DOI: 10.1002/ejoc.200600653

# Recent Advances in Asymmetric Organocatalytic 1,4-Conjugate Additions

**Svetlana B. Tsogoeva*[a]**

**Keywords:** 1,4-Conjugate addition / Michael addition / Asymmetric reactions / Chiral amines / Multicomponent reactions / Organocatalysis

Recent progress in the field of asymmetric organocatalytic 1,4-conjugate addition reactions, regarded as belonging among the more synthetically important carbon–carbon bond-forming reactions, is described. The focus is on some recent advances in the following selected reactions: additions of various nucleophiles to α,β-unsaturated cyclic and acyclic enals, enones, vinyl sulfones and nitro olefins, addition of malonates and/or ketones to acyclic enones, or of aldehydes and ketones to vinyl ketones and nitro olefins, together with some multicomponent domino reactions.


## 1. Introduction

Among the numerous asymmetric carbon–carbon bond-forming reactions, catalytic asymmetric conjugate additions play a prominent role.[1] These 1,4-additions in particular have in recent years been the subject of numerous advances aimed at the discovery of efficient chiral catalysts.[2] Recent developments include metal-mediated enantioselective conjugate addition reactions of stabilized and nonstabilized carbanions[3] and the asymmetric catalysis of intermolecular conjugate addition of appropriate enolates to acceptor-substituted olefins, usually known as the Michael reaction.[4]

More recently, asymmetric organocatalysis has emerged as a new, powerful, and environmentally friendly methodology for the catalytic production of enantiomerically pure organic compounds and also as one of the most rapidly growing and competitive research areas in synthetic organic chemistry.[5] Clearly, an elegant and economically attractive way to introduce chirality into a Michael and/or Michael-type acceptor is through a chiral organocatalyst, due to the versatility of this class of compounds.[5] Many different variants of this synthetic approach have been described recently, and an overview of selected recent developments in these asymmetric organocatalytic 1,4-conjugate additions is presented here.

[a] Institute of Organic Chemistry
University of Erlangen-Nürnberg,
Henkestraße 42, 91054 Erlangen, Germany
Fax: +49-9131-85-26865
E-mail: tsogoeva@chemie.uni-erlangen.de

## 2. Conjugate Additions to Enones

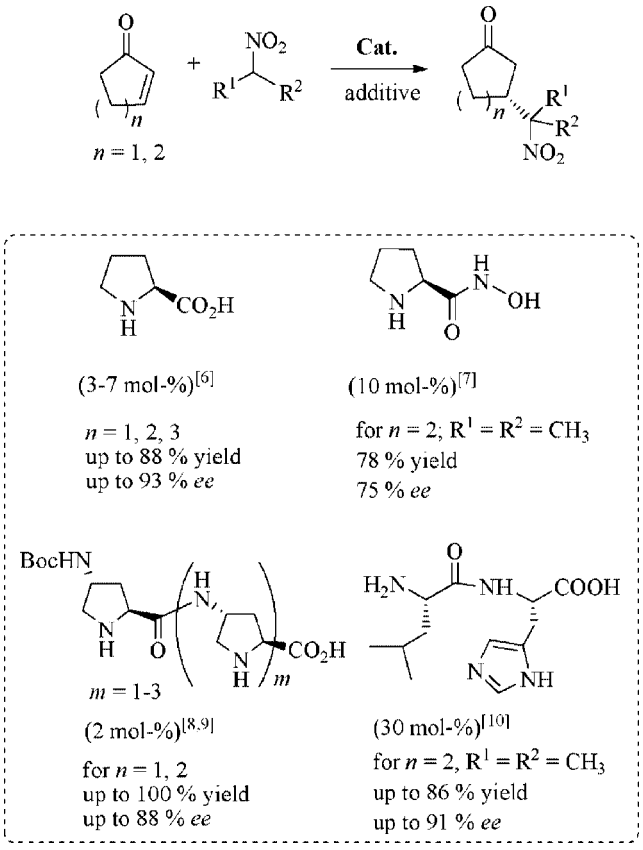
### 2.1. Conjugate Additions of Nitro Alkanes to Cycloalkenones

The products of 1,4-additions of nitro alkanes to α,β-unsaturated enones are useful precursors for a variety of structures such as aminocarbonyl compounds, aminoalkanes, and pyrrolidines. Efforts toward achieving asymmetric conjugate additions of nitro alkanes to α,β-unsaturated ketones have been the subject of several recent reports.

Hanessian and co-workers[6] described catalytic asymmetric conjugate additions of various nitro alkanes to cyclic enones (cyclopentenone, cyclohexenone, and cycloheptenone) in the presence of L-proline (3–7 mol-%) as a catalyst and *trans*-2,5-dimethylpiperazine as an additive (Scheme 1). The reaction proceeds with good to high enantioselectivities of 62–93% *ee* and in yields of up to 88%. The highest enantioselectivity was found with 2-nitropropane and cyclohexenone (93% *ee*).

*Svetlana B. Tsogoeva, born in 1973, studied chemistry at St.-Petersburg State University, Russia, where she completed her doctoral thesis on the "Synthesis of Modified Analogues of Steroid Estrogens" in 1998 in the group of Prof. Shavva. After a one and half year postdoctoral stay with Prof. Göbel at Johann Wolfgang Goethe University, Frankfurt/Main, Germany, in July 2000 she joined Degussa AG Fine Chemicals Division in Hanau-Wolfgang, Germany, as a research scientist. In January 2002 she was appointed Junior Professor of Chemistry at Georg August University of Göttingen, Germany, and in December 2006 she was appointed Professor of Chemistry at Friedrich Alexander University of Erlangen-Nürnberg, Germany. Her research is currently focused on asymmetric organocatalysis, as well as the synthesis of natural product hybrids.*



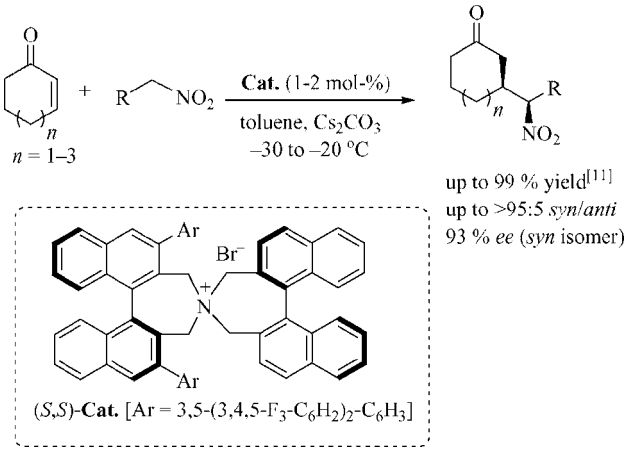

Scheme 1.

The same group showed[7] for the first time that proline-hydroxamic acid can also act as an effective catalyst for this reaction, albeit with more modest enantioselectivity (75% *ee*) and a slower reaction time than L-proline (Scheme 1).

Subsequently we demonstrated[8,9] that an asymmetric version of the addition of different nitro alkanes to cyclic enones can be successfully achieved with short peptides based on 4-*trans*-aminoproline as catalysts (Scheme 1). In the presence of the di-, tri-, and/or tetrapeptide as the catalyst (2 mol-%) and *trans*-2,5-dimethylpiperazine as an additive, the products have been formed in up to 100% yield and with up to 88% *ee*.

Using the conjugate addition of 2-nitropropane to cyclohex-2-en-1-one as an example, we further showed,[10] for the first time, that the combination of the dipeptide H-Leu-His-OH and (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine as co-catalysts produced a new catalytic system for C–C bond-formation reactions (Scheme 1). Although neither co-catalyst was sufficiently effective independently in terms of yield or enantioselectivity, their combination resulted in a drastic increase in yields (up to 86%) and selectivities (up to 91% *ee*), indicating the possibility of synergistic effects.

Recently, Maruoka and co-worker[11] have demonstrated the effectiveness of the chiral phase-transfer catalysis of an *N*-spiro chiral quaternary ammonium bromide possessing a 3,5-bis(3,4,5-trifluorophenyl)phenyl substituent (Scheme 2) for highly diastereo- and enantioselective conjugate additions of nitro alkanes to cyclic α,β-unsaturated ketones.

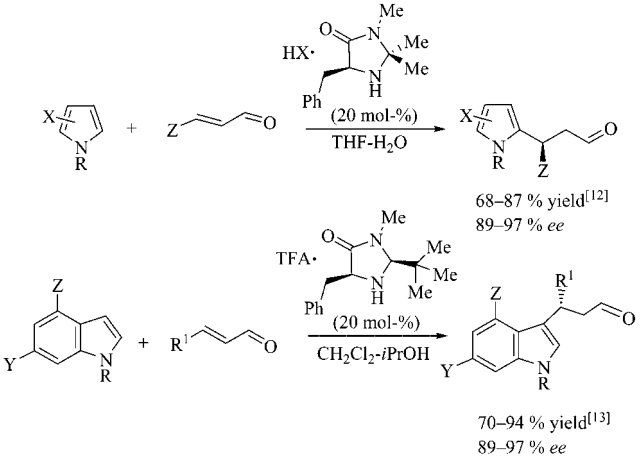



Scheme 2.

This study implies the potential to elaborate even more versatile catalyst systems for the synthetically attractive conjugate addition chemistry of nitro alkanes.

### 2.2. Conjugate Additions to α,β-Unsaturated Acyclic Enals, Enones, and Vinyl Sulfones

MacMillan and co-workers[12,13] successfully established the potential of a novel mechanistic paradigm – amine catalysis – to provide "unconventional" chemoselectivity in asymmetric conjugate additions of pyrroles and indoles to enals in the presence of chiral imidazolidinone catalysts (Scheme 3).

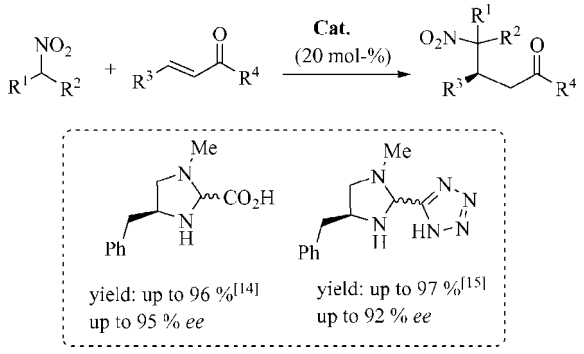



Scheme 3.

Recently, Jørgensen and co-workers[14,15] have disclosed organocatalyzed enantioselective conjugate additions of nitro alkanes to acyclic α,β-unsaturated enones in the pres-

ence of two novel imidazoline catalysts (Scheme 4). The adducts were obtained with high yields and enantioselectivities (up to 96%, 95% *ee* and 97%, 92% *ee*).




Scheme 4.

The observed stereochemistries of the products were explained in terms of the formation of the catalyst-substrate iminium intermediate **A**, in which the benzyl group of the catalyst shields the *re*-face of the enone, leaving the *si*-face open for attack (Figure 1). The favored status of the intermediate **A** may be due either to steric interactions between the methyl group of the ketone and the benzyl group, or to the possibility of a π-stacking interaction between the two aromatic rings.

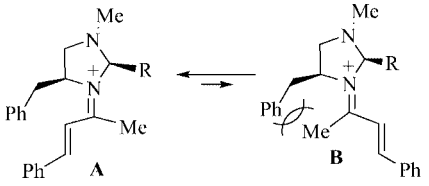
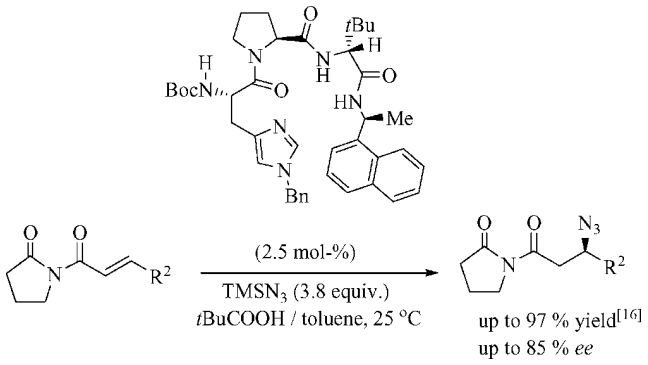



Figure 1. Possible catalyst–substrate iminium intermediates.

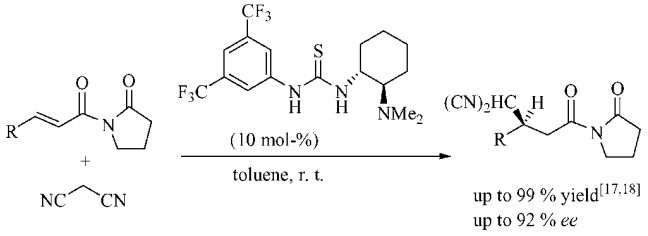
Miller et al.[16] have shown that simple β-turn peptides containing a τ-(benzyl)-His residue act as enantioselective catalysts for conjugate additions of azide to α,β-unsaturated carbonyl compounds (Scheme 5). In the presence of the β-turn tripeptide as the catalyst (2.5 mol-%) the products have been formed in excellent yields (79–97%) and with 45–85% *ee* values. Substrates that possess a γ-branch on the acrylate moiety display more enantioselective reactions. Cyclohexyl-substituted acrylate undergoes efficient conversion to azide with 85% *ee*. In addition, this reaction also represents an attractive route to β-amino acids.

Takemoto et al.[17,18] successfully developed the first highly enantioselective organocatalytic conjugate additions of malononitrile to α,β-unsaturated imides in the presence of a bifunctional thiourea (Scheme 6). The presence of the pyrrolidinone moiety in the α,β-unsaturated imides has been demonstrated to play a key role in the thiourea-catalyzed 1,4-conjugate additions. The reaction is applicable to a variety of α,β-unsaturated imides bearing aryl and alkyl groups as β substituents, and high yields (up to 99%) and




Scheme 5.

enantioselectivities (up to 92% *ee*) are attained. However, additions of other carbon nucleophiles such as malonates and β-keto esters did not give the desired products, owing to their low reactivities.




Scheme 6.

The authors proposed a ternary complex of catalyst, malononitrile, and imide as a plausible transition state in which imide and the anion of malononitrile coordinate to the thiourea moiety and to the tertiary amine group of catalyst, respectively, through hydrogen-bonding interactions (Figure 2).

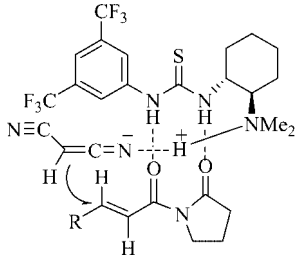
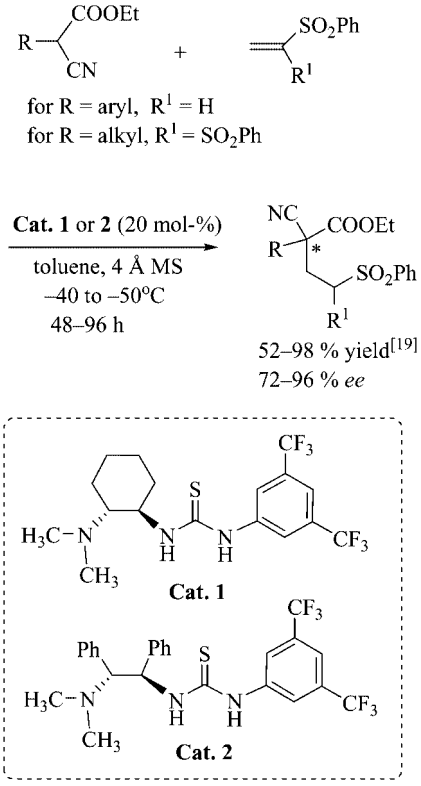


Figure 2. Proposed transition state.

Very recently, Chen and co-workers[19] have described a highly efficient organocatalytic method for asymmetric conjugate additions of α-substituted cyanoacetates to vinyl sulfones. This reaction was synergistically promoted by readily available bifunctional thiourea–tertiary amine organocatalysts (Scheme 7).

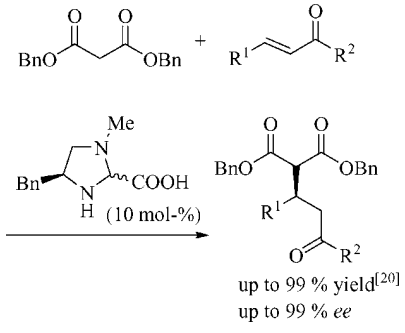



Scheme 7.

This is the first enantioselective catalytic reaction that might involve a double hydrogen-bonding interaction between the NH of thiourea and a sulfone functionality. The scope of the reaction is substantial: α-aryl or alkyl cyanoacetates could be successfully applied, and good to high enantioselectivities (72–96% *ee*) were achieved.

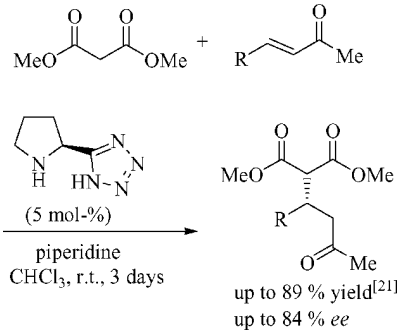
### 2.3. Conjugate Additions of Malonates and/or Ketones to Acyclic Enones

The first highly enantioselective organocatalytic 1,4-conjugate additions of malonates to α,β-unsaturated enones, in the presence of an imidazolidine catalyst, were developed by Jørgensen and co-workers[20] (Scheme 8). The reaction proceeds for a wide range of α,β-unsaturated enones with high yields (up to 99%) and excellent enantioselectivities (up to 99% *ee*).



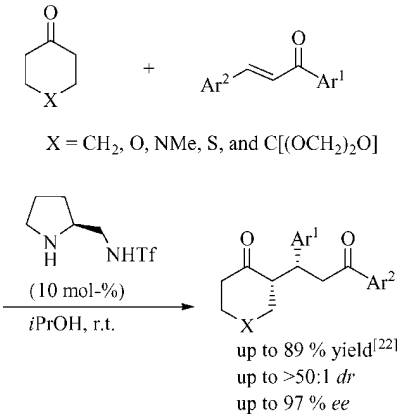

Scheme 8.

Ley et al.[21] demonstrated that the tetrazole analogue of proline acted as a useful organocatalyst for asymmetric additions of malonates to a range of enones, with good to excellent enantioselectivities (Scheme 9). The function of the base (e.g., piperidine) has not been fully established, since changing the base affects not only yields but also the enantioselectivities.




Scheme 9.

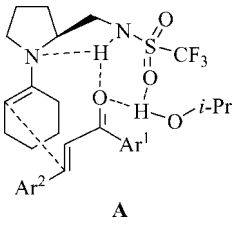
Enantioselective catalytic conjugate addition reactions of ketones to enones remain challenging. Studies probing this issue have been reported very recently by Wang's group,[22] who developed the first highly enantioselective, organocatalytic Michael addition reactions of unmodified ketones to chalcones (Scheme 10). This process, catalyzed by (*S*)-pyrrolidinesulfonamide, was carried out under mild reaction conditions to afford synthetically useful 1,5-dicarbonyl compounds in high yields (up to 89%) and with high to excellent levels of enantio- (up to 97% *ee*) and diastereoselectivity (up to >50:1 *dr*).




Scheme 10.

To account for the high levels of enantio- and diastereoselectivity of Michael addition reactions between cyclic ketones and unsaturated ketones, Wang et al. suggested a possible model **A** (Figure 3). It was proposed that the NH proton may provide transition state stabilization through a hydrogen bonding interaction with the chalcone carbonyl group. Furthermore, the $CF_3SO_2$ group was assumed to participate in an additional H-bonding interaction with the carbonyl group through *i*PrOH, providing a tighter transition state and thus higher stereoselectivities.[22]



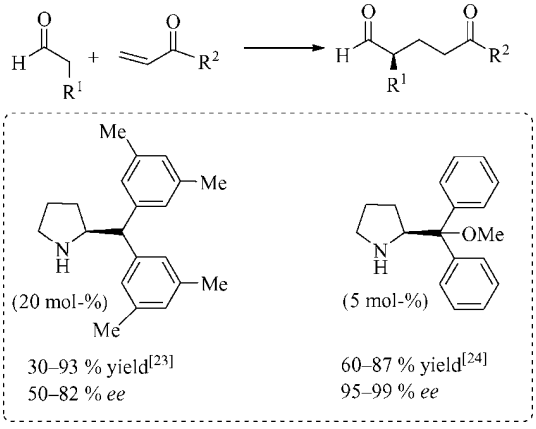
**A**

Figure 3. Proposed transition state **A**.

## 3. Direct Michael Additions of Unmodified Aldehydes and Ketones to Vinyl Ketones and Nitro Olefins

A potentially advantageous strategy in terms of atom economy involves direct additions of unmodified carbonyl compounds to Michael-type acceptors. Because of difficulties in controlling reactions of enolates or enols of aldehydes, however, there had until recently been no examples of catalytic asymmetric conjugate additions of naked aldehydes.

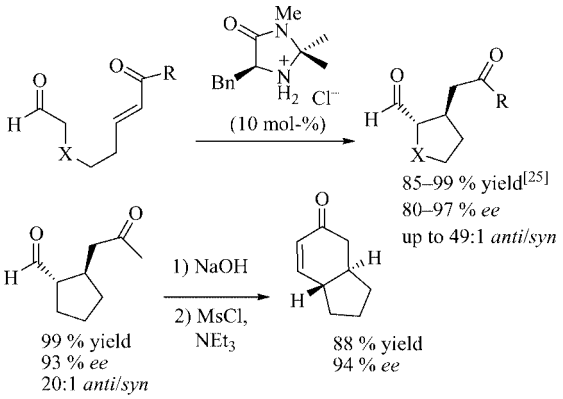
Melchiorre and Jørgensen[23] developed the first organocatalytic direct enantioselective Michael additions of simple aldehydes to vinyl ketones (Scheme 11). The reactions proceed with the formation of optically active substituted 5-keto aldehydes in moderate to high yields (30–93%) and with good enantioselectivities (50–82% *ee*), in the presence of (*S*)-2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine at a 20 mol-% loading as the catalyst.




Scheme 11.

Recently, Chi and Gellman have reported[24] that diphenylprolinol methyl ether can catalyze the same intermolecular Michael additions with high enantioselectivities (95–99%) at significantly lower (5 mol-%) catalyst loadings (Scheme 11).

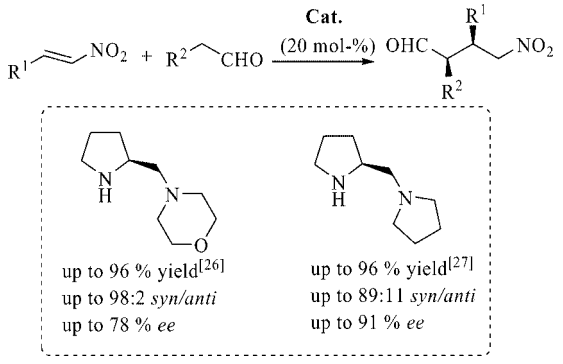
List and Hechavarria Fonseca[25] reported the first catalytic asymmetric intramolecular Michael reactions of aldehydes catalyzed by a MacMillan imidazolidinone. The process gave cyclic keto aldehydes in excellent yields, with high enantioselectivities, and under very mild and convenient reaction conditions (Scheme 12). This reaction can be included as part of a tandem process, as the keto aldehyde products readily undergo aldolization to give enones.




Scheme 12.

Michael reactions of aldehydes and ketones with nitro olefins represent a convenient route to valuable building blocks in organic synthesis.[4a] The nitro functionality can easily be transformed into a nitrile oxide, ketone, amine, or carboxylic acid, etc., providing a wide range of synthetically interesting compounds.

Barbas III et al.[26,27] have described highly diastereoselective direct catalytic Michael reactions involving the addition of unmodified aldehydes to nitro olefins in the presence of (*S*)-2-(morpholinomethyl)pyrrolidine and (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine as catalysts (Scheme 13). The reactions proceed in good to high yields (up to 96%) in a highly *syn*-selective manner (up to 98:2), with up to 91% *ee* values.

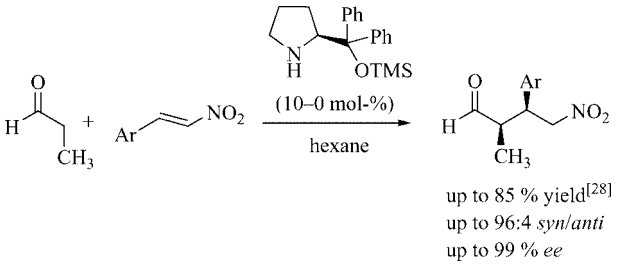



Scheme 13.

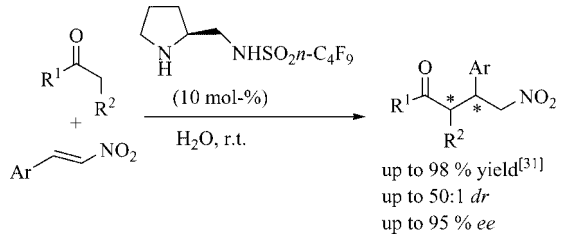
With the development of highly enantioselective Michael reactions of aldehydes and nitro alkenes, Hayashi and coworkers[28] showed that silylation of the prolinol can dramatically improve its catalytic activity (Scheme 14). The reaction has broad applicability with respect both to the Michael acceptor and to the donor; in most of the cases examined the adducts were obtained in nearly optically pure form (99% *ee*) and with excellent *syn* diastereoselectivities.

Chiral (*S*)-pyrrolidine trifluoromethanesulfonamide has been shown by the Wang group[29,30] to serve as an effective catalyst for direct Michael additions of aldehydes and ketones to nitro olefins (Scheme 15). Studies with linear chain aldehydes revealed that these substrates reacted much




Scheme 14.



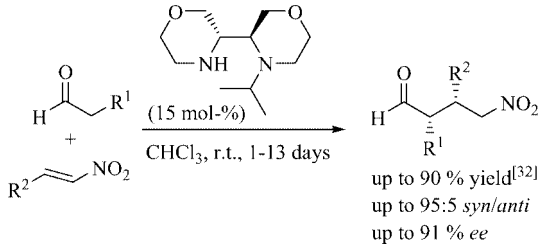

Scheme 16.

more rapidly than the more hindered α,α-dialkyl aldehydes. More significantly, reactions with β-nitrostyrenes bearing either electron-withdrawing or electron-donating substituents occurred with excellent levels of enantio- (94–99% *ee*) and diastereoselectivity (up to 50:1 *dr*).

The generality of Michael addition reactions between ketones and nitro olefins promoted by (*S*)-pyrrolidine trifluoromethanesulfonamide was also explored. Excellent levels of enantio- (97% *ee*) and diastereoselectivity (up to 50:1 *dr*) accompanied the reactions of cyclohexanone, but, in contrast, almost no reaction occurred in the cases of five- and seven-membered ring cyclic ketones, presumably due to difficulties in the formation of enamines. The electronic natures of the substituents on the nitro olefins had no effect on stereoselectivity; excellent levels of enantio- (96–99% *ee*) and diastereoselectivity are observed (Scheme 15).

The development of organocatalysts that promote reactions in the environmentally clean, safe, and cheap solvent water is a significant goal. More recently, Wang's group has reported[31] a recyclable and reusable fluorous (*S*)-pyrrolidine sulfonamide organocatalyst for promotion of highly enantio- and diastereoselective Michael addition reactions of aldehydes and ketones with nitro olefins in water (Scheme 16). They demonstrated that fluorous (*S*)-pyrrolidine sulfonamide is a robust catalyst that is effective in water and can be readily separated and reused without significant loss of catalytic activity and stereoselectivity.

Very recently, Alexakis and co-workers[32] have developed new 3,3′-bimorpholine derivatives for asymmetric conjugate additions of various aldehydes to different nitro olefins (Scheme 17). Interestingly, the natures of aromatic nitro olefins had no influence either on the stereoselectivity or on the yield, but non-aromatic groups on the nitro olefins played a crucial role in terms of reactivity. Although the stereoselectivity was maintained, the reactivity, and consequently the yield, decreased dramatically in the case of nitro olefins bearing saturated cyclic systems (e.g. $R^2$ = *c*Hex).

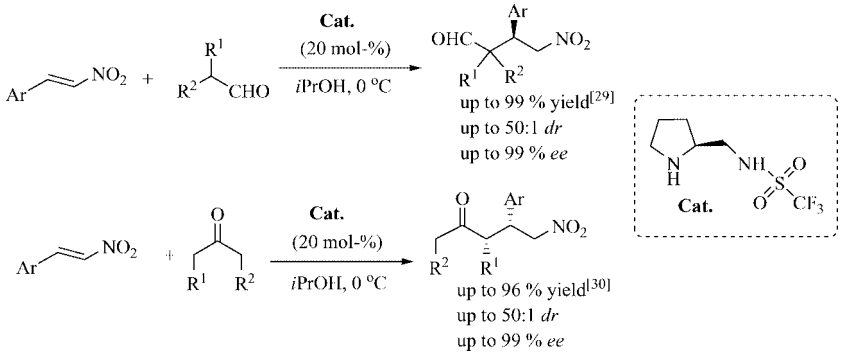



Scheme 17.

Barbas,[33] List,[34] and Enders[35] with co-workers independently reported the first organocatalytic additions of acetone to *trans*-β-nitrostyrene in the presence of L-proline as the catalyst. Other amines also seemed to be potentially interesting as organocatalysts, and several examples using amines in asymmetric catalytic Michael additions have been reported recently.

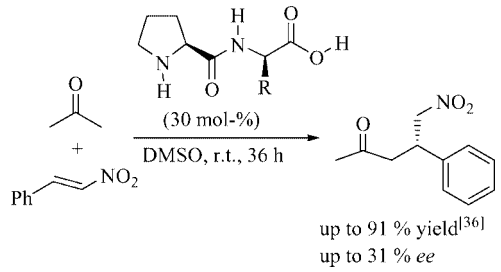
List and Martin[36] have shown that N-terminal prolyl peptides are promising asymmetric aminocatalysts (Scheme 18).

Alexakis et al.[37–39] reported additions of aldehydes and ketones to nitrostyrene catalyzed by chiral 2,2′-bipyrrolidines (Scheme 19). With acetone the reactions gave nonnegligible quantities of dinitro adduct, but the addition of a catalytic amount of *p*TSA (0.15 equiv.) completely eliminated the formation of this byproduct and also produced an increase in the reaction rate.

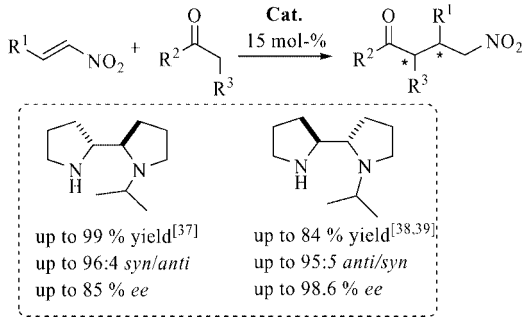



Scheme 15.



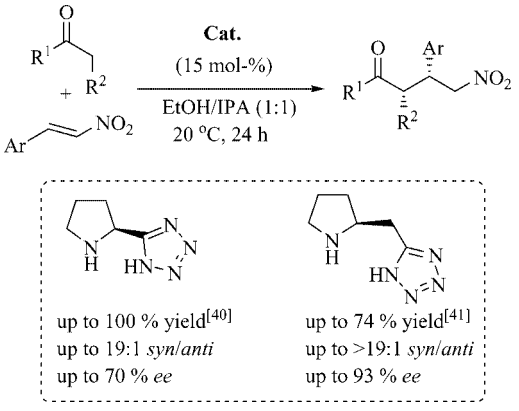

Scheme 18.




Scheme 19.

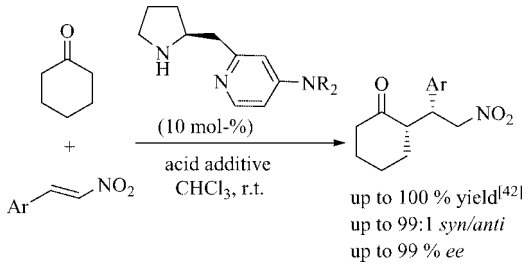
Catalytic Michael additions of unsymmetrical ketones such as methyl ethyl ketone and methyl propyl ketone raised the issue of regioselectivity.[37] When the enamine was formed under kinetic conditions, the less hindered methyl group reacted preferentially, in a low to moderate regioisomer ratio (43:57 and 33:67, respectively). In the presence of *p*TSA or the hydrochloride catalyst, the formation of the enamine under thermodynamic conditions inverted the regioselectivity to 74:26.[37]

Several advances in asymmetric additions of ketones to nitroolefins with the aid of two proline-derived tetrazole catalysts have been discovered by Ley et al.[40,41] (Scheme 20). The results are a definite improvement on those previously reported in the literature for this reaction with L-proline.[33–35] These organocatalysts far outperfom L-proline in terms of yield, enantioselectivity, reaction times, and stoichiometry.




Scheme 20.

Kotsuki et al.[42] have developed a new direct method for asymmetric Michael addition reactions of ketones to nitro olefins in the presence of new pyrrolidine-pyridine conjugate base catalysts, which are easily prepared from L-prolinol. The reaction was highly efficient in terms of productivity (up to 100% yield), enantioselectivity (up to 99% *ee*), and *syn* diastereoselectivity (up to 99:1 *syn*/*anti*, Scheme 21). To account for the highly enantio- and diastereoselective Michael addition reactions, Kotsuki's group proposed an acyclic synclinal transition state, in which the pyridinium ring must effectively shield the *si*-face of an enamine double bond, as depicted in Figure 4.




Scheme 21.

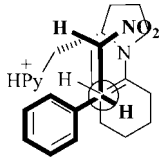
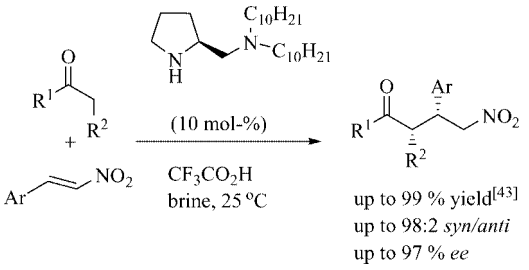


Figure 4. Proposed acyclic synclinal transition state.

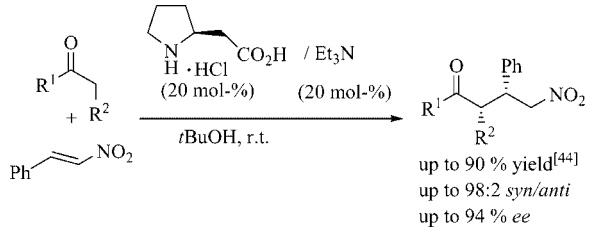
Since several studies had indicated that amine catalysts behave as initiators of polymerization, Barbas III et al.[43] very recently hypothesized that, if the anion intermediate derived from the addition of the amine catalyst to β-nitrostyrene could be stabilized, polymerization should be inhibited and the chemical yield should be improved. They found that the best results were obtained when brine was used as a solvent, providing excellent yields and high levels of diastereo- and enantioselectivity. The authors also reported that yield and enantioselectivity were essentially the same in seawater taken directly from the Pacific Ocean. Addition of TFA to the reaction in brine improved chemical yields by acceleration of enamine formation. The diamine/TFA bifunctional catalyst system thus demonstrated excellent reactivity (up to 99% yield), diastereoselectivity (up to 98:2 *dr*), and enantioselectivity (up to 97% *ee*) in brine (Scheme 22).

Oriyama et al.[44] envisaged that (*S*)-homoproline might catalyze highly enantioselective carbon–carbon bond formation and developed asymmetric Michael addition reactions of ketones to β-nitrostyrene and its derivatives in the presence of (*S*)-homoproline as a chiral organocatalyst (Scheme 23). The reaction was highly diastereoselective (up to 98:2 *dr*) and enantioselective (over 90% *ee*).

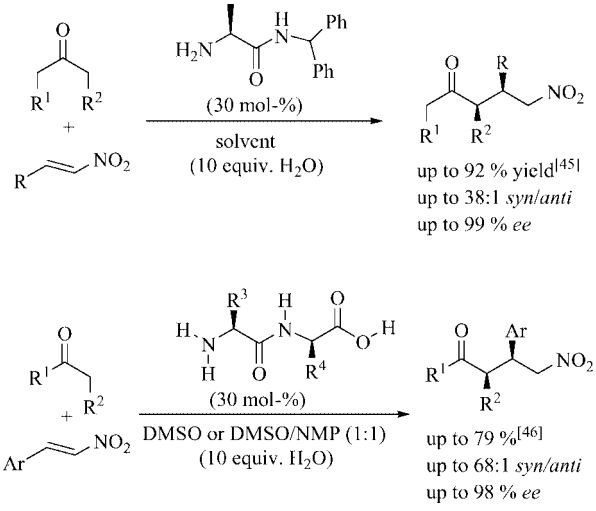



Scheme 22.




Scheme 23.

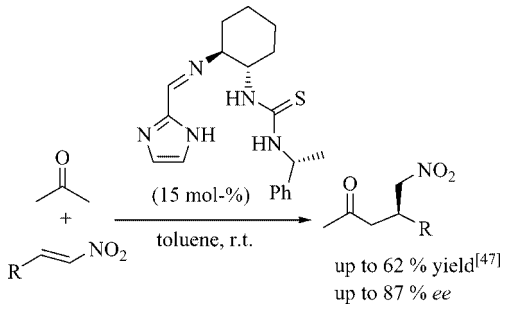
Córdova and co-workers[45,46] have reported that highly modular amino acid derivatives and simple dipeptides with a catalytic primary amine residue catalyze direct asymmetric Michael additions of ketones to nitro olefins with high stereoselectivity to furnish the corresponding γ-nitro ketones with up to 38:1 *dr*/99% *ee* and 68:1 *dr*/98% *ee*, respectively (Scheme 24).




Scheme 24.

A different vista has been opened up by some recent contributions from our and other research groups, who have shown that chiral thiourea-based bifunctional compounds can act as efficient organocatalysts for asymmetric Michael reactions between ketones and nitro olefins.[47–50]

Recently we synthesized[47] some novel bifunctional organocatalysts bearing both a thiourea moiety and an imidazole group on a chiral scaffold, and applied them in nitro-Michael addition reactions (Scheme 25). In the case studied (addition of acetone to *trans*-β-nitrostyrene) the selected chiral bifunctional organocatalyst gave enantioselectivities (87% *ee*) superior to those generated by L-proline (0–12% *ee*)[33–35] and/or proline derivatives (31–42% *ee*).[36,39,41]




Scheme 25.

Although a remarkable improvement in the *ee* value (87% *ee*) was achieved with this novel bifunctional organocatalyst, the yield was only moderate (up to 62%, Scheme 25). In view of the fact that secondary and primary amines with ketones reversibly form enamines,[5,33–35,39] which can further react with electrophiles, we have further designed and synthesized[48,49] new chiral bifunctional organocatalysts possessing both a thiourea moiety and an amine group as a base (Scheme 26).

The use of proline-based chiral thioureas, in the presence of 0.15 equiv. of AcOH and 2 equiv. of $H_2O$ as additives, gave the product in only 3% *ee* and in only moderate yields (up to 55%). Notably, much higher catalytic activities were displayed under the same reaction conditions by catalysts containing just a primary amine group in place of the proline moiety (84–91% *ee*, 85–98% yields).

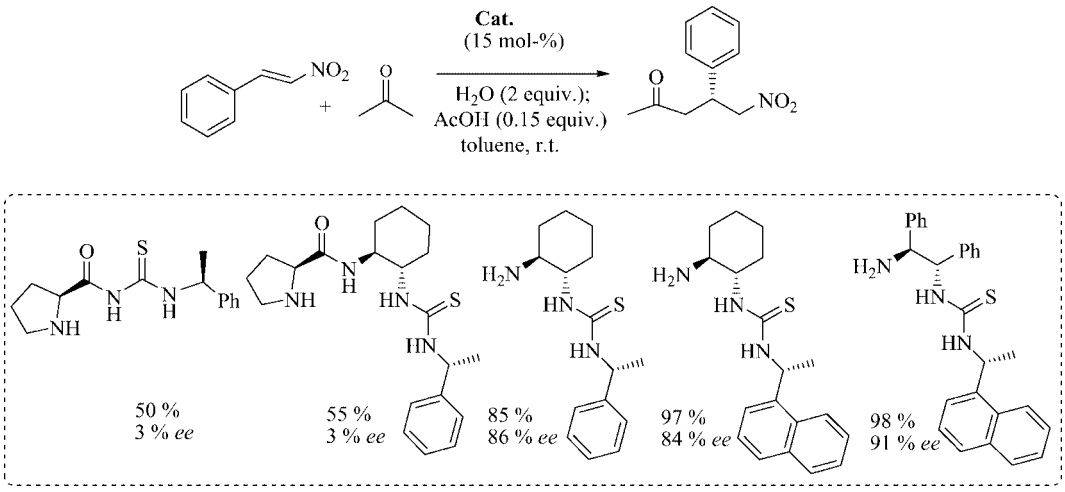
To explain the predominant production of (*R*) adducts we have computationally determined the first-order saddle points ("transition state structures") for the formation of both (*R*) and (*S*) enantiomers with one of the new catalysts.[48] Our results gave clear evidence that only one oxygen atom of the nitro group is bound to the thiourea moiety (Figure 5).

We have demonstrated for the first time that chiral thioureas derived from primary amines can catalyze asymmetric nitro-Michael additions, giving high yields (82–99%) and enantioselectivities (90–98% *ee*) and good diastereoselectivities (up to 83:17 *syn*/*anti*) for acetone, cyclic ketones (e.g., cyclohexanone and tetrahydrothiopyran-4-one), and different aromatic nitro olefins. Surprisingly, additions of unsymmetrical ketones such as methyl ethyl ketone to β-nitrostyrene under the same conditions gave the opposite diastereomer (14:86 *syn*/*anti*) with very high enantiocontrol (>99% *ee*; Scheme 27).[49]

From these results we proposed the plausible transition state model **A**, which reasonably explains the relative (*syn*) and absolute configurations of the Michael adducts. To explain the inversion of diastereoselectivity with methyl ethyl ketone as a substrate we assumed the formation of the (*Z*) enamine intermediate **B** (Figure 6).[49]

Very recently, another primary amine/thiourea catalyst system was reported by Jacobsen and Huang[50] for ketone/




Scheme 26.

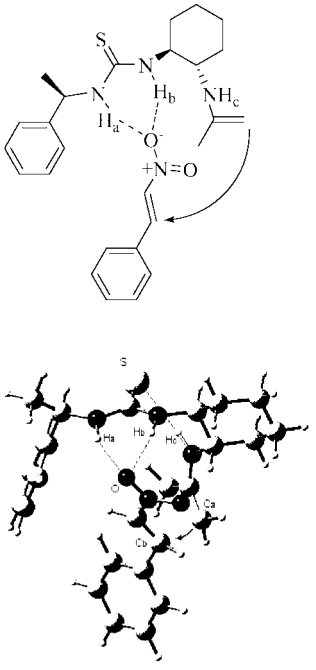
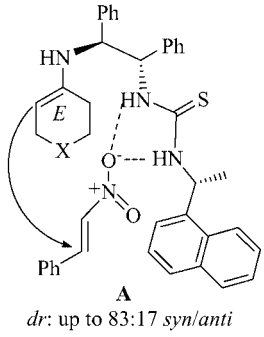


Figure 5. Transition state structure for the formation of the (*R*) enantiomer (DFT calculations with Gaussian03 program package).



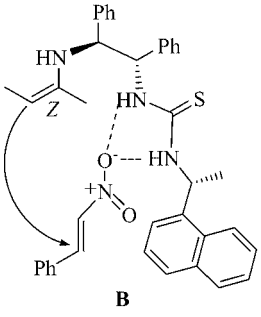
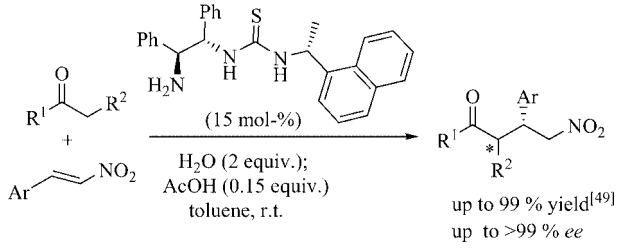




Figure 6. Proposed transition states for Michael reactions of symmetrical (**A**) and unsymmetrical ketones (**B**) with *trans*-β-nitrostyrene.

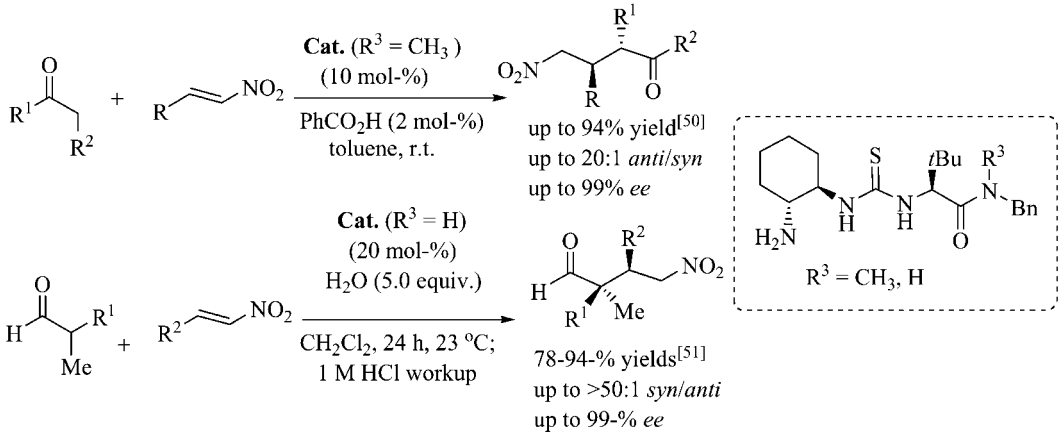



Scheme 27.

nitro alkene Michael reactions (Scheme 28). A wide range of aromatic and heteroaromatic nitro alkenes underwent reactions with acetone in high yields and with good enantioselectivities in the presence of the new thiourea/amine catalyst and on addition of catalytic amounts of weak acids, such as benzoic acid. Nitro alkenes bearing β-substituents proved to be viable electrophilic reacting partners in the presence of added benzoic acid. The catalyst displayed a marked bias toward activation of ethyl ketones, allowing regio- and diastereoselective formation of a variety of branched products bearing contiguous tertiary stereocenters. *N*-Alkyl ethyl ketones afforded Michael adducts with complete regioselectivity, high enantiomeric excesses (up to 99% *ee*), and diastereoselectivity favoring the *anti* isomers (up to 20:1 *dr*).

Jacobsen and co-workers[51] have also shown that a similar chiral primary amine/thiourea catalyst is highly effec-

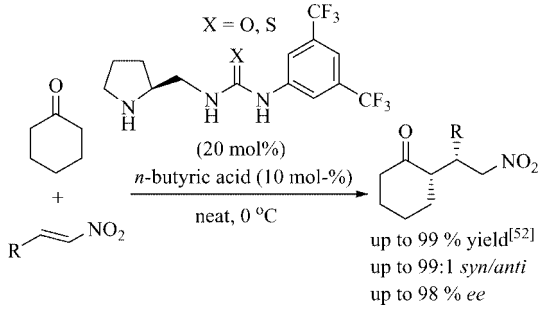
  




Scheme 28.

tive in the addition of α,α-disubstituted aldehydes to nitro alkenes, generating synthetically versatile nitro aldehyde adducts. Simultaneous activation of both nucleophile and electrophile allows this challenging transformation to take place under mild reaction conditions and with broad substrate scope (Scheme 28).

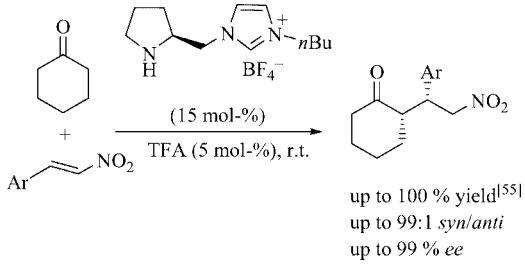
Tang and co-workers[52] have recently synthesized two pyrrolidine/urea(thiourea)-based bifunctional organocatalysts, which have been applied to asymmetric Michael reactions of cyclohexanone with both aryl- and alkylnitro olefins. Addition of catalytic amounts of organic acids was capable of increasing the reaction rate dramatically without any deterioration in enantiomeric excess (Scheme 29). When *n*-butyric acid was used as an additive, *trans*-nitro olefins were converted into the desired products rapidly, with high diastereoselectivities (up to 99:1 *dr*) and good to high enantioselectivities (up to 98% *ee*).




Scheme 29.

Interesting results were also observed by Toma et al.[53] for Michael additions in an ionic liquid. 1-Butyl-3-methylimidazolium hexafluorophosphate ([bmim]$PF_6$) was shown to be a good solvent for L-proline-catalyzed additions of aldehydes and ketones to β-nitrostyrene. Aldehydes proved to be much better donors than ketones, which were in turn better than β-diketones, indane-1,3-dione being the exception. Reactions with ketones require elevated temperatures to achieve good yields of products.

Functional ionic liquids have recently been receiving growing attention, due to their advantages as reusable homogeneous supports, reaction media, and reagents. Important progress in the development of chiral ionic liquids (CILs) has also been made in the last few years.[54] Quite recently, Luo, Cheng, and co-workers[55] synthesized a series of pyrrolidine-type CILs by starting from L-proline as the "chiral pool" source and examined the application of these CILs in asymmetric Michael additions. The reactions were carried out in neat mixtures in the presence of 15 mol-% of catalyst and 5 mol-% of TFA as co-catalyst. Consistently with previous reports,[37–39,43,48–50,52] the use of an acidic co-catalyst was essential in their catalytic system (Scheme 30).



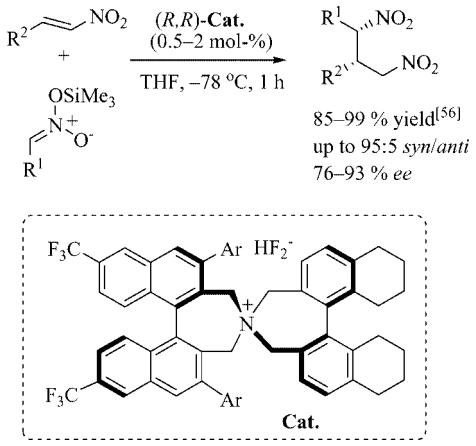

Scheme 30.

## 4. Conjugate Addition Reactions of Silyl Nitronates, Malonates, β-Keto Esters, and Pentane-2,4-dione to Nitro Olefins

Maruoka and co-workers[56] have very recently achieved efficient and highly diastereo- and enantioselective formal conjugate additions of nitro alkanes to nitro alkenes with the aid of a novel chiral quaternary ammonium bifluoride catalyst in combination with silyl nitronates (Scheme 31).

This strategy greatly expands the applicability of conjugate addition chemistry involving organonitro compounds and provides a reliable route to optically active 1,3-dinitro compounds, which are synthetically useful intermediates for a wide range of valuable 1,3-difunctionalized organic molecules.

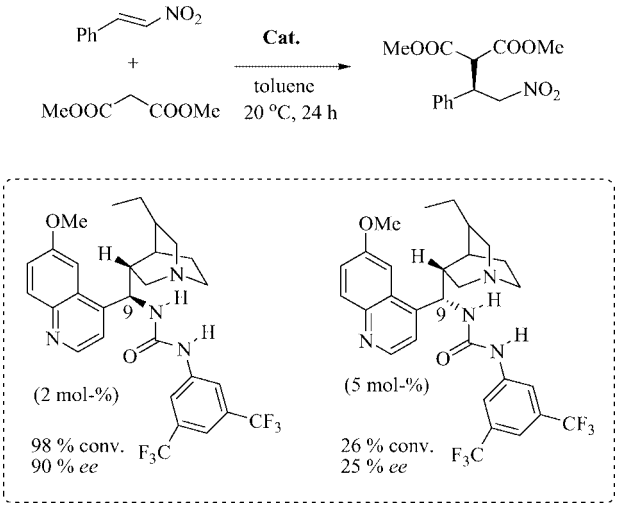



Scheme 31.

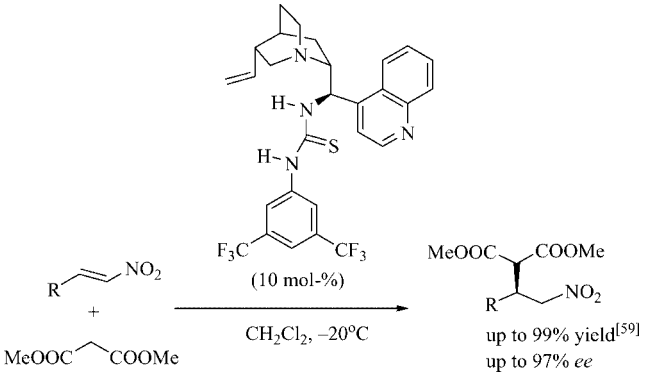
Deng et al.[57] developed a new class of chiral bifunctional organocatalysts based on cinchona alkaloids. These catalysts are easily accessible from either quinine or quinidine and have been shown to be highly efficient for synthetically important C–C bond-forming asymmetric additions of 1,3-dicarbonyl compounds to β-nitrostyrenes. It was demonstrated that the readily available 6′-demethylated quinine and quinidine alkaloids are considerably more active and selective catalysts than their natural 6′-methylated analogues. A wide range of nitro alkenes bearing aryl, heteroaryl, and alkyl groups were treated with dimethyl malonate in THF at –20 °C in the presence of quinine catalyst (Scheme 32).

Connon and McCooey[58] modified the cinchona alkaloid structural backbone by substituting the hydroxy group at C9 with an aryl(thio)urea moiety and applied the new bifunctional compounds as efficient organocatalysts for asymmetric additions of dimethyl malonate to nitro alkenes. Interestingly, the inversion of the absolute configuration at C9 in these thio(urea)-substituted systems dramatically improved catalyst activity and selectivity (Scheme 33).

A new 9-amino (9-deoxy) epicinchonine thiourea derivative was identified by Dixon et al.[59] as an effective bifunctional organocatalyst and was found to induce high enantioselectivity in malonate ester addition reactions to a range of nitroolefins (Scheme 34). Aliphatic nitro olefins reacted more slowly than their aromatic counterparts and slight deterioration in enantioselectivity was witnessed.

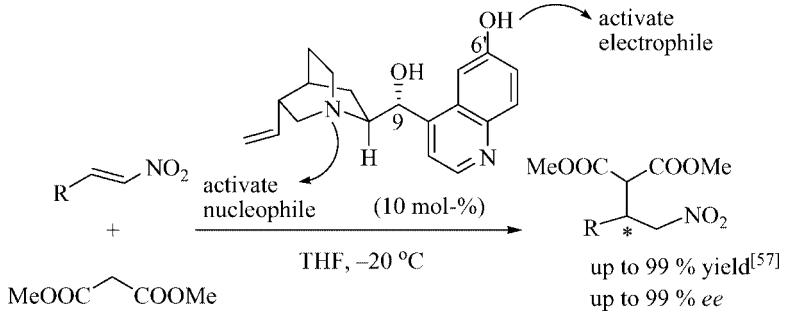



Scheme 33.



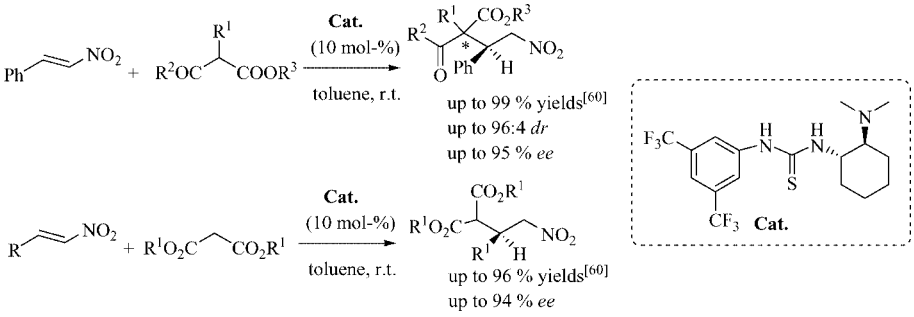

Scheme 34.

Takemoto and co-workers[60] have reported for the first time that a novel bifunctional catalyst (bearing a thiourea moiety and a tertiary amino group on a chiral scaffold) permits Michael reactions of α-substituted β-keto esters to nitro olefins with high enantioselectivity (up to 95% *ee*) and diastereoselectivity (up to 96:4; Scheme 35). They also examined the scope of Michael reactions of nitro olefins with a series of malonates in the presence of the same catalyst. The ester group size in the malonates had a marginal effect on the enantioselectivities of the Michael adducts (up to




Scheme 32.




Scheme 35.

94% *ee*), but large ester groups such as *tert*-butyl ester decreased the reactivities of the malonates.

The authors have proposed that the bifunctional thiourea catalyst interacts with a nitro group of the nitro olefin, enhancing its electrophilicity, while at the same time the tertiary amine activates the nucleophile through hydrogen bonding (Figure 7).

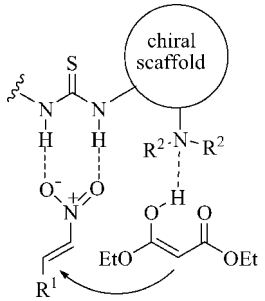
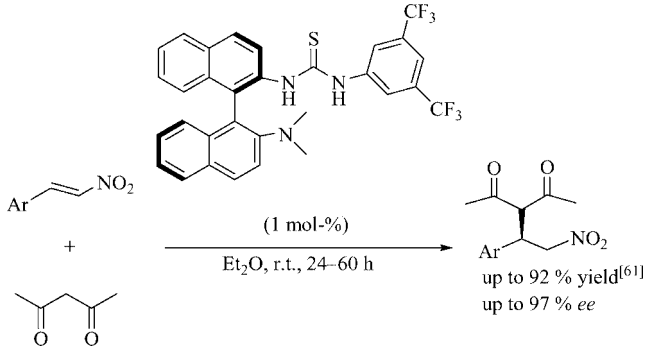



Figure 7. Proposed double activation with the bifunctional organocatalysts.

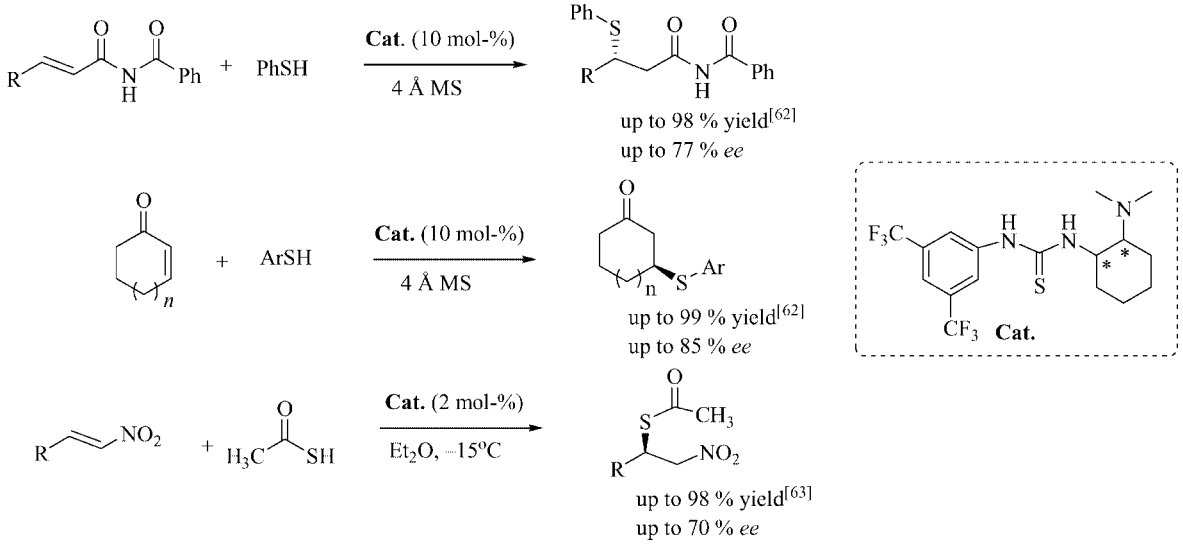
Recently, Wang and co-workers[61] have developed a new bifunctional binaphthyl-derived amine thiourea, which serves as an efficient organocatalyst for asymmetric Michael additions of 1,3-diketones to nitro olefins. Because of its high catalytic activity, utilization of the catalyst in amounts as low as 1 mol-% is sufficient for the process (Scheme 36). Moreover, the Michael addition products can readily be converted into the valuable α-substituted-β-amino acid building blocks.




Scheme 36.

## 5. Conjugate Additions of Thio Derivatives to α,β-Unsaturated Carbonyl Compounds and Nitro Olefins

Cheng et al.[62] successfully applied Takemoto's catalyst in asymmetric 1,4-additions of arylthiols to α,β-unsaturated

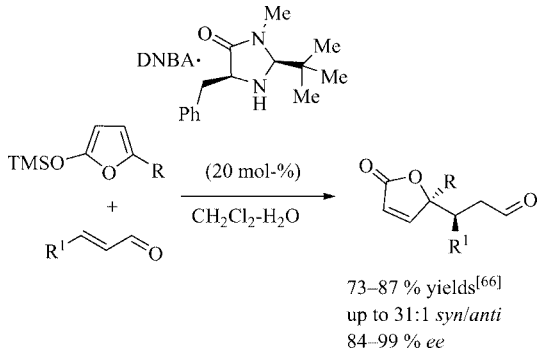



Scheme 37.

carbonyl compounds. The reactions showed good substrate scope and up to 85% *ee* values have been achieved (Scheme 37).

Very recently, Wang and co-worker[63] have developed a method for organocatalytic, enantioselective 1,4-addition reactions of thioacetic acid with a range of *trans*-β-nitrostyrenes. The processes, promoted by the same chiral amine thiourea organocatalyst, take place in high yields (91–98%) with up to 70% *ee*s under mild reaction conditions (Scheme 37). This study represents the first example of the use of a chiral organocatalyst to catalyze 1,4-conjugate addition reactions of a less reactive thioacid with β-nitrostyrenes.




Scheme 38.

## 6. Multicomponent Domino (Cascade, Tandem) Reactions Involving 1,4-Conjugate Additions

An impressive number of domino reactions[64] (also known as cascade or tandem reactions) have been accomplished in recent years.[65] All of these reaction sequences were initiated by an inorganic or organometallic catalyst, or by thermal reactions. Recently, MacMillan[66,67] List,[68] and Jørgensen[69] have developed new strategies for organocatalysis allowing increasingly rapid access to structural complexity from simple starting materials and catalysts through domino processes, while achieving high levels of enantiocontrol.

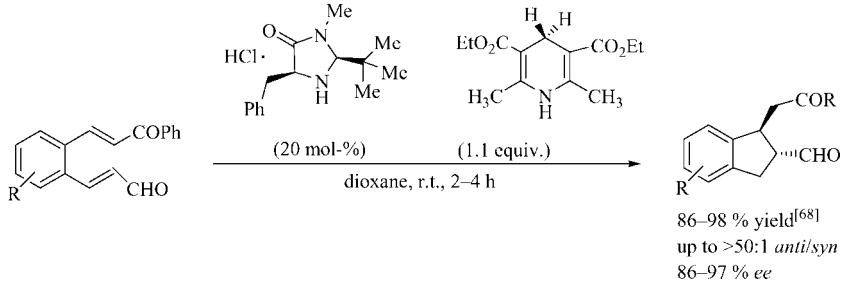
The first enantioselective organocatalytic Mukaiyama–Michael reaction using α,β-unsaturated aldehydes was accomplished by MacMillan and co-workers.[66] The use of iminium catalysis has provided a new strategy for enantioselective additions of 2-silyloxy furans to unsaturated aldehydes to generate a variety of butenolide systems. The imidazolidinone amine catalyst (20 mol-%) has been found to mediate 1,4-conjugate additions of a wide variety of substituted and unsubstituted silyloxy furans to unsaturated aldehydes (Scheme 38).

List et al.[68] have developed highly efficient and chemo-, regio-, diastereo-, and enantioselective organocatalytic tandem conjugate reduction-Michael cyclizations of enal enones (Scheme 39). They have demonstrated that treatment of the enal enone with Hantzsch dihydropyridines in the presence of catalytic amounts of an imidazolidinone organocatalyst provides cyclic keto aldehydes in high yields (up to 98%) and enantiomeric excesses (up to 97% *ee*). The authors assume that the reaction proceeds through an iminium catalytic conjugate reduction followed by an in situ enamine catalytic asymmetric Michael cyclization.

Jørgensen and co-workers[69] have recently reported a novel and simple approach to the synthesis of highly functionalized molecules containing two adjacent stereocenters, presenting an organocatalytic asymmetric multicomponent domino and a conjugated addition reaction to provide α,β-unsaturated aldehydes through the use of 2-{bis[3,5-bis(trifluoromethyl)phenyl](trimethylsilanyloxy)methyl}-pyrrolidine as organocatalyst (Scheme 40). The multicomponent reactions proceed to give enantiopure aminothiols in moderate to good yields (38–72%) and with excellent *ee* values (97–99%). Furthermore, organocatalyzed thiol additions to α,β-unsaturated aldehydes were shown to take place in good yields (73–87%) and with high enantioselectivities (89–97% *ee*).

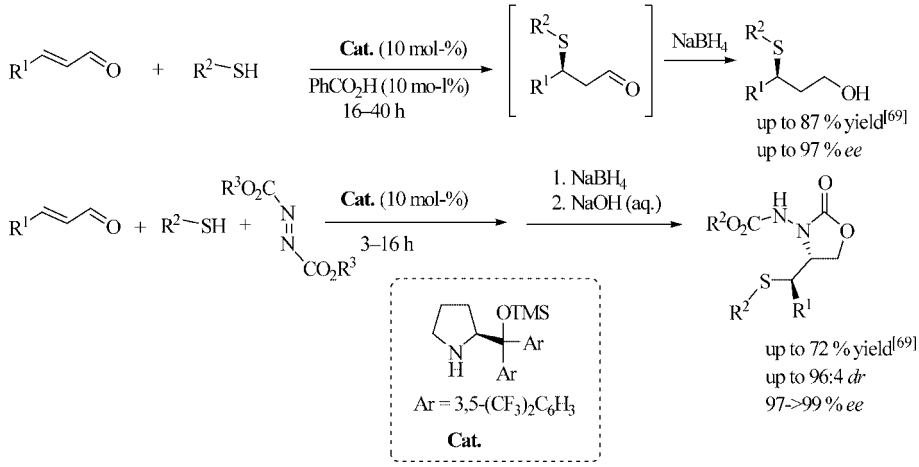
Wang et al.[70] have developed highly enantioselective tandem Michael-aldol reactions of α,β-unsaturated aldehydes with 2-mercaptobenzaldehydes promoted by (*S*)-diphenylpyrrolinol silyl ether. The method affords one-pot access to chiral and synthetically useful thiochromenes with good to high yields (72–97%) and enantioselectivities (85–95% *ee*, Scheme 41).

Very recently, Enders and co-workers[71] have developed chemo-, diastereo- and enantioselective three-component domino reactions, accomplished with the proline-derived organocatalyst, to afford tetrasubstituted cyclohexene carbaldehydes (Scheme 42). The four stereogenic centers are generated in three consecutive carbon–carbon bond-forming steps with high diastereo- and enantioselectivity.

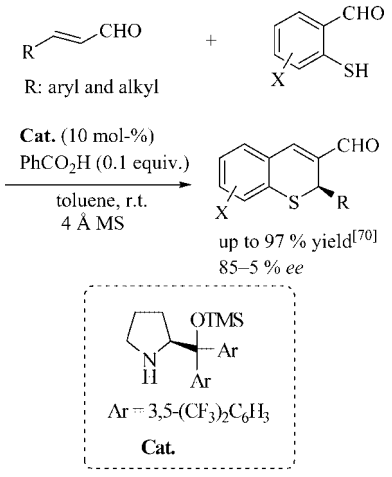



Scheme 39.

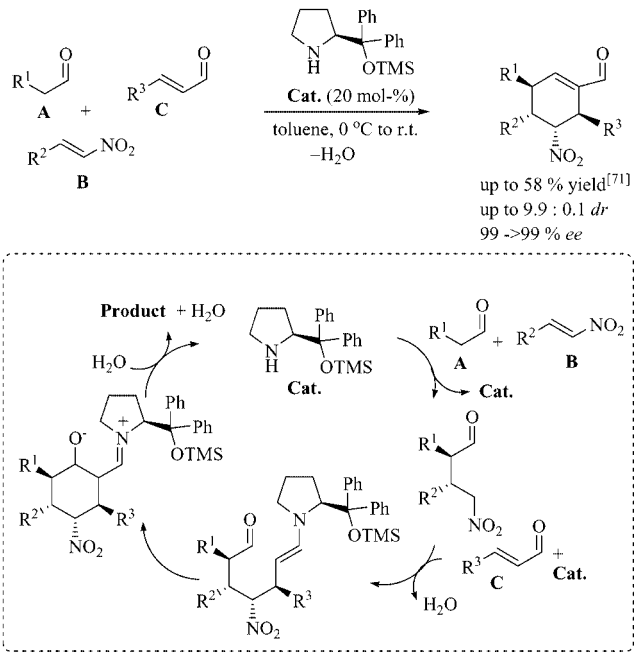
  




Scheme 40.




Scheme 41.




Scheme 42.

The authors proposed that, in the first step, the catalyst activates component **A** by enamine formation, which then selectively adds to the nitro alkene **B** in a Michael-type reaction. The subsequent hydrolysis regenerates the catalyst, which could form the iminium ion of the α,β-unsaturated aldehyde **C** to accomplish the second conjugate addition with the previously formed nitro alkane (Scheme 42).

This approach combines all the advantages of domino reactions as well as asymmetric organocatalysis and provides a simple and flexible route to polyfunctional cyclohexene building blocks.

## 7. Conclusions

The 1,4-conjugate addition is definitely one of the most versatile tools for the preparation of valuable building blocks in organic synthesis. Considerable progress in this field has been made in the last few years through the employment of chiral organocatalysts. Notably, highly effective asymmetric organocatalytic additions of various nucleophiles to α,β-unsaturated cyclic and acyclic enals, enones, vinyl sulfones, and nitro olefins, addition of malonates and/or ketones to acyclic enones, or of aldehydes and ketones to vinyl ketones and nitro olefins, as well as multi-component domino reactions have been developed.

The high degree of enantio- and diastereocontrol that can be achieved in different 1,4-conjugate addition reactions has been shown by examination of L-proline, chiral pyrrolidine derivatives, imidazolidinones, N-spiro chiral quaternary ammonium bromide, bimorpholine derivatives, short peptides, thiourea-based bifunctional compounds, and cinchona alkaloid derivatives – as well as chiral ionic liquids – as effective new asymmetric organocatalysts.

The ever expanding contributions to asymmetric organocatalytic 1,4-conjugate addition reactions confirm that this field of research continues to be very attractive for synthetic chemists and further exciting discoveries of novel chiral organocatalysts are to be expected in the near future.

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Received: July 27, 2006
Published Online: March 1, 2007

  