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A Porphyrin-Inspired Iron Catalyst for Asymmetric Epoxidation of Electron-Deficient Olefins

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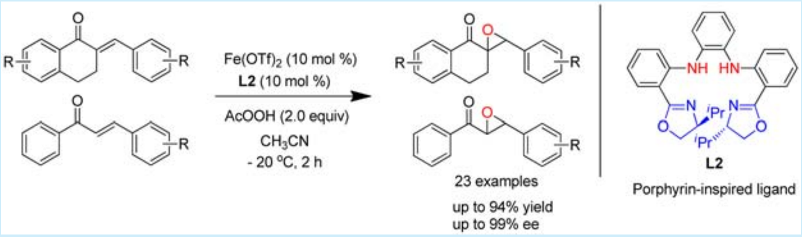
S *Supporting Information*

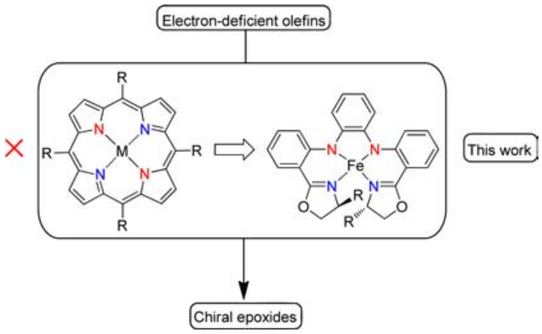


ABSTRACT: An in situ formed porphyrin-inspired iron complex that catalyzes asymmetric epoxidation of di- and trisubstituted enones is described. The reaction provides highly enantioenriched *α*,*β*-epoxyketones (up to 99% ee). The practical utility of the new catalyst system is demonstrated by the gram-scale synthesis of optically pure epoxide. Hammett analysis suggests that the transition state of the reaction is electron-demanding and the active oxidant is electrophilic.

The past decades have witnessed rapid progress in the asymmetric epoxidation of olefins with chiral organocatalysts[1] and metal-based catalysts.[2] Among existing catalytic approaches, iron-catalyzed asymmetric epoxidation should offer many remarkable advantages, as iron is abundant, cheap, and relatively nontoxic in comparison to other metals and shows variable oxidation states.[3] However, iron-catalyzed asymmetric epoxidations that can be refined to find application in the preparation of fine chemicals and pharmaceuticals remain scarce.[4] In view of toughening environmental concerns, numerous efforts have been dedicated to the development of iron-based biomimetic or bioinspired systems for asymmetric epoxidation owing to metalloenzyme-catalyzed reactions usually exhibiting high reactivity and operating under a green process.[5] Among them, asymmetric epoxidation based on iron porphyrins, which are the mimics of the cytochrome P450 active site, has been the most extensively studied. Since the initial success achieved in asymmetric epoxidation using an iron porphyrin catalyst by Groves in 1983, other catalytic systems based on iron porphyrins have also been developed and a high level of enantioselectivity for certain classes of electron-rich olefins such as styrene derivatives using an environmentally unfriendly oxidant has been achieved.[6] However, asymmetric epoxidation of the challenging electron-deficient olefins with iron porphyrins has not been reported until now.

We recently developed a new type of porphyrin-inspired N_4 ligands bearing chiral oxazoline moieties derived from a chiral amino alcohol that fulfilled the structural requirements of the porphyrin ligand in some way. The porphyrin-inspired ligands have been successfully applied in the manganese-catalyzed asymmetric epoxidation of electron-rich olefins and asymmetric sulfoxidation.[5d,7] Meanwhile, we demonstrated that the ligands possessed excellent tolerance for oxidation reactions. With this background in mind, it was envisioned that we could develop a highly enantioselective asymmetric epoxidation catalyst for electron-deficient olefins exploring the iron in combination with the porphyrin-inspired ligands (Scheme 1). Herein, we report an efficient and highly enantioselective epoxidation method of electron-deficient olefins by an in situ formed porphyrin-inspired chiral iron complex in high yields (up to 94%) with excellent enantioselectivities (up to 99% ee), as well as application of the method to the gram-scale synthesis of optically pure epoxide.

Scheme 1. Strategy of Asymmetric Epoxidation of Electron-Deficient Olefins



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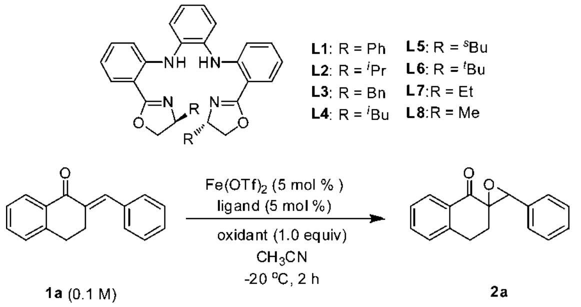
The development of a general and efficient strategy for asymmetric epoxidation of trisubstituted cyclic enones is highly valuable and desirable, as trisubstituted cyclic *α,β*-epoxyketones, which possess a chiral quaternary carbon center, are valuable and versatile ubiquitous structural motifs in organic synthesis and biologically active compounds.[4c,8] Therefore, we began our studies with trisubstituted cyclic enones **1a** as the model substrate to assay the best reaction conditions. To evaluate the ligands, the epoxidation of **1a** was initially performed in acetonitrile at −20 °C with the iron complexes generated in situ from 5 mol % Fe(OTf)$_2$ and 5 mol % ligand in the presence of *m*-CPBA (Table 1, entries 1−8) . To our delight, ligand **L2** was identified as the ligand being the most favorable in view of enantioselectivity and yield. Subsequently, the oxidant loading of *m*-CPBA was examined. We found that the best result was achieved upon addition of 2 equiv of *m*-CPBA (Table 1, entries 9 and 10). It is worthy of note that the enantioselectivity increased when the catalyst loading was raised to 10 mol % (Table 1, entry 11). Finally, the identity of the oxidant was investigated. When *m*-CPBA was replaced with H$_2$O$_2$ or *t*-BOOH, no desired product was obtained (Table 1, entries 12 and 13). Gratifyingly, using CH$_3$CO$_3$H as the oxidant led to further improvement in terms of enantioselectivity and yield (Table 1, entry 14).

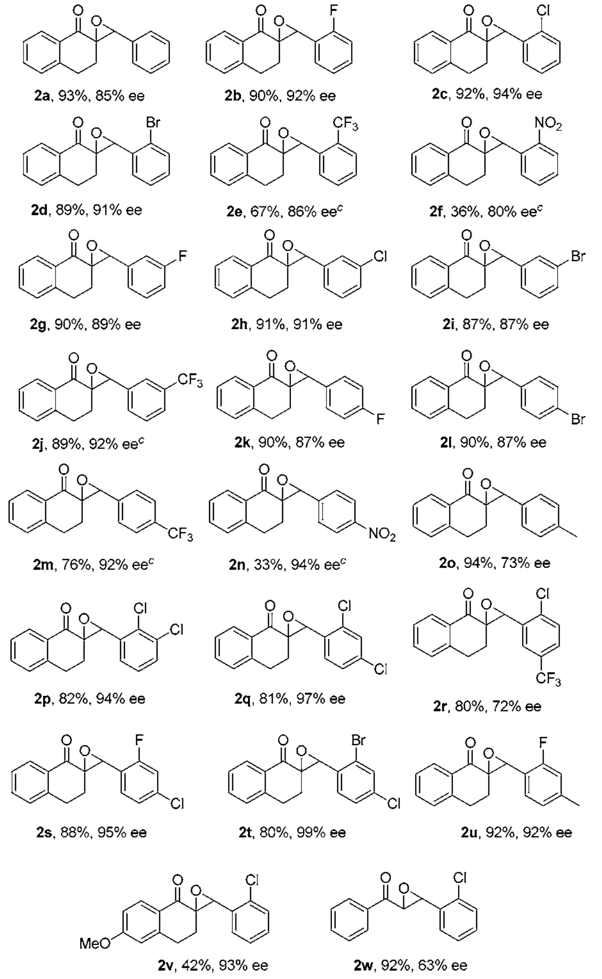
Table 1. Screening the Reaction Conditions



entry	ligand	oxidant	% yield[a]	% ee[b]
1	**L1**	*m*-CPBA	53	54
2	**L2**	*m*-CPBA	54	78
3	**L3**	*m*-CPBA	–	–
4	**L4**	*m*-CPBA	48	64
5	**L5**	*m*-CPBA	54	65
6	**L6**	*m*-CPBA	50	72
7	**L7**	*m*-CPBA	40	65
8	**L8**	*m*-CPBA	54	64
9[c]	**L2**	*m*-CPBA	82	79
10[d]	**L2**	*m*-CPBA	89	79
11[e]	**L2**	*m*-CPBA	90	82
12[f]	**L2**	H$_2$O$_2$	–	–
13[g]	**L2**	*t*-BuOOH	–	–
14[h]	**L2**	CH$_3$CO$_3$H	93	85

[a]Isolated yield. [b]Determined by chiral HPLC analysis. [c]*m*-CPBA (1.5 equiv). [d]*m*-CPBA (2.0 equiv). [e]*m*-CPBA (2.0 equiv), Fe(OTf)$_2$ (10 mol %), **L2** (10 mol %). [f]H$_2$O$_2$ (2.0 equiv), Fe(OTf)$_2$ (10 mol %), **L2** (10 mol %). [g]*t*-BuOOH (2.0 equiv), Fe(OTf)$_2$ (10 mol %), **L2** (10 mol %). [h]CH$_3$CO$_3$H (2.0 equiv), Fe(OTf)$_2$ (10 mol %), **L2** (10 mol %).

Scheme 2. Substrate Scope of Epoxidation[a,b]



2a, 93%, 85% ee
2b, 90%, 92% ee
2c, 92%, 94% ee
2d, 89%, 91% ee
2e, 67%, 86% ee[c]
2f, 36%, 80% ee[c]
2g, 90%, 89% ee
2h, 91%, 91% ee
2i, 87%, 87% ee
2j, 89%, 92% ee[c]
2k, 90%, 87% ee
2l, 90%, 87% ee
2m, 76%, 92% ee[c]
2n, 33%, 94% ee[c]
2o, 94%, 73% ee
2p, 82%, 94% ee
2q, 81%, 97% ee
2r, 80%, 72% ee
2s, 88%, 95% ee
2t, 80%, 99% ee
2u, 92%, 92% ee
2v, 42%, 93% ee
2w, 92%, 63% ee

[a]Reaction conditions: substrate (0.1 mmol), 30% CH$_3$CO$_3$H (0.2 mmol, diluted with 0.1 mL CH$_3$CN), Fe(OTf)$_2$ (10 mol %), **L2** (10 mol %), CH$_3$CN (1.5 mL), −20 °C, 2 h. [b] Isolated yield. The ee values were determined by chiral HPLC. [c] *m*-CPBA (0.2 mmol) was used as oxidant.

With the optimized conditions in hand, we next set out to explore the substrate scope using a variety of di- and trisubstituted enones (Scheme 2). Introducing a halogen substituent at the *ortho*-position of phenyl groups of the olefin side led to a significant increase in enantioselectivity relative to the *para*- and *meta*-position, probably because of steric hindrance which is favorable in controlling the enantioselectivity (Scheme 2, entries **2b**−**d** versus **2g**−**i**, **2k**, and **2l**). Presumably as a result of the electron effect, the substrates containing strong electron-withdrawing substituents such as nitro or trifluoromethyl groups at the *ortho*- and *para*-position resulted in a deleterious effect on the yield, albeit with good to excellent enantioselectivity (Scheme 2, entries **2e**, **2f**, **2m**, and **2n**). Interestingly, when there was an electron-withdrawing trifluoromethyl group at the *meta*-position, excellent enantioselectivity and yield were obtained (Scheme 2, entry **2j**). A substrate bearing methyl at the *para*-position gave the highest yield (Scheme 2, entry **2o**), whereas a substrate with a nitro group at the *para*-position led to the lowest one under identical conditions (Scheme 2, entry **2n**), which strongly suggested that the electronic properties of substrates played a crucial role in the yields of the asymmetric epoxidation. Encouraged by these findings, we turned our attention to the cyclic enones derivatives with two substituents on the phenyl rings. Gratifyingly, the ee values of the desired epoxides except **2r** were excellent (Scheme 2, entries **2p**−**v**). To extend the substrate scope further, we expected that the disubstituted enone derivative would also be epoxidized. Fortunately, the present epoxidation could also be successfully applied to a chalcone derivative, giving the corresponding epoxide in high yields with moderate enantioselectivity (Scheme 2, entry **2w**).

To probe the nature of active oxidant, competitive asymmetric epoxidations of *p*-substituted cyclic enones were conducted under optimized conditions. We found a good linear correlation between the $\log(k_X/k_H)$ and σ_p^+ with negative $\rho^+ = -0.52$ which indicated that the transition state of the reaction was electron-demanding and the active oxidant was electrophilic (Figure 1).[2n,9] The above results provided solid evidence against our catalyst system processing though a nucleophilic Weitz–Scheffer-type epoxidation mechanism.[10]

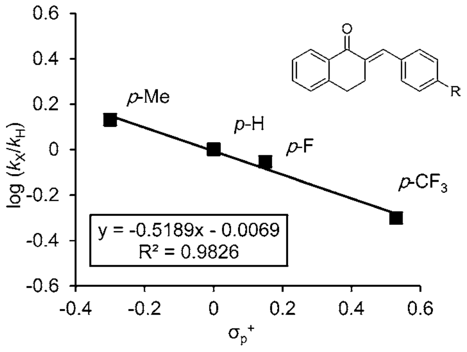
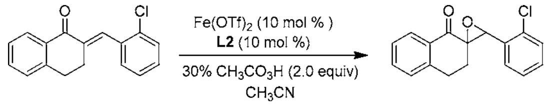


Figure 1. Hammett plots of $\log(k_X/k_H)$ vs σ_p^+ for the epoxidation of *para*-substituted cyclic enones.

To further evaluate the practical utility of the catalyst system, the epoxidation of cyclic enone **1c** was carried out on gram scale under the optimized conditions, and the desired product **2c** was furnished with 82% yield and 91% ee after a prolonged reaction time (Scheme 3).

Scheme 3. Gram-Scale Synthesis of Epoxide 2c

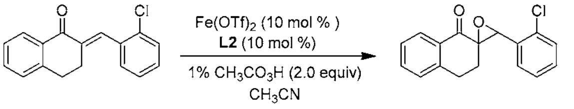


1c:1.0 g

2c: 82% yield, 91% ee

It is well-known that the primary difficulty in the use of peracetic acid as the oxidant is the extremely explosive nature of the compound. This hazard can be minimized or prevented by the use of a low or dilute concentration of peracetic acid. To investigate the influence of the concentration of peracetic acid on yield and enantioselectivity, the experiment was performed at 1% peracetic acid, affording the desired product **2c** in 84% yield and 94% ee (Scheme 4). The result proved that the reaction could be conducted at a low concentration of peracetic acid which made the whole procedure safe.

Scheme 4. Reaction under Low Concentration of Peracetic Acid



1c (0.1 M)

2c: 84% yield, 94% ee

In summary, we have successfully developed a highly efficient and general catalytic asymmetric epoxidation method that employs an inexpensive and easily available porphyrin-inspired chiral iron complex, allowing for the epoxidation of a wide variety of multisubstituted enones in excellent yields with ee values up to 99%. Hammett analysis confirmed that the active oxidant was electrophilic, and the practical utility of the catalyst system was demonstrated by the gram-scale synthesis of the optically active epoxide. In addition, good results were still maintained when a low concentration of peracetic acid was used in our catalyst system. Further studies on the precise mechanism and extension of the catalyst to other reactions are underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, compound characterization data, and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. (b) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497. (c) Juliá, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 929. (d) Carde, L.; Davies, H.; Geller, T. P.; Roberts, S. M. *Tetrahedron Lett.* **1999**, *40*, 5421. (e) Porter, M. J.; Skidmore, J. *Chem. Commun.* **2000**, 1215. (f) Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 6844. (g) Lattanzi, A. *Org. Lett.* **2005**, *7*, 2579. (h) Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964. (i) Yi, H.; Zou, G.; Li, Q.; Chen, Q.; Tang, J.; He, M.-y. *Tetrahedron Lett.* **2005**, *46*, 5665. (j) Lu, X.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 8134. (k) Wang, X.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6070. (l) Bondzic, B. P.; Urushima, T.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2010**, *12*, 5434. (m) Nagano, M.; Doi, M.; Kurihara, M.; Suemune, H.; Tanaka, M. *Org. Lett.* **2010**, *12*, 3564. (n) Palumbo, C.; Mazzeo, G.; Mazziotta, A.; Gambacorta, A.; Loreto, M. A.; Migliorini, A.; Superchi, S.; Tofani, D.; Gasperi, T. *Org. Lett.* **2011**, *13*, 6248. (o) Capobianco, A.; Russo, A.; Lattanzi, A.; Peluso, A. *Adv. Synth. Catal.* **2012**, *354*, 2789. (p) Wong, M.-K.; Ho, L.-M.; Zheng, Y.-S.; Ho, C.-Y.; Yang, D. *Org. Lett.* **2001**, *3*, 2587. (q) Kawai, H.; Okusu, S.; Yuan, Z.; Tokunaga, E.; Yamano, A.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 2221.

(2) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (c) Matsumoto, K.; Sawada, Y.; Saito, B.; Sakai, K.; Katsuki, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4935. (d) Sawada, Y.; Matsumoto, K.; Kondo, S.; Watanabe, H.; Ozawa, T.; Suzuki, K.; Saito, B.; Katsuki, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3478. (e) McGarrigle, E. M.; Gilheany, D. G. *Chem. Rev.* **2005**, *105*, 1563. (f) Enders, D.; Zhu, J.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1725. (g) Yu, H.-B.; Zheng, X.-F.; Lin, Z.-M.; Hu, Q.-S.; Huang, W.-S.;

Pu, L. *J. Org. Chem.* **1999**, *64*, 8149. (h) Elston, C. L.; Jackson, R. F.; MacDonald, S. J.; Murray, P. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 410. (i) Wu, M.; Wang, B.; Wang, S.; Xia, C.; Sun, W. *Org. Lett.* **2009**, *11*, 3622. (j) Ottenbacher, R. V.; Bryliakov, K. P.; Talsi, E. P. *Adv. Synth. Catal.* **2011**, *353*, 885. (k) Wang, B.; Miao, C.; Wang, S.; Xia, C.; Sun, W. *Chem.—Eur. J.* **2012**, *18*, 6750. (l) Berkessel, A.; Guenther, T.; Wang, Q.; Neudörfl, J. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 8467. (m) Cussó, O.; Garcia-Bosch, I.; Font, D.; Ribas, X.; Lloret-Fillol, J.; Costas, M. *Org. Lett.* **2013**, *15*, 6158. (n) Ottenbacher, R. V.; Samsonenko, D. G.; Talsi, E. P.; Bryliakov, K. P. *ACS Catal.* **2014**, *4*, 1599. (o) Liao, S.; List, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 628. (p) Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9474. (q) Wang, X.; Shi, L.; Li, M.; Ding, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6362. (r) Chu, Y.; Liu, X.; Li, W.; Hu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2012**, *3*, 1996. (s) Qian, Q.; Tan, Y.; Zhao, B.; Feng, T.; Shen, Q.; Yao, Y. *Org. Lett.* **2014**, *16*, 4516. (t) Wang, C.; Yamamoto, H. *J. Am. Chem. Soc.* **2014**, *136*, 1222. (u) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345.

(3) (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.

(4) (a) Gelalcha, F. G.; Bitterlich, B.; Anilkumar, G.; Tse, M. K.; Beller, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7293. (b) Nishikawa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2011**, *133*, 8432. (c) Wang, B.; Wang, S.; Xia, C.; Sun, W. *Chem.—Eur. J.* **2012**, *18*, 7332. (d) Cussó, O.; Garcia-Bosch, I.; Ribas, X.; Lloret-Fillol, J.; Costas, M. *J. Am. Chem. Soc.* **2013**, *135*, 14871. (e) Wang, X.; Miao, C.; Wang, S.; Xia, C.; Sun, W. *ChemCatChem* **2013**, *5*, 2489. (f) Niwa, T.; Nakada, M. *J. Am. Chem. Soc.* **2012**, *134*, 13538. (g) Luo, L.; Yamamoto, H. *Eur. J. Org. Chem.* **2014**, *35*, 7803.

(5) (a) Que, L.; Tolman, W. B. *Nature* **2008**, *455*, 333. (b) Murphy, A.; Dubois, G.; Stack, T. *J. Am. Chem. Soc.* **2003**, *125*, 5250. (c) Nehru, K.; Kim, S. J.; Kim, I. Y.; Seo, M. S.; Kim, Y.; Kim, S.-J.; Kim, J.; Nam, W. *Chem. Commun.* **2007**, 4623. (d) Dai, W.; Li, J.; Li, G.; Yang, H.; Wang, L.; Gao, S. *Org. Lett.* **2013**, *15*, 4138. (e) Yeung, H.-L.; Sham, K.-C.; Tsang, C.-S.; Lau, T.-C.; Kwong, H.-L. *Chem. Commun.* **2008**, 3801.

(6) (a) Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791. (b) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628. (c) Collman, J. P.; Zhang, X.; Lee, V. J.; Brauman, J. I. *J. Chem. Soc., Chem. Commun.* **1992**, 1647. (d) Mansuy, D.; Battioni, P.; Renaud, J.-P.; Guerin, P. *J. Chem. Soc., Chem. Commun.* **1985**, 155. (e) Rose, E.; Ren, Q. Z.; Andrioletti, B. *Chem.—Eur. J.* **2004**, *10*, 224. (f) Collman, J. P.; Wang, Z.; Straumanis, A.; Quelquejeu, M.; Rose, E. *J. Am. Chem. Soc.* **1999**, *121*, 460.

(7) (a) Dai, W.; Li, J.; Chen, B.; Li, G.; Lv, Y.; Wang, L.; Gao, S. *Org. Lett.* **2013**, *15*, 5658. (b) Dai, W.; Li, G.; Wang, L.; Chen, B.; Shang, S.; Lv, Y.; Gao, S. *RSC Adv.* **2014**, *4*, 46545. (c) Dai, W.; Shang, S.; Chen, B.; Li, G.; Wang, L.; Ren, L.; Gao, S. *J. Org. Chem.* **2014**, *79*, 6688.

(8) (a) Wang, B.; Tu, Y. Q. *Acc. Chem. Res.* **2011**, *44*, 1207. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.

(9) Garcia-Bosch, I.; Ribas, X.; Costas, M. *Adv. Synth. Catal.* **2009**, *351*, 348.

(10) (a) Diez, D.; Nunez, M. G.; Anton, A. B.; García, P.; Moro, R.; Garrido, N.; Marcos, I. S.; Basabe, P.; Urones, J. G. *Curr. Org. Synth.* **2008**, *5*, 186. (b) Christian, C. F.; Takeya, T.; Szymanski, M. J.; Singleton, D. A. *J. Org. Chem.* **2007**, *72*, 6183. (c) Kelly, D. R.; Roberts, S. M. *Pept. Sci.* **2006**, *84*, 74.