective (*e.g.* 80% *ee* + 80% *ee* = 97.5% *ee*).



Scheme 1. Example of the Horeau Principle (*e.g.* 80% $ee_{(1)}$ + 80% $ee_{(2)}$ = 97.5% $ee_{(1+2)}$).

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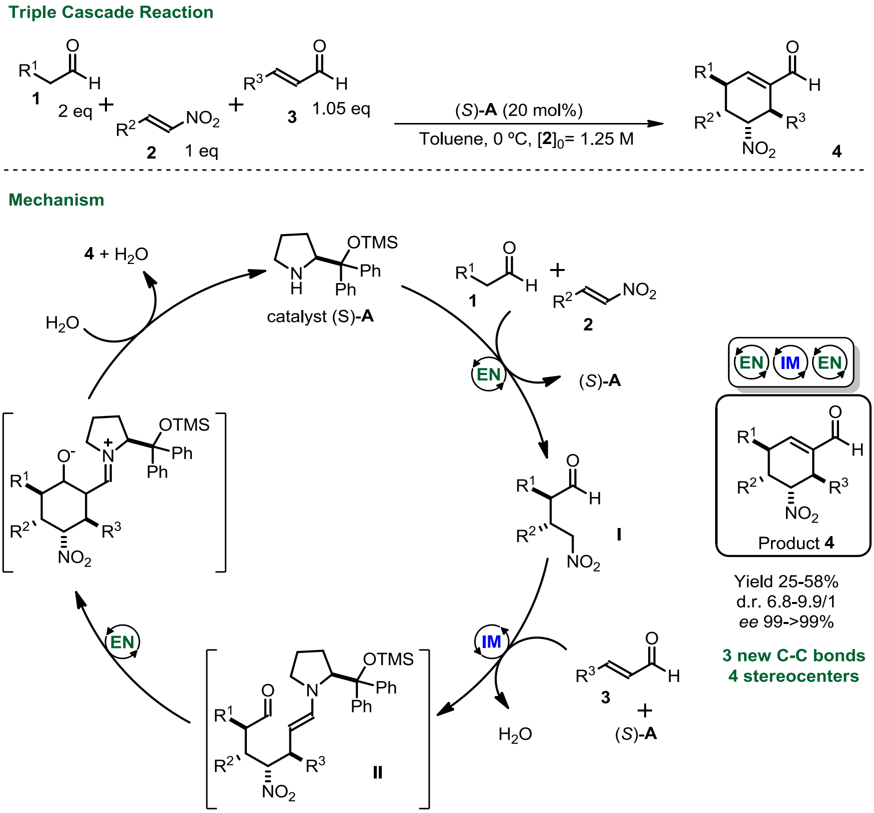
[5] J. P. Vigneron, M. Dhaenens, A. Horeau. Nouvelle Methode Pour Porter au Maximum la Purete Optique d'un Produit Partiellement Dedouble sans l'Aide d'Aucune Substance Chirale. *Tetrahedron*, **1973**, *29*, 1055.

The synthetic potential of asymmetric aminocatalytic cascade reactions has been also validated by their recent applications to the total synthesis of natural products.[6,7]

One of the most venerable examples of aminocatalyzed cascade reactions was developed by Enders and co-workers in 2006.[8] They reported an asymmetric organocatalytic triple cascade reaction for the construction of tetra-substituted cyclohexenecarbaldehydes **4** from easily available starting substrates such as enals **3**, nitroalkenes **2**, and enolizable aldehydes **1** (Scheme 2).



Scheme 2. Multicomponent Enamine/Iminium Ion/Enamine Cascade Reaction.

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[6] S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan. Collective Synthesis of Natural Products by Means of Organocascade Catalysis. *Nature*, **2011**, *475*, 183.

[7] C. Grondal, M. Jeanty, D. Enders. Organocatalytic Cascade Reactions as a New Tool in Total Synthesis. *Nat. Chem.*, **2010**, *2*, 167.

[8] D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe. Control of Four Stereocentres in a Triple Cascade Organocatalytic Reaction. *Nature*, **2006**, *441*, 861.

In this work, they obtained the sequential creation of three bonds and four contiguous stereogenic centers by a highly enantioselective combination of enamine/iminium ion/enamine activation. In the first step, the commercially available α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether catalyst **A** activates the linear aldehyde **1** through enamine formation toward a highly stereoselective Michael addition to the nitro-olefin **2**. In the second step, the chiral amine, by way of the iminium ion activation of α,β-unsaturated aldehyde **3,** promotes an intermolecular conjugate addition of the transiently generated nitroalkane nucleophilic intermediate **I**. The last step is an intramolecular enamine-catalyzed aldol reaction, where the less hindered aldehyde of intermediate **II** acts as a nucleophile, followed by the elimination of water. The triple cascade reaction affords cyclohexene-carboxaldehyde **4** with moderate to good yields (30-58%) but complete enantioselectivity (>99% *ee*).

In 2007, Jørgensen and co-workers developed a mechanistically distinct organocatalytic cascade reaction for the direct synthesis of cyclohexenes from malononitriles or related compounds and enals (Scheme 3).[9] The reaction occurs *via* an iminium ion/iminium ion/enamine sequence involving activated methylene substrates, and affording the final cyclohexenes **6** in good yields and with essentially perfect stereoselectivity. Activated methylene compounds, such as malonates and malononitrile, possess a fairly low pK_a (from 11 to 16 in DMSO).[10,11] Their acidity confers them an ambident nucleophilic profile, which permits to use the methylene active compounds in two consecutive conjugate additions. The reaction does indeed proceeds *via* a Michael addition of the ambident nucleophile **5** to the iminium ion generated by the condensation of catalyst **B** on the enal **3**. The resulting prochiral carbon nucleophile **II** is reactive enough to participate in an intermolecular, iminium ion catalyzed conjugate addition with another molecule of **3**. The last intramolecular aldolization/dehydration sequence, driven by enamine activation, afforded the desired spiro-derivative **6**.

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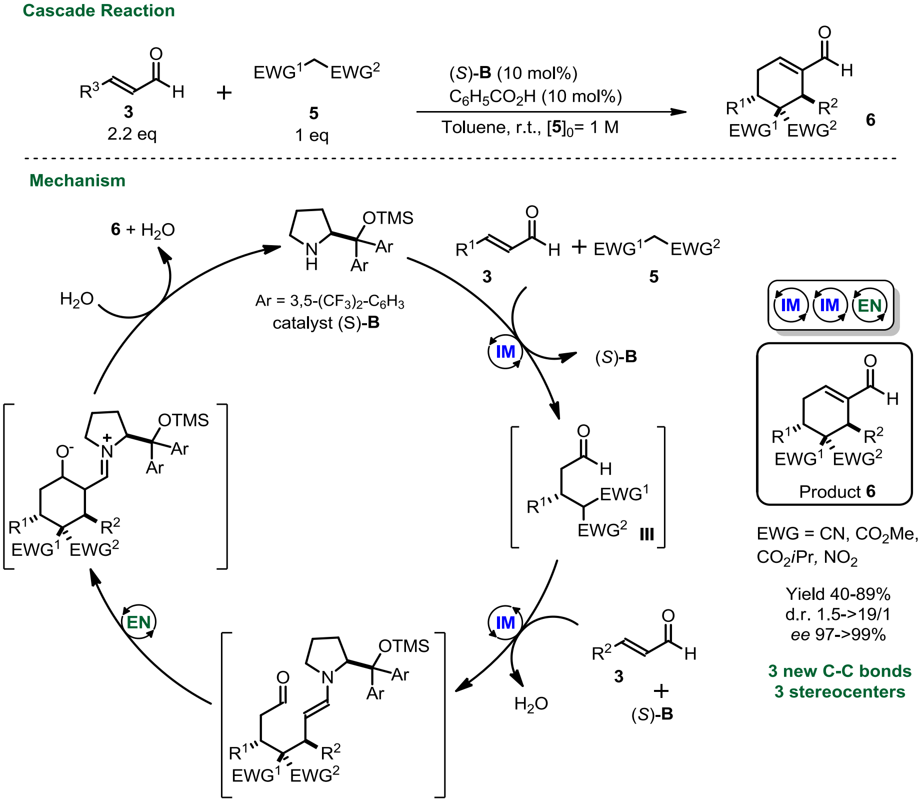
[9] A. Carlone, S. Cabrera, M. Marigo, K. A. Jørgensen. A New Approach for an Organocatalytic Multicomponent Domino Asymmetric Reaction. *Angew. Chem. Int. Ed.*, **2007**, *46*, 1101.

[10] a) W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, N. R. Vanier. Equilibrium Acidities of Carbon Acids. VI. Establishment of an Absolute Scale of Acidities in Dimethyl Sulfoxide Solution. *J. Am. Chem. Soc.*, **1975**, *97*, 7006. b) W. N. Olmstead, F. G. Bordwell. Ion-Pair Association Constants in Dimethyl Sulfoxide. *J. Org. Chem.*, **1980**, *45*, 3299.

[11] E. M. Arnett, S. G. Maroldo, S. L. Schilling, J. A. Harrelson. Ion Pairing and Reactivity of Enolate Anions. 5. Thermodynamics of Ionization of β-Di- and Tricarbonyl Compounds in Dimethyl Sulfoxide Solution and Ion Pairing of Their Alkali Salts. *J. Am. Chem. Soc.*, **1984**, *106*, 6159.



Scheme 3. Multicomponent Iminium Ion/Iminium Ion/Enamine Cascade Reaction.

An expansion of the synthetic utility of aminocatalytic enantioselective cascade reactions was possible with the use of a different substrate: α,β-unsaturated ketones. The activation of enones with chiral amines offers an alternative pathway to capitalize upon the enamine and iminium ion technique, allowing for the design of novel cascade sequences.

This concept relies on the aminocatalytic activation of α,β-unsaturated aliphatic ketones to form the corresponding iminium ion, which exists in equilibrium with the cross-conjugated dienamine, an intermediate which is characterized by a nucleophilic character (Scheme 4). This equilibrium means that not only the classical iminium ion/enamine sequence is viable, but it can be possible to switch the intrinsic electrophilic behavior of the iminium ion, channeling the reaction manifold toward a nucleophilic α-site alkylation.[12]

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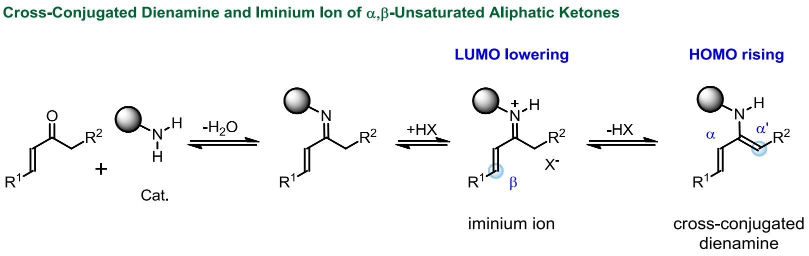
[12] L.-Y. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli, P. Melchiorre. Organocascade Reactions of Enones Catalyzed by a Chiral Primary Amine. *Angew. Chem. Int. Ed.*, **2009**, *48*, 7196.



Scheme 4. Aminocatalyzed Reaction of Enones – Exploiting the Cross-Conjugated Dienamine.

Exploiting this enamine/iminium ion tandem sequence, in 2009, our group reported the use of primary amines to activate α,β-unsaturated aliphatic ketones in the context of an asymmetric synthesis of complex spirocyclic oxindoles (Scheme 5).[13,14] This peculiar scaffold is featured in a number of natural products as well as medicinally relevant compounds (Figure 2). However, its stereocontrolled synthesis, in particular installing the challenging spiro-quaternary stereocenter, represents a difficult synthetic problem.

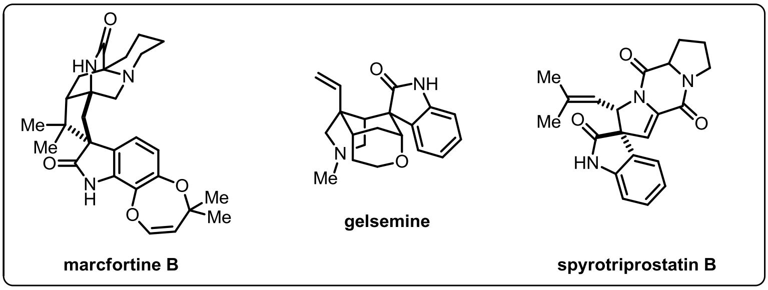


Figure 2. Examples of Natural Product Containing Spirocyclic Oxindoles.

The ability of the 9-amino(9-deoxy)*epi* cinchona alkaloid **HQN** to promote a highly enantioselective enamine/iminium ion cascade reaction on the of strongly activated Michael acceptors **8** (derived from 2-oxindole) was exploited (Scheme 5). Two factors were central to the

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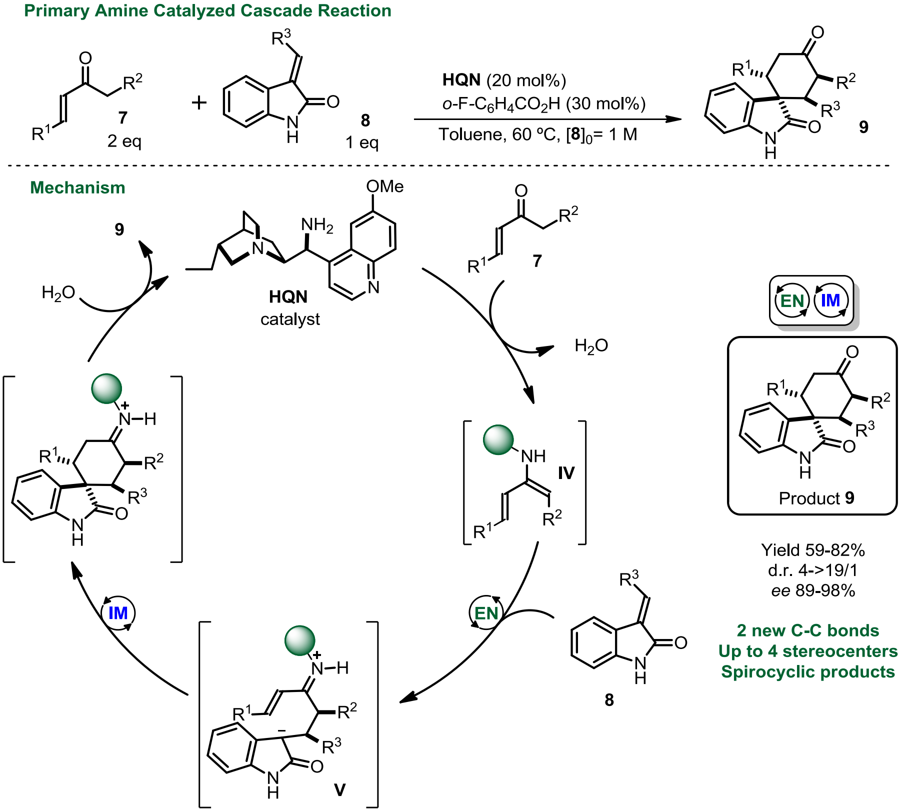
[13] G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli, P. Melchiorre. Targeting Structural and Stereochemical Complexity by Organocascade Catalysis: Construction of Spyrocyclic Oxindoles Having Multiple Stereocenters. *Angew. Chem. Int. Ed.*, **2009**, *48*, 7200.

[14] The use of secondary amine catalysis to promote the stereoselective Diels-Alder reactions of enones as dienes *via* the transient formation of cross-dienamine **IV** depicted in Scheme 4 was pioneered by Carlos Barbas: this is why this intermediate is known as the “Barbas’ dienamine”: a) R. Thayumanavan, B. Dhevalapally, K. Sakthivel, F. Tanaka, C. F. Barbas III. Amine-catalyzed Direct Diels–Alder Reactions of α,β-Unsaturated Ketones with Nitro Olefins. *Tetrahedron Lett.*, **2002**, *43*, 3817; b) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, Organocatalytic Asymmetric Domino Knoevenagel/Diels–Alder Reactions: A Bioorganic Approach to the Diastereospecific and Enantioselective Construction of Highly Substituted Spiro[5,5]undecane-1,5,9-triones. *Angew. Chem. Int. Ed.*, **2003**, *42*, 4233.

successful implementation of novel cascade reactions of enones: (i) the identification of a suitable acidic co-catalyst, which could facilitate the equilibrium between the iminium ion and the nucleophilic cross-conjugated dienamine intermediate (Scheme 4); (ii) the identification of a suitable compound **8**, which could first act as a Michael acceptor, intercepting the nucleophilic dienamine intermediate **IV** generated by the condensation of the catalyst **HQN** with the α,β-unsaturated ketone **7**. Then the resulting carbon centered nucleophile **V** selectively engages itself in an intramolecular, iminium ion conjugate addition to afford the spiro-oxindole derivative **9** (Scheme 5).



Scheme 5. Primary Amine Catalyzed Cascade Reaction.

With this report the authors provided a solution to the problem of accessing complex nature inspired molecules characterized by spirocyclic cores.

Given the potential of cascade reactions to assemble, in a single step, complex chiral molecules in almost enantiopure form, we wondered whether this strategy could be useful for the enantioselective synthesis of a different class of spirocyclic compounds: the spiro-benzofuranones. This scaffold is featured in a number of natural products that exhibit biological activities ranging from anti-oxidant properties to a potential application in anticancer and Alzheimer's therapy (Figure 3).[15]

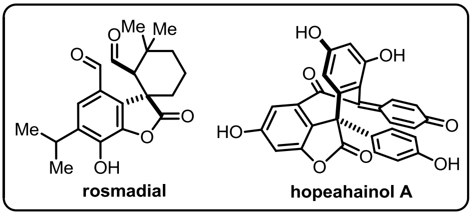


Figure 3. Natural Occurring and Biologically Active Benzofuranones

2.2 Results and Discussion

2.2.1. *Approach A* – Enamine/Iminium Ion/Enamine Cascade Sequence

We approached the synthetic problem by exploiting the established ability of the chiral diphenyl prolinol silyl ether catalyst (*S*)-**A** to integrate orthogonal activation modes of aldehydes (enamine and iminium ion activation) into more elaborate cascade sequences. Inspired by previous studies from our laboratory[13] and the triple cascade reaction developed by Enders,[8] we recognized compound **10** (Scheme 6), bearing the benzofuranone moiety, as the key for the design of novel organocascade processes. Compound **10** seemed well-tailored to first act as a Michael acceptor and then to generate, after the conjugate addition, a nucleophilic intermediate able to continue the cascade. Given this reactivity profile, we included compound **10** as the third component of a three-component cascade strategy that exploited the catalytic ability of the secondary amine (*S*)-**A** to realize an enamine/iminium ion/enamine sequential activation of aldehydes **1** and α,β-unsaturated aldehydes **3** (Scheme 6).

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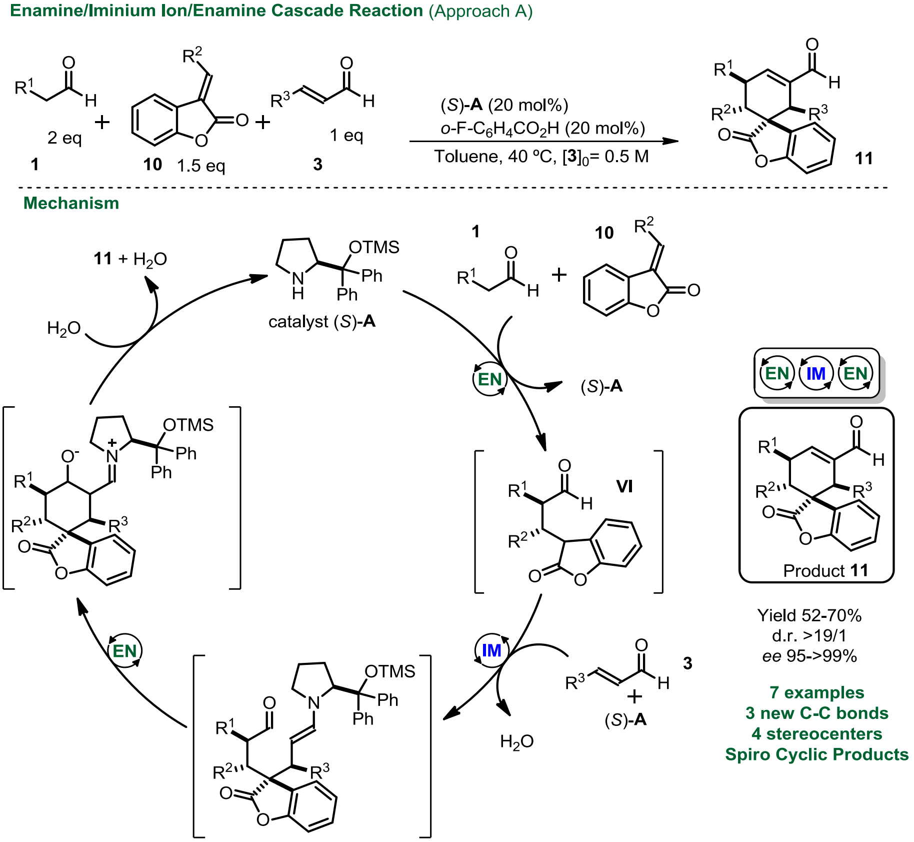
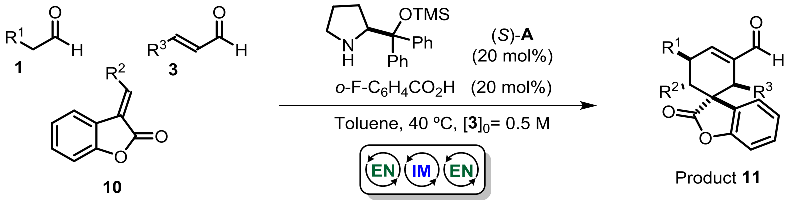
[15] K. C. Nicolau, T. R. Wu, Q. Kang, D. Y.-K. Chen. Total Synthesis of Hopeahainol A and Hopeanol. *Angew. Chem. Int. Ed.*, **2009**, *48*, 3440.



Scheme 6. Enamine/Iminium Ion/Enamine Cascade Sequence – *Approach A.*

This reaction proceeds at 40 °C in the presence of the catalytic salt **A** · *ortho*-F-$C_6H_4CO_2H$ (20 mol%) in toluene by way of a catalyzed Michael/Michael/aldol condensation sequence. As shown in Table 1, this triple organocascade provided access to complex spiro benzofuranones **11** with almost perfect control of the stereochemistry. Aromatic and aliphatic groups as well as ester moieties at the β-position of the benzofuranone-based compounds **10** were well tolerated. Moreover, different aldehydic substrate combinations could be used without affecting the stereochemical outcome of the reaction (see Table 1).

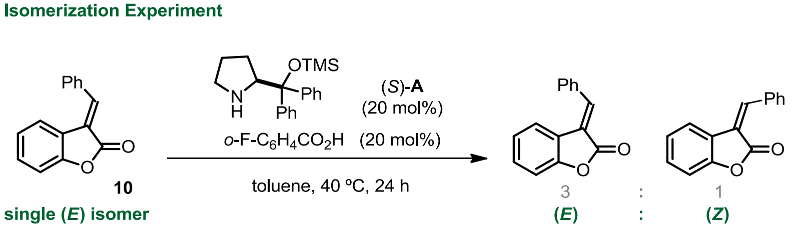
Table 1. *Approach A* – Substrate Scope.[a]



Entry	R^1	R^2	R^3	**11**	Yield (%)^b	d.r.^{c}	*ee* (%)^d
1	Me	Ph^e	Ph	**a**	56	>19 : 1	>99
2	Me	Ph^f	Ph	**a**	58	>19 : 1	>99
3	Me	*p*-Cl-C_6H_4	Ph	**b**	57	>19 : 1	99
4	Me	*p*-NO_2-C_6H_4	Ph	**c**	52	>19 : 1	>99
5	Me	Propyl	Ph	**d**	56	>19 : 1	>99
6	Me	CO_2Et	Ph	**e**	54	>19 : 1	>99
7	Me	CO_2Et	Me	**f**	70	>19 : 1	95
8	Allyl	CO_2Et	Ph	**g**	57	>19 : 1	>99

[a] Reactions carried out using 2 equiv of aldehyde **1**, 1.5 equiv of **10** and [**3**]$_0$ = 0.5 M in toluene on a 0.20 mmol scale at 40 °C. Reaction time 48 h. [b] Yield of the isolated product. [c] A single diastereoisomer was always detected by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Reaction carried out using isomerically pure **10** having an (*E*) geometry. [f] Reaction carried out using a 3 : 1 mixture of (*E*) and (*Z*) isomers of **10**.

With the aim of obtaining two different diastereoisomers of product **11**, we tested the possibility of using different double-bond geometries of **10**. However, we found that pure (*E*)-**10** underwent partial double bond isomerization under the reaction conditions, until equilibration was reached (3:1 mixture of *E*/*Z* isomers). This excluded the possibility of modulating the diastereoselectivity of the reaction by using geometrically distinct starting substrates, and also raised questions about the mechanism of the reaction.



Scheme 7. Isomerization of **10** Under the Reaction Condition.[16]

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[16] The same isomerization event has been observed when subjecting the *E* isomer of **10** to the optimized conditions of *Approach C* (see section 2.2.3).

Using a 3:1 mixture of the *E*/*Z*-isomers of compound **10** led to the same stereochemical outcome as when employing the geometrically pure *E*-isomer (Table 1, entries 1 and 2, a single stereoisomer was obtained, de and *ee* >99%). The stereo-convergence of the triple cascade can be rationalized on the basis of two different mechanism: *i*) a reversible enamine catalyzed Michael addition step between aldehydes **1** and **10**, leading to intermediate **VI** (Scheme 5): a rapid equilibrium may account for a dynamic kinetic resolution process driven by an extremely productive matched pair combination between the chiral iminium ion (generated by condensation of catalyst **A** and enal **3**) and only one out of the possible eight stereoisomers of intermediate **VI**. *ii*) Alternatively, the *E*- and *Z*-isomers of **10** might be characterized by a different reactivity and the double-bond isomerization allows continuous regeneration of the faster reacting isomer. Unfortunately, to date we were not able to isolate the intermediate **VI**, which would be key to support or discard our hypotheses.

From a synthetic standpoint, this stereo-convergent catalytic path delineates a more practical protocol, since a mixture of **10** can be used without affecting the stereochemical outcome of the cascade.

2.2.2. *Approach B* - Iminium Ion/Iminium Ion/Enamine Cascade Sequence

The ability to address a particular synthetic problem through separate approaches is a general validation for the versatility and reliability of a chemical strategy. A central goal of our organocascade catalysis studies was to demonstrate the potential of accessing enantiomerically pure spiro-benzofuranone cyclohexane derivatives using complementary organocascade reactions, based on distinct catalytic machineries. For a second cascade reaction we decided to exploit the relatively low pK_a of benzofuranones **12** (pK_a of 13.5 in DMSO).[17] We thought to exploit the ambident nucleophilic profiles of such compounds in an iminium ion/iminium ion/enamine sequence, a cascade reaction reminiscent of the previous work of Jørgensen described in Scheme 3.[9] With this aim, we designed a cascade reaction with α,β-unsaturated aldehydes **3** as shown in Scheme 8.

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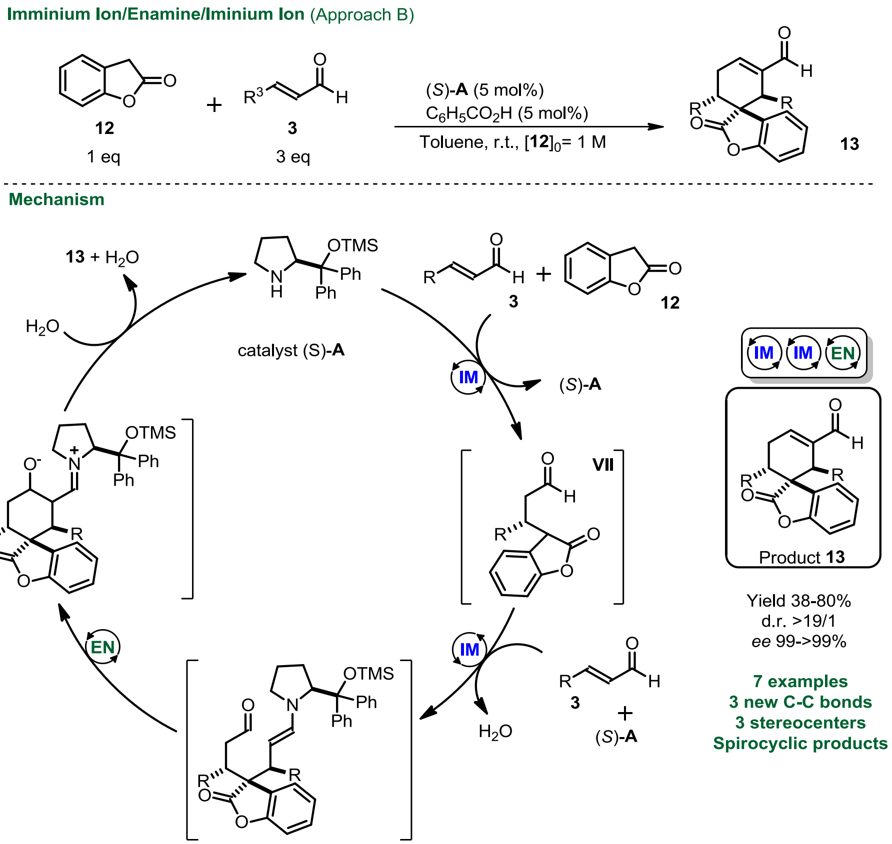
[17] F. G. Bordwell, H. E. Fried. Heterocyclic Aromatic Anions with 4n + 2 π-Electrons. *J. Org. Chem.*, **1991**, *56*, 4218.

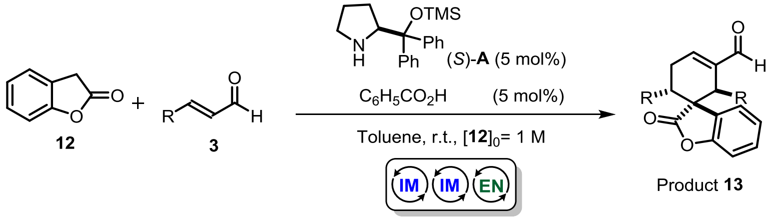


Scheme 8. Iminium Ion/Enamine/Iminium Ion – *Approach B.*

The relatively high acidity of **12** makes it possible to use its inherent ambident nucleophilic profile in a double Michael addition sequence, much in the same way as the previously discussed case with malononitriles (Scheme 3). The reaction proceeds *via* a double iminium ion catalyzed Michael addition followed by an intramolecular aldolization/dehydration sequence driven by enamine activation (Scheme 8).

Our organocascade strategy was evaluated conducting the reactions in toluene at room temperature for 16 hours, under an aerobic atmosphere.

Table 2. *Approach B* – Substrate Scope.[a]



Entry	R	**13**	Yield (%)[b]	d.r.[c]	*ee* (%)[d]
1	Ph	**a**	75	>19 : 1	>99
2[e]	Ph	**a**	68	>19 : 1	>99
3	*p*-NO_2-C_6H_4	**b**	59	>19 : 1	>99
4	*p*-MeO-C_6H_4	**c**	54	>19 : 1	>99
5	*p*-Cl-C_6H_4	**d**	80	>19 : 1	99
6	2-Furyl	**e**	49	>19 : 1	99
7	Me	**f**	51	19 : 1	>99
8	CO_2Et	**g**	38	>19 : 1	99

[a] Reactions carried out using 3 equiv of aldehyde **3** and [**12**]$_0$ = 1 M in toluene on a 0.20 mmol scale at r.t.. Reaction time 16 h. [b] Yield of the isolated product. [c] A single diastereoisomer was always detected by ^1H NMR analysis of the crude mixture. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Reaction carried out with 1 mol% of catalyst **A** and 1 mol% of the acid at 40 °C for 16 h.

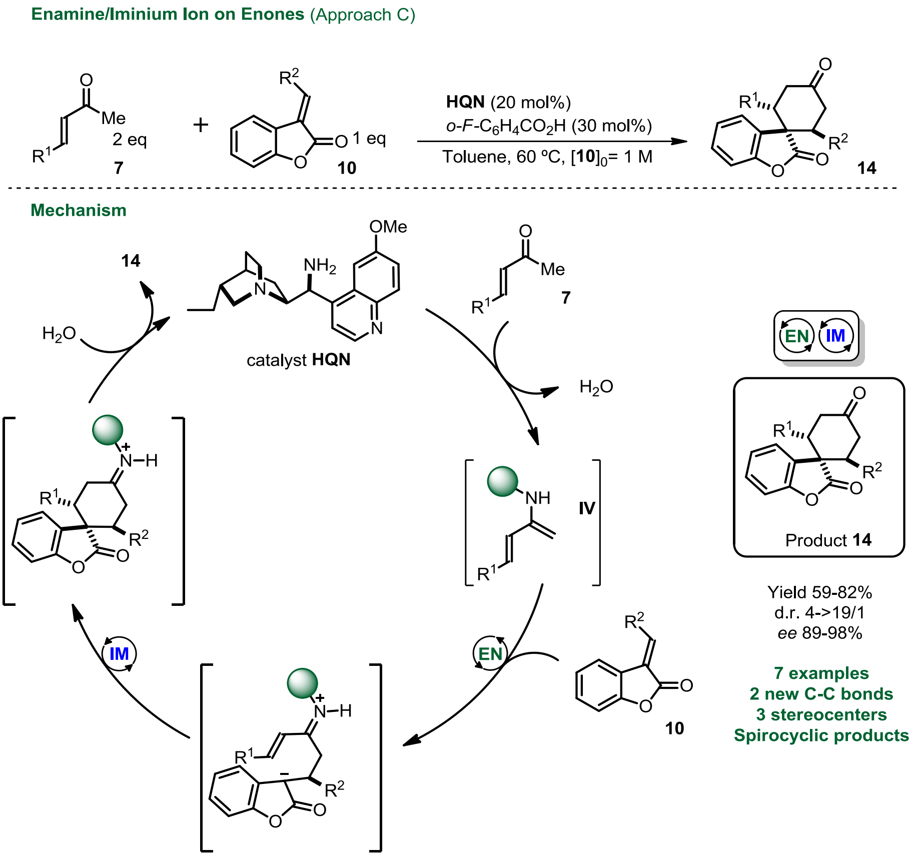
Optimization studies again identified the chiral secondary amine **A** as the catalyst of choice for this transformation, which performed better in presence of an acidic co-catalyst such as benzoic acid in a one to one ratio (Table 2). A catalyst loading of 5 mol% was found to be optimal. Still, a catalyst loading as low as 1 mol% afforded the enantiopure spiro benzofuranone **13** as a single stereoisomer (out of the possible 8), with a good yield and in a reasonable reaction time of 16 hours (entry 2).

As highlighted in Table 2, there appears to be significant tolerance toward structural and electronic variation of the enal **3** β-substituent, enabling access to a variety of complex spiro-compounds **13** bearing three stereocenters. Different substituents at the aromatic moiety, regardless of their electronic properties, and a hetero-aromatic substituent were well-tolerated (entries 1–6). Crotonaldehyde and ethyl *trans*-4-oxo-2-butenoate were also suitable substrates for the cascade (entries 7 and 8).

2.2.3. *Approach C* - Enamine/Iminium Ion Cascade Sequence

To make our approach more versatile, we sought to use a different aminocatalytic tool to design a third cascade pathway: the activation of α,β-unsaturated aliphatic ketones with primary amines. Central to the implementation of this strategy was the ability of the primary amine 9-

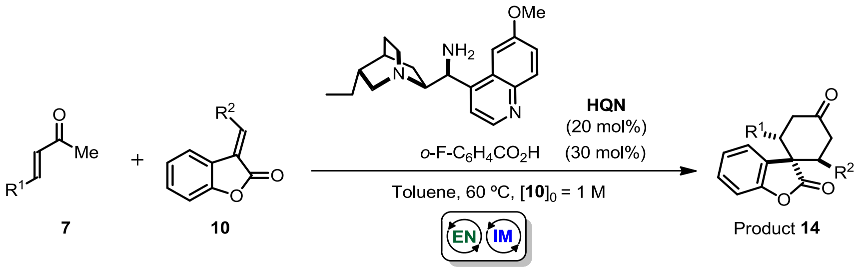
amino(9-deoxy)*epi* hydroquinine **HQN** to facilitate the formation of the nucleophilic dienamine intermediate **IV** (influencing the equilibrium with the iminium ion generated *in situ* by condensation with enone **7**) while selectively directing the reaction manifold toward a stepwise double-Michael addition sequence (Scheme 9).[13]



Scheme 9. Enamine/Iminium Ion on Ketones – *Approach C.*

The best results in terms of both yield and stereoselectivity were achieved using 20 mol% of amine **HQN** in combination with an acidic co-catalyst, such as *ortho*-fluorobenzoic acid (30 mol%). The results shown in Table 3 illustrate how this cascade enabled access to a variety of complex spiro-compounds **14** with good diastereomeric and enantiomeric ratios (Table 3).

Table 3. *Approach C* – Substrate Scope.[a]



Entry	R^1	R^2	**14**	Yield (%)[b]	d.r.[c]	*ee* (%)[d]
1[e]	Ph	Ph	**a**	70	5.5 :1	>99
2[f]	Ph	Ph	**a**	71	6.3 : 1	>99
3	Ph	*p*-Cl-C_6H_4	**b**	75	3.5 : 1	97
4	Ph	*p*-NO_2-C_6H_4	**c**	82	2 : 1	98
5	Ph	Propyl	**d**	40	>19 : 1	91
6	Ph	CO_2Et	**e**	77	2.2 : 1	85
7	*p*-Cl-C_6H_4	Ph	**f**	85	3.5 : 1	97
8	3-Thienyl	Ph	**g**	91	4 : 1	96

[a] Reactions carried out using 2 equiv of enones **7** and [**10**]$_0$ = 0.5 M in toluene on a 0.20 mmol scale at 60 °C. Reaction time 48 h. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Reaction carried out using isomerically pure **10** having an (*E*) geometry. [f] Reaction carried out using a 3 : 1 mixture of (*E*) and (*Z*) isomers of **10**.

As already observed for the enamine/iminium ion/enamine cascade reaction (*approach A*, section 2.2.1) the use of isomerically pure **10** or its 3:1 mixture did not affect the stereochemical outcome of the reaction (entries 1 and 2, Table 3).

2.3 Conclusions

Three distinct catalytic machineries have been developed to access densely functionalized spirocyclic molecules in an essentially enantiomerically pure form. The three different aminocatalytic cascade reactions led to the facile generation of benzofuranone derivatives bearing a spiro-center, which are structural elements present in many biologically active compounds. In view of the abundance of benzofuranone-derived natural products, these methods could be useful in asymmetric synthesis.

These results demonstrate that aminocatalytic cascades are a tool versatile enough to solve synthetic problems using different yet complementary approaches.

2.4 Experimental Section

2.4.1. General Informations

The ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts (δ) for ^1H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$ @ 7.26 ppm ^1H NMR, 77.0 ppm ^{13}C NMR). Coupling constants are given in Hz. Carbon substitution was determined by DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Chromatographic purification of products was accomplished using flash chromatography (FC) on silica gel (35-70 mesh) according to the method of Still.[18] Thin layer chromatography (TLC) analysis was performed throughout this work using Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm), using UV light as the visualizing agent and an acidic mixture of ceric ammonium molybdate or basic aqueous potassium permangante ($KMnO_4$), and heat as developing agents. High-resolution mass spectra (HRMS) were obtained from the ICIQ High Resolution Mass Spectrometry Unit on a Waters GCT gas chromatograph coupled time-of-flight mass spectrometer (GC/MS-TOF) with electron ionisation (EI). X-ray data was obtained from the ICIQ X-Ray Unit using a Bruker-Nonius diffractometer equipped with an APPEX 2 4K CCD area detector. Optical rotations are reported as follows: $[\alpha]_D^T$ (c in g per 100 mL, solvent). All reactions were performed in the air and using commercial solvents, without any precautions to exclude moisture unless otherwise noted.

The ^1H and ^{13}C NMR spectra and HPLC are available in the literature and are not reported in the present manuscript.[1]

2.4.2. Materials

Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[19] Catalysts (*S*) and (*R*)-**A** were purchased from Aldrich and used as received. Chiral primary amine catalysts, 9-amino(9-deoxy)*epi* hydroquinine **HQN** and its pseudoenantiomer 9-amino(9-deoxy)*epi* hydroquinidine were prepared from commercially available hydroquinine and hydroquinidine, respectively, following the literature procedure.[20] α,β-Unsaturated enones (*E*)-4-(4-chlorophenyl)but-3-en-2-one **7f** and

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[18] W. C. Still, M. Kahn, A. J. Mitra. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.,* **1978**, *43*, 2923.

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

[20] C. Cassani, R. Martín-Rapún, E. Arceo, F. Bravo, P. Melchiorre. Synthesis of 9-Amino(9-deoxy)epi Cinchona Alkaloids, General Chiral Organocatalysts for the Stereoselective Functionalization of Carbonyl Compounds. *Nat. Protoc.* **2013**, *8*, 325.

(*E*)-4-(thiophen-3-yl)but-3-en-2-one **7g**, were prepared according to the literature procedure,[21] whereas the enal (*E*)-3-(4-chlorophenyl)acrylaldehyde **3d** was prepared using the Wittig olefination reaction from commercially available 4-chloro benzaldehyde and (triphenylphosphoranylidene)acetaldehyde.

All the other enals **3**, aldehydes **1** and unsaturated ketones **7** were purchased from Aldrich or Alfa Aesar and used as received. 1-Benzofuran-2(3H)-one **5** is commercially available.

All the Michael acceptors bearing a benzofuranone moiety (**10**) were prepared according to literature procedures.[22] 3-Benzylidenebenzofuran-2(3H)-one **10a** was obtained as a 3:1 mixture of *E*/*Z* isomer; isolation of the pure E isomer has been accomplished by standard chromatography on silica gel. (*E*)-3-(4-Chlorobenzylidene)benzofuran-2(3H)-one, (*E*)-3-(4-nitrobenzylidene)benzofuran-2(3H)-one, and (*E*)-3-butylidenebenzofuran-2(3H)-one were all synthesized as a mixture *E*/*Z* isomers, and used without further purification.

(*E*)-Ethyl 2-(2-oxobenzofuran-3(2H)-ylidene)acetate was synthesized as a single *E* isomer.

2.4.3. Determination of the Enantiomeric Purity

HPLC analysis on chiral stationary phase was performed on an Agilent 1200-series instrumentation. Daicel Chiralpak IA or IC columns with *i*-PrOH/hexane as the eluent were used. HPLC traces were compared to racemic samples prepared by performing the reactions using a 1:1 mixture of (*S*)- and (*R*)-**A** as the catalyst for the synthesis of compounds **4** and **6**. Racemic mixtures for compounds **8** were obtained by mixing the two antipodes obtained performing distinct reactions with catalyst 9-amino(9-deoxy)*epi* hydroquinine **HQN** and the pseudo-enantiomer 9-amino(9-deoxy)*epi* hydroquinidine.

2.4.4. Determination of Diastereomeric Ratios

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

2.4.5. Absolute and Relative Configuration Determination

The absolute and relative configurations of compound **11b**, **13d**, and **14b** were assigned by X-ray crystallographic analysis. CCDC 781708, 780474, 781524, respectively, contain the supplementary crystallographic data for those compounds. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

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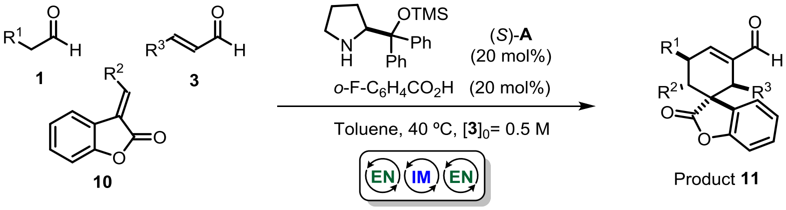
[21] K. Zumbansen, A. Döhring, B. List. Morpholinium Trifluoroacetate-Catalyzed Aldol Condensation of Acetone with both Aromatic and Aliphatic Aldehydes. *Adv. Syn. Cat.*, **2010**, *352*, 1135.
[22] M. Msaddek, M. Rammah, K. Ciamala, J. Vebrel, B. Laude. A New and Efficient Synthesis of Pyridazin-3(2H)-ones *via* 1,3-Dipolar Cycloaddition. *Synthesis*, **1997**, *12*, 1495.

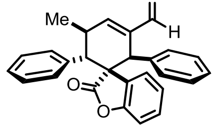
2.4.6. General Procedure for the Organocatalytic Triple Cascade proceeding *via* Enamine/Iminium Ion/Enamine Activation of Aldehydes (*Approach A*)

All the reactions were carried out in an ordinary vial equipped with a Teflon-coated stir bar, with no precautions to exclude moisture in undistilled toluene. Catalyst **A** (0.04 mmol, 20 mol%), aldehyde **1** (0.4mmol) and *ortho*-fluoro benzoic acid (20 mol%) were stirred in toluene (0.1 mL) at room temperature for 10 minutes. The cascade was started by adding a solution of benzofuranone derivative **10** (0.3 mmol) and aldehyde **3** (0.2 mmol), dissolved in 0.1 mL of toluene. The vial was sealed and heated up to 40 °C, and stirring was continued till completion of the reaction, as monitored by TLC (generally 48 hours). The crude reaction was then flushed through a short plug of silica, using CH_2Cl_2/Et_2O 1/1 as the eluent. Solvent was removed *in vacuo* and, after NMR analysis to determine the diastereomeric ratio of the process, the residue was purified by flash column chromatography (silica gel) to yield the desired spiro-compounds **11**.



(1''R,2''R,3''S,4''S)-4''-methyl-2-oxo-1'',3''-diphenyl-2H-spiro[benzofuran-3,2''-cyclohex[5']ene]-6''-carbaldehyde (**11a**).

11a

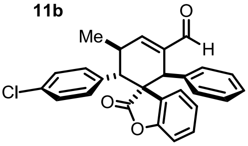


The reaction was carried out at 40 °C following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 20/1) in 56% yield and >99% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 90/10 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ=254 nm: τ_{major} = 7.56 min, τ_{minor}= 11.2 min. HRMS *calcd.* for ($C_{27}H_{22}O_3$+Na): 417.1467, found 417.1483. $[\alpha]_D^{25}$= -180.9 (c = 0.57, $CHCl_3$, >99% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (d, *J* = 7.2 Hz, 3H), 3.15 (d, *J* = 11.2 Hz, 1H), 3.53-3.57 (m, 1H), 4.07 (s, 1H), 5.41(d, *J* = 7.2 Hz, 1H), 6.57 (t, *J* = 7.2, 1H), 6.68 (bs, 1H), 6.74 (d, *J* = 8.4, 1H), 6.88-7.02 (m, 6H), 7.17-7.24 (m,3H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.42 (bs, 1H), 9.56 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 34.9, 46.0, 50.0, 54.3, 109.8, 122.5, 126.7, 127.41, 127.46, 128.1, 128.4, 128.6, 137.9, 138.0, 152.4, 156.1, 177.3, 192.4 ppm.

(1''R,2''R,3''S,4''S)-3''-(4-chlorophenyl)-4''-methyl-2-oxo-1''-phenyl-2H-spiro[benzofuran-3,2''-cyclohex[5']ene]-6''-carbaldehyde (11b).

11b



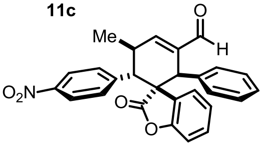
The reaction was carried out at 40 °C following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 20/1) in 57% yield and 99% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 95/5 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{major} = 10.2 min, τ_{minor} = 19.7 min. HRMS *calcd.* for ($C_{27}H_{21}ClO_3$+Na): 451.1077, found 451.1089. $[\alpha]_D^{25}$= -148.5 (c = 0.76, $CHCl_3$, 99% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (d, *J* = 7.2 Hz, 3H), 3.13 (d, *J* = 10.4 Hz, 1H), 3.45-3.53 (m, 1H), 4.06 (s, 1H), 5.38 (d, *J* = 8.0 Hz, 1H), 6.59 (t, *J* = 7.6 Hz, 1H), 6.67 (bs, 1H), 6.77-7.02 (m, 6H), 7.16-7.22 (m, 3H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.40 (bs, 1H), 9.55 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 34.9, 45.9, 49.4, 54.2, 110.1, 122.7, 126.5, 127.1, 127.5, 128.6, 128.9, 133.2, 136.6, 137.4, 137.9, 152.3, 155.5, 177.0, 192.3 ppm.

The absolute configuration of 4b was unambiguously determined by single crystal X-ray analysis.

(1''R,2''R,3''S,4''S)-4''-methyl-3''-(4-nitrophenyl)-2-oxo-1''-phenyl-2H-spiro[benzofuran-3,2''-cyclohex[5']ene]-6''-carbaldehyde (11c).

11c

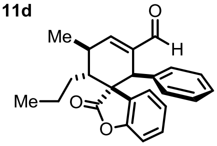


The reaction was carried out at 40 °C following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 7/1) in 52% yield and >99% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 80/20 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{major} = 7.4 min, τ_{minor} = 13.6 min. HRMS *calcd.* for ($C_{27}H_{21}NO_5$+Na): 462.1317, found 462.1331. $[\alpha]_D^{25}$= -199.9 (c = 0.61, $CHCl_3$, >99% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (d, *J* = 7.2 Hz, 3H), 3.30 (d, *J* = 10.4 Hz, 1H), 3.54-3.59 (m, 1H), 4.09 (s, 1H), 5.40 (d, *J* = 8.4 Hz, 1H), 6.60 (t, *J* = 8.0 Hz, 1H), 6.68 (bs, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.98-7.23 (m, 6H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.41(bs, 1H), 7.88 (d, *J* = 9.6 Hz, 2H), 9.56 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 34.7, 45.9, 50.0, 54.0, 110.3, 122.9, 123.6, 123.7, 126.4, 126.5, 128.3, 129.3, 137.0, 138.0, 145.9, 147.2, 152.2, 154.6, 176.6, 192.1 ppm.

(1'R,2'R,3'R,4'S)-4'-methyl-2-oxo-1'-phenyl-3'-propyl-2H-spiro[benzofuran-3,2'-cyclohex[5]ene]-6'-carbaldehyde (**11d**).

11d

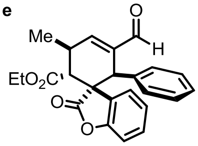


The reaction was carried out at 40 °C following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 20/1) in 56% yield and >99% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 80/20 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{major} = 5.1 min, τ_{minor} = 6.3 min. HRMS *calcd*. for ($C_{24}H_{24}O_3$+Na): 383.1623, found 383.1605. $[\alpha]_D^{25}$= -148.2 (c = 0.55, $CHCl_3$, >99% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.57 (t, *J* = 8.0 Hz, 3H), 0.88-1.14 (m, 4H), 1.46 (d, *J* = 7.6 Hz, 3H), 2.01-2,06 (m,1H), 2.96-3.05 (m, 1H), 3.89 (s, 1H), 5.46 (d, *J* = 7.6 Hz, 1H), 6.73 (t, *J* = 8.0 Hz, 1H), 7.05-7.28 (m, 8H), 9.47 (s,1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 19.2, 21.2, 33.0, 34.7, 41.3, 45.8, 53.4, 110.2, 122.8, 126.4, 127.8, 128.0, 128.1, 128.9, 137.5, 153.0, 156.7, 177.1, 192.4 ppm.

(1'R,2'S,3'R,4'S)-ethyl 6'-formyl-4'-methyl-2-oxo-1'-phenyl-2H-spiro[benzofuran-3,2'-cyclohex[5]ene]-3'-carboxylate (**11e**).

11e

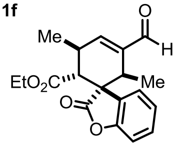


The reaction was carried out at 40 °C following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 10/1) in 54% yield and >99% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 95/5 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{major} = 21.5 min, τ_{minor} = 22.9 min. HRMS *calcd.* for ($C_{24}H_{22}O_5$+Na): 413.1365, found 413.1366. $[\alpha]_D^{25}$= -97.6 (c = 0.55, $CHCl_3$, >99% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (t, *J* = 7.2 Hz, 3H), 1.44 (d, *J* = 8.0 Hz, 3H), 3.01 (d, *J* = 11.2 Hz, 1H), 3.43-3.48 (m, 1H), 3.75-3.83 (m, 2H), 3.99 (s, 1H), 5.50 (d, *J* = 8.0 Hz, 1H), 6.71 (t, *J* = 8.0 Hz, 1H), 7.05-7.09 (m, 3H), 7.19-7.31 (m, 5H), 9.50 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 18.5, 32.2, 45.1, 50.4, 50.6, 61.3, 110.3, 122.9, 126.2, 126.6, 128.22, 128.29, 129.5, 136.7,137.8, 154.4, 171.2, 192.0 ppm.

(1'S,2'R,5'S,6'R)-ethyl 3'-formyl-2',5'-dimethyl-2-oxo-2H-spiro[benzofuran-3,1'-cyclohex[3]ene]-6'-carboxylate (**11f**).

11f



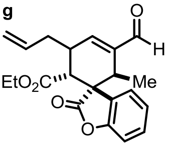
The reaction was carried out at 40 °C following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a colourless oil by column chromatography (hexane/AcOEt = 10/1) in 70% yield and 95% *ee*.

HPLC analysis ona Daicel Chiralpak IC column: 80/20 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{minor} = 6.5 min, τ_{major} = 7.1 min. HRMS *calcd.* for ($C_{19}H_{20}O_5$+Na): 351.1208, found 351.1215. $[\alpha]_D^{25}$= +69.3 (c = 0.61, CHCl3, 95% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, *J* = 7.6 Hz, 3H), 1.21 (d, *J* = 7.2 Hz, 3H), 1.30 (d, *J* = 7.2 Hz, 3H), 2.88 (q, *J* = 7.2 Hz, 1H), 2.99 (d, *J* = 10.8 Hz, 1H), 3.32-3.37 (m, 1H), 3.79-3.89 (m, 2H), 6.78 (d, *J* = 3.2 Hz, 1H), 7.08-7.34 (m, 4H), 9.50 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 17.3, 18.5, 32.4, 33.7, 49.9, 50.0, 61.4, 111.0, 123.5, 125.8, 127.5, 129.6, 140.9, 154.1, 171.3, 192.9 ppm.

(1'S,2'R,6'R)-ethyl 5'-allyl-3'-formyl-2'-methyl-2-oxo-2H-spiro[benzofuran-3,1'-cyclohex[3]ene]-6'-carboxylate (**11g**).

11g

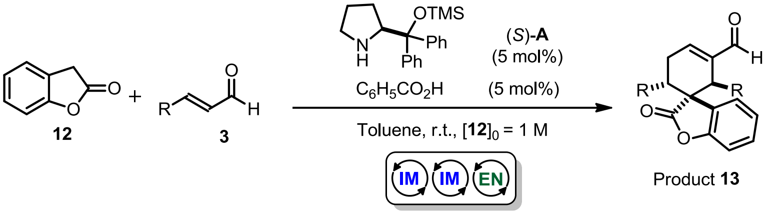


The reaction was carried out at 40 °C following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 10/1) in 57% yield and >99% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 90/10 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm : τ_{minor} = 12.7 min, τ_{major} = 13.2 min. HRMS *calcd.* for ($C_{26}H_{24}O_5$+Na): 439.1521, found 439.1507. $[\alpha]_D^{25}$= -99.5 (c = 0.77, $CHCl_3$, >99% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.8 (t, *J* = 7.2 Hz, 3H), 2.33-2.41 (m, 1H), 2.65-2.71 (m, 1H), 3.16 (d, *J* = 12 Hz, 1H), 3.50-3.56 (m, 1H), 3.78 (q, *J* = 7.2 Hz, 2H), 3.97 (s, 1H), 5.30-5.35 (m, 2H), 5.51 (d, *J* = 8.4 Hz, 1H), 5.93- 6.03 (m, 1H), 6.7(t, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 2H), 7.18-7.31 (m, 6H), 9.50 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 36.5, 36.6, 45.1, 48.0, 50.5, 61.3, 110.3, 119.7, 122.9, 126.4, 126.5, 128.20, 128.23, 129.5, 133.6, 136.9, 138.8, 152.2, 153.0, 171.2, 191.9 ppm.

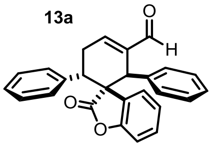
2.4.7. General Procedure for the Organocatalytic Triple Cascade of Aldehydes proceeding *via* an Iminium Ion/Iminium Ion/Enamine Sequence (*Approach B*)

All the reactions were carried out with no precautions to exclude moisture in undistilled toluene. In an ordinary vial equipped with a Teflon-coated stir bar, (*S*)-(–)-α,α-Diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **A** (0.01 mmol, 20 μL of a 0.5 M toluene stock solution, 5 mol%) was added to 180 μL of toluene. After the addition of benzoic acid (0.01 mmol, 1.2 mg, 5 mol%), the solution was stirred for 5 minutes at room temperature before adding the aldehyde **3** (0.6 mmol, 3 equiv). The mixture was then allowed to stir for 5 minutes further at room temperature before the addition of 2-Cumarone **12** (26.8 mg, 0.2 mmol). The vial was sealed, and the stirring continued at room temperature for 16 h. The crude reaction was then flushed through a short plug of silica, using CH_2Cl_2/Et_2O 1/1 as the eluent. Solvent was removed *in vacuo* and, after NMR analysis to determine the diastereomeric ratio of the process, the residue was purified by flash column chromatography (silica gel) to yield the desired product **13**.



(1''R,2''R,3''S)-2-oxo-1'',3''-diphenyl-2H-spiro[benzofuran-3,2''-cyclohex[5']ene]-6''-carbaldehyde (**13a**)

13a



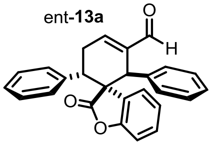
The reaction was carried out following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/diethyl ether = 8/2) in 75% yield and >99% de and *ee*. HPLC analysis on a Daicel Chiralpak IC column: 80/20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 12.9 min, τ_{minor} = 23.1 min; HRMS *calcd.* for ($C_{26}H_{20}O_3$+Na): 403.1310, found 403.1318. $[\alpha]_D^{25}$ = -167.7 (c = 1.00, $CHCl_3$, >99% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.01 (td, 1H, J_d = 20.5 Hz, J_t = 5.7 Hz), 3.38-3.49 (m, 1H), 3.65 (dd, 1H, J_1= 11.4 Hz, J_2 = 5.8 Hz), 4.09 (s, 1H), 5.44 (dd, 1H, J_1 = 7.7 Hz, J_2 = 0.9 Hz), 6.58 (dt, 1H, J_t = 7.6 Hz, J_d= 0.9 Hz), 6.63-6.79 (m, 2H), 6.87-7.06 (m, 6H), 7.08-7.48 (m, 5H), 9.55 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.3 (CH2), 42.4 (CH), 46.0 (CH), 53.5 (C), 109.9 (CH), 122.9 (CH), 126.7 (CH), 127.3 (C), 127.4 (CH), 128.1 (CH), 128.2 (C), 128.2 (CH), 128.4 (CH), 128.7 (CH), 137.7 (CH), 138.8 (CH), 139.3 (C), 150.6 (CH), 152.5 (C), 177.0 (C), 192.2 (CH) ppm.

Performing the reaction in the presence of 1 mol% of the catalyst **A** at 40 °C afforded similar results: full conversion, 68% isolated yield, de and *ee* >99%

(1''S,2''S,3''R)-2-oxo-1'',3''-diphenyl-2H-spiro[benzofuran-3,2''-cyclohex[5']ene]-6''-carbaldehyde. (ent-**13a**)

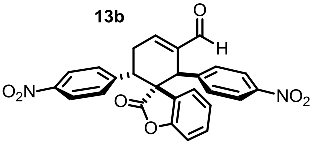
ent-**13a**



The reaction was carried out following the general procedure using (*R*)-(+)-α,α-Diphenyl-2-pyrrolidinemethanol trimethylsilyl ether as catalyst to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/diethyl ether = 8/2) in 72% yield and >99% *ee*. HPLC analysis on a Daicel Chiralpak IC column: 80/20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{minor} = 12.9 min, τ_{major} = 23.1 min;. $[\alpha]_D^{25}$= +132.9 (c = 1.06, $CHCl_3$, >99% *ee*).

(1''R,2''R,3''S)-1'',3''-bis(4-nitrophenyl)-2-oxo-2H-spiro[benzofuran-3,2''-cyclohex[5']ene]-6''-carbaldehyde (13b)

13b

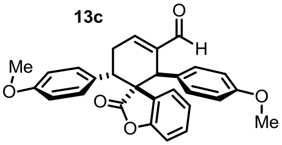


The reaction was carried out following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a yellow solid by column chromatography (hexane/diethyl ether = 6/4) in 59% yield and >99% de and *ee*. HPLC analysis on a Daicel Chiralpak IC column: 70/30 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 45.3 min, τ_{minor} = 54.1 min; HRMS *calcd.* for ($C_{26}H_{17}N_2O_7$+Na): 469.1036, found 469.1048. $[\alpha]_D^{25}$ = -258.5 (c = 1.07, $CHCl_3$, >99% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 3.08 (td, 1H, J_d = 20.5 Hz, J_t = 5.4 Hz), 3.45-3.53 (m, 1H), 3.66 (dd, 1H, J_1 =11.3 Hz, J_2 = 5.6 Hz), 4.21 (s, 1H), 5.50 (dd, 1H, J_1 = 7.6 Hz, J_2 = 0.9 Hz), 6.67 (dt, 1H, J_t = 7.5 Hz, J_d 0.9= Hz), 6.83-6.95 (m, 2H), 7.04-7.13 (m, 3H), 7.37-7.50 (m, 2H), 7.88-7.92 (m, 2H), 8.00-8.11 (m, 1H), 8.24-8.36 (m,1H), 9.57 (s, 1H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ 30.8 (CH2), 42.5 (CH), 45.6 (CH), 52.6 (C), 111.0 (CH),123.4 (CH), 123.5 (C), 123.8 (CH), 125.6 (C), 125.8 (CH), 129.2 (CH), 130.0 (CH), 138.6 (C), 144.7 (C),145.6 (C), 147.4 (C), 147.8 (C), 150.3 (CH), 152.4 (C), 175.8 (C), 191.5 (CH) ppm.

(1''R,2''R,3''S)-1'',3''-bis(4-methoxyphenyl)-2-oxo-2H-spiro[benzofuran-3,2''-cyclohex[5']ene]-6''-carbaldehyde (13c)

13c

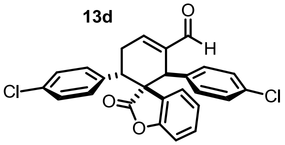


The reaction was carried out following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a pale yellow solid by column chromatography (hexane/diethyl ether = 7/3) in 54% yield and >99% de and *ee*. HPLC analysis on a Daicel Chiralpak IC column: 70/30 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 18.0 min, τ_{minor} = 38.1 min; HRMS *calcd.* for ($C_{28}H_{24}O_5$+Na): 463.1521, found 463.1533. $[\alpha]_D^{26}$ = -215.1 (c = 1.08, $CHCl_3$, >99% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.98 (td, 1H, J_d = 20.7 Hz, *J*t 5.6= Hz), 3.32-3.44 (m, 1H), 3.58 (dd, 1H, J_1 = 11.4 Hz, J_2 = 5.8 Hz), 3.65 (s, 3H), 3.84 (s, 3H), 4.05 (s, 1H), 5.58 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.0 Hz), 6.54-6.58 (m, 2H), 6.59-6.78 (m, 3H), 6.80 (d, 1H, *J* = 8.0), 6.83-6.87 (m, 2H), 6.91-6.99 (m, 1H), 7.02 (dt, 1H, J_d = 1.3 Hz, *J*t = 7.7 Hz), 7.11-7.22 (m, 1H), 7.34-7.37 (m, 1H), 9.55 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.4 (CH2), 41.4 (CH), 45.0 (CH), 53.7 (C), 55.0(CH3), 55.3 (CH3), 109.8 (CH), 113.4 (C), 113.6 (CH), 122.5 (CH), 126.7 (CH), 127.4 (C), 128.5 (CH), 129.1 (CH), 129.7 (C), 130.7 (C), 139.4 (C), 150.3 (CH), 152.4 (C), 158.5 (C), 159.2 (C), 177.0 (C), 192.2 (CH) ppm.

(1''R,2''R,3''S)-1'',3''-bis(4-chlorophenyl)-2-oxo-2H-spiro[benzofuran-3,2''-cyclohex[5']ene]-6''-carbaldehyde (13d)

13d



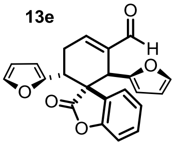
The reaction was carried out following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/diethyl ether = 7/3) in 80% yield and 99% *ee*. HPLC analysis on a Daicel Chiralpak IC column: 70/30 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 10.4 min, τ_{minor} = 17.8 min; HRMS *calcd.* for ($C_{26}H_{18}Cl_2O_3$+Na): 471.0531, found 471.0535. $[\alpha]_D^{26}$ = -198.1 (c = 1.32, $CHCl_3$, 99% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 3.01 (td, 1H, J_d = 20.4 Hz, J_t 5.2= Hz), 3.35-3.46 (m, 1H), 3.52 (dd, 1H, J_1 =11.4 Hz, J_2 = 5.7 Hz), 4.07 (s, 1H), 5.57 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.2 Hz), 6.55-6.74 (m, 2H), 6.82-6.90 (m, 3H), 7.00-7.04 (m, 3H), 7.07(dt, 1H, J_d = 1.4 Hz, J_t = 8.0 Hz), 7.12-7.26 (m, 2H), 7.38-7.46 (m, 2H), 9.55 (s, 1H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ 31.2 (CH2), 41.8 (CH), 45.3 (CH), 53.1 (C), 110.4 (CH), 122.9 (CH), 126.4 (CH), 126.6 (C), 128.5 (CH), 128.7 (CH), 129.2 (CH), 129.5 (CH), 133.4 (C), 134.2 (C), 136.1 (C), 137.1 (C), 139.1 (C), 150.4 (CH), 152.5 (C), 195.5 (CH) ppm.

The absolute configuration of 6d was unambiguously determined by single crystal X-ray.

(1''R,2''R,3''S)-1'',3''-bis(4-chlorophenyl)-2-oxo-2H-spiro[benzofuran-3,2''-cyclohex[5']ene]-6''-carbaldehyde (13e)

13e

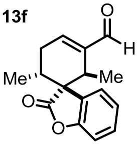


The reaction was carried out following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/diethyl ether = 7/3) in 49% yield and 99% *ee*. HPLC analysis on a Daicel Chiralpak IC column: 80/20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 15.3 min, τ_{minor} = 24.9 min; HRMS *calcd.* for ($C_{22}H_{16}O_5$+Na): 383.0895, found 383.0913. $[\alpha]_D^{26}$ = -163.9 (c = 0.84, $CHCl_3$, 99% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.96 (td, 1H, J_d = 20.9 Hz, J_t = 5.4 Hz), 3.31-3.42 (m, 1H), 4.06 (dd, 1H, J_1 = 11.2 Hz, J_2 = 5.8 Hz), 4.21 (s, 1H), 5.84 (d, 1H, *J* = 3.2 Hz), 5.86-5.90 (m, 1H), 6.01 (dd, 1H, J_1 = 3.2 Hz, J_2 = 1.8 Hz), 6.08 (d, 1H, *J* = 3.2 Hz), 6.35 (dd, 1H, J_1 = 3.2 Hz, J_2 = 1.9 Hz), 6.83 (dt, 1 H, J_t = 7.6 Hz, J_d = 0.9 Hz), 6.89 (d, 1H, *J* = 7.9 Hz), 7.02-7.04 (m, 1H), 7.13 (dt, 1H, J_t = 7.6 Hz, J_d = 1.0 Hz), 7.20-7.24 (m, 1H), 7.37-7.39 (m, 1H), 9.51(s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.6 (CH2), 37.0 (CH), 38.9 (CH), 52.0 (C), 107.2 (CH), 110.1(CH), 110.2 (CH), 110.8 (CH), 110.9 (CH), 123.4 (CH), 125.2 (CH), 127.6 (C), 129.2 (CH), 137.2 (C), 141.9 (CH), 142.1 (CH), 150.2 (CH), 151.4 (C), 152.6 (C), 152.7 (C), 191.7 (CH) ppm.

(1'R,2'R,6'R)-2',6'-dimethyl-2-oxo-2H-spiro[benzofuran-3,1'-cyclohex[3]ene]-3'-carbaldehyde (13f)

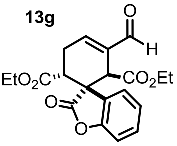
13f



The reaction was carried out following the general procedure to furnish the crude product (d.r. 19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a yellowish oil by column chromatography (hexane/diethyl ether = 8/2) in 51% yield and >99% de and *ee*. HPLC analysis on a Daicel Chiralpak IC column: 80/20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 13.3 min, τ_{minor} = 17.5 min; HRMS *calcd.* for ($C_{16}H_{16}O_3$+Na): 279.0997, found 297.0994. $[\alpha]_D^{26}$ = -21.8 (c = 1.40, $CHCl_3$, 99% *ee*).
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.74 (d, 3H, *J* = 6.8 Hz), 1.21 (d, 3H, *J* = 6.9 Hz), 2.43-2.68 (m, 3H), 2.90 (q, 1H, *J* = 6.9 Hz), 6.92-6.96 (m, 1H), 7.10-7.22 (m, 3H), 7.30-7.35 (m, 1H), 9.48 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9 (CH3), 17.2 (CH3), 29.3 (CH), 32.1 (CH2), 33.5 (CH), 52.7 (C), 111.0 (CH), 123.7 (CH), 125.7 (CH), 128.9 (C), 129.0 (CH), 142.3 (C), 150.4 (CH), 153.4 (C), 176.6 (C), 193.1 (CH) ppm.

(1'R,2'R,6'R) - diethyl 3'-formyl-2-oxo-2H-spiro [benzofuran-3,1'-cyclohex[3]ene]-2',6'-dicarboxylate (13g)

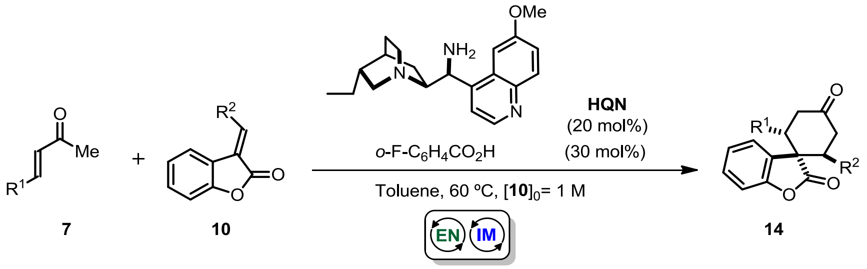
13g



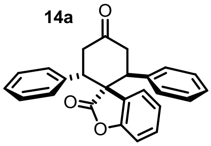
The reaction was carried out following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a colourless oil by column chromatography (hexane/diethyl ether = 8/2) in 38% yield and *ee* 99%. HPLC analysis on a Daicel Chiralpak IC column: 80/20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 10.9 min, τ_{minor} = 13.9 min; HRMS *calcd.* for ($C_{20}H_{20}O_7$+Na): 395.1107, found 395.1111. $[\alpha]_D^{25}$ = -75.5 (c = 1.23, $CHCl_3$, 99% *ee*).
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.97 (t, 3, *J* = 7.2 Hz), 1.10 (t, 3H, *J* = 7.2 Hz), 3.02 (td, 1H, J_d = 20.0 Hz, J_t = 5.7 Hz), 3.12-3.23 (m, 1H), 3.71 (s, 1H), 3.85-4.04 (m, 4H), 4.08-4.17 (m, 1H), 7.02-7.18 (m, 3H), 7.24-7.27 (m, 1H), 7.37 (dt, 1H, J_t = 7.8 Hz, J_d = 1.3 Hz), 9.54 (s, 1H).ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8 (CH3), 13.9 (CH3), 27.2 (CH2), 42.6 (CH), 45.2 (CH), 46.25 (C), 61.5 (CH2), 61.7 (CH2), 111.2 (CH), 123.9 (CH), 124.0 (CH), 127.1 (C), 130.2 (CH), 135.7 (C), 150.7 (CH), 153.6 (C), 170.2 (C), 171.4 (C), 174.78 (C),191.7 (CH) ppm.

2.4.8. General Procedure for the Organocatalytic Tandem Double Michael Additions Proceeding *via* Enamine/Iminium Ion Activation Sequence (*Approach C*)

All the reactions were carried out in an ordinary vial equipped with a Teflon-coated stir bar, with no precautions to exclude moisture in undistilled toluene. Catalyst **HQN** (0.02 mmol, 20 mol%), enone **7** (0.4 mmol) and *o*-fluoro-benzoic acid (30 mol%) were stirred in toluene (0.1 mL) at room temperature for 10 minutes. The cascade was started by adding a solution of benzofuranone derivative **10** (0.2 mmol) dissolved in 0.1 mL of toluene. The vial was sealed and heated up to 60 °C, and stirring was continued till completion of the reaction, as monitored by TLC (generally 72 hours). The crude reaction was then flushed through a short plug of silica, using CH_2Cl_2/Et_2O 1/1 as the eluent. Solvent was removed *in vacuo* and, after NMR analysis to determine the diastereomeric ratio of the process, the residue was purified by flash column chromatography (silica gel) to yield the desired spiro-compounds **14**.

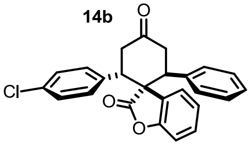


(2'S,6'S)-2',6'-diphenyl-2H-spiro[benzofuran-3,1'-cyclohexane]-2,4'-dione (**14a**)



The reaction was carried out at 60 °C following the general procedure to furnish the crude product as a 6.3/1 mixture of diastereoisomer (dr. 6.3:1 determined by integration of ^{1}H NMR signal: δ_{minor} 6.45 d, δ_{major} 6.06 ppm, d). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 90/10) in 70% yield (as a single of diastereoisomer) and >99% *ee*. HPLC analysis on a Daicel Chiralpak IC column: 80/20 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{minor} = 12.8 min, τ_{major} = 15.1 min. HRMS *calcd.* for ($C_{25}H_{20}NO_3$+Na): 391.1310, found 391.1329. $[\alpha]_D^{25}$= -195.8 (c = 0.76, $CHCl_3$, >99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.76 (d, *J* =13.2 Hz, 1H), 2.95 (dd, *J* = 5.2 Hz, *J* = 16 Hz, 1H), 3.61 (dd, *J* = 6.0 Hz, *J* = 15.6 Hz,1H), 3.68-3.71 (m, 1H), 3.76-3.87 (m, 1H), 6.04 (d, *J* = 7.2 Hz, 1H), 6.73-6.86 (m, 4H), 6.93-6.96 (m, 2H), 7.03-7.07 (m, 4H), 7.24-7.29 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.8, 42.6, 45.9, 47.5, 110.2, 123.1,126.0, 127.7, 127.9, 128.0, 128.41, 128.49, 129.0, 129.5, 137.3, 139.0, 152.5, 177.9, 209.7 ppm.

(1'S,2'S,6'S)-2'-(4-chlorophenyl)-6'-phenyl-2H-spiro[benzofuran-3,1'-cyclohexane]-2,4'-dione (**14b**)



The reaction was carried out at 60 °C following the general procedure to furnish the crude product as a 3.5/1 mixture of diastereoisomer (d.r. 3.5:1 determined by integration of ^{1}H NMR signal: δ_{major} 6.25 d, δ_{minor} 6.05 ppm. d). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 90/10) in 75% yield (as a 3:1 mixture of diastereoisomer) and 97% *ee*. HPLC analysis on a Daicel Chiralpak IC column: 80/20 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: Major diastereoisomer (97% *ee*): τ_{minor}

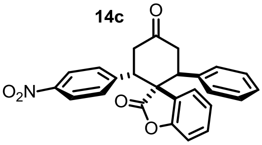
= 13.9 min, τ_{major} = 14.9 min; Minor diastereoisomer (>99% *ee*): τ_{minor} = 13.2 min, τ_{major} = 16.3 min. HRMS *calcd.* for ($C_{25}H_{19}ClO_3$+Na): 425.0920, found 425.0937. $[\alpha]_D^{25}$ = -155.7 (c = 0.78, $CHCl_3$, dr 3.5:1, 97% ee_{major}, >99% ee_{minor}).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.73-2.79 (m, 1H), 2.91-2.97 (m, 1H), 2.53-2.67 (m, 3H), 3.54 (dd, *J* = 6.12, 16.2 Hz, 1H), 3.67-3.85 (m, 4H), 6.03 (d, *J* = 7.6 Hz, 1H minor), 6.23 (d, *J* = 8.0 Hz, 1H major), 6.74-6.93 (m, 8H), 7.0-7.10 (m, 5H), 7.21-7.27 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.6, 41.7, 42.4, 42.5, 45.3, 46.0, 46.7, 47.4, 55.2, 55.3, 110.45, 110.46, 123.3, 123.4, 125.7, 125.8, 127.62, 127.69, 127.8, 128.0, 128.1, 128.4, 128.5, 128.62, 128.65, 129.27, 129.29, 129.3, 129.4, 130.7, 133.9, 135.8, 136.9, 137.4, 152.5, 177.6, 177.7, 209.1, 209.3 ppm.

The absolute configuration of 8b was unambiguously determined by single crystal X-ray.

(1'S,2'S,6'S)-2'-(4-nitrophenyl)-6'-phenyl-2H-spiro[benzofuran-3,1'-cyclohexane]-2,4'-dione (**14c**)

14c

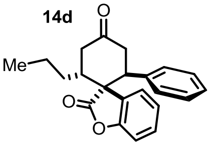


The reaction was carried out at 60 °C following the general procedure to furnish the crude product as a 2/1 mixture of diastereoisomer (d.r. 2:1 determined by integration of ^{1}H-NMR signal: δ_{major} 6.46 d, δ_{minor} 6.08 ppm d). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 7/1) in 82% yield (as a 2:1 mixture of diastereoisomers) and 98% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 80/20 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: Major diastereoisomer (98% *ee*): τ_{major} = 13.3 min, τ_{minor} = 16.3 min; Minor diastereoisomer can't be separated. HRMS *calcd.* for ($C_{25}H_{19}NO_5$+Na): 436.1161, found 436.1173. $[\alpha]_D^{25}$= -240.2 (c = 0.8, $CHCl_3$, d.r .2:1, 98% ee_{major}).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.75-2.82 (m, 1H), 2.97 (dd, *J* = 4.76, 16.2 Hz, 1H, minor), 3.07 (dd, *J* = 7.76, 16.56 Hz, 1H, major), 3.62 (dd, *J* = 6.4, 16 Hz, 1H, major), 3.45 (dd, *J* = 5.6, 16.32 Hz, 1H, minor), 3.69-3.73 (m, 2H), 3.78-3.96 (m, 4H), 6.05 (d, *J* = 8. Hz, 1H, minor), 6.42 (d, *J* = 8. Hz, 1H, major), 6.73-6.93 (m, 7H), 7.02- 7.05(m, 8H), 7.24-7.30 (m, 3H), 7.90 (d, *J* = 8.4 Hz, 2H, minor), 8.09 (d, *J* = 8.8 Hz, 2H, major)ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.1, 41.6, 42.0, 42.1, 45.6, 46.3, 46.7, 47.5, 54.9, 55.6, 110.6, 110.8, 123.5, 123.62, 123.64, 123.8, 125.0, 125.8, 127.0, 127.3, 128.0, 128.1, 128.3, 128.5, 128.6, 129.1, 129.5, 129.6, 129.7, 130.1, 138.4, 144.7, 145.9, 152.4, 152.5, 177.4, 208.3, 208.6 ppm.

(1'R,2'S,6'R)-2'-phenyl-6'-propyl-2H-spiro[benzofuran-3,1'-cyclohexane]-2,4'-dione (**14d**)

14d



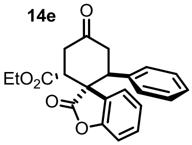
The reaction was carried out at 60 °C following the general procedure to furnish the crude product as a single diastereoisomer. The title compound was isolated as a white solid by preparative TLC (toluene/AcOEt = 100/1) in 40% yield (as a single diastereoisomer) and 91% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 80/20 hexane/*i*-

PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{minor} = 5.67 min, τ_{major} = 6.23 min; HRMS *calcd.* for ($C_{22}H_{22}O_3$+Na): 357.1467, found 357.1456. $[\alpha]_D^{25}$= -118.2 (c =0.55, $CHCl_3$, dr 1.5:1, 98% ee_{major}, 88% ee_{minor}).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (t, *J* = 7.2 Hz, 3H), 1.03-1.12 (m, 1H), 1.25-1.43 (m, 3H), 2.53-2.67 (m, 3H), 3.07 (dd, *J* = 4.0 Hz, 15.6, 1H), 3.55-3.65 (m, 2H), 6.78-6.81 (m, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 7.07-7.28 (m, 5H), 7.39 (d, *J* = 8.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 20.4, 33.3, 40.5, 42.0, 47.2, 55.8, 110.9, 124.0, 124.9, 127.8, 128.0, 128.3, 128.4, 129.0, 129.3, 137.0, 153.0, 178.1, 209.9 ppm.

(1'S,2'R,6'S)-ethyl 2,4'-dioxo-6'-phenyl-2H-spiro[benzofuran-3,1'-cyclohexane]-2'-carboxylate (14e)

14e

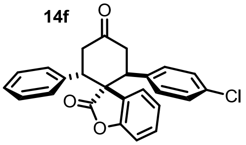


The reaction was carried out at 60 °C following the general procedure to furnish the crude product as a 2.2/1 mixture of diastereoisomer (d.r. 2.2:1 determined by HPLC). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 10/1) in 77% yield (as a 2.2:1 mixture of diastereoisomers) and 85% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 90/10 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: Major diastereomer (85% *ee*): τ_{major} = 16.35 min, τ_{minor} = 17.45 min; Minor diastereomer (>99% *ee*):τ_{major} = 14.7 min, $[\alpha]_D^{25}$= -57.2 (c= 0.58, $CHCl_3$, 2.2:1 d.r., 85% ee_{major}, >99%ee_{minor}).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.0 (t, *J* = 7.2 Hz, 3H), 2.63-2.68 (m, 1H), 2.80-2.86 (m, 1H), 3.32 (dd, *J* = 5.6, 1.6 Hz, 1H), 3.42-3.63 (m, 2H), 6.75-6,91 (m, 3H), 7.06-7.29 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.73, 13.76, 38.3, 39.6, 41.9, 42.2, 46.4, 46.6, 50.60, 50.61, 52.3, 52.5, 61.6, 61.8, 110.6, 110.7, 122.2, 123.9, 124.1, 124.4, 127.9, 128.0, 128.2, 128.40, 128.44, 129.4, 129.8, 136.2, 136.3, 153.0, 153.2, 170.0, 170.8, 175.7, 176.7, 206.2, 207.2 ppm.

(1'R,2'S,6'S)-2'-(4-chlorophenyl)-6'-phenyl-2H-spiro[benzofuran-3,1'-cyclohexane]-2,4'-dione (14f)

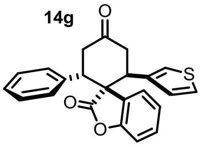
14f



The reaction was carried out at 60 °C following the general procedure to furnish the crude product as a 4/1 mixture of diastereoisomers (d.r. 3.5:1 determined by integration of ^{1}H NMR signal: δ_{major} 6.05 d, δ_{minor} 6.24 ppm. d). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 85/15) in 85% yield (as a 3.4:1 mixture of diastereoisomers) and 97% *ee*. HPLC analysis on a Daicel Chiralpak IC column: 80/20 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: Major diastereomer (97% *ee*): τ_{minor} = 12.9 min, τ_{major} = 15.9 min; Minor diastereomer (96% *ee*): τ_{minor} = 13.5 min, τ_{major} = 14.5 min. HRMS *calcd.* for ($C_{25}H_{19}Cl\ O_3$+Na): 425.0920, found 425.0938. $[\alpha]_D^{25}$= -130.6 (c = 1.07, $CHCl_3$, dr 4:1, 97% ee_{major}, 96% ee_{minor}).

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.71-2.84 (m, 1H), 2.91-3.01 (m, 1H), 3.53.3.88 (m, 4H), 6.05 (d, 1H, *J* = 7.5 Hz major), 6.24 (d, 1H, *J* = 7.5 Hz minor), 6.75.-6.98 (m, 6H), 7.01-7.13 (m, 3H), 7.22-7.34 (m, 3H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 41.7 (CH2), 42.5 (CH2), 45.3 (CH), 47.5 (CH), 55.3 (C), 110.5 (CH), 123.3 (CH), 125.8 (CH), 127.6 (C), 128.0 (CH), 128.1 (CH), 128.5 (CH), 128.6 (C), 128.6 (C), 128.7 (C), 129.3 (CH), 129.4 (CH), 129.5 (CH), 130.8 (C), 133.7 (C), 135.9 (C), 138.8 (C), 152.5 (C), 177.7 (C), 209.2 (C) ppm.

(1'R,2'S,6'R)-2'-phenyl-6'-(thiophen-3-yl)-2H-spiro[benzofuran-3,1'-cyclohexane]-2,4'-dione (14g)


14g

The reaction was carried out at 60 °C following the general procedure to furnish the crude product as a 4/1 mixture of diastereoisomers (d.r. 4:1 determined by integration of ^{1}H-NMR signal: δ_{major} 6.02 d, δ_{minor} 6.07 ppm. d). The title compound was isolated as a white solid by column chromatography (hexane/Acetone = 95/5) in 91% yield (as a 4:1 mixture of diastereoisomers) and 96% *ee*. HPLC analysis on a Daicel Chiralpak IA column: 95/5 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: Major diastereomer (96% *ee*): τ_{minor} = 18.7 min, τ_{major} = 24.4 min; Minor diastereomer (93% *ee*): τ_{minor} = 17.3 min, τ_{major} = 19.6 min. $[\alpha]_D^{25}$= -99.1 (c = 0.78, CHCl$_3$, dr 4:1, 96% ee_{major}, 93% ee_{minor}).

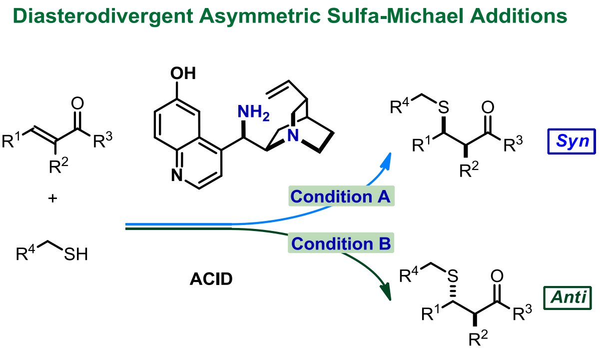
^{1}H NMR (400 MHz, CDCl$_3$): δ 2.72-2.95 (m, 2H), 3.54.3.84 (m, 4H), 3.94 (dd, 1H, *J*1 = 13.7, *J*2= 4.2 Hz), 6.02 (d, 1H, *J* = 7.5 Hz major), 6.07 (d, 1H, *J* = 7.5 Hz minor), 6.47 (dd, 1H, *J*1= 5.2, *J*2= 1.4 Hz), 6.70-6.73 (m, 1H), 6.75-6.88 (m, 2H), 6.91-6.94 (m, 2H), 6.99 (dd, 1H, *J*1= 4.9, *J*2= 2.9 Hz), 7.02-7.16 (m, 2H), 7.26-7.30 (m, 2H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 41.5 (CH), 41.8 (CH2), 42.9 (CH2), 47.3 (CH), 55.1 (C), 110.4 (CH), 122.9 (CH), 123.3 (CH), 125.7 (C), 125.8 (CH), 125.9 (CH), 126.8 (CH), 128.0 (C), 128.1 (CH), 128.5 (CH), 128.6 (CH), 129.1 (CH), 129.5 (CH), 138.2 (C), 139.1 (C), 139.7 (C), 152.8 (C), 177.9 (C), 209.3 (C) ppm.

Chapter III

Diastereodivergent Asymmetric Sulfa-Michael Additions of α-Branched Enones

Target

Fully control the diastereo- and enantio-selectivity of the asymmetric conjugate addition of alkyl thiols to α-substituted α,β-unsaturated ketones, a class of carbonyls that has never before succumbed to a catalytic approach, using a single chiral organic catalyst.



Tool

The ability of the cinchona primary amine catalyst to activate hindered carbonyl compounds.[1]

3.1 Background

3.1.1 Activating a Challenging Carbonyl Substrate

In the past decade, asymmetric aminocatalysis has become a fundamental synthetic strategy for the stereoselective functionalization of carbonyl compounds.[2,3] In particular, the iminium ion activation of α,β-unsaturated carbonyl compounds has served for the design of highly enantioselective Michael additions of a wide variety of nucleophiles (Scheme 1). Initial studies have mainly focused on chiral secondary aminocatalysts, such as the phenylalanine-derived

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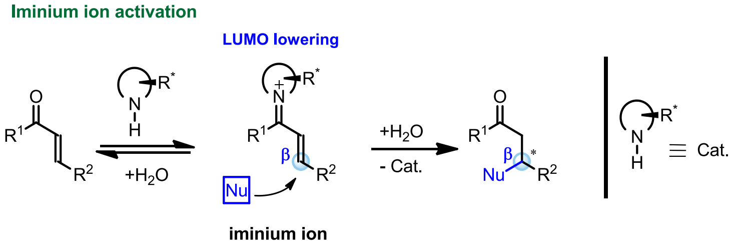
[1] The work discussed in this chapter has been published, see: X. Tian, C. Cassani, Y. Liu, A. Moran, A. Urakawa, P. Galzerano, E. Arceo, P. Melchiorre. Diastereodivergent Asymmetric Sulfa-Michael Additions of α-Branched Enones using a Single Chiral Organic Catalyst. *J. Am. Chem. Soc.*, **2011**, *133*, 17934. Experimental part developed together with X. Tian (optimization of the *syn*-selective system).

[2] P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli. Asymmetric Aminocatalysis-Gold Rush in Organic Chemistry. *Angew. Chem. Int. Ed.*, **2008**, *47*, 6138.

[3] S. Bertelsen, K. A. Jørgensen. Organocatalysis - After the Gold Rush. *Chem. Soc. Rev.*, **2009**, *38*, 2178.

imidazolidinones (MacMillan catalyst),[4] to effectively activate simple enals.



Scheme 1. Iminium Ion Activation Mode. Nu = nucleophile.

In the last few years, researchers have recognized that chiral primary amines offer new opportunities for expanding the applicability and synthetic potential of iminium ion activation. In particular, 9-amino(9-deoxy)*epi* cinchona alkaloids, primary amines easily derived from natural sources,[5] have enabled the stereoselective functionalization of a variety of sterically hindered carbonyl compounds, which cannot be functionalized using secondary amines (Figure 1).

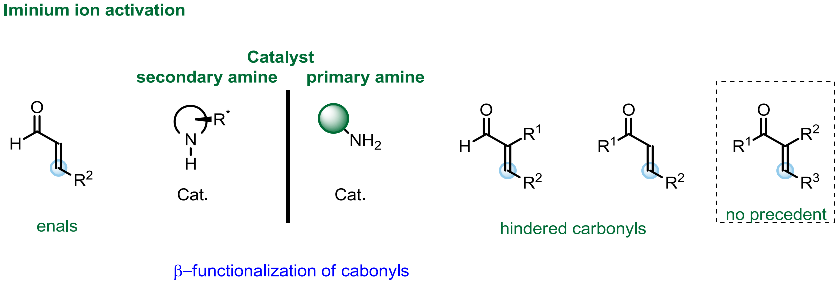


Figure 1. Classes of α,β-Unsaturated Carbonyl Compounds Amenable to Iminium Ion Activation with Chiral Primary Amines.

The unique ability of the cinchona-based primary amines in generating congested covalent intermediates with hindered carbonyl compounds allowed the iminium ion activation of challenging substrates, such as enones and α-branched enals.[6,7] However, catalytic activation of α,β-disubstituted unsaturated ketones remains an elusive and difficult target, in particular when considering that an alternative asymmetric metal-catalyzed strategy for the functionalization of this compound class is also lacking.

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[4] G. Lelais, D. W. C. MacMillan. Modern Strategies in Organic Catalysis: The Advent and Development of Iminium Activation, *Aldrichimica Acta*, **2006**, *39*, 79.

[5] P. Melchiorre. Cinchona-Based Primary Amine Catalysis in the Asymmetric Functionalization of Carbonyl Compounds. *Angew. Chem. Int. Ed.*, **2012**, *51*, 9748.

[6] P. Ricci, A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Mechiorre. Organocatalytic Asymmetric Sulfa-Michael Addition to α,β-Unsaturated Ketones. *Adv. Synth. Catal.*, **2008**, *350*, 49.

[7] P. Galzerano, F. Pesciaioli, A. Mazzanti, G. Bartoli, P. Melchiorre. Asymmetric Organocatalytic Cascade Reactions with α-Substituted α,β-Unsaturated Aldehydes. *Angew. Chem. Int. Ed.*, **2009**, *48*, 7892.

3.1.2 Aminocatalyzed Sulfa-Michael Addition (SMA)

Since the first asymmetric organocatalyzed variant reported by Wynberg in 1981,[8] the sulfa-Michael addition (SMA) reaction has become a bench-mark for the asymmetric β-functionalization of α,β-unsaturated carbonyls. Moreover, among the existing methods for the preparation of chiral sulfur containing molecules, the asymmetric SMA is nowadays of prime importance.[9]

Our research group has recently demonstrated the versatility of cinchona-based primary amines in the context of the stereoselective iminium-ion catalyzed SMA of alkyl thiols to both α,β-unsaturated enones[6] and α-branched α,β-unsaturated aldehydes[7] (Figure 2a and b respectively).

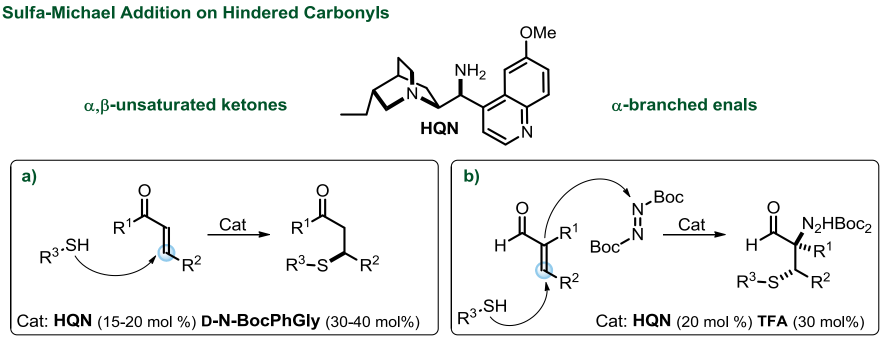

Figure 2. Precedent Aminocatalytic SMA on: a) Enones;[6] b) α-Branched Enals.[7] TFA= trifluoroacetic acid; D-N-BocPhGly = Boc-D-α-phenylglycine.

Both reports rely on the ability of **HQN**, a quinine-based primary amine, to effectively engage in the iminium ion formation with encumbered carbonyls while promoting the asymmetric SMA with high selectivity.

3.1.3 Relative and Absolute Stereocontrol

Asymmetric catalysis relies on a chiral agent to control the stereochemical outcome of a reaction. If the desired product has just one chiral center, it is usually straightforward to prepare either enantiomer by using the appropriate enantiomer of the catalyst. Reactions that generate two chiral centers in one product represent a much harder challenge. There is no obvious means of modifying a catalyst to modulate the relative configuration of two stereogenic centers; in

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[8] H. Hiemstra, H. Wynberg. Addition of Aromatic Thiols to Conjugated Cycloalkenones, Catalyzed by Chiral β-Hydroxy Amines. A Mechanistic Study on Homogeneous Catalytic Asymmetric Synthesis. *J. Am. Chem. Soc.*, **1981**, *103*, 417.

[9] For a review, see: D. Enders, K. Lüttgen, A. Narine. Asymmetric Sulfa-Michael Additions. *Synthesis*, **2007**, 959.

some cases, it may be necessary to pursue entirely different approaches to bond construction in order to obtain each distinct diastereoisomer (Figure 3).

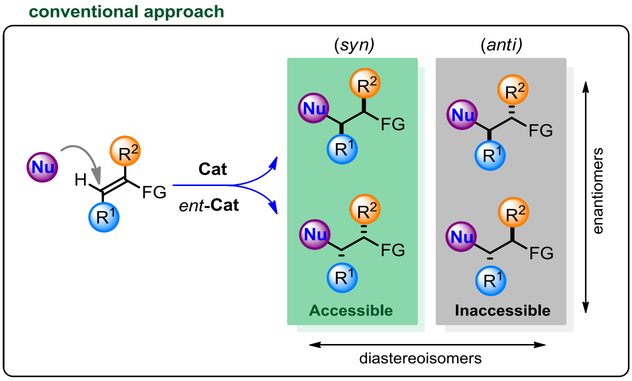

Figure 3. Typical Scenario for Enantio- and Diastereo-selective Addition Reaction in which the Judicious Choice of the Catalyst Enantiomer Enables the Selective Synthesis of only a Single Enantiomeric Pair of the Product.

Conjugate additions to α,β-disubstituted unsaturated carbonyls generate two adjacent stereocenters through an addition/protonation tandem sequence. Obviously, all attempts to design a stereocontrolled variant of this process must address the challenge of diastereo- as well as enantio-selectivity.

In the case of the iminium ion activated addition on α,β-disubstituted unsaturated ketones, this requires the ability of a chiral catalyst to (i) effectively activate the highly hindered keto-moiety, while (ii) selectively shielding one of the two faces of the electrophilic unsaturated π-system to forge the β-stereocenter with high fidelity. Finally, (iii) strict control over the transient enamine geometry is necessary to ensure a catalyst-directed protonation event (Figure 4).

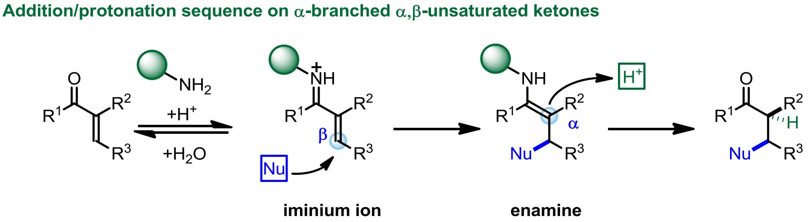

Figure 4. Catalytic Activation of α-Branched Enones.

From a wider perspective, the complex stereoselectivity issues inherent to this type of chemical transformation provided us the opportunity to face the challenge of accessing the complete matrix of stereoisomers using a single chiral catalyst.

Mirror image products (complementary enantioselectivity) can be individually provided by the enantiomeric pair of a chiral catalyst. However, researchers are largely still not able to modulate the diastereoselectivity (control over the relative stereochemistry) using a single chiral catalyst. A diastereochemical switch generally requires the use of distinct chiral catalysts[10,11,12] or ligands,[13] the addition of different Lewis acids,[14] or tailored substrate modifications.[15] Less explored is the approach of changing the reaction conditions to tune the functions of a single catalyst (Figure 5).[16]

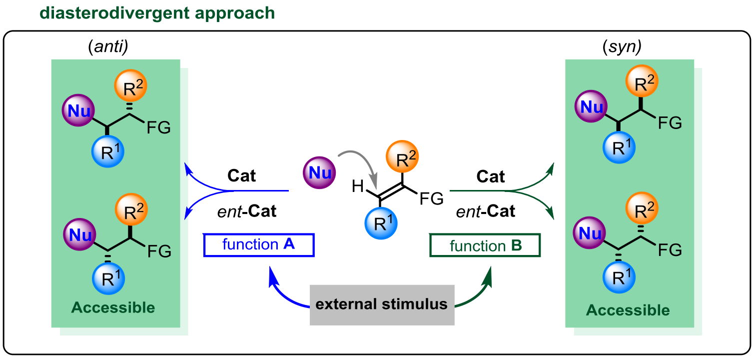

Figure 5. Diastereodivergent Approach Based on a Single Chiral Catalyst.

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[10] B. Wang, F. Wu, Y. Wang, X. Liu, L. Deng. Control of Diastereoselectivity in Tandem Asymmetric Reactions Generating Nonadjacent Stereocenters with Bifunctional Catalysis by Cinchona Alkaloids. *J. Am. Chem. Soc.*, **2007**, *129*, 768.

[11] For strategies that use two cyclic specific aminocatalysts to achieve the modular control of the enforced sense of enantio- and diastereoinduction in tandem reactions, see: a) B. Simmons, A. M. Walji, D. W. C. MacMillan. Cycle-Specific Organocascade Catalysis: Application to Olefin Hydroamination, Hydro-oxidation, and Amino-oxidation, and to Natural Product Synthesis. *Angew. Chem. Int. Ed.*, **2009**, *48*, 4349. b) Y.Chi, S. T. Scroggins, J. M. J. Fréchet. One-Pot Multi-Component Asymmetric Cascade Reactions Catalyzed by Soluble Star Polymers with Highly Branched Non-Interpenetrating Catalytic Cores. *J. Am. Chem. Soc.*, **2008**, *130*, 6322.

[12] S. Krautwald, D. Sarlah, M. A. Schafroth, E. M. Carreira. Enantio- and Diastereodivergent Dual Catalysis: α-Allylation of Branched Aldehydes. *Science*, **2013**, *340*, 1065.

[13] a) X.-X. Yan, Q. Peng, Q. Li, K. Zhang, J. Yao, X.-L. Hou, Y.-D. Wu. Highly Diastereoselective Switchable Enantioselective Mannich Reaction of Glycine Derivatives with Imines. *J. Am. Chem. Soc.*, **2008**, *130*, 14362. b) M. Luparia, M. T. Oliveira, D. Audisio, F. Frébault, R. Goddard, N. Maulide. Catalytic Asymmetric Diastereodivergent Deracemization. *Angew. Chem. Int. Ed.*, **2011**, *50*, 12631.

[14] a) A. Nojiri, N. Kumagai, M. Shibasaki. Linking Structural Dynamics and Functional Diversity in Asymmetric Catalysis. *J. Am. Chem. Soc.*, **2009**, *131*, 3779. b) G. Lu, T. Yoshino, H. Morimoto, S. Matsunaga, M. Shibasaki. Stereodivergent Direct Catalytic Asymmetric Mannich-Type Reactions of α-Isothiocyanato Ester with Ketimines. *Angew. Chem. Int. Ed.*, **2011**, *50*, 4382.

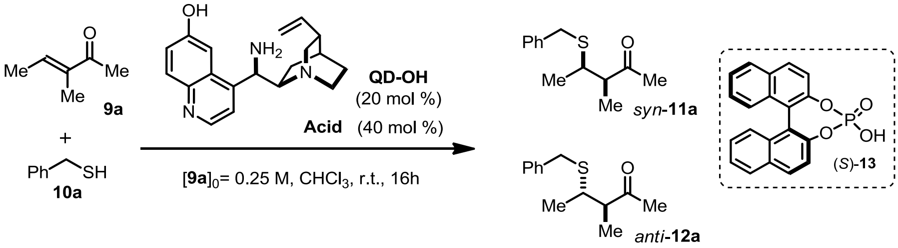
[15] J. D. Huber, J. L. Leighton. Highly Enantioselective Imine Cinnamylation with a Remarkable Diastereochemical Switch. *J. Am. Chem. Soc.*, **2007**, *129*, 14552.

[16] a) J. Gao, S. Bai, Q. Gao, Y. Liu, Q. Yang. Acid Controlled Diastereoselectivity in Asymmetric Aldol Reaction of Cycloketones with Aldehydes Using Enamine-Based Organocatalysts. *Chem. Commun.*, **2011**, *47*, 6716. b) M. Bandini, P. G. Cozzi, A. Umani-Ronchi. Salen as a Chiral Activator: *anti* versus *syn* Switchable Diastereoselection in the Enatioselective Addition of Crotyl Bromide to Aromatic Aldehyde. *Angew. Chem. Int. Ed.*, **2000**, *39*, 2327. c) A. B. Northrup, D. W. C. MacMillan. Two-Step Synthesis of Carbohydrates by Selective Aldol Reactions. *Science*, **2004**, *305*, 1752.

3.2 Preliminary Results

The unique versatility of the cinchona-based primary amines to functionalize hindered substrates with constantly high stereoselectivity was recently tested against the most severe of trials, the activation of α,β-disubstituted unsaturated ketones. Considering the synthetic usefulness of simple alkyl S-centered nucleophiles, we focused on the conjugate addition of benzylmercaptan **10a** to the α-branched enone **9a** as the model reaction. We first screened the effect of the acidic co-catalyst (Table 1).

Table 1. Preliminary Results.[a]



entry	Acid	pK_a	Conv (%)[b]	d.r.[b] syn/anti	ee (%)[c] syn-11a	ee (%)[c] anti-12a
1	no	-	29	5 : 1	65	49
2	CH_3CO_2H	4.76	35	7 : 1	77	17
3	$PhCO_2H$	4.20	40	9 : 1	82	59
4	*2*-Naphtoic acid	4.17	45	7 : 1	83	43
5	*o*-F-$C_6H_4CO_2H$	3.27	42	**6 : 1**	**89**	55
6	*o*-OH-$C_6H_4CO_2H$	2.98	24	2 : 1	73	93
7	*o*-NO_2-$C_6H_4CO_2H$	2.17	15	1.3 : 1	72	86
8[d]	TFA	0.23	13	1 : 1.15	3	92
9[d]	(*S*)-**13**	<2	28	1 : 1.3	35	93
10[e]	(*S*)-**13**	<2	62[f]	**1 : 6.2**	<5	**98**

[a] Reactions carried out at r.t. on a 0.05 mmol scale using 2 equiv of **10a** and [**9a**]$_0$ = 0.25 M in $CHCl_3$. Reaction time 16h. pK_a values refer to water. [b] Determined by ^1H NMR analysis of the crude mixture. [c] Determined by GC analysis on a chiral stationary phase. [d] Reaction carried out using 30 mol% of the acid. [e] Reaction performed in acetone at 40 °C, [**9a**]$_0$= 0.5 M, 10 mol% of a 1:1 ratio of **QD-OH**:(*S*)-**13** was used. [f] Yield of the isolated product **12a** after 60 h of reaction time. TFA = trifuoroacetic acid.

This transformation generates two adjacent stereocenters through a conjugate addition/protonation tandem sequence, leading to the *syn*-**11a** and *anti*-**12a** products. In the absence of an acidic additive, the catalyst afforded the selective formation of the *syn* product **11a** with a moderate level of enantiomeric excess (*ee*) (entry 1). Under these conditions, the catalytic profile of amine **QD-OH** is dictated by the tertiary bridgehead amine, which likely channels the SMA reaction through a general base-catalyzed mechanistic pathway.

We then sought to favor the iminium ion activation of the enone **9a** by the addition of an acid co-catalyst that, by protonating the quinuclidine moiety, would suppress the chemical handle necessary for base-catalysis while providing the acidic conditions required for iminium ion formation.[17] The primary amines deriving from the cinchona alkaloids are indeed characterized by a dichotomous catalytic behavior. These organic molecules can execute their catalytic functions using both covalent and non-covalent-based organocatalysis. It is a remarkable coincidence that the free base catalyst (acting as a general base activator) provides a similar selectivity with respect to the **QD-OH**/benzoic acid system, which operates under iminium ion activation (compare entries 1 and 3-7 in Table 1).

Various benzoic acid derivatives were tested and, together with **QD-OH**, they effectively promoted the SMA reaction, imparting a good level of *syn* diastereoselection and moderate to good enantio-induction (entries 3-7). Evaluation of the reaction media indicated chloroform as the best solvent. Notably, a 1 : 2 ratio of amine to *ortho*-fluorobenzoic acid offered an effective catalytic system for achieving *syn* diastereoselectivity while inferring high enantiomeric excess (*ee* = 88%, Table 1, entry 5).

Surprisingly, the use of stronger acid (pK_a in water <2.5, Table 1**,** entries 6-9) greatly altered the stereochemical outcome of the reaction. The loss of diastereocontrol was accompanied by a remarkable decrease in the enantiomeric excess of the *syn*-**11a** adduct, while the *anti*-**12a** optical purity grew up to 93% *ee* (Table 1, entries 8 and 9). We thus undertook extensive optimization studies (not shown) to identify a catalytic system capable of a high level of *anti* diastereoinduction. These optimization studies showed that the combination of amine **QD-OH** with the commercially available chiral phosphoric acid (*S*)-**13** in a 1:1 ratio (10 mol %), led to the *anti* diastereoisomer **12a** with good diastereoselectivity and excellent enantioselectivity when acetone was used as the solvent at 40 °C (entry 10, Table 1).

Further experiments, detailed in Table 2, were conducted to determine whether the addition/protonation reaction sequence was entirely under the control of the catalyst and not governed by thermodynamic factors. The absence of any substantial diastereoselectivity in the presence of a strong base or an achiral iminium-forming catalyst (Table 2, entries 1 and 2) excluded the possibility of a selective pathway induced by substrate control. Moreover, control experiments indicated that the *anti*-**12a** adduct is the thermodynamic product. Indeed, in the absence of any catalyst, a thermally induced reaction at 100 °C gave the final product in a *syn/anti* ratio of 1 : 4 (Table 2 entry 3). No epimerization was observed when the products *syn*-**11a** and *anti*-**12a** were mixed with the amino catalyst under the reaction conditions.

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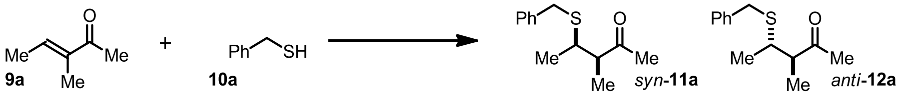
[17] The iminium ion formation from primary amines is greatly accelerated by the presence of an acid, see: J. Hine. Bifunctional Catalysis of α-Hydrogen Exchange of Aldehydes and Ketones. *Acc. Chem. Res.*, **1978**, *11*, 1 and references therein.

Table 2. Achiral Base and Iminium Ion Activation.[a]



entry	Catalyst *(mol%)*	*Acid (mol%)*	Conv. (%)[b]	d.r.[b] *syn/anti*
1	DBU (20)	no	67	1:1.6
2	$BnNH_2$ (30)	TFA (30)	60	1.8:1
3[c]	-	-	full	1:4

[a] Reactions carried out using 2 equiv of **10a** and $[\mathbf{9a}]_0$ = 0.5 M in toluene on a 0.05 mmol scale at r.t.. Reaction time = 16 h. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] Neat reaction performed at 100 °C. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; $BnNH_2$ = benzylamine.

3.3 Further Observations

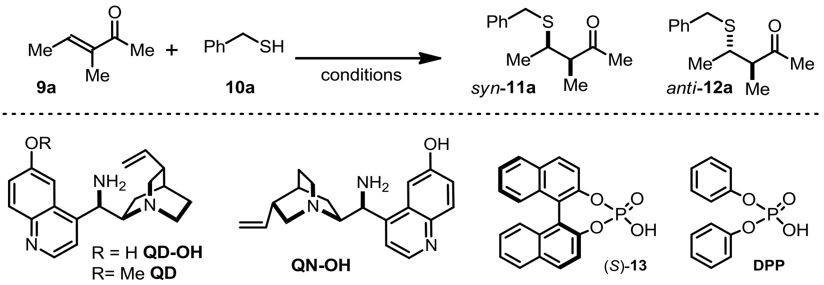
The initial results indicated that the pK_a of the acidic additive and the reaction media can be used to switch the sense of the catalyst's diastereoselection, thereby affording either the enantioenriched *syn* or *anti* product on demand. To gain more insight into the factors responsible for the uncommon diastereo-switching behavior of amine **QD-OH**, we further studied the model SMA reaction of **10a** and enone **9a** (Table 3).

First, we evaluated the influence of the hydroxyl group at the 6' position of the catalyst scaffold. The primary amine **QD**, directly derived from natural quinidine, in combination with benzoic acid, promoted the *syn* SMA reaction of **10a** and **9a** in chloroform leading to product *syn*-**11a** with slightly lower stereoselectivity than catalyst **QD-OH** (compare entries 1 and 2, Table 3).

In marked contrast, when amine **QD** was mixed with the chiral phosphoric acid (*S*)-**13** in acetone to promote the SMA reaction, the *anti* diastereoisomer **12a** was obtained with very high enantioselectivity but with essentially no control over the relative stereochemistry (compare entries 3 and 4, Table 3). The results underline how the hydrogen bonding donor moiety at the 6' position of the cinchona scaffold was essential to channel the reaction toward an *anti*-diastereoselective pathway.

The *anti*-diastereoselective pathway, however, was also strictly dependent on the choice of solvent and the nature of the strong acid employed. The amine **QD-OH**/*ortho*-fluorobenzoic acid combination, which proved to be effective for promoting the *syn*-diastereoselective reaction in chloroform, led to poor stereocontrol when used in acetone (entry 5, Table 3), while the amine **QD-OH**/(*S*)-**13** catalyst salt did not provide relative stereocontrol in chloroform (entry 6, Table 3). Moreover, when a strong acid other than the phosphoric acid derivative was used in combination with amine **QD-OH** (*e.g.*, TFA, entry 7, Table 3), a complete loss of diastereoselectivity was observed although the *anti*-**12a** isomer was generated with very high enantiomeric purity. These results suggest that the constructive cooperation of three crucial parameters is necessary for inducing the *anti*-diastereoselectivity. These parameters are (i) the hydroxyl group at the 6' position of the catalyst **QD-OH**, (ii) the nature of the reaction medium, and (iii) the strong hydrogen-bonding ability of the phosphate anion. Each of these factors, individually, is necessary but not alone sufficient for switching the catalyst's diastereochemical preference.

Table 3. Catalyst's Scaffold, Solvent and Acid Effect.[a]



entry	Catalyst (*mol%*)	Acid *(mol%)*	Solvent	T (°C)	Conv (%)[b]	d.r.[b] *syn/anti*	*ee* (%)[c] *syn/anti*
1	**QD-OH**(20)	*o*-F-$C_6H_4CO_2H$(40)	$CHCl_3$	25	42	6:1	88/59
2	**QD**(20)	*o*-F-$C_6H_4CO_2H$(40)	$CHCl_3$	25	26	7:1	77/n.d.
3	**QD-OH**(10)	(*S*)-**13**(30)	acetone	40	62	1:6.2	<5/98
4	**QD**(10)	(*S*)-**13**(30)	acetone	40	25	1:1.7	n.d/97
5	**QD-OH**(20)	*o*-F-$C_6H_4CO_2H$(40)	acetone	25	35	2.1:1	30/83
6	**QD-OH**(20)	(*S*)-**13** (30)	$CHCl_3$	40	28	1:1.3	35/93
7	**QD-OH**(10)	TFA(10)	acetone	40	18	1:1.7	n.d./89
8	**QD-OH**(20)	-	acetone	40	14	4.5:1	<5/<5
9	-	(*S*)-**13**(40)	acetone	40	18	4.2:1	<5/<5
10	**QD-OH**(10)	(*R*)-**13**(10)	acetone	40	39	1:5.2	n.d./96
11	**QD-OH**(10)	**DPP**(10)	acetone	40	52	1:6.2	<5/98
12	**QN-OH**(10)	(*S*)-**13**(10)	acetone	40	51	1:4.2	n.d./92
13	**QN-OH**(10)	(*R*)-**13**(10)	acetone	40	43	1:3.9	n.d./94
14	**QN-OH**(10)	**DPP**(10)	acetone	40	66	1:2.5	n.d./94

[a] Reactions carried out using 2 equiv of **10a** and [**9a**]$_0$ = 0.25M in $CHCl_3$ or acetone on a 0.05 mmol scale. Reaction time 16 h. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] Determined by GC analysis on a chiral stationary phase. TFA = trifuoroacetic acid; DPP = diphenyl hydrogen phosphate.

Within this context, it is intriguing to consider how combining the amine **QD-OH** and the acid **13** results in a unique mechanistic pathway. The two discrete catalysts, when operating individually under general base and Brønsted acid catalysis respectively, still promoted the SMA addition in acetone but inducing a *syn*-selective racemic pattern (entries 8 and 9, Table 3).

Finally, to gain insight into the specific role played by the two chiral entities of the **QD-OH**/**13** catalyst salt, we used the mismatched catalysts combination to promote the *anti*-SMA reaction (compare entries 3 and 10, Table 3). The combination of amine **QD-OH** with (*R*)-**13** provided lower reactivity and slightly decreased stereoselectivity (96% *ee* against 98% *ee*). This suggests that the chiral primary amine is the main cause of the enantioselectivity of the process, while the chiral phosphoric acid co-catalyst is needed to induce an *anti*-diastereoselective pathway. The minor influence of the phosphoric acid chiral backbone on the enantioselectivity of the final product prompted us to investigate the effect of diphenyl hydrogen phosphate (**DPP**) as the achiral co-catalyst. As shown in Table 3 (entry 11), **DPP** led to comparable results, in terms of reactivity and stereoselectivity, to those obtained with the chiral acid **13**. This further supported the notion that, while the hydrogen-bonding ability of the phosphate counteranion strongly influences the structural assembly of the iminium intermediate (*vide infra*), its chirality is not essential for the stereochemical outcome of the asymmetric transformation.

Interestingly, the opposite configuration of the SMA product could be accessed by simply selecting the appropriate enantiomer of the aminocatalyst. Thus, combining the pseudo-enantiomeric catalyst **QN-OH** (derived from quinine) with (*R*)-**13**, (*S*)-**13**, or **DPP**, affords *anti*-**12a** with the opposite absolute configuration while maintaining a high level of selectivity (entries 12-14, Table 3).

Mechanistic Considerations.

We propose that the same general mechanism (covalent organocatalysis through the iminium ion activation of α-branched enones) is operative in the two stereodivergent chemical pathways. The conceptual framework for rationalizing the diastereodivergent behavior of amine **QD-OH** is as follows: the addition of acidic additives and the change of the reaction medium induce a three-dimensional structural modification of the active intermediate's framework (Figure 6). Altering the chiral catalyst conformation may in turn reflect on different catalyst-substrate specific interactions and distinct transition state structures that could direct the transformation through diastereodivergent pathways.

Changing the reaction conditions, including solvent and temperature,[18] or using light,[19] has already been reported in asymmetric catalysis in order to modulate the chiral environment in which an enantioselective catalytic reaction takes place, thus leading to enantiodivergent reaction outcomes. This strategy provided individual access to either of the product enantiomers from a single enantiomer of the chiral synthetic catalyst. Our results suggest that the synthetic potential of chiral molecules whose catalytic function changes in response to an external stimulus can be further expanded to attack challenging problems in chemical synthesis: modulating the enforced sense of diastereoselectivity on demand using a single chiral catalyst.

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[18] Y. Sohtome, S. Tanaka, K. Takada, T. Yamaguchi, K. Nagasawa. Solvent-Dependent Enantiodivergent Mannich-Type Reaction: Utilizing a Conformationally Flexible Guanidine/Bisthiourea Organocatalyst. *Angew. Chem. Int. Ed.*, **2010**, *49*, 9254.

[19] J. Wang, B. L. Feringa. Dynamic Control of Chiral Space in a Catalytic Asymmetric Reaction Using a Molecular Motor. *Science*, **2011**, *331*, 1429.

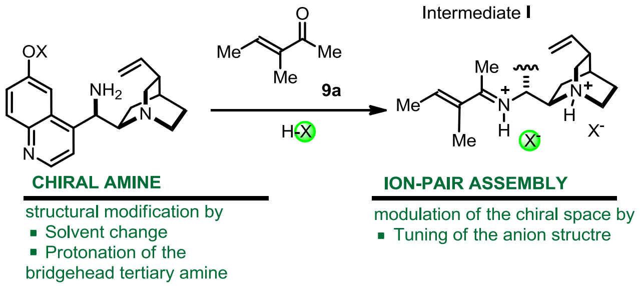

Figure 6. Switching the Diastereoselectivity of the Chiral Amine **QD-OH** by Exploiting the Catalyst's Conformational Flexibility and the Tunable Nature of the Ion Pair Intermediate **I**. H-X: acidic additive.

The following two factors may explain the induced alteration of the chiral space where the sulfa-Michael reaction takes place (Figure 6):

(i) *Flexibility of the Cinchona Scaffold*. Cinchona alkaloid derivatives like **QD-OH** possess a high degree of conformational flexibility in solution,[20] and three-dimensional structural switches can be induced by different chemical stimuli, such as solvent change[20a] or protonation of the N-quinuclidine moiety.[21] Since the catalytic function of the cinchona scaffold is intimately related to its spatial architecture, a conformational change may induce an alternative environment in which the C-S bond forming step takes place, allowing for a change in the diastereoselectivity. It has already been shown how modulation of the solvent polarity directly reflects on the ability of a cinchona catalyst to induce a preferred geometry in the product formed during an asymmetric transformation.[22] In this respect, vibrational circular dichroism (VCD), circular dichroism (CD) and nuclear magnetic resonance (NMR) spectroscopic analyses of the **QD-OH**/*ortho*-fluorobenzoic acid and **QD-OH**/diphenyl hydrogen phosphate combinations have been carried out. These studies have been conducted by Dr. Atsushi Urakawa, group leader at ICIQ, and Dr. Antonio Moran, a postdoctoral fellow working in our group, in the frame of a collaborative mechanistic investigation. Their experiments have provided insight into the conformational behavior of each

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[20] a) T. Bürgi, A. Baiker. Conformational Behavior of Cinchonidine in Different Solvents: A Combined NMR and ab Initio Investigation. *J. Am. Chem. Soc.*, **1998**, *120*, 12920. b) G. D. H. Dijkstra, R. M. Kellogg, H. Wynberg, J. S. Svendsen, I. Marko, K. B. Sharpless. Conformational Study of Cinchona Alkaloids. A Combined NMR, Molecular Mechanics, and X-ray Approach. *J. Am. Chem. Soc.*, **1989**, *111*, 8069. c) A. Urakawa, D. M. Meier, H. Rüegger, A. Baiker. Conformational Behavior of Cinchonidine Revisited: A Combined Theoretical and Experimental Study. *J. Phys. Chem. A*, **2008**, *112*, 7250.

[21] R. A. Olsen, D. Borchardt, L. Mink, A. Agarwal, L. J. Mueller, F. Zaera. Effect of Protonation on the Conformation of Cinchonidine. *J. Am. Chem. Soc.*, **2006**, *128*, 15594.

[22] M. Aune, A. Gogoll, O. Matsson. Solvent Dependence of Enantioselectivity for a Base-Catalyzed 1,3-Hydrogen Transfer Reaction. A Kinetic Isotope Effect and NMR Spectroscopic Study. *J. Org. Chem.*, **1995**, *60*, 1356.

catalytic system in chloroform and acetone. Interestingly, it was found that, whereas the two catalytic salts did not show clear chiroptical distinctions, a change of the solvent greatly altered their ground-state conformations.

(ii) *Modular Nature of the Ion-Pair Molecular Assembly.* Amine **QD-OH**, which bears a pendant primary amino moiety, can effectively condense with hindered carbonyls,[23] in the presence of an acidic additive to form a reactive catalytic species, the iminium ion intermediate (intermediate **I** in Figure 6). The distinctive feature of such an ion pair assembly as a chiral molecular catalyst is that its stereocontrolling ability can be fine-tuned by structurally modifying both the cation and the anion.[24] We investigated further to evaluate the influence of the counteranions on the catalyst's function. Previous observations indicated that substituting the carboxylate with a phosphate anion induces the functional change in the ion-pair molecular assembly **I**. The results detailed in Figure 7 show how the *syn* to *anti* switch of the catalyst's diastereoselectivity seems to strongly depend on the hydrogen-bonding ability of the acid-anion.[25]

Indeed phosphates are strong H-bond acceptors. (*S*)-**13** or **DPP** can induce a catalyst conformational change, promoting an *anti*-selective reaction manifold. However, when bulkier phosphates (which bind more weakly to the catalyst) are used, a *syn*-selective pathway for the SMA reaction is dominant. This is presumably because of the reduced binding ability of the anion, which cannot induce a change in the catalyst conformation.

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[23] G. Bencivenni, P. Galzerano, A. Mazzanti, G. Bartoli, P. Melchiorre. Direct asymmetric vinylogous Michael Addition of Cyclic Enones to Nitroalkenes *via* Dienamine Catalysis. *Proc. Natl. Acad. Sci. USA,* **2010**, *107*, 20642.

[24] The foundations for rationalizing the influence of chiral counteranion on both the reactivity and stereoselectivity of iminium ion catalysis have been established. List and co-workers have recently introduced asymmetric counterion directed catalysis (ACDC) as an efficient strategy for enantioselective transformations that proceed *via* cationic species, including iminium ion intermediates, see: M. Mahlau, B. List. Asymmetric Counteranion-Directed Catalysis: Concept, Definition, and Applications. *Angew. Chem. Int. Ed.*, **2013**, *52*, 518.

[25] C. Yang, X.-S. Xue, J.-L. Jin, X. Li, J.-P. Cheng. Theoretical Study on the Acidities of Chiral Phosphoric Acids in Dimethyl Sulfoxide: Hints for Organocatalysis. *J. Org. Chem.*, **2013**, *78*, 7076.

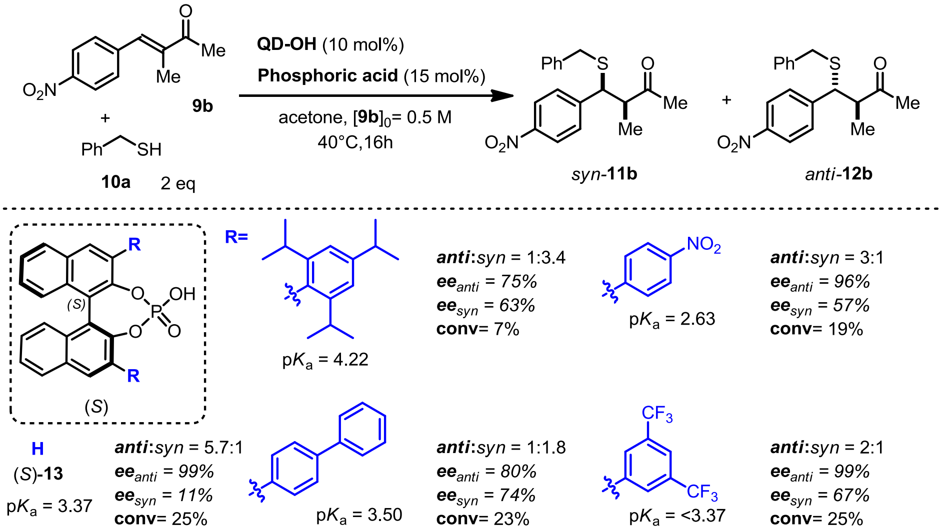

Figure 7. Correlation between the Catalyst's Selectivity Switch and the Hydrogen-Bonding Ability of the Phosphate Anion.[26]

Together with the conformational flexibility of amine **QD-OH**, the use of structurally different counteranions can provide distinct chiral environments in which the enantioselective SMA reaction can take place. This creates an opportunity for the design of a programmable organocatalyst with multiple stereochemical preferences. We are aware that important information on the active catalytic species can be obtained by characterizing the covalent reactive intermediate, the iminium ion assembly **I** (Figure 6) generated by condensation of the cinchona-based primary amine with the carbonyl compound. This would provide a more reliable picture of the mechanism. In general, however, the nature of ion pairs in iminium ion-catalyzed reactions is poorly understood and only very recently it became the focus of different mechanistic studies.[27]

Our attempts to detect the covalent active intermediate **I** by CD and NMR spectroscopic studies did not produced informative results.

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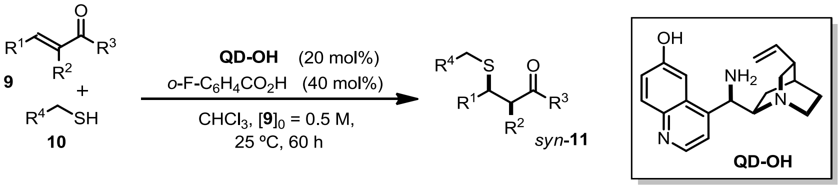
[26] When bulkier phosphates than (*S*)-**13** are used, a *syn*-selective pathway is dominant, presumably due to a weaker binding ability of the anion. Interestingly, the inductive effect of electron withdrawing groups (p-NO_2 and CF_3 moieties) at the 3- and 3'-substituents of phosphoric acids preserved the *anti*-diastereoselectivity. The pK_a values are measured DMSO, as given in ref 25. For the CF_3 substituted phosphoric acid the pK_a value is not available: inductive effects should presumably render this compound more acidic than **13**.

[27] a) A. Moran, A. Hamilton, C. Bo, P. Melchiorre. A Mechanistic Rationale for the 9-Amino(9-deoxy)*epi* Cinchona Alkaloids Catalyzed Asymmetric Reactions *via* Iminium Ion Activation of Enones. *J. Am. Chem. Soc.*, **2013**, *135*, 9091. b) O. Lifchits, M. Mahlau, C. M. Reisinger, A. Lee, C. Farès, I. Polyak, G. Gopakumar, W. Thiel, B. List. *J. Am. Chem. Soc.*, **2013**, *135*, 6677.

3.4 Optimization and Scope of the *syn*-SMA

The first cycle of optimization experiments revealed that *ortho*-fluorobenzoic acid was the preferred acidic co-catalyst to induce a *syn*-selective SMA (see Table 1, entry 5). This prompted us to initiate a second screening of the reaction conditions using this acidic co-catalyst. Chloroform was identified as the best reaction medium while a 1 : 2 ratio of amine **QD-OH** to *ortho*-fluorobenzoic acid offered the most effective catalytic system. The number of equivalents of thiol was increased to three to ensure a faster reaction time. These reaction conditions were selected to evaluate the scope of the *syn*-SMA (Table 4).

Table 4. Substrate Scope – *syn*-Selective SMA.[a]



entry	R^1	R^2	R^3	R^4	**11**	Yield(%)[b]	d.r.[c] *syn/anti*	*ee* (%)[d] *syn*-**11**
1	Me	Me	Me	Ph	**a**	68	5.1:1	86
2	4-NO_2-C_6H_4	Me	Me	Ph	**b**	79	5.1:1	88
3[e]	4-NO_2-C_6H_4	Me	Me	Ph	**b**	50	3.5:1	77
4	Ph	Me	Me	Ph	**c**	54	3.5:1	85
5	4-Br-C_6H_4	Me	Me	Ph	**d**	60	3.8:1	89
6	4-NO_2-C_6H_4	Et	Me	Ph	**e**	68	9.3:1	87
7	4-NO_2-C_6H_4	Me	Et	Ph	**f**	40	5.0:1	81
8	Et	Ph	Me	Ph	**g**	60	2.8:1	73
9	Me	Me	Me	4-MeO-C_6H_4	**h**	56	4.9:1	90
10	Me	Me	Me	4-Cl-C_6H_4	**i**	65	5.0:1	89
11	Me	Me	Me	$CH=CH_2$	**j**	60	7.8:1	87
12	Me	Me	Me	CO_2Et	**k**	68	5.5:1	61

[a] Reactions carried out using 3 equiv of **10** and [**9**]$_0$ = 0.5 M in $CHCl_3$ on a 0.2 mmol scale at 25 °C. Reaction time 60 h.[b] Yields of the isolated product. [c] Determined by ^1H NMR analysis of the crude mixture. [d] Determined by GC or HPLC analysis on a chiral stationary phase. [e] Reaction performed at 15 °C over 5 days with catalyst **QN-OH** leading to the opposite enantiomer: *syn*-(3*S*,4*R*)-**11b**.

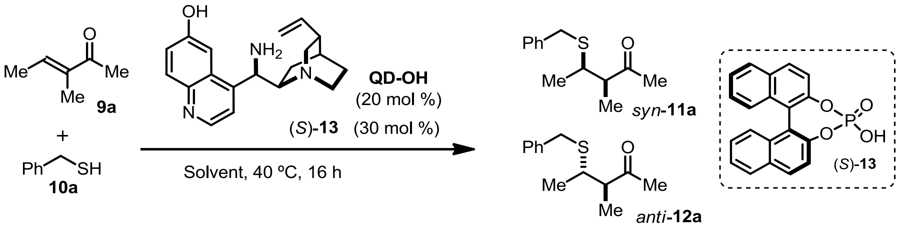
The catalytic system showed a wide substrate generality and high levels of diastereoselectivity and enantiocontrol. Both aliphatic and aromatic substituents at the β-position were well-tolerated (Table 4, entries 1-7). The presence of a more sterically demanding group at the branched R^2 α-position or at the R^3 position did not drastically influence the reactivity profile of the catalytic system with the corresponding *syn*-adducts **11e-g** being obtained in good chemical yield and high levels of stereocontrol (entries 6-8). Remarkably, a broad range of alkyl mercaptans, containing either aromatic groups or a vinyl moiety, could be used in the *syn*-

selective SMA reaction (entries 9-11). Moreover, a thioglycolate derivative also was found to be a suitable nucleophilic component of this reaction (entry 12).

3.5 Optimization and Scope of the *anti*-SMA

The observation that strong acids and in particular (*S*)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (*S*)-**13**, completely reversed the diastereoselectivity of the SMA reaction leading to the *anti*-product with good enantioselectivity (entry 9, Table 1), prompted us toward a further optimization of the reaction conditions. Results of a solvent screening are reported in Table 5.

Table 5. Solvent Screening – *anti*-Selective SMA[a]



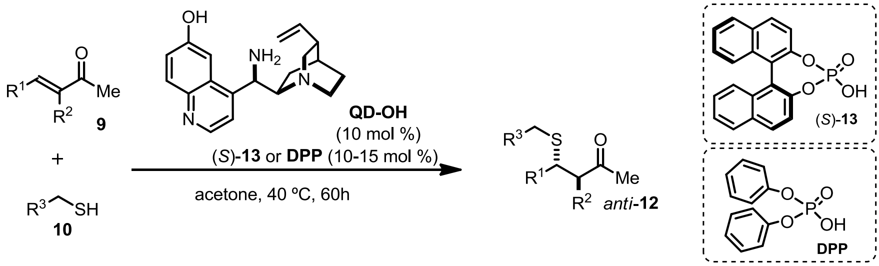
entry	solvent	Conv (%)[b]	d.r.[b] *syn*/*anti*	*ee* (%)[c] *syn*-**11a**	*ee* (%)[c] *anti*-**12a**
1	DMSO	51	8:1	<5	<5
2	EtOH	74	1.8:1	31	84
3	THF	<10	1:1	45	93
4	AcOEt	49	1:1	24	93
5	$CHCl_3$	28	1:1.3	36	93
6	DMF	34	1:2	26	90
7	Dioxane	42	1:2.1	33	97
8	DCE	14	1:2.7	37	96
9	H_2O	0	-	-	-
10	**Acetone**	**37**	**1:6.2**	**53**	**97**
11	Acetone $_{(anh.)}$	38	1:6.2	50	97

[a] Reactions carried out using 1.2 equiv of **10a** and [**9a**]$_0$ = 0.25 M in the specified solvent on a 0.05 mmol scale at 40 °C. Reaction time = 16 h. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by GC analysis on a chiral stationary phase. DMSO = dimethylsulfoxide; THF = tetrahydrofuran; DMF = N,N-dimethylformamide; DCE = 1,2-dichloroethane; Dioxane = 1,4 dioxane; anh. =anhydrous.

The solvent plays a crucial role in determining the stereochemical outcome of the reaction. Clearly, the use of acetone strongly increases the diastereoselectivity, by favoring the *anti*-product formation (entry 10). Performing the reaction with dry acetone resulted in no change in the outcome of the reaction, suggesting that water does not affect the reactivity or the selectivity of the SMA. Extensive reaction screening showed that a 1 to 1 acid/catalyst combination was optimal for substrates bearing aliphatic groups, while an acid/catalyst ratio of 1.5 to 1 ensured better selectivity in the SMA of β-aromatic substituted enones. Careful tuning of the reagent concentration and the temperature allowed us to decrease the catalyst loading to 10 mol%.

With the optimized condition for the *anti*-SMA in hands we investigated the substrate scope of the reaction. Since the chirality of the acid co-catalyst was only marginally responsible for the stereoselectivity of the process, achiral and cheaper phosphoric acids were also tested in the reaction (see Table 3). Between them, diphenyl hydrogen phosphate **DPP** was chosen as the most effective alternative: the results, obtained employing it as the acidic co-catalyst, are reported between parentheses in Table 6.

Table 6. Substrate Scope – *anti*-Selectivity.[a]



entry	R^1	R^2	R^3	**12**	Yield(%)[b]	d.r.[c] *syn/anti*	*ee* (%)[d] *anti*-**12**
1	Me	Me	Ph	**a**	80 (68)	6.2:1 (6.1:1)	98 (98)
2	Me	Me	Ph	**a**	43 (66)	3.9:1 (3.0:1)	94 (94)[e]
3	4-NO_2-C_6H_4	Me	Ph	**b**	77(56)	5.7:1	99 (96)
4[e]	4-NO_2-C_6H_4	Me	Ph	**b**	48	2.8:1	97
5	CH_2Bn	Me	Ph	**c**	69	8.2:1	97
6	Ph	Me	Ph	**d**	41(44)	5.2:1 (5.1:1)	99 (95)
7	4-NO_2-C_6H_4	Et	Ph	**e**	35	1.8:1	98
8	4-MeO-C_6H_4	ME	Ph	**f**	42	4.2:1	99
9	4-Br-C_6H_4	Me	Ph	**g**	59(38)	6.5:1 (6.3:1)	99 (96)
10	4-Cl-C_6H_4	Me	Ph	**h**	58(59)	5.3:1 (5.3:1)	99 (98)
11	2-thiophenyl	Me	Ph	**i**	44	4.2:1	98
12	CO_2Et	Me	Ph	**j**	56	5.2:1	96
13	Me	Me	4-MeO-C_6H_4	**k**	42(68)	7.1:1 (7.0:1)	98 (98)
14	Me	Me	4-Cl-C_6H_4	**l**	58(71)	7.2:1 (4.2:1)	94 (97)
15	Me	Me	$CH=CH_2$	**m**	73	4.8:1	98
16	Me	Me	CO_2Et	**n**	50(65)	2.4:1 (2.0:1)	92 (83)

[a] Results in parentheses refer to the reactions catalyzed by the **QD-OH**/diphenyl phosphoric acid (**DPP**) combination. Reactions carried out using 2 equiv of **10** and $[\mathbf{9}]_0$ = 0.5 M in acetone on a 0.2 mmol scale at 40 °C. Reaction time = 60 h. When the β-substituent of enones **9** is an aromatic group, 15 mol% of the phosphoric acid (*S*)-**13** has been used. Other substrates perform better in the presence of 10 mol% of (*S*)-**13**. *ee* value refers to the major *anti*-**12** compound. [b] Yields of the isolated product. [c] Determined by ^{1}H NMR analysis of the of the crude mixture. [d] Determined by GC or HPLC analysis on a chiral stationary phase. [e] Reaction performed with catalyst **QN-OH**, leading to the opposite enantiomer of *anti*-**12**.

The *anti*-selective SMA protocol, powered by the phosphoric acid (*S*)-**13** (10 mol%, 1:1 with **QD-OH** when the β-substituent is aliphatic, 1.5:1 when aromatic) offers a wide scope for both the electrophilic and nucleophilic components, affording the desired adducts **12** with a synthetically useful diastereomeric ratio and very high enantioselectivity (*ee*'s ranging from 92 to 99%). The results reported in Table 6 illustrate how a variety of substituents at the β-position can be accommodated without affecting the efficacy of the catalytic system. Different substituents at the aromatic moiety, regardless of their electronic properties, and an ester group are tolerated (entries 1-12). Moreover, using different alkyl thiols opens up fast access to optically active chiral sulfur compounds bearing orthogonally removable S-protecting groups (entries 13-16). Importantly, variation in the steric contribution of the R^2 ketone substituent has a strong influence on the *anti*-catalytic system. An ethyl group at the R^2 position drastically reduces the reaction efficiency (entry 7), while every substituent on the carbonylic carbon, different from the methyl, suppresses the *anti*-selective reaction.

3.6 Switching Diastereo-selection during the Reaction

We then wondered if it would be possible to switch the diastereoselectivity of catalyst **QD-OH** on demand during the course of the reaction and in the same reaction flask. We thought that, between the two acids of choice selected for the diastereodivergent reactions, the stronger acid, namely the achiral phosphoric acid **DPP**, would reset the previous function by creating a tighter chiral ion pair with the catalyst.

Initially, we used a combination of **QD-OH** and *ortho*-fluorobenzoic acid to select the *syn*-directing pathway for the reaction between thiol **10a** and enone **9b** in chloroform, leading to the adduct *syn*-**11b** (Figure 8). Then, the use of 1:1 molar ratio of the phosphoric acid **DPP** ($pK_a \approx 1.9$ in H_2O) to amine **QD-OH** likely leads to a quantitative association with the quinuclidine tertiary amine moiety, the most basic site of the catalyst, thus displacing *ortho*-fluorobenzoic acid ($pK_a = 3.27$ in H_2O) from the acid-base equilibrium with **QD-OH**. Acetone (2:1 ratio to the original chloroform) was added followed by a different enone substrate **9a** in the same flask. An *anti*-selective addition of thiol **10a** to **9a** proceeded to afford *anti*-**12a** with a high level of stereocontrol, demonstrating the change in catalyst function.[28] In this experiment, both *syn*- and *anti*-products were synthesized in the same reaction flask using a single catalyst, and then individually isolated by chromatographic purification.

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[28] The catalyst's *syn*-preference is deactivated when the achiral phosphoric acid (DPP) is added to the reaction medium. A control experiment revealed that catalyst **QD-OH** (20 mol%), when mixed with 40 mol% of *ortho*-fluorobenzoic acid and 20 mol% of (*S*)-**13** in acetone, is programmed for an *anti*-directing function. The reaction between **9a** and **10a** afforded the *anti*-adduct **12a** with 4.6:1 dr and 97% ee_{anti}. The chiral acid (*S*)-**13** was also used to switch the diastereoselectivity of catalyst **QD-OH** during the course of the reaction, in a similar experiment to that detailed in Figure 8.

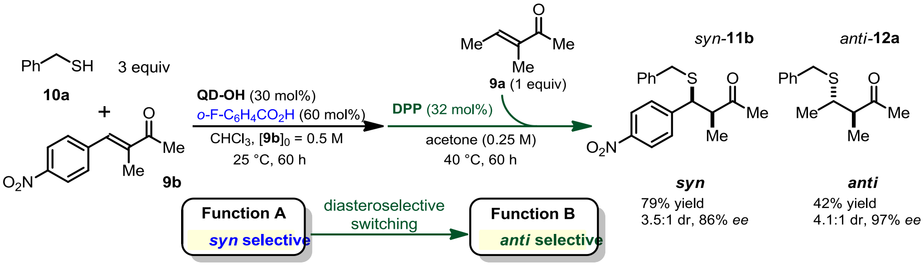


Figure 8. Switching Diastereoselectivity during the Course of the Reaction.

3.7 Accessing the Full-Matrix of Stereoisomers

After the optimization of the two *syn*- and *anti*-pathways, the ability to selectively orientate the reaction manifolds toward complementary diastereochemical outcomes using a single chiral catalyst was exploited to access the full matrix of possible stereoisomeric products of the SMA reaction (Figure 9). When carried out in chloroform, the *ortho*-fluorobenzoic acid/**QD-OH** combination induces a *syn*-selective outcome of the SMA of **10a** to enone **9b** (bearing an aryl β-substituent). In acetone, the phosphoric acid (*S*)-**13** switches the catalyst's induction toward *anti*-selectivity. The same designer acid-induced diastereoselectivity switching behavior was observed with the *pseudo*-enantiomeric catalyst **QN-OH**, derived from quinine, thus allowing access to the full matrix of possible stereo-isomeric products of the SMA reaction.

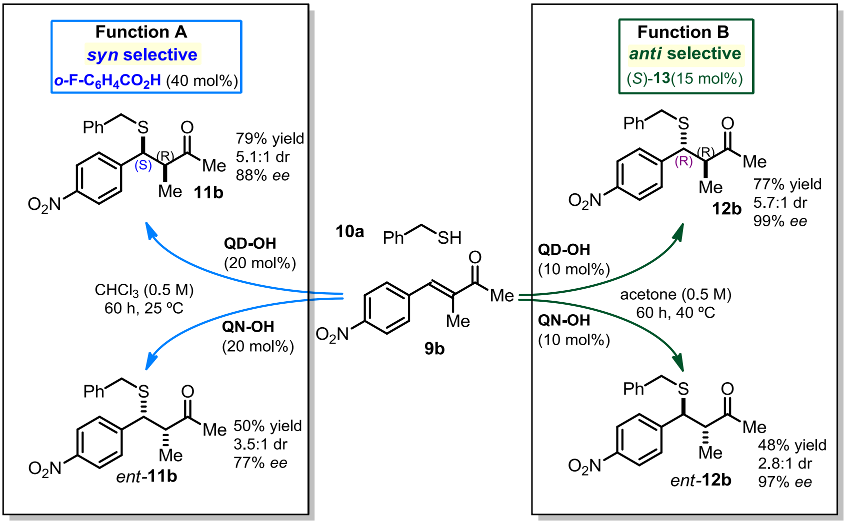
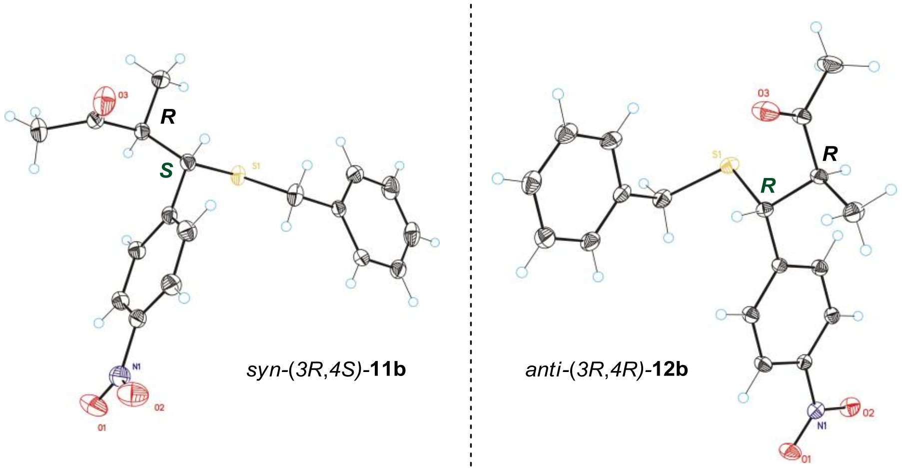


Figure 9. Accessing the Full Matrix of the Stereoisomers of the SMA Reaction.

The relative and absolute configurations of the *syn*- and *anti*-products **11b** and **12b** were unambiguously determined by anomalous dispersion X-ray diffraction analysis (Figure 10).



syn-(3*R*,4*S*)-**11b**

anti-(3*R*,4*R*)-**12b**

Figure 10. X-Ray Structure of **11b** and **12b**.[29]

The fact that the products are not diastereomeric at the α but at the β carbon (the site of the initial nucleophilic attack) is rather intriguing. The opposite absolute configuration at the β carbon-sulfur stereogenic center of the *syn*- and *anti*-products **11b** and **12b** was largely unexpected, since the conjugate addition step (in contrast to the protonation step) must be under the stereocontrol of the catalyst. This inspired us to carefully consider an alternative explanation for the observed stereochemical outcome: specifically that the switch of the catalyst functions is connected with completely unrelated mechanisms of catalysis.

3.8 Another Mechanistic Hypothesis

We based our thought on the dichotomous catalytic profile of the 6'-hydroxy-9-amino(9-deoxy)*epi* quinidine catalyst **QD-OH**. We have already commented on the potential for this amine to use two completely distinct modes of catalysis for activating the reagents of the SMA reaction, executing its catalytic functions using both covalent and non-covalent-based organocatalysis.[23,30]

In the early 1980s, Wynberg showed that the basic bridgehead nitrogen in the quinuclidine core of the cinchona derivatives can be used in an asymmetric SMA reaction to activate thiols *via* a

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[29] Crystallographic data for compounds **11b** and **12b** are available free of charge from the Cambridge Crystallographic Data Centre, accession numbers CCDC 804889 and CCDC 804888 respectively.

[30] B. Tan, P. J. Chua, Y. Li, G. Zhong. Organocatalytic Asymmetric Tandem Michael-Henry Reactions: A Highly Stereoselective Synthesis of Multifunctionalized Cyclohexanes with Two Quaternary Stereocenters. *Org. Lett.*, **2008**, 10, 2437.

general base-catalysis mechanism (intermediate **II** in Figure 11).[8] Recently, the introduction of a primary amino moiety has led to the identification of cinchona-based primary amines of type **QD-OH** as effective covalent-based activators of carbonyl compounds *via* iminium ion formation (intermediate **I** in Figure 11). In particular, we have demonstrated its unique versatility in the context of the stereoselective iminium ion promoted SMA of alkyl thiols to both α,β-unsaturated enones and α-branched α,β-unsaturated aldehydes.[6,7]

Such a dichotomous catalytic profile of the cinchona catalyst **QD-OH** may offer the possibility of designing a programmable organocatalyst able to exert distinct catalytic functions. The challenge is to identify a suitable chemical stimulus to power and switch the functions of catalyst **QD-OH** between general base catalysis and iminium ion activation. In principle, an acidic additive could be used to modulate the catalyst behavior. The intrinsic catalytic profile of amine **QD-OH** is influenced by the tertiary amino moiety, which channels the SMA reaction through a general base mechanistic pathway (intermediate **II** in Fig. 11). However, adding an acidic co-catalyst with a suitable pK_a could switch the catalytic potential toward the iminium activation of the enone (intermediate **I** in Fig. 11). The change of function could be driven by two concomitant factors: the protonation of the quinuclidine moiety, which would prevent general base catalysis, while providing the acidic conditions required for iminium ion formation.

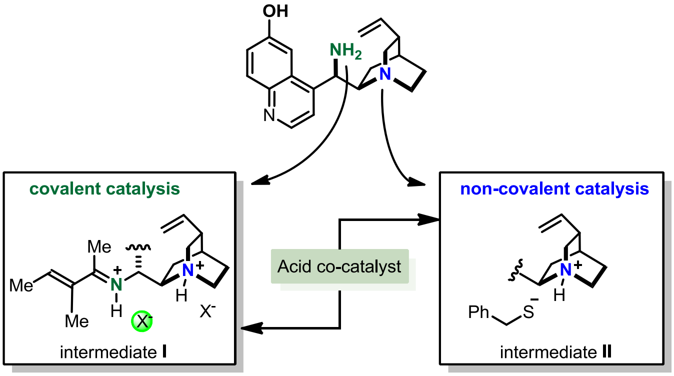

Figure 11. Dichotomous Catalysis Modes of **QD-OH**.

The opposite absolute configuration at the β carbon-sulfur stereogenic center of the *syn*- and *anti*-products **11b** and **12b** could be considered as evidence that the chiral amine **QD-OH** is catalyzing two stereo-divergent, mechanistically unrelated conjugate addition pathways when properly powered by an external signal (an appropriate acid). This mechanistic interpretation, however, would require the oxymoron of a base-catalyzed reaction proceeding under acidic conditions. The *syn*-selective reaction, indeed, proceeds in the presence of a weak acid (*ortho*-fluorobenzoic acid, Figure 12, center). However, it is of interest that this process, when promoted by **QD-OH** alone (Figure 12, left), thus working as a purely chiral-base, provides very similar results in terms of stereochemical outcome. It is indeed a remarkable casualty that the free base catalyst **QD-OH** (a general base catalyst) gives rise to similar selectivity with respect to the **QD-OH**/*ortho*-fluorobenzoic acid system, considering the latter as iminium ion promoter. In contrast, and in line with this hypothesis, a strong acid (pK_a < 2.5, Figure 12, right) greatly altered the stereochemistry of the model reaction, leading to the formation of the final product with the opposite configuration at the β-position.

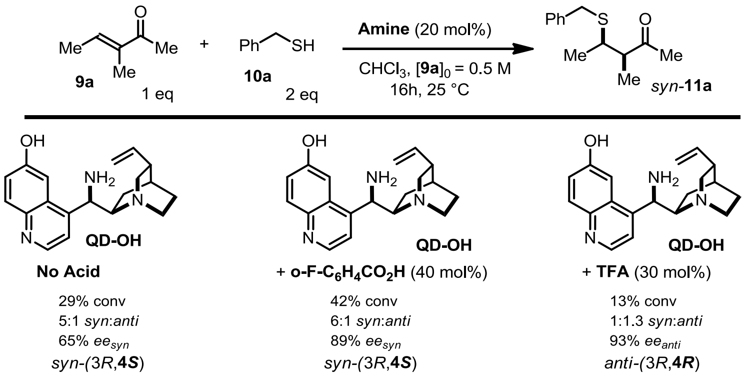

Figure 12. The Effect of the Acid.

It would be reasonable to propose that the relatively weak acidity of *ortho*-fluoro benzoic acid (pK_a = 3.27 in H_2O) may not lead to a quantitative association with the quinuclidine tertiary amine in **QD-OH**, thus providing the conditions for the catalyst **QD-OH** to still function as a general base activator using the tertiary moieties.[31] Nevertheless, to suggest that simple general base catalysis could occur under these acidic conditions is an extraordinary claim. Extraordinary claims require extraordinary evidence but, despite our many attempts, such evidence is still lacking.

At the present stage of investigation and mechanistic study, we consider that the more plausible mechanistic picture is the one described previously, where the same general mechanism (iminium ion activation) is operative in both pathways.

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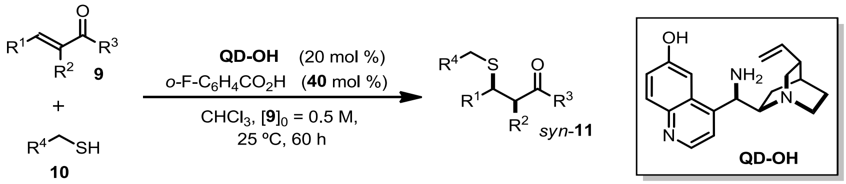
[31] Even though general base-catalysis is normally inhibited when an acidic additive is present, the use of a cinchona catalyst to act as a chiral base in the presence of benzoic acid is not without precedent, see: L. Liu, S. Zhang, F. Xue, G. Lou, H. Zhang, S. Ma, W. Duan, W. Wang, Catalytic Enantioselective Henry Reactions of Isatins: Application in the Concise Synthesis of (S)-(-)-Spirobrassinin. *Chem. Eur. J.*, **2011**, *17*, 7791.

3.9 Conclusions

We have described the possibility of using a single chiral catalyst to fully control the stereochemical outcome of the asymmetric conjugate addition of alkyl thiols to α,β-disubstituted unsaturated ketones, an elusive class of Michael acceptors. The judicious choice of a designer acidic additive and reaction medium switches the catalyst’s diastereoselectivity, establishing a direct connection between the enantioselective catalyst and the operator (the chemist). In this study, all the unique features of cinchona-based primary amines, including the flexibility of the cinchona scaffold and the modular nature of the ion pair assembly, both of which can be modified using external stimuli such as different acids and solvents, have been synergistically combined.

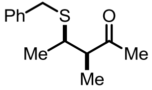
3.10 Experimental Section

3.10.1 General Procedure for the *syn*-Selective SMA of α-Branched Enones.



All the reactions were carried out in freshly distilled chloroform, without any precaution to exclude air and moisture (open air chemistry on the bench top). An ordinary vial equipped with a Teflon-coated stir bar and a plastic screw cap was charged with 6’-hydroxy-9-amino(9-deoxy)*epi* quinidine **QD-OH** (0.04 mmol, 12.4 mg, 20 mol%) and 0.4 mL of chloroform. Then, *ortho*-fluorobenzoic acid (0.08 mmol, 13.0 mg, 40 mol%) was added in one portion and the resulting solution was stirred at ambient temperature for 10 minutes. The SMA reaction was started by the sequential addition of the α,β-unsaturated α-branched ketone **9** (0.2 mmol) and the aliphatic thiol **10** (0.6 mmol, 3 equiv). The vial was sealed and immerged in a water bath (thermostated at 25 °C) and stirring continued over 60 hours. The crude mixture was flushed through a short plug of silica, using dichloromethane/diethyl ether 1:1 as the eluent (5 mL). Solvent was removed under reduced pressure and the crude mixture was analyzed by ^{1}H NMR spectroscopy to determine the diastereomeric ratio (d.r.) of the reaction. The SMA adducts **11** were isolated by flash column chromatography or preparative TLC.

(3R,4R)-4-(benzylthio)-3-methylpentan-2-one

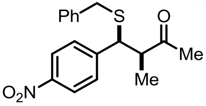


11a

(**11a**) The reaction was carried out at 25 °C following the general procedure to furnish the crude product as a 5.1:1 mixture of diastereoisomers: d.r. determined by integration of ^{1}H NMR signal: δminor 1.08 (d), δmajor 1.14 ppm (d). The title compound was isolated as a colorless oil by column chromatography (hexane/AcOEt = 50:1) in 68% yield and 86% *ee*. The enantiomeric excess was determined by GC analysis on chiral stationary phase (Astec CHIRALDEX G-TA column): 50 °C to 150 °C (ramp of 12 °C per minute), then isotherm at 150 °C, flow rate 1.000 mL/min: τ_{minor} = 39.3 min, τ_{major}= 40.2 min. HRMS *calcd.* for ($C_{13}H_{18}OS+Na$): 245.0976, found245.0969. $[\alpha]_D^{25}$= -34.3 (c = 0.65, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (d, *J* = 7.2, 3H, minor), 1.14 (d, *J* = 7.2, 3H, major), 1.29 (d, *J* = 6.9, 3H), 2.06 (s, 3H), 2.56-2.63 (m, 1H), 2.91-2.98 (m, 1H), 3.73 (q, *J* = 13.6, 2H), 7.21-7.26 (m, 1H), 7.28-7.33 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 20.3, 29.3, 35.5, 41.8, 52.4, 127.2, 128.6, 129.0, 138.4, 210.6 ppm.

(3R,4S)-4-(benzylthio)-3-methyl-4-(4-nitrophenyl)butan-2-one



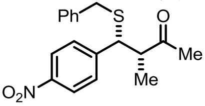
11b

(**11b**) The reaction was carried out at 25 °C following the general procedure to furnish the crude product as a 5.1:1 mixture of diastereoisomers: d.r. determined by integration of ^{1}H NMR signal: δminor 0.81 (d), δmajor 1.27 ppm (d). The title compound was isolated as a yellow solid by column chromatography (hexane/AcOEt = 10:1) in 79% yield and 88% *ee*. The enantiomeric excess was determined by HPLC analysis on a Daicel Chiralpak IA column: 97/3 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{major} = 13.8 min, τ_{minor} = 17.0 min. HRMS *calcd.* for ($C_{18}H_{19}NO_3S+Na$): 352.0983, found 352.0988. $[\alpha]_D^{26}$ -307.8 (c = 0.70, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (d, *J* = 6.8, 3H, minor), 1.27 (d, *J* = 7.2, 3H, major), 1.88 (s, 3H, major), 2.21 (s, 3H, minor), 2.95-3.03 (m, 1H), 3.35 (d, *J* = 13.2, 1H), 3.54 (d, *J* = 13.2, 1H), 3.98 (d, *J* = 9.8, 1H), 7.13-7.16 (m, 2H), 7.20-7.29 (m, 3H), 7.43 (d, *J* = 8.6, 2H), 8.15 (d, *J* = 8.6, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2, 29.6, 35.6, 36.5, 50.3, 50.9, 52.4, 123.8, 123.8, 123.8, 127.4, 127.4, 128.6, 128.6, 129.0, 129.0, 129.1, 129.4, 129.5, 137.0, 137.1, 147.0, 149.3, 209.1 ppm.

The relative and absolute configuration for *syn*-3b was unambiguously determined by anomalous dispersion X-ray crystallographic analysis.

(3S,4R)-4-(benzylthio)-3-methyl-4-(4-nitrophenyl)butan-2-one

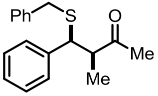


ent-**11b**

(*ent*-**11b**) The reaction was carried out at 15 °C over 5 days following the general procedure but using the quinine-based catalyst **QN-OH**, to furnish the crude product as a 3.5:1 mixture of diastereoisomers: d.r. determined by integration of ^{1}H NMR signal: δminor 0.81 (d), δmajor 1.27 ppm (d). The title compound was isolated as a yellow solid by column chromatography (hexane/AcOEt = 10/1) in 50% yield and 77% *ee*. Optical purity analyzed by HPLC analysis on a Daicel Chiralpak IA column: 97/3 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{minor} = 13.6 min, τ_{major} = 15.8 min. $[\alpha]_D^{25}$= +125.8 (c = 0.80, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ 0.81 (d, *J* = 7.2, 3H, minor), 1.27 (d, *J* = 7.2, 3H, major), 1.89 (s, 3H), 2.92-3.02 (m, 1H), 3.35 (d, *J* = 13.5, 1H), 3.54 (d, *J* = 13.5, 1H), 3.97 (d, *J* = 9.6, 1H), 7.13-7.16 (m, 2H), 7.21-7.29 (m, 3H), 7.43 (d, *J* = 8.4, 2H), 8.14 (d, *J* = 8.4,2H) ppm.

(3R,4S)-4-(benzylthio)-3-methyl-4-phenylbutan-2-one

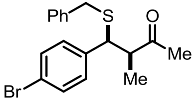


11c

(**11c**) The reaction was carried out at 25 °C following the general procedure to furnish the crude product as a 3.5:1 mixture of diastereoisomers; d.r. determined by integration of ^1H NMR signal: δminor 0.80 (d), δmajor 1.23 ppm (d). The title compound was isolated as a colorless oil by preparative TLC (toluene) in 54% yield and 85% *ee*. The enantiomeric excess was determined by HPLC analysis on a Daicel Chiralpak IC column: 98/2 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{major} = 8.84 min, τ_{minor} = 9.33 min. HRMS *calcd.* for ($C_{18}H_{20}OS+Na$): 307.1133, found 307.1138. $[\alpha]_D^{25}$= -140.7 (c = 0.55, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ 0.80 (d, *J* = 5.6, 3H, minor), 1.23 (d, *J* = 6.0, 3H, major), 1.81 (s, 3H, major), 2.06 (s, 3H, minor), 2.91-3.01 (m, 1H), 3.34 (d, *J* = 13.2, 1H), 3.48 (d, *J* = 13.2, 1H), 3.91 (d, *J* = 10.2, 1H), 7.16-7.17 (d, *J* = 4, 1H), 7.21- 7.28 (m, 5H), 7.30-7.32 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.0, 16.3, 29.1, 29.6, 35.2, 35.9, 51.1, 51.9, 52.4, 52.8, 127.1, 127.5, 127.6, 128,5, 128.5, 128.6, 128.7 ,128.7, 129.0, 129.1, 137.7, 137.9, 140.9,210.1, 210.6 ppm.

(3R,4S)-4-(benzylthio)-4-(4-bromophenyl)-3-methylbutan-2-one

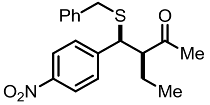


11d

(**11d**) The reaction was carried out at 25 °C following the general procedure to furnish the crude product as a 4:1 mixture of diastereoisomers; d.r. determined by integration of ^1H NMR signal: δminor 0.80 (d), δmajor 1.22 ppm (d). The title compound was isolated as a colorless oil by preparative TLC (toluene) in 60% yield and 89% *ee*. The enantiomeric excess was determined by HPLC analysis on a Daicel Chiralpak IC column: 98/2 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{major} = 9.7 min, τ_{minor} =10.9 min. HRMS *calcd.* for ($C_{18}H_{19}BrOS+Na$): 385.0238, found 385.0248. $[\alpha]_D^{25}$= -236.3 (c = 0.6, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ 0.80 (d, *J* = 6.8, 3H, minor), 1.22 (d, *J* = 7.6, 3H, major), 1.84 (s, 3H, major), 2.17 (s, 3H, minor), 2.89-2.96 (m, 1H), 3.33 (d, *J* = 13.2, 1H), 3.49 (d, *J* = 13.2, 1H), 3.86 (d, *J* = 9.2, 1H), 7.14-7.19 (m, 4H), 7.21-7.29 (m, 3H), 7.41-7.45 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.1, 16.2, 29.3, 29.7, 35.3, 36.0, 50.4, 51.1, 52.2, 52.6, 121.2, 127.2, 128.6, 128.6, 129.1 129.1 130.3, 130.4, 131.7, 131.8 137.6, 140.3, 209.7 ppm.

(R)-3-((S)-(benzylthio)(4-nitrophenyl)methyl)pentan-2-one

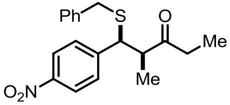


11e

(**11e**) The reaction was carried out at 25 °C following the general procedure to furnish the crude product as a 9.3:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δminor 0.73 (t), δmajor 0.86 ppm (t). The title compound was isolated as a yellow solid by column chromatography (hexane/AcOEt = 30/1) in 68% yield and 87% *ee*. The enantiomeric excess was determined by HPLC analysis on a Daicel Chiralpak IC column: 90/10 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{major} = 11.1 min, τ_{minor} = 12.1 min. HRMS *calcd.* for ($C_{19}H_{21}NO_3S$-H): 342.1164, found 342.1161. $[\alpha]_D^{25}$= -327.3 (c = 0.78, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.68 (t, *J* = 7.6, 3H, minor) 0.85 (t, *J* = 7.6, 3H, major), 1.77-1.87 (m, 4H), 1.94-2.03 (m, 1H), 2.96-3.02 (ddd, *J* = 3.5, 8.9, 10.6, 1H), 3.33 (d, *J* = 13.6, 1H), 3.54 (d, *J* = 13.6, 1H), 3.93 (d, *J* = 10.2, 1H), 7.16-7.18 (m, 2H), 7.25-7.32 (m, 3H), 7.41 (d, *J* = 9.3, 1H), 8.14 (d, *J* = 8.4, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.7, 23.4, 31.4, 35.3, 49.4, 58.7, 123.7, 123.8, 127.4, 128.6, 128.6, 128.9, 129.3, 129.5, 137.1, 147.0, 149.2, 209.2 ppm.

(1S,2R)-1-(benzylthio)-2-methyl-1-(4-nitrophenyl)pentan-3-one

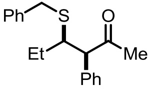


11f

(**11f**) The reaction was carried out at 25 °C following the general procedure to furnish the crude product as a 5.0:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δminor 0.77 (t), δmajor 1.0 ppm (t). The title compound was isolated as a yellow solid by column chromatography (hexane/AcOEt = 40:1) in 40% yield and 81% *ee*. Optical purity analyzed by HPLC analysis on a Daicel Chiralpak IA column: 97/3 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{major} = 10.3 min, τ_{minor} = 12.8 min; HRMS *calcd.* for ($C_{19}H_{21}NO_3S$ -H): 342.1164, found 342.1151. $[\alpha]_D^{25}$= -178.3 (c =0.70, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77 (t, *J* = 7.2, 3H, major), 1.0 (t, *J* = 7.2, 3H, minor), 1.27(d, *J* = 7.2, 3H) 1.87-1.97 (m, 1H), 2.28-2.38 (m, 1H), 2.95-3.02 (m, 1H), 3.36 (d, *J* = 13.2, 1H), 3.52 (d, *J* = 13.2, 1H), 3.98(d, *J* = 9.8, 1H), 7.13-7.15 (m, 2H), 7.21-7.32 (m, 3H), 7.42 (d, *J* = 8.2, 2H), 8.13(d, *J* = 8.2, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.45, 15.8, 35.6, 36.0, 51.2, 51.6, 123.7, 123.8, 127.4, 128.6, 128.8, 128.9, 129.4, 137.1, 149.5, 211.8 ppm.

(3R,4R)-4-(benzylthio)-3-phenylhexan-2-one



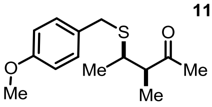
11g

(**11g**) The reaction was carried out at 25 °C following the general procedure to furnish the crude product as a 2.8:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δminor 0.76 (t), δmajor 0.97 ppm (t). The title compound was isolated as a colorless oil by column chromatography (hexane/AcOEt = 100/1) in 60% yield and 73% *ee* (single diastereomer). Optical purity analyzed by HPLC analysis on a Daicel Chiralpak AD column: 99/1 hexane/*i*-PrOH, flow rate

1.0 mL/min, λ = 254 nm: τ_{minor} = 6.1 min, τ_{major} = 7.0 min. HRMS *calcd.* for ($C_{19}H_{22}OS+Na$): 321.1289, found 321.1294. $[\alpha]_D^{25}$ = -94.08 (c = 0.80, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.2, 3H), 1.43-1.54 (m, 1H), 1.62-1.72 (m, 1H,), 2.08 (s, 3H), 3.10-3.22 (m, 3H), 3.79 (d, *J* = 10.4, 1H), 7.06-7.09 (m, 2H), 7.16-7.26 (m, 5H), 7.30-7.36 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.2, 26.9, 30.6, 36.3, 49.5, 64.6, 126.9, 127.8, 128.4, 128.7, 129.1, 129.6, 136.8, 138.3, 207.7 ppm.

(3R,4R)-4-((4-methoxybenzyl)thio)-3-methylpentan-2-one

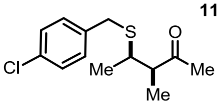


11h

(**11h**) The reaction was carried out at 25 °C following the general procedure to furnish the crude product as a 4.9:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δminor 1.09 (d), δmajor 1.15 ppm (d). The title compound was isolated as a colorless oil by column chromatography (hexane/AcOEt = 30/1) in 56% yield and 90% *ee*. The enantiomeric excess was determined by GC analysis on Astec CHIRALDEX GS15 TA column: 50 °C to 150 °C (ramp of 12 °C per minute), then isotherm at 150 °C for 40 minutes, and then from 150 °C to 170 °C(ramp of 12 °C per minute), flow rate 1.000 mL/min, τ_{minor} = 67.4 min, τ_{major} = 68.3 min. HRMS *calcd.* for ($C_{14}H_{20}O_2S+Na$): 275.1082, found 275.1090. $[\alpha]_D^{25}$= -27.7 (c = 0.70, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (d, *J* = 6.8, 3H, minor), 1.15 (d, *J* = 7.6, 3H, major), 1.28 (d, *J* = 7.2, 3H), 2.08 (s, 3H), 2.54-2.61 (m, 1H), 2.91-2.97 (m, 1H), 3.70 (q, *J* = 12.8, 2H), 3.8 (s, 3H), 6.82-6.86 (m, 2H), 7.21-7.25 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 20.3, 29.3, 34.9, 41.8, 52.3, 55.4, 114.0, 130.1, 130.3, 1508.8, 210.8 ppm

(3R,4R)-4-((4-chlorobenzyl)thio)-3-methylpentan-2-one

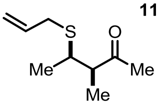


11i

(**11i**) The reaction was carried out at 25 °C following the general procedure to furnish the crude product as a 5.0:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δminor 1.08 (d), δmajor 1.14 ppm (d). The title compound was isolated as a colorless oil by column chromatography (hexane/AcOEt = 50:1) in 65% yield and 89% *ee*. The enantiomeric excess was determined by GC analysis on Astec CHIRALDEX GTA column: 50 °C to 170 °C (ramp of 12 °C per minute), then isotherm at 170 °C, flow rate 1.000 mL/min: τ_{minor} = 44.2 min, τ_{major} = 45.4 min. HRMS *calcd*. for ($C_{13}H_{17}ClOS+Na$): 279.0586, found 279.0599. $[\alpha]_D^{25}$= -35.4 (c= 0.70, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (d, *J* = 7.2, 3H, minor), 1.14 (d, *J* = 7.2, 3H, major), 1.26 (d, *J* = 6.8, 3H), 2.08 (s, 3H), 2.53-2.62 (m, 1H), 2.88-2.96 (m, 1H), 3.68 (q, *J* = 13.5, 2H), 7.23-7.28 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 20.3, 29.3, 34.9, 42.0, 52.3, 128.7, 130.3, 132.9, 136.9, 210.6 ppm.

(3R,4R)-4-(allylthio)-3-methylpentan-2-one

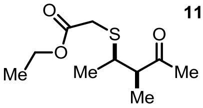


11j

(**11j**). The reaction was carried out at 25 °C following the general procedure to furnish the crude product as a 7.8:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δminor 1.11 (d), δmajor 1.18 ppm (d). The title compound was isolated as a colorless oil by column chromatography (hexane/AcOEt = 50:1) in 60% yield and 87% *ee*. The enantiomeric excess was determined by GC analysis on Astec CHIRALDEX G-TA column: 50 °Cto 130 °C (ramp of 12 °C per minute), then isotherm at 130 °C, flow rate 1.0 mL/min: τ_{minor} = 14.6 min, τ_{major} = 15.0 min. HRMS *calcd.* for ($C_9H_{16}OS$+Na): 195.0820, found 195.0809. $[\alpha]_D^{25}$ = +8.82 (c = 0.80, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, *J* = 6.8, 3H, minor), 1.18 (d, *J* = 7.4, 3H, major), 1.27 (d, *J* = 6.8, 3H), 2.18 (s, 3H), 2.58-2.65 (m, 1H), 2.97-3.04 (m, 1H), 3.11-3.20 (m, 2H), 5.07-5.15 (m, 2H), 5.74-5.83 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 20.3, 29.5, 34.1, 41.3, 52.3, 117.2, 134.6, 210.8 ppm.

ethyl 2-(((2R,3R)-3-methyl-4-oxopentan-2-yl)thio)acetate

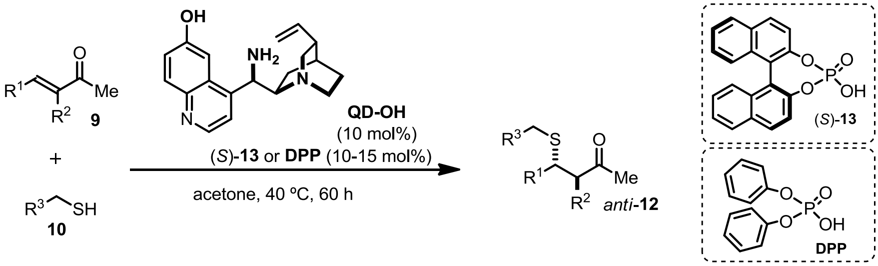


11k

(**11k**) The reaction was carried out at 25 °C following the general procedure to furnish the crude product as a 5.5:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δminor 1.10 (d), δmajor 1.19 ppm (d). The title compound was isolated as a colorless oil by column chromatography (hexane/AcOEt = 20/1) in 68% yield and 61% *ee*. Optical purity analyzed by HPLC analysis on a Daicel Chiralpak IA column: 98:2 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{major} = 16.4 min, τ_{minor} = 17.5 min. HRMS *calcd.* for ($C_{10}H_{18}O_3S$ +Na): 241.0874, found 241.0861. $[\alpha]_D^{25}$= -8.11 (c = 0.70, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (d, *J* = 7.2, 3H, minor), 1.19 (d, *J* = 7.2, 3H, major), 1.25-1.31 (m, 6H), 2.18 (s, 3H), 2.59-2.66 (m, 1H, major), 2.69-2.76 (m, 1H, minor), 3.18-3.29 (m, 3H), 4.14-4.20 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4, 14.0, 14.2, 17.3, 20.0, 29.0, 29.4, 32.7, 33.3, 41.7, 43.1, 51.4, 52.2, 61.5, 170.6, 210.4 ppm.

3.10.2 General Procedure for the *anti*-Selective SMA of α-Branched Enones.



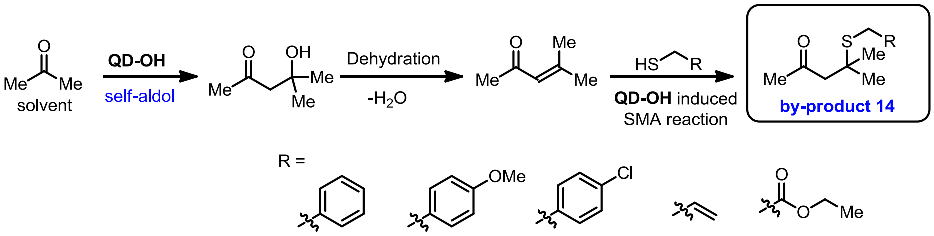
Method A: SMA of enones **9** bearing an *aliphatic* group at the β-position (1:1 ratio of **QD-OH** to (*S*)-**13**).

All the reactions were carried out in acetone (HPLC grade reagent) without any precaution to exclude air and moisture (open air chemistry on the benchtop). An ordinary vial equipped with a Teflon-coated stir bar and a plastic screw cap was charged with 6’-hydroxy-9-amino(9-deoxy)*epi* quinidine **QD-OH** (0.02 mmol, 6.2 mg, 10 mol%) and 0.4 mL of acetone. Then, (*S*)-(+)-1,1'-Binaphthalene-2,2'-diyl hydrogen phosphate (*S*)-**13** (0.02 mmol, 7.0 mg, 10 mol%) was added in one portion and the resulting solution was stirred at room temperature for 10 minutes. The SMA reaction was started by the sequential addition of the α,β-unsaturated α-branched ketone **9** (0.2 mmol) and the aliphatic thiol **10** (0.4 mmol, 2 equiv). The vial was closed and immerged in a silicon bath (thermostated at 40 °C) and stirring continued over 60 hours. The crude mixture was flushed through a short plug of silica, using dichloromethane/diethyl ether 1:1 as the eluent (5 ml). Solvent was removed *in vacuo* and the diastereomeric ratio (d.r.) was determined by ^{1}H NMR analysis of the crude mixture. The SMA adducts **12** were isolated by flash column chromatography or preparative TLC. The reactions catalyzed by amine **QD-OH**/diphenyl phosphate (**DPP**) combination have been performed following the same experimental procedure (1:1 ratio of **QD-OH** to **DPP** when R^1 is an aliphatic group).

Method B: SMA of enones **9** bearing an *aromatic* group at the β-position (1:1.5 ratio of **QD-OH** to (*S*)-**13** or **DPP**).

All the reactions were carried out in acetone (HPLC grade reagent) without any precaution to exclude air and moisture (open air chemistry on the benchtop). An ordinary vial equipped with a Teflon-coated stir bar and a plastic screw cap was charged with 6’-hydroxy-9-amino(9-deoxy)*epi* quinidine **QD-OH** (0.02 mmol, 6.2 mg, 10 mol%) and 0.4 mL of acetone. Then, (*S*)-(+)-1,1'-Binaphthalene-2,2'-diyl hydrogen phosphate (*S*)-**13** (0.015 mmol, 10.5 mg, 15 mol%) was added in one portion and the resulting solution was stirred at room temperature for 10 minutes. The SMA reaction was started by the sequential addition of the α,β-unsaturated α-branched ketone **9** (0.2 mmol) and the aliphatic thiol **10** (0.4 mmol, 2 equiv). The vial was closed and immerged in a silicon bath (thermostated at 40 °C) and stirring continued over 60 hours. The crude mixture was flushed through a short plug of silica, using dichloromethane/diethyl ether 1:1 as the eluent (5 ml). Solvent was removed *in vacuo* and the diastereomeric ratio (d.r.) was determined by ^{1}H NMR analysis of the crude mixture. The SMA adducts **12** were isolated by flash column chromatography or preparative TLC. The reactions catalyzed by amine **QD-OH**/diphenyl phosphate (**DPP**) combination have been performed following the same experimental procedure (1:1.5 ratio of **QD-OH** to **DPP** when R^1 is an aromatic group).

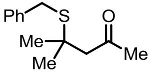
By-Product. During the extensive optimization studies, we decided to test acetone as the reaction media, fully aware of the possible secondary pathways that such a solvent might initiate. This was a crucial decision, since acetone greatly improved the diastereo-induction of the process. However, a small amount (ranging from 10 to 20%) of a by-product **14** derived from the SMA addition of thiols **10** to the in situ formed enone, *i.e.* 4-methylpent-3-en-2-one, generated by a **QD-OH** catalyzed self aldol-condensation of acetone, was always detected (Scheme 2). Indeed, in all of the *anti*-selective reactions the formation of the byproduct **14** was observed and because of its affinity with the products in a few cases it was not possible the perfect purification of the desired product.



Scheme 2. Byproduct **14** Formation.

The purification of the *anti* SMA adduct **12** by flash chromatography is trivial for most of the cases. Difficulties were encountered when 3-methyl-3-penten-2-one **9a** is used as the Michael-acceptor, as in this case the corresponding SMA product **12** and the by-product **14** are structural-isomers. Thus, separation by standard chromatography results problematic. In the following experimental section, when needed, the amount of the byproduct **14** still present after chromatography purification of the SMA adduct, and affecting the isolated yield, is specified.

14a

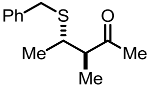


The by-product **14a** is a structural isomer of the SMA adducts **11** and **12** when the enone **9a** is used.

HRMS *calcd.* for ($C_{13}H_{18}ONaS$): 245.0976, found 245.0969. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.46 (S, 6H), 2.14 (s, 3H), 2.69 (s, 2H), 3.79 (s, 2H), 7.20-736 (m. 5H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 28.6, 32.4, 33.48, 44.5, 54.8, 127.1, 128.7, 129.1, 138.1, 206.9 ppm.

(3R,4S)-4-(benzylthio)-3-methylpentan-2-one

12a

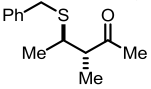


(**12a**). The reaction was carried out following the general procedure (Method A) to furnish the crude product as a 6.2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δmajor 1.10 ppm (d), δminor 1.31 ppm (d). The title compound was isolated by flash column chromatography (hexane/diethyl ether = 90/10) in 80% overall yield, together with by-product **14** (**12a** to **14** ratio 89:11, calculated by ^{1}H NMR). The enantiomeric excess was determined to be 98% by GC analysis on Astec CHIRALDEX G-TA column: isotherm 150 °C, flow rate 1.000 mL/min, τ_{major} = 28.46 min., τ_{minor} = 29.26 min. $[\alpha]_D^{25}$ = +48.9 (c =1.195, $CHCl_3$, 98% *ee*, 6.2:1 d.r.); HRMS *calcd.* for ($C_{13}H_{18}OS$+Na): 245.0976, found 245.0969.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (d, 3H, *J* = 7.01 Hz), 1.17 (d, 3H, *J* = 6.96 Hz), 2.06 (s, 3H), 2.58-2.67 (m, 1H), 2.93-3.01(m, 1H), 3.71 (d, 2H, *J* = 1.76 Hz), 7.20-7.36 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.6, 17.7, 28.9, 35.9, 40.6, 51.8, 127.2, 128.6, 128.9, 138.3, 210.6 ppm.

(3S,4R)-4-(benzylthio)-3-methylpentan-2-one

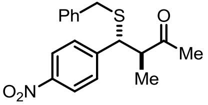
ent-**12a**



(ent-**12a**). The reaction was carried out following the general procedure (Method A) but using **QN-OH** derived from quinine, to furnish the crude product as a 3.9:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δmajor 1.10 ppm (d), δminor 1.31 ppm (d). The title compound was isolated by flash column chromatography (hexane/diethyl ether = 90/10) in 44% overall yield, together with by-product **14** (ent-**12** to **14** ratio 66:34, calculated by ^{1}H NMR). The enantiomeric excess was determined to be 94% by GC analysis on Astec CHIRALDEX G-TA column: isotherm 150 °C, flow rate 1.000 mL/min, τ_{major} = 29.26 min., τ_{minor} = 28.46 min. $[\alpha]_D^{26}$= -42.0 (c = 0.7, $CHCl_3$, 94% *ee*, 2.7:1 d.r.).

(3R,4R)-4-(benzylthio)-3-methyl-4-(4-nitrophenyl)butan-2-one

12b



(**12b**) The reaction was carried out following the general procedure (Method B) to furnish the crude product as a 5.7:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δmajor 3.84 ppm (d), δminor 3.97 ppm. The title compound was isolated by column chromatography (hexane/diethyl ether = 95/5) in 77% yield and 99% *ee*, 5.7:1 d.r. The *ee* value was determined by HPLC analysis on a Daicel Chiralpak IA column: 96:4 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 12.3 min, τ_{minor} = 10.7 min. $[\alpha]_D^{26}$= +249.2 (c = 1.03, $CHCl_3$, 99% *ee*, 5.7:1 d.r.); HRMS *calcd.* for ($C_{18}H_{19}NO_3S$+Na): 352.1001, found 352.0983.

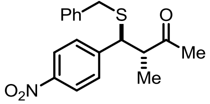
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (d, 3H, *J* = 6.97 Hz), 2.22 (s, 3H), 2.91-3.01 (m, 1H), 3.49 (dd, 2H), 3.83 (d, 1H, *J* = 10.76 Hz), 7.12-7.16 (m, 2H), 7.19-7.30 (m, 3H), 7.32-7.38 (m, 2H), 8.12-8.18

(m, 2H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 16.2, 29.7, 36.5, 50.3, 51.8, 123.9, 127.5, 128.6, 129.1, 129.5, 137.0, 147.2, 148.4, 209.5 ppm.

The relative and absolute configuration for *anti*-**12b** was unambiguously inferred by anomalous dispersion Xray crystallographic analysis.

(3S,4S)-4-(benzylthio)-3-methyl-4-(4-nitrophenyl)butan-2-one

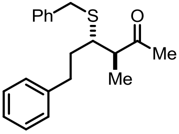
ent-**12b**



(*ent*-**12b**) The reaction was carried out following the general procedure (Method B) but using **QN-OH** derived from quinine, to furnish the crude product as a 2.8:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δmajor 3.84 ppm (d), δminor 3.97 ppm (d). The title compound was isolated by column chromatography (hexane/diethyl ether = 95/5) in 48% yield and 94% *ee*, 2.2:1 d.r. The *ee* value was determined by HPLC analysis on a Daicel Chiralpak IA column: 96:4 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 10.7 min, τ_{minor} = 12.3 min. $[\alpha]_D^{26}$= -151.6 (c = 0.93, CHCl$_3$, 94% *ee*, 2.2:1 d.r.).

(3R,4S)-4-(benzylthio)-3-methyl-6-phenylhexan-2-one

12c



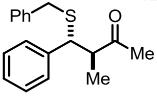
(**12c**) The reaction was carried out following the general procedure (Method A) to furnish the crude product as a 8.2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δmajor 1.08 ppm (d), δminor 1.14 ppm (d).

The title compound was isolated by chromatography on preparative TLC (toluene/diethyl ether, 10:1) in 71% overall yield. *Ee*: 97%, d.r.: 12.3:1. The *ee* was determined by HPLC analysis on a Daicel Chiralpak IC column: 99/1 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 10.72 min, τ_{minor} = 11.07 min. $[\alpha]_D^{26}$= +12.9 (c = 0.90, CHCl$_3$, 97% *ee*, 12.3:1 d.r.); HRMS *calcd.* for ($C_{20}H_{24}OS$+Na): 335.1446, found 335.1448.

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.08 (d, 3H, *J* = 7.00 Hz), 1.57-1.74 (m, 2H), 1.90 (S, 3H), 2.49-2.85 (m, 4H), 3.72 (s, 2H), 7.00-7.37 (m, 10H) ppm. ^{13}C NMR (400 MHz, CDCl$_3$): δ 12.4, 29.0, 32.7, 32.8, 36.6, 45.6, 51.2, 126.0, 127.2, 128.5, 128.6, 128.4, 129.2, 138.5, 141.8, 210.5 ppm.

(3R,4R)-4-(benzylthio)-3-methyl-4-phenylbutan-2-one

12d

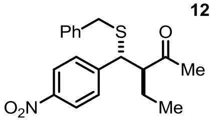


(**12d**) The reaction was carried out following the general procedure (Method B) to furnish the crude product as a 5.2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δmajor 3.37 ppm (d), δminor 3.27 ppm (d). The title compound was isolated by chromatography on preparative TLC (toluene/hexane, 8:2) in 41% yield and 99% *ee*. The *ee* was determined by HPLC analysis on a Daicel Chiralpak IC column: 95/5 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 8.5 min, τ_{minor} = 12.3 min. $[\alpha]_D^{26}$= +195.9 (c= 0.70, $CHCl_3$, 99% *ee*, 13.1:1 d.r.); HRMS *calcd.* for ($C_{18}H_{20}OS$+Na): 307.1133, found 307.1139.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (d, 3H, *J* = 7.00 Hz), 2.19 (s, 3H), 2.87-2.97 (m, 1H), 3.47 (dd, 2H), 3.72 (d, 1H, *J* = 11.21 Hz), 7.14-7.36 (m, 10H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.3, 29.1, 36.0, 51.2, 52.5, 127.1, 127.6, 128.5, 128.6, 128.7, 128.8, 129.1, 137.8, 140.2, 210.6 ppm.

(R)-3-((R)-(benzylthio)(4-nitrophenyl)methyl)pentan-2-one

12e

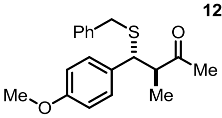


(**12e**) The reaction was carried out following the general procedure (Method B) to furnish the crude product as a 1.8:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δmajor 0.71 ppm (d), δminor 0.85 ppm (d). The title compound was isolated by column chromatography (hexane/diethyl ether = 95/5) in 35% yield, together with by-product **14** (**12e** to **14** ratio 68:32, calculated by ^{1}H NMR). Enantiopurity: 98% *ee* in the major diastereomer and 73% *ee* in the minor diastereomer. The *ee* was determined by HPLC analysis on a Daicel Chiralpak IA column: 90/10 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm. Major diastereoisomer: τ_{major} = 13.0 min, τ_{minor} = 14.2 min; minor diastereoisomer: τ_{major} = 10.4 min, τ_{minor} = 11.3 min. $[\alpha]_D^{26}$= +56.1 (c = 0.96, $CHCl_3$, 98% *ee*, 1.8:1 d.r.); HRMS *calcd.* for ($C_{19}H_{21}NO_3S$+Na): 366.1140, found 366.1153.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (t, 3H, *J* = 7.50 Hz), 1.21-1.38 (m, 2H), 2.24 (s, 3H), 2.86 (dt, 1H, *J*t = 10.70; *J*d = 3.75 Hz), 3.49 (dd, 2H), 3.77 (d, 1H, *J* = 11.15 Hz), 7.12-7.19 (m, 2H), 7.22-7.46 (m, 5H), 8.14-8.22 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.5, 24.6, 31.4, 36.4, 49.9, 58.8, 123.9, 127.5, 129.1, 129.4, 136.9, 148.7, 149.3, 209.8 ppm.

(3R,4R)-4-(benzylthio)-4-(4-methoxyphenyl)-3-methylbutan-2-one

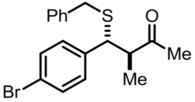
12f



(**12f**) The reaction was carried out following the general procedure (Method B) to furnish the crude product as a 4.2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δmajor 3.39 ppm (d), δminor 3.32 ppm (d). The title compound was isolated by column chromatography (hexane/diethyl ether = 90/10) in 42% of combined yield with byproduct **14** (8% calculated by ^{1}H NMR) and 99% *ee*. After purification, the dr was 16:1. The *ee* was determined by HPLC analysis on a Daicel Chiralpak IC column: 98/2 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 16.7 min, τ_{minor} = 20.2 min. $[\alpha]_D^{27}$= +174.9 (c = 1.06, $CHCl_3$, 99% *ee*, 16:1 d.r.); HRMS *calcd.* for ($C_{19}H_{22}O_2S$+Na): 337.1249, found 337.1238.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (d, 3H, *J* = 7.09 Hz), 2.15 (s, 3H), 2.83-2.93 (m, 1H), 3.46(dd, 2H), 3.69 (d, 1H, *J* = 10.83 Hz), 3.83 (s, 3H), 6.84-6.89 (m, 2H), 7.14-7.36 (m, 7H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 29.1, 35.9, 50.6, 52.7, 55.4, 114.0, 127.1, 128.5, 129.1, 129.8, 132.0, 137.9, 159.0, 210.8 ppm.

(3R,4R)-4-(benzylthio)-4-(4-bromophenyl)-3-methylbutan-2-one

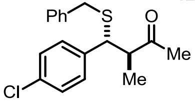


12g

(**12g**) The reaction was carried out following the general procedure (Method B) to furnish the crude product as a 6.5:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δmajor 3.69 ppm (d), δminor 3.85 ppm (d). The title compound was isolated by chromatography on preparative TLC (toluene/hexane/diethyl ether, 2:2:1) in 59% yield and 99% *ee*. The *ee* was determined by HPLC analysis on a Daicel Chiralpak IC column: 98/2 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 14.1 min, τ_{minor} = 15.0 min. $[\alpha]_D^{27}$= +186.2 (c = 0.66, $CHCl_3$, 99% *ee*, 6.5/1 d.r.); HRMS *calcd.* for ($C_{18}H_{19}BrOS$+Na): 385.0238, found 385.0246.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (d, 3H, *J* = 6.99 Hz), 2.17 (s, 3H), 2.83-2.93 (m, 1H), 3.47(Second Order System, 2H), 3.69 (d, 1H, *J* = 10.89 Hz), 7.09-7.30 (m, 7H), 7.42-7.48 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ δ 16.2, 29.3, 36.1, 50.5, 52.2, 121.3, 127.3, 128.6, 129.1, 130.4, 131.8, 137.5, 139.4, 210.2 ppm.

(3R,4R)-4-(benzylthio)-4-(4-chlorophenyl)-3-methylbutan-2-one

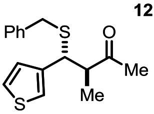


12h

(**12h**) The reaction was carried out following the general procedure (Method B) to furnish the crude product as a 5.3:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δmajor 3.70 ppm (d), δminor 3.87 ppm (d). The title compound was isolated by chromatography on preparative TLC (toluene/hexane/diethyl ether, 2:2:1) in 58% yield and 99% *ee*, 5.2:1 d.r. The *ee* was determined by HPLC analysis on a Daicel Chiralpak IC column: 98/2 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 14.1 min, τ_{minor} = 15.3 min. $[\alpha]_D^{27}$= +193.3 (c = 0.73, $CHCl_3$, 99% *ee*, 5.2/1 d.r.); HRMS *calcd.* for ($C_{18}H_{19}ClOS$+Na): 341.0743, found 341.0742.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (d, 3H, *J* = 7.07 Hz), 2.17 (s, 3H), 2.83-2.92 (m, 1H), 3.48(Second Order System, 2H), 3.70 (d, 1H, *J* = 10.85 Hz), 7.13-7.31 (m, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 29.3, 36.1, 50.4, 52.3, 127.3, 128.6, 128.8, 129.1, 130.1, 133.2, 137.5, 138.9, 210.2 ppm.

(3R,4R)-4-(benzylthio)-3-methyl-4-(thiophen-3-yl)butan-2-one

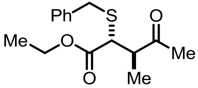


12i

(**12i**) The reaction was carried out following the general procedure (Method B) to furnish the crude product as a 4.2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δmajor 0.82 ppm (d), δminor 1.26 ppm (d). The title compound was isolated by chromatography on preparative TLC (toluene/acetone, 50:1) in 44% yield and 98% *ee*. The *ee* was determined by HPLC analysis on a Daicel Chiralpak IC column: 98/2 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 10.2 min, τ_{minor} = 11.8 min. $[\alpha]_D^{27}$= +162.1 (c = 1.05, $CHCl_3$, 98% *ee*, 4.2:1 d.r.); HRMS *calcd.* for ($C_{16}H_{18}OS_2$+Na): 313.0697, found 313.0692.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (d, 3H, *J* = 7.09 Hz), 2.14 (s, 3H), 2.86-2.97 (m, 1H), 3.48 (dd, 2H), 3.90 (d, 1H, *J* = 10.50 Hz), 7.00-7.06 (m, 1H), 7.16-7.33 (m, 7H), ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 29.1, 36.1, 46.2, 52.2, 123.1, 126.5, 127.0, 127.2, 128.5, 129.1, 137.8, 140.9, 210.4 ppm.

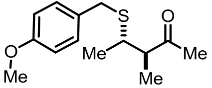
(2R,3R)-ethyl 2-(benzylthio)-3-methyl-4-oxopentanoate



12j

(**12j**) The reaction was carried out following the general procedure (Method A) to furnish the crude product as a 5.2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δmajor 3.37 ppm (d), δminor 3.27 ppm (d). The title compound was isolated by flash column chromatography (hexane/diethyl ether = 95:5) in 56% overall yield, together with by-product **14** (**12j** to **14** ratio 86:14, calculated by ^{1}H NMR). *Ee*: 96%, d.r.: 5.2:1. The *ee* was determined by HPLC analysis on a Daicel Chiralpak IC column: 90/10 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 25.0 min, τ_{minor} = 17.9 min. $[\alpha]_D^{26}$= +60.3 (c = 0.51, CHCl3, 96% *ee*, 5.2:1 d.r.); HRMS *calcd.* for ($C_{15}H_{20}O_3S$+Na): 303.1039, found 303.1031.
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (d, 3H, *J* = 6.91 Hz), 1.27 (t, 3H, *J* = 7.24 Hz), 2.08 (s, 3H), 2.95-3.04 (m, 1H), 3.37 (d, 1H, *J* = 9.96 Hz), 3.83 (s, 2H), 4.16 (q, 2H, *J* = 7.10 Hz), 7.23-7.34 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 15.6, 29.3, 37.2, 48.0, 48.2, 61.5, 127.5, 128.7, 129.4, 137.5, 171.5, 209.2 ppm.

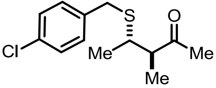
(3R,4S)-4-((4-methoxybenzyl)thio)-3-methylpentan-2-one



12k

(**12k**) The reaction was carried out following the general procedure (Method A) to furnish the crude product as a 7.1:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δmajor 1.10mppm (d), δminor 1.29 ppm (d). The title compound was isolated by flash column chromatography (hexane/ethyl acetate = 30:1) in 53% overall yield, together with by-product **14** (**12k** to **14** ratio 78:22, calculated by ^{1}H NMR). *Ee*: 98%, d.r.: 7.1:1. The *ee* was determined by GC analysis on Astec CHIRALDEX G-TA column: 50 to 150 °C (ramp of 12 °C per minute), then isotherm at 150 °C for 40 minutes and then from 150 to 170 °C (ramp of 12 °C per minute), flow rate 1.000 mL/min, τ_{major} = 64.4 min., τ_{minor} = 64.7 min. $[\alpha]_D^{26}$= +47.3 (c = 1.06, $CHCl_3$, 98% *ee*, 7.1:1 d.r.); HRMS *calcd.* for ($C_{14}H_{20}O_2S$+Na): 275.1082, found 275.1092.
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (d, 3H, *J* = 7.00 Hz), 1.17 (d, 3H, *J* = 7.00 Hz), 2.08 (s, 3H), 2.60-2.66 (m, 1H), 2.92-2.99 (m, 1H), 3.69 (d, 2H, *J* = 2.58 Hz), 3.79 (s, 3H), 6.82-6.87 (m, 2H), 7.21-7.27 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.7, 17.8, 29.0, 35.4, 40.6, 51.8, 55.4, 114.1, 130.1, 158.8, 210.5 ppm.

(3R,4S)-4-((4-chlorobenzyl)thio)-3-methylpentan-2-one

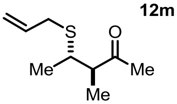


12l

(**12l**) The reaction was carried out following the general procedure (Method A) to furnish the crude product as a 7.2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δmajor 1.11 ppm (d), δminor 1.28 ppm (d). The title compound was isolated by flash column chromatography (hexane/ethyl acetate = 50:1) in 62% overall yield, together with by-product **14** (**12l** to **14** ratio 74:26, calculated by ^{1}H NMR). *Ee*: 94%, d.r.: 7.2:1. The *ee* was determined by GC analysis on Astec CHIRALDEX column: 50 to 150 °C (ramp of 12 °C per minute), then isotherm at 150 °C, flow rate 1.000 mL/min, τ_{major} = 41.1 min., τ_{minor} = 41.9 min. $[\alpha]_D^{26}$= +28.4 (c = 1.02, $CHCl_3$, 98% *ee*, 7.2:1 d.r.); HRMS *calcd.* for ($C_{13}H_{17}ClOS$+Na): 279.0586, found 279.0594.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (d, 3H, *J* = 6.98 Hz), 1.16 (d, 3H, *J* = 7.05 Hz), 2.09 (s, 3H), 2.57-2.66 (m, 1H), 2.88-2.97 (m, 1H), 3.67-3.69 (m, 2H), 7.23-7.29 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.0, 17.9, 28.6, 35.3, 40.8, 51.9, 128.8, 130.3, 132.9, 136.9, 210.5 ppm.

(3R,4S)-4-(allylthio)-3-methylpentan-2-one

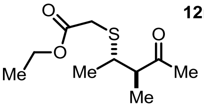


12m

(**12m**) The reaction was carried out following the general procedure (Method A) to furnish the crude product as a 4.8:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δmajor 1.13 ppm (d), δminor 1.29 ppm. The title compound was isolated by flash column chromatography (hexane/ethyl acetate = 50/1) in 73% overall yield, together with by-product **14** (**12m** to **14** ratio 86:14, calculated by ^{1}H NMR). *Ee*: 98%, d.r. 4.8:1. The major diastereoisomer has been isolated by semi-preparative HPLC, using Zorbax C18 as column, 50/50 MeOH/H2O, flow rate 1.00 mL/min, λ = 215, 254 nm: major diastereoisomer τ_{major} = 15.85 min. The *ee* of the major diastereoisomer was determined by GC analysis on Astec CHIRALDEX GTA column: 50 to 130 °C (ramp of 12 °C per minute), than 130 °C, flow rate 1.000 mL/min, τ_{major} = 14.19 min., τ_{minor} = 14.97 min. $[\alpha]_D^{26}$= +39.1 (c = 0.63, $CHCl_3$, 98% *ee*, 7.8:1 d.r.); HRMS *calcd.* for ($C_9H_{16}OS$+Na): 195.0820, found 195.0815.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, 3H, *J* = 6.95 Hz), 1.19 (d, 3H, *J* = 7.02 Hz), 2.17 (s, 3H), 2.67-2.73 (m, 1H), 3.02-3.09 (m, 1H), 3.16(d, 2H, *J* = 7.13 Hz), 5.08-5.18 (m,1H), 5.76-5.86 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.5, 17.6, 34.5, 39.8, 51.5, 53.4, 117.0, 134.6, 210.4 ppm.

ethyl 2-(((2S,3R)-3-methyl-4-oxopentan-2-yl)thio)acetate



12n

(**12n**) The reaction was carried out following the general procedure (Method A) to furnish the crude product as a 2.4:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δmajor 1.11 ppm (d), δminor 1.20 ppm (d). The title compound was isolated by flash column chromatography (hexane/ethyl acetate = 20/1) in 50% overall yield, together with by-product **14** (**12n** to **14** ratio 58:42, calculated by ^{1}H NMR). *Ee*: 92%, d.r.: 2.4:1. The *ee* was determined by GC analysis on Astec CHIRALDEX G-TA column: 50 to 130 °C (ramp of 12 °C per minute), then isotherm 150 °C, flow rate 1.0 mL/min, τ_{major} = 39.5 min., τ_{minor} = 41.1 min. $[\alpha]_D^{26}$= +23.0 (c = 1.98, $CHCl_3$, 96% *ee*, 2.4:1 d.r.); HRMS *calcd.* for ($C_{10}H_{18}O_3S$+Na): 241.0870, found 214.0874.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, 3H, *J* = 7.00 Hz), 1.20-1.30 (m, 6H), 2.18 (s, 3H), 2.70-2.76 (m, 1H), 3.21-3.24 (m, 2H), 3.25-3.30(m, 1H), 4.15-4.22 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 28.2, 31.4, 32.3, 41.8, 44.6, 54.5, 61.6, 171.1, 206.5 ppm.

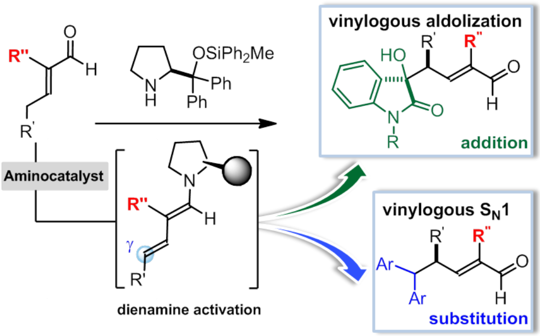
Chapter IV

Asymmetric γ-Substitution and γ-Addition of α-Branched Enals

Target

Address a difficult problem in catalytic reaction design: the remote enantioselective functionalization of unmodified carbonyl compounds.

Demonstrate the potential of vinylogous nucleophilicity induced by dienamine activation within a nucleophilic substitution and addition reaction pathway.



Tool

The ability of chiral secondary amines to condense with hindered carbonyls, such α-branched enals, and promote vinylogous nucleophilicity within a high stereo- and regio-selective reaction pathway.[1]

4.1 Background

Asymmetric aminocatalysis has greatly expanded the chemist’s ability to stereoselectively functionalize unmodified carbonyls compounds. Over the past decade, enamine and iminium ion activations have become reliable synthetic platforms for generating stereogenic centers at the α- and β-positions of aldehydes and ketones with very high level of stereo-control. More recently, the chemist’s interest has shifted toward the use of aminocatalysis for targeting even more remote stereogenic centers. The first success in the design of direct vinylogous processes

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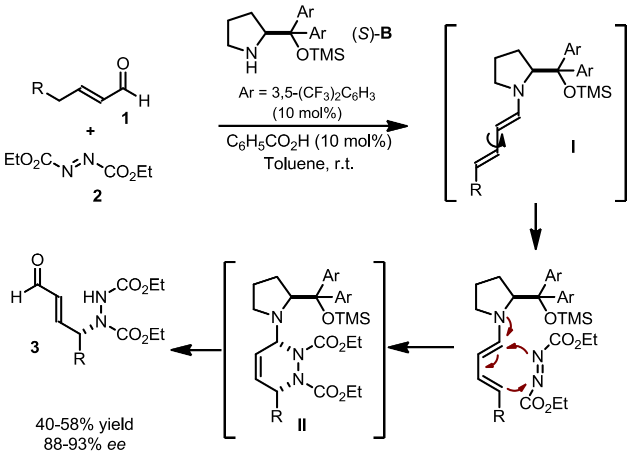
[1] The work discussed in this chapter has been published, see: a) C. Cassani, P. Melchiorre. Direct Catalytic Enantioselective Vinylogous Aldol Reaction of α-Branched Enals with Isatins. *Org. Lett*, **2012**, *14*, 5590; b) M. Silvi, C. Cassani, A. Moran, P. Melchiorre. Secondary Amine-Catalyzed Asymmetric γ-Alkylation of α-Branched Enals *via* Dienamine Activation. *Helv. Chim. Acta*, **2012**, *95*, 1985. Experimental part developed together with M. Silvi (γ-alkylation of α-branched enals).

was achieved in 2006 by Jørgensen and co-workers with the direct, enantioselective γ-amination of α,β-unsaturated aldehydes (Scheme 1).[2]



Scheme 1. The First Example of Dienamine Activation: Diels-Alder Type Reaction.[2]
Me = methyl; Et = ethyl; TMS = trimethylsilyl.

The diaryl prolinol trimethylsilyl ether catalyst (*S*)-**B**, together with benzoic acid, effectively generated the transient electron-rich dienamine **I** after condensation with aldehyde **1**. It was demonstrated that the reaction proceeds, *via* a [4+2] cycloaddition pathway, with the *cis* isomer of **I** reacting with the diethyl azodicarboxylate **2**, which acts as the dienophile. This gives origin to the cyclic aminal intermediate **II**, which opens and hydrolyzes under the reaction conditions, leading to the final product **3** and the free catalyst (*S*)-**B**.

With this report the authors introduced the concept of dienamine activation basing their strategy on the electronic transmission through double bonds.[3] The dienamine activation mode relies on the propagation of the HOMO raising effects, inherent to enamine activation, through the vinylogous space offered by the π-system of unsaturated carbonyl compounds (Figure 1).

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[2] S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen. Dienamine Catalysis: Organocatalytic Asymmetric γ-Amination of α,β-Unsaturated Aldehydes. *J. Am. Chem. Soc.*, **2006**, *128*, 12973.

[3] In 1935, R. C. Fuson formulated the principle of vinylogy to explain how the electronic influence of a functional group may be transmitted to a distant point within the molecule when the two positions are connected by conjugated double-bond linkages. R. C. Fuson. The Principle of Vinylogy. *Chem. Rev.*, **1935**, *16*, 1.

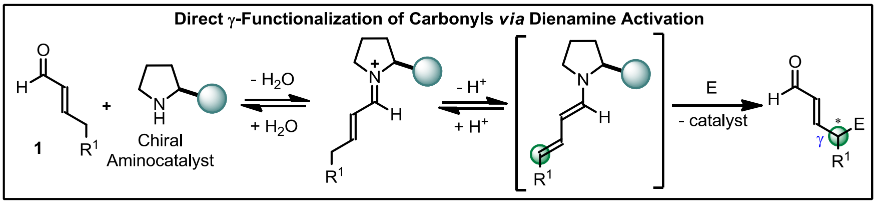
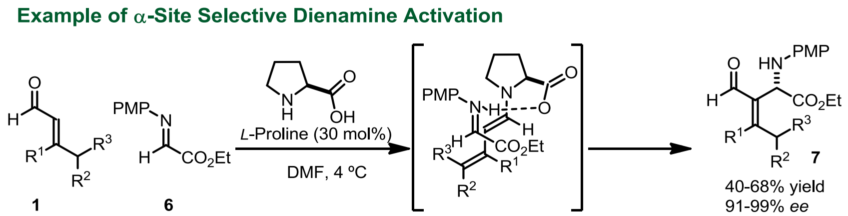


Figure 1. Dienamine Activation as a Remote Functionalization Strategy in Organocatalysis. E = electrophile.

Combining asymmetric aminocatalysis with the principle of vinylogy, dienamine activation has greatly expanded the chemists' ability to functionalize carbonyl compounds at remote positions, such as the γ carbon atom.[4]

In spite of its potential, the approach initially found limited application. This was probably because the γ-amination of unsaturated aldehydes **1** followed a [4+2] cycloaddition path (Scheme 1), instead of a more general nucleophilic addition pathway. Moreover, initial studies suggested that chiral secondary amines, such as proline and its derivatives, activated γ-enolizable unsaturated aldehydes toward the formation of the dienamine intermediate, but generally promoted α-site selective alkylation *via* an enamine pathway in the presence of suitable electrophiles (Scheme 2).[5,6]



Scheme 2. An Example of a Mannich Type Reaction for the Formation of aza-Morita-Baylis–Hillman-Type Products.[5] PMP: *para*-methoxy phenyl.

The peculiar Diels–Alder mechanism of the initial γ-amination chemistry and the difficult control of the site selectivity meant that the strategy found rapid applications in cycloaddition processes exclusively. γ-Site selective transformation based on dienamine activation remained limited to few exceptions due to the many challenges offered by this activation mode.

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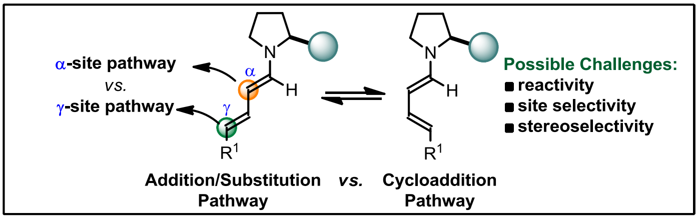
[4] a) H. Jiang, Ł. Albrecht, K. A. Jørgensen. Aminocatalytic Remote Functionalization Strategies. *Chem. Sci.*, **2013**, *4*, 2287. b) I. D. Jurberg, I. Chatterjee, R. Tannert, P. Melchiorre. When Asymmetric Aminocatalysis Meets the Vinylogy Principle. *Chem. Commun.*, **2013**, *49*, 4896.

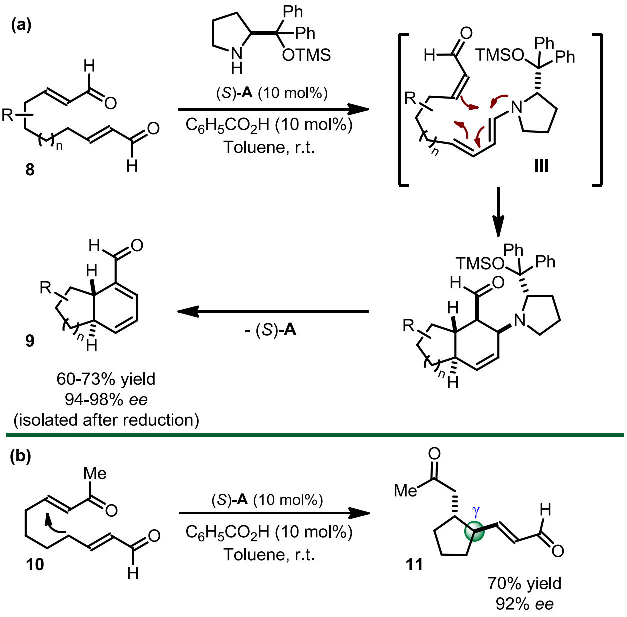
[5] N. Utsumi, H. Zhang, F. Tanaka, C. F. Barbas III. A Way to Highly Enantiomerically Enriched aza-Morita–Baylis–Hillman–Type Products. *Angew. Chem. Int. Ed.*, **2007**, *46*, 1878.

[6] E. Marquez-Lopez, R. P. Herrera, T. Marks, W. C. Jacobs, D. Könning, R. M. de Figueiredo, M. Christmann, Crossed Intramolecular Rauhut-Currier-Type Reactions *via* Dienamine Activation. *Org. Lett.*, **2009**, *11*, 4116.



Scheme 3. Designing Vinylogous Processes by means of Dienamine Activation: Challenges.

The first use of dienamine activation in a direct nucleophilic γ-addition was successfully reported by the Christmann group in 2008, as a single isolated example within the framework of a [4+2] type reaction of α,β-unsaturated aldehydes (Scheme 4a and 4b).[7]



Scheme 4. (a) Intramolecular Diels-Alder Reaction of Dienals *via* Dienamine Activation. (b) The First Example of Direct Vinylogous Nucleophilic Addition. Ph = phenyl.

The transient formation of the electron-rich dienamine **III** from the bis-aldehydic compound **8** initiated a pericyclic reaction that led to product **9** with excellent enantioselectivity (Scheme 4a). Only when a keto moiety replaced one of the aldehydic functions in **8** (compound **10**), a change

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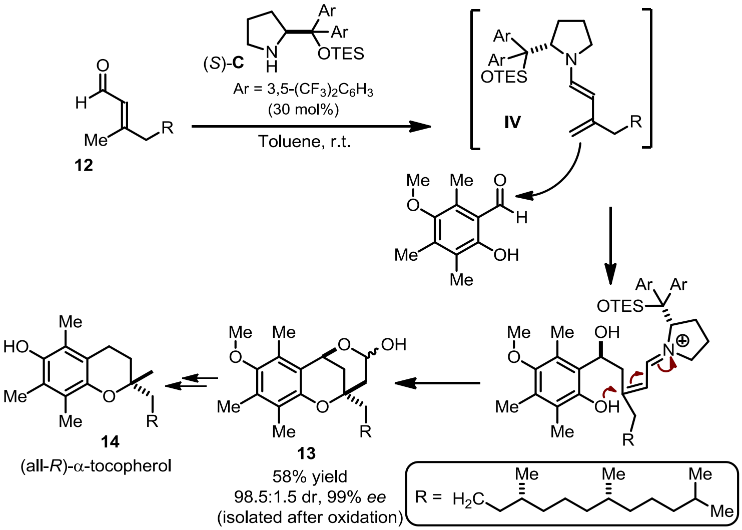
[7] R. M. de Figueiredo, R. Fröhlich, M. Christmann, Amine-Catalyzed Cyclizations of Tethered α,β-Unsaturated Carbonyl Compounds. *Angew. Chem. Int. Ed.*, **2008**, *47*, 1450.

in the reaction manifold was observed and, instead of the expected cyclo-addition path, a vinylogous Michael addition was observed leading to product **11**.

Another example of dienamine activation in the context of vinylogous nucleophilic addition reaction was reported by Woggon in 2008.[8] In this case a terminal dienamine **IV**, formed upon condensation of the catalyst **C** with the β-methyl substituted enal **12**, was responsible for the initial step in a domino sequence. The vinylogous aldol/*oxa*-Michael reactions, as presented in Scheme 5, led to the formation of **13**, an advanced intermediate *en-route* toward the synthesis of α-tocopherol **14,** which is one of the most significant members of the vitamin E family.



Scheme 5. Tandem Reaction Sequence for the Total Synthesis of α-Tocopherol. TES = triethylsilyl.

This report provided a powerful annulation strategy while also demonstrating the potential of dienamine activation to streamline the total synthesis of natural compounds. In the Woggon approach, the direct vinylogous aldol reaction was integrated at the beginning of a cascade sequence. However, a discrete, intermolecular, vinylogous addition reaction using dienamine activation of unmodified α,β-unsaturated carbonyl substrates, without needing to implement it within a cascade sequence, remained elusive.

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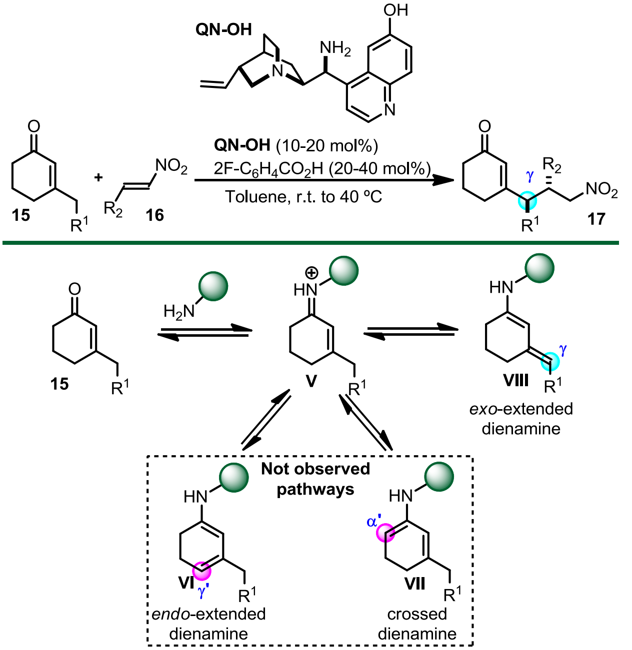
[8] K. Liu, A. Chougnet, W.-D. Woggon. A Short Route to α-Tocopherol. *Angew. Chem. Int. Ed.*, **2008**, *47*, 5827.

In 2010, our research group reported an important advancement in the field of remote functionalization of carbonyl compounds utilizing Cinchona-based primary amine catalyst.[9] It was shown that the 6'-hyroxy-9-amino quinine derivative **QN-OH** could promote the direct, vinylogous Michael addition of β-substituted cyclohexenone derivatives **15** to nitroalkenes **16** proceeding by dienamine activation (Scheme 6).[10]



Scheme 6. Dienamine-Promoted Vinylogous Michael Addition Reaction.

The already known ability of cinchona-derived amines to condense and activate hindered carbonyl substrates was exploited to generate the active dienamine intermediate of the keto-derivative **15**. Remarkably, the reaction occured with high levels of both enantio- and diastereo-control and with excellent γ-site selectivity. Key to reaction development was the unique ability

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[9] P. Melchiorre. Cinchona-based Primary Amine Catalysis in the Asymmetric Functionalization of Carbonyl Compounds. *Angew. Chem. Int. Ed.,* **2012**, *51*, 9748.

[10] G. Bencivenni, P. Galzerano, A. Mazzanti, G. Bartoli, P. Melchiorre. Direct Asymmetric Vinylogous Michael Addition of Cyclic Enones to Nitroalkenes *via* Dienamine Catalysis. *Proc. Natl. Acad. Sci. USA,* **2010**, *107*, 20642.

of the cinchona-derived amine to coax the selective formation of the *exo*-cyclic extended dienamine **VIII** over the *endo*-isomer **VI** or the *cross*-conjugated dienamine **VII**.[11]

Interestingly, while primary amine catalyst **QN-OH** led exclusively to the *exo*-cyclic extended dienamine intermediate **VIII**, chiral secondary amines, in the presence of the same reagent combination, induced the formation of the crossed-conjugated dienamine **VI**, catalyzing a Diels-Alder-type reaction pathway.[12]

4.1.1. Vinylogous Aldol Reaction

The concept of vinylogous reactivity has already been studied and applied in asymmetric metal catalysis. A milestone for this concept is the vinylogous aldol reaction. This reaction was successfully realized, employing preformed silyl enolethers and $TiCl_4$ as a Lewis acid, for the first time by Mukaiyama and Ishida in 1975.[13] This reactivity has been intensely used for the construction of densely adorned δ-hydroxylated α,β-unsaturated carbonyls. The presence of these functional groups in many biologically active compounds, in particular within polyketide structures, has provided the impetus for developing highly stereoselective, catalytic, vinylogous aldol reactions, as well as the direct application of these methodologies in the total synthesis of natural products.[14]

Also in this field of investigation, organocatalysis has emerged as a complementary and effective approach to asymmetric metal catalysis. The best examples in this context have been provided with a) the vinylogous and bisvinylogous Mukaiyama aldol reaction published by List in 2011 and b) the guanidine catalyzed direct reaction of furanone derivatives reported by Terada in 2010 (Scheme 7a and 7b, respectively).[15,16]

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[11] The regiocontrolled formation of the extended dienamine **VIII** finds support in related enolization studies demonstrating that, under certain conditions, the selective formation of the thermodynamic *exo*-cyclic enolate is strongly favoured, see: S. Saito, M. Shiozawa, M. Ito, H. Yamamoto. Conceptually New Directed Aldol Condensation using Aluminum tris(2,6-diphenylphenoxide). *J. Am. Chem. Soc.*, **1998**, *120*, 813.

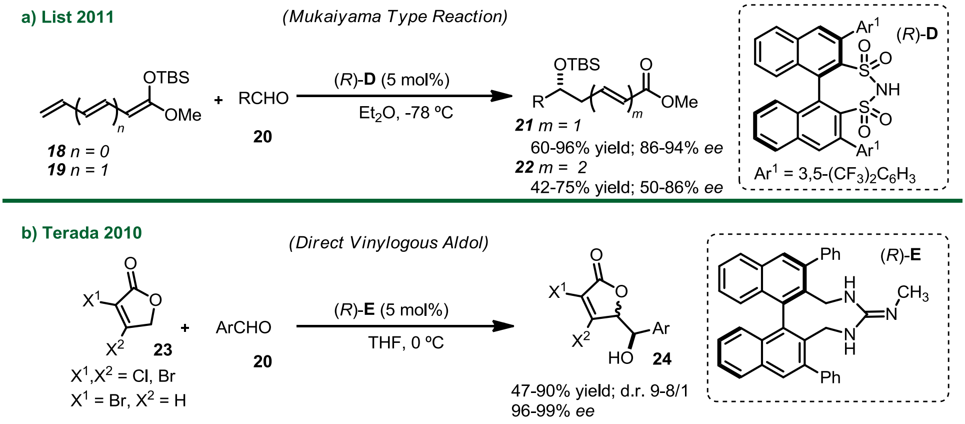
[12] D.-Q. Xu, A.-B. Xia, S.-P. Luo, J. Tang, S. Zhang, J.-R. Jiang, Z.-Y. Xu. In Situ Enamine Activation in Aqueous Salt Solutions: Highly Efficient Asymmetric Organocatalytic Diels–Alder Reaction of Cyclohexenones with Nitroolefins. *Angew. Chem. Int. Ed.*, **2009**, *48*, 3821.

[13] T. Mukaiyama, A. Ishida. A Convenient Method for the Preparation of δ-Alkoxy-α,β-Unsaturated Aldehydes by Reaction of Acetals with 1-Trimethylsiloxy-1,3-Butadiene. *Chem. Lett.*, **1975**, 319.

[14] a) S. E. Denmark, S. Fujimori. Total Synthesis of RK-397. *J. Am. Chem. Soc.*, **2005**, *127*, 8971; b) X. Jiang, B. Liu, S. Lebreton, J. K. De Brabander. Total Synthesis and Structure Revision of the Marine Metabolite Palmerolide *J. Am. Chem. Soc.*, **2007**, *129*, 6386.

[15] L. Ratjen, P. García-García, F. Lay, M. E. Beck, B. List. Disulfonimide-Catalyzed Asymmetric Vinylogous and Bisvinylogous Mukaiyama Aldol Reactions. *Angew. Chem. Int. Ed.*, **2011**, *50*, 754.

[16] H. Ube, N. Shimada, M. Terada. Asymmetric Direct Vinylogous Aldol Reaction of Furanone Derivatives Catalyzed by an Axially Chiral Guanidine Base. *Angew. Chem. Int. Ed.*, **2010**, *49*, 1858.



Scheme 7. Examples of Organocatalyzed Vinylogous Aldol Reaction.[15,16]

Despite the progresses in the organocatalyzed vinylogous aldol reaction, the scope of the nucleophilic substrate has remained very narrow. Most of the methodologies developed so far are based on a Mukaiyama-type process, which requires preformed silyl enolethers (for example the organocatalytic approaches depicted in Scheme 7a). In contrast to this technique are the approaches where the nucleophilic enolate equivalents are generated *in situ*, so that makes possible the direct γ-aldol reaction of unmodified substrates. However, until now the direct approaches have been limited to the use of cyclic carbonyl substrates, as exemplified in Scheme 7b. As a consequence, these transformations could provide access to a small number of geometrically diverse molecules.[17]

Our target was to realize an effective and enantioselective discrete vinylogous aldol reaction of an unmodified acyclic unsaturated carbonyl substrate. As already mentioned, one of the main challenges in vinylogous reactivity is related to the site-selectivity, since the dual nucleophilic nature of the active dienamine intermediate makes the reaction at both the α- and γ-position competitive (Scheme 2 and 3). We thought to channel the reactivity toward the γ-site selectivity by sterically hindering the α-position of the dienamine intermediate. To do this, we investigated the possibility of using α-branched enals as substrates, since the extra substituent should lower or even suppress the reactivity at the α-site for steric reasons.[18]

The aminocatalytic activation of such hindered carbonyl compounds is not trivial, due to the difficulties associated with the chiral aminocatalyst condensation. The activation of α-branched

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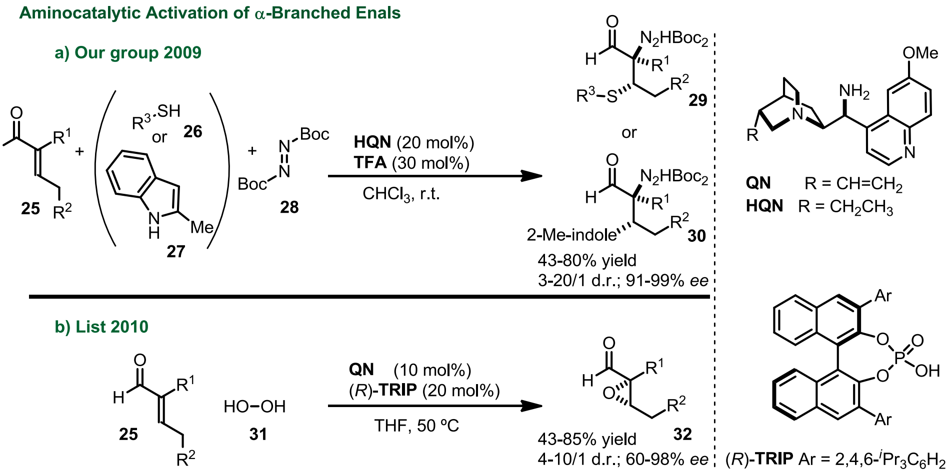
[17] S.V. Pansare, E. K. Paul. The Organocatalytic Vinylogous Aldol Reaction: Recent Advances. *Chem. Eur. J.*, **2011**, *17*, 8770.

[18] For the γ-site alkylation of α-branched enals under dienamine activation and via a S_N1 pathway, see: G. Bergonzini, S. Vera, P. Melchiorre. Cooperative Organocatalysis for the Asymmetric γ-Alkylation of α-Branched Enals. *Angew. Chem. Int. Ed.*, **2010**, *49*, 9685.

enals was successfully achieved by exploiting the unique ability of the cinchona-based primary amine to covalently interact with sterically demanding partners. This was demonstrated by our group, in 2009, and by the group of List in 2010 (Scheme 8a and 8b, respectively).[19,20]



Scheme 8. Aminocatalytic Activation of α-Branched Enals.[19,20] TFA = trifluoroactic acid.

These two cascade reactions, promoted by quinine-derived catalysts, followed an iminium ion/enamine activation sequence (concept discussed in detail in Chapter **II**) to generate the products **29**, **30**, and **32** with high level of enantio- and diastereo-selectivity. These promising results, albeit obtained in the context of the β-functionalization of α-branched enals, encouraged us to test the primary amine catalysts in the vinylogous aldol addition reaction.

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[19] P. Galzerano, F. Pesciaioli, A. Mazzanti, G. Bartoli, P. Melchiorre. Asymmetric Organocatalytic Cascade Reactions with α-Substituted α,β -Unsaturated Aldehydes. *Angew. Chem. Int. Ed.*, **2009**, *48*, 7892.

[20] O. Lifchits, C. M. Reisinger, B. List. Catalytic Asymmetric Epoxidation of α-Branched Enals. *J. Am. Chem. Soc.*, **2010**, *132*, 10227.

4.2 Direct Vinylogous Aldol Reaction

With the idea of the nucleophile already in mind, we focus on the identification of a suitable electrophile to develop a vinylogous aldol process, which would lead to enantioenriched δ-hydroxylated α,β-unsaturated carbonyls.

After a short screening, isatin derivatives **26** were found to be good candidates for the transformation. The inherent reactivity and the presence of the 3-substituted 3-hydroxyoxindole scaffold in many biologically active compounds (Figure 2) make it an even more appealing substrate for our investigations (Scheme 9).[21]

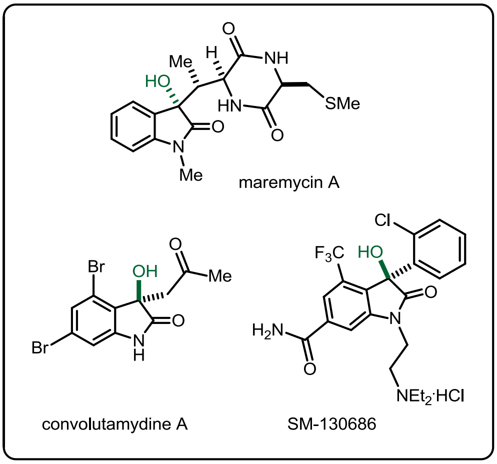
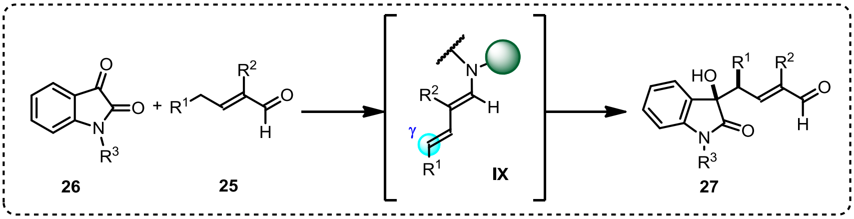


Figure 2. 3-Hydroxyoxindole Moiety in Biologically Active Compounds.

Our initial studies focused on the addition of (*E*)-2-methylpent-2-enal **25a** to N-benzyl protected isatin **26a** (Table 1). The combination of enal **25a** and the cinchona-catalysts was key for developing the sulfa-Michael/amination cascade and the epoxidation reported in Scheme 8. However, despite extensive efforts, we have not succeeded in translating the α-branched enal/cinchona-based catalyst system to the vinylogous aldol process. The use of 20 mol% of the cinchona primary amine catalyst **QD** and **QD-OH** led to the desired product **27a**, but with poor stereocontrol (entries 1 and 2 in Table 1). Different combinations of acid and solvent could not improve the performance of this system.



Scheme 9. Model Reaction for Direct γ-Aldolization through Dienamine Activation.

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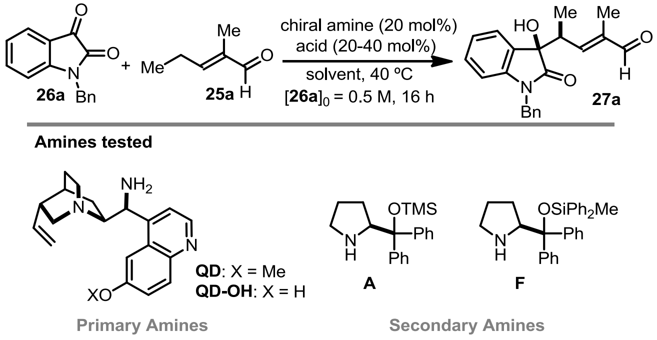
[21] G. Bergonzini, P. Melchiorre. Dioxindole in Asymmetric Catalytic Synthesis: Routes to Enantioenriched 3-Substituted 3-Hydroxyoxindoles and the Preparation of Maremycin A. *Angew. Chem. Int. Ed.*, **2012**, *51*, 971.

Table 1. Screening of the Reaction Conditions.[a]



Entry	amine	acid	solvent	conv (%)[b]	*d.r.*[c]	*ee* (%)[c]
1	**QD**	TFA	$CHCl_3$	42	6:1	<5
2	**QD-OH**	TFA	$CHCl_3$	67	2.8:1	42
3	**A**	BA	toluene	35	1:1	40
4	**A**	BA	EtOH	>95	1.2:1	75
5	**F**	BA	EtOH	>95	1.2:1	83
6[d]	**F**	BA	EtOH	>95	1.4:1	89
7[d]	**F**	BA	MeCN	30	3:1	92
8[d]	**F**	BA	MeCN/EtOH[e]	49	2.7:1	92
9[d]	**F**	CF_3-BA	MeCN/EtOH[e]	59	3.2:1	91
10[d,f]	**F**	CF_3-BA	MeCN/EtOH[e]	87	3.2:1	90

[a] BA: benzoic acid; CF_3-BA: 2,6-$(CF_3)_2$-$C_6H_3CO_2H$; TFA: trifluoroacetic acid. Catalyst **QD** and **QD-OH** were used with 2 equiv. of TFA, while **A** and **F** required a 1:1 combination with the acid. Reactions carried out on a 0.05 mmol scale using 2 equiv. of enal **25a** and [**26**]$_0$ = 0.5 M in the solvent. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction performed at 25 °C. [e] Reaction performed in a 9:1 MeCN/EtOH mixture. [f] 10 mol % of amine **F** and of CF_3-BA was used. Reaction time: 40 h; [**26a**]$_0$ = 2 M. Yield value refers to the isolated compound after chromatography.

The quest for a more stereoselective catalyst prompted us to undertake an extensive catalyst screening. This led to an unexpected observation: the commercially available diphenylprolinol silyl ether **A**[22] could indeed catalyze the vinylogous aldol process (Table 1, entry 3).[23] This stands in contrast to the catalytic profiles of secondary amines that are generally unable to efficiently activate sterically hindered carbonyl compounds, such as α,β-disubstituted enals of type **25**. The activation of α-branched enals generally requires the use of primary amine catalysts[19,20,24] and,

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[22] K. L. Jensen, G. Dickmeiss, H. Jiang, Ł. Albrecht, K. A. Jørgensen. The Diarylprolinol Silyl Ether System: A General Organocatalyst. *Acc. Chem. Res.*, **2012**, *45*, 248.

[23] Interestingly, among the most classic secondary amine catalysts (including proline and imiazolinones) the Hayashi-Jørgensen catalyst **A** and other silyl protected diphenylprolinol ethers were the only able to promote the reaction.

[24] K. Ishihara, K. Nakano. Design of an Organocatalyst for the Enantioselective Diels−Alder Reaction with α-Acyloxyacroleins. *J. Am. Chem. Soc.*, **2005**, *127*, 10504.

except for two examples,[25] the use of secondary amines is limited to the iminium ion activation of highly reactive α-branched acroleins.[26]

Despite the moderate level of stereoselectivity initially achieved with catalyst **A**, we were encouraged by the unanticipated efficiency of secondary amine catalyst to direct the reaction toward a γ-site selective aldolization through dienamine activation of α-branched enals. Examination of the reaction media revealed that the catalytic process was greatly influenced by polarity, solvents with a high dielectric constant strongly increasing both reactivity and stereoselectivity (Table 1, entries 4-10). Gratifyingly, the stereocontrol was also sensitive to catalyst structural modifications, the bulkier silyl protective group of catalyst **F** leading to a significant improvement (compare entries 4 and 5). This particular modification of the Hayashi-Jørgensen catalyst **A** was introduced for the first time by Seebach.[27]

A second cycle of optimization using catalyst **F** established a 9:1 acetonitrile/ethanol mixture as the best reaction medium, while revealing that the nature of the acidic additives was also crucial for modulating catalyst efficiency (entries 8 and 9). The use of a 1:1 combination of amine **F** (10 mol%) and 2,6-bis(trifluoromethyl) benzoic acid in a more concentrated reaction system ([**26a**]$_0$ = 2 M) provided the product **27a** with synthetically useful results over a 40 h reaction time and at room temperature (entry 10: **27a** isolated in 87% yield, 3.2:1 dr, and 90% *ee*).

These conditions were selected to evaluate the scope of the vinylogous aldol process on a series of differently substituted aldehydes and isatin derivatives (Table 2). Different substituents, including heteroatom-containing moieties, could be accommodated at the γ-position without affecting the site selectivity, while slightly increasing the enantioselectivity of the vinylogous aldol process (*ee* up to 95%, entries 2-4). More encumbered aliphatic substituents in the α-position were also well-tolerated (entries 5 and 6). Concerning the scope of the isatin derivatives **26**, different substitution patterns were well-tolerated, regardless of their electronic properties (Table 2, entries 7-14). Although the vinylogous aldolization proceeds with poor to moderate control over the relative configuration, it is possible to easily isolate the diastereoisomers, by simple chromatography, upon $NaBH_4$ reduction of adducts **27**. This testifies to the synthetic utility of the process. Proof of concept has been provided for the alcohol derivatives obtained

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[25] (a) L. Deiana, P. Dziedzic, J. Vesely, I. Ibrahem, R. Rios, J. Sun, A. Cordova. Catalytic Asymmetric Aziridination of α,β-Unsaturated Aldehydes. *Chem. Eur. J.*, **2011**, *17*, 7904. (b) E.-M. Tanzer, L. E. Zimmer, W. B. Schweizer, R. Gilmour. Fluorinated Organocatalysts for the Enantioselective Epoxidation of Enals: Molecular Preorganisation by the Fluorine-Iminium Ion Gauche Effect. *Chem. Eur. J.*, **2012**, *18*, 11334.

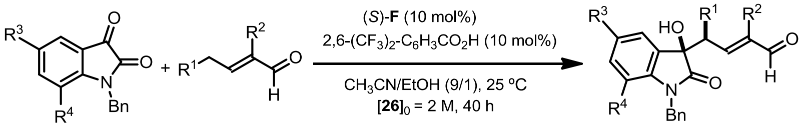
[26] B. P. Bondzic, T. Urushima, H. Ishikawa, Y. Hayashi. Asymmetric Epoxidation of α-Substituted Acroleins Catalyzed by Diphenylprolinol Silyl Ether. *Org. Lett.*, **2010**, *12*, 5434.

[27] U. Grošelj, D. Seebach, D. M. Badine, W. B. Schweizer, A. K. Beck, I. Krossing, P. Klose, Y. Hayashi, T. Uchimaru. Structures of the Reactive Intermediates in Organocatalysis with Diarylprolinol Ethers. *Helv. Chim. Acta*, **2009**, *92*, 1225.

from **27a**, **27h**, and **27j** (Table 2, entries 1, 8, and 10; isolated yields reported in parentheses refer to the reduced products).

The absolute and relative configuration of the major diastereoisomer of compound **27h** was determined by anomalous dispersion X-ray crystallographic analysis: (*S*) absolute configuration was observed at the newly formed γ-stereocenter.[28]

Table 2. Scope of the Direct Vinylogous Aldolization.[a]



26 **25** **27**

Entry	R^1	R^2	R^3	R^4	**27**	yield (%)[b]	*d.r.*[c]	*ee* (%)[d]
1	Me	Me	H	H	**a**	87 (47)	3.2:1	90 (76)
2	Bn	Me	H	H	**b**	68	2.5:1	95 (77)
3	CH_2SMe	Me	H	H	**c**	89	1.6:1	94(70)
4	CH_2NHCbz	Me	H	H	**d**	63	3:1	94(70)
5[e]	Bn	Bn	H	H	**e**	65	1.5:1	90 (78)
6[e]	Et	Et	H	H	**f**	28[f]	1.5:1	94
7	Me	Me	Cl	H	**g**	92	1.7:1	86(73)
8	Bn	Me	Cl	H	**h**	69(35)	1.6:1	92(78)
9	Me	Me	Br	H	**i**	68	1.9:1	85(78)
10	Me	Me	Me	H	**j**	76(44)	3.8:1	92(81)
11	Me	Me	NO_2	H	**k**	87	1.5:1	87(75)
12	Me	Me	CF_3O	H	**l**	71	2.9:1	89(63)
13	Me	Me	Me	Me	**m**	65	3.9:1	91(77)
14	Me	Me	H	Br	**n**	88	2.4:1	92(71)

[a] Reactions performed on a 0.2 mmol scale using 2 equivalent of **25**. *E*/*Z* ratio of **25** >95:5; no double bond scrambling was observed during the reaction. Only the (*E*)-isomer of the aldol products **27** was detected. [b] Yield of the isolated product **27** after chromatographic purification on silica gel. Values between parentheses (entries 1, 8 and 10) refer to the yield of the isolated major diastereomer of the alcohols obtained after $NaBH_4$ reduction of compounds **27**. [c] Determined by ^1H NMR analysis of the crude mixture. [d] *Ee* value of the major diastereomer, as determined by HPLC analysis. Values between parentheses refer to the *ee*'s of the minor diastereomers of **27**. [e] 20 mol % of catalyst **F** was used. [f] Yield of the isolated major diastereomer of **27f**.

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[28] Crystallographic data for compound **27h** are available free of charge from the Cambridge Crystallographic Data Centre, accession number CCDC 885390.

4.2.1. α-Aryl Substituted Aldehydes

We then carried out further explorations to fully delineate the reaction scope. Unexpectedly, the presence of an aryl substituent at the R^2-branched position of enal **25** led to a different product distribution. As depicted in Table 3, reacting (*E*)-2-phenylpent-2-enal **25b** with isatin **26** gave rise to the formation of the spirooxindole lactol **28**. We then started a screening of the reaction conditions for this particular class of aldehydes. We found that the use of the bulkier catalyst **F** was not necessary since the commercially available amine **A** was delivering the desired product in almost enantiopure form with similar diastereoselectivity. The solvent of choice was determined to be toluene and screening of the concentration and temperature parameters led to the optimized reaction conditions (see Table 3). Finally, we explored the synthetic potential of this catalytic asymmetric approach. As reported in Table 3, the reactions proceed readily at room temperature, and quantitative conversion was obtained in convenient reaction times. Despite the moderate level of relative stereocontrol, both diastereoisomers of the spirolactols **28** were formed in enantiomerically pure form and isolated as a single stereoisomer after chromatography on silica gel.

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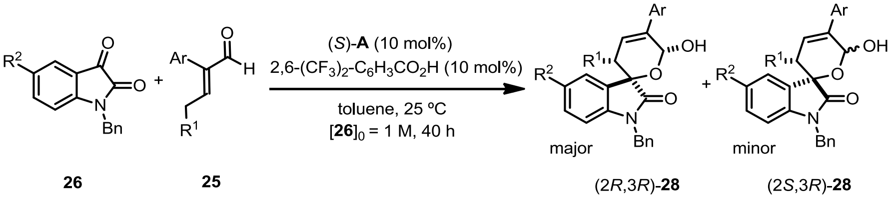
Table 3. Scope of the Hetero-Diels-Alder Type Reaction on α-Aryl Enals.[a]

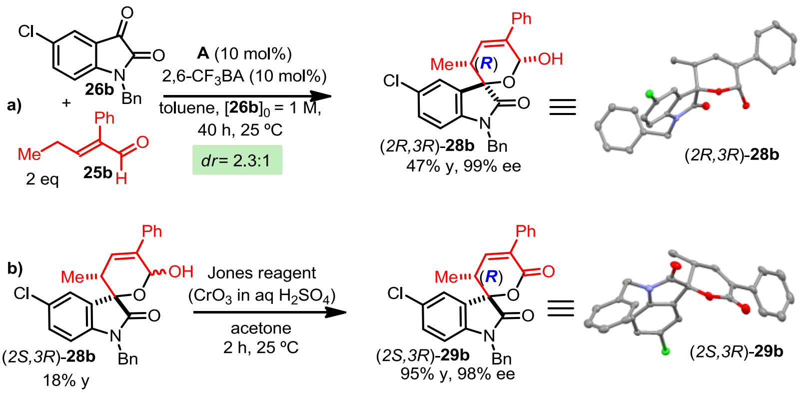


Entry	R^1	Ar	R^2	28	yield (%)[b] major/minor	*d.r.*[c]	*ee* (%)[d] major/minor
1	Me	Ph	H	**a**	45/22	2.2:1	99/99
2	Me	Ph	Cl	**b**	47/18	2.3:1	99/98
3[e]	Me	Ph	Me	**c**	63/19	3.0:1	99/98
4[e]	Me	Ph	NO_2	**d**	45/31	1.3:1	99/97
5[e]	Et	Ph	H	**e**	36/-	2.2:1	99/-
6[e]	Me	4-Cl-C6H4	H	**f**	69/22	3.2:1	99/98

[a] Reactions performed on a 0.2 mmol scale using 2 equiv of **25**. *E*/*Z* ratio of **25** >95:5; no double bond scrambling was observed during the reaction. [b] Yield of the isolated diastereomerically pure compounds (2*R*,3*R*)-**28** and (2*S*,3*R*)-**28**, which can be separated by chromatography. [c] Determined by ^1H NMR analysis of the crude mixture. [d] Determined by HPLC analysis on chiral stationary phase. Values between parentheses refer to the *ee*'s of the minor diastereoisomers of **27**. [e] 20 mol% of catalyst **A** was used.

To gain more information about the two diastereoisomers of the product, we performed X-ray analysis of the corresponding crystalline structures.

Simple oxidation of the minor (2*S*,3*R*)-**28b** isomer granted access to the spirooxindole dihydropyran-2-one **29b** (Scheme 10b). X-ray analyses established an (*R*) absolute configuration at the γ-stereocenter for both the diastereomeric products **28b**, in contrast with the stereochemistry observed in products **27**.



Scheme 10. The Stereochemical Outcome of the Reactions of α-Aryl Substituted Enals.[29]
2,6-CF$_3$BA=2,6-(CF$_3$)$_2$-C$_6$H$_3$CO$_2$H

4.2.2. Mechanistic Studies

The classical "steric control approach" generally invoked to rationalize the stereochemical outcome of a process catalyzed by **A** is consistent with the asymmetric induction observed when using an α-alkyl substituted enal of type **25a** (Table 2). Indeed, the efficient shielding by the chiral fragment in **F** determines the selective engagement of the isatin **27** with the *Si* face of the dienamine intermediate **X** (Figure 3). In contrast, this model, which is based on the direct addition of isatin from the unshielded face of **X**, cannot account for the (*R*)-absolute configuration of the γ stereocenter observed for products **28** (Table 3 and Scheme 10). The striking difference in the stereochemistry between products **27** and **28** led us to consider that a mechanistically distinct pathway may be operative for the α-aryl substituted enal **25b**. In analogy with related studies by Jørgensen and colleagues on the γ-functionalization of linear enals *via* dienamine activation, we envisaged a possible pericyclic [4+2] cycloaddition pathway.[2] To test this hypothesis, the two

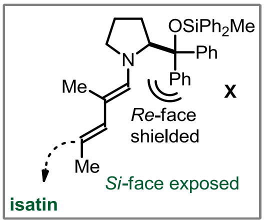


Figure 3. Proposed Stereochemical Model.

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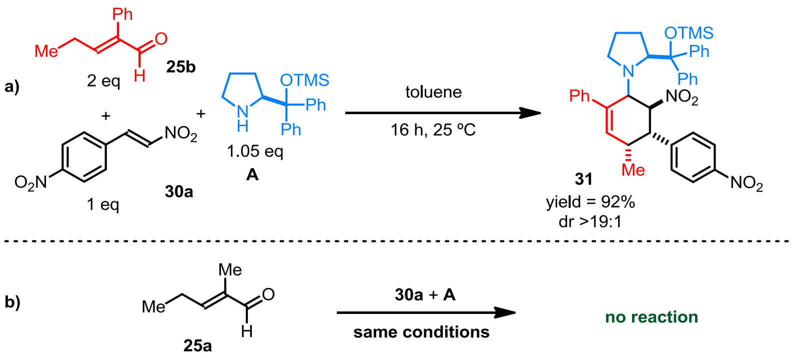
[29] Crystallographic data for compounds, (2R,3R)-**28b** and (2S,3R)-**29b** are available free of charge from the Cambridge Crystallographic Data Centre, accession numbers CCDC 885391 and CCDC 885392 respectively.

different enal substrates **25a** and **25b** were individually mixed with the amine catalyst **A** (1.05 equiv) and the nitrostyrene derivative **30a**, a dienophile that can react in concerted pericyclic processes catalyzed by amine **A** (Scheme 11).[30]



Scheme 11. Mechanistic Investigation.[31]

While the enal bearing a methyl substituent was found to be totally unreactet (Scheme 11b), aldehyde **25b** led to the fast and quantitative formation of the Diels-Alder-type product **31** with perfect stereocontrol (Scheme 11a). After chromatographic purification, the cyclic adduct **31** was characterized by X-ray crystallographic analysis.[31,32]

Although an extensive mechanistic investigation is required, a preliminary interpretation is possible. The initial observations are in agreement with a hetero-Diels-Alder (HDA) process being operative with enal **25b** bearing a phenyl α-substituent. A simple rotation around the C-C single bond of dienamine **Xb** would produce the intermediate **XIIb**, having the required *s-cis* geometry to engage in a pericyclic path (Figure 4). The HDA process with isatin would result in the labile hemiaminal ether intermediate **XIII**, which can easily hydrolyze to the lactol product **28** while releasing the catalyst **A**. It is to be noted that the stable cyclic adduct **31** in Scheme 11 is not amenable to this hydrolysis event.

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[30] (a) Ł. Albrecht, G. Dickmeiss, F. Cruz Acosta, C. Rodríguez-Escrich, R. L. Davis, K. A. Jørgensen. Asymmetric Organocatalytic Formal [2+2]-Cycloadditions *via* Bifunctional H-Bond Directing Dienamine Catalysis. *J. Am. Chem. Soc.*, **2012**, *134*, 2543. (b) Z.-J. Jia, Q. Zhou, Q.-Q Zhou, P.-Q Chen, Y.-C. Chen. *exo*-Selective Asymmetric Diels–Alder Reaction of 2,4-Dienals and Nitroalkenes by Trienamine Catalysis. *Angew. Chem. Int. Ed.*, **2011**, *50*, 8638.

[31] Crystallographic data for compound **31** are available free of charge from the Cambridge Crystallographic Data Centre, accession number CCDC 885695.

[32] The use of **30a**, the *p*-nitro derivative of the nitrostyrene, is needed only to access an easier crystallization of the product **27**. The reaction has the same chemical outcome using nitrostyrene. Compound **27** was crystallized from a hot mixture in hexane, then cooled at room temperature and slowly evaporated.

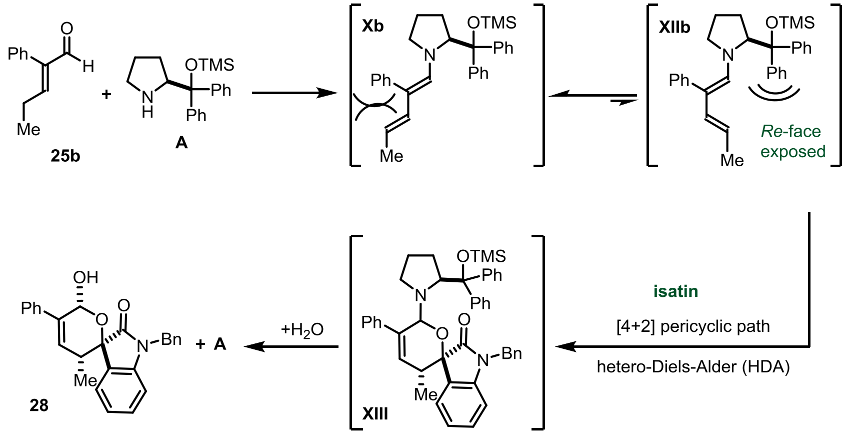
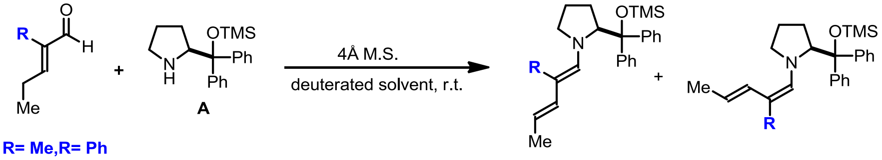


Figure 4. Possible Reaction Mecanism for the [4+2] Pericylcic Pathway.

NMR Analysis of the Active Intermediates

With the aim to identify a possible correlation between the dienamine geometry and the chemical outcome of the reaction, we carried out preliminary conformational investigations of the two reactive intermediates.

We used NMR spectroscopic analysis to gain information on the ground-state conformational behavior of the dienamine intermediates **Xa** and **Xb,** which are actively involved in the stereodefining step (Scheme 12). When mixing the aminocatalyst **A** with enal **25a** or **25b** (bearing a methyl or a phenyl α-branched substituent, respectively) in different deuterated solvents and in the presence of 4 Å molecular sieves, the corresponding dienamine intermediates **X** were formed.



Scheme 12. Formation of the Reactive Intermediates.

Experiments in deuterated chloroform resulted in the formation of the desired dienamines having two different geometries, in a ratio of roughly 3 to 1 for both the aldehydes **25a** and **25b** (**X** and **XI**) (Scheme 12 and Figure 5).

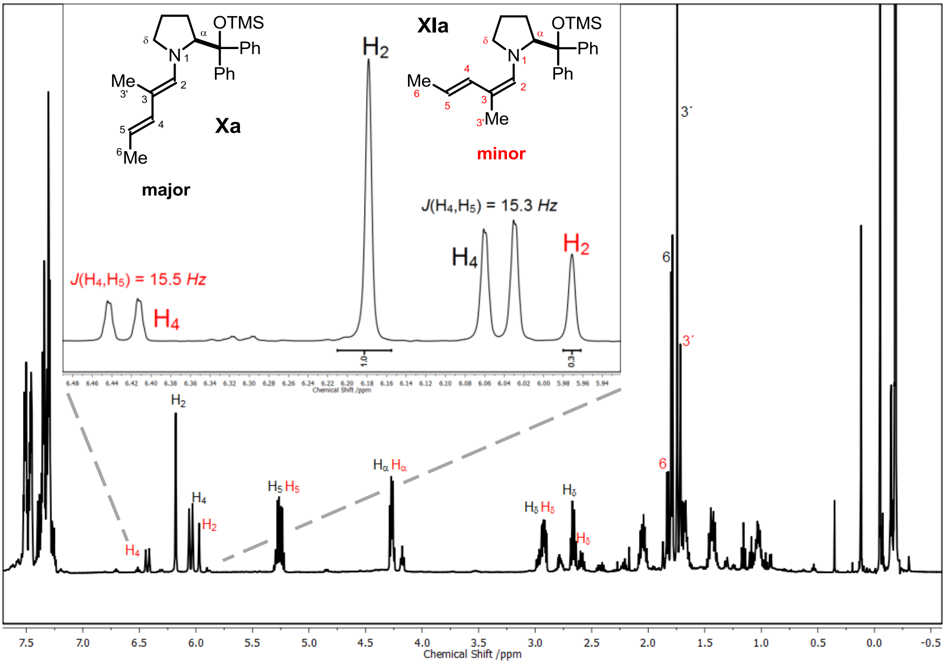


Figure 5. ^{1}H NMR of **Xa** and **XIa** in CDCl$_3$.

Several topological elements have the same geometry in the major and the minor isomers **X** and **XI**, respectively. In the case of **Xa** and **XIa** the presence of strong NOESY cross-peak between the H_2 and H_α indicates a s-*trans*-conformation of the single bond connecting N_1-C_2 (Figure 6). Additionally, the 15.5 and 15.3Hz coupling constants between H_4 and H_5 for the intermediates **Xa** and **XIa**, respectively, are evidence of an (*E*)-configured C_4=C_5 bond. Finally, the NOE cross-peak between $H_{3'}$ and H_5 (proton signal overlap for the major and the minor species) suggests an s-*trans*-conformation around the C_3-C_4 bond. The two dienamine conformers differ in the configuration of the C_2=C_3 bond. The major isomer **Xa** has an (*E*)-configured C=C bond, assigned on the basis of the two NOESY cross-peaks between $H_{3'}$ and H_δ, and H_4 and H_2 (Figure 6).

In contrast, the minor isomer **XIa** has a (*Z*)-configured C=C bond, as assigned on the basis of the two diagnostic NOESY signals $H_{3'}$/H_2 and H_4/H_δ.

Overall, these studies establish the (*E*)-s-*trans*-(*E*) as the most populated ground-state conformation of the major isomer, while the minor isomer has a (*Z*)-s-*trans*-(*E*) topology.

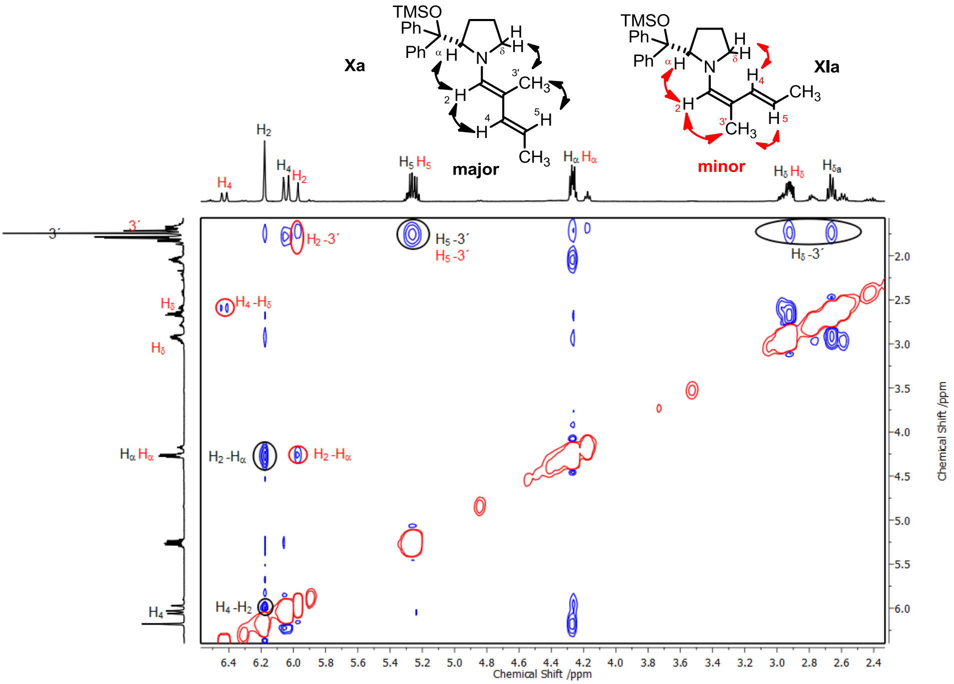


Figure 6. NOESY of **Xa** and **XIa** in $CDCl_3$.

Surprisingly, the nature of the α-branched substituent did not alter the conformational preference, indeed the same sets of isomers, with similar relative population, were found for **Xb** and **XIb** (the dienamines relative to the α-aromatic enal).

Finally, we carried out conformational studies in toluene-d_8 and CD_3CN, the deuterated analogs of the reaction medium for the γ-aldolization and HDA type reactions. In both of the cases two isomers, having the same topological arrangement as in $CDCl_3$, were detected. Nevertheless, the major (*E*)-s-trans-(*E*) dienamine of type **X** was formed in a much higher relative abundance (**X/XI** 10:1 in toluene-d_8; and **X/XI** 7 : 1 in CD_3CN).

For what concern the α-aryl enal **25b**, the NMR studies have shown that, in an environment similar to the reaction conditions, the only detectable isomers are **Xb** and **XIb** (in a ratio of 10:1). However, to account for the observed stereochemical ourcome of the process when using **25b**, it appears that the reactive isomer involved in the stereoselective event should have a different geometry of the C_4=C_5 double bond (intermediate **XIIb** in Figure 4). A similar scenario, where the less stable intermediate of type **XIIb** is responsible for the reactivity and stereoselectivity of the dienamine promoted reaction, has been already proposed and supported by computational studies for the γ-amination of enals reported by Jørgensen.[2]

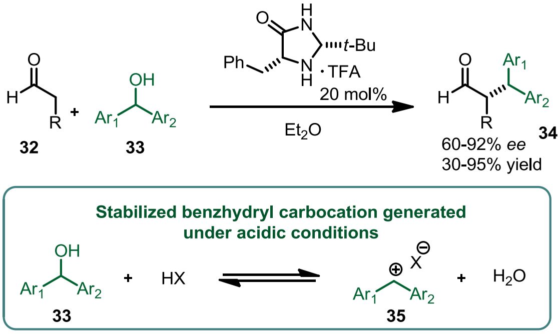
4.3 Direct γ-Alkylation of α-Branched Enals

After developing a highly enantioselective direct vinylogous aldol reaction of α-branched enals by employing secondary amine catalysts, we investigated the possibility to expand the use of such a catalytic system to different vinylogous reactions. To better show the flexibility of this approach, we decided to focus on a different class of transformations: nucleophilic *substitution* reactions.

4.3.1. Background of Aminocatalyzed Alkylation Reactions

The S_N1-type alkylation of carbonyl compounds based on the *in situ* generation of stabilized carbocations is nowadays an established technique and a benchmark for nucleophilic substitution reactions. This reactivity was investigated in organocatalysis with pioneering reports by Melchiorre[33] and Cozzi,[34] in which the direct and stereoselective α-alkylation of aldehydes was realized using enamine activation.

In particular, the direct nucleophilic substitution of benzhydryl alcohols **33**, developed by Cozzi and coworkers represents an appealing methodology for the preparation of α-alkylated aldehydes, as water is the only by-product of the transformation (Scheme 13).



Scheme 13. Enamine-catalyzed asymmetric α-alkylation of aldehydes via an S_N1-type reaction. *t*-Bu = *tert*-butyl. Ar = aryl.

Key to the development of the chemistry was the possibility of intercepting stable carbocations **35**, generated *in situ* under acidic conditions from benzhydrol derivatives **33**, with enamine intermediates. The careful choice of the acidic co-catalyst is important for the outcome of the

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[33] R. R. Shaikh, A. Mazzanti, M. Petrini, G. Bartoli, P. Melchiorre. Proline-Catalyzed Asymmetric Formal α-Alkylation of Aldehydes *via* Vinylogous Iminium Ion Intermediates Generated from Arylsulfonyl Indoles. *Angew. Chem. Int. Ed.*, **2008**, *47*, 8835.

[34] P. G. Cozzi, F. Benfatti, L. Zoli. Organocatalytic Asymmetric Alkylation of Aldehydes by S_N1-Type Reaction of Alcohols. *Angew. Chem. Int. Ed.*, **2009**, *48*, 1313.

reaction since the acid needs to be strong enough to allow for the *in situ* generation of the stabilized carbocation.

The reactivity and the formation of stable carbocations from benzhydrol substrates of type **33** were extensively studied by the group of Professor Herbert Mayr. They introduced the electrophilicity (*E*) and nucleophilicity (*N*) parameters for carbocations or related electrophiles and a plethora of nucleophiles (a small collection is reported in Figure 7).[35]

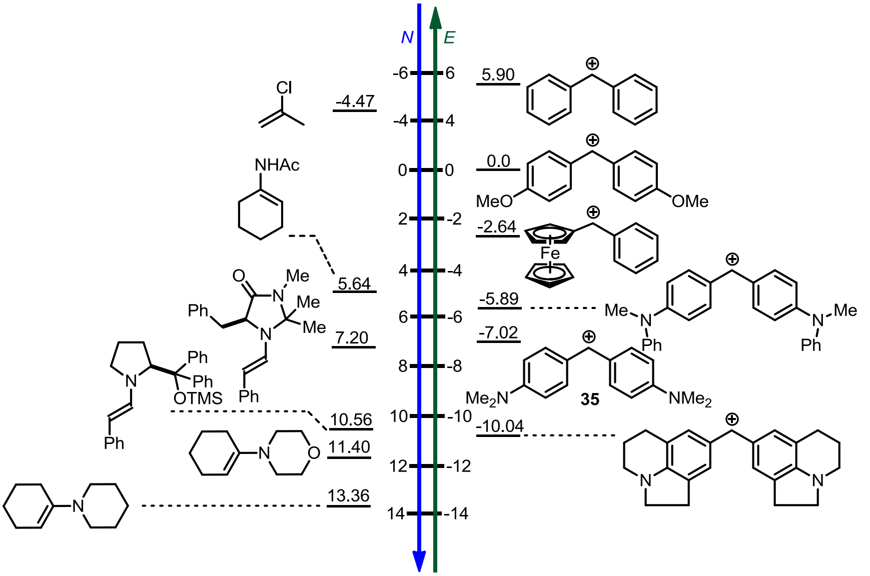

Figure 7. Selection of E and N values. Ac = acetate.

The acquired database contains parameters *E*, *N*, and *s* which allow the calculation of the rate constants for combinations of electrophiles with nucleophiles by applying the following equation (Eq. 1):

$$\log k\,(20\,°\mathrm{C}) = s\,(N + E) \qquad \text{(Eq.1)}$$

where *E* represents the electrophilicity of the carbocations while nucleophiles are characterized by two parameters, the nucleophilicity parameter *N* and the slope parameter s, the latter of which can be neglected for qualitative considerations (s ≈ 1).

This equation allows for a semi-quantitative prediction of a rate constant of a reaction and whether the process will take place or not in a reasonable time frame. Considerations on the rate constant (second-order rate constant $k > 10^{-4}\ \mathrm{M^{-1}s^{-1}}$ is required to give 50% of conversion in less than 3 h for a bi-molecular reaction which initial concentration is 1 M in both reactants) led

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[35] H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, H. Schimmel. Reference Scales for the Characterization of Cationic Electrophiles and Neutral Nucleophiles. *J. Am. Chem. Soc.*, **2001**, *123*, 9500.

to the conclusion that electrophiles can be expected to react with nucleophiles at room temperature in less than three hours when $E + N > -5$. Higher values of $E + N$ would correspond to faster reaction rate until the limit in which the reaction is under diffusion control. This situation may be not desirable if the aim is to conduct a catalyzed asymmetric transformation since it may raise issues of selectivity, thus making it difficult to transfer the stereochemical information with high fidelity.

According to Figure 7, enamines ($N \approx 12$) and bis(4-dimethylamino-phenyl)methanol **33**, which forms a stable carbocation **35** ($E = -7.02$),[36] can lead to a productive reaction. Other alcohols that form more reactive carbocations, such as benzhydrol which is placed at the top of Figure 7, showed instead no reactivity in the α-alkylation of aldehydes.

Based on this background, Cozzi successfully developed an aminocatalytic asymmetric S_N1-type alkylation of aldehydes.[34]

Assuming that, the dienamine intermediates might be characterized by similar level of nucleophilicity as the enamines, our group started the development of the direct γ-alkylation of aldehydes (Scheme 14).[18] This unprecedented transformation was accomplished using an interwoven activation pathway that successfully integrates dienamine activation and Brønsted acid catalysis simultaneously (Figure 8). To achieve this result, the ability of cinchona primary amines to activate hindered carbonyl such as α-branched enals **25** was again exploited.

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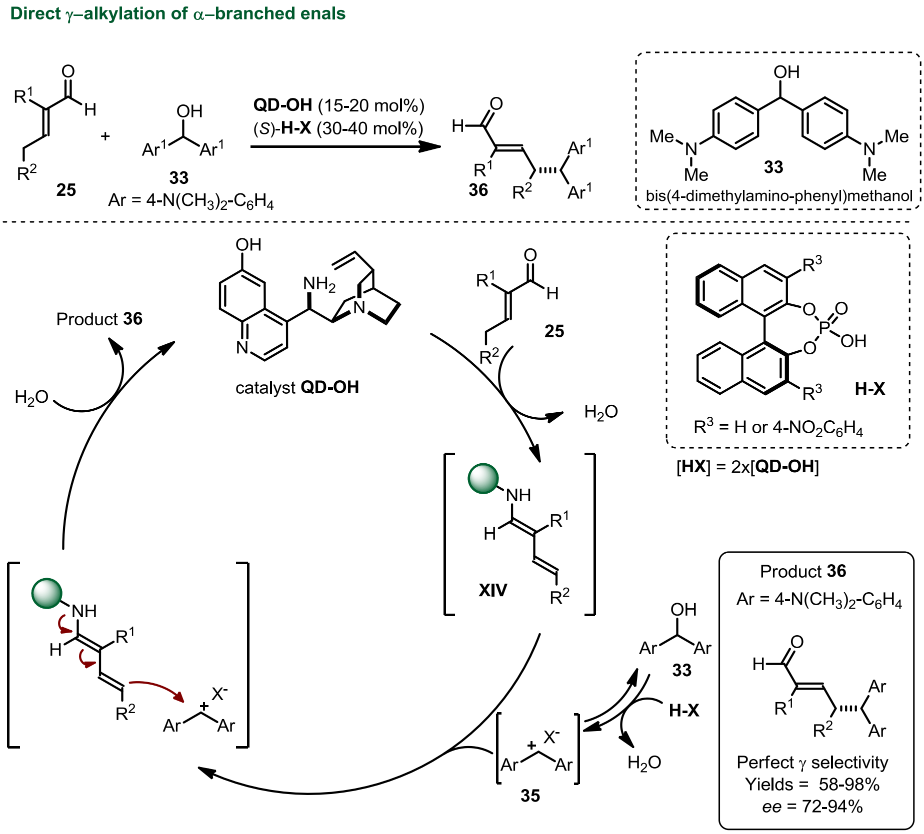
[36] The 4,4'-bis(dimethylamino)diphenylmethane carbocation has a half-life of 10-20 seconds, see: R. A. McClelland, V. M. Kanagasabapathy, N. S. Banait, S. J. Steeken. Flash-Photolysis Generation and Reactivities of Triarylmethyl and Diarylmethyl Cations in Aqueous Solutions. *J. Am. Chem. Soc.*, **1989**, *111*, 3966.



Scheme 14. Direct γ-Alkylation of α-Branched Enals.

In this reaction, a benzydryl carbocation **35** is *in situ* generated through an acid promoted elimination of water and then trapped by the transient dienamine intermediate **XIV**. The reaction requires two equivalents of a chiral Brønsted acid in order to proceed in a stereoselective and effective fashion, leading to the product with absolute γ-site selectivity and high enantioselectivity (see Figure 8 for a mechanistic proposal). The strong effect of the matched/mismatched-pair combinations supports a highly constructive and synergistic cooperation of the dienamine and Brønsted acid catalysts, an observation which highlights the importance of the chirality of the acid co-catalyst for this transformation.

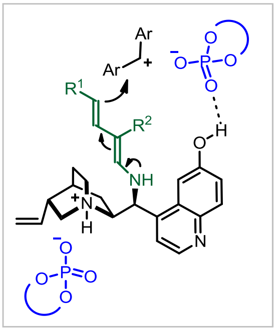
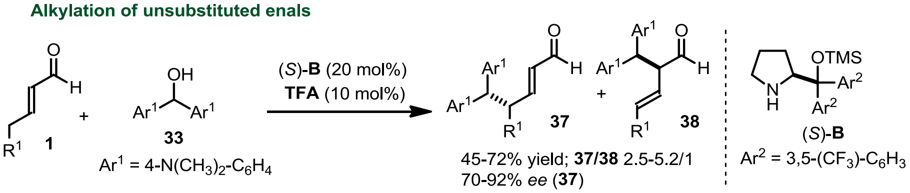


Figure 8. Proposed Mechanism

The main drawback of this catalytic system was the need for a high amount of chiral catalysts (up to 60 mol%), a primary amine cinchona derivative **QD-OH** (15-20 mol%) together with the double amount of the chiral phosphoric acid (30-40 mol%).

It is of note that, at the same time, an independent study by Christmann and co-workers established the ability of a secondary-amine catalyst, specifically the diphenylprolinol silyl ether **B**, to promote the S_N1-type alkylation of unsubstituted linear enals (Scheme 15).[37] However, the catalytic system provided moderate control over the site selectivity (competing α- *vs* γ-site alkylation) and a high level of stereocontrol only for selected examples.



Scheme 15. γ-Alkylation of Enals using Secondary Aminocatalysts.

The quest for a more convenient and simple γ-alkylation protocol prompted us to investigate the possibility of employing the catalytic system that we successfully developed for the vinylogous γ-aldolization of α-branched enals. We focused on the opportunity for the chiral secondary amine catalysts to promote the dienamine formation, condensing with α-branched enal, and to trap the *in situ* generated benzydril carbocation in an enantioselective fashion.

4.3.2. Results and Discussion

As a model reaction, we chose the direct γ-alkylation of (*E*)-2-methylpent-2-enal **25a** with bis[4-(dimethylamino)phenyl]methanol **33**. The standard in terms of efficiency and enantioselectivity for this transformation has been set during our previous investigations on cinchona-based primary-amine catalysis (Table 4, entry 1).[18] The combination of **A** with 30 mol% of 2,6-bis(trifluoromethyl)benzoic acid (the acid co-catalyst of choice for the γ-aldol reaction) led to compound **36a** as the sole product with good enantiomeric purity, albeit in a poor yield (entry 2).

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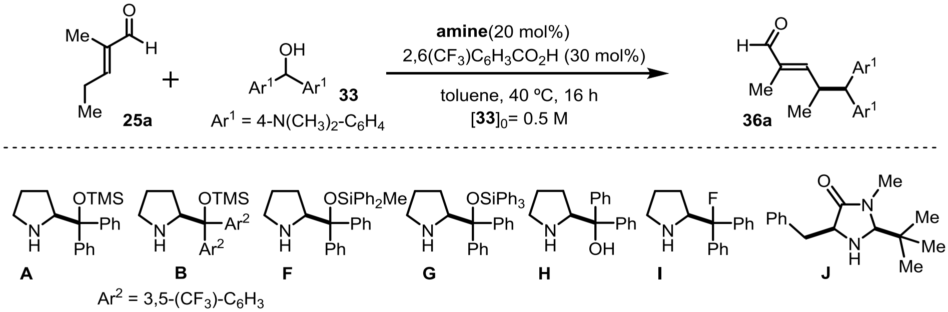
[37] J. Stiller, E. Marqués-López, R. P. Herrera, R. Fröhlich, C. Strohmann, M. Christmann. Enantioselective α- and γ-Alkylation of α,β-Unsaturated Aldehydes Using Dienamine Activation. *Org. Lett.*, **2011**, *13*, 70.

Table 4. Secondary Amine Catalysts Screening. [a]



Entry	catalyst	conv (%)[b]	*ee* (%)[c]
1[d]	**QD-OH**	98	89
2	**A**	10	81
3	**B**	3	75
4	**F**	18	88
5	**G**	13	84
6	**H**	n.r.	-
7	**I**	<5	71
8	**J**	n.r.	-

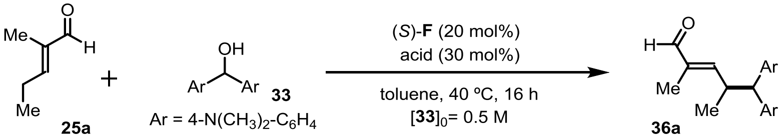
[a] Reactions performed on a 0.1 mmol scale using 2 equiv of **25a**. *E*/*Z* ratio of **25** >95:5. [**33**]$_0$ = 0.5 M in toluene at 40 °C. Reaction time 16 h. [b] Determined by ^{1}H NMR analysis of the crude mixture; n.r. = no reaction. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction conducted in $CHCl_3$ at 50 °C and catalyzed by the combination of 15 mol% of the primary amine **QD-OH** and 30 mol% of the chiral phosphoric acid. Result taken from reference 18.

Despite the poor reactivity initially achieved with catalyst **A**, we were encouraged by the ability of secondary amine catalyst to direct the reaction toward a γ-site selective alkylation through dienamine activation. In remarkable analogy with our precedent studies connected with the vinylogous aldol chemistry, both reactivity and stereocontrol were sensitive to catalyst structural modifications, with the bulkier silyl protective group of catalyst **F** leading to a significant improvement (compare entries 2 and 4). Further increasing the steric hindrance of the pendant silyl group did not provide higher stereoselectivity (entry 5). Interestingly, other widely employed chiral secondary amines (proline or the second-generation MacMillan imidazolidinone **J**) were not able to promote the transformation (entries 7 and 8).

Screening of the reaction media showed a correlation between the polarity of the solvent with both reactivity and enantioselectivity. Solvents with a high dielectric constant strongly increased the reactivity but at the expense of the enantioselectivity.

We then found that the nature of the acidic additives was also crucial for modulating the catalyst efficiency, in particular in terms of reactivity. Upon investigation of a variety of acid co-catalysts (Table 5; reactions performed in toluene as the solvent), inexpensive and easily available saccharin was identified as the most promising additive toward the design of an effective amine **F**-based catalytic system (Table 5, entry 9).

Table 5. Screening of the Acid Co-catalyst. [a]



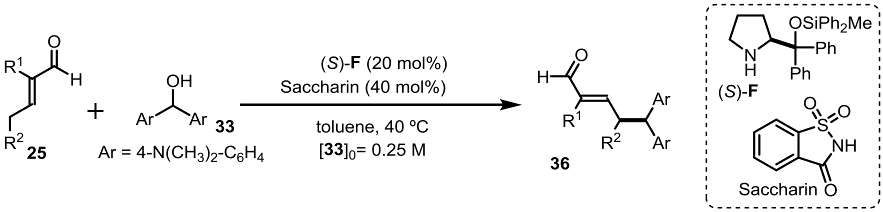
Entry	acid	conv (%)[b]	*ee* (%)[c]
1	2,6-$(CF_3)_2$-$C_6H_3CO_2H$	18	88
2	2,6-$(F)_2$-$C_6H_3CO_2H$	28	91
3	*p*-NO_2-$C_6H_4CO_2H$	24	88
4	*o*-NO_2-$C_6H_4CO_2H$	29	91
5	2,6-$(NO_2)_2$-$C_6H_3CO_2H$	83	82
6	CF_3CO_2H	29	88
7	TsOH	6	71
8[d]	DPP	27	91
9	Saccharin	71	88

[a] Reactions performed on a 0.1 mmol scale using 2 equiv of **25a**, with $[\mathbf{33}]_0 = 0.5$ M, in toluene at 40 °C. Reaction time 16 h. TsOH = *p*-toluensulfonic acid, DPP = diphenyl phosphate [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction carried out using 4 equivalents of **25a**.

Further optimization experiments carried out with 20 mol% of the catalyst **F** in toluene established a 2 : 1 saccharin/amine ratio as the most effective combination, while revealing that the reagent concentration was also crucial for modulating the efficiency. Performing the reaction at 40 °C with an excess of enal **25a** (4 equiv.) and in higher dilution ($[\mathbf{25a}]_0 = 0.25$ M), the product **36a** was obtained in synthetically useful yield and enantioselectivity after 24 h reaction time (**36a** isolated in 88% yield and 93% *ee*). These conditions were selected to evaluate the scope of the secondary amine catalyzed γ-alkylation of α-branched enals (see Table 6).

As shown in Table 6, different alkyl substituents, including a heteroatom-containing moiety (entry 6), can be accommodated at the enal γ-position without affecting either the site-selectivity or the enantioselectivity of the vinylogous S_N1-type process (entries from 1 to 6). Remarkably, γ-aryl-substituted enals are competent substrates for this catalytic system (entries 7 – 9). For these substrates, the γ-alkylation protocol opens a direct access to enantiomerically enriched benzylic stereogenic center. Different aliphatic substituents in the α-position of the enals are well-tolerated, enabling access to a broad variety of multifunctional molecules with complete γ-site selectivity and moderate-to-high levels of enantioselectivity (entries 10 and 11). As a limitation of the system, 2-phenylpent-2-enal, bearing a Ph group at the α-position, reacted smoothly providing the corresponding product **36l** with a modest level of stereocontrol (40% *ee*; entry 12).

Table 6. Aldehyde Scope for the Direct γ-Alkylation. [a]

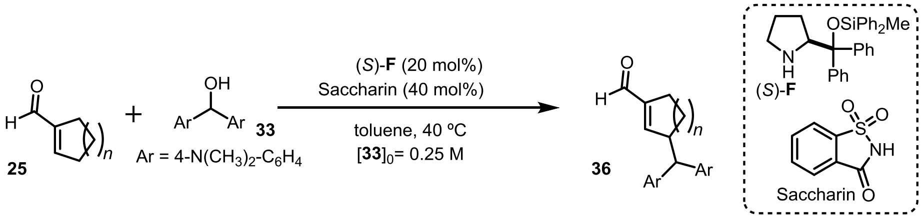


Entry	R^1	R^2	**36**	time (h)	Yield (%)[b]	*ee* (%)[c]
1	Me	Me	**a**	24	88	93
2	Me	Et	**b**	32	74	96
3[d]	Me	*i*Pr	**c**	48	63	94
4	Me	Allyl	**d**	50	82	94
5	Me	Bn	**e**	43	59	95
6	Me	$MeSCH_2$	**f**	48	40	90
7	Me	Ph	**g**	6	92	92
8	Me	4-MeO-C_6H_4	**h**	6	88	94
9	Me	4-Cl-C_6H_4	**i**	5.5	92	91
10[d]	Et	Et	**j**	78	82	92
11	Bn	Bn	**k**	48	83	94
12	Ph	Me	**l**	26	82	40

[a] Reactions performed on a 0.2mmol scale using 4 equiv of **33**, with [**10**]$_0$ = 0.25 M, in toluene at 40 °C. [b] Yield of the isolated product **36** after chromatographic purification. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction carried out in toluene with [**25**]$_0$ = 0.5 M.

We also explored the possibility of extending the chiral secondary amine-induced vinylogous nucleophilicity to cyclic α-branched enals. The protocol developed for the linear substrates can be translated to cyclopent-1-ene-1-carboxaldehyde **25m** and cyclohex-1-ene-1-carboxaldehyde **25n**, maintaining a good level of reactivity but with only moderate stereoselectivity (Table 7). Notably, the five-membered substrate proved to be very reactive as the reaction reached completion within 4 h (entry 1).

Table 7. Asymmetric γ-Alkylation of Cyclic α-Branched Enals.[a]

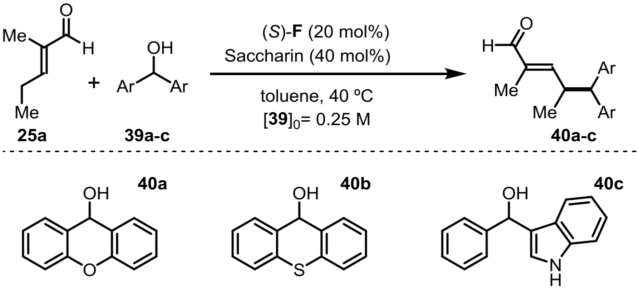


Entry	*n*	**36**	time (h)	Yield (%)[b]	*ee* (%)[c]
1	1	**m**	4	76	68
2	2	**n**	32	86	63

[a] Reactions performed on a 0.2mmol scale using 4 equiv of **25**, with $[\mathbf{34}]_0 = 0.25$M, in toluene at 40 °C. [b] Yield of the isolated product **36** after chromatographic purification. [c] Determined by HPLC analysis on a chiral stationary phase.

To further delineate the reaction scope, we tested other alcohols able to generate stable carbocations through acid-catalyzed ionization (see Table 8). Xanthydrol **39a** and thioxanthydrol **39b** reacted smoothly under the reaction conditions, leading to the γ-alkylated products **40a** and **40b**, respectively, with synthetically useful results (Table 8, entries 1 and 2).[34]

Table 8. Electrophile Precursor Scope. [a]



Entry	**40**	time (h)	Yield (%)[b]	d.r. (%)[c]	*ee* (%)[d]
1[e]	**a**	30	65	-	81
2[f]	**b**	30	78	-	81
3	**c**	25	52[g]	1.3:1	87/92

[a] Reactions performed on a 0.2mmol scale using 4 equivalents of **25a**, with $[\mathbf{39}]_0 = 0.25$ M, in toluene at 40 °C. [b] Yield of the isolated product **40** after chromatographic purification. [c] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Reaction performed in MeCN with $[\mathbf{39b}]_0$=0.5 M; 2,4-NO_2-$C_6H_3CO_2H$ was used as the acidic additive. [f] Reaction performed in MeCN with $[\mathbf{39c}]_0$=0.5 M. [g] Yield of the product obtained as a mixture of diastereoisomers.

(1H-Indol-3-yl)(phenyl)methanol **39c** can be used to easily access relevant indole-containing compounds in high enantiomeric excess, but with low control of the diastereoselection (Table 8, entry 3).[34,38]

The absolute configuration of compound **40b** was unambiguously determined by anomalous-dispersion X-ray crystallographic analysis: an (*S*) absolute configuration at the newly formed γ-stereogenic center was inferred.[39]

Also in this case the classical "steric control approach" well accounts for the stereochemical outcome of the reaction. With the support of results obtained in the studies of the dienamine intermediate we propose the stereochemical model shown in Figure 9.

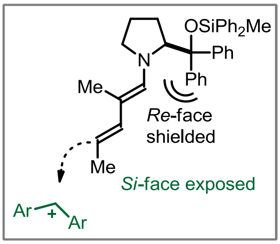


Figure 9. Proposed Stereochemical Model.

4.4 Conclusions

By exploiting the underscored ability of secondary amine catalysts to promote dienamine activation of α-branched enals, we could expand the synthetic potential of this activation mode to develop two mechanistically different reactions. We successfully realized the first example of a discrete catalytic and enantioselective vinylogous aldol reaction of an unmodified acyclic unsaturated carbonyl substrate. Preliminary mechanistic studies suggest that, depending on the nature of the α-branched enal substituents, two divergent reaction mechanisms can be operating, leading to different products and stereochemical outcomes. The same catalytic concept was also applied in a nucleophilic substitution reaction, namely a direct γ-selective S_N1-type alkylation. This study showed once again the ability of secondary amines to effectively condense with hindered carbonyls, like α-branched enals, and control the remote stereochemistry of the resulting dienamine active species.

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[38] B. Han, Y.-C. Xiao, Y. Yao, Y.-C. Chen. Lewis Acid Catalyzed Intramolecular Direct Ene Reaction of Indoles. *Angew. Chem., Int. Ed.*, **2010**, *49*, 10189.

[39] Crystallographic data for compound **40b** are available free of charge from the Cambridge Crystallographic Data Centre, accession numbers CCDC 894226.

4.5 Experimental Section

Materials.

Commercial grade reagents and solvents were purchased from Sigma Aldrich, Fluka, and Alfa Aesar and used as received, without further purification; otherwise, where necessary, they were purified as recommended. The cinchona-based primary amine catalyst 6’-hydroxy-9-amino-9-deoxy*epi*quinidine **QD-OH**, was prepared from commercially available quinidine following the literature procedure. Chiral secondary amine catalyst **A**, **B**, **H**, **I** and **J** are commercially available (Aldrich or Alfa Aeser); **A** was purified by flash column chromatography prior to use and stored at 4 °C under argon to avoid undesired desilylation that would affect the catalytic potential of the amine. Catalyst **F** was synthesized following the procedure reported in the literature.[27]

The N-benzyl protected isatins **26** were easily synthesized from the corresponding commercially available unprotected isatins, according to the following procedure: a solution of N-H isatin (5 mmol in 40 ml of dry DMF) was slowly added to a suspension of sodium-hydride (1.04 g, 60% dispersion in paraffin liquid, 1.3 equiv) in dry DMF (100ml) at 0 °C over a period of 10 minutes. The mixture was stirred at the same temperature for further 30 minutes. Then benzylbromide (6 mmol, 1.2 equiv) was added dropwise at the same temperature. The mixture was slowly warmed up at room temperature and stirring continued until the reaction was over (complete consumption of the starting N-H isatin, as judge by analytical TLC). The reaction was cooled at 0 °C and quenched with water (750 ml). The suspension was then filtered and the filtrated recrystallized from EtOAc and hexane to give the final product **26**.

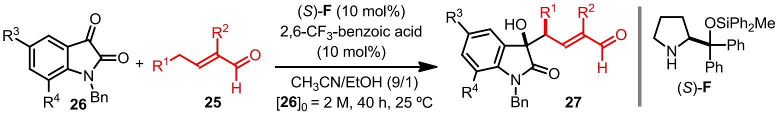
Most of the α-branched enals **25** are commercially available and were purchased from Aldrich or Alfa Aeser and used as received. Otherwise, they were synthesized according to the following procedure.

Preparation of α-Branched Enals.

A mixture of linear aliphatic aldehyde (1 equiv) and the appropriate triphenylphosphorane (1.5 equiv) was dissolved in THF and refluxed for 16 h. The solution was then allowed to reach room temperature; the solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography (silica gel) to yield the desired product α-branched enals **25** (yield 40-50 %).

Note: For all the α-branched enals **25**, a E/Z ratio >95:5 was determined by ^{1}H NMR analysis. No double bond scrambling was observed neither during the catalytic reaction (checked by analysis of the crude reaction mixture) nor mixing the enal with a catalytic amount of catalyst **F**.

4.5.1. General Procedure for the Vinylogous Aldol Reaction (*Procedure A*)

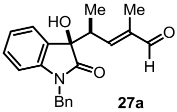


All the reactions were carried out in a 9/1 mixture of acetonitrile and ethanol without any precaution for excluding air and moisture (open air chemistry on the benchtop). An ordinary vial equipped with a Teflon-coated stir bar and a plastic screw cap was charged with (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol methyldiphenylsilyl ether **F** (9.00 mg, 0.02 mmol, 10 mol%) and 2,6-bis(trifluromethyl)benzoic acid (5.2 mg, 0.02 mmol, 10 mol%). Then the solvent mixture (100 µL) and the α-branched enal **25** (0.4 mmol) were sequentially added and the resulting solution stirred at ambient temperature for 5 minutes. The reaction was started by the addition of the N-benzyl protected isatin derivative **26** (0.2 mmol). The vial was sealed and immerged in a water bath (thermostated at 25 °C) and stirring continued over 40 hours. Then the crude mixture was flushed through a short plug of silica, using dichloromethane/diethyl ether 1:1 as the eluent (5 ml). Solvent was removed under reduced pressure and the crude mixture was analyzed by ^{1}H NMR spectroscopy to determine the diastereomeric ratio. The product **27** was isolated by flash column chromatography using the specified eluent.

Determination of Yield and Conversion in the Optimization Studies.

The conversion of the starting materials and the yield of the products in the optimization studies related to the model reaction depicted in Table 1 of this chapter were determined by ^{1}H NMR spectroscopy adding an internal standard in the crude reaction: 2,5-dimethylfuran: δ 2.26 ppm (s, 6H), 5.84 (s, 2H). Since in all instances the conversion of isatin **26a** was equal to the yield of product **27a**, in some cases the yield was determined by integration of the signals of the unreacted isatin **26a** in the ^{1}H NMR spectra (N-benzyl isatin **26a** NMR signal @ δ 4.92 ppm (s) and product **27a** signal @ 9.34 (s) and 9.21 (s); double checked with the product signals @ 6.42 (d) and 6.16 (d)).

(*S*,*E*)-4-((*R*)-1-benzyl-3-hydroxy-2-oxoindolin-3-yl)-2-methylpent-2-enal (27a)

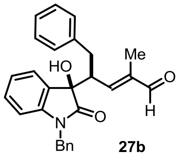


27a

The reaction was carried out according to the general procedure to furnish the crude product as a 3.2:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 6.44 ppm (d), δ_{minor} 6.21 ppm (d). The title compound was isolated as a mixture of diastereoisomers (R_f = 0.24 hexane/ethyl acetate 9/1) in 87% yield (white solid). The enantiomeric excess was determined to be 90% for the major diastereoisomer (76% *ee* for the minor) by HPLC analysis on a Daicel Chiralpak IB column: 95:5 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 26.7 min, τ_{minor} = 62.5 min. $[\alpha]_D^{28}$= +61.0 (c = 0.79, $CHCl_3$, d.r. 3.2/1, $_{major}$ 90% *ee*, $_{minor}$ 76% *ee*). HRMS *calcd*. for ($C_{21}H_{21}NO_3$+Na): 358.1419, found 358.1419.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33 (s, 1H), 7.39 (d, 1H, J_1 = 7.3 Hz, J_2 = 1.1 Hz), 7.35-7.19 (m, 7H), 7.08 (dt, 1H, J_d = 7.6 Hz, J_t = 0.9 Hz), 6.78 (d, 1H, J = 7.8 Hz), 6.42 (dq, 1H, J_d = 10.5 Hz, J_q= 1.3 Hz), 5.05 (d, 1H, J = 15.6 Hz), 4.71 (d, 1H, J = 15.6 Hz), 3.49-3.39 (m, 1H), 1.74 (d, 3H, J = 1.2 Hz), 1.00 (d, 3H, J = 6.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 177.3, 151.7, 142.9, 141.3, 135.5, 130.2, 129.0, 128.3, 128.1, 127.6, 127.5, 124.7, 123.3, 109.7, 78.4, 44.2, 41.5, 14.1, 9.8 ppm.

(*S,E*)-4-((*R*)-1-benzyl-3-hydroxy-2-oxoindolin-3-yl)-2-methyl-5-phenylpent-2-enal (27b)



27b

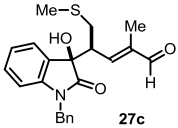
The reaction was carried out following the general procedure to furnish the crude products as a 2.5:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 9.18 ppm (s), δ_{minor} 9.11 ppm (s).

The title compound was isolated as a mixture of diastereoisomers (R_f = 0.3 hexane/ethyl acetate 8/2) in 68% yield (white solid). The enantiomeric excess was determined to be 95% for the major diastereoisomer (77% ee for the minor) by HPLC analysis on a Daicel Chiralpak IA column: 90/10 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 22.9 min, τ_{minor} = 41.0min.

$[\alpha]_D^{26}$= +149.0 (c = 1.0, $CHCl_3$, d.r. 2.5/1, $_{major}$ 95% ee, $_{minor}$ 77% ee). HRMS *calcd*. for ($C_{27}H_{25}NO_3$+Na): 434.1732, found 434.1740.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (s, 1H), 7.46 (d, 1H, J_1 = 7.4 Hz, J_2 = 0.9 Hz), 7.37-6.69 (m, 12H), 6.81 (d, 1H, J = 7.7 Hz), 6.31 (dq, 1H, J_d = 10.8 Hz, J_q= 1.2 Hz), 5.05 (d, 1H, J = 15.8 Hz), 4.73 (d, 1H, J = 15.8 Hz), 3.66 (td, 1H, J_t = 11.0 Hz, J_d= 3.3 Hz), 3.08 (dd, 1H, J_1 = 13.4 Hz, J_2= 11.2 Hz), 1.26 (d, 3H, J = 1.3 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.8, 177.2, 149.5, 143.2, 142.8, 138.4, 135.4, 130.4, 129.1, 129.0, 128.6, 128.5, 128.0, 127.6, 127.5, 126.6, 124.5, 123.5, 109.9, 78.1, 49.5, 44.2, 35.1, 9.5 ppm.

(*S,E*)-4-((*R*)-1-benzyl-3-hydroxy-2-oxoindolin-3-yl)-2-methyl-5-(methylthio)pent-2-enal (27c)



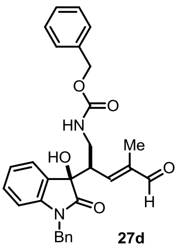
27c

The reaction was carried out following the general procedure **A** to furnish the crude products as a 1.6:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 6.12 ppm (d), δ_{minor} 5.89 ppm (d).

The title compound was isolated as a mixture of diastereoisomers (R_f = 0.28 hexane/ethyl acetate 8/2) in 89% yield (colourless solid). The enantiomeric excess was determined to be 95% for the major diastereoisomer (77% *ee* for the minor) by HPLC analysis on a Daicel Chiralpak IB column: 95:5 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 32.0 min, τ_{minor} = 97.4 min. $[\alpha]_D^{26}$= +103.5 (c = 0.68, $CHCl_3$, d.r. 1.6/1, $_{major}$ 95% ee, $_{minor}$ 77% ee).

HRMS calc. for ($C_{22}H_{23}NO_3S$+Na): 404.1296, found 404.1286. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.17 (s, 1H), 7.38 (d, 1H, J = 7.7 Hz), 7.34-7.15 (m, H), 7.06 (dt, 1H, J_d = 7.6 Hz, J_t = 0.8 Hz), 6.78 (d, 1H, J = 7.8 Hz), 6.14 (dq, 1H, J_d = 10.9 Hz, J_q= 1.4 Hz), 5.02 (d, 1H, J = 15.5 Hz), 4.70 (d, 1H, J = 15.5 Hz), 3.68 (bs, 1H), 3.65-3.55 (m, 1H), 2.94 (dd, 1H, J_1 = 13.1 Hz, J_2 = 4.6 Hz), 2.54 (dd, 1H, J_1 = 13.0 Hz, J_2 = 10.0 Hz), 2.07 (s, 3H), 1.66 (d, 3H, J = 1.3 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.8, 176.7, 148.8, 143.3, 143.3, 142.5, 135.4, 130.4, 129.0, 128.2, 127.4, 124.3, 123.5, 109.7, 77.9, 46.5, 44.2, 33.3, 16.1, 10.1 ppm.

benzyl ((*R,E*)-2-((*R*)-1-benzyl-3-hydroxy-2-oxoindolin-3-yl)-4-methyl-5-oxopent-3-en-1-yl)carbamate (27d).

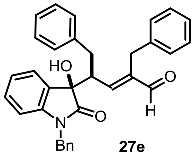


27d

The reaction was carried out following the general procedure to furnish the crude products as a 3.0:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 6.01 ppm (bd), δ_{minor} 5.91 ppm (bd).

The title compound was isolated as a mixture of diastereoisomers (R_f = 0.25 hexane/ethyl acetate 7/3) in 63% yield (white solid). The enantiomeric excess was determined to be 94% for the major diastereoisomer by HPLC analysis on a Daicel Chiralpak IB column: 85/15 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 27.4 min, τ_{minor} = 45.1 min. $[\alpha]_D^{26}$= +55.5 (c = 0.90, $CHCl_3$, d.r. 3.0/1, 94% ee_{major}, 74% ee_{minor}). HRMS calc. for ($C_{29}H_{28}N_2O_5$+Na): 507.1896, found 507.1911. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (bs, 1H), 7.50-7.13 (m, 14H), 7.05 (t, 1H, J_t = 7.4 Hz), 6.73 (d, 1H, J = 7.8 Hz), 6.10 (bd, 1H, J = 10.0 Hz), 5.34-5.25 (m, 1H), 5.07-5.03 (m, 1H), 4.99 (d, 1H, J = 15.6 Hz), 4.66 (d, 1H, J = 15.6 Hz), 3.82-3.73 (m, 1H), 3.64-3.47 (m, 2H), 1.50 (bs, 3H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ194.7, 176.6, 153.7, 147.2, 143.3, 142.2, 136.4, 135.4, 130.3, 129.4, 129.0, 128.6, 128.2, 127.5, 124.1, 123.6, 109.6, 77.2, 66.9, 47.2, 44.0, 40.0, 9.7 ppm.

(*S,E*)-2-benzyl-4-((*R*)-1-benzyl-3-hydroxy-2-oxoindolin-3-yl)-5-phenylpent-2-enal (27e).



27e

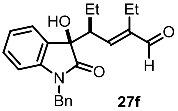
The reaction was carried out following the general procedure (using 20% mol of catalyst loading) to furnish the crude products as a 1.5:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 9.32 ppm (s), δ_{minor} 9.24 ppm (s).

The title compound was isolated as a mixture of diastereoisomers (hexane/ethyl acetate 10/1) in 65% yield (white solid). The enantiomeric excess was determined to be 90% for the major diastereoisomer by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 9.3min, τ_{minor} = 11.7 min. $[\alpha]_D^{26}$= +92.5 (c = 0.75, $CHCl_3$, d.r. 1.5/1, $_{major}$ 90% *ee*, $_{minor}$ 76% *ee*). HRMS calc. for ($C_{33}H_{29}NO_3$+Na): 510.2045, found 510.2021.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32(bs, 1H), 7.36-6.93 (m, 20H), 6.79 (bd, 1H, J = 7.8 Hz), 6.76-6.71 (m, 2H), 6.48 (d, 1H, J = 11.0Hz), 5.00 (d, 1H, J = 15.9 Hz), 4.72 (d, 1H, J = 15.9 Hz), 3.72 (td, 1H, J_t

= 11.0 Hz, J_d = 3.4 Hz), 3.41 (d, 1H, J = 15.1 Hz), 3.02-2.95 (m, 1H), 2.92 (d, 1H, J = 15.0 Hz), 2.87 (bs, 1H), 2.39 (dd, 1H, J_1 = 13.3 Hz, J_2 = 10.7 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 177.0, 150.9, 146.0, 142.4, 138.3, 138.1, 135.3, 130.2, 129.1, 129.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.5, 126.6, 126.0, 124.7, 123.4, 109.8, 77.9, 49.3, 44.1, 35.4, 29.7 ppm.

(*S,E*)-4-((*R*)-1-benzyl-3-hydroxy-2-oxoindolin-3-yl)-2-ethylhex-2-enal (27f)



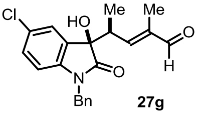
27f

The reaction was carried out following the general procedure (using 20% mol of the catalyst **D**/acid combination) to furnish the crude products as a 1.5:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 6.22 ppm (d), δ_{minor} 5.87 ppm (d).

The title compound was isolated as a single diastereoisomer (hexane/ethyl acetate 10:1) in 28% yield (white solid). The enantiomeric excess was determined to be 94% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 9.1 min, τ_{minor} = 12.9 min. $[\alpha]_D^{26}$= +84.5 (c = 1.45, $CHCl_3$, 94% *ee*). HRMS *calcd*. for ($C_{23}H_{25}NO_3$+Na): 386.1732, found 386.1739.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.35(s, 1H), 7.37 (dd, 1H, J_1 = 7.4 Hz, J_2= 1.0 Hz), 7.34-7.22 (m, 6H), 7.07 (td, 1H, J_t = 7.5 Hz, J_d= 1.0 Hz), 6.77 (d, 1H, J = 7.8 Hz), 6.22 (d, 1H, J = 11.0Hz), 5.01 (d, 1H, J = 15.4 Hz), 4.74 (d, 1H, J = 15.4 Hz), 3.26 (td, 1H, J_t = 11.1 Hz, J_d = 3.0 Hz), 2.96 (bs, 1H), 2.36-2.23 (m, 2H), 1.67-1.58 (m ,1H), 1.20-1.10 (m, 1H), 0.95 (t, 3H, J = 7.5 Hz), 0.76 (t, 3H, J = 7.5 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.9, 177.4, 150.4, 149.3, 142.9, 135.5, 1302, 129.0, 128.0, 127.6, 124.7, 123.3, 109.8, 78.2, 48.6, 44.2, 21.7, 18.1, 13.4, 12.1 ppm.

(*S,E*)-4-((*R*)-1-benzyl-5-chloro-3-hydroxy-2-oxoindolin-3-yl)-2-methylpent-2-enal (27g)



27g

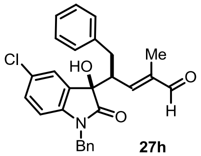
The reaction was carried out following the general procedure to furnish the crude products as a 1.7:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 6.36 ppm (d), δ_{minor} 6.17 ppm (d).

The title compound was isolated as a mixture of diastereoisomers (R_f = 0.30 hexane/ethyl acetate 8/2) in 92% yield (white solid). The enantiomeric excess was determined to be 86% for the major diastereoisomer (73% *ee* for the minor) by HPLC analysis on a Daicel Chiralpak IA column: 90:10 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 15.3 min, τ_{minor} = 22.2 min. $[\alpha]_D^{26}$= +31.0 (c = 1.15, $CHCl_3$, d.r. 1.7/1, $_{major}$ 86% *ee*, $_{minor}$ 73% *ee*). HRMS *calcd*. for ($C_{21}H_{20}NO_3Cl$+Na): 392.1029, found 392.1038.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.36 (s, 1H), 7.39 (d, 1H, J = 2.1 Hz), 7.37-7.18 (m, 7H), 6.72 (d, 1H, J = 8.5 Hz), 6.39 (dq, 1H, J_d = 10.2 Hz, J_q= 1.3 Hz), 5.05 (d, 1H, J = 15.7 Hz), 4.72 (d, 1H, J = 15.7 Hz), 3.49-3.39 (m, 1H), 1.77 (d, 3H, J = 1.3 Hz), 1.05 (d, 3H, J = 6.8 Hz) ppm. ^{13}C NMR (100 MHz,

$CDCl_3$): δ 195.0, 176.9, 150.8, 141.6, 141.4, 135.0, 130.1, 129.1, 128.9, 128.3, 127.5, 127.4, 125.2, 110.7, 78.4, 44.3, 41.5, 14.0, 9.9 ppm.

(*S,E*)-4-((*R*)-1-benzyl-5-chloro-3-hydroxy-2-oxoindolin-3-yl)-2-methyl-5-phenylpent-2-enal (27h)



27h

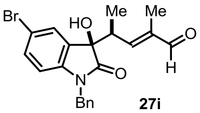
The reaction was carried out following the general procedure to furnish the crude products as a 1.6:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 6.23 ppm (d), δ_{minor} 5.94 ppm (d).

The title compound was isolated as a mixture of diastereoisomers (R_f = 0.30 hexane/ethyl acetate 8/2) in 69% yield (white solid). The enantiomeric excess was determined to be 92% for the major diastereoisomer (78% *ee* for the minor) by HPLC analysis on a Daicel Chiralpak IA column: 52.5/2.5/50 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 7.9 min, τ_{minor} = 9.2 min. $[\alpha]_D^{26}$= +80.0 (c = 0.77, $CHCl_3$, d.r. 1.6/1, $_{major}$ 92% *ee*, $_{minor}$ 78% *ee*). HRMS *calcd*. for ($C_{27}H_{24}NO_3Cl$+Na): 468.1342, found 468.1358.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (s, 1H), 7.42 (d, 1H, *J* = 2.2 Hz), 7.36-7.12 (m, 9H), 7.05-7.01 (m, 2H), 6.71 (d, 1H, *J* = 8.4 Hz), 6.42 (dq, 1H, J_d = 10.9 Hz, J_q= 1.3 Hz), 5.02 (d, 1H, *J* = 15.4 Hz), 4.73 (d, 1H, *J* = 15.4 Hz), 3.62 (td, 1H, J_t = 10.9 Hz, J_d= 3.6 Hz), 3.34 (bs, 1H), 3.07 (dd, 1H, J_1 = 13.6 Hz, J_2= 3.1 Hz), 2.49 (dd, 1H, J_1 = 13.6 Hz, J_2= 10.9 Hz), 1.27 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.6, 176.8, 148.7, 143.5, 141.2, 138.1, 134.9, 130.4, 130.3, 129.2, 129.0, 128.6, 128.3, 127.6, 126.7, 125.0, 110.9, 78.0, 49.5, 44.3, 34.9, 9.5 ppm.

Crystals of compound **27h** were obtained by slow evaporation of a mixture of hexane/diethyl ether at room temperature. (CCDC 885390)

(*S,E*)-4-((*R*)-1-benzyl-5-bromo-3-hydroxy-2-oxoindolin-3-yl)-2-methylpent-2-enal (27i).



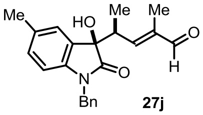
27i

The reaction was carried out following the general procedure to furnish the crude products as a 1.9:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 6.35 ppm (d), δ_{minor} 6.19 ppm (d). The title compound was isolated as a mixture of diastereoisomers (R_f = 0.30 hexane/ethyl acetate 8/2) in 68% yield (white solid). The enantiomeric excess was determined to be 85% for the major diastereoisomer (78% *ee* for the minor) by HPLC analysis on a Daicel Chiralpak IA column: 90:10 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 8.3 min, τ_{minor} = 11.5 min. $[\alpha]_D^{26}$= +51.0 (c = 1.33, $CHCl_3$, d.r. 1.9/1, $_{major}$ 85% *ee*, $_{minor}$ 78% *ee*). HRMS *calcd*. for ($C_{21}H_{20}NO_3Br$+Na): 436.0524, found 436.0533.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 7.50 (d, 1H, *J* = 2.0 Hz), 7.39-7.23 (m, 7H), 6.64 (d, 1H, *J* = 8.3 Hz), 6.36 (dq, 1H, J_d = 10.4 Hz, J_q= 1.4 Hz), 5.01 (d, 1H, *J* = 15.6Hz), 4.67 (d, 1H, *J* = 15.6 Hz), 3.51 (bs, 1H), 3.47-3.36 (m, 1H), 1.74 (d, 3H, *J* = 1.4 Hz), 1.05 (d, 3H, *J* = 6.9 Hz) ppm. ^{13}C NMR

(100 MHz, $CDCl_3$): δ 195.1, 176.9, 150.9, 141.9, 141.6, 134.9, 132.9, 130.6, 129.1, 128.2, 127.9, 127.5, 116.1, 111.2, 78.4, 44.2, 41.5, 14.1, 9.8 ppm.

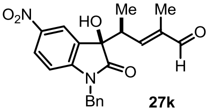
(*S,E*)-4-((*R*)-1-benzyl-3-hydroxy-5-methyl-2-oxoindolin-3-yl)-2-methylpent-2-enal (27j).


27j

The reaction was carried out following the general procedure to furnish the crude products as a 3.8:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 6.42 ppm (d), δ_{minor} 6.22 ppm (d). The title compound was isolated as a mixture of diastereoisomers (R_f = 0.30 hexane/ethyl acetate 8/2) in 76% yield (white solid). The enantiomeric excess was determined to be 95% for the major diastereoisomer (81% ee for the minor) by HPLC analysis on a Daicel Chiralpak IA column: 49:2:49 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 7.4 min, τ_{minor} = 10.3 min. $[\alpha]_D^{26}$= +66.7 (c = 1.345, $CHCl_3$, d.r. 3.8/1, $_{major}$ 95% *ee*, $_{minor}$ 81% *ee*). HRMS *calcd*. for ($C_{22}H_{23}NO_3$+Na): 372.1576, found 372.1586.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.36 (s, 1H), 7.35-7.19 (m, 6H), 7.06 (bd, 1H, *J* = 7.9 Hz), 6.68 (d, 1H, *J* = 7.9 Hz), 6.46 (dq, 1H, J_d = 10.5 Hz, J_q= 1.3 Hz), 5.02 (d, 1H, *J* = 15.6 Hz), 4.69 (d, 1H, *J* = 15.6 Hz), 3.49-3.41 (m, 2H), 2.34 (s, 3H), 1.76 (d, 3H, *J* = 1.3 Hz), 1.02 (d, 3H, *J* = 6.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 177.4, 152.1, 141.2, 140.5, 135.6, 132.9, 130.4, 128.9, 128.5, 127.9, 127.6, 127.4, 125.4, 109.5, 78.6, 44.1, 41.5, 21.2, 14.2, 9.8 ppm.

(*S,E*)-4-((*R*)-1-benzyl-3-hydroxy-5-nitro-2-oxoindolin-3-yl)-2-methylpent-2-enal (27k)

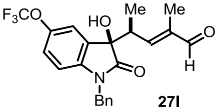

27k

The reaction was carried out following the general procedure to furnish the crude products as a 1.5:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 6.33 ppm (d), δ_{minor} 6.15 ppm (d).

The title compound was isolated as a mixture of diastereoisomers (R_f = 0.30 hexane/ethyl acetate 7/3) in 87% yield (white solid). The enantiomeric excess was determined to be 87% for the major diastereoisomer (75% *ee* for the minor) by HPLC analysis on a Daicel Chiralpak IA column: 49/2/49 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 10.7 min, τ_{minor} = 14.0 min. $[\alpha]_D^{26}$= +80.3 (c = 0.80, $CHCl_3$, d.r. 1.5/1, $_{major}$ 87% *ee*, $_{minor}$ 75% *ee*). HRMS *calcd*. for ($C_{21}H_{20}N_2O_5$+Na): 403.1270, found 403.1270.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 8.35-8.25 (m, 2H), 7.39-7.23 (m, 5H), 6.88 (d, 1H, *J* = 6.7 Hz), 6.33 (dq, 1H, J_d = 10.4 Hz, J_q= 1.4 Hz), 5.09 (d, 1H, *J* = 15.4 Hz), 4.78 (d, 1H, *J* = 15.4 Hz), 3.55-3.39 (m, 1H), 3.26 (bs, 1H), 1.71 (d, 3H, *J* = 1.4 Hz), 1.08 (d, 3H, *J* = 6.7 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 178.3, 151.2, 141.3, 140.3, 136.9, 136.1, 132.0, 128.7, 127.5, 126.8, 124.6, 123.8, 103.1, 77.4, 44.8, 41.8, 14.0, 9.8 ppm.

(*S,E*)-4-((*R*)-1-benzyl-3-hydroxy-2-oxo-5-(trifluoromethoxy)indolin-3-yl)-2-methylpent-2-enal (27l)



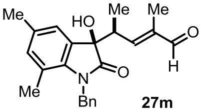
27l

The reaction was carried out following the general procedure to furnish the crude products as a 2.9:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 6.28 ppm (d), δ_{minor} 6.16ppm (d).

The title compound was isolated as a mixture of diastereoisomers (R$_f$ = 0.30 hexane/ethyl acetate 8/2) in 71% yield (white solid). The enantiomeric excess was determined to be 89% for the major diastereoisomer (63% *ee* for the minor) by HPLC analysis on a Daicel Chiralpak IA column: 49/2/49 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 8.2 min, τ_{minor} = 10.5 min. HRMS *calcd*. for ($C_{22}H_{20}NO_4F_3$+Na): 442.1242, found 442.1259.

^{1}H NMR (400 MHz, CDCl$_3$): δ 9.28 (s, 1H), 7.36-7.26 (m, 6H), 7.14-7.10 (m, 1H), 6.76 (d, 1H, *J* = 8.4 Hz), 6.28 (dq, 1H, J_d = 10.3 Hz, J_q= 1.2 Hz), 5.06 (d, 1H, *J* = 15.6 Hz), 4.70 (d, 1H, *J* = 15.6 Hz), 3.45-3.37 (m, 1H), 3.02 (bs, 1H), 1.70 (d, 3H, *J* = 1.2 Hz), 1.07 (d, 3H, *J* = 6.6 Hz) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 194.9, 177.1, 150.5, 145.1, 141.6, 1414, 134.9, 129.2, 128.4, 127.6, 123.3, 118.6, 110.3, 78.3, 44.4, 41.7, 13.9, 9.8 ppm.

(*S,E*)-4-((*R*)-1-benzyl-3-hydroxy-5,7-dimethyl-2-oxoindolin-3-yl)-2-methylpent-2-enal (27m)



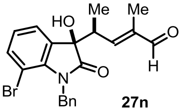
27m

The reaction was carried out following the general procedure to furnish the crude products as a 3.9:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 6.23 ppm (d), δ_{minor} 6.12 ppm (d) in deutereted toluene.

The title compound was isolated as a mixture of diastereoisomers (R$_f$ = 0.30 hexane/ethyl acetate 10/1) in 65% yield (pale-pink solid). The enantiomeric excess was determined to be 91% for the major diastereoisomer (77% *ee* for the minor) by HPLC analysis on a Daicel Chiralpak IA column: 48.5:3:48.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 6.4 min, τ_{minor} = 7.7 min. $[\alpha]_D^{26}$= +64.5 (c = 1.40, CHCl$_3$, d.r. 3.9/1, $_{major}$ 90% *ee*, $_{minor}$ 77% *ee*). HRMS *calc.* for ($C_{23}H_{25}NO_3$+Na): 386.1732, found 386.1751.

^{1}H NMR (400 MHz, CDCl$_3$): δ 9.40 (s, 1H), 7.32-7.20 (m, 3H), 7.17-7.12 (m, 2H), 7.08 (bs, 1H), 6.81 (bs, 1H), 6.47 (dq, 1H, J_d = 10.4 Hz, J_q= 1.4 Hz), 5.15 (s, 1H), 5.10 (s, 1H), 3.48-3.38 (m, 2H), 2.28 (s, 3H), 2.21 (s, 3H), 1.73 (d, 3H, *J* = 1.4 Hz), 1.06 (d, 3H, *J* = 6.9 Hz) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 195.3, 178.5, 152.4, 141.1, 138.5, 137.3, 134.6, 132.9, 129.0, 127.5, 125.9, 123.3, 120.2, 77.6, 45.3, 41.6, 20.9, 18.8, 14.3, 9.8 ppm.

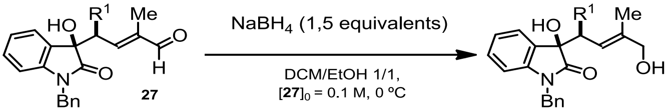
(*S,E*)-4-((*R*)-1-benzyl-7-bromo-3-hydroxy-2-oxoindolin-3-yl)-2-methylpent-2-enal (27n)



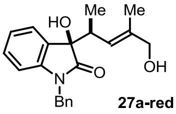
The reaction was carried out following the general procedure to furnish the crude products as a 2.4:1 mixture of diastereoisomers; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 6.29 ppm (d), δ_{minor} 6.38 ppm (d). The title compound was isolated as a mixture of diastereoisomers (R_f = 0.30 hexane/ethyl acetate 8/2) in 88% yield (white solid). The enantiomeric excess was determined to be 92% for the major diastereoisomer (71% ee for the minor) by HPLC analysis on a Daicel Chiralpak IA column: 49:2:49 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 8.2 min, τ_{minor} = 10.3 min. $[\alpha]_D^{26}$= +38.6 (c = 1.15, $CHCl_3$, d.r. 2.4/1, $_{major}$ 92% *ee*, $_{minor}$ 71% *ee*). HRMS *calcd*. for ($C_{21}H_{20}NO_3Br$+Na): 436.0524, found 436.0508.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.30 (s, 1H), 7.43 (dd, 1H, J_1 = 8.1 Hz, J_2= 1.2 Hz), 7.36 (dd, 1H, J_1 = 7.4 Hz, J_2= 1.2 Hz), 7.33-7.21 (m), 7.19-7.14 (m, 1H), 6.97 (dd, 1 H, J_1 = 8.2 Hz, J_2= 7.3 Hz), 6.35 (dq, 1H, J_d = 10.6 Hz, J_q= 1.5 Hz), 5.46 (d, 1H, J = 16.1 Hz), 5.29 (d, 1H, J = 16.1 Hz), 3.45-3.33 (m, 2H), 1.69 (d, 3H, J = 1.3 Hz), 1.03 (d, 3H, J = 6.7 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 178.3, 151.1, 141.4, 140.3, 136.9, 136.2, 132.0, 127.6, 126.8, 126.5, 124.6, 123.7, 103.1, 77.4, 44.8, 41.8, 14.0, 9.8 ppm.

4.5.2. General Procedure for the Reduction of Products 27

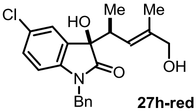


0.1 mmol of adducts **27a, 27h,** and **27j** were transferred in a vial and dissolved in 1 mL of a DCM/ethanol mixture (1 to 1 v/v) and cooled to 0 °C (ice bath). After the addition of $NaBH_4$ (1.5 equivalents, added in small portions) the mixture was stirred until the reaction was considered complete by TLC analysis (typically 1-2h). The reaction was then quenched with water and the compound extracted with diethyl ether. The aqueous phase was washed three times with diethyl ether and the combined organic phases dried over sodium sulphate. Solvent was removed under reduced pressure and the crude mixture was purified by chromatography column. Separation of the two diastereoisomers was straightforward, securing access to diastereomerically pure alcohol adducts.



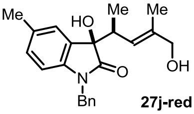
Compound **27a** was reduced to the corresponding alcohol following the general procedure. The crude was purified by flash column chromatography (gradient from hexane/ethyl acetate 7/3 to 1/1, R_f = 0.15 in hexane/ethyl acetate 7/3) to afford compound **27a-red** as a single diastereoisomer in

71% yield (colorless solid, 47% overall yield).
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.44-7.39 (m, 1H), 7.36-7.26 (m, 5H), 7.22 (td, 1H, J_t = 7.9 Hz, J_d = 1.3 Hz), 7.05 (td, 1H, J_t = 7.9 Hz, J_d = 1.3 Hz), 6.75 (d, 1H, J = 7.9 Hz), 5.48 (d, 1H, J = 10.3 Hz), 5.07 (d, 1H, J = 15.3 Hz), 4.70 (d, 1H, J = 15.3 Hz), 4.02 (bs, 1H), 3.25-3.17 (m, 1H), 3.03 (bs, 1H), 1.71 (s, 3H), 0.88 (d, 3H, J = 6.8 Hz) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ 177.9, 143.1, 139.0, 135.8, 129.6, 129.1, 128.9, 127.9, 127.6, 124.9, 123.8, 122.9, 109.4, 78.9, 68.6, 44.1, 40.2, 15.1, 14.4 ppm.



27h-red

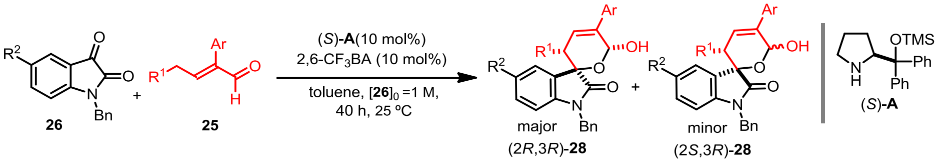
Compound **27h** was reduced to the corresponding alcohol following the general procedure. Chromatographic purification on silica gel (gradient from hexane/ethyl acetate 8:2 to 6/4, R$_f$ = 0.2 in hexane/ethyl acetate 7/3) afforded the reduced adduct **27h-red** as single diastereoisomer in 55% yield (colorless solid, 35% overall yield). Since the alchohl was not solid, the major diastereoisomer was then re-oxidized to the aldehyde adduct **27h** in order to get suitable crystals for X-ray crystallographic analysis. Oxidation of the alcohol **27h-red:** compound**27h-red** was transferred in a round bottom flask, then DCM (1.5 ml, 0.05M) and activated MnO$_2$ (10 equivalents) were added and the stirring continued over a period of 16 hours. The mixture was filtered on celite and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (hexane/ethyl acetate 7/3) to give the pure **27h** as single diastereoisomer in a 32% overall yield.



27j-red

Compound **27j** was reduced to the corresponding alcohol following the general procedure. Chromatographic purification on silica gel (gradient from hexane/ethyl acetate 7/3 to hexane/ethyl acetate 1/1, R$_f$ = 0.15 in hexane/ethyl acetate 7/3) to afford compound **27j-red** as single diastereo isomer in 74% yield (colorless solid, 44% overall yield). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.34-7.29 (m, 5H), 7.23-7.20 (m, 1H), 7.02 (d, 1H, J = 7.7 Hz), 6.63 (d, 1H, J = 8.0 Hz), 5.49 (d, 1H, J = 10.5 Hz), 5.05 (d, 1H, J = 15.8 Hz), 4.69 (d, 1H, J = 15.8 Hz), 4.02 (bs, 1H), 3.23-3.15 (m, 1H), 2.95 (bs, 1H), 2.95 (bs, 1H), 2.31 (s, 3H), 1.72 (s, 3H), 0.88 (d, 3H, J = 6.8 Hz) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ *177.8*, 140.7, 138.9, 135.9, 132.6, 129.8, 129.2, 129.1, 128.9, 127.8, 127.6, 125.6, 124.0, 109.1, 78.9, 68.7, 44.1, 40.2, 21.2, 15.1, 14.4 ppm

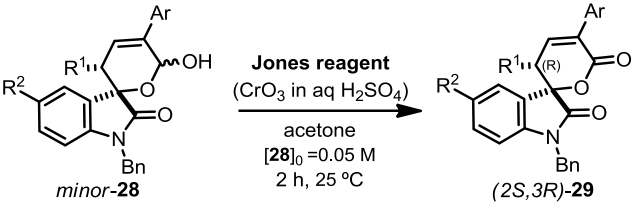
4.5.3. General Procedure for the Hetero-Diels-Alder-type Reaction of α-Aryl Substituted Enals (*Procedure B*)



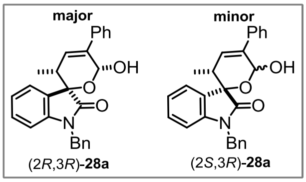
All the reactions were carried out in toluene (synthesis grade, >99%) without any precaution for excluding air and moisture (open air chemistry on the benchtop). An ordinary vial equipped with a Teflon-coated stir bar and a plastic screw cap was charged with (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **A** (6.5 mg, 0.02 mmol, 10 mol%) and 2,6-bis(trifluromethyl)benzoic acid (5.2 mg, 0.02 mmol, 10 mol%). Then the solvent (200 μL) and the α-branched enal **25** (0.4 mmol) were sequentially added and the resulting solution stirred at ambient temperature for 5 minutes. The reaction was started by the addition of the N-benzyl protected isatin derivative **26** (0.2 mmol). The vial was sealed and immerged in a water bath (thermostated at 25 °C) and stirring continued over 40 hours. Then the crude mixture was flushed through a short plug of silica, using dichloromethane/diethyl ether 1:1 as the eluent (5 ml). Solvent was removed under reduced pressure and the crude mixture was analyzed by ^{1}H NMR spectroscopy to determine the diastereomeric ratio. The two diastereoisomers for product **28** were isolated by flash column chromatography using the specified eluent.

While the major isomers, the spirooxindole lactols (2*R*,3*R*)-**28** are stable compounds that can be stored after isolation, the minor isomers (the (2*S*,3*R*)-**28** adducts) are stable on the bench only for 2-3 days. In addition, given the difficulties of determining their enantiomeric excess by HPLC analysis, spirooxindole lactols (2*S*,3*R*)-**28** were oxidized suddenly after their isolation. The procedure for the oxidation is as follows:

4.5.4. Procedure for the Oxidation of Lactol 28 to Lactons 29

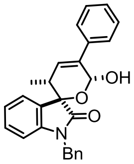


The oxidation of compounds **28** to the corresponding lactones **29** was performed following a slightly modified procedure reported in literature.[40] 0.1 mmol of compound **28** were placed and dried in a 5 ml vial, followed by the sequential addition of acetone (0.5 mL) and the Jones reagent (dropwise, 0.2 mL). The mixture was stirred at room temperature over 2 hours, then diluted with diethyl ether and quenched with water. The aqueous phase was washed three times with diethyl ether and the combined organic phases dried over sodium sulphate. Solvent was removed under reduced pressure and the crude mixture was purified by chromatography on silica gel (typically with hexane/ethyl acetate 9/1 as the eluent) to afford the pure spirooxindole dihydropyran-2-ones (2*S*,3*R*)-**29**.
Jones reagent was prepared carefully diluting a solution of CrO_3 (5g) in 5 mL of H_2SO_4 with 25 mL of water at 0 °C.



The reaction was carried out following the general procedure **B** to furnish the crude products as a mixture of 2.2:1 diastereoisomers (2*R*,3*R*)-**28a**/(2*S*,3*R*)-**28a**; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 6.13 ppm (bs), δ_{minor} 6.22 ppm and 6.25 ppm (bs). (2*R*,3*R*)-**28a**/(2*S*,3*R*)-**28a** were individually isolated by chromatographic purification on silica gel (gradient from hexane/diethyl ether 9/1 to 8/2).

(2'R,3'R,6'R)-1-benzyl-6'-hydroxy-3'-methyl-5'-phenyl-3',6'-dihydrospiro[indoline-3,2'-pyran]-2-one


*(2R,3R)-**28a***

The major diastereoisomer (2*R*,3*R*)-**28a** was isolated as single diastereoisomer (R_f = 0.3 hexane/diethyl ether 8/2) in 45% yield (white solid). The enantiomeric excess was determined to be 99% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 4.8 min, τ_{minor} = 5.7 min. $[\alpha]_D^{26}$= -59.0 (c = 1.60, $CHCl_3$, 99% *ee*). HRMS *calcd*. for ($C_{26}H_{23}NO_3$+Na): 420.1576, found 420.1571.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.51 (m, 2H), 7.35-7.30 (m, 3H), 7.28-7.17 (m, 7H), 7.06 (td, 1H, J_t = 7.5 Hz, J_d= 0.9 Hz), 6.67 (d, 1H, *J*= 7.7 Hz), 6.06-6.04 (m, 1H), 5.85 (d, 1H, *J*= 12.8 Hz), 5.09 (d, 1H, *J*= 12.7 Hz), 5.00 (d, 1H, *J*= 15.5 Hz), 4.65 (d, 1H, *J*= 15.5 Hz), 3.03-2.96 (m, 1H), 0.87 (d, 3H, *J*= 7.5 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 142.8, 137.7, 137.2, 135.4, 130.1, 129.7, 129.0, 128.6, 127.9, 127.5, 126.7, 126.6, 124.0, 123.9, 109.5, 92.1, 78.6, 44.3, 36.9, 14.8 ppm.

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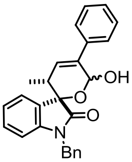
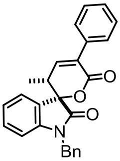
[40] A. Füstner, T. Nagano, *J. Am. Chem. Soc.*, **2007**, *129*, 1906.

(2'S,3'R)-1-benzyl-6'-hydroxy-3'-methyl-5'-phenyl-3',6'-dihydrospiro[indoline-3,2'-pyran]-2-one



(2S,3R)-**28a**

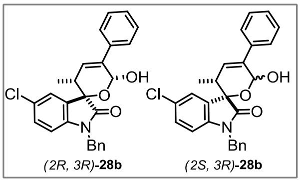


(2S,3R)-**29a**

The minor (2*S*,3*R*)-**28a** isomer was isolated as a 1/1 mixture of anomers (R_f = 0.20 hexane/ethyl acetate 8/2) in 22% yield (white solid). The title compound was directly oxidized to the corresponding lactone (2*S*,3*R*)-**29a** using Jones reagent following the reported procedure. The corresponding lactone was obtained as a single diastereoisomer and isolated after chromatography column (R_f = 0.3 hexane/diethyl ether 8/2) in 95% yield.

(2*S*,3*R*)-**29a.** The enantiomeric excess was determined to be 99% by HPLC analysis on a Daicel Chiralpak IA column: 50/50 hexane/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 5.1 min, τ_{minor} = 6.1 min. HRMS *calcd*. for ($C_{26}H_{21}NO_3$+Na): 418.1419, found 418.1407.

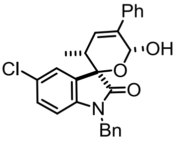
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.55 (m, 2H), 7.48-7.23 (m, 10H), 6.97 (td, 1H, J_t = 7.7 Hz, J_d= 0.9 Hz), 6.84 (d, 1H, *J*= 7.9 Hz), 5.02 (d, 1H, *J*= 15.6 Hz), 4.86 (d, 1H, *J*= 15.6 Hz), 3.66 (qd, 1H, J_q = 7.2 Hz, J_d= 2.4 Hz), 0.98 (d, 3H, *J*= 7.3 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 162.1, 144.9, 143.4, 135.1, 134.8, 132.5, 131.2, 129.1, 128.8, 128.3, 128.3, 128.1, 127.4, 125.1, 125.0, 123.3, 110.3, 84.6, 44.3, 34.6, 14.6 ppm.



(2R, 3R)-**28b** *(2S, 3R)*-**28b**

The reaction was carried out following the general procedure **B** to furnish the crude products as a mixture of 2.3:1 diastereoisomers (2*R*,3*R*)-**28b**/(2*S*,3*R*)-**28b**; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 6.12 ppm (bs), δ_{minor} 6.19 ppm and 6.23 ppm (bs). (2*R*,3*R*)-**28b**/(2*S*,3*R*)-**28b** were individually isolated by chromatographic purification on silica gel (gradient from hexane/diethyl ether 9/1 to 8/2).

(2'R,3'R,6'R)-1-benzyl-5-chloro-6'-hydroxy-3'-methyl-5'-phenyl-3',6'-dihydrospiro[indoline-3,2'-pyran]-2-one



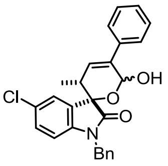
(2R, 3R)-**28b**

(2*R*,3*R*)-**28b** was isolated as a single diastereoisomer (R_f = 0.3 hexane/diethyl ether 8/2) in 47% yield (white solid). The enantiomeric excess was determined to be 99% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 5.5 min, τ_{minor} = 6.9 min. $[\alpha]_D^{26}$= -20.7 (c = 1.3, $CHCl_3$, 99% *ee*). HRMS *calcd*. for ($C_{26}H_{22}NO_3Cl$+Na): 454.1186, found 454.1183.

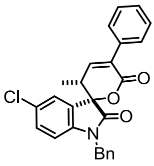
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.57 (m, 2H), 7.42-7.18 (m, 11H), 6.65 (d, 1H, *J*= 8.5 Hz), 6.12-6.09 (m, 1H), 5.91 (s, 1H), 5.04 (d, 1H, *J*= 15.8 Hz), 4.69 (d, 1H, *J*= 15.8 Hz), 3.07-2.99 (m, 1H), 0.94 (d, 3H, *J*= 7.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 141.2, 137.4, 137.2, 134.9, 131.4, 130.0, 129.4, 129.1, 128.6, 128.1, 127.9, 127.5, 126.7, 126.3, 124.6, 110.5, 92.1, 44.4, 36.9, 14.7 ppm.

Crystals of compound (2*R*,3*R*)-**28b** (major diastereomer) were obtained by slow evaporation of a mixture of hexane/diethyl ether at room temperature. (CCDC 885391)

(2'S,3'R)-1-benzyl-5-chloro-6'-hydroxy-3'-methyl-5'-phenyl-3',6'-dihydrospiro[indoline-3,2'-pyran]-2-one



(2S, 3R)-**28b**

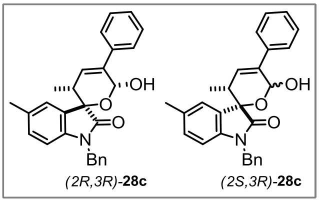


(2S, 3R)-**29b**

(2*S*,3*R*)-**28b** was isolated as a 1/1 mixture of anomers (R_f = 0.20 hexane/ethyl acetate 8/2) in 17% yield (white solid). The title compound was directly oxidized to the corresponding lactone (2*S*,3*R*)-**29b** using the Jones reagent following the reported procedure. The corresponding lactone was obtained as a single diastereoisomer and isolated after chromatography column (R_f = 0.3 hexane/diethyl ether 8/2) in 98% yield. (2*S*,3*R*)-**29b.** The enantiomeric excess was determined to be 99% by HPLC analysis on a Daicel Chiralpak IA column: 40/60 hexane/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 7.3 min, τ_{minor} = 9.3 min. HRMS *calcd*. for ($C_{26}H_{21}NO_3$+Na): 418.1419, found 418.1407.

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.58-7.53 (m, 2H), 7.48-7.40 (m, 3H), 7.38-7.21 (m, 8H), 6.84 (t, 1H, *J* = 2.8 Hz), 6.70 (d, 1H, *J*= 8.4 Hz), 4.99 (d, 1H, *J*= 15.6 Hz), 4.85 (d, 1H, *J*= 15.6 Hz), 3.65 (qd, 1H, J_q = 7.5 Hz, J_d= 2.9 Hz), 1.00 (d, 3H, *J*= 7.3 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 171.7, 161.6, 144.6, 141.8, 134.6, 134.6, 132.6, 131.1, 129.2, 128.9, 128.7, 128.7, 128.3, 128.3, 127.4, 126.6, 125.5, 111.4, 84.3, 44.4, 34.5, 14.5 ppm.

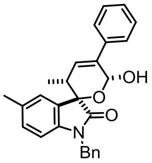
Crystals of compound (2*S*,3*R*)-**29b** were obtained by slow evaporation of a mixture of hexane/diethyl ether at room temperature. (CCDC 885392)



(2R,3R)-**28c** *(2S,3R)*-**28c**

(2*R*,3*R*)-**28c** *and* (2*S*,3*R*)-**29c.** The reaction was carried out following the general procedure **B**, using 20 mol% of the catalyst, to furnish the crude products as a mixture of 3.0:1 diastereoisomers (2*R*,3*R*)-**28c**/(2*S*,3*R*)-**28c**; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 6.11 ppm (bs), δ_{minor} 6.19 ppm and 6.22 ppm (bs). (2*R*,3*R*)-**28c**/(2*S*,3*R*)-**28c** were individually isolated by chromatographic purification on silica gel (gradient from hexane/diethyl ether 9/1 to 8/2) as described below.

(2'R,3'R,6'R)-1-benzyl-6'-hydroxy-3',5-dimethyl-5'-phenyl-3',6'-dihydrospiro[indoline-3,2'-pyran]-2-one



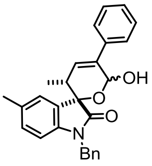
(2R,3R)-**28c**

(2*R*,3*R*)-**28c** was isolated as a single diastereoisomer (R_f = 0.3 hexane/diethyl ether 8/2) in 63% yield (white solid). The enantiomeric excess was determined to be 99% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 4.5 min, τ_{minor} = 5.6 min. $[\alpha]_D^{27}$= -30.8 (c = 1.25, $CHCl_3$, 99% ee). HRMS *calcd*. for ($C_{27}H_{25}NO_3$+Na): 434.1732, found 434.1716.

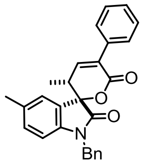
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.56 (m, 2H), 7.42-7.25 (m, 10H), 7.20-7.17 (m, 1H), 7.04 (d, 1H, *J*= 8.3 Hz), 6.61 (d, 1H, *J*= 8.2 Hz), 6.11-6.09 (m, 1H), 6.10 (bs, 1H), 5.89 (dq, 1H, J_d= 12.6 Hz, J_q= 1.2 Hz), 5.20 (d, 1H, *J*= 12.7 Hz), 5.04 (d, 1H, *J*= 15.6 Hz), 4.70 (d, 1H, *J*= 15.6 Hz), 4.70 (d, 1H, *J*= 15.8 Hz), 3.08-2.99 (m, 1H), 2.32 (s, 3H), 0.94 (d, 3H, *J*= 7.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8, 140.3, 137.7, 137.2, 135.5, 133.7, 130.4, 129.7, 129.0, 128.6, 127.9, 127.8, 127.5, 126.7, 126.7, 124.7, 109.3, 92.2, 78.7, 44.3, 36.9, 21.2, 14.9 ppm.

(2'S,3'R,6'R)-1-benzyl-6'-hydroxy-3',5-dimethyl-5'-phenyl-3',6'-dihydrospiro[indoline-3,2'-pyran]-2-one



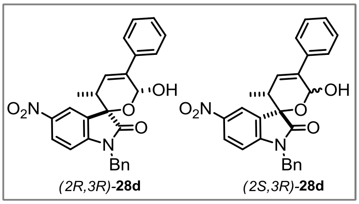
(2S,3R)-**28c**



(2S,3R)-**29c**

(2*S*,3*R*)-**28c** was isolated as a 1/1 mixture of anomers (R_f = 0.20 hexane/ethyl acetate 8/2) in 17% yield (white solid). The title compound was directly oxidized to the corresponding lactone (2*S*,3*R*)-**29c** using the Jones reagent following the reported procedure. The corresponding lactone **29c** was obtained as a single diastereoisomer and isolated after chromatography column (R_f = 0.3 hexane/ethyl acetate 9/1) in 94% yield.

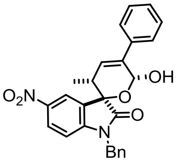
(2*S*,3*R*)-**29c.** The enantiomeric excess was determined to be 98% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 4.5 min, τ_{minor} = 5.3 min. $[\alpha]_D^{26}$= -73.63 (c = 0.4, $CHCl_3$, 98% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.54 (m, 2H), 7.48-7.39 (m, 3H), 7.36-7.22 (m, 5H), 7.18 (bs, 1H), 7.05 (bd, 1H, *J* = 7.8 Hz), 6.83 (d, 1H, *J* = 2.6 Hz), 6.65 (d, 1H, *J*= 8.1 Hz), 4.99 (d, 1H, *J*= 15.7 Hz), 4.83 (d, 1H, *J*= 15.7 Hz), 3.65 (qd, 1H, J_q = 7.4 Hz, J_d= 2.7 Hz), 2.63 (s, 3H), 0.98 (d, 3H, *J*= 7.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 162.2, 145.1, 140.9, 135.2, 135.0, 132.9, 132.5, 131.4, 129.1, 128.8, 128.7, 128.4, 128.0, 127.4, 125.8, 125.0, 110.1, 84.8, 44.4, 34.6, 21.3, 14.6 ppm.



(2*R*,3*R*)-**28d** (2*S*,3*R*)-**28d**

(2*R*,3*R*)-**28d** and (2*S*,3*R*)-**28d.** The reaction was carried out following the general procedure **B,** using 20 mol % of the catalyst, to furnish the crude products as a mixture of 1.3:1 diastereoisomers (2*R*,3*R*)-**28d**/(2*S*,3*R*)-**28d**; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 6.14 ppm (bs), δ_{minor} 6.18 ppm and 6.22 ppm (bs). (2*R*,3*R*)-**28d**/(2*S*,3*R*)-**28d** were individually isolated by chromatographic purification on silica gel (gradient hexane/ethyl acetate 9/1 to hexane/ethyl acetate 7/3) as described below.

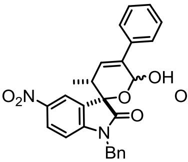
(2'R,3'R,6'R)-1-benzyl-6'-hydroxy-3'-methyl-5-nitro-5'-phenyl-3',6'-dihydrospiro[indoline-3,2'-pyran]-2-one



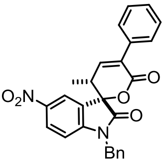
(2*R*,3*R*)-**28d**

(2*R*,3*R*)-**28d** was isolated as mixture of diastereoisomers (18/1) (R_f = 0.3 hexane/diethyl ether 7/3) in 45% yield (white solid). The enantiomeric excess of (2*R*,3*R*)-**4d** was determined to be 99% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 6.3 min, τ_{minor} = 9.2 min. $[\alpha]_D^{26}$= +15.4 (c = 0.85, $CHCl_3$, 99% ee). HRMS *calcd*. for ($C_{26}H_{22}N_2O_5$+Na): 465.1426, found 465.1429. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, 1H, *J*= 2.4 Hz), 8.22 (dd, 1H, J_1= 8.7 Hz, J_1= 2.3 Hz), 7.60-7.55 (m, 5H), 7.43-7.26 (m, 9H), 6.82 (d, 1H, *J*= 8.7 Hz), 6.12-6.09 (bs, 1H), 5.93 (d, 1H, *J*= 12.9 Hz), 5.10 (d, 1H, *J*= 15.5 Hz), 4.77 (d, 1H, *J*= 15.5 Hz), 4.73 (d, 1H, *J*= 12.3 Hz), 3.16-3.07 (m, 1H), 0.93 (d, 3H, *J*= 7.4 Hz) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 148.3, 144.5, 137.3, 137.2, 134.2, 130.8, 129.3, 128.7, 128.5, 128.1, 127.5, 127.1, 126.7, 125.9, 120.1, 109.3, 77.9, 11.6, 36.8, 14.7 ppm.

(2'S,3'R,6'R)-1-benzyl-6'-hydroxy-3'-methyl-5-nitro-5'-phenyl-3',6'-dihydrospiro[indoline-3,2'-pyran]-2-one



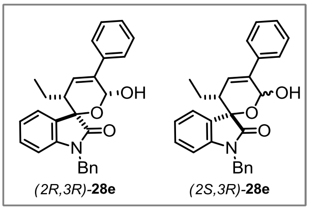
(2*S*,3*R*)-**28d**



(2*S*,3*R*)-**29d**

(2*S*,3*R*)-**28d** was isolated as a 1/1 mixture of anomers (R_f = 0.20 hexane/ethyl acetate 8/2) in 17% yield (white solid). The title compound was directly oxidized to the corresponding lactone (2*S*,3*R*)-**29d** using the Jones reagent and following the reported procedure. The corresponding lactone was obtained as a single diastereoisomer and isolated after chromatography column (R_f = 0.3 hexane/ethyl acetate 8/2) in 94% yield.

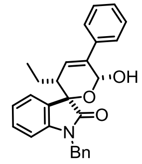
(2*S*,3*R*)-**29d.** The enantiomeric excess was determined to be 97% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 7.3 min, τ_{minor} = 9.3 min. $[\alpha]_D^{27}$= -122.75 (c = 0.75, $CHCl_3$, 97% ee). HRMS *calcd.* for ($C_{26}H_{20}N_2O_5$+Na): 463.1270, found 463.1266. ^{1}H NMR (400 MHz, $CDCl_3$): δ 831 (d, 1H, *J* = 2.3 Hz), 8.24 (dd, 1H, J_1= 8.6 Hz, J_2= 2.2 Hz), 7.59-7.54 (m, 2H), 7.50-7.27 (m, 9H), 6.89 (d, 1H, *J* = 8.8 Hz), 6.86 (d, 1H, *J* = 2.9 Hz), 5.06 (d, 1H, *J* = 15.8 Hz), 4.93 (d, 1H, *J* = 15.8 Hz), 3.67 (qd, 1H, J_q = 7.3 Hz, J_d = 2.0 Hz), 1.03 (d, 3H, *J* = 7.5 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 172.1, 162.2, 145.1, 140.9, 135.2, 135.0, 132.9, 132.5, 131.4, 129.1, 128.8, 128.7, 128.4, 128.0, 127.4, 125.8, 125.0, 110.1, 84.8, 44.4, 34.6, 21.3, 14.6 ppm.



(2*R*,3*R*)-**28e** (2*S*,3*R*)-**28e**

(2*R*,3*R*)-**28e** and (2*S*,3*R*)-**28e.** The reaction was carried out following the general procedure **B,** using 20 mol % of the catalyst, to furnish the crude products as a mixture of 2.2:1 diastereoisomers (2*R*,3*R*)-**28e**/(2*S*,3*R*)-**28e**; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 6.31 ppm (bs), δ_{minor} 6.38 ppm and 6.40 ppm (bs). The reaction conversion was approximately 60% after 72 hours reaction time.

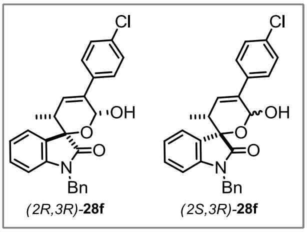
(2'R,3'R,6'R)-1-benzyl-3'-ethyl-6'-hydroxy-5'-phenyl-3',6'-dihydrospiro[indoline-3,2'-pyran]-2-one



(2*R*,3*R*)-**28e**

(2*R*,3*R*)-**28e** was isolated as a single diastereoisomer (R_f = 0.3 hexane/diethyl ether 8/2) in 36% yield (white solid). The enantiomeric excess of (2*R*,3*R*)-**28e** was determined to be 99% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 4.8 min, τ_{minor} = 5.6 min. $[\alpha]_D^{26}$= -51.5 (c = 0.65, $CHCl_3$, 99% *ee*). HRMS *calcd*. for ($C_{27}H_{25}NO_3$+Na): 434.1737, found 434.1716.

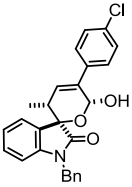
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.26-7.57 (m, 2H), 7.41-7.36 (m, 3H), 7.36-7.21 (m, 7H), 7.21 (td, 1H J_t= 2.8 Hz, J_d= 0.7 Hz), 6.74 (d, 1H, *J*= 7.7 Hz), 6.31-6.28 (m, 1H), 5.90 (bd, 1H, *J*= 11.8 Hz), 5.08 (bd, 1H, *J*= 11.8 Hz), 5.04 (d, 1H, *J*= 15.6 Hz), 4.72 (d, 1H, *J*= 15.6 Hz), 2.80-2.75 (m, 1H), 1.35-1.24 (m, 1H), 1.16-1.06 (m, 1H), 0.92 (t, 1H, *J*= 7.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 178.1, 142.9, 137.9, 137.4, 135.3, 130.1, 129.9, 129.0, 128.6, 127.9, 127.8, 127.5, 126.7, 123.9, 123.9, 109.4, 92.1, 77.9, 44.2, 43.7, 21.5, 11.7 ppm.



(2*R*,3*R*)-**28f** (2*S*,3*R*)-**28f**

(2*R*,3*R*)-**28f** and (2*S*,3*R*)-**28f.** The reaction was carried out following the general procedure **B**, using 20 mol% of catalyst, to furnish the crude products as a mixture of 3.2:1 diastereoisomers (2*R*,3*R*)-**28f**/(2*S*,3*R*)-**28f**; d.r. determined by integration of ^{1}H NMR signal: δ_{major} 6.12 ppm (bs), δ_{minor} 6.22 ppm and 6.28 ppm (bs). (2*R*,3*R*)-**28f**/(2*S*,3*R*)-**28f** were individually isolated by chromatographic purification on silica gel (gradient from hexane/diethyl ether 9/1 to hexane/ethyl acetate 8/2) as described below.

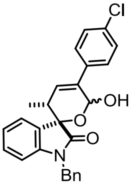
(2'R,3'R,6'R)-1-benzyl-5'-(4-chlorophenyl)-6'-hydroxy-3'-methyl-3',6'-dihydrospiro[indoline-3,2'-pyran]-2-one



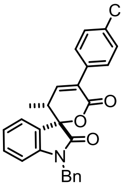
(2R,3R)-**28f**

(2*R*,3*R*)-**28f** was isolated as single diastereoisomer (R_f = 0.3 hexane/diethyl ether 8/2) in 69% yield (white solid). The enantiomeric excess of (2*R*,3*R*)-**28f** was determined to be 99% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 5.6 min, τ_{minor} = 8.2 min. $[\alpha]_D^{27}$= -60.0 (c = 1.05, $CHCl_3$, 99% *ee*). ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.58-7.53 (m, 2H), 7.40-7.25 (m, 10H), 7.17-7.12 (m, 1H), 6.77 (d, 1H, *J*= 7.8 Hz), 6.14-6.11 (bs, 1H), 5.86 (d, 1H, *J*= 12.8 Hz), 5.20 (d, 1H, *J*= 12.6 Hz), 5.07 (d, 1H, *J*= 15.5 Hz), 4.74 (d, 1H, *J*= 15.5 Hz), 3.10-3.39 (m, 1H), 0.94 (d, 3H, *J*= 7.3 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 177.9, 142.7, 136.2, 136.1, 135.3, 133.7, 130.2, 129.6, 129.0, 128.7, 128.0, 127.5, 127.0, 124.0, 123.9, 109.5, 91.9, 78.6, 44.3, 36.9, 14.8 ppm.

(2'S,3'R,6'R)-1-benzyl-5'-(4-chlorophenyl)-6'-hydroxy-3'-methyl-3',6'-dihydrospiro[indoline-3,2'-pyran]-2-one



(2S,3R)-**28f**

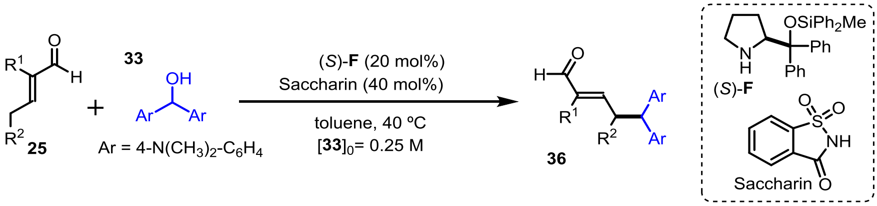


(2S,3R)-**29f**

(2*S*,3*R*)-**28f** was isolated as a 1/1 mixture of anomers (R_f = 0.20 hexane/ethyl acetate 8/2) in 22% yield (white solid). The title compound was directly oxidized to the corresponding lactone (2*S*,3*R*)-**29f** using the Jones reagent and following the reported procedure. The corresponding lactone was obtained as a single diastereoisomer and isolated by chromatography column (R_f = 0.3 hexane/ethyl acetate 9/1) in 98% yield.

(2*S*,3*R*)-**29f.** The enantiomeric excess was determined to be 98% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 5.7 min, τ_{minor} = 7.0 min. HRMS *calcd*. for ($C_{26}H_{20}NO_3Cl+Na$): 452.1017, found 452.1029. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.54-7.49 (m, 2H), 7.43-7.38 (m, 2H), 7.37-7.24 (m, 7H), 6.98 (td, 1H, J_t= 7.7 Hz, J_d= 0.7 Hz), 6.84 (d, 1H, *J* = 2.8 Hz), 6.78 (d, 1H, *J* = 7.9 Hz), 5.02 (d, 1H, *J* = 15.6 Hz), 4.85 (d, 1H, *J* = 15.6 Hz), 3.62 (td, 1H, J_t= 7.4 Hz, J_d= 2.8 Hz), 0.99(d, 3H, *J*= 7.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 172.10, 161.9, 145.1, 143.4, 135.1, 135.0, 133.2, 131.5, 131.3, 129.7, 129.1, 128.9, 128.1, 127.4, 125.0, 124.9, 123.4, 110.4, 84.5, 44.4, 34.7, 14.7 ppm.

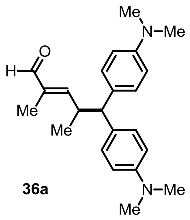
4.5.5. General Procedure for the γ-Alkylation of α-Branched Enals



All the reactions were carried out in toluene (synthesis grade, >99%) without any precaution for excluding air and moisture. An ordinary 1 mL vial equipped with a Teflon-coated stir bar and a plastic screw cap was charged with 0.1 mmol of the alcohol **33** (or **18a-c**), 0.02 mmol of (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol methyldiphenylsilyl ether **F** and 0.4 mmol of the enal **25** in 400 μL of toluene ($[\mathbf{33}]_0$= 0.25 M). Then 0.04 mmol of saccharin was added. The vial was sealed and immerged in a water bath (thermostated at 40 °C) and stirring continued for the time specified in the tables. The reaction mixture assumes a green color that disappears upon complete consumption of the alcohol **33** (generally 24-36 hours). Upon completion of the reaction (as verified by TLC analysis) the mixture is directly charged on silica gel and subjected to chromatographic purification with hexane:diethyl ether or toluene:diethyl ether as the eluent. All the products are stable if conserved in sealed vials flushed with argon and stored at 0 °C in the absence of any trace of acids (for spectroscopic analysis, basified chloroform pre-treated with K_2CO_3 was employed).

Known and previously unreported compounds products were fully characterized. The absolute configuration of the γ-alkylated products **36** was assigned by comparison of the optical rotation to known compounds,[18] while the absolute configuration for compound **40b** was unambiguously determined by anomalous dispersion X-ray crystallographic analysis (CCDC 894226).

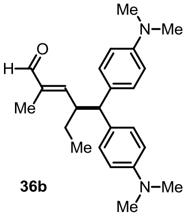
(S)-5,5-bis(4-(dimethylamino)phenyl)-2,4-dimethylpent-2-enal (**36a**)



36a

The reaction was carried out following the general procedure. After 24 hours the title compound was isolated by flash column chromatography (eluent hexane:diethyl ether 4:1) as a colorless oil (31 mg, 0.088 mmol, 88% yield). The enantiomeric excess was determined to be 93% by HPLC analysis on a Daicel Chiralpak IA column: 95/5 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 254 nm: τ_{major} = 8.4 min, τ_{minor} = 9.6 min. $[\alpha]_D^{26}$= + 30.4 (*c* = 0.73, $CHCl_3$, 93% *ee*). ^1H NMR (500 MHz, $CDCl_3$) δ 9.24 (s, 1H), 7.17 – 7.10 (m, 2H), 7.07 – 7.00 (m, 2H), 6.72 – 6.63 (m, 2H), 6.61 – 6.54 (m, 2H), 6.32 (dq, *J* = 9.9, 1.4 Hz, 1H), 3.62 (d, *J* = 10.5 Hz, 1H), 3.50 – 3.40 (m, 1H), 2.86 (s, 6H), 2.90 (s, 6H), 1.74 (d, *J* = 1.4 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.6, 160.1, 149.1, 149.0, 137.6, 132.1, 132.0, 128.6, 128.3, 112.8, 112.6, 56.2, 40.7, 40.6, 38.2, 19.0, 9.3 ppm.

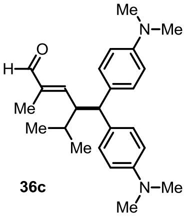
(S)-4-(bis(4-(dimethylamino)phenyl)methyl)-2-methylhex-2-enal (**36b**)



36b

The reaction was carried out following the general procedure. After 32 hours the title compound was isolated by flash column chromatography (eluent hexane:diethyl ether 5:1) as a white solid (27 mg, 0.074 mmol, 74% yield). The enantiomeric excess was determined to be 96% by HPLC analysis on a Daicel Chiralpak IA column: 95/5 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 254 nm: τ_{major} = 8.4 min, τ_{minor} = 9.5 min. $[\alpha]_D^{25}$= + 7.1 (*c* = 1.24, $CHCl_3$, 96% *ee*). HRMS *calcd.* for ($C_{24}H_{32}ON_2+H^+$): 365.2593, found 365.2596. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.20 – 7.11 (m, 2H), 7.09 – 6.92 (m, 2H), 6.76 – 6.63 (m, 2H), 6.63 – 6.52 (m, 2H), 6.23 (dq, *J* = 10.3, 1.3 Hz, 1H), 3.69 (d, *J* = 10.3 Hz, 1H), 3.30 (qd, *J* = 10.3, 3.2 Hz, 1H), 2.90 (s, 6H), 2.85 (s, 6H), 1.74 (d, *J* = 1.3 Hz, 3H), 1.71 – 1.65 (m, 1H), 1.26 – 1.20 (m, 1H), 0.80 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.5, 158.9, 149.1, 148.9, 139.4, 132.1, 132.1, 128.5, 128.3, 112.8, 112.6, 54.8, 45.3, 40.7, 40.6, 26.5, 11.5, 9.9 ppm.

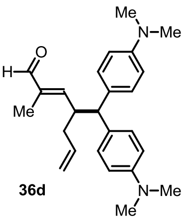
(S)-4-(bis(4-(dimethylamino)phenyl)methyl)-2,5-dimethylhex-2-enal (**36c**)



36c

The reaction was carried out following the general procedure but with [**33**]$_0$ = 0.5 M. After 48 hours the title compound was isolated by flash column chromatography (eluent hexane:diethyl ether 4:1) as a white solid (24 mg, 0.063 mmol, 63% yield). The enantiomeric excess was determined to be 94% by HPLC analysis on a Daicel Chiralpak IA column: 80/20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 254 nm: τ_{major} = 4.7 min, τ_{minor} = 5.8 min. $[\alpha]_D^{26}$= - 12.5 (*c* = 0.70, $CHCl_3$, 94% *ee*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.22 – 7.15 (m, 2H), 7.06 – 7.00 (m, 2H), 6.70 – 6.66 (m, 2H), 6.55 – 6.51 (m, 2H), 6.30 (dq, *J* = 11.1, 1.3 Hz, 1H), 3.85 (d, *J* = 11.1 Hz, 1H), 3.38 (td, *J* = 11.1, 3.1 Hz, 1H), 2.90 (s, 6H), 2.84 (s, 6H), 1.92 (heptd, *J* = 7.0, 3.1 Hz, 1H), 1.71 (d, *J* = 1.3 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.5, 156.2, 149.1, 148.9, 140.5, 132.3, 132.0, 128.3, 128.1, 112.9, 112.6, 52.7, 48.6, 40.7, 40.6, 29.8, 22.1, 15.7, 10.1 ppm.

(S)-4-(bis(4-(dimethylamino)phenyl)methyl)-2-methylhepta-2,6-dienal (**36d**)

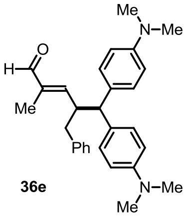


36d

The reaction was carried out following the general procedure. After 50 hours the title compound was isolated by flash column chromatography (eluent in gradient hexane:diethyl ether 4:1 – 3:1) as a white solid (31 mg, 0.082 mmol, 82% yield). The enantiomeric excess was determined to be 94% by HPLC analysis on a Daicel Chiralpak IA column: 94/6 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 254 nm: τ_{major} = 8.2 min, τ_{minor} = 8.9 min.

$[\alpha]_D^{27}$= -12.9 (*c* = 1.00, $CHCl_3$, 94% *ee*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.21 – 7.13 (m, 2H), 7.08 – 6.99 (m, 2H), 6.73 – 6.66 (m, 2H), 6.61 – 6.53 (m, 2H), 6.25 (dq, *J* = 10.4, 1.3 Hz, 1H), 5.66 (ddt, *J* = 17.3, 10.2, 7.2 Hz, 1H), 5.00 – 4.89 (m, 2H), 3.74 (d, *J* = 10.4 Hz, 1H), 3.55 – 3.41 (m, 1H), 2.91 (s, 6H), 2.85 (s, 6H), 2.42 – 2.32 (m, 1H), 2.10 – 1.98 (m, 1H), 1.70 (d, *J* = 1.3 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.4, 158.0, 149.2, 149.0, 139.2, 135.4, 131.7(x2), 128.6, 128.3, 116.8, 112.9, 112.6, 54.4, 43.6, 40.7, 40.6, 37.8, 9.9 ppm.

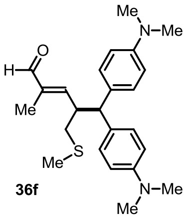
(S)-4-benzyl-5,5-bis(4-(dimethylamino)phenyl)-2-methylpent-2-enal (**36e**)



36e

The reaction was carried out following the general procedure. After 43 hours the title compound was isolated by flash column chromatography (eluent hexane:diethyl ether 4:1) as a white solid (25 mg, 0.059 mmol, 59% yield). The enantiomeric excess was determined to be 95% by HPLC analysis on a Daicel Chiralpak IC column: 85/15 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 254 nm: τ_{major} = 19.4 min, τ_{minor} = 21.0 min. $[\alpha]_D^{26}$= + 5.2 (*c* = 0.94, $CHCl_3$, 95% *ee*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.29 – 7.21 (m, 2H), 7.21 – 7.09 (m, 3H), 7.07 – 6.96 (m, 4H), 6.77 – 6.71 (m, 2H), 6.61 – 6.52 (m, 2H), 6.22 (dq, *J* = 10.3, 1.3 Hz, 1H), 3.79 (d, *J* = 10.3 Hz, 1H), 3.63 (qd, *J* = 10.3, 3.2 Hz, 1H), 3.02 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.93 (s, 6H), 2.85 (s, 6H), 2.42 (dd, *J* = 13.4, 10.3 Hz, 1H), 1.19 (d, *J* = 1.3 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.3, 157.3, 149.2, 149.0, 139.8, 139.6, 131.8, 131.7, 129.1, 128.6, 128.2, 128.1, 126.0, 113.1, 112.6, 54.9, 46.4, 40.7, 40.6, 39.8, 9.1 ppm.

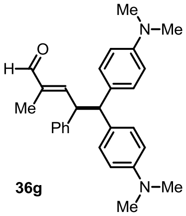
(S)-5,5-bis(4-(dimethylamino)phenyl)-2-methyl-4-((methylthio)methyl)pent-2-enal (**36f**)



36f

The reaction was carried out following the general procedure. After 48 hours the title compound was isolated by flash column chromatography (eluent in gradient hexane:diethyl ether 5:1 – 4:1) as a yellowish solid (16 mg, 0.040 mmol, 40% yield). The enantiomeric excess was determined to be 90% by HPLC analysis on a Daicel Chiralpak IA-3 column: 97/3 hexane/*i*-PrOH, flow rate 0.80 mL/min, λ = 254 nm: τ_{major} = 14.0 min, τ_{minor} = 15.0 min. $[\alpha]_D^{25}$= +19.7 (*c* = 1.07, $CHCl_3$, 90% *ee*). HRMS *calcd.* for ($C_{24}H_{32}N_2OS+H^+$): 397.2314, found 397.2333. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.20 – 7.14 (m, 2H), 7.06 – 7.01 (m, 2H), 6.72 – 6.66 (m, 2H), 6.61 – 6.54 (m, 2H), 6.31 (dq, *J* = 10.3, 1.4 Hz, 1H), 3.89 (d, *J* = 10.3 Hz, 1H), 3.64 (tdd, *J* = 10.3, 8.7, 3.6 Hz, 1H), 2.91 (s, 6H), 2.86 (s, 6H), 2.73 (dd, *J* = 12.8, 3.6 Hz, 1H), 2.48 (dd, *J* = 12.8, 8.7 Hz, 1H), 2.02 (s, 3H), 1.74 (d, *J* = 1.4 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.3, 156.6, 149.2, 149.0, 140.1, 131.1(x2), 128.5, 128.4, 113.0, 112.6, 53.9, 43.6, 40.7, 40.6, 38.6, 16.7, 10.0 ppm.

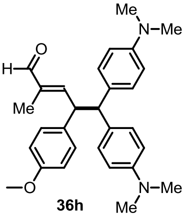
(S)-5,5-bis(4-(dimethylamino)phenyl)-2-methyl-4-phenylpent-2-enal (**36g**)



36g

The reaction was carried out following the general procedure. After 6 hours the title compound was isolated by flash column chromatography (eluent hexane:diethyl ether 4:1) as a white solid (38 mg, 0.092 mmol, 92% yield). The enantiomeric excess was determined to be 92% by HPLC analysis on a Daicel Chiralpak IA column: 93/7 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 254 nm: τ_{major} = 8.3 min, τ_{minor} = 9.2 min. $[\alpha]_D^{26}$= + 6.9 (*c* = 1.05, $CHCl_3$, 92% *ee*). ^1H NMR (400 MHz $CDCl_3$) δ 9.25 (s, 1H), 7.23 – 7.17 (m, 2H), 7.17 – 7.09 (m, 5H), 6.96 – 6.91 (m, 2H), 6.65 – 6.59 (m, 3H), 6.54 – 6.45 (m, 2H), 4.50 (t, *J* = 10.9 Hz, 1H), 4.26 (d, *J* = 10.9 Hz, 1H), 2.89 (s, 6H), 2.83 (s, 6H), 1.70 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 157.0, 149.1, 148.7, 141.7, 137.9, 131.2, 131.1, 128.7(x2), 128.5, 128.3, 126.5, 112.6, 112.5, 55.4, 50.3, 40.6(x2), 9.5 ppm.

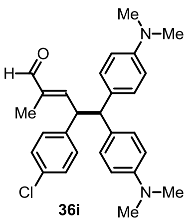
(S)-5,5-bis(4-(dimethylamino)phenyl)-4-(4-methoxyphenyl)-2-methylpent-2-enal (**36h**)



36h

The reaction was carried out following the general procedure. After 5.5 hours the title compound was isolated by flash column chromatography (eluent hexane:diethyl ether 2:1) as a white solid (39 mg, 0.088 mmol, 88% yield). The enantiomeric excess was determined to be 94% by HPLC analysis on a Daicel Chiralpak IC-3 column: 80/20 hexane/*i*-PrOH, flow rate 0.80 mL/min, λ = 254 nm: τ_{major} = 25.9 min, τ_{minor} = 30.8 min. $[\alpha]_D^{26}$= -2.1 (*c* = 1.00, $CHCl_3$, 94% *ee*). ^1H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.14 – 7.03 (m, 4H), 6.99 – 6.92 (m, 2H), 6.79 – 6.72 (m, 2H), 6.66 – 6.57 (m, 3H), 6.55 – 6.47 (m, 2H), 4.47 (dd, *J* = 11.1, 9.9 Hz, 1H), 4.21 (d, *J* = 11.1 Hz, 1H), 3.74 (s, 3H), 2.89 (s, 6H), 2.83 (s, 6H), 1.70 (d, *J* = 1.3 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.4, 158.0, 157.4, 149.1, 148.7, 137.6, 133.8, 131.4, 131.2, 129.2, 128.7(x2), 113.9, 112.6, 112.5, 55.5, 55.1, 49.4, 40.6(x2), 9.4 ppm.

(S)-4-(4-chlorophenyl)-5,5-bis(4-(dimethylamino)phenyl)-2-methylpent-2-enal (**36i**)

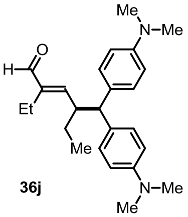


36i

The reaction was carried out following the general procedure. After 6 hours the title compound was isolated by flash column chromatography (eluent hexane:diethyl ether 3:1) as a white solid (41 mg, 0.092 mmol, 92% yield). The enantiomeric excess was determined to be 91% by HPLC analysis on a Daicel Chiralpak IA-3 column: 90/10 hexane/*i*-PrOH, flow rate 0.80 mL/min, λ = 254 nm: τ_{minor} = 10.1 min, τ_{major} = 10.9 min. $[\alpha]_D^{26}$= +12.4 (*c* = 1.00, $CHCl_3$, 91% *ee*). ^1H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.20 – 7.14 (m, 2H), 7.12 – 7.03 (m, 4H), 6.95 – 6.89 (m, 2H), 6.64 – 6.55 (m, 3H), 6.53 – 6.48 (m, 2H), 4.47 (dd, *J* = 11.1, 9.7 Hz, 1H), 4.18 (d, *J* = 11.1 Hz, 1H), 2.89 (s, 6H), 2.83 (s, 6H), 1.67 (d, *J* = 1.3 Hz, 3H) ppm. ^{13}C NMR

(100, MHz, $CDCl_3$) δ 195.1, 156.1, 149.2, 148.8, 140.4, 138.4, 132.1, 130.8, 130.7, 129.6, 128.7, 128.6, 128.6, 112.6, 112.5, 55.5, 49.7, 40.6(x2), 9.5 ppm.

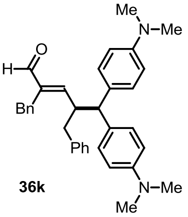
(S)-4-(bis(4-(dimethylamino)phenyl)methyl)-2-ethylhex-2-enal (**36j**)



36j

The reaction was carried out following the general but with $[\mathbf{33}]_0$ = 0.5 M. After 78 hours, the title compound was isolated by flash column chromatography (eluent hexane:diethyl ether 4:1) as a white solid (31 mg, 0.082 mmol, 82% yield). The enantiomeric excess was determined to be 92% by HPLC analysis on a Daicel Chiralpak IC column: 90/10 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 254 nm: τ_{major} = 15.7 min, τ_{minor} = 18.4 min. $[\alpha]_D^{27}$= -16.7 (*c* = 0.85, $CHCl_3$, 92% *ee*). ^1H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.19 – 7.13 (m, 2H), 7.06 – 7.00 (m, 2H), 6.71 – 6.65 (m, 2H), 6.59 – 6.53 (m, 2H), 6.16 (d, *J* = 10.6 Hz, 1H), 3.70 (d, *J* = 10.2 Hz, 1H), 3.35 – 3.23 (m, 1H), 2.90 (s, 6H), 2.84 (s, 6H), 2.22 (q, *J* = 7.5 Hz, 2H), 1.73 – 1.62 (m, 1H), 1.26 – 1.20 (m, 1H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.80 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 158.5, 149.1, 149.0, 144.9, 132.1, 131.8, 128.6, 128.4, 112.8, 112.6, 54.8, 45.0, 40.7, 40.7, 26.5, 18.2, 12.8, 11.6 ppm.

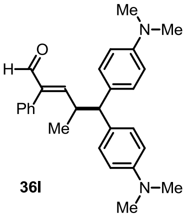
(S)-2,4-dibenzyl-5,5-bis(4-(dimethylamino)phenyl)pent-2-enal (**36k**)



36k

The reaction was carried out following the general procedure. After 48 hours, the title compound was isolated by flash column chromatography (eluent in gradient toluene:diethyl ether 97:3 – 95:5) as a white solid (42 mg, 0.083 mmol, 83% yield). The enantiomeric excess was determined to be 94% by HPLC analysis on a Daicel Chiralpak IA column: 96/4 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 254 nm: τ_{minor} = 11.8 min, τ_{major} = 12.5 min. $[\alpha]_D^{26}$= -33.6 (*c* = 1.00, $CHCl_3$, 94% *ee*). ^1H NMR (500 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.24 – 7.19 (m, 5H), 7.15 – 7.12 (m, 3H), 7.03 – 7.00 (m, 2H), 6.88 – 6.82 (m, 2H), 6.76 – 6.72 (m, 4H), 6.49 – 6.44 (m, 2H), 6.38 (d, *J* = 10.2 Hz, 1H), 3.77 (d, *J* = 10.3 Hz, 1H), 3.70 – 3.63 (m, 1H), 3.12 (d, *J* = 15.1 Hz, 1H), 3.01 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.93 (s, 6H), 2.85 (s, 6H), 2.69 (d, *J* = 15.1 Hz, 1H), 2.46 (dd, *J* = 13.4, 9.4 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.8, 158.8, 149.2, 148.9, 142.3, 139.3, 138.8, 131.4, 131.4, 129.4, 128.7, 128.5, 128.5, 128.3, 128.1, 126.2, 125.7, 113.0, 112.6, 54.9, 46.4, 40.7, 40.6, 39.8, 29.3 ppm.

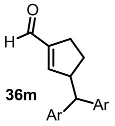
(S)-5,5-bis(4-(dimethylamino)phenyl)-4-methyl-2-phenylpent-2-enal (**36l**)



36l

The reaction was carried out following the general procedure. After 26 hours, the title compound was isolated by flash column chromatography (eluent hexane:diethyl ether 4:1) as a yellowish oil (34 mg, 0.082 mmol, 82% yield). The enantiomeric excess was determined to be 40% by HPLC analysis on a Daicel Chiralpak IA column: 95/5 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 254 nm: τ_{major} = 9.9 min, τ_{minor} = 12.8 min. $[\alpha]_D^{25}$= + 38.9 (*c* = 1.30, $CHCl_3$, 40% ee). ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.48 – 7.39 (m, 3H), 7.08 – 6.98 (m, 4H), 6.92 – 6.87 (m, 2H), 6.65 – 6.60 (m, 2H), 6.59 – 6.51 (m, 3H), 3.63 (d, *J* = 10.5 Hz, 1H), 3.41 – 3.28 (m, 1H), 2.88 (s, 6H), 2.87 (s, 6H), 1.07 (d, *J* = 6.5 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 161.4, 149.1(x2), 142.8, 133.1, 132.0, 131.6, 129.3, 128.5(x2), 128.2, 127.8, 112.8, 112.6, 56.5, 40.7 (x2), 38.5, 19.7 ppm.

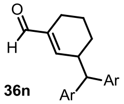
3-(bis(4-(dimethylamino)phenyl)methyl)cyclopent-1-enecarbaldehyde (**36m**)



36m

The reaction was carried out following the general procedure. After 4 hours, the title compound was isolated by flash column chromatography (eluent toluene:diethyl ether from 96:4 to 95:5) as a yellowish oil (26 mg, 0.076 mmol, 76% yield). The enantiomeric excess was determined to be 68% by HPLC analysis on a Daicel Chiralpak IA column: 90/10 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 254 nm: τ_{major} = 11.2 min, τ_{minor} = 12.2 min. $[\alpha]_D^{27}$= + 76.2 (*c* = 1.00, $CHCl_3$, 68% *ee*). HRMS *calcd.* for ($C_{23}H_{27}N_2O+H^+$): 349.2280, found 349.2263. ^1H NMR (500 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.18 – 7.10 (m, 4H), 6.72 – 6.64 (m, 5H), 3.77 – 3.68 (m, 1H), 3.60 (d, *J* = 11.2 Hz, 1H), 2.91 (s, 6H), 2.90 (s, 6H), 2.62 – 2.51 (m, 1H), 2.50 – 2.40 (m, 1H), 2.17 – 2.06 (m, 1H), 1.71 – 1.60 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.4, 156.3, 149.1, 149.1, 147.0, 132.6, 132.1, 128.4, 128.3, 112.9, 112.8, 55.0, 51.8, 40.7, 29.3, 27.8 ppm.

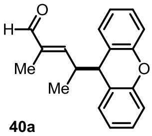
3-(bis(4-(dimethylamino)phenyl)methyl)cyclohex-1-enecarbaldehyde (**36n**)



36n

The reaction was carried out following the general procedure. After 32 hours, the title compound was isolated by flash column chromatography (eluent toluene:diethyl ether 5:1) as a yellowish solid (31 mg, 0.086 mmol, 86% yield). The enantiomeric excess was determined to be 63% by HPLC analysis on a Daicel Chiralpak IA column: 90/10 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 254 nm: τ_{major} = 8.5 min, τ_{minor} = 9.9 min. $[\alpha]_D^{26}$= + 8.7 (*c* = 1.00, $CHCl_3$, 63% *ee*). ^1H NMR (500 MHz, $CDCl_3$) δ 9.28 (s, 1H), 7.20 – 7.11 (m, 4H), 6.73 – 6.65 (m, 4H), 6.65 – 6.61 (m, 1H), 3.56 (d, *J* = 11.2 Hz, 1H), 3.20 – 3.09 (m, 1H), 2.92 (s, 6H), 2.90 (s, 6H), 2.33 – 2.25 (m, 1H), 2.11 – 2.03 (m, 1H), 1.87 – 1.76 (m, 1H), 1.77 – 1.70 (m, 1H), 1.56 – 1.47 (m, 1H), 1.27 – 1.19 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.9, 154.6, 149.1, 149.1, 141.5, 132.0, 131.4, 128.6, 128.3, 113.0, 112.9, 54.9, 41.0, 40.7, 40.7, 28.0, 21.7, 20.6 ppm.

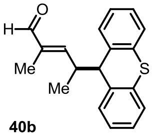
(S)-2-methyl-4-(9H-xanthen-9-yl)pent-2-enal (**40a**)



40a

The reaction was carried out following the general procedure but with [**39a**]$_0$ = 0.5 M and using 2,4-dinitrobenzoic acid as the acidic additive (40% mol) in acetonitrile. After 30 hours, the reaction mixture was subjected to flash column chromatography purification (eluent hexane:diethyl ether 95:5) obtaining a mixture of the product and xanthone (this compound shows fluorescence at 354 nm). This mixture was finally purified on preparative TLC using methylene chloride as eluent (product R_f=0.6) affording the product as a white solid (18 mg, 0.065 mmol, 65% yield). The enantiomeric excess was determined to be 81% by HPLC analysis on a Daicel Chiralpak IA column: 95/5 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 254 nm: τ_{minor} = 5.6 min, τ_{major} = 5.8 min. $[\alpha]_D^{26}$= + 13.8 (*c* = 1.00, $CHCl_3$, 81% *ee*). HRMS *calcd.* for ($C_{19}H_{18}O_2$+Na^+): 301.1204, found 301.1210. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.29 – 7.22 (m, 2H), 7.22 – 7.14 (m, 2H), 7.13 – 7.04 (m, 4H), 6.11 (dq, *J* = 10.3, 1.4 Hz, 1H), 3.98 (d, *J* = 5.0 Hz, 1H), 3.00 (dqd, *J* = 10.3, 6.8, 5.0 Hz, 1H), 1.36 (d, *J* = 1.4 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 155.8, 153.0, 152.9, 139.4, 129.2, 129.0, 128.1, 123.3, 123.2, 123.0, 122.7, 116.5, 116.4, 45.0, 42.4, 16.7, 8.8 ppm.

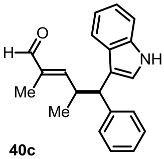
(S)-2-methyl-4-(9H-thioxanthen-9-yl)pent-2-enal (**40b**)



40b

The reaction was carried out following the general procedure but with [**39b**]$_0$ = 0.5 M. and using acetonitrile as the solvent. After 30 hours, the title compound was isolated by flash column chromatography (eluent hexane:diethyl ether 10:1) as a white solid (23 mg, 0.078 mmol, 78% yield). The enantiomeric excess was determined to be 81% by HPLC analysis on a Daicel Chiralpak IA column: 90/10 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 254 nm: τ_{minor} = 6.2 min, τ_{major} = 8.4 min. $[\alpha]_D^{26}$= - 106.7 (*c* = 0.85, $CHCl_3$, 81% *ee*). HRMS *calcd.* for ($C_{19}H_{18}OS$+Na^+): 317.0976, found 317.0961. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.31 (s, 1H), 7.54 – 7.45 (m, 1H), 7.44 – 7.33 (m, 1H), 7.35 – 7.24 (m, 3H), 7.21 – 7.03 (m, 3H), 6.28 (dq, *J* = 10.5, 1.3 Hz, 1H), 3.84 (d, *J* = 9.8 Hz, 1H), 3.52 – 3.37 (m, 1H), 1.18 (d, *J* = 1.3 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 157.1, 139.7, 136.2, 135.7, 132.7, 132.5, 130.3, 129.8, 127.2, 126.9, 126.8, 126.7, 126.2, 126.0, 55.0, 33.2, 18.6, 8.5 ppm.

(E)-5-(1H-indol-3-yl)-2,4-dimethyl-5-phenylpent-2-enal (**40c**)



40c

The reaction was carried out following the general procedure. After 25 hours, the title compound was isolated by flash column chromatography (eluent in gradient toluene:diethyl ether 98:2 – 95:5) as a white solid (16 mg, 0.052 mmol, 52% yield) as a mixture of diastereoisomers in a ratio of 1.3:1 (checked by ^{1}H NMR on the crude mixture) with an enantiomeric excess respectively of 87% and 92%. The enantiomeric excess was determined by HPLC analysis on a Daicel Chiralpak IA column: 80/20 hexane/i-PrOH, flow rate 1.00 mL/min, $\lambda = 254$ nm: $T_{minor} = 6.5$ min, $T_{major} = 14.5$ min and $\tau_{minor} = 5.7$ min, $\tau_{major} = 7.5$ min. HRMS *calcd.* for ($C_{21}H_{21}NO+Na^+$): 326.1521, found 326.1522. ^1H NMR (400 MHz, C_6D_6) δ 9.17 (s, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.23 – 6.89 (m, 10H), 6.59 – 6.50 (m, 1H), 6.01 (d, *J* = 9.9 Hz, 1H), 3.98 (d, *J* = 9.0 Hz, 1H), 3.41 – 3.31 (m, 1H), 1.62 (d, *J* = 1.4 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (100 MHz, C_6D_6) δ 195.1, 158.5, 144.4, 139.2, 138.7, 137.4, 129.4, 129.2, 127.4, 123.2, 122.2, 120.6, 120.4, 118.9, 112.3, 49.8, 39.5, 19.9, 10.2 ppm.

Chapter V

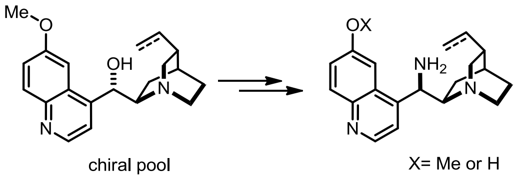
Synthesis of 9-Amino(9-deoxy)epi Cinchona Alkaloids

Summary

We have developed two procedures for the synthesis of primary amines derived from cinchona alkaloids, valuable catalysts used in the asymmetric functionalization of carbonyl compounds.

The two procedures were optimized following two different approaches: a laboratory oriented synthesis (*Approach A*) and a more scalable industrial method of preparation *(Approach B)*.[1]

FROM CHIRAL POOL TO AMINOCATALYST



Two different ways of synthesis.

Multigram approach (5 g and 20 g).

5.1 Background

The emergent field of asymmetric aminocatalysis,[2,3] which exploits the ability of chiral primary[4] and secondary[5] amines to *in situ* generate active intermediates *via* the reversible condensation with unmodified carbonyl reagents, has greatly expanded the chemist's resources to catalytically and asymmetrically functionalize carbonyl compounds. The use of enantiopure chiral cyclic

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[1] The work discussed in this chapter has been published, see: C. Cassani, R. Martín-Rapún, E. Arceo, F. Bravo, P. Melchiorre. Synthesis of 9-amino(9-deoxy)*epi* cinchona alkaloids, general chiral organocatalysts for the stereoselective functionalization of carbonyl compounds. *Nat. Protoc.*, **2013**, *8*, 325. Experimental part developed together with R. Martín-Rapún.

[2] B. List. Emil Knoevenagel and the Roots of Aminocatalysis. *Angew. Chem. Int. Ed.*, **2010**, *49*, 1730.

[3] P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli. Asymmetric Aminocatalysis-Gold Rush in Organic Chemistry. *Angew. Chem. Int. Ed.*, **2008**, *47*, 6138.

[4] L.-W. Xu, J. Luo, Y. Lu. Asymmetric Catalysis with Chiral Primary Amine-based Organocatalysts. *Chem. Commun.*, **2009**, 1807.

[5] K. L. Jensen, G. Dickmeiss, H. Jiang, Ł. Albrecht, K. A. Jørgensen. The Diarylprolinol Silyl Ether System: A General Organocatalyst. *Acc. Chem. Res.*, **2011**, *45*, 248.

secondary amine catalysts, in particular L- or D-proline and its derivatives,[5,6] has demonstrated excellent versatility and efficiency, providing a reliable synthetic platform for the asymmetric functionalization of linear aldehydes and enals at their α,[7] β,[8] γ, [9] δ,[10] and even ε positions.[11]

The recent developments have indicated how the appropriate choice of a primary amine catalyst can overcome the steric restrictions that secondary amines often encounter in the activation of bulky carbonyl compounds, such as simple ketones as well as α-branched substituted aldehydes and ketones, and their α,β-unsaturated counterparts. Particularly, primary amines derived from 9-amino(9-deoxy)*epi* cinchona alkaloids,[12] easily prepared from natural sources,[13] have been recognized as a reliable and general catalyst class with a high synthetic potential for asymmetric aminocatalysis.[14] Among the possible scaffolds offered by this well-known chiral pool subset, the most frequently used are the quinine **1** and quinidine **3** derivatives (Figure 1).

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[6] B. List. Proline-catalyzed Asymmetric Reactions. *Tetrahedron*, **2002**, *58*, 5573.

[7] G. Lelais, D. W. C. MacMillan. Modern Strategies in Organic Catalysis: The Advent and Development of Iminium Activation. *Aldrichimica Acta*, **2006**, *39*, 79.

[8] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan. New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels−Alder Reaction. *J. Am. Chem. Soc.*, **2000**, *122*, 4243.

[9] S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen. Dienamine Catalysis: Organocatalytic Asymmetric γ-Amination of α,β-Unsaturated Aldehydes. *J. Am. Chem. Soc.*, **2006**, *128*, 12973.

[10] L. Dell'Amico, Ł. Albrecht, T. Naicker, P. H. Poulsen, K. A. Jørgensen. Beyond Classical Reactivity Patterns: Shifting from 1,4- to 1,6- Additions in Regio- and Enantioselective Organocatalyzed Vinylogous Reactions of Olefinic Lactones with Enals and 2,4-Dienals. *J. Am. Chem. Soc.*, **2013**, *135*, 8063.

[11] Z.-J. Jia, H. Jiang, J.-L. Li, B. Gschwend, Q.-Z. Li, X. Yin, J. Grouleff, Y.-C. Chen, K. A. Jørgensen. Trienamines in Asymmetric Organocatalysis: Diels−Alder and Tandem Reactions. *J. Am. Chem. Soc.*, **2011**, *133*, 5053.

[12] L. Jiang, Y.-C. Chen. Recent Advances in Asymmetric Catalysis with Cinchona Alkaloid-based Primary Amines. *Catal. Sci. Technol.*, **2011**, 1, 354.

[13] a) U. Sundermeier, C. Döbler, G. M. Mehltretter, W. Baumann, M. Beller. Synthesis of 9-N-Cinchona Alkaloid Peptide Hybrid Derivatives: Preparation and Conformational Study of 9-N-Acylamino(9-deoxy)cinchona Alkaloids. *Chirality*, **2003**, *15*, 127. b) B. Vakulya, S. Varga, A. Csampai, T. Soos. Highly Enantioselective Conjugate Addition of Nitromethane to Chalcones using Bifunctional Cinchona Organocatalysts. *Org. Lett.*, **2005**, *7*, 1967. c) S. H. McCooey, S. J. Connon. Readily Accessible 9-*Epi*-Amino Cinchona Alkaloid Derivatives Promote Efficient, Highly Enantioselective Additions of Aldehydes and Ketones to Nnitroolefins. *Org. Lett.*, **2007**, *9*, 599.

[14] P. Melchiorre. Cinchona-based Primary Amine Catalysis in the Asymmetric Functionalization of Carbonyl Compounds. *Angew. Chem. Int. Ed.*, **2012**, *51*, 9748.

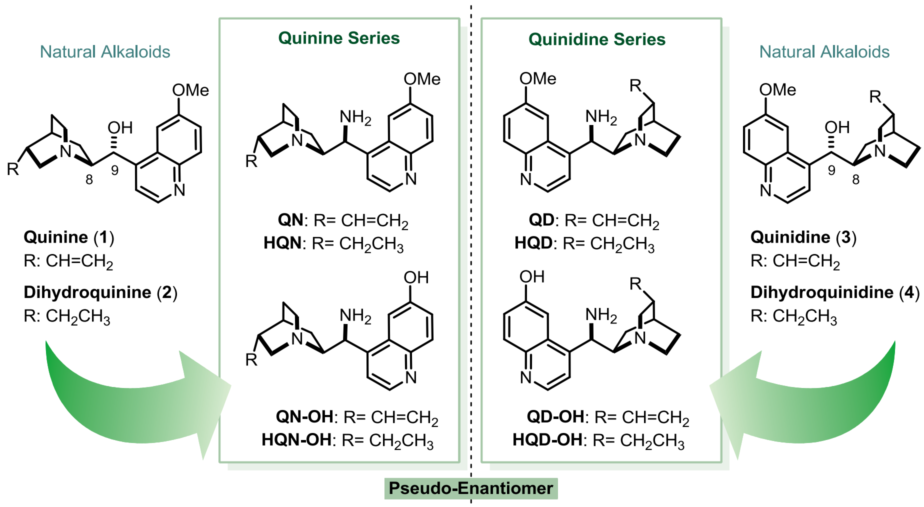

Figure 1. 9-amino(9-deoxy)*epi* Cinchona Derivatives.

These cinchona-based primary amines, which combine a primary amine functionality and a Lewis base in the same structure, have enabled the stereoselective functionalization of a variety of sterically hindered carbonyl compounds, which cannot be functionalized using secondary amines and which are also challenging substrates for metal catalysis. Remarkably, this single catalyst class can activate structurally different carbonyl compounds with consistently high levels of stereocontrol, while making use of the different aminocatalytic activation modes: iminium ion,[15] enamine,[16] dienamine,[17] trienamine[18] and vinylogous iminium ion.[19]

In addition, primary amines derived from cinchona alkaloids are used as precursors in the synthesis of another class of bifunctional organocatalysts which incorporate a fragment able to act as a hydrogen bond donor (Figure 2). These urea, thiourea and squaramide cinchona alkaloid

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[15] G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre. Organocatalytic Asymmetric Friedel−Crafts Alkylation of Indoles with Simple α,β-Unsaturated Ketones. *Org. Lett.*, **2007**, *9*, 1403.

[16] P. Kwiatkowski, T. D. Beeson, J. C. Conrad, D. W. C. MacMillan. Enantioselective Organocatalytic α-Fluorination of Cyclic Ketones. *J. Am. Chem. Soc.*, **2011**, *133*, 1738.

[17] G. Bergonzini, S. Vera, P. Melchiorre. Cooperative Organocatalysis for the Asymmetric γ-Alkylation of α-Branched Enals. *Angew. Chem. Int. Ed.*, **2010**, *49*, 9685.

[18] X.-F. Xiong, Q. Zhou, J. Gu, L. Dong, T.-Y. Liu, Y.-C. Chen. Trienamine Catalysis with 2,4-Dienones: Development and Application in Asymmetric Diels–Alder Reactions. *Angew. Chem. Int. Ed.*, **2012**, *51*, 4401.

[19] X. Tian, Y. Liu, P. Melchiorre. Aminocatalytic Enantioselective 1,6-Additions of Alkyl Thiols to Cyclic Dienones: Vinylogous Iminium Ion Activation. *Angew. Chem. Int. Ed.*, **2012**, *51*, 6439.

derivatives have emerged in the last years as versatile catalysts in a variety of useful asymmetric reactions.[20]

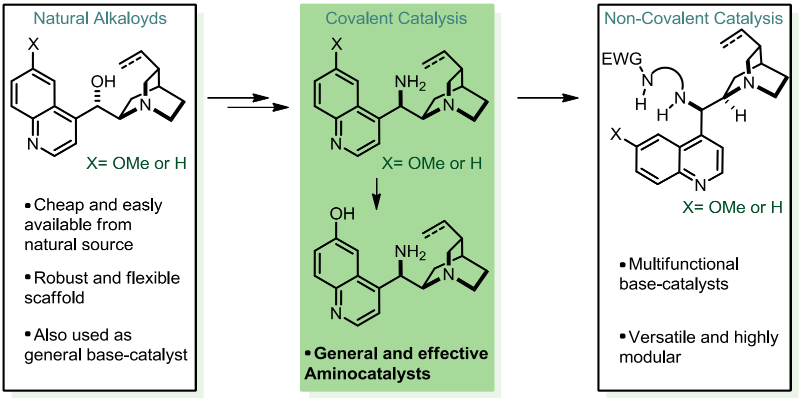

Figure 2. The Three Main Classes of Cinchona-Based Organocatalysts.

Cinchona alkaloid-derived primary amine catalysts are readily available from inexpensive starting materials that in nature only occur in diastereoisomeric pairs: quinine **1** (Figure 1**,** left) and quinidine **3** (Figure 1, right). In an asymmetric process, the diastereoisomeric pair generally acts as pseudo-enantiomeric catalysts, thus granting access to both enantiomers of one particular chiral product of a reaction.

In the naturally occurring alkaloids, the spatial configurations at C8 and at C9 are different (for example, (8*S*-9*R*) in quinine) with the hydroxyl group (at C9) and the nitrogen of the quinuclidine ring pointing away from each other in the preferred conformation.[21] Conversely, 9-*epi* alkaloids have an "unnatural" configuration with *R* (or *S*) configuration at both C8 and C9. Studies with cinchona-based primary amine catalysts with "natural" absolute configurations have constantly provided moderate results in terms of selectivity and reactivity, in large contrast with the high levels of stereocontrol achieved with the 9-epimer analogues in asymmetric reactions of carbonyl compounds.[13c]

The unique ability of cinchona-based primary amines to condense and activate hindered carbonyl compounds through asymmetric transformations greatly expanded the chemists ability

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[20] a) M. Kotke, P. R. Schreiner. In *Hydrogen Bonding in Organic Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA. **2009**, 141. b) S. J. Connon. Asymmetric Catalysis with Bifunctional Cinchona Alkaloid-Based Urea and Thiourea Organocatalysts. *Chem. Commun.*, **2008**, 2499. c) J. P. Malerich, K. Hagihara, V. H. Rawal. Chiral Squaramide Derivatives are Excellent Hydrogen Bond Donor Catalysts. *J. Am. Chem. Soc.*, **2008**, *130*, 14416.

[21] T. Bürgi, A. Baiker. Conformational Behavior of Cinchonidine in Different Solvents: A Combined NMR and *ab Initio* Investigation. *J. Am. Chem. Soc.*, **1998**, *120*, 12920.

to directly functionalize sterically demanding substrates. There are many features which make this class of catalyst so effective and widely used in asymmetric aminocatalysis (see section 1.2.5). Remarkable developments have been reported in the last few years, and further progress and discoveries can be expected in the near future.

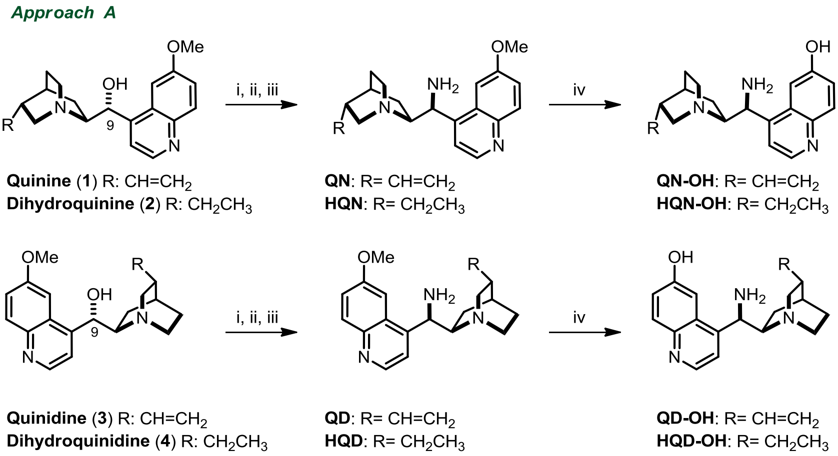
For this reason, and for the intensive use we made of these catalysts in our laboratory, we focused in scaling-up and improving the synthesis of these catalysts. Thanks to the expertise acquired with the use of such molecules in our laboratory and to the possibility of working in close contact with the technology development unit of CSOL (Catalyst Selection and Optimization Laboratory) at ICIQ, we successfully optimized two different protocols for the synthesis of these aminocatalysts: *Approach A* and *Approach B*.

Approach A: Basing on reported protocols, we described an improved and detailed synthesis which meets the needs of an organic synthesis laboratory: simplicity, robustness and pragmatism, all of which allow quantities of 5g to be synthesized in a reproducible way. This approach allows the one-pot syntheses of four cinchona-based primary amines from the alkaloids quinine **1**, dihydroquinine **2,** quinidine **3** and dihydroquinidine **4** respectively. This was achieved by means of a Mitsunobu reaction to introduce an azide group, followed by reduction and hydrolysis. Demethylation with BBr_3 provided direct access to the bifunctional aminocatalysts bearing the free hydroxyl moiety.

Approach B: In collaboration with CSOL we could participate in the development of a more scalable and cost-effective protocol for the synthesis of the same 9-amino(9-deoxy)*epi* cinchona derivatives and their demethylated counterparts. This approach provided a synthetic route more convenient for large scale synthesis (tested up-to 20 g-scale). In this procedure, the azides, formed from the O-mesylated derivatives of quinine and quinidine only, are selectively reduced with $LiAlH_4$ to afford catalysts **QN** and **QD**, while hydrogenation (Pd/C) provides **HQN** and **HQD**. A further reaction using alkylthiolate affords the bifunctional (-OH free) catalysts in a process in which the less expensive quinine and quinidine are the only starting materials used.

5.2 *Approach A*

On the basis of previously reported syntheses of these compounds, amination of the alcohol at C9 in the cinchona alkaloids can be performed by introducing an azide *via* the Mitsunobu protocol.[13] The Mitsunobu reaction has been largely employed in organic synthesis, usually for the inversion of the configuration of secondary alcohol compounds. This reaction is characterized by high stereoselectivity, mild reaction conditions and compatibility with the presence of other functionalities. The Mitsunobu protocol involves the reaction of an alcohol and a nucleophile, in the presence of triaryl or trialkylphosphine (Ph_3P in this case) and diisopropyl azodicarboxylate (DIAD). The general approach to prepare the primary amines **QN**, **HQN**, **QD** and **HQD** is outlined in Scheme 1. The commercially available diphenylphosphoryl azide (DPPA) is the azide source of choice, a safer approach than directly using hydrazoic acid. Along with the desired product, which contains the newly formed C-N bond with inversion of configuration at C9, the byproducts phosphine oxide ($Ph_3P{=}O$) and diisopropyl hydrazine 1,2-dicarboxylate are produced in the reaction. In order to avoid isolation of the azide product, a reduction is performed in the same pot, where the N_3-functionalized product reacts with an excess of triphenylphosphine, according to the Staudinger reaction. This leads to aminophosphorane products (with a $Ph_3P{=}N$- group) which can be readily transformed into an amino function ($-NH_2$) by subsequent hydrolysis. In this way, the synthesis can be carried out through a sequence of one-pot transformations (Scheme 1).



Scheme 1. (i)PPh_3, DIAD, DPPA, THF, 0-45 °C; (ii) PPh_3, 45 °C; (iii) H_2O, 45 °C; then HCl_{aq} then NH_4OH; (iv) BBr_3, DCM, -78 to 25 °C.

Commercially available alkaloids quinine **1**, dihydroquinine **2,** quinidine **3** and dihydroquinidine **4** were subjected to the same reaction sequence in a similar manner and, subsequently, the obtained crude mixtures were treated with aqueous HCl solution and the products were purified as hydrochloride salts by crystallization. Neutralization using a NH_4OH aqueous solution affords the free primary amines **QN**, **QD**, **HQN** and **HQD**. Demethylation was performed on these -OMe derivatives following a reported procedure with BBr_3 to obtain the -OH derivatives **QN-OH**, **QD-OH**, **HQN-OH**, and **HQD-OH**, respectively.[22] In general, this is an operationally simple and relatively fast procedure for the synthesis of quinine and quinidine derived primary amines and

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[22] W. Chen, W. Du, Y.-Z. Duan, Y. Wu, S.-Y. Yang, Y.-C. Chen. *Angew. Chem. Int. Ed.*, **2007**, *46*, 7667.

their respective demethylated counterparts in a 5 g-scale that is highly convenient for laboratory practice. Detailed experimental procedures are given in the experimental section (5.4).

5.2.1. General Comments to *Approach A*

The use of this approach provides access to eight cinchona-based primary amines in sufficient amounts for laboratory scale reactions. However, this approach suffers from an important limitation for larger scale production: *(a)* The use of expensive and/or low atom economy reagents such as triphenylphosphine, DIAD and DPPA. This results in the generation of a considerable amount of waste; more specifically, large amounts of triphenyphosphine oxide generated both in the Mitsunobu reaction and in the Staudinger azide reduction can be difficult to remove when scaling up the reaction and may impact downstream processing. *(b)* The -OMe analogues (**QN**, **QD**, **HQN** and **HQD**) are first isolated as hydrochloride salts from aqueous solution by evaporation of the water, a time consuming process that requires a large amount of energy. *(c)* The hazardous and corrosive reagent BBr_3 requires particular care in its manipulation and would require the use of a suitable reactor (*e.g.*, glass lined or hast-alloy). (*d)* The low temperature of the demethylation reaction (-78 °C) is generally not achievable either at larger scale-up or at pilot plant reactors.

These limitations, in addition to the use of relatively expensive starting materials such as dihydroquinidine and, particularly, dihydroquinine, prompted us to devise a modified and more economic synthesis. The studies, carried out by the technology development unit of CSOL, lead to a new procedure which is based on the combination of previously reported individual steps. This approach is more cost-effective and convenient than the *Approach A.*

5.3 *Approach B*

O-mesylated cinchona derivatives **5** and **6**, derived from quinine **1** and quinidine **3**, can be easily prepared under mild conditions, according to previous reference, by mesylation with methanesulfonyl chloride at the C9-position (Scheme 2).[23]

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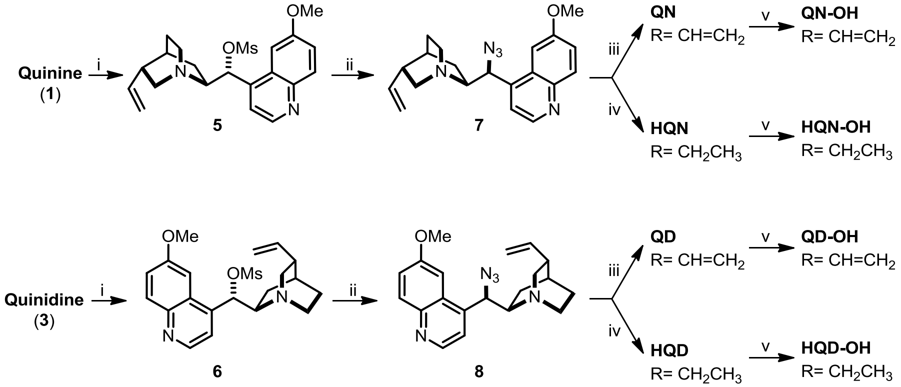
[23] M.H. Franz, S. Röper, R. Wartchow, H. M. R. Hoffmann. The First and Second Cinchona Rearrangement. Two Fundamental Transformations of Alkaloid Chemistry. *J. Org. Chem.*, **2004**, *69*, 2983.

Approach B



Scheme 2. (i) MsCl, TEA, THF, 0 °C; (ii) NaN_3, DMF, 65 °C; (iii) $LiAlH_4$, THF, 0 °C, then HCl, then NH_4OH; (iv) H_2, Pd/C, MeOH, then HCl, then NH_4OH; (v) NaSEt, DMSO, 80 °C.

Sodium azide in N,N-dimethylformamide (DMF) is then used to obtain the azide products **7** and **8** by nucleophilic displacement (S_N2) of the methanesulfonate function by the azide ion, which proceeds with inversion of configuration and without racemization.[24] Selective reduction of the azido group in **7** and **8** with lithium aluminium hydride gives a primary amino group, affording catalysts **QN** and **QD** (iii, Scheme 2). Alternatively, when the reduction of **7** and **8** is performed under hydrogen pressure using Pd/C as catalyst (iv, Scheme 2), 9-amino(9-deoxy)*epi* cinchona derivatives **HQN** and **HQD** are obtained. **QN**, **QD**, **HQN** and **HQD** are purified *via* the formation and precipitation of their hydrochloride salts in organic solvents. After recovering of the free primary amines **QN**, **QD**, **HQN** and **HQD** by treatment with aqueous NH_4OH, demethylation of **QN**, **QD**, **HQN** and **HQD** can be performed using sodium ethyl thiolate in DMSO (this is a modification of the procedure reported for the demethylation of quinidine,[25] since the original procedure results in decomposition) to afford catalysts **QN-OH**, **QD-OH**, **HQN-OH** and **HQD-OH** respectively (v, Scheme 2). This results in a highly convenient synthetic process in which the whole collection of primary amine catalysts is prepared from the less expensive alkaloids quinine **1** and quinidine **3**.

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[24] K. Kacprzak, B. Gierczyk. Clickable 9-Azido-(9-deoxy)-cinchona Alkaloids: Synthesis and Conformation. *Tetrahedron Asymmetry*, **2010**, *21*, 2740.

[25] F. Xu, E. Corley, M. Zacuto, D. A. Conlon, B. Pipik, G Humphrey, J Murry, D. Tschaen. Asymmetric Synthesis of a Potent, Aminopiperidine-Fused Imidazopyridine Dipeptidyl Peptidase IV Inhibitor. *J. Org. Chem.*, **2010**, *75*, 1343.

5.3.1. General Comments to *Approach B*

The synthetic route outlined in Scheme 2 (*Approach B*) addresses the issues intrinsic to the *Approach A* (indicated above), and it is therefore more suitable for scale-up. The synthetic solutions provided, offer some practical advantages that can be rationalized as follows: *(a)* The Mitsunobu reagents are replaced by the more affordable methanesulfonyl chloride and sodium azide. *(b)* The azides can be reduced selectively in the presence of the double bond or, alternatively, both groups can be reduced simultaneously, thus enabling access to the dihydro-derivatives and introducing divergence in the synthesis. These azides, which are also intermediates generated *in situ* in *Approach A*, do not pose a major concern from a process safety point of view since their exothermic degradation, as obtained from Dynamic Scanning Calorimetry (DSC) analysis, have a start temperature for the exothermic event at over 60 °C above the reaction temperature (The temperatures for the start of exothermic event of the azides derived from quinine and quinidine are *ca.* 140 °C and 130 °C, respectively; in a similar experiment, we found that sodium azide does not show any exothermic event in the range from 30 to 300 °C. A safety margin of 50 °C between the exothermic event and the reaction temperature, even in the absence of adiabatic data, is generally accepted as sufficient from a process safety perspective). *(c)* The -OMe derivatives (**QN**, **QD**, **HQN** and **HQD**) are isolated from the organic solution by precipitation of the hydrochloride salts. (In this respect, whilst the trihydrochloride salts of compounds **QN**, **QD** and **HQD** are very convenient because of their easy manipulation, in the case of **HQN** we choose to precipitate the more crystalline monohydrochloride salt, since the trihydrochloride tends to form a jelly-like solid difficult to filter and wash). *(d)* Thiolates (*e.g.*, sodium ethylthiolate) can be used as mild reagents in the demethylation reaction, giving a clean reaction profile. *(e)* Extreme temperatures are avoided. *(f)* The reactions are scalable at least to 20 g-scale.

Despite the problems circumvented by the synthetic route made available through *Approach B*, several disadvantages need also to be considered. Lithium aluminium hydride is a moisture sensitive reagent and can create work-up and waste disposal challenges; for example, removal of the solids formed in the reaction work-up can be cumbersome. Despite these potential problems, multi-kilogram scale use of $LiAlH_4$ is very common. Regarding the use of sodium azide, although the approach through the azides **7** and **8** provides a unique method for accessing the whole set of the eight primary amine catalysts from quinine **1** and quinidine **3**, its use introduces some issues due to its toxicity and safety concerns. The equipment employed has to be free of heavy metal contaminants (lead, copper, silver, mercury, etc.), since their salts can detonate due to thermal or mechanical stress. Sodium azide waste has to be treated with care and at all times under basic conditions, as protic, acidic or neutral solutions would generate poisonous and explosive HN_3.[26] In this respect, the reagent diphenylphosphoryl azide (DPPA) used in *Approach A* provides fewer concerns from a process safety perspective because it gets reduced in the subsequent Staudinger reduction, and examples of its use at high scale can also be found.

Approach A and *Approach B* offer different advantages and disadvantages (summarized in Table 1), but both synthetic routes are highly reproducible, effective and convenient ways to prepare 9-amino(9-deoxy)*epi* cinchona primary amines.

Table 1. Comparison between *Approaches A* and *B*.

Approach A Mitsunobu – Staudinger – BBr_3 route	***Approach B*** S_N2 – $LiAlH_4$ or Pd/C – Thiolate route
QN and **QN-OH** synthesized from quinine **1** **QD** and **QD-OH** synthesized from quinidine **3** **HQN** and **HQN-OH** synthesized from dihydroquinine **2** **HQD** and **HQD-OH** synthesized from dihydroquinidine **4**	**QN**, **QN-OH**, **HQN**, **HQN-OH** synthesized from quinine **1** **QD**, **QD-OH**, **HQD**, **HQD-OH** synthesized from quinidine **3**
Expensive starting materials (dihydroquinine and dihydroquinidine) for the synthesis of **HQN**, **HQN-OH**, **HQD** and **HQD-OH**	Inexpensive quinine and quinidine are the only starting materials used. Divergent synthesis by taking advantage of selective-non selective reducing methods.
One-pot process to obtain **QN**, **QD**, **HQN** and **HQD** hydrochlorides One-pot process plus demethylation step to afford **QN-OH**, **QD-OH**, **HQN-OH** and **HQD-OH**	Three steps to obtain **QN**, **QD**, **HQN** and **HQD** without intermediate isolation. Four steps to obtain **QN-OH**, **QD-OH**, **HQN-OH** and **HQD-OH**
Expensive and low atom economy reagents, generation of waste during Mitsunobu and Staudinger reduction (triphenylphosphine oxide, hydrazine derived from DIAD).	More affordable MsCl and NaN_3 are used. Toxic N_3 residues are generated. The use of $LiAlH_4$ might difficult the work-up.
Hydrochlorides of -OMe derivatives **QN**, **QD**, **HQN** and **HQD** isolated by water evaporation (time and energy consuming process).	Hydrochlorides of -OMe derivatives **QN**, **QD**, **HQN** and **HQD** isolated by precipitation from organic medium.
Use of extremely corrosive BBr_3.	Use of less corrosive thiolates.
Requires -78 °C for the demethylation step (iv, Scheme 2)	Extremely low temperature is avoided, all reactions occur in the range from 0 to 80 °C
The procedure has not been described on a scale greater than 5 g.	The reactions are scalable to, at least, 20 g.

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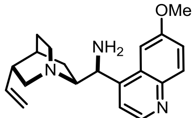
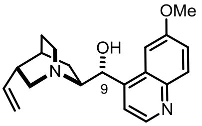
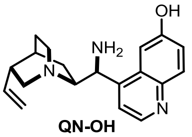
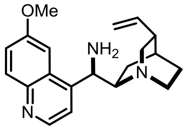
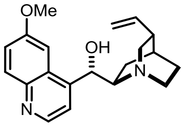
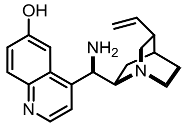
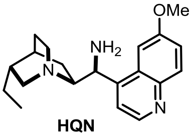
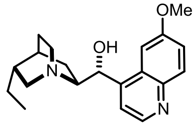
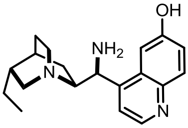
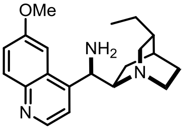
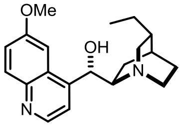
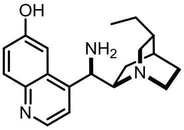
[26] M. E. Kopach, M. M. Murray, T. M. Braden, M. E. Kobierski, O. L. Williams. Improved Synthesis of 1-(Azidomethyl)-3,5-bis-(trifluoromethyl)benzene: Development of Batch and Microflow Azide Processes. *Org. Process Res. Dev.*, **2009**, *13*, 152.

5.4 Experimental Section

This procedure is organized in a modular fashion. Refer to Table 2 and, and highlight the sections of the procedure that are required for the synthesis of your compound of interest.

Table 2. Reaction Roadmap and Typical Yields.

Target compound	Starting Material	Modules for Approach 1 *(Typical yield)*	Modules for Approach 2 *(Typical yield)*
 **QN**	 **Quinine (1)**	1) MODULE A 2) MODULE B 3) MODULE D *(60-70%)*	1) MODULE H 2) MODULE I 3) MODULE K 4) MODULE D *(45-55%)*
 **QN-OH**	**QN**	1) MODULE E 2) MODULE G *(60-70%)*	1) MODULE N *(55-65%)*
 **QD**	 **Qunidine (3)**	1) MODULE A 2) MODULE C 3) MODULE D *(50-60%)*	1) MODULE H 2) MODULE I 3) MODULE L 4) MODULE D *(45-55%)*
 **QD-OH**	**QD**	1) MODULE E 2) MODULE F *(45-55%)* 1) MODULE E 2) MODULE G *(60-70%)*	1) MODULE N *(55-65%)*

Target compound	**Starting Material**	**Modules for Approach 1 (*Typical yield*)**	**Modules for Approach 2 (*Typical yield*)**
 **HQN**	 **Dihydroquinine (2)**	1) MODULE A 2) MODULE B 3) MODULE D *(55-65%)*	
	Quinine (1)		1) MODULE H 2) MODULE J 3) MODULE M 4) MODULE D *(55-65%)*
 **HQN-OH**	**HQN**	1) MODULE E 2) MODULE G *(60-70%)*	1) MODULE N *(55-65%)*
 **HQD**	 **Dihydroqunidine (4)**	1) MODULE A 2) MODULE C 3) MODULE D *(55-65%)*	
	Quinidine (3)		1) MODULE H 2) MODULE J 3) MODULE L 4) MODULE D *(50-60%)*
 **HQD-OH**	**HQD**	1) MODULE E 2) MODULE G *(60-70%)*	1) MODULE N *(55-65%)*

5.4.1. Experimental *Approach A*

A Synthesis of *9-amino(9-deoxy)epi quinine and quinidine derivatives* QN, QD, HQN and HQD

(i) Set a previously oven-dried two-necked, 250 mL round-bottom flask with a condenser, rubber septa and a stirring bar. Evacuate the air under vacuum and refill with nitrogen gas (three times).

(ii) Add 15.4 mmol of cinchona alkaloid quinine **1**, dihydroquinine **2,** quinidine **3** or dihydroquinidine **4** (5 g in the case of quinine) and 4.85 g (18.5 mmol) of PPh_3 in the flask under nitrogen atmosphere.

(iii) Add 60 mL of anhydrous THF to the flask with a syringe or a cannula and stir for 5 min or until the solid is completely dissolved.

(iv) Cool down the reaction mixture to 0 °C using a water-ice bath and stir the solution for further 5 min.

(v) Slowly add 3.64 mL (18.5 mmol) of DIAD with a syringe to the cold solution (addition time 5-6 min). (The solution changes from colorless to pale orange/yellowish)

(vi) 5 min after the addition, add 4.0 mL (18.5 mmol) of DPPA dropwise (addition time 15 min) and after stirring for further 15 min at 0 °C remove the cooling bath to let the mixture warm-up to room temperature (20-25°C).

(vii) Stir the reaction mixture at room temperature for 4h. During this period, the mixture becomes a yellowish suspension.

(viii) Move the reaction flask to a heating bath at 45 °C and continue stirring at this temperature for 2 h. An homogeneous solution is formed again. Completeness of the reaction can be checked by the disappearance of the spots corresponding to compound starting alkaloids in thin layer chromatography (eluent ethyl acetate/methanol 10/1; R_f starting alkaloids of ≈0.05) and simultaneous formation of a new spot (eluent ethyl acetate/methanol 10/1; $R_f \approx 0.5$-0.6) (both starting materials and intermediates display a bright blue spot under UV lamp at 365nm).

(ix) Add to the mixture another portion of PPh_3 (triphenylphosphine), 4.85 g (18.5 mmol) in one portion. A prolonged but moderate gas evolution is observed.

(x) Leave the reaction stirring at the same temperature for 2 h. 45 °C.

(xi) Add 3.5 mL of water and stir the solution for additional 4 h at 45 °C.

■ **PAUSE POINT:** The solution can be left stirring overnight (16 h) to ensure full conversion.

(xii) Let the reaction mixture cool down to room temperature and then transfer the solution to a 500 mL round bottom flask using DCM (15 mL) to rinse the reaction flask.

(xiii) Remove the solvents under vacuum with the help of a rotary evaporator.

(xiv) Add a magnetic stirrer to the round bottom flask and 80 mL DCM. Then stir the mixture until a homogeneous solution is obtained.

(xv) Slowly add 80 mL of an aqueous HCl solution (2 M) and stir vigorously (stir so that the phases are in close contact) for 10 min more.

(xvi) Remove the stirrer and transfer the solution to a 250 mL separation funnel (2 portions of 5 mL of aqueous solution of HCl (2 M) and DCM (5 mL) can be used to complete the transfer and rinse the round bottom flask).

(xvii) Remove the organic phase and wash the aqueous phase twice with DCM (2 x 40 mL).

(xviii) Transfer the aqueous solution into a 250 mL round bottom flask (wash the funnel with 10 mL of methanol) and remove the solvent under reduced pressure (First with a rotary evaporator; then residual solvents are carefully removed by using a high-vacuum pump). A bright yellow solid is obtained.

■ **PAUSE POINT:** The solid obtained can be stored under air for weeks with no noticeable decomposition.

B Purification of the hydrochloride salts of compounds QN and HQN by recrystallization.

(i) A reflux condenser is attached to the top of the flask. The salt is dissolved in the minimum amount of methanol possible to fully dissolve the solid (50 to 100 mL of MeOH; the exact amount of solvent will vary depending on the compound and on the water content of the solvent) while heating the mixture to reflux.

(ii) Slowly add ethyl acetate (10-15 mL) in small portions until the opalescence becomes persistent.

▲**CRITICAL STEP**: the presence of water in the salt may alter the outcome of the recrystallization. If the salt is not well dried, smaller amounts of solvent are necessary to dissolve the material, and this may affect the purity of the recrystallized product.

(iii) Let the flask cool down to room temperature before putting it in the refrigerator (0-4 °C temperature).

(iv) Generally the recrystallization takes place overnight.

▲**CRITICAL STEP**: This class of compounds recrystallizes as a solid (jelly solid in the case of **HQN**) swelled by solvent. This does not compromise the purity of the final primary amine.

(v) Separate the solid by filtration over filter paper and wash it with 5-10 mL of cold ethyl acetate (previously cooled down to 5-10 °C using an ice-water bath). The solvent in the mother liquid can be removed under vacuum and a second recrystallization can be carried out on the remaining solid, following the same procedure reported in **Module B steps i-v**.

(vi) Transfer the solid into a round bottom flask and dry under high-vacuum.

■**PAUSE POINT:** the solid obtained can be stored under air for months with no noticeable decomposition.

C Purification of the hydrochloride salts of compounds QD and HQD by hot reslurry.

(i) Add 150 mL of MeOH to the flask. The bright yellow solid will partially dissolve leading to a suspension of a white solid in a yellow solution.

(ii) Warm-up the flask to 40-45 °C for 5 to 6 min, moving the flask in circles so that the solid in suspension becomes a fine dust with no blocks.

(iii) Add 20 mL of ethyl acetate.

(iv) Let the flask cool down to room temperature before putting it in a refrigerator (0-4 °C temperature) for at least 3-4 h.

(v) Separate the solid by filtration over filter paper and wash it with cold ethyl acetate (5-10 mL) and hexane (10-15 mL).

(vi) Transfer the solid to a round bottom flask and dry under high-vacuum.

■**PAUSE POINT:** the solid obtained can be stored under air at room temperature for months without noticeable decomposition.

D Neutralization of the salt and formation of the free amines QN, HQN, QD and HQD

(i) Transfer 3 g of the salt obtained in **MODULE B step vi** or **MODULE C step vi** or **MODULE K step x** or **MODULE L step x** or **MODULE M step viii** to a 100 mL round-bottom flask.

(ii) Add a stirrer and 20 mL of DCM to the flask.

(iii) Slowly add 15 mL of a 5 M aqueous solution of NH_4OH to the suspension (the suspension turns into a colorless biphasic mixture) and stir vigorously (stir so that the phases are in close contact) the biphasic system for 5 min.

(iv) Transfer the mixture into a 50 mL separation funnel using DCM to wash the flask (3+3 mL).

(v) Collect the organic phase and wash two more times the aqueous phase with DCM (with two portions of 15 mL).

(vi) Dry the organic phase with Na_2SO_4 (with approximately 2 g of sodium sulfate for 2-5 minutes) filter through a fritted glass filter connected to a 100 mL round-bottom flask and remove the solvents under reduced pressure.

! CAUTION: The primary amines (**QN**, **HQN**, **QD** or **HQD**) are obtained as very viscous oils that often form foams during the evaporation of the solvents.

■ **PAUSE POINT:** the oil obtained (compounds **QN**, **HQN**, **QD** or **HQD**) can be stored under air in the refrigerator (4 °C) for months without noticeable decomposition.

E Synthesis of the hydrobromide salts of *9-amino(9-deoxy)epi* cinchona *alkaloids derivatives* QN-OH, HQN-OH, QD-OH and HQD-OH

(i) Transfer 2 g of **QN**, **HQN**, **QD** or **HQD** dissolved in a small amount of DCM to a previously dried 100 mL round-bottom flask. Remove the solvent under high vacuum. Then connect the flask to a previously dried addition funnel. Evacuate the air under vacuum and refill with nitrogen gas (three times).

! CAUTION: The primary amines derived from cinchona alkaloids are obtained as very viscous oils and often generate foams during a fast evaporation of the solvents.

(ii) Set a rubber septum and a stirring bar on the 100 mL flask containing the 2 g of the amine under argon.

! CAUTION: Due to the formation of a thick suspension during the following process, stirring may result difficult. For this reason, the choice of a big stirring bar is recommended.

▲**CRITICAL STEP**: All the glassware for this step has to be previously dried (overnight in the oven). The use silicone grease is recommended to seal the junctions and the key of the funnel. The rubber septa will be probably damaged during the process of addition of BBr_3. To maintain the argon overpressure in the system it is possible to use also an argon balloon or other inlet connected with needles to the system; in the case of using balloons it is very important (especially during the addition of BBr_3) to often verify that the needles are not obstructed.

(iii) Add, under argon, 60 mL of anhydrous DCM in the flask and stir at room temperature until a clear solution is obtained.

(iv) Place the round-bottom flask in a bath at -78 °C and stir for 5 min.

(v) Add 4.4 mL (45.4 mmol) of BBr_3 to the funnel.

! CAUTION: BBr_3 is very corrosive and highly harmful. It is important to use all the precaution and the personal protection to avoid inhalation and eye and skin contact during the manipulation of this compound. Wear chemical goggles and appropriate protective gloves and clothing to prevent skin exposure. Work under adequate ventilation inside a chemical fume hood. Syringes or glassware used to transfer the BBr_3 should be quenched (by washing with cold methanol and then water) right after use.

(vi) Slowly add the BBr_3 over a period of 30 min and stir at the same temperature for other 30 min. The clear solution turns into a bright-yellow suspension.

(vii) Change the temperature of the bath to -40 °C and stir for additional 2 h.

(viii) Leave the mixture warm up to room temperature and stir for 12 h more.

(ix) QUENCHING: cool down the mixture to -10 °C (internal temperature), add 20 mL of non-anhydrous diethyl ether to the funnel connected to the flask and add it slowly to the mixture (5 min).

(x) Stir at -10 °C (internal temperature) for 10 min.

(xi) Let the system warm up to room temperature and stir for further 20 min.

(xii) Filter the solid on paper washing with diethyl ether (2 x 5 mL) and dry under vacuum.

■ **PAUSE POINT:** the solid obtained can be stored under air in the refrigerator (4 °C) for weeks without noticeable decomposition.

F **Purification of QD-OH**

(i) **Purification of the hydrobromide salt (Steps i-iii)** Add to 2 g of the salt obtained in **MODULE E Step xii**, 8 mL of MeOH and warm up until reflux.

(ii) Cool down the suspension to room temperature before putting it in the refrigerator (0-4 °C temperature) for at least 2h.

(iii) Filter the white solid on a filter paper and wash it with diethyl ether (2 x 5 mL).

(iv) **Neutralization of the salts and formation of the free amine (Steps iv-vii)** Transfer the solid into a 100 mL round-bottom flask equipped with a stirrer. Then add 25 mL of DCM.

(v) Add to the suspension 10 mL of water and slowly add 5 M aqueous solution of NH_4OH (3-5 mL) until the water phase arrives to a value of pH of 9 (higher or lower pH values may lower the final yield) and the solid is dissolved, and stir for additional 10 min. If during this period solid agglomeration is observed, more DCM (10-15 mL) can be added until a homogeneous solution is obtained.

(vi) Transfer the biphasic mixture into a separation funnel and collect the organic phase. Wash the aqueous phase with DCM (3 x 20 mL).

(vii) Dry the combined organic phase on Na_2SO_4, filter and remove the solvent under reduced pressure (a pale orange solid is formed).

■ **PAUSE POINT:** The solid obtained can be stored under nitrogen in the refrigerator (4 °C) for weeks without noticeable decomposition.

G **Purification of QN-OH, HQN-OH, QD-OH and HQD-OH by column chromatography.**

(i) **Neutralization of the salt and formation of the free amine (Steps i-v)**Add 2 g of the salt obtained in **MODULE E Step xii** to a 100 mL round bottom flask and add a stirrer, 60 mL of DCM and 30 mL of water.

(ii) Add to the suspension around 3-5 mL of 5 M aqueous NH_4OH solution until the aqueous phase attains a pH value of 9 and all the solid is dissolved (higher or lower pH values may lower the final yield), stir for further 10 min. If during this period solid agglomeration is observed, more DCM (10-15 mL) can be added until a homogeneous solution is obtained.

(iii) Transfer the biphasic mixture in a separation funnel washing the round-bottom flask with DCM (2 x 5 mL).

(iv) Collect the organic phase and wash the aqueous phase 3 times with 35 mL of DCM.

(v) Dry the combined organic phases with Na_2SO_4, filter and remove the solvent under reduced pressure (a pale orange solid is obtained).

(vi) **Column (Steps vi-ix).** Prepare a column of 2.5-3 cm of inner diameter with 20 g of silica gel 60A (35-70 µm particle size) and condition it with EtOAc.

(vii) Introduce the compound into the column using DCM.

(viii) Elute the column with a mixture 10/1/1 of (EtOAc/MeOH/5 M aqueous NH_4OH) until the product comes out. In these conditions the desired product has an R_f of 0.30.

(ix) After evaporation of the fractions containing the desired product a pale orange solid is obtained.

■ **PAUSE POINT:** The solid obtained can be stored in the fridge under nitrogen atmosphere for weeks with no noticeable decomposition.

5.4.2. Experimental *Approach B*

H Inversion of configuration at C9 in quinine 1 and quinie 2 through the preparation of azides 7 and 8

(i) **Synthesis of quinine and quinidine *O*-mesylates 5 and 6 (Steps i-xv)** Prepare a dry 3-necked 500 mL round-bottom flask with a thermometer, a 100 mL addition funnel and a Teflon coated stirring bar.

(ii) Add 20 g (61.6 mmol) of cinchona alkaloid quinine **1** or quinidine **3**. Evacuate the air under vacuum and refill with nitrogen gas (three times).

(iii) Add 90 mL of anhydrous THF (using a measuring cylinder) and stir the mixture for 5 min. A suspension is obtained.

(iv) Transfer 34 mL (246.6 mmol) of triethylamine (using the measuring cylinder) to the reaction mixture.

(v) Cool down the reaction mixture using a water-ice bath and stir the mixture while the internal temperature stabilizes at 0-4 °C.

(vi) Load the addition funnel with methanesulfonyl chloride (11.4 mL, 148.0 mmol) dissolved in anhydrous THF (40 mL).

(vii) Add the methanesulfonyl chloride solution dropwise. Typical addition time is 30 min.

! CAUTION: The reaction is exothermic and the internal temperature will rise if the addition is performed too fast.

(viii) Once the addition is finished the ice bath and the addition funnel can be removed. The reaction mixture is stirred at room temperature for additional 3.5 h. Completeness of the reaction can be checked by the disappearance of **1** or **2** spots in thin layer chromatography (eluent ethyl acetate/methanol/aq. NH_4OH (5 M) 100/5/1; R_f (quinine **1**): 0.21; R_f (quinidine **2**): 0.20; R_f (**5**): 0.50; R_f (**6**): 0.54). Starting materials **1** and **2** display a bright blue spot under UV lamp at 365nm.

(ix) Cool down the reaction mixture using a water-ice bath and stir the mixture while the internal temperature stabilizes at 0-4 °C.

(x) Load an aqueous solution of $NaHCO_3$ (3.5 % w/w) (140 mL) in a 250 mL addition funnel and connect it to the round-bottom flask.

(xi) Add the aqueous solution dropwise while stirring. Typical addition time is 30 min. Upon addition, separate yellow transparent organic and aqueous layers are formed.

! CAUTION: The reaction is exothermic and the internal temperature will rise if the addition is performed too fast.

(xii) Separate the aqueous and the organic layers using a 500 mL separation funnel, and then extract the aqueous layer with ethyl acetate (2 × 40 mL).

(xiii) Combine the organic layers and use the separation funnel to remove the newly formed aqueous layer. Transfer the organic layer to a 1 liter round-bottom flask.

(xiv) Remove the solvents under reduced pressure. Residual water can be removed by adding ethyl acetate (10 mL) and submitting the mixture to reduced pressure (twice).

(xv) Dry the crude under vacuum (1.0×10^{-1} mbar for 2 h).

! CAUTION: **5** and **6** are obtained as very viscous oils and often generate foams during fast evaporation of the solvents or when drying under vacuum.

▲CRITICAL STEP: The presence of water has a negative impact in the yield of the next step due to side reactions, mainly the substitution of the mesyl with a hydroxy group.

■PAUSE POINT: The obtained crude products **5** or **6** are oils that may solidify on standing providing white to off-white solids. Crude **5** and **6** can be stored under air in the refrigerator for at least four weeks, with no noticeable decomposition.

(xvi) **Synthesis of azides 7 and 7 (Steps xvi-xxviii)** Prepare a dry 3-necked 500 mL round-bottom flask with a thermometer, a condenser and a Teflon coated stirring bar. Evacuate the air under vacuum and refill with nitrogen gas (three times).

(xvii) Add 6 g (92.5 mmol) of sodium azide.

(xviii) Add dry *N*,*N*-dimethylformamide (DMF) (40 mL) and start stirring. A suspension is obtained.

(xix) Dissolve crude **5** or **6** from **step xv** in dry DMF (60 mL) and transfer the solution to the 3-necked round-bottom flask, all at once. Use additional DMF (20 mL) to rinse all the starting material into the reaction vessel. A yellow suspension is obtained.

(xx) Heat the reaction mixture so that the internal temperature is 65 °C (oil bath temperature around 70 °C).

(xxi) Stir the reaction at 65 °C. After 8 hours the reaction is usually complete but it can be left overnight (16 hours) stirring at 65 °C to ensure full conversion. Completeness of the reaction can be checked by the disappearance of **5** or **6** spots in thin layer chromatography (eluent ethyl acetate/methanol 20/1; R_f (**5**): 0.36; R_f (**6**): 0.25; R_f (**7**): 0.49; R_f (**8**): 0.40). Products **7** and **8** display a bright blue spot under UV lamp at 365nm.

(xxii) Stop heating, allow the reaction mixture to reach room temperature and then cool it down with a water-ice bath while stirring.

(xxiii) Load an aqueous solution of NaOH (1 M) (120 mL) in a 250 mL addition funnel and connect it to the 3-necked round bottom flask.

(xxiv) Add the aqueous solution dropwise while stirring. Typical addition time is 30 min. Upon addition, the product, which is insoluble in water, separates as a yellow oil.

! CAUTION: The reaction is exothermic and temperature will rise if the addition is performed too fast.

! CAUTION: Sodium azide must be extracted in basic media. Do not use acids as poisonous gases may be formed.

(xxv) Transfer the mixture to a 500 mL separation funnel and extract the aqueous solution with three portions of *tert*-butyl methyl ether (MTBE) (3 × 40 mL) to recover the product. Combine the organic layers.

! CAUTION: Don't use chlorinated solvents for extraction as unstable and explosive azides (diazidomethane and triazidomethane) may be formed.

(xxvi) Wash the organic layer with aqueous NaOH (40 mL). Combine the aqueous layers containing NaN_3 and dispose of them in an appropriate waste container.

(xxvii) Dry the organic phase with Na_2SO_4, filter the solution to a 250 mL round-bottom flask and concentrate under vacuum with a rotary evaporator.

(xxviii) Dry the crude product **7** or **8** under vacuum (1.0×10^{-1} mbar for 1 h).

■PAUSE POINT: 7 and **8** are yellow oils that can be stored under air for months with no noticeable decomposition.

I Preparation of crude QN and QD

(i) Prepare a dry 3-necked 1 liter round-bottom flask with septa, a thermometer and a Teflon coated stirring bar. Evacuate the air under vacuum and refill with nitrogen gas (three times).

(ii) Dissolve crude **7** or **8** from **MODULE H Step xxviii** in dry THF (300 mL) in the round-bottom flask.

(iii) Cool down the reaction mixture using a water-ice bath and stir the mixture while the internal temperature gets to 0-4 °C.

(iv) Slowly add lithium aluminium hydride solution in THF (2.4 M) (15.4 mL, 37.0 mmol) *via* syringe through a rubber septum. (Alternatively, 1 M solution of lithium aluminium hydride in THF can be used, affording similar results). A typical addition time is 1 h. Upon addition the colour of the reaction mixture turns first to orange and then to red.

! CAUTION: Extremely flammable hydrogen gas is released during this reaction with concomitant appearance of foams. The reaction is exothermic and the temperature will rise if the addition is performed too fast.

(v) Stir the reaction at 0-4 °C. After 4 hours the reaction is typically finished (can be left overnight at 0-4 °C). Completeness of the reaction can be checked by the disappearance of **7** or **8** spots in thin layer chromatography (eluent ethyl acetate/methanol 20/1; R_f (**7**): 0.49; R_f (**8**): 0.40).

(vi) Slowly add ethyl acetate (100 mL) to quench the reaction while stirring at 0 °C.

(vii) Load an aqueous solution of NH_4OH (0.5 M) (250 mL) in a 250 mL addition funnel and connect it to the 3-necked round-bottom flask.

(viii) Add the aqueous solution dropwise while stirring. Typical addition time is 30 min. Upon addition, separate yellow transparent organic and milky aqueous layers are formed.

! CAUTION: Extremely flammable hydrogen gas is released during this reaction with concomitant appearance of foams. The reaction is exothermic and the temperature will rise if the addition is performed too fast.

(ix) Separate the aqueous and the organic layers using a 1 liter separation funnel, and then further extract the aqueous layer with ethyl acetate (2 × 100 mL).

(x) Combine the organic layers and wash with an aqueous solution of NH_4OH (0.5 M) (2 × 40 mL).

(xi) With a rotary evaporator concentrate the organic layer to 100 mL under reduced pressure.

(xii) Transfer the mixture to a separation funnel and remove the newly formed aqueous layer.

(xiii) Transfer the organic phase to a 1 liter round-bottom flask and remove all solvents under reduced pressure with a rotary evaporator.

(xiv) Residual water can be removed by adding ethyl acetate (40 mL) and submitting the mixture to reduced pressure (twice).

(xv) Dry the crude under vacuum (1.0×10^{-1} mbar for 2 h).

■ **PAUSE POINT:** The crude products **QN** and **QD** are thick yellow oils that can be stored under air for months without noticeable decomposition.

J Preparation of crude HQN and HQD

(i) Dissolve crude **7** or **8** (as obtained after **MODULE H Step xxviii**) in methanol (40 mL) once again and transfer the yellow solution to a high pressure reactor (100 mL).

(ii) Weigh out palladium on carbon 5 wt. % (2 g) and add it to the yellow solution.

(iii) Seal the reactor, purge it three times with hydrogen (pressurizing it at 5 bar with hydrogen and subsequently venting). Finally pressurize it at 20 bar. Start the magnetic stirring at room temperature.

! CAUTION: Extremely flammable hydrogen gas is released during purging.

! CAUTION: Before charging hydrogen, test for leaks in the reactor by pressurising with N_2, and ensuring the pressure is kept constant for some minutes.

(iv) After 2 hours stirring at room temperature, purge the reactor with hydrogen (3 times at 5 bar), and finally pressurize it at 20 bar.

! CAUTION: Extremely flammable hydrogen gas is released during purging.

(v) Stir the reaction 22 h at room temperature. The reaction is best monitored by the consumption of H_2, completeness being achieved when the pressure of H_2 does not decrease.

(vi) After 22 h, carefully release the pressure of the reactor. Purge it with nitrogen gas (3 times at 5 bar).

! CAUTION: Extremely flammable hydrogen gas is released.

(vii) Prepare a pad of packed celite (28 grams, about 3 cm high) soaked with ethyl acetate on a fritted glass filter, and filter the reaction mixture through it.

(viii) Wash the pad of celite with ethyl acetate until the filtrating solution shows no colour.

(ix) The filtrate is a yellow solution. Transfer it to a 1 liter round-bottom flask. After removing the solvents with a rotary evaporator, the crude is obtained as a yellow oil.

! CAUTION: The primary amines derived from cinchona alkaloids are obtained as very viscous oils and often generate foams during fast evaporation of the solvents or when drying under vacuum.

(x) Dry the crude thus obtained under vacuum (2 h, 1.0 × 10^{-1} mbar).

■ **PAUSE POINT:** The products **HQN** and **HQD** are thick yellow oils that can be stored under air for months with no noticeable decomposition.

K Precipitation of QN · QD HCl

(i) Prepare a dry 3-necked 250 mL round-bottom flask with a thermometer, a condenser and a Teflon coated stirring bar.

(ii) Dissolve crude **QN** from **MODULE I step xv** in methanol (75 mL) and transfer the solution to the round-bottom flask.

(iii) Slowly add hydrogen chloride solution in 2-propanol (5-6 M) (27.5 mL) *via* syringe to the stirred solution. Upon addition, the solution turns from yellow to red and then to dark orange.

(iv) Heat the solution to 55 °C (internal temperature) and stir the solution for 5 min.

(v) Load the addition funnel with ethyl acetate (75 mL) and add it slowly while stirring. Instant clouding occurs upon addition of ethyl acetate.

(vi) After 5 min stirring at 55 °C, allow the solution reaching room temperature slowly.

(vii) In less than 2 hours a pale yellow precipitate is formed.

(viii) Cool the mixture in a water-ice bath. Stir the suspension for 1 hour.

(ix) Collect the pale yellow solid by filtration using a 125 mL fritted glass filter; wash the solid with a mixture of methanol and ethyl acetate (1:1) (2 x 20 mL).

▲**CRITICAL STEP**: If the product is of a marked yellow colour it may contain impurities probably due to a too large amount of ethyl acetate for the precipitation. If that is the case, dissolve the solid in 75 mL of methanol at 55 °C, and repeat from **MODULE K step iv** using less ethyl acetate for the precipitation in **MODULE K step v**.

(x) Dry **QN · 3 HCl** under vacuum (1.0 × 10^{-1} mbar for 24 h, 35 °C).

■**PAUSE POINT:** the solid obtained can be stored under air for months with no noticeable decomposition.

L Precipitation of QD· 3 HCl and HQD · 3 HCl

(i) Prepare a dry 3-necked 1 liter round-bottom flask with a thermometer, a condenser, a 100 mL addition funnel and a Teflon coated stirring bar.

(ii) Dissolve crude **QD** or **HQD** (from **MODULE I step xv** or **MODULE J step x**) in methanol (450 mL) and transfer the solution to the round-bottom flask. Start the stirring.

(iii) Heat the solution to 55 °C (internal temperature) and stir the solution for 5 min.

(iv) Slowly add hydrogen chloride solution in 2-propanol (5-6 M) (27.5 mL) *via* syringe while stirring. Upon addition, the solution turns from yellow to red and then to dark orange.

(v) Stir the mixture at 55 °C for 5 min. The solution becomes turbid.

(vi) Allow the reaction mixture to cool to room temperature while stirring. A white precipitate is formed.

(vii) After 2 h load the addition funnel with ethyl acetate (60 mL) and add it slowly on the mixture.

(viii) Cool the mixture with a water-ice bath. Stir the suspension for 1 hour.

(ix) Collect the white solid by filtration using a 125 mL fritted glass filter of porosity 3, wash the solid with a methanol and ethyl acetate mixture (1:1) (2 x 30 mL).

▲**CRITICAL STEP**: If the product is of a marked yellow colour it may contain impurities probably due to a too large amount of ethyl acetate for the precipitation. If that is the case, suspend the solid in 450 mL of methanol at 55 °C, and repeat from **MODULE L step vi** using less ethyl acetate in **MODULE L step vii**.

(x) Dry **QD · 3 HCl** or **HQD · 3 HCl** under vacuum (1.0×10^{-1} mbar for 24 h, 35 °C).

■**PAUSE POINT:** the solid obtained can be stored under air for months with no noticeable decomposition.

M Precipitation of HQN · HCl

(i) Prepare a dry 3-necked 100 mL round-bottom flask with a thermometer, a condenser and a Teflon coated stirring bar.

(ii) Dissolve 3.7 g of dry crude **HQN** from **MODULE J step x** in acetonitrile (19 mL) and transfer it to the round-bottom flask.

(iii) Heat the solution to 55 °C (internal temperature) and stir the solution for 5 min.

(iv) Slowly add hydrogen chloride 4 M solution in 1,4-dioxane (2.8 mL) *via* syringe. With the first drops, some white gummy precipitate forms in the yellow solution which rapidly equilibrates to a white powder after a few seconds stirring.

▲**CRITICAL STEP:** Hydrogen chloride must be added slowly and carefully. If too much hydrogen chloride is added the precipitate turns yellow, loses its powder quality and may contain impurities.

(v) Stir at 55 °C for 5 min and then allow the mixture reaching room temperature.

(vi) Stir for 1 h at room temperature.

(vii) Collect the white solid by filtration using a fritted glass filter, wash it twice with acetonitrile (2 × 5 mL) and let it dry on the fritted glass filter.

▲**CRITICAL STEP:** The product should be white. Yellow colour is indicative of the presence of impurities. If that is the case, wash it exhaustively with acetonitrile on the fritted glass filter. If this is not successful, suspend the solid in hot acetonitrile (5 mL) and repeat the filtration step described in **MODULE M step vii**.

(viii) Dry the white solid **HQN · HCl** under vacuum (1.0×10^{-1} mbar for 24 h, 35 °C).

■ **PAUSE POINT:** the solid obtained can be stored under air for months with no noticeable decomposition.

N Synthesis of 9-amino(9-deoxy)*epi* cinchona alkaloids derivatives QN-OH, HQN-OH, QD-OH and HQD-OH

(i) Prepare a dry 10 mL round-bottom flask with a septum and a Teflon coated stirring bar.

(ii) Weigh out sodium ethanethiolate (740 mg, 8.8 mmol) in the round-bottom flask.

! CAUTION: This material already has an unpleasant odour and should be manipulated inside a well-ventilated fume hood or in a closed flask. Sodium ethanethiolate liberates a toxic gas of unpleasant odour if in contact with non-basic water.

(iii) Prepare a solution of **QN** (500 mg, 1.5 mmol) (or **HQN** or **QD** or **HQD**) obtained in **MODULE D step vi** in DMSO (1 mL) and add it to the thiolate. Use additional DMSO (0.5 mL) to rinse all the starting material inside the reaction vessel.

(iv) Connect a condenser to the round-bottom flask and set a nitrogen inlet on top of it.

(v) Heat the mixture to 80 °C and stir for 72 h. Completeness of the reaction can be checked by the disappearance of **QN-OH, HQN-OH, QD-OH** or **HQD-OH** spots in thin layer chromatography (eluent ethyl acetate/methanol/aq. NH_4OH (5 M) 100/10/5; R_f (**QN**): 0.41; R_f (**QN-OH**): 0.27; R_f (**HQN**): 0.33; R_f (**HQN-OH**): 0.20; R_f (**QD**): 0.29; R_f (**QD-OH**): 0.14; R_f (**HQD**): 0.24; R_f (**HQD-OH**): 0.12).

(vi) Allow the reaction mixture reach room temperature.

(vii) Add water (10 mL). The pH of the resulting aqueous phase is about 14.

! CAUTION: Manipulate the reaction mixture in the fume hood. All waste solutions containing thiolate residues should be treated with bleach before their disposal in the appropriate solvent waste container.

(viii) Wash the aqueous phase with dichloromethane (3 x 5 mL) in a 25 mL separation funnel.

(ix) Transfer the aqueous layer to a 25 mL round-bottom flask with a stirring bar.

(x) Add dropwise a saturated aqueous solution of ammonium chloride to lower the pH to 9 (3 mL) while stirring. A white suspension is formed.

(xi) Extract the aqueous layer with dichloromethane (6 x 5 mL) in the 25 mL separation funnel.

(xii) Dry the organic phase with anhydrous Na_2SO_4, filter the Na_2SO_4 and remove the solvents under vacuum with a rotary evaporator (pressure 500 mbar with a water bath temperature at 35 °C).

(xiii) Prepare a column of 2 cm of inner diameter with 5 g of silica gel 60A (35-70 µm particle size) and condition it with EtOAc.

(xiv) Introduce the compound into the column using DCM.

(xv) Start eluting the column with ethyl acetate (50 mL).

(xvi) Change the eluent to a 100:10 mixture of ethyl acetate and methanol (50 mL).

(xvii) Change the eluent to a 100:10:1 mixture of ethyl acetate, methanol and concentrated aqueous NH_4OH and go on with this eluent until the desired product elutes from the column.

(xviii) After evaporation of the fractions containing the desired product, a pale orange solid is obtained: dry it under vacuum (1.0×10^{-1} mbar for 24 h, 35 °C).

5.4.3. Timing

MODULE A (Synthesis of (**QN**, **QD**, **HQN** and **HQD** hydrochloride salts): (Steps i-xviii) 17 h
MODULE B (Work up of compounds **QN** and **HQN**) (Steps i-vi): 16 h
MODULE C (Work up of compounds **QD** and **HQD**) (Steps i-vi): 4 h 30 min
MODULE D (Neutralization of the salt and formation of **QN**, **QD**, **HQN** and **HQD**) (Steps i-vi): 1 h 30 min
MODULE E (Synthesis of *9-amino(9-deoxy)epi* cinchona *alkaloids derivatives* **QN-OH**, **QD-OH**, **HQN-OH** and **HQD-OH**) (Steps i-xii)**:** 18 h
MODULE F (Purification of **QD-OH**)(Steps i-vii): 3 h 30 min
MODULE G (Purification of **QN-OH**, **QD-OH**, **HQN-OH**, and **HQD-OH** by column chromatography) (Steps i-ix): 2 h 30 min
MODULE H (Inversion of configuration at C9 in compounds **1** and **3** through the preparation of azides **7** and **8**) Steps i-vii: 50 min; Steps viii-xi, 4 h; Steps xii-xiv, 2 h; Step xv, 2 h. Steps xvi-xx, 40 min (it is possible to carry out steps i-xx within one work day); Step xxi, 8-24 h; Steps xxii-xxiv, 1 h; Steps xxv-xxvii, 1 h; Step xviii, 1 h .
MODULE I (Preparation of crude **QN** and **QD**): Steps i-iv, 1 h 30 min, Step v, 4-24 h; Steps vi-xiv, 3 h; Step xv, 1 h.
MODULE J (Preparation of crude **HQN** and **HQD**) Steps i-iii, 20 min, Step iv, 2 h 20 min; Step v, 22 h; Step vi, 20 min; Steps vii-ix, 2 h; Step x, 2 h.
MODULE K (Precipitation of **QN · 3 HCl**) Steps i-vi, 45 min, Step vii, 2 h; Step viii, 1 h 20 min; Step ix, 30 min; Step x, 24 h.
MODULE L (Precipitation of **QD · 3 HCl** and **HQD · 3 HCl**) Steps i-v, 45 min, Steps vi-viii, 3 h; Step ix, 30 min; Step x, 24 h.
MODULE M (Precipitation of **HQN · HCl**) Steps i-v, 40 min; Step vi, 1 h; Step vii, 10 min h; Step viii, 24 h.
MODULE N (Synthesis of 9-amino(9-deoxy)*epi* cinchona alkaloids derivatives **QN-OH**, **QD-OH**, **HQN-OH** and **HQD-OH**) Steps i-iv, 30 min; Step v, 72 h; Steps vi-xii, 2h; Steps xiii-xviii, 2 h.

5.4.4. Analytical Data

^{1}H and ^{13}C NMR spectra.

5: white solid, ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.79 (d, 1H, J= 4.5 Hz), 8.04 (d, 1H, J = 9.2 Hz), 7.44 (bs, 1H), 7.40 (dd, 1H, J_1 = 9.2, J_2 = 2.6 Hz), 7.36 (bs, 1H), 6.17 (bs, 1H), 5.82 (ddd, 1H, J_1 = 17.4, J_2 = 10.0, J_3 = 7.2 Hz), 5.04 – 4.96 (m, 2H), 3.95 (s, 3H), 3.39 (bs, 1H), 3.16 – 3.03 (m, 1H), 3.03 – 2.88 (m, 1H), 2.70 – 2.44 (m, 5H), 2.33 – 2.17 (m, 1H), 2.15 – 2.00 (m, 1H), 1.95 – 1.86 (m, 1H), 1.83 – 1.69 (m, 1H), 1.70 – 1.59 (m, 1H) and 1.59 – 1.43 (m, 1H).

7: yellow oil, ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.79 (d, 1H, J = 4.5 Hz), 8.08 (d, 1H, J = 9.2 Hz), 7.47 (bs, 1H), 7.43 (dd, 1H, J_1 =9.2, J_2 = 2.7 Hz), 7.34 (d, 1H, J = 4.5 Hz), 5.76 (ddd, 1H, J_1 = 17.4, J_2 = 10.4, J_3 = 7.3 Hz), 5.06 – 4.93 (m, 3H), 3.98 (s, 3H), 3.43 – 3.27 (m, 2H), 3.26 – 3.16 (m, 1H), 2.98 – 2.88 (m, 1H), 2.88 – 2.78 (m, 1H), 2.40 – 2.23 (m, 1H), 1.73 – 1.65 (m, 1H), 1.65 – 1.49 (m, 2H), 1.47 – 1.34 (m, 1H) and 0.85 – 0.70 (m, 1H).

6: white solid, ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.79 (d, 1H, J = 4.5 Hz), 8.05 (d, 1H, J = 9.3 Hz), 7.45 (bs, 1H), 7.41 (dd, 1H, J_1 =9.2, J_2 = 2.7 Hz), 7.33 (bs, 1H), 6.21 (bs, 1H), 6.03 (ddd, 1H, J_1 =17.1, J_2 = 10.5, J_3 = 7.3 Hz), 5.13 (dt, 1H, J_d =10.5, J_t = 1.4 Hz), 5.11 (dt, 1H, J_d =17.0, J_t = 1.5 Hz), 3.96 (s, 3H), 3.32 (bs, 1H), 2.89 (d, 2H, J = 8.9 Hz), 2.82 – 2.55 (m, 4H), 2.35 – 2.20 (m, 1H), 2.17 – 2.01 (m, 1H), 2.01 – 1.90 (m, 1H), 1.89 – 1.82 (m, 1H), 1.68 (m, 1H) and 1.61 – 1.50 (m, 2H).

8: yellow oil, ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.77 (d, 1H, J = 4.5 Hz), 8.05 (d, 1H, J = 9.2 Hz), 7.43 (bs, 1H), 7.41 (dd, 1H, J_1 = 9.1, J_2 = 2.7 Hz), 7.35 (d, 1H, J = 4.5 Hz), 5.86 (ddd, 1H, J_1 =17.0, J_2 = 11.0, J_3 = 6.4 Hz), 5.12 – 5.02 (m, 3H), 3.96 (s, 3H), 3.38 – 3.19 (m, 1H), 3.19 – 3.09 (m, 1H), 3.09 – 2.82 (m, 3H), 2.37 – 2.22 (m, 1H), 1.71 – 1.61 (m, 1H), 1.61 – 1.42 (m, 2H), 1.18 – 1.05 (m, 1H) and 1.01 – 0.84 (m, 1H).

QN · 3 HCl: pale yellow solid; ^{1}H NMR (500 MHz, D$_2$O) δ 9.04 (d, 1H, J = 5.8 Hz), 8.30 (d, 1H, J = 9.3 Hz), 8.16 (d, 1H, J = 5.7 Hz), 7.94 (dd, 1H, J_1 = 9.3, J_2 = 2.5 Hz), 7.84 (d, 1H, J = 2.5 Hz), 5.91 (ddd, 1H, J_1 =17.2, J_2 = 10.6, J_3 = 6.4 Hz), 5.55 (d, 1H, J = 10.8 Hz), 5.27 (ddd, 1H, J_1 =17.3, J_2 = 1.5, J_3 = 1.0 Hz), 5.25 (ddd, 1H, J_1 =10.6, J_2 = 1.5, J_3 = 1.0 Hz, 1H), 4.37 – 4.24 (m, 1H), 4.13 (s, 3H), 4.04 – 3.94 (m, 1H), 3.85 (dd, 1H, J_1 = 13.3, J_2 = 10.5 Hz), 3.64 – 3.43 (m, 2H), 3.03 – 2.88 (m, 1H), 2.21 – 2.00 (m, 3H), 1.99 – 1.84 (m, 1H) and 1.24 – 1.12 (m, 1H). ^{13}C {^{1}H} NMR (125 MHz, D$_2$O) δ 161.4, 146.8, 141.0, 137.1, 134.5, 129.6, 128.4, 123.7, 121.1 (broad), 116.9, 102.7, 59.3, 56.7, 53.9, 48.8 (broad), 42.5, 35.6, 25.3, 23.5 and 23.2.

QD · 3 HCl: white solid; ^{1}H NMR (500 MHz, D$_2$O) δ 9.07 (d, 1H, J = 5.8 Hz), 8.29 (d, 1H, J = 9.4 Hz), 8.22 (d, 1H, J = 5.7 Hz), 7.93 (dd, 1H, J_1 =9.4, J_2 = 2.5 Hz), 7.78 (d, 1H, J = 2.5 Hz), 5.89 (ddd, 1H, J_1 =17.4, J_2 = 10.8, J_3 = 5.4 Hz), 5.67 (d, 1H, J = 10.6 Hz), 5.32 (ddd, 1H, J_1 =10.5 Hz, J_2 = 1.5 Hz, J_3 = 0.5 Hz), 5.31 (ddd, 1H, J_1 =17.5 Hz, J_2 = 1.5 Hz, J_3 = 0.5 Hz,), 4.35 (q, 1H, J = 9.6 Hz), 4.13 (s, 3H), 3.83 – 3.74 (m, 1H), 3.75 – 3.65 (m, 2H), 3.65 – 3.55 (m, 1H), 2.97 – 2.88 (m, 1H), 2.14 – 2.05 (m, 2H), 2.05 – 1.95 (m, 1H), 1.59 – 1.49 (m, 1H) and 1.41 – 1.33 (m, 1H). ^{13}C {^{1}H} NMR (125 MHz, D$_2$O) δ 161.4, 146.6, 141.0, 136.3, 134.5, 129.6, 128.7, 123.7, 121.1, 116.9, 102.0, 59.8, 56.8, 49.6, 48.1 (broad), 46.9, 35.1, 25.1, 23.0 and 21.8.

HQN · HCl: white solid; ^{1}H NMR (500 MHz, D$_2$O) δ 8.71 (d, 1H, J = 4.7 Hz), 7.98 (d, 1H, J = 9.5 Hz), 7.68 – 7.22 (m, 3H), 4.01 (s, 3H), 3.94 – 3.77 (m, 2H), 3.72 (dd, 1H, J_1 = 12.9, J_2 = 10.5 Hz), 3.52 – 3.24 (m, 1H), 3.03 (ddd, 1H, J_1 =12.8, J_2 = 5.9, J_3 = 2.6 Hz), 2.07 – 1.90 (m, 3H), 1.91 – 1.83 (m, 1H), 1.82 – 1.68 (m, 1H), 1.52 – 1.29 (m, 2H), 1.11 – 0.91 (m, 1H) and 0.85 (t, 3H, J = 7.4 Hz). ^{13}C {^{1}H} NMR (125 MHz, D$_2$O) δ 157.7, 147.4, 146.2 (broad), 142.9, 130.0, 127.2, 121.8, 118.5 (broad), 101.2, 61.5, 55.7, 55.3, 49.5 (broad), 40.9, 34.2, 25.8, 24.0, 23.7, 23.3 and 10.7.

HQD · 3 HCl: white solid; ^{1}H NMR (500 MHz, D$_2$O) δ 9.09 (d, 1H, J = 5.7 Hz), 8.31 (d, 1H, J = 9.4 Hz), 8.24 (d, 1H, J = 5.8 Hz), 7.94 (dd, 1H, J = 9.3, 2.5 Hz), 7.84 (d, 1H, J = 2.5 Hz), 5.74 (d, 1H, J = 10.2 Hz), 4.41 – 4.29 (m, 1H), 4.13 (s, 3H), 3.76 (dd, 1H, J_1 = 13.5, J_2 = 10.3 Hz), 3.71 – 3.63 (m, 1H), 3.63 – 3.51 (m, 1H), 3.39 (ddd, 1H, J_1 = 13.5, J_2 = 8.6, J_3 = 2.5 Hz), 2.18 – 2.03 (m, 1H), 2.03 – 1.91 (m, 3H), 1.60 – 1.46 (m, 2H), 1.46 – 1.30 (m, 2H) and 0.91 (t, 3H, J = 7.4 Hz). ^{13}C {^{1}H} NMR (100 MHz, D$_2$O) δ 161.5, 146.6, 141.0, 134.6, 129.6, 128.7, 123.8, 121.1 (broad), 102.0, 59.8, 56.8, 49.5, 49.2, 48.1 (broad), 34.1, 24.5, 23.7, 22.7, 22.4 and 10.5.

QN: yellowish oil, $[\alpha]_D$ = + 100.5 (c 1.00 in $CHCl_3$ at 24 °C), ^1H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, 1H, J = 4.5 Hz), 8.01 (d, 1H, J = 9.4 Hz), 7.64 (bs, 1H), 7.46-7.41 (m, 1H), 7.36 (dd, 1H, J_1 = 9.3, J_2 = 2.8 Hz), 5.78 (ddd, 1H, J_1 = 17.3, J_2 = 10.1, J_3 = 7.5 Hz), 5.01-4.90 (m, 2H), 4.67-4.51 (m, 2H), 3.94 (s, 3H), 3.26 (dd, 1H, J_1 = 13.7, J_2 = 10.0 Hz), 3.23-3.15 (m, 1H), 3.12-2.98 (m, 1H), 2.84-2.74 (m, 2H), 2.31-2.23 (m, 1H), 2.12-1.93 (m, 2H) 1.64-1.59 (m, 1H), 1.58-1.48 (m, 2H), 1.45-1.36 (m, 1H) and 0.79-0.71 (m, 1H). $^{13}C\ \{^1H\}$ NMR (125 MHz, $CDCl_3$, 213 K): δ 157.3, 148.0, 146.8, 143.9, 141.6, 131.6, 128.5, 121.5, 119.4, 114.5, 100.2, 61.9, 55.5, 55.5, 50.3, 40.7, 39.6, 27.6, 27.0 and 25.6.

QN-OH: pale orange solid, $[\alpha]_D$ = + 96.9 (c 1.00 in $CHCl_3$ at 25 °C), ^1H NMR (500 MHz, CD_3OD) δ 8.61 (d, 1H, J = 4.6 Hz), 7.91 (d, 1H, J = 9.1 Hz), 7.57 (bs, 1H), 7.54 (d, 1H, J = 4.6 Hz), 7.38 (dd, 1H, J_1 = 9.1, J_2 = 2.5 Hz), 5.87 (ddd, 1H, J_1 = 17.5, J_2 = 10.4, J_3 = 7.5 Hz), 5.05 (d, 1H, J = 17.1 Hz), 5.00 (d, 1H, J = 10.4 Hz), 4.71 – 4.58 (m, 1H), 3.36 – 3.26 (m, 2H), 3.26 – 3.15 (m, 1H), 2.94 – 2.80 (m, 2H), 2.44 – 2.30 (m, 1H), 1.73 – 1.52 (m, 3H), 1.52 – 1.36 (m, 1H) and 0.77 (dd, 1H, J_1 = 13.6, J_2 = 7.4 Hz). $^{13}C\ \{^1H\}$ NMR (125 MHz, CD_3OD) δ 158.4, 148.2, 147.5, 144.2, 142.6, 131.5, 130.6, 123.7, 120.4 (broad), 115.1, 105.5 (broad), 63.2 (broad), 56.8, 41.7, 40.7, 28.8, 28.4 and 26.7.

QD: yellowish oil, $[\alpha]_D$ = + 74.3 (c 1.00 in $CHCl_3$ at 25 °C), ^1H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, 1H, J = 4.5 Hz), 8.02 (d, 1H, J = 9.2 Hz), 7.73-7.49 (m, 2H), 7.37 (dd, 1H, J_1 = 9.4, J_2 = 2.8 Hz), 5.88 (ddd, 1H, J_1 = 17.1, J_2 = 10.6, J_3 = 6.6 Hz), 5.08 (dt, 1H, J_d = 8.8, J_t = 1.6 Hz), 5.06-5.03 (m, 1H), 4.75-4.60 (m, 1H), 3.96 (s, 3H), 3.11-2.88 (m, 5H), 2.34-2.22 (m, 1H), 2.15-1.94 (m, 2H), 1.64-1.59 (m, 1H), 1.58-1.49 (m, 2H), 1.17-1.09 (m, 1H) and 1.00-0.90 (m, 1H). $^{13}C\ \{^1H\}$ NMR (125 MHz, $CDCl_3$, 213 K): δ 157.2, 147.9, 147.5, 143.8, 140.5, 131.4, 128.4, 122.1, 119.6, 114.4, 99.5, 62.6, 55.4, 49.1, 48.9, 46.6, 38.7, 26.8, 25.9 and 24.2.

QD-OH: pale orange solid, $[\alpha]_D$ = + 62.0 (c 1.00 in $CHCl_3$ at 25 °C), ^1H NMR (500 MHz, CD_3OD) δ 8.61 (d, 1H, J = 4.6 Hz), 7.91 (d, 1H, J = 9.1 Hz), 7.60 – 7.52 (m, 2H), 7.38 (dd, 1H, J_1 = 9.1, J_2 = 2.6 Hz), 5.89 (ddd, 1H, J_1 = 17.3, J_2 = 10.4, J_3 = 6.9 Hz), 5.10 (dt, 1H, J_d = 13.9, J_t = 1.6 Hz), 5.08 – 5.06 (m, 1H), 4.68 (d, 1H, J = 10.2 Hz), 3.25 – 2.91 (m, 5H), 2.34 (q, 1H, J = 8.5 Hz), 1.68 – 1.47 (m, 3H) and 1.13 – 0.95 (m, 2H). $^{13}C\ \{^1H\}$ NMR (125 MHz, CD_3OD) δ 158.3, 148.3, 147.6, 144.2, 141.2, 131.5, 130.6, 123.7, 120.6 (broad), 115.6, 105.6 (broad), 63.4 (broad), 50.3, 48.1, 40.6, 29.0, 27.1 and 25.9.

HQN: yellowish oil, $[\alpha]_D$ = + 83.1 (c 1.00 in $CHCl_3$ at 25 °C), ^1H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, 1H, J = 4.6 Hz), 8.00 (d, 1H, J = 9.2 Hz), 7.62 (bs, 1H), 7.50 – 7.38 (m, 1H), 7.35 (dd, 1H, J_1 = 9.1, J_2 = 2.6 Hz), 4.63 – 4.46 (m, 1H), 3.93 (d, 3H, J = 1.2 Hz), 3.21 (dd, 1H, J_1 = 13.7, J_2 = 9.9 Hz), 3.18 – 3.10 (m, 1H), 3.08 – 2.95 (m, 1H), 2.74 (ddd, 1H, J_1 = 14.7, J_2 = 10.4, J_3 = 4.7 Hz), 2.52 – 2.43 (m, 1H), 2.11 (bs, 3H), 1.62 – 1.15 (m, 7H), 0.78 (t, 3H, J = 7.3 Hz) and 0.75 – 0.66 (m, 1H).$^{13}C\ \{^1H\}$ NMR (125 MHz, $CDCl_3$, 213 K) δ 157.1, 147.8, 146.8, 143.7, 131.3, 128.4, 121.3, 119.2, 100.0, 61.6, 57.0, 55.3, 50.1, 40.7, 36.3, 28.0, 27.2, 25.1, 24.3 and 12.0.

HQN-OH: pale orange solid, $[\alpha]_D$ = + 58.6 (c 0.81 in $CHCl_3$ at 25 °C), ^1H NMR (400 MHz, CD_3OD) δ 8.61 (d, 1H, J = 4.7 Hz), 7.91 (d, 1H, J = 9.1 Hz), 7.61 – 7.50 (m, 2H), 7.37 (dd, 1H, J_1 = 9.1, J_2 = 2.6 Hz), 4.70 – 4.57 (m, 1H), 3.41 – 3.32 (m, 1H), 3.28 – 3.17 (m, 1H), 2.93 – 2.80 (m, 1H), 2.63 (ddd, 1H, J_1 = 13.5, J_2 = 4.8, J_3 = 2.4 Hz), 1.79 – 1.51 (m, 4H), 1.51 – 1.31 (m, 4H), 0.87 (t, 3H, J = 7.4 Hz) and 0.78 (dd, 1H, J_1 = 13.5, J_2 = 7.2 Hz).$^{13}C\ \{^1H\}$ NMR (125 MHz, CD_3OD) δ 158.7, 148.1 (broad), 147.5, 144.2, 131.5, 130.4, 123.8, 123.7 (broad), 105.5 (broad), 63.1 (broad), 58.0, 41.8, 38.0, 28.3, 28.2, 26.3, 26.1 and 12.2.

HQD: yellowish oil, $[\alpha]_D$ = + 33.5 (c 1.00 in $CHCl_3$ at 25 °C), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, 1H, *J* = 4.5 Hz), 8.02 (d, 1H, *J* = 9.2 Hz), 7.63 (bs, 1H), 7.55 – 7.45 (m, 1H), 7.37 (dd, 1H, J_1 = 9.3, J_2 = 2.7 Hz), 4.77 – 4.53 (m, 1H), 3.95 (s, 3H), 3.08 – 2.84 (m, 4H), 2.62 (ddd, 1H, J_1 = 14.1, J_2 = 7.3, J_3 = 2.3 Hz), 2.07 (bs, 2H), 1.64 – 1.26 (m, 7H), 1.12 – 1.00 (m, 1H), 0.98 – 0.91 (m, 1H), and 0.86 (t, 3H, *J* = 7.2 Hz). ^{13}C {^{1}H} (125 MHz, $CDCl_3$) δ 157.0, 147.8, 147.4, 143.7, 131.4, 128.4, 121.8, 119.5, 99.5, 62.6, 55.2, 49.0, 48.9, 48.9, 36.5, 26.7, 25.6, 25.0, 23.9 and 11.9.

HQD-OH: pale orange solid, $[\alpha]_D$ = + 27.5 (c 1.03 in $CHCl_3$ at 25 °C), ^{1}H NMR (400 MHz, CD_3OD) δ 8.60 (d, 1H, *J* = 4.7 Hz), 7.90 (d, 1H, *J* = 9.1 Hz), 7.55 (d, 1H, *J* = 4.7 Hz), 7.52 (bs, 1H), 7.37 (dd, 1H, J_1 = 9.1, J_2 = 2.6 Hz), 4.67 (d, 1H, *J* = 10.2 Hz), 3.22 – 2.94 (m, 4H), 2.77 (dd, 1H, J_1 = 12.8, J_2 = 7.1 Hz), 1.71 – 1.49 (m, 4H), 1.49 – 1.27 (m, 2H), 1.08 – 0.98 (m, 2H) and 0.90 (t, 3H, *J* = 7.4 Hz). ^{13}C {^{1}H} NMR (125 MHz, CD_3OD) δ 159.2, 148.2, 147.2, 144.1, 131.4, 130.7, 124.2, 120.4 (broad), 105.4 (broad), 63.6 (broad), 50.3, 49.9, 38.3, 27.7, 27.1, 26.6, 25.7 and 12.3.