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A new methodology for the oxidation of sulfides with Fe(III) catalysts

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A variety of sulfides were converted to the corresponding sulfoxide derivatives with 70% t-BuOOH (water) as the oxidant in the presence of catalytic quantity of Fe₂(SO₄)₃. The method described has a wide range of applications, involves simple work-up, exhibits chemoselectivity/enantioselectivity and proceeds under mild reaction conditions. The resulting products are obtained in good yield within a reasonable time. Copyright © 2012 John Wiley & Sons, Ltd.

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Introduction

Oxidation reactions are of fundamental importance in nature, and are key transformations in organic synthesis. Sulfides are regarded as vital intermediates in organic chemistry owing to their versatile usage in fundamental research.^[1-3] Optically pure sulfoxides represent valuable compounds in asymmetric synthesis, being frequently used as chiral auxiliaries^[2] and in the pharmaceutical industry due to their important biological activities.^[4–9] The most investigated approach for the synthesis of enantiomerically enriched sulfoxides is the asymmetric oxidation of prochiral sulfides by chemical and enzymatic systems.^[10,11] Enantioselective oxidation of sulfides with titanium, manganese, and vanadium complexes has been widely studied in detail.^[12,13]

In particular, Bolm found that 30% H_2O_2 is an effective and environmentally friendly oxidant for sulfoxidation catalyzed by the *in situ* vanadium Schiff base complexes derived from chiral amino alcohols,^[14–28] and found that the more sterically hindered Schiff base ligand gave higher *ee* values than the less crowded ligands.^[14–18]

Iron is one of the most abundant metals in the universe.^[19] It is inexpensive, environmentally benign, and relatively non-toxic in comparison to other metals. Conversely, iron is relatively underrepresented in this field, and the few systems developed so far fail in terms of efficiency and practicability.^[20-22] Most involve structurally complex iron porphyrins and iodosylbenzene^[23-27] or alkyl hydroperoxides^[27] as terminal oxidant, and the enantioselectivities are only moderate (<55% ee).^[24,25] The iron complex [Fe₂O(pb)₄ $(H_2O)_2](ClO_4)_4]$ (where pb is (-)-4,5-pinene-2,2'-bipyridine) as a catalyst for sulfide oxidations with H₂O₂ was reported by Fontecave and coworkers, but the enantioselectivity remained rather low (max. 40% ee).^[28,29] Asymmetric oxidations could then be achieved by the use of chiral iron complexes. Recently Bolm and Legros reported a new enantioselective sulfide oxidation, which provides optically active sulfoxides with up to 90% ee by using an iron catalyst formed in situ from [Fe(acac)₃] and a Schiff base.^[30] In general, the product was isolated after 16 h of reaction time and the isolated yield of the various products varied from low to moderate. In fact, in the presence of substituted benzoic acids as additive the ee increased remarkably.^[31] In 2004 Bryliakov and Talsi reported that the iodosylbenzene (salen)–iron(III) complex [Fe^{III}CI–(salen*)] (OIPh) is an efficient catalyst for the asymmetric oxidation of sulfides.^[32]

Water as a reaction medium has been applied to a variety of oxidation reactions.^[33,34] With regard to asymmetric oxidation of sulfides to sulfoxides in water, only a few examples including the use of cyclodextrin derivatives,^[35] chiral micelles,^[36–39] or biological catalysts^[40] exist. Although both biological catalysts and the use of cyclodextrins sometimes give sulfoxides with high enantioselectivities in water, these methods lack practicality and generality due to their low to moderate optical yields and high substrate specificity. Recently, Katsuki and Egami investigated a highly enantioselective Fe(salan) complex/aqueous hydrogen peroxide system in water for the asymmetric oxidation of sulfides.^[41]

A careful review of the literature^[42–45] suggests that simple Fe(III) salts have not been evaluated so far for the process of sulfoxidation and issues related to enantioselectivity.^[46] With this goal in mind, the following objectives of study were summarized: (1) to evaluate the catalytic activity of simple iron salts like FeCl₃, Fe₂(SO₄)₃ and Fe₂O₃ towards sulfoxidation; (2) optimization of reaction parameters; (3) application of optimized reaction conditions to a variety of sulfide substrates; (4) determination of enantioselectivity; and (5) possibility of devising an environmentally friendly process.

Herein we report a new methodology for asymmetric oxidation of sulfides, by using 70% *t*-BuOOH as the oxidant, with Fe₂(SO₄)₃ as catalyst and (*R*,*R*)-(-)-*N*,*N'*-bis(3,5-di-*t*-butylsalicylidene)-1, 2-cyclohexanediamine (salen) as a chiral ligand in water at 100°C. The over-oxidized product was not observed in our system as compared to the literature.^[41]

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Results and Discussion

Oxidation of Sulfide

The reaction conditions for the oxidation of sulfides were optimized using methyl(4-tolyl)sulfane as a suitable substrate in the presence of different solvents, oxidants, and 5 mol% of different Fe(III) salts. Iron sulfate was found to be the best catalyst among the various Fe(III) salts (Table 1, entry 3 vs. 6 and 7). The catalyst and ligand were optimized by using different concentrations. The results show that 1 mol% salen with 5 mol% iron sulfate were the best concentrations for transformation to occur within a reasonable time period. When 2 mol% of salen was used, no appreciable change with respect to yield and *ee* was found. In fact, in the case of 0.5 mol%, the *ee* dropped with low yield. Low catalyst loading did not produce better results.

The results are summarized in Table 1. The oxidation of methyl (4-tolyl)sulfane to 1-methyl-4-(methylsulfinyl)benzene was found to be extremely facile in the presence of $5 \text{ mol}\% \text{ Fe}_2(\text{SO}_4)_3$, salen (1 mol%) as ligand and 1 equiv. of 70% t-BuOOH solution in water. The same reaction took 6 h in the presence of 1 equiv. of 5 M t-BuOOH solution in decane with lower isolated yield (80%) of the product. Water was found to be the best solvent (Table 1, entry 3). The reaction was found to be extremely sluggish under ambient conditions or with lower mol% of Fe(III) salts. With 1 equiv. of 30% H₂O₂ solution, the reaction went to completion in a much longer period of time (Table 1, entry 5 vs. entry 2). With higher amounts of oxidant the reaction mixture contains some sulfone in addition to the required sulfoxide. It is important to disclose here that the reaction fails completely when performed with Fe(II) sources like FeCl₂ and Mohr's salt. Gas chromatography-mass spectrometry (GC-MS) of the crude reaction mixtures did not reveal the presence of any sulfone, making this methodology 100% selective. This developed method was used to convert different aromatic sulfides to the corresponding sulfoxides. The results have been depicted in Table 2.

A variety of different aromatic sulfides were successfully converted to the corresponding sulfoxides and these were isolated in high yields after subsequent work-up and column chromatography. Again, no sulfone product was seen in the crude reaction mixtures. The catalytic system did not show any selectivity (Table 2, entries 3, 5, 8, 19 and 20). Only racemic mixtures were obtained in these cases.

The kinetic studies of the sulfoxidation with methyl(4-tolyl) sulfane and (4-chlorophenyl)(methyl)sulfane were explored in detail. High-pressure liquid chromatography (HPLC) was used to determine the various starting materials and products present as a function of time. The concentration of reactant and product for the oxidation of methyl(4-tolyl)sulfane is shown in Fig. 1. The concentration of the sulfide decreases steadily while that of the sulfoxide increases and we have calculated the rate of such reactions. As an example let us consider the conversion of methyl(4-tolyl)sulfane to the corresponding sulfoxides. The Van't Hoff differential method was used to determine the order (n) and rate constant (k) (Fig. 2). From Fig. 2, the rate of the reaction at different concentrations can be estimated by evaluating the slope of the tangent at each point on the curve corresponding to that of methyl phenyl sulfide. With these data, $log_{10}(rate)$ vs. $log_{10}(concentration)$ is plotted. The order (n) and rate constant (k) are given by the slope of the line and its intercept on the log₁₀(rate) axis. From Fig. 2, it is clear that this reaction proceeds with second-order kinetics (n = 2 with second-order kinetics (n = 2.01) and the rate constant $k = 0.1089 \text{ L mol}^{-1} \text{ min}^{-1}$. For the other substrate, the order of the reaction is n = 2.16 with rate constants $k = 0.2324 \text{ L mol}^{-1} \text{ min}^{-1}$.

The postulated mechanism of oxidation (Scheme 1) catalyzed by Fe(III) may be written based upon reports available in the literature.^[44]

The role of Fe(III) is to form the active oxidant-substrate complex. With Fe(II) this intermediate is Fe(III), which is a stable oxidation state of Fe. This explains why FeCl₂ and Mohr's salt do not catalyze this reaction. Thereafter, transfer of oxygen to sulfur leads to the formation of product. The metal first binds with *t*-BuOOH and forms Fe(IV) active oxidant. This species reacts with the sulfide and forms oxidant-substrate complex and the transfer of oxygen takes place. The reaction rate is dependent on the concentrations of the Fe(IV) active oxidant and sulfide substrate. This is supported by the kinetic studies suggesting second order of reaction.

The work-up for these coupling reactions involves extraction of the aqueous reaction mixture with ethyl acetate, subsequent removal of solvent, followed by flash chromatography of the crude product. We are pleased to disclose that the aqueous phase containing $Fe_2(SO_4)_3$ can be recycled repeatedly without much loss in activity of the reaction or yield (Table 3).

$\overbrace{\text{solvent, reflux}}^{\text{oxidant, catalyst}} \overbrace{\text{solvent, reflux}}^{\text{oxidant, catalyst}} \overbrace{\text{solven, reflux}$								
Entry	Catalyst	Solvent	Oxidant	Time (h) ^b	Yield (%) ^c			
1	$Fe_2(SO_4)_3$	CH ₂ Cl ₂	t-BuOOH	14	85			
2	$Fe_2(SO_4)_3$	MeCN	t-BuOOH	12	85			
3	$Fe_2(SO_4)_3$	H ₂ O	t-BuOOH	2	93			
Ļ	$Fe_2(SO_4)_3$	MeNO ₂	t-BuOOH	18	78			
5	Fe ₂ (SO ₄) ₃	H ₂ O	H_2O_2	14	88			
5	FeCl₃	H ₂ O	t-BuOOH	16	85			
7	Fe ₂ O ₃	H ₂ O	t-BuOOH	12	80			

Table 1. Optimization of reaction conditions for the conversion of methyl(4-tolyl)sulfane to 1-methyl-4-(methylsulfinyl)benzene with different solvents, oxidants and iron salts^a

^aMethyl(4-tolyl)sulfane (1 mmol), salen (1 mol%), 70 % *t*-BuOOH (water) (1 equiv.) and Fe(III) salts (5 mol%) refluxed in water. ^bMonitored using TLC until all the sulfide was consumed.

^clsolated yield after column chromatography of the crude product.

Table 2. Fe₂(SO₄)₃-catalyzed selective oxidation of sulfides to sulfoxides^a





Entry	Substrate	Time (h) ^b	Yield (%) ^c	<i>ee</i> (%) ^d	Config. ^e
1		2.00	93	98.1	(S)-(—)
2	s	2.00	81	98.7	(S)-(—)
3	s s	2.00	90	_	_
4	Br — S	2.30	89	97.9	(<i>S</i>)-(—)
5	⟨¯}–s∖	2.10	91	—	—
6	ci—	2.30	90	97.7	(<i>S</i>)-(—)
7	Br S	2.50	91		
8	s-	4.00	90	_	_
9	3211 →	2.00	92	99.4	(<i>S</i>)-(—)
10		2.00	90	81.5	(<i>S</i>)-(—)
11	ci—	2.30	90	97.7	(<i>S</i>)-(—)
12		2.00	88	98.8	(S)-(—)
13	s	2.00	91	—	_
14	Br SS	2.20	90	98.2	(<i>S</i>)-(—)
15		0.30	92	_	_
16	∕∕_S	0.10	91	—	_
17	SS	1.50	89	95.7	(<i>R</i>)-(—)



^bMonitored using TLC until all sulfide was found consumed.

^cIsolated yield after column chromatography of the crude reaction mixture.

^dEnantiomeric excess were determined by HPLC with a chiral stationary phase.

^eAbsolute configurations were assigned by comparing the optical rotations and HPLC retention times with the literature.



Figure 1. Concentration versus time in the oxidation of methyl(4-tolyl)sulfane with 5 mol% (Fe)₂(SO₄)₃, salen (1 mol%) and 1 equiv. 70% *t*-BuOOH in H₂O at 100°C.

Conclusions

A variety of aromatic sulfides were converted to the corresponding sulfoxide derivatives with 70% *t*-BuOOH (water) as the oxidant in the presence of salen as the ligand and catalytic



Figure 2. Van't Hoff differential plot for the oxidation of methyl(4-tolyl)sulfane with 5 mol% (Fe)₂(SO₄)₃, salen (1 mol%) and 1 equiv. 70 % *t*-BuOOH in H₂O at 100°C.

quantity of $Fe_2(SO_4)_3$. The method described has a wide range of applications, does not involve cumbersome work-up, exhibits chemoselectivity/enantioselectivity and proceeds under mild reaction conditions, and the resulting products are obtained in good yields within a reasonable time. The over-oxidized product sulfone was not observed.



Scheme 1. Mechanism of oxidation.

Table 3. Results for the oxidation of methyl(4-tolyl)sulfane in differentcycles ^a						
Cycle No.	Time (h) ^b	Yield (%) ^c				
1	2	93				
2	2	93				
3	2.05	92.8				
4	2.05	92.8				

^aReactions performed in water with $Fe_2(SO_4)_3$ (5 mol%) and 70 % *t*-BuOOH (1 equiv.) under reflux condition.

^bMonitored using TLC until all sulfide was consumed.

^cIsolated yield after column chromatography of the crude product.

Experimental

Instruments

High-resolution ¹H NMR and ¹³C NMR (100 MHz) were recorded on a Bruker Avance 400 MHz spectrometer and the chemical shifts are reported in units of ppm relative to trimethylsilane (0.00 ppm) for ¹H and ¹³C NMR, where CDCl₃ is used as a solvent. Mass spectra of the sample were recorded on a Micro mass quadrupole time-of-flight QToF instrument, low-resolution electrospray ionization (ESI) mass spectrometer using methanol solvent. GC-mass spectra were recorded using a Jeol JMS GC-Mate II instrument. HPLC analysis was carried out using a Waters instrument fitted with a Waters 515 pump and 2487 dual λ absorbance detector. Suitable methods were developed with different proportions of MeCN and alcohol.

Materials

All the substrates used in this study were purchased from Aldrich and used as received. The solvents, along with H_2O_2 and *t*-BuOOH, were purchased from Ranchem, India. Solvents were purified using standard methods. The iron salts used for this study were purchased from Aldrich.

Typical Procedure for Sulfoxidation

To a stirred solution of sulfide (1 mmol), salen (1 mol%) and Fe₂ $(SO_4)_3$ (5 mol%) in 2.5 ml water, 70% *t*-BuOOH (water) (0.90 ml, 1 mmol) was added. The reaction mixture was set to reflux. The progress of the reaction was monitored using thin-layer chromatography (TLC) periodically until all sulfide was found to consumed.

The product was extracted from water by washing with ethyl acetate and purified by column chromatography using ethyl acetate and hexane as eluent. The spectral data of the various sulfoxides were found to be satisfactory, in accordance with the literature.

Determination of Enantioselectivity

The enantiomeric excesses of purified sulfoxide products were determined by using HPLC fitted with a chiralcel OJ-H column with 0.8 ml min⁻¹ flow rate of hexane and isopropanol (8:2) on the basis of retention time reported in the literature.^[47]

Kinetic Studies

To the stirred solution of sulfide (1 mmol), salen (1 mol%) and Fe₂ (SO₄)₃ (5 mol%) in 2.5 ml water, 70% *t*-BuOOH (1 mmol) was added. The reaction mixture was set to reflux. 0.2 ml of reaction mixture was taken after regular time intervals. The reaction mixture was treated with 10% Na₂S₂O₃ to quench the excess *t*-BuOOH. The crude product was extracted from water by washing with ethyl acetate. All the volatiles were removed to yield the crude product. HPLC (C-18 column, methanol as eluent with 0.5 ml min⁻¹ flow rate) was used for kinetic studies.

SUPPORTING INFORMATION

Supporting information may be found in the online version of this article.

Acknowledgments

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