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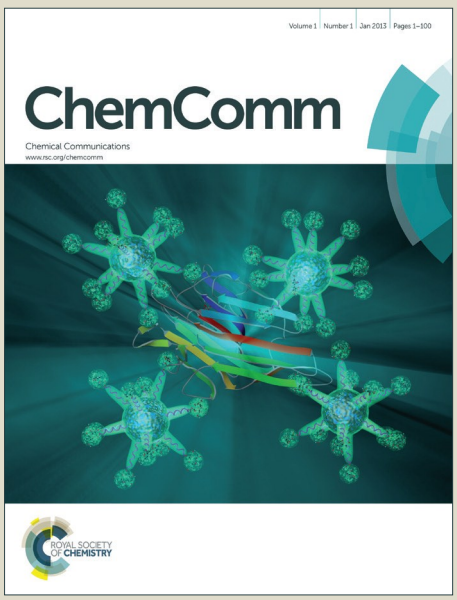

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COMMUNICATION

Highly efficient oxidation of alcohols catalyzed by a porphyrin-inspired manganese complex

Wen Dai,[a] Ying Lv,[a] Lianyue Wang,[a] Sensen Shang,[a] Bo Chen,[a] Guosong Li[a] and Shuang Gao*[a]

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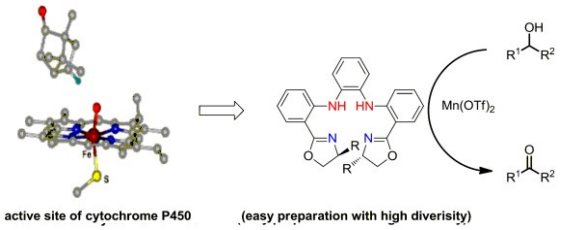
A novel strategy for catalytic oxidation of a variety of benzylic, allylic, propargylic, and aliphatic alcohols to the corresponding aldehydes or ketones by an in situ formed porphyrin-inspired manganese complex in excellent yields (up to 99%) has been successfully developed.

The selective oxidation of alcohols to carbonyl compounds is among the most important and extensively used class of oxidation reactions in organic synthesis.[1] The past decades have witnessed significant progress in the catalytic methods for oxidation of alcohols with organocatalysts or metal-based catalysts which offer economic and environmental benefits over traditional stoichiometric oxidants.[2] Owing to metalloenzyme-catalyzed reactions usually exhibiting exquisite substrate specificity and operating under mild conditions, widespread interest has been directed toward the development of bioinspired or biomimetic alcohol oxidation methods.[3] Since the initial breakthrough accomplished in oxidation of alcohols using copper complex miming the galactose oxidase (GAO) by Stack et al. and Wieghardt et al. in 1983,[1e, 4] other bioinspired or biomimetic catalytic systems have also been developed and selective oxidation of a broad range of alcohols has been achieved.[5] However, only limited examples of oxidation of alcohols based on metalloporphyrins, which are the mimics of the cytochrome P450 active site, have been previously described and refined to find application in industrial and fine-chemical synthesis.[6] This unfortunate situation is mainly attributed to notoriously difficult synthesis of porphyrin ligands.

We recently developed a new type of porphyrin-inspired N_4 ligands which were easily prepared, structurally diverse, sterically and electronically tunable as well as fulfilled the structural requirements of the porphyrin ligand in some way.[7] The porphyrin-inspired ligands which possess excellent tolerance for oxidation reactions have been successfully applied in asymmetric epoxidation of olefins and asymmetric sulfoxidation.[7-8] Meanwhile, manganese-catalyzed oxidation of



Scheme 1 Strategy for the development of oxidation of alcohols method.

alcohols should offer many remarkable advantages, as manganese is abundant, easily available and relatively nontoxic and shows variable oxidation state.[9] With this background in mind, it was envisioned that we could develop a highly effective, selective, and broad-scope catalyst system for oxidation of alcohols exploring the manganese in combination with the porphyrin-inspired N_4 ligands (Scheme 1). We disclose herein a porphyrin-inspired manganese catalyst system that enables selective oxidation of benzylic, allylic, propargylic and aliphatic alcohols to the corresponding aldehydes or ketones in high yields (up to 99%). High chemoselectivity, mild conditions and easy scalability make this catalyst system highly practical.

Initially, we chose cinnamyl alcohol **1a** as the model substrate to examine the effect of carboxylic acid (CA). The reactions were conducted with **1a** (0.2 mmol), CA (1.0 equiv), H_2O_2 (4.0 equiv), and 2.5 mol% of catalyst which was generated from $Mn(OTf)_2$ and **L4**, in acetonitrile at 0 °C. When the acetic acid was used, the corresponding cinnamaldehyde **2a** was obtained in 24% yield (Table 1, entry 1). Replacing the acetic acid with a wide variety of aliphatic acids including branched and cyclic carboxylic acid led a significant improvement in yield (entries 2-9). Among them, the adamantane carboxylic acid (**aca**) provided the best result (entry 9). In addition to the aliphatic acids, the aromatic carboxylic acids were also tested and compatible with our catalyst system with high yield (entries 10 and 11). Subsequently, the oxidant loading was examined. We found that 6 equiv of H_2O_2 were necessary in order to achieve the best result (entries 12 and 13). After testing CA loading, the amount

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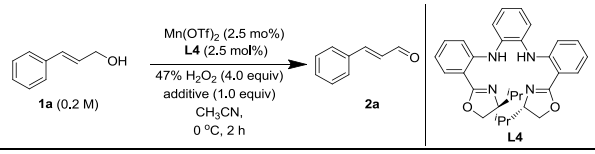
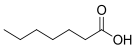
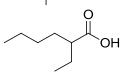
Electronic Supplementary Information (ESI) available: Experimental procedures and compound characterization data. See DOI: 10.1039/x0xx00000x

Table 1 Screening of the identity and amount of additives.



entry	additive	H_2O_2 (equiv.)	yield(%)[a]
1	CH_3COOH	4	24
2		4	36
3		4	44
4		4	56
5		4	48
6		4	31
7		4	56
8		4	42
9		4	60
10		4	46
11		4	49
12	**aca**	6	76
13	**aca**	8	78
14[b]	**aca**	6	75
15[c]	**aca**	6	65

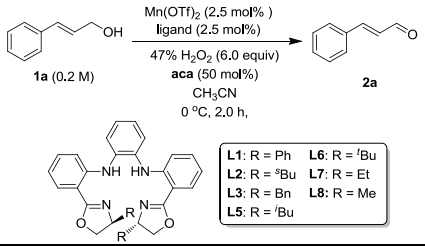
[a]Determined by GC. [b]**aca** (50 mol%). [c]**aca** (30 mol%).

of CA was successfully lowered to 50 mol% with no decrease of yield (entry 14). Further reducing the CA loading to 30 mol% resulted an obvious decrease in yield (entry 15).

Further examinations were focused on ligand screening. From the evaluation of various ligands containing oxazoline moieties derived from chiral amino alcohol, we identified **L2** as the ligand providing the best result (Table 2, entries 1–7). It is noteworthy that decreasing the amount of catalyst to 1.0 mol% failed to bring about deterioration of yield (entry 8). Remarkably, further lowering the catalyst loading to 0.5 mol% resulted a significant decrease in yield (entry 9). Finally, the ratio of $Mn(OTf)_2$ and **L2** was investigated. Best result was obtained with a ratio of 1:1. (see the supporting information, Table S1).

With the optimal conditions in hand, exploration of substrate scope was carried out, and the results were summarized in Table 3. A variety of conjugated allylic alcohols were smoothly converted into their corresponding *α,β*-unsaturated aldehyde or ketones with excellent yields (entries 1–4). The unconjugated allylic alcohol 1-Octen-3-ol was less reactive, affording the corresponding ketone in 34% yield (entry 5). The catalyst system was next applied to oxidation of benzylic primary and secondary alcohols. 1-Arylethanols with

Table 2 Investigation of effect of ligand structure.

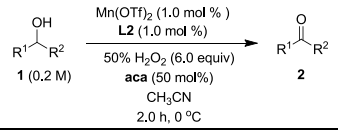


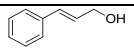
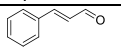
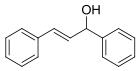
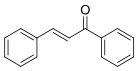
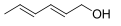
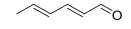
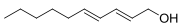
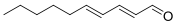
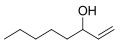
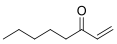
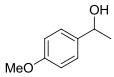
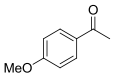
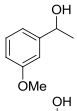
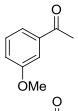
entry	ligand	% yield[a]
1	**L1**	55
2	**L2**	85
3	**L3**	73
4	**L5**	37
5	**L6**	56
6	**L7**	84
7	**L8**	52
8[b]	**L2**	86
9[c]	**L2**	74

[a]Determined by GC. [b]$Mn(OTf)_2$ (1.0 mol%), **L2** (1.0 mol%). [c]$Mn(OTf)_2$ (0.5 mol%), **L2** (0.5 mol%).

electron-donating and -withdrawing substituents at the aromatic ring proceeded well to give the corresponding acetophenone derivatives in good to excellent yields (entries 6–9). For annular benzylic secondary alcohols, the substrates could be successfully oxidized into the desired product in excellent yield (entries 10–13). Excellent yield was preserved for the oxidation of benzylic secondary alcohols bearing condensed aromatic ring and sterically hindered structure (entries 14–15). In the case of alcohol bearing electron-withdrawing group, only moderate yield was obtained (entry 16). Alcohols containing heterocycles could also serve as good substrate and afford the corresponding ketones in good yield (entries 17–19). When the reactions of aliphatic secondary alcohols including linear and cyclic alcohols were carried out, the ketones were formed in moderate yield (entries 20–22). In addition to the secondary alcohols, the primary benzylic alcohols were also investigated. Gratifyingly, good yield was also achieved (entries 23–24). To further explore the generality of the current catalyst system, we investigated the oxidation of propargylic alcohols. The reaction of the secondary propargylic alcohols provided the corresponding ketones in moderate to excellent yields (entries 25–27). Meanwhile, the excellent yield was obtained for the oxidation of the terminal alkyne 1-phenyl-2-propyn-1-ol (entry 28). The present system was also applicable to the primary propargylic alcohol, although the yield was moderate (entry 29). To investigate the intramolecular chemoselectivity of secondary over primary alcohol, 1-phenyl-1,2-ethanediol was chosen as the substrate. Moderate yield was obtained for the oxidation of the secondary alcohol and no trace of aldehyde was observed, which indicated our catalyst system possessed high chemoselectivity for secondary alcohols (entry 30). Finally, the

Table 3 Substrate scope



entry	substrate	product	% yield[a]
1			86[b]
2			92
3			99[b]
4			88[b]
5			34[b]
6			95
7			84
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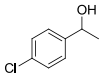
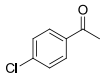
9			70
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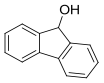
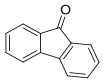
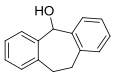
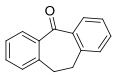
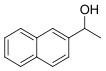
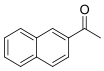
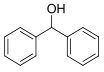
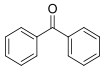
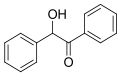
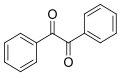
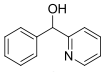
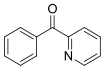
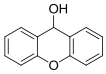
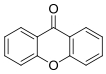
11			86
12			90
13			93
14			90
15			89
16			48
17			80
18			90
19			88
20			41[b]
21			38[b]
22			25[b]
23			74
24			75

Table 3 Substrate scope (*Contd.*)

entry	substrate	product	% yield[a]
25			70
26			91
27			58[b]
28			85
29			40
30			56

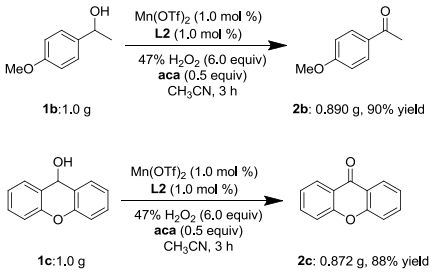
[a]Isolated yields. [b]Determined by GC.

successful results of oxidation of alcohols prompted us to further explore the oxidative kinetic resolution of racemic alcohols. Unfortunately, only low to moderate ee value was obtained (see the supporting information, Table S2).

To gain insight into the nature of active oxidant, competitive oxidation of *p*-substituted 1-phenylethanol were performed under the optimized conditions. We found good linear correlation between the log (k_X/k_H) and σ_p^+ with negative ρ^+ = -0.38 which demonstrated that transition state of the reaction was electron-demanding and the active oxidant was electrophilic (Fig. 1).[5g, 10] Then the KIE for this manganese catalyzed oxidation of 1-Phenylethanol was 3.0, which was basically consistent with that of the manganese-catalyzed alcohols oxidation reported by Nam et al. (KIE 2.2) and Sun et al. (KIE 2.1).[5f, 5g] Moreover, the current catalyst system has excellent selectivity for the oxidation of alcohols to the corresponding aldehydes or ketones. It may be inferred from these results that a high-valent Mn-oxo species would be an active intermediate in current catalyst system and carboxylic acid additive may play a key role in the activation of H_2O_2 to form the high-valent Mn-oxo species, although the exact structure of the catalyst is not clear.

To further evaluate the practical utility of the catalyst system, the oxidation of 1-(4-methoxyphenyl)ethanol **1b** and xanthydrol **1c** was carried out on gram scale under the optimized conditions, affording the desired product **2b** and **2c** in 90% yield and 88% yield after a prolonged reaction time, respectively (Scheme 2).

Fig. 1 Hammett plots of Log (k_X/k_H) vs σ_p^+ for the oxidation of *para*-substituted 1-phenylethanol.



Scheme 2 Gram-scale synthesis of **2b** and **2c**.

In summary, we have successfully developed a highly efficient and general catalytic oxidation of alcohols method that employs an inexpensive and easily available porphyrin-inspired manganese complex, allowing for the oxidation of a wide variety of benzylic, allylic, propargylic and aliphatic alcohols to corresponding aldehydes or ketones in high yields. Mild conditions, high chemoselectivity, and easy scalability make this catalyst system highly practical. Moreover, Hammett analysis confirmed that active oxidant was electrophilic. Further work on the mechanistic study and extension of the strategy to other synthetic application are currently underway.

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Notes and references

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