Asymmetric Oxidation of Sulfides with Optically Active Hydroperoxides Prepared by Singlet Oxygenation of Thiazolidine Derivatives

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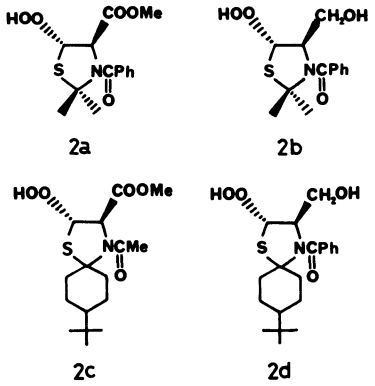
Synopsis. Asymmetric oxidation of prochiral sulfides with optically active hydroperoxides prepared in situ by photo-sensitized oxygenation, gives chiral sulfoxides with moderate optical yields which are enhanced by addition of $Ti(OPr^i)_4$.

Asymmetric oxidation of sulfides is an essential and universal entry for synthesizing optically active sulfoxides with easy performance and less limitation, among several preparative methods with a variety of cptical yields.[1-7] However, the simplest oxidation with optically active peroxy acids resulted in low optical yields (0—5% e.e.),[1] in contrast to those with mixed oxidation systems, especially with modified Sharpless oxidation system (91% e.e.),[5,6] and electrochemical method (≈85% e.e.),[4] which were reported recently. The main reason is considered to be due not only to the distance between the chiral and reaction centers, but also to the lack of close interaction in the transition state. There has hitherto been no appropriate experimental verification for such a hypothesis, but the use of chiral hydroperoxide shortens the distance and therefore it would be expected to enhance the optical yield.

Although organic hydroperoxide is a relatively weak but useful oxidant for many organic substaces such as sulfides, to our knowledge it has not previously been used as a chiral oxidant for asymmentric oxidation of sulfides. In this paper, the optically active hydroperoxides that we have recently prepared by singlet oxygenation of thiazolidine derivatives,[8] are examined in the asymmetric oxidation of prochiral sulfides (Eq. 1).



The asymmetric oxidation was carried out in a single reaction adding a prochiral sulfide to a solution of a hydroperoxide freshly prepared in situ by photosensitized oxidation of thiazolidine derivative **1**. The results obtained for a few sulfides with four hydroperoxdes, are summarized in Table 1.

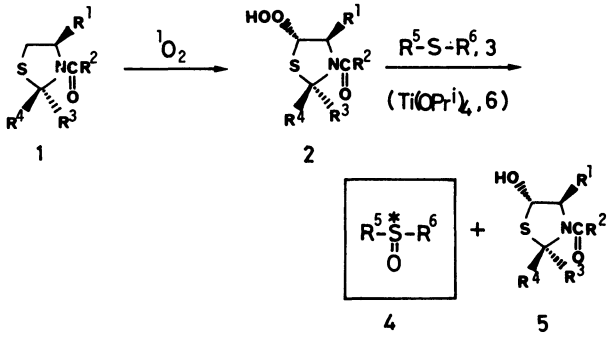


Fig. 1.

Table 1. Asymmetric Oxidation of Prochiral Sulfides with Optically Active Hydroperoxides

Run	Oxidant	Sulfide	Sulfoxide yield/%	Abs. confgn.	Optical purity/%[a]
1	**2a**	p-TolSMe(**4a**)	84	(+)-R	10.0(11)
2	**2b**	**4a**	95	(+)-R	3.6(7)
3	**2c**	**4a**	95	(−)-S	26.7(22)
4	**2a**	$PhSC_6H_4$-OMe-p(**4b**)	79	(+)-R	7.4
5	**2d**	$PhCH_2SBu^t$(**4c**)	93	(−)-S	9.2
6	**2c**	$PhCH_2STol$-p(**4d**)	80	(−)-S	17.2
7	**2a**+**6**	**4a**	59	(−)-S	10.3(12)
8	**2c**+**6**	**4a**	75	(−)-S	—[b](37)
9	**2c**+**6**	**4b**	41	(−)-S	5.3
10	**2c**+**6**	**4c**	80	(−)-S	25.8
11	**2c**+**6**	**4d**	81	(−)-S	21.3

a) Optical purity determined from specific optical rotation of purified sulfoxide (as for max. rotation, see Ref. 7. Parenthesis indicates enantiomer excess calculated from ^1H NMR integration using shift reagent Eu(hfc)3(tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato], europium derivative) (error: ±ca. 5%). b) Not determined.

Table 1 indicates that some asymmetric induction on the sulfur atoms of the sulfides took place. The chemical yields of the sulfoxide product were satisfactory, while the optical purities were not high. However, these values are higher than those obtained in asymmetric oxidation with peroxy acids.[1] Direct comparison may be difficult because of the structural differences of the parent skeleton between these two oxidants. Among the hydroperoxieds used,[9] **2c** afforded good results with higher optical yields. As shown in Table 1 the absolute configuration of the excess enantiomer is variable depending on the structure not only of the hydroperoxides but also of the substrate sulfides. We believe that Mislow's suggestion is always operative where a small energy difference in the transition state would change the reaction course so as to give different results.[1]

The effect of the addition of $Ti(OPr^i)_4$ was examined, in expectation of a closer interaction in the transition state in the light of both the Sharpless[6,10] and the modified Sharpless[5] systems for asymmetric oxidations. In fact, enhancement of the optical purity was observed in the case of sulfides **4a** and **4b** (Runs 3 and 7, and 6 and 11). The absolute configuration, however, was changed by addition of **6** from *dextro* to *levo* rotatory for sulfide **4a** (Runs 1 and 7).

In this paper the first asymmetric oxidation of prochiral sulfides with optically active hydroperoxides is described. Since the increasing bulkiness of the oxidant peroxy acids does not always give rise to higher asymmetric induction,[1] the short distance between the reaction and chiral centers is important as well as the close interaction in the transition state during the oxidation. Therefore, the hypothesis that the low asymmetric induction in the peroxy acid oxidation is carried by two factors, is then justified by the results obtained here. Rough calculations[11] indicate the distances for peroxy acids are 361 pm and for hydroperoxide 225 pm. Such clear shortening of the distance in the hydroperoxide unambiguously causes the higher asymmetric induction. Addition of $Ti(OPr^i)_4$ (**6**) seems to affect the closeness in the transition state to some extent, although the exact structure of the transition state is still uncertain.[10]

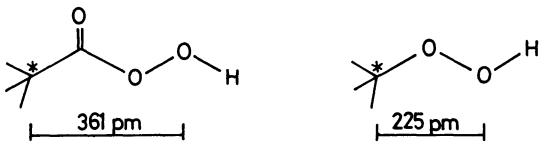


Fig. 2.

Experimental

Thiazolidines (**1**) were prepared from L-cysteine as described in the previous paper.[8] Sulfoxides (**4**) as products and alcohols (**5**)[12] as by-products were identified by reported physical and spectral data.

General Procedure. a) Without $Ti(OPr^i)_4$. A mixture of a thiazolidine derivative (**1**, 1—5 mmol) and TPP (5,10,15,20-tetraphenylporphyrin, 15 mg mmol^{-1} of **1**) in dry THF ([C]=0.05—0.15 M (1 M=1 mol dm^{-3})) was photo-irradiated with a 500 W halogen lamp with bubbling dry oxygen at −30 °C. The reacton took 2 to 10 hs depending on the substrate (**1**) used.[8,12] To the resulting solution containing **2**, aprochiral sulfide (**3**, 2—10 mmol) was added and mixed well at −30 °C. The mixture was allowed to stand at −30 °C for 3 h and then at room temperature for a few hours in the dark to avoid further photo-oxidation of **3**. The resulting mixture was concentrated under reduced pressure and the residue was subjected to silica-gel chromatography (eluent: benzene-ethyl acetate-methanol=20:4:1). The products were eluted in the following order: TPP, sulfide **3**, sulfoxide **4**, and alcohol **5**. When further purification was necessary, the sulfoxide was purified by preparative high pressure liquid chromatography of sufficient sample for measurement of the optical rotation.

b) With $Ti(OPr^i)_4$. To the hydroperoxide (**2**) solution, $Ti(OPr^i)_4$ (1—5 mmol, equimolar of **1**) and then sulfide **3** (2—10 mmol) were added subsequently at −30 °C. After the same treatment as above, to the reaction mixture concentrated, water (1—5 cm^3) and alumina (5—30 cm^3) were added. After allowing to stand for a few hours at room temperature and then drying with evaporator and vacuum pump, the resulting powder was poured onto the top of the column and chromatographed.

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