JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

Iron-Catalyzed Asymmetric Epoxidation of β,β-Disubstituted Enones

Yasuhiro Nishikawa and Hisashi Yamamoto*

Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637, United States

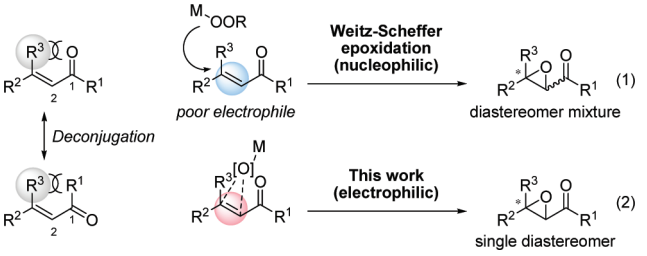
Supporting Information

ABSTRACT: The combination of $Fe(OTf)_2$ and novel phenanthroline ligands enables the catalytic asymmetric epoxidation of acyclic β,β-disubstituted enones, which have been a heretofore inaccessible substrate class. The reaction provides highly enantioenriched α,β-epoxyketones (up to 92% ee) that can be further converted to functionalized β-ketoaldehydes with an all-carbon quaternary center.

The catalytic asymmetric epoxidation of olefins is a powerful strategy for the synthesis of chiral molecules. Thus, numerous efforts have been dedicated to achieving greater efficiency with less expensive and environmentally benign catalysts and oxidants as well as applicability to a variety of substrate classes.[1] Among various useful methods, the development of an iron-catalyzed asymmetric epoxidation should provide us with many advantages, as iron is the most abundant transition metal on the earth and relatively nontoxic.[2−4] In addition, understanding the mechanism of iron-catalyzed oxidations, which play important roles in biological metabolism, may lead to new insights in biocatalysis and resulting drug design.[5] Actually, the biomimetic asymmetric epoxidation of styrene derivatives with iron porphyrin complexes was first reported in 1999,[6,7] although it has drawbacks such as the difficult synthesis of the required chiral porphyrin ligands. After studies pursuing non-heme iron catalysts that could be easily prepared and modified, Beller and co-workers reported that the best results were obtained using iron-catalyzed asymmetric epoxidation of stilbene derivatives with excellent enantioselectivity.[4c,d] However, the high selectivity was obtained for only one specific substrate with 10 mol % catalyst loading. Therefore, it is apparent that iron has yet to be fully introduced in asymmetric epoxidations.

Obviously, the extension of the accessible substrate classes for catalytic asymmetric epoxidation would be desirable. To the best of our knowledge, a general method for the catalytic asymmetric epoxidation of *acyclic* β,β-disubstituted enones is still lacking, probably because of stereocongestion at the β-carbon in the Weitz−Scheffer-type epoxidation, which is commonly employed to access α,β-epoxycarbonyl compounds (eq 1 in Scheme 1).[1d,8] In the case of acyclic enones, a β-substituent (R^3 group) increases the steric repulsion not only between the β-carbon and the nucleophile but also between the R^3 group and the acyl group, which causes the substrate to break conjugation to avoid repulsion. As a result, the electrophilicity of the double bond in acyclic β,β-disubstituted enones is thought to be weaker than that in cyclic or non-β-substituted enones.[9] In contrast, the deconjugation described above should increase the reactivity toward electrophilic epoxidation (eq 2 in Scheme 1).[9c,i] Herein is a solution to the catalytic asymmetric epoxidation of acyclic β,β-disubstituted enones with a newly designed iron complex.

Scheme 1. Epoxidation of Acyclic β,β-Disubstituted Carbonyl Compounds

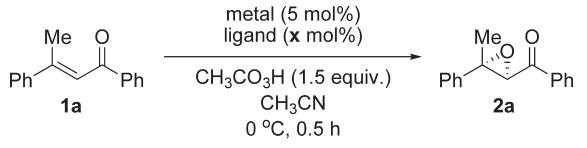


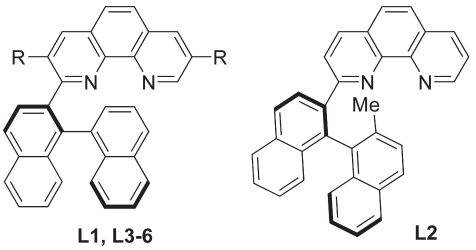
We initially investigated the epoxidation of readily available (*E*)-dypnone (**1a**) as a model substrate using a variety of complexes consisting of iron metals and phenanthroline ligands attached to binaphthyl moieties (Table 1). A preliminary screening of reaction conditions showed that peracetic acid as a terminal oxidant is crucial in producing epoxides.[10] When **1a** was reacted with 5 mol % $FeCl_2$ and monophenanthroline ligand **L1** in the presence of peracetic acid solution in acetonitrile, the epoxidation resulted in only low conversion of starting material and low selectivity (entry 1). Replacing $FeCl_2$ with $Fe(OTf)_2$ led to a significant improvement in terms of reactivity and enantioselectivity (entry 2). Thus, we turned our attention to the effects of various monophenanthroline ligands. Introduction of a methyl group at the 2′-position in the binaphthyl group dramatically diminished the reactivity and selectivity (entry 3). To our delight, we found that the introduction of a phenyl group at the 3- and 8-positions in the phenanthroline moiety, which would be expected to restrict the rotation of the bond between the binaphthyl group and the phenanthroline moiety, resulted in significantly increased enantioselectivity (entry 4). After testing various ligands bearing aromatic groups on the phenanthroline rings (entries 4−7), we identified **L5** as the ligand providing the best yield and enantioselectivity (entry 6). A study of the ligand/metal ratio implied that an iron complex coordinated by two phenanthroline ligands induces high enantioselectivity (entries 6, 8, and 9). Furthermore, the catalyst loading was successfully lowered to 2.5 mol % with only a slight decrease in the yield and selectivity (entry 10). It should be noted that only one diastereomer of the epoxide was observed during the course of this study, while Weitz−Scheffer-type epoxidation of trisubstituted α,β-carbonyl compounds often suffers from low diastereocontrol.[9e,g,11] In addition, this

Received: March 1, 2011
Published: May 10, 2011

   dx.doi.org/10.1021/ja201873d | *J. Am. Chem. Soc.* 2011, 133, 8432–8435

Table 1. Screening of Reaction Conditions





				2a	
entry	metal	ligand (R)	x	% yield[a]	% ee[b]
1	$FeCl_2$	**L1** (H)	10	17	3
2	$Fe(OTf)_2$	**L1** (H)	10	95	57
3	$Fe(OTf)_2$	**L2** (−)	10	<5	17
4	$Fe(OTf)_2$	**L3** (Ph)	10	93	83
5	$Fe(OTf)_2$	**L4** (*o*-Tol)	10	72	75
6	**$Fe(OTf)_2$**	**L5** (***m*-xylyl**)	**10**	**88 (80)[c]**	**91**
7	$Fe(OTf)_2$	**L6** (*m*-$Et_2C_6H_3$)	10	64	86
8	$Fe(OTf)_2$	**L5** (*m*-xylyl)	5	73	78
9	$Fe(OTf)_2$	**L5** (*m*-xylyl)	15	25	53
10[d]	$Fe(OTf)_2$	**L5** (*m*-xylyl)	5	81	86

[a] Determined using ^1H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard. [b] Determined by chiral HPLC analysis. [c] The value in parentheses is the isolated yield. [d] 2.5 mol % $Fe(OTf)_2$ was used.

diastereospecific epoxide formation in our catalytic system implies a concerted pathway unlike the stepwise mechanism proposed previously.[12n]

Next, X-ray crystallographic analysis was carried out on a single crystal grown in an acetonitrile solution of $Fe(OTf)_2$ and 2 equiv of *rac*-**L3**. As illustrated in Figure 1, an octahedral, mononuclear $[Fe(\mathbf{L3})_2(CH_3CN)(OTf)](OTf)$ complex was identified in which two homochiral phenanthroline ligands coordinate the iron center in a cis topology, affording a pseudo-C_2-symmetric iron complex. Although the bidentate phenanthroline ligands can in principle adopt many possible diastereomers on the iron center, including the hetero- or homocombination of *rac*-**L3**, only the diastereomer shown above was selectively crystallized.[13] This selective complexation can be explained by the $\pi-\pi$ interactions between the naphthyl groups and diphenylphenanthroline. However, the relationship between this selective formation of an iron−ligand complex and the enantioselectivities, as well as the actual structure of the catalyst in the reaction medium, is still unclear.[12]

With the optimized conditions in hand, we next examined the scope of substrates using the $Fe(OTf)_2$−**L5** complex (Table 2). The epoxidations of β,β-disubstituted enones having different electronic characters on the phenacyl groups proceeded smoothly in good yields with excellent enantioselectivities (entries 1−5). Sterically different types of aromatic substituents were also tolerated (entries 6−8). While an electron-deficient aromatic group at the β-position had no influence on the epoxidation (entry 9), an electron-rich group such as a naphthyl group at the β-position

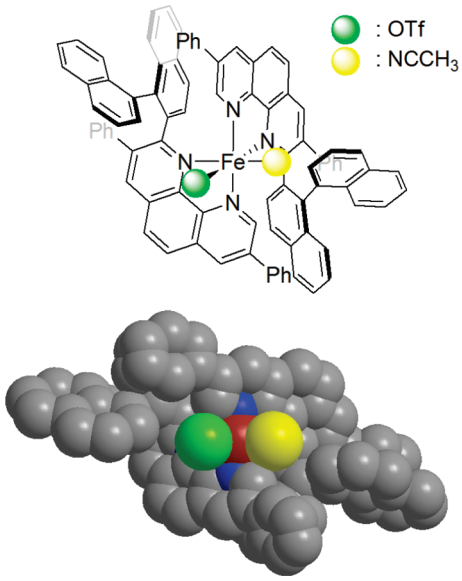


Figure 1. X-ray structure of $[Fe(\mathbf{L3})_2(CH_3CN)(OTf)](OTf)$ shown as a CPK model. Thermal ellipsoids correspond to 50% probability. H atoms and noncoordinating molecules have been omitted for clarity. For clarity, the triflate group and CH_3CN have been replaced by green and yellow atoms, respectively. See the Supporting Information for details. C, gray; N, blue; Fe, red.

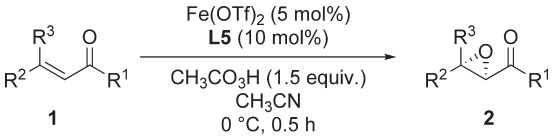
had a deleterious effect on the yield of the product, probably because of the instability of the epoxide obtained under the acidic conditions, although the high enantioselectivity was still maintained (entry 10). On the other hand, the substrate bearing an alkyl substituent at the β-position turned out to have inferior reactivity and selectivity relative to aromatic substrates (entry 11). The substrate with an ethyl group as the R^3 substituent kept the high enantiomeric excess (entry 12). Notably, a single diastereomer was obtained even when (*Z*)-dypnone was employed, although the enantioselectivity was poor (entry 13). This fact could further support the proposal that the reaction proceeds via a concerted pathway.

Gratifyingly, we realized that this chiral iron−phenanthroline system can be applied not only to α,β-enones but also to a nonactivated olefin such as *trans*-α-methylstilbene with good enantioselectivity (eq 1 in Scheme 2).[14] With this result in hand, we conducted an intermolecular competition reaction to determine the nature of the active oxidant (eq 2 in Scheme 2).[15] The competition reaction between electron-deficient alkene **1a** and electron-rich alkene **1n** showed a 2.4:1 preference for the latter with comparable enantioselectivities, confirming the electrophilic nature of the active oxidant.

The utility of chiral α,β-epoxyketones was demonstrated as shown in Scheme 3. The obtained α,β-epoxyketones **2a** and **2l** were converted into the corresponding β-ketoaldehydes **3a** and **3l** bearing all-carbon quaternary centers via Lewis acid-mediated rearrangement without significant loss of enantiomeric excess (eq 1 in Scheme 3).[16] Unlike reaction with the substrate having a phenacyl group, the iron-catalyzed epoxidation of alkyl-substituted substrate **1o** gave the rearranged product **3o** as a major compound concomitant with the corresponding epoxide (eq 2 in Scheme 3). Eventually, the pure rearranged product **3o** was successfully obtained in 35% yield over two steps by treatment of the mixture with $BF_3 \cdot OEt_2$ at room temperature. Furthermore, the

dx.doi.org/10.1021/ja201873d | *J. Am. Chem. Soc.* 2011, 133, 8432–8435

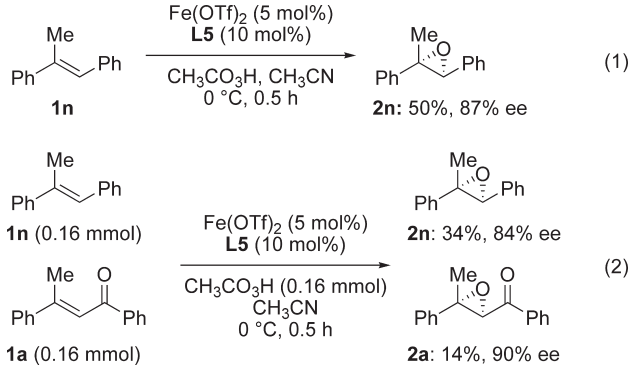
Table 2. Substrate Scope of Epoxidations



entry	1	R^1	R^2	R^3	2	% yield[a]	% ee[b]
1	**1a**	Ph	Ph	Me	**2a**	80	91
2	**1b**	*p*-$MeOC_6H_4$	Ph	Me	**2b**	78	90
3	**1c**	*p*-MeC_6H_4	Ph	Me	**2c**	77	92
4	**1d**	*p*-FC_6H_4	Ph	Me	**2d**	78	92
5	**1e**	*p*-$CF_3C_6H_4$	Ph	Me	**2e**	70	89
6	**1f**	*m*-MeC_6H_4	Ph	Me	**2f**	67	90
7	**1g**	*o*-MeC_6H_4	Ph	Me	**2g**	61	92
8	**1h**	2-naphthyl	Ph	Me	**2h**	88	90
9	**1i**	Ph	*p*-ClC_6H_4	Me	**2i**	88	92
10	**1j**	Ph	2-naphthyl	Me	**2j**	45	92
11	**1k**	Ph	*n*-C_3H_7	Me	**2k**	20	50
12	**1l**	Ph	Ph	Et	**2l**	72	92
13	**1m**	Ph	Me	Ph	**2m**	33	6

[a] Isolated yields. [b] Determined by chiral HPLC analysis.

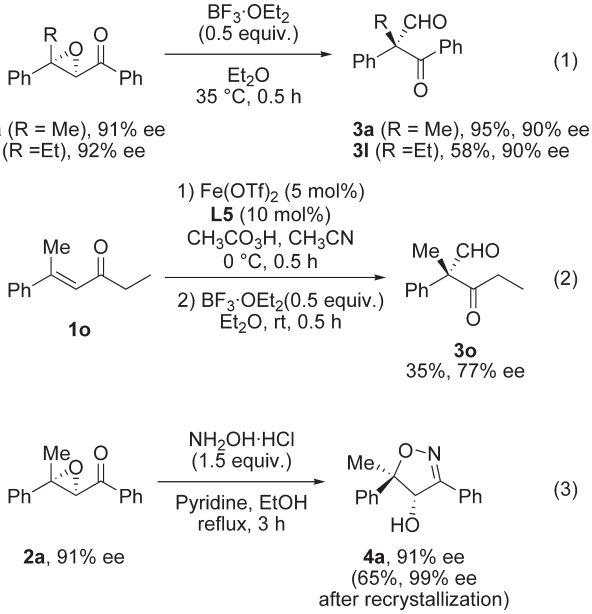
Scheme 2. Asymmetric Epoxidation with a Nonactivated Olefin and a Competitive Experiment Using Electron-Rich and Electron-Deficient Olefins



chiral α,β-epoxyketones can be transformed to 2-isoxazolidines,[17] which are important intermediates in the preparation of a variety of compounds with 1,3-difunctional groups, such as β-hydroxyketones[18] and γ-aminoalcohols.[19] Treatment of **2a** with hydroxylamine hydrochloride in the presence of pyridine furnished highly substituted 2-isoxazoline **4a** in optically pure form (eq 3 in Scheme 3).[20]

In summary, we have developed the first iron-catalyzed asymmetric epoxidation of acyclic β,β-disubstituted enones. Essential for success was the use of the iron complex consisting of $Fe(OTf)_2$ and 2 equiv of a carefully designed phenanthroline ligand. X-ray crystallography revealed a pseudo-C_2-symmetric iron−ligand complex. Moreover, the construction of chiral all-carbon quaternary centers was also realized via Lewis acid-mediated rearrangement of the obtained chiral epoxides. Furthermore, this work provides a new strategy for designing pseudo-C_2-symmetric orthophenanthroline ligand-based catalysts, which should have a vast potential for transition-metal-catalyzed organic synthesis in general.

Scheme 3. Transformations of Optically Active α,β-Epoxyketones



■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures; characterization of compounds **L1**−**6**, **1a**−**m**, **1o**, **2a**−**n**, **3a**, **3l**, **3o**, and **4a**, including ^1H NMR and ^{13}C NMR spectra and HPLC analysis; complete ref 17a; and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
yamamoto@uchicago.edu

■ ACKNOWLEDGMENT

This work was partially supported by the National Institutes of Health (5R01GM068433) and the Uehara Memorial Foundation (Y.N.). We thank Dr. Ian M. Steele for X-ray structure determination and Antoni Jurkiewicz for his NMR expertise.

■ REFERENCES

(1) For recent reviews of asymmetric epoxidation, see: (a) Adolfsson, H.; Shi, Y. In *Modern Oxidation Methods*; Bäckvall, J.-E., Ed.; Wiley-VCH: Weinheim, Germany, 2004; pp 21 ff. (b) Matsumoto, K.; Katsuki, T. In *Catalytic Asymmetric Synthesis*, 3rd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2010; pp 839 ff. (c) Lane, B. S.; Burgess, K. *Chem. Rev.* **2003**, *103*, 2457. (d) Díez, D.; Núñez, M. G.; Antón, A. B.; García, P.; Moro, R. F.; Garrido, N. M.; Marcos, I. S.; Basabe, P.; Urones, J. G. *Curr. Org. Synth.* **2008**, *5*, 186. (e) Matsumoto, K.; Sawada, Y.; Katsuki, T. *Pure Appl. Chem.* **2008**, *80*, 1071. (f) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958.

(2) For reviews of iron catalysis, see: (a) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317. (b) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.

(3) For the seminal work on non-heme iron-catalyzed epoxidation, see: White, M. C.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 7194.

(4) For examples of non-heme iron-catalyzed asymmetric epoxidation, see: (a) Francis, M. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 937. (b) Marchi-Delapierre, C.; Jorge-Robin, A.; Thibon, A.; Ménage, S. *Chem. Commun.* **2007**, 1166. (c) Gelalcha, F. G.; Bitterlich, B.; Anilkumar, G.; Tse, M. K.; Beller, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7293. (d) Gelalcha, F. G.; Anilkumar, G.; Tse, M. K.; Brückner, A.; Beller, M. *Chem.—Eur. J.* **2008**, *14*, 7687. (e) Yeung, H.-L.; Sham, K.-C.; Tsang, C.-S.; Lau, T.-C.; Kwong, H.-L. *Chem. Commun.* **2008**, 3801.

(5) Costas, M.; Mehn, M. P.; Jensen, M. P.; Que, L. *Chem. Rev.* **2004**, *104*, 939.

(6) (a) Collman, J. P.; Wang, Z.; Straumanis, A.; Quelquejeu, M.; Rose, E. *J. Am. Chem. Soc.* **1999**, *121*, 460. (b) Rose, E.; Ren, Q.-Z.; Andrioletti, B. *Chem.—Eur. J.* **2004**, *10*, 224.

(7) For chiral porphyrin catalysts, see: Rose, E.; Andrioletti, B.; Zrig, S.; Quelquejeu-Ethève, M. *Chem. Soc. Rev.* **2005**, *34*, 573 and references therein.

(8) The asymmetric epoxidation of (*E*)-dypnone with a stoichiometric amount of chiral peroxide (40% yield, 72% ee) has been reported. See: Adam, W.; Rao, P. B.; Degen, H.-G.; Saha-Möller, C. R. *Eur. J. Org. Chem.* **2002**, 630.

(9) For examples of catalytic asymmetric epoxidations of trisubstituted α,β-carbonyl compounds, see: (a) Bentley, P. A.; Bickley, J. F.; Roberts, S. M.; Steiner, A. *Tetrahedron Lett.* **2001**, *42*, 3741. (b) Adam, W.; Rao, P. B.; Degen, H.-G.; Levai, A.; Patonay, T.; Saha-Möller, C. R. *J. Org. Chem.* **2002**, *67*, 259. (c) Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792. (d) Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 6844. (e) Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964. (f) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *Synlett* **2006**, 3529. (g) Wang, X.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 1119. (h) Wang, X.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6070. (i) Wang, B.; Wu, X.-Y.; Wong, O. A.; Nettles, B.; Zhao, M.-X.; Chen, D.; Shi, Y. *J. Org. Chem.* **2009**, *74*, 3986.

(10) *m*CPBA also afforded an epoxide in a comparable yield, while other oxidants such as H_2O_2, sodium percarbonate, *tert*-butyl hydroperoxide, and cumene hydroperoxide were ineffective. See: Dubois, G.; Murphy, A.; Stack, T. D. P. *Org. Lett.* **2003**, *5*, 2469.

(11) Moiseev, A. G.; Neckers, D. C. *Synthesis* **2005**, 2901.

(12) For selected mechanistic studies, see: (a) Chen, K.; Costas, M.; Kim, J.; Tipton, A. K.; Que, L. *J. Am. Chem. Soc.* **2002**, *124*, 3026. (b) Quiñonero, D.; Musaev, D. G.; Morokuma, K. *Inorg. Chem.* **2003**, *42*, 8449. (c) Fujita, M.; Que, L. *Adv. Synth. Catal.* **2004**, *346*, 190. (d) Mairata i Payeras, A.; Ho, R. Y. N.; Fujita, M.; Que, L. *Chem.—Eur. J.* **2004**, *10*, 4944. (e) Bassan, A.; Blomberg, M. R. A.; Siegbahn, P. E. M.; Que, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 2939. (f) Quiñonero, D.; Morokuma, K.; Musaev, D. G.; Mas-Ballesté, R.; Que, L. *J. Am. Chem. Soc.* **2005**, *127*, 6548. (g) Bukowski, M. R.; Comba, P.; Lienke, A.; Limberg, C.; Lopez de Laorden, C.; Mas-Ballesté, R.; Merz, M.; Que, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3446. (h) Mas-Ballesté, R.; Costas, M.; van den Berg, T.; Que, L. *Chem.—Eur. J.* **2006**, *12*, 7489. (i) Duban, E. A.; Bryliakov, K. P.; Talsi, E. P. *Eur. J. Inorg. Chem.* **2007**, 852. (j) Bautz, J.; Comba, P.; Lopez de Laorden, C.; Menzel, M.; Rajaraman, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 8067. (k) Mas-Ballesté, R.; Que, L. *J. Am. Chem. Soc.* **2007**, *129*, 15964. (l) Comba, P.; Rajaraman, G. *Inorg. Chem.* **2008**, *47*, 78. (m) Company, A.; Feng, Y.; Güell, M.; Ribas, X.; Luis, J.; Que, L.; Costas, M. *Chem.—Eur. J.* **2009**, *15*, 3359. (n) Benet-Buchholz, J.; Comba, P.; Llobet, A.; Roeser, S.; Vadivelu, P.; Wadepohl, H.; Wiesner, S. *Dalton Trans.* **2009**, 5910. (o) Lyakin, O. Y.; Bryliakov, K. P.; Britovsek, G. J. P.; Talsi, E. P. *J. Am. Chem. Soc.* **2009**, *131*, 10798. (p) Li, F.; England, J.; Que, L. *J. Am. Chem. Soc.* **2010**, *132*, 2134.

(13) (a) Knof, U.; Zelewsky, A. v. *Angew. Chem., Int. Ed.* **1999**, *38*, 302. (b) Knight, P. D.; Scott, P. *Coord. Chem. Rev.* **2003**, *242*, 125.

(14) See the Supporting Information for another example.

(15) It has been reported that non-heme iron complexes may generate either nucleophilic or electrophilic intermediates upon treatment with peroxide-based oxidants. See: Fujita, M.; Costas, M.; Que, L. *QJ. Am. Chem. Soc.* **2003**, *125*, 9912.

(16) (a) Domagala, J. M.; Bach, R. D. *J. Am. Chem. Soc.* **1978**, *100*, 1605. (b) Domagala, J. M.; Bach, R. D. *J. Org. Chem.* **1984**, *49*, 4181. (c) Sankararaman, S.; Nesakumar, J. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3173.

(17) 3-Arylisoxazolidine derivatives show a variety of biological activities. For examples, see: (a) Olson, R. E.; et al. *J. Med. Chem.* **1999**, *42*, 1178. (b) Pruitt, J. R.; Pinto, D. J.; Estrella, M. J.; Bostrom, L. L.; Knabb, R. M.; Wong, P. C.; Wright, M. R.; Wexler, R. R. *Bioorg. Med. Chem.* **2000**, *10*, 685.(c) Burgey, C. S.; Nguyen, D. N.; Paone, D. V.; Potteiger, C. M.; Vacca, J. P. U.S. Pat. Appl. 2011/0003822 A1, Jan 6, 2011. (d) Mihara, J.; Murata, T.; Yamazaki, D.; Yoneta, Y.; Shibuya, K.; Shimojo, E.; Goergens, U. Pat. Appl. WO 2008/122375 A2, Oct 16, 2008.

(18) (a) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826. (b) Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.* **1982**, *23*, 3123.

(19) (a) Jäger, V.; Schwab, W.; Buss, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 601. (b) Schwab, W.; Jäger, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 603.

(20) Ito, S.; Sato, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2739.