Asymmetric Organocatalysis: From Infancy to Adolescence

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In memory of Albert I. Meyers

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After an initial period of validating asymmetric organocatalysis by using a wide range of important model reactions that constitute the essential tools of organic synthesis, the time has now been reached when organocatalysis can be used to address specific issues and solve pending problems of stereochemical relevance. This Review deals with selected studies reported in 2006 and the first half of 2007, and is intended to highlight four main aspects that may be taken as testimony of the present status and prospective of organocatalysis: a) chemical efficiency; b) discovery of new substrate combinations to give new asymmetric syntheses; c) development of new catalysts for specific purposes by using mechanistic findings; and d) applications of organo-catalytic reactions in the asymmetric total synthesis of target natural products and known compounds of biological and pharmaceutical relevance.

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1. Introduction

Asymmetric organic synthesis using metal-free low-molecular-weight organic molecules as catalysts was first reported in the form of a proline-catalyzed intramolecular asymmetric aldol reaction of a triketone by two industrial research groups in 1971.[1,2] This approach, which is now commonly known as organocatalysis, was almost ignored for three decades, but has blossomed rapidly since the turn of the century. Numerous research groups around the world are now exploring the potential of the method.[3–5] A variety of key asymmetric carbon–carbon and carbon–heteroatom bond-forming reactions (such as, Diels–Alder and 1,3-dipolar cycloadditions, direct aldol condensation, Mannich and Michael reactions, epoxidation, hydride transfer, nitroalkane addition to enones, α-halogenation, and amination of alde-hydes) can be carried out by using organocatalytic methods. Under optimized conditions and the use of natural or newly designed chiral catalysts,[6] these reactions lead to the formation of products in very high yield and almost complete enantiomeric purity. Organocatalysis during these years has been often referred to as a research topic in its infancy. This time is now over, and the field of organocatalysis has now reached adolescence. Today the scope of organocatalysis spans from the generation of complex molecular systems to the consideration of technical synthesis processes, particularly in regard to environmentally friendly techniques. Mechanistic schemes and basic operational procedures have been estab-lished, thus giving great confidence in the success of many challenging endeavors that rely on organocatalyzed key steps. A few introductory comments are needed before a range of selected examples is provided to illustrate our views expressed above.

A look at a modern book of organic chemistry cannot fail to impress how this fundamental discipline has progressed in the second half of the 1900s mainly because of the discovery of asymmetric synthetic methods that are promoted by metal complexes with chiral organic ligands. Milestones in this field are represented by the wide scope of transition-metal-catalyzed coupling reactions,[7] asymmetric hydrogenation of olefins,[8] and olefin metathesis,[9] particularly with Pd, Pt, and Rh catalysts. The titanium-catalyzed asymmetric epoxidation of olefins and osmium-catalyzed asymmetric dihydroxylation of olefins[10] are also landmark discoveries. The power of these methods made many once unthinkable syntheses possible. However, despite the large consensus by the chemical community of the important role of metal catalysts in synthesis and the ongoing search for new systems, the apparent drawbacks cannot be ignored anymore. These include the high cost and effort for the preparation of the catalysts, the use of noxious metals, which, although present in trace amounts, contaminate the final organic product, the lack of orthogonality with a wide range of functional groups, and in some cases the need to operate under rigorously anhydrous or anaerobic conditions. Organocatalysts, some of which are natural products (including amino acids which very likely played a key role in prebiotic systems),[11] appear to provide an answer to the above problems. After an initial phase of investigation on the scope of organocatalysis by using model systems, the time has now been reached where this approach—in combination with other modern reaction con-cepts and synthetic tools—can be applied to the construction of more sophisticated targets.

We highlight in this Review four main aspects which in our opinion show, more than others, the present status and future prospects of organocatalysis (Figure 1). The vastness of the field has necessitated limiting the content of this Review to synthetic transformations promoted by either amino or Brønsted acid organocatalysts. This choice has been dictated by their predominance in the field of organocatalysis and the

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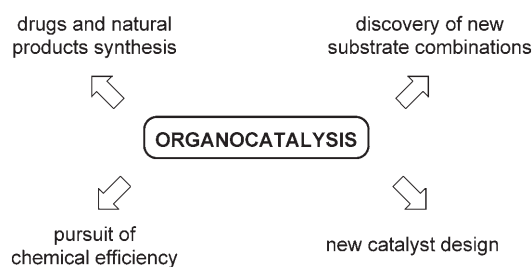   E-mail: adn@unife.it
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Figure 1. Current objectives in asymmetric organocatalysis.

similarity of their mechanisms: both cases involve activation of a carbonyl group towards nucleophilic attack by lowering the lowest unoccupied molecular orbital (LUMO). The examples reported herein are a selection of the significant contributions which in our opinion have major importance for the area and appeared in the literature in 2006 or the first half of 2007.

2. Chemical Efficiency

The great potential of asymmetric domino processes[12] to generate chemical efficiency through the formation of multiple new bonds and stereocenters in a one-pot system is amply documented. This strategy avoids time-consuming and costly processes such as the purification of intermediates and the protection or deprotection of functional groups. These favorable features stimulated the development of a range of asymmetric organocatalytic domino reactions.[5k] While reports on this area of organocatalysis appeared in the early 2000s, mainly from the research group of Barbas,[13] it was only at the end of 2005 that this organocatalytic strategy began to be intensively investigated.[14] Secondary amines capable of both enamine and iminium catalysis in tandem sequences were mainly used as organocatalysts. In this way, the sequential introduction of the nucleophile and electrophile components in the substrate and—in principle—the formation of two new stereocenters can be achieved. Three main approaches with different activation sequences can be envisaged: iminium-enamine, enamine-enamine, and enamine-iminium sequences.[5k] Quite recently, Jørgensen and co-workers reported on the asymmetric synthesis of highly functionalized tetrahydrothiophenes by a Michael–aldol

domino reaction in which a proline derivative was used as the catalyst (iminium-enamine sequence),[15] while Hong et al. performed an unprecedented enantioselective proline-catalyzed [3+3] cycloaddition of α,β-unsaturated aldehydes by a domino reaction, in which enamine and iminium catalytic cycles proceeded simultaneously on the same substrate.[16] However, the most striking result in this field was achieved by Enders et al., who developed a highly stereoselective synthesis of tetrasubstituted cyclohexene carbaldehydes with four new stereocenters (Scheme 1).[17] Thus, a linear alkyl aldehyde, a nitroalkene, and an α,β-unsaturated aldehyde underwent a three-component condensation catalyzed by the trimethylsilyl (TMS) protected diphenylprolinol **1**.
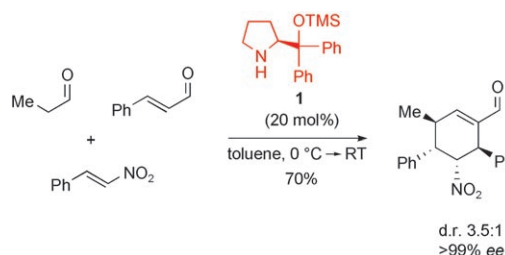
Scheme 1. Michael–Michael–aldol domino sequence.

It has been suggested that this domino reaction takes place through a triple cascade process constsiting of a Michael-Michael–aldol sequence (enamine-iminium-enamine activation, Scheme 2). The formation of only 2 of the 16 possible stereoisomers is indicative of an excellent level of chemical efficiency. The high stereocontrol was explained as arising from the diastereo- and enantioselectivity of the first Michael addition and the enhancement of this selectivity in the next steps by sterically favorable interactions (Scheme 2). Moreover, the good chemoselectivity registered for each step of the cascade process was the result of an ingenious synthesis design. Accordingly, the enamine of the alkyl aldehyde reacted much faster with the nitroalkene than with the less reactive α,β-unsaturated aldehyde (Michael acceptor), and the final product (the cyclohexene carbaldehyde) was sterically too hindered to undergo a Michael addition.

The synthesis of chiral cyclohexene carbaldehydes by an amino-catalyzed asymmetric multicomponent domino process was also reported in 2007 by Jørgensen and co-work-
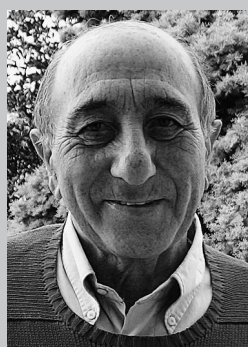
Alessandro Dondoni has been Professor of Organic Chemistry at the University of Ferrara since 1975. He has been the recipient of several awards including the A. Mangini Gold Medal by the Italian Chemical Society (1996), the Avogadro-Minakata Prize of the Chemical Society of Japan (1999), the Ziegler–Natta Prize of the German Chemical Society (1999), and the Lincei Prize in Chemistry (1999). His research interests include the development of new synthetic methods, asymmetric and diastereoselective synthesis, the use of heterocycles as synthetic auxiliaries, and carbohydrate chemistry.
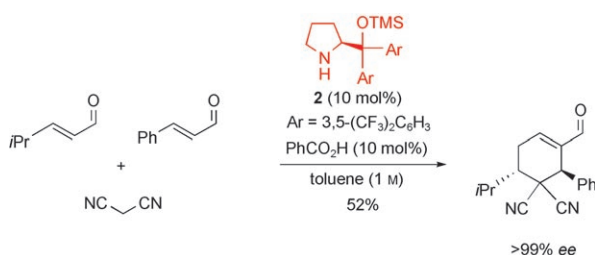
Alessandro Massi, born in Bologna, Italy, received his MSc (1994) and PhD (1999) from the University of Bologna and Ferrara, respectively. He spent one year at Cambridge University (UK) working under Professor S. V. Ley and then joined the group of Professor A. Dondoni in Ferrara, where he currently holds the position of Research Associate. His main research interest is the development of new methodologies for the high-throughput solution-phase synthesis of bioactive compounds.
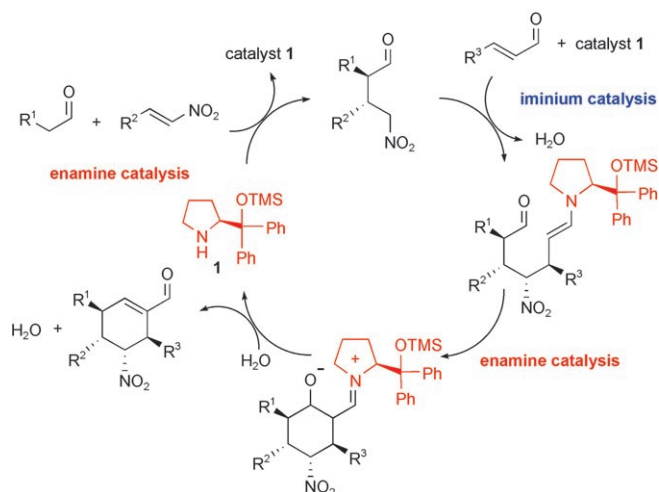
Scheme 2. Proposed catalytic cycle for the domino reaction shown in Scheme 1.

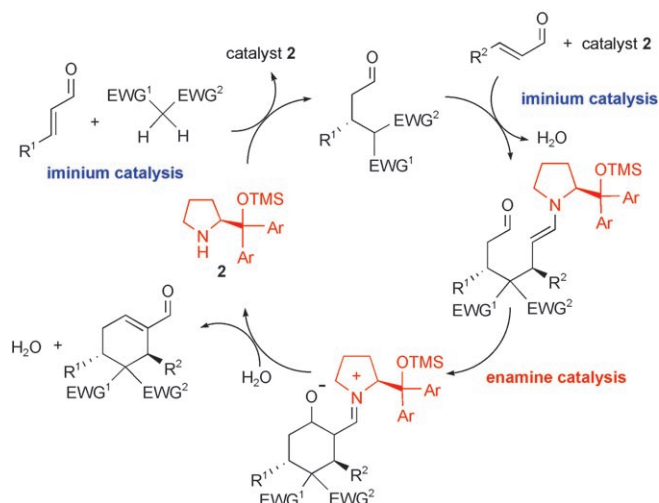**Scheme 4.** Proposed catalytic cycle for the domino reaction shown in Scheme 3. EWG = electron-withdrawing group.

ers.[18] As shown by the example in Scheme 3, the starting reagents were two different α,β-unsaturated aldehydes and an activated methylene compound such as malononitrile. The use of pyrrolidine derivative **2** as the secondary amine organocatalyst led to a substituted cyclohexene carbaldehyde with two stereocenters. Compounds with an additional, third, stereocenter were obtained by using cyanoacetates as the activated methylene reagents.


Scheme 3. Michael–Michael–aldol domino sequence.

This domino reaction was interpreted as proceeding through an unprecedented iminium-iminium-enamine sequential activation of the α,β-unsaturated aldehydes by the secondary amine catalyst (Scheme 4). The progression of the reaction sequence was dependent on the choice of the two aldehydes. Isopropylacrolein was a quite suitable aldehyde, because it afforded a sterically hindered product in the first cycle which reacted very slowly in the second cycle. Thus, in this way the domino process afforded exclusively one regioisomer and one diastereoisomer with excellent enantiomeric excess.

The validity of the multicomponent organocatalytic domino approach to cyclic aldehydes bearing several stereocenters was further demonstrated. Hayashi et al. reported on the tandem Michael–Henry reaction sequence of a nitroalkene and a dialdehyde such as pentane-1,5-dialdehyde.[19] When this reaction was carried out in the presence of the TMS-protected diphenylprolinol **1** catalyst, a chiral trisubsti-

tuted cyclohexane carbaldehyde was obtained with high diastereo- and enantioselectivity (Scheme 5). The high efficiency of this reaction was maintained for a range of nitroalkenes with different substituents R.
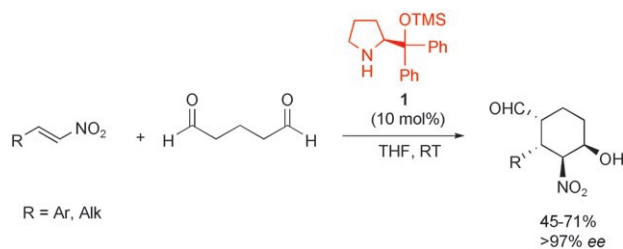

Scheme 5. Michael–Henry domino sequence.

Another impressive example came from Enders et al., with their report on the one-pot synthesis of chiral tricyclic carbaldehydes by a triple Diels–Alder cascade sequence catalyzed by the prolinol derivative **1** (Scheme 6).[20] The same research group also demonstrated that catalyst **1** promoted the domino Michael–aldol reaction of γ-nitroketones and α,β-unsaturated aldehydes to form chiral cyclohexene carbaldehydes with a tetrasubstituted double bond (Scheme 7).[21]

A remarkable achievement in the field of organocatalyzed cascade reactions was disclosed by Zhou and List, who reported on studies involving the combined application of amino-catalysis and asymmetric Brønsted acid catalysis.[22] To demonstrate the efficacy of combining the two catalytic principles in a domino process, a sequence of aldolization, conjugate reduction, and reductive amination was used for the highly stereoselective synthesis of pharmaceutically relevant 3-substitued cyclohexylamines from 2,6-diketones. The catalyst used in this triple organocatalytic cascade reaction was the binaphthyl hydrogen phosphate (R)-TRIP (**3**). The Hantzsch ester **4** was used as a reducing agent and an achiral p-alkoxyaniline used as the promoter (Scheme 8). The reaction began with an intramolecular enamine-catalyzed
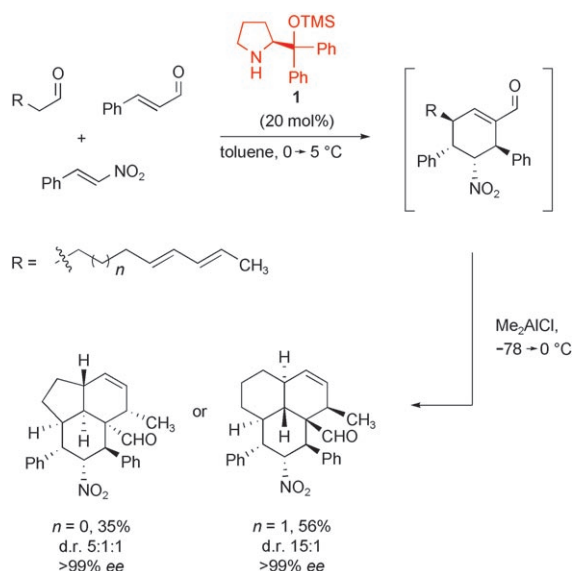
Scheme 6. Triple Diels–Alder cascade.
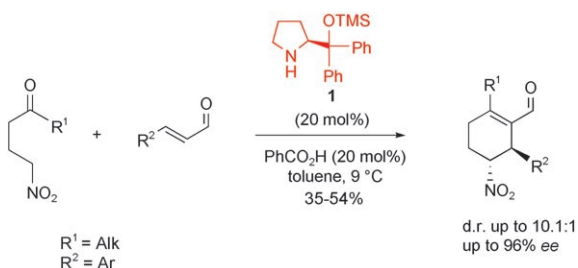
Scheme 7. Domino reaction of γ-nitroketones and enals.
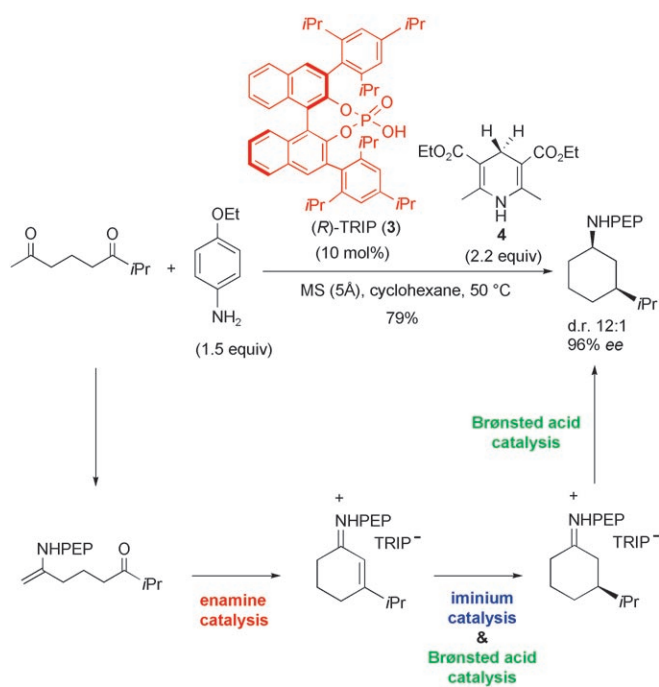
Scheme 8. Combination of enamine, iminium, and Brønsted acid catalysis. PEP = p-ethoxyphenyl.

aldolization, followed by a combined iminium and Brønsted acid catalyzed conjugate reduction. The final acid-catalyzed reductive amination then afforded the target cis-3-substituted cyclohexylamine with two stereocenters and the aryl amine promoter as a substituent.

In the middle of 2007 Ramachary and Kishor found that asymmetric organocatalytic multicomponent cascade reactions provided one of the best ways to achieve chemically efficient biomimetic syntheses.[23] The authors described a proline-catalyzed reaction cascade consisting of a Knoevenagel reaction, a hydrogenation, and a Robinson annulation, wherein a cyclic β-diketone, an aldehyde, a Hantzsch ester, and a methyl vinyl ketone furnished a Wieland–Miescher ketone analogue (Scheme 9). The reaction of 1,3-cyclohexandione with aldehydes afforded the condensed bicyclic dicarbonyl products in good to high yields and with excellent enantioselectivities.
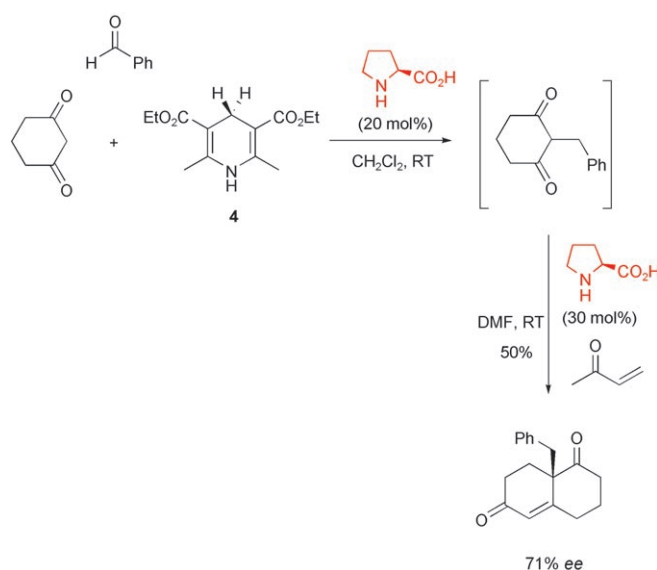
**Scheme 9.** Sequence of Knoevenagel reaction, hydrogenation, and Robinson annulation.

The Huisgen 1,3-dipolar cycloaddition and the Diels–Alder reaction represent the most efficient intermolecular processes for the formation of heterocycles and carbocycles. The high synthetic value of these reactions relies on their complete atom economy. Another recent case of a highly efficient organocatalytic reaction is represented by the 1,3-dipolar cycloaddition of an azomethine ylide to α,β-unsaturated aldehydes with diphenylprolinol **5** as the catalyst.[24] This reaction afforded chiral pyrrolidine aldehydes as single regioisomers in high yields and with excellent diastereo- and enantioselectivities (Scheme 10). Quite interestingly, a further stereocenter was formed by the stereoselective removal of one carboxylate group from the initial cycloadduct, thus affording a tetrasubstituted enantiomerically pure pyrrolidine derivative.

Recent impressive achievements in chemical efficiency have focused on economic and ecological aspects of organo-
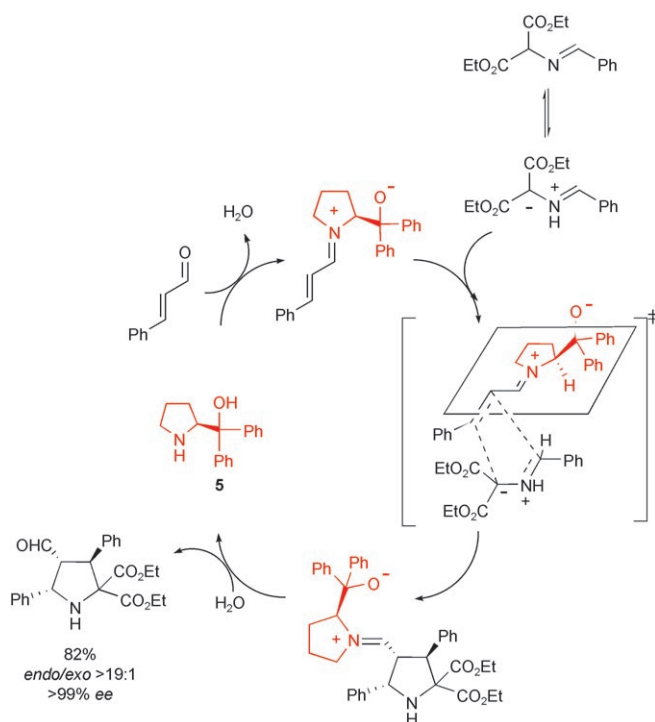
Scheme 10. Proposed catalytic cycle for the [3+2] cycloaddition of an azomethine ylide and α,β-unsaturated aldehydes.

catalysis. This further improvement in the methodology is a clear indication of the high level of reliability and generality reached by this catalytic concept over the last few years. Thus, for example, the use of alternative reaction media such as ionic liquids and water as well as new techniques based on new energy sources such as microwave irradiation were considered to reduce the impact on the environment and reduce hazards as well as shorten the reaction time. Efficiency was also pursued by simplifying the post-reaction phases such as workup, product isolation, and recycling of the catalyst. Particularly noteworthy is the study by Bolm and co-workers on a solvent-free proline-catalyzed asymmetric aldol reaction in a ball mill,[25] as well as the study by Cheng and co-workers who developed a series of pyrrolidine–ionic liquid conjugates **6** and demonstrated their potential as highly efficient organocatalysts for Michael reactions (Scheme 11).[26] The notable feature of catalyst **6** is the presence of the ionic liquid unit, which acts both as a phase tag for easy recycling of the catalyst and as a chiral-induction group to ensure high stereoselectivity.
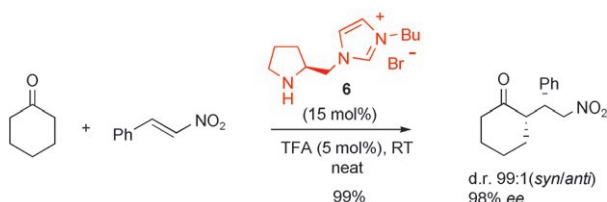
Scheme 11. Example of the application of a functionalized chiral ionic liquid as the organocatalyst for a Michael addition. TFA = trifluoroacetic acid.

The role of water as a solvent, co-solvent, or just as an additive in organocatalytic reactions has been discussed in an interesting and constructive debate.[27] The research groups of Barbas, Hayashi, and Pericàs investigated proline-catalyzed direct asymmetric aldol reactions "in the presence of water". As clarified by Hayashi,[27b] these reactions proceed in a concentrated organic phase, with water being present as a second phase that influences the reaction in the organic phase. These reactions differ from those performed "in water", where the reactants participating in the reaction are dissolved homogeneously in water. Although the use of water as a solvent does not a priori exclude the need for an organic solvent for product isolation, and the energetic balance of such a process is not always favorable,[27a] water is without doubt a low cost, safe, and environmentally friendly reaction medium. However, the use of water is often precluded in asymmetric catalytic reactions because of inhibition of the catalyst activity and loss of selectivity through modification of stereoelectronic interactions in the transition state. Indeed, Barbas and co-workers showed that in the presence of proline the expected aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde did not take place in water, while the reaction proceeded smoothly in dimethylsulfoxide with high diastereo- and enantioselectivity.[28] Hence, on the basis of the finding that class I aldolase enzymes catalyze enantioselective aldol reactions in water (by an enamine mechanism), these researchers designed catalyst **7** (Scheme 12 a). They assumed that appropriate hydrophobic groups on the proline scaffold would be able to assemble with hydrophobic reactants in water to form an emulsion and sequester the transition state from water. Indeed, it was found that **7** in the presence of an equimolar amount of trifluoroacetic acid as an additive catalyzed the above model reaction in water to afford the
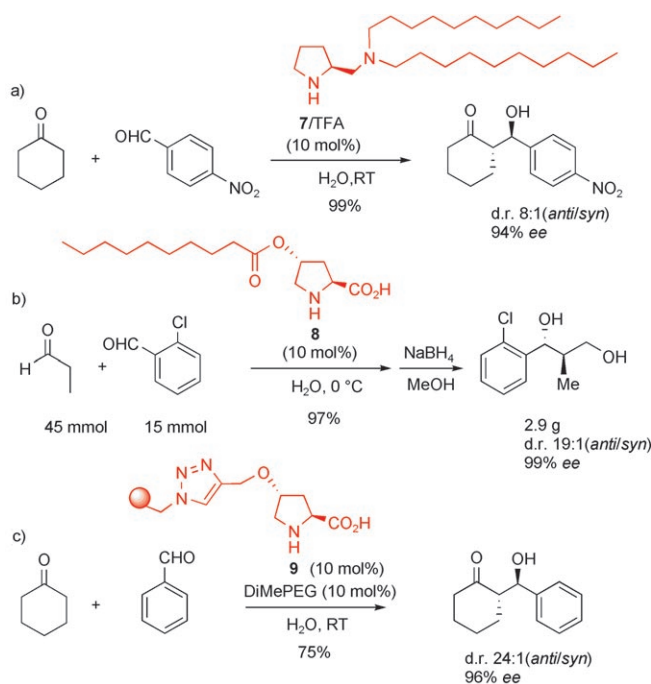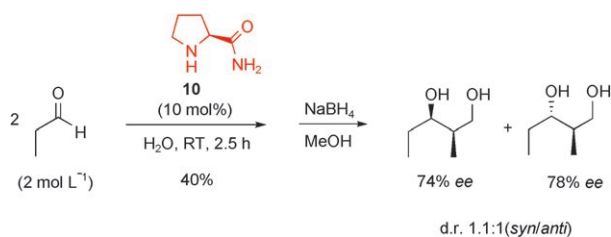

Scheme 12. Direct asymmetric aldol reactions of aldehydes and ketones "in the presence of water". DiMePEG = dimethyl polyethylene glycol.

target aldol in high yield, with good *anti* diastereoselectivity, and with very high enantioselectivity. The substrate scope was also demonstrated by using various combinations of aryl aldehydes and ketones.[28] An additional significant improvement of this methodology relied on the use of equimolar amounts of donor and acceptor reaction partners (aldol reactions in organic solvents need a large excess of the donor substrate). The concept of forcing the assembly of the reagents in organocatalytic aqueous cross-aldol reactions of aldehydes through hydrophobic interactions in emulsions was also adopted by Hayashi et al.[29] They prepared the proline catalyst **8**, which has a long alkyl chain at the 4-position of the ring. The catalytic activity of **8** was tested in the challenging direct cross-aldol reaction of propanal with *o*-chlorobenzaldehyde "in the presence of water". This reaction proceeded smoothly with high diastereo- and enantioselectivity without the need for any acid additive (Scheme 12b).[29a]

A further step toward the generation of an optimized highly efficient procedure for the organocatalytic aqueous aldol reaction was established by Pericàs and co-workers.[30] They addressed the issue of catalyst recycling by preparing the polymer-supported proline derivative **9** (Scheme 12c) by a Cu[I]-catalyzed azide–alkyne cycloaddition (click chemistry).[31] The polystyrene portion of **9**, which served as a phase tag and a highly hydrophobic moiety, allowed an easy recovery of the catalyst by simple filtration of the resin and, at the same time, induced excellent stereocontrol over the aldol reaction when water was used as the solvent. It was also found that the presence of a catalytic amount of the water-soluble DiMePEG ($M \approx 2000$) in the reaction mixture improved the yield of the aldol product by facilitating diffusion of the polymeric catalyst.

Since the first reports from the research groups of Barbas, Hayashi, and Pericàs,[28–30] several publications by different research groups have appeared on asymmetric organocatalytic aldol reactions "in the presence of water".[32] Only a single study documenting a direct enantioselective aldol reaction "in water" has been disclosed so far. After screening 19 amino acids and some dipeptides, Hayashi and co-workers discovered that L-prolinamide **10** was capable of promoting the homoaldolization of water-soluble propanal at room temperature in 40% yield (within 2.5 h) and with good enantioselectivity (Scheme 13).[33] Despite the lack of generality and a detailed mechanistic investigation, this finding is of great interest, not least because the reaction investigated constitutes a fundamental step in the biosynthesis of important natural molecules such as carbohydrates and terpenes.
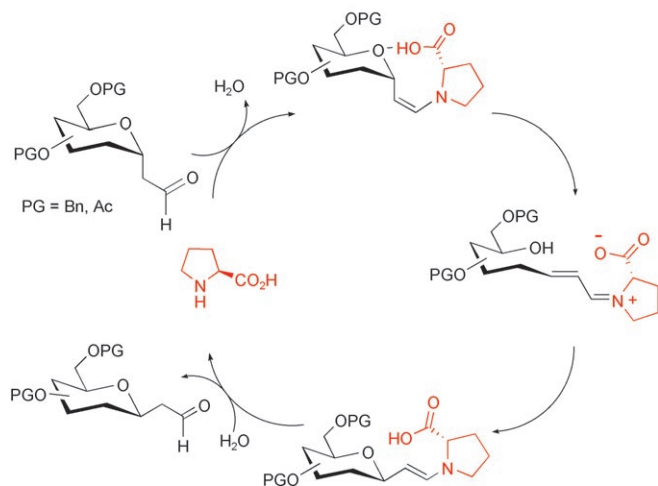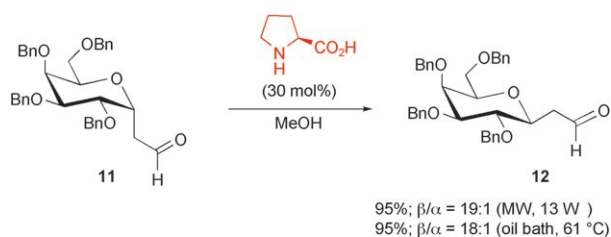
The application of microwave dielectric heating in organocatalyzed reactions has also been investigated with the aim of improving their efficiency by reducing the long reaction time (5–96 h) and high catalyst loading (≥ 10 mol%). A thermal microwave-induced acceleration of the reaction rate of asymmetric organocatalysis had already been demonstrated in the pioneering work of Westermann and Neuhaus in 2005.[34] The main challenge in this approach remained the identification of a reaction window that allowed for both a high reaction rate and a high enantioselectivity. These optimal conditions were found for Mannich,[35] aldol,[36] Michael,[36] and Diels–Alder[36] reactions in two independent studies carried out by the research groups of Bolm and Alexakis. The reactions were in all cases investigated at constant microwave irradiation at low power (10–15 W) with a simultaneous cooling of the reaction vial. The catalyst loading in the case of the Mannich reaction was reduced from 20 to 0.5 mol% while maintaining good reactivity and selectivity (Scheme 14).[35]
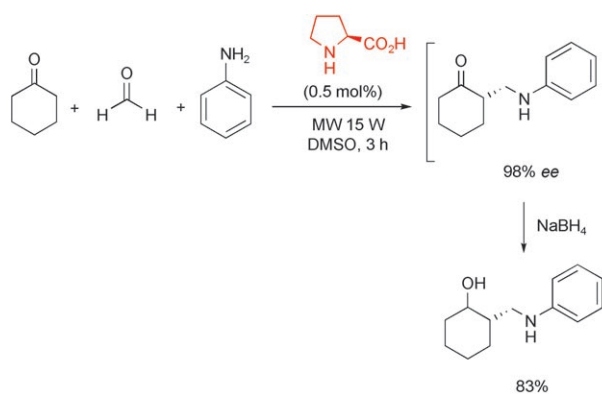
Scheme 14. Microwave (MW) assisted organocatalytic asymmetric Mannich reaction.

The effect of microwaves on organocatalytic reactions was recently reconsidered by Kappe and co-workers.[37] These researchers excluded the occurrence of a specific or nonthermal microwave effect in asymmetric organocatalysis because they could reproduce the results obtained by the research groups of Bolm and Alexakis[35,36] when the reactions were carried out at the same temperature and length of time by conventional heating. A key element of this investigation was an accurate measurement of the internal reaction temperature by a fiber-optic probe device (in place of a conventional infrared probe that is typically installed outside the vessel wall). In the course of a study on the microwave-assisted proline-catalyzed anomerization of α-*C*-glycosylmethyl aldehydes **11** into the corresponding β anomers **12** (Scheme 15),[38] Dondoni and co-workers found no nonthermal microwave effect. The same reaction efficiency was observed when the reaction performed under optimized microwave irradiation conditions was carried out in a preheated oil bath. The authors suggested that the reaction proceeds through the generation of an enamine followed by β elimination and intramolecular hetero-Michael reactions, as depicted in Scheme 15.
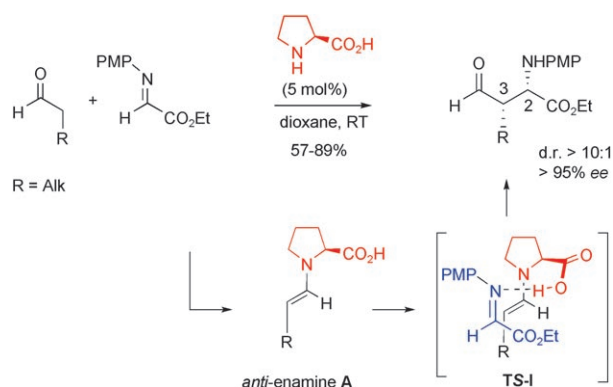

Scheme 13. Direct asymmetric aldol reaction "in water".

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Scheme 15. Microwave-assisted organocatalytic anomerization of α-*C*-glycosylmethyl aldehydes. PG = protecting group, Bn = benzyl.

Scheme 16. Proline-catalyzed Mannich reaction of unmodified aldehydes with *N*-*p*-methoxyphenyl (PMP) protected α-imino ethyl glyoxylate.

3. Development of New Catalysts

The possibility of controlling the stereochemistry of a reaction by using a suitable catalyst is a key criterion for evaluating the synthetic value of an asymmetric synthesis. In the area of organocatalysis, the lack of mechanistic details has very often precluded the design of suitable catalysts and, as a consequence, stereoselective synthetic pathways. While in the majority of amino-catalyzed reactions, control over the enantioselectivity can be obtained by changing the absolute configuration of the catalyst (for example by switching from (*S*)- to (*R*)-proline), control over the diastereoselectivity is a quite difficult task that requires the design of new catalysts.

A demonstrative example of the developmental potential in this area is provided by the Mannich reaction. The direct asymmetric Mannich reaction of unmodified aldehydes with protected α-imino glyoxylates is a highly effective carbon–carbon bond-forming reaction that affords enantiomerically enriched amino acids and amino alcohols. The biological functions of these compounds depend on the absolute and relative configuration of substituents at the C2- and C3-positions. Despite the high demand for *syn*- and *anti*-Mannich products for biomedical investigations, only the *syn*-selective direct asymmetric Mannich reaction was developed (by using L-proline as the catalyst). The excellent level of diastereo- and enantioselectivity of this transformation was explained as being due to the preferential *anti* conformation of the *E*-enamine intermediate **A**, whose double bond points away from the carboxylic group (Scheme 16). This activated species

intercepts the imine acceptor as shown in the transition state **TS-I** to give the *syn*-Mannich adduct.[39]

The first highly stereoselective amino-catalyzed *anti*-diastereoselective Mannich reaction (*anti*-Mannich reaction) was reported by Maruoka and co-workers at the end of 2005.[40] The inversion of the diastereoselectivity was considered to occur through a reversal of the enamine facial selectivity observed in the L-proline-catalyzed reactions. Consequently, this would produce *anti*-Mannich adducts with the opposite absolute configuration at the C3 stereocenter. The authors used the axially chiral organocatalyst **13**, a derivative of the catalyst they had previously employed in the direct asymmetric aldol reaction between acetone and aldehydes.[41] The key feature of **13** was the large distance between the amino and the acid groups. This separation favored the preferential formation of the *syn*-enamine intermediate **B**, thus affording the *anti*-Mannich product via transition state **TS-II** (Scheme 17).
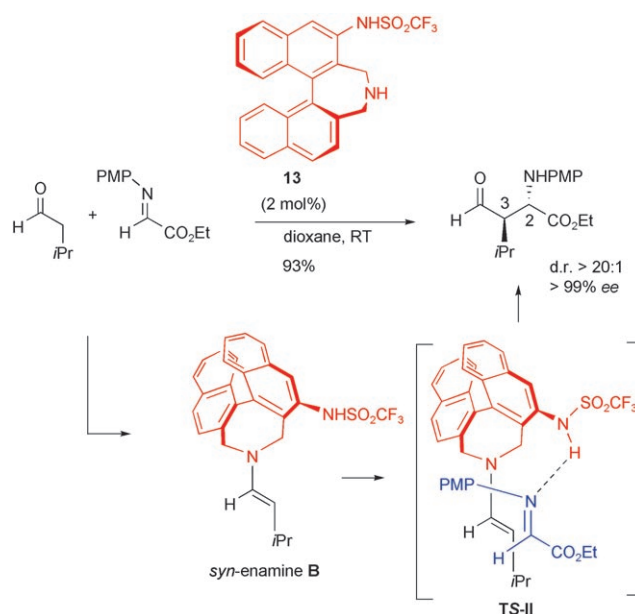
Scheme 17. First highly stereoselective amino-catalyzed *anti*-Mannich reaction of unmodified aldehydes with protected α-imino glyoxylates.

Almost concomitantly with the successful *anti*-Mannich reaction of aldehydes with α-imino glyoxylates by Maruoka and co-workers,[40] Barbas, Houk, and co-workers designed and prepared the chiral pyrrolidine-based amino acid **14** as a potential catalyst for the same transformation (Scheme 18).[42]
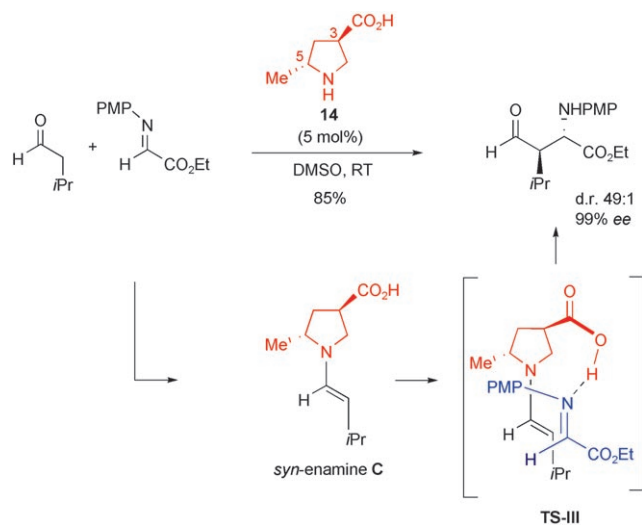
Scheme 18. Catalyst design for *anti*-Mannich reactions of unmodified aldehydes with protected α-imino glyoxylates.

This study represented the first rational design of a suitable catalyst for *anti*-Mannich reactions by means of computational studies. The reversal of diastereoselectivity with respect to the proline-catalyzed reactions was induced by the formation of the *syn*-enamine intermediate **C**. Important structural features of catalyst **14** are the methyl group at C5 of the pyrrolidine ring and the *trans* carboxy group at the distal C3-position. This arrangement fixed the *E*-enamine intermediate **C** in a *syn* conformation and at the same time directed the nucleophilic *si* attack of the protected imine as shown in the transition state **TS-III**. The efficiency of catalyst **14** was demonstrated by the synthesis of a range of *anti*-Mannich products in excellent chemical and stereochemical yields.

The extension of the above strategy to unmodified ketones as donor components proved to be unsuccessful because the reaction rate was exceptionally low.[43] This result was explained by the slow formation of the enamine intermediate because of steric interactions between the ketones and the methyl group of the catalyst **14**. Hence, Barbas and co-workers prepared catalyst **15**, which has only the 3-carboxylic acid group as the stereodirecting group. It was assumed that although *anti*-enamine **D** and *syn*-enamine **E** would have similar free energies, only the nucleophilic carbon atom of **E** would be properly positioned to react with the imine acceptor via the transition state **TS-IV** (Scheme 19). This hypothesis was confirmed by the high level of enantio- and *anti*-diastereoselectivity observed for the Mannich reactions of several linear and cyclic ketones with protected α-imino glyoxylates in the presence of pyrrolidine 3-carboxylic acid **15**.[43]
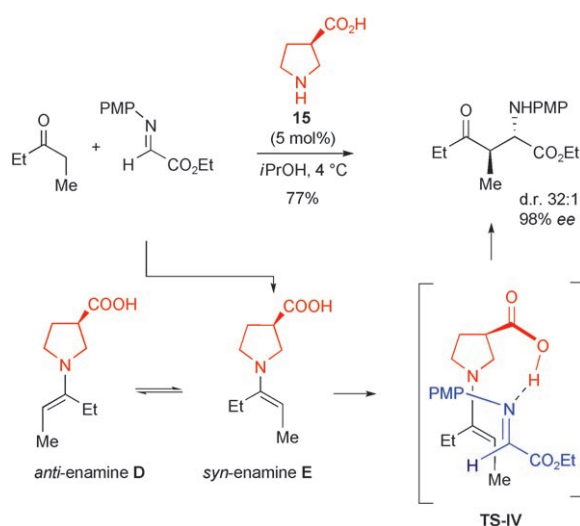
Scheme 19. Organocatalytic *anti*-Mannich reactions of unmodified ketones with protected α-imino glyoxylates.

The pyrrolidine catalysts **14** and **15** were also tested in the Mannich reactions of α-hydroxyketones with imines to give the important *anti*-1,2-amino alcohols.[44] However, these catalysts were less than optimal for this transformation, with the Mannich adducts being obtained in good yield but only moderate diastereo- and enantioselectivity. Hence, a novel catalyst design was considered on the basis of earlier observations of the preferential formation of a *Z*-enamine from hydroxyacetone and the primary amine of the lysine residue of aldolase antibodies.[45] Accordingly, it was hypothesized that with primary amines as catalysts and α-hydroxyketones as substrates, the *Z*-enamine **G** would predominate over the *E*-enamine **F**, thus resulting in the formation of *anti*-Mannich adducts via the transition state **TS-V** (Scheme 20). A variety of natural acyclic amino acids were screened as
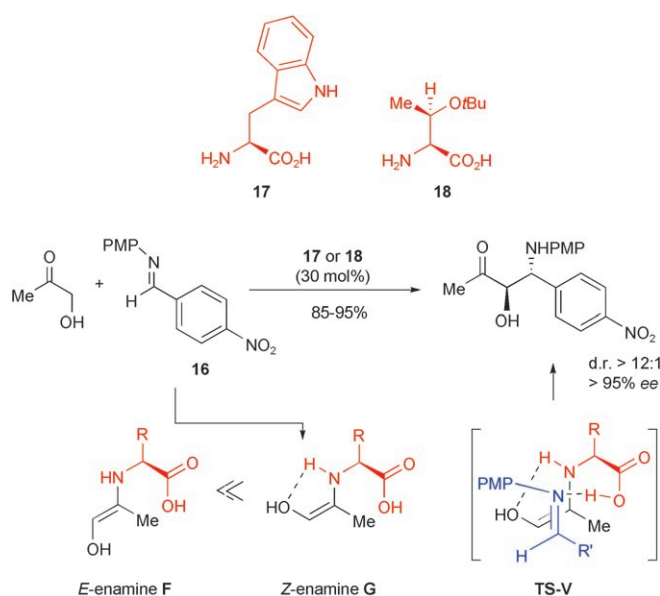
Scheme 20. Organocatalytic asymmetric synthesis of *anti*-1,2-amino alcohols.

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catalysts for the Mannich reaction of hydroxyacetone with imine **16**. The best diastereo- and enantioselectivities were obtained using either L-Trp (**17**) or *O-t*Bu-L-Thr (**18**) catalysts.[44]

Catalysts **17** and **18** could also be used for the direct three-component Mannich reaction of hydroxyacetone with *p*-anisidine and aromatic or aliphatic aldehydes in organic solvents. These reactions afforded *anti*-1,2-amino alcohols in good to excellent yields.[44] The same one-pot transformation in water was investigated by Lu and co-workers, who used several amino acids as catalysts.[46] No desired product was formed when hydroxyacetone was used as the donor. On the other hand, optimal results were obtained by using the *O*-benzyl derivative of hydroxyacetone in combination with the *O*-TBDPS-protected (TBDPS = *tert*-butyldiphenylsilyl) L-Thr catalyst **19** (Scheme 21).
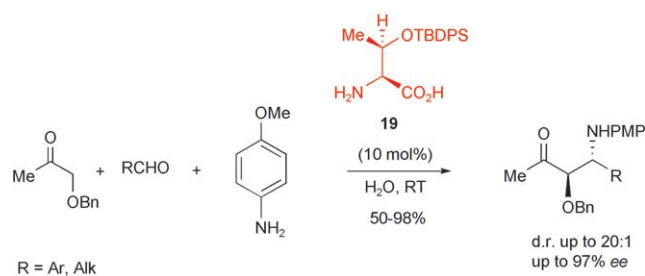

Scheme 21. Direct asymmetric organocatalytic three-component *anti*-Mannich reaction in water.

In a parellel investigation, Gong and co-workers used another strategy for organocatalytic Mannich reactions, namely the application of Brønsted acid catalysis. By using this approach they were able to perform the unprecedented direct three-component Mannich reaction of cyclic, acyclic, and aromatic ketones with aromatic aldehydes and substituted anilines.[47] Based on mechanistic considerations, an approach was envisaged wherein the use of chiral phosphoric acids as catalysts would exert dual activation of both the ketone donor and imine acceptor via the transition state **TS-VI**. Indeed, the use of catalyst **20** or **21** at very low concentrations (0.5 and 2.0 mol%, respectively) promoted the formation of *anti*-β-amino carbonyl derivatives in high yield and excellent stereoselectivity from a broad range of substrates (Scheme 22).

Other studies focused on the design of amino catalysts for *syn*-aldol reactions. With only a few exceptions,[48] most organocatalytic enantioselective cross-aldol reactions are known to provide *anti*-aldol adducts as major products.[11a,c,28–30,49] A detailed discussion on the structural features of recently designed *anti*-aldol catalysts is beyond the scope of this Review. Leading references to this topic, which itself could constitute the subject of a review, can be found in Refs. [32h,44,50].

One of the most interesting results in the area of catalyst design is the development of difunctional Brønsted acid catalysts, which contain acid, basic, or nucleophilic functional groups in addition to the Brønsted acid functionality. Although a number of these catalysts were already
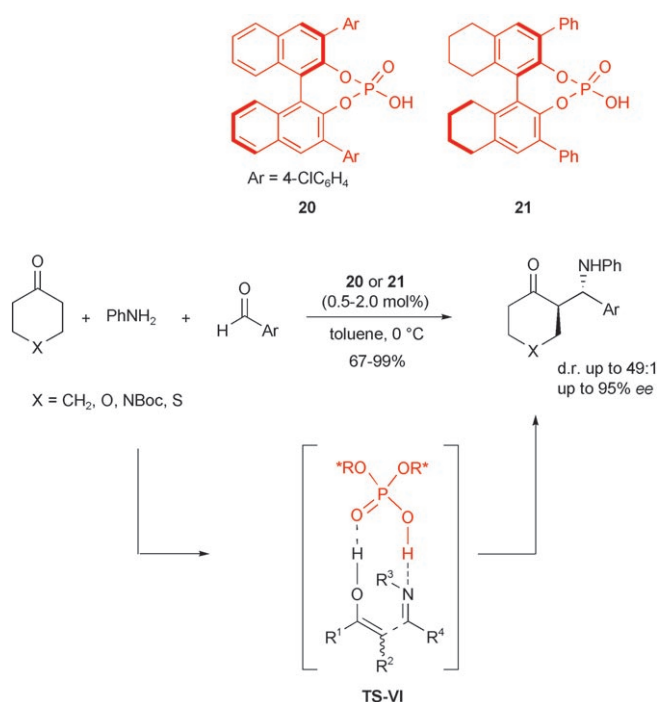
Scheme 22. Direct asymmetric Brønsted acid catalyzed *anti*-Mannich reaction. Boc = *tert*-butoxycarbonyl.

reported,[51] it was only from 2006 that dual electrophile/nucleophile activation strategies were explored intensively. The majority of the newly designed difunctional catalysts incorporate known hydrogen-bond-donor motifs (thiourea, 2,2′-dihydroxy-1,1-′binaphthyl (binol), and phosphoric acid) and different nucleophile-activating groups in their structure. Difunctional thioureas have undoubtedly played a major role in this modern field of catalysis, as demonstrated by their successful applications in three fundamental reactions of carbonyl compounds, that is, 1,2-additions,[52] 1,4-additions,[53] and acyl transfer reactions.[54] A representative example is the first highly enantioselective organocatalytic nitroaldol (Henry) reaction of aromatic aldehydes[52f] (a reaction that normally proceeds with only moderate enantioselectivity). Inspired by studies on the use of cinchona alkaloids for nucleophile activation by general base catalysis,[6d] Hiemstra and co-workers prepared the difunctional catalyst **22**, which contains an activated thiourea moiety and a basic quinuclidine nitrogen atom in a well-defined chiral environment (Scheme 23). Compound **22** proved to be an efficient catalyst for the Henry reaction of nitromethane with a range of aromatic and heteroaromatic aldehydes having different stereoelectronic properties. The observed high enantioselectivity was explained by activation of the aldehyde by the thiourea moiety (through the formation of two hydrogen bonds) and activation of the nitromethane by the basic quinuclidine nitrogen atom.[52f]

Another interesting example of difunctional catalysis was reported by Sasai and co-workers. The authors designed catalyst **23**, which constitutes the effective Brønsted acid binol motif to which was attached a side chain bearing a pyridine ring. The catalyst proved effective in the aza-Morita–Baylis–
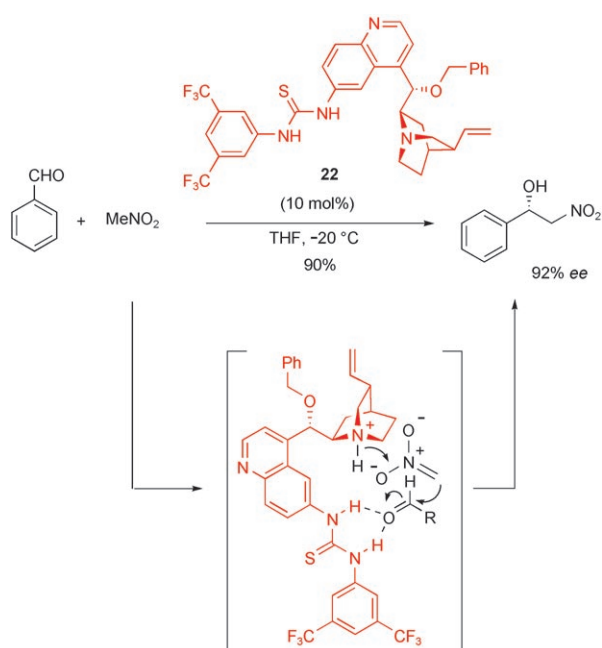
Scheme 23. Asymmetric organocatalytic Henry reaction with electrophile/nucleophile activation.

Hillman reaction of α,β-unsaturated carbonyl compounds with aryl *N*-tosylimines (Scheme 24).[55]
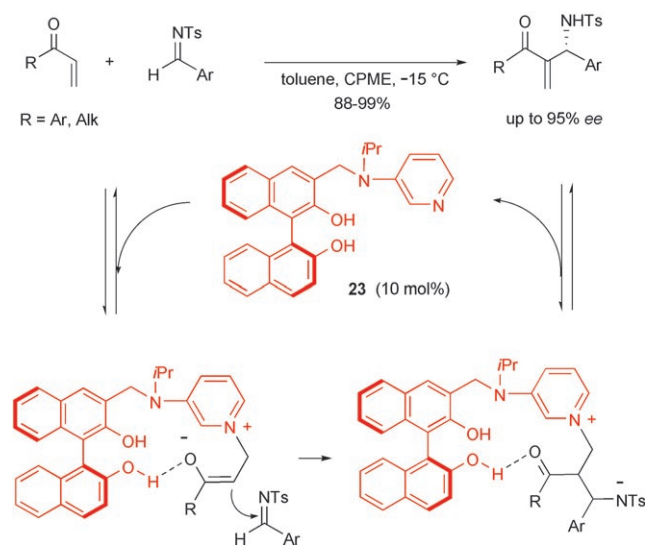
Scheme 24. Aza-Morita–Baylis–Hillman reaction with difunctional catalysis. CPME = cyclopentyl methyl ether, Ts = *p*-toluenesulfonyl.

As already mentioned in this section, chiral phosphoric acids can be considered as difunctional catalysts because of the presence of the Lewis basic P=O moiety. Terada et al. used catalyst **24** in the aza-ene-type reaction of *N*-benzoylimines **25** with enamides or enecarbamates **26** to give the chiral imine adduct **27** in high enantiomeric purity (Scheme 25).[56] It was suggested that catalyst **24** electrophilically activates **25** through the acidic proton and at the same time accepts the NH proton of **26** through the Lewis basic phosphoryl oxygen
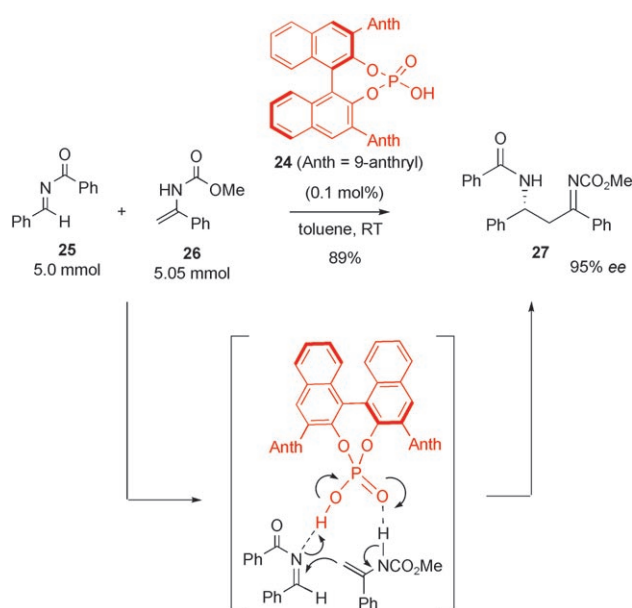
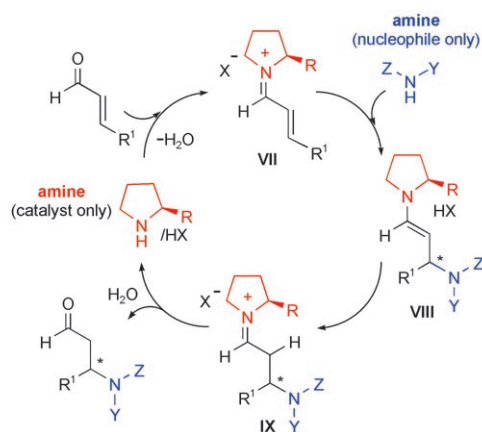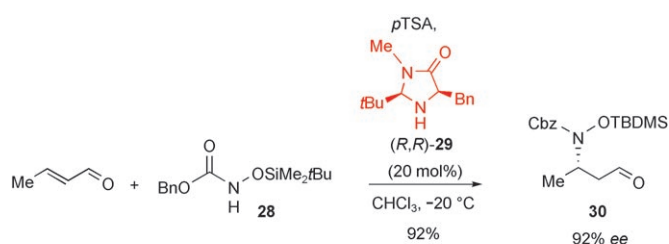**Scheme 25.** Organocatalytic enantioselective aza-ene reaction.

atom. This dual activation scheme appears to be supported by the high catalytic efficiency of **24**, as this catalyst could be used at an extremely low concentration (0.1 mol%), even in large scale reactions, without any notable loss of enantioselectivity.

4. Discovery of New Substrate Combinations

The impact of organocatalysis on modern organic synthesis is highlighted by the way it inspired numerous novel combinations of substrates that paved the way to unprecedented synthetic routes. Only a few of the relevant reports that have appeared in the last two years are commented upon here. These correspond to representative studies on reactions performed for the first time as a catalytic asymmetric version, and novel synthetic approaches that were complementary or superior to those based on metal catalysis in terms of chemical feasibility, practicality, and stereochemical outcome.

The study by MacMillan and co-workers on the first highly chemo- and enantioselective organocatalytic conjugate amination of α,β-unsaturated aldehydes represents a significant example.[57] This challenging approach required the identification of an amine that functioned as a nucleophile in a 1,4-addition without activating the iminium ion (racemic pathway). At the same time, a second amine needed to be found that performed as an iminium catalyst and not as a nucleophile (consumption of the catalyst). Moreover, the amine nucleophile needed to have moderate basicity to ensure an irreversible proton transfer during the stereodefining addition step. This would lead to the intermediate **VIII** in an enantioenriched form (Scheme 26). In contrast, an equilibrium protonation in this key step would result in the formation of racemic **VIII**.

In consideration of the above requirements, the *N*-silyloxycarbamates of type **28** were selected as the *N*

Scheme 26. Enantioselective organocatalytic conjugate addition of an amine. Cbz = benzyloxycarbonyl, TBDMS = *tert*-butyldimethylsilyl.

nucleophiles: the *O*-silyl group enhanced the nucleophilicity of the nitrogen atom, while the carbamate group made the intermediate **VIII** effectively nonbasic. The imidazolidinone amines developed by MacMillan and co-workers were considered as suitable catalysts because of their capacity to participate in asymmetric iminium activation with enals and enones while avoiding heteroconjugate addition.[58] Thus, it was observed that the combination of imidazolidinone **29** and *p*-toluenesulfonic acid (*p*TSA), which forms a chiral cyclic iminium salt in solution, catalyzed the model reaction of *tert*-butyldimethylsilyloxy carbamate **28** with crotonaldehyde effectively to give the β-amino aldehyde **30** in high enantiomeric purity (Scheme 26). The broad substrate scope of this organocatalytic conjugate amination reaction was demonstrated by varying the carbamate moiety and the α,β-unsaturated component.

Another significant example of a novel substrate combination in the area of amino-catalysis is represented by the organocatalytic enantioselective synthesis of α-hydroxy phosphonates developed by Zhao and co-workers.[59] As close analogues of α-amino acids,[60] these compounds have recently been found to serve as inhibitors of medicinally important enzymes such as renin or HIV protease and polymerase. Although the origin of their biological activity is still not completely understood, it is well-known that only one enantiomer is responsible for the observed activity. The most straightforward access to chiral tertiary α-hydroxy phosphonates (for example, **31**; Scheme 27a) is undoubtedly the direct asymmetric phosphoaldol reaction, that is, the cross-aldol reaction of a ketone (donor) with an α-keto phosphonate (acceptor). Unfortunately, this synthetic transformation had never been reported in the literature, even with
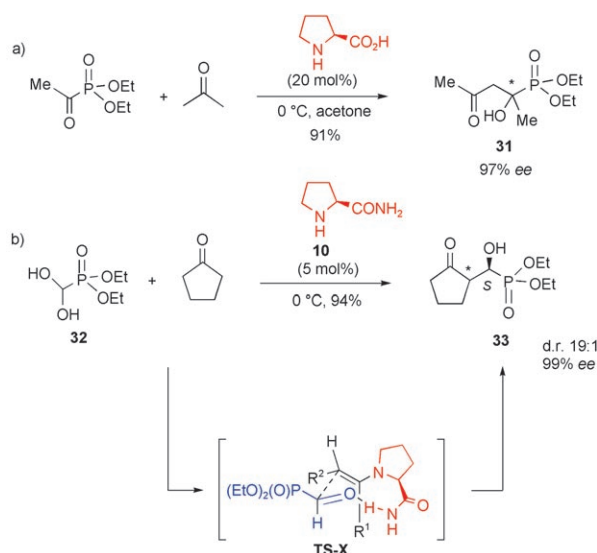

Scheme 27. Organocatalytic synthesis of tertiary and secondary α-hydroxy phosphonates.

nonchiral reagents. The reason for this is very likely the high susceptibility of the phosphonate group of α-keto phosphonates toward nucleophilic attack and its good leaving group ability. These properties may have prevented the use of preformed enolates and enamines in the phosphoaldol reaction. Nonetheless, Zhao and co-workers demonstrated that the enamine generated in situ from a ketone and a catalytic amount of L-proline reacted with the α-keto phosphonate under optimized conditions to afford the tertiary α-hydroxy phosphonate derivative exclusively. Quite rewardingly, the formation of the 1,3-diketone by-product through phosphonate elimination appeared to be totally suppressed. The high yields and excellent enantioselectivities found in the direct phosphoaldol reactions of different ketones and α-keto phosphonates demonstrated the effectiveness of enamine catalysis for this transformation.[59a]

The cross-aldol reaction of various ketones (including cyclic ketones) and diethyl formyl phosphonate hydrate (**32**) was also investigated (Scheme 27b).[59b] L-Prolinamide (**10**) was the optimal catalyst in this process. L-Proline was ineffective, presumably because phosphonate **32** is incompatible with its acidity. The hydrate form of the diethyl formyl phosphonate was used because of the high instability of the free aldehyde. Dodda and Zhao used this catalytic strategy to prepare an array of diverse secondary α-hydroxy phosphonates in very high enantiomeric purity. A representative example of this class of chiral phosphonates is **33**, which is derived from the reaction with cyclopentanone. The formation of 2S-configured α-hydroxy phosphonates as major products was explained by a preferential *si* attack of the enamine on the keto phosphonate to give the transition state **TS-X**. In this arrangement there is only a minor steric interaction between the bulky phosphonate group and the axial alkyl (R[1]) group.[59b]

A significant advancement in the area of Brønsted acid catalysis and asymmetric catalysis in general was provided by the work of MacMillan and co-workers on the one-pot

enantioselective reductive amination of ketones to give chiral secondary amines.[61] An enantioselective version of this reaction had not previously been explored, even by using metal-centered Lewis acid catalysts. Inspired by the mechanism of the amino acid biosynthesis (in which transferase enzymes catalyze the formation of ketimine derivatives of pyruvate), MacMillan and co-workers envisaged replacing enzymes and cofactors with hydrogen-bond donors and NADH analogues, respectively. The application of this strategy followed the pioneering work of Rueping et al., who first reported on the chiral phosphoric acid catalyzed reduction of preformed ketimines, with Hantzsch dihydro-pyridines used as the hydride source.[62] MacMillan and co-workers optimized their model one-pot reductive coupling of acetophenone and *p*-anisidine by using *ortho*-triphenylsilyl-binol phosphoric acid **34** as the catalyst and the ethyl Hantzsch ester **4** as the hydride source (Scheme 28). The
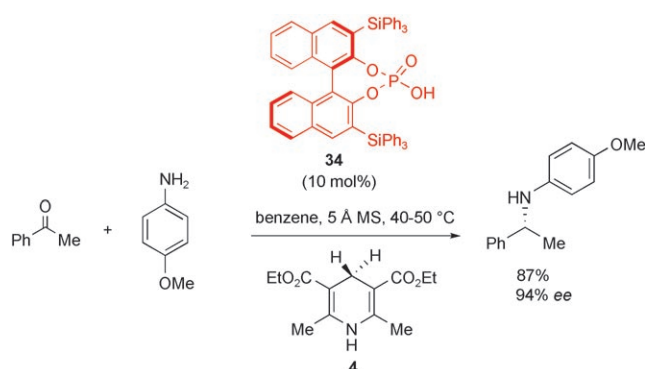
Scheme 28. Enantioselective organocatalytic reductive amination of methyl ketones.

reaction was successfully applied to the enantioselective reductive amination of aromatic and aliphatic ketones with various aromatic amines, including heteroaromatic derivatives. Unfortunately, experimental and computational data demonstrated the limited applicability of this methodology to imines derived from methyl ketones.[61]

The scope of the organocatalytic asymmetric reductive amination involving the use of a chiral phosphoric acid catalyst and a Hantzsch ester as the hydride source was extended by List and co-workers to α-branched alkyl aldehydes.[63] The successful transformation of these substrates was even more challenging than the transformation of ketones. It was hypothesized that an α-branched alkyl aldehyde in the presence of an amine and a chiral Brønsted acid may undergo a fast equilibration into the two enantiomers through an imine/enamine tautomerization (Scheme 29). Consequently, enantiomerically enriched products can be formed if the reduction of the iminium ion of one of the two imine enantiomers is faster than the reduction of the other (dynamic kinetic resolution). List and co-workers found the optimal reaction conditions (solvent, temperature, and use of molecular sieves) for the reductive amination of 2-phenylpropanal (**35**) with *p*-anisidine by using catalyst **36** at low loading (5 mol%) and dihydropyridine **37**. The wide scope of the method was demonstrated by the transformation
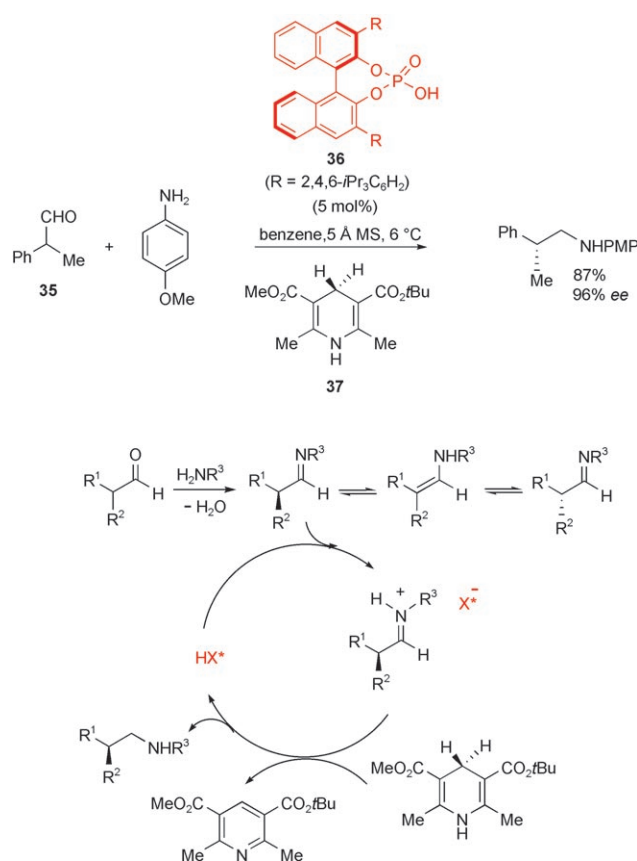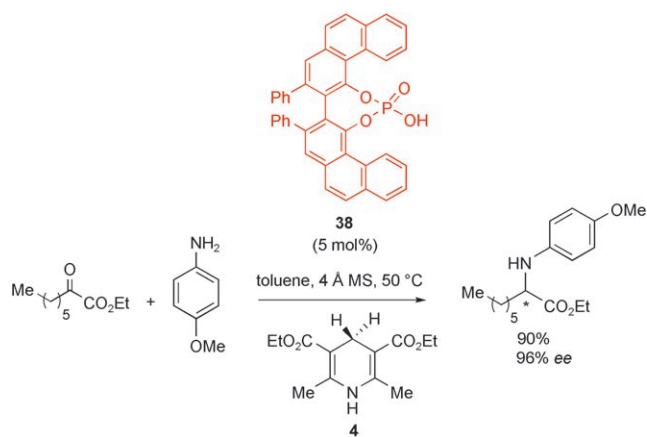

Scheme 29. Organocatalytic reductive amination of aldehydes by dynamic kinetic resolution.

of a series of aliphatic and aromatic aldehydes with different amines.[63]

Spurred on by the work of MacMillan and co-workers,[61] Antilla and co-workers later carried out the first one-pot reductive amination of α-keto esters to α-amino esters.[64] They first demonstrated that the asymmetric reduction of preformed alkyl- and aryl-substituted α-imino esters proceeded in good yield and excellent enantioselectivity in the presence of the chiral vapol-phosphoric acid **38** (vapol = 2,2′-diphenyl-4-biphenanthrol) as catalyst. The MacMillan catalyst **34** was virtually inactive in this reaction. Subsequently, they found that the reaction could be carried out—albeit for only a few examples—in a one-pot procedure, with alkyl-substituted α-imino esters generated in situ from the corresponding α-keto esters and *p*-anisidine (Scheme 30).[64]

Asymmetric organocatalysis proved to nicely complement metal catalysis by giving the product with the opposite configuration. The study by Rueping et al. on the asymmetric Brønsted acid catalyzed Nazarov cyclization of divinylke-tones[65] constitutes a representative example of this useful facet of organocatalysis. The Nazarov reaction belongs to the class of electrocyclic reactions and its synthetic utility has been widely demonstrated by the straightforward syntheses of a number of five-membered rings, some of which were identified in the structures of important natural products.[66,67] While the asymmetric metal-catalyzed variant of the Nazarov reaction of divinylketones typically provided *trans*-cyclopen-

Scheme 30. Enantioselective organocatalytic reductive amination of α-keto esters.

tenones (by a conrotatory ring closure),[67c] the organocatalytic version using the chiral phosphoric acid derivative **39** produced the corresponding *cis* stereoisomers as major products (Scheme 31).[65] A mechanistic rationalization for this unprecedented organocatalytic transformation consisted of the initial catalytic protonation of divinylketone by the chiral Brønsted acid (*BH), followed by conrotatory 4π electrocyclization to give the oxyallyl cation **XII**. A successive proton exchange between the substrate and the catalyst in
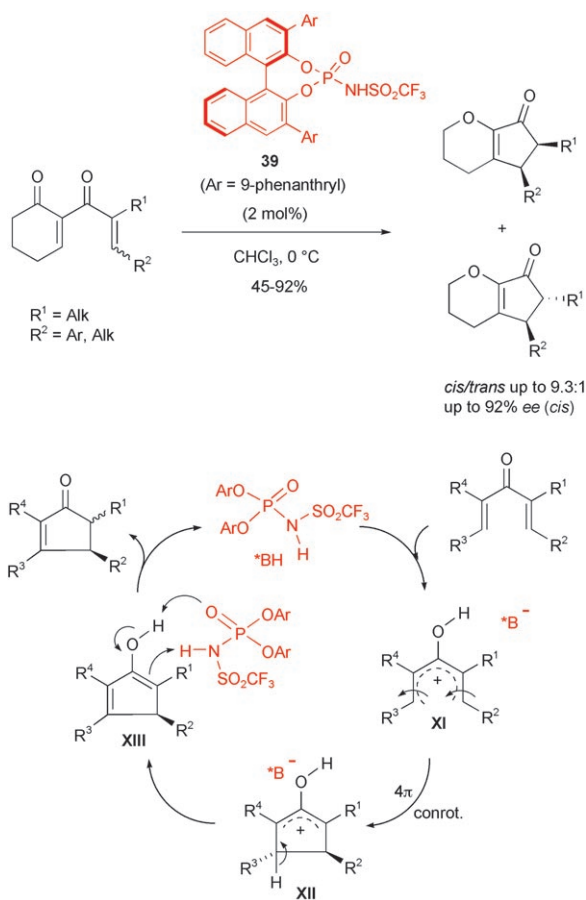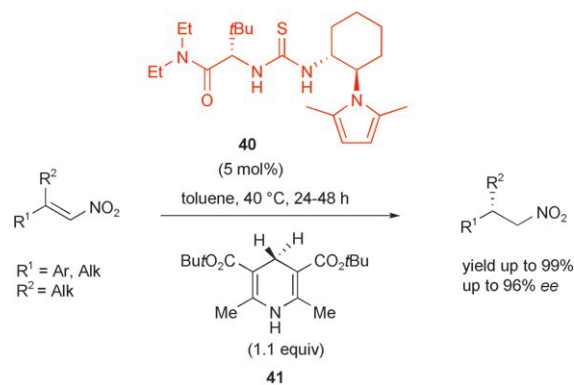

Scheme 31. Organocatalytic asymmetric Nazarov cyclization.

intermediate **XIII** would lead to formation of the cylopentenone and regeneration of the catalyst. The important features of this novel asymmetric Nazarov reaction are the mild reaction conditions, the low catalyst loading (2 mol%), and the high enantioselectivities obtained for a large number of synthesized cyclopentenones.[65]

The practicality of synthetic procedures may represent a further advantage of an organocatalytic strategy over the corresponding metal-catalyzed variant. One example is the catalytic enantioselective conjugate reduction of β,β-disubstituted nitroolefins. Early work by Czekelius and Carreira led to a copper-catalyzed version of this challenging reaction through the use of a mixture of phenylsilane and methyl hydrogen siloxane polymer (PMHS) as a reducing agent.[68a] However, the method was quite laborious. Optimal conditions[68b] required the initial generation of the chiral copper complex by slowly mixing the commercially available bisphosphane ligand (*R*)-1-[(*S*)-2-diphenylphosphanyl)ferrocenyl]ethyldicyclohexylphosphane (josiphos) with CuF$_2$. This operation was followed by the sequential addition of optimized amounts of PMHS, phenylsilane/water, nitromethane, phenylsilane/nitroolefin, and finally phenylsilane over a total period of 17 h.

The synthetic procedure disclosed by List and co-workers for this transformation appeared to be much more practical.[69] Stirring the mixture of β,β-disubstituted nitroolefin, Jacobsen-type thiourea[70] catalyst **40**, and Hantzsch ester **41** in toluene at 40°C for a suitable time (24–48 h) resulted in the formation of the target chiral β-branched nitroalkane derivative in high yield and with good enantioselectivity (Scheme 32).[69] It is worth noting that although catalyst **40** and reductant **41** are not commercially available, they can easily be prepared by straightforward procedures.[69,71]

Scheme 32. Organocatalytic asymmetric reduction of β,β-nitroolefins.

5. Drugs and Natural Products Synthesis

The ultimate validation of any synthetic method is its successful application to the synthesis of structurally complex molecular targets, especially those of biological or pharmaceutical relevance. Organocatalysis appeared to have all the credentials for use in drug and natural product synthesis, and the first successes were achieved recently.[5j] In many of these examples, however, the organocatalytic step is carried out at

the very beginning of the synthesis, and therefore an intermediate is formed whose structure is quite remote from that of the final product. In some cases the resulting product is a stereoisomer of an earlier reported compound produced by different approaches. More significant are those syntheses in which a target natural product or drug is formed by an organocatalytic reaction that is a key step, especially when they are more efficient than the organometallic-catalyzed versions. In this context a few selected examples reported from 2006 to the middle of 2007 are illustrated below.

Garden, Tomasini, and co-workers described the synthesis of (R)-convolutamydine A (**43**, Scheme 33).[72] This natural
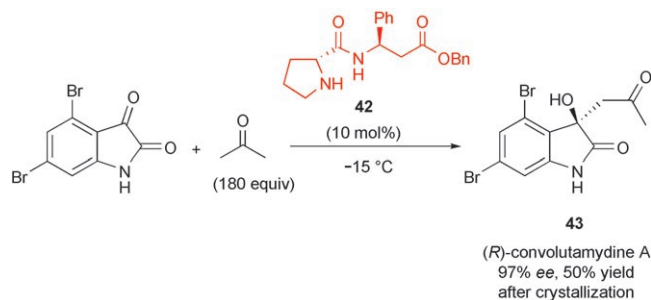
Scheme 33. Total synthesis of (R)-convolutamydine A (**43**).

product is a member of a group of alkaloids isolated in 1995 from the Floridian marine bryozoan *Amathia convolute*. It exhibits a potent activity in the differentiation of promyelocytic HL-60 human leukemia cells.[73] The structure of **43** consists of a 4,6-dibromo-3-hydroxyoxindole with a 2-oxopropyl side chain at the asymmetric quaternary carbon atom. The synthesis of **43** was achieved by the organocatalytic aldol reaction of acetone with 4,6-dibromoisatin (Scheme 33), an approach that had been used in an earlier study by Tomasini and co-workers for the coupling of acetone and isatin.[74] The catalyst employed was the D-prolinamide **42**, which induced the formation of the quaternary carbon atom with the correct *R* configuration (the L-proline derivative afforded the *S* enantiomer preferentially). Under optimized conditions the natural product was obtained in almost quantitative yield. Although the enantioselectivity was modest, highly enantiomerically enriched (R)-**43** (97% *ee*) was obtained in 50% yield after crystallization. The structure of the product with the *R* configuration at C3 was confirmed by single-crystal X-ray diffraction studies. Interestingly, the optical rotation of the synthetic material ($\alpha_D = 41.4$) was much higher than that reported for the natural sample ($\alpha_D = 27.4$).
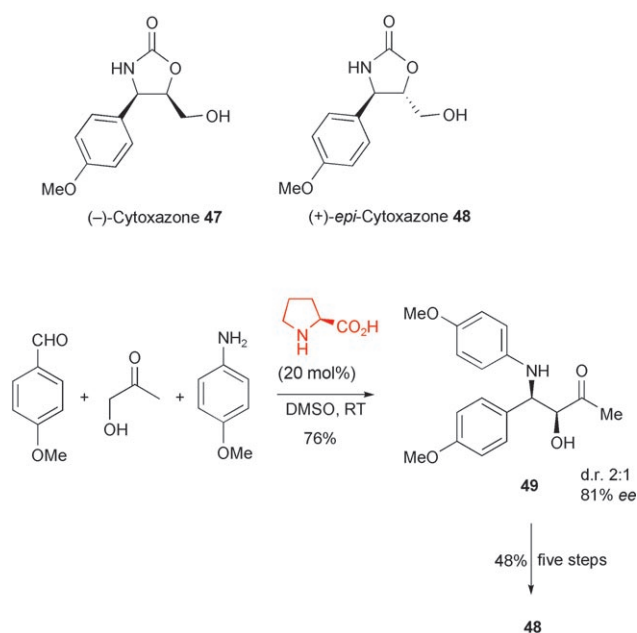
An insightful example of the advantages of the organocatalytic approach over catalytic organometallic reactions is the stereoselective total synthesis of the indole alkaloid *ent*-dihydrocorynantheol (**46**) by Itoh et al. (Scheme 34).[75] This natural product belongs to the corynantheine group of alkaloids, which have attracted substantial interest over the years because they exhibit antiparasitic, antiviral, and analgesic activity.[76] The synthesis relied on a very efficient L-proline-catalyzed initial step involving the known 9-tosyl-3,4-dihydro-β-carboline (**44**) and 3-ethyl-3-buten-2-one to give
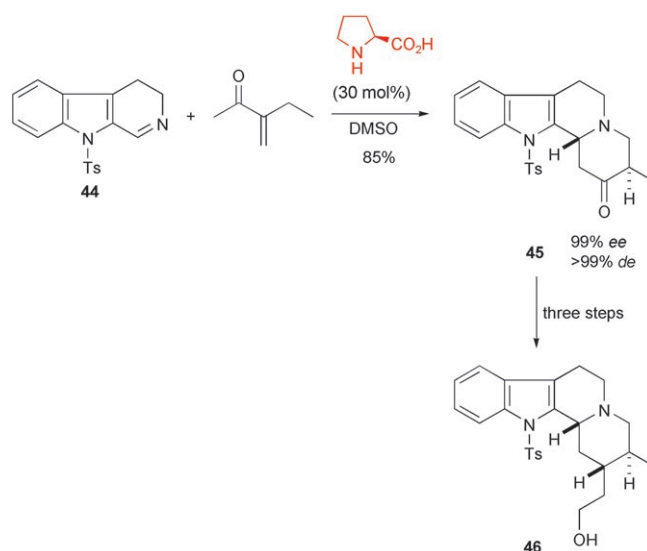
Scheme 34. Total synthesis of *ent*-dihydrocorynantheol (**46**).

exclusively product **45** with high stereoselectivity. In this way the skeleton of the target product with the correct configuration of the two stereocenters was formed in a single organocatalytic step. This process was considered to occur by a Mannich–Michael reaction sequence rather than a Diels–Alder reaction. The transformation of **45** into the target molecule *ent*-dihydrocorynantheol (**46**) was achieved by standard reactions: a Wittig reaction of the carbonyl group and the stereoselective reduction of the resulting olefin. Product **46** was obtained from the carboline **44** in four steps and in 38% overall yield. It is worth noting that this synthesis is much more concise and simple than the synthesis of *ent*-**46**, that is, the natural product dihydrocorynantheol.[76] This was synthesized by Dieters and Martin starting from indole-3-acetic acid by a series of organometallic reactions (two ring-closing metathesis and a zirconocene-catalyzed carbomagnesation) in eight steps and in 26% overall yield.[76]

The enantioselective total synthesis of the chiral oxazolidinone (−)-cytoxazone (**47**), a cytokine modulator, was carried by Paraskar and Sudulai by a Ti-catalyzed Sharpless asymmetric epoxidation of allyl alcohol.[77] The same researchers reported the synthesis of the stereoisomer (+)-*epi*-cytoxazone (**48**) by an L-proline-catalyzed asymmetric Mannich reaction (Scheme 35).[77] They took advantage of earlier work by List on a direct organocatalytic three-component Mannich reaction.[39c] List had pointed out that a successful reaction can be performed because of two factors: 1) the chiral enamine derived from a ketone and proline reacts faster with an imine than with an aldehyde, and 2) the formation of an imine from an aldehyde and a primary amine is faster than the concurrent aldolization. Hence, the key asymmetric step of the synthesis of **48** by Paraskar and Sudulai involved the initial construction of the *syn*-amino alcohol **49** (Scheme 35) by condensation of *p*-anisaldehyde with *p*-anisidine and hydroxyacetone in the presence of an L-proline catalyst. Although **49** was formed with just fair stereoselectivity (d.r. 2:1, 81% *ee*), its elaboration to **48** was accomplished in five steps by ring closure to form an

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Scheme 35. Structures of (−)-cytoxazone (**47**) and epimer (+)-*epi*-cytoxazone (**48**), and the synthesis of **48**.

oxazolidinone, and transformation of the acetyl group to a primary hydroxymethyl group.

Nicolaou et al. used an organocatalytic strategy in the total synthesis of the natural product biyouyanagin A,[78] which is a drug-discovery lead compound (anti-HIV agent) and a Japanese natural medicine. Two synthetic routes emerged from a retrosynthetic analysis which involved a symmetry-allowed photoinduced [2+2] cycloaddition of the disubstituted cyclohexadiene **52 a** (*ent*-7-epizingiberene) or **52 b** (*ent*-zingiberene, Scheme 36). These approaches allowed the unambiguous assignment of the configuration of the C24 stereocenter in the alkyl side chain of biyouyanagin A. The synthesis of terpenoids **52 a** and **52 b** was elegantly carried out by an organocatalytic process (Scheme 36). *O*-Methyl diphenylprolinol (**50**) in the presence of 3,4-dihydroxybenzoate promoted the enamine-mediated asymmetric Michael addition of (*S*)-citronellal to methyl vinyl ketone to give a ketoaldehyde intermediate that underwent an intramolecular aldol condensation. In this way the cyclohexenone **51 a** was obtained in good yield (72%) and high diastereoselectivity (93% *de*). This enone was then transformed into terpene **52 a** by known methods. In the same way, the diastereoisomer **52 b** was prepared starting from (*R*)-citronellal. These compounds were subjected to [2+2] photo-cycloaddition with hyperolactone C (**53**), with both cycloadditions leading to the rapid chemo-, regio-, and stereoselective formation of the cyclobutane ring to give diastereoisomers **54 a** (24*S*) and **54 b** (24*R*), the latter of which is the natural product biyouyanagin A.

Key steps in natural product synthesis rely on earlier exploratory research on simple model substrates. The approach to the biomimetic iminium ion catalyzed asymmetric hydrogenation of α,β-unsaturated aldehydes developed by MacMillan and co-workers[58d] and List and co-workers[79] set the basis for the regio- and enantioselective reduction of
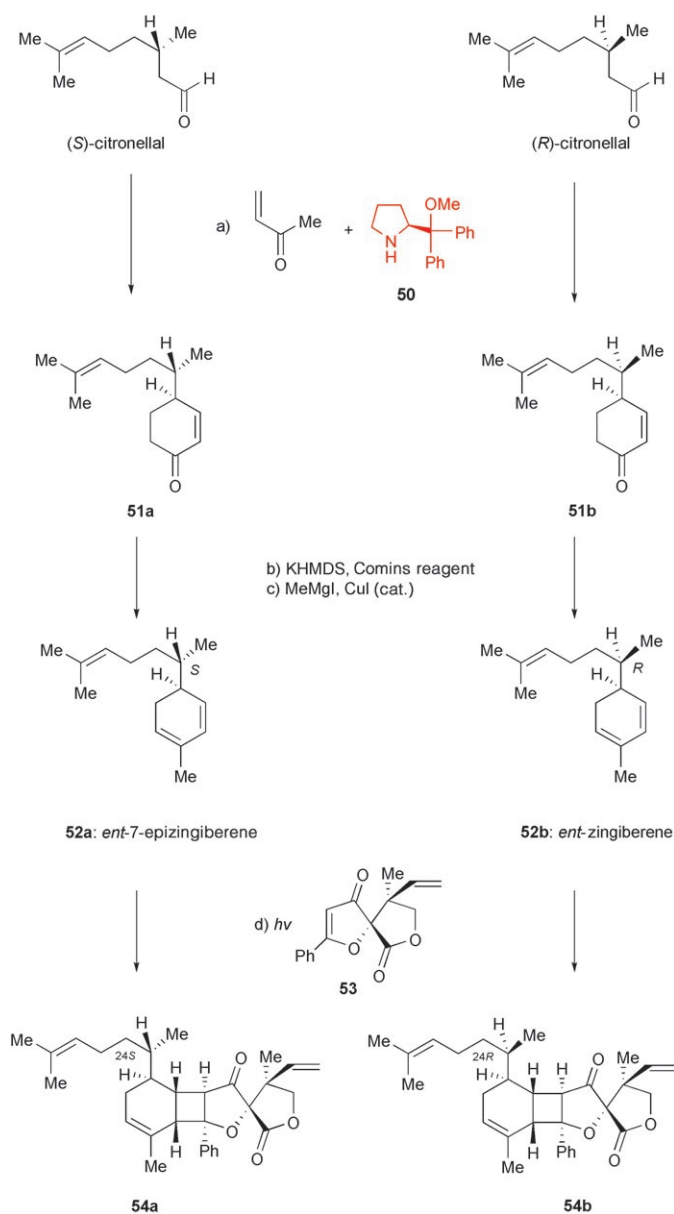
Scheme 36. Total synthesis of biyouyanagin A (**54 b**).
HMDS = 1,1,1,3,3,3-hexamethyldisilazane.

polyunsaturated natural aldehydes. Although the general use of a Hantzsch dihydropyridine as the reductant and synthetic nicotinamide-adenine dinucleotide (NADH) analogue had already been established, the remarkable advancement made by Mayer and List[80] was the use of a chiral counteranion to induce asymmetry in the reduction of substituted α,β-unsaturated aldehydes. Mayer and List used the morpholinium salt **55**, which features a sterically hindered chiral phosphate as counteranion (Scheme 37).[80] With this, they achieved the reduction of (*E*)-citral to (*R*)-citronellal (a perfume ingredient and intermediate in the industrial synthesis of menthol) and the reduction of farnesal to (*R*)-dihydrofarnesal (a pheromone of several bumble bee species and a constituent of the scent of orchids as well as the blossom fragrance of lemon tree flowers). The enantioselectivity of the
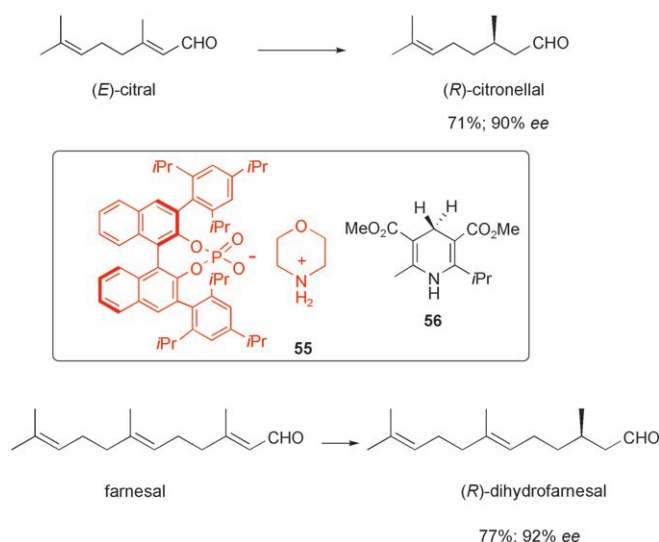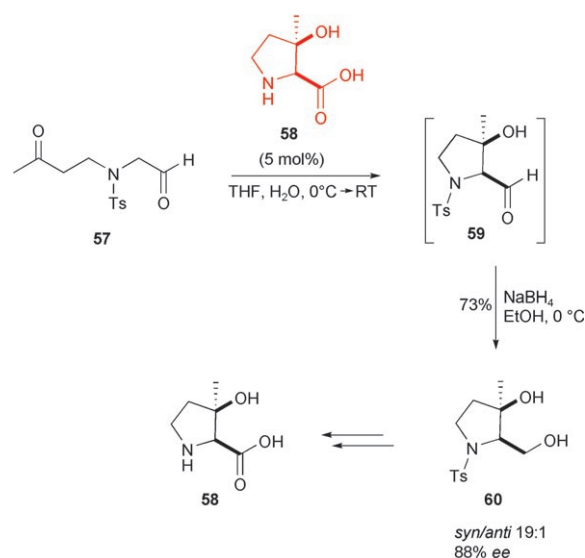
Scheme 37. Hydrogenation of citral and farnesal.

Scheme 38. Organocatalytic synthesis of (2S,3R)-3-hydroxy-3-methyl-proline (**58**).

hydrogen transfer process from the Hantzsch ester **56** to citral with this catalyst was much higher than the values achieved earlier by List and co-workers[79b] and by MacMillan and co-workers[58d] who used chiral imidazolidinone salts. As these reactions proceeded through an iminium-type activation, only the double bond adjacent to the carbonyl group was reduced, while the other double bonds remained unaffected.[81] As catalytic asymmetric hydrogenation processes are currently carried out by the use of metal catalysts or stoichiometric amounts of metal hydrides, organocatalysis provides a substantial advancement in respect to cost, safety, and practicability of these processes.

In the course of their organocatalytic approach to (2S,3R)-3-hydroxy-3-methylproline (**58**), a required component for the assembly of polyoxypeptins, Hamada and co-workers discovered an interesting case of asymmetric autocatalysis.[82] They observed that the addition of a small amount of product **58** to the ketoaldehyde **57** acted as an efficient catalyst for the intramolecular asymmetric aldol reaction (Scheme 38). The resulting chiral aldehyde **59** was reduced in situ to the alcohol **60**, which was isolated in very good yield and high stereochemical purity. Finally, **60** was readily transformed into the target product **58**. This represents a nice example wherein a natural product synthesis led to the discovery of a new organocatalytic process.

The key role of carbohydrates in biological processes[83] and their potential as drug candidates[84] stimulated the interest of leading research groups in organocatalysis on the de novo synthesis of common and rare sugar molecules. This is probably the area in which the utility of organocatalysis is most evident, as it provided access to a range of products of great relevance in biological and medicinal sciences which were difficult to access from natural sources or by synthetic methods. This research topic was pioneered by Barbas and co-workers in 2002[11e, 13c] and more thoroughly investigated by Northrup and MacMillan[49g] in 2004. Numerous subsequent studies—particularly by the research groups of Enders,[85] Barbas,[86] and Córdova[87]—established and then demon-

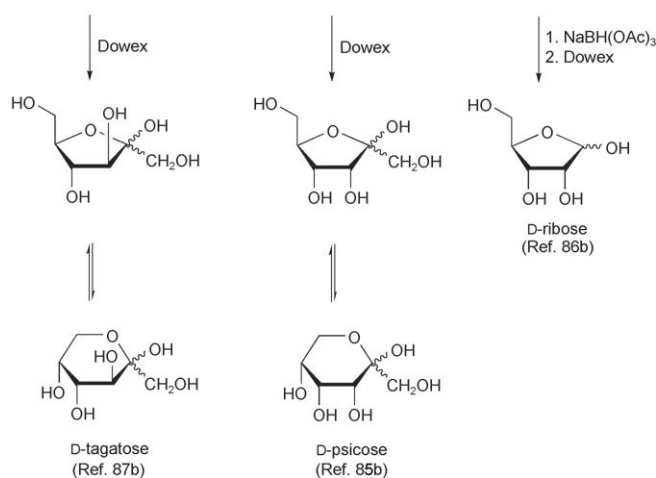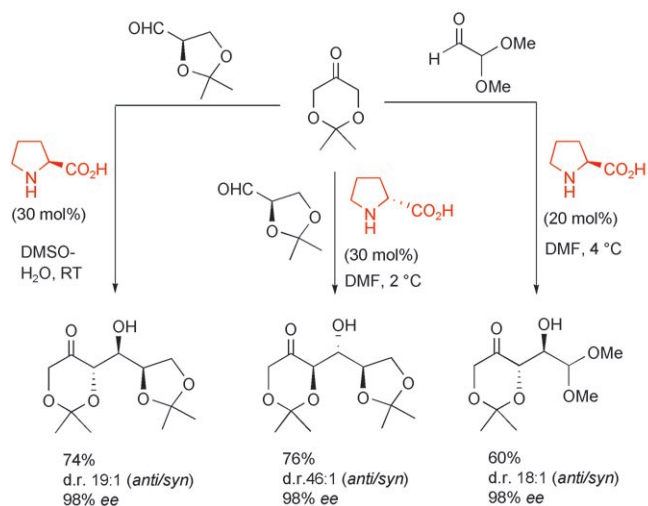strated the biomimetic $C_3 + C_n$ strategy based on the asymmetric coupling of 2,2-dimethyl-1,3-dioxan-5-one (donor) with aldehyde acceptors in the presence of proline or proline derivatives as catalysts.[88] Three selected examples dealing with the synthesis of D-ribose, D-psicose, and D-tagatose are reported in Scheme 39.
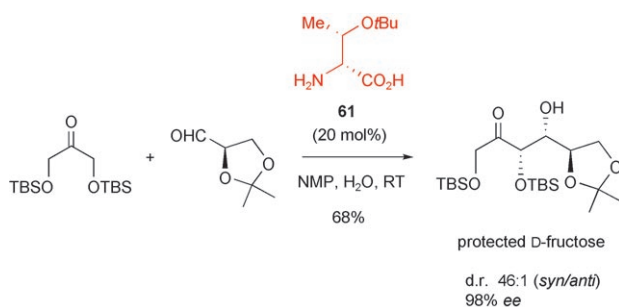
More recently Grondal and Enders have extended the scope of this approach to the synthesis of protected D- and L-aldopentoses by stereodivergent reduction of the carbonyl group of ketoses formed in the organocatalytic step.[89] This $C_3 + C_n$ strategy is essentially identical to the synthesis of natural carbohydrates by phosphate aldolase catalyzed aldol addition of dihydroxyacetone phosphate to aldehydes. The proline catalyst was thus regarded as an organocatalytic mimic of aldolase enzymes. In view of the preferred formation of *anti*-aldol products, (S)-proline was considered to be a mimic of D-tagatose aldolase and (R)-proline to be a mimic of L-fuculose aldolase.

Full control over the diastereoselectivity of the aldol reaction to provide *syn*-configured 1,2-diols was achieved by Barbas and co-workers by using amino acid catalysts that mimick L-rhamnulose phosphate and D-fructose diphosphate.[50c,d] The reaction of *tert*-butyldimethylsilyl (TBS) protected dihydroxyacetone with the acetonide of D-glyceraldehyde in the presence of a catalytic amount of O-*t*Bu-D-Thr (**61**) occurred with high diastereo- and enantioselectivity to give protected D-fructose in good yield (Scheme 40). Hence, the *syn*-configured diol was formed. Therefore, it appears that the appropriate choice of amino acid catalysts and protected variants of dihydroxyacetone can make accessible a wide range of D and L sugars.

A still neglected topic in the area of organocatalytic carbohydrate chemistry is the preparation of sugar building blocks[38] and biologically relevant glycoconjugates.[90] The organocatalyzed α-amination of C-glycosylmethyl aldehydes **62** is the key step in a synthesis of C-glycosylglycines.[91] In these non-natural α-amino acids the sugar fragment is directly

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Scheme 39. The biomimetic $C_3 + C_n$ strategy for the synthesis of carbohydrates.

Scheme 40. Synthesis of protected D-fructose. NMP = N-methyl-2-pyrrolidinone.

linked to the chiral α-amino acid group (glycinyl moiety) through an anomeric carbon–carbon bond (Scheme 41). The importance of C-glycosyl amino acids as key building blocks for the co-translation synthesis of non-natural glycopeptides is widely recognized.[92] Furthermore, C-glycosylglycines have been used for the preparation of C-nucleoside antibiotics,[93] and they are inhibitors of bacterial synthetases.[94] However, all the reported synthetic methods to C-glycosylglycines
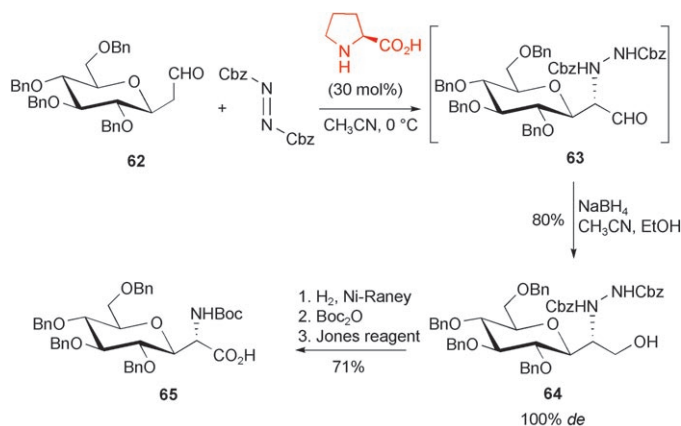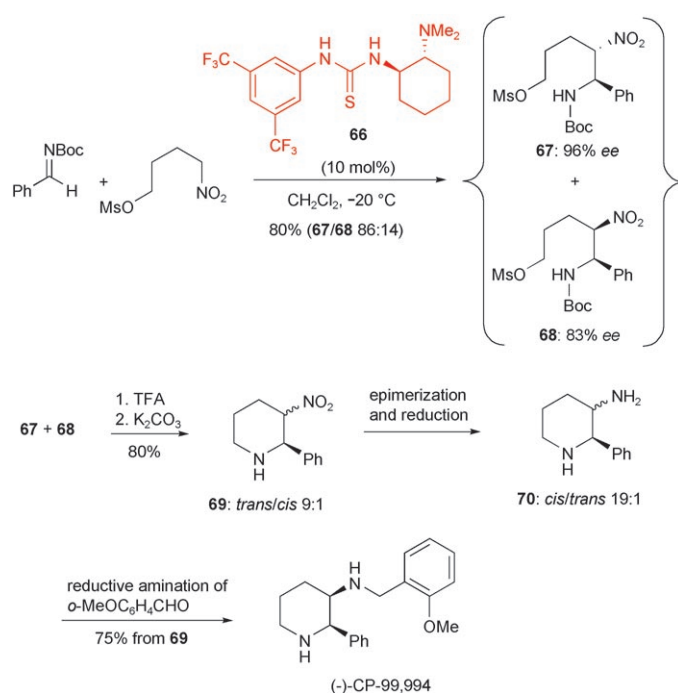

Scheme 41. Organocatalytic synthesis of C-glycosylglycines. CBz = benzyloxycarbonyl.

suffer from various drawbacks, such as low stereoselectivity, the numerous steps involved, and the lack of generality.[92a, 95] Organocatalysis offers the opportunity to overcome these major limitations. Dondoni et al. found that the proline-catalyzed α-amination of **62** proceeded efficiently to afford, after reduction of the intermediate aldehyde **63**, the α-hydrazino alcohol **64** as a single stereoisomer. This compound in turn was easily converted into the target C-glycosylglycine **65**, suitably protected for its subsequent co-translation insertion into a peptidic chain.[91]

Organocatalysis also plays a primary role in the synthesis of low-molecular-weight drug candidates. The aza-Henry reaction (nitro-Mannich reaction) was used by Takemoto and co-workers[96] for the short asymmetric synthesis of the chiral piperidine derivative CP-99,994 (Scheme 42). The previous asymmetric syntheses of this potent neurokinin-1 receptor antagonist were mainly based on the use of metal complexes as catalysts but suffered by several drawbacks, for example, low overall yield and enantioselectivity or a lengthy synthetic route.[97] Notably, the synthesis of Takemoto and co-workers proceeded in five steps without the need to separate the diastereoisomeric intermediates. The catalyst employed was the chiral thiourea **66**, which served as an activator of both the nitroalkane and imine reactants. The transition state is relatively complex and is dominated by hydrogen-bonding interactions. This difunctional catalyst is an elegant improvement over the chiral thiourea and tertiary amine system developed by Jacobsen and co-workers as an organocatalyst for the aza-Henry reaction.[53d, 98] The use of **66** catalyzed efficiently the first asymmetric carbon–carbon bond-forming step (an aza-Henry reaction) en route to CP-99,994 without the need for any external amine. Accordingly, the N-Boc-protected benzaldimine reacted with 4-methoxy-nitrobutane in the presence of this catalyst to give the desired cis-diastereoisomer **68** as a minor product, although in very high enantiomeric purity. The two isomers **67** and **68** were cyclized as a mixture to give the piperidine **69**, predominately as the trans isomer, of course. This was almost completely epimerized and then reduced to the required cis-amino-piperidine **70**. The reductive amination of the latter with o-anisaldehyde finally afforded the target product (−)-CP-

Scheme 42. Organocatalytic synthesis of CP-99,994, a neurokinin-1 receptor antagonist. Ms = methanesulfonyl.

99,994 in high purity, as evident from a comparison of the optical rotation with the literature value.

Another remarkable synthesis of an interesting drug candidate was reported by Gong and co-workers. They developed a highly enantioselective protocol for the asymmetric Biginelli reaction in which they used a chiral phosphoric acid as the organocatalyst.[99] The reaction involved the one-pot acid-catalyzed three-component condensation of an aldehyde, a β-ketoester, and (thio)urea to give the chiral 3,4-dihydropyrimidin-2-one derivatives **71** (DHPMs, Scheme 43). The DHPM scaffold is a privileged structure that, depending on the substitution patterns, shows a variety of important pharmacological properties. The absolute configuration of the C4 stereocenter in the DHPM ring dramatically influences the biological activity of these molecules. An asymmetric variant with an ytterbium-based catalyst for the Bignelli synthesis was already known,[100] but the discovery of a metal-free synthesis by using the Brønsted acid catalyst **21**, which
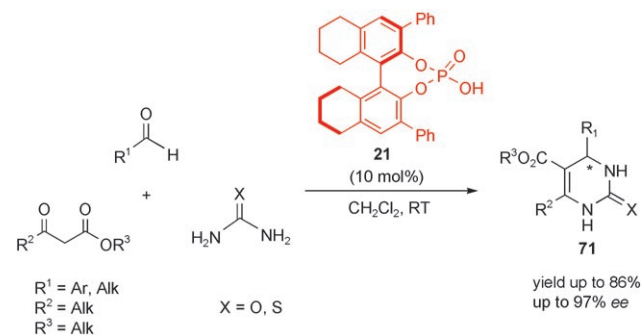

Scheme 43. Enantioselective organocatalytic three-component Biginelli reactions.

avoided contamination of the products with traces of metal was an important on advancement. This catalyst matched or even improved the levels of the conversion and stereoselectivity of the corresponding Lewis acid catalyzed reactions, while maintaining the same substrate scope.[99]

6. Summary and Outlook

The objectives of asymmetric organocatalysis has without doubt substantially changed in the last two years. After the impressive initial years which led to numerous remarkable results regarding the stereochemical control of model reactions, the new trend is to focus on the synthesis of complex compounds that are difficult to access by common methods. The search for new organocatalysts is particulary important for the advancement of one of the central themes of modern organic synthesis: the creation of new structure classes with a wide range of chemical and stereochemical properties. Organocatalysis is ideally suited for this purpose since it allows the structure of basic molecular fragments to be modified efficiently. A number of organocatalytic reactions promoted by customized catalysts show great resemblance to enzymatic reactions.

Organocatalysis plays an ever increasing and important role in synthetic methodology. The growing number of applications in the total synthesis of natural products and pharmaceutically or biologically active compounds bear testimony to this trend. The question is now whether organocatalysis has reached complete maturity and only needs some refinements or whether it is open to new concepts. In this respect it is notable that the newly developed radical-chemistry approach was recently the topic of a Highlight.[101] In this approach, SOMO-enamine activation (SOMO = the singly occupied molecular orbital) relies upon the hypothesis that one-electron oxidation of a transient enamine intermediate will give a three-π-electron SOMO-activated species (Scheme 44).[102b] The coupling of the cationic radical species
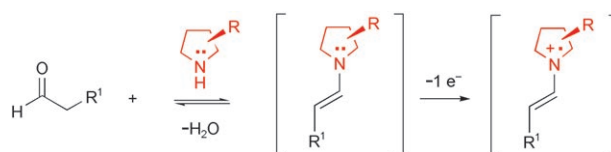
Scheme 44. SOMO catalysis through single-electron oxidation of a transient enamine intermediate.

that is formed with suitable π-rich nucleophiles should provide the opportunity for numerous organocatalytic transformations, which are difficult or impossible to perform with established iminium and enamine catalysis.

This area of organocatalytic enantioselective SOMO activation was founded by MacMillan and co-workers[102] and by Sibi et al.[103] Density functional theory calculations showed that the MacMillan imidazolidinone **29** was the most suitable catalyst for the generation of the SOMO-activated cation. Moreover, the enantiodifferentiated structure of this

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cation was expected to give rise to enantioselective additions.[102a] MacMillan and co-workers described the α-allylation of aldehydes through a catalytic enantioselective double oxidation procedure (Scheme 45). The first oxidative step,
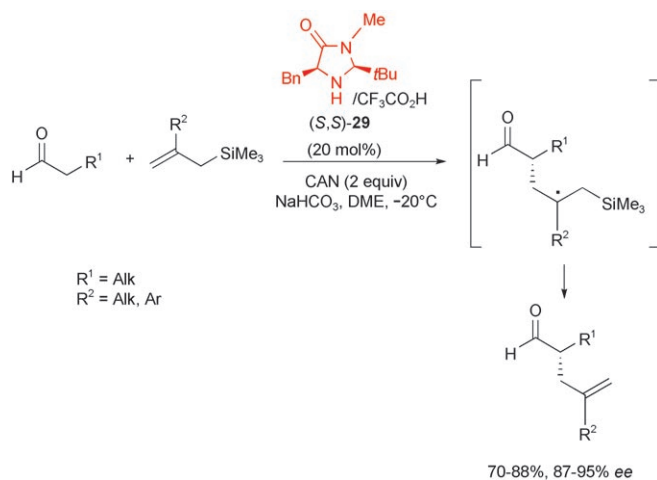
Scheme 45. Enantioselective α-allylation of aldehydes by SOMO catalysis. DME = 1,2-dimethoxyethane.

performed by cerium ammonium nitrate (CAN), served to generate the SOMO-enamine (a radical cation). This reacted with the allylsilane, a π-rich olefin, to give a neutral radical adduct from which the TMS group was removed in a second oxidative step by CAN. Overall, the reaction afforded an α-allyl aldehyde (Scheme 45).[102a] The α-enolation of aldehydes was carried out by the same synthetic route but using enolosilanes as the π-rich nucleophiles. In this case the isolated product was a γ-ketoaldehyde.[102b]

While the approach of MacMillan and co-workers involved the formation of a C−C bond, Sibi and Hasegawa developed an organocatalytic radic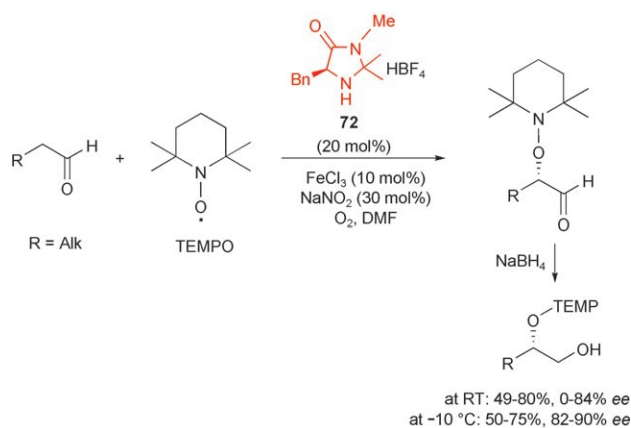al-mediated C−O bond-forming reaction.[103] These authors reported the synthesis of α-aminoxy aldehydes,[104] a class of compounds that are, however, accessible by organocatalysis by using nitrosobenzene as the aminoxylating agent and proline as the catalyst.[105]

Scheme 46. Enantioselective α-aminoxylation of aldehydes by SOMO catalysis.

In the approach used by Sibi and Hasegawa, the SOMO-enamine radical, generated by the use of a catalytic amount of FeCl$_3$ (as a single electron transfer reagent) and NaNO$_2$/O$_2$ (as cooxidant), was treated with a preformed persistent aminoxyl radical such as 2,2,6,6-tetramethyl-1-piperidinoxyl (free radical, TEMPO) in the presence of the MacMillan oxazolidinone organocatalyst **72** (Scheme 46). This reaction led in situ to the α-aminoxylated aldehyde followed by reduction to the corresponding primary alcohol.

SOMO activation is a new highly promising strategy for organocatalysis which has great potential given the numerous radical-based C−X (X = C, O, N, S, halogen) bond-forming reactions that can be carried out in a catalytic and asymmetric manner.

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