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ASYMMETRIC SYNTHESIS OF CHIRAL SULFOXIDES *VIA* MICROBIAL OXIDATION OF SULFIDES

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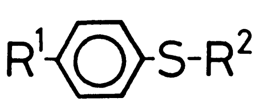
Incubation of alkyl aryl and allyl aryl sulfides with growing cells of *Corynebacterium equi* IFO 3730 gave the corresponding optically active sulfoxides of high enantiomeric excess.

Optically active sulfoxides constitute a group of useful chiral auxiliary for asymmetric synthesis.1) The most practical method for obtaining chiral sulfoxides is diastereomeric separation of *l*-menthyl sulfinates, followed by the reaction with Grignard reagents.2) This method, however, is limited by the availability of starting materials. Asymmetric oxidation of sulfides by the aid of chiral peroxides has been known, but the optical yields were not so high.3) On the other hand, enzymatic oxidation of sulfides presents another effective way for preparing chiral sulfoxides.4) In the course of our studies on organic transformations utilizing microorganisms as asymmetric catalysts,5) we have found that *Corynebacterium equi* IFO 3730 is capable of enantioselectively oxidizing alkyl aryl and allyl aryl sulfides (**1**) resulting in the formation of optically active sulfoxides (**2**).



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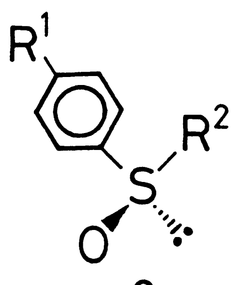

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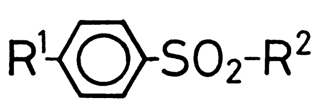

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In a 500-ml Sakaguchi flask, were added 50 ml of the sterilized inorganic medium,[6] 1 ml of hexadecane and 0.1 to 0.2 ml of 1, and the mixture was inoculated with 2 to 5 ml of a suspension of *C. equi*, previously grown in the same medium without 1. The whole mixture was incubated for 3 days at 30 °C on a reciprocatory shaker. The broth was extracted three times with 50 ml portions of ethyl acetate, and the combined extracts were concentrated under reduced pressure. Removal of remaining hexadecane by column chromatography on silica gel gave a mixture which consisted of 1, 2, and sulfone 3 amounting to almost quantitative recovery of sulfur containing compounds. The molar ratio of three compounds in each case determined by NMR. Then, the oxidation products were isolated and purified by centrifugal TLC (Harrison Research) and identified as 2 and 3 comparing their NMR, IR, and mass spectra with those of authentic specimen

Table 1. Asymmetric Oxidation of Alkyl Aryl Sulfide with *C. equi*

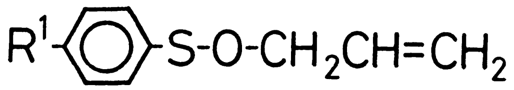
Entry	R^1	R^2	1[a] (ml)	Ratio (%)[b] 3	2[c]	recovered 1	$[\alpha]_D^{19}$ of 2[d]	% e.e.
1	H	n-$C_{10}H_{21}$	0.2	31	25	44	+140°	98.7[e]
2	H	n-$C_{10}H_{21}$	0.1	88	7	5		
3	H	n-C_4H_9	0.2	0	29	71	+193°	100[e]
4	H	n-C_4H_9	0.1	19	81	0		
5	H	CH_3	0.1	0	100	0	+106°	75[f]
6	H	$CH_2{=}CHCH_2$	0.1	27	38	36	+176°[g]	100[e]
7	CH_3	n-$C_{10}H_{21}$	0.2	10	55	35	+124°	91.6[e] (89)[h]
8	CH_3	n-C_4H_9	0.1	3	79	19	+162°	87.3[e] (87)[i]
9	CH_3	CH_3	0.1	0	33	67	+138°	82[j]
10	CH_3	$CH_2{=}CHCH_2$	0.1	23	67	10	+227°[g]	92.4[e]

a) Sulfide added to 50 ml of the medium. b) In all cases, total recoveries of sulfur containing compounds were nearly quantitative, except for entry 5 (yield of sulfoxide, 18%). c) Yield of 2 are not optimized. In case of oxidation of allyl phenyl sulfide (entry 6), the best isolated yield of the sulfoxide was 56%. d) Measured in acetone, unless otherwise stated. e) Determined by HPLC according to the method of Pirkle *et al.*[7] f) Compared with Ref. 9.
g) Measured in ethanol. h) Compared with the authentic sample prepared by the method described in Ref. 2. i) Compared with Ref. 10. j) Compared with Ref. 2.

prepared by the oxidation of **1** with hydrogen peroxide in acetic acid. The results are summarized in Table 1.

As can be seen from the ratios of products and recovered sulfides, the carbon numbers of alkyl chain exerted a remarkable effect on the reaction course. While the formation of sulfones dominated in case that the alkyl chains were long, the oxidation of aryl methyl sulfides solely gave the corresponding sulfoxides, suggesting that aryl methyl sulfoxides are hardly oxidized by this microbial oxidation. The similar effect of the numbers of the alkyl chain has been also observed in the oxidation of terminal olefins[5b] and secondary alcohols[7] by this bacterium.

The optical purities of resulting sulfoxides were determined by HPLC[8] and/or comparing the values of their specific rotation with those of authentic samples prepared by the reaction of *l*-menthyl sulfinates with Grignard reagents[2] and with reported values.[2, 9, 10] In genaral, phenyl sulfides gave higher optical yields than *p*-tolyl sulfides. Alkyl chains of sulfides also affected the optical yields of oxidation. The optical purities of aryl methyl sulfoxides were lower than the other sulfoxides with longer alkyl chains in both phenyl and *p*-tolyl compounds. It is noteworthy that the optical purities of allylic sulfoxides are extremely high in this microbial oxidation. Although allylic sulfoxides has been demonstrated to racemize easily because of the equilibrium between sulfenate ester (**4**),[11] allyl phenyl sulfoxides was obtained in optically pure form. The fact that despite a long reaction time (3 days at 30 °C), the optical yields are high could be deduced to the high polarity of the reaction medium.[11a]



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The absolute configuration of the sulfoxides is considered to be (*R*), judging from the positive sign of the optical rotation. As Table 1 shows, high enantioselectivities have been achieved in all the cases. Two possibilities are considered to account for these selectivities: One is enantioselective oxidation of sulfides, and the other is non-stereoselective formation of *dl*-sulfoxides followed by the selective oxidation of (*S*)-sulfoxides to sulfones. Chemical yields higher than 50% in several cases indicate that the former reaction path is operating.

Thus, microbial oxidation of sulfides by *C. equi* IFO 3730 appeared to be a covenient method for obtaining optically active sulfoxides. Further synthetic applications of this method are the subject of an on-going study.

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6) The medium consists of $(NH_4)_2HPO_4$ (10 g), K_2HPO_4 (2 g), $MgSO_4\cdot7H_2O$ (0.3 g), $FeSO_4\cdot7H_2O$ (10 mg), $ZnSO_4\cdot7H_2O$ (8 mg), $MnSO_4\cdot4H_2O$ (8 mg), yeast extract (0.2 g), and H_2O to make 1000 ml (pH 7.2).

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