Organic &
Biomolecular Chemistry

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View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 1801

Received 10th December 2012,
Accepted 18th January 2013

DOI: 10.1039/c3ob27398a

www.rsc.org/obc

Asymmetric Michael reactions catalyzed by a highly efficient and recyclable quaternary ammonium ionic liquid-supported organocatalyst in aqueous media†

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A novel ionic liquid-support organocatalyst, which contains the quaternary ammonium ion moiety, was recently developed and successfully applied to the asymmetric Michael reaction in the presence of a newly developed ionic liquid-supported (ILS) benzoic acid as co-catalyst. For the reactions studied, in which various aldehydes and nitroolefins were examined, excellent diastereo- and enantioselectivities were obtained with low catalyst loading. Also, the catalyst could be recycled for ten times without significant loss of enantioselectivity.

The ability to carry out asymmetric organocatalyzed reactions in aqueous media has many advantages, and this area of research has attracted the attention of many researchers in recent years.[1] Water has unique physical properties, which make it a very desirable medium for various reactions and it is an environmental safe liquid and also relatively cheap.[2] Over the years, many water-compatible organocatalysts have been developed and applied to a wide range of organic transformations, in which the asymmetric products are obtained with high stereoselectivities.[3,4] Such organocatalysts typically contain large hydrophobic groups, which serve to concentrate the organic phase and assemble the hydrophobic reactants in water. A problem encountered with the use of such catalysts however, is that difficulty is typically encountered in the separation of the product phase from the catalyst, which is typically soluble in the organic phase. Another problem encountered is that large amounts of the catalysts that are usually used, typically 10–30 mol%, present an environmental challenge for disposal.

Water-compatible recyclable and environmentally benign organocatalysts recently developed in our lab are specifically designed to address some of the problems described earlier in the use of other catalysts.[5] Ever since List, Lerner and Barbas reported that L-proline is an efficient enantioselective catalyst for a direct intermolecular aldol reaction,[6] different types of proline-derived catalysts have been developed. In this research, we have developed a new type of ionic-liquid supported organocatalyst, which contains an ammonium ion moiety (catalyst **1**). Ionic liquids have a unique combination of physical properties, such as extremely high polarity, they lack measurable vapor pressure and they are thermally and chemically stable,[7] which makes them ideal to be used as reusable homogenous supports for catalysts and co-catalysts. In addition, they are very polar molecules, which have been shown to synergistically enhance reaction rates of various reactions.[8] For this quaternary ammonium ILS organocatalyst, the bulky benzyl group introduces steric bulk in addition to the other bulky groups on the catalyst; they will serve to increase the stereoselectivity. Even though quaternary ammonium ILS catalysts have been introduced before and successfully used to catalyze asymmetric reactions,[9] they lack the added bulkiness found in this catalysis.

We have recently reported the development and use of a new type of diarylprolinol silyl ether as a water-soluble organocatalyst for the highly asymmetric Michael addition of aldehydes to nitroolefins in water with high enantioselectivity; these catalysts are easily recycled from the organic products by separation of the aqueous phase.[10] A major challenge that was discovered in the use of this catalytic system however, is the separation of the co-catalyst, typically benzoic acid, from the reaction products. Since benzoic acid and the organic products are both typically soluble in the organic phase, separation of the products from the catalytic system is extremely difficult.[11] In order to address this problem, we have developed recently a new type of co-catalyst that contains an ionic liquid moiety, shown in Table 1. We have demonstrated that this ionic liquid-supported (ILS) benzoic acid is an effective, water-soluble, and recyclable co-catalyst in aqueous media.[12]

In this research, the effectiveness of this new catalytic system shown in Table 1 was examined by studying the Michael reaction of *n*-pentanal and β-nitrostyrene by using benzoic acid and our recently developed ionic liquid-supported (ILS) benzoic acid as an additive. For the broad

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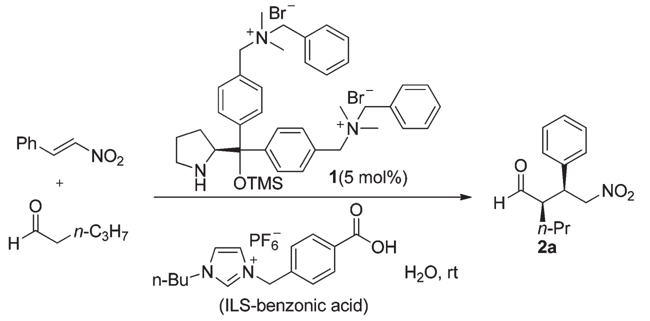
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ob27398a

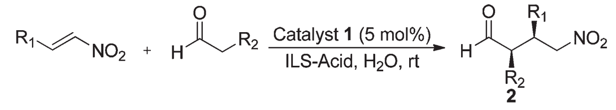
Table 1 Optimization of the Michael addition reaction conditions[a]



Entry	Acid	Acid (eq.)	Time (h)	Yield[b] (%)	*syn*/*anti*[c]	ee[d] (%)
1	Benzoic acid	6	36	99	94 : 6	99
2	Benzoic acid	10	24	99	94 : 6	99
3	**ILS benzoic acid**	**6**	**18**	**99**	**96 : 4**	**>99**
4	ILS benzoic acid	10	18	99	97 : 3	>99
5	ILS benzoic acid	3	19	99	93 : 7	>99

[a] Reactions performed on 0.4 mmol scale using catalyst **1**, acid, *n*-pentanal (2 equiv.), and water (0.5 mL). [b] Yields of isolated product. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC.

Table 2 Organocatalytic asymmetric Michael reaction using aldehydes and nitroalkenes[a]



Entry	R^1	R^2	Time (h)	Yield[b] (%)	*syn*/*anti*[c]	ee[d] (%)
1	Ph	*n*-Pr	18	99/**2a**	96 : 4	>99
2	Ph	i-Pr	70	73/**2b**	98 : 2	>99
3	Ph	*n*-Bu	16	99/**2c**	98 : 2	>99
4	Ph	*n*-C_5H_{11}	21	98/**2d**	98 : 2	99
5	Ph	*n*-C_7H_{15}	60	94/**2e**	98 : 2	>99
6	4-MeO–C_6H_4	*n*-Pr	60	87/**2f**	94 : 6	99
7	3-MeO–C_6H_4	*n*-Pr	30	96/**2g**	95 : 5	>99
8	2-Furan	*n*-Pr	20	99/**2h**	99 : 1	>99
9	4-Br–C_6H_4	*n*-Pr	42	94/**2i**	92 : 8	>99
10	*n*-Bu	Bn	20	75/**2j**	96 : 4	99

[a] Reactions performed on 0.4 mmol scale using catalyst **1**, acid, *n*-pentanal (2 equiv.), and water (0.5 mL). [b] Yields of isolated product. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC.

spectrum of reactions that are essential for organic synthesis, the catalyzed asymmetric Michael reaction of aldehyde with nitroolefins is especially important.[13] This type reaction is especially important because it is one of the most powerful reactions for carbon–carbon bond formation and also affords synthetically useful γ-nitro carbonyl compounds with excellent diastereoselectivities both in nature and in modern organic synthesis.[14] Screening of the type acid and their ratios was investigated to optimize the reaction conditions; the results are summarized in Table 1.

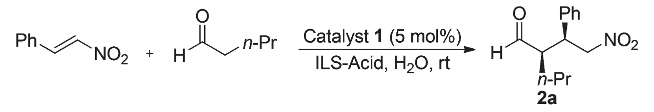
Initially, the reaction was performed in water with 5 mol% of the catalyst and 6 eq. of benzoic acid as additive. The reaction afforded the product with 99% yield with excellent selectivity after 36 hours (Table 1, entry 1). However, the reaction time was shorter when 10 eq. of benzoic acid was used (Table 1, entry 2); further increase of the amount of acid did not improve in the reaction time. When 6 eq. of the ILS benzoic acid was used as additive, the reaction was completed within 18 hours with excellent yield and excellent stereoselectivity (Table 1, entry 3). However, an increase in amount of ILS benzoic did not improve the results (Table 1, entry 4), and by decreasing the amount of ILS benzoic acid, a decrease in the diastereoselectivity of the reaction was observed (Table 1, entry 5). Thus, the conditions for entry 3 were taken as optimized conditions to be used to test the reaction scope.

The scope of the Michael addition reactions between a series of aldehydes and nitroolefins by using the catalytic system was studied in water and the results are summarized in Table 2. From these results, it is obvious that all aldehydes can efficiently undergo Michael reactions with different aryl-substituted nitrostyrenes as well as aliphatic nitroolefins in presence of 5 mol% of the catalyst and 6 eq. of the additive ILS benzoic acid at room temperature to give the Michael adducts **2a–j** in moderate to high yields (73–99%) with excellent enantio- (up to >99% ee) and diastereoselectivities (*syn*/*anti* ratio up to 99/1). Also, nitroolefins bearing electron-withdrawing and electron-donating aromatic substituents, as well as a heterocyclic aromatic group were excellent Michael acceptors for *n*-pentanal (Table 2, entries 1, 6–9). Furthermore, this catalytic system is also highly effective for Michael addition of aldehyde to aliphatic nitroolefin at room temperature for providing product **2j** in good yield and excellent stereoselectivities (Table 2, entry 10).

The recyclability of this catalytic system was examined for the reaction of *trans*-β-nitrostyrene and *n*-pentanal. After the reaction was completed, the reaction mixture was extracted by a solvent mixture of Et_2O–hexane (1 : 8). The product was obtained after evaporation of the organic solvent and purified by silica gel column chromatography. The recovered aqueous phase, which contains the catalyst and co-catalyst, was reused for the next cycle directly by addition of fresh portions of *n*-pentanal and *trans*-β-nitrostyrene. As shown in Table 3, the recovered catalytic system retained good activity and high levels of enantioselectivity for at least ten cycles despite some progressive loss of activity observed in cycles 2–10. However, the enantioselectivity was not affected and remains above 99% up to 8 catalytic cycles. These results demonstrate that this catalytic system is recyclable and effective for the asymmetric conjugate addition reactions between aldehydes and nitroolefins in water with excellent stereoselectivities.

In summary, a newly developed organocatalyst when used in combination with ILS-benzoic acid results in a highly efficient catalytic system for the Michael additions of aldehydes to nitroolefins in water. This new catalytic system displays remarkable features. Not only does it give excellent enantioselectivities and high diastereoselectivities for a wide

Table 3 Recycling studies of water-soluble catalyzed Michael addition of *n*-pentanal to *trans*-β-nitrostyrenes[a]



Cycle	Time (h)	Yield[b] (%)	*syn*/*anti*[c]	ee[d] (%)
1	9	96	97 : 3	>99
2	20	95	97 : 3	>99
3	24	96	96 : 4	>99
4	27	94	97 : 3	>99
5	28	90	99 : 1	>99
6	38	85	94 : 6	>99
7	44	70	92 : 8	99
8	45	66	90 : 10	99
9	48	45	90 : 10	98
10	60	46	86 : 14	98

[a] Reactions performed on 0.4 mmol scale using catalyst **1**, acid, *n*-pentanal (2 equiv.), and water (0.5 mL). [b] Yields of isolated product. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC.

range of nitroolefins, including aromatic and aliphatic nitroolefins, but it can be easily reused for at least 10 times without significant loss of stereoselectivities. In addition, only 5 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. These remarkable advantages make this approach an effective and practical use in the synthesis of fine chemicals.

Acknowledgements

We are grateful to the Robert A. Welch Foundation (T-1460) and the National Science Foundation (CHE-1213287) for financial support of this research.

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