Electronic Effects of Substituents in Sulfides: Mechanism Elucidation of Vanadium Catalyzed Sulfoxidation

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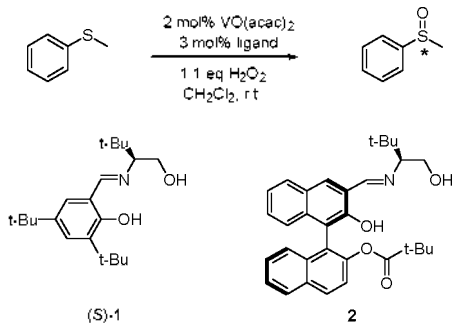
The synthetic methodology for chiral sulfoxide, which has been used as the key step in the synthesis of various pharmaceutical compounds such as lansoprazol and omeprazol, is one of the major challenges in medicinal chemistry. The method has been mainly developed in two ways; one is the diastereselective sulfoxidation using chiral auxiliaries and the other is asymmetric oxidation of prochiral sulfides.[1-4] In order to synthesize wide range of chiral sulfoxides, the latter is more attractive, especially with chiral transition metal complex.

Asymmetric sulfoxidation catalyzed by the chiral vanadium complex derived with a tricoordinated Schiff base **1** developed by Bolm,[3a] attracted our attention because of the facile preparation of the ligand as well as the operational simplicity such as open-vessel reaction, *in-situ* generation of catalyst and the use of aqueous hydrogen peroxide as the terminal oxidant.[3] We have recently demonstrated that the vanadium complex of BINOL-based chiral Schiff base **2** can catalyze the enantioselective sulfoxidation of sulfides with high enantioselectivity (Scheme 1).[4]

Despite the potential of the reaction in asymmetric synthesis, the mechanism of the reaction has not been well understood. In our effort to improve the stereoselectivity of the reaction in relation with the mechanistic study, we tested the steric effect of the ligand in the reaction using Schiff bases **3** and **4**. Although the stereoselectivities of the reactions with **3** and **4**, were not improved compared with the reaction with Schiff base **1**, we observed an unusual substituent effect in the sulfoxidation of substituted thioanisoles. Thus, here we report the result and discuss about the mechanism of vanadium catalyzed oxidation of sulfides.



Scheme 1. Various Schiff bases for Vanadium catalyzed asymmetric sulfoxidation.

Schiff bases **3** and **4** were prepared from the reaction between 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde and the corresponding amino alcohols synthesized according to the literature procedures (Figure 1)[4b] and applied to the enantioselective sulfoxidation of various sulfides. The results are summarized in Table 1 along with the result obtained with Schiff base **1**.

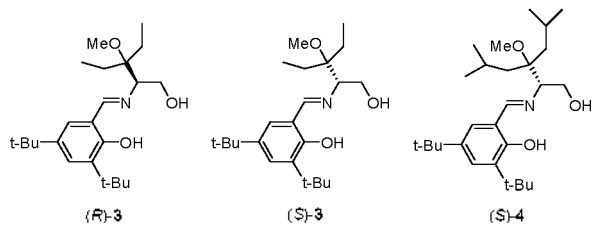


Figure 1. New chiral Shiff bases with sterically hindered amino alcohols.

Table 1. Asymmetric sulfoxidation of various sulfides.

Entry	Sulfide	Schiff base	Yield (%)[a]	ee (%)[b]	Config.[c]
1	C_6H_5-S-CH_3	(*S*)-**1**	79 (73)	65	(*S*)
2		(*S*)-**3**	86	64	(*R*)
3		(*R*)-**3**	84	64	(*S*)
4		(*S*)-**4**	91	64	(*R*)
5	*p*-MeO-C_6H_4-S-CH_3	(*S*)-**1**	36	50	(*S*)
6		(*S*)-**4**	59	47	(*R*)
7	*p*-Me-C_6H_4-S-CH_3	(*S*)-**1**	45	60	(*S*)
8		(*S*)-**3**	54	61	(*R*)
9		(*S*)-**4**	56	59	(*R*)
10	*p*-Br-C_6H_4-S-CH_3	(*S*)-**1**	61	52[d]	(*S*)
11		(*S*)-**4**	62	56[d]	(*R*)
12	*p*-NO_2-C_6H_4-S-CH_3	(*S*)-**1**	54	52[e]	(*S*)
13		(*S*)-**4**	64	48[e]	(*R*)
14	C_6H_5-CH_2-S-C_6H_5	(*S*)-**1**	60	61[f]	(*S*)
15		(*S*)-**3**	67	58[f]	(*R*)
16		(*S*)-**4**	42	53[f]	(*R*)

[a]Isolated yield. [b]Determined by HPLC analysis with a Daicel Chiralcel OD column, unless otherwise mentioned. [c]Absolute configuration determined by comparison of $[\alpha]^D$ with literature values. [d]Determined by ^{1}H-NMR (400 MHz) analysis using (*R*)-binaphthol as a shift reagent. [e]Determined by ^{1}H-NMR (400 MHz) analysis using (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol as a shift reagent. [f]Determined by HPLC analysis with a Daicel Chiralcel OJ column.

In the sulfoxidation of thioanisole with **3** and **4**, thioanisole sulfoxides were obtained in 84 ~ 91% yield with 64% ee (entries 2-4). It was found that an over oxidation of the sulfoxide to sulfone was not significant in these reactions and only a trace amount of the sulfone were observed. As has been reported in the literature,[3,4] the stereochemical outcome of sulfoxide was clearly dominated by the chirality of the Schiff base (entries 2 and 3). In the oxidation of thioanisole with either Schiff bases (*S*)-**1** or (*R*)-**3** which are similar in a spatial arrangement of substituents on the chiral center, (*S*)-thioanisole sulfoxide was produced as the major stereoisomer (entries 1 and 3). Unfortunately, the Schiff bases **3** and **4** did not improve enantioselectivities compared with ligand **1**. However, yields obtained with these ligands were slightly higher than that with **1**.

Interestingly, in the sulfoxidation of para-substituted thioanisoles, unexpected electronic effects of substituents toward the chemical yield and the enantiomeric excess were observed. Para-substituted thioanisoles containing either electron donating or electron withdrawing group were oxidized to their sulfoxides with a low yield and a low enantioselectivity compared to thioanisole. All three Schiff bases employed in this study showed similar tendency (entries 5-13).

Since the yield of the reaction within a given time is related to the rate of the reaction, a Hammett plot could be obtained using the logarithm of the relative chemical yields of substituted thioanisoles with respect to thioanisole and substituent constants (σ_p). A Hammett plot using enantiomeric excess was also drawn in Figure 2. We chose the Schiff base **1** in order to minimize the steric effect in obtaining the Hammett plot.

As shown in Figure 2, a nonlinear Hammett plot was obtained. While the slope of the plot at the region of electron donating substituents was positive, negative slope was observed in the region of electron withdrawing substituents. The unusual deviation from the straight line indicates a mechanistic change-over induced by the substituents.[5]

To explain this phenomenon, we suggest the mechanism as shown in Scheme 2.[6] Initially, it has been proposed that the active hydroperoxo vanadium complex **5** has the exo-structure, in which R group on imine subunit is in the face opposite to the oxo ligand based on NMR experiment and computational study.[6a-c] The sulfide approaches to the catalyst **5** in an orientation with the phenyl group pointing away from R group. Then an electron pair of sulfides coordinates to the electron poor vanadium atom and the intermediate **6A** is formed to minimize the steric interaction between sulfide and the ligand to produce (*S*)-enantiomer of aryl sulfoxide as obtained in our experiment. Then, the partially electropositive sulfur atom in **6A** is attacked by the electron rich oxygen atom of hydroperoxyl group as shown in **6C** state, to generate intermediate **6D** that eventually gives the sulfoxide and metal complex **7**.

In this scheme, the rate determining step might be either first (k_A) or second step (k_B) dependent upon substituents. For thioanisoles with electron-donating substituents, the coordination of sulfide bond to vanadium may be fast with increasing nucleophilicity of sulfide. However, the following nucleophilic oxygen transfer from the hydroperoxide to electropositive sulfur atom at **6A** through **6C** might be the rate determining step (k_B) that results the lower yield for sulfides with the more electron donating group (entries 5 and 7). Therefore,

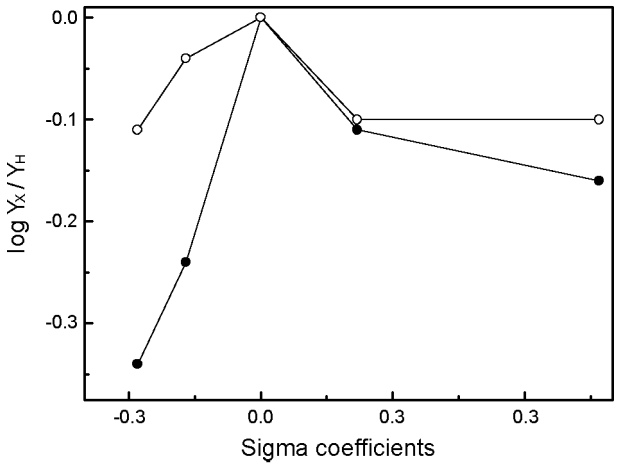
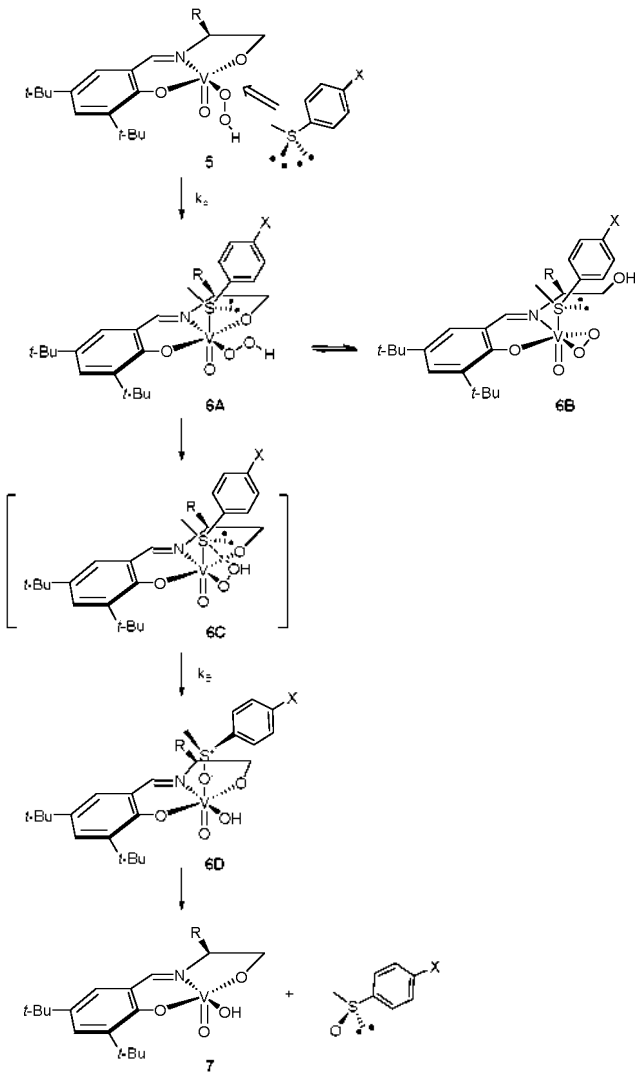


Figure 2. Correlation of the log Y_X/Y_H, where Y_X is the yield for substituted thioanisole and Y_H is the yield for thioanisole, with substituent constants (σ_p); the chemical yield (shaded circle) and the enantiomeric excess (open circle).



Scheme 2. Proposed mechanism for enantioselective sulfoxidation.

the slope in the Hammett plot is expected to be positive.

For thioanisoles with electron-withdrawing substituents, the coordination step (k_A) of sulfide to generate **6A** might be the rate determining step because of the low electron density at sulfur atom. At the intermediate **6A**, the coordinated sulfide is electropositive enough to be readily oxidized by the nucleophilic hydroperoxide. Thus, the negative slope in the Hammett plot can be obtained (entries 10 and 12). This rate limiting step changeover induced by substituents can successfully explain the curved Hammett plot.

The low enantioselectivities for electron rich or poor sulfides could also be explained using the mechanism. For *p*-Br or *p*-NO_2-thioanisole, the distance between sulfur and vanadium in **6A** which is the intermediate after the rate limiting step might be longer compared to that of thioanisole, resulting less facial discrimination by the ligand. If the life time in intermediate **6A** is long caused by slow rate determining oxygen transfer step for *p*-OMe and *p*-Me-thioanisole, the possibility to go to the intermediate **6B**, in which the steric effect of chiral center may be low, is increased causing the decreased enantioselectivities (entries 5 and 7).[6f,g]

In summary, we prepared Schiff bases **1**, **3** and **4** and examined the enantioselective oxidation of para-substituted thioanisoles and benzyl phenyl sulfide catalyzed by the vanadium-Schiff base complex. We found the unusual electronic effect in the reaction and suggested the oxidation mechanism.

Experimental

Generals. Melting points were determined on a Laboratory Devices INC. the Digital Melting Point Analyzer MEL-TEMP 3.0. The ^{1}H and ^{13}C NMR spectra were obtained using Jeol JNM-AL300 spectrometer at 300 MHz and 75 MHz and Varian AS-400 spectrometer at 400 MHz, 100 MHz respectively with tetramethylsilane as the internal reference. HRMS spectra were obtained on a Jeol JMS-700 spectrometer. HPLC was performed on a Young Lin SP-930D liquid chromatography coupled with a Young Lin UV-730D spectrophotometeric detector.

Synthesis of chiral Schiff base. Equivalent amount of amino alcohol and salicylic aldehyde were dissolved in an appropriate volume of ethanol. The mixture was stirred at room temperature until all starting material was consumed on TLC for about 3 hours. The mixture was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography.

(*R*)-**3**; $[\alpha]_{22}^{D}$ -60.2 (*c* 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.26 (brs, 1H), 8.35 (s, 1H), 7.41 (s, 1H), 7.40 (s, 1H), 7.13 (s, 1H), 4.07 (dd, 1H, J_1 = 4.5 Hz, J_2 = 11.0 Hz), 3.75 (dd, 1H, J_1 = 11.0 Hz, J_2 = 7.8 Hz), 3.43 (dd, 1H, J_1 = 7.8 Hz, J_2 = 4.5 Hz), 3.30 (s, 3H), 1.78-1.23 (m, 4H), 1.44 (s, 9H), 1.31 (s, 9H), 0.98 (t, 3H, J = 7.5 Hz), 0.86 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.58, 157.99, 140.22, 136.67, 127.27, 126.29, 117.67, 80.05, 75.91, 63.24, 49.87, 35.02, 34.11, 31.44, 29.36, 25.84, 25.37, 8.50, 7.29. HRMS (*m/z*): calculated for $C_{23}H_{40}NO_3$: 378.3008, found: 378.3013.

(*S*)-**3**; $[\alpha]_{22}^{D}$ +56.6 (*c* 0.2, $CHCl_3$).

(*S*)-**4**; $[\alpha]_{22}^{D}$ +55.4 (*c* 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.40 (brs, 1H), 8.37 (s, 1H), 7.41 (s, 1H), 7.40 (s, 1H), 7.13 (s, 1H), 4.06 (dd, J_1 = 4.5 Hz, J_2 = 11.0 Hz, 1H), 3.73(dd, J_1 = 11.0 Hz, J_2 = 7.8 Hz, 1H), 3.52 (dd, J_1 = 7.8 Hz, J_2 = 4.5 Hz, 1H), 3.30 (s, 3H), 2.03-1.85 (m, 2H), 1.57 (d, J = 5.7 Hz, 2H), 1.48-1.45 (m, 2H), 1.44 (s, 9H), 1.32 (s, 9H), 1.01-0.93 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.93, 158.07, 140.12, 136.69, 127.24, 126.26, 117.74, 81.28, 76.58, 63.29, 50.00, 42.33, 42.17, 35.04, 34.12, 31.47, 29.37, 24.81, 24.61, 24.59, 24.25, 24.02, 23.54. HRMS (*m/z*): calculated for $C_{27}H_{47}NO_3$: 434.3634, found: 434.3636.

Asymmetric sulfoxidation. Vanadyl acetylacetonate (5.3 mg, 0.02 mmol) and the Schiff base (0.03 mmol) were dissolved in CH_2Cl_2 (3 mL) then stirred 10 minutes at room temperature. After the addition of the sulfide (1.0 mmol), the solution was cooled to 0 °C and 30% H_2O_2 (0.13 mL, 1.1 mmol) was added. The mixture was stirred for 24 hr at 0 °C and quenched with sat. Na_2SO_3 aqueous solution. The resulting solution was extracted with CH_2Cl_2. The organic layer was briefly dried $MgSO_4$, filtered and concentrated under reduce pressure. The crude product was purified by flash column chromatography.

Phenyl methyl sulfoxide: Daicel Chiral OD column; 254 nm; 9% isopropyl alcohol in hexane, 0.5 mL/min, 25 °C, retention time: (*R*) = 22.0 min, (*S*) = 27.3 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 2H), 7.52 (m, 3H), 2.93 (s, 3H).

***p*-Tolyl methyl sulfoxide:** Daicel Chiral OD column; 254 nm; 4% isopropyl alcohol in hexane, 1.0 mL/min, 25 °C, retention time; (*R*) = 18.3 min, (*S*) = 20.0 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, 2H, J = 8.16 Hz), 7.30 (d, 2H, J = 8.20 Hz), 2.71 (s, 3H), 2.42 (s, 3H).

***p*-Methoxyphenyl methyl sulfoxide:** Daicel Chiral OD column; 254 nm; 20% isopropyl alcohol in hexane, 0.5 mL/min, 25 °C, retention time; (*R*) = 30.0 min, (*S*) = 32.7 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, 2H, J = 9.28 Hz), 7.05 (d, 2H, J = 8.79 Hz), 3.86 (s, 3H), 2.71 (s, 3H).

***p*-Bromophenyl methyl sulfoxide:** Optical purity confirmed by ^{1}H NMR in presence of (*R*)-binaphthol as a shift reagent; (*S*) = 2.70 ppm, (*R*) = 2.68 ppm. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, 2H, J = 8.40 Hz), 7.52 (d, 2H, J = 8.40 Hz), 2.72 (s, 3H).

***p*-Nitrophenyl methyl sulfoxide:** Optical purity confirmed by ^{1}H NMR in presence of (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl) ethanol as a shift reagent; (*S*) = 2.53, (*R*) = 2.55 ppm. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, 2H, J = 8.76 Hz), 7.86 (d, 2H, J = 8.74 Hz), 2.81 (s, 3H).

Benzyl phenyl sulfoxide. Daicel Chiral OJ column; 254 nm; 20% isopropyl alcohol in hexane, 1.0 mL/min, 25 °C, retention time: (*R*) = 20.1 min, (*S*) = 12.6 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.36 (m, 5H), 7.29-7.23 (m, 3H), 6.98 (d, 2H, J = 6.6 Hz), 4.05 (dd, 2H, J_1 = 38.8 Hz, J_2 = 12.8 Hz).

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