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Accounts

Discovery and Application of Asymmetric Reaction by Multi-Functional Thioureas

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Novel bifunctional organocatalysts, which possess a thiourea moiety and an amino group, were designed and synthesized. We discovered that bifunctional thiourea bearing a tertiary amino group significantly accelerated several nucleophilic addition reactions of active methylene compounds to electron-deficient double bonds. In these reactions, the double hydrogen-bonding activation of electrophiles bearing nitro, imide, and carbamate groups by the thiourea moiety and simultaneous deprotonation of nucleophiles by the dimethylamino group of bifunctional thiourea proved to play a crucial role for enhancing both reaction rate and enantioselectivity. We have demonstrated the utility of PEG-bound thiourea as a homogeneous catalyst. Although the reaction rate was somewhat decreased with PEG-bound thiourea, immobilization to a PEG support proved to facilitate the recovery and reuse of thiourea catalyst without affecting the chemical yield and enantioselectivity. A newly designed thiourea catalyst provided sufficient activation of organoboronic acids to facilitate the enantioselective Petasis transformation of quinolines even at low temperatures. A high degree of stereocontrol was achieved in the reaction of various quinolines and organoboronic acids by using a combination of H_2O and $NaHCO_3$ as additives.

1. Introduction

New concepts and methods for controlling stereochemistry are emerging continuously, allowing sustainable chemical transformations.[1] In the last ten years, the development of chiral organocatalysts has become a field of central importance for asymmetric synthesis.[2,3] This field has grown at an extraordinary level; thus, it is clear that there is a lot of interest in organocatalysis not only from academia but also from industry. Organocatalysts have several advantages over metal catalysts. Especially, chemical transformations using organocatalyst seem to be attractive for the preparation of pharmaceutical products that do not tolerate metal contamination.

Urea and thiourea have been intensively investigated in the area of molecular recognition due to their strong hydrogen-bonding activity.[2j] Kelly et al. and Etter et al. reported that urea and thiourea not only recognized organic compounds but also activated them as a general acid catalyst.[4] Recently, novel urea and thiourea derivatives have been developed as organocatalysts and their versatility as a general acid has been successfully demonstrated by several groups.[3,5–9] However, the application of these catalysts to enantioselective reactions seems to be somewhat limited, because ureas are weaker acids than metallic Lewis acids. Therefore, our laboratory introduced chiral bifunctional thiourea, which accelerates a variety of enantioselective reactions as a result of dual activation of electrophile and nucleophile. In this account, we offer a comprehensive overview of our recent studies on bifunctional urea/thiourea-mediated asymmetric nucleophilic reactions.

2. Chiral Amino Thiourea

2.1 Design of Thiourea Having a Chiral Amino Moiety. Since Curran's pioneering work,[5] various types of nucleophilic addition reactions have been found to be effectively promoted by a catalytic amount of well-designed ureas and thioureas by several research groups.[2] However, there is only limited information on how to design a chiral urea/thiourea catalyst for asymmetric reactions. Based on the results of Schreiner's achiral diarylthiourea catalyst **1**,[6] we have designed the new thioureas **2a–2d** bearing a chiral scaffold and a basic functionality in expectation of dual activation[1] to promote several nucleophilic addition reactions (Figure 1).[10] It is assumed that weak tertiary amine bases can coexist with thiourea moiety in a molecule without deactivating each other.[11] From an X-ray crystallographic structure of **2a**, both the dimethylamino group and the thiourea moiety are revealed to be located in equatorial positions on a chair-formed cyclohexane ring. That means that thiourea **2a** has an ideal conformation for dual activation. In catalytic cycles and processes, non-covalent interaction such as hydrogen bonding is an essential tool for activating both electrophile and nucleophile.

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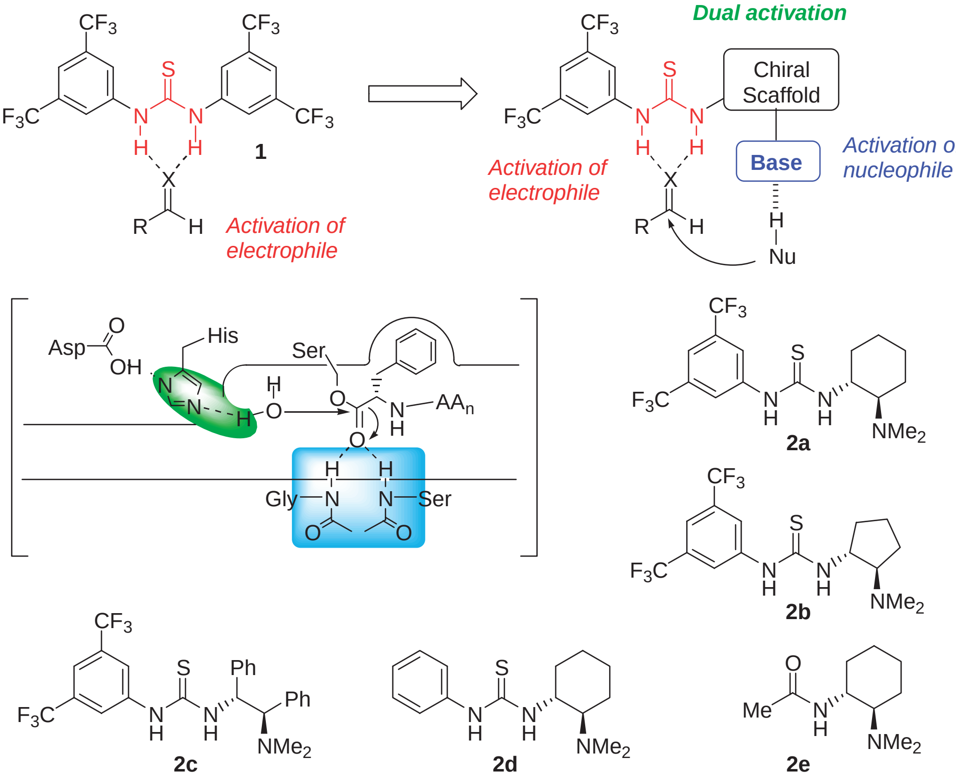
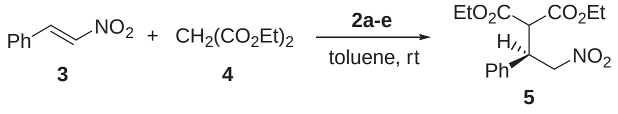


Figure 1. Design of bifunctional thioureas having a chiral amino moiety.

Due to analogies with catalytic action of enzymes, organocatalysts can be regarded as minimum versions of metal-free enzymes. Our thiourea catalysts were also designed based on the mechanism of serine protease, which is known as a hydrolytic enzyme.

2.2 Michael Addition to Electron-Deficient C=C Bonds. In order to test the viability of chiral thioureas **2a**–**2d**, the electrophile of choice was nitroolefin, since nitrobenzene derivatives were shown to exhibit eight-membered hydrogen bonding with diarylthiourea by co-crystallization experiments.[4g] To compare the reactivity and selectivity between thiourea and amide, amide **2e** was also prepared. We first explored the Michael reactions[12] of β-nitrostyrene (**3**) with diethyl malonate (**4**) as a nucleophile which would be deprotonated by the tertiary amino group (Table 1).[10] Reaction was carried out in toluene with 2 equiv of diethyl malonate (**4**) and 10 mol % of catalysts **2a**–**2e**. As expected, thiourea **2a** gave the best results in terms of chemical yield and enantioselectivity (Entry 1). These results indicated that both rigidity of the chiral diamine scaffold and cooperative function of two N–H bonds and the tertiary amino group in the catalyst were crucial for the enantioselective Michael reaction (Entries 1–5). Further studies on the Michael addition demonstrated that 1,3-diketones and β-ketoesters could be used as a nucleophile.

Table 1. Michael Addition to β-Nitrostyrene (**3**) Catalyzed **2a**–**2e**[a)]

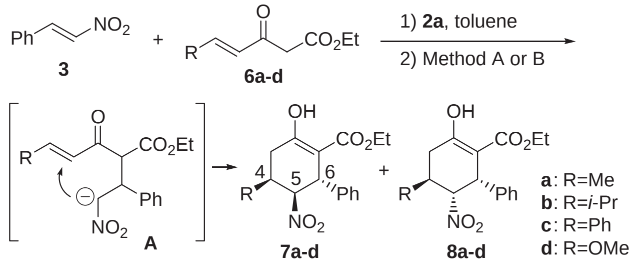


Entry	Thiourea	Time/h	Yield/%	ee/%
1	**2a**	24	86	93
2	**2b**	48	56	84
3	**2c**	48	52	64
4	**2d**	48	58	80
5	**2e**	24	14	35

a) Reaction was carried out in the presence of catalyst (10 mol %) in toluene.

The catalytic tandem construction of multiple stereogenic centers is a challenging problem.[13] In particular, the development of efficient methods using organocatalysts has been of great importance from both economic and environmental points of view. For this purpose, we next investigated a tandem Michael addition of γ,δ-unsaturated β-ketoesters **6a**–**6d** to β-nitrostyrene (**3**) for providing valuable building blocks for organic synthesis (Table 2).[14] Reaction of **6a** was carried out in toluene with 10 mol % of catalysts **2a** at room temperature (Entry 1). The reaction of **6a** proceeded cleanly to provide the tandem Michael adduct **7a** as a single product in 65% yield with 86% ee. The result demonstrates that the bifunctional thiourea **2a** catalyzed both the inter- and intramolecular Michael additions. Unfortunately, the same treatment of **6b** bearing a more bulky isopropyl group as that of **6a** provided only Michael adduct **A** but not **7b**. After several experiments, we found that the subsequent treatment of the obtained Michael adducts with 0.1 equiv of 1,1,3,3-tetramethylguanidine (TMG) (Method A) or with 0.1 equiv of KOH (Method B) gave rise to the desired 5,6-anti-4,5-syn products **7a**–**7d** with good diastereoselectivities (Entries 2–7). Based on these results, it was revealed that the high diastereoselectivity of the intramolecular Michael addition would be attributed to the reaction substrates, but not to the catalysts employed. Reexamination of the reaction of **6a** using Method A revealed that **7a** could be prepared as a single product with higher enantioselectivity than that obtained by the one-pot method (Entries 1 and 2). The reaction of phenyl-substituted derivative **6c** gave a mixture of diastereoisomers **7c** and **8c** in a ratio of 95/5 by Method A (Entry 4). Similarly, the methoxy-substituted derivative **6d** afforded an 82/18 mixture of **7d** and **8d** (Entry 5). Since the diastereomers **8c** and **8d** seemed to be generated by a base-catalyzed epimerization of the major products **7c** and **7d**, we screened a variety of bases. Consequently, replacement of TMG with KOH in ethanol was revealed to suppress the epimerization, affording **7c** and **7d** in good yield as a single isomer, respectively (Entries 6 and 7). It is worthy to note that this was the first report of successful asymmetric synthesis of three contiguous stereogenic centers by the tandem Michael reaction with nitroalkenes.

Table 2. Tandem Michael Addition to β-Nitrostyrene (**3**) Catalyzed Thiourea **2a**



Entry	Substrate	T/°C	Method	Yield/%	de/%	ee/%
1	**6a**	rt	—[a)]	65	>99	86
2	**6a**	−20	A[b)]	87	>99	92
3	**6b**	rt	A[b)]	71	>99	88
4	**6c**	−40	A[b)]	79	90	89
5	**6d**	rt	A[b)]	63	64	85
6	**6c**	−40	B[c)]	62	>99	92
7	**6d**	rt	B[c)]	79	>99	84

a) Reaction was carried out without any base. b) Method A: TMG (0.1 equiv), CH_3CN, 0 °C. c) Method B: KOH (0.1 equiv), EtOH, 0 °C.

The stereoselective formation of **7a–7d** is rationally explained by considering the transition state **B** shown in Figure 2. The transition state **B**, giving the major adducts **7a–7d**, would be energetically more stable than the other transition state **C**, giving the minor adducts **8a–8d**, due to the steric hindrance between the phenyl ring and the nitronate anion.

Having established the two-step procedure to synthesize chiral 4-nitrocyclohexanones, we next applied this manipulation to the total synthesis of (−)-epibatidine, an alkaloid isolated from the skin of the Ecuadorian frog *Epibatidores tricolor* in 1992 by Daly et al. (Scheme 1).[15] Treatment of nitroolefin **9** and unsaturated β-ketoester **10** under the Method B conditions afforded the cyclic product **12** in 77% yield via Michael adduct **11**. Although the ee of **12** was revealed to be only 75%, the enantiomeric excess was improved to 99% by recrystallization of **13**, which was obtained from **12** by Pd-catalyzed decarboxylation, stereoselective hydride reduction of ketone, and elimination of methanol. To complete the total synthesis of (−)-epibatidine, we undertook the 1,4-hydride reduction of nitrocycloalkene **13** with $NaBH_3CN$, mesylation, and reduction with zinc dust, giving the final compound (−)-epibatidine as a single product.

Bifunctional thiourea **2a** could be expected to activate an imide moiety through double hydrogen-bonding interaction in a similar manner as the nitro group of nitroolefin. Therefore, we next investigated the enantioselective Michael addition of malononitrile to α,β-unsaturated carboxylic acid derivatives having imide moiety (Table 3).[16,17] Among several α,β-unsat-

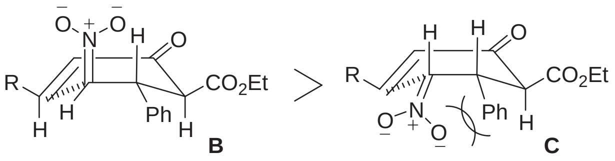
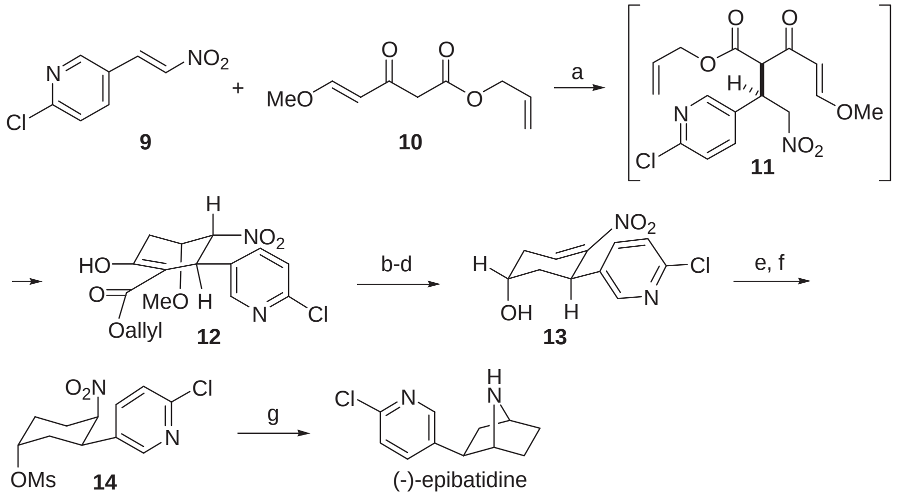
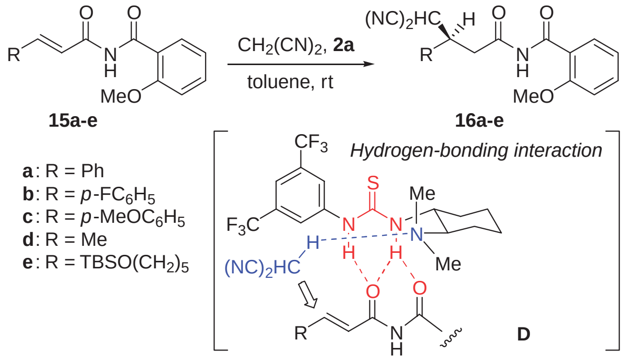


Figure 2. Diastereoselective formation of **7a–7d**.



Scheme 1. Synthesis of (−)-epibatidine using tandem Michael addition. Reagents and conditions: a) **2a**, toluene; KOH, EtOH, 77% (75% ee); b) $Pd(OAc)_2$, PPh_3, HCO_2H, Et_3N, THF, 99%; c) L-Selectride, THF, 71%; d) NaOMe, *t*-BuOH, 71%; e) $NaBH_3CN$, AcOH, MeOH, 87% (β-NO_2-isomer/α-NO_2-isomer = 9/1); f) MsCl, Et_3N, DMAP, CH_2Cl_2, 91%; g) Zn, AcOH, THF, 85%.

Table 3. Michael Addition to *N*-Acylamides **15a**–**15e** Catalyzed by Thiourea **2a**[a)]



Entry	*N*-Acylamide	Time/h	Yield/%	ee/%
1	**15a**	14	95	91
2	**15b**	7	99	92
3	**15c**	24	92	90
4	**15d**	3	96	90
5	**15e**	5	95	93

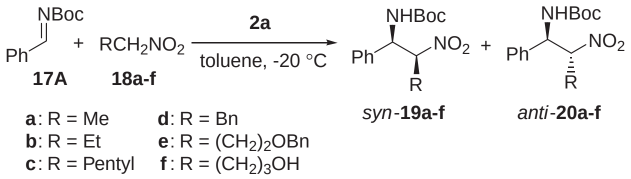
a) Reaction was carried out in the presence of catalyst **2a** (10 mol %) in toluene.

urated acid derivatives investigated, *N*-acyl-2-methoxybenzamide **15a** exhibited high reactivity. The reaction of **15a** was complete after 14 h to afford the desired product **16a** in 95% yield with 91% ee (Entry 1). The reaction could be applied to a wide range of substrates **15b**–**15e** bearing various β-substituents (Entries 2–5). Furthermore, functionalized nucleophiles such as $CH_2(CN)(CO_2Me)$ and CH_3NO_2 worked well under similar reaction conditions. The reaction could take place via the transition state **D**, where a nucleophile, activated by the amino group of **2a**, can attack the β-position of the imide.

2.3 Addition to Electron-Deficient C=N and N=N Bond. The development of stereoselective carbon–carbon bond-forming reactions that create contiguous stereogenic centers bearing heteroatom functionality can provide valuable building blocks for organic synthesis. To extend the synthetic versatility of the thiourea-catalyzed reactions, we next investigated nucleophilic addition to electron-deficient C=N and N=N bonds. Recently, several studies on nucleophilic reaction with imines have been reported.[8]

The aza-Henry (nitro-Mannich) reaction, that is, nucleophilic addition of nitroalkanes to imines, is a useful carbon–carbon bond-forming process.[18] The obtained β-nitroamines can be transformed into valuable compounds such as vicinal diamines and α-amino acids by reduction and Nef reaction of the nitro moiety. We envisaged that the desired nitronate anion could be produced from nitroalkane with the bifunctional thiourea **2a** via hydrogen-bonding activation by the thiourea moiety and subsequent deprotonation by the neighboring tertiary amino group.[19] Our initial experiments showed that thiourea **2a** catalyzed the aza-Henry reaction of nitromethane with *N*-Boc-imines (Boc = *t*-butoxycarbonyl) to give the adduct with high enantioselectivity. On the basis of the above results, the reaction of *N*-Boc-imine **17A** with prochiral nitroalkanes **18a**–**18f** was explored to prepare useful chiral building blocks having contiguous stereogenic centers (Table 4). As expected, the reaction proceeded in a diastereo- and enantioselective manner, and the corresponding *syn*-β-nitroamines **19a**–**19f** were always obtained as major products. Thiourea **2a** efficiently promoted the reaction of nitroethane **18a** to furnish a mixture of β-nitroamines **19a** and **20a** in 92% yield with good diastereoselectivity (*syn*-**19a**/*anti*-**20a** = 90/10) (Entry 1). In addition, the enantioselectivity of the major product *syn*-**19a** was high (93% ee). Various types of nitroalkanes bearing aryl, alcohol, ether, and ester groups can be used as nucleophiles (Entries 2–6).

Table 4. Aza-Henry Reaction of Imine **17** Catalyzed Thiourea **2a**[a)]



Entry	Nitroalkane	Yield/%	dr	ee/%
1	**18a**	92	90:10	93
2	**18b**	90	88:12	95
3	**18c**	82	93:7	99
4	**18d**	84	83:17	97
5	**18e**	86	93:7	94
6	**18f**	80	92:8	89

a) Reaction was carried out in the presence of catalyst **2a** (10 mol %) in toluene.

To account for the current highly stereoselective reaction, we propose a ternary complex **H** of catalyst **2a**, imine, and nitronate as a plausible transition state, which can be considered to be generated through route a or route b (Figure 3). In any event, the thiourea moiety would play a crucial role in activation of *N*-Boc-imine **17A** in the nucleophilic addition step and/or nitroalkanes **18a**–**18f** in the deprotonation step.

Synthetic versatility of the addition products is demonstrated by the transformation to chiral piperidine derivatives such as CP-99,994 (Scheme 2). Mesylate **21** was treated with *N*-Boc-imine **17A** in the presence of thiourea **2a** (10 mol %) to give aza-Henry adducts as a mixture of diastereomers (**22**/**23** = 86/14). The enantiomeric excesses of **22** and **23** were 96% ee and 83% ee, respectively. Removal of the *N*-Boc group and subsequent treatment with aqueous K_2CO_3 gave the cyclized products **24** as a 9/1 mixture of trans and cis isomers. The synthesis of CP-99,994 was achieved in three-steps from products **24** via epimerization of the C3-position, reduction of the nitro group, and reductive amination of *o*-anisaldehyde.

In recent years, enantioselective direct Mannich reaction has attracted much attention in approaches toward chiral β-amino acid derivatives.[20,21] We became interested in the possibility of using thiourea **2a** in direct Mannich reactions and investigated the catalytic activity of **2a** in the reaction of imines with malonate **4** (Table 5).[22] Among the several imines examined, *N*-Boc-imine **17A** worked well to give the product **25A** with 88% ee after being stirred at room temperature for 24 h (Entry 1). The degree of selectivity was shown to be dependent on the reaction temperature; thus, changing the temperature from

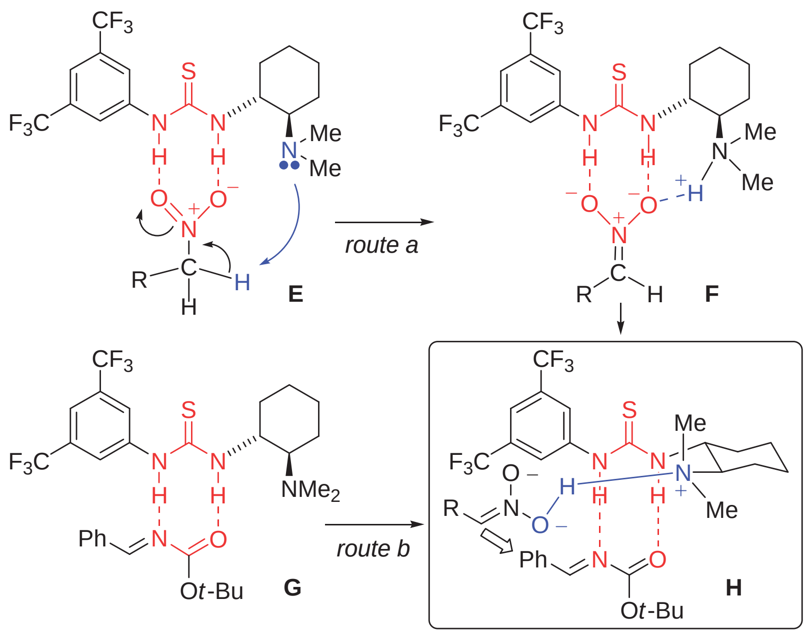
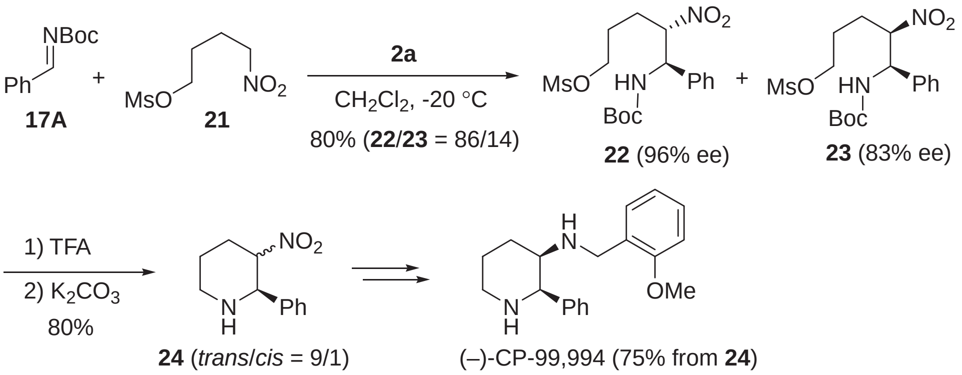
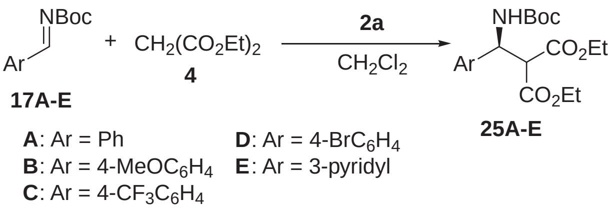


Figure 3. Proposed reaction process.



Scheme 2. Synthesis of (−)-CP-99,994.

Table 5. Direct Mannich Reaction Catalyzed by Thiourea **2a**[a)]



A: Ar = Ph
B: Ar = 4-MeOC$_6$H$_4$
C: Ar = 4-CF$_3$C$_6$H$_4$
D: Ar = 4-BrC$_6$H$_4$
E: Ar = 3-pyridyl

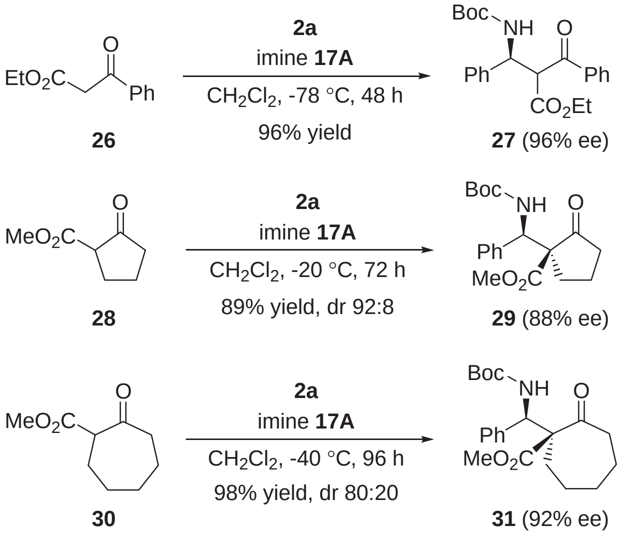
Entry	Imine	T/°C	Time/h	Yield/%	ee/%
1	**17A**	rt	24	77	88
2	**17A**	0	48	84	94
3	**17B**	−20	72	82	93
4	**17C**	−78	24	91	96
5	**17D**	−78	24	84	98
6	**17E**	−78	48	73	97

a) Reaction was carried out in the presence of catalyst **2a** (10 mol %) in CH$_2$Cl$_2$.

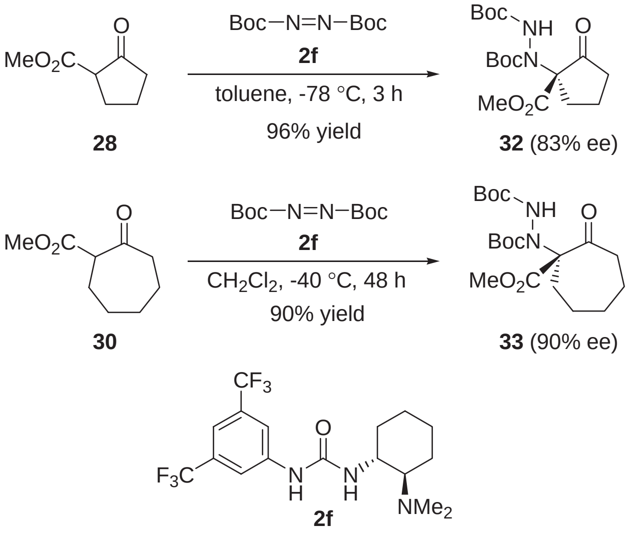
room temperature to 0 °C led to a moderate increase in enantioselectivity to 94% ee (Entry 2). Excellent chemical yield and high enantioselectivity were also obtained in the reaction of other *N*-Boc-imines **17B–17E** (Entries 3–6).

Asymmetric Mannich reaction with an unsymmetrical nucleophile allows the generation of two stereogenic centers in a single carbon–carbon bond-forming process; thus, the control of both enantio- and diastereoselectivities is a challenging task. Next, we tried the reaction with prochiral nucleophile **26** (Scheme 3). Although the adduct **27** was obtained with excellent ee, valuable diastereoselectivity was not observed probably due to epimerization. Therefore, we next focused on reaction with cyclic 1,3-dicarbonyl compounds **28** and **30** having a substituent at the 2-position. As expected, thiourea **2a** worked well as an effective catalyst for the control of both enantio- and diastereoselectivities to give adducts **29** and **31** with good selectivities.

From the viewpoint of development of neuroactive glutamate analogs, cyclic α-amino acids have attracted great attention. The highly enantioselective amination of β-ketoesters or



Scheme 3. Direct Mannich reaction with unsymmetrical nucleophiles.



Scheme 4. Hydrazination catalyzed thiourea **2f**.

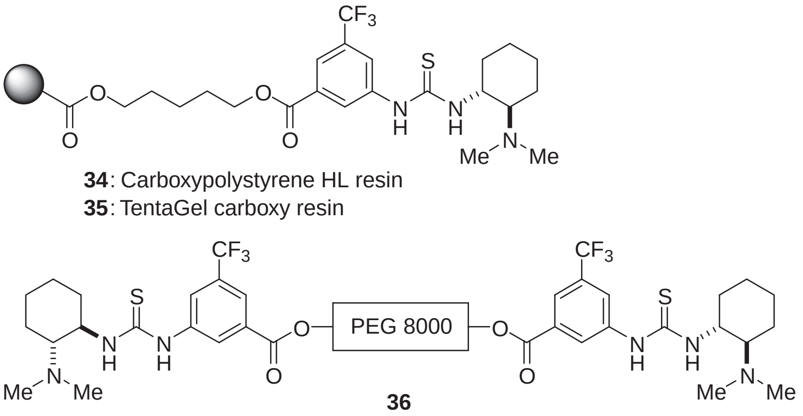


Figure 4. Polymer-supported thiourea catalysts.

α-cyanoesters have been reported.[23] In contrast, to the best our knowledge, the use of cyclic β-ketoesters has met with limited success in organocatalytic α-hydrazination.[24] The hydrazination of ketoesters was examined by using di-*tert*-butyl azodicarboxylate (Scheme 4).[25] We found that the urea **2f** was preferred for this reaction due to the instability of thiourea **2a** under the reaction conditions. The cyclic 1,3-dicarbonyl compounds **28** and **30** were reacted well, giving the corresponding addition products **32** and **33** with good enantioselectivities.

3. Catalysts Anchored to Polymer Support

The thiourea-catalyzed reactions suffered from the difficulty of recovering thiourea catalyst **2a**. Immobilization facilitates the recovery and reuse of catalyst from the reaction mixture. Therefore, we next planned to develop a new and effective thiourea catalyst anchored to polymer support.[26]

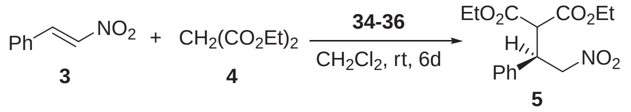
To attach the thiourea to polymer supports, an ester moiety was introduced in place of the trifluoromethyl group of original thiourea **2a** (Figure 4). At first, we used cross-linked polystyrene such as carboxypolystyrene HL resin and TentaGel carboxy resin purchased from Novabiochem. To enhance the catalytic activity of resin-bound thioureas, we introduced a spacer generated from 1,5-pentanediol. The resin-bound catalysts **34** and **35** were prepared in ca. 0.79 and ca. 0.19 $\mathrm{mmol\,g^{-1}}$ loading levels, respectively, which were determined by quantification of fluoride by elemental analysis. Since soluble non cross-linked polymer supports offer certain advantages over insoluble polymers in terms of ease of analysis and the establishment of homogeneous conditions, a soluble immobilizing catalyst **36** was also prepared by directly connecting two amino thiourea moieties to poly(ethylene glycol) (PEG 8000). The purity of the catalyst was determined to be ca. 80% by ^{1}H NMR analysis.

The viability of thioureas **34**–**36** as catalysts was the next focus of our efforts; thus, the catalytic enantioselective Michael addition to β-nitrostyrene (**3**) was investigated (Table 6). The resin-bound catalysts **34** and **35** showed lower catalytic activities as compared with soluble immobilizing catalyst **36**. It is assumed that the difference of activity between **34** and **35** was attributed to the difference of their loading levels. The catalytic activity of **36** was enhanced under homogeneous conditions using CH_2Cl_2 as solvent. The Michael reaction of **3** with diethyl malonate afforded the Michael adduct

(*S*)-**5** in 71% yield with 86% ee, after being stirred at room temperature for 6 days (Entry 4). Furthermore, the tedious workup to recover the catalyst was eliminated in the polymer support methodology. The catalyst **36** was solidified by the addition of diethyl ether and reused without further treatment after recovery by filtration. In the repeated use of the recovered catalyst, (*S*)-**5** was obtained in 74% yield with 90% ee.

Tandem Michael reaction of **3** also proceeded smoothly to give the cyclic product **7a** in 63% yield with 76% ee. The catalyst **36** was reused for the second and third reactions, affording **7a** in 64% yield with 76% ee and in 63% yield with 79% ee, respectively (Scheme 5).

Table 6. Michael Addition to β-Nitrostyrene (**3**) Catalyzed Thiourea **34–36**[a)]



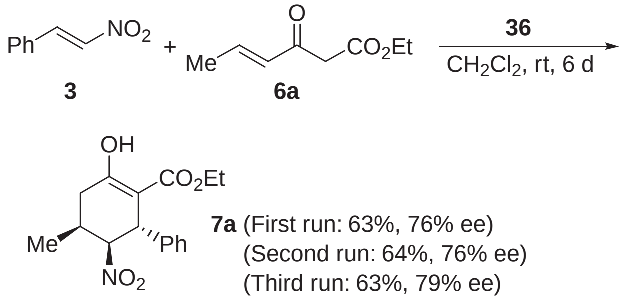
Entry	Thiourea	Yield/%	ee/%
1	**34** (First run)	37	87
2	**34** (Second run)	25	85
3	**35** (First run)	4	88
4	**36** (First run)	71	86
5	**36** (Second run)	74	90

a) Reaction was carried out in the presence of catalyst (10 mol %) in CH_2Cl_2 for 6 days.

4. Catalysts Having a Chelating Functionality

4.1 Design of New Thiourea Catalysts. Our laboratory introduced the chiral thioureas **2a** and **36** as a bifunctional organocatalyst. These catalysts accelerated the aza-Henry reaction and the Michael reaction of nitroolefins or α,β-unsaturated imides as a result of dual activation of electrophile and nucleophile. However, the scope of suitable nucleophiles for catalysts **2a** and **36** was mainly limited to active methylene compounds. Therefore, we have designed new catalysts having a chelating functionality, which might activate metallic nucleophiles (Figure 5).

The use of organoboronic compounds has many advantages in organic synthesis from both economical and environmental points of view. As a modern variation of the Mannich reaction using organoboronic acids, the Petasis reaction has recently been of great importance in synthetic chemistry.[27,28] The standard Petasis reaction is a three-component condensation of amine, aldehyde, and vinyl- or arylboronic acid (Figure 6). However, the full potential of this reaction remains unrealized, and its stereocontrol is a subject of current interest. Studies on asymmetric induction have achieved some remarkable success, particularly in diastereoselective processes using chiral α-hydroxyaldehydes.[29] However, there are no reports on catalytic enantioselective processes using chiral catalysts. In the Petasis reaction, the formation of reactive "ate" complex such as **I** is assumed to play an important role for the reactivity and selectivity. On the basis of this mechanism, we considered that the



Scheme 5. Tandem reaction catalyzed thiourea **36**.

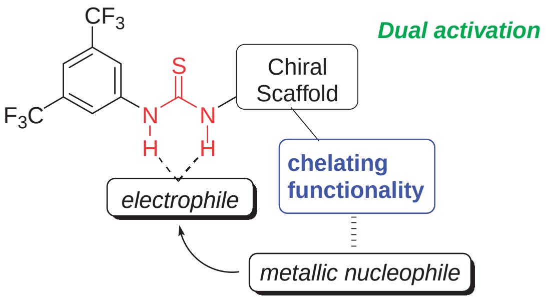


Figure 5. Newly designed catalysts.

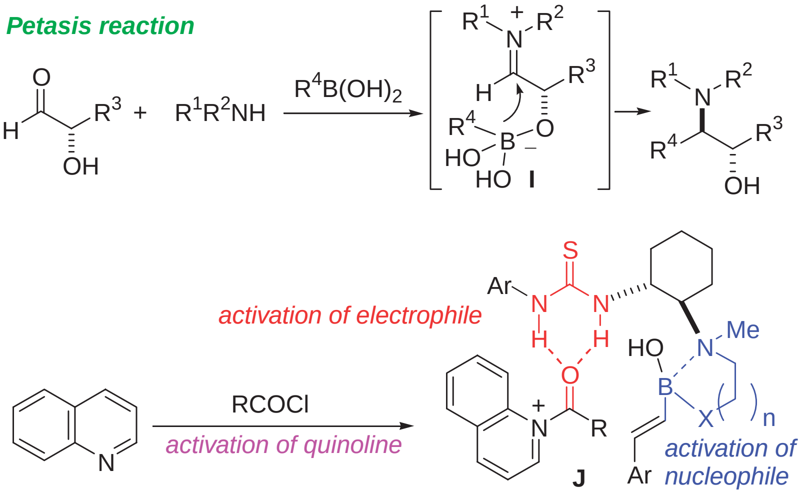


Figure 6. Concept of new catalyst for Petasis-type reaction.

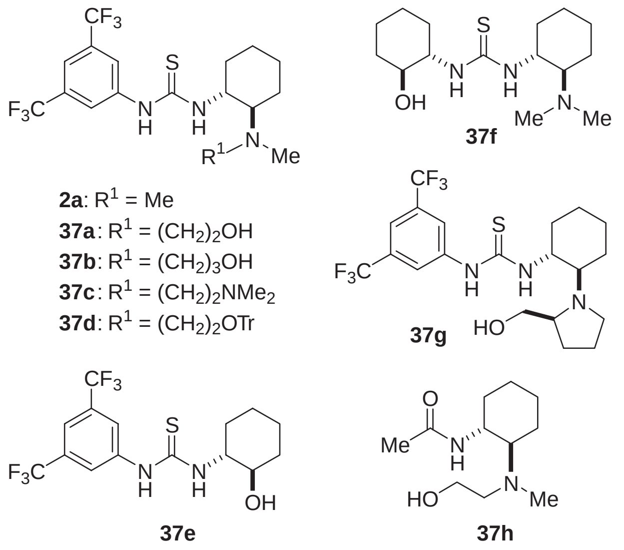


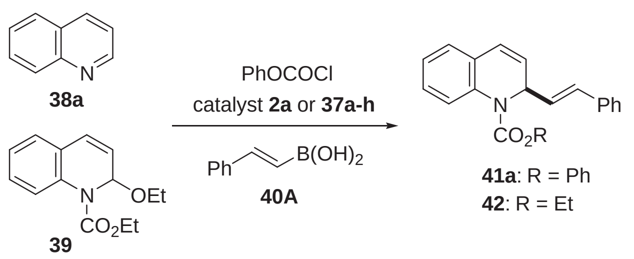
Figure 7. Newly designed catalysts **37a–37h**.

catalytic generation of a chiral ternary complex **J** from catalyst, electrophile, and organoboronic acids would be crucial for the success of enantioselective transformations. We studied the enantioselective reaction of activated quinolines with vinyl boronic acid.[30,31] In our concept, the thiourea moiety of the catalyst acts as a Brønsted acid and activates electrophiles such as N-acylated quinolinium salts.[32] We also expected that the thiourea moiety controls the distribution of s-trans/s-cis isomers of the amide bond in *N*-phenoxycarbonyl quinolinium salt. Additionally, the greater reactivity of catalyst-activated electrophiles and organoboronic acids could enable reaction at low temperatures.

Our newly designed catalyst **37a–37h** has a chiral chelating aminoalcohol functionality, which could activate the organoboronic acids by coordinating to the boron center and direct the stereochemical outcome of the reaction (Figure 7).[33]

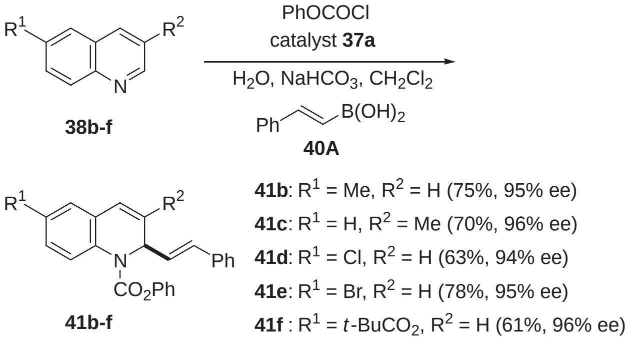
4.2 Petasis-Type Transformation of Quinolines. We first explored the utility of new functionalized catalysts **37a–37h** in the transformation of quinoline **38a** with vinylboronic acid **40A** into 1,2-adduct (Table 7).[34,35] As an activating reagent, the addition of phenyl chloroformate (2 equiv) promoted the reaction at −65 °C, while practically no reaction occurred in the absence of activating reagent. A protic solvent such as EtOH increased the addition rate, although no enantioselectivity was observed. Good stereocontrol was achieved with the use of aprotic and nonpolar solvents such as CH_2Cl_2 and toluene; thus reactions were run in CH_2Cl_2 at −65 °C for 24 h. Original catalyst **2a** could not be applied to stereocontrol in enantioselective Petasis processes (Entry 1). In contrast, the use of new thiourea **38a** with an α-aminoalcohol functionality (10 mol %) increased the chemical efficiency to give the 1,2-adduct **41a** in 70% yield with 90% ee without formation of a 1,4-adduct (Entry 2). The activating reagent affected the enantioselectivity. The addition of EtOCOCl, BnOCOCl, AcCl, BzCl, Tf_2O, Ac_2O, and Boc_2O instead of phenyl chloroformate led to lower ee. Although the dihydroquinoline **39** showed excellent reactivity toward **40A**, stereocontrol was not achieved and the racemic product **42** was obtained in 68% yield (Entry 3).[36] Several catalysts **37b–37h** were also tested to determine the role of the aminoalcohol moiety (Entries 4–10). An α-aminoalcohol functionality on the catalyst was necessary for valuable stereocontrol, as shown in the reaction with catalyst **37g** as well as **37a** (Entry 9). The effect of a thiourea moiety in catalysts was confirmed by using the simple 1,2-amino alcohol catalyst **37h** (Entry 10). As expected, catalyst **37h** also showed excellent catalytic activity in this process, although the enantioselectivity was decreased. The addition of H_2O as a proton source increased the enantioselectivity with a decrease in the yield (Entry 11), and the combination of H_2O and $NaHCO_3$ improved the chemical yield (Entry 12). The remarkable effect of H_2O and $NaHCO_3$ is assumed to be the in situ regeneration of catalyst **37a** promoted by a proton source and removal of the resulting boronic acid by base.

Table 7. Petasis-Type Reaction Using Catalysts **2a** and **37a–37h**[a]



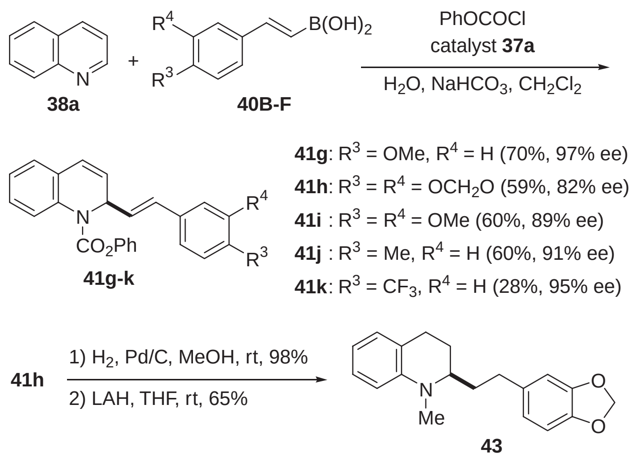
Entry	Catalyst	Substrate	Additive	Yield/%	ee/%
1	**2a**	**38a**	none	34	−9
2	**37a**	**38a**	none	70	90
3[b]	**37a**	**39**	none	68	rac
4	**37b**	**38a**	none	47	27
5	**37c**	**38a**	none	31	4
6	**37d**	**38a**	none	44	rac
7	**37e**	**38a**	none	33	rac
8	**37f**	**38a**	none	57	rac
9	**37g**	**38a**	none	60	68
10	**37h**	**38a**	none	70	50
11	**37a**	**38a**	H_2O	27	93
12	**37a**	**38a**	H_2O and $NaHCO_3$	65	94

a) Reaction was carried out in the presence of catalyst (10 mol %) in CH_2Cl_2 at −65 °C. b) Reaction was carried out without PhOCOCl.



Scheme 6. Reaction of **38b–38f** with **40A** using catalyst **37a**.

An outstanding level of enantioselectivity was also achieved in the reaction of other quinolines **38b–38f** (Scheme 6). Under analogous conditions, the reaction of quinoline **41c** proceeded



Scheme 7. Reaction of **38a** with **40B–40F** using catalyst **37a**.

smoothly despite the presence of a methyl group at the 3-position. The reaction of quinolines is frequently plagued by the generation of regioisomeric 1,2- and 1,4-adducts; thus, it is also specifically noteworthy that this reaction provides a powerful method for the enantio- and regioselective synthesis of 1,2-adduct.

Various boronic compounds **40B–40F** were tested (Scheme 7). The reaction with electron-rich boronic acids took place even at −78 °C to give the adducts **41g–41i**. Although the formation of **41k** which has an electron-withdrawing substituent was remarkably diminished, a high degree of stereocontrol was achieved. The absolute configuration was determined by converting the adduct **41h** into (+)-galipinine (**43**).

5. Conclusion and Outlook

Chiral amino thiourea catalyzed asymmetric additions of several nucleophiles to electron-deficient unsaturated compounds such as nitroolefins, α,β-unsaturated imides, imines, and azodicarboxylates. The structure–activity relationship of amino thiourea catalysts revealed that thiourea **2a** was the best catalyst for accelerating the reaction with various active methylenes such as malonates, β-ketoesters, 1,3-diketones, nitroalkanes, malononitrile, and so on. In these reactions, a strong hydrogen-bonding ability of the thiourea moiety as well as an appropriate Brønsted basicity of the tertiary amine would be crucial for high enantioselectivity. Furthermore, immobilization of chiral thiourea catalyst was studied. The PEG-bound thiourea showed better catalytic activity than those bound to carboxypolystyrene HL resin and TentaGel carboxy resin. In the presence of PEG-bound thiourea, Michael and tandem Michael reactions of *trans*-β-nitrostyrene proceeded enantioselectively.

New catalysts having a chelating functionality, which activates a metallic nucleophile, were designed and synthesized. An organocatalyst **37a** provided sufficient activation of organoboronic acids to facilitate stereocontrol in the Petasis transformation of quinolines as a result of the catalytic generation of a chiral complex as well as the dual activation of an electrophile and nucleophile.

From the standpoint of sustainable chemistry, these organocatalyst-mediated reactions would be desirable tools for preparing organic compounds and therefore, more sophisticated multi-functional organocatalysts should be created for the development of new methodologies for multi-component and tandem reactions.

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