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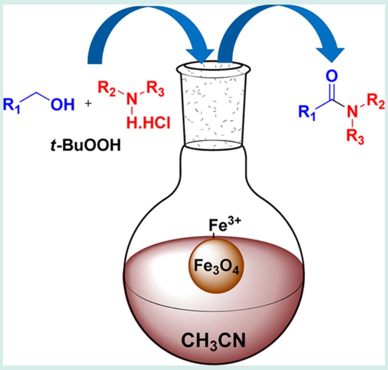
Superparamagnetic $Fe(OH)_3@Fe_3O_4$ Nanoparticles: An Efficient and Recoverable Catalyst for Tandem Oxidative Amidation of Alcohols with Amine Hydrochloride Salts

Marzban Arefi,[†] Dariush Saberi,[‡] Meghdad Karimi,[†] and Akbar Heydari*,[†]

[†]Chemistry Department, Tarbiat Modares University, P.O. Box 14155-4838, Tehran 46417-76489, Iran
[‡]Fisheries and Aquaculture Department, College of Agriculture and Natural Resources, Persian Gulf University, Bushehr 75169, Iran

Supporting Information

ABSTRACT: Magnetic $Fe(OH)_3@Fe_3O_4$ nanoparticles were successfully prepared and characterized. This magnetic nanocomposite was employed as an efficient, reusable, and environmentally benign heterogeneous catalyst for the direct amidation of alcohols with amine hydrochloride salts. Several derivatives of primary, secondary and tertiary amides were synthesized in moderate to good yields in the presence of this catalytic system. The catalyst was successfully recycled and reused up to six times without significant loss of its catalytic activity.



KEYWORDS: *oxidative amidation, tandem oxidation, magnetic nanoparticles, iron oxide, heterogeneous catalyst*

INTRODUCTION

Amide bond formation is one of the most important and often used reactions in the synthesis of natural products, polymers, pharmaceuticals, and fine chemicals.[1] Owing to the importance of the amide functionality in biological systems and pharmaceutical chemistry (more than 25% of available drugs contain an amide unit[2]), the development of an efficient and practical protocol for the amide bond formation remains a great challenge in organic chemistry. Traditionally, amides are synthesized by the reaction of an amine with a carboxylic acid (or their derivatives) or by using a coupling reagent.[3] These methodologies are generally expensive and produce a significant amount of chemical waste.[4] However, these traditional methods suffer from poor atom-efficiency or the use of highly hazardous reagents. To circumvent these problems, another alternative amide formation protocols have been explored. These includes, the Staudinger reaction,[5] the Schmidt reaction,[6] the Beckmann rearrangement,[7] dehydrogenative amidation of alcohols,[8] hydroamidation of alkynes,[9] amino carbonylation of haloarenes,[10] direct amide synthesis from alcohols with amines or nitroarenes,[8c,11] transamidation of primary amides,[12] and oxidative amidation of aldehydes.[13] Although significant achievements were made, most of the strategies mentioned above have not been applied in industry owing to drawbacks such as the use of expensive transition metals and harsh reaction conditions. Among the amide formation protocols, the tandem oxidative amidation of alcohols with amine salts has received sustained attention over the past few years. These methods require the use of transition metals, such as copper,[14] zinc,[15] ruthenium,[8a,11b,16] rhodium[17] and iridium[18] or heterogeneous catalysts, such as Au/TiO_2 system,[19] Au/DNA nanohybrids,[8b] and alumina-supported silver clusters.[20]

Iron is abundant, inexpensive, safe, and environmentally benign. On the other hand, a variety of iron salts as well as complexes are commercially available. So to compete with these methods involving expensive metals, studies on iron-catalyzed formation of amides from aldehydes or alcohols have been paid more attention in this area. In this context, Gaspa et al. reported the base-free iron-catalyzed oxidative amidation of alcohols with *N*-chloroamines, generated from toxic and non-atom-economic *N*-chlorosuccinimide.[21] Recently, Ghosh et al. reported a tandem oxidative amidation of benzyl alcohols with amine salts using $Fe(NO_3)_3$-(2,2,6,6-tetramethylpiperidin-1-yl)oxyl as catalyst, molecular oxygen and *tert*-butyl hydroperoxide as the oxidants.[22] Other iron salts, such as $FeCl_2$[23] and $FeSO_4{\cdot}7H_2O$,[24] have also been used for synthesis of amides from aldehydes and amine hydrochloride salts. Although, these iron-catalytic systems, for the preparation of amides, promote the drawbacks existing with the other transition metal catalytic systems, the separation of the desired product and the catalyst

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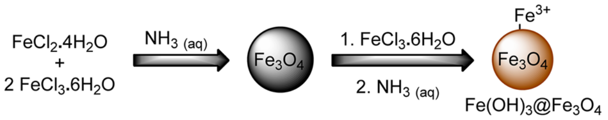
from the reaction mixture can be challenging in these homogeneous catalytic methodologies.

In recent years, magnetic nanoparticles-supported catalysts have been successfully deployed in a variety of important organic transformations.[25] Because they are highly stable and they can be separated from the reaction mixture by using an external magnet for further using. In continuation of our efforts in using magnetic nanoparticles as a catalyst support in organic reactions,[26] herein, we describe an inexpensive, magnetically reusable and environmentally friendly catalytic system ($Fe(OH)_3@Fe_3O_4$) for the direct oxidative amidation of alcohols with amine hydrochloride salts.

■ RESULTS AND DISCUSSION

As can be seen in Scheme 1, our catalytic system was prepared through a simple pathway (for details see Experimental Procedures).

Scheme 1. Preparation of Magnetic $Fe(OH)_3@Fe_3O_4$ Nanoparticles



The prepared catalyst was characterized using some instrumental techniques, such as XRD, SEM, TEM, TGA, and VSM. The XRD pattern of this catalyst is shown in Figure 1. In particular, seven characteristic peaks at 2*θ* equal 21.5°, 35.4°, 41.7°, 50.9°, 63.7°, 68.0°, and 75.1°, which correspond to the Miller indices values {*hkl*} of {111}, {220}, {311}, {400}, {422}, {511}, and {440}, respectively. The XRD pattern resembles that of Fe_3O_4 nanoparticles and no signal is observed from the $Fe(OH)_3$ phase, indicating that the $Fe(OH)_3$ compound is amorphous. Nanoparticles morphology was evaluated by SEM (Figure 2) and TEM (Figure 3) images. Core−shell structure and spherical in shape with a smooth surface morphology of the particles are clearly seen in these images. On the other hand, these images confirm that the particle size is below 40 nm. TGA recorded under nitrogen atmosphere for Fe_3O_4 (Figure 4A) and $Fe(OH)_3@Fe_3O_4$ MNPs (Figure 4B) determining this catalyst consisting 9.4 wt % of $Fe(OH)_3$ and 90.6 wt % of Fe_3O_4 (see Supporting Information). The magnetic feature of the catalyst was confirmed by vibrating sample magnetometry (VSM). Magnetizing (emu/g) as a function of applied field (Oe) is depicted in Figure 5. The magnetization curve demonstrate that these $Fe(OH)_3@Fe_3O_4$ nanoparticles (Possessed magnetic saturation

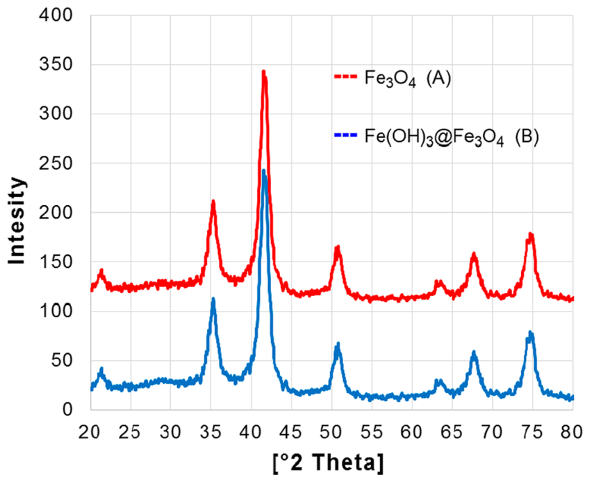


Figure 1. XRD pattern of Fe_3O_4 and $Fe(OH)_3@Fe_3O_4$.

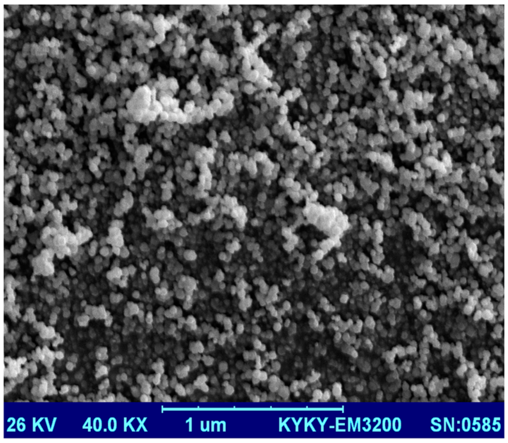


Figure 2. SEM image of the catalyst.

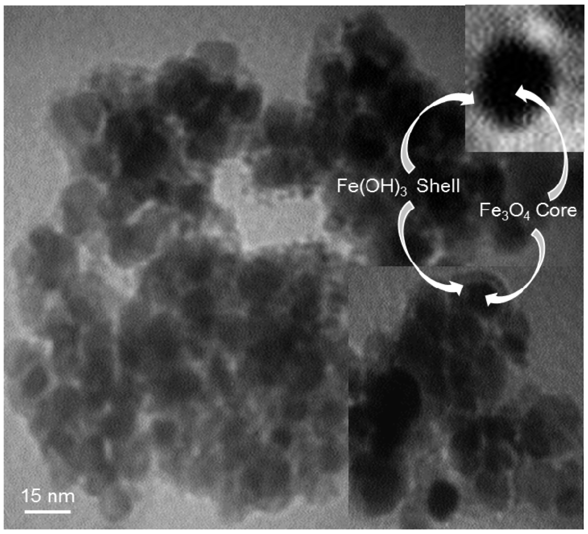


Figure 3. TEM image of the catalyst.

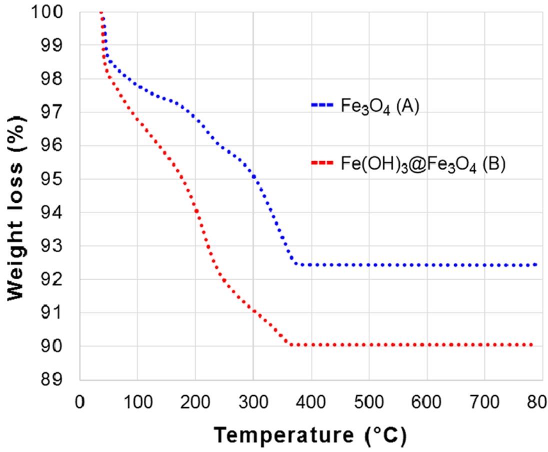


Figure 4. TGA results of Fe_3O_4 and $Fe(OH)_3@Fe_3O_4$.

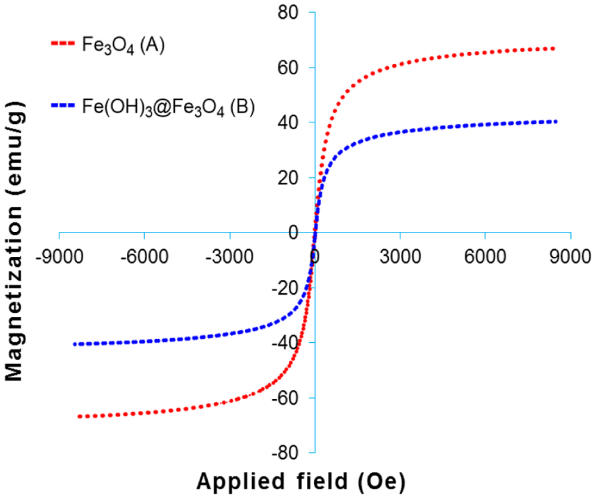


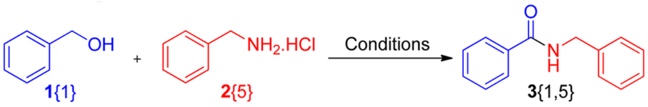
Figure 5. Magnetization curve of Fe_3O_4 and the catalyst.

(Ms) about 40.0 emu/g) have superparamagnetic properties which accounts for easy recovery of this catalyst.

The catalytic activity of $Fe(OH)_3@Fe_3O_4$ MNPs was tested in tandem oxidative amidation of alcohols with amine hydrochloride salts. Initially, the reaction of benzyl alcohol with benzylamine hydrochloride salt was tested as the model reaction under the following conditions: benzyl alcohol **1**{*1*} (0.5 mmol, 1 equiv), benzyl amine hydrochloride salt **2**{*5*} (0.75 mmol, 1.5 equiv), *t*-BuOOH (3.0 equiv), $CaCO_3$ (1.5 equiv), CH_3CN (1.0 mL), under Ar atmosphere at 25 °C. Under these conditions, after 6 h of reaction time, the corresponding product, *N*-benzylbenzamide **3**{*1,5*}, was formed in just 18% yield. To increase the yield of the product, various conditions were screened that the results are summarized in Table 1.

As shown in Table 1, raising the reaction temperature to 80 °C resulted in a drastic improvement in the yield (Table 1, entries 1−3). Increasing the temperature to 100 °C caused a significant decrease in the efficiency (Table 1, entry 4). We reasoned that the lower yields at higher temperatures could be due to the partial over oxidation of benzyl alcohol to benzoic acid as a side product. Screening the solvent indicated that acetonitrile is the best solvent among several others (Table 1, entries 5−7). Subsequently, the other oxidants (H_2O_2, *m*-CPBA, and UHP) did not give the results better than that of *t*-BuOOH (70 wt % in H_2O) (Table 1, entries 8−10). Meanwhile, the product was not observed in the absence of the oxidant (Table 1, entry 11). Other experiments were carried out to investigate the effect of the base on the reaction. Our study showed that lower yields are obtained when other bases such as Cs_2CO_3, K_2CO_3, and Na_2CO_3 are employed (Table 1, entries 12−14). Further study showed that the catalyst was essential for this transformation. In the absence of the catalyst only <5% of the amide product was formed (Table 1, entry 15). Finally, the effect of catalyst loading on efficiency was investigated and 20 mg per 0.5 mmol of benzyl alcohol was the best (Table 1, entries 16 and 17). In addition, the low efficiency of the reaction in the presence of Fe_3O_4 nanoparticles showed that iron ions, coated on the magnetic nanoparticles, plays a major role as catalyst (Table 1, entry 18). Therefore, the optimum conditions for this reaction were as follows: 20 mg of $Fe(OH)_3@Fe_3O_4$ at 80 °C with the respective acetonitrile as the solvent, $CaCO_3$ as the base and *t*-BuOOH as the oxidant.

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (mg)	oxidant	base	solvent	temp (°C)	yield (%)[b]
1	20	*t*-BuOOH	$CaCO_3$	CH_3CN	25	18
2	20	*t*-BuOOH	$CaCO_3$	CH_3CN	60	40
3	20	*t*-BuOOH	$CaCO_3$	CH_3CN	80	87
4	20	*t*-BuOOH	$CaCO_3$	CH_3CN	100	51
5	20	*t*-BuOOH	$CaCO_3$	DMF	80	10
6	20	*t*-BuOOH	$CaCO_3$	H_2O	80	35
7	20	*t*-BuOOH	$CaCO_3$	DMSO	80	42
8	20	*m*-CPBA[c]	$CaCO_3$	CH_3CN	80	<10
9	20	UHP[d]	$CaCO_3$	CH_3CN	80	<10
10	20	H_2O_2	$CaCO_3$	CH_3CN	80	28
11	20		$CaCO_3$	CH_3CN	80	
12	20	*t*-BuOOH	Cs_2CO_3	CH_3CN	80	43
13	20	*t*-BuOOH	K_2CO_3	CH_3CN	80	48
14	20	*t*-BuOOH	Na_2CO_3	CH_3CN	80	59
15		*t*-BuOOH	$CaCO_3$	CH_3CN	80	<5
16	30	*t*-BuOOH	$CaCO_3$	CH_3CN	80	87
17	15	*t*-BuOOH	$CaCO_3$	CH_3CN	80	38
18	20[e]	*t*-BuOOH	$CaCO_3$	CH_3CN	80	28

[a] Reaction conditions: benzyl alcohol **1**{*1*} (0.5 mmol, 1 equiv), benzyl amine hydrochloride salt **2**{*5*} (0.75 mmol, 1.5 equiv), oxidant (3 equiv), base (1.5 equiv), solvent (1 mL), under Ar atmosphere, 6 h. [b] Yield of the isolated product is based on the alcohol. [c] *meta*-Chloroperoxybenzoic acid. [d] Urea hydrogen peroxide. [e] 20 mg of Fe_3O_4 nanoparticles were used.

The above optimized protocol was extended to the direct oxidative amidation. So, various types of amine hydrochloride salts and alcohols were subjected to this reaction and wide range of primary, secondary and tertiary amides were synthesized in moderate to good yields (Table 2). The diversity of alcohols and various amine hydrochloride salts is depicted in Figures 6 and 7.

Generally speaking, electron-donating groups such as methoxy or methyl, on the benzyl alcohol, give the better yields than the electron with-drawing groups,such as bromo, chloro, fluoro,or nitro. Under the optimized conditions, a variety of aryl alcohols were reacted with ammonium hydrochloride salt and the corresponding primary amides were prepared in moderate to good yields (Table 2, entries 1−5). Heteroaromatic alcohols (e.g., furfuryl alcohol and thiophen-2-ylmethanol) were also efficiently transformed, affording the corresponding amides in moderate yields (Table 2, entries 6, 7, 20,and 32). To further establish the general utility of this transformation, we were encouraged to test the synthesis of secondary amides. As shown in Table 2, secondary amides were obtained in good yields under these conditions. The reaction is sensitive to steric hindrance as the reaction with *tert*-butylamine hydrochloride salt gave the corresponding amide in moderate yield (Table 2, entry 10). In the case of enantiomerically pure amines, according to chiral HPLC data (on products in Table 2, entries 12−14 and 15−20), no racemization was observed. The reaction is compatible with several functional groups such as alcohol (Table 2, entry 13), ester (Table 2, entry 14) and ether (Table 2, entries 27−32). Following the successful synthesis of primary and secondary amides with this heterogeneous catalytic system, we were

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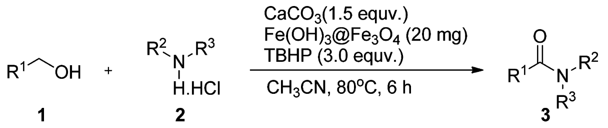
Table 2. Amide Bond Formation in the Presence of the $Fe(OH)_3@Fe_3O_4$ Catalyst[a]



entry	product	yield (%)[b]
1	3{*1,1*}	79
2	3{*2,1*}	49
3	3{*3,1*}	51
4	3{*5,1*}	71
5	3{*6,1*}	69
6	3{*9,1*}	52
7	3{*10,1*}	54
8	3{*1,2*}	89
9	3{*1,3*}	77
10	3{*1,4*}	49
11	3{*1,5*}	87
12	3{*1,6*}	89
13	3{*1,7*}	73
14	3{*1,8*}	65
15	3{*2,6*}	60
16	3{*3,6*}	59
17	3{*8,6*}	68
18	3{*5,6*}	87
19	3{*6,6*}	70
20	3{*9,6*}	57
21	3{*1,9*}	75
22	3{*1,11*}	64
23	3{*1,10*}	68
24	3{*1,12*}	80
25	3{*1,13*}	70
26	3{*1,14*}	68
27	3{*1,15*}	79
28	3{*7,15*}	72
29	3{*3,15*}	57
30	3{*8,15*}	65
31	3{*5,15*}	82
32	3{*9,15*}	55

[a] Reaction conditions: alcohol **1**{*1−10*}(0.5 mmol, 1 equiv), amine hydrochloride salt **2**{*1−15*} (0.75 mmol, 1.5 equiv), CH_3CN (1 mL), $CaCO_3$ (1.5 equiv), *t*-BuOOH (3 equiv), catalyst (20 mg), 80 °C, under Ar atmosphere, 6 h. [b] Isolated yields.

encouraged to extend the scope of this protocol to the formation of more challenging tertiary amides. Delightfully, various salts of secondary amines carried out this reaction and the corresponding tertiary amides obtained in good yields (Table 2, entries 21−32). Finally, several alkyl alcohols were employed as the substrates but their corresponding amides could not be detected.

On the basis of the results and literature reports,[13c,27] we propose a plausible free radical mechanism for this tandem reaction as shown in Scheme 2.

Initially, the aldehyde is generated from the alcohol in the presence of *tert*-butylperoxyl and *tert*-butoxyl radicals that can be formed from eqs 1 and 2, respectively (Scheme 3).[28]

Subsequently, this generated aldehyde can react with the free amine, obtained from the reaction of the amine salt with $CaCO_3$, to form hemiaminal intermediate (III).[24,29] The *tert*-butylperoxyl radical, formed by the Fe^{III}-*t*-BuOOH catalytic system, abstracts hydrogen from hemiaminal (III) to give intermediate (IV). Finally, hydrogen abstraction by *tert*-butoxyl radical leads to formation of the corresponding amide. Being radical reaction pathway was confirmed by adding free radical inhibitor, 2,4-di-*tert*-butyl-4-methylphenol to the reaction mixture and lack of product formation.

After establishing the activity and versatility of the $Fe(OH)_3@Fe_3O_4$ catalyst for synthesis of amides from alcohols and amine hydrochloride salts, the recyclability and reusability of it was tested in the preparation of compound **3**{*1,5*} under the optimized reaction conditions. After completion of the reaction, the catalyst was removed from the reaction mixture by simple decantation using an external magnet, washed with ethanol, dried at ambient temperature and reused for the next cycle. The catalyst recycled up to six times in this amidation reaction without any significant loss of its catalytic activity (Figure 8). The TEM and SEM images as well as XRD pattern of the reused catalyst showed that the morphology and size of the catalyst after recycling six times does not change significantly (see Supporting Information page S27).

■ CONCLUSIONS

In conclusion, we have demonstrated a novel protocol for the formation of amides in the presence of the cheap and magnetically separable $Fe(OH)_3@Fe_3O_4$ catalyst. This catalyst exhibited high catalytic activity for amide bond formation. By using this catalytic system, all types of amides (primary, secondary and tertiary amides) were obtained in moderate to good yields. Its advantages include a straightforward preparation, facile separation from the reaction medium and recyclability up to six times.

■ EXPERIMENTAL PROCEDURES

All experiments were carried out under argon. All chemicals and solvents were purchased from commercial suppliers and used without further purification. FT-IR spectra were obtained over the region 400−4000 cm^{-1} with a Nicolet IR100 FT-IR with spectroscopic grade KBr. The powder X-ray diffraction spectrum was recorded at room temperature using a Philips X-

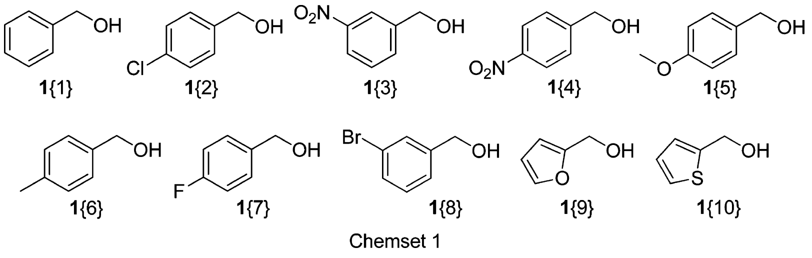


Figure 6. Diversity of alcohol **1**{*1−10*}.

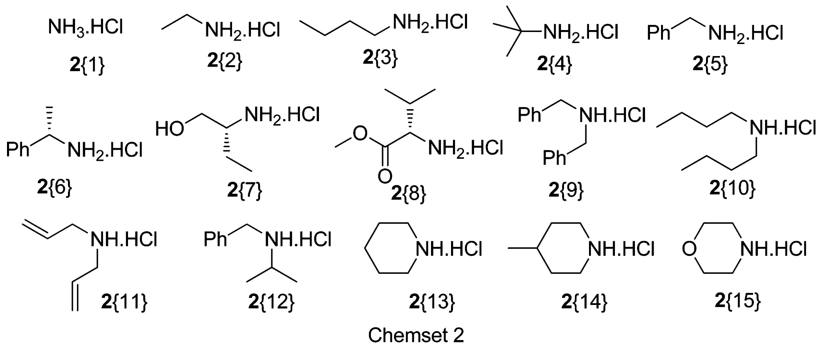
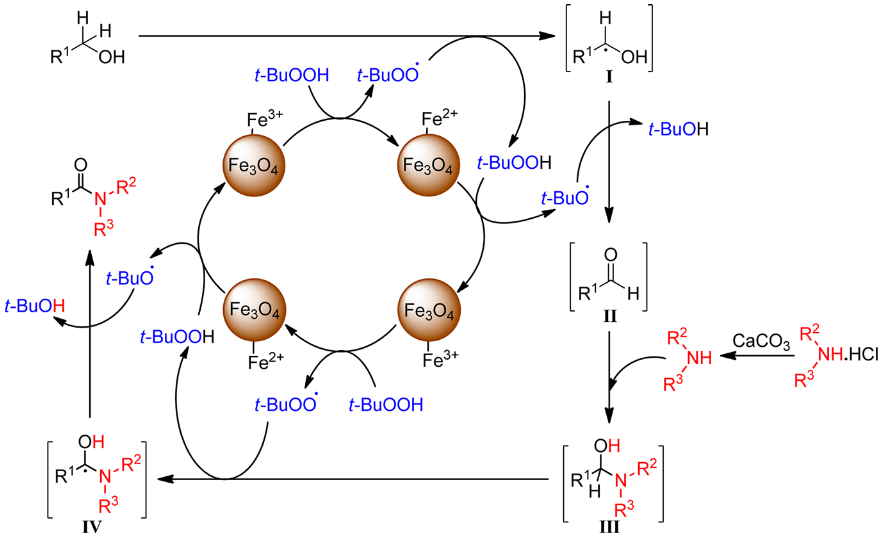


Figure 7. Diversity of amine hydrochloride salt **2**{*1*−*15*}.

Scheme 2. Proposed Mechanism for $Fe(OH)_3@Fe_3O_4$ Catalyzed Tandem Oxidative Amidation of Alcohols with Amine Hydrochloride Salts



Scheme 3. Decomposition of *t*-BuOOH Assisted by an Iron Compound

$$Fe^{3+} + t\text{-BuOOH} \longrightarrow Fe^{2+} + t\text{-BuOO}^{\bullet} + H^{+} \quad (1)$$

$$Fe^{2+} + t\text{-BuOOH} + H^{+} \longrightarrow Fe^{3+} + t\text{-BuO}^{\bullet} + H_2O \quad (2)$$

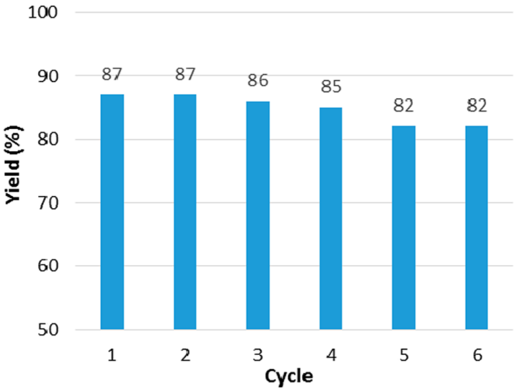


Figure 8. Recycling of the catalyst in the preparation of compound 3{*1*,*5*}.

Pert 1710 diffractometer with Co K*α* (*α* = 1.79285 Å) voltage: 40 kV, current: 40 mA and in the range 20°−80° (2*θ*) with a scan speed of 0.02°/s. The morphology of catalyst was studied with scanning electron microscopy using SEM (Philips XL 30 and S-4160) on gold coated samples. The magnetic properties of $Fe(OH)_3@Fe_3O_4$ were obtained by a vibrating magnetometer/Alternating Gradient Force Magnetometer (VSM/AGFM, MDK Co., Iran, www.mdk-magnetic.com). Transmission electron microscopy (TEM) were carried out at 120 kV (Philips model CM120). Thermal gravimetric analysis (TGA) was performed on a Thermal Analyzer with a heating rate of 20 °C min^{-1} over a temperature range of 25−1100 °C under flowing compressed N_2. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance (DPX 250 MHz and DRX 400 MHz) in pure deuterated $CDCl_3$ solvent with tetramethylsilane (TMS) as internal standard.

Catalyst Preparation. The nanosized $Fe(OH)_3@Fe_3O_4$ was synthesized via a modified procedure reported by Song et al.[30] The superparamagnetic catalyst was prepared by dissolving the mixture of 4 mmol $FeCl_3\cdot6H_2O$ and 2 mmol $FeCl_2\cdot4H_2O$ salts in 40 mL of deionized water under vigorous stirring. An ammonia solution (25% (w/w)) was added in dropwise manner over 5 min to the stirring mixture to maintain the reaction pH about 11. The resulting black dispersion was stirred vigorously for 1h at room temperature and then was refluxed for 1h. Fe_3O_4 nanoparticles were magnetically gathered and the residue was repeatedly washed with water and ethanol. Subsequently, as-prepared Fe_3O_4 nanoparticles and 15 mmol of $FeCl_3\cdot6H_2O$ were ultrasonically dispersed into 10 mL of ethanol. After totally dissolution and dispersion, the nanoparticles were separated from the ethanol solution by magnetic decantation and dried at 80 °C for 4h. $Fe(OH)_3@Fe_3O_4$ nanoparticles were obtained by dropwise addition of aqueous ammonia (25% (w/w), 5 mL) to the dried brown nanoparticles under vigorous stirring. Finally, the products of $Fe(OH)_3@Fe_3O_4$ were magnetically separated, washed with water, and dried in an oven at 373 K overnight for further usage.

General Procedure for the Direct Amidation of Alcohols with Amine Hydrochloride Salts. To a mixture of catalyst (20 mg, 3.5 mol %), amine hydrochloride salt (0.75 mmol, 1.5 equiv) and $CaCO_3$ (75.1 mg, 1.5 equiv) in CH_3CN (1 mL) were added alcohol (0.5 mmol, 1 equiv), and *t*-BuOOH (70 wt % in H_2O, 3 equiv) under argon atmosphere. The mixture was stirred at 80 °C for 6 h. After completion, the reaction mixture was allowed to cool to room temperature. It was then diluted with EtOAc and the catalyst was separated with an external magnet and washing twice with EtOAc. The mixture was extracted with EtOAc, the volatiles were removed under reduced pressure, and the crude product was purified by column chromatography to afford the desired product.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, ^1H NMR, ^{13}C NMR, and mass spectra, and chiral HPLC data of selected amides. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/co5001844.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: heydar_a@modares.ac.ir. Fax: (+98)-21-82883455. Phone: (+98)-21-82883444.

Notes

The authors declare no competing financial interest.

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