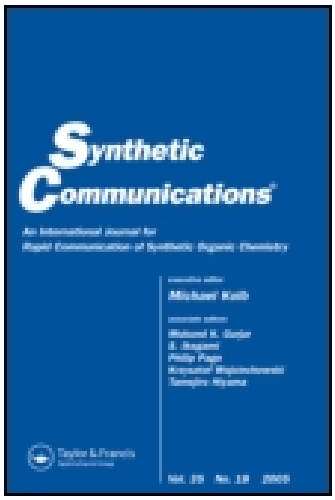

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An Economic Approach to Chiral Thiosulfinates by Enantioselective Oxidation with Hydroperoxide

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ABSTRACT

Some novel chiral ligands and $VO(acac)_2$ were utilized to catalytic asymmetric oxidation of disulfides. The optically active thiosulfinates were obtained.

Key Words: Asymmetric catalysis; Chiral thiosulfinates; Enantioselective oxidation; Hydroperoxide.

There have been numerous reports in which the sulfinyl group has acted as a removable source of diastereoselection in asymmetric synthesis. While

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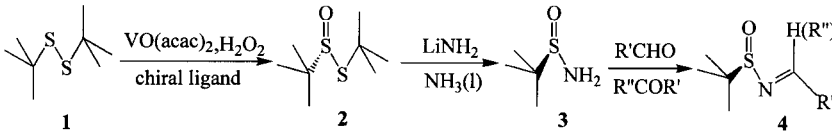

Scheme 1.

tert-butanesulfinimines were new chiral nitrogen intermediates for preparation of a range of chiral amines,[1] including α-branched amines,[2–5] tertiary carbinamines,[2,6–8] α-and β-amino acid,[9–11,12–14] 1,2- and 1,3-amino alcohol,[15–19] α-trifluoromethyl amines.[20,21] As shown in Scheme 1. Ellman and coworkers described a method[22,23] for preparing enantiomerically enriched tert-butyl tert-butanethiosulfinate **2** in the first example of an asymmetric catalytic oxidation upon tert-butyl disulfide **1**. Reaction of $LiNH_2$ with **2** provided the sulfinamide **3** in high yield with absolute stereospecificity, **3** condensed with aldehydes or ketones to provide tert-butanesulfinimine **4**. But the chiral ligand was prepared by the condensation of 3,5-di-tert-butylsalicylaldehyde and (*S*)-tert-leucinol, which is expensive and difficult to synthesize.

Now, we wish to report the results of the catalytic asymmetric oxidation of tert-butyl disulfide in the presence of cheap and easily available chiral ligands (Figure 1) **5a–i**, **6a–c**, **7a–b**. Ligand 5 was formed from condensation of 3,5-di-tert-butylsalicylaldehyde and amino alcohols, which are from reduction of natural L-amino acids,[24] except ligand **5f**. While ligand **6** was synthesized from amino acid esters. Reduction of Schiff base ligands[25] provided ligand **7**.

We investigated the effects of R_1 in ligand **5a–i** on the e.e.% of tert-butanethiosulfinate **2**, the results are summerized in Table 1. Compared with entry 1–6, we found that the bulkiness of R_1 in ligand **5a–i** do affect the enantioselectivity of **2**. The larger R_1 is, the higher enantioselectivity the catalyst shows. Because another hydroxyl group at opposite position of R_1 can also cooperate with VO(IV), the e.e.% of **2** in entry 9 is very low. The opposite cooperation is also affect e.e.% of **2** in entry 7 and 8.

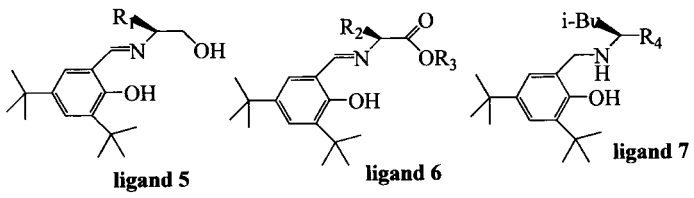

Figure 1. Chiral ligands **5**, **6** and **7**.

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Table 1. Asymmetric oxidation of tert-butyl disulfide with ligand.

	5a–i			
Entry	Ligand 5	R_1	Yield (%)[a,b]	e.e. (%)[d]
1	5a	Me	49.8	49.0
2	5b	Bn	92.8	62.1
3	5c	i-Bu	87.6	65.5
4	5d	s-Bu	80.8	65.9
5	5e	i-Pr	53.3	67.3
6	5f	t-Bu	63.4	88.3[c]
7	5g	4-OH-Bn	30.2	29.6
8	5h	1-indolyl-methylene	45.7	44.2
9	5i	1-OH-Et	41.2	4.24

[a]Isolated yield.
[b]Product was confirmed by ^{1}HNMR and elemental analysis.
[c]Determined by HPLC analysis using chiral column (DAICEL CHIRALPAK AS, hexanes/2-propanole = 97/3).
[d]Estimated from the specific rotation.

Ligand **6a** in Table 2 can seldom catalyze the oxidation of tert-butyl disulfide, because ester group can not cooperate with VO(IV). For containing hydroxyl group in R_2, ligand **6b** and **6c** can lightly catalyze the reaction. with enantioselectivity.

In Table 3, reduced Schiff base ligands can also catalytically oxide tert-butyl disulfide, but the enantioselectivity is almost lost, and nearly racemic products are obtained. Probably because ligand **7a** and **7b** do not contain the conjugated construction of C═N double bond and aromatic ring, and no appropriate complexes can be formed during the reaction.

Table 2. Asymmetric oxidation of tert-butyl disulfide with ligand.

	6a–c				
Entry	Ligand 6	R_2	R_3	Yield (%)[a]	e.e. (%)
1	6a	Me	Et	5.6	4.24
2	6b	HO–CH_2	Et	15.5	12.1
3	6c	HO–CH_2	i-amyl	13.7	14.7

[a]Isolated yield.

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Table 3. Asymmetric oxidation of tert-butyl disulfide with ligand.

		7a–b		
Entry	Ligand 7	R_4	Yield (%)[a]	e.e. (%)
1	7a	HO–CH2	25.8	6.05
2	7b	COOH	32.6	4.84

[a]Isolated yield.

In order to compare the efficiency of this oxidation between alkyl disulfides and aryl disulfides, we make a further study of asymmetric oxidation of *p*-tolyl disulfide in Sch. 2 with ligand **5b–f** listed in Table 4. Because of lower density of electron cloud of sulfur, yield and e.e.% of *p*-tolyl *p*-toluenethiosulfinate is lower.

EXPERIMENTAL

General Procedure

1.50×10^{-4} mol (0.50 mol%) $VO(acac)_2$ dissolved in 2.5 mL anhydrous chloroform under nitrogen in a 50 mL tube, followed by the addition of 1.56×10^{-4} mol (0.52 mol%) chiral ligand (**5a–i**, **6b**, **6c**, **7a–b**) and 12 mL chloroform, The resulting solution was stirred 20 min. before 5.78 mL

Table 4. Asymmetric oxidation of *p*-tolyl disulfide with ligand.

		5b–f		
Entry	Ligand 5[d]	R_1	Yield (%)[a,b]	e.e. (%)[c]
1	5b	Bn	41.3	35.0
2	5c	i-Bu	35.4	38.5
3	5d	s-Bu	46.5	32.7
4	5e	i-Pr	35.7	36.9
5	5f	t-Bu	48.0	34.5

[a]Isolated yield.
[b]Product was confirmed by ^{1}H NMR and elemental analysis.
[c]Determined by HPLC analysis using chiral column (DAICEL CHIRALPAK AS, hexanes/2-propanole = 90/10).
[d]All reactions were performed at 25°C with 2.6 mol % ligand.

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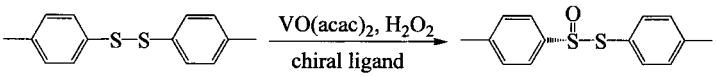

Scheme 2.

(0.03 mol) tert-butyl disulfide was added, followed by 4.5 mL 30% H_2O_2 in a slow steady steam. The cooling bath temperature was maintained at $15 \sim 20^{\circ}C$. After 4 days the organic phase was separated, washed with saturated brine, dried with Na_2SO_4 and concerntrated. Column chramatography on silica gel (200–300 mesh) using petroluem/ethyl acetate = 15 : 1 as elutant furnished **2** as a white crystalline solid with main configuration of R. The results are shown in Tables 1, 2, and 3, with different chiral ligands.

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