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Polymer-Immobilized Pyrrolidine-Based Chiral Ionic Liquids as Recyclable Organocatalysts for Asymmetric Michael Additions to Nitrostyrenes under Solvent-Free Reaction Conditions

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Keywords: Immobilized chiral ionic liquids / Asymmetric Michael additions / Organocatalysis / Nitrostyrenes / Solvent-free reactions

A polymer immobilized pyrrolidine-based chiral ionic liquid **5a** was synthesized and was found to be a highly efficient catalyst for the Michael additions of ketones and aldehydes to nitrostyrenes, which afforded the corresponding adducts in good yields (up to 97 %), excellent enantioselectivities (up to >99 % *ee*) and high diastereoselectivities (up to >99:1 *dr*) under solvent-free reaction conditions. In addition, the catalyst **5a** could be reused at least eight times without a significant loss of its catalytic activity and stereoselectivity.

Introduction

Asymmetric carbon–carbon bond and carbon–heteroatom bond-forming reactions are among the most challenging endeavors in organic synthesis, and much attention has been paid to design and application of organocatalysts for asymmetric reactions in recent years.[1] The asymmetric Michael addition reactions of nucleophiles to nitroalkenes have attracted much attention from a large number of organic chemists working in the area of an easy transformation of the versatile nitro functionality into an amine, nitrile oxide, ketone, carboxylic acid, hydrogen atom, etc.[2] In the past decade, various enantioselective processes have been developed by using chiral ligand–metal complexes[3] and metal-free chiral organocatalysts[1c–1f] as catalysts. The organocatalytic asymmetric Michael addition of ketones with nitroolefins was pioneered by List[4] and Barbas,[5] independently. Since then, interest in the field of asymmetric Michael addition has increased intensively, and various effective organocatalysts have been developed, such as modified L-prolines,[6] pyrrolidine-based diamines,[7] chiral diamines,[8] chiral guanidines,[9] cinchona alkaloid based bifunctional organocatalysts,[10] urea(thiourea)-based bifunctional organocatalysts,[11] etc. Environmental concerns associated with chemical processes have encouraged the development of environmentally more friendly methodologies for organic reactions. In recent years, immobilization of chiral organocatalysts on supports has received considerable interest. Much effort has been spent to develop asymmetric organic reactions catalyzed by supported organocatalysts. L-Proline supported on silical gel, polymers, and ionic liquids has been successfully used in aldol reactions.[12] Recently, some recyclable organocatalysts, such as fluorous pyrrolidine sulfonamides,[13] ionic liquid supported pyrrolidine-based catalysts,[14] and polymer-supported thiourea catalysts[15] for the asymmetric Michael addition of ketones and aldehydes with nitroolefins have also been developed. We were pleased to find that the novel designed polymer-supported pyrrolidine-based organocatalysts **5a**, **5b** and **5c**, which were easily prepared from (*S*)-Boc-L-proline as shown in Scheme 1, catalyzed the reactions of ketones and aldehydes with aryl-substituted nitroolefins smoothly at room temperature in high yields with excellent diastereoselectivities and enantioselectivities under solvent-free reaction conditions (Scheme 1).

Results and Discussion

Initially, various solvents and additives were examined at room temperature using **5a** as a catalyst and (*E*)-β-nitrostyrene as a substrate. The Michael addition of cyclohexanone to nitrostyrene was chosen as a model reaction. As shown in Table 1, the Michael addition reactions proceeded smoothly in polar solvents, such as CH_3CN, EtOH, DMF and H_2O, to generate the products in moderate to excellent yields with excellent enantioselectivities and diastereoselectivities (Entries 1–4, Table 1), whereas using Et_2O, CH_2Cl_2 and THF as solvents resulted in poor yields and similar enantioselectivities and diastereoselectivities (Entries 5–7,

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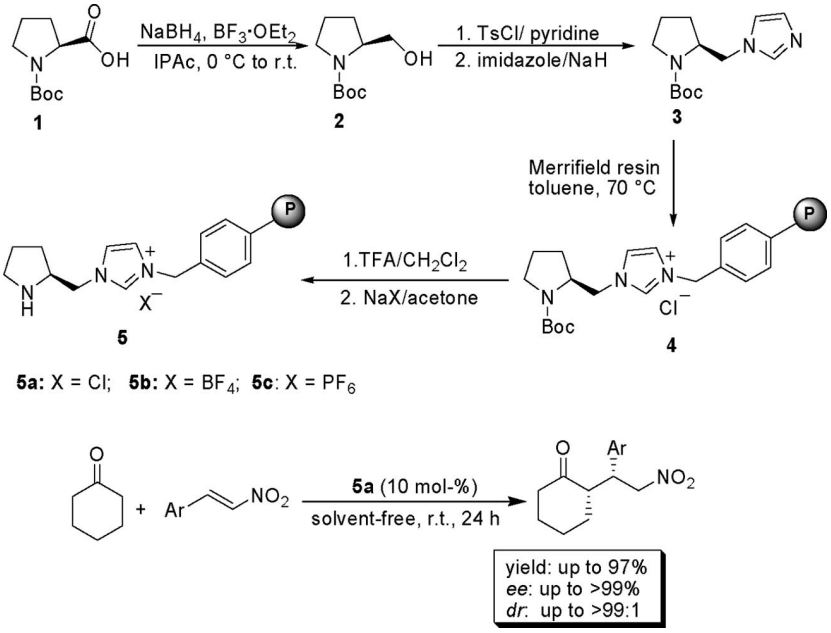
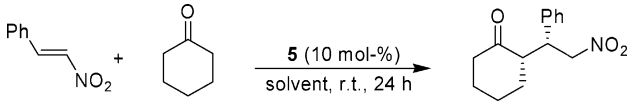


Scheme 1. Synthesis of polymer-immobilized pyrrolidine-based chiral ionic liquids **5a**, **5b** and **5c** and their applications in the Michael additions.

Table 1). The Michael additions also proceeded smoothly in nonpolar solvents, such as toluene and hexane, to give the products in excellent yields with excellent enantioselectivities and diastereoselectivities (Entries 8–9, Table 1). However, a slightly higher yield with similar enantioselectivity and diastereoselectivity were observed under solvent-free reaction conditions (Entry 10, Table 1). Moreover, a slightly higher enantioselectivity and almost the same diastereoselectivity were achieved when the reaction temperature was lowered to 0 °C, without a significant decrease of the reaction rate (Entry 14, Table 1). Interestingly, the addition of a catalytic amount of an organic acid, such as TFA, could reduce dramatically the reaction rate along with a loss of enantiomeric excess (Entry 11, Table 1). It was also found that the reaction was accomplished as it was carried out for more than 24 h (Entry 12, Table 1). It should be noted that good isolated yield, *ee* and *dr* were obtained when up to 10 mol-% of **5a** active units was added to the reaction mixture. A lower yield of the Michael addition product was isolated when less than 10 mol-% of **5a** loading was used in the reaction (Entry 13, Table 1). Under standard reaction conditions, but use of catalysts **5b** and **5c** instead of **5a**, the Michael adducts were also obtained, and the exchange of Br^- for BF_4^- and PF_6^-, respectively, has no obvious effects on both the activities and selectivities (Entries 15 and 16, Table 1).

Under the optimized reaction conditions for Michael additions of nitroolefins with ketones, which involve the use of 5 mol-% of **5a** as catalyst in the absence of solvent at room temperature for 24 h, the reactions of a variety of nitroolefins with different substituents and ketones and aldehydes were investigated, and the results are summarized in Table 2. Various styrene-type nitroolefins reacted smoothly with cyclohexanone in high yields with excellent diastereoselectivities and enantioselectivities (Entries 1–16, Table 2). Generally, substituents on aryl groups slightly influenced the diastereoselectivities and enantioselectivities, as well as the yields. For example, phenyl rings in nitroolefins with both electron-withdrawing and -donating

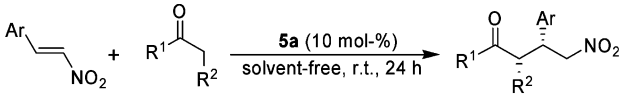
Table 1. Optimization of the reaction conditions.[a]

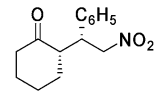
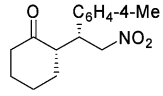
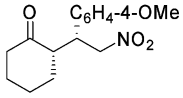
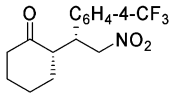
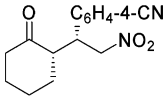
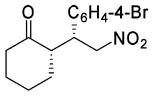
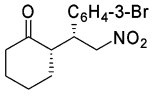
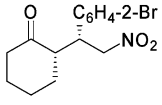
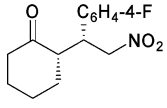
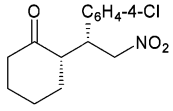
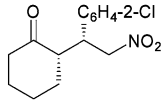
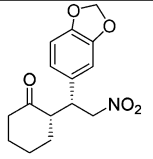
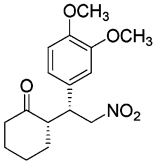
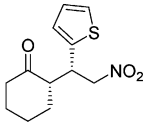
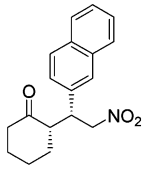
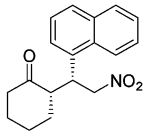
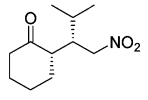
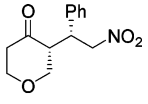
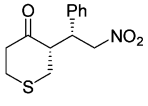
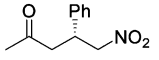
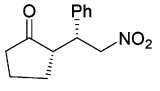
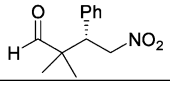


Entry	Catalyst	Solvent	Yield[b] (%)	*ee*[c] (%)	*dr*[d]
1	**5a**	CH_3CN	86	98	98:2
2	**5a**	EtOH	90	98	99:1
3	**5a**	DMF	75	99	98:2
4	**5a**	H_2O	80	99	99:1
5	**5a**	Et_2O	25	98	98:2
6	**5a**	CH_2Cl_2	40	98	98:2
7	**5a**	THF	36	98	98:2
8	**5a**	hexane	94	98	98:2
9	**5a**	toluene	95	99	98:2
10	**5a**	neat	97	99	99:1
11[e]	**5a**	neat	90	91	97:3
12[f]	**5a**	neat	82	98	99:1
13[g]	**5a**	neat	78	98	99:1
14[h]	**5a**	neat	95	>99	99:1
15	**5b**	neat	91	98	99:1
16	**5c**	neat	94	99	99:1

[a] Nitrostyrene (1.0 mmol), cyclohexanone (2.0 mmol), catalyst **5** (contains 0.10 mmol of active loading), in solvent (2 mL) at room temperature for 24 h. [b] Isolated yields. [c] Determined by HPLC using chiralpak AD-H column. [d] Diasteromeric ratio, *dr* (*syn*/*anti*), determined by ^1H NMR spectroscopy. [e] 5 mol-% TFA was added at room temperature, and the reaction time was 48 h. [f] The reaction time was 12 h. [g] 5 mol-% of catalyst **5a** was added. [h] The reaction temperature was 10 °C.

Table 2. Michael additions of ketones and an aldehyde to (*E*)-β-nitrostyrenes catalyzed by **5a**.[a]



Entry	Product	Yield[b] (%)	*ee*[c] (%)	*dr*[d]
1		97	99	99:1
2		96	>99	>99:1
3		96	99	99:1
4		98	>99	>99:1
5		97	96	95:5
6		96	99	99:1
7		93	96	98:2
8		96	98	99:1
9		97	97	98:2
10		97	99	99:1
11		94 82	93 96	95:5 97:3
12		94	98	98:2
13		92	>99	>99:1
14		90	>99	99:1
15		90	>99	>99:1
16		86	98	98:2
17		69	91	93:7
18		91	95	95:5
19		87	93	96:4
20		98 98[e]	51 57	–
21		96 84[e]	46 51	75:25 81:19
22		76	84	–

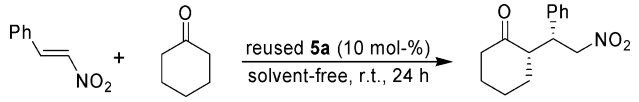
[a] Nitroolefin (1.0 mmol), ketone or aldehyde (2.0 mmol), **5a** (contains 0.10 mmol of active loading), under solvent-free reaction conditions at room temperature for 24 h. [b] Isolated yields. [c] Determined by HPLC using chiralpak AD-H column. [d] Diasteromeric ratio, *dr* (*syn*/*anti*), determined by ^{1}H NMR spectroscopy. [e] At 0 °C for 48 h.

groups gave the desired products with high selectivities (up to >99:1 *dr* and up to >99% *ee*) in excellent yields. Unfortunately, a medium yield but good enantioselectivity of product was obtained when an aliphatic substituted nitroolefin was used as substrate (Entry 17, Table 2). Moreover, the Michael reactions were evaluated with other ketones,

and it was found that tetrahydrothiopyran-4-one and tetrahydro-4*H*-pyran-4-one were also suitable substrates as Michael donors (Entries 18 and 19, Table 2). However, acetone, cyclopentanone and isobutyraldehyde served as efficient Michael donors to generate the desired adducts with excellent yields, but moderate to good enantioselectivities (Entries 20–22, Table 2).

The recyclability of polystyrene-immobilised pyrrolidine **5a** was also surveyed. After carrying out the reaction, the reaction solution was vacuum-filtered using a sintered-glass funnel and washed with CH_2Cl_2 (2 mL), Et_2O (2 mL), C_2H_5OH (2 mL), and hexane (2 mL). After being dried, **5a** can be reused directly without further purification, and it could be recovered, recycled and used for eight consecutive trials without loss of its activity and enantioselectivity (Entries 1–8, Table 3).

Table 3. Successive trials by using recoverable organocatalyst **5a**.[a]



Trial	Yield[b] (%)	*ee*[c] (%)	*dr*[d]
1	97	99	98:2
2	94	99	98:2
3	95	98	98:2
4	89	99	98:2
5	91	99	98:2
6	88	99	98:2
7	89	99	97:3
8	87	99	98:2

[a] Nitrostyrene (1.0 mmol), cyclohexanone (2.0 mmol), reused **5a** (contains 0.10 mmol of active loading) under solvent-free reaction conditions at room temperature for 24 h. [b] Isolated yields. [c] Determined by HPLC using chiralpak AD-H column. [d] Diastereomeric ratio, *dr* (*syn*/*anti*), determined by ^{1}H NMR spectroscopy.

Conclusions

We have developed a new type of polymer-immobilized pyrrolidine-based chiral ionic liquid, which is capable of catalyzing Michael addition reaction of ketones and aldehydes with nitrostyrenes in high yields, excellent enantioselectivies and diastereoselectivities. In comparison with the traditional methods, this new method has particular advantages: (i) recyclability of the catalyst up to 8 times without significant loss of catalytic activity and stereoselectivity; (ii) broad substrate applicability; (iii) high yields, excellent enantioselectivities and diastereoselectivities; (iv) solvent-free reaction conditions without any organic solvents in the reaction mixture; and (v) simple and easy experimental operation. Further investigation on the application of this kind of supported organocatalysts in asymmetric catalysis is still underway in our laboratory.

Supporting Information (see footnote on the first page of this article): Experimental details, preparation of polymer-immobilized pyrrolidine-based chiral ionic liquids, experimental procedure for Michael addition reactions, spectral and HPLC data.

Acknowledgments

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[1] For selective reviews and examples, see: a) P. L. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; b) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724; c) D. Almasi, D. A. Alonso, C. Najera, *Tetrahedron: Asymmetry* **2007**, *18*, 299–365; d) special issue on organocatalysis: *Acc. Chem. Res.* **2004**, *37*(8); e) organocatalysis in organic synthesis: *Tetrahedron* **2006**, *62*(2–3); f) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701–1716.
[2] O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894.
[3] For selected examples, see: a) J. Ji, D. M. Barnes, J. S. Zhang, A. King, S. J. Wittemberg, H. E. Morton, *J. Am. Chem. Soc.* **1999**, *121*, 10215–10216; b) C. A. Luchaco-Cullis, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 8192–8193; c) A. Alexakis, C. Benhaim, S. Rosset, M. Humam, *J. Am. Chem. Soc.* **2002**, *124*, 5262–5263; d) A. Rimkus, N. Sewald, *Org. Lett.* **2003**, *5*, 79–80; e) M. Watanabe, A. Ikagawa, H. Wang, K. Murata, T. Ikariya, *J. Am. Chem. Soc.* **2004**, *126*, 11148–11149; f) D. A. Evans, D. Seidel, *J. Am. Chem. Soc.* **2005**, *127*, 9958–9959; g) M. Janka, W. He, I. E. Haedicke, F. R. Fronczek, A. J. Frontier, R. Eisenberg, *J. Am. Chem. Soc.* **2006**, *128*, 5312–5313.
[4] B. List, P. Pojarlier, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423–2425.
[5] J. M. Betancort, K. Sakthivel, R. Thayumanavan, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 4441–4444.
[6] L. Q. Gu, G. Zhao, *Adv. Synth. Catal.* **2007**, *349*, 1629–1632.
[7] a) T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.* **2004**, *126*, 9558–9559; b) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967; c) S. V. Pansare, K. Pandya, *J. Am. Chem. Soc.* **2006**, *128*, 9624–9625; d) Vishnumaya, V. Singh, *Org. Lett.* **2007**, *9*, 1117–1119.
[8] a) O. Andrey, A. Alexakis, G. Bernardinelli, *Org. Lett.* **2003**, *5*, 2559–2561; b) S. Mosse, M. Laars, K. Kriis, T. Kanger, A. Alexakis, *Org. Lett.* **2006**, *8*, 2559–2562.
[9] M. Terada, H. Ube, Y. Yaguchi, *J. Am. Chem. Soc.* **2006**, *128*, 1454–1455.
[10] a) H. M. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907; b) J. X. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481–4483.
[11] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; b) J. Wang, H. Li, W. H. Duan, L. S. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4713–4716; c) S. B. Tsogoeva, S. W. Wei, *Chem. Commun.* **2006**, 1451–1453; d) M. P. Lalonde, Y. G. Chen, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 6366–6370; e) H. B. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170–7171; f) C. L. Cao, M. C. Ye, X. L. Sun, Y. Tang, *Org. Lett.* **2006**, *8*, 2901–2904; g) Y. J. Cao, Y. Y. Lai, X. Wang, Y. J. Li, W. J. Xiao, *Tetrahedron Lett.* **2007**, *48*, 21–24.
[12] a) M. Benaglia, G. Celentano, F. Cozzi, *Adv. Synth. Catal.* **2001**, *343*, 171–175; b) M. Benaglia, M. Cinquini, A. Puglisi, F. Cozzi, G. Celentano, *Adv. Synth. Catal.* **2002**, *344*, 533–542; c) F. Calderon, R. Fernandez, F. Sanchez, A. F. Mayoralas, *Adv. Synth. Catal.* **2005**, *347*, 1395–1403; d) W. S. Miao, T. H. Chan, *Adv. Synth. Catal.* **2006**, *348*, 1711–1718.
[13] L. S. Zu, J. Wang, H. Li, W. Wang, *Org. Lett.* **2006**, *8*, 3077–3079.
[14] a) S. Z. Luo, X. L. Mi, L. Zhang, S. Liu, H. Xu, J. P. Cheng, *Angew. Chem. Int. Ed.* **2006**, *45*, 3093–3097; b) B. K. Ni, Q. Y. Zhang, A. D. Headley, *Green Chem.* **2007**, *9*, 737–739.
[15] H. Miyabe, S. Tuchida, M. Yamauchi, Y. Takemoto, *Synthesis* **2006**, 3295–3300.

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