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Efficient Benzylic and Aliphatic C–H Oxidation with Selectivity for Methylenic Sites Catalyzed by a Bioinspired Manganese Complex

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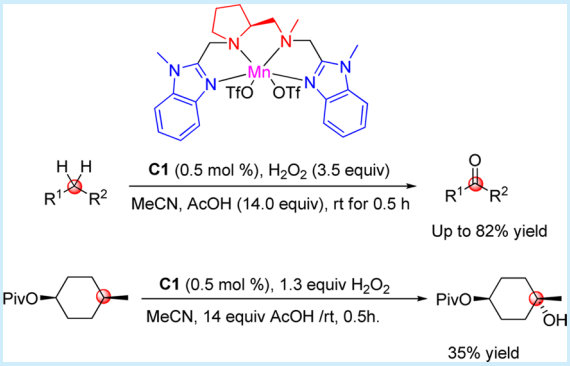
Supporting Information

ABSTRACT: A benzimidazole-based nonheme manganese complex efficiently catalyzes benzylic, aliphatic C–H as well as tertiary C–H oxidation with hydrogen peroxide as the oxidant in the presence of acetic acid as additive. ^{18}O labeling experiments suggest the reaction may proceed via a high-valent manganese-oxo intermediate.



Direct oxidation and functionalization of C–H bonds under mild conditions is an appealing methodology toward the complex molecule synthesis and the elaboration of simple hydrocarbon feedstocks into value-added hydroxyl and carbonyl compounds.[1] Biological C–H bond functionalization is primarily performed by iron-containing enzymes that utilize dioxygen as the terminal oxidant, such as methane monooxygenase (MMO) and Rieske dioxygenase.[2] Inspired by these metal enzymes, a variety of biomimetic catalytic models involving transition metals had been developed and applied to catalyze C–H bond oxidation during the past decades.[3] Bioinspired nonheme iron complexes, containing tetradentate N4 ligands, such as the tripodal TPA (TPA = tris(2-pyridylmethyl)amine) and linear MEP (MEP = *N*,*N*′-dimethyl-*N*,*N*′-bis(2-pyridylmethyl)ethylene-1,2-diamine), can perform stereospecific alkane hydroxylation using H_2O_2 as the oxidant.[4] These extensive studies involving nonheme iron catalysts have provided key insights into the mechanisms about the alkane C–H oxidation. In 2007, White and co-workers reported that the $[Fe(S,S\text{-PDB})(CH_3CN)_2](SbF_6)_2$ (PDB = *N*,*N*′-bis(2-pyridylmethyl)-2,2′-bipyrrolidine) catalyst catalyzes the hydroxylation of complex organic molecules with synthetically useful yields, but in the presence of acetic acid.[5] Costas et al. demonstrated that the Fe-MCPP complex can efficiently oxidize C–H bonds under lower catalyst loadings.[6] Later, White applied the same iron catalyst to achieve the methylene oxidation of a broad range of hydrocarbons.[7] Recent work by Costas et al. showed that $[Fe\text{-}(^{Me,Me}Pytacn)]^{2+}$ (^{Me,Me}Pytacn = 1-(6-methyl-2-pyridylmethyl)-4,7-dimethyl-1,4,7-triazacyclononane), pinene-containing nonheme iron catalysts and analogues can mediate the methylene oxidation under mild conditions and lower catalyst loadings.[8]

Despite previous advances in the oxidations of C–H bond-catalyzed nonheme iron catalysts, the efficiency of catalysts need to be further improved from the viewpoint of synthetic use. In the course of our investigations with nonheme catalysts for the enantioselective epoxidation of olefins, manganese complexes generally display higher turnover numbers (TONs) than those of iron complexes.[9−11] Most significantly, one of the manganese complexes (*S*-PEB-Mn, Figure 1) based on ligands

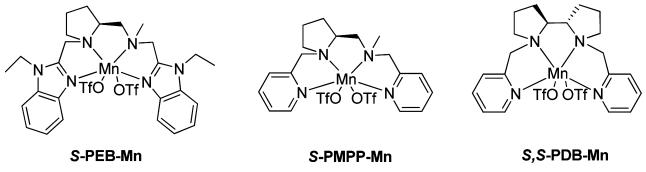


Figure 1. Previous reported nonheme Mn complexes.

with chiral diamine derived from proline and two benzimidazoles as sp^2 nitrogen units can efficiently catalyze the asymmetric epoxidation of olefins, even in a 0.01 mol % catalyst loading.[9d] Despite the fact that nonheme Mn catalyzed C–H oxidations with H_2O_2 have been less investigated,[12] Nam et al. reported that Bn-TPEN-Mn(IV)-oxo complex shows high reactivity in oxidation of C–H bond of ethylbenzene.[13] Bryliakov et al. reported the aminopyridine manganese

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complexes (Figure 1) demonstrate excellent efficiency and stereospecificity in the oxidation of aliphatic C−H bonds with acetic acid as the additive.[14] Herein, we report a manganese complex that can catalyze the selective oxidation of secondary C−H groups and tertiary C−H groups by using H_2O_2 as the oxidant in the presence of acetic acid.

The *S*-PMB ligand (**L1**) could be prepared easily in good yield according to the previous method for the synthesis of *S*-PEB ligand (Figure 2).[9c,d] The crystal structure of *S*-PMB-

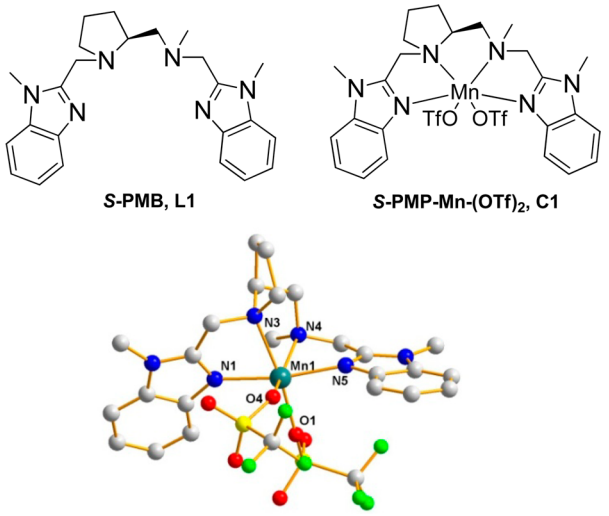
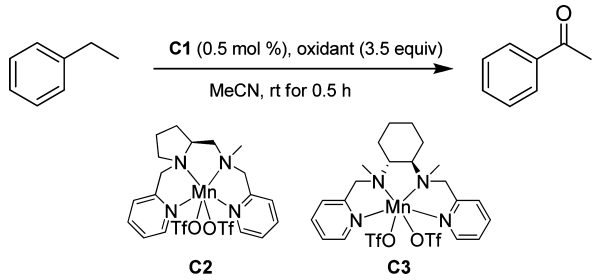


Figure 2. Ligand *S*-PMB (**L1**) and crystal structure of the corresponding nonheme manganese complex *S*-PMB-Mn(OTf)$_2$ (**C1**).

Mn(OTf)$_2$ (**C1**) shows a slightly distorted octahedral manganese center in a *cis*-α conformation, in which the two benzimidazole rings are *trans* to each other and the two triflate anions are *cis* to each other.[15] The room temperature solution magnetic moment determined using the method of Evans is 6.1 μB for manganese complex, consistent with high-spin (S = 5/2) manganese(II).[16]

The manganese complex **C1** was tested as catalyst (0.5 mol %) for the ethylbenzene oxidation in acetonitrile at room temperature. H_2O_2 (3.5 equiv) was added to a reaction tube under argon over a period of 30 min by using a syringe pump. The reaction gave no product in the absence of acetic acid (Table 1, entry 1). To our delight, the reaction provided acetophenone in 48% yield by using 6.0 equiv of acetic acid as the additive (Table 1, entry 2). After optimization, best result (68% yield of acetophenone, Table 1, entry 3) was obtained when the acetic acid was increased to 14.0 equiv with respect to the substrate. These reaction conditions were adopted by Costas et al. in the epoxidation of olefins[10,11] and Bryliakov et al. in the oxidation of unactivated aliphatic C−H bonds.[14] It should be noted that α-methylbenzyl alcohol (1% yield) and α-methylbenzyl alcohol acetate (6% yield) were observed on the basis of the GC and GC−MS analysis. These results also indicate the formation of acetophenone by further oxidation of α-methylbenzyl alcohol.[12e] Various oxidants, such as AcOOH, PhIO, *m*-CPBA, and *t*BuOOH, were tested in the oxidation reaction; only AcOOH as the oxidant led to a comparable result (Table 1, entries 5−8). Other manganese complexes, *S*-PMPP-Mn(OTf)$_2$ (**C2**) and *R*,*R*-MCP-Mn(OTf)$_2$ (**C3**)[17] were also tested, but both proved not to be efficient ones (Table 1, entries 9, 10).

Table 1. Screening the Reaction Conditions[a]



entry	catalyst	oxidant	AcOH/equiv	yield[b]
1	**C1**	H_2O_2	0	NR
2	**C1**	H_2O_2	6	48
3	**C1**	H_2O_2	14	68[c]
4	none	H_2O_2	14	NR
5	**C1**	AcOOH	–	60
6	**C1**	*m*-CPBA	0	trace
7	**C1**	PhIO	0	NR
8	**C1**	*t*BuOOH	0	trace
9	**C2**	H_2O_2	14	15
10	**C3**	H_2O_2	14	6

[a]Reaction conditions: 3.5 equiv of oxidant diluted with 0.5 mL of CH_3CN was delivered by syringe pump over 30 min to a stirred solution of catalyst **C1** (2.0×10^{-3} mmol, 0.5 mol %), HOAc (5.6 mmol), and substrate (0.4 mmol) in 1.0 mL of CH_3CN at rt under Ar atmosphere. [b]GC yield with nitrobenzene as an internal standard. [c]1% yield of α-methylbenzyl alcohol and 6% yield of α-methylbenzyl acetate as the byproducts.

After the optimized conditions were identified, a series of derivatives of ethylbenzene containing different substituted groups on the aromatic ring were subjected to the oxidation reactions catalyzed by the Mn complex **C1**. Most of the tested substrates gave the corresponding ketone in >60% yields (Table 2, entries 1−3; Table S1, Supporting Information (SI), entries 1−4). Only oxidation of 4-ethylbiphenyl resulted in a 23% yield of ketone, an additional 5% is acetic ester byproduct (Table S1 (SI), entry 4). In the case of oxidation of toluene, trace amount of benzyl alcohol and benzaldehyde were observed (Table S1 (SI), entry 5). Other benzylic compounds with bulkier groups were also explored; the reaction provided the benzophenone in a 70% yield for the oxidation of diphenylmethane (Table 2, entry 4). An enhanced yield was afforded for the oxidation of 1,2-diphenylethane because of the substrate having both identical benzylic sites (Table 2, entry 6). Oxidation of the benzylic sites in cycloalkanes bearing aromatic rings was also accomplished. The oxidation of 1,2,3,4-tetrahydronaphthalene occurs preferentially at one of the both benzylic sites with a 51% yield of ketone and a 10% yield of acetic ester with two equiv of H_2O_2 (Table 2, entry 7). On the other hand, 51% yield of 1,4-naphthoquinone was obtained through the desaturation reaction by using of 6.0 equiv of H_2O_2 (Table S1 (SI), entry 9). Xanthene could be transformed into carbonyl compound in a 55% yield and an additional 10% yield of acetic ester (Table 2, entry 8). Furthermore, oxidation of cyclohexane under optimized conditions afforded cyclohexanone in 61% yield together with 4% yield of cyclohexanol (Table 2, entry 10). On the other hand, oxidation at the C3 site was mainly observed in the case of *tert*-butylcyclohexane because of the steric influence; a total 49% yield of C3 and C4 ketones were formed (Table 2, entry 12, C3/C4 = 3.7/1).

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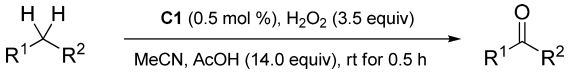
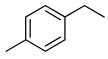
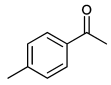
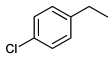
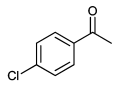
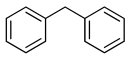
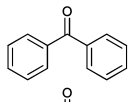
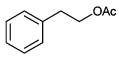
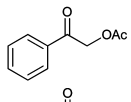
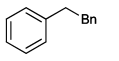
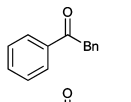
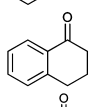
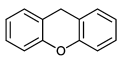
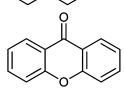
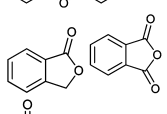
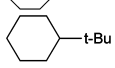
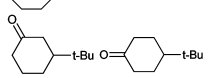
Table 2. Scope of the Oxidation of Benzylic and Aliphatic C−H Bonds[a]



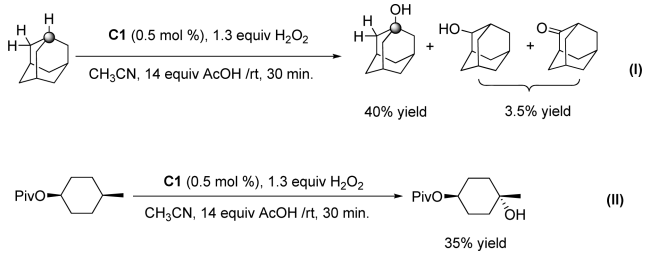
entry	substrate	product	yield[b]
1			(68)
2			(82)
3			67(77)
4			70
5			15
6			75
7[c]			51
8[d]			55
9			20/53
10[e]			(61)
11[f]			(54)
12		 (3.7 : 1)	40(49)

[a]Reaction conditions: 3.5 equiv of oxidant diluted with 0.5 mL of CH_3CN was delivered by syringe pump over 30 min to a stirred solution of catalyst **C1** (2.0×10^{-3} mmol, 0.5 mol %), HOAc (5.6 mmol), and substrate (0.4 mmol) in 1.0 mL of CH_3CN at rt under Ar atmosphere. [b]Isolated yield (GC yields in the parentheses). [c]With 2.0 equiv of H_2O_2 as oxidant, 10% yield acetic ester as a byproduct. [d]10% yield acetic ester as a byproduct. [e]4% yield of alcohol. [f]5% yield of alcohol.

The oxidation of adamantine was also examined by using 1.3 equiv of H_2O_2, which gave 1-adamantanol as the main product in 40% yield (Scheme 1(I); 2-adamantanol and 2-adamantanone were obtained in 3.5% yield, totally). The hydroxylation occurs at the more electron-rich tertiary C−H groups, and it indicates that the catalytic system possess an electrophilic nature. We also chose *cis*-4-methylcyclohexyl-1-pivalate as a substrate to evaluate the capability of complex **C1** to stereospecific hydroxylates tertiary C−H bonds. As expected, the catalyst exhibits a good selectivity for tertiary C−H bonds with excellent retention of configuration (Scheme 1(II)).[6]

To gain further insights into this reaction, we measured the kinetic isotope effect (KIE) in the oxidation of cyclohexane by using excess substrate and limited H_2O_2. The competing experiment of cyclohexane and the deuterated cyclohexane

Scheme 1. Oxidation of Adamantane and *cis*-4-Methylcyclohexyl-1-pivalate



under the standard oxidation conditions shows a KIE value of 3.9, which indicates that the C−H cleavage is the rate-limiting step (see SI). Isotopic labeling experiments were also carried out to reveal the reaction mechanism. Under standard conditions, oxidation of ethylbenzene in the presence of 20 equiv of $H_2{}^{18}O$ resulted in 13.3% of ^{18}O incorporation into acetophenone (see SI). The high-valent manganese-oxo species may be involved in the catalytic process, since oxygen exchange between the high-valent manganese-oxo species and labeled water could take place via tautomerism.[4h,18] Despite the use of AcOOH or H_2O_2/AcOH as the oxidant showing similar reactivity in the oxidations mediated by nonheme catalysts, the specific role of acetic acid has not yet been clarified.[9−11] A control experiment was performed under the standard reaction conditions but without substrate; 700 equiv of H_2O_2 was added to the reaction system in CD_3CN (1.0 equiv of Mn complex **C1** and 2800 equiv of acetic acid). After 30 min, no detectable AcOOH was observed on the basis of the ^{13}C NMR spectrum (see SI).[19] It suggests that acetic acid may serve as a key additive to promote fast O−O heterolysis of Mn^{III}−OOH intermediates.[20]

In summary, a bioinspired manganese complex based on the ligand with a more rigid diamine derived from proline and two benzimidazoles was successfully applied to the benzylic and aliphatic C−H oxidation under mild conditions. The present nonheme manganese catalyst exhibits good performance in the oxidation of secondary benzylic, aliphatic C−H bonds as well as tertiary C−H groups and provides oxidation products in synthetically valuable yields. Further investigations into the mechanism and applications of this nonheme system are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Procedures for C−H bond catalytic oxidation reactions, characterization of Mn complex **C1** and the products, NMR copies of the products, and crystal data (CIF). 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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