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Cyclohexene Promoted the Efficient Biomimetic Oxidation of Alcohols to Carbonyl Compounds Catalyzed by Manganese Porphyrin under Mild Conditions

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Summary of main observation and conclusion Selective oxidation of alcohols to corresponding carbonyl compounds is one of the most important processes both in academic and application research. As one kind of biomimetic catalysts, metalloporphyrins-catalyzed aerobic oxidation of alcohols with aldehyde as hydrogen donator is gathering much attention. However, using olefins as another kind hydrogen donator for the aerobic oxidation of alcohols was not been reported. In this study, a system comprising managenese porphyrin and cyclohexene for the biomimetic aerobic oxidation of alcohols to carbonyl compounds was developed. The catalytic system exhibited excellent catalytic performance and selectivity towards the corresponding products for most primary and secondary alcohols under mild conditions. Based on the results obtained from experiments as well as *in situ* EPR (Electron Paramagnetic Resonance) and UV–vis spectroscopy, the role of cyclohexene was demonstrated.

Background and Originality Content

The selective oxidation of alcohols to carbonyl compounds is one of the most important processes because the products are valuable in organic synthesis[1]. Numerous methods for the oxidation of alcohols have been developed involve the use of stochiometric oxidants such as chromium oxides[2], TBHP (*tert*-butyl hydrogen peroxide)[3], hydrogen peroxide[4] etc., which causes environmental and high cost problems. From the viewpoints of enviroment and cost, selective oxidation of alcohols with molecular oxygen is extremely valuable and particularly attractive. The aerobic oxidation of alcohols catalyzed by TEMPO (2,2,6,6-tetramethylpiperidyl-l-oxy) or its derivatives in absence of transition metal is gathering much attention[5]. And variety of methods were reported on the aerobic oxidation of alcohols catalyzed by metal catalysts like ruthenium[6], manganese[7], cobalt[8], and Au-Pd alloy nanoparticles[9] or vanadium oxide[10] presented excellent activity.

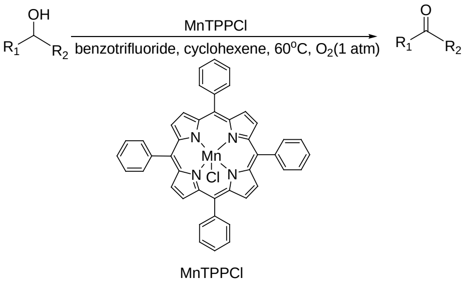
Particularly, most common transition metals like iron and copper are also efficient for the aerobic oxidation of alcohols[11]. Ma group reported a general an practical catalytic protocol of $Fe(NO_3)_3{\cdot}9H_2O$/TEMPO/NaCl to accomplish the selective aerobic oxidation of alcohols to aldehydes or ketones at room temperature[12]. Copper complexes bearing redox-active ligands catalyzed the aerobic oxidation of alcohols to aldehydes efficiently without using any additives at room temperature[13]. Most recently, $Cu(NO_3)_3{\cdot}3H_2O$/TEMPO or (4-HO) TEMPO catalyst presented excellent performance in the selective aerobic oxidation of alcohols to corresponding aldehydes using readily available reagents, at room temperature with O_2 or ambient air as the oxidant[14].

There is always imbalance between conversion and selectivity in the aerobic catalytic oxidation reaction. This is mainly due to the harsh conditions for activating molecular oxygen in the oxidation process[15]. Therefore, it is of great concern to achieve the activation of dioxygen under mild conditions. Metalloporphyrins-mediated biomimetic catalytic system is the promising approach due to the similar reactivity as enzyme-catalyzed oxidation, which has been gathering much attention in recent years[16].

In bio-oxidation mediated by cytochrome P450 enzymes, hydroxylation can be achieved by utilizing NAD(P)H (nicotinamide adenine dinucleotide (phosphate)) as the hydrogen donator for activating molecular oxygen[17]. Therefore, aldehydes acts as NAD(P)H-like hydrogen donator are widely used to activate dioxygen in metalloporphyrins-catalyzed oxidation system[18]. Other compounds that containing active α-hydrogen are desired to have the efficiency of molecular oxygen activation. Recently, our group reported the biomimetic aerobic epoxidation of olefins with isopropylbenzene as hydrogen donator, with excellent conversion and selectivity up to 94%[19]. The biomimetic aerobic oxidation of cyclohexane and diphenylmethane in the presence of cyclohexene as hydrogen donator were also reported recently[20].

However, the selective aerobic oxidation of alcohols in presence of cyclohexene as hydrogen donator catalyzed by metalloporphyrins with molecular oxygen as oxidant is still limited. As part of our ongoing interests in biomimetic catalytic oxidations process with dioxygen, the aerobic oxidation of alcohols to carbonyl compounds catalyzed by manganese porphyrin in the presence of cyclohexene has been developed in this work (*Scheme* 1). The catalytic system exhibited excellent catalytic performance and selectivity towards the corresponding products for most primary and secondary alcohols under mild conditions. Based on the results obtained from experiments as well as *in situ* EPR and UV–vis spectroscopy, a plausible mechanism for the alcohol aerobic oxidation catalyzed by MnTPPCl (*meso*-triphenylporphyrin manganese chloride) in presence of cyclohexene was proposed.

Scheme 1 Aerobic oxidation of alcohols catalyzed by manganese porphyrins in presence of cyclohexene



Results and Discussion

Catalytic performance

Using benzyl alcohol as testing substrate, the reactivity and selectivity of catalytic system involved metalloporphyrins and cyclohexene were explored (Figure 1). In the control experiments, that is the reaction was conducted in absence of either MnTPPCl or cyclohexene, almost no oxidation occurred after 60 min stirring. Then, about 25% benzyl alcohol was converted to corrresponding aldehyde in excellent selectivity when the oxidation was carried out with either MnTPPCl or cyclohexene alone. However, the simultaneous presence of MnTPPCl and cyclohexene could make the oxidation exhaustivity. This result indicates that the synergistic action plays significant role in the biomimetic catalytic oxidation of alcohols.

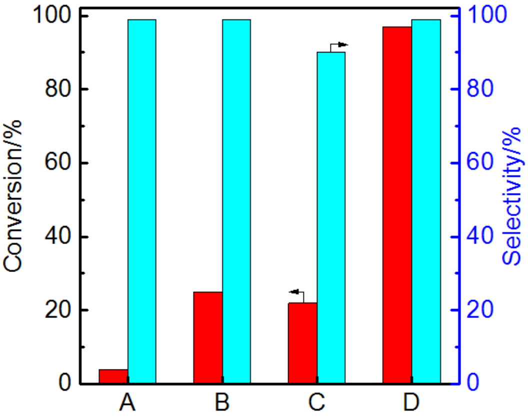


Figure 1. Aerobic oxidation of benzyl alcohol. Benzyl alcohol (2.0 mmol), MnTPPCl (0.1 mol%), benzotrifluoride (5 mL), O_2 bubbling, 60°C, 60 min. A: In absence of catalyst and cyclohexene; B: MnTPPCl (0.1 mol%); C: cyclohexene (1.0 mmol); D: in presence of MnTPPCl (0.1 mol%) and cyclohexene (1.0 mmol).

Followed, the activities of different metalloporphyrins that have same ligand but different metal ions were tested. Comparison among the tested catalysts revealed that manganese porphyrins (MnTPPCl) exhibited higher catalytic activity than iron, copper, cobalt and zinc porphyrins (entries 1-5, Table 1). These catalytic performance differences could be ascribed to the stability of high-valent species during the oxidation[21]. Manganese complexes have been reported to be efficient for alcohols oxidation due to its various multiple valence**[22]**. Meng group also reported the aerobic oxidation of benzyl alcohol to benzaldehyde with 95% yield by using decacarbonyldimanganese [$Mn_2(CO)_2$] as catalyst at 120°C**[23]**.

Interestingly, the selectivity of benzaldehyde was excellent whatever metalloporphyrins catalyst was used in this biomimetic oxidation system.

The selective oxidation of benzyl alcohol with different amount of cyclohexene were examined. The conversion of benzyl alcohol increased as cyclohexene amount rose (entries 6 and 7, Table 1). But the large excess amount of cyclohexene could promote over-oxidation of benzaldehyde to benzoic acid (entry 7, Table 1). The effect of solvent on the aerobic oxidation of benzyl alcohol with MnTPPCl catalyst and cyclohexene was also examined. As shown in Table 1, the efficiency of alcohol oxidation is closely related with the polarity of the used solvents (entries 8~10, Table 1). The strong electrophilic effect of benzotrifluoride was most favorable to the alcohol oxidation. Moderate yield of benzaldehyde was obtained using ethyl acetate and acetonitrile (entries 9 and 10, Table 1). The remarkable differences could be attributed to two aspects. Beside the solvation effect, benzotrifluoride is favorable to improve the stability of free radicals[24].

The oxidation was greatly influenced by the reaction temperature (entries 11 and 12, Table 1). With increasing temperature, benzyl alcohol conversion increased as temperature rose. But the selectivity towards the over-oxidation product (benzoic acid) increased when the oxidation was conducted at 70 °C (entry 12, Table 1).

Table 1. Optimization of reaction conditions for the oxidation of benzyl alcohol by MnTPPCl and cyclohexene[a]

Entry	Catalyst	Amount of cyclohexene (mmol)	Solvent	Conv. (%)	Select. (%)
1	FeTPPCl	1.0	Benzotrifluoride	80	>99
2	MnTPPCl	1.0	Benzotrifluoride	97	>99
3	CuTPP	1.0	Benzotrifluoride	72	>99
4	CoTPP	1.0	Benzotrifluoride	82	>99
5	ZnTPP	1.0	Benzotrifluoride	83	>99
6	MnTPPCl	0.5	Benzotrifluoride	62	>99
7[b]	MnTPPCl	1.5	Benzotrifluoride	98	92(8)
8	MnTPPCl	1.0	Toluene	76	>99
9	MnTPPCl	1.0	Ethyl acetate	45	>99

10	MnTPPCl	1.0	Acetonitrile	52	>99
11[c]	MnTPPCl	1.0	Benzotrifluoride	69	>99
12[d]	MnTPPCl	1.0	Benzotrifluoride	99	81(19)

[a] Benzyl alcohol (2.0 mmol), solvent (5 mL), catalyst (0.1 mol%), O_2 bubbling, 60 °C, 60 min.

[b] The numbers in parentheses indicate the selectivity of benzoic acid.

[c] 50 °C.

[d] [illegible]0 °C, the numbers in parentheses indicate the selectivity of benzoic acid.

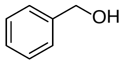
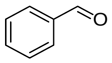
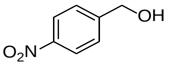
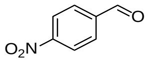
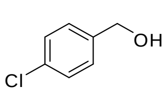
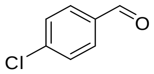
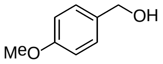
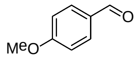
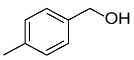
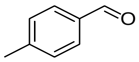
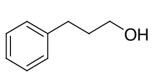
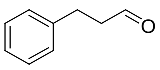
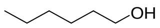
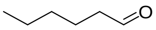
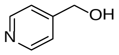
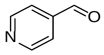
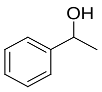
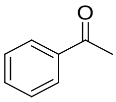
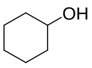
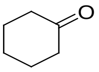
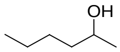
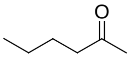
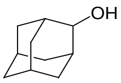
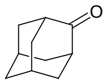
To further identify the scope of alcohol reactions in presence of MnTPPCl and cyclohexene, the study was extended to include various benzylic alcohols, primary and secondary alcohols and the results are summarized in Table 2.

The catalytic system appeared efficient towards most benzylic primary alcohols, in which alcohols were smoothly converted to corresponding aldehydes with high yields (entries 1~6, Table 2). The efficiency for the oxidation of benzylic primary alcohols in this catalytic system was dependent on the electronic property of the *para* substituents of the substrate. Compared to benzylic alcohols with electron-donating groups, electron-withdrawing groups seemed unfavorable for forming carbonyl compounds, in which longer reaction time was necessary. It could be attributed to the electronic effect promoting β-hydride elimination. The catalytic system showed also excellent efficiency towards the oxidation of saturated primary aliphatic alcohols, such as 3-phenylpropanol and 1-hexanol (entries 6 and 7, Table 2). The present catalyticic system was also efficient for basic substrates like 4-pyridinemethanol. It was converted with high conversion (87%) within 90 min (entry 8, Table 2). Furthermore, MnTPPCl with cyclohexene system was found to be efficient for the oxidation of most secondary to the corresponding ketones (entries 9-12, Table 3). Even sterically hindered 2-adamantanol could smoothly be converted into corresponding ketone with yield of 92% (entry 12, Table 2).

Plausible mechansim

The profile of benzyl alcohol oxidation catalyzed by MnTPPCl and cyclohexene in presence of molecular oxygen is shown in Figure 2. The conversion of benzyl alcohol slowly increased within the first [illegible] min. Then, the reaction rate rapidly increased. It is clear that there is an induction period during the catalytic oxidaiton process, which exihibited the features of the radical reaction. For verifying the free-radical mechanism, 2,6-*di*-*tert*-butylphenol (1 mmol), serving as the free-radical inhibitor, was used. After the addition of this inhibitor, the oxidation was subsequently quenched.

Table 2. Oxidation of various alcohols catalyzed by MnTPPCl with cyclohexene[a]

Entry	Substrate	Product	Time /min	Conv. /%	Select. /%
1			60	97	>99
2			90	90	>99
3			90	92	>99
4			60	99	>99
5			60	99	>99
6			60	96	>99
7			60	95	>99
8			90	87	>99
9			60	96	>99
10			60	97	>99
11			60	93	>99
12			90	92	>99

[a] Substrate (2.0 mmol), MnTPPCl (0.1 mol%), benzotrifluoride (5 mL), cyclohexene (1.0 mmol), O_2 bubbling, 60 °C.

As has been previously reported, high-valent species was generally produced in the oxidation catalyzed by metalloporphyrins[25]. The *in situ* UV–vis spectra were recorded on a spectrophotometer connected to an AvaSpec-2048 spectrometer under the given reaction conditions, and the obtained spectra were presented in Figure 3.

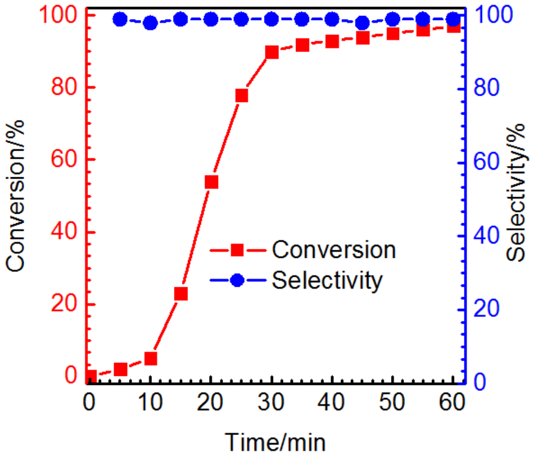


Figure 2. Reaction profile of benzyl alcohol aerobic oxidation catalyzed by MnTPPCl in presence of cyclohexene. Benzyl alcohol (2.0 mmol), benzotrifluoride (5 mL), MnTPPCl (0.1 mol%), cyclohexene (1.0 mmol), O_2 bubbling, 60 °C.

The spectrophotometer was programmed for acquiring UV–vis spectrum every 5 min. As shown in Figure 3, as the reaction proceeded, the Soret band gradually decreased at 477 nm. Meanwhile, a red shift with 5 nm in the Soret band from 477 nm to 482 nm was observed. The color bleach of mixture solution from dark green to yellow was also observed. Such changes in the *in situ* UV–vis spectra have been reported to be attributed to the generation of the oxidize active species ($PorMn^V=O$) during oxidation[26].

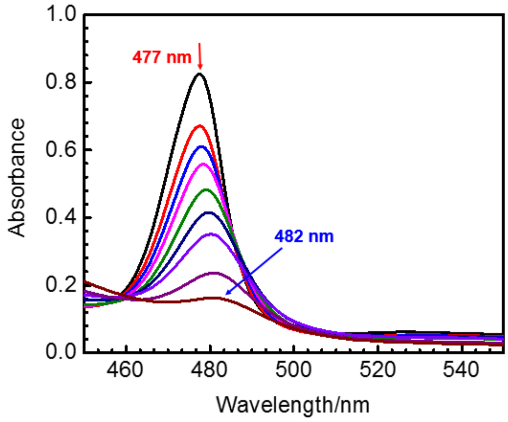


Figure 3. *In situ* UV-vis spectra for benzyl alcohol aerobic oxidation catalyzed by MnTPPCl in presence of cyclohexene (interval 5 min). Benzyl alcohol (2.0 mmol), benzotrifluoride (5 mL), MnTPPCl (0.1 mol%), cyclohexene (1.0 mmol), O_2 bubbling, 60 °C.

To obtain more insights into the role of cyclohexene in the oxidation of alcohols catalyzed by manganese porphyrins, *in situ* EPR spectra was used to record the signal changes of free radicals. The catalytic oxidation in benzotrifluoride was carried out in a Wilmad WG-810-A quartz-flat cell. A mixture of benzotrifluoride solution comprised MnTPPCl, cyclohexene, and PBN (free-radical spin-trapping agent). The cell was sealed after filling dioxygen. EPR analyses were performed under a microwave frequency of 9.05 GHz at 333 K. The results were showed in Figure 4.

According to previous reports, the α-hydrogen atom of cyclohexene was easily abstracted under high temperature, affording an allylic radical[27]. As shown in Figure 4A, two stable PBN radical adducts were obtained when the oxidation of cyclohexene was carried out in molecular oxygen without MnTPPCl (Figure 4A, ***a***). Adduct **1** was characterized by hyperfine splitting constant (a_{N1} = 15.2 G, a_{H1} = 3.6 G, g = 2.0033), adduct **2** was characterized by hyperfine splitting constants, (a_{N2} = 14.0 G, a_{H2} = 2.3 G, g = 2.0033). Allylic radical can combine with dioxygen quickly to generate allylic peroxyl radical. According to our previous works, adduct **1** should be assigned to carbon-centred cyclohexenyl radical ($C_6H_9\bullet$), adduct **2** is assigned to cyclohexenyl peroxyl radical ($C_6H_9OO\bullet$)[20a].

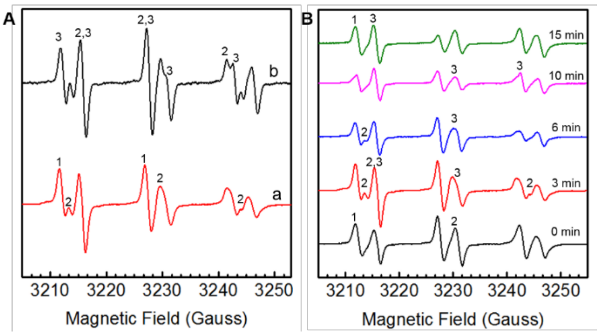


Figure 4. A: *in situ* EPR spectra of cyclohexene aerobic oxidation at 333K, (a) without MnTPPCl, (b) catalyzed by MnTPPCl; B: *in situ* EPR spectra of benzyl alcohol oxidation catalyzed by MnTPPCl and cyclohexene at 333K.

When MnTPPCl catalyst was added in the mixture, the signal of adduct **1** disappeared gradually, while another radical signal constantly increased (adduct **3**). Adduct **3** was characterized by hyperfine splitting constant (a_{N3} = 15.5 G, a_{H3} = 3.4 G, g = 2.0031). Therefore, the manganese porphyrin catalyst has been suggested to be favorable for the transfer of radical **2** to radical **3**. The radical transfer involves the participation of manganese porphyrins catalyst. High-valent Mn species and cyclohexenyl alkoxyl radical could be generated from the heterolysis of O-O bond in cyclohexenyl peroxyl radical ($C_6H_9OO\bullet$). Hence, the radical should be assigned to cyclohexenyl alkoxyl radical ($C_6H_9O\bullet$)[20b].

Figure 4B shows time courses of *in situ* EPR spectra towards benzyl alcohol oxidation catalyzed by MnTPPCl and cyclohexene. As reaction progresses, the radical transformation of radical **2** to radical **3** was further confirmed. The active cyclohexenyl alkoxyl radical can react with one cyclohexene molecule to produce cyclohexen-1-ol and one cyclohexenyl radical ($C_6H_9\bullet$).

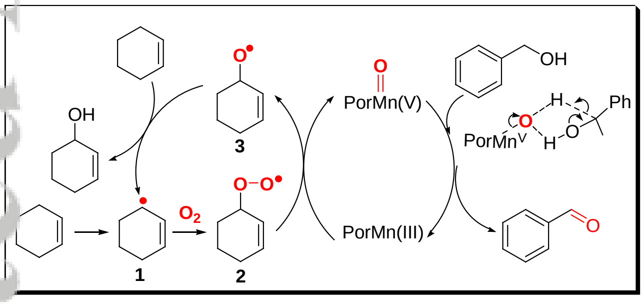
Based on the above discussions, a plausible mechanism was proposed for the aerobic oxidation of alcohols to carbonyl compounds in the presence of MnTPPCl and cyclohexene, as shown in *Scheme 2*.

The reaction initiated from the generation of cyclohexenyl radical (**1**, $C_6H_9\bullet$), which is derived from the abstraction of hydrogen at the allylic position under reaction temperature conditions. Cyclohexenyl peroxyl radical (**2**, $C_6H_9OO•$) is rapidly formed by the insertion of oxygen. Subsequently, cyclohexenyl alkoxyl radical (**3**, $C_6H_9O•$) and PorMn(V)=O were generated from the O-O bond cleavage of cyclohexenyl peroxyl radical (**2**, $C_6H_9OO•$). Cyclohexenyl alkoxyl radical is an active oxy radical, which can react with another cyclohexene molecule to produce 2-cyclohexen-ol and cyclohexenyl radical. The formation of benzaldehyde is attibuted to the reaction of benzyl alcohol with Mn-oxo species, followed by the β-hydride elimination.

Conclusions

In this study, a system comprising managenese porphyrin and cyclohexene for the biomimetic aerobic oxidation of alcohols to carbonyl compounds was developed. The catalytic system exhibited excellent catalytic performance and selectivity towards the corresponding products for most primary and secondary alcohols under mild conditions. Based on the results obtained from experiments as well as *in situ* EPR and UV–vis spectroscopy, a plausible mechanism for the alcohol oxidation catalyzed by managenese porphyrin in presence of cyclohexene was presented. The role of cyclohexene was to generate Mn-oxo species through the propagation of free radical that generated from cyclohexene.

Scheme 2 Plausible mechanism for the aerobic oxidation of benzyl alcohol catalyzed by MnTPPCl in presence of cyclohexene



Experimental

Materials and methods

Alcohols and the corresponding carbonyl comppounds, cyclohexene, *N-tert*-butyl-alpha-phenylnitrone (PBN) were purchased from J&K Scientific Ltd. Other reagents were of analytical grade and used without further purification unless indicated. Metalloporphyrin catalysts were prepared according to previous procedures[28].

FT-IR spectra were obtained on a Bruker 550 spectrometer. The UV–vis spectra were recorded on a Shimadzu UV-2450 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 M spectrometer. Elemental analysis data were received on a Vario EL III system. Mass spectra were obtained on a Shimadzu LCMS-2010A. The *in situ* UV–vis spectra were recorded on a spectrophotometer connected to an AvaSpec-2048 spectrometer. The *in situ* EPR (Electron Paramagnetic Resonance) spectroscopy measurements were performed on a JESFA-200 (JEOL, Japan) spectrometer using PBN as a free-radical spin-trapping agent.

General procedures for the biomimetic catalytic oxidation of alcohols

The catalytic oxidation of alcohols were carried out in a magnetically stirred glass reaction tube fitted with a reflux condenser. Using benzyl alcohol as a model substrate, a typical procedure was as follows: A solution of benzotrifluoride (5 mL), benzyl alcohol (2 mmol), cyclohexene (2.0 mmol), MnTPPCl ($2×10^{-3}$ mmol, 0.1mol% based substrate) and 0.5 mmol naphthalene (inert internal standard) were added in the tube. Then the mixture was stirred at 60°C for 60 min with the bubbled molecular oxygen. The consumption of benzyl alcohol and formation of benzaldehyde were monitored by GC (Shimadzu GC-2010 plus) and GC-MS (Shimadzu GCMS-QP2010). Each catalytic reaction was repeated three times.

Oxidation of alcohol monitored by *in situ* UV–vis spectroscopy

Catalytic oxidation was carried out in the stainless-steel reactor (Parr 5510) equiped with a reflux condenser. The reaction mixture contained solvent (benzotrifluoride), catalyst (MnTPPCl), alcohol and cyclohexene were added into the reactor. The reactor sealed and dioxygen bubbled through the mixture. The reaction mixture was heated to 60 °C. The *in situ* UV–vis spectra of MnTPPCl were recorded on the AvaSpec-2048 spectrometer, which was equipped with a high-pressure, high-temperature probe and connected to the stainless-steel reactor. The spectrophotometer was programmed at 5 min intervals.

Oxidation of alcohol monitored by *in situ* EPR spectroscopy

Aerobic catalytic oxidation in benzotrifluoride was performed in a Wilmad WG-810-A quartz-flat cell with a mixture of the solution of MnTPPCl as well as cyclohexene, alcohol and PBN. A JESFA-200 (JEOL, Japan) spectrometer was utilized to record *in situ* EPR spectra. The cell was sealed after filling dioxygen. EPR analyses were performed at a microwave frequency of 9.05 GHz at 333K. Instrument conditions for all analyses were as follows: microwave frequency, 9.05 GHz; modulation amplitude, 2 mT; modulation frequency, 100 kHz; power, 0.998 mW; and time constant, 0.03 s. All spectra represent the signal-averaged sum of six scans unless otherwise noted.

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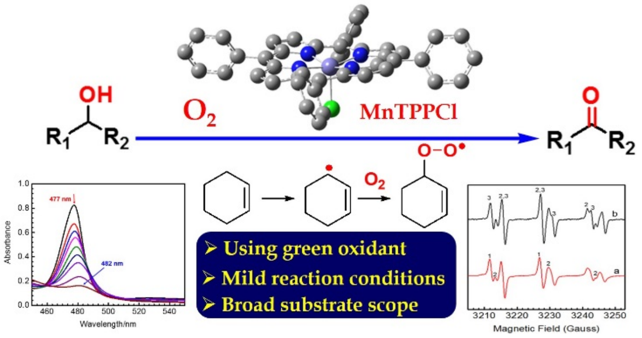

ao-Hui Liu, Hai-Yang Yu, Can Xue, Xian-Tai Zhou,* Hong-Bing Ji*

A system comprising managenese porphyrin and cyclohexene for the biomimetic aerobic oxidation of alcohols to carbonyl compounds was developed.

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