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Asymmetric Epoxidation of Alkenes Catalyzed by a Porphyrin-Inspired Manganese Complex

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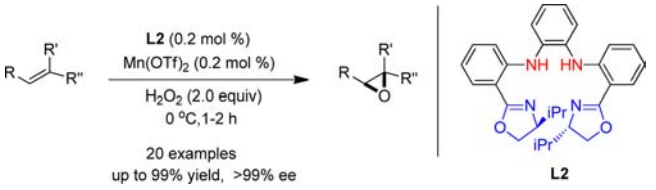
ABSTRACT



A novel strategy for catalytic asymmetric epoxidation of a wide variety of olefins by a porphyrin-inspired chiral manganese complex using H_2O_2 as a terminal oxidant in excellent yield with up to greater than 99% ee has been successfully developed.

Optically active epoxides are without question one of the most valuable and versatile building blocks in organic synthesis.[1] Ever since the pioneering work of the Sharpless epoxidation of allylic alcohols and the Katsuki–Jacobsen epoxidation of unfunctionalized alkenes, there has been great progress in asymmetric epoxidation (AE) over the past decades.[2] Despite these advances, the demand for less expensive, environmentally more benign catalytic systems for the AE of olefins is urgently needed and of great significance. Therefore, considerable efforts have been directed toward the development of bioinspired or biomimetic AE catalysts mimicking the reactivity of natural metalloenzymes owing to metalloenzyme-catalyzed oxidations often exhibiting exquisite substrate specificity and operating under mild conditions through inherently green processes in recent years.[1,3] Metalloporphyrins as P450 enzyme mimics have been shown to be a class of versatile catalysts.[4] Groves and Meyers reported the first AE catalyzed by a chiral iron–porphyrin complex in 1983; after that, numerous efforts have been dedicated to synthesizing various chiral porphyrins as potential asymmetric epoxidation catalysts.[5] To date, however, the catalytic AE of olefins based on

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metalloporphyrins has not been developed into a practical methodology for preparation of fine chemicals and pharmaceutically important small molecules. First, this unfortunate situation is largely attributed to the formidable challenges associated with the synthesis of chiral porphyrins and the highly planar structure of porphyrin ligands that prohibits the introduction of chirality around the metal center. In addition, the oxidant is more often iodosylbenzene and 2,6-dichloropyridine *N*-oxide, which are not considered environmentally friendly.

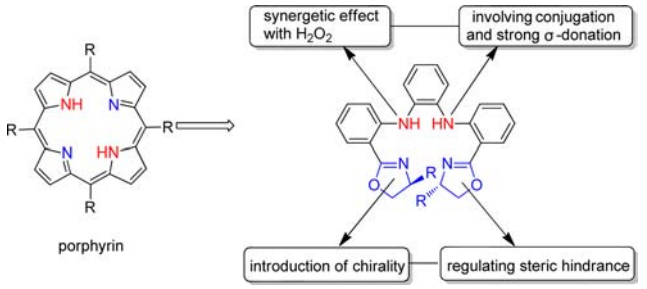

Figure 1. Design strategy for chiral ligand.

Recently, in view of the difficulty in the synthesis of chiral porphyrin, Niwa and Nakada developed an easily prepared 1,8-(bisoxazolyl)-carbazole iron complex with porphyrin-like properties for the AE of *trans*-stilbene derivatives applying iodosobenzene in the presence of sodium tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF).[6] Unfortunately, the types of substrates are limited, and the oxidant is environmentally unfriendly. With this background in mind, it was envisioned that we could develop a new alternative to porphyrins that fulfills structural requirements of the porphyrins in some way, which possesses a long conjugation and strong donor moieties and can also obtain good results for the AE of a relatively wide range of substrates using an environmentally benign oxidant. To our delight, we designed and synthesized a totally new type of tetradentate nitrogen based ligands that can be simply prepared, are structurally diverse, and are sterically tunable as well as allows easy introduction of chirality (Figure 1). The tetradentate ligands have relatively long conjugation and two N−H moieties that exhibit strong σ-donation. Moreover, Katsuki and co-workers disclosed that N−H groups in the organometallic catalyst have a significant synergetic effect in the epoxidation of olefins with hydrogen peroxide as the terminal oxidant in terms of activity and enantioselectivity.[7] In addition, the enantioselective introduction and steric hindrance could be regulated by the chiral oxazolines, which can be synthesized from commercially available α or β amino acids. Herein, we report a general AE method of olefins by a porphyrin-inspired chiral manganese complex using H_2O_2 as the terminal oxidant in high yields with excellent enantioselectivities (up to greater than 99% ee), as well as application of the method to the gram-scale synthesis of optically pure epoxide and chiral drug *S*-Levcromakalim.

For our investigations, we chose chromene **1a** as the model substrate because its product is of potential value as a pharmaceutical intermediate.[8] Initially, when **1a** was reacted with 0.2 mol % iron metals and ligand **L2** in the presence of H_2O_2/AcOH in acetonitrile, no epoxidation was observed (Table 1, entries 1 and 2). By replacing iron metals with $MnCl_2$, the epoxidation resulted in only low conversion of the starting material (Table 1, entry 3). Gratifyingly, using $Mn(OTf)_2$ led to a significant improvement in terms of reactivity and enantioselectivity (95% yield, 95% ee; Table 1, entry 5). Besides $Mn(OTf)_2$, $Mn(OAc)_2$ could also be used, although the yield was slightly lower than that obtained by using $Mn(OTf)_2$ (Table 1, entry 4). After testing the loading of acetic acid, we identified that the best results were achieved upon addition of acetic acid (5.0 equiv) with respect to the substrate (Table 1, entries 5−7). Preliminary results indicated that the reaction temperature had certain effects on the yield and enantioselectivity (Table 1, entries 5, 8, and 9). The ee values could be promoted when the temperature was decreased to 0 °C. The ee values remained the same by further lowering the temperature to −20 °C. Subsequently, examination of various ligands showed that **L2** was the best choice regarding yield and enantioselectivity under the optimized conditions (Table 1, entries 5 and 10−13). Finally, the catalyst loading was successfully lowered to 0.1 mol % with only a slight decrease in the yield (Table 1, entry 14).

With the optimized conditions in hand, we turned our attention to examining the scope of substrates using the $Mn(OTf)_2$−**L2** complex (Table 2). As expected, a wide variety of olefins could be efficiently epoxidized efficiently within short reaction times, providing the corresponding chromene derivatives (entries 1−15), indene (entry 16), 1,2-dihydronaphthalene (entry 17), and *trans*-stilbene epoxides (entry 18) in high yields and excellent enantioselectivities. It is noteworthy that various electron-withdrawing

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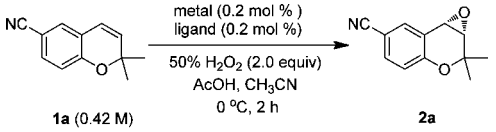
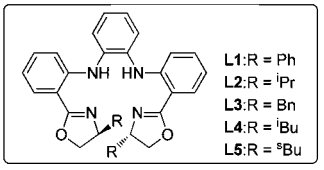
Table 1. Screening of Reaction Conditions





entry	metal	ligand	AcOH [equiv]	% yield[a]	% ee[b]
1	$FeCl_2$	**L2**	5	–	–
2	$Fe(OTf)_2$	**L2**	5	–	–
3	$MnCl_2$	**L2**	5	<5	–
4	$Mn(OAc)_2$	**L2**	5	78	94
5	$Mn(OTf)_2$	**L2**	5	95	95
6	$Mn(OTf)_2$	**L2**	3	32	84
7	$Mn(OTf)_2$	**L2**	6	88	94
8[c]	$Mn(OTf)_2$	**L2**	5	89	94
9[d]	$Mn(OTf)_2$	**L2**	5	92	90
10	$Mn(OTf)_2$	**L1**	5	15	84
11	$Mn(OTf)_2$	**L3**	5	72	92
12	$Mn(OTf)_2$	**L4**	5	30	88
13	$Mn(OTf)_2$	**L5**	5	66	92
14[e]	$Mn(OTf)_2$	**L2**	5	89	92

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] −20 °C. [d] 30 °C. [e] $Mn(OTf)_2$ (0.1 mol %), **L2** (0.1 mol %), 3 h.

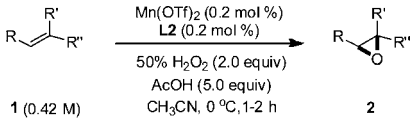
and -donating substituents such as halogen, nitro, nitrile, ester, and hydroxymethyl were equally well tolerated. In addition, a good yield and moderate enantioselectivity were also obtained for the reaction of terminal olefin (entry 19).

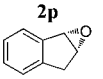
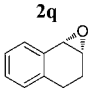
Gratifyingly, a moderate yield and enantioselectivity could also be obtained for the reaction of electron-deficient 4-methoxychalcone (Table 2, entry 20). With this result in hand, we performed an intermolecular competition reaction between **1a** and **3a** to determine the nature of the active oxidant (Scheme 1). It was found that an electron-rich alkene showed an obvious advantage compared to an electron-deficient compound in yield and enantioselectivity, suggesting that the nature of the active oxidant is possibly electrophilic. However, more work is required to determine the mechanistic aspect.

To further evaluate the practical utility, the epoxidation of chromene **1a** was carried out on gram scale, and the desired product was furnished with 92% yield and 94% ee (Scheme 2). Moreover, the ligand **L2** could be recovered via procedures of extraction and silica gel column chromatography, respectively. The absolute configuration of epoxide **2a** was determined to be *S*,*S* by comparison of the

(9) (a) Hashihayata, T.; Ito, Y.; Katsuki, T. *Tetrahedron* **1997**, *53*, 9541–9552. (b) Liao, S.; List, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 628–631.

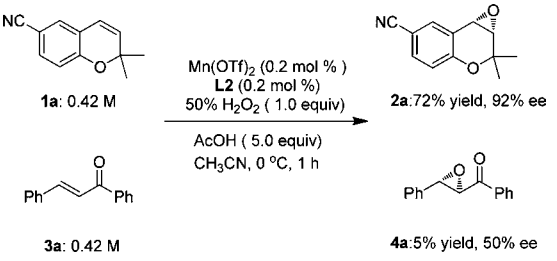
Table 2. Substrate Scope of Epoxidation



entry	alkene	product	% yield[a]	% ee[b]
1	R = CN (**1b**)	**2b**	95	95
2	R = Cl (**1c**)	**2c**	93	96
3	R = Br (**1d**)	**2d**	90	96
4	R = NO_2 (**1e**)	**2e**	93	94
5	R = COOMe (**1f**)	**2f**	95	96
6	R = Ph (**1g**)	**2g**	98	94
7	R = CH_2OH (**1h**)	**2h**	96	>99
8	R = NHAc (**1i**)	**2i**	90	95
9	7-NO_2 (**1j**)	**2j**	91	92
10	R = CN (**1k**)	**2k**	98	90
11	R = Br (**1l**)	**2l**	91	94
12	R = NO_2 (**1m**)	**2m**	92	92
13	R = COOMe (**1n**)	**2n**	97	90
14	R = Ph (**1o**)	**2o**	99	96
15	R = NHAc (**1p**)	**2p**	99	98
16		 **2q**	93	84
17		 **2r**	99	96
18	R = Ph	**2t**	95	92
19	R = H		98	47
20	R = 4-MeO C_6H_4CO	**2u**	62	56

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

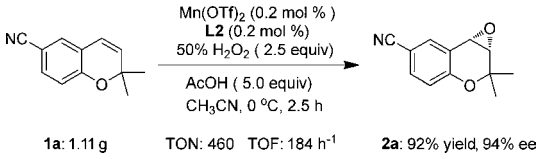
Scheme 1. Competitive Experiment between **1a** and **3a**



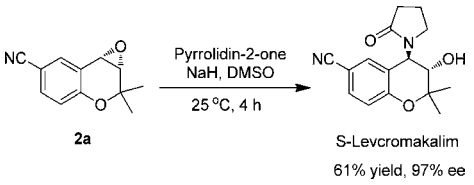
HPLC retention times and optical rotation with data reported in literature.[9]

Finally, to broaden the application of our methodology, we focused on the gram-scale synthesis of an antihypertensive drug *S*-Levcromakalim (Scheme 3). Treatment of the (*S*,*S*)-epoxidate **2a** with pyrrolidin-2-one under

Scheme 2. Gram-Scale Synthesis of Epoxide **2a**



Scheme 3. Gram-Scale Synthesis of the Chiral Drug *S*-Levcromakalim



the conditions reported in the literature yielded the *S*-Levcromakalim with up to 97% ee.[10]

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In summary, we have successfully developed a highly efficient and general catalytic AE method that employs a low loading of an inexpensive and easily prepared porphyrin-inspired chiral manganese complex and H_2O_2, allowing for general epoxidation of a wide variety of olefins in excellent yield with ee values up to greater than 99%. To the best of our knowledge, this is the first example of a porphyrin-inspired system for AE with H_2O_2 under environmentally friendly and mild conditions. Moreover, this work provides a new strategy for designing ligand-based catalysts, which play one of the central roles in homogeneous catalysis. Mechanistic study and extension of the strategy to other reactions are in progress.

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

The authors declare no competing financial interest.