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Review

Advances in asymmetric organocatalytic reactions catalyzed by chiral primary amines

Fangzhi Peng, Zhihui Shao *

Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming 650091, People's Republic of China

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Abstract

A short review on the development and application of chiral primary amine catalysts in organocatalytic enantioselective reactions has been described.

Keywords: Chiral primary amines; Organocatalysis; Asymmetric reactions

Contents

1. Introduction

The asymmetric organocatalysis, in which small chiral organic molecules catalyzed enantioselective reactions, has grown explosively to become the main focus of research in asymmetric synthesis [1–6]. Over the past few years, a number of chiral organocatalysts have been developed for different asymmetric transformations. Among them, chiral secondary amines are probably the most intensively used organocatalysts so far. In contrast, chiral primary amine catalysts are largely neglected, probably due to unfavorable imine-enamine equilibria. Recently, chiral primary amines have emerged as new and powerful cat-

* Corresponding author. Tel.: +86 871 5031119; fax: +86 871 5035538.
E-mail address: zhihui_shao@hotmail.com (Z. Shao).

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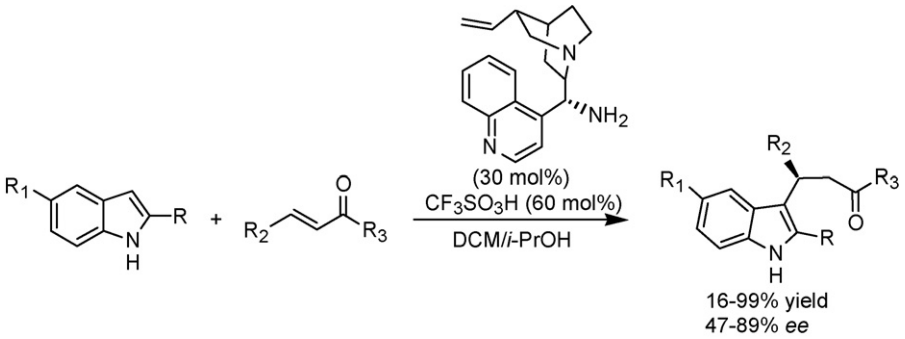


Scheme 1. Asymmetric Friedel–Crafts alkylations of indoles with α, β-unsaturated ketones..

alysts for enantioselective organocatalytic reactions. In this review, the development and application of chiral primary amine catalysts in enantioselective organocatalytic reactions have been described.

2. Asymmetric organocatalytic reactions catalyzed by chiral primary amines

Asymmetric organocatalytic reactions promoted by chiral primary amines occur through two types of activation modes: enamine catalysis and iminium catalysis [7]. Aldehydes or ketones are activated by enamine formation, and α,β-unsaturated carbonyl compounds are activated by iminium-ion formation.

2.1. Iminium catalysis

2.1.1. Friedel-Crafts alkylation of indoles with α,β-unchelating unsaturated ketones

The catalytic asymmetric Friedel-Crafts alkylation of indoles with α,β-unsaturated carbonyl compounds is an important method for the synthesis of chiral indole derivatives [8,9]. In 2002, Austin and MacMillan [10] presented the first enantioselective organocatalytic Friedel-Crafts indole alkylation of α,β-unsaturated aldehydes in the presence of a chiral imidazolidinone catalyst. Nevertheless, such a catalytic system was ineffective for the stereoselective addition of indoles to α,β-unsaturated ketones and poor enantioselectivity (25% e.e.) has been observed [11].

The first enantioselective organocatalytic Friedel–Crafts alkylation of indoles with simple α,β-unsaturated ketones was developed by Chen et al. [12] (Scheme 1). This process, catalyzed by a chiral primary amine derived from natural cinchonine, afforded chiral indole derivatives in moderate to good yields (16–99%) and enantioselectivities (47– 89% e.e.).

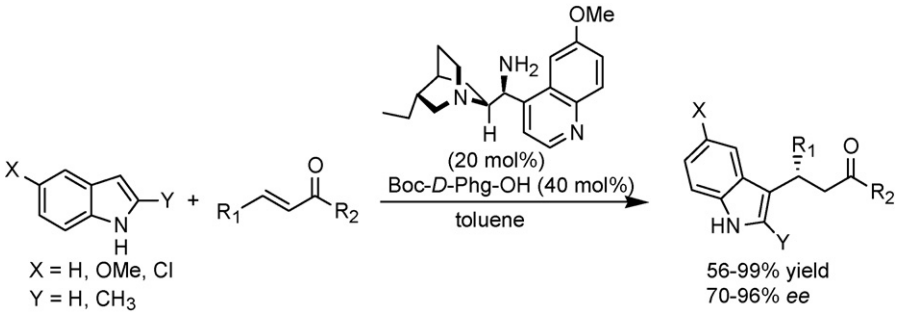
This is the first organocatalytic enantioselective Friedel–Crafts alkylation of indoles with nonchelating α,β-unsaturated ketones [13,14].

More recently, Bartoli et al. [15] have developed a new method for organocatalyzed enantioselective Friedel–Crafts alkylation of indoles with simple α,β-unsaturated ketones in the presence of a primary amine salt, in which both the cation and the anion are chiral (Scheme 2). The reactions gave the enantioenriched β-indolyl derivatives in good yields and with up to 96% e.e.

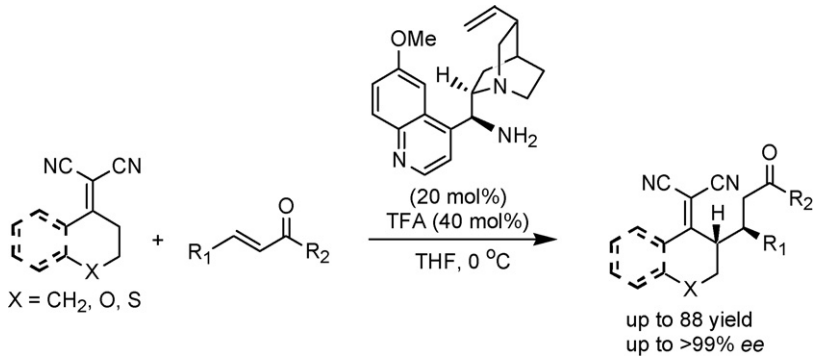
It should be noted that chiral secondary amines such as L-proline and the MacMillan second generation imidazolidinone catalyst have been found to be ineffective for enantioselective Friedel–Crafts alkylation of indoles with α,β-unsaturated ketones. The relative bulkiness of secondary amines was thought to be unfavorable for the generation of congested iminium ions from α,β-unsaturated ketones.

2.1.2. Vinylogous Michael addition of α,α-dicyanoalkenes toα,β-unsaturated ketones

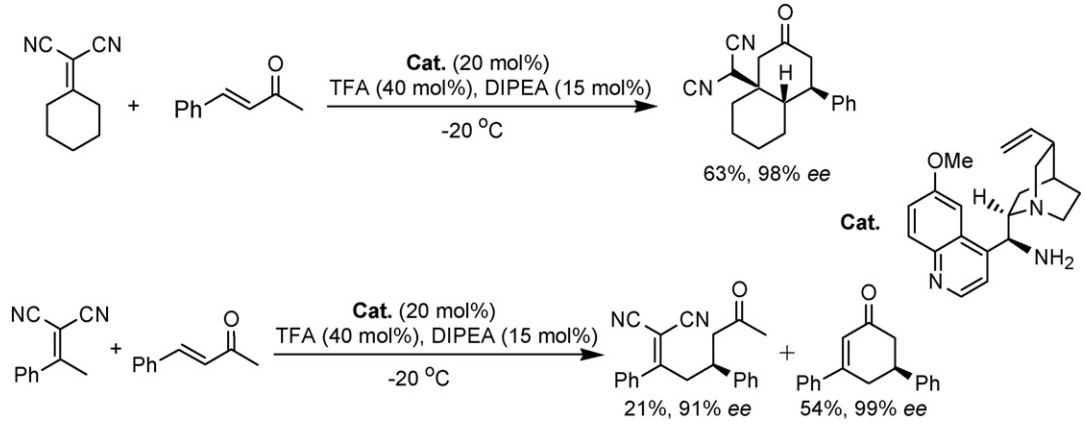
The first highly enantioselective vinylogous Michael addition of α,α-dicyanoalkenes to α,β-unsaturated ketones, in the presence of a chiral primary aminocatalyst derived from quinine, was developed by Xie et al. [16] (Scheme 3). The reaction is applicable to a variety of α,α-dicyanoalkenes and substituted α,β-unsaturated enones. High e.e. values and excellent diastereoselectivity were observed in all the reactions tested. The secondary amine catalysts such as L-proline and its derivatives have been found to be completely inert for the vinylogous



Scheme 2. Asymmetric Friedel–Crafts alkylation of indoles with simple enones.



Scheme 3. Asymmetric vinylogous Michael addition of α,α-dicyanoalkenes to α,β-unsaturated ketones.



Scheme 4. Asymmetric vinylogous Michael addition of acyclic β-phenyl-α,α-dicyanoalkenes and aliphatic cyclic dicyanoalkenes.

Michael addition of α,α-dicyanoalkenes to α,β-unsaturated ketones as the relative bulkiness of secondary amines might be unfavorable for the formation of iminium ions with α,β-unsaturated ketones.

Notably, when acyclic β-phenyl-α,α-dicyanoalkenes and aliphatic cyclic dicyanoalkenes were used as substrates, domino Michael–Michael reactions occurred (Scheme 4). This is the first report of enantioselective domino reactions catalyzed by a chiral primary amine.

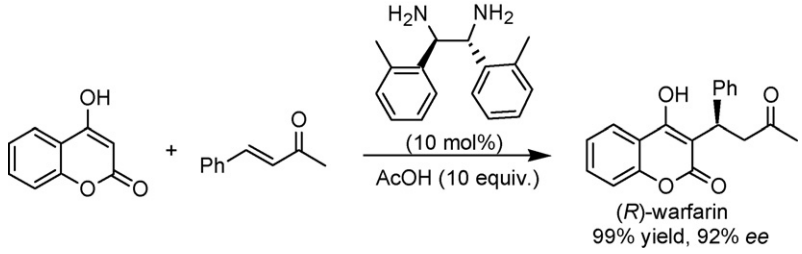
2.1.3. *Michael addition of cyclic 1,3-dicarbonyls to α,β-unsaturated ketones*

The synthesis of warfarin, a widely prescribed anticoagulant for treating thrombosis has attracted attention [17–21]. One of the direct and appealing routes to warfarin and related important compounds is Michael addition of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated ketones. In 2003, Halland et al. [20] developed the first organocatalytic asymmetric Michael addition of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated ketones, and (*R*)-warfarin was directly prepared in 96% yield and 82% e.e.Kim et al. [22] have developed a novel primary diamine catalyst for enantioselective oragnocatalytic Michael addition of 4-hydroxycoumarin to *trans*-4-phenyl-3-buten-2-one, affording (*R*)-warfarin in 99% yield and 92% e.e. (Scheme 5).

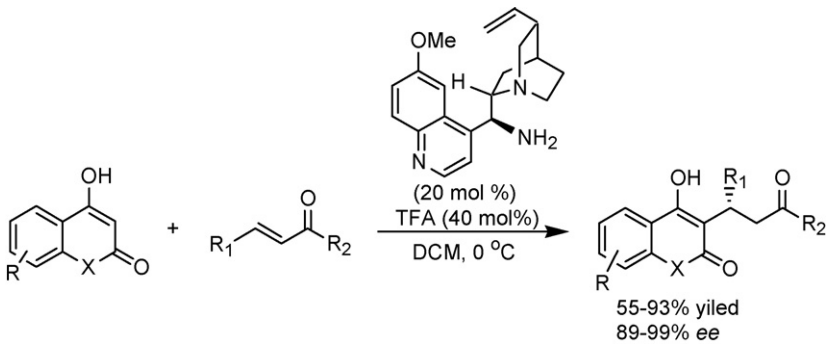
Recently, Xie et al. [23] have described efficient enantioselective Michael addition of cyclic 1,3-dicarbonyls to α,β-unsaturated ketones catalyzed by a chiral primary amine derived from quinine (Scheme 6). This versatile Michael addition furnished (*S*)-warfarin (88% yield, 96% e.e.) and other Michael adducts in good yields (55–93%) and with excellent enantioselectivities (89–99% e.e.).

2.1.4. *Cycloaddition of α-substituted acroleins*

2.1.4.1. [4 + 2] Cycloadditon of α-acyloxyacroleins with dienes. The enantioselective Diels–Alder reaction is one of the most powerful organic transformations in organic synthesis and



Scheme 5. Organocatalytic asymmetric synthesis of (*R*)-warfarin.



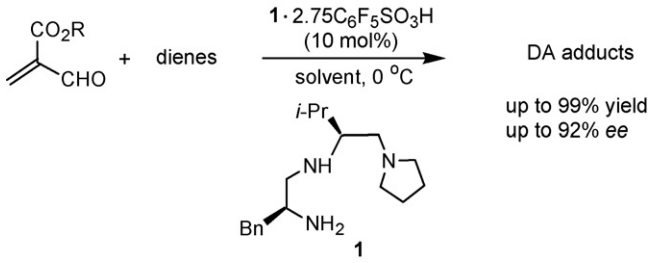
Scheme 6. Asymmetric Michael addition of 1,3-dicarbonyl compounds to α,β-unsaturated ketones.

a most appealing approach to many important chiral building blocks for the total synthesis of bioactive natural products [24]. A few years ago, MacMillan and co-workers [25,26] reported the first highly enantioselective organocatalytic Diels–Alder reaction of dienes with α-unsubstituted acroleins in the presence of the secondary amine salts. Nevertheless, these salts failed to activate α-substituted acroleins, probably due to poor generation of the corresponding iminium ions with α-substituted acroleins.

In 2005, Ishihara and Nakano [27] reported the first highly enantioselective organocatalytic Diels–Alder reaction of dienes with α-substituted acroleins by employing an ammonium salt of $C_6F_5SO_3H$ with chiral triamine 1 bearing a primary amino function group (Scheme 7). The reactions, in the presence of 10 mol% catalyst, were smoothly conducted at 0 °C. Good enantioselectivities (74–92% e.e.) were achieved.

Recently, Sakakura et al. [28] developed a new chiral primary diamine salt catalyst for asymmetric Diels–Alder reaction of α-substituted acroleins with dienes (Scheme 8). The catalyst is easily prepared in situ by mixing chiral 1,1′-binaphthyl-2,2′-diamine and Tf_2NH. The chiral primary diamine salt catalyst demonstrated excellent reactivity (up to 98% yield) and enantioselectivity (up to 94% e.e.).

2.1.4.2. [2 + 2] Cycloaddition of α-acyloxyacroleins with unactivated alkenes. The first enantioselective organocatalytic [2 + 2] cycloaddition reactions of α-acyloxyacroleins with unactivated alkenes, in the presence of **1**·2.6HNTf$_2$ were developed by Ishihara and Nakano [29] (Scheme 9). The cycloadducts were obtained in moderate to good yields (up to 89%) and in a highly *anti*-selective manner (up to 96:4), with up to 95% e.e. values. Interestingly **1**·2.75$C_6F_5SO_3H$ and **1**·2.75TfOH were inert for this reaction.

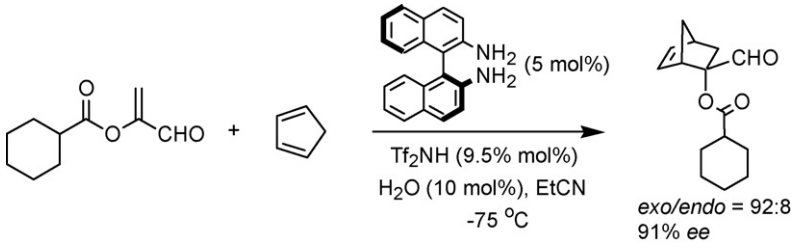


Scheme 7. Organocatalytic enantioselective Diels–Alder reaction of dienes with α-substituted acroleins.

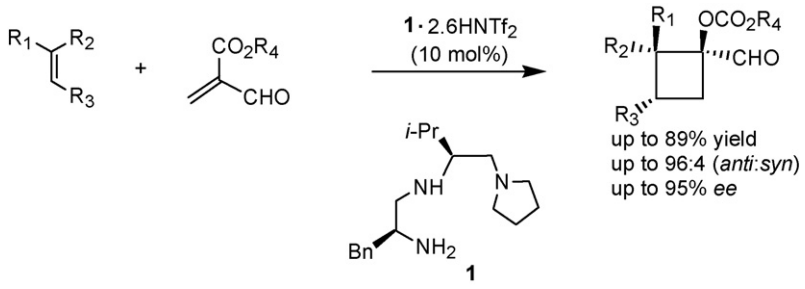
The authors proposed that, in the first step, Michael addition of alkenes to a *Z*-iminium intermediate, which would be generated from α-acyloxyacroleins and **1**·2.6HNTf$_2$, then the resulting tertiary carbocation intermediate would be intramolecularly cyclized (Scheme 10).

2.1.4.3. 1,3-Dipolar cycloaddition of cyclic enones. Chen et al. [30] have very recently developed the first highly enantioselective 1,3-dipolar cycloaddition of cyclic enones with azomethine imines (Scheme 11). This process, catalyzed by a multifunctional primary amine derived from quinine, afforded chiral five-membered heterocycle compounds in good to high yields (up to 99%) and with excellent levels of enantio- (up to 95% e.e.) and diastereoselectivity (dr > 50:1).

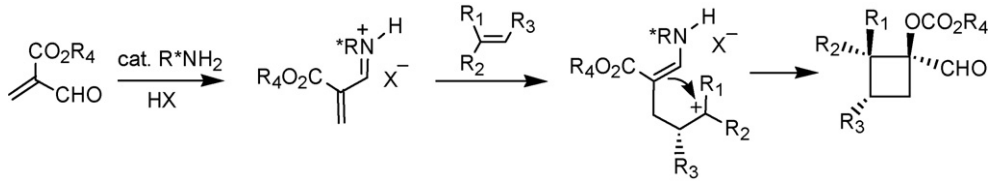
To account for the high levels of enantio- and diastereoselectivity of 1,3-dipolar cycloaddition of cyclic enones with azomethine imines, Chen et al. proposed a plausible catalytic model as depicted in Fig. 1, in which the ketiminium cation between catalyst and cyclic enone might adopt a *trans*-conformation, and the hydroxyl group of catalyst may provide an additional enantiocontrol through a hydrogen bonding interaction with the carbonyl group of dipole. Moreover, the steric



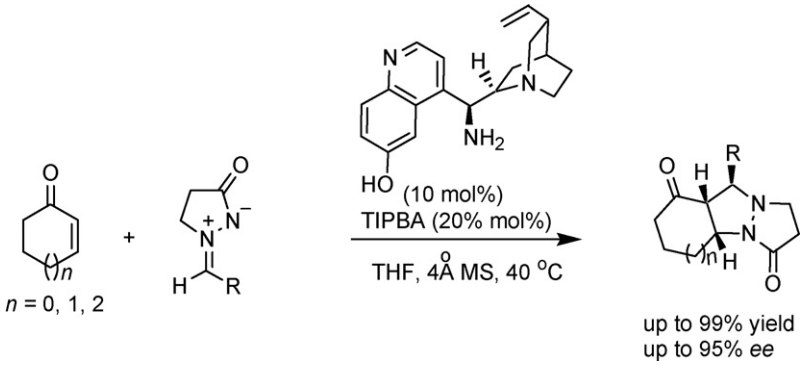
Scheme 8. Asymmetric Diels–Alder reaction of α-substituted acroleins with dienes.



Scheme 9. Enantioselective [2 + 2] cycloaddition of unactivated alkenes with α-acyloxyacroleins.



Scheme 10. Proposed mechanism for the [2 + 2] cycloaddition of unactivated alkenes with α-acyloxyacroleins.



Scheme 11. Asymmetric 1,3-dipolar cycloaddition of cyclic enones and azomethine imines.

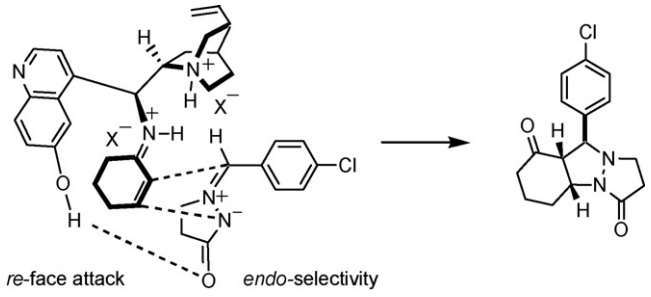


Fig. 1. Proposed 1,3-dipolar cycloaddition mode.

hindrance from the ion pair of the tertiary amine moiety would further enforce the high *endo*- and *re*-face selectivity of the cycloaddition product.

2.1.5. Transfer hydrogenation of α,β-unsaturated ketones

Martin and List [31] have described a highly efficient organocatalytic method for asymmetric hydrogenation of α,β-unsaturated ketones (Scheme 12). This reaction was synergistically promoted by a primary amine salt, in which both the cation and the anion are chiral.

2.1.6. Conjugate addition of 2-nitropropane to cyclohex-2-en-1-one

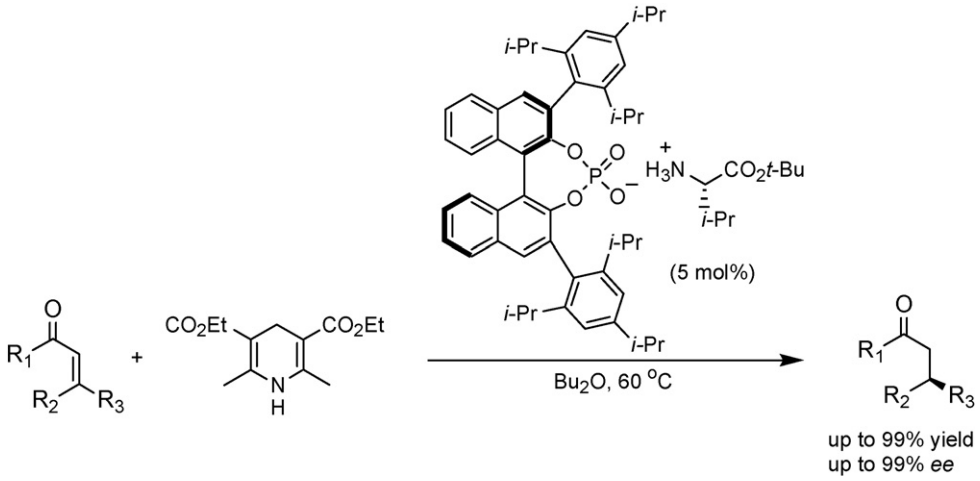
Tsogoeva and Jagtap [32] have demonstrated the effectiveness of the combination of the dipeptide H-Leu-His-OH and (1*R*, 2*R*)-(+)-1,2-diphenylethylenediamine as co-catalysts for catalytic asymmetric conjugate addition of 2-nitropropane to cyclohex-2-en-1-one (Scheme 13). Although neither co-catalyst was sufficiently effective independently in terms of yield nor enantioselectivity, their combination resulted in a drastic increase in yields (up to 86%) and selectivities (up to 91% e.e.), indicating the possibility of synergistic effects.

2.2. Enamine catalysis

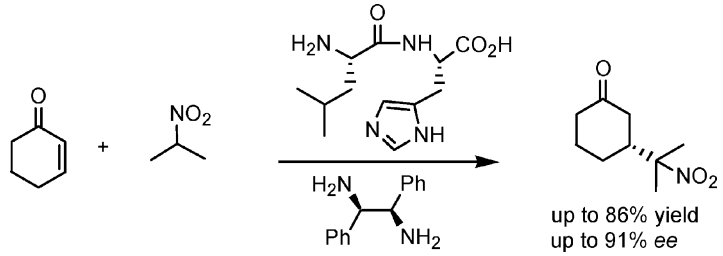
2.2.1. Michael addition of aldehydes and ketones to nitro olefins

Michael reactions of aldehydes and ketones with nitro olefins represent a convenient access to the versatile difunctional nitroketones in an atom-economical manner, and development of asymmetric organocatalysts for such processes has been the focus of recent research effort [6].

Xu and Cordova [33] have demonstrated for the first time that simple primary amino acid derivatives can catalyze the direct



Scheme 12. Asymmetric hydrogenation of α,β-unsaturated ketones.



Scheme 13. Enantioselective conjugate addition of 2-nitropropane to cyclohex-2-en-1-one.

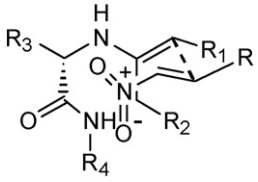


Fig. 2. Plausible transition state for the primary amino acid amide catalyzed asymmetric additions of ketones to nitro olefins.

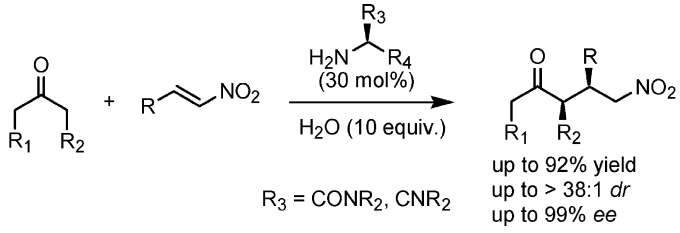
enantioselective addition of ketones to nitro olefins, furnishing the corresponding γ-nitroketones in high yields with up to >38:1 dr and up to 99% e.e. (Scheme 14).

To account for the observed *syn*-diatereoselectivity and the absolute configuration of products, Cordova and Xu proposed a plausible transition state, in which *si*-face of the nitroalkene is approached by the *re*-face of the catalytically generated enamine (Fig. 2).

Xu et al. [34] have also shown that simple di- and tripeptides derived from alanine can act as useful catalysts for asymmetric Michael addition of ketones to nitro olefins.

Simple chiral primary amines derived from cinchona alkaloids have been shown by McCooey and Connon [35] to promote highly enantio- and diastereoselective Michael-type addition reactions between enolizable carbonyl compounds and nitroalkenes (Scheme 15). The reaction has exceptionally broad scope: ketones (cyclic/acyclic), aldehydes (straight-chain/α,α-disubstituted), and a variety of nitro olefins are tolerated.

The development of chiral bifunctional thiourea organocatalysts for enantioselective reactions has attracted much interest in the last years [36,37]. Tsogoeva and Wei [38–40] have demonstrated for the first time that chiral primary amine-thiourea catalysts can catalyze asymmetric addition of ketones to nitro olefins, giving high yields (up to 82–99%), enantioselectivities (90–99% e.e.) and diastereoselectivities (up to 83:17 *syn/anti*) for acetone, cyclic ketones (Scheme 16). 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% e.e.).



Scheme 14. Asymmetric additions of ketones to nitro olefins promoted by chiral primary amino acid derivatives.

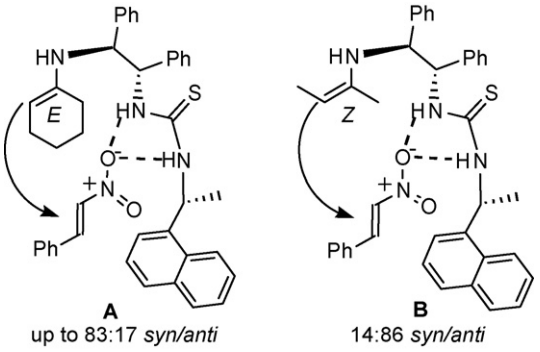


Fig. 3. Proposed transition states for Michael reactions of symmetrical (**A**) and unsymmetrical ketones (**B**) with *trans*-β-nitrostyrene.

The authors proposed a 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, they assumed the formation of the *Z*-enamine intermediate B (Fig. 3). The transition state geometries in this Michael addition have been calculated and analyzed [39,40].

Meanwhile, Huang and Jacobsen [41] developed another new primary amine-thiourea catalyst for the addition of ketones to nitro olefins (Scheme 17). A wide range of aromatic and heteroaromatic nitroalkenes underwent reaction with acetone in high yields and enantioselectivities by the addition of catalytic amounts of weak acids, such as benzoic acid. Nitroalkenes bearing aliphatic 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.

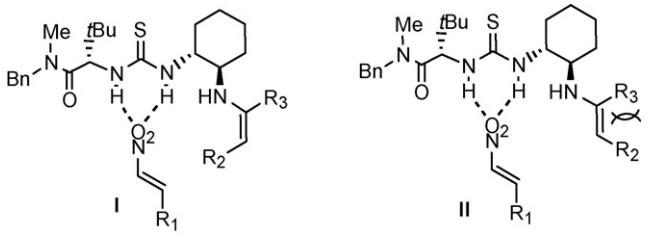


Fig. 4. Proposed intermediates in Michael reactions catalyzed by primary amine-thiourea. (I) Favored Z-enamine. (II) Disfavored *E*-enamine.

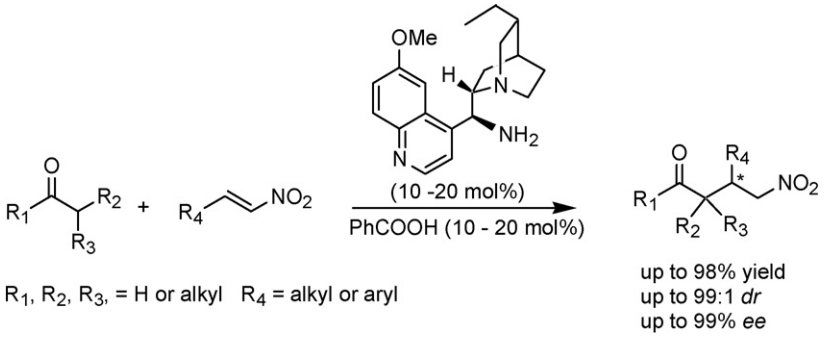
The *anti*-diastereoselectivity was explained by formation a *Z*-enamine intermediate. *E*-enamine is not favored due to steric repulsion between R_2 and R_3 (Fig. 4).

Lalonde et al. [42] have also shown that a similar chiral primary amine-thiourea is highly effective catalyst in the direct conjugate addition of α,α-disubstituted aldehydes to nitro olefins, generating synthetically versatile nitroaldehyde adducts (Scheme 18).

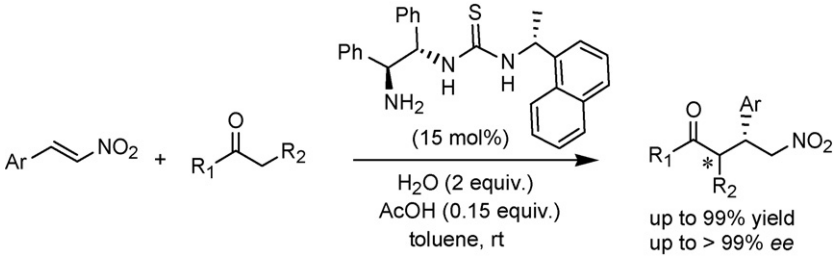
Liu et al. [43] have very recently synthesized a new class of bifunctional primary amine-thiourea catalysts based on saccharides. These simple catalysts were shown to be highly enantioselective for direct Michael addition of aromatic ketones to a range of nitro olefins (up to 98% e.e.) (Scheme 19).

To account for the observed absolute configuration (*S*) of the conjugate adduct, the authors proposed a transition state assembly (Fig. 5), in which the *si*-face of the nitroalkene is attacked by enamine intermediate, generated from ketone and the primary amine group of bifunctional catalyst. The attack of the enamine to the *re*-face of the nitro olefin is restricted by the cyclohexyl scaffold of the catalyst.

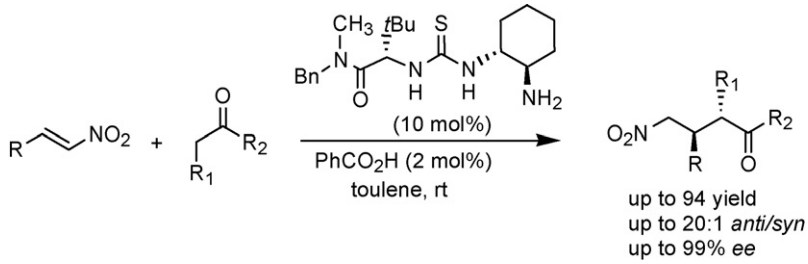
The chiral functionalized salt catalysts have recently received growing attention, due to their tuneable features for various



Scheme 15. Enantioselective additions of aldehydes and ketones to nitro olefins catalyzed by cinchona alkaloid derivatives.



Scheme 16. Asymmetric addition of ketones to nitro olefins catalyze by chiral primary amine-thiourea.



Scheme 17. Enantioselective conjugate addition of ketones to nitroalkenes promoted by a chiral primary amine-thiourea catalyst.

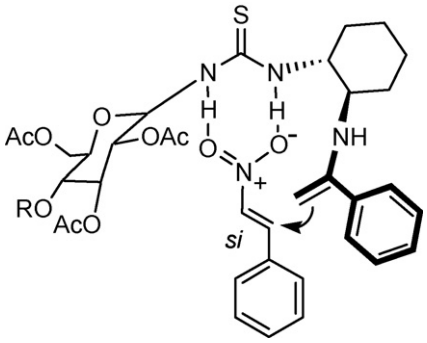


Fig. 5. Proposed transition state model.

chemical tasks. Quite recently, Xiong et al. [44] synthesized three types of primary amine-salt catalysts: chiral anion salt, chiral cation salt and chiral cation-chiral anion salt, which have been applied to asymmetric addition of ketones to nitro olefins (Scheme 20). Michael addition adducts were obtained in good yields (up to 99%), high diastereoselectivities (up to 96:4 dr), and enantioselectivities (up to 96% e.e.), in the presence of these primary amine-salts as catalysts.

2.2.2. Mannich reactions

The Mannich reaction is one of the most important carbon–carbon bond-forming reactions for the production of nitrogenous molecules.

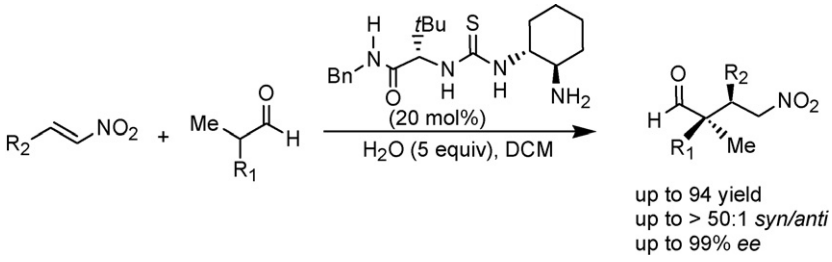
The first highly enantioselective primary amine and amino acid-catalyzed Mannich-type reactions were developed by Ibrahem et al. [45] (Scheme 21). The reactions gave β-amino carbonyl products in good yields (up to 90% yields) in highly *syn*-selective manner (up to >19:1), with up to >99% e.e. values.

The authors proposed the direct asymmetric Mannich reactions catalyzed by chiral primary amine and amino acid occurred via the six-membered chair-like transition states I and II, respectively, for which the *si*-face of the catalytically generated chiral enamine is approached by the *si*-face of the in situ generated acceptor imine (Fig. 6).

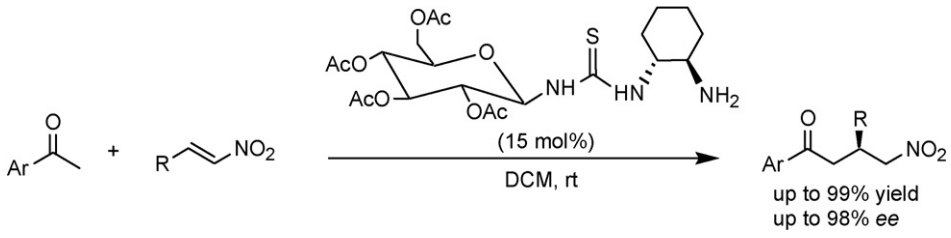
The development of organocatalysts that promote reactions in the environmentally clean, safe, and cheap solvent water is a significant goal. More recently, Cheng et al. [46] have reported a threonine-derived catalyst for promoting direct asymmetric three-component Mannich reactions of *O*-benzyl hydroxyacetone with *p*-anisidine and aldehydes in a purely aqueous system (Scheme 22). The reactions are *anti*-selective and highly enantioselective, and applicable to both aromatic and aliphatic aldehydes.

This study is the first demonstration that direct three-component Mannich reactions can be promoted by a chiral primary amino acid in water.

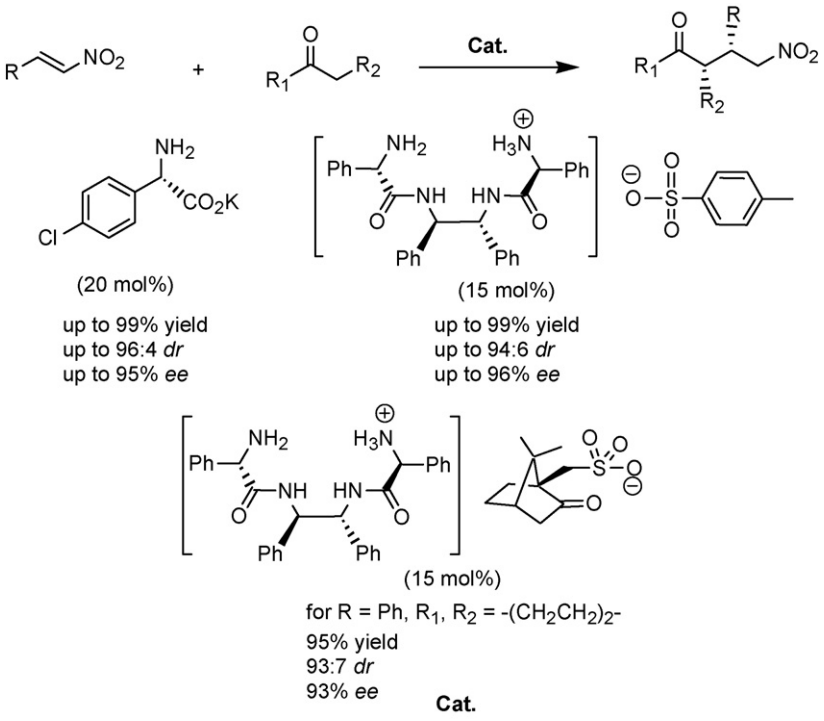
Cheng et al. [47] have also shown that a similar catalyst is highly effective in the direct *anti*-selective Mannich reactions of *O*-TBS-hydroxyacetone with various *N*-tosylimines derived



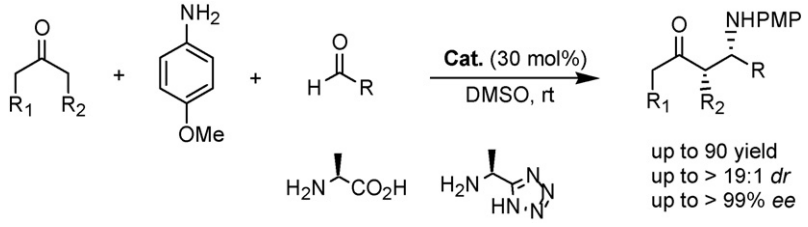
Scheme 18. Asymmetric conjugate addition of α,α-disubstituted aldehydes to nitroalkenes.



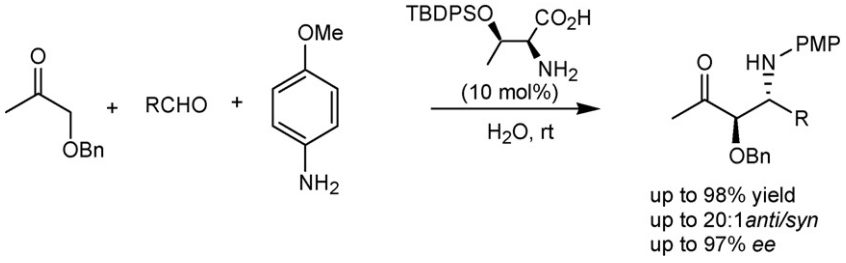
Scheme 19. Enantioselective Michael addition of aromatic ketones to nitro olefins promoted by chiral primary amine-thiourea catalysts based on saccharides.



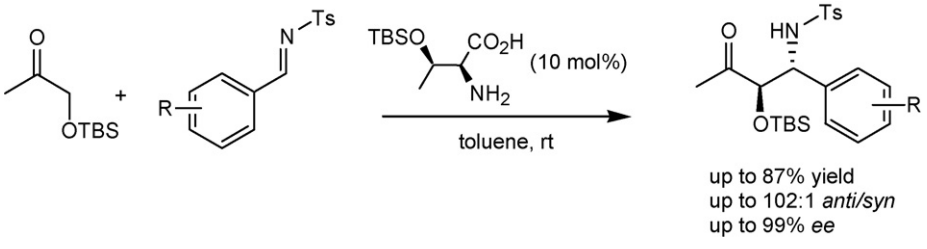
Scheme 20. Chiral functionalized salts-catalyzed asymmetric Michael addition of ketones to nitro olefins.



Scheme 21. Direct three-component asymmetric Mannich reactions catalyzed by an acyclic chiral amine or amino acid.



Scheme 22. Asymmetric three-component Mannich reactions in water.



Scheme 23. Organocatalytic asymmetric Mannich reactions of N-tosylimines.

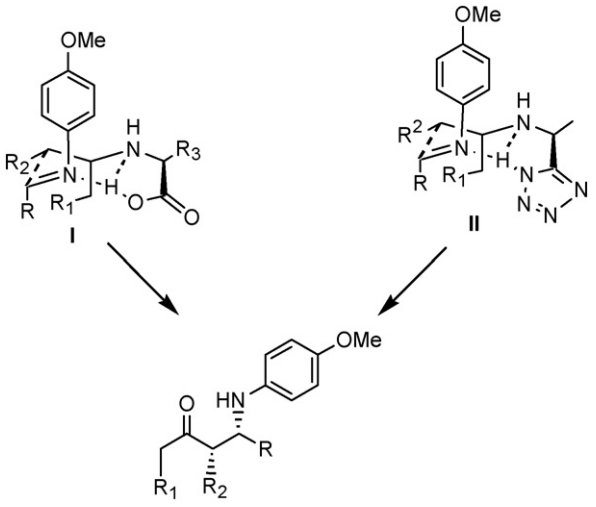


Fig. 6. Plausible transition states I and II for the direct three-component asymmetric Mannich reactions.

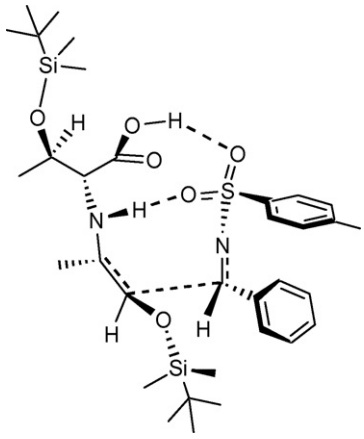


Fig. 7. Calculated transition state for the *anti*-Mannich product formation.

from aromatic aldehydes (Scheme 23). The 1,2-amino alcohols have been obtained in good yields (up to 87%) and with enantioselectivities of 99%.

The formation of the major *anti*-product was explained via a calculated transition state as depicted in Fig. 7. Both sulfone oxygen atoms are involved in hydrogen bondings, and the formation of *Z*-enamine is facilitated by hydrogen bonding. The predominant isomer can be formed via the attack of *N*-tosylimine by the enamine from the *si*-face.

The involvement of both oxygen atoms of sulfone in hydrogen bonding network to stabilize the transition state is unprecedented, and may have implications for the design of novel organocatalytic systems.

Ramasastry et al. [48] have described highly enantioselective organocatalytic Mannich reactions involving the unmodified α-hydroxyketones in the presence of primary amine-containing amino acids (Scheme 24). The reactions provide enantiomerically enriched 1,2-amino alcohols in good yields (up to 95%) in a highly *anti*-selective manner (up to >19:1), and with up to 98% e.e. values.

2.2.3. Direct α-amination of aromatic ketones

Liu et al. [49] reported the first highly enantioselective direct α-amination of aromatic ketones catalyzed by chiral primary amines derived from cinchona alkaloids (Scheme 25). Excellent enantioselectivities (88–99% e.e.) have been achieved for a broad spectrum of aryl ketones. The presence of 4 Å molecular sieves was of great assistance for the high conversions and enantiocontrol.

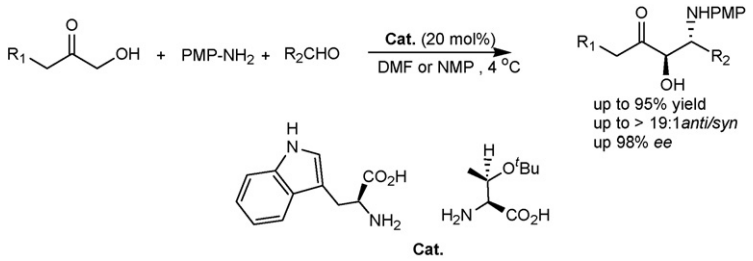
To account for the high levels of enantioselectivity of amination reactions, Chen et al. proposed a catalytic model as depicted in Fig. 8. It was suggested that the in situ formed enamine between the ketone and the catalyst may adopt the *E*-conformation, which directs the α-methyl group away from the catalyst. Furthermore, the protonated quinuclidine moiety of the catalyst would act as a synergistic Brønsted acid for the activation of electrophilic diethyl azodicarboxylate through hydrogen bonding. The preferred chiral product would be produced by the *si*-face attacking the enamine intermediate.

2.2.4. Aldol reactions

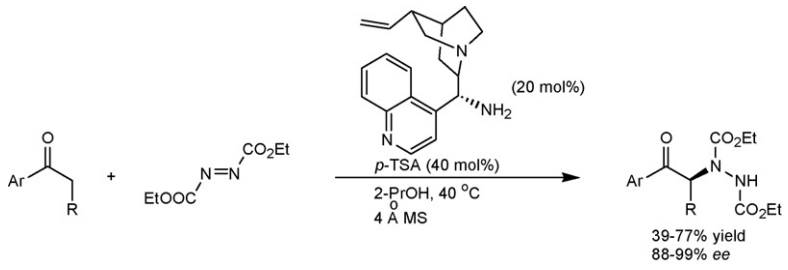
The direct catalytic asymmetric aldol reaction is one of the most powerful methods for constructing carbon-carbon bonds in organic synthesis. An exciting new development in this reaction is the use of chiral organic molecule catalysts.

In 2005, Amedjkouh [50] and Cordova et al. [51,52] independently reported that chiral primary amino acids can catalyze direct asymmetric intermolecular aldol reactions [53] (Scheme 26). It was demonstrated that water played a beneficial role in the primary amino acids-catalyzed aldol reactions, and might assist enamine formation via a proton relay.

Tsogoeva and Wei [54] initially demonstrated that the primary amine containing peptides are potential catalysts in asymmetric aldol reaction between acetone and aromatic aldehydes (Scheme 27). Good yields (up to 96%) and enantioselectivities (up to 76% e.e.) were obtained with electron-deficient aromatic aldehydes in the presence of H-Leu-His-OH.



Scheme 24. Catalytic asymmetric *anti*-Mannich reactions involving unmodified α-hydroxyketones.



Scheme 25. Enantioselective direct α-amination of aromatic ketones.

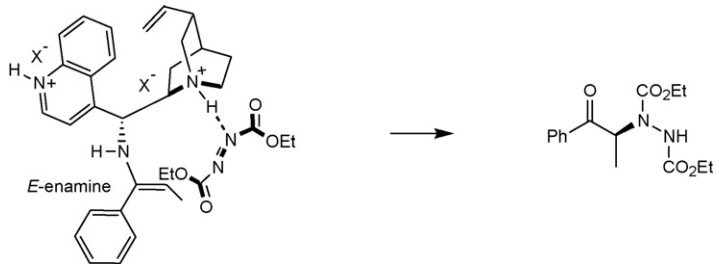
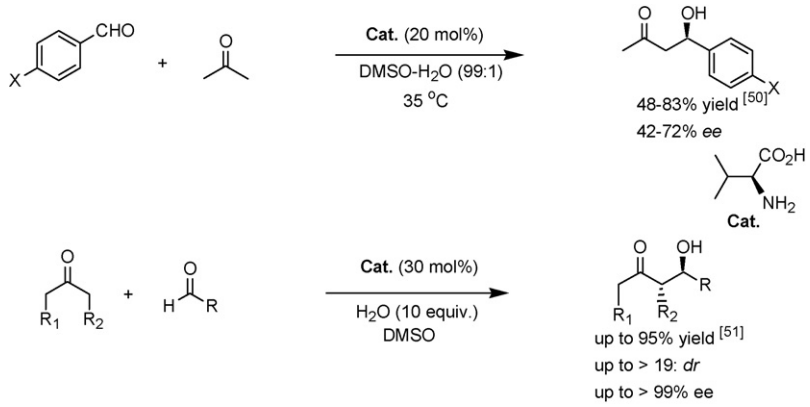


Fig. 8. Proposed catalytic reaction mode through concerted activation.



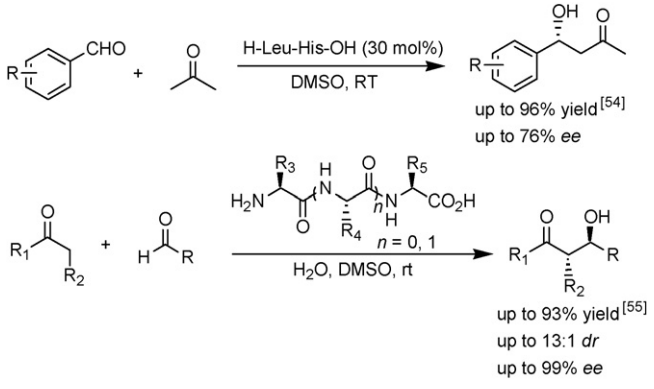
Scheme 26. Primary amino acids-catalyzed direct asymmetric intermolecular aldol reactions.

Zou et al. [55] have shown that simple peptides and their analogues having a primary amino group as the catalytic residue serve as effective catalysts for the direct asymmetric aldol reactions of cyclic ketones and aldehydes (Scheme 27).

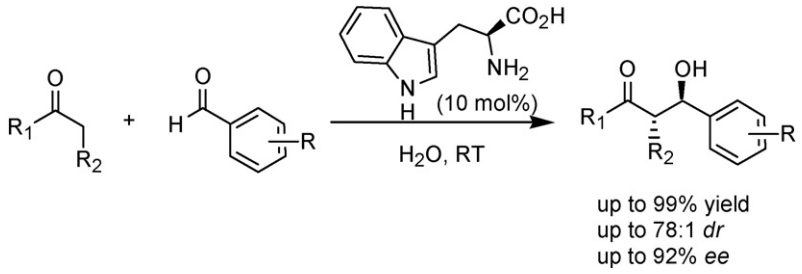
Recently, Jiang et al. [56] developed the highly enantioselective organocatalytic aldol reactions between cyclic ketones and aromatic aldehydes, catalyzed by a natural hydrophobic amino acid with a primary amino function group, in a purely aqueous system (Scheme 28). This process was carried out in mild conditions to furnish β-hydroxy carbonyl compounds in good yields (up to 99%) and with good to high enantio- (up to 92% e.e.) and diastereoselectivity (up to 78:1 dr).

Wu et al. [57] have also shown that threonine derived primary amino acids are effecient organocatalysts for the direct asymmetric aldol reactions of cyclohexanone and TBS-protected α-hydroxyacetone in water (Scheme 29).

Ramasastry et al. [48] have successfully developed highly enantioselective direct aldol reactions involving the unmodified α-hydroxyketones by employing primary amine-containing amino acids as catalysts (Scheme 30). The reactions provide enantiomerically enriched *syn*-1,2-diols in good yields (up to >95%) with high enantioselectivities (98% e.e.) and good diastereoselectivities (up to 18:1 *syn/anti*).



Scheme 27. Asymmetric aldol reactions catalyze by the primary amine containing peptides.

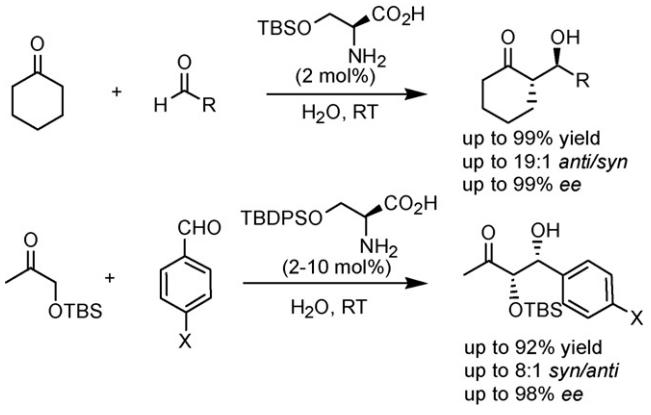


Scheme 28. L-Tryptophan-catalyzed direct aldol reactions in water.

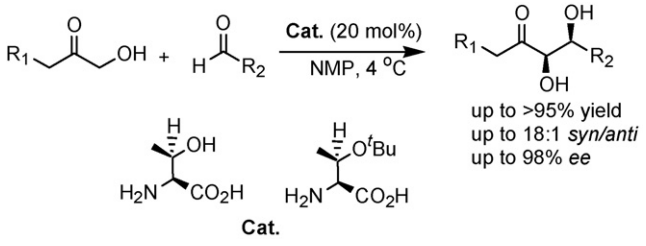
Luo et al. [58] have disclosed asymmetric direct aldol reactions of linear aliphatic ketones with aromatic aldehydes in the presence of a simple chiral primary catalyst (Scheme 31). A range of aromatic aldehydes underwent reaction with acetone in high yields and enantioselectivity at room temperature. The reaction of ethyl ketones occurred preferentially at the methylene carbon in good regioselectivity (4:1–20:1 *b/l*), favoring the branched aldol products with high enantioselectivity (87–96% e.e.) and diastereoselectivity (up to 12:1 *syn/anti)*. On the other hand, the reaction of longer ketones, such as methyl propyl ketone and methyl *i*-butyl ketone, produced linear products instead of the branched ones with good regioselectivity (5:1- > 20:1 *l/b*) and enantioselectivity (85–88% e.e.).

To account for the observed *syn*-diastereoselectivity, the authors proposed a *Z*-enamine transition state, in which the protonated tertiary amine serves as a directing hydrogen-bonding donor, as depicted in Fig. 9.

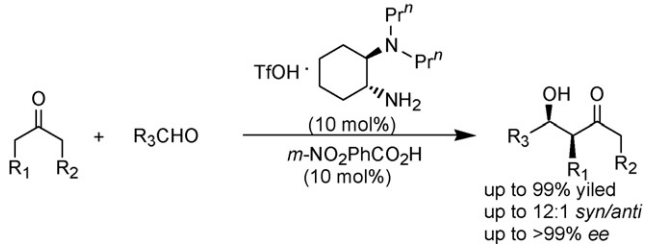
More recently, Zheng et al. [58] have demonstrated the effectiveness of a chiral primary amine derived from cinchonine for highly enantioselective organocatalytic aldol reactions of alde-



Scheme 29. Asymmetric aldol reactions catalyzed by threonine derived primary amino acids in water.



Scheme 30. Enantioselective direct aldol reactions involving the unmodified α-hydroxyketones.



Scheme 31. Chiral primary amine-catalyzed asymmetric aldol reactions of linear aliphatic ketones.

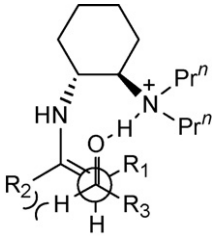
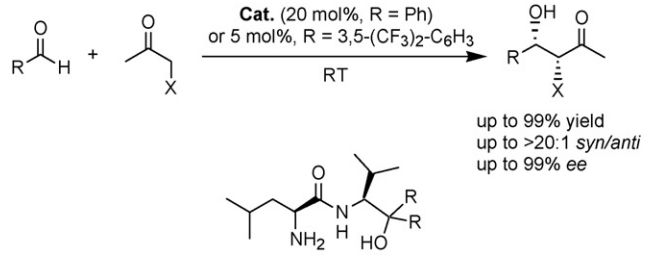
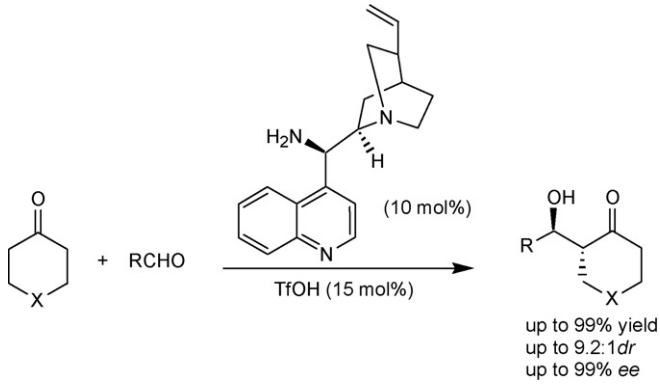


Fig. 9. Proposed transition state for the reaction of acyclic ketone.



Scheme 32. Asymmetric *syn*-aldol reactions of hydroxyacetone and acyclic ketones with aldehydes.



Scheme 33. Enantioselective direct aldol reaction catalyzed by cinchona derived primary amines.

hydes with cyclic ketones (Scheme 32). The *anti*-adducts were obtained in up to 99% yield, with good diastereoselectivities (up to 9.2: 1 dr) and excellent enantioselectivities (up to 99% e.e.).

Wu et al. [59] designed two multifunctional primary amine catalyst for the direct syn-aldol reactions (Scheme 32). These catalysts can be readily prepared from L-valine, demonstrating excellent diastereoselectivity (up to >20/1) and enantioselectivity (up to 99% e.e.).

More recently, Zheng et al. [60] have demonstrated the effectiveness of a chiral primary amine derived from cinchonine for highly enantioselective organocatalytic aldol reactions of aldehydes with cyclic ketones (Scheme 33). The anti-adducts were obtained in up to 99% yield, with good diastereoselectivities (up to 9.2:1 dr) and excellent enantioselectivities (up to 99% e.e.).

3. Conclusion

The chiral primary amines have been established as new and powerful organocatalysts for different asymmetric transformations. Remarkable progress in this area has been made in the past few years, and many chiral primary amine catalysts have been developed. It can be expected that further exciting discoveries of novel chiral primary amine catalysts will appear in the near future.

Acknowledgement

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References

[1] E.R. Jarvo, S.J. Miller, Tetrahedron 58 (2002) 2481–2495.
[2] P.I. Dalko, L. Moisan, Angew. Chem. Int. Ed. 43 (2004) 5138–5175.
[3] A. Berkessel, H. Groger, Asymmetric Organocatalysis, Wiley-VCH, Weinheim, 2005.
[4] J. Seayad, B. List, Org. Biomol. Chem. 3 (2005) 719–724.
[5] G. Lelais, D.W.C. MacMillan, Aldrichim. Acta 39 (2006) 79–87.
[6] S.B. Tsogoeva, Eur. J. Org. Chem. (2007) 1701–1716.
[7] B. List, Chem. Commun. (2006) 819–824.
[8] M. Bandini, A. Melloni, A. Umani-Ronchi, Angew. Chem. Int. Ed. 43 (2004) 550–556.
[9] K.A. Jørgensen, Synthesis (2003) 1117–1125.
[10] J.F. Austin, D.W.C. MacMillan, J. Am. Chem. Soc. 124 (2002) 1172–1173.
[11] D.-P. Li, Y.-C. Guo, Y. Ding, W.-J. Xiao, Chem. Commun. (2006) 799–801.
[12] W. Chen, W. Du, L. Yue, R. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, Org. Biomol. Chem. 5 (2007) 816–821.
[13] M. Bandini, M. Fagioli, P. Melchiorre, A. Melloni, A. Umani-Ronchi, Tetrahedron Lett. 44 (2003) 5843–5846.
[14] M. Bandini, M. Fagioli, M. Garavelli, A. Melloni, V. Trigari, A. Umani-Ronchi, J. Org. Chem. 69 (2004) 7511–7518.
[15] G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, Org. Lett. 9 (2007) 1403–1405.
[16] J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y.-C. Chen, Y. Wu, J. Zhu, J.-G. Deng, Angew. Chem. Int. Ed. 46 (2007) 389–392.
[17] A.S. Demir, C. Tanyeli, V. Gulbeyaz, H. Akgun, Turk. J. Chem. 20 (1996) 139–145.
[18] A. Robinson, H.-Y. Li, J. Feaster, Tetrahedron Lett. 37 (1996) 8321–8324.
[19] G. Cravotto, G.M. Nano, G. Palmisano, S. Tagliapietra, Tetradedron: Asymmetry 12 (2001) 707–709.
[20] N. Halland, T. Hansen, K.A. Jørgensen, Angew. Chem. Int. Ed. 42 (2003) 4955–4957.
[21] Y. Tsuchiya, Y. Hamashima, M. Sodeoka, Org. Lett. 8 (2006) 4851–4854.
[22] H. Kim, C. Yen, P. Preston, J. Chin, Org. Lett. 8 (2006) 5239–5242.
[23] J.-W. Xie, L. Yue, W. Chen, W. Du, J. Zhu, J.-G. Deng, Y.-C. Chen, Org. Lett. 9 (2007) 413–415.
[24] E.J. Corey, Angew. Chem. Int. Ed. 41 (2002) 1650–1667.
[25] K.A. Ahrendt, C.J. Borths, D.W.C. MacMillan, J. Am. Chem. Soc. 122 (2000) 4243–4244.
[26] A.B. Northrup, D.W.C. MacMillan, J. Am. Chem. Soc. 124 (2002) 2458–2460.
[27] K. Ishihara, K. Nakano, J. Am. Chem. Soc. 127 (2005) 10504–10505.
[28] A. Sakakura, K. Suzuki, K. Nakano, K. Ishihara, Org. Lett. 8 (2006) 2229–2232.
[29] K. Ishihara, K. Nakano, J. Am. Chem. Soc. 129 (2007) 8930–8931.
[30] W. Chen, W. Du, Y.-Z. Duan, Y. Wu, S. -Y, Y.-C. Yang, Chen, Angew. Chem. Int. Ed. 46 (2007) 7667–7670.
[31] N.J.A. Martin, B. List, J. Am. Chem. Soc. 128 (2006) 13368–13369.
[32] S.B. Tsogoeva, S.B. Jagtap, Synlett (2004) 2624–2626.
[33] Y. Xu, A. Cordova, Chem. Commun. (2006) 460–462.
[34] Y. Xu, W. Zou, H. Sunden, I. Ibrahem, A. Cordova, Adv. Synth. Catal. 348 (2006) 418–424.
[35] S.H. McCooey, S.J. Connon, Org. Lett. 9 (2007) 599–602.
[36] M.S. Taylor, E.N. Jacobsen, Angew. Chem. Int. Ed. 45 (2006) 1520–1543.
[37] S.J. Connon, Chem. Eur. J. 12 (2006) 5418–5427.
[38] S.B. Tsogoeva, S. Wei, Chem. Commun. (2006) 1451–1453.
[39] D.A. Yalalov, S.B. Tsogoeva, S. Schmatz, Adv. Synth. Catal. 348 (2006) 826–832.
[40] S. Wei, D.A. Yalalov, S.B. Tsogoeva, S. Schmatz, Catal. Today 121 (2007) 151–157.
[41] H. Huang, E.N. Jacobsen, J. Am. Chem. Soc. 128 (2006) 7170–7171.
[42] M.P. Lalonde, Y. Chen, E.N. Jacobsen, Angew. Chem. Int. Ed. 45 (2006) 6366–6370.
[43] K. Liu, H.-F. Cui, J. Nie, K.-Y. Dong, X.-J. Li, J.-A. Ma, Org. Lett. 9 (2007) 923–925.
[44] Y. Xiong, Y. Wen, F. Wang, B. Gao, X. Liu, X. Huang, X. Feng, Adv. Synth. Catal. 349 (2007) 2156–2166.
[45] I. Ibrahem, W. Zou, M. Engqvist, Y. Xu, A. Cordova, Chem. Eur. J. 11 (2005) 7024–7029.
[46] L. Cheng, X. Wu, Y. Lu, Org. Biomol. Chem. 5 (2007) 1018–1020.
[47] L. Cheng, X. Han, H. Huang, M.W. Wong, Y. Lu, Chem. Commun. (2007) 4143–4145.
[48] S.S.V. Ramasastry, H.L. Zhang, F. Tanaka, C.F. Barbas III, J. Am. Chem. Soc. 129 (2007) 288–289.
[49] T.-Y. Liu, H.-L. Cui, Y. Zhang, K. Jiang, W. Du, Z.-Q. He, Y.-C. Chen, Org. Lett. 9 (2007) 3671–3674.
[50] M. Amedjkouh, Tetrahedron: Asymmetry 16 (2005) 1411–1414.
[51] A. Cordova, W.B. Zou, I. Ibrahem, E. Reyes, M. Engqvist, W.-W. Liao, Chem. Commun. (2005) 3586–3588.
[52] A. Bassan, W. Zou, E. Reyes, F. Himo, A. Cordova, Angew. Chem. Int. Ed. 44 (2005) 7028–7032.
[53] S. Pizzarellol, A.L. Weber, Science 303 (2004) 1151.
[54] S.B. Tsogoeva, S. Wei, Tetrahedron: Asymmetry 16 (2005) 1947–1951.
[55] W. Zou, I. Ibrahem, P. Dziedzic, H. Sunden, A. Cordova, Chem. Commun. (2005) 4946–4948.
[56] Z. Jiang, Z. Liang, X. Wu, Y. Lu, Chem. Commun. (2006) 2801–2803.
[57] X. Wu, Z. Jiang, H.-M. Shen, Y. Lu, Adv. Synth. Catal. 349 (2007)812–816.
[58] S. Luo, H. Xu, J. Li, L. Zhang, J.-P. Cheng, J. Am. Chem. Soc. 129 (2007) 3074–3075.
[59] X.-Y. Xu, Y.-Z. Wang, L.-Z. Gong, Org. Lett. 9 (2007) 4247–4249.
[60] B.-L. Zheng, Q.-Z. Liu, C.-S. Guo, X.-L. Wang, Long He, Org. Biomol. Chem. 5 (2007) 2913–2915.