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Michael additions in water of ketones to nitroolefins catalyzed by readily tunable and bifunctional pyrrolidine–thiourea organocatalysts

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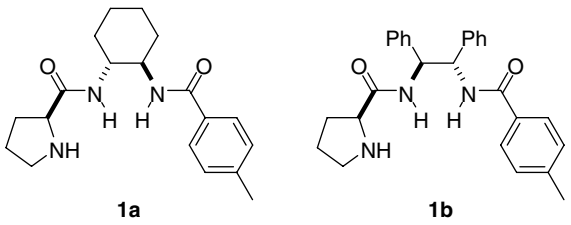
Abstract—An operationally trivial and environmentally benign procedure for direct Michael addition has been developed. The reaction of various ketones with nitroolefins can be performed in water to afford the corresponding nitro compounds in high yields in the presence of a pyrrolidine–thiourea organocatalyst at 35 °C. The reaction exhibits a high stereoselectivity, with high enantioselectivities (up to 99%) as well as diastereoselectivities (up to 99:1) being achieved under the optimal conditions.

One of the fundamental and challenging goals to scientists is to perform organic reactions in water because water is an environmentally friendly and safe medium although widely accepted as 'a contaminant in organic synthesis'.[1] Another challenge is to stereoselectively synthesize enantiopure organic molecules, concerning the importance of chirality for biologically active molecules.[2] In this context, it is of great importance to carry out an enantioselective organic reaction in water. Over the past 30 years, remarkable progress in this area has been achieved with the use of metal-based catalytic processes, although great care has to be taken to reduce the expenses and the possible contamination of the product by metals.[3] Recently, enantioselective organocatalysis has become a rapidly expanding subfield of asymmetric catalysis with attendant potential for saving in cost, operational complexity and chemical waste in comparison to chiral metal catalysis.[4,5] The pivotal feature of organocatalysts, generally insensitive to oxygen and moisture in our natural atmosphere, provides an excellent opportunity to develop organocatalytic asymmetric reactions in aqueous media. Such benefits of organocatalysis, indeed, have been recently demonstrated in the literatures.[6]

The Michael addition is an important carbon–carbon bond-forming reaction. Since the pioneering works of List[7] and Barbas,[8] organocatalytic asymmetric Michael additions have been intensively investigated,[9,10] and in doing so some elegant thiourea organocatalysts, such as primary and tertiary amine–thiourea based catalysts[11] have been successfully developed for this reaction. To the best of our knowledge, however, the secondary amine–thiourea catalyzed reactions have been rarely reported.[12] We have previously reported that the secondary amine–diamide compounds **1** (Fig. 1), which can be easily prepared from commercially available chiral 1,2-diamines and L-proline, are highly efficient and bifunctional organocatalysts for direct aldol reactions.[13]



1a **1b**

Figure 1. Representative examples of tunable and bifunctional secondary amine–diamide catalysts **1a**–**b**.

Keywords: Organocatalysis; Michael addition; Pyrrolidine–thiourea; Cyclohexanone; Water.

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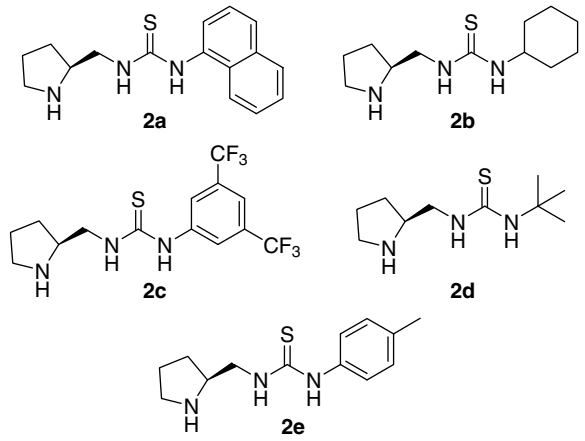
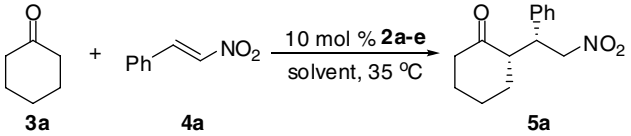


Figure 2. Tunable and bifunctional pyrrolidine–thiourea catalysts.

As part of our ongoing project on designing new organocatalysts for organic transformations,[13,14] we reasoned that the chiral molecule incorporating a pyrrolidine unit and an appropriate thiourea motif should be a tunable and bifunctional organocatalyst. Accordingly, we designed and synthesized five pyrrolidine–thiourea based catalysts **2a**–**e** (Fig. 2), and their catalytic activities were evaluated in the direct Michael addition reactions of ketones to nitroolefins in water. In this letter, we wish to disclose the preliminary results of this research.

Most recently, Barbas[6f] and Wang[6h] independently reported Michael reactions of ketones and aldehydes with nitroolefins in brine and water, respectively, using diamine/TFA and (*S*)-pyrrolidine sulfonamide as catalysts. Based on these seminal works, we initially conducted the Michael reaction of cyclohexanone with β-nitrostyrene using **2a**/PhCOOH[15] as the catalyst in brine and distilled water, respectively. As shown in Table 1, distilled water is a more suitable solvent for this reaction in terms of chemical yields (Table 1, entry 1 vs 2). Initial catalyst screening indicated that secondary amine–thiourea catalysts **2a**–**e** displayed an excellent catalytic activity toward the formation of 2-(1′-phenyl-2′-nitroethyl) cyclohexanone (**5a**) in water with great stereoselectivities (Table 1, entries 1 and 3–6). In particular, the use of 10 mol % **2e** and 10 mol % benzoic acid was the most effective catalyst system for achieving the highest diastereo- and enantioselectivities (Table 1, entry 6). Decreasing the amount of cyclohexanone (10–5 equiv) did not affect the chemical yield of **5a**, but slightly reduced both diastereoselectivity and enantioselectivity (Table 1, entry 6 vs 7).

Table 1. The catalyst screening for Michael addition of cyclohexanone (**3a**) to β-nitrostyrene (**4a**) in water[a]

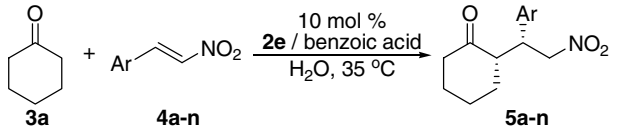


Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	dr[c] (*syn*:*anti*)	ee[d] (%)
1	**2a**	H_2O	10	89	95:5	90
2	**2a**	Brine	10	63	96:4	93
3	**2b**	H_2O	17	87	94:6	90
4	**2c**	H_2O	12	94	95:5	91
5	**2d**	H_2O	12	90	98:2	93
6	**2e**	H_2O	12	90	98:2	96
7[e]	**2e**	H_2O	12	90	96:4	94

[a] Unless specified, the reaction was carried out with cyclohexanone (**3a**, 5 mmol) and **4a** (0.5 mmol) in the presence of catalyst (0.05 mmol) and benzoic acid (0.05 mmol) in water (1 mL) at 35 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis of the mixture of *syn*/*anti* products.
[d] Determined by chiral HPLC analysis (chiralpak AS-H, hexane/2-propanol = 75/25).
[e] 5 equiv of **3a** was used.

The Michael additions of cyclohexanone to a variety of nitroolefins were effected using **2e**/PhCOOH as the catalyst system, and the results are summarized in Table 2. It was found that the reaction had a wide substrate scope with respect to nitroolefins (Table 2, entries 1 and 3–15). In general, nitroolefins with both electron-withdrawing and electron-donating aryl group reacted efficiently (72–98% yield) with high to excellent levels of enantioselectivity (ee up to 99%) and diastereoselectivity (dr up to 99:1). Other aromatic styrenes could also participate in this catalytic process (Table 2, entries 13–15). Significantly, stereoselectivities of the reaction in water were even better than those in the organic solvent, *n*-hexane (Table 2, entry 1 vs 2).

Table 2. Michael additions of cyclohexanone (**3a**) to nitroolefins (**4a**–**n**) catalyzed by **2e**/benzoic acid in water[a]



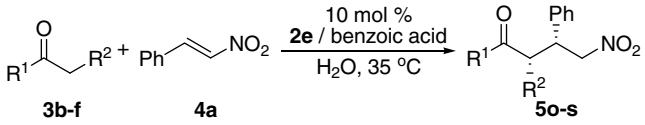
Entry	Ar	Product	Time (h)	Yield[b] (%)	dr[c] (*syn*:*anti*)	ee[d] (%)
1	Ph	**5a**	12	90	98:2	96
2[e]	Ph	**5a**	11	93	96:4	92
3	*p*-ClPh	**5b**	12.5	83	97:3	99
4	*o*-ClPh	**5c**	12.5	91	99:1	95
5	*p*-BrPh	**5d**	12.5	93	98:2	>99
6	2,4-ClPh	**5e**	2.5	86	>99:1	>99
7	*m*-BrPh	**5f**	23.5	72	95:5	93
8	*p*-FPh	**5g**	11	89	95:5	92
9	*o*-FPh	**5h**	12	84	99:1	94
10	*p*-MePh	**5i**	12.5	87	97:3	94
11	*m*-PhOPh	**5j**	34	73	94:6	88
12	*p*-MeOPh	**5k**	12	98	95:5	91
13	1-Naphthyl	**5l**	12.5	87	98:2	94
14	2-Furyl	**5m**	3.5	87	87:13	79
15	2-Thienyl	**5n**	6	90	92:8	88

[a] The reaction was conducted with **2e** (0.05 mmol), benzoic acid (0.05 mmol), **4** (0.5 mmol), and 10 equiv **3a** in 1 mL H_2O at 35 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis of the mixture of *syn*/*anti* product.
[d] Determined by chiral HPLC analysis (chiralpak AS-H, AD-H, OD-H).
[e] *n*-Hexane was used as the solvent.

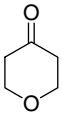
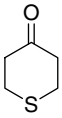
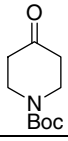
In order to expand the generality of this catalytic system, the Michael additions of other cyclic and acyclic ketones to β-nitrostyrene (**4a**) were examined using **2e**/PhCOOH as catalyst. As shown in Table 3, the reaction of acetone with β-nitrostyrene afforded the desired product **5o** in 65% isolated yield with 57% ee (Table 3, entry 1). Heterocyclic ketones worked very well in this reaction to exhibit moderate to good stereoselectivities with the ee and dr up to 89% and 99/1, respectively (Table 3, entries 2–4). In the case of tetrahydro-4*H*-thiopyran-4-one and *N*-Boc-piperidone, the addition of a small amount of CH_2Cl_2 (100 μL) to the reaction system was necessary to make the reaction efficient, because both substrates were solids and could not be readily suspended in water.

In summary, we have successfully developed a series of bifunctional pyrrolidine–thiourea organocatalysts, with the catalytic activity being tuned easily by simply changing the thiourea scaffold. These catalysts have proven to be robust and can be efficiently used in the direct Michael additions of ketones to various nitroolefins in water. High yields (up to 98%) and great stereoselectivities (up to 99:1 dr and 99% ee) make the current research very valuable. Further studies focusing on the full scope of these catalysts in asymmetric catalysis in both aqueous and organic media are currently in progress in this laboratory.

Table 3. Enantioselective Michael additions of various ketones to β-nitrostyrene catalyzed by **2e**/benzoic acid in water[a]



3b-f **4a** **5o-s**

Entry	Ketone	Product	Time (h)	Yield[b] (%)	dr[c] (*syn*:*anti*)	ee[d] (%)
1		**5o**	64	65	—	57
2		**5p**	42	80	99:1	88
3[e]		**5q**	11	90	98:2	89
4[e]		**5r**	11	88	97:3	63

[a] Unless otherwise specified, the reaction was carried out with 10 equiv of ketones (**3b**–**f**) and 0.5 mmol **4a** in the presence of 0.05 mmol **2e** and 0.05 mmol benzoic acid at 35 °C in 1 mL H_2O.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis of the mixture of *syn*/*anti* product.
[d] Determined by chiral HPLC analysis (chiralpak AS-H, AD-H).
[e] 100 μL of CH_2Cl_2 was added.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.037.

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15. We have checked TFA, HOAc, $HClO_4$, PhCOOH, and *p*-TsOH as the co-catalyst, and found that PhCOOH is the best one for the title reaction.