

Article

Aqueous asymmetric aldol reaction catalyzed by nanomagnetic solid acid SO₄²⁻/Zr(OH)₄-Fe₃O₄

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ARTICLE INFO

Article history: Received 13 July 2014 Accepted 2 September 2014 Published 20 March 2015

Keywords: Solid acid catalyst Magnetism Aldol reaction Asymmetric catalysis Aqueous phase

ABSTRACT

Magnetic solid acid catalysts SO₄²⁻/Zr(OH)₄-Fe₃O₄ were prepared using magnetic Fe₃O₄ nanoparticles, ZrOCl₂·8H₂O, and sulfuric acid as starting materials in the calcination temperature range 110–650 °C. The properties of the magnetic solid acid, such as loaded SO_{4²⁻} content, acid distribution, surface morphology, and porous structure, were characterized. In the aqueous asymmetric aldol reaction of various benzaldehydes with strong electron-withdrawing groups ($R = NO_2$ and CN), good to excellent catalytic performance (83%-100% yield, 86.0%-95.6% ee anti, and anti/syn = 88–96/12–4) was achieved. These nanomagnetic solid acids can be quantitatively recycled from the reaction mixture using an external magnet and reused five times without significant loss of catalytic activity.

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1. Introduction

The asymmetric aldol reaction is one of the most important C-C bond-forming reactions and creates the optically active β -hydroxy carbonyl structural unit found in many natural products and drugs [1–4]. Most asymmetric aldol reactions involve the directed aldol reaction in the presence of acidic promoters, including organic and inorganic acids, which are used to activate aldehydes electrophilically. Unfortunately, organic acids such as TfOH and F₃CCO₂H have high solubility in the organic phase, which results in impurities in the catalytic products owing to difficult separation. Furthermore, liquid inorganic acids are highly corrosive to industrial equipment. Therefore, the choice of the solid acid in the aldol reaction is a crucial decision [5-10].

Magnetic nanoparticles (MNPs) with large specific surface areas and good textural properties are currently an area of extensive research, particularly for applications in catalysis and

adsorption processes owing to their unique superparamagnetism, low toxicity, simple preparation, low cost, and ease of recovery [11-13]. To combine the advantages of MNPs and solid acids, magnetic solid acids have been developed and widely applied in catalytic nitration [14], the Hantzsch reaction [15], esterification [16,17], hydrolysis reactions [18,19], the acetal reaction of benzaldehyde with ethylene glycol [20], and coupling reactions of aryl bromides with heterocycles [21]. However, the application of magnetic solid acids in asymmetric catalytic reactions is seldom reported.

In this paper, the nanomagnetic solid acids SO_{4²⁻}/Zr(OH)₄-Fe₃O₄ [22–24] were applied to the asymmetric aldol reaction of cyclohexanone with various substituted benzaldehydes for the first time. Good to excellent catalytic performance for the benzaldehydes with strong electron-withdrawing groups (83%-100% yield, 86.0%–95.6% ee anti, and anti/syn = 88–96/12–4) was satisfactorily achieved. These magnetic solid acids can be easily recovered in quantitative yield using an external magnet

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This work was supported by the National Natural Science Foundation of China (21071116).

DOI: 10.1016/S1872-2067(14)60222-9 | http://www.sciencedirect.com/science/journal/18722067 | Chin. J. Catal., Vol. 36, No. 3, March 2015

and possessed good tolerance in catalytic cycles with no significant loss of catalytic performance.

2. Experimental

2.1. Preparation of nanomagnetic solid acid SO4²⁻/Zr(OH)4-Fe₃O4

The suspension of nano-Fe₃O₄ (2.32 g, 10.0 mmol, Aladdin, 99.5%) in distilled water (20 mL) was well stirred at 65 °C, and aqueous ZrOCl₂·8H₂O solution (20 mL, Aladdin, 99.9%) with molar ratios of ZrOCl₂·8H₂O:Fe₃O₄ = 0.2, 0.5, 1.0, 2.0, or 5.0 was added dropwise. The pH of the reaction medium was adjusted to 13 by ammonia spirit and stirred for another 4 h. The supernatant was decanted by magnetic separation using an external magnet, and the obtained magnetic solids Zr(OH)₄/Fe₃O₄ were washed with distilled water until the solution was neutral and no Cl- ions were present and dried at 110 °C in vacuo. After three nitrogen replacement, grinding, immersing in 0.5 mol/L sulfuric acid for 3 h, and separating using an external magnet, the samples were dried at 110 °C to obtain nanomagnetic solid acids, which were designated as SZF1-5 for ZrOCl2·8H2O:Fe3O4 ratios of 0.2, 0.5, 1.0, 2.0, and 5.0, respectively [25,26]. SZF₃ was calcined in a muffle furnace at 300 or 650 °C for 3 h to give the nanomagnetic solid acids SZF₃-300 and SZF₃-650, respectively.

2.2. Characterization of catalysts

Magnetic hysteresis loops were measured on a vibrating sample magnetometer (VSM, HH-15, China) using Ni as the standard substance. The powder was strongly pressed and fixed in a small cylindrical plastic box for the magnetization measurements. Thermogravimetry-differential thermal analysis (TG-DSC) spectra of the as-synthesized samples were measured on an SBTQ600 thermal analyzer (TA, USA) with a heating rate of 20 °C/min from 40 to 800 °C under N_2 (100 mL/min). The total acidity of the samples was determined by temperature-programmed desorption (TPD) of NH₃. The measurements were carried out by an automatic TPD apparatus (PCA-1200, China). The sample was kept at 50 °C for 60 min in a flow of NH₃. The amount of desorbed NH₃ was determined after heating the sample up to 700 °C with a heating rate of 10 °C/min. N₂ adsorption-desorption analysis was performed at -196 °C on an Autosorb-1 apparatus (Quantachrome, USA). All samples were degassed at 130 °C for 12 h before measurements, and the surface area and pore size distribution were calculated by the BET and BJH models, respectively. After being well-dispersed in water (10 mg sample in 10 mL of H_2O) for 10 min under ultrasonic irradiation, sputtered over copper wire, and evaporated under infrared radiation for 10 min, the as-synthesized samples were observed by transmission electron microscopy (TEM) using a JEM 2100 transmission electron microscope under an accelerating rate voltage of 200 kV to show their surface morphologies (JEOL, Japan).

Accurately weighed nanomagnetic solid acid (100.0 mg) was soaked in 6 mol/L HCl (50 mL) under vigorous stirring for 3 h and filtered. Saturated BaCl₂ was added to the filtrate and BaSO₄ precipitated out. After BaSO₄ was filtered, dried under reduced pressure, and accurately weighed, the $SO_{4^{2-}}$ content was calculated.

2.4. General asymmetric aldol reaction

9-Amino-9-deoxy-epi-cinchonidine (epi-CDNH2) was prepared according to a literature procedure [27]. In a vial (25 mL), the mixture of nanomagnetic solid acid SZF_3 (35.0 mg), epi-CDNH₂ (11.0 mg, 0.0375 mmol), cyclohexanone (0.98 g, 10.0 mmol, Adamas-beta, 99.5%), and deionized water (2.0 mL) was stirred at room temperature for 15 min. Then, p-nitrobenzaldehyde (76 mg, 0.50 mmol, Adamas-beta, 99%) was added and allowed to react at 25 °C for 48 h. After the reaction was complete, the SZF₃ catalyst was magnetically separated using an external magnet and directly reused in the next experiment. The resulting reaction mixture was extracted with ethyl acetate (3 \times 20 mL). The combined organic phases were dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography eluted with petroleum ether/ethyl acetate (v/v = 10/1 to 2/1) to give pure 2-(hydroxy(4-methoxyphenyl)methyl)cyclohexanone. The anti/syn (Dr) ratio was determined by 1H NMR in CDCl₃, in which the chemical shifts of syn- and anti-CHOH protons were at δ = 5.32 ppm (d) with 3 = 1.3 Hz and δ = 4.74 ppm (d) with ³*J* = 8.8 Hz, respectively. The enantiomeric excess (ee) was determined by high-performance liquid chromatography (HPLC) (Agilent Technologies 1200 Series) with a 254 nm UV-vis detector using a Daicel chiralpak Chiral OD column (4.6 mm \times 250 mm), eluting with *n*-hexane/ iso-propanol (95/5) with a flow rate of 0.5 mL/min at 20 °C.

3. Results and discussion

3.1. Chemical composition of nanomagnetic solid acid

The chemical compositions of the magnetic solid acids SZF_{1-5} are listed in Table 1. Although the molar ratios of $ZrOCl_2:Fe_3O_4$ in the preparation of $Zr(OH)_4$ – Fe_3O_4 varied greatly in the range 0.2–5.0, the formed $Zr(OH)_4$ could be loaded onto nano- Fe_3O_4 in 72%–75% yield. The content of $Zr(OH)_4$ in SZF_{1-5} determined by the inductively coupled plasma (ICP) method increased from 13.9% to 71.2% with the increasing

Table 1	
Chemical compositions of the various magnetic solid acids.	

Entry	Catalyst	Molar ratio of ZrOCl ₂ :Fe ₃ O ₄	Loaded Zr(OH) ₄ (wt%)	SO ₄ ²⁻ content (wt%)
1	SZF_1	1:5	13.9	6.8
2	SZF ₂	1:2	20.3	14.3
3	SZF ₃	1:1	33.9	20.7
4	SZF_4	2:1	50.1	17.2
5	SZF ₅	5:1	71.2	12.3

molar ratio of ZrOCl₂:Fe₃O₄. It is noteworthy that the SO₄²⁻ contents in the magnetic solid acids SZF₁₋₅ showed a close relationship with the loaded Zr(OH)₄. The immersed SO₄²⁻ contents in SZF₁₋₅ first increased with increasing loaded amount of Zr(OH)₄. However, when the loaded Zr(OH)₄ exceeded 33.9%, the SO₄²⁻ content gradually decreased owing to the accumulation of Zr(OH)₄ on the outer surface of nano-Fe₃O₄.

3.2. Magnetic properties

The magnetic properties of the representative solid acids SZF₁, SZF₃, and SZF₃' (SZF₃ reused five times) were examined through vibrating sample magnetometry. Their hysteresis loops at room temperature are shown in Fig. 1. VSM analysis showed that the magnetic solid acids SZF1, SZF3, and SZF3' possessed saturated magnetization values of 55.58, 39.21, and 46.44 emu/g, respectively. The saturated magnetization values of SZF₁, SZF₃, and SZF₃' were all sufficiently high to meet the needs of magnetic separation. The zero coercivity and resonance of each magnetization loop confirmed the superparamagnetism behavior at 25 °C for all of the samples, which is very beneficial for the catalyst's rapid dispersion and magnetic separation. Unexpectedly, the magnetic susceptibility of SZF3' increased from 39.21 to 46.44 emu/g. The most likely reason for this phenomenon is the decrease in SO_{4²⁻} content from 20.7 wt% (SZF₃) to 12.8 wt% (SZF₃'), which was verified by the decrease in the catalytic performance.

3.3. TG analysis

Using solid acid SZF₃ as an example, the thermal decomposition was characterized by TG-DSC. From the TG-DSC results shown in Fig. 2, there are three types of peaks for SZF₃. An endothermic peak with a gradual weight loss of 6.08% below 200 °C, which was verified by the DSC curve, was mainly attributed to desorption of surface-bound or intercalated water in the pores. Another gradual weight loss peak of 2.41% at 200–600 °C resulted from the dehydration of Zr(OH)₄ to form amorphous ZrO₂ [28] and the transformation of zirconia from



Fig. 1. Magnetization curves of the nanomagnetic solid acids (1) SZF_1 , (2) SZF_3 , and (3) SZF_3' .



Fig. 2. TG-DSC curves of magnetic solid acid SZF₃.

the tetragonal to the monoclinic phase [29]. Accompanied by an endothermic peak centered at 721 °C in the DSC curve, the peak with a sharp weight loss of 8.06% at 600–780 °C corresponded to the removal of the SO_4^{2-} group [14].

3.4. NH₃-TPD analysis

The NH₃-TPD profiles of the magnetic solid acids SZF₃, SZF₃-300, and SZF₃-650 are shown in Fig. 3. Magnetic solid acid SZF₃ with 0.952 mmol/g acidity showed a broad NH₃ desorption peak, including four peaks centered at 146, 257, 389, and 539 °C, which indicated that the surface acid strengths were not homogeneously distributed. In general, the broad NH3 desorption peak was divided into two types of desorption peaks based on Gaussian fitting: the first broad medium temperature (MT) desorption signal in the range 100–300 °C, corresponding to NH₃ adsorbed on the acid sites at medium strengths; and the second broad high-temperature (HT) peak in the range of 300-650 °C, suggesting the presence of very strong acid sites [29]. Unfortunately, the MT and HT desorption signals of SZF₃-300 and SZF₃-650 sharply decreased with increasing calcination temperature from 110 to 650 °C for 3 h. Especially for magnetic solid acid SZF₃-650, little NH₃ adsorption demonstrated weak acidity (0.178 mmol/g), which was also evidenced by its poor catalytic performance in the following asymmetric aldol reaction.



Fig. 3. NH₃-TPD profiles of magnetic solid acids (1) SZF₃, (2) SZF₃-300, and (3) SZF₃-650.



Fig. 4. TEM profiles of (a) nano-Fe₃O₄ and (b) magnetic solid acid SZF₃.

3.5. Surface morphology and porous structure

The TEM images of nano-Fe₃O₄ and magnetic solid acid SZF₃ are shown in Fig. 4. The micrograph of nano-Fe₃O₄ clearly shows uniform square crystallites of about 60-80 nm in diameter. After Fe₃O₄ was coated with Zr(OH)₄ and immersed in 0.5 mol/L sulfuric acid, the obtained magnetic solid acid SZF₃ with 80-100 nm in diameter shows about 10-20 nm growth of particle size. The N₂ adsorption-desorption isotherm of magnetic solid acid SZF₃ (Fig. 5) is a type II isotherm in classic definitions, agreed well with the normal form obtained with a non-porous or macroporous adsorbent. This indicates that magnetic solid acid SZF3 was a typical microporous material, which was verified by its BJH pore size distribution plot (inset of Fig. 5). Based on the multipoint BET method and the BJH method, the BET specific surface area and pore volume of magnetic solid acid SZF₃ were calculated to be 15.8 m²/g and 0.029 mL/g, respectively.

3.6. XRD results

Figure 6 shows the high-angle powder XRD patterns of nano-Fe₃O₄, Zr(OH)₄–Fe₃O₄, and SO₄^{2–}/Zr(OH)₄–Fe₃O₄. The XRD pattern of nano-Fe₃O₄ shows the typical peaks at 18.12°, 30.08°, 35.45°, 43.06°, 53.49°, 57.00°, 62.62°, and 74.05°, which correspond to the (111) (d = 5.68 Å), (220) (d = 3.44 Å), (311) (d = 2.94 Å), (400) (d = 2.44 Å), (422) (d = 1.99 Å), (511) (d = 1.87



Fig. 5. N₂ adsorption-desorption isotherms and pore size distribution (insert) of magnetic solid acid SZF₃.



Fig. 6. Powder XRD patterns of (1) nano-Fe₃O₄, (2) $Zr(OH)_4$ -Fe₃O₄, and (3) $SO_4^{2-}/Zr(OH)_4$ -Fe₃O₄.

Å), (440) (d = 1.72 Å), and (533) (d = 1.48 Å) reflections, respectively [30]. After Zr(OH)₄ and SO_{4²⁻} were consecutively loaded on nano-Fe₃O₄, there was no significant change in the various characteristic diffraction peaks, which indicated that Zr(OH)₄ and SO_{4²⁻} were well-dispersed on/in the internal and external surfaces of nano-Fe₃O₄.

3.7. Catalytic performance in asymmetric aldol reaction

3.7.1. Effect of reaction temperature and magnetic solid acids

The asymmetric aldol reaction between 4-nitrobenzaldehyde and cyclohexanone was used as a model reaction to investigate the catalytic performance of the as-synthesized magnetic solid acids [31,32]. From Fig. 7, the catalytic reaction temperature had a great influence on the yield and enantioselectivity of the aldol adduct. With increasing reaction temperature, the yield of the aldol adduct increased, whereas the enantioselectivity markedly decreased. Considering these two contradictory factors, the optimal temperature of 25 °C was chosen for the following screening tests.

Furthermore, the catalytic performance of various magnetic solid acids (SZF₁₋₅) in the aldol reaction of 4-nitrobenzaldehyde with cyclohexanone was evaluated, and the results are listed in Table 2. It was found that the SO_4^{2-} content had a significant influence on the yield of the aldol adduct. Magnetic solid acid



Fig. 7. Asymmetric aldol reaction of 4-nitrobenzaldehyde with cyclohexanone at different temperatures.

 Table 2

 Asymmetric aldol reaction catalyzed by various magnetic solid acids.

O ₂ N	CHO +	$\frac{\text{Cat., rt}}{\text{epi-CDNH}_2 (7.5 \text{ m})}$	ol%) O ₂ N	OH O
Entry	Catalyst	Isolated yield (%)	ee anti ^c (%)	Dr (anti/syn) °
1	SZF1	74	84.0	81/19
2	SZF ₂	85	84.3	79/21
3	SZF ₃	96	83.1	81/19
4	SZF ₄	87	82.9	81/19
5	SZF ₅	80	85.1	82/18
6	_	54	20.4	70/30
7	SZF3 a	>99	90.8	91/9
8	TfOH ^b	>99	96.8	93/7
9	Zr(OH)4/SO42-	98	91.2	90/10

Reaction conditions: Catalyst (20.0 mg), epi-CDNH₂ (11.0 mg, 0.0375 mmol), cyclohexanone (0.98 g, 10.0 mmol), p-nitrobenzaldehyde (76.0 mg, 0.5 mmol), H₂O (2.0 mL), 25 °C, 48 h.

^aSZF₃ (30.0 mg), 72 h. ^bTfOH (10.0 mg), 12 h.

^cDetermined by chiral HPLC (AD-H column).

SZF₃ with 20.7% SO₄²⁻ content produced the highest yield (96%, entry 3). However, the stereoselectivity was insensitive to the SO_{4²⁻} content. The enantioselectivity (82.9%-85.1% ee anti) and diastereoselectivity (anti/syn = 79-82/21-18) changed little when the SO42- content varied in the range 6.8%-20.7%. Unfortunately, in the absence of magnetic solid acid, the aldol reaction afforded unsatisfactory catalytic results (54% yield, 20% ee anti, and anti/syn = 70/30, entry 6). In particular, compared with an organic acid (>99% yield, 96.8% ee anti, and anti/syn = 93/7), magnetic solid acid SZF₃ gave similar diastereoselectivity (anti/syn = 91/9) and lower enantioselectivity (90.8% ee anti) in excellent yield (>99%) (entries 7 and 8). Considering the possible effect of the bonding interaction between $Zr(OH)_4$ and Fe_3O_4 on the catalytic performance, Zr(OH)₄/SO₄²⁻ was prepared according to the same procedure as SZF₃ in the absence of Fe₃O₄. A similar yield and stereoselectivity of aldol products were obtained (entry 9), which indicated that the bonding interaction between Zr(OH)₄ and Fe₃O₄ had little effect on the catalytic performance.

3.7.2. Effect of calcination temperature and magnetic solid acid amount

It is well known that the calcination temperature of the solid acid strongly affects the form of the SO₄^{2–} group [14]. To investigate the influence of the calcination temperature and the amount of SZF₃, the aldol reaction was performed under the optimized conditions. From Fig. 8, after calcining at 110 °C, magnetic solid acid SZF₃ gave the highest catalytic performance (>99% yield, 92.1% ee *anti*, and *anti/syn* = 89/11). With increasing the calcination temperature from 110 to 650 °C, the enantioselectivity and yield decreased for different amounts of catalyst SZF₃ (5.0–55.0 mg). In particular, the enantioselectivity and yield of the aldol adduct sharply decreased when the calcination temperature reached 650 °C. The main reason might be the removal of the SO₄^{2–} group with increasing temperature, which was verified by the sharp mass loss at 600–780 °C (Fig. 2) and the decreased acidity of catalyst SZF₃-650 (Fig. 3).

3.7.3. Reaction with various substituted benzaldehydes

Encouraged by the remarkable results under the above reaction conditions, the substrate scope was extended to a wide variety of benzaldehydes with *ortho*, *meta*, and *para* substituents. The catalytic results are summarized in Table 3. For the benzaldehydes with strong electron-withdrawing substituents (R = NO₂ and CN), the aldol reactions exhibited good to excellent enantioselectivity (86.0%–95.6% ee *anti*) and diastereoselectivity (*anti/syn* = 88–96/12–4) with 83%–100% yield (entries 1–6). However, the benzaldehydes with weak electron-withdrawing substituents (R = Cl and Br) gave moderate to good enantioselectivity (70.9%–85.9% ee *anti*) and disappointing yield (19%–76%) although good to excellent diastereoselectivity (*anti/syn* = 88–96/12–4) was achieved. Unfortunately, the benzaldehydes with electron-donating substituents (R = CH₃ and OCH₃) did not proceed smoothly.

3.7.4. Recovery and reuse of catalyst

At the end of the catalytic aldol reaction, magnetic solid acid SZF_3 could be easily and quantitatively separated from the reaction mixture using an external magnet and directly reused in



Fig. 8. Effect of calcination temperature and amount of SZF₃ used on the enantioselectivity (a) and yield (b) of the aldol adduct. Reaction conditions: *epi*-CDNH₂ (11.0 mg, 0.0375 mmol), cyclohexanone (0.98 g, 10.0 mmol), *p*-nitrobenzaldehyde (76 mg, 0.50 mmol), and 2.0 mL H₂O.

Table 3

Asymmetric aldol reaction of various benzaldehydes with cyclohexanone.

$R \xrightarrow{(i)} CHO + CHO + Cat., rt \xrightarrow{(i)} R \xrightarrow{(i)} R$							
Entry	R	Isolated yield (%)	ee <i>anti</i> ^b (%)	Dr (anti/syn) ^b			
1	4-NO2	>99	92.1	89/11			
2	3-NO2	95	90.9	81/19			
3	$2-NO_2$	83	95.9	96/4			
4	4-CN	91	92.5	84/16			
5	3-CN	94	86.0	88/12			
6	2-CN	92	87.4	88/12			
7	4-Cl ^a	76	72.8	94/6			
8	3-Cl ^a	67	82.2	96/4			
9	2-Cl ^a	38	81.9	93/7			
10	2,4-Cl ^a	39	85.9	89/11			
11	4-Br ^a	19	70.9	88/12			

Reaction conditions: SZF₃ (35.0 mg), *epi*-CDNH₂ (11.0 mg, 0.0375 mmol), cyclohexanone (0.98 g, 10.0 mmol), benzaldehyde (0.5 mmol), H₂O (2.0 mL), 25 °C, 48 h.

^a Reaction time 72 h. ^b Determined by chiral HPLC (AD-H column).

cycle tests. Figure 9 shows the catalytic results of reused magnetic solid acid SZF₃ in the aqueous asymmetric aldol reaction of cyclohexanone with 4-nitrobenzaldehyde. To our surprise, the yield and enantioselectivity unexpectedly increased during the first three cycles. In the third cycle, magnetic solid acid SZF₃ produced the highest enantioselectivity (94.7% ee *anti*) owing to the increased dispersion in the aqueous medium. It is noteworthy that 91.3% yield, 90.2% ee *anti*, and *anti/syn* = 78/22 were obtained in the fifth run. The slight decrease in catalytic performance was because of the loss of SO_{4²⁻} (20.7 to 12.8 wt%) in the catalytic process.

3.7.5. Large-scale asymmetric aldol reaction

A large-scale asymmetric aldol reaction between cyclohexanone (9.8 g, 0.10 mol) and 4-nitrobenzaldehyde (3.8 g, 25 mmol) was performed at 25 °C for 48–72 h in the presence of *epi*-CDNH₂ (110.0 mg, 0.375 mmol) and SZF₃ (350.0 mg). Good catalytic performance (96% yield, *anti/syn* = 90/10,



Fig. 9. Reusability of magnetic solid acid SZF3 in cycle experiment.

93.2% ee *anti*) was observed. After the completion of the aldol reaction, solid acid SZF₃ was filtered for reuse. Furthermore, *epi*-CDNH₂ was also recovered by extraction with dilute hydrochloric acid (10%), alkalization with an excess of concentrated ammonia, and extraction with CH₂Cl₂. The catalytic system could be reused and gave satisfactory results (87% yield, *anti/syn* = 89/11, 90.4% ee *anti*) in the third cycle.

4. Conclusions

With the purpose of realizing environmentally benign and friendly processes in asymmetric reactions, a series of sulfated zirconium hydroxide compounds loaded on nano-Fe₃O₄ were prepared, characterized, and applied in the aqueous asymmetric aldol reaction of various benzaldehydes with cyclohexanone for the first time. These magnetic solid acids, which could be easily and quantitatively separated from the reaction mixture using an external magnet, showed good to excellent catalytic performance for benzaldehydes with strong electron-withdrawing substituents and possessed good tolerance in five consecutive runs without a significant loss of catalytic performance.

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