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

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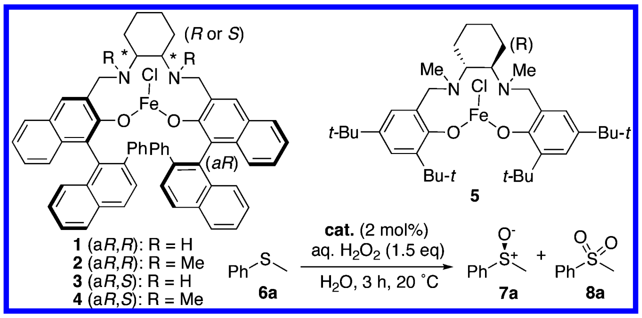
Enhancement of ecological sustainability as well as selectivities in chemical transformation is of primary importance for realizing green chemistry. Ecological sustainability of an organic reaction depends on the reagent(s),[1] solvent,[2] and workup procedure used for transformation. Thus, intensive 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 H_2O_2 in acetonitrile.[9] Bolm et al. achieved highly enantioselective sulfoxidation using a V− or Fe−Schiff base complex/aqueous H_2O_2-dichloromethane system.[7b,8e,i,k] In 2005, Strukul et al. reported the first enantio- and chemoselective sulfoxidation using a Pt/BINAP/H_2O_2/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) complexes[11] are efficient catalysts for asymmetric sulfoxidation using H_2O_2 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 H_2O_2[15] (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, 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).

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 (*R*)[d]
3	**2**	25	2	10 (*S*)[d]
4	**3**	89	5	88 (*S*)[d]
5	**4**	91	9	96 (*S*)[d]
6[e]	**4**	47	1	95 (*S*)[d]
7[f]	**4**	92 (90)[g]	8	96 (*S*)[d]
8	**5**	21	<1	<5 (*R*)[d]

[a] The reactions were carried out in water on a 0.2 mmol scale in the presence of 30% H_2O_2 and Fe(salan) complexes (2 mol %) at 20 °C, unless otherwise mentioned. [b] Determined by ^{1}H 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).

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

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Scheme 1. Oxidation of Racemic Sulfoxide Using the **4**/H_2O_2 System

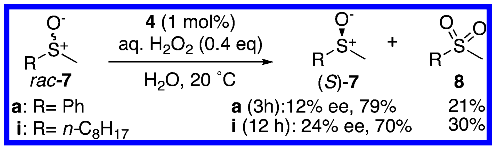
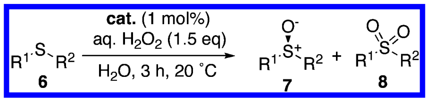


Table 2. Asymmetric Oxidation of Various Sulfides Using **4**[a]



entry	R^1	R^2		yield of **7**[b] (%)	yield of **8**[b] (%)	ee of **7**[c] (%)
1	*p*-MePh	Me	**b**	91 (88)	9	96 (*S*)[d]
2	*p*-MeOPh	Me	**c**	92 (88)	8	95 (*S*)[d]
3	*p*-ClPh	Me	**d**	76 (72)	24	94 (*S*)[d]
4	*o*-ClPh	Me	**e**	97 (86)	<1	96 (*S*)[d]
5	*o*-MeOPh	Me	**f**	99 (90)	<1	95 (*S*)[d]
6[e]	*o*-MeOPh	Me	**f**	80 (77)	<1	93 (*S*)[d]
7	Ph	Et	**g**	78 (73)	22	81 (*S*)[d]
8	$PhCH_2$	Me	**h**	93 (85)	7	87 (*S*)[d]
9	*n*-C_8H_{17}	Me	**i**	82 (73)	18	89 (*S*)[d]
10	*n*-$C_{12}H_{25}$	Me	**j**	82 (79)	18	94 (*S*)[d]
11	*c*-C_6H_{11}	Me	**k**	91 (73)	9	88 (*S*)[d]

[a] The reactions were carried out on a 0.2 mmol scale in water (0.5 mL) in the presence of 30% H_2O_2 (1.5 equiv) and **4** (1 mol %) at 20 °C, unless otherwise mentioned. [b] Determined by ^1H NMR (400 MHz) spectroscopic analysis. The values in parenthesis are isolated yields that were obtained on a 0.4 or 0.5 mmol scale. [c] Determined by HPLC analysis as reported in Supporting Information. [d] Assigned as reported in Supporting Information. [e] The reaction run on a 10 mmol scale with 0.01 mol % of **4** for 6 h in the presence of 30% H_2O_2 (1.2 equiv).

sulfoxide **7e** exclusively with 96% ee (entry 4). It is noteworthy that the oxidation of *o*-methoxy-substituted sulfide gave the corresponding sulfoxide **7f** exclusively with almost the same enantioselectivity as **7e** (entry 5), and the turnover number of **4** amounted to 8000 (entry 6). The results suggested that the presence of an *o*-substituent significantly suppresses over-oxidation. The oxidation of ethyl phenyl sulfide **6g** proceeded with somewhat reduced enantioselectivity of 81% ee (entry 7). To our delight, the present oxidation could be successfully applied to oxidation of alkyl methyl sulfides (**6h**−**k**), giving the corresponding sulfoxides of 87−94% ee (entries 8−11). Although slight over-oxidation was observed, the enantiomer differentiation (k_{rel}) measured in the oxidation of racemic methyl octyl sulfoxide was as small as 4.5 (Scheme 1).

The mechanism of iron-catalyzed sulfoxidation is not well-understood.[8k,14] In the present oxidation, mixing of solid **4** with sulfide in water immediately gives a biphasic liquid system. ^1H NMR analysis of the system (1:1 **4**/sulfide/D_2O) showed the broadened signals of the sulfide, indicating the formation of a sulfide-coordinated **4**. The generation of the biphasic system should increase substrate concentration around **4**. Thus, regardless of a heterogeneous system, the reaction in water proceeded as rapidly as that in methanol. Higher enantioselectivity was also observed in water than in methanol (see Supporting Information).

In summary, we have achieved highly enantioselective sulfoxidation with wide scope of application in water in the absence of a surfactant by using a novel Fe(salan) complex/aqueous hydrogen peroxide system. The reaction can be carried out in ambient air and at 20 °C with remarkably high catalyst turnover number. Further study on the mechanism of this sulfoxidation is now proceeding in our laboratory.

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Supporting Information Available: Experimental procedures, ^1H NMR spectra data for sulfoxides, and HPLC condition. This material is available free of charge via the Internet at http://pubs.acs.org.

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