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Magnetically recoverable catalyst for the asymmetric Henry reaction based on a substituted imidazolidine-4-one copper(II) complex supported by Fe₃O₄·SiO₂ nanoparticles

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ABSTRACT

The preparation and characterization of a heterogeneous recyclable catalyst based on Cu(II) complex of magnetic nanoparticles Fe_3O_4 ·SiO₂ with (2*R*,5*S*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one is described. The ligand molecules were attached to the surface by means of coordination bonds. The catalyst was characterized using DLS, FT-IR spectroscopy, SEM, and microanalysis. The reaction of substituted aldehydes with nitromethane catalyzed with this complex proceeded with high yields (82–99%) and high enantioselectivity (68–94%). The reaction rate decreased due to the formation of aggregated forms of the catalyst nanoparticles whose size (115–834 nm) depends on their concentration in the reaction medium. After a tenfold recycling of the catalyst, the catalytic activity slightly decreased (~10%); however, no change in enantioselectivity was observed (~94% ee). The efficiency of the catalyst prepared was also verified in the preparation of an intermediate of synthesis of the medical drug (*R*)-Salmeterol (yield 72%; 91% ee).

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1. Introduction

All catalyzed reactions are connected with the problem of separating the product from the catalyst. After the separation of the product, the reuse of homogeneous catalysts is often impossible or economically and technologically demanding. Thus, the used catalysts become constituents of hazardous waste, which has to be further processed or disposed of.¹ The necessity of research and developing recyclable catalysts is particularly desirable in the cases of catalysts containing heavy metals.¹ From the point of view of sustainable technologies, it is advantageous to immobilize homogeneous catalysts by attaching them to solid carriers, which enable easy separation and thus also the possibility of their reuse.²⁻¹³ Suitable carriers of homogeneous catalysts include, polymers.^{4,5} However, currently a much more efficient alternative, both economically and technologically, is the application of homogeneous catalysts anchored on magnetic carriers since their magnetic separation is very simple.⁶⁻¹³ Often, the magnetic carrier is the nanoparticles of a magnetite (Fe₃O₄).^{14,15} It is advantageous to cover the surface of these particles with a layer of silicon dioxide (Fe₃O₄·SiO₂), which ensures high chemical resistance and, at the

http://dx.doi.org/10.1016/j.tetasy.2015.10.003 0957-4166/© 2015 Elsevier Ltd. All rights reserved. same time, enables a covalent anchoring of suitable organic molecules to their surface.¹⁵ Magnetic nanoparticles, both as such or surface-modified ones, have already found applications particularly in medicine.^{16,17} Recently, a number of review articles have been published,^{6–13} which describe the use of magnetic nanoparticles as carriers of many catalysts, inclusive of the enantioselective ones.¹³

The enantioselective variant of the Henry reaction represents a reaction between an α -carbon atom of an aliphatic nitro compound and a carbonyl carbon, which produces enantiomerically pure nitroethanols.^{16–21} Our previous paper²⁰ described the preparation and characterization of a colloidal recyclable catalyst of such an asymmetric Henry reaction. The catalyst was based on a complex of (2R,5S)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one with a cupric salt of block copolymer of methoxypoly(ethylene glycol)-b-poly(L-glutamic acid). In this case, the bond between the polymeric carrier and the chiral ligand was mediated by a coordination bond with the central Cu(II) ion. Using this catalyst, we prepared the corresponding functionalized (S)-2-nitroethanols with chemical yields of 70-98% and enantioselectivities of 61–92% ee.²⁰ Such a catalytic system exhibits a considerable advantage in being easily prepared by coordination reactions between the carrier salt and the ligand. This way of anchoring eliminates the necessity of synthesizing a ligand containing a functional group



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intended for covalent anchoring of the ligand on the carrier. Due to the high stability of the complex in the reaction medium, it was possible to recycle the catalyst ten times with a minimum decrease in enantioselectivity and chemical yield.²⁰ However, this catalyst has a disadvantage in the necessity of its isolation from the reaction medium by means of (not very environmentally friendly) precipitation with diethyl ether. Herein our aim was to prepare and characterize a recyclable catalyst for the asymmetric variant of Henry reaction¹⁹ based on a magnetically separable carrier. Since the preparation of the catalyst had to be simple, we examined the possibility of coordination anchoring of imidazolidine-4-one ligands on a suitably modified surface of Fe₃O₄·SiO₂ particles. In addition to the characterization of the synthesized catalyst, we also wanted to prove its catalytic efficiency and the possibility of recycling in the Henry reaction, and compare its properties with analogous catalysts.

2. Results and discussion

The application of magnetic particles requires their size distribution to vary within a narrow range from 10^0 nm to 10^2 nm, depending on the purpose of their application.⁷ The smaller the particles of the colloidal solution are, the larger their surface is, and the higher is the rate of reaction taking place on the surface. On the other hand, very small and well-stabilized particles suffer from the disadvantage in that the rate of their separation from reaction medium is disproportionately lowered.^{22,23} For the preparation of the catalyst, we used the nanoparticles of Fe₃O₄·SiO₂–NH₂ (1.42%, N) prepared earlier.¹⁷ These were submitted to reaction with *cis*-aconitic acid anhydride,²⁴ which represents a simple method for the preparation of particles functionalized with carboxylic groups (Fe₃O₄·SiO₂–(COOH)₂) (Scheme 1).

Subsequent reaction with basic copper carbonate gave the corresponding salt (Fe₃O₄·SiO₂-(COO)₂Cu) onto which we coordinated the enantiomerically pure ligand (2R,5S)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one **L**, which we prepared as described in the literature.²¹

The synthesized catalyst Fe_3O_4 ·SiO₂-(COO)₂CuL (Chart 1) was then characterized by means of microanalysis, infrared spectroscopy (FT-IR), determination of the specific surface area, and scanning electron microscopy (SEM) and dynamic light scattering (DLS). The results of the microanalysis showed that the catalyst Fe_3O_4 ·SiO₂-(COO)₂CuL particles contain 3.64–3.84% of nitrogen and 4.27–4.35% of copper. The content of the coordinated ligand calculated on the basis of these analyses was 672–685 µmol/g.

Figure 1 shows the FT-IR spectra of starting nanoparticles $Fe_3O_4 \cdot SiO_2 - NH_2^{17}$ and modified nanoparticles $Fe_3O_4 \cdot SiO_2 - (COOH)_2$, $Fe_3O_4 \cdot SiO_2 - (COO)_2Cu$ and $Fe_3O_4 \cdot SiO_2 - (COO)_2CuL$. The spectrum of $Fe_3O_4 \cdot SiO_2 - NH_2$ (Fig. 1, A) contains valence bands of primary amino



Chart 1. Structure of magnetically separable catalyst Fe₃O₄·SiO₂-(COO)₂CuL.



Figure 1. FT-IR spectra of Fe_3O_4 ·SiO₂-NH₂ (A), Fe_3O_4 ·SiO₂-(COOH)₂ (B), Fe_3O_4 ·SiO₂-(COO)₂Cu (C), and Fe_3O_4 ·SiO₂-(COO)₂CuL (D).

group at the wave numbers from 1556 to 1484 cm^{-1.25} A deformation multiple band of this amino group was found at 682 cm^{-1.26} Furthermore, the spectrum contains the absorption band Fe–O of magnetic nucleus at 564 cm⁻¹, while the absorption band at 1089 cm⁻¹ belonging to asymmetric valence vibration of Si–O–Si group, or (as the case may be) valence vibration of Si–O–Fe group.²⁵ In the spectrum of Fe₃O₄·SiO₂–(COOH)₂ (Fig. 1, B), the bands²⁶ presumed to belong to amide I (C=O, valence vibration) 1650 cm⁻¹ and to amide II (N–H and C–N vibrations) 1550 cm⁻¹ are almost hidden in the left part of the broad strong band at 1510 cm⁻¹. However, the spectrum does not contain the typical absorption bands of valence vibration C=O and the broad absorption band of hydrogen bonds of –COOH group (3300–2500 cm⁻¹).²⁶ On the other hand, we found



Scheme 1. Preparation of particles of Fe₃O₄·SiO₂-(COO)₂Cu.

the characteristic, very strong absorption band of asymmetric valence vibrations of -COO⁻ group at 1510 cm⁻¹, which indicates that the acid is present in the form of its salt.²⁶ In this case, it is the ammonium salt, which is supported by the presence of the absorption band of asymmetric valence vibrations of -NH₃⁺ at 3404 cm^{-1} and the pair of bands at 3329 cm^{-1} and 3200 cm^{-1} corresponding to the valence vibrations of group -NH₂.²⁶ This is the reason as to why the spectra of Fe_3O_4 ·SiO₂-(COOH)₂ (Fig. 1B) and Fe_3O_4 ·SiO₂-(COO)₂Cu (Fig. 1C) are almost identical, the presumed exchange of -NH₃⁺ ions for Cu²⁺ ions being almost indistinguishable by means of IR. In the spectrum of the catalyst Fe₃O₄·SiO₂-(COO)₂-CuL (Fig. 1D), there appeared a distinct band with wave number ca 1600 cm⁻¹, which corresponds to the C=C valence vibration of 2functionalized pyridine.^{20,26} The ligand coordination is also supported by the distinct strenghtening of the bands about the wave number of 2965 cm⁻¹ belonging to C–H vibrations of aliphatic bonds²⁶ of the ligand molecule.

The textural characteristics of Fe₃O₄·SiO₂-NH₂ and Fe₃O₄·SiO₂-(COO)₂CuL (surface area, micro-pore volume and total pore volume) based on the determination of the nitrogen adsorption/ desorption isotherms are summarized in Table 1. In particular, the changes in S_{BET} illustrate a pronounced reduction of the surface area, which was accessible for nitrogen molecules due to the organic phase introduction. The particles Fe₃O₄·SiO₂-(COO)₂CuL with the anchored catalyst exhibited a decrease in S_{BET} by 46% related to particles Fe₃O₄·SiO₂-NH₂. The change in pore volume is even more dramatic; volumes decrease from $0.165 \text{ cm}^3/\text{g}$ $(Fe_3O_4:SiO_2-NH_2)$ to 0.018 cm³/g for the sample of catalyst $(Fe_3O_4:SiO_2-(COO)_2CuL)$. The volume of micro-pores is negligible in both samples as is evidenced by values less than 0.002 cm³/g. Interaction parameter C in BET equation is slightly decreasing with increasing content of organic phase, which indicates a decreasing wettability of surface by nitrogen.

The catalyst particles of Fe_3O_4 ·SiO₂-(COO)₂CuL were represented by means of scanning electron microscopy (SEM) (Fig. 2). Figure 2 shows that the particles have spherical shapes and agglomerate over the course of drying. A comparison of Figure 2A and B does not show any significant differences between the morphologies of freshly prepared catalysts and after operation of ten reaction cycles.

The synthesized catalyst Fe_3O_4 ·SiO₂-(COO)₂CuL was further tested for the Henry reaction of various aldehydes with nitromethane in ethanol at 10 °C (Table 2).

Table 2 presents the values of conversion and enantiomeric excess for the reactions of individual aldehydes in comparison with the results previously published,²¹ where the catalyst was ligand L combined with cupric acetate. The application of catalyst Fe₃O₄·SiO₂-(COO)₂CuL gave the corresponding 2-nitroethanols with an (*R*)-configuration in excess. Table 2 shows that the application of a heterogeneous catalyst generally led to negligible or only a mild decrease in the enantioselectivity. Only in the series of reactions of 4-substituted benzaldehydes, did we observe a more significant decrease in the enantioselectivity (Table 2, entries 3–5; Δ up to –24%). On the other hand, in the case of pentanal, we observed an increase in enantioselectivity as compared with the homogeneous catalyst (Table 2, entry 7; Δ +7% ee). The catalyst

Table 1 BET surface area (S_{BET} in m²/g), volume of micro-pores (V_{μ} in cm³/g) and total volume of pores (V_{tot} in cm³/g determined at relative pressure 0.98) of the prepared particles

Sample	BET isotherm		$V_{\mu} (\mathrm{cm}^3/\mathrm{g})$	$V_{\rm tot}~({\rm cm^3/g})$
	$S_{\text{BET}}(m^2/g)$	С		
Fe_3O_4 ·SiO ₂ -NH ₂	22	66 52	0.0009	0.165
$\operatorname{Fe}_{3}\operatorname{O}_{4}\operatorname{SIO}_{2}$ -(COO) ₂ CuL	10	52	0.0001	0.018

Fe₃O₄·SiO₂-(COO)₂CuL was also tested in the synthesis of (*R*)-1-(2,2-dimethyl-4*H*-benzo[*d*-1,3]dioxin-6-yl)-2-nitroethanol, which is an intermediate in the synthesis of (*R*)-Salmeterol, a medical drug used as a long-acting β 2-adrenoreceptor agonist (trade name Serevent[®]).²⁷ In this case, the obtained yield was 72% with 91% ee, which was analogous to the results obtained with the homogeneous catalyst L/Cu(OAc)₂ under comparable conditions²⁸ (Scheme 2).

All of the reactions studied were performed by stirring the dispersed system containing the corresponding aldehyde, nitromethane, ethanol and catalyst $Fe_3O_4 \cdot SiO_2 - (COO)_2CuL$. After the reaction, the catalyst was simply separated by means of an external magnet and reused in the next reaction cycle (Fig. 3). From this point of view, Sheldon's filtration test was performed,²⁹ which involved the separation of the heterogeneous catalyst part way through a reaction, followed by continuation of the reaction in the absence of the immobilized catalyst. The result was negative, with the reaction stopping completely after filtration.

The possibility of recycling the catalyst $Fe_3O_4 \cdot SiO_2 - (COO)_2CuL$ was tested for the reaction of pivalaldehyde with nitromethane (Fig. 4). Figure 4 shows that after 10 reaction cycles no significant changes in the enantioselectivity occur (~94% ee). However, the conversion exhibited a slow decrease from 88% down to 78%. The slight lowering of the catalyst activity in the reaction of pivaloy-laldehyde with nitromethane is documented in Figure 5, where the conversion-time dependence is presented for the fresh catalyst and for the ten times reused catalyst.

This decrease in catalyst activity cannot be explained by the loss in the number of reaction centers, because neither the content of the nitrogen nor the content of copper was decreased in the ten times reused catalyst (3.66% N; 4.31% Cu). In the case of washing out of the ligand itself (if a case of lower stability of the complex would be presumed), a decrease in enantioselectivity would have to be observed. Therefore, the decrease in activity can be explained either by partial inhibition or a gradual loss of the catalyst due to handling.²¹

The average hydrodynamic size of catalyst particles was determined (DLS) in the reaction mixture of nitromethane, 2-methoxybenzaldehyde and ethanol at 10 °C and at the concentrations of Fe₃O₄·SiO₂-(COO)₂CuL from 0.12 mg/mL to 12 mg/mL. The increasing concentration of catalyst was connected with the increase in the hydrodynamic size of particles: 115 ± 34 nm (0.12 mg/mL), 450 ± 39 nm (0.5 mg/mL), 593 ± 27 nm (1.2 mg/mL), 774 ± 46 nm (5 mg/mL), and 834 ± 92 nm (12 mg/mL). At catalyst concentrations of below 0.12 mg/mL, the hydrodynamic size of the catalyst particles did not decrease any further. These results show that a reversible formation of the aggregates takes place in the reaction medium, and the distribution of their dynamic size values is determined by the character of medium and by concentration of the catalyst.

Figure 6 (Table 3) presents the conversion-time dependences for the reaction of nitromethane with 2-methoxybenzaldehyde in the presence of various amounts of the catalyst Fe₃O₄·SiO₂-(COO)₂CuL, namely in the range of 0.12-12 mg/mL (0.05-5 mol %). The obtained enantiomeric excess values were in the presence of different amounts of the catalyst and were almost comparable (81-87% ee). Within the above-mentioned concentration range, the catalyst is well dispersed in the reaction medium and represents more or less aggregated nanoparticles of hydrodynamic size values from \sim 115 nm to \sim 830 nm, depending on its concentration (according to DLS, Table 3). It was also proved that the intensity of stirring of reaction mixture does not affect the observed reaction rate. The time dependence in Figure 6 shows that between the catalyst concentrations 0.5-1.2 mg/mL, the effect is only negligible. However, the increase in catalyst concentration above 1.2 mg/mL results in a deceleration of the reaction. Such concentration

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Figure 2. SEM of particles Fe₃O₄·SiO₂-(COO)₂CuL, freshly prepared (A) and used after 10 cycles (B).

increase causes an increase in the size of aggregated particles of catalyst, which lowers its specific surface with concomitant decrease observed in reaction rate. On the other hand, lowering the catalyst concentration below 0.5 mg/mL also caused deceleration of the reaction. A distinct drop in reaction rate was observed, at the catalyst concentration of 0.12 mg/mL (~115 nm). This indicates that the particles have a larger specific surface (a factor accelerating the reaction), the ratio catalyst/substrate is already too low at this concentration. In summary, in the heterogeneously

catalyzed reaction of nitromethane with 2-methoxybenzaldehyde, the optimum concentration of the catalyst $Fe_3O_4 \cdot SiO_2 - (COO)_2CuL$ was in the range of ca 0.5–1.2 mg/mL, where the observed deceleration of the reaction was approximately fivefold in comparison with the homogeneous catalyst (Table 3). From the standpoint of reaction rate and approaching a homogeneous system, it is usually much more advantageous to use a catalyst with particle size values in the range of 10^0-10^1 nm.⁸ However, in our case the acceleration of reaction would require not only size lowering of catalyst

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Table 2

Henry reaction of nitromethane with various aldehydes catalyzed by L/Cu(OAc)₂ complex and recoverable catalyst Fe₃O₄·SiO₂-(COO)₂CuL

Entry	Aldehyde (R)	L/Cu(OAc) ₂ ^a		Fe ₃ O ₄ ·SiO ₂ -(COO) ₂ CuL ^b	
		Yield ^c (%)	ee ^d (%)	Yield ^c (%)	ee ^d (%)
1	Ph	97	92	93	87
2	2-MeOC ₆ H ₄	97	92	99	86
3	4-ClC ₆ H ₄	97	90	90	80
4	$4-BrC_6H_4$	97	92	90	68
5	$4-PhC_6H_4$	97	92	99	81
6	cyclohexyl	86	92	82	92
7	n-Butyl	82	87	87	94
8	t-Butyl	87	96	88	94

^a Results published²¹ in our previous work (24 h).

^b Reaction time 96 h.

^c Values are isolated yields after chromatographic purification.

^d Enantiomeric excess determined by HPLC using Chiralcel OD-H.



Scheme 2. Enantioselectivities of homogeneous L/Cu(OAc)₂ complex and heterogeneous catalyst Fe₃O₄·SiO₂-(COO)₂CuL in the preparation of (R)-Salmeterol.



Figure 3. Principle of separation and recycling of catalyst Fe₃O₄·SiO₂-(COO)₂CuL.

particles, but simultaneously it would be necessary to increase the content of the anchored homogeneous catalyst above 685 μ mol/g. Nevertheless, our partially aggregated catalyst offers the advantage of easy and fast magnetic separation from the reaction medium (several minutes). In the case of small and well-stabilized nanoparticles, the magnetic separation is often very difficult.^{22,23}

3. Conclusion

The heterogeneous complex Fe_3O_4 ·SiO₂-(COO)₂CuL was synthesized and tested as an enantioselective, magnetically separable and

recyclable catalyst of the Henry reaction of functionalized aldehydes with nitromethane. The main criteria of evaluation of the effect of immobilization on the effectiveness of the catalyst were its effects on overall reaction yield, enantioselectivity, possibility recycling, and the effect of recycling on the above-mentioned parameters. In comparison with the original homogeneous catalyst (87%; 96% ee), the best result was obtained in the reaction of pivalaldehyde with nitromethane (88%; 94% ee). On the other hand, a mild decrease in enantioselectivity was observed in the reactions of aromatic aldehydes. As is often the case with the application of heterogeneous catalysts, the reactions proceeded approximately five times more slowly than the reaction catalyzed by the corresponding homogeneous catalyst. From the standpoint of reaction rate, the optimum concentration of the catalyst was in the range of ca 0.5-1.2 mg/mL Fe₃O₄·SiO₂-(COO)₂CuL. It was also found, that above ca 1.2 mg/mL, the rate of reaction of 2-methoxybenzaldehyde with nitromethane decreased with increasing concentration of the catalyst. This decrease is due to the lowering of the specific surface of the catalyst caused by an increase in the size of the aggregates formed. Thanks to the high stability of the complex in the reaction medium, it was possible to simply synthesize, separate and recycle the catalyst. After tenfold recycling of the heterogeneous catalyst, the yields were lowered by only ca 10% without any observable decrease in the enantioselectivity. The catalyst Fe₃O₄·SiO₂-(COO)₂CuL used in the synthesis gives (R)-1-(2,2-dimethyl-4H-benzo[d-1,3]dioxin-6-yl)-2-nitroethanol [intermediate for medical drug (R)-Salmeterol; 72%; 91% ee], which is a result comparable with that obtained with the analogous homogeneous catalysis (76%; 90% ee). The synthesized catalyst, which is

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Figure 4. Proof of recoverability of catalyst Fe_3O_4 ·SiO₂-(COO)₂CuL (up to 10 times) in the asymmetric Henry reaction of MeNO₂ with t-C₄H₉CHO.



Figure 5. The time (h) dependence of conversion (%) of the Henry reaction of MeNO₂ with *t*-C₄H₉CHO catalyzed by fresh catalyst (\blacklozenge) and catalyst after 10 cycles (\blacksquare) (Fe₃O₄·SiO₂-(COO)₂CuL; 5 mol %, 10 °C).



Figure 6. The time dependence (h) of conversion (%) for the reaction of MeNO₂ with 2-methoxybenzaldehyde catalyzed by homogeneous catalyst L/Cu(OAc)₂ 3.32 mg/mL (\bullet) and different amounts of heterogeneous catalyst [Fe₃O₄·SiO₂-(COO)₂CuL]: 0.5 mg/mL (\bullet); 1.2 mg/mL (\blacksquare); 5 mg/mL (\bullet); 12 mg/mL (\bigcirc) at 10 °C.

Table 3

The dependence of half-life (h) of reaction of MeNO₂ with 2-methoxybenzaldehyde on concentration (mg/mL; mol %) and hydrodynamic size distribution (nm) of recoverable catalyst Fe₃O₄·SiO₂-(COO)₂CuL (ethanol; 10 °C)

Fe ₃ O ₄ ·SiO ₂ -(COO) ₂ CuL		Hydrodynamic size	Half-life of	
mg/mL	mol %	distribution (nm)	reaction (h)	
0.12	0.05	115 ± 34	>80	
0.5	0.2	450 ± 39	16	
1.2	0.5	593 ± 27	14	
5	2	774 ± 46	23	
12	5	834 ± 92	40	
3.32*	5*	_	3*	

* For homogeneous catalyst complex L/Cu(OAc)₂.

easily magnetically separable and recyclable, meets a number of contemporary requirements imposed by 'green' and sustainable chemistry with concomitant preserving of high application potential in practical enantioselective Henry reactions.

4. Experimental

4.1. General

If not stated otherwise, the starting chemicals and solvents were obtained from Sigma-Aldrich or Fluka and used without further purification. Infrared diffuse reflectance spectra were measured using the FT-IR Nexus of Thermo Nicolet corp. spectrophotometer in the range 4000–400 cm^{-1} with resolution of 4 cm^{-1} using a dry KBr powder containing 3 wt % of the sample. The number of scans was 128 at the mirror velocity 0.158 cm s^{-1} . The obtained diffuse reflection spectra (R) were converted to absorption spectra using the Kubelka–Munk (KM) function as $KM(R) = (1 - R)^2/(2R)$.³⁰ Arithmetic average of five spectra was used for increasing intervals of noise. Finally, the KM spectra were converted to (%) transmittance ((%) *T*) spectra by equation: (%) $T = 10^{(2 - KM)}$ and the transmittance on the y axis in Figure 1 is labeled as Intensity. The average particle size and size distribution of the conjugate Fe₃O₄·SiO₂-(COO)₂CuL were determined by dynamic light scattering using a Zetasizer Nano ZS. Measurements were taken in the reaction mixture at 25 °C with scattering angle of 173° using disposable sizing cuvettes. The microanalyses were performed on an apparatus of FISONS Instruments, EA 1108 CHN. The determination of Cu was carried out with an Aavanta P double beam atomic absorption spectrometer in the flame atomization mode. Microwave digestion of samples was carried out in the Speedwave TM MWS-3+ microwave system with the maximum total output of the microwave generator 1450 W. Quantification of Cu concentrations was performed establishing calibration curve by linear regression. The SEM of prepared particles was carried out on an electron microscope JEOL JSM-7500F apparatus. In order to increase its conductivity, the sample was coated with an Au layer (0.2 nm) with the help of dust sprinkling equipment Balzers. The BET surface area and pore size distribution of the samples were determined according to the N₂ adsorption isotherms. Nitrogen, used as adsorptive, was supplied by Linde corp. Adsorption isotherms of nitrogen at -196 °C were determined using an ASAP 2020 instrument and evaluated by MicroActive Software. The specific surface area was calculated according to BET methodology.³¹ The pore size distributions were determined by means of BJH algorithm³² using Harkins–Jura equation for calculation of adsorbed layer thickness.³³

4.2. Synthesis

4.2.1. Preparation of Fe₃O₄·SiO₂-(COOH)₂

The Fe₃O₄·SiO₂NH₂ particles (500 mg, 1.42%, N; 115 ± 60 nm (DLS)¹⁷) were dispersed in dry pyridine (40 mL) by using ultrasound (450 W) under nitrogen for 30 min. A solution of *cis*-aconitic anhydride (600 mg, 3.84 mmol) in 1,4-dioxane (2 mL) was added dropwise to the prepared dispersion and the reaction mixture was mixed at 25 °C. After 6 days, the particles were separated by using external magnet, then refluxed for one hour in ethanol (40 mL) and lastly washed with water (3 × 30 mL) and methanol (3 × 30 mL) and dried in vacuum at 40 °C. Yield: 310 mg particles of Fe₃O₄·SiO₂-(COOH)₂; FT-IR (KBr), cm⁻¹: 3587, 3564, 3404, 3329, 3200, 2924, 2854, 2544, 1804, 1650, 1550, 1510, 1429, 1403, 1128, 1088, 1052, 986, 938, 877, 819, 775, 752, 735, 715, 630, 603, 511, 488, 462, 450, 430, 415; Elemental analysis: Found: C, 8.38; H, 1.12; N, 1.37.

4.2.2. Preparation of Fe₃O₄·SiO₂-(COO)₂Cu

The Fe₃O₄·SiO₂–(COOH)₂ particles (240 mg) and CuCO₃·Cu(OH)₂ (220 mg, 1 mmol) were dispersed in an ethanol/water mixture (1/1; 10 mL) by using ultrasound (450 W) under nitrogen for 30 min. The mixture was stirred at room temperature overnight; after 15 min of sonication, the dispersed particles were separated by using an external magnet. The same procedure was repeated three times to remove the unreacted excess of CuCO₃·Cu(OH)₂ and then washed with water (6 × 30 mL) and ethanol (3 × 30 mL) and dried in vacuum at 40 °C. Yield: 250 mg particles of Fe₃O₄·SiO₂–(COO)₂Cu; FT-IR (KBr), cm⁻¹: 3587, 3564, 3404, 3330, 3200, 2854, 2527, 2852, 2545, 1804, 1650, 1550, 1510, 1430, 1403, 1128, 1088, 1053, 986, 938, 877, 819, 775, 751, 735, 714, 631, 600, 509, 486, 460, 425, 419; Elemental analysis: Found: C, 7.58; H, 1.12; N, 1.48; Cu, 6.26.

4.2.3. Preparation of Fe₃O₄·SiO₂-(COO)₂CuL

The Fe₃O₄·SiO₂-(COO)₂Cu particles (100 mg) were dispersed in methanol (7 mL) by ultrasound (450 W) under nitrogen for 30 min. The solution ligand L (40 mg, 0.18 mmol) in methanol (10 mL) was added to dispersion. The particles were separated with an external magnet after mixing for 24 h at 25 °C and lastly washed by methanol (3 × 20 mL). The product was dried under vacuum drying at 40 °C overnight. Yield: 120 mg particles of Fe₃O₄·SiO₂-(COO)₂CuL; FT-IR (KBr), cm⁻¹: 3587, 3564, 3388, 3334, 3076, 2965, 2933, 2874, 2546, 1803, 1696, 1605, 1594, 1569, 1502, 1429, 1396, 1326, 1297, 1264, 1205, 1122, 1088 1050, 997, 944, 874, 819, 754, 735, 714, 620, 599, 508, 486, 469, 427, 420, 409, 398; Elemental analysis: Found: C, 20.83; H, 2.69; N, 3.62; Cu, 4.27.

4.3. General procedure for the asymmetric Henry reaction

A mixture of Fe₃O₄·SiO₂-(COO)₂CuL (30 mg, 0.02 mmol), and nitromethane (0.54 mL, 10 mmol) in absolute ethanol (2 mL) was stirred for 1 h at room temperature. The mixture was then cooled at 10 °C and the aldehyde (0.4 mmol) was added. The mixture was stirred for 96 h. The solvents were removed under reduced pressure, and the crude product was purified by column or flash chromatography (AcOEt/hexane; 1/4 (v/v). The enantiomeric excess was determined by HPLC. The characterization data for all enantiomers of the nitroalcohols were in accordance with data published previously.²¹

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