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PAPER

Copolymer-supported heterogeneous organocatalyst for asymmetric aldol addition in aqueous medium†

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In the current study, a convenient and simple way is presented to synthesize a novel type of supported heterogeneous organocatalyst in 21–81% yield by the copolymerization of 9-amino-9-deoxy-*epi*-cinchonine organocatalyst with acrylonitrile using AIBN as radical initiator. The chemical compositions (*x*/*y*) and weight-average molecular weights of copolymers **1a–d** were determined by ^{1}H NMR and GPC analysis respectively. Their porous and layered structure, and surface morphology were characterized by nitrogen adsorption–desorption, XRD and TEM. In the asymmetric aldol addition of *p*-nitrobenzaldehyde to cyclohexanone and 1-hydroxy-2-propanone in water, all the supported organocatalysts **1a–d** afforded excellent isolated yields (90.2–94.7%) and stereoselectivities (96.8–97.8%ee *anti*, *anti*/*syn* = 91/9). The highest catalytic property (96% yield, *anti*/*syn* = 90/10 and 99%ee *anti*) in water as the sole solvent was achieved under the optimized conditions. Compared with cyclohexanone, cyclopentanone and acetone showed the less desired enantioselectivities in the same aldol reactions. At the end of the aldol reaction, the copolymer-supported organocatalyst **1a** was readily recovered in 95–98% yield from reaction mixture by simple filtration using an organic membrane. Even in the fifth run, there was no significant loss in catalytic activity and stereocontrol (94.3% yield, 97.2%ee *anti*, *anti*/*syn* = 90/10). After continuous reuse five times, there was some drop in catalytic activity and stereoselectivity.

Introduction

It is clear by now that modern asymmetric catalysis is built on three rather than two pillars, namely biocatalysis, metal catalysis and organocatalysis. The last two decades have witnessed a spectacular advancement in new catalytic methods based on organic molecules. In many cases, these small organic compounds result in extremely high enantioselectivities. Chiral organocatalysts[1] are stable to moisture and air, and free from toxic, rare, and expensive metals. However, some of them are expensive owing to the cost of the chemical transformations in the synthetic procedure. Thus, the development of recyclable chiral organocatalysts is currently a highly sought after goal in green chemistry. One of the strategies is heterogenizing homogeneous organocatalysts,[2] including the attachment to porous silica gel,[3] organic polymer[4] and biopolymer,[5] and magnetic nanoparticles.[6] On the other hand, chemical reactions in which water is used as the sole solvent have attracted a great deal of attention because water is an environmentally friendly and safe medium, which avoids the problem of pollution that is inherent with organic solvents.[7] Therefore, from a concept of green chemistry, both the easy, complete separation and subsequent recycling of homogeneous organocatalysts from reaction media and catalytic reactions in water are urgently desired.

The aldol condensation is one of the most important carbon–carbon bond-forming reactions, which creates the β-hydroxy carbonyl structural unit found in many natural products and drugs. Among the successful strategies, chiral organocatalysts have been seen as a simplified version of enzymes. Several prominent chiral organocatalysts have been developed for the aldol reaction, and some of them provided aldol-adducts excellently and stereoselectively, even in aqueous medium.[8] 9-Amino-9-deoxy-*epi*-cinchonine, one of the cinchona derived primary amines, is regarded as an outstanding representative of these organocatalysts, and has been employed as an efficient organocatalyst with excellent catalytic properties in asymmetric aldol addition,[9] Diels–Alder reaction,[10] Friedel–Crafts reaction,[11] Henry reaction,[12] Mannich reaction,[13] Michael addition,[14] hydrogenation,[15] epoxidation,[16] 1,3-dipolar cycloaddition,[17] decarboxylation,[18] and methanolytic desymmetrization.[19] Due to the virtue of its excellent catalytic performance and the defect of its being expensive, it is necessary that amino-9-deoxy-*epi*-cinchonine should be easily separated from the reaction mixture and reused after the completion of catalytic reaction. Unfortunately, very

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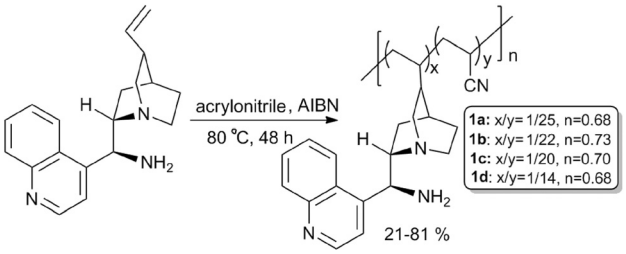
† Electronic supplementary information (ESI) available: XRD of **1a–d**; IR spectra of **1a–d**; thermogravimetric curves of **1a–d**; N_2 adsorption–desorption analysis of **1a–d**; some of the HPLC spectra. See DOI: 10.1039/c2ob25106j



Scheme 1 The synthetic route to the supported organocatalysts **1a–d**.

little research work focused on the theme of recycling amino-9-deoxy-*epi*-cinchonine and its derivatives has been reported.[20]

In this paper, by the simple copolymerization of 9-amino-9-deoxy-*epi*-cinchonine organocatalyst with acrylonitrile in the presence of AIBN as radical initiator,[21] copolymer-supported organocatalysts **1a–d** with different chemical compositions (*x*/*y*) of 9-amino-9-deoxy-*epi*-cinchonine were prepared for the first time in one synthetic step under mild conditions (Scheme 1). In the asymmetric direct aldol addition of *p*-nitrobenzaldehyde to cyclohexanone, the high catalytic properties (96% yield, *anti*/*syn* = 90/10 and 99%ee *anti*) and reusability for five times without significant loss in catalytic properties were achieved using water as a sole reaction medium.

Results and discussion

Characterization of copolymer-supported organocatalyst

Chemical composition. The novel analogues, copolymer-supported organocatalysts **1a–d**, which possessed different loading amounts of 9-amino-9-deoxy-*epi*-cinchonine, were prepared under different molar ratios of 9-amino-9-deoxy-*epi*-cinchonine and acrylonitrile in DMF at 80 °C for 48 h in the presence of AIBN as radical initiator. The chemical compositions (*x*/*y*) in the copolymers **1a–d** could be determined by the ^{1}H NMR method. By the comparative investigation of ^{1}H NMR of 9-amino-9-deoxy-*epi*-cinchonine, acrylonitrile and the copolymers **1a–d**, it was found that the five hydrogens neighboured on the nitrogen atom in 9-amino-9-deoxy-*epi*-cinchonine moiety and one hydrogen neighboured on the cyano group were in the range of 2.5–3.5 ppm, and the absorption peaks in 7.3–9.2 ppm range were attributed to the six aromatic hydrogens in the quinoline moiety (Fig. 1). Therefore, according to the ^{1}H NMR principle that peak area is directly proportional to the number of hydrogen, the molar ratios of *x* to *y* in the co-polymers **1a–d** could be calculated to be 1/25, 1/22, 1/20 and 1/14 respectively. Unfortunately, similar chemical compositions in the copolymers **1a–d** were obtained, even at high initial molar ratios (10 : 1) of acrylonitrile to 9-amino-9-deoxy-*epi*-cinchonine. GPC analysis showed that weight-average molecular weights of the polymers **1a–d** were between 0.7 and 1.2 kDa and PDI values between 1.7 and 2.2, which may be not accurate since linear polyacrylonitrile standards were used for calibration while the supported organocatalysts **1a–d** were brush polymers.

The covalent attachment of chiral 9-amino-9-deoxy-*epi*-cinchonine on the frame of the copolymers **1a–d** was also successfully corroborated and verified by infrared spectra in the range of

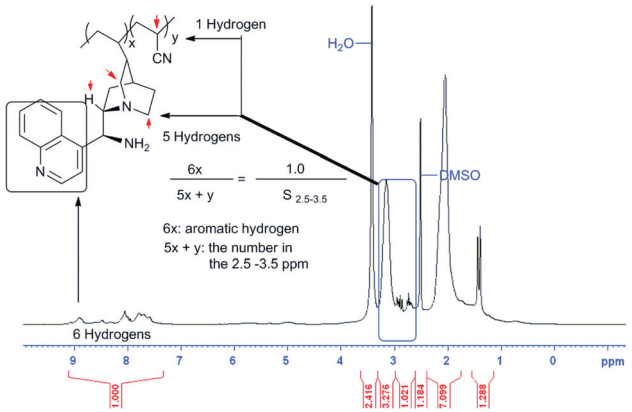


Fig. 1 ^{1}H NMR spectra of copolymer-supported organocatalyst **1d**.

4000–400 cm^{-1} shown in ESI.† The broad, strong and wide absorption band extending from 3700 to 2500 cm^{-1} and centered at 3450 cm^{-1} was assigned to the O–H stretching vibration, which was indicative of the presence of hydrogen bonds between adsorbed water on the internal surface. With the increase of *y* values from 14 to 25, the stretching vibrations of –C≡N at 2244 cm^{-1} and C–H at 2940 and 2890 cm^{-1} were strengthened in turn from **1d** to **1a**. The moderate absorption bands at 1651 and 619 cm^{-1} were attributed to the stretching vibration mode and flexural vibration of the quinoline moiety, respectively.

The thermal stabilities of the copolymer-supported organocatalysts **1a–d** were investigated by using TGA. From the DTG and TG curves, it can be deduced from the weight loss below 150 °C that 3.4–4.3% of the surface-bound or intercalated water was absorbed in the internal pores, and the process was endothermic, verified by DSC curves. Accompanied by the exothermic peaks in the DSC curves, the sharp and slow weight losses in the temperature range of 150–550 °C and 550–800 °C corresponded to the initial and deep decompositions of the appended organic fragments, respectively. The total weight losses of supported organocatalysts **1a–d** in the temperature range of 150–800 °C were 46.4, 53.3, 51.3 and 49.9% respectively.

Porous and layered structure. In Table 1 were listed, for all the as-synthesized copolymers **1a–d**, BET-specific surface areas, average pore diameters and pore volumes by BJH analysis. Due to the winding round each other of cyano resin chains and the supporting pillar of 9-amino-9-deoxy-*epi*-cinchonine, the supported organocatalysts **1a–d** possessed porous structures with the surface area (20–41.2 m^2 g^{-1}), average pore diameters (8.2–10.1 Å) and pore volumes (8.4–20.7 cc g^{-1}) shown in Table 1. However, it was found that the surface areas, average pore diameters and pore volumes decreased successively with the increase of immobilized 9-amino-9-deoxy-*epi*-cinchonine, which showed that the more 9-amino-9-deoxy-*epi*-cinchonine was immobilized, the more space was occupied. In addition, the layered structures of the copolymer-supported organocatalysts **1a–d** (d = 5.3 Å at 2θ = 17°), which can be determined from the 00*n* peaks in the powder XRD pattern (*via* the Bragg equation, $n\lambda = 2d \sin\theta$), were observed unexpectedly owing to the ordered overlapping of cyano resin chains.

Table 1 Porous properties of the synthesized copolymers **1a–d**[a]

Cat.	Surface area[b] [m^2 g^{-1}]	Average pore diameter[c] [Å]	Pore volume[d] [cc g^{-1}]	Interlayer distance [Å]
1a (y = 25)	41.2	10.1	20.7	5.4
1b (y = 22)	35.9	8.4	15.1	5.3
1c (y = 20)	30.3	10.0	15.2	5.3
1d (y = 14)	20.5	8.2	8.4	5.3
1a (7th)	38.6	9.5	18.9	5.4

[a] Degassed at 80 °C for 12 h. [b] Based on the multipoint BET method. [c] Based on the desorption data using BJH method. [d] Based on the desorption data of BJH method.

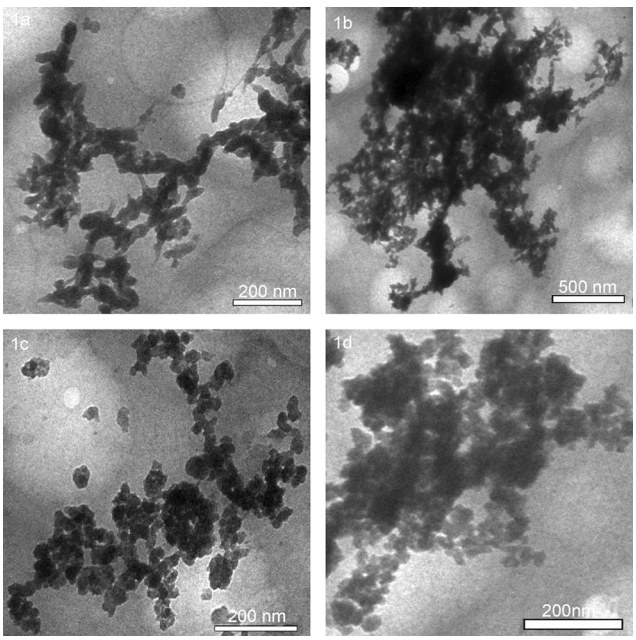


Fig. 2 The TEM images of copolymer-supported organocatalysts **1a–d**.

Surface morphology. Taking into account the intimate relationship between physical surface property of supported organocatalyst and its catalytic performance, it was necessary that the copolymer-supported organocatalysts **1a–d** should be well clarified by TEM and SEM to understand the surface morphology and particle size in water. After being well-dispersed in water (5 mg sample in 1 mL of H_2O) for 30 min under ultrasonic radiation, sputtered over copper wire, and evaporated under infrared radiation for 10 min, the TEM images were observed under an accelerating rate voltage of 200 keV. From Fig. 2, it can be seen that the filiform structures were produced with widths of 20–30 nm and lengths up to hundreds of micrometers. Based on the interlayer d-spacings of the copolymer-supported organocatalysts **1a–d** (d = 5.3 Å) determined by XRD, it can be deduced that each filiform chain consisted of ordered stacks of 40–60 cyano resin chains. Due to being well-dispersed in water, the TEM images could be identified as efficiently elaborating the surface morphologies of the copolymer-supported organocatalysts **1a–d** in aqueous solution, which seemed to simulate the

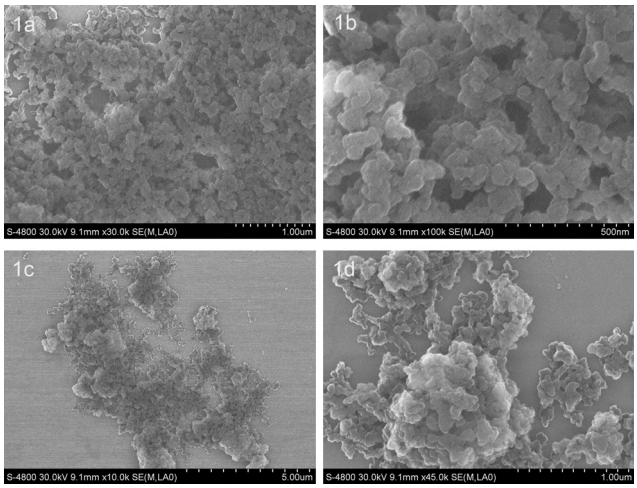


Fig. 3 The SEM images of copolymer-supported organocatalysts **1a–d**.

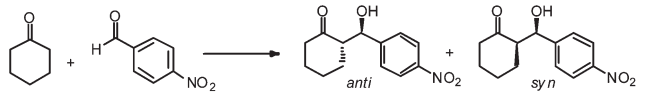
"true" states of the catalysts **1a–d** in the asymmetric aldol addition in water. The SEM images with aggregates larger than 5 μm in size, which were observed in the solid state, could be considered to mirror surface morphologies of catalysts **1a–d** in the solid state (Fig. 3).

Asymmetric aldol reaction

We first examined the copolymer-supported organocatalyst **1a** in a model reaction, the asymmetric aldol addition of *p*-nitrobenzaldehyde to cyclohexanone, which was conducted in different solvents for 48 h at room temperature. As shown in Table 2, the solvent played an important role in the catalytic activity, diastereoselectivities and enantioselectivity of aldol adducts and a series of solvents were screened. Taking the solubility of copolymer-supported organocatalyst **1a** in various solvents into account, the aldol additions could be carried out homogeneously in DMF, DMSO and CH_3CN, and heterogeneously in other solvents such as H_2O, toluene and THF. In nonpolar or less polar solvents, the aldol product was apparently retarded with low yields (18.3–37.4%) and poor stereocontrol (0–15.7%ee *anti*, Table 2, entries 1–5). However, the reaction proceeded smoothly in polar solvents such as H_2O, DMF and ethanol in the moderate to high yields (49.4–94.7%) and with the excellent stereocontrol (86.8–97.6%ee *anti*, *anti*/*syn* = 94–71/6–29, Table 2, entries 6–14). To our delight, the excellent yield and stereoselectivity (94.7% yield, *anti*/*syn* = 89/11, and 97.6%ee *anti*) could be obtained, although the aldol reaction was carried out heterogeneously in water (Table 2, entry 7). Predicated on these data, the influence of solvents on the stereoselectivities was related to the different conformations of 9-amino-9-deoxy-*epi*-cinchonine in different solvents.[22]

The influence of catalyst loading, used amount and reaction time on catalytic performance was further examined. As mentioned above, by the copolymerization using different initial molar ratios of organocatalyst 9-amino-9-deoxy-*epi*-cinchonine to acrylonitrile, different incorporation levels (x/y = 1/25, 1/22, 1/20 and 1/14) of 9-amino-9-deoxy-*epi*-cinchonine in **1a–d** were

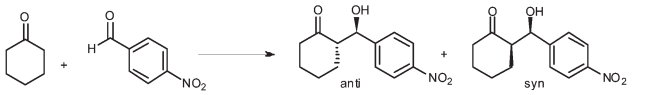
Table 2 The effect of various solvents in the yields, diastereoselectivities and enantioselectivities of aldol adducts[a]



Entry	Solvent	Yield[b] [%]	%ee *anti*[c]	%ee *syn*[c]	Dr (*anti*/*syn*)[d]
1	Et_2O	21.4	0.0	21.3	52/48
2	PhMe	27.3	14.4	19.7	58/42
3	$CH_3CO_2C_2H_5$	26.9	3.6	8.6	43/57
4	$CHCl_3$	37.4	15.7	11.5	57/43
5	CH_2Cl_2	18.3	0.0	3.4	58/42
6	EtOH	49.4	91.4	51.3	89/11
7	H_2O	94.7	97.6	73.0	89/11
8	THF	64.3	86.8	15.0	71/29
9	DMSO	51.8	95.1	61.7	82/18
10	DMSO/H_2O = 5/1	55.2	94.2	58.1	79/21
11	MeCN	56.5	97.0	2.3	94/6
12	MeCN/H_2O = 5/1	62.2	92.4	37.7	86/14
13	DMF	51.7	90.0	27.7	81/19
14	DMF/H_2O = 5/1	57.2	92.5	35.2	91/9

[a] Reaction conditions: *p*-nitrobenzaldehyde (37.3 mg, 0.25 mmol), cyclohexanone (473.5 mg, 4.8 mmol, 0.5 mL), 5 mol% **1a**, 10 mol% TfOH, 25 °C, 2 mL of solvent, 48 h. [b] Isolated yield. [c] Determined by chiral HPLC using Daicel Chiralpak AD-H chiral column. [d] Determined by ^{1}H NMR.

Table 3 The effect of catalyst loading, used amount, reaction time and temperature on the catalytic performance[a]



Entry	Variable	Yield[c] [%]	%ee *anti*[d]	%ee *syn*[d]	Dr (*anti*/*syn*)
1	**1a**	94.7	97.8	73.4	91/9
2	**1b**	93.5	97.8	74.2	91/9
3	**1c**	90.2	97.2	70.2	90/10
4	**1d**	91.8	96.8	72.0	90/10
5[b]	1.0 mol%	55.0	90.0	45.3	78/22
6[b]	2.5 mol%	78.3	95.0	68.0	85/15
7[b]	5.0 mol%	94.6	98.1	61.1	90/10
8[b]	7.5 mol%	95.6	97.9	69.7	90/10
9[b]	10.0 mol%	96.8	95.5	66.1	90/10
10[b]	12 h	63.6	95.0	57.5	90/10
11[b]	24 h	74.7	96.0	60.1	91/9
12[b]	36 h	85.3	97.8	61.5	91/9
13[b]	48 h	96.1	99.0	61.2	90/10
14[b]	72 h	96.6	97.0	60.0	91/9
15[b]	10 °C	77.3	93.5	44.0	81/19
16[b]	20 °C	95.5	95.6	66.5	90/10
17[b]	25 °C	96.1	99.0	61.2	90/10
18[b]	30 °C	93.5	96.4	59.7	89/11
19[b]	40 °C	87.8	91.3	55.1	80/20

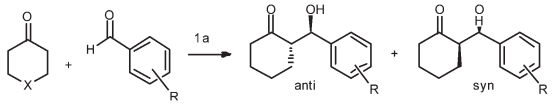
[a] Reaction conditions: *p*-nitrobenzaldehyde (37.3 mg, 0.25 mmol), cyclohexanone (473.5 mg, 4.8 mmol, 0.5 mL), 5 mol% **1a**, 10 mol% TfOH, 25 °C, 2 mL of solvent. [b] Cat. **1a**. [c] Isolated yield. [d] Determined by chiral HPLC using Daicel Chiralpak AD-H chiral column.

obtained. In the direct aldol addition of *p*-nitrobenzaldehyde to cyclohexanone, all the supported organocatalysts **1a–d** possessed excellent isolated yields (90.2–94.7%) and stereoselectivities (96.8–97.8%ee *anti*, 70.2–74.2%ee *syn*, *anti*/*syn* = 91/9) without significant difference (Table 3, entries 1–4). However, due to the larger specific surface area, pore diameter and pore volume of **1a** than that of the others (Table 1), better catalytic performance (94.7%, 97.8%ee *anti*, 73.4%ee *syn*, *anti*/*syn* = 91/9) was observed, although the supported organocatalysts **1a** contained a relatively low incorporation of 9-amino-9-deoxy-*epi*-cinchonine. Therefore, using supported organocatalyst **1a** as an example, the optimized catalytic conditions were investigated in detail to be 7.5 mol% of catalyst in combination with 10 mol% triflic acid as an additive, water as sole solvent and 48 h at room temperature (Table 3, entries 5–19).

The optimized protocol was then expanded to a wide variety of aldehydes, cyclic and open-chain ketones to investigate catalytic performances. The results indicated that the aldol reaction catalyzed by supported organocatalyst **1a** was dramatically dependent on the electronic effect of the substituent as that of its parent 9-amino-9-deoxy-*epi*-cinchonine in homogeneous catalysis. For example, *o*-, *m*- and *p*-nitrobenzaldehydes smoothly underwent the aldol reaction with cyclohexanone in good to excellent yields (81.0–95.8%) and excellent stereoselectivities (96.6–98.7%ee *anti*, *anti*/*syn* = 90–98/10–2) (Table 4, entries 1–3). Compared with their corresponding "blank" reaction using 9-amino-9-deoxy-*epi*-cinchonine as catalyst (Table 4, entries 21–23), supported organocatalyst **1a** was found to be less reactive (48 h) to obtain similar yields, for *o*-, *m*- and *p*-nitrobenzaldehydes. In general, homogeneous organocatalyst 9-amino-9-deoxy-*epi*-cinchonine only needed 6–9 h to obtain good yield (>90%) at room temperature. The excellent stereoselectivity (97.2%ee *anti*) and good yield (87.2%) were also obtained for the electron-withdrawing cyano group (Table 4, entry 4). Unsubstituted aromatic aldehyde, benzaldehyde, was less reactive in 59.6% yield with good enantioselectivity (92.3%ee *anti*) and moderate *anti*/*syn* = 72/28 (Table 4, entry 10). Unfortunately, the substrates with electron-donating groups at the aromatic ring were not suitable for aldol reaction. For example, 4-methoxybenzaldehyde reacted with cyclohexanone for 48 h yielding the corresponding product in only 22.2% yield and 91.4%ee *anti* (Table 4, entry 9). The other substituted groups such as CH_3, F, Cl, Br showed the same results (Table 4, entries 5–8). It was worth notice that, under the same catalytic conditions, *o*-, *m*- and *p*-nitrobenzaldehydes catalyzed by **1a** afforded the same (2*S*,1′*R*)-configuration as their corresponding homogeneous catalysis.[23] However, the heterogeneous catalyst system gave improved diastereoselectivities (Table 4, entries 2, 3) and enantioselectivity (Table 4, entry 1).

Cyclopentanone was also employed in the same aldol reaction. Unfortunately, the less desired enantioselectivities compared with cyclohexanone were found. For example (Table 4, entries 11–13), *p*-, *m*- and *o*-nitrobenzaldehydes afforded the corresponding products in 87.8, 71.4 and 81.6% yields and 85.8, 80.0 and 62.2%ee *anti* respectively. In almost all cases of cyclopentanone, the diastereoselectivity was not high (Table 4, entries 11–20). Furthermore, the aldol addition of *p*-nitrobenzaldehyde to an alkyl chain ketone such as acetone and 1-hydroxy-2-propanone was preliminarily investigated. Under the optimized conditions, 1-hydroxy-2-propanone gave (3*S*,4*R*)-3,4-dihydroxy-4-(4-nitrophenyl)butan-2-one with the preferable results (91.2% yield, 98.6%ee *syn*, *syn*/*anti* = 80/20).[23a] On the other hand, the aldol reaction between acetone and 4-nitrobenzaldehyde was

Table 4 The enantioselective direct aldol reactions of aldehydes and cyclic ketones[a]



Entry	R	X	Yield[b] [%]	%ee *anti*[c]	%ee *syn*[c]	Dr (*anti*/*syn*)[d]
1	*o*-NO_2	CH_2	81.0	98.0	39.2	98/2
2	*m*-NO_2	CH_2	87.6	96.6	39.0	92/8
3	*p*-NO_2	CH_2	95.8	98.7	68.6	90/10
4	*p*-CN	CH_2	87.2	97.2	67.2	88/12
5	*p*-F	CH_2	19.8	96.4	42.6	96/4
6	*p*-Cl	CH_2	35.5	97.0	38.4	99/1
7	*p*-Br	CH_2	18.4	95.8	7.8	95/5
8	*p*-CH_3	CH_2	18.3	92.4	32.6	93/6
9	*p*-OCH_3	CH_2	22.2	91.4	77.8	67/33
10	*p*-H	CH_2	59.6	92.3	35.5	72/28
11	*p*-NO_2	—[e]	87.8	85.8	25.2	88/12
12	*m*-NO_2	—[e]	71.4	80.0	58.4	67/33
13	*o*-NO_2	—[e]	81.6	62.2	24.8	77/23
14	*p*-F	—[e]	26.9	81.2	24.8	93/7
15	*p*-Cl	—[e]	30.4	81.4	31.8	81/19
16	*p*-Br	—[e]	17.8	61.2	26.8	66/34
17	*p*-CH_3	—[e]	41.1	81.0	15.8	79/21
18	*p*-OCH_3	—[e]	32.7	82.0	34.0	94/6
19	*p*-H	—[e]	18.9	76.6	10.0	39/61
20	*p*-CN	—[e]	92.3	89.0	71.0	70/30
21[f]	*o*-NO_2	CH_2	83	95	−44	98/2
22[f]	*m*-NO_2	CH_2	98	98	36	86/16
23[f]	*p*-NO_2	CH_2	97	99	22	84/16

[a] Reaction conditions: *p*-nitrobenzaldehyde (37.3 mg, 0.25 mmol), cyclohexanone (473.5 mg, 4.82 mmol, 0.5 mL), 7.5 mol% **1a**, 10 mol% TfOH, 25 °C, 48 h, 2 mL of water. [b] Isolated yield. [c] Determined by chiral HPLC using Daicel Chiralpak AD-H chiral column. [d] Determined by ^{1}H NMR. [e] Cyclopentanone. [f] 9-Amino-9-deoxy-*epi*-cinchonine as "blank" reaction (25 °C, 6 h).

also studied in acetone aqueous solution. However, the aldol adduct, (*S*)-4-hydroxy-4-(4-nitrophenyl)butan-2-one, was obtained in moderated yield (78%) and with poor enantioselectivity (44%ee).

The recovery and reuse of catalyst

At the end of aldol reaction, the copolymer-supported organocatalyst **1a** was readily recovered in 95–98% recovered yields from reaction mixture by simple filtration using an organic membrane. The supported organocatalyst **1a** was washed with ethyl acetate, stirred in ammonia water for 2 h, filtered, dried under reduced pressure and reused in the following recycle experiments. Fig. 4 shows the supported organocatalyst **1a** had excellent catalytic performance and stability. Even in the fifth run, there was no loss in catalytic activity and stereocontrol. However, after being continuously reused five times, there were some small drops in catalytic activity and stereoselectivity. In order to seek the reason why the catalytic property decreased slightly, TEM, TGA and nitrogen adsorption–desorption isotherm were used to monitor the change of surface morphology, weight percent of organic moiety and pore structure. Compared with fresh catalyst **1a**, a similar surface morphology in the seventh run was observed.

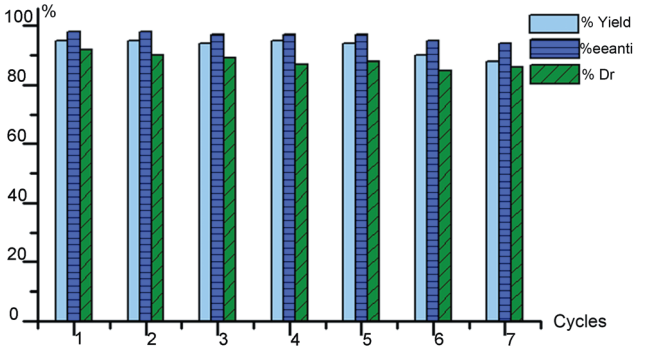


Fig. 4 The stability of supported organocatalyst **1a** in direct asymmetric aldol addition of *p*-nitrobenzaldehyde to cyclohexanone in water.

However, it was found that the organic weight loss of organic moiety in the temperature range of 150–800 °C increased from 46.4 to 49.4%, and the surface area, average pore diameter and pore volume slightly decreased from 42.1, 10.1 and 20.7 to 38.6 $m^2\ g^{-1}$, 9.5 Å and 18.9 cc g^{-1} respectively. Furthermore, the aldol addition of *p*-nitrobenzaldehyde to cyclohexanone without the addition of recycled **1a** was carried out in the filtered aqueous medium of 7th recycle experiment under the same conditions. As expected, no optically active aldol product was observed by using HPLC, which was indicative of no leaching of active component 9-amino-9-deoxy-*epi*-cinchonine from the backbone of copolymer. Therefore, considering the increased organic weight loss (3.0%) by TGA and decreased surface area and pore volume, it was concluded that the adsorbed reactants, products, or impurity occupied some pores, covered the catalytic active sites and resulted in the decrease in catalytic property.

Conclusions

In conclusion, we have synthesized a novel type of supported heterogeneous organocatalyst by the simple copolymerization of the organocatalyst 9-amino-9-deoxy-*epi*-cinchonine with acrylonitrile in the presence of AIBN as radical initiator. From a concept of green chemistry, these copolymer-supported heterogeneous organocatalysts possessed three virtues: simple synthetic procedure, the easy, perfect separation and subsequent recycling from the reaction media, and catalytic aldol reactions in water. In the asymmetric aldol addition of *p*-nitrobenzaldehyde to cyclohexanone in water, all the supported-organocatalysts **1a–d** possessed excellent isolated yields (90.2–94.7%) and stereoselectivities (96.8–97.8%ee, *anti*, *anti*/*syn* = 91/9). Furthermore, they could maintain high catalytic performance and stability in water without a loss in catalytic activity and stereocontrol, even in the fifth run.

Experimental section

General remarks

All chemicals were purchased and used without any further purification. 9-Amino-9-deoxy-*epi*-cinchonine was synthesized according to the reference and ascertained by ^{1}H and ^{13}C NMR.[24]

Instrumentation and methods

TLC, where applicable, was performed on pre-coated aluminium-backed plates and spots were made visible by quenching ultraviolet (UV) fluorescence (λ = 254 nm). Fourier transform infrared spectra were recorded on a Perkin-Elmer Model GX Spectrometer using a KBr pellet method with polystyrene as a standard. Thermogravimetric analysis (TGA) was performed on a SBTQ600 Thermal Analyzer (USA) with a heating rate of 20 °C min^{-1} over a temperature range of 40–800 °C under flowing compressed N_2 (100 mL min^{-1}). ^1H NMR were performed on a Bruker AV-300 NMR instrument at ambient temperature at 300 MHz. All chemical shifts were reported downfield in ppm relative to the hydrogen resonance of TMS. The interlayer spacings were obtained on a DX-1000 automated X-ray power diffractometer (XRD), using Cu Kα radiation and internal silicon powder as a standard with all samples. The patterns were measured between 2.00° and 20.00° (2θ) with a step size of 1° min^{-1} and X-ray tube settings of 40 kV and 2.5 mA. The morphologies of as-synthesized samples were determined by a Hitachi model H-800 transmission electron microscope (TEM). N_2 adsorption–desorption analysis was carried out at 77 K on an Autosorb-1 apparatus (Quantachrome). The specific surface areas and pore diameters were calculated by the BET and BJH model respectively. C, H, and N elemental analysis was obtained from an EATM 1112 automatic elemental analyzer instrument (Thermo, USA). Gel permeation chromatography (GPC) was performed using a 515 HPCC pump and a Waters styragel HT3 column (Mw 500–30 000) with a 2414 refractive index detector from Waters. Experiments were performed at 35 °C using THF as fluent, flow rate of 0.7 mL min^{-1}, and molecular weights are reported *versus* polyacrylonitrile standards. Optical rotatory power was measured on Model 341 polarimeter (Perkin Elmer). The *anti*/*syn* ratio was determined by ^1H NMR of crude product in $CDCl_3$; CHOH *d*: *syn* 5.48 ppm, J = 3.0 Hz; *anti*: 4.90 ppm, J = 9.0 Hz. The enantiomeric excess (%ee) was determined on HPLC with a Daicel Chiralpak AD-H column (n-hexane/2-propanol = 80/20) under 20 °C, 254 nm and 0.5 mL min^{-1} conditions.

Preparation of copolymer-supported organocatalysts 1a–d

A dried flask (100 mL) was flushed three times with Ar_2 atmosphere, to this was added 5 mL 9-amino-9-deoxy-*epi*-cinchonine (0.29 g, 1 mmol) DMF solution, 10 mL acrylonitrile (0.53 g, 10 mmol) DMF solution and 2 mL AIBN (0.03 g, 0.2 mmol) DMF solution, consecutively. The reaction mixture was heated to 80 °C for 48 h and poured into 50 mL of methanol. The pale yellow precipitate was filtered, washed with methanol (10 mL × 3) and dried under reduced pressure to obtain pale yellow copolymer-supported organocatalyst **1a** 0.67 g in 81% yield. In addition, by changing the initial molar ratio of acrylonitrile to 9-amino-9-deoxy-*epi*-cinchonine (8/1, 5/1 and 2/1), the other supported organocatalysts **1b–d** were also obtained in 62, 45 and 28% yields, respectively.

1a: $[\alpha]^{20}_{D(589)}$ = +14.0 (0.5 g mL^{-1}, DMF), anal. calcd for $C_{63.9}H_{66.6}N_{19.0}$: C, 69.71; H, 6.05; N, 24.16; Found: C, 71.03; H, 6.34; N, 23.02. **1b**: $[\alpha]^{20}_{D(589)}$ = +15.8 (0.5 g 100 mL^{-1}, DMF), anal. calcd for $C_{62.1}H_{65.0}N_{18.3}$: C, 69.90; H, 6.09; N, 24.01; Found: C, 70.83; H, 6.27; N, 22.92. **1c**: $[\alpha]^{20}_{D(589)}$ = +17.6 (0.5 g 100 mL^{-1}, DMF), anal. calcd for $C_{55.3}H_{58.1}N_{16.1}$: C, 70.01; H, 6.13; N, 23.79; Found: C, 72.58; H, 6.39; N, 22.82. **1d**: $[\alpha]^{20}_{D(589)}$ = +24.6 (0.5 g 100 mL^{-1}, DMF), anal. calcd for $C_{41.5}H_{44.2}N_{11.6}$: C, 70.74; H, 6.28; N, 22.98; Found: C, 71.97; H, 6.44; N, 21.54.

Asymmetric aldol reaction in water

In a 5 mL vial, supported organocatalyst **1a** (30 mg, 0.019 mmol) and TfOH (5.6 mg, 0.038 mmol), water (1 mL) and cyclohexanone (474 mg, 4.8 mmol) were added consecutively. After stirring at room temperature for 5 min in a closed system, *p*-nitrobenzaldehyde (37.3 mg, 0.25 mmol) was added and left under stirring for 48 h at 25 °C (monitored by TLC). The reaction mixture was centrifuged to recover supported organocatalyst **1a** and extracted with ethyl acetate (15 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to recover cyclohexanone. The crude products were purified by flash column chromatography eluting with petroleum ether/ethyl acetate (v/v = 10/1) to remove the unreacted *p*-nitrobenzaldehyde and then petroleum ether/ethyl acetate (v/v = 2/1) as an eluent to afford the pure aldol adduct. The *anti*/*syn* ratio and enantioselectivities (%ee) were determined by ^1H NMR and HPLC analysis.

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