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# Aerobic oxidation of secondary alcohols using NHPI and iron salt as catalysts at room temperature



Hanqing Zhao<sup>a</sup>, Wei Sun<sup>b</sup>, Chengxia Miao<sup>b,\*</sup>, Quanyi Zhao<sup>a,\*</sup>

<sup>a</sup> School of Pharmacy, Lanzhou University, Lanzhou 730000, People's Republic of China

<sup>b</sup> State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, People's Republic of China

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# ABSTRACT

Aerobic oxidation of various alcohols has been accomplished by using a novel catalytic system, *N*-hydroxyphthalimide (NHPI) combined with  $Fe(NO_3)_3$ ·9H<sub>2</sub>O. Secondary alcohols, especially benzylic and aliphatic alcohols, were smoothly transformed into corresponding ketones with up to 92% yields at room temperature under one atmosphere pressure of oxygen. The influences of reaction conditions such as solvent, different metal catalyst, catalyst loading and the structure of alcohols on the promotion effect were studied. And a possible radical mechanism for the oxidation of secondary alcohols in  $Fe(NO_3)_3$ ·9H<sub>2</sub>O/NHPI/O<sub>2</sub> system was proposed.

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# 1. Introduction

The selective oxidation of alcohols into their corresponding carbonyl compounds is a frequently used transformation in organic synthesis [1–5], and most of the resulting carbonyl compounds are important synthetic intermediates in chemicals and pharmaceuticals [6,7], hence many scientists tried their best to develop a wide variety of methods for oxidation of alcohols. Traditional oxidants mainly include permanganate [8], manganese (IV) oxide [9,10], chromium (VI) oxide [11], and ruthenium reagents [12,13]. In general, these oxidants are needed at least a stoichiometric amount and usually bring about noxious byproducts. Therefore, oxygen as clean oxidant for the selective oxidation of alcohols to carbonyl compounds under mild conditions is more attractive since the main by-product is water [14–16]. And NHPI is recognized as one of powerful catalysts for aerobic oxidation of various organic compounds [17–22].

Up to now, very few catalytic systems have more advantages than using NHPI for the oxidation of alcohols with  $O_2$  as terminal oxidant [23–26], thus, either from the viewpoint of green or sustainable chemistry, developing a highly efficient catalytic system based on NHPI is very interesting and valuable. However, because oxygen molecule cannot be activated directly by NHPI in the absence of co-catalyst at room temperature, a co-catalyst is required for this catalytic reaction. Iron has a number of advantages over other transition metals for it's relatively non-toxic, cheap and environmentally friendly [27], and iron-based catalyst systems have been applied in a variety of organic transformations [28–36], especially in some oxidation reactions using oxygen as oxidant [37–39]. Therefore, we supposed iron salts have a potential as good co-catalysts in NHPI catalytic system and applied NHPI and iron salts as the catalytic system to the oxidation of alcohols. As we expected, a series of secondary aliphatic and aromatic alcohols were smoothly converted to corresponding ketones at room temperature under an atmosphere pressure of oxygen (Scheme 1).

# 2. Experimental

# 2.1. General remarks

All starting materials and catalysts were purchased from commercial suppliers and used without further purification. Column chromatography was generally performed on silica gel (200–300 mesh) and TLC inspections were on silica gel GF254 plates.

GC–MS spectra were recorded on an Agilent Technologies 7890A GC-system with an Agilent 5975 inert Mass Selective Detector (EI) and a HP-5MS column (0.25 mm  $\times$  30 m, Film: 0.25  $\mu$ m). <sup>1</sup>H NMR and  $^{13}$ C NMR spectra were recorded on a Bruker spectrometer 400 MHz using CDCl<sub>3</sub> as the solvent with TMS as an internal reference.

<sup>\*</sup> Corresponding authors. Tel.: +86 931 8915686; fax: +86 931 8915686. E-mail addresses: chxmiao@licp.cas.cn (C. Miao), zhaoqy@lzu.edu.cn (Q. Zhao).



Scheme 1. Oxidation of secondary alcohols into corresponding ketones at room temperature in the presence of Fe(NO<sub>3</sub>)<sub>3</sub>.9H<sub>2</sub>O and NHPI under an atmosphere pressure of oxygen.

# 2.2. General procedure of oxidation of secondary alcohols

Substrate (1 mmol) and the desired amounts of  $Fe(NO_3)_3 \cdot 9H_2O$ and NHPI were added to 1.5 mL of acetonitrile in a 15 mL test tube. The solution was maintained for 20 h under an atmospheric pressure of  $O_2$  and at 25 °C. After the reaction was quenched by  $Na_2S_2O_3$ solution, 60 mg of nitrobenzene, serving as an internal standard, was added to the reaction system. The solution was centrifuged and the supernatant was diluted with diethyl ether and dried with anhydrous  $Na_2SO_4$  for 30 min. The products were analyzed by GC, and further confirmed by GC–MS. The isolated yield was obtained through column chromatography generally performed on silica gel (200–300 mesh).

# 3. Results and discussion

#### 3.1. Influence of metal salts

The exploratory experiments were started by testing this protocol and screening the metal salts using  $\alpha$ -phenylethanol as the model substrate in the presence of NHPI (10 mol%) under the identical conditions (Table 1). Initially, a variety of iron salts were used and their reaction activities were evaluated. We found only Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O as co-catalyst could obtain high conversion and selectivity (Table 1, entry 8), other iron salts were almost inert for the reaction (Table 1, entries 1–7); moreover, Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O, NHPI and oxygen were essential to the aerobic

Table 1

Screening of metal salt as catalyst for the oxidation of  $\alpha$ -phenylethanol.<sup>a</sup>

Entry	Metal salt	Conv. (%) <sup>b</sup>	Yield (%) <sup>b</sup>
1	K <sub>4</sub> [Fe(CN) <sub>6</sub> ]·3H <sub>2</sub> O	NR <sup>c</sup>	-
2	$K_3[Fe(CN)_6]$	NR <sup>c</sup>	-
3	$Fe_2(SO_4)_3 \cdot XH_2O$	NR <sup>c</sup>	-
4	FeCl <sub>2</sub> ·4H <sub>2</sub> O	NR <sup>c</sup>	-
5	FeCl <sub>2</sub>	NR <sup>c</sup>	-
6	FeCl <sub>3</sub>	6	-
7	Fe(OTf) <sub>2</sub>	9	8
8	Fe(NO <sub>3</sub> ) <sub>3</sub> .9H <sub>2</sub> O	84	83
9	-	NR <sup>c</sup>	-
10 <sup>d</sup>	$Fe(NO_3)_3 \cdot 9H_2O$	20	19
11 <sup>e</sup>	$Fe(NO_3)_3 \cdot 9H_2O$	NR <sup>c</sup>	-
12	$Co(NO_3)_2 \cdot 6H_2O$	6	6
13	$Cu(NO_3)_2 \cdot 3H_2O$	39	39
14	$Zr(NO_3)_4 \cdot 5H_2O$	56	55
15	$Mg(NO_3)_2 \cdot 6H_2O$	NR <sup>c</sup>	-
16	$Ni(NO_3)_2 \cdot 6H_2O$	NR <sup>c</sup>	-
17	$Zn(NO_3)_2 \cdot 6H_2O$	NR <sup>c</sup>	-
18	$Al(NO_3)_3 \cdot 9H_2O$	Trace	Trace
19	$In(NO_3)_3 \cdot 5H_2O$	Trace	Trace

 $^a$   $\alpha-Phenylethanol$  (1 mmol), metal salt (5 mol%), NHPI (10 mol%), acetonitrile (1.5 mL),  $O_2$  (1 atm), room temperature, 20 h.

<sup>b</sup> Determined by GC using nitrobenzene as an internal standard.

<sup>c</sup> NR = No reaction.

<sup>d</sup> Under dinitrogen atmosphere.

e Without NHPI.

oxidation of  $\alpha$ -phenylethanol (Table 1, entries 9–11). Obtaining 19% of acetophenone under dinitrogen atmosphere may ascribe to the oxidation of  $Fe(NO_3)_3 \cdot 9H_2O$  [40]. The results suggested that the anions of iron salts had a great effect on the oxidation of  $\alpha$ -phenylethanol. That's to say, nitrate ion may play an important role in the oxidation. Subsequently, a series of nitrates were investigated to test whether the metal cation also had certain effect for the reaction (Table 1, entries 12-19). The results showed Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O and Zr(NO<sub>3</sub>)<sub>4</sub>·5H<sub>2</sub>O could give 39% and 55% yields respectively (Table 1, entries 13 and 14). As for Co(NO<sub>3</sub>)<sub>2</sub>.6H<sub>2</sub>O, only 6% yield was provided (Table 1, entry 12), and for other nitrates, no products were detected (Table 1, entries 15–19). The results indicated that metal cation also has some influence on the reaction. Among tested metal salts, Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O exhibited best activity. Maybe, this good performance is attributed to the synergistic effect between iron cation and nitrate anion.

#### 3.2. Influence of different solvent

The effect of the solvents on the oxidation of alcohols was also evaluated (Table 2). It is clear that the solvent has an important effect on the reaction. Under the same condition, the conversion of  $\alpha$ -phenylethanol to acetophenone was achieved in higher yield in acetonitrile compared to other solvents such as DMSO, THF, dichloroethane, and toluene and so on (Table 2, entry 1 vs entries 2–7).

# 3.3. Influence of the amount of $Fe(NO_3)_3 \cdot 9H_2O$ and NHPI

Subsequently, the influence of the amount of  $Fe(NO_3)_3 \cdot 9H_2O$ and NHPI on the oxidation was examined under the identical reaction conditions, as listed in Table 3. The yield of acetophenone was 14% in the presence of 0.5 mol%  $Fe(NO_3)_3 \cdot 9H_2O$  and 5 mol% NHPI (Table 3, entry 5). And the yield increased to 75% when the amount of  $Fe(NO_3)_3 \cdot 9H_2O$  reached to 5 mol% (Table 3, entries 2–4), but there was almost no change by further increasing  $Fe(NO_3)_3 \cdot 9H_2O$ to 8 mol% (Table 3, entry 1). Therefore, 5 mol% of  $Fe(NO_3)_3 \cdot 9H_2O$ is a desired catalyst loading. Based on that, the desired loading amount of the NHPI was investigated also (Table 3, entries 6–10).

Table 2	
Solvent op	timizatior

Entry	Solvent	Conv. (%) <sup>b</sup>	Yield (%) <sup>b</sup>
1	Acetonitrile	84	83
2	CH <sub>2</sub> Cl <sub>2</sub>	38	38
3	ClCH <sub>2</sub> CH <sub>2</sub> Cl	7	7
4	THF	13	13
5	DMSO	NR <sup>c</sup>	-
6	H <sub>2</sub> O	NR <sup>c</sup>	-
7	Toluene	NR <sup>c</sup>	-

<sup>a</sup>  $\alpha$ -Phenylethanol (1 mmol), Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O (5 mol%), NHPI (10 mol%), solvent (1.5 mL), O<sub>2</sub> (1 atm), room temperature, 20 h.

<sup>b</sup> Determined by GC using nitrobenzene as an internal standard.

<sup>c</sup> NR = No reaction.

# Table 3

The influence of the amount of  $\text{Fe}(\text{NO}_3)_3.9\text{H}_2\text{O}$  and NHPI on the oxidation of  $\alpha\text{-phenylethanol.}^a$ 

Entry	$Fe(NO_3)_3{\cdot}9H_2O(mol\%)$	NHPI (mol%)	Conv. (%) <sup>b</sup>	Yield (%) <sup>b</sup>
1	8	5	77	76
2	5	5	76	75
3	2	5	53	53
4	1	5	27	27
5	0.5	5	14	14
6	5	12	89	86
7	5	10	84	83
8	5	5	76	75
9	5	2	64	63
10	5	1	48	48

 $^a\,$   $\alpha-Phenylethanol\,(1$  mmol),  $O_2\,(1$  atm), acetonitrile (1.5 mL), room temperature, 20 h.

<sup>b</sup> Determined by GC using nitrobenzene as an internal standard.

Good performance was shown with 10 mol% of NHPI (Table 3, entry 7).

# 3.4. Aerobic oxidation of various secondary alcohols catalyzed by *Fe*(NO<sub>3</sub>)<sub>3</sub>.9H<sub>2</sub>O and NHPI

In order to survey the scope of the substrates, we applied the present catalyst system to a variety of secondary alcohols as

#### Table 4

Oxidation of secondary benzylic alcohols.<sup>a</sup>

tabulated in Tables 4 and 5. Obviously, all secondary benzylic alcohols were converted into corresponding ketones in moderate to high yields, and aliphatic secondary alcohols gave moderate yields; as for decan-4-ol, only 17% yield was obtained (Tables 4 and 5). The different rates probably have some relationships with the inductive effects and steric effects of the substituents. But for an identical substituent at different site on the benzene rings, the substituent group on benzene ring is more away from the alcohol hydroxyl, the yield is higher (Table 4, entries 2 and 3, 4 and 5, 6 and 7, 8 and 9). The hydroxyl of aliphatic secondary alcohols is closer terminal of the carbon chain, they are oxidized easier (Table 5, entries 1 and 2).

As for the reaction mechanism, it was recognized that PINO radical generated *in situ* plays an important role in NHPI participant system [41]. In order to prove this point, the reaction was carried out with  $\alpha$ -phenylethanol as the substrate under optimized reaction conditions. 1,1-Diphenylethylene, which acts as a radical scavenger [42], was added to the reaction system. When 10 mol% of 1,1-diphenylethylene was used, the yield of the reaction decreased from 84% to 47%. And it was shown that the reaction was inhibited completely by adding 50 mol% of 1,1-diphenylethylene (Scheme 2). The phenomena indicated that the mechanism of the reaction should proceed by a free-radical pathway and PINO radical is still a key intermediate.

At present, it is not easy to show how  $Fe(NO_3)_3 \cdot 9H_2O$  works in the process of generation of PINO radical. However, according to the above results, we speculate that there is a synergistic effect



#### Table 4 (Continued)



<sup>a</sup> Alcohol (1 mmol), NHPI (10 mol%), Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O (5 mol%), acetonitrile (1.5 mL), O<sub>2</sub> (1 atm), at room temperature, 48 h.

<sup>b</sup> Isolated yield.

<sup>c</sup> Determined by GC using nitrobenzene as an internal standard.

between iron cation and nitrate anion. In addition, we considered that the Fe<sup>3+</sup> can be converted into Fe<sup>2+</sup> in the process of reaction. In order to confirm metal chemical state,  $K_3$ [Fe(CN)<sub>6</sub>] solution was added to the reaction system after the reaction lasts for ten hours. The solution turned to Prussian blue from brownish yellow, which indicates the generation of Fe<sup>2+</sup> during the reaction [43].

Based on the previous reports and our aforementioned results, we propose a possible mechanism delineated in Scheme 3. Initially, PINO radical is generated from NHPI in the presence of  $Fe(NO_3)_3 \cdot 9H_2O$  and  $O_2$ , then the PINO radical abstracts the hydrogen atom from  $\alpha$ -phenylethanol to produce  $\alpha$ -hydroxy carbon radical and regenerate NHPI. And then  $\alpha$ -hydroxy carbon radical

# Table 5

Oxidation of secondary aliphatic alcohols.<sup>a</sup>



 $^{a}$  Alcohol (1 mmol), NHPI (10 mol%), Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O (5 mol%), O<sub>2</sub> (1 atm), acetonitrile (1.5 mL), at room temperature, 48 h.

<sup>b</sup> Determined by GC using nitrobenzene as an internal standard.



Scheme 2. The effect of 1,1-diphenylethylene on generation of acetophenone.



Scheme 3. Proposed mechanism of  $\alpha$ -phenylethanol oxidation catalyzed by NHPI/Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O with O<sub>2</sub>.

is transformed into a peroxy radical by O<sub>2</sub>. Finally, it is converted into acetophenone and H<sub>2</sub>O<sub>2</sub> through the formation of  $\alpha$ -hydroxy hydroperoxide [23,44]. Besides, hydrogen peroxide could also oxidize the alcohols to carbonyl compounds under the help of NHPI and Fe(NO<sub>3</sub>)<sub>3</sub>.9H<sub>2</sub>O [45].

# 4. Conclusions

We have developed a novel catalytic system, including NHPI and  $Fe(NO_3)_3 \cdot 9H_2O$ , for the aerobic oxidation of alcohols at room temperature in the presence of 1 atm  $O_2$ . Various secondary benzilic and aliphatic alcohols which are insusceptible to be oxidized by NHPI alone could be oxidized to the corresponding carbonyl compounds in satisfactory yields in this catalytic system. And a radical mechanism involving PINO was proposed based on the previous report and our results and more investigations for the proposed mechanism are under the way in our laboratory. We anticipate that this protocol will be of broad interest and use to the chemical industries.

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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. 2014.06.007.

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- [45] α-Phenylethanol (1 mmol) was reacted with Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O (5 mol%), NHPI (10 mol%) and H<sub>2</sub>O<sub>2</sub> (2 mmol) in 1.5 mL acetonitrile under N<sub>2</sub> at room temperature for 48 h. The GC analysis showed that conversion of α-phenylethanol was 66% and yield of acetophenone was 64%.