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Highly Efficient Oxidation of Secondary Alcohols to Ketones Catalyzed by Manganese Complexes of N_4 Ligands with H_2O_2

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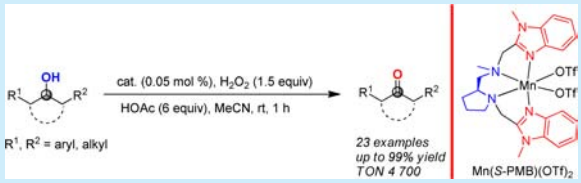
Supporting Information

ABSTRACT: The manganese complex Mn(*S*-PMB)$(CF_3SO_3)_2$ was proven to be highly efficient in the catalytic oxidation of several benzylic and aliphatic secondary alcohols with H_2O_2 as the oxidant and acetic acid as the additive. A maximum turnover number of 4700 was achieved in the alcohol oxidation. In addition, the Hammett analysis unveiled the electrophilic nature of this manganese catalyst with N_4 ligand.



Several nonheme enzymes are capable of realizing highly efficient and selective oxidation for specific organic substrates in vivo.[1] To mimic these metalloenzyme functions, many research groups have committed themselves to the studies of biomimetic models, which generally consist of small inorganic complexes.[2] Faithful synthetic nonheme catalysts were successfully demonstrated to be highly active in a serious of oxidation reactions, such as the C−H oxidation of alkanes,[3] epoxidation of olefins,[4] and other oxidation reactions.

Specifically, the oxidation of alcohols to their respective aldehydes and ketones is one of the fundamental transformations; as such, classes of catalytic methods have already been established.[5] The seminal works of bioinspired complex-catalyzed oxidation of alcohols were published in 1998 by Stack et al.[6] (Figure 1, ligands **1a**−**d**) and Wieghardt et al.[7] (Figure 1, ligand **2**), respectively. These groups' copper complexes showed high activity and selectivity in the aerobic oxidation of alcohols, mimicing galactose oxidase (GAO).[8]

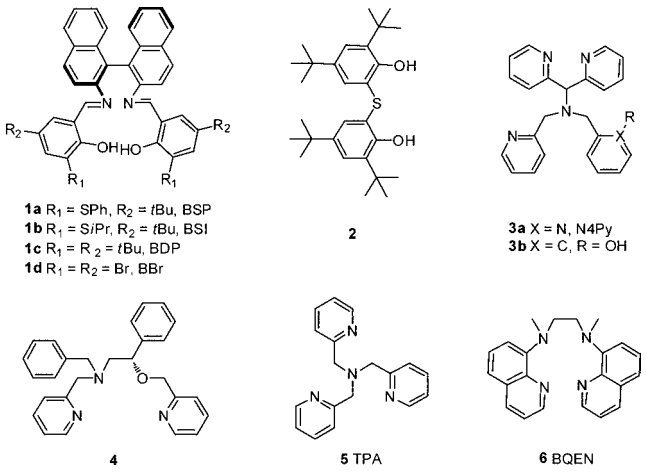


Figure 1. Selected structures of previously nonheme ligands.

Following these developments, diverse nonheme ligands and their metal complexes were designed, synthesized, and applied to the oxidation of alcohols. In 2001, Feringa et al.[9] reported a highly efficient and HOTf (OTf = CF_3SO_3)-accelerated alcohol oxidation (up to 65% yield) catalyzed by a nonheme μ-oxo diiron(III) complex with a N4Py-related pentadentate ligand (Figure 1, ligands **3a** and **3b**). Meanwhile, Bauer et al.[10] prepared a set of bi- and tridentate aminopyridine ligands and corresponding iron complexes (Figure 1, ligand **4**), which showed catalytic activity in the oxidation of alcohols, including especially the good chemical selectivity of secondary alcohols over primary alcohols. With regard to the nature of iron-based systems, a 2005 report from Nam et al.[11] provided detailed mechanistic insights into the oxidation of alcohol with in situ generated oxoiron(IV) complexes bearing nonheme ligands such as N4Py and TPA (Figure 1, ligands **3a** and **5**). Later, a manganese complex, [Mn(BQEN)]$(OTf)_2$ (Figure 1, ligand **6**), was also proven to be an efficient catalyst in alcohol oxidation with peracetic acid as the oxidant.[12] The mechanistic experiments predicted a metal-based mechanism rather than auto-oxidation in this manganese system. Furthermore, the oxidation of alcohol catalyzed by other catalytic nonheme systems was reported, as were the mechanisms concerning metal−oxo intermediates.[13]

Our group has dedicated the past few years to several catalytic oxidations, particularly asymmetric epoxidation with nonheme metal complexes as the catalysts. Notably, we found that replacing the pyridines on ligands of *S*-PMPP[14] (Figure 2, **L2**) and MCP[15] (Figure 2, **L3**) with benzimidazoles caused the iron and manganese complexes with proline−benzimidazole-based ligands (Figure 2, analogues of **L1**) to exhibit highly

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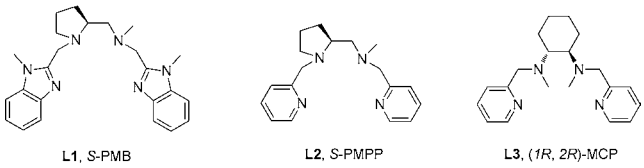
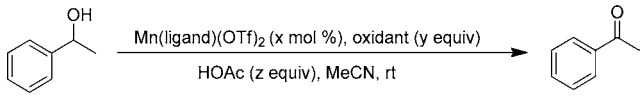


Figure 2. Ligands studied in this work.

improved efficiencies and enantioselectivities in the asymmetric epoxidation of various alkenes.[16] Subsequent selective oxidations of benzylic and aliphatic C−H bonds proved the analogue catalyst Mn(*S*-PMB)$(OTf)_2$[17] to be active and superior to the analogue complexes with ligands of pyridine moieties. These findings indicate a possibility that the manganese catalyst could promote the oxidation of alcohols even in a low catalyst loading. In an attempt to expand the application of nonheme system, herein, we employed the manganese complex Mn(*S*-PMB)$(OTf)_2$ to the oxidation of a series of secondary alcohols. To our delight, various alcohols were oxidized to ketones with good to excellent yields. In addition, the primary mechanisms, that is, the Hammett and kinetic isotope effects (KIE), were also involved in this work.

First, we chose 1-phenylethanol as a model substrate to screen the optimal conditions. As can be seen in Table 1, almost no reaction occurred without manganese catalyst or acetic acid (AA) (Table 1, entries 1 and 2). Afterward, the substrate was fully converted to the acetophenone in the presence of 0.1 mol % of Mn(**L1**)$(OTf)_2$ with 6 equiv of AA as the additive (Table 1, entry 4). Reduction in the catalyst loading led to a decreased yield (Table 1, entry 5). However, extending the reaction time to 1 h established the optimized conditions with full conversion and excellent yield with 0.05 mol % of catalyst and 1.5 equiv of H_2O_2 (Table 1, entry 6). It should be noted that a moderate of yield was obtained even with 0.01 mol % catalyst after 2 h, which underscored the efficiency and stability of this manganese catalyst (TOF = 2 350 h^{-1} and TON = 4 700, respectively) (Table 1, entries 7 and 8). However, under the optimized conditions, manganese complexes coordinated with ligands **L2** and **L3** both showed poorer activity, which likely demonstrates the advantages of benzimidazole over the pyridine moiety[14,16a] of the nitrogen ligands in some catalytic oxidations. Moreover, a variety of oxidants always involved in biomimetic catalysis were compared, and all showed inferiority to the "Mn(Ligand)-$(OTf)_2$-HOAc-H_2O_2" system (see the Supporting Information, Table S1). Oxidative kinetic resolution of the secondary alcohol was also observed with limited oxidant; unfortunately, the ee value was still low (Table 1, entry 12).

Table 1. Screening Reaction Conditions[a]



entry	complex *x*	oxidant *y*	AcOH *z*	time (h)	GC conv (%)	GC yield (%)
1	none (0)	H_2O_2 (1.3)	6	0.5	trace	trace
2	Mn**L1** (0.1)	H_2O_2 (1.3)	0	0.5	trace	trace
3	Mn**L1** (0.1)	H_2O_2 (1.3)	6	0.5	82	82
4	Mn**L1** (0.1)	H_2O_2 (1.5)	6	0.5	99	99
5	Mn**L1** (0.05)	H_2O_2 (1.5)	6	0.5	83	82
6	Mn**L1** (0.05)	H_2O_2 (1.5)	6	1	99	98
7	Mn**L1** (0.02)	H_2O_2 (1.5)	6	2	87	86
8	Mn**L1** (0.01)	H_2O_2 (1.5)	6	2	51	47
9	Mn**L1** (0.05)	H_2O_2 (1.5)	5	1	92	92
10	Mn**L2** (0.05)	H_2O_2 (1.5)	6	1	42	37
11	Mn**L3** (0.05)	H_2O_2 (1.5)	6	1	24	22
12[b]	Mn**L1** (0.05)	H_2O_2 (0.8)	6	0.5	52	

[a]Reaction conditions: hydrogen peroxide (50% aqueous solution) with 0.5 mL of MeCN was delivered through syringe pump over 0.5−2 h to a stirred solution of catalyst (0.01−0.1 mol %), acetic acid (0−6 equiv), internal standard (nitrobenzene), and substrate (0.5 mmol) in 1.0 mL of MeCN in the air at room temperature (entries 1−12). [b]Reaction at 0 °C for 0.5 h; 27% ee was observed.

After the optimized conditions were established, we oxidized a variety of benzylic and aliphatic secondary alcohols to the corresponding ketones. From the results listed in Table 2, good to excellent yields were accomplished in most cases. For example, the steric hindrance of the groups on the side chain had an obvious impact and the activities decreased in the order of Me > Et > *i*-Pr > *t*-Bu (Table 2, entries 1−4). For annular benzylic secondary alcohols, the substrates were fully converted but with the exception of partial benzylic C−H oxidation products (Table 2, entries 5−7). However, in the oxidation of diphenylmethanol, a 30% yield of benzophenone was produced under the optimal conditions in Table 1. Unexpectedly, the highest conversion and yield were achieved with the use of 14 equiv of AA[18] (Table 2, entry 8), which was previously adopted by Costas et al.[19] and Talsi et al.[20] in alkene epoxidation catalyzed by manganese complexes of N_4 ligands, respectively. Similarly, for alcohols with a strong electron-withdrawing group or heteroatom, we gained good yields of ketones (Table 2, entries 9 and 10) with large amounts of AA. In the case of substituted 1-phenylethanol, strong electron-donating groups led to poor results, even under the condition **B** (Table 2, entries 12 and 13). In the oxidation of the substrate-bearing ester, the oxidation proceeds well with a 79% isolated yield (Table 2, entry 14). In the case of allyl alcohol, both enone and epoxyketone were obtained (Table 2, entry 15). To our delight, generally good yields were reached only with 0.05 mol % of manganese catalyst in the cases of both linear and cyclic aliphatic secondary alcohols, which are sometimes thought of as inactive substrates (Table 2, entries 16−21). However, the steric effects was obvious in the example of 2-admantanol, and larger amounts of catalyst and acid were needed (Table 2, entry 22). To explore the intramolecular chemoselectivity of secondary over primary alcohols, we chose 1-phenyl-1,2-ethanediol as the substrate and got a much higher selectivity (83%) and isolated yield (78%) for secondary alcohol oxidation than that of the iron system recently reported by Bauer et al.[10b] In addition, intermolecular competition of secondary and primary alcohols was also investigated (see the Supporting Information). Likewise, the secondary alcohol was preferentially converted to the ketone while the primary alcohol was hardly oxidized in the present catalytic system.

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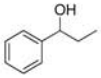
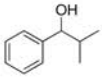
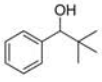
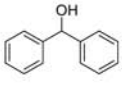
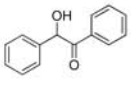
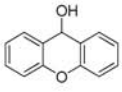
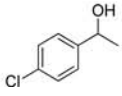
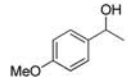
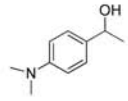
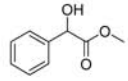
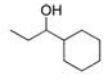
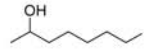
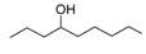
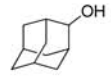
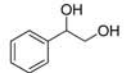
Table 2. Substrates Scope[a]

entry	substrate	conditions (A[b]/B[c])	GC conv (%)	GC yield[d] (%)
1		A	99	98
2		A	92	91(75)
3		A	88	84(75)
4		A	70	60(55)
5		A	99	66(61)/(9[e])
6		A	99	62(56)/(13[f])
7		A	99	(70)/(7[g])
8		A B	33 99	(30) (90)
9		B	73	(70)
10		B	99	(86)
11		B	99	(95)
12		B	55	15
13		B	-	-
14		B	86	(79)
15		B	96	43(27)/30(23[h])
16		A	95	91
17		A	84	58
18		A	97	84
19		A	90	75
20		A	94	85
21		A	90	66
22		B	95	68
23		B	99	83(78)

[a]Reaction conditions: hydrogen peroxide (50% aqueous solution) diluted with 0.5 mL of MeCN was delivered through a syringe pump over 1 h to a stirred solution of catalyst, HOAc, internal standard (decane), and substrate (0.5 mmol) in 1.0 mL of MeCN in the air at room temperature. [b]Method A: catalyst (0.05 mol %), HOAc (6 equiv). [c]Method B: catalyst (0.2 mol %), HOAc (14 equiv). [d]Isolated yields are shown in parentheses. [e]Yield of 1*H*-indene-1,3(2*H*)-dione. [f]Yield of naphthalene-1,4-dione. [g]Yield of 7,8-dihydro-5*H*-benzo[7]annulene-5,9(6*H*)-dione. [h]Oxiran-2-yl-(phenyl)methanone.

In order to gain more insight into the alcohol oxidation, we then investigated the influences of *para*-substituents on the benzene ring. Therefore, competitive experiments of several substituted 1-phenylethanol were carried out (see the Supporting Information for details). The relative activities (K_{rel} values) were plotted against the *para*-substitutent constant σ and an acceptable Hammett correlation was obtained. The negative ρ value of −1.2 indicated the electrophilic nature of this manganese catalyst, which conformed to the experimental results.

Then the primary KIE value was determined, and 1-(4-chlorophenyl)ethanol was selected as the mediation in the competitive experiments due to the overlaps of peaks in GC for 1-phenylethanol and its deuterated alcohol (see the Supporting Information for details). The KIE for this manganese-catalyzed oxidation of secondary alcohol was 2.1, which seemed to be consistent with that of the $[Mn(BQEN)]^{2+}$ reported by Nam et al. (KIE 2.2)[12] and in situ $[Mn(TPEN)]^{2+}$ complex reported by Feringa et al. (KIE 2.2)[21] in the oxidation of benzyl alcohol. Combined with the excellent selectivity for acetophenone, it may be concluded that the hydroxyl radical was not likely involved in the process while a high-valent Mn−oxo species might have been an active intermediate in this catalytic system. In addition, acetic acid may play a key role in the activation of

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H_2O_2 to form the Mn−oxo species with the manganese complex during the process.[17,22]

In summary, we exhibited a highly efficient biomimetic manganese-catalyzed oxidation for a variety of secondary benzylic and aliphatic alcohols. The substituent effects and kinetic isotope effects revealed that a high-valent Mn−oxo speices might be involved. Further investigations concerning expanding the reaction scopes and mechanistic insights are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and NMR copies. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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