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Asymmetric Oxidation Catalysis by a Porphyrin-Inspired Manganese Complex: Highly Enantioselective Sulfoxidation with a Wide Substrate Scope

Wen Dai,[†,‡,§] Jun Li,[†,‡] Bo Chen,[†,‡,§] Guosong Li,[†,‡] Ying Lv,[†,‡] Lianyue Wang,[†,‡] and Shuang Gao*[,†,‡]

Dalian Institute of Chemical Physics, the Chinese Academy of Sciences, Dalian, 116023, People's Republic of China, Dalian National Laboratory for Clean Energy, People's Republic of China, and University of Chinese Academy of Sciences, Beijing 100049, People's Republic of China

sgao@dicp.ac.cn

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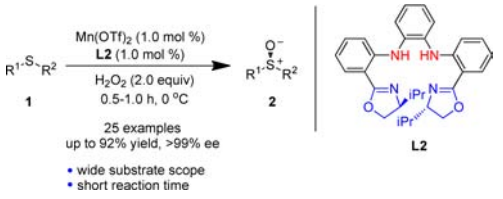
ABSTRACT



The first genuinely promising porphyrin-inspired manganese-catalyzed asymmetric sulfoxidation method using hydrogen peroxide has been successfully developed, allowing for rapidly oxidizing (0.5−1.0 h) a wide variety of sulfides in high yields with excellent enantioselectivities (up to >99% ee).

Optically pure sulfoxides are extremely useful versatile building blocks and chiral auxiliaries in organic synthesis.[1] They have also been extensively applied in constituting many bioactive compounds, including several marketed pharmaceuticals such as modafinil, sulindac, and esomeprazole.[2] During the past few decades, intense effort has been devoted to the development of various synthetic methods toward enantioenriched sulfoxides.[3] Among the available approaches developed, it is widely appreciated that the asymmetric sulfoxidation is the most powerful and reliable route. Since the initial breakthrough achieved in asymmetric sulfide oxidation using modified Sharpless epoxidation catalysts by Kagan in 1984,[4] other catalytic systems based on titanium,[5] vanadium,[6] iron,[7] aluminum,[8] and copper[9] have also been developed; a high level enantioselectivity for certain classes of sulfides such as simple aryl alkyl sulfides has been achieved.

[†] Dalian Institute of Chemical Physics.
[‡] Dalian National Laboratory for Clean Energy.
[§] University of Chinese Academy of Sciences.

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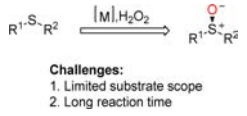
However, asymmetric oxidation of the challenging sulfides, e.g., those with sterically hindered, long or branched alkyl substituents, has been slow to develop, despite the broad pharmaceutical and synthetic utility of these types of enantiopure sulfoxides. In addition, each system has obvious limitations that include relatively harsh reaction conditions, long reaction times, or expensive catalysts. Consequently, the discovery of a highly efficient and practical catalytic method that enables enantioselective oxidation of sulfides remains an attractive goal (Scheme 1).

Scheme 1. Challenges in Asymmetric Sulfoxidation



Manganese catalysts have been widely and successfully applied in asymmetric epoxidation.[10] However, Mn-catalyzed asymmetric sulfoxidation has largely been neglected. The research groups of Jacobsen,[11] Katsuki,[12] Fontecave,[13] Golchoubian,[14] and Halterman[15] have all used a Mn-based system for asymmetrically oxidizing sulfides, but with limited success. Recently, we reported easily prepared and structurally diverse porphyrin-inspired chiral ligands for asymmetric epoxidation in our laboratory, and we demonstrated that the new N-containing ligands exhibit excellent tolerance for oxidation reactions and efficiently induce high enantioselectivity.[10d] With this background in mind, it was envisioned that we could develop a highly enantioselective asymmetric sulfoxidation catalyst system exploring the manganese in combination with the porphyin-inspired ligands (Scheme 2). Herein, we report the first genuinely promising porphyrin-inspired Mn-catalyzed asymmetric sulfoxidation method using hydrogen peroxide, allowing for rapidly (0.5−1.0 h) oxidizing a wide variety of sulfides in high yields with excellent enantioselectivities (up to >99% ee).

(8) For aluminum-catalyzed oxidation of sulfides, see: (a) Yamaguchi, T.; Matsumoto, K.; Saito, B.; Katsuki, T. *Angew. Chem.* **2007**, *119*, 4813. (b) Fujisaki, J.; Matsumoto, K.; Matsumoto, K.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *133*, 56. (c) Matsumoto, K.; Yamaguchi, T.; Katsuki, T. *Chem. Commun.* **2008**, 1704.

(9) For copper-catalyzed oxidation of sulfides, see: (a) O'Mahony, G. E.; Ford, A.; Maguire, A. R. *J. Org. Chem.* **2012**, *77*, 3288. (b) Kelly, P.; Lawrence, S. E.; Maguire, A. R. *Synlett* **2007**, *2007*, 1501.

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(14) Hosseinpoor, F.; Golchoubian, H. *Tetrahedron Lett.* **2006**, *47*, 5195.

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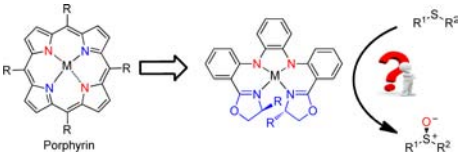
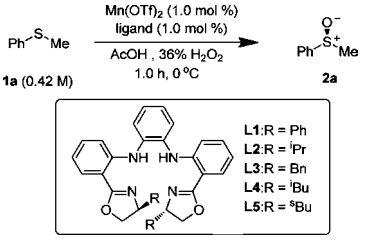
Thus the antiulcer drug esomeprazole was obtained on gram scale through the newly developed asymmetric sulfoxidation reaction. Notably, besides the direct asymmetric sulfoxidation, the oxidative kinetic resolution of omeprazole provides an alternative approach for the synthesis of esomeprazole, which further underscores the practical utility of our methodology.

Scheme 2. Strategy for the Development of Asymmetric Sulfoxidation Method



First, we examined the asymmetric oxidation of thioanisole with 1.0 equiv of 36% hydrogen peroxide in the presence of $Mn(OTf)_2$ and various ligands in acetonitrile at 35 °C and found that the structure of the ligands influenced their catalytic and chiral inducing abilities. The reaction with ligand **L2** was the best choice regarding yield and enantioselectivity (Table 1, entries 1−5). When 1.5 equiv of hydrogen peroxide was used, the yield increased to 90% (Table 1, entry 6). Preliminary results indicated that the

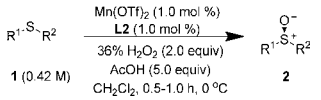
Table 1. Screening of Reaction Conditions

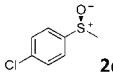
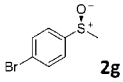
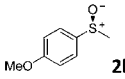
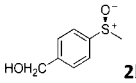
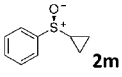
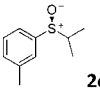
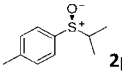
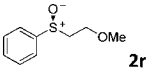
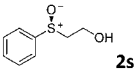
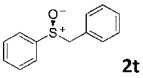
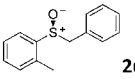
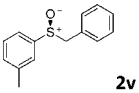
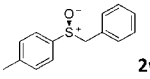
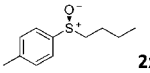
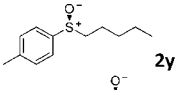


entry	solvent	ligand	H_2O_2 (equiv)	AcOH (equiv)	yield (%)[a]	ee (%)[b]
1[c]	CH_3CN	**L1**	1	5	45	56
2[c]	CH_3CN	**L2**	1	5	79	60
3[c]	CH_3CN	**L3**	1	5	76	58
4[c]	CH_3CN	**L4**	1	5	66	40
5[c]	CH_3CN	**L5**	1	5	76	56
6[c]	CH_3CN	**L2**	1.5	5	90	52
7	CH_3CN	**L2**	1.5	5	92	66
8	MeOH	**L2**	1.5	5	97	66
9	CH_2Cl_2	**L2**	1.5	5	96	74
10	CH_2Cl_2	**L2**	1.5	4	76	68
11	CH_2Cl_2	**L2**	1.5	6	86	79
12	THF	**L2**	1.5	5	<5	–
13	CCl_4	**L2**	1.5	5	<5	–
14	toluene	**L2**	1.5	5	10	0
15	cyclohexane	**L2**	1.5	5	12	0
16	dioxane	**L2**	1.5	5	<5	–
17	*n*-hexane	**L2**	1.5	5	<5	–
18	CH_2Cl_2	**L2**	2	5	82	97

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] Run at 35 °C.

Table 2. Substrate Scope of Asymmetric Sulfoxidation



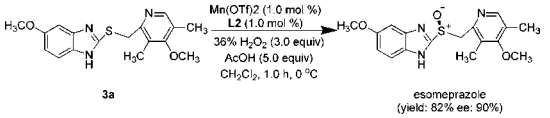
entry	product	yield (%)[a]	ee (%)[b]
1	 **2a**	82	97 (*R*)[c]
2	 **2b**	79	92 (*R*)[c]
3	 **2c**	82	97 (*R*)[c]
4	 **2d**	74	>99 (*R*)[c]
5	 **2e**	84	>99 (*R*)[c]
6	 **2f**	80	>99 (*R*)[c]
7	 **2g**	77	>99 (*R*)[c]
8	 **2h**	69	95 (*R*)[c]
9	 **2i**	72	>99 (*R*)[c]
10	 **2j**	80	>99(*R*)[c]
11	 **2k**	81	98(*R*)[c]
12	 **2l**	78	>99(*R*)[c]
13	 **2m**	74	91 (*R*)[c]
14	 **2n**	86	97 (*R*)[c]
15	 **2o**	92	>99 (*R*)[c]
16	 **2p**	84	94 (*R*)[c]
17	 **2q**	81	>99 (*R*)[c]
18	 **2r**	79	>99 (*R*)[c]
19	 **2s**	82	>99 (*R*)[c]
20	 **2t**	84	>99 (*R*)[c]
21	 **2u**	86	>99 (*R*)[c]
22	 **2v**	88	>99 (*R*)[c]
23	 **2w**	81	>99 (*R*)[c]
24	 **2x**	82	97 (*R*)[c]
25	 **2y**	76	87 (*R*)[c]
26	 R = dodecyl **2ab**	88	33 (*R*)[c]

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] Assigned by HPLC elution order with know literature data (see SI for details).

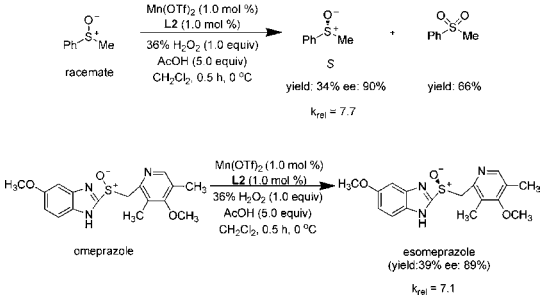
reaction temperature had a significant effect on the enantioselectivity. The ee values could be promoted when the temperature was decreased to 0 °C (Table 1, entry 7). Among the solvents examined, dichloromethane gave the desired sulfoxide in the highest yield with excellent enantioselectivity (96% yield, 74% ee; Table 1, entries 8, 9 and 12−17). After testing the loading of acetic acid, the best results were achieved upon addition of acetic acid (5.0 equiv) with respect to the substrate (Table 1, entries 9−11) Gratifyingly, the ee values improved significantly with a slight decrease in the yield by the use of 2.0 equiv of hydrogen peroxide (82% yield, 97% ee; Table 1, entry 18). This result might be attributed to the oxidative kinetic resolution process. Benzoic acid and heptanoic acid were also found to be a suitable additive for this reaction, although a slightly lower yield was observed (see the Supporting Information (SI)).

Having identified the optimized conditions, the scope of the asymmetric sulfoxidation was investigated. As shown in Table 2, a variety of aryl methyl sulfides could be efficiently converted into the corresponding sulfoxides within a short time in high yields with excellent enantioselectivities (entries 1−12). The high yield and excellent enantioselectivity were preserved irrespective of the electronic

Scheme 3. Gram-Scale Synthesis of Esomeprazole



Scheme 4. Oxidative Kinetic Resolution of Racemic Methyl Phenyl Sulfoxide and Omeprazole



nature and position of the substituent on the aromatic ring. It is noteworthy that sulfides with branched or longer alkyl groups instead of methyl could also be oxidized in good yields with generally excellent enantioselectivities (entries 24, 25 and 13−17). Good yields and excellent enantioselectivities could be achieved even for the methoxyethyl sulfide **2r** and hydroxyethyl sulfides **2s** (entries 18 and 19). Gratifyingly, the enantioselectivity obtained with sterically hindered aryl benzyl sulfides was unprecedented and remarkable (>99% ee, entries 20−23). In addition, a good yield and moderate enantioselectivity were also obtained for an aryl alkyl sulfide (entry 26).

Esomeprazole is a proton pump inhibitor for the treatment of gastresophageal reflux disease. It should be noted that titanium mediated sulfoxidation has been developed to prepare esomeprazole.[16] To further evaluate the practical utility of our methodology, we focused our attention on the gram scale synthesis of esomeprazole. Treatment of **3a** which is the key intermediate for the formal synthesis of the esomeprazole under the optimized conditions furnished the esomeprazole (*S*)-enantiomer in 82% yield with up to 90% ee (Scheme 3).

As already noted, there existed a kinetic resolution process in the current system. In view of this aspect, we performed an experiment under the optimized conditions using racemic methyl phenyl sulfoxide and found that the oxidation of the (*R*)-enantiomer was obviously preferential to the (*S*)-enantiomer with a relative ratio of 7.7. To broaden the application of our methodology in oxidative kinetic resolution, we synthesized the esomeprazole by the kinetic resolution of omeprazole. The reaction was carried out under the optimized conditions and furnished the desired product in 39% yield with up to 89% ee (Scheme 4).

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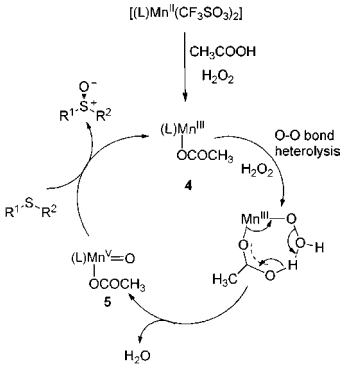
Scheme 5. Proposed Catalytic Cycle



Although the precise reaction mechanism is not entirely clear, we proposed a possible catalytic cycle based on our work and the pertinent literature (Scheme 5).[17] The (L)Mn(II) is initially converted to the intermediate **4**. Then the active species Mn(V)-oxo complex **5** is formed by the heterolysis of the O−O bond of the intermediate **4**. The active species **5** oxidizes sulfides to corresponding sulfoxides along with the formation of intermediate **4**.

In summary, we have successfully achieved a highly enantioselective asymmetric sulfoxidation by a low loading of a readily available porphyrin-inspired manganese complex and hydrogen peroxide within a short time (0.5−1.0 h), thus allowing for general sulfoxidation of a wide range of substrates in good yields with remarkable enantioselectivities (up to >99% ee). The elucidation of the precise reaction mechanism and extension of the system to other reactions are proceeding in our laboratory.

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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.