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Fe(salan)-Catalyzed Asymmetric Oxidation of Sulfides with Hydrogen Peroxide in Water

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Enhancement of ecological sustainability as well as selectivities in chemical transformation is of primary importance for realizing green chemistry. Ecological sustainability of an organic reaction depends on the reagent(s),¹ solvent,² and workup procedure used for transformation. Thus, intensive effort has been devoted to development of asymmetric reactions using highly atom-efficient and green reagent(s) that co-produce only innocuous waste. For example, asymmetric oxidation using molecular oxygen or aqueous hydrogen peroxide that produces only water as the co-product is a topic of current interest, and quite a few atom-efficient methods using them have been reported.¹ On the other hand, significant effort has also been devoted to development of asymmetric reactions in water, and a few efficient methods that use a metal complex as the catalyst have been reported: Kobayashi et al. reported highly enantioselective reactions in water with chiral Lewis acid–surfactant combined catalysts.³ Asymmetric oxidation in water has also been actively studied.⁴ However, few highly enantioselective oxidations with molecular oxygen or aqueous hydrogen peroxide in water have been reported.^{4b} Still, realization of asymmetric reaction using a chiral catalyst in water without a surfactant is a challenge.

Optically active sulfoxides are found in many bioactive compounds as a subunit,⁵ and they also serve as chiral auxiliaries.⁶ Thus, many methods for asymmetric sulfoxidation have been developed,⁷ and some of them use aqueous hydrogen peroxide as the oxidant.^{7b,8} Jacobsen et al. reported a Mn(salen) complex catalyzed enantioselective sulfoxidation using aqueous H₂O₂ in acetonitrile.⁹ Bolm et al. achieved highly enantioselective sulfoxidation using a V- or Fe–Schiff base complex/aqueous H₂O₂-dichloromethane system.^{7b,8e,i,k} In 2005, Strukul et al. reported the first enantio- and chemoselective sulfoxidation using a Pt/BINAP/H₂O₂/surfactant (SDS) system in water, albeit with modest enantioselectivity.^{4b} However, substrates of these previous methods are largely limited to alkyl aryl sulfides.^{7,10} We have recently demonstrated that *cis*-β-Ti(salen)^{8b} and *cis*-β-Al(salalen) complexes¹¹ are efficient catalysts for asymmetric sulfoxidation using H₂O₂ as oxidant, while they are less efficient in water probably due to high oxophilicity of titanium and aluminum ions. We expected that a combination of a less oxophilic metal ion and a more donor ONNO ligand, such as the salan ligand^{8j,12} that is the fully reduced salen (or reduced salalen) ligand, would enable enantioselective sulfoxidation in water. It is known that various iron complexes serve as catalysts for oxidation, and the iron ion makes complexes with di- and trinitrogen ligands.^{13,14} Herein, we report widely applicable asymmetric oxidation of sulfides using a Fe(salan) complex/aqueous hydrogen peroxide system in water.

Oxidation of methyl phenyl sulfide was first examined with complexes **1**–**5** at 20 °C with 1.5 equiv of H₂O₂¹⁵ (Table 1). The reactions with **1** and **2** were slow, and the enantioselectivities were low (entries 2 and 3). On the other hand, the reactions with **3** and **4** proceeded smoothly with good and high enantioselectivities,

Table 1. Oxidation of Methyl Phenyl Sulfide Using Fe(salan) Complexes as Catalyst^a

entry	cat.	yield of 7a ^b (%)	yield of 8a ^b (%)	ee of 7a ^c (%)
1	none	4	0	
2	1	30	2	10 (<i>R</i>) ^d
3	2	25	2	10 (<i>S</i>) ^d
4	3	89	5	88 (<i>S</i>) ^d
5	4	91	9	96 (<i>S</i>) ^d
6 ^e	4	47	1	95 (<i>S</i>) ^d
7 ^f	4	92 (90) ^g	8	96 (<i>S</i>) ^d
8	5	21	<1	<5 (<i>R</i>) ^d

^a The reactions were carried out in water on a 0.2 mmol scale in the presence of 30% H₂O₂ and Fe(salan) complexes (2 mol %) at 20 °C, unless otherwise mentioned. ^b Determined by ¹H NMR (400 MHz) spectroscopic analysis. ^c Determined by HPLC analysis as reported in Supporting Information. ^d Assigned as reported in Supporting Information. ^e The reaction run for 0.5 h. ^f The reaction run with 1 mol % of **4**. ^g Isolated yield (on a 0.4 mmol scale).

respectively, though slight over-oxidation was observed (entries 4 and 5). We also examined the reaction with **4** for 0.5 h and found that the enantioselectivity was 95% ee, suggesting that the over-oxidation was a poorly enantiomer-differentiating process (vide infra) (entry 6). Moreover, reduction of the loading of **4** scarcely affected the yield and the enantioselectivity (entry 7). The reaction with **5** showed poor enantioselectivity (entry 8).

In order to estimate the effect of over-oxidation on enantioselectivity, we examined oxidation of racemic sulfoxide (*rac*-**7a**) under the present conditions (Scheme 1),¹⁶ and the oxidation of the (*R*)-enantiomer was found to be ca. 2.5 times as fast as that of the (*S*)-enantiomer. This agrees with the results described in Table 1.

We next examined the oxidation of other alkyl aryl sulfides with **4** as the catalyst under the optimized conditions (Table 2). Similar levels of yields and enantioselectivities were obtained in the oxidation of **6b** and **6c** carrying an electron-donating group at the *p*-position, respectively (entries 1 and 2). On the other hand, substantial over-oxidation was observed in the oxidation of *p*-chloro-substituted sulfide **6d**, and the corresponding sulfoxide of 94% ee was obtained in decent yield (76%) together with sulfone **8d** (24%) (entry 3), while oxidation of *o*-chloro-substituted sulfide **6e** gave

