Review

Development of Chiral Thiourea Catalysts and Its Application to Asymmetric Catalytic Reactions

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We have developed several multifunctional thiourea catalysts bearing a tertiary amine or an 1,2-amino alcohol in expectation of their synchronous activation of a nucleophile and an electrophile through both acid-base and hydrogen-bonding interactions. From these studies, it was revealed that the weak acidity of thioureas compared with metallic Lewis acids could be overcome by this modification. The bifunctional aminothiourea could be used efficiently for a wide range of diastereoselective and enantioselective nucleophilic reactions such as Michael addition of 1,3-dicarbonyl compounds to nitroolefines, aza-Henry reaction of nitroalkanes to *N*-Boc imines, and hydrazination of cyclic β-keto esters. We also discovered that multifunctional thiourea catalyst, bearing an 1,2-amino alcohol moiety, significantly accelerated the Petasis-type reaction of alkenylboronic acids to *N*-phenoxycarbonyl quinolinium salts, prepared from quinolines and phenyl chloroformate, to afford 1,2-addition products with high enantioselectivity (up to 97% ee). Furthermore, to expand the synthetic applicability of the thiourea-catalyzed asymmetric reactions, tandem organocatalyzed reactions were explored to establish the concise one-pot synthesis of chiral densely functionalized three-, five-, and six-membered compounds.

Key words organocatalyst; asymmetric reaction; thiourea; hydrogen bond; Michael addition; dual activation

1. Introduction

Over the past decade, the research area of asymmetric organocatalysis has grown rapidly to become one of the most exciting current fields in organic chemistry.[1—9] Since small chiral organic molecules act as catalytically active species in asymmetric organocatalysis, these organocatalysts are metal-free, usually nontoxic, readily accessible, and often very robust. A significant advantage of many organocatalysts is the capability of multipoint recognition of substrates similar to enzymes. Thus, there is a lot of interest in organocatalysis not only from academia but also from industry.

The most commonly used organocatalysts such as proline derivatives interact with their substrates *via* a covalent bond. Recently, hydrogen-bond donors such as ureas/thioureas,[10—23] BINOL/diols,[24—32] and phosphoric acids[33—40] have been also recognized as efficient organocatalysts. Novel urea and thiourea derivatives were developed as organocatalysts and their potential as a general acid has been successfully demonstrated by several groups.[41—73] However, their application to enantioselective reactions was somewhat limited in the early stage, because thioureas are weaker acids than metallic Lewis acids. In 2003, we first introduced a chiral bifunctional thiourea bearing a tertiary amino group,[74,75] by which a wide range of asymmetric reactions were dramatically promoted with high enantioselectivity on the basis of the dual-activation protocol[76—80] of electrophile and nucleophile. In this review, we provide a comprehensive overview of our recent studies on bifunctional thiourea-mediated asymmetric nucleophilic reactions.[81—90]

2. Chiral Bifunctional Amino Thiourea-Catalyzed Reactions

At the time we started this study, several enantioselective nucleophilic additions catalyzed by chiral urea/thiourea derivatives had been already reported by Jacobsen's group.[41—44] However, the application of these catalysts to enantioselective reactions was somewhat limited. To enhance the catalytic activity of thiourea catalysts, we designed chiral bifunctional thioureas bearing a tertiary amino group in expectation of their dual activation of both electrophiles and nucleophiles to promote a wide range of nucleophilic addition reactions.

2.1. Preparation of Bifunctional Amino Thiourea Catalysts[8] Based on the results of the reported thiourea-catalyzed reactions,[10—14] a variety of bifunctional amino thioureas such as **2a**—**c** were designed by replacing one of

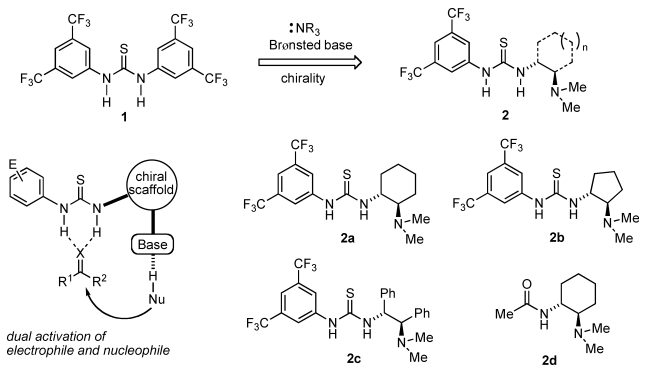

Fig. 1. Concept and Design of Bifunctional Thioureas **2a**—**c** and Amide **2d**

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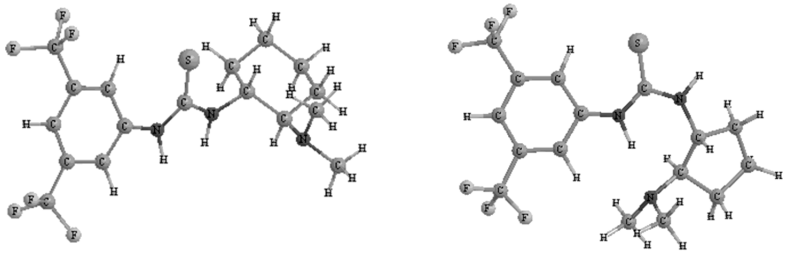
the aryl rings of diaryl thiourea **1** by cyclic and acyclic 2-(*N*,*N*-dimethylamino)ethane derivatives as a chiral scaffold. To compare the reactivity and selectivity between thiourea and amide, bifunctional amide **2d** was also prepared (Fig. 1).

From the X-ray crystallographic structure of **2a**, both the dimethylamino group and the thiourea moiety of **2a** are obviously located in equatorial positions on a chair-formed cyclohexane ring of the catalyst. That means that **2a** has an ideal conformation for the dual activation of both nucleophiles and electrophiles. On the other hand, thiourea **2b** bearing a 2-(*N*,*N*-dimethylamino)cyclopentyl moiety was revealed to possess a different conformation to that of **2a**, where two N–H bonds of thiourea **2b** are oriented toward anti direction due to the intramolecular hydrogen bond between the tertiary amine and the ArN–H group (Fig. 2).

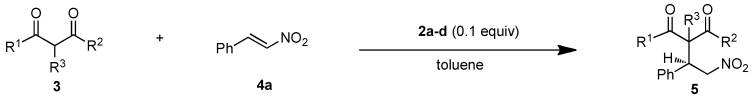
2.2. Enantioselective Michael Addition of 1,3-Dicarbonyl Compounds to Nitroolefins We initially examined the Michael reaction[91—95] of *β*-nitrostyrene **4** with 2 eq of diethyl malonate **3a** in toluene with 10 mol% of catalysts **2a**—**d** (Table 1, entry 1). As expected, thiourea **2a** gave the best results in terms of chemical yield and enantioselectivity. These results indicated that both rigidity of the chiral diamine scaffold and cooperative function of two N–H bonds in the catalyst were crucial for the enantioselective Michael

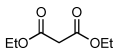
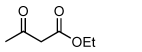
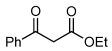
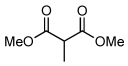
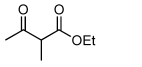
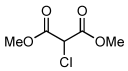
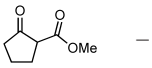
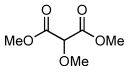
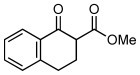


2a **2b**

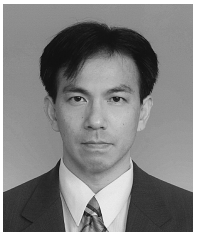
Fig. 2. X-Ray Crystallographic Structure of **2a** and **2b**

Table 1. Thiourea-Catalyzed Michael Addition of 1,3-Dicarbonyl Compounds **3** to *β*-Nitrostyrene **4a**



Entry	Ketoester	Temp. (°C)	Time (h)	Yield (%)	ee (%)	Entry	Ketoester	Temp. (°C)	Time (h)	Yield (%)	de (%)	ee (%)
1		**2a** rt **2b** rt **2c** rt **2d** rt	24 48 48 24	86 56 52 14	93 84 64 35	6		rt	0.5	91	11	89
2		rt	1	80	89	7		−40	14	93	16	94
3		rt	36	82	93	8		rt	6	89	55	91
4		rt	1	Quant.	89	9		−50	24	96	85	93
5		rt	28	89	94	10		rt	2	97	90	90

Yoshiji Takemoto is Professor of the Graduate School of Pharmaceutical Sciences at Kyoto University. He was born in Osaka in 1960 and received his BSc (1983) and PhD (1988) from Osaka University. After working as a postdoctoral fellow with Prof. R. A. Holton at Florida State University from 1988 and with Dr. S. Terashima at Sagami Chemical Research Center from 1989, he joined the Faculty of Pharmaceutical Sciences, Osaka University, as an Assistant Professor in 1990. He moved to the Graduate School of Pharmaceutical Sciences, Kyoto University, as an Associate Professor in 1998 and was promoted to Professor in 2000. He has been awarded the Takeda Award in Synthetic Organic Chemistry, Japan (1992), Thomson Scientific Research Front Award (2007), and The PSJ Award for Divisional Scientific Promotions (2009). His research interests are in the areas of transition-metal chemistry, organocatalyst chemistry, and the total synthesis of natural products.



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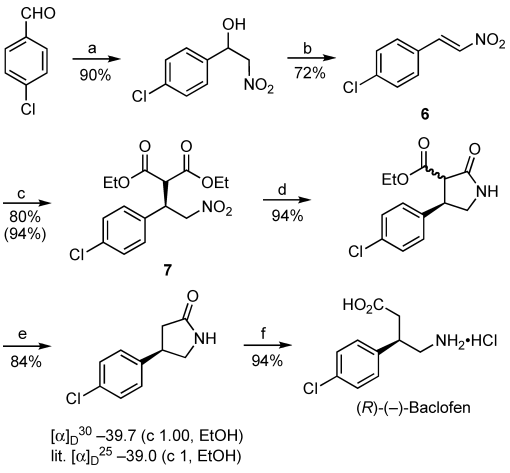
reaction. In addition, 1,3-diketone and β-ketoesters as well as α-substituted malonates could be used as a nucleophile to give the corresponding adducts **5** in good yields with 89—94% ee (entries 2—7). It should be noted that the reaction with prochiral nucleophiles such as α-substituted β-ketoesters also occurred in good diastereoselective and enantioselective manner, resulting in the construction of contiguous stereogenic centers containing a chiral quaternary carbon (entries 8—10).

Baclofen is a lipophilic analog of GABA (γ-aminobutylic acid) that is widely used as an antispastic agent. Although baclofen is commercialized in its racemic form, it has been reported that its biological activity resides exclusively in the (*R*)-enantiomer. We therefore applied the Michael reaction for the synthesis of (*R*)-(−)-baclofen (Chart 1). The reaction of 4-chlorobenzaldehyde with nitromethane and subsequent dehydration of the resultant alcohol provided nitroolefin **6**, which was reacted with diethyl malonate in the presence of 10 mol% of **2a** to afford the adduct **7** in 80% yield with 94% ee. Enantiomerically pure **7** (>99% ee) was obtained after single recrystallization from hexane and EtOAc. Reduction of **7** with nickel borite was followed by successive hydrolysis with NaOH and 6 N HCl, affording enantiomerically pure (*R*)-(−)-baclofen as its hydrochloric salt with 38% overall yield in 6 steps from 4-chlorobenzaldehyde.



Reagents and Conditions: (a) $MeNO_2$, NaOMe, MeOH, rt, 15 h; (b) MsCl, Et_3N, THF, rt, 1 h; (c) Diethyl malonate, **2a**, toluene, rt, 24 h (>99% ee after single recrystallization from Hexane/AcOEt); (d) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, rt, 7.5 h; (e) NaOH, EtOH, rt, 45 h; then toluene, reflux, 6.5 h; (f) 6N HCl, reflux, 24 h.

Chart 1. Total Synthesis of (*R*)-Baclofen

3. Chiral Multifunctional Thioureas with Coordinating Ability

As described above, our laboratory introduced the chiral aminothiourea **2a** as a bifunctional organocatalyst. Although the catalyst efficiently accelerated a variety of asymmetric reactions such as Michael addition, aza-Henry reaction, Mannich reaction, and hydrazination as a result of dual activation of electrophile and nucleophile,[81—90] the scope of suitable nucleophiles for catalysts **2a** was mainly limited to active methylene compounds. We therefore turned our attention toward the development of new catalysts having coordinating or chelating functionality, which might activate metallic nucleophiles.

3.1. Design of New Thioureas Bearing 1,2-Amino Alcohol Among organometallic reagents, organoborones have many advantages in organic synthesis from both economical and environmental points of view. We chose the Petasis reaction as a case study. The standard Petasis reaction is a three-component condensation of amine, aldehyde, and vinyl or aryl boronic acid (Fig. 3).[96—100] Although studies on asymmetric induction have achieved some remarkable success, particularly in diastereoselective processes using chiral α-hydroxyaldehydes,[101—104] there are no reports on catalytic enantioselective processes using chiral catalysts. On the basis of this mechanism, we designed a new thiourea bearing a 1,2-amino alcohol, which can coordinate to organoboronic acids. The resulting chiral binary complex **A** generated from catalyst and organoboronic acids would be capable of capturing a substrate by two-point recognition through the double hydrogen bonding and Lewis acid–Lewis base interaction. Moreover, by forming the ternary complex **B** consisting of *N*-acylquinolinium salt and **A**, the R group of organoboronic acid would be transferred to the coordinated substrate smoothly and stereoselectively as in an intramolecular reaction.

3.2. Petasis-Type Transformation of Quinolines We studied the enantioselective reaction of activated quinolines with styryl boronic acids.[105—110] In our concept, the thiourea

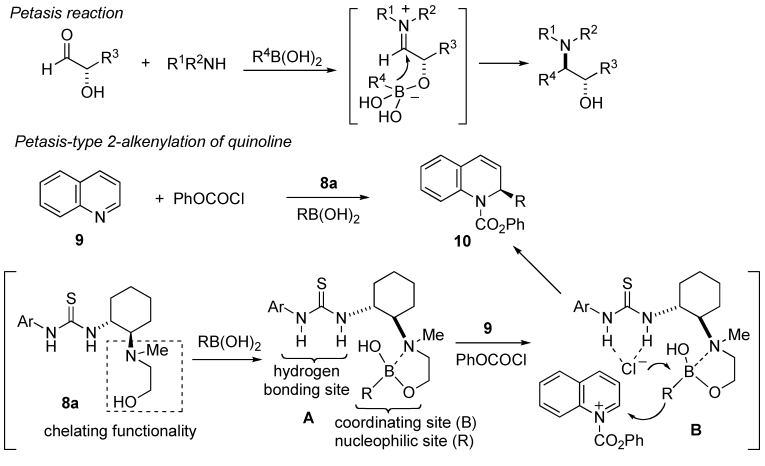


Fig. 3. Concept and Design of New Thiourea Catalyst for Petasis-Type Reaction

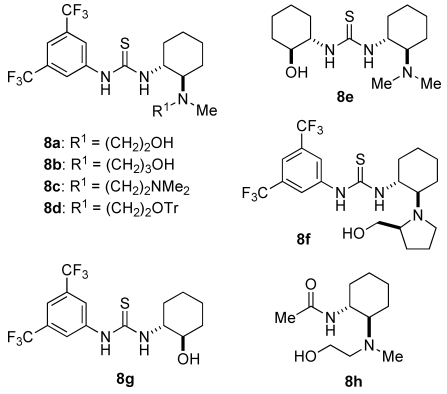
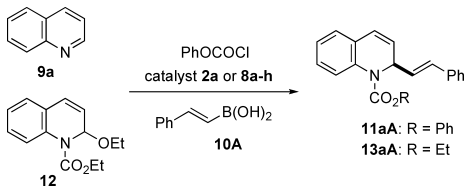


Fig. 4. Newly Designed Catalysts **8a**—**h**

Table 2. Petasis-Type Reaction of Quinoline Using Various Catalysts **2** and **8**[a)]



Entry	Substrate	Catalyst	Yield (%)	ee (%)
1	**9a**	**2a**	34	−9
2	**9a**	**8a**	70	90
3	**9a**	**8b**	47	27
4	**9a**	**8c**	31	4
5	**9a**	**8d**	44	rac
6	**9a**	**8e**	33	rac
7	**9a**	**8f**	57	rac
8	**9a**	**8g**	60	68
9	**9a**	**8h**	70	50
10[b)]	**12**	**8a**	68	rac
11[c)]	**9a**	**8a**	27	93
12[d)]	**9a**	**8a**	65	94

a) Reaction was carried out in the presence of catalyst (10 mol%) in CH_2Cl_2 at −65 °C. *b*) Without PhOCOCl. *c*) Addition of H_2O (CH_2Cl_2 : H_2O = 10 : 1). *d*) Addition of H_2O (CH_2Cl_2 : H_2O = 10 : 1) and $NaHCO_3$ (2 eq).

moiety of the catalyst binds to the chloride anion of the *N*-acylated quinolinium salt and forms chiral *N*-acyliminium chloride–thiourea complex through counterion interaction, from which the desired addition product would be obtained.[111)]

We investigated the catalytic efficiency of new functionalized catalysts **8a**—**h** (Fig. 4) in the transformation of quinoline **9a** with (*E*)-styrylboronic acid **10A** into 2-alkylated dihydroquinoline (Table 2).[112,113)] The addition of phenyl chloroformate (2 eq) as a *N*-acylating reagent was essential to undergo the reaction in CH_2Cl_2 at −65 °C. Among the new catalysts prepared, thiourea **8a** gave the best results to afford the 1,2-adduct **11aA** in 70% yield with 90% ee without formation of 1,4-adduct (entries 1—9). The dihydroquinoline **12**, an equivalent of *N*-acylquinolinium salt, showed excellent reactivity toward **10A**; the racemic product **13aA** was obtained in 68% yield (entry 10). Moreover, the addition of H_2O as a proton source increased the enantioselectivity with a decrease in 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 due to *in situ* regeneration of catalyst **8a** by removing HCl and boronic acid by the base.

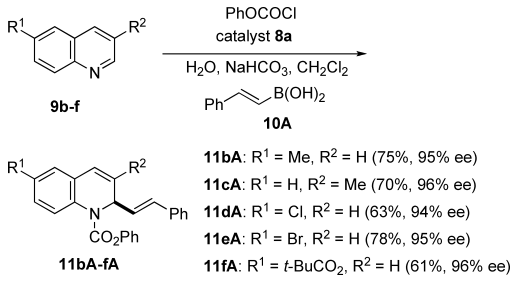


Chart 2. Petasis-Type Reaction of **9b**—**f** with **10A** Using Catalyst **8a**

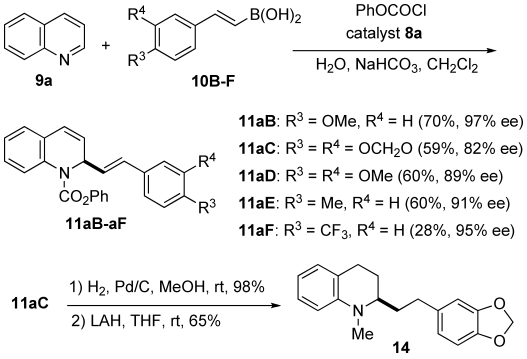


Chart 3. Petasis-Type Reaction of **9a** with **10B**—**F** Using Catalyst **8a**

Various quinolines **9b**—**f** (Chart 2) and boronic acids **10B**—**F** (Chart 3) were tolerated under the optimized conditions to give the corresponding products with high ee. The reaction of quinolines is frequently plagued by generation of regioisomeric 1,2- and 1,4-adducts; thus it is also noteworthy that this reaction provides a powerful method for the enantioselective and regioselective synthesis of 1,2-adducts. The potential of this method was clearly demonstrated by the short-step synthesis of (*R*)-(+)-galipinine **14** from quinoline **9a**.

4. Development of Asymmetric Thiourea-Catalyzed Domino Reactions

One of the current topics in organic synthesis is the development of multicomponent domino reactions for the efficient and stereoselective construction of complex molecules from simple precursors in a single process.[114—116)] These reactions are expected to circumvent serious problems of routine synthesis such as costly protecting-group strategies and lengthy purification procedures after each synthetic step. Organocatalytic domino reactions would be highly promising and efficient tools from the perspective of biomimetic synthesis, because similar principles are often found in the biosynthesis of natural products.

4.1. Asymmetric Synthesis of 4-Nitrocyclohexanones

The enantioselective construction of multiple stereogenic centers in a single operation has been the subject of recent research. In particular, such methods have been developed to synthesize highly functionalized chiral cyclohexanes **C** due to their versatility as synthetic intermediates for natural products such as epibatidine and pancratistatin. For this purpose, we planned to develop a tandem Michael addition of γ,δ-unsaturated β-ketoesters **A** to nitroalkenes **B** for the asymmet-

ric synthesis of (−)-epibatidine (Chart 4).[117,118] We investigated the tandem Michael addition of γ,δ-unsaturated-β-ketoesters **15a**—**d** to nitrostyrene **4a** in the presence of bifunctional thiourea **2a** (Table 3). Although the reaction with **15a** proceeded cleanly to provide the tandem Michael adduct **17a** as a single product in 65% yield with 86% ee (entry 1), the same treatment of **15b** bearing a bulky δ-substituent provided only Michael adduct **16b** but not **17b**. The subsequent treatment of the Michael adducts **16a**, **b** with 0.1 eq of 1,1,3,3-tetramethylguanidine (TMG) in CH_3CN provided 3,4-*anti*-4,5-*syn* adducts **17a**, **b** exclusively. In sharp contrast, a mixture of diastereoisomers **17c**, **d** and **18c**, **d** was obtained in the same reaction of **16c**, **d** (entries 2—5). Fortunately, only switching the base from TMG to KOH gave **17c**, **d** exclusively in better yields with higher enantioselectivities (entries 6, 7). It is noteworthy that this was the first report of successful asymmetric synthesis of three contiguous stereogenic centers by the tandem Michael reaction with nitroalkenes.

We next applied this manipulation to the total synthesis of (−)-epibatidine, a potent nicotinic acetylcholine receptor agonist (Chart 5).[117,118] Treatment of nitroolefin **19** and unsaturated β-ketoester **20** under the conditions described above afforded the tandem Michael adduct **21** in 77% yield. Although the ee of **21** was revealed only 75%, the enantiomeric excess was improved to 99% by recrystallization of **22**, which was obtained by a three-step sequence from **21**: Pd-catalyzed decarboxylation, stereoselective hydride reduction of ketone, and elimination of methanol. To accomplish the total synthesis of (−)-epibatidine, we undertook the 1,4-hydride reduction of nitrocycloalkene **22** with $NaBH_3CN$, mesylation, and reduction with zinc dust, giving the final compound (−)-epibatidine as a single product.

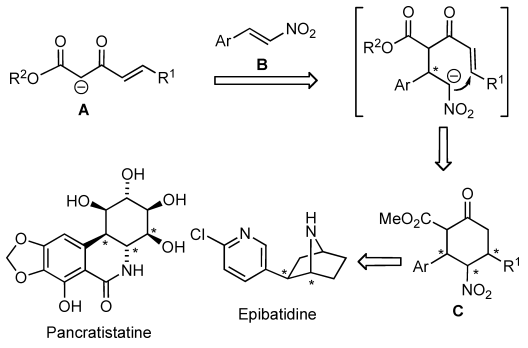
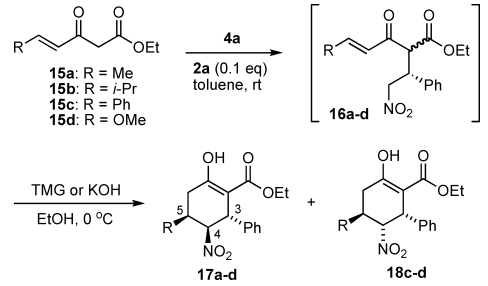


Chart 4. Tandem Michael Reaction for Chiral 4-Nitrocyclohexanones

Table 3. Tandem Michael Reaction of **15a**—**d** with β-Nitrostyrene **4a**

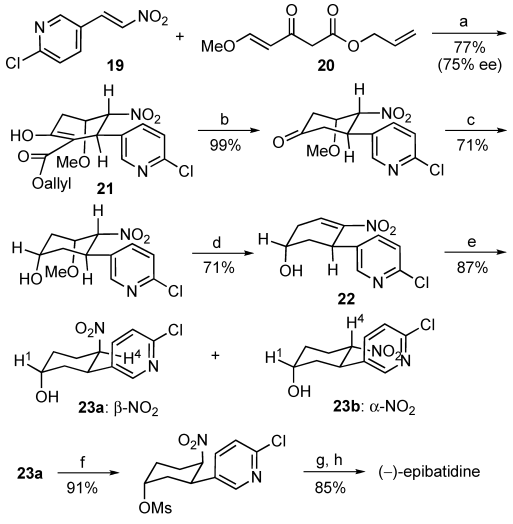


Entry	15	Temp. (°C)	Method	Yield (%)	de (%)	ee (%)
1	**15a**	rt	—[a]	65	>99	86
2	**15a**	−20	A[b]	87	>99	92
3	**15b**	rt	A[b]	71	>99	88
4	**15c**	−40	A[b]	79	90	89
5	**15d**	rt	A[b]	63	64	85
6	**15c**	−40	B[c]	62	>99	92
7	**15d**	rt	B[c]	76	>99	84

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

4.2. Asymmetric Synthesis of Multifunctionalized Pyrrolidines The [3+2] cycloaddition reactions have been employed as one of the most powerful synthetic tools to provide a variety of five-membered carbocycles as well as heterocycles. The cycloaddition of azomethine ylides with olefins affords highly functionalized pyrrolidines, which are structural motifs of biologically active natural products and pharmaceuticals.[119] Although many studies on the asymmetric [3+2] cycloaddition of azamethine ylides using chiral Lewis acids as well as chiral organocatalysts have been reported,[120—122] there is only one report on the organocatalyzed version with nitroolefin and, furthermore, the level of asymmetric induction is still moderate (up to 63% ee).[123,124] To achieve a highly enantioselective [3+2] cycloaddition of azomethine ylides with nitroolefins, we planned the one-pot stepwise synthesis of highly functionalized pyrrolidines **25** using thiourea-catalyzed Michael addition of α-amino malonate imine **24** into nitroolefin **4** *via* **D** and subsequent intramolecular aza-Henry reaction of the resulting intermediate **E** (Chart 6).[125]

The reaction of **24A** and **4a** in the presence of **2a** (10 mol%) proceeded even at 0 °C in toluene to give only Michael adduct **26Aa** in 90% yield with 90% ee. We then examined the subsequent aza-Henry reaction of **26Aa** (Table 4). Although no aprotic solvents were effective for this cyclization, the desired pyrrolidine **25Aa** was formed in 95% conversion, the reaction being carried out in EtOH (entries 1—4). Further investigation revealed that the desired pyrrolidine **25Aa** was predominantly produced in one-pot with high



Reagents and Conditions: (a) **2a**, toluene, 0 °C; KOH, EtOH, 0 °C; (b) $Pd(OAc)_2$, PPh_3, HCO_2H, Et_3N, THF, rt; (c) L-Selectride, THF, –78°C; (d) NaOMe, *tert*-BuOH; (e) $NaBH_3CN$, AcOH, MeOH, –20°C, **23a**/**23b** = 9/1; (f) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C; (g) Zn, AcOH, THF, rt; (h) $CHCl_3$, 60 °C.

Chart 5. Enantioselective Total Synthesis of (−)-Epibatidine

diastereoselectivity (dr=98 : 1 : 1), when 30 eq of 2,2,2-trifluoroethanol (TFE) was added to the reaction mixture at 0 °C after completion of the initial Michael addition (entries 5—8). The cooperation of both thiourea and TFE is crucial to accelerate the intramolecular aza-Henry reaction. The stereochemistry of the major diastereomer of **25Aa** was fully assigned by X-ray crystallographic analysis to be (3*R*,4*R*,5*R*) configuration.

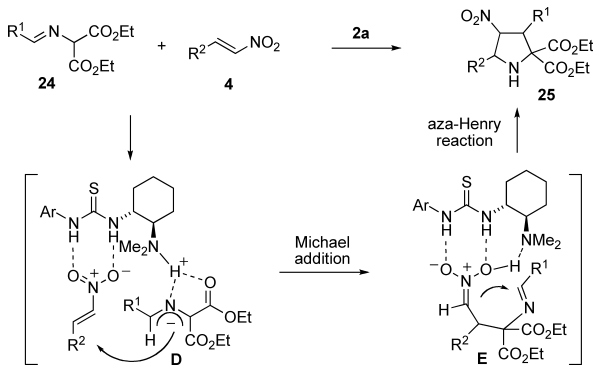
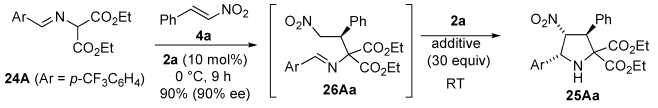


Chart 6. Formal [3+2] Cycloaddition of Azomethine Ylide **24**

Table 4. Investigation of Intramolecular Aza-Henry Reaction[a)]



Entry	Solvent	Additive	Time (h)	25Aa	
				% Conv.[b)]	Dr[c,d)]
1	Toluene	—	48	0	
2	CH_2Cl_2	—	48	0	
3	Dioxane	—	48	0	
4	EtOH	—	48	95	92 : 7 : trace
5	Toluene	EtOH	24	6	99 : trace
6	Toluene	TFE	24	99	89 : 10 : 1
7[e)]	Toluene	TFE	24	85	97 : 2 : trace
8[f)]	Toluene	TFE	24	0	

a) The reaction was carried out with **26Aa** in the absence or in the presence of an additive (30 eq) at room temperature. *b*) The conversion yield was determined by ^{1}H-NMR. *c*) The diastereomeric ratio was determined by ^{1}H-NMR. *d*) The stereochemistry of the minor adducts was not determined. *e*) The reaction was carried out at 0 °C. *f*) The reaction was performed in the absence of **2a**.

As shown in Table 5, high diastereoselective and enantioselectivities were achieved in the reaction of **24A**—**D** with various nitroolefins **4a**—**g** having an electron-rich, electron-deficient aromatic group or heteroaromatic group (entries 1—7). In contrast, removal of an electron-withdrawing substituent or introduction of electron-donating group from the aryl group (R^1) of **24** led to a decrease in enantioselectivity (entries 8—10).

The stereochemical outcome in the sequential [3+2] cycloaddition can be rationalized by the following plausible mechanism (Fig. 5). According to our previous reports,[74,75)] (*R*)-**26Aa** would be produced predominantly through a ternary complex of **2a**, **24A**, and **4a**. The resulting nitroalkane **26Aa** would be deprotonated by the amino group of **2a**, furnishing the corresponding nitronate anion, which is stabilized by assistance of the thiourea moiety of **2a**. Moreover, an external acidic proton of TFE might activate the imine moiety of **26Aa** and stabilize a transition state by the hydrogen bond. Consequently, good diastereoselectivity of **25Aa** is observed in the cyclization step.

4.3. Asymmetric Synthesis of 2-Nitrocyclopropanecarboxylic Acids 2-Nitrocyclopropanecarboxylic acid derivatives are recognized as versatile precursors for biologically active compounds[126—129)] as well as useful building blocks for the synthesis of highly functionalized molecular targets.[130—133)] Therefore catalytic and enantioselective construction of these motifs is a valuable challenge for synthetic chemists. Asymmetric Michael addition followed by intramolecular nucleophilic substitution is a representative process for this purpose.[134—137)] We explored a convenient

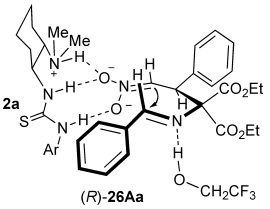
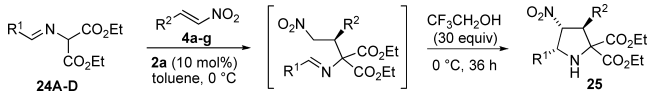


Fig. 5. Proposed Transition State for Major Adduct **25Aa**

Table 5. Formal [3+2] Cycloaddition of Various α-Amino Malonate and Nitroolefins[a)]



Entry	**24** (R^1)	**4** (R^2)	Product	% Yield[b)]	Dr[c,d)]	% ee[e)]
1	**24A** (4-$CF_3C_6H_4$)	**4a** (C_6H_5)	**25Aa**	84	98 : 1 : 1	92
2	**24A** (4-$CF_3C_6H_4$)	**4b** (4-$MeOC_6H_4$)	**25Ab**	81	95 : 4 : 1	91
3	**24A** (4-$CF_3C_6H_4$)	**4c** (4-ClC_6H_4)	**25Ac**	72	98 : 1 : 1	90
4	**24A** (4-$CF_3C_6H_4$)	**4d** (3-ClC_6H_4)	**25Ad**	75	98 : 1 : 1	90
5	**24A** (4-$CF_3C_6H_4$)	**4e** (2-ClC_6H_4)	**25Ae**	52	94 : 4 : 2	92
6	**24A** (4-$CF_3C_6H_4$)	**4f** (2-thienyl)	**25Af**	86	91 : 5 : 4	84
7	**24A** (4-$CF_3C_6H_4$)	**4g** (1-naphthyl)	**25Ag**	75	96 : 3 : 1	88
8	**24B** (4-ClC_6H_4)	**4a** (C_6H_5)	**25Ba**	80	98 : 1 : 1	91
9	**24C** (C_6H_4)	**4a** (C_6H_5)	**25Ca**	78	96 : 3 : 1	80
10	**24D** (4-$CH_3C_6H_4$)	**4a** (C_6H_5)	**25Da**	83	96 : 2 : 2	54

a) The reaction was carried out with **24A**—**D**, **4a**—**g**, and **2a**. *b*) Isolated yield. *c*) Diastereomeric ratio was determined by ^{1}H-NMR. *d*) The stereochemistry of the minor adducts was not determined. *e*) Ee was determined by HPLC analysis using a chiral column.

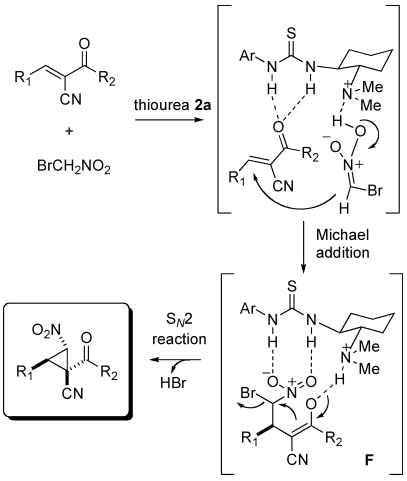
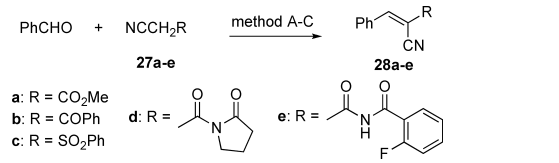


Fig. 6. Cyclopropanation Using Bromonitromethane

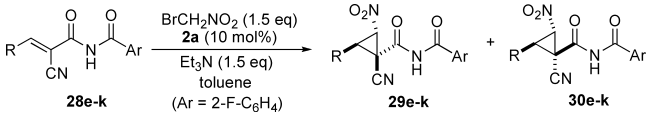
Table 6. Knoevenagel Condensation of α-Cyano Compounds **27a**—**e**



Entry	Substrate	Method[a]	Time (h)	Product	Yield (%)[b]
1	**27a**	A	24	**28a**	54
2	**27a**	B	7	**28a**	22
3	**27a**	C	26	**28a**	68
4	**27b**	C	24	**28b**	85
5	**27c**	C	17	**28c**	88
6	**27d**	C	6	**28d**	59
7	**27e**	C	25	**28e**	72

a) Method A: AcOH (10 mol%), morpholine (10 mol%), toluene, Dean–Stark refluxing; method B: ZnO (5 eq), DMF, rt; method C: **2a** (10 mol%), toluene, reflux. *b*) Isolated yield.

Table 7. Enantioselective Nitrocyclopropanation of **28e**—**k** with $BrCH_2NO_2$



Entry	Substrate (R)	Additive	Temp.	Time (h)	Yield of **29** and **30**[a]	ee of **29** (%)[b]
1	**28e** (Ph)	None	rt	24	11 (>99 : 1)	97
2	**28e** (Ph)	K_2CO_3	rt	24	27 (>99 : 1)	82
3	**28e** (Ph)	Pyridine	rt	19	7 (>99 : 1)	90
4	**28e** (Ph)	Et_3N	rt	2	55 (>99 : 1)	96
5	**28e** (Ph)	Et_3N	−60 °C	24	84 (63 : 37)	97
6	**28f** (4-MeC_6H_4)	Et_3N	−60 °C	24	81 (62 : 38)	99
7	**28g** (4-BrC_6H_4)	Et_3N	−20 °C	5	76 (58 : 42)	98
8	**28h** (3-ClC_6H_4)	Et_3N	−20 °C	2	80 (50 : 50)	98
9	**28i** (2-ClC_6H_4)	Et_3N	−20 °C	1	79 (63 : 37)	98
10	**28j** (1-naphthyl)	Et_3N	−20 °C	1	81 (73 : 27)	98

a) Isolated yield. *b*) Determined by HPLC.

protocol for preparing target molecules efficiently using tandem organocatalyzed reactions. We envisioned that if the Michael reaction with bromonitromethane proceeds efficiently, there is a chance that the Michael adduct obtained **F** would cyclize concurrently *via* the organocatalyzed intramolecular *SN*2 reaction to give the desired 2-nitrocyclopropanecarboxylic acids stereoselectively (Fig. 6).[138]

In the course of our study on Knoevenagel condensation for preparation of the requisite α-cyano-α,β-unsaturated ester, ketone, sulfone, and imide **28a**—**e** from benzaldehyde and several α-substituted nitriles **27a**—**e**, we discovered that bifunctional thiourea **2a** could be used as an effective catalyst comparable to the standard reaction conditions.[139—141] In practice, the heating of nitriles **27a**—**e** and benzaldehyde with 10 mol% of thiourea **2a** for several hours provided the corresponding *E*-isomers **28a**—**e** exclusively in good yields (Table 6).

From the study on the reaction of **28a**—**e** and bromonitromethane with a stoichiometric amount of thiourea **2a**, α,β-unsaturated imide **28e** gave the best result in terms of enantioselectivity of 2-nitrocyclopropane **29e**. We then examined the catalytic asymmetric cyclopropanation of **28e** with 10 mol% of **2a** in the presence of several bases (Table 7). As expected, catalytic reaction with no additional base resulted in recovery of most of the starting material and gave the cycloadduct **29e** in 11% yield with small amounts of Michael adduct (4%) (entry 1). After several investigations of bases, Et_3N was found the best additive, and gave **29e** in 55% yield as a single product (entries 2—4). The excellent enantioselectivity of the product was maintained in the catalytic reaction even with an excess amount of achiral base such as Et_3N. On the other hand, when the same reaction was performed at lower temperature, the chemical yield was enhanced to 84% and we obtained a mixture of **29e** and diastereoisomer **30e**, which was a C3 epimer of **29e**, in a ratio of 63 : 37 (entry 5). Concerning the scope of this catalytic reaction, the catalytic reaction of **28f**—**j** proceeded in good yields with high enantioselectivities regardless of the electron-withdrawing and electron-donating groups of the aryl group (entries 1, 2, 5).

5. Conclusion

We designed a variety of novel bifunctional organocatalysts that possess a thiourea moiety and an amino group. The

structure–activity relationship of these catalysts revealed that thiourea **2a** was the best catalyst for all reactions examined. The optimized catalyst was successfully applied to a wide range of asymmetric reactions as well as tandem reactions using various nucleophiles such as malonates, β-ketoesters, 1,3-diketones, nitroalkanes, malononitrile, and α-cyanoacetate into nitroolefins, *N*-Boc aldimines, α,β-unsaturated imides, and azodicarboxylate. In these reactions, the double hydrogen-bonding activation of electrophiles bearing nitro, imide, and carbamate groups by the thiourea moiety and simultaneous deprotonation of the nucleophiles by the dimethylamino group of bifunctional thiourea **2a** were shown to play a crucial role for enhancing both reaction rate and enantioselectivity. Furthermore, new catalysts having a chelating functionality, which activates a metallic nucleophile, were designed and synthesized. An organocatalyst **8a** provided sufficient activation of organoboronic acids to facilitate stereocontrol in the Petasis transformation of quinolines.

From the perspective of sustainable chemistry, these organocatalyst-mediated reactions would be desirable tools for preparing organic compounds and, therefore, more sophisticated multifunctional organocatalysts should be created for the development of new methodologies for multicomponent and tandem reactions and of a system for recycling organocatalysts.

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