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Cytochrome P-450 model reactions: Efficient and highly selective oxidation of alcohols with tetrabutylammonium peroxymonosulfate catalyzed by Mn-porphyrins

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Abstract—A novel biomimetic method for rapid oxidation of a wide range of benzylic, allylic, aliphatic, primary and secondary alcohols to the related aldehydes and ketones using Bu_4NHSO_5 catalyzed by Mn(TPP)OAc/pyridine system with high to excellent yields and excellent selectivity has been developed. The high turnover rates obtained in this catalytic system represent a high efficiency and also relative stability of Mn-porphyrin catalyst towards oxidative degradation. The presence of an electron-withdrawing group on the phenyl ring of both benzyl alcohol and porphyrin ligand increases the reactivity of substrate as well as catalytic activity of Mn-porphyrin catalyst in the oxidation reaction.

1. Introduction

The oxidation of alcohols into aldehydes and ketones is a ubiquitous transformation in synthetic chemistry as well as in chemical industry for the preparation of many drugs, vitamins and fragrances.[1,2] The plethora of reagents available to accomplish this key reaction is a testimony to show that it is extremely valuable.[3] This process is also very important from biological point of view. For example, the copper metalloenzyme, galactose oxidase (GOase) and their model compounds are efficient catalysts for oxidation of alcohols.[4] It has also been known that cytochrome P-450, a monooxygenase enzyme, catalyzes oxidation of alcohols to the corresponding carbonyl compounds.[5] However, despite the extensive applications of metalloporphyrins as synthetic models of cytochrome P-450 in catalytic oxidation of hydrocarbons, epoxidation of olefins and oxidation of sulfur-containing compounds using various oxygen sources,[6] much less attention has been devoted for oxidation of alcohols to their carbonyl derivatives.[7] Recently, we have developed a highly efficient oxidation system using tetrabutylammonium peroxymonosulfate (Bu_4NHSO_5) as organic salt of Oxone® ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$), in combination with Mn(TPP)OAc (TPP = *meso*-tetraphenylporphyrin) as a biomimetic catalyst in the presence of imidazole as co-catalyst for rapid and selective oxidation of hydrocarbons,[8a] and various organosulfur compounds.[8b] We noticed that in the oxidation of saturated hydrocarbons using this catalytic system,[8a] the higher yields of the ketones were obtained than the alcohols. This result prompted us to apply this oxidation system for the oxidation of alcohols to carbonyl compounds. Herein, we wish to report an efficient and highly selective oxidation method for conversion of various alcohols to the corresponding carbonyl compounds using Bu_4NHSO_5 catalyzed by simple Mn(TPP)OAc in the presence of pyridine (Py) as co-catalyst in CH_3CN under mild conditions (Scheme 1). The electronic effect of the substituents in the alcohol and porphyrin ligand of the catalyst on their reactivities has also been investigated in this work.

2. Results and discussion

In order to optimize the best reaction conditions, the oxidation of benzyl alcohol was used as a model

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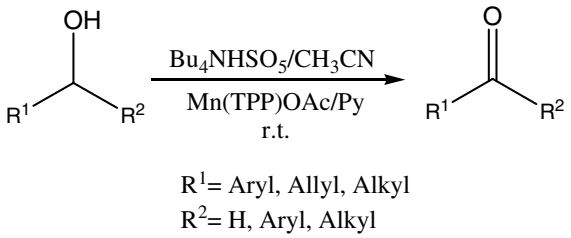


Scheme 1.

reaction. The oxidation of benzyl alcohol using Bu_4NHSO_5 in the absence and in the presence of the Mn(TPP)OAc catalyst proceeded slowly and led to the low yields of benzaldehyde (23% and 43%, respectively) after 48 h in CH_2Cl_2. We noticed that the nitrogen bases acting as the axial ligands in metalloporphyrins[9] had a significant effect on the yields and also reaction rates in this system. We therefore examined several nitrogen bases as axial ligands in this catalytic system for oxidation of benzyl alcohol to benzaldehyde (Table 1). Among the axial ligands tested, pyridine showed to be the best in terms of yield and reaction rate. We also found that the optimal ligand/catalyst ratio necessary to obtain the fastest conversion was 10/1 (entry 1 in Table 1 compared to entry 2 in Table 2). Then we tried the effect of solvent in this reaction and acetonitrile was found to be the solvent of choice in terms of yield and reaction rate (Table 2). Application of these optimized conditions in the oxidation of benzyl alcohol led to benzaldehyde in 95% yield within 5 min.

Table 1. Influence of axial ligands on the Mn(TPP)OAc-catalyzed oxidation of benzyl alcohol with Bu_4NHSO_5 in CH_2Cl_2[a]

Entry	Axial ligands	Benzaldehyde[b] (%)
1	Pyridine	83
2	4-*tert*-Butyl pyridine	79
3	Imidazole	70
4	2-Picoline	55
5	None	43[c]

[a] The reactions were run at rt under air for 10 min and the molar ratio for benzyl alcohol/Bu_4NHSO_5/axial ligand/Mn(TPP)OAc is 100:190:1:1.
[b] GC yield based on starting alcohol.
[c] The reaction was run for 48 h.

Table 2. Solvent dependence in the Mn(TPP)OAc/Py-catalyzed oxidation of benzyl alcohol with Bu_4NHSO_5 [a]

Entry	Solvent	Benzaldehyde[b] (%)
1	CH_3CN	95
2	CH_2Cl_2	90
3	$CHCl_3$	88
4	$(CH_3)_2CO$	83
5	MeOH	52
6	EtOH	38

[a] The reactions were run at rt under air for 5 min and the molar ratio for benzyl alcohol/Bu_4NHSO_5/Py/Mn(TPP)OAc is 100:190:10:1.
[b] GC yield based on starting alcohol.

To test the scope and limitation of this oxidation method, a wide range of primary and secondary aliphatic, allylic and benzylic alcohols were subjected to oxidation under these optimized conditions (Table 3). Inspection of the results in Table 3 displays the high efficiency and excellent selectivity of this general method. The system works well for the oxidation of primary and secondary saturated alcohols to their carbonyls in high to excellent yields (Table 3, entries 1–4). The quantitative conversion of less reactive primary aliphatic alcohols to the corresponding aldehydes with excellent yields (94% and 98%) and without any overoxidation to carboxylic products is a notable feature of this oxidation method (Table 3, entries 1 and 2).

We also obtained the promising results in the oxidation of allylic systems (Table 3, entries 5 and 6). The employment of the reaction conditions to allylic alcohols gave the corresponding α,β-unsaturated carbonyls in high yields with no amounts of epoxidation products.[10]

Next, we oxidized a wide range of primary and secondary benzylic alcohols having various substitutions containing electron-donating or electron-withdrawing groups in high to excellent yields (Table 3, entries 7–19) without any carboxylic acids, which has been observed in the oxidation of aldehydes with Oxone®.[11]

It seems that the efficiency of oxidation in this catalytic system is very dependent on the electronic and steric requirements of the substrate. Electron-donating and electron-withdrawing substituents on the phenyl ring of benzyl alcohols have a pronounced effect on the rate of oxygenation. To examine the electronic influence of substituent on the reactivity of alcohol in the oxidation reaction, we determined the turnover number (TON) of Mn(TPP)OAc catalyst in the oxidation of different benzylic alcohols having electron-donating or electron-withdrawing groups after 1 min (Table 4, entries 1–3). It was observed that the presence of –OMe as an electron-donating substituent decreases the TON in comparison with molecule having no substituent on the ring (Table 4, entries 2 and 3; 2475 vs 3050). Whereas, a substrate with an electron-withdrawing $–NO_2$ group on the phenyl ring displays a higher TON per min (Table 4, entries 1 and 2; 3825 vs 3050) under the same conditions. However, the lower yields of *ortho*-substituted benzyl alcohols in comparison to *para*-derivatives in this study (Table 3, entries 12–19) can be related to their steric hindrance. Obviously, the high turnover rates of Mn(TPP)OAc catalyst obtained in the oxidation of various alcohols (Table 4) indicate well the high efficiency and also relative stability of Mn-catalyst towards oxidative degradation in this oxidation system.[12]

Also, to compare both the relative reactivities of alcohols and the catalytic activities of Mn-catalysts in this method, three different *para*-substituted Mn-porphyrins have been investigated in the oxidation of electronically and structurally different benzylic alcohols (Fig. 1). The higher activity of electron-poor Mn[T(4-NO_2P)P]OAc catalyst in this study compared to those of Mn(TPP)OAc and Mn[T(4-OMeP)P]OAc under similar

Table 3. Oxidation of various alcohols using Bu_4NHSO_5 catalyzed by Mn(TPP)OAc/Py system in CH_3CN [a]

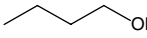
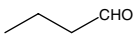
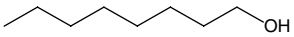
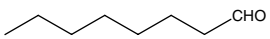
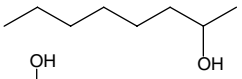
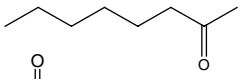
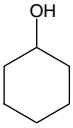
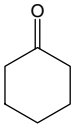
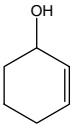
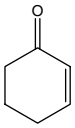
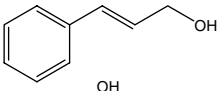
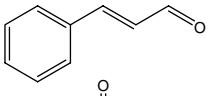
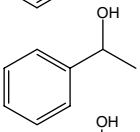
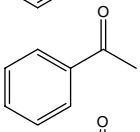
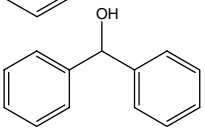
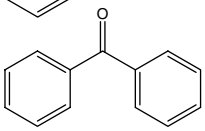
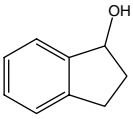
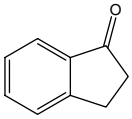
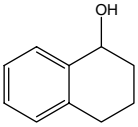
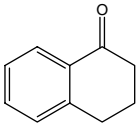
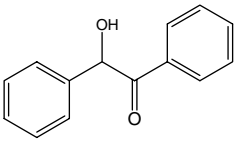
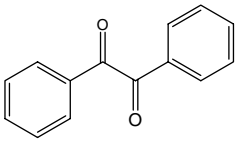
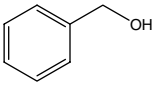
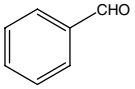
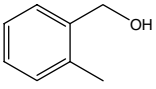
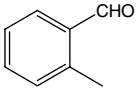
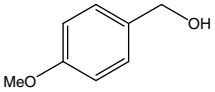
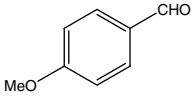
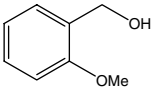
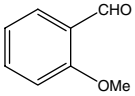
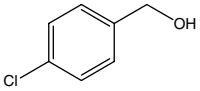
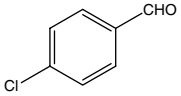
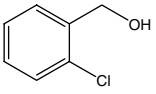
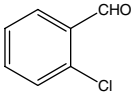
Entry	Alcohols	Product[b]	Yield[c] (%)
1			98
2			94
3			80
4			84
5			86 (80)[d]
6			84 (79)[d]
7			97 (91)[d]
8			94
9			95 (88)[d]
10			96
11			90[d]
12			95 (90)[d]
13			88
14			89
15			85
16			95
17			90

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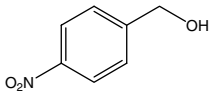
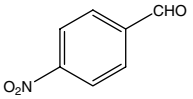
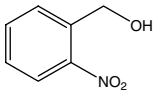
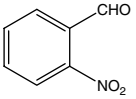
Table 3 (*continued*)

Entry	Alcohols	Product[b]	Yield[c] (%)
18			100 (94)[d]
19			91

[a] The reactions were run under air at rt and the molar ratio for alcohol/Bu_4NHSO_5/Py/Mn(TPP)OAc was 100:190:10:1.
[b] All products were identified by their IR, ^1H NMR and GC–MS spectral data in comparison with authentic samples.
[c] GC yield based on starting alcohol after 5 min except for entries 1–3 which are analyzed after 20 min.
[d] Isolated yield.

Table 4. Turnover numbers of Mn(TPP)OAc in the oxidation of different alcohols using Bu_4NHSO_5 [a]

Entry	Alcohol	Yield[b]	TON per min[c]
1	4-NO_2-benzyl alcohol	76.5	3825
2	Benzyl alcohol	61	3050
3	4-OMe-benzyl alcohol	49.5	2475
4	2-Cyclohexene-1-ol	48	2400
5	Cyclohexanol	30.5	1525

[a] The reactions were run under air in CH_3CN and the molar ratio for alcohol/Bu_4NHSO_5/Py/Mn(TPP)OAc is 5000:9500:10:1.
[b] GC yield after 1 min.
[c] Turnover number (TON) is the ratio of the number of moles of product to the number of moles of catalyst.

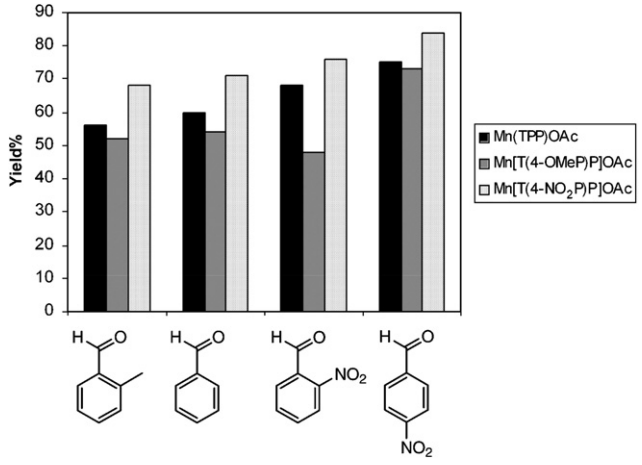


Figure 1. The comparison of catalytic activity of Mn(TPP)OAc, Mn[T(4-OMeP)P]OAc, and Mn[T(4-NO_2P)P]OAc in the oxidation of different benzylic alcohols with molar ratio of 100:100:10:1 for alcohol/oxidant/Py/catalyst in CH_2Cl_2 after 5 min.

conditions, especially in the oxidation of benzyl alcohols containing an electron-withdrawing substituent, reflects the increasing effect of an electron-deficient group on the catalytic activitiy of Mn-porphyrin catalyst (cytochrome P-450 model reactions)[13] as well as on reactivity of substrate in this catalytic method (Fig. 1). Further work with other Mn-porphyrin catalysts and also a wide range of axial ligands is underway in this area.

3. Conclusion

In conclusion, Mn(TPP)OAc in combination with pyridine is an excellent biomimetic catalyst for activation of Bu_4NHSO_5 in rapid oxidation of alcohols to the related aldehydes and ketones in high to excellent yields with excellent selectivity under mild conditions. The presence of an electron-withdrawing group on the phenyl ring of both benzyl alcohol and porphyrin ligand increases the reactivity of substrate as well as catalytic activity of Mn-porphyrin catalyst. The applicability of this simple methodology to a wide variety of primary and secondary benzylic, allylic, and also saturated cyclic and alicyclic alcohols with excellent selectivity combined with high turnover rates and relative stability of Mn-catalyst makes it more attractive.

4. Experimental

4.1. General remarks

$Mn(OAC)_2{\cdot}4H_2O$, Oxone®, tetrabutylammonium hydrogen sulfate, nitrogen bases and alcohols were purchased from Merck or Fluka Chemical Companies. Bu_4NHSO_5 was prepared by Trost method or other modified procedures.[14] The free base porphyrins: $TPPH_2$,[15] T(4-OMeP)PH_2,[15] T(4-NO_2P)PH_2,[16] $TDCPPH_2$[17] and $TMPH_2$[17] were prepared and purified by methods reported previously. Mn(Por)OAc complexes were obtained using the $Mn(OAc)_2{\cdot}4H_2O$ according to the procedure of Alder et al.[18] Purity determinations of the products were accomplished by GC on a Shimadzu GC-16A instrument using a 25 m CBP1-S25 (0.32 mm ID, 0.5 μm coating) capillary column. IR spectra were recorded on a Perkin Elmer 780 instrument. NMR spectra were recorded on a Brucker Avance DPX 250 MHz instrument. Mass spectra were recorded on a Shimadzu GC-MS-QP5050A.

4.2. Typical procedure for oxidation of benzyl alcohols using Bu_4NHSO_5 catalyzed by Mn(TPP)OAc/Py system in CH_3CN

To a mixture of benzyl alcohol (1 mmol, 0.108 g), Mn(TPP)OAc (0.01 mmol, 0.726 mg) and pyridine (0.1 mmol, 7.9 mg, 8 μl) in CH_3CN (2 ml) was added freshly

prepared Bu_4NHSO_5 (1.9 mmol, 1 g). Reaction mixture was stirred at 25 °C for appropriated reaction time, which was monitored by GC (Table 3). After completion of the reaction, the desired product was isolated by column chromatography eluted with *n*-hexane/ethyl acetate (10:1). Evaporation of the solvent gave benzaldehyde in 90% yield (0.096 g). Liquid (bp: 178 °C). IR (neat) cm^{-1}: 1701, 1600, 1460, 1312, 1204, 827, 749; ^1H NMR (250 MHz) δ (ppm) 7.45–7.67 (m, 3 H), 7.87–7.90 (m, 2H), 10.02 (s, 1H); ^{13}C NMR (63 MHz) δ (ppm) 128.8, 129.7, 134.4, 136.5, 192.3; MS *m*/*z* 106 $[M]^+$.

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