Epoxidation Catalysts

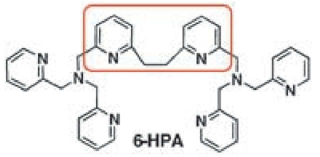
DOI: 10.1002/ange.200501825

A Diiron Center Stabilized by a Bis-TPA Ligand as a Model of Soluble Methane Monooxygenase: Predominant Alkene Epoxidation with H_2O_2**

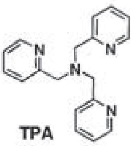
Masahito Kodera, Motoharu Itoh, Koji Kano, Takuzo Funabiki, and Marius Reglier*

Models of soluble methane monooxygenase (sMMO)[1] are useful for studying peroxodiiron(III) and oxodiiron(IV) intermediates in O–O activation,[1] as well as for developing an efficient oxidation catalyst.[2] Our synthetic efforts to obtain models for dimetal biosites yielded a series of dinucleating polypyridine ligands.[3] The diiron complex of the hexapyridine ligand efficiently catalyzes the oxidation of alkanes and forms a thermally stable peroxo complex.[3d–f] Diiron complexes of tris(2-pyridylmethyl)amine (TPA) and related ligands are known as effective sMMO models.[4] However, such ligands do not stabilize the diiron core in solution,[5] and the resulting complexes display varied reactivity, depending on them being mono- or diiron complexes.[6,7] Iron complexes of TPA derivatives catalyze alkene oxidation with H_2O_2 to give the 1,2-*cis*-diol and epoxide, and Rieske dioxygenase-type monoiron active species have been proposed.[6] However, predominant epoxidation was observed with the iron complex of the ligand *N,N′*-dimethyl-*N,N′*-bis(2-pyridylmethyl)ethane-1,2-diamine (MEP), which is similar to TPA, and an sMMO-type diiron species was proposed.[7] Therefore, a TPA-containing dinucleating ligand capable of stabilizing a diiron core in solution would be useful for the development of an effective sMMO model.

We prepared 1,2-bis[2-{bis(2-pyridylmethyl)aminomethyl}-6-pyridyl]ethane (6-HPA) as a bis-TPA dinucleating ligand. Herein, we describe the synthesis, structure, and application of the diiron complex of 6-HPA as a highly useful sMMO model. The complex can catalyze epoxidation with H_2O_2 with high yields and large turnover numbers. Spectral studies showed that a peroxodiiron(III) complex is formed as an intermediate. ^{18}O-labeling studies demonstrated that the O atoms of μ-oxo and μ-peroxo groups in the peroxo intermediate were incorporated equivalently into the epoxide. Thus, the oxo- and peroxo-derived O atoms in the active species scramble one another.



6-HPA



TPA

6-HPA forms the diiron complexes $[Fe_2(6\text{-HPA})(O)(OH_2)_2](ClO_4)_4$ (**1**) and $[Fe_2(6\text{-HPA})(TfO)_4]$ (**2**; TfO = triflate). The structure of **1** was revealed by X-ray structure analysis (Figure 1).[8] The distances and angles of the diiron core in **1** are almost equivalent to those in a corresponding diiron(III) complex of TPA, $[Fe_2(TPA)_2(O)(OH_2)_2](ClO_4)_3$ (**3**),[9] which indicates that 6-HPA stabilizes the diiron core without distortion. The ESI mass spectrum of **1** exhibited a major peak at *m/z* 1033 arising from $\{[Fe_2(6\text{-HPA})(O)(OH_2)_2](ClO_4)_3\}^+$, and the spectrum of **3** showed two major peaks at *m/z* 362 and 445 that resulted from the monoiron species and two minor peaks at *m/z* 923 and 1007 arising from the diiron species. These results clearly show that 6-HPA specifically stabilizes the diiron core of **1** in solution.

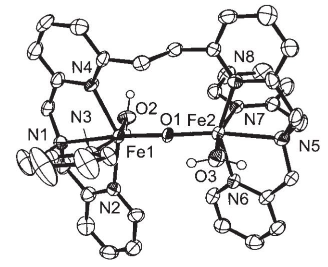


Figure 1. ORTEP view (40% probability) of the structure of the cation in **1**. Selected distances [Å] and angles [°]: Fe1···Fe2 3.607(3), Fe1-O1 1.795(2), Fe2-O1 1.812(2), Fe1-O2 2.084(7), Fe2-O3 2.059(2), Fe1-N1 2.244(1), Fe1-N2 2.151(5), Fe1-N3 2.114(1), Fe1-N4 2.187(7), Fe2-N5 2.235(5), Fe2-N6 2.152(7), Fe2-N7 2.120(9), Fe2-N8 2.196(6); Fe1-O1-Fe2 179.2.

Efficient and predominant epoxidation of alkenes with H_2O_2 catalyzed by **1** was achieved, and the results are summarized in Table 1.[10] Cyclooctene was converted to the epoxide and 1,2-*cis*-diol in 75 and 2% yields, respectively. In an effort to determine the durability of **1** as a catalyst, an experiment with repeated additions of H_2O_2 was performed under similar conditions, in which the turnover number of **1** exceeded 100. For other alkenes, the epoxide was formed

Table 1: Oxygenation of alkenes with H_2O_2 catalyzed by **1** and **2**.

	Yield[a] [%] (turnover number) epoxide/*cis*-1,2-diol	
alkene [IP (eV)][b]	**1**	**2**
cyclooctene [8.98]	75(7.5)/2(0.2)[c] 70(105)/2(3.0)[d]	42(4.2)/24(2.4)[c]
trans-β-methylstyrene [8.08]	91(9.1)/0[c]	
cis-β-methylstyrene [8.48]	79(7.9)/0[c]	
styrene [8.49]	63(6.3)/0[c]	
1-octene [9.52]	37(3.7)/0[c]	

[a] Yield based on the H_2O_2 used. [b] IP is the ionization potential of the alkene. [c] 10 equiv of H_2O_2 was added. [d] 150 equiv of H_2O_2 was added.

---

[*] Prof. Dr. M. Kodera, M. Itoh, Prof. Dr. K. Kano, Dr. T. Funabiki
Department of Molecular Science and Technology
Faculty of Engineering, Doshisha University
Kyotanabe, Kyoto 610-0321 (Japan)
Fax: (+81) 774-65-6848
E-mail: mkodera@mail.doshisha.ac.jp

Dr. M. Reglier
Université Paul Cezanne
Escadrille Normandie-Niemen
13397 Marseille Cedex 20 (France)

[**] This work was supported by a Grant-in-Aid for Scientific B (14340210) from the JSPS. TPA = tris(2-pyridylmethyl)amine.

predominantly and the 1,2-*cis*-diol was not detected. The *trans*-epoxide was obtained from *trans*-β-methylstyrene in 91 % yield. Given the large turnover number and high epoxide yield, it can be stated that **1** is an effective sMMO model. The epoxide yield increased with decreasing ionization potential (IP)[11] of the alkene (Table 1); *trans*-β-methylstyrene, which had the lowest IP value, gave the highest epoxide yield. Moreover, epoxidation was not stereospecific, as *cis*- and *trans*-epoxides were obtained from *cis*-β-methylstyrene with an RC value of 63 %.[12] These data indicate that the first step in the epoxidation represents a one-electron oxidation of the alkene by an active species, and that the radical cation generated undergoes a *cis*-to-*trans* configuration change. As 6-HPA stabilizes the diiron core of **1** in solution, the active species generated from **1** must be a dinuclear complex relevant to sMMO.

Interestingly, when the diiron(II) complex **2**, which does not have bridging oxo or hydroxo groups, was used as a catalyst for the oxygenation of cyclooctene, the 1,2-*cis*-diol was a main product (see Table 1). When 1 equiv of H_2O_2 was added to **2**, the epoxide/*cis*-1,2-diol product ratio was 0.15:0.85. With an increase in the amount of H_2O_2 added, the yield of epoxide was increased and that of *cis*-1,2-diol was decreased according to the following epoxide/*cis*-1,2-diol ratios: 0.26:0.74, 0.53:0.47, and 0.64:0.36 for 2, 5, and 10 equiv of H_2O_2 added, respectively. These results clearly show that **2** mainly produces *cis*-1,2-diol, and **1** gradually generated by oxidation of **2** with H_2O_2 mainly produces epoxide. This finding indicates that the μ-oxo bridge in **1** plays an essential role for the sMMO-type reactivity.

Addition of 2 equiv of H_2O_2 to a solution of **1** in CH_3CN at −40 °C generated a green species **4** that exhibited absorption bands at 490 ($\varepsilon = 1130\ \text{M}^{-1}\text{cm}^{-1}$), 670 (1060), and 882 nm (sh, 370). These data are similar to those of the peroxodiiron complex $[Fe_2(O)(O_2)(6\text{-}Me_3\text{-}TPA)_2](ClO_4)_2$ (**5**; 6-Me_3-TPA = tris(6-methyl-2-pyridylmethyl)amine).[13] The cold-spray ionization (CSI) mass spectrum of **4** showed a parent peak at *m*/*z* 865 arising from a peroxodiiron complex, $\{[Fe_2(O)(O_2)(6\text{-}HPA)](ClO_4)\}^+$, as the strongest peak (Figure 2). The ion exhibited an isotope intensity pattern that matched the calculated one. Upon addition of $H_2{}^{18}O_2$ instead of $H_2{}^{16}O_2$, the mass of the ion increased by four units. These results indicate that **4** is best formulated as $[Fe_2(O)(O_2)(6\text{-}HPA)](ClO_4)_2$. Spontaneous decomposition of **4** in CH_3CN monitored at 680 nm obeyed first-order kinetics with $k = 1.6 \times 10^{-3}\ \text{s}^{-1}$ at 243 K (the half-life $\tau_{1/2} = 7.2$ min). This value was equivalent to that of **5** under the same conditions.[13] Compound **4** was as stable as **5** but without steric hindrance, as was the case with the Me groups of 6-Me_3-TPA in **5**. When *trans*-β-methylstyrene was added to the solution of **4** generated as described above at −40 °C, the decay of **4** was not accelerated at all. The mixture was analyzed after warming to room temperature; the epoxide yield was increased to almost quantitative.

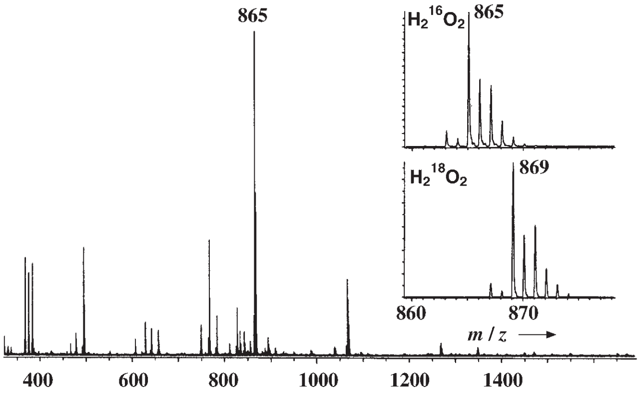
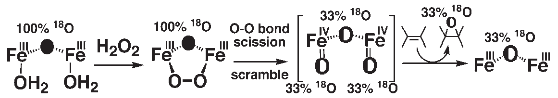


Figure 2. CSI mass spectrum of **4** obtained at −40 °C in CH_3CN. The isotope patterns assignable to $\{[Fe_2(O)({}^{16}O_2)(6\text{-}HPA)](ClO_4)\}^+$ and $\{[Fe_2(O)({}^{18}O_2)(6\text{-}HPA)](ClO_4)\}^+$ are shown in the insets.

Isotope-labeling experiments with *trans*-β-methylstyrene as substrate were carried out by using $H_2{}^{18}O_2$ and μ-^{18}O-**1** under argon to gain insight into the O–O activation mechanism. Upon addition of 10 equiv of $H_2{}^{18}O_2$ to **1**, ^{18}O was incorporated into 94 % of the epoxide, whereas addition of 1 or 3 equiv of $H_2{}^{16}O_2$ to μ-^{18}O-**1** resulted in incorporation of ^{18}O into 31 or 17 % of the epoxide, respectively. Thus, μ-^{18}O is incorporated into the epoxide in addition to $H_2{}^{18}O_2$. This finding can be explained if it is assumed that a dioxo-μ-oxodiiron(IV) moiety is generated from **4** as an active species via homolytic scission of the O–O bond, and that three O atoms in the active species scramble one another. Accordingly, with $H_2{}^{16}O_2$ (1 equiv)/μ-^{18}O-**1**, 33 % of each oxo group in the active species was labeled with ^{18}O, and thus the theoretical yield of the ^{18}O-epoxide was 33 % (Scheme 1). Similarly, with $H_2{}^{16}O_2$ (3 equiv)/μ-^{18}O-**1** or $H_2{}^{18}O_2$ (10 equiv)/**1**, the yield of ^{18}O-epoxide is estimated to be 16 or 95 %, respectively. The theoretical values of 33, 16, and 95 % agree with the experimental results of 31, 17, and 94 %, respectively.



Scheme 1. Incorporation of the ^{18}O atom on labeling with μ-^{18}O-**1**.

Further experiments with an excess amount of $H_2{}^{18}O$ or under $^{18}O_2$ revealed the unique reactivity of the active species. With $H_2{}^{18}O/H_2{}^{16}O_2$/**1** (1000:10:1), only 1.5 % of the epoxide was labeled with ^{18}O, which shows that O-atom exchange of the active species with H_2O was much slower than O-atom transfer to the alkene.[14] When the reaction was carried out with $H_2{}^{16}O_2$ (10 equiv)/**1** under $^{18}O_2$, 5 % of the epoxide was labeled with ^{18}O. This result suggests that a one-electron oxidation of the alkene by the active species occurs to form a radical cation and a diiron(III),(IV) species, as ^{18}O labeling from $^{18}O_2$ must occur by autoxidation of the radical cation. The remaining 95 % of nonlabeled epoxide could be accounted for by O-atom transfer from the resultant diiron(III),(IV) species to the radical cation. We are presently attempting to detect the diiron(III),(IV) and diiron(IV) species, which would be generated from **1** and H_2O_2 via the peroxo intermediate **4**.

Experimental Section

6-HPA: An aqueous solution of NaOH (2.3 M, 5 mL) was added dropwise with vigorous stirring to a solution of TPA (0.77 g, 3.87 mmol) and 1,2-bis(6-bromomethyl-2-pyridyl)ethane·2 HBr (1.03 g, 1.94 mmol) in water (5 mL) at room temperature. The reaction mixture was stirred for 24 h at room temperature and then extracted with $CHCl_3$. The extracts were dried over Na_2SO_4 and the product 6-HPA was isolated as a white solid (0.71 g, 60 %). Mp.: 133.5–135.0 °C. Elemental analysis (%) calcd for $C_{38}H_{38}N_8$: C 75.22, H 6.31, N 18.34; found: C 74.99, H 6.34, N 18.34. ^1H NMR (Me_4Si, in $CDCl_3$): $\delta = 8.52$ (dq, 4 H, py′-6), 7.65 (m, 6 H, py-4 and py′-4), 7.49 (s, 4 H,py′-3), 7.36 (d, 2 H, py-5), 7.13 (s, 4 H, py′-5), 6.96 (d, 2 H, py-3), 3.89 (s, 8 H, $pyCH_2N(CH_2py)_2$), 3.86 (s, 4 H, $pyCH_2N(CH_2py)_2$), 3.19 ppm (s, 4 H, CH_2); ^{13}C NMR (Me_4Si, in $CDCl_3$): $\delta = 160.3$, 159.3, 158.5 (py-2, py-6, py′-2), 148.8 (py′-6), 136.4, 136.2, 122.6, 121.7, 120.9, 119.9 (py-4, py′-4, py′-3, py′-5, py-5, py-3), 60.0, 59.9 (methylene), 38.0 ppm (ethylene). FAB MS: m/z 607 $[M+H]^+$.

1: 6-HPA (60.5 mg, 0.1 mmol) was dissolved in water (1 mL), a solution of $Fe(ClO_4)_3 \cdot 9H_2O$ (103 mg, 0.2 mmol) in water (1 mL) was added, and the mixture was stirred overnight. **1** precipitated as a brown powder (yield 86.5 %) and was recrystallized from C_6H_6/CH_3CN to give crystals suitable for X-ray structure analysis. Elemental analysis (%) calcd for $C_{38}H_{50}N_8Cl_4O_{23}Fe_2$: C 36.80, H 4.06, N 9.03, Fe 9.00; found: C 36.62, H 4.03, N 9.04, Fe 8.73. UV/Vis absorption (in CH_3CN): $\lambda_{max} = 515\ nm^{-1}$ ($\varepsilon_{max} = 110\ M^{-1}cm^{-1}$). IR (KBr disk): $\tilde{\nu} = 3072$, 3032 (aromatic C–H), 2959, 2924 (aliphatic C–H), 1607, 1572 (pyridine ring), 1113, 1084 (ClO_4), 810 cm^{-1} (Fe–O–Fe). ESI MS: m/z 1033 $[M-2H_2O-ClO_4]^+$, 466 $[M-2H_2O-2ClO_4]^{2+}$.

μ-^{18}O-**1:** 6-HPA (20.3 mg, 33 μmol) and $Fe(ClO_4)_3 \cdot 9H_2{}^{18}O$ (35.9 mg, 67 μmol) were dissolved in $H_2{}^{18}O$ (1 mL) and the mixture was stirred overnight. μ-^{18}O-**1** precipitated as a brown powder (yield 65 %) and was recrystallized from dry C_6H_6/CH_3CN. IR (KBr disk): $\tilde{\nu} = 3069$, 3034 (aromatic C–H), 2953, 2922 (aliphatic C–H), 1607, 1572 (pyridine ring), 1092 (ClO_4), 768 cm^{-1} (Fe–O–Fe). ESI MS: m/z 1035 $[M-2H_2{}^{18}O-ClO_4]^+$, 467 $[M-2H_2{}^{18}O-2ClO_4]^{2+}$, 278 $[M-2H_2{}^{18}O-3ClO_4]^{3+}$.

2: A solution of 6-HPA (30.75 mg, 0.051 mmol) in CH_2Cl_2 (1 mL) was added to a solution of $Fe^{II}(TfO)_2 \cdot 2CH_3CN$ (40.1 mg, 0.11 mmol) in THF (2 mL) and the mixture was stirred overnight under Ar. Complex **2** precipitated as a pale yellow powder, and was isolated by filtration (46.8 mg, yield 70 %) and recrystallized from CH_2Cl_2/CH_3CN/Et_2O under Ar. Elemental analysis (%) calcd for $C_{42}H_{38}N_8F_{12}S_4O_{12}Fe_2$: C 38.37, H 2.91, N 8.52, Fe 8.50; found: C 38.29, H 2.89, N 8.31, Fe 8.19. UV/Vis absorption (in CH_3CN): λ_{max} ($\varepsilon_{max}\ M^{-1}cm^{-1}$) = 355 (1600), 540 nm^{-1} (20). IR (KBr disk): $\tilde{\nu} = 3119$, 3082 (aromatic C–H), 2984, 2926 (aliphatic C–H), 1607, 1576, 1466, 1447 (pyridine ring), 1283, 1254, 1167, 1030 cm^{-1} (CF_3SO_3). ESI MS (in CH_3CN): m/z 1165 $[M-CF_3SO_3]^+$, 508 $[M-2CF_3SO_3]^{2+}$, 289 $[M-3CF_3SO_3]^{3+}$.

Isotope-labeling experiments were carried out under similar conditions in the presence of an excess amount of $H_2{}^{18}O$ or under $^{18}O_2$. The epoxidation reaction was also performed with μ-^{18}O-**1**/H_2O_2 ratios of 1:1 and 1:3 under Ar. The resultant mixtures were analyzed by GC-MS, and the rate of ^{18}O labeling was determined from the isotope-intensity pattern.

Received: May 26, 2005

Keywords: alkenes · epoxidation · iron · isotopic labeling · peroxo ligands

---

[1] a) M. Costas, M. P. Mehn, M. P. Jensen, L. Que, Jr., *Chem. Rev.* **2004**, *104*, 939; b) E. Y. Tshuva, S. J. Lippard, *Chem. Rev.* **2004**, *104*, 987.

[2] a) Y. Mekmouche, S. Ménage, C. Toia-Duboc, M. Fontecave, J.-B. Galey, C. Lebrun, J. Pécaut, *Angew. Chem.* **2001**, *113*, 975; *Angew. Chem. Int. Ed.* **2001**, *40*, 949; b) A. Murphy, G. Dubois, T. D. P. Stack, *J. Am. Chem. Soc.* **2003**, *125*, 5250; c) K. Kamata, K. Yonehara, Y. Sumida, K. Yamaguchi, S. Hikichi, N. Mizuno, *Science* **2003**, *300*, 964.

[3] a) M. Kodera, K. Katayama, Y. Tachi, K. Kano, S. Hirota, S. Fujinami, M. Suzuki, *J. Am. Chem. Soc.* **1999**, *121*, 11006; b) M. Kodera, Y. Kajita, Y. Tachi, K. Katayama, K. Kano, S. Hirota, S. Fujinami, M. Suzuki, *Angew. Chem.* **2004**, *116*, 338; *Angew. Chem. Int. Ed.* **2004**, *43*, 334; c) M. Itoh, J. Nakazawa, K. Maeda, K. Kano, T. Mizutani, M. Kodera, *Inorg. Chem.* **2005**, *44*, 691; d) M. Kodera, H. Shimakoshi, K. Kano, *Chem. Commun.* **1996**, 1737; e) M. Kodera, H. Shimakoshi, M. Nishimura, H. Okawa, S. Iijima, K. Kano, *Inorg. Chem.* **1996**, *35*, 4967; f) M. Kodera, Y. Taniike, M. Itoh, Y. Tanahashi, H. Shimakoshi, K. Kano, S. Hirota, S. Iijima, M. Ohba, H. Okawa, *Inorg. Chem.* **2001**, *40*, 4821.

[4] a) Y. Dong, H. Fujii, M. P. Hendrich, R. A. Leising, G. Pan, C. R. Randall, E. C. Wilkinson, Y. Zang, L. Que, Jr., B. G. Fox, K. Kauffman, E. Münck, *J. Am. Chem. Soc.* **1995**, *117*, 2778; b) C. Kim, Y. Dong, L. Que, Jr., *J. Am. Chem. Soc.* **1997**, *119*, 3635; c) Y. Dong, Y. Zang, L. Shu, E. C. Wilkinson, L. Que, Jr., *J. Am. Chem. Soc.* **1997**, *119*, 12683; d) H.-F. Hsu, Y. Dong, L. Shu, V. G. Young, Jr., L. Que, Jr., *J. Am. Chem. Soc.* **1999**, *121*, 5230.

[5] J. Kim, Y. Dong, E. Larka, L. Que, Jr., *Inorg. Chem.* **1996**, *35*, 2369.

[6] a) K. Chen, M. Costas, J. Kim, A. K. Tipton, L. Que, Jr., *J. Am. Chem. Soc.* **2002**, *124*, 3026; b) M. Costas, L. Que, Jr., *Angew. Chem.* **2002**, *114*, 2283; *Angew. Chem. Int. Ed.* **2002**, *41*, 2179; c) M. Fujita, M. Costas, L. Que, Jr., *J. Am. Chem. Soc.* **2003**, *125*, 9912.

[7] a) M. C. White, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 7194; b) J. Y. Ryu, J. Kim, M. Costas, K. Chen, W. Nam, L. Que, Jr., *Chem. Commun.* **2002**, 1288.

[8] Rigaku AFC7R/CCD diffractometer, 12-kW rotating-anode generator. $C_{50}H_{54}Cl_4Fe_2N_8O_{19}$, $M_w = 1324.52$, red crystals, $0.20 \times 0.30 \times 0.50$ mm, monoclinic, $P2_1/c$ (No. 14), $a = 13.522(3)$, $b = 18.669(3)$, $c = 24.486(5)$ Å, $\beta = 101.364(4)°$, $V = 6060.1(20)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.452\ g\,cm^{-3}$, $2\theta_{max} = 55°$, $Mo_{K\alpha}$ ($\lambda = 0.71069$), $T = -50$ °C, total number of independent reflections 61013 ($R_{int} = 0.086$), number of reflections used 32710 ($I > 3.00\sigma(I)$), $R = 10.0$, $R_w = 16.1$, GOF = 1.213, $\mu = 7.30\ cm^{-1}$, full-matrix least squares on *F*. CCDC-274091 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] B. R. Whittlesey, Z. Pang, R. A. Holwerda, *Inorg. Chim. Acta* **1999**, *284*, 124.

[10] In a typical reaction, a solution of H_2O_2 (21 μmol) in CH_3CN was added over 30 min to a solution of **1** (2.1 μmol) and cyclooctene (2.1 mmol) in CH_3CN (3.0 mL) by using a syringe pump under Ar with stirring at 25 °C. The mixture was analyzed by gas–liquid chromatography with nitrobenzene as internal standard.

[11] a) T. G. Traylor, F. Xu, *J. Am. Chem. Soc.* **1988**, *110*, 1953; b) J. M. Garrison, D. Ostovic, T. C. Bruice, *J. Am. Chem. Soc.* **1989**, *111*, 4960; c) M. S. Workentin, B. D. Wagner, J. Lusztyk, D. D. M. Wayner, *J. Am. Chem. Soc.* **1995**, *117*, 119.

[12] When the RC value is 100%, the reaction is stereospecific and when the RC value is 0%, the reaction is completely non-stereospecific. (RC) (%) of epoxide = 100 × (*cis*−*trans*)/(*cis*+*trans*); see reference [6].

[13] Y. Dong, Y. Zang, L. Shu, E. C. Wilkinson, L. Que, Jr., *J. Am. Chem. Soc.* **1997**, *119*, 12683.

[14] M. S. Seo, J.-H. In, S. O. Kim, N. Y. Oh, J. Hong, J. Kim, L. Que, Jr., W. Nam, *Angew. Chem.* **2004**, *116*, 2471; *Angew. Chem. Int. Ed.* **2004**, *43*, 2417.