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Tetrahedron Letters 49 (2008) 2173–2176
Tetrahedron Letters

Polystyrene-immobilized pyrrolidine as a highly stereoselective and recyclable organocatalyst for asymmetric Michael addition of cyclohexanone to nitroolefins

Tao Miao [a], Lei Wang [a,b,*]

[a] Department of Chemistry, Huaibei Coal Teachers College, Huaibei, Anhui 235000, PR China
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, PR China

Received 1 November 2007; revised 23 December 2007; accepted 8 January 2008
Available online 11 January 2008

Abstract

Polystyrene-immobilized pyrrolidine **4** has been developed as a highly efficient, reusable, and stereoselective organocatalyst for the asymmetric Michael addition of cyclohexanone to nitroolefins. In the presence of trifluoroacetic acid, **4** catalyzed the reaction of cyclohexanone to a variety of nitroolefins with high yields (up to >99%) and excellent diastereoselectivities (up to >99:1 dr), and enantioselectivities (up to >99% ee). Furthermore, **4** could be recovered and recycled by a simple filtration of the reaction solution and used for more than 10 consecutive trials without significant loss of its catalytic activity.

Keywords: Polystyrene-immobilized pyrrolidine; Organocatalyst; Asymmetric Michael addition; Cyclohexanone; Nitroolefins

The Michael addition is one of the most important carbon–carbon bond-formation reactions in organic synthesis, and thus, it is absolutely necessary to develop the enantioselective catalytic protocols for this cornerstone reaction.[1] Asymmetric organocatalytic Michael addition has attracted much attention in the recent few years due to its environmental friendliness and the generation of multiple stereogenic centers in a single step. So far quite a number of chiral small organic molecules have been developed as stereoselective catalysts for this transformation.[2–4] L-Proline was first used to catalyze the intermolecular Michael addition of carbon nucleophiles to nitroolefins. However, it afforded the adducts with poor enantioselectivity, albeit with good diastereoselectivity.[2] Recently, various catalysts were designed and synthesized based on proline and applied to this reaction, and significantly improved efficiencies, diastereoselectivities, and enantioselectivities were obtained.[3,4] Most of these catalysts take advantage of the carboxylic acid function of proline to install steric shielding substrate-orienting functional groups. Barbas[5] and Alexakis[6] have shown that aminomethylpyrrolidine and 2,2′-bipyrrolidine derivatives could serve as useful asymmetric catalysts for the Michael addition reactions. Furthermore, Jorgensen and co-workers[7] reported an asymmetric Michael addition reaction catalyzed by chiral imidazoline catalysts.

Although these catalytic processes provide a unique methodology in asymmetric Michael addition reactions, development of new, effective catalysts is still desirable.[8] Recently, there are some reports on the asymmetric reactions using immobilized proline and its derivatives on PEG, mesoporous support, and ionic liquid.[9,10] To develop highly enantioselective and efficient chiral organocatalysts with broad substrate applicability and easy recyclability in this field is essential.[11]

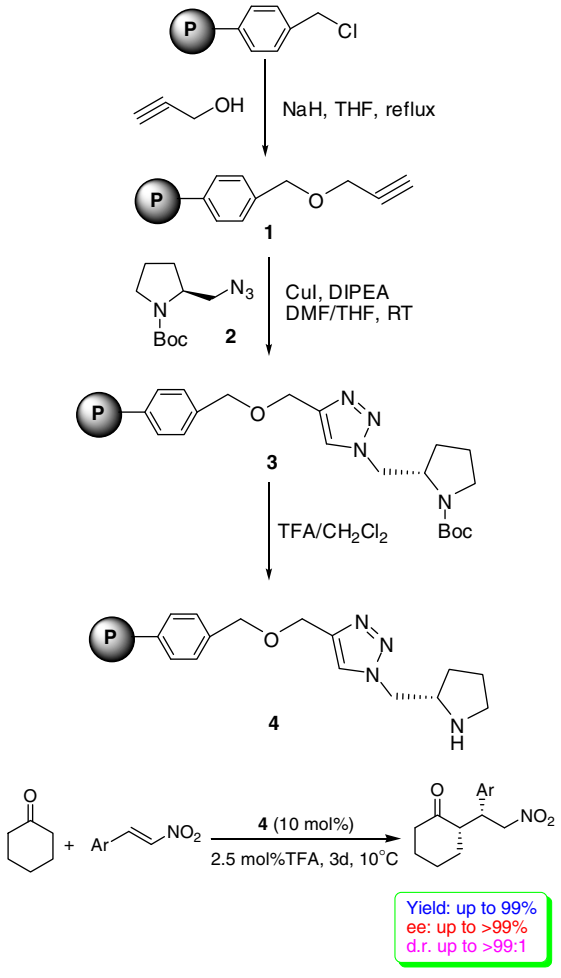
Herein, we wish to report a new catalyst **4**, a polystyrene-immobilized pyrrolidine unit for achieving high stereoselectivity in the asymmetric Michael addition of

* Corresponding author. Tel.: +86 561 380 2069; fax: +86 561 309 0518.
E-mail address: leiwang@hbcnc.edu.cn (L. Wang).

0040-4039/$ - see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2008.01.026

cyclohexanone to nitroolefins. **4** and its analogs were not only reported by our group in the abstract of Chinese Journal of Organic Chemistry,[12] but also reported by Pericás's group.[13] In the presence of trifluoroacetic acid, **4** catalyzed the reaction of cyclohexanone and a variety of nitroolefins with high yields (up to >99%) and excellent diastereoselectivities (up to >99:1 dr) and enantioselectivities (up to >99% ee). Furthermore, **4** could be recovered and recycled by a simple filtration of the reaction solution and used for more than 10 consecutive trials without significant loss of its catalytic activity (Scheme 1).

Polystyrene-immobilized pyrrolidine **4** was easily prepared starting from the commercially available Merrifield resin (2% DBV, loading 2.0 mmol/g active Cl from Aldrich Company) according to Scheme 1. Merrifield resin reacted with propargyl alcohol in the presence of sodium hydride in anhydrous THF under reflux condition for 12 h to generate functionalized resin **1**. Then, **1** reacted with an organic azide **2** in the presence of cuprous iodide and DIPEA in DMF/THF co-solvents at room temperature via click chemistry to give the corresponding 1,2,3-triazole **3**. After the removal of the *N*-Boc protecting group using trifluoroacetic acid (TFA) in CH_2Cl_2, the desired polystyrene-immobilized pyrrolidine **4** was obtained in a nearly quantitative yield.



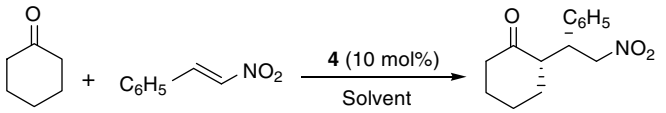
Scheme 1.

In our initial screening experiments, the asymmetric Michael addition of cyclohexanone to nitrostyrene catalyzed by polystyrene-immobilized pyrrolidine **4** was chosen as the model reaction. When we searched for a Michael addition protocol of cyclohexanone and nitrostyrene, we observed that cyclohexanone could react with nitrostyrene in the presence of polystyrene-immobilized pyrrolidine **4** (10 mol % of catalyst active unit loading) in ethanol at room temperature for 72 h to afford the desired product in 85% yield with good stereoselectivity (87% ee and 90% dr). Encouraged by this result, we continued our research to improve the yield of product and the stereoselectivity by the optimization of reaction conditions.

The solvent played an important role in the asymmetric Michael addition of cyclohexanone to nitrostyrene. In the presence of trifluoroacetic acid, when the reactions were conducted in EtOH, THF, toluene, CH_2Cl_2, and CH_3CN, products with good enantioselectivities and diastereoselectivities were isolated (Table 1, entries 1–5). When excess amount of cyclohexanone was added to the reaction mixture as solvent and substrate instead of additional solvents, excellent yield of desired product (97%) was obtained with very high ee (>99%) and dr (>99:1) (Table 1, entry 7). However, a lower yield (85%) and ee (92%) were observed in the absence of TFA (Table 1, entry 6).

The effect of reaction temperature and time on the Michael reaction was also investigated. The results were listed in Table 2. At room temperature (25 °C), the reaction took place smoothly with excellent isolated yield, good enantioselectivity, and high diastereoselectivity (Table 2, entry 1). An excellent enantioselectivity (>99% ee) was obtained along with excellent yield and dr when the reaction was performed at 10 °C. Meanwhile, a lower yield was observed when the reaction was performed at 0 °C. It is interesting to note that isolated yields, both of ee

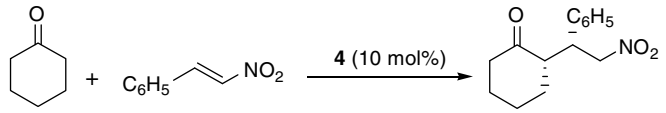
Table 1
Effect of solvent on the Michael reaction[a]



Entry	Solvent	Yield[b] (%)	ee[c] (%)	dr[d]
1	EtOH	70	92	99:1
2	THF	68	72	99:1
3	Toluene	55	56	95:5
4	CH_2Cl_2	62	70	95:5
5	CH_3CN	65	83	97:3
6	Cyclohexanone[e]	85	92	99:1
7	Cyclohexanone	97	>99	>99:1

[a] Nitrostyrene (1.00 mmol), cyclohexanone (4.00 mmol), catalyst **4** (10 mol %), TFA (2.5 mol %) in solvent (2 mL) at 10 °C for 72 h.
[b] Isolated yields.
[c] Determined by HPLC using chiral column.
[d] Diastereomeric ratio, dr (*syn/anti*), determined by ^{1}H NMR.
[e] In the absence of TFA.

Table 2
Effect of reaction temperature and time on the Michael reaction[a]



Entry	T (°C)	t (h)	Yield[b] (%)	ee[c] (%)	dr[d]
1	25	72	99	95	99:1
2	0	72	74	>99	>99:1
3	10	72	97	>99	>99:1
4	10	48	88	>99	>99:1
5	10	96	97	>99	>99:1
6[e]	10	72	90	>99	>99:1
7[f]	10	72	98	>99	>99:1

[a] Nitrostyrene (1.00 mmol), cyclohexanone (2 mL), catalyst **4** (10 mol % active unit loading), TFA (2.5 mol %) at the reaction temperature and time indicated in the table.
[b] Isolated yields.
[c] Determined by HPLC using chiral column.
[d] Diastereomeric ratio, dr (*syn/anti*), determined by ^{1}H NMR.
[e] In the presence of **4** (5 mol %).
[f] In the presence of **4** (20 mol %).

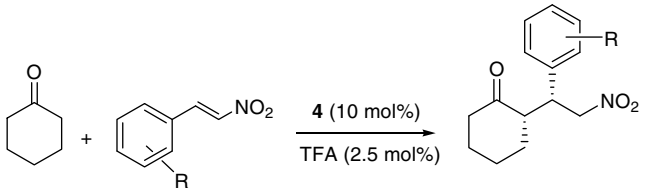
and dr, were maintained up to >99% when 10 mol % of polystyrene-immobilized pyrrolidine **4** active unit loading was added to the reaction mixture. A lower yield of the Michael addition reaction product was isolated when less than 10 mol % of **4** loading was used in the reaction. It was found that the reaction was accomplished more than 72 h.

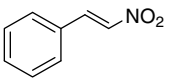
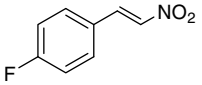
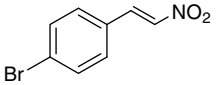
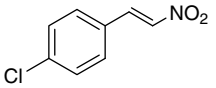
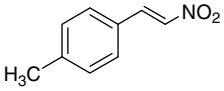
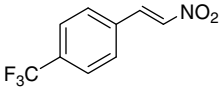
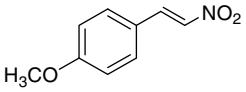
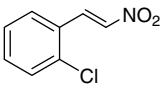
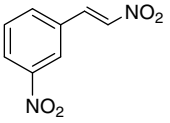
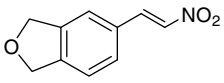
We have investigated the reactions using a variety of nitrostyrenes as the substrates under the standard reaction conditions and the results are summarized in Table 3. As shown in Table 3, high isolated yields were obtained for all the selected nitroolefins regardless of the electronic nature of the aromatic substituent R. Most of the nitroolefins, especially *para* substitution ones, were obtained in nearly optically pure form (>99% ee) and with excellent dr (99:1 to >99:1) in most of the cases examined (Table 3, entries 1, 4, 5, and 7). This addition was also tolerant of *ortho* or *meta* substitution in nitroolefins and led to good yields with good enantioselectivities and diastereoselectivities (90% ee, 98:2 dr and 88% ee, 97:3 dr, respectively, for entries 8 and 9, Table 3).

The recyclability of polystyrene-immobilized pyrrolidine **4** 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), respectively. It can be reused directly without further purification. The **4** could be recovered, recycled and used for 10 consecutive trials without loss of activity (Table 4).

Typical procedure for the asymmetric Michael addition of cyclohexanone to nitroolefins: An oven-dried round-bottomed flask was charged with polystyrene-immobilized pyrrolidine **4** (150 mg, $f = 0.697$ mmol/g, contains 0.10 mmol of active pyrrolidine unit), nitroolefin (1.0 mmol), TFA (0.025 mmol), and cyclohexanone

Table 3
Polystyrene-immobilized pyrrolidine catalyzed Michael addition of cyclohexanone to nitrostyrenes[a]

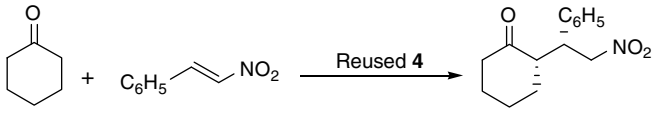


Entry	Nitrostyrene	Yield[b] (%)	ee[c] (%)	dr[d]
1		97	>99	>99:1
2		94	92	>99:1
3		90	>99	98:2
4		92	99	>99:1
5		88	>99	99:1
6		91	96	99:1
7		85	>99	>99:1
8		92	90	98:2
9		95	88	97:3
10		89	96	99:1

[a] Nitrostyrene (1.00 mmol), cyclohexanone (2 mL), catalyst **4** (10 mol % active unit loading), TFA (2.5 mol %) at 10 °C for 72 h.
[b] Isolated yields.
[c] Determined by HPLC using chiral column.
[d] Diastereomeric ratio, dr (*syn/anti*), determined by ^{1}H NMR.

(2 mL) (*Note*: bulk solution of TFA in cyclohexanone was freshly prepared and employed in the reaction, 40 μL of TFA in 100 mL of cyclohexanone). The reaction mixture was stirred at 10 °C for 72 h. After the reaction mixture was vacuum filtered using a sintered glass funnel and washed with CH_2Cl_2 (2 × 2 mL), the combined organics were dried over Na_2SO_4, filtered, concentrated, and the residue was purified by flash chromatography on silica gel to give the desired asymmetric Michael addition product.

Table 4
Successive trials by using recoverable catalyst **4**[a]



Trial	Yield[b] (%)	ee[c] (%)	dr[d]
1	97	>99	99:1
2	95	>99	99:1
3	96	>99	99:1
4	93	>99	99:1
5	95	>99	99:1
6	94	>99	99:1
7	93	>99	99:1
8	90	>99	99:1
9[e]	88	>99	99:1
10[e]	89	>99	99:1

[a] Nitrostyrene (1.00 mmol), cyclohexanone (2 mL), reused catalyst **4** (10 mol %), TFA (2.5 mol %) at 10 °C for 72 h.
[b] Isolated yields.
[c] Determined by HPLC using chiral column.
[d] Diastereomeric ratio, dr (*syn*/*anti*), determined by ^{1}H NMR.
[e] 10 °C for 96 h.

In conclusion, we have developed polystyrene-immobilized pyrrolidine as a highly stereoselective and recyclable organocatalyst for the asymmetric Michael addition of cyclohexanone to nitroolefins. Polystyrene-immobilized pyrrolidine **4** catalyzed the reaction of cyclohexanone to a variety of nitroolefins with high yields (up to >99%) and excellent diastereoselectivities (up to >99:1 dr) and enantioselectivities (up to >99% ee) in the presence of trifluoroacetic acid. Furthermore, **4** could be recovered and recycled by a simple filtration and used for more than 10 consecutive trials without significant loss of its catalytic activity.

Acknowledgment

We gratefully acknowledge financial support by the National Natural Science Foundation of China (Nos. 20572031, 20772043).

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