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Vanadium-Catalyzed Enantioselective Sulfoxidation and Concomitant, Highly Efficient Kinetic Resolution Provide High Enantioselectivity and Acceptable Yields of Sulfoxides

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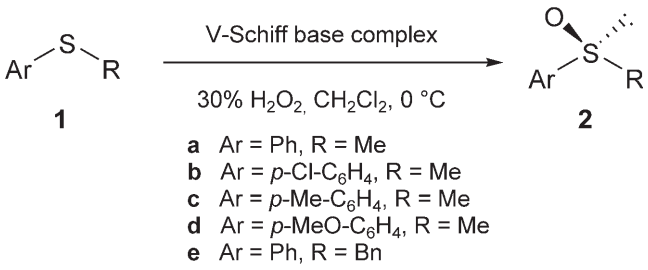
Abstract: Simple, inexpensive, preformed vanadium-Schiff base complexes were facilely prepared and used in enantioselective sulfoxidation. Both the amount of aqueous H_2O_2 and reaction time greatly influenced the ee values and yields of chiral sulfoxides. High enantioselectivities (up to 99% ee) and reasonable yields (>40%) for various chiral sulfoxides were achieved by combining enantioselective sulfoxidation and appropriate concomitant kinetic resolution.

Keywords: asymmetric catalysis; kinetic resolution; Schiff bases; sulfoxides; vanadium

Optically pure sulfoxides are a valuable class of compounds, which are extensively used as chiral auxiliaries and intermediates in current organic synthesis,[1] and also for important drugs, such as esomeprazole.[2] Catalytic enantioselective oxidation of sulfides is an efficient synthetic method for chiral sulfoxides.[1a,3] Recently, the enantioselective oxidation of sulfides catalyzed by chiral complexes of transition metals, such as titanium,[4] vanadium,[5] iron,[6] manganese,[7] has been extensively researched. In particular, Bolm found that vanadium-Schiff base complexes derived from chiral *tert*-leucinol are effective catalysts for sulfoxidation with aqueous H_2O_2 as an environmentally friendly oxidant (Scheme 1).[5a] Berkessel,[5b] Katsuki,[5c] Anson,[5d] and Ahn[5e] improved the Bolm's protocol. However, the Schiff base ligands are usually derived from expensive chiral *tert*-leucinol or 1-amino-2-indanol and complicated salicylaldedhyde analogues, which decreases their practical value.

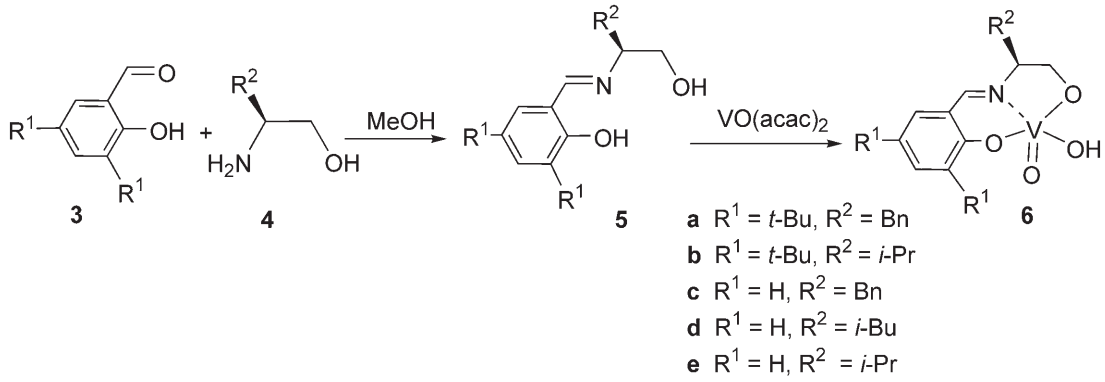


Scheme 1. Vanadium-catalyzed enantioselective oxidation of sulfides

The kinetic resolution of racemic sulfoxides, and oxidation of sulfides accompanying kinetic resolution catalyzed by titanium often gave high ee values of sulfoxides, but low yields.[4b,8] Recently Chan developed a one-pot, titanium-catalyzed tandem sulfoxidation and kinetic resolution process, which proceeded at different temperatures and gave extremely high ee values and acceptable yields of chiral sulfoxides.[9]

Katsuki found that 10% sulfone was observed in the case of methyl *p*-nitrophenyl sulfide as substrate during vanadium-catalyzed sulfoxidation;[5c] and Bolm found that when *p*-methoxybenzoic acid or its lithium salt was added in the iron complex, 10–15% sulfones were observed in cases of >90% ee sulfoxides obtained,[6b] which suggests that kinetic resolution could occur during vanadium- and iron-catalyzed sulfoxidation. To our knowledge, vanadium-catalyzed enantioselective oxidation of sulfides and concomitant kinetic resolution has not yet been studied in detail.[10]

During the continuation of our studies on enantioselective sulfoxidation,[11] we envisaged that, by combining appropriate kinetic resolution and enantioselective sulfoxidation, complexes of simple Schiff bases and vanadi-



Scheme 2. Synthesis of chiral Schiff bases and preformed vanadium-Schiff base complexes.

um might provide chiral sulfoxides with high ee values as well as acceptable yields.

In the previous studies, 50 mol % excess amounts of the expensive ligands were usually adopted in the vanadium-catalyzed sulfoxidation.[5] The excess ligands were wasted and the *in situ* catalysts made elucidation of the mechanism more difficult.[5g] We managed to prepare the preformed vanadium-Schiff base complexes without the need for excess ligands (Scheme 2).

In this paper we report the synthesis of simple, inexpensive, preformed chiral vanadium-Schiff base complexes and their application in asymmetric sulfide oxidation accompanying kinetic resolution.

Generally, when a salicylaldehyde **3** (1 equiv.) was reacted with a chiral amino alcohol **4** (1 equiv.) in anhydrous methanol, the yellow-colored simple chiral Schiff base **5** was instantly formed, which is pure enough for ^{1}H NMR determination. Then 1 equiv. of $VO(acac)_2$ was added to the Schiff base solution, and a brown to violet precipitate or solution was formed after 3 hours under reflux. After removal of methanol, the vanadium-Schiff base complex **6** was obtained. The complexes **6c** and **6d** were characterized by IR, FAB-FT-ICR-MS, and ^{51}V NMR. In order to compare them with the *in situ* catalysts, chiral Schiff bases derived from 3,5-di-*tert*-butylsalicylaldedyde and chiral phenylalaninol and valinol were prepared with a similar procedure.

Some preformed catalysts and some *in situ* catalysts were tested in the oxidation of thioanisole (**1a**) and *p*-chlorophenyl methyl sulfide (**1b**). The results are showed in Table 1. The data of Table 1 show that preformed catalysts gave slightly higher enantioselectivity in the asymmetric oxidation of **1a** (entries 3 *vs.* 1, 2; 5 *vs.* 4; 7 *vs.* 6) and of **1b** (entries 9 *vs.* 8). Probably VO $(acac)_2$ and Schiff bases had not completely been transformed into complexes with stirring for a short time at room temperature before aqueous H_2O_2 was added, and then the residual $VO(acac)_2$ was turned into diperoxovanadium $[VO(O_2)O_2H]$, which oxidized sulfides into racemic sulfoxides. Several simple, preformed vanadium-Schiff base complexes **6c**, **6d** and **6e** exhibited similar ee values and yields (entries 7, 10 and 11). Among them, two simple complexes **6c** and **6d** derived from salicylaldehyde and phenylalaninol and isoleucinol were adopted for further investigation in the sulfoxidation accompanying kinetic resolution.

The ees were slightly increased when 2 mol % **6c** and **6d** were used (data not given). When 5 mol % **6c** and **6d** and 1.2 equivs. H_2O_2 were used, much higher ee values were achieved (82.5% ee for **6d**) (Table 2, entries 3 and 4). Therefore the effect of aqueous H_2O_2 on the oxidation of the model substrate thioanisole was screened (Table 2). When the amount of 30% H_2O_2 was raised from 0.8 to 2.0 equiv, ee values increased steadily (entries 1, 3, 5 and 7 for **6c**; entries 2, 4, 6 and 8 for **6d**).

Table 1. The effects of the preformed catalysts and the *in situ* catalysts.[a]

Entry	Ligand or complex	Substrate	Yield [%]	ee [%][b]
1[c]	**5a**	**1a**	93	39
2[c]	**5a**	**1a**	60	27
3	**6a**	**1a**	93.5	45.3
4[c]	**5b**	**1a**	50	29
5	**6b**	**1a**	82.6	51.4
6	**5c**	**1a**	94.1	55.6
7	**6c**	**1a**	76.0	59.2
8	**5c**	**1b**	95.0	56.3
9	**6c**	**1b**	82.4	60.1
10	**6d**	**1a**	86.3	55.7
11	**6e**	**1a**	78.1	55.9

[a] Reaction conditions: the *in situ* catalyst from $VO(acac)_2$ (0.01 mmol) and Schiff base ligand (0.015 mmol) or vanadium-Schiff base complexes (0.01 mmol), thioanisole (1 mmol) and aqueous H_2O_2 (30%; 1.1 mmol) in CH_2Cl_2 at 0 °C for 4 hours, unless otherwise mentioned.

[b] The ee values were determined by HPLC. The absolute configuration was assigned by comparison with literature values. All of the major isomers are in the *S* form.

[c] Data cited from literature:[5f,g] 1 mol % $VO(acac)_2$, 1.5 mol % Schiff base, at 1 °C for 1 hour and then at 20 °C for 12 hours or 15 hours.

Table 2. The effects of the amount of aqueous H_2O_2 on enantioselective sulfoxidation and concomitant kinetic resolution catalyzed by **6c** and **6d**.[a]

Entry	H_2O_2 [equivs.]	Catalyst	Yield [%]	ee [%][b]
1	0.8	**6c**	68.5	63.3
2	0.8	**6d**	64.4	67.3
3	1.2	**6c**	72.8	72.4
4	1.2	**6d**	78.2	82.5
5	1.6	**6c**	60.3	83.6
6	1.6	**6d**	58.4	90.0
7	2.0	**6c**	41.2	98.9
8	2.0	**6d**	40.6	99.0

[a] Reaction conditions: vanadium complexes (0.01 mmol), thioanisole (1 mmol) and 30% H_2O_2 (0.8 mmol to 2.0 mmol) in CH_2Cl_2 at 0 °C for 8 hours.
[b] See Table 1.

Table 3. The effects of time on enantioselective sulfoxidation and accompanying kinetic resolution catalyzed by **6c** and **6d**.[a]

Entry	Time [h]	Catalyst	Yield [%]	ee [%][b]
1	2	**6c**	69.4	77.0
2	2	**6d**	66.4	73.1
3	4	**6c**	65.1	85.8
4	4	**6d**	52.4	91.0
5	6	**6c**	46.3	91.0
6	6	**6d**	48.7	93.5
7	8	**6c**	41.2	98.9
8	8	**6d**	40.6	99.0

[a] Reaction conditions: vanadium complexes (0.05 mmol), thioanisole (1 mmol) and 30% H_2O_2 (2.0 mmol) in CH_2Cl_2 at 0 °C for the given time.
[b] See Table 1.

But the yields increased in the beginning when H_2O_2 increased from 0.8 to 1.2 equivs. (entries 1 and 3 for **6c**; entries 2 and 4 for **6d**), and then decreased when H_2O_2 rose from 1.2 to 2.0 equivs. (entries 3 to 8). The reason for this is that an insufficient amount of H_2O_2 cannot completely transform the sulfide into the sulfoxide (entries 1 and 2), and surplus H_2O_2 causes kinetic resolution of the resulting sulfoxide (entries 5 to 8). During the course of the kinetic resolution, vanadium-Schiff base complexes mainly transformed the undesired (*R*)-form sulfoxide into sulfone, and higher concentration of aqueous H_2O_2 accelerated the progress. Thus, the sulfoxide predominant in the (*S*)-form was obtained in up to 99% ee as well as more than 40% yield (entries 7 and 8).

Next we screened the effect of reaction time for the oxidation of thioanisole with 2.0 equivs. of H_2O_2 catalyzed by **6c** and **6d** (Table 3). When the time was increased from 2 hours to 8 hours, yields of the sulfoxide decreased steadily but ee values boosted up rapidly (entries 1, 3, 5 and 7 for **6c**; entries 2, 4, 6 and 8 for **6d**). The rapid increase of ee values implies that the kinetic resolution of the resulting sulfoxide catalyzed by the vanadium complexes were of extremely high efficiency, that is, oxidation of the undesired isomer of the resulting sulfoxide was highly selectivity.

Besides, the tendency of yields indicates that 2 hours were enough to completely oxidize thioanisole (**1a**) under the reaction condition, and suggests that the rate of oxidation of thioanisole (**1a**) catalyzed by the preformed complexes was very fast.

High ee values (85–91% ee) and good yields (52–65%) have been achieved after 4 hours (entries 3 and 4). Taking into account the acceptable yields of chiral sulfoxides and the different reaction rates for various sulfides, 4 hours was the reaction time of choice for other substrates.

Based on the above investigations, 2.0 equivs. of 30% H_2O_2 and 4 hours were adopted for sulfoxidation of other substrates (Table 4). Relative to the model substrate

Table 4. Substrates tested in enantioselective sulfoxidation and accompanying kinetic resolution catalyzed by vanadium-Schiff base complexes **6c** and **6d**.[a]

Entry	Substrate	Catalyst	Yield [%]	ee [%][b]
1	**1a**	**6c**	65.1	85.8
2	**1a**	**6d**	52.4	91.0
3	**1c**	**6c**	59.4	81.2
4	**1c**	**6d**	62.3	86.1
5	**1d**	**6c**	76.3	76.8
6	**1d**	**6d**	77.2	78.0
7	**1b**	**6c**	60.3	92.1
8	**1b**	**6d**	31.2	99.2
9	**1e**	**6c**	58.8	86.4
10	**1e**	**6d**	58.6	83.2

[a] Reaction conditions: vanadium complexes (0.05 mmol), sulfide (1 mmol) and 30% H_2O_2 (2.0 mmol) in CH_2Cl_2 at 0 °C for 4 hours.
[b] See Table 1.

PhSMe, ee values decreased slightly and yields remained relatively stable when *p*-TolSMe (**1c**) was used (entries 3 *vs.* 1, 4 *vs.* 2). In the case of *p*-$MeOC_6H_4SMe$ (**1d**), ee values decreased evidently (76–78% ee), but yields (76–77%) are higher (entries 5 *vs.* 1, 6 *vs.* 2). When *p*-ClC_6H_4 SMe (**1b**) was used as substrate, large improvements of enantioselectivity (92–99% ee) and lower yields were observed. These results suggest that electron-donating groups on the phenyl group of the substrates slow down the rate of sulfoxidation and kinetic resolution, while electron-drawing substituents on the phenyl group of the substrates accelerate the reaction rate of sulfoxidation and kinetic resolution when vanadium-Schiff base complexes are used as catalysts. It is interesting that higher enantioselectivity (83–86% ee) and yield (58%) were obtained for PhSBn (**1e**). As a whole, for various substrates, the ee values were good to excellent, and yields were good when the inexpensive, preformed **6c** and **6d** were used as catalysts (entries 1 to 8).

In conclusion, we have successfully developed cheap preformed complexes from simple Schiff bases and $VO(acac)_2$ and a practical process for high ees and acceptable yields of chiral sulfoxides. In the course of enantioselective sulfoxidation, the kinetic resolutions catalyzed by the preformed complexes were of high efficiency, and the kinetic resolution provided high enantioselectivities as well as good yields of PhSOMe. Furthermore, the catalysts are generally efficient for the enantioselective oxidation of various substituted sulfides. The derived principles are probably suitable for other vanadium catalysts in asymmetric sulfoxidation.

Experimental Section

Synthesis of Vanadium-Schiff Base Complexes

A mixture of 5 mmol of salicylaldehyde **3**, 5 mmol of (*S*)-2-aminoalcohol **4** and 15 mL of methanol was heated to reflux for 2 hours, which gave the yellow Schiff base. Then, 5 mmol of $VO(acac)_2$ were added into the resulting solution. After one hour at reflux, a brown precipitate of **6c** appeared in the solution, others gave a dark-red to purple solution. Vanadium-Schiff base complexes were obtained by filtration (for **6c**) or by removing the solvent under reduced pressure.

***Vanadium complex of (S)-2-(N-salicylidene)-amino-3-phenyl-1-propanol* (6c):** Brown solid; yield: 85–95%; IR: $\nu =$ 3432 (br), 1625, 1601, 1544, 1446, 1298, 991, 741, 701, 594 cm^{-1}; FAB-FT-ICR-MS: $m/z = 336.0440$ $[M-H]^-$, calcd. for $C_{16}H_{15}NO_4V$: 336.0446; ^{51}V NMR (131.3 MHz, CH_2Cl_2): $\delta = 529.7$, 536.6, 550.0, and 562.9.

***Vanadium complex of (2S,3S)-2-(N-salicylidene)-amino-3-methyl-1-pentanol* (6d):** Black solid; yield: quantitative; IR: $\nu =$ 3300 (br), 1626, 1603, 1544, 1469, 1446, 1400, 1295, 1052, 988, 761, 745, 551 cm^{-1}; FAB-FT-ICR-MS: $m/z = 302.0608$ $[M-H]^-$, calcd. for $C_{13}H_{17}NO_4V$: 302.0602; ^{51}V NMR (131.3 MHz, CH_2Cl_2): $\delta = 535.6$, 536.7, 540.5, 548.3, 559.0.

General Procedures for Enantioselective Oxidation of Sulfides Catalyzed by Vanadium Complexes

Vanadium-Schiff base complex (0.01 mmol) and 1 mmol sulfide were dissolved in CH_2Cl_2 (2 mL) in an ice/water bath. To the solution, 30% H_2O_2 (0.8 to 2.0 mmol) was added dropwise. The mixture was stirred for 2 to 8 hours 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.

Supporting Information

^1H NMR and ^{13}C NMR spectra of ligand **5c**, ^1H NMR and ^{13}C NMR spectra of ligand **5d**, FAB-FT-ICR-MS, ^{51}V NMR and IR spectra of catalyst **6c**, FAB-FT-ICR-MS, ^{51}V NMR and IR spectra of catalyst **6d**, some chiral HPLC diagrams of racemic and optical active *p*-PhSOMe, and some chiral HPLC diagrams of racemic and optical active *p*-ClPhSOMe.

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