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Published on Web 06/28/2006

Thiourea-Catalyzed Asymmetric Michael Addition of Activated Methylene Compounds to α,*β*-Unsaturated Imides: Dual Activation of Imide by Intra- and Intermolecular Hydrogen Bonding

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Abstract: A thiourea-catalyzed asymmetric Michael addition of activated methylene compounds to α,*β*-unsaturated imides derived from 2-pyrrolidinone and 2-methoxybenzamide has been developed. In the case of 2-pyrrolidinone derivatives, the reaction with malononitrile proceeded in toluene with high enantioselectivity, providing the Michael adducts in good yields. However, the nucleophiles that could be used for this reaction were limited to malononitrile due to poor reactivity of the substrate. Further examination revealed that *N*-alkenoyl-2-methoxybenzamide was the best substrate among the corresponding benzamide derivatives bearing different substituents on the aromatic ring. Indeed, several activated methylene compounds such as malononitrile, methyl α-cyanoacetate, and nitromethane could be employed as a nucleophile to give the Michael adducts in good to excellent yields with up to 93% ee. The results of spectroscopic experiments clarified that this enhanced reactivity can be attributed to the intramolecular hydrogen-bonding interaction between the N−H of the imide and the methoxy group of the benzamide moiety. Thus, the key to the success of the catalytic enantioselective Michael addition is dual activation of the substrate by both intramolecular hydrogen bonding in the imide and intermolecular hydrogen bonding with thiourea **1a**, as well as the activation of a nucleophile by the tertiary amine of the bifunctional thiourea.

Introduction

The catalytic asymmetric formation of a carbon−carbon bond is one of the most challenging fields in organic chemistry. From the viewpoint of the availability of substrates and the versatility of enantiomerically enriched addition products, asymmetric Michael addition of enolate equivalents to α,*β*-unsaturated carbonyl acceptors has been extensively studied.[1] Considerable effort has been directed to the development of Lewis acid-promoted addition of enol silyl ethers to α,*β*-unsaturated carbonyl compounds (Mukaiyama−Michael reaction) through the use of various types of chiral ligands.[2,3] Direct catalytic asymmetric Michael additions of aldehydes, ketones, and 1,3-dicarbonyl compounds attract considerable attention due to their simple manipulation and high atom economy, and successful results have recently been reported by several groups.[4−7] However, the acceptors used in these Michael additions of 1,3-dicarbonyl compounds generally have been limited to enones[4−6] and nitroalkenes.[7] Similarly, although organocatalysts possessing chiral secondary amines[8] or thioureas[9] have been shown to be efficient catalysts for the Michael reaction with such acceptors, there have been no reports on their application to α,*β*-unsaturated acid derivatives. Therefore, the development of general and highly enantioselective versions with α,*β*-unsaturated acid derivatives still remains a challenging goal. Two

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10.1021/ja061364f CCC: $33.50

groups independently achieved initial breakthroughs on these problems.[10,11] Kanemasa discovered a catalytic double-activation method using chiral Lewis acid and achiral amine catalysts for the enantioselective Michael reaction of 1-alkenoyl-3,5-dimethylpyrazole with several nucleophiles such as nitromethane and cyclohexadione derivative.[10] Jacobsen also reported that the Salen−Al complex-catalyzed Michael addition of malononitrile and 2-substituted cyanoacetates to α,*β*-unsaturated imides proceeded with high enantioselectivity.[11] Quite recently, Evans developed the Ni(II)-catalyzed conjugate reaction of *β*-keto esters with unsaturated *N*-acyl-1,3-thiazolidine-2-thiones.[12] However, because there have been no reports concerning the asymmetric reaction without a metallic catalyst, we investigated the thiourea-catalyzed asymmetric Michael reaction of 1,3-dicarbonyl compounds to α,*β*-unsaturated carboxylic acid derivatives based on our previous results with nitroolefins.[9a,b] We expected that an imide moiety could be activated by bifunctional thiourea **1a**[13,14] through a hydrogen-bonding interaction[15,16] in a manner similar to that of the nitro group (Figure 1). A similar concept was successfully applied by Schreiner to the thiourea-catalyzed Diels−Alder reaction of chiral *N*-alkenoly-1,3-oxazolidinone with cyclopentadiene.[15c] In practice, we developed the first organocatalyst-mediated enantioselective Michael reactions of malononitrile to *N*-alkenoyl-2-pyrrolidinone.[13b] Further examination of this reaction revealed that *N*-alkenoyl-2-methoxybenzamide was a more reactive substrate than *N*-alkenoylpyrrolidinone and the corresponding benzamide derivatives, and several activated methylene compounds such as malononitrile, methyl α-cyanoacetate, and nitromethane could

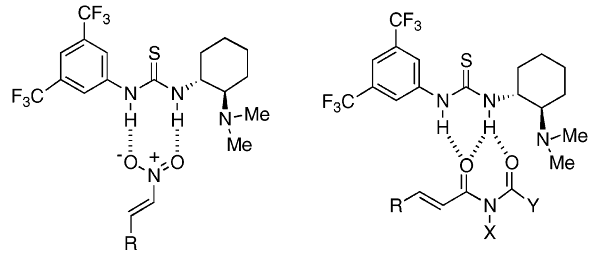

Figure 1. Hydrogen-bond interaction with thiourea **1a**.

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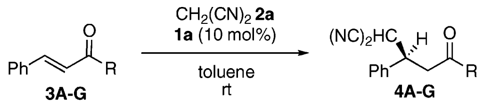
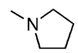
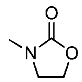
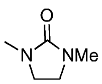
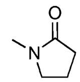
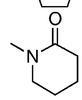
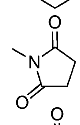
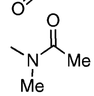
Table 1. Enantioselective Michael Addition of Malonotrile **2a** with α,β-Unsaturated Acid Derivatives **3A**−**G**[a]



entry	substrate (R)		product	time (h)	yield (%)[b]	ee (%)[c]
1	**3A**		**4A**	48	0	–
2	**3B**		**4B**	96	89	83
3	**3C**		**4C**	120	59	81
4	**3D**		**4D**	60	93	87
5	**3E**		**4E**	140	42	59
6	**3F**		**4F**	48	0	–
7	**3G**		**4G**	216	27	56

[a] The reaction was conducted with **1a** (10 mol %), **2a** (2 equiv), and **3A**−**G** in toluene (0.5 M solution). [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of **4A**−**G** using a chiral column.

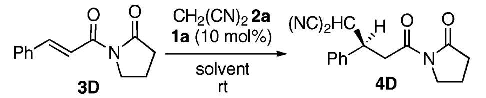
be used as a nucleophile to give the Michael adducts with up to 93% ee. We report here the details of the organocatalytic enantioselective Michael reactions of different nucleophiles with various α,β-unsaturated imides as well as a mechanistic investigation of Michael addition.

Results and Discussion

Investigation of the Reaction Conditions for the Thiourea-Catalyzed Asymmetric Michael Reaction of Malononitrile. Although we reported that the bifunctional thiourea-catalyzed Michael reaction of 1,3-dicarbonyl compounds such as methyl malonate and β-keto esters with nitroalkenes proceeded with high enantioselectivity of up to 93% ee,[9a,b] the same reaction with α,β-unsaturated acid derivatives gave no addition products. To extend the synthetic utility of bifunctional thiourea **1a** in the asymmetric reaction, we then undertook screening of proper Michael acceptors other than nitroalkenes by using malononitrile as a reactive nucleophile. For this purpose, α,β-unsaturated imides seem to have an ideal structure to form hydrogen bonds with the thiourea catalyst **1a** as shown in Figure 1.[15]

We first investigated the Michael addition of malononitrile **2a** to several types of α,β-unsaturated acid derivatives **3A**−**G** (Table 1). The reaction of **2a** (2 equiv) with **3A**−**G** (a 0.5 M toluene solution) was carried out at room temperature in the presence of 10 mol % of **1a**. Although the conjugate addition of **2a** with amide **3A** gave no desired product, the same reaction with *N*-acyl-1,3-oxazolidinone **3B**[15c] was complete after 96 h, giving the Michael adduct **4B** in 89% yield (entries 1 and 2). The enantioselectivity of **4B** was revealed to be 83% ee by HPLC analysis. We expected to enhance the hydrogen-bonding interaction with thiourea **1a**, and thus used *N*-acyl-1,3-imidazolidinone **3C**, which possesses a cyclic urea moiety, as a Michael acceptor, but both the chemical yield and the enantioselectivity decreased to afford the adduct **4C** in 59% yield with 81% ee (entry 3). In contrast, with **3C**, *N*-acylpyrrolidinone **3D** exhibited good reactivity to **2a**, providing the corresponding product **4D** in 93% yield with the best enantioselectivity (87% ee) (entry 4).

Table 2. Reaction of α,β-Unsaturated Imide **3D** in Various Solvent[a]



entry	solvent	concentration (M)	**1a** (mol %)	time (h)	yield (%)[b]	ee (%)[c]
1	MeOH	0.5	10	72	22	7
2	THF	0.5	10	120	57	62
3	CH_3CN	0.5	10	120	58	44
4	CH_2Cl_2	0.5	10	72	77	81
5	toluene	0.5	10	60	93	87
6	toluene	0.5	5	120	94	88
7	toluene	0.5	1	168	50	86
8	toluene	0.1	10	168	92	93

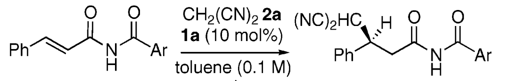
[a] The reaction was conducted with **1a**, **2a** (2 equiv), and **3D**. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of **4D** using a chiral column.

The use of *N*-acylpiperidinone **3E** and acyclic imide **3G** for the Michael addition reaction resulted in a significant decrease in both chemical yield and enantioselectivity (entries 5 and 7). In contrast to the results with **3D**, the reaction of **2a** with *N*-acylpyrrolidine-2,5-dione **3F** under the same conditions did not occur at all, leading to recovery of the starting material (entry 6). With a good Michael acceptor, *N*-acylpyrrolidinone **3D**, we examined the optimal reaction conditions for the Michael addition (Table 2). The use of a polar solvent such as methanol and acetonitrile significantly lowered the stereoselectivity. Among the solvents examined, toluene was the best solvent in terms of chemical yield and enantioselectivity (entries 1−5). The amount of the catalyst **1a** could be reduced to 1 mol % without affecting the enantioselectivity, but the chemical yield of the product was reduced (entries 6 and 7). Although the best enantioselectivity (93% ee) was obtained in a 0.1 M solution of the substrate, the reaction required a prolonged reaction time (7 d) (entry 8).

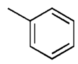
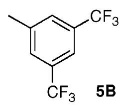
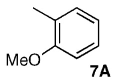
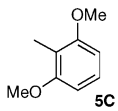
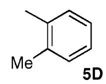
To overcome this problem, we reexamined the *N*-acylbenzamide derivatives **5A**−**D** and **7A**, which are considered to be potential Michael acceptors for Lewis acid-catalyzed Michael reactions[17] (Table 3). All reactions were carried out in a 0.1 M solution of the substrate with 2 equiv of **2a** and 10 mol % of **1a**. As expected, the reaction of **2a** with **5A** proceeded smoothly and was complete within 26 h, giving the corresponding adduct **6A** in 84% yield with 88% ee (entry 1). When the more electron-deficient substrate **5B**, bearing a 3,5-bis(trifluoromethyl)phenyl group, was subjected to the same reaction conditions, a miserable result was obtained in terms of chemical yield due to the poor solubility of **5B** in the reaction solvent (entry 2). Surprisingly, the electron-rich substrate **7A** exhibited high reactivity in the

(17) (a) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1999**, *121*, 8959. (b) Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2003**, *125*, 4442. (c) Sibi, M. P.; Prabagaran, N.; Ghorpade, S. G.; Jasperse, C. P. *J. Am. Chem. Soc*. **2003**, *125*, 11796. (d) Vanderwal, C. D.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2004**, *126*, 14724.

Table 3. Thiourea-Catalyzed Michael Addition of **2a** with *N*-Cinnamoylbenzamide Derivatives **5A**−**D** and **7A**[a]



5A-D, **7A** **6A-D**, **8A**

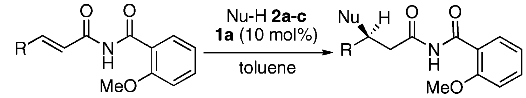
entry	substrate (Ar)	product	time (h)	yield (%)[b]	ee (%)[c]
1	 **5A**	**6A**	26	84	88
2	 **5B**	**6B**	94	28	89
3	 **7A**	**8A**	14	95	91
4	 **5C**	**6C**	75	90	62
5	 **5D**	**6D**	24	93	89

[a] The reaction was conducted with **1a** (10 mol %), **2a** (2 equiv), and **5A**−**D**, **7A** in toluene (0.1 M solution). [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of **6A**−**D** and **8A** using a chiral column.

Michael addition; the reaction was complete after only 14 h, and the desired product **8A** was obtained in 95% yield with 91% ee (entry 3). In contrast to this result, the reaction of 2,6-dimethoxybenzimide **5C** led to significant decreases in both the reaction rate and the enantioselectivity (entry 4). By comparing the result of 2-methylbenzimide **5D** with that of **7A**, the 2-methoxy group was proved to play an important role for the acceleration of the conjugate reaction. We assumed that the intramolecular hydrogen bonding between NH and OMe groups of **7A** enhanced the electrophilicity of the *N*-alkenoyl moiety of the imide **7A** due to the decrease of electron density of the nitrogen atom as well as coplanar orientation of the 2-methoxybenzamide moiety (entries 3 and 5). These results demonstrated that the 2-methoxybenzimide **7A** was the best choice for a substrate in all respects.

Scope and Limitation of the Thiourea-Catalyzed Asymmetric Michael Reaction with 2-Methoxybenzimides. Having established the optimal reaction conditions for the enantioselective Michael reaction of malononitrile **2a**, we next screened a series of substrates **7A**−**E** bearing various β-substituents and nucleophiles **2a**−**c**. As illustrated in Table 4, 2-methoxybenzimides **7B**−**E** underwent conjugate addition of malononitrile **2a** in the presence of catalyst **1a** in high yield and ee, and these results were almost independent of steric hindrance and the electronic properties of the β-substituents. The reactions with aryl-substituted imides **7B** and **7C** proceeded with high enantioselectivity to furnish the addition adducts **8B** and **8C**, while the rate of the reaction was somewhat decreased for **7C** (R = *p*-methoxyphenyl) due to the electron-rich substrate (entries 1, 2). Similarly, imides **7D** and **7E** bearing alkyl groups as the β-substituent underwent a clean reaction as well, giving the corresponding adducts **8D** and **8E** with 90−93% ee (entries 3, 4). In contrast to the Michael addition with *N*-acylpyrrolidinone **3D** mentioned above,[13b] the present reaction with 2-methoxybenzimides **7A**−**E** occurred smoothly to afford the desired products **8A**−**E** within 3−24 h. Encouraged by this result, we next investigated the Michael addition of other nucleophiles, such as methyl α-cyanoacetate **2b**, but the reaction was sluggish even with **7A**. After many experiments, the desired Michael adducts **9A** and **9B** were obtained in good yield by simply heating the reaction mixture at 80 °C (entries 5, 6). It is noteworthy that the enantioselectivity of the products **9A**,**B** remained fairly high (82−85% ee) even at high temperature. In contrast to the aromatic imides **7A**,**B**, the reaction of aliphatic imides **7D** and **7E** with **2b** occurred even at room temperature, providing **9D** and **9E** with somewhat higher enantioselectivity (92% ee) (entries 7, 8). Furthermore, it was revealed that nitromethane **2c** could be used as a nucleophile for the Michael addition with imides **7**, whereas the reaction took place slowly even at 60 °C. The corresponding Michael adducts **10A**,**B** and **10D**,**E** were produced in moderate to good yields with up to 87% ee (entries 9−12). Consequently, we succeeded in the first organocatalyzed enantioselective Michael addition of methyl α-cyanoacetate **2b** and nitromethane **2c** with 2-methoxybenzimides **7A**,**B** and **7D**,**E** by using bifunctional thiourea **1a**.

Table 4. Thiourea-Catalyzed Michael Addition of **2a**−**c** with Various α,β-Unsaturated Imides **7A**−**E**[a]



7A-E **8A-E, 9A-E, 10A-E**

2a: Nu = $CH(CN)_2$, **2b**: Nu = $CH(CN)(CO_2Me)$, **2c**: Nu = CH_2NO_2
A: R = Ph, **B**: R = *p*-FC_6H_5, **C**: R = *p*-$MeOC_6H_5$, **D**: R = Me,
E: R = $TBSO(CH_2)_5$

entry	7	2	temp (°C)	time (h)	product	yield (%)[b]	ee (%)[c]
1	**7B**	**2a**	rt	7	**8B**	99	92
2	**7C**	**2a**	rt	24	**8C**	92	90
3	**7D**	**2a**	rt	3	**8D**	96	90
4	**7E**	**2a**	rt	5	**8E**	95	93
5	**7A**	**2b**	80	52	**9A**	94[d]	82[e]
6	**7B**	**2b**	80	48	**9B**	91[d]	85[e]
7	**7D**	**2b**	rt	87	**9D**	90[d]	92[e]
8	**7E**	**2b**	rt	137	**9E**	96[d]	92[e]
9	**7A**	**2c**	60	168	**10A**	56	87
10	**7B**	**2c**	60	168	**10B**	60	86
11	**7D**	**2c**	rt	135	**10D**	91	83
12	**7E**	**2c**	rt	256	**10E**	82	80

[a] The reaction was conducted with **1a**, **2a**−**c** (2−40 equiv), and **7A**−**E**. [b] Isolated yield. [c] Enantiomeric excess (ee) was determined by HPLC analysis of **8**−**10** using a chiral column. [d] Product was obtained as a mixture of two diastereoisomers. [e] The ee values were estimated from ee of the decarboxylated nitrile.

The absolute configurations of the Michael adducts **8B**, **9B**, and **10A** were determined by their transformation to known compounds **11**,[11a] **12**,[11a] and **13**[18] (Scheme 1). Treatment of **8B** with a catalytic amount of $Er(OTf)_3$ in methanol provided the corresponding methyl ester **11** ($[\alpha]^{24}_D = +17$: *c* 1.2, CH_3CN) in 96% yield. In the case of **9B**, the obtained product **9B** was converted into nitrile **12** in two steps according to the reported procedure[11a] ($[\alpha]^{25}_D = +7$: *c* 1.1, CH_3CN). Based on a comparison of their specific rotations with those of authentic

(18) Felluga, F.; Gombac, V.; Pitaco, G.; Valentin, E. *Tetrahedron: Asymmetry* **2005**, *16*, 383.

Scheme 1. Transformation of Michael Adducts to Methyl Esters **11**−**13**

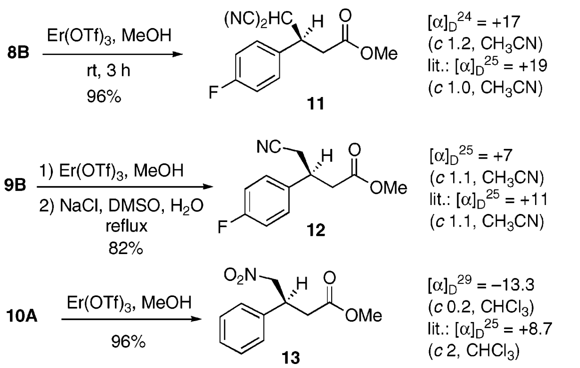


Table 5. ^{1}H NMR and IR Experiments of Imides **5A**, **7A**, **5c**, and **5D**

imide	^{1}H NMR ($CDCl_3$, 0.015 M)	IR ($CHCl_3$, 0.01 M)
5A	8.59 (NH)	3405 (N−H)
	7.86 (H_α)	1680 (C═O)
	7.95 (H_β)	1619 (C═C)
7A	10.30 (NH)	3330 (N−H)
	7.86 (H_α)	1671 (C═O)
	7.91 (H_β)	1619 (C═C)
5C	8.19 (NH)	3393 (N−H)
	7.75 (H_α)	1679 (C═O)
	7.89 (H_β)	1620 (C═C)
5D	8.21 (NH)	3391 (N−H)
	7.76 (H_α)	1680 (C═O)
	7.94 (H_β)	1618 (C═C)

samples (**11**, $[\alpha]^{25}_D = +19$, *c* 1.0, CH_3CN; **12**, $[\alpha]^{25}_D = +11$, *c* 1.1, CH_3CN),[11a] the absolute configurations of **8B** and **9B** were determined to be *R* and *S*, respectively. The same treatment of **10A** as **8B** afforded the corresponding methyl esters **13** ($[\alpha]^{29}_D = -13.3$: *c* 0.20, $CHCl_3$), whose configuration was confirmed to be *S* by comparison of its specific rotation with that of the authentic sample,[18] and those of the other adducts **8A**, **8C**−**E**, **9A**, and **10B** were presumed on the basis of the above results. Consequently, these results indicated that all nucleophiles tend to attack the Michael acceptors from the same side in the presence of **1a**, regardless of the functional groups of the nucleophiles.

Mechanistic Studies. To gain insight into the different reactivity of the imides **7A** and **5A**−**D**, we performed experiments using IR and ^{1}H NMR spectroscopy. The results are summarized in Table 5. Although almost all of the ^{1}H NMR signals such as the vinylic protons (H_α and H_β) of **5A**, **5C**,**D**, and **7A** possessed similar chemical shifts; the signal of the N−H proton of **7A** was observed downfield as compared to those of **5A** and **5C**,**D**. In addition, the stretching absorption of the N−H bond in the IR spectrum of **7A** (0.01 M) appeared at a slightly lower wavenumber (3330 cm^{-1}) than those of **5A** and **5C**,**D** (3391−3405 cm^{-1}). On the basis of these facts, we speculated that intramolecular hydrogen bonding between the imide N−H moiety and the methoxy group was formed in the case of **7A**, by which the α,β-unsaturated carbonyl moiety of 2-methoxybenzimide **7A** would be more reactive as a Michael acceptor than the other imides. To identify additional hydrogen bonding between 2-methoxybenzimides **7** and thiourea **1a**, we took the ^{1}H NMR spectra of **7A** in the presence of different amounts of **1a**. In contrast to nitroolefins[9a,b] and *N*-Boc imines,[13a,c] the formation of a substrate−catalyst complex **7A·1a** in toluene-d_8

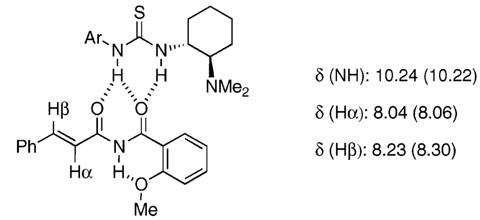


Figure 2. ^{1}H NMR of a 1:1 mixture of **1a** and **7A** in toluene-d_8 (0.02 M) (the values in parentheses are chemical shifts of **7A** without **1a**).

was supported by ^{1}H NMR spectroscopic experiments, as shown in Figure 2.[19] The chemical shift of the imide N−H of **7A** was gradually shifted downfield with an increase in the ratio of **1a** to **7A**. When **1a** was mixed with **7A** (**1a**/**7A** = 1/1), the chemical shift of N−H was shifted from 10.22 to 10.24 ppm. In contrast, the chemical shifts of H_α and H_β of **7A** were gradually shifted upfield with an increase in the amount of **1a**. This implies that the acidic protons (NH) of **1a** interacted with two carbonyl oxygens of the imide **7A**, as shown in Figure 2.[20]

To obtain further information about the reaction mechanism, we carried out kinetic studies on the Michael reaction. When the reaction was carried out with a large excess of **2a**, plotting ln([**7A**]/[**7A**^{0}]) versus time gave a straight line ($R^2 = 0.9988$, A in Figure 3), which indicates that the reaction is first-order with respect to **7A**. Although the order with regard to nucleophile **2a** could not be determined due to the poor solubility of the substrate **7A**, when the order with regard to the catalyst was also examined by plotting the kinetic rate constant (k_{obs}) against the loading of **1a** (B in Figure 3), the reaction was shown to be first-order with respect to **1a**. In addition, Figure 3 shows the relationship (Michaelis−Menten plot) between the substrate concentration [S_0] of **7A** and reaction rate (VM/min) (C in Figure 4). This result unambiguously indicates that equilibrium between catalyst **1a** (or a binary complex of **1a** and malononitrile **2a**) and substrate **7A** exists in the thiourea-catalyzed Michael addition. Therefore, the reaction constants of K_M, V_{max}, and k_{cat} were calculated from the Lineweaver−Burk plot ($R^2 = 0.9936$, D in Figure 4): $K_M = 0.300$ M, $V_{max} = 4.42 \times 10^{-3}$ M/min, $k_{cat} = 0.442$ min^{-1}, $k_{cat}/K_M = 1.47$ (1/M·min).

On the basis of these results, we propose a ternary complex of catalyst **1a**, malononitrile **2a**, and imide **7** as a plausible transition state (Figure 5). Successive interaction of malononitrile **2a** and 2-methoxybenzimide **7** with catalyst **1a** took place through the deprotonation of **2a** by the tertiary amine of **1a** and the coordination of **7** to the thiourea moiety of **1a**, producing ternary complex **A**, which is composed of **1a**, **7**, and the anion of malononitrile **2a**. Consequently, the activated nucleophile attacks the imide **7** from the front of ternary complex **A**, giving the (*R*)-adduct **8** predominantly. This proposed mechanism is consistent with the experimental results described above.

1,2-Nucleophilic Addition of Hard Nucleophiles to the Michael Adducts. To transform the obtained Michael adducts into advanced compounds, a wide range of reactions have been developed.[10−12,17] However, these reactions have required a catalytic amount of additional Lewis acids or a stoichiometric

(19) A similar phenomenon was observed on the ^{1}H NMR titration studies of malononitrile **2a** with thiourea **1a**. The chemical shift of the methylene protons of malononitrile **2a** was shifted from 0.92 to 0.95 ppm by the addition of 1.0 equiv of thiourea **1a** in toluene-d_8 (0.02 M).

(20) At this stage, it is not clear why the chemical shifts of H_α and H_β of **7A** shifted upfield with an increase of additional amounts of **1a**. The same upfield-shifts were observed in the ^{1}H NMR spectra of **5A** and **5C**.

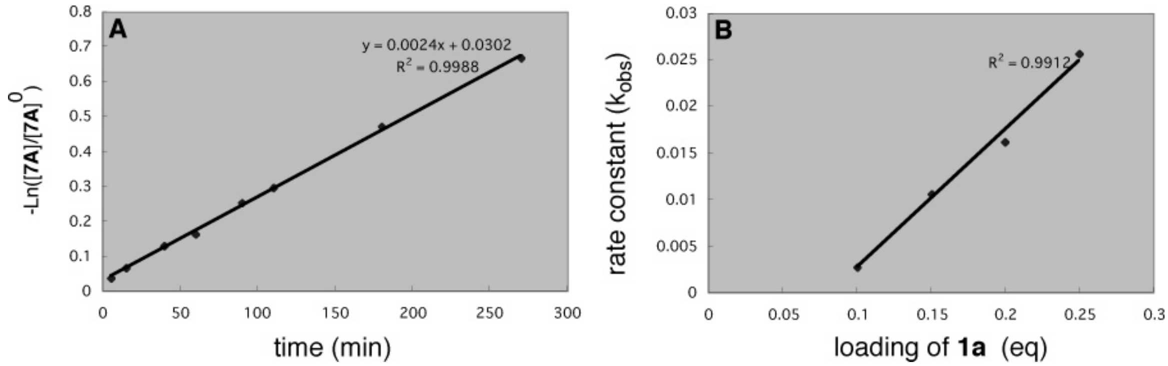


Figure 3. Kinetic studies on the Michael reaction of malonotrile **2a** to imide **7A** in the presence of **1a**.

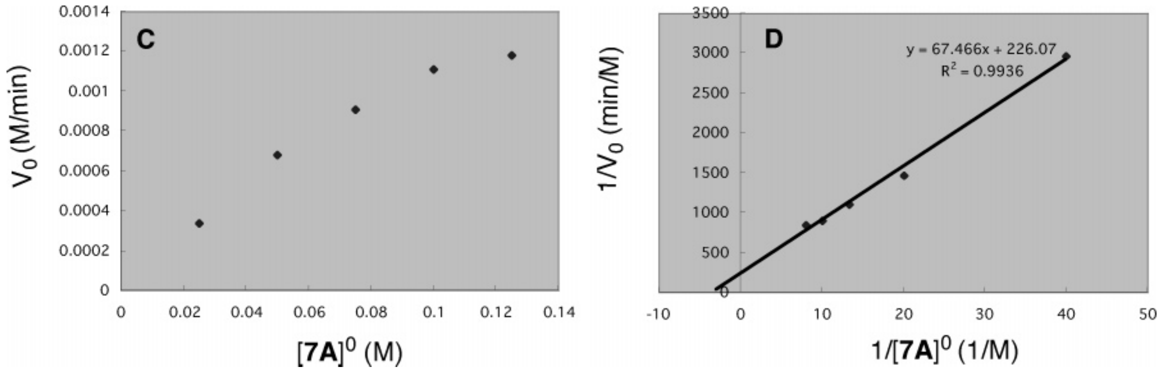


Figure 4. Michaelis−Menten and Lineweaver−Burk plots of the Michael reaction of **2a** with **7A**.

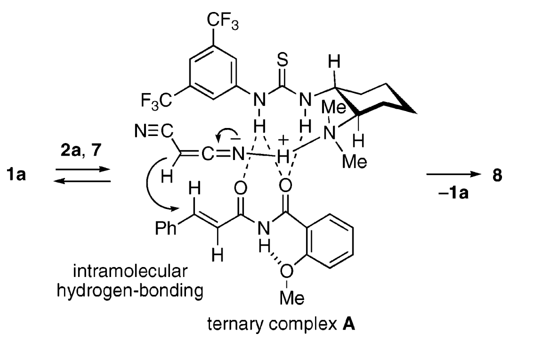
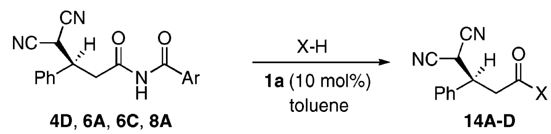


Figure 5. Plausible reaction mechanism of the Michael addition of imide **7** with malonotrile **2a** in the presence of **1a**.

amount of bases. From an atom-economical point of view, it would be desirable to develop a new method for the subsequent reaction, which does not demand additional catalyst. The bifunctional thiourea catalyst **1a** was designed on the basis of a mechanism of hydrolytic enzymes such as serine protease.[21] This means that the thiourea **1a** might catalyze the transformation of the imides to other carboxylic acid derivatives.[14j,m] Therefore, we next explored the one-pot transformation of **7** into carboxylic acid derivatives such as ester, amide, and Weinreb amide by tandem Michael addition of soft nucleophile and 1,2-nucleophilic addition of a hard nucleophile. Because we have already developed the asymmetric Michael addition of malononitrile **2a** to imides **7**, a key to the success of one-pot transformation would be the second reaction of the Michael adducts **8** with hard nucleophiles (Table 6). Therefore, we first examined the reaction of several Michael adducts **4D**, **6A**, **6C**, and **8A** with methanol as a hard nucleophile. The reaction was

Table 6. Thiourea-Catalyzed Transformation of Imides **4D**, **6A**, **6C**, and **8A** into Various Carboxylic Acid Derivatives **14A**−**D**



14A: X = OMe, **14B**: X = OBn, **14C**: X = NHBn, **14D**: X = NMe(OMe)

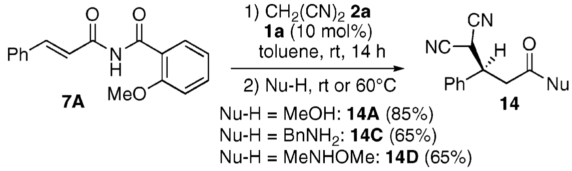
entry	substrate	reaction conditions	product	yield[a]
1	**4D**	MeOH (neat), 60 °C, 24 h	**14A**	82
2	**6A**	MeOH (neat), rt, 24 h	**14A**	94
3	**6C**	MeOH (neat), rt, 24 h	**14A**	88
4	**8A**	MeOH (neat), rt, 24 h	**14A**	87
5[b]	**8A**	MeOH (neat), rt, 24 h	**14A**	9
6	**8A**	BnOH (neat), rt, 88 h	**14B**	89
7	**8A**	$BnNH_2$ (2 equiv), rt, 3 h	**14C**	77
8	**8A**	MeNHOMe (3 equiv), 60 °C, 20 h	**14D**	75

[a] Isolated yield. [b] Without thiourea catalyst **1a**.

carried out in methanol in the presence of 10 mol % **1a**. In the case of **4D**, the reaction required heating at 60 °C to go to completion and provided the methyl ester **14A** in 82% yield (entry 1). In contrast to this result, the same reaction of benzimides **6A**, **6C**, and **8A** proceeded at room temperature to give the desired product **14A** in good yields, respectively (entries 2−4). Distinct from the Michael addition of soft nucleophiles, these benzimides exhibited almost the same reactivities to methanol. However, the yield of **14A** was low without thiourea catalyst **1a**, while the reaction occurred slowly (entry 5). Similarly, benzyl alcohol could be employed as a nucleophile for this transformation, affording the corresponding ester **14B** in 89% yield (entry 6). Although the amide **14C** could be obtained by treatment of **8A** with benzylamine (2 equiv) in toluene at room temperature, the reaction with *N*,*O*-dimethylhydroxyamine required heating at 60 °C to furnish the desired

(21) Wharton, C. W. In *Comprehensive Biological Catalysis*; Sinnott, M., Ed.; Academic Press: London, 1998; Vol. 1, pp 345−379.

Scheme 2. One-Pot Transformation of **7A** into **14A**, **14C**, and **14D**



Weinreb amide **14D**. Having established the optimal reaction conditions for the 1,2-nucleophilic addition of hard nucleophiles, we finally undertook the one-pot reaction of α,β-unsaturated imide **7A** with malononitrile **2a** and methanol (Scheme 2). After the Michael addition of **2a** to **7A** under the standard conditions, methanol was added to the reaction mixture and the resulting mixture was stirred at room temperature to provide the desired methyl ester **14A** in 85% yield. Similarly, the one-pot reactions of **7A** with $BnNH_2$ and MeNHOMe proceeded efficiently, giving the corresponding adducts **14C** and **14D** in good yields. In this way, we succeeded in the tandem reaction of enantioselective Michael addition of soft nucleophile and the 1,2-nucleophilic addition of a hard nucleophile with a single chiral organocatalyst.

Conclusion

We successfully developed the first highly enantioselective organocatalytic Michael addition of several soft nucleophiles **2a**−**c** with α,β-unsaturated imides **4D** and **7A**−**E** using a bifunctional thiourea **1a**. Although the pyrrolidinone moiety of α,β-unsaturated imides **4D** is demonstrated to play a key role in the Michael reaction of malononitrile **2a**, the *N*-alkenoylbenzamide derivatives **5** and **7** are more promising Michael acceptors in terms of reaction rate and stereoselectivity. Among them, *N*-alkenoyl-2-methoxybenzamides **7** is the best Michael acceptor. The high reactivity of **7** can be attributed to intramolecular hydrogen bonding between the imide N−H moiety and the methoxy group of the benzamide. The reaction can be applied to a variety of α,β-unsaturated imides **7A**−**E** bearing aryl and alkyl groups as a β-substituent, with high enantioselectivity. Furthermore, the Michael addition of other carbon-nucleophiles such as methyl α-cyanoacetate **2b** and nitromethane **2c** with **7A**−**E** also proceeds at elevated temperature, giving the corresponding Michael adducts with good enantioselectivity. Subsequent treatment of the obtained Michael adducts with hard nucleophiles such as alcohol, amine, and *N*,*O*-dimethylhydroxyamine in the presence of thiourea **1a** promotes the 1,2-nucleophilic addition into imides to afford the corresponding ester, amide, and Weinreb amide in good yield. Thus, different soft and hard nucleophiles can be introduced to *N*-alkenoyl-2-methoxybenzamides **7** in a highly regio- and enantioselective manner by using a single chiral catalyst.

Acknowledgment. This work was supported by grants from the 21st Century COE Program “Knowledge Information Infrastructure for Genome Science”, Grant-in-Aid for Scientific Research on Priority Areas (17035043) from MEXT, and JSPS KAKENHI (16390006).

Supporting Information Available: Experimental procedures and characterization of the products and other detailed results. This material is available free of charge via the Internet at http://pubs.acs.org.

JA061364F