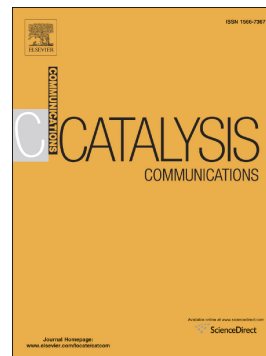


## Accepted Manuscript

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An efficient catalyst system for selective oxidation of alcohols  
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Fe(NO<sub>3</sub>)<sub>3</sub>/2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ): An efficient Catalyst System for Selective Oxidation of Alcohols under Aerobic Conditions

Yongke Hu, Lei Chen, Bindong Li\*

*School of Chemical Engineering, Nanjing University of Science and Technology,  
Nanjing 210094, PR China*

E-mail: [libindong@njut.edu.cn](mailto:libindong@njut.edu.cn)

## Abstract

A practical and efficient catalyst system for the oxidation of alcohols to carbonyl compounds using catalytic amounts of DDQ and Fe(NO<sub>3</sub>)<sub>3</sub> with air as the environmentally benign oxidant has been developed. A variety of benzylic, heterocyclic, allylic and propargylic alcohols were smoothly converted into aldehydes or ketones in good to excellent yields. In case of large-scale reaction for the oxidation of benzyl alcohol, benzaldehyde was obtained in 93% isolated yield. Moreover, a possible reaction mechanism was proposed.

## Introduction

The selective oxidation of alcohols into corresponding aldehydes or ketones is a fundamental transformation in organic chemistry and the carbonyl compounds are widely used as important precursors for pharmaceuticals, perfumes and organic intermediates [1, 2]. Traditional methods for this transformation involve the use of stoichiometric amount of oxidants such as MnO<sub>2</sub> [3], chromium oxides [4], activated DMSO [5] and hypervalent iodine [6], which produce large amounts of toxic waste and cause pollution to the environment. From the viewpoints of green and sustainable chemistry, molecular oxygen as a green oxidant has attracted great attention because molecular oxygen is inexpensive, abundant and water is produced as the only

innocuous by-product [7, 8]. Thus, considerable efforts have been devoted to developing green and facile approaches for the oxidation of alcohols with molecular oxygen as the terminal oxidant. Over the past decades, numerous protocols have been developed and showed high efficiency in aerobic alcohol oxidation with transition metal catalysts or metal-free catalysts [9, 10]. Among all the catalytic system the ones based on stable nitroxyl radical such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and *N*-hydroxyphthalimide (NHPI) in combination with co-catalysts are the most reported [11-14].

In recent years, a new organocatalyst, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has been recognized as an powerful oxidant for numerous organic transformation [15]. Although DDQ is efficient for alcohol oxidation [16], aromatization [17], oxidative cyclization [18] and deprotection [19], stoichiometric or even excess amounts of DDQ are required. In addition, the stoichiometric use of DDQ produces equimolar quantities of the corresponding hydroquinone (DDQH<sub>2</sub>) byproduct, which makes purification difficulties on the large scale synthesis. To date, few works have been reported for the alcohol oxidation using substoichiometric quantities of DDQ. Helquist and co-workers described a practical, chemoselective method for the oxidation of alcohols by employing 20 mol% of DDQ as the oxidant and 6 equiv of Mn(OAc)<sub>3</sub> as the co-oxidant (Scheme 1, a) [20]. However, the use of excess amounts of Mn(OAc)<sub>3</sub> made this protocol environmentally unfriendly. Gao and co-workers developed a transition-metal-free catalytic system by using low catalytic amount of DDQ and NaNO<sub>2</sub> with molecular oxygen as terminal oxidant, but this

catalytic system was limited for the oxidation of benzylic alcohols containing electron-withdrawing groups (Scheme 1, b) [21]. Subsequently, Moody and co-workers reported a similar catalyst system with catalytic amount of DDQ and  $\text{NaNO}_2$  or *tert*-butyl nitrite under visible light irradiation (Scheme 1, c) [22]. Both Gao's and Moody's work were nitrite-based protocols, the sodium nitrite was employed as co-catalyst and AcOH was also required. In the presence of AcOH and oxygen, nitric oxide was generated in situ by sodium nitrite, which was a sufficiently strong oxidant to recycle the  $\text{DDQH}_2$ . As we know,  $\text{DDQH}_2$  cannot be directly oxidized to DDQ by molecule oxygen in the absence of co-catalyst under mild conditions. Hence, the development of an efficient and inexpensive co-catalyst in combination with catalytic amount of DDQ for the aerobic oxidation of alcohols under mild conditions is still highly desired.

Iron, a cheap, non-toxic, and earth-abundant metal, has been developed as a catalyst for many organic reactions, especially in some oxidation reactions using oxygen as oxidant [23]. The mainly catalytic systems were based on TEMPO in combination with Fe salts as the co-catalyst. In 2005, Wang et al. first reported  $\text{FeCl}_3$ /TEMPO/ $\text{NaNO}_2$  catalyst system for the alcohol oxidation [24]. Further developments of the  $\text{Fe}(\text{NO}_3)_3$ /TEMPO catalyst system were reported by Ma et al. and  $\text{Fe}(\text{NO}_3)_3$  was proven to be an efficient and promising catalyst for the alcohol oxidation (Scheme 1, d) [25-28]. Therefore, we hypothesized  $\text{Fe}(\text{NO}_3)_3$  has a potential as good co-catalyst in DDQ catalytic system for the oxidation of alcohols.

Herein, we wish to report a facile and efficient approach for the oxidation of alcohols to carbonyl compounds by using catalytic amount of DDQ as catalyst, cheap and nontoxic  $\text{Fe}(\text{NO}_3)_3$  as the co-catalyst and air as the terminal oxidant (Scheme 1, e). A variety of aldehydes and ketones were obtained in moderate to excellent yields.

## Result and discussion

Initially, benzyl alcohol (**1a**) was employed as model substrate to optimize reaction conditions including catalysts, solvents and reaction time under air. As shown in Table 1, different iron catalysts such as  $\text{Fe}_2(\text{SO}_4)_3$ ,  $\text{FeCl}_3$ ,  $\text{FeCl}_2$ ,  $\text{Fe}(\text{acac})_3$  and  $\text{Fe}(\text{NO}_3)_3$  were screened in the presence of 3 mol% DDQ at 60 °C under air balloon (Table 1, entries 1-5). To our delight,  $\text{Fe}(\text{NO}_3)_3$  showed higher catalytic activity than other iron salts and product **2a** was isolated in 80% yield (Table 1, entry 5). Next, the influence of the catalyst loading and reaction time on the reaction was investigated. It was found that 3 h and 10 mol% of  $\text{Fe}(\text{NO}_3)_3$ , 5 mol% of DDQ were sufficient for this transformation (Table 1, entries 6-9). Among all the solvents screened, 1,2-dichloroethane gave the best result compared with other solvents such as toluene,  $\text{CH}_3\text{OH}$ ,  $\text{CH}_2\text{Cl}_2$  and  $\text{H}_2\text{O}$  (Table 1, entries 10-13). In addition, we attempted different reaction temperatures, and 60 °C was the better choice (Table 1, entries 14 and 15). Therefore, we chose 10 mol%  $\text{Fe}(\text{NO}_3)_3$ , 5 mol% DDQ in 1,2-dichloroethane at 60 °C under air as the standard reaction conditions (Table 1, entry 7).

With the optimal reaction condition in hand, the substrate scope and limitation of this catalytic system were examined. Firstly, we investigated the oxidation of a variety of primary alcohols under standard conditions. To our delights, both electron-donating

groups and electron-withdrawing groups were well tolerated in the reactions. It was observed that benzylic alcohols bearing electron-donating groups were fully converted to the desired products (Table 2, **2b-2g**). However, the electron-withdrawing groups such as -F, Br, -Cl, -NO<sub>2</sub> and -CF<sub>3</sub> substituted benzylic alcohols provided slightly low yields of corresponding aldehydes (Table 2, **2h-2m**). Notably, 4-chlorobenzylalcohol and 4-nitrobenzylalcohol were smoothly transformed to the desired products, which was superior to the previous works reported by Gao's and Helquist's group. Benzyl alcohols with methylthiol and hydroxyl substitution gave the corresponding products in 93% and 74% yields, which indicated that methylthiol and hydroxyl substitution on the phenyl group was unaffected under the standard reaction conditions (Table 2, **2n** and **2o**). For the piperonyl alcohol, 4-phenylbenzyl alcohol and 1-naphthalenemethanol, they were oxidized to the desired products in moderate to good yields (Table 2, **2p-2r**). In the case of unsaturated alcohols such as cinnamyl alcohol,  $\alpha$ -methylcinnamyl alcohol and 3-phenylprop-2-yn-1-ol were also well tolerated in this reaction (Table 2, **2s-2u**). In addition, heterocyclic alcohols such as 2-furanemethanol and 2-thiophenemethanol were tested successively and transformed smoothly with acceptable yields (Table 2, **2v-2w**).

The oxidation of secondary alcohols was also tested and the results were summarized in Table 3. As expected, all secondary benzylic alcohols were converted into corresponding ketones in moderate to high yields (Table 3, **4a-4p**). It was worthy to note that when the length of the side chain increasing, the products yield reduced,

which indicated that the steric hindrance of the groups on the side chain had an obvious impact on this transformation (Table 3, **4a-4c**). Similarly, the reaction activity decreased, when the size of the ring on the side of the hydroxyl enlarging (Table 3, **4i-4k**). In addition, it was found that secondary propargylic alcohols such as 1-phenylprop-2-yn-1-ol and 1-phenyl-1-pentyn-3-ol were also smoothly oxidized to the desired ketones with good yields (Table 3, **4o and 4p**). Unfortunately, both primary and secondary aliphatic alcohols were failed to afford the desired products under standard conditions (Table 2, **2x** and Table 3, **4q**). The important advantage of this catalytic system is that the use of air as the terminal oxidant instead of pure dioxygen also results in good yields.

To further confirm the practicality and efficiency of this catalyst system, a large-scale experiment for the oxidation of **1a** was conducted under standard conditions. Product of **2a** was successfully obtained in 93% isolated yield (Scheme 2). The result suggested that this catalyst system was amenable to scale up.

In order to explore the reaction mechanism, the following control experiments were carried out and the results were illustrated in Scheme 3. When the reaction was conducted in the presence of  $\text{NaNO}_3$  or  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ , only 10% and 29% yield of benzaldehyde was isolated, respectively. Besides, the yield of benzaldehyde increased to 76% by employing 30 mol%  $\text{NaNO}_3$  combined with 10 mol%  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  in the reaction. These results indicated that  $\text{Fe}^{3+}$  as well as  $\text{NO}_3^-$  was essential in this reaction. Additionally, we considered that the  $\text{Fe}^{3+}$  can be transformed into  $\text{Fe}^{2+}$  in the process of oxidation. In order to demonstrate the metal chemical state, a small

quantity of the reaction mixture was added discontinuously to the  $K_3[Fe(CN)_6]$  solution. The Prussian blue precipitate appeared rapidly and existed throughout the aerobic oxidation of benzyl alcohol even after the completion of the reaction, which indicated the generation of  $Fe^{2+}$  during the reaction. However, when the reaction mixture was in the absence of DDQ, the Prussian blue precipitate was not obtained. Based on the results above and pertinent literature [25, 29-31], a plausible mechanism for the oxidation of alcohols catalyzed by  $Fe(NO_3)_3/DDQ$  was presented in Scheme 4. Firstly, DDQ oxidized alcohols to carbonyl compounds and itself was converted to  $DDQH_2$ . Then  $DDQH_2$  reduced the  $Fe^{3+}$  to  $Fe^{2+}$ . The  $NO_3^-$  was to be a source of  $NO_2$ , which played an important role in the oxidation of  $Fe^{2+}$  to  $Fe^{3+}$  and then  $NO_3^-$  was reduced to  $NO_2^-$  [32-35]. Finally,  $NO_3^-$  could be easily regenerated by the oxidation of  $NO_2^-$  with molecular oxygen.

## Conclusion

In summary, we have developed a highly efficient  $Fe(NO_3)_3/DDQ$ -catalyzed system for the oxidation of alcohols with air serving as the environmentally friendly terminal oxidant. This catalytic system exhibits excellent substrate tolerance and a variety of benzylic, heterocyclic, allylic and propargylic alcohols are selectively transformed to the corresponding aldehydes and ketones in moderate to good yields. In addition, a plausible reaction mechanism has been proposed and further applications of this catalytic system are under way in our laboratory.

## References



- [1] M. Hudlicky, *Oxidations in organic chemistry*, American Chemical Society, Washington, DC, 1990.
- [2] R.C. Larock, *Comprehensive organic transformations: a guide to functional group preparations.*, Wiley-VCH, New York, 1999.
- [3] R.J. Taylor, M. Reid, J. Foot, S.A. Raw, *Acc. Chem. Res.* 38 (2005) 851-869.
- [4] M.E. Gonzalez-Nunez, R. Mello, A. Olmos, R. Acerete, G. Asensio, *J. Org. Chem.* 71 (2006) 1039-1042.
- [5] M. Marx, T.T. Tidwell, *J. Org. Chem.* 49 (1984) 788-793.
- [6] D.B. Dess, J.C. Martin, *J. Org. Chem.* 48 (1983) 4155-4156.
- [7] T. Punniyamurthy, S. Velusamy, J. Iqbal, *Chem. Rev.* 105 (2005) 2329-2363.
- [8] Z. Shi, C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* 41 (2012) 3381-3430.
- [9] T. Mallat, A. Baiker, *Chem. Rev.* 104 (2004) 3037-3058.
- [10] R. Prebil, G. Stavber, S. Stavber, *Eur. J. Org. Chem.* 2014 (2014) 395-402.
- [11] B.L. Ryland, S.S. Stahl, *Angew. Chem. Int. Ed.* 53 (2014) 8824-8838.
- [12] Q. Cao, L.M. Dornan, L. Rogan, N.L. Hughes, M.J. Muldoon, *Chem. Commun.* 50 (2014) 4524-4543.
- [13] S.S. Yasutaka Ishi, Takahiro Iwahama, *Adv. Synth. Catal.* 343 (2001) 393-427.
- [14] Y. Hu, L. Chen, B. Li, *Catal. Commun.* 83 (2016) 82-87.
- [15] D. Walker, J.D. Hiebert, *Chem. Rev.* 67 (1967) 153-195.
- [16] H.D. Becker, A. Bjoerk, E. Adler, *J. Org. Chem.* 45 (1980) 1596-1600.
- [17] J.R. Manning, H.M. Davies, *J. Am. Chem. Soc.* 130 (2008) 8602-8603.
- [18] L. Liu, P.E. Floreancig, *Org. Lett.* 11 (2009) 3152-3155.

- [19] M.A. Rahim, S. Matsumura, K. Toshima, *Tetrahedron Lett.* 46 (2005) 7307-7309.
- [20] C.C. Cosner, P.J. Cabrera, K.M. Byrd, A.M.A. Thomas, P. Helquist, *Org. Lett.* 13 (2011) 2071-2073.
- [21] L. Wang, J. Li, H. Yang, Y. Lv, S. Gao, *J. Org. Chem.* 77 (2012) 790-794.
- [22] K. Walsh, H.F. Sneddon, C.J. Moody, *Org. Lett.* 16 (2014) 5224-5227.
- [23] I. Bauer, H.-J. Knoelker, *Chem. Rev.* 115 (2015) 3170-3387.
- [24] N. Wang, R. Liu, J. Chen, X. Liang, *Chem. Commun.* (2005) 5322-5324.
- [25] S.M. Ma, J.X. Liu, S.H. Li, B. Chen, J.J. Cheng, J.Q. Kuang, Y. Liu, B.Q. Wan, Y.L. Wang, J.T. Ye, Q. Yu, W.M. Yuan, S.C. Yu, *Adv. Synth. Catal.* 353 (2011) 1005-1017.
- [26] J. Liu, S. Ma, *Org. Biomol. Chem.* 11 (2013) 4186-4193.
- [27] L. Wang, S. Shang, G. Li, L. Ren, Y. Lv, S. Gao, *J. Org. Chem.* 81 (2016) 2189-2193.
- [28] X. Wang, X. Liang, *Chinese J. Catal.* 29 (2008) 935-939.
- [29] Z.L. Shen, J.L. Dai, J. Xiong, X.J. He, W.M. Mo, B.X. Hu, N. Sun, X.Q. Hu, *Adv. Synth. Catal.* 353 (2011) 3031-3038.
- [30] Z.L. Shen, M. Chen, T.T. Fang, M.C. Li, W.M. Mo, B.X. Hu, N. Sun, X.Q. Hu, *Tetrahedron Lett.* 56 (2015) 2768-2772.
- [31] Y. Hu, L. Chen, B. Li, *RSC Adv.* 6 (2016) 65196-65204.
- [32] P. Bar-On, M. Mohsen, R. Zhang, E. Feigin, M. Chevion, A. Samuni, *J. Am. Chem. Soc.* 121 (1999) 8070-8073.
- [33] C. Miao, H. Zhao, Q. Zhao, C. Xia, W. Sun, *Catal. Sci. Technol.* 6 (2016)

1378-1383.

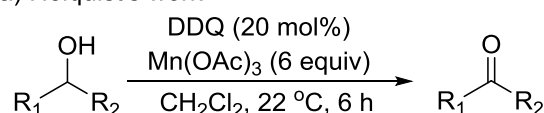
[34] M.H.C.L. Dressen, J.E. Stumpel, B.H.P. van de Kruijs, J. Meuldijk, J.A.J.M.

Vekemans, L.A. Hulshof, *Green Chem.* 11 (2009) 60-64.

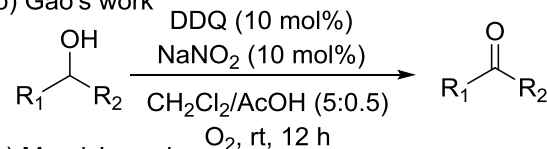
[35] Y.C. Zhang, F.L. Lu, X.H. Cao, J.Q. Zhao, *RSC Adv.* 4 (2014) 40161-40169.

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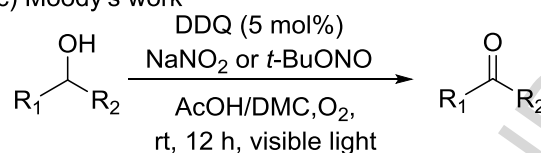
a) Helquist's work



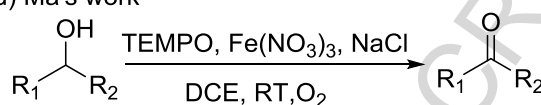
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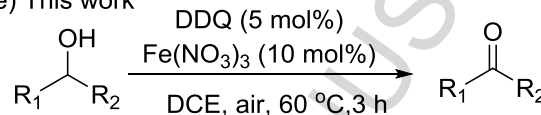
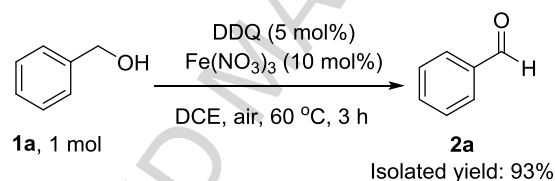
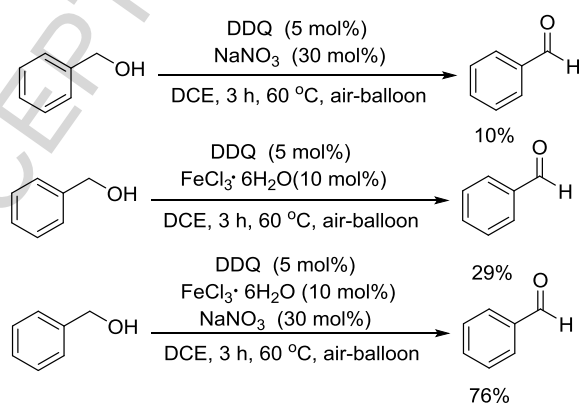
c) Moody's work

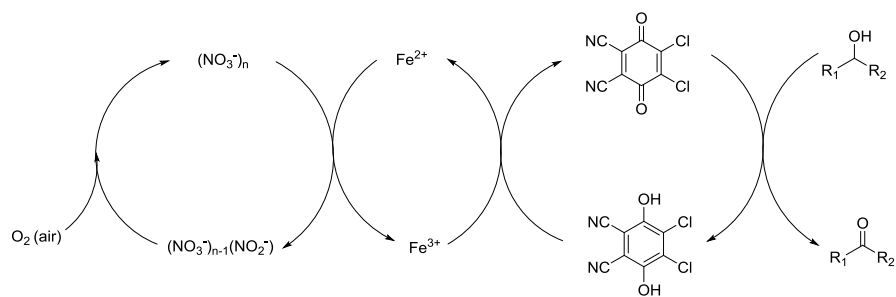


d) Ma's work

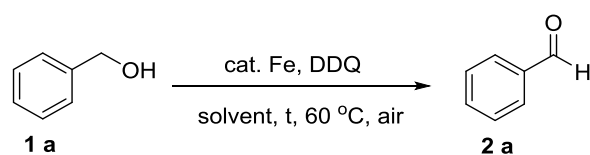


e) This work

**Scheme 1.** Methods for the oxidation of alcohols with DDQ**Scheme 2.** Aldehyde formation in the large-scale.**Scheme 3.** Control experiments.

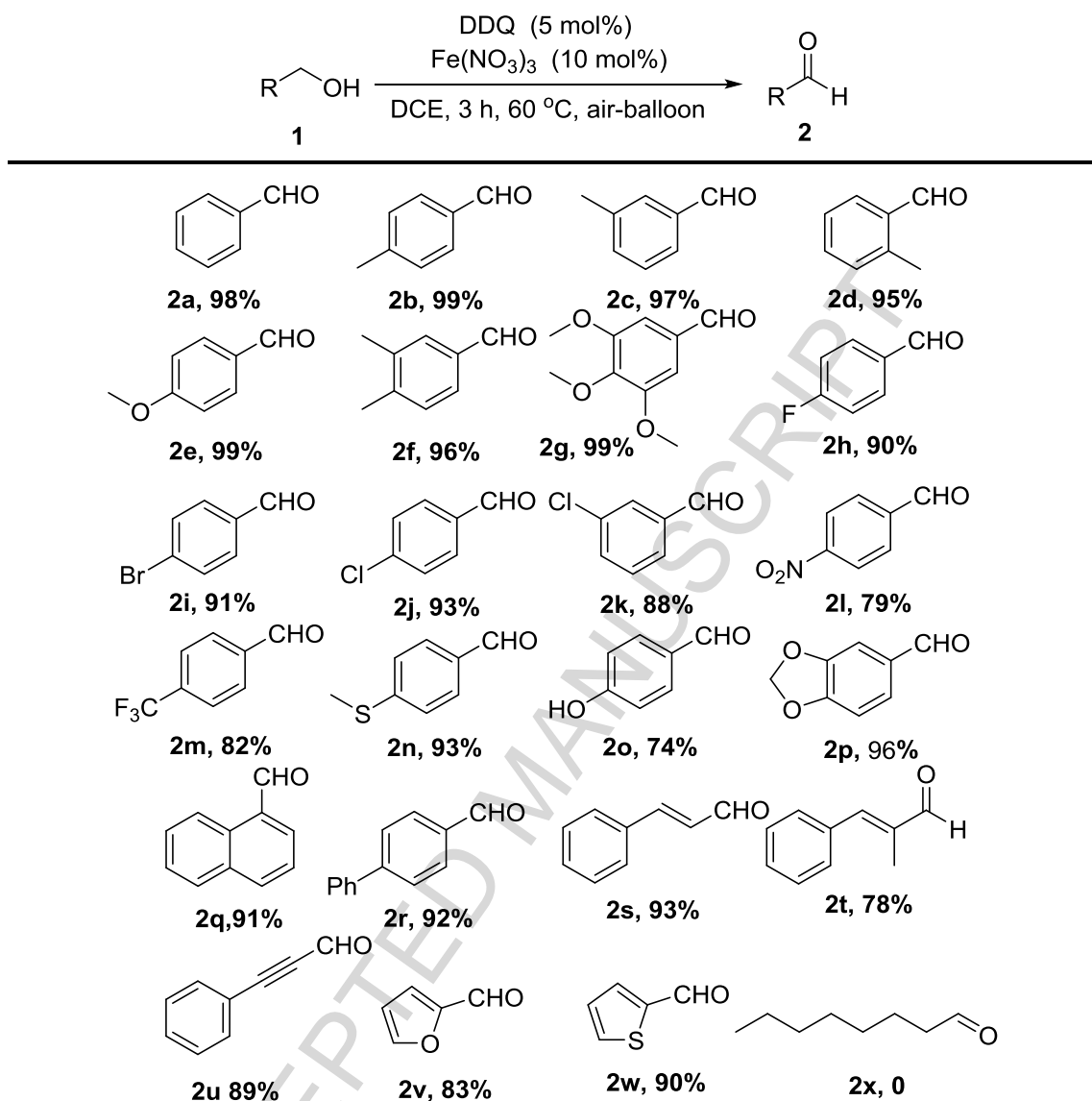


**Scheme 4.** Proposed reaction mechanism.

**Table 1.** Optimization of reaction conditions<sup>a</sup>

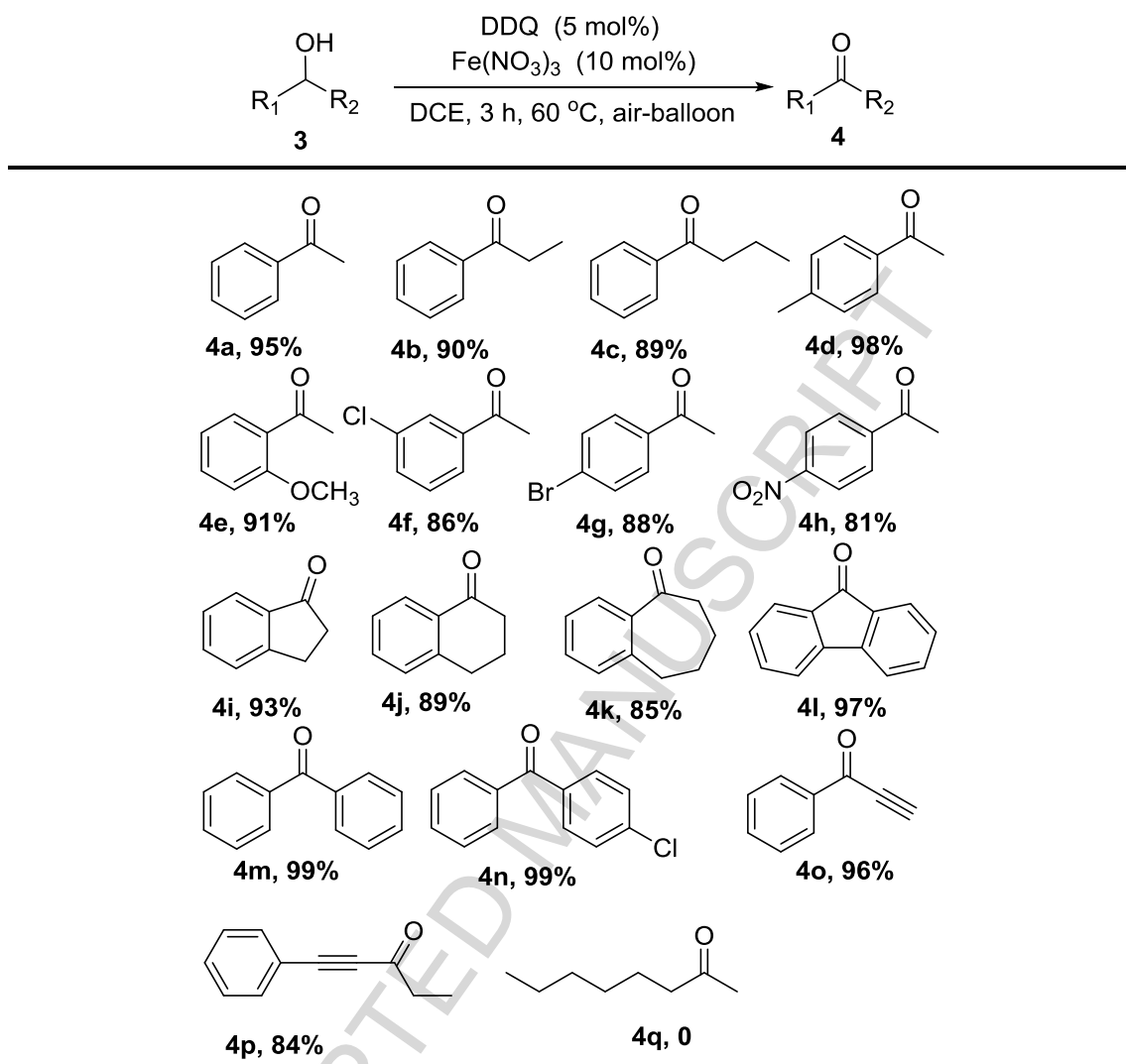
Entry	Fe catalyst (mol %) <sup>b</sup>	DDQ (mol %)	Solvent	Time (h)	Yield (%) <sup>c</sup>
1	Fe <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub> ·9H <sub>2</sub> O (5)	3	DCE	4	16
2	FeCl <sub>3</sub> ·6H <sub>2</sub> O (5)	3	DCE	4	25
3	FeCl <sub>2</sub> ·4H <sub>2</sub> O (5)	3	DCE	4	18
4	Fe(acac) <sub>3</sub> (5)	3	DCE	4	12
5	Fe(NO <sub>3</sub> ) <sub>3</sub> (5)	3	DCE	4	80
6	Fe(NO <sub>3</sub> ) <sub>3</sub> (5)	5	DCE	4	91
<b>7</b>	<b>Fe(NO<sub>3</sub>)<sub>3</sub> (10)</b>	<b>5</b>	<b>DCE</b>	<b>3</b>	<b>98</b>
8	Fe(NO <sub>3</sub> ) <sub>3</sub> (15)	10	DCE	3	98
9	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	5	DCE	2	89
10	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	5	Toluene	3	75
11	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	5	MeOH	3	69
12	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	5	CH <sub>2</sub> Cl <sub>2</sub>	3	92
13	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	5	H <sub>2</sub> O	3	20
14 <sup>d</sup>	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	5	DCE	3	96
15 <sup>e</sup>	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	5	DCE	3	90

<sup>a</sup> Reaction condition: **1a** (1 mmol), Fe catalyst, DDQ, solvent (2 mL) in a 10 mL Schlenk tube, at 60 °C, under air balloon. <sup>b</sup> Fe(NO<sub>3</sub>)<sub>3</sub> = Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O unless otherwise noted. <sup>c</sup> Isolated yield. <sup>d</sup> Reaction at 65 °C <sup>e</sup> Reaction at 55 °C

**Table 2.** Aerobic oxidation of primary alcohols to aldehydes catalyzed by DDQ/Fe(NO<sub>3</sub>)<sub>3</sub><sup>a</sup>

<sup>a</sup>Reaction conditions: **1** (1 mmol), Fe(NO<sub>3</sub>)<sub>3</sub> (10 mol%), DDQ (5 mol%), DCE (2 mL) in a 10 mL Schlenk tube, at 60 °C for 3 h, under air balloon. Isolated yield.

**Table 3.** Aerobic oxidation of secondary alcohols to ketones catalyzed by DDQ/ $\text{Fe}(\text{NO}_3)_3$ <sup>a</sup>



<sup>a</sup>Reaction conditions: **1** (1 mmol),  $\text{Fe}(\text{NO}_3)_3$  (10 mol%), DDQ (5 mol%), DCE (2 mL) in a 10 mL Schlenk tube, at 60 °C for 3 h, under air balloon. Isolated yield.



**Highlights**

- $\text{Fe}(\text{NO}_3)_3$  and DDQ as the catalysts with air as the terminal oxidant.
- Various aldehydes and ketones were obtained in good to excellent yields.
- A plausible mechanism was proposed.

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