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SHORT COMMUNICATION

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Benzoylthiourea–Pyrrolidine as Another Bifunctional Organocatalyst: Highly Enantioselective Michael Addition of Cyclohexanone to Nitroolefins

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Asymmetric Michael addition of cyclohexanone to nitrostyrenes in the presence of organocatalyst **1** (10 mol-%) and 2,4-dichlorobenzoic acid (10 mol-%) afforded the corresponding synthetically valuable γ-nitroketones in moderate to good yields with high diastereoselectivities (up to >99:1 *dr*) and high enantioselectivities (up to >99 % *ee*) under mild conditions.

Introduction

In recent years, organocatalytic asymmetric catalysis has been identified as one of the most economical and powerful approaches to access a great variety of enantiomerically enriched compounds that are widely used in drug discovery and chemical synthesis.[1] Advantages of organocatalytic reactions, including mild reaction conditions, environmental benignity, and facile recovery of the catalysts, render some features of green chemistry to these processes.[2] The strategies for organocatalysis include the formation of temporary covalent bonds (enamine[3,4] or iminium[5] catalysis), hydrogen-bonding interactions (urea or thiourea catalysis),[6] Brønsted acid–base interactions,[7] and ion-pair interactions (phase-transfer catalysts).[8] The combination of some of these strategies may lead to unexpected synergistic effects, and the success of bifunctional organocatalysts in a wide array of asymmetric processes provides a good example.[9] (Thio)urea–pyrrolidine[10] and sulfamide–pyrrolidine[11] have been reported and were successfully used as bifunctional organocatalysts in asymmetric catalysis. Essential to these bifunctional catalysts is their capability to form two or more H-bonds with a reaction component. Such H-bonding interactions not only further activate the reactant but also direct it to a well-defined orientation that is required for asymmetric induction.[12] To the best of our knowledge, the 3,5-bis(trifluoromethyl)phenyl substituent has been frequently used in thiourea catalysis.[6a,6e,6f,6g,10b,10c] The presence of electron-withdrawing groups serves to decrease the pK_a of the N–H bonds, which increases their H-bond donating ability. Learning from the concept of bioisosterism in medicinal chemistry, we envisaged that the cheaper and generally more available benzoyl or *p*-toluenesulfonyl group would be a better choice. Benzoylthiourea and sulfonylurea, which are structural relatives of (thio)urea and expected to provide strong acidity to the N–H bonds, could possibly be introduced to the chiral amine to serve as a versatile core activation unit for bifunctional catalysis. Therefore, we designed benzoylthiourea/sulfonylurea–pyrrolidine-based catalysts and analogues **1**–**4** (Figure 1) and found that benzoylthiourea–pyrrolidine **1** was excellent for catalyzing the asymmetric Michael addition of cyclohexanone to nitroolefins. In this paper, we report the preliminary results.

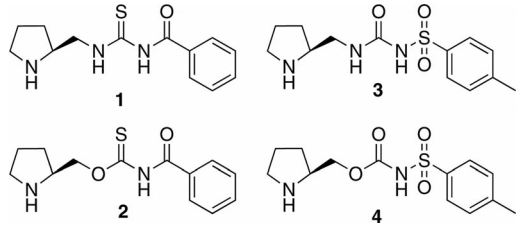

Figure 1. Bifunctional organocatalysts **1**–**4**.

Results and Discussion

Benzoylthiourea/sulfonylurea–pyrrolidines 1–4 were easily prepared from benzoyl isothiocyanate or *p*-toluenesulfonyl isocyanate and (*S*)-*tert*-butyl-2-(aminomethyl)-pyrrolidine-1-carboxylate or (*S*)-*tert*-butyl-2-(hydroxymethyl)pyrrolidine-1-carboxylate in two steps in 26–55% overall yield (see the Experimental Section).

Initially, various solvents and additives were examined in the model asymmetric Michael addition of cyclohexanone to β-nitrostyrene. The results are summarized in Table 1. The conjugate addition was first examined in different sol-

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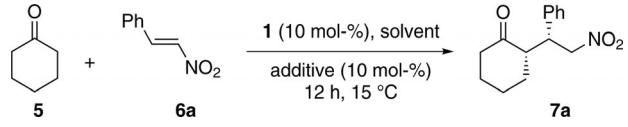
vents at 15 °C with benzoic acid as the additive. Among the various organic solvents tested, dichloromethane, toluene, and no solvent were better in terms of diastereoselectivity and enantioselectivity (90, 91, and 93%*ee*, respectively; Table 1, entries 1, 2, and 5). If the reaction was performed in polar solvents (THF, EtOH, and DMSO), the yield of **7a** was very poor (Table 1, entries 3, 4, and 6). Toluene was then selected as the solvent to study the influence of the additive and catalyst. The addition of a carboxylic acid was found to be an essential factor for this reaction. In the absence of a carboxylic acid, or in the presence of trifluoroacetic acid (TFA), the reaction proceeded slowly (Table 1, entries 10 and 11). Almost the same level of enantioselectivity was observed for substituted benzoic acid as for unsubstituted benzoic acid (91%*ee*; Table 1, entry 2), 2-nitrobenzoic acid (94%*ee*; Table 1, entry 7), 4-methylbenzoic acid (95%*ee*; Table 1, entry 8), and 2,4-dichlorobenzoic acid (94%*ee*; Table 1, entry 9). 2,4-Dichlorobenzoic acid was the best choice in terms of diastereoselectivity and reaction rate.

Table 1. Effects of solvents and additives on the reaction of cyclohexanone to nitrostyrene.[a]



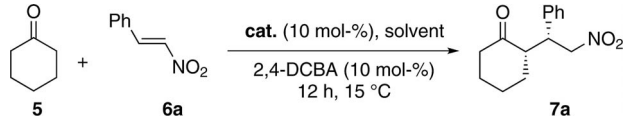
5 6a 7a

Entry	Additive[b]	Solvent	Yield [%][c]	*dr* (*syn*/*anti*)[d]	*ee* [%][d]
1	BA	CH_2Cl_2	95	89:11	90
2	BA	toluene	93	94:6	91
3	BA	THF	40[e]	97:3	95
4	BA	MeOH	20[e]	94:6	93
5	BA	neat	90	82:18	93
6	BA	DMSO	20[e]	94:6	87
7	*o*-NBA	toluene	65[e]	98:2	94
8	*p*-MBA	toluene	66	98:2	95
9	2,4-DCBA	toluene	92	99:1	94
10	TFA	toluene	trace[e]	–	–
11	none	toluene	80[d]	97:3	93

[a] All reactions were carried out with **5** (100 mg, 1.0 mmol) and **6a** (18.7 mg, 0.13 mmol) in the presence of catalyst **1** (10 mol-%). [b] BA = benzoic acid, *o*-NBA = 2-nitrobenzoic acid, *p*-MBA = 4-methylbenzoic acid, 2,4-DCBA = 2,4-dichlorobenzoic acid, TFA = trifluoroacetic acid. [c] Yield of the isolated product after chromatography on silica gel. [d] Determined by chiral HPLC with a Chiralpak AS-H column and *n*-hexane/2-propanol as eluents. [e] Reaction time = 24 h.

Chiral catalysts **2**–**4** were screened by employing these optimized conditions, and the results are summarized in Table 2. Compounds **2**–**4**, however, proved incapable of catalyzing this model reaction. The inefficiency of **2**–**4** may be due to their poor solubility in toluene (for **3** and **4**) and/or the lower acidity of the protons (for **2** and **4**). Catalysts **2**–**4** were then re-examined in other solvents, and the data are also listed in Table 2. In THF and DMF, and under neat conditions, catalyst **3** gave moderate conversions and asymmetric inductions (Table 2, entries 9, 11, and 12). In 2010, Carter and Yang introduced alkylbenzenesulfonyl groups into proline–sulfonamide organocatalysts that were used to perform Michael additions.[13] Carter and Yang's work suggests that in the future we can add appropriate hydrophobic groups into the structure of **3** to improve its catalytic efficiency. In addition, catalysts **2** and **4** were still inactive in THF, DMSO, and DMF, as well as under neat conditions.

Table 2. Screening of the catalysts.[a]



5 6a 7a

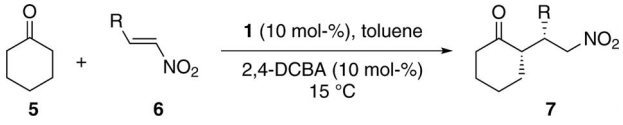
Entry	Cat.	Solvent	Yield [%][b]	*dr* (*syn*/*anti*)[c]	*ee* [%][c]
1	**1**	toluene	92	99:1	94
2	**2**	toluene	0	–	–
3	**3**	toluene	0	–	–
4	**4**	toluene	0	–	–
5	**2**	THF	0	–	–
6	**2**	DMSO	0	–	–
7	**2**	DMF	0	–	–
8	**2**	neat	0	–	–
9	**3**	THF	44	93:7	86
10	**3**	DMSO	0	–	–
11	**3**	DMF	40	94:6	83
12	**3**	neat	66	95:5	75
13	**4**	THF	0	–	–
14	**4**	DMSO	0	–	–
15	**4**	DMF	0	–	–
16	**4**	neat	0	–	–

[a] All reactions were carried out with **5** (100 mg, 1.0 mmol) and **6a** (18.7 mg, 0.13 mmol) in the presence of the catalyst (10 mol-%). [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by chiral HPLC with a Chiralpak AS-H column and *n*-hexane/2-propanol as eluents.

Under the optimized conditions, a variety of nitroolefins with different structures were investigated, and the results are shown in Table 3. Various styrene-type nitroalkenes reacted smoothly with cyclohexanone to provide the corresponding adducts in moderate to excellent yields with excellent diastereoselectivities and enantioselectivities (Table 3, entries 1–9). Excellent diastereoselectivities and enantioselectivities were observed regardless of the electronic nature of the aromatic R substituent, although the nature of the substituent on the benzene ring did exhibit a slight influence on the reaction rate and yield. If an electron-donating substituent was introduced onto the benzene ring, the reaction proceeded slowly (Table 3, entries 2 and 9). In addition, thiophenyl- and furyl-containing nitroalkenes as Michael acceptors gave moderate yields but good stereoselectivities (Table 3, entries 10 and 11). An aliphatic aldehyde nitroalkene also appeared to be a good candidate for this asymmetric Michael addition reaction (Table 3, entry 12).

Cyclopentanone, acetophenone, acetone, and isobutyraldehyde were subsequently examined in the **1**-catalyzed Michael addition with nitrostyrene (**6a**). Unfortunately, as depicted in Scheme 1, the results were not satisfactory. Acetone and cyclopentanone gave moderate yields and stereoselectivities, and no product was obtained for acetophenone or isobutyraldehyde as the nucleophile.

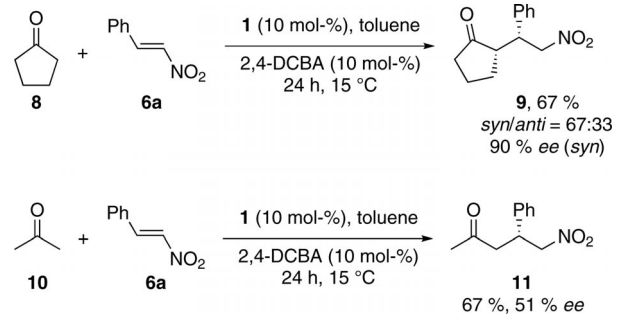
Table 3. Catalytic Michael addition of cyclohexanone to nitroalkenes.[a]



5 6 7

Entry	R	Time [h]	Yield [%][b]	*dr* (*syn*/*anti*)[c]	*ee* [%][c]
1	Ph	12	92	99:1	94
2	4-MeC_6H_4	36	60	98:2	93
3	2,4-$Cl_2C_6H_3$	12	80	>99:1	97
4	4-BrC_6H_4	12	98	98:2	97
5	3-$NO_2C_6H_4$	12	98	97:3	98
6	2-ClC_6H_4	12	90	>99:1	95
7	4-ClC_6H_4	12	85	98:2	96
8	4-FC_6H_4	12	88	98:2	96
9	3,4-$(MeO)_2C_6H_3$	72	trace	–	–
10	2-thiophenyl	72	65	95:5	91
11	2-furyl	72	56	92:8	89
12	isopropyl	72	66	79:21	>99

[a] All reactions were carried out with **5** (100 mg, 1.0 mmol) and **6** (0.13 mmol) in the presence of catalyst **1** (10 mol-%). [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by chiral HPLC with a Chiralpak AS-H column and *n*-hexane/2-propanol as eluents.



8 6a 10 6a

Scheme 1. Michael addition of ketones and aldehyde to **6a**.

On the basis of the experimental results, a possible transition state for the **1**-catalyzed Michael addition is presented in Figure 2. Catalyst **1** is proposed as a bifunctional catalyst. Pyrrolidine reacts with the carbonyl compound to form an enamine and the benzoylthiourea–activated nitroolefin through hydrogen bonding. The enamine attacks the nitroolefin from the *Re* face to afford the product.

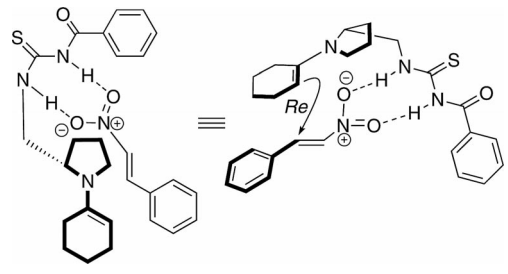


Figure 2. Possible stereochemical model.

Conclusions

In conclusion, we have developed new benzoylthiourea–pyrrolidine **1** as a novel bifunctional organocatalyst for the asymmetric Michael addition of ketones to nitroalkenes. Moderate to excellent diastereoselectivities and enantioselectivities were obtained for the addition of cyclohexanone to a variety of nitroalkenes under mild conditions. Application of this new type of organocatalyst in other asymmetric reactions is underway in our laboratory.

Experimental Section

General Procedure for the 1-Catalyzed Asymmetric Michael Addition of Ketones to Nitroalkenes: A solution of catalyst **1** (0.013 mmol) and cyclohexanone (0.1 mL, 0.1 mmol) in toluene (0.2 mL) was stirred at room temperature for 30 min. Then, 2,4-dichloridebenzoic acid (2.5 mg, 0.013 mmol) was added, and the reaction mixture was stirred for 15 min. To the resulting mixture was added nitroalkene (0.13 mmol) at 15 °C. After the reaction was complete (monitored by TLC), the mixture was purified by column chromatography on silica gel (200–300 mesh, petroleum ether/ethyl acetate = 10:1) to afford the product.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data, and copies of the ^1H NMR and ^{13}C NMR spectra for all key intermediates and final products.

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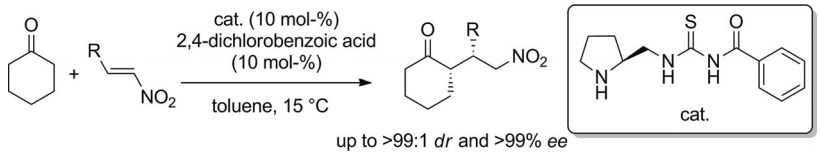
Bifunctional Organocatalyst



A benzoylthiourea–pyrrolidine catalyst was synthesized and used in the asymmetric Michael addition of ketones to nitroalkenes. The corresponding synthetically valuable γ-nitroketones were obtained in moderate to good yields with high levels of diastereo- and enantioselectivities (up to >99:1 *dr* and up to >99% *ee*).

Keywords: Organocatalysis / Diastereoselectivity / Enantioselectivity / Michael addition / Nitroalkenes

