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Core-shell silica magnetic microspheres supported proline as a recyclable organocatalyst for the asymmetric aldol reaction

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ABSTRACT

L-4-Hydroxyproline has been successfully grafted onto the core-shell structural silica magnetic microspheres and characterized by elemental analysis, thermo gravimetric analysis (TGA), vibrating sample magnetometry (VSM), high resolution transmission electron microscopy (HRTEM) and Fourier transform infrared (FT-IR). The chiral immobilized catalyst demonstrated high catalytic activity (up to 92%), diastereoselectivity (up to 85:15) and enantioselectivity (up to 80%) in the asymmetric aldol reaction between aldehyde acceptors and ketone donors. On the other hand, the synthesized catalyst could be rapidly separated from the reaction mixture through an external magnetic field and reused up to five runs without any obvious loss of activity, indicating its easy-separated property and excellent recyclability.

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1. Introduction

Since reported as a catalyst for the asymmetric aldol reaction by List et al. [1] in 2000, L-proline has attracted a wild spread attention in the field of asymmetric catalysis. Compared with metal catalysts, L-proline, as a non-metallic organocatalyst, has a lot of advantages, such as milder reaction conditions, lower price, easier immobilization and recovery, better stability and less pollution. Besides the aldol reactions [2–5], L-proline has also been applied to many other asymmetric reactions. Quite a few researchers successively used proline and its derivatives as catalysts for Michael addition reactions [6–9]. Mannich reactions were also usually catalyzed by proline [10–15]. Bui and Barbas III [16] reported that L-proline could act as catalysts in both steps of the Robinson annulation reaction. The research work of Thayumanavan et al. [17], Ramachary et al. [18], and Sabitha et al. [19] revealed the proline's catalytic activities for Diels–Alder reactions, respectively.

At the same time, immobilization and recycling of L-proline have received considerable concerns in recent years. Although Lproline is not very expensive, the studies of supported proline and its derivatives still have important significance. Supported proline catalysts 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. Moreover, immobilization gives the possibility to explore modifications of the properties of the supported catalysts by employing specific characteristics of the supports. Several types of supports such as polymer, silica, ionic liquid, cyclodextrin and magnetite are usually considered for the immobilizations of proline and its derivatives. Gruttadauria and his co-workers [20] used polystyrene-supported, proline-based organic catalysts for the direct asymmetric aldol reaction. Zou et al. [21] investigated the catalytic behaviors of PVC-TEPA-supported L-proline in the aldol reaction. Lu et al. [22] synthesized L-proline functionalized polymers as supported organocatalysts. Zamboulis et al. [23] grafted L-proline onto the heterogenized silica for catalyzing the asymmetric aldolization. Doyagüez et al. [24] catalyzed the asymmetric aldol reaction by proline on mesoporous materials. Miao and Chan [25] prepared an ionic-liquid-anchored proline catalyst which was efficient and recyclable for asymmetric aldol reaction. Luo et al. [26] used proline functionalizing chiral ionic liquids as highly efficient asymmetric organocatalysts in Michael addition reaction. Immobilizations of proline and its derivatives into the β -cyclodextrin cavity as catalysts for direct asymmetric aldol reactions were also reported [27,28].

Magnetic materials, especially Fe₃O₄ and γ -Fe₂O₃, have many outstanding properties such as superparamagnetism and low toxicity. Fe₃O₄ coated with silica was commonly applied as the support of metal and non-metal catalysts [29–33]. These silica magnetic microspheres have large surface area and can be functionalized easily. In catalytic applications, the magnetic particles have high stability, which can be used in kinds of organic and inorganic solutions and easy to be separated from the reaction mixture by magnetic decantation.

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In our present work, L-4-hydroxyproline has been successfully anchored onto the $Fe_3O_4@SiO_2$ nanoparticles, consequently named $Fe_3O_4@SiO_2$ -Pro, and confirmed by corresponding characterization means. Moreover, the catalytic performances and recycling utilization rate of the catalyst $Fe_3O_4@SiO_2$ -Pro in the asymmetric aldol reaction were investigated. Although the catalyst based on proline and magnetite has been studied [31,34], our catalyst had much more excellent mechanical strength and recyclability compared with those related reports. Furthermore, the effects of the catalyst support $Fe_3O_4@SiO_2$ for the reaction got a discussion.

2. Experimental

2.1. Preparation of the catalyst Fe₃O₄@SiO₂-Pro

The core-shell structural silica magnetic nanoparticles as supports of the catalyst were synthesized according to the previously published methods [35]. Then, the catalyst Fe₃O₄@SiO₂-Pro was prepared by steps showed in Fig. 1.

2.1.1. Synthesis of compound 2

In ice bath, benzyl chloroformate (24 mmol, 4.09 g) was added dropwise to a mixture of L-4-hydroxyproline (20 mmol, 2.62 g) and NaHCO₃ (60 mmol, 5.04 g) in acetone (20 mL) and distilled water (40 mL) under continuous stirring. The resulting mixture was kept stirring in ice environment for 30 min and followed by reacting at room temperature for 2 h. Then the pH value of the reaction system was adjusted to 3–4 with 1 mol/L HCl. Acetone was removed by vacuum distillation and the aqueous phase was extracted by CH₂Cl₂ (4×30 mL). The organic layer was dried on anhydrous Na₂SO₄, filtered and evaporated. (2S,4R)-1-benzyloxycarbonyl-4-hydroxyproline (compound 2) was obtained as colorless oil (4.51 g, yield 85%).

2.1.2. Synthesis of compound 3

Triethylamine was added to the solution of compound 2 (15 mmol, 3.98 g) and benzyl bromide (16.5 mmol, 2.82 g) in THF (25 mL) at 0 °C. After the mixture was stirred for 18 h at room temperature, the solvent was evaporated in vacuo. The residue was dissolved in 50 mL of CH₂Cl₂, washed with HCl (1 N), H₂O, Na₂CO₃ (5%), and H₂O, and then dried over Na₂SO₄. The solvent was evaporated, and the residue was purified by column chromatography on silica gel (hexane/AcOEt, 2:1) to afford (2S,4R)-1,2-dibenzyloxycarbonyl-4-hydroxypyrrolidine (compound 3) as pale yellow oil (2.66 g, yield 50%).

2.1.3. Synthesis of compound 4

The solution of compound 3 (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-dibenzyloxycarbonyl-4-(3-triethoxysilylpropylaminocarboxy) pyrrolidine (compound 4) as a brown oil (yield 83%).

2.1.4. Synthesis of compound 5

Compound 4 (2 mmol, 1.20 g) was hydrogenated over palladium on carbon (0.16 g, 10%) in methanol (40 mL) for 7 h at room temperature under H₂ atmosphere (3 atm). The catalyst Pd/C was filtered off, and the filtrate was concentrated in vacuo yielding (2S,4R)-2-carboxy-4-(3-triethoxysilylpropylaminocarboxy) pyrrolidine (compound 5) quantitatively as pale yellow oil. No purification was possible due to the instability of the product.

2.1.5. Preparation of Fe₃O₄@SiO₂-Pro

The solution of the proline derivative (compound 5, 1g) in toluene (20 mL) was added into the suspension of the inorganic support of Fe₃O₄@SiO₂ (3g) in a mixture of toluene/water (40 mL/40 μ L). The mixture was refluxed for 24 h. The solid was then filtered and washed with several solvents of different polarity (MeOH, AcOEt, CH₂Cl₂, hexane and ether) abundantly, to remove the remaining non-supported proline derivative. The brown yellow solid was dried at 40 °C under vacuum.

Several catalysts with different amount of proline were also prepared through adjusting the proportion of the proline derivative and $Fe_3O_4@SiO_2$.

2.2. Characterizations of the catalyst Fe₃O₄@SiO₂-Pro

The synthesized catalyst Fe₃O₄@SiO₂-Pro was confirmed by corresponding characterization means. The C, H and N contents in Fe₃O₄@SiO₂-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 °C min⁻¹. Magnetic measurements of Fe₃O₄@SiO₂ and Fe₃O₄@SiO₂-Pro were investigated by a quantum design vibrating sample magnetometry (VSM) at room temperature in an applied magnetic field sweeping from -15 to 15 kOe. The morphology and microstructure of Fe₃O₄@SiO₂-Pro were characterized by high-resolution transmission electron microscopy (HRTEM). The HRTEM images were obtained through Tecnai G2 F30 electron microscope operating at 300 kV. 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.

2.3. Reaction procedures for activity evaluation of catalyst Fe₃O₄@SiO₂-Pro in the direct aldol reaction

2.3.1. Optimization experiments of reaction conditions

4-Nitrobenzaldehyde (0.5 mmol, 76 mg), cyclohexanone and corresponding kinds and amounts of catalysts were added in the solvent. The reaction mixture was stirred for 24-72 h at room temperature and treated with 10 mL of saturated ammonium chloride solution and extracted with ethyl acetate (3×10 mL). The organic layer was dried over anhydrous Na₂SO₄, and concentrated in vacuo. The products were isolated by column chromatography on silica gel (hexane/AcOEt, 4:1). The 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 $Fe_3O_4@SiO_2-Pro(20 mol%)$ and corresponding aldehyde (0.5 mmol) and ketone (2 mmol) were stirred in 2 mL ethanol for 24–72 h at room temperature. The mixture was treated with 10 mL of saturated ammonium chloride solution and extracted with ethyl acetate (3×10 mL). The organic layer was dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with hexanes/ethyl acetate. The 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 Fe₃O₄@SiO₂-Pro

4-Nitrobenzaldehyde (0.5 mmol, 76 mg), catalyst $Fe_3O_4@SiO_2$ -Pro (20 mol%), cyclohexanone (2 mmol, 196 mg) and ethanol (2 mL) were mixed and stirred at room temperature for 48 h. The catalyst $Fe_3O_4@SiO_2$ -Pro was removed by an external magnetic field,



Fig. 1. Synthesis of Fe₃O₄@SiO₂-Pro.

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 Fe₃O₄@SiO₂-Pro

Through elemental analysis of C, H and N, the proline content of $Fe_3O_4@SiO_2$ -Pro was evaluated to be 0.693 mmol/g.

The results of TGA analysis for Fe₃O₄@SiO₂ and Fe₃O₄@SiO₂-Pro were depicted in Fig. 2. The weight losses of both Fe₃O₄@SiO₂ and Fe₃O₄@SiO₂-Pro below 200 $^{\circ}$ C can be assigned to the release of physisorbed and chemisorbed water on the surface of the silica shell. The weight loss at the temperature range of 200–600 °C in the TGA curve of Fe₃O₄@SiO₂-Pro (Fig. 2b) was mainly attributed to the decomposition of organic groups from the grafted proline. Meanwhile, the weight loss above 200 °C was also possibly caused by the loss of structural water within amorphous SiO₂. In this way, the slow slope appeared at the temperature range of 200-600 °C in the TGA curve of Fe₃O₄@SiO₂ (Fig. 2a) can be explained. The total weight loss was evaluated to be 10% and 23% for Fe₃O₄@SiO₂ and Fe₃O₄@SiO₂-Pro, respectively. Through the TGA analysis, the proline content of Fe₃O₄@SiO₂-Pro was evaluated to be 0.605 mmol/g, which was close to the CHN elemental analysis result (0.693 mmol/g). The little difference between the results of the proline content in Fe₃O₄@SiO₂-Pro was mainly attributed to the difference of detection methods and the instrument error of the two detection means.

The magnetic property of the synthesized catalyst was examined through VSM analysis. The hysteresis loops of the silica magnetic nanoparticles before and after grafting proline measured



Fig. 2. TGA curves of (a) Fe₃O₄@SiO₂ and (b) Fe₃O₄@SiO₂-Pro.

at room temperature were given in Fig. 3. The saturation magnetization value of $Fe_3O_4@SiO_2$ -Pro was measured to be 2.04 emu/g. The zero coercivity and resonance of each magnetization loop evidenced the superparamagnetism of the magnetic materials which was very useful for the catalyst's rapid dispersion and separation. As shown in the lower right corner of Fig. 3, the nanoparticles of $Fe_3O_4@SiO_2$ -Pro had a good dispersion in the solvent of ethanol, and an excellent magnetic separation capability appeared when there was a magnet near the vessel.



Fig. 3. Magnetization curves of (a) Fe₃O₄@SiO₂ and (b) Fe₃O₄@SiO₂-Pro.

The HRTEM images shown in Fig. 4 revealed that the silica–magnetite composites prepared as supports of the catalyst had good spherical morphologies and regular core–shell structures. Grafting proline onto the $Fe_3O_4@SiO_2$ did not lead to a significant increase in the size of the individual particles. The average particle size of as-synthesized catalyst was about 80 nm and the diameter of the magnetic core was about 10 nm.

Through the seeded sol–gel approach, the thickness of silica shell of the $Fe_3O_4@SiO_2$ particles can be conveniently adjusted by controlling the addition amount of silica source (TEOS) [35]. With the increase of the particle sizes, the magnetic property of the particles certainly would decrease, which was unfavorable for

the separation of the catalyst from the reaction mixture. Generally, compared with the large-size support solid, nanoparticles with small particle sizes have larger specific surface area and better dispersion in the solvent, which can have beneficial effects to the catalysis. However, it easily leads to an agglomeration in the process of reaction, and then seriously affects the activity of the catalyst when the particle size is too small. In this paper, the distribution of the particle sizes was controlled in a range of 60–100 nm. The particles of the catalyst did not agglomerate and kept high activity even after five runs, evidenced by the HRTEM images of the reused catalyst (Fig. 4e and f) and the recycling experiments (Table 3).

The FT-IR spectra of Fe₃O₄@SiO₂, Fe₃O₄@SiO₂-Pro, and Fe₃O₄@SiO₂-Pro after five runs were illustrated in Fig. 5. The strong absorption band at 1095 cm⁻¹ was attributed to Si–O–Si vibrations, indicating the presence of SiO₂. Compared to the FT-IR spectrum of Fe₃O₄@SiO₂, there were two new peaks near 1560 and 1635 cm⁻¹ obviously appearing in that of Fe₃O₄@SiO₂-Pro, corresponding to bending vibration of the N–H groups in proline. These results demonstrated that L-4-hydroxyproline has been successfully grafted on the surface of Fe₃O₄@SiO₂ and the original structure of silica magnetic particles was retained.

3.2. Activity evaluations of Fe₃O₄@SiO₂-Pro

With the synthesized catalyst $Fe_3O_4@SiO_2$ -Pro in hand, its catalytic activity was evaluated in the asymmetric aldol reaction at room temperature.

The well-documented aldol reaction between 4nitrobenzaldehyde and cyclohexanone was chosen as a model to optimize the reaction conditions (Table 1). In all cases, the desired aldol product was obtained as a mixture of diastereomers.

In order to find out the optimum molar ratio of substrates, different stoichiometric ratios of 4-nitrobenzaldehyde and cyclohexanone (1:1, 1:2, 1:4, 1:10 and 1:20) were used in the experiments respectively (entries 1–5). When the stoichiometric



Fig. 4. HRTEM images of (a), (b) Fe₃O₄@SiO₂, (c), (d) Fe₃O₄@SiO₂-Pro and (e), (f) Fe₃O₄@SiO₂-Pro after five runs.

Table 1

Optimization conditions for the direct aldol reaction catalyzed by Fe₃O₄@SiO₂-Pro.



^a Isolated yield of mixture of all four diastereomers.

^b Determined by chiral HPLC (Chiralpak AD-H column, 95:5 n-hexane/isopropanol, 1 mL/min, detected at 254 nm).

^c The molar ratios of 4-nitrobenzaldehyde and cyclohexanone were 1:1, 1:2, 1:10, 1:20 respectively, and 1:4 was always used in the other groups of experiments. ^d Catalysts with different amount of proline (0.412 mmol/g, 0.791 mmol/g, 1.17 mmol/g) were used respectively, and catalyst with 0.693 mmol/g of proline was always

used in the other groups of experiments. ^e n.d. = not determined.

^f The mass equal to 20 mol% Fe₃O₄@SiO₂-Pro was added.



Fig. 5. FT-IR spectra of (a) $Fe_3O_4@SiO_2$, (b) $Fe_3O_4@SiO_2$ -Pro and (c) $Fe_3O_4@SiO_2$ -Pro after five runs.

ratio was changed from 1:1 to 1:4, the yield had a significant increase and became flat after 1:4. In all experiments with different stoichiometric ratios, good enantioselectivities were always obtained. So the molar ratio of 1:4 was chosen in the subsequent experiments.

Several catalysts with different amount of proline were designed (0.412 mmol/g, 0.791 mmol/g, 1.17 mmol/g) for comparison. Obvious differences were not observed in the data of their catalytic activities given in Table 1 (entries 6–8), when 20 mol% of proline was added in the all reactions. However, when the content of proline in $Fe_3O_4@SiO_2$ -Pro was too low, the amount of the support would be over-used in the reaction. On the other hand, when the

content of proline per unit mass of the catalyst was too high, the mechanical loss of the catalyst solid in the process of recycling would cause more loss of proline in the catalyst, which possibly decreased the catalytic activity seriously. Therefore, from an economic point of view, 0.693 mmol/g was the reasonable proline content in Fe₃O₄@SiO2-Pro.

Regrettably, H₂O, as an environmentally friendly solvent, was eliminated owing to its restraint for the activity of the catalyst (entry 10). However, the reaction proceeded with high yield and good enantioselectivity in ethanol (entry 3). Therefore, ethanol, another low-polluting solvent, was chosen as the most suitable solvent for this reaction. 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 participating, the reaction almost hardly occurred (entry 11). Meanwhile, Fe₃O₄@SiO₂ nanoparticles also had a catalytic activity in the aldol reaction (entry 12), due to the silanol groups on the silica shell, which were considered as very weak acids. The weakly acidic surface hydroxyl groups often form hydrogen bonds with oxygenates and the H-bonds probably catalyzed the aldol reactions in this work [36]. This result seemed to demonstrate that the solid support Fe₃O₄@SiO₂ also acted via its acidic sites in the Fe₃O₄@SiO₂-Pro catalyzing aldol reactions. However, the products of this group of controlled experiment were racemic, which revealed that proline played a very important catalytic role in the asymmetric aldol reaction. The yield and enantioselectivity did not improve apparently after increasing the catalyst loading from 20 to 30 mol%. And although a good enantioselectivity was still obtained, the yield was poor when the amount of catalyst was reduced to 10 mol%. From an economical point of view, 20 mol% was the preferred catalyst loading. Compared to reacting for 48 h, the yield of reacting for 24 h was lower, although the enantiomeric excess values (ee values) were quite similar. And little decrease even appeared both in the yield and enantioselectivity when the reaction proceeded for 72 h. So the optimum reaction time was decided to be 48 h.

Under the optimized conditions, the catalyst $Fe_3O_4@SiO_2$ -Pro was tested in aldol reactions between a variety of aromatic

37

24

96

Table 2

5

6

7

Evaluation of the catalyst $Fe_3O_4@SiO_2$ -Pro for the direct aldol reactions between different aromatic aldehydes and ketones.



72

72

24

4-0-N ^a Isolated yield of mixture of all four diastereomers.

4-02N

4-0₂N

b Determined by chiral HPLC (Chiralpak AD-H column, 95:5 n-hexane/isopropanol, 1 mL/min, detected at 254 nm).

30

4^c

d

^c 0.025 mmol of acetic acid was added.

^d Acetone was used as the ketone component.

^e Determined by chiral HPLC (Chiralpak OB-H column, 85:15 n-hexane/isopropanol, 1 mL/min, detected at 254 nm).



^a Isolated yield of mixture of all four diastereomers.

^b Determined by chiral HPLC (Chiralpak AD-H column, 95:5 n-hexane/isopropanol, 1 mL/min, detected at 254 nm).

aldehyde acceptors and ketone donors (Table 2). 4-Cyanobenzaldehyde was a good acceptors and gave the desired anti products in good yield with high diastereoselectivity and enantioselectivity (entry 1), which indicated that the aromatic aldehydes carrying strong electron withdrawing groups such as nitro or cyano group were good substrates for the aldol reaction. Unfortunately, attempts changing the substituting group positions onto the aromatic aldehydes resulted in lower ee values, although the yields remained good (entries 2 and 3). These phenomena were probably due to the electronic and steric effects of aromatic aldehydes. The formation of aldol products related with the electron accepting capacity of the substituent group on aldehydes and the steric hindrance at position 4 on the aromatic ring played a positive role for enantioface discrimination in transition state [37]. Good ee values were still obtained when other cyclic ketones including cyclopentanone, cycloheptanone and cyclooctanone were used as donors, whereas the yields had a significant drop with the increasing of the carbon numbers onto the cyclic ketones (entries 4-6). Acetone was also proved to be a suitable donor providing excellent yield with moderate enantioselectivity (entry 7).

The silica magnetic microspheres supported catalyst can be easily separated from the reaction media and subsequently reused through an external magnetic field, which is one of the outstanding advantages associated with supporting catalysts onto magnetic materials. The possibility of the reuse of Fe₃O₄@SiO₂-Pro in the reaction between 4-nitrobenzaldehyde and cyclohexanone was studied and the results were shown in Table 3. This magnetic nanoparticles supported proline can be reused up to five runs without any significant loss of activity. Recently, Wang et al. [31] and Riente et al. [34] designed organocatalysts based on proline derivatives as active centers and magnetic nanoparticles as support and investigated their catalytic performances in the asymmetric Michael addition reactions, successively. Both of their catalysts have high activities and enantioselectivity in the reactions. However, the same phenomenon occurred in the recycling tests of the catalysts that after the third run, a significant decrease in catalytic activity was observed, although the enantioselectivity was maintained. Compared with their reports, our catalyst had much more excellent mechanical strength and recyclability.

45.55

64:36

Through elemental analysis, the catalyst Fe₃O₄@SiO₂-Pro did not have an obvious change in proline content (0.622 mmol/g) after being reused for five times. As was shown in Fig. 5c, the FT-IR spectrum of Fe₃O₄@SiO₂-Pro after five runs still kept the characteristic peaks of proline compared with that of fresh catalyst (Fig. 5b). From the HRTEM images (Fig. 4e and f), it can be seen that the reused catalyst did not have an obvious agglomeration and still retained the good spherical morphology and regular core-shell structure, which revealed that the synthesized catalyst Fe₃O₄@SiO₂-Pro had an excellent mechanical strength and recyclability.

4. Conclusion

A new chiral immobilized organocatalyst based on proline as active sites and silica magnetic nanoparticles as supports has been successfully prepared and applied to the asymmetric aldol reaction between aromatic aldehydes and ketones. Moderate to good

ee^b (%) anti (syn)

79(7)

23 (20)

6(40)

99(27)

91 (96)

11 (79)

43^e

yields, diastereoselectivities and enantioselectivities were shown in the activity evaluation experiments. This synthesized catalyst had excellent magnetic separation ability, mechanical strength and recyclability, evidenced by being extensively reused without any substantial loss of activity.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j. molcata.2012.07.017.

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