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Organocatalytic enantioselective Michael addition of thioacetic acid to enones

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Abstract—An enantioselective, organocatalytic Michael addition reaction of thioacetic acid with enones has been developed. The process, catalyzed by a chiral bifunctional amine thiourea, furnishes products in excellent yields with up to 63% ee.

The preparation of sulfur-containing molecules has long been a mainstay of organic synthesis as a result of their broad application to organic and medicinal chemistry.[1] Conjugate addition of sulfur-centered nucleophiles to α,β-unsaturated carbonyls serves as a powerful synthetic method in this area of sulfur chemistry.[2–5] While an asymmetric version of this Michael addition process would furnish enantiomerically enriched adducts, to date reports of this reaction are sparse.[4,5] A great deal of effort has been directed toward the use of strong nucleophilic thiols as a Michael donor.[4,5] However, the employment of weakly nucleophilic thioacid (RCOSH) for the Michael addition reaction has not been explored. From a synthetic perspective, the resulting thioester can be readily transformed into versatile SH group under various, mild reaction conditions.[6] Along this line, recently, we have disclosed an organocatalytic enantioselective approach for the Michael addition of thioacetic acid to β-nitrostyrenes in high yields (91–98%) with up to 70% ee.[7] In our continuing effort in the area, we wish to describe the results of an investigation which has led to the development of an efficient method for carrying out enantioselective Michael addition reactions of thioacetic acid with α,β-unsaturated ketones by using a bifunctional amine thiourea.

In the exploratory investigation, we surveyed six bifunctional organocatalysts[8–10] including Takemoto's catalyst **I**,[11,12] chiral binaphthyl-derived amine thiourea **II**,[13] developed in our laboratory, a quinine-based thiourea **III**,[14] and cinchona alkaloids quinine **IV**, quinidine **V**, and quinine-OH **VI**.[15] These catalysts can provide two site activations of substrates (Fig. 1). Subsequently, such synergistic activation by two functionalities on the catalyst can lead to specific control of the transition state structure, thus resulting in products with good yields and high stereocontrol.[16] To test their catalytic ability to promote asymmetric Michael addition, a reaction between *trans*-chalcone **1a** and thioacetic acid **2** in the presence of 10 mol % catalyst in Et_2O at rt was carried out. Examination of the results of the studies reveals that the organocatalyzed processes proceeded smoothly (3–4 h) in high yields ($\geqslant$90%), but the enantioselectivities varied significantly (Table 1). Among the organocatalysts probed, catalyst **I** displayed the highest enantioselectivity (58% ee, Table 1, entry 1). No or lower ee was observed for other organocatalysts (entries 2–6). Utilization of thiobenzoic acid (**2b**) as a Michael donor resulted in longer time (12 h), lower yield (41%) and poorer 33% ee (Table 1, entry 7).

A survey of solvents revealed that the reaction media had a significant effect on this process. For example, the reaction carried out in Et_2O and THF gave highest enantioselectivities (58%, 58%, respectively, Table 2, entries 1 and 3). Lower enantioselectivities were observed when other solvents were used in the processes (Table 2, entries 4–9). By lowering the temperature to 0 °C for reaction in Et_2O, interestingly the enantioselectivity was decreased to 44% ee (Table 2, entry 2). Thus, Et_2O was selected as the reaction medium for reactions to probe the scope of the asymmetric processes at room temperature.

Keywords: Amine thiourea; Asymmetric organocatalysis; Enones; Michael addition reaction; Thioacetic acid.
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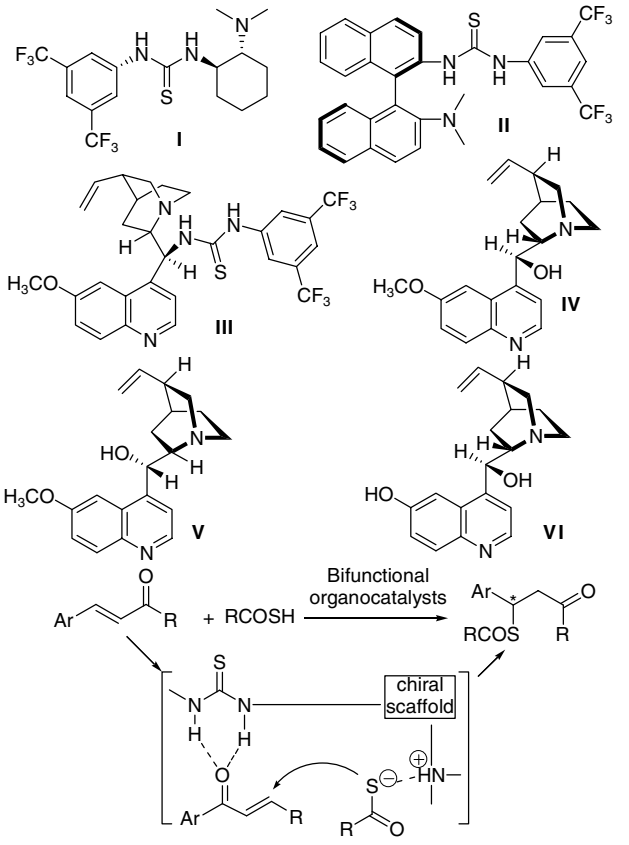
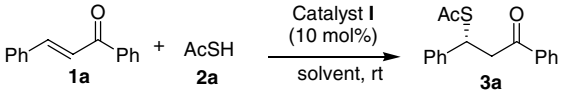


Figure 1. Organocatalysts for asymmetric Michael addition reactions.

To demonstrate the generality of direct Michael reactions catalyzed by thiourea **I**, reactions of a variety of enones **1** with thioacetic acid **2** in Et_2O at rt were explored (Table 3). All processes took place smoothly to give products in excellent yields (>95%) with moderate ee (33–65% ee, entries 1–2 and 4–10). Relatively low ee values were observed for the chalcones containing electron-withdrawing groups (Table 3, entries 2 and 4–6). However, the chalcones containing neutral or electron-donating groups gave products with higher enantioselectivities (entries 1 and 7–9). The reaction is also applicable to heterocyclic systems (e.g., thiophene, entry 10) with 55% ee. When *trans*-4-phenyl-3-buten-2-one was used as Michael acceptor, the reaction occurred in high yield (93%) with lower ee (15%) (entry 11). Interestingly, no ee was observed for enone containing aliphatic substituents at both ends (entry 12). In a controlled study, in the absence of catalyst **I**, the reaction proceeded much slower with lower yield (24 h, 75% yield) (Table 3, entry 3). This indicates that the catalyst can facilitate the process. The absolute configuration of **3g** was determined by X-ray crystallography to be *R* (Fig. 2).[17]

Table 2. Effect of solvents on the asymmetric Michael addition reactions[a]

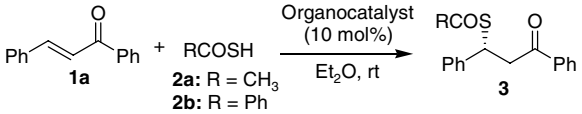


Entry	Solvent	*t* (h)	Yield[b] (%)	ee[c] (%)
1	Et_2O	3	95	58
2[d]	Et_2O	8	93	44
3	THF	4	93	58
4	Toluene	4	90	27
5	CH_2Cl_2	4	92	43
6	$CHCl_3$	4	92	47
7	CH_3CN	4	91	35
8	Dioxane	4	92	38
9	Benzene	4	90	24

[a] See footnote a in Table 1.
[b] Isolated yield after chromatographic purification.
[c] Determined by chiral HPLC analysis (Chiralpak AS-H).
[d] The reaction was run at 0 °C.

In conclusion, we have developed a catalytic variant of the asymmetric Michael addition reactions between chalcones and thioacetic acid. The reactions are catalyzed by bifunctional amine thiourea **I**, affording synthetically useful thioesters in excellent yields with moderate enantioselectivities. The full scope and the further improvement of enantioselectivity of the process and its application in the synthesis of biologically active molecules are under investigation.

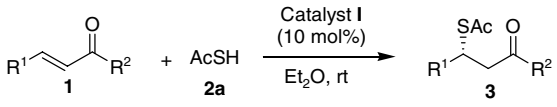
Table 1. Asymmetric Michael addition of thioacid (**2**) to *trans*-chalcone (**1a**) catalyzed by organocatalysts[a]

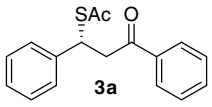
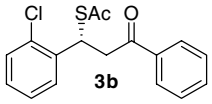
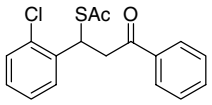
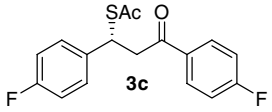
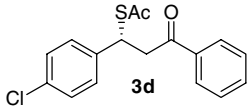
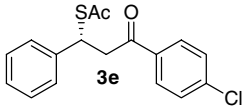
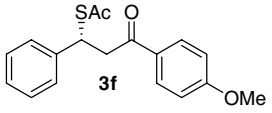
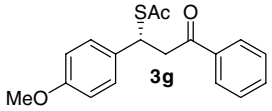
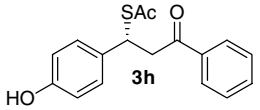
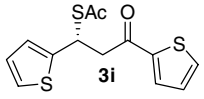
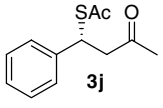
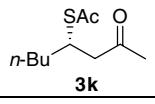


Entry	Catalyst	R	*t* (h)	Yield[b] (%)	ee[c] (%)
1	**I**	Me	3	95	58
2	**II**	Me	4	90	0
3	**III**	Me	4	91	26
4	Quinine **IV**	Me	4	92	12
5	Quinidine **V**	Me	4	91	0
6	Hydroquinine **VI**	Me	4	92	8
7	**I**	Ph	12	41	33

[a] Unless otherwise specified, the reaction was carried out using **1a** (0.1 mmol) and **2** (0.2 mmol) in the presence of 10 mol % catalyst in 0.5 mL of solvent at room temperature.
[b] Isolated yields after chromatographic purification.
[c] Determined by chiral HPLC analysis (Chiralpak AS-H).

Table 3. Catalytic asymmetric Michael addition of thioacetic acid to chalcones[a]



Entry	Product	*t* (h)	Yield[b] (%)	ee[c] (%)
1	 **3a**	3	95	58
2	 **3b**	3	97	51
3[d]		24	75	0
4	 **3c**	3	100	33
5	 **3d**	3	97	37
6	 **3e**	3	96	48
7	 **3f**	3	97	50
8	 **3g**	3	97	53
9	 **3h**	24	95	65
10	 **3i**	3	97	55
11	 **3j**	10	93	15
12	 **3k**	12	90	0

[a] See footnote a in Table 1 and Supplementary data.
[b] Isolated yield after chromatographic purification.
[c] Determined by chiral HPLC analysis (Chiralpak AS-H).
[d] The reaction was run without catalyst **I**.

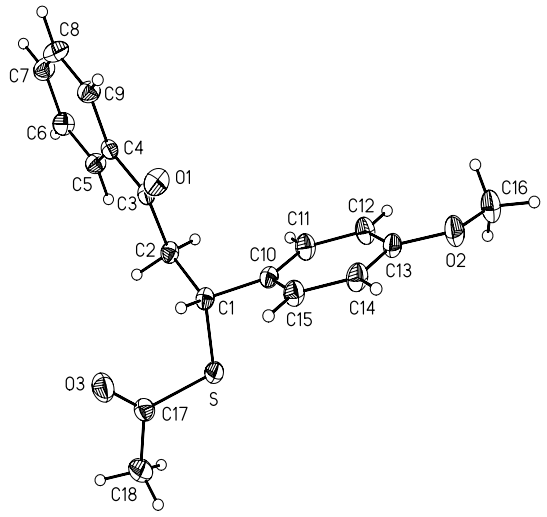


Figure 2. X-ray crystal structure of **3g**.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.02.140.

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17. See Supplementary data for X-ray crystallographic information; CCDC 283456 also contains Supplementary crystallographic data. These data can be obtained free of charge via www.ccdc.cam.ac.uk.