A highly efficient non-heme manganese complex in oxygenation reactions†

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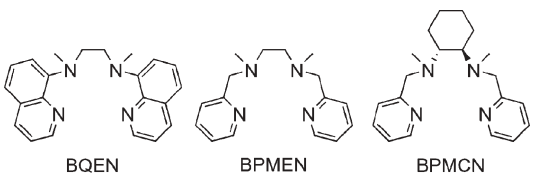
A non-heme manganese(II) complex shows a high catalytic activity in the epoxidation of olefins by iodosyl benzene and in the oxidation of olefins, alcohols and alkanes by peracetic acid; a mechanism involving metal-based oxidants is proposed for the oxidation reactions.

Metal-catalyzed oxygenations of organic substrates are of significant importance in both synthetic chemistry and industrial processes.[1] Since metalloenzymes catalyze the oxygenation reactions with high regio- and stereoselectivity under mild conditions, biomimetic oxygenation reactions using their model compounds have attracted much attention in the communities of bioinorganic and oxidation chemistry.[2] For example, it has been demonstrated that synthetic iron complexes of heme and non-heme ligands are capable of mimicking the chemistry of cytochrome P450 (CYP 450) and non-heme iron enzymes, respectively, and that the oxygenation reactions by the model compounds proceed *via* a mechanism involving metal-based oxidants (*e.g.*, high-valent iron-oxo intermediates).[3] Similarly, manganese porphyrins have been extensively investigated as chemical models of CYP 450 in various oxygenation reactions.[4] Manganese complexes bearing non-heme ligands, such as salen- and tacn-derived ligands,[5] have shown promise as versatile catalysts in olefin epoxidation and alkane hydroxylation.[6,7] Very recently, Stack and co-workers[8] reported a highly efficient epoxidation reaction using peracetic acid as the terminal oxidant, in which terminal olefins are epoxidized to the corresponding epoxides in the presence of non-heme Mn(II) catalysts (*e.g.*, $Mn(BPMEN)(CF_3SO_3)_2$ and $Mn(BPMCN)(CF_3SO_3)_2$).[5] We now report a mononuclear non-heme manganese complex, $Mn(BQEN)(CF_3SO_3)_2$ (**1**),[5] that shows a high catalytic activity and stereo- and regioselectivity in the oxidation of olefins, alcohols and alkanes under mild conditions.



The manganese complex **1** was synthesized by reacting equimolar amounts of $Mn(CF_3SO_3)_2$ and the ligand BQEN[9] in CH_3CN. Addition of diethyl ether into the reaction solution afforded colorless crystals suitable for crystallographic analysis. The crystal structure of **1** reveals a *cis*-α coordination mode around the distorted octahedral metal center (Fig. 1), similar to the structure of the iron analogue.[9] The electrospray ionization mass spectrum (ESI MS) of **1** exhibits a prominent ion peak at a mass-to-charge ratio (*m*/*z*) of 546.2, whose mass and isotope distribution pattern corresponds to $[Mn(II)(BQEN)(CF_3SO_3)]^+$ (calculated *m*/*z* of 546.1) (ESI,† Fig. S1). The X-band EPR spectrum of **1** exhibits an intense signal at $g = 2.0$ (ESI,† Fig. S2), indicating a high-spin ($S = 5/2$) Mn^{II} species.[8c] The high-spin state of **1** was further confirmed by determining the magnetic moment of 5.4 μ_B at 25 °C with the ^1H NMR method of Evans.[10]

The catalytic activity of **1** was first investigated in olefin epoxidation by iodosyl benzene (PhIO) and then compared to that of $Mn(BPMEN)(CF_3SO_3)_2$ (**2**) and $Mn(BPMCN)(CF_3SO_3)_2$ (**3**) under identical conditions (Table 1). In the epoxidation of cyclohexene, cyclohexene oxide was the major product with the formation of small amounts of allylic oxidation products such as cyclohexenol and cyclohexenone (entry 1). The epoxidation of *cis*- and *trans*-stilbene produced *cis*- and *trans*-stilbene oxide, respectively, with the formation of trace amounts of isomerized stilbene oxide products (entries 3 and 4), demonstrating that the olefin epoxidation by **1** and PhIO is highly stereospecific. It is worth noting that the formation of isomerized products was often observed in non-heme manganese complex-catalyzed olefin epoxidations.[6,11] In the competitive epoxidation of *cis*- and

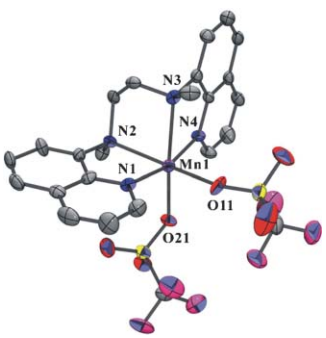


Fig. 1 Molecular structure of $Mn(BQEN)(CF_3SO_3)_2$ (**1**) showing 30% probability thermal ellipsoids.‡[1] Hydrogen atoms have been omitted for clarity. The average Mn–N and Mn–O distances are 2.27 and 2.16 Å, respectively. The absolute configuration of the amine nitrogen atoms in the stereoisomer is N2-*R* and N3-*R*. See ESI† for the crystal data and structure refinement of **1** (Table S1) and selected bond distances and angles (Table S2). CCDC 650716. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b708976g

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, Tables S1 and S2, and Fig. S1 and S2. See DOI: 10.1039/b708976g

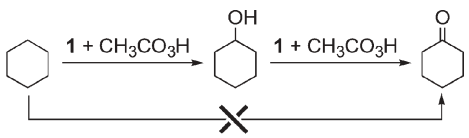
Table 1 Epoxidation of olefins by PhIO catalyzed by non-heme manganese(II) complexes[a]

Entry	Substrate	Product(s)	Yield[b,c] (%) 1	2	3
1	Cyclohexene	Cyclohexene oxide	82 (4)	45 (3)	45 (3)
		Cyclohexenol	3 (1)	10 (2)	8 (2)
		Cyclohexenone	3 (1)	11 (2)	8 (2)
2	Cyclooctene	Cyclooctene oxide	95 (4)	35 (2)	26 (2)
3	*cis*-Stilbene	*cis*-Stilbene oxide	33 (2)	16 (2)	12 (2)
		trans-Stilbene oxide	3 (1)	7 (1)	13 (2)
		Benzaldehyde	23 (3)	24 (3)	20 (3)
4	*trans*-Stilbene[d]	*cis*-Stilbene oxide	0	0	0
		trans-Stilbene oxide	35 (2)	17 (2)	24 (2)
		Benzaldehyde	23 (3)	20 (3)	27 (3)
5	*cis*-Stilbene[e] + *trans*-stilbene	*cis*-Stilbene oxide + *trans*-stilbene oxide	16 (2) + 40 (3)	4 (1) + 24 (2)	8 (1) + 22 (2)

[a] *Reaction conditions*: Solid PhIO (100 equiv. per Mn) was added to a reaction solution containing manganese catalyst (1 mM) and substrate (0.5 M) in CH_3CN (2 mL) at 25 °C. After 30 min stirring, the reaction solution was filtered and directly analyzed by GC, GC-MS, or HPLC. [b] Product yields are based on the amount of PhIO added. [c] The numbers in parentheses represent a standard deviation of three experiments. [d] Reaction was carried out with *trans*-stilbene (0.25 M) and PhIO (50 equiv. per Mn) in acetone due to the low solubility of the substrate. [e] Equimolar amounts (0.25 M each) of *cis*- and *trans*-stilbene and PhIO (50 equiv. per Mn) were used in acetone.

trans-stilbene, the ratio of *cis*- to *trans*-stilbene oxide was determined to be 0.4 (entry 5), indicating the preference of *trans*-olefin epoxidation to *cis*-olefin epoxidation by the intermediate generated in the reaction of **1** and PhIO. This result is markedly different from those frequently observed in competitive olefin epoxidations, in which *cis*-stilbene epoxidation is favored over *trans*-stilbene epoxidation due to the steric hindrance caused by the phenyl groups of *trans*-stilbene.[12] In contrast to the excellent catalytic activity of **1**, low epoxide yields and reduced selectivities were observed in olefin epoxidations by **2** and **3** (Table 1). To the best of our knowledge, **1** is the most effective non-heme manganese catalyst that affords high epoxide yields, small amounts of allylic oxidation products, and a high stereospecificity in the epoxidation of olefins by PhIO. However, only trace amounts of oxygenated products were produced in the hydroxylation of cyclohexane by **1** and PhIO (*e.g.*, <4% based on the PhIO added), indicating that **1** is not an effective catalyst in alkane hydroxylation by PhIO (*vide infra*).

We then studied the oxidation of olefins, alcohols and alkanes using peracetic acid as the terminal oxidant in the presence of Mn(II) catalysts, inspired by the pioneering work of Stack and co-workers who demonstrated that **3** is an excellent catalyst in the epoxidation of terminal olefins by peracetic acid.[8] The results in Table 2 show that the product yields are very high and that the catalytic activity of **1** is comparable to that of **3**. In the epoxidation of olefins, epoxides were the sole products detected (entries 1–4), and excellent product yields were obtained even in the epoxidation of terminal olefins.[8] Alcohols were converted to the corresponding ketone or aldehyde products (entries 5–7), and a kinetic isotope effect (KIE) of 2.2 was determined in an intermolecular competitive oxidation of benzyl alcohol and benzyl-d_7 alcohol (entry 12).[13]



(1)

Table 2 Oxidation of olefins, alcohols, and alkanes by peracetic acid catalyzed by non-heme manganese complexes[a]

Entry	Substrate	Product(s)	Yield[b,c] (%) 1	3
A. Olefin epoxidation				
1	Cyclohexene	Cyclohexene oxide	95 (3)	95 (3)
2	Cyclooctene	Cyclooctene oxide	95 (3)	95 (3)
3	1-Hexene	1,2-Epoxyhexane	96 (3)	98 (2)
4	1-Octene	1,2-Epoxyoctane	95 (3)	98 (2)
B. Alcohol oxidation				
5	Cyclohexanol	Cyclohexanone	80 (5)	96 (3)
6	Cyclooctanol	Cyclooctanone	78 (5)	96 (3)
7	Benzyl alcohol	Benzaldehyde	70 (5)	98 (2)
C. Alkane hydroxylation				
8	Cyclohexane	Cyclohexanol & cyclohexanone	4 (1) & 41 (3)	3 (1) & 32 (3)
9	*cis*-1,2-Dimethylcyclohexane	*cis*-1,2-Dimethylcyclohexanol	58 (4)	55 (4)
		2,3- and 3,4-Dimethylcyclohexanol and -one	20 (3)	20 (3)
10	*trans*-1,2-Dimethylcyclohexane	*trans*-1,2-Dimethylcyclohexanol	18 (2)	13 (2)
		2,3- and 3,4-Dimethylcyclohexanol and -one	30 (3)	30 (3)
11	Adamantane[d]	Adamantan-1-ol	20 (2)	9 (1)
		Adamantan-2-ol + adamantan-2-one	1 (1)	1 (1)
D. Competitive oxidation reactions[e]				
12	Benzyl alcohol + benzyl-d_7 alcohol	Benzaldehyde + benzaldehyde-d_6	66 (3) + 30 (2)	66 (3) + 32 (2)
13	Cyclohexane + cyclooctanol	Cyclohexanol & cyclohexanone + cyclooctanone	0 + 90 (2)	0 + 98 (2)
14	Cyclohexane + cyclohexane-d_{12}	Cyclohexanol + cyclohexanol-d_{12}	22 (2) + 8 (1)	26 (2) + 10 (1)
		Cyclohexanone + cyclohexanone-d_{10}	30 (2) + 4 (1)	23 (2) + 5 (1)
15	*cis*-1,2-Dimethylcyclohexane[f] + *trans*-1,2-dimethylcyclohexane	*cis*-1,2-Dimethylcyclohexanol + *trans*-1,2-dimethylcyclohexanol	52 (3) + 8 (1)	46 (3) + 8 (1)

[a] *Reaction conditions*: Peracetic acid (100 equiv per Mn, 32 wt% solution) was added to a reaction solution containing manganese catalyst (1 mM) and substrate (0.5 M) over 20 min *via* a syringe method in CH_3CN (2 mL) at 25 °C. After 10 min stirring, the reaction solution was directly analyzed by GC and GC-MS. [b] Product yields are based on the amount of CH_3CO_3H added. [c] The numbers in parentheses represent a standard deviation of three experiments. [d] Low concentration of adamantane (0.25 M) was used due to the low solubility. [e] Equimolar amounts of competing substrates (0.25 M each) and oxidant (50 mM) were used unless otherwise noted. [f] Other products, such as 2,3- and 3,4-dimethylcyclohexanol and -one, were formed (~30%).

In alkane hydroxylation, ketone was the dominant product formed in the hydroxylation of cyclohexane (entry 8), and the ketone formation was the result of the further oxidation of alcohols at a fast rate (entry 13) [eqn. (1)]. By carrying out an intermolecular competitive hydroxylation with cyclohexane and cyclohexane-d_{12} (entry 14), a KIE value of 2.5 was determined for the formation of alcohol. The alkane hydroxylation was found to be highly stereospecific, in which the hydroxylation of *cis*-1,2-dimethylcyclohexane afforded *cis*-1,2-dimethylcyclohexanol with >99% retention and the hydroxylation of *trans*-1,2-dimethylcyclohexane yielded *trans*-1,2-dimethylcyclohexanol with no formation of its epimer (entries 9 and 10). In a competitive hydroxylation of *cis*- and *trans*-1,2-dimethylcyclohexane, the ratio of *cis*- to *trans*-1,2-dimethylcyclohexanol was ~6.0 (entry 15), indicating that the intermediate generated in the reactions of **1** and **3** with CH_3CO_3H reacts faster with *cis*-alkane than *trans*-alkane. The alkane hydroxylation was also highly regioselective, in which the oxidation took place rigorously at the tertiary C–H bond in the hydroxylation of adamantane (entry 12); the ratio of 3°/2° oxygenated products was 60 after statistical corrections.§[14] The ESI MS and EPR spectra of **1**, taken after the completion of the oxidation reaction, were identical to those of the starting Mn complex (ESI,† Fig. S1 and S2), indicating that **1** is resistant against the ligand destruction. However, the catalytic activity decreases drastically upon the addition of further peracetic acid to the reaction solution. A control reaction, carried out with $Mn(CF_3SO_3)_2$ instead of **1**, revealed that only trace amounts of oxygenated products were formed in the hydroxylation of cyclohexane by CH_3CO_3H, implying that there is a significant ligand effect in generating an active oxidant and/or tuning the reactivity of the intermediate toward oxygenation reactions.

Finally, we carried out ^{18}O-labeled experiments to understand the source of oxygen found in oxygenated products.[7b,15] When the alkane hydroxylation was carried out in the presence of $H_2{}^{18}O$, no ^{18}O-incorporation from the labeled water into alcohol products was observed. This result implies that the active species generated in the reaction of **1** and CH_3CO_3H does not exchange with $H_2{}^{18}O$ at a fast rate. In addition, no ^{18}O-incorporation was observed in oxygenated products when the alkane hydroxylation by **1** and CH_3CO_3H was carried out under $^{18}O_2$ atmosphere, demonstrating that the oxygen in oxygenated products derived from the oxidant, not from molecular oxygen.

In conclusion, all the results presented above strongly support that the epoxidation of olefins by PhIO and the oxidation of olefins, alcohols and alkanes by CH_3CO_3H does not occur *via* an auto-oxidation reaction but *via* a mechanism involving metal-based oxidants. Then, what are the oxygenating intermediates involved in the PhIO and CH_3CO_3H reactions? Based on the observations that the intermediates generated in the PhIO and CH_3CO_3H reactions showed different reactivities in alkane hydroxylation and different product distributions in competitive oxygenations, we may propose that the intermediates involved in the catalytic oxygenation reactions by PhIO and CH_3CO_3H are different. However, all our efforts to characterize the reactive species spectroscopically failed at this moment. It should be noted that the nature of oxygenating intermediates in manganese complex-catalyzed oxygenation reactions has been poorly understood.[16] Future studies will focus on elucidating the structure of oxygenating intermediates and the effect of non-heme ligands in tuning the oxidizing power of the intermediates.

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Notes and references

‡ We make no claim to be reporting a chiral synthesis, and the Flack value [0.20(3)] does not allow an unequivocal determination of absolute structure of **1**. What is shown in Fig. 1 has N2-*R* and N3-*R* stereochemistry.

§ The amount of 1-adamantanol was divided by the sum of 2-adamantanol and 2-adamantanone, and then multiplied by 3 to correct the number of tertiary and secondary C–H bonds.

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5 salen = *N*,*N*′-Bis(salicylidene)ethylenediamine, tacn = 1,4,7-triazacyclononane, BPMEN = *N*,*N*′-dimethyl-*N*,*N*′-bis(2-pyridylmethyl)ethane-1,2-diamine, BPMCN = *N*,*N*′-dimethyl-*N*,*N*′-bis(2-pyridylmethyl)cyclohexane-(1*R*,2*R*)-diamine, BQEN = *N*,*N*′-dimethyl-*N*,*N*′-bis(8-quinolyl)-ethane-1,2-diamine.

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