Organocatalysis

Enantioselective Michael Addition to α,β-Unsaturated Imides Catalyzed by a Bifunctional Organocatalyst**

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The catalytic asymmetric formation of a carbon–carbon bond represents one of the most challenging fields in organic chemistry. A number of asymmetric Michael additions to α,β-unsaturated carbonyl acceptors catalyzed by chiral catalysts have been reported.[1] However, the acceptors employed in the asymmetric Michael additions of 1,3-dicarbonyl compounds generally have been restricted to enones[2–4] and nitroalkenes.[5] Similarly, although organocatalysts that bear chiral secondary amine groups have been shown to be efficient catalysts for the Michael reaction with such acceptors,[6] their applications to α,β-unsaturated acid derivatives seems to be difficult. Therefore, the development of general and highly enantioselective versions of the reactions of α,β-unsaturated acid derivatives still remains a challenging goal. Quite recently, two groups achieved the initial breakthroughs on these problems. The Jacobsen and Kanemasa groups independently reported the highly enantioselective metal-catalyzed Michael additions of malononitrile, which is equivalent to a 1,3-dicarbonyl compound, to α,β-unsaturated imides.[7,8] However, there have been no reports of such asymmetric Michael addition without any metal catalysts. Herein, we report the first enantioselective Michael reactions of malononitrile to acyclic α,β-unsaturated imides in the presence of a chiral organocatalyst.

Although we recently reported that the bifunctional-thiourea-catalyzed Michael reaction of 1,3-dicarbonyl compounds to nitroalkenes proceeded with high enantioselectivity (up to 93% *ee*),[9] the same reaction of other nucleophiles such as malononitrile to nitroalkenes gave the corresponding product with low enantioselectivity. To extend the synthetic utility of the bifunctional thiourea **1a** in the asymmetric reaction, we undertook the screening of proper Michael acceptors other than nitroalkenes to react with malononitrile. For the purpose, α,β-unsaturated imides seem to have an ideal structure to form hydrogen bonds with the thiourea catalyst **1a** as shown in Scheme 1.[10,11]

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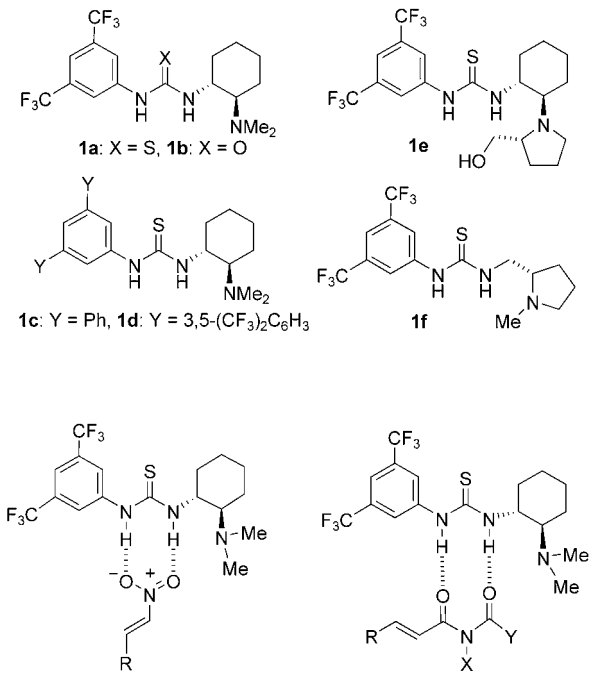
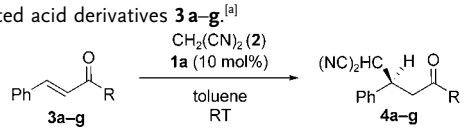


Scheme 1. Hydrogen-bond interaction with thiourea **1a**.

We first investigated the Michael addition of malononitrile (**2**) to several types of α,β-unsaturated acid derivatives **3a**–**g** (Table 1). The reaction of **2** (2 equiv) with a solution of imides **3** in toluene (0.5 M) was carried out at room temperature in the presence of **1a** (10 mol%). Although the conjugate addition of **2** with amide **3a** gave no desired product, the same reaction with *N*-acyl-1,3-oxazolidinone **3b**[10e] was completed after 96 h to give the Michael adduct **4b** in 89% yield (Table 1, entries 1 and 2). The enantiopurity of **4b** was revealed to be 83% ee by means of HPLC analysis. In the hope of enhancing the hydrogen-bonding interaction with thiourea **1a**, we employed *N*-acyl-1,3-imidazolidinone **3c**, which bears a cyclic urea moiety, as a Michael acceptor, but both the yield of **4c** and enantioselectivity were poorer (59%, 81% *ee*; Table 1, entry 3). In contrast with **3c**, *N*-acylpyrrolidinone **3d** was revealed to be a good acceptor of **2**, providing the corresponding product **4d** in 93% yield with the best enantioselectivity (87% *ee*) (Table 1, entry 4). Use of *N*-acylpiperidinone **3e** and acyclic imide **3f** for the Michael addition reaction resulted in a significant decrease in both chemical yield and enantioselectivity (Table 1, entries 5 and 6). On the other hand, the conjugate addition of **2** with imide **3g** proceeded smoothly, but the enantioselectivity (84% *ee*) was somewhat lower than that with **3d** (Table 1, entry 7). Notably, the same reaction with **3d** under dilute conditions (0.1 M solution in toluene) improved the stereoselectivity up to 93% *ee*.

Table 1: Enantioselective Michael addition of malononitrile **2** with α,β-unsaturated acid derivatives **3a**–**g**.[a]



Entry	Substrate (R)	Product	*t* [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**	216	27	56
7	**3g**	**4g**	8	94	84

[a] The reaction was conducted with **1a** (10 mol%), **2** (2 equiv), and **3a**–**g** in toluene (0.5 M). [b] Yield of isolated product. [c] The *ee* values were determined by HPLC analysis of **4a**–**g** with a chiral column.

Encouraged by the excellent results obtained with *N*-acylpyrrolidinone **3d** and thiourea **1a**, we explored the effectiveness of a bifunctional urea **1b** and other bifunctional thioureas **1c**–**f** for the Michael addition (Table 2). The reaction of **2** with **3d** in the presence of urea **1b** gave a similar result, affording the desired product **4d** in somewhat lower yield (78%, 87% *ee*; Table 2, entry 1). However, the introduction of phenyl and 3,5-bis(trifluoromethyl)phenyl groups on the aromatic ring of **1a** as well as modification of its dimethylamino group led to significant decrease in reaction rate and enantioselectivity (Table 2, entries 2–4). Furthermore, the (*N*-methylpyrrolidin-2-yl)methyl derivative **1f** was not catalytically active in the Michael reaction and resulted in a low yield of **4d**. These results demonstrated that the original thiourea **1a** was the best choice as a chiral organocatalyst.

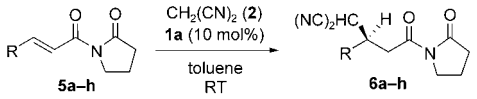
Table 2: Enantioselective Michael addition of **2** and imide **3d** in the presence of several bifunctional thioureas **1a**–**f**.

Entry	**1**	*t* [h]	Yield [%][a]	*ee* [%][b]
1	**b**	48	78	87 (*R*)
2	**c**	120	66	60 (*R*)
3	**d**	120	78	69 (*R*)
4	**e**	120	61	48 (*R*)
5	**f**	120	13	3 (*S*)

[a] Yield of isolated product. [b] Determined by HPLC analysis of **4d** with a chiral column.

Having established the optimal reaction conditions for the enantioselective Michael reaction of malononitrile (**2**), we next screened a series of analogues **5a**–**h**, which bear various β substituents. As illustrated in Table 3, imides **5a**–**h** underwent conjugate addition of **2** in the presence of catalyst **1a** in high yields and enantioselecivities, which were almost independent of the β substituents in terms of steric hindrance and electronic properties. The reaction with aryl-substituted

Table 3: Asymmetric Michael addition of **2** and various α,β-unsaturated imides **5a–h** with **1a**.

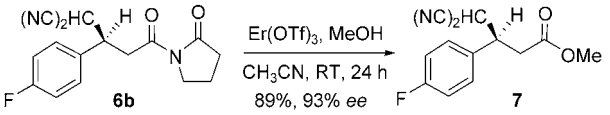


Entry	**5** (R)	*t* [h][a]	**6**	Yield [%][a, b]	*ee* [%][a, c]
1	**a** (*p*-ClC_6H_4)	72 (192)	**a**	85 (88)	89 (93)
2	**b** (*p*-FC_6H_4)	48 (168)	**b**	99 (84)	88 (93)
3	**c** (*p*-$MeOC_6H_4$)	216	**c**	77	85
4	**d** (1-naphthyl)	48 (168)	**d**	93 (87)	88 (93)
5	**e** (2-furyl)	192	**e**	79	85
6	**f** ($PhCH_2CH_2$)	24 (144)	**f**	96 (98)	88 (94)
7	**g** (Me)	24 (120)	**g**	82 (86)	84 (93)
8	**h** (*t*Bu)	168	**h**	78	92

[a] The values in parentheses were obtained from reactions carried out in a 0.1 M solution. [b] Yield of isolated products, after chromatography, of reactions carried out in a 0.5 M solution. [c] Determined by chiral HPLC analysis.

imides **5a–c** proceeded with high enantioselectivity to furnish the addition adducts **6a–c**, while the rate of the reaction was somewhat lower for **5c** (R = *p*-methoxyphenyl) owing to the electron-rich substrate (Table 2, entries 1–3). Similarly, imides **5d–e** bearing 1-naphthyl and furyl groups as the β substituent underwent clean reaction as well, and gave the corresponding adducts **6d–e** with 85–88% *ee* (Table 2, entries 4–5). In contrast to the previously reported Michael addition with nitroalkenes,[9] the present reaction of **2** with imides **5f–h**, which bear alkyl groups as the β substituent, occurred smoothly to afford the desired products **6f–h** in good yields with high enantioselectivities similar to those of **5a–e**. The highest enantioselectivity (92% *ee*) was obtained under the standard conditions in the case of *tert*-butyl derivative **5h**. Furthermore, it is noteworthy that when the reactions were carried out in a 0.1M solution, the all the corresponding products were obtained with higher enantioselectivities (> 93% *ee*).

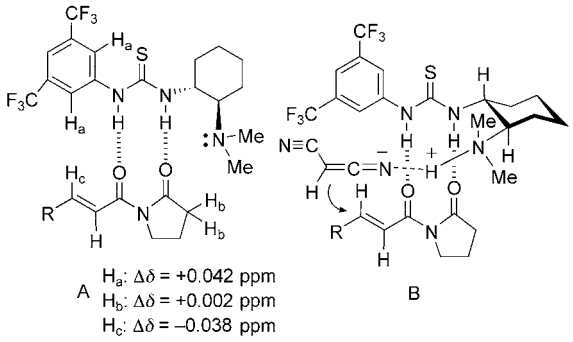
The absolute configuration of the Michael adduct **6b** was determined by the transformation of **6b** into a known compound **7**[7b] (Scheme 2). Treatment of **6b** with a catalytic



Scheme 2. Transformation of Michael adduct **6b** to methyl ester **7**.

amount of $Er(OTf)_3$ in methanol provided methyl ester **7** ($[\alpha]_D^{24} = +22$; $c = 0.70$, CH_3CN) in 89% yield. By comparing $[\alpha]_D$ value with that of an authentic sample ($[\alpha]_D^{24} = +19$; $c = 1.0$, CH_3CN),[7b] the absolute configuration of **6b** was determined to be *R*, and those of the other adducts **6a** and **6c–h** were also assumed to be *R* based on this result.

The formation of a substrate–catalyst complex **1a**·**3d** (**A**; R = Ph) was supported by ^1H NMR spectroscopic experiments (1:1 mixture of **1a** and **3d** in [D_8]toluene), as shown in Scheme 3. From these results, we propose a ternary complex



Scheme 3. ^1H NMR spectroscopic experiments of a substrate–catalyst complex **A** and proposed transition state **B** for the Michael reaction with **1a**.

B of catalyst **1a**, malononitrile (**2**), and imide **5** as a plausible transition state in which **5** and the anion of **2** coordinate to the thiourea moiety and the tertiary amine group of **1a**, respectively, through hydrogen-bonding interactions. The predominant production of *R* adducts is reasonably explained by this transition-state model.

In summary, we have developed the first highly enantioselective organocatalytic Michael reaction of malononitrile (**2**) with α,β-unsaturated imides **5a–h** in the presence of a bifunctional thiourea **1a**. The pyrrolidinone moiety of α,β-unsaturated imides is demonstrated to play a key role in the thiourea-catalyzed Michael reaction. The reaction is applicable to a variety of α,β-unsaturated imides that bear aryl and alkyl groups as a β substituent, and high enantioselectivities are attained. Unfortunately, the Michael addition of other carbon nucleophiles such as malonates and β-ketoesters with **4d** gave no desired products owing to their low reactivities. Further investigations into the mechanism and synthetic application are underway and will be reported in due course.

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