In situ Formation of Peracetic Acid in Iron-Catalyzed Epoxidations by Hydrogen Peroxide in the Presence of Acetic Acid

Megumi Fujita, Lawrence Que, Jr.*

Department of Chemistry and Center for Metals in Biocatalysis, University of Minnesota, Minneapolis, Minnesota 55455, USA
Fax: (+1)-612-624-7029, e-mail: que@chem.umn.edu

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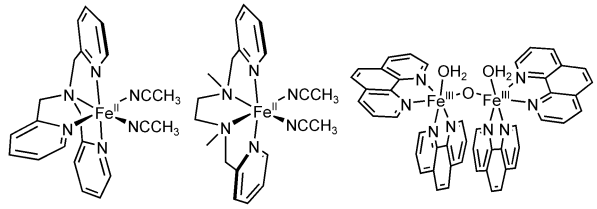
Abstract: Iron complexes (tpa)Fe(OTf)$_2$ (**1**) and (bpmen)Fe(OTf)$_2$ (**2**) [tpa = tris-(2-pyridylmethyl)-amine; bpmen = *N,N'*-bis-(2-pyridylmethyl)-*N,N'*-dimethyl-1,2-ethylenediamine] were found to catalyze the *in situ* formation of AcOOH from H_2O_2 and AcOH in the course of olefin oxidations. While oxidation of cyclooctene by H_2O_2 catalyzed by **1** gives nearly equimolar epoxide and *cis*-diol products, introduction of AcOH to the reaction greatly enhances the selectivity for epoxidation. The resulting product distribution is nearly identical to that of cyclooctene oxidation by AcOOH catalyzed by **1**. The *in situ* generation of AcOOH from H_2O_2 and AcOH in epoxidation catalyzed by some iron complexes opens a possibility to attain AcOOH-type efficiency of epoxidation using H_2O_2 as a terminal oxidant.

Keywords: dihydroxylation; epoxidation; hydrogen peroxide; iron; N ligands; peracetic acid

Epoxidation of olefins is an important reaction in organic synthesis. While organic peracids such as 3-chloroperbenzoic acid are widely used as reagents, the major drawback is the toxicity of the organic acid byproduct.[1] Peracetic acid (AcOOH) and hydrogen peroxide (H_2O_2) are more desirable oxidants because of the non-toxic byproducts (acetic acid and water, respectively). Although AcOOH by itself is capable of epoxidation, it requires prolonged reaction time and often elevated reaction temperature compared to 3-chloroperbenzoic acid.[2] AcOOH is readily prepared by the reaction of concentrated aqueous H_2O_2 and AcOOH with a strong acid catalyst, typically sulfuric acid.[2] On the other hand, H_2O_2 is a more challenging oxidant to utilize in epoxidation. Unlike AcOOH, H_2O_2 by itself is a very poor epoxidation reagent (except under alkaline conditions where it epoxidizes electron-deficient olefins[3]), and it is prone to metal-based decomposition. Development of catalytic epoxidation methods with H_2O_2[4] or AcOOH[5] thus stands as an important objective.

Non-heme iron complexes have recently been investigated as oxidation catalysts for olefins.[5–8] We reported that [(tpa)Fe(CH$_3$CN)$_2$]$^{2+}$ (**1**) and [(bpmen)Fe(CH$_3$CN)$_2$]$^{2+}$ (**2**) (Scheme 1) catalyze epoxidation by H_2O_2, accompanied by differing extents of *cis*-dihydroxylation.[7] Jacobsen found **2** with SbF_6^- counterions to be an efficient epoxidation catalyst with H_2O_2 in the presence of AcOH under synthetically more practical conditions.[8] Similarly, Stack recently reported [{(phen)$_2$Fe^{III}(OH$_2$)}$_2$(μ-O)]$^{4+}$ (**3**) as a highly efficient catalyst for epoxidation by AcOOH.[5b] Our interest in developing bio-inspired epoxidation catalysts prompted us to investigate how the reaction conditions utilized by the three different groups may relate to each other. In the course of this study, we have determined that **1** and **2** catalyze *in situ* formation of AcOOH from H_2O_2 and AcOH, affording the possibility of developing an olefin epoxidation system with high efficiency with the use of inexpensive components.

(tpa)Fe^{II}(OTf)$_2$ (1): We have carried out the most extensive investigation on **1**, because the **1**-catalyzed oxidation of cyclooctene with H_2O_2 gives an epoxide/*cis*-diol ratio of close to 1, which serves as a sensitive indicator of mechanism.[7b–d] The product distribution was examined under oxidant-limiting conditions (substrate:oxidant:catalyst = 500 : 4.5~14.5 : 1, Conditions **A**) to obtain accurate product ratios and to minimize effects of possible alteration of a catalyst over time or over-



Scheme 1. Iron complexes studied.

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oxidation of diol products. The effects of adding AcOH on the oxidation of cyclooctene by H_2O_2 or AcOOH catalyzed by **1** are summarized in Table 1 (entries 1 to 11). When 14.5 equivs. (per Fe) H_2O_2 were gradually added to the solution of cyclooctene and **1** in acetonitrile, 4.3 equivs. epoxide and 5.9 equivs. *cis*-diol were formed (entry 1), with overall yield of 70% based on the oxidant, consistent with our earlier reports. Notably, the introduction of 2–100 equivs. AcOH into the reaction mixture significantly enhanced the selectivity for epoxidation and resulted in near quantitative conversion of oxidant to desired products (Figure 1; Table 1, entries 1–5). The suppression of *cis*-diol formation with the addition of AcOH increases the potential utility of **1** as an olefin epoxidation catalyst.

Entry 6 shows the effect of using 10 equivs. AcOOH as oxidant instead of H_2O_2. The amount of epoxide obtained was over three-fold higher than that obtained in the absence of a catalyst (entry C3, Table 1), suggesting that **1** catalyzes olefin epoxidation by AcOOH as well. Interestingly, the reaction in entry 6 afforded 11.7 equivs. epoxide and 2.0 equivs. *cis*-diol, a combined yield that exceeded the number of equivalents of AcOOH added. This result may be rationalized by the

Table 1. Cyclooctene oxidation (Conditions **A**).

Entry	Oxidant and Other Components[a]				Products[a]			Total Yield [%][d]
	AcOOH	H_2O_2	AcOH	H_2O	Epoxide[b]	*cis*-Diol[c]	Epoxide:Diol	
[(tpa)Fe^{II}(OTf)$_2$] (1)								
1		14.5			4.3(5)	5.9(8)	0.7:1	70
2		14.5	2		6.5	6.8	1:1	92
3		14.5	17		11.8	2.7	4:1	100
4		14.5	29		12.7	2.1	6:1	102
5		14.5	100		13.1	0.8	16:1	96
6	10	4.5	17		11.7(3)	2.0(2)	6:1	94
7		4.5			1.5	1.9	1:1	76
8		4.5	17		3.1	0.8	4:1	87
9	10	4.5	34		12.0	1.6	8:1	94
10	10	4.5	100		12.7	1.5	8:1	98
11	10	4.5	200		12.8	1.5	8:1	99
12	10	4.5	17	840[e]	10.5	3.0	4:1	93
No catalyst								
C1		*14.5*			*0.3(1)*	*0.0*	*No diol*	*2*[f]
C2		*14.5*	*17*		*0.3(1)*	*0.0*	*No diol*	*2*[f]
C3	*10*	*4.5*	*17*		*3.4(1)*	*0.0*	*No diol*	*23*[f]
[(tpa)Zn^{II}(OTf)$_2$]								
C4		*14.5*			*0.3(1)*	*0.0*	*No diol*	*2*[f]
C5		*14.5*	*29*		*0.5*	*0.0*	*No diol*	*3*[f]
C6	*10*	*4.5*	*17*		*2.8*	*0.0*	*No diol*	*19*[f]
Zn^{II}(OTf)$_2$								
C7		*14.5*			*0.4(2)*	*0.0*	*No diol*	*3*[f]
C8		*14.5*	*29*		*0.2*	*0.0*	*No diol*	*1*[f]
C9	*10*	*4.5*	*17*		*3.1*	*0.0*	*No diol*	*21*[f]
tpa ligand								
C10		*14.5*			*0.3(2)*	*0.0*	*No diol*	*2*[f]
C11		*14.5*	*17*		*0.1(0)*	*0.0*	*No diol*	*<1*[f]
C12	*10*	*4.5*	*17*		*3.4(2)*	*0.0*	*No diol*	*23*[f]
[(bpmen)Fe^{II}(OTf)$_2$] (2)								
21		14.5			13.0(3)	0.7(1)	19:1	94
22		14.5	34		14.8(2)	0.4(1)	34:1	105
23	10	4.5	17		14.1(2)	0.3(0)	47:1	99
[{(phen)$_2$Fe^{III}(OH$_2$)}$_2$(μ-O)](ClO$_4$)$_4$ (3)								
31		14.5		>53	1.7(2)	0.2(0)	11:1	13
32		14.5	29	>53	1.0(0)	0.2(0)	5:1	8
33	10	4.5	17	>53	9.1(2)	0.0	No diol	63

[a] Amounts expressed as equivalents formed per mol iron catalyst.
[b] Retention of configuration was >94% for all cases except for C3 (75%) and C9 (67%).
[c] Retention of configuration was >99% for all cases.
[d] Total yield of the epoxide and the diol based on the total peroxide content.
[e] ^{18}O-Labeled water (95% ^{18}O).
[f] Various unidentified byproducts were observed.

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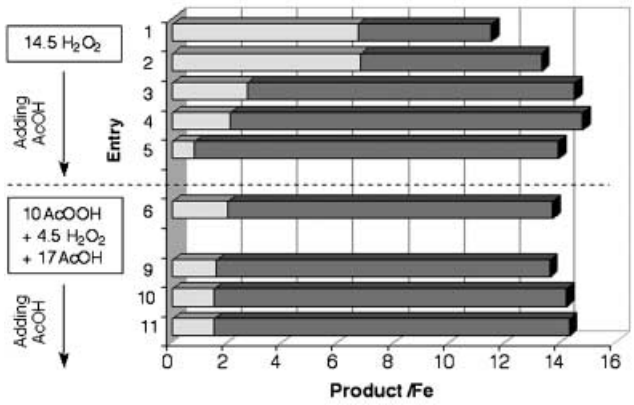

Figure 1. Effect of AcOH on epoxide and diol yields from cyclooctene (from Table 1). Comparison of product yields from **1**-catalyzed oxidation of cyclooctene, expressed as equivalents formed per mol iron catalyst. Light color: *cis*-diol; dark color: epoxide. Entry numbers correspond to those in Table 1.

fact that, in the commercial preparation we used, 10 equivs. AcOOH also contained 4.5 equivs. H_2O_2 and *ca.* 17 equivs. AcOH, so there was clearly some contribution of H_2O_2 to the oxidation yield. Assuming that the 2.0 equivs. of diol derived only from the residual H_2O_2, then 1.5 equivs. epoxide may be expected from the H_2O_2 component, as suggested by the experiment in entry 7 where only 4.5 equivs. H_2O_2 were used as oxidant. Another control experiment with 4.5 equivs. H_2O_2 and 17 equivs. AcOH (entry 8) afforded more epoxide and less diol. As already shown in entries 1 to 5, the addition of increasing amounts of AcOH to the oxidations by H_2O_2 resulted in a larger yield of epoxide and a smaller amount of diol. Similarly, adding more AcOH to the oxidations by AcOOH (entries 9 – 11) further enhanced epoxide formation and suppressed diol formation (see also Figure 1). The near identity of the epoxide/diol ratio and total product yield in entries 3 – 6 strongly suggests the possibility that **1** can catalyze the *in situ* formation of AcOOH from H_2O_2 and AcOH and then utilize the incipient AcOOH for epoxidation. Such *in situ* conversion of H_2O_2 to AcOOH is not commonly observed in oxidation catalysis but has been reported for metal-free haloperoxidases in acetate buffer.[9] However, to our best knowledge, **1** is the first iron catalyst shown to catalyze formation of AcOOH from H_2O_2/AcOH and its subsequent activation for substrate oxidations.

Control experiments supported this mechanistic hypothesis. Cyclooctene oxidation with AcOOH in the absence of a catalyst (entry C3, Table 1) formed 3.4 equivs. epoxide. (The epoxide yield in the presence of **1** (entry 1) is >3 times higher, *vide supra.*) Non-redox-active Lewis acids such as (tpa)Zn(OTf)$_2$ and Zn(OTf)$_2$ were tested as well for their ability to catalyze either *in situ* AcOOH generation or olefin epoxidation (entries C4 – C9), but they were ineffective. These results imply that the redox active Fe center is crucial in the catalytic behavior of complex **1**.

Lastly, an isotope labeling experiment using $H_2{}^{18}O$ (95% labeled) was carried out to ascertain the source of the epoxide oxygen in the oxidation by AcOOH. The product distribution was only slightly affected by addition of 840 equivs. of labeled water (see entry 12 *vs.* 6). There was no ^{18}O incorporated into the epoxide product from the labeled water under the conditions of entry 12. Our previous labeling studies showed that cyclooctene oxide formed from H_2O_2/**1** in the presence of excess $H_2{}^{18}O$ exhibited approximately 10% ^{18}O incorporation *via* a putative HO-Fe^{V}=O intermediate.[7c, d] This lack of ^{18}O incorporation from $H_2{}^{18}O$ in the AcOOH reaction indicates minimal involvement of the **1**/H_2O_2 pathway in epoxide formation and strongly suggests an alternative mechanism wherein the iron center activates the peracid for epoxidation.

(bpmen)Fe^{II}(OTf)$_2$ (2): In contrast to **1**, the selectivity for epoxidation in the **2**-catalyzed oxidation of cyclooctene by H_2O_2 is already quite high in the absence of AcOH (epoxide/diol = 8) (entry 21, Table 1).[7c] Addition of AcOH further enhanced the selectivity for epoxidation and improved the overall yield (entry 22), and the *cis*-diol yield became nearly negligible (< 3%). These observations are consistent with those reported by Jacobsen.[8] The effect of AcOH and the similarity between the [H_2O_2 + AcOH] run and the AcOOH run (entry 23) parallel the results from catalyst **1**. Thus it appears that both **1** and **2** catalyze *in situ* AcOOH formation from H_2O_2 and AcOH as well as AcOOH epoxidation, but the AcOH effect on H_2O_2 oxidation is much less dramatic with **2** than with **1**.

[{(phen)$_2$Fe^{III}(OH$_2$)}$_2$(μ-O)](ClO$_4$)$_4$ (3): Stack reported that the oxo-bridged diion(III) complex **3** was an excellent epoxidation catalyst with AcOOH as oxidant.[5b] Indeed the epoxide yield in our experiment (entry 33) was quite high, 91% when calculated based only on the number of equivalents of AcOOH introduced. However, the corresponding experiments with an equivalent amount of H_2O_2 (entry 31) or with H_2O_2 and AcOH (entry 32) showed that **3** is not a good catalyst for epoxidation with H_2O_2 as oxidant nor does it catalyze *in situ* formation of AcOOH from H_2O_2 and AcOH.

1-Octene Oxidation, Conditions B: The AcOH-enhanced epoxidation catalysts **1** and **2** have been examined for the oxidation of a terminal olefin, 1-octene, by H_2O_2 under more practical, substrate-limiting conditions (1-octene:H_2O_2:Fe = 1 : 1.5 : 0.03, Conditions **B**), in the presence or absence of AcOH, following the conditions used for [(bpmen)Fe(NCCH$_3$)$_2$](SbF$_6$)$_2$ (**2b**) by Jacobsen and coworkers.[8] We have previously reported H_2O_2-only oxidation under similar conditions with [LFe(NCCH$_3$)$_2$](ClO$_4$)$_2$ series, including L = tpa and bpmen.[7d] In this study we have examined the role of

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AcOH under these conditions and compared our results with those reported for **2b**.

Enhancement of epoxidation by AcOH was observed under these conditions as well, with both catalysts **1** and **2**. With **1**, the epoxide/diol ratio favored epoxide with > 3 equivs. of AcOH per 1-octene (entries 1–4, Table 2). The selectivity for epoxide increased from 16% to 46% upon addition 20 equivs. of AcOH per 1-octene, although the degree of mass loss also became higher (entry 4). The same trend was observed with catalyst **2**, but a smaller amount of AcOH (0.5 equiv. per 1-octene) was sufficient to suppress the diol formation to a negligible level (entry 6), while the selectivity for epoxide was enhanced from 52% to 64%. The only difference between **2** and **2b** was the counteranion (TfO^- *vs.* SbF_6^-), which can be readily displaced by solvent upon dissolution in CH_3CN, but the epoxidation yield with **2** was not as high as that of **2b** with either H_2O_2 alone or with added AcOH (entries 5–9). Jacobsen also noted that the SbF_6^- salt was a better catalyst than the ClO_4^- salt, so the counteranions seem to have effects on the catalyst efficiency.

Although Jacobsen proposed that the role of AcOH was to generate the acetate-bridged diiron(III) complex $[(bpmen)Fe^{III}(\mu\text{-}O)(\mu\text{-}\kappa^2\text{-}OAc)Fe^{III}(bpmen)]^{3+}$ *in situ* that was responsible for epoxidation catalysis, our current investigation suggests that iron-catalyzed *in situ* generation of AcOOH from H_2O_2 and AcOH must play a significant role in the epoxidation mechanism.

In conclusion, complexes **1** and **2** were found to catalyze *in situ* generation of AcOOH in the epoxidation of olefins by H_2O_2 in the presence of AcOH. Addition of AcOH to olefin oxidation by H_2O_2/**1** greatly enhanced the selectivity for epoxidation over *cis*-dihydroxylation. Optimization of the conditions to achieve greater efficiency and investigation of the range of applicable olefins are currently in progress. Attaining AcOOH-like epoxidation character from H_2O_2 and AcOH by means of metal catalysis as found in this study may be advantageous for developing H_2O_2-based epoxidation catalysts.

Experimental Section

The AcOOH reagent (Aldrich, 32 wt % in dilute acetic acid) contains < 6.0% H_2O_2 and approx. 40–45% acetic acid according to the reagent description. Iodometric titration showed that the peroxide content was 1.45 times higher than the described AcOOH content; thus the 0.45 equiv. was presumed to come from H_2O_2. This is equivalent to 6.4 wt % of the reagent, reasonably matching the reagent description. The AcOH content was calculated to be 1.6–1.8 equivs. of AcOOH based on the reagent description, and found to be 1.9 equivs. based on the AcOH/AcOOH ratio in the ^{13}C NMR spectrum. In this study, the AcOH/AcOOH ratio of the reagent was assumed to be 1.7. The H_2O_2 solutions in acetonitrile were diluted from a 35 wt % aqueous solution (Aldrich). Acetonitrile was distilled from CaH_2 under argon. Preparations of the iron complexes **1**, **2**, and **3** were described previously.[5b,7c,10,11]

Reaction Conditions A

Solvent acetonitrile and the oxidant solutions in acetonitrile were dried over $MgSO_4$ and filtered before use in order to control the water content. The concentration of the oxidant was not affected by this drying process, confirmed by iodometric titration. To a stirred solution of cyclooctene

Table 2. 1-Octene oxidation (Conditions **B**)

Entry	AcOH/1-octene[a]	/Fe[b]	Conversion [%][c]	Epoxide [%][d]	Diol [%][d]	Selectivity for Epoxide [%][e]	Mass loss [%][f]
$[(tpa)Fe^{II}(OTf)_2]$ (1)							
1	0	0	38(2)	6(0)	33(4)	16	–
2	0.5	17	31(4)	9(1)	27(7)	30	–
3	3	100	53(0)	23(2)	19(0)	44	11
4	20	667	74(0)	34(0)	18(0)	46	22
$[(bpmen)Fe^{II}(OTf)_2]$ (2)							
5	0	0	94(1)	49(1)	7(0)	52	38
6	0.5	17	99(1)	63(1)	1(0)	64	35
$[(bpmen)Fe^{II}(NCCH_3)_2](SbF_6)_2$ (2b)[g]							
7	0	0	98	70		71	28
8	0.055	1	> 99	85		85	14
9	0.5	9	> 99	82		82	17

[a] Equivalents per 1-octene.
[b] Equivalents per Fe.
[c] Conversion [%] = [1 – (remaining substrate/initial amount of substrate)] × 100.
[d] Yields are based on the substrate.
[e] Selectivity for epoxide [%] = (Epoxide yield [%]/Conversion [%]) × 100.
[f] Mass loss [%] = Conversion [%] – (Epoxide [%] + Diol [%]).
[g] From Ref.[8] with 1-decene and catalyst loading 5.5 mol %.

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(1.05 mmol), a catalyst (2.1 μmol Fe) and additives (if applicable) in 2.6 mL of acetonitrile was added a solution of either H_2O_2 (70 mM, 0.435 mL for 14.5 equivs./Fe) or AcOOH (70 mM of AcOOH content, 0.300 mL for 10 equivs./Fe AcOOH) in acetonitrile at the rate of 14 μL/min *via* a syringe pump at r.t. under air. After 5 min of additional stirring, esterification reagents (acetic anhydride or propionic anhydride 0.5–1.0 mL and 1-methylimidazole, 0.1–0.3 mL) and an internal standard (naphthalene, 13.7 mM in acetonitrile, 0.50 mL) were added.[12] After 15 min of stirring, chloroform and ice were added, and the organic layer was washed with 1 N H_2SO_4, saturated $NaHCO_3$, and water, respectively, and dried over $MgSO_4$. The solution was analyzed by GC for product yields.

Reaction Conditions B

Solvent and oxidant solutions were not dried. To a solution of 1-octene (0.24 mmol) and a catalyst (3 mol % Fe) in 1.5 mL of acetonitrile was added, if applicable, AcOH (7 μL, 0.13 mmol for 0.5 equiv/1-octene) and the mixture was cooled in an ice/water bath. To this stirred solution was added a solution of H_2O_2 in acetonitrile (0.36 mmol, 1.5 equivs., 0.36 M, 1.0 mL), precooled in an ice/water bath, *via* a syringe pump over 40 sec (with AcOH) or 2.5 min (no AcOH). After 5 min, esterification reagents and an internal standard were added and product yields were analyzed in the same manner as for Conditions A.

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References and Notes

[1] H. Heaney, *Top. Curr. Chem.* **1993**, *164*, 1–19.

[2] D. Swern, *Organic Peroxides*, John Wiley & Sons, New York, **1970**, Vol. 1.

[3] J.-P. Schirmann, S. Y. Delavarenne, *Hydrogen Peroxide in Organic Chemistry*, Edition et documentation industrielle, Paris, **1979**.

[4] Recent review, see: B. S. Lane, K. Burgess, *Chem. Rev.* **2003**, *103*, 2457–2473.

[5] a) A. Murphy, G. Dubois, T. D. P. Stack, *J. Am. Chem. Soc.* **2003**, *125*, 5250–5251; b) G. Dubois, A. Murphy, T. D. P. Stack, *Org. Lett.* **2003**, *5*, 2469–2472.

[6] W. Nam, R. Ho, J. S. Valentine, *J. Am. Chem. Soc.* **1991**, *113*, 7052–7054.

[7] a) C. Kim, K. Chen, J. Kim, L. Que, Jr. *J. Am. Chem. Soc.* **1997**, *119*, 3635–3636; b) K. Chen, L. Que, Jr. *Angew. Chem. Int. Ed.* **1999**, *38*, 2227–2229. c) K. Chen, M. Costas, J. Kim, A. K. Tipton, L. Que, Jr., *J. Am. Chem. Soc.* **2002**, *124*, 3026–3035; d) K. Chen, M. Costas, L. Que, Jr., *J. Chem. Soc. Dalton Trans.* **2002**, 672–679; e) J. Y. Ryu, J. Kim, M. Costas, K. Chen, W. Nam, L. Que, Jr., *Chem. Commun.* **2002**, 1288–1289; f) M. Fujita, M. Costas, L. Que, Jr., *J. Am. Chem. Soc.* **2003**, *125*, 9912–9913.

[8] M. C. White, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 7194–7195.

[9] M. Picard, J. Gross, E. Lübbert, S. Tölzer, S. Krauss, K.-H. van Pée, A. Berkessel, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1196–1199.

[10] M. H. Lim, J.-U. Rohde, A. Stubna, M. R. Bukowski, M. Costas, R. Y. N. Ho, E. Münck, W. Nam, L. Que, Jr, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 3665–3670.

[11] S. Ménage, J. M. Vincent, C. Lambeaux, G. Chottard, A. Grand, M. Fontecave, *Inorg. Chem.* **1993**, *32*, 4766–4773.

[12] This esterification procedure was implemented to facilitate the analysis of the diol products. It has been confirmed that this step does not affect the yield of epoxides.

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