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A chiral benzoylthiourea–pyrrolidine catalyst for the highly enantioselective Michael addition of ketones to chalcones

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ABSTRACT

A benzoylthiourea–pyrrolidine catalyst was developed for the asymmetric Michael addition of ketones to chalcones. The corresponding products were obtained in high yields with high level of diastereoselectivities (up to 99:1 dr) and high level of enantioselectivities (up to 94% ee) under mild conditions.

The formation of carbon–carbon bonds is central to organic chemistry, indeed to chemistry in general.[1] One essence of synthetic organic chemistry leading to the formation of various valuable molecules is how to efficient generation of a carbon–carbon bond. For a long time chemists have focused considerable and consistent attentions on the development of efficient and operationally simple protocols for the formation of carbon–carbon bonds.[2] The Michael reaction is generally regarded as one of the most efficient carbon–carbon bond forming reactions.[3] The importance of this methodology has stimulated significant interest in the development of catalytic, asymmetric versions of the process.[4,5] Although in 1973 Langstrom and Bergson firstly reported the enantioselective Michael addition catalyzed by 2-(hydroxymethyl)-quinuclidine,[6] organocatalytic Michael reaction has blossomed rapidly since the turn of the century.[7] Forming of iminium[8] or enamine[9] intermediate temporarily, hydrogen bonding interactions[10] and steric hindrance[11] are mainly involved in organocatalytic Michael reaction. Chiral proline,[8,9] thioureas or ureas,[10] cinchona alkaloid[6,7a] and guanidines[12] have been developed and applied to asymmetric Michael reaction.

Chalcones, belonging to the flavonoid family, is one of the major classes of natural products with widespread distribution in fruits, vegetables, spices, tea and soy based foodstuff. Chalcones and their structural analogues have been reported to possess many useful properties, including anti-inflammatory, antimicrobial, antifungal, antioxidant, cytotoxic, antitumor and anticancer activities.[13] Organocatalytic Michael additions of nucleophiles (such as nitroalkanes,[14] malonates,[15] cyanoacetates,[16] hydroxylamines,[17] malononitrile,[18] thiols,[19] cyanomethylphosphonate,[20] butenolide,[21] and sodium bisulfite et al.[22]) to chalcones have been reported. Asymmetric addition of simple cyclic ketones with chalcones catalyzed by organocatalysts, however, still remains a challenge, probably due to the low reactivity and high steric hindrance of the substrates.[23] Wang et al. accomplished the addition of ketones to chalcones for the first time with high enantioselectivity using a chiral pyrrolidinylmethylsulfonamide catalyst and obtained the desired products with moderate yields and good enantioselectivities and diastereomeric ratios.[23a] Wang and co-workers then reported the Michael addition of cyclohexanone to chalcones catalyzed by a pyrrolidine-pyridine base.[23b] Wang et al. developed a C_2-symmetric tetraamine catalyst for the asymmetric addition of ketones to chalcones.[23c,d] The corresponding adducts were obtained in good yields with high levels of diastereo- and enantioselectivities under mild conditions. A proline-based organic phosphane was discovered by Li'group and successfully applied to catalyze the addition of cyclohexanone or cyclopentanone to chalcones.[23e] Our group in 2012 reported the pyrrolidine-based imides which can catalyze the addition of cyclic ketones to chalcones smoothly.[23f]

Recently, we have developed the novel bifunctional benzoylthiourea–pyrrolidine **1** (Fig. 1) which was found to be efficient in the asymmetric Michael reaction of ketones to nitroalkenes.[6b]

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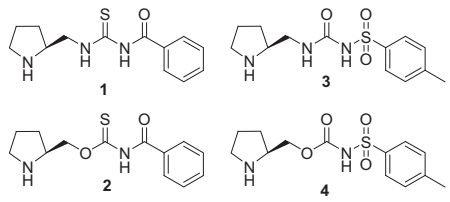


Figure 1. Bifunctional organocatalysts of **1**∼**4**.

Considering the consistency of catalytic mechanism, herein we tested the benzoylthiourea/sulfonylurea–pyrrolidine catalysts **1**∼**4** (Fig. 1) in the addition of cyclic ketones to lower activated Michael acceptors chalcones. The experimental results showed this catalytic system performed well over a broad scope of substrates, furnishing various 1,5-diketone compounds in high diastereoselectivity (up to 99:1) and excellent enantioselectivity (up to 94% ee) under mild conditions.

Using **1** as the catalyst, the effects of the solvent, additive, and the catalyst loading on the model asymmetric Michael addition of cyclohexanone **5a** to chalcone **6a** were thoroughly investigated, and the results are summarized in Table 1. Initially, the reaction was performed by using 10 mol % of **1** in a few solvents at 20 °C with benzoic acid as the additive. Among the various organic solvents tested, DCM, toluene, and no solvent(neat) were better in terms of both the diastereoselectivity and enantioselectivity, with 87% ee, 91% ee and 92% ee in enantioselectivity, respectively (Table 1, entries 1, 2, and 6). When the reaction proceeded in polar solvents (DMSO, THF and *i*-PrOH), almost no product was obtained (Table 1, entries 3–5). We also found that the yield of **7a** was increased obviously by augmenting the catalyst loading from 0.1 to 0.3 equiv (Table 1, entries 7–9). Considering both the reaction rate and stereoselectivity, neat was then selected as the optimal reaction condition in the study of the influence of the additive. In the absence of any carboxylic acid or in the presence of TFA, acetic acid or HCl, the reaction proceeded slowly and the yield of **7a** was lower or very poor (Table 1, entries 10–13). When 2,4-dichlorobenzoic acid was added as co-catalyst the reaction proceeded smoothly while with unsatisfied yield (Table 1, entry 14, 60% yield). Benzoic acid is the best choice because of the higher of enantioselectivity and reaction rate (Table 1, entry 9, 96:4 dr, 94% ee). In addition, decreasing cyclohexanone(**5a**) loading was deteriorated to the yield and stereoselectivity of **7a** (Table 1, entry 15).

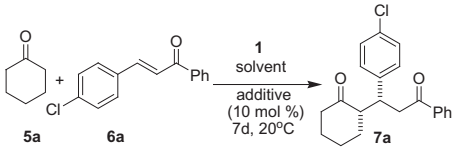
Catalysts **2**∼**4** were then screened employing above optimized conditions (Table 1, entry 9), and the results were summarized in Table 2. Catalysts **2**∼**4**, however, proved incapable of catalyzing this model reaction. Inefficiency of **2**∼**4** may be due to their poor solubility in cyclohexanone(neat) (**3** and **4**) and/or less of acidic protons (**2** and **4**). Catalysts **2**, **3** and **4** were then reexamined in other polar solvents such as DMF, DMSO, and *i*-PrOH. To our disappointment, solubilities improvement of catalysts did not generate satisfactory results. Probably polar solvents themselves are against this catalytic system.

With the optimized reaction conditions in hand, a variety of chalcones bearing different substituent groups were investigated, and the results are summarized in Table 3. These chalcones reacted smoothly with cyclohexanone to provide the corresponding adducts in moderate to excellent yields with excellent diastereoselectivities and enantioselectivities (Table 3, entries 1–13). Excellent diastereoselectivities (up to >99/1 dr) and enantioselectivities (up to 94% ee) were observed regardless of the electronic nature of the aromatic substituent. While the nature of the substituent on the benzene ring exhibited slight influence on the reaction rate and yield: when electron-donating substituent was introduced to the benzene ring, low to moderate yields were obtained (Table 3, entries 7 and 11). To our satisfaction, thiophenyl contained chalcone as Michael acceptor gave good yield and stereoselectivity (Table 3, entry 13).

Other ketones (cyclopentanone, acetone and cycloheptanone) were then tested as the Michael donors for this catalytical system (Fig. 2). Cyclopentanone and acetone gave the adducts with good enantioselectivities (79% and 50% ee, respectively). However, when cycloheptanone was used as substrate, the reaction proceeded slowly and only moderate enantioselectivity was obtained.

On the basis of the experimental results, the possible transition state for the **1**-catalyzed Michael addition was presented. As

Table 1
Screening of reaction conditions for the addition of cyclohexanone to chalcone **6a**[a]



Entry	Additive	Catalyst loading (mol %)	Solvent	Yield[b] (%)	dr (*syn*/*anti*)[c]	ee[c] (%)
1	Benzoic acid	10	DCM	59	86:14	87
2	Benzoic acid	10	Toluene	48.1	94:6	91
3	Benzoic acid	10	DMSO	Trace	–	–
4	Benzoic acid	10	DMF	0	–	–
5	Benzoic acid	10	*i*-PrOH	0	–	–
6	Benzoic acid	10	Neat	79	95:5	92
7	Benzoic acid	30	DCM	79	96:4	94
8	Benzoic acid	30	Toluene	68	96:4	93
9	Benzoic acid	30	Neat	95	96:4	94
10	No additive	30	Neat	52	87:13	90
11	TFA	30	Neat	0	–	–
12	Acetic acid	30	Neat	Trace	–	–
13	HCl	30	Neat	0	–	–
14	2,4-Dichlorobenzoic acid	30	Neat	60	90:10	90
15	Benzoic acid	30	Neat[d]	78	95:5	92

[a] All reactions were carried out with cyclohexanone (**5a**; 0.5 mL, absolutely excess) and chalcone (**6a**; 63 mg, 0.26 mmol) in the presence of catalyst **1**.
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determined by chiral HPLC on a Chiralpak AS-H column with *n*-hexane and 2-propanol as eluents.
[d] Cyclohexanone(**5a**; 0.3 mL), chalcone (**6a**; 63 mg, 0.26 mmol) in the presence of catalyst **1**.

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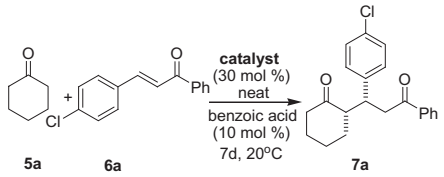
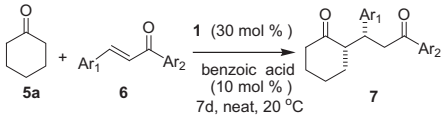
Table 2
Screening of catalysts[a]



Entry	Catalyst	Yield[b] (%)	dr (*syn*/*anti*)[c]	ee[c] (%)
1	1	95	96:4	94
2	2	0	–	–
3	3	Trace	–	–
4	4	0	–	–

[a] All reactions were carried out with cyclohexanone (**5a**; 0.5 mL, absolutely excess) and chalcone (**6a**; 63 mg, 0.26 mmol) in the presence of catalyst (30 mol %).
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determined by chiral HPLC on a Chiralpak AS-H column with n-hexane and 2-propanol as eluents.

Table 3
Catalytic asymmetric Michael addition of cyclohexanone to chalcones[a]



Entry	Ar_1	Ar_2	Yield[b] (%)	dr (*syn*/*anti*)[c]	ee[c] (%)
1	4-ClC_6H_4	Ph	95	96:4	94
2	Ph	Ph	98	91:9	89
3	3-$NO_2C_6H_4$	Ph	95	87:13	87
4	2,4-$Cl_2C_6H_3$	Ph	90	99:1	91
5	4-BrC_6H_4	Ph	88	97:3	90
6	4-FC_6H_4	Ph	92	95:5	90
7	4-$CH_3C_6H_4$	Ph	85	98:2	94
8	Ph	4-BrC_6H_4	94	97:3	78
9	Ph	4-$NO_2C_6H_4$	91	96:4	87
10	Ph	4-FC_6H_4	78	98:2	90
11	Ph	4-$CH_3C_6H_4$	66	99:1	75
12	Ph	4-ClC_6H_4	89	98:2	87
13	2-Thiophenyl	2-Thiophenyl	95	85:15	87

[a] All reactions were carried out with cyclohexanone (**5a**; 0.5 mL, absolutely excess) and chalcone (**6**; 63 mg, 0.26 mmol) in the presence of catalyst **1** (30 mol %).
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determined by chiral HPLC on a Chiralpak AS-H column with *n*-hexane and 2-propanol as eluents.

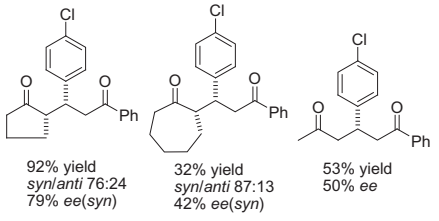


Figure 2. Michael adducts of chalcone **6a** with other ketones.

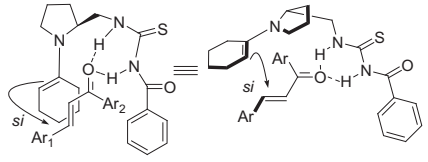


Figure 3. Tentative transition state.

shown in Figure 3, benzoylthiourea–pyrrolidine catalyst **1** was proposed as a bifunctional catalyst. The pyrrolidine reacted with carbonyl compounds to form an enamine and the benzoylthiourea-activated chalcone via N–H hydrogen bonds. The enamine attacked the chalcone from the *si*-face to afford the product.

In conclusion, we have successfully developed a procedure for catalytic asymmetric Michael addition reaction of cyclic ketones with chalcones. Moderate to excellent diastereoselectivities and enantioselectivities were obtained for the addition of ketones to a variety of chalcones under benzoylthiourea–pyrrolidine **1**. The presence of a brønsted acid with proper acidity, such as benzoic acid, proved to be critical for the excellent performance of this catalyst system. The application of this new type of organocatalyst in other asymmetric reactions is underway in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.04.005.

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