Asymmetric Michael Addition of Arylthiols to α,β-Unsaturated Carbonyl Compounds Catalyzed by Bifunctional Organocatalysts

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Abstract: Bifunctional chiral organocatalysts comprising thiourea and tertiary amine groups were synthesized. They act as efficient catalysts for asymmetric Michael addition of arylthiols to α,β-unsaturated carbonyl compounds. Enantioselectivity up to 85% has been achieved. Asymmetric α-protonation reaction (up to 60% ee) can be obtained in the presence of the bifunctional catalyst.

Key words: bifunctional organocatalyst, thiourea, hydrogen bonding, asymmetric Michael addition, asymmetric protonation

Hydrogen bonding as a force for promoting chemical reactions has attracted increasing attention, and the development of hydrogen bonding activated asymmetric catalysis has been a rapidly growing area in synthetic organic chemistry over the past few years.[1] Apart from proline and proline-derived organocatalysts-catalyzed direct aldol, Mannich, amination and aminoxylation reactions,[2] more and more organocatalysts in connect with hydrogen bonding activation have been reported.[3] In the domain of urea and thiourea catalysts,[4] remarkable advances were made by Jacobsen in a serials of asymmetric reactions promoted by urea or thiourea containing Schiff base catalysts.[5] More recently, Takemoto developed an excellent bifunctional organocatalyst comprising tertiary amine and thiourea moiety for the enantioselective 1,4- or 1,2-addition reactions through hydrogen bonding interaction with nitro group.[6] However, the asymmetric catalysis involving hydrogen bonding between carbonyl compounds and thiourea (urea) has largely been left unexplored.[7] Here we would like to report the synthesis of thiourea and tertiary amine-based chiral organocatalysts and the application in the asymmetric Michael addition of arylthiols to α,β-unsaturated carbonyl compounds.[8]

Natural cinchona alkaloids and their derivatives have been widely used in the asymmetric organocatalysis.[9] The bulky tertiary amine unit plays a very important role by activating nucleophilic agent. Therefore, a thiourea moiety bearing a 3,5-bis(trifluoromethyl)phenyl group was introduced in the 9-position[10] of cinchonidine **2a** or cinchonine **2b** to give the novel bifunctional catalysts **1a** or **1b** in two steps, respectively, in over 60% yields (Scheme 1). Their catalytic activities in the asymmetric Michael addition of phenylthiol to α,β-unsaturated imide **7a**[11] were tested. We envisage that the thiourea would activate the carbonyl electrophile through double hydrogen bonding,[12] in connect with tertiary amine activating the nucleophile. High catalytic activity was observed at 10 mol% catalyst loading in CH_2Cl_2. Unfortunately, only poor enantioselectivity was obtained for both catalysts with almost quantitative yields (Table 1, entries 1 and 2), probably owing to the improper positions of two functional groups. On the other hand, bifunctional catalyst **1c**, prepared[6,13] smoothly from (*R*,*R*)-1,2-diphenylethylenediamine in 45% overall yield (Scheme 1), showed better enantioselectivity (entry 3). More satisfactory results were achieved by (*S*,*S*)-1,2-cyclohexanediamine-derived **1d** (Scheme 1, Takemoto's catalyst,[6] entry 4, 60% ee). It seems that the more rigid skeleton of chiral 1,2-cyclohexanediamine is vital to give better enantioselectivity, the Takemoto's catalyst **1d** was further modified in consideration of the electronic and steric reasons.[14] It was found that both catalytic activity and enantioselectivity were decreased when **1e** was used probably due to the lower electron-withdrawing ability of 4-trifluomethylphenyl group (entry 5). In addition, lower enantioselectivity was also observed when bulky catalyst **1f** was applied (entries 6). Nevertheless, slightly better ee was obtained using catalyst **1g** with a strong electron-withdrawing group, while reactivity was decreased probably owing to the bulky structure (entry 7, 62% ee). It should be noted that better and more reproducible results could be achieved in the presence of freshly dried 4Å MS. Furthermore, almost racemic product was obtained when 10% (v/v) methanol was added to the CH_2Cl_2 solution (entry 8). The findings indicated that the hydrogen-bonding activation of carbonyl group by thiourea moiety was significant for the control of enantioselectivity since trace water or proton solvent would affect the weak interaction.

While screened out the best bifunctional organocatalyst **1d** for the Michael addition, more reaction conditions were investigated in order to improve the enantioselectivity. Solvent was found to have dramatic effects on the catalytic performance. Similar results were obtained using toluene as the solvent (Table 1, entry 9). However, very poor enantioselectivity was observed when THF was used (entry 10). Product with reversed configuration was obtained in MeOH solution while with low enantioselectivity (entry 11). No beneficial effect in enantioselectivity was observed when 20 mol% catalyst loading was applied

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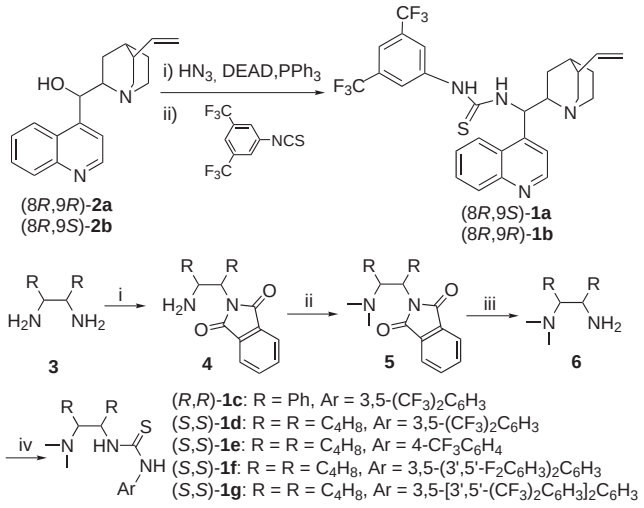
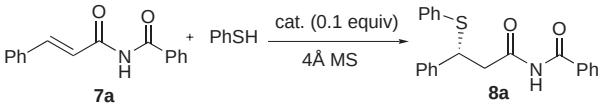


Scheme 1 *Conditions*: (i) phthalic anhydride, TsOH, toluene; (ii) HCOOH, HCHO; (iii) $N_2H_4 \cdot H_2O$, EtOH; (iv) ArNCS, toluene.

Table 1 Optimization of Reaction Conditions for Michael Addition of Phenylthiol to Unsaturated Imide **7a**[a]



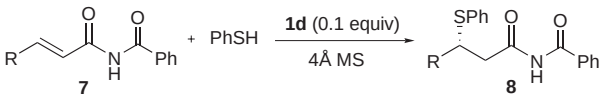
Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	ee (%)[c,d]
1	**1a**	CH_2Cl_2	20	2	99	7
2	**1b**	CH_2Cl_2	20	2	99	17
3	**1c**	CH_2Cl_2	20	2	99	39
4	**1d**	CH_2Cl_2	20	4	98	60
5	**1e**	CH_2Cl_2	20	5	98	56
6	**1g**	CH_2Cl_2	20	12	97	53
7	**1h**	CH_2Cl_2	20	10	97	62
8[e]	**1d**	CH_2Cl_2	20	12	96	6
9	**1d**	Toluene	20	4	98	59
10	**1d**	THF	20	12	98	4
11	**1d**	MeOH	20	12	97	25[f]
12[g]	**1d**	CH_2Cl_2	20	3	98	60
13	**1d**	CH_2Cl_2	0	12	98	67
14	**1d**	CH_2Cl_2	–40	72	95	75

[a] Reactions were carried out at 0.1 mmol scale in 0.5 mL solvent and 20 mg 4Å MS were added.
[b] Isolated yield.
[c] The ee was determined by HPLC analysis on chiral column.
[d] The absolute configuration was determined to be *R* by the rotation after conversion to ethyl ester.[8g]
[e] 10% (v/v) MeOH was added.
[f] *S*-configuration was obtained.
[g] 20 mol% catalyst was used.

(entry 12). On the other hand, better enantioselectivity could be achieved when the reaction was conducted at lower temperature (entry 13, 0 °C, 67% ee), and up to 75% ee was obtained at –40 °C while the reaction time should be extended (entry 14). However, almost no reaction happened when the temperature was further decreased to –78 °C.

With the optimized reaction conditions in hand, the scope and limitations of the bifunctional thiourea-tertiary amine catalyst **1d** promoted Michael addition were investigated.[15] A series of α,β-unsaturated imides **7** were reacted with phenylthiol catalyzed by 10 mol% **1d** at –40 °C. The results were summarized in Table 2. It was found that the reactions were not very sensitive to substitution patterns of acceptors. Similar enantioselectivity was obtained in the reactions of phenylthiol with α,β-unsaturated imides bearing various aryl or alkyl substitutions. In general over 70% ee was obtained except a *t*-butyl group was substituted at β-position (Table 2, entry 5, 55% ee). The best result was achieved when a linear alkyl substitution was introduced (entry 6, 77% ee). However, lower enantioselectivity was observed while 2-naphthylthiol was used (entry 7).

Table 2 Michael Addition of Thiol to Unsaturated Imide Catalyzed by **1d**[a]

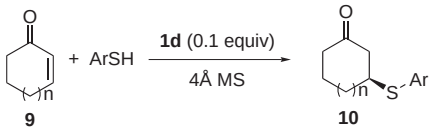


Entry	R	Time (h)	Yield (%)[b]	ee (%)[c]
1	C_6H_5	72	98	75
2	*p*-MeO-C_6H_4	72	97	70
3	Cyclohexyl	72	96	73
4	$CH(CH_3)_2$	84	92	72
5	$C(CH_3)_3$	84	90	55
6	$(CH_2)_2CH_3$	72	95	77
7[d]	$(CH_2)_2CH_3$	72	96	67

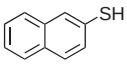
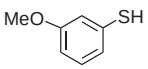
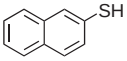
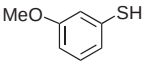
[a] Reactions were carried out at 0.1 mmol scale in 0.5 mL CH_2Cl_2 at –40 °C and 20 mg 4Å MS were added.
[b] Isolated yield.
[c] The ee was determined by HPLC analysis on chiral column.
[d] 2-Naphthylthiol as the Michael addition donor.

Since the single carbonyl group of ketone or aldehyde can also form double hydrogen bonding to thiourea moiety,[16] the asymmetric Michael additions between cyclic enones and thiols were also investigated in the presence of catalyst **1d**. The results were summarized in Table 3. In the model reaction of phenylthiol and cyclohenxen-2-one, better enantioselectivity (80% ee) was obtained compared with the above reactions of acyclic unsaturated imides (Table 3, entry 1). The enantioselectivity could be raised to 85% at 0 °C (entry 2). But the ee lowered down when

Table 3 Michael Addition of Arylthiol to Enone Catalyzed by **1d**[a]



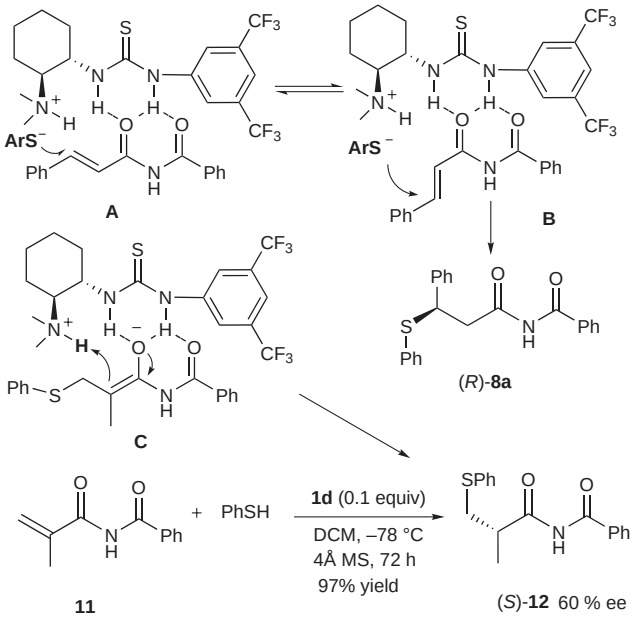
9 **10**

Entry	ArSH	Enone	Temp (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	PhSH		20	4	99	80[d]
2			0	12	97	85[d]
3			–35	40	95	81[d]
4			0	8	98	71
5			0	8	99	77
6	PhSH		0	12	95	76
7	PhSH		0	10	97	68
8			0	12	96	63
9			0	12	98	74

[a] Reactions were carried out at 0.1 mmol scale in 0.5 mL CH_2Cl_2 and 20 mg 4Å MS were added.
[b] Isolated yield.
[c] The ee was determined by HPLC analysis on chiral column.
[d] The absolute configuration was determined to be *S* by the rotation.[8f]

the reaction temperature was further decreased (entry 3). Thus, the reaction scope was studied at 0 °C. In general, slightly lower enantioselectivity was observed for other substrates. Over 70% ee was obtained for the Michael addition of arylthiols to six-membered cyclic enones (entries 4–6). On the other hand, moderate enantioselectivity (63–74% ee) was gained when cyclopenten-2-one was used as the substrate (entries 7–9).

Like the catalytic model of malonates with nitroolefins[6] in the presence of bifunctional catalyst **1d**, the plausible mechanism for the Michael addition of arylthiols to α,β-unsaturated carbonyl compounds is proposed (Scheme 2, complexes **A** and **B**). The formation of double hydrogen bonding between thiourea moiety and imide,[11] in addition to the concerted activation of thiol by the tertiary amine, is essential for the enantioselective discrimination. On the basis of the configuration of **8a**, the reaction would proceed through complex **B** to give the *R*-product. We also found that the asymmetric protonation could be achieved in the reaction of phenylthiol and α-prochiral imide **11** (Scheme 2).[17] Up to 60% ee was obtained on α-carbon center of **12** with *S*-configuration[18] when the reaction was conducted at –78 °C. We speculate that the ammonium group may act as the proton source after the conjugate addition of thiol anion to the β-carbon, while the thiourea moiety stabilizes the more stable *Z*-enolate through hydrogen bonding interaction (complex **C**). Further protonation study is in progress in our group.



Scheme 2

In conclusion, we report that chiral organocatalysts bearing tertiary amine and thiourea moiety can efficiently catalyze the asymmetric Michael addition of thiols to α,β-unsaturated carbonyl compounds in a concerted double activation way. The reactions showed good substrate scope and up to 85% ee was obtained. Moreover, we demonstrated for the first time that this type of bifunctional organocatalysts[6] could serve as chiral proton catalysts and asymmetric α-protonation (up to 60% ee) has been obtained. Further study in asymmetric protonation reaction and application of the bifunctional catalysts in other asymmetric reactions are actively under investigation.

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(15) **General Experimental Procedure for (*S*,*S*)-1d-Catalyzed Asymmetric Michael Addition.** Phenylthiol (12 μL, 0.11 mmol) was added to the stirred solution of α,β-unsaturated imide **7a** (25.1 mg, 0.1 mmol) and **1d** (4.2 mg, 0.01 mmol) in 0.5 mL CH_2Cl_2 at –40 °C. The reaction was stirred for 72 h. Flash chromatography eluting with petroleum ether–EtOAc (10:1) gave the product as a white solid (35.3 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.47 (s, NH), 7.78–7.76 (m, 2 H), 7.62–7.59 (m, 1 H), 7.51–7.47 (m, 2 H), 7.36–7.32 (m, 4 H), 7.29–7.19 (m, 6 H), 4.85 (dd, *J* = 1.6, 8.4 Hz, 1 H), 3.77 (dd, *J* = 8.4, 15.6 Hz, 1 H), 3.62 (dd, *J* = 8.4, 15.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 165.6, 140.8, 133.9, 133.3, 133.1, 132.4, 128.9, 128.8, 128.4, 127.8, 127.7, 127.6, 127.4, 48.2, 43.8. ESI-MS: *m*/*z* = 360.1 $[M - H]^-$; ee was determined by HPLC on Daicel Chiralcel OD (20% 2-propanol in hexane, 0.5 mL/min, t_S = 10.8 min, t_R = 12.1 min, 75% ee).
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