Chiral amines as organocatalysts for asymmetric conjugate addition to nitroolefins and vinyl sulfones *via* enamine activation

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Over the last decade the potential of organocatalysis has successfully been demonstrated. In particular, chiral amines such as pyrrolidine analogues have emerged as a broadly applicable class of organocatalyst for asymmetric conjugate addition *via* enamine activation. This Feature Article documents the development of these catalysts, emphasizing the design and mechanistic features that supply high selectivity in asymmetric Michael reactions.

Introduction and background

Besides transition metal complexes and enzymes, organocatalysis has recently emerged as a new field in asymmetric synthesis.[1,2] The efficiency and the scope of organocatalysis, and particularly aminocatalysis, have been broadly established. Covalently bonded aminocatalysts operate through two mechanisms by converting the carbonyl substrates either into activated nucleophiles (enamine intermediates) or electrophiles (iminium intermediates). In iminium catalysis,[3] the addition of the amine catalyst to the carbonyl substrate generates an iminium ion as the active species, with lowered LUMO energy, which can react with a nucleophile; whereas in enamine catalysis,[4] the deprotonation of the iminium ion provides the enamine nucleophilic intermediate, with increased HOMO energy, which can attack an electrophile (Scheme 1).[5,6]

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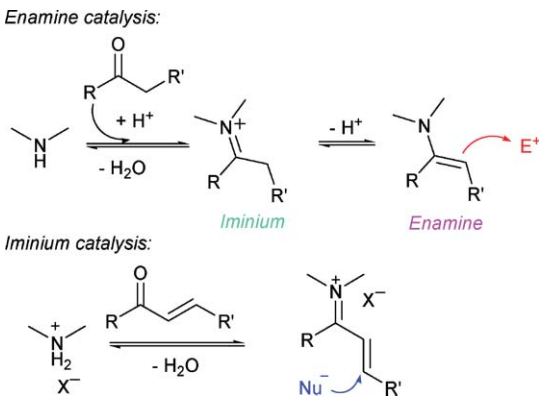
Despite the novelty of the word, organocatalysis is an old story.[7] The first asymmetric enamine catalysis was developed in the 1970s by Wiechert and co-workers, and Hajos and Parrish for the intramolecular aldol reaction catalyzed by L-proline. Surprisingly, this process was not exploited until lately. Inspired by their work on Class I aldolase enzymes[8] and



Scheme 1 Enamine and iminium catalysis.

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Sarah Sulzer-Mossé, born in Montpellier (France) in 1977, studied chemistry at the High School of Chemistry in Lyon (CPE Lyon), and completed her diploma thesis in organic chemistry at the Claude Bernard University, Lyon with Pr. M. A. Ciufolini. After a one year experience at Firmenich SA (Geneva, Switzerland), she started her PhD in 2003 under the supervision of Pr. A. Alexakis at the University of Geneva, Switzerland. Her research interests include the development of new methods in asymmetric organocatalysis, especially the organocatalyzed Michael addition of carbonyl compounds.

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Alexandre Alexakis was born in Alexandria in 1949. He graduated from Paris VI University in 1970 and received his PhD in 1975. After a postdoctoral stay at Johns Hopkins University, he joined the CNRS at Pierre et Marie Curie University in 1977, being appointed Directeur de Recherche in 1985. In 1994, he was awarded the Silver Medal of the CNRS. In 1996, he moved from the CNRS to Pierre et Marie Curie University as a full Professor (1st class), then to the University of Geneva in 1998. In 2002, he was awarded the Novartis Lectureship Award. His research focuses on asymmetric synthesis and methodologies, using both metal catalysts, particularly copper reagents, and non-metallic catalysts (organocatalysis).

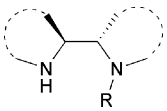


Fig. 1 Diamine models as organocatalysts for asymmetric conjugate addition.

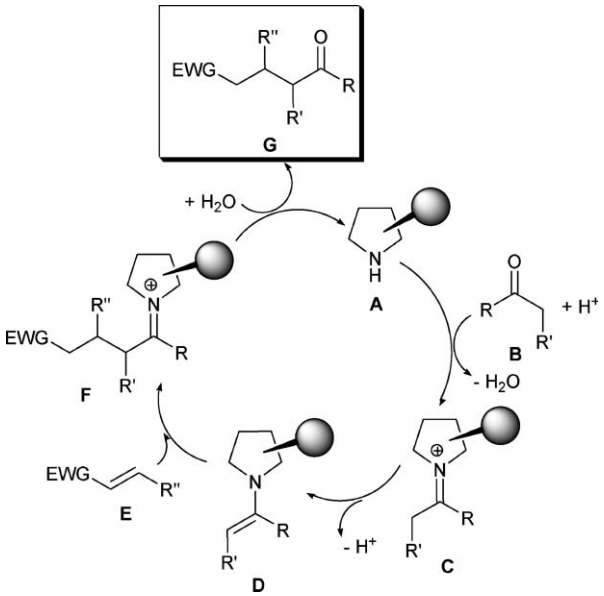
following the first example of an asymmetric aldol reaction catalyzed by heterobimetallic complexes,[9] List and Barbas *et al.* reported pioneering studies in 2000 on the intermolecular aldol reaction and pointed out the rediscovery of enamine catalysis.[10] In the same year, the first highly enantioselective example of iminium catalysis for the Diels–Alder reaction was described by MacMillan.[11] The remarkable selectivity of these reactions prompted further research activity in organocatalysis. Thus, our laboratory was interested in aminocatalysis and especially enamine catalysis using bicyclic five- and six-membered ring diamines (Fig. 1) for asymmetric conjugate addition, which represents one of the most important C–C bond forming reactions in organic chemistry.[12]

Enantiopure vicinal diamines are of great importance in organic chemistry because of their presence in many biological active compounds and their use as versatile chiral ligands or auxiliaries in asymmetric synthesis.[13] In the course of our studies on C_2-symmetrical chiral diamines,[14] we have recently disclosed a new asymmetric synthesis of optically pure 2,2′-bipyrrolidine,[15] which can also be easily obtained from photodimerization of the pyrrolidine followed by a resolution with tartaric acid.[16] Due to its pyrrolidine backbone, this chiral secondary diamine can be compared to L-proline. Consequently, following the pioneering findings of L-proline catalyzed enantioselective conjugate addition of ketones to nitroolefins,[17] we decided to study bipyrrolidine derivatives as organocatalysts for asymmetric Michael reactions.

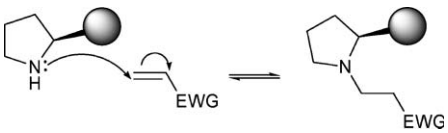
In this Feature Article, we will focus on our contributions to enamine catalysis for asymmetric intermolecular conjugate addition while including examples from other groups.[18] Therefore, we will give a short overview on our research aimed at the synthesis of 2,2′-bipyrrolidine derivatives and their applications in the enantioselective Michael reaction of aldehydes and ketones to nitroolefins and vinyl sulfones. Furthermore, we will discuss the benefits of microwave (MW) activation in these organocatalytic reactions. Likewise, we will examine 3,3′-bimorpholine derivatives as a new class of organocatalyst for asymmetric conjugate addition of aldehydes to the latter Michael acceptors.

Mechanistic insights

Small chiral amines may catalyze the asymmetric conjugate addition of ketones and aldehydes to Michael acceptors by transforming the carbonyl group into an enamine intermediate. The mechanism is outlined in Scheme 2. Firstly, an iminium ion **C** is generated by the reversible reaction between a chiral amine catalyst **A** and a carbonyl compound **B**; **C** can be more easily deprotonated to form the enamine nucleophilic intermediate **D**, owing to the increase in C–H acidity. This carbanion equivalent, **D**, can react with the electron deficient olefin **E** in order to create the new C–C bond. The subsequent



Scheme 2 Enamine catalysis in asymmetric conjugate addition of aldehydes and ketones.



Scheme 3 Catalyst's trapping.

hydrolysis of the α-modified iminium ion **F** affords the Michael adduct **G** and restores the aminocatalyst **A**, which is suitable for a new catalytic cycle.

This cycle could be limited by the availability of the amine catalyst which could be trapped by the electrophilic substrate (Scheme 3). Consequently, the reversibility of this trapping is crucial for the occurrence of the desired Michael reaction.

The selectivity of the intermolecular conjugate addition could be explained in terms of the potential electronic or steric transition states (Fig. 2 and 3). The geometry of the enamine, *E* or *Z*, would essentially be determined by the catalyst structure. According to steric hindrance, the thermodynamically favorable *E*-enamine, coming from either aldehyde or ketone, would mainly be formed unless other specific bonding interactions would favor the *Z*-enamine. Besides controlling the geometry of the enamine, the chiral substituent on the catalyst framework governs the shift of the equilibrium between the enamine

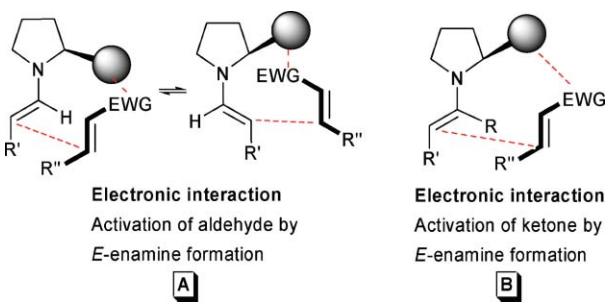


Fig. 2 Electronic transition states.

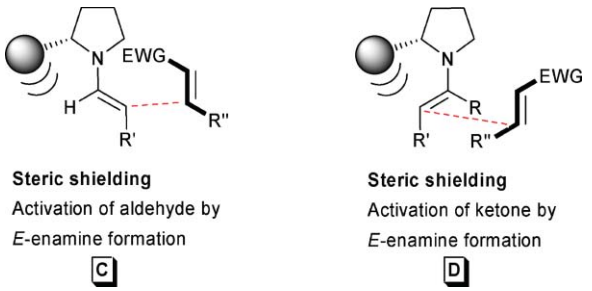


Fig. 3 Steric shielding transition states.

rotamers, which therefore influences the facial selectivity. The relative size of the two sides of the enamine depends on the carbonyl substrates. The smallest group, hydrogen for aldehydes, leads to the formation of the relatively more stable *Re*-rotamer; whereas in the case of ketones, the less hindered moiety is the double bond which gives preferentially the *Si*-rotamer as long as other interactions are not involved.

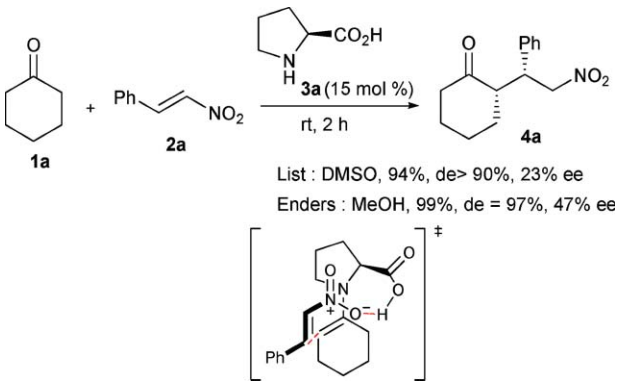
Finally, the nucleophilic *E*-enamine may attack the Michael acceptor *via* an acyclic synclinal transition state[19] through two different pathways. Hence, the face-selectivity is determined by electronic or steric interactions as shown respectively in Fig. 2 and 3. In both aldehyde and ketone cases, as illustrated in Fig. 2 (**A** and **B**), electronic interactions would be rationalized by hydrogen bonding in L-proline, tetrazole or thiourea catalysts. Consequently, the conjugate addition to the Michael acceptor would arise from the same face as the chiral substituent (Fig. 2 **A** and **B**). Actually, stabilizing H-bonding in transition state Fig. 2 **B** could counterbalance repulsive steric interactions and could force the *E*-enamine to adopt the apparently disfavored *anti*-enamine conformation, namely the *Re*-rotamer (Fig. 2 **B**).

On the other hand, steric shielding could be involved in the determination of the facial selectivity. Indeed, the bulky group on the catalyst framework could prevent the H-bonding interaction, forcing the attack from the opposite side to the chiral substituent, as depicted in Fig. 3 (**C** and **D**). In this context, the less hindered *Si*,*Si* transition state *via* an *anti*-enamine (Fig. 3 **C**) is usually well favored for aldehydes compared to the *Re*,*Re* approach for the ketones *via* a *syn*-enamine (Fig. 3 **D**).

In conclusion, the preferred diastereo- and enantioselectivity rely on electronic or steric interactions, and obviously on the absolute configuration of the aminocatalyst.

Asymmetric conjugate addition of ketones to nitroolefins

Recently, the interest in synthesizing γ-nitro ketones as valuable synthons in organic chemistry is in a constant state of effervescence. The first example was reported by List *et al.*[17] in which L-proline **3a** catalyzed the conjugate addition of ketones to nitroolefins in DMSO as the solvent (Scheme 4). Although the enantioselective outcome was only modest, good yields with high diastereoselectivities were achieved which illustrated the efficiency of the enamine catalysis for the Michael reaction. From a synthetic point of view, the Michael adducts were readily transformed to the corresponding optically active pyrrolidines by hydrogenation.



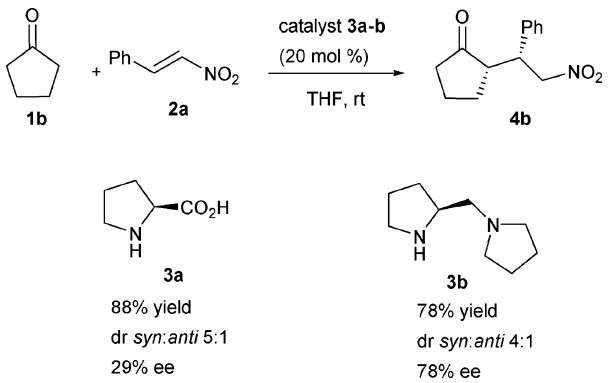
Scheme 4 L-Proline **3a** catalyzed Michael reaction of cyclohexanone **1a** to nitrostyrene **2a**.

Following this seminal study, methanol was demonstrated by Enders and Seki[20] to be the optimal solvent, obtaining a better enantioselectivity (Scheme 4). The formation of the (*S*,*R*) adduct **4a** in the L-proline catalyzed conjugate addition of ketones to nitroalkenes could be accounted for by electronic interactions (Fig. 2 **B** and Scheme 4).

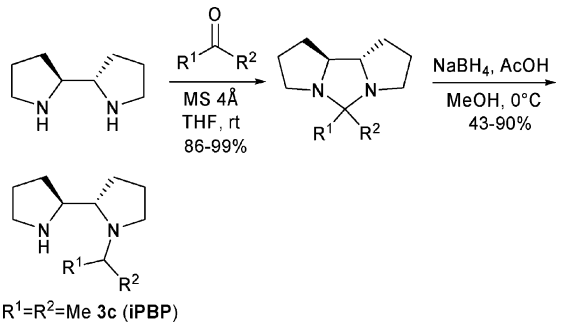
It should be pointed out that the solvent is of crucial importance for the reaction rate, diastereo- and enantioselectivity of asymmetric organocatalyzed conjugate additions.

Thus, further investigation by Barbas *et al.*[21] identified (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **3b** as an aminocatalyst that considerably improved the asymmetric conjugate addition of ketones to nitroolefins in comparison with L-proline (Scheme 5). These results suggested that L-proline catalysis requires a lone pair on the electrophile to induce high stereocontrol through H-bonding with its carboxylic acid as shown in aldol, Mannich and related reactions.[2,4] The obvious conclusion of this study is the efficiency of a chiral diamine bearing secondary and tertiary amine groups.

With this analogy in mind, our group synthesized *N*-alkyl-2,2′-bipyrrolidine derivatives as a new class of organocatalyst and applied them to the asymmetric Michael reaction of ketones to nitroalkenes.[22] A wide range of diamines were prepared in good overall yield using our simple methodology based on imidazolidine or so-called aminal formation followed by its reduction (Scheme 6).[22b]

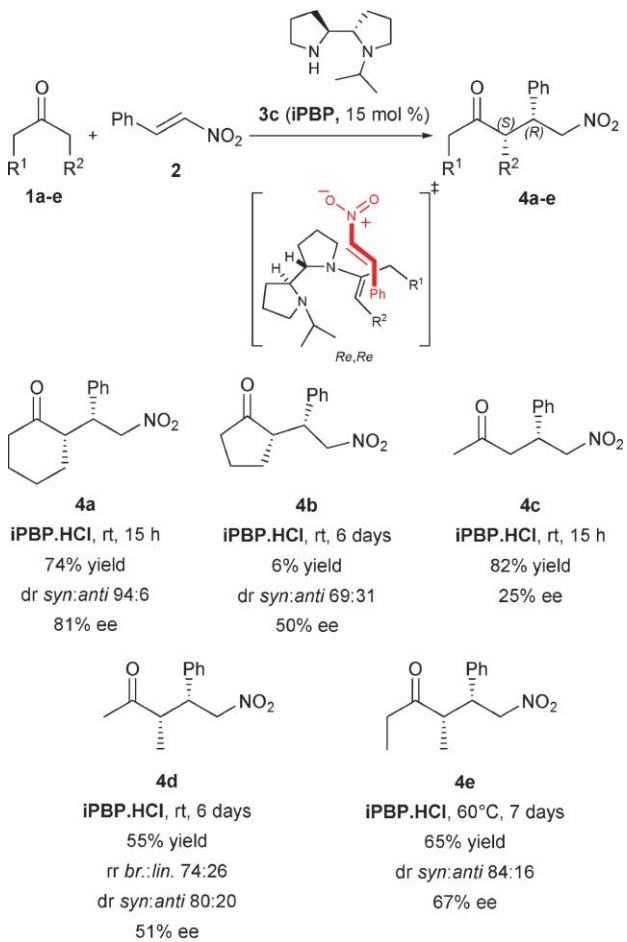


Scheme 5 L-Proline **3a** compared to diamine **3b** for conjugate addition of cyclopentanone **1b** to nitrostyrene **2a**.

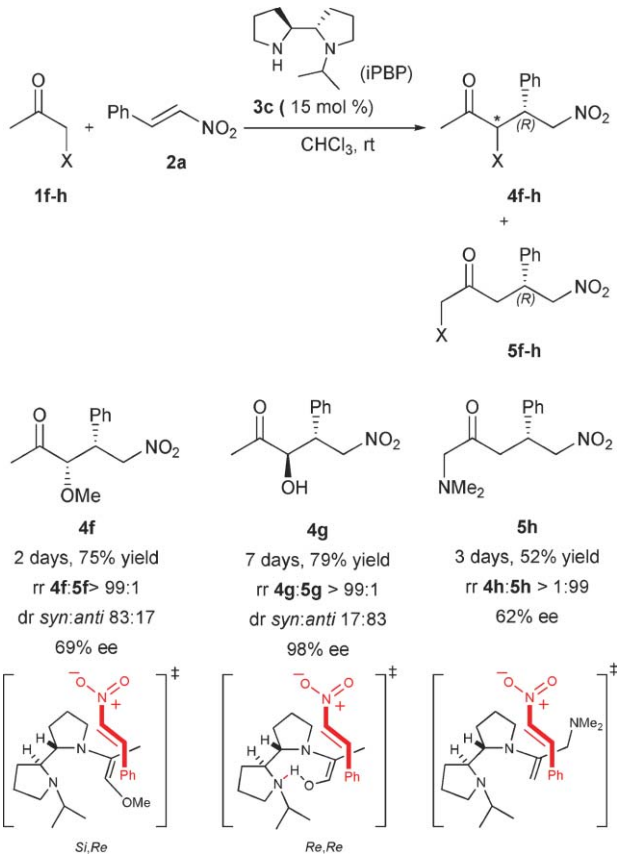


Scheme 6 Synthesis of *N*-alkyl-2*S*,2′*S*-bipyrrolidine derivatives.

According to preliminary results, the *N*-*i*Pr-2,2′-bipyrrolidine **3c** (*i*PBP) appeared to be the most effective candidate. The best asymmetric outcome for the conjugate addition to nitrostyrene **2a** was reached with cyclohexanone **1a** as the substrate and catalyst *i*PBP·HCl, affording γ-nitro ketone **4a** in 81% ee (Scheme 7). The acid co-catalyst accelerated the C–C bond forming process by increasing the rate of enamine formation.[23] It is worth noting that no reaction occurred without an acid additive in the cases of cyclic ketones **1a–b** and pentanone **1e**. The *syn*-selectivity is in accordance with Seebach's model based on steric shielding (Fig. 3 **D**) in which there are favorable electrostatic interactions between the



Scheme 7 (*S*,*S*)-*i*PBP **3c** catalyzed conjugate addition of ketones **1a–e** to nitrostyrene **2a**.

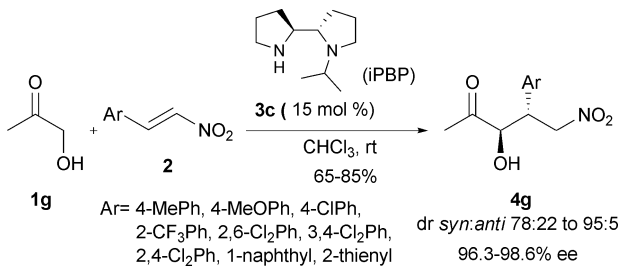


Scheme 8 (*S*,*S*)-*i*PBP **3c** catalyzed conjugate addition of α-heterosubstituted ketones **1f–h** to nitrostyrene **2a**.

nitrogen of the enamine and the nitro group (Scheme 7). The isopropyl substituent would promote the selective formation of the *E*-enamine and induce a marked bias toward the *Re*,*Re* approach (Scheme 7).

The challenging problem of regioselectivity in non-symmetrical ketones (Scheme 7, **1d**) was eluded by the use of α-heterosubstituted substrates **1f–h** (Scheme 8).[22b,24] The enhancement of acidity, due to the introduction of an oxygen atom, allowed exclusive formation of the enol-enamine, favoring branched adducts **4f–g**; whereas substitution by a nitrogen atom inverted this behaviour, providing solely the terminal enamine and, thereby, the linear adduct **4h**. Oddly, hydroxyacetone **1g** underwent reaction with nitrostyrene **2a** in favor of the *anti*-isomer with high regio- and enantioselectivity. The excellent enantioselectivity, as well as the diastereoselectivity, stemmed from efficient binding between the tertiary amine (N–*i*Pr), as a Lewis base, and the hydroxy group, as a H-bond donor, leading to the formation of the *Z*-enamine and rigidifying the transition state. The addition of hydroxyacetone **1g** was then extended to a variety of β-arylnitroolefins with high enantioselectivity regardless of the substitution pattern (Scheme 9).

These precedents provided the basis for the development of various chiral pyrrolidine organocatalysts, some of which are illustrated in Scheme 10. It should be pointed out that both free catalysts and protonated ones catalyzed the Michael reaction of ketones to nitroolefins with high *syn*-selectivity. Probably, acid additives could improve the overall rate of the reaction by affecting the outcome of the enamine forming step



Scheme 9 (*S*,*S*)-*i*PBP **3c** catalyzed conjugate addition of hydroxyacetone **1g** to β-arylnitroolefins **2**.

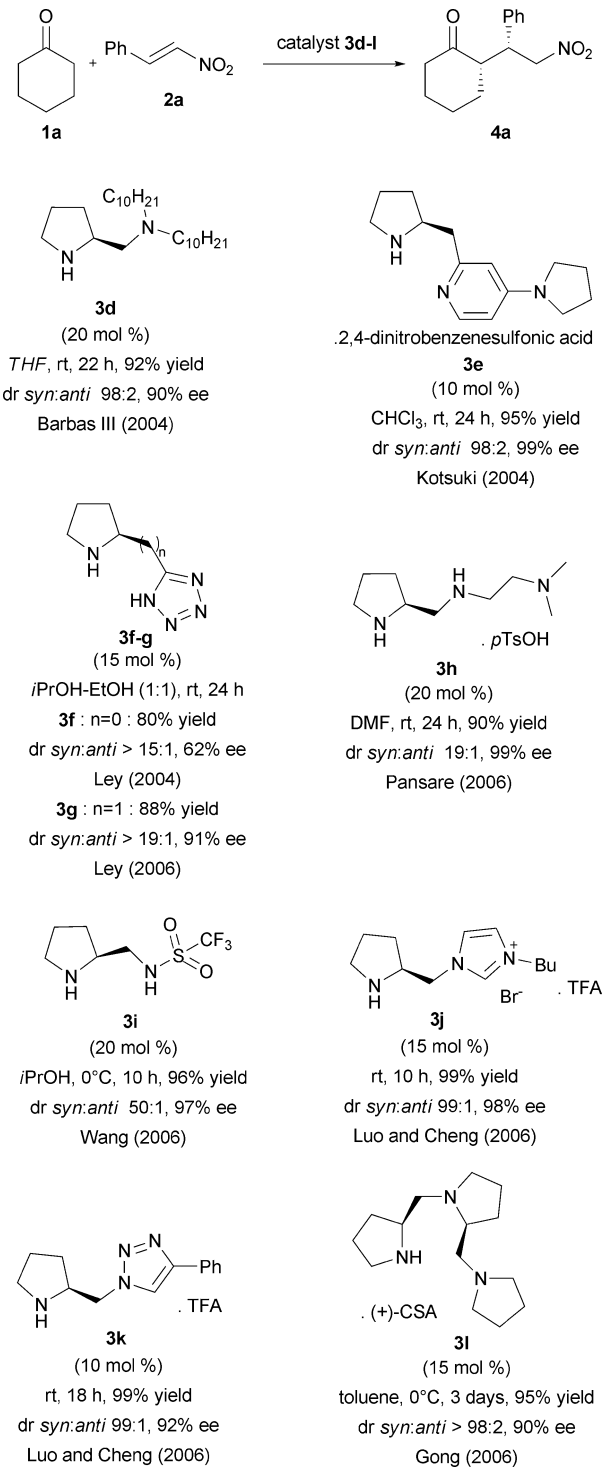
and could orient the substrates by hydrogen bonding.[23] The reactivity as well as the selectivity depended on the right combination of amine catalyst and protic acids, and the solvent. Mostly, the stereochemical outcome relied on the donor substrates, *i.e.* the ketone. Indeed, in contrast to cyclopentanone or acyclic ketones, cyclohexanone has shown excellent asymmetric results (up to 99% ee). Commonly, a large excess of ketone (~10 eq.) was provided to enforce an equilibrium favoring the Michael adduct. It is also worth noting that a relative high catalyst loading (10–20 mol%) is required to induce efficient asymmetric catalysis.

Thus, Barbas *et al.* reported the promotion of the conjugate addition of cyclohexanone **1a** to nitrostyrene **2a** by using diamine **3d** bearing hydrophobic alkyl groups.[25a] The stereochemistry of the product could be rationalized by approach of the nitrostyrene **2a** from the less hindered *Re*-face of the enamine according to steric shielding (Fig. 3 **D**). Later, the same group demonstrated the excellent reactivity and selectivity of the diamine **3d** in combination with trifluoroacetic acid (TFA) and in brine as the solvent.[25b]

Kotsuki *et al.* designed a new pyrrolidine-pyridine base catalyst such as **3e**, which is easily prepared from L-prolinol.[26] Given the importance of the proximity of the pyrrolidine-pyridine functionality, it is postulated that this basic functionality could facilitate the enamine formation and the resulting pyridinium ring could effectively shield one face of the enamine double bond (Fig. 3 **D**). Hence, the reaction was highly efficient in terms of yield and stereocontrol (up to 99% ee).

Ley *et al.* replaced proline's carboxylic acid group with tetrazole, a bioisostere of this functionality, to give **3f**,[27] and successfully applied it to the conjugate addition of ketones to nitroolefins.[28a] In comparison with L-proline, this organocatalyst **3f** far outperformed it in every respect (Scheme 4 catalyst **3a** *vs.* Scheme 10 catalyst **3f**). Interestingly, the reaction worked well using a relatively small amount of ketone (1.5 eq.). The improved activity could be ascribed either to the difference in hydrogen-bonding strengths between the tetrazole and the carboxylic acid functionality or to the increased size of the tetrazole moiety or to the enhanced solubility of the tetrazole analogue **3f**. Further optimization led to the development of homoproline tetrazole catalyst **3g** which afforded high selectivity for a wide range of ketones and nitroolefins (up to 93% ee).[28b] Either the bulkier homotetrazole side chain (Fig. 3 **D**) or easier binding abilities (Fig. 2 **B**) could explain the improvement in enantioselectivity.

More recently, protonated proline-derived triamine catalysts **3h** were developed by Pansare and Pandya for the highly



Scheme 10 Chiral pyrrolidine **3d–l** catalyzed conjugate addition of cyclohexanone **1a** to nitrostyrene **2a**.

enantioselective conjugate addition of cyclic six-membered ketones to nitroalkenes (up to 99% ee).[29] The high enantioselection suggested that H-bond donation might be effected by the catalyst in its protonated form (Fig. 2 **B**).

Wang *et al.* reported an interesting new pyrrolidine sulfonamide **3i** which efficiently mediated asymmetric conjugate addition of ketones to nitroolefins.[30a] The enhanced catalytic activity and selectivity of catalyst **3i** relative to

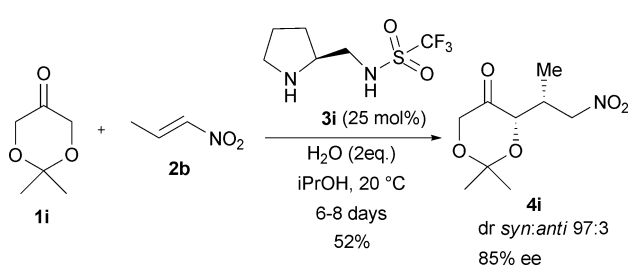
L-proline **3a** are a consequence of the acidic and steric bulk properties of the NHTf group. Computational studies ascribed the activity of the organocatalyst **3i** to the formation of both intramolecular and intermolecular hydrogen bonds. The selectivity seemed to originate from the steric hindrance between the bulky sulfonamide group and the alkyl substituent of the enamine intermediate. The same group also developed a recyclable and reusable fluorous pyrrolidine sulfonamide for promoting highly enantio- and diastereoselective Michael reactions of ketones and aldehydes to nitroolefins in water.[30b]

Chiral ionic liquids such as **3j** were also identified by Luo and Cheng *et al.* as both maintaining the unique properties of an ionic liquid and representing a proficient catalyst for the Michael reaction (up to 99% ee).[31a] The use of an acidic co-catalyst was essential for accelerating the reaction rate. The ionic liquid moiety could not only act as a phase tag to facilitate recycling and reuse of the catalyst **3j** but could also induce high selectivity *via* steric shielding (Fig. 3 **D**) under neat conditions. Subsequently, with the intention of constructing a chiral pyrrolidine library with structural diversity, Luo and Cheng *et al.* explored the utility of click chemistry and proved pyrrolidine-triazole skeleton **3k** to be a new class of valuable organocatalysts for the Michael reaction. The polar and planar triazole moiety was responsible for potent space shielding.[31b,c]

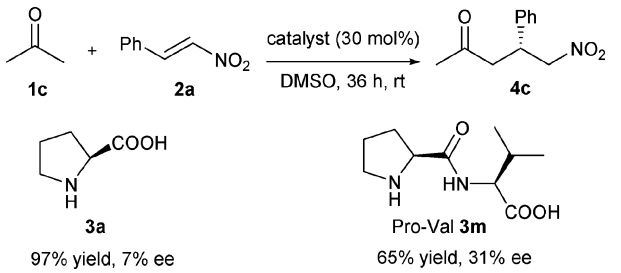
A new triamine bearing three pyrrolidine cores **3l** has also been employed by Gong *et al.* in this reaction.[32] The catalysis and the selectivity were significantly increased in the presence of (+)-camphorsulfonic acid (CSA). The chirality of the stereogenic center of the acid had little effect on the enantioselectivity which suggested a possible match–mismatch effect. Once again, steric shielding might be a reason for supporting the stereochemical outcome (Fig. 3 **D**).

In addition, it is worth noting that Benaglia *et al.* developed a poly(ethyleneglycol)-supported proline as a recyclable aminocatalyst for the asymmetric synthesis of γ-nitro ketones which could be obtained in lower yields and similar enantioselectivities in comparison with L-proline.[33]

Interestingly, Enders *et al.* have employed the protected dihydroxyacetone[34] (DHA) derivative **1i** as the donor substrate in the Michael reaction with various nitroalkenes (Scheme 11).[35] The best asymmetric outcome was obtained by pyrrolidine sulfonamide **3i**, providing 1,4-adduct **4i** in high diastereo- and enantioselectivity (up to 86%). The addition of water accelerated the reaction and increased the yield with a shorter reaction time. The stereocontrol could be governed by electronic interactions *via* hydrogen bonding (Fig. 2 **B**).



Scheme 11 Pyrrolidine sulfonamide **3i** catalyzed conjugate addition of protected DHA **1i** to nitroolefin **2b**.

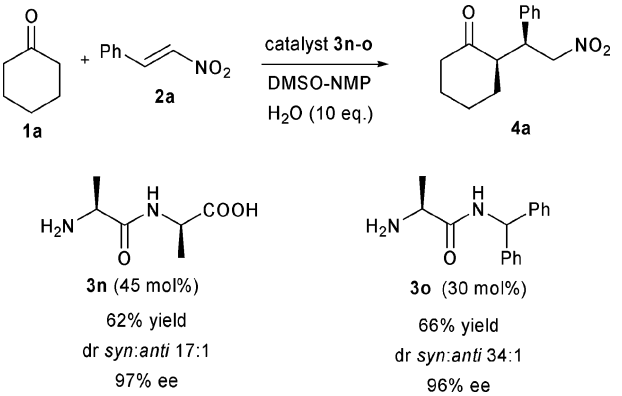


Scheme 12 L-Proline **3a** compared to dipeptide **3m** for conjugate addition of acetone **1c** to nitrostyrene **2a**.

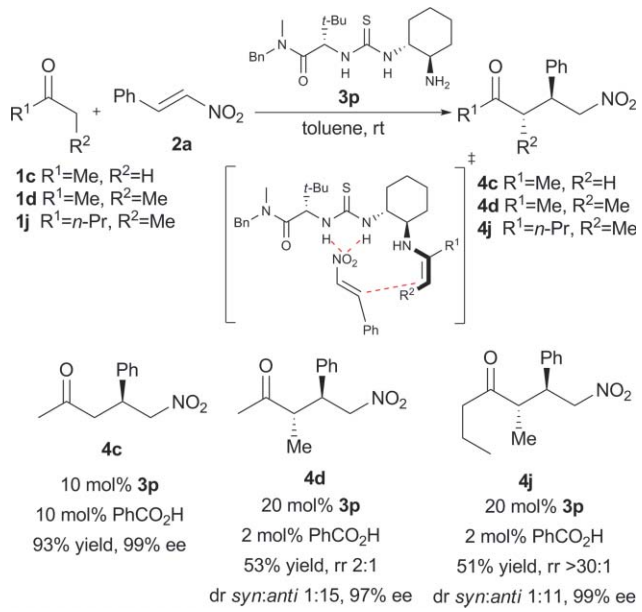
The use of peptides in the conjugate addition of acetone **1c** to nitrostyrene **2a** was innovatively introduced by List and Martin (Scheme 12).[36] A relative improvement with N-terminal prolyl peptides in comparison with L-proline was observed.

Córdova *et al.* screened various simple dipeptides to catalyze the Michael reaction (Scheme 13).[37] Alanine-alanine derivative **3n**, with a primary amine at the terminus, promoted the addition of a wide range of cyclic ketones to nitroolefins with enantioselectivities up to 98% ee. A small excess of water was added to increase the efficiency and *N*-methyl-2-pyrrolidinone (NMP) was used as a co-solvent. Hydrogen bonding, due to the presence of acid and amide groups and water, could plausibly be involved in the transition state based on Seebach's acyclic synclinal model. Soon after, the same group also investigated the use of primary acyclic amino acid derivative **3o** as an efficient organocatalyst for the conjugate addition (Scheme 13).[38]

More recently, thiourea derivatives were also demonstrated to hold promise as hydrogen-bonding catalysts for enamine activation.[39] Jacobsen and Huang reported a new bifunctional catalyst **3p** to induce high selectivity for a broad substrate scope with respect to nucleophilic and electrophilic reacting partners (up to 99% ee, Scheme 14).[40] A catalytic amount of benzoic acid suppressed side reactions such as double alkylation and accelerated the reaction. The selective formation of the *anti*-diastereomers stood in contrast to previous results. It has been suggested that the stereochemical outcome could arise from a *Z*-enamine intermediate. The thiourea moiety could probably participate in the transition state by binding nitroolefins which allowed high regio- and stereocontrol.

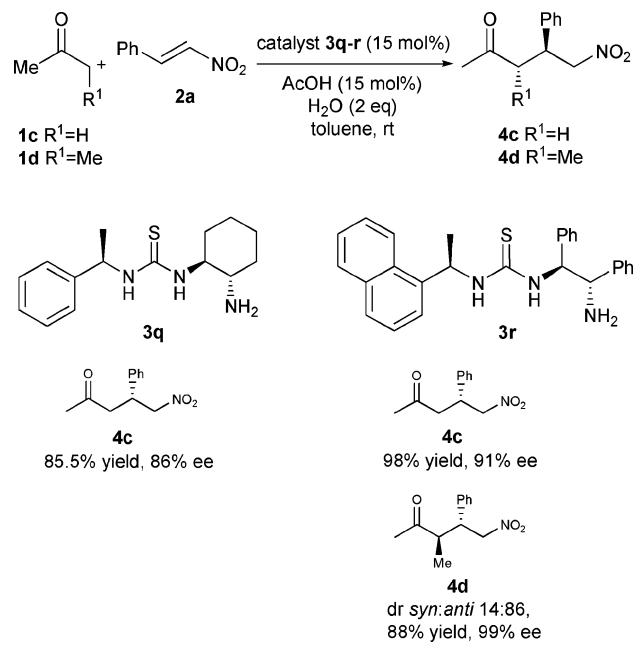


Scheme 13 Amino acid derivatives **3n–o** catalyzed conjugate addition of cyclohexanone **1a** to nitrostyrene **2a**.

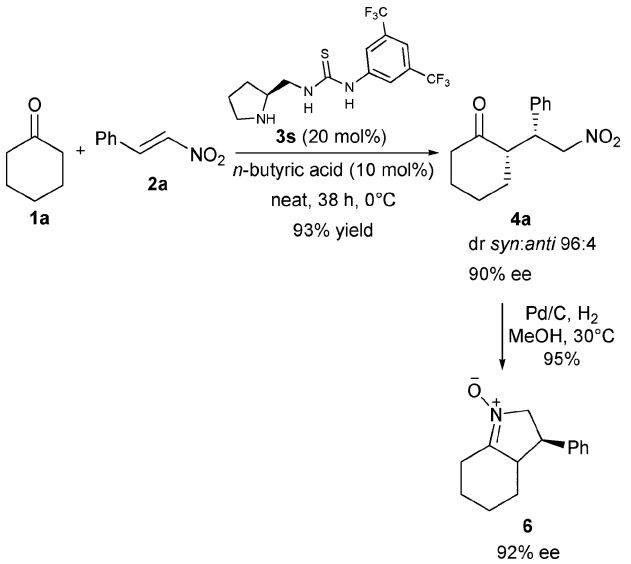


Scheme 14 Thiourea-primary amine bifunctional catalyst **3p** catalyzed conjugate addition of ketones **1c–d,j** to nitrostyrene **2a**.

The thiourea **3q** developed by Tsogoeva *et al.* has also functioned as an efficient organocatalyst for the Michael reaction (84–92% ee, Scheme 15).[41] The combination of water and acetic acid was found to be the optimal conditions. Computational studies have shown that only one oxygen atom of the nitro group was bonded to the thiourea moiety. A more potent thiourea catalyst **3r** was described by the same group for this reaction under the same conditions (90–99% ee, Scheme 15).[42] The *syn*-selectivity for cyclic ketones was observed, as commonly reported in the literature, whereas acyclic ketones generated the *anti*-diastereomers which could



Scheme 15 Thiourea-primary amine bifunctional catalysts **3q–r** catalyzed conjugate addition of ketones **1c–d** to nitrostyrene **2a**.



Scheme 16 Pyrrolidine-thiourea **3s** catalyzed conjugate addition of cyclohexanone **1a** to nitrostyrene **2a** followed by nitrone **6** formation.

be attributed to the formation of the *Z*-enamine as mentioned by Jacobsen.

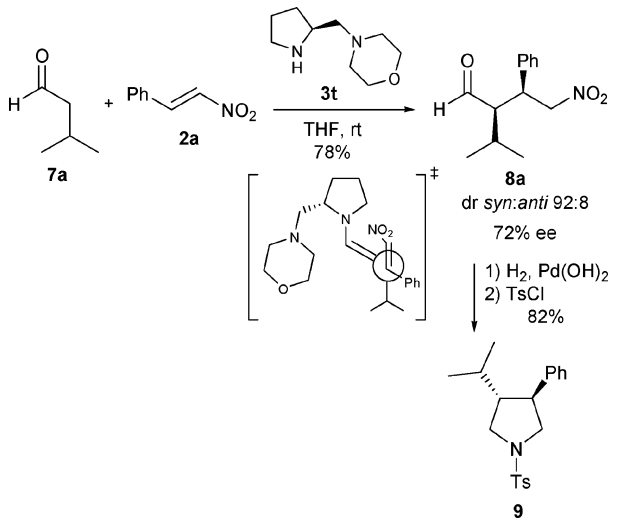
Tang *et al.* made another important contribution to this field by designing a new pyrrolidine-thiourea based catalyst **3s** (Scheme 16).[43] The use of bifunctional catalyst **3s** in combination with *n*-butyric acid in solvent-free conditions turned out to be an excellent system to catalyze the conjugate addition of ketones to nitroolefins (up to 98% ee). H-bonding interactions were postulated to account for the high stereoinduction, which is consistent with proline and tetrazole activation (Fig. 2 **B**). The synthetic utility of the γ-nitrocyclohexanone **4a** was emphasized by the preparation of the corresponding nitrone **6** in 95% yield without erosion of enantioselectivity.

A similar pyrrolidine-thiourea catalyst bearing a *para*-methyl instead of bis-*meta*-trifluoromethyl groups was independently described by Xiao *et al.* and allowed a slight improvement of selectivity in water as the solvent (adduct **4a**: 90% yield, dr *syn* : *anti* 98 : 2, 96% ee).[44]

Asymmetric conjugate addition of aldehydes to nitroolefins and vinyl sulfones

Viewed as more reactive compounds, aldehydes turned out to be interesting donor substrates for the organocatalyzed Michael reaction. Most of the catalysts discussed above are well suited for the conjugate addition of aldehydes. Similarly to studies on ketones, acid co-catalysts suppressed side reactions and fostered the Michael reaction. Typically, both aldehydes and ketones showed *syn*-selectivity but gave the opposite enantiomers in accordance with the transition states in Fig. 2 **A** and Fig. 3 **C**.

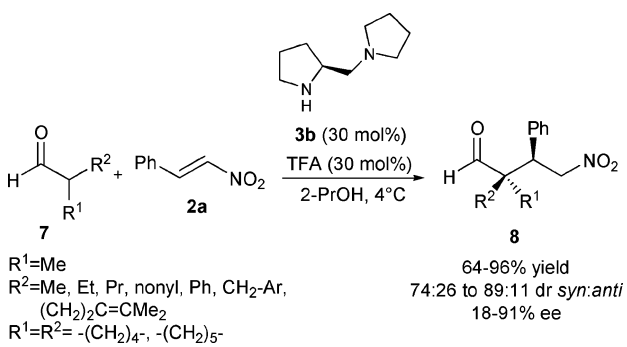
The first report of the utilization of unmodified aldehydes for the Michael reaction to nitroolefins with chiral secondary amine catalysts was disclosed by Barbas *et al.* (Scheme 17).[25a,45] A large number of pyrrolidine derivatives were evaluated and under catalytic conditions (20 mol%) up to 86% ee was



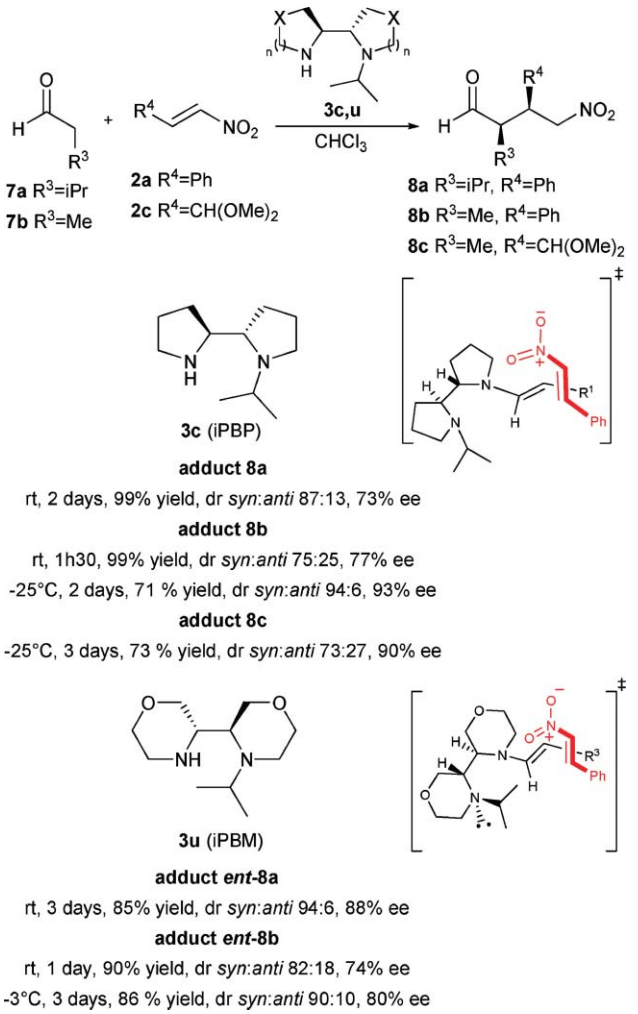
Scheme 17 Diamine **3t** catalyzed conjugate addition of isovaleraldehyde **7a** to nitrostyrene **2a**.

obtained with (*S*)-2-(morpholinomethyl)pyrrolidine **3t** for branched aldehydes. With respect to yield and selectivity, L-proline **3a** was a poor catalyst for this class of Michael reaction. These useful synthons could be further converted into 3,4-disubstituted pyrrolidines **9** by reductive amination. According to steric shielding (Fig. 3 **C**), approach of the nitroolefin from the less hindered *Si*-face of the enamine could explain the stereochemistry. Later, the scope of the reaction was extended by the same group to the formation of quaternary carbon centers with high enantioselectivities (up to 91% ee) by using diamine **3b** in combination with TFA (Scheme 18).[46] The reaction was also proved to be possible in brine as solvent with a slight decrease in selectivity.[25b]

For the sake of comparison, our group explored this chemistry with our 2,2′-bipyrrolidine derivative **3c** (*i*PBP) (Scheme 19).[22] Linear aldehydes such as propionaldehyde **7b** (up to 93% ee) provided a higher reaction rate and selectivity than branched aldehydes such as isovaleraldehyde **7a** (up to 73% ee). For the less hindered aldehydes, decreasing the temperature allowed the enantio- and diastereoselectivity to increase while maintaining enough reactivity. To generalize the scope of the reaction, the addition of the best substrate, propionaldehyde **7b**, to a wide range of nitroolefins was successfully examined with ee's up to 95%. As shown



Scheme 18 Diamine **3b** catalyzed conjugate addition of α,α-disubstituted aldehydes **7** to nitrostyrene **2a**.

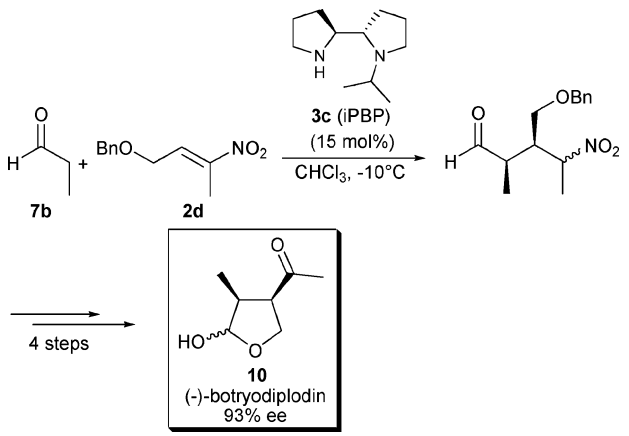


Scheme 19 Diamine **3c** (*i*PBP) compared to diamine **3u** (*i*PBM) for conjugate addition of aldehydes **7a–b** to nitrostyrene **2a**.

previously by Barbas, the steric hindrance influenced the transition state, favouring the *Si*,*Si* approach. In addition, NMR investigations[22b] revealed that not only the character of the Michael acceptor but also the availability of the catalyst, which could sometimes be trapped by electrophilic substrates, had an influence on the reaction rate. An improvement in selectivity for bulky aldehydes was further achieved by our group with diamine **3u** (*i*PBM), incorporating the morpholine structural motif instead of the pyrrolidine motif (Scheme 19).[47] It could be suggested that the reactivity relies on the nucleophilicity of the enamine intermediate.[48] Hence, the more nucleophilic enamine of *i*PBP **3c** showed a higher reaction rate than the enamine of *i*PBM **3u**. From a synthetic point of view, the potential to add propionaldehyde **7b** with high enantioselectivity regardless of the nitroolefin by using catalyst **3c** (*i*PBP) was demonstrated by the first asymmetric synthesis of (−)-botryodiplodin **10** (Scheme 20).[22b,49]

A chiral spiro diamine prepared by Royer *et al.* was also proved to catalyze the conjugate addition of isovaleraldehyde **7a** to nitrostyrene **2a** in moderate enantioselectivity without diastereocontrol.[50]

As highlighted in the previous section on ketones,[30] Wang *et al.*'s chiral pyrrolidine sulfonamide **3i** promoted the



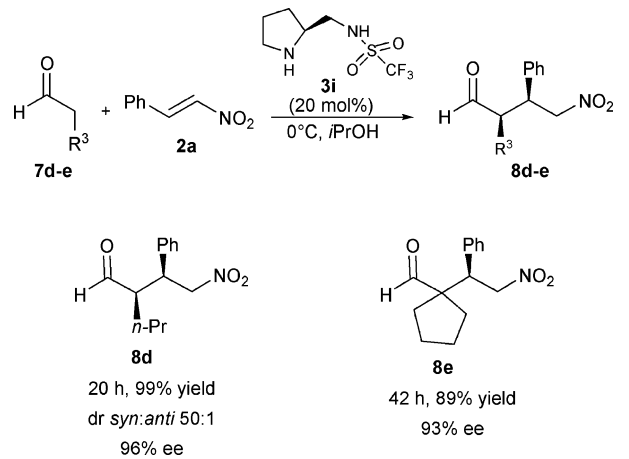
Scheme 20 Asymmetric synthesis of (−)-botryodiplodin **10** using *i*PBP-catalyzed conjugate addition.

Michael addition of aldehydes to nitroolefins with high levels of enantio- (89–99% ee) and diastereoselectivity (⩾20 : 1 dr *syn* : *anti*) (Scheme 21).[30a,51]

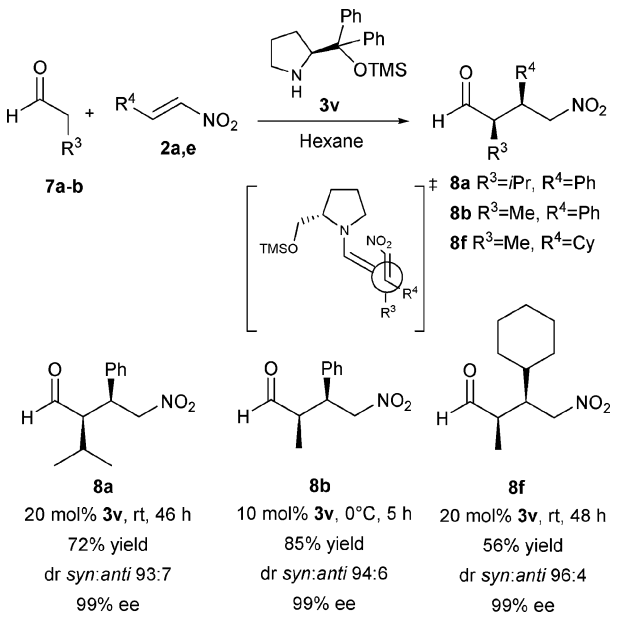
Innovatively, diphenylprolinol silyl ether **3v** was found to be exceptionally effective in the asymmetric catalysis of the Michael reaction of aldehydes and nitroalkenes (Scheme 22).[52] The broad applicability with respect to both the Michael acceptors and the donor substrates was displayed by the achievement of the nearly perfect enantioselectivity (99% ee) and the excellent diastereoselectivity in most of the cases related to steric shielding. Later, a recyclable and reusable diphenylprolinol silyl ether surrogate bearing an *n*-C_8F_{17} fluorous tag was developed by Wang *et al.* for this reaction.[53]

The efficiency of diphenylprolinol silyl ether **3v** was demonstrated by Enders *et al.* in a triple cascade organocatalytic reaction for the synthesis of tetra-substituted cyclohexene carbaldehydes **12** (Scheme 23).[54] The four stereogenic centers were generated in a Michael–Michael–aldol sequence with high diastereo- and enantioselectivity (>99% ee).

Lately, simple (*S*)-prolinol was employed by Vicario *et al.* to promote the Michael reaction of aldehydes to β-nitroacrolein dimethyl acetal **2c**, leading to the highly functionalized



Scheme 21 Pyrrolidine sulfonamide **3i** catalyzed conjugate addition of aldehydes **7d–e** to nitrostyrene **2a**.

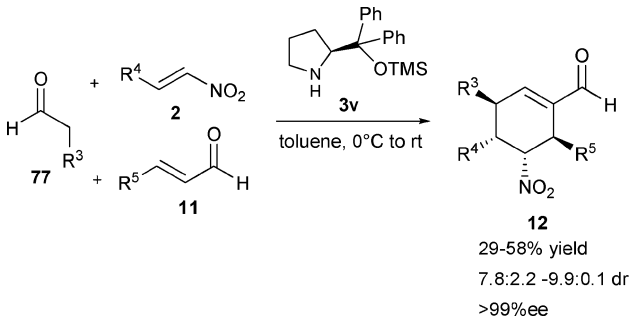


Scheme 22 Diphenylprolinol silyl ether **3v** catalyzed conjugate addition of aldehydes **7a–b** to nitroolefins **2a,e**.

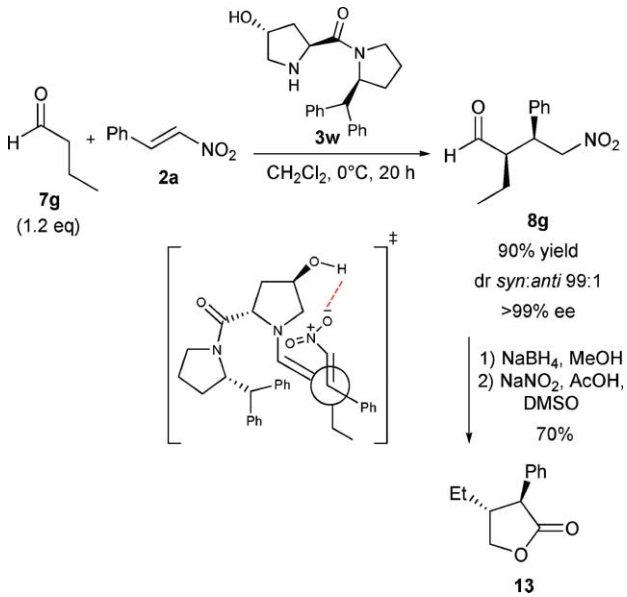
compound **8c** with two differentiated formyl groups with, however, lower enantioselectivity (80% ee) than catalyst **3c** (Scheme 19).[55] Interestingly, the reaction could be performed using equimolar amounts of substrates and low catalyst loading (10 mol%).

Importantly, Palomo *et al.* reported a new model of organocatalyst **3w** for the conjugate addition that included both a bulky α-group and a hydrogen bond donor directing γ′-group (Scheme 24).[56] The *trans*-4-hydroxyprolylamide **3w** could be used in only 5 mol% catalyst loading and gave adducts in high yields with high selectivities (91–99% ee). The synthetic interest was highlighted by the simple synthesis of γ-butyrolactones **13**, which are common structural units of natural products.

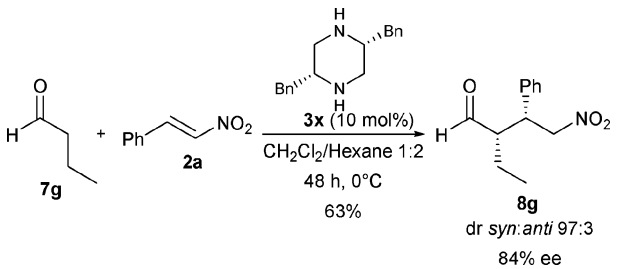
Very recently, Barros and Phillips investigated the impact of chiral 2,5-disubstituted piperazines **3x** as organocatalysts to synthesize γ-nitro aldehydes (Scheme 25).[57] A concise survey of various aldehydes and β-arylnitroolefins identified butyraldehyde **7g** as the most efficient donor substrate leading to the best asymmetric outcome, ascribed to valuable steric shielding (85% ee).



Scheme 23 Diphenylprolinol silyl ether **3v** catalyzed three component domino reaction.



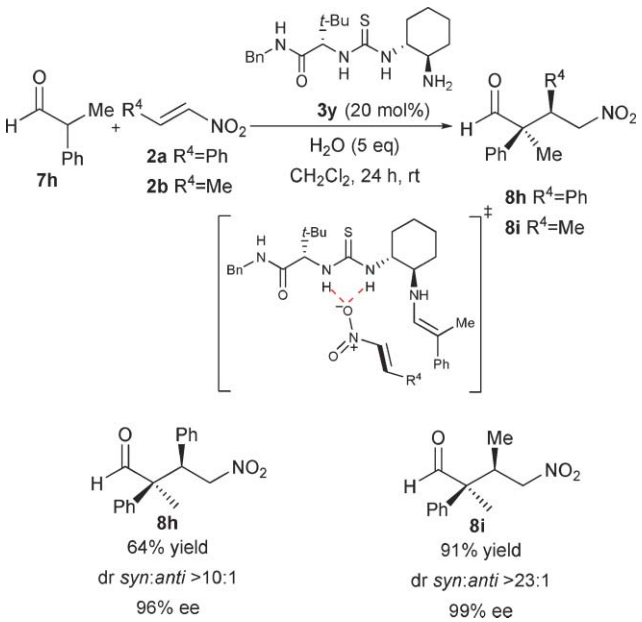
Scheme 24 *trans*-4-Hydroxyprolylamide **3w** catalyzed conjugate addition of butyraldehyde **7g** to nitrostyrene **2a** and γ-butyrolactone synthesis.



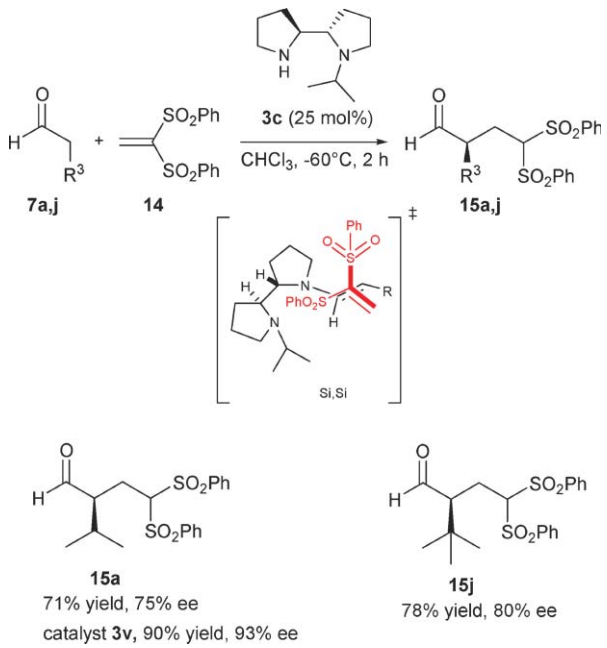
Scheme 25 Chiral piperazine **3x** catalyzed conjugate addition of butyraldehyde **7g** to nitrostyrene **2a**.

Inspired by his work on ketones depicted in the previous section,[40] Jacobsen *et al.* further explored the primary amine-thiourea catalyzed addition of α,α-disubstituted aldehydes to nitroolefins (Scheme 26).[58] Bifunctional catalyst **3y**, bearing a secondary amide, proved to be broadly applicable and generated compounds with contiguous quaternary and tertiary stereogenic centers with high levels of selectivity (92–99% ee). The remarkable stereoinduction could be tied to simultaneous activation of both the nucleophile and electrophile through covalent *E*-enamine catalysis and hydrogen bonding, respectively.

Finally, pioneering findings on enantioselective enamine catalysis using vinyl sulfones as Michael acceptors were reported by our group (Scheme 27).[59] Although sulfones are still recognized as useful intermediates in organic synthesis,[60] the use of organocatalysis in this area remains elusive.[61,62] Delightfully, 1,4-adducts were obtained in good yields and enantioselectivities (up to 80% ee) with our diamine **3c** (*i*PBP). Very recently, the enantiomeric excess of 1,4-adduct **15a** could be improved to 93% ee with organocatalyst **3v**.[63] The more hindered the aldehyde, the better the stereoinduction. According to advanced studies, the reactivity depended on the



Scheme 26 Primary amine-thiourea derivative **3y** catalyzed conjugate addition of aldehyde **7h** to nitroolefins **2a–b**.

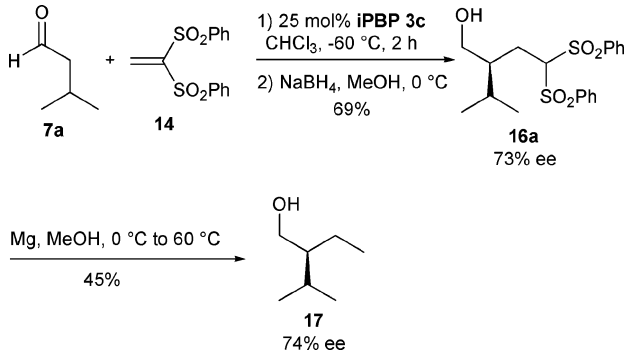


Scheme 27 *i*PBP **3c** catalyzed conjugate addition of aldehydes **7a,j** to vinyl sulfone **14**.

presence of geminal-bis-sulfone groups on the olefin **14**. The determination of the absolute configuration, after suitable transformations (Scheme 28), allowed us to postulate a *Si*,*Si* transition state model, as shown previously for nitroolefins.

Organocatalyzed asymmetric conjugate addition *via* modern technologies

New technologies represent attractive topics as they open completely new possibilities for chemical industry. The

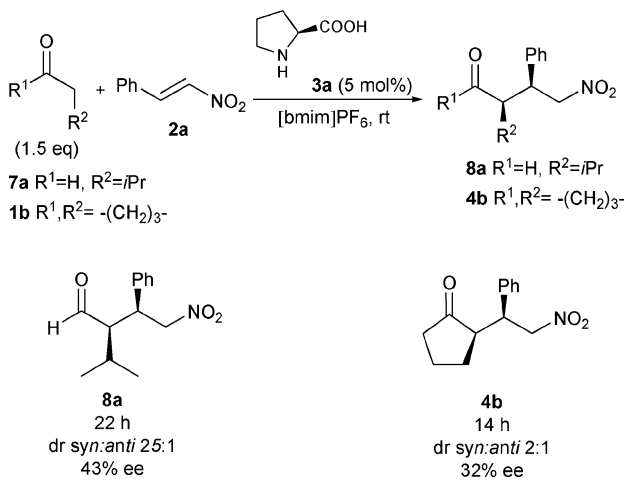


Scheme 28 Synthetic transformations of the sulfone groups to determine the absolute configuration of 1,4-adduct **15a** (Scheme 27).

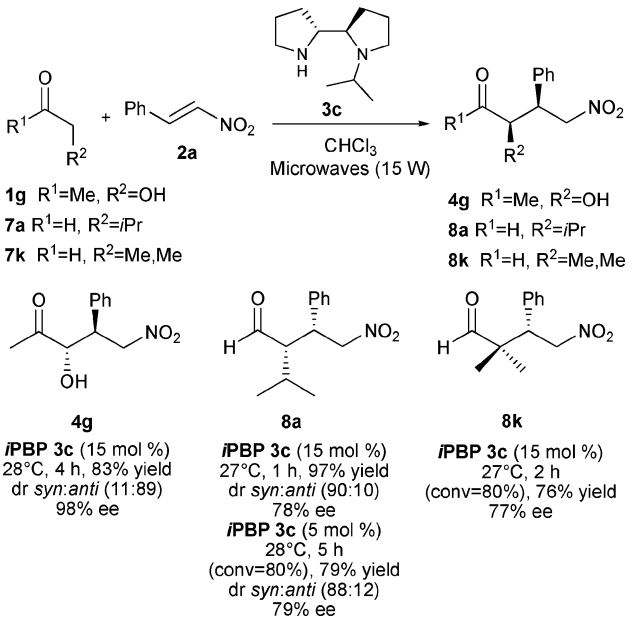
combination of organocatalysis and some modern technologies has yet been considered to promote asymmetric conjugate addition.

Accordingly, Toma *et al.* carried out L-proline catalyzed Michael reactions of ketones and aldehydes to nitroalkenes in an ionic liquid as a "green" solvent.[64] Only moderate selectivity could be reached using [bmim]PF_6 and a small amount of catalyst loading (5 mol%) (Scheme 29).

Although affording high enantio- and diastereoselectivities, most of the organocatalyzed reactions have a long reaction time and a high catalyst loading. Consequently, our group considered that microwave activation would remove these drawbacks.[65] Indeed, since the initial experiments in the mid-1980s, MW energy has shown tremendous benefits to organic synthesis and now represents a reliable tool for organic chemists.[66,67] The impact of microwave activation was especially displayed in our *i*PBP-catalyzed conjugate addition of hindered aldehydes and hydroxyacetone to nitrostyrene (Scheme 30).[68] In all cases, reaction times were dramatically shortened without loss of selectivity. Most importantly, the catalyst loading could be decreased from 15 mol% to 5 mol% with isovaleraldehyde **7a** while maintaining good reactivity. Hence, microwave technology improved our previous results (Scheme 8 and Scheme 19 *vs.* Scheme 30).



Scheme 29 L-Proline **3a** catalyzed conjugate addition of isovaleraldehyde **7a** and cyclopentanone **1b** to nitrostyrene **2a** in ionic liquid as solvent.



Scheme 30 *i*PBP-catalyzed conjugate addition *via* microwave activation.

Conclusions

In summary, many highly successful examples of organocatalyzed asymmetric conjugate addition of aldehydes and ketones to nitroolefins and vinyl sulfones *via* enamine activation have emerged in a matter of six years. The aminocatalysts can be easily tuned from both steric and electronic standpoints in order to induce efficient stereocontrol. The versatile chiral Michael adducts can be transformed into useful building blocks for natural product synthesis. Hence, new developments in this recent area will undoubtedly continue through the design of greatly active and selective organocatalysts in order to overcome synthetic challenges.

Acknowledgements

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