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Efficient Asymmetric Oxidation of Sulfides and Kinetic Resolution of Sulfoxides Catalyzed by a Vanadium−Salan System

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Abstract: The asymmetric oxidation of sulfides to chiral sulfoxides with hydrogen peroxide in good yield and high enantioselectivity has been catalyzed very effectively by chiral vanadium−salan [*N*,*N*′-alkyl bis(salicylamine)] complex. The salan ligand shows results superior in terms of reactivity and enantioselectivity to those of salen [*N*,*N*′-alkylene bis(salicylideneimine)] analogue, and provides the sulfoxide with opposite configuration. The high enantioselectivity of this reaction is the direct result of the asymmetric oxidation. The efficient kinetic resolution of racemic sulfoxides catalyzed by the vanadium−salan system is also described.

Enantiopure sulfoxides constitute a class of the most efficient and versatile chiral controllers and useful synthons in asymmetric synthesis, and they are of great interest in the pharmaceutical industry as biologically significant compounds.[1] The synthesis of chiral nonracemic sulfoxides with high enantiomeric purity has been a subject of constant interest over the past two decades. The following two types of procedures have been most commonly employed for the preparation of chiral sulfoxides: (1) an approach that consists of the synthesis of a sulfinylating agent with an electrophilic sulfur of known configuration, followed by the reaction with an organometallic regent,[2] and (2) the direct asymmetric oxidation of the easily available prochiral sulfides.[3] In the latter procedure, catalytic asymmetric oxidation of sulfides with chiral metal complexes or enzymes is undoubtedly the most attractive and economical method because of its simplicity. Following the initial reports by Kagan[4] and Modena[5] on the use of a modified Sharpless reagent, most of the metal-catalyzed enantioselective oxidation of sulfides are based on the use of chiral titanium or manganese complexes.[6] In contrast, vanadium catalysts have been less extensively investigated.[7] The first example of vanadium-catalyzed asymmetric sulfoxidation, in which alkyl peroxide was used as the oxidant, was reported by Fujita.[7a] Subsequently, Bolm reported a highly selective and promising catalyst system in which a combination of the amino alcohol-derived Schiff base with vanadium was employed, and the oxidation proceeded in up to 85% enantiomeric excess, with very low catalyst loading and with hydrogen peroxide as a nontoxic and inexpensive stoichiometric oxidant.[7b] Employing this catalyst system, Ellman has successfully and extensively studied the catalytic asymmetric oxidation of *tert*-butyl disulfide.[8] Very recently, Bolm reported the iron-catalyzed version of this system for the asymmetric sulfide oxidation.[7d] An oxidation catalyst system for the sulfoxidation of sulfide that combines high catalytic efficiency and excellent enantioselectivity remains an important goal.

Nitrogen-containing ligands are one of the most common types of chiral ligands, which are becoming applicable for catalytic asymmetric synthesis.[9] It has been reported that the chiral ligands containing a secondary amino group (sp^3-hybridized nitrogen atom) are superior in terms of reactivity and enantioselectivity to imino analogues (sp^2-hybridized nitrogen atom).[10] Herein, we wish to report a catalytic asymmetric oxidation of sulfides to sulfoxides with excellent enantioselectivity by means of a facile and efficient procedure using chiral vanadium−salan complexes as the catalysts. Kinetic resolution of racemic sulfoxides catalyzed by an identical system is also described.

The readily obtainable tetradentate salan ligands **1** and **2**, which are based on the (*R*,*R*)-1,2-diaminocyclo-

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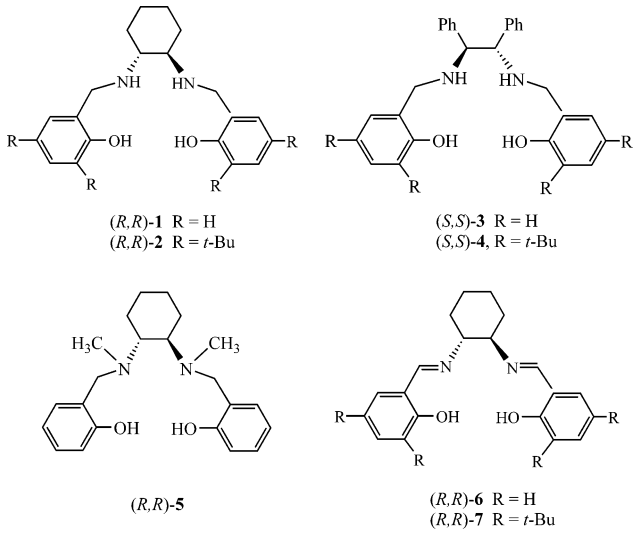


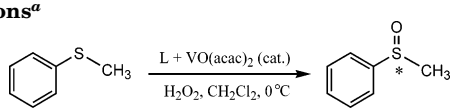
FIGURE 1. Structures of ligands used in this study.

hexane backbone, ligands **3** and **4**, which are derived from (*S,S*)-1,2-diamino-1,2-diphenylethane, and ligand **5**, in which there are two tertiary nitrogen atoms, were chosen as chiral auxiliaries (Figure 1). Ligands **1**−**4** were prepared by the reduction of their corresponding Schiff base salen precursor with sodium borohydride in absolute methanol in very high yields,[11] while ligand **5** was synthesized by the treatment of **1** in THF with *n*-butyllithium and iodomethane successively. These salan ligands have been employed in the formation and characterization of different metal complexes,[12] while, to the best of our knowledge, only one example of their chemistry in asymmetric catalysis has been reported.[10b]

Following Bolm's protocol,[7b] in which the catalyst was formed in situ from the reaction of $VO(acac)_2$ and chiral ligand, where hydrogen peroxide was used as an oxidant, we studied the reactivity and enantioselectivity of the oxidation of sulfide using methyl phenyl sulfide as a model substrate. The influence of parameters such as the nature of the ligand and the metal/ligand ratio, together with the effects of the temperature and the solvent, has been examined. The results were collected in Table 1.

All of the catalysts bearing amine ligands showed good catalytic reactivity, with the yields ranging from 71 to 91%, but with different selectivity in the range between 21 and 95% ee. Ligands (**1** and **2**) with a cyclohexane backbone showed better selectivity than those with a 1,2-diphenylethane backbone (**3** and **4**). The secondary amine ligand **1** gave the best result (entry 2) in terms of selectivity, but when **1** was methylated to tertiary amine **5**, the selectivity decreased to only 21% and 37% ee in $CHCl_3$ and CH_2Cl_2 (entries 16 and 17), respectively. Surprisingly, in contrast with other systems,[13] the sterically demanding substituents such as the *t*-Bu group in the salicyl component induced a negative effect in the enantioselectivity of the reaction in our system.

TABLE 1. Catalyzed Asymmetric Oxidation of Methyl Phenyl Sulfide Using Various Ligands under Different Conditions[a]



entry	ligand	solvent	time (h)	$VO(acac)_2$: ligand	yield (%)[b]	ee (%)[c]	configuration[d]
1	**1**	CH_2Cl_2	12	1:1.5	84	70	*R*
2	**1**	$CHCl_3$	16	1:1.5	81	95	*R*
3[e]	**1**	$CHCl_3$	16	1:1.5	80	62	*R*
4[f]	**1**	$CHCl_3$	16	1:1.5	78	95	*R*
5[g]	**1**	$CHCl_3$	16	1:1.5	67	93	*R*
6	**1**	$CHCl_3$	16	1:1.2	80	94	*R*
7	**1**	$CHCl_3$	16	1:1	78	91	*R*
8	**1**	CCl_4	20	1:1.5	71	45	*R*
9	**1**	CH_3CN	6	1:1.5	91	37	*R*
10	**1**	THF	14	1:1.5	83	66	*R*
11	**1**	toluene	18	1:1.5	70	22	*R*
12	**2**	CCl_4	20	1:1.5	82	63	*R*
13	**2**	$CHCl_3$	18	1:1.5	78	51	*R*
14	**3**	$CHCl_3$	16	1:1.5	76	31	*S*
15	**4**	$CHCl_3$	16	1:1.5	75	22	*S*
16	**5**	$CHCl_3$	20	1:1.5	82	21	*R*
17	**5**	CH_2Cl_2	20	1:1.5	83	37	*R*
18	**6**	$CHCl_3$	16	1:1.5	37	5	*S*
19	**7**	$CHCl_3$	16	1:1.5	42	10	*S*

[a] Unless otherwise noted, all reactions were carried out at 0 °C with $VO(acac)_2$ loading of 2 mol % and 1.5 mmol of H_2O_2 (30%). [b] Isolated yields; amount of sulfone < 5%. [c] Ee values were determined by HPLC with a Daicel Chiralcel OD-H column. [d] Absolute configuration was assigned by comparison of optical rotation reported in the literature.[14] [e] Reaction performed at 25 °C. [f] Reaction performed at −20 °C. [g] Performed with a 5% H_2O_2 solution.

For comparison, the imine salen ligands **6** and **7** (Figure 1) were also examined in this oxidation system (entries 18 and 19). The reactivity and especially the selectivity are very poor, which is consistent with the results obtained for a VO/salen/CHP system.[7a] It is noteworthy that the products resulting from amine ligands **1** and **2** are of *R* configuration, which is the reverse of that of corresponding salen ligands **6** and **7** (the major product is of *S* configuration). This may be due to the electronic difference and the stereogenic character of nitrogen atoms in salan ligands, which resulted from the coordination of nitrogen atoms to the central metal. The influence of the chirality of the nitrogen atom in the ligand on the catalytic selectivity deserves more investigation.

The nature of the solvent was revealed to have a remarkable effect upon the enantioselectivity and chemical yield. Of the six solvents we investigated, $CHCl_3$ gave the highest enantioselectivity and good chemical yield using **1** as the chiral ligand. When CH_2Cl_2 and THF were used as solvents, moderate ee values were obtained (entries 1 and 10). CH_3CN gave the highest chemical yield but lower ee values (entry 9). Thus, $CHCl_3$ proved to be the best solvent in terms of selectivity. A variation of the reaction temperature from 0 to 25 °C caused a sharp decrease in the ee value to 62% (entry 3), but there was no significant change when the reaction was carried out at −20 °C (entry 4). Moreover, there was a slight decrease when the metal/ligand ratio changed from 1:1.5 to 1:1.1 (entries 2, 5, and 7). The use of dilute hydrogen peroxide (5%) caused a slight decrease in chemical yield but no significant change in selectivity (entry 5).

We thus used **1** as the chiral ligand for enantioselective oxidation of a variety of sulfides using $VO(acac)_2$ as a cat-

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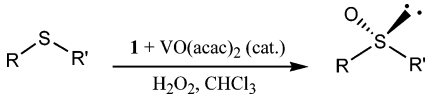
TABLE 2. Vanadium-Catalyzed Enantioselective Oxidation of Sulfides Using Chiral Ligand 1[a]



entry	R	R′	sulfoxide (%)[b]	ee (%)[c]	configuration[d]
1	Ph	CH_3	81	95	*R*
2	*p*-$CH_3C_6H_4$	CH_3	78	66	*R*
3	*p*-^{i}PrC_6H_4	CH_3	80	85	*R*
4	*m*-BrC_6H_4	CH_3	83	92	*R*
5	*o*-BrC_6H_4	CH_3	86	83	*R*
6	*p*-ClC_6H_4	CH_3	71	58	*R*
7	*p*-FC_6H_4	CH_3	80	51	*R*
8	*o*-$NO_2C_6H_4$	CH_3	72	60	*R*
9	*m*-$NO_2C_6H_4$	CH_3	62	64	*S*
10	*m*-$CH_3OC_6H_4$	CH_3	82	81	*R*
11	*p*-$CH_3OC_6H_4$	CH_3	83	75	*R*
12	Ph	CH_2Ph	78	72	*R*
13	*p*-$CH_3C_6H_4$	CH_2Ph	84	66	*R*
14	*t*-Bu	CH_3	83	76	/
15	*t*-Bu	*i*-Pr	76	63	/
16	*t*-Bu	*n*-Bu	83	72	/

[a] All reactions were carried out in $CHCl_3$ at 0 °C for 16−20 h. Molar ratio: substrate/H_2O_2/VO(acac)$_2$/**1** = 1:1.5:0.02:0.03. [b] Isolated yields. [c] Ee values of entries 1−13 were determined by HPLC with a Daicel Chiralcel OB-H or OD-H column, while those of entries 14−16 were determined by ^{1}H NMR analysis. [d] Absolute configuration was assigned by comparison of optical rotation reported in the literature.[14]

alyst precursor. The reactions were carried out at 0 °C in $CHCl_3$ under air with 1.5 equiv of H_2O_2 as an oxidant. The results are summarized in Table 2. Good chemical yields of isolated products, in the range of 62−86%, were obtained for all cases, with these being almost independent of the structure of the sulfides. All the products of aryl alkyl sulfides obtained were of *R* configuration except for entry 9. The enantioselectivity varied from 51 to 95% depending on the nature of the sulfide. The change of the aryl group in the methyl sulfide to probe electronic effects displayed no regular trends in the enantioselectivity. The highest ee value was observed for the phenyl group, but lower enantioselectivities were obtained both for the electron-donating and electron-accepting groups attached to the phenyl ring. Moreover, good enantioselectivities were also achieved even for the dialkyl sulfide (entries 14−16). The method appears to be fairly general for the enantioselective oxidation of sulfide.

In most cases, the high ee values of the sulfoxides were caused by two independent stereoselective processes, i.e., the asymmetric oxidation producing sulfoxide and its subsequent kinetic resolution via further oxidation to sulfone.[15] To our delight, sulfones were formed only in very low quantities (<5%) in the reaction processes using the catalytic system described here. From the time profile of the oxidation of methyl phenyl sulfide (Figure 2), it can be seen that the ee of sulfoxide does not change significantly during the reaction process. On the basis of these studies, it is deduced that the high ee values of the sulfoxides do not arise from a selectivity enhancement caused by kinetic resolution of the chiral sulfoxide but are the direct result of the enantioselective oxidation. On the other hand, a nonlinear effect was not observed in our catalytic system; this is presumably because the catalytic species contains only one ligand in the configuration-determining step.

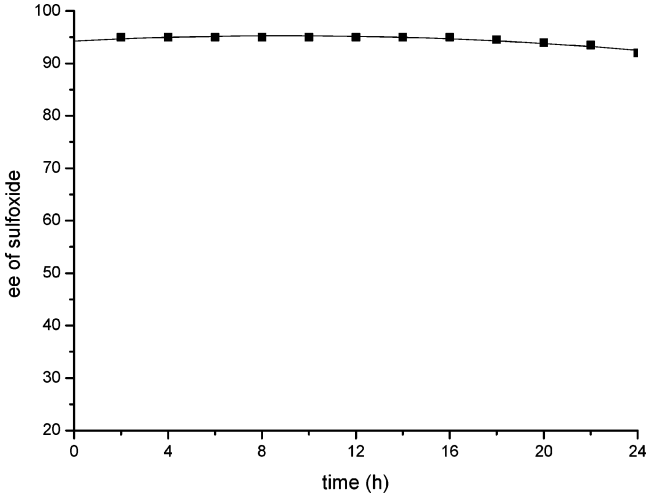
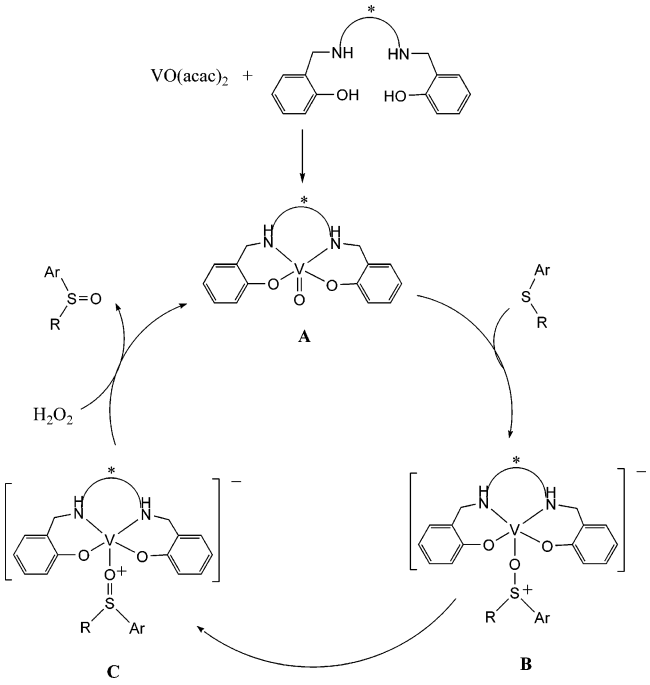


FIGURE 2. Time profile of the enantioselectivity (% ee of methyl phenyl sulfoxide) in the oxidation of methyl phenyl sulfide in entry 1 of Table 2.

SCHEME 1. Proposed Mechanism for the Asymmetric Sulfide Oxidation



A proposed mechanism for the catalytic asymmetric oxidation of sulfide is shown in Scheme 4. The reaction of salan ligand with VO(acac)$_2$ gave a salan−oxovanadium complex **A** as a catalyst species.[7a] As no Hammett correlations were found in this reaction, the process of oxygen transfer might not involve the formation of discrete intermediate sulfur radicals or cations but, most

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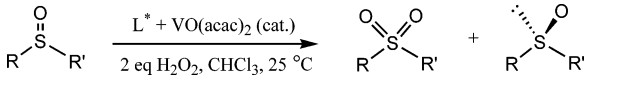
TABLE 3. Kinetic Resolution of Racemic Sulfoxides Catalyzed by Vanadium−Salan System[a]



entry	R	R′	sulfoxide (%)[b]	ee (%)[c]	configuration[d]
1	Ph	CH_3	32	92	*S*
2	*p*-$CH_3C_6H_4$	CH_3	29	98	*S*
3	*p*-^{i}PrC_6H_4	CH_3	28	87	*S*
4	*m*-BrC_6H_4	CH_3	30	78	*S*
5	*o*-BrC_6H_4	CH_3	26	93	*S*
6	*p*-ClC_6H_4	CH_3	30	86	*S*
7	Ph	CH_2Ph	26	93	*S*
8	*p*-$CH_3C_6H_4$	CH_2Ph	27	91	*S*

[a] All reactions were carried out in $CHCl_3$ at 25 °C for 20−24 h. Molar ratio: substrate/H_2O_2/VO(acac)$_2$/**1** = 1:2:0.05:0.075. [b] Isolated yields. [c] Ee values were determined by HPLC with a Daicel Chiralcel OB-H or OD-H column. [d] Absolute configuration was assigned by comparison of optical rotation reported in the literature.[14]

likely, proceeds by a concerted mechanism.[16] Nucleophilic attack of sulfur on the oxygen atom, which could be regarded as a remote nucleophilic attack on the metal, formed intermediate **B**. Reaction of intermediate **C** with hydrogen peroxide gave the chiral sulfoxide and regenerated species **A**.

Kinetic resolution of racemic sulfoxides has also emerged as a promising method for obtaining optically pure sulfoxides, as racemic sulfoxides are readily prepared by direct oxidative methods. Although several examples have been reported, only a few examples of kinetic resolutions have been effective for obtaining sulfoxides of high ee.[17] It is of interest to study the kinetic resolution of racemic sulfoxides with the vanadium−salan catalyst.

After optimization studies, combination of VO(acac)$_2$ (5 mol %), chiral ligand **1** (7.5 mol %), and H_2O_2 (2 equiv) in $CHCl_3$ at 25 °C proved to be the best reaction conditions for the asymmetric kinetic resolution of racemic sulfoxides. The kinetic resolutions of different racemic sulfoxides were accomplished under the above conditions, and the results are presented in Table 3. From the results, it can be seen that kinetic resolution of racemic sulfoxides could be also achieved by catalysis with chiral vanadium−salan complex **1** to give the sulfoxides in moderate chemical yields and good to excellent ee values, with the methyl *p*-tolyl sulfoxide providing the best result of up to 98% ee (entry 2). The stereoselectivity factor k_{rel} is 7.3 for the resolution of methyl phenyl sulfoxide (entry 1).[4d] It is clear that the chiral vanadium−salan complex recognizes (*R*)- and (*S*)-sulfoxides and catalyzes predominantly the oxidation of (*R*)-sulfoxide. Once again, it strongly supported that the high ee values of the catalytic oxidation of sulfides were not the result of kinetic resolution. We would like to mention that both *R* and *S* forms of optical active sulfoxides can be obtained with the same salan−vanadium catalyst system through the oxidation of sulfides and the kinetic resolution of racemic sulfoxides, respectively.

In summary, the asymmetric oxidation of sulfides as well as the kinetic resolution of sulfoxides with hydrogen peroxide under air catalyzed by a salan−vanadium catalyst provides an efficient procedure for the preparation of chiral sulfoxides in both good chemical yields and excellent enantiomeric purity. An important characteristic of the new catalytic system is that it provided chiral sulfoxides in higher ee values and with opposite enantioselection as compared with that of the corresponding salen system. Moreover, the high enantioselectivity of the asymmetric oxidation of sulfides did not arise from a selectivity enhancement caused by kinetic resolution of the chiral sulfoxide but was the direct result of the enantioselective oxidation. The *R* and *S* forms of sulfoxides can be obtained by the enantioselective oxidation of sulfides or the kinetic resolution of sulfoxides, respectively, catalyzed by the identical salan−vanadium catalyst system. Investigations are currently underway to understand the oxidation mechanism.

Experimental Section

General Procedure for the Asymmetric Oxidation of Sulfides. VO(acac)$_2$ (5.2 mg, 0.02 mmol) and the ligand (0.03 mol) were dissolved in a reaction tube in $CHCl_3$ (4 mL), and the solution was stirred for 1 h, with the color of the solution turning gradually from blue to deep brown. The sulfide (1 mmol) was added into the tube after the system was cooled to 0 °C. After the solution was stirred for another 10 min, the hydrogen peroxide (30%, 1.5 mmol) was added dropwise. The mixture was stirred for 16 h at 0 °C. Then, 10 mL of H_2O was added into the mixture. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 1.5/1). The fractions of sulfoxide were mixed.[18] The enantioselectivities were determined by chiral HPLC (Daicel UV detector (254 nm), flow rate 0.5 mL/min). The reaction can be scaled up to 10 mmol without significant change of chemical yield and ee value.

General Procedure for the Kinetic Resolution. VO(acac)$_2$ (0.05 mmol) and the ligand (0.075 mol) were dissolved in a reaction tube in $CHCl_3$ (4 mL), and the solution was stirred for 1 h, with the color turning gradually from blue to deep brown. After the addition of the racemic sulfoxide (1 mmol) and the dropwise addition of 30% H_2O_2 (2.0 mmol), the resulting mixture was stirred for 20 h at ambient temperature. Then, 10 mL of H_2O was added into the reaction mixture. The aqueous layer was separated and extracted with CH_2Cl_2, and the combined organic layer was dried over anhydrous Na_2SO_4. After the solvent was removed, the crude product was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 1.5/1).

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Supporting Information Available: Characterization data for ligands **1**−**5** and the sulfoxides. This material is available free of charge via the Internet at http://pubs.acs.org.

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