LETTER

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Substituent effects and mechanism elucidation of enantioselective sulfoxidation catalyzed by vanadium Schiff base complexes

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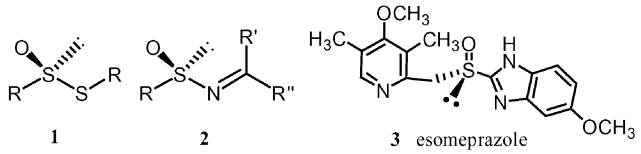
The effects of substituents of the Schiff base ligands on oxovanadium-catalyzed enantioselective sulfoxidation were first systematically studied, and a rational mechanism of enantioselective sulfoxidation based on our experimental data and the reported data is proposed.

Introduction

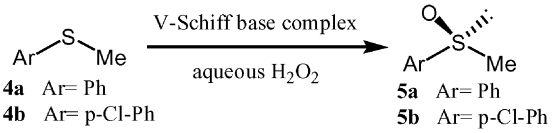
Chiral sulfoxides are widely used as chiral auxiliaries and as chiral drugs.[1] For example, the important intermediates thiosulfinate **1** and sulfinamide **2** have extensive application in organic synthesis;[1a] esomeprazole **3** (the *S* form of omeprazole) has a much better curative effect for stomach ulcers than the *R* form and racemic omeprazole (Scheme 1).[1d,2]

Recently, enantioselective oxidation of sulfides catalyzed by chiral complexes of transition metals, such as titanium,[3] vanadium,[4] iron,[5] or manganese,[6] has been extensively researched. 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 (Scheme 2).[4a] Bolm found that the Schiff base ligand derived from 3-*tert*-butyl-5-nitrosalicylaldehyde with high steric hindrance gave higher ee values than that derived from 5-nitrosalicylaldehyde.[4a] In a preliminary study, we surprisingly discovered that some ligands derived from 3,5-di-*tert*-butylsalicylaldehyde gave even lower enantioselectivity than those derived from less sterically hindered salicylaldehyde. Furthermore, to our best knowledge, the effects of substituents of Schiff base ligands on enantioselective sulfoxidation have not been systematically studied, and there is no appropriate mechanism of vanadium-catalyzed enantioselective sulfoxidation. Here we evaluate the effects of substituents of Schiff base ligands on enantioselective sulfoxidation. Furthermore, based on our experimental results and the reported data, a rational mechanism for vanadium-catalyzed enantioselective sulfoxidation is proposed.



1 **2** **3** esomeprazole

Scheme 1 Some applications of sulfoxides.



4a Ar= Ph
4b Ar= p-Cl-Ph

5a Ar= Ph
5b Ar= p-Cl-Ph

Scheme 2 Vanadium-catalyzed enantioselective oxidation of sulfides with aqueous H_2O_2.

Results and discussion

Chiral Schiff base ligands **8** were prepared from salicylaldehyde analogues **6** and chiral amino alcohols **7**, as shown in Scheme 3, and were fully characterized by ^{1}H NMR, ^{13}C NMR, IR and ESI-MS. The preformed vanadium complexes **9** were characterized with IR. There existed all characteristic absorbing peaks of C=N (about 1625 cm^{-1}), and V=O (987–995 cm^{-1}) for vanadium complexes **9**. In addition, **9e** was also further characterized by FAB-HRMS. The FAB-FT-ICRMS spectrum of **9e** demonstrated a predominant peak at 336.0440 ($[M - H]^-$, $C_{16}H_{15}NO_4V$, calculated: 336.0446), which accords with the structure **9e** as shown in Scheme 3. Thus, the preformed vanadium complexes **9** probably have the general structure as shown in Scheme 3.

The vanadium complexes **9** were applied to the asymmetric sulfoxidation of thioanisole **4a**,[7] as shown in Scheme 2. The results of enantioselective sulfoxidation catalyzed by vanadium–Schiff base complexes are listed in Table 1. For all of the catalysts **9**, the configurations of the products are all *S* form (entries 1–13), which suggests all of the reactions had a similar transitional state.

Surprisingly, for the tested complexes **9**, when the hydrogen atom on the 2,4-salicylaldehyde moieties was replaced by a *tert*-butyl slightly lower ee values resulted, except for the ligand derived from phenylglycinol (entries 1 *vs.* 2, 3 *vs.* 4, 5 *vs.* 6, 7 *vs.* 8). The catalysts derived from valinol, isoleucinol and phenylalaninol gave similar ee values (entries 1, 3, 5 or entries 2, 4, 6). It is easy to understand that a low ee value was obtained when the smaller alaninol derived catalyst **9i** was adopted (entry 9). Furthermore, there exists a certain relation between the R_1 and R_2 and the ee values, that is, a small R_1 group will cooperate with a larger R_2, and a large R_1 will cooperate with a smaller R_2. When R_1 is bulky *tert*-butyl, bulky R_2 groups, for example 2-*exo*-bornyl, 2-phenylethyl, decreased the enantioselectivity.[4b]

It seems that there exists a bulky group on Berkessel's Schiff base **10** (Scheme 4). But in fact, its stereo structure is like that of **11**, and the two naphthyl groups form a dihedral angle of a certain degree. Thus, the naphthyl groups construct a shield,

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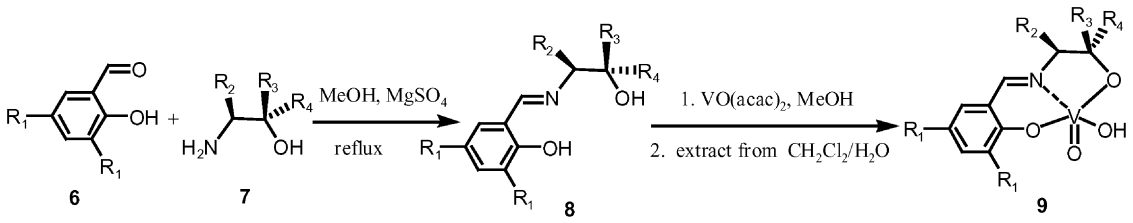


a R_1= R_3=R_4=H, R_2= i-Pr **b** R_1= t-Bu, R_2= i-Pr, R_3=R_4=H
c R_1= R_3=R_4=H, R_2= i-Bu **d** R_1= t-Bu, R_2= i-Bu, R_3=R_4=H
e R_1= R_3=R_4=H, R_2= Bn **f** R_1=t-Bu, R_2= Bn, R_3=R_4=H
g R_1= R_4=H, R_2=R_3= Ph **h** R_1= t-Bu, R_2= Ph, R_3=R_4=H
i R_1= R_3=R_4=H, R_2= Me **j** R_1= t-Bu, R_2= i-Pr, R_3=R_4=Ph

Scheme 3 Synthesis of Schiff base ligands **8** and vanadium–Schiff base complexes **9**.

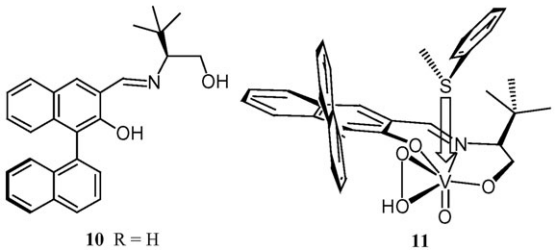
which limits the orientation of attack of anisole and thus improves the enantioselectivity (**11**). Katsuki's[4c] and Ahn's[4e] Schiff bases have similar stereo structures and demonstrate better enantioselectivity in asymmetric sulfoxidation.

R_3 and R_4 also affected the enantioselectivity of sulfoxidation (entries 8 and 10). In particular, when R_3 and R_4 are both bulky phenyls, a very low ee value was obtained. This is because the symmetric bulky groups decrease the asymmetry of the surroundings, and suggests that the V–O bond of the amino alcohol moiety never breaks down during the sulfoxidation. If V–O bond is easily broken during the reaction, little influence on enantioselectivity is expected. The facts seem not to coincide with Bryliakov's conclusion.[8]

The complexes **9a**, **9c** and **9e** were used in sulfoxidation of *p*-chlorophenyl methyl sulfide **4b**, and enantioselectivity of up to 68.1% ee was achieved (entries 11–13).

Although Fujita's[9] and Ellman's[10] oxovanadium Schiff base complexes contain oxovanadium alkoxide VO(OR) fragments, a VO(OH) fragment exists in the structures of the algal bromo/iodoperoxidases and the fungal chloroperoxidase,[11] which suggests that the VO(OR) in Fujita's and Ellman's single crystals will be converted into VO(OH) in the presence of water. The FAB-FT-ICRMS spectrum of vanadium–Schiff base complex **9e** extracted from water verified the existence of a VO(OH) fragment. Based on those facts, we deduced a mechanism of enantioselective sulfoxidation as shown in Scheme 5.

Five-coordinate oxovanadium Schiff base complex **12** is the start of the catalytic cycle. The hydroxyl of the oxovanadium complex **12** is in exchange with hydroperoxide to release H_2O.



10 R = H **11**

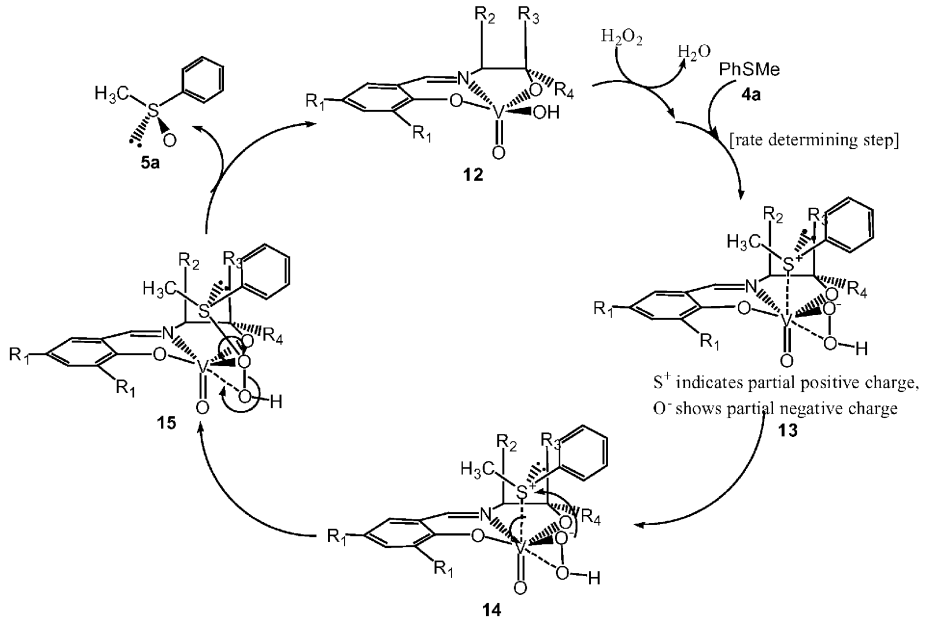
Scheme 4 Berkessel's Schiff base (**10**) and its stereo structure.

Then an electron pair from thioanisole coordinates with the vanadium of the complex (**13**), which is the rate-determining step. Due to steric repulsion, the other lone pair of electrons on thioanisole will point to the amino alcohol moiety and the bulky phenyl will locate between the R_3 group and V(O_2H) (**13**), which will determine the absolute configuration of the product sulfoxide. The coordinated thioanisole will show a partial positive charge, and the hydroperoxyl shows some negative charge; and S–V–O is in a space-favorable triangle (**13**). Therefore, the oxygen atom of hydroperoxyl attacks the sulfur atom of sulfide (to produce the *S* form of the sulfoxide) and an electron pair of the S–V bond moves to vanadium (**14**). Sequentially, the electrons of the V–O(–O–H) bond will turn to the S–O bond, which triggers the breaking of the O–O bond of hydroperoxyl and then the hydroxyl of hydroperoxyl and the vanadium form V–OH (**14**). Thus the *S*-sulfoxide is released from the cycle and the five-coordinate oxovanadium complex **12** is recovered. A new catalytic cycle will occur.

Table 1 Enantioselective sulfoxidation catalyzed by chiral vanadium–Schiff base complexes (in italics when R_1 = t-Bu)[a]

Entry	Complex	Substrate	Yield (%)[b]	Ee (%)[c]
1	**9a**	**4a**	78.1	55.9
2	*9b*	**4a**	*82.6*	*51.4*
3	**9c**	**4a**	86.3	55.7
4	*9d*	**4a**	*63.0*	*48.6*
5	**9e**	**4a**	76.0	59.2
6	*9f*	**4a**	*93.5*	*45.3*
7	**9g**	**4a**	67.4	48.4
8	*9h*	**4a**	*88.7*	*45.1*
9	**9i**	**4a**	51.6	6.7
10	*9j*	**4a**	*75.4*	*2.9 (3.6)*[d]
11	**9a**	**4b**	74.4	68.1
12	**9c**	**4b**	68.2	57.5
13	**9e**	**4b**	71.9	60.1

[a] Reaction conditions: vanadium Schiff base complexes (0.01 mmol), sulfide (1 mmol) and aqueous H_2O_2 (30%; 1.1 mmol) in CH_2Cl_2 (2 ml) in an ice–water bath (about 4 °C) for 4 h, unless otherwise mentioned. [b] Isolated yield after column chromatography. [c] The ee values were measured on the isolated product and determined by HPLC analysis on a Daicel chiralcel OD-H column. The absolute configurations were assigned by comparing optical rotations and/or HPLC elution order with known literature data. All configurations of sulfoxides are *S* form. [d] The datum was obtained using an ice–salt bath for 5 h.



Scheme 5 Proposed mechanism for enantioselective sulfoxidation catalyzed by vanadium–Schiff base complexes.

The oxygen atoms of the product sulfoxide and the hydroxyl in the oxovanadium complex all are from H_2O_2, which agrees with Ellman's observation.[10]

Conclusion

The effects of substituents of Schiff base ligands on enantioselective sulfoxidation were systematically examined. Some interesting results were obtained. Based on the experimental data and the reported facts, a reasonable mechanism of enantioselective sulfoxidation was proposed.

Acknowledgements

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7 The general procedure for the sulfoxidation reactions is as follows. Vanadium–Schiff base complex (0.01 mmol) and 1 mmol sulfide were dissolved in CH_2Cl_2 (2 mL) with an ice–water bath. To the mixture, 30% H_2O_2 (0.13 mL, 1.1 mmol) was added dropwise. The mixture was stirred for 2 to 16 h in an ice–water bath. The resulting solution was diluted with CH_2Cl_2 and washed with water and then with saturated NaCl solution. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using petroleum ether and ethyl acetate (2 : 1) as eluent.

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