J|A|C|S COMMUNICATIONS

Published on Web 12/15/2009

Diarylprolinol Silyl Ether Salts as New, Efficient, Water-Soluble, and Recyclable Organocatalysts for the Asymmetric Michael Addition on Water

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The organocatalytic asymmetric Michael reaction of aldehydes to nitroolefins is a key transformation in organic synthesis.[1] Many chiral organocatalysts have been developed to exhibit high activities and enantioselectivities for this cornerstone transformation in recent years.[2] However, a major problem associated with these organocatalytic systems is that high catalyst loading (normally 10−30 mol %) and large excess amounts of Michael donors (up to 10 equiv of aldehydes) are generally required for the reactions to be completed in reasonable time scales with good enantioselectivity. Furthermore, the high polarity and volatility of organic solvents, such as DMSO, DMF, or CH_2Cl_2, which are typically used for these reactions, are also a major problem from a green chemistry perspective. Therefore, the design and synthesis of highly active organocatalysts aimed at lowering catalyst loading, reducing the quantity of donor sources, and being active in an aqueous system[3] has proved to be a significant challenge. Most importantly would be the challenge to facilitate these expensive organocatalysts' recovery and reuse. Although initial strategies toward organocatalyst recycling using solid-phase, ionic liquid support, and fluorous technologies have been developed,[4] these methods result in low catalytic activity and enantioselectivity for aldehydes due to heterogeneous conditions,[4a] use several different polar organic solvents for catalyst recovery,[4b] or require expensive fluorous solvents for phase separation.[4c] In this paper, we provide the first example of organocatalysis using diarylprolinol silyl ether salts (Figure 1)[5] as efficient, water-soluble, and recyclable organocatalysts for the asymmetric Michael addition on pure water.[6,7] This new approach successfully combines the high efficiency and selectivity of homogeneous catalysis with the ease of separation and recyclability of heterogeneous catalysis.

It has been described that the addition of Brønsted acids to amine-catalyzed reactions can promote the formation of enamine, thereby improving chemical yields and increasing stereoselectivity.[8] In addition, Brønsted acid and the dimethylamine of the catalyst can form ammonium salts, which should not only enhance the aqueous solubility of the catalyst but also provide an easy recycling of catalysts by capitalizing on their solubility characteristics. To test this hypothesis, we carried out a model reaction on pure water of *n*-pentanal and *trans*-*β*-nitrostyrene in the presence of catalysts **1**−**2**. Screening of acid additives and their ratios to the catalyst was performed to optimize the reaction conditions. Some representative results are summarized in Table 1. Initially, the Michael addition reaction was conducted in water with 3 mol % of catalyst **2** and 3 mol % of benzoic acid as additive. The yield of Michael adduct **5a** is good (85%) with a high diastereoselectivity of 94/6 (*syn*/*anti*) and enantioselectivity of 98% ee after 24 h at room temperature (entry 1). When the amount of benzoic acid was increased to 15 mol % and 20 mol %, respectively, the reaction yields were slightly increased with comparable diastereo- and enantioselectivities (entries 2−3).

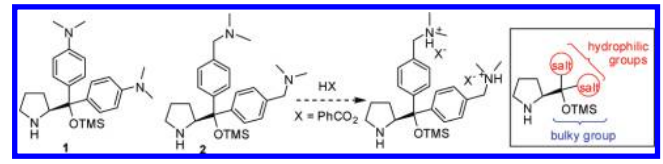
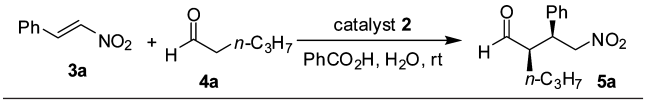


Figure 1. New design of water-soluble recyclable organocatalysts.

Table 1. Optimization of the Michael Reaction Conditions[a]



entry	catalyst loading (%)	amount of acid (%)	*t* (h)	yield (%)[b]	*syn*/*anti*[c]	ee (%)[d]
1	3	$PhCO_2H$ (3)	24	85	94/6	98
2	3	$PhCO_2H$ (15)	21	92	95/5	97
3	3	$PhCO_2H$ (20)	24	94	94/6	97
4	**3**	**$PhCO_2H$ (30)**	**5**	**97**	**97/3**	**>99**
5	3	$PhCO_2H$ (40)	5	98	96/4	98
6	3	CF_3CO_2H (30)	48	trace	−	−
7	3	CH_3CO_2H (30)	48	trace	−	−
8	3	TsOH (30)	48	trace	−	−
9	2	$PhCO_2H$ (20)	24	90	92/8	97
10	1	$PhCO_2H$ (13)	48	trace	−	−
11[e]	cat. **1** (10)	$PhCO_2H$ (40)	24	76	65/35	93/90

[a] Reactions performed on 0.5 mmol scale using catalyst **2**, benzoic acid, *n*-pentanal (2 equiv), and water (0.5 mL). [b] Yields of isolated product. [c] Determined by ^1H NMR. [d] Determined by chiral HPLC. [e] 10 mol % of catalyst **1** was used.

Interestingly, the reaction rate was greatly accelerated by increasing the amount of benzoic acid to 30 mol % affording the Michael adduct in slightly improved diastereo- and enantioselectivity (*syn*/*anti*: 97/3; ee: 99%) (entry 4). Comparable yield and selectivity were observed with a further increase of the benzoic acid loading (entry 5). When other acids, such as CF_3CO_2H, CH_3CO_2H, and TsOH, were used as additives, only trace amounts of Michael adducts were observed (entries 6−8). The catalyst loading can be reduced to 2 mol % without significantly compromising the enantioselectivity, but a longer reaction period is needed (entry 9). When the catalyst loading was further reduced to 1 mol %, only a trace amount of the product was observed after 48 h (entry 10). However, catalyst **1**, in which the dimethylamino group is connected to a phenyl ring, led to lower yield (76%) and stereoselectivity (*syn*/*anti*: 65/35; 93% ee for *syn* isomer and 90% ee for *anti* isomer, respectively), even with 10 mol % catalyst loading (entry 11). The absolute stereochemistry of major *syn* product **5a** was determined to be 2*R*,3*S* by comparing its optical rotation with literature values.[2b] The absolute stereochemical results can be explained by related transition state models previously discussed for (*S*)-diphenylprolinol silyl ether catalyzed Michael reactions.[2b]

10.1021/ja9093583

Next, the reaction of *trans*-β-nitrostyrene and *n*-pentanal was chosen as the model to examine the recyclability of the catalytic system (5 mol % of catalyst **2** was used). After the reaction was completed, the reaction mixture was extracted two times by adding a mixture solvent of Et_2O−hexane (1:8). The product was obtained by simple evaporation of the organic phase and further purification by flash silica gel chromatography. The recovered aqueous phase was used again for the next cycle directly by addition of the new reagent benzoic acid and new reactants *n*-pentanal and *trans*-β-nitrostyrene. As shown in Table 2, the catalytic activity of catalyst **2** dropped gradually after four cycles, but the yield of cycle 8 dropped dramatically to 15% even with prolonged reaction time to 24 h. However, the enantioselectivity was not affected and remains above 99% throughout all catalytic cycles. These results demonstrate that catalyst **2** is the best recyclable organocatalyst developed so far for the asymmetric Michael reactions between aldehydes and nitroolefins on water with excellent stereoselectivities as well as a very simple, practical, and green procedure for catalytic system recovery.

Table 2. Recycling Studies of Water-Soluble **2**-Catalyzed Michael Addition of *n*-Pentanal to *trans*-β-Nitrostyrene[a]

cycle	*t* (h)	yield (%)	*syn*/*anti*	ee (%)	cycle	*t* (h)	yield (%)	*syn*/*anti*	ee (%)
1	5	97	97/3	99	5	6	93	96/4	99
2	5	96	97/3	99	6	8	95	97/3	99
3	5	97	96/4	99	7	12	68	97/3	99
4	5	97	97/3	99	8	24	15	96/4	99

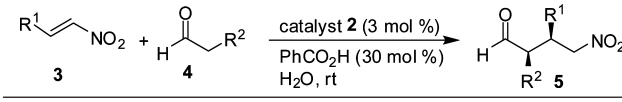
[a] Reactions performed on 0.6 mmol scale using catalyst **2**, benzoic acid, *n*-pentanal (2 equiv), and water (0.8 mL).

The scope of the Michael reactions using catalyst **2** on water was examined with a variety of aldehydes and nitroolefins (Table 3). As demonstrated in Table 3, not only linear aldehydes (entries 1−4) but also a branched aldehyde (entry 5) can be all employed successfully as the Michael donors to afford the products **5a**−**e** in high yields (84→99%) and excellent enantioselectivities (ee: up to >99%). Nitroolefins bearing electron-deficient and electron-rich aromatic substituents and heteroaromatic group were excellent Michael acceptors for *n*-pentanal (entries 6−11). Furthermore, catalyst **2** is also highly effective for Michael addition of aldehyde to aliphatic nitroolefin at room temperature for 5 h providing product **5l** in good yield and excellent stereoselectivities (*syn*/*anti*: 98/2, ee: 99%) (entry 12). However, the α,α′-disubstituted aldehyde isobutyraldehyde was found to be a poor Michael donor with low yield of the Michael adduct formed.[2b]

The large-scale (10 mmol) preparation of the Michael product of *n*-pentanal to *trans*-β-nitrostyrene under standard reaction conditions was also investigated to give product **5a** in 96% yield with excellent stereoselectivities (98% ee; *syn*/*anti*: 97/3).[5] Notably, after the reaction was completed, the product was isolated by simple phase separation and no organic solvent is required for the workup step.

We have developed a novel strategy for the catalytic asymmetric Michael addition of aldehydes to nitroolefins on water providing the Michael adducts with excellent diastereo- and enantioselectivities. There are several advantages in the present reaction: (a) the diarylprolinol silyl ether **2** catalyst is readily available; (b) a broad range of nitroolefins, including aromatic and aliphatic introolefins, are accessible; (c) the reaction can be conducted under mild conditions using only 3 mol % of catalyst and a slight excess amount of aldehydes (2 equiv); (d) the catalytic system can be easily recovered and reused for at least six times without significant loss of catalytic activity and stereoselectivities; (e) no organic solvent is required except in the purification step. These remarkable advantages will make this approach suitable not only for laboratory-scale research but also for industrial applications.

Table 3. Organocatalytic Asymmetric Michael Reaction Using Aldehydes and Nitroalkenes[a]



entry	R^1	R^2	product	*t* (h)	yield (%)[b]	*syn*/*anti*[c]	ee (%)[d]
1	Ph	*n*-Pr	**5a**	5	97	97/3	>99
2	Ph	*n*-Bu	**5b**	5	94	97/3	99
3	Ph	n-C_5H_{11}	**5c**	8	99	98/2	99
4	Ph	n-C_7H_{15}	**5d**	22	99	97/3	99
5	Ph	*i*-Pr	**5e**	21	84	97/3	>99
6	*p*-BrC_6H_4	*n*-Pr	**5f**	24	86	96/4	>99
7	*o*-ClC_6H_4	*n*-Pr	**5g**	24	74	97/3	98
8	*o*-$CF_3C_6H_4$	*n*-Pr	**5h**	72	78	96/4	>99
9	*m*-$MeOC_6H_4$	*n*-Pr	**5i**	12	96	95/5	99
10	*p*-$MeOC_6H_4$	*n*-Pr	**5j**	22	83	95/5	98
11	2-furyl	*n*-Pr	**5k**	5	93	97/3	>99
12	*n*-Bu	Bn	**5l**	5	76	98/2	99

[a] Reactions performed on 0.5 mmol scale using catalyst **2**, benzoic acid, aldehydes (2 equiv), and water (0.5 mL). [b] Yields of isolated product. [c] Determined by ^1H NMR. [d] Determined by chiral HPLC.

Acknowledgment. We are grateful to the Robert A. Welch Foundation (T-0014), NSF-REU (Grant No. 0851966), and Office of Graduate Studies & Research at Texas A&M University-Commerce for financial support of this research.

Supporting Information Available: Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA9093583