P. Melchiorre, M. Marigo et al.

DOI: 10.1002/anie.200705523

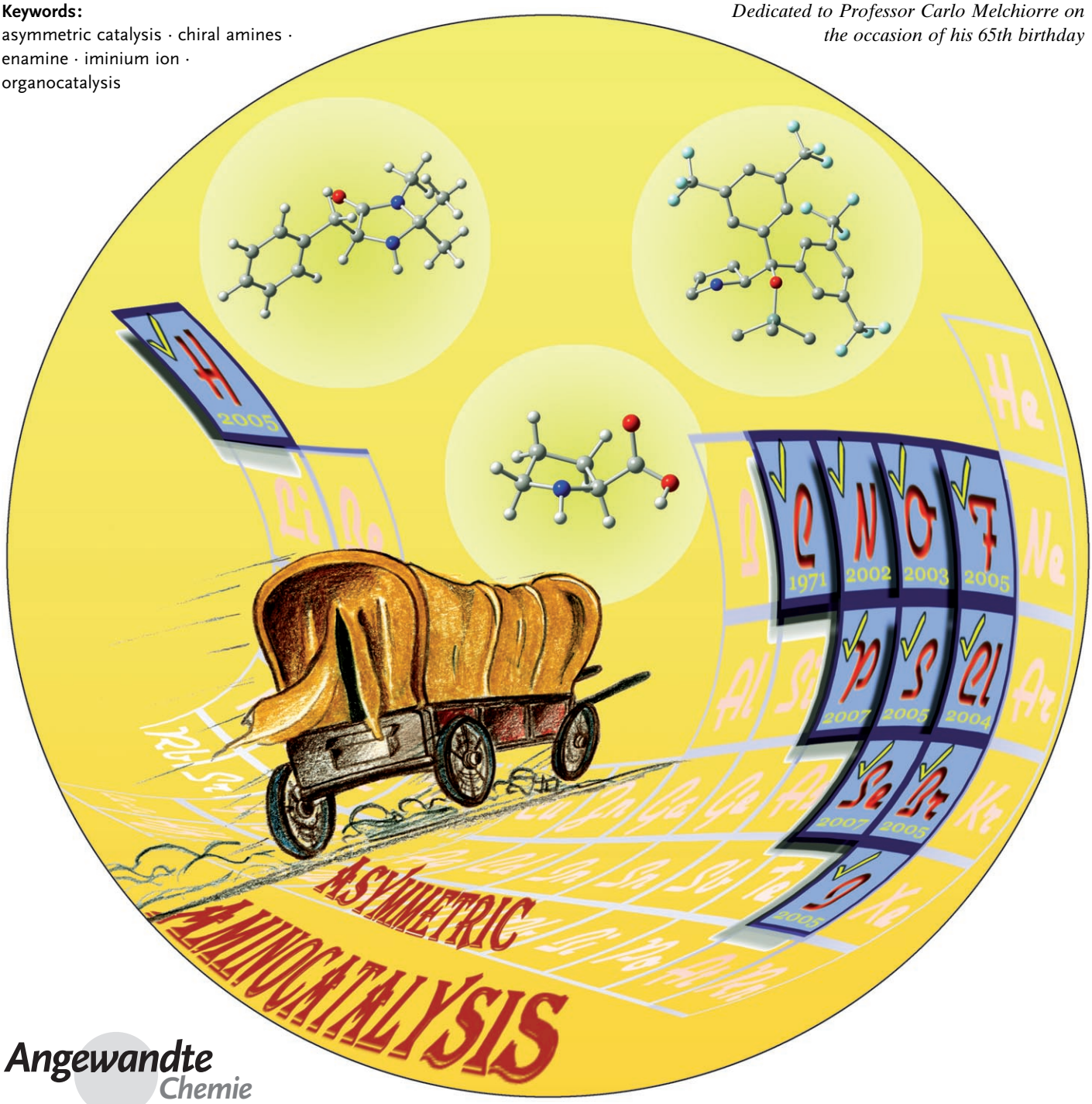
Organocatalysis

Asymmetric Aminocatalysis—Gold Rush in Organic Chemistry

Paolo Melchiorre, Mauro Marigo,* Armando Carlone, and Giuseppe Bartoli*

Keywords:
asymmetric catalysis · chiral amines · enamine · iminium ion · organocatalysis

Dedicated to Professor Carlo Melchiorre on the occasion of his 65th birthday



Catalysis with chiral secondary amines (asymmetric aminocatalysis) has become a well-established and powerful synthetic tool for the chemo- and enantioselective functionalization of carbonyl compounds. In the last eight years alone, this field has grown at such an extraordinary pace that it is now recognized as an independent area of synthetic chemistry, where the goal is the preparation of any chiral molecule in an efficient, rapid, and stereoselective manner. This has been made possible by the impressive level of scientific competition and high quality research generated in this area. This Review describes this "Asymmetric Aminocatalysis Gold Rush" and charts the milestones in its development. As in all areas of science, progress depends on human effort.

From the Contents

1. Introduction

Nowadays, asymmetric organocatalysis is recognized as an efficient and reliable strategy for the stereoselective preparation of valuable chiral compounds.[1] The use of purely organic molecules as chiral catalysts complements the traditional organometallic and biological approaches to asymmetric catalysis, thus enabling synthetic chemists to move closer to being able to construct any chiral scaffold in an efficient, rapid, and stereoselective manner. Asymmetric organocatalysis offers alternatives to the activation of substrates, and can deliver unique, orthogonal, or complementary selectivities compared to metal-catalyzed processes. In addition, it offers some attractive benefits: The metal-free organic catalysts are generally nontoxic, readily available, and stable. These properties allow most reactions to be performed in wet solvent and in air, which increases the reproducibility and operational simplicity.

Asymmetric organocatalysis is impressive because of its synthetic utility and because it gained its prominent role in such a short period of time: from 2000 to now! Although it was known for a long time that chiral small organic molecules were able to promote different transformations in a stereoselective fashion, it was not until two seminal reports by List, Lerner, and Barbas,[2] and MacMillan and co-workers on catalysis by chiral secondary amines[3] that the potential of this approach was realized. Following these publications, numerous high quality studies on catalysis by chiral secondary amines (asymmetric aminocatalysis) were reported.[4] This was quickly extended to different organocatalytic activation concepts,[5–7] and the "asymmetric aminocatalysis gold rush" was on.

"The California Gold Rush (1848–1855) began on January 24, 1848, when gold was discovered at Sutter's Mill. As news of the discovery spread, some 300000 people came to California from the rest of the United States and abroad. While most of the newly arrived were Americans, the Gold Rush also attracted tens of thousands from Latin America, Europe, Australia, and Asia. At first, the prospectors retrieved the gold from streams and riverbeds using simple techniques, such as panning, and later developed more sophisticated methods of gold recovery that were adopted around the world."

This excerpt[8] about the California Gold Rush could also describe the development of asymmetric aminocatalysis. The "asymmetric aminocatalysis gold rush" was started by a few leading research groups. Now, thousands of researchers from academia and the chemical industry are involved in this field. As a result, new ideas, new approaches, and creative thinking have flowed freely, substantially raising the level of quality.

Instead of providing an exhaustive list of catalysts and reactions, this Review aims to critically describe the developments achieved in the last eight years, charting the ideas, challenges, and milestone reactions that were essential for the progress of the field. It is remarkable how, whenever this stream of innovation seemed to lose momentum, a new breakthrough reaction was disclosed. A large number of challenging concepts were developed independently (and almost simultaneously) by different research groups. This developed into tremendous scientific competition which has guided asymmetric aminocatalysis towards excellent levels of development, and opened up new synthetic opportunities that were considered inaccessible only a few years before. This "aminocatalytic gold rush" emphasizes a general aspect of science: progress depends on human effort.

Undoubtedly, we are not at the end of the story, and asymmetric aminocatalysis will be further developed in the

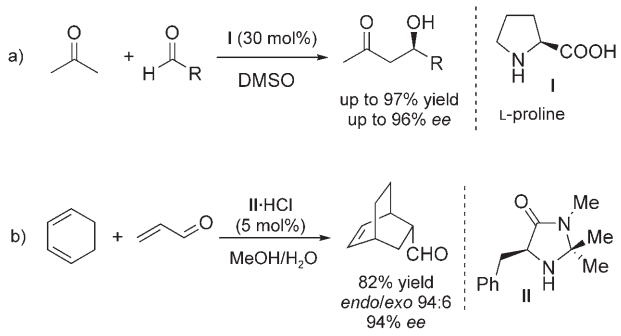
[*] Dr. P. Melchiorre, A. Carlone, Prof. G. Bartoli
Department of Organic Chemistry "A. Mangini"
Alma Mater Studiorum—Università di Bologna
Viale Risorgimento 4, 40136 Bologna (Italy)
Fax: (+39) 051-209-3654
E-mail: p.melchiorre@unibo.it
Dr. M. Marigo
Nuevolution A/S
Rønnegade 8, 2100 Copenhagen (Denmark)
E-mail: marigoma@libero.it

near future. Thus, we will discuss possible future challenges and describe some of the new research lines arising from the latest studies, such as dienamine activation and singly occupied molecular orbital (SOMO) catalysis.

2. Activation Modes in Aminocatalysis

In 2000, two seminal reports established the possibility of employing simple, chiral cyclic secondary amines to efficiently catalyze the asymmetric functionalization of carbonyl compounds. List, Lerner, and Barbas reported that a catalytic amount of the proteinogenic amino acid L-proline (**I**) was able to promote the enantioselective direct aldol reaction between an unmodified ketone, such as acetone, and a variety of aldehydes (Scheme 1 a).[2] Soon after this publication, MacMillan and co-workers described the first amine-catalyzed asymmetric Diels–Alder reaction, and demonstrated the effectiveness of the newly designed imidazolidinone catalyst (**II**) in the activation of α,β-unsaturated aldehydes (Scheme 1 b).[3]

Besides offering alternative asymmetric and catalytic methods for two fundamental C–C bond-forming reactions, these studies constituted the basis for two novel organocatalytic activation modes of carbonyl compounds, thereby establishing the origin of asymmetric aminocatalysis. Both activation modes were based on covalent active intermediates generated by the condensation of chiral cyclic amines with a carbonyl group. The principle for aminocatalytic activation emulates the mechanism of the activation of carbonyl compounds by Lewis acids. This is a well-established strategy



Scheme 1. a) Proline-catalyzed intermolecular aldol reaction between acetone (donor) and aldehydes (acceptors). b) Imidazolidinone **II** catalyzed asymmetric Diels–Alder reaction.

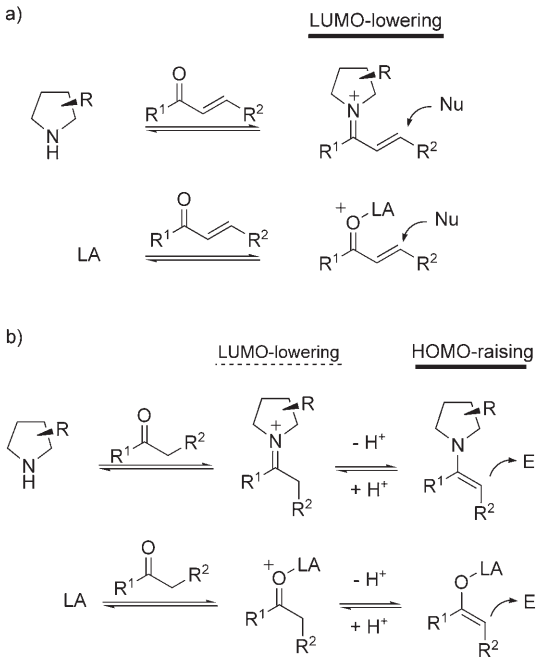
for enantioselective catalysis, in which rate acceleration occurs through the reversible binding of the Lewis acid to isolated or conjugated π systems, thereby resulting in an redistribution of the electronic density toward the positively charged metal center (Scheme 2). The reversible condensation of a chiral secondary amine with carbonyl compounds to form positively charged iminium ion intermediates mimics the electronic situation of the π orbitals in Lewis acid catalysis. Thus, the energy of the lowest unoccupied molecular orbital (LUMO) of the system is effectively lowered. For conjugated π systems, the electronic redistribution induced by the iminium intermediates facilitates nucleophilic additions, including conjugate additions and pericyclic reactions (LUMO activation). In the case of isolated π systems, the lowering of the LUMO energy increases the acidity of the

Paolo Melchiorre was born in 1973 in Camerino (Italy). He completed his PhD in Chemistry (2003) at Bologna University under the supervision of Prof. Achille Umani-Ronchi. After research with Prof. Karl Anker Jørgensen at the Center for Catalysis, Aarhus University (Denmark), he joined the research group of Prof. Giuseppe Bartoli at Bologna University, where he is currently an Assistant Professor. He was the recipient of the "G. Ciamician" Medal awarded by the Italian Chemical Society (2007). His interests focus on the discovery and mechanistic elucidation of new asymmetric organocatalytic processes.

Armando Carlone was born in Campobasso (Italy) in 1979. In 2000 he spent one year at the University of Utrecht (The Netherlands) working on colloids. In 2003 he stayed at Paris VI-Jussieu (France) working on organometallic compounds. In 2003 he completed his MSc in Industrial Chemistry in Bologna under the supervision of Prof. Alfredo Ricci. In 2005 he started PhD research on asymmetric organocatalysis at the University of Bologna under the supervision of Prof. Giuseppe Bartoli and Dr. Paolo Melchiorre. In 2006 he spent nine months in Aarhus (Denmark) in Prof. Karl Anker Jørgensen's research group.

Mauro Marigo was born in Sacile (Italy) in 1975. He received his MSc in 2001 from Trieste University under the supervision of Dr. Erica Farnetti. In 2001 he moved to Aarhus University (Denmark), and in 2005 obtained his PhD under the supervision of Prof. Karl Anker Jørgensen. From 2004 to 2006 he was actively involved in the field of organocatalysis. He currently works for Nuevolution A/S in Copenhagen (Denmark).

Giuseppe Bartoli graduated from the University of Bologna in 1967 with a Laurea in Industrial Chemistry. He was Assistant Professor of Organic Chemistry at the University of Bari (Italy) from 1968, then moved to the University of Bologna (Italy) as Associate Professor, and then to the University of Camerino in 1986 as Full Professor. In 1993 he returned to the University of Bologna where he is currently Professor of Organic Chemistry. From 2001 to 2007, he was Head of the Department of Organic Chemistry "A. Mangini".



Scheme 2. Comparison of the activation of carbonyl compounds by a Lewis acids (LA) and by aminocatalysis. E = electrophiles, Nu = nucleophiles.

α proton. This induces a fast deprotonation, which leads to the generation of the enamine—a nucleophilic enolate equivalent (HOMO activation). Here too, the raising of the energy of the highest occupied molecular orbital (HOMO) leads to activation of the carbonyl compounds, similar to the generation of activated nucleophiles by Lewis acids.

The potential of asymmetric aminocatalysis for the highly enantioselective functionalization of a broad range of carbonyl compounds was quickly recognized and stimulated a massive growth of interest and competition.

By exploiting the HOMO-raising activation pathway (enamine catalysis),[9] a vast number of α-functionalizations of aldehydes and ketones with carbon- and heteroatom-based electrophilic reagents has been accomplished.[10] The LUMO-lowering approach (iminium ion catalysis)[9] enabled the asymmetric introduction of several nucleophiles to the β position of unsaturated aldehydes and ketones (Figure 1).[11] Two new methods for the enantioselective functionalization of carbonyl compounds have recently been described: Dienamine catalysis accounts for the γ-functionalization of α,β-unsaturated aldehydes, which proceeds by reaction of the electron-rich dienamine intermediate with electrophilic dienophiles.[12] A fourth aminocatalytic pathway involves the formation of a single unpaired electron in the activated enamine intermediate (SOMO catalysis).[13] The use of all these aminocatalytic strategies has enabled chemists to stereoselectively incorporate all the non-inert "nonmetals" into carbonyl compounds. At present, aminocatalysis is considered a well-established and reliable tool in asymmetric synthesis.

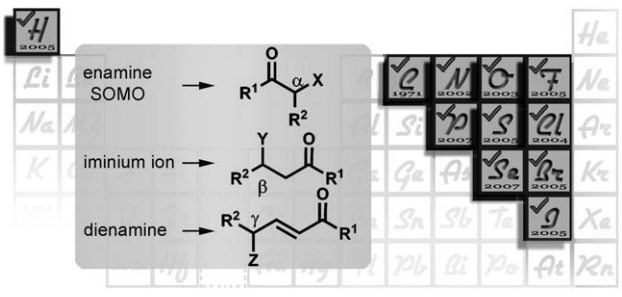


Figure 1. Asymmetric aminocatalytic reaction pathways.

3. Proline Catalysis

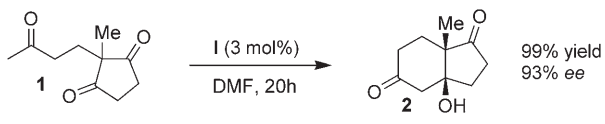
> *"…quegli che pigliavano per altore altro che la natura, maestra de' maestri, s'affaticavano invano.."*
> *"...those who took inspiration from anywhere but nature, master of masters, were laboring in vain..."*
> Leonardo da Vinci (1500)[14]

Nature has inspired scientists for millennia, offering them the necessary tools to accomplish their goals. Natural molecules provide chemists with a nearly limitless fount of stereochemically defined complex architectures, and we can learn much from nature in regard to asymmetric synthesis: enzymatic catalysis promotes stereoselective processes with very high fidelity.

In proline catalysis,[15] a simple natural amino acid efficiently imitates the concept of enzymatic catalysis. Proline catalysis has been developed extensively and with such impressive results that proline has been considered the "simplest enzyme" in nature.[16]

3.1. Lessons from Nature

List, Lerner, and Barbas[2] established proline as an efficient catalyst for the asymmetric intermolecular aldol reaction (Scheme 1 a) and provided the prototype reaction for enamine-centered asymmetric catalysis. Their seminal discovery stems from two fundamental observations from different chemical areas: organic and biochemistry.[4g] The pioneering research by Hajos, Parrish, Eder, Sauer, and Wiechert in the early 1970s on the proline-catalyzed intramolecular aldol cyclization of triketone **1**[17] (Scheme 3) first showed the potential for a simple natural molecule to act as a highly enantioselective chiral catalyst for a fundamental chemical transformation. Hajos and Parrish interpreted their results as "a simplified model of a biological system in which (*S*)-proline plays the role of an enzyme".[17d] They advanced two possible mechanisms, one of which was based on a postulated



Scheme 3. The Hajos–Parrish–Eder–Sauer–Wiechert reaction.[17]

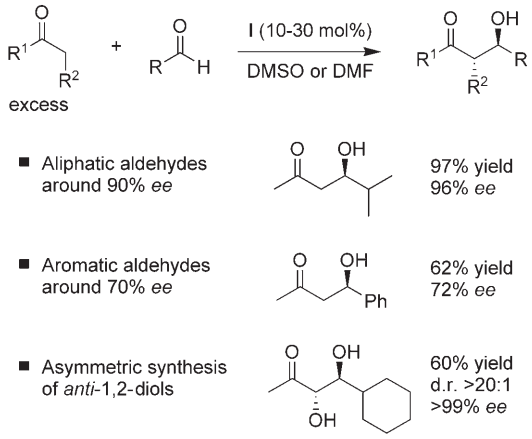
enamine intermediate as the nucleophilic counterpart.[18] However, the great potential of this discovery was not realized by the chemical community for 30 years.

The second series of studies dates to the late 1990s. The research group of Lerner and Barbas was involved in the design of catalysts for aldolase antibodies that were able to promote intermolecular aldol reactions by a chemical mechanism analogous to that employed by the natural Type I aldolase enzymes.[19] These enzymes use an enamine-based mechanism to catalyze the direct aldolization of two unmodified carbonyl compounds.[20] Their studies were aimed at expanding the scope and versatility of aldolase enzymes, while preserving their exceptional catalytic efficiency. During these studies, they found that the aldolase antibody 38C2 was an effective catalyst for enantiodifferentiating aldol cyclodehydration reactions, including the Hajos–Parrish–Eder–Sauer–Wiechert reaction.[21]

These findings highlighted a close mechanistic analogy between proline- and enzyme-catalyzed aldol reactions, with the enamine activation being at the heart of both strategies. They thus suggested the potential employment of proline as a catalyst for the direct asymmetric intermolecular aldolization of unmodified carbonyl compounds—the actual aldolase reaction.

3.2. The Mechanism of Proline-Catalyzed Aldolization

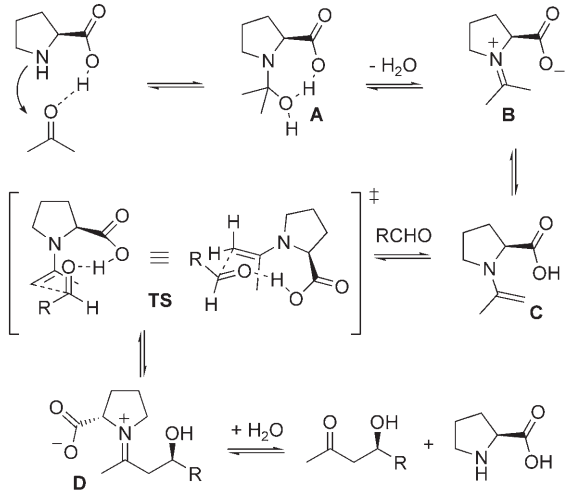
The proline-catalyzed asymmetric intermolecular aldol reaction with aldehyde acceptors was successfully extended to different types of ketone donors, including cyclic substrates (Scheme 4).[22]



Scheme 4. The proline-catalyzed intermolecular aldol reaction of unmodified ketones with aldehydes.

The use of an excess of the ketone component allows the isolation of the cross-aldol products in good yields and high enantiomeric excess (*ee*). The enantioselectivity depends on the nature of aldehydic substituents: aromatic aldehydes give around 70% *ee*, whereas branched substituents give greater than 90% *ee*. Guided by studies initially performed with aldolase antibodies[21b] and by the mechanistic parallel with proline, the use of hydroxyacetone as a donor for the highly diastereo- and enantioselective proline-catalyzed addition to aldehydes was next investigated.[22b,c] This powerful procedure furnishes synthetically useful *anti*-1,2-diols, which complement the Sharpless *syn*-dyhydroxylation of these important building blocks.

From a mechanistic standpoint, the proline-catalyzed intermolecular aldol reaction of acetone with a variety of aldehydes proceeds through an enamine-based mechanism,[22b,c] as summarized in Scheme 5. The high levels of



Scheme 5. The proposed mechanism for the direct asymmetric intermolecular aldolization of acetone. The transition state contains a single proline molecule.

reactivity and selectivity induced by proline stem from the simultaneous exploitation of both amino acid functionalities. Primarily, the nucleophilicity associated with the nitrogen atom of the pyrrolidine portion of proline facilitates the condensation with a carbonyl substrate. This yields a tetrahedral carbinolamine intermediate **A** which then collapses to an electrophilic iminium ion **B**. Although this intermediate can be susceptible to nucleophilic attack, it can also evolve to a nucleophilic enamine intermediate **C** through an α-deprotonation step. This last process mimics the condensation of the active-site lysine residue with a carbonyl substrate in Type I aldolases. The carboxylic acid moiety of the enamine intermediate can then direct the approach of the electrophilic carbonyl group through formation of a specific hydrogen bond. This provides both preorganization of the substrates in a highly structured transition state **TS** and stabilization of the forming alkoxyde. The crucial formation of the enamine aldol bond occurs together with hydrogen transfer from the carboxylic acid,[23] which is *anti* to the *E*-enamine double bond, and actually controls the facial selectivity of the process. The aldehyde acceptor is attacked on the *Re* face to place the aldehydic substituent R in a pseudoequatorial arrangement. The resulting iminium ion **D** is then hydrolyzed to release the desired aldol product and the proline, which can proceed in another catalytic cycle. This type of transition state

involves a single proline at the carbon–carbon bond-forming step and is based on the formation of an enamine intermediate. It is closely related to the mechanism of enzymatic aldol catalysis, and it has been widely supported by experimental evidence[24] and theoretical investigations.[25]

Recent studies have elucidated the role of water in proline-mediated aldol reactions. Although water suppresses the formation of the active enamine intermediate through Le Chatelier's principle, its presence also increases the total concentration of the catalyst, thereby reducing parasitic equilibria and the consequent proline degradation pathways. The net effects of such complex and dichotomic roles of water in aldol transformations are strictly dependent on the reaction conditions and on the nature of the reactants employed.[26]

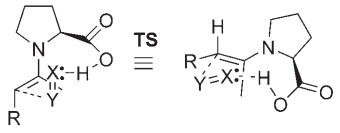
Interestingly, the mechanism of the intermolecular aldolization involving one proline molecule is not consistent with the formerly accepted mechanism of the Hajos–Parrish–Eder–Sauer–Wiechert reaction advanced by Agami and co-workers. To account for the weak nonlinear effect and concentration-dependent stereoselectivity observed, they proposed the involvement of two proline molecules in the transition state of the intramolecular aldol reaction.[27] Importantly, these observations prompted Kagan and co-workers to include this example in their seminal report on the nonlinear correlation in asymmetric catalysis between the enantiomeric excess of the catalyst and the enantiopurity of the product.[28] The apparent discrepancy was resolved by experiments carried out by Houk, List, and colleagues, which revealed a linearity between the enantiomeric excess of the proline catalyst and the product in both intra- and intermolecular aldolizations.[29] At the time, the differences observed in the two studies was explained by the fact that Agami's experiment was based on only five data points and on optical rotation measurements, a relatively inaccurate method compared to HPLC analysis on a chiral stationary phase.[29]

Further investigations by Blackmond and co-workers on proline-catalyzed aldol reactions revealed a more complex behavior.[30] It was found that the optical purity of the aldol product is largely independent of the *ee* value of the proline when a high catalyst concentration is used, so that the dissolved proline is in equilibrium with the solid proline. For such a scalemic system, the solution composition at the eutectic point is fixed and the *ee* value of dissolved proline in DMSO is about 50%, regardless of the overall *ee* value of the proline employed. This type of solid–liquid phase behavior, which is common to many proteinogenic amino acids, constitutes a new and efficient mechanism that gives rise to asymmetric amplification. It thus supports the idea that catalysis by amino acids may have played a role in the prebiotic evolution of homochirality (see also Section 7.1).[31] Further studies on nonlinear effects arising from physical phase behavior led Blackmond and co-workers to introduce "the concept of a kinetic conglomerate phase [that] can rationalize the findings of Kagan and co-workers in a manner that remains compatible with the currently accepted one-proline reaction mechanism and reconciles reports of both linearity and nonlinearity" of proline-catalyzed aldolization.[32] This behavior, which has deep implications for the interpretation of nonlinear effects in mixed-phase systems, depends on the temporal evolution of the *ee* value of the catalyst in solution and is sensitive to factors such as mixing times and water content.

Significantly, all the above experimental and theoretical studies[33] support a unified mechanism of intra- and intermolecular proline-catalyzed aldolization. Understanding enamine catalysis was essential to expanding the asymmetric proline catalysis beyond nature's aldol transformations by replacing the aldehydic counterpart with diverse electrophilic components.

3.3. Proline in Action

Extensive mechanistic investigations of proline-catalyzed aldol reactions have demonstrated that the formation of a carbon–carbon bond requires both the enamine intermediate and proton transfer from the proline carboxylic acid to the forming alkoxyde. As well as providing electrophilic activation and stabilization of the transition state (**TS**), this specific hydrogen-bonding interaction determines the stereoselectivity of the process by directing the electrophile approach from the upper face of the enamine. This bifunctional activation by



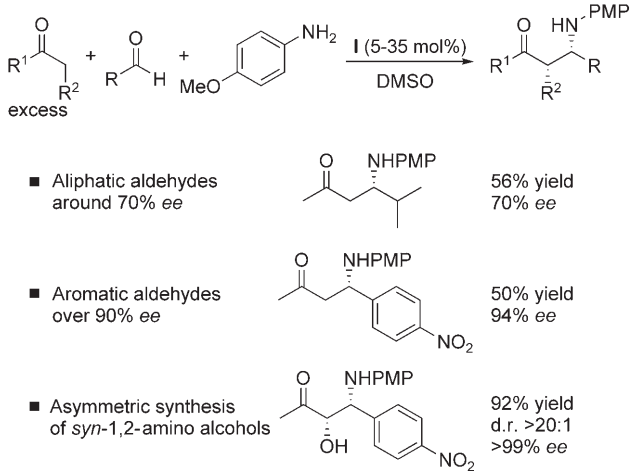
proline might be extended to electrophilic substrates with a basic lone pair of electrons that can efficiently interact with the carboxylic moiety of proline. This condition is generally found in electrophilic substrates Y=X that have a lone pair of electrons centered on the heteroatom X of a double bond.

The intriguing prospect arose that the applicability of proline catalysis may be far more general than originally thought. Catalytic amounts of proline could be used to generate enamines as chiral enolate equivalents, which could then react with a series of different electrophiles. It would thus be possible to access stereochemically complex molecules from simple, unmodified, and readily available precursors by employing operationally simple procedures. These ideas greatly increased the interest in proline catalysis and prompted the start of a remarkable competition.

3.4. The "Proline Gold Rush"

3.4.1. Beyond Aldol Reactions

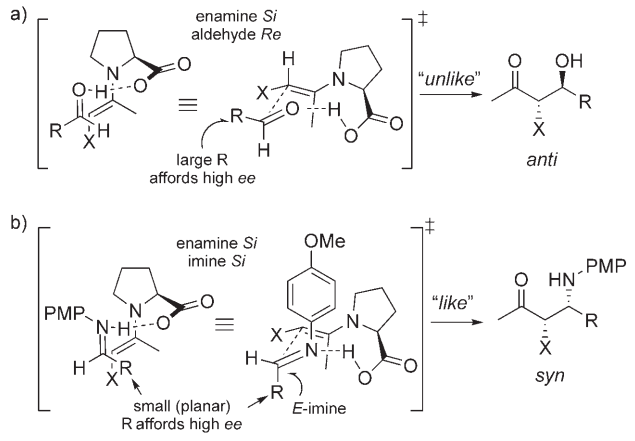
Following the studies on the proline-catalyzed intermolecular asymmetric aldolization, List applied the enamine activation strategy to realize the first, direct, catalytic, and asymmetric Mannich reaction between an aldehyde, *p*-anisidine, and a ketone, without prior formation of an enolate or imine (Scheme 6).[34] The Mannich reaction constitutes one of the most powerful organic transformations for the construction of chiral nitrogen-containing molecules.[35] In addi-



Scheme 6. The proline-catalyzed asymmetric Mannich reaction. PMP = *p*-methoxy phenyl.

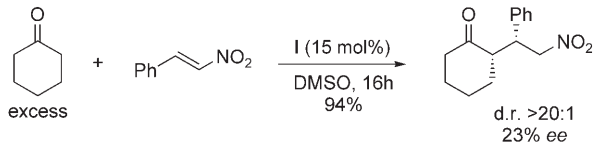
tion to its synthetic value, this organocatalytic approach established the possibility of using electrophiles other than aldehydes, and thus represents a cornerstone in the area of proline catalysis. Under the mild conditions of proline catalysis, which allows the in situ generation of the imine, the direct three-component Mannich reaction of various ketones has been accomplished to furnish the desired products in high yield and enantioselectivity: the aldol derivatives were not detected. Notably, the use of α-oxygenated ketones results in complete regioselectivity for the hydroxy-substituted alkyl chain, and allows the highly chemo-, diastereo-, and enantioselective synthesis of *syn*-1,2-amino alcohols.[34b]

An intriguing aspect of the proline-catalyzed Mannich reaction concerns the reversal of the observed diastereo- and enantioselectivity with respect to aldol reactions (Scheme 7). While the facial selectivity of the enamine (*Si* when X is of highest priority) is common to both transformations, the facial selectivity of the electrophile is opposite, thereby resulting in "*like*" topicity for the Mannich reaction and in "*unlike*" topicity for aldolization (Scheme 7). The discordant stereochemical outcomes have been rationalized on the basis of transition-state models involving an intramolecular proton transfer from the carboxylic moiety to the lone pair of electrons on the N or O atoms.[36] This specific hydrogen-bonding interaction occurs readily when the enamine double bond is *anti* to the carboxylic acid group of proline. In Zimmerman–Traxler-type transition states, the aldehyde substituent assumes a pseudoequatorial conformation in the aldol transformation, thus allowing the nucleophilic attack to occur on the aldehydic *Re* face. In contrast, the major stability of the *E* imine in the Mannich reaction forces the substituent R into a pseudoaxial arrangement (imine *Si* face exposed).



Scheme 7. Reversal of the stereoselectivities in proline-catalyzed aldol (a) and Mannich reactions (b).

The demonstration of the ability of proline to efficiently activate different types of electrophiles such as imines toward highly selective transformations provided the impetus for seeking alternative and suitable electrophilic components. Indeed, List et al.[37] as well as Barbas and co-workers[38] independently demonstrated that Michael acceptors such as nitro olefins react with unmodified ketones under proline catalysis (Scheme 8).[39a] Although the resulting γ-nitro

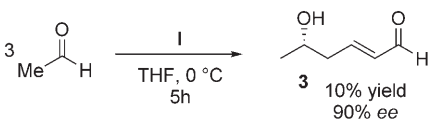


Scheme 8. The proline-catalyzed Michael reaction.

ketones are produced in very poor optical purity, the extension of the concept of enamine activation to fundamental chemical transformations such as Michael reactions paved the way for the future optimization[39] of highly efficient and enantioselective protocols based on newly designed organocatalysts (Section 5). Moreover, these studies highlighted the stringent necessity for the specific interaction between the electrophilic components and the carboxylic moiety of proline to enforce excellent stereocontrol. When this interaction is not optimal, as in the case of Michael acceptors, the enantioselectivity is very modest.

3.4.2. Aldehydes as Donors

In 2001, an important breakthrough was advanced by Barbas and co-workers, who established the possibility of employing α-unbranched aldehydes, in addition to unmodified ketones, as donors in enamine catalysis.[40] In particular, they described the proline-catalyzed direct self-aldolization of acetaldehyde to afford (5*S*)-hydroxy-(2*E*)-hexenal (**3**) in 90% *ee* (Scheme 9).[40a] The involvement of "naked" aldehyde donors in proline catalysis had a profound impact on

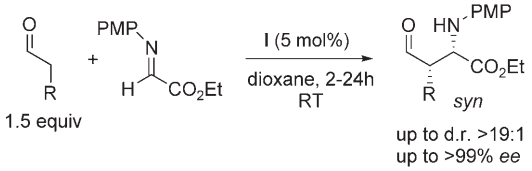


Scheme 9. The first use of aldehydes as donors in proline catalysis.

asymmetric aminocatalysis, encouraging the development of new aldehyde-based transformations with a wide range of electrophilic partners. Aldehydes quickly gained a central role in organocatalysis because of their high reactivity in reactions catalyzed by enamines and iminium ions and because of their great versatility as building blocks.

3.4.3. Proline-Catalyzed Nucleophilic Additions

The notions that proline-catalysis could be extended to different classes of electrophiles and could involve unmodified aldehydes as donors led to the development of highly stereoselective, organocatalytic transformations that had not before been realized through traditional stoichiometric enamine reactions[41] or transition-metal catalysis. The first fruitful combination of these concepts was achieved by Barbas and co-workers, who disclosed the use of unmodified aliphatic aldehydes in the direct catalytic asymmetric Mannich addition to preformed *N*-PMP-protected α-imino ethyl glyoxylate (PMP = *p*-methoxyphenyl, Scheme 10).[42] This

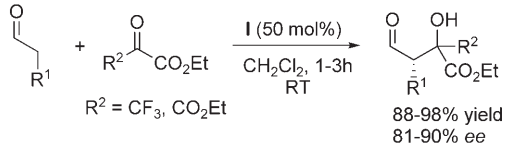


Scheme 10. Unmodified aldehydes as donors in the Mannich reaction.

proline-catalyzed transformation provides synthetically useful amino acid derivatives with excellent enantioselectivity and high *syn* diastereoselectivity. Interestingly, the use of a low catalyst loading (5 mol%) and a small excess of the aldehyde component (1.5 equiv) does not affect the efficiency of the catalytic system. From an atom-economy standpoint, these conditions constitute a significant improvement over the previously reported proline-catalyzed transformations with unmodified ketones.[22,42b]

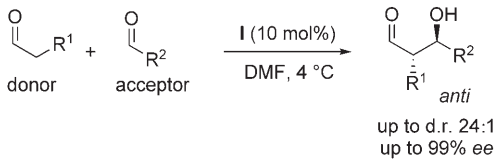
The remarkably high stereoselectivity associated with the proline-promoted Mannich transformations, and their synthetic usefulness, led to the investigation of several substrates. Hayashi et al. and Córdova independently developed the direct and enantioselective one-pot, three-component Mannich reaction between two different aldehydes and *p*-anisidine.[43] This method requires one aldehydic substrate to selectively function as the donor while the other constitutes the acceptor. This chemoselective and *syn*-stereoselective route gives highly enantioenriched β-amino aldehydes. Recently, reaction conditions were identified that allow the use of the preformed *N*-Boc-imine (Boc = *tert*-butoxycarbonyl) in proline-catalyzed Mannich reactions.[44] Despite the difficulty in employing aliphatic imines, these studies introduced important synthetic advances: The easy and efficient removal of the N-protecting group allows easy access to unfunctionalized chiral amines.

The ability of proline to generate an active enamine intermediate from enolizable aldehydes was exploited by Jørgensen and co-workers in their development of the first direct asymmetric aldol addition of aldehydes to activated ketones (Scheme 11).[45] This transformation represented the first intermolecular organocatalytic aldol reaction involving ketone acceptors. The use of different unsymmetrical ketones as acceptors in proline-catalyzed aldolizations was later accomplished, which allowed the concise synthesis of compounds with a quaternary carbon center.[46]



Scheme 11. Unmodified aldehydes as donors in the aldol reaction.

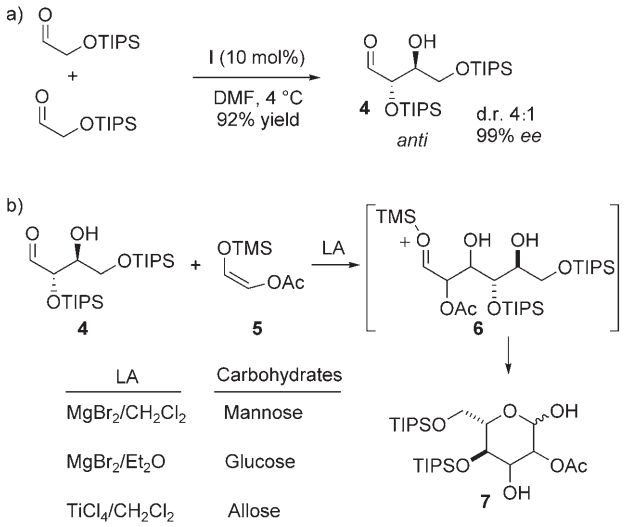
An impressive advance in the area of aldol chemistry was reported by Northrup and MacMillan, who documented the first direct enantioselective catalytic cross-aldol reaction of two unmodified aldehydes: a powerful transformation (Scheme 12).[47] This reaction requires that the non-equivalent aldehydes selectively partition into two discrete components—the nucleophilic donor and the electrophilic acceptor. The formation of by-products arising from dehydration of the products or from a self-aldolization process is suppressed by using DMF as the solvent and by the slow addition (syringe pump) of the aldehyde donors. Under these conditions, the presence of proline (10 mol%) results in the chemo- and diastereoselective aldol cross-coupling of α-alkyl aldehydes to furnish highly enantioenriched *anti*-hydroxy aldehydes.



Scheme 12. Asymmetric direct cross-coupling reaction of aldehydes.

The crucial observation that the aldehydic products of this reaction resist further aldol reactions with proline, prompted Northrup, MacMillan et al. to extend this methodology to the coupling of α-oxygenated aldehydes (Scheme 13).[48] The proline-catalyzed aldolization provides selective access to the dimerization product **4** in a stereoselective fashion, thus setting the stage for a two-step de novo synthesis of carbohydrates.[49]

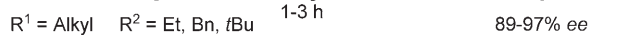
Although **4** is relatively inert to enamine addition, it can be activated by Lewis acids to undergo a selective Mukaiyama aldol-type addition with an α-oxy-enolsilane **5** to provide a transient oxocarbenium ion **6**, which rapidly undergoes cyclization to the pyran ring of the hexoses **7**. Interestingly, the selective preparation of either mannose, glucose, or allose can be accomplished by tuning the experimental conditions.[49] Different tactics, based on an iterative aldol reaction or on the addition of an dihydroxyacetone equivalent to



Scheme 13. Iterative two-step synthesis of carbohydrates by aldol reactions: a) proline-catalyzed aldol dimerization of an α-oxyaldehyde, b) Lewis acid promoted Mukaiyama aldol reaction. TIPS = triisopropylsilyl, TMS = trimethylsilyl.

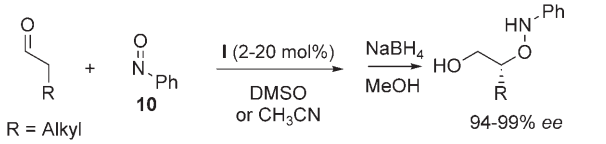
aldehydes, have been exploited for the direct proline-catalyzed de novo synthesis of carbohydrates.[50] These studies highlight the ability of proline to effect the clean and rapid asymmetric synthesis of stereochemically defined complex molecules using simple achiral building blocks.

The next milestone of the "proline gold rush" was the extension of the enamine activation concept to the direct functionalization of aldehydes and ketones with an α-heteroatom. In nearly all areas of organic chemistry, a fundamental role is played by optically active molecules containing a stereogenic carbon atom attached to a heteroatom adjacent to a carbonyl moiety. In 2002, Jørgensen and co-workers and List almost simultaneously reported an efficient and simple method for the direct highly enantioselective α-amination of aldehydes.[51] This expanded the applicability of proline catalysis beyond the established C–C bond-forming processes (Scheme 14). The use of azodicarboxylates **8** as the electrophilic nitrogen source and 10 mol% proline in aprotic solvents furnishes the α-hydrazino aldehydes in good yield and high enantioselectivity. Given the tendency of the α-aminated products to slowly racemize, the in situ reduction with $NaBH_4$ leads to the configurationally stable 2-hydrazino alcohols **9**. These are versatile intermediates for accessing important chiral building blocks such as oxazolidinones and α-amino acid derivatives. The proline-catalyzed direct α-amination was later successfully extended to include ketones and α,α-disubstituted aldehydes, and was also applied in the total synthesis of biologically active compounds.[52] From a mechanistic standpoint,[53] this transformation is part of the general bifunctional activation mode of proline—the azodicarboxylate is activated towards enamine attack by the hydrogen bond of the carboxylic acid group.

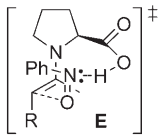


Scheme 14. The first proline-catalyzed asymmetric α-heterofunctionalization of aldehydes (α-amination).

In this context, the direct asymmetric α-oxygenation of aldehydes (Scheme 15), with nitrosobenzene **10** used as the oxygen electrophilic source, provides the best evidence for the high efficiency associated with the catalytic behavior of proline. In addition to imparting high stereocontrol, as in other proline-catalyzed transformations, the hydrogen bond in the transition state **E** is selectively formed with the nitrogen atom of nitrosobenzene, because of the enhanced Brønsted basicity with respect to the oxygen atom. This accounts for the high regiocontrol of the reaction in terms of the desired addition at the oxygen atom.[54]

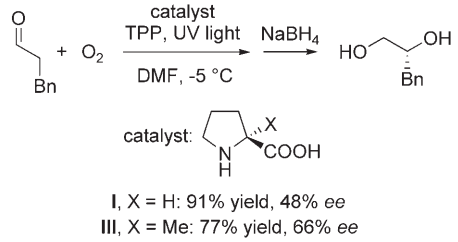


Scheme 15. Proline-catalyzed asymmetric α-oxygenation of aldehydes.



On this basis, three different research groups separately exploited the ability of proline to control both the O/N selectivity and enantioselectivity of the direct α-oxygenation of aldehydes (Scheme 15).[55] The α-oxyaldehyde products are oligomeric in solution and are most conveniently isolated as the corresponding alcohols after in situ reduction with $NaBH_4$. Nonetheless, these oligomeric aldehydes smoothly undergo reactions typical of aldehydes, and direct transformations performed on the crude reaction mixture allow the synthesis of useful, optically active scaffolds.[56]

A very interesting application of the organocatalytic α-oxidation strategy was the asymmetric incorporation of singlet molecular oxygen, generated by the UV irradiation of molecular oxygen or air in the presence of tetraphenylporphyrin (TPP) as the sensitizer, under enamine catalysis conditions (Scheme 16). Córdova et al. demonstrated the effectiveness of proline and, in particular, of the related α-methylproline (**III**) for catalyzing the α-oxidation of

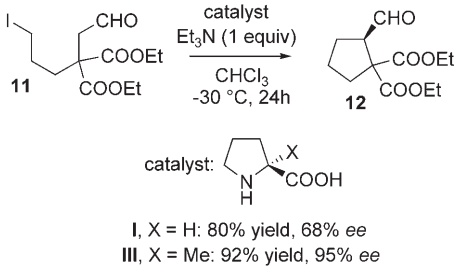


Scheme 16. An asymmetric reaction with molecular oxygen.

aldehydes to afford optically active terminal diols from renewable materials.[57]

3.4.4. Proline-Catalyzed Nucleophilic Substitution

In 2004, the massive competition in proline catalysis led this strategy toward an excellent standard of efficiency. The unusual activation mode of catalysis allowed a number of different electrophiles to be stereoselectively incorporated into carbonyl compounds through highly enantioselective nucleophilic additions. On the other hand, the need for an available lone pair of electrons in the electrophiles to achieve such levels of stereocontrol set considerable limits for proline catalysis. Within this context, Vignola and List presented the first catalytic asymmetric intramolecular α-alkylation of haloaldehydes under enamine catalysis, an unprecedented and highly useful transformation.[58] Proline and its derivative α-methylproline (**III**) can effectively cyclize 6-halo aldehydes **11** to give cyclopentancarbaldehydes **12** in excellent yields and enantioselectivity (Scheme 17).



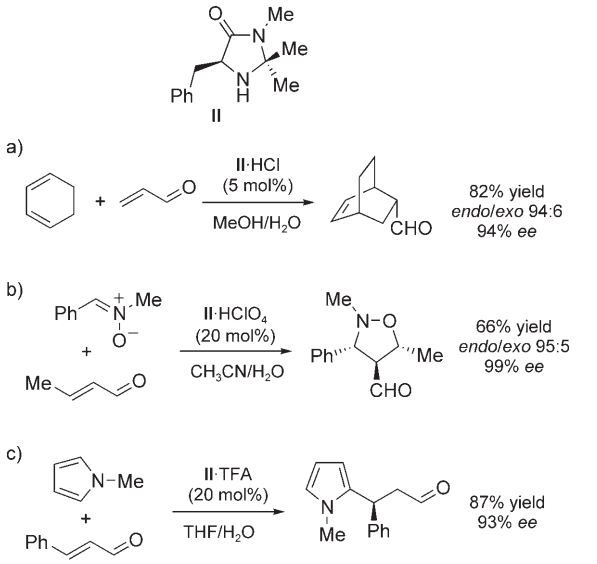
Scheme 17. Proline-catalyzed asymmetric nucleophilic substitution.

This study represented a fundamental breakthrough in the field of asymmetric aminocatalysis, and the described catalytic system also solves the challenging problems of catalyst deactivation by N-alkylation or possible product racemization. This first nucleophilic substitution reaction that proceeds through enamine activation opened up unexplored routes that allowed the "aminocatalysis gold rush" to continue (see Section 5).

4. Iminium Catalysis

The asymmetric Diels–Alder reaction between α,β-unsaturated aldehydes and various dienes catalyzed by imidazolidinone **II** represents a milestone for asymmetric organocatalysis.[3] With this study, MacMillan and co-workers introduced the novel catalytic activation concept termed iminium catalysis, which led to the development of a large range of asymmetric transformations involving unsaturated carbonyl compounds.

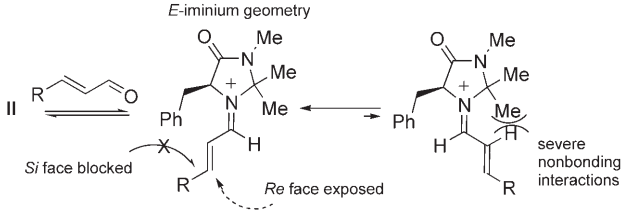
This organocatalytic activation mode exploits the reversible condensation of a chiral amine, such as **II**, with an unsaturated aldehyde to form an iminium ion intermediate. In this system, a rapid equilibrium exists between an electron-deficient and an electron-rich state, which effectively lowers the LUMO energy of the π system and enhances its susceptibility toward nucleophilic attack.[59] Importantly, further studies on LUMO-lowering organocatalysis by MacMillan and co-workers established the effectiveness of the readily available chiral imidazolinone **II** to promote mechanistically distinct transformations of α,β-unsaturated aldehydes in a highly enantioselective fashion (Scheme 18).[60] It is important to point out that the nature of the anion of the catalytically active salt is essential for modulating both the reactivity as well as the stereoselectivity of the process.



Scheme 18. Asymmetric iminium catalysis by imidazolidinone **II**: a) Diels–Alder reaction,[3] b) [3+2] cycloaddition with nitrones,[60a] and c) Friedel–Crafts alkylation of pyrroles.[60b]

4.1. MacMillan's Imidazolidinone Catalysts

Central to the success of imidazolidinone **II** as a stereoselective iminium activator is its ability to effectively and reversibly form a reactive iminium ion intermediate with high levels of both configurational control and π-facial discrimination (Scheme 19). The activated iminium intermediate

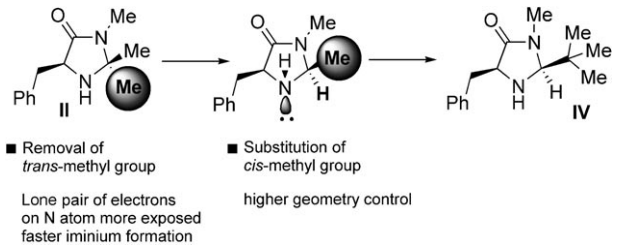


Scheme 19. Control of the configuration of the iminium ion and π-facial shielding by the imidazolidinone catalyst **II**.

predominantly exists in the *E* conformation to avoid problematic nonbonding interactions between the double bond of the substrate and the *gem*-dimethyl groups on the catalyst. The selective π-facial blocking of the imidazolidinone frame-

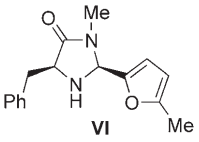
work by the benzyl group leaves the *Re* face of the iminium ion exposed for the nucleophilic attack, thereby resulting in a highly enantioselective bond formation.

Having identified imidazolidinone **II** as an efficient catalyst to mediate the asymmetric addition of pyrroles to unsaturated aldehydes,[60b] MacMillan and co-workers sought to also extend this organocatalytic Friedel–Crafts strategy to heteroaromatic indole and furan derivatives, which are less-activated π nucleophiles.[61] The poor results in terms of both reactivity and enantioselectivity obtained in the reaction catalyzed by **II** highlighted the need for a new, more reactive, and versatile amine catalyst, which would allow for the enantioselective catalytic addition of less reactive nucleophiles. Kinetic studies on the reaction with imidazolidinone **II** as the catalyst suggested that the formation of the iminium ion and the C–C bond-forming step both influence the reaction rate. On this basis, it was theorized that replacement of the *trans*-methyl group (with respect to the benzyl moiety) with a hydrogen atom would reduce the steric hindrance on the participating free lone pair of electrons on the nitrogen atom, thereby increasing its nucleophilic tendency to rapidly form an iminium ion and increasing the overall rate of reaction (Scheme 20). At the same time, replacement of the *cis*-methyl

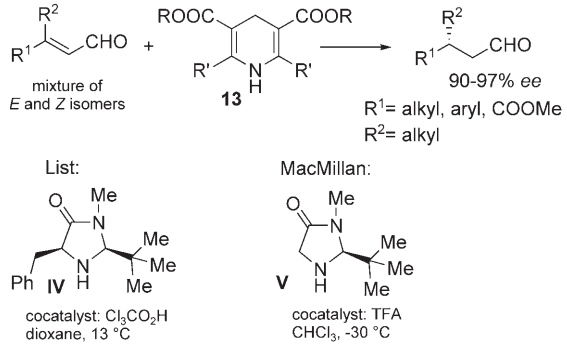


Scheme 20. Logical development of imidazolidinone catalysts.

group with a larger substituent, such as a *tert*-butyl moiety, provided increased control over the geometry of the iminium ion and better coverage of the blocked *Si* enantioface. Furthermore, the lack of a methyl group in catalyst **IV** allowed the nucleophile to approach the *Re* face of the formed chiral iminium ion without steric hindrance.[61,62]



Since its introduction in 2002, the new imidazolidinone catalyst **IV** has been applied successfully to the catalysis of a wide range of asymmetric transformations of unsaturated aldehydes, including cycloaddition reactions and conjugate additions with different nucleophiles.[63] Importantly, iminium catalysis can deliver unique, orthogonal, or complementary selectivities compared to established metal-catalyzed transformations, as in the synthesis of butenolides by the Mukaiyama–Michael addition of silyloxyfurans to enals.[63b] Perhaps the most impressive validation of this concept has been offered by the metal-free, organocatalytic asymmetric transfer hydrogenation of α,β-unsaturated aldehydes. The metal-catalyzed hydrogenations of double bonds are by far the most predominant asymmetric transformations applied to industrial processes. Their usefulness was recognized with the award of the Nobel Prize in Chemistry to Knowles and Noyori in 2001. The development of organocatalytic asymmetric reductions with hydride would thus be useful to solve toxicity concerns about the complete removal of metal impurities. The research groups of MacMillan and List demonstrated that iminium catalysis is a suitable strategy for accomplishing the highly enantioselective reduction of enals by using synthetic Hantzsch dihydropyridines **13** as hydride donors (Scheme 21).[64]



Scheme 21. Iminium ion catalyzed transfer hydrogenation. TFA = trifluoroacetic acid.

Interestingly, List and co-workers employed imidazolidinone **IV** as the catalyst, whereas MacMillan and co-workers designed the new organocatalyst **V** to impart high stereocontrol and reactivity. Both processes are enantioconvergent, since the formation of an *E*- or *Z*-configured double bond does not influence the sense of the asymmetric induction and furnishes the same product enantiomer. This stereoconvergent outcome has been rationalized by assuming a fast isomerization (an equilibrium iminium–dienamine intermediate, Section 7.3.1) induced by the catalyst. These results, which enhance the synthetic value of such approaches, are in marked contrast to most metal-mediated hydrogenations, wherein the configuration of the double bond dictates enantiospecific reductions.

4.2. Iminium Ion Activation of Unsaturated Ketones

Stereoselective Michael additions to α,β-unsaturated ketones represents a challenging objective in asymmetric catalysis. In metal-catalyzed asymmetric processes, the steric and electronic similarity of the two carbonyl substituents does not generally permit high levels of discrimination between the free lone pairs of electrons in the metal-association step, which is an essential requirement for achieving high stereocontrol in the conjugate addition.

The activation as an iminium ion, which overcomes the necessity of coordination to a specific lone pair of electrons, can in principle constitute a suitable and general method for accomplishing highly stereoselective transformations of enones. However, the inherent problems of forming highly substituted iminium ions from ketones, along with the issue

associated with a more difficult control over the configuration of the iminium ion, have complicated the development of an efficient chiral organocatalyst for ketones. The first advance in this challenging area came from the MacMillan research group, with the development of a new imidazolidinone catalyst (**VI**) that allowed the first catalytic Diels–Alder reaction with simple α,β-unsaturated ketones.[65] Whereas oxazolidinones **II** and **IV**, which are valuable activators of aldehydes as iminium ions, were almost inactive and non-selective with this type of substrates, catalyst **VI** allowed enantioselective access to substituted cyclohexenyl ketones.

Imidazolidinone **VI**, however, has not demonstrated a wide generality as a ketone activator.[65b] In this context, important expansions of iminium catalysis to the asymmetric additions of acyclic enones[66] came from Jørgensen and co-workers, who introduced chiral secondary amine catalysts **VII** and **VIII**.[67] These readily available organocatalysts have broad applicability in the conjugate addition of unsaturated ketones. They promote the highly enantioselective addition of different carbogenic nucleophiles such as nitroalkanes,[67a] malonates,[67b] and β-keto-esters[67c] or -sulfones,[67d] thus providing access to useful building blocks for organic synthesis (Figure 2). Despite the relative low activity of **VII** and

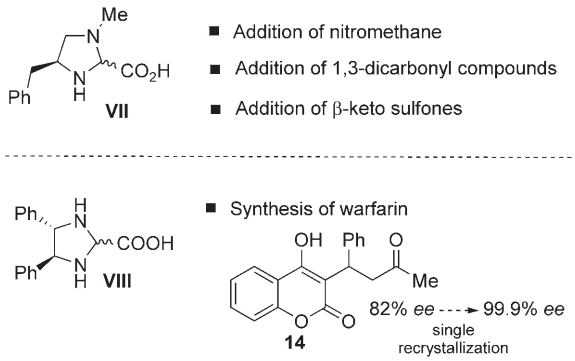


Figure 2. Catalysts that activate acyclic enones as iminium ions.

VIII (the reaction time being generally on the order of four or more days), their utility as iminium activators has been further attested to by the one-pot direct synthesis of enantioenriched biological active compounds, such as the anticoagulant warfarin (**14**).[67e]

At the end of 2004, thanks to contributions from the research groups of MacMillan and, later, Jørgensen, iminium catalysis assumed a prominent role in asymmetric synthesis as an established catalytic method for the asymmetric β-functionalization of unsaturated carbonyl compounds. This field, together with enamine catalysis, began to attract the interest of many researchers from both academia and the chemical industry, who recognized the synthetic potential of such strategies. At the time, enamine and iminium catalysis were still considered two divergent and separate aminocatalytic pathways, which allowed discrete types of transformations. This view would shortly be challenged by the idea of combining the two aminocatalytic activation modes. In the next two chapters, we will discuss the theoretical context that provided the suitable conditions for the merging of enamine and iminium catalysis, and the associated synthetic consequences.

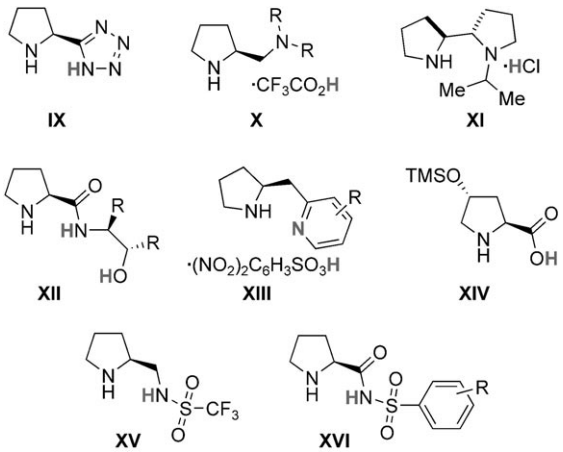
5. Beyond Proline

> *"…dove la Natura finisce di produrre le sue spezie, l'uomo quivi comincia con le cose naturali, con l'aiutoro di essa Natura, a creare infinite spezie…"*
> *"…where nature finishes producing its species, there man begins with natural things to make, with the aid of this nature, an infinite number of species…"*
> Leonardo da Vinci[68]

Deciphering the molecular logic behind the bifunctional activation mode of proline was invaluable for the development of asymmetric aminocatalysis (Section 3). However, the scientific community realized that, to expand the scope of enamine catalysis it was necessary to design new families of chiral amine catalysts.

5.1. "Improving" Proline

The most straightforward approach to a new catalyst began with the derivatization of proline. The design of new organocatalysts has focused on the introduction of tunable hydrogen-bonding donor groups to improve the dual activation ability while preserving the molecular scaffold created by nature as a central design element. A series of modifications of the structure of proline was accomplished by different research groups, who aimed mainly at improving the solubility



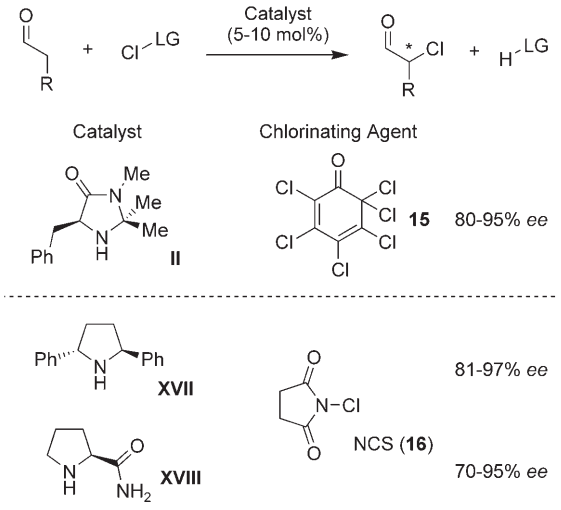
and/or enhancing the acidity of the directing acid proton. In this research area, the aldol reaction and the conjugate addition of carbonyl compounds to nitrostyrene derivatives were often chosen as benchmark reactions.[69] It is remarkable that these catalysts showed major improvements in terms of reactivity or enantioselectivity in some specific transformation, yet all lacked the generality of the natural amino acid proline (**I**).

Reactions catalyzed by proline or by its synthetic analogues quickly reached very high levels of efficiency, but the requirement of an available lone pair of electrons in the electrophiles represented a serious limitation. To overcome this problem, the researchers began to focus on exploitating different catalytic patterns that do not require a specific hydrogen-bonding interaction to impart high stereocontrol. In particular, chiral cyclic amines with bulky substituents, instead of the acidic functional group, could control the stereoselectivity by using the steric hindrance of the chiral architecture. This new tactic opened up new opportunities for the transformation of new reagents not suitable for proline catalysis.

5.2. Enantioselective Chlorination

Until 2004, there were few successful enamine-catalyzed reactions in which alternative secondary amines were used.[70] In this context, the α-chlorination of aldehydes represented a huge step forward in the establishment of organocatalysis as a versatile and reliable synthetic strategy. Two important mechanistic goals were simultaneously achieved: Firstly, the reaction expanded the scope of enamine catalysis to intermolecular nucleophilic substitution reactions, and secondly, it was definitively demonstrated that enamine catalysis is not limited to proline. The reaction is also very important because it provides easy access to a large number of simple but extremely versatile building blocks.[71] The almost simultaneous publications by the research groups of MacMillan[72] and Jørgensen[73] are a nice example of how organocatalysis can deliver more that one solution for the same problem. The two alternative protocols are based on very different catalysts and chlorine sources, but furnish similarly excellent results.

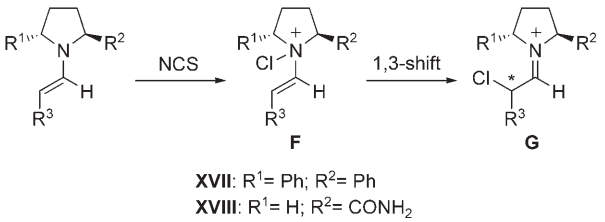
Scheme 22 shows the excellent results obtained with the MacMillan catalyst **II** in combination with perchlorinated quinone **15**,[72] and with 2,5-diphenylpyrrolidine (**XVII**) when *N*-chlorosuccinimide (**16**) is the chlorine source. Interestingly,



Scheme 22. The enantioselective amino-catalyzed chlorination of aldehydes. LG = leaving group.

the very simple prolinamide **XVIII** also shows very good reactivity and good enantioselectivity.[73] The authors also described how the products of the reaction could easily be converted into terminal epoxides, amino acids, or amino alcohols, while maintaining the high enantiomeric excess.

To gain insight into the reaction mechanism, the Jørgensen research group began a more detailed investigation of the α-chlorination reaction.[74] This study was triggered mainly by the apparently minimum degree of face-shielding provided by the two α substituents in the C_2-symmetric diphenylpyrrolidine **XVII**, but also by the "catalyst generality" observed. In fact, although proline promoted an almost nonselective transformation (< 25% *ee*), an unusually large number of diverse enantiomerically pure amines catalyzed the formation of the α-chlorinated products with promising levels of asymmetric induction.[73] These studies led to the proposal of a new mechanism for the α-chlorination of aldehydes catalyzed by the chiral pyrrolidine **XVII**. It was suggested that, in this case, the chlorination does not take place directly at the α-carbon atom, but involves a two-step process constituting the initial chlorination of the nitrogen atom of the enamine, followed by a fast [1,3] sigmatropic shift, as summarized in Scheme 23. This theory was corroborated by a



Scheme 23. Mechanistic studies on the direct α-chlorination of aldehydes.

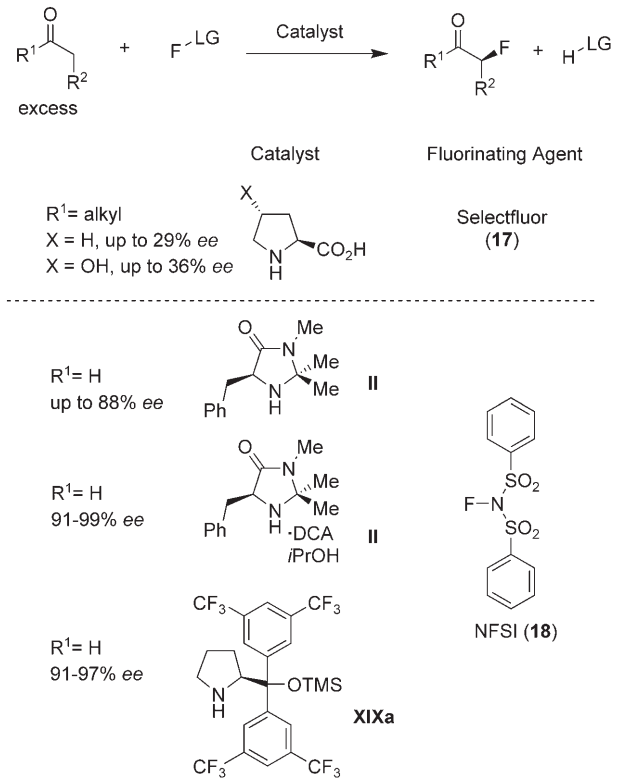
series of experimental results and DFT calculations, although the key intermediate **F** could not be detected.[74] Very recently, this mechanism was supported by studied by Metzger and co-workers, who used electrospray ionization mass spectroscopy to successfully intercept and characterize the N-chlorinated intermediate **F** formed when prolinamide **XVIII** was used as the catalyst.[75] The reaction rate appears to be independent of the conversion of the two reagents, and it can be significantly increased by adding simple acids and water. The presented data suggest that the rate-determining step of this chlorination reaction is the hydrolysis of the iminium ion **G** (Scheme 23). This is notably different to the aldol reaction, where computational analysis suggests that the formation of a C–C bond is the rate-determining step.[25,26]

The enantioselective chlorination was a milestone in the field of aminocatalysis. It became the inspiration for, and the beginning of, a series of enantioselective α-halogenations[76] of both aldehydes and ketones, which culminated in the successful development of the particularly challenging α-fluorination of aldehydes.

5.3. Enantioselective Fluorination Reactions

The electrophilic fluorination reaction whetted the scientific appetite of many chemists.[77] The large electronegativity and small van der Walls radius of the fluorine atom clearly differentiates it from the other halogens. This helps explain the great interest in this reaction. The potential applications of the fluorinated products were also a strong incentive to optimize this reaction. Fluorine substituents usually affect the overall physicochemical properties of a molecule.[77c] For example, the addition of fluorine atom to a biologically active compound can significantly improve its metabolic stability.

The race towards an efficient α-fluorination of carbonyl compounds led to the publication of four independent contributions in a very short period of time (Scheme 24).

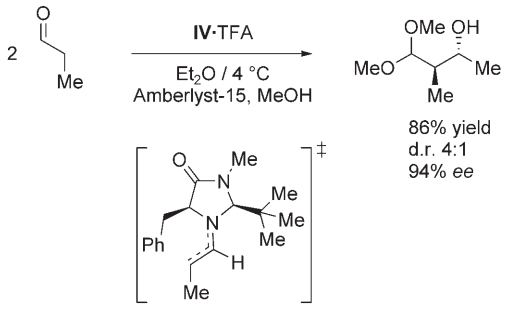


Scheme 24. The enantioselective amino-catalyzed α-fluorination of carbonyl compounds. LG = leaving group, DCA = dichloroacetic acid.

The first α-fluorination of aldehydes and ketones was reported by Enders and Hüttl.[78] They described how different chiral amines catalyzed the α functionalization of carbonyl compounds by using selectfluor (**17**) as the source of electrophilic fluorine. However, the maximum enantiomeric excess observed in the fluorination of cyclohexanone was only 36% *ee*. Barbas and co-workers[79] applied the imidazolidinone catalyst **II** to the reaction of aldehydes with the milder electrophilic fluorine source *N*-fluorodibenzenesulfonimide (NFSI, **18**). Despite the moderate catalyst turnover (catalyst loading 30–100 mol%), high levels of stereocontrol were achieved (up to 88% *ee*). Beeson and MacMillan[80] reported that the imidazolidinone **II** is a much more efficient catalyst for this transformation if used in combination with 10 mol% of an appropriate acid and 2-propanol. These improved reaction conditions, with a much lower catalyst loading, provide the fluorinated aldehydes in moderate to high yields and up to 99% *ee*. Jørgensen and co-workers[81] found that (*S*)-2-[bis-(3,5-bis-trifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine (**XIXa**; see Section 5.5) was also a suitable catalyst for the α-fluorination of aldehydes with **18**. Products were obtained in good yields and with excellent selectivities (91–97% *ee*) under mild conditions and using only 1 mol% of the catalyst. Interestingly, it was demonstrated that the catalytic system controls the stereochemical output of the reaction by means of two distinct, but clearly connected, patterns. The main one, of course, is the highly stereoselective formation of the C–F bond. Studies on the kinetic and the positive nonlinear effects in the reaction also indicated that the system is capable of "metabolizing" the minor enantiomer by catalyzing a selective second α-fluorination.[81]

5.4. Imidazolidinone Catalysts in Enamine Catalysis

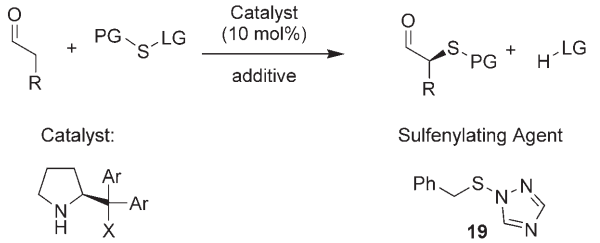
In addition to promoting highly enantioselective conjugate additions of different nucleophiles to α,β-unsaturated compounds (Section 4), the MacMillan imidazolidinone catalysts **II** and **IV** proved to effectively participate in HOMO-raising enamine activation with aldehydes. The shift from the iminium to activation by imidazolidinones followed mechanistic considerations: a computational study on the aldol reaction indicated the involvement of a late transition state, thus suggesting that the development of the iminium π bond preceeds formation of the carbon–carbon bond.[25] On this basis, MacMillan and co-workers hypothesized that the ability of the chiral amine to control the iminium geometry in the transition state might be a crucial factor for achieving high enantiofacial discrimination in the enamine additions. The efficiency of imidazolidinones in activating carbonyl groups as iminium ions imparting high level of geometric control led to the authors wondering if the same chiral amine scaffolds might readily function as highly selective enamine catalysts. This hypothesis was validated by performing an asymmetric enamine-aldol reaction catalyzed by imidazolidinone **IV** (Scheme 25),[82] and was further corroborated by the halogenation[72,79–80] of aldehydes (see Sections 5.2 and 5.3) and by other asymmetric enamine-based transformations.[83]



Scheme 25. Imidazolidinone **IV** as an enamine catalyst.

5.5. Diaryl Prolinol Ethers in Enamine and Iminium Catalysis

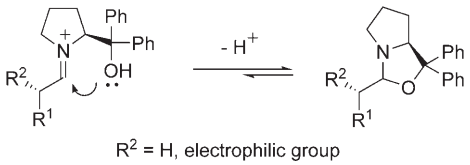
The excellent results obtained in the halogenation reactions revealed the tremendous potential of the organocatalytic approach. This approach opened up unexplored possibilities for many asymmetric nucleophilic substitutions that proceed through activation as enamines. When the organocatalytic chlorination reaction first appeared in the literature, the organocatalytic electrophilic α-sulfenylation reaction of aldehydes was already being studied. In early 2005, Jørgensen and co-workers published the first highly enantioselective version of this elusive yet important transformation, which was not possible with other asymmetric catalytic methods (Scheme 26).[84]



Scheme 26. The enantioselective amino-catalyzed sulfenylation of aldehydes. LG = leaving group, PG = protecting group.

The novel sulfenylating agent 1-benzylsulfanyl-1,2,4-triazole (**19**) represents the best compromise in terms of stability, reactivity, ease of preparation, and synthetic utility for this reaction. In addition to the value of this transformation,[84c] the highlight of this study is without doubt the synthesis of a new class of organocatalysts. Simple protection of the oxygen atom of the inactive diphenylprolinol (**XIXb**) with a trimethylsilyl (TMS) group produced the catalyst **XIXc**, excellent in terms of both yield (90%) and enantioselectivity (77% *ee*). A small modification of the aromatic moieties of the catalyst led to the optimized Jørgensen catalyst (*S*)-2-[bis(3,5-bis(trifluoromethyl)phenyl)trimethylsilanyloxymethyl]pyrrolidine (**XIXa**), which catalyzes the formation of sulfenylated products in high yield and in over 95% *ee*.[84a]

Diphenylprolinol (**XIXb**) is an amino alcohol which was first synthesized in the 1930s.[85a] It was used by Enders et al.[85b] as a chiral auxiliary and by Corey et al. as a ligand in Lewis acid catalyzed reactions.[85c] The compound rarely demonstrated useful catalytic activity when used as an enamine activator, although in some transformations it could induce high stereocontrol.[86] The poor yields obtained with **XIXb** were explained by the larger size of the substituents relative to catalyst **XX**, which, in contrast, often showed good activity and low levels of stereocontrol.[70b,c] Jørgensen and co-workers, however, suggested that the reason for the disappointing behavior of **XIXb** was the formation of unreactive hemiaminal species (Scheme 27).[87] It was not the size but the chemical reactivity of the free hydroxy group that was the deciding factor. A simple protection of this functionality consequently restored the high activity.



Scheme 27. The hemiaminal equilibrium.

Outstanding enantiomeric excess and a consistent absolute configuration were observed for the transformations catalyzed by diarylprolinol silyl ethers. These findings are in agreement with a transition state that minimizes the steric interactions between the bulky substituents on the pyrrolidine ring and the reactive carbon atom (*E-anti* configuration of the enamine).[88] At the same time, the catalyst structure guarantees an excellent shielding of the *Si* face of the enamine, and the overall result is an almost complete stereocontrol in the reaction (Figure 3). Furthermore, the sterically encumbered

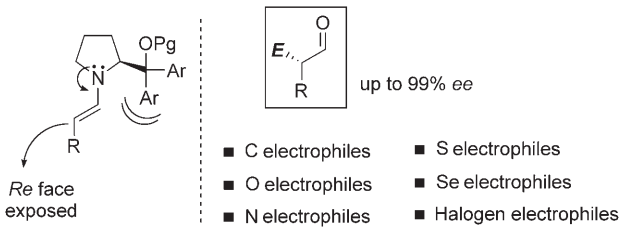


Figure 3. Enantioselectivity in the reactions catalyzed by diaryl prolinol ethers through enamine activation.

chiral amine seems to prevent racemization of the optically active products, as exemplified by the sulfenylation[84a] and fluorination reactions.[81] Notably, the proposed model, which explains the activity and the asymmetric induction, does not rely upon the structure of the electrophile. This points to the possible use of this new class of catalysts in reactions other than the α-sulfenylation reaction.[89] The more general potential of this type of catalyst was soon confirmed by its application in the previously described α-fluorination reaction.

Interestingly, a few months after these first publications by Jørgensen and co-workers on the use of O-silyl derivatives of diarylprolinol as efficient enamine-based organocatalysts, Hayashi et al. demonstrated the efficiency of these type of catalysts as highly stereoselective promoters of the asymmetric conjugate addition of aldehydes to nitroalkenes, a benchmark C–C bond-forming reaction.[90] The ability of catalysts **XIXa–e** to promote asymmetric nucleophilic additions other than substitution reactions was exploited, for example, in enantioselective conjugate additions,[87,91] arylations,[92] Man-

nich reactions,[87] and aminomethylation reactions.[93] C–N (α amination[87] and oxyamination[94]) and C–O bond-forming reactions[57b] also take place under similar conditions and afford the same excellent enantioselectivities. The "journey" around the periodic table continues with the publication of α-bromination,[87] α-selenenylation,[95] the previously described α-fluorination, and α-sulfenylation reactions (Figure 3).

Just as the MacMillan catalysts, which were designed for iminium ion catalysis, turned out to be effective for enamine catalysis, so the diaryl prolinol silyl ethers (designed for application in enamine-catalyzed reactions) found application in iminium ion catalysis. The addition of C-,[96] N-,[97] O-,[98] S-,[99] and P-based[100] nucleophiles to α,β-unsaturated aldehydes was reported to be highly enantioselective in the presence of catalytic amounts of Jørgensen catalyst **XIXa** or its derivatives (Figure 4). Here too, the excellent stereoselectivities

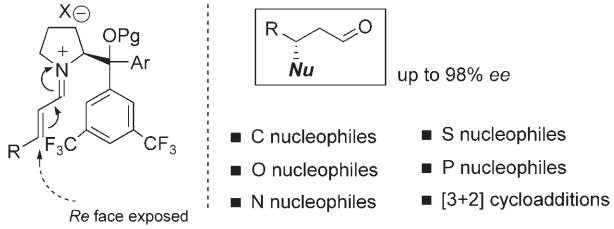


Figure 4. Enantioselectivity in the reactions catalyzed by diaryl prolinol ethers through activation as iminium ions.

reported are closely connected to the size of the substituents on the catalyst. The configuration of the iminium ion in the transition state is such that steric repulsions are minimized. The chiral fragment extends enough to provide efficient face-shielding to the more distant β-carbon atom. The addition of catalytic amounts of an organic acid usually increases the rate of this kind of transformation. There is most likely a relationship between the energy of the LUMO of the iminium ion and the nature of its counteranion. However, the role of these additives has not been completely clarified and might not be the same in all situations. It is commonly accepted that acids are able to increase the rate of the overall catalytic process by accelerating the formation of the enamine and/or its hydrolysis. (A new perspective on the role of the counteranion in asymmetric iminium catalysis can be found in Section 7.2.)

In both models (Figure 3 and 4), the efficiency of the O-protected diaryl prolinols seems to be related only to the size of the substituents on the catalyst and not to their chemical nature. The first consequence of this is that fine-tuning of the catalytic activity can easily be achieved by subtle modification of the aryl structure. The smaller[87,90] (and often, therefore, more reactive) catalyst **XIXc** with the phenyl substituents could be applied in some transformations, while maintaining outstanding levels of selectivity. The research groups of Gellman,[91a] Hayashi,[96f] and Wang[98b] reported that it is also possible to change the protecting group on the oxygen atom (methyl, *tert*-butyldimethylsilyl (TBDMS), or triethylsilyl (TES)) to modulate the reactivity and improve the chemical stability of the catalyst. More recently, Palomo et al. described excellent results in a series of enantioselective transformations with a catalyst bearing long aliphatic chains in place of the aryl groups.[101]

There are two further properties of O-protected diaryl prolinols that need to be mentioned. First, they are poor catalysts for the homo-aldol reaction of aldehydes under the mild conditions in which they are usually applied. This is very important since the formation of such by-products often forces the use of a large excess of aldehyde when other chiral amines are used as the organocatalysts. Secondly, the catalysts are compatible with different reaction media. Successful applications have been reported in a variety of solvents ranging from the apolar and aprotic hexane and toluene to polar and protic solvents such as ethanol or water.

5.6. General Catalysts and Specific Designs

The development of new enantioselective reactions is the ultimate goal for organic chemists involved in this highly competitive and stimulating research field. The combined efficiency of the natural "universal catalyst" proline and the synthetic MacMillan catalysts and the silyl-protected diaryl prolinol catalysts is a precious tool for synthetic chemists, who can avoid screening large numbers of catalysts when searching for the optimal conditions for new asymmetric processes. The successes obtained using these catalytic systems increased the enthusiasm of chemists to investigate ever more challenging combinations of electrophiles and nucleophiles. However, the progress obtained should not just be measured by the number of new reactions that have been discovered. Aminocatalysis is not limited to the application of a few efficient organocatalysts. The most important achievement has been a deeper understanding of the complex mechanisms associated with the multistep catalytic processes.

The development of the efficient *anti*-selective Mannich reaction is just one example of how aminocatalysis has already become a versatile tool for synthetic organic chemists. This reaction represents a difficult task, since proline is able to catalyze exclusively the formation of the *syn* product with excellent levels of stereocontrol (Section 3.4). Activation by the acidic proton results in the *Si* face of the enamine approaching the *Si* face of the imine with the formation of a nine-membered ring transition state (Figure 5a; see Section 3.4.1 for a mechanistic discussion). A highly enantioselective *anti*-selective Mannich reaction was later reported by Jørgensen and co-workers: by using organocatalyst **XIXa**, the products could be obtained with moderate to good diastereoselectivities (*anti*:*syn* 4:1–15:1) and in up to 98% *ee* (Figure 5b).[87] However, organocatalysts that have general applicability do not perform at their optimum ability in every single transformation.

The results obtained by the research group of Maruoka[102] and by Barbas, Houk, and co-workers[103] with specifically designed catalysts demonstrate the full power of the aminocatalytic approach. Maruoka and co-workers used their familiarity with axial chirality[6a] and their initial investigations on non-natural axially chiral amino acids as enamine

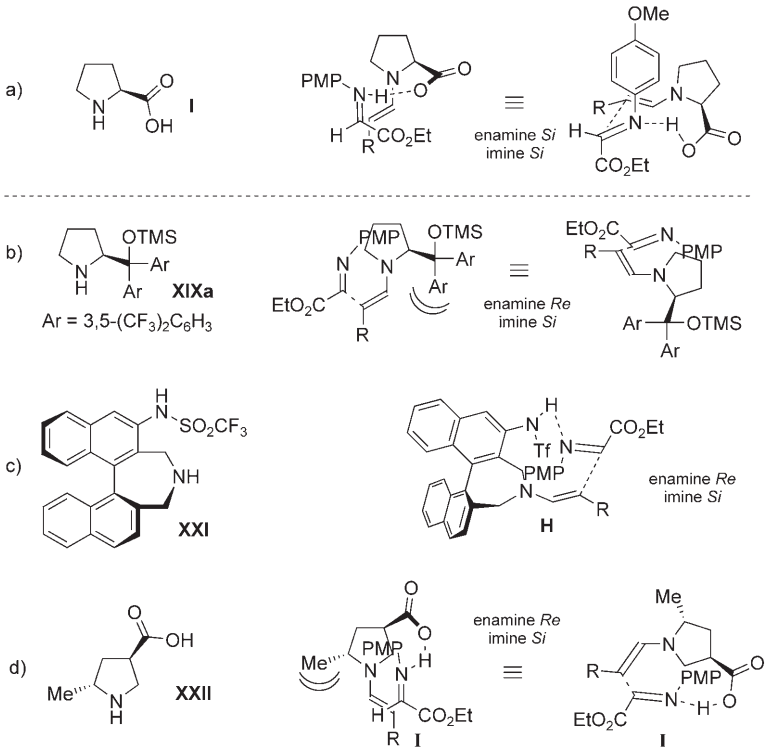


Figure 5. Highly efficient control of the relative and absolute configuration in the Mannich reaction. a) Proline-catalyzed *syn*-Mannich reaction. b)–d) Amino-catalyzed *anti*-selective Mannich reactions.

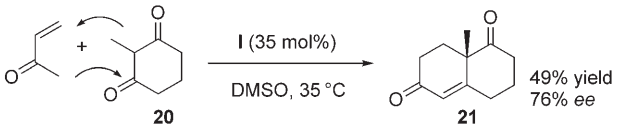
catalysts.[104] The extraordinary chiral amino sulfonamide **XXI** is capable of catalyzing the *anti*-selective Mannich reaction with a diastereoselectivity of at least 11:1 and 97% *ee* for all the substrates tested (Figure 5c).[102] The ten-membered-ring transition state **H** in which the *Si* face of the imine approaches the *Re* face of the *E* enamine is the only one that can fully benefit from the double activation of the aldehyde (by the seven-membered ring amine) and of the electrophile (by the acidic proton of the sulfonamide). Houk et al. found an elegant solution to the issues raised by the *anti*-selective Mannich reaction. The most important feature is the control of the enamine conformation and the correct positioning of the key proton activation of the imine (ten-membered-ring transition state **I**, Figure 5d).[103] Their experience with proline-catalyzed reactions[4d,g] and computational investigations[25] prompted the authors to introduce two important modifications to the proline structure: they moved the carboxylic acid from position 2 to position 3 of the pyrrolidine ring, and an additional methyl group was introduced at position 5. The resulting active catalyst **XXII** has almost complete control over both the diastereomeric and enantiomeric ratios, despite its simple molecular structure.

The general and readilyy available catalysts[105] represent an important starting point for the investigation of new reactions. However, aminocatalysis will face problems of increasing complexity and diversity in the near future. It is realistic to assume that these problems will also be solved by using different catalysts, rationally designed to perform best in a single application.

6. Amino-Catalyzed Domino Reactions

The synthesis of complex, optically active molecules is usually the result of multistep syntheses and often requires the isolation and purification of many intermediates. In contrast, the biosynthesis of complex natural products is achieved by highly regulated catalytic cascade reactions that do not require these time-consuming and costly operations. Once more, the efficiency of nature is a fount of inspiration, and the design of catalytic enantioselective domino transformations has become an essential goal.[106] Such an approach might reduce the great need for protecting groups, which is a serious limitation in the overall atom economy of every synthesis. The knowledge accumulated on the mechanism of enamine and iminium catalysis has allowed the integration of these activation modes into more elaborate reaction sequences, with the aim of securing direct and simple access to complex products.[107]

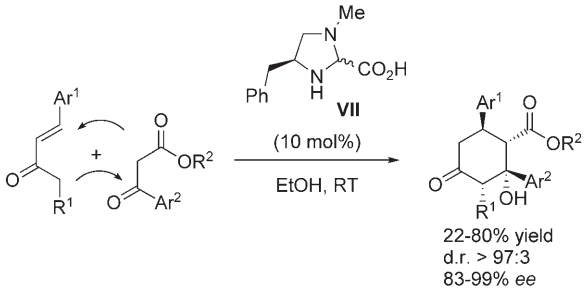
The first example of an organocatalytic domino reaction was presented in 2000 by Bui and Barbas (Scheme 28).[108] In this Robinson annulation,[17] L-proline (**I**) first catalyzes the conjugate addition of 2-methyl-1,3-cyclohexadie-



Scheme 28. Asymmetric Robinson annulation (iminium ion/enamine-catalyzed domino reaction).

none **20** to methyl vinyl ketone. The achiral intermediate is then converted into tetrahydronaphthalene-1,6(2*H*,7*H*)-dione **21** in 49% yield and 76% *ee*.

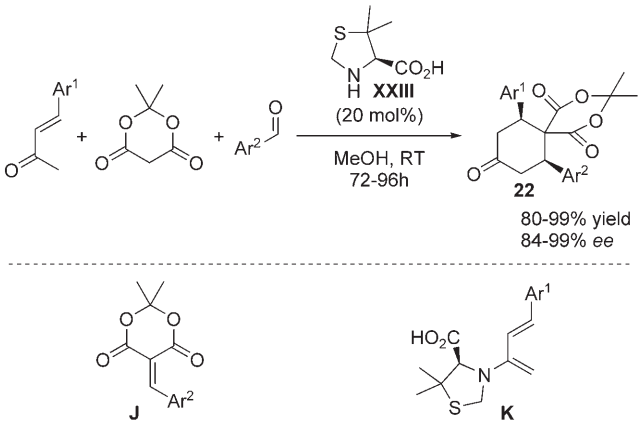
In 2004, Jørgensen and co-workers described a new domino reaction involving β-ketoesters and unsaturated ketones (Scheme 29),[67c] with a mechanism closely related to the Robinson annulation. The chiral imidazolidinone **VII** catalyzes the enantioselective Michael addition (Section 4.2) of 1,3-dicarbonyl compounds to the enone through activation



Scheme 29. Asymmetric conjugate addition/aldol reaction.

as an iminium ion, followed by a diastereoselective ring closure. Interestingly, under the described reaction conditions, the dehydratation does not occur and products with up to four stereocenters were obtained diastereomerically pure (d.r. > 97:3) and with excellent enantiomeric excess.

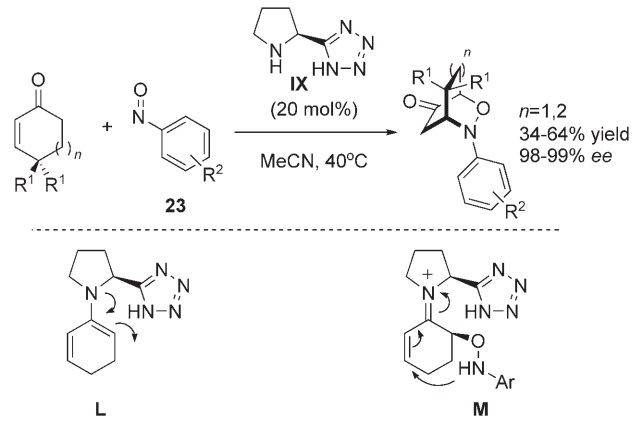
In 2003, Barbas and co-workers started an interesting series of investigations on the coupling of three components through sequential Knoevenagel and Diels–Alder reactions.[109] One example of the efficiency and broad scope of their approach is summarized in Scheme 30.[109b] In the first step, the aldehyde reacts with Meldrum acid to form the



Scheme 30. Asymmetric Knoevenagel/Diels–Alder reaction.

reactive dienophile **J**. In the second step, the chiral dienamine intermediate **K**, formed by condensation of 5,5-dimethylthiazolidinium-4-carboxylate (**XXIII**) with the enone, reacts in a highly diastereoselctive manner with the product **J** of the Knoevenagel condensation. The optically active products **22** of the Diels–Alder reaction are obtained with up to 99% *ee* after hydrolysis of the catalyst.

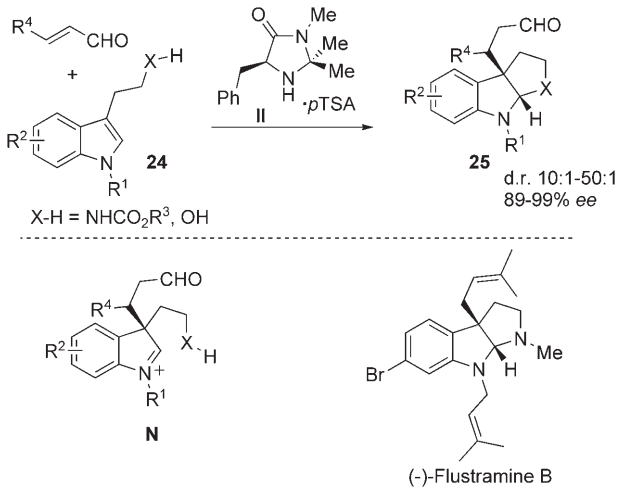
Another important example of an organocatalyzed domino reaction involving unsaturated ketones was reported by Yamamoto and co-workers (Scheme 31).[110] Here, the catalyst combines different characteristics of aminocatalysis to promote both steps in the addition of cyclic enones to



Scheme 31. Domino enamine/iminium ion catalyzed reaction.

nitrosobenzene or its derivatives **23**. Initial condensation of the proline-based tetrazole **IX** with cyclic enones generates the electron-rich dienamine intermediate **L**, which chemoselectively reacts with the oxygen atom of the nitrosobenzene **23** (see Section 3.4.3). In the second stereodefining step, the iminium ion **M**, formed from **IX** and the α,β-unsaturated product, undergoes the conjugate intramolecular addition that closes the six-membered ring with up to 99% *ee*.

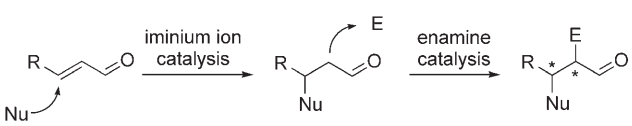
The first example of a domino reaction involving α,β-unsaturated aldehydes was presented in 2004 by the MacMillan research group.[111] First, the nucleophilic indole **24** attacks the chiral iminium ion formed from the imidazolidinone **II** and the α,β-unsaturated aldehyde (Scheme 32). This highly



Scheme 32. Domino conjugate addition/cyclization reaction.

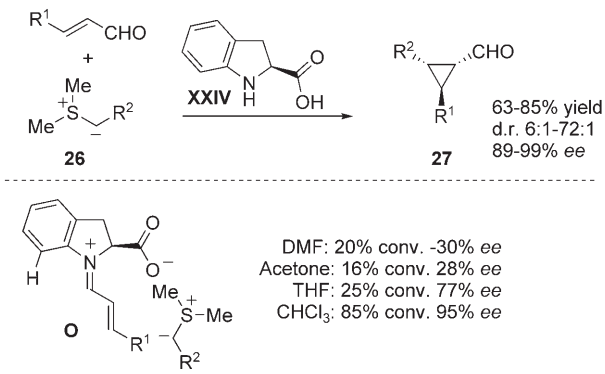
enantioselective formation of a quaternary all-carbon-substituted stereocenter is then followed by the trapping of the indolinium ion **N** by the appended alcohol or carbamate-protected amino moieties. The pyrroloindolines **25** are thus synthesized in high yields and with excellent diastereomeric and enantiomeric ratios in one single and simple operation. Many analogues of naturally occurring compounds could be accessed by this approach. For example, (−)-flustramine B was synthesized in just five steps starting from the product of an organocatalytic reaction.

A different approach to aminocatalyzed domino reactions is based on the conjugate addition of a nucleophile to α,β-unsaturated aldehydes followed by the α-functionalization of the resulting saturated aldehydes (Scheme 33). The catalyst has an active role in both steps of this sequence: initially it forms the activated iminium ion species and later it forms the electron-rich enamine intermediate.



Scheme 33. Domino iminium ion/enamine catalyzed reaction. Nu = nucleophile, E = electrophile.

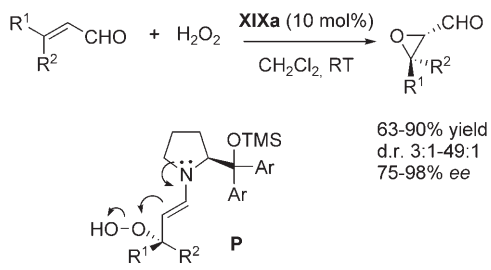
In 2005, Kunz and MacMillan applied 2-carboxylic acid dihydroindole (**XXIV**) as a catalyst in the reaction between α,β-unsaturated aldehydes and stabilized sulfur ylides **26** (Scheme 34). The cylopropane derivatives **27** were formed in good yields, high diastereoselectivity, and very good enantiomeric excess (up to 96% *ee*).[112]



Scheme 34. Organocatalytic cyclopropanation.

The authors advanced a peculiar mechanism of chiral induction, termed "direct electrostatic activation" (DEA). The interaction between the carboxylate group on the chiral fragment and the thionium substituents helps the nucleophilic reagent to get in close to the β-carbon atom of the iminium ion (see intermediate **O**, Scheme 34), thereby facilitating the formation of a carbon–carbon bond. Catalyst **XXIV** achieves higher enantioselectivities than proline (46% *ee*), because of better control over the conformation of the iminium ion through steric repulsion between the olefin substrate and the hydrogen atom of the aromatic ring. The postulated DEA mechanism is supported by solvent studies. A slower reaction and poor enantiomeric excess was observed in polar solvents, which can disrupt the described charge–charge interaction. The inversion of the absolute configuration observed in DMF can probably be associated with a different enantiodifferentiating pathway, in which the face-shielding of the carboxylate substituent prevails over the now weak or absent charge–charge interaction.

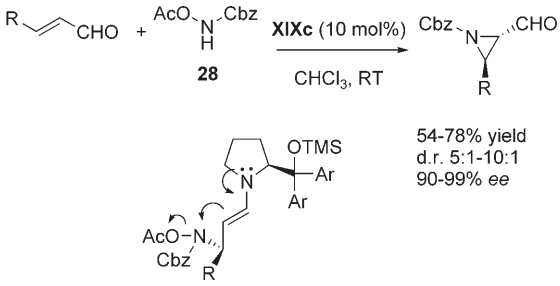
Shortly after, Jørgensen and co-workers demonstrated that the O-TMS diaryl prolinol **XIXa** can catalyze the direct epoxidation of β-mono or disubstituted α,β-unsaturated aldehydes under very mild conditions (Scheme 35).[113]



Scheme 35. Organocatalytic epoxidation.

Although the reaction seems to proceed best in dichloromethane, it is efficient in many different solvents, including alcohols and water. Hydrogen peroxide (35% in water) was used as the oxidant to achieve very good yields and excellent diastereomeric ratios and enantioselectivities. The mechanism first involves activation of the unsaturated aldehydes as an iminium ion and then nucleophilic addition of the hydrogen peroxide. The newly formed enamine intermediate **P** attacks the electrophilic peroxide unit and closes the three-membered ring. The protocol is also applicable to α,β-disubstituted acrolein derivatives. Mixtures of *E* and *Z* olefins are transformed with very good stereoselectivity. Such a stereoconvergent outcome, independent of the configuration of the double bond, has been observed in other iminium-catalyzed transformations (see Section 4.1).

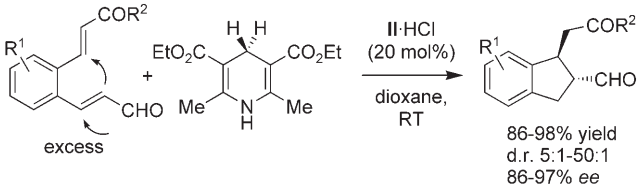
Approximately two years after these ground-breaking discoveries, the Córdova research group reported the asymmetric aziridination of α,β-unsaturated aldehydes (Scheme 36).[114] The key factor for the success of this



Scheme 36. Organocatalytic aziridination. Cbz = benzyloxycarbonyl.

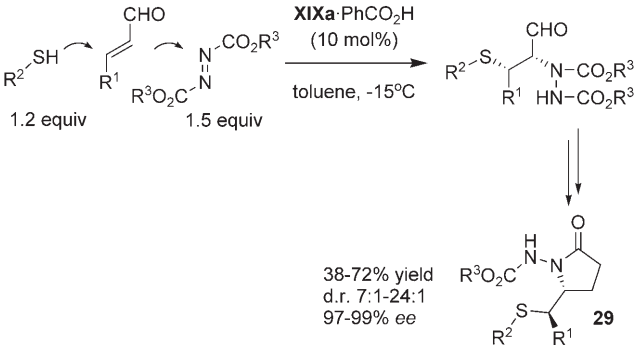
aminocatalytic asymmetric transformation was the choice of the nitrogen source **28**. The valuable aziridine scaffolds with an easily removable benzyl carbamate protecting group were obtained directly with very high enantiomeric excess (90–99% *ee*) by using the smallest of the Jørgensen-type catalysts **XIXc** (Ar = Ph).

Fundamental developments in the application of the iminium ion–enamine activation strategy were independently and simultaneously reported by the research groups of List, Jørgensen, and MacMillan. List and co-workers disclosed a domino organocatalytic hydrogenation/Michael cyclization. They used the HCl salt of MacMillan catalyst **II** and obtained excellent yields and levels of stereocontrol under very mild reaction conditions (Scheme 37).[115]



Scheme 37. Organocatalytic hydrogenation/Michael cyclization sequence.

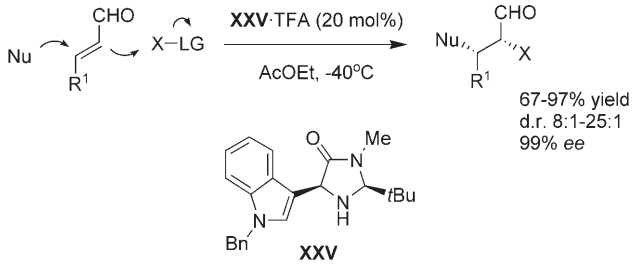
The research groups of Jørgensen[99] and MacMillan[116] went one step further by applying the iminium ion/enamine activation strategy to develop a series of new multicomponent reactions in which the two stereoselective steps are intermolecular reactions. Jørgensen and co-workers combined the first highly enantioselective organocatalytic addition of thiols to α,β-unsaturated aldehydes in an α-amination reaction (Scheme 38).[99] The products were further reduced and



Scheme 38. Aminocatalytic sulfa-Michael addition/amination sequence.

cyclizated in a one-pot process to afford **29** in good yields with excellent diastereomeric ratios and enantiomeric excess. One important aspect of this reaction is that moderate to good yields could be maintained when all three components were present in an approximately equimolar ratio in the multicomponent reaction.

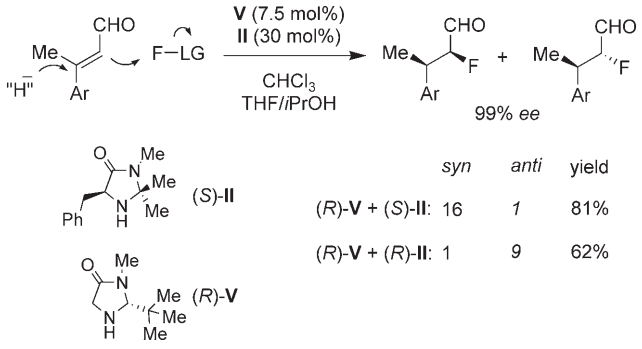
MacMillan and co-workers used a variation of their chiral imidazolidinones (**XXV**) to combine the enantioselective conjugate addition of a large number of diverse carbon-based nucleophiles with an α-chlorination (Scheme 39).[116]



Scheme 39. Aminocatalytic conjugate addition/halogenation. LG = leaving group.

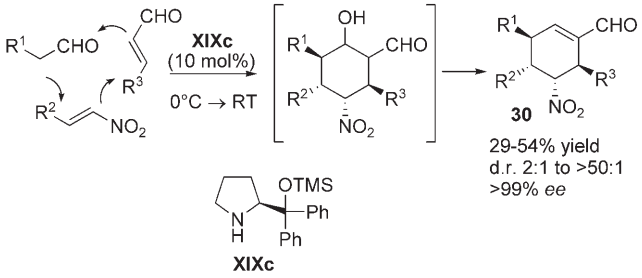
An extremely appealing feature of these domino sequences was observed by the research groups of both Jørgensen[117] and MacMillan.[116] They found that the interaction between the chiral catalyst and the chiral intermediate, resulting from the first conjugate addition, induces a remarkable enantioenrichment in the final enamine step. This approach affords rapid access to products with generally over 99% *ee*.

Furthermore, MacMillan and co-workers performed a series of investigations that significantly expanded the scope of this approach.[116] It was demonstrated clearly that organocatalysts with different iminium ion/enamine activities can coexist, thus allowing the preparation of both diastereoisomers of the optically active products. The Hantzsch ester **13** and NFSI (**18**) constitute the nucleophile and the electrophile, respectively, in a domino hydrogenation/fluorination reaction which, according to the catalyst combination, can give *syn* or *anti* addition products in good yield and with 99% *ee* (Scheme 40).



Scheme 40. Aminocatalytic *syn*- or *anti*-diastereoselective hydrogenation/fluorination reaction. LG = leaving group.

Enders and co-workers found success in the even more ambitious synthetic task of controlling four stereocenters in a triple domino reaction by using the aminocatalyst to perform an outstanding sequential enamine/iminium/enamine activation sequence (Scheme 41).[118,119] The O-TMS diphenylprolinol catalyst (**XIXc**) first controls a Michael addition of the aliphatic aldehydes to nitrostyrene derivatives. In the second step, the chiral amine catalyzes the conjugate addition of the nitroalkane intermediate to α,β-unsaturated aldehydes. The last step is an aldol reaction, where the less-hindered aldehyde acts as a nucleophile, which is followed by the elimination of water. The highly functionalized products **30** are obtained in essentially enantiopure form in a simple single operation.[118a]

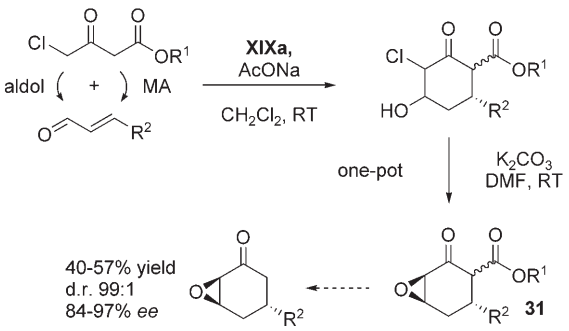


Scheme 41. Aminocatalytic enamine/iminium ion/enamine catalyzed domino reaction.

In parallel with the rush to reach the limits (three reaction partners and/or three catalytic steps) of aminocatalyzed domino reactions, the different research groups began a series of investigations that focused on the assembly of functionalized cyclic structures that could represent good

starting points for the synthesis of naturally occurring or biologically active compounds. Most of the recent organocatalytic domino reactions have a common strategy. The Michael addition is generally the first step. It creates a stereocenter with excellent enantiomeric excess but also the "tool" that links together, for example, an α,β-unsaturated aldehyde with a second bifunctional building block. Five- and six-membered rings were the main targets of initial experiments since they are kinetically or thermodynamically favored.

As a first example, Jørgensen and co-workers reported a domino conjugate addition and aldol reaction, followed by an in situ base-catalyzed intramolecular alkylation (Scheme 42).[120] The chiral catalyst controls only the first



Scheme 42. Organocatalytic iminium ion/cyclization.

step in this synthesis, while the weak base catalyzes the aldol condensation. Such transformations catalyzed by iminium ions are compatible with different organic as well as inorganic bases. Moreover, the enantiomeric excess in the overall process is not affected by their presence. The products **31** of this one-pot conjugate addition and Darzens condensation are obtained in good yield, remarkably so given the complexity of these molecules. More importantly, the first stereocenter, forged by the catalyst, induces complete stereocontrol over the other steps. After hydrolysis and decarboxylation of the ester group, the product containing three stereocenters is diastereomerically pure with up to 97% *ee*.

The principle of the most successful domino reactions is presented in Figure 6. As previously mentioned, the first step is often a conjugate addition, where the nucleophilic partner of the α,β-unsaturated aldehyde can be an activated methylene group (C–C bond formation).[121] Alternatively C–S, C–N, and C–O bonds can be formed using thiols,[122] amines,[123] and alcohols,[124] respectively. In the cyclization step, the newly formed saturated aldehyde can act as an electrophile (Figure 6a; for example, for aldol,[122c] nitroaldol,[121g,i] and Morita–Baylis–Hillman (MBH) reactions[121j] or carbamate addition[121k]) or as a nucleophile (Figure 6b). In this last case, the intramolecular α functionalization might occur via an enamine intermediate, as was presented earlier by the research groups of MacMillan, List, and Jørgensen. Examples involving aldol[122–124] (often followed by elimination), alkylation,[121c,d] or Michael additions[121f] have already been reported by different research groups. The optically active

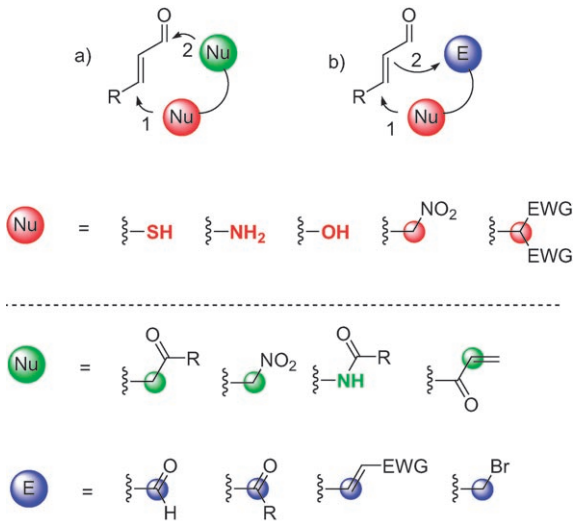


Figure 6. Organocatalytic iminium ion/cyclizations promoted by diaryl prolinol ethers and basic or acid co-catalysts. a) Domino nucleophilic additions to α,β-unsaturated aldehydes. b) Domino β- and α-functionalization of α,β-unsaturated aldehydes. EWG = electron-withdrawing group.

cyclized products with up to five[121i] newly formed stereocenters are always characterized not just by an excellent enantiomeric excess but, generally, by high to excellent diastereomeric ratios.

It is impossible to predict how extensive the application of organocatalyzed domino reactions will be in organic synthesis since every new report seems to expand the possibilities of this approach. When these ideas are combined with the possibility of one-pot oxidation, reduction, reductive amination, or Wittig reactions, the limits seem set only by the imagination of the chemists. It also seems reasonable that the particular thermodynamic and kinetic aspects of the different intramolecular steps will enable the broad generality of proline and of the different variations of the MacMillan or Jørgensen catalysts to be complemented by new and specifically designed catalyst structures. A host of new possibilities would appear if the concept of the coexistence of different organocatalysts, as introduced by MacMillan and co-workers,[116] could be exploited to control and engineer both the absolute and relative configuration of all the stereocenters of these complex optically active products. Furthermore, reactions catalyzed by iminium ions and enamines take place in the presence of strong acids and strong bases. They therefore seem perfectly suited to be combined with other organocatalytic strategies in even more efficient multicomponent or one-pot sequences, as was recently demonstrated by List and co-workers (Section 7.2).

7. New Directions

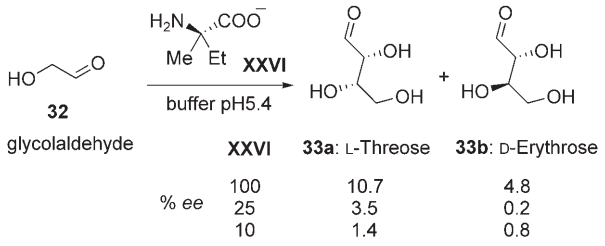
Asymmetric aminocatalysis has become established as a reliable and powerful tool for modern synthetic chemistry. It can deliver unique and divergent carbonyl activation pathways, complementing and often overcoming the inherent

restrictions of classic asymmetric methods. This has prompted recent research towards more ambitious objectives. The fundamental principles of aminocatalysis have been established, and now it can be combined with concepts from other areas of chemistry to develop previously unknown transformations.

7.1. Catalysis with Chiral Primary Amines

Chiral secondary amine catalysts have been the "stars" in asymmetric aminocatalytic. By contrast, little attention has been paid to the development of chiral primary amine catalysts. Yet, primary amine catalysis is effectively exploited by natural enzymes such as Type I aldolases and decarboxylases, both of which contain catalytically active lysine residues.[20] Moreover, since the pioneering studies in the early 1970s on intramolecular aldol cyclizations,[17] it was established that natural amino acids other than proline (such as L-phenylalanine) can promote enamine-based asymmetric transformations.[125] The notion of unfavorable imine–enamine equilibria may explain the low level of interest in the use of primary amines.[126] A more important reason is perhaps 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.

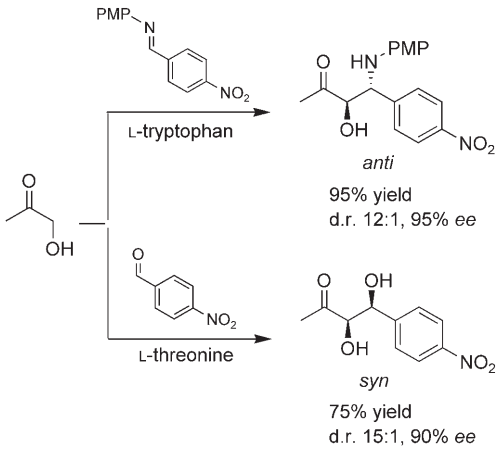
In 2004, Pizzarello and Weber reported on the catalytic influence of two nonracemic primary amino acids, alanine and isovaline, on a water-based prebiotic model of sugar synthesis by self-aldolization of glycol aldehydes **32** (Scheme 43).[31a]



Scheme 43. Primary amino acids as prebiotic asymmetric catalysts.

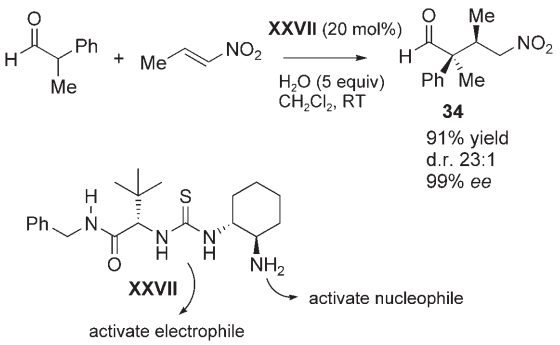
The choice of isovaline **XXVI** was due to the observation that this chiral amino acid is the most abundant in meteorites. The aminocatalyzed aldol condensation, carried out in aqueous triethylammonium acetate buffer (pH 5.4 at 50 °C), produced tetroses **33** with low enantiomeric excess. However, the asymmetric effect of the catalysts was still observed at the low levels of catalyst *ee* values found in meteorites. This finding corroborated the already proposed idea[127] that aminocatalytic reactions might have played a crucial role in the prebiotic asymmetric synthesis of the building blocks of life. This report generated a great drive towards the investigation of asymmetric amplification with amino acids as catalysis and its implication to the prebiotic evolution of homochirality (Section 3.2).[30,31] It also drew renewed attention towards primary amines as potentially useful organocatalysts.

Along these lines, some recent reports have demonstrated the ability of simple derivatives of natural and unnatural primary amino acids to efficiently promote important processes such as aldol[128] and Michael reactions.[129] An interesting application was described by Barbas and co-workers, who used L-tryptophan and L-threonine to catalyze the asymmetric *syn*-aldol and *anti*-selective Mannich reactions of hydroxy ketones (Scheme 44).[130] This approach represents an important synthetic advance, as it complements the ability of proline catalysis to afford only *syn*-1,2-amino alcohols and *anti*-1,2-diols (Section 3.4).



Scheme 44. Primary amines in enamine catalysis.

Catalysis with primary amines encompasses the classical activation modes of proline-derived catalysts, but also offers the unique possibility of effecting processes between sterically demanding partners. It thus overcomes the inherent difficulties of chiral secondary amines in generating congested covalent intermediates. An important example of the potential of primary amines for enamine activation was reported by Jacobsen and co-workers,[131] who employed a new bifunctional organocatalyst **XXVII** for the highly enantioselective direct conjugate addition of α,α-disubstituted aldehydes[132] to nitroalkenes (Scheme 45). Originally, such catalysts with primary amine groups and thiourea units were introduced independently by Tsogoeva and Wey as well as by Huang and

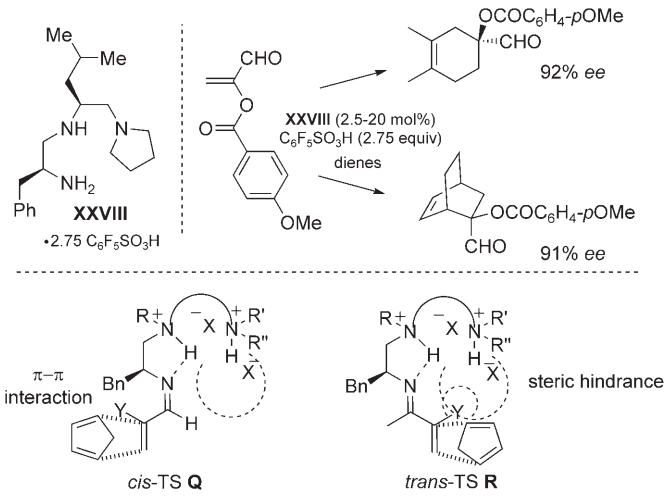


Scheme 45. Bifunctional catalysts by primary amine and thiourea groups.

Jacobsen for the organocatalytic asymmetric addition of ketones to nitroalkenes.[133] However, the innovative aspect of this study was the use of a challenging class of carbonyl compounds as nucleophilic counterparts—because of the inherent steric bias of the enamine intermediate—and the consequent construction of products **34** with two adjacent stereogenic carbon atoms (one of which is quaternary). The bifunctional catalyst **XXVII** combines the benefits associated with a primary amine moiety and a Brønsted acidic thiourea unit, an established framework which can effectively activate electrophiles through the formation of two hydrogen bonds.[5,134] These reports highlight how the capacity to extrapolate and combine concepts from different areas of organocatalysis is a crucial requirement for future progress.

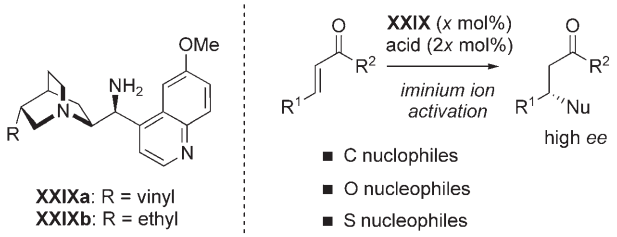
Chiral primary amine derivatives have recently also been employed to activate challenging classes of unsaturated carbonyl compounds as iminium ions, thereby overcoming the restrictions associated with secondary amine catalysis. For example, the efficient activation of α-substituted α,β-unsaturated aldehydes by the MacMillan imidazolidinone catalysts or by Jørgensen-type catalysts is generally not possible because of steric constraints. Ishihara and Nakano succeeded in this important goal by identifying a novel primary amine organocatalyst **XXVIII** for the first enantioselective Diels–Alder reaction with α-substituted acroleins.[135] In particular, α-acyloxyacroleins underwent *exo*-selective cycloaddition with a variety of dienes in very good yields and high enantioselectivity (Scheme 46). Notably, development of the best organocatalyst for this transformation was by a mechanism-guided design strategy based on a postulated five-membered cyclic *cis* or *trans* transition state (TS). Exploiting the π–π attractive interaction between the benzyl moiety of the catalyst and the π system of the iminium intermediate in the *cis*-TS **Q** and maximizing the steric hindrance between the counterion ($C_6F_5SO_3^-$), the catalyst architecture, and H_2C=CY in *trans*-TS **R**, catalyst **XXVIII** is able to promote the Diels–Alder reaction with high enantiocontrol.

The asymmetric β-functionalization of unsaturated ketones by iminium ion activation represents another difficult



Scheme 46. Primary amines in iminium catalysis: Diels–Alder reaction of α-substituted acroleins.

task, as sluggish reaction rates are usually observed under secondary chiral amine catalysis, probably because of the generation of only small amounts of the catalytically active adducts (see Section 4.2). Also in this context, primary amines could overcome the inherent limitations of the established organocatalysts. In particular, it was demonstrated that the salts of 9-amino-9-deoxyepiquinine (**XXIXa**) and 9-amino-9-deoxyepihydroquinine (**XXIXb**), prepared in a single step by a Mitsunobu reaction on the OH group of readily available cinchona alkaloids, are effective catalysts for the activation of enones (Scheme 47).[136] By choosing the appropriate counter-



Scheme 47. Primary amine salts as activators of enones as iminium ions.

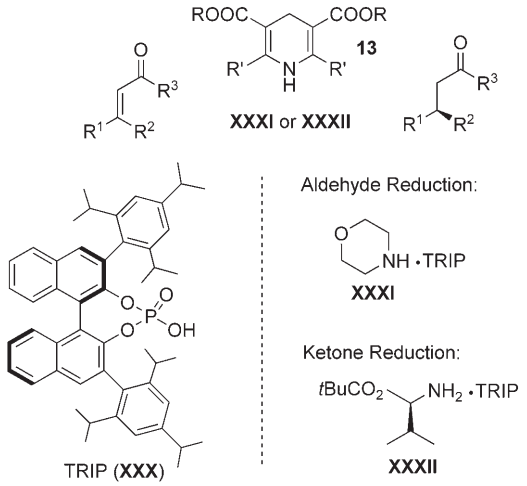
anions (such as from TFA or the chiral D-*N*-Boc phenylglycine), it was possible to tune the reactivity and the selectivity of the catalyst system, thereby allowing the highly enantioselective conjugate addition of a series of different nucleophiles. In addition to their generality as activators in iminium catalysis, catalysts **XXIX** have also been successfully employed for the asymmetric α functionalization of ketones via enamine intermediates.[137]

The recent results obtained by using chiral primary amines have shown the potential of this approach. It seems reasonable to expect that future studies on both enamine and iminium catalysis will expand the range of possible electrophiles or nucleophiles that can be stereoselectively introduced into ketones, and thereby approach the excellent levels of efficiency already reached in the aminocatalyzed functionalization of aldehydes. On the other hand, transformations involving α-substituted α,β-unsaturated carbonyl compounds still represent an important challenge. It is likely that much effort will be devoted to the design of novel catalysts to address this synthetic problem.

7.2. Asymmetric Aminocatalysis by Chiral Counteranions

List and co-workers recently introduced a novel strategy for enantioselective synthesis: asymmetric counterion-directed catalysis (ACDC).[138] This approach exploits the fact that most chemical transformations proceed via charged intermediates or transition states. High stereocontrol can thus be induced by the use of suitable chiral catalysts able to form chiral ion pairs.[139] Accordingly, catalytic reactions proceeding through cationic intermediates can be performed enantioselectively by introducing a chiral counteranion into the catalyst. The List research group applied this concept to

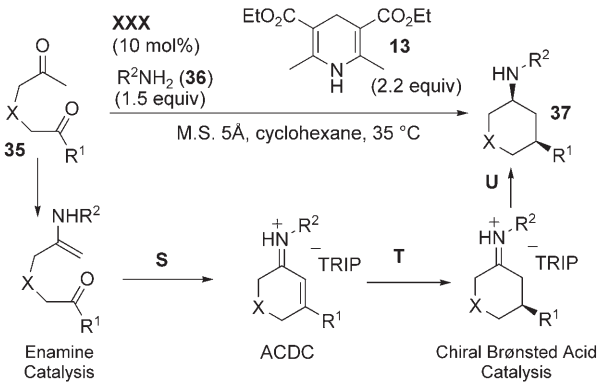
iminium catalysis, since the fundamental covalent intermediates derived from the condensation of amine catalysts and carbonyl compounds are positively charged. As a proof of concept, the asymmetric biomimetic transfer hydrogenation of α,β-unsaturated aldehydes was studied.[138a] This transformation had already been achieved by employing salts of chiral secondary amines (Section 4.1).[64] By applying ACDC, it was demonstrated that the catalytic ammonium salt **XXXI**, made by combining an achiral secondary amine such as morpholine and the chiral phosphoric acid 3,3′-bis(2,4,6-triisopropylphenyl)1,1′-diylhydrogen phosphate (**XXX**, TRIP), can function as a highly enantioselective iminium catalyst in the conjugate reduction of enals (Scheme 48).[138a] The use of the chiral binaphthol-based phosphoric acid derivatives as the counteranions was inspired by their recent application as highly efficient chiral Brønsted acids to catalyze highly stereoselective nucleophilic additions to imines.[5a–d]



Scheme 48. Asymmetric counterion directed catalysis (ACDC).

The ACDC approach was later extended to the asymmetric transfer hydrogenation of α,β-unsaturated ketones.[138b] To obtain high reactivity as well asymmetry in the process, the new salt **XXXII**, which consists of a chiral primary amine and a chiral anion, was developed as the catalyst. Efficient activation relies on the proven ability of primary amines to form congested iminium ion intermediates from ketones, together with the benefits of asymmetric counteranion-directed catalysis.

The potential of this new concept is far from being fully disclosed.[138c] An impressive example of its utility was recently demonstrated by Zhou and List. They combined ACDC and Brønsted acid activations in a new triple organocascade sequence to give pharmaceutically relevant substituted cyclohexylamines **37** (Scheme 49).[140] Starting from 2,6-diketones **35** and Hantzsch ester **13**, the combination of an achiral primary amine such as *p*-alkoxy anilines **36** with a catalytic amount of TRIP (**XXX**) promotes an aldolization/dehydration step (**S**) by enamine activation. This step is followed by asymmetric conjugate reduction proceeding through ACDC (**T**) and a final Brønsted acid catalyzed



Scheme 49. Combining aminocatalysis and ACDC.

reductive amination (**U**) to give the product.[141] Interestingly, both the amine and the phosphoric acid are essential for promoting the first two reaction steps, and, of a series of chiral acids tested, only TRIP gave the observed *cis* selectivity in the final reductive step.

It is unclear why the the potential role of the counterion in iminium catalysis was underrated for so long, particularly when considering that strong counterion effects on both reactivity and selectivity had already been found in early studies of aminocatalytic activation. The introduction of ACDC into aminocatalysis illustrates how the "aminocatalysis gold rush" may be sustained by "thinking out of the box" and by combining ideas from different areas of organocatalysis, for example, catalysis by chiral hydrogen-bond donors[5] and phase-transfer catalysis.[6,139] Notably, it was recently demonstrated how the ACDC strategy can be applied not only to purely organic catalysts, but also to organometallic systems, thus providing new opportunities for asymmetric catalysis.[142] These reports illustrate how concepts of organocatalysis are starting to positively influence other established synthetic areas.

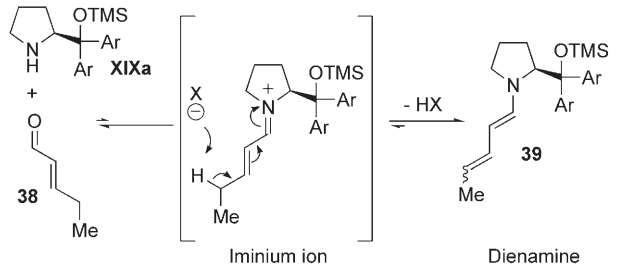
7.3. New Activation Modes

Asymmetric aminocatalysis, with activation as enamines and iminium ions, has resulted in a number of highly chemo- and stereoselective α- and β-functionalizations of carbonyl compounds with electrophilic and nucleophilic reagents, respectively. The current goal for the progress and implementation of organocatalysis is the exploration of new activation modes that will allow transformations that cannot be realized by other means. Along these lines, two new activation concepts based on the use of chiral secondary amines have recently been introduced which enable the γ-functionalization of α,β-unsaturated aldehydes and the challenging α-alkylations of aldehydes.

7.3.1. Dienamine Catalysis for γ-Functionalization of α,β-Unsaturated Aldehydes

The addition of nucleophiles to α,β-unsaturated aldehydes is one of the most important strategies in organo-

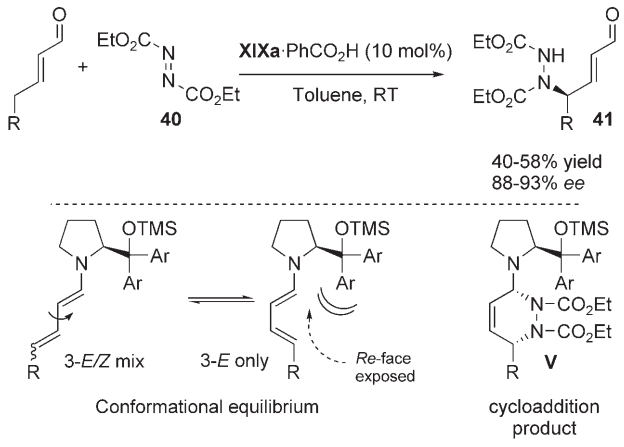
catalysis, and the key intermediate in these catalytic processes is the highly electrophilic iminium ion. However, Jørgensen and co-workers[12] reported that the concentration of the iminium ion formed in the reaction between catalyst **XIXa** and (*E*)-pent-2-enal (**38**) is so low under conditions generally used for 1,4-additions that it could not be detected by ^{1}H NMR spectroscopy. The negatively charged counterion can easily extract the γ proton of the iminium ion and, as a result, the electron-rich dienamine **39** is the most abundant species in solution (Scheme 50).



Scheme 50. HOMO activation of α,β-unsaturated aldehydes to form dienamines.

Dienamines are well-known compounds, and their transient formation has been proposed as an important step in organocatalytic domino reactions involving α,β-unsaturated ketones (Section 6). The equilibrium between the iminium ion and dienamine was also invoked as the reason for the enantioconvergence observed in the enantioselective amino-catalyzed transfer hydrogenation reaction (Section 4.2). However, the possibility of taking advantage of these reactive intermediates for the γ functionalization of α,β-unsaturated carbonyl compounds had surprisingly been ignored.

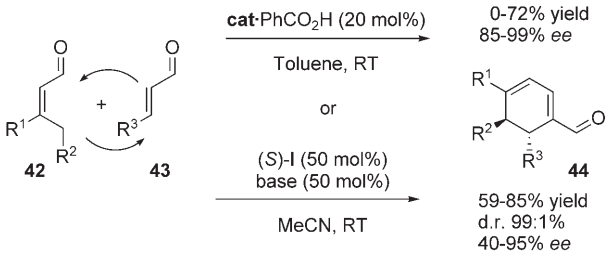
Based on the results of a simple spectroscopic experiment, Jørgensen and co-workers developed the first γ-amination of α,β-unsaturated aldehydes (Scheme 51).[12] The chiral amine **XIXa** catalyzes the nucleophilic addition of a number of α,β-unsaturated aldehydes with aliphatic substituents in the β position to diethyl azodicarboxylate (DEAD, **40**). The products **41** were obtained in moderate yield and with very



Scheme 51. Dienamine-catalyzed γ-amination of α,β-unsaturated aldehydes.

similar enantiomeric excess (88–93% *ee*). The high enantiomeric excess observed seems not to be consistent with the direct functionalization of the γ-carbon atom, since the dienamine is present as a *Z*/*E* mixture: a racemic product would be expected if the two isomers have similar reactivity. On the basis of the experimental evidence and computational investigations, the authors proposed that the γ-amination of α,β-unsaturated aldehydes might be the result of a [4+2] cycloaddition between the (*E*,s-*cis*,*E*)-dienamine and diethyl azodicarboxylate (**40**) as the dienophile. The hydrolysis of the cyclic aminal intermediate **V** leads to the release of the catalyst and the optically active product **41**.

The research group of Hong applied dienamine catalysis to a highly enantioselective Robinson annulation of α,β-unsaturated aldehydes.[143,144] The authors proposed that, in this case, the products **44** are the result of a domino conjugate addition/aldol/elimination reaction rather than a [4+2] cycloaddition (Scheme 52).[143] The nucleophilic addition of the

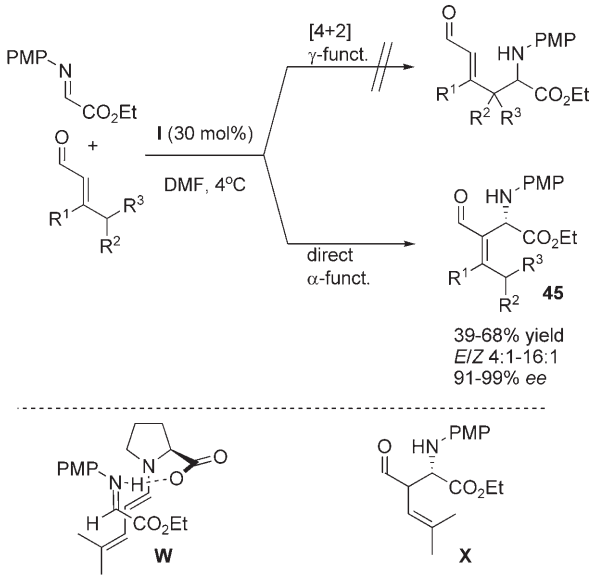


Scheme 52. Asymmetric Robinson annulation of α,β-unsaturated aldehydes initiated by the formation of a dienamine. R^1 = alkyl or H; cat. = (*S*)-**XIXc** (or (*R*)-**XIXd**); base = Et_3N or (−)-sparteine.

dienamine, formed by reaction of enals **42** with the chiral amine (**XIXc, XIXd**, or **I**), to the Michael acceptor **43** proceeds with moderate to good yields and generally with high enantiomeric excess. The catalyst might be necessary not just for the formation of the dienamine, but also for the simultaneous activation of the Michael acceptor **43** as an iminium ion and/or in the cyclization step. It is also very interesting how, in this case, catalysts **XIXc** (derived from L-proline) and L-proline (**I**) promote the formation of products with the same absolute configuration.[145] It is therefore possible that the complex mechanism of the reaction and of the chiral induction might not be the same for both catalytic systems and for all the substrates. When both α,β-unsaturated aldehydes can act as nucleophiles ($R^3 = CH_2R$), the chemoselectivity observed is in accordance with the preferred formation of the most substituted dienamine. In general, diaryl prolinols lead to very enantioselective reactions (up to 99% *ee*). However, the application of catalyst **XIXc**,**d** is possible only in the case of β-disubstituted pronucleophiles (R^1 = alkyl); proline is a good catalyst for a wider range of reagent combinations. For example, dimerization of (*E*)-4-oxobut-2-enyl acetate (R^1 = H, R^2 = OAc, $R^3 = CH_2OAc$) took place only in the presence of proline (**I**); the product was obtained with 95% *ee* and used as a starting point for the synthesis of (+)-palitantin.

Previous examples underscore how the dienamine equilibrium can be used to perform a new series of γ-function-

alization of carbonyl compounds. However, a recent paper by Barbas and co-workers demonstrated that the reactivity of this conjugate enamine can be selectively controlled.[146] Proline (**I**) catalyzes the direct α-functionalization of α,β-unsaturated aldehydes with N-PMP-protected α-imino ethyl glyoxylate instead of the addition at the γ-carbon atom (Scheme 53). The products **45** of the aza-Morita–Baylis–Hillman (MBH) reaction are formed in moderate yields (39–68% yield), but with excellent enantioselectivities (up to



Scheme 53. Comparison of dienamine catalysis by γ-functionalization and α-functionalization. Mannich reaction for the formation of aza-Morita–Baylis–Hillman-type products. Structure **W** shows the Bifunctional proline catalysis, structure **X** is a nonconjugated intermediate.

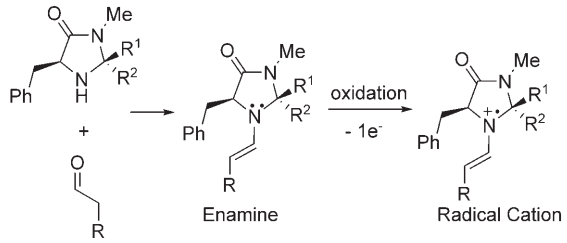
99% *ee*). In the transition state **W**, he simultaneous activation of the imine by the acid functionalities of proline probably compensates for the higher energy required for the formation of an intermediate **X** that is not stabilized by conjugation. Isomerization of the double bond that leads to the final product **45** can occur spontaneously or is catalyzed by proline itself or by additives such imidazole.

Dienamine catalysis offers a number of new possibilities to synthetic chemists.[147] The high reactivity of these conjugate enamines can be controlled by careful choice of catalyst, reagents, and conditions. The few examples reported showed that the highly enantioselective γ-functionalization of α,β-unsaturated carbonyl compounds can be achieved by [4+2] cycloadditions or as a result of a direct nucleophilic γ-addition. Furthermore, dienamine catalysis is also a valuable strategy for the preparation of highly functionalized MBH-type products that cannot easily be prepared by conventional methods.

7.3.2. ***Radical Aminocatalysis***

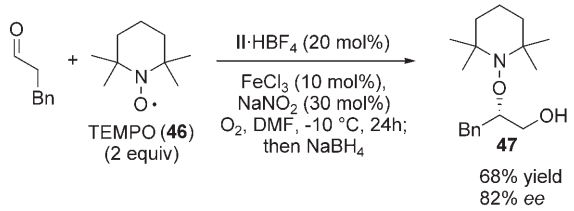
Recently, the research groups of MacMillan[13a–b] and Sibi[13c] almost simultaneously introduced a new aminocatalytic activation concept, termed singly occupied molecular orbital (SOMO) catalysis, which is based on radical intermediates.[148] These reports represent a breakthrough in the aminocatalytic field and link distant research areas such as organocatalysis and radical chemistry. Thus, this approach allows a shift from processes involving charged intermediates to radical catalysis. The reports introduced a totally different synthetic paradigm that goes beyond the established reactivity and expands the field of asymmetric aminocatalysis.

From a chemical viewpoint, SOMO catalysis exploits the susceptibility of the transient enamine (generated by condensation of aldehydes and a chiral amine) to undergo selective oxidation relative to other reaction components. It thus generates a radical cation with three π electrons and a singly occupied molecular orbital (SOMO), which is more activated toward subsequent chemical attack than the aldehyde starting material (Scheme 54).



Scheme 54. The principle of SOMO catalysis.

Sibi and Hasegawa exploited aminocatalytic SOMO activation for the stereoselective α-oxygenation of aldehydes. They used the MacMillan imidazolidinone **II** as the catalyst and a substoichiometric amount of $FeCl_3$ for single-electron transfer (SET) in the presence of $NaNO_2/O_2$ as a cooxidant to regenerate the radical active intermediate from the enamine (Scheme 55).[13c] The use of TEMPO (**46**), a persistent radical

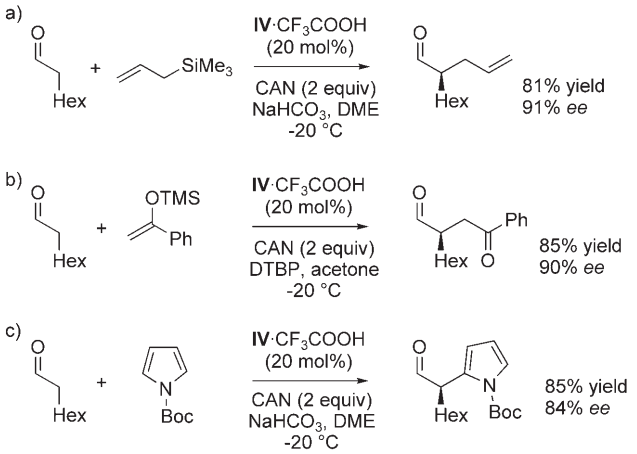


Scheme 55. SOMO catalysis for the α-oxygenation of aldehydes.

reagent, to intercept the radical cationic species affords the desired oxygenated adducts **47** in moderate to high enantioselectivity. Although the same products are accessible by the highly stereoselective proline-catalyzed addition of aldehydes to nitrosobenzene and molecular oxygen (Section 3.4.3), this study represented a significant proof of concept for SOMO catalysis.

MacMillan and co-workers demonstrated the real value of the novel activation strategy by applying SOMO catalysis to the highly enantioselective α-alkylation of aldehydes, a fundamental yet challenging C–C bond-forming transforma-

tion for asymmetric synthesis and organocatalysis[13a,b] (see Section 3.4.4 for an intramolecular organocatalytic variant). The cationic radical intermediates are generated by oxidation of the enamine, formed by condensation of aldehydes with the second generation imidazolidinone catalyst **IV**, with cerium ammonium nitrate (CAN, Scheme 56). After reaction with π-electron-rich silylated reagents (the actual alkylating agents)



Scheme 56. Asymmetric α-allylation (a), α-enolation (b), and α-arylation (c) of aldehydes by SOMO catalysis. DTBP = 2,6-di-*tert*-butylpyridine, DME = 1,2-dimethoxyethane.

a second oxidation by CAN and removal of the silyl group afford the α-functionalized aldehydes with high enantiopurity. Interestingly, the enantiofacial discrimination observed in the SOMO-activated intermediate arises from the same structural features of the catalyst **IV** that are responsible for the steric shielding in enamine–iminium intermediates.

SOMO catalysis was applied to asymmetric α-allylation[13a] and α-enolation[13b] of aldehydes and also to α-arylation by using N-Boc-protected pyrrole as the somophile[13a] (Scheme 56). It should be noted that, in these transformations, the α-carbon atom of the aldehyde reacts with nucleophilic reagents. Formally, this activation mode reverses the common polar reactivity (umpolung) of enamine intermediates, thereby allowing reactions that are not possible with established catalysis concepts.

SOMO catalysis will almost certainly have a major impact on asymmetric aminocatalysis, with many applications expected in the near future.[149] New possibilities for SOMO activation may be offered by the extension of this tactic to different aldehydes and ketones, and to other classes of reagents typical of radical chemistry.

8. Summary and Outlook

> *"Gold! Gold! Gold from the American River!"*

This simple cry is the most famous quote from the Californian Gold Rush.[150a] Shouted on the streets of San Francisco in 1848 by merchant S. Brannan, it caused a record population explosion, with the city's population growing from about 1000 in 1848 to 25000 full-time residents in 1850.[150b] Similarly, organic chemists have been attracted by the seminal reports on secondary amine catalysis by List, Lerner, and Barbas,[2] and by MacMillan and co-workers.[3] The rediscovery of enamine chemistry and its application in catalytic enantioselective reactions had greater consequences than expected. The initial results of a few leading research groups prompted the explosion of organocatalysis, a fast-growing research field with a scope that now goes beyond aminocatalyzed reactions. However, chiral amine catalysts play a key role in this unstoppable stream of discovery, and the combined efforts of many highly skilled individuals have turned asymmetric aminocatalysis into a well-established and reliable synthetic strategy. This approach has great potential, since organocatalysts are generally readily available, very robust, and less toxic than organometallic complexes. It is important to stress the operational simplicity of these reactions: Limited specialist equipment is required since reactions usually take place under very mild conditions, do not need inert atmospheres, and might be carried out under neat conditions or in environmentally friendly solvents. Furthermore, several examples have demonstrated how aminocatalyzed reactions may be readily scaled-up without detrimental effects on the yield or enantiomeric excess.

As is true of any field that has reached a certain stage of maturity, new developments will focus on more ambitious objectives, thus increasing the high standards of innovation and practicality. There is now a deep understanding of the complex mechanisms associated with the multistep processes inherent to aminocatalysis. This knowledge is beginning to form a reliable platform for the rational design of new catalysts and new reactions. Recent studies have demonstrated that it is now possible to engineer and prepare specific catalysts to efficiently address important issues relating to the synthesis of challenging and previously inaccessible target molecules. Moreover, asymmetric aminocatalysis is becoming an invaluable tool for the direct preparation of enantiopure complex molecules through domino and multicomponent reactions. Such regulated catalytic cascade sequences, which are typical of biological systems, do not require time-consuming and costly operations, such as isolation or purification of intermediates. In this context, this strategy may be a key element in the design of sustainable processes for the synthesis of drugs and relevant biologically active compounds.[151]

Finally, a critical goal for the continued expansion of aminocatalysis will be the design and implementation of new activation concepts to enable previously unknown transformations to be carried out. The recent introduction of ACDC and SOMO catalysis, in addition to their major synthetic implications, illustrates how important it is to extrapolate and mix ideas from different areas of chemistry. This Review has highlighted some of the amazing results which have been already achieved; however, we can certainly assert that the "asymmetric aminocatalysis gold rush" is still on.[152]

We thank Stefano Barbaresco for drawing the "Pioneers' Wagon" in the frontispiece. Finally, P.M. thanks Amleto Piazzi for all his invaluable advices.

Received: December 3, 2007

[1] For general reviews on asymmetric organocatalysis, see: a) *Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**; b) M. J. Gaunt, C. C. C. Johansson, A. McNally, N. C. Vo, *Drug Discovery Today* **2007**, *12*, 8 – 27; c) B. List, J. W. Yang, *Science* **2006**, *313*, 1584 – 1586; d) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719 – 724; e) *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis* (Eds.: A. Berkessel, H. Gröger) Wiley-VCH, Weinheim, **2004**; f) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248 – 5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138 – 5175; for special issues on asymmetric organocatalysis, see: g) *Adv. Synth. Catal.* **2004**, *346*, 1007 – 1249 (Eds.: B. List, C. Bolm); h) *Acc. Chem. Res.* **2004**, *37*, 487 – 631 (Eds.: K. N. Houk, B. List); for a recent review on the immobilization of organic catalysts, see: i) F. Cozzi, *Adv. Synth. Catal.* **2006**, *348*, 1367 – 1390.

[2] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395 – 2396.

[3] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243 – 4244.

[4] For recent reviews on asymmetric aminocatalysis, see: a) B. List, *Chem. Commun.* **2006**, 819 – 824; b) M. Marigo, K. A. Jørgensen, *Chem. Commun.* **2006**, 2001 – 2011; c) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84 – 96; d) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580 – 591; e) E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481 – 2495; f) B. List, *Synlett* **2001**, 1675 – 1686; for an excellent essay that provides historical context to the development of enamine/iminium ion based organocatalysis, see: g) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44 – 50; *Angew. Chem. Int. Ed.* **2008**, *47*, 42 – 47.

[5] For reviews on asymmetric catalysis by chiral hydrogen-bonding donors, see: a) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550 – 1573; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520 – 1543; b) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999 – 1010; c) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418 – 5427; d) S. J. Connon, *Angew. Chem.* **2006**, *118*, 4013 – 4016; *Angew. Chem. Int. Ed.* **2006**, *45*, 3909 – 3912; e) C. Bolm, T. Rantanen, I. Schiffers, L. Zani, *Angew. Chem.* **2005**, *117*, 1788 – 1793; *Angew. Chem. Int. Ed.* **2005**, *44*, 1758 – 1763; f) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299 – 4306; g) P. M. Pihko, *Angew. Chem.* **2004**, *116*, 2110 – 2113; *Angew. Chem. Int. Ed.* **2004**, *43*, 2062 – 2064; h) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289 – 296.

[6] For reviews on asymmetric phase-transfer catalysis, see: a) T. Ooi, K. Maruoka, *Angew. Chem.* **2007**, *119*, 4300 – 4345; *Angew. Chem. Int. Ed.* **2007**, *46*, 4222 – 4266; b) M. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506 – 517; c) B. Lygo, B. I. Andrews, *Acc. Chem. Res.* **2004**, *37*, 518 – 525; d) K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013 – 3028.

[7] For reviews on chiral bases-catalyzed transformations, see: a) T. Marcelli, T. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2006**, *118*, 7658 – 7666; *Angew. Chem. Int. Ed.* **2006**, *45*, 7496 – 7504; b) S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621 – 631; c) S. France, D. J. Guerin, S. J. Miller, T. Letcka, *Chem. Rev.* **2003**, *103*, 2985 – 3012.

[8] Quotation from The California Gold Rush: *Wikipedia, the free encyclopedia.* Retrieved September 19, 2007. http://en.wikipedia.org/wiki/California_Gold_Rush#_note-BancroftGoldGoldGold.

[9] The definitions of enamine catalysis and iminium catalysis have been given by List in Ref. [4f]: "There are two aminocatalytic pathways. Iminium catalysis directly utilizes the higher reactivity of the iminium ion in comparison to the carbonyl species and facilitates Knoevenagel-type condensations, cyclo- and nucleophilic additions, and cleavage of σ-bonds adjacent to the α-carbon. Enamine catalysis on the other hand involves catalytically generated enamine intermediates that are formed via deprotonation of an iminium ion, and react with various electrophiles or undergo pericyclic reactions."

[10] For a review on asymmetric enamine catalysis, see: a) B. List, *Acc. Chem. Res.* **2004**, *37*, 548 – 557; b) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471 – 5569; see also Ref. [4].

[11] For a review on asymmetric iminium ion catalysis, see: a) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79 – 87; b) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416 – 5570; for recent general reviews on organocatalytic asymmetric conjugate additions, see: c) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701 – 1716; d) D. Almaşi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299 – 365; e) J. L. Vicario, D. Badia, L. Carrillo, *Synthesis* **2007**, 2065 – 2092.

[12] S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973 – 12980.

[13] a) T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582 – 585; b) H.-Y. Jang, J.-B. Hong, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**, *129*, 7004 – 7005; c) M. P. Sibi, M. Hasegawa, *J. Am. Chem. Soc.* **2007**, *129*, 4124 – 4125; for recent highlights, see: d) S. Mukherjee, B. List, *Nature* **2007**, *447*, 152 – 153; e) S. Bertelsen, M. Nielsen, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 7500 – 7503; *Angew. Chem. Int. Ed.* **2007**, *46*, 7356 – 7359.

[14] The original sentence by Leonardo da Vinci, "*Trattato della Natura*", 1500.

[15] a) B. List, *Tetrahedron* **2002**, *58*, 5573 – 5590; b) H. Gröger, J. Wilken, *Angew. Chem.* **2001**, *113*, 545 – 548; *Angew. Chem. Int. Ed.* **2001**, *40*, 529 – 532.

[16] M. Movassaghi, E. N. Jacobsen, *Science* **2002**, *298*, 1904 – 1905.

[17] a) Z. G. Hajos, D. R. Parrish, German Patent DE 2102623, 29 July, **1971**; b) U. Eder, G. Sauer, R. Wiechert, German Patent DE 2014757, 7 October, **1971**; c) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492 – 493; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496 – 497; d) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615 – 1621.

[18] An enamine mechanism was already suggested in 1970s, see: K. L. Brown, L. Damm, J. D. Dunitz, A. Eschenmoser, R. Hobi, C. Kratky, *Helv. Chim. Acta* **1978**, *61*, 3108 – 3135; see also Ref. [22b,c].

[19] a) J. Wagner, R. A. Lerner, C. F. Barbas III, *Science* **1995**, *270*, 1797 – 1800; b) C. F. Barbas III, A. Heine, G. Zhong, T. Hoffmann, S. Gramatikova, R. Björnestedt, B. List, J. Anderson, E. A. Stura, E. A. Wilson, R. A. Lerner, *Science* **1997**, *278*, 2085 – 2092; c) G. Zhong, R. A. Lerner, C. F. Barbas III, *Angew. Chem.* **1999**, *111*, 3957 – 3960; *Angew. Chem. Int. Ed.* **1999**, *38*, 3738 – 3741.

[20] A. Heine, G. DeSantis, J. G. Luz, M. Mitchell, C.-H. Wong, *Science* **2001**, *294*, 369 – 374, and references therein.

[21] a) T. Hoffmann, G. Zhong, B. List, D. Shabat, J. Anderson, S. Gramatikova, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **1998**, *120*, 2768 – 2779; b) G. Zhong, T. Hoffmann, R. A. Lerner, S. Danishefsky, C. F. Barbas III, *J. Am. Chem. Soc.* **1997**, *119*, 8131 – 8132.

[22] a) B. List, P. Pojarliev, C. Costello, *Org. Lett.* **2001**, *3*, 573 – 576; b) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386 – 7387;

c) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260 – 5267.
[23] The idea of intramolecular carboxylic acid catalysis (Brønsted cocatalyst) proposed by List, Lerner, and Barbas in Ref. [2] can be traced back to a review in 1976: M. E. Jung, *Tetrahedron* **1976**, *32*, 3 – 31.
[24] B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5839 – 5842; for studies demonstrating a linear relationship between the *ee* value of L-proline and that of the aldol product, see Refs. [4f] and [22c].
[25] a) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 11273 – 11283; b) K. N. Rankin, J. W. Gauld, R. J. Boyd, *J. Phys. Chem. A* **2002**, *106*, 5155 – 5159; c) S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 2475 – 2479; d) C. Allemann, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong, K. N. Houk, *Acc. Chem. Res.* **2004**, *37*, 558 – 569.
[26] a) N. Zotova, A. Franzke, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.* **2007**, *129*, 15100 – 15101; for previous studies on the effect of water, see: b) P. M. Pihko, K. M. Laurikainen, A. Usano, A. I. Nyberg, J. A. Kaavi, *Tetrahedron* **2006**, *62*, 317 – 328.
[27] For a review of their work, see: C. Agami, *Bull. Soc. Chim. Fr.* **1988**, *3*, 499 – 507.
[28] C. Puchot, O. Samuel, E. Duñach, S. Zhao, C. Agami, H. B. Kagan, *J. Am. Chem. Soc.* **1986**, *108*, 2353 – 2357.
[29] L. Hoang, S. Bahmanyar, K. N. Houk, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 16 – 17.
[30] a) M. Klussmann, H. Iwamura, S. P. Mathew, D. H. Wells, Jr., U. Pandya, A. Armstrong, D. G. Blackmond, *Nature* **2006**, *441*, 621 – 623; see also: b) Y. Hayashi, M. Matsuzawa, J. Yamaguchi, S. Yonehara, Y. Matsumoto, M. Shoji, D. Hashizume, H. Koshino, *Angew. Chem.* **2006**, *118*, 4709 – 4713; *Angew. Chem. Int. Ed.* **2006**, *45*, 4593 – 4597.
[31] a) S. Pizzarello, A. L. Weber, *Science* **2004**, *303*, 1151; b) R. Breslow, M. S. Levine, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 12979 – 12980; c) S. Pizzarello, *Chem. Biodiversity* **2007**, *4*, 680 – 693.
[32] M. Klussmann, S. P. Mathew, H. Iwamura, D. H. Wells, Jr., A. Armstrong, D. G. Blackmond, *Angew. Chem.* **2006**, *118*, 8157 – 8160; *Angew. Chem. Int. Ed.* **2006**, *45*, 7989 – 7992.
[33] a) F. R. Clemente, K. N. Houk, *Angew. Chem.* **2004**, *116*, 5890 – 5892; *Angew. Chem. Int. Ed.* **2004**, *43*, 5766 – 5768; b) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 9922 – 9923.
[34] a) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336 – 9337; b) B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827 – 833; for similar studies, see: c) W. Notz, K. Sakthivel, T. Bui, G. Zhong, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 199 – 201.
[35] For a recent review on asymmetric organocatalytic Mannich reactions, see: A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, 5797 – 5815.
[36] S. Bahmanyar, K. N. Houk, *Org. Lett.* **2003**, *5*, 1249 – 1251.
[37] B. List, P. Pojarliev, J. Martin, *Org. Lett.* **2001**, *3*, 2423 – 2425.
[38] In Ref. [22c] the use of proline to catalyze Michael additions of acetone to nitrostyrene to afford racemic products was described. For related pioneering studies on Michael additions by enamine catalysis, see: J. M. Betancort, K. Sakthivel, R. Thayumanavan, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 4441 – 4444.
[39] For an improved proline-based protocol, see: a) D. Enders, A. Seki, *Synlett* **2002**, 26 – 28. See also Ref. [40b]; for selected examples on the use of different secondary amine catalysts, see: b) O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147 – 1168, and references therein; c) T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.* **2004**, *126*, 9558 – 9559; d) S. V. Pansare, K. Pandya, *J. Am. Chem. Soc.* **2006**, *128*, 9624 – 9625; e) C. Palomo, S. Vera, A. Mielgo, E. Gómez-Bengoa, *Angew. Chem.* **2006**, *118*, 6130 – 6133; *Angew. Chem. Int. Ed.* **2006**, *45*, 5984 – 5987, and references therein.
[40] a) A. Córdova, W. Notz, C. F. Barbas III, *J. Org. Chem.* **2002**, *67*, 301 – 303; for the first asymmetric Michael addition of aldehydes to nitroalkenes by using proline-derived secondary amines as catalysts, see: b) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737 – 3740; for related studies, see: c) H. Hagiwara, T. Okabe, T. Hakoda, T. Hoshi, H. Ono, V. P. Kamat, T. Suzuki, M. Ando, *Tetrahedron Lett.* **2001**, *42*, 2705 – 2707.
[41] For a seminal paper, see: a) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, R. Terrel, *J. Am. Chem. Soc.* **1963**, *85*, 207 – 222; also see: b) *The Chemistry of Enamines* (Ed.: Z. Rappaport), Wiley, New York, **1994**.
[42] a) A. Córdova, S. Watanabe, F. Tanaka, W. Notz, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1866 – 1867; for a similar Mannich strategy in which ketones were employed as donors, see: b) A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1842 – 1843; an interesting autocatalytic mechanism in which the chiral product acts as catalyst for its own formation has been observed for this reaction: c) M. Mauksch, S. B. Tsogoeva, I. M. Martynova, S. Wei, *Angew. Chem.* **2007**, *119*, 397 – 400; *Angew. Chem. Int. Ed.* **2007**, *46*, 393 – 396 .
[43] a) Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji, K. Sakai, *Angew. Chem.* **2003**, *115*, 3805 – 3808; *Angew. Chem. Int. Ed.* **2003**, *42*, 3677 – 3680; b) A. Córdova, *Chem. Eur. J.* **2004**, *10*, 1987 – 1997.
[44] a) J. W. Yang, M. Stadler, B. List, *Angew. Chem.* **2007**, *119*, 615 – 617; *Angew. Chem. Int. Ed.* **2007**, *46*, 609 – 611; see also: b) J. Vesely, R. Rios, I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 421 – 425; for the first proline-catalyzed asymmetric Mannich reaction of a ketone and N-Boc imines (two examples), see: c) D. Enders, C. Grondal, M. Vrettou, *Synthesis* **2006**, 3597 – 3604; see also: d) D. Enders, M. Vrettou, *Synthesis* **2006**, 2155 – 2158.
[45] A. Bøgevig, K. Kumaragurubaran, K. A. Jørgensen, *Chem. Commun.* **2002**, 620 – 621.
[46] a) O. Tokuda, T. Kano, W.-G. Gao, T. Ikemoto, K. Maruoka, *Org. Lett.* **2005**, *7*, 5103 – 5105; b) P. Dambruoso, A. Massi, A. Dondoni, *Org. Lett.* **2005**, *7*, 4657 – 4660; c) S. Samanta, C.-G. Zhao, *J. Am. Chem. Soc.* **2006**, *128*, 7442 – 7443.
[47] a) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798 – 6799; for an intramolecular variant, see: b) C. Pidathala, L. Hoang, N. Vignola, B. List, *Angew. Chem.* **2003**, *115*, 2891 – 2894; *Angew. Chem. Int. Ed.* **2003**, *42*, 2785 – 2788; for a highlight on cross-aldol reactions, see: c) B. Alcaide, P. Almendros, *Angew. Chem.* **2003**, *115*, 884 – 886; *Angew. Chem. Int. Ed.* **2003**, *42*, 858 – 860.
[48] A. B. Northrup, I. K. Mangion, F. Hettche, D. W. C. MacMillan, *Angew. Chem.* **2004**, *116*, 2204 – 2206; *Angew. Chem. Int. Ed.* **2004**, *43*, 2152 – 2154.
[49] A. B. Northrup, D. W. C. MacMillan, *Science* **2004**, *305*, 1752 – 1755.
[50] a) D. Enders, C. Grondal, *Angew. Chem.* **2005**, *117*, 1235 – 1238; *Angew. Chem. Int. Ed.* **2005**, *44*, 1210 – 1212; b) J. Casas, M. Engqvist, I. Ibrahem, B. Kaynak, A. Córdova, *Angew. Chem.* **2005**, *117*, 1367 – 1369; *Angew. Chem. Int. Ed.* **2005**, *44*, 1343 – 1345.
[51] a) 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; b) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656 – 5657; for proline-catalyzed α-amination of ketones, see: c) N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254 –

6255; for a review, see: d) R. O. Duthaler, *Angew. Chem.* **2003**, *115*, 1005 – 1008; *Angew. Chem. Int. Ed.* **2003**, *42*, 975 – 978.

[52] a) H. Vogt, S. Vanderheiden, S. Bräse, *Chem. Commun.* **2003**, 2448 – 2449; b) J. T. Suri, D. D. Steiner, C. F. Barbas III, *Org. Lett.* **2005**, *7*, 3885 – 3888.

[53] Nonlinear effects have been reported in the proline-catalyzed α-amination and α-aminoxylation of propanal, see: a) S. P. Mathew, H. Iwamura, D. G. Blackmond, *Angew. Chem.* **2004**, *116*, 3379 – 3383; *Angew. Chem. Int. Ed.* **2004**, *43*, 3317 – 3321; b) H. Iwamura, S. P. Mathew, D. G. Blackmond, *J. Am. Chem. Soc.* **2004**, *126*, 11770 – 11771; these effects are probably not related to the catalytic reaction mechanism, as previously supposed, but instead to the ternary phase behavior of proline in the solvent, see Refs. [30a,b] and [32].

[54] For quantum mechanical computational studies, see: a) P. H.-Y. Cheong, K. N. Houk, *J. Am. Chem. Soc.* **2004**, *126*, 13912 – 13913; b) A. Córdova, H. Sundén, A. Bøgevig, M. Johansson, F. Himo, *Chem. Eur. J.* **2004**, *10*, 3673 – 3684.

[55] a) G. Zhong, *Angew. Chem.* **2003**, *115*, 4379 – 4382; *Angew. Chem. Int. Ed.* **2003**, *42*, 4247 – 4250; b) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808 – 10809; c) Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, *Tetrahedron Lett.* **2003**, *44*, 8293 – 8296.

[56] For analogous proline-catalyzed α-aminoxylations of ketones, see: a) A. Bøgevig, H. Sundén, A. Córdova, *Angew. Chem.* **2004**, *116*, 1129 – 1132; *Angew. Chem. Int. Ed.* **2004**, *43*, 1109 – 1112; b) Y. Hayashi, J. Yamaguchi, T. Sumiya, M. Shoji, *Angew. Chem.* **2004**, *116*, 1132 – 1135; *Angew. Chem. Int. Ed.* **2004**, *43*, 1112 – 1115; for a review, see: c) J. M. Janey, *Angew. Chem.* **2005**, *117*, 4364 – 4372; *Angew. Chem. Int. Ed.* **2005**, *44*, 4292 – 4300.

[57] a) A. Córdova, H. Sundén, M. Engqvist, I. Ibrahem, J. Casas, *J. Am. Chem. Soc.* **2004**, *126*, 8914 – 8915; see also b) I. Ibrahem, G.-L. Zhao, H. Sundén, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 4659 – 4663; for a similar reaction with ketones, see: c) H. Sundén, M. Engqvist, J. Casas, I. Ibrahem, A. Córdova, *Angew. Chem.* **2004**, *116*, 6694 – 6697; *Angew. Chem. Int. Ed.* **2004**, *43*, 6532 – 6535.

[58] N. Vignola, B. List, *J. Am. Chem. Soc.* **2004**, *126*, 450 – 451.

[59] The experimental basis of the iminium activation strategy are rooted in established synthetic methodologies, such as reductive amination or in the Diels–Alder investigations by Jung and colleagues, who demonstrated that the iminium ion intermediates are more reactive than the corresponding unsaturated aldehydes, see: M. E. Jung, W. D. Vaccaro, K. R. Buszek, *Tetrahedron Lett.* **1989**, *30*, 1893 – 1896; for a personal account by D. W. C. MacMillan on the rationale behind this new organocatalytic concept, see Ref. [1a], chap. 3, pp. 95–120.

[60] a) W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874 – 9875; b) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370 – 4371.

[61] a) J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172 – 1173; very recently, the MacMillan research group developed organocatalytic and enantioselective vinyl and Friedel–Crafts alkylations with trifluoroborate salts that allow π-neutral or π-deficient substrates to function as suitable nucleophiles for iminium catalysis with enals, see: b) S. Lee, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**, *129*, 15438 – 15439.

[62] For theoretical studies of asymmetric alkylations of pyrrole and indole organocatalyzed by imidazolidinone catalysts, see: R. Gordillo, J. Carter, K. N. Houk, *Adv. Synth. Catal.* **2004**, *346*, 1175 – 1185.

[63] For selected examples on: conjugate addition of electron-rich benzenes, see: a) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 7894 – 7895; Mukaiyama–Michael additions, see: b) S. P. Brown, N. C. Goodwin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 1192 – 1194; addition of amines, see: c) Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 9328 – 9329; [4+3] cycloadditions, see: d) M. Harmata, S. K. Ghosh, X. Hong, S. Wacharasindhu, P. Kirchhoefer, *J. Am. Chem. Soc.* **2003**, *125*, 2058 – 2059; intramolecular Diels–Alder (IMDA) reactions, see: e) R. M. Wilson, W. S. Jen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 11616 – 11617; f) S. A. Selkälä, A. M. P. Koskinen, *Eur. J. Org. Chem.* **2005**, 1620 – 1624.

[64] a) S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 32 – 33; b) J. W. Yang, M. T. Hechavarria Fonseca, N. Vignola, B. List, *Angew. Chem.* **2005**, *117*, 110 – 112; *Angew. Chem. Int. Ed.* **2005**, *44*, 108 – 110; for an achiral organocatalytic approach including one moderately enantioselective example, see: c) J. W. Yang, M. T. Hechavarria Fonseca, B. List, *Angew. Chem.* **2004**, *116*, 6829 – 6832; *Angew. Chem. Int. Ed.* **2004**, *43*, 6660 – 6662.

[65] a) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458 – 2460; for the use of **VI** in the asymmetric transfer hydrogenation of cyclic enones, see: b) J. B. Tuttle, S. G. Ouellet, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 12662 – 12663; for theoretical studies on the iminium catalyzed Diels–Alder reactions with unsaturated aldehydes and ketones, see: c) R. Gordillo, K. N. Houk, *J. Am. Chem. Soc.* **2006**, *128*, 3543 – 3553.

[66] For previous studies on the addition of carbogenic nucleophiles to cyclic enones with proline or proline derivatives as catalysts, see: a) M. Yamaguchi, T. Shiraishi, M. Hirama, *J. Org. Chem.* **1996**, *61*, 3520 – 3530, and references therein; b) S. Hanessian, V. Pharm, *Org. Lett.* **2000**, *2*, 2975 – 2978.

[67] a) N. Halland, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 8331 – 8338; b) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 685 – 689; *Angew. Chem. Int. Ed.* **2003**, *42*, 661 – 665; c) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem.* **2004**, *116*, 1292 – 1297; *Angew. Chem. Int. Ed.* **2004**, *43*, 1272 – 1277; d) J. Pulkkinen, P. S. Aburel, N. Halland, K. A. Jørgensen, *Adv. Synth. Catal.* **2004**, *346*, 1077 – 1080; e) N. Halland, T. Hansen, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 5105 – 5107; *Angew. Chem. Int. Ed.* **2003**, *42*, 4955 – 4957; see also: f) H. Kim, C. Yen, P. Preston, J. Chin, *Org. Lett.* **2006**, *8*, 5239 – 5242.

[68] Leonardo da Vinci, *Disegni Anatomici* in the Royal Library of Windsor. English translation: *The Literary Works* of Leonardo da Vinci, compiled and edited from the original manuscripts by J.-P. Richter, commentary by C. Pedretti, Phaidon, Oxford, **1977**, p. 102.

[69] Selected examples for catalyst **IX**: a) A. Hartikka, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2004**, *15*, 1831 – 1834; b) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem.* **2004**, *116*, 2017 – 2020; *Angew. Chem. Int. Ed.* **2004**, *43*, 1983 – 1986; c) A. J. A. Cobb, D. A. D. Longbottom, D. M. Shaw, S. V. Ley, *Chem. Commun.* **2004**, 1808 – 1809; see also Ref. [4c]; catalyst **X**: d) N. Mase, F. Tanaka, C. F. Barbas III, *Angew. Chem.* **2004**, *116*, 2474 – 2477; *Angew. Chem. Int. Ed.* **2004**, *43*, 2420 – 2423; e) N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2527 – 2530; f) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 734 – 735; g) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966 – 4967; see also Refs. [39d, 40b]; catalyst **XI**: h) S. Sulzer-Mossé, A. Alexakis, *Chem. Commun.* **2007**, 3123 – 3135, and references therein; see also Ref. [39b]; catalyst **XII**: i) Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 5262 – 5263; j) Z. Tang, Z.-H. Yang, X.-H. Chen, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *J. Am. Chem. Soc.* **2005**, *127*, 9285 – 9289; catalyst **XIII**: see Ref. [39c]; catalyst

XIV: k) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem.* **2006**, *118*, 972 – 975; *Angew. Chem. Int. Ed.* **2006**, *45*, 958 – 961; catalyst **XV**: l) W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393 – 1395; *Angew. Chem. Int. Ed.* **2005**, *44*, 1369 – 1371; m) W. Wang, H. Li, J. Wang, *Tetrahedron Lett.* **2005**, *46*, 5077 – 5079, and references therein; catalyst **XVI**: n) A. Berkessel, B. Koch, J. Lex, *Adv. Synth. Catal.* **2004**, *346*, 1141 – 1146.

[70] See Ref. [4d] and references therein. For selected examples, see: a) A. Alexakis, O. Andrey, *Org. Lett.* **2002**, *4*, 3611 – 3614; b) K. Juhl, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 1536 – 1539; *Angew. Chem. Int. Ed.* **2003**, *42*, 1498 – 1501; c) P. Melchiorre, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 4151 – 4157.

[71] a) N. De Kimpe, R. Verhé, *The Chemistry of α-Haloketones, α-Haloaldehydes, and α-Haloimines*, Wiley, New York, **1990**; for a recent application of the organocatalyzed α-chlorination of aldehydes in the synthesis of naturally occurring compounds, see: b) B. Kang, R. Britton, *Org. Lett.* **2007**, *9*, 5083 – 5086.

[72] M. P. Brochu, S. P. Brown, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2004**, *126*, 4108 – 4109.

[73] N. Halland, A. Braunton, S. Bechmann, M. Marigo, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 4790 – 4791.

[74] N. Halland, M. A. Lie, A. Kjærsgaard, M. Marigo, B. Schiøtt, K. A. Jørgensen, *Chem. Eur. J.* **2005**, *11*, 7083 – 7090.

[75] C. A. Marquez, F. Fabbretti, J. O. Metzger, *Angew. Chem.* **2007**, *119*, 7040 – 7042; *Angew. Chem. Int. Ed.* **2007**, *46*, 6915 – 6917.

[76] a) M. Marigo, S. Bechmann, N. Halland, A. Braunton, K. A. Jørgensen, *Angew. Chem.* **2004**, *116*, 5623 – 5626; *Angew. Chem. Int. Ed.* **2004**, *43*, 5507 – 5510; b) S. Bertelsen, N. Halland, S. Bechmann, M. Marigo, A. Braunton, K. A. Jørgensen, *Chem. Commun.* **2005**, 4821 – 4823.

[77] For a recent highlight on the asymmetric fluorination of carbonyl compounds, see: a) P. M. Pihko, *Angew. Chem.* **2006**, *118*, 558 – 561; *Angew. Chem. Int. Ed.* **2006**, *45*, 544 – 547; for the first asymmetric catalytic α-fluorination, see: b) L. Hintermann, A. Togni, *Angew. Chem.* **2000**, *112*, 4530 – 4533; *Angew. Chem. Int. Ed.* **2000**, *39*, 4359 – 4362; for the benefits associated to life sciences molecules bearing fluorine atoms, see: c) A. M. Thayer, *Chem. Eng. News* **2006**, *84*(23), 15 – 24; d) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881 – 1886.

[78] D. Enders, M. R. M. Hüttl, *Synlett* **2005**, 991 – 993.

[79] D. D. Steiner, N. Mase, C. F. Barbas III, *Angew. Chem.* **2005**, *117*, 3772 – 3776; *Angew. Chem. Int. Ed.* **2005**, *44*, 3706 – 3710.

[80] T. D. Beeson, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 8826 – 8828.

[81] 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.

[82] I. K. Mangion, A. B. Northrup, D. W. C. MacMillan, *Angew. Chem.* **2004**, *116*, 6890 – 6892; *Angew. Chem. Int. Ed.* **2004**, *43*, 6722 – 6724.

[83] a) M. T. Hechavarria Fonseca, B. List, *Angew. Chem.* **2004**, *116*, 4048 – 4050; *Angew. Chem. Int. Ed.* **2004**, *43*, 3958 – 3960; b) T. J. Peelen, Y. Chi, S. H. Gellman, *J. Am. Chem. Soc.* **2005**, *127*, 11598 – 11599.

[84] 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; for an earlier non-asymmetric version, see: b) W. Wang, H. Li, J. Wang, L. Liao, *Tetrahedron Lett.* **2004**, *45*, 8229 – 8231; c) A. Armstrong, L. Challinor, J. H. Moir, *Angew. Chem.* **2007**, *119*, 5465 – 5468; *Angew. Chem. Int. Ed.* **2007**, *46*, 5369 – 5372; for classical asymmetric methods, see: d) D. Enders, T. Schäfer, O. Piva, A. Zamponi, *Tetrahedron* **1994**, *50*, 3349 – 3362; e) D. Enders, T. Schäfer, W. Mies, *Tetrahedron* **1998**, *54*, 10239 – 10252.

[85] a) J. Kapfhammer, A. Matthes, *Hoppe-Seylers Z. Physiol. Chem.* **1933**, *223*, 43 – 52; b) D. Enders, H. Kipphardt, P. Gerdes, L. J. Breña-Valle, V. Bhushan, *Bull. Soc. Chim. Belg.* **1988**, *100*, 1580 – 1581; see, for example: c) E. J. Corey, T. Shibata, T. W. Lee, *J. Am. Chem. Soc.* **2002**, *124*, 3808 – 3809.

[86] For early observations on the high stereocontrol but low turnover inherent to the diphenylprolinol catalyst (**XIXb**), see Refs. [70b,c] and [73]; for asymmetric transformations based on activation as an iminium ion in which **XIXb** proved to be the best organocatalyst, see: a) J.-W. Xie, L. Yue, D. Xue, X.-L. Ma, Y.-C. Chen, Y. Wu, J. Zhu, J.-G. Deng, *Chem. Commun.* **2006**, 1563 – 1565; b) J. L. Vicario, S. Reboredo, D. Badía, L. Carrillo, *Angew. Chem.* **2007**, *119*, 5260 – 5262; *Angew. Chem. Int. Ed.* **2007**, *46*, 5168 – 5170.

[87] J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296 – 18304.

[88] a) P. Dinér, A. Kjærsgaard, M. A. Lie, K. A. Jørgensen, *Chem. Eur. J.* **2008**, *14*, 122 – 127; b) D. Seebach, A. K. Beck, D. M. Badine, M. Limbach, A. Eschenmoser, A. M. Treasurywala, R. Hobi, W. Prikoszovich, B. Linder, *Helv. Chim. Acta* **2007**, *90*, 425 – 471.

[89] For a recent highlight on the impact of diaryl prolinol ethers in aminocatalysis, see: C. Palomo, A. Mielgo, *Angew. Chem.* **2006**, *118*, 8042 – 8046; *Angew. Chem. Int. Ed.* **2006**, *45*, 7876 – 7880.

[90] a) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284 – 4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212 – 4215; for an application of a recyclable fluorous diphenylprolinol silyl ether in the same reaction, see:b) L. Zu, H. Li, J. Wang, X. Yu, W. Wang, *Tetrahedron Lett.* **2006**, *47*, 5131 – 5134; for recent improvements, see: c) S. Zhu, S. Yu, D. Ma, *Angew. Chem.* **2008**, *120*, 555 – 558; *Angew. Chem. Int. Ed.* **2008**, *47*, 545 – 548.

[91] a) Y. Chi, S. H. Gellman, *Org. Lett.* **2005**, *7*, 4253 – 4256; b) S. Sulzer-Mossé, M. Tissot, A. Alexakis, *Org. Lett.* **2007**, *9*, 3749 – 3752; after the submission of this Review, an organocatalytic oxidative dearomatization/intramolecular conjugate addition was reported, see: c) N. T. Vo, R. D. M. Pace, F. O'Hara, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 404 – 405.

[92] J. Alemán, S. Cabrera, E. Maerten, J. Overgaard, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 5616 – 5619; *Angew. Chem. Int. Ed.* **2007**, *46*, 5520 – 5523.

[93] a) Y. Chi, S. H. Gellman, *J. Am. Chem. Soc.* **2006**, *128*, 6804 – 6805; see also: b) Y. Chi, E. P. English, W. C. Pomerantz, W. S. Horne, L. A. Joyce, L. R. Alexander, W. S. Fleming, E. A. Hopkins, S. H Gellman, *J. Am. Chem. Soc.* **2007**, *129*, 6050 – 6055; c) I. Ibrahem, G.-L. Zhao, A. Córdova, *Chem. Eur. J.* **2007**, *13*, 683 – 688.

[94] a) C. Palomo, S. Vera, I. Velilla, A. Mielgo, E. Gómez-Bengoa, *Angew. Chem.* **2007**, *119*, 8200 – 8202; *Angew. Chem. Int. Ed.* **2007**, *46*, 8054 – 8056; previously, a different chiral secondary amine was successfully employed for the asymmetric α-oxyamination of aldehydes, see: b) T. Kano, M. Ueda, J. Takai, K. Maruoka, *J. Am. Chem. Soc.* **2006**, *128*, 6046 – 6047.

[95] a) M. Tiecco, A. Carlone, S. Sternativo, F. Marini, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2007**, *119*, 7006 – 7009; *Angew. Chem. Int. Ed.* **2007**, *46*, 6882 – 6885; see also: b) H. Sundén, R. Rios, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 7865 – 7869; for earlier-non asymmetric versions, see: c) W. Wang, J. Wang, H. Lao, *Org. Lett.* **2004**, *6*, 2817 – 2820; d) J. Wang, H. Li, Y. Mei, B. Lou, D. Xu, D. Xie, H. Guo, W. Wang, *J. Org. Chem.* **2005**, *70*, 5678 – 5687.

[96] For selected examples on conjugate additions, see: a) S. Brandau, A. Landa, J. Franzén, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2006**, *118*, 4411 – 4415; *Angew. Chem. Int. Ed.* **2006**, *45*, 4305 – 4309; b) H. Gotoh, R. Masui, H. Ogino, M. Shoji, Y. Hayashi, *Angew. Chem.* **2006**, *118*, 7007 – 7010; *Angew.*

Chem. Int. Ed. **2006**, *45*, 6853 – 6856; c) H. Gotoh, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2007**, *9*, 5307 – 5309; d) L. Zu, H. Xie, H. Li, J. Wang, W. Wang, *Adv. Synth. Catal.* **2007**, *349*, 2660 – 2664; e) D. Enders, M. H. Bonten, G. Raabe, *Synlett* **2007**, 885 – 888; for cycloaddition reactions, see: f) H. Gotoh, Y. Hayashi, *Org. Lett.* **2007**, *9*, 2859 – 2862; g) R. Rios, I. Ibrahem, J. Vesely, G.-L. Zhao, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 5701 – 5705.

[97] a) P. Dinér, M. Nielsen, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 2029 – 2033; *Angew. Chem. Int. Ed.* **2007**, *46*, 1983 – 1987; b) I. Ibrahem, R. Rios, J. Vesely, G.-L. Zhao, A. Córdova, *Chem. Commun.* **2007**, 849 – 851; c) I. Ibrahem, R. Rios, J. Vesely, G.-L. Zhao, A. Córdova, *Synthesis* **2008**, 1153 – 1157; for an intramolecular reaction, see: d) S. Fustero, D. Jimenez, J. Moscardo, S. Catalan, C. S. del Pozo, *Org. Lett.* **2007**, *9*, 5283 – 5286.

[98] a) S. Bertelsen, P. Dinér, R. L. Johansen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 1536 – 1537; for tandem oxa-Michael/aldol sequences, see Ref. [124]; see also: b) H. Li, J. Wang, T. E-Nunu, L. Zu, W. Jiang, S. Wei, W. Wang, *Chem. Commun.* **2007**, 507 – 509.

[99] M. Marigo, T. Schulte, J. Franzen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 15710 – 15711; for tandem sulfa-Michael/aldol sequences, see: Ref. [122].

[100] a) A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Melchiorre, *Angew. Chem.* **2007**, *119*, 4588 – 4590; *Angew. Chem. Int. Ed.* **2007**, *46*, 4504 – 4506; b) I. Ibrahem, R. Rios, J. Vesely, P. Hammar, L. Eriksson, F. Himo, A. Córdova, *Angew. Chem.* **2007**, *119*, 4591 – 4594; *Angew. Chem. Int. Ed.* **2007**, *46*, 4507 – 4510; c) E. Maerten, S. Cabrera, A. Kjærsgaard, K. A. Jøorgensen, *J. Org. Chem.* **2007**, *72*, 8893 – 8903.

[101] C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, Á. Puente, S. Vera, *Angew. Chem.* **2007**, *119*, 8583 – 8587; *Angew. Chem. Int. Ed.* **2007**, *46*, 8431 – 8435.

[102] a) T. Kano, Y. Yamaguchi, O. Tokuda, K. Maruoka, *J. Am. Chem. Soc.* **2005**, *127*, 16408 – 16409; for the use of axially chiral sulfonamide **XXI** as the organocatalyst of direct *syn*-selective cross-aldol reactions, see: b) T. Kano, Y. Yamaguchi, Y. Tanaka, K. Maruoka, *Angew. Chem.* **2007**, *119*, 1768 – 1770; *Angew. Chem. Int. Ed.* **2007**, *46*, 1738 – 1740.

[103] a) S. Mitsumori, H. Zhang, P. Ha-Yeon Cheong, K. N. Houk, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 1040 – 1041; b) for a more detailed study published after submission of this Review, see: H. Zhang, S. Mitsumori, N. Utsumi, M. Imai, N. Garcia-Delgado, M. Mifsud, K. Albertshofer, P. H. Yeon Cheong, K. N. Houk, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2008**, *130*, 875 – 886.

[104] T. Kano, J. Takai, O. Tokuda, K. Maruoka, *Angew. Chem.* **2005**, *117*, 3115 – 3117; *Angew. Chem. Int. Ed.* **2005**, *44*, 3055 – 3057; see also Ref. [94b].

[105] Both enantiomers of the MacMillan imidazolidinones and Jørgensen-type catalysts can be readily prepared on multigram scales and/or they are commercially available.

[106] For an excellent review on cascade reactions in total synthesis, see: a) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292 – 7344; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134 – 7186; for a review on asymmetric multicomponent reactions, see: b) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628 – 1661; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602 – 1634.

[107] For reviews on organocatalytic domino reactions, see: a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590 – 1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570 – 1581; b) G. Guillena, D. J. Ramón, M. Yus, *Tetrahedron* **2007**, *63*, 693 – 700.

[108] T. Bui, C. F. Barbas III, *Tetrahedron Lett.* **2000**, *41*, 6951 – 6954.

[109] a) D. B. Ramachari, N. S. Chowdari, C. F. Barbas III, *Synlett* **2003**, *12*, 1910 – 1914; 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; c) D. B. Ramachary, K. Anebouselvj, N. S. Chowdari, C. F. Barbas III, *J. Org. Chem.* **2004**, *69*, 5838 – 5849; d) B. Dhevalapally, D. B. Ramachari, C. F. Barbas III, *Chem. Eur. J.* **2004**, *10*, 5323 – 5331.

[110] a) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962 – 5963; for a similar approach in which imines were employed instead of nitrosobenzene (formal aza-Diels–Alder reaction) and proline, see: b) H. Sundén, I. Ibrahem, L. Eriksen, A. Córdova, *Angew. Chem.* **2005**, *117*, 4955 – 4958; *Angew. Chem. Int. Ed.* **2005**, *44*, 4877 – 4880.

[111] 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.

[112] R. K. Kunz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 3240 – 3241.

[113] M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang, K. A. Jorgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964 – 6965.

[114] J. Vesely, I. Ibrahem, G.-L. Zhao, R. Rios, A. Córdova, *Angew. Chem.* **2007**, *119*, 792 – 795; *Angew. Chem. Int. Ed.* **2007**, *46*, 778 – 781.

[115] J. W. Yang, M. T. Hechavarria Fonseca, B. List, *J. Am. Chem. Soc.* **2005**, *127*, 15036 – 15037.

[116] Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051 – 15053.

[117] For an intermolecular domino amination/amination reaction, see: H. Jiang, J. B. Nielsen, M. Nielsen, K. A. Jorgensen, *Chem. Eur. J.* **2007**, *13*, 9068 – 9075.

[118] a) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861 – 863; see also: b) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe, B. Wendt, *Angew. Chem.* **2007**, *119*, 471 – 473; *Angew. Chem. Int. Ed.* **2007**, *46*, 467 – 469; c) D. Enders, M. R. M. Hüttl, G. Raabe, J. W. Bats, *Adv. Synth. Catal.* **2008**, *350*, 267 – 279.

[119] For an alternative iminium ion/iminium ion/enamine domino reaction, see: A. Carlone, S. Cabrera, M. Marigo, K. A. Jorgensen, *Angew. Chem.* **2007**, *119*, 1119 – 1122; *Angew. Chem. Int. Ed.* **2007**, *46*, 1101 – 1104.

[120] M. Marigo, S. Bertelsen, A. Landa, K. A. Jorgensen, *J. Am. Chem. Soc.* **2006**, *128*, 5475 – 5479.

[121] For Michael/aldol sequences, see: a) A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen, *Chem. Commun.* **2006**, 4928 – 4930; b) J. Wang, H. Li, H. Xie, L. Zu, X. Shen, W. Wang, *Angew. Chem.* **2007**, *119*, 9208 – 9211; *Angew. Chem. Int. Ed.* **2007**, *46*, 9050 – 9053; for Michael/α-alkylation sequences, see: c) R. Rios, J. Vasely, H. Sundén, I. Ibrahem, G.-L. Zhao, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 5835 – 5839; d) R. Rios, H. Sundén, J. Vasely, G.-L. Zhao, P. Dziedzic, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 1028 – 1032; e) H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886 – 10894; for double Michael sequence, see: f) L. Zu, H. Li, H. Xie, J. Wang, W. Jiang, Y. Tang, W. Wang, *Angew. Chem.* **2007**, *119*, 3806 – 3808; *Angew. Chem. Int. Ed.* **2007**, *46*, 3732 – 3734; for a Michael/Henry sequence, see: g) Y. Hayashi, T. Okano, S. Aratake, D. Hazelard, *Angew. Chem.* **2007**, *119*, 5010 – 5013; *Angew. Chem. Int. Ed.* **2007**, *46*, 4922 – 4925; for a nitro-Michael/aldol sequence, see:h) D. Enders, A. A. Narine, T. R. Benninghaus, G. Raabe, *Synlett* **2007**, 1667 – 1670; for a nitro-Michael/Henry sequence, see: i) E. Reyes, H. Jiang, A. Milelli, P. Elsner, R. G. Hazell, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 9362 – 9365; *Angew. Chem. Int. Ed.* **2007**, *46*, 9202 – 9205; for a Michael/MBH sequence, see: j) S. Cabrera, J. Alemán, P. Bolze, S. Bertelsen, K. A. Jørgensen, *Angew. Chem.* **2008**, *120*, 127 – 131; *Angew. Chem. Int. Ed.* **2008**, *47*, 121 – 125; see also: k) R. Rios, I. Ibrahem, J. Vesely, H. Sundén, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 8695 – 8699.

[122] For tandem sulfa-Michael/aldol sequences, see: a) W. Wang, H. Li, J. Wang, L. Zu, *J. Am. Chem. Soc.* **2006**, *128*, 10354 – 10355; b) R. Rios, H. Sundén, I. Ibrahem, G.-L. Zhao, L. Eriksson, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 8547 – 8551; c) S. Brandau,

E. Maerten, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 14986 – 14991; for a sulfa-Michael/Michael sequence, see: d) H. Li, L. Zu, H. Xie, J. Wang, W. Jiang, W. Wang, *Org. Lett.* **2007**, *9*, 1833 – 1835.

[123] For an aza-Michael/aldol sequence, see: H. Sundén, R. Rios, I. Ibrahem, G.-L. Zhao, L. Eriksen, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 827 – 832.

[124] For tandem oxa-Michael/aldol sequences, see: a) T. Govender, L. Hojabri, F. M. Moghaddam, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2006**, *17*, 1763 – 1767; b) H. Sundén, I. Ibrahem, G.-L. Zhao, L. Eriksson, A. Córdova, *Chem. Eur. J.* **2007**, *13*, 574 – 581; see also Ref. [98b].

[125] a) N. Cohen, *Acc. Chem. Res.* **1976**, *9*, 412 – 417, and references therein; b) S. Danishefsky, P. Cain, *J. Am. Chem. Soc.* **1975**, *97*, 5282 – 5283.

[126] a) R. A. Clark, D. C. Parker, *J. Am. Chem. Soc.* **1971**, *93*, 7257 – 7261; b) D. R. Boyd, W. B. Jennings, L. C. Waring, *J. Org. Chem.* **1986**, *51*, 992 – 995; c) B. Capon, Z.-P. Wu, *J. Org. Chem.* **1990**, *55*, 2317 – 2324, and references therein.

[127] See, for example: a) N. S. Chowdari, D. B. Ramachary, A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 9591 – 9595; b) A. Córdova, W. Notz, C. F. Barbas III, *Chem. Commun.* **2002**, 3024 – 3025.

[128] For selected examples, see: a) A. Bassan, W. Zou, E. Reyes, F. Himo, A. Córdova, *Angew. Chem.* **2005**, *117*, 7190 – 7194; *Angew. Chem. Int. Ed.* **2005**, *44*, 7028 – 7032; b) X. Wu, Z. Jiang, H.-M. Shen, Y. Lu, *Adv. Synth. Catal.* **2007**, *349*, 812 – 816; c) S. Luo, H. Xu, J. Li, L. Zhang, J.-P. Cheng, *J. Am. Chem. Soc.* **2007**, *129*, 3074 – 3075, and references therein; d) A. V. Malkov, M. A. Kabeshov, M. Bella, O. Kysilka, D. A. Malyshev, K. Pluhackova, P. Kocovsky, *Org. Lett.* **2007**, *9*, 5473 – 5476.

[129] a) Y. Xu, W. Zou, H. Sundén, I. Ibrahem, A. Córdova, *Adv. Synth. Catal.* **2006**, *348*, 418 – 424; b) Y. Xu, A. Córdova, *Chem. Commun.* **2006**, 460 – 462, and references therein.

[130] S. S. V. Ramasastry, H. Zhang, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2007**, *129*, 288 – 289.

[131] M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 6514 – 6518; *Angew. Chem. Int. Ed.* **2006**, *45*, 6366 – 6370.

[132] For the asymmetric α-fluorination of α-branched aldehydes catalyzed by a chiral primary amine based on non-biaryl atropisomerism, see: S. Brandes, B. Niess, M. Bella, A. Prieto, J. Overgaard, K. A. Jørgensen, *Chem. Eur. J.* **2006**, *12*, 6039 – 6052; for the asymmetric functionalization of α-branched aldehydes catalyzed by secondary chiral amines, see Refs. [52] and [69d,e,l,m].

[133] 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.

[134] For a bifunctional catalyst with secondary amine and thiourea groups, see: Y.-J. Cao, H.-H. Lu, Y.-Y. Lai, L.-Q. Lu, W.-J. Xiao, *Synthesis* **2006**, 3795 – 3800, and references therein.

[135] K. Ishihara, K. Nakano, *J. Am. Chem. Soc.* **2005**, *127*, 10504 – 10505.

[136] For the asymmetric addition of carbon nucleophiles, see: 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) J.-W. Xie, L. Yue, W. Chen, W. Du, J. Zhu, J.-G. Deng, Y.-C. Chen, *Org. Lett.* **2007**, *9*, 413 – 415; c) W. Chen, W. Du, L. Yue, R. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Org. Biomol. Chem.* **2007**, *5*, 816 – 821; d) G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403 – 1405; e) W. Chen, W. Du, Y.-Z. Duan, Y. Wu, S.-Y. Yang, Y.-C. Chen, *Angew. Chem.* **2007**, *119*, 7811 – 7814; *Angew. Chem. Int. Ed.* **2007**, *46*, 7667 – 7670; oxygen nucleophiles, see: f) A. Carlone, G. Bartoli, M. Bosco, F. Pesciaioli, P. Ricci, L. Sambri, P. Melchiorre, *Eur. J. Org. Chem.* **2007**, 5492 – 5495; sulfur nucleophiles, see: g) P. Ricci, A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Melchiorre, *Adv. Synth. Catal.* **2008**, *350*, 49 – 53; see also Ref. [67f].

[137] a) S. H. McCooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599 – 602; b) T.-Y. Liu, H.-L. Cui, Y. Zhang, K. Jiang, W. Du, Z.-Q. He, Y.-C. Chen, *Org. Lett.* **2007**, *9*, 3671 – 3674; c) B.-L. Zheng, Q.-Z. Liu, C.-S. Guo, X.-L. Wang, L. He, *Org. Biomol. Chem.* **2007**, *5*, 2913 – 2915.

[138] 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; for asymmetric transfer hydrogenation of cyclic enones by employing salts of chiral secondary amines, see Ref. [65b]; for the use of a catalyst primary amine salt, in which both the cation and the anion are chiral, for the activation of α,β-unsaturated ketones as iminium ions, see also Ref. [36d–g]; c) after the submission of this Review, ACDC was applied to the asymmetric epoxidation of enals, see: X. Wang, B. List, *Angew. Chem.* **2008**, *120*, 1135 – 1139; *Angew. Chem. Int. Ed.* **2008**, *47*, 1119 – 1122.

[139] The use of chiral, cationic catalysts in asymmetric reactions involving anionic achiral intermediates is at the heart of phase-transfer catalysis; see Ref. [6].

[140] J. Zhou, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 7498 – 7499.

[141] For pioneering studies on the asymmetric reduction of preformed imines catalyzed by chiral phosphoric acids, see: a) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781 – 3783; for asymmetric reductive amination catalyzed by phosphoric acids, see: b) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84 – 86; for a similar study, including an example of a prototypical reductive amination protocol, see: c) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590 – 7593; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424 – 7427.

[142] a) G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496 – 499; b) S. Mukherjee, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 11336 – 11337; c) M. Rueping, A. P. Antonchick, C. Brinkmann, *Angew. Chem.* **2007**, *119*, 7027 – 7030; *Angew. Chem. Int. Ed.* **2007**, *46*, 6903 – 6906.

[143] B.-C. Hong, M.-F. Wu, H.-C. Tseng, G.-F. Huang, C.-F. Su, J.-H. Liao, *J. Org. Chem.* **2007**, *72*, 8459 – 8471.

[144] For preliminary reports with moderate selectivities, see: a) B.-C. Hong, M.-F. Wu, H.-C. Tseng, J.-H. Liao, *Org. Lett.* **2006**, *8*, 2217 – 2220; b) B. J. Bench, C. Liu, C. R. Evett, C. M. H. Watanabe, *J. Org. Chem.* **2007**, *72*, 8459 – 8471.

[145] For a discussion on the origin of stereoselectivity in proline catalysis (electronic shielding) and in catalysis by diaryl prolinol ethers (steric shielding) see Sections 3.3 and 5.5, respectively.

[146] 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; for a later expansion of this protocol to N-Boc-protected imines, see: b) J. Vesely, P. Dziedzic, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 6900 – 6904.

[147] After the submission of this Review, dienamine catalysis was applied to the asymmetric cyclization of tethered α,β-unsaturated carbonyl compounds, see: R. M. de Figueiredo, R. Fröhlich, M. Christmann, *Angew. Chem.* **2008**, *120*, 1472 – 1475; *Angew. Chem. Int. Ed.* **2008**, *47*, 1450 – 1453; this report underscores the ability of γ-activation to promote different intramolecular transformations: Diels–Alder (IMDA) reactions, conjugate addition to enones, and aldol reactions.

[148] For the non-enantioselective SOMO activation of enamines generated by using a stoichiometric amount of an amine, see: K. Narasaka, T. Okauchi, K. Tanaka, M. Murakami, *Chem. Lett.* **1992**, 2099 – 2102.

[149] After the submission of this Review, SOMO catalysis was used for the first asymmetric catalytic α-vinylation of aldehydes, by

using vinyl trifluoroborate salts used as the coupling reagents for radical-based processes, see: H. Kim, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2008**, *130*, 398 – 399.

[150] a) H. H. Bancroft, *Hystory of California*, *Vol. 2*3, 1848 – 1858; **1888**, pp. 55–56; b) J. S. Holliday, *Rush for Riches; Gold Fever and the Making of California*, Oakland Museum of California and University of California Press, **1999**, p. 51.

[151] R. Marcia de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575 – 2600.

[152] Note added in proof: Several new articles have been published since the submission of this Review that further expand the scope of asymmetric aminocatalysis. Of particular interest, for example, is the use of acetaldehyde as a nucleophile in enamine-catalyzed reactions: a) Mannich reaction: J. W. Yang, C. Chandler, M. Stadler, D. Kampen, B. List, *Nature* **2008**, *452*, 453 – 455; b) Aldol reaction: Y. Hayashi, T. Itoh, S. Aratake, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 2112 – 2114; *Angew. Chem. Int. Ed.* **2008**, *47*, 2082 – 2084; c) Michael Reaction: P. García-García, A. Ladépêche, R. Halder, B. List, *Angew. Chem.* **2008**, *120*, 4797 – 4799; *Angew. Chem. Int. Ed.* **2008**, *47*, 4719 – 4721; d) Y. Hayashi, T. Itoh, M. Ohkubo, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 4800 – 4802; *Angew. Chem. Int. Ed.* **2008**, *47*, 4722 – 4724; Highlight: e) B. Alcaide, P. Almendros, *Angew. Chem.* **2008**, *120*, 4710 – 4712; *Angew. Chem. Int. Ed.* **2008**, *47*, 4632 – 4634; a new approach toward the control of both the relative and absolute stereochemistry in asymmetric domino reactions: f) Y. Chi, S. T. Scroggins, J. M. J. Fréchet, *J. Am. Chem. Soc.* **2008**, *130*, 6322 – 6323; a new application of dienamine catalysis in domino reactions (dienamine–iminium ion) and synthesis of natural products:g) K. Liu, A. Chougnet, W.-D. Woggon, *Angew. Chem.* **2008**, DOI: 10.1002/ange.200801765; *Angew. Chem. Int. Ed.* **2008**, DOI: 10.1002/anie.200801765; a recent review of asymmetric organocatalysis: h) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716 – 4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638 – 4660.