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Bifunctional primary amine-thioureas in asymmetric organocatalysis

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Research disclosed since the demonstration of the first examples of primary amine-thiourea organocatalysis in 2006 has shown that primary amine-based thioureas can successfully catalyze a diverse variety of highly enantioselective transformations providing a wide range of versatile organic compounds. Recent remarkable progress with these chiral catalysts is summarized in this review.

Introduction

Asymmetric organocatalysis has emerged as a powerful and environmentally friendly and mild methodology for the catalytic production of enantiomerically pure natural products, chiral drugs, building-blocks, and important molecules for materials chemistry.[1,2] In many cases, the effectiveness of organocatalysts relies on the hydrogen bonding interactions: *e.g.* non-covalent catalysis with thioureas and ureas, diols and amidinium cations.[3,4] Particularly, thiourea derivatives have become a subject of considerable interest for catalyst design in recent years.[4] Pioneering examples include the work of Jacobsen,[5] Schreiner[6] and Takemoto,[7] who showed that thiourea-based organocatalysts can successfully be used in different important C–C bond formation reactions.

Over the past decade bifunctional compounds, bearing both a thiourea moiety and an amine group on a chiral scaffold, have emerged as particularly useful organocatalysts and found numerous applications for organic synthesis. Besides impressive developments with tertiary and secondary amine-thioureas,[8,9] more recently, significant progress has been achieved with primary amine-thiourea organocatalysts of general structure presented in Fig. 1, first introduced in 2006 by the Tsogoeva group[10] and the Jacobsen group.[11] Chiral primary amines as organocatalysts possess a particular appeal because of their known occurrence in the catalytic sites of several enzymes, such as type I aldolases, dehydratases, and decarboxylases.[12] Demonstration of the potential of primary amine-thioureas as attractive new organocatalysts,[10,11]

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Christina M. Heckel was born in 1987 in Pegnitz, Germany. She received her B.Sc. and M.Sc. degrees in Molecular Science from the University of Erlangen-Nuremberg. In 2012, she began her doctoral studies under the supervision of Professor S. B. Tsogoeva working on organocatalytic domino reactions and one-pot processes towards nitrogen-containing heterocycles.

has stimulated the interest of different research groups to develop new useful enantioselective transformations, employing primary amine-thioureas.

Over the last decade, several excellent general reviews on organocatalysis using thioureas were published.[3,4,8,9,13–17] Additionally, advances in organocatalysis using chiral primary amines[18,19] and some of their derivatives[20] were also highlighted. However, up to now, there is no systematical overview exclusively on bifunctional primary amine-thiourea organocatalysis.

This perspective illustrates recent progress in organic synthesis using different primary amine-thioureas summarized in Fig. 1. Results published after 2006 through to the beginning of 2013 are presented. The different contributions have been organized into sections according to the individual organic reaction catalyzed by primary amine-thiourea organocatalysts in the following order: nitro-Michael reactions, 1,4-conjugate additions to enones and enals, domino aza-Michael–Henry reaction, Mannich-type reactions, α-alkylation of aldehydes, Nazarov cyclizations, intramolecular [5 + 2] cycloadditions, Diels–Alder, vinylogous aldol, domino Michael-aldol and multicomponent Biginelli reactions.

Nitro-Michael additions

Among the numerous asymmetric C–C bond formation reactions, the conjugate Michael addition plays a particularly prominent role.[21] Employing nitroolefins as Michael acceptors opens the way to synthetically useful C–C, C–N and C–O bond-forming reactions. For example, the Michael reaction of ketones with nitroolefins represents a convenient access to γ-nitro ketones which are valuable synthons in organic synthesis.

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Svetlana B. Tsogoeva is a professor of organic chemistry at the Friedrich-Alexander-University of Erlangen-Nuremberg, since February 2007. She was born in 1973, studied chemistry at St. Petersburg State University, where she completed her doctoral thesis in 1998. Then, she moved to the Johann Wolfgang Goethe-University, Frankfurt am Main, for postdoctoral research. In July 2000 she joined the Degussa AG Fine Chemicals Division as a research scientist. In January 2002 she was appointed as a first junior professor in Germany at the Georg-August-University of Göttingen. Her research is currently focused on asymmetric organocatalysis, catalysis by metal complexes and synthesis of natural product hybrids for medicinal chemistry.

Over the past decade, much effort has been devoted to the development of an organocatalytic version of this reaction.[21]

In 2006, Tsogoeva and co-workers introduced the bifunctional organocatalyst **1**, bearing both a thiourea moiety and a primary amine group on a chiral scaffold, as an effective catalyst in the addition of acetone to different aromatic nitroolefins giving the products γ-nitro ketones in good to high yields (85.5–93%) and enantioselectivities (84–92% ee) (Scheme 1).[10,22]

To explain the predominant production of *R* adducts, the transition state structures for the formation of both ***R*** and ***S*** enantiomers with the new bifunctional organocatalyst **1** have been computationally determined.[22] The obtained results gave clear evidence that only one oxygen atom of the nitro group is bound to the thiourea moiety (Fig. 2).

Based on these results, a plausible reaction mechanism for chiral thiourea-amine **1** catalysis was proposed (Scheme 2). According to Scheme 2, the formation of the acetone enamine occurs following the formation of an iminium ion intermediate, supported by acid additive (AcOH). This C-nucleophile attacks the *trans*-β-nitrostyrene activated through hydrogen bonding with the thiourea moiety to give the intermediate **A**. The existence of the intermediate **A** in the reaction mixture was confirmed using the ESI-MS method (Scheme 2). At the last step, the regeneration of the catalyst through hydrolysis of the imine **A** is facilitated by water.

In 2006, the new bifunctional thiourea-amine **2** has further been disclosed to catalyze the Michael reaction of ketones (acetone and cyclic ketones) with different aromatic nitroolefins in 82–99% yield, with 90–99% enantioselectivities and good diastereoselectivities (*syn* : *anti* up to 83 : 17) (Scheme 3).[10,23] Interestingly, the addition of a nonsymmetrical ketone such as methylethylketone to β-nitrostyrene under the same conditions, led to the opposite diastereomer (*syn* : *anti* 14 : 86) with a very high ee value (>99%).

To explain these results, the plausible transition-state model (**B**), which reasonably explains the relative (*syn*) and absolute configuration of the Michael adducts was proposed. To explain the inversion of diastereoselectivity with methylethylketone as a substrate, the formation of the *Z* enamine intermediate **C** was proposed (Fig. 3).[10]

In 2006, Jacobsen and Huang reported another interesting primary amine-thiourea organocatalyst **3** for analogous nitro-Michael addition of ketones to nitroolefins.[11] Additions of various *n*-alkyl ethyl ketones (R^1 = Et, *n*-Pr, *n*-Bu, *p*-pentyl; R^2 = Me) to nitrostyrene afforded Michael adducts with complete regioselectivity (<30 : 1 rr), high enantiomeric excess (up to 99%) and up to 20 : 1 dr favoring the *anti* diastereomer (Scheme 4). Interestingly, while the reaction of nitrostyrene with lower *n*-alkyl ethyl ketone, methylethylketone, provided a product with modest regioselectivity (2 : 1 branched/linear), a branched product (>30 : 1 rr) was obtained with methoxyacetone as the Michael donor. Notably, nitroalkenes bearing aliphatic β-substituents have also proved to be viable Michael acceptors under the reaction conditions.

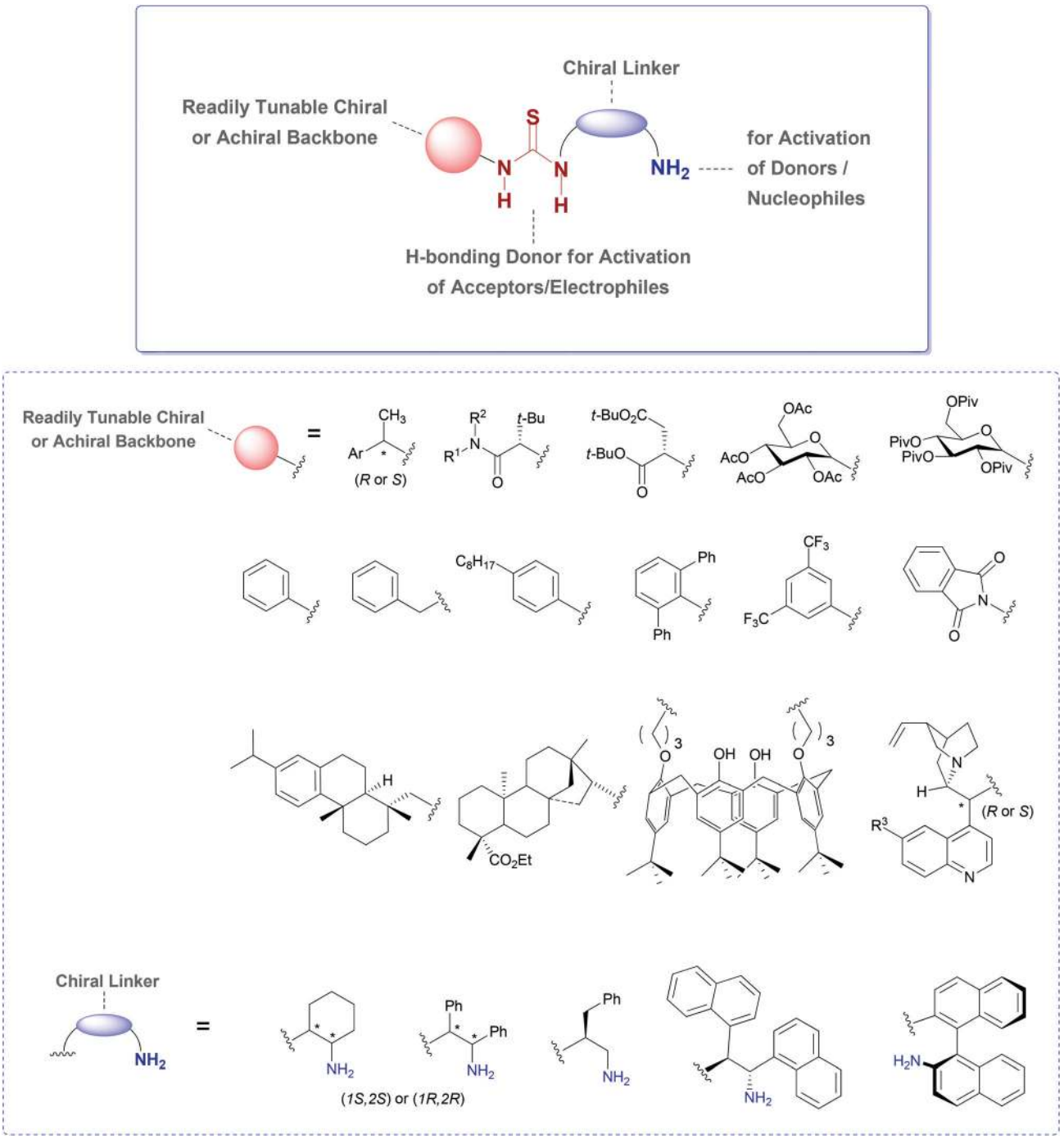
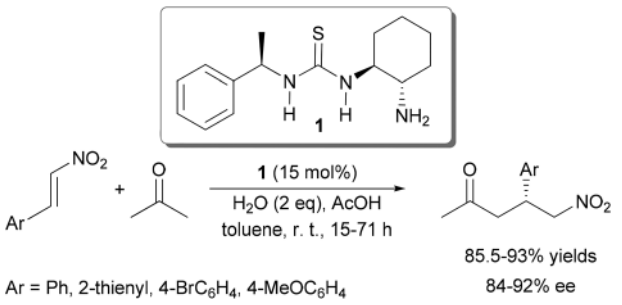


Fig. 1 Schematic and general representation of primary amine-thiourea organocatalysts for dual activation of the substrates.

Subsequently, the application of the related organocatalysts **4** and **5** to the conjugate addition of α,α-disubstituted aldehydes to nitroalkenes was studied by Jacobsen and co-workers.[24] While catalyst **5**, derived from diphenylethylene diamine, afforded excellent results in the reaction of 1-nitro-hex-1-ene with 2-phenylpropionaldehyde, diaminocyclohexane-derived catalyst **4** was found to be more broadly applicable (Schemes 5 and 6). High enantioselectivity and a useful to high level of diastereoselectivity were obtained with a wide range of substrates by using primary amine-thiourea **4** (Scheme 6).

In 2007, Ma and co-workers developed a new class of bifunctional primary amine-thiourea catalysts based on saccharides.[25] In particular, catalyst **6** has shown excellent enantioselectivities for direct Michael addition of aromatic ketones to a series of aromatic-, heteroaromatic-, and alkylsubstituted nitroolefins (Scheme 7, Fig. 4). The addition of acetophenone to different aromatic- and heteroaromatic substituted



Scheme 1

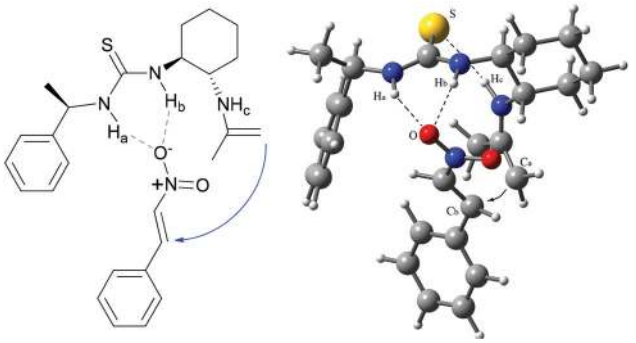
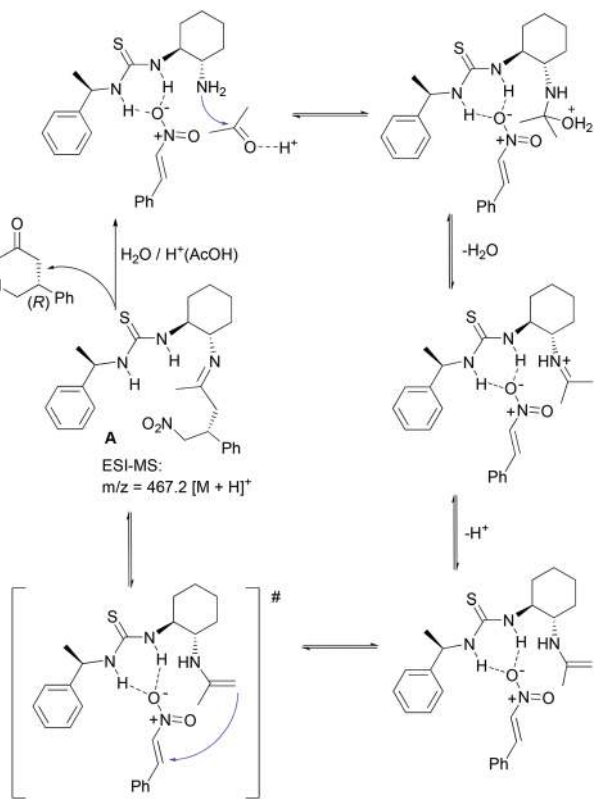
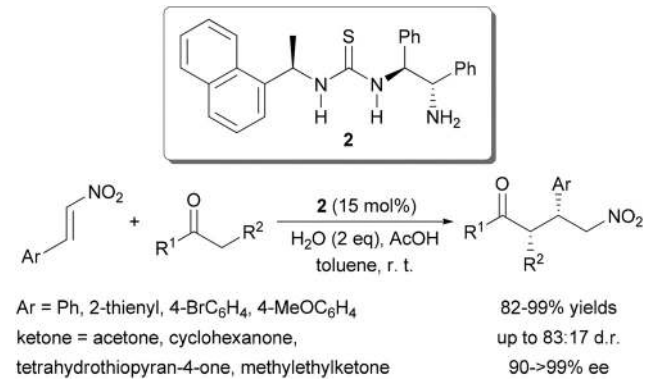


Fig. 2 Transition state structure for the formation of the *R* enantiomer (DFT calculations at the B3LYP/6-31G(d) level).



Scheme 2



Scheme 3

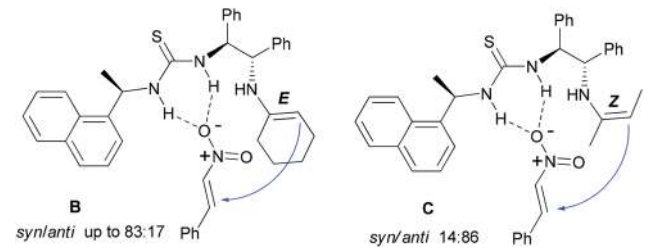
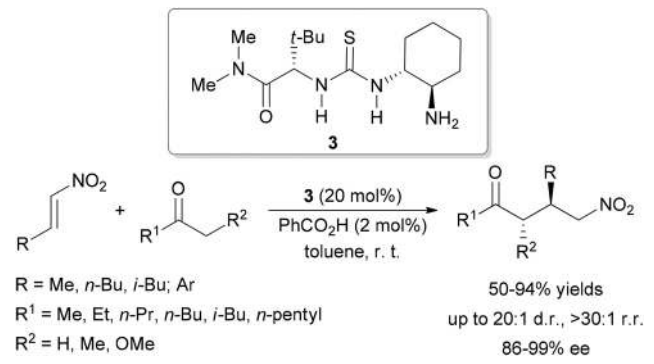
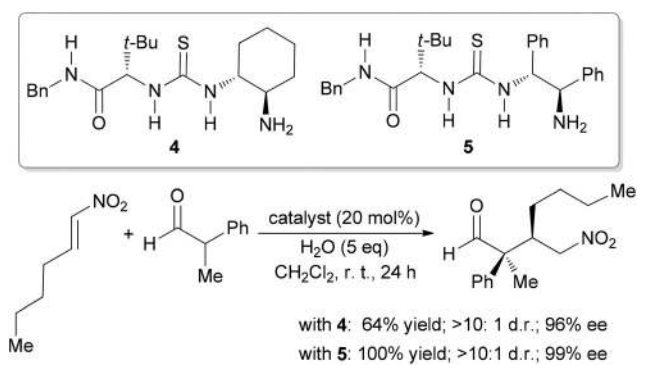


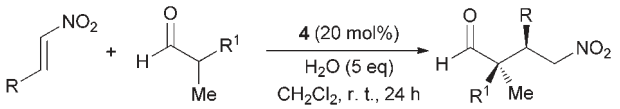
Fig. 3 Proposed transition states for the Michael reaction of symmetrical (B) and nonsymmetrical ketones (C) with *trans*-β-nitrostyrene.



Scheme 4

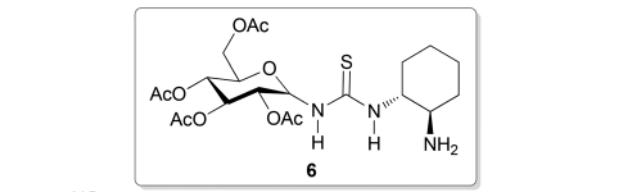


Scheme 5



R = Me, CF_3, *n*-Bu, Ph, 4-$MeOC_6H_4$, 2-furyl, 2-$CF_3C_6H_4$, $PhCH_2OCH_2$, 4-FC_6H_4, 3-pyridyl, 2-thienyl, 4-BrC_6H_4,
R^1 = Ph, $TBSOCH_2$, PhO, *n*-Pr, 4-$MeOC_6H_4CH_2O$, $Me_2CH{=}CHCH_2CH_2$

Scheme 6



Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4/2-BrC_6H_4 (44:56), 4-ClC_6H_4, 2-naphthyl
R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-BrC_6H_4, 2-ClC_6H_4, 2-naphthyl, 2-furyl, Et

Scheme 7

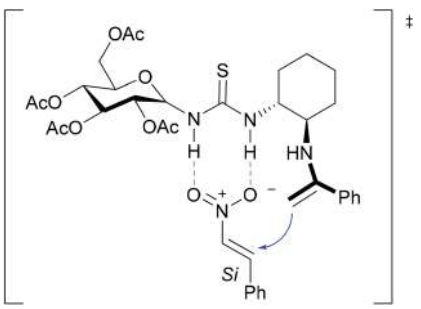
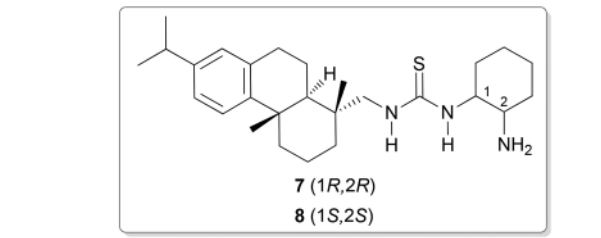


Fig. 4 Proposed transition state structure.

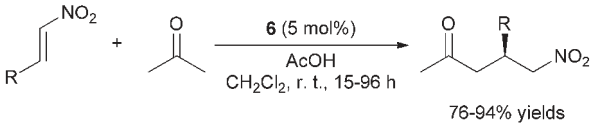
nitroolefins took place in 65–99% yield with high enantioselectivities (94–98% ee). The same catalytic system was applicable to various aromatic methyl ketones in moderate to high yields (42–92%) with 95–97% ee.

A new class of primary amine-thiourea catalysts **7** and **8** based on dehydroabietic amine, which has been applied to the doubly stereo-controlled synthesis of γ-nitro heteroaromatic ketones, was developed by the group of Wang in 2009 (Scheme 8).[26] Almost in all cases, the reactions proceeded smoothly, affording the desired products of the (*S*) or (*R*) configuration (*S*-product with **7** and *R*-product with **8**) with



R = Ph, 2-furyl, 2-thienyl, 4-FC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 2-MeC_6H_4
R^1 = Me, Ph, 2-furyl, 2-thienyl, 5-methylfuryl, 2,5-dimethylfuryl, 2-thiazolyl, 4-FC_6H_4, 4-ClC_6H_4, 3-MeC_6H_4, 3-BrC_6H_4

Scheme 8



R = 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-CNC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 2-ClC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 2,4-$Cl_2C_6H_3$, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-furyl

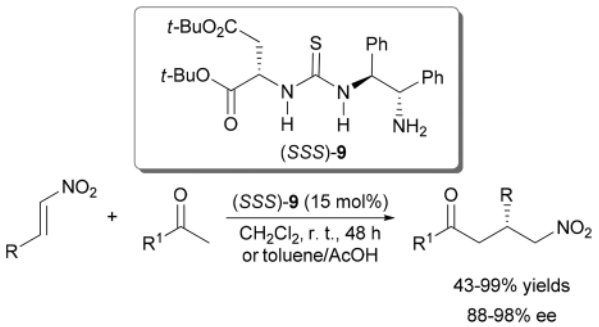
Scheme 9

excellent enantioselectivities (98–>99% ee) in moderate to high yields. Notably, the decrease of the catalyst loading to 0.5–1 mol% did not affect the enantioselectivity, but a decrease in yield was observed.

Later, Wu and co-workers studied further the saccharide-based catalytic system, developed by Ma and co-workers. They reported that the reactivity and the enantioselectivity could be improved when acid additives were used as co-catalysts (Scheme 9).[27] The reactions proceeded in the presence of 5 mol% of the Ma catalyst **6**, and gave chiral Michael adducts in good yields (76–94%) with high to excellent enantioselectivities (88–96%).

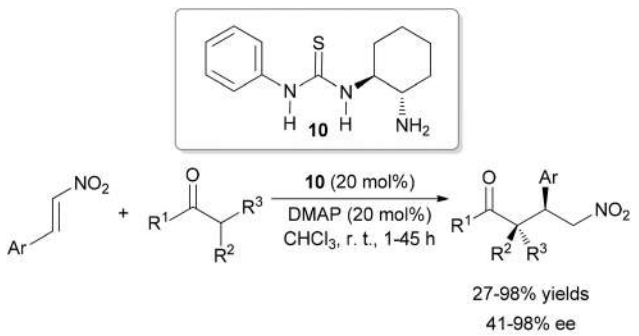
New primary amine-thioureas based on *tert*-butyl esters of (*S*)-α-amino acids and (1*S*,2*S*)-diphenylethylenediamine, for example catalyst (*S*,*S*,*S*)-**9**, able to catalyze asymmetric Michael additions with high enantioselectivities were reported by Kokotos.[28] The reaction between acetophenone and various aromatic nitroolefins took place in CH_2Cl_2 in 43–71% yield with high ee values (95–98%). The same transformation with acetone was performed in toluene in the presence of AcOH (15 mol%) in 69–99% yield with 88–92% ee (Scheme 10).

In 2009, the group of Yan applied a simple chiral thiourea catalyst **10** derived from cyclohexane-1,2-diamine to the conjugate addition of aldehydes to nitroalkenes.[29] Excellent enantioselectivities and yields were obtained for a variety of aryl and



R = 4-MeOC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 4-FC$_6$H$_4$, 2-furyl; R^1 = Ph, Me

Scheme 10



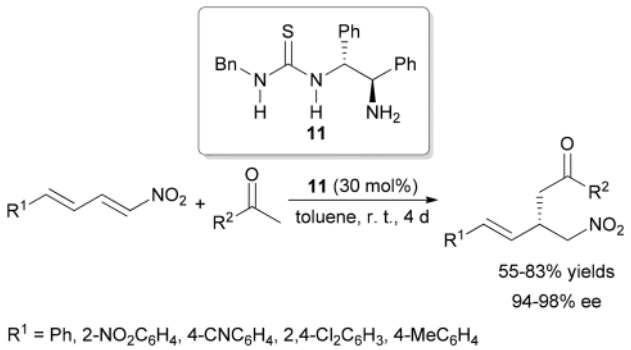
Ar = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 2-furyl, 2-thienyl, Ph-CH=CH,1-naphthyl
R^1 = H, Me, R^2, R^3 = Me; R^2 = H, R^3 = Me; R^2 = H, R^3 = Et
R^1, R^2, R^3 = (CH$_2$)$_4$

Scheme 11

heteroaryl nitroalkenes (Scheme 11). However, with ketones, lower enantioselectivities and yields were observed. The use of base additives, for example DMAP, in the transformation, is essential for good yields and excellent enantioselectivities.

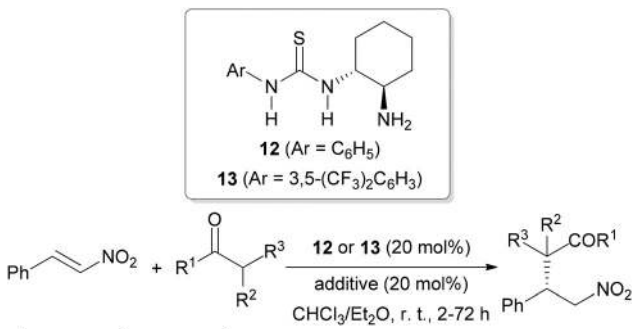
In the same year, the group of Wu reported the successful asymmetric nitro-Michael addition of aromatic ketones to various nitrodienes catalyzed by primary amine-thiourea catalyst **11**, providing the desired Michael adducts in good yields (up to 83%) and excellent enantioselectivities up to 98% ee (Scheme 12).[30] The catalysis of electron-deficient aromatic methyl ketones to acetophenone usually provided the expected Michael products in better yields than the experiments with non-substituted or electron-rich aromatic methyl ketones, whereas the enantioselectivity remained constantly high. Notably, the best yield of 83% was achieved using a Michael donor with a rather bulky 2-naphthyl residue.

The effect of hydrogen-bonding interactions between bifunctional organocatalysts and the reactants of conjugate additions involving *trans*-β-nitrostyrene or (*E*)-methyl 2-oxo-4-phenylbut-3-enoate and isobutyraldehyde or acetone, respectively, was investigated in 2009 by the Yan group.[31] Different hydrogen bond donors, like ureas, thioureas, sulfamides or amides were tested. With primary amine-thiourea catalysts **12**



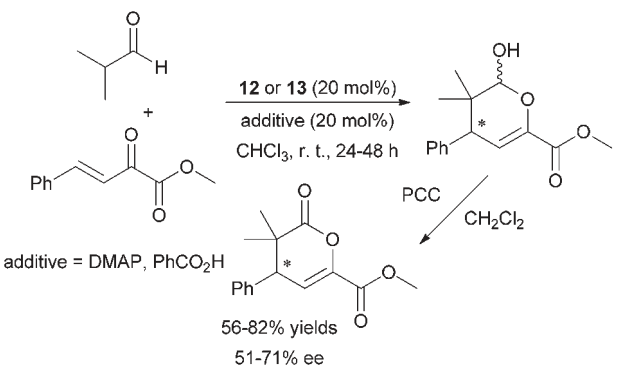
R^1 = Ph, 2-NO$_2$C$_6$H$_4$, 4-CNC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$, 4-MeC$_6$H$_4$
R^2 = Ph, 4-NO$_2$C$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-naphthyl

Scheme 12



R^1 = H, Me; R^2 = H, Me; R^3 = H, Me
additive = DMAP, PhCO$_2$H, imidazole

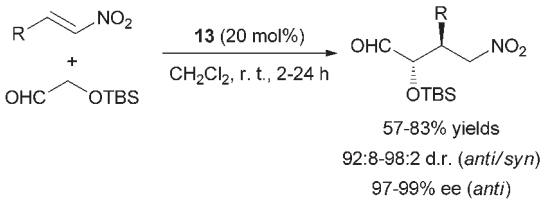
Scheme 13



Scheme 14

and **13**, moderate to high yields (58–95%) and good to excellent enantioselectivities (64–98% ee) were achieved (Schemes 13 and 14). The investigations showed that the acidity of the thiourea–N–H bonds of the catalysts is not proportional to their catalytic activity and it can be assumed that the catalytic behavior of a catalyst, concerning activity and enantioselectivity, is more dependent on reaction substrates and conditions than on N–H-acidity and hydrogen-bonding modes.

The first *anti*-selective nitro-Michael reaction of aldehydes with nitroolefins catalyzed by primary amine-thiourea catalysts



R = Ph, 4-BrC_6H_4, 4-MeC_6H_4, 3-BrC_6H_4, 3,4-$Cl_2C_6H_3$, 2-$CF_3C_6H_4$, 2,6-$Cl_2C_6H_3$, 2-thienyl, *n*-C_7H_{15}

Scheme 15

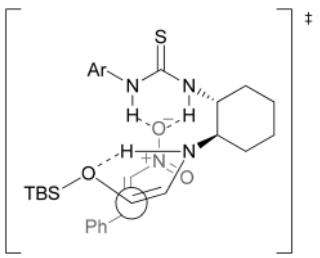
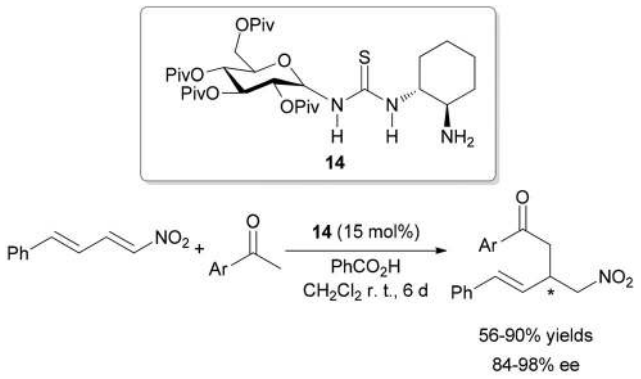


Fig. 5 Proposed synclinal transition-state model.

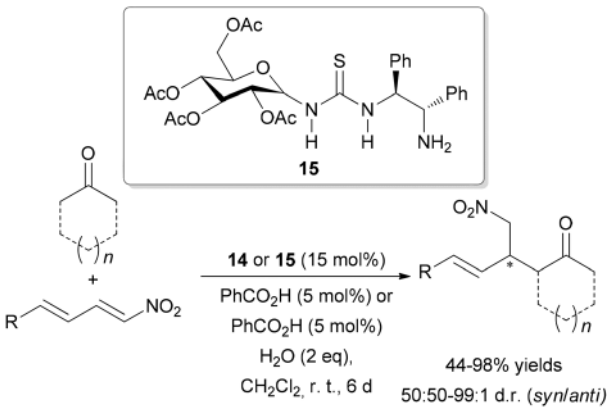
13 was reported by Barbas III and Uehara in 2009.[32] The diverse Michael adducts derived from the conversion of TBS-protected hydroxyacetaldehyde with electron-deficient, electron-rich and sterically hindered nitrostyrenes were obtained in moderate to high yields (57–83%) with excellent diastereo- and enantioselectivities (98 : 2 d.r. and up to 99% ee) (Scheme 15, Fig. 5). Due to the *anti*-selectivity of this reaction, the *Z*-enamine was considered to be the reactive species which might be stabilized by intramolecular hydrogen bonding.

In 2010, Ma and co-workers reported the effective Michael-type addition of selected acyclic and cyclic ketones to aryl nitrodienes in the presence of readily available bifunctional thioureas derived from simple saccharides.[33] Pivaloyl protected thiourea catalyst **14** was identified as the most active one for the addition of phenyl nitrodiene to a variety of substituted aryl methyl ketones (Scheme 16). Only 1,4-addition



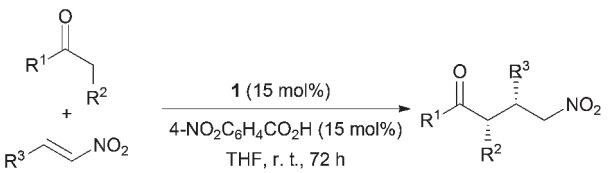
Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 2-naphthyl, 1,3-benzodioxolyl, 2-Py, 3-Py, 2-furyl, 2-thienyl

Scheme 16



R = Ph, 2-$NO_2C_6H_4$, 4-$MeOC_6H_4$
ketone = acetophenone, cyclohexanone, cyclopentanone, dihydropyran-4-one,dihydrothiopyran-4-one, acetone, methyl isobutyl ketone

Scheme 17



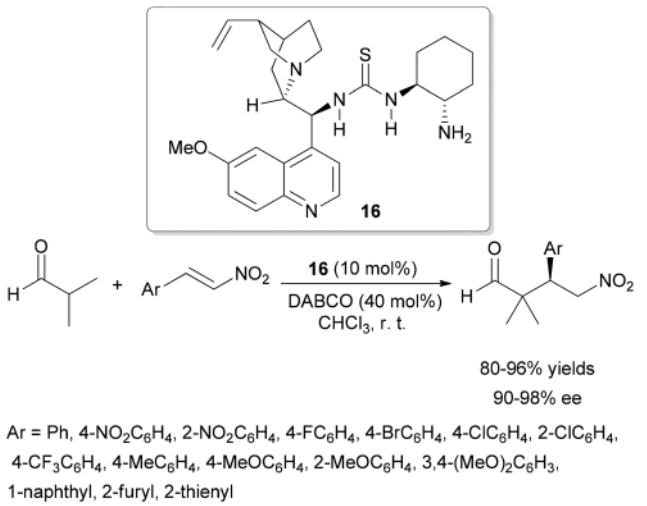
R^1 = Ph, 3-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, -$(CH_2)_4$-; R^2 = H, -$(CH_2)_4$-
R^3 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 2-BrC_6H_4, 2-furyl, 2-thienyl

Scheme 18

products were isolated in high yields (up to 90%) and excellent enantioselectivities (up to 98% ee).

Thiourea-amine **14** failed to catalyze the addition of phenyl nitrodienes to aliphatic ketones, like cyclohexanone or acetone. These transformations were accomplished through acetyl protected thiourea catalyst **15** with benzoic acid and water as additives providing yields up to 98%, high enantioselectivities (84–99% ee) and poor to high diastereoselectivities (50 : 50 to 99 : 1) (Scheme 17).

Primary amine-thiourea catalyst **1**, developed in the Tsogoeva group, was applied in 2010 by Xu and co-workers for the enantioselective Michael addition of a wide range of substituted acetophenones to aryl nitroolefines.[34] By varying the reaction parameters, co-catalyst 4-nitrobenzoic acid and THF were found to provide the best results. Under these conditions, good to high yields (70–98%) and excellent enantioselectivities (89–99% ee) were achieved (Scheme 18). The interaction between the nitroolefin and the catalyst was indicated by ^{1}H-NMR monitoring.



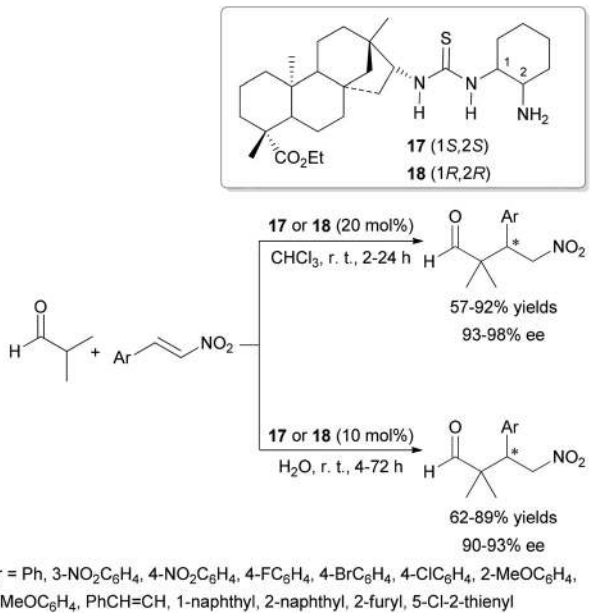
Scheme 19

The group of Chen developed a highly enantioselective Michael addition of isobutyraldehyde to nitroolefins catalyzed by a cinchona-alkaloid derived primary amine-thiourea organocatalyst **16**.[35] With a catalyst loading of 10 mol% and the addition of 40 mol% DABCO, the reactions of a broad spectrum of substituted nitroolefins proceeded in high yields (80–96%) and good enantioselectivities (up to 98% ee, Scheme 19).

In 2011, Tao and Tang developed an isosteviol-derived amine-thiourea organocatalyst for the same nitro-Michael addition using isobutyraldehyde and nitroolefins as starting compounds.[36] They were able to perform the reaction in organic solvents like chloroform as well as in aqueous medium, which required a lower catalyst loading and longer reaction times than the comparable reactions in organic media. In both cases, moderate to high yields (up to 92%) and excellent enantioselectivities (90–98% ee) were reached (Scheme 20, Fig. 6). For catalyst **17**, the (*S*)-enantiomer was predominantly formed, whereas catalyst **18** delivered the (*R*)-enantiomer. These experimental results were confirmed by computational calculations of the transition states.

The substrate scope of the above mentioned enantioselective Michael addition of ketones to aryl nitrodienes catalyzed by bifunctional thiourea catalyst (1*R*,2*R*)-**11** was further expanded by He and Wu in 2012.[37] The various experiments performed with a range of aliphatic ketones like butanone, 3-pentanone or cyclohexanone provided the desired Michael products with modest to high yields (25–97%) and, with one exception, excellent enantioselectivities (up to 99% ee). However, only low diastereoselectivities (69 : 31 to 83 : 17) were reported (Scheme 21).

Kokotos and co-workers applied successfully di-*tert*-butyl aspartate-derived catalyst **9** to the Michael addition of aryl methyl ketones to nitroolefins.[38] Both diastereomers, (*S*,*S*,*S*)-**9** and (*R*,*R*,*S*)-**9**, were tested to reveal the most suitable combination of the absolute configurations of stereogenic centers. With the optimal organocatalyst (*R*,*R*,*S*)-**9**, derived from



Scheme 20

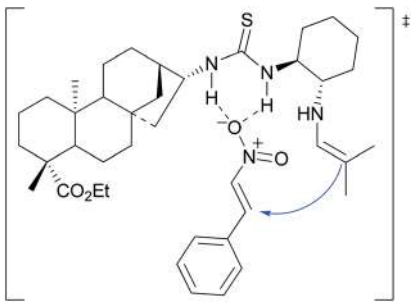
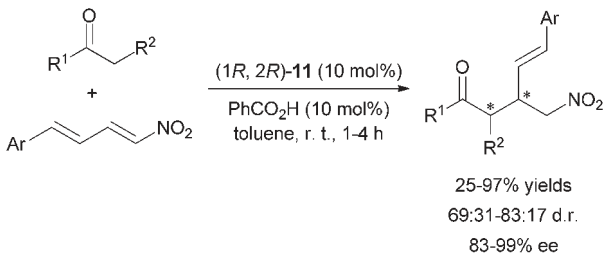
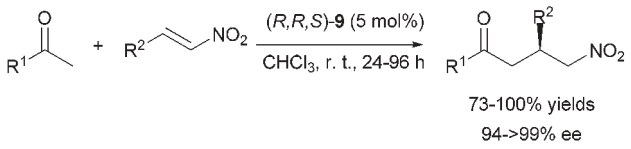


Fig. 6 Proposed structure for the formation of the (*S*)-enantiomer.



Scheme 21

(1*R*,2*R*)-diphenylethylenediamine, the Michael addition was performed with high yields (73–100%) and excellent enantioselectivities (94–99% ee), while the catalyst loading could be reduced from 15 to 5 mol% (Scheme 22, Fig. 7). To highlight the utility of this methodology, the efficient synthesis of (*S*)-baclofen, (*R*)-baclofen and (*S*)-phenibut was demonstrated.



R^1 = Me, Ph, 4-$NO_2C_6H_4$, 4-CNC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 4-$AcOC_6H_4$, 4-HOC_6H_4, 2-furyl
R^2 = Ph, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 2-furyl, 3-$NO_2C_6H_4$

Scheme 22

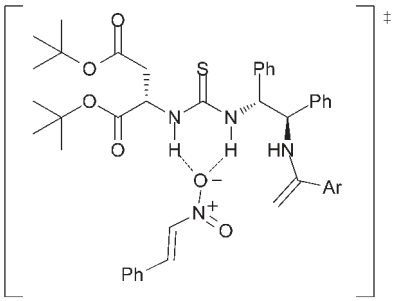
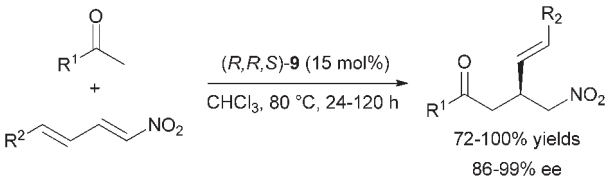
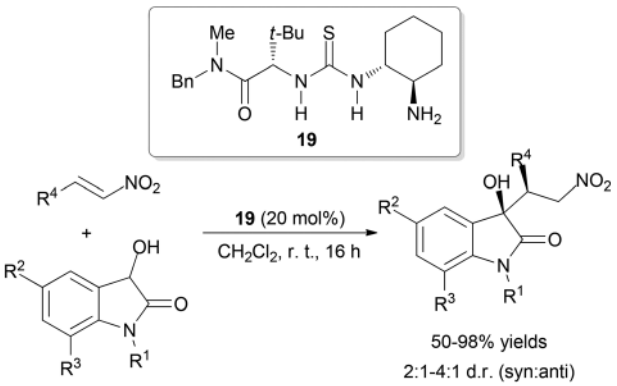


Fig. 7 Proposed transition state structure.



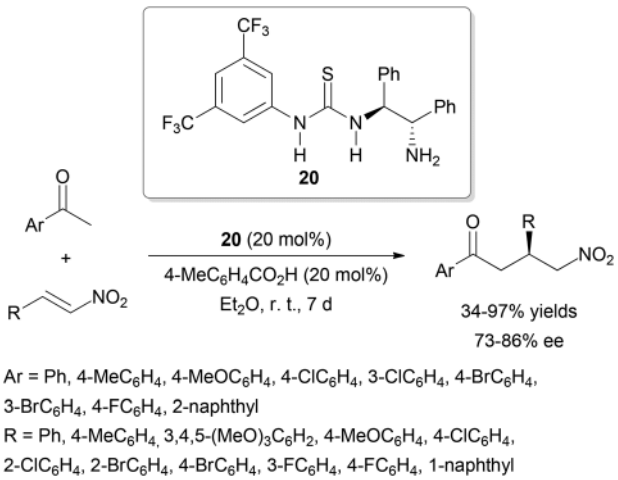
R^1 = Me, Ph, 4-$NO_2C_6H_4$, 4-CNC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-PhC_6H_4, 4-$AcOC_6H_4$, 4-$MeOC_6H_4$, 2-naphthyl, 2-furyl
R^2 = Ph, 4-$MeOC_6H_4$, 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-ClC_6H_4

Scheme 23



R^1 = H, Me, Bn; R^2 = H, Me, Br; R^3 = H, Me, Br
R^4 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 2-BrC_6H_4, 2-furyl, 3-thienyl

Scheme 24



Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3-ClC_6H_4, 4-BrC_6H_4, 3-BrC_6H_4, 4-FC_6H_4, 2-naphthyl
R = Ph, 4-MeC_6H_4, 3,4,5-$(MeO)_3C_6H_2$, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-ClC_6H_4, 2-BrC_6H_4, 4-BrC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 1-naphthyl

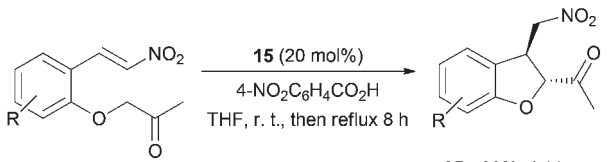
Scheme 25

In addition, the same group proved that the same catalyst (*R*,*R*,*S*)-**9** is also able to catalyze the nitro-Michael addition of a variety of aryl methyl ketones and acetone, respectively, to diverse substituted nitrodienes.[39] By elevation of the reaction temperature and pressure, the reaction time was reduced in most cases to an acceptable length whereas the enantioselectivity remained at a high level. With a broad range of substituted ketones and nitrodienes, high to quantitative yields and excellent enantioselectivities were achieved (Scheme 23).

In 2012, Melchiorre and co-workers reported a successful catalytic asymmetric 1,4-addition of 3-hydroxy-substituted oxindoles to aryl nitroalkenes.[40] Primary amine-thiourea catalyst **19** was found to be the most suitable catalyst for this type of reaction and after optimization of the reaction conditions, yields of up to 98%, diastereoselectivities of up to 4 : 1 d.r. and excellent enantioselectivities were observed (Scheme 24). A structure/stereoselectivity correlation study revealed the importance of the primary amine function and the amido moiety. Additionally, slight changes on one of the catalyst chiral centers lead to a significant drop in enantioselectivity.

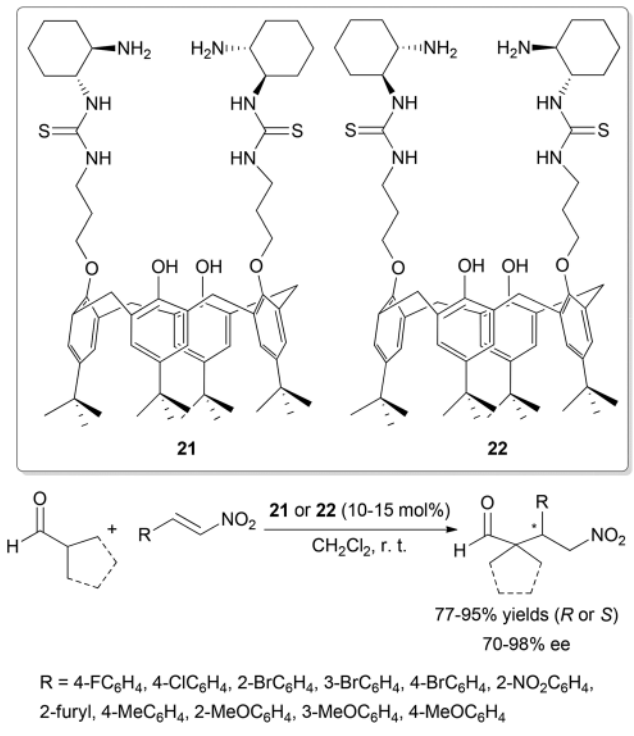
Similar to the discussed publications, Wang and co-workers reported in 2010 the asymmetric Michael addition of aryl methyl ketones to aromatic nitroolefins catalyzed by a simple 1,2-diphenyl ethylenediamine derived thiourea catalyst **20**.[41] With a range of different substrates bearing moieties with different electronic properties and steric hindrance, poor to high yields and good to high enantioselectivities were accomplished (Scheme 25).

More recently, primary amine-thiourea organocatalyzed intramolecular nitro-Michael addition with formation of *trans*-dihydrobenzofurans was developed by the group of Wang and Zhou.[42] In the presence of an (*R*,*R*)-1,2-diphenylethylamine derived primary amine-thiourea bearing a glucosyl scaffold, the corresponding *trans*-dihydrobenzofurans were obtained in high yields with excellent enantioselectivities (up to >99% ee) (Scheme 26). An *in situ* isomerization occurring at high



R = H, 5-F, 5-Cl, 5-Br, 5-NO_2, 7-MeO, 5-MeO, 7-Me, 6-Me, 5-Me, 4,5-CH=CH-CH=CH

Scheme 26



R = 4-FC_6H_4, 4-ClC_6H_4, 2-BrC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 2-$NO_2C_6H_4$, 2-furyl, 4-MeC_6H_4, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$

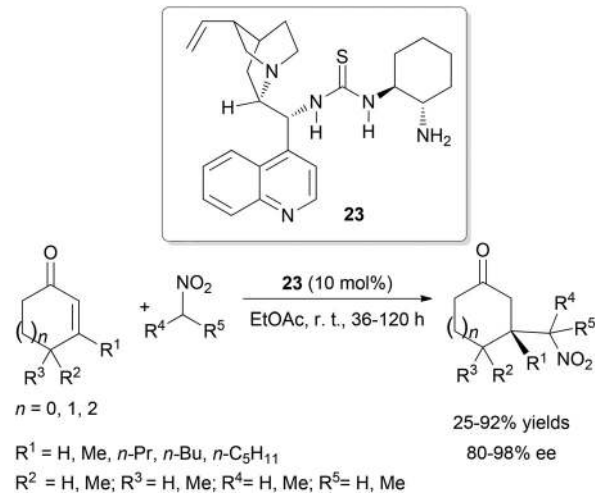
Scheme 27

temperature gave good to excellent *trans* : *cis* ratios as well (84 : 16–96 : 4).

In 2013, Sirit and Durmaz described a new type of chiral bifunctional primary amine-thiourea catalysts **21** and **22** derived from calix[4]arene. These catalysts were successfully applied to promote Michael addition of aldehydes with nitroalkenes affording (*R*)- or (*S*)-adducts in yields up to 95% with high enantioselectivities (Scheme 27).[43]

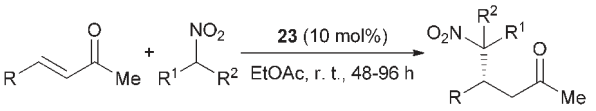
1,4-Conjugate additions to α,β-unsaturated ketones and aldehydes

In 2008, Liang and Ye developed a new type of organocatalyst consisting of 1,2-diaminocyclohexane and 9-aminocinchona alkaloid derivatives for asymmetric Michael addition of nitroalkanes to ketones.[44] For example, catalyst **23** with a primary amine function activating and arranging cyclic enone,



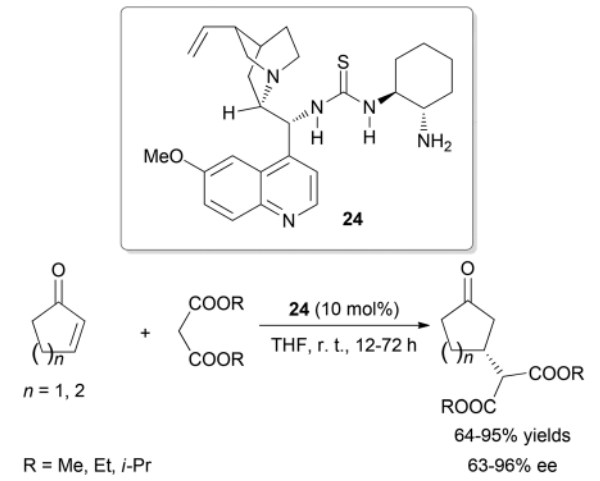
R^1 = H, Me, *n*-Pr, *n*-Bu, *n*-C_5H_{11}
R^2 = H, Me; R^3 = H, Me; R^4 = H, Me; R^5 = H, Me

Scheme 28



R^1 = H, Me; R^2 = H, Me
R = Ph, 4-$NO_2C_6H_4$, 4-MeC_6H_4, 2-MeC_6H_4, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-ClC_6H_4, 2-thienyl, *n*-Pr, *n*-Bu

Scheme 29

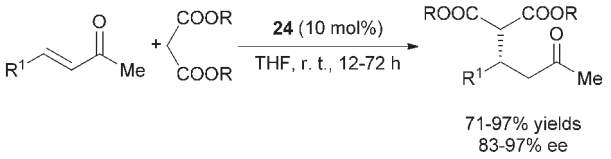


R = Me, Et, *i*-Pr

Scheme 30

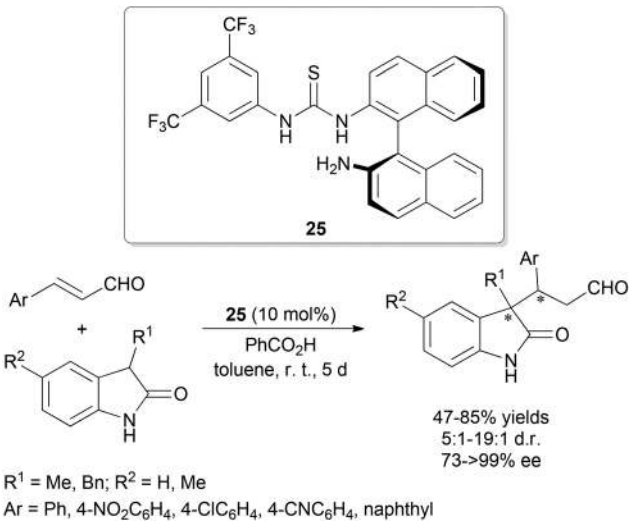
provided products in up to 92% yield with good enantioselectivities (80–98% ee) (Scheme 28). The same system **23** was shown to catalyze the reactions with acyclic enones in 60–98% yield with moderate ee values (73–86%) (Scheme 29).

On the other hand, the catalyst **24** was found to be more efficient for the addition of malonates to unsaturated ketones.[45] Thus, using cyclic enones, the Michael adducts were obtained in good yields with 63–96% ee (Scheme 30). The



R = Me, Et
R^1 = Ph, 4-ClC_6H_4, 2-BrC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, *n*-Pr, *n*-Bu, 2-thienyl

Scheme 31



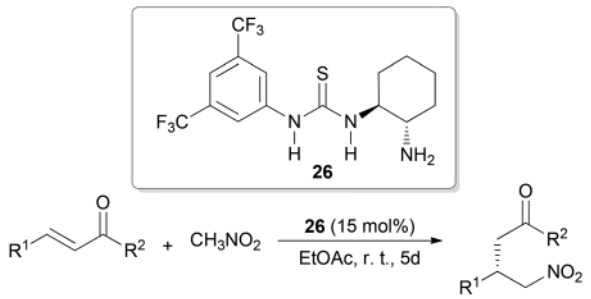
R^1 = Me, Bn; R^2 = H, Me
Ar = Ph, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-CNC_6H_4, naphthyl

Scheme 32

reaction conditions also allowed to perform the reaction with the sterically hindered α,β-unsaturated ketones (Scheme 31). Moreover, electron-withdrawing and electron-donating groups could be introduced into the aromatic ring with a little effect on efficiency or enantioselectivity.

In 2009, Melchiorre applied a chiral amine-thiourea catalyst to asymmetric conjugate addition of oxindoles to α,β-unsaturated aldehydes.[46] Thus, oxindoles reacted with enals in the presence of 10 mol% of chiral primary amine-thiourea **25** in good yields with up to 99% ee (Scheme 32). Whereas the thiourea moiety activated the oxindole, stabilizing its enol form, the primary amine activated the unsaturated aldehydes through iminium ion formation. Without additive the reaction was not efficient (39% yield, 97% ee). Interestingly, replacement of the primary amine moiety with a tertiary one (NMe_2) in the catalyst scaffold led to a complete loss of catalytic activity.

Wang and co-workers slightly improved the outcome of the conjugate addition of nitroalkanes to enones using the catalyst **26**.[47] The protocol provided a catalytic approach to the preparation of nitroketones with excellent enantioselectivities (92–99% ee). The reaction proceeded with acyclic and cyclic enones, as well as with other nitroalkanes, for example, nitroethane (82% yield, 94% ee). However, 15 mol% of



R^1 = Ph, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, 3,4-$(OCH_2O)C_6H_3$, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 4-FC_6H_4, 4-BrC_6H_4, 2-IC_6H_4, 2-furyl, $PhCH_2$, $PhCH_2CH_2$, *trans*-PhCH=CH
R^2 = Me, Et, *i*-Pr, $AcOCH_2$, $PhCO_2CH_2$; R^1, R^2 = -$(CH_2)_4$-

Scheme 33

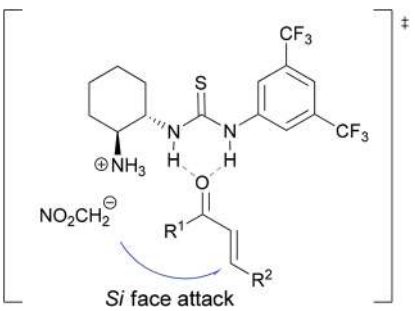
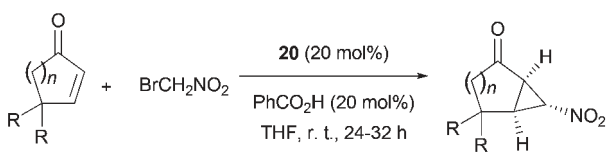


Fig. 8 Proposed transition state structure.

catalyst was used and the reaction time was extended to 5 days (Scheme 33, Fig. 8).

In 2010, the group of Yan has successfully applied the catalyst **20** to the conjugate addition of bromonitromethane to cyclic α,β-unsaturated ketones (Scheme 34, Fig. 9).[48] Excellent enantioselectivities and yields were obtained for cyclohex-2-enone and 4,4-dimethylcyclohex-2-enone. Good enantioselectivity and moderate yield was achieved for cyclohept-2-enone. Cyclopent-2-enone provided the corresponding product with good enantioselectivity in poor yield. Acyclic unsaturated ketones, such as chalcone and benzylidene acetone, were not reactive under the reaction conditions. Without additive, the reaction resulted in poor yield (35%).

In 2010, Liang and Ye showed that the catalyst **23** exhibits catalytic activity in the asymmetric Michael addition of triazole



n = 1, 2
R = H, Me

Scheme 34

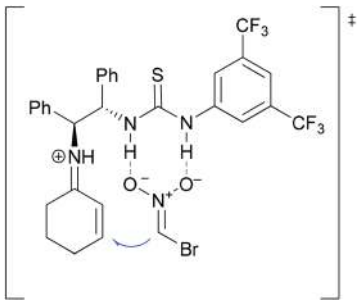
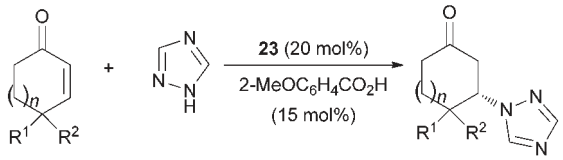


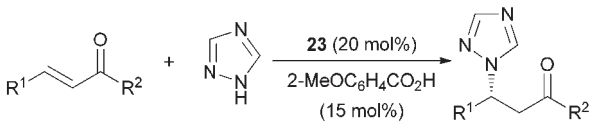
Fig. 9 Proposed transition state structure.



n = 1, 2
R^1 = H, Me; R^2 = H, Me

81-98% yields
87-93% ee

Scheme 35



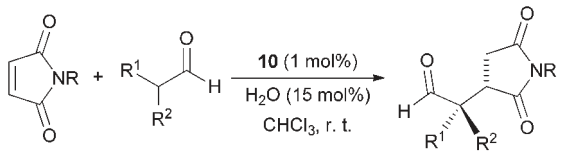
43-96% yields
69-80% ee

R^1 = Ph, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-FC$_6$H$_4$, 3-FC$_6$H$_4$, 4-FC$_6$H$_4$, 2-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-BrC$_6$H$_4$, 2-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 2-naphthyl
R^2 = Me, Ph

Scheme 36

to enones.[49] The most efficient additive was found to be 2-methoxybenzoic acid. In the presence of the additive the reaction with cyclic enones (cyclohex-2-enone, 4,4-dimethylcyclohex-2-enone, cyclopent-2-enone) gave products in high yields with 87–93% ee (Scheme 35). However, Michael adducts of acyclic aryl enones with triazole were obtained in good yields, but with mostly moderate enantioselectivities (69–80%) (Scheme 36).

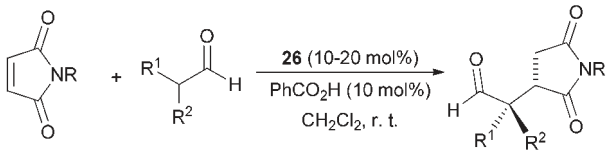
The catalyst **10**, previously reported by Yan, was applied by Duan and Wang for conjugate addition of α,α-disubstituted aldehydes to maleinimides.[50] High enantioselectivities, good yields, but low diastereoselectivities were obtained using very low catalyst loading (1 mol%) and small amounts of water (Scheme 37). The reactions of maleimides with electron-neutral, electron-donating and electron-withdrawing groups with isobutyraldehyde proceeded smoothly to give diverse succinimides. The electron-withdrawing group slowed down the reaction, however, the use of higher catalyst loading (15 mol%) could increase the reaction rate.



68-91% yields
1.2:1-11:2 d.r.
75-99% ee

R = Ph, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, Bn
R^1 = R^2 = Me; R^1, R^2 = -(CH$_2$)$_4$-, -(CH$_2$)$_5$-

Scheme 37



85-99% yields
1:1-9:1 d.r.
91->99% ee

R = Ph, 4-MeC$_6$H$_4$,3-CF$_3$C$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 3-MeC$_6$H$_4$, Bn, *n*-Pr, *i*-Pr
R^1 = Me, Et; R^2 = Me, Et, *n*-Pr, Ph, 4-*t*-BuBn; R^1, R^2 = -(CH$_2$)$_5$-

Scheme 38

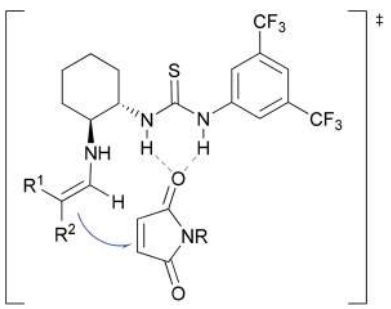
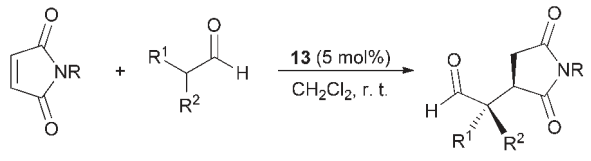


Fig. 10 Proposed transition state structure.

Ye and co-workers have explored the scope of this reaction.[51] They have shown that the use of the catalyst **26** and benzoic acid as an additive provided succinimides in 85–99% yield with 91–>99% ee (Scheme 38, Fig. 10). However, catalyst loadings were higher (up to 20 mol% for sterically hindered 2-aryl-substituted aldehydes). Additionally, in this case, heating of the reaction mixture to 35 °C was necessary. Low diastereoselectivities were observed in all experiments. Thus, the reactions of the 2-alkyl-substituted aldehydes with minimal steric differentiation between the α-substituents provided a 1 : 1 diastereomeric ratio.

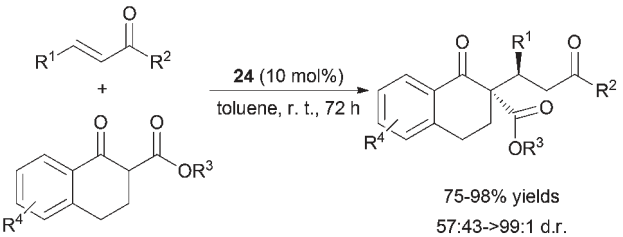
Nearly the same activity in this reaction was reported by Wang and Xu for catalyst **13**, which is simply an opposite enantiomer of **26**.[52] It provided Michael adducts in 55–98% yield and enantioselectivities up to 99% ee using 5 mol% catalyst



55-98% yields
1:1-1:1.3 d.r.
93-99% ee

R = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-FC$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 3-HOC$_6$H$_4$, 2-FC$_6$H$_4$, Me, Bn
R^1 = Me, Bn; R^2 = Me; R^1, R^2 = -(CH$_2$)$_5$-

Scheme 39



75-98% yields
57:43->99:1 d.r.
15-97% ee

R^1 = Me, *n*-Pr, *n*-Bu, *n*-C$_5$H$_{11}$, *n*-Hex, *i*-Bu, CH$_2$Bn
R^2 = Me, Et, *n*-Bu, Ph; R^1, R^2 = -(CH$_2$)$_3$-, -(CH$_2$)$_4$-
R^3 = Me, Et
R^4 = H, 7-OMe, 6-OMe, 6-Br, 6-Cl

Scheme 40

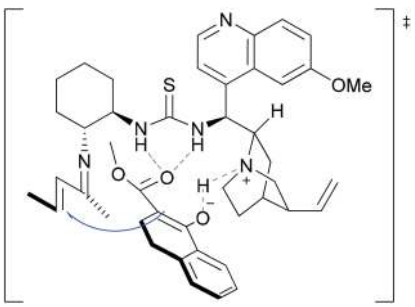
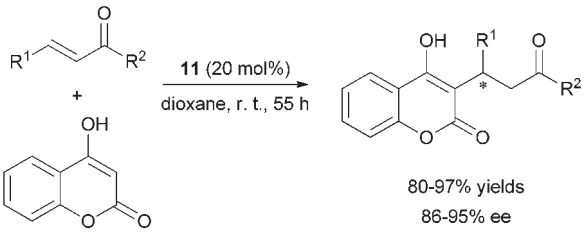


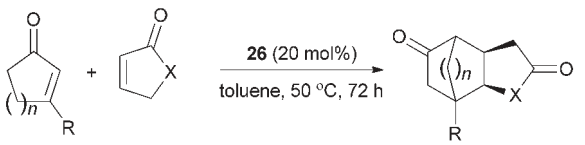
Fig. 11 Proposed transition state structure.



80-97% yields
86-95% ee

R^1 = Me, Et
R^2 = Ph, 3-FC$_6$H$_4$, 4-FC$_6$H$_4$, 2-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 2-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-furyl, 2-thienyl, 1-naphthyl

Scheme 41



n = 1, 2 X = O, S, NH

60-90% yields
>30:1 d.r.

R = H, Me, Et, *n*-Pr, *n*-Bu, *n*-C$_5$H$_{11}$, *i*-Bu, *c*-Hex, Bn, (CH$_2$)$_2$Ph

Scheme 42

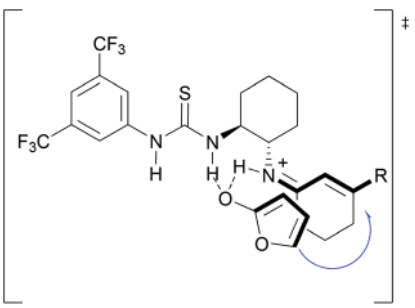


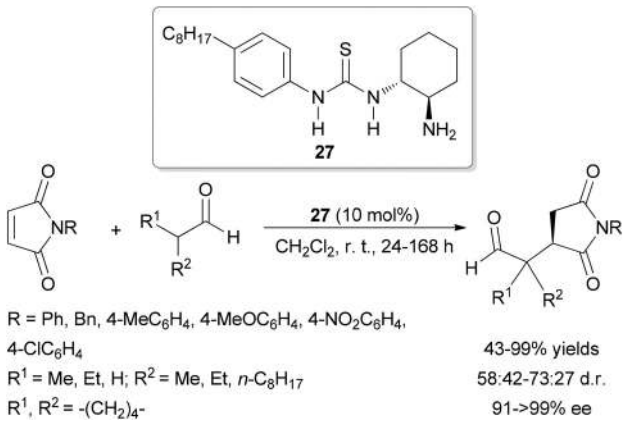
Fig. 12 Proposed transition state structure.

loading (Scheme 39). However, no diastereoselectivity was observed in all experiments.

An efficient approach for the enantioselective Michael additions of β-alkyl-β-keto esters to β-substituted α,β-unsaturated ketones has been developed by Ye.[53] The Michael products were obtained in the presence of catalyst **24** in good to excellent yields (75–98%) with excellent diastereoselectivities (up to >99 : 1 dr) and enantioselectivities (up to 97% ee) (Scheme 40, Fig. 11). However, a moderate ee value was achieved using benzylideneacetone and no reaction was observed with the more bulky Michael acceptors.

In 2011, Wang and co-workers developed an efficient procedure for the addition of 4-hydroxycoumarin to α,β-unsaturated ketones for the preparation of (*S*)-warfarin and its analogues.[54] Naphthyl α,β-unsaturated ketones, as well as aromatic α,β-unsaturated ketones with electron-withdrawing and electron-donating substituents, afforded corresponding products with high enantioselectivities (86–95% ee) in 80–97% yield (Scheme 41). Substituents in the aromatic ring slightly affected the yields and enantioselectivities. Heteroaromatic α,β-unsaturated ketones and bulkier alkyl enone also gave satisfactory yields and enantioselectivities.

The group of Ye described the catalytic reaction of 2(5*H*)-furanone with β-substituted cyclic enones proceeding *via* diastereoselective tandem Michael–Michael addition providing bicyclo[2.2.2]octan-2-one derivatives in good to excellent yields (65–90%) with excellent diastereoselectivities.[55] The procedure was also applied to α,β-unsaturated γ-butenolides with sulfur and nitrogen atoms. The corresponding S- and N-heterocyclic products were isolated in 60–85% yield (Scheme 42, Fig. 12).

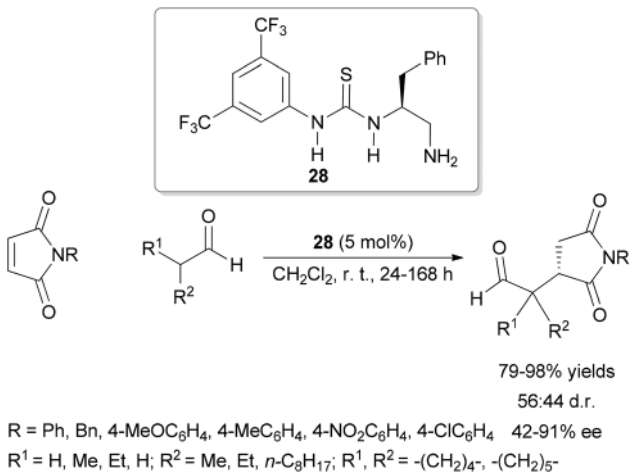


Scheme 43

In 2011, Miura and co-workers reported another example of conjugate addition of α,α-disubstituted aldehydes to maleinimides.[56] The authors have suggested a new catalyst **27** providing chiral succinimides in high yields (43–99%) with excellent enantioselectivities (99% ee in almost all experiments). The reaction was performed with maleimides bearing electron-neutral, electron-donating and electron-withdrawing groups in the presence of 10 mol% catalyst at room temperature (Scheme 43). Notably, catalytic activity and enantioselectivity of the catalyst did not change significantly over up to three repetitive reaction cycles.

The same authors suggested another primary amine-thiourea organocatalyst prepared from L-phenylalanine for this reaction.[57] Thus, Michael addition in the presence of the derivative **28** (5 mol%) gave succinimides in higher yields (79–98%), but with slightly lower enantioselectivities (42–91%) (Scheme 44, Fig. 13). Obviously, the transformation proceeds *via* a known enamine intermediate which was indicated by the stereochemistry of products.

A novel class of chiral multifunctional thioureas bearing a chiral lipophilic beyerane scaffold and a primary amino group



Scheme 44

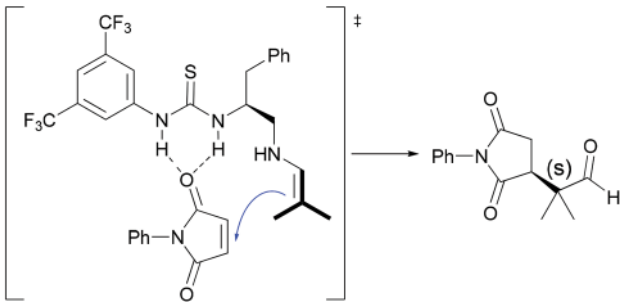
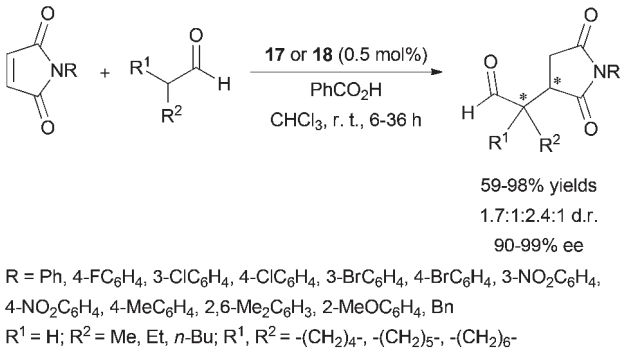


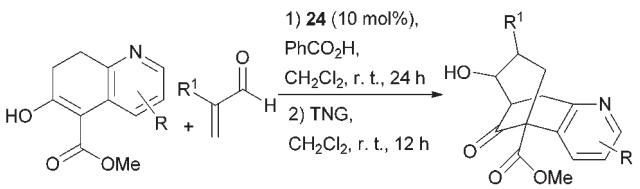
Fig. 13 Proposed transition state structure.



Scheme 45

was designed by Tao and co-workers.[36,58] The catalysts **17** and **18** were successfully applied to conjugate addition of α,α-disubstituted aldehydes to maleinimides (Scheme 45). The corresponding succinimides were obtained in 59–98% yield with excellent enantioselectivities using low catalyst loading (0.5 mol%).

In 2012, the group of Yao reported the first example of a highly enantioselective organocatalytic method for the construction of the bicyclo[3.3.1]nona-2,6-dien-9-one core of (−)-huperzine.[59] In the presence of the catalyst **24**, a variety of substituted β-tetralones smoothly underwent the tandem Michael-aldol reactions, providing the corresponding bridged products in 75–88% yield with up to 92% ee (Scheme 46, Fig. 14). On the other hand, the reaction with acrolein demonstrated very poor enantioselectivity (15% ee). With longer branched chains at the α-carbon of the aldehydes, the ee values were moderate (75–78%). When the β-substituted



Scheme 46

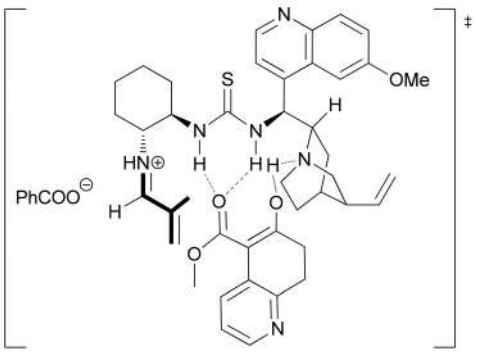
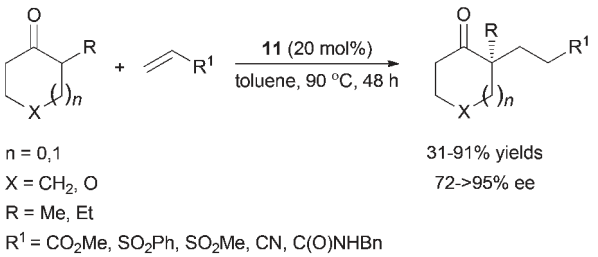


Fig. 14 Proposed transition state.



Scheme 47

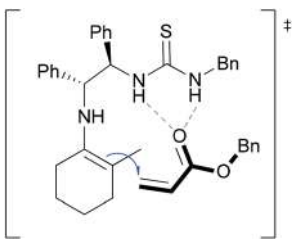
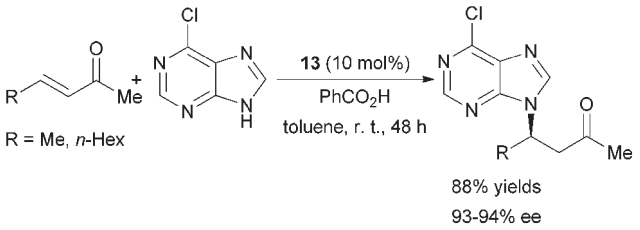


Fig. 15 Proposed transition state.

α,β-unsaturated aldehydes were used as the Michael acceptors, the reaction did not proceed. Probably, in this case, the formation of favorable supramolecular interactions in the transition state was impossible.

Carter and Kang applied catalyst **11** for enantioselective synthesis of α,α-disubstituted cycloalkanones.[60] Five- and six-membered cycloalkanones afforded the desired products in excellent yields and enantioselectivities (Scheme 47, Fig. 15). 2-Methylcycloheptanone gave none of the desired products. 2-Ethyl cyclohexanone provided a lower yield than the parent 2-methyl cyclohexanone.

Recently, Huang and Wang demonstrated that the primary amine-thiourea **13** catalyzes the aza-Michael addition of purine bases to α,β-unsaturated ketones.[61] Thus, the reaction of 6-chloro-9*H*-purine with 3-penten-2-one in the presence of benzoic acid proceeded in 88% yield with high enantioselectivity (93% ee). 3-Decen-2-one gave the corresponding adduct in 88% yield with 94% ee (Scheme 48, Fig. 16). The



Scheme 48

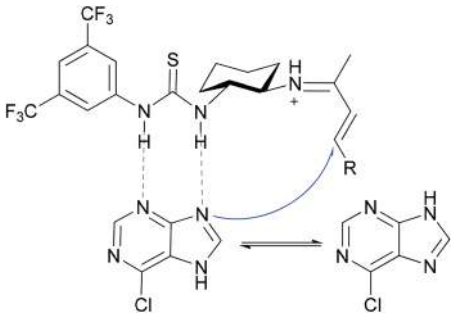
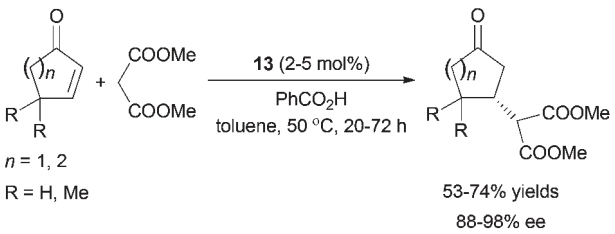


Fig. 16 Proposed transition state structure.

transformation was utilized for the synthesis of enantio-enriched non-natural nucleoside analogues.

The same catalyst has demonstrated higher activity with the addition of malonates to unsaturated ketones in comparison with catalyst **24**.[62] The group of Kwiatkowski has shown that the use of 2–5 mol% of the compound **13** allowed to perform the reaction of malonates with cyclic unsaturated ketones in moderate yields with ee values of 88–98% (Scheme 49, Fig. 17). Moreover, the addition to acyclic ketones proceeded in yields up to 96% with excellent enantioselectivities (92–97%)



Scheme 49

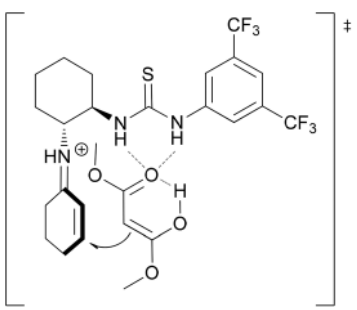
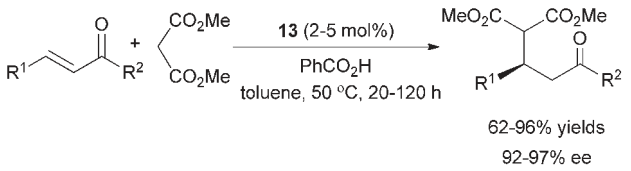
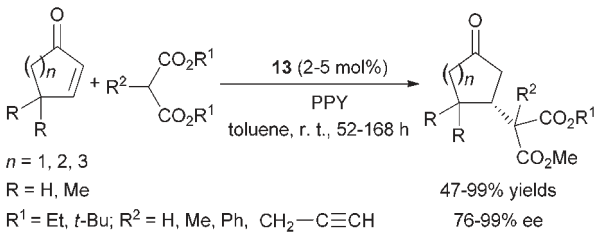


Fig. 17 Proposed transition state structure.



Scheme 50



Scheme 51

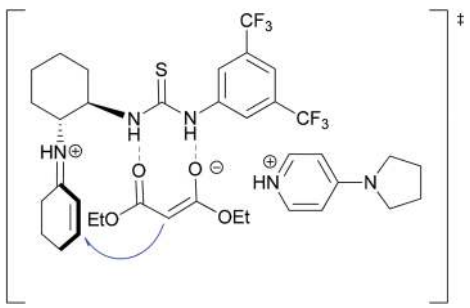


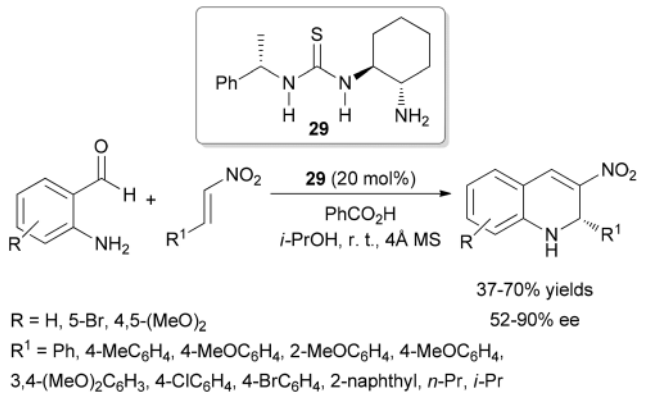
Fig. 18 Proposed transition state structure.

(Scheme 50). Notably, the efficiency of the Michael addition was significantly improved by the addition of weak acids and increasing the temperature to 50 °C.

In the presence of catalyst **13** and 4-pyrrolidinopyridine (PPY), the same reaction provided Michael adducts in better yields with excellent enantioselectivities already at room temperature (Scheme 51, Fig. 18).[63] The suggested procedure is particularly useful for the synthesis of complex molecules bearing sterically congested stereogenic centers. The presence of a free primary amine moiety in the catalyst was shown to be essential, since the dimethylamine homologue and bisthiourea provided no catalytic activity. The role of PPY was facilitating proton abstraction.

Domino aza-Michael–Henry reaction

In 2009, Xu and co-workers described an aza-Michael–Henry domino reaction of 2-aminobenzaldehydes with nitroolefins employing catalyst (*S*,*S*,*S*)-**29**, which is a diastereomer of primary amine-thiourea (*S*,*S*,*R*)-**1**. The reaction afforded



Scheme 52

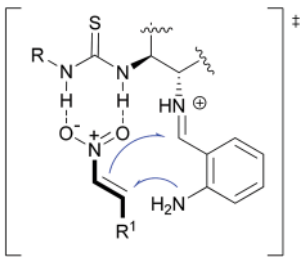


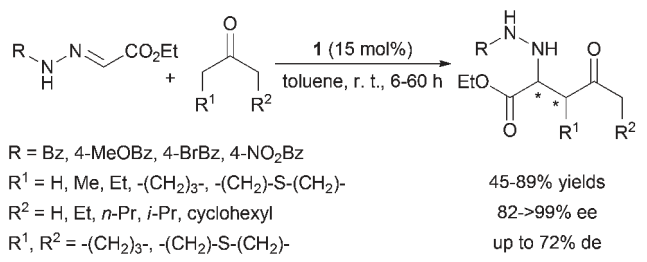
Fig. 19 Proposed transition state structure.

3-nitro-1,2-dihydroquinolines in up to 70% yield with up to 90% ee (Scheme 52, Fig. 19).[64] Synergistic activation of both reactants through stereoselective covalent activation and hydrogen-bonding interactions was proven by the ESI-MS method.

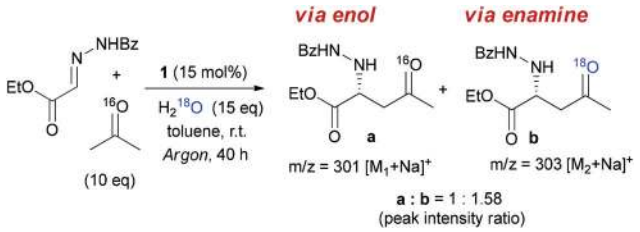
Mannich-type reaction

In 2008, Tsogoeva and co-workers demonstrated that bifunctional primary amine derived chiral thiourea **1** can successfully catalyze the asymmetric Mannich-type reaction of unmodified ketones with readily available and stable α-hydrazono esters.[65] The reaction does not require preformed enolate equivalents and provides the corresponding products in up to 89% yield and good to excellent enantioselectivities (82–>99% ee, Scheme 53).

Employing DFT calculations (in collaboration with the Computer Chemistry Center, FAU Erlangen) and ^{18}O-



Scheme 53



Scheme 54

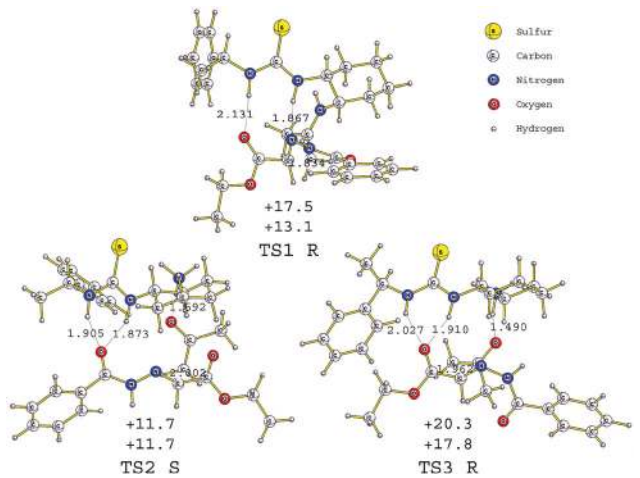


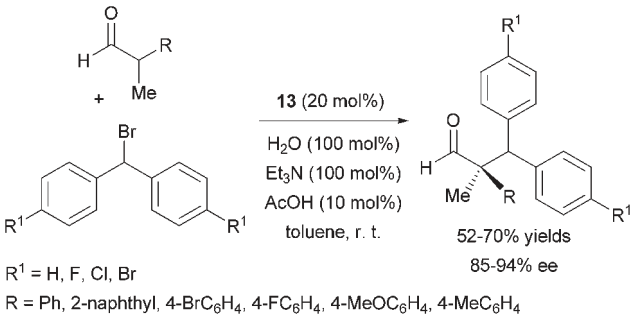
Fig. 20 Transition state structures located for the enamine (TS1, *R product*) and enol (TS2, *S product*; TS3, *R product*) mechanisms, respectively. Computed at the B3PW91/6-31G(d) (top number) and MP2/6-31G(d)//B3PW91/6-31G(d) (bottom number) levels of theory.

incorporation studies by ESI-MS methods, the first piece of evidence for involvement of both the enol and enamine mechanisms in the primary amine-thiourea catalyzed Mannich-type reaction of acetone with *N*-benzoylhydrazone was presented (Scheme 54).

Interestingly, while ESI-MS measurements indicated that both mechanistic pathways are active (with some predominance of the enamine mechanism), computational studies (Fig. 20) revealed a preference for the enol over enamine mechanism.

α-Alkylation of α-branched aldehydes

In 2010, Jacobsen and co-workers showed that primary amine-thiourea catalysts can efficiently catalyze enantioselective alkylation of α-arylpropionaldehydes with diarylbromomethane.[66] Thus, in the presence of catalyst **13** corresponding products were obtained in 52–70% yield with 85–94% ee (Scheme 55, Fig. 21). The reaction was considered to proceed *via* S_N1-like substitution mechanism induced by bromide anion binding to the thiourea and benzhydryl cation formation, which was supported by competition experiments and catalyst structure–activity studies.



Scheme 55

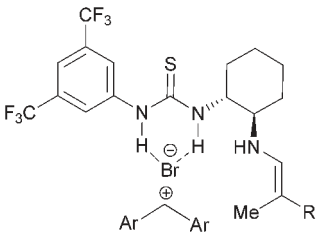
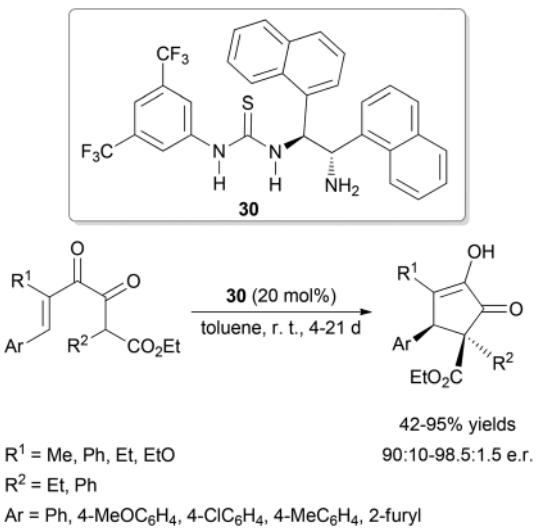


Fig. 21 Proposed electrophile activation mode.

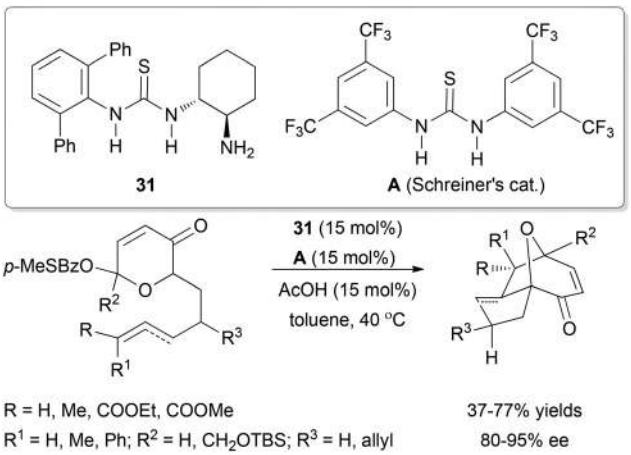


Scheme 56

Cyclizations and cycloadditions

An asymmetric Nazarov cyclization of diketoesters catalyzed by amine-thiourea catalysts was examined by Tius and co-workers in 2010.[67] The primary amine catalyst **30** was found to be the most effective, providing products in 42–95% yield and up to 98.5 : 1.5 e.r. (Scheme 56).

In 2011, a dual catalyst system consisting of a chiral primary amine-thiourea and an achiral thiourea was developed by Jacobsen and co-workers (Scheme 57, Fig. 22).[68] The system represents an example of cooperative catalysis for an



Scheme 57

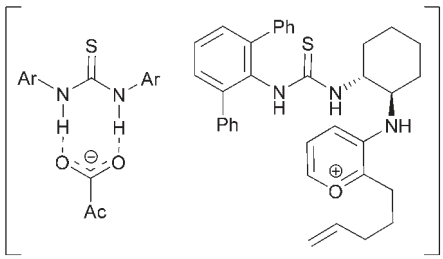


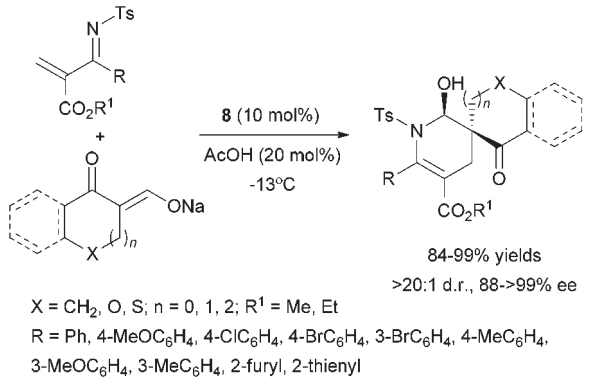
Fig. 22 Proposed mechanism of cooperative catalysis.

intramolecular [5 + 2] cycloaddition based on oxidopyrylium intermediates and provides a facile access to tricyclic structures in moderate yields (37–77%) and good to high enantioselectivities (80–95%). The role of **A** (Schreiner's catalyst) was supposed to be a carboxylate-binding agent, acting cooperatively with **31** to generate the reactive ion pair.

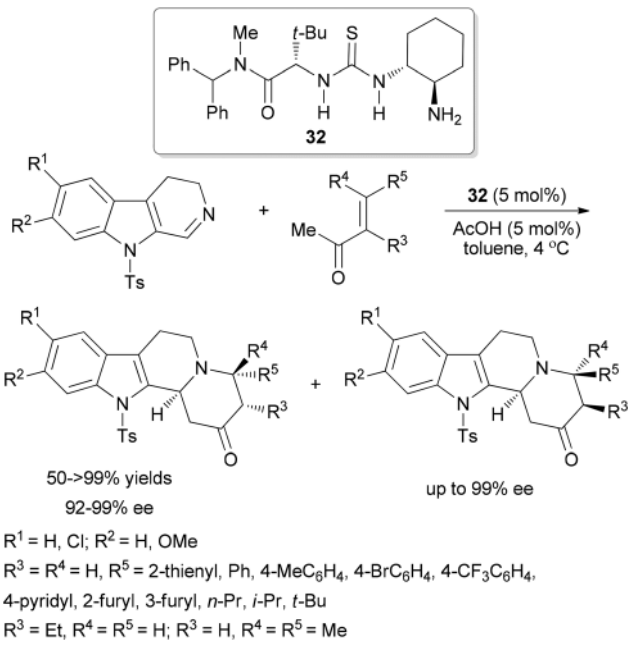
An efficient *in situ* generation/activation strategy for the first highly enantioselective inverse-electron-demand Diels–Alder reaction using catalyst **8** was reported by Wang and co-workers in 2012.[69] The transformation provides a method for the enantioselective construction of densely functionalized azaspirocyclic products in 84–99% yield, with 88–>99% ee (Scheme 58).

Recently, in the Jacobsen group, a highly enantio- and diastereoselective synthesis of indolo- and benzoquinolizidine derivatives has been developed through the formal aza-Diels–Alder reaction of enones with cyclic imines.[70] Good to excellent yields (50–>99%) and high ee values (92–99% ee) of adducts were observed with enones bearing β-aryl, heteroaryl and linear and/or branched alkyl substituents (Scheme 59). Interestingly, in the absence of a catalytic amount of AcOH, low turnover by the thiourea catalyst **32** was achieved, although the enantioselectivity remained high.

In 2013, Wang and co-workers described the first example of the organocatalytic asymmetric Michael/cyclization tandem reaction of 4-hydroxycoumarin with nitroalkenes.[71] Adducts of



Scheme 58

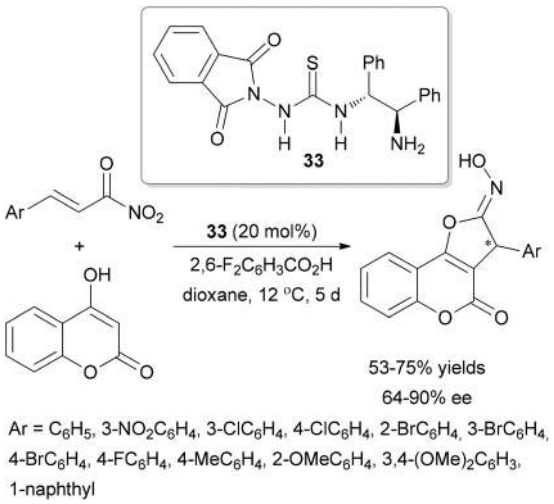


Scheme 59

2,3-dihydrofuro[3,2-*c*]-coumarin have been obtained in moderate yields (53–75%) and good enantioselectivities (64–90% ee) in the presence of 20 mol% chiral catalyst **33** (Scheme 60).

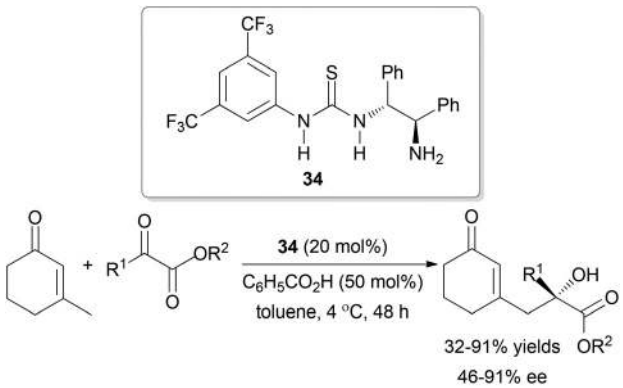
Asymmetric vinylogous aldol reaction

Recently, the enantioselective direct vinylogous aldol reaction of 3-methyl 2-cyclohexen-1-one with α-keto esters has been developed by Melchiorre (Scheme 61).[72] The key to the success of the transformation was dual activation of both substrates: H-bond-directing activation of a bifunctional primary amine-thiourea catalyst **34** and dienamine catalysis. This was corroborated by NMR studies and MS investigations. The products were obtained in good yields with 46–91% ee.



Ar = C_6H_5, 3-$NO_2C_6H_4$, 3-ClC_6H_4, 4-ClC_6H_4, 2-BrC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 2-$OMeC_6H_4$, 3,4-$(OMe)_2C_6H_3$, 1-naphthyl

Scheme 60

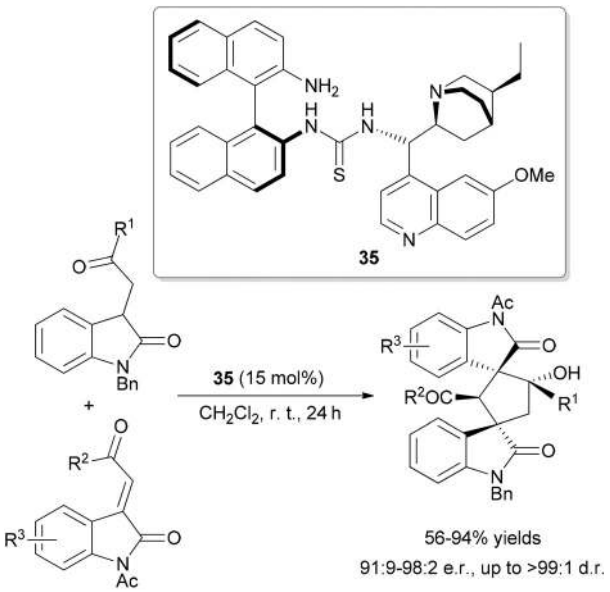


R^1 = 4-BrC_6H_4, 4-ClC_6H_4, 4-IC_6H_4, 4-FC_6H_4, 2-FC_6H_4, 2,4-F2C_6H_3, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-thienyl, Me, *c*-Hex, $CH_2CH_2CO_2Bn$
R^2 = Bn, Et, Anth

Scheme 61

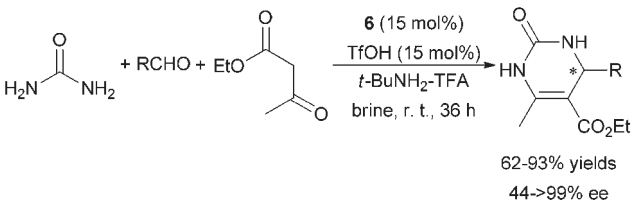
Domino Michael-aldol reaction

The first asymmetric catalytic domino process between 3-substituted oxindoles and methyleneindolinones in the presence of chiral primary amine-thiourea **35** was reported by Barbas III in 2011. The reaction proceeded with good stereocontrol to give bispirooxindole derivatives with three quaternary stereocenters in 56–94% yield (Scheme 62).[73]



R^1 = Ph, 4-FC_6H_4, 3-$MeOC_6H_4$, 2-furanyl, 2-thienyl, Me
R^2 = Ph, 4-ClC_6H_4, 2-MeC_6H_4; R^3 = H, 5-F, 5-Br

Scheme 62



R = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-FC_6H_4, 3-MeC_6H_4, 2-ClC_6H_4

Scheme 63

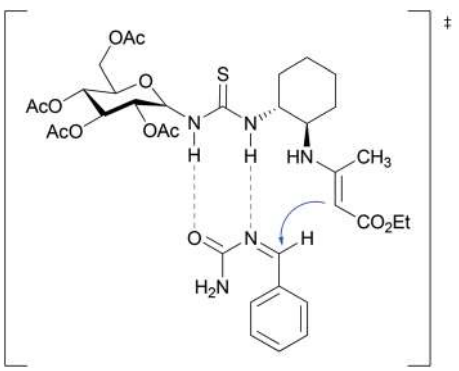


Fig. 23 Proposed transition state structure.

Multicomponent Biginelli reactions

In 2009, an enantioselective multicomponent Biginelli reaction catalyzed by a chiral bifunctional primary amine-thiourea **6** and a Brønsted acid as the combined catalyst with *tert*-butylammonium trifluoroacetate as additive was developed by Miao and Chen.[74] Chiral dihydropyrimidines were obtained in moderate to high yields with 15–99% ee. Later, the authors have demonstrated that the same reaction can be efficiently performed in aqueous media in the presence of **6** (15 mol%) and trifluoromethane sulfonic acid in 62–93% yield with 44–>99% ee (Scheme 63, Fig. 23).[75]

Conclusions and outlook

Considerable advances in the field of organocatalysis have been made in recent years by employing chiral primary amine-thiourea organocatalysts and asymmetric synthesis using these bifunctional compounds became arguably a facile tool in organic chemistry.

Since the introduction of the first primary amine-thioureas to organocatalysis in 2006, a remarkable number of new primary amine-thiourea frameworks have been developed (Fig. 2), able to effectively catalyze several important transformations: nitro-Michael reactions, 1,4-conjugate additions to enones and enals, domino aza-Michael–Henry reaction, Mannich-type reactions, α-alkylation of aldehydes, Nazarov cyclizations, intramolecular [5 + 2] cycloadditions, aza-Diels–Alder, vinylogous aldol and multicomponent Biginelli reactions.

Although much recent progress has been made with primary amine-thioureas, there is still large room for improvement in terms of catalyst loading and substrate scope in the reaction systems discussed in this review. Without question, the full potential and power of primary amine-thiourea catalysis has not been realized yet. Thus, further exciting discoveries of new primary amine-thiourea catalyzed transformations and further developments with this versatile type of bifunctional organocatalysis are to be expected in the near future with the advent of more systematic studies into the reaction mechanisms.

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