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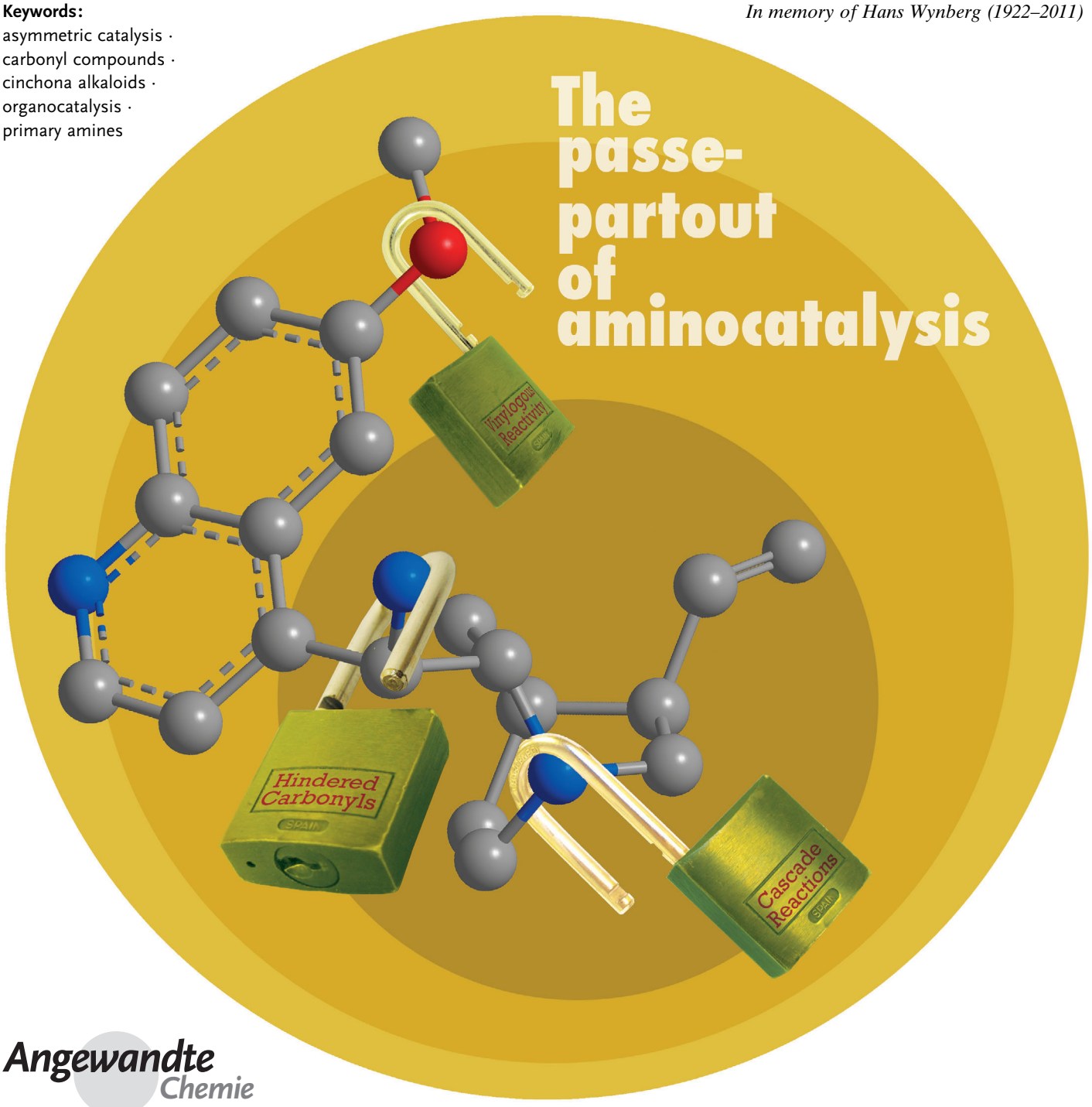
Asymmetric Organocatalysis

Cinchona-based Primary Amine Catalysis in the Asymmetric Functionalization of Carbonyl Compounds

*Paolo Melchiorre**

Keywords:
asymmetric catalysis · carbonyl compounds · cinchona alkaloids · organocatalysis · primary amines

In memory of Hans Wynberg (1922–2011)



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Asymmetric aminocatalysis exploits the potential of chiral primary and secondary amines to catalyze asymmetric reactions. It has greatly simplified the functionalization of carbonyl compounds while ensuring high enantioselectivity. Recent advances in cinchona-based primary amine catalysis have provided new synthetic opportunities and conceptual perspectives for successfully attacking major challenges in carbonyl compound chemistry, which traditional approaches have not been able to address. This Review outlines the historical context for the development of this catalyst class while charting the landmark discoveries and applications that have further expanded the synthetic potential of aminocatalysis.

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1. Introduction

The functionalization of carbonyl compounds is among the most important classical synthetic reactions. Indeed, carbonyl compound chemistry has been called "the backbone of organic synthesis".[1] Enantioselective versions of this chemistry have historically offered a potent synthetic way of producing valuable chiral molecules. Recently, the classical organometallic-based approach has been enriched by the possibility of using chiral primary and secondary amines as efficient catalysts, a strategy known as "asymmetric aminocatalysis".[2] Exploiting fundamental and well-established mechanistic patterns, and mainly using the chemistry of simple enamine and iminum ion intermediates,[3] aminocatalysis has greatly expanded the chemist's ability to asymmetrically functionalize carbonyl compounds. This success is mainly because of the possibility of directly generating the catalytically active intermediates in situ from unmodified reagents through their reversible condensation with the aminocatalysts. Most widely used are certain chiral cyclic secondary amines, in particular proline[4] and its derivatives, including diarylprolinol ethers[5] and phenylalanine-derived imidazolidinones.[6] They have been called the "privileged organocatalysts", or the workhorses[3a] of enantioselective organocatalysis.[7] Insightful perspectives have recently addressed the historical origins of aminocatalysis mediated by secondary amines,[8] which nowadays provides a reliable synthetic platform for the asymmetric functionalization of aldehydes at their α, β, γ, or even ε positions.[2]

In the last five years, researchers have recognized that chiral primary amines offer new opportunities for expanding the applicability and synthetic potential of aminocatalysis.[9] In particular, 9-amino(9-deoxy)-*epi*-cinchona alkaloids, primary amines easily derived from natural sources,[10] have enabled the stereoselective functionalization of a variety of sterically hindered carbonyl compounds, which cannot be functionalized using secondary amines and which are often unsuccessful substrates for metal-based approaches too. It is remarkable how this single catalyst class can activate carbonyl compounds characterized by completely different structural features and steric bias (e.g. simple ketones as well as α-branched substituted aldehydes and ketones, and their α,β-unsaturated counterparts), while exploiting the different aminocatalytic activation modes (iminium ion, enamine, dienamine, and trienamine activations,[11] Figure 1). The consistently high level of stereocontrol inferred by these nature-derived aminocatalysts testifies to their impressive versatility and reliability.

Instead of providing an exhaustive list of reactions that have been made possible by cinchona-based primary amine catalysis (readers can refer to recently written Reviews),[9b–d] we seek to provide the historical context for the development of this nature-derived catalyst class while discussing the new synthetic perspectives opened up by recent studies. Of particular interest is the ability of cinchona-based primary amine catalysts to impart unique mechanistic pathways, thus complementing and enriching the established reactivity profile of secondary amine catalysis. Chemists can thus attack difficult problems connected with the preparation of chiral molecules, which traditional approaches have not been able to address.

2. Historical Background and Mechanistic Considerations

> "*If I have seen further it is by standing on the shoulders of giants*"
> Isaac Newton (1676)[12]

We have long known that nature routinely exploits primary amines in its catalytic machinery. Since the 1960s, it has been recognized that natural enzymes, such as acetoace-

[*] Prof. Dr. P. Melchiorre
ICREA—Institució Catalana de Recerca i Estudis Avançats
Passeig Lluís Companys 23, 08010 Barcelona (Spain)
Prof. Dr. P. Melchiorre
ICIQ—Institute of Chemical Research of Catalonia
Avenida Països Catalans 16, 43007 Tarragona (Spain)
E-mail: pmelchiorre@iciq.es
Homepage: http://www.iciq.es/portal/862/default.aspx

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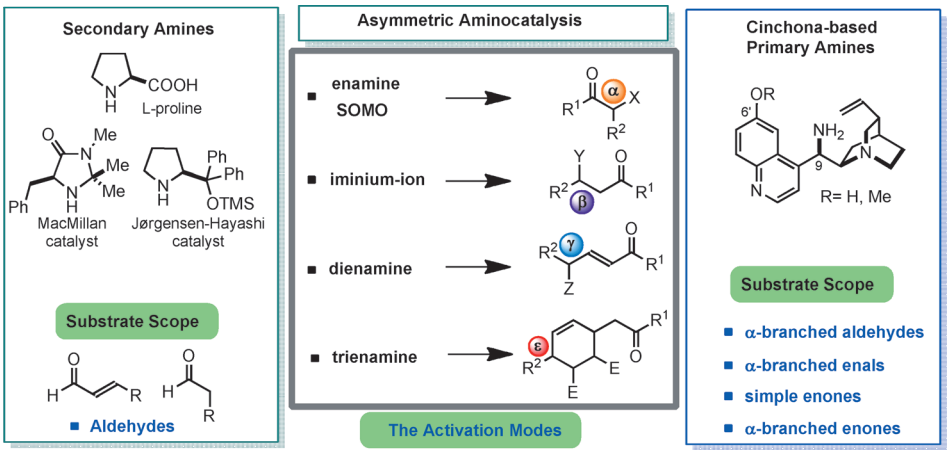
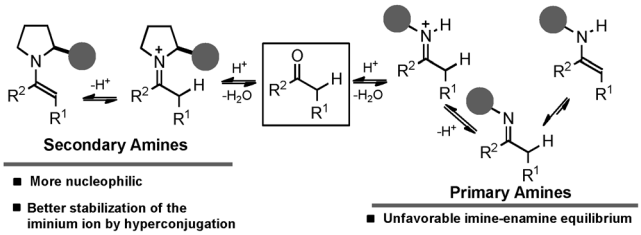


Figure 1. The state-of-the-art of asymmetric aminocatalysis: five distinct activation modes enable the direct, highly stereoselective functionalization of unmodified carbonyl compounds. Enamine and SOMO (singly occupied molecular orbital) activations both account for the direct α functionalization of saturated carbonyl compounds. Iminium ion catalysis represents a reliable way of enantioselectively introducing a nucleophile at the β position of α,β-unsaturated enals and enones. Dienamine catalysis accounts for the γ-functionalization of α,β-unsaturated carbonyl compounds with electrophilic reagents. Trienamine catalysis exploits the transient formation of a trienamine intermediate that can react as a diene in stereoselective Diels–Alder processes to forge two stereocenters at the β and ε position. While secondary amine-based catalysts provide an exceptionally effective way of functionalizing aldehydes, the cinchona-based primary amines offer the unique possibility of effecting processes between sterically demanding partners, thus greatly expanding the substrate scope of aminocatalysis. For in-depth discussions of the mechanisms connected with the aminocatalytic activation modes, see Ref. [2].

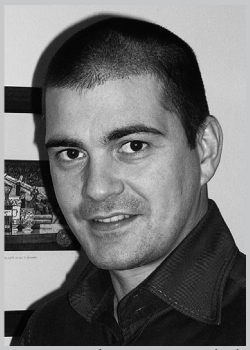
tate decarboxylases and Type I aldolases use the γ-amino group of lysine residues to form a covalently bound reactive catalytic species (the iminium ion and its enamine tautomer) upon condensation with a keto substrate.[13] In the 1930s, Kai J. Pedersen[14] and Frank H. Westheimer[15] published pioneering studies on the decarboxylation of acetoacetate and the dealdolization of diacetone alcohol, respectively. In these works, they observed that primary amines can be even more effective than closely related secondary amines in non-enzymatic reactions in which iminium ion and enamine intermediates are implicated. In the early 1970s, initial studies on intramolecular aldol cyclizations[16] established that natural amino acids other than proline (such as L-phenylalanine) can catalyze synthetically relevant asymmetric transformations through an enamine-based mechanism.[16c,d]

It may thus seem surprising that chiral primary amines have only attracted interest in the late stages of the impressive investigations into asymmetric aminocatalysis, which began in 2000 with all the intensity and competitiveness of a gold rush.[2a,b] Looking back, we must consider the excitement generated by the advent of proline in the field of asymmetric catalysis and the consequent great emphasis placed on cyclic secondary amines as organocatalysts.[17] The organic chemistry community was fascinated by the ability of a simple natural amino acid to impart almost perfect stereocontrol in a variety of fundamental reactions, while using a peculiar bifunctional activation mode that strictly imitated the concept of enzymatic catalysis.[4c]

From a chemical reactivity standpoint, various factors may explain the initial low levels of interest in primary amine catalysis. The fundamental studies by Gilbert Stork on the synthetic utility of enamines as nucleophiles of many organic transformations[18] established the superior efficiency of cyclic secondary amines in forming stable enamine intermediates. Stork's legacy taught chemists that five-membered ring amines (e.g. pyrrolidine) form iminium ion and enamine intermediates with non-hindered carbonyl compounds more readily than most other amines, a consequence of the increased nucleophilicity imparted by the cyclic strain.[19] In contrast, primary amines offer the challenges of reduced nucleophilicity, less effective stabilization of the iminium ion intermediates by hyperconjugation,[19,20a] and an unfavorable imine–enamine equilibrium.[20] Generally, primary and secondary enamines rearrange spontaneously to the more stable imine (Scheme 1).[20b–d]



Scheme 1. Secondary versus primary amines in condensation with non-hindered carbonyl compounds: cyclic secondary amines win.



Paolo Melchiorre was born in 1973 in Camerino (Italy). He earned his M.Sc. degree (1999) and then his PhD in Chemistry (2003) from Bologna University under the supervision of A. Umani-Ronchi and P. G. Cozzi. After a research period with K. A. Jørgensen at Center for Catalysis, Aarhus University (Denmark), he joined the research group of G. Bartoli at Bologna University, where he became Assistant Professor in 2007. In 2009 He moved to Tarragona (Spain) as an ICREA Research Professor and an ICIQ Senior Group Leader. His research interests include the discovery and mechanistic elucidation of asymmetric organocatalytic processes.

However, a close inspection of the literature precedents may provide some rationalizations for the recently recognized potential of chiral primary amines (in particular when placed on the privileged molecular architecture of cinchona alkaloids) to encompass the classical activation modes of proline-derived catalysts, while offering the unique possibility of extending the scope of aminocatalysis to include sterically demanding carbonyl compounds.

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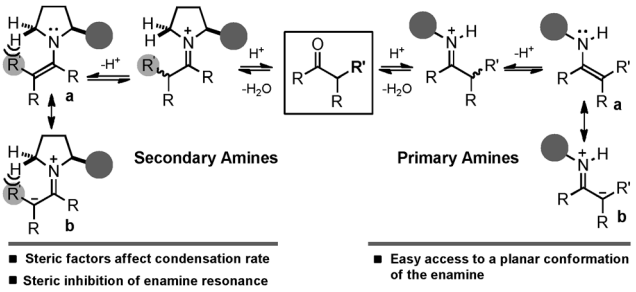
2.1. Chiral Primary Amines at Work

One fascinating aspect of chemical research, and scientific progress in general, is that the knowledge and investigations of our scientific progenitors serve as foundations for future developments.[12] Thus, the preceding systematic studies of the fundamental processes involved in the formation of enamine and iminium ion intermediates (the key species of aminocatalysis) have provided the conceptual framework for rationalizing the superior ability of primary amine catalysis (with respect to secondary amines) to effectively functionalize sterically biased carbonyls.

A reconsideration of the extensive studies by Jack Hine provides useful elements for an in depth comparison of the reactivity of primary and secondary amines when condensing with hindered aldehydes and ketones (Scheme 2).[21] The



Scheme 2. Secondary versus primary amines in condensation with sterically hindered carbonyl compounds: primary amines win. The π conjugation of the enamine system can be represented as resonance between the two structures **a** and **b**.

equilibrium constants for iminium ion formation (deduced by rate constants for the catalysis of the deuterium exchange of deuterated carbonyls) indicated how steric factors greatly affect the reactivity of secondary amines, while primary amines are less influenced by the structural features of the carbonyl compounds. Indeed, in spite of the particular rapidity of iminium ion formation from acetone,[22d] pyrrolidine is less effective than primary amines in condensation with an α-branched aldehyde, such as isobutyraldehyde.[22] In addition, it was demonstrated that secondary enamines hydrolyzed (thus, reacted) much faster than the corresponding tertiary enamines.[23] Again, this can be attributed to steric factors,[24] since bulky substituents on the double bond and the nitrogen atom make it difficult for the resulting enamine system to achieve a near to planar conformation: this geometry is required to maximize overlap between the π-orbital of the carbon–carbon double bond and the lone pair orbital on the nitrogen atom.[23b,c] The steric inhibition of the resonance among structures **a** and **b** (Scheme 2) is more pronounced for tertiary than for secondary enamines, since the secondary enamines always bear a small hydrogen substituent[22f] on the nitrogen atom that secures π conjugation, that is, the zwitterionic structure **b** substantially contributes to the resonance of the secondary enamine system.

2.2. Why the Cinchona Scaffold?

Cinchona alkaloids, simple organic molecules generously provided by nature, have historically played a privileged role in asymmetric catalytic synthesis.[25] The first organocatalytic enantioselective reaction was carried out exactly one century ago by Georg Bredig and Paul S. Fiske using quinine and quinidine as the chiral inducers.[26] About 50 years later, Horst Pracejus demonstrated the possibility of reaching high levels of enantioselectivity in the asymmetric catalytic preparation of chiral molecules, again using a cinchona derivative as the catalyst.[27] The pioneering studies by Hans Wynberg in the 1970s began a new era for asymmetric catalysis using cinchona derivatives. He demonstrated how the basic bridgehead nitrogen atom in the quinuclidine core can be used in general Brønsted base catalysis.[28] This privileged molecular scaffold has also had an impact on the field of asymmetric aminocatalysis. This influence is because the introduction of a primary amine moiety recently led to the identification of 9-*epi*-amino cinchona derivatives as effective covalent-based activators of hindered carbonyl compounds (Figure 2).

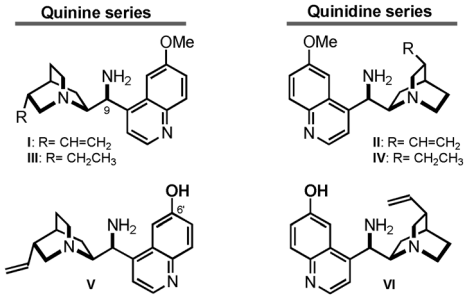


Figure 2. The 9-amino-9-deoxy-*epi*-cinchona alkaloids derived from (hydro)quinine and (hydro)quinidine constitute a pseudo-enantiomeric pair (formally they are diastereoisomers), allowing access to both antipodes of the chiral product of a reaction. The hydroxy group at the 6′ position in catalysts **V**–**VI**, as a result of the improved hydrogen-bonding ability, is often used to modulate the stereoselectivity as well as the catalytic activity.

What makes the cinchona scaffold such a well-suited highly selective and general chiral catalyst? Its easy availability has been a factor since the dawn of asymmetric catalytic synthesis. But there are other factors too.

2.2.1. The Flexibility of the Cinchona Scaffold

Cinchona alkaloid derivatives are characterized by a high degree of conformational flexibility in solution,[29] thus they exist in solution as a mixture of conformers. Three-dimensional structural modifications can be induced by different chemical stimuli, such as a solvent change[29a] or protonation of the *N*-quinuclidine moiety.[30] Since the catalytic function of the cinchona scaffold is intimately related to its spatial architecture, a conformational change may induce a different catalytic behavior.[31] Preliminary investigations on conformational behavior of the amine **VI** have used vibrational circular dichroism (VCD) and nuclear magnetic resonance (NMR) spectroscopic analyses. They have shown that the nature of

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the medium greatly alters the ground-state conformations.[32] The degree of flexibility of the cinchona catalysts can also account for their wide tolerance toward substrates having a different steric bias, since slight structural modifications can modulate the three-dimensional catalytic assembly to accommodate a variety of reactants.

2.2.2. The Multifunctional Nature of the Cinchona Scaffold

Their multifunctional character is a key factor in the successful and wide use of cinchona alkaloids in asymmetric catalysis.[25] A discussion on the versatility of cinchona derivatives as effective catalysts of many different asymmetric transformations is beyond the scope of this Review. However, it is important to note that, in 1981, Wynberg first demonstrated the possibility for natural cinchona alkaloids to act as efficient bifunctional catalyst:[28a] using both the quinuclidine moiety, in general base catalysis, and the hydroxy group on C9, in hydrogen-bonding interactions, they can simultaneously activate the electrophilic and nucleophilic reagents of a reaction. This multifunctional behavior also strongly influences and assists the catalysis function of 9-*epi* amino cinchona derivatives when they operate through covalent-based modes of activation.

In the cinchona-based diamines, 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 atom in the quinuclidine core can greatly contribute to the catalysis[33] while altering the electronic nature of the primary amine (Figure 3).

Generally an acid co-catalyst is needed to power the catalytic functions of amines **I**–**VI**. This is because condensation with carbonyls is greatly accelerated under acidic conditions:[34] otherwise, the carbonyl compounds remain almost inactive toward the aminocatalytic transformations.

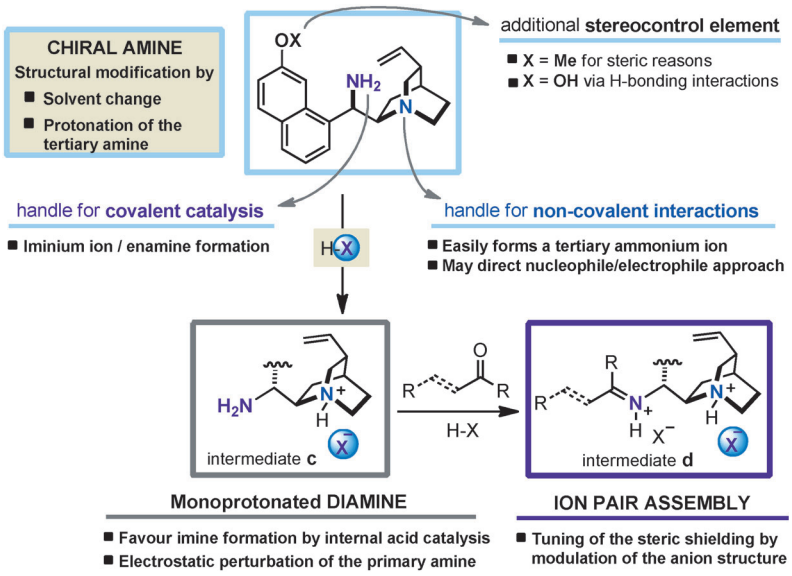

Figure 3. The multifunctional nature of cinchona-based primary aminocatalysts; X: anion, H–X: acid cocatalyst.

For the enamine activation of enolizable carbonyls, an equimolar amount of the acid with respect to the amino-catalyst is often used. A twofold 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 **c** in Figure 3), which represents the active catalyst governing the formation of the covalent intermediate.[35] The charged catalytic species **c** may strongly influence the rate of imine formation through internal acid catalysis, since the tertiary ammonium ion may favor the dehydration of the intermediate carbinolamines by proton transfer. This possibility finds support upon previous investigations by Hine and co-workers, 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.[36] To the same extent, the positively charged protonated tertiary amine in **c** can greatly alter the electronic nature of the vicinal primary amine. Such electrostatic perturbation may decrease the basicity (or the proton affinity) of the primary amino moiety, lowering its propensity to be protonated, thus facilitating its nucleophilic attack on the carbonyl compound under acidic conditions. This electrostatic mechanism closely resembles the micro-environment effect that is operative in many enzymes (operating via enamine intermediates) to lower the pK_a of the catalytically active lysine residue, as originally proposed by Westheimer more than 45 years ago.[37]

A distinct feature of the iminium ion assembly formed by condensation of the cinchona-based primary amine with a carbonyl compound is that its ability to stereocontrol a reaction can be fine-tuned by structurally modifying the anion (X within the intermediate **d** in Figure 3).[38] Indeed, the nature and the three-dimensional arrangement of the counteranion surrounding the tertiary ammonium salt has a direct influence on the catalysis, and may exert a more decisive (and deep) influence than expected. Some of the more significant consequences of the counteranion effect are discussed in this Review.

2.3. The First Applications of Cinchona-based Primary Amines in Aminocatalysis

In early 2007, three different research groups, independently and almost at the same time, introduced 9-amino-9-deoxy-*epi*-cinchona alkaloids as effective catalysts of the stereoselective functionalization of hindered carbonyl compounds. While Chen and co-workers,[39] and my research group[40] applied this catalyst class to the iminium ion activation of simple α,β-unsaturated ketones, Connon and co-workers[41] demonstrated the potential of cinchona-based primary amines for the enamine activation of ketones and α-branched substituted aldehydes. The concomitant publication of these studies provided another example of the scientific competition which has characterized the development of asymmetric aminocatalysis. From a synthetic point of view, these results suggested the attrac-

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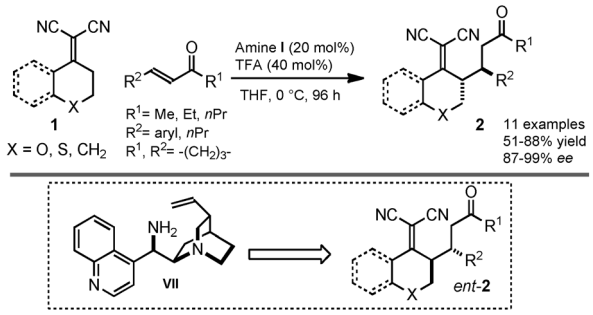
tive prospect that the synthetic potential of aminocatalysis could be expanded beyond the limits of secondary amine catalysis (which was restricted to the functionalization of unhindered aldehydes and enals). Indeed, catalysis with cinchona-derived primary amines was shown to encompass the classical activation modes of proline-derived catalysts (enamine and iminium ion activation), while offering the possibility of effecting processes between sterically demanding partners that could not be functionalized using established methods.

2.3.1. Enantioselective Michael Additions of Simple Enones under Iminium Ion Activation

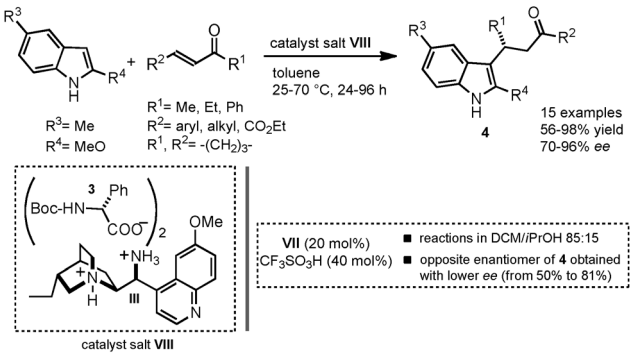
The reporting of cinchona-derived primary amines as iminium ion-based catalysts dates back to the beginning of 2007, when Chen's group developed the asymmetric Michael addition of α,α-dicyanoalkenes **1** to simple enones (Scheme 3).[39a] The combination of 20 mol% of 9-amino-9-deoxy-



Scheme 3. Iminium ion activation of α,β-unsaturated ketones.

epi-quinine **I** with a twofold excess of trifluoroacetic acid (TFA, 40 mol%) provided the adducts **2** with complete *anti* diastereoselectivity[42] and high enantiocontrol. Synthetically noteworthy was that the cinchonine derivative **VII** (a member of the quinidine series) granted access to the other antipode of products **2** preserving the high stereoselectivity. Other features of the catalytic system were the broad range of enones successfully activated by catalyst **I**, ranging from differently substituted linear substrates to include the cyclohexenone, and the observation that an equimolar amount of the TFA co-catalyst (1:1 ratio with amine) markedly affected the enantioselectivity as well as the catalytic efficiency.

Shortly after, the ability of the primary amine **VII** to effectively condense with α,β-unsaturated ketones was exploited in the asymmetric Friedel–Crafts-type alkylation of indoles (Scheme 4).[39b] Notably, chiral secondary amines were previously shown to be inadequate for reaching a high level of stereoselectivity and reactivity in this synthetically relevant transformation.[43] Chen and co-workers used the cinchonine-based catalyst **VII** in combination with 2 equivalents of trifluoromethanesulfonic acid to catalyze the chemo- and stereoselective addition to both β-alkyl and aryl enones in good yield yet moderate enantiomeric excesses. At the same time, my research group was studying the same transformation using the hydroquinine-derived catalyst **III**.[40]



Scheme 4. Asymmetric Friedel–Crafts alkylation of indoles with simple enones.

In agreement with Chen's study, a moderate level of enantioselectivity (around 60% *ee*) was observed when using a strong acid co-catalyst (i.e. TFA). The key element to engineering a more-selective catalyst was the use of a chiral acid. Indeed, the catalytic amine salt **VIII**, made by combining two chiral entities, such as **III** and D-N-Boc phenylglycine D-**3**, promoted the Friedel–Crafts alkylation inferring a higher level of stereocontrol (*ee* in the 90% range, Scheme 4). Interestingly, the enantioselectivity of the reaction was not affected by the temperature, and this allowed us to thermally drive the reaction to completion in a reasonable time. The ability to preserve the high level of induction under more drastic conditions is another useful peculiarity of amino cinchona catalysts.[42]

At that time, sporadic examples of asymmetric reactions of hindered unsaturated carbonyls catalyzed by primary amines were known, with the catalysts specifically designed for particular transformations.[44] The demonstration that the same catalyst class was successful in the asymmetric Michael addition of two different carbon-centered nucleophiles[39,40] suggested that cinchona-based primary amines could become a general catalytic platform for the iminium ion activation of enones. In addition, the possibility of modulating the stereoselectivity using a chiral acidic co-catalyst offered a versatile strategy for securing consistently high levels of enantioselectivity. These features, together with the synthetic possibility of carrying out stereocontrolled conjugate addition to α,β-unsaturated ketones [historically challenging substrates for metal- and organocatalytic approaches][9] attracted the interest of many practitioners of organocatalysis. As a result, cinchona-derived primary amines were applied to a variety of highly enantioselective conjugate additions, not restricted to simple α,β-unsaturated enones. Section 3.1 details the main achievements and progress that have allowed researchers to better understand the potential of this catalyst class as general iminium ion activators of sterically hindered carbonyl compounds.

2.3.2. Enamine Activation of Enolizable Carbonyl Compounds

In parallel with the studies on the iminium ion activation of enones, cinchona-based primary amines were also shown to hold great potential in the α-functionalization of enolizable

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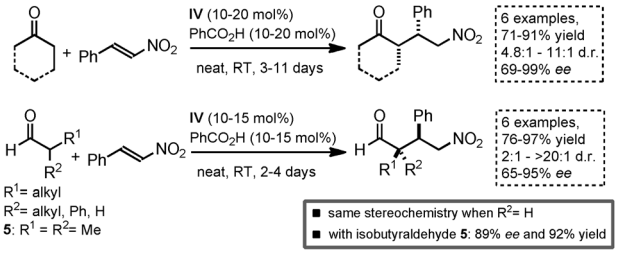
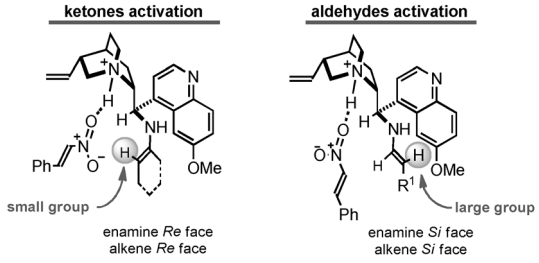
sterically hindered carbonyl compounds.[41] Specifically, the 9-*epi* hydroquinidine-derived catalyst **IV** proved effective in the Michael addition of nitroalkenes by enamine activation of linear and cyclic ketones as well as linear and α-branched aldehydes (Scheme 5). This C–C bond forming reaction has historically been a benchmark for measuring the efficiency of novel secondary[45] and primary[46] aminocatalysts.



Scheme 5. Enamine activation of ketones and aldehydes.

The use of "neat conditions" (that is, without solvent) and an equimolar amount of benzoic acid afforded the corresponding products with high *syn* diastereoselectivity and enantiocontrol. The primary amine catalyst having the natural absolute configuration at C9 led to poor results in terms of selectivity and reactivity, a general trend successively confirmed in other cinchona-derived primary amine-catalyzed transformations.[47] It is intriguing to consider that catalyst **IV** provided the highest levels of stereocontrol thus far reported in the enamine-catalyzed reactions with isobutyraldehyde **5**. This substrate served as a model for the pioneering studies by Hine to demonstrate the higher reactivity of primary over secondary amines when condensing with hindered aldehydes (see Section 2.1).[22]

Interestingly, aldehydes and ketones led to the corresponding Michael adducts with consistent *syn* diastereoselectivity but opposite absolute configuration. This observation, together with the necessity of an acid co-catalyst to ensure an effective process, prompted a bifunctional mode of activation to be proposed, in which the protonated quinuclidine moiety activates the nitroalkenes through hydrogen-bonding interactions and the primary amine is engaged in the enamine formation (Scheme 6). The stereochemical outcome, which was rationalized on the basis of the classical acyclic synclinal transition-state model proposed by Seebach,[48] provided the first evidence of the unique potential of the cinchona primary amine to react with carbonyl compounds which have completely different steric constraints. Achieving high stereocontrol in enamine-based reactions is strictly connected with the ability of the catalyst to sterically differentiate the two rotational enamine isomers that allow maximal overlap between the nitrogen lone pair and the π orbital of the adjacent C=C system (see also Scheme 2 and discussion in Section 2.1). In the activation of ketones, the catalyst recognizes the enamine vinylic proton as the less-hindered group. The opposite is true with enamines generated from aldehydes, where the substituent at the double bond plays the role of the stereochemical-defining element (the large group).[49] The cinchona-based primary amine seems able to adapt its flexible structure to ensure configurational control and π-facial discrimination of the covalent intermediate, the factors essential for enforcing high levels of enantioselectivity in aminocatalytic reactions proceeding through enamine and iminium ion.



Scheme 6. Reversal of the absolute configuration in the enamine catalyzed reactions with ketones and aldehydes. The "like" topicity of the Michael reaction is preserved while the facial selectivity of the enamine (which dictates the absolute stereochemistry of the whole process) is the opposite. The vinyl moiety has been assigned the highest priority.

2.4. The Consequences

The initial investigations highlighted the great potential of cinchona-derived primary amines to expand the scope of aminocatalysis. Three features attracted the interest of the researchers: 1) the ability to activate both (α,β-unsaturated) ketones and α-substituted aldehydes while 2) inferring constantly high levels of stereocontrol, and 3) using divergent, mechanistically unrelated carbonyl activation modes, either via electrophilic iminium ions or nucleophilic enamines. This provided the foundation for developing asymmetric functionalizations of sterically hindered carbonyl compounds that were previously inaccessible.

Probably the most important factor in boosting progress in the field was the possibility of using a single catalyst class. An analogy is found in the area of secondary amine catalysis, where the incredibly high efficiency demonstrated by the "privileged" aminocatalysts have consolidated the strategy as a reliable and powerful synthetic tool for the chemo- and enantioselective functionalization of unhindered aldehydes. Indeed, a versatile and easily available catalyst that constantly assures high levels of enantioselectivity represents a fundamental starting point for the development of new asymmetric processes. By avoiding large screening of catalysts when setting up the optimal reaction conditions, researchers can focus on exploring novel reactivity patterns and developing challenging and non-conventional transformations. This happened with cinchona primary amines, initially in the α- and β-functionalization of ketones and enones via enamine and iminium ion activations, respectively.

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3. Functionalization of Ketones and Simple Enones

3.1. Iminium Ion Activation of Simple Enones

Since its introduction in 2007, the cinchona primary amines **I**–**IV** were successfully applied to the catalysis of a wide range of asymmetric transformations of α,β-unsaturated ketones, including conjugate additions with different nucleophiles and cycloaddition reactions. The possibility of functionalizing substrates that are almost inaccessible to chiral secondary amine catalysis[50] provided impetus for the rapid growth of the field.

3.1.1. Conjugate Additions

Key to reaction developments was the general efficiency of the cinchona-based catalysts in activating α,β-unsaturated ketones via iminium ion formation while enforcing constantly high levels of enantioselectivity, regardless of the type of nucleophiles used. This resulted in the highly chemo- and stereoselective additions of C-,[51] N-,[52] O-,[53] and S-centered[54] nucleophiles to enones (Figure 4).

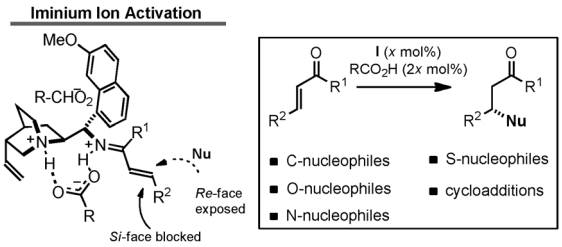
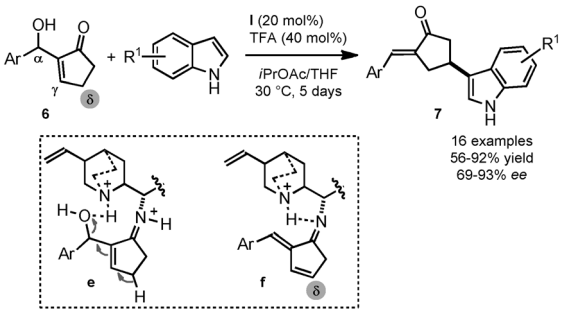


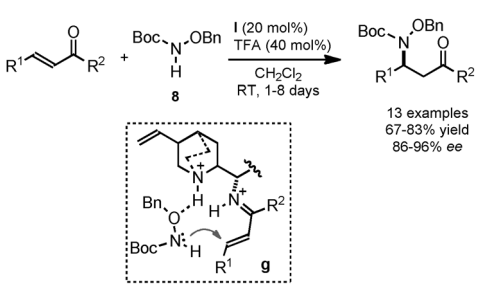
Figure 4. Stereoselectivity model for the iminium ion activation of enones with 9-amino-9-deoxy-*epi*-quinine **I**; RCO_2H: acidic cocatalyst.

Many classical carbon nucleophiles were used in C–C bond-forming processes toward the synthesis of useful chiral building blocks, testifying to the versatility and usefulness of the cinchona-based methodologies.[51] More importantly, the reliability of the iminium ion-based system brought about the development of novel and unconventional functionalizations of enones. One example is the enantioselective reaction of cyclopent-2-enone-derived Morita–Baylis–Hillman (MBH) alcohols **6** with indoles.[55] As shown in Scheme 7, the use of 9-amino-9-deoxy-*epi*-quinine **I** in the presence of a twofold excess of TFA resulted in an unanticipated yet exclusive δ-regioselectivity, leading to products **7**. Alcohol derivatives **6** are generally involved in conjugate addition or allylic substitution with nucleophiles, to afford α- or γ-substituted products, respectively. The cinchona primary amine **I** channels the reaction toward a specific δ-selective pathway. The necessity for an acidic co-catalyst (otherwise the system remains completely inactive) supports the formation of the iminium intermediate **e**, which assists the dehydration event through a hydrogen-bonding interaction with the protonated quinuclidine moiety. The resulting intermediate **f**, whose transient formation has been supported by ESI mass spectrometry analyses, is then selectively attacked at the δ-position by indole while the cinchona scaffold provides effective face shielding of the butadiene intermediate. The origin of the regioselectivity of the dehydration-conjugate-type addition has not yet been completely elucidated (both electronic and steric effects appear to be important). However, this example attests to the unique reactivity profiles induced by cinchona primary amines. Indirectly, this chemistry provided a clue for the possible condensation (thus, iminium ion activation) of catalyst **I** with α-substituted α,β-unsaturated ketones (for the realization of this target, see Section 5.3).

Owing to its intrinsic reversible nature, the development of an asymmetric conjugate addition of enones with nitrogen-centered nucleophiles (aza-Michael reactions) provided a more severe testing ground for the effectiveness of cinchona-based primary amines in promoting synthetically useful yet challenging transformations.[56] The application of iminium catalysis to the asymmetric β-amination of unsaturated carbonyl compounds is a difficult target. This is because the challenge of chemoselectivity is added to the already present issue of stereoselectivity. Indeed, two adequate amine components must be identified that can coexist while individually functioning as the 1,4-addition nucleophile (without interacting with the carbonyl group to form an iminium intermediate) and the iminium catalyst, selectively. Once again, the combination of amine **I** and 2 equivalents of TFA provided an effective catalyst system of the direct aza-Michael addition of Boc-protected *N*-benzyloxyamine (Boc = *tert*-butoxycarbonyl) **8** to a variety of enones, leading to β-amino ketones in good yield and high enantioselectivity (Scheme 8).[52] Key to success was a bifunctional activation mode where the nucleophile **8** was synergistically activated by hydrogen-bonding interactions with the protonated quinuclidine moiety (intermediate **g**).



Scheme 7. An unexpected δ-selective substitution of MBH alcohols.



Scheme 8. Bifunctional catalysis of the aza-Michael reaction.

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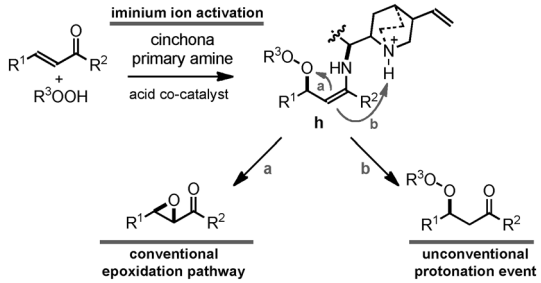
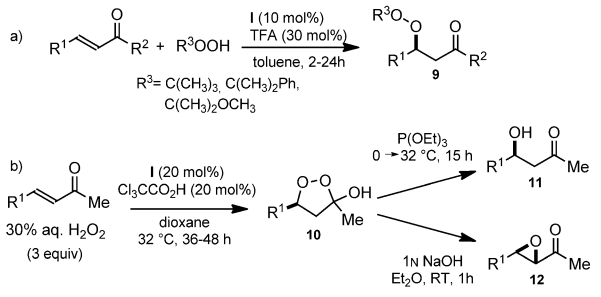
The catalytic enantioselective oxa-Michael reaction, specifically the peroxidation of enones, was developed independently and almost at the same time by the research groups of Deng and List.[53a,b] The chemistry nicely demonstrated one of the main aspects of cinchona primary amine catalysis: the possibility of channeling the reaction toward unconventional and previously inaccessible pathways. As depicted in Scheme 9, the cinchona catalyst directs the stereoselective



Scheme 9. The unconventional peroxidation driven by cinchona primary amine catalyst: pathway b.

nucleophilic addition of the hydroperoxide to enone through iminium activation to form the corresponding enamine intermediate **h**. The conventional reactivity would anticipate an intramolecular nucleophilic substitution that breaks the weak peroxide bond, the classical pathway toward the formation of enantioenriched epoxides.[57] The cinchona catalyst, however, has shown the uncommon potential for channeling the reaction toward the peroxidation pathway (b in Scheme 9). The key aspect is related to the conformational rigidity imposed by the cinchona scaffold to the enamine intermediate **h**, which cannot adopt the geometry required for the intramolecular nucleophilic attack to the electrophilic oxygen atom. While the epoxidation pathway is greatly inhibited, the protonated quinuclidine can act as a proton source to partition the reaction selectively toward the peroxidation.

Following this peculiar reactivity, Deng and co-workers developed an alkyl-peroxidation of linear enones to the corresponding chiral keto-alkylperoxides **9** using a combination of the quinine derivative **I** and TFA and different hydroperoxides, such as *tert*-butyl, cumene, and α-methoxy isopropyl hydroperoxide (Scheme 10a).[53a] Shortly after, the

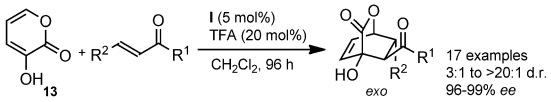


Scheme 10. a) Alkyl-peroxidation and b) hydro-peroxidation of linear enones.

interrupted epoxidation pathway was exploited by List and co-workers to develop a hydroperoxidation reaction. Aliphatic unsaturated ketones, in the presence of hydrogen peroxide, are converted by a catalytic amount of **I** and trichloroacetic acid into the corresponding peroxyhemiketals **10** with high enantioselectivity (Scheme 10b).[53b] Importantly, in situ reduction of peroxides **10** mediated by $P(OEt_3)$ or a basic work-up provided direct access to enantioenriched β-hydroxy ketones **11** or epoxides **12**, respectively.

3.1.2. Cycloaddition Reactions

Asymmetric catalytic Diels–Alder transformations, and pericyclic reactions at large, have been intensely researched because they offer a powerful and atom-economical way to rapidly access chiral cyclic compounds.[58] It is probably not by chance that iminium ion activation has been invented to implement an asymmetric [4+2] cycloaddition: indeed, the LUMO-lowering activation that allows α,β-unsaturated aldehydes to function as effective dienophiles in a highly enantioselective pericyclic path provided the first demonstration of the potential of secondary amine-mediated iminium catalysis.[6] The scope of the asymmetric catalytic Diels–Alder reaction has greatly expanded, yet simple acyclic α,β-unsaturated ketones have, for a long time, remained elusive dienophiles. Although secondary amine-based iminium catalysis has provided a first solution to this problem,[50a] cinchona primary amines have greatly expanded the applicability of the iminium catalyzed Diels–Alder reaction of enones. It was found that 9-amino-9-deoxyepiquinine **I** in combination with TFA catalyzes the conversion of 2-pyrone **13** and a series of β-aryl, β-alkyl, and unsubstituted enones into the corresponding cycloadducts with moderate to high *exo*-selectivity and excellent enantioselectivity (Scheme 11).[59] Remarkably, in the absence of any acid, the



Scheme 11. Diels–Alder reaction of simple enones.

reaction follows a different reaction pathway, leading to the corresponding Michael adduct, providing evidence that further confirms the importance of the acidic co-catalyst to modulate the catalyst activity as well as the selectivity of the process.

Pericyclic reactions have provided the ground for an important advance in the field of cinchona-based primary amine catalysis. In 2007, Chen's group introduced the 6′-hydroxy-9-amino derivatives **V** and **VI** (see Figure 2 and Scheme 12).[60] These multifunctional chiral catalysts greatly influenced future developments in the functionalization of sterically congested carbonyl compounds (see Sections 3.1.3 and 5). During studies on the [3+2] dipolar cycloaddition of cyclic enones with azomethine imines **14** (Scheme 12), Chen and co-workers found that the generally selective catalyst **I** afforded the desired tricyclic product **15** with moderate

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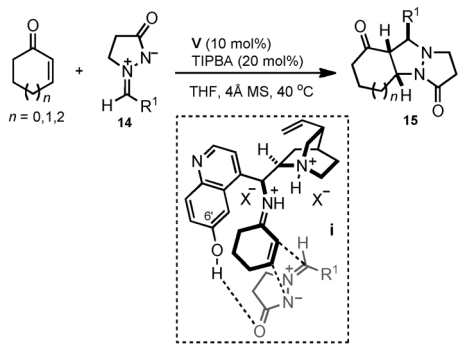


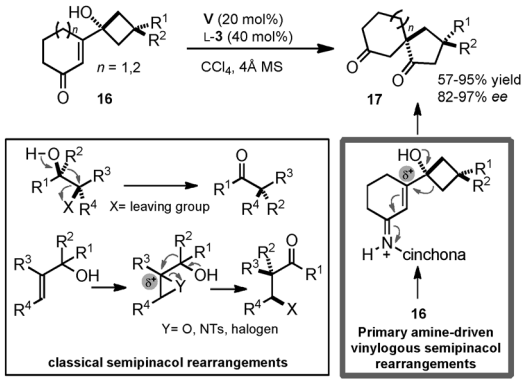
Scheme 12. The multifunctional catalyst **V**; TIPBA: 2,4,6-triisopropylbenzenesulfonic acid, X = counteranion.

enantioselectivity (*ee* values in the 50% range). Chen and co-workers speculated that they could achieve higher stereocontrol by using a bifunctional catalyst capable of simultaneously activating the two reaction partners of the cycloaddition. This cooperative prospect was translated to experimental reality with 6′-hydroxy-9-amino-9-deoxyepiquinine **V**. Through the hydroxy moiety at the 6′ position of the quinoline ring, **V** productively engaged in hydrogen-bonding interactions with the dipole of **14** (intermediate **i**, Scheme 12), ultimately channeling the transformation towards a highly stereoselective path (up to 95% *ee*).[60]

3.1.3. The Impact of 6′-Hydroxy-9-Amino Derivatives

Soon after its introduction, the multifunctional catalyst **V** was used to develop a conceptually novel transformation. A series of spirocyclic diketons **17** bearing all-carbon quaternary stereocenters (Scheme 13)[61] was constructed by the asymmetric vinylogous α-ketol rearrangement through semipinacol-type 1,2-carbon migration catalyzed by a combination of amine **V** and L-*N*-Boc phenylglycine (L-**3**).

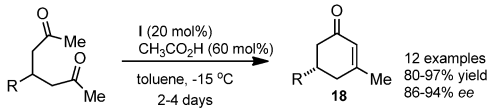
From a synthetic standpoint, the chemistry provided stereocontrolled access to difficult-to-make congested cyclic structures. More importantly, this study extended the classical 1,2-sigmatropic migration of the semipinacol rearrangement[61b] to an unprecedented vinylogous version. The iminium activation of the designed α-hydroxy enones **16** resulted in an electron-deficient electrophilic center next to the tertiary hydroxy moiety, which was able to drive the 1,2-carbon migration. Notably the two main features of this study, the asymmetric synthesis of spirocyclic compounds and the concept of vinylogy,[62] have often been associated with cinchona-based primary amines (see Sections 3.3.2, 5.1, and 5.2).



Scheme 13. An unprecedented vinylogous α-ketol rearrangement.

3.2. Enamine Activation of Ketones

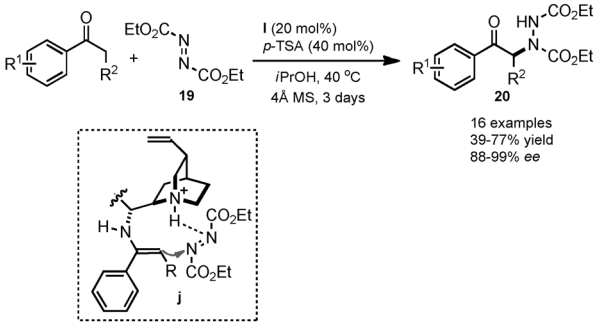
A distinctive feature of cinchona-based primary amines is their ability to participate in both enamine and iminium ion activations of hindered carbonyl compounds. After the initial report on the enamine-catalyzed Michael addition to nitroalkenes (Section 2.3.2), the quinine derivative **I** was successfully applied in another fundamental C–C bond-forming reaction: enantioselective intramolecular aldolization.[63] Specifically, List and co-workers reinvestigated the cyclodehydration of 4-substituted 2,6-heptandiones to cyclohexenones **18**, an aldol reaction which requires the catalyst to differentiate enantiotopic groups (Scheme 14).[63a] Although



Scheme 14. Intramolecular aldol reaction under enamine catalysis.

intense studies were previously devoted to this transformation, a highly enantioselective version remained elusive for a long time. Neither use of proline as the catalyst,[64a,b] nor applying the aldolase antibody 38C2[64c] reached high levels of stereocontrol. The realization of this sought-after reaction shows how cinchona primary amines, and aminocatalysis in general, have greatly expanded the chemist's ability to asymmetrically functionalize unmodified carbonyl compounds.

The development of the direct α-amination of aromatic ketones provided other important hints concerning the versatility of the cinchona-based primary amines (Scheme 15).[65] The use of diethyl azodicarboxylate (DEAD, **19**) as the electrophilic nitrogen source and amine **I** furnished the α-heteroatom functionalized ketones **20** with



Scheme 15. Direct α-amination of aryl ketones; *p*-TSA: *p*-toluenesulfonic acid.

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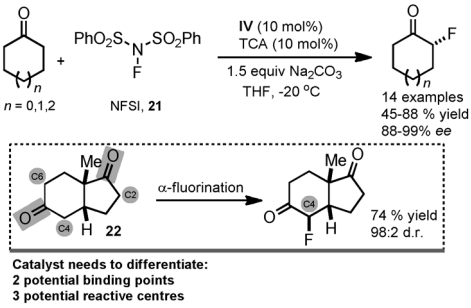
high enantioselectivity, expanding the applicability of enamine activation beyond the established C–C bond-forming processes. In addition, this study indicated that sterically encumbered aryl ketones, generally unsuitable substrates for aminocatalysis, can be efficiently functionalized. Mechanistically, it was proposed that the azodicarboxylate is activated towards enamine attack by hydrogen bonding with the protonated quinuclidine moiety (intermediate **j**), a mechanistic rationale often invoked in enamine-promoted transformations with cinchona aminocatalysts.

Recently, MacMillan and co-workers described the chemo- and highly enantioselective α-fluorination of cyclic ketones using hydroquinidine derivative **IV** as the catalyst and *N*-fluoro dibenzenesulfonimide (NFSI, **21**) as a mild electrophilic fluorine source (Scheme 16).[66] Several aspects of this

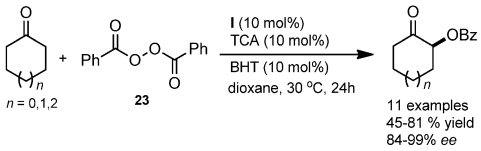


Scheme 16. α-Fluorination of cyclic ketones, TCA: trichloroacetic acid.

study deserve to be highlighted. Mechanistically, it was demonstrated that enamine catalysis by cinchona-based primary amines is not limited to addition reactions but has synthetic potential for nucleophilic substitutions too. From a synthetic standpoint, the α-fluorination of ketones has remained an elusive yet sought after transformation since 2005, when researchers developed the corresponding α-fluorination of aldehydes using chiral secondary aminocatalysts.[67] The interest in this reaction can be understood when considering the distinctive physical properties (a consequence of the large electronegativity and small van der Walls radius of the fluorine atom) that make stereodefined organofluorine compounds valuable to the pharmaceutical, agrochemical, and polymer industries.[68]

The approach to solving the "ketone fluorination problem" also tells us something important about the properties of cinchona-based primary aminocatalysis. The optimal catalytic system was identified by high-throughput evaluation of a large and diverse set of catalyst structures, including primary and secondary amines. The use of a robotic platform to automate the parallel execution of around 400 small-scale reactions and to determine the utility of a library of 250 novel and known organocatalysts indicated the unique efficiency of the cinchona catalyst **IV**, which greatly outperformed all the other candidates. Remarkably, the catalytic system has demonstrated impressive carbonyl chemoselectivity as well as α-carbonyl positional selectivity in the fluorination of cyclic ketones that incorporate pre-existing stereogenicity. An illustrative example is the diastereoselective fluorination of the hydrogenated Hajos–Parrish ketone **22** (selectively reacting at C4, Scheme 16).

The ability of cinchona primary amines to promote asymmetric nucleophilic substitution reactions and α-heteroatom functionalizations of carbonyl compounds was further exploited to develop the α-benzoyloxylation of cyclic ketones (Scheme 17).[69] The method uses anhydrous benzoyl peroxide



Scheme 17. α-Oxygenation of cyclic ketones, TCA: trichloroacetic acid.

23 and 10 mol% of the radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol (BHT) to avoid possible benzoyl radical side reactions, and leads to synthetically relevant chiral α-oxygenated ketones with high optical purity.

3.3. Cascade Reactions

Enantioselective cascade catalysis is a potent synthetic solution to the stereoselective construction of molecular complexity.[70] This bio-inspired strategy works by combining multiple asymmetric transformations in a cascade sequence. From simple precursors, it provides rapid access to complex molecules containing multiple stereocenters.[71] The ability of the cinchona-based primary amines to activate (α,β-unsaturated) ketones by enamine and/or iminium ion formation makes them perfectly suited to cascade catalysis. This is because of the possibility of integrating orthogonal activation modes into more elaborate reaction sequences.

3.3.1. Iminium Ion/Enamine Tandem Sequence

The initial approach to designing aminocatalyzed domino reactions was based on the conjugated addition of a nucleophile to α,β-unsaturated ketones followed by the α-functionalization of the resulting saturated ketones. In this well-defined sequence, the cinchona aminocatalyst has an active role in both steps, initially forming the activated iminium ion species **k** and later the electron-rich enamine intermediate **l** (Figure 5). This tandem sequence provided the reactivity framework for developing synthetically palatable transformations, such as the asymmetric epoxidation,[72] aziridination,[73] and cyclopropanation[74] of enones. Key to the success was the identification of suitable compounds that first act as nucleophiles under iminium ion catalysis, affording a stereoselective addition step, and then become electrophilic to facilitate the enamine-catalyzed cyclisation event.

Following this cascade approach, cinchona amine catalysts have solved the challenge of the direct, highly enantioselective epoxidation and aziridination of cyclic enones, a historically difficult substrate class for these venerable transformations.[75] Cyclic enones are readily epoxidized with excellent

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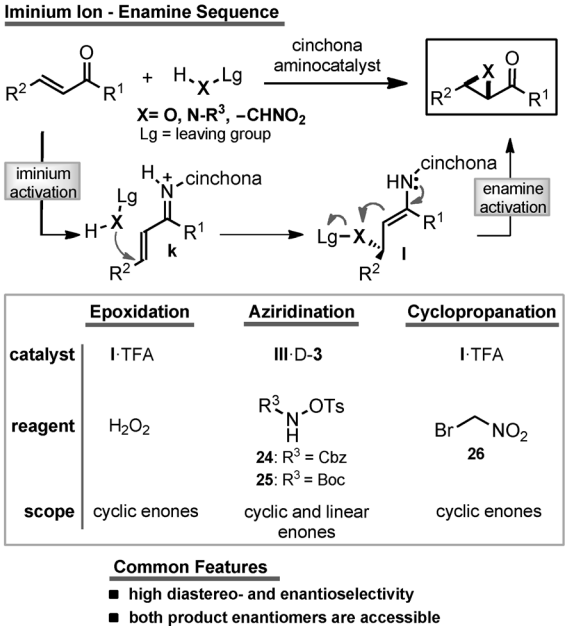
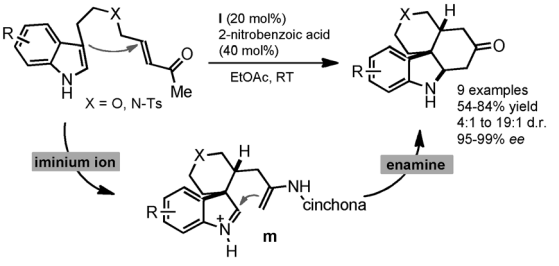


Figure 5. Iminium ion/enamine cascades of enones to epoxides, aziridines, and cyclopropanes.

enantioselectivity upon treatment with hydrogen peroxide and a combination of amine **I** and TFA,[72] while benzyl and *tert*-butyl tosyloxycarbamates **24** and **25** can be used to access *N*-Cbz or *N*-Boc protected *trans* keto-aziridines, respectively, under the catalysis of a salt made by combining the hydroquinine derivative **III** and D-*N*-Boc phenylglycine D-**3**.[73b] Both strategies are characterized by high control over the relative and absolute configuration, but only the aziridination chemistry has been successfully expanded to include linear α,β-unsaturated ketones[73a] (see Section 3.1.1 for the unconventional peroxidation pathway observed while attempting to epoxidize linear enones). The asymmetric cyclopropanation was conducted in the presence of quinine derivative **I** and TFA, and using bromonitromethane **26** as the reagent.[74] In this case as well, the scope was limited to cyclic enones, which were converted into the corresponding nitrocyclopropane products in high yields and stereoselectivities.

A slightly modified iminium ion/enamine cascade sequence catalyzed by the quinine primary amine **I** was recently designed for directly synthesizing complex tetracyclic indolines (Scheme 18).[76]



Scheme 18. Michael–Mannich cascade to densely fused indolines; Ts: tosyl.

The cascade involves an intramolecular Friedel–Crafts-type alkylation of the indolyl enone to generate an electrophilic spirocyclic indolenine intermediate **m**, which is then trapped by the enamine formed in situ. Notably, the enamine **m** engaged in the cyclization step (a Mannich reaction) is the less-substituted isomer, while the reaction shown in Figure 5 is driven by the internal enamine **l**, which has a trisubstituted double bond.

3.3.2. ***Enamine/Iminium Ion Tandem Sequence***

The chemistry of the iminium ion intermediate **k** depicted in Figure 5 is mainly characterized by the enhanced susceptibility of the β carbon atom toward nucleophilic attack, a result of the lowered energetic potential of the LUMO π-system. This reactivity platform has been extensively exploited, providing the foundations for a large portion of the chemistry described in the previous sections of this Review, including the cascade reactions detailed in Figure 5 and Scheme 18. A reconsideration of the reactivity profiles inherent to the iminium ion **k** opened up new possibilities for designing cascade reactions of enones based on a distinct reactivity framework. As shown in Figure 6, the intermediate **k**, formed upon protonation of the imine precursor (generated in situ by catalyst condensation with the α,β-unsaturated ketone) with a suitable acidic co-catalyst, increases the acidity of the α-proton. The conjugate base of the acidic co-catalyst may potentially drive a tautomerization event toward the cross-conjugated dienamine **n**,[77] which has nucleophilic character. This situation potentially allows a switching of the intrinsic electrophilic behavior of the iminium ion **k**, channeling the reaction toward a nucleophilic α-site alkylation. Two factors were central to the successful implementation of novel cascade reactions of enones: 1) the identification of a suitable acidic co-catalyst, which could facilitate the equilibrium between the iminium ion **k** and the nucleophilic cross-conjugated dienamine intermediate **n**;

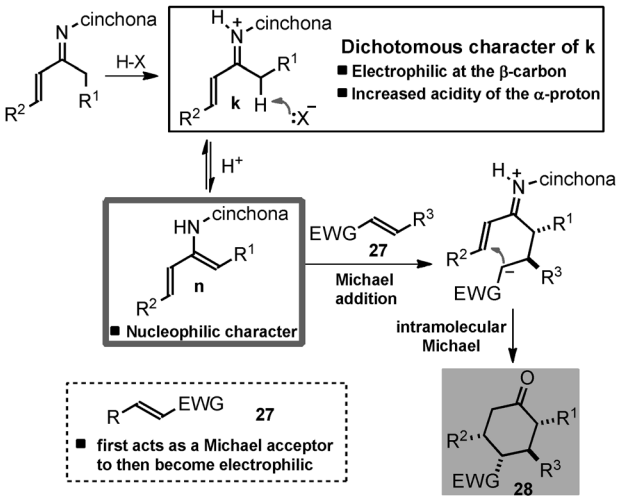


Figure 6. Design plan for an enamine/iminium ion cascade sequence; EWG: electron-withdrawing group.

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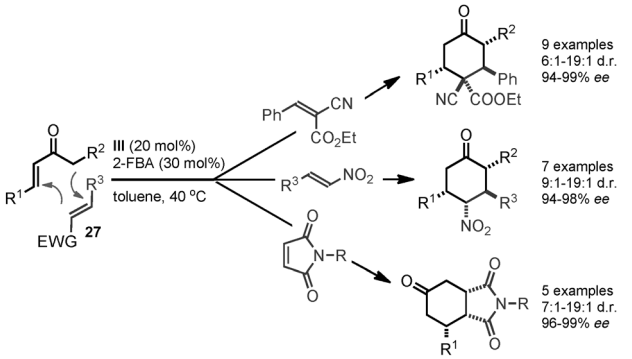
2) the identification of a suitable compound **27**, which could first act as a Michael acceptor, intercepting the dienamine **n**, and then become nucleophilic, thus selectively engaging in an intramolecular, iminium ion catalyzed conjugate addition to afford the cyclic product of type **28** (Figure 6). This cascade plan uses a pathway mirroring the chemistry reported in Figure 5 in that the α,β-unsaturated ketones are activated toward a well-defined enamine/iminium ion tandem sequence.

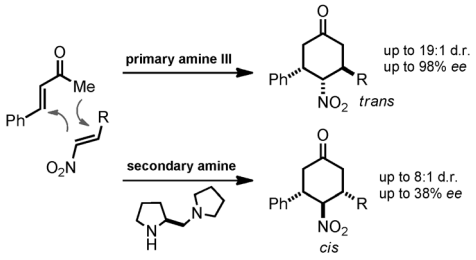
This reactivity plan was successfully implemented using cinchona-based primary amine **III** and 2-fluoro benzoic acid (2-FBA) as the co-catalyst, and applied to a range of electrophilic compounds of type **27**. The chemistry furnishes a one-step access to complex cyclohexane scaffolds, having three or four stereogenic centers, with excellent optical purity (Scheme 19).[78] Depending on the reaction partner, cyclohexanones with all-carbon quaternary stereocenters and bicyclic scaffolds were constructed with high efficiency.



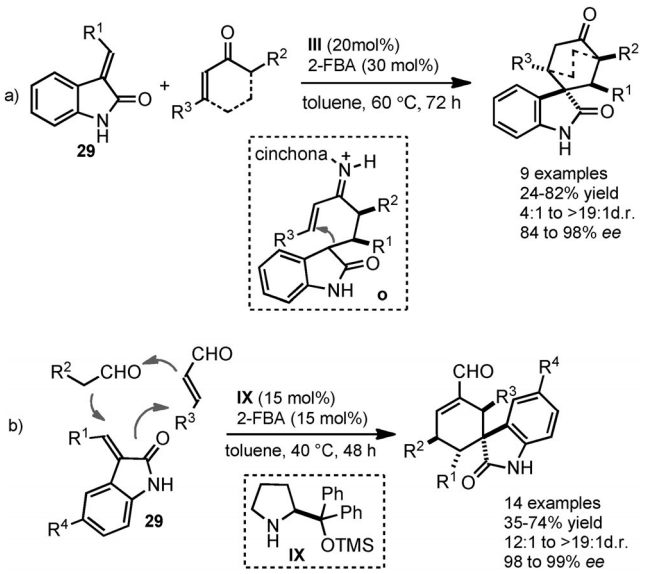
Scheme 19. Organocascade with enones: combinations with cyanocinnamates, nitroalkenes, and maleimides.

The ability of cinchona primary amine catalysis to impart unique reactivity profiles is noteworthy, not least because the use of chiral secondary amines in the same transformation gave a different stereochemical outcome and a poor enantioselectivity (Scheme 20).[77a,79]

The double-Michael addition cascade sequence of enones was then applied to the one-step, highly stereoselective synthesis of complex spirocyclic oxindoles starting from simple precursors (Scheme 21 a). Both linear and cyclic enones were successfully converted into the corresponding



Scheme 20. The different behavior of cinchona-primary amine and a proline derivative.



Scheme 21. Complementary organocascade strategies for the construction of spirocyclic oxindoles: a) chiral primary amine **III** selectively activates enones toward a double conjugate addition, exploiting an enamine/iminium activation sequence; b) chiral secondary amine **IX** promotes a triple organocascade by way of an enamine/iminium ion/enamine activation of aldehydes.

complex products under catalysis by **III** and 2-fluoro benzoic acid. Central to this study was the design of a suitable Michael acceptor **29**, bearing the oxindole moiety, which, after the first conjugate addition, generates the nucleophilic intermediate **o**. The second intramolecular conjugate addition step directly forges the spiro-stereocenter with high fidelity.[80]

Although the spiro-oxindole core features in a number of natural products as well as medicinally relevant compounds, its stereocontrolled synthesis, particularly installing the challenging spiro-quaternary stereocenter, poses a great synthetic problem.[81] Remarkably, a complementary organocascade strategy was devised, based on activating aldehydic compounds under secondary amine catalysis. This led to similar spirocyclohexene oxindoles with very high stereocontrol (Scheme 21 b).[80,82] The complementary approaches depicted in Scheme 21 are based on mechanistically distinct domino sequences. They highlight the potential of organocascade catalysis to face up to challenging synthetic problems using disparate tactics. From the perspective of aminocatalysis, this study indicated how primary amine catalysis can reach and complement the impressive level of efficiency inherent to the chemistry driven by chiral secondary amines.

4. Functionalization of α-Substituted Aldehydes and Enals

The potential of cinchona-based primary amines to effectively functionalize α-branched aldehydes under enamine activation was recognized early by the initial investigations of McCooey and Connon (Section 2.3.2).[41] The versatility of this catalyst class has allowed researchers to success-

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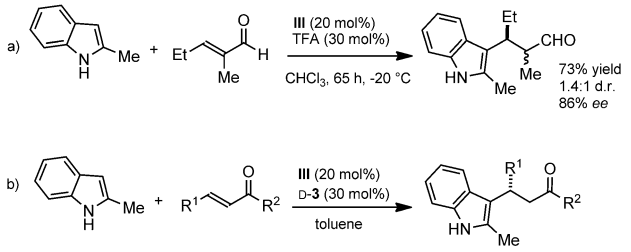
fully address the difficult issue of the iminium ion activation of α,β-disubstituted enals.

4.1. Iminium Ion Activation of α,β-Disubstituted Enals

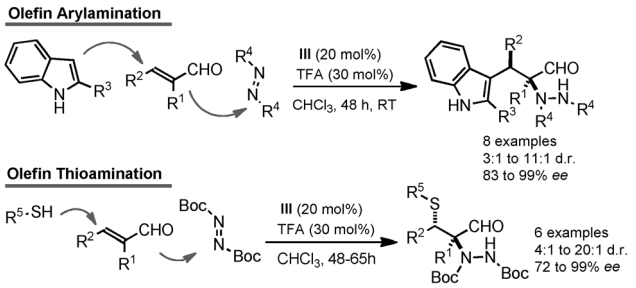
α-Branched α,β-unsaturated aldehydes have long been challenging substrates for asymmetric catalysis. Neither metal-based methodologies nor asymmetric aminocatalysis have provided a way to stereoselectively functionalize this sterically congested compound class.[83] Cinchona primary amines have a unique ability to engage in iminium ion formation with encumbered enones while enforcing high geometry control and face discrimination. In early 2009, it was hypothesized whether this ability could be translated into the challenging class of α,β-disubstituted enals.[84] Preliminary investigations revealed that the TFA salt of the quinine-based amine **I** promoted the Friedel–Crafts alkylation of 2-methyl-1*H*-indole with (*E*)-2-methylpent-2-enal with good enantioselectivity. This result indicated that a selective π-facial shielding of the iminium intermediate was effective (Scheme 22 a). The poor diastereocontrol, however, demonstrated that the following enamine-based protonation step escaped catalyst control.



Scheme 22. a) Iminium activation of α-branched enals in the Friedel–Crafts alkylation of indoles; b) opposite stereochemical outcome with enones.

This result further consolidated the unique ability of the cinchona primary amine to recognize carbonyl compounds which have completely different steric constraints. Remarkably, the observed opposite absolute configuration of the β-stereocenter in the Friedel–Crafts alkylation of indoles with enones and α-branched enals under catalysis by the same quinine-derived catalyst **III** (Scheme 22 a,b and Scheme 4) strictly resembled the enantiodivergent stereochemical outcome of the Michael addition of aldehydes and ketones to nitroalkenes under enamine activation (Scheme 6 and discussion therein). It appears that the flexible nature of the cinchona amine structure can ensure configurational control and π-facial discrimination, regardless of the steric bias inherent in the covalent iminium intermediate.

The issue of the modest control over the relative stereochemistry in the **III**-catalyzed Michael addition to enals (Scheme 22 a) was by-passed by designing a three-component cascade reaction, because using a more encumbered electrophile (with respect to a proton) generally engenders higher diastereocontrol. Two organocascade reactions that combine two intermolecular and stereoselective steps were successfully developed (Scheme 23).[84] The olefin aryl-amination and thio-amination processes follow a defined Michael addition-amination pathway under an iminium ion/



Scheme 23. Organocascade catalysis with α-branched α,β-unsaturated aldehydes: Friedel–Crafts/amination strategy and sulfa-Michael/amination strategy.

enamine sequence, in which the indole or the thiol acts as the nucleophile and the azodicarboxylate as the electrophile. The chemistry affords straightforward access to valuable precursors of α-amino acids that have two adjacent stereogenic centers with high optical purity.

The same iminium ion/enamine tandem sequence successively served for the enantioselective epoxidation of α-monosubstituted and α,β-disubstituted enals,[85] substrate classes that had long been inaccessible to asymmetric epoxidation catalysis. The study introduced interesting elements of novelty. The best catalytic system was identified by synergistically combining amine **I** with 2 equivalents of the chiral phosphoric acid derivatives **30** and **31** (Figure 7). A dramatic case of "matched" chiral induction was observed when using the (*R*)-enantiomer of the phosphoric acids. In addition, the chiral acid was responsible for the high stereocontrol achieved in the epoxidation of α-monosubstituted enals.

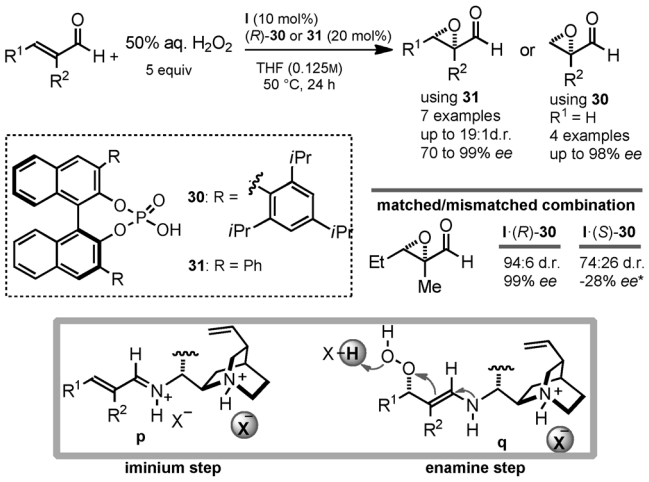


Figure 7. Epoxidation of α-branched enals; X: phosphate anion; * the opposite enantiomer was formed.

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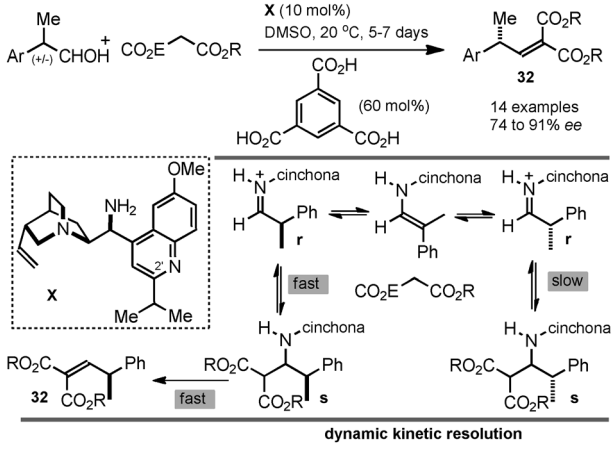
All the evidence supports the notion that the chiral phosphoric acid, in cooperation with the cinchona primary amine, provides additional enantio-discrimination in both the iminium ion step, serving as chiral counteranion (intermediate **p**), as well as in the enamine-driven cyclization, acting as a Brønsted acid (intermediate **q**). This study first showed the peculiar efficiency and compatibility of cinchona primary amines and phosphoric acids, a privileged combination that has found other synthetically relevant applications dealing with the functionalization of sterically encumbered carbonyl compounds (Section 5).

Interestingly, the cinchona-based catalyst was not able to effectively activate α-unsubstituted enals, which are the ideal substrates of chiral secondary aminocatalysis, instead it gave the corresponding epoxide in a process which had low reactivity and low stereocontrol. This intriguing limitation of the cinchona catalyst, observed in other transformations too, further underscores the complementary nature of primary and secondary amine catalysts.

4.2. Enamine Activation of α-Branched Aldehydes

The modern perspective and the new methodological opportunities provided by asymmetric organocatalysis have allowed chemists to redefine the synthetic power of many fundamental C–C bond forming transformations: highly stereoselective aminocatalytic variants of the aldol, Mannich, Michael, and Diels–Alder reactions have been successfully developed. However, it was only with the advent of cinchona-based primary amines that a venerable reaction, the Knoevenagel condensation,[86] succumbed to a catalytic asymmetric approach. This transformation, which more than a century ago led the historical foundations for the development of modern aminocatalysis,[8a] has never been made enantioselective. To finally achieve this target, List and co-workers designed a cinchona amine-catalyzed dynamic kinetic resolution of racemic α-branched aldehydes (Scheme 24).[86b] The system exploits the ability of the cinchona catalyst to form the covalent intermediate and to then drive a continuous racemization through an iminium ion/enamine tautomerization, which is the vehicle for interconversion. The enantioselectivity of the process arises from the different rates at which the intermediate diastereomeric iminium ions **r** are converted into the Mannich adducts **s** or, if **s** is generated reversibly, the stereoselectivity reflects the different kinetics of dehydration leading to the Knoevenagel product **32**.



Scheme 24. An old reaction revisited: the Knoevenagel condensation.

Remarkably, the use of a modified cinchona-derived primary amine **X**, bearing a substituent at the 2′ position of the quinoline ring, afforded slightly higher stereoselectivity with respect to the quinine analogue **I** (88% versus 91% *ee*). The modified catalyst class of type **X** may serve in future endeavors for fine tuning the stereoselectivity of the cinchona-amine catalyzed processes.

5. New Directions

Progress within the field of cinchona-based primary amine catalysis has been largely influenced and guided by previous studies on chiral secondary amines.[2] In only five years, this approach has almost equaled the high level of efficiency and reliability of aminocatalysis by proline-derived catalysts, offering the unique possibility of effecting processes between sterically demanding carbonyl compounds. Recent findings have suggested that the role of cinchona primary amines is not limited to expanding the substrate scope while still using established activation modes. The use of cinchona primary amines may yet redefine the frontiers of carbonyl functionalization providing novel opportunities to successfully attack previously elusive synthetic problems.

5.1. Dienamine Catalysis

The direct, catalytic, and stereoselective functionalization of carbonyl compounds at the γ position is a difficult target for asymmetric synthesis. Of the few useful approaches devised to date, the concept of vinylogous nucleophilicity is the most powerful (Figure 8).[62] However, designing asymmetric catalytic versions is not simple. Indeed, every approach to vinylogous reactions overlays the challenge of site-selectivity onto the already present issue of stereo-selectivity. Organic chemists classically address the critical regiochemical issue by preparing preformed, stable dienolate equivalents. Logically, this approach would be improved by avoiding the stoichiometric pre-activation of the vinylogous nucleophilic components. However, examples of direct, catalytic, and asymmetric vinylogous reactions are rare.[87] Secondary amine catalysis has recently provided a potentially general reactivity framework for designing direct vinylogous processes: dien-

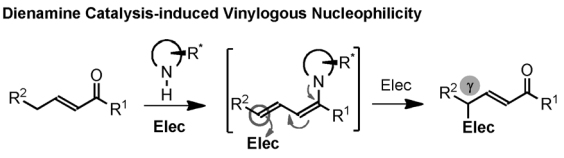


Figure 8. Dienamine catalysis and the concept of vinylogy; Elec: electrophile.

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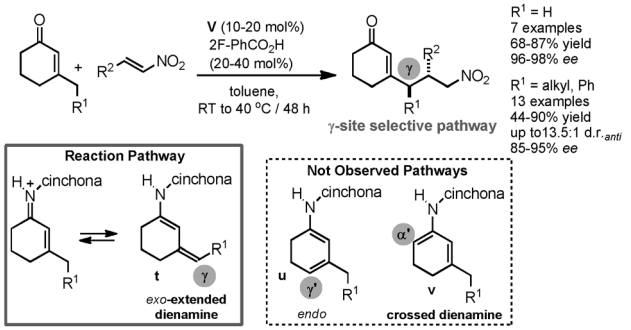
amine catalysis. Introduced in 2006 by Jørgensen and coworkers[88a] to promote the direct, enantioselective γ-amination of α,β-unsaturated aldehydes, it exploits the ability of chiral amine catalysts to form a nucleophilic dienamine intermediate in situ when they condense with γ-enolizable unsaturated carbonyls (Figure 8).

Surprisingly, dienamine catalysis has since found only limited application in asymmetric synthesis,[88b–d] probably because γ-amination of enals was originally proposed to follow a particular [4+2] cycloaddition path,[88a] instead of a more general nucleophilic addition route.[89] Recently, cinchona-based primary amine catalysis has greatly expanded the potential of this approach, promoting vinylogous nucleophilicity within Michael addition patterns, upon selective activation of unmodified cyclic α,β-unsaturated ketones (Scheme 25).

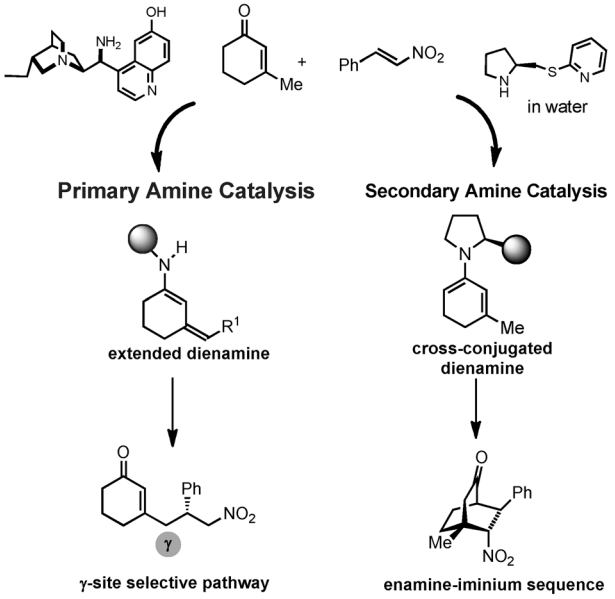


Scheme 25. Vinylogous Michael addition.

Specifically, the multifunctional 6′-hydroxy-9-amino quinine derivative **V** (Section 3.1.3) catalyzed the unprecedented, direct, vinylogous Michael addition of β-substituted cyclohexenone derivatives to nitroalkenes under dienamine catalysis.[90] Catalyst **V** ensured complete γ-site selectivity, with the two stereocenters at the γ and δ positions of the carbonyl moiety forged with very high fidelity. Remarkably, **V** can communicate its inherent stereochemical information while forging the new stereocenter at the δ position, several atoms away from the catalyst binding point within the covalent dienamine intermediate.

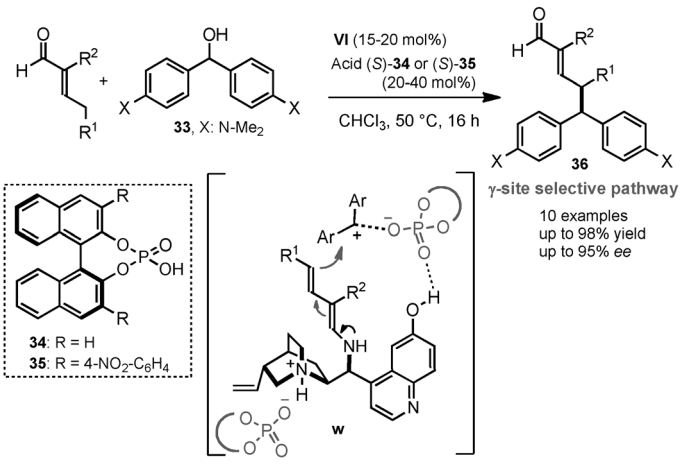
Central to success was the potential of the cinchona-derived catalyst to easily condense with an enone substrate to form the iminium ion intermediate, and then to coax the selective formation of the *exo*-cyclic extended dienamine **t** over the *endo*-adduct **u** or the cross-conjugated dienamine **v** (this intermediate is preferentially formed with acyclic enones, see Section 3.2.3 and Figure 6 for discussions). Exploitation of the ability of catalyst **V** (in combination with an acidic co-catalyst) to perturb the iminium–dienamine equilibrium, taken together with thermodynamic factors,[91] which govern the regioselective formation of the *exo*-cyclic dienamine intermediate **t**, resulted in an exclusive γ-site selective pathway.

Interestingly, primary amine catalysis can impart unique mechanistic pathways. A recent report has demonstrated that a chiral secondary amine and the cinchona-based primary amine behave in completely different ways when exposed to the very same reagent combination, namely β-methyl cyclohexenone and nitrostyrene, catalyzing a Diels–Alder reaction[92] and a vinylogous pathway,[90] respectively (Scheme 26).



Scheme 26. Primary amine versus secondary amine catalysis.

The logical extension to consolidating dienamine catalysis as a useful template for the γ-functionalization of carbonyl compounds was its application to nucleophilic substitution reactions. The 6′-hydroxy-9-amino quinidine **VI** was used to catalyze the direct asymmetric γ-alkylation of α-substituted linear α,β-unsaturated aldehydes with bis(4-dimethylaminophenyl)methanol **33** by an S_N1 pathway (Scheme 27).[93] This unprecedented transformation was accomplished using an interwoven activation pathway that successfully integrates dienamine catalysis and Brønsted acid catalysis simultaneously. The combination of amine **VI** with the chiral phosphoric acids **34** or **35** led to the γ-alkylated compound **36** as the



Scheme 27. Vinylogous substitution reaction in the S_N1-type γ-alkylation of α-branched enals.

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sole product of the reaction and it is formed with high optical purity. Mechanistically, the phosphoric acid induces the formation of a chiral contact ion pair (the reactive carbocationic alkylating agent) from alcohol **33**[94] that may synergistically engage in a matched combination with the chiral covalent dienamine intermediate (arising from the condensation of primary amine **VI** with enal). A cooperative catalytic system is thus operative, in which both the electrophilic and nucleophilic chiral intermediates interact through a network of noncovalent interactions (intermediate **w**).

It was demonstrated that dienamine catalysis is not limited to cyclic scaffolds, but has synthetic potential in the functionalization of acyclic, sterically hindered unsaturated carbonyl compounds. This possibility was interesting from a synthetic perspective. Moreover, the alkylation of α-unbranched enals took place with perfect γ-site selectivity under primary amine catalysis, but with very poor stereocontrol (under 10% *ee*).[95] This lack of control was presumably due to the poor *E*/*Z* geometry control of the dienamine intermediate. There thus arose the interesting prospect that α-branched enals, which are very difficult substrates for enamine and iminium ion catalysis, have the structural properties (namely the α-substituent) to bias the dienamine geometry, a necessary requirement for forging a stereogenic center at the γ position with high fidelity.

5.2. Trienamine Catalysis

The previous Section has detailed how the application of the HOMO-raising activation strategy to enolizable α,β-unsaturated carbonyl compounds results in the formation of a dienamine intermediate (Figure 8), whose intrinsic vinylogous nucleophilicity can be used for the direct asymmetric functionalization of unmodified carbonyl compounds at their γ position. Recent findings have demonstrated that the HOMO-raising electronic effect can be further propagated within poly-conjugated enals and enones of type **37**, thus leading to the in situ formation of trienamine intermediates (species **x** in Figure 9).[11,96] These covalent species can readily participate in Diels–Alder processes in which they act as activated chiral dienes, thus intercepting a variety of electron-deficient dienophiles. The chemistry allows the rapid construction of stereochemically dense cyclohexenyl rings **38** adorned with different molecular architectures and with high stereocontrol. Remarkable features of the resulting methods are 1) the perfect regioselectivity, in which the two novel carbon–carbon bonds form exclusively at the β and ε position

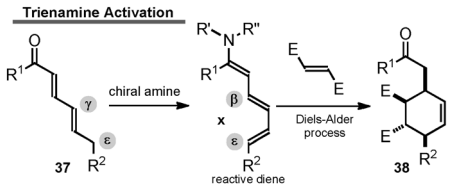
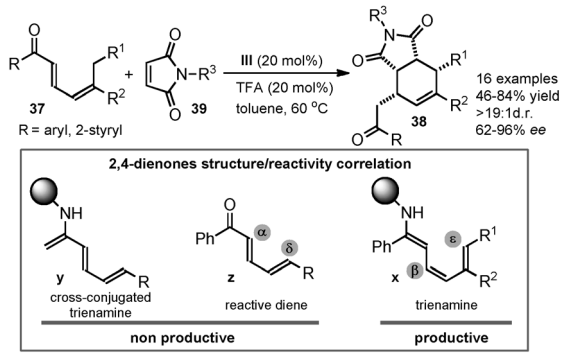


Figure 9. Further extending the marriage between the vinylogy principle and the HOMO-raising activation approach leads to the trienamine activation strategy; E: electron-withdrawing group.

of the original carbonyl **37**, and 2) the impressive ability of the aminocatalysts to communicate their inherent stereochemical information while forging the new stereocenter at the ε position, six atoms away from the catalyst binding point within the covalent trienamine intermediate.

The viability of the trienamine activation was established in a collaborative project between the research groups of Chen and Jørgensen.[11a] The efficiency of chiral secondary amines to activate aldehydic substrates provided the synthetic ground for developing asymmetric Diels–Alder processes based on the transient generation of extended conjugated trienamine intermediates of type **x** ($R^1 = H$, Figure 9).[11] Chen and co-workers, thanks to the effectiveness of the cinchona-based primary aminocatalyst **III**, have successfully extended trienamine activation to 2,4-dienones.[96] Still, this was not a trivial achievement: building up on experimental observations, a logical and careful design of the dienones was needed to effectively channel the reaction toward a productive pericyclic pathway induced by the trienamine intermediate **x** (Scheme 28). Indeed, the presence of an aryl group (R = Ph in



Scheme 28. Challenges arising from the trienamine activation of 2,4-dienones; TFA: trifluoroacetic acid; the black circle represents the catalyst scaffold.

37) instead of an enolizable methyl substituent at the α position of the carbonyl was essential to suppress the detrimental formation of the cross-conjugated trienamine intermediate **y**, which completely inhibited the reactivity. Afterwards, a γ,γ-disubstituted pattern ($R^2 = Me$ in **37**) was envisioned to prohibit a non-catalyzed Diels–Alder process of the dienone **z**, which is an intrinsically reactive diene conjugated between the α- and δ-carbon atoms, assuring in this way an amine-catalyzed β,ε-regioselective cyclization.

The Diels–Alder reaction of maleimides **39** with a wide variety of structurally distinct dienones **37** under the trienamine activation by the primary aminocatalyst **III** afforded the corresponding cyclic compounds **38** in high optical purity (Scheme 28). The chemistry was also extended to completely different classes of dienophiles, such as methylene-indolinones, olefinic cyanoacetates, or nitroalkenes (results not detailed in Scheme 28) preserving a very high degree of regio-, stereo-, and *endo*-selectivity.[96]

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5.3. Iminium Ion Activation of α,β-Disubstituted Enones and Beyond

The unique versatility of the cinchona-based primary amines to functionalize hindered substrates, with constantly high stereoselectivity, was recently tested in the most severe of trials, the activation of α,β-disubstituted unsaturated ketones. This class of carbonyl compounds has never before succumbed to a catalytic approach.[97] Along with the inherent problems of forming congested iminium ions, the catalyst must bias between two sterically encumbered carbonyl substituents. In addition, since conjugate additions to linear α-branched enones generate two adjacent stereocenters through an addition–protonation sequence, the design of a stereocontrolled process must address the challenge of diastereo- as well as enantioselectivity. To address these challenges (Figure 10) the aminocatalyst must: 1) condense with the highly hindered keto moiety, while 2) selectively shielding one face of the iminium intermediate, to forge the β-stereocenter with high fidelity. Finally, 3) strict control over the geometry of the transiently generated enamine is necessary to ensure a catalyst-directed protonation event.

The multifunctional 6′-hydroxy-9-amino quinidine derivative **VI** successfully addressed all the requirements, catalyzing the stereoselective sulfa-Michael addition (SMA) of different alkyl thiols to a range of linear α-branched enones (Scheme 29).[32a] The catalytic potential of the cinchona primary amine went even further, addressing an unmet challenge in asymmetric catalytic synthesis: modulation of the enforced sense of diastereoselectivity using a single catalyst through fairly simple modifications of the reaction conditions.[98] Indeed, the judicious choice of acidic additives and reaction media switches the sense of the catalyst's diastereoselection, thereby affording either the *syn* or *anti* products with high enantioselectivity.

This potential was exploited to access the full range of possible stereoisomeric products **42** of the SMA reaction (Figure 11). The *ortho*-fluoro benzoic acid/catalyst **VI** combination induced a *syn* selective outcome to the SMA of benzylthiol **40** to enone **41**, when carried out in chloroform. In acetone the phosphoric acid (*S*)-1,1′-binaphthalene-2,2′-diyl hydrogen phosphate **34** switched the catalyst's induction toward *anti*-selectivity. The same designed acid-induced diastereo-switching behavior was observed with the quasi-enantiomeric catalyst **V**, derived from quinine.

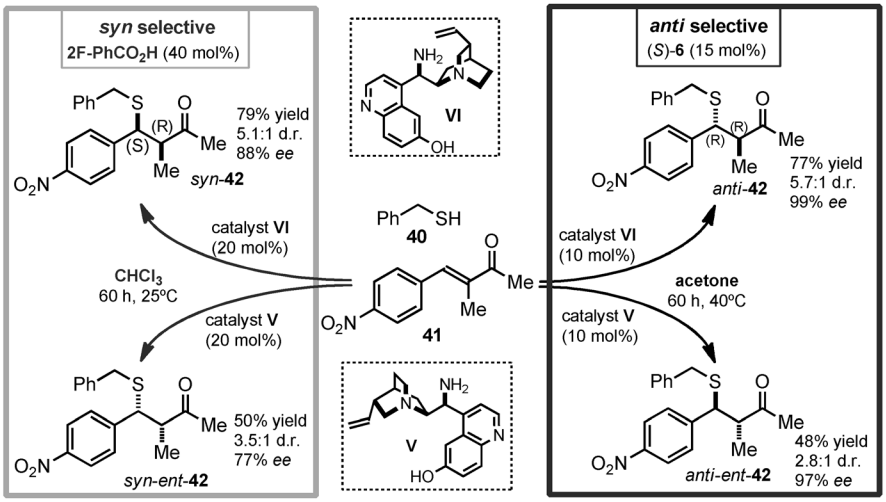


Figure 11. Accessing the full range of the stereoisomers of the SMA reaction using a single chiral catalyst.

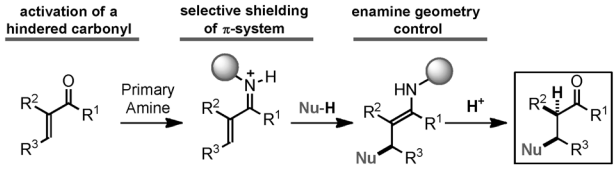
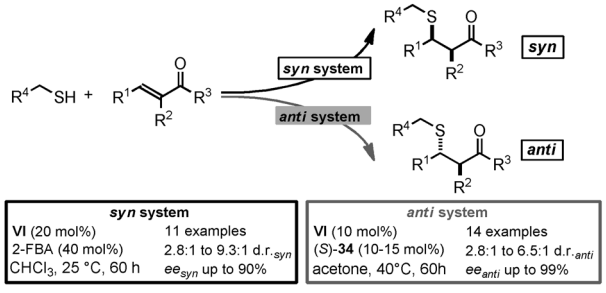


Figure 10. Challenges arising from the iminium ion activation of α-branched enones.



Scheme 29. Switching the diastereoselectivity of the SMA of α-branched enones; 2-FBA: 2-fluoro benzoic acid.

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.[99] Looking to the future, understanding how to induce (and maybe even program) such a synergic cooperation could provide the possibility of preparing a chiral catalyst whose catalysis function changes in response to an external chemical stimulus, thus greatly increasing the potential of cinchona primary amine catalysis.

6. Conclusion

This Review seeks to provide a useful guide to rationalizing how cinchona-based primary amines have expanded (and will probably continue to expand) the potential of asymmetric aminocatalysis. Progress was spurred by the need to overcome the intrinsic limitations of chiral secondary amine catalysis, which was restricted to the functionalization of unhindered aldehyde compounds. Early investigations were largely influenced by previous studies on secondary

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amines catalysis, and demonstrated that primary amines could encompass the classical activation modes, while offering the possibility of effecting processes between sterically demanding partners. This resulted in more exciting achievements than originally hoped. That is because a single catalyst class, the cinchona-based amines, was shown to effectively activate different carbonyl compounds, which are characterized by completely distinct structural features and steric bias, and to infer consistently high levels of stereocontrol. As such, researchers are closer to realizing the "dream" of a general aminocatalyst, able to activate nearly all the carbonyl compound classes.

The reliability and impressive versatility of the cinchona amines have motivated researchers toward more ambitious objectives, providing a general and solid catalytic platform from where successfully attacking those major challenges connected with the preparation of chiral molecules that cannot be addressed by traditional approaches. It is clear, however, that, to sustain future methodological innovation, a deeper understanding of the complex mechanisms associated with the multistep processes inherent to primary aminocatalysis is required. This is particularly true for the cinchona-based primary amine catalysts. The lack of information about the active conformer of this catalyst class stands in sharp contrast to the extensive experimental studies that have delineated its reactivity. It is anticipated that the "tools of the trade" of traditional physical organic chemistry will play a decisive role in the near future to elucidate reaction mechanisms and elements of stereocontrol.[100] To fully exploit the potential of this nature-inspired catalyst class, it will thus be crucial to combine computational methods, spectroscopic measurements and X-ray crystallography to detect, analyze, and characterize the reactive intermediates involved in cinchona-based primary amine catalysis.

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[1] R. E. Ireland, *Organic Synthesis*, Prentice-Hall, Englewood Cliffs, **1969**.

[2] For recent Reviews on aminocatalysis: a) S. Bertelsen, K. A. Jørgensen, *Chem. Commun.* **2009**, 2178–2189; b) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232–6265; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171; c) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; d) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79–87. For a discussion on the mechanisms of the α-, β-, and γ-functionalizations of aldehydes and enals by secondary amines, see: e) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun.* **2011**, *47*, 632–649.

[3] For the characterization of covalent reactive intermediates formed during organocatalysis by condensation of chiral secondary amines with aldehydes, see: a) D. Seebach, U. Grošelj, D. M. Badine, W. B. Schweizer, A. K. Beck, *Helv. Chim. Acta* **2008**, *91*, 1999–2034; b) D. Seebach, R. Gilmour, U. Grošelj, G. Deniau, C. Sparr, M.-O. Ebert, A. K. Beck, *Helv. Chim. Acta* **2010**, *93*, 603–634; c) M. B. Schmid, K. Zeitler, R. M. Gschwind, *Angew. Chem.* **2010**, *122*, 5117–5123; *Angew. Chem. Int. Ed.* **2010**, *49*, 4997–5003; d) M. B. Schmid, K. Zeitler, R. M. Gschwind, *Chem. Sci.* **2011**, *2*, 1793–1803.

[4] a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; b) B. List, *Tetrahedron* **2002**, *58*, 5573–5590; c) M. Movassaghi, E. N. Jacobsen, *Science* **2002**, *298*, 1904–1905.

[5] a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804–807; *Angew. Chem. Int. Ed.* **2005**, *44*, 794–797; b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284–4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215; c) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304; For a Review on the impact diarylprolinol ethers have had in aminocatalysis, see: d) K. L. Jensen, G. Dickmeiss, H. Jiang, Ł. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248–264.

[6] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244. See also Ref. [2d].

[7] The impressive developments in aminocatalysis have triggered a renaissance in catalysis mediated by small organic chiral molecules (organocatalysis), a relatively new and popular field within the domain of enantioselective synthesis. For general Reviews on asymmetric organocatalysis: a) E. N. Jacobsen, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20618–20619; b) *Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**; c) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308.

[8] a) B. List, *Angew. Chem.* **2010**, *122*, 1774–1779; *Angew. Chem. Int. Ed.* **2010**, *49*, 1730–1734; b) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44–50; *Angew. Chem. Int. Ed.* **2008**, *47*, 42–47.

[9] For a Review on primary amine catalysis: a) L.-W. Xu, J. Luo, Y. Lu, *Chem. Commun.* **2009**, 1807–1821. For Reviews focusing on the reasons (and the coincidences) that have brought about the development of cinchona-based primary amines, see: b) L. Jiang, Y.-C. Chen, *Catal. Sci. Technol.* **2011**, *1*, 354–365; c) G. Bartoli, P. Melchiorre, *Synlett* **2008**, 1759–1771; d) Y.-C. Chen, *Synlett* **2008**, 1919–1930.

[10] The catalysts, in both the pseudo-enantiomeric forms, are easily prepared in a single step by a Mitsunobu reaction of the OH group of readily available natural cinchona alkaloids. For the first synthesis of 9-amino(9-deoxy)-*epi*-cinchona alkaloids, see: H. Brunner, J. Bügler, B. Nuber, *Tetrahedron: Asymmetry* **1995**, *6*, 1699–1702.

[11] Last among the aminocatalytic activation modes, trienamine catalysis has been recently discovered by a collaborative project between the groups of Chen and Jørgensen. The activation strategy exploits the condensation of a chiral secondary amine with 2,4-dienals to form a trienamine intermediate that can engage with different dienophiles in a highly stereoselective Diels–Alder reaction: a) Z.-J. Jia, H. Jiang, J.-L. Li, B. Gschwend, Q.-Z. Li, X. Yin, J. Grouleff, Y.-C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053–5061. For other examples based on trienamine intermediates, see: b) H. Jiang, B. Gschwend, Ł. Albrecht, S. G. Hansen, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 9032–9036; c) Z.-J. Jia, Q. Zhou, Q.-Q. Zhou, P.-Q. Chen, Y.-C. Chen, *Angew. Chem.* **2011**, *123*, 8797–8800; *Angew. Chem. Int. Ed.* **2011**, *50*, 8638–8641; d) Y. Liu, M.

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Nappi, E. Arceo, S. Vera, P. Melchiorre, *J. Am. Chem. Soc.* **2011**, *133*, 15212 – 15218.

[12] This is an excerpt from a letter that Isaac Newton wrote to Robert Hooke in 1676. It is an apt comment on how science, and indeed the whole of civilization, is a series of incremental advances, each building on what went before.

[13] a) G. A. Hamilton, F. H. Westheimer, *J. Am. Chem. Soc.* **1959**, *81*, 6332 – 6333; b) R. A. Laursen, F. H. Westheimer, *J. Am. Chem. Soc.* **1966**, *88*, 3426 – 3430; c) C. Y. Lai, N. Nakai, D. Chang, *Science* **1974**, *183*, 1204 – 1206; d) A. Heine, G. DeSantis, J. G. Luz, M. Mitchell, C.-H. Wong, *Science* **2001**, *294*, 369 – 374, and references therein.

[14] a) K. J. Pedersen, *J. Phys. Chem.* **1934**, *38*, 559 – 571; b) K. J. Pedersen, *J. Am. Chem. Soc.* **1938**, *60*, 595 – 571.

[15] a) F. H. Westheimer, H. Cohen, *J. Am. Chem. Soc.* **1938**, *60*, 90 – 94; b) F. H. Westheimer, W. A. Jones, *J. Am. Chem. Soc.* **1941**, *63*, 3283 – 3286.

[16] a) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492 – 493; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496 – 497; b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615 – 1621; c) N. Cohen, *Acc. Chem. Res.* **1976**, *9*, 412 – 417, and references therein; d) S. Danishefsky, P. Cain, *J. Am. Chem. Soc.* **1975**, *97*, 5282 – 5283.

[17] The seminal papers by List, Lerner, and Barbas and by MacMillan and co-workers (Refs. [4a] and [6], respectively), both published in 2000, indicated the potential of cyclic secondary amines to efficiently catalyze the asymmetric functionalization of carbonyl compounds. The asymmetric aminocatalysis "gold rush" was on. See Ref. [2].

[18] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, R. Terrell, *J. Am. Chem. Soc.* **1963**, *85*, 207 – 222.

[19] a) P. W. Hickmott, *Tetrahedron* **1982**, *38*, 1920 – 2050; b) *Chemistry of Enamines* (Ed.: Z. Rappaport), Wiley, Chichester, **1994**.

[20] a) J. Hine, R. A. Evangelista, *J. Am. Chem. Soc.* **1980**, *102*, 1649 – 1655. Enamines are normally stable only when the nitrogen atom does not bear a hydrogen; otherwise, the imine form predominates, see: b) B. Witkop, *J. Am. Chem. Soc.* **1956**, *78*, 2873 – 2882; c) R. A. Clark, D. C. Parker, *J. Am. Chem. Soc.* **1971**, *93*, 7257 – 7261; d) D. R. Boyd, W. B. Jennings, L. C. Waring, *J. Org. Chem.* **1986**, *51*, 992 – 995.

[21] J. Hine, *Acc. Chem. Res.* **1978**, *11*, 1 – 7, and references therein.

[22] Studies on the iminium ion formation from primary amines: a) J. Hine, B. C. Menon, J. H. Jensen, J. Mulders, *J. Am. Chem. Soc.* **1966**, *88*, 3367 – 3373; b) J. Hine, F. A. Via, *J. Am. Chem. Soc.* **1972**, *94*, 190 – 194; see also: c) F. Tanaka, R. Thayumanavan, N. Mase, C. F. Barbas III, *Tetrahedron Lett.* **2004**, *45*, 325 – 328. Studies on the iminium ion formation from secondary amines: d) J. Hine, J. Mulders, *J. Org. Chem.* **1967**, *32*, 2200 – 2205; e) J. Hine, R. C. Dempsey, R. A. Evangelista, E. T. Jarvi, J. M. Wilson, *J. Org. Chem.* **1977**, *42*, 1593 – 1599. For the conformational isomerization of imines derived from isobutyraldehyde and primary amines: f) J. Hine, C. H. Yeh, *J. Am. Chem. Soc.* **1967**, *89*, 2669 – 2676.

[23] a) B. Capon, Z.-P. Wu, *J. Org. Chem.* **1990**, *55*, 2317 – 2324, and references therein; b) F. Johnson, *Chem. Rev.* **1968**, *68*, 375 – 413, p. 392 therein; c) J. E. Anderson, D. Casarini, L. Lunazzi, *Tetrahedron Lett.* **1988**, *29*, 3141 – 3144.

[24] One of the most important factors in determining the physical and chemical properties of enamines is the ability of the system to place the nitrogen substituent coplanar with the double bond, an essential requirement for maximizing conjugation between the nitrogen lone pair and π C=C system. Hence, a large structural difference between secondary and tertiary enamines might be expected when the tertiary enamines are hindered by the substituents on the nitrogen and on the double bond.

[25] a) C. E. Song, *Cinchona Alkaloids in Synthesis and Catalysis*, Wiley-VCH, Weinheim, **2009**; b) T. Marcelli, H. Hiemstra, *Synthesis* **2010**, 1229 – 1279; c) T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691 – 1693.

[26] G. Bredig, P. S. Fiske, *Biochem. Z.* **1912**, *46*, 7 – 23.

[27] H. Pracejus, *Justus Liebigs Ann. Chem.* **1960**, *634*, 9 – 22.

[28] a) H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417 – 430; b) H. Wynberg, *Top. Stereochem.* **1986**, *16*, 87 – 129.

[29] a) T. Bürgi, A. Baiker, *J. Am. Chem. Soc.* **1998**, *120*, 12920 – 12926; b) G. D. H. Dijkstra, R. M. Kellogg, H. Wynberg, J. S. Svendsen, I. Marko, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, *111*, 8069 – 8076; c) A. Urakawa, D. M. Meier, H. Rüegger, A. Baiker, *J. Phys. Chem. A* **2008**, *112*, 7250 – 7255.

[30] R. A. Olsen, D. Borchardt, L. Mink, A. Agarwal, L. J. Mueller, F. Zaera, *J. Am. Chem. Soc.* **2006**, *128*, 15594 – 15595.

[31] It has already been shown how modulation of the solvent polarity directly reflects on the ability of a cinchona catalyst to induce a preferred handedness in the product formed during an asymmetric transformation, see: M. Aune, A. Gogoll, O. Matsson, *J. Org. Chem.* **1995**, *60*, 1356 – 1364.

[32] See the Supplementary Information, pp. S28–S45 in: a) X. Tian, C. Cassani, Y. Liu, A. Moran, A. Urakawa, P. Galzerano, E. Arceo, P. Melchiorre, *J. Am. Chem. Soc.* **2011**, *133*, 17934 – 17941. See also: b) H. Brunner, P. Schmidt, M. Prommesberger, *Tetrahedron: Asymmetry* **2000**, *11*, 1501 – 1512.

[33] Cinchona-based primary amines, in the absence of acids and as free bases, have been used to promote asymmetric transformations under general base catalysis, see: a) B. Tan, P. J. Chua, Y. Li, G. Zhong, *Org. Lett.* **2008**, *10*, 2437 – 2440; b) B. Tan, X. Zhang, P. J. Chua, G. Zhong, *Chem. Commun.* **2009**, 779 – 781. Thus, catalysts **I** – **VI** are characterized by a dichotomous catalytic behavior. This is because they can execute their catalytic functions using both covalent and noncovalent-based organocatalysis.

[34] a) G. J. S. Evans, K. White, J. A. Platts, N. C. O. Tomkinson, *Org. Biomol. Chem.* **2006**, *4*, 2616 – 2627; b) W. P. Jenks, *Catalysis in Chemistry and Enzymology*, *Section B*, *Part 1*, McGraw-Hill, New York, Chap. 10, **1969**.

[35] Many authors have proposed a bifunctional activation mode for the cinchona-based primary amines where the non-protonated quinuclidine moiety assists the approach of the reagents to the covalently bound intermediate through noncovalent interactions (generally Brønsted base activation). Although possible, this peculiar mechanism of catalysis is unlikely to be operative under the acidic conditions in which the aminocatalytic reactions are generally performed.

[36] a) J. Hine, M. S. Cholod, W. K. Chess, Jr., *J. Am. Chem. Soc.* **1973**, *95*, 4270 – 4276; b) J. Hine, F. A. Via, *J. Org. Chem.* **1977**, *42*, 1972 – 1978; c) J. M. Sayer, B. Pinsky, A. Schonbrunn, W. Washtien, *J. Am. Chem. Soc.* **1974**, *96*, 7998 – 8009. See also Ref. [21].

[37] a) S. Warren, B. Zerner, F. H. Westheimer, *Biochemistry* **1966**, *5*, 817 – 823; b) F. C. Kokesh, F. H. Westheimer, *J. Am. Chem. Soc.* **1971**, *93*, 7270 – 7274; c) F. H. Westheimer, *Tetrahedron* **1995**, *51*, 3 – 20; d) M.-H. Ho, J.-F. Ménétret, H. Tsuruta, K. N. Allen, *Science* **2009**, *459*, 393 – 397.

[38] The foundations for rationalizing the influence of chiral counteranions on both the reactivity and stereoselectivity of iminium catalysis have been established by List and co-workers. They have introduced asymmetric counterion directed catalysis (ACDC) as an efficient strategy for enantioselective transformations that proceed via cationic species, including iminium-ion intermediates, see: a) S. Mayer, B. List, *Angew. Chem.* **2006**, *118*, 4299 – 4301; *Angew. Chem. Int. Ed.* **2006**, *45*, 4193 – 4195; b) N. J. A. Martin, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13368 – 13369.

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[39] a) J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y.-C. Chen, Y. Wu, J. Zhu, J.-G. Deng, *Angew. Chem.* **2007**, *119*, 393 – 396; *Angew. Chem. Int. Ed.* **2007**, *46*, 389 – 392; b) W. Chen, W. Du, L. Yue, R. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Org. Biomol. Chem.* **2007**, *5*, 816 – 821.

[40] G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403 – 1405.

[41] S. H. McCooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599 – 602.

[42] The high level of diastereoselectivity of this transformation is more ascribable to the particular nucleophile **1** used than to a general feature of the cinchona-based primary amines. Generally, these catalysts infer constantly high enantioselectivity but poor diastereocontrol when promoting the conjugate addition of prochiral carbon nucleophiles to α,β-unsaturated ketones. Another peculiarity of the amino cinchona catalysts is the ability to preserve the high level of induction under drastic conditions (temperature and pressure) see: a) P. Kwiatkowski, K. Dudziński, D. Łyżwa, *Org. Lett.* **2011**, *13*, 3624 – 3627; b) S. Fustero, C. del Pozo, C. Mulet, R. Lazaro, M. Sánchez-Roselló, *Chem. Eur. J.* **2011**, *17*, 14267 – 14272.

[43] a) D.-P. Li, Y.-C. Guo, Y. Ding, W.-J. Xiao, *Chem. Commun.* **2006**, 799 – 801. For an overview of the catalytic asymmetric Friedel – Crafts alkylations, see: b) *Catalytic Asymmetric Friedel – Crafts Alkylations* (Eds.: M. Bandini, A. Umani-Ronchi), Wiley-VCH, Weinheim, **2009**.

[44] For the iminium activation of α-substituted acroleins, see: a) K. Ishihara, K. Nakano, *J. Am. Chem. Soc.* **2005**, *127*, 10504 – 10505. For the activation of α,β-unsaturated eketones, see: b) H. Kim, C. Yen, P. Preston, J. Chin, *Org. Lett.* **2006**, *8*, 5239 – 5242; c) S. B. Tsogoeva, S. B. Jagtap, *Synlett* **2004**, 2624 – 2626. See also Ref. [38b].

[45] For selected examples: a) B. List, P. Pojarliev, J. Martin, *Org. Lett.* **2001**, *3*, 2423 – 2425; b) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737 – 3740; c) O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147 – 1168; see also Ref. [5b].

[46] a) S. B. Tsogoeva, S. Wei, *Chem. Commun.* **2006**, 1451 – 1453; b) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170 – 7171; c) M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 6514 – 6518; *Angew. Chem. Int. Ed.* **2006**, *45*, 6366 – 6370.

[47] For cinchona-based primary amines as well as for another general and effective catalyst, namely the cinchona *epi*-C9-(thio)urea catalyst, the natural stereochemistry at the C9 always provided poor results with respect to the 9-epimer analogues. For an overview of the applications of cinchona thiourea catalyst, see: S. J. Connon, *Chem. Commun.* **2008**, 2499 – 2510.

[48] In this transition state, the thermodynamically stable *E* enamine reacts with *E* nitroolefins in a synclinal arrangement, in which the actual donor and acceptor atoms are situated close to each other: a) D. Seebach, J. Goliński, *Helv. Chim. Acta* **1981**, *64*, 1413 – 1423; b) D. Seebach, A. K. Beck, J. Golinski, J. N. Hay, T. Laube, *Helv. Chim. Acta* **1985**, *68*, 162 – 172.

[49] In the case of the ketone, the enamine may adopt a Z configuration to minimize steric interactions. However, this geometry would result in an *anti* diastereoselective pathway, a stereochemical outcome achieved using other chiral primary aminoacatlysts, see Ref. [46a,b]. The intriguing ability of the cinchona primary amines to infer *syn* diastereoselectivity, although not rationalized, provides another example of the unique reactivity profiles they may impart.

[50] For a discussion of challenging issues associated with the iminium activation of enones by chiral secondary amines, see: a) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458 – 2460; for other applications of chiral secondary amines, see: b) J. B. Tuttle, S. G. Ouellet, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 12662 – 12663; c) N. Halland, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 8331 – 8338; d) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem.* **2004**, *116*, 1292 – 1297; *Angew. Chem. Int. Ed.* **2004**, *43*, 1272 – 1277.

[51] For a comprehensive list of carba-Michael reactions, see Refs. [9b–d]. For selected examples: a) J.-W. Xie, L. Yue, W. Chen, W. Du, J. Zhu, J.-G. Deng, Y.-C. Chen, *Org. Lett.* **2007**, *9*, 413 – 415; b) M. W. Paixão, N. Holub, C. Vila, M. Nielsen, K. A. Jørgensen, *Angew. Chem.* **2009**, *121*, 7474 – 7478; *Angew. Chem. Int. Ed.* **2009**, *48*, 7338 – 7342; c) C. Liu, Y. Lu, *Org. Lett.* **2010**, *12*, 2278 – 2281.

[52] X. Lu, L. Deng, *Angew. Chem.* **2008**, *120*, 7824 – 7827; *Angew. Chem. Int. Ed.* **2008**, *47*, 7710 – 7713. See also Ref. [73a].

[53] a) X. Lu, Y. Liu, B. Sun, B. Cindric, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 8134 – 8135; b) C. M. Reisinger, X. Wang, B. List, *Angew. Chem.* **2008**, *120*, 8232 – 8235; *Angew. Chem. Int. Ed.* **2008**, *47*, 8112 – 8115; c) A. Carlone, G. Bartoli, M. Bosco, F. Pesciaioli, P. Ricci, L. Sambri, P. Melchiorre, *Eur. J. Org. Chem.* **2007**, 5492 – 5495.

[54] P. Ricci, A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Melchiorre, *Adv. Synth. Catal.* **2008**, *350*, 49 – 53.

[55] Z. Qiao, Z. Shafiq, L. Liu, Z.-B. Yu, Q.-Y. Zheng, D. Wang, Y.-J. Chen, *Angew. Chem.* **2010**, *122*, 7452 – 7456; *Angew. Chem. Int. Ed.* **2010**, *49*, 7294 – 7298.

[56] The aza-Michael type addition of enals under iminium activation was pioneered by MacMillan and co-workers, see: a) Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 9328 – 9329. For a metal-based approach with enones, see: b) M. S. Taylor, D. N. Zalatan, A. M. Lerchner, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 1313 – 1317.

[57] The epoxidation of enals driven by iminium/enamine tandem sequence and using a chiral secondary amine is a well-established, enantioselective method: M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang, K. A. Jorgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964 – 6965.

[58] a) E. J. Corey, *Angew. Chem.* **2002**, *114*, 1724 – 1741; *Angew. Chem. Int. Ed.* **2002**, *41*, 1650 – 1667; b) Y. Hayashi, *Catalytic asymmetric Diels – Alder reactions* in *Cycloaddition Reactions in Organic Synthesis* (Eds.: S. Kobayashi, K. A. Jørgensen), Wiley-VCH, Weinheim, **2001**.

[59] R. P. Singh, K. Bartelson, Y. Wang, H. Su, X. Lu, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 2422 – 2423.

[60] W. Chen, W. Du, Y. Duan, Y. Wu, S.-Y. Yang, Y.-C. Chen, *Angew. Chem.* **2007**, *119*, 7811 – 7814; *Angew. Chem. Int. Ed.* **2007**, *46*, 7667 – 7670.

[61] a) E. Zhang, C.-A. Fan, Y.-Q. Tu, F.-M. Zhang, Y.-L. Son, *J. Am. Chem. Soc.* **2009**, *131*, 14626 – 14627; for a Review on semipinacol rearrangement strategy, see: b) B. Wang, Y.-Q. Tu, *Acc. Chem. Res.* **2011**, *44*, 1207 – 1222.

[62] The principle of vinylogy was formulated by Fuson in 1935 as the transmission of electronic effects through a conjugated π-system: R. C. Fuson, *Chem. Rev.* **1935**, *16*, 1 – 27. In the context of aminocatalysis, this principle accounts for the use of γ-enolisable α,β-unsaturated carbonyl compounds as precursors of nucleophilic dienolate equivalents, formally inverting the usual reactivity of this compound class (vinylogous nucleophilicity).

[63] a) J. Zhou, V. Wakchaure, P. Kraft, B. List, *Angew. Chem.* **2008**, *120*, 7768 – 7771; *Angew. Chem. Int. Ed.* **2008**, *47*, 7656 – 7658. For intermolecular aldol reactions promoted by cinchona primary amines, see: b) B.-L. Zheng, Q.-Z. Liu, C.-S. Guo, X.-L. Wang, L. He, *Org. Biomol. Chem.* **2007**, *5*, 2913 – 2915; c) P. Li, J. Zhao, F. Li, A. S. C. Chan, F. Y. Kwong, *Org. Lett.* **2010**, *12*, 5616 – 5619. For aldol reactions under enamine activation by primary amines, see: d) S. Pizzarello, A. L. Weber, *Science* **2004**, *303*, 1151; e) S. S. V. Ramasastry, H. Zhang, F. Tanaka,

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C. F. Barbas III, *J. Am. Chem. Soc.* **2007**, *129*, 288 – 289. See also Ref. [16d].

[64] a) C. Agami, H. Sevestre, *J. Chem. Soc. Chem. Commun.* **1984**, 1385 – 1386; b) C. Agami, N. Platzer, H. Sevestre, *Bull. Soc. Chim. Fr.* **1987**, *2*, 358 – 360; c) B. List, R. A. Lerner, C. F. Barbas III, *Org. Lett.* **1999**, *1*, 59 – 61.

[65] a) T.-Y. Liu, H.-L. Cui, Y. Zhang, K. Jiang, W. Du, Z.-Q. He, Y.-C. Chen, *Org. Lett.* **2007**, *9*, 3671 – 3674; for the pioneering proline-catalyzed α-amination of aldehydes, see: b) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem.* **2002**, *114*, 1868 – 1871; *Angew. Chem. Int. Ed.* **2002**, *41*, 1790 – 1793; c) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656 – 5657; for proline-catalyzed α-amination of ketones, see: d) N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254 – 6255.

[66] P. Kwiatkowski, T. D. Beeson, J. C. Conrad, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 1738 – 1741.

[67] a) M. Marigo, D. Fielenbach, A. Braunton, A. Kjærsgaard, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 3769 – 3772; *Angew. Chem. Int. Ed.* **2005**, *44*, 3703 – 3706; b) D. D. Steiner, N. Mase, C. F. Barbas III, *Angew. Chem.* **2005**, *117*, 3772 – 3776; *Angew. Chem. Int. Ed.* **2005**, *44*, 3706 – 3710; c) T. D. Beeson, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 8826 – 8828. The best result in the α-fluorination of cyclohexanone using chiral secondary amines (4-hydroxyproline) led to 56% yield and 34% *ee*, see: d) D. Enders, M. R. M. Hüttl, *Synlett* **2005**, 991 – 993.

[68] a) A. M. Thayer, *Chem. Eng. News* **2006**, *84*, 15 – 24; b) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881 – 1886; c) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359 – 4369.

[69] a) O. Lifchits, N. Demoulin, B. List, *Angew. Chem.* **2011**, *123*, 9854 – 9857; *Angew. Chem. Int. Ed.* **2011**, *50*, 9680 – 9683; for the pioneering contribution on the α-benzoyloxylation of aldehydes under secondary aminocatalysis: b) T. Kano, H. Mii, K. Maruoka, *J. Am. Chem. Soc.* **2009**, *131*, 3450 – 3451. For a recent Review of organocatalyzed asymmetric α-oxygenation of carbonyls, see: c) T. Vilaivan, W. Bhanthumnavin, *Molecules* **2010**, *15*, 917 – 958.

[70] Reviews on cascade reactions: a) L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**; b) Special Issue on: Rapid Formation of Molecular Complexity in Organic Synthesis: E. J. Sorensen, H. M. L. Davies, *Chem. Soc. Rev.* **2009**, *38*, 2969 – 3276; Reviews on organocascade reactions: c) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167 – 178; d) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590 – 1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570 – 1581; e) A. M. Walji, D. W. C. MacMillan, *Synlett* **2007**, 1477 – 1489.

[71] In addition to creating multiple stereocenters in a one-step process, the combination of multiple asymmetric transformations in a cascade sequence also imparts increased enantiomeric excess to the final product when compared to the corresponding discrete transformations. The Horeau principle provides the mathematical foundation for rationalizing the enantioenrichment observed along successive cascade cycles. J. P. Vigneron, M. Dhaenens, A. Horeau, *Tetrahedron* **1973**, *29*, 1055 – 1059.

[72] X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6070 – 6071.

[73] a) F. Pesciaioli, F. De Vincentiis, P. Galzerano, G. Bencivenni, G. Bartoli, A. Mazzanti, P. Melchiorre, *Angew. Chem.* **2008**, *120*, 8831 – 8834; *Angew. Chem. Int. Ed.* **2008**, *47*, 8703 – 8706; b) F. De Vincentiis, G. Bencivenni, F. Pesciaioli, A. Mazzanti, G. Bartoli, P. Galzerano, P. Melchiorre, *Chem. Asian J.* **2010**, *5*, 1652 – 1656.

[74] J. Lv, J. Zhang, Z. Lin, Y. Wang, *Chem. Eur. J.* **2009**, *15*, 972 – 9779.

[75] a) *Aziridines and Epoxides in Organic Synthesis* (Ed.: A. Yudin), Wiley-VCH, New York, **2006**. For a synthetically relevant application of cinchona amine-catalyzed epoxidation and aziridination, see: b) H. Jiang, N. Holub, K. A. Jørgensen, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20630 – 20635.

[76] a) Q. Cai, C. Zheng, J.-W. Zhang, S.-L. You, *Angew. Chem.* **2011**, *123*, 8824 – 8828; *Angew. Chem. Int. Ed.* **2011**, *50*, 8665 – 8669; for a pioneering contribution of organocascade catalysis based on the trapping of the indolinium ion intermediate, see: b) J. F. Austin, S. G. Kim, C. J. Sinz, W. J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482 – 5487.

[77] The use of secondary amine catalysis to promote the stereoselective Diels–Alder reactions of enones as dienes via the transient formation of dienamine **n** was pioneered by Barbas: this is why intermediate **n** is known as the "Barbas' dienamine": a) R. Thayumanavan, B. Dhevalapally, K. Sakthivel, F. Tanaka, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 3817 – 3820; b) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Angew. Chem.* **2003**, *115*, 4365 – 4369; *Angew. Chem. Int. Ed.* **2003**, *42*, 4233 – 4237. See also: c) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962 – 5963; d) H. Sundén, R. Rios, Y. Xu, L. Eriksson, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 2549 – 2555.

[78] L.-Y. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7332 – 7335; *Angew. Chem. Int. Ed.* **2009**, *48*, 7196 – 7199.

[79] Conclusive evidence supporting a [4+2] cycloaddition reaction or a stepwise double Michael addition sequence has not been provided.

[80] G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7336 – 7339; *Angew. Chem. Int. Ed.* **2009**, *48*, 7200 – 7203.

[81] a) S. Kotha, A. C. Deb, K. Lahiri, E. Manivannan, *Synthesis* **2009**, 165 – 193, and references therein; b) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902 – 8912; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748 – 8758.

[82] The rationale behind the secondary amine-based approach arises from the spectacular studies on the triple organocascade, see: a) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861 – 863. For a different approach to spirooxindoles using cinchona-based amine catalyst, see: b) L.-L. Wang, L. Peng, J.-F. Bai, Q.-C. Huang, X.-Y. Xu, L.-X. Wang, *Chem. Commun.* **2010**, *46*, 8064 – 8066.

[83] Iminium ion activation of α-acyloxy acroleins using chiral primary amines has been used to design a stereoselective Diels–Alder process, see Ref. [44a]. For a more recent example, see: a) T. Kano, Y. Tanaka, K. Osawa, T. Yurino, K. Maruoka, *Chem. Commun.* **2009**, 1956 – 1958. Metal-mediated activation of α-branched unsaturated compounds is generally based on the use of bidentate chelating carbonyl compounds: see for example: b) M. P. Sibi, J. Coulomb, L. M. Stanley, *Angew. Chem.* **2008**, *120*, 10061 – 10063; *Angew. Chem. Int. Ed.* **2008**, *47*, 9913 – 9915, and references therein.

[84] P. Galzerano, F. Pesciaioli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 8032 – 8034; *Angew. Chem. Int. Ed.* **2009**, *48*, 7892 – 7894.

[85] O. Lifchits, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2010**, *132*, 10227 – 10229.

[86] a) E. Knoevenagel, *Chem. Dtsch. Ber. Ges.* **1894**, *27*, 2345 – 2346; b) A. Lee, A. Michrowska, S. Sulzer-Mosse, B. List, *Angew. Chem.* **2011**, *123*, 1745 – 1748; *Angew. Chem. Int. Ed.* **2011**, *50*, 1707 – 1710.

[87] For Reviews on vinylogous processes, see: a) G. Casiraghi, F. Zanardi, G. Appendino, G. Rassu, *Chem. Rev.* **2000**, *100*, 1929 – 1972; b) S. E. Denmark, J. R. Heemstra, Jr., G. L. Beutner, *Angew. Chem.* **2005**, *117*, 4760 – 4777; *Angew. Chem. Int. Ed.*

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2005, *44*, 4682 – 4698. For a catalytic asymmetric γ-functionalization of furanones by a direct vinylogous Michael addition: c) B. M. Trost, J. Hitche, *J. Am. Chem. Soc.* **2009**, *131*, 4572 – 4573. For a potentially general method based on nucleophilic phosphine catalysis, see: d) Y. Fujiwara, J. Sun, G. C. Fu, *Chem. Sci.* **2011**, *2*, 2196 – 2198, and references therein.

[88] a) S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973 – 12980. For other examples of dienamine catalysis by secondary amines: b) R. M. de Figueiredo, R. Fröhlich, M. Christmann, *Angew. Chem.* **2008**, *120*, 1472 – 1475; *Angew. Chem. Int. Ed.* **2008**, *47*, 1450 – 1453; c) K. Liu, A. Chougnet, W.-D. Woggon, *Angew. Chem.* **2008**, *120*, 5911 – 5913; *Angew. Chem. Int. Ed.* **2008**, *47*, 5827 – 5829. For a Review: d) D. B. Ramachary, Y. V. Reddy, *Eur. J. Org. Chem.* **2012**, 865 – 887.

[89] A major problem with dienamine catalysis by secondary amines is the site selectivity: proline and its derivatives can activate γ-enolizable unsaturated aldehydes toward the formation of the dienamine intermediate, but generally promote a α-site selective alkylation step by enamine catalysis in the presence of suitable electrophiles: a) N. Utsumi, H. Zhang, F. Tanaka, C. F. Barbas III, *Angew. Chem.* **2007**, *119*, 1910 – 1912; *Angew. Chem. Int. Ed.* **2007**, *46*, 1878 – 1880; b) B. Han, Y.-C. Xiao, Z.-Q. He, Y.-C. Chen, *Org. Lett.* **2009**, *11*, 4660 – 4663.

[90] G. Bencivenni, P. Galzerano, A. Mazzanti, G. Bartoli, P. Melchiorre, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20642 – 20647.

[91] The regiocontrolled formation of the extended dienamine **t** finds support upon related enolization studies demonstrating that, under certain conditions, the selective formation of the thermodynamic *exo*-cyclic enolate of type **t** is strongly favored over both the *endo*-isomer and the kinetic cross-conjugated dienolate. This inherent behavior of β-substituted cyclohexenones has found a wonderful application in the direct, vinylogous aldol reaction, see: S. Saito, M. Shiozawa, M. Ito, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 813 – 814. In analogy with the report by Yamamoto and co-workers, the complete γ-site selectivity induced by the amine **V** may arise from catalyst steric effects, which inhibit base deprotonation at the α′ position, while thermodynamic factors account for the formation of the reactive *exo*-dienamine **t**.

[92] a) D.-Q. Xu, A.-B. Xia, S.-P. Luo, J. Tang, S. Zhang, J.-R. Jiang, Z.-Y. Xu, *Angew. Chem.* **2009**, *121*, 3879 – 3882; *Angew. Chem. Int. Ed.* **2009**, *48*, 3821 – 3824. See also: b) G. N. Stowe, K. D. Janda, *Tetrahedron Lett.* **2011**, *52*, 2085 – 2087.

[93] G. Bergonzini, S. Vera, P. Melchiorre, *Angew. Chem.* **2010**, *122*, 9879 – 9882; *Angew. Chem. Int. Ed.* **2010**, *49*, 9685 – 9688.

[94] The in situ formation under acidic conditions of stabilized benzhydryl carbocation from **33** has been used for the α-alkylation of aldehydes by enamine catalysis: a) P. G. Cozzi, F. Benfatti, L. Zoli, *Angew. Chem.* **2009**, *121*, 1339 – 1342; *Angew. Chem. Int. Ed.* **2009**, *48*, 1313 – 1316; for related studies: b) R. R. Shaikh, A. Mazzanti, M. Petrini, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2008**, *120*, 8835 – 8838; *Angew. Chem. Int. Ed.* **2008**, *47*, 8707 – 8710; c) A. R. Brown, W.-H. Kuo, E. N. Jacobsen, *J. Am. Chem. Soc.* **2010**, *132*, 9286 – 9288.

[95] Chiral secondary amine catalysis has been used in the γ-alkylation of α-unbranched enals, see: J. Stiller, E. Marqués-López, R. P. Herrera, R. Fröhlich, C. Strohmann, M. Christmann, *Org. Lett.* **2011**, *13*, 70 – 73.

[96] X.-F. Xiong, Q. Zhou, J. Gu, L. Dong, T.-Y. Liu, Y.-C. Chen, *Angew. Chem.* **2012**, *124*, 4477 – 4480; *Angew. Chem. Int. Ed.* **2012**, *51*, 4401 – 4404.

[97] For a chiral auxiliary-controlled asymmetric tandem sulfa-Michael/Meerwein-Ponndorf-Verley reduction of α-branched enones, see: a) K. Nishide, M. Ozeki, H. Kunishige, Y. Shigeta, P. K. Patra, Y. Hagimoto, M. Node, *Angew. Chem.* **2003**, *115*, 4653 – 4655; *Angew. Chem. Int. Ed.* **2003**, *42*, 4515 – 4517. For a Review on sulfa-Michael reactions, see: b) D. Enders, K. Lüttgen, A. Narine, *Synthesis* **2007**, 959 – 980.

[98] For strategies based on the contemporary use of two specific cyclic 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, *Angew. Chem.* **2009**, *121*, 4413 – 4417; *Angew. Chem. Int. Ed.* **2009**, *48*, 4349 – 4353; b) Y. Chi, S. T. Scroggins, J. M. J. Fréchet, *J. Am. Chem. Soc.* **2008**, *130*, 6322 – 6323.

[99] Further detailed investigations are required to understand the origin of the diastereo-switching behavior. Present observations detailed in Ref. [32] are consistent with the fact that the conformational flexibility of amine **VI** and the use of structurally different counteranions provide distinct chiral environments in which the enantioselective SMA reaction can take place.

[100] R. R. Knowles, E. N. Jacobsen, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20678 – 20685.

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