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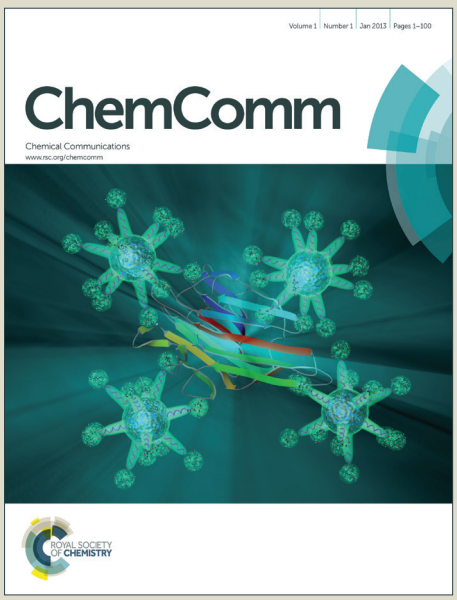

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FEATURE ARTICLE

Recent advances in asymmetric organocatalysis mediated by bifunctional amine-thioureas bearing multiple hydrogen-bonding donors

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Organocatalysis has proven to be one of the most rapidly developing and competitive research areas in asymmetric catalysis since 2000, and has become a third branch besides biocatalysis and transition metal catalysis. In this feature article, recent progresses from our research group on asymmetric organocatalysis, focusing on fine-tunable amine-thiourea catalysis, are described. Design of novel bifunctional amine-thiourea organocatalysts based upon the synergistic activation strategy via multiple hydrogen bonds and their applications in asymmetric C–C, C–N, and C–S bond-forming reactions under mild conditions are discussed in detail. The most attractive feature of the newly designed fine-tunable amine–thiourea catalysts is the incorporation of multiple hydrogen bonding donors and stereogenic centers.

Introduction

Asymmetric organocatalysis has experienced tremendous advances over the past decade.[1] Numerous stereoselective transformations, including new processes as well as fascinating domino sequences appropriate for the synthesis of natural products[2] and industrial applications,[3] have been developed. There are various activation strategies including non-covalent catalysis via hydrogen-bonding,[4] phase transfer,[5] Brønsted acid,[6] Brønsted base[7] and covalent catalysis via Lewis base.[8] Among commonly used chiral organic molecules, amine-thioureas have been intensively investigated for promoting carbon–carbon and carbon–heteroatom bond formation via hydrogen-bonding interactions between substrates and catalysts.[9]

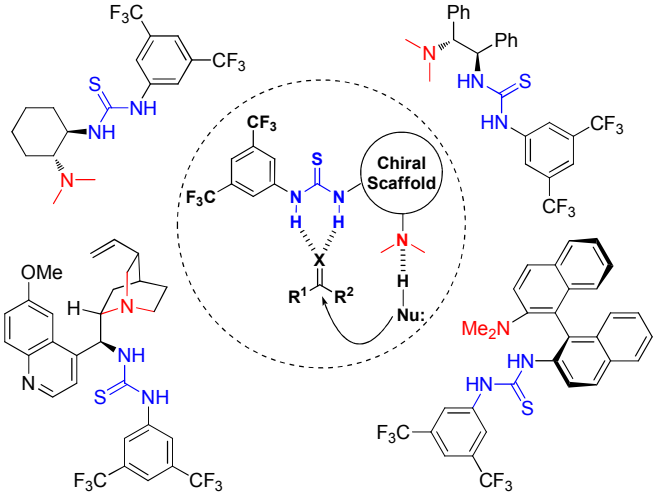


Figure 1. Reported representative bifunctional amine-thiourea catalysts and the dual activation model.

As an organic molecule with hydrogen-bond donor capability, thiourea-based organocatalyst evolved as an efficient class due to its unique characteristic of dual hydrogen-bonding donor. A number of research groups have proven that catalysts with bifunctional moieties could promote asymmetric transformations more efficiently.[10] The concept of "bifunctionality" was realized when a Lewis basic functional group was introduced into the catalyst along with hydrogen-bond donors (Figure 1), which work synergistically to achieve the activation of both nucleophile and electrophile in a catalytic asymmetric reaction.

Regarding the significance of the double hydrogen-bonding interactions between thiourea motif and substrate in amine-thiourea catalyzed enantioselective transformations,[10] we envisaged that amine-thiourea catalysts bearing multiple hydrogen-bonding donors could facilitate the formation of additional hydrogen bonds,[11] and thus remarkably improve their catalytic activity (Figure 2). To our knowledge, the strategy of multiple hydrogen-bonding synergistic activation was utilized in the design and preparation of chiral amine-thiourea organocatalysts for the first time.

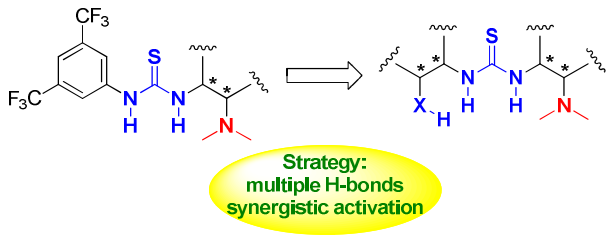
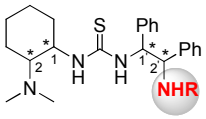
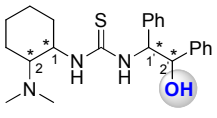


Figure 2. Design of novel bifunctional amine-thiourea catalysts bearing multiple hydrogen-bonding donors.

The attractive features of the newly designed fine-tunable amine-thiourea catalysts include: 1) multiple hydrogen-bonding donors and up to four stereogenic centers, 2) enhanced adjustability of the electronic effect and steric effect, and 3) commercial availability of enantioenriched diamines and amino alcohols. The bifunctional amine-thiourea catalysts **I** and **II** (Figure 3) showed excellent performances in the catalytic asymmetric Michael addition, nitro-Mannich reaction, amination reaction, and sulfa-Michael addition, resulting in high stereoselectivity with broad substrate scope. In this article, we wish to review our research efforts on the design and development of these bifunctional amine-thiourea organocatalysts and their applications in organocatalytic asymmetric C–C, C–N, and C–S bond-forming reactions.



(1*R*,2*R*,1'*S*,2'*S*)-**I-A:** R = Ts
(1*R*,2*R*,1'*R*,2'*R*)-**I-B:** R = Ts
(1*R*,2*R*,1'*R*,2'*R*)-**I-C:** R = Ms
(1*R*,2*R*,1'*R*,2'*R*)-**I-D:** R = 3,5-$(CF_3)_2C_6H_3SO_2$



(1*R*,2*R*,1'*S*,2'*S*)-**II-A**
(1*R*,2*R*,1'*R*,2'*R*)-**II-B**
(1*R*,2*R*,1'*S*,2'*R*)-**II-C**
(1*R*,2*R*,1'*R*,2'*S*)-**II-D**

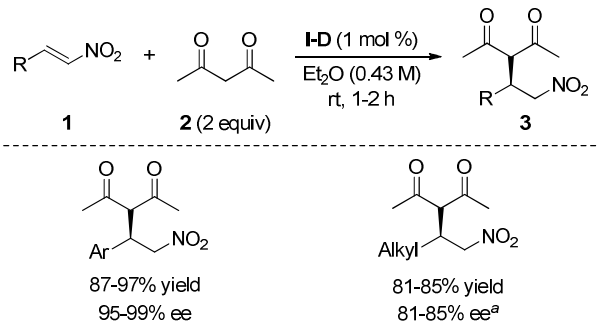
Figure 3. Novel bifunctional amine-thiourea organocatalysts bearing multiple hydrogen-bonding donors.

Michael addition

Michael addition is an important synthetic tool and represents one of the most powerful and efficient methods for the generation of carbon–carbon bonds in synthetic chemistry.[12] In particular, a great deal of effort has been devoted to developing organocatalytic asymmetric Michael additions of carbonyl compounds with nitroalkenes.[13]

As a model reaction to evaluate the catalytic efficiency of the novel bifunctional amine-thiourea organocatalysts bearing multiple hydrogen-bonding donors, we selected Michael addition of acetylacetone **2** to nitroolefin **1a** (Scheme 1). In the presence of 10 mol % of Takemoto's catalyst,[10f,g] the reaction was finished in about 1 h, giving the anticipated adduct in 80% yield with 89% ee. To our delight, in the following assessment of the newly designed catalysts, high catalytic reactivity was achieved (less than 0.5 h reaction time). While catalyst **I-A** promoted the model reaction in 97% yield with only 76% ee, its isomer **I-B** led to a superior enantioselectivity of 93% ee. This reveals that the (*R*,*R*)-cyclohexanediamine moiety matched the (*R*,*R*)-1,2-diphenylethenediamine moiety, and the configuration of the adduct was controlled mainly by the former, while the enantioselectivity could be significantly improved by the latter. Replacement of the Ts group in **I-B** with a less bulky Ms group led to diminished enantioselectivity probably due to the less steric demanding of catalyst **I-C**. The best enantioselectivity of 97% ee was obtained with **I-D** as the catalyst, which is likely ascribed to the additional strong hydrogen-bonding donor from $NHSO_2Ar$ bearing two electron-withdrawing CF_3 groups on the phenyl ring.[14] Further optimization revealed that the catalyst loading could be reduced to as low as 1 mol % without loss of enantioselectivity or reaction efficiency.

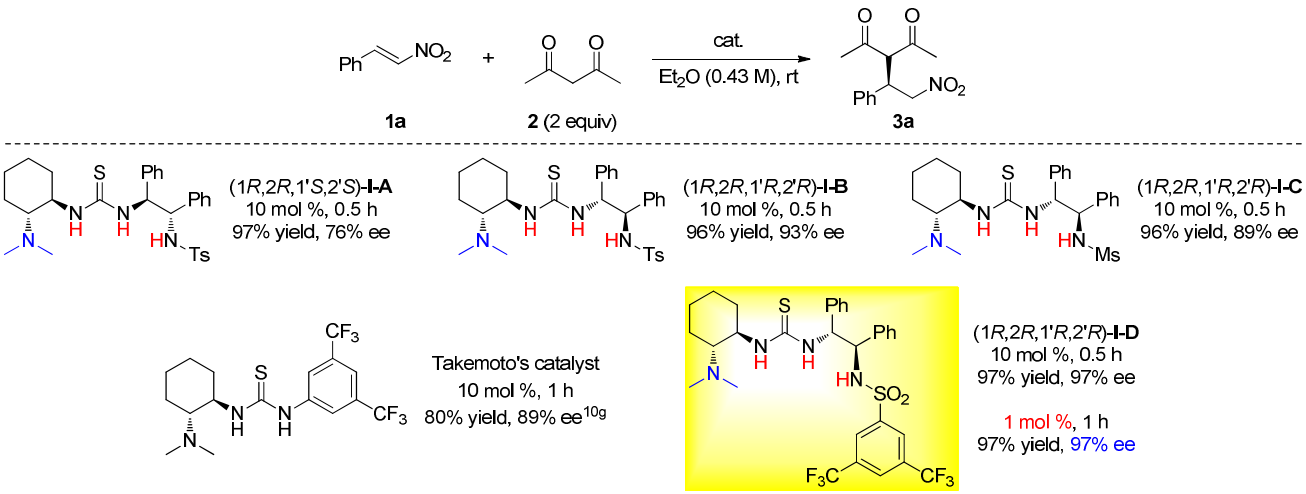
The substrate scope of the **I-D**-catalyzed Michael addition of acetylacetone **2** to nitroolefins **1** are summarized in Scheme 2.[14] Not only aromatic nitroolefins but also less reactive aliphatic nitroolefins were well tolerated, affording the expected adducts in good yield with high enantioselectivity (up to 99% ee).



[a] 5 mol % catalyst was used and the reactions completed in 16-28 h.

Scheme 2 Asymmetric Michael addition of acetylacetone **2** to nitroolefins **1** catalyzed by organocatalyst **I-D**.

Other diketones were also examined in this asymmetric Michael addition with **I-D** as the catalyst. As exemplified in Scheme 3, 1,3-diphenylpropane-1,3-dione **4** was first employed as a Michael donor affording the adduct **5** in 95% yield with 85% ee. 2-Acetylcyclopentanone **6** was also tolerated in this catalytic system.



Scheme 1 Catalytic asymmetric Michael addition of acetylacetone **2** to nitroolefin **1a** catalyzed by bifunctional amine-thiourea catalysts.

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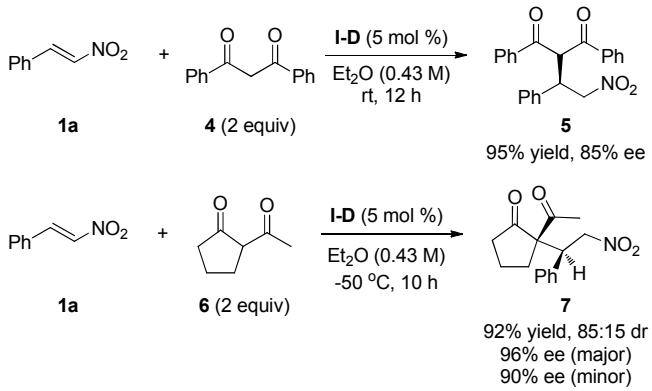
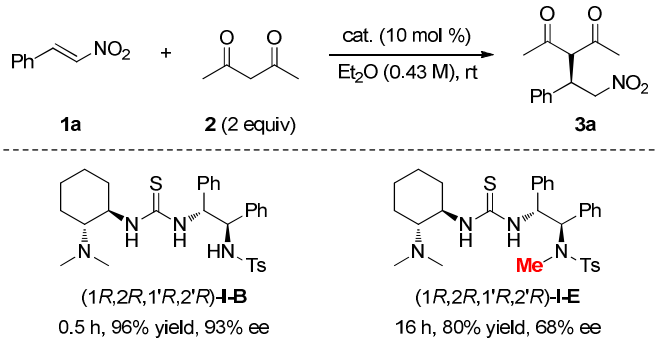


Scheme 3 Asymmetric Michael addition of other diketones to nitroolefin **1a** catalyzed by **I-D**.

To further validate the role of the multiple hydrogen-bonding donors played in this catalytic system, we carried out a control experiment with 10 mol % of methylated **I-E** as the catalyst (Scheme 4). The model Michael addition became extremely sluggish and the adduct was produced in 80% yield with 68% ee even after 16 h, which reveals that the third hydrogen-bonding donor, NH of sulfonamide, plays a crucial role in promoting this Michael addition reaction, in terms of both enantioselectivity and reactivity.



Scheme 4 Results for the asymmetric Michael addition of acetylacetone **2** to nitroolefin **1a** catalyzed by **I-B** and **I-E**.

Considering the structural similarity between 1,3-diketone and β-ketoester, we next tried to extend the application of our catalytic system to the Michael addition of α-substituted β-ketoester **8a** to nitroolefin **1a**, aiming at constructing two contiguous tertiary and quaternary stereogenic centers. However, the product **9a** was formed with very low diastereoselective control (nearly 1:1 dr) and only moderate to good enantioselective control (Scheme 5, left side).[15] On the basis of these experimental results and the reported transition state model for the Michael addition of β-ketoesters to nitroolefins,[10g] we envisaged that replacing the bulky sulfonamide $NHSO_2Ar$ group with a less bulky OH group in the homologous amine-thioureas would promote the formation of

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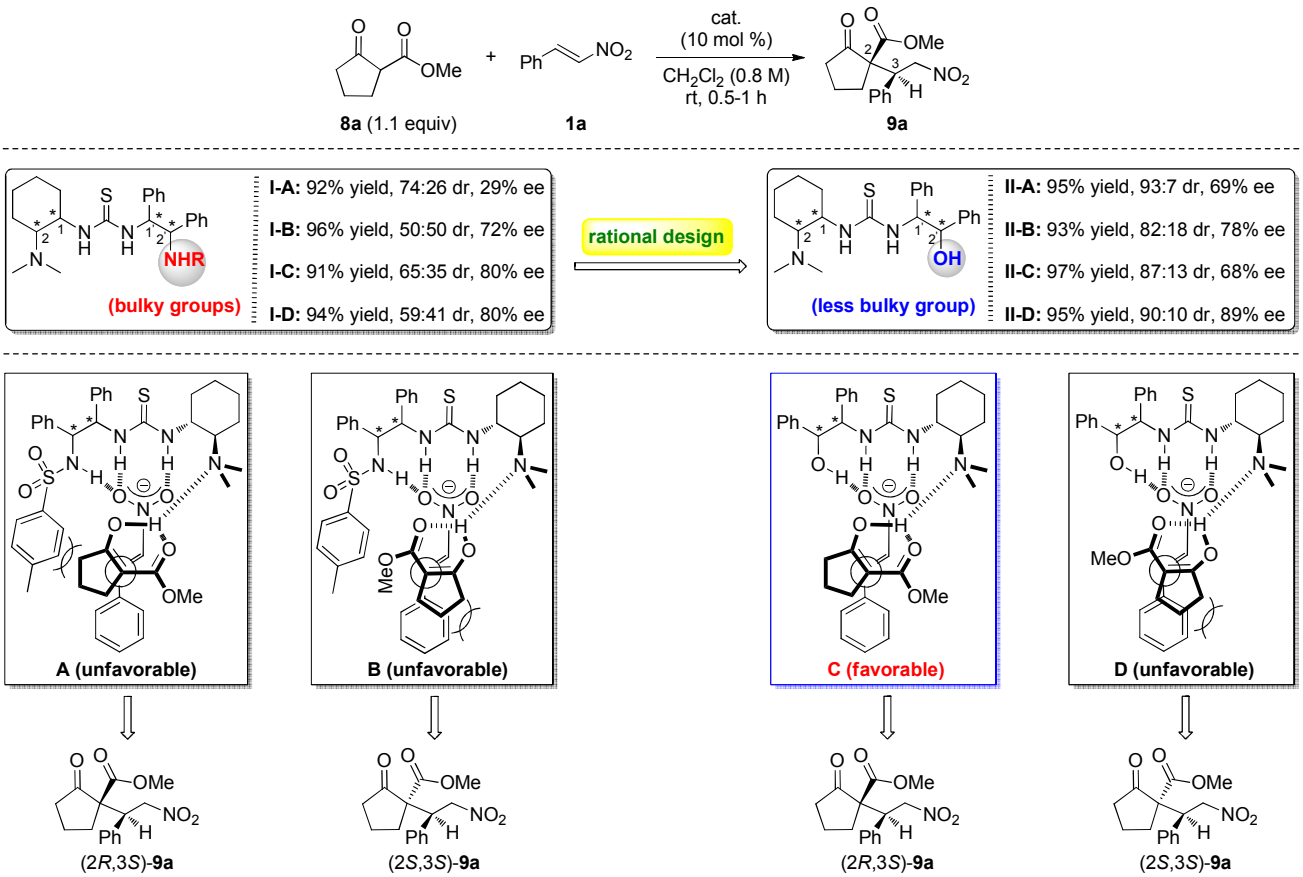
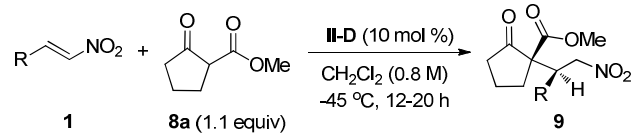


Scheme 5 Asymmetric Michael addition of α-substituted β-ketoester **8a** to nitroolefin **1a** and rational design of novel fine-tunable and less bulky amine-thiourea organocatalysts **II** bearing multiple hydrogen-bonding donors.

more favorable transition state, thus improving the diastereoselectivity and enantioselectivity. To our delight, this reaction promoted by the rationally designed organocatalysts **II** gave the adduct with significantly improved stereoselectivity, which supported our hypothesis (Scheme 5, right side).

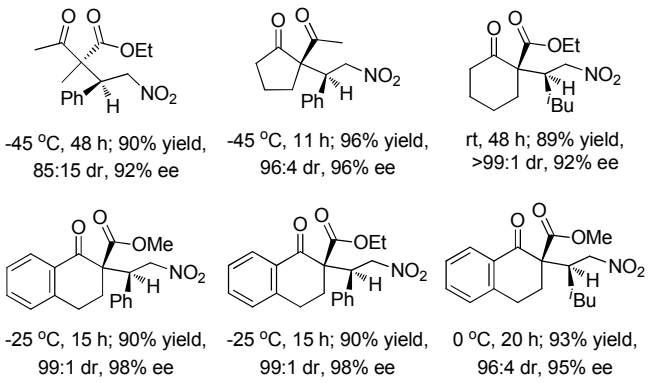
The fine-tunable bifunctional amine-thiourea organocatalyst **II-D** showed excellent diastereoselectivity and enantioselectivity with broad substrate scope in the catalytic enantioselective Michael addition of α-substituted β-ketoester **8a** to nitroolefins **1** (Scheme 6).[15] Multiple hydrogen-bonding donors play an important role in enhancing the yields and stereoselectivities in these reactions, providing a facile access to highly functionalized compounds bearing adjacent tertiary and quaternary stereogenic centers in a single step.



[a] Carried out at 0 °C.

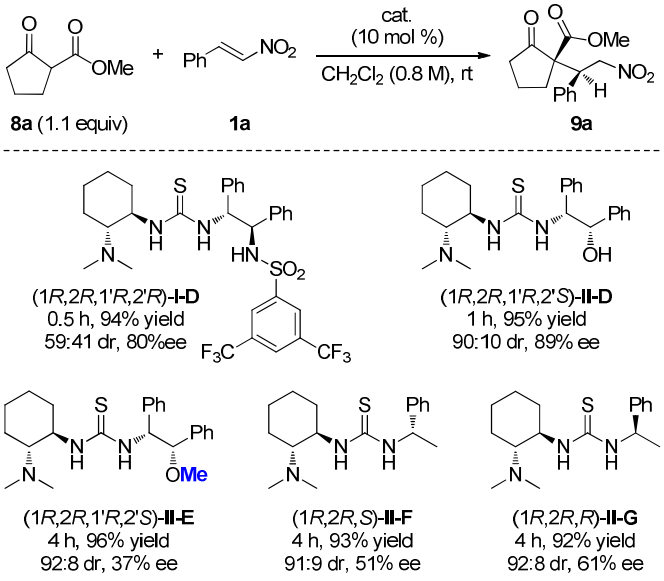
Scheme 6 Asymmetric Michael addition of α-substituted β-ketoester **8a** and nitroolefins **1** catalyzed by organocatalyst **II-D**.

To further examine the scope of this reaction, some other trisubstituted substrates were also tested using catalyst **II-D**. As presented in Scheme 7, various α-substituted 1,3-dicarbonyl compounds were proved to be suitable substrates with high diastereo- and enantioselectivity.



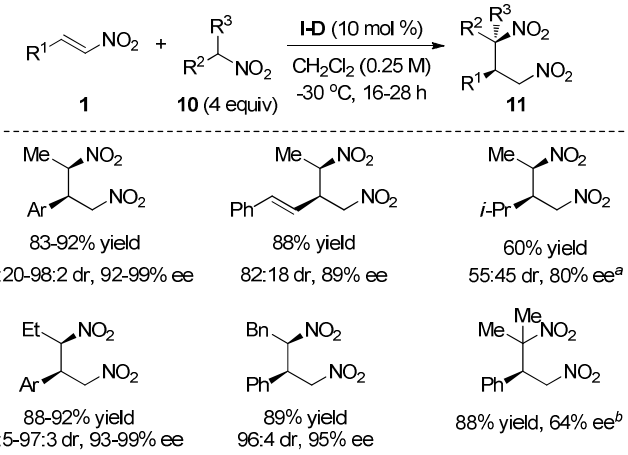
Scheme 7 Michael addition of nitroolefins **1** with other cyclic and acyclic trisubstituted carbon nucleophiles catalyzed by organocatalyst **II-D**.

Control experiments were conducted to demonstrate the key role of the additional hydrogen-bonding donor from the less bulky OH group played in the above catalytic system (Scheme 8). In sharp contrast to the amine-thiourea **II-D**, the methylated or less bulky catalysts **II-E**, **II-F**, and **II-G** all led to significantly diminished enantioselectivity and the reaction proceeded a little sluggishly under the same conditions, although the diastereoselective control remained. Such control experimental results were consistent with the proposed transition state of the reaction (Scheme 5).



Scheme 8 Control experiments to evaluate the roles of the multiple hydrogen-bonding donors and the steric effect played in organocatalyst **II-D**.

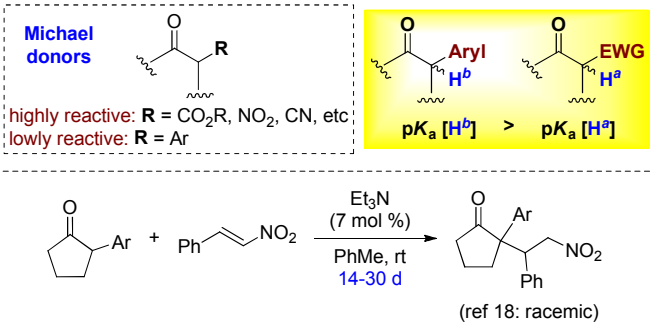
Another example of successful promotion of Michael addition using bifunctional amine-thiourea **I-D** is the challenging *syn*-selective asymmetric Michael addition of nitroalkanes **10** with nitroolefins **1** (Scheme 9).[16] This catalytic system worked well with broad substrate scope, producing a variety of 1,3-dinitro compounds **11** with high stereoselectivity under mild reaction conditions. The obtained adducts with two adjacent stereogenic centers could be easily transformed into optically active 1,3-diamines, which are of great significance and synthetic value.[17]



[a] For 48 h. [b] Carried out at rt for 20 h without solvent.

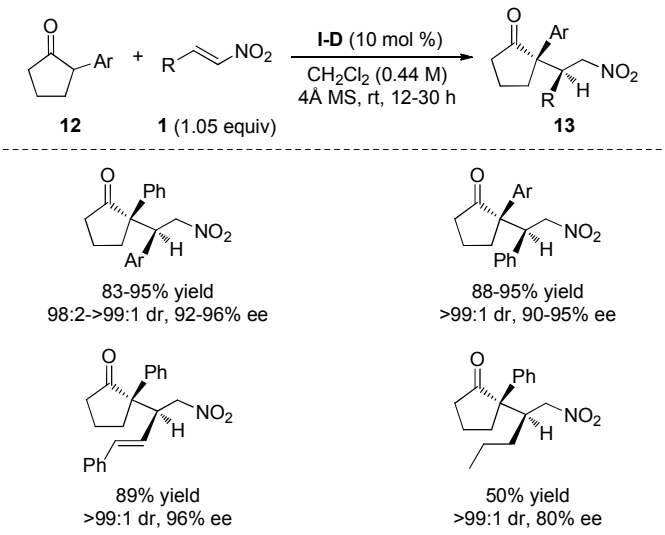
Scheme 9 Asymmetric direct Michael addition reaction of nitroalkanes **10** to nitroolefins **1** using organocatalyst **I-D**.

In sharp contrast to employing carbonyl substrates with electron-withdrawing groups such as CO_2R, NO_2, or CN at the α-position as nucleophiles, α-aryl substituted carbonyl compounds have rarely been used as the nucleophile in asymmetric reaction (Scheme 10). To our knowledge, only one example of racemic version using α-aryl cyclopentanones as the nucleophile and nitroolefin as the electrophile had been reported before our investigation of the asymmetric version. The racemic example used Et_3N as the catalyst and the reaction was accomplished in 14–30 days.[18] The long reaction time was required likely due to the higher pK_a value of the α-proton and disfavored steric hindrance of the aromatic substituent.



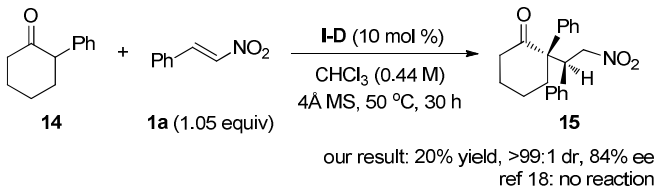
Scheme 10 A challenging Michael addition reaction with α-aryl substituted carbonyl compounds as Michael donors.

We reported an unprecedented enantioselective Michael addition of α-aryl cyclopentanones **12** with nitroolefins **1** catalyzed by organocatalyst **I-D** (Scheme 11).[19] This catalytic system affords the expected adducts **13** bearing adjacent tertiary and quaternary stereocenters with excellent asymmetric induction (>98:2 dr and 80-96% ee) and broad substrate scope. To demonstrate the utility of this methodology, the optically active conjugate adduct was converted to synthetically valuable molecules such as cyclic imine, nitrone, and fused pyrrolidine without loss of stereoselectivity.[20]



Scheme 11 Asymmetric Michael addition of α-aryl cyclopentanones **12** and nitroolefins **1** catalyzed by bifunctional organocatalyst **I-D**.

Encouraged by the above results, we subsequently examined a more challenging nucleophile α-phenyl cyclohexanone **14**, which failed to undergo Michael addition in the literature.[18] To our gratification, the reaction took place with catalyst **I-D** and the anticipated product **15** was obtained in 20% yield with 84% ee (Scheme 12). Such success further validated the catalytic efficiency of our bifunctional amine-thiourea catalyst bearing multiple hydrogen-bonding donors.



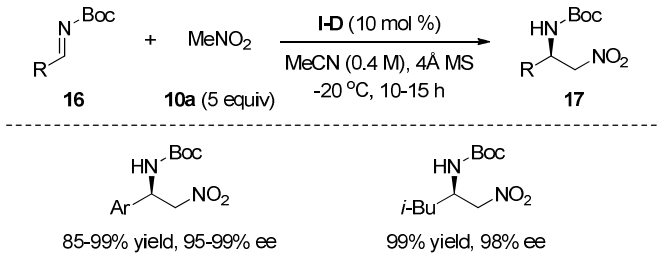
Scheme 12 Michael addition of nitroolefin **1a** with α-phenyl cyclohexanone **14** catalyzed by organocatalyst **I-D**.

Nitro-Mannich reaction

The addition of nitroalkanes to imines, called the nitro-Mannich (or *aza*-Henry) reaction, is a very useful approach to form C–C bond in organic synthesis.[21] Synthetically valuable β-nitro amines generated in this method could be easily transformed into 1,2-diamines[22] and α-aminocarbonyl compounds.[23]

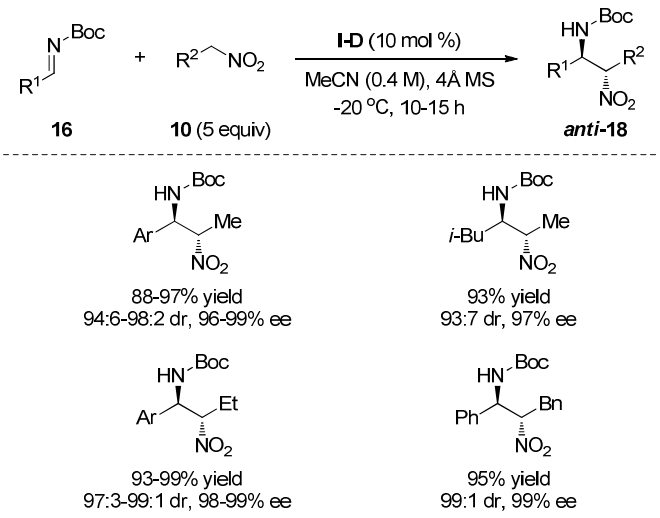
Over the last decade, much attention has been devoted to the development of catalytic asymmetric protocols for this reaction.[24] In 2007, Shibasaki reported a nitro-Mannich reaction catalyzed by a heterobimetallic Cu-Sm-Schiff base complex, affording nitroamines in high yields with excellent stereoselectivities.[25] The significance of this reaction lies in the fact that this is the first highly *syn*-selective nitro-Mannich reaction. However, for *anti*-selective nitro-Mannich reaction, few organocatalysts could afford high *anti*-selectivity of greater than 10:1 with good enantioselectivity for a broad substrate scope.[24e,f]

We reported a highly enantioselective nitro-Mannich reaction in 2008.[26] Promoted by the bifunctional amine-thiourea catalyst **I-D**, various *N*-Boc aldimines **16** reacted smoothly with nitromethane **10a** affording the expected adducts in high yields (85-98%) with excellent enantioselectivities (97-99% ee) (Scheme 13). An attractive feature of the current method is the exceptional compatibility with heteroaromatic and aliphatic *N*-Boc aldimines.



Scheme 13 Asymmetric nitro-Mannich reaction of *N*-Boc aldimines **16** with nitromethane **10a** using organocatalyst **I-D**.

The highly enantioselective *anti*-nitro-Mannich reaction was also realized with organocatalyst **I-D** for the first time.[26] Our exploration of the reaction of *N*-Boc aldimines **16** with several other nitroalkanes **10** led to the formation of two contiguous nitrogen-containing stereocenters. As shown in Scheme 14, the desired *anti*-adducts **18** were attained in high yields (up to 99%) with excellent diastereo- and enantioselectivities (up to 99:1 dr and 99% ee). Notably, higher diastereoselectivity was observed with **I-D** as the catalyst, comparing to that when employing Takemoto's catalyst.[24f]



Scheme 14 Highly *anti*-selective catalytic asymmetric nitro-Mannich reaction of *N*-Boc aldimines **16** with nitroalkanes **10**.

A plausible transition state model was postulated for this reaction as shown in Figure 4. We propose that the synergistic dual activation of both *N*-Boc aldimines and nitroalkanes by amine-thiourea catalyst **I-D** is very important to achieve high *anti*-selectivity in this catalytic asymmetric nitro-Mannich reaction. The thiourea and sulfonamide moieties would interact with *N*-Boc aldimine by means of hydrogen-bonding interactions, while the vicinal tertiary amine would serve as a common base to produce the nitronate simultaneously. It is believed that the less sterically hindered **TS-1** is more favorable than **TS-2**. Therefore, the stereoselective formation of the C–C bond via **TS-1** affords the observed *anti*-adduct.

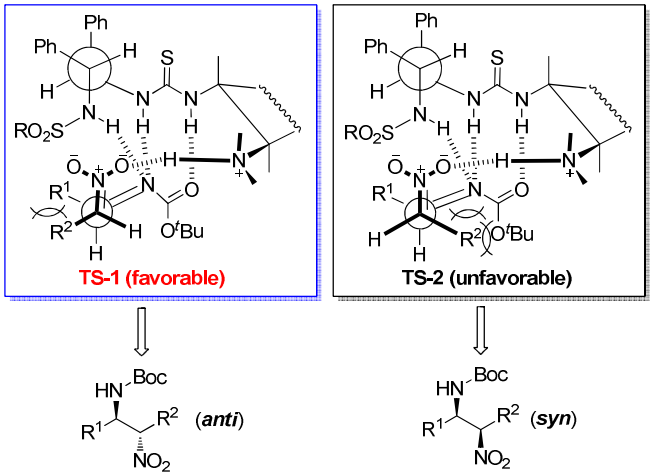
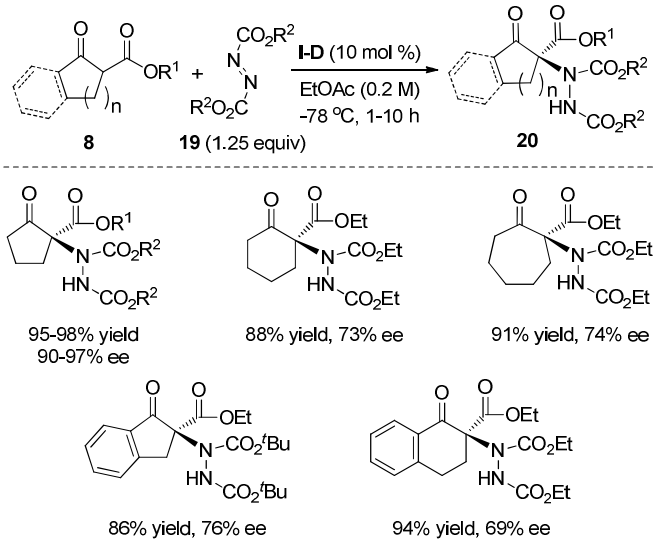


Figure 4. Proposed transition state model leading to *anti*-adducts.

Amination reaction

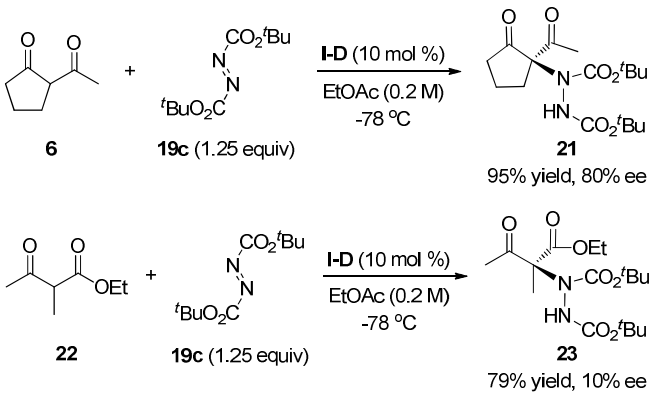
Optically active α-amino acid derivatives are prevalent in numerous natural alkaloids, as well as biologically and pharmaceutically significant building blocks in organic synthesis.[27] The asymmetric amination of β-ketoesters with azodicarboxylates provides an effective approach for the construction of α,α-disubstituted amino acid derivatives featuring a nitrogen-containing quaternary stereocenter.[28] Considerable attention has been paid to the development of catalytic asymmetric strategies for this reaction over the last decade.[29]

We described an efficient asymmetric amination reaction of cyclic β-ketoesters **8** with dialkyl azodicarboxylates **19** mediated by chiral bifunctional amine-thioureas. Catalyst **I-D** showed the best performance for this transformation and provided optically active α,α-disubstituted amino acid derivatives **20** with up to 97% ee (Scheme 15).[30]



Scheme 15 Enantioselective amination of various cyclic β-ketoesters **8** with dialkyl azodicarboxylates **19** catalyzed by organocatalyst **I-D**.

The asymmetric amination of 2-acetylcyclopentanone **6** was also investigated. As shown in Scheme 16, the desired adduct **21** was generated in 95% yield with 80% ee under the optimized reaction conditions. However, only 10% ee was observed when acyclic β-ketoester **22** was employed with this catalytic system.



Scheme 16 Asymmetric amination of 2-acetylcyclopentanone (**6**) and ethyl 2-methyl-3-oxo-butylate (**22**) with dialkyl azodicarboxylate **19c**.

Sulfa-Michael addition

Chiral sulfur-containing molecules are key structural units in natural products,[31] and also have been found be highly valuable in synthetic organic chemistry and biologically active pharmaceuticals.[32] Among the existing approaches, enantioselective sulfa-Michael addition of thiols to electron-deficient olefins is one of the most significant and straightforward methods to synthesize optically pure sulfur-containing compounds.[33] Consequently, considerable efforts have been devoted to the development of catalytic asymmetric protocols for this reaction over the last several years.[34]

Organofluorine molecules play a significant and unique role in the fields of pharmaceutical and material science.[35] Among fluorinated organic compounds, chiral trifluoromethylated molecules are particularly important in agricultural and pharmaceutical chemistry.[36] One such case is (*R*)-γ-trifluoromethyl γ-sulfone hydroxamate (Figure 5), a potent inhibitor of MMP-3 (stromelysin-1), in which a unique trifluoromethyl substituent is linked to the stereocenter. Zanda disclosed a method to obtain both enantiomers of γ-trifluoromethyl γ-sulfone hydroxamate through the key step of a sulfa-Michael addition reaction of *p*-methoxythiophenol with 4,4,4-trifluorocrotonamide bearing a chiral oxazolidin-2-one or oxazolidine-2-thione group.[37] However, this chiral-auxiliary-induced sulfa-Michael addition produced the pivotal intermediate as a mixture of the two diastereoisomers in nearly 1:1 ratio.

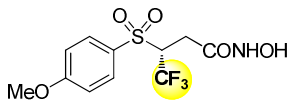
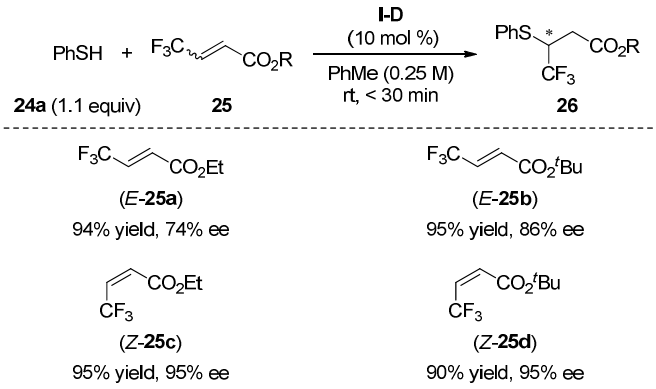


Figure 5. The potent inhibitor of MMP-3 (stromelysin-1): (*R*)-γ-trifluoromethyl γ-sulfone hydroxamate.

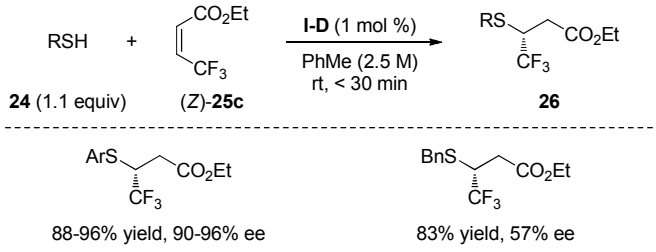
In order to develop an efficient catalytic asymmetric protocol for the synthesis of the key intermediate of MMP-3 (stromelysin-1), the sulfa-Michael addition of thiophenol **24a** to (*E*)-4,4,4-trifluorocrotonate **25a** was investigated with catalyst **I-D**. The expected product was obtained in high yield yet with

only moderate enantioselectivity (74% ee).[38] The effects of the ester moiety and geometry of the double bond were then explored. As shown in Scheme 17, the bulkier *tert*-butyl ester gave higher enantioselectivity, and switching the double bond geometry from *E* to *Z* resulted in formation of the opposite enantiomer with better enantioselectivity. The (*Z*)-4,4,4-trifluorocrotonate **25c** gave the best outcomes in terms of both yield and enantioselectivity.



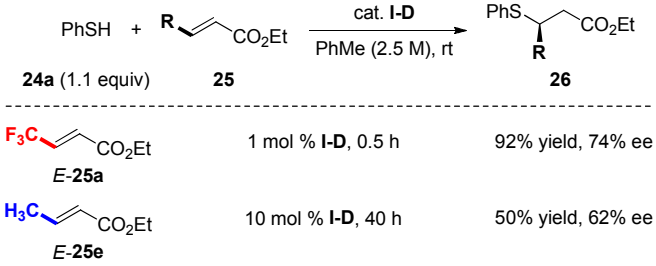
Scheme 17 Asymmetric sulfa-Michael addition of thiophenol **24a** to 4,4,4-trifluorocrotonates **25** catalyzed by bifunctional organocatalyst **I-D**.

We achieved the first catalytic enantioselective sulfa-Michael addition of thiols **24** to (*Z*)-4,4,4-trifluorocrotonate **25c** promoted by bifunctional amine-thiourea **I-D** with as low as 1 mol % catalyst loading, affording the adducts in high yield (up to 96%) with excellent enantioselectivity (up to 96% ee) (Scheme 18).[38] This could be used as a straightforward method to construct chiral building blocks featuring a sulfur atom and a unique CF_3 group at the stereocenter.



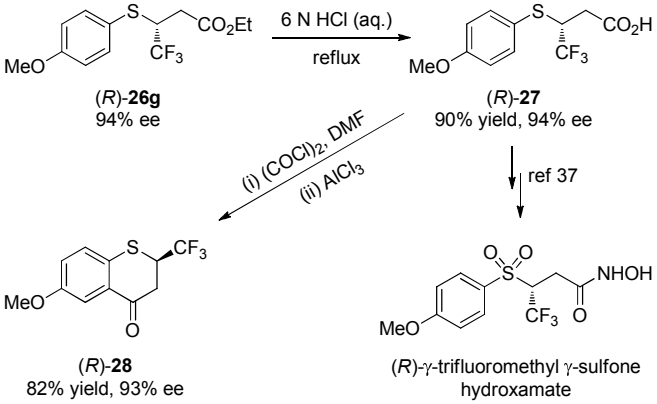
Scheme 18 Asymmetric sulfa-Michael addition of thiols **24** to (*Z*)-ethyl 4,4,4-trifluorocrotonate **25c** with organocatalyst **I-D**.

A control experiment was performed with ethyl crotonate **25e** as the Michael acceptor to probe the role of CF_3 group played in the above reaction (Scheme 19). This reaction turned to be much slower and afforded the adduct with only 62% ee, which revealed that the C=C bond in 4,4,4-trifluorocrotonate was substantially activated through the σ-electron-withdrawing nature of CF_3 group.



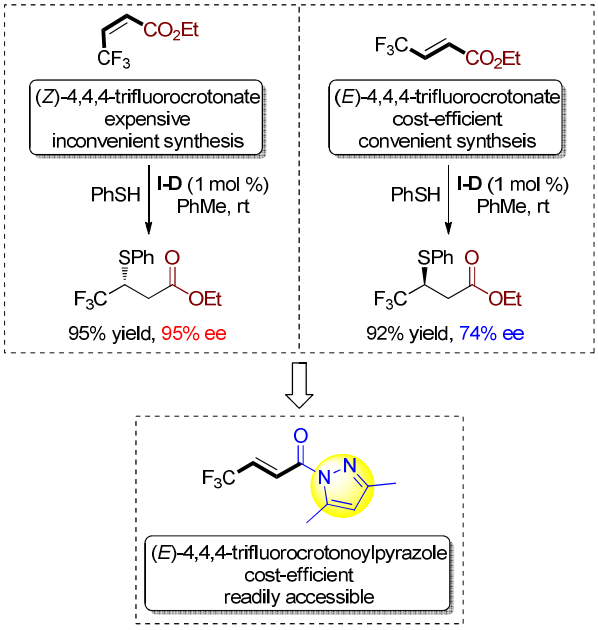
Scheme 19 Control experiments to evaluate the role of the electron-withdrawing CF_3 group played in the sulfa-Michael addition reaction.

To illustrate the application of this reaction, we investigated the preparation of (*R*)-**27**, a key intermediate to synthesize stromelysin-1 (Scheme 20). The ethyl ester group of (*R*)-**26g** could be easily hydrolyzed to deliver the crucial intermediate (*R*)-**27** under mild reaction conditions. Synthetically valuable thiochroman-4-one (*R*)-**28** was also obtained by means of two sequential reactions in a one-pot protocol with retention of enantioselectivity.[39]



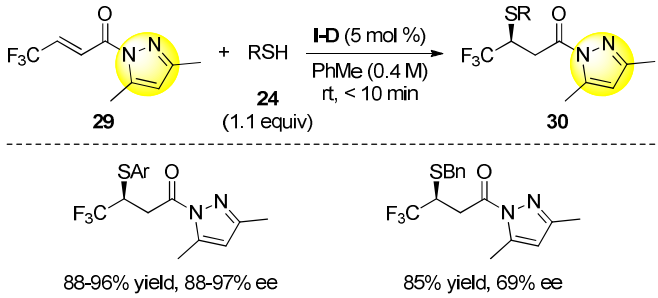
Scheme 20 Synthetic transformations of the Michael adduct (*R*)-**26g**.

However, there is a synthetic limitation of the above methodology due to the difficulty to access (*Z*)-4,4,4-trifluorocrotonate. When the cost-efficient (*E*)-4,4,4-trifluorocrotonate was employed as the Michael acceptor, only moderate enantioselective control was obtained (Scheme 21).[38] We envisaged that replacement of the ester moiety in (*E*)-ethyl 4,4,4-trifluorocrotonate with an *N*-acylpyrazole moiety, which contains an additional hydrogen-bonding acceptor, would efficiently improve its reactivity and stereoselectivity via the enhanced hydrogen-bonding interactions between the electrophile and the bifunctional amine-thiourea catalyst.



Scheme 21 New strategy of employing (*E*)-4,4,4-trifluorocrotonoylpyrazole as the Michael acceptor.

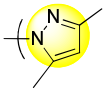
After extensive exploration, we disclosed an effective strategy to achieve the enantioselective sulfa-Michael addition of thiols **24** to the readily accessible (*E*)-4,4,4-trifluorocrotonoylpyrazole **29** mediated by bifunctional amine-thiourea **I-D** in high yield (up to 96%) with good to excellent enantioselectivity (up to 97% ee) (Scheme 22).[40] The method presented here opened up a new and practical way to construct valuable chiral building blocks featuring both a sulfur atom and a CF_3 group at the same stereocenter. Furthermore, it is worth to note that the enantiomeric excess of the adducts could be easily improved by a simple recrystallization.



Scheme 22 Asymmetric sulfa-Michael addition of thiols **24** to (*E*)-4,4,4-trifluorocrotonoylpyrazole **29** with organocatalyst **I-D**.

Control experiments were performed to probe the roles that the pyrazole and CF_3 moieties played in the above reaction (Table 1): replacement of the ester group with an amide group in the Michael acceptors led to a superior level of both reactivity and enantioselectivity. These results indicated that the introduction of the pyrazole moiety[41] was shown to be essential for a better chelation due to the additional hydrogen-bond acceptor in the moiety and therefore higher stereoselectivity. Moreover, the electrophilicity was also enhanced by the σ-electron-withdrawing CF_3 group.

Table 1 Control experiments to evaluate the roles of the pyrazole motif and the electron-wthdrawing CF_3 group

entry	R^1	R^2	I-D (mol %)	time	yield (%)	ee (%)
1	CF_3		1	10 min	92	93
2	Me		10	15 h	90	80
3	Ph		10	28 h	82	63
4	CF_3		1	30 min	92	74
5	Me	OEt	10	40 h	50	62
6	Ph		10	48 h	trace	ND

A proposed dual activation model explaining the observed stereochemistry of the above sulfa-Michael addition is shown in Figure 6. The hydrogen-bonding interactions between thiourea/sulfonamide moieties and the substrate (*E*)-4,4,4-trifluorocrotonoylpyrazole would enhance its electrophilicity towards the nucleophilic attack of thiols. Meanwhile, the vicinal tertiary amine would serve as a common base to improve the nucleophilicity of thiols. The attack of a thiol to the *Si*-face of (*E*)-4,4,4-trifluorocrotonoylpyrazole yields the (*S*)-adduct.

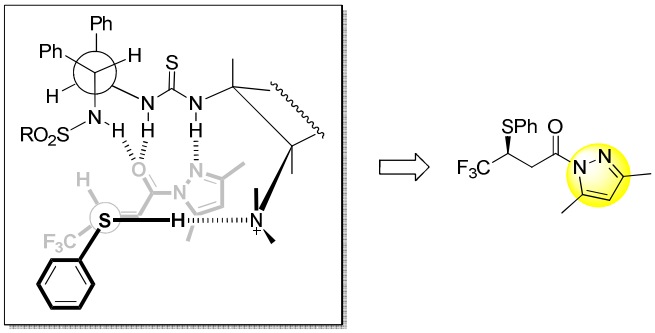
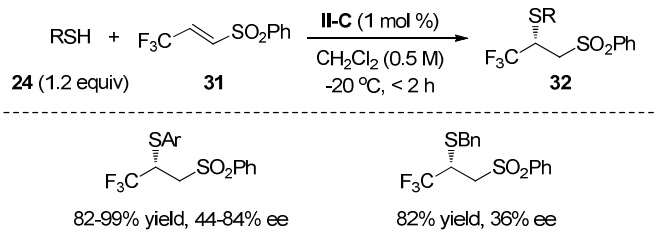


Figure 6. Proposed transition state model leading to (*S*)-adduct.

Recently, we reported an enantioselective sulfa-Michael addition of thiols **24** to (*E*)-3,3,3-trifluoropropenyl phenyl sulfone **31** promoted by bifunctional amine-thiourea organocatalyst **II-C** (Scheme 23).[42] This catalytic system provides the expected trifluoromethylated sulfones **32** featuring a unique CF_3 group at the stereocenter in high yield with moderate to good enantioselectivity.

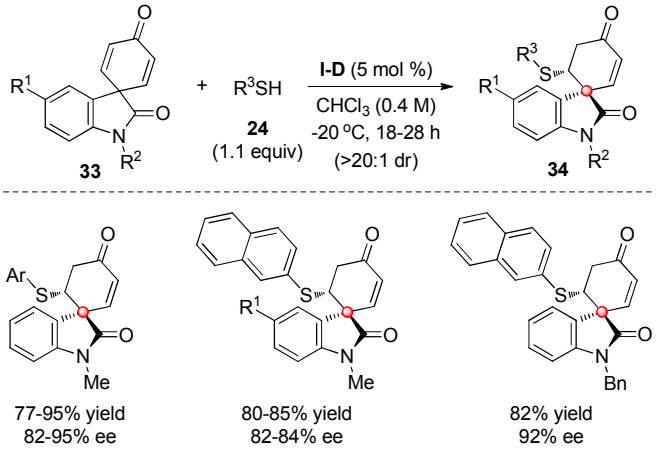


Scheme 23 Asymmetric sulfa-Michael addition of thiols **24** to (*E*)-3,3,3-trifluoropropenyl phenyl sulfone **31** with organocatalyst **II-C**.

Spirocyclic oxindoles widely emerge in a great deal of natural products and bioactive compounds,[43] especially those containing an all-carbon quaternary stereocenter at the C-3

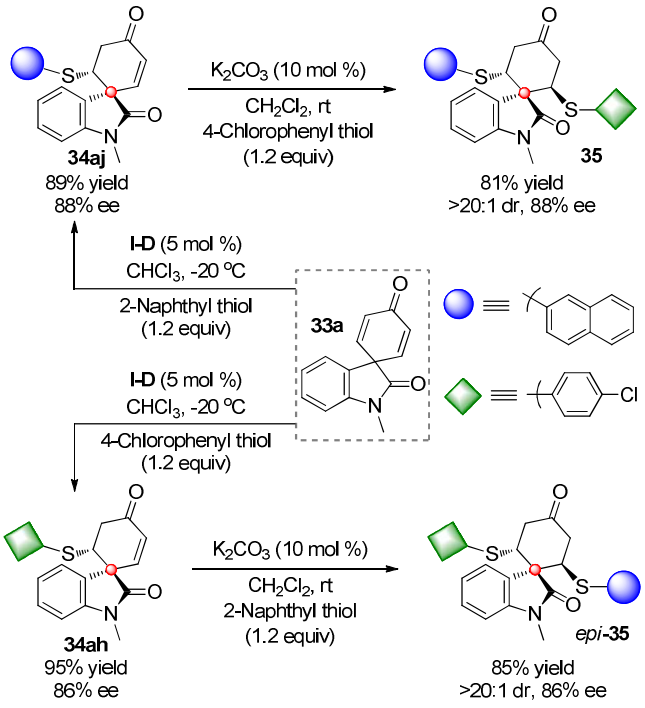
position.[44] Enantioselective desymmetrization is an effective strategy to generate optically enriched compounds containing multiple stereocenters, which is realized by differentiation of two enantiotopic groups on the easily accessible prochiral or symmetric molecules.[45,46]

We disclosed the desymmetrization of spiro cyclohexadienone oxindoles **33** via an efficient enantioselective sulfa-Michael addition catalyzed by bifunctional amine-thiourea **I-D** (Scheme 24),[47] which provides expeditious access to highly functionalized chiral spirocyclic oxindoles **34** containing adjacent quaternary and tertiary stereogenic centers with excellent levels of stereoselectivity. This catalytic system displayed broad substrate scope with high reactivity (up to 95% yield) and good stereoselective control (>20:1 dr and up to 95% ee).



Scheme 24 Enantioselective desymmetrization of spiro cyclohexadienone oxindoles **33** via asymmetric sulfa-Michael addition with organocatalyst **I-D**.

The inclusion of an α,β-unsaturated enone moiety could increase the possible structural and stereochemical complexity of the sulfa-Michael adducts **34** (Scheme 25): subsequent inorganic base-mediated sulfa-Michael addition with a second thiol could afford **35** or *epi*-**35** with 2,6-*trans* configuration in a highly diastereoselective fashion (>20:1 dr) by means of simply switching the order of addition of the thiols.



Scheme 25 Synthesis of compounds **35** and *epi*-**35** via double sulfa-Michael addition by switching the adding sequence of thiols.

A possible transition state model for the addition of thiols to spiro cyclohexadienone oxindole is shown in Figure 7. The bifunctional character of the organocatalyst enables simultaneous activation of spiro cyclohexadienone oxindoles with the thiourea and sulfonamide-NH via hydrogen-bonding interactions and thiols with the vicinal tertiary amine, thus producing the desired Michael adduct via organocatalyzed enantioselective desymmetrization.

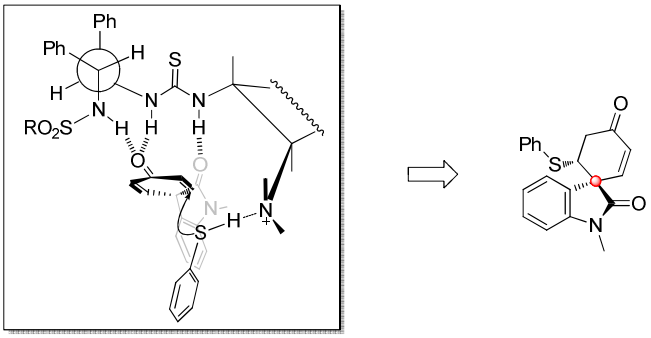
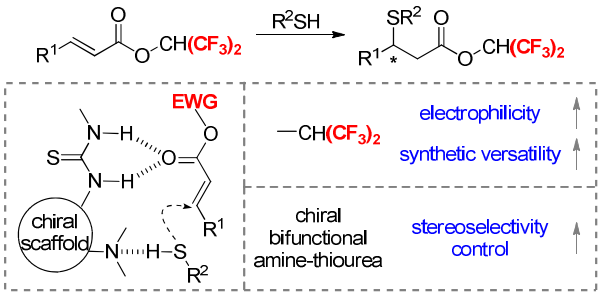


Figure 7. Proposed transition state model for the organocatalytic asymmetric desymmetrization.

Diverse electron-deficient olefins have been used as acceptors in catalytic stereoselective sulfa-Michael addition. However, it is surprising that the readily available and inexpensive α,β-unsaturated esters have rarely been employed as the substrates in this reaction, which could probably be attributed to their relatively low electrophilicity. To our knowledge, except for the example of employing (*Z*)-ethyl 4,4,4-trifluorocrotonate bearing a σ-electron-withdrawing CF_3 group as the specific Michael acceptor reported by our group,[38] only one case of α,β-unsaturated ester-involved asymmetric sulfa-Michael addition mediated by metal-complex at low

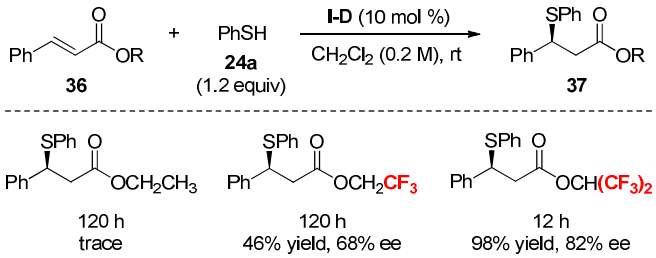
temperature was achieved.[34a] Nevertheless, there were several drawbacks in that catalytic system, especially *ortho*-substituted thiophenols must be used as the nucleophile in order to obtain higher enantioselective control. Thus, developing a versatile method for the enantioselective sulfa-Michael addition of thiol nucleophiles to readily accessible α,β-unsaturated esters is still challenging and of great importance.

In consideration of the important role of hexafluoroisopropyl ester motif played in asymmetric transformations,[48] we envisioned that the electrophilicity of α,β-unsaturated esters can be improved by introducing an electron-withdrawing moiety, such as hexafluoroisopropyl group, thereby enhancing the reactivity towards nucleophilic attack of thiol nucleophiles with high enantioselectivity, and thus can tackle the challenging catalytic enantioselective sulfa-Michael addition with α,β-unsaturated esters as Michael acceptors (Scheme 26).



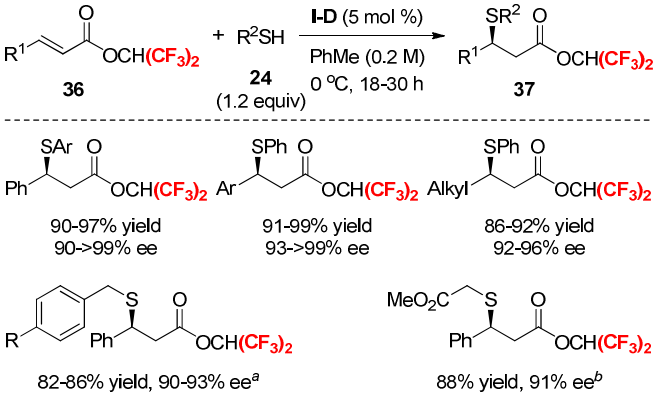
Scheme 26 Strategies for the challenging catalytic asymmetric sulfa-Michael addition employing α,β-unsaturated esters as Michael acceptors.

The reactions between different α,β-unsaturated cinnamate esters with thiophenol were initially studied to estimate their electrophilicity. As shown in Scheme 27, the electrophilicity of cinnamate was improved by replacing the ethyl group with a trifluoroethyl group yet long reaction time was still required, which preliminarily supported our hypothesis on electrophilicity improvement of α,β-unsaturated esters with electron-deficient moiety and stereoselective control through the synergistic hydrogen-bonding interactions. As expected, introduction of the bulkier and more electron-deficient hexafluoroisopropyl moiety remarkably led to higher reactivity and enantioselectivity.



Scheme 27 Ester moiety effect on catalytic asymmetric sulfa-Michael addition of thiophenol **24a** with various α,β-unsaturated esters.

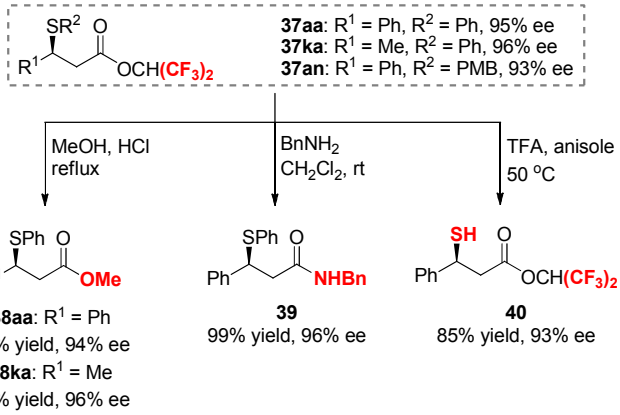
We developed an unprecedented highly enantioselective sulfa-Michael addition of thiols **24** with various α,β-unsaturated hexafluoroisopropyl esters **36** catalyzed by bifunctional amine-thiourea **I-D** (Scheme 28).[49] The reaction showed good substrate scope for both thiols and α,β-unsaturated hexafluoroisopropyl esters, producing the desired adducts **37** in high yield (up to 99%) with excellent enantioselectivity (up to >99% ee).



[a] For 48 h. [b] Carried out at -30 °C for 40 h.

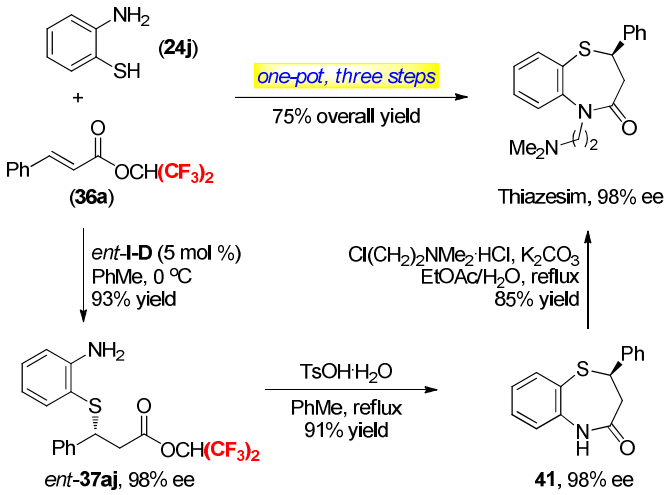
Scheme 28 Catalytic asymmetric sulfa-Michael addition of thiols **24** to α,β-unsaturated hexafluoroisopropyl esters **36** catalyzed by organocatalyst **I-D**.

The optically active Michael adducts **37** containing a highly reactive hexafluoroisopropyl ester moiety were easily converted to important chiral building blocks as exemplified in Scheme 29. Treatment of **37aa** and **37ka** with methanol in the presence of concentrated HCl furnished the corresponding methyl esters. The amide **39** was obtained in quantitative yield without loss of enantiomeric excess via treatment with benzylamine in simple protocol. On the other hand, synthetically useful β-mercapto ester **40** could be obtained in good yield with retention of optical purity through efficient cleavage of the PMB group in **37an** under mild reaction conditions.[32d]



Scheme 29 Synthetic transformations of the sulfa-Michael adducts.

A concise preparation of (*R*)-thiazesim, an antidepressant agent,[50] was performed to demonstrate the synthetic potential of the current methodology. The key step in the synthetic route to the target compound was an efficient *ent*-**I-D**-catalyzed enantioselective sulfa-Michael addition of 2-aminothiophenol with hexafluoroisopropyl cinnamate (Scheme 30). The treatment of the Michael adduct *ent*-**37aj** with a catalytic amount of $TsOH \cdot H_2O$ in PhMe under reflux followed by *N*-alkylation of the generated cyclic amide **41** afforded (*R*)-thiazesim in high yield with excellent enantioselectivity. It is worth noting that those three step transformations could be performed sequentially in one-pot delivering the enantioenriched target compound in 75% overall yield with 98% ee.



Scheme 30 Concise synthesis of (*R*)-thiazesim.

Conclusions

In this feature article, we have summarized our recent efforts on asymmetric organocatalysis mediated by the elaborately designed and fine-tunable bifunctional amine-thioureas. The examples, reported over the last few years, confirmed that bifunctional amine-thioureas bearing multiple hydrogen-bonding donors have found a place as powerful organocatalysts for asymmetric synthesis. The success of bifunctional catalysis in which multiple hydrogen-bonding donors in the thiourea/sulfonamide moieties and a basic tertiary amine group work synergistically has highlighted the fundamental principle of biocatalysis. Thus, as in a mimic of enzymatic catalysis, both electrophile and nucleophile are activated simultaneously to promote a chemical transformation in a highly efficient and selective manner. Moreover, these organocatalysts could be prepared from commercially available or readily accessible scaffolds. Further applications of these bifunctional amine-thiourea catalysts in asymmetric transformations can be expected in the near future.

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Notes and references

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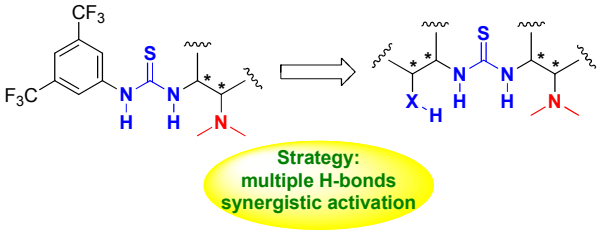
Graphical abstract:



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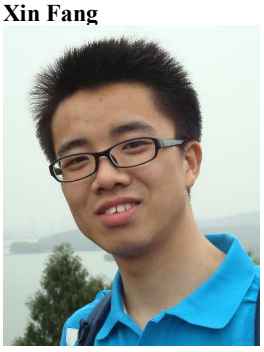

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