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Pyrrolidine–Thiourea as a Bifunctional Organocatalyst: Highly Enantioselective Michael Addition of Cyclohexanone to Nitroolefins

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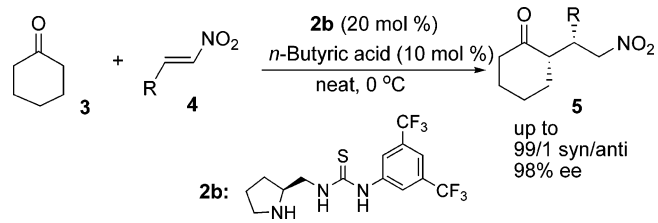
ABSTRACT



Asymmetric Michael additions of cyclohexanone to both aryl and alkyl nitroolefins in the presence of 20 mol % of organocatalyst 2b and 10 mol % of *n*-butyric acid afford adducts 5 with high diastereoselectivities and enantioselectivities.

Much attention has been paid to the design and application of organocatalysts recently. Of the developed organocatalysts in asymmetric catalysis,[1] proline and its derivatives have proven to be powerful and applied successfully to enamine chemistry.[2,3] Recently, urea(thiourea)-based organocatalysts have been widely used in asymmetric catalysis[4] due to their strong activation of carbonyl and nitro groups through efficient double-hydrogen-bonding interactions.[5] We envi-

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(2) For selected reviews on proline and its derivatives catalyzed reactions: (a) List, B. *Acc. Chem. Res.* **2004**, *37*, 548−557. (b) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580−591. (c) Duthaler, R. O. *Angew. Chem., Int. Ed.* **2003**, *42*, 975−978. (d) List, B. *Tetrahedron* **2002**, *58*, 5573−5590. (e) Gröger, H.; Wilken, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 529−532.

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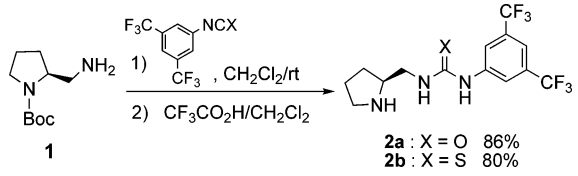
sioned that an appropriate combination of urea (thiourea) and pyrrolidine in a chiral scaffold could result in a potential bifunctional organocatalyst. Therefore, we designed two pyrrolidine−urea based catalysts **2a** and **2b** as shown in Scheme 1 and found that both of them were excellent for

Scheme 1. Synthesis of **2a** and **2b**



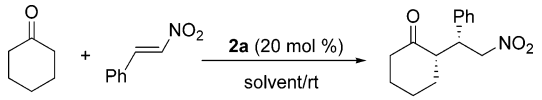
catalyzing the asymmetric Michael addition of cyclohexanone to nitroolefins.[6−11] In this paper, we report the preliminary results.

The organocatalytic asymmetric Michael addition of ketone with nitroolefins was pioneered by List and Barbas, independently.[7h,8] Since then, Barbas,[7h,i,9] Alexakis,[10] and Kotsuki[11] have shown that aminomethylpyrrolidine, 2,2′-bipyrrolidine, and pyrrolidine−pyridine derivatives could serve as powerful asymmetric catalysts for such a Michael addition. In these cases, high diastereoselectivities and enantioselectivities were achieved. Very recently, Wang reported the reactions of aldehydes with nitroolefins catalyzed by pyrrolidine sulfonamide with high diastereo- and enantioselectivities.[6b] These protocols provide unique methodology in asymmetric Michael addition. However, to the best of our knowledge, no example was described on the reaction of cyclohexanone with alkyl nitroolefins to date, probably due to the fact that they are less reactive than aryl nitroolefins.[10b]

We were pleased to find that the newly designed pyrrolidine−ureas **2a** and **2b**, which were easily prepared from L-proline as shown in Scheme 1,[12] catalyzed the reaction of cyclohexanone with both alkyl- and arylnitroolefins smoothly in good to high yields with high diastereoselectivities and excellent enantioselectivities.

Initially, various solvents and additives were examined at room temperature using **2a** as a catalyst and *trans*-nitroolefin **4a** as a substrate. As shown in Table 1, in polar solvents

Table 1. Effects of Solvents and Additives on the Reaction of Cyclohexanone to *trans*-Nitrostyrene[a]



3 4a 5a

entry	solvent	*T*/°C	*t* (d)	conv[b] (%)	syn/anti[b]	ee[c] (%)
1	MeOH	25	6	trace		
2	*i*-PrOH	25	4	trace		
3	THF	25	6	trace		
4	hexane	25	4	73	90/10	80
5	benzene	25	2	68	92/8	67
6	benzene[d]	25	1	100	90/10	77
7	benzene[e]	25	0.5	100	94/6	80
8	neat[e,f]	25	0.5	100	94/6	87
9	neat[e,f]	0	1.5	100	97/3	89
10[g]	neat[e,f]	0	1.5	100	96/4	90

[a] Unless otherwise noted, all reactions were carried out in solvent (1 mL) using **3** (0.25 mL, 10 equiv) and **4** (0.25 mmol, 1 equiv) in the presence of 20 mol % of **2a**. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis (chiralpak AD-H, hexane/2-propanol = 90/10). [d] Acetic acid (10 mol %) was added. [e] *n*-Butyric acid (10 mol %) was added. [f] 20 equiv of cyclohexanone was used. [g] **2b** as a catalyst, 0 °C.

such as MeOH, *i*-PrOH, and THF, only a trace amount of the desired adduct was observed (entries 1−3), whereas in nonpolar solvents, such as hexane and benzene, the Michael addition reaction proceeded smoothly to give product **5a** in moderate to excellent conversions with good to high enantioselectivities (entries 4 and 5). Interestingly, the addition of a catalytic amount of organic acids could increase dramatically the reaction rate (entries 6 and 7) without a loss of enantiomeric excess. For example, when *n*-butyric acid was used as an additive, *trans*-nitroolefin was converted into the desired product rapidly with high diastereoselectivity (94/6) and good enantioselectivity (80%) (entry 7). In solvent-free condition, the ee was improved to 87%, which further increased to 89% ee when the reaction temperature was lowered to 0 °C without a significant reduction of the reaction rate (entry 9). The use of catalyst **2b** instead of **2a** under the same conditions gave 90% ee (entry 10).

Under the optimized conditions, a variety of nitroolefins with different structures were investigated, and the results are summarized in Table 2. Various styrene-type nitroolefins

(5) (a) Maher, D. J.; Connon, S. J. *Tetrahedron Lett.* **2004**, *45*, 1301−1305. (b) Okino, T.; Hoashi, Y.; Takemoto, Y. *Tetrahedron Lett.* **2003**, *44*, 2817−2821. (c) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289−296. (d) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407−414. (e) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217−220. (f) Curran, D. P.; Kou, L. H. *Tetrahedron Lett.* **1995**, *36*, 6647−6650. (g) Curran, D. P.; Kou, L. H. *J. Org. Chem.* **1994**, *59*, 3259−3261.

(6) (a) Xu, Y.-M.; Córdova, A. *Chem. Commun.* **2006**, 460−462. (b) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369−1371. (c) Kotrusz, P.; Toma, S.; Schmalz, H.-G.; Adler, A. *Eur. J. Org. Chem.* **2004**, 1577−1583.

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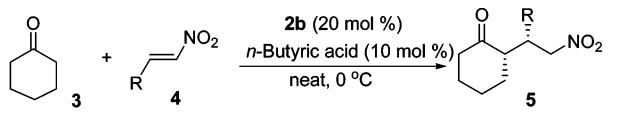
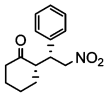
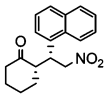
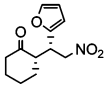
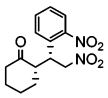
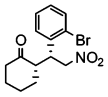
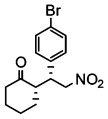
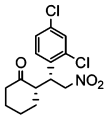
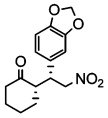
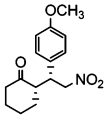
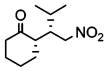
(11) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558−9559.

(12) For the synthesis of compound **1**: Dahlin, N.; Boegevig, A.; Adolfsson, H. *Adv. Synth. Catal.* **2004**, *346*, 1101−1105.

Table 2. Michael Addition Reactions of Cyclohexanone to *trans*-Nitroolefins Catalyzed by **2b**[a]



entry	product		*t* (h)	syn/anti[b]	yield (%)[c]	ee (%)[d]
1		**5a**	38	96/4	93	90
2		**5b**	60	99/1	93	95
3		**5c**	36	91/9	99	90
4		**5d**	38	96/4	95	97
5		**5e**	29	99/1	88	96
6		**5f**	38	95/5	90	95
7		**5g**	49	97/3	89	97
8		**5h**	38	94/6	87	98
9		**5i**	44	97/3	95	88
10		**5j**	6d	>99/1	63	94

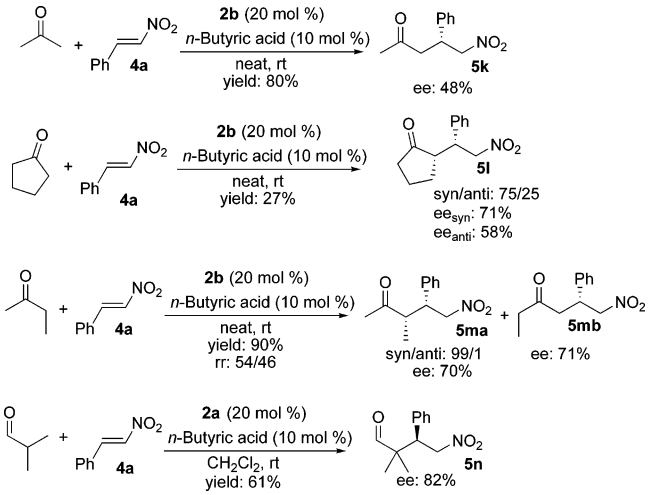
[a] All reactions were carried out using **3** (0.5 mL, 20 equiv) and **4** (0.25 mmol, 1 equiv) in the presence of 20 mol % of neat **2b**. [b] Determined by ^{1}H NMR of the crude products. [c] Isolated yield. [d] Determined by chiral HPLC analysis.

reacted smoothly with cyclohexanone in excellent diastereoselectivities and high enantioselectivities (entries 1−9). Generally, substituents on aryl groups slightly influenced the diastereoselectivities and enantioselectivities as well as the yields. For example, nitroolefins bearing both electron-withdrawing and electron-donating aryl groups gave the desired products with high selectivities (dr up to 99/1 and ee up to 98%) in excellent yields. Noticeably, alkylnitroolefins also worked well in this reaction. For example, (*E*)-3-methyl-1-nitrobut-1-ene gave the corresponding product with high diastereoselectivity (99/1) and enantioselectivity (94% ee) in good yield (63%).

The relative and absolute configurations of the Michael adducts are shown in Table 2. The relative configurations were assigned by comparison of ^{1}H and ^{13}C NMR of the products with the known compounds. The absolute configurations of products **5b**, **5c**, and **5i** were determined by comparing the optical rotations with the corresponding known compounds.

The asymmetric addition of other ketones and aldehyde to nitrostyrene **4a** using **2** as a catalyst was also investigated. As shown in Scheme 2, acetone gave the desired product

Scheme 2. Reactions of Acetone and Isobutyl Aldehyde with **4a**



5k in 80% yield with 48% ee. Methyl ethyl ketone also worked well to give the desired products in excellent yield with moderate enantioselectivity (70%) but poor regioselectivity (54/46). Cyclopentanone and cycloheptanone are less active. Cyclopentanone gave only 27% yield with morderate selectivities and cycloheptanone failed to afford the desired adduct. Isobutyl aldehyde proved a good substrate and furnished the corresponding adducts **5n** with good ee (82%) in moderate yield (61%).

On the basis of the experimental results described above, a stereochemical model was developed to account for the high enantioselectivity and diastereoselectivity of the present reaction. As shown in Figure 1, pyrrolidine−urea-based catalyst **2a** was proposed as a bifunctional catalyst. The pyrrolidine reacted with carbonyl compounds to form an enamine and the urea-activated nitroolefin via a hydrogen bond. The enamine attacked the nitroolefin from the *re*-face to afford the product, which was consistent with the experimental results.

The present reaction is potentially useful in organic synthesis. For example, nitro compound **5a** was readily converted into 3-phenyloctahydroindole,[14] and we also found that, in the presence of Pd/C, **5a** was easily hydrogenated into the corresponding nitrone **6** in 95% yield without loss of ee (eq 1).[3c] The structure of nitrone **6** was determined by

(13) For the detailed experimental procedure, see Supporting Information.

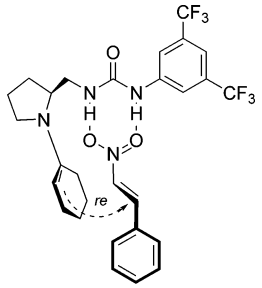


Figure 1. Possible stereochemical model.

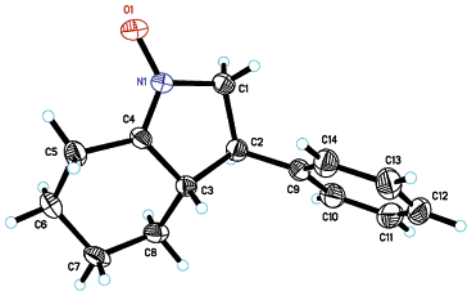
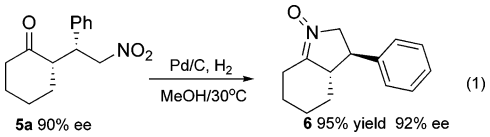


Figure 2. X-ray crystal structure of compound **6**.

NMR, mass spectra and further confirmed by X-ray analysis, which was in full accordance with the relative configuration as described above (Figure 2).



In conclusion, we have designed and synthesized two pyrrolidine−urea (thiourea)-based bifunctional organocatalysts, which have been successfully applied to the asymmetric Michael reaction of cyclohexanone with both aryl- and alkylnitroolefins. The high yield, high diastereoselectivity, and high enantioselectivity make the current reaction potentially useful. Further investigations on the application of these catalysts (**2a**, **2b**) in asymmetric catalysis are in progress.

Acknowledgment. We are grateful for the financial support from the Natural Sciences Foundation of China and The Science and Technology Commission of Shanghai Municipality.

Supporting Information Available: Characterization data for all new compounds, absolute configuration of compounds noted in Table 2, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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