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Highly Enantioselective Organocatalytic Sulfa-Michael Addition to α,β-Unsaturated Ketones

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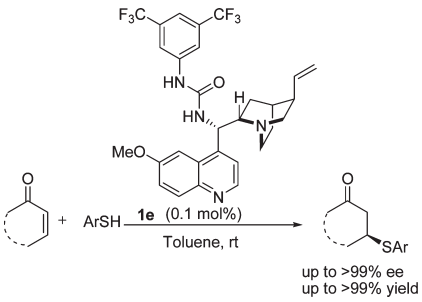

A cinchona alkaloid-derived urea was found to be an efficient organocatalyst for catalyzing enantioselective conjugate addition between thiols and various α,β-unsaturated ketones to provide optically active sulfides with high chemical yields (up to >99%) and enantiomeric excess (up to >99% ee). The reaction was performed with 0.1 mol % of catalyst in toluene at room temperature. A transition state model has been proposed to explain the stereochemical outcome of the reaction.

The catalytic asymmetric Michael addition is one of the most powerful transformations in asymmetric synthesis.[1] In recent years, a remarkable progress has been made in organocatalytic version of this reaction.[2] Among various type of this reaction, sulfa-Michael addition provides direct access to optically active sulfides that are versatile precursors for the synthesis of biologically interesting compounds.[3]

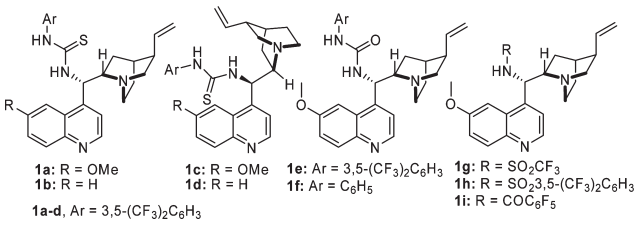

FIGURE 1. Homochiral Brønsted acids.

Successful catalytic systems for the asymmetric version of this reaction include cinchona alkaloid derivatives,[4] heterobimetallic complexes,[5] chiral metal complexes,[6] and organocatalysts.[7] Despite all the progress made in this area, most of the current catalytic systems have certain limitations such as lower substrate scope, low reaction temperatures, relatively high catalyst loading (~20 mol %), and use of additives such as molecular sieves. Hence, it is desirable to develop a catalytic system that can overcome some of the limitations associated with the existing methodologies. Recently, chiral bifunctional thiourea derivatives[8] have appeared to be efficient organocatalysts for the different Michael addition reaction. Among them, cinchona alkaloid-derived thioureas have found wide applications in many enantioselective transformations.[9] As a part of our ongoing program on the development of homochiral Brønsted acids for asymmetric catalysis, we have investigated the reaction of thiols with α,β-unsaturated ketones catalyzed by homochiral Brønsted acids

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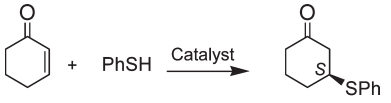
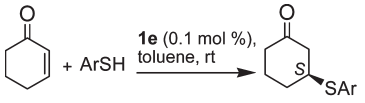
TABLE 1. Optimization of Reaction Condition for the Enantioselective Michael Addition of Thiol to α,β-Unsaturated Enones[a]



entry	catalyst	mol (%)	time (h)	yield (%)	ee (%)[b]
1	**1a**	10	0.5	>99	69
2	**1a**	5	0.5	>99	75
3	**1a**	1	2	>99	86
4	**1a**	0.5	2	>99	88
5	**1a**	0.5	2	>99	61[c]
6	**1a**	0.5	12	98	81[d]
7	**1a**	0.5	12	95	66[e]
8	**1a**	0.5	2	>99	66[f]
9	**1b**	0.5	2	>99	30
10	**1c**	0.5	2	>99	−70
11	**1d**	0.5	2	>99	−44
12	**1e**	0.5	2	>99	92
13	**1f**	0.5	4	>99	84
14	**1g**	0.5	2	>99	4
15	**1h**	0.5	2	>99	8
16	**1i**	0.5	2	>99	10
17	**1e**	0.1	5	>99	94

[a]Reactions were carried out on a 0.5 mmol scale with 0.6 mmol of thiol in 1 mL of toluene at room temperature, unless noted otherwise. [b]Determined by HPLC using chiral column. [c]4 Å molecular sieves were added. [d]Reaction was carried out at 0 °C. [e]Reaction was carried out at −15 °C. [f]CH_2Cl_2 was used as a solvent.

TABLE 2. Enantioselective Michael Addition of Different Aryl Thiols to Cyclohexenone[a]



entry	Ar	time (h)	product	yield (%)	ee (%)[b]
1	C_6H_5	5	**2a**	>99	94
2	2-MeC_6H_4	7	**2b**	>99	95
3	4-MeC_6H_4	7	**2c**	>99	92
4	2,4-$Me_2C_6H_3$	9	**2d**	>99	88
5	2,6-$Me_2C_6H_3$	10	**2e**	>99	99
6	2-EtC_6H_4	8	**2f**	>99	90
7	2-naphthyl	6	**2g**	97	93
8	4-$^tBuC_6H_4$	8	**2h**	>99	92
9	2-$MeOC_6H_4$	10	**2i**	>99	97
10	4-$MeOC_6H_4$	8	**2j**	>99	>99
11	2-FC_6H_4	5	**2k**	>99	90
12	4-FC_6H_4	5	**2l**	>99	91
13	2,4-$F_2C_6H_3$	5	**2m**	>99	85
14	2-ClC_6H_4	6	**2n**	>99	91
15	4-ClC_6H_4	6	**2o**	>99	92
16	2-BrC_6H_4	10	**2p**	95	90
17	4-BrC_6H_4	10	**2q**	97	89

[a]Reactions were carried out on a 0.5 mmol scale with 0.6 mmol of thiol in 1 mL of toluene at room temperature, unless noted otherwise. [b]Determined by HPLC using chiral column.

(Figure 1). In this Note, we wish to report the highly enantioselective organocatalytic conjugate addition of thiols with α,β-unsaturated ketones.

At the outset, sulfa-Michael reaction of thiophenol with cyclohexenone was examined using thiourea **1a**. Treatment of thiol with cyclohexenone in the presence of 10 mol % of the catalyst **1a** in toluene at room temperature furnished Michael adduct **2a** in 69% ee (Table 1, entry 1). To our delight, on decreasing the catalyst loading from 10 to 0.5 mol %, the enantioselectivity increased to a great extent, with no appreciable change in chemical yield of the reaction (Table 1, entries 2−4). Increase in enantioselectivity with low catalyst loading indicates the formation of a more stereocontrolled transition state at low local catalyst concentration. Addition of 4 Å molecular sieves had negative effect on the enantioselectivity of the reaction (Table 1, entry 5). Role of water on the enantioselectivity enhancement was not clear. But, we believe that it plays a crucial role in stabilizing the transition state via weak hydrogen bonding. However, using water as a reaction medium led to racemic product.[10]

Lowering the reaction temperature to 0 °C and −15 °C did not show any effect on the chemical yield, but the enantioselectivity decreased when the reactions were carried out at lower temperatures (Table 1, entries 6 and 7). However, on changing the reaction medium to CH_2Cl_2,[10] the product was formed in high yield and moderate enantioselectivity (Table 1, entry 8).

After optimizing reaction conditions with **1a**, various chiral Brønsted acid catalysts **1b**−**i** with different hydrogen bond donating arms were screened in the above reaction, and the results are summarized in Table 1. However, the enantioselectivities varied greatly depending on the organocatalyst used. The poor enantioselectivity with catalysts **1b**−**d** and **1g**−**i** emphasize the correct relative orientation of acidic and basic functional groups and importance of double hydrogen bonding in the catalyst's chiral scaffold. The lower enantiomeric excess with catalyst **1f** clearly indicates that CF_3 substituent on the aromatic ring is crucial for the observed enantioselectivity (Table 1, entries 12 and 13). Finally, we were pleased to find that lowering the catalyst loading to 0.1 mol % had a positive effect on the enantioselectivity and the product **2a** was obtained in 94% ee while a good level of conversion was maintained (Table 1, entry 17).

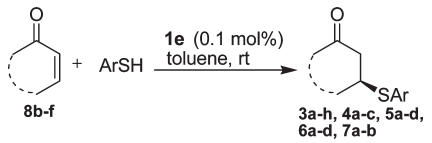
Having identified the optimized condition for this reaction, a variety of aromatic thiols were then tested by using cyclohexenone as an acceptor (Table 2). High enantioselectivities were obtained in almost all the cases. It is noteworthy that not only the steric hindrance of the substituents at the aromatic rings but also the electronic nature has no effect on the enantioselectivity.

To extend the scope of the reaction, Sulfa-Michael addition of other cyclic and acyclic enones was studied (Table 3). Excellent enantioselectivities were achieved with wide variety of cyclic and acyclic enones. Interestingly, 4,4-dimethyl cyclohexenone furnished the corresponding Michael adducts in excellent enantioselectivities (up to >99% ee) and yields (Table 3, entries 1−8). Apart from cyclohexenone, cyclic enones such as cyclopentenone and cycloheptenone also afforded the Michael adducts in high enantioselectivities (Table 3, entries 9−15). The reaction was then extended to acyclic enones and a variety of aryl thiols were screened. Again, high enantioselectivities were obtained in almost all the cases (Table 3, entries 16−21).

The proposed transition state model to explain the stereochemical outcome of the reaction is shown in Figure 2. We

(10) Other solvents were also screened for this reaction using the catalyst **1a**, but its enantioselectivity was found to be inferior in comparison to toluene: H_2O (0%), EtOH (0%), CH_3NO_2 (17%), DCE (65%), THF (45%), *o*-xylene (62%), $CHCl_3$ (42%), and CH_3CN (16%).

TABLE 3. Enantioselective Michael Addition between Different Aryl Thiols and Enones[a]



entry	enone	Ar	time (h)	yield (%)	ee (%)[b]
1		C_6H_5	10	**3a** (>99)	92
2		2-naphthyl	12	**3b** (96)	91
3		2-MeC_6H_4	12	**3c** (96)	90
4		4-MeC_6H_4	10	**3d** (>99)	>99
5	**8b**	2-$MeOC_6H_4$	14	**3e** (94)	97
6		4-$MeOC_6H_4$	12	**3f** (98)	90
7		4-ClC_6H_4	10	**3g** (>99)	91
8		4-^{t}BuC_6H_4	12	**3h** (92)	91
9		C_6H_5	8	**4a** (>99)	80
10		2-MeC_6H_4	10	**4b** (98)	90
11	**8c**	2-$MeOC_6H_4$	14	**4c** (98)	88
12		C_6H_5	10	**5a** (98)	92
13		2-MeC_6H_4	12	**5b** (98)	92
14	**8d**	2-$MeOC_6H_4$	18	**5c** (95)	92
15		2,6-$Me_2C_6H_3$	18	**5d** (93)	91
16		2-naphthyl	12	**6a** (95)	82
17		2-MeC_6H_4	10	**6b** (98)	90
18	**8e**	4-ClC_6H_4	8	**6c** (97)	87
19		4-FC_6H_4	8	**6d** (92)	86
20		2-MeC_6H_4	10	**7a** (97)	94
21	**8f**	2,6-$Me_2C_6H_3$	12	**7b** (96)	99

[a]Reactions were carried out on a 0.5 mmol scale with 0.6 mmol of thiol in 1 mL of toluene at room temperature, unless noted otherwise. [b]Determined by HPLC using chiral column.

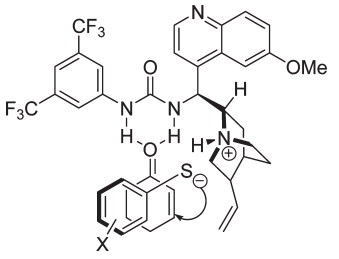


FIGURE 2. Proposed transition state model.

believe that the enone is activated by the urea moiety through double hydrogen bonding, while the thiol is activated by the basic quinuclidine nitrogen atom and the approach of thiol to the *Si* face of enone leads to the formation of the major stereoisomer.

In conclusion, we have developed a highly enantioselective organocatalytic sulfa-Michael addition to enones promoted by a quinine-derived urea catalyst. The stereochemical outcome has been explained with the help of a transition state model. This protocol offers several advantages such as operational simplicity, mild reaction conditions, low catalyst loading (0.1 mol %), and high enantioselectivities (up to >99% ee) and yields.

Experimental Section

General Procedure for the Enantioselective Organocatalytic Michael Addition of Thiols with α,β-Unsaturated Ketones. 1. Thiophenol (66 mg, 0.6 mmol) was added to a mixture of 2-cyclohexenone **8a** (48 mg, 0.5 mmol) and the catalyst **1e** (50 μL 0.01 M stock solution in dry toluene, 0.289 mg, 0.0005 mmol) in dry toluene (1.0 mL) at the room temperature. The reaction mixture was stirred, and the progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was concentrated in vacuum, and the crude product was purified over silica gel by column chromatography. The product **2a** was obtained in >99% (102 mg) yield and 94% ee. The enantiomeric excess of the Michael adduct was determined by chiral HPLC on chiralpak AD column [*n*-hexane/2-propanol 98:2]; flow rate 1 mL/min; λ = 254 nm; t_R(major) = 13.85 min (*S*), t_R(minor) = 17.98 min (*R*); $[\alpha]_D^{25} = -85.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.66−1.77 (m, 2H), 2.11−2.16 (m, 2H), 2.26−2.39 (m, 3H), 2.66−2.69 (m, 1H), 3.39−3.42 (m, 1H), 7.26−7.35 (m, 3H), 7.41−7.42(m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.0, 31.2, 40.8, 46.1, 46.7, 127.7, 129.0, 132.9, 133.2, 208.7. IR (NaCl cell, CH_2Cl_2, cm^{-1}): 2943, 1712. HRMS (ES+) calcd for $C_{12}H_{15}OS$ $[M + H]^+$: 207.0844; found: 207.0845.

2. 2-Thionaphthol (96 mg, 0.6 mmol) was added to a mixture of (*E*)-4,4-dimethyl-1-phenylpent-2-en-1-one **8e** (94 mg, 0.5 mmol) and the catalyst **1e** (50 μL 0.01 M stock solution in dry toluene, 0.289 mg, 0.0005 mmol) in dry toluene (1.0 mL) at the room temperature. The reaction mixture was stirred, and the progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was concentrated in vacuum and the crude product was purified over silica gel by column chromatography. The product **6a** was obtained in 95% (166 mg) yield and 82% ee. The optical purity was determined by HPLC on chiralpak AD column [*n*-hexane/2-propanol 95:5]; flow rate 1 mL/min; λ = 254 nm; t_R(minor) = 8.40 min (*S*); t_R(major) = 9.54 min (*R*); $[\alpha]_D^{25} = -125.4$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (s, 9H), 3.34−3.36 (m, 2H), 4.01 (dd, *J* = 7.5, 5.5 Hz, 1H), 7.37−7.42 (m, 4H), 7.49−7.55 (m, 2H), 7.67−7.73 (m, 3H), 7.83−7.89 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.9, 36.3, 41.2, 55.5, 125.7, 126.4, 127.4, 127.7, 128.2, 128.4, 128.6, 128.7, 128.9, 132.0, 133.1, 133.8, 134.8, 137.3, 198.8. IR (KBr pellet, cm^{-1}): 2923, 1590; mp = 65 °C. HRMS (ES+) calcd for $C_{23}H_{25}OS$ $[M + H]^+$: 349.1626; found: 349.1626.

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Supporting Information Available: General experimental procedures, characterization data including ^{1}H NMR spectra, ^{13}C NMR spectra for all new compounds, and HPLC chromatograms for Michael adducts. This material is available free of charge via the Internet at http://pubs.acs.org.