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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Highly Enantioselective Michael Reaction between α,β-Unsaturated Ketone and Malonic Acid Half-thioester

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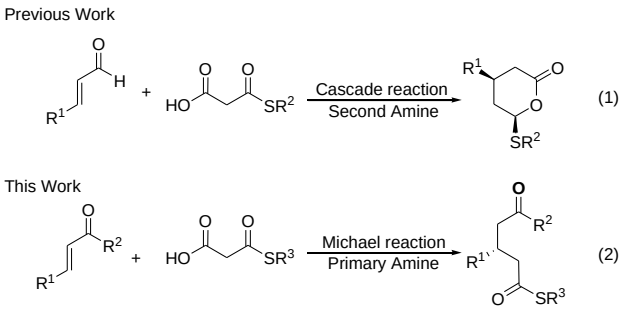
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

We disclose herein an efficient enantioselective organocatalytic Michael reactions between α,β-unsaturated ketones and malonic acid half thioesters (MAHTs). The reactions are catalyzed by a primary amine to generate Michael addition products in good to excellent yields (62-87%) with high to excellent enantioselectivities (80-98%).

The asymmetric Michael reaction is one of the most useful and powerful tools to form new carbon-carbon bond between various nucleophiles and α,β-unsaturated carbonyl compounds.[1] Since 2000, chemists have developed primary and secondary amine organocatalysts to catalyze the asymmetric Michael reaction by forming an iminium intermediate with a carbonyl compound.[2-3] Besides, chemists are also inspirited by the ability of nature. In the biosynthesis of polyketides, requiring the generation of ester enolates, the use of strong bases is avoided by using the more acidic malonic acid half thioesters.[4] By far, chemists have paid much attention on the decarboxylative reactions of malonic acid half thioesters (MAHTs).[5] As the precursors of ester enolates, malonic acid half thioesters (MAHTs) allows a mild base to form the ester enolates. This feature makes MAHT as an ideal substrate in organocatalytic reaction.

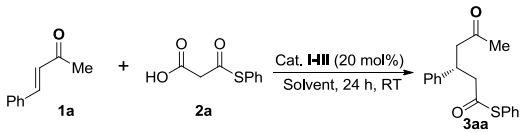
In the decarboxylative processes of MAHTs, various electrophiles have been used as the reaction partners under either metal[6] or metal-free conditions.[7] Recently, the catalytic enantioselective decarboxylative Michael addition reactions of MAHTs have also been well studied.[8] However, to the best of our knowledge, the examples of enantioselective decarboxylative Michael reactions between α,β-unsaturated carbonyl compounds and MAHTs are still rare. In 2012, our group reported a facile synthesis of 4-substituted 3,4-dihydrocoumarins and 3-hydroxyoxindoles through an organocatalytic decarboxylation process.[9] More recently, our group firstly reported an enantioselective decarboxylative synthesis of δ-lactone through enals and MATHs in the presence of chiral prolinol amine organocatalysts (Scheme 1, (1)).[10] It should be noted that our methodology provided a straightforward way to generate a valuable chiral δ-lactone scaffold, which has potential biological significance in the field of medicinal chemistry. As part of our continued interest in this area, we here reported our new discovery regarding the highly enantioselective Michael reactions between α,β-unsaturated ketones and MAHTs (Scheme 1, (2)).

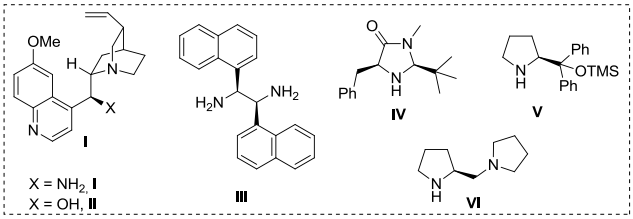


Scheme 1. Organocatalytic Decarboxylation between α,β-Unsaturated Carbonyls and Malonic Half-thioesters.

Our investigation began with α,β-unsaturated ketone **1a** and MAHT **2a** in the presence of organocatalysts **I**-**III**. To our delight, primary amine catalyst **I** could afford the Michael product **3aa** in 65% yield and 90% ee using DCM as the solvent at room temperature (Table 1, entry 1). Catalyst **II** gave no desired product. This result indicated that the amino group is critical for catalyst activity. Catalyst **III** also gave no reaction, which possibly caused by the absence of tertiary amine functional group in catalytic structure. We also examined secondary amine catalysts. As shown in Table 1 (entries 4 and 5), catalysts **IV** and **V** both gave poor activities. Lastly, catalyst **VI**, bearing both a secondary amine group and a tertiary amine group, was found to give no desired product **3aa**, but starting material 2a was fully converted to by product S-phenyl ethanethioate (entry 6). The plausible reason is that tertiary amine promoted the decarboxylation of MAHTs to generate S-phenyl ethanethioate. From above results, we envisioned that catalyst's activity is largely associated with a combination of primary and tertiary amine functional groups. After identifying catalyst **I** as the best catalyst for this reaction,

Table 1. Exploration of the Decarboxylative Michael Reaction of MAHTs **2a** to *trans*-4-Phenyl-3-buten-2-one **1a**.[a]





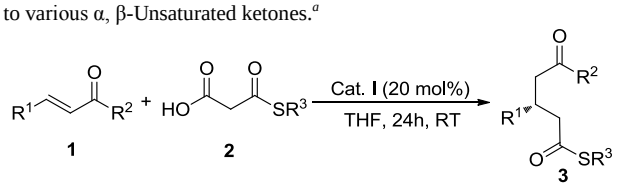
Entry	Catalyst	Solvent	T/°C	Yield (%)[b]	*ee* (%)[c]
1	**I**	DCM	RT	65	90
2	**II**	DCM	RT	trace	-
3	**III**	DCM	RT	trace	-
4	**IV**	DCM	RT	trace	-
5	**V**	DCM	RT	trace	-
6	**VI**	DCM	RT	trace	-
7	**I**	DCE	RT	56	88
8	**I**	Toluene	RT	54	92
9	**I**	Xylenes	RT	52	90
10	**I**	$PhCF_3$	RT	52	84
11	**I**	EtOAc	RT	68	95
12[d]	**I**	EtOAc	0	<10	-
13	**I**	IPA	RT	44	84
14	**I**	1,4-Dioxane	RT	53	98
15	**I**	Et_2O	RT	76	93
16	**I**	CH_3CN	RT	52	57
17	**I**	THF	RT	81	97
18[e]	**I**	THF	RT	72	96

[a] Reactions were conducted with *trans*-4-phenyl-3-buten-2-one **1a** (0.20 mmol), MAHT **2a** (0.50 mmol) in the solvent (1.0 mL) at RT for 24h.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] 0 °C.
[e] 10 mol% of **I**, 48 h.

further optimizations revealed that the solvent is the crucial factor for this process. For instance, when the reactions were carried out in toluene, xylenes and $PhCF_3$, moderate results (52-54% yields, 84-92% ee) were obtained (Table 1, entries 8-10). If EtOAc or Et_2O was used as the solvent, the yield would increase to 68% and 76% with the ee values maintained (Table 1, entries 11 and 15). If we changed the solvent as 1,4-dioxane or DCE, similar results (53-56% yield, 88-98% ee) were observed (Table 1, entries 7, 11). However, if we choose CH_3CN as the solvent, the yield was similar as other solvents, but ee value would decrease to 57% (Table 1, entry 16). Finally, THF was selected as the best solvent. When the reaction was conducted in THF, the Michael product **3aa** would be obtained in 81% yield and 97% ee (Table 1, entry 17). However, if we conducted the reaction at 0°C using EtOAc as the solvent, the yield would significantly diminished to <10% (Table 1, entry 9). Therefore, we decided to conduct the reaction at room temperature. If the catalyst loading was reduced to 10 mol%, the yield will slightly decrease to 72% after 48 h, but ee value was still maintained (Table 1, entries 18). Finally, the best result was achieved by performing the Michael reaction in the presence of 20 mol% of catalyst **I** at room temperature using THF as solvent (Table 1, entry 17).

With the optimized reaction conditions in hand, we then investigated the scope of this transformation by varying α,β-unsaturated ketones **1**. As summarized in table 2, the optimized reaction conditions allowed various α,β-unsaturated ketones containing different groups, regardless of electron-donating or electron-withdrawing properties, giving the corresponding

Table 2. Enantioselective Decarboxylative Michael Reaction of MAHTs to various α, β-Unsaturated ketones.[a]



Entry	R^1	R^2	R^3	Yield (%)[b]	*ee* (%)[c]
1	Ph	Me	Ph	81	97
2	4-FC_6H_4	Me	Ph	76	97
3	4-*i*-PrC_6H_4	Me	Ph	87	97
4	4-allyloxy C_6H_4	Me	Ph	71	96
5	4-$BnOC_6H_4$	Me	Ph	78	97
6	3-$MeOC_6H_4$	Me	Ph	75	97
7	2-furyl	Me	Ph	85	98
8	2-thiophenyl	Me	Ph	76	97
9	Me	Me	Ph	78	97
10	Me	Et	Ph	70	98
11	Ph	Me	4-ClC_6H_4	73	95
12	Ph	Me	2-$MeOC_6H_4$	80	98
13	Ph	Me	3,4-$(MeO)_2$ C_6H_4	71	96
14	-(CH_2CH_2)-		Ph	62	80

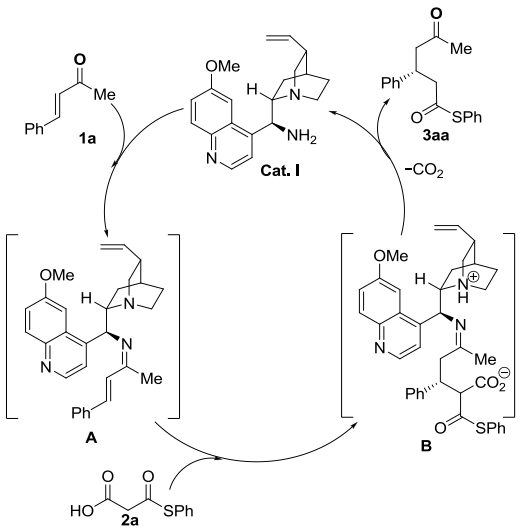
[a] Reactions were conducted with α, β-unsaturated ketones **1** (0.20 mmol), MAHT **2** (0.50 mmol) in THF (1.0 mL) at RT for 24h.
[b] Isolated yield after column chromatography.
[c] Determined by HPLC analysis.

products in good to high yields (71-87%) and high to excellent ee values (96-97%) (Table 1, entries 1-6). It is noteworthy that heterocyclic rings such as furan and thiophene rings were also tolerated in substrates, affording the desired products in high yields and excellent ee values (Table 2, entries 7-8). Notably, for alkyl α,β-unsaturated ketones, a slightly inferior result was obtained (Table 2, entries 9-10). In addition, cyclic enone also indicated a moderate catalytic activity and enantioselectivity in this system (Tabe 2, entry 14, 62% yield, 80% ee). Next, we examined the scope of malonic acid half thioesters. To our delight, a number of MAHTs were participated in this process and afforded high yields and high ee values (Table 2, entries 11-13). The absolute configuration of **3** (R^1 = 4-BrC_6H_4, R^2 = Me, R^3 = Ph) was determined by X-ray crystallography, and the other products were assigned by analogy.[11]

As shown in scheme 2, a plausible mechanism is proposed to explain the reaction process. First of all, α, β-unsaturated ketone **1a** can be activated the primary amine group of catalyst **I** through the formation of iminium intermediate **A**. Notably, due to the less steric hindrance, primary amine group is more active than secondary amine group in proceeding to form iminium intermediate. Then the Michael reaction took place between iminium intermediate **A** and malonic acid half thioester **2a** to form the intermediate **B**, which released the catalyst **I** and CO_2 to generate the final product **3aa**. In this step, the tertiary amine group of catalyst **I** assists the decarboxylation process by working as a base. We envisioned that a combination of primary amine group and tertiary amine group is the best choice to allow the catalyst to exhibit a high reaction activity.

In summary, an efficient enantioselective organocatalytic

decarboxylative Michael reaction between α,β-unsaturated ketones and malonic acid half thioesters (MAHTs) has been developed. The reaction is catalyzed by a chiral primary amine to give the Michael addition products in high yields and good to excellent enantioselectivities. Considering the large variety and ready availability of the starting materials (α,β-unsaturated ketones) and the operational simplicity, we believe that this work will have a widely practical use in the future and will attract more research attentions to this area. Such studies are actively under way in our laboratory, and more results will be reported in due course.



Scheme 2. A proposed reaction mechanism.

Experimental

To a solution of *trans*-4-Phenyl-3-buten-2-one **1a** (29.2 mg, 0.2 mmol), catalyst **I** (12.9 mg, 0.04 mmol) and THF (1.0 mL) was added malonic acid half thioester **2a** (98.1 mg, 0.50 mmol) in one portion. The reaction mixture was kept stirring at room temperature for 24 h. The crude product was purified by silica gel flash chromatography, eluted by hexane/EtOAc = 10:1 to afford the desired product **3aa** as colorless oil (48.3 mg, 81% yield); HPLC (Chiralpak IC, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 15.6 min, t_R (minor) = 20.5 min, *ee* = 97%; $[\alpha]^{25}_D$ = -74.2 (*c* = 1.01 in DCM).

Acknowledgements

Financial support from China Hubei Collaborative Innovation 2011 Project and National Natural Science Foundation of China (21202136) are greatly appreciated.

Notes and references

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11 CCDC 903996 (**3,** R^1 = 4-BrC_6H_4, R^2 = Me, R^3 = Ph) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.