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Oxidative kinetic resolution of heterocyclic sulfoxides with a porphyrin-inspired manganese complex by hydrogen peroxide

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ABSTRACT

We have successfully reported here the low loading porphyrin-inspired high-valent manganese (IV)-oxo complex was applied in oxidative kinetic resolution (OKR) of racemic heterocyclic sulfoxides using the environmentally benign hydrogen peroxide for the first time. This approach allows for rapid OKR (0.5 h) of a variety of racemic sulfoxides (including pyridine, pyrimidine, pyrazine, thiazole, benzothiazole, thiophene) in excellent enantioselectivity (up to > 99% ee), simultaneously generating the corresponding sulfones in high yield (up to 80%). The catalytic system also showed an unexceptionable chemoselectivity for the sulfoxide substrates with hydroxyl groups in which only the sulfoxide group was oxidized. The practical utility of the method has been demonstrated in the OKR of gram-scale sulfoxides.

Introduction

The nonracemic sulfoxides are extensively used as chiral auxiliaries, ligands and intermediates in modern organic synthesis chemistry and valuable well-marketed pharmaceutical (e.g., esomeprazole, modafinil).[1] Therefore, the efficient synthesis of enantiopure sulfoxides have aroused great interest to numerous chemists.[2] Although the synthesis of chiral sulfoxides is mainly carried out through the asymmetric oxidation of thioether since the initial breakthrough completed in asymmetric thioether oxidation by the groups of Kagan and Modena in 1984,[3] it is a high research value how to convert racemic sulfoxides to optically pure sulfoxides because the synthesis of the racemic sulfoxides is becoming increasingly concise and can be purchased in lower prices.[4] The tiny sulfones which has wide industrial utility were often found to form in the most of the process of conventional asymmetric oxidation of thioether.[5] Sulfone moieties are widely used in medicine (e.g., bicalutamide, eletriptan, and Vioxx), plastics, herbicides, basic organic synthesis and other industries.[6] To date, the method of synthesis of sulfones is really scanty except sulfides directly oxidized into sulfones in organic synthesis.[7] And the oxidative kinetic resolution (OKR) can be a perfect method to be used for obtaining both chiral sulfoxides and sulfones from the conversion of racemic sulfoxide. So it is a great of significance to explore a highly efficient method of OKR of racemic sulfoxides to acquire high ee value of sulfoxides and high yield of sulfones. To the best of our knowledge, several cases of the OKR of racemic sulfoxides in the literature involve metal-salen complex (e.g. titanium,[1f] vanadium,[8] iron,[9] aluminum,[10] and copper[11]) with hydrogen peroxide have been reported. The optical purity of aryl alkyl sulfoxides up to >99% ee have been achieved (such as Maguire,[12] Zeng and Zhao[13] and Chan[14]). But the above catalytic systems have apparent disadvantages, including limited substrate scope or long reaction times (Scheme 1). And the existing report mostly focused on the OKR of aromatic sulfoxides, the OKR of heterocyclic sulfoxides have not been reported yet. As we all know, the sulfoxide substances with heteroatoms are more difficult to be carried out in a electrophilic reaction. Therefore, to develop a efficient catalytic system for the OKR of heterocyclic sulfoxides is still an attractive target.

We have developed a porphyrin-inspired manganese complexes with hydrogen peroxide way to conduct catalytic oxidation of sulfide to chiral sulfoxide.[15] We found a oxidation kinetic resolution process should exist in the oxidation reaction. Here we reported a high-efficiency method of OKR involves porphyrin-inspired manganese complexes with hydrogen peroxide to applicate in the desymmetrization of racemic heterocyclic sulfoxides. With the low-loading catalyst (0.01 equiv), higher efficiency(0.5 h), more moderate reaction condition(−30 °C), and more green oxidant

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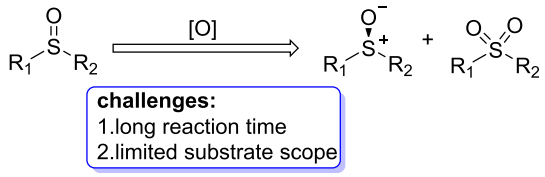


Scheme 1. Challenges in oxidative kinetic resolution of sulfoxides.

(H_2O_2), a wide range of sulfoxides in high ee value were obtained by the OKR of heterocyclic sulfoxides along with the corresponding sulfones in high yield. The OKR of heterocyclic sulfoxides are perfectly carried out and some new optically pure sulfoxides and sulfones were obtained. And the OKR of the sulfoxide substrates with hydroxyl groups demonstrate that this catalytic system has a favorable chemoselectivity. The further practical utility has achieved in the OKR of omeprazole and gram-scale sulfoxides.

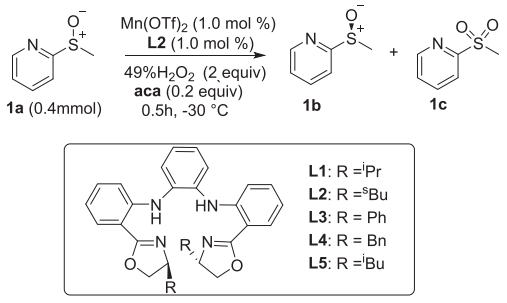
Results and discussion

Initially, we selected 2-(methylsulfinyl)pyridine(**1a**) as the model substrate to explore the feasibility of oxidant. $Mn(OTf)_2$ (1.4 mg, 0.004 mmol) and **L2** (2.0 mg, 0.004 mmol) were dissolved in acetonitrile (1.5 mL) , and the mixture was stirred at room temperature for 12 h. To the solution of manganese complex were added substrate (0.4 mmol), 0.2 equiv of adamantane carboxylic acid(**aca**) (14.4 mg, 0.08 mmol), and 65% aqueous tert-butyl hydroperoxide (28.8 mg, 0.32 mmol). Then decreased the temperature to −30 °C, and the reaction mixture was stirred at −30 °C for 0.5 h. When tert-butyl hydroperoxide was used as a oxidant, the chiral sulfoxide **1b** was obtained in 14% yield and 73% ee (Table 1, entry 1). Substituting oxidant with two another peroxide oxidants including cumyl hydroperoxide and 49% hydrogen peroxide result in a significant upgrade in yield (entry 2,3). Hydrogen peroxide provided the best result (entry 3). Subsequently, we demonstrated that 2 equiv of H_2O_2 can be achieved the pleasant result when the oxidant quantity was investigated (entry 4–8).

Except for **L2**, further ligand screening investigations were focused on **L1**, **L3**, **L4** and **L5**. Among them, we failed to get a better result than **L2** from the ligands containing chiral amino alcohol introductory oxazoline moieties (Table 1, entries 9–12). Moreover, we also tested pivalic acid as additive, but the effect is unsatisfactory than **aca** (entry 13).

Under the established optimized conditions, we took the initiative to investigate the substrate scope for a series of representative sulfoxides (Table 2). An efficient conversion which varieties of racemic pyridyl sulfoxides into the corresponding chiral sulfoxides and sulfones within a short time in appreciable yields with excellent enantioselectivities could be happened (**1b**–**5b** and **1c**–**5c**). The excellent enantioselectivity and high yields are independent to the electronic character and site of the substituents on the aromatic ring with heteroatoms. It is more attention, good yields and excellent enantioselectivity were retained when methyl was replaced by a longer alkyl chain (propyl and isobutyl) (**3b**, **3c** and **4b**, **4c**). Obviously, a higher ee value could be achieved when the substrates of pyrimidinyl and pyrazinyl sulfoxides were involved in the reaction (**6b**–**11b**, **6c**–**11c**). Stimulated by good results, the thiazolyl and thienyl sulfoxides caused our attention. Satisfactorily, the same good results still can be obtained (**12b**, **13b** and **16b**).

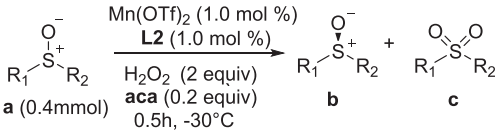
Table 1
Screening of Reaction Condition.

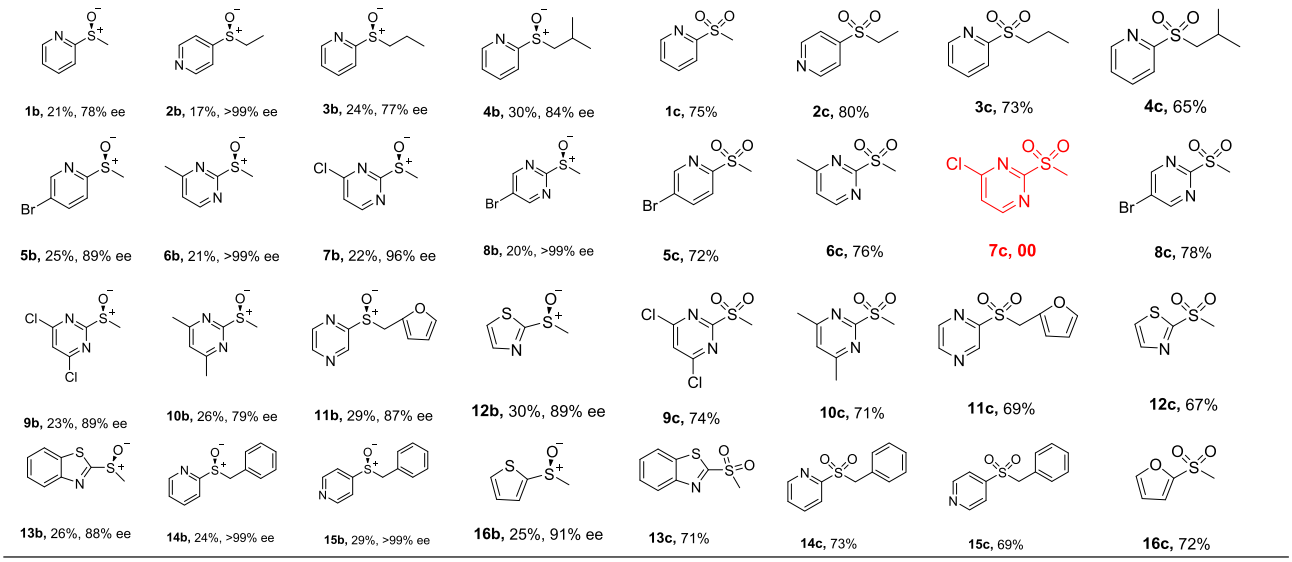


Entry	ligand	additive	H_2O_2 (equiv)	yield(%)[a]	ee(%)[b]
1[c]	**L2**	**aca**	–	14	73
2[d]	**L2**	**aca**	–	35	39
3	**L2**	**aca**	0.8	46	48
4	**L2**	**aca**	1.2	34	60
5	**L2**	**aca**	1.6	27	71
6	**L2**	**aca**	1.8	25	73
7	**L2**	**aca**	2.0	23	78
8	**L2**	**aca**	2.2	17	83
9	**L1**	**aca**	2.0	36	57
10	**L3**	**aca**	2.0	58	26
11	**L4**	**ca**	2.0	62	48
12	**L5**	**aca**	2.0	81	9
13[e]	**L2**	–	2.0	38	44

[a] The yield were determined by GC and nitrobenzene as interior label.
[b] The ee values were determined by chiral HPLC.
[c] Tert-Butyl hydroperoxide (0.8 equiv).
[d] Cumyl hydroperoxide (0.8 equiv).
[e] P ivalic acid.

Table 2
Substrate Scope of Oxidative Kinetic Resolution of Sulfoxides.



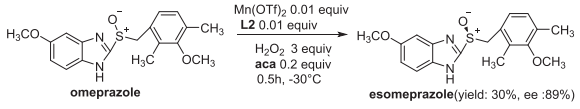


[a] Isolated yield.
[b] The ee values were determined by chiral HPLC.
[c] The sulfone(**7c**) needs to be stored under N_2 at 0 °C, so we cannot get the product in our experimental conditions.[6g]

Furthermore, in order to display the high efficiency of the oxidized system, we tested the sterically hindered heterocyclic benzyl sulfoxides. Fortunately, the hodiernal oxidation could also be favourably applied to heterocyclic benzyl sulfoxides, the corresponding chiral sulfoxides and sulfones were acquired with high yields and excellent enantioselectivity (>99% ee, **14b**, **14c** and **15b**, **15c**).

In addition, we selected the substrate **17a** and **18a** with hydroxyl groups as the reactants and extended the reaction time to 1 h. We found only **17b**, **17c** and **18b**, **18c** were obtained and no C—H bond and O—H bond oxidazed product were obtained (proved by GC–MS). It indicated that the catalytic system showed a favorable chemoselectivity (Scheme 2).

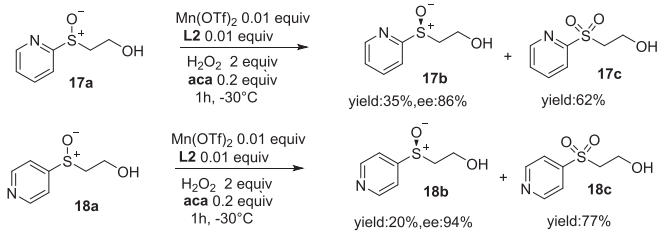
In order to explore the applicability of the methodology, the OKR of omeprazole was carried out and 30% yield esomeprazole that is a chiral proton pump inhibitor for the treatment of gastroesophageal reflux disease[1a] was obtained in 89% ee with 3.0 equiv H_2O_2 (Scheme 3).



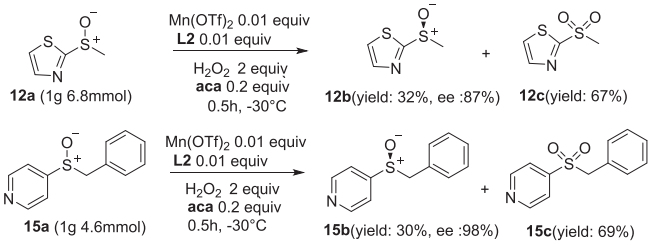
Scheme 3. Synthesis of Esomeprazole.

To further evaluate the practicability prospect of the catalytic system, the OKR of thiazole derivative **12a** and pyridine derivative **15a** were amplified to gram-scale under the optimized conditions, furnishing the conceivable product **12b** with 32% yield and 87% ee, **12c** 67% yield and **15b** was provided with 30% yield and 98% ee, **15c** 69% yield (Scheme 4).

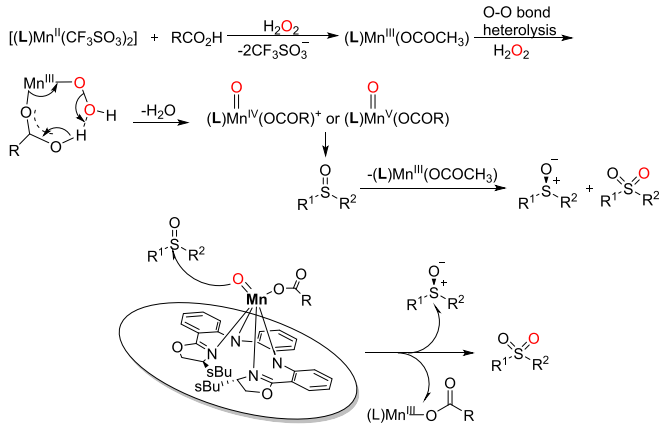
We suggested that the OKR mechanism was the similar to our previous study (Scheme 5).[5b,5c] First, the original conversion is (L)Mn(II) to the intermediate **M**. Then, the intermediate **M**



Scheme 2. Evidence Experiment of Chemoselectivity.



Scheme 4. Gram-scale Oxidative Kinetic Resolution of Sulfoxide **12a** and **15a**.



Scheme 5. Proposed Mechanism and Transition State Model.

species ($L^{+\cdot}$)$Mn^{IV}O$ complexes (**N**) or (L)$Mn^{V}O$ complexes (**N′**). No formation of (L)$Mn^{V}O$ species (**N′**) had been proved in the via the heterolysis of the O—O bond to generate the active asymmetric oxidation of sulfides by a porphyrin-inspired manganese complex with H_2O_2 via DFT calculations by Dai, et al.[15] At last, the coupled high-valent species **N** oxidizes sulfoxides to corresponding sulfones and keep a single configuration of sulfoxide simultaneously formed the intermediate **M**.

Conclusions

In summary, we have described a highly efficient OKR process to a diversity of racemic heterocyclic sulfoxides by the porphyrin-inspired Mn-oxo complex and hydrogen peroxide for the first time. In the procedure, the general OKR of a broad range of heterocyclic sulfoxide substrates was occurred in a mild reaction condition with high yields (up to 35%) and supernormal enantioselectivities (up to >99% ee) with an excellent chemoselectivity. At the same time, a high yield synthetic method of sulfone by a low loading catalyst with environmentally benign oxidant was proposed. The reaction process which one enantiomer reacts faster than the other was determined by a similar mechanism that forming a high-valent manganese-oxo complex via the carboxylic acid-assisted pathway to oxidize the enantiomers. In addition, the catalytic system has been practically applied to synthesis of esomeprazole and the OKR of gram-scale substrate.

Acknowledgments

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A. Supplementary data

Experimental procedures, analytical data, and copies of the ^{1}H and ^{13}C NMR spectra and ee value for all products (**1b**–**18b**) and (**1c**–**18c**).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2017.12.012.

References

1. (a) Wojaczyńska E, Wojaczyński J. *Chem Rev*. 2010;110:4303–4356;
(b) Fernández I, Khiar N. *Chem Rev*. 2003;103:3651–3705;
(c) Adrio J, Carretero JC. *J Am Chem Soc*. 1999;121:7411–7412;
(d) Chen MS, Prabagaran N, Labenz NA, White MC. *J Am Chem Soc*. 2005;127:6970–6971;
(e) Mariz R, Luan X, Gatti M, Linden A, Dorta R. *J Am Chem Soc*. 2008;130:2172–2173;
(f) Bürgi JJ, Mariz R, Gatti M, Drinkel E, Luan X, Blumentritt S, Linden A, Dorta R. *Angew Chem Int Ed*. 2009;48:2768–2771;
(g) Maezaki N, Sakamoto A, Nagahashi N, et al. *J Org Chem*. 2000;65:3284–3291;
(h) Carreno MC, Des Mazery R, Urbano A, Colobert F, Solladié G. *Org Lett*. 2004;6:297–299.
2. (a) Romanowski G, Kira J. *Polyhedron*. 2016;117:352–358;
(b) Tang J, Yao PF, Xu XL, et al. *RSC Adv*. 2016;6:44154–44162;
(c) Zhang Y, Tan R, Zhao G, Luo X, Xing C, Yin D. *J Catal*. 2016;335:62–71;
(d) Jahier C, Touzani R, Kadiri SE, Nlate S. *Inorg Chim Acta*. 2016;450:81–86.
3. (a) Ligtenbarg AG, Hage R, Feringa BL. *Coord Chem Rev*. 2003;237:89–101;
(b) Pitchen P, Dunach E, Deshmukh M, Kagan H. *J Am Chem Soc*. 1984;106:8188–8193;
(c) Deshmukh M, Duñach E, Juge S, Kagan H. *Tetrahedron Lett*. 1984;25:3467–3470;
(d) Di Furia F, Modena G, Seraglia R. *Synthesis*. 1984;1984:325–326.
4. (a) Sturala J, Bohacova S, Chudoba J, Metelkova R, Cibulka R. *J Org Chem*. 2015;80:2676–2699;
(b) Leow WR, Ng WK, Peng T, et al. *J Am Chem Soc*. 2016;139:269–276;
(c) Hassanpour A, Acuña-Parés F, Luis JM, et al. *Chem Commun*. 2015;51:14992–14995;
(d) Zhao L, Zhang H, Wang Y. *J Org Chem*. 2016;81:129–136;
(e) Chatterjee S, Paine TK. *Angew Chem*. 2016;128:7848–7853.
5. (a) Rioz-Martínez A, de Gonzalo G, Pazmiño DET, Fraaije MW, Gotor V. *Eur J Org Chem*. 2010;33:6409–6416;
(b) Dai W, Li G, Wang L, et al. *RSC Adv*. 2014;4:46545–46554;
(c) Dai W, Li J, Chen B, et al. *Org Lett*. 2013;15:5658–5661;
(d) Drago C, Caggiano L, Jackson RFW. *Angew Chem*. 2005;117:7387–7389;
(e) Boruah JJ, Ahmed K, Das S, et al. *J Mol Catal*. 2016;425:21–30.
6. (a) Shavnya A, Coffey SB, Smith AC, Mascitti V. *Org Lett*. 2013;15:6226–6229;
(b) Niklas W, Char J, Xavier F, Thibault C. *Angew Chem*. 2017;129:5708–5711;
(c) Schellhammer PF. *Expert Opin Pharmacother*. 2002;3:1313–1328;
(d) Tfelt-Hansen P, De Vries P, Saxena PR. *Drugs*. 2000;60:1259–1287;
(e) Gronowitz S, Nikitidis G, Hallberg A, Servin R. *J Org Chem*. 1988;53:3351–3353;
(f) Davey DD, Adler M, Arnaiz D, et al. *J Med Chem*. 2007;50:1146–1157.
7. (a) Fareghi-Alamdari R, Zekri N, Moghadam AJ, Farsani MR. *Catal Commun*. 2017;98:71–75;
(b) Zhao W, Yang C, Cheng Z, Zhang Z. *Green Chem*. 2016;18:995–998;
(c) Shyam P, Jang HY. *J Org Chem*. 2017;82:1761–1767;
(d) Fukuda N, Ikemoto T. *J Org Chem*. 2010;75:4629–4631;
(e) Xu L, Cheng J, Trudell ML. *J Org Chem*. 2003;68:5388–5391.
8. (a) Bolm C, Bienewald F. *Angew Chem Int Ed*. 1996;34:2640–2642;
(b) Drago C, Caggiano L, Jackson RF. *Angew Chem*. 2005;117:7387–7389.
9. (a) Legros J, Bolm C. *Chem A Eur J*. 2005;11:1086–1092;
(b) Egami H, Katsuki T. *J Am Chem Soc*. 2007;129:8940–8941;
(c) Bryliakov KP, Talsi EP. *Chem Eur J*. 2007;13:8045–8050.
10. Yamaguchi T, Matsumoto K, Saito B, Katsuki T. *Angew Chem*. 2007;119:4813–4815.
11. O'Mahony GE, Ford A, Maguire AR. *J Org Chem*. 2012;77:3288–3296.
12. Kelly P, Lawrence SE, Maguire AR. *Eur J Org Chem*. 2006;2006:4500–4509.
13. Zeng Q, Wang H, Wang T, Cai Y, Weng W, Zhao Y. *Adv Synth Catal*. 2005;347:1933–1936.
14. Jia X, Li X, Xu L, et al. *Adv Synth Catal*. 2004;346:723–726.
15. Dai W, Shang S, Lv Y, Li G, Li C, Gao S. *ACS Catal*. 2017;7:4890–4895.