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## An Economic Approach to Chiral Thiosulfates by Enantioselective Oxidation with Hydroperoxide

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### ABSTRACT

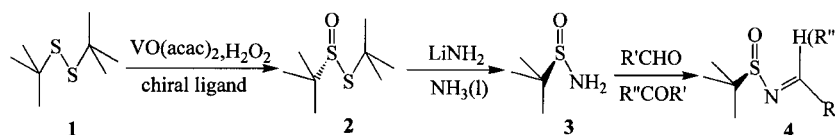
Some novel chiral ligands and  $\text{VO}(\text{acac})_2$  were utilized to catalytic asymmetric oxidation of disulfides. The optically active thiosulfates were obtained.

*Key Words:* Asymmetric catalysis; Chiral thiosulfates; 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,<sup>[1]</sup> including  $\alpha$ -branched amines,<sup>[2–5]</sup> tertiary carbinamines,<sup>[2,6–8]</sup>  $\alpha$ - and  $\beta$ -amino acid,<sup>[9–11,12–14]</sup> 1,2- and 1,3-amino alcohol,<sup>[15–19]</sup>  $\alpha$ -trifluoromethyl amines.<sup>[20,21]</sup> As shown in Scheme 1. Ellman and coworkers described a method<sup>[22,23]</sup> 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  $\text{LiNH}_2$  with **2** provided the sulfonamide **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,<sup>[24]</sup> except ligand **5f**. While ligand **6** was synthesized from amino acid esters. Reduction of Schiff base ligands<sup>[25]</sup> 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 summarized 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.

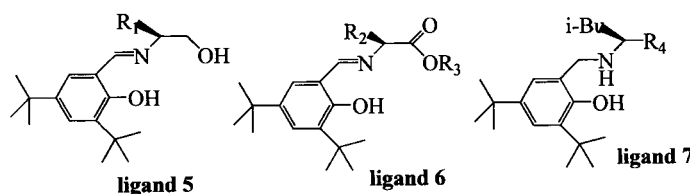


Figure 1. Chiral ligands **5**, **6** and **7**.



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

<b>5a–i</b>				
Entry	Ligand 5	R <sub>1</sub>	Yield (%) <sup>a,b</sup>	e.e. (%) <sup>d</sup>
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 <sup>c</sup>
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

<sup>a</sup>Isolated yield.

<sup>b</sup>Product was confirmed by <sup>1</sup>HNMR and elemental analysis.

<sup>c</sup>Determined by HPLC analysis using chiral column (DAICEL CHIRALPAK AS, hexanes/2-propanol = 97/3).

<sup>d</sup>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<sub>2</sub>, 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.

<b>6a–c</b>					
Entry	Ligand 6	R <sub>2</sub>	R <sub>3</sub>	Yield (%) <sup>a</sup>	e.e. (%)
1	6a	Me	Et	5.6	4.24
2	6b	HO–CH <sub>2</sub>	Et	15.5	12.1
3	6c	HO–CH <sub>2</sub>	i-amyl	13.7	14.7

<sup>a</sup>Isolated yield.



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

<b>7a–b</b>				
Entry	Ligand 7	R <sub>4</sub>	Yield (%) <sup>a</sup>	e.e. (%)
1	7a	HO–CH <sub>2</sub>	25.8	6.05
2	7b	COOH	32.6	4.84

<sup>a</sup>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

$1.50 \times 10^{-4}$  mol (0.50 mol%) VO(acac)<sub>2</sub> dissolved in 2.5 mL anhydrous chloroform under nitrogen in a 50 mL tube, followed by the addition of  $1.56 \times 10^{-4}$  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.

<b>5b–f</b>				
Entry	Ligand 5 <sup>d</sup>	R <sub>1</sub>	Yield (%) <sup>a,b</sup>	e.e. (%) <sup>c</sup>
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

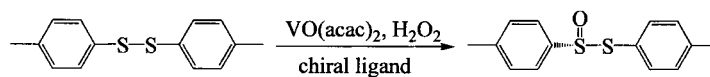
<sup>a</sup>Isolated yield.

<sup>b</sup>Product was confirmed by <sup>1</sup>H NMR and elemental analysis.

<sup>c</sup>Determined by HPLC analysis using chiral column (DAICEL CHIRALPAK AS, hexanes/2-propanol = 90/10).

<sup>d</sup>All reactions were performed at 25°C with 2.6 mol % ligand.





Scheme 2.

(0.03 mol) *tert*-butyl disulfide was added, followed by 4.5 mL 30%  $\text{H}_2\text{O}_2$  in a slow steady stream. The cooling bath temperature was maintained at  $15 \sim 20^\circ\text{C}$ . After 4 days the organic phase was separated, washed with saturated brine, dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Column chromatography on silica gel (200–300 mesh) using petroleum/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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