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## 1. Introduction

The asymmetric aldol reaction is one of the most important carbon–carbon bond-forming strategies in organic synthesis, which can be used in the generation of various compounds with biological and optical activities. Generally, there are three kinds of catalysts for the aldol reaction, which are the biocatalysts,<sup>1-3</sup> chiral metal complexes<sup>4,5</sup> and metal-free small molecular organocatalysts.<sup>6–8</sup> Among these catalysts, the third one has attracted intense attention in recent years owing to its economical advantage, operationally simple and environmentally friendly features. Since List *et al.*<sup>9</sup> successfully demonstrated that L-proline can highly catalyze the simple aldol reaction of acetone and aldehydes, numerous highly-efficient small organic molecular catalysts based on proline and its derivatives have been designed for varieties of asymmetric reactions<sup>10–15</sup> and rapidly grown to their adolescence from infancy.

Compared with homogeneous catalysts, supported proline can be easily recovered from the reaction mixture and keep stable catalytic activity and selectivity after being reused for many times, which is meaningful for the environmental protection and energy conservation. Since the PEG-supported proline catalyst was successfully prepared and applied in the

# The high catalytic activity and reusability of the proline functionalized cage-like mesoporous material SBA-16 for the asymmetric aldol reaction proceeding in methanol—water mixed solvent<sup>+</sup>

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The cage-like mesoporous material SBA-16 has been successfully functionalized with l-4-hydroxyproline and characterized by Fourier transform infrared (FT-IR) spectroscopy, Small-angle X-ray powder diffraction (XRD), N<sub>2</sub> sorption detection, transmission electron microscopy (TEM), elemental analysis and thermo gravimetric analysis (TGA). This chiral non-metallic catalyst avoided heavy metal pollution during the preparing and using process, and demonstrated high catalytic activity (up to 91%), diastereoselectivity (up to 97 : 3) and enantioselectivity (up to 83%) in the asymmetric aldol reaction between aldehyde acceptors and ketone donors with methanol $-H_2O$  as solvent. Moreover, the synthesized catalyst could be easily separated from the reaction mixture by filtration and reused for up to five runs without any obvious loss of activity, indicating its excellent recyclability.

> asymmetric aldol condensations,16 a significant amount of efforts have been devoted to immobilization and recycling of Lproline.<sup>17-21</sup> Different types of support materials, such as polymer, ionic liquids, magnetite, carbon and silica materials have been used in connection with the immobilization of proline. Huerta et al.22 investigated the catalytic behaviors of a watersoluble L-proline-functionalized catalytic polymer in the aldol reaction. A kind of basic chiral ionic liquids on the basis of commercially available (S)-proline was designed by Vasiloiu and his co-workers,23 and utilized as organocatalyst in asymmetric aldolization. Riente et al.24 immobilized the (S)-a,a-diphenylprolinol trimethylsilyl ether onto superparamagnetic Fe<sub>3</sub>O<sub>4</sub> nanoparticles and used it as a highly active, magnetically recoverable and reusable catalyst for the asymmetric Michael addition reaction. An effective heterogeneous L-proline catalyst for the direct asymmetric aldol reaction using graphene oxide as support was reported by Tan and his company.25 Hsiao et al.26 prepared the mesoporous SBA-15 modified with chiral proline derivatives for catalyzing the addition of diethylzinc to benzaldehvde.

> Among various supports of the heterogeneous catalysts, the mesoporous materials are very promising for their large specific surface area and regularly arranged pore structure. Unlike the widely-used channel-like materials MCM-41 or SBA-15, the recently synthesized SBA-16 is a new type of ordered silicon material with cage-like mesoporous framework, which is suitable for processing large molecules because of their unique structure and pore connectivity. This mesoporous cage-like material has tunable cage size (4–10 nm) and tunable pore entrance size (generally less than 4 nm). The isolated



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nanocages are three-dimensionally interconnected by pore entrances. Such architectures can probably eliminate pore blocking and allow a fast transport of reactants and products.<sup>27</sup> Recently, due to its excellent physical and chemical properties, SBA-16 has played an important role in the immobilization of catalysts.<sup>28-32</sup>

In our previous work, a kind of magnetic catalyst based on proline as active component and  $Fe_3O_4$  (a)SiO<sub>2</sub> as support was successfully synthesized and demonstrated high catalytic activity, diastereoselectivity and enantioselectivity in the direct aldol reactions.<sup>33</sup> Upon the consideration that the threedimensional mesoporous cage-like material SBA-16 has a superior ability in reducing the diffusion resistance,<sup>28</sup> which is crucial factor for designing high-performance catalyst, another heterogeneous catalyst, proline anchored into the cage-like mesoporous material SBA-16 was designed, consequently named SBA-16-Pro and confirmed by corresponding characterization means. Furthermore, the catalytic activity, stereoselectivity and reusability of the catalyst SBA-16-Pro were evaluated in the asymmetric aldol reaction.

#### 2. Experimental

#### 2.1. Preparation of the catalyst SBA-16-Pro

**2.1.1. Synthesis of SBA-16.** The mesoporous cage-like material SBA-16 as support of catalyst was synthesized according to the previously published methods.<sup>29</sup>

Pluronic F127 (EO<sub>106</sub>PO<sub>70</sub>EO<sub>106</sub>, 1.48 g) and Pluronic P123  $(EO_{20}PO_{70}EO_{20}, 0.24 \text{ g})$  were used as the templates. After the mixed templates were completely dissolved in a solution of 60 mL of distilled water and 8.9 mL of concentrated hydrochloric acid (37%), the solution was further stirred at 40 °C for 4 h. Then, 5.6 mL of tetraethylorthosilicate (TEOS) was added dropwise to the solution. After being stirred for 40 min, the resultant suspension was transferred into an autoclave. The autoclave was placed under static conditions at 40 °C for 24 h. After that, the temperature was raised up to 100 °C and kept for 32 h. After the hydrothermal treatment, the precipitated solid was isolated by filtration and washed with distilled water and ethanol, then dried in vacuum at 60 °C for 24 h, yielding white solid powders. This powder sample was then subjected to calcination at 550 °C for 10 h, and the mesoporous cage-like material SBA-16 was eventually obtained.

**2.1.2. Preparation of SBA-16-Pro.** After successful synthesis of SBA-16, the catalyst SBA-16-Pro was prepared by steps displayed in Scheme 1.

The solution of (2S,4R)-1,2-dibenzyloxycarbonyl-4-hydroxy pyrrolidine, (compound 1, 10 mmol, 3.55 g), triethoxysilylpropyl isocyanate (15 mmol, 3.71 g), and triethylamine (20 mmol, 2.02 g) in THF (25 mL) was refluxed for 24 h and then cooled to room temperature. After removal of solvent under vaccum, the crude product was purified by column chromatography on silica gel (hexane/AcOEt, 3 : 1) to give 4.99 g of (2S,4R)-1,2-dibenzy-loxycarbonyl-4-(3-triethoxysilylpropylaminocarboxy) pyrrolidine (compound 2) as a brown oil (yield 83%).

Compound 2 (2 mmol, 1.20 g) was hydrogenated over palladium on carbon (0.16 g, 10%) in methanol (40 mL) for 7 h



Scheme 1 Preparation of the catalyst SBA-16-Pro.

at room temperature under  $H_2$  atmosphere (3 atm). The catalyst Pd/C was filtered off, and the filtrate was concentrated *in vacuo* yielding (2S,4R)-2-carboxy-4-(3-triethoxysilylpropyla-minocarboxy) pyrrolidine (compound 3) quantitatively as pale yellow oil. No purification was possible due to the instability of the product.

The solution of the proline derivative (compound 3, 1 g) in toluene (20 mL) was added into the suspension of the inorganic support of SBA-16 (1 g) in a mixture of toluene/water (40 mL/ 40  $\mu$ L). The mixture was refluxed for 24 h. The solid was then filtered and washed with several solvents of different polarity (MeOH, AcOEt, CH<sub>2</sub>Cl<sub>2</sub>, hexane and ether) abundantly, to remove the remaining non-supported proline derivative. The light yellow solid SBA-16-Pro was dried at 40 °C under vacuum.

#### 2.2. Characterization of the catalyst SBA-16-Pro

The synthesized catalyst SBA-16-Pro was confirmed by corresponding characterization means. Fourier transform infrared (FT-IR) spectra were recorded on a Nicolet NEXUS 670 FTIR spectrometer with a DTGS detector, and samples were measured with KBr pellets. Small-angle X-ray powder diffraction (XRD) measurements were performed on a Rigaku D/max-2400 diffractometer using  $Cu-K_{\alpha}$  radiation as the X-ray source in the  $2\theta$  range of 0.5-4°. N<sub>2</sub> physical sorption was carried out on micromeritics ASAP2020 volumetric adsorption analyzer (before the measurements, samples were out gassed at 120 °C for 6 h). The Brunauer-Emmett-Teller (BET) surface area was evaluated from data in the relative pressure range from 0.05 to 0.20. The total pore volume of each sample was estimated from the amount adsorbed at the highest  $P/P_0$  (above 0.99). Pore diameters were determined from the adsorption branch using Barrett-Joyner-Halenda (BJH) method. The morphology and microstructure of SBA-16-Pro were characterized by transmission electron microscopy (TEM). The TEM images were obtained through Tecnai G2 F30 electron microscope operating at 300 kV. The C, H and N contents in SBA-16-Pro were determined by Elementar Analysensysteme GmbH varioEL cube. Thermal gravimetric analysis (TGA) was measured under nitrogen atmosphere to 800 °C with a Perkin Elmer Thermal Analyzer at a heating rate of 10  $^{\circ}$ C min<sup>-1</sup>.

# 2.3. Reaction procedures for activity evaluation of catalyst SBA-16-Pro in the direct aldol reaction

**2.3.1.** Optimization experiments of reaction conditions. 4-Nitrobenzaldehyde (0.5 mmol, 76 mg), cyclohexanone (2 mmol, 196 mg) and corresponding kinds and amounts of catalysts were added in the solvent. The reaction mixture was stirred for 12–96 h at room temperature. After separation of the catalyst, the mixture was treated with 10 mL of saturated ammonium chloride solution and extracted with ethyl acetate ( $3 \times 10$  mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The products were isolated by column chromatography on silica gel (hexane/AcOEt, 4 : 1). The diastereomeric and enantiomeric excess of products was determined by chiral high performance liquid chromatography (HPLC) using CHIRALPAK AD-H column with *n*-hexane and isopropyl alcohol (95 : 5) as eluants.

2.3.2. The direct aldol reactions between different aldehydes and ketones. The catalyst SBA-16-Pro (20 mol%) and corresponding aldehyde (0.5 mmol) and ketone (2 mmol) were stirred in 2 mL MeOH/H<sub>2</sub>O (v/v = 10 : 1) for 24–72 h at room temperature. After separation of the catalyst, the mixture was treated with 10 mL of saturated ammonium chloride solution and extracted with ethyl acetate ( $3 \times 10$  mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with hexanes/ethyl acetate. The diastereomeric and enantiomeric excess of products was determined by chiral HPLC using CHIRALPAK AD-H and OB-H columns with *n*-hexane and isopropyl alcohol as eluants.

2.3.3. Recycling tests of catalyst SBA-16-Pro. 4-Nitrobenzaldehyde (0.5 mmol 76 mg), cyclohexanone (2 mmol, 196 mg), catalyst SBA-16-Pro (20 mol%) and 2 mL MeOH/H<sub>2</sub>O (v/v = 10 : 1) were mixed and stirred at room temperature for 48 h. The catalyst SBA-16-Pro was removed by filtration, washed with MeOH and AcOEt for several times and dried under vacuum. Then another portion of reactants was added. The products in every recycling test were isolated by column chromatography and analyzed by chiral HPLC.

## 3. Results and discussion

#### 3.1. Characterizations of the catalyst SBA-16-Pro

The FT-IR spectra of SBA-16, SBA-16-Pro and SBA-16-Pro after five runs were displayed in Fig. 1. The bands approximately at 960 cm<sup>-1</sup> and 1095 cm<sup>-1</sup> were assigned to the typical silanol groups (Si–OH) stretching mode and Si–O–Si vibrations, respectively, which were commonly found in the silica-based materials. The band at 1640 cm<sup>-1</sup> observed in the spectra of both SBA-16 and SBA-16-Pro was related to the water absorbed on the solid surface.<sup>28</sup> Compared to the spectrum of SBA-16, there were three new peaks near 2970, 1710 and 1560 cm<sup>-1</sup> obviously appearing in that of SBA-16-Pro, corresponding to the stretching vibrations of C–H, carboxylic C=O, and the bending vibration of N–H in proline, respectively. These results demonstrated that SBA-16 was successfully functionalized by



Fig. 1 FT-IR spectra of (a) SBA-16, (b) SBA-16-Pro, (c) SBA-16-Pro after five runs.

L-4-hydroxyproline and the original structure of the silicon material SBA-16 was retained.

Small-angle powder XRD patterns of SBA-16 and SBA-16-Pro were illustrated in Fig. 2. The synthesized SBA-16 showed an intense peak at  $0.85^{\circ}$  attributable to the (110) reflection and two poorly resolved weak peaks at  $1.2^{\circ}$  and  $1.5^{\circ}$  due to the (200) and (211) reflections, respectively.<sup>30</sup> These results indicated that SBA-16 was a kind of mesoporous material with the ordered cubic Im3m structure. The SBA-16-Pro still kept the main diffraction (110) peak, however, its intensity obviously decreased and the diffraction (200) and (211) peaks completely disappeared revealing that the proline was successfully grafted into the mesoporous SBA-16 and did not seriously destroy the structure of SBA-16, which could be confirmed by N<sub>2</sub> sorption detection.

The nitrogen adsorption-desorption isotherms and pore size distributions of corresponding samples were depicted in Fig. 3. Both SBA-16 and SBA-16-Pro exhibited type IV isotherm patterns with typical H2 hysteresis loop, demonstrating that the cage-like structure of SBA-16 was maintained even after grafted with proline. From the textural parameters determined by N<sub>2</sub> sorption and listed in Table 1, the decreases in BET surface area,



Fig. 2 Small-angle powder XRD patterns of (a) SBA-16 and (b) SBA-16-Pro.



Fig. 3 N<sub>2</sub> sorption isotherms and pore size distributions of (a) SBA-16 and (b) SBA-16-Pro.

Table 1 Structural parameters of SBA-16 and SBA-16-Pro

Samples	BET surface area $(m^2 g^{-1})$	Pore volume $(cm^3 g^{-1})$	Pore size (nm)
SBA-16	698.28	0.869	4.98
SBA-16-Pro	459.17	0.434	3.78

pore volume and pore size were observed for SBA-16-Pro. These changes pointed to the fact that proline was not only immobilized on the external surface of SBA-16, but also into the interior of it.

The TEM images shown in Fig. 4 provided more information about SBA-16, fresh and reused catalyst SBA-16-Pro. The support material SBA-16 presented a cubic array of uniform channels (Fig. 4a). After modifications with proline, the ordered bodycentered cubic mesostructure was still well maintained (Fig. 4b).

Through elemental analysis of C, H and N, the proline content of SBA-16-Pro was evaluated to be 1.68 mmol  $g^{-1}$ .

SBA-16 and SBA-16-Pro were further characterized with TGA (Fig. 5). It could be seen that the weight losses of both SBA-16 and SBA-16-Pro below 200 °C were very slight, which should be assigned to the release of physisorbed and chemisorbed water existing on the surface and in the channels of the mesoporous

silica materials. The weight of SBA-16 did not have an obvious loss throughout the temperature rising process (Fig. 5a), demonstrating that SBA-16 material as the support of catalyst had a strong thermal stability. The TGA curve of SBA-16-Pro (Fig. 5b) got a sharp drop at the temperature range of 200–600 °C, and then became flat above 600 °C. This part of weight loss was mainly caused by the decomposition of organic groups from the grafted proline. Through the TGA analysis, the total weight loss of SBA-16-Pro was evaluated to be 35%, and the proline content into the catalyst SBA-16-Pro was evaluated to be 1.62 mmol g<sup>-1</sup>, which was close to the CHN elemental analysis result (1.68 mmol g<sup>-1</sup>). The little difference between the results of the proline content in SBA-16-Pro was mainly attributed to the difference of detection methods and the instrument error of the two detection means.

#### 3.2. Activity evaluations of SBA-16-Pro

With the synthesized catalyst SBA-16-Pro in hand, its catalytic activity was evaluated in the asymmetric aldol reaction.

The well-documented aldol reaction between 4-nitrobenzaldehyde and cyclohexanone was chosen as a model to optimize the reaction conditions (Table 2). The solvent, amount of catalyst, reaction temperature and time, as influencing factors for the reaction, were investigated one by one. In all



Fig. 4 TEM images of (a) SBA-16, (b) SBA-16-Pro and (c) SBA-16-Pro after five runs.



Fig. 5 TGA curves of (a) SBA-16 and (b) SBA-16-Pro.



Scheme 2 The reaction between 4-nitrobenzaldehyde and cyclohexanone.

cases, the desired aldol product was obtained as a mixture of diastereomers.

Regrettably, H<sub>2</sub>O, as an environmentally friendly solvent, could not be used directly in the reaction, because plenty of water had a restraint for the activity of the catalyst<sup>34</sup> (entry 1). Meanwhile, the reaction proceeded with much higher yield in alcohols (entries 2 and 3), especially in methanol, compared with other kinds of solvent (entries 4 and 5), revealing that the catalytic efficiency of SBA-16-Pro in hydrophilic solvent was better than that in hydrophobic solvent. It could be observed that when the reaction took place in singe solvent, the enantioselectivity was generally non-ideal. It has been reported that small amount of water is sometimes beneficial in the prolinecatalyzed aldol reaction.35 Therefore, the mixed solvent Methanol-H<sub>2</sub>O was tried to be used in place of single solvent Methanol (entries 7 to 10), in which the catalyst solid had a good dispersion. Interestingly, the reactions in Methanol-H<sub>2</sub>O mixture exhibited a progressive increase of stereoselectivity as the volume ratio of Methanol-H<sub>2</sub>O was changed from 100 : 1 to 10:1. However, when 1:1 of Methanol-H<sub>2</sub>O volume ratio was used, the yield dropped drastically and the enantioselectivity began to decrease. On the basis of these results, the mixed Methanol-H<sub>2</sub>O, which was cheap and available, was chosen as

Table 2	Optimization	conditions for	the direct ald	dol reaction	catalyzed b	y SBA-16-Pro
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O U	O ∐	OH O
O <sub>2</sub> N H	+	x mol% catalyst, solvent Time, Temperature

Entry	Catalyst	Loading (mol%)	Time (h)	Temperature (°C)	Solvent	$\operatorname{Yield}^{a}(\%)$	$dr^b$ (anti : syn)	$ee^{b}$ (%)
1	SBA-16-Pro	20	48	RT	$H_2O$	<5	n.d. <sup><i>c</i></sup>	n.d.
2	SBA-16-Pro	20	48	RT	MeOH	97	98:2	49
3	SBA-16-Pro	20	48	RT	EtOH	82	90:10	56
4	SBA-16-Pro	20	48	RT	$CH_2Cl_2$	47	59:41	46
5	SBA-16-Pro	20	48	RT	$CHCl_3$	50	59:41	50
6	SBA-16-Pro	20	48	RT	No solvent	69	97:3	62
7	SBA-16-Pro	20	48	RT	$MeOH/H_2O(100:1)$	95	94:6	74
8	SBA-16-Pro	20	48	RT	$MeOH/H_2O(50:1)$	94	93:7	86
9	SBA-16-Pro	20	48	RT	$MeOH/H_2O(10:1)$	91	97:3	83
10	SBA-16-Pro	20	48	RT	$MeOH/H_2O(1:1)$	44	80:20	77
11	_	_	48	RT	$MeOH/H_2O(10:1)$	n.d.	n.d.	n.d.
12	SBA-16	d	48	RT	$MeOH/H_2O(10:1)$	n.d.	n.d.	n.d.
13	L-4-Hydroxyproline	20	48	RT	$MeOH/H_2O(10:1)$	98	82:18	68
14	SBA-16-Pro <sup>e</sup>	20	48	RT	$MeOH/H_2O(10:1)$	70	95:5	76
15	SBA-16-Pro	5	48	RT	$MeOH/H_2O(10:1)$	62	95:5	84
16	SBA-16-Pro	10	48	RT	$MeOH/H_2O(10:1)$	82	80:20	82
17	SBA-16-Pro	30	48	RT	$MeOH/H_2O(10:1)$	94	82:18	78
18	SBA-16-Pro	40	48	RT	$MeOH/H_2O(10:1)$	92	98:2	74
19	SBA-16-Pro	20	48	40	$MeOH/H_2O(10:1)$	86	>99:1	61
20	SBA-16-Pro	20	48	60	$MeOH/H_2O(10:1)$	63	99:1	18
21	SBA-16-Pro	20	12	RT	$MeOH/H_2O(10:1)$	33	>99:1	77
22	SBA-16-Pro	20	24	RT	$MeOH/H_2O(10:1)$	71	96:4	75
23	SBA-16-Pro	20	72	RT	$MeOH/H_2O(10:1)$	93	90:10	78
24	SBA-16-Pro	20	96	RT	$MeOH/H_2O(10:1)$	91	>99:1	77
					( )			

<sup>*a*</sup> Isolated yield of mixture of all four diastereomers. <sup>*b*</sup> Determined by chiral HPLC (Chiralpak AD-H column, 95:5 *n*-hexane/isopropanol, 1 mL min<sup>-1</sup>, detected at 254 nm). <sup>*c*</sup> n.d. = not determined. <sup>*d*</sup> The mass equal to 20 mol% SBA-16-Pro was added. <sup>*e*</sup> After the reaction proceeded for 24 h, the catalyst SBA-16-Pro was separated from the system by filtration and the left reaction mixture kept being stirring for another 24 h.

Table 3 Evaluation of the catalyst SBA-16-Pro for the direct aldol reactions between different aromatic aldehydes and ketones

$$\begin{array}{c} O \\ R_1 \\ H \end{array}^{+} R_2 \\ R_3 \end{array} \xrightarrow{\begin{array}{c} 20 \text{ mol}\% \text{ SBA-16-Pro} \\ \text{MeOH-H}_2 O, \text{ time, RT} \end{array}} \begin{array}{c} O \\ R_1 \\ R_3 \\ R_3 \end{array} \xrightarrow{\begin{array}{c} 0 \\ \text{H} \\ R_3 \end{array}} R_2$$

				-: (1)			h (ac)
Entry	$R_1$	$R_2$	$R_3$	Time (h)	Yield <sup>a</sup> (%)	dr <sup>o</sup> (anti : syn)	ee <sup>o</sup> (%) anti (syn)
1	2-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> -	-(CH <sub>2</sub> ) <sub>4</sub> -		48	76	88:12	95
2	$3-O_2NC_6H_4-$	-(CH <sub>2</sub> ) <sub>4</sub> -		48	90	96:4	80
3	$4-NCC_6H_4-$	-(CH <sub>2</sub> ) <sub>4</sub> -		48	88	80:20	82
4	4-ClC <sub>6</sub> H <sub>4</sub> -	-(CH <sub>2</sub> ) <sub>4</sub> -		48	78	90:10	85
5	$C_6H_5-$	-(CH <sub>2</sub> ) <sub>4</sub> -		48	63	8:92	(93)
6	2-Thienyl–	-(CH <sub>2</sub> ) <sub>4</sub> -		48	71	88:12	92
7	2-Furanyl–	-(CH <sub>2</sub> ) <sub>4</sub> -		48	77	97:3	84
8	4-MeOC <sub>6</sub> H <sub>4</sub> -	-(CH <sub>2</sub> ) <sub>4</sub> -		60	46	95:5	83
9	4-MeC <sub>6</sub> H <sub>4</sub> -	-(CH <sub>2</sub> ) <sub>4</sub> -		60	41	97:3	91
10	$4-O_2NC_6H_4-$	-(CH <sub>2</sub> ) <sub>3</sub> -		48	97	56:44	>99%
11	$4-O_2NC_6H_4-$	-(CH <sub>2</sub> ) <sub>5</sub> -		72	41	53:47	58
12	$4-O_2NC_6H_4-$	$CH_3$	н	24	95	—	38 <sup>c</sup>
13	$4-O_2NC_6H_4-$	$C_6H_5-$	Н	72	n.d.	n.d. <sup>d</sup>	n.d.
14	$4-O_2NC_6H_4-$	$4-O_2NC_6H_4-$	Н	72	n.d.	n.d.	n.d.

<sup>*a*</sup> Isolated yield of mixture of all four diastereomers. <sup>*b*</sup> Determined by chiral HPLC (Chiralpak AD-H column, 95 : 5 *n*-hexane/isopropanol, detected at 254 nm). <sup>*c*</sup> Determined by chiral HPLC (Chiralpak OB-H column, 85 : 15 *n*-hexane/isopropanol, 1 mL min<sup>-1</sup>, detected at 254 nm). <sup>*d*</sup> n.d. = not determined.

the solvent of the reaction, and the volume ratio was 10:1. It was also noteworthy that excellent diastereoselectivity, moderate yield and enantioselectivity were obtained when the reaction proceeded in solvent-free condition. Several groups of controlled experiments were arranged to investigate the influence of the catalyst's amount for the reaction. It could be seen that when no catalyst or just the support material SBA-16 participating, the reaction almost hardly occurred (entries 11 and 12), which demonstrated that proline played a very important catalytic role in the asymmetric aldol reaction. On the other hand, when the homogeneous proline was used as catalyst in the reaction, a superior yield was obtained, but its enantioselectivity was not as good as that of heterogeneous catalyst SBA-16-Pro (entry 13). That is possibly because in some cases, there is a strong interaction between active sites and supports which can improve the activity and stability of catalysts.<sup>36</sup> Compared with the heterogeneous catalyst, supported catalyst has some special characteristics in the structure. The steric hindrances of the active centers immobilized on the support and the restrictions from the channels of the mesoporous material SBA-16 were beneficial for the chiral induction in the catalysis of the asymmetric aldol reaction. Furthermore, the yield and enantioselectivity did not improve apparently after increasing the catalyst loading from 20 to 40 mol% (entries 17 and 18). And although good enantioselectivities were still obtained, the yields were low when the amount of catalyst was reduced to 5 and 10 mol% (entries 15 and 16). From an economical point of view, 20 mol% was the preferred catalyst loading. With the reaction temperature rising, not only the enantioselectivities, but also the yields appreciably decreased (entries 19 and 20). The drop of yield was mainly attributed to the occurrence of side reaction

(Scheme 2). The results of the aldol reactions proceeding for difference time were summarized (entries 21 to 24). When the reaction time increased from 12 to 48 h, the yield had a significant growth, and almost reached equilibrium after 48 h. Moreover, the enantiomeric excess value (ee values) of the product obtained at 48 h was the best. So the optimum reaction time was decided to be 48 h.

Under the optimized conditions, the catalyst SBA-16-Pro was tested in aldol reactions between a variety of aromatic aldehyde acceptors and ketone donors, and the results were summarized in Table 3. It was obvious that good yields with excellent ee values were still obtained after changing the substituting group positions onto the aromatic aldehydes (entries 1 and 2). Meanwhile, 4-cyanobenzaldehyde and 4-chlorobenzaldehyde were good acceptors and gave the desired anti products in good

 Table 4
 Recycling experiments of the catalyst SBA-16-Pro for the aldol reaction between 4-nitrobenzaldehyde and cyclohexanone

$$O_{\rm p,N}$$
  $H$   $+$   $H$   $+$  H  $+$   $H$   $+$  H  $+$   $H$   $+$  H  $+$   $H$   $+$  H  $+$   $H$   $+$   $H$   $+$  H  $+$   $H$   $+$   $H$   $+$  H  $+$  H  $+$  H  $+$   $H$   $+$  H  $+$ 

Run	Yield <sup><math>a</math></sup> (%)	$dr^b$ (anti : syn)	$ee^{b}$ (%)
1	91	97:3	83
2	92	98:2	77
3	88	99:1	78
4	87	95:5	81
5	90	92:8	81

<sup>*a*</sup> Isolated yield of mixture of all four diastereomers. <sup>*b*</sup> Determined by chiral HPLC (Chiralpak AD-H column, 95 : 5 *n*-hexane/isopropanol, 1 mL min<sup>-1</sup>, detected at 254 nm).

yield with high diastereoselectivity and enantioselectivity (entries 3 and 4), which indicated that the aromatic aldehydes carrying electron withdrawing groups were good substrates for the aldol reaction. Moreover, when benzaldehyde, 2-thenaldehyde and furfural were used as aldehyde acceptors, good ee values were all obtained, and the yield gradually increased with the aromaticity of aldehyde weakening (entries 5 to 7). The dr and ee values were ideal, when the reaction proceeded between cyclohexanone and benzaldehyde with electron donating group, whereas the yield had an apparent decrease (entries 8 and 9). The ee values were still good when other cyclic ketones including cyclopentanone and cycloheptanone were used as donors, although the increase of the carbon numbers onto the cyclic ketones led the yields to have a significant drop (entries 10 and 11). Acetone was also proved to be a suitable donor providing excellent yield with moderate enantioselectivity (entry 12). However, attempts using acetophenone derivatives as ketone donors in this reaction were unsuccessful. The corresponding target products were almost not detected, so acetophenone derivatives were not suitable substrates in this reaction system (entries 13 and 14).

The catalyst SBA-16-Pro can be easily separated from the reaction media by filtration and subsequently reused in the next cycle. The reusability of the synthesized catalyst in the reaction between 4-nitrobenzaldehyde and cyclohexanone was studied. As shown in Table 4, This SBA-16 material supported proline could be reused up to five runs without a significant loss of activity, proving that the catalyst had excellent mechanical strength and recyclability. Through elemental analysis, the catalyst SBA-16-Pro did not have an obvious change in proline content (1.55 mmol  $g^{-1}$ ), which still remained 92% of original porline, after being reused for five times. The FT-IR spectrum of SBA-16-Pro after five runs (Fig. 1c) still kept the characteristic peaks of proline compared with that of fresh catalyst (Fig. 1b). From the TEM images (Fig. 4c), it could be seen that the cagelike structure of the reused catalyst was still observed although the channel had a little collapse locally. For better exploring the effect of the leached proline for the reaction result, another experiment for comparison was arranged (Table 2, entry 14). 20 mol% of catalyst SBA-16-Pro was added into the reaction system. After the reaction proceeded for 24 h, the catalyst solids were separated from the system by filtration and the left reaction mixture kept being stirring for another 24 h. It was noticed that the yield and ee value did not have an apparent change after the catalyst solids SBA-16-Pro being separated, revealing that the proline leaching form the support during the reaction process was very little and even could not make an obvious influence on the yield of aldol reaction.

Varieties of supported-type catalysts based on proline or proline derivatives as active sites have been designed and exhibited moderate to good catalytic activities and stereoselectivities for kinds of asymmetric reactions.<sup>19</sup> However, as reported, some supported proline catalysts existed problem in the recycling process. Compared with the literature,<sup>24,37</sup> our catalyst had much more excellent mechanical strength and recyclability, evidenced by being extensively reused without any substantial loss of activity.

## 4. Conclusions

A new chiral metal-free organocatalyst based on proline as active site and mesoporous cage-like material SBA-16 as support has been successfully prepared and used in the asymmetric aldol reaction between aromatic aldehydes and ketones. Moderate to good yields, diastereoselectivities and enantioselectivities exhibited in the activity evaluation experiments. This synthesized catalyst avoided heavy metal pollution during the preparing and using process, and had excellent mechanical strength and reusability, evidenced by being extensively reused without any substantial loss of activity.

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