JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

A Non-Heme Iron(III) Complex with Porphyrin-like Properties That Catalyzes Asymmetric Epoxidation

Takashi Niwa* and Masahisa Nakada*

Department of Chemistry and Biochemistry, School of Advanced Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo, 169-8555, Japan

Supporting Information

ABSTRACT: In this report, we describe an iron(III) complex containing a carbazole-based tridentate ligand that catalyzes highly enantioselective asymmetric epoxidation of (*E*)-alkenes at room temperature. The non-heme iron(III) complex has a five-coordinated trigonal-bipyramidal structure, and its two-electron oxidized state has the similar electronic structure as that of iron porphyrins.

Metalloporphyrins exist as catalytic centers in various enzymes, realizing surprising chemical transformations with high efficiency.[1] Interest in these systems has focused on not only their biological and medical importance but also their potential utility as efficient catalysts in organic synthesis.[2] Hence, numerous studies of metalloporphyrins to elucidate the reaction mechanisms of enzymes that contain them have been reported thus far.[3−8] Cytochrome P450 oxidases are well-understood enzymes that contain iron porphyrins as catalytic centers.[9,10] These enzymes catalyze the oxidation of nonpolar compounds including drugs, steroids, and pollutants using dioxygen as a terminal oxidant with excellent efficiency.[11] Because of their efficient catalysis, the reaction mechanism of cytochrome P450 oxidases in metabolic reactions[12−15] as well as asymmetric catalysis has been extensively explored in order to better understand the reaction mechanism of iron porphyrin derivatives.[16,17] However, the number of highly efficient and practical metalloporphyrin-type catalysts that enable enantioselective transformations has been limited. This unfortunate situation is attributable to the limited variations within porphyrin ligands, which possess a highly planar structure that prohibits flexibility in design as well as the introduction of chirality near the metal center. Moreover, the preparation of a porphyrin ligand bearing a variety of functional groups requires many steps, rendering the screening and optimization of a desired catalyst difficult.

In 1983, Groves and co-workers reported the first asymmetric epoxidation catalyzed by a chiral iron porphyrin complex.[18] However, despite considerable efforts to develop asymmetric catalysis with chiral metalloporphyrins,[17,19,20] an easily available and practical iron porphyrin catalyst has not been reported until now.

The unique properties of iron porphyrins are attributed to the structure of the porphyrin ligand, which has a highly conjugated planar structure with strong donor moiety. The challenge lies in finding a new surrogate ligand that fulfills these structural requirements that can also accommodate the introduction of a chiral environment near the iron center. We envisioned that a 1,8-(bisoxazolyl)carbazole ligand developed in our laboratory could serve this purpose even though it is a tridentate and not tetradentate ligand (Figure 1). The carbazole-based tridentate ligand has planarity, relatively long π-conjugation, and an acidic N−H that can become anionic and exhibit strong σ-donation. Moreover, since the chiral oxazolines that coordinate to the iron center are easily prepared from α-amino acids, the chiral environment is easily introduced and effectively tunable. 1,8-(Bisoxazolyl)carbazole ligands were developed for asymmetric catalysis in Nozaki-Hiyama-Kishi reactions in our laboratory,[21] and we have demonstrated that these ligands induce high enantioselectivity and have excellent tolerance for redox reactions.

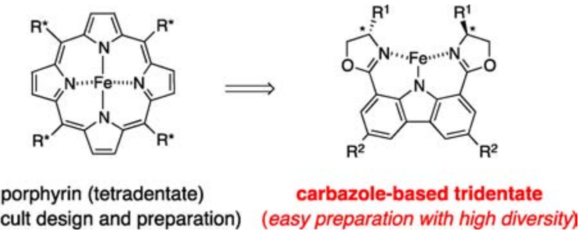


Figure 1. Carbazole-based tridentate ligand as a surrogate porphrin ligand.

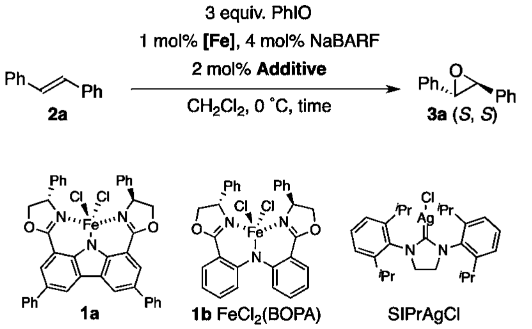
Herein, we report the development of a non-heme iron(III) complex bearing a carbazole-based tridentate ligand that displays iron porphyrin-like properties and catalyzes the asymmetric epoxidation of (*E*)-alkenes with excellent enantioselectivity.[22−24] The two-electron oxidized state of the complex confers upon it a similar electronic state as those found in iron porphyrins,[25] even though the tridentate carbazole ligand and porphyrins have different numbers of binding sites. We demonstrate that the unique catalysis of iron porphyrins can be mimicked by this iron complex bearing a carbazole-based tridentate ligand, which features simple and straightforward preparation as well as plenty extensive capacity for fine-tuning.

We found that the cationic iron(III) complex of **1a**, which was prepared from $FeCl_2 \cdot 4H_2O$, the tridentate carbazole ligand, and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl] borate (NaBARF), catalyzed the asymmetric epoxidation of *trans*-stilbene (**2a**) to afford the desired chiral epoxide **3a** with

Received: May 2, 2012
Published: August 6, 2012

moderate yield and high enantioselectivity (Table 1, entry 1).[26] The yield was diminished owing to the competitive formation of diphenylacetaldehyde. No epoxidation was observed in the absence of NaBARF (entry 2). The yield and enantioselectivity were improved when SIPrAgCl (SIPr=*N*,*N*′-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene), a silver salt which has been commonly used as a SIPr donor to various transition metals, was used in the reaction (entry 3). Interestingly, no epoxidation occurred in the presence of iron complex **1b** that features a tridentate bis(oxazolinylphenyl)amine (BOPA) ligand,[27] which lacks the C−C bond between the two phenyl rings that is present in the carbazole-based tridentate ligand (entry 4). These results indicate that the π-conjugation system of the carbazole-based tridentate ligand is required for the catalytic activity of the iron complex in the epoxidation reaction.

Table 1. Asymmetric Epoxidations of 2a with Catalytic Iron Complexes of 1a and 1b



entry	complex	additive	time (min)	yield (%)[a]	ee (%)[b]
1	**1a**	None	30	35	83
2[c]	**1a**	None	60	trace	NA[d]
3	**1a**	SIPrAgCl	60	55	88
4	**1b**	SIPrAgCl	60	trace	NA[d]

[a]Isolated yields. [b]Ee determined by HPLC. For HPLC conditions, see Supporting Information. [c]Reaction in the absence of NaBARF. [d]Not available.

To explore the epoxidation mechanism and the similarity between the cationic complex of **1a** and iron porphyrins, iron complexes including the intermediates in the epoxidation were analyzed using several techniques (Figure 2). The structure of the iron complex **1a** was estimated to be the same as that of **1c** based on the X-ray crystal structure of **1c** (Figure 2a),[28] which has a five-coordinated trigonal-bipyramidal structure. We next turned our attention to iron intermediates in the epoxidation and analyzed the mixture of iron complex **1a**, NaBARF, and SIPrAgCl (Figure 2b) using several different techniques. The mixture containing intermediate **A**, which was prepared by stirring **1a**, NaBARF, and SIPrAgCl in dichloromethane at room temperature for 10 min, was obtained as a yellow-green solution. The UV−vis spectrum of this solution exhibited strong absorbance at 347 nm ($\varepsilon = 2.0 \times 10^4$ M^{-1} cm^{-1}) and a very weak, broad signal centered at 710 nm ($\varepsilon = 2.7 \times 10^3$ M^{-1} cm^{-1}, Figure 2c). Electron paramagnetic resonance (EPR) spectroscopy analysis of a frozen solution of **A** showed multiple strong signals around $g = 4.1$ with hyperfine splitting and a weak signal around $g = 2.0$ at −196 °C (Figure S1-a). Because the observed spectrum was similar to those of typical iron porphyrins that possess an intermediate-spin state ($S = 3/2$),[29] this result indicates that the intermediate **A** has $S = 3/2$ spin state as well.

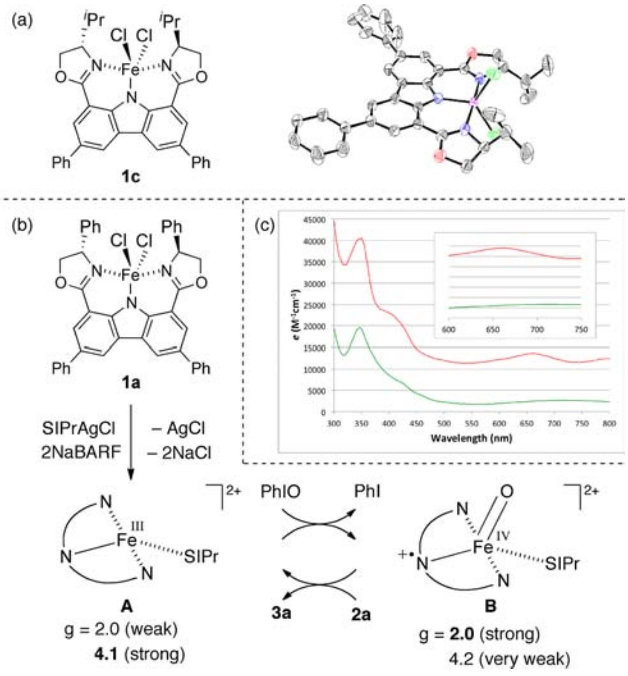


Figure 2. Proposed reaction mechanism of the asymmetric epoxidation and spectra of the intermediates. (a) X-ray crystal structure of the iron complex **1c**. Hydrogen atoms have been omitted for clarity. Black: carbon, red: oxygen, blue: nitrogen, green: chlorine, purple: iron. (b) Proposed reaction mechanism of the asymmetric epoxidation. The *g* values and shapes written below each compound were obtained by EPR spectroscopy. (c) UV−vis spectra of a solution containing **A** (green line, measured at 20 °C) and **B** (red line, measured at −10 °C). The inset shows enlargement of the area between 600 and 725 nm.

Studies focused on the oxidation mechanism of P450 oxidases and iron porphyrins with iodosobenzene have proposed several candidates for the intermediate: (i) an iron(V)−oxo complex, (ii) an iron(IV)−oxo complex bearing a π-cation radical, and (iii) an iodosobenzene activated by an iron(III) complex, which acts as a Lewis acid without any redox change.[5,30] To the best of our knowledge, the consensus reached through a great number of analyses using several techniques as well as theoretical studies is that candidate (ii) is the intermediate.

In this context, analyses of intermediates in the epoxidation were conducted. A green solution including oxidized intermediate **B** was prepared by combining the solution containing **A** with iodosobenzene at −23 °C and stirring for 10 min. The color of the solution changed to yellow at room temperature within several minutes, which indicated low stability of the intermediate **B**. A UV−vis spectrum of the resulting solution was recorded at −10 °C, which showed that a new signal appeared at 660 nm ($\varepsilon = 1.4 \times 10^4$ M^{-1} cm^{-1}). This absorption band has typically been observed in the UV−vis spectrum of iron(IV)−oxo species,[31] and therefore is suggestive that oxidation of the iron complex **A** proceeds in a similar manner to that of iron porphyrins. EPR analysis of a mixture containing **B** at −196 °C revealed a sharp and symmetrical signal centered at $g = 2.0$ (Figure S1-b).[32] This result suggests that **B** has the low spin state $S = 1/2$, and the observed unpaired electron is attributable to a π-radical in the ligand.

Notably, a nearly identical change was observed in both the EPR spectra (Figure S2) and the UV−vis spectra (Figure S3) even in the absence of SIPr ligand. Furthermore, the EPR spectrum of iron(V)-oxo complex has been reported, which shows multiple asymmetrical signals owing to anisotropy of the d-orbital of the iron and differs from ours.[33] This fact could rule out the possibility that **B** is the (i) iron(V)−oxo complex.

On the basis of the above results and discussion, although further studies are still required, we propose that the key intermediate in the epoxidation is the (ii) iron(IV)−oxo complex bearing a π-cation radical, and the iron complex bearing the carbazole ligand has similar properties to those of iron porphyrins, at least as they concern the oxidation reaction.

Next, the scope of the asymmetric epoxidation of alkenes using cationic complex of **1a** was investigated (Figure 3).[34]

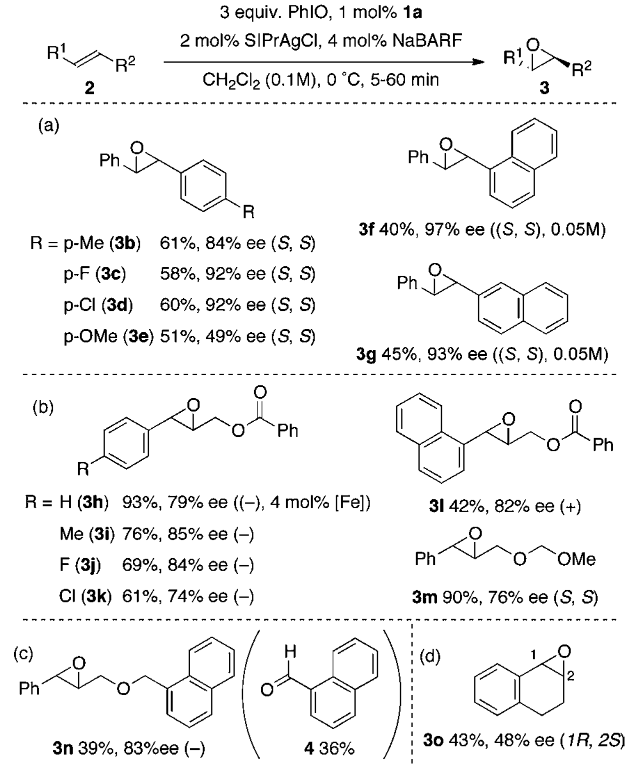


Figure 3. Scope of the asymmetric epoxidation with the cationic iron complex of **1a**. Various (*E*)-alkenes were transformed to the corresponding chiral epoxides under the optimized conditions. Substrate scope includes (a) stilbene derivatives and (b) cinnamyl alcohol derivatives. (c) Direct benzylic oxidation is observed in the reaction of **2n**. (d) Epoxidation of (*Z*)-alkene **2o** afforded the desired epoxide with reduced enantioselectivity. The isolated yield and enantiomeric excess are given below each product. Ee's were determined by HPLC. See Supporting Information for experimental details.

Epoxidation of *trans*-stilbene derivatives (Figure 3a) as well as cinnamyl alcohol derivatives (Figure 3b) smoothly afforded chiral (*S*, *S*)-epoxides with excellent enantioselectivity, whereas moderate selectivity was observed in the epoxidation of substrates bearing an electron-rich aromatic group. The epoxidation of alkene **2n** under the optimized conditions afforded the desired epoxide **3n** along with aldehyde **4** as a byproduct (Figure 3c). Formation of **4** suggests that the catalytic epoxidation proceeds via an iron oxo complex, which is known to promote benzylic oxidation.[35] The epoxidation of 1,2-dihydronaphthalene (**3o**) afforded the product with low enantioselectivity (Figure 3d). To the best of our knowledge, the catalytic asymmetric epoxidation of (*E*)-alkenes with the cationic complex of **1a** and SIPrAgCl shows the highest enantioselectivity and yield compared with the previously reported asymmetric epoxidations using other chiral iron porphyrins. Although the Shi epoxidation affords the product with excellent enantioselectivity and yield,[36] the iron complex developed in our laboratory has advantages in low catalyst loading (1 mol %), short reaction time (<1 h), and availability of both enantiomers of the ligand, which allows us to prepare the chiral epoxide with the desired stereochemistry.

In summary, we have reported the first non-heme iron(III) complex displaying porphyrin-like properties that catalyzes highly enantioselective asymmetric epoxidation. It was discovered that the two-electron oxidation of the cationic iron(III) complex of **1a** generates an iron(IV) cation radical species, which has the same electronic structure as that of iron porphyrins in spite of their different numbers of binding sites. The carbazole-based tridentate ligand has been shown to be a good surrogate for traditional porphyrins, allowing for flexibility in design as well as simple and straightforward preparation. The non-heme iron(III) complex we have developed opens up new avenues for utilizing metalloporphyrin chemistry to accelerate the development of ideal and practical new artificial catalysts for other useful transformations. The highly enantioselective catalytic asymmetric epoxidation of (*E*)-alkenes shown here is a model for these kinds of investigations. Further studies on characterization of the intermediate, mechanism of chiral induction, as well as substrate scope, are in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

EPR and UV−vis spectra, HPLC data, experimental procedures, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*niw@aoni.waseda.jp; mnakada@waseda.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported in part by The Grant-in-Aid for Scientific Research on Innovative Areas “Organic Synthesis based on Reaction Integration. Development of New Methods and Creation of New Substances” (No. 2105), The Grant-in-Aid for Young Scientists (B) (24750096), and the Global COE program “Center for Practical Chemical Wisdom” by MEXT, and a Waseda University Grant for Special Research Projects. We are grateful to Mr. K. Yoshiya, Profs. T. Yamaguchi and K. Ishihara (Waseda University) for performing UV−vis spectrometer, and also to Prof. Tsunehiko Higuchi (Nagoya City University) for helpful discussion.

■ REFERENCES

(1) Kaim, W.; Schwederski, B. *Bioinorganic Chemistry: Inorgnic Elements in the Chemistry of Life*; John Wiley & Sons Inc.: New York, 1994.

(2) Guengerich, F. P. *Drug. Metab. Rev.* **2004**, *36*, 159.

(3) Traylor, T. G. *Pure. Appl. Chem.* **1991**, *63*, 265.

(4) Watanabe, Y. *J. Biol. Inorg. Chem.* **2001**, *6*, 846.

(5) Fujii, H. *Coord. Chem. Rev.* **2002**, *226*, 51.

(6) Tani, F.; Matsu-ura, M.; Nakayama, S.; Naruta, Y. *Coord. Chem. Rev.* **2002**, *226*, 219.

(7) Groves, J. T. *J. Inorg. Biochem.* **2006**, *100*, 434.

(8) Shaik, S.; Hirao, H.; Kumar, D. *Acc. Chem. Res.* **2007**, *40*, 532.

(9) Denisov, I. G.; Makris, T. M.; Sligar, S. G.; Schlichting, I. *Chem. Rev.* **2005**, *105*, 2253.

(10) Jung, C.; de Vries, S.; Schünemann, V. *Arch. Biochem. Biophys.* **2011**, *507*, 44.

(11) Rittle, J.; Green, M. T. *Science* **2010**, *330*, 933.

(12) Dawson, J. H.; Sono, M. *Chem. Rev.* **1987**, *87*, 1255.

(13) Mansuy, D.; Battioni, P.; Battioni, J.-P. *Eur. J. Biochem.* **1989**, *184*, 267.

(14) Beri, P.; Chandra, R. *Drug Metab. Rev.* **1993**, *25*, 49.

(15) Hansch, C.; Zhang, L. *Drug Metab. Rev.* **1993**, *25*, 1.

(16) Stephenson, N. A.; Bell, A. T. *J. Mol. Catal. A: Chem.* **2007**, *275*, 54.

(17) Rose, E.; Andrioletti, B.; Zrig, S.; Quelquejeu-Ethève, M. *Chem. Soc. Rev.* **2005**, *34*, 573.

(18) Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791.

(19) Naruta, Y.; Ishihara, N.; Tani, F.; Maruyama, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 158.

(20) Rose, E.; Ren, Q.-Z.; Andrioletti, B. *Chem.—Eur. J.* **2004**, *10*, 224.

(21) (a) Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 1140. (b) Suzuki, T.; Kinoshita, A.; Kawada, H.; Nakada, M. *Synlett* **2003**, 570. (c) Inoue, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 2977. (d) Inoue, M.; Nakada, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 252. (e) Inoue, M.; Nakada, M. *Heterocycles* **2007**, *72*, 133. (f) Inoue, M.; Suzuki, T.; Kinoshita, A.; Nakada, M. *Chem. Rec.* **2008**, *8*, 169.

(22) For a review of iron-catalyzed epoxidations, see: Adolfsson, H. In *Modern Oxidation Methods*, 2nd ed; Bäckvall, J.-E., Ed.; Wiley-VCH: Weinheim, 1998; p 64.

(23) For recent examples of asymmtric epoxidations with non-heme iron complexes, see: (a) Francis, M. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 937. (b) Rose, E.; Ren, Q.-Z.; Andrioetti, B. *Chem.—Eur. J.* **2004**, *10*, 224. (c) Marchi-Delapieere, C.; Jorge-Robin, A.; Thibon, A.; Ménage, S. *Chem. Commun.* **2007**, 1166. (d) Gelalcha, F. G.; Bitterlich, B.; Anilkumar, G.; Tse, M. K.; Beller, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7293. (e) Gelalcha, F. G.; Anilkumar, G.; Tse, M. K.; Brückner, A.; Beller, M. *Chem.—Eur. J.* **2008**, *14*, 7687. (f) Yeung, H.-L.; Sham, K.-C.; Tsang, C.-S.; Lau, T.-C.; Kwong, H.-L. *Chem. Commun.* **2008**, 3801. (g) Nishikawa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2011**, *133*, 8432. (h) Lyakin, O. Y.; Ottenbacher, R. V.; Bryliakov, K. P.; Talsi, E. P. *ACS Catal.* **2012**, *2*, 1196. (i) Wang, B.; Wang, S.; Xia, C.; Sun, W. *Chem.—Eur. J.* **2012**, *18*, 7332.

(24) For examples of asymmtric dihydroxylations catalyzed by non-heme iron complexes, see: (a) Costas, M.; Tipton, A. K.; Chen, K.; Jo, D.-H.; Que, L., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 6722. (b) Suzuki, K.; Oldenburg, P. D.; Que, L., Jr. *Angew. Chem., Int. Ed.* **2008**, *47*, 1887.

(25) Groves, J. T.; Haushalter, R. C.; Nakamura, M.; Nemo, T. E.; Evans, B. J. *J. Am. Chem. Soc.* **1981**, *103*, 2884.

(26) Use of hydrogen peroxide as a terminal oxidant caused decomposition of the catalyst with evolving dioxygen.

(27) Inagaki, T.; Phong, L. T.; Furuta, A.; Ito, J.-i.; Nishiyama, H. *Chem.—Eur. J.* **2010**, *16*, 3090.

(28) Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data centre as supplementary publication numbers CCDC 867843. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, U.K. [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

(29) Mansuy, D.; Morgenstern-Badarau, I.; Lange, M.; Gans, P. *Inorg. chem.* **1982**, *21*, 1427.

(30) Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 5786.

(31) For iron(IV)—oxo porphyrins, see: (a) Groves, J. T.; Watanabe, Y. *J. Am. Chem. Soc.* **1986**, *108*, 507. (b) Bell, S. R.; Groves, J. T. *J. Am. Chem. Soc.* **2009**, *131*, 9640.

(32) A spin concentration of a single peak at $g = 2.0$ of a solution containing **B** was 0.43 mM while the starting concentration of Fe(III) precursor was 1.36 mM. This result could suggest formation of intermediates other than **B**. The signal (Figure S1-b) seems to have small hyperfine splitting though we have no evidence that it is indeed due to hyperfine interaction.

(33) Tiago de Oliveira, F.; Chanda, A.; Banerjee, D.; Shan, X.; Mondal, S.; Que, L., Jr.; Bominaar, E. L.; Muenck, E.; Collins, T. J. *Science* **2007**, *315*, 835.

(34) Interestingly, the epoxidation of styrene was low yielding owing to the formation of phenylacetaldehyde.

(35) Costas, M. *Coord. Chem. Rev.* **2011**, *255*, 2912.

(36) Wong, O. A.; Wang, B.; Zhao, M.-X.; Shi, Y. *J. Org. Chem.* **2009**, *74*, 6335. For a review of Shi epoxidation, see: Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958.