

ASYMMETRIC OXIDATION OF RACEMIC SULFIDE.  
 STEREOCHEMISTRY OF ENANTIOMER DIFFERENTIATION REACTION

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Summary: Stereochemistry of the oxidation of racemic 2-methyl-2,3-dihydrobenzothiophene with optically active hydroperoxides prepared by photooxidation of thiazolidine derivatives was studied and found to be reverse to that with modified Sharpless oxidation system.

The enantiomer differentiation reaction is one of the advantageous methods for obtaining optically active compounds. Despite much study on the asymmetric oxidation of sulfides with optically active compounds or systems,<sup>1</sup> no report has appeared on the asymmetric oxidation of racemic sulfides. Recently, we have reported<sup>2</sup> the chirality transfer from optically active hydroperoxide (2) derived via a photochemical singlet oxygenation of 1,<sup>3</sup> where prochiral sulfides were oxidized to chiral sulfoxides in higher optical yields than those with peroxy acids.<sup>1a</sup> Meanwhile, 2-methyl-2,3-dihydrobenzothiophene 4 was shown to be a good choice of substrate for studies of stereochemistry of the asymmetric oxidation with monooxygenase cytochrome P-450.<sup>4</sup> In continuing research, the asymmetric oxidation of racemic 4 with the hydroperoxides 2 has been carried out and interesting stereochemical results have been obtained, especially in comparison with those oxidized with the modified Sharpless oxidation system.

The reaction was achieved in one pot as described below. A mixture of thiazolidine derivative (1, 3 mmol) and TPP (meso-tetraphenylporphyrin, 15 mg/

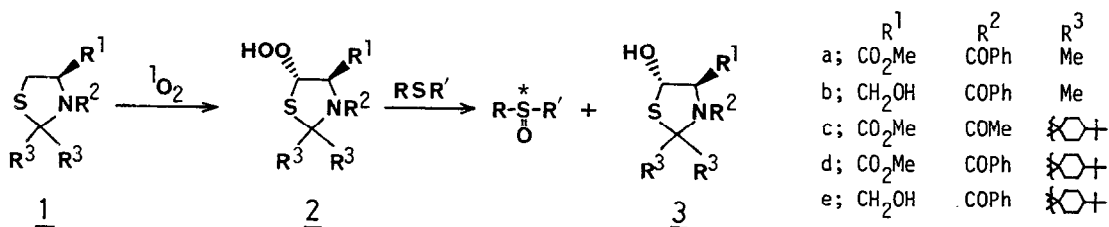


Table 1 Asymmetric Oxidation of Racemic 2-Methyl-2,3-dihydrobenzothiophene 4 with Optically Active Hydroperoxides and Effect of  $Ti(O^iPr)_4$

Run	Oxidant	Yield/%	cis:trans	e.e./% <sup>a,b</sup>			
				cis		trans	
				A	B	A	B
1	<u>2a</u>	91	27 : 73	15.7	15.4	3.2	4.0
2	<u>2b</u>	61	20 : 80		14.2		4.4
3	<u>2c</u>	84	21 : 79		42.4		23.8
4	<u>2a</u> + $Ti(O^iPr)_4$	72	10 : 90		20.0		32.0
5	<u>2c</u> + $Ti(O^iPr)_4$	95	7 : 93		60.0		72.0
6 <sup>c</sup>	<u>2c</u> + $Ti(O^iPr)_4$	80	5 : 95		29.4		43.0
7 <sup>d</sup>	<u>2c</u> + $Ti(O^iPr)_4$	93	9 : 91		27.5		50.0
8	<u>2d</u> + $Ti(O^iPr)_4$	95	10 : 90		ND <sup>e</sup>		32.0
9	<u>2e</u> + $Ti(O^iPr)_4$	74	10 : 90		26.2		29.1
10	f	95	5 : 95		60.0		82.0

a) Excess isomers are  $5_{SS}$  for cis form and  $5_{RS}$  for trans form, respectively(see Table 2).

b) Method A is based on specific optical rotation( calculated maximum rotation from data of ref. 4:  $[\alpha]_D^{-94}$ (acetone) for  $5_{SS}$  and  $+132$ (acetone) for  $5_{RS}$ , respectively). Method B is from analysis of  $^1H$  NMR spectrum with chiral shift reagent  $Eu(hfc)_3$ . c) Solvent is dichloromethane. d) Equimolar amount of water is added. e) not determined. f) modified Sharpless system(0.45 equivalent of  $tBuOOH$  vs. 4 was used as oxidant).<sup>1e</sup>

mmol of 1) in dry THF([C]= ca. 0.1 M) was photoirradiated with a 500W halogen lamp under bubbling oxygen at  $-30$  °C. After the reaction(4.5 - 7.5 h), racemic sulfide(4, 6.6 mmol) was added to the solution and the mixture was allowed to stand at that temperature and then at room temperature(3.5 + 3.0 h). The products separated chromatographically were recovered sulfide(4), alcohol reduced(3), and desired sulfoxide(5).<sup>5,6</sup>

The sulfoxide was a mixture of cis and trans isomers from methyl signals of  $^1H$  NMR which determined their ratio. The two isomers were separated by high pressure liquid chromatography. The e.e. value of each isomer was easily determined by  $^1H$  NMR using chiral shift reagent  $Eu(hfc)_3$ (tris[3-(heptafluoropropyl-hydroxymethylene)d-camphorato]europium(III)), or from specific rotational values according to the literature.<sup>4</sup> Results with the use of a variety of chiral hydroperoxides(2a - 2e) and effect of  $Ti(O^iPr)_4$  are summarized in Table 1.

Inspection of data of Table 1(runs 1 - 3) reveals the oxidation with the hydroperoxide alone strongly preferred trans isomer to the cis one. Such selectivity is not obtainable with  $NaIO_4$ (48:52) and MCPBA(m-chloroperbenzoic acid, 47:53).<sup>4</sup> The e.e. of cis isomer was always higher than that of the trans. Highest e.e. was obtained with the use of 2c.

Addition of  $\text{Ti}(\text{O}^i\text{Pr})_4$  (3 mmol) furthermore promoted the selective formation of trans sulfoxide and remarkably enhanced the e.e. of both isomers. However, the e.e. of trans isomer in turn was higher than that of the cis one in any case (runs 1, 3, 4, and 5). Here, the use of 2c (run 5) also produced the best result of all in which the highest e.e. was obtained (cis: 60.0 and trans: 72.0, respectively). Probably,  $\text{Ti}(\text{O}^i\text{Pr})_4$  contributes tight interaction in the transition state of the oxidation by ligand exchange.<sup>7</sup>

The oxidation in dichloromethane (a less polar solvent) which is believed to provide higher e.e. in peroxy acid oxidation,<sup>1a,3</sup> however, resulted in lower e.e. than that in THF (run 6). The modified Sharpless oxidation system consists of mixed functions of  $t\text{BuOOH}$  - diethyl tartrate -  $\text{Ti}(\text{O}^i\text{Pr})_4$  -  $\text{H}_2\text{O}$ ,<sup>1e</sup> which affords high diastereoselectivity and e.e. under the reported conditions (run 10). It is an excellent system at the present time. Addition of water which is required in that system was not effective (run 7).<sup>1e</sup>

The enantiomer differentiation in a typical oxidation is clearly shown in Table 2. The most interesting result is the completely reverse enantiomer differentiation between our system and modified Sharpless system, in spite of the similar diastereoselectivity. The major sulfoxide produced by our system is

Table 2 Enantiomer Differentiation in the Oxidation of Racemic 4 with Optically Active Hydroperoxides 3. Relative Yield of Each Isomer, Calculated from Data of Run 5 of Table 1\*

Substrate	Products and Relative Yields	Enantiomer Differentiation				
		<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; text-align: center;">2(S)- 19% (87%)</td> <td style="width: 50%; text-align: center;">2(R)- 62%</td> </tr> <tr> <td style="width: 50%; text-align: center;">2(R)- 81% (13%)</td> <td style="width: 50%; text-align: center;">2(S)- 74%</td> </tr> </table>	2(S)- 19% (87%)	2(R)- 62%	2(R)- 81% (13%)	2(S)- 74%
2(S)- 19% (87%)	2(R)- 62%					
2(R)- 81% (13%)	2(S)- 74%					
Oxidation Selectivity at Sulfur Atom	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; text-align: center;">1(R)- 86%(10%)</td> <td style="width: 50%; text-align: center;">1(S)- 14%(90%)</td> </tr> <tr style="border-top: 1px dashed black;"> <td style="width: 50%; text-align: center;">1(R)- 72%</td> <td style="width: 50%; text-align: center;">1(S)- 80%</td> </tr> </table>	1(R)- 86%(10%)	1(S)- 14%(90%)	1(R)- 72%	1(S)- 80%	
1(R)- 86%(10%)	1(S)- 14%(90%)					
1(R)- 72%	1(S)- 80%					
* Yield in parenthesis is that calculated from data of modified Sharpless system (Run 10, Table 1).						

5<sub>RS</sub> obtained in 80% while in the other case 5<sub>SR</sub> was mainly formed in 86%. Therefore, our system favors sulfide 4<sub>S</sub> while the modified Sharpless system requires sulfide 4<sub>R</sub> during the oxidation. Thereby, the predominant transformation necessarily gives rise to discriminating oxidation at sulfur, whose selectivities are 72% l(R) and 80% l(S), respectively.

Thus, the present work could indicate very clearly the stereochemical course of the asymmetric oxidation of racemic sulfide 4 in which the reverse enantiomer differentiation was observed between our and the modified Sharpless systems. Namely, use of these two systems is of significance for obtaining two different enantiomers in high optical purities. This work will be described in detail in a full article.

#### REFERENCES AND FOOTNOTES

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5. Both sulfide 4 and sulfoxide 5 had identical spectroscopic data with those reported.<sup>4</sup> Spectroscopic data of the alcohol 3 confirmed its structure which was consistent with those published.<sup>6</sup>
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