A Novel Recyclable Organocatalytic System for the Highly Asymmetric Michael Addition of Aldehydes to Nitroolefins in Water

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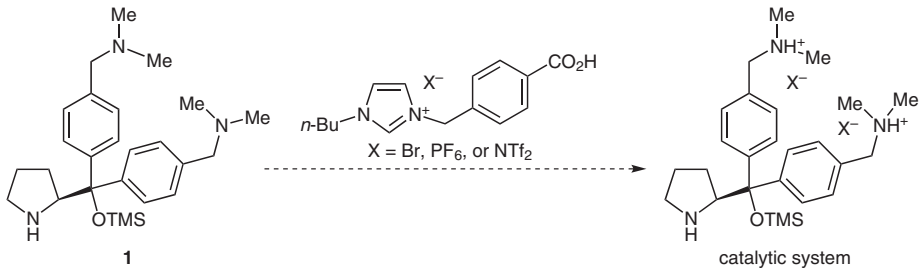
Abstract: A novel strategy for the asymmetric Michael addition of aldehydes to nitroolefins with a catalytic system of organocatalyst **1** in combination with ionic-liquid-supported (ILS) benzoic acid in water has been developed. The Michael adducts of this system give excellent diastereo- and enantioselectivities. A notable feature of this organocatalytic system is that the catalyst can be recycled more than 12 times without significant loss of enantioselectivity. In addition, the synthetic methodology presented is simple, practical, and environmentally benign.

Key words: aldehydes, asymmetric catalysis, green chemistry, ionic liquids, Michael addition

Asymmetric organocatalysis that can be performed in water has received growing attention and has become a very active field of research in recent years. Owing to the unique physical properties of water, it is a desirable medium, in which various reactions can be carried out since it is an environmentally safe liquid and also relatively cheap.[1] Many water-compatible asymmetric organocatalysts have been developed and applied to a wide range of organic transformations, in which the asymmetric products are obtained with high stereoselectivities.[2] These organocatalysts typically have a common feature in that they were specifically designed as water-insoluble and contain large hydrophobic groups, which accurately serve as 'concentrated organic phase' and assemble with hydrophobic reactants in water and sequester the formation of transition state from water.[3] The basic problem associated with these organocatalytic systems, however, is the separation of the product phase from the catalyst, which is soluble. In addition, large catalytic amounts, typically 10–30 mol% are normally used, and the catalysts are typically very difficult to separate and recycle for further use.

To overcome these problems, the development of water-soluble recyclable organocatalysts is highly desirable to expand the various applications of organocatalysis and also to address important issues, such as the development of environmentally benign catalysts that have practical and industrial applications. One aspect of our research involves the development of environmentally unique organocatalysts for asymmetric organic reactions in water.[4] We have recently reported for the first time the development and use of diarylprolinol silyl ether **1** as a water-soluble organocatalyst for the highly asymmetric Michael addition of aldehydes to nitroolefins in water with high enantioselectivity; the catalytic system is easily recycled from the product by separation of the aqueous phase.[4b] However, such a system has the disadvantage that it requires the addition of the co-catalyst benzoic acid (10 equiv of catalyst) in each cycle and since benzoic acid and the organic products are both soluble, separation of the products from the catalytic system is extremely difficult.[2o,5] To further optimize the catalytic system, we now report on the use of diarylprolinol silyl ether **1** in combination with the easily prepared ionic-liquid-supported (ILS) benzoic acid as an effective, water-soluble, and recyclable organocatalyst in water (Scheme 1). The new catalyst system can be used for the asymmetric Michael addition of aldehydes to nitroolefins to afford the Michael adducts with high diastereo- and enantioselectivities. Most important is that the new catalyst can be recovered and reused for at least 10 times without a significant loss of its ability to affect the outcome of the asymmetric induction.

The ILS benzoic acids **3** and **4a**,**b** with an imidazolium cation and bromide, PF_6, or NTf_2 anions were synthesized



Scheme 1 New design of water-soluble recyclable organocatalysts

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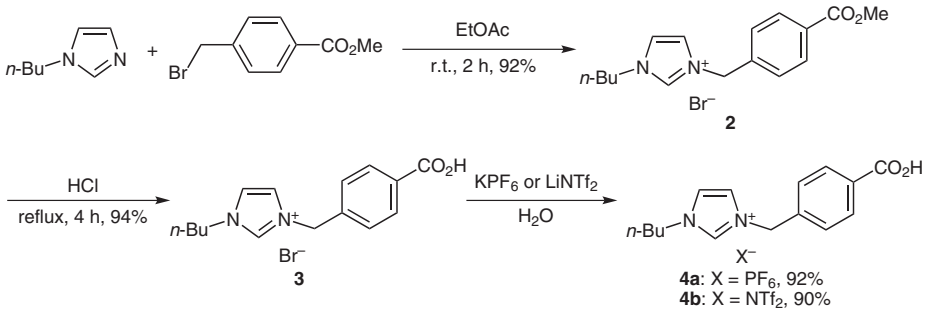
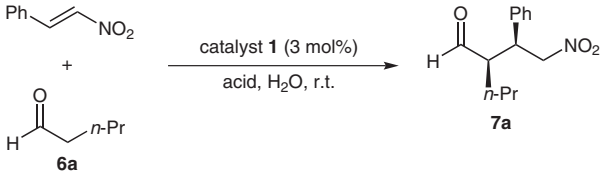


Scheme 2 Synthesis of ionic liquid-supported benzoic acid

by a sequence of reactions, which includes the alkylation of 1-butylimidazole with methyl 4-(bromomethyl)benzoate, hydrolysis of ester **2** in concentrated HCl, followed by the transformation of bromide **3** into PF_6 **4a** or NTf_2 **4b** by anion exchange in water (Scheme 2). Total yields of compounds **3** and **4a**,**b** were 78–86%.

With ILS benzoic acids **3** and **4a**,**b** in hand, we started testing their efficiency as additives in combination with organocatalyst **1** for the Michael addition of *n*-pentanal to *trans*-β-nitrostyrene in water, using 3 mol% catalyst loading in the presence of 2 equivalents of aldehyde. Representative results are summarized in Table 1. Initially, the Michael addition reaction was conducted in water with 30 mol% of ILS benzoic acid **4a** as additive. The reaction displayed an outstanding activity and selectivity, and the Michael product **7a** was obtained in 98% yield with diastereoselectivity of 94:6 (*syn*/*anti*) and enantioselectivity of 98% ee after five hours at room temperature (Table 1, entry 1). When the amount of **4a** was decreased from 30 mol% to 21 mol%, the reaction gave comparable yield and diastereo- and enantioselectivities (Table 1, entry 2). In a comparison using the same amount of non-supported benzoic acid versus ILS benzoic acid as additive, the ILS benzoic acid gave superior results with respect to the reaction time and selectivities (5 h vs 24 h; dr: 96:4, ee: 99% vs dr: 94:6, ee: 97).[4b] These results indicate an important role of the ionic liquid moiety, which can increase the catalytic activity and selectivity. By further decreasing the amount of additive **4a** from 21 mol% to 15 mol%, 9 mol%, and 6 mol%, respectively, comparable yields and enantioselectivities were obtained. However, the diastereoselectivies dropped gradually and prolonged reaction time was needed, especially in the use of 3 mol% ILS **4a** (Table 1, entries 3–6). It was found that in the presence of ILS **3** and **4b** where the anions are bromide and NTf_2, respectively, the reaction either gave very poor reactivity or relative lower stereoselectivity, compared to those obtained when ILS **4a** with PF_6 as anion was used (Table 1, entries 7, 8). The absolute stereochemistry of major *syn* product **7a** was determined to be 2*R*,3*S* by comparing its optical rotation with literature values.[6] The absolute stereochemical results can be explained by the transition-state models previously discussed for (*S*)-diphenylprolinol silyl ether catalyzed Michael reactions.[5]

Table 1 Optimization of the Michael Reaction Conditions[a]



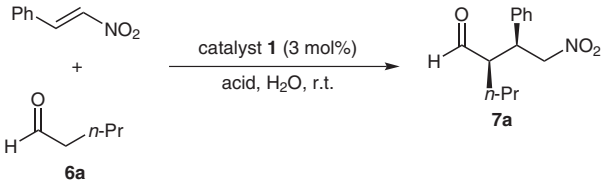
Entry	Acid	Amount of acid (%)	Time (h)	Yield (%)[b]	*syn*/*anti*[c]	ee (%)[d]
1	**4a**	30	5	98	97:3	98
2	**4a**	**21**	**5**	**97**	**96:4**	**99**
3	**4a**	15	5	98	93:7	99
4	**4a**	9	5	97	88:12	97
5	**4a**	6	5	98	82:18	98
6	**4a**	3	7	97	79:21	99
7	**3**	21	48	trace	–	–
8	**4b**	21	7	88	95:5	96

[a] Reactions performed on 0.5 mmol scale using catalyst **1**, acid, *n*-pentanal (2 equiv), and H_2O (0.5 mL).
[b] Isolated yields of pure product.
[c] Determined by ^1H NMR spectroscopy.
[d] Determined by chiral HPLC of the *syn* product.

Next, the recyclability of catalytic system (5 mol% of catalyst **1** and 35 mol% of additive ILS benzoic acid **4a** were used) was studied in a reaction of *n*-pentanal with *trans*-β-nitrostyrene. Upon completion of the reaction, the reaction mixture was extracted two times with diethyl ether. The product was obtained by simple evaporation of the diethyl ether 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 reactants *n*-pentanal and *trans*-β-nitrostyrene. As shown in Table 2, the catalyst **1** catalytic system could be recovered and reused for at least 11 times without any loss of enantioselectivity (99% ee) despite slightly prolonged reaction times were needed after cycle 5. The observation of the gradual drop in activity and diastereoselectivity of catalyst could be explained by catalyst's leaching into the organic solvent (Et_2O) or by its transformation into catalytically less-active desilylated compound.[7] However,

these results demonstrate that catalyst **1** in combination with additive **4a** is the best recyclable organocatalytic system developed so far for the asymmetric Michael reactions between aldehydes and nitroolefins in water with excellent stereoselectivities as well as a very simple, practical, and green procedure for catalytic system recovery. In contrast, other recyclable chiral organocatalysts, such as polymer-supported pyrrolidine and fluorous pyrrolidine sulfonamide, which have been used to catalyze this reaction in aqueous medium, all have the disadvantage of requiring high catalyst loading (10–20 mol%) and the use of large excess of aldehydes (5–20 equivalents).[8] In addition, low catalytic activity and enantioselectivities (48–62% ee) were observed for these systems since heterogeneous reaction conditions[6a] or expensive fluorous solvents were required for phase separation.[6b]

Table 2 Recycling Studies of Water-Soluble **1** Catalyzed Michael Addition of *n*-Pentanal to *trans*-β-Nitrostyrene[a]

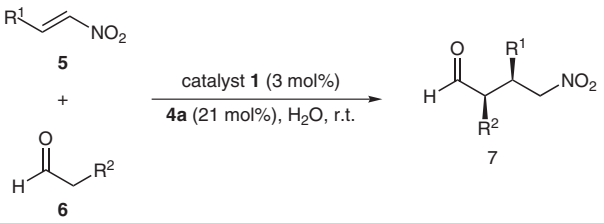


Cycle	Time (h)	Yield (%)	*syn*/*anti*	ee (%)
1	5	97	96:4	99
2	5	96	96:4	99
3	5	95	96:4	99
4	5	95	95:5	99
5	5	94	95:5	99
6	6	94	95:5	99
7	8	92	95:5	99
8	11	89	95:5	99
9	16	88	94:6	99
10	24	78	93:7	99
11	24	64	90:10	99
12	30	55	88:12	98

[a] Reactions performed on 0.5 mmol scale using catalyst **1**, acid **4a**, *n*-pentanal (2 equiv), and H_2O (0.5 mL).

Based on the excellent results obtained with the model reaction and the catalytic system in Table 1, the reaction conditions of entry 2 (Table 1) were chosen to investigate the scope of the Michael reactions using a range of aldehydes and nitrostyrenes in the presence of 3 mol% of catalyst **1**. Good to excellent yields and excellent stereoselectivities were obtained for a variety of aldehydes and nitroolefins reacting at room temperature, and the results are summarized in Table 3. As demonstrated in Table 3, not only *n*-pentanal, but also other linear aldehydes, such as *n*-hexanal, *n*-hepanal, and *n*-nonanal, can be all employed successfully as the Michael donors to afford the products **7a–d** in excellent yields (95–98%) and stereoselectivities (*syn*/*anti*: up to 97:3, 99% ee) except that a longer reaction time is required for the long-chain *n*-nonanal (Table 3, entries 1–3 vs entry 4). An aldehyde bearing a substituent on the β-position also provided product **7e** in high yield with near optical purity (Table 3, entry 5). Nitroolefins bearing both electron-deficient and electron-rich aromatic substituents were excellent Michael acceptors for *n*-pentanal (Table 3, entries 6–8). The heteroaromatic nitroolefin was also a suitable substrate as Michael donor affording the product **7i** in excellent stereoselectivity and yield (Table 3, entry 9). Furthermore, catalyst **1** is also highly effective for Michael addition of aldehyde to aliphatic nitroolefin at room temperature for five hours providing product **7j** in good yield and excellent stereoselectivities (*syn*/*anti*: 95:5, 99% ee) (Table 3, entry 10).

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



Entry	R^1	R^2	Product	Time (h)	Yield (%)[b]	*syn*/*anti*[c]	ee (%)[d]
1	Ph	*n*-Pr	**7a**	5	98	96:4	99
2	Ph	*n*-Bu	**7b**	5	96	96:4	99
3	Ph	n-C_5H_{11}	**7c**	8	95	96:4	99
4	Ph	n-C_7H_{15}	**7d**	20	98	97:3	99
5	Ph	*i*-Pr	**7e**	20	85	95:5	>99
6	4-BrC_6H_4	*n*-Pr	**7f**	24	85	95:5	99
7	3-$MeOC_6H_4$	*n*-Pr	**7g**	10	93	94:6	99
8	4-$MeOC_6H_4$	*n*-Pr	**7h**	24	81	96:4	99
9	2-furyl	*n*-Pr	**7i**	5	91	99:1	99
10	*n*-Bu	Bn	**7j**	5	74	95:5	99

[a] Reactions performed on 0.5 mmol scale of nitroolefin using catalyst **1**, acid **4a**, aldehyde **6** (2 equiv), and H_2O (0.5 mL).
[b] Isolated yields of pure product.
[c] Determined by ^1H NMR spectroscopy.
[d] Determined by chiral HPLC of the *syn* product.

The large-scale (10 mmol) preparation of the Michael product of *n*-pentanal to *trans*-β-nitrostyrene under standard reaction conditions was also investigated. After the reaction was completed, the reaction mixture was separated into two phases. The aqueous layer was removed by the

simple two-phase separation. The organic phase was purified by flash chromatography on silica gel to give the Michael product in 96% yield with excellent diastereoselectivity (*syn*/*anti*: 96:4) and enantioselectivity (99% ee). Notably, the procedure is green and practical, and no organic solvent is required for the workup step.

In summary, a highly efficient organocatalyst in combination with ILS-benzoic acid as a catalytic system for Michael additions of aldehydes to nitroolefins in water has been developed. This new catalytic system displays remarkable features. Not only does it give excellent enantioselectivities and high diastereoselectivities for a wide range of nitroolefins, including aromatic and aliphatic introolefins, but it can be easily recovered and reused for at least 12 times without significant loss of stereoselectivities. In addition, only 3 mol% of catalyst and a slight excess of donor aldehydes (2 equiv) are required. Moreover, no organic solvent is required except during the final purification step and the reaction can be easily scaled up in which similar results are obtained. These remarkable advantages make this approach more suitable for practical use in the fine chemical synthesis. Further studies focusing on the scope of this unique organocatalyst-catalyzed asymmetric transformations are currently under investigation and will be reported in due course.

Commercial reagents were used as received, unless otherwise stated. Merck 60 silica gel was used for chromatography, and Whatman silica gel plates with fluorescence UV254 were used for thin-layer chromatography (TLC) analysis. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 spectrometer. All the compounds synthesized Table 3 are known compounds. The relative and absolute configurations of the products were determined by comparison with the known ^{1}H NMR and ^{13}C NMR spectra and chiral HPLC analysis.

Compound 2

To a solution of methyl 4-bromomethylbenzoate (3.0 g, 13.1 mmol) in EtOAc (5 mL) was added *n*-butylimidazole (1.7 mL, 13.1 mmol). The reaction mixture was stirred at r.t. for 2 h under exclusion of moisture. The white solid precipitated formed was filtered and dried to give **2**; yield: 4.0 g (86%).

^{1}H NMR (400 MHz, CD_3OD): δ = 9.23 (s, 1 H), 8.04–8.02 (m, 2 H), 7.71–7.68 (m, 2 H), 7.54–7.52 (d, *J* = 4 Hz, 2 H), 5.54 (s, 1 H), 4.27–3.23 (t, *J* = 8.0 Hz, 2 H), 3.88 (s, 3 H), 1.91–1.84 (m, 2 H), 1.41–1.31 (m, 2 H), 0.98–0.94 (m, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 168.9, 140.1, 137.6, 132.7, 131.6, 129.6, 124.2, 124.0, 53.9, 50.8, 48.4, 33.0, 20.4, 13.7.

Compound 3

A solution of compound **2** (4.0 g, 11.2 mmol) in concd HCl (11 mL) was heated under reflux for 4 h. Then the reaction mixture was cooled to r.t. and subsequently extracted with Et_2O (3 × 5 mL). The aqueous phase was concentrated under reduced pressure and the residue was dried in a desiccator to give the product **3**; yield: 3.2 g (94%).

^{1}H NMR (400 MHz, CD_3OD): δ = 9.23 (s, 1 H), 8.04–8.02 (m, 2 H), 7.71–7.68 (m, 2 H), 7.54–7.52 (d, *J* = 4.0 Hz, 2 H), 5.54 (s, 1 H), 4.27–3.23 (t, *J* = 8.0 Hz, 2 H), 1.91–1.83 (m, 2 H), 1.41–1.31 (m, 2 H), 0.98–0.94 (t, *J* = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 168.9, 140.1, 137.6, 132.7, 131.6, 129.6, 124.2, 124.0, 53.9, 50.8, 48.4, 33.0, 20.4, 13.7.

HRMS (ESI+): *m*/*z* (%) calcd for $[C_{15}H_{19}N_2O_2]^+$: 259.1446; found: 259.1443.

Compound 4a

To a solution of compound **3** (3.0 g, 8.8 mmol) in H_2O (5 mL) was added KPF_6 (1.6 g, 8.8 mmol), and the reaction mixture was stirred for 4 h. White precipitate was formed, which was filtered and dried under reduced pressure to give the compound **4a**; yield: 3.6 g (92%).

^{1}H NMR (400 MHz, CD_3OD): δ = 9.02 (s, 1 H), 8.05–8.03 (d, *J* = 8.0 Hz, 2 H), 7.64–7.60 (d, *J* = 15.6 Hz, 2 H), 7.49–7.47 (d, *J* = 8.4 Hz, 2 H), 5.47 (s, 1 H), 4.22–3.19 (t, *J* = 7.6 Hz, 2 H), 1.90–1.82 (m, 2 H), 1.40–1.30 (m, 2 H), 0.97–0.94 (t, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 169.0, 140.1, 137.5, 132.8, 131.6, 129.5, 124.2, 124.0, 53.6, 50.8, 33.0, 20.4, 13.7.

HRMS (ESI+): *m*/*z* (%) calcd for $[C_{15}H_{19}N_2O_2]^+$: 259.1446; found: 259.1449.

HRMS (ESI–): *m*/*z* (%) calcd for $[PF_6]^-$: 144.9642; found: 144.9642.

Compound 4b

To a solution of compound **3** (3.0 g, 8.8 mmol) in H_2O (5 mL) was added $LiNTf_2$ (2.5 g, 8.8 mmol), and the mixture was stirred for 5 h at r.t. A colorless oil was formed, which was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the product **4b**; yield: 4.2 g (89%).

^{1}H NMR (400 MHz, CD_3OD): δ = 9.04 (s, 1 H), 8.06–8.04 (d, *J* = 8.4 Hz, 2 H), 7.65–7.61 (d, *J* = 14.8 Hz, 2 H), 7.48–7.46 (d, *J* = 87.2 Hz, 2 H), 5.47 (s, 1 H), 4.23–4.19 (t, *J* = 7.2 Hz, 2 H), 1.90–1.82 (m, 2 H), 1.40–1.30 (m, 2 H), 0.97–0.94 (t, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 166.3, 137.3, 134.7, 130.0, 128.9, 126.8, 119.6 (q, *J* = 319.4 Hz, 1C), 50.9, 48.9, 30.2, 17.7, 10.9.

HRMS (ESI+): *m*/*z* (%) calcd for $[C_{15}H_{19}N_2O_2]^+$: 259.1446; found: 259.1455.

HRMS (ESI–): *m*/*z* (%) calcd for $[N(SO_2CF_3)_2]^-$: 279.9173; found: 279.9156.

Michael Reaction of Aldehydes and Nitroolefins; General Procedure

Aldehyde **6** (1 mmol), catalyst **1** (7 mg, 0.015 mmol), nitroolefin **5** (0.5 mmol), and ILS benzoic acid **4a** (0.105 mmol, 7 times of catalyst **1**), and H_2O (0.5 mL) were added in a vial at r.t. The reaction mixture was stirred until complete conversion of the starting materials (monitored by TLC) and then extracted with Et_2O (2 × 4 mL). The combined organic phases were concentrated under vacuum to give the crude product, which was purified by flash column chromatography (silica gel, hexane–EtOAc) to afford the Michael adduct. The *syn*/*anti*-ratio was determined by ^{1}H NMR spectroscopy of the crude mixture and the enantiomeric excess (ee) was determined by HPLC on a chiral phase (Table 3).

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