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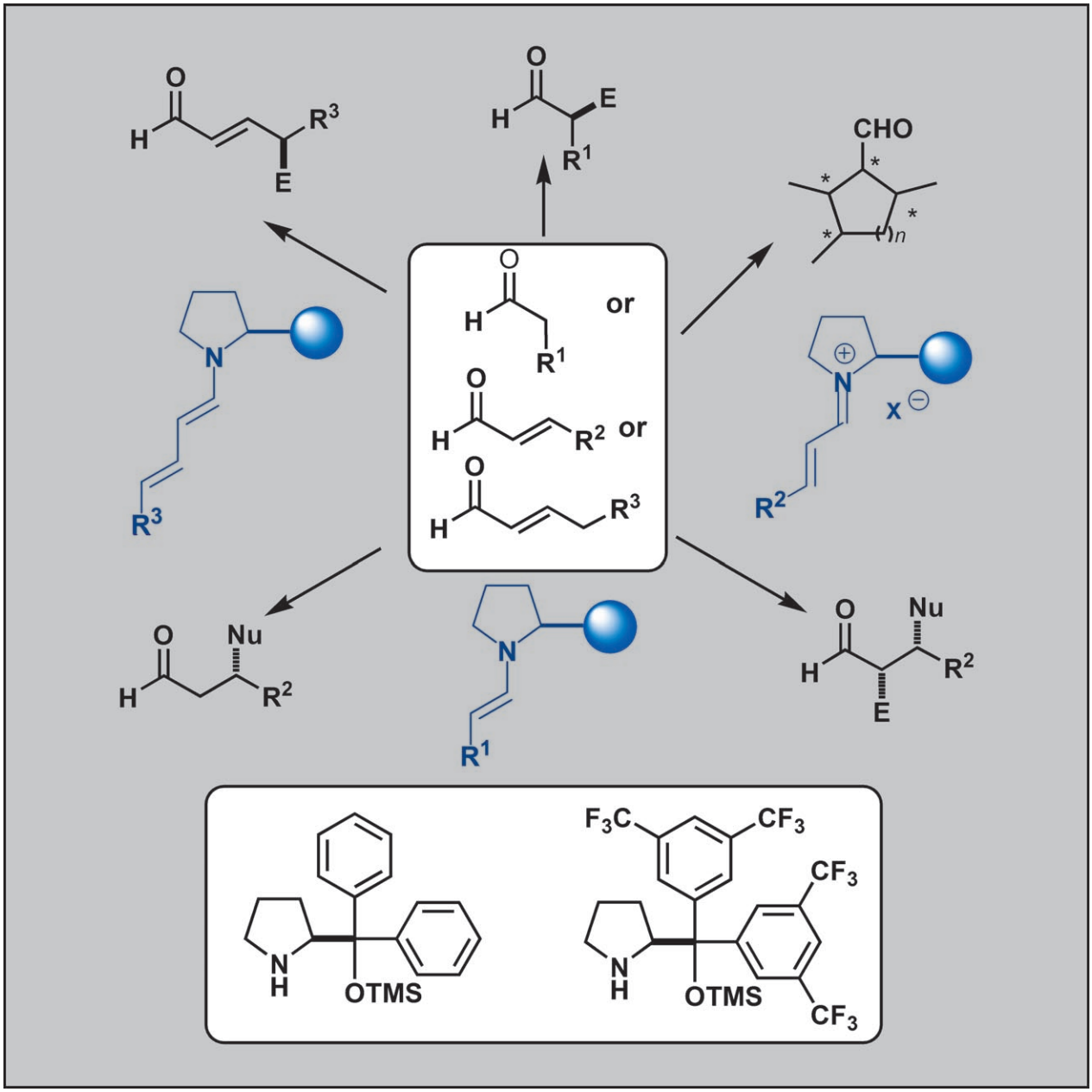
α,α-Diarylprolinol Ethers: New Tools for Functionalization of Carbonyl Compounds

Antonia Mielgo and Claudio Palomo*[a]



Abstract: α,α-Diaryl(dialkyl)prolinol ethers constitute a potent organocatalyst family which has been shown to be very general for a broad range of reactions involving enamine and iminium ion activation or a combination of both. The reactions are characterized by an efficient steric control approach and can lead to a variety of α-, β-, γ-, and α,β-functionalized carbonyl compounds with excellent stereocontrol. As a full expression of their catalytic activity, these compounds are also excellent promoters of elegant cascade processes and valuable catalysts in water-compatible systems.

Keywords: asymmetric catalysis · enamine activation · iminium ion activation · organocatalysis · tandem reactions

1. Introduction

Inspired by nature, where enantioselective reactions[1] are efficiently performed by enzymes,[2] synthetic chemists have developed new strategies to enantioselectively synthesize chiral compounds. While the end of the last century has been dominated by the use of transition-metal catalysts to achieve this goal,[3] the use of organocatalysts is reaching its golden age[4] in the 21st century.

Organocatalysis, which can be defined as the "acceleration of chemical reactions with an ideal substoichiometric amount of organic compounds, which do not contain any metal atom,"[4e] has been known since Marckwald carried out the decarboxylation of a malonic acid derivative in the presence of brucine in 1904, this reaction being the first example of an enantioselective transformation.[5] Despite this fact, it has only been over the last decade that the use of organic molecules as catalysts has emerged as an important area of research. Organocatalyzed reactions present an attractive complement to metal-catalyzed processes because of their lower cost and benign environmental impact in comparison to organometallic catalysis.

Chiral secondary amines are probably the most commonly used organocatalysts today.[6] They can activate the α-C–H and β-C–H bonds of carbonyl compounds and transform them into a C–X (X = heteroatom) or C–C bond via enamine[7] or iminium ion[8] formation, respectively. Saturated carbonyl compounds are easily activated for their α-functionalization in the presence of a chiral secondary amine through an enamine intermediate wherein the energy of the HOMO orbital is raised. This enamine, in the presence of an adequate electrophile, forms a C–X or C–C bond. Hydrolysis of the intermediate releases the chiral amine, which can then undergo a new catalytic cycle to give an α-functionalized carbonyl compound (Figure 1). Alternatively, when α,β-unsaturated carbonyl compounds are the substrates of

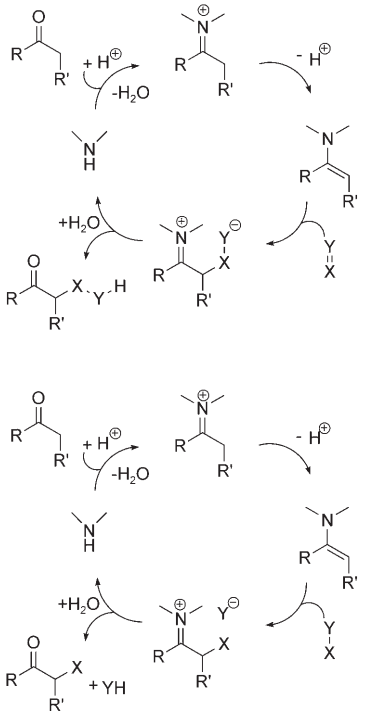


Figure 1. Enamine catalysis of nucleophilic addition and substitution reactions to afford α-functionalized carbonyl compounds (arrows may be considered equilibria).

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choice, activation takes place through an iminium ion intermediate, wherein the energy of the LUMO orbital is decreased, thereby facilitating the transfer of the chirality in the presence of the appropriate nucleophile to the β-position to yield a β-functionalized carbonyl compound (Figure 2). In addition, and owing to their capability of promoting several types of reactions through different activation modes, these secondary amines have experienced a recent development in tandem and/or domino reactions,[9] which proceed consecutively and under the same reaction conditions to construct complex frameworks from simple molecules.

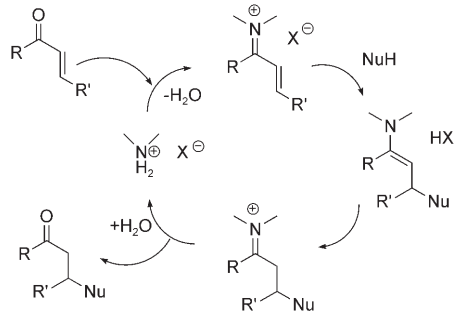


Figure 2. The iminium catalytic cycle to afford β-functionalized carbonyl compounds (arrows may be considered equilibria).

In general, in all these processes the configuration of the final adducts can be controlled either by hydrogen-bond interactions between acidic protons of the chiral amine and the incoming electrophile/nucleophile (Figure 3A) or by steric hindrance coming from the secondary amine (Figure 3B) for enamine activation, which guides the approach of the electrophile/nucleophile from the less hindered face of the enamine.

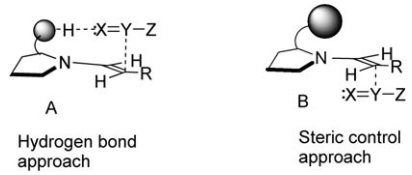


Figure 3. Pictogram showing two complementary modes of chiral pyrrolidines by enamine catalysis; typical examples are: model A: L-proline, through a hydrogen bond; model B: diarylprolinol ethers, through steric control.

Abstract in Spanish: Los trimetilsilil éteres derivados del prolinol han emergido como potentes organocatalizadores que permiten la funcionalización de compuestos carbonílicos tanto vía enamina como ión iminio. Actualmente se han descrito diferentes procedimientos para la alfa, beta, gamma y alfa-beta funcionalización, así como procesos en cascada y multicomponentes de gran interés para la comunidad científica. En esta revisión se presentan los últimos avances en este contexto.

Among the chiral secondary amines developed to date as fairly general and efficient organocatalysts are the amino acid proline[7] and MacMillan's imidazolidinones.[8] However, recently prolinol ethers, particularly α,α-diarylprolinol ethers,[10] have also emerged as fairly general organocatalysts. These catalysts work through steric control (Figure 3B) and have been applied to a large variety of organocatalytic transformations affording α-, β-, and, more recently, γ-functionalized carbonyl compounds, including also tandem or multicomponent processes. As a result, the number of publications in this field describing the use of these amine-based catalysts, particularly **1** and **2** (Figure 4), has increased dramatically within the last two years.[11] The goal of this Focus Review is to give an overview of all the

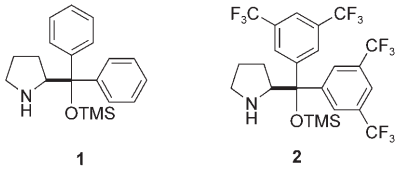
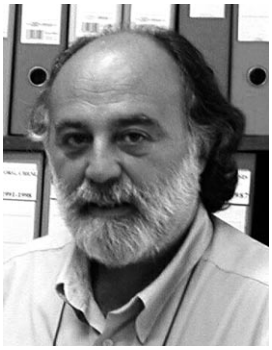


Figure 4. Prototypical α,α-diarylprolinol ether catalysts. TMS = trimethylsilyl.



Claudio Palomo was born in Barcelona (Spain) in 1951. He studied chemistry at the Instituto Químico de Sarriá, in Barcelona, where he received his Chemical Engineering Degree in 1975. After two years working in industry, he obtained his Licenciatura in chemistry in 1979 at the University of Barcelona. In the same year he joined the Organic Chemistry Department at the University of the Basque Country with Prof. R. Mestres. In 1983, he took his PhD in Organic Chemistry, and after two years of postdoctoral work at the same university, he became Associate Professor. In 1989 he was promoted to Full Professor in Organic Chemistry and two years later he joined, as visiting professor, the research group of Prof. H. Rapoport at the University of California at Berkeley. His work focus is asymmetric catalysis and the design and implementation of molecular entities with biological properties.

Antonia Mielgo was born in San Sebastian (Spain) and studied chemistry at the University of the Basque Country. She obtained her Licenciatura in 1989 and completed her Doctorate in 1996 with Prof. Palomo on β-lactam chemistry. After a two-year postdoctoral stay with Prof. C. Gennari at the University of Milan on combinatorial chemistry, she joined the team of Prof. Claudio Palomo at San Sebastián in 1998. Since 2003, she has been Associate Professor at the same university. Her main interest is asymmetric catalysis.

achievements in the functionalization of carbonyl compounds promoted by this kind of organocatalysts.

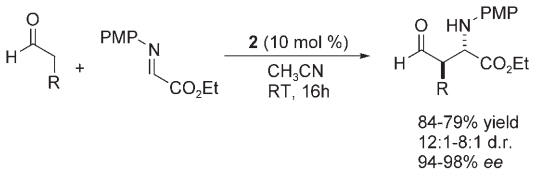
2. α-Functionalization of Aldehydes

Prolinol ether derivatives have been successfully applied to C–C, C–N, C–O, C–X (X = halogen), C–S, and C–Se bond-forming reactions from carbonyl compounds and suitable electrophiles. In all these transformations activation of the α-C–H bond adjacent to the carbonyl group takes place by enamine formation.

2.1. Carbon-Carbon Bond-Forming Reactions

2.1.1. The Mannich Reaction

The Mannich reaction is a highly effective carbon–carbon bond-forming reaction that may be used for the preparation of enantiomerically enriched amino acids, amino alcohols, and their derivatives.[12] Because of the utility of these types of synthons, the demand for Mannich reactions that selectively afford *anti* or *syn* products is high. Enantioselective *anti*-Mannich reactions are, however, considerably rarer.[12,13] In this area, remarkably significant is the Mannich reaction of aldehydes with glyoxylate-derived imines catalyzed by **2**, which turned out to be highly *anti*-selective (Scheme 1) as



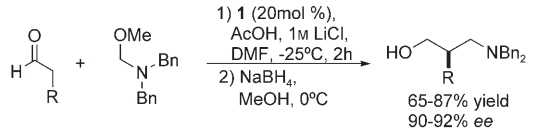
Scheme 1. Organocatalyzed enantioselective *anti*-Mannich reaction of aldehydes with glyoxylate-derived imines.

reported by Jørgensen.[11b] Later, Córdova[14] described that the same reaction is also catalyzed by **1** (10 mol %). It is worth noting that only a few types of organocatalysts, pyrrolidine-3-carboxylic acids[15] and chiral aminosulfonamides,[16] have been reported to afford *anti*-Mannich adducts with high diastereo- and enantioselectivities. These results complement those reported with L-proline, where high *syn* diastereoselectivities are observed.[17]

Gellman and Chi[18] and Córdova[19] independently described the α-aminomethylation of aldehydes through a catalytic asymmetric Mannich reaction involving a formaldehyde-derived iminium electrophile and by using **1** as organocatalyst together with AcOH and LiCl (Scheme 2). The expected adducts are reduced in situ to afford the γ-amino alcohols in good yields and excellent enantioselectivities.

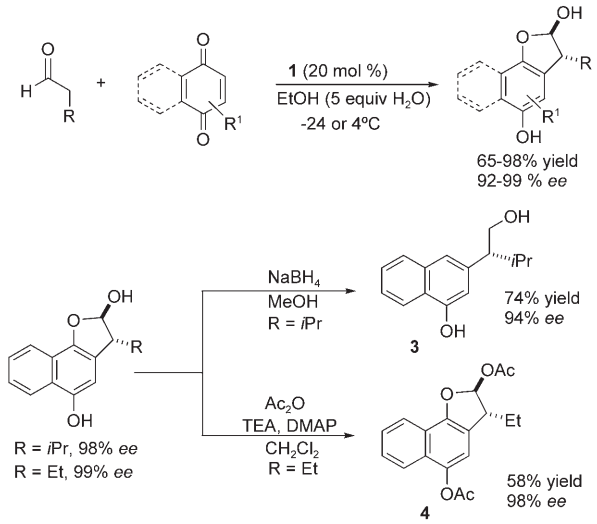
2.1.2. α-Arylation

The direct enantioselective α-arylation of aldehydes is challenging because of the importance of the optically active ar-



Scheme 2. Enantioselective aminomethylation reaction of aldehydes.

omatic compounds formed. Very recently, Jørgensen reported the first highly asymmetric α-arylation of aldehydes promoted by diphenylylprolinol trimethylsilyl ether **1** using quinones as the aromatic partner and leading to optically active α-arylated aldehydes which are isolated as their hemiacetal form (Scheme 3).[20] The formed α-arylated products if subjected to reduction with sodium borohydride lead to quinones **3**. Furthermore, both hydroxyl groups can be acetylated by Ac_2O to afford **4**. Surprisingly, catalyst **2** was not active in this reaction, as it did not lead to any arylated product.



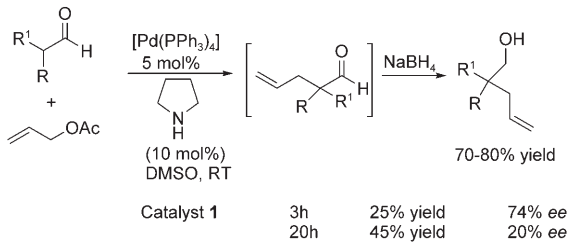
Scheme 3. Enantioselective α-arylation of aldehydes with quinones.

The proposed mechanism for this reaction consists of two catalytic cycles. The first cycle, in which the stereogenic center is formed, is the reaction of the enamine intermediate with the quinone, and the second one is a series of proton-transfer reactions leading to the optically active arylated aldehyde that has a dihydroquinone functionality. The proton-transfer reactions might involve H_2O, as no reaction occurs in its absence.

2.1.3. α-Allylation

The α-alkylation of carbonyl compounds is a fundamental carbon–carbon bond-forming reaction in organic synthesis. Organocatalytic alkylation of enamine intermediates with allyl and benzyl bromides promoted by pyrrolidine derivatives has proven to be difficult, presumably owing to N-alkylation of the catalyst.[21] In 2006 Córdova[22] reported the

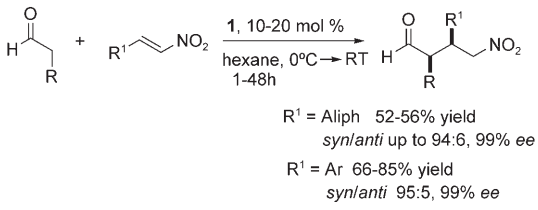
first direct catalytic intermolecular α-allylic alkylation of aldehydes and ketones by using transition-metal chemistry and organocatalysis. The reaction is mediated by a combination of palladium and enamine catalysis promoted by pyrrolidine, which furnishes racemic α-allyl carbonyl compounds in high yields. However, preliminary studies on the catalytic asymmetric version of this reaction (Scheme 4) showed that either (*S*)-proline or **1** provides α-allylic alkylated alcohols both in low yields and enantioselectivities after in situ reduction of the corresponding aldehydes.



Scheme 4. α-Allylic alkylation of aldehydes.

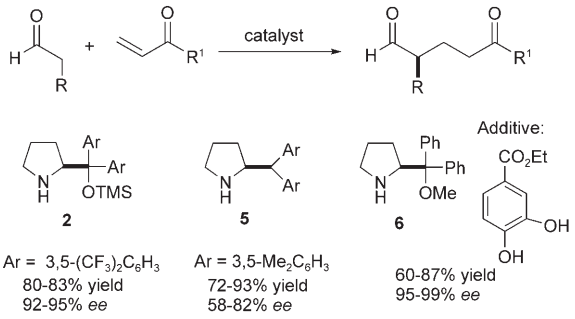
2.1.4. The Michael Addition of Aldehydes to Nitroalkenes, Vinyl Ketones, Maleimides, Vinyl Sulfones, and Vinyl Phosphonates

Asymmetric conjugate additions for C–C bond formation are another important challenge in organic synthesis.[23] The enantioselective version of this process has also been explored with diarylprolinol ether derivatives by both enamine and iminium ion activation. In the first case, Michael addition reactions of aldehydes to nitroalkenes[24], vinyl ketones, maleimides, vinyl sulfones, and phosphonates have been reported within the last two years. Hayashi et al.[11c,25] have documented the conjugate addition of aldehydes to nitroalkenes catalyzed by **1** (Scheme 5). Under these conditions the reaction is very effective with nitrostyrenes, while with β-alkyl-substituted nitroalkenes moderate yields are obtained.



Scheme 5. Conjugate addition of aldehydes to nitroalkenes.

In a related context the Michael reaction between aldehydes and methyl vinyl ketone was carried out with good enantioselectivities using **2** as catalyst (10 mol%, Scheme 6).[11b] In this case, the reaction had to be run a relatively high temperature (40 °C) in ethanol in order to obtain the final products in good yields and in acceptable reaction times. Nevertheless the author reported a slight nonlinear



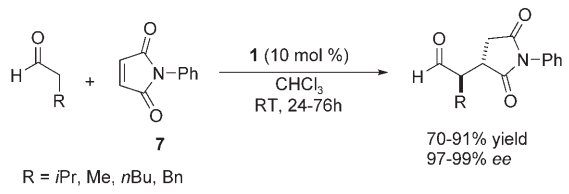
Scheme 6. Conjugate addition of aldehydes to vinyl ketones catalyzed by **2**, **5**, and **6**.

effect in the same reaction using a related catalyst, **5**, which pointed toward the hypothesis that two molecules of the catalyst were involved in the reaction mechanism and therefore a possible iminium-type activation of the electrophile might occur.[26]

On the other hand, Gellman and Chi[27] showed the utility of diphenylprolinol methyl ether **6** in the conjugate addition of aldehydes to vinyl ketones (methyl and ethyl vinylketones) under optimized conditions (5 mol% of catalyst, neat, 4 °C, 24–48 h, Scheme 6) and suggested that in this case, the reaction proceeded exclusively by enamine activation of the aldehyde. Optimum results were achieved when the reactions were carried out in the presence of a catechol derivative as a cocatalyst, which apparently activates the enone by hydrogen-bond interaction to the carbonyl oxygen.

The amine catalyst **6** was also employed by Tanaka, Barbas III, et al.[28] for the Michael addition reaction of phthalimidoacetaldehyde to nitroolefins to afford the Michael adducts in good enantioselectivity (*ee* values from 86% to 94% for *syn* and 60% to 86% for *anti*), albeit with poor diastereomeric ratios, typically 2:1. An interesting aspect is that reactions carried out in $CHCl_3$/brine mixtures proved to be slightly faster than the same reactions performed in $CHCl_3$ alone.

Very recently Córdova et al.[29] presented the conjugate addition of aldehydes to maleimide **7** catalyzed by **1** (Scheme 7) to afford the corresponding α-substituted succinimides in good to high yields and with 97–99% *ee*.



Scheme 7. Conjugate addition of aldehydes to maleimides.

The first enantioselective organocatalytic conjugate additions of aldehydes to both vinyl sulfones and vinyl phosphonates were reported by Alexakis et al.[30] Nevertheless, while

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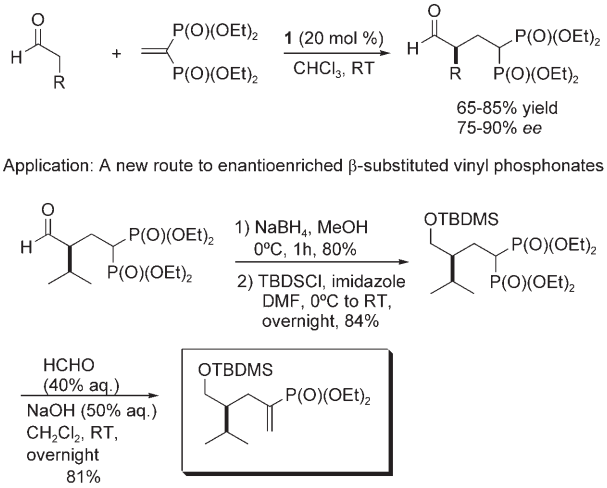
the reaction with vinyl sulfones proceeds with modest enantioselectivity and exhibits a great extent of retroaddition,[30a] the addition reaction of aldehydes to vinyl phosphonates occurs in high yields and with enantioselectivities up to 97% *ee* (Scheme 8).[30b] This latter process provides synthetically useful chiral γ-geminal phosphonate aldehydes which can be easily converted in a few steps into chiral β-substituted vinyl phosphonates, a class of intermediates with potential synthetic utility.



Scheme 8. Conjugate addition of aldehydes to vinyl phosphonates and application to the synthesis of β-substituted vinyl phosphonates.

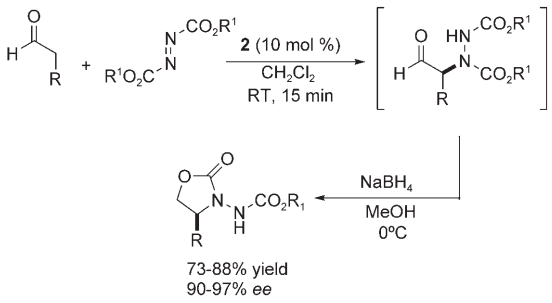
All the above procedures involve aldehydes as Michael donors. It appears that ketones are poor substrate donors for this reaction as judged by the lack of reactivity between cyclohexanone and dimethyl 2-(4-nitrobenzylidene)malonate in the presence of catalyst **1**.[31]

2.2. α-Heterofunctionalization

The organocatalytic α-heterofunctionalization of carbonyl compounds via enamine has been thoroughly investigated and numerous different secondary amine-based catalysts have been developed.[32] Among of them, α,α-diarylprolinol ethers have provided useful entries to α-amino, α-hydroxy, α-halo, α-thio, and α-seleno carbonyl compunds, particularly aldehydes.

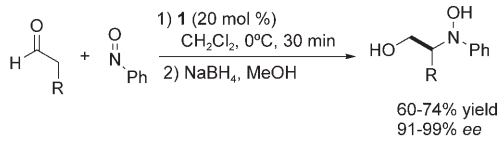
2.2.1. α-Amination

While many examples on enolate-based asymmetric α-aminations of carbonyl compounds are known,[33] it is only rather recently that direct catalytic methods have emerged.[34] The direct α-amination of aldehydes with azadicarboxylates was independently developed by List[35] and Jørgensen[36] using L-proline as the catalyst.[37] In both cases the configuration (*R*) of the main enantiomer is controlled by hydrogen-bond interactions. A complementary route has been provided by Jørgensen[11b] using catalyst **2** (Scheme 9), which leads to the opposite enantiomer (*S*). The α-aminated derivatives were isolated in high yields and excellent enantioselectivities as the corresponding oxazolidinones after reduction of the aldehyde moiety and subsequent cyclization.



Scheme 9. Organocatalyzed enantioselective β-amination of aldehydes.

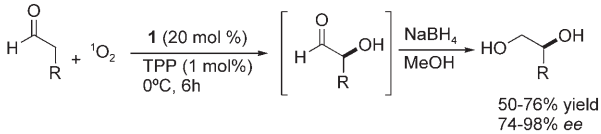
Nitrosobenzene has proven to be another promising reagent for the α-amination of carbonyl compounds.[38] Owing to its high reactivity towards nucleophiles, controlling the regioselectivity of either nitrogen or oxygen to preferentially react with the nucleophile is a challenge of fundamental importance. Organocatalyzed reactions of nitrosobenzene and carbonyl compounds with proline and its derivatives have been actively investigated to afford α-oxygenated compounds as the major products.[39] In sharp contrast only two contributions on organocatalyzed direct nitrosoaldol reactions of aldehydes that take place preferentially at the nitrogen atom have been reported.[40] Recently it was found that catalyst **1** promotes a highly regio- and enantioselective direct oxyamination reaction of aldehydes (Scheme 10).[41] The product itself or water coming from enamine formation has been proposed to activate the oxyamination reaction through hydrogen-bond coordination to the oxygen atom of nitrosobenzene.



Scheme 10. Enantioselective oxyamination of aldehydes with nitrosobenzene.

2.2.2. α-Hydroxylation

Direct enantioselective α-oxidation of aldehydes using molecular oxygen and catalyst **1** was presented by Córdova in 2006 (Scheme 11).[42] The corresponding diols are obtained

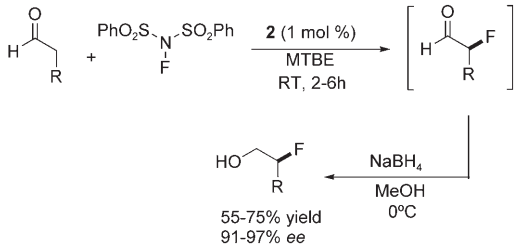


Scheme 11. Enantioselective α-hydroxylation of aldehydes. TPP = tetraphenylporphine.

after in situ reduction in moderate to good yields and with up to 98% *ee*, thus providing a route to enantioenriched 1,2-diols. Electrophilic singlet molecular oxygen was photochemically or chemically generated.

2.2.3. α-Halogenation

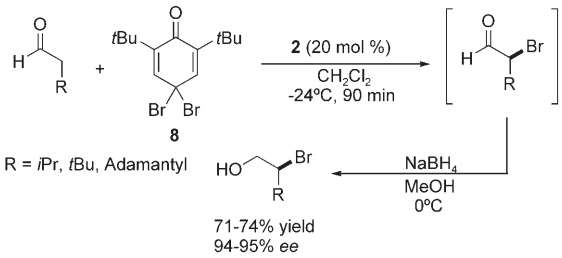
Various chiral amines can catalyze the direct enantioselective α-halogenation of carbonyl compounds.[32] For example, the enantioselective α-fluorination[43] of aldehydes was achieved almost simultaneously by Jørgensen,[11b,44] Barbas III,[45] and MacMillan[46] in high yields and enantioselectivities. While Barbas III and MacMillan used imidazolidinone derivatives as catalysts, Jørgensen found diarylprolinol silyl ether **2** as an efficient catalyst for this transformation (Scheme 12). A screening showed that with catalyst **2** high



Scheme 12. Organocatalyzed enantioselective α-fluorination of aldehydes.

asymmetric induction is obtained, and after optimization of the reaction conditions it was found that by decreasing the catalyst amount to 1 mol% and using a slight excess of aldehyde higher yields are provided, while the high enantiomeric excess is maintained. The corresponding optically active fluoro alcohols could be isolated in moderate to high yields and with excellent enantioselectivity after $NaBH_4$ reduction. The activity of the catalyst turned out to be highly dependent on the solvent. Thus, in solvents such as methylene chloride or acetonitrile, desilylation of the catalyst was observed. This side reaction did not take place in methyl *tert*-butyl ether at room temperature, allowing the diminution of the amount of the catalyst to 1 mol%. In this case, a comparison of the properties of catalyst **2** with the imidazolidinone catalyst used by both Barbas III[45] and MacMillan[46] shows that both systems give excellent enantioselectivities. However, higher catalytic activity of **2** leads to shorter reaction times. The higher reaction rate observed using **2** allows a lower catalytic loading (0.25 to 1 mol%), while the imidazolidinone system required 2.5 to 100 mol%. Other complementary catalysts such as L-proline,[44,47] L-proline amide,[44] and (*R,R*)-2,5-diphenylpyrrolidine[44] all gave poor yields and enantioselectivities.

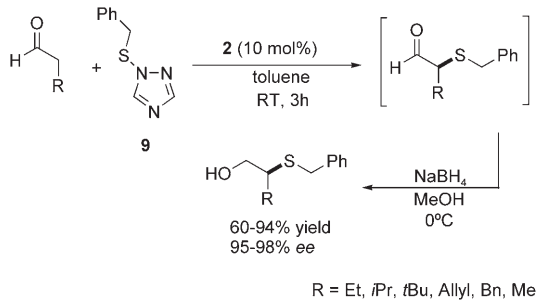
In 2005 Jørgensen's group presented the α-bromination of aldehydes with compound **8** in the presence of catalyst **2** with excellent asymmetric induction (Scheme 13).[11b] Compared to the use of (*R,R*)-2,5-diphenylpyrrolidine previously used by the same group for the same transformation,[48] catalyst **2** has several advantages, such as easier synthesis of the catalyst and no need for mixed solvents and additives such as benzoic acid and water. Furthermore, **2** gives superior enantioselectivities.



Scheme 13. Organocatalyzed enantioselective α-bromination of aldehydes.

2.2.4. α-Sulfenylation

The first report concerning the α-sulfenylation of ketones and aldehydes appeared in 2004, but no enantioselectivities were reported.[49] Later on, the group of Jørgensen showed that a highly enantioselective α-sulfenylation of aldehydes is feasible by using **2** as the catalyst and **9** as the sulfur electrophile (Scheme 14).[11] Under these conditions and after $NaBH_4$ reduction the corresponding α-sulfenylated alcohols were isolated in high yields and excellent enantioselectivities.

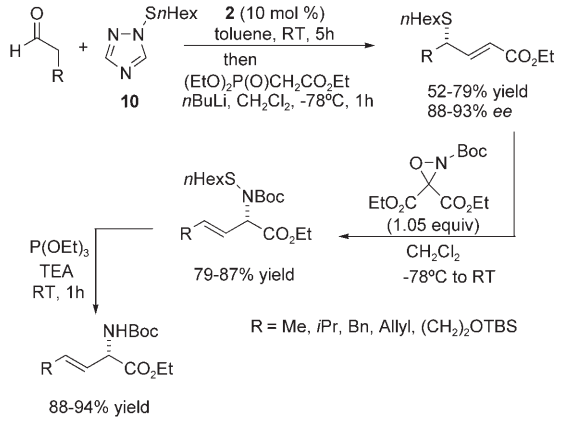


Scheme 14. Organocatalyzed enantioselective α-sulfenylation of aldehydes.

More recently, Armstrong et al.[50] documented an original protocol for the enantioselective synthesis of vinyl glycines (Scheme 15), which combines the above organocatalytic α-sulfenylation of aldehydes with an olefination step and a stereospecific [2,3]-sigmatropic rearrangement. In this case the one-pot organocatalytic α-sulfenylation/olefination is achieved with **10** as the sulfur source and catalyst **2**.

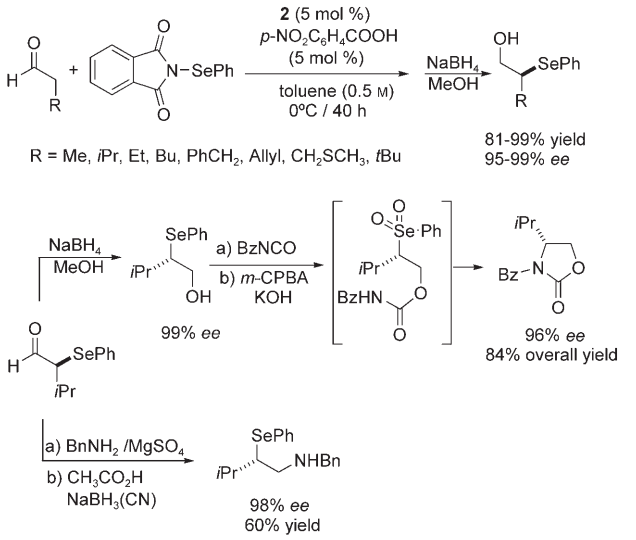
2.2.5. α-Selenenylation

The only access to chiral α-seleno aldehydes reported until very recently relied on a "chiral pool" approach that involved multistep procedures.[51] However, Marini, Melchiorre, et al.[52] have just presented the first organocatalytic α-selenenylation of aldehydes promoted by **2** in the presence of *para*-nitrobenzoic acid in toluene at 0°C. The α-



Scheme 15. One-pot asymmetric α-sulfenylation/olefination of aldehydes followed by [2,3]-sigmatropic rearrangement .

seleno aldehydes were reduced in situ to the corresponding alcohols, which were obtained in excellent yields and enantioselectivities (Scheme 16). Under the same reaction conditions the use of benzoic acid as an additive afforded similar enantioselectivities, but lower yields. The method proved successful for aldehydes with a wide range of substituents, including alkyl, alkenyl, and heterosubstituted groups. In addition, this organocatalytic enantioselective α-selenenylation reaction provides highly versatile chiral building blocks for different synthetic transformations that lead to valuable optically active compounds, as outlined in Scheme 16.



Scheme 16. Organocatalyzed enantioselective α-selenenylation of aldehydes and their synthetic transformations.

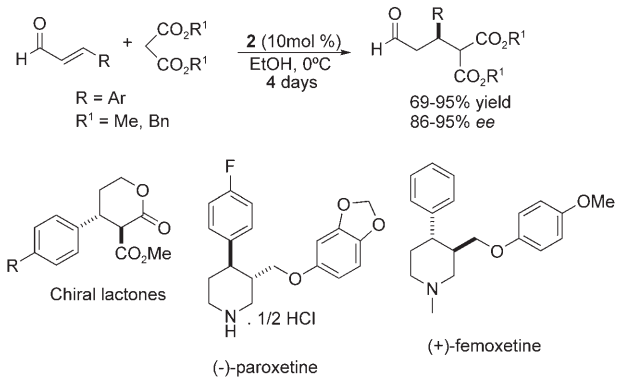
3. β-Functionalization of Carbonyl Compounds

Chiral secondary amines are also effective catalysts for enantioselective β-addition to α,β-unsaturated carbonyl compounds.[23] In this case, the catalyst activates the substrate through the iminium ion mechanism,[8] thereby facilitating the addition of the nucleophile to the β-carbon atom. This reaction protocol has been developed organocatalytically in the presence of diarylprolinol ether derivatives for a number of different reactions, including the formation of C–C, C–N, C–O, C–S, and C–P bonds, as summarized below.

3.1. Carbon–Carbon Bond-Forming Reactions

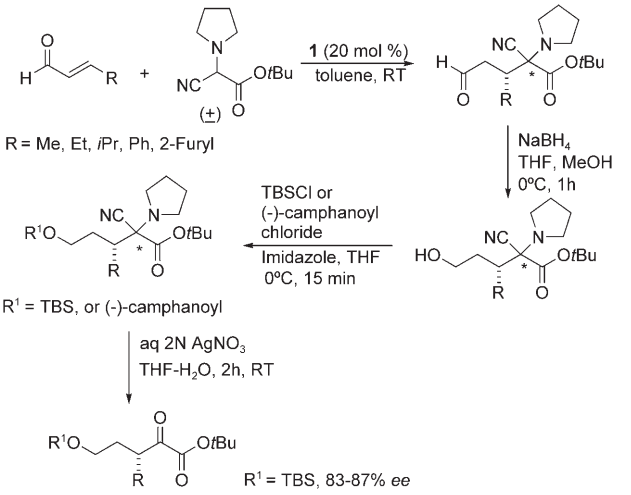
3.1.1. The Michael Addition of Carbon-Centered Nucleophiles to α,β-Unsaturated Aldehydes

The β-functionalization of carbonyl compounds through the Michael addition reaction of carbon-centered nucleophiles has been investigated using active methylenes, aminonitriles, and α,α-dicyanoolefins as donors. For example, the conjugate addition of malonates to β-aryl-substituted α,β-unsaturated aldehydes catalyzed by **2** yields Michael adducts in good yields and excellent enantioselectivities (Scheme 17).[53] Among the solvents examined for this transformation, primary alcohols were optimal and the best results were obtained with MeOH and EtOH; in the latter, full conversion was attained after four days with excellent enantiomeric excess (89–92% *ee*), while in MeOH and, in spite of the higher *ee* value, conversion was much lower compared to EtOH. In all the other tested solvents (CH_2Cl_2, Et_2O, CH_3CN, DMSO, hexane, H_2O, acetone) no or low conversion was observed with the exception of DMSO (46% conversion, 81% *ee*). On the other hand, aliphatic α,β-unsaturated aldehydes did not react with only malonates, but reacted with both the malonates and ethanol (solvent) under these reaction conditions. This protocol has been successfully applied to the synthesis of lactones, (−)-paroxetine, and (+)-femoxetine.



Scheme 17. Conjugate addition of malonates to α,β-unsaturated aldehydes.

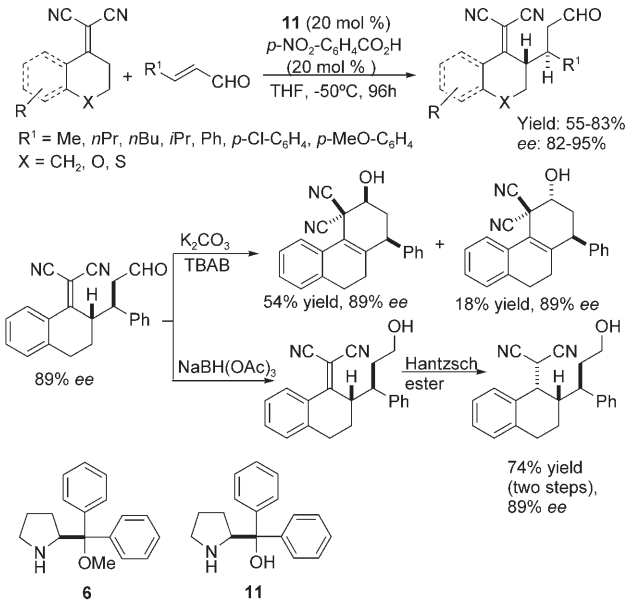
Recently Enders et al.[54] reported the first asymmetric conjugate glyoxylation of β-alkyl- and β-aryl-substituted α,β-unsaturated aldehydes employing racemic aminonitriles as donors and in the presence of **2** as the catalyst (Scheme 18). After reduction and TBS protection or conver-



Scheme 18. Conjugate glyoxylation of α,β-unsaturated aldehydes.

sion into camphanoyl derivatives of the resulting alcohols, the final 3-substituted 2-ketoesters were obtained in acceptable yields over the four steps.

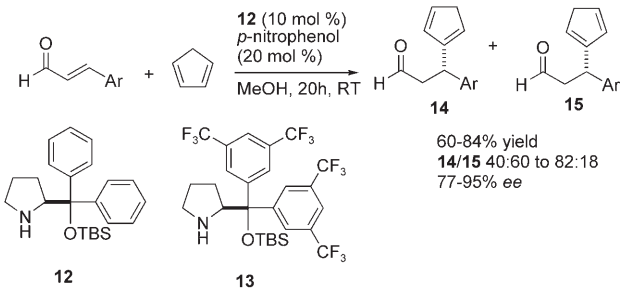
Prolinols have previously been reported to fail to activate enals owing to the formation of unreactive protonated cyclic *N,O*-acetals.[11b,55] However, using catalyst **11** Deng et al.[56] presented the first highly regio-, chemo-, diastereo-, and enantioselective direct vinylogous Michael addition of α,α-dicyanoolefins to β-alkyl- and β-aryl-substituted α,β-unsaturated aldehydes (Scheme 19). Under the same conditions, a slightly lower *ee* value was obtained with the methyl ether derivative **6**. On the other hand, this methodology provides facile access to various attractive enantioenriched multifunctional compounds.



Scheme 19. Vinylogous Michael addition of α,α-dicyanoolefins to α,β-unsaturated aldehydes and elaboration of the Michael adducts.

3.1.2. The "Ene" and Diels–Alder Reactions with α,β-Unsaturated Aldehydes

The asymmetric ene reaction is a useful carbon–carbon bond-forming reaction.[57] Although several excellent examples have been reported, no highly enantioselective intermolecular reactions using an alkene as the enophile was known until Hayashi reported the intermolecular ene reaction of cyclopentadiene with β-aryl α,β-enals catalyzed by diphenylprolinol silyl ether **12** (Scheme 20).[58] In this reaction the additive is also important: The strong trifluoroacetic acid does



Scheme 20. Asymmetric ene reaction of cyclopentadiene with α,β-enals. TBS = *tert*-butyldimethylsilyl.

not promote the reaction in methanol and only affords the dimethyl acetal of cinnamaldehyde instead. When 20 mol% of *p*-nitrophenol was employed in combination with the catalyst, the reaction rate increased and good yields and excellent enantioselectivies were attained. Strikingly, catalyst **13** showed complete inactivity in the present reaction.

This reaction is also the first in which cyclopentadiene acts as the ene component in an ene reaction with α,β-enals, despite the numerous reports of it acting as a diene in the Diels–Alder reaction. MacMillan[59] was the first who showed the effectiveness of the iminium activation strategy for the Diels–Alder reaction[60] giving the corresponding *endo* adducts in excellent enantioselectivities. Interestingly, when the "ene" reaction shown in Scheme 20 is performed under acidic conditions, its course changes dramatically. When cinnamaldehyde and cyclopentadiene were treated with catalyst **12** in the presence of CF_3CO_2H in toluene, the corresponding Diels–Alder adduct was obtained in good optical purity in spite of the low yield. Most remarkably, the *exo* isomer was produced predominantly.[61] After optimization 3,5-bis(trifluoromethyl) phenyl-substituted catalyst **16** was found to be a superior catalyst for the reaction affording the Diels–Alder adducts in high *exo* selectivity and excellent enantioselectivities (Scheme 21).

Catalysts **1** and **17** have also proven to be good in promoting the reaction between some 3-substituted-but-2-enals and α,β-unsaturated aldehydes to afford the [4+2] adducts in high enantioselectivities (Scheme 22).[62] Nonetheless, in the case of 4-methyl-2-pentenal ($R^1 = iPr$) more than 40% of the aldol dehydrated product **18** was also obtained.

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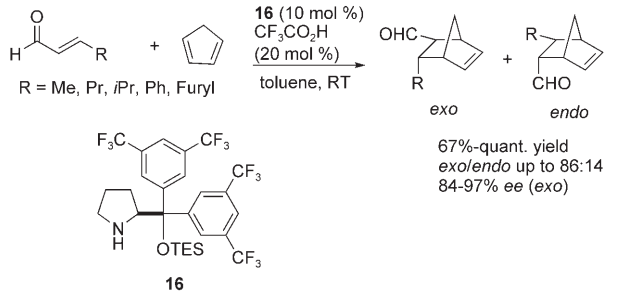
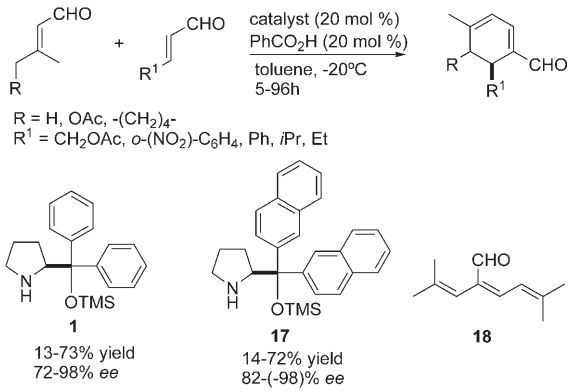


Scheme 21. Enantioselective *exo*-Diels–Alder reaction between cyclopentadiene and α,β-enals. TES = triethylsilyl.

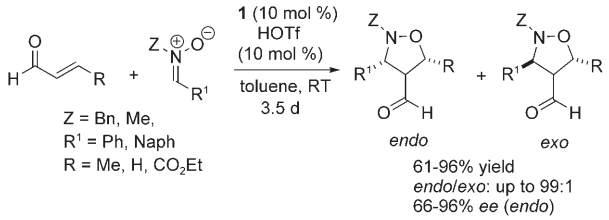


Scheme 22. [4+2] reactions of α,β-unsaturated aldehydes catalyzed by **1** and **17**.

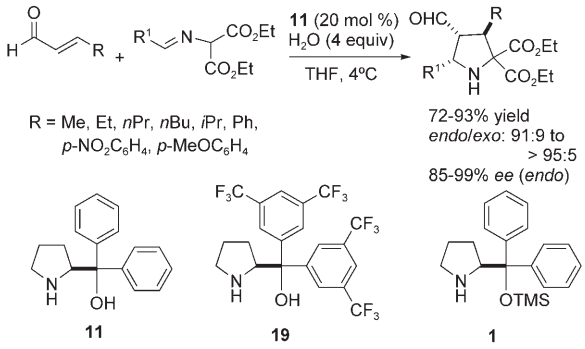
3.1.3. 1,3-Dipolar Cycloaddition Reactions with α,β-Unsaturated Aldehydes

The catalytic asymmetric [3+2] cycloaddition reaction can be considered as one of the most powerful and reliable tools for the enantioselective synthesis of five-membered heterocyclic systems.[63] Within the context of organocatalysis two significant contributions using prolinol ether derivatives, which complement the first breakthrough in this area,[64] have been reported. One is the 1,3-dipolar cycloaddition reaction of nitrones to α,β-unsaturated aldehydes catalyzed by the triflate salt of **1** to provide oxazolidines in high yields and excellent diastereo- and enantioselectivities (Scheme 23).[65] The cycloaddition seems to be quite general with respect to both the nitrone and the dipolarophile structure. Independently, Córdova et al.[66] showed that this reaction can be performed starting from hydroxylamines and saturated aldehydes without the need of preparing the nitrone in a separate step.

The other contribution on this subject was recently reported by Vicario and implies the first organocatalytic enantioselective [3+2] cycloaddition reaction between α,β-unsaturated aldehydes and azomethine ylides promoted by either catalyst **11** or **19** (Scheme 24).[67,68] The reaction proceeds with complete regioselectivity and with very high diastereo- and enantioselectivity to furnish almost stereoisomerically pure, highly functionalized polysubstituted pyrrolidines in excellent yields. After optimization THF was found to be the best solvent for this reaction, and remarkably, the authors observed that the inclusion of water as an additive resulted in significant acceleration of the reaction to furnish the expected cycloadducts in better yield in the same reaction time. The incorporation of acid additives, however, led to significantly lower yields under the same conditions. The necessity of the free OH group in the catalyst structure was verified by the lack of catalytic activity of the protected derivative **1**. Almost simultaneously Córdova et al.[69] presented an organocatalytic asymmetric multicomponent 1,3-dipolar cycloaddition starting from an aldehyde, an amino acid derivative, and an α,β-unsaturated aldehyde to give highly functionalized pyrrolidines. In this case the authors report the inactivity of catalyst **11** for this reaction and present catalyst **1** as the best, which affords the expected cycloadducts in moderate yields (50–63%) and diastereoselectivity, but with excellent enantioselectivity (90–98% *ee*).



Scheme 23. [3+2] Cycloaddition of α,β-unsaturated aldehydes and nitrones.



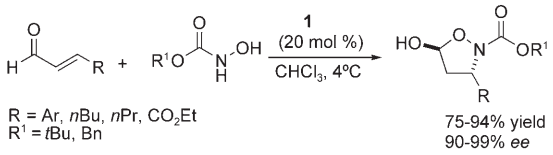
Scheme 24. [3+2] Cycloaddition reaction of azomethine ylides with α,β-unsaturated aldehydes.

3.2. β-Heterofunctionalization

The conjugate addition of heteroatom-centered nucleophiles to enals in the presence of α,α-diarylprolinol ether derivatives has also been the focus of intensive research. Several different types of nucleophiles, such as nitrogen-, oxygen-, sulfur-, and phosphorous-based Michael donors, have been shown to be successful in forming the corresponding C–X bond with high enantioselectivity.

3.2.1. C–N Bond-Forming Reactions: The Aza-Michael Reaction

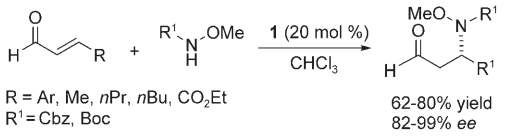
The aza-Michael reaction, in which an amine is added to the β-position of a carbonyl compound, has found a multitude of applications in organic synthesis.[70] The resulting β-amino carbonyl compounds are constituents of many natural products and can be used as chiral intermediates for the preparation of pharmaceutical agents. For example, Córdova et al. reported the conjugate addition of simple *N*-hydroxy carbamates to enals with high yields and enantioselectivities in the presence of **1** (Scheme 25).[71] In this case the Michael



Scheme 25. Aza-Michael reaction of N-protected hydroxylamines to enals catalyzed by **1** and subsequent 1,2-addition to afford 5-hydroxyisoxazolidines.

adduct underwent intramolecular 1,2-addition to furnish 5-hydroxyisoxazolines. This approach complements the first metal-induced[72] and metal-free[73] catalytic contributions on the conjugate addition of carbamates to α,β-unsaturated carbonyl compounds.

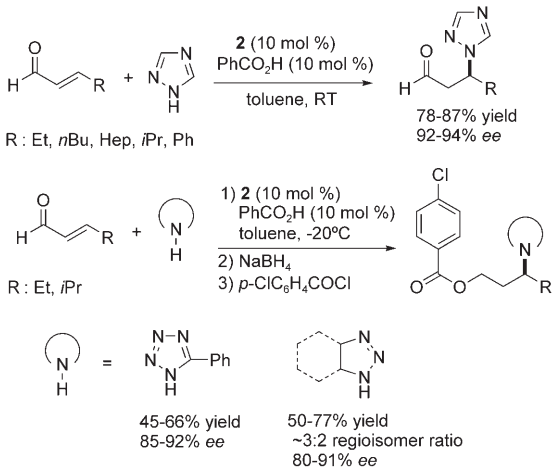
Similarly α,α-diphenylprolinol trimethylsilyl ether **1** efficiently catalyzes the enantioselective conjugate addition of *N*-methoxycarbamates to α,β-unsaturated aldehydes[74] (Scheme 26). Moreover, the reaction may be linked in cas-



Scheme 26. Direct catalytic conjugate addition reactions between *N*-methoxycarbamates and α,β-unsaturated aldehydes.

cade with organocatalytic Mannich reactions to give the corresponding protected chiral diamines with high enantioselectivity (see Section 6.3.3).

Nitrogen heterocycles are another group of nucleophiles employed in enantioselective organocatalytic aza-Michael reactions. In this context, Jørgensen and co-workers[75] reported a study on the conjugate addition of 1,2,4-triazole, 1,2,3-triazole, 1,2,3-benzotriazole, and 5-phenyltetrazole to α,β-unsaturated aldehydes using **2** as catalyst (Scheme 27). The reaction with 1,2,4-triazole proceeded with complete regioselectivity and high enantioselectivity at room temperature, while in the reactions with other heterocycles, the temperature turned out to be a key parameter to be controlled



Scheme 27. Enantioselective conjugate additions of N-heterocycles to α,β-unsaturated aldehydes.

because of the tendency shown by the adducts to racemize at room temperature. This led to the need for in situ reduction/esterification of the obtained adducts. Furthermore, while the reaction with 5-phenyltetrazole proceeded with complete regioselectivity, the use of 1,2,3-triazoles led to the formation of mixtures of regioisomers, which were separated by chromatography and isolated as highly enantioenriched compounds.

3.2.2. C–O Bond-Forming Reactions: The Oxa-Michael Reaction

The stereoselective addition of oxygen-centered nucleophiles to Michael acceptors has received little attention over the years despite the potential utility of the resulting products in synthesis. The relative weakness of O nucleophiles, together with problems associated with reaction reversibility, has hampered the development of general methods for this transformation.[76] As a result, stereoselective variants of this reaction have been mainly limited to O-conjugate addition reactions of chiral alkoxides to highly activated acceptors,[77] intramolecular hemiacetal alkoxide conjugate additions,[78] and some examples of tandem organocatalytic–asymmetric ring-closure processes involving a phenol (see Section 6.3.1). The first enantioselective intermolecular addition reaction of O nucleophiles was presented by Vanderwal and Jacobsen[79] in 2004 wherein aromatic oximes successfully added to α,β-unsaturated imides in the presence of salen–aluminiun complexes. Very recently Jørgensen et al.[80] reported the first organocatalytic intermolecular β-hydroxylation of enals through a Michael addition of aromatic oximes in the presence of **2** as catalyst (Scheme 28). Under these conditions and after $NaBH_4$ reduction the corresponding alcohols are isolated in good yields and excellent enantioselectivities. Deprotection of the oxime function by hydrogenation allows access to 1,3-diols. One limitation of this methodology is that α,β-unsaturated aldehydes having aromatic substituents do not react under these reaction conditions.

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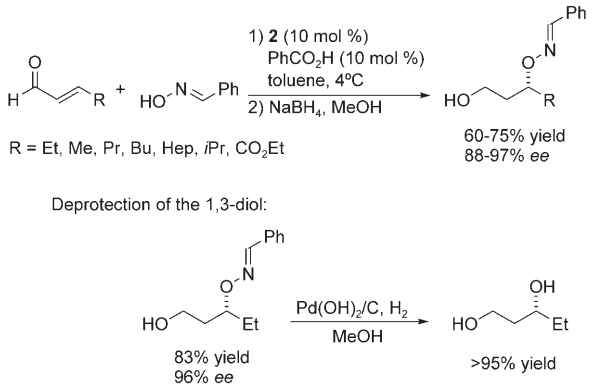
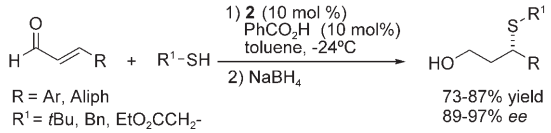


Scheme 28. Enantioselective β-hydroxylation of α,β-unsaturated aldehydes by Michael addition of oximes.

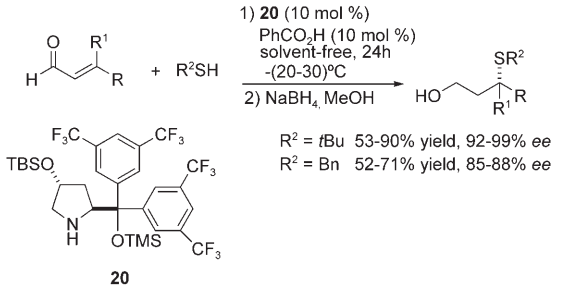
3.2.3. C–S Bond-Forming Reactions: The Sulfa-Michael Reaction

The addition of thiols to electron-deficient olefins is an important tool in the formation of C–S stereocenters.[81] The iminium-activation strategy has been applied successfully in a series of conjugate additions of thiols to conjugated carbonyl compounds. Most of these transformations involve domino processes wherein bifunctional aromatic thiols act as nucleophiles in the first step and incorporate an additional electrophilic functionality (see Sections 6.3.4 and 6.3.5). Jørgensen and co-workers reported the use of **2** as an effective catalyst in the intermolecular Michael-type addition of thiols to α,β-unsaturated aldehydes (Scheme 29).[82] β-Aliphatic and β-aromatic enals reacted with several aliphatic thiols in good yields and excellent enantioselectivities, both determined following reduction of the first-formed β-thioaldehydes to the β-thioalcohols. At room temperature, the Michael adducts were found to rapidly racemize. However, by performing the reactions at low temperature (−20–30 °C), racemization could be suppressed, but addition of an acid cocatalyst was required, presumably to catalyze iminium ion formation. This protocol was also applied to a multicomponent domino sulfa-Michael amination process (see Section 7.1, Scheme 57).



Scheme 29. Enantioselective conjugate addition of thiols to α,β-unsaturated aldehydes.

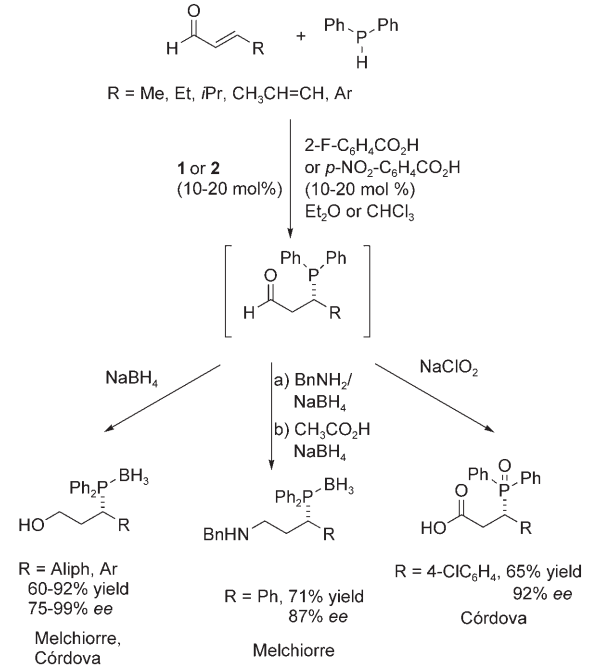
More recently Oriyama[83] presented a solvent-free organocatalytic conjugate addition of thiols to enals catalyzed by **20** (Scheme 30). The reaction proceeds without any organic solvent, albeit in water or brine the reaction also takes place, giving the corresponding chiral sulfides in high enantioselectivities (92–99 % *ee*) for *tert*-butyl mercaptan and slightly lower enantioselectivities (85–88 % *ee*) for benzyl mercaptan.



Scheme 30. Enantioselective conjugate addition of thiols to enals. TBS = *tert*-butyldimethylsilyl.

3.2.4. C–P Bond-Forming Reactions: The Phospha-Michael Reaction

The phospha-Michael addition, that is, the addition of a phosphorous nucleophile to an electron-deficient alkene, represents one of the most versatile and powerful tools for the formation of P–C bonds since many different electrophiles and P nucleophiles can be combined with each other.[84] However, a very limited number of examples can be found in the literature on organocatalytic enantioselective phospha-Michael additions.[85] Recently, a general procedure for carrying out the conjugate addition of diphenylphosphine to α,β-unsaturated aldehydes was almost simultaneously described by Melchiorre[86] and Córdova[87] (Scheme 31). This transformation presents inherent difficulties because of the reversibility of the nucleophilic attack

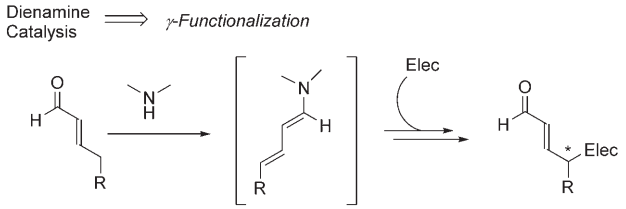


Scheme 31. Enantioselective hydrophosphination of α,β-unsaturated aldehydes catalyzed by **1** or **2** and applications of the adducts.

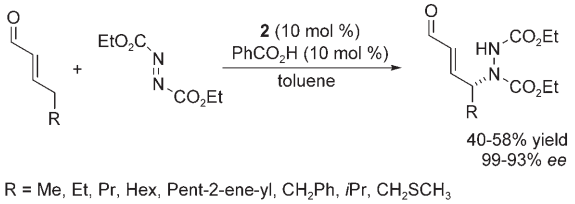
and competition between 1,2- and 1,4-addition to the enal. Melchiorre presented the catalytic system **2**/*p*-nitrobenzoic acid as the most promising one for this transformation in Et_2O at room temperature whilst Córdova reported catalysts **1** and **2** in combination with 2-fluorobenzoic acid for the same reaction in chloroform at 4 °C. In both cases the corresponding β-formylphosphines were reduced in situ with $NaBH_4$ to the air-stable alcohol derivatives. The reaction was efficient and highly enantioselective for α,β-unsaturated aldehydes with either aliphatic or aromatic β-substituents. The utility of this hydrophosphination was also demonstrated by the one-pot conversion of the aldehyde intermediates into enantioenriched 3-amino-phosphine derivatives by in situ reductive amination and by the synthesis of β-phosphine oxide acids.

4. γ-Functionalization of Carbonyl Compounds

As previously outlined, and despite the fundamental analogies in the structure of the catalysts and substrates, the mechanisms for the α- and β-functionalization of carbonyl compounds promoted by secondary amines are different. In this context, Jørgensen and co-workers[88] documented a new mechanism for the functionalization of α,β-unsaturated carbonyl compounds, which seems to occur through a dienamine intermediate (Scheme 32). They disclosed that secondary amines, and in particular **2**, can invert the common reactivity of α,β-unsaturated aldehydes, thereby transforming an electron-poor alkene into an electron-rich diene. As an example of this inverted reactivity, the authors reported the electrophilic γ-amination of α,β-unsaturated aldehydes with diethylazodicarboxylate (DEAD) to give the γ-aminated products in high enantioselectivity, although in moderate yields (Scheme 33). Computational and experimental investigations indicate that this γ-amination might be the result of a [4+2] cycloaddition reaction between DEAD and the chiral dienamine formed in situ with the catalyst.[89]



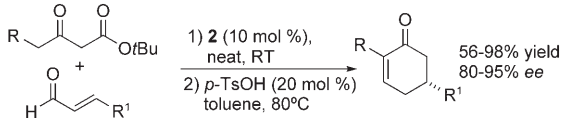
Scheme 32. Dienamine catalysis.



Scheme 33. Organocatalytic γ-amination of α,β-unsaturated aldehydes.

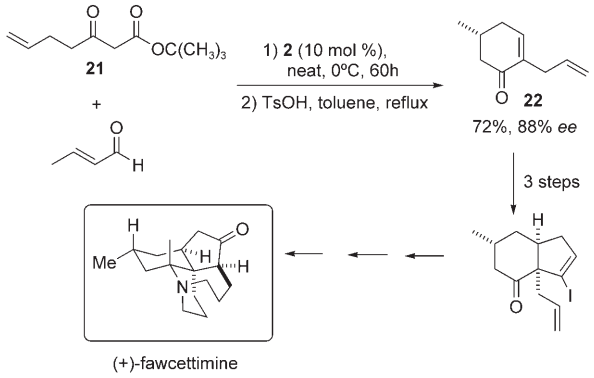
5. Enamine- or Iminium-Induced Tandem Reactions

Some examples which combine reactions that occur via enamine or iminium catalysis with a subsequent reaction at a remaining carbonyl moiety have been reported. In 2006, the **2**-catalyzed one-pot Michael–aldol reaction of α,β-unsaturated aldehydes and β-ketoesters was reported for the preparation of cyclohexenones.[90] The first step of the process is the Michael addition of the active methylene to the enal by iminium activation, followed by the aldol reaction at the formyl group. In this case, the final intramolecular aldol reaction required assistance by heating of the mixture in the presence of an acid cocatalyst, which also induced a hydrolysis/decarboxylation process, leading to the formation of target compounds, with excellent yields and enantioselectivities (Scheme 34).



Scheme 34. One-pot Michael–aldol reaction of enals and β-ketoesters.

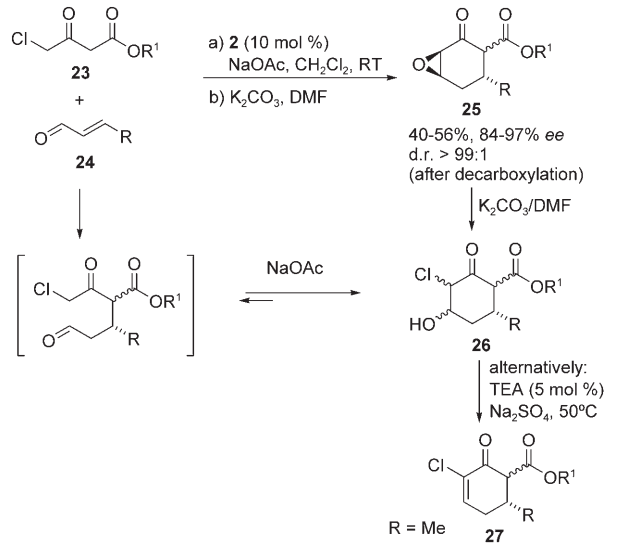
Using an analogous methodology Toste et al. presented the organocatalytic Robinson annulation reaction between ketoester **21** and crotonaldehyde, which gave 2-allylcyclohexanone **22** in 88 % *ee* and 72 % yield (Scheme 35).[91]



Scheme 35. Organocatalytic asymmetric synthesis of dienone **22**.

Moreover, the reaction performed well on a multigram scale, providing nearly 10 g of product **22** in a single run, to give a key substrate en route to (+)-fawcettimine, a class of *Lycopodium* alkaloids.[92]

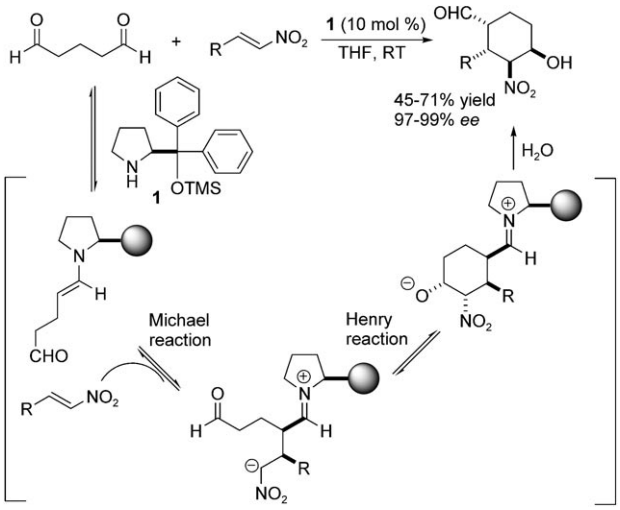
Highly functionalized epoxycyclohexanone derivatives **25** with up to four stereocenters can be obtained by a **2**-catalyzed domino Michael/Darzens reaction (Scheme 36).[93]



Scheme 36. Asymmetric Michael/Darzens reaction for the synthesis of epoxycyclohexanone derivatives.

This process starts with the conjugate addition of the γ-chloro-β-ketoester **23** to the activated enal **24**. The Michael addition is followed by a Darzens reaction facilitated by NaOAc, to promote first the aldol addition, and then by K_2CO_3 for the final intramolecular S_N2 displacement to form the epoxide. The overall yields and enantioselectivities are good, but the diastereocontrol is only moderate as the stereocenter between the ketone and ester is not configurationally stable, which explains the diastereomeric ratio (d.r. from 4:1 to 7:1). Nevertheless, after decarboxylation only one diastereomer can be detected (>99% diastereomeric purity). The high stereocontrol of the remaining stereocenters is a consequence of the intramolecular epoxide formation, as only one conformation of **26** is energetically favored. The authors postulate a reversible aldol addition whereby the diastereomers of **26** are in equilibrium, and irreversible epoxide formation to afford the products in overall good yield. Alternatively, depending on the base, the reaction can be directed towards the synthesis of 2-chlorocyclohex-2-enones **27**. Oddly, starting from 4-bromoacetoacetate and under similar conditions cyclopentane derivatives are obtained (see Scheme 48).

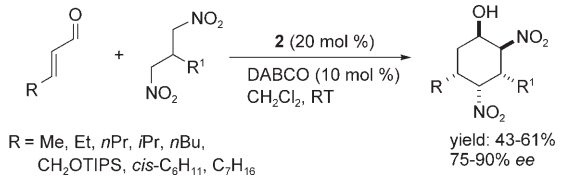
In this context and as a further application of diaryl prolinol ether derivatives in asymmetric reactions, Hayashi[94] presented a highly enantioselective tandem Michael/Henry reaction promoted by **1**, which affords, in a single operation, substituted chiral nitrocyclohexanecarbaldehydes with excellent diastereo- and enantioselectivities and control of four stereogenic centers (Scheme 37). Different organic solvents were tested in this reaction (CH_2Cl_2, toluene, *N*,*N*-dimethylformamide, hexane, and THF), and although the reaction



Scheme 37. Catalytic asymmetric tandem Michael/Henry.

proceeded in all cases, the best yields and diastereoselectivities were attained in THF. Water was also examined, but the reactions in this solvent scarcely proceeded. The reaction is fast with electron-deficient aryl-substituted nitroalkenes, while it is slow with electron-rich, aryl-substitued ones. Not only aromatic groups but also heteroaromatic groups, such as furan and indole could be successfully employed as the β-substituent of the nitroalkene. β-Alkyl-substituted nitroalkenes may also participate in this reaction.

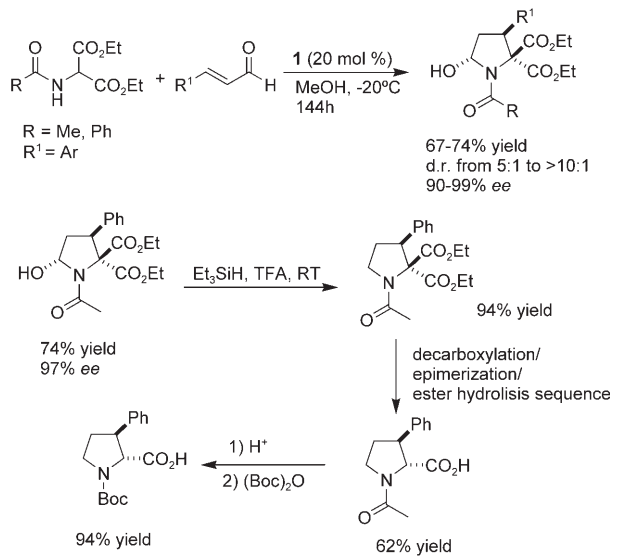
Very recently, Jørgensen et al. reported an elegant approach for the organocatalytic construction of pentasubstituted cyclohexanes carrying five contigous stereocenters in one pot. The transformation is based on the Michael/Henry reaction of an α,β-unsaturated aldehyde and a dinitroalkane, promoted by **2** in the presence of DABCO as the base additive (Scheme 38).[95] This novel domino reaction proceeds



Scheme 38. Organocatalytic nitro-Michael/Henry catalyzed by **2.**

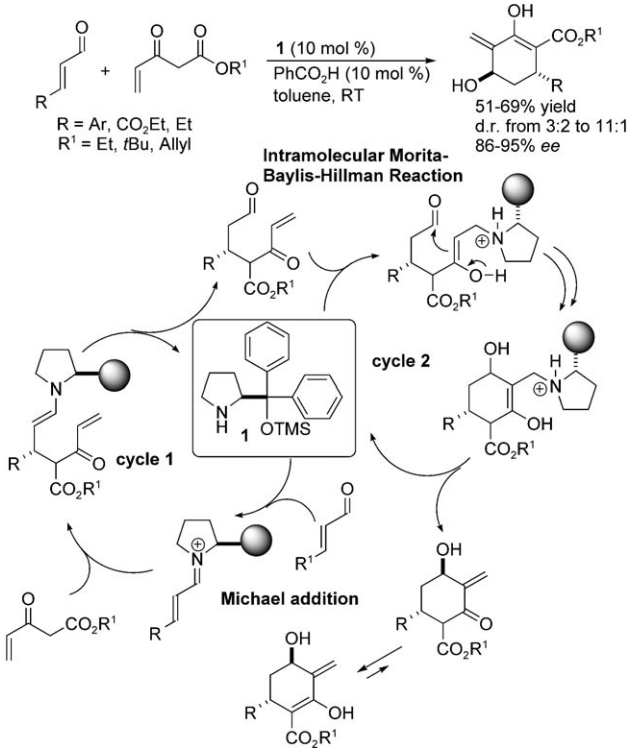
with moderate to good yields and with high diastereo- and enantioselectivity.

5-Hydroxypyrrolidines are accessible trough a **1**-catalyzed organocatalytic tandem reaction between 2-acylaminomalonates and α,β-unsaturated aldehydes and are formed in high yields with 90–99% *ee* (Scheme 39).[96] The first step implies the Michael addition to the iminium formed from the enal, which is followed by the nitrogen addition to the formyl group. Elaboration of the resulting adducts trough a decarboxylation/epimerization/ester hydrolysis sequence affords 3-substituted prolines.



Scheme 39. Organocatalytic asymmetric synthesis of 5-hydroxypyrrolidines and 3-substituted proline derivatives.

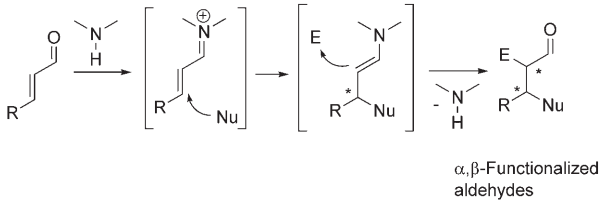
Another interesting application of prolinol ethers as catalysts has been recently disclosed by Jørgensen et al. and implies the **1**-promoted organocatalytic asymmetric tandem Michael/Morita–Baylis–Hillman reaction between enals and Nazarov reagent (Scheme 40).[97] The reaction proceeds in high enantio- and diastereoselectivity for a wide range of α,β-unsaturated aldehydes and different β-ketoesters. Interestingly, mechanistic studies indicate that **1** acts as the catalyst in both steps.



Scheme 40. Organocatalytic Michael/Morita-Baylis–Hillman reaction.

6. α,β-Functionalization of Carbonyl Compounds: Iminium/Enamine-Based Consecutive Creation of C–H, C–C, and C–X bonds

Another strategy for developing organocatalytic domino or cascade processes[9] involves first iminium activation and reaction with a nucleophile; and secondly, in contrast to the previous examples in Section 5, the trapping of the resulting enamine by an electrophile. This iminium/enamine approach uses enals or enone systems to afford double-substituted (α,β-functionalized) products which in general contain two stereocenters (Scheme 41).



Scheme 41. The concept of iminium–enamine activation in domino processes for α,β-functionalization.

In this section the new formed bonds are classified according to the following example: reactions in which a C–H bond is formed at the β-position of the carbonyl functionality (first step of the domino process that takes place through iminium ion activation) and a C–C bond is formed at the α-position (second step of the process that takes place via an enamine intermediate) are referred to as "carbon–hydrogen/carbon–carbon bond-forming reactions". In a similar way, carbon–carbon/carbon–carbon bond-forming reactions and carbon–heteroatom/carbon–carbon bond-forming reactions have been developed within this context.

6.1. Carbon–Hydrogen/Carbon–Carbon Bond-Forming Reactions

6.1.1. The Reductive Mannich Reaction

Despite the importance of direct catalytic Mannich reactions (see above) there was no report of a direct catalytic asymmetric reductive Mannich-type transformation until Zhao and Córdova in 2006 presented the first example by an organocatalytic asymmetric domino sequence.[98] Thus, in the presence of **1** and benzoic acid as catalysts and employing a metal-free asymmetric transfer hydrogenation followed by a domino enantioselective Mannich-type reaction, three contiguous stereocenters were assembled in a stereoselective fashion in one pot starting from α,β-unsaturated aldehydes. The first step of the process is the asymmetric hydrogenation, which takes place by iminium ion activation and is ach-

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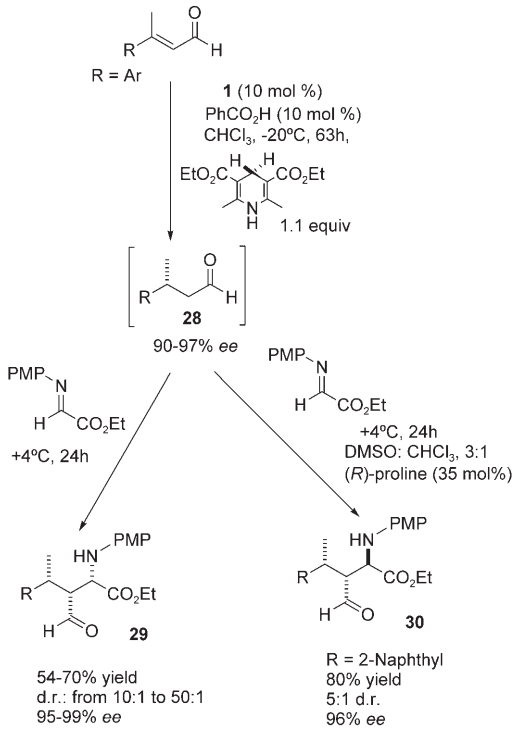
ieved by using Hantzsch ester[99] in the presence of benzoic acid (Scheme 42). In the second step the enamine intermediate coming from the first step reacts with *N*-*p*-methoxyphen-



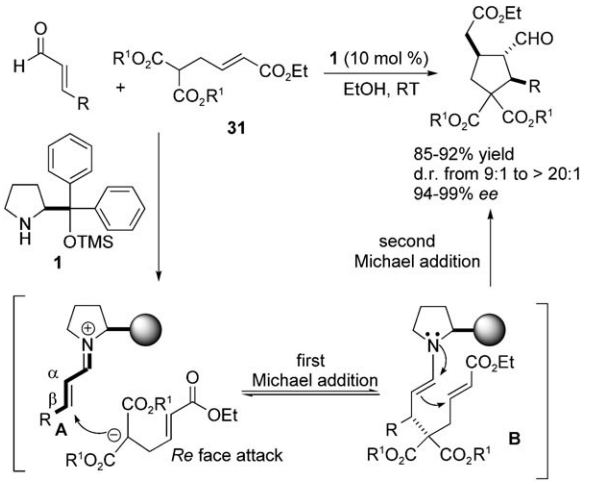
Scheme 42. Direct catalytic enantioselective reductive Mannich-type reactions.

yl-protected α-iminoglyoxylate as the electrophile in a Mannich-type reaction. The reactions are carried out with β-aryl-substituted enals in chloroform at −20 °C and furnish amino acid derivatives in good yields with up to 50:1 d.r. and up to 99 % *ee*. Notably, the second C–C bond-forming step leads to a higher enantioselectivity of the Mannich products **29** as compared to the transfer hydrogenation products **28**. When (*R*)-proline in 35 mol % together with the α-iminoglyoxylate is added to the reaction mixture after the reduction step, diastereoisomer **30** is produced with high enantioselectivity. Apparently, the presence of catalyst **1** does not interfere in this latter process.

6.2. Carbon–Carbon/Carbon–Carbon Bond-Forming Reactions

6.2.1. Double Michael Addition Reactions

Recently an unprecedent synthesis of highly functionalized chiral cyclopentanes[100] by catalytic enantio- and diastereoselective double Michael addition reactions was reported by Tang, Wang, et al.[101] Thus, α,β-unsaturated aldehydes react with the α,β-unsaturated esters of type **31** in the presence of **1** as catalyst (Scheme 43). Under these conditions the cascade process takes place efficiently to give chiral cyclopen-

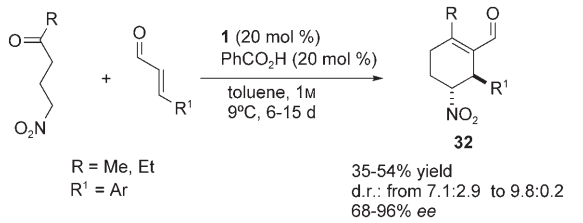


Scheme 43. Cascade double Michael addition reactions promoted by catalyst **1** for the one-pot formation of chiral cyclopentanes.

tanes in excellent yields with excellent *ee* values and good d.r. ratios. The results show that the size of the R^1 group of the malonate ester moiety in **31** has a limited effect on the process. Several β-aryl substituted enals proved to be good substrates for this transformation, and an example of a β-alkyl unsaturated aldehyde is also reported, which shows a similarly good result. One important feature of this approach is that the reactivity of the α,β-unsaturated system **31** that participates in the second conjugate addition reaction through enamine **B** must be high enough to allow for the intramolecular Michael reaction, but lower than that of the α,β-unsaturated iminium **A**, which was derived from the initial α,β-unsaturated aldehyde.

6.2.2. Tandem Michael/Aldol Reactions

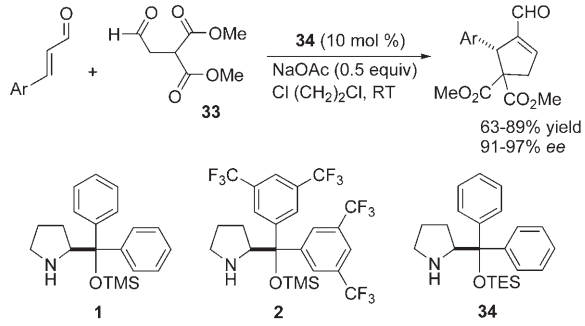
Chiral substituted cyclohexanes **32** are accessible from γ-nitroketones and α,β-unsaturated aldehydes in the presence of catalyst **1** (Scheme 44).[102] In the first step the catalyst acti-



Scheme 44. Asymmetric organocatalytic synthesis of cyclohexenecarbaldehydes from γ-nitroketones and α,β-unsaturated aldehydes.

vates the enal by iminium ion formation, and this species reacts then with the nitroketone in a Michael addition. In the second step, the resultant enamine intermediate undergoes an intramolecular aldol reaction with release of catalyst **1** for re-entry into the catalytic cycle. Finally the cyclohexene is formed upon elimination of water from the aldol.

More recently, Wang and co-workers[103] reported another Michael/aldol protocol that leads to cyclopentenes. The reaction between **33** and different aromatic enals in the presence of prolinol triethylsilyl ether **34** and NaOAc affords at room temperature highly functionalized chiral cyclopentenes in high yields and excellent enantioselectivities (Scheme 45).

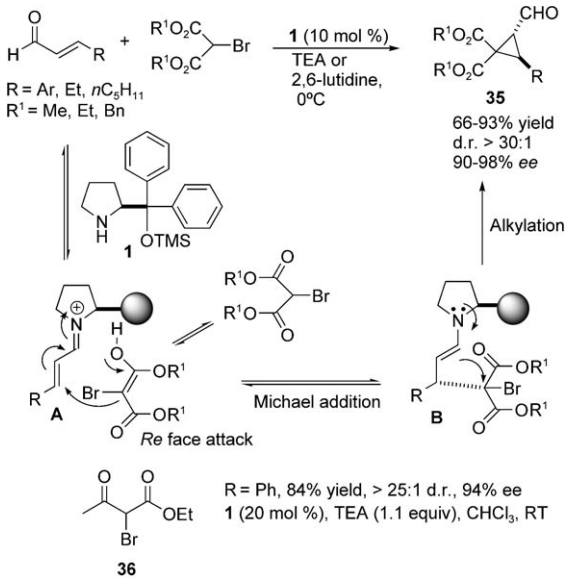


Scheme 45. Cascade Michael–aldol condensation reaction of enals with **33**.

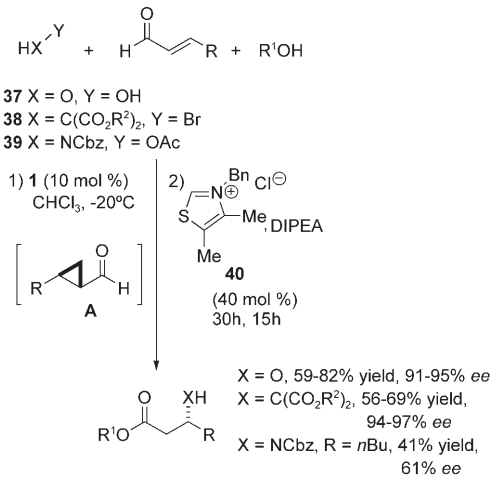
Prolinol ether **1** affords slightly lower *ee* values, while in the presence of **2** no reaction takes place. On the other hand, with β-alkyl-substituted enals almost no reaction occurs.

6.2.3. Tandem Michael/Alkylation Reactions

Iminium/enamine-based tandem Michael/alkylation reactions promoted by diarylprolinol ether derivatives have proven to be another interesting tool for the construction of chiral cyclopropanes[104] and cyclopentanones.[100] The reaction between bromomalonates and enals in the presence of **1** and triethylamine (TEA) or 2,6-lutidine as HBr scavenger gives the corresponding 2-formylcyclopropanes **35** in high yields and diastereomeric ratios and excellent asymmetric induction[105] (Scheme 46). Strikingly, catalyst **2** was not effective in this case, leading only to traces of the expected product. On the other hand, ethyl-2-bromo-3-oxobutanoate **36** proves also to be a good substrate for the same reaction with cinnamaldehyde.[105a] The proposed mechanism involves the activation of the enal by the amine catalyst through an iminium intermediate **A**, in which an efficient *Si*-face shielding leads to the stereoselective *Re*-facial nucleophilic conjugate addition by the 2-bromosubstituted malonates and β-keto esters. Next, the generated chiral enamine intermediate **B** performs an intramolecular nucleophilic attack through an alkylation reaction to produce the cyclopropane. The intramolecular ring closure pushes the equilibrium forward and makes this step irreversible.



Scheme 46. Organocatalytic cyclopropanation of enals with α-bromomalonates and ethyl-2-bromo-3-oxobutanoate **36**.

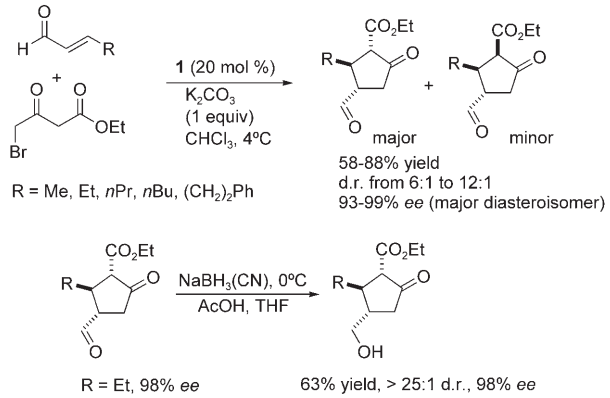


Scheme 47. One-pot catalytic tandem asymmetric epoxidation/esterification, cyclopropanation/esterification, and aziridination/esterification of enals.

More recently a one-pot combination of amine and heterocyclic carbene[106] catalysis (AHCC) was disclosed for the asymmetric synthesis of β-hydroxy, β-malonate, and β-amino esters from α,β-unsaturated aldehydes, which are obtained in good to high yields with up to 97% *ee* (Scheme 47).[107] The mechanism implies as first step iminium activation of the enal followed by enantioselective conjugate addition of nucleophiles **37**, **38**, and **39**. Subsequent intramolecular cyclization by the in situ generated chiral enamine would furnish the corresponding 2-epoxy (X=O), 2-cyclopropyl [X=C-(CO_2R^1)], and 2-aziridine[108] (X=NCbz) aldehydes **A**. Next, the base-generated heterocyclic carbene catalysts would catalyze the C–O, C–C, or C–N bond cleavage ring opening followed by concomitant oxidation of the aldehyde and subsequent esterification.

One-pot organocatalytic domino Michael/α-alkylation reactions have also proven to be useful for the enantioselective synthesis of functionalized cyclopentanones and cyclopentanols. Thus, **1** efficiently catalyzes the reaction of 4-bromo-β-ketoesters with α,β-unsaturated aldehydes to afford trisubstituted cyclopentanones in good to high yields, moderate diastereoselectivity (6:1–12:1), and excellent

enantioselectivities for the major diastereomer (93–99%; Scheme 48).[109] The presence of base was essential for the reaction to proceed. Moreover, the resulting cyclopentanones were also reduced with $NaBH_3(CN)$ to the corresponding cyclopentanols.



Scheme 48. Organocatalytic enantioselective synthesis of functionalizaed cyclopentanones and cyclopentanols from the reaction of enals with 4-bromo-β-ketoesters.

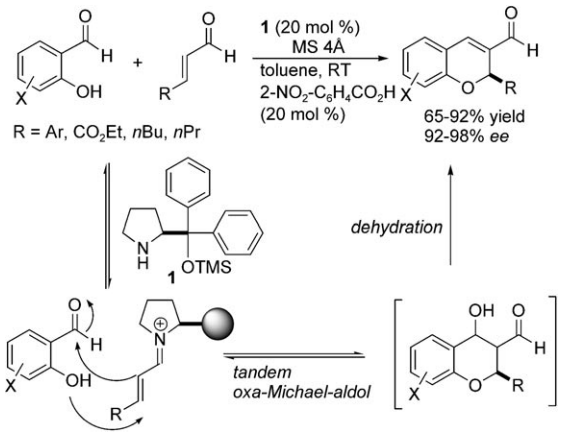
6.3. Carbon–Heteroatom/Carbon–Carbon Bond-Forming Reactions

6.3.1. Tandem Oxa-Michael/Aldol Reactions

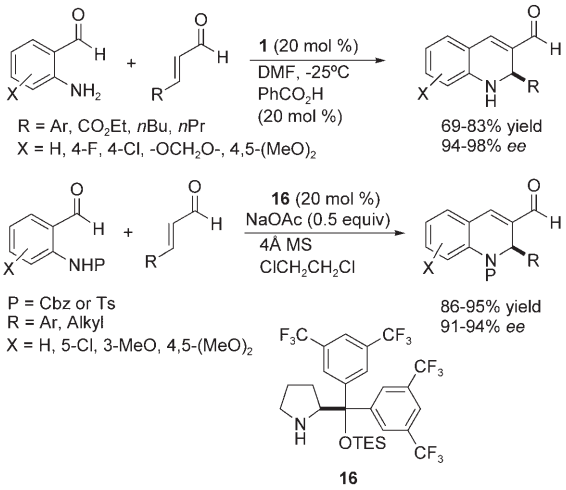
Asymmetric domino oxa-Michael-intramolecular aldol–dehydration sequences constitute a very effective and straightforward entry to enantioenriched benzopyranes, also known as chromenes, widespread elements in natural products and in lead compounds with proved pharmacological activities.[110] In this context, three independent reports documented the use of catalyst **1** for the above transformation.[111–113] Arvidsson et al.[111] demonstrated that benzopyranes can be obtained through an organocatalytic domino reaction sequence starting from α,β-unsaturated aldehydes, salicylic aldehyde, and **1** as promoter of the process. Investigation of the effect of different basic and acid additives led to the conclusion that the best conditions involved the absence of any external additive. However, under these conditions enantioselectivities are poor, typically 50% *ee*. Córdova and Wang, almost simultaneously, presented the same version but using organic acid additives.[112,113] Thus, enals efficiently react with salicylic aldehyde in the presence of either **1** (20 mol%)/2-nitrobenzoic acid (20 mol%),[112] or **1** (30 mol%)/benzoic acid (30 mol%)[113] and molecular sieves (4 Å) to facilitate the dehydration step (Scheme 49). Under these conditions excellent enantioselectivities are attained.

6.3.2. Tandem Aza-Michael/Aldol Reactions

Starting from 2-aminobenzaldehydes and α,β-unsaturated aldehydes the aza version of the above oxa-Michael intramolecular aldol–dehydration sequence leads to 1,2-dihydroquinolines with excellent chemo- and enantioselectivity (Scheme 50).[114,115] It was shown, for example, that catalyst **1**



Scheme 49. Organocatalytic asymmetric domino oxa-Michael/aldol condensation between salicylaldehydes and enals.



Scheme 50. Organocatalytic asymmetric domino aza-Michael/aldol condensation between 2-aminobenzaldehydes and enals promoted by **1** and **16**.

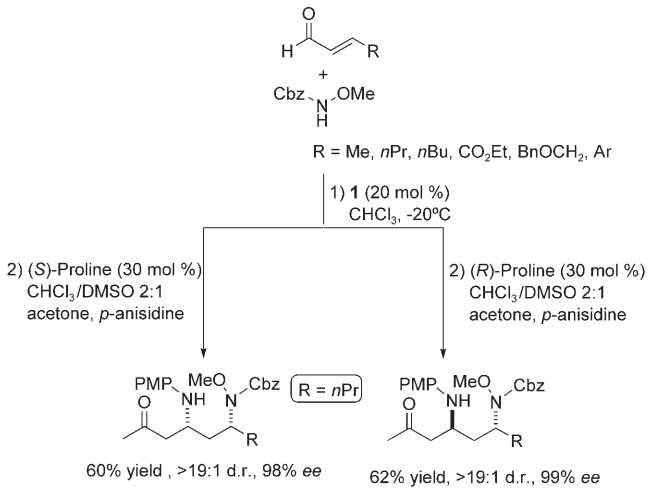
in combination with benzoic acid promotes the reaction of nonprotected 2-aminobenzaldehydes[114] with β-aryl and β-alkoxycarbonyl α,β-unsaturated aldehydes in DMF as solvent. With β-alkyl α,β-unsaturated aldehydes the highest asymmetric induction was achieved in CH_3CN without addition of an organic acid.

Almost simultaneously to Córdova's work, Wang[115] reported the same reaction starting from N-protected 2-aminobenzaldehydes and using catalyst **16**, NaOAc, and molecular sieves (4 Å) in 1,2-dichloroethane as the solvent. The expected adducts were obtained in good yields and high enantioselectivities (Scheme 50).

6.3.3. Tandem Aza-Michael/Mannich Reactions

As reported in Section 3.2.1 catalyst **1** is an efficient promoter of the conjugate addition of *N*-methoxycarbamates to enals (Scheme 26).[74] This reaction when linked in cascade with an L-proline-promoted Mannich reaction gives direct

access to orthogonally protected chiral diamine derivatives with excellent chemo- and enantioselectivities (Scheme 51). This is probably due to the difference in reactivity between chiral pyrrolidine **1** and proline in the separate reactions.

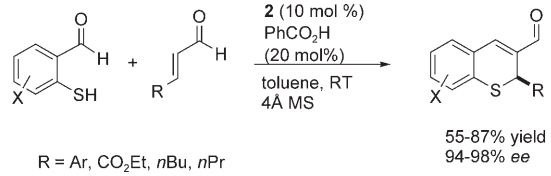


Scheme 51. One-pot asymmetric cascade aza-Michael/Mannich reactions using a combination of **1** and proline.

6.3.4. Tandem Sulfa-Michael/Aldol Reactions

At room temperature adducts coming from sulfa-Michael reactions have been found to rapidly racemize.[81–83] Domino processes initiated by the sulpha-Michael addition can also be used as an alternative strategy for avoiding racemization of the conjugate adducts by equilibration. For these reasons, much of the progress in this area has stemmed from the use of bifunctional thiol derivatives in which an additional electrophilic functionality has been introduced. In this context, the **2**-catalyzed sulfa-Michael addition of 2-mercapto-1-phenylethanone to α,β-unsaturated aldehydes has proven to be an excellent method for the synthesis of enantioenriched tetrahydrothiophenes (Scheme 52).[116] Moreover, the authors found that two different regioisomers can be selectively obtained by slight modification of the reaction conditions. For example, when the reaction was carried out in the presence of an acid cocatalyst, 2-benzoyl-5-alkyltetrahydrothiophen-4-ols were obtained, but under basic conditions, a completely different isomer was observed. These results were interpreted in terms of an iminium–enamine cascade process in the first case, with the acid cocatalyst facilitating the formation of the iminium intermediate. However, under basic conditions, hydrolysis of the enamine intermediate might occur and, therefore, a final intramolecular base-catalyzed aldol reaction with the more reactive aldehyde moiety as electrophile would lead to the final product. In this second case, the basic conditions employed could also promote the uncatalyzed sulfa-Michael reaction, thereby leading to the observed decrease in the enantioselectivity.

In a similar approach, the Michael reaction of 2-mercaptobenzaldehydes with α,β-unsaturated aldehydes has resulted in a very straightforward and effective method for the enantioselective preparation of 2*H*-1-benzothiopyrans (Scheme 53).[117] In this case the domino sequence ended

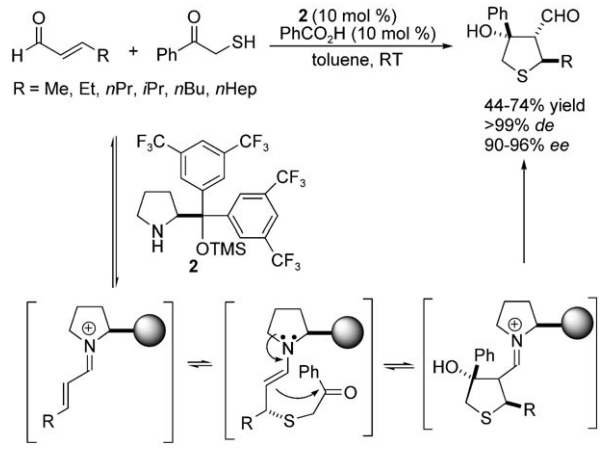


Scheme 53. Organocatalytic asymmetric domino sulfa-Michael/aldol condensation between 2-mercapto-benzaldehyde and enals.

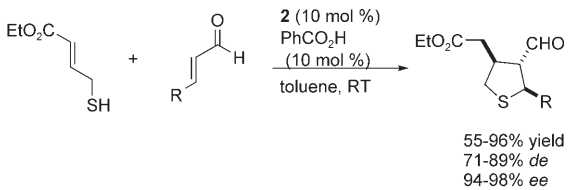
with the dehydration of the aldol intermediate, either during the reaction itself or during purification by chromatography on silica gel. Cyclic enones can also be employed as electrophiles in the reaction to give the corresponding adducts, albeit with poor *ee* values.[118]

6.3.5. Tandem Sulfa-Michael/Michael Reactions

A novel organocatalytic enantioselective thiol-initiated domino double Michael addition reaction of α,β-unsaturated aldehydes with *trans*-ethyl-4-mercapto-2-butenoate in the presence of **2** was recently documented (Scheme 54).[119] The process furnishes highly functionalized tetrahydrothiophenes with the generation of three new stereogenic centers in high yield and excellent enantioselectivities and high stereoselectivities.



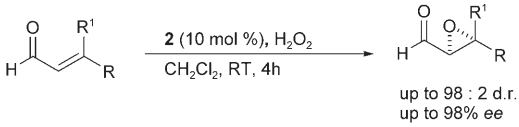
Scheme 52. Organocatalytic asymmetric domino sulfa-Michael/aldol condensation between 2-mercapto-1-phenylethanone and enals promoted by **2**.



Scheme 54. Catalyst **2**-promoted domino sulfa-Michael–Michael reactions of α,β-unsaturated aldehydes with *trans*-ethyl-4-mercapto-2-butenoate.

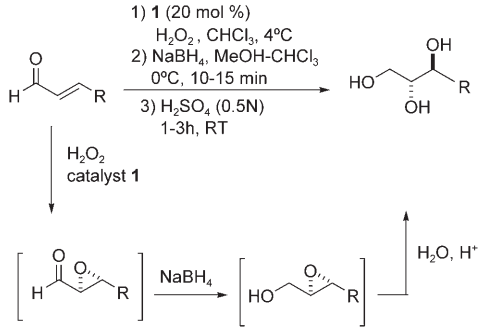
6.3.6. Epoxidation of α,β-Unsaturated Carbonyl Compounds

Chiral epoxides are very important building blocks for the synthesis of enantiomerically pure complex molecules, in particular of biologically active compounds.[120] The asymmetric epoxidation of functionalized and unfunctionalized olefins has emerged as a very versatile and important synthetic tool in organic synthesis.[120,121] In this context, diarylprolinol silyl ethers have also been investigated as organocatalysts in the epoxidation of α,β-unsaturated carbonyl compounds. Jørgensen et al.[122] demonstrated that catalyst **2** is efficient in promoting the epoxidation of enals in the presence of hydrogen peroxide to afford the expected epoxides in excellent diastereomeric ratios and enantioselectivities (Scheme 55). In contrast, L-proline and other pyrrolidine-based catalysts gave poor or low conversion and low enantiomeric excess.[122,123]



Scheme 55. Epoxidation of α,β-unsaturated aldehydes.

In a similar way, Córdova et al.[124] documented a tandem organocatalytic asymmetric synthesis of 1,2,3-triols (Scheme 56). Thus, TMS-protected diphenylprolinol **1** effi-



Scheme 56. Organocatalytic asymmetric synthesis of 1,2,3-prim,sec,sec-triols.

ciently catalyzes the asymmetric epoxidation of enals with hydrogen peroxide followed by in situ reduction with $NaBH_4$ and epoxide opening using sulfuric acid. Under these conditions the tandem sequence with β-aryl-substituted enals affords the corresponding terminal triols in good overall yield over the three steps, moderate diastereoselectivities (from 2:1 to 3:1), and 95–98% *ee* for the major diastereomer. The reaction with aliphatic enals is highly diastereoselective and gives the corresponding triols with up to greater than 50:1 d.r. and 68–73% *ee*. The reaction can also be applied to the enantioselective synthesis of 3-aryl-3-chloro-1,2-propandiols by employing aqueous HCl (2N) in the last step of the reaction sequence.

6.3.7. Aziridination of α,β-Unsaturated Carbonyl Compounds

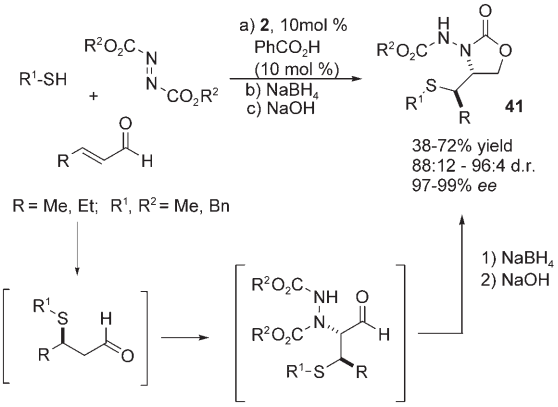
Aziridines are nitrogen-containing heterocycles of great importance as versatile chiral building blocks in organic synthesis.[125] As previously mentioned, aziridination of α,β-unsaturated aldehydes is successfully achieved in the presence of **1** and acetoxycarbamates as the nucleophilic agents (see Scheme 47). The reaction is highly chemo- and enantioselective, and the corresponding Boc- or Cbz-protected 2-formylaziridines are isolated in good to high yields with 84–99% *ee*. The resulting α,β-aziridine aldehydes can also be converted in one step into the corresponding Boc- or Cbz-protected β-amino acid esters in the presence of a thiazolium catalyst generated in situ.

7. Multicomponent Reactions

One of the challenges in organocatalysis is to implement various reaction concepts in a multicomponent domino reaction to achieve multibond formation in a one-pot operation.[9] In this section we summarize multicomponent reactions promoted by prolinol ether derivatives wherein more than two substrates are involved. The reactions are sorted by their activation sequences.

7.1. Iminium–Enamine Activation: C–X/C–X Bond-Forming Reactions

As described in Section 3.2.3, Jørgensen and co-workers reported the use of **2** together with benzoic acid as an effective catalyst system in the intermolecular Michael-type addition of thiols to α,β-unsaturated aldehydes (Scheme 29).[82] They also applied this protocol to a multicomponent domino sulfa-Michael amination process, disclosing the first enantioselective, organocatalytic conjugate thiol-addition/amination reaction in a C–X/C–X bond-forming sequence. First, the iminium activated enal undergoes a conjugate addition with the soft thionucleophile (Scheme 57). The resulting enamine is then trapped by the azodicarboxylate to

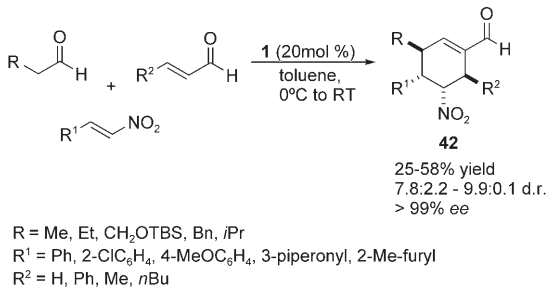


Scheme 57. Asymmetric conjugate thiol addition/amination sequence.

afford the thio- and hydrazino-substituted aldehydes with high diastereocontrol and very high enantiomeric purity. This domino reaction is then followed by in situ reduction of the aldehyde carbonyl with $NaBH_4$ and formation of the oxazolidinones **41** under basic conditions. The corresponding yields are quite good, as they result for a four-step one-pot procedure. It is important to mention that the reaction temperature has a great influence with regard to the stereoselectivity and the reaction rate. The sulfa-Michael addition is very fast at ambient temperature, but under these conditions the Michael product racemizes easily. If the reaction temperature is lowered to −15 °C, the racemization can be prevented but the reaction rate is strongly slowed down. The problem was solved by employing benzoic acid as a cocatalyst, which leads to higher reaction rates.

7.2. Enamine–Iminium–Enamine Activation: C−C/C−C/C−C Bond-Forming Reactions

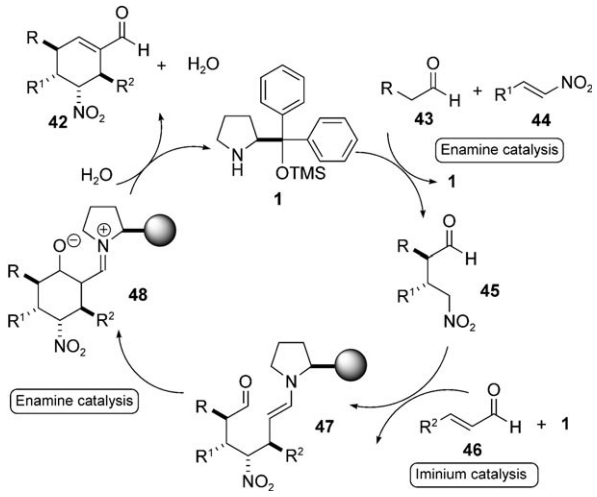
Enders et al. were the first who presented an elegant example of the control of four stereocenters in a triple C−C cascade organocatalytic reaction. The approach involves reaction between a linear aldehyde, a nitroalkene, and an α,β-unsaturated aldehyde promoted by catalyst **1** to afford tetrasubstituted cyclohexene carbaldehydes with high diastereoselectivity and essentially complete enantiocontrol (Scheme 58).[126] This multicomponent reaction proceeds



Scheme 58. Michael/Michael/aldol sequence promoted by **1** leading to cyclohex-1-ene-carbaldehydes.

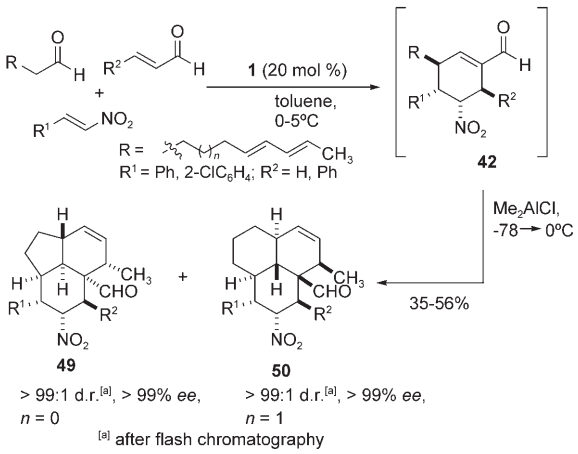
through a Michael/Michael/aldol condensation sequence that includes the consecutive and highly chemo-, regio-, and stereoselective formation of three C−C bonds. An advantage of this approach is clearly the fact that R, R^1, and R^2 can be easily varied from aliphatic, aromatic, and heteroaromatic to functionalized residues by employing a 1:1:1 ratio of the three susbtrates.

In this case the catalytic cycle starts with enamine activation of the linear aldehyde **43** (Scheme 59), which then selectively adds to the nitroalkene **44** in a Michael reaction, in analogy to the reaction proposed by Hayashi (see Scheme 5). The subsequent hydrolysis liberates the catalyst, which is now able to form the iminium ion of the α,β-unsaturated aldehyde **46** to accomplish the conjugate addition with nitroalkane **45**. In the subsequent third step, an enamine intermediate **47** leads to an intramolecular aldol condensation via **48**. Hydrolysis completes the catalytic cycle and releases the tetrasubstituted cyclohexene carbaldehyde **42**.



Scheme 59. Proposed catalytic cycle of a triple cascade reaction affording cyclohex-1-ene-carbaldehydes (arrows may be considered equilibria).

This multicomponent domino reaction was recently extended by a highly stereoselective intramolecular Diels–Alder reaction.[127] The domino reaction is followed by a Lewis acid mediated intramolecular [4+2] cycloaddition, which leads to complex tricyclic frameworks **49**–**50**. In this tetradomino reaction, five C−C bonds are formed with the diastereo- and enantioselective construction of up to eight new stereogenic centers in a one-pot operation (Scheme 60).

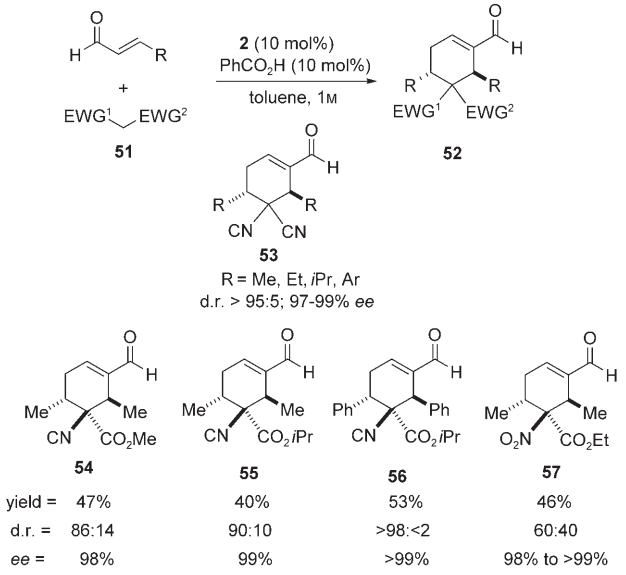


Scheme 60. Michael/Michael/aldol condensation/Diels–Alder domino sequence.

7.3. Iminium–Iminium–Enamine Activation: C−C/C−C/C−C Bond-Forming Reactions

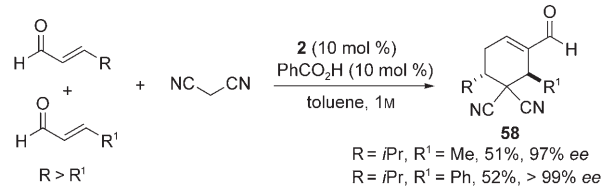
Recently a new approach for an enantioselective concurrent multicomponent domino organocatalytic reaction following a sequential iminium–iminium–enamine catalysis, which en-

ables the consecutive formation of three new carbon–carbon bonds, was presented by Jørgensen and co-workers.[128] In a first instance the authors investigated the reaction between enals and different active methylene compounds (Scheme 61). The process furnishes cyclohex-1-ene-carbaldehyde derivatives of type **52**–**57** in good to high yields, moderate to good diastereomeric ratios, and excellent enantioselectivities. The reaction proceeds well for both β-aliphatic and β-aromatic aldehydes and the best d.r. values are obtained for malononitrile. For nucleophiles **51** having two different electron-withdrawing groups, for example cyanoacetates, the results show that better diastereocontrol is attained by increasing the size of the ester group.



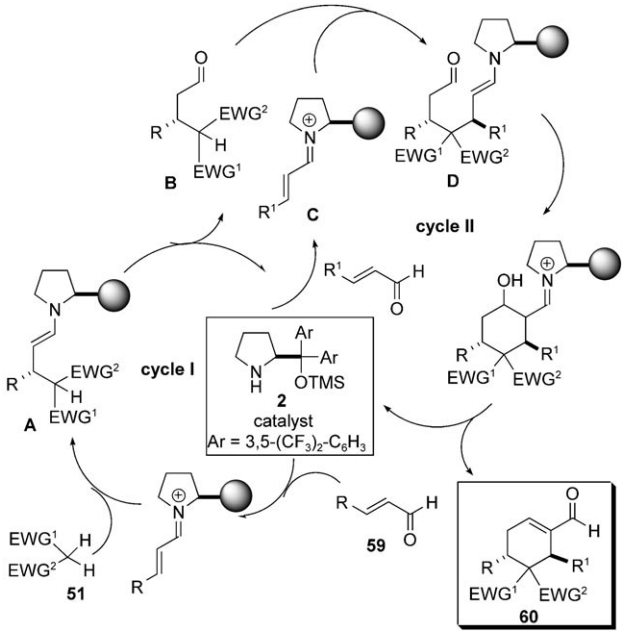
Scheme 61. Reactions of α,β-unsaturated aldehydes with activated methylene compounds catalyzed by **2.**

The authors have also extended this concept for the combination of two different enals with malononitrile. It was shown that it is possible to control the reaction sequence with regard to the α,β-unsaturated aldehydes by choosing the appropriate R and R^1 groups (Scheme 62). For this purpose the enals, with the R substituent, need to be unreactive enough in cycle II (see Scheme 63) so that cycle I would be complete prior to the beginning of the formation of adduct **D**. This was successfully attained by using the R isopropyl group. Interestingly, the sequence can be applied to enals with alkyl and aryl R^1 substituents, providing the respective cyclohex-ene-carbaldehyde **58** as exclusively one regioisomer and one diastereomer, formed with excellent enantiomeric excess.



Scheme 62. Organocatalytic domino reaction with two different α,β-unsaturated aldehydes catalyzed by **2.**

The stereoselective formation of these cyclohex-1-ene-carbaldehyde derivatives can be explained by iminium–iminium–enamine sequential activation of the enals by catalyst **2** as outlined in Scheme 63. In the first step (cycle I), aldehyde **59** reacts with catalyst **2** to give the iminium ion intermediate. Malononitrile, or another activated methylene compound **51**, reacts as a nucleophile with this intermediate to give **A**, which is then hydrolized to yield compound **B** with regeneration of the catalyst. Then, catalyst **2** re-enters the second cycle (cycle II) to form iminium intermediate **C**, which subsequently reacts with **B** to generate an additional stereocenter (if $EWG^1 = EWG^2$) in intermediate **D**. At this stage, the final product, cyclohex-1-ene-carbaldehyde derivative **60**, which has up to three stereocenters (if $EWG^1 \neq EWG^2$), is formed from the enamine intermediate that mediates the ring-closure reaction by an intramolecular aldol reaction, followed by elimination of water.



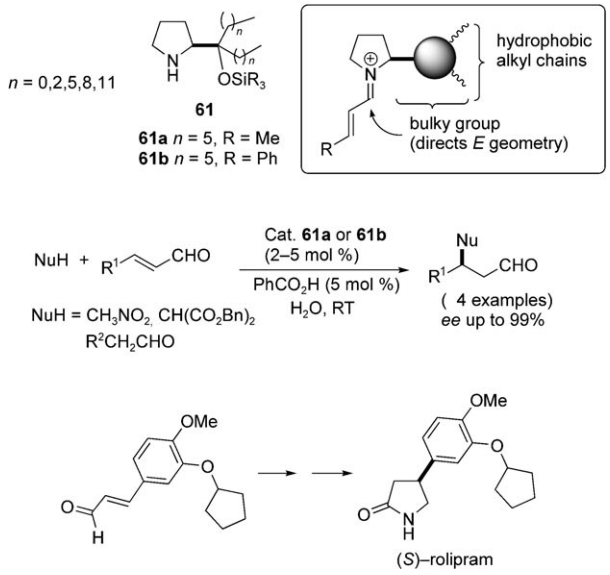
Scheme 63. Proposed mechanism for the organocatalytic multicomponent domino synthesis of cyclohex-1-ene-carbaldehydes catalyzed by **2.**

8. Reactions in Water

In the most recent decades, chemists have begun investigating the possibility of using water as solvent for organic reactions[129] because of potential benefits from industry[130] and biological implications. As for the field of asymmetric syn-

thesis, the development of water-compatible catalytic methods still remains challenging, basically because most metal catalysts are unstable toward hydrolysis.[131] Water can also interfere with organocatalysis given its capacity for disrupting H bonds and other polar interactions. Different chiral secondary amines have been shown to be viable organocatalysts in varying degrees of an aqueous environment for several C–C bond-forming processes known to proceed through activation of the substrate carbonyl by enamine formation.[132,133] In this context diarylprolinol ether derivatives have shown certain water compatibility in some enamine-based organocatalytic reactions.[20,28,67,83] However, in other enamine-based organocatalytic reactions carried out in the presence of water, diarylprolinol ethers led to less successful results. This is the case, for example, for the Michael addition of aldehydes to vinyl phosphonates catalyzed by **1** (see Scheme 8),[30b] which gives low yields and enantioselectivities when carried out in water/ethanol mixtures.

Similar results have been observed in aqueous systems using amine catalysis by formation of iminium species. Jørgensen demonstrated that epoxidations of enals can be successfully achieved in the presence of **2** in water/EtOH solutions.[122] In a similar way the **2**-catalyzed conjugate 1,4-additions of β-ketoesters to α,β-unsaturated aldehydes takes place efficiently in the presence of water as the only solvent to afford the expected adducts in high yields and enantioselectivities.[98] However, the parent addition of malonates and malononitriles appears to work sluggishly if at all.[53,128] The recently presented tandem Michael–Henry reaction by Hayashi in the presence of **1** as catalyst[88] (see Scheme 34, Section 5) constitutes another water-noncompatible example. More recently a complementary family of prolinol ether derivatives, α,α-dialkylprolinol silyl ethers **61**, has been presented as a good alternative for carrying out the conjugate addition of carbon-centered nucleophiles to enals in the presence of water (Scheme 64).[134] The concept of the catalyst design is based on the use of the prolinol ether platform owing to its excellent properties as a catalyst, together with the introduction of hydrophobic alkyl chains.[135] After optimization, catalysts **61a** and **61b** were found to be the best in promoting the conjugate addition of nitromethane, benzyl malonate, and saturated aldehydes to enals, providing high enantioselectivities. In addition the methodology was sussessfully applied to the synthesis of the *S* isomer of rolipram (Scheme 64), a type IV phosphodiesterase inhibitor, which was obtained through a conjugate addition of nitromethane to the adequate enal, followed by oxidation, esterification, and hydrogenation of the resulting adduct.



Scheme 64. Conjugate addition of carbon-centered nucleophiles to enals catalyzed by **61a** and **61b** in the presence of water.

9. Conclusion and Prospects

From the data presented in this Focus Review one can conclude that α,α-diaryl(dialkyl)prolinol ethers constitute a potent organocatalyst family which has been shown to be very general for a vast range of transformations. These include the α-, β-, γ-, and α,β-functionalization of carbonyl compounds. In addition, as an exciting full expression of their catalytic activity, these derivatives have also emerged as promising promoters of very elegant cascade processes. Moreover, new α,α-dialkylprolinol ethers have proven to be valuable catalysts in promoting Michael additions via iminium ions in water-compatible systems. During the last two years we have witnessed an increasing number of publications reporting the use of these new general organocatalysts, and for sure new contributions on their application to new reactions and new tandem processes can be anticipated.[136]

Acknowledgements

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[1] Y. Izumi, *Angew. Chem.* **1971**, *83*, 956–966; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 871–881.
[2] a) C.-H. Wong, G. Withesides, *Enzymes in Organic Chemistry*, Pergamon Press, Oxford, **1994**; b) K. Drauz, H. Waldmann, Eds. ; *Enzyme Catalysis in Organic Synthesis: A Comprehensive Handbook*; Wiley-VCH, Weinheim, **2002**, *Vols. 1–3*; c) *Catalytic Antibodies*, (Ed.: E. Keinan), Wiley-VCH, Weinheim, **2005**.
[3] a) I. Ojima, Ed. ; *Catalytic Asymmetric Synthesis*, VCH, Weinheim, **1993**; b) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**; c) *Stereoselective Synthesis* (Eds.: G. Helmchen, R.W. Hoffmann, J. Mulzer, E. Schaumann), (Houben-Weyl), Thieme, Stuttgart, **1996**; d) *Comprehensive Asymmetric Catalysis, Vols. 1–3* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; e) *Comprehensive Asymmetric Catalysis*, (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Suppl. 2; Springer, Berlin, **2004**; f) D. J. Ramón, M. Yus, *Chem. Rev.* **2006**, *106*, 2126–2208.
[4] For general reviews, see: a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840–3864; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748; b) M. Benaglia, A. Puglivi, F. Cozzi, *Chem. Rev.* **2003**, *103*, 3401–

3440; c) B. List, C. Bolm, *Adv. Synth. Catal.* **2004**, *346*, 1021–1022 (thematic issue on Organic Catalysis, nos. 9+10); d) K. N. Houk, B. List, Guest, *Acc. Chem. Res.* **2004**, *37*, 487 (thematic issue on Asymmetric Organocatalysis, no. 8); e) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; f) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH, Weinheim, **2005**; g) P. Kočovskỳ, A. V. Malkov, *Tetrahedron* **2006**, *62*, 255 (thematic issue on Organocatalysis in Organic Synthesis nos. 2+3). For a recent brief overview on the state of the art, see: h) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724. For a recent essay on organocatalysis, see: i) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44–50; *Angew. Chem. Int. Ed.* **2008**, *47*, 42–47.

[5] W. Marckwald, *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 394–354.

[6] For other amine-based catalysts, see: cinchona alcaloids: a) K. Kacprzak, J. Gawronski, *Synthesis* **2001**, 961–998; cupreines and cupreidines: b) T. Marcelli, J. H. Van Maarseven, H. Hiemstra, *Angew. Chem.* **2006**, *118*, 7658–7666; *Angew. Chem. Int. Ed.* **2006**, *45*, 7496–7504; guanidines: c) T. Ishikawa, T. Isobe, *Chem. Eur. J.* **2002**, *8*, 552–557; d) T. Ishikawa, T. Kumamoto, *Synthesis* **2006**, 737–752.

[7] For the uncovering of the enamine activation concept in asymmetric catalysis, see: a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396. For reviews, see: b) B. List, *Tetrahedron* **2002**, *58*, 5573–5590; c) B. List, *Acc. Chem. Res.* **2004**, *37*, 548–557; d) B. List, *Chem. Commun.* **2006**, 819–824.

[8] For the uncovering of the iminium activation concept in asymmetric catalysis, see: a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874–9875. For a review, see: b) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79–87.

[9] For recent reviews on tandem and/or domino reactions, see: a) *Domino Reactions in Organic Synthesis* (Eds.: L. F. Tietze, G. Brasche, K. M. Gerike), Wiley-VCH, Weinheim, **2006**; b) J.-C. Wasilke, S. J. Obreg, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001–1020; c) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628–1661; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602–1634; d) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581; e) Ch. J. Chapman, Ch. G. Frost, *Synthesis* **2007**, 1–21.

[10] For a previous review, see: C. Palomo, A. Mielgo, *Angew. Chem.* **2006**, *118*, 8042–8046; *Angew. Chem. Int. Ed.* **2006**, *45*, 7876–7880.

[11] For the first reports on the use of catalysts **1** and **2**, see: a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804–807; *Angew. Chem. Int. Ed.* **2005**, *44*, 794–797; b) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304; c) Y. Hayashi, H. Gotoh, T. Hayasi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284–4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215.

[12] For reviews on Mannich reactions, see: a) A. Ting, S. E. Schaus *Eur. J. Org. Chem.* **2007**, 5797–5815; b) M. M. B. Marques *Angew. Chem.* **2006**, *118, 356–360; Angew. Chem. Int. Ed.* **2006**, 45, 348–352; *Angew. Chem. Int. Ed.* **2006**, *45*, 348–352; c) J. A. Ma, *Angew. Chem.* **2003**, *115*, 4426–4435; *Angew. Chem. Int. Ed.* **2003**, *42*, 4290–4299; d) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102–112.

[13] For some *anti*-Mannich reactions based on metal catalysis, see: a) S. Kobayashi, H. Ishitani, M. Ueno, *J. Am. Chem. Soc.* **1998**, *120*, 431–432; b) S. Harada, S. Handa, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2005**, *117*, 4439–4442; *Angew. Chem. Int. Ed.* **2005**, *44*, 4365–4368; c) B. M. Trost, J. Jaratjaroonphong, V. Reutrakul, *J. Am. Chem. Soc.* **2006**, *128*, 2778–2779.

[14] I. Ibrahem, A. Córdova, *Chem. Commun.* **2006**, 1760–1762.

[15] H. Zhang, S. Mitsumori, N. Utsumi, M. Imai, N. García-Delgado, M. Midsuf, K. Albertshofer, P. H.-Y. Cheong, K. N. Houk, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2008**, *130*, 875–886.

[16] a) T. Kano, Y. Yamaguchi, O. Tozuda, K. Maruoka, *J. Am. Chem. Soc.* **2005**, *127*, 16408–16409; b) T. Kano, Y. Hato, K. Maruoka, *Tetrahedron Lett.* **2006**, *47*, 8467–8469.

[17] a) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337; b) A. Córdova, S.-I. Watanabe, F. Tanaka, W. Notz, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1866–1867; c) B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827–833. See also reference 12.

[18] a) Y. Chi, S. H. Gellman, *J. Am. Chem. Soc.* **2006**, *128*, 6804–6805. Recently the same authors reported a diastereoselective version of this reaction in the presence of L-proline as the catalyst and using a chiral *N,O*-acetal as the iminium precursor: 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.

[19] I. Ibrahem, G.- L. Zhao, A. Córdova, *Chem. Eur. J.* **2007**, *13*, 683–688.

[20] 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.

[21] For a case where intramolecular alkylation occurs, see: N. Vignola, B. List, *J. Am. Chem. Soc.* **2004**, *126*, 450–451.

[22] I. Ibrahem, A. Córdova, *Angew. Chem.* **2006**, *118*, 1986–1990; *Angew. Chem. Int. Ed.* **2006**, *45*, 1952–1956.

[23] For general reviews on organocatalytic conjugate additions, see: a) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701–1716; b) D. Almasi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299–365; c) J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, *14*, 2065–2092.

[24] For a review on organocatalytic conjugate additions to nitroalkenes, see: a) S. Sulzer, A. Alexakis, *Chem. Commun.* **2007**, 3123–3135; b) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894.

[25] For an application of a recyclable fluorous diphenyl prolinol silyl ether in the same reaction, see: L. Zu, H. Li, J. Wang, X. Yu, W. Wang, *Tetrahedron Lett.* **2006**, *47*, 5131–5134.

[26] P. Melchiorre, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 4151–4157.

[27] Y. Chi, S. H. Gellmann, *Org. Lett.* **2005**, *7*, 4253–4256.

[28] K. Albertshofer, R. Thayumanavan, N. Utsumi, F. Tanaka, C. F. Barbas III, *Tetrahedron Lett.* **2007**, *48*, 693–696.

[29] G.- L. Zhao, Y. Xu, H. Sundén, L. Eriksson, M. Sayah, A. Córdova, *Chem. Commun.* **2007**, 734–735.

[30] a) S. Mossé, A. Alexakis, *Org. Lett.* **2005**, *7*, 4361–4364; b) S. Sulzer-Mossé, M. Tissot, A. Alexakis, *Org. Lett.* **2007**, *9*, 3749–3752.

[31] C.- L. Cao, X.- L. Sun, J.- L. Zhou, Y. Tang, *J. Org. Chem.* **2007**, *72*, 4073–4076.

[32] For reviews on organocatalytic enantioselective α-heterofunctionalization of carbonyl compounds, see: a) G. Guillena, D. J. Ramón, *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492; b) M. Marigo, K. A. Jørgensen, *Chem. Commun.* **2006**, 2001–2011.

[33] For reviews on α-aminations of carbonyl compounds, see: a) *Modern Amination Methods* (Ed.: A. Ricci), Wiley-VCH, Weinheim, **2000**; b) C. Greck, B. Drouillat, C. Thomassingy, *Eur. J. Org. Chem.* **2004**, 1377–1385.

[34] For recent advances in catalytic α-aminations and α-oxygenations of carbonyl compounds, see: J. M. Janey, *Angew. Chem.* **2005**, *117*, 4364–4372; *Angew. Chem. Int. Ed.* **2005**, *44*, 4292–4300.

[35] B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656–5657.

[36] 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.

[37] For a review on proline-catalyzed α-aminations, see: R. O. Duthaler, *Angew. Chem.* **2003**, *115*, 1005–1008; *Angew. Chem. Int. Ed.* **2003**, *42*, 975–978.

[38] For reviews on nitroso compounds, see: a) P. Zuman, P. Shah, *Chem. Rev.* **1994**, *94*, 1621–1641; b) L. Joghyuk, L. Chen, A. H. West, G. B. Richter-Addo, *Chem. Rev.* **2002**, *102*, 1019–1065; c) H.

Yamamoto, M. Kawasaki, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 595–607. Also see Ref. [34].

[39] For reviews, see: a) P. Merino, T. Tejero, *Angew. Chem.* **2004**, *116*, 3055–3058; *Angew. Chem. Int. Ed.* **2004**, *43*, 2995–2997; b) B. Plietker, *Tetrahedron: Asymmetry* **2005**, *16*, 3453–3459; c) H. Yamamoto, N. Momiyama, *Chem. Commun.* **2005**, 3514–3525.

[40] a) H.- M. Guo, L. Cheng, L.-F. Cun, L.-Z. Ghong, A.-Q. Mi, Y.-Z. Jiang, *Chem. Commun.* **2006**, 429–431; b) T. Kano, M. Ueda, J. Takai, K. Maruoka, *J. Am. Chem. Soc.* **2006**, *128*, 6046–6047.

[41] C. Palomo, S. Vera, I. Velilla, A. Mielgo, E. Gómez-Bengoa, *Angew. Chem.* **2007**, *119*, 8200–8202; *Angew. Chem. Int. Ed.* **2007**, 4636, 8054–8056.

[42] I. Ibrahem, G.- L. Zhao, H. Sundén, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 4659–4663.

[43] For reviews on asymmetric α-fluorination, see: a) H. Ibrahem, A. Togni, *Chem. Commun.* **2004**, 1147–1155; b) G. K. S. Prakash, P. Beier, *Angew. Chem.* **2006**, *118*, 2228–2230; *Angew. Chem. Int. Ed.* **2006**, *45*, 2172–2174; c) P. M. Pihko, *Angew. Chem.* **2006**, *118*, 558–561; *Angew. Chem. Int. Ed.* **2006**, *45*, 544–547.

[44] M. Marigo, D. Fielenbach, A. Braunton, A. Kjæsgaard, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 3769–3772; *Angew. Chem. Int. Ed.* **2005**, *44*, 3703–3706.

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

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

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

[48] S. Bertelsen, N. Halland, S. Bachmann, M. Marigo, A. Braunton, K. A. Jørgensen, *Chem. Commun.* **2005**, 4821–4823.

[49] W. Wang, H. Li, J. Wang, L. Liao, *Tetrahedron Lett.* **2004**, *45*, 8229–8231.

[50] A. Armstrong, L. Challinor, J. H. Moir, *Angew. Chem.* **2007**, *119*, 5465–5468; *Angew. Chem. Int. Ed.* **2007**, *46*, 5369–5372.

[51] a) J. N. Fitzner, R. G. Shea, J. E. Fankhauser, P. B. Hopkins, *J. Org. Chem.* **1985**, *50*, 417–419; b) R. G. Shea, J. N. Fitzner, J. E. Fankhauser, A. Spaltenstein, P. A. Carpino, R. M. Peevey, D. V. Pratt, B. J. Tenge, P. B. Hopkins, *J. Org. Chem.* **1986**, *51*, 5243–5252.

[52] 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. For an independent report for the same type of reaction, see: b) H. Sundén, R. Rios, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 7865–7869. For a preliminary work on this reaction with other pyrrolidine derivatives leading to almost racemic products, see: c) W. Wang, J. Wang, H. Li, *Org. Lett.* **2004**, *6*, 2817–2820.

[53] 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.

[54] D. Enders, M. H. Bonten, G. Raabe, *Synlett* **2007**, 885–888.

[55] a) S. Karlsson, H.-E. Högberg, *Tetrahedron: Asymmetry* **2002**, *13*, 923–926; b) S. Karlsson, H.-E. Högberg, *Eur. J. Org. Chem.* **2003**, 2782–2791.

[56] J.-W. Xie, L. Yue, D. Xue, X.- L. Ma, Y.-Ch. Chen, Y. Wu, J. Zhu, J.-G. Deng, *Chem. Commun.* **2006**, 1563–1565.

[57] a) K. Mikami, K. Terada in *Comprehensive Asymmetric Catalysis*, *Vol. III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yammamoto), Springer, Berlin, **1999**, pp. 1143–1174; b) K. Mikami, M. Shimizu, *Chem. Rev.* **1992**, *92*, 1021; c) D. J. Berrisford, C. Bolm, *Angew. Chem.* **1995**, *107*, 1862–1864; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1717–1719; d) L. C. Dias, *Curr. Org. Chem.* **2000**, *4*, 305–342.

[58] H. Gotoh, R. Masui, H. Ogino, M. Shoji, Y. Hayashi, *Angew. Chem.* **2006**, *118*, 7007–7010; *Angew. Chem. Int. Ed.* **2006**, *45*, 6853–6856.

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

[60] For recent reviews on enatioselective Diels–Alder reactions, see: a) D. A. Evans, J. S. Johnson in *Comprehensive Asymmetric Catalysis*, (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, New York, **1999**; *Vol. III*, pp. 1177; b) J. E. Corey, *Angew. Chem.* **2002**, *114*, 1724–1741; *Angew. Chem. Int. Ed.* **2002**, *41*, 1650–1667; c) Y. Hayashi, Catalytic Asymmetric Diels–Alder Reactions in *Cycloaddition Reactions in Organic Synthesis* (Eds.: S. Kobayashi, K. A. Jørgensen), Wiley-VCH, Weinheim, Germany, **2002**, pp. 5–55.

[61] H. Gotoh, Y. Hayashi, *Org. Lett.* **2007**, *9*, 2859–2862.

[62] 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.

[63] For reviews, see: a) H. Pellisier, *Tetrahedron* **2007**, *63*, 3235–3285; b) I. Coldham, R. Hufton, *Chem. Rev.* **2005**, *105*, 2765–2810; c) K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863–910.

[64] W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874–9875.

[65] S. S. Chow, M. Nevaleinen, C. A. Evans, C. W. Johannes, *Tetrahedron Lett.* **2007**, *48*, 277–280.

[66] R. Rios, I. Ibrahem, J. Vesely, G.- L. Zhao, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 5701–5705.

[67] a) J. L. Vicario, S. Reboredo, D. Badía, L. Carrillo, *Angew. Chem.* **2007**, *119*, 5260–5262; *Angew. Chem. Int. Ed.* **2007**, *46*, 5168–5170. For [3+2] cycloadditions of azomethine imines, see: b) W. Chen, X.-H. Yuan, R. Li, W. Du, Y. Wu, L.-S. Ding, Y.-C. Chen, *Adv. Synth. Catal.* **2006**, *348*, 1818–1822.

[68] For reviews on cycloadditions with azomethine ylides, see: a) G. Pandey, P. Banarjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484–4517; b) S. Husinec, V. Savic, *Tetrahedron: Asymmetry* **2005**, *16*, 2047–2061; c) C. Nájera, J. M. Sansano, *Angew. Chem.* **2005**, *117*, 6428–6432; *Angew. Chem. Int. Ed.* **2005**, *44*, 6272–6276.

[69] I. Ibrahem, R. Rios, J. Vesely, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 6252–6257.

[70] For general information, see: a) P. Pelmuter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, **1992**. For reviews, see: b) M. Liu, M. P. Sibi, *Tetrahedron* **2002**, *58*, 7991–8035; c) J. L. Vicario, L. Badía, L. Carrillo, J. Etxebarria, E. Reyes, N. Ruiz, *Org. Prep. Proced. Int.* **2005**, *37*, 513–538; d) L.-W. Xu, C.-G. Xia *Eur. J. Org. Chem.* **2005**, 633–639.

[71] I. Ibrahem, R. Rios, J. Vesely, G.- L. Zhao, A. Córdova, *Chem. Commun.* **2007**, 849–851.

[72] C. Palomo, M. Oiarbide, R. Halder, M. Kelso, E. Gómez-Bengoa, J. M. García, *J. Am. Chem. Soc.* **2004**, *126*, 9188–9189.

[73] Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 9328–9329.

[74] J. Vesely, I. Ibrahem, R. Rios, G.- L. Zhao, Y. Xu, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 2193–2198.

[75] P. Dinér, M. Nielsen, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 2029–2033; *Angew. Chem. Int. Ed.* **2007**, *46*, 1983–1987.

[76] For more information on this subject, see: a) I. C. Stewart, R. G. Bergman, F. D. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 8696–8697; b) P. B. Kisanga, P. Ilankumaran, B. M. Fetterly, J. G. Verkade, *J. Org. Chem.* **2002**, *67*, 3555–3560.

[77] For the conjugate addition of (6*S*)-methyl δ-lactol to alkylidene-, arylidene-, and heteroarylidene-malonate derivatives, see: a) D. J. Buchanan, D. J. Dixon, F. A. Hernandez-Juan, *Org. Lett.* **2004**, *6*, 1357–1360. For the conjugate addition of (6*S*)-methyl δ-lactol to nitroalkenes, see: b) N. J. Adderley, D. J. Buchanan, D. J. Dixon, D. I. Lainé, *Angew. Chem.* **2003**, *115*, 4373–4376; *Angew. Chem. Int. Ed.* **2003**, *42*, 4241–4244; c) D. J. Buchanan, D. J. Dixon, F. A. Hernandez-Juan, *Org. Biomol. Chem.* **2004**, *2*, 2932–2934; d) D. J. Buchanan, D. J. Dixon, M. S. Scott, D. I. Lainé, *Tetrahedron: Asymmetry* **2004**, *15*, 195–197. For the oxa-Michael addition of (−)-*N*-formylnorephedrine to nitroalkenes, see: e) D. Enders, A. Haertwig, G. Raabe, J. Runsink, *Angew. Chem.* **1996**, *108*, 2540–2542; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2388–2390; f) D. Enders, A. Haertwig, G. Raabe, J. Runsink, *Eur. J. Org. Chem.* **1998**, 1771–1792; g) D. Enders, A. Haertwig, J. Runsink, *Eur. J. Org. Chem.* **1998**, 1793–1802.

[78] D. A. Evans, J. A. Gauchet-Prunet, *J. Org. Chem.* **1993**, *58*, 2446–2453.

[79] Ch. D. Vanderwal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 14724–14725.

[80] S. Bertelsen, P. Dinér, R. Lyng Johansen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 1536–1537.
[81] For a recent review on sulfa-Michael reactions, see: D. Enders, K. Lüttgen, A. A. Narine, *Synthesis* **2007**, *7*, 959–980.
[82] M. Marigo, T. Schulte, J. Franzén, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 15710–15711.
[83] T. Ishino, T. Oriyama, *Chem. Lett.* **2007**, *36*, 550–551.
[84] For a general review on phospha-Michael reactions, see: D. Enders, A. Saint-Dizier, M.-I. Lannou, A. Lenzen, *Eur. J. Org. Chem.* **2006**, 29–49.
[85] For more information on this topic, see: G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, A. Mazzanti, L. Sambri, P. Melchiorre, *Chem. Commun.* **2007**, 722–724.
[86] A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Melchiorre, *Angew. Chem.* **2007**, *119*, 4588–4590; *Angew. Chem. Int. Ed.* **2007**, *46*, 4504–4506.
[87] 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.
[88] S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973–12980.
[89] For an example where a dienamine acts as nucleophile forming a C–C bond at the α-position, see: N. Utsumi, H. Zhang, F. Tanaka, C. F. Barbas III, *Angew. Chem.* **2007**, *119*, 1910–1912; *Angew. Chem. Int. Ed.* **2007**, *46*, 1878–1880.
[90] A. Carlone, M. Marigo, C. North, A. Landa, A. Jørgensen, *Chem. Commun.* **2006**, 4928–4930.
[91] X. Linghu, J. J. Kennedy-Smith, F. D. Toste, *Angew. Chem.* **2007**, *119*, 7815–7817; *Angew. Chem. Int. Ed.* **2007**, *46*, 7671–7673.
[92] X. Ma, D. R. Gang, *Nat. Prod. Rep.* **2004**, *21*, 752–772.
[93] M. Marigo, S. Bertelsen, A. Landa, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 5475–5479.
[94] Y. Hayashi, T. Okano, S. Aratake, D. Hazelard, *Angew. Chem.* **2007**, *119*, 5010–5013; *Angew. Chem. Int. Ed.* **2007**, *46*, 4922–4925.
[95] 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.
[96] R. Ríos, I. Ibrahem, J. Vesely, H. Sundén, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 8695–8699.
[97] 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.
[98] G.- L. Zhao, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 7417–7421.
[99] For reviews on Hantzsch ester, see: a) H. Adolfsson, *Angew. Chem.* **2005**, *117*, 3404–3406; *Angew. Chem. Int. Ed.* **2005**, *44*, 3340–3342; b) S.-Li You, *Chem. Asian J.* **2007**, *2*, 820–827; c) S. J. Connon, *Org. Biomol. Chem.* **2007**, *5*, 3407–3417.
[100] For selected reviews on the synthesis of cyclopentanes, see: a) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49–92; b) C. E. Masse, J. S. Panek, *Chem. Rev.* **1995**, *95*, 1293–1316.
[101] 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.
[102] D. Enders, A. A. Narine, T. R. Benninghaus, G. Raabe, *Synlett* **2007**, 1667–1670.
[103] 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.
[104] For recent reviews, see: a) W. A. Donaldson, *Tetrahedron* **2001**, 57, 8589–8627; b) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977–1050; c) J. M. Fox, N. Yang, *Curr. Org. Chem.* **2005**, *9*, 719–732; d) A. Reichelt, S. F. Martin, *Acc. Chem. Res.* **2006**, *39*, 433–442.
[105] a) R. Ríos, H. Sundén, J. Veseley, G.- L. Zhao, P. Dziedzic, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 1028–1032; b) H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886–10894.
[106] For reviews of carbenes in asymmetric organocatalysis, see: a) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534–541; b) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 3046–3058; *Angew. Chem. Int. Ed.* **2007**, *46*, 2988–3000.
[107] G.-L. Zhao, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 5976–5980.
[108] For another contribution on organocatalytic aziridination of α,β-unsturated aldehydes promoted by **1**, see: 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.
[109] R. Rios, J. Vesely, H. Sundén, I. Ibrahem, G.-L. Zhao, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 5835–5839.
[110] For an overview and examples, see: a) G. Zeni, R. C. Larok, *Chem. Rev.* **2004**, *104*, 2285–2310; b) K. C. Nicolaou, J. A. Pfefferkon, A. J. Roecker, G.-Q. Cao, S. Barluenga, H. J. Mitchell, *J. Am. Chem. Soc.* **2000**, *122*, 9939–9953; c) K. C. Nicolaou, J. A. Pfefferkon, H. J. Mitchell, A. J. Roecker, S. Barluenga, G.-Q. Cao, R. L. Affleck, J. E. Lillig, *J. Am. Chem. Soc.* **2000**, *122*, 9954–9967; d) K. C. Nicolaou, J. A. Pfefferkon, S. Barluenga, H. J. Mitchell, A. J. Roecker, G.-Q. Cao, *J. Am. Chem. Soc.* **2000**, *122*, 9968–9976.
[111] T. Govender, L. Hojabri, F. M. Moghaddam, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2006**, *17*, 1763–1767.
[112] a) H. Sundén, I. Ibrahem, G.- L. Zhao, L. Eriksson, A. Córdova, *Chem. Eur. J.* **2007**, *13*, 574–581. For another contribution with α,β-unsaturated cyclic ketones, see: b) R. Rios, H. Sundén, I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 2181–2184.
[113] H. Li, J. Wang, T. E-Nunu, L. Zu, W. Jiang, S. Wei, W. Wang, *Chem. Commun.* **2007**, 507–509.
[114] H. Sundén, R. Rios, I. Ibrahem, G.- L. Zhao, L. Eriksson, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 827–832.
[115] H. Li, J. Wang, H. Xie, L. Zu, W. Jiang, E. N. Duesler, W. Wang, *Org. Lett.* **2007**, *9*, 965–968.
[116] S. Brandau, E. Maerten, A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 14986–14991.
[117] 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.
[118] R. Rios, H. Sundén, I. Ibrahem, G.- L. Zhao, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 8679–8682.
[119] H. Li, L. Zu, H. Xie, J. Wang, W. Jiang, W. Wang, *Org. Lett.* **2007**, *9*, 1833–1835.
[120] a) G. J. Smith, *Synthesis* **1984**, *8*, 629–656; b) P. Besse, H. Veschambre, *Tetrahedron* **1994**, *50*, 8885–8927.
[121] a) *Aziridines and Epoxides in Organic Synthesis* (Ed.: A. K. Yudin), Wiley-VCH, Weinheim, **2006**; b) T. Katutsi in *Comprehensive Asymmetric Catalysis*, *Vol. II* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 621–693; c) A. Armstrong, *Angew. Chem.* **2004**, *116*, 1484–1486; *Angew. Chem. Int. Ed.* **2004**, *43*, 1460–1462.
[122] a) M. Marigo, J. Franzén, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964–6965; b) W. Zhuang, M. Marigo, K. A. Jørgensen, *Org. Biomol. Chem.* **2005**, *3*, 3883–3885.
[123] a) H. Sundén, I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 99–103; b) G.- L. Zhao, I. Ibrahem, H. Sundén, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 1210–1224. For a non-enamine-based epoxidation of enones promoted by prolinol derivatives, see: c) A. Lattanzi, *Org. Lett.* **2005**, *7*, 2579–2582; d) A. Lattanzi, *Adv. Synth. Catal.* **2006**, *348*, 339–346; e) A. Lattanzi, A. Russo, *Tetrahedron* **2006**, *62*, 12264–12269; f) Y. Li, X. Liu, Y. Yang, G. Zhao, *J. Org. Chem.* **2007**, *72*, 288–291.
[124] G.- L. Zhao, P. Dziedzic, I. Ibrahem, A. Córdova, *Synlett* **2006**, 3521–3524.
[125] For reviews, see: a) E. N. Jacobsen in *Comprehensive Asymmetric Catalysis*, *Vol. II* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 607–618; b) J. B. Sweeney, *Chem. Soc. Rev.* **2002**, *31*, 247–258; c) M. McCoull, F. A. Davis, *Synthesis* **2000**, 1347–1365. See also Ref. [121a].
[126] D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, 441, 861–863.
[127] 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.

[128] A. Carlone, S. Cabrera, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 1119–1122; *Angew. Chem. Int. Ed.* **2007**, *46*, 1101–1104.

[129] General reviews: a) *Organic Synthesis in Water* (Ed.: P. A. Grieco), Blackie Academic & Profesional, London, **1998**; b) U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751–2772; c) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095–3165; d) C. J. Li, L. Cheng, *Chem. Soc. Rev.* **2006**, *35*, 68–82.

[130] For a critical recent essay, see: D. G. Blackmond, A. Armstrong, V. Coombe, A. Wells, *Angew. Chem.* **2007**, *119*, 3872–3874; *Angew. Chem. Int. Ed.* **2007**, *46*, 3798–3800.

[131] For successful metal catalysis in aqueous systems, see: a) *Aqueous-Phase Organometallic Catalysis* (Eds.: B. Cornils, W. A. Herrman), WILEY-VCH, Weinheim, **1998**; b) S. Kobayashi, C. Ogawa, *Chem. Eur. J.* **2006**, *12*, 5954–5960; c) S. Kobayashi, M. Sugiura, H. Kitagawa, W. W.- L- Lam, *Chem. Rev.* **2002**, *102*, 2227–2302; d) D. Sinou, *Adv. Synth. Catal.* **2002**, *344*, 221–237.

[132] Aldol reactions: a) T. J. Dickerson, K. D. Janda, *J. Am. Chem. Soc.* **2002**, *124*, 3220–3221; 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) P. Dziedzic, W. Zou, J. Hafren, A. Cordova, *Org. Biomol. Chem.* **2006**, *4*, 38–40; d) P. M. Pihko, K. M. Laurikainen; A. Usano, A. I. Nyberg, J. A. Kaavi, *Tetrahedron* **2006**, *62*, 317–328; A. Usano, A. I. Nyberg, J. A. Kaavi, *Tetrahedron* **2006**, *62*, 317–328; e) Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya, M. Shoji, *Angew. Chem.* **2006**, *118*, 5653–5655; *Angew. Chem. Int. Ed.* **2006**, *45*, 5527–5529; f) D. Font, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2006**, *8*, 4653–4655; g) Y. Wu, Y. Zhang, M. Yu, G. Zhao, S. Wang, *Org. Lett.* **2006**, *8*, 4417–4420; h) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas, *J. Am. Chem. Soc.* **2006**, *128*, 734–735. Mannich reaction: i) L. Cheng, X. Wu, Y. Lu, *Org. Biomol. Chem.* **2007**, *5*, 1018–1020. Michael reactions: j) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967; k) L. Zu, J. Wang, H. Li, W. Wang, *Org. Lett.* **2006**, *8*, 3077–3079; l) Z.-Y. Yan, Y.-N. Niu, H.- L. Wei, L.-Y. Wu, Y.-B. Zhao, Y.- M. Liang, *Tetrahedron: Asymmetry* **2007**, *17*, 3288–3293; m) S. Luo, X. Mi, S. Liu, H. Xu, J.-P. Cheng, *Chem. Commun.* **2006**, 3687–3689; n) Y.- J. Cao, Y.-Y. Lai, X. Wang, Y.- J. Li, W.- J. Xiao, *Tetrahedron Lett.* **2007**, *48*, 21–24; o) V. Singh, V. K. Singh, *Org. Lett.* **2007**, *9*, 1117–1119.

[133] For a recent exchange discussion on enamine-based organocatalysis carried out in systems containing water, see: a) A. P. Brogan, T. J. Dikerson, K. D. Janda, *Angew. Chem.* **2006**, *118*, 8278–8280; *Angew. Chem. Int. Ed.* **2006**, *45*, 8100–8102; b) Y. Hayashi, *Angew. Chem.* **2006**, *118*, 8281–8282; *Angew. Chem. Int. Ed.* **2006**, *45*, 8103–8104; See also Ref. [127].

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

[135] For the favorable role played by hydrophobic alkyl chains in water-compatible enamine-mediated catalysis, see Ref. [132e,h,j].

[136] After submission and manuscript revision the following papers appeared. For a review on enamine catalysis: a) A. Erkkilä, I. Majander, P. M. Phiko, *Chem. Rev.* **2007**, *107*, 5416–5470. For a review on iminium catalysis: b) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569. For an intramolecular nitrogen-based conjugate addition: c) S. Fustero, D. Jiménez, J. Moscardó, S- Catalán, C. del Pozo, *Org. Lett.* **2007**, *9*, 5283–5286. For β-amination and selective diamination of α,β-unsaturated aldehydes, see: d) H. Jiang, J. B. Nielsen, M. Nielsen, K. A. Jørgensen, *Chem. Eur. J.* **2007**, *13*, 9068–9075. For the β-phosphonylation of enals, see: e) E. Maerten, S. Cabrera, A. Kjaesgaard, K. A. Jørgensen, *J. Org. Chem.* **2007**, *72*, 8893–8903. For the Michael addition of nitroalkanes to enals, see: f) H. Gotoh, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2007**, *9*, 5307–5309; g) L. Zu, H. Xie, H. Li, J. Wang, W. Wang, *Adv. Synth. Catal.* **2007**, *349*, 2660–2664; h) Y. Wang, P. Li, X. Liang, T. Y. Zhang, J. Ye, *Chem. Commun.* **2008**, 1232–1234. For the conjugate addition of aldehydes to nitroalkenes in water, see: i) S. Zhu, S. Yu, D. Ma, *Angew. Chem.* **2008**, *120*, 555–558; *Angew. Chem. Int. Ed.* **2008**, *47*, 545–548. For an oxidative dearylation of *p*-substituted phenols followed by an intramolecular Michael addition, see: j) N. T. Vo, R. D. M. Pace, F. O'Hara, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 404–405. For domino thia-Michael aldol reactions, see: k) G.- L. Zhao, J. Vesely, R. Rios, I. Ibrahem, H. Sundén, A. Córdova, *Adv. Synth. Catal.* **2008**, *350*, 237–242. For a domino Michael/Michael/aldol condensation sequence, see: l) D. Enders, M. R. M. Hüttl, G. Raabe, J. W. Bats, *Adv. Synth. Catal.* **2008**, *350*, 267–279. For a direct crossed-aldol reaction of acetaldehyde, see: m) Y. Hayashi, T. Itoh, S. Aratake, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 2112–2114; *Angew. Chem. Int. Ed.* **2008**, *47*, 2082–2084. For a formal aza-[3+3] cycloaddition reaction, see: n) Y. Hayashi, H. Gotoh, R. Masui, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 4076–4079; *Angew. Chem. Int. Ed.* **2008**, *47*, 4012–4015. For a cascade sequence initiated by the 1,4-addition of 2-hydroxy-1,4-napthtoquinones to enals to afford pyranonaphtoquinones and β-lapachones, see: o) M. Rueping, E. Sugiono, E. Merino, *Angew. Chem.* **2008**, *120*, 3089–3092; *Angew. Chem. Int. Ed.* **2008**, *47*, 3046–3049.For a formal aza [3+3] cycloaddition reaction for the enantioselective formation of enantioenriched piperidines: p) Y. Hayashi, H. Gotoh, R. Masui, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 4076-4079; *Angew. Chem. Int. Ed.* **2008**, *47*, 4012-4015. For an organocatalytic enamine-iminium-enamine sequence involving cyanoacrylates: q) O. Penon, A. Carlone, A. Mazzanti, M. Locatelli, L. Sambri, G. Bartoli, P. Melchiorre, *Chem. Eur. J.* **2008**, DOI: 10.1002/chem.200800440. For one-pot catalytic asymmetric cascade synthesis of cycloheptane derivatives: r) J. Vesely, R. Rios, I. Ibrahem, G.-L. Zhao, L. Erikson, A. Córdova, *Chem. Eur. J.* **2008**, DOI: 10.1002/chem.200701918. For an organocatalytic double Michael reaction of 7-oxohept-2-enoates and nytrostyrene: s) B.-C. Hong, R. Y. Nimje, M.-F. Wu, A. A. Sadani, *Eur. J. Org. Chem.* **2008**, 1449-1457. For conjugate additions of thioesters to enals: t) D. A. Alonso, S. Kitagaki, N. Utsumi, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2008**, DOI: 10.1002/anie.200801088. For asymmetric Michael reaction of acetaldehyde to nitroalkenes: u) P. García-García, A. Ladépêche, R. Halder, B. List, *Angew. Chem. Int. Ed.* **2008**, DOI: 10.1002/anie.200800847. v) Y. Hayashi, T. Itoh, M. Ohkube, H. Ishikawa, *Angew. Chem. Int. Ed.* **2008**, DOI: 10.1002/anie.200801130. For an organocatalytic one-pot synthesis of substituted 1,4-dihydropyridines: w) P. T. Franke, R.-L. Johansen, S. Bertelsen, K. A. Jørgensen, *Chem. Asian J.* **2008**, 3, 216-264. For the Michael addition of aldehydes to nitroethylene: x) Y. Chi, L. Guo, N. A. Kopf, S. H. Gellman, *J. Am. Chem. Soc.* **2008**, *130*, 5608-5609. For the Michael addition of malonates to enals in water: y) A. Ma, S. Zhu, D. Ma, *Tetrahedron Lett.* **2008**, *49*, 3075-3077. For a general review on organocatalysis: z) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 2-26; *Angew. Chem. Int. Ed.* **2008**, *47*, 2-25.

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