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Enantioselective sulfa-Michael addition of thioacids to α,β-unsaturated ketones with bifunctional organocatalyst

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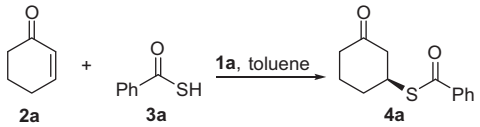
ABSTRACT

Organocatalytic conjugate addition of thioacids to α,β-unsaturated ketones has been studied in the presence of *cinchona* alkaloid derived urea catalyst. Both the enantiomers of products are accessible with the same level of enantioselectivity using *pseudoenantiomeric* quinine/quinidine derived catalysts. The catalytic process provides optically active thioesters with high chemical yields (up to 99%) and useful enantioselectivity (up to 83% ee). The reaction was performed with 1 mol % of catalyst in toluene at room temperature. A transition state model has been proposed to explain the stereochemical outcome of the reaction.

Sulfur containing chiral frameworks are common in valuable biologically active natural products and pharmaceutical agents.[1] The asymmetric reaction of sulfur-centered nucleophiles with electron-deficient olefins, viz. sulfa-Michael addition (SMA), offers a convenient and practical method for the preparation of enantiomerically enriched sulfur containing molecules.[2] In recent years, a great deal of efforts have been directed toward the development of enantioselective sulfa-Michael addition. Asymmetric protonation in sulfa-Michael addition to α-substituted acrylates enabled access to stereogenic center in the addition/protonation product β to sulfur atom.[3] Tandem sulfa-Michael/aldol and sulfa-Michael/Michael have also been investigated.[4] Unfortunately, enantioselective sulfa-Michael addition promoted by both chiral metal-complexes and organocatalysts have been limited to the use of aromatic[5] and aliphatic thiols.[6] The optically active thioethers, obtained by the asymmetric 1,4-addition of aromatic thiols to enones, could not be easily cleaved selectively or transformed into versatile thiol groups. After the pioneer report of Gawronski et al.,[7a] enantioselective Michael addition of thioacids to α,β-unsaturated ketones has become a useful method for the preparation of optically active keto-thioesters,[7] which could easily be converted into versatile thiol groups under mild reaction conditions.[8] Organocatalytic asymmetric conjugate addition of thioacetic acid to β-nitroalkenes has also been reported.[9] Most of the reported methods have limited substrate scope and low stereoselectivity. Thus, there is still a need to develop catalyst systems for the Michael addition reaction of thioacids to α,β-unsaturated carbonyls, which can show substrate generality and high enantioselectivity. In recent years, the asymmetric Michael addition reactions promoted by chiral bifunctional thiourea derivatives derived from cinchona alkaloids have been recognized as an effective method for asymmetric carbon–carbon and carbon–hetero bond formation.[10] We have recently reported an effi-

Table 1
Effect of catalyst loading and temperature on enantioselective sulfa-Michael addition of thiobenzoic acid to 2-cyclohexenone[a]



2a **3a** **4a**

Entry	**1a** (mol %)	Temp (°C)	Time (h)	Yield (%)	ee[b] (%)
1	10	rt	2	99	29
2	5	rt	5	99	56
3	2	rt	10	99	59
4[c]	1	rt	18	99	64
5	0.5	rt	36	99	64
6	0.1	rt	48	90	49
7	1	10	24	99	60
8	1	0	24	97	60
9	1	−15	36	94	59
10	1	−30	48	90	49
11	1	−60	48	81	44

[a] Reactions were carried out with 0.2 mmol of **2a** and 0.24 mmol of **3a** in 1 mL of toluene, unless noted otherwise.
[b] Determined by HPLC using Chiralcel OD-H column.
[c] Absolute stereochemistry of the product was determined to be (*S*).[12]

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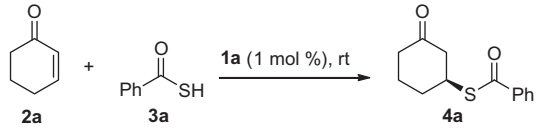
Table 2
Effect of solvent on enantioselective sulfa-Michael addition of thiobenzoic acid to 2-cyclohexenone[a]



2a **3a** **4a**

Entry	Solvent	Time (h)	Yield (%)	ee[b] (%)
1	Toluene	18	99	64
2	*m*-Xylene	18	99	46
3	*n*-Hexane	18	99	44
4	CH_2Cl_2	14	99	41
5	$CHCl_3$	14	99	46
6	DCE	14	99	34
7	THF	18	99	30
8	Et_2O	18	99	44
9	1,4-Dioxane	18	99	42
10	Acetonitrile	12	99	12

[a] Reactions were carried out with 0.2 mmol of **2a** and 0.24 mmol of **3a** in 1 mL of solvent at rt, unless noted otherwise.
[b] Determined by HPLC using Chiralcel OD-H column.

cient catalytic asymmetric sulfa-Michael addition reaction of aromatic thiols to α,β-unsaturated ketones.[11]

In our continuing efforts, we chose to explore the unique reactivity profile of thioacids by its addition to α,β-unsaturated ketones. Here, we report catalytic asymmetric sulfa-Michael addition of thioacids to α,β-unsaturated ketones catalyzed by a bifunctional *epi-quinine* amine urea.

In our previous report, quinine derived urea **1a** was found to be an efficient organocatalyst in the enantioselective Michael addition of aromatic thiols to α,β-unsaturated ketones.[11] With the understanding of activation modes of **1a**, we selected it as pivot point for the enantioselective addition of thioacid to α,β-unsaturated carbonyl compound. Treatment of 2-cyclohexenone with thiobenzoic acid in the presence of 10 mol % of the catalyst **1a** in toluene at room temperature furnished the Michael adduct **2a** in a 29% ee and quantitative yield (Table 1, entry 1). The initial results encouraged us to carry out detailed investigation to improve the selectivity. To our delight, decrease in catalyst loading from 10 to 1 mol % led to increase in the enantioselectivity, without affecting the chemical yield of the reaction. When the reaction was carried out with 0.5 mol % of catalyst loading, the enantioselectivity did not improve and a longer reaction time was required for the completion of the reaction. However, further lowering the catalyst loading to 0.1 mol % resulted in the decrease of enantioselectivity and yield of the reaction.

Thus, with optimized catalyst amount, the effect of temperature was investigated. Lowering the reaction temperature did not show much effect on the chemical yield, but the enantioselectivity decreased gradually (Table 1, entries 7–11). The lower enantioselectivity at lower temperature may be due to the different arrangement of transition state. Although a drop in enantioselectivity with lowering temperature is generally uncommon, very similar trend of the enantioselectivity dependence on reaction temperature has been observed for thiourea catalyzed several Michael addition reactions.[3g,7c,11,13] Subsequently, the effect of solvent was studied (Table 2). Among various solvents used for the reaction, toluene was found to be the best in terms of selectivity.

After initial optimization of the reaction conditions with catalyst **1a**, various cinchona alkaloid derived thiourea catalysts (Fig. 1) were screened in the above reaction, and the results are

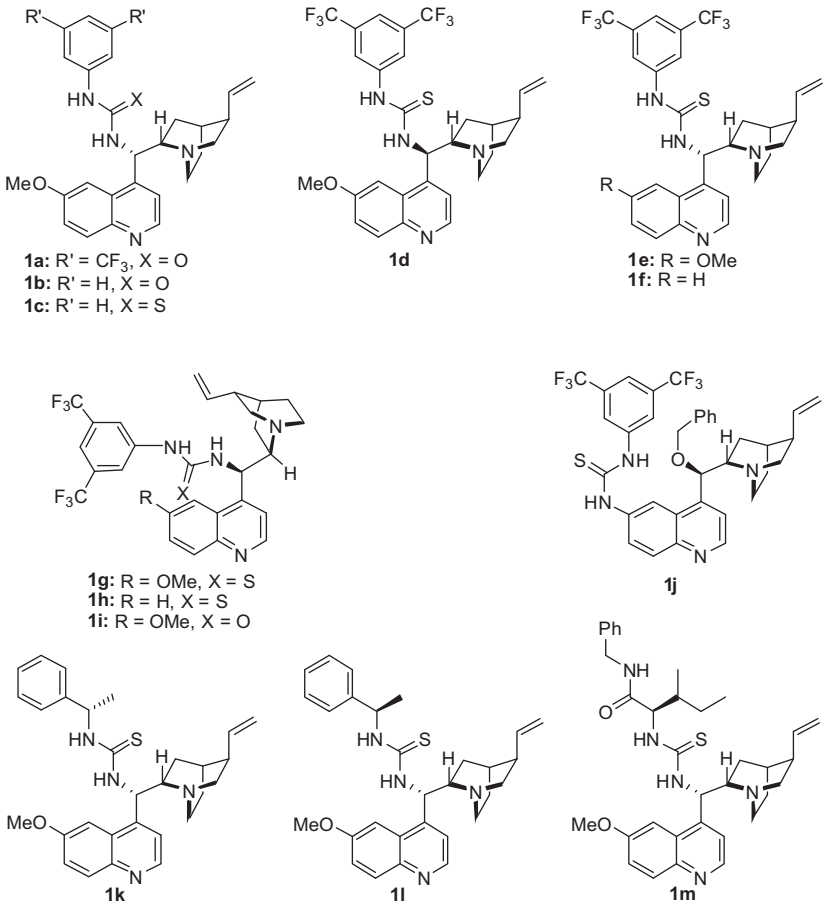
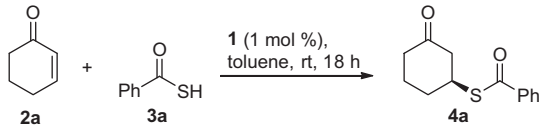


Figure 1. Chiral bifunctional urea/thiourea catalysts.

Table 3
Screening of different chiral catalysts[a]



2a 3a 4a

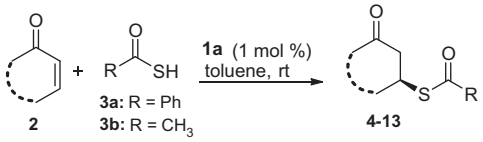
Entry	Catalyst	Yield (%)	ee[b] (%)
1	**1a**	99	64
2	**1b**	99	56
3	**1c**	99	49
4	**1d**	99	05
5	**1e**	99	59
6	**1f**	99	58
7[c]	**1g**	99	58
8[c]	**1h**	99	56
9[c]	**1i**	99	62
10	**1j**	99	10
11	**1k**	99	42
12	**1l**	99	54
13	**1m**	99	25
14[d]	**1a**	99	82

[a] Reactions were carried out with 0.2 mmol of **2a** and 0.24 mmol of **3a** in 1 mL of toluene at rt, unless noted otherwise.
[b] Determined by HPLC using Chiralcel OD-H column.
[c] Opposite enantiomer was obtained as major.
[d] Thioacetic acid was used as a nucleophile and reaction was continued for 24 h.

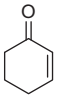
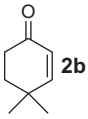
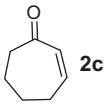
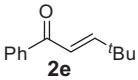
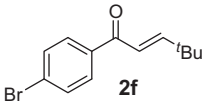
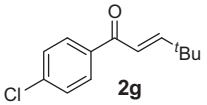
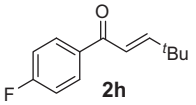
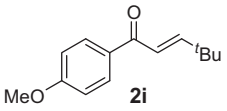
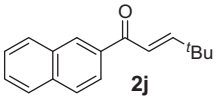
summarized in Table 3. Intensive screening of several chiral catalysts disclosed the significant impact of the substituent and catalyst's chiral scaffold on the enantioselectivity. Slightly lower enantioselectivity with catalysts **1b** and **1c** compared to **1a** indicates that CF_3 substituent on the aromatic ring of the catalyst is crucial (Table 3, entries 2 and 3). A very low enantioselectivity with *epi-quinine* derived catalyst **1d** emphasizes the importance of the correct relative orientation of thiourea and quinuclidine functional groups in the catalyst's chiral scaffold (Table 3, entry 4). Thioureas **1e** and **1f** also were tested in the reaction, however urea **1a** was found to be superior over the corresponding thiourea **1e** catalyst. Sulfa-Michael addition product **4a**, enriched in the opposite enantiomer, was obtained with catalysts **1g–i** (Table 3, entries 7–9). Thus, access to both enantiomers was found to be possible with the same level of enantioselectivity. When 6′-cinchona thiourea **1j** was used for the reaction, poor enantioselectivity was observed (Table 3, entry 10). The result indicates that the appropriate distance between acidic and basic groups is important for high enantioselectivity. Catalysts **1k–m** having additional chiral centers were also employed in the above reaction, but poor enantioselectivities were observed. Finally, the enantioselectivity increased to a great extent by changing the nucleophile from thiobenzoic acid to thioacetic acid (Table 3, entry 14).

With the optimized reaction conditions in hand, a variety of α,β-unsaturated ketones were tested with both thiobenzoic and thioacetic acids as Michael donors and the results are summarized in Table 4. Moderate to good enantioselectivities were obtained in both the cases of 2-cyclohexenone and substituted cyclohexenone (Table 4, entries 1–6). For a few typical cases, both the enantiomers have been achieved with the same level of enantioselectivity by using two *pseudoenantiomeric* catalysts **1a** and **1i**. Interestingly, useful ee's have been achieved with 2-cycloheptenone (Table 4, entries 7–9). However, low enantioselectivity was obtained with cyclopentenone (Table 4, entries 10 and 11). Acyclic α,β-unsaturated ketones offered lower enantioselectivities in most of the cases as compared to cyclic enones. Acyclic enones with 4-halogenated aromatics provided enantioselectivities in the range of 25–46% (Table 4, entries 14–19). Having electron donating substituent on

Table 4
Enantioselective sulfa-Michael addition between thioacids and α,β-unsaturated ketones[a]



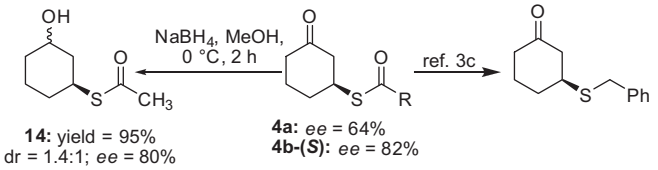
2 **3a:** R = Ph **3b:** R = CH_3 4-13

Entry	Enone **2**	**3**	Time (h)	Yield (%)/ product	ee[b] (%)
1	 **2a**	**3a**	18	99 **4a**	64
2[c]		**3b**	24	99 **4b-(*S*)**	82
3[d]		**3b**	24	99 **4b-(*R*)**	79
4	 **2b**	**3a**	30	99 **5a**	63
5		**3b**	36	99 **5b-(*R*)**	81
6[d]		**3b**	36	99 **5b-(*S*)**	80
7	 **2c**	**3a**	18	99 **6a**	60
8		**3b**	24	99 **6b-(*S*)**	83
9[d]		**3b**	24	99 **6b-(*R*)**	80
10	 **2d**	**3a**	18	99 **7a**	35
11		**3b**	24	99 **7b**	50
12	 **2e**	**3a**	24	99 **8a**	32
13		**3b**	30	96 **8b**	42
14	 **2f**	**3a**	24	95 **9a**	27
15		**3b**	30	92 **9b**	40
16	 **2g**	**3a**	24	99 **10a**	40
17		**3b**	30	98 **10b**	46
18	 **2h**	**3a**	24	99 **11a**	25
19		**3b**	30	99 **11b**	33
20	 **2i**	**3a**	28	92 **12a**	5
21		**3b**	36	90 **12b**	24
22	 **2j**	**3a**	24	99 **13a**	24
23		**3b**	30	95 **13b**	42

[a] Reactions were carried out with 0.2 mmol of **2**, 0.24 mmol of **3,** and 0.002 mmol of **1a** in 1 mL of toluene at rt, unless noted otherwise.
[b] Determined by HPLC using chiral column.
[c] Absolute stereochemistry of the product was determined to be (*S*).[12]
[d] Catalyst **1i** was used and opposite enantiomer was obtained as major.

the aromatic ring of the acyclic enone resulted in poor enantioselectivities (Table 4, entries 20 and 21).

Finally, the synthetic utility of the catalytic process have been demonstrated in Scheme 1. The sulfa-Michael addition product **4b-(*S*)** was successfully transformed into the corresponding 3-hydroxyl thioester **14** in a high yield almost without any loss of enantioselectivity. Additionally, **14** could easily be converted



Scheme 1. Synthesis of chiral 3-hydroxyl thioester and thioethers.

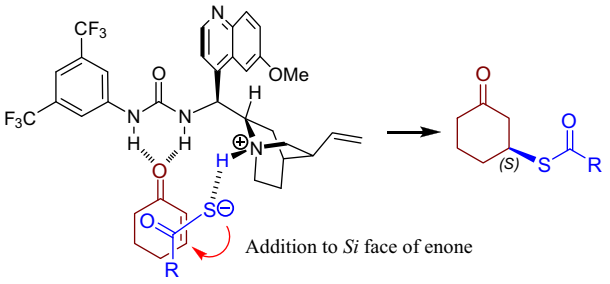


Figure 2. Possible transition state model.

into 1,3-*O*,*S*-diacetate.[7a] In principle, the thioester could also be transformed into the corresponding thioether.[3c]

A possible transition state model is shown in Figure 2 to explain the stereochemical outcome of the reaction. We believe that enone is activated by the urea moiety of the catalyst through double hydrogen bonding, while the thioacid is activated by the tertiary nitrogen of the quinuclidine moiety. Michael addition of thioacid to the *Si* face of the enone leads to the formation of the major stereoisomer.

In conclusion, we have developed a catalytic variant of the asymmetric sulfa-Michael addition of thioacids to α,β-unsaturated ketones. Quinine derived bifunctional organocatalyst **1a** can efficiently catalyze the reaction between thioacids and enones affording synthetically useful thioesters in excellent yields with moderate to good enantioselectivities. Both the enantiomers of products have been achieved with the same level of enantioselectivities by using two *pseudoenantiomeric* catalysts. The resulting thioesters have been converted into the corresponding 3-hydroxy thioester. The full scope and further control over enantioselectivity of the reaction are currently under investigation in our laboratory.

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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.2012.02.052.

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