Surfactant-type asymmetric organocatalyst: organocatalytic asymmetric Michael addition to nitrostyrenes in water†

Sanzhong Luo,*[a] Xueling Mi,[b] Song Liu,[b] Hui Xu[a] and Jin-Pei Cheng*[ab]

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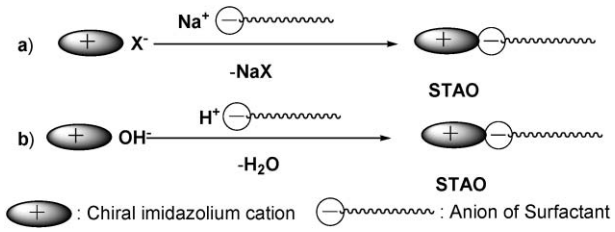
A surfactant-type asymmetric organocatalyst (STAO) catalyzed highly efficient Michael addition to nitroalkenes with high stereoselectivities in water without using any organic solvents or additional additives.

Catalytic asymmetric reactions in water have been the subject of considerable research efforts in the past decade because water is an inexpensive, safe and environmentally benign reaction medium and it often exerts a synergistic effect on the reactivity and selectivity.[1] Asymmetric organocatalysts have been recognized as the "simplest enzyme" mimic.[2] However, unlike enzymatic reactions in nature, organocatalytic processes have typically been carried out in organic solvents and, if using bulk water as the reaction medium, low yields or low selectivity are usually observed.[2a,3]

Surfactants are frequently employed in order to perform reactions in water[1,4] and this strategy has also been attempted in organocatalysis, but met with only limited success.[5] Based on our previous work on chiral ionic-liquid-type organocatalysts,[6] we envisaged that surfactant type asymmetric organocatalysts (STAOs) that were obtained by replacing the anions with surfactant sulfate or sulfonate (Scheme 1) might act as efficient asymmetric catalysts in water. This kind of catalyst would simultaneously function as an asymmetric catalyst to promote the reactions and at the same time as a surfactant to assist in solubilizing the organic substrates. This hypothesis should be conceivable because (1) according to recent studies, ionic liquids with long-chain alkyl sulfate anions still maintain the properties of surfactants and could efficiently solubilize organic substrates in water;[7] and (2) surfactants with catalytic head groups such as



Scheme 1 Synthesis of surfactant-type asymmetric organocatalysts (STAOs) by (a) anion metathesis and (b) neutralization.

[a]*Beijing National Laboratory for Molecular Sciences (BNLMS), Centre for Molecular Science, Institute of Chemistry, Chinese Academy of Science, Beijing, 100080, China. E-mail: luosz@iccas.ac.cn; Fax: +86-10-62554449; Tel: +86-1062554446*
[b]*Department of Chemistry and State-key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin, 300071, China.*

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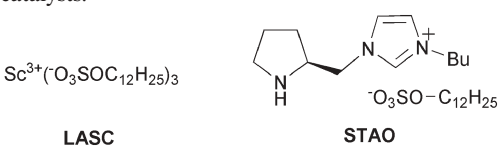
Lewis acid–surfactant combined catalysts (LASCs) developed by Kobayashi *et al.*[8] and independently by Engberts and co-workers,[9] have been successfully applied to a range of organic reactions in water. Recently, LASCs in combination with chiral ligands have been used as asymmetric catalysts in water.[10] These studies encouraged us to anticipate that a surfactant appended with a catalytic head-group (in most cases, a catalytic counterion) would suffice for smooth catalysis in pure water and that an extension to asymmetric catalysis would be achieved by changing achiral catalytic groups for chiral ones such as those in surfactant-type asymmetric organocatalysts (STAOs). In fact, asymmetric catalysis in water has previously been attempted using surfactants with chiral head-groups, albeit with low enantioselectivity.[4,11] To the best of our knowledge, no highly efficient catalyst of the chiral surfactant type has been reported up to now. To test our hypothesis, Michael addition of cyclohexanone to nitrostyrene was carried out in water using a series of surfactant-type asymmetric organocatalysts.[12]

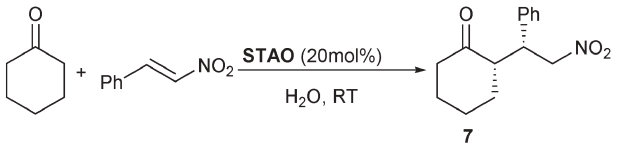


Previously, we have reported chiral ionic-liquid-type catalysts (for example, **1a**) as highly efficient organocatalysts for Michael addition to nitroolefins under neat conditions.[6] Although this type of organocatalyst is well soluble in water, our initial efforts on an aqueous version of the reaction using chiral ionic liquids such as **4–6** were unsuccessful (Table 1, entries 1–4 and 12). The reactions in water resulted in poor yields or even no desired product but insoluble material. For example, the reaction catalyzed by chiral ionic liquids such as **1a** and **3a** afforded no desired product or poor yield (Table 1, entries 1 and 11), due to the polymerization of β-nitrostyrene in water.[13] Increasing the side-chain length of the imidazolium cation improved the product yields, but the polymerization pathway still dominated (Table 1, entries 3–4).

Surfactant effect was also examined in our study. Chiral ionic liquid **1a** in combination with SDS (20 mol%) gave 27% yield of Michael addition product along with polymerized by-product (Table 1, entry 5). Further increase of the SDS loading amount showed no improvement in the reaction and only traces of product were observed (Table 1, entry 6).

Inspired by the success of LASCs, we then synthesized surfactant-type asymmetric organocatalysts (Fig. 1) simply by anion metathesis of chiral imidazolium bromides with surfactant sodium salts or by neutralization of chiral imidazolium hydroxides with surfactant Brønsted acid (Scheme 1). To our delight, the reactions catalyzed by these catalysts provided much better yields

Table 1 Screening of surfactant-type asymmetric organocatalysts (STAOs) for Michael addition of cyclohexanone (5.0 equiv.) to β-nitrostyrene in water



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Entry	Catalyst	*t*/h	Yield (%)[a]	*syn* : *anti*[b]	ee (%)[c]
1	**1a**	24	np[d,e]	—	—
2	**4**	12	np[d,e]	—	—
3	**5**	24	14[e]	nd[f]	nd
4	**6**	24	25[e]	nd	nd
5[g]	**1a**	12	27[e]	95 : 5	88
6[h]	**1a**	12	Trace[e]		
7	**1b**	12	56	97 : 3	93
8	**1c**	12	56	96 : 4	92
9[i]	**1c**	24	50	96 : 4	93
10	**2**	22	40	94 : 6	90
11	**3a**	12	20[e]	nd	nd
12[j]	**3a**	12	Trace[e]		
13	**3b**	12	56	96 : 4	97
14	**3c**	12	93	97 : 3	97
15[k]	**3c**	12	37	99 : 1	96
16[l]	**3c**	23	77 (94)[m]	97 : 3	97
17[n]	**3c**	12	48	96 : 4	96

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis (Chiralcel AD-H). [d] Conversion > 99%, np = no products. [e] Polymerization of the starting material was observed. [f] nd = not determined. [g] 20 mol% of SDS (sodium dodecylsulfate) was added. [h] one equivalent of SDS was used. [i] 7 mol% of trifluoroacetic acid was added. [j] 20 mol% of sodium dodecylbenzenesulfonate was added. [k] Reaction under solvent-free conditions. [l] 15 mol% of **3c** was used. [m] Yields based on recovery of nitrostyrene. [n] Stirring was ceased after 30 min.

of the desired Michael addition products and the polymerization pathway became less prominent in these cases (Table 1, entries 7–10 and 13–17). For example, although chiral ionic liquid-type catalysts such as **1a** and **3a** were ineffective in water, a simple switch of the bromide with dodecyl sulfate (**2b** and **3b**, respectively) led to remarkably improved performance and the Michael addition products were isolated in moderate yields with up to

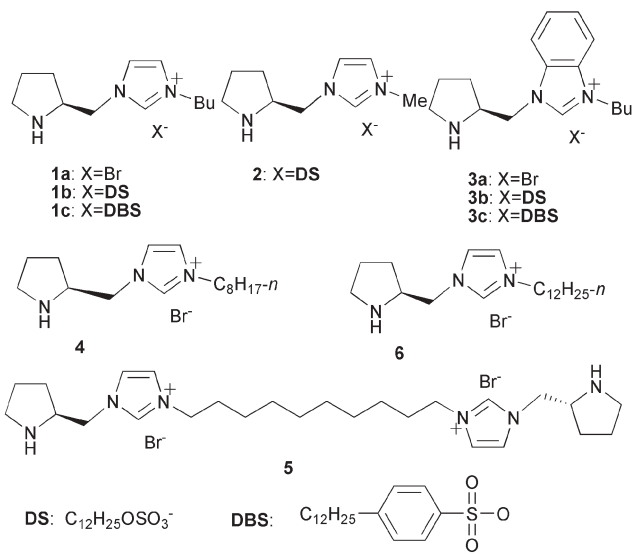


Fig. 1 Synthetic catalysts for screening.

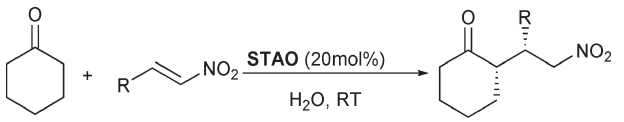
97% ee. Further screening (Fig. 1) identified **3c** as our current optimal catalyst. In the presence of 20 mol% of **3c**, the Michael addition of cyclohexanone to nitrostyrene afforded 93% yield and 97% ee in 12 h (Table 1, entry 14). In sharp contrast, simple combination of **2** with sodium dodecylbenzenesulfonate in water resulted in almost complete polymerization (Table 1, entry 12). These results along with the inefficiency of **3c** under neat conditions (Table 1, entry 15) indicated the unique properties of **3c** as a highly efficient asymmetric organocatalyst in water. The loading of **3c** could be reduced to 15 mol% without comprising the stereoselectivity (Table 1, entry 16).

The catalysis by surfactant-type asymmetric organocatalysts was generally carried out in pure water without any co-catalyst. Acidic additives such as trifluoroacetic acid (TFA), previously reported as essential co-catalysts in chiral ionic-liquid catalysis,[6] was no longer necessary in the aqueous reaction (Table 1, entry 8 *vs.* 9). The reaction was initialized simply by mixing substrates with **3c** in water, and the reaction mixture immediately turned to a white colloid type solution upon stirring (see ESI†). During the reaction, vigorous stirring should be maintained. When stirring was stopped after the initial 30 min, the reaction became sluggish and afforded only 48% yield after 12 h (Table 1, entry 17). These results suggest that the reaction should occur through interfacial catalysis.[8] When stirring is maintained, it enhances the interfacial collisions in a colloid-type solution and, as a consequence, leads to fast reaction and *vice versa*.[8,14] At this stage, the high activity of **3c** in inhomogeneous aqueous solution is not fully understood and may be rationalized by considering the hydrophobic effect in an aqueous micellar system.[4,15]

The Michael addition product **7** obtained from the aqueous reaction had the (1′*R*, 2*S*) absolute stereochemistry, which is the same as that of the product obtained from chiral ionic-liquid catalysis under neat conditions. Therefore, this stereoselectivity could also be explained by the Seebach–Golinski model as previously proposed.[6,12,16]

We next probed the substrate scope of **3c** (Table 2). Both electron-rich and electron-deficient nitrostyrenes were shown to be excellent Michael acceptors for cyclohexanone and the reactions all occurred smoothly in pure water. The desired Michael products

Table 2 STAO **3c** catalyzed asymmetric Michael addition in water



Entry	R	Product	Time/h	Yield (%)[a]	*syn* : *anti*[b]	ee (%)[c]
1	Ph	**7**	12	93	97 : 3	97
2	4-ClPh	**8**	12	64	97 : 3	97
3	2-ClPh	**9**	12	>99	99 : 1	98
4	2-BrPh	**10**	12	99	99 : 1	98
5	3-NO_2Ph	**11**	36	83	97 : 3	97
6	4-MePh	**12**	12	90	97 : 3	95
7	4-MeOPh	**13**	15	84	99 : 1	94
8	2,4-$(MeO)_2$Ph	**14**	23	98	94 : 6	91
9	2-Naphthyl	**15**	15	84	97 : 3	96
10[d]	Ph	**16**	24	80	97 : 3	61

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis (Chiralcel AD-H). [d] The Michael donor is isovaleraldehyde.

were obtained in good yields (64–99%) and showed excellent diastereoselectivity (*syn* : *anti* ⩾94 : 6) and enantioselectivity (⩾91% ee) (Table 2, entries 1–9). The stereoselectivities are comparable with those of the reactions catalyzed by Kotsuki's pyrrolidine-pyridines in organic solvent[12c] and our previous results with chiral ionic-liquid catalysis under neat conditions.[6] Most recently, Takabe and co-workers reported a diamine–TFA catalytic system for asymmetric Michael reaction in brine.[3d] In comparison, our surfactant-type catalyst **3c** demonstrated clearly better stereoselectivity than Takabe's catalyst in most of the cases examined. For example, Takabe reported optimized 89% ee and *syn* : *anti* 95 : 5 for the reaction of cyclohexanone and β-nitrostyrene, while in our case the reaction catalyzed by **3c** gave 97% ee and *syn* : *anti* 97 : 3 (Table 2, entry 1).

Acyclic ketone donors such as acetone have also been tested under the optimized conditions but with little success. The reaction of acetone with β-nitrostyrene resulted in trace product with most of the starting material decomposed.[17] Preliminary studies indicated that the reaction worked with aldehyde donors such as isovaleraldehyde (Table 2, entry 10). The Michael addition of isovaleraldehyde to nitrostyrene gave the desired product in good yield, high diastereoselectivity (*syn* : *anti*= 97 : 3) and moderate enantioselectivity (61% ee).

Generally, the desired products were gradually precipitated or separated from the water solution. In cases where phase separation did not occur at the end of the reaction, the product phase could be separated by centrifuging the mixture for a while. Therefore, the Michael products could be separated from the bulk water without using any organic solvent.

To conclude, we have developed surfactant-type asymmetric organocatalysts (STAOs) that were demonstrated to be efficient asymmetric organocatalysts in pure water with no need of any organic solvents or additional additives. The catalysts (*e.g.* **3c**) could catalyze Michael addition to nitroalkenes with high reactivity and excellent diastereoselectivity and enantioselectivity in water.[18] Further studies on broadening the scope of surfactant-type asymmetric organocatalysts in water and on developing reusable STAOs are currently under way in our laboratory and will be reported in due course.

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