

Simple Iron Catalyst for Terminal Alkene  
Epoxidation

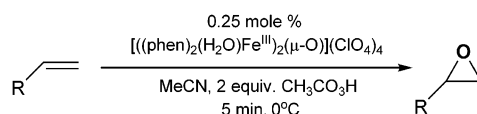
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## ABSTRACT



A  $\mu$ -oxo-iron(III) dimer,  $[(\text{phen})_2(\text{H}_2\text{O})\text{Fe}^{\text{III}}]_2(\mu\text{-O})(\text{ClO}_4)_4$ , is an efficient epoxidation catalyst for a wide range of alkenes, including terminal alkenes, using peracetic acid as the oxidant. Low catalyst loadings, in situ catalyst preparation from common reagents, fast reaction times (<5 min at 0 °C), and enhanced reaction performance at high substrate concentrations combine to create a temporally and synthetically efficient procedure for alkene epoxidation.

Epoxidation of terminal and certain classes of electron-deficient alkenes remains a challenging task in organic chemistry. Transition metal catalysts have been developed that dramatically enhance the selectivity and the rate of epoxidation of such olefins.<sup>1–9</sup> However, few of these catalysts are simply prepared and provide rapid conversion with high selectivities. Herein we report an in situ-prepared ferric phenanthroline catalyst that efficiently epoxidizes terminal and trans olefins within 5 min using peracetic acid as the final oxidant.

Uncatalyzed epoxidation of alkenes with peroxydicarboxylic acids is a fundamental reaction in organic chemistry that is commercially exploited to epoxidize internal alkenes of fatty acids. Peracetic acid is capable of epoxidizing more electron-

deficient terminal alkenes, albeit at elevated reaction temperatures and with extended reaction times that significantly reduce the selectivity of the reaction.<sup>10</sup> Metal-catalyzed variants of this reaction can reduce these limitations by enhancing the reaction rates and lowering the reaction temperatures. In fact, several chiral  $[\text{Mn}^{\text{III}}(\text{salen})]^{1+}$  complexes are known to efficiently epoxidize aromatic or substituted alkenes with high ees using peroxydicarboxylic acids at  $-80$  °C.<sup>11,12</sup> Unfortunately, these catalysts are ineffective epoxidizing agents for most terminal and trans olefins.<sup>13–16</sup> We have recently reported a cationic  $\text{Mn}^{\text{II}}$  complex,  $[\text{Mn}^{\text{II}}((R,R)\text{-mcp})](\text{CF}_3\text{SO}_3)_2$ , that rapidly and efficiently epoxidizes electron-deficient olefins in >85% isolated yields using 0.1% catalyst and peracetic acid.<sup>1,17</sup> In contrast to the planar ligation of **salen**, the neutral tetradentate

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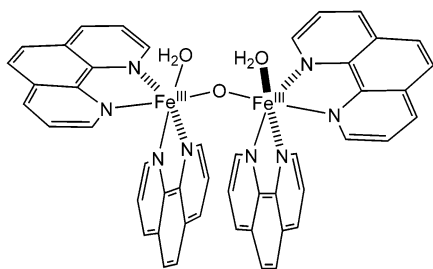
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(17) **mep** = *N,N'*-dimethyl-*N,N'*-bis(2-pyridylmethyl)-ethane-1,2-diamine; **(R,R)-mcp** = *N,N'*-dimethyl-*N,N'*-bis(2-pyridylmethyl)-cyclohexane-1*R,2R*-diamine.

amine (***R,R***)-**mcp** enforces the cis coordination of an octahedrally ligated metal with two exogenous, adjacent ligands. A similar coordination is found in Jacobsen's recently reported iron catalyst,  $[\text{Fe}^{\text{II}}(\text{mep})]^{2+}$ , that efficiently epoxidizes terminal olefins in the presence of  $\text{H}_2\text{O}_2$  and acetic acid.<sup>2,17</sup> The Lewis acidity of these cationic complexes, in conjunction with the cis-positioned exogenous ligands, provides not only an appropriate coordination for the formation of a potent oxidant but also one that is accessible to trans olefins.<sup>1,2</sup>

Two phenanthroline ligands (**phen**) ligate iron in a cis coordination similar to that of **mcp** or (***R,R***)-**mcp**. The ferric species prefer to dimerize in the presence of water, leading to a common structural motif, a ferric  $\mu$ -oxo dimer such as  $[\{(\text{phen})_2(\text{H}_2\text{O})\text{Fe}^{\text{III}}\}_2(\mu\text{-O})](\text{ClO}_4)_4$  (**1**) or  $[\{(\text{phen})_2(\text{H}_2\text{O})\text{Fe}^{\text{III}}\}_2(\mu\text{-O})](\text{NO}_3)_4$  (**2**) (Figure 1). The bridging oxide



**Figure 1.** Schematic drawing of  $[\{(\text{phen})_2(\text{H}_2\text{O})\text{Fe}^{\text{III}}\}_2(\mu\text{-O})]^{4+}$ .

ligand and the exogenous water ligands occupy the adjacent cis sites of each iron site.<sup>18–20</sup> **1** and **2** are simply formed by aerobic mixing of ferric perchlorate or ferric nitrate with 2 equiv of **phen** in MeCN/ $\text{H}_2\text{O}$ .<sup>20</sup> The preorganized, oxidatively robust nature of **phen** has motivated a great deal of interest in its metal complexes for oxidation catalysis. In fact, the  $\mu$ -oxo ferric dimer has been extensively investigated for alkane hydroxylation and sulfide oxidation with  $\text{H}_2\text{O}_2$  or alkyl hydroperoxides,<sup>20–24</sup> but investigation of the epoxidation chemistry has been limited.<sup>20</sup>

When **1** is combined with commercial peracetic acid, efficient and rapid (<5 min) epoxidation occurs with a wide range of electron-rich and electron-poor alkenes at 0 °C. Low loadings of catalyst (0.25 mol %) are sufficient for high conversions, and comparable product yields are found using either isolated **1** or in situ-prepared **1** (Table 1). Under

**Table 1.** Epoxidation of Alkenes with **1** and Peracetic Acid<sup>a</sup>

alkene	0.25 mole % <b>1</b> MeCN, 2 equiv. $\text{CH}_3\text{CO}_3\text{H}$ , 5 min, 0 °C		
	conversion <sup>b</sup> ± 2%	GC yield ± 2%	isolated <sup>c</sup> % yield
<b>1</b> cyclooctene	100	100	90
<b>2</b> cyclohexene	100	98	85
<b>3</b> 2-methyl-2-hexene	100	90	
<b>4</b> <i>cis</i> -2-heptene	100	97	
<b>5</b> <i>trans</i> -2-heptene	100	99	
<b>6</b> 1-heptene	97	94	88
<b>7</b> vinylcyclohexane	95	93	90
<b>8</b> 1-octene	98	96	92
<b>9</b> styrene <sup>d</sup>	100	63	
<b>10</b> <i>trans</i> - $\beta$ -methyl styrene	100	96	96
<b>11</b> <i>cis</i> - $\beta$ -methyl styrene	100	74	
<b>12</b> <i>trans</i> -methyl-cinnamate <sup>e</sup>	87	87	86
<b>13</b> butadiene <sup>e</sup>	96	95	
<b>14</b> butadiene monooxide	<1	<1	
<b>15</b> ethyl sorbate <sup>f</sup>	100	100	89
<b>16</b> ethyl crotonate	<1	<1	
<b>17</b> 4-vinyl-1-cyclohexene <sup>g</sup>	100	99 <sup>h</sup>	
<b>18</b> 2-cyclohexen-1-ol	96	77	
<b>19</b> allyl acetate	8	8	

<sup>a</sup> Reaction conditions: olefin (1.1 M in  $\text{CH}_3\text{CN}$ ), **1** (0.25 mol %), and 32%  $\text{CH}_3\text{CO}_3\text{H}$  (2 equiv) added rapidly at 0 °C, 5 min. <sup>b</sup> Yields determined by GC using nitrobenzene or decane as an internal standard. Averaged over at least three runs. <sup>c</sup> Isolated yields determined as an average of three runs on gram-scale reactions. <sup>d</sup> Used 0.38 mol %. <sup>e</sup> Reaction performed at –15 °C, 5 min, and no diepoxide product was detected. <sup>f</sup> Only the 4,5-monoepoxide product was detected. <sup>g</sup> Used 3 equiv of  $\text{CH}_3\text{CO}_3\text{H}$ , 0.5 mol % **2**. <sup>h</sup> Diepoxide product only.

identical reaction conditions excluding **1**, insignificant epoxidation of terminal alkenes is observed.<sup>25</sup> While 32% peracetic acid is commercially available, a 24% peracetic acid solution is easily prepared by stirring 50%  $\text{H}_2\text{O}_2$  with  $\text{CH}_3\text{CO}_2\text{H}$  with 1%  $\text{H}_2\text{SO}_4$  at room temperature overnight.<sup>26,27</sup> Since **1** and **2** have comparable reactivity, **2** should be used in large-scale reactions given the potential dangers of perchlorate metal complexes.

These epoxidation reactions are readily scaled to gram quantities without significant loss of efficiency, and high alkene concentrations (>0.5 M) generally provide the highest yields. As these epoxidation reactions are both exothermic and fast, gram-scale reactions need to be performed in high surface to volume flasks cooled by an ice bath. Slow addition of a catalyst solution over 5 min to an efficiently stirred solution generally ensures efficient heat dissipation. Larger scale reactions (0.1 mol) generally need to be initially cooled to ca. –30 °C.<sup>28</sup>

(25) Under the epoxidation conditions described, simple iron salts are ineffective epoxidation catalysts.

(26) Supporting Information provides the details for the preparation of a 24% peracetic acid solution. The peracetic acid content is readily quantified using  $^{13}\text{C}$  NMR.

(27)  $\text{H}_2\text{O}_2$  added to an acetic acid/sulfuric acid/MeCN media with **1** does not appreciably epoxidize (<1%) terminal alkenes at 0 °C in 5 min.

(28) These larger scale reactions require ~30 min at –30 °C. See Supporting Information.

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Unfunctionalized terminal olefins are readily epoxidized, but more electron-deficient terminal olefins such as butadiene monooxide (entry 14) or allyl acetate (entry 19) define a boundary of electron-deficient substrates for this catalytic system. Allylic alcohols are efficiently epoxidized, although alcohol oxidation can be a significant side reaction; 2-cyclohexen-1-ol (entry 18) is oxidized to 2,3-epoxycyclohexan-1-ol (77%), 2-cyclohexenone (19%), and a small amount of 2,3-epoxycyclohexanone (4%). As 2-cyclohexenone is unreactive under the oxidizing conditions, the 2,3-epoxycyclohexanone results from a secondary oxidation of the initial 2,3-epoxycyclohexan-1-ol product.

Epoxidation of styryl olefins (entries 9–12) under the acidic conditions of the reported reaction may be considered to be unconventional due to the acid sensitivity of the styryl epoxide products. Yet, most styryl substrates are efficiently epoxidized. Styrene and *cis*- $\beta$ -methyl styrene (entries 9 and 11) show lower selectivities for the epoxide product due to the formation of phenylacetaldehyde (37%) and propiophenone (26%), respectively, during the course of the reaction. Appropriate control experiments indicate that these carbonyl products do not result from epoxide opening and rearrangement, suggesting a secondary oxidation pathway or oxidant.<sup>29</sup>

Compared to  $[\text{Mn}^{\text{II}}(\text{R,R})\text{-mcp}]^{2+}$ , the active oxidant created with peracetic acid and **1** is a less potent epoxidizing agent, providing an opportunity for regiospecific epoxidation of polyenes.<sup>1</sup> The two *trans*-alkenes of ethyl sorbate are electronically distinct, yet  $[\text{Mn}^{\text{II}}(\text{R,R})\text{-mcp}]^{2+}$  with peracetic acid epoxidizes them in a 4:1 product ratio of monoepoxides. Use of **1** and peracetic acid epoxidizes only the more electron-rich alkene (entry 15). Indiscriminant epoxidation of butadiene is also found with  $[\text{Mn}^{\text{II}}(\text{R,R})\text{-mcp}]^{2+}$ , while **1** exclusively forms the monoepoxide product, providing a convenient route to this useful epoxide synthon (entries 13 and 14).<sup>30</sup>

The nature of the active oxidant has been probed by intermolecular competition reactions. A competitive reaction of cyclooctene and vinylcyclohexane shows a 100:1 preference for the former at low conversion (~20%) confirming the electrophilic nature of the active oxidant. The 5:1 preference for epoxidation of *cis*-2-heptene over *trans*-heptene contrasts with the reactivity of “planar” salen- or porphyrin-based catalysts that are chemoselective for *cis*-olefins. The retention of the original *cis* stereochemistry in the epoxide product of *cis*-2-heptene with **1** (<1% *trans*-epoxide) supports a nonradical oxidation process.

Aside from the intermolecular competition studies, the nature of the active species has been difficult to assess. In the presence and absence of commercial peracetic acid, UV-vis, EPR, and magnetic susceptibility measurements of **1** show insignificant changes, suggesting that the predominant species in solution is a strongly antiferromagnetically coupled  $\mu$ -oxo ferric dimer. However, a strong pH dependence on the efficiency of the epoxidation reaction implicates impor-

tant metal speciation and ligand exchange rates. Reactions performed with commercial peracetic acid (1%  $\text{H}_2\text{SO}_4$ ) result in a reaction solution pH of ~2, and the epoxidation of vinyl cyclohexane is complete within 5 min with >90% yield (Table 1). In contrast, strong acid free peracetic acid as the oxidant creates a reaction solution pH of ~5, and only ~20% epoxidation is observed in 5 min.<sup>31</sup> The epoxidation efficiency of **1** with strong acid free peracetic acid is restored by adjusting the pH to 2 with either  $\text{HClO}_4$  or  $\text{H}_2\text{SO}_4$ , accentuating the proton sensitivity of this reaction.

Given the complex composition of the peracetic acid oxidant ( $\text{H}_2\text{O}$ ,  $\text{HSO}_4^{1-}$  ( $\text{p}K_{\text{a}} = 2.0$ ),  $\text{CH}_3\text{CO}_2\text{H}$  ( $\text{p}K_{\text{a}} = 4.7$ ),  $\text{CH}_3\text{CO}_3\text{H}$  ( $\text{p}K_{\text{a}} = 8.2$ )) and the sequential  $\text{p}K_{\text{a}}$  values of the water molecules ligated to  $[\text{((phen)}_2(\text{H}_2\text{O})\text{Fe}^{\text{III}})_2(\mu\text{-O})]^{4+}$  ( $\text{p}K_{\text{a}} = 5.0$  and  $6.5$ ),<sup>32</sup> this proton dependence is understandable. Assuming a tetracationic  $\mu$ -oxo ferric dimer as the resting state catalyst of **1**, water displacement at one or both ferric sites by a monodentate or bridging peracetic acid molecule, respectively, must precede the formation of the active oxidant. Lower pHs ensure facile water exchange from the metal, as hydroxide or acetate ligation to the iron will be minimized. Bisulfate, perchlorate, or nitrate ligation to the iron site(s) do not appear to be competitive with other ligands under the reaction conditions. Whether one or both of these sites is necessary for activation of the peracetic acid is currently unknown. However, the inactivity of  $[\text{((phen)}_2(\text{Cl})\text{Fe}^{\text{III}})_2(\mu\text{-O})](\text{Cl})_2$  with strongly ligated chlorides suggests that labile coordination sites are required. Chloride inhibition of other oxidation reactions with iron catalysts has been previously noted.<sup>33</sup>

A related  $\mu$ -oxo ferric dimer,  $[\text{((mep)}_2(\mu\text{-O})(\mu\text{-OAc}))^{3+}$  (**3**), is proposed by Jacobsen as the resting state of their efficient epoxidation catalyst that uses  $\text{H}_2\text{O}_2$  in acetic acid/MeCN.<sup>2</sup> Que has reported dramatically different reactivity of **3**.<sup>34</sup> Yet, the conditions used in each report are quite different; Jacobsen's include HOAc, while those of Que are more neutral and do not include acetic acid. In our hands, **3** is an efficient terminal olefin epoxidation catalyst under acidic conditions. Curiously,  $[\text{((phen)}_2\text{Fe}^{\text{III}})_2(\mu\text{-O})(\mu\text{-OAc}))^{3+}$ ,<sup>20</sup> a complex structurally similar to **3**, is an impotent terminal alkene epoxidation catalyst under comparable acidic conditions. These differences highlight the sensitivity of the epoxidation reaction not only to the catalyst but to the reaction conditions as well (i.e., pH).

In this paper we have demonstrated that iron complexes, easily synthesized from inexpensive and commercially available compounds, are efficient catalysts for the epoxidation of alkenes using peracetic acid as the oxidant. The temporal efficiency of both the in situ catalyst preparation and the epoxidation reaction itself provide significant advantages over other epoxidation procedures for terminal olefins. This system constitutes a second example of a bioinspired non-

(31) For initial formation of epoxide at various pHs, see Supporting Information.

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(30) Butadiene reactions were performed on a 0.025 mol scale and isolated as solutions in pentane or toluene.

heme iron complex capable of efficient epoxidation of olefins. Experiments aimed toward understanding the nature of the oxidative species are underway.

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**Supporting Information Available:** Experimental procedures for preparation of the catalysts and the peracetic acid solutions and the epoxidation of olefins with **1** and **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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