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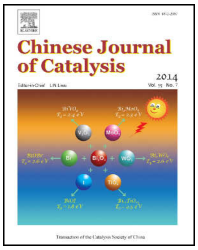

Communication

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 execellent enantioselectivity (up to 96%) using water as solvent.

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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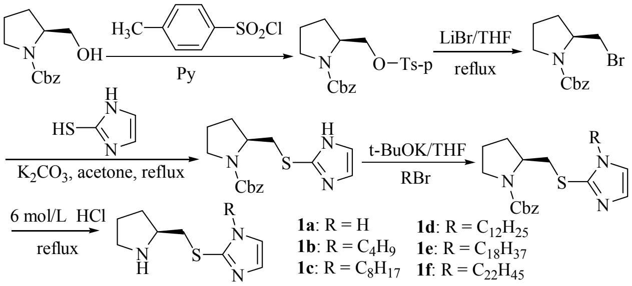


Scheme 1. Synthesis of the catalysts.

strategy to improve mass diffusion limitation in water-oil biphasic 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 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).

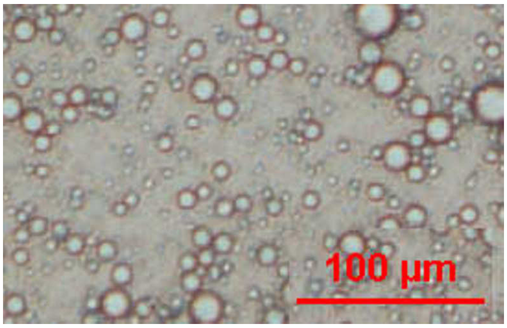
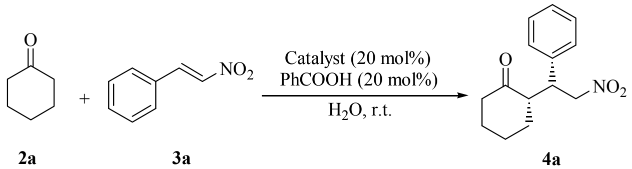


Fig. 1. Microscope images of the emulsion system formed with **1d**.

Table 1
Catalysts screened for the reaction of cyclohexanone **2a** and nitroolefin **3a**.[a]



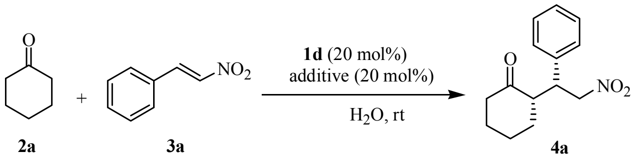
Entry	Catalyst	Conversion[b] (%)	ee[c] (%)
1	**1a**	61	91
2	**1b**	62	93
3	**1c**	69	92
4	**1d**	85	92
5	**1e**	97	84
6	**1f**	75	91
7[d]	**1d**	94	87
8[e]	**1d**	99	83
9[f]	**1d**	99	87

[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 ^{1}H NMR.
[c] Determined by chiral HPLC analysis.
[d] 0.5 mL CH_2Cl_2 was used.
[e] 0.5 mL $CHCl_3$ was used.
[f] The reaction was carried out in neat condition.

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 CF_3COOH, 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 enantioselectiv-

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_3COOH	12	16	92
8	CH_3CH_2COOH	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 absolutely configuration was determined to be (S,S) by comparing with the $[\alpha]^{25}_{D}$ in the literature.
[d] No additive was added.