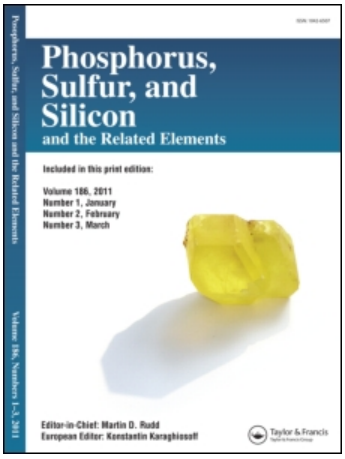


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# ASYMMETRIC OXIDATION OF β-HYDROXYSULFIDES. THE ROLE OF THE HYDROXY GROUP

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In the asymmetric oxidation of prochiral β-hydroxysulfides to the corresponding sulfoxides, by using a recently developed modified Sharpless reagent, it has been observed that the presence of the hydroxy group in the molecule of the substrate is not playing a significant role in determining the extent of the enantioselection, at variance with the asymmetric epoxidation of allylic alcohols where formation of alkoxytitanium complexes is believed to be a crucial process, thus indicating some important difference in the oxidation mechanisms.



In the Sharpless asymmetric epoxidation of allylic alcohols,[1] several pieces of evidence, including theoretical calculations,[2] point to a major role played by the hydroxy group in determining the very high enantioselectivities achieved. A direct evaluation of the relevance of the hydroxy group, which is believed to allow the formation of alkoxytitanium ground state complexes,[3] could be attained by comparing the results of the epoxidation of a model allylic alcohol with those of the epoxidation of a structurally similar, unfunctionalized alkene. Unfortunately, owing to the rather small oxidizing power of the *t*-$BuO_2H$/Ti(IV) catalytic system,[4] the epoxidation of simple olefins with such reagent is not feasible. On the other hand the *t*-$BuO_2H$/Ti(IV) system is effective enough to carry out the oxidation of sulfides to sulfoxides.[4] This is likely due to the greater nucleophilicity of sulfur as compared with that of double bond. In fact, we have recently developed a procedure for the asymmetric oxidation of prochiral sulfides by using a modified (sulfide: $RO_2H$:Ti:DET-1:2:1:4) Sharpless reagent.[5]

Fairly high e.e. values (up to 90%) have been obtained in the oxidation of unfunctionalized sulfides such as *p*-tolyl methyl sulfide.[5]

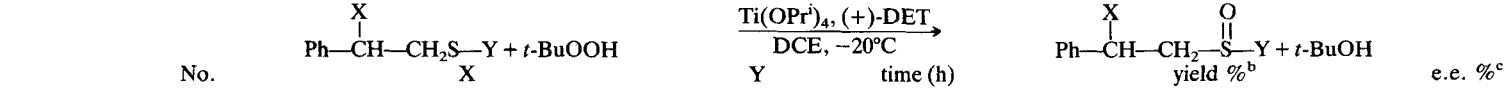
The procedure has been found to be particularly effective for the asymmetric oxidation of 1,3-dithiolanes[6,7] allowing to obtain in some cases, after crystallization, the almost enantiomerically pure (e.e. > 98%) *S*-oxides. Based on these results, a procedure for the optical resolution of carbonyl compounds has been developed.[6,7]

Interestingly, results obtained in our laboratory[5a] as well as literature data[8] appear to indicate that the enantioselectivity observed with β-hydroxy sulfides is not larger than that of comparable unfunctionalized sulfides, as it could have been expected on the basis of the analogy with allylic alcohols.

We have deemed worthwhile to investigate this feature in some more detail. The results of such investigation are reported in Table I.

TABLE I

Asymmetric oxidation of β-hydroxysulfides with the t-BuOOH/(+)-DET/Ti(IV) catalytic system[a]




| No. | X | Y | time (h) | yield %[b] | e.e. %[c] |
|---|---|---|---|---|---|
| 1 | —OH | *t*-Bu- | 5 | 73 | 47[d] |
| 2 | —O—$SiMe_3$ | *t*-Bu- | 15 | 76 | 58[d] |
| 3 | —OH | Ph- | 14 | 88 | 18[e] |
| 4 | —OAc | Ph- | 20 | 53 | 21[f] |
| 5 | —OH | o—Tol- | 14 | 83 | 24[g] |
| 6 | —OH | Naftyl- | 21 | 69 | 20[h] |

[a] Under the conditions described in the Experimental Section; [b] Based on the oxidant; [c] The reaction leads to the formation of two diastereomers (ratios ranging from 54:46 to 74:26). The e.e. values refer to the major diastereomer; [d] From $^1$H-NMR spectra run in the presence of $Eu(tfc)_3$ in $CDCl_3$ from the splitting of the $C(CH_3)_3$ singlet; [e] Determined after oxidation to sulfone by polarimetric measurement, $[\alpha]_D^{25}$ (max) = +30.3 ($c$ = 2, $CHCl_3$), see experimental section; [f] After hydrolysis and oxidation to sulfone; [g] As note e. $[\alpha]_D^{25}$ (max) = +45.01 ($c$ = 2, $CHCl_3$); [h] As note e. $[\alpha]_D^{25}$ (max) = +4.09 ($c$ = 2, $CHCl_3$).

The most noteworthy feature exhibited by the data of Table I is the scarce effect of the hydroxy group on the enantioselectivity. This is evident if one compares the e.e. values of entries **1** and **2** and entries **3** and **4**. Such a behavior is not completely surprising in the light of previous kinetic and thermodynamic results[9] which indicated that, at variance with allylic alochols, β-hydroxysulfides do not form ground state alkoxy complexes with vanadium (V) whose coordination chemistry is rather similar to that of titanium (IV). Although the difference of e.e. values is too small to allow a firm conclusion, it could nevertheless be argued that the substitution of the hydroxy group with $OSiMe_3$ or OAc causes an increase of the enantioselectivity. Having ruled out the formation of alkoxytitanium species, it is likely that the better results for **2** and **4** are related to some specific effect of the two groups which are also bulkier than OH.

Interestingly, in the series of β-hydroxysulfides examined, a dialkyl sulfide such as **1** provides better results than arylalkyl sulfides such as **3**, **4** and **5**.

The opposite behavior is observed in the oxidation of unfunctionalized sulfides where the largest e.e. values are obtained with the arylmethyl derivatives.[10] This might suggest that the hydroxy group is eventually playing a role, though a minor one, likely in the transition state of the oxidation.[9,11,12]

Finally, the data of the Table confirm what seems to be a general feature of sulfide asymmetric oxidations, i.e. the low sensitivity of the enantioselection to the nature of the aryl group bound to the sulfur atom.[10] In fact, in passing from phenyl, **4**, to *o*-tolyl, **5**, and naftyl, **6**, almost no variation of e.e. values is observed.

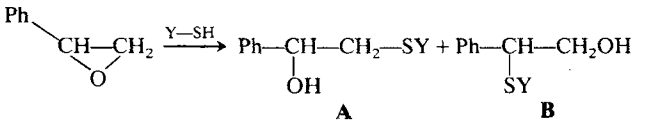
The data reported above may be of some help in the effort directed toward the understanding the mechanism of sulfide asymmetric oxidations which appears to differ, particularly as far as substrate coordination is concerned, from that of allylic alcohol epoxidations.



## EXPERIMENTAL SECTION

*Materials.* $Ti(OPr^i)_4$, tert-butyl hydroperoxide and (+)-diethyltartrate were purified by distillation. Dicholoroethane was subsequently washed with $H_2SO_4$ (96%) and water before distillation over $P_2O_5$. All other chemicals, highly pure commercial samples, were used as received.

β-Hydroxysulfides **1–6** were prepared according to a reported procedure[13] by condensation of the corresponding thiols with styrene epoxide in the presence of metallic sodium in ethanol. The reaction generally leads to the formation of the two isomers **A** and **B**:




which are separated by low pressure (4–5 atm) liquid chromatography (silica gel < 0.063 mm); the identity of β-hydroxysulfides **A** was established on the basis of their $^1$H-NMR spectra. The optically active compounds **A**, used for determining the e.e. values by polarimetry, have been obtained starting from the commercially available (+)-(S)-styrene epoxide (Fluka) of optical purity > 97%.

Compound **1**. **A**:**B** = 4:1; final yield (**A**) 77%; $^1$H-NMR ($CDCl_3$) 1.28 (s, 9H), 2.61 (m, 1H), 2.91 (m, 1H), 4.88 (s, 1H), 5.41 (m, 1H), 7.28–7.48 (m, 5H).

Compound **2**. was obtained from **1** by reaction with $Me_3SiCl$ in DMF; yield 78%; $^1$H-NMR ($CDCl_3$) 0.06 (s, 9H), 1.29 (s, 9H), 2.85 (m, 2H), 4.75 (m, 1H), 7.35 (m, 5H).

Compound **3**. **A**:**B** = 2:1.6, final yield (**A**) 46%; $^1$H-NMR 2.90 (m, 1H), 3.30 (m, 1H), 5.27 (m, 1H), 7.22–7.43 (m, 6H), 7.55–7.72 (m, 2H), 7.72–7.82 (m, 2H).

From the optically active sulfide $[\alpha]_D^{25} = -9.41$ ($c = 2$, $CHCl_3$), after oxidation with MCPBA, the corresponding sulfone $[\alpha]_D^{25}$ (max) = +30.3 ($c = 2$, $CHCl_3$) has been obtained. Its optical rotation has been used for the determination of the e.e. values of the reactions.

Compounds **4**. was obtained by reaction of **3** with acetic anhydride in pyridine; yield 84%; $^1$H-NMR ($CDCl_3$) 2.15 (s, 3H), 3.16 (m, 2H), 6.21 (m, 1H), 7.24–7.36 (m, 6H), 7.46–7.60 (m, 2H), 7.60–7.75 (m, 2H).

Compound **5**. **A**:**B** = 2:1.8, final yield (**A**) 41%; $^1$H-NMR 2.40 (s, 3H), 2.80 (m, 1H), 3.05 (m, 1H), 3.25 (m, 1H), 4.75 (m, 1H), 7.14–7.50 (m, 4H), 7.95 (m, 3H). Optically pure sulfide $[\alpha]_D^{25} = +0.44$ ($c = 2$, $CHCl_3$), and sulfone $[\alpha]_D^{25}$ (max) = +45.01 ($c = 2$, $CHCl_3$).

Compound **6**. **A**:**B** = 2:1.2; final yield (**A**) 41%; $^1$H-NMR 2.94 (m, 1H), 3.36 (m, 1H), 3.79 (broad s, 1H), 5.31 (m, 1H), 7.16–7.35 (m, 5H), 7.50–7.69 (m, 1H), 7.86–8.08 (m, 3H), 8.30 (s, 1H). Optically pure sulfide $[\alpha]_D^{25} = -63.77$ ($c = 2$, $CHCl_3$) and sulfone $[\alpha]_D^{25}$ (max) = +4.09 ($c = 2$, $CHCl_3$).

*Oxidation procedures.* In all cases the oxidation reactions have been carried out by mixing a solution (15 ml) of $Ti(OPr^i)_4$ (1 mL, 3.4 mmol) in DCE with a solution (15 ml) of (+)-R,R-DET (2.3 mL, 13.4 mmol) in DCE at 25°C, under stirring. The temperature was then lowered to −20°C. TBHP (0.66 mL, 6.7 mmol) and the sulfide (17.5 mmol) were subsequently added. The reaction mixture was kept at −20°C until the oxidant was totally consumed (iodometric titer). Addition of 1 mL of water to this cooled solution produces a gel which is stirred and warmed up to 25°C. The solution is filtered on celite and the organic layer washed several times with water, dried over $MgSO_4$ and concentrated. The sulfide in excess was separated by column chromatography on silica gel recovering the mixture of the two diasteroisomeric sulfoxides from which the diasteroisomeric ratio is obtained by $^1$H-NMR. The separation of the two diasteromers is then attained by low-pressure liquid chromatography on silica gel. The enantiomeric excesses have been determined for the major diasteroisomer by $^1$H-NMR in the presence of $Eu(tfc)_3$ in the case of entries 1 and 2. In all other cases (entries 3–6) the major sulfoxide was further oxidized to sulfone with meta-chloroperbenzoic acid and the optical yield calculated from the $[\alpha]_D^{25}$ (max) values of optically pure authentic sulfones.



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