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Mechanistic Insights into the Enantioselective Epoxidation of Olefins by Bioinspired Manganese Complexes: Role of Carboxylic Acid and Nature of Active Oxidant

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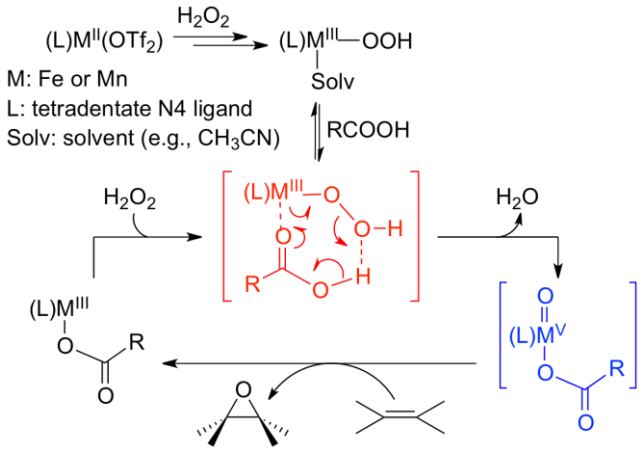
ABSTRACT: Bioinspired manganese and iron complexes bearing nonporphyrinic tetradentate N4 ligands are highly efficient catalysts in asymmetric oxidation reactions by hydrogen peroxide (H_2O_2), in which carboxylic acid is employed as an essential additive to improve product yields and stereo-, regio-, and enantioselectivities. The metal catalysts should possess two *cis*-binding sites for oxidant (e.g., H_2O_2) and carboxylic acid to generate high-valent metal-oxo species as active oxidants via "carboxylic acid-assisted" mechanism. In the present study, we have investigated the role(s) of carboxylic acid and the nature of reactive intermediate(s) in the manganese complex-catalyzed enantioselective epoxidation of olefins, by employing nonheme manganese catalysts, such as **1** bearing a tetradentate N4 ligand (L^{N4}) and **2** bearing a pentadentate N5 ligand (L^{N5}), and using various oxidants, such as H_2O_2, alkyl hydroperoxides, and iodosylbenzene (PhIO). As expected, **1** possessing two *cis*-binding sites is an effective catalyst irrespective of the oxidants in the presence of carboxylic acid. In contrast, **2** possessing only one binding site is not an effective catalyst in the reactions of H_2O_2 and alkyl hydroperoxides even in the presence of carboxylic acid. However, unexpectedly, **2** turns out to be an effective catalyst in the asymmetric epoxidation of olefins by PhIO in the presence of carboxylic acid. The latter result indicates that a manganese complex, which cannot bind carboxylic acid as an auxiliary ligand, can afford a high enantioselectivity, probably through a second-sphere coordination interaction between carboxylic acid and the oxo group of a presumed manganese-oxo oxidant. We have also provided indirect evidence supporting that a high-valent Mn(V)-oxo species is the active oxidant in the catalytic asymmetric epoxidation reactions.

KEYWORDS: Asymmetric Epoxidation, Manganese Catalyst, Carboxylic Acid Additive, Mechanism, Manganese-Oxo

INTRODUCTION

The selective oxidation of hydrocarbons under mild conditions is of great current interest in enzymatic reactions as well as in synthetic organic chemistry.[1,2] In enzymatic reactions, metalloenzymes, such as heme and nonheme iron enzymes, catalyze a diverse array of important oxidative transformations, including olefin epoxidation and alkane hydroxylation reactions.[2] Inspired by the high reactivity and selectivity shown by heme and nonheme iron enzymes, synthetic iron porphyrins, nonheme iron complexes, and related manganese complexes have been employed as catalysts in the oxidation of organic substrates.[3-5] One notable example is the recent development in the (asymmetric) epoxidation of olefins and the C-H bond hydroxylation of alkanes by hydrogen peroxide (H_2O_2) catalyzed by nonheme iron and manganese complexes.[6,7] In the catalytic oxidation reactions, carboxylic acid (e.g., acetic acid) is an essential component for high product yields and stereo-, regio-, and enantioselectivities.[6,7] Indeed, Jacobsen and co-workers reported for the first time that the catalytic epoxidation of aliphatic olefins by a nonheme iron complex and H_2O_2 afforded high product yields in the presence of acetic acid,[8] followed by using the catalytic system (e.g., nonheme iron catalysts/H_2O_2/carboxylic acid) in C-H selective oxidation reactions by White and co-workers.[9] Shul'pin and co-workers also reported that manganese complexes catalyzed the epoxidation of olefins by H_2O_2 in the presence of acetic acid.[10] Later, Que and co-workers invoked a carboxylic acid-assisted O-O bond cleavage mechanism, in which a highly reactive nonheme Fe(V)-oxo species was generated via a heterolytic O-O bond cleavage of an Fe(III)-OOH precursor in the presence of acetic acid (Scheme 1).[5b,11] The catalytic systems (e.g., nonheme iron and manganese catalysts/H_2O_2/carboxylic acid) were then successfully developed in asymmetric oxidation reactions by the groups of Bryliakov/Talsi, Costas, and Sun.[6,7,12-14] Of particular note is the report by Bryliakov/Talsi and co-workers that the steric bulk of carboxylic acid additives affects the epoxidation enantioselectivity, implying that the carboxylic acid molecule is involved in the enantioselectivity-determining step, presumably acting as an auxiliary ligand.[12a] Very recently, we succeeded in using a catalytic amount of sulfuric acid (H_2SO_4), instead of using a large amount of carboxylic acid, to achieve the asymmetric oxidation of organic substrates by nonheme manganese complexes and H_2O_2.[15] These results demonstrate unambiguously that carboxylic acid (and sulfuric acid) plays an important role in improving the catalytic activity as well as the enantioselectivity in the asymmetric oxidation



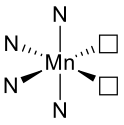
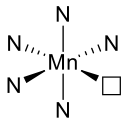
Scheme 1. Proposed Carboxylic Acid-Assisted Heterolytic O-O Bond Cleavage Mechanism

reactions by nonheme metal catalysts and H_2O_2.

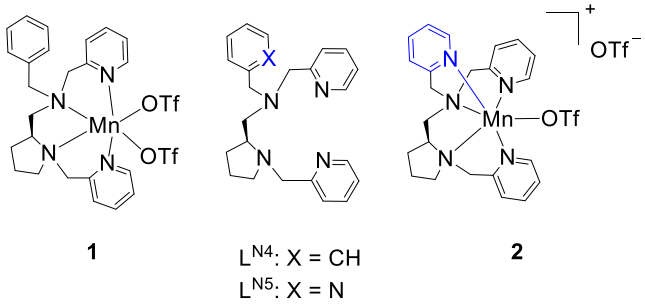
Another important factor, which is crucial to achieve the efficient asymmetric olefin epoxidation by metal complexes and H_2O_2 in the presence of carboxylic acid, is the structure (and topology) of the iron and manganese catalysts. The metal catalysts bearing tetradentate N4 ligands should possess two *cis*-labile sites for the binding of both oxidant (e.g., H_2O_2) and carboxylic acid to facilitate the heterolytic O-O bond cleavage of metal(III)-hydroperoxo intermediates (Scheme 1, red-colored structure) and form metal(V)-oxo species as active oxidants (Scheme 1, blue-colored structure).[5-7] Indeed, mononuclear nonheme Fe(V)-oxo species have been trapped and characterized using various spectroscopic techniques,[12,16-18] such as electron paramagnetic resonance (EPR), stopped-flow UV–vis, and variable-temperature mass spectrometry (VT-MS), along with density functional theory (DFT) calculations,[19] supporting the intermediacy of the Fe(V)-oxo species in the catalytic oxidation reactions. Thus, the availability of two *cis*-binding sites in nonheme metal catalysts is crucial for the generation of high-valent metal(V)-oxo intermediates by activating H_2O_2 in the presence of carboxylic acid additive.

As mentioned above, it is clear that carboxylic acid (or sulfuric acid) plays a key role in generating high-valent metal-oxo intermediates for the selective oxidation reactions (Scheme 1, red- and blue-colored structures). However, the carboxylic acid effect on the enantioselectivity in the epoxidation reactions is still unclear and remains elusive. Moreover, the nature of the active oxidant(s) responsible for the catalytic epoxidation reactions needs to be clarified, especially in nonheme manganese systems; there has been a controversy on the structure of the active oxidant, such as M(V)-oxo versus M(III)-(acyl)hydroperoxo (M = Mn and Fe) species.[16c,20] As our ongoing efforts to develop and understand the catalytic asymmetric oxidation reactions using earth-abundant metal catalysts and environmentally benign oxidants, we have investigated the manganese complex-catalyzed enantioselective epoxidation of olefins, by employing nonheme manganese catalysts bearing tetradentate N4 (L^{N4}) and pentadentate N5 (L^{N5}) ligands (see Table 1 for the Mn core structures of catalysts and Scheme 2 for the structures of ligands and Mn(II) complexes) and using various

Table 1. Summary of Asymmetric Epoxidation Reactions by Manganese Complexes and Various Oxidants in the Presence of Carboxylic Acid[a]

oxidant		
H_2O_2	✓	✗
alkyl hydroperoxides	✓	✗
PhIO	✓	✓

[a]The square represents the binding site(s) for oxidant and carboxylic acid. The tick and cross stand for excellent and poor reactivity, respectively.



Scheme 2. Structures of Ligands and Manganese Complexes Used in This Study

oxidants, such as H_2O_2, alkyl hydroperoxides, and iodosylbenzene (PhIO). We now report that the manganese complex bearing the tetradentate N4 (L^{N4}) ligand, **1** (Scheme 2, left structure), is an effective catalyst irrespective of the oxidants in the presence of carboxylic acid additive, whereas the manganese complex bearing the pentadentate N5 (L^{N5}) ligand, **2** (Scheme 2, right structure),[21] is not an effective catalyst in the reactions of H_2O_2 and alkyl hydroperoxides under the identical reaction conditions (see Table 1 for the summary of the asymmetric epoxidation of olefins by various oxidants catalyzed by **1** and **2**). Interestingly, **2** turns out to be a highly efficient catalyst giving high product yields with a high enantioselectivity in the asymmetric epoxidation of olefins by PhIO in the presence of carboxylic acid (Table 1). Other mechanistic aspects, such as the nature of the active manganese oxidant and the formation mechanism of the manganese oxidant, are also discussed in the present study.

RESULTS AND DISCUSSION

Synthesis and Characterization of Manganese Catalysts. We used two manganese(II) catalysts in this study, such as **1** with a tetradentate N4 ligand (denoted as L^{N4}, L^{N4} = (*S*)-*N*,*N*-bis(2-picolinyl)-*N*-benzyl-2-pyrrolidinemethanamine) and **2** with a pentadentate N5 ligand (denoted as L^{N5}, L^{N5} = (*S*)-*N*,*N*,*N*-tris(2-picolinyl)-2-pyrrolidinemethanamine) (see Scheme 2 for the structures of L^{N4}, L^{N5}, **1**, and **2**). The ligands were synthesized by

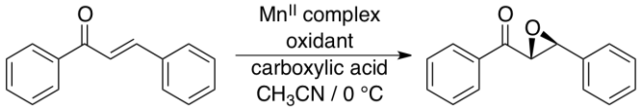
introducing one benzyl and two 2-picolinyl groups for L^{N4} and three 2-picolinyl groups for L^{N5} to the L-proline-derived chiral skeleton (*S*)-2-pyrrolidinemethanamine. The Mn(II) complexes, $[Mn^{II}(L^{N4})(OTf)_2]$ (**1**) and $[Mn^{II}(L^{N5})(OTf)](OTf)$ (**2**), were synthesized by treating the ligands with an equimolar amount of $Mn(OTf)_2$ ($OTf^- = CF_3SO_3^-$) in CH_3CN under an Ar atmosphere (Experimental Section for the synthesis and characterization of ligand L^{N4} and **1**; see also Supporting Information (SI), Figure S1 for the schematic drawings for the synthesis of ligands and Mn catalysts). The crystal structure of **1** exhibits a hexa-coordinated manganese complex in *cis-α* topology with two triflate ligands, indicating that two labile sites are available for the binding of oxidant and carboxylic acid (Scheme 2, left structure; also see SI, Tables S1 and S2 for crystallographic data and Figure S2 the X-ray crystal structure). In contrast, **2** contains a single triflate ligand bound to the manganese center, implying that only one labile site is available for the binding of either oxidant or carboxylic acid (Scheme 2, right structure).[21]

Catalytic Reactions by 1 and 2 under Various Conditions. The catalytic activity of **1** possessing two *cis*-binding sites was compared with that of **2** possessing only one binding site, by carrying out the asymmetric epoxidation of chalcone with various oxidants, such as H_2O_2, *tert*-butyl hydroperoxide (TBHP), cumyl hydroperoxide (CHP), and PhIO, in the absence and presence of 2-ethylhexanoic acid (EHA), which is a frequently used carboxylic acid in the oxidation of organic substrates by H_2O_2 catalyzed by nonheme Fe and Mn complexes.[12a,22] The reaction conditions are described in the schematic diagram and footnote in Table 2, and the product yields as well as the enantiomeric excess (*ee*) values of the epoxide product are listed in Table 2. The results are divided into two sub-sections for discussion, such as one with H_2O_2 and alkyl hydroperoxides and the other with PhIO.

(i) Reactions with H_2O_2 and Alkyl Hydroperoxides. The epoxidation of chalcone by **1** and H_2O_2 did not yield the epoxide product in the absence of carboxylic acid (i.e., EHA; Table 2, entry 1). However, when the identical reaction was carried out in the presence of EHA, chalcone oxide was produced with a high yield and a good enantioselectivity (Table 2, entry 2; see also SI, Figures S3 and S4 for NMR and HPLC analyses). The carboxylic acid effect was also observed in the catalytic epoxidation of chalcone by **1** and alkyl hydroperoxides, such as TBHP and CHP (Table 2, entries 3 and 4 for TBHP and entries 5 and 6 for CHP). Thus, as demonstrated previously,[6,7,12,13] in the olefin epoxidation reactions by H_2O_2 and alkyl hydroperoxides catalyzed by **1**, the binding of carboxylic acid at the manganese center promotes the heterolytic O-O bond cleavage of the manganese-hydro(alkyl)peroxo precursors, resulting in the formation of a high-valent manganese-oxo species as an active oxidant via the "carboxylic acid-assisted" mechanism (Scheme 3, pathways *a* and *c*).[5b,11]

When the catalytic epoxidation of chalcone by **1** and H_2O_2 was carried out in protic solvent (i.e., trifluoroethanol (TFE)) in the absence of the carboxylic acid additive, chalcone oxide was produced with a high yield but the *ee* value was low (Scheme 4). Interestingly, when the epoxidation reaction was carried out in the presence of EHA under the identical conditions, we observed the formation of chalcone oxide *not only* with a high product yield *but also* with a good enantioselectivity (Scheme 4); the *ee* value was increased from 31% in the absence of EHA to 86% in the presence of EHA. These

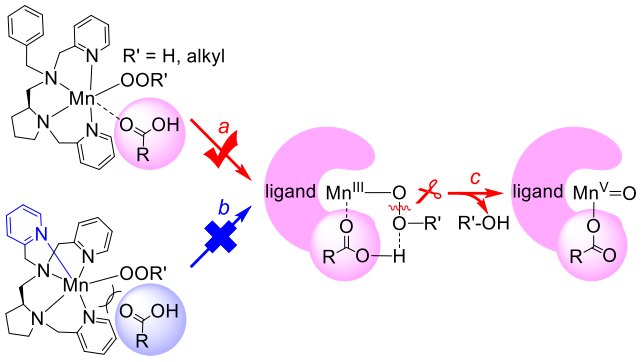
Table 2. Asymmetric Epoxidation of Chalcone by Mn Catalysts under Various Conditions[a]



entry	cat.	oxidant	EHA (equiv)	conv. (%)	yield (%)	*ee* (%)
1	**1**	H_2O_2	0	<1	<1	n. d.
2			5	75	71	89
3		TBHP	0	46	43	19
4			5	99	97	90
5		CHP	0	39	33	5
6			5	99	96	90
7		PhIO	0	33	30	32
8			5	99	97	89
9		$PhI(OAc)_2$	0	99	94	75
10	**2**	H_2O_2	0	<1	<1	n. d.
11			5	<1	<1	n. d.
12		TBHP	0	15	11	n. d.
13			5	16	12	n. d.
14		CHP	0	7	5	n. d.
15			5	11	7	n. d.
16		PhIO	0	41	37	25
17			5	72	70	78
18		$PhI(OAc)_2$	0	76	71	66

[a]Reaction conditions: chalcone (0.20 mmol), catalyst (2.0 mol%), oxidant (2 equiv to substrate), and 2-ethylhexanoic acid (EHA; 0 or 5 equiv to substrate) in CH_3CN at 0 °C for 2 h.

results are rationalized with the roles of protic solvent and carboxylic acid for the efficient formation of an active Mn-oxo species and the enhanced epoxidation enantioselectivity, respectively. That is, a Mn(III)-hydroperoxo species is converted to a Mn-oxo intermediate via an "alcohol-assisted" heterolytic O-O bond cleavage; this "alcohol-assisted" mechanism is similar to the "water-assisted" mechanism proposed previously by Que and co-workers.[5b,23] Indeed, it has been shown in iron porphyrin systems that the O-O bond of iron(III)-hydroperoxo porphyrin species is heterolytically cleaved in protic solvents (e.g., methanol), thereby

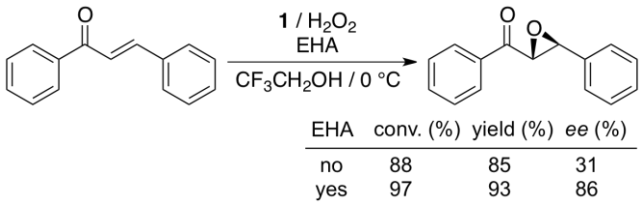


Scheme 3. *cis*-Binding Sites Required for the Formation of Active Manganese-Oxo Species in the Reactions of H_2O_2 and Alkyl Hydroperoxides

affording high product yields in the catalytic epoxidation of olefins by iron(III) porphyrin complexes and H_2O_2.[24] More importantly, the observation that the *ee* value was increased dramatically in the presence of carboxylic acid is the direct evidence that carboxylic acid plays an important role in tuning the epoxidation enantioselectivity via either coordinated or non-coordinated carboxylic acid (vide infra).

In the epoxidation reactions using **2** as a catalyst, product yields were low in the reactions of H_2O_2 and alkyl hydroperoxides even in the presence of carboxylic acid (Table 2, entries 10 – 15), probably due to the single binding site available at the Mn center in **2** (Scheme 3, pathway *b*; see also the structure in Table 1 and Scheme 2). These results demonstrate again the importance of the two *cis*-binding sites to form an active Mn-oxo intermediate via the "carboxylic acid-assisted" mechanism (Schemes 1 and 3). In addition, the present results lead us to propose that a pyridyl group coordinating at the manganese center in **2** cannot be replaced by carboxylic acid (vide infra). If carboxylic acid can coordinate to Mn center by replacing a pyridyl group in L^{N5}, the reactivity of **2** would be similar to that of **1** in the epoxidation of olefins by H_2O_2 and alkyl hydroperoxides; however, **2** is not an effective catalyst in these reactions (Table 2, entries 11, 13, and 15). We therefore conclude that the low catalytic activity of **2** in the epoxidation reactions by H_2O_2 and alkyl hydroperoxides even in the presence of carboxylic acid additive is due to the lack of two *cis*-binding sites for oxidant and carboxylic acid at the Mn center in **2** (Scheme 3, pathway *b*)

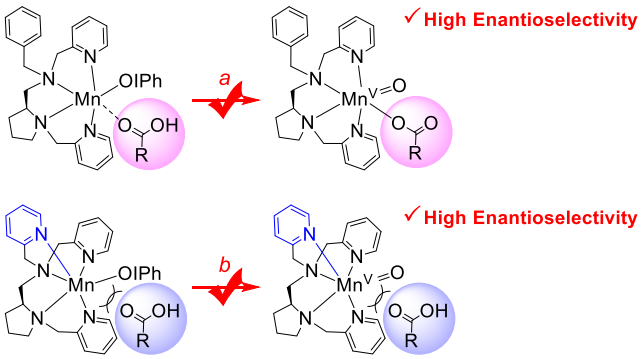
(ii) Reactions with PhIO. Iodosylbenzene (PhIO) is a single oxygen atom donor, which does not require the O-O bond cleavage step in generating high-valent metal-oxo intermediates. Therefore, different from the reactions of H_2O_2 and alkyl hydroperoxides, the catalytic activities of **1** and **2** bearing tetradentate N4 and pentadentate N5 ligands, respectively, would be similar in the reactions using PhIO as a terminal oxidant. In order to verify this hypothesis, we carried out the epoxidation of chalcone by PhIO catalyzed by **1** and **2** in the absence and presence of carboxylic acid. First, in the absence of carboxylic acid, the product yields and the *ee* values were low in the reactions of **1** and **2** (Table 2, entries 7 and 16). The low *ee* values were not unexpected, since carboxylic acid plays an important role in tuning epoxidation enantioselectivity (vide supra). Interestingly, when the identical reactions were carried



EHA	conv. (%)	yield (%)	*ee* (%)
no	88	85	31
yes	97	93	86

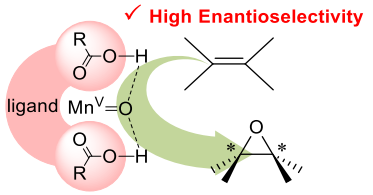
Scheme 4. Epoxidation of Chalcone by 1 and H_2O_2 in Protic Solvent[a]

[a]Reaction conditions: chalcone (0.20 mmol), **1** (2.0 mol%), H_2O_2 (0.40 mmol), and EHA (0 or 1.0 mmol) at 0 °C for 2 h.



Scheme 5. Formation of Active Manganese-Oxo Species in the Reactions of 1 and 2 with PhIO

out in the presence of carboxylic acid, *not only* the product yields *but also* the *ee* values increased dramatically in the reactions of **1** and **2** (Table 2, entries 8 and 17). These results demonstrate that highly reactive and enantioselective manganese-oxo intermediates were formed in the reactions of **1** and **2** with PhIO in the presence of carboxylic acid (Scheme 5). In addition, there are several important points that should be addressed here: First, in the catalytic epoxidation of chalcone by **1**, the *ee* value obtained in the reaction of PhIO was virtually the same as those obtained in the reactions of H_2O_2 and alkyl hydroperoxides (Table 2, entries 2, 4, and 6 for peroxides and entry 8 for PhIO), suggesting that a common intermediate (e.g., Mn-oxo species) was generated as an active oxidant in all of the reactions. If different oxidants (e.g., Mn-oxidant adducts such as Mn-OOH(R) or Mn-OIPh) were involved in the catalytic epoxidation reactions, the *ee* values of the epoxide product would be different depending on the terminal oxidants. Second, it is notable that the *ee* value obtained in the reaction of **2** and PhIO was high. It has been shown above that carboxylic acid cannot bind to **2** by replacing one of the pyridyl groups in L^{N5}. Nonetheless, the *ee* value was increased from 25% in the absence of carboxylic acid to 78% in the presence of carboxylic acid. The latter result implies that the enantioselectivity can be affected by non-coordinated carboxylic acid molecule(s), probably via a second-sphere hydrogen-bonding interaction between the H-atom(s) of the carboxylic acid and the oxo group of the manganese-oxo species (Scheme 6). It has been shown previously that secondary coordination sphere effects play an important role in selectivity and reactivity in a number of catalytic and enzymatic reactions.[25] However, to the best of our knowledge, this is the first example showing that the epoxidation



Scheme 6. Proposed Second-Sphere Hydrogen-Bonding Interaction That Controls the Epoxidation Enantioselectivity

enantioselectivity can be affected by the non-coordinated carboxylic acid(s); as discussed briefly above, carboxylic acid molecule(s) modulates the enantioselectivity of Mn-oxo species through a hydrogen-bonding interaction with the manganese-oxo moiety. Indeed, it has been shown recently that the reactivity of high-valent metal-oxo species is greatly influenced by the presence of protons, probably through a hydrogen-bonding interaction between metal-oxo moiety and proton(s).[26,27] Finally, the increased product yields in the reactions of **1** and **2** with PhIO in the presence of carboxylic acid are due to the increased solubility of the polymeric PhIO by the carboxylic acid (eq 1) (see the data in the columns of conversion and yield in Table 2, entries 7 and 8 for **1** and entries 16 and 17 for **2**). This speculation is evidenced by using $PhI(OAc)_2$, which is soluble in CH_3CN, as a terminal oxidant (Table 2, entries 9 and 18); the product yields as well as the *ee* values were high in these reactions.

$$PhIO + 2\ RCO_2H \rightleftharpoons PhI(RCO_2)_2 + H_2O \qquad (1)$$

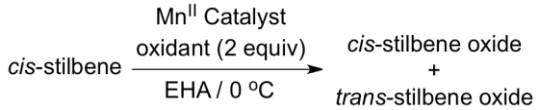
In this section, we have discussed the carboxylic acid effect in the asymmetric epoxidation of chalcone by various oxidants, such as H_2O_2, alkyl hydroperoxides, and` PhIO, catalyzed by two mononuclear nonheme manganese complexes bearing tetradentate N4 and pentadentate N5 ligands; one of the significant observations is that the enantioselectivity in epoxidation can be affected by non-coordinated carboxylic acid molecule(s), probably via a second-sphere coordination interaction between carboxylic acid and the oxo group of a manganese-oxo oxidant. The carboxylic acid effect was also shown in the epoxidation of other olefins, such as cyclooctene, styrene, and 1-octene, in which the product yields were dependent significantly on the presence of carboxylic acid and the availability of two *cis*-binding sites in the Mn catalysts (SI, Tables S3 – S5).

Nature of Reactive Intermediate(s). There has been a long-standing debate on one oxidant (e.g., high-valent metal-oxo species) versus multiple oxidants (e.g., high-valent metal-oxo plus metal-oxidant adducts) in the catalytic oxidation of organic substrates.[28,29] The mechanism of the O-O bond cleavage of metal-hydro(alkyl)peroxo intermediates for the formation of high-valent metal-oxo species (e.g., homolysis versus heterolysis) has also been of great interest in the community of bioinorganic/biomimetic chemistry.[30] In this section, we report the nature of active oxidant(s) and the O-O bond cleavage mechanism in the catalytic epoxidation of olefins by manganese catalysts, **1** and **2**, with various oxidants in the presence of carboxylic acid.

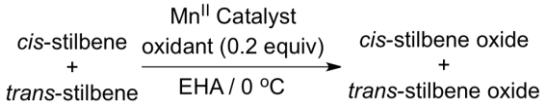
(i) Mechanistic Studies in Olefin Epoxidation. We have shown above that the *ee* values of epoxide product formed in the catalytic epoxidation of chalcone by **1** with various oxidants, such as H_2O_2, alkyl hydroperoxides, and PhIO, were the same within experimental

Table 3. Epoxidation of *cis*-Stilbene (Gray Area) and Competitive Epoxidation of *cis*- and *trans*-Stilbenes (Orange Area)

(1) Epoxidation of *cis*-stilbene[a,c]



(2) Competitive epoxidation of *cis*- vs *trans*-stilbenes[b,c]

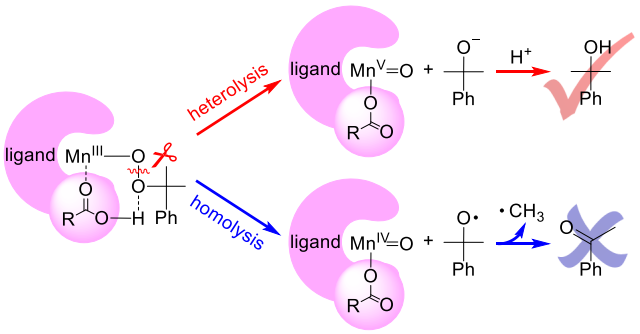


entry	cat.	oxidant	(1) ratio of *cis*- to *trans*-stilbene oxide products[d]	(2) ratio of *cis*- to *trans*-stilbene oxide products[e]
1	**1**	H_2O_2	40/1	1/4
2		TBHP	40/1	1/4
3		CHP	40/1	1/4
4		PhIO	40/1	1/4
5	**2**	PhIO	40/1	1/4

Reaction conditions: [a]*cis*-Stilbene (0.20 mmol), oxidant (2 equiv); [b]*cis*-stilbene (0.10 mmol) + *trans*-stilbene (0.10 mmol), oxidant (0.040 mmol, 0.2 equiv); [c]catalyst (2.0 mol%), EHA (5 equiv), in CH_3CN/CH_2Cl_2 (3:1 v/v) at 0 °C for 2 h. [d]Products from epoxidation of *cis*-stilbene; [e]products from the competitive epoxidation of *cis*- and *trans*-stilbenes.

error (e.g., ~90%) when the reactions were carried out in the presence of carboxylic acid (Table 2, entries 2, 4, 6, and 8). These results suggest that a common intermediate was generated as an active oxidant in all of the reactions. Herein, we carried out the epoxidation of *cis*-stilbene and the competitive epoxidation of *cis*- and *trans*-stilbenes and compared the ratios of *cis*- and *trans*-stilbene oxide products, to support that one oxidant is indeed responsible for the epoxidation reactions (see the reaction Schemes shown in Table 3).

First, in the oxidation of *cis*-stilbene, *cis*-stilbene oxide was produced predominantly with a trace amount of *trans*-stilbene oxide and the ratio of *cis*- to *trans*-stilbene oxide products was 40:1 in all of the reactions (see Table 3, the gray-colored column; SI, Figure S5 for NMR analysis); it was shown previously that *cis*-olefin oxides were produced in the epoxidation of *cis*-olefins by nonheme manganese catalysts in the presence of carboxylic acid additive.[20a] In the epoxidation of *trans*-stilbene, *trans*-stilbene oxide was exclusively produced in all of the reactions (SI, Table S6). These results demonstrate that the epoxidation of olefins is highly stereospecific. We then performed a competitive epoxidation reaction with *cis*- and *trans*-stilbenes, since it has been often used as a mechanistic probe to propose one oxidant versus multiple oxidants



Scheme 7. Heterolytic vs Homolytic O–O Bond Cleavage Mechanisms

in catalytic oxidation reactions.[31] Interestingly, the ratios of *cis*- to *trans*-stilbene oxide products were the same irrespective of the oxidants and catalysts used (see Table 3, the orange-colored column; SI, Figure S6 for NMR analysis), providing strong evidence that one oxidant is responsible for the olefin epoxidation by manganese catalysts with PhIO, H_2O_2, TBHP, and CHP in the presence of carboxylic acid. We presume that a Mn-oxo species is generated as an active oxidant in the epoxidation reactions, although we cannot distinguish Mn(IV)-oxo versus Mn(V)-oxo from the mechanistic studies (vide infra). As discussed above, if Mn-oxidant adducts are involved in the competitive epoxidation reactions, then the ratio of *cis*- to *trans*-stilbene oxides would be different depending on the terminal oxidants.

We then analyzed products derived from the CHP reactions to understand the mode of the O-O bond cleavage of the presumed Mn(III)-alkylperoxo precursor; CHP has been often used as an oxidant probe to propose the O-O bond homolysis versus heterolysis mechanisms.[32] As shown in Scheme 7, cumyl alcohol is the product in the heterolytic O–O bond cleavage pathway (SI, Figure S7 for HPLC analysis), whereas the homolytic O–O bond cleavage pathway affords acetophenone as a product. Since cumyl alcohol was formed quantitatively in the epoxidation of chalcone and other olefins by CHP catalyzed by **1** in the presence of carboxylic acid, we conclude that the O-O bond of Mn-(hydro)alkylperoxo is cleaved heterolytically.

(ii) Reactivity of a Synthetic Mn(IV)-Oxo Complex. Two high-valent Mn-oxo complexes, such as Mn(IV)-oxo and Mn(V)-oxo, can be considered as the intermediate generated in the reactions of **1** with PhIO, H_2O_2, TBHP, and CHP. Since mononuclear nonheme Mn(IV)-oxo complexes have been successfully synthesized recently,[33-36] we attempted to synthesize a Mn(IV)-oxo species of **1** by following the literature procedures.[33b] Addition of 5 equiv of PhIO to **1** in CH_3CN at –40 °C resulted in the formation of a yellowish-green intermediate (**3**), with a broad absorption band at λ_{max} = 590 nm (ε = ~500 M^{-1} cm^{-1}) (Figure 1a; see also SI, Figure S8 for natural decay). The intermediate **3** was characterized with coldspray ionization time-of-flight mass spectrometer (CSI-TOF MS) and electron paramagnetic resonance (EPR) spectroscopy. The CSI-TOF MS of **3** exhibits a prominent peak at m/z = 474.2, whose mass and isotope distribution pattern correspond to $[(L^{N4})Mn^{IV}(O)(OCH_3)]^+$ (calculated m/z = 474.2) (Figure 1b). When **3** was prepared with an isotopically ^{18}O-labeled $PhI^{18}O$, a mass shift from 474.2 to 476.2 was observed (Figure 1b, inset), indicating

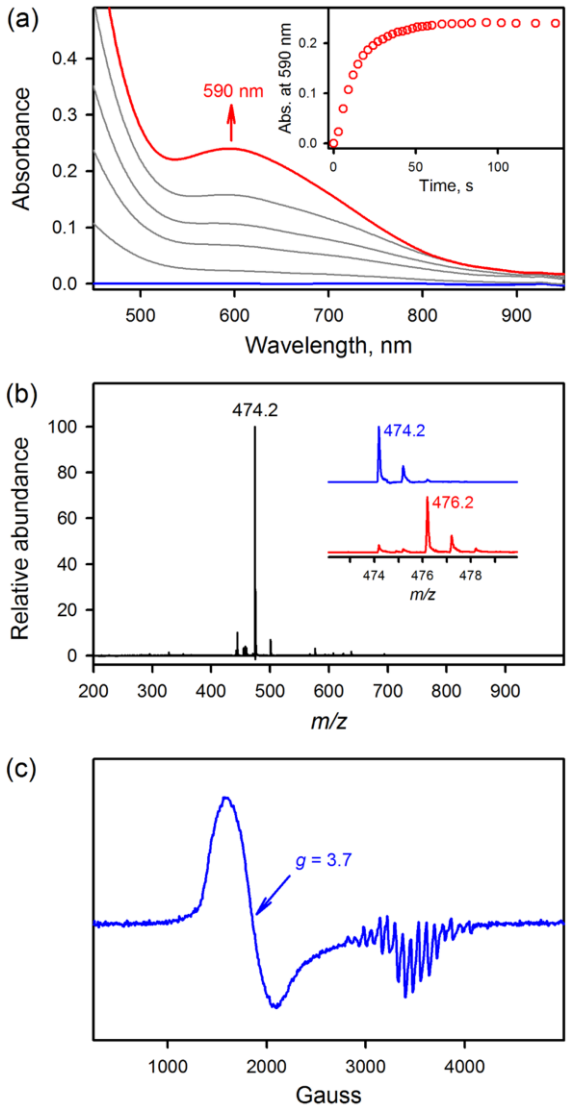


Figure 1. (a) UV-vis absorption spectral changes showing the formation of **3** (red line) observed in the reaction of **1** (0.50 mM, blue line) and PhIO (2.5 mM) in CH_3CN at –40 °C. Inset shows the time course monitored at 590 nm for the formation of **3**. (b) CSI-TOF MS spectrum of **3**. Inset shows the isotope distribution patterns of **3**-^{16}O (blue line) and **3**-^{18}O (red line). (c) X-band CW-EPR spectrum of **3** recorded at 5 K. The signal at g = 3.7 is characteristic of S = 3/2 high-spin manganese(IV) species. The signals around at g = 2.0 with impurity scale (<3%) are assignable to the dimanganese(III,IV) species.

that **3** contains one oxygen atom. The X-band CW-EPR spectrum of **3**, recorded in a frozen solution at 5 K, exhibits signals corresponding to high-spin (S = 3/2) Mn^{IV} species (Figure 1c).[33-35] Based on the spectroscopic characterization, the intermediate **3** is assigned as $[Mn^{IV}(O)(L^{N4})]^{2+}$.

Then, the reactivity of **3** was examined in olefin epoxidation reactions, by adding substrates to the solution of **3** generated in situ in CH_3CN at –40 °C. The UV-vis spectrum of **3** was intact upon addition of chalcone or cyclooctene (25 mM; 50 equiv to **3**) (SI, Figure S9), suggesting that **3** is not capable of epoxidizing olefins at –40 °C. Further, **3** even in the presence of carboxylic acid (e.g., EHA)

did not react with olefins (SI, Figure S9). In contrast, under the identical reaction conditions, the catalytic epoxidation of chalcone by H_2O_2 in the presence of carboxylic acid (EHA) in CH_3CN at –40 °C afforded the epoxide product with 67% yield (see Experimental Section for detailed reaction procedures). Based on the results of the stoichiometric and catalytic reactions, we are able to exclude the Mn(IV)-oxo species as a potent intermediate responsible for the olefin epoxidation, since the synthetic Mn(IV)-oxo complex was not reactive with olefins. The remaining candidate that can be considered as an active oxidant is a Mn(V)-oxo species, although such a mononuclear nonheme Mn(V)-oxo species bearing neutral tetradentate N4 and pentadentate N5 ligands has never been detected in any stoichiometric and catalytic reactions. Nonetheless, as proposed in a number of cases,[6,7,12,14,16-20,22,23] we believe that a Mn(V)-oxo species is the active oxidant that effects the olefin epoxidation reaction.

CONCLUSION

In bioinspired catalytic systems (e.g., nonheme iron and manganese catalysts/H_2O_2/carboxylic acid) for the (asymmetric) epoxidation of olefins, carboxylic acid is an essential additive that improves the catalytic activity and enantioselectivity of the metal complexes. In this work, we have performed mechanistic studies to understand the carboxylic acid effect and the nature of the active intermediate(s) in the manganese complex-catalyzed enantioselective epoxidation of olefins, by employing nonheme manganese catalysts (e.g., **1** and **2**) and various oxidants (e.g., H_2O_2, TBHP, CHP, and PhIO). The results obtained herein are summarized as follows:

(1) The catalytic systems of **1**/H_2O_2-TBHP-CHP/carboxylic acid afford high product yields with good enantioselectivities, whereas the catalytic systems of **2**/H_2O_2-TBHP-CHP/carboxylic acid are inefficient. Given that **1** has two *cis*-binding sites but **2** has only one binding site, the results demonstrate the significance of two *cis*-binding sites to form an active Mn-oxo oxidant via the "carboxylic acid-assisted" mechanism.

(2) In protic solvent, the product yield is high in the catalytic system of **1**/H_2O_2 even in the absence of carboxylic acid (e.g., an "alcohol-assisted" heterolytic O-O bond cleavage), but the enantioselectivity is low. The enantioselectivity is increased upon addition of carboxylic acid, demonstrating that carboxylic acid modulates the epoxidation enantioselectivity.

(3) The enantioselectivity in the catalytic system of **2**/PhIO is dramatically increased upon addition of carboxylic acid. Since carboxylic acid cannot bind to the manganese center in **2**, we propose that the epoxidation enantioselectivity can be modulated by the non-coordinated carboxylic acid molecule(s), probably through a second-sphere hydrogen-bonding interaction between the non-coordinated carboxylic acid molecule(s) and the Mn-oxo moiety.

(4) Irrespective of the oxidants, the catalytic systems of **1**/H_2O_2-TBHP-CHP-PhIO/carboxylic acid afford virtually the same *ee* values in the asymmetric epoxidation of olefins. In addition, the ratios of *cis*- to *trans*-stilbene oxide products are the same in the competitive epoxidation of *cis*- versus *trans*-stilbenes as well as in the *cis*-stilbene epoxidation. These results demonstrate that a common intermediate (e.g., Mn-oxo) is generated as an active oxidant in all of the catalytic systems.

(5) A synthetic Mn(IV)-oxo complex of **1** is shown to be incompetent in epoxidizing olefins, leading us to exclude Mn(IV)-oxo as an active oxidant and propose Mn(V)-oxo species as the most plausible active oxidant in the catalytic olefin epoxidation reactions.

In future studies, it will be of great interest if mononuclear nonheme Mn(V)-oxo species bearing neutral tetradentate N4 and pentadentate N5 ligands are synthesized and their chemical properties are unveiled in (asymmetric) oxidation reactions.[37]

EXPERIMENTAL SECTION

Materials. All chemicals were purchased from commercial sources with the maximum purity available and used as received unless mentioned otherwise. Anhydrous solvents were purified using standard methods.[38] **2** was prepared according to published procedures (see SI, Figure S1 for the synthetic method).[21] Manganese catalysts were purified before use by recrystallization with acetonitrile and ether.

Synthesis of L^{N4} and Its Manganese Complex. The precursor compound of L^{N4}, (*S*)-2-(benzylaminomethyl)pyrrolidine, was synthesized according to a literature method.[39] Then, ligand L^{N4} was synthesized by reacting (*S*)-2-(benzylaminomethyl)pyrrolidine with 2-picolylchloride hydrochloride in the presence of KI and triethylamine (Et_3N) in CH_3CN at 25 °C, as reported previously (see SI, Figure S10 for ^1H and ^{13}C NMR spectra).[21] Finally, $[Mn^{II}(L^{N4})(OTf)_2]$ (**1**) was synthesized by reacting $Mn(OTf)_2$ with equimolar amounts of L^{N4} in CH_3CN at 25 °C (see SI, Figure S1). Crystals of **1** suitable for X-ray diffraction were obtained by diffusing ether into the CH_3CN solution. CCDC 1587411 (in the Cambridge Crystallographic Data Centre) contains the supplementary crystallographic data for **1**.

Instruments and Analysis Methods. ^1H and ^{13}C NMR spectra were recorded using a Bruker Avance III 400MHz spectrometer. ^1H and ^{13}C NMR spectroscopic chemical shifts (ppm) were referenced to the residual solvent peaks. High resolution mass spectra (HRMS) were recorded on an Agilent 6530 Q-TOF mass spectrometer with an ESI source. Optical rotation was recorded with a Perkin-Elmer 341 polarimeter (sodium lamp, 1-dm cuvette, c in g/100 ml, 20 °C). X-ray crystallographic data were collected at 173 K on a Bruker Smart APEX II diffractometer equipped with Cu Kα radiation (λ = 1.54184 Å). GC-MS analyses were performed with Agilent 7890A/5975C GC-MS system with an HP-5 MS column. HPLC analysis for measuring *ee* values was performed with a SHIMADZU system (SHIMADZU LC-20AT pump, SHIMADZU LC-20A Absorbance Detector) with a Chiralpak OD-H column (Daicel Chemical Industries, LTD). HPLC analysis for product(s) derived from the decomposition of the cumyl hydroperoxide was performed using an Agilent 1260 infinity instrument with an Agilent Zorbax SB-C18 column. GC analysis for *ee* values, conversion and yields were performed with an Agilent 7890 GC instrument with a CP-Chirasil-Dex CB column. UV-vis spectra were recorded on an Agilent 8454 spectrophotometer equipped with a variable-temperature liquid-nitrogen cryostat (UNISOKU Scientific Instruments). X-band CW-EPR spectra were recorded at 5 K using an X-band Bruker EMX-plus spectrometer equipped with a dual mode cavity (ER 4116DM). Low temperatures were achieved and controlled with Oxford Instruments ESR900 liquid Helium quartz cryostat fitted with an Oxford Instruments ITC503 temperature and gas flow controller [experimental parameters; microwave frequency = 9.647 GHz, microwave power = 1.0 mW, modulation amplitude = 10 G, gain =

1×10^4, modulation frequency = 100 kHz, time constant = 40.96 ms, conversion time = 85.00 ms]. CSI-TOF MS spectra were collected on a JMS-T100CS (JEOL) mass spectrometer equipped with a CSI source. Typical measurement conditions were as follows: needle voltage: 2.2 kV, orifice 1 current: 50-500 nA, orifice 1 voltage: 0 to 20 V, ring lens voltage: 10 V, ion source temperature: 5 °C, spray temperature: –40 °C. The CSI-TOF mass spectra of **3** and **3**-^{18}O were obtained by infusing the reaction solution directly into the ion source through pre-cooled tube under high N_2 gas pressure.

Typical Procedure for Catalytic Olefin Epoxidations. Substrate (0.20 mmol), carboxylic acid additive (1.0 mmol, 5 equiv to substrate), and manganese catalyst (4.0 μmol, 2.0 mol% to substrate) were dissolved in CH_3CN (2 mL), and the mixture was thermostated at 0 °C. Then the desired oxidant (0.40 mmol, 2 equiv to substrate) was added in one portion for TBHP, CHP and PhIO or over 0.5 h via a syringe pump for H_2O_2 upon stirring. After stirring for 2 h, saturated $NaHCO_3$ and $Na_2S_2O_3$ aqueous solutions were added to quench the reaction. For *cis*-, *trans*-stilbene, and chalcone, the mixture was dried over anhydrous Na_2SO_4 and filtered through a short column of silica gel, which was subsequently rinsed with ethyl acetate. After evaporation, internal standard CH_2Br_2 was added to the residue. Products were analyzed by ^{1}H NMR to determine the conversion and yield. For cyclooctene and styrene, the resulting solution was extracted with ether before GC analysis. Products were analyzed by GC in the presence of decane as the internal standard. It should be noted that the CH_3CN-CH_2Cl_2 (v/v 3:1) mixed solvent was used for *cis*- and *trans*-stilbene because of the solubility of substrates. Besides, to compare with stoichiometric reactions by $Mn^{IV}(O)$ species, catalytic epoxidation of chalcone by **1** was also performed at –40 °C (reaction conditions: [chalcone] = 25 mM, [EHA] = 125 mM, [**1**] = 0.50 mM, and [H_2O_2] = 50 mM).

Product Analysis for the Oxidation of Chalcone by Cumyl Hydroperoxide. Chalcone (0.20 mmol), EHA (1.0 mmol; 5 equiv to substrate) and **1** (4.0 μmol, 2.0 mol% to substrate) were dissolved in CH_3CN (2.0 mL) and thermostated at 0 °C. Then cumyl hydroperoxide (40 μmol) was added to reaction solution in one portion upon stirring. After 5 min, the mixture was filtered through a short plug of silica gel to remove the metal complex and analyzed by HPLC (Agilent Zorbax SB-C18 column; H_2O : CH_3CN (v/v 50:50); flow rate 1.0 ml min^{-1}; monitoring at 215 nm; 30 °C). Quantitative analysis was conducted on the basis of comparison between HPLC peak integrations of reaction solutions and authentic samples, and cumyl alcohol was demonstrated as the sole product with >99% yield based on the cumyl hydroperoxide used (SI, Figure S7 for HPLC analysis).

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

Tables S1 – S6 and Figures S1 – S15 (PDF).

Crystallographic data for [$Mn^{II}(L^{N4})(OTf)_2$] (**1**) (CIF)

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Notes

The authors declare no competing financial interest.

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