# NHPI and Ferric Nitrate: A Mild and Selective System for Aerobic Oxidation of Benzylic Methylenes

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# NHPI and Ferric Nitrate: A Mild and Selective System for Aerobic Oxidation of Benzylic Methylenes

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A mild and selective system comprising *N*-hydroxyphthalimide (NHPI) and $Fe(NO_3)_3\cdot 9H_2O$ was developed for oxidation of benzylic methylenes with an atmospheric pressure of molecular oxygen at 25 °C. The influences of reaction conditions such as solvent, different metal catalyst and catalyst loading were studied, as well as the kinetics of the oxidation reaction. Various benzylic methylene substrates could be oxidized to the corresponding carbonyl compounds in satisfactory yields with this catalytic system. Hammett analysis suggested that the substrates with electron-donating groups would have higher oxidation rates. Isotopic ($^{18}O$) labeling experiments provided evidence of the participation of nitrate anion in the catalytic cycle. And a possible radical mechanism involving PINO (phthalimide-*N*-oxyl) abstracting the hydrogen atom and nitrate participation for the oxidation of benzylic methylenes in $Fe(NO_3)_3\cdot 9H_2O$/NHPI/$O_2$ system was proposed.

## Introduction

The direct functionalization of C-H bonds is a long-lasting challenge in modern organic chemistry.[1] Among them, oxidation of C-H bonds is one of the most efficient methods to construct carbonyl compounds.[2] Traditionally, a stoichiometric amount of hazardous oxidant such as manganese dioxide, potassium dichromate or chromic acid was employed for these transformations, generally generating large amounts of wastes and unwanted by-products.[3] Molecular oxygen is a convenient and green oxidant for catalytic chemistry due to its economic and environmentally benign features.[4] However, $O_2$ is a relatively unreactive oxidant toward the oxidation of inert C-H bonds. Therefore, the direct oxidation of C-H bonds with molecular oxygen as the oxidant is still regarded as one of the main challenges.[5] To overcome this impediment, various catalysts have been applied to oxygen activation and subsequent C-H bonds oxidation.[6] In recent years, NHPI (*N*-hydroxyphthalimide) has been recognized as a valuable catalyst for the activation of C-H bond via hydrogen abstraction by intermediate PINO radical.[7] And the formation of the PINO radicals from its precursor NHPI can be achieved by using various mediators with oxygen as the oxidant, including anthraquinone derivatives, 2,2'-azobisisobutyronitrile (AIBN), oximes, aldehyde, $HNO_3$, quaternary ammonium salts, bromine and transition metal salts and so on.[8-14] In spite of the impressive progress made in this area, the oxidation using molecular oxygen as the oxidant at mild conditions is still difficult and the reaction usually occurs under high temperature to overcome the high activation barriers. And oxygen at higher temperature, which exists as diradical in the ground state, takes part preferably in nonselective radical reactions. So low temperature may be benefit for the selectivity of the reaction. However, there are only few reports for achieving oxidation of C-H bond involving NHPI as catalyst under low temperature. Initially, Ishii and co-workers successfully converted alkylbenzenes into the corresponding carboxylic acids under atmospheric dioxygen at ambient temperature using NHPI and $Co(OAc)_2$ system in 1997.[15] In addition, Einhorn also reported an efficient system for aerobic oxidation of benzylic compounds catalyzed by *N*-hydroxy-3,4,5,6-tetra-phenylphthalimide (NHTPPI) and CuCl at 35 °C.[16] On the other hand, iron is relatively non-toxic, cheap and environmentally friendly and iron-based catalyst systems have been applied in a variety of organic transformations.[17] Although NHPI combined with iron salts has also been used in various oxidations, such as oxidation of alcohols, oxidative coupling of NHPI with toluene, and oxidation of indane in aqueous media and so on, $H_2O_2$ was used as the oxidant in some systems. The detailed research on the substrate scope, kinetics and mechanism of aerobic oxidation for benzylic C-H bond has not been reported.[18] Our continued efforts in oxidation promoted us to study in detail to use iron salts as the mediator for the transformation of NHPI to PINO, which continued to achieve the aerobic oxidation of benzylic C-H bond under mild conditions.[19] Delightedly, NHPI combined with $Fe(NO_3)_3\cdot 9H_2O$ successfully realized aerobic oxidation of benzylic methylenes to corresponding carbonyl compounds at 25 °C with an atmospheric pressure of molecular oxygen, giving moderate to high yields (Scheme 1).

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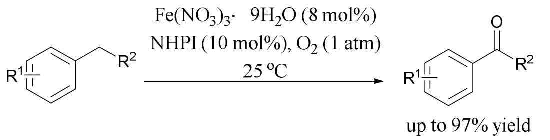


**Scheme 1** Aerobic oxidation of benzylic methylenes.

## Results and discussion

Our study commenced with the oxidation of diphenylmethane as the model substrate in the presence of NHPI (5 mol%) at 25 °C with an atmosphere pressure of molecular oxygen, and the screening of different parameters was summarized in Table 1. Initially, the activities of a variety of iron salts were evaluated (Table 1, entries 1-5). Only $Fe(NO_3)_3{\cdot}9H_2O$ as co-catalyst gave moderate conversion and good selectivity (Table 1, entry 5). Further experiments indicated $Fe(NO_3)_3{\cdot}9H_2O$ and NHPI were essential to the aerobic oxidation of diphenylmethane (Table 1, entries 6 and 7). The results also suggested that the anions of iron salts had a great effect on the oxidation of diphenylmethane. Subsequently, a series of nitrates were also investigated to test whether there was certain relationship between the metal cation and the reaction activity (Table 1, entries 8-15). Unfortunately, most of the other nitrates were inert for the oxidation reaction and the substrate almost recovered (Table 1, entries 9-15). Only in the case of $Cu(NO_3)_2{\cdot}3H_2O$ as the co-catalyst resulted in the ketone in a 31% yield (Table 1, entry 8). Besides, the effect of the solvents on the oxidation was also evaluated (Table 1, entries 5 and 16-20). It was indicated that acetonitrile as solvent exhibited better catalytic activity compared to other solvents such as DMSO, dichloromethane, toluene and so on (Table 1, entry 5), perhaps for the retard of the side reaction, such as nitration.[20] Taken together, it is the combination of $Fe(NO_3)_3$ and NHPI that is necessary to efficiently catalyze the benzylic methylene oxidation.

**Table 1** Screening of metal salts and solvents for the aerobic oxidation of diphenylmethane[a]

| Entry | Metal salt | Solvent | Conv. (%)[b] | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $K_3[Fe(CN)_6]$ | $CH_3CN$ | NR[c] | - |
| 2 | $Fe_2(SO_4)_3{\cdot}9H_2O$ | $CH_3CN$ | 3 | trace |
| 3 | $FeCl_2{\cdot}4H_2O$ | $CH_3CN$ | NR[c] | - |
| 4 | $FeCl_3{\cdot}6H_2O$ | $CH_3CN$ | 28 | 24 |
| 5 | $Fe(NO_3)_3{\cdot}9H_2O$ | $CH_3CN$ | 74 | 73 |
| 6 | - | $CH_3CN$ | NR[c] | - |
| 7[d] | $Fe(NO_3)_3{\cdot}9H_2O$ | $CH_3CN$ | NR[c] | - |
| 8 | $Cu(NO_3)_2{\cdot}3H_2O$ | $CH_3CN$ | 34 | 31 |
| 9 | $Zr(NO_3)_4{\cdot}5H_2O$ | $CH_3CN$ | 6 | 3 |
| 10 | $Al(NO_3)_3{\cdot}9H_2O$ | $CH_3CN$ | 7 | 4 |
| 11 | $Co(NO_3)_2{\cdot}6H_2O$ | $CH_3CN$ | 5 | trace |
| 12 | $Mg(NO_3)_2{\cdot}6H_2O$ | $CH_3CN$ | 4 | trace |
| 13 | $Ni(NO_3)_2{\cdot}6H_2O$ | $CH_3CN$ | 4 | trace |
| 14 | $Zn(NO_3)_2{\cdot}6H_2O$ | $CH_3CN$ | 3 | trace |
| 15 | $In(NO_3)_3{\cdot}5H_2O$ | $CH_3CN$ | 4 | trace |
| 16 | $Fe(NO_3)_3{\cdot}9H_2O$ | $CH_2Cl_2$ | 9 | 4 |
| 17 | $Fe(NO_3)_3{\cdot}9H_2O$ | ethyl acetate | 25 | 22 |
| 18 | $Fe(NO_3)_3{\cdot}9H_2O$ | Dimethyl sulphoxide | NR[c] | - |
| 19 | $Fe(NO_3)_3{\cdot}9H_2O$ | $H_2O$ | NR[c] | - |
| 20 | $Fe(NO_3)_3{\cdot}9H_2O$ | toluene | NR[c] | - |

[a] Reaction conditions: diphenylmethane (1 mmol), metal salt (5 mol%), NHPI (5 mol%), acetonitrile (1.5 mL), $O_2$ (1 atm), 25 °C, 40 h. [b] Determined by GC using biphenyl as an internal standard. [c] NR = No reaction. [d] Without NHPI.

Additionally, the dosage of $Fe(NO_3)_3{\cdot}9H_2O$ and NHPI was further examined at 25 °C with an atmosphere pressure of molecular oxygen as the oxidant, as listed in Table 2. In the presence of 5 mol% $Fe(NO_3)_3{\cdot}9H_2O$ and 2 mol% NHPI, only 23% yield was obtained (Table 2, entry 1). The yield increased to 72% when the amount of NHPI reached to 10 mol% (Table 2, entry 3), but almost no change was observed by further increasing NHPI to 12 mol% (Table 2, entry 4). Therefore, 10 mol% of NHPI is considered as the desired catalyst loading. Further studies indicated that good result was obtained with 8 mol% of $Fe(NO_3)_3{\cdot}9H_2O$ (Table 2, entries 3, 5 and 6).

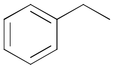
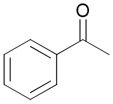
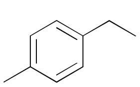
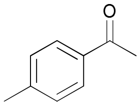
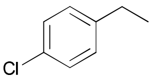
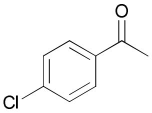
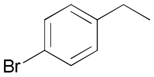
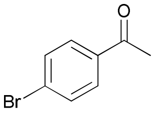
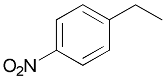
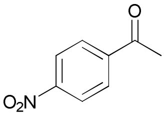
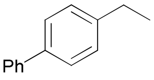
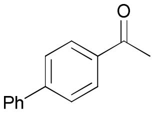
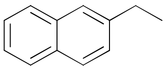
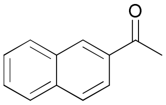
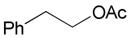
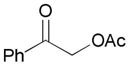
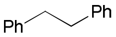
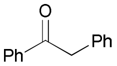
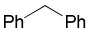
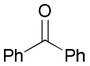
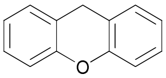
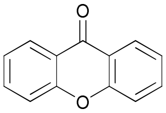
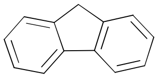
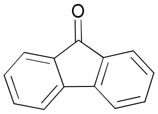
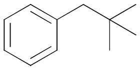
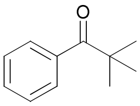
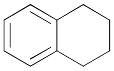
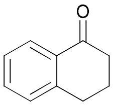
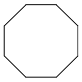
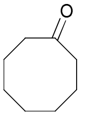
**Table 2** The influence of the dosage of $Fe(NO_3)_3{\cdot}9H_2O$ and NHPI on aerobic oxidation of diphenylmethane[a]

| Entry | $Fe(NO_3)_3{\cdot}9H_2O$ (mol%) | NHPI (mol%) | Conv. (%)[b] | Yield (%)[b] |
|---|---|---|---|---|
| 1 | 5 | 2 | 27 | 23 |
| 2 | 5 | 8 | 63 | 60 |
| 3 | 5 | 10 | 74 | 72 |
| 4 | 5 | 12 | 77 | 73 |
| 5 | 8 | 10 | 84 | 84 |
| 6 | 10 | 10 | 86 | 85 |

[a] Reaction conditions: diphenylmethane (1 mmol), $O_2$ (1 atm), acetonitrile (1.5 mL), 25 °C, 40 h. [b] Determined by GC using biphenyl as an internal standard.

With a set of optimized conditions in hand, the scope of the substrates with methylene was investigated and the results were tabulated in Table 3. First, a variety of ethylbenzene derivatives containing different substituted groups on the aromatic ring were subjected to the oxidation system with NHPI and $Fe(NO_3)_3{\cdot}9H_2O$ as the catalysts. The results demonstrated that all the tested ethylbenzene derivatives could be oxidized to the desired ketones in moderate to good yields (Table 3, entries 1-8). For example, the oxidation of 4-ethylbiphenyl provided an 83% yield under optimized conditions (Table 3, entry 7). However, ethylbenzene derivatives bearing OAc or Ph on the methyl group only gave 23% and 24% yields respectively (Table 3, entries 9 and 10). Notably, diphenylmethane, 9H-xanthene and 9H-fluorene demonstrated excellent reactivities, providing 84% to 97% yields (Table 3, entries 11-13). In the case of oxidation of neopentylbenzene, the reaction did not take place, perhaps due to the steric hindrance of tertiary butyl (Table 3, entry 14). In addition, tetrahydronaphthalene was oxidized to corresponding ketone in a 50% yield (Table 3, entry 15). Non-activated substrate was also tested, 14% yield of cyclooctanone was observed for the oxidation of cyclooctane

**Table 3** Selectively aerobic oxidation of C-H bonds of various methylenes by NHPI and $Fe(NO_3)_3{\cdot}9H_2O^a$

| Entry | Substrate | Product | Yield(%)$^b$ |
|---|---|---|---|
| 1 |  |  | 70$^c$ |
| 2 |  |  | 79$^c$ |
| 3$^d$ | | | 57$^c$ |
| 4 |  |  | 63$^c$ |
| 5 |  |  | 60$^c$ |
| 6 |  |  | 54$^c$ |
| 7 |  |  | 83 |
| 8 |  |  | 51 |
| 9 |  |  | 23 |
| 10 |  |  | 24 |
| 11 |  |  | 84$^c$ |
| 12 |  |  | 97 |
| 13 |  |  | 90 |
| 14 |  |  | trace |
| 15 |  |  | 50 |
| 16 |  |  | 14$^c$ |

[a] Reaction conditions: substrate (1 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (8 mol%), NHPI (10 mol%), acetonitrile (1.5 mL), $O_2$ (1 atm), 25 °C, 40 h. [b] Isolated yield. [c] Determined by GC using biphenyl as an internal standard. [d] t = 20 h.

catalyzed by $Fe(NO_3)_3{\cdot}9H_2O$/NHPI system (Table 3, entry 16). Additionally, we compared the reaction outcomes catalyzed by $Fe(NO_3)_3{\cdot}9H_2O$/NHPI system with that of NHPI/$Co(OAc)_2$ system developed by Ishii in 1997.[15] Obviously, the dosage of $Co(OAc)_2$ in Ishii's system was very low. The present $Fe(NO_3)_3{\cdot}9H_2O$/NHPI system showed higher selectivity for the production of ketone (Ishii system, 12% and 17% alcohol as by-product with 47% and 31% ketone respectively).

Furthermore, we studied the kinetics of the oxidation and wanted to get some hints for the possible mechanism. Fig. 1 presented the kinetic curves of benzophenone accumulation over reaction time under the optimized experimental conditions. The results also indicated that the rate was quick during initial 7 h, then the reaction rate reduced gradually.

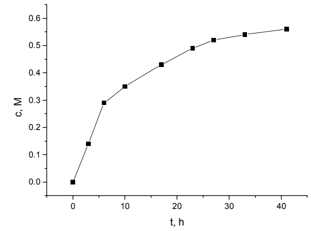


**Fig. 1** Benzophenone accumulation in the oxidation of diphenylmethane catalyzed by NHPI ($6.67\times10^{-2}$ M) and $Fe(NO_3)_3{\cdot}9H_2O$ ($5.33\times10^{-2}$ M) in the presence of $O_2$ (1 atm) in acetonitrile.

On the other hand, we determined the dependences of the initial rate of benzophenone formation ($W_0$) on the concentration of each reagent. The dependence of the oxidation rate on the concentration of NHPI is linear in the range of a concentration from 0 to $6.67\times10^{-2}$ M (Fig. 2), similar to the result of $Fe(NO_3)_3{\cdot}9H_2O$ (Fig. 3).

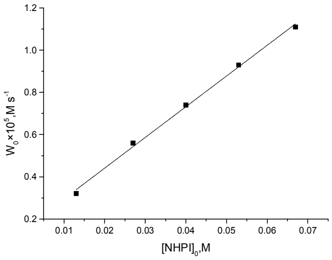


**Fig. 2** Dependences of benzophenone initial accumulation rate $W_0$ on the concentration of NHPI. (Reaction conditions: diphenylmethane (1 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (8 mol%) , $O_2$ (1 atm), acetonitrile (1.5 mL), at 25 °C, 4 h)

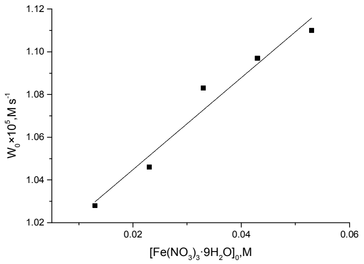


**Fig. 3** Dependences of benzophenone initial accumulation rate $W_0$ on the concentration of $Fe(NO_3)_3 \cdot 9H_2O$. (Reaction conditions: diphenylmethane (1 mmol), NHPI (10 mol%) , $O_2$ (1 atm), acetonitrile (1.5 mL), at 25 °C, 4 h)

The effect of *para*-substituents of ethylbenzene derivatives on the oxidation has also been investigated. The experiments were carried out in $CH_3CN$ (1.5 mL) at 25 °C under an atmospheric pressure of molecular oxygen by mixing equimolar amount (1 mmol) of *para*-substituted ethylbenzene ($p$-Y-$C_8H_{10}$, Y = MeO, Me, H, Cl, Br or $NO_2$) and ethylbenzene catalyzed by NHPI (10 mol%) and $Fe(NO_3)_3 \cdot 9H_2O$ (8 mol%) for 1 hour. The relative rates for these *para*-substituted ethylbenzene derivatives, $k_{rel}$, were evaluated by monitoring the reactions with gas chromatography (Table 4). When the log$k_{rel}$ values determined for each *para*-substituted ethylbenzene were plotted against the substituent constants σ, Hammett correlations were obtained (Fig. 4). A good linear correlation between the log$k_{rel}$ and σ [with a negative ρ of -1.3 indicating an electron-demanding transition state] was found, demonstrating the more electron-rich substrates with higher oxidation rates.

**Table 4** Listing of $k_{rel}$ and σ values for the oxidation of *para*-substituted ethylbenzene derivatives

| Entry | Y | $k_{rel}$ | σ |
|---|---|---|---|
| 1 | MeO | 0.64 | -0.27 |
| 2 | Me | 0.31 | -0.17 |
| 3 | H | 0 | 0 |
| 4 | Cl | -0.19 | 0.23 |
| 5 | $NO_2$ | -0.87 | 0.78 |

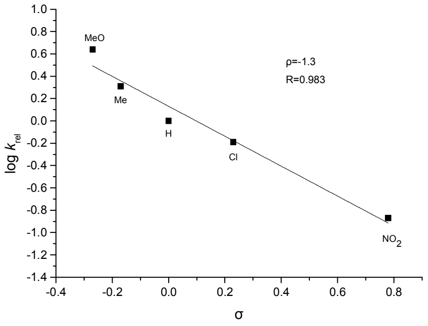
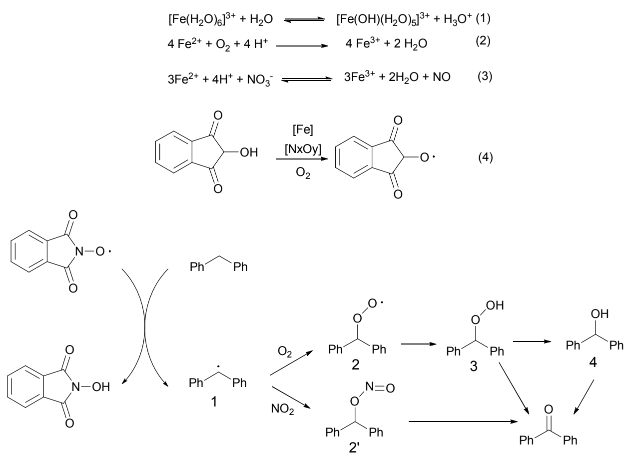


**Fig. 4** Hammett correlation studies (log$k_{rel}$ vs σ) for oxidation of *para*-substituted ethylbenzene derivatives catalyzed by $Fe(NO_3)_3 \cdot 9H_2O$ and NHPI with an atmospheric pressure of molecular oxygen as oxidant.

In order to further understand the mechanism of the reaction, we have therefore studied oxidation of diphenylmethane with $Fe(NO_3)_3 \cdot 9H_2O$/NHPI under an $^{18}O_2$ atmosphere. The incorporation of $^{18}O$ into the products also has been determined (Figure S1). The result showed that the percentage of the products containing $^{18}O$ was 53%, which indicated that $O_2$ is not the only oxygen source for the production of benzophenone. Then we supplemented a blank experiment that diphenylmethane (1 mmol) was catalyzed by $Fe(NO_3)_3 \cdot 9H_2O$ (8 mol%) and NHPI (10 mol%) in 1.5 mL acetonitrile under argon at 25 °C for 40 h. And the GC analysis showed that yield of benzophenone was 30%. The results indicated that only $Fe(NO_3)_3 \cdot 9H_2O$ also had certain oxidation ability and partial oxygen of the product should derive from nitrate. Moreover, Hulshof reported that the changes of the valence state of the iron and nitrogen oxides existed in the oxidation of benzyl alcohol by iron(III)nitrate.[20] Besides, we supplemented a control experiment that diphenylmethane (1 mmol) was catalyzed by $FeCl_3 \cdot 6H_2O$ (8 mol%), $NaNO_3$ (24 mol%) and NHPI (10 mol%) in 1.5 mL acetonitrile under $O_2$ at 25 °C for 40 h. The GC analysis showed that the yield of benzophenone was 70%. Then we replaced $NaNO_3$ with $NaNO_2$ and found the yield of benzophenone turned to 51%. The results indicate that nitrate anion plays an important role in the reaction and $NO_3^-$ and $NO_2^-$ could be converted into the real intermediate in the process of the reaction.

Accordingly, iron cation and nitrate anion were necessary for the reaction. However, the change of iron cation and the transformation of nitrate with the help of iron cation were not clear up to now. According to our experimental results and previous report, we proposed a possible mechanism as shown in Scheme 2. Based on our previous report on the oxidation of alcohols catalyzed by NHPI and $Fe(NO_3)_3 \cdot 9H_2O$, $Fe^{3+}$ could be transformed into $Fe^{2+}$ during the reaction detected by addition of $K_3[Fe(CN)_6]$ solution.[19c] After the reaction, we tested the pH of the system which indicated to be a weakly acidic environment, probably for the hydrolysis of hydrated ferric ion (Scheme 2, (1)).[20a,21] $Fe^{3+}$ has strong oxidizing ability and $Fe^{2+}$ could be oxidized to $Fe^{3+}$ with the help of $O_2$ or $NO_3^-$ under acidic condition (Scheme 2, (2) and (3)).[22] The reaction may be initiated by hydrogen-atom abstraction from the hydroxyimide group of NHPI by iron compound and $N_xO_y$ under oxygen atmosphere (Scheme 2, (4)).[12b,22,23,24] Then PINO abstracts the hydrogen atom from diphenylmethane to produce corresponding radical **1**, which subsequently reacts with molecular oxygen or $NO_2$ producing peroxy radical **2** or nitrite **2'**.[25] Then intermediate **2** accepts hydrogen to providing **3**, which then loses water and is transformed into the desire ketone product. The hydroperoxidate intermediate **3** may also be transformed into the benzyl alcohol derivative **4**, which under further oxidation provides corresponding ketone. Besides, the desired product could be also produced by the elimination or arrangement of **2'**. [20a]



**Scheme 2** Proposed mechanism for oxidation of diphenylmethane catalyzed by NHPI and $Fe(NO_3)_3{\cdot}9H_2O$ with $O_2$.

## Experimental

### General Remarks

All starting materials and catalysts were purchased from commercial suppliers without further purification. $^{18}O_2$ was purchased from Sigma-Aldrich. Column chromatography was generally performed on silica gel (200-300 mesh) and TLC inspections were on silica gel GF254 plates.

GC analysis was performed on Agilent Technologies 6820 with a flamed-ionization detector and a HP-5MS column (0.25 mm × 30 m, Film: 0.25 μm). 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 × 30 m, Film: 0.25 μm). $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a Bruker spectrometer 400 MHz using $CDCl_3$ as the solvent with TMS as an internal reference.

### General procedure for oxidation of benzylic methylenes

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 stirred for 40 h under an atmospheric pressure of $O_2$ at 25 °C controlled with water bath. After the reaction, 30 mg of biphenyl or nitrobenzene 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 minutes. The products were analyzed by GC, and further confirmed by GC-MS or NMR. The isolated yield was obtained through column chromatography generally performed on silica gel (200-300 mesh).

## Conclusions

We have developed a system including NHPI and $Fe(NO_3)_3{\cdot}9H_2O$ for aerobic oxidation of benzylic methylenes at 25 $^oC$ in the presence of 1 atm $O_2$. Various benzylic methylenes could be oxidized to the corresponding carbonyl compounds in satisfactory yields in this catalytic system. Hammett analysis suggested that the substrates with electron-donating groups would have higher oxidation rates. Isotopic ($^{18}O$) labeling study provided evidence of the participation of nitrate anion in the catalytic cycle. And a radical mechanism involving PINO abstracting the hydrogen atom and dioxygen and nitrate anion participation in the catalytic cycle was proposed. Further investigations toward the scope and mechanism are underway in our laboratory.

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# NHPI and Ferric Nitrate: A Mild and Selective System for Aerobic Oxidation of Benzylic Methylenes

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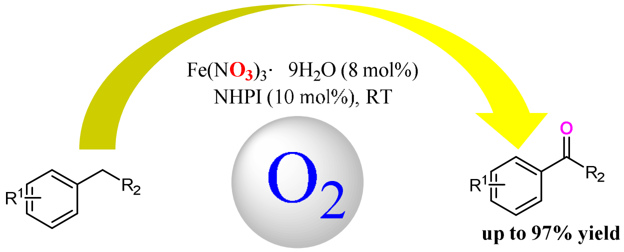

NHPI and ferric nitrate was developed for efficient oxidation of benzylic methylenes with 1 atm of oxygen at 25 $^{o}$C, providing up to 97% yield.