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Enantioselective oxidation of sulfides with hydrogen peroxide catalyzed by vanadium complex of sterically hindered chiral Schiff bases

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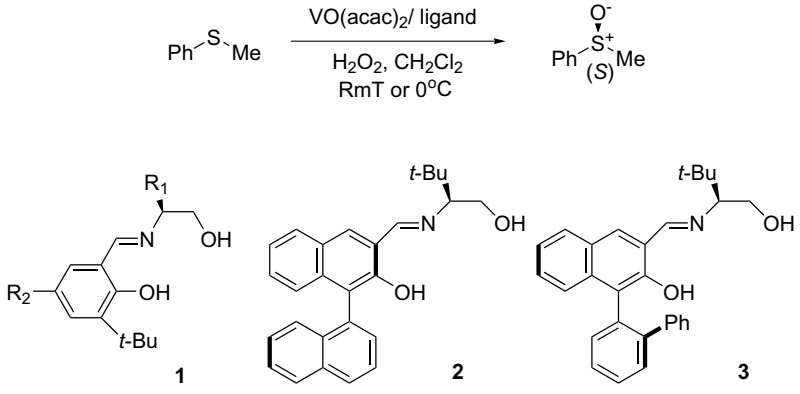
Abstract—Sterically hindered chiral Schiff base ligands **4a**–**d** were prepared from an aldehyde derived from BINOL. The vanadium complexes of the ligands catalyze an efficient, enantioselective H_2O_2-promoted sulfoxidation of alkyl aryl sulfides, and enantioselectivities as high as 98–99% ee are observed in the sulfoxidation of benzyl aryl sulfides.

Chiral sulfoxides are an important class of compounds as chiral auxiliaries in asymmetric carbon–carbon bond forming reactions[1] and as bioactive ingredients in the pharmaceutical industry.[2] As part of our research for the synthesis of lansoprazole,[3] a drug used to heal and relieve symptoms of gastric or duodenal ulcers, we have been interested in the synthesis of chiral sulfoxides, particularly using an asymmetric oxidation of sulfides. The enantioselective oxidation of sulfides catalyzed by chiral complexes of transition metals such as titanium,[4] manganese,[5] iron[6] or vanadium[7] has been extensively studied in recent years for the synthesis of optically active sulfoxides. Especially, the catalytic system of a chiral vanadium-tridentate ligand **1** reported by Bolm[7b] has received a great attention recently because of its simplicity and high activity using hydrogen peroxide, an environmentally benign oxidant (Scheme 1). The enantioselectivity of the reaction has been further improved by Berkessel[7d] and Katsuki[7e] employing ligands derived from a chiral binaphthalene (**2**) and a chiral biphenyl (**3**), respectively.

We were particularly interested in Berkessel's ligand because the catalytic system might be improved by



Scheme 1.

Keywords: Enantioselective sulfoxidation; Chiral sulfoxide; Hydrogen peroxide.
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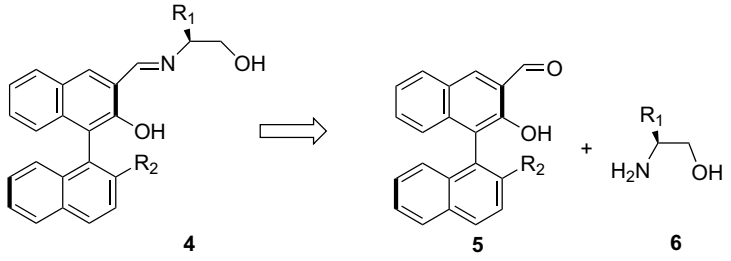
introducing a substituent onto the binaphthyl subunit such as ligand **4** (Scheme 2). It had been reported that the steric effect of the substituent, R_1 of ligand **1** is important to get a high enantioselectivity in the vanadium catalyzed asymmetric oxidation of sulfides.[7h] We thought that R_2 as well as R_1 of the ligand **4** might also provide an improvement in the enantioselectivity as had been observed in the asymmetric epoxidation of olefins catalyzed by a chiral manganese salen complex.[8] Thus, here we want to report the enantioselective sulfoxidation of aryl sulfides catalyzed by chiral vanadium complexes derived from the chiral Schiff base **4**.

Initially, we expected that the ligand **4a**, which contains sterically hindered *t*-butyl group at R_1 and *t*-butyl ester at R_2 might give a good enantioselectivity in the vanadium catalyzed oxidation of sulfide. Thus, the Schiff-base (*R*,*S*)-**4a**,[9] prepared from the aldehyde (*R*)-**5a**[8] derived from (*R*)-BINOL and (*S*)-*t*-leucinol, was applied to the asymmetric sulfoxidation of thioanisole at room temperature.[10] The reaction produced (*S*)-methyl phenyl sulfoxide in 86% yield with an enantioselectivity of 82% ee (Table 1, entry 1), which is better than the reported result obtained with **2** (71% ee). Since the ligand **4a** showed a good enantioselectivity at room temperature, we decided to study the asymmetric sulfoxidation in detail. At first, we ran the reaction at 0 °C to see the temperature effect with thioanisole and obtained the enantioselectivity of 86% ee (entry 2). The result is better than the Berkessel's result (78% ee)[7d] studied with ligand **2** at 0 °C, and similar to the results reported by Katsuki[7e] and Anson.[7f] Interestingly, (*S*,*S*)-**4a** whose binaphthyl subunit is in *S*-configuration also gave the same (*S*)-isomer of methyl phenyl sulfoxide as the major enantiomer,

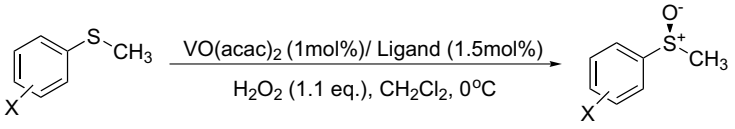


(*R*,*S*)-**4a**, R_1 = *t*-Bu, R_2 = -OOC-*t*-Bu
(*R*,*S*)-**4b**, R_1 = *t*-Bu, R_2 = -OOC-CH_3
(*R*,*S*)-**4c**, R_1 = *t*-Bu, R_2 = -O-$SiPh_2$(*t*-Bu)
(*R*)-**4d**, R_1 = H, R_2 = -OOC-*t*-Bu

5a, R_2 = -OOC-*t*-Bu
5b, R_2 = -OOC-CH_3
5c, R_2 = -O-$SiPh_2$(*t*-Bu)

Scheme 2.

Table 1. Asymmetric sulfoxidation of methyl aryl sulfide



Entry	Sulfide	Schiff base	Yield[a] (%)	Ee[b] (%)	Config.[c]
1	C_6H_5–S–CH_3	(*R*,*S*)-**4a**	86	82[d]	*S*
2		(*R*,*S*)-**4a**	90	**86**	*S*
3		(*S*,*S*)-**4a**	95	72	*S*
4		(*R*,*S*)-**4b**	95	78	*S*
5		(*R*,*S*)-**4c**	66	45	*S*
6	*p*-MeO–C_6H_4–S–CH_3	(*R*,*S*)-**4a**	82	77	*S*
7	*p*-Me–C_6H_4–S–CH_3	(*R*,*S*)-**4a**	86	**87**	*S*
8	*p*-Br–C_6H_4–S–CH_3	(*R*,*S*)-**4a**	77	73[e]	*S*
9	*p*-NO_2–C_6H_4–S–CH_3	(*R*,*S*)-**4a**	76	68[f]	*S*
10	*o*-Br–C_6H_4–S–CH_3	(*R*,*S*)-**4a**	78	31	*S*
11		(*S*,*S*)-**4a**	89	42	*S*
12		(*R*,*S*)-**4b**	79	40	*S*
13	C_6H_5–S–CH_3	(*R*)-**4d**	46	0[d]	

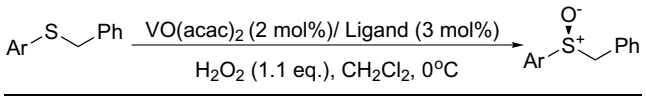
[a] Isolated yield.
[b] Determined by HPLC with a Daicel Chiralcel OD column.
[c] Absolute configuration of the major product was determined by comparison of its sign of optical rotation with literature data.
[d] Room temperature reaction.
[e] Determined by ^{1}H NMR (400 MHz) analysis using (*R*)-(+)-2,2′-dihydroxy-1,1′-binaphthyl as a shift reagent.
[f] Determined by ^{1}H NMR (400 MHz) analysis using (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol as a shift reagent.

however, with an inferior enantioselectivity (72% ee, entry 3). As shown in entry 13, the ligand without a chiral center at the imine subunit such as **4d** did not give any enantioselectivity in the reaction. Thus, the configuration of sulfoxide must be greatly affected by the configuration of aminoalcohol used in the ligand synthesis. To improve the enantioselectivity, a sterically hindered substituent R_2 such as *tert*-butyldiphenylsilyloxy group was introduced (ligand **4c**). However, the selectivity obtained with **4c** was low (entry 5) and even worse than the enantioselectivity obtained with **4b** (entry 4) containing acetyl group at R_2, indicating that a proper steric hindrance has to be introduced at R_2. Thus, ligand **4a** showed the best enantioselectivity in the oxidation of thioanisole among the ligands that we prepared.

Oxidations of various alkyl substituted-aryl sulfides were also examined with ligand **4a** (entry 6–11). Most of the reactions showed good enantioselectivities reaching 87% ee (entry 7) except *ortho*-substituted substrates (entries 10–12). Sulfones expecting from an oxidation of the corresponding sulfoxides were formed only to a minor extent (less than 3%). Interestingly, (*S*,*S*)-**4a** was shown to be the better catalyst compared to (*R*,*S*)-**4a** in the oxidation of methyl *o*-bromophenyl sulfide (entries 10 and 11). The result contrasts with the oxidation of thioanisole (entries 2 and 3).

We also examined the oxidation of benzyl 4-substituted phenyl sulfides with ligand **4a** (Table 2). Surprisingly, the reaction proceeded with an excellent enantioselectivity. In the sulfoxidation of benzyl phenyl sulfide, (*S*)-benzyl phenyl sulfoxide was obtained in 99% ee (entry 1). This is the best record that has been observed in the sulfoxidation of benzyl phenyl sulfide with a vanadium catalyst. Further, in the oxidation of benzyl 4-bromophenyl sulfide, (*S*)-benzyl 4-bromophenyl sulfoxide, a versatile intermediate for the syntheses of various chiral sulfoxides using a substitution reaction[4l] was also obtained in 98% ee (entry 3). These results demonstrate the potential of our catalytic system. It is difficult to provide a reasonable explanation for the high enantioselectivities observed with our catalytic system at the present stage. However, the low enantioselectivity obtained with (*R*,*S*)-**4b** (entry 5) suggests that the pivaloyl group of (*R*,*S*)-**4a**-vanadium catalyst may interact with the benzyl group of incoming aryl benzyl sulfides under the catalytic condition to give the high face selection in the sulfide oxidation.

Table 2. Asymmetric sulfoxidation of aryl benzyl sulfide



Entry	Ligand	Ar	Yield[a] (%)	Ee[b] (%)	Config.[c]
1	(*R*,*S*)-**4a**	Ph	78	**99**	*S*
2	(*R*,*S*)-**4a**	*p*-MeC_6H_4	90	94	*S*
3	(*R*,*S*)-**4a**	*p*-BrC_6H_4	85	**98**	*S*
4	(*R*,*S*)-**4a**	*p*-$MeOC_6H_4$	81	67	*S*
5	(*R*,*S*)-**4b**	Ph	67	69	*S*

[a] Isolated yield.
[b] Determined by HPLC using Daicel Chiralcel OJ column.
[c] Absolute configuration of the major product was determined by comparison of its sign of optical rotation with literature data.

In summary, we were able to optimize the Berkessel's catalytic system for the asymmetric oxidation of alkyl aryl sulfides. The Schiff base ligand **4a** showed an excellent enantioselectivity reaching 99% ee in the oxidation of benzyl aryl sulfide.

Acknowledgements

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9. A solution of **5a** (100 mg, 0.25 mmol) and (*S*)-*t*-leucinol (35 mg, 0.30 mmol) in ethanol (6 mL) was stirred at room temperature. After 3 h, the solution was concentrated under reduced pressure. Flash column chromatography of the residue provided **4a** (115 mg, 92%): mp 97–98 °C; $[\alpha]_D^{22}$ +17 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.61 (s, 1H), 8.01–7.94 (m, 3H), 7.86–7.84 (m, 1H), 7.48–7.40 (m, 3H), 7.34–7.26 (m, 3H), 7.12–7.11 (m, 1H), 3.97–3.91 (m, 1H), 3.74–3.70 (m, 1H), 3.03 (dd, $J_1 = 9.44$ Hz, $J_2 = 2.73$ Hz, 1H), 1.63 (s, 2H), 0.97 (s, 9H), 0.78 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.2, 165.7, 154.5, 146.9, 135.0, 133.6, 133.4, 131.7, 129.0, 128.3, 128.2, 128.1, 127.1, 126.3, 126.1, 125.3, 125.0, 124.4, 123.4, 122.0, 120.2, 115.6, 81.7, 62.4, 38.6, 33.3, 27.1, 26.5. Anal. Calcd for $C_{32}H_{35}NO_4 \cdot H_2O$: C, 74.54; H, 7.23; N, 2.72. Found C, 74.76; H, 6.85; N, 2.63%.
10. The general procedure used for the sulfoxidation reactions is as follows: Vanadyl acetylacetonate (5.3 mg, 0.02 mmol), and a ligand (0.03 mmol) were dissolved in CH_2Cl_2 (3 mL), and stirred 10 min at room temperature. After the addition of a sulfide (1.0 mmol), 30% H_2O_2 (0.13 mL, 1.1 mmol) was added. The mixture was stirred for 24 h at room temperature or 0 °C and quenched with satd Na_2SO_3 solution. The resulting solution was extracted with CH_2Cl_2. The organic layer was briefly dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography.