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Synthesis of New Chiral Ligands Based on Thiophene Derivatives for Use in Catalytic Asymmetric Oxidation of Sulfides

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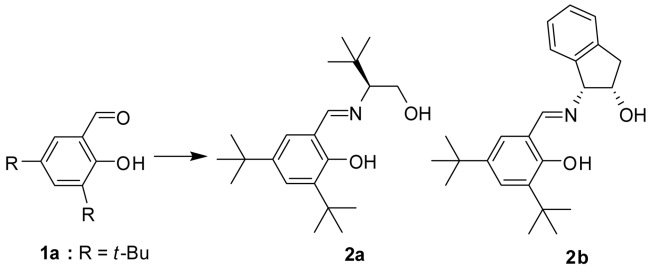
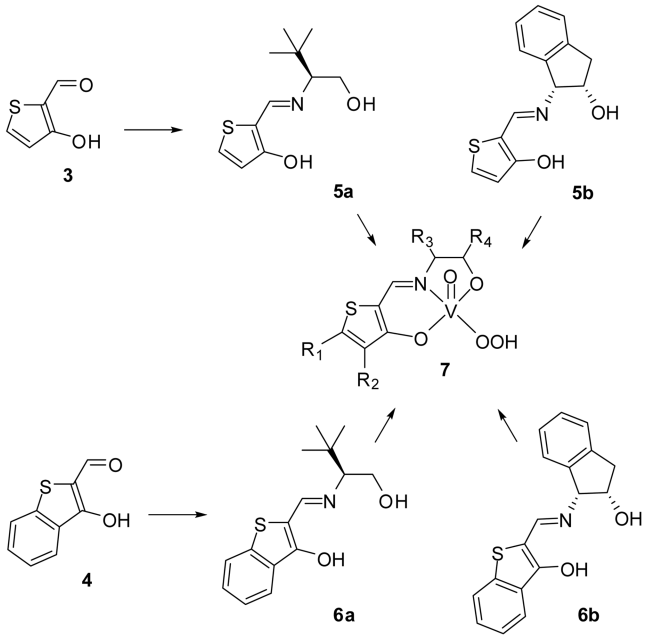
Chiral sulfoxides are important functional groups for various applications.[1,2] For example, the biological activities of sulfoxide containing drugs such as omeprazole are strongly related to the chirality of the sulfoxide group; for this reason, esomeprazole, the enantiomerically pure form of omeprazole, was later developed. There are several chiral sulfoxide based drugs that have been introduced by the pharmaceutical industry including armodafinil, aprikalim, oxisurane, and ustiloxin. Chiral sulfoxides have also been utilized as chiral auxiliaries in asymmetric syntheses of chiral intermediates.[2]

Chiral sulfoxides can be obtained either by resolution of racemic mixtures or by asymmetric oxidation of sulfides.[3] Among the numerous sulfoxidation methods, the asymmetric oxidation of sulfides by hydrogen peroxide in the presence of a chiral catalyst is expected to be the most attractive method because of its high atom economy and the use of a "green oxidant", hydrogen peroxide.[4] Our interest in the asymmetric oxidation of sulfides by hydrogen peroxide was also motivated by the desire to develop an efficient method to synthesize drugs such as esomeprazole.[5] In this regard, reactions catalyzed by vanadium complexes of the Bolm type,[4a] such as the tridentate chiral Schiff bases **2a** and **2b** (Scheme 1) were chosen since they have previously been used to prepare chiral sulfoxides with good enantioselectivities.[4g]

Recently, in an effort to improve catalytic activity, we designed new tridentate Schiff base ligands **5** and **6**, which we hypothesized would show catalytic asymmetric sulfoxidation activity similar to ligand **2** (Scheme 2). The angles θ_5 and θ_6 of aldehyde **3**, the starting material for ligand **5**, were calculated by the MM2 program to be larger than θ_2 and θ_3 of salicylaldehyde, respectively, due to the five-membered thiophene ring (Figure 1). However, the distance between O7 and O8 of **3**, which is related to the bite angle of the metal-ligand complex **5**, is similar to the distance between O8 and O9 of salicylaldehyde due to the small angle θ_4 of **3** compared with θ_1. These data indicate that the



Scheme 1. Tridentate chiral Schiff bases.



Scheme 2. New tridentate chiral ligands based on thiophene derivatives.

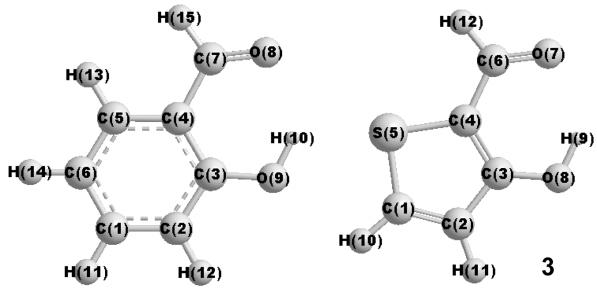


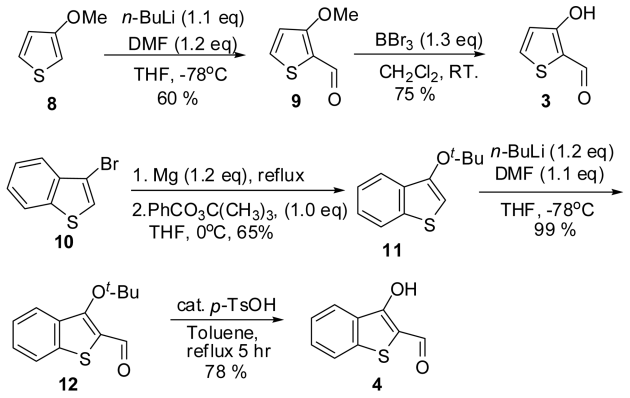
Figure 1. Calculated properties of salicylaldehyde and 3-hydroxythiophene-2-carbaldehyde **3**.

reaction of tridentate ligand **5** with $VO(acac)_2/H_2O_2$ can produce the vanadium complex **7** which has been assumed as the active catalyst in the sulfoxidation reaction. In fact, the vanadium complex with ligand **5** showed a good catalytic activity in the sulfoxidation of sulfide by hydrogen peroxide. Thus, we report here the detailed study of the asymmetric sulfoxidation catalyzed by the new vanadium complexes prepared from the tridentate ligands **5** and **6**.

The 3-hydroxythiophene-2-carbaldehyde derivatives **3** and **4**, key compounds for the syntheses of **5** and **6**, are known compounds and have been used for the preparation of metal complexes. However, detailed methods for their preparation are not well documented.[6] Thus, we prepared the compounds according to scheme 3 starting from the commercially available reagents 3-methoxythiophene and 3-bromobenzothiophene. In the synthesis of 3-hydroxythiophene-2-carbaldehyde **3**, the formylation step gave a mixture of 3-methoxythiophene-2-carbaldehyde and 3-methoxythiophene-5-carbaldehyde in a ratio of 60:40. The regioselectivity, although low, can be rationalized by neighboring group participation of the methoxy group to give predominantly lithiation at the 2-thiophene position. Fortunately, the two formylated compounds were easily separated using silica gel column chromatography.

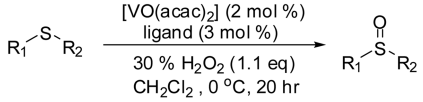
Benzothiophene carbaldehyde **4** was synthesized from 3-bromobenzothiophene (**10**) in three steps (Scheme 3). First, 3-*t*-butoxybenzothiophene was prepared in 65% yield by reaction of the Grignard reagent derived from compound **10** with *t*-butyl peroxybenzoate.[7] Then, formylation and dealkylation of compound **11** provided carbaldehyde **4** in 78% yield. Chiral Schiff bases **5a**, **5b**, **6a**, and **6b** were obtained from the reaction between the aldehydes (**3** and **4**) and the chiral aminoalcohols (*S*)-*t*-leucinol and (1*R*,2*S*)-1-amino-2-indanol (Scheme 2).

Next, we examined the catalytic activity of these chiral Schiff bases in the asymmetric oxidation of thioanisole (Table 1). Vanadium complex catalysts, generated *in situ*, were used for the oxidation reaction. For comparison purposes, Schiff bases **2a**, **b** were also synthesized. In the sulfoxidation of thioanisole, the yields obtained with **5a**, **b** and **6a**, **b** were similar to the yields with **2a**, **b**, respectively, indicating that catalytic activity of the new ligands was



Scheme 3. Synthetic methods for compounds **3** and **4**.

Table 1. Enantioselective oxidation of sulfides with H_2O_2 catalyzed by vanadium Schiff bases[a]



Entry	Ligand	R_1	R_2	Yield (%)[b]	Ee (%)[c]	Config[g]
1	**2a**	Ph	CH_3	93	66	(*S*)
2	**2b**			81	56	(*R*)
3	**5a**			83	41	(*S*)
4	**5b**			84	62	(*R*)
5	**6a**			89	28	(*S*)
6	**6b**			88	68	(*R*)
7	**2a**	*p*-Br-Ph		61	52[d]	(*S*)
8	**6b**			86	62[d]	(*R*)
9	**2a**	*p*-NO_2-Ph		59	48[e]	(*S*)
10	**6b**			65	41[e]	(*R*)
11	**2a**	*p*-Me-Ph		45	60	(*S*)
12	**6b**			80	70	(*R*)
13	**2a**	*p*-OMe-Ph		36	50	(*S*)
14	**6b**			63	75	(*R*)
15	**2a**	2-Naphthyl		65	64	(*S*)
16	**5b**			71	44	(*R*)
17	**6b**			84	79	(*R*)
18	**2a**	Phenyl	Benzyl	60	61[f]	(*S*)
29	**5b**			84	60[f]	(*R*)
20	**6b**			88	67[f]	(*R*)

[a]Reaction conditions: sulfide (1.0 mmol), ligand (0.03 mmol), $VO(acac)_2$ (0.02 mmol), 30% H_2O_2 (1.1 mmol), CH_2Cl_2 (3.0 mL). [b]Isolated yield. [c]Determined by HPLC with a Daicel Chiralcel OD column. [d]Determined by ^{1}H-NMR (300 MHz, $CDCl_3$) analysis using (*R*)-2,2'-dihydroxy-1,1'-binaphthyl as a shift reagent. [e]Determined by ^{1}H-NMR (300 MHz, $CDCl_3$) analysis using (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol as a shift reagent. [f]Determined by HPLC with a Daicel Chiralcel OJ column. [g]Absolute configuration of the major product was determined by comparison of its sign of optical rotation with data from the literature.

comparable to the well-studied ligands **2a**, **b** (entries 1-6). Unfortunately, the enantioselectivites obtained with our new ligands, **5a** (41% ee) and **6a** (28% ee), were inferior to those with **2a** (66% ee). Interestingly, the Schiff bases **5b** and **6b**, prepared with the sterically hindered (1*R*,2*S*)-1-amino-2-indanol, gave the chiral thioanisole sulfoxide with good enantioselectivities, 62% ee and 68% ee (entries 4 and 6) respectively, which were better than the results with **2b** (56% ee, entry 2). Although these enantioselectivities were similar, they demonstrate the potential of our newly designed ligands in the asymmetric sulfoxidation reaction. The absolute configuration of the sulfoxide obtained with ligands **2**, **5**, and **6** was dependent upon the configuration of the amino alcohol moiety, indicating that the Schiff bases **5** and **6** behaved similarly to the Schiff base **2** in this reaction.

Various para-substituted phenyl methyl sulfides were also examined in the catalytic oxidation reaction with ligands **2a** and **6b** (entry 7-14) to check for a substituent effect. In all cases, the yields and enantioselectivities with Schiff base **6b** were better than with Schiff base **2a** except for para-nitrothioanisole (entries 7-14). As shown in Table 1, a

general pattern was observed in the asymmetric sulfoxidations catalyzed by Bolm type catalysts such as **2a** that thioanisoles substituted with either electron withdrawing or electron donating groups gave lower yields and enantioselectivities compared with the non-substituted thioanisole.[5a] In the case of **6b**, this substituent effect was similarly observed with respect to yield; however, unlike **2a**, Schiff base **6b** provided good enantioselectivities with thioanisoles containing electron donating groups (entries 6, 12, and 14).

Finally, oxidations of other sulfides such as 2-methylsulfanyl naphthalene and phenyl benzyl sulfide were also examined with the Schiff bases **2a**, **5b**, and **6b** (entries 15-20). As was observed with thioanisoles, Schiff base **6b** resulted in good enantioselectivities in contrast to **2a**. In the oxidation of sulfides catalyzed by the vanadium complexes, only trace amounts of the sulfone were observed. Kinetic resolution of racemic phenyl methyl sulfoxide with the vanadium complex of Schiff base **6b** was not successful (less than 8% ee).[4a,b] From this result, we believe that the enantioselectivities obtained with Schiff bases derived from **4** and **5** originate mainly from the asymmetric oxidation of the sulfide and not from kinetic resolution.

In conclusion, we discovered that the vanadium complexes of new Schiff base ligands **5** and **6** prepared from thiophene derivatives efficiently catalyze the asymmetric oxidation of sulfides by hydrogen peroxide to provide sulfoxides with enantioselectivities up to 79% ee and in yields up to 89%. Notably, Schiff base **6b** showed better or similar enantioselectivity than the well-studied Schiff base **2a**. These results suggest possible applications of Schiff bases derived from **3** and **4** in other catalytic asymmetric reactions.

Experimental Section

3-Hydroxythiophene-2-carbaldehyde (3). To a solution of 3-methoxythiophene (17.5 mmol) in THF (20 mL) at −78 °C, *n*-BuLi (19.3 mmol) was added. After stirring for 1 hr, DMF (21.1 mmol) was added. The solution was stirred for 1 hr at room temperature and water was added. Crude product, 3-methoxythiophene-2-carbaldehyde was obtained by extraction with CH_2Cl_2 (60 % yield). To a solution of 3-methoxythiophene-2-carbaldehyde (7.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C, BBr_3 (8.4 mmol) was added slowly. After being stirred for one day at room temperature, water was added to the reaction mixture. Product was extracted by CH_2Cl_2. After flash column chromatography, a pure product was obtained in 75 % yield. mp 91-92 °C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.69 (brs, 1H), 9.64 (s, 1H), 7.60 (d, 1H, J = 5.1 Hz), 6.78 (d, 1H, J = 5.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.67, 166.25, 136.41, 119.62, 115.55. HRMS (70 eV, EI) *m/z* calcd for $C_5H_4O_2S$: 127.9932; found: 127.9930.

3-Hydroxybenzothiophene-2-carbaldehyde (4). To a solution of 3-*t*-butoxybenzo[b]thiophene (4.85 mmol) in THF (20 mL) at −78 °C, *n*-BuLi (5.82 mmol) was added. After stirring for 1 hr, DMF (5.33 mmol) was added. The solution was stirred for 1 hr at room temperature and water was added. Crude product, 3-*t*-butoxy-2-thianaphthenaldehde, was obtained by extraction with CH_2Cl_2 (99% yield). The mixture of 3-*t*-butoxy-2-thianaphthenaldehde (5.61 mmol) and *p*-TsOH (0.28 mmol) in toluene (10 mL) was heated to reflux for 5 hr. After evaporation of solvent and flash column chromatography, a pure product was obtained in 78% yield. mp 109-110 °C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.75 (s, 1H), 8.02 (d, 1H, J = 8.1 Hz), 7.77 (d, 1H, J = 8.0 Hz), 7.56 (dd, 1H, J_1 = 8.1 Hz, J_2 = 8.0 Hz), 7.43 (dd, 1H, J_1 = 8.1 Hz, J_2 = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.69, 161.83, 141.66, 130.18, 130.03, 124.91, 123.94, 123.61, 112.59. FTIR (KBr cast) 3055, 1613, 1520, 1464, 1418, 1376, 1323, 1268, 1100, 1064, 944. HRMS (70 eV, EI) *m/z* calcd for $C_9H_6O_2S$: 178.0089; found: 178.0080.

General Procedure for the Preparation of Chiral Tridentate Ligands. To the refluxing solution of aldehyde in ethanol, chiral aminoalcohol was added. The mixture was heated for 2 hr more. Cooling of the solution at room temperature gave pure crystalline product.

(*S*)-5a: yield: 75%, $[\alpha]_D^{22}$ −145.8 (*c* 0.1, THF), mp 115-116 °C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54 (d, 1H, J = 5.7 Hz), 7.43(s, 1H), 6.25 (d, 1H, J = 5.7 Hz), 3.93 (dd, 1H, J_1 = 11.8 Hz, J_2 = 2.9 Hz), 3.64 (dd, 1H, J_1 = 11.8 Hz, J_2 = 9.7 Hz), 2.97 (dd, 1H, J_1 = 9.7 Hz, J_2 = 2.9 Hz), 1.01 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 185.85, 152.81, 141.10, 123.83, 103.29, 73.41, 61.14, 33.12, 26.66. FTIR (KBr cast) 3233, 2962, 1633, 1538, 1477, 1433, 1399, 1368, 1314, 1241, 1180, 1107, 1077, 1056, 1013. HRMS (70 eV, EI) *m/z* calcd for $C_{11}H_{17}NO_2S$: 227.0980; found: 227.0985.

(1*R*,2*S*)-5b: yield: 82%, $[\alpha]_D^{22}$ +290.5 (*c* 0.1, CH_3OH), mp 144-145 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (d, 1H, J = 5.7 Hz), 7. 43 (s, 1H), 7.32-7.26 (m, 4H), 6.28 (d, 1H, J = 5.7 Hz), 4.82 (d, 1H, J = 4.8 Hz), 4.66 (m, 1H), 3.15 (dd, 1H, J_1 = 16.2 Hz, J_2 = 5.7 Hz), 3.01 (dd, 1H, J_1 = 16.2 Hz, J_2 = 5.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.56, 150.84, 142.29, 141.31, 138.29, 129.00, 127.26, 125.72, 125.03, 124.16, 104.27, 73.65, 66.21, 38.93. FTIR (KBr cast) 3206, 2944, 1632, 1532, 1478, 1458, 1438, 1367, 1300, 1217, 1178, 1115, 1078, 1055, 989. HRMS (70 eV, EI) *m/z* calcd for $C_{14}H_{13}NO_2S$: 259.0667; found: 259.0667.

(*S*)-6a: yield: 93%, $[\alpha]_D^{22}$ −136.6 (*c* 0.05, THF), mp 43-44 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83 (d, 1H, J = 7.9 Hz), 7.44-7.37 (m, 2H), 7.29-7.21 (m, 2H), 4.01 (dd, 1H, J_1 = 11.7 Hz, J_2 = 3.0 Hz), 3.70 (dd, 1H, J_1 = 11.7 Hz, J_2 = 9.8 Hz), 3.02 (dd, 1H, J_1 = 9.8, Hz, J_2 = 3.0 Hz), 1.03 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.07, 152.15, 144.54, 133.73, 130.72, 124.51, 123.75, 123.33, 101.97, 73.34, 61.88, 33.25, 26.72. HRMS (70 eV, EI) *m/z* calcd for $C_{15}H_{19}NO_2S$: 277.1137; found: 277.1138.

(1*R*,2*S*)-6b: yield: 95%, $[\alpha]_D^{22}$ +289.0 (*c* 0.05, THF), mp 201-202 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (d, 1H, J = 7.6 Hz), 7.51-7.43 (m, 2H), 7.31-7.21 (m, 6H), 4.89 (bs, 1H), 4.71 (d, 1H, J = 3.2 Hz), 3.19 (dd, 1H, J_1 = 16.4 Hz, J_2 = 5.6 Hz), 3.03 (dd, 1H, J_1 = 16.4 Hz, J_2 = 3.2 Hz), 1.89 (bs, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.77, 165.56, 163.33, 148.91, 138.52, 135.49, 131.33, 129.08, 127.48, 125.65, 125.10, 124.91. 123.85, 123.54, 10x, 74.13, 66.37, 39.34. FTIR (KBr cast) 3263, 2955, 1631, 1593, 1540, 1462, 1444,

1284, 1075. HRMS (70 eV, EI) *m/z* calcd for $C_{18}H_{15}NO_2S$: 309.0824; found: 309.0811.

General Procedure for the Catalytic Asymmetric Sulfoxidation. Vanadyl acetylacetonate (5.3 mg, 0.02 mmol) and the ligand (0.03 mmol) were dissolved in CH_2Cl_2 (3 mL) and were stirred 10 minutes at room temperature. After addition of the sulfide (1.0 mmol), the solution was cooled to 0 ^oC, and 30% H_2O_2 (0.13 mL, 1.1 mmol) was added. The mixture was stirred for 20 hr and was quenched with saturated Na_2SO_3 solution. The resulting solution was extracted with CH_2Cl_2. The organic layer was briefly dried over $MgSO_4$, filtered, and concentrated under reduce pressure. The crude product was purified by flash column chromatography.

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