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Silica-supported pyrrolidine–triazole, an insoluble, recyclable organocatalyst for the enantioselective Michael addition of ketones to nitroalkenes

Ya-Bin Zhao, Lin-Wei Zhang, Lu-Yong Wu, Xing Zhong, Rong Li, Jian-Tai Ma *

College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, PR China

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ABSTRACT

A highly efficient, silica-supported organocatalyst for the Michael addition of ketones to nitroalkenes is successfully developed. A 1,2,3-triazole ring, constructed via a click 1,3-dipolar cycloaddition, plays a dual role of grafting the chiral pyrrolidine onto the silica surface and of providing a structural element complementary to the pyrrolidine. The supported catalyst demonstrated high activity and enantioselectivity; furthermore, it can be readily reused four times without significant loss of catalytic activity.

1. Introduction

Organocatalytic, asymmetric carbon–carbon and carbon–heteroatom bond-forming reactions have been extensively investigated in recent years.[1] Within this field, the organocatalyzed asymmetric Michael addition remains an important challenge,[2] the conjugate addition of ketones to nitroalkenes is particularly interesting and challenging because it can generate two contiguous stereocenters in a single step. These Michael adducts are versatile building blocks for the preparation of agricultural and pharmaceutical compounds.[3] As a result, different catalysts, quite often based on proline, have been developed, providing useful solutions for almost every reaction involving classical carbonyl chemistry.[4]

Recently, a significant amount of effort has been devoted towards modification of the proline motif. A series of proline derivatives, particularly chiral pyrrolidine–triazoles, which are made through copper-mediated 1,3-dipolar cycloaddition between azides and alkynes (click chemistry),[5] have been found to be very effective in asymmetric Michael addition reactions.[6,7] These organocatalysts are generally considered environmentally benign because the use of metals is avoided. However, it would be even more desirable and economical to develop an immobilized, easily recoverable, and reusable catalyst to perform this reaction.[8]

Since Benaglia et al. utilized PEG-supported L-proline-catalyzed asymmetric aldol condensations,[9] much effort has been devoted to the recovery of the L-proline-based organocatalysts.[10] Different types of supports, such as PEG, mesoporous, and ionic liquids,[11,12] have been used in connection with organocatalysts recovery. Unfortunately, most insoluble solid-supported chiral catalysts often suffer from low catalytic activity and enantioselectivity.[13] Recently, attempts to work with supported chiral pyrrolidine–triazole[14,15] catalysts in asymmetric Michael additions have shown improved catalytic properties over homogeneous counterparts and have led to high enantioselectivities, while offering important operational advantages.[16]

The stereoselective reaction in water or neat environments is another important research area, which avoids the problems of waste disposal that are inherent with organic solvents. However, the asymmetric reaction in water has proven to be very difficult, although a small amount of water is beneficial in some proline derivative-mediated reactions. We found that the pyrrolidine–triazole substituted proline, especially bridged with amine, is capable of catalyzing asymmetric Michael addition reaction under environmentally benign conditions, with high diastereoselectivity and enantioselectivity. These findings and our current interest in the application of solid-supported ligands in the asymmetric Michael addition led us to explore silica-supported triazole–pyrrolidine **1**, (Fig. 1) connecting through an amine tether as a recyclable catalyst. For optimal performance, ligands to be supported must be designed to allow anchoring through positions remote from the catalytic sites, in this way, interference by the bulky solid backbone will be avoided. We envisioned that the implementation of a click-reaction in the synthetic scheme towards a ligand should lead to a novel class of chiral silica-supported pyrrolidine-type triazoles **1**, which would catalyze the Michael addition of carbonyl compounds to nitroalkenes.

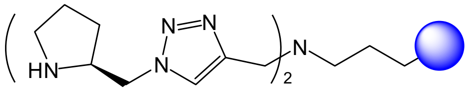

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Figure 1.

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* Corresponding author. Tel.: +86 931 8912596; fax: +86 931 8912582.
E-mail address: majiantai@lzu.edu.cn (J.-T. Ma).

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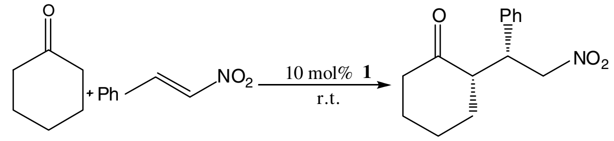
2. Results and discussion

As has been mentioned in the preceding section, we have recently described the synthesis and application of a new type of silica-supported catalyst **1** (shown in Scheme 1). Compound **3** was prepared from Boc-(*S*)-proline in four steps.[6,7,17] The other coupling partner, 3-aminopropyl functionalized silica **4** was treated with propargyl bromide under basic conditions (K_2CO_3 in acetone) to provide the alkyne-functionalized silica **5**. Azide **2** was then grafted onto **5** by a Cu(I)-catalyzed Huisgen cycloaddition to afford, upon deprotection with TFA, immobilized catalyst **1**.

The catalytic activity of the silica-supported organocatalyst **1** was evaluated in the Michael addition reaction of cyclohexanone to β-nitrostyrene at room temperature. Initial attempts to carry out the reaction in DMSO led to incomplete conversion of β-nitrostyrene (Table 1, entry 1). Variation of the solvent to H_2O or $CHCl_3$ did not improve the yield of reaction (entries 2 and 3); interestingly, the best conversion and highest enantioselectivities with catalyst **1** were achieved under neat conditions. The addition of 5 mol % of TFA decreased the reaction yield[18] (entries 5–8), while decreasing the catalyst loading led to lower yield, although the diastereoselectivity and ee were maintained (Table 1, entry 9).

Under the optimized conditions, a variety of nitroalkenes and ketones were investigated to establish the generality of this methodology (Table 2). All reactions were performed at room temperature in the presence of 10 mol % of **1** for 72 h. As shown in Table 2, all aromatic β-nitroalkenes are good acceptors and give the desired *syn* adducts in good yields with high diastereo- and enantioselectivity. No significant dependence on the electronic or steric properties of the substrate was observed (entries 1–10), with the exception of 2-naphthyl-nitroalkene, where a slight decrease in enantioselectivity was observed, whereas the reaction yield remained excellent (entry 11). Unfortunately, attempts using aliphatic nitroalkenes gave lower yields and ees. On the other hand, the use of ketones other than cyclohexanones had a dramatic effect on the performance of the catalyst. Thus, the use of cyclopentanone and 3,3-dimethyl-1,5-dioxaspiro[5.5]undecan-9-one as a Michael donor resulted in a significant drop in both yield and enantioselectivity (entries 13 and 14), acetone also proved to be a suitable Michael donor providing good yield with moderate enantioselectivity (entry 12).

Table 1
Optimization of the reaction conditions[a]



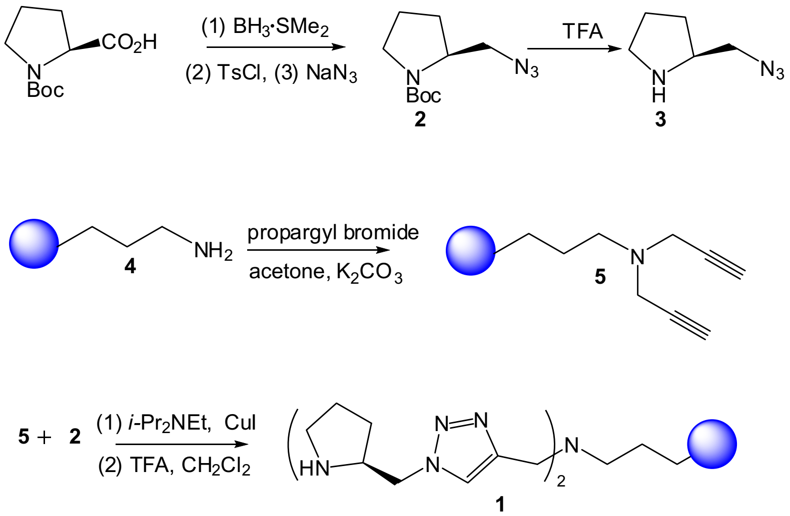
Entry	Solvent	Additive	Yield[c] (%)	dr (*syn*/*anti*)[d]	ee[f] (%)
1	DMSO	—	80	94:6	89
2	H_2O	—	83	93:7	90
3	$CHCl_3$	—	Trace	—	—
4	No solvent	—	97	96:4	91
5	$CHCl_3$	TFA[b]	Trace	—	—
6	H_2O	TFA	75	93:7	82
7	DMSO	TFA	70	93:7	87
8	No solvent	TFA	88	96:4	88
9[e]	No solvent	—	65	95:5	90

[a] Unless otherwise noted, the reaction was conducted using cyclohexanone (2 mmol), β-nitrostyrene (0.1 mmol), 10 mol % catalyst **1**, and reaction mixture was stirred at room temperature for 72 h.
[b] TFA = trifluoroacetic acid, 0.005 mmol was used.
[c] Isolated yield.
[d] Determined by ^1H NMR.
[e] 5 mol % catalyst was used.
[f] Determined by chiral HPLC analysis (Chiralpak AD-H, hexane-2-propanol = 90:10).

In addition to these characteristics, the recyclability and reusability of silica-supported catalyst **1** is noteworthy (Table 3). The reaction of cyclohexanone and β-nitrostyrene was chosen as a model study. Thus, after the reaction mixtures were quenched by filtration, the catalyst was washed with EtOAc and simply dried for reuse. As shown in Table 3, the supported catalyst exhibited good catalytic activity with high diastereo- and enantioselectivity up to the fourth cycle.

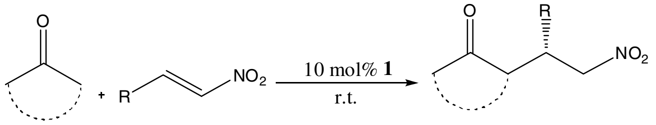
3. Conclusion

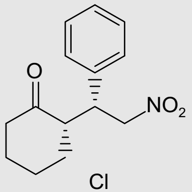
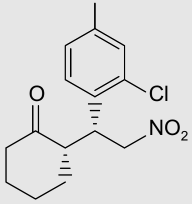
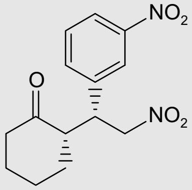
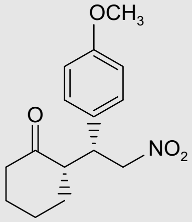
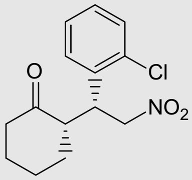
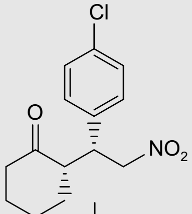
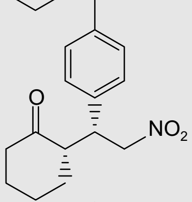
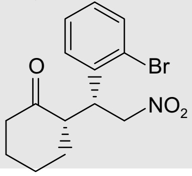
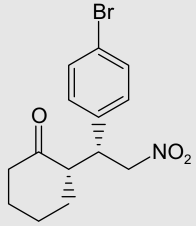
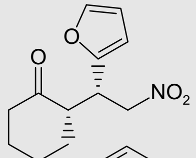
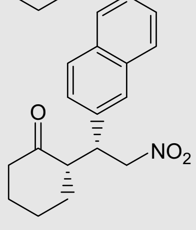
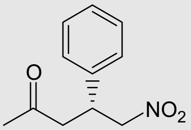
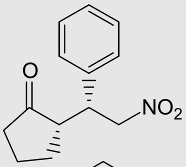
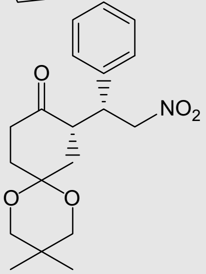
In conclusion, a new silica-supported organocatalyst has been prepared and successfully applied to the asymmetric Michael addition reaction of ketones to nitroalkenes. The reactions proceeded smoothly at room temperature to give high yields (up to 98%), excellent diastereoselectivities (*syn*/*anti* ratio up to 20:1), and excellent enantioselectivities (ee up to 93%). Furthermore, this procedure permits extensive recycling of the catalyst without substantial loss of activity. On the basis of the current work, it seems likely that a number of asymmetric reactions could be performed equally well with this immobilized organocatalyst. The design of the



Scheme 1.

Table 2
Scope of different ketone with nitroolefins[a]



Entry	Product	Yield[b] (%)	dr (*syn*/*anti*)[c]	ee[d] (%)
1		97	96:4	91
2		97	>20:1	88
3		97	93:7	87
4		98	>20:1	84
5		96	>20:1	89
6		97	>20:1	93
7		98	96:4	85
8		97	>20:1	87
9		96	96:4	89
10		97	94:6	88
11		94	>20:1	77
12		95	–	40
13		55	23:14	43:56[e]
14		68	95:5	65

[a] Reactions were performed on a 0.1 mmol nitroalkene, 2 mmol ketone and 10 mol % catalyst **1**.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC analysis (Chiralpak AD-H).
[e] ee (%) is *syn*:*anti*.

Table 3
Recycling studies of silica-supported catalyst **1** in the Michael reaction of cyclohexanone to β-nitrostyrene

Cycle	1	2	3	4
Yield[a] (%)	97	96	93	95
dr (*syn*/*anti*)[b]	96:4	97:3	95:5	94:6
ee[c] (%)	91	90	90	91

[a] Isolated yield.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC analysis (Chiralpak AD-H).

improved catalysts and their application to other types of reactions are currently underway in our laboratory.

4. Experiment

4.1. General

All commercial solvents and reagents were used without further purification, and all reactions were carried out directly under open air, unless otherwise stated. ^{1}H NMR spectra were recorded on Varian Mercury Plus 300 or 400 MHz NMR spectrometer, and ^{13}C NMR spectra at 75 MHz or 100 MHz. Mass spectra were recorded by the EI method or HRMS method. Nicolet NEXUS 670 FTIR spectrometer was used for IR spectra. HPLC analysis was performed on Waters 600 using a ChiralPak AD-H column with 2-propanol in hexanes as the eluent.

4.2. General procedure for the asymmetric Michael addition reactions of ketones to nitroalkenes

To a mixture of nitroalkenes (0.1 mmol), the catalyst **1** (0.01 mmol) was added to ketone (2 mmol). The suspension was stirred vigorously at room temperature and monitored by TLC. After the reaction, the mixture was filtrated, the catalyst was washed with AcOEt (3 × 15 mL), and simply dried for reuse. The organic layer was separated and rotary evaporated, and purified by flash column chromatography on silica gel using a mixture of ethyl acetate/petroleum ether = 1:20 to 4:1 to give the Michael adduct.

4.3. Synthesis of silica-supported catalyst 1

(a) 3-Aminopropyl functionalized silica catalyst **4**.[19]
Elemental analysis (%): N, 1.71, C, 6.55, H, 1.68; Loading: 1.22 mmol/g.

(b) Silica-supported catalyst **5**.
3-Aminopropyl functionalized silica (1 g, loading = 1.22 mmol/g) was treated with propargyl bromide (4.3 g, 36.6 mmol), K_2CO_3 (1.2 equiv) and refluxed in acetone for 48 h. The reaction mixture was then filtered and sequentially washed with water (250 mL), DMF (250 mL), THF (250 mL), THF–MeOH 1:1 (250 mL), MeOH (250 mL), and THF (250 mL). The solid was dried in vacuo for 24 h at 40 °C. Elemental analysis (%): N, 1.27, C, 15.58, H, 2.07; Loading: 0.91 mmol/g.

(c) Cycloaddition of **5** with *N*-Boc-(2*S*)-2-azidomethyl-pyrrolidine **2**.
N-Boc-(2*S*)-2-Azidomethyl-pyrrolidine **2** (181 mg, 0.8 mmol), *N*,*N*-diisopropylethylamine (1.12 mL, 6.4 mmol), and copper(I) iodide (0.006 g, 0.003 mmol) were added to a suspension of **5** (1 g, loading = 0.91 mmol/g) and stirred in DMF–THF 1:1 (20 mL) at 35 °C for 24 h, then collected by filtration and sequentially washed with water (250 mL), DMF (250 mL), THF (250 mL), THF–MeOH 1:1 (250 mL), MeOH (250 mL), and THF (250 mL). The solid was dried in vacuo for 24 h at 40 °C. Elemental analysis (%): N, 3.23, C, 18.73, H, 2.50; Loading: 0.26 mmol/g.

(d) Deprotection.
Firstly, 1 g (loading = 0.26 mmol/g) of the silica resulting from the previous step was immersed with 10 mL of CH_2Cl_2. After 10 min, 10 mL of trifluoroacetic acid was added and stirred for 24 h, after which the reaction mixture was filtered. After filtration, silica-supported proline 1 was sequentially washed with THF (with 2% of Et_3N, 250 mL), water (250 mL), THF (250 mL), THF–MeOH 1:1 (250 mL), MeOH (250 mL), and THF (250 mL). The solid was dried in vacuo for 24 h at 40 °C. Elemental analysis (%): N, 3.15, C, 15.60, H, 2.17; Loading: 0.25 mmol/g.

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18. It should be noted that the addition of TFA had little effect on the diastereoselectivity and enantioselectivity, presumably because the stereogenic center α to the carbonyl carbon is prone to racemization. This would be even faster in water or aqueous acidic condition, however, the system used is neat and without acid, thus can avoid this undesired reaction and give high diastereo- and enantioselectivity.
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