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Selective Aerobic Oxidation of 4-Ethylnitrobenzene to 4-Nitroacetophenone Promoted by Metalloporphyrins

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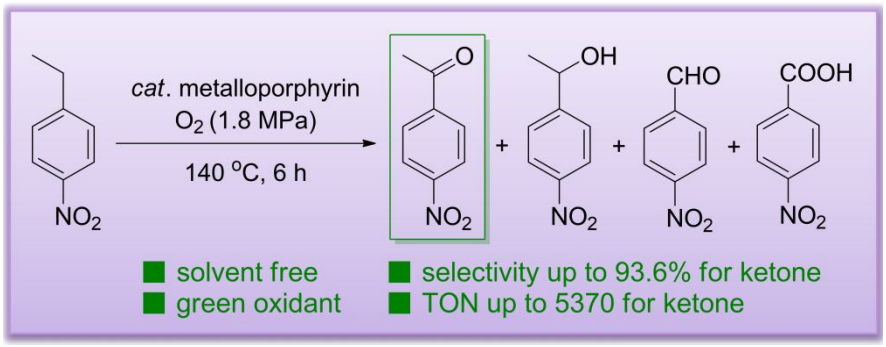

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ABSTRACT: A solvent-free and environment-friendly process for the oxidation of 4-ethylnitrobenzene to 4-nitroacetophenone promoted by metalloporphyrins was developed in pressure reactor using O_2 as clean oxidant. The activities and reaction selectivities of the metalloporphyrins could be significantly affected by their central metal ions, the nature and position of the substituted groups, which were systematically investigated by employing more than 60 metalloporphyrins. Generally, the Fe(III)- and Mn(II)-porphyrins exhibited high activities. Moreover, metalloporphyrins with electron-withdrawing substituents on the *para*-positions of the phenyl rings showed activities with an order of T(*p*-Br)PPM < T(*p*-Cl)PPM < T(*p*-F)PPM. The substituent positions effect on the activities of T(*o*-Cl)PPM > T(*m*-Cl)PPM > T(*p*-Cl)PPM, and T(*o*-OMe)PPM < T(*m*-OMe)PPM < T(*p*-OMe)PPM were observed. Furthermore, selectivites over 90.0% and TON of 5370 could be achieved for the desired ketone. Especially, the T(*p*-Cl)PPMn demonstrated a selectivity of up to 93.6% and a conversion of 51.9% with only 3.3% acid and no alcohol observed, and the selectivity was nearly keeping the same for a large-scale experiment (100 g).

KEYWORDS: solvent-free, aerobic oxidation, 4-ethylnitrobenzene, 4-nitroacetophenone, metalloporphyrin, ARC

INTRODUCTION: Selective side-chain oxidation of alkyl aromatic compounds to valuable ketones, alcohols, aldehydes or carboxylic acids catalyzed by designed catalysts has been attracting a great deal of attentions in recent years.[1-3] 4-Nitroacetophenone is an essential

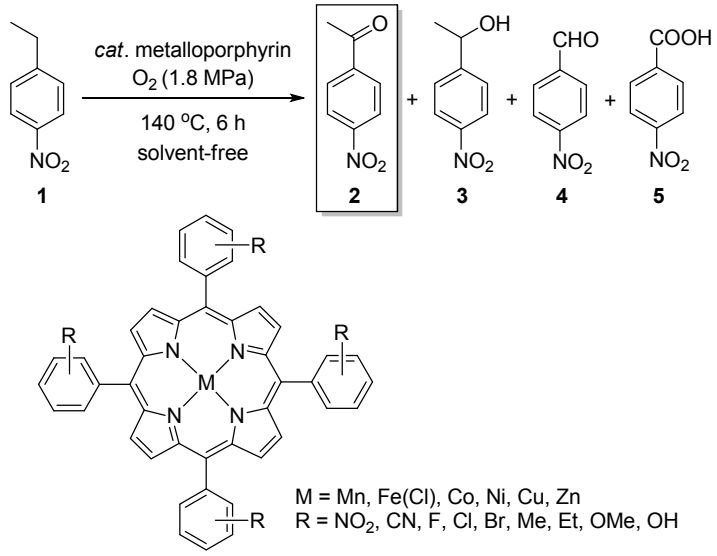
intermediate for pharmaceutical industry, agricultural and widely used in synthesizing chirality compounds.[4-6] The 4-nitroacetophenone cannot be synthesized through Friedel–Crafts acylation of cheap nitrobenzene, thus, direct constructing carbonyl from 4-ethylnitrobenzene through highly selective oxidation of C-H bond is one of the most efficient method to prepare 4-nitroacetophenone.[7] Traditionally, stoichiometric amount of hazardous oxidants, such as $KMnO_4$,[8] H_2O_2,[9] TBHP[10] or Ozone[11] were employed in direct oxidation inert α-H of alkylarenes catalyzed by metal catalysts,[12] nanometer materials,[13] MOFs,[14] mesoporous materials[15] or organic metal compounds[16] and great progress has been made. The oxidation of 4-ethylnitrobenzene to 4-nitroacetophenone were also developed by using various of catalysts, like sodium o-iodobenzenesulfonate,[17] co-doped material,[18] *cis*-$[Ru(dtbpy)_2Cl_2]$[19] and nanocatalyst.[20] However, some problems are still needed to be resolved, for example, the development of environmentally friendly oxidants and mild reaction conditions, the design of economical catalysts and enhancement of the reaction selectivity.

In contrast, molecular oxygen as a clean, and atom-economical oxidant for large-scale production has attracted considerable attentions in chemical industry.[21] However, the triplet-state nature of molecular oxygen hampers its reaction with hydrocarbon molecule in singlet state, hence, the aerobic oxidation processes are largely dependent on the development of catalysts to realize the preparation of corresponding products.[22] Moreover, because of the unique chemical and physical properties, metalloporphyrins have played an important role in molecule bonding,[23]

photochemical catalysis,[24] biomimetic catalyst,[25] and especially the selective aerobic oxidation reactions.[26] Inspired by the distinctive molecular structure and capability of heme and related enzymes,[27-34] several mono-substituted or multi-substituted tetraphenyl porphyrins bionic catalytic systems have been reported.[35] Many specific advantages of metalloporphyrins in oxidation systems have been demonstrated, like easily modified molecular structures,[36] low catalyst loading,[37] high reaction selectivity.[38] Metalloporphyrins promoted highly selective functionalization of the side-chain C-H bond of alkyl aromatic compounds provides an environmentally friendly and convenient approach for the biomimetic catalytic oxidation reactions. However, systematic investigation of the effect of ring-substituent groups and their positions on the catalytic activities and selectivities of the metalloporphyrins is quite rare.

The aerobic oxidation of 4-ethylnotrobenzene (**1**) is a very complicated reaction process (Scheme 1) involving radical mechanism. Besides the desired product 4-nitroacetophenone (**2**), there may be also other byproducts, like 1-(4-nitrophenyl)ethanol (**3**), 4-nitrobenzaldehyde (**4**), and 4-nitrobenzoic acid (**5**) **(**Scheme 1**)**. To increasing the selectivity of the aerobic oxidation, we tried to regulate the central metal irons, the substituent groups and their positions of metalloporphyrins to realize a considerable catalytic activity and selectivity.

Scheme 1. Aerobic Oxidation of 4-Ethylnitrobenzene Promoted by Metalloporphyrins.



EXPERIMENTAL SECTION

The oxidation of 4-ethylnitrobenzene with pure O_2 gas (1.8 MPa) was performed in a pressure reactor with solvent-free. Compared with the reported procedure in an open reactor with O_2 gas bubbling, this solvent-free procedure can save a plenty of O_2 gas, and avoid the loss of 4-ethylnitrobenzene. Importantly, this can significantly reduce emission of organic pollutants and solid waste to the surrounding environment, and avoid the explosion risk caused by high concentration of organic emissions.

Chemicals and reagents. All commercial reagents were purchased and used without further purification. Oxygen (99.99% of purity) provided by Jingong Gas Company in Hangzhou of China.

General procedure of 4-ethylnitrobenzene oxidation. The aerobic oxidation of 4-ethylnitrobenzene was carried out in a 100 mL pressure reactor. In a typical experiment, 4-ethylnitrobenzene (4.53 g, 30 mmol) and metalloporphyrin (0.01 mol%) were charged to the pressure reactor. After being sealed tightly, the pressure reactor was flushed with O_2 gas to 0.4 MPa, and then the gas was released very slowly to avoid the loss of the 4-ethylnitrobenzene. This procedure was repeated once again and then the reactor was pressurized with O_2 gas to 1.8 MPa. Then the pressure reactor content was heated to 140 ^oC in an oil bath and stirred at 140 rpm for 6.0 h. After that, the pressure reactor was taken out of the oil bath and cooled down to room temperature. Then the excess O_2 gas was released slowly to give the reaction mixture containing oxidation products and the 4-ethylnitrobenzene.

Safety concerns. Aerobic oxidation of hydrocarbons is usually exothermic reaction. For safety reasons, the thermal stabilities of the reactant, products and reaction mixture were typically screened by thermogravimetric analysis (TGA), differential screening calorimetry (DSC) and accelerating rate calorimetry (ARC) (Figure 1 and S2). The TGA of ketone **2** showed an obviously weight lost at about 145 ^oC due to thermal volatilization. However, acid **5** exhibited a significantly decomposition at 245-250 ^oC (Figure 1a, b). The ARC test curves showed an exotherm event and pressure raising at about 250 ^oC, which could be attributing to the gas generation, like nitrogen oxides and carbon oxides, from the decomposition of the acid **5**. This

was also consistent with the TGA result. Fortunately, the reaction temperature in this work is less than 145 °C, without the risk of explosion.

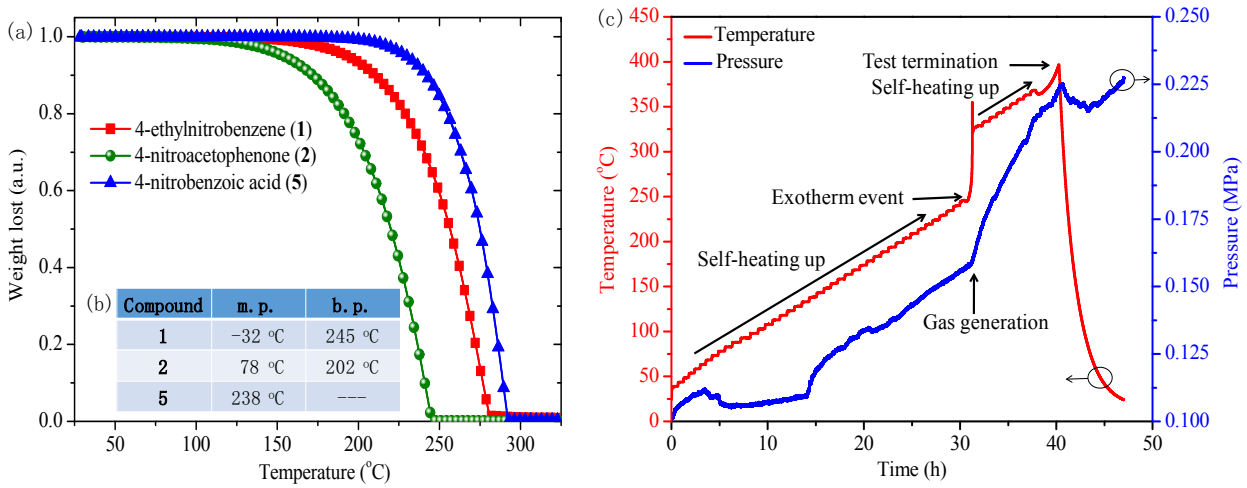


Figure 1. (a) TGA curves for **1**, **2** and **5**. (b) The melting point (m.p.) and boiling point (b. p.) of the **1**, **2** and **5** at 760 mmHg. (c) ARC test temperature and pressure history for a mixture of **1** (0.24 g), **2** (0.24 g) and **5** (0.01 g).

Sampling and analytical methods. The reaction mixture obtained above was transferred out and then diluted to 100 ml in a volumetric flask with methanol. Then sampling 2 ml by pipette transferred to another 50 ml volumetric flask, and 4-nitrotoluene (**6**) (69.3 mg, 0.5 mmol, 99% purity) was added as internal reference. The mixture was then diluted to 50 ml, in order to that the sample concentration was applicable for the detector of HPLC to display regular chromatographic peaks. Then quantitative measurements of the 4-ethylnitrobenzene (**1**), ketone **2**, alcohol **3**, aldehyde **4** and acid **5** were performed by HPLC analysis using the corresponding

calibration curves in Figure 2 (see supporting information for details). The conversion of 4-ethylnitrobenzene (**1**) was determined by the total amount of the yield of all oxidized products in order to eliminate the experiments errors, because of the volatility of 4-ethylnitrobenzene.

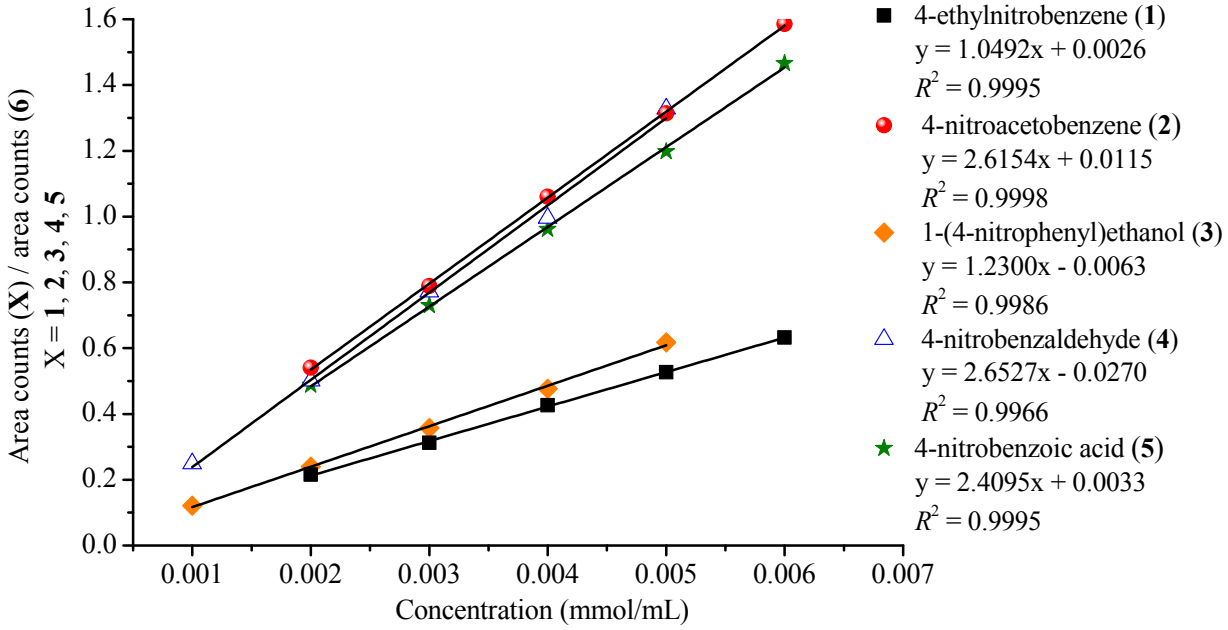


Figure 2. Calibration curves for compounds **1**, **2**, **3**, **4** and **5**.

RESULTS AND DISCUSSIONS:

It is a challenge to achieve both high selectivity and high yield for the 4-nitroacetophenone (**2**) of the aerobic oxidation. However, the selectivity and yield can be improved by adding various metalloporphyrins though adjusting their central metal ions and porphyrin ligands. In this study, the 1-(4-nitrophenyl)ethanol (**3**) and over-oxidation product 4-nitrobenzoic acid (**5**) involving C-C bond cleavage also generate, which were observed in our recent report of metal-free aerobic oxidation of nitro-substituted alkylarenes.[39] However, the 4-nitrobenzaldehyde (**4**) was not

observed in the HPLC analysis in this study attributing to its instability in the reaction system, and was quickly further oxidized to acid **5**.

Effect of central metal ions: In the absence of metalloporphyrin, the aerobic oxidation of the 4-ethylnitrobenzene could proceed under 1.8 MPa O_2 at 140 ^oC, to give 14.5% conversion with 11.5%, 2.7% and 0.3% yields for the ketone **2**, alcohol **3** and acid **5** respectively, and a selectivity of 79.3% for the desired product ketone **2** was obtained (Table 1, entry 1). Then, metalloporphyrins T(*p*-F)PPM with various transition metal ions, like Mn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, were used to investigate their activities and selectivities in the aerobic oxidation. All the conversions were significantly enhanced after adding only 0.01 mol% metalloporphyrins. The T(*p*-F)PPMn, T(*p*-F)PPFeCl and T(*p*-F)PPCo showed high activities with conversions of 43.6%, 54.5% and 48.7% respectively, and considerable yields of 37.2%, 47.3% and 41.5% respectively for ketone **2** (Table 1, entries 2, 3 and 4). The T(*p*-F)PPFeCl and T(*p*-F)PPCo gave the highest selectivity of 86.8% (Table 1, entries 3, 4). These phenomena can be explained by the fact that the different valences of the central metal ions caused corresponding redox potential make the activation of Fe^{2+}/Fe^{3+} be more positive than other ions.[40] By contrast, the valance of Zn^{2+} is difficult to change, making T(*p*-F)PPZn show low activity in the aerobic oxidation.[41]

Table 1. **Effect of the Central Metal Ions of Metalloporphyrins in the Aerobic Oxidation of 4-Ethylnitrobenzene**[a]

entry	T(*p*-F)PPM	conversion[b] (%)	yield[b] (%)			selectivity[b] (%)		
			ketone	alcohol	acid	ketone	alcohol	acid
1	——	14.5	11.5	2.7	0.3	79.3	18.6	2.1
2	T(*p*-F)PPMn	43.6	37.2	3.8	2.6	85.3	8.7	6.0
3	T(*p*-F)PPFeCl	54.5	47.3	3.8	3.4	86.8	7.0	6.2
4	T(*p*-F)PPCo	48.7	41.5	3.0	4.2	86.8	6.3	8.8
5	T(*p*-F)PPNi	25.9	21.3	3.7	0.9	82.2	14.3	3.5
6	T(*p*-F)PPCu	38.8	31.3	5.3	2.2	80.6	13.7	5.7
7	T(*p*-F)PPZn	36.9	30.5	2.4	4.0	82.6	6.5	10.8

[a] 30 mmol scale, 0.01 mol% T(*p*-F)PPM, O_2 (1.8 MPa), 140 °C, 6.0 h. [b] By HPLC analysis.

Effect of ligands. Besides the central metal ions discussed above, the ligands of the metalloporphyrins, like the electronic properties and positions of the substituents on the porphyrins, can also significantly affect the electron density of the metal ions, and further adjust the activities of the metalloporphyrins and the selectivities of the aerobic oxidations. Hence, the effect of the ligands should be also studied systematically.

The environmentally friendly Fe(III)-porphyrins with various electron withdrawing and donating groups of the *para*-positions on the phenyl rings were investigated firstly (Table 2). Basically, with the increase of the electron withdrawing capacity of the substituents, the activities of the Fe(III)-porphyrins were also enhanced except the T(*p*-NO_2)PPFeCl (Table 2, entries 2-6). The T(*p*-CN)PPFeCl exhibited the highest reaction activity with conversion of 63.1%, and a yield of 53.7% for the desired ketone **2** (Table 2, entry 3), this was corresponding to a turnover number (TON) of up to 5370, and over 20 times higher than the reported catalysts,[11,14,42-46] like ZJU-18,[14] CoSBA-15,[42] cobalt(II) Salen complex,[43]

Ru^{III}(TDCPP)(Ph)(OEt_2)[44] (see supporting information Table S2). All the Fe(III)-porphyrins with electron donating groups showed similar activities (Table 2, entries 7-9) except the T(*p*-OH)PPFeCl (Table 2, entry 10). Compared with the blank experiment, the T(*p*-OH)PPFeCl acted as an inhibitor for the aerobic oxidation, this could be attributed to the high activity of the phenolic hydroxyl groups to quench the free radicals in the reaction system. To our delighted, most of the Fe(III)-porphyrins demonstrated high reaction selectivity of over 85.0% for desired ketone **2**. Notably, the T(*p*-Br)PPFeCl and T(*p*-Et)PPFeCl exhibited high reaction selectivity of up to 90.7%, 91.0% (Table 2, entries 6, 8), and the activity of the T(*p*-Et)PPFeCl was also over 50% (Table 2, entry 8). Thus, the reaction condition needs to be further optimized to get higher activity and selectivity.

Table 2. Aerobic Oxidation of 4-Ethylnitrobenzene Promoted by T(*p*-R)PPFeCl[a]

entry	T(*p*-R)PPFeCl	conversion[b] (%)	yield[b] (%)			selectivity[b] (%)		
			ketone	alcohol	acid	ketone	alcohol	acid
1	—	14.5	11.5	2.7	0.3	79.3	18.6	2.1
2	T(*p*-NO_2)PPFeCl	46.3	38.9	3.7	3.7	84.0	8.0	8.0
3	T(*p*-CN)PPFeCl	63.1	53.7	4.3	5.1	85.1	6.8	8.2
4	T(*p*-F)PPFeCl	54.5	47.3	3.8	3.4	86.8	7.0	6.2
5	T(*p*-Cl)PPFeCl	49.1	42.2	2.8	4.1	85.9	5.7	8.4
6	T(*p*-Br)PPFeCl	35.4	32.2	3.2	0.0	90.7	9.0	0.0
7	T(*p*-Me)PPFeCl	55.2	47.7	4.0	3.4	86.4	7.2	6.2
8	T(*p*-Et)PPFeCl	51.3	46.7	1.0	3.6	91.0	2.0	7.0
9	T(*p*-OMe)PPFeCl	55.1	47.7	4.0	3.4	86.6	7.3	6.2
10	T(*p*-OH)PPFeCl	2.6	2.1	0.5	0.0	80.7	19.2	0.0

[a] 30 mmol scale, 0.01 mol% T(*p*-R)PPFeCl, O_2 (1.8 MPa), 140 °C, 6.0 h.
[b] By HPLC analysis.

Then, the activities and selectivities of the Co(II)-, Ni(II)- and Mn(II)-porphyrins, which showed reasonable activities for their fluorinated derivatives observed above, were also investigated (Tables 3-5). The reaction activities of the Co(II)-porphyrins were improved with

the increase of the electron withdrawing capacity of the substituents, especially for the *p*-F, *p*-Cl, and *p*-Br substituted Co(II)-porphyrins, and similar effect was also observed for the discussed Fe(III)-porphyrins. Compared with the Fe(III)-porphyrins, most Co(II)- and Ni(II)-porphyrins showed lower activities. However, the T(*p*-Br)PPCo demonstrated higher activity than that of the T(*p*-Br)PPFeCl (44.7% vs 35.4%), and had a high reaction selectivity of 87.5% for ketone **2** (Table 3, entry 6), which was also the highest among all the Co(II)-porphyrins. As expected, the T(*p*-OH)PPCo and T(*p*-OH)PPNi also showed very poor activities (Table 3, entry 10; Table 4, entry 10). Moreover, the Mn(II)-porphyrins with electron withdrawing substituents, like -F, -Cl, and -Br, demonstrated even higher activities compared with the discussed Co(II) and Ni(II)-porphyrins. Unexpectedly, the T(*p*-OH)PPMn could significantly promote the aerobic oxidation, which was much different with the Fe(III)-, Co(II) and Ni(II)-based T(*p*-OH)PPM, this can be attributed to the high reaction activity of the central metal ion Mn^{2+}. Furthermore, these three type metalloporphyrins with electron-withdrawing substituents usually exhibited higher reaction activities than their metalloporphyrins with electron-donating substituents.

Generally, all the Co(II)-, Ni(II)- and Mn(II)-porphyrins exhibited reaction selectivities over 80% for the desired product ketone **2**. The selectivities were enhanced if decreasing the electron-withdrawing ability of the Co(II)-porphyrins (Table 3, entries 2-6), and similar results were also observed for the Co(II)-porphyrins with electron-donating groups (Table 3, entries 7-9). Moreover, the Ni(II)- and Mn(II)-porphyrins bearing electron-withdrawing groups usually

exhibited higher selectivities than these with electron-donating groups (Tables 4, 5). The T(*p*-Cl)PPNi demonstrated the highest activity (46.2%) and selectivity (87.7%) compared to other Ni(II)-porphyrins (Table 4, entry 5). Similar result was also observed for the T(*p*-Cl)PPMn. Especially, the T(*p*-Cl)PPMn gave the selectivity of up to 93.6% for ketone **2** with only a little acid **5**, which was easily removed from the reaction mixture, and no alcohol **3** was observed, importantly, the conversion was also over 50% (Table 5, entry 5).

Table 3. Aerobic Oxidation of 4-Ethylnitrobenzene Promoted by T(*p*-R)PPCo[a]

entry	T(*p*-R)PPCo	conversion[b] (%)	yield[b] (%)			selectivity[b] (%)		
			ketone	alcohol	acid	ketone	alcohol	acid
1	—	14.5	11.5	2.7	0.3	79.3	18.6	2.1
2	T(*p*-NO_2)PPCo	36.1	28.6	5.9	1.6	79.2	16.3	4.4
3	T(*p*-CN)PPCo	45.9	37.5	5.7	2.7	82.0	12.4	5.9
4	T(*p*-F)PPCo	48.7	41.5	3.0	4.2	85.2	6.1	8.6
5	T(*p*-Cl)PPCo	48.4	41.8	3.2	3.4	86.4	7.0	7.6
6	T(*p*-Br)PPCo	44.7	39.1	3.2	2.4	87.5	7.2	5.4
7	T(*p*-Me)PPCo	40.7	33.0	5.9	1.8	81.1	14.5	4.4
8	T(*p*-Et)PPCo	44.4	36.5	4.9	3.0	82.2	11.0	6.8
9	T(*p*-OMe)PPCo	44.5	38.8	2.9	2.8	87.2	6.5	6.3
10	T(*p*-OH)PPCo	1.3	0.6	0.0	0.7	46.2	0.0	53.8

[a] 30 mmol scale, 0.01 mol% T(*p*-R)PPCo, O_2 (1.8 MPa), 140 °C, 6.0 h.
[b] By HPLC analysis.

Table 4. Aerobic Oxidation of 4-Ethylnitrobenzene Promoted by T(*p*-R)PPNi[a]

entry	T(*p*-R)PPNi	conversion[b] (%)	yield[b] (%)			selectivity[b] (%)		
			ketone	alcohol	acid	ketone	alcohol	acid
1	—	14.5	11.5	2.7	0.3	79.3	18.6	2.1
2	T(*p*-NO_2)PPNi	25.1	21.4	3.6	0.1	85.3	14.3	0.4
3	T(*p*-CN)PPNi	33.3	26.8	4.1	2.4	80.5	12.3	7.2
4	T(*p*-F)PPNi	25.9	21.3	3.7	0.9	82.2	14.3	3.5
5	T(*p*-Cl)PPNi	46.2	40.5	3.0	2.7	87.7	6.5	5.8
6	T(*p*-Br)PPNi	35.4	30.1	3.4	1.9	85.0	9.6	5.4
7	T(*p*-Me)PPNi	40.7	33.0	5.9	1.8	81.1	14.5	4.4
8	T(*p*-Et)PPNi	34.0	27.2	5.0	1.8	80.0	14.7	5.3
9	T(*p*-OMe)PPNi	37.2	29.4	6.2	1.6	79.0	16.7	4.3
10	T(*p*-OH)PPNi	8.0	6.1	1.6	0.3	76.3	20.0	3.8

[a] 30 mmol scale, 0.01 mol% T(*p*-R)Ni, O_2 (1.8 MPa), 140 °C, 6.0 h.
[b] By HPLC analysis.

Table 5. Aerobic Oxidation of 4-Ethylnitrobenzene Promoted by T(*p*-R)PPMn[a]

entry	T(*p*-R)PPMn	conversion[b] (%)	yield[b] (%)			selectivity[b] (%)		
			ketone	alcohol	acid	ketone	alcohol	acid
1	——	14.5	11.5	2.7	0.3	79.3	18.6	2.1
2	T(*p*-NO_2)PPMn	34.2	29.2	2.4	2.6	85.4	7.0	7.6
3	T(*p*-CN)PPMn	47.6	40.5	3.4	3.7	85.1	7.1	7.8
4	T(*p*-F)PPMn	43.6	37.2	3.8	2.6	85.3	8.7	6.0
5	T(*p*-Cl)PPMn	51.9	48.6	0.0	3.3	93.6	0.0	6.4
6	T(*p*-Br)PPMn	51.0	44.5	3.1	3.4	87.3	6.1	6.7
7	T(*p*-Me)PPMn	44.5	38.8	2.9	2.8	87.2	6.5	6.3
8	T(*p*-Et)PPMn	50.9	38.2	4.0	8.7	75.0	7.9	17.1
9	T(*p*-OMe)PPMn	51.3	42.6	3.4	5.3	83.0	6.6	10.3
10	T(*p*-OH)PPMn	32.4	19.6	3.5	9.3	60.5	10.8	28.7

[a] 30 mmol scale, 0.01 mol% T(*p*-R)PPMn, O_2 (1.8 MPa), 140 °C, 6.0 h.
[b] By HPLC analysis.

Encouraged by these results, we next also examined the aerobic oxidation promoted by the T(*p*-R)PPZn, whose valance were difficult to change (Table 6). Most of the T(*p*-R)PPZn exhibited relatively low activities with conversions less than 50%, however, they showed high selectivities over 80% except the T(*p*-OH)PPZn. Surprisingly, the T(*p*-NO_2)PPZn demonstrated a very high activity with conversion up to 58.7%, by contrast, other nitro-based metalloporphyrins, like T(*p*-NO_2)PPFeCl, T(*p*-NO_2)PPCo, T(*p*-NO_2)PPNi and T(*p*-NO_2)PPMn, all showed very low activities. Besides, the T(*p*-NO_2)PPZn also exhibited the highest selectivity of 86.7% for ketone **2** with only 4.1% alcohol among all the T(*p*-R)PPZn. Additionally, the T(*p*-OH)PPZn also showed remarkably reaction activity with nearly double conversion yield compared to the blank experiment, although the reason was still unclear.

Table 6. Aerobic Oxidation of 4-Ethylnitrobenzene Promoted by T(*p*-R)PPZn[a]

entry	T(*p*-R)PPZn	conversion[b] (%)	yield[b] (%)			selectivity[b] (%)		
			ketone	alcohol	acid	ketone	alcohol	acid
1	—	14.5	11.5	2.7	0.3	79.3	18.6	2.1
2	T(*p*-NO_2)PPZn	58.7	50.9	2.4	5.4	86.7	4.1	9.2
3	T(*p*-CN)PPZn	26.9	22.6	3.3	1.0	84.0	12.3	3.7
4	T(*p*-F)PPZn	36.9	30.5	2.4	4.0	82.7	7.9	10.8
5	T(*p*-Cl)PPZn	26.6	22.8	3.1	0.7	85.7	11.7	2.6
6	T(*p*-Br)PPZn	44.6	37.2	5.3	2.1	83.4	11.9	4.7
7	T(*p*-Me)PPZn	40.7	35.3	4.0	1.4	86.7	9.8	3.4
8	T(*p*-Et)PPZn	32.4	26.0	5.0	1.4	80.2	15.4	4.3
9	T(*p*-OMe)PPZn	40.4	34.1	3.9	2.4	84.4	9.7	5.9
10	T(*p*-OH)PPZn	28.6	21.7	5.8	1.1	75.9	20.3	3.8

[a] 30 mmol scale, 0.01 mol% T(*p*-R)PPZn, O_2 (1.8 MPa), 140 °C, 6.0 h.
[b] By HPLC analysis.

Effect of substituent position. The above studies focused on the various metalloporphyrins bearing substituents on the *para*-positions of the phenyl rings. Next, metalloporphyrins with substituents on the *meta*- and *ortho*-positions of the phenyl rings, which had greater effect on the spatial configuration of the metalloporphyrins, were also investigated.

Table 7. Aerobic Oxidation of 4-Ethylnitrobenzene Promoted by T(*o/m/p*-Cl)PPM[a]

entry	T(*o*/*m*/*p*-Cl)PPM	conversion[b] (%)	yield[b] (%)			selectivity[b] (%)		
			ketone	alcohol	acid	ketone	alcohol	acid
1	T(*o*-Cl)PPFeCl	55.3 ↑	48.7	3.2	3.4	88.1	5.8	6.1
2	T(*m*-Cl)PPFeCl	54.2	46.9	3.6	3.6	86.5	6.6	6.6
3	T(*p*-Cl)PPFeCl	49.1	42.2	2.8	4.1	85.9	5.7	8.4
4	T(*o*-Cl)PPCo	61.8 ↑	52.7	5.1	4.0	85.3	8.3	6.5
5	T(*m*-Cl)PPCo	53.7	46.0	4.2	3.5	85.7	7.8	6.5
6	T(*p*-Cl)PPCo	49.0	41.8	3.8	3.4	85.3	7.8	6.9
7	T(*o*-Cl)PPMn	55.0 ↑	47.8	3.2	4.0	86.9 ↓	5.8	7.3
8	T(*m*-Cl)PPMn	53.6	47.7	2.0	3.9	89.0	3.7	7.3
9	T(*p*-Cl)PPMn	51.9	48.6	0.0	3.3	93.6	0.0	6.4
10	T(*o*-Cl)PPZn	42.2 ↑	38.1	3.1	1.0	90.3	7.3	2.4
11	T(*m*-Cl)PPZn	29.7	25.1	3.6	1.0	84.5	11.4	3.4
12	T(*p*-Cl)PPZn	26.6	22.8	3.1	0.7	85.7	11.7	2.6

[a] 30 mmol scale, 0.01 mol% T(*o*/*m*/*p*-Cl)PPM, O_2 (1.8 MPa), 140 °C, 6.0 h.
[b] By HPLC analysis.

Based on the high activities and selectivities for T(*p*-Cl)PPNi and T(*p*-Cl)PPMn (Table 4, entry 5 and Table 5, entry 5), the electron-withdrawing group, -Cl, was employed firstly to examine the substituent position effect (Table 7). All the Fe(III)-, Co(II)-, Mn(II)- and Zn(II)-porphyrins exhibited improved reaction activities with an order of T(*p*-Cl)PPM < T(*m*-Cl)PPM < T(*o*-Cl)PPM. The selectivities for all the T(*o*/*m*/*p*-Cl)PPM were over 85.0%, especially, the T(*o*-Cl)PPZn also demonstrated a selectivity of over 90.0%, comparable to that of the T(*p*-Cl)PPMn. Moreover, compared to the activities, the selectivities showed an opposite trend for the T(*o*/*m*/*p*-Cl)PPMn (Table 7, entries 7-9). These results indicated that the large steric hindrance of the phenyl groups on the T(*o*/*m*/*p*-Cl)PPM could significantly promote their reaction activities, but had little effect on the selectivity. This could be attributed to greater steric hindrance preventing the self-aggregation of the metalloporphyrins to stimulate their activities.[28]

The substituent position effect of the electron-donating group for the T(*o*/*m*/*p*-OMe)PPM was also examined (Table 8). Unlike the previous results for the T(*o*/*m*/*p*-Cl)PPM, the T(*o*/*m*/*p*-OMe)PPM showed an activities order of T(*o*-Cl)PPM < T(*m*-Cl)PPM < T(*p*-Cl)PPM. Their selectivities were in a range of 81.1-88.3%, which were relatively lower than these of the T(*o*/*m*/*p*-Cl)PPM. Moreover, the selectivities of the T(*o*/*m*/*p*-OMe)PPCo exhibited similar trend to their activities (Table 8, entries 4-6), however, the T(*o*/*m*/*p*-OMe)PPZn gave an opposite result (Table 8, entries 10-12).

Table 8. Aerobic Oxidation of 4-Ethylnitrobenzene Promoted by T(*o/m/p*-OMe)PPM[a]

entry	T(*o/m/p*-OMe) PPM	conversion[b] (%)	yield[b] (%)			selectivity[b] (%)		
			ketone	alcohol	acid	ketone	alcohol	acid
1	T(*o*-OMe)PPFeCl	42.6	36.8	3.0	2.8	86.4	5.9	5.5
2	T(*m*-OMe)PPFeCl	50.6	44.7	3.3	2.6	88.3	6.5	5.1
3	T(*p*-OMe)PPFeCl	55.1	47.7	4.0	3.4	86.6	7.3	6.2
4	T(*o*-OMe)PPCo	34.2	28.3	3.8	2.1	82.7	11.1	6.1
5	T(*m*-OMe)PPCo	42.7	35.5	4.4	2.8	83.1	10.3	6.6
6	T(*p*-OMe)PPCo	44.5	38.8	2.9	2.8	87.2	6.5	6.3
7	T(*o*-OMe)PPMn	20.7	17.3	2.6	0.8	83.6	12.6	3.9
8	T(*m*-OMe)PPMn	50.2	40.7	6.2	3.3	81.1	12.4	6.6
9	T(*p*-OMe)PPMn	51.3	42.6	3.4	5.3	83.0	6.6	10.3
10	T(*o*-OMe)PPZn	15.5	13.5	2.0	0.0	87.1	12.9	0.0
11	T(*m*-OMe)PPZn	42.3	36.3	3.6	2.4	85.8	8.5	5.7
12	T(*p*-OMe)PPZn	40.4	34.1	3.9	2.4	84.4	9.7	5.9

[a] 30 mmol scale, 0.01 mol% T(*o/m/p*-OCH_3)PPM, O_2 (1.8 MPa), 140 °C, 6.0 h.
[b] By HPLC analysis.

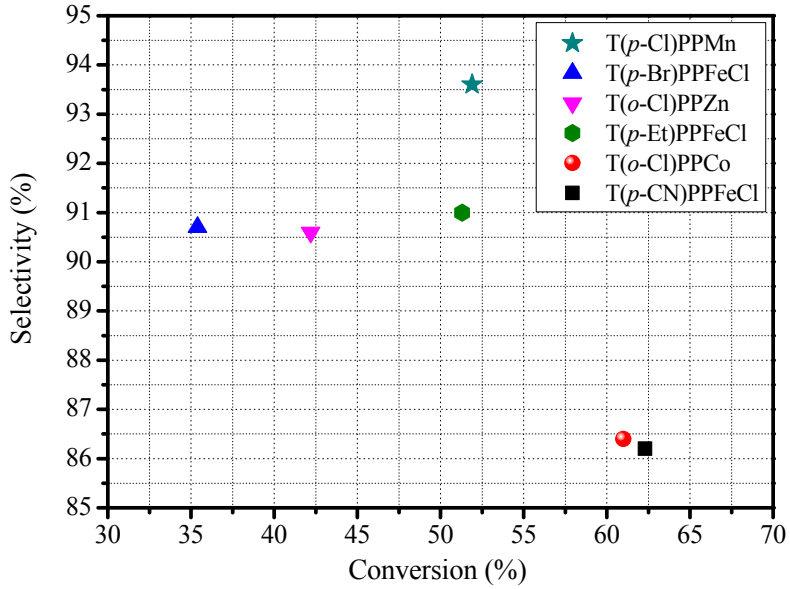


Figure 3. The activities and selectivties comparison of T(*p*-Cl)PPMn, T(*p*-Br)PPFeCl, T(*o*-Cl)PPZn, T(*p*-Et)PPFeCl, T(*o*-Cl)PPCo and T(*p*-CN)PPFeCl.

On the basis of the above results, it is demonstrated that the T(*p*-CN)PPFeCl and T(*o*-Cl)PPCo exhibited very high activities with conversion yields over 60% (Figure 3). Moreover, most of the metalloporphyrins showed high selectivites over 80.0%, and over 90.0% selectivities could be achieved for the T(*p*-Br)PPFeCl, T(*p*-Cl)PPMn, T(*o*-Cl)PPZn and T(*p*-Et)PPFeCl

(Figure 3). Especially, the T(*p*-Cl)PPMn demonstrated a selectivity and conversion of up to 93.6%, 51.9% respectively, and a yield of 48.6% for ketone, with only a little acid (6.4%) and no alcohol observed. This high selectivity makes us confidently to scale up the reaction.

Reaction time effect and large-scale experiment. Reaction time effect was also carefully investigated on the aerobic oxidation promoted by 0.01 mol% T(*p*-Cl)PPMn in 30.0 mmol scale (4.53 g) in a 100 mL pressure reactor. The selectivity continues to increase in the first six hours, and then begins to decline (Figure 4a). This is attributed to the increase of the over-oxidation product **5** (Figure 4b). The 1-(4-nitrophenyl) ethanol (**3**) can be obviously detected only in the first five hours. The isolated yields after column chromatography for the desired ketone **2** were consistent with the conversion yields obtained from the HPLC analyses (Table 9 entries 6-8).

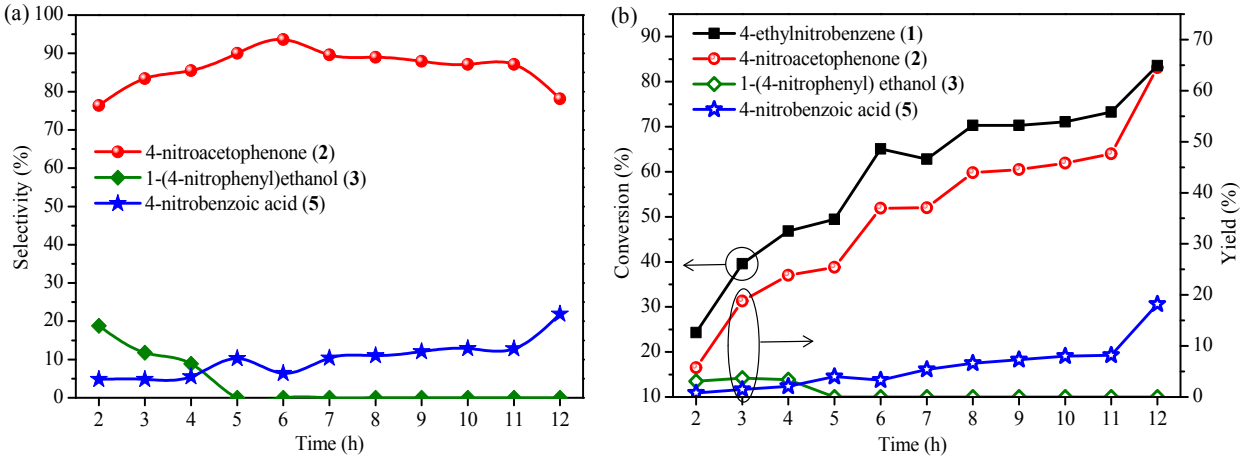


Figure 4. (a) Product selectivties and (b) conversion and product yields versus reaction time for the aerobic oxidation of **1** in a 30.0 mmol scale promoted by 0.01 mol% T(*p*-Cl)PPMn under O_2 (1.8 MPa) at 140 °C in a 100 mL pressure reactor.

Table 9. Reaction time effect of the aerobic oxidation of 4-ethylnitrobenzene promoted by T(*p*-Cl)PPMn

entry	time (h)	conversion[b] (%)	yield[b] (%)			selectivity[b] (%)		
			ketone	alcohol	acid	ketone	alcohol	acid
1	2.0	16.5	12.6	3.1	0.8	76.4	18.8	4.8
2	3.0	31.3	26.1	3.7	1.5	83.4	11.8	4.8
3	4.0	37.0	32.5	3.4	2.1	87.8	9.2	5.7
4	5.0	38.8	34.8	0.0	4.0	90.0	0.0	10.3
5	6.0	51.9	48.6	0.0	3.3	93.6	0.0	6.4
6	7.0	52.0	46.6 (49.2)[c]	0.0	5.4	89.6	0.0	10.4
7	8.0	59.8	53.2 (54.3)[c]	0.0	6.6	89.0	0.0	11.0
8	9.0	60.5	53.2 (55.1)[c]	0.0	7.3	87.9	0.0	12.1
9	10.0	61.9	53.9	0.0	8.0	87.1	0.0	12.9
10	11.0	64.0	55.8	0.0	8.2	87.1	0.0	12.8
11	12.0	83.1	64.9 (66.0)[c]	0.0	18.2	78.1	0.0	21.9

[a] 30 mmol scale, 0.01 mol% T(*p*-Cl)PPMn, O_2 (1.8 MPa), 140 °C, 6.0 h. [b] By HPLC analysis.
[c] Isolated yields after column gromatography in the parentheses.

Before scaling up the experiment, the safety was further evaluated with a real reaction mixture (1.0 g) and additional T(*p*-Cl)PPMn (0.24 mg) (Figure 5). The ARC test curves also showed an exotherm event and pressure raising at about 250 °C. This result is similar to the curves of the ARC test temperature and pressure history for a mixture of **1** (0.24 g), **2** (0.24 g) and **5** (0.01 g), which was discussed above. However, the pressure is much bigger, attributing to the more reaction mixture and the additional T(*p*-Cl)PPMn.

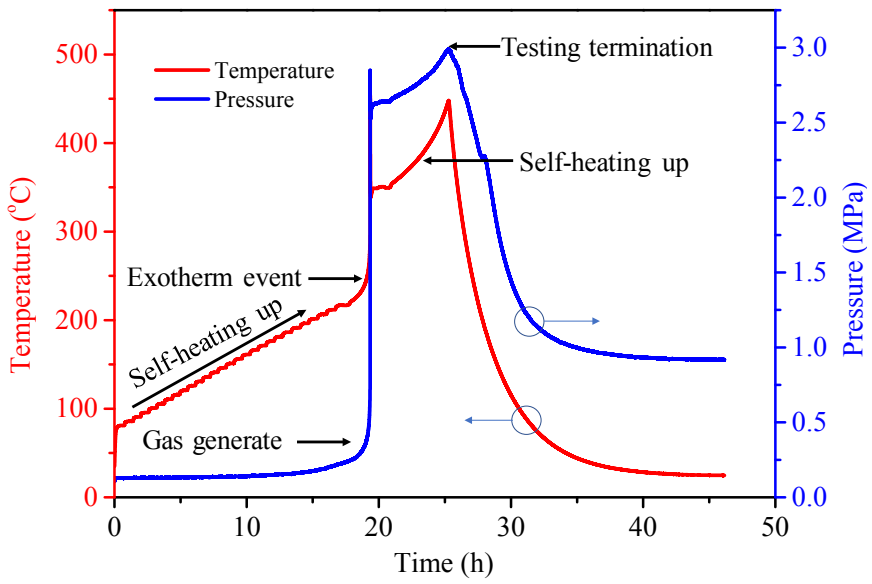
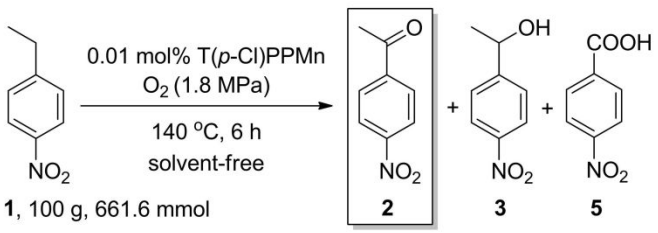


Figure 5. ARC test temperature and pressure history for a real reaction mixture (1.0 g) and T(*p*-Cl)PPMn (2.4 mg).



product	content (wt%)[d]			
	1	**2**	**3**	**5**
39.21 g[a]	0.0	99.3	0.0	0.7
5.35 g[b]	0.0	87.2[e]	0.0	12.8[e]
59.94 g[c]	86.6	9.4	3.7	0.4

[a] Product from crystallization. [b] Product from second crystallization. [c] Residue from mother solution. [d] By HPLC analysis. [e] By ^{1}H NMR.

conversion/**1** (%)	total yield (%)			selectivity (%)		
	2	**3**	**5**	**2**	**3**	**5**
48.2	45.1	2.0	1.1	93.5	4.2	2.3

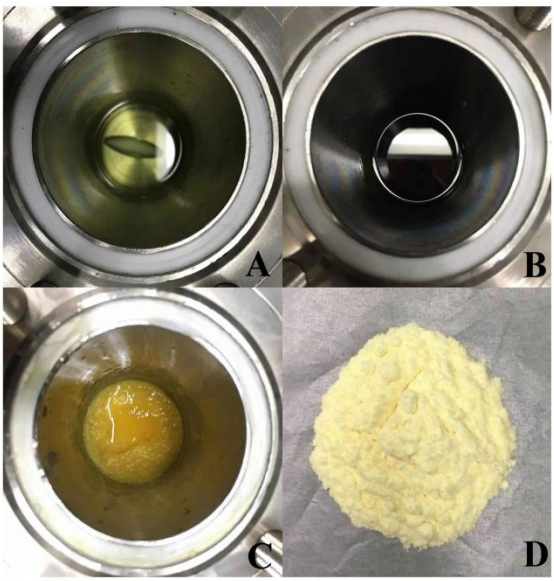


Figure 6. (left) Large-scale experiment. (right) 100 g **1** in a 250 mL pressure reactor (A); a mixture of 100 g **1** and 0.01 mol% T(*p*-Cl)PPMn (B); reaction mixture under O_2 (1.8 MPa) at 140 °C for 6 h (C); the 39.21 g product **2** obtained by crystallization (D).

Large-scale experiment was set up in 661.6 mmol scale (100 g) in a 250 mL pressure reactor. The reaction could proceed smoothly with a 48.2% conversion and 93.5% selectivity (Figure 6, left) and gave a yellow reaction mixture (Figure 6, right, C). The desired product ketone **2** (39.21 g, >99.0% purity) could be easily separated by crystallization in ethanol in a light yellow solid (Figure 6, right, D). Another 5.35 g ketone **2** could be obtained by adding some hexane to the mother solution to give a total isolated yield of 40.8% (see Supporting information for details). Compared with the above result, this lower conversion and the generation of alcohol **3** were due to the relatively smaller contact area between the reactants and the O_2 gas.

It should be noted that the metalloporphyrin, T(*p*-Cl)PPMn, completely decomposed through the color change before and after the reaction (Figure 6, right, A-C). Similar phenomena were also observed in aerobic oxidation promoted by other metalloporphyrins discussed above. Also, the bleach or degradation of the metalloporphyrins in reaction systems were reported by Cunningham,[47-49] Nasrollahi[50] and Khazaei's group.[51] The composition of the reaction mixture was also confirmed by a UV-Vis spectra analyses (Figure 7). The high energy strong absorption bands below 450 nm are assigned to $^1(\pi\text{-}\pi^*)$ transitions of the phenyl groups of in the 4-ethylnitrobenzene, T(*p*-Cl)PPMn and T(*p*-Cl)PP. It can be seen clearly that the strong absorption band for Soret band at 477 nm and two reletively weak absorption bands for the Q bands at 582 and 617 nm. Also, the porphyrin T(*p*-Cl)PP exhibits four Q bands at 514, 549, 588 and 647 nm.

However, after reaction, all the characteristic absorption bands of 450-700 nm for the T(*p*-Cl)PPMn and T(*p*-Cl)PP disappeared, indicating the decompsition of the T(*p*-Cl)PPMn, and also the porphyrin rings are not existing. The reaction could continue if the reaction time was prolonged (Table 9). These results demonstrated that the metalloporphyrins were not catalysts, but acted as initiators in our reaction system.

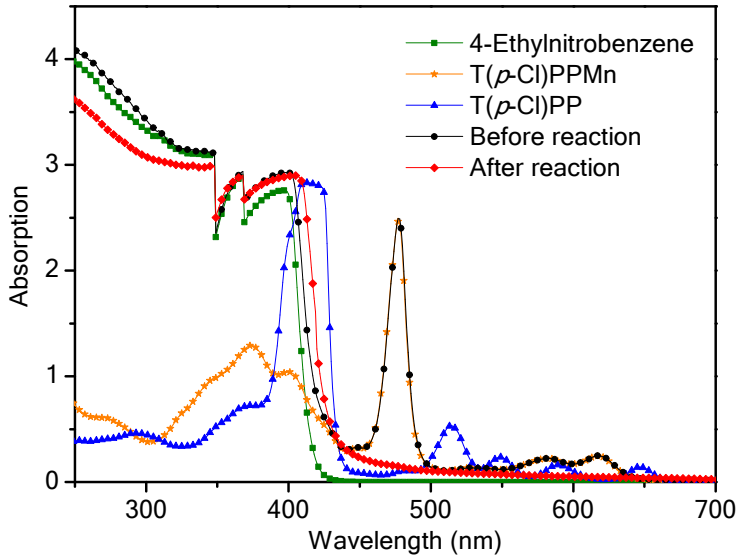


Figure 7. UV-Vis spectra of 4-ethylnitrobenzene (0.3 M), T(*p*-Cl)PPMn (3.0×10^{-5} M), T(*p*-Cl)PP (3.0×10^{-5} M), and mixture of before reaction and after reaction. Wherein the concentrations of 4-ethylnitrobenzene (0.3 M) and T(*p*-Cl)PPMn (3.0×10^{-5} M) in the mixture before reaction are the same with their pure samples.

CONCLUSION

A solvent-free process for the oxidation of 4-ethylnitrobenzene to 4-nitroacetophenone promoted by metalloporphyrins was developed in pressure reactor using O_2 as clean oxidant. This process

is environment-friendly and can also avoid the loss of the raw material and O_2. More than 60 metalloporphyrins had been employed to systematically explore the central metal ion effect and the ligand effect on the reaction activities and selectivities. Generally, the Fe(III)- and Mn(II)-porphyrins exhibited higher activities than these of the Co(II)-porphyrins, and Ni(II)- and Zn(II)-porphyrins usually showed poor activities. Moreover, the Fe(III)-, and Co(II)-porphyrins with electron-withdrawing substituents on the *para*-positions of the phenyl rings showed activities with an order of T(*p*-Br)PPM < T(*p*-Cl)PPM < T(*p*-F)PPM. The substituent position effect on the reaction activities of T(*o*-Cl)PPM > T(*m*-Cl)PPM > T(*p*-Cl)PPM, and T(*o*-OMe)PPM < T(*m*-OMe)PPM < T(*p*-OMe)PPM were observed, where the M could be Fe(III), Co(II), Mn(II) or Zn(II). The T(*p*-CN)PPFeCl and T(*o*-Cl)PPCo exhibited very high activities with conversion yields over 60% (Figure 2). Furthermore, most of the metalloporphyrins showed high selectivites over 80.0%, and over 90.0% selectivities could be achieved for the T(*p*-Br)PPFeCl, T(*p*-Cl)PPMn, T(*o*-Cl)PPZn and T(*p*-Et)PPFeCl (Figure 2). Especially, the T(*p*-Cl)PPMn demonstrated a selectivity and conversion of up to 93.6%, 51.9% respectively, and a yield of 48.6% for ketone, with only a little acid (6.4%) and no alcohol observed, and the selectivity was nearly keeping the same for a large-scale experiment (100 g). TON of up to 5370 could be achieved for the desired ketone promoted by T(*p*-CN)PPFeCl, which was over 20 times higher than the best reported catalysts.[42] Several efficient metalloporphyrins with high selectivities were developed for the aerobic oxidation of the of 4-ethylnitrobenzene, which could provide an efficient alternative process for the preparation of the 4-nitroacetophenone.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Details of sampling and analytical methods, NMR and HRMS spectra of the products (PDF).

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Notes

The authors declare no competing financial interest.

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