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Communication

An amphiphilic organic catalyst for the direct asymmetric Michael addition of cycloketone to nitroolefins in water

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ABSTRACT

A series of amphiphilic proline-derived mercapto imidazole organic catalysts were synthesized and shown to be very effective with an acid cocatalyst for the asymmetric Michael addition reaction of ketones to nitroolefins with high diastereoselectivity (up to 99:1) and excellent enantioselectivity (up to 96%) using water as solvent.

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Water is environmentally benign, safe and cheap compared to organic solvents, and therefore the use of water as the reaction solvent has received much attention in the field of green chemistry. However, the incompatibility between organic reactants and water limits its applications.

The Michael addition is one of the most powerful methods for the formation of C–C bonds in organic synthesis [1]. Since List et al. [2] reported the proline-catalyzed asymmetric Michael addition reaction, the direct asymmetric Michael addition of unmodified carbonyl compounds into nitro olefins has been regarded as an efficient synthesis route for chiral γ -nitro carbonyl compounds [3–7], which serve as versatile building blocks for the synthesis of complex organic molecules [8,9]. Meanwhile, effective organocatalytic Michael addition reactions in an aqueous system have also been reported by several research groups [10–12]. In 2006, Barbas III's group developed a

catalytic direct asymmetric Michael reaction of ketones to nitroolefins that can be performed in brine using an amphiphilic protonated diamine organic catalyst [10]. In the same year, Luo et al. [11] synthesized surfactant-type organic catalysts (SATO) for the same reactions in water. In case, high enantioselectivity up to 98% and diastereoselectivity up to 99% were observed. Recently, Syu et al. [12] reported a new second amine catalyst bearing a sulfide which showed high catalytic activity toward the direct asymmetric Michael reaction of cyclohexanone and aromatic nitroolefins using water as the solvent. In the above cases, reactions involving aliphatic nitroolefins were not reported [13–15]. Therefore, the development of a new method for asymmetric Michael addition to aliphatic nitroolefins using water as solvent is in demand.

Recently, the development of amphiphilic organic catalysts that form an emulsion system has proved to be a promising

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Scheme 1. Synthesis of the catalysts.

strategy to improve mass diffusion limitation in water-oil bi-phasic organocatalytic systems [16–19]. As our continuing effort to develop new chiral emulsion organocatalytic systems, we envisioned that the strategy of emulsion catalysis would increase the reactivity of aliphatic nitroolefins in the aqueous Michael addition reaction because of the increased frequency of contact between the catalyst, that has a long carbon chain, and the substrates. In this communication, we report a new amphiphilic proline-derived mercapto imidazole organic catalyst, which forms an emulsion system in the reaction mixture by self-assembly.

A series of proline-based organic catalysts bearing a mercapto imidazole motif (Scheme 1) with different hydrophobic alkyl chains were designed and synthesized in five steps from commercially available N-Cbz-L-prolinol. The details for the synthesis of the catalysts were given in the Supporting Information.

The model asymmetric Michael reaction of cyclohexanone **2a** to β -trans-nitroolefin **3a** was conducted in water by using 20 mol% catalyst loading at room temperature. The results are given in Table 1. All the catalysts promoted this reaction (Table 1, entries 1–6), especially catalysts **1d–1f** bearing hydrophobic

Table 1

Catalysts screened for the reaction of cyclohexanone **2a** and nitroolefin **3a**.^a

Entry	Catalyst	Conversion ^b (%)	ee ^c (%)
1	1a	61	91
2	1b	62	93
3	1c	69	92
4	1d	85	92
5	1e	97	84
6	1f	75	91
7 ^d	1d	94	87
8 ^e	1d	99	83
9 ^f	1d	99	87

^a Unless otherwise noted, all reactions were carried out at room temperature in water (0.5 mL), catalyst **1** (20 mol%), benzoic acid (20 mol%), **2a** (1.2 mmol), **3a** (0.20 mmol), reaction time 5 h.

^b Determined by ¹H NMR.

^c Determined by chiral HPLC analysis.

^d 0.5 mL CH₂Cl₂ was used.

^e 0.5 mL CHCl₃ was used.

^f The reaction was carried out in neat condition.

Fig. 1. Microscope images of the emulsion system formed with **1d**.

alkyl chains with different lengths, which exhibited higher activities in metastable emulsion states (Fig. 1). Catalyst **1d** with a dodecane moiety was the most efficient. The reaction also proceeded efficiently in an organic solvent or under neat condition. However, small decreases in enantioselectivity were observed (Table 1, entries 7–9).

An extensive study of various acids other than benzoic acid highlighted the importance of the nature of the acidic counterpart. As illustrated in Table 2, the activity varied dramatically with the different acids. Only 63% yield after 72 h was achieved when no additive was added (Table 2, entry 9). In the presence of the strong acid CF₃COOH, only a trace of the desired product was detected (Table 2, entry 7). The reactions with the relatively weak acids such as aliphatic and aromatic acids as the additive gave products in higher yield (up to 99% yield, Table 2, entries 1–6, 8). On the basis of both the reactivity and enantioselectivity, 4-nitrobenzoic acid was chosen.

Under the optimal reaction conditions, a variety of nitrostyrenes bearing different substitutions were investigated. The results are summarized in Table 3. Various styrene-type nitroalkenes reacted smoothly with cyclohexanone to provide the corresponding adducts in good yield with high enantioselectivity.

Table 2

Influence of the additive on the reaction of cyclohexanone **2a** and nitroolefin **3a**.^a

Entry	Additive	Time (h)	Yield ^b (%)	ee ^c (%)
1	benzoic acid	12	83	92
2	4-methylbenzoic acid	12	87	93
3	4-methoxybenzoic acid	12	89	93
4	4-hydroxybenzoic acid	12	90	92
5	4-nitrobenzoic acid	12	99	93
6	Salicylic acid	12	99	92
7	CF ₃ COOH	12	16	92
8	CH ₃ CH ₂ COOH	12	81	93
9 ^d	—	72	63	90

^a Unless otherwise noted, all reactions were carried out at room temperature in water (0.5 mL), catalyst **1d** (20 mol%), benzoic acid (20 mol%), **2a** (1.2 mmol), **3a** (0.20 mmol).

^b Isolated yield based on **3a**.

^c Determined by chiral HPLC analysis. The absolute configuration was determined to be (S,S) by comparing with the [α]_D²⁵ in the literature.

^d No additive was added.

Table 3Michael addition of ketones **2** to nitroolefins **3**.^a

$ \begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\ \\ \text{X} \end{array} + \text{R}-\text{CH}=\text{CH}-\text{NO}_2 \xrightarrow[\text{H}_2\text{O, rt}]{\text{1d (20 mol\%)} \\ p\text{-Nitrobenzoic acid (20 mol\%)}} \begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\ \\ \text{X} \end{array} \begin{array}{c} \text{R} \\ \\ \text{CH}_2-\text{CH}-\text{NO}_2 \end{array} $											
2a X = CH ₂ ; 2b X = O						4					
Entry	Product	Time (h)	Yield ^b (%)	d.r. ^c (syn:anti)	ee ^c (%)	Entry	Product	Time (h)	Yield ^b (%)	d.r. ^c (syn:anti)	ee ^c (%)
1		12	99	99:1	93	7		72	71	87:13	90
2		24	73	97:3	94	8		96	87	99:1	86
3		36	84	96:4	92	9		96	70	99:1	94
4		8	69	99:1	94	10		50	61	99:1	91
5		60	92	95:5	96	11		72	70	99:1	90
6		24	76	95:5	95						

^a All reactions were carried out at room temperature in water (0.5 ml), **1d** (20 mol%), benzoic acid (20 mol%), **2a** (1.2 mmol), **3a** (0.20 mmol).^b Isolated yield based on **3a**.^c Determined by chiral HPLC analysis.

ity (Table 3, entries 1–6). The electronic nature of the substituents on the benzene ring of nitroolefin **3** influenced slightly the enantioselectivity (90%–95% ee) and activity. Nitroolefin containing thiophenyl was also a suitable substrate as a Michael acceptor (Table 3, entry 7). In addition, the cyclohexanone derivative **2b** proved to be an available donor in this catalytic system (Table 3, entry 8). Noticeably, aliphatic substituted nitroolefins were also good candidates for this asymmetric Michael addition reaction although they showed slightly lower reactivity than the β -aryl-nitroolefins (Table 3, entries 9–11).

Cyclopentanone was also investigated as a donor in the **1d**-catalyzed Michael addition with **3a** (Scheme 2). The reaction proceeded smoothly and showed moderate diastereoselectivity and good enantioselectivity.

In summary, we have designed and synthesized a class of novel amphiphilic organic catalysts which were successfully

used in the asymmetric Michael addition of cyclohexanone with nitroolefins in water. The emulsion state was crucial for achieving high activity and enantioselectivity.

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Scheme 2. Michael addition of **5** with **3a**.

Graphical Abstract

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Michael addition was catalyzed by a new amphiphilic proline-derived mercapto imidazole organic catalyst using water as solvent with high diastereoselectivity (99:1 d.r.) and excellent enantioselectivity (96% ee).

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一种新型双亲性有机小分子催化剂在水相体系中催化环己酮与硝基烯烃 直接不对称Michael加成反应

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摘要: 设计合成了一系列基于脯氨酸巯基咪唑衍生物的新型双亲性有机小分子催化剂, 在水相中加入酸作为助催化剂, 可以高效高选择性的催化环己酮与硝基烯烃的不对称Michael加成反应, 非对映选择性和对映选择性分别高达99:1和96%.

关键词: 不对称催化; 乳液; 有机催化; 迈克尔加成

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