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Recognition and activation by ureas and thioureas: stereoselective reactions using ureas and thioureas as hydrogen-bonding donors†

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Hydrogen-bonding interaction plays a crucial role in the molecular recognition and activation processes of various biologically important reactions that are mediated by enzymes and antibodies in living organisms. Recently, it has been shown that a hydrogen-bonding donor can be used as a general acid catalyst for various types of reactions in organic chemistry. In this article, we describe enantioselective reactions catalyzed by urea and thiourea derivatives as general acid catalysts as well as diastereoselective reactions. This perspective provides an overview of this rapidly growing field.

1 Introduction

Over the past decade, it has been established that small organic molecules, called organocatalysts, can be used as efficient catalysts for various asymmetric reactions.[1] Such organocatalysts do not contain any metals, and are therefore advantageous from environmental as well as resource perspectives. These catalysts hold considerable promise as cheap, stable, moisture-insensitive, reproducible, and easy-to-construct alternatives to well-studied metal-based catalysts. From a mechanistic point of view, organocatalysts are sometimes regarded as artificial enzymes. Due to the recent progress in this research area, most enzymatic reactions can be reproduced/mimicked in terms of chemical yield and even stereoselectivity by using organocatalysts. Furthermore, due to the relatively weak interactions between organocatalyst and substrate, so-called "product inhibition" is generally not a problem in organocatalyst-mediated reactions. Among various interactions, hydrogen-bonding is a slightly old but powerful tool for activating Lewis basic substrates as general acid catalysts. Therefore, much effort has been directed toward the development of new Brønsted acid catalysts, which has led to the discovery of several types of hydrogen-bonding donors such as ureas/thioureas, diols, and phosphoric acids.[2,3]

Urea and thiourea derivatives have been intensively investigated in the area of molecular recognition due to their strong hydrogen-bonding activity.[4] They can be used to recognize carboxylic acids, sulfonic acids, nitrates, and others through multi-hydrogen bonding. Recently, several groups have reported that urea and thiourea not only recognized organic compounds but also activated them as an acid catalyst. The original concept was reported by Kelly *et al.* in the Diels–Alder reaction catalyzed by biphenylene diols (bis-hydrogen-bonded complex **A** in Fig. 1).[5] The subsequent discovery by Etter and co-workers that diaryl ureas possessing electron-withdrawing substituents readily form cocrystals with a variety of proton acceptors such as carbonyl compounds (Etter's urea **B**) inspired the impressive development of chiral urea catalysts.[6] Furthermore, a similar dual-hydration model (**C**) was proposed by Jorgensen to explain the accelerating effect of water on the Diels–Alder reaction and the Claisen rearrangement.[7]

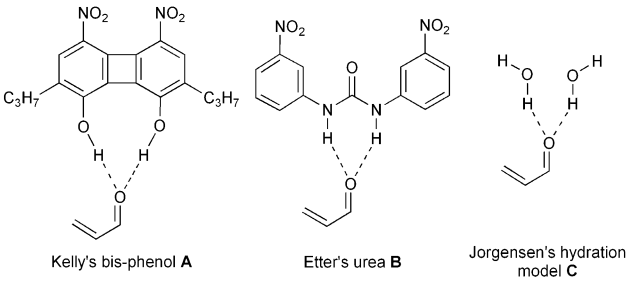

Fig. 1 Bis-hydrogen-bonding interaction.

Thus far, urea and thiourea derivatives have been successfully used for a variety of diastereo- and enantioselective reactions and the versatility of these urea derivatives as general acids has been demonstrated by several groups. However, the application of these catalysts to enantioselective reactions seems to be somewhat limited, since ureas are weaker acids than metallic Lewis acids. Therefore, quite recently, a bifunctional thiourea catalyst has been designed and prepared to overcome this problem,[8] and it has been shown that such a catalyst is effective for use in catalytic asymmetric reactions. Since this report, the dual-activation of bifunctional ureas has been shown to be useful and applicable to a variety of asymmetric reactions. In this

† This paper is dedicated to the memory of the late Professor Kiyoshi Tanaka.

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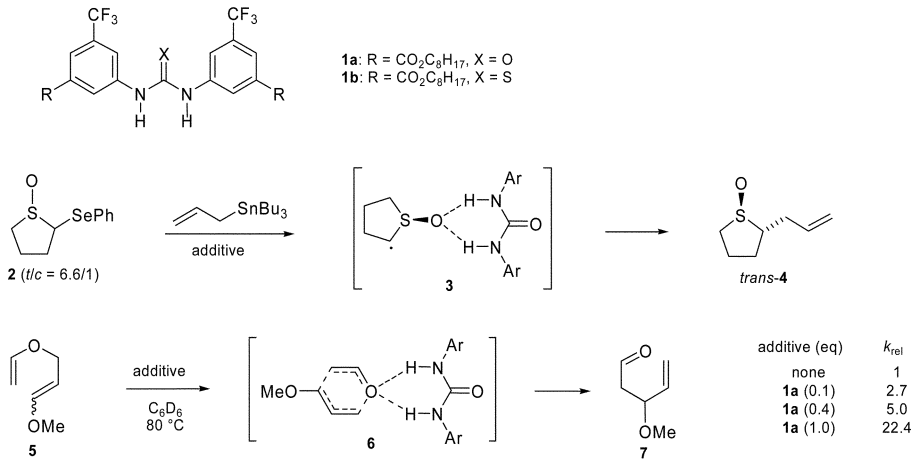


Scheme 1 Acceleration of allylation and Claisen rearrangement of **2** and **5** with diarylurea **1a**.

Table 1 Allylation of phenylseleno sulfoxide **2**

Entry	Solvent	Additive	**4** (t/c)	Yield (%)
1	Benzene	None	2.5/1	60
2	AcOH	None	6.7/1	51
3	CF_3CH_2OH	None	8.1/1	83
4	THF	$ZnBr_2$ (0.5 M)	8.0/1	60
5	Benzene	Urea **1a** (0.2 eq)	3.7/1	57
6	Benzene	Urea **1a** (1.0 eq)	7.0/1	81

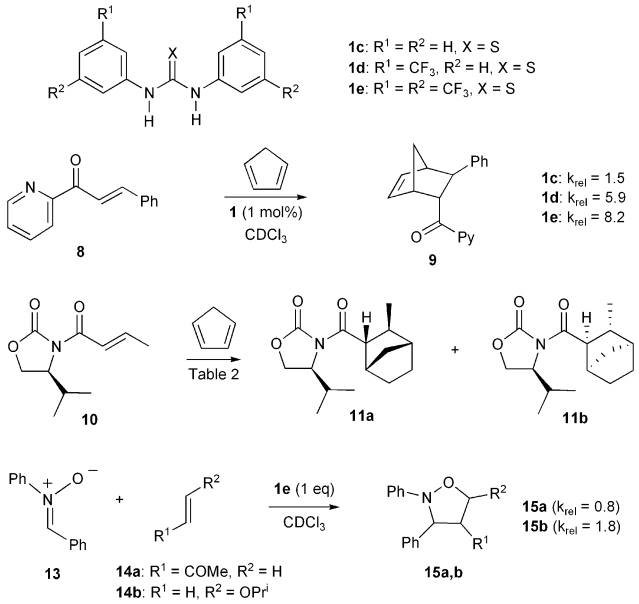
perspective, we attempt to offer a comprehensive overview of asymmetric reactions mediated by these urea/thiourea catalysts.

2 Diastereoselective reactions using urea and thiourea catalysts

Curran apparently was the first to use urea derivatives for general acid-promoted reactions. The new diarylurea **1a** was designed by combining the ideas and observations of Kelly, Etter, and Jorgensen. To facilitate the synthesis and to increase the solubility of the catalyst, a trifluoromethyl group and an octyl ester are introduced to the aromatic rings of **1a** (Scheme 1).[9]

The radical-mediated allylation reaction of α-(phenylseleno)-sulfoxide **2** with allyltributylstannane was examined to evaluate the ability of **1a** to diastereoselectivity.[9a] As shown in Table 1, an increase in the amount of urea **1a** increases both the *trans*/*cis* ratio and the combined yield of **4**. The addition of 1 equiv of **1a** enhanced the diastereoselectivity comparable to the best solvent and also improved the chemical yield (entry 6 *vs.* entries 1–4). The increase in the *trans*/*cis* ratio of the product **4** was explained by the intermediacy of complexed radical **3**, in which the coordination of the urea shields one face. Furthermore, complexed radical **3** may be more electrophilic than the free radical, and thus favorable polar effects were proposed to accelerate its rate of addition to allylstannane. Catalysts of types **1a–b** were also used for some Claisen rearrangements, in which they provided a one- to five-fold rate acceleration at 80–100 °C.[9b] A 22-fold increase in the rearrangement rate of **5** to **7** was observed when 1 equiv of **1a** was added. Although thiourea **1b** was also examined for this rearrangement, the rate acceleration was moderate (k_{rel}: 3–4). The bis-hydrogen bonded transition state model **6** was proposed as an explanation for the accelerating effects of urea **1a** on the Claisen rearrangement of **5**.

Based on Curran's studies, Schreiner and co-workers developed a remarkable array of thiourea catalysts for the Diels–Alder reaction between enone **8** and cyclopentadiene in terms of their solubility in a variety of solvents and simplified preparation. In addition, the thiocarbonyl group is a much weaker hydrogen-bond acceptor (Scheme 2).[10a] From experiments with thioureas **1c–e** they identified thiourea **1e**, which has two trifluoromethyl groups at the 3,5-positions of the aromatic



Scheme 2 Cycloaddition reactions with electron-deficient thioureas **1c–e**.

rings, as the most efficient catalyst. Thioureas such as **1d** and **1e**, bearing electron-withdrawing substituents at the meta- and para-positions, have a significant accelerating effect due to their rigid conformation (**D** in Fig. 2), which minimizes the entropic penalty upon complexation with carbonyl compounds. In addition, they studied the complexation between thiourea **1e** and *N*-acyloxazolidinone **10** by a combination of dynamic NMR, low-temperature IR, and high-level computational methods (DFT), and elucidated the structure of the complex **1e**·**10** like **12A** and **12B** (Fig. 3).[10b] These findings are further supported by the Diels–Alder reaction of **10** with cyclopentadiene (Table 2). Since the uncatalyzed reaction did not occur at room temperature, prolonged heating was required to obtain the cycloadducts **11a** and **11b** in a ratio of 36/64 (entry 1). In marked contrast, catalytic amounts of Lewis acids such as $AlCl_3$ accelerated the reaction enormously to give **11a** and **11b** in good yield with high diastereoselectivity (entry 2). Similarly, thioureas **1d** and **1e** catalyzed the reaction well enough so that it could be carried out

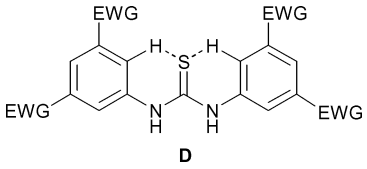


Fig. 2 Attractive S–H interaction of **1e**.

Table 2 Diels–Alder reactions between **10** and cyclopentadiene

Entry	Reaction conditions	% Yield (**11a** : **11b**)
1	Benzene, 130 °C	55 (36 : 64)
2	$AlCl_3$ (0.25 eq), $CHCl_3$, −78 °C	95 (92 : 8)
3	Urea **1d** (0.25 eq), $CHCl_3$, rt	74 (77 : 23)
4	Urea **1e** (0.25 eq), $CHCl_3$, rt	78 (81 : 19)

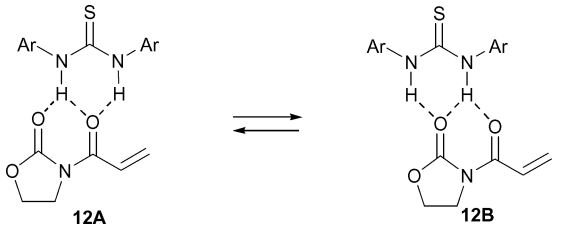
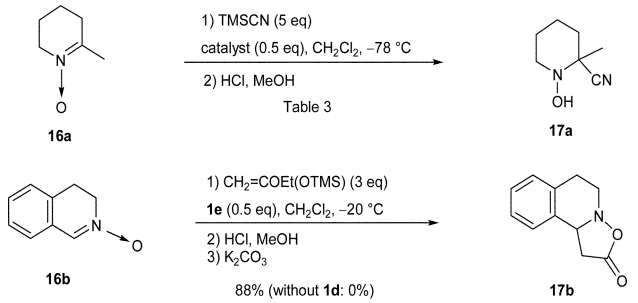


Fig. 3 Plausible hydrogen-bonding interaction between **1** and **10**.

at 23 °C with appreciable yields (entries 3 and 4). In the thiourea-catalyzed reactions, the de's are also enhanced and product **11a** was obtained as a major product as in entry 2. Since **11a** would be produced *via* the conformation **12A** and **12B**, these results are consistent with the above discussion. To verify the proposal that the interaction between the thiourea and the carbonyl groups causes the observed accelerations, 1,3-dipolar cycloadditions of *N*-benzylideneaniline *N*-oxide **13** with dipolarophiles such as methyl vinyl ketone **14a** and *iso*-propyl vinyl ether **14b** were investigated.[10a] While the addition of an equimolar amount of **1e** did not have an accelerating effect on the reaction with electron-deficient olefin **14a**, modest enhancement of the reaction rate was observed in the reaction with electron-rich olefin **14b**. These results support the proposition that the thiourea catalysts operate by hydrogen-bonding to the most Lewis-basic group and reduce the HOMO–LUMO gap in an analogous manner as Lewis acids.

Later, Schreiner's catalyst **1e** was used for the activation of nitrones, γ-crotonolactone, and methyl acrylate in nucleophilic addition reactions by three research groups.

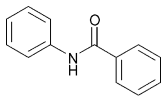
We found that thioureas promoted the addition of TMSCN and ketene silyl acetals to various nitrones **16** to give the corresponding hydroxyamines **17** in good yields (Scheme 3).[11] As in Schreiner's reports, a positive correlation was observed between the acidity of the N–H bond of amides, ureas and thioureas and their catalytic activities, and bidentate coordination of the thiourea to the nitrone was shown to be important for catalytic activation (Table 3). Among the catalysts examined, thiourea **1e** was the best catalyst for the nucleophilic addition of TMSCN and ketene silyl acetals. The postulated hydrogen-bonding interaction between nitrone **16** and **1e** is supported by ^1H and ^{13}C NMR experiments.



Scheme 3 Thiourea-catalyzed nucleophilic addition to nitrones **16**.

Nagasawa and co-workers investigated the urea-catalyzed hetero-Michael reaction of α,β-unsaturated carbonyls (Scheme 4).[12] The reaction of pyrrolidine with γ-crotonolactone **18** was carried out in the presence of ureas, thioureas, and guanidine as catalysts and the accelerating activities of the catalysts were determined by measuring $t_{1/2}$ (Table 4). As expected, the

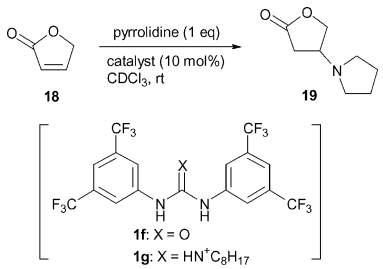
Table 3 Organocatalyst-mediated addition of TMSCN to nitrone **16a**



Entry	Organocatalyst	Time/min	Cy (%)
1	—	300	79
2	**E**	180	83
3	**1c**	45	81
4	**1d**	15	75
5	**1e**	15	81

Table 4 Organocatalyst-mediated hetero-Michael reaction of pyrrolidine to **18**

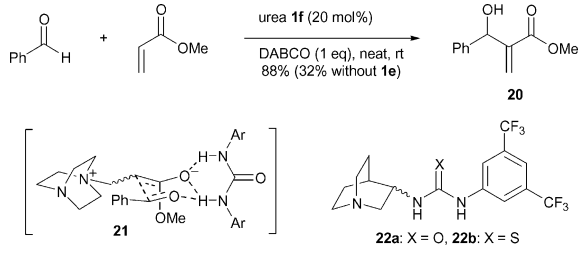
Entry	Catalyst	$t_{1/2}$ (min)	Rel. increase (k_{rel})
1	None	96	
2	**1c**	37	2.6
3	**1e**	<4	>24
4	**1f**	<4	>24
5	**1g**	14	6.9



Scheme 4 Hetero-Michael reaction of pyrrolidine to **18** with catalysts **1c** and **1e–g**.

reaction rates with catalyst **1e** were increased more than 24-fold over the uncatalyzed reaction. Thiourea **1e** was a more efficient catalyst for the hetero-Michael reaction than urea **1f** and guanidine **1g**. In addition, the authors stated that the catalytic activity of these urea compounds is correlated with their ability to alter the chemical shifts of protons adjacent to the lactone **18**.

The three-component Morita–Baylis–Hillman reaction is a promising carbon–carbon bond-forming process, since multifunctional products can be obtained from relatively simple starting materials. However, a significant drawback associated with these transformations are low reaction rates. Various types of catalysts have been used to accelerate the reaction by either activating the aldehyde component or stabilizing the nucleophilic betaine intermediate. In 2004, Connon and co-workers developed a dual-activation method for this reaction using two different electrophiles with urea **1f** (Scheme 5).[13] To examine the catalysts' abilities to promote Morita–Baylis–Hillman processes, the pseudo-first-order rate constants for the reaction between methyl acrylate (10 equiv) and benzaldehyde catalyzed by both DABCO (1 equiv) and catalysts were determined (Table 5). The



Scheme 5 DABCO-promoted Baylis–Hillman reaction catalyzed by ureas **1f** and **22a,b**.

Table 5 Baylis–Hillman reaction with H-bonding catalysts

Entry	Catalyst	$10^{-2}k_{obs}/h^{-1}$	k_{rel}
1	None	0.46	1
2	**1e** (20 mol%)	1.73	3.7
3	**1f** (20 mol%)	3.06	6.7
4	MeOH (40 mol%)	1.15	2.5
5	H_2O (40 mol%)	0.72	1.6

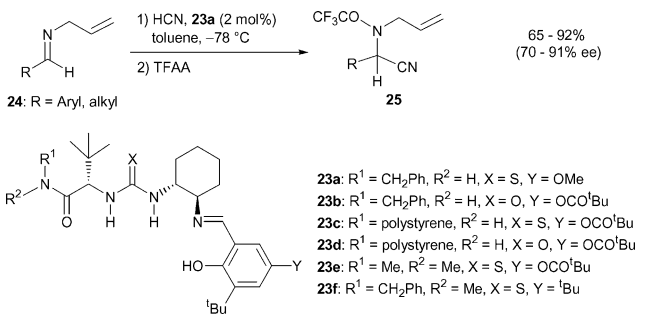
results revealed that though both ureas and thioureas accelerated the reaction relative to the uncatalyzed process, urea **1f** was superior to thiourea **1e** in terms of stability and efficiency. However, the urea-catalyzed reaction was completely suppressed in the presence of equimolar TBAA (tetrabutylammonium acetate), and the desired product **20** could not be obtained. The authors postulated that the catalysts operate mainly *via* binding of a Zimmerman–Traxler-type transition state **21** for addition of the resulting enolate anion to the aldehyde. In view of the compatibility of urea with DABCO, tertiary amino/aryl urea hybrid catalysts **22** were prepared and tested in the same reaction, but the performance of **22a** and **22b** was disappointing, and both gave inferior results compared to DABCO.

3 Enantioselective reactions using chiral urea and thiourea catalysts

3.1. Reactions of aldimines and ketoimines with Schiff-base catalysts (Jacobsen's catalyst)

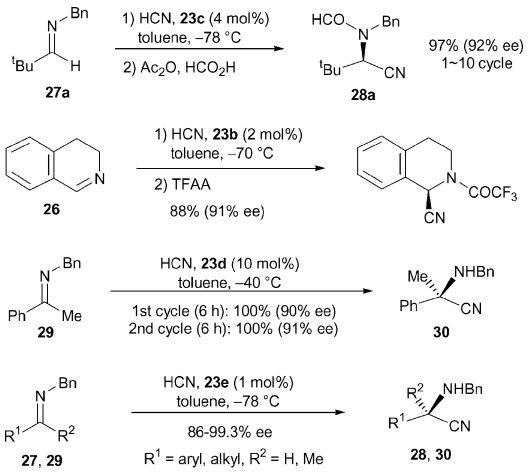
The most remarkable advances in the field of urea and thiourea catalysts were achieved by Jacobsen's group.[14–18] They focused on the activation of alkyl- or acyl-substituted imines and identified and optimized a series of urea- and thiourea-containing Schiff-base catalysts for various types of asymmetric reactions such as Strecker, Mannich, hydrophosphonylation, nitro-Mannich, and acyl Pictet–Spengler reactions.

In 1998, Jacobsen *et al.* first reported the asymmetric Strecker reaction of *N*-allyl aldimines **24** with Schiff-base urea catalyst **23a**, which was identified and optimized from a parallel synthetic library (Scheme 6).[14a] The three components (L-*tert*-leucine, (*R*,*R*)-1,2-diaminocyclohexane, and 3-*tert*-butyl-5-methoxysalicylaldehyde) of **23a** are crucial for good enantioselectivity (70–91% ee) in the product **25**.



Scheme 6 Asymmetric Strecker reaction of **24** with Schiff base catalysts **23**.

Later, the 5-pivaloyl-substituted Schiff base **23b** and resin-bound catalyst **23c** proved to be superior catalysts for the enantioselective Strecker reaction of *N*-allyl or *N*-benzyl aromatic and aliphatic imines **24** and **27** as well as cyclic imine **26** by further optimization (up to 97% ee) (Scheme 7).[14b] Catalyst **23c** was reused for up to 10 cycles with no loss of catalyst reactivity or product enantioselectivity in the Strecker reaction of *N*-benzyl imine **27** to **28**. They succeeded in the highly enantioselective addition of HCN to methylketoimines **29** for the first time using recyclable resin-bound urea catalyst **23d** as well as **23b** (up to 95% ee).[14c,d] Both spectral experiments and high-level calculations suggest that the *Z*-isomer of imines preferentially interacts



Scheme 7 Optimization of a highly enantioselective catalyst **23b–e** for Strecker reaction of aldimines **27** and ketoimines **29**.

with both urea hydrogens of the catalyst in a bridging mode (Fig. 4). Based on a consideration of this reaction mechanism, thiourea **23e** was identified as the most enantioselective Strecker catalyst (up to 99.3% ee).[14e]

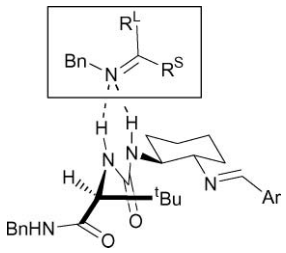
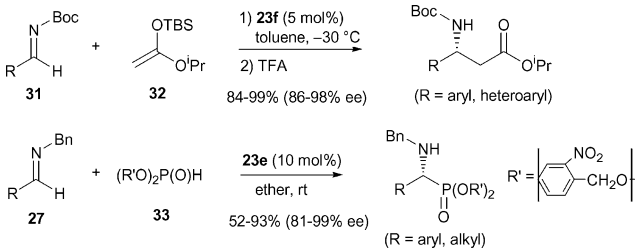


Fig. 4 The proposed mechanism of the Strecker reaction using **23b**.

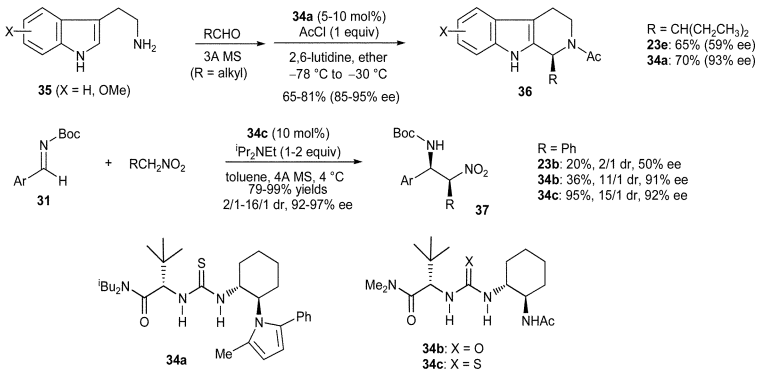
Subsequently, they succeeded in developing catalytic Mannich and hydrophosphonylation reactions of *N*-Boc imines **31** and *N*-benzyl imines **27** by tuning the Schiff base catalysts (**23f** and **23e**) and nucleophiles (silyl ketene acetal **32** and phosphite **33**), respectively (Scheme 8).[15,16]



Scheme 8 Thiourea-catalyzed enantioselective Mannich reaction and hydrophosphonylation.

Recently, they discovered that urea- and thiourea-catalysts **34** without a Schiff-base moiety promoted the acyl-Pictet–Spengler reaction with high enantioselectivity (Scheme 9).[17] After initial failure in the direct Pictet–Spengler reaction of imines, *N*-acyliminium ions were revealed to be suitable substrates for the urea-catalyzed cyclization. The enantioselectivity of the reaction strongly depended on the structure of the catalysts, as well as the acylating agent and reaction solvent. The reaction of tryptamine **35** and an appropriate aldehyde in the presence of acetyl chloride and **34a** occurred smoothly to provide the cyclized product **36** with high enantioselectivity (85–93% ee), while the same treatment of **35** [R = $CH(CH_2CH_3)_2$] in the presence of Schiff-base catalyst **23e** gave **36** in only 59% ee.

Similarly, in the Henry (nitro-Mannich) reaction of *N*-Boc imines **31** with nitroalkanes, the simple acetamide thiourea **34c**



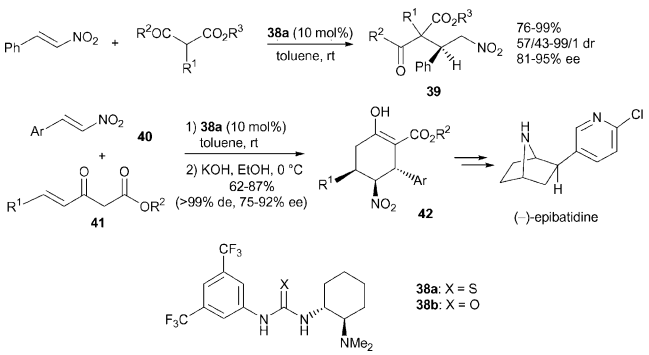
Scheme 9 Highly enantioselective catalytic acyl-Pictet–Spengler reaction and nitro-Mannich reaction.

was demonstrated to be an excellent catalyst, and gave the *syn* adducts **37** with high enantio- and diastereoselectivity (up to 97% ee and 16/1 dr) in the presence of Hünig's base (Scheme 9).[18] In this study, they found that the addition of powdered 4 Å molecular sieves improved the reproducibility of the process and provided higher diastereoselectivity in the products.

3.2. Reactions with bifunctional urea and thiourea catalysts

Although Jacobsen's group has shown that some urea and thiourea derivatives connected to suitable amino acids catalyze several types of asymmetric reactions with excellent enantioselectivity,[14–18] the substrates used in their reactions are somewhat restricted to aldimines and ketoimines. This limitation was overcome by the development of bifunctional urea and thiourea catalysts **38**, **43**, **46**, and **61**. With the use of these catalysts, Michael reactions of various electron-deficient alkenes bearing nitro, ketone, and carboxylic acid derivatives proceeded smoothly to give the addition products in good yield with excellent enantioselectivity.

While the nitro group is well known to interact with urea and thiourea through hydrogen bonding,[4] there have been no reports concerning the urea-catalyzed reaction of nitro compounds. In 2003, we first discovered that bifunctional thiourea **38a**, bearing a tertiary amine, promoted the Michael addition of diethyl malonate with β-nitrostyrene to give the addition product **39** with up to 93% ee (Scheme 10).[8,19a] Since both a thiourea moiety and a dimethylamino group are essential for rate acceleration and high enantioselectivity, the bifunctional catalyst **38a** can be considered to activate both nitroolefins and nucleophiles simultaneously and to control the approach of these substrates stereoselectively (Fig. 5). Indeed, the X-ray crystallography of **38a** indicates that amino groups and thiourea N–H orient towards the same direction (Fig. 6). Therefore, nucleophiles can approach nitroolefins in an ideal way, when both thiourea and amino group interact with nitroolefin and nucleophile, respectively. This hypothesis agrees with the experimental result in Scheme 10, and it encouraged us to employ the catalyst **38a** in



Scheme 10 Bifunctional thiourea-catalyzed Michael addition of 1,3-dicarbonyl compounds **41** to nitroolefins.

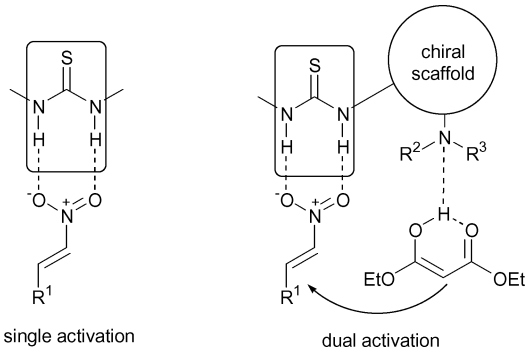


Fig. 5 Dual activation concept using bifunctional thiourea.

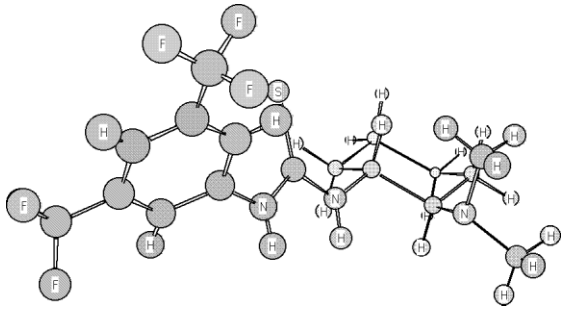
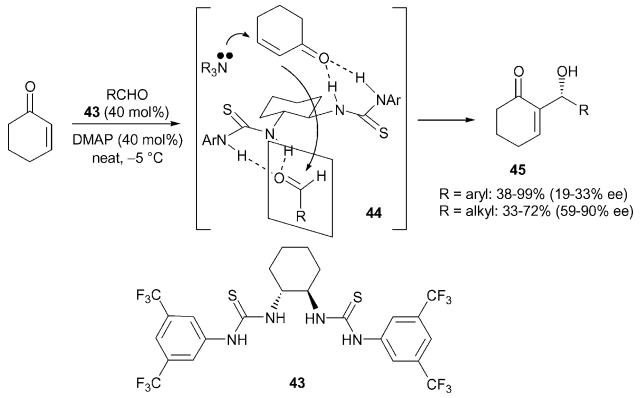


Fig. 6 X-Ray crystal structure of bifunctional thiourea **38a**.

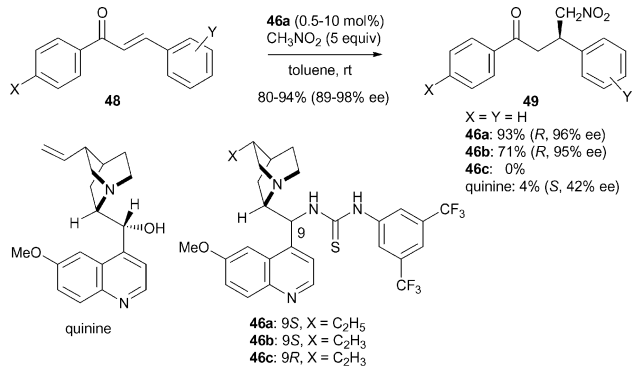
Michael reactions of various 1,3-dicarbonyl compounds. When the same reaction was carried out with prochiral 1,3-dicarbonyl compounds, moderate to good diastereoselectivities (57/43–99/1) were observed together with high enantioselectivities (81–95% ee). Furthermore, we succeeded in the stereoselective preparation of chiral cyclohexanes **42** by applying the above protocol to the double Michael reaction of γ,δ-unsaturated β-ketoester **41** with nitroolefin **40**.[19b] The three contiguous stereogenic centers of **42** were constructed with excellent diastereoselectivity and good enantioselectivity. The asymmetric synthesis of (−)-epibatidine was accomplished from one of the intermediates **42** in seven steps in 30% overall yield.

Nagasawa's group developed the bis-thiourea-catalyzed asymmetric Baylis–Hillman reaction of cyclohexenone with aldehydes (Scheme 11).[20] They found that the bis-thiourea catalyst **43** promoted the reaction of cyclohexenone with benzaldehyde in the presence of an additive (0.4 equiv) such as DMAP and imidazole to afford the allylic alcohol **45** (DMAP: −5 °C, 88%, 33% ee; imidazole: rt, 40%, 57% ee). Higher enantioselecitivities were obtained in the reaction with aliphatic aldehydes (up to 90% ee). Transition state **44**, in which both the aldehyde and the enone coordinate to the thiourea groups of **43** through hydrogen-bonding interactions, is proposed to explain the stereochemistry of the product.



Scheme 11 Asymmetric Baylis–Hillman reaction of cyclohexenone with bis-thiourea **43**.

Later, the enantioselective Michael addition of nitromethane to acyclic enones using bifunctional cinchona alkaloid-based thioureas was described by Soós' group (Scheme 12).[21] They designed the new bifunctional catalysts **46a–c** to enhance the Lewis acidity of the original cinchona alkaloids such as quinine by replacing the hydroxy group with a thiourea moiety. Interestingly, catalysts **46a–b** with an unnatural C-9 configuration showed high activity in this process compared with quinine and thiourea **46c** with a natural C-9 configuration. These results indicate that the introduction of a more acidic thiourea moiety to quinine is necessary to obtain efficient catalytic activity and **46a** is the best catalyst in terms of chemical yield and enantioselectivity. With catalyst **46a** (10 mol%), chalcones **48** bearing electron-withdrawing or electron-donating substituents underwent clean reactions to afford the corresponding adducts **49** with high enantioselectivities (89–98% ee).

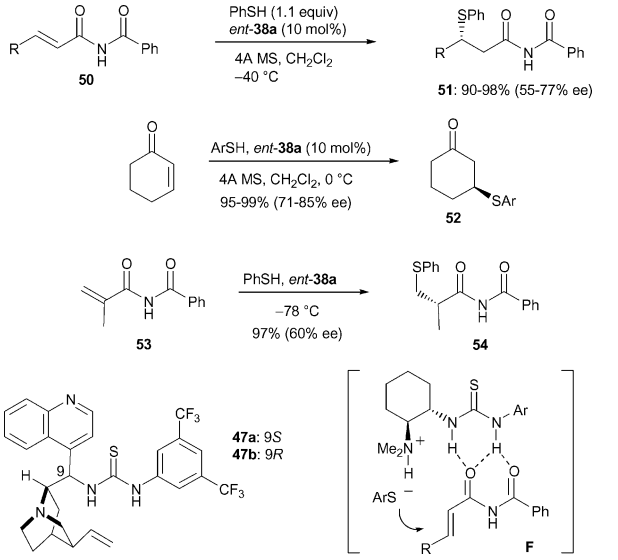


Scheme 12 Michael addition of nitromethane to chalcones **48** with bifunctional chinchona organocatalyst **46**.

To date, the asymmetric Michael addition to α,β-unsaturated carboxylic acid derivatives has been reported by two research groups using the same bifunctional thiourea catalyst **38a**.

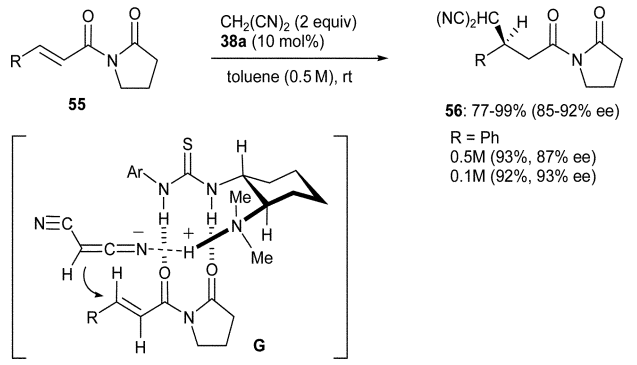
Wu *et al.* examined the catalytic activities of various thioureas in the asymmetric Michael addition of phenylthiol to α,β-unsaturated imide **50**, and found that the thiourea catalysts **47a,b** derived from cinchonine and cinchonidine were not effective for the reaction independent of the C-9 configuration, and the best result (95%, 77% ee) was obtained when the reaction (**50**: R = *n*-Pr) was conducted with 10 mol% *ent*-**38a** (antipode of **38a**) in CH_2Cl_2 at −40 °C (Scheme 13).[22] This protocol can be applied to cyclic enones. For example, the same thiourea-catalyzed reaction of 2-cyclohexenone and phenylthiol at 0 °C gave the product **52** in 97% yield with 85% ee. Furthermore, they investigated the asymmetric protonation of α-prochiral imide **53** with phenylthiol and *ent*-**38a**, which gave the addition product **54** with an *S*-configuration with 60% ee.

During studies to expand the synthetic utility of **38a** in the asymmetric reaction, we also discovered that α,β-unsaturated



Scheme 13 Asymmetric Michael addition of arylthiols to imides **50** with *ent*-**38**.

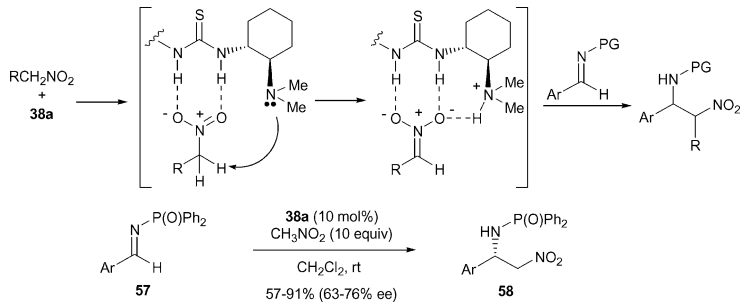
imides **55** were suitable Michael acceptors for the thiourea-catalyzed conjugate addition of malononitrile (Scheme 14).[23] Indeed, the reaction of *N*-acylpyrrolidinones **55** with malononitrile (2 equiv) and **38a** (10 mol%) in toluene at room temperature provided the Michael adducts **56** in good yields (77–99%). The enantioselectivities were almost independent of the β-substituents in terms of steric hindrance and electronic properties (84–92% ee). In contrast, the concentration of the reaction mixture somewhat affects the stereoselectivities. When the reactions were carried out in a 0.1 M solution, the corresponding products were obtained with higher enantioselectivities (> 93% ee). The reaction mechanism of both reactions is not clear at this stage, but different transition state models have been proposed by the two research groups (**F** in Scheme 13 and **G** in Scheme 14).



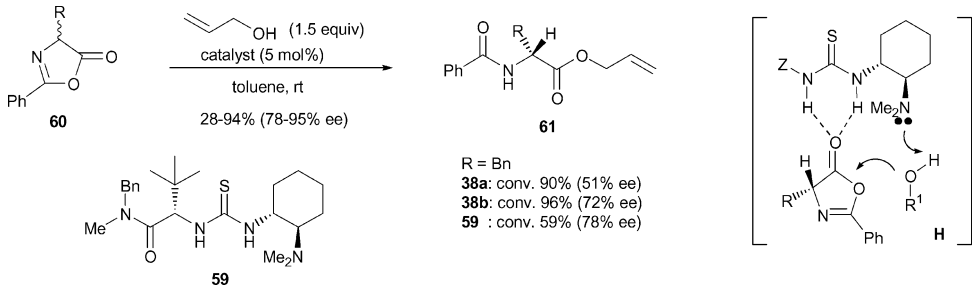
Scheme 14 Asymmetric Michael addition of $CH_2(CN)_2$ to imides **55** with **38a**.

Recent studies have revealed that bifunctional thiourea catalysts could be used in the 1,2-addition reactions of several nucleophiles to imines and ketones as well as Michael addition reactions.

Since Jacobsen's group previously reported that Schiff-base urea catalysts efficiently activated *N*-Boc imines, we explored the nitro-Mannich reaction of several imines with nitromethane in the presence of the bifunctional catalyst **38a**(Scheme 15).[24] In this reaction, we expected that the corresponding nitronate anion could be effectively produced from nitroalkane by thiourea **38a** *via* hydrogen-bonding activation through the thiourea moiety and subsequent intra- or intermolecular deprotonation by the dimethylamino group. Consequently, the reaction of the nitronate with the activated imine proceeds enantioselectively to give the optically active β-nitroamine. In practice, the thiourea-catalyzed nitro-Mannich reaction of *N*-phosphinoylimine **57**



Scheme 15 Enantioselective aza-Henry reaction of **57** catalyzed by bifunctional thiourea **38a**.

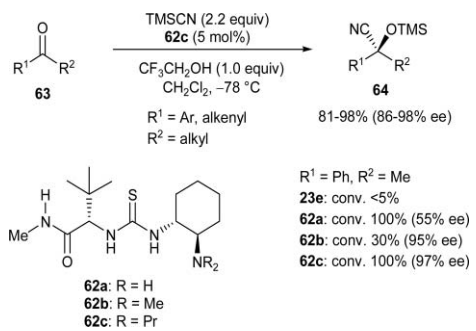


Scheme 16 Enantioselective dynamic kinetic resolution of azlactones **60** with bifunctional thiourea **59**.

with nitromethane in dichloromethane at room temperature resulted in the corresponding β-nitroamines **58** in good yields, but the enantioselectivities were moderate to good (63–76% ee). After our report, a more enantioselective nitro-Mannich reaction has been reported by Jacobsen's group, as described above.[18]

With the aim of establishing a method for the synthesis of chiral *N*-acyl amino acid esters **61**, Berkessel's group studies the dynamic kinetic resolution of azlactones **60** using bifunctional urea-catalyzed alcoholysis (Scheme 16).[25] Among the many bifunctional ureas and thioureas examined, they identified **38a,b** as a first-generation catalyst and allyl alcohol was selected as an optimal nucleophile.[25a] In further studies, they noted that the electron-deficient arylamino group of the catalyst could be replaced by a *tert*-leucine amide, and discovered the best catalyst **59** as a second-generation catalyst.[25b] The reaction of azlactones **60** with allyl alcohol at room temperature in the presence of 5 mol% catalyst **59** furnished the *N*-benzoylamino acid allyl esters **61** with up to 95% ee. The same treatment of **60** with mono- and bis-ureas without the amine functionality as well as (−)-quinine and dimeric cinchona alkaloids such as $(DHQD)_2PHAL$ and $(DHQD)_2AQN$ resulted in recovery of the starting material or low enantioselectivity. Based on NMR experiments, which support the formation of a substrate-catalyst complex, the plausible transition state model **H** is proposed.

The catalytic asymmetric cyanation of carbonyl compounds is among the most important and well-studied reactions in asymmetric catalysis. Quite recently, Jacobsen also reported the application of bifunctional thiourea catalysts to the catalytic cyanosilylation of ketones **63** into cyanohydrins **64** (Scheme 17).[26]



Scheme 17 Bifunctional thiourea-catalyzed enantioselective cyanosilylation of ketones **63**.

Thiourea **62c**, bearing propyl groups as amine substituents, proved to be an excellent catalyst for the highly enantioselective reaction (up to 97% ee) of a wide range of ketones **63** such as alkyl aryl ketones and α,β-unsaturated ketones. In this reaction, the addition of 1.0 equivalent of 2,2,2-trifluoroethanol is crucial for catalytic activity and high enantioselectivity. The electronic, rather than steric, differentiation of the two ketone substituents is speculated to be the source of asymmetric induction.

Conclusion

Recent developments in the area of urea- and thiourea-catalyzed stereoselective reactions have been summarized. The development of organocatalysts that bind to and activate a substrate through two hydrogen bonds offers attractive alternatives to metal-catalyzed reactions. Since the first report of urea–Lewis base complexes in early 1990 by Etter's group, not only have various types of organic reactions catalyzed by urea and thiourea derivatives been reported, but also novel multi-functional ureas and thioureas have been designed and synthesized. Of particular significance are the enantioselective reactions catalyzed by the Schiff-base ureas and bifunctional thioureas. From the standpoint of sustainable chemistry, these organocatalyst-mediated reactions seem to be desirable tools for preparing organic compounds and therefore the further development of more multi-functional organocatalysts should be increasingly important. For example, few urea-catalyzed asymmetric reactions of aldehydes and ketones have been developed. For this purpose, a new design concept is required. However, since the detailed mechanisms of these reactions are often not available, the rational design of multi-functional organocatalysts utilizing hydrogen bonds and hydrophobic interactions may be very difficult at this stage without basic knowledge on how to control reactivity and selectivity. Therefore, computational techniques may help to facilitate the discovery of novel catalyst structures. Furthermore, the development of new methodologies for multi-component and tandem reactions and of a system for recycling organocatalysts such as immobilization on a solid support as well as improvements in activity and selectivity through the design of multi-functional catalysts should have great practical potential in these organocatalyst-mediated reactions. Finally, I hope that many more exciting and practical advances will be forthcoming in this important area.

Acknowledgements

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