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Enantioselective Oxidation of Sulfinic Acid Esters with the Aid of a Microorganism†

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Incubation of racemic arenesulfinic acid esters with a bacterial strain gave the corresponding sulfonates leaving behind optically active sulfinates via enantioselective oxidation. The substrates having longer alkyl chains as alcohol component were smoothly oxidized, and electron donating substituents on aromatic ring accelerated the reaction.

Microbial transformation of synthetic substrates has become increasingly important in recent years.[1] Among them, microbial oxidation of sulfides is one of the most useful, as it provides a facile method for the preparation of chiral sulfoxides.[2] However, practically no study has been reported on enzymatic reaction of sulfinic acid esters. Two types of reaction are possible for these compounds, *i.e.*, oxidation to sulfonates and hydrolysis to afford sulfinic acids and alcohols. Thus microbial reaction of sulfinic esters is of interest not only from the standpoint of examining the interaction of enzymes on synthetic substrates, but also it would add a new entry for preparation of optically active molecules. Enantioselective conversion of racemic sulfinates is expected to afford optically active sulfinates, which are versatile synthons of optically active sulfoxides.[3] We have already developed asymmetric oxidation of alkyl aryl sulfides[4] and enantioselective hydrolysis of arenesulfinyl carboxylic acid esters[5] using *Rhodococcus equi* IFO 3730, which is a commercially available type culture strain. These results indicate that this bacterium has two enzyme systems, one to oxidize a sulfinyl group, and another to hydrolyze an ester with differentiation of chirality of a sulfur atom. Accordingly, we applied this microorganism to the conversion of sulfinic esters.

Racemic ethyl *p*-toluenesulfinate and seed culture of *R. equi* were simultaneously added to a sterilized inorganic medium[6] containing hexadecane as a sole source of carbon. The mixture was incubated for 7 days at 30 °C. Purification of the organic extract by preparative TLC afforded an oxidation product, ethyl *p*-toluenesulfonate,[7] and starting sulfinate of high optical purity. Its enantiomeric excess (e.e.) was determined by HPLC analysis (CHIRALCEL OB Daicel Chemical Industries Ltd.). The absolute configuration was

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†Dedicated to Professor Emeritus Osamu Simamura of The University of Tokyo on the occasion of his 80th birthday.

determined to be (*R*), by comparison of the sign of optical rotation with that of an authentic specimen after derivation to methyl *p*-tolyl sulfoxide[8] according to Andersen method.[9] These results suggest that one enantiomer is oxidized faster than the other. However, the combined yield of the sulfinate and sulfonate was less than 50%. As the sulfonate was found to be stable in the medium under incubation conditions, low material balance is

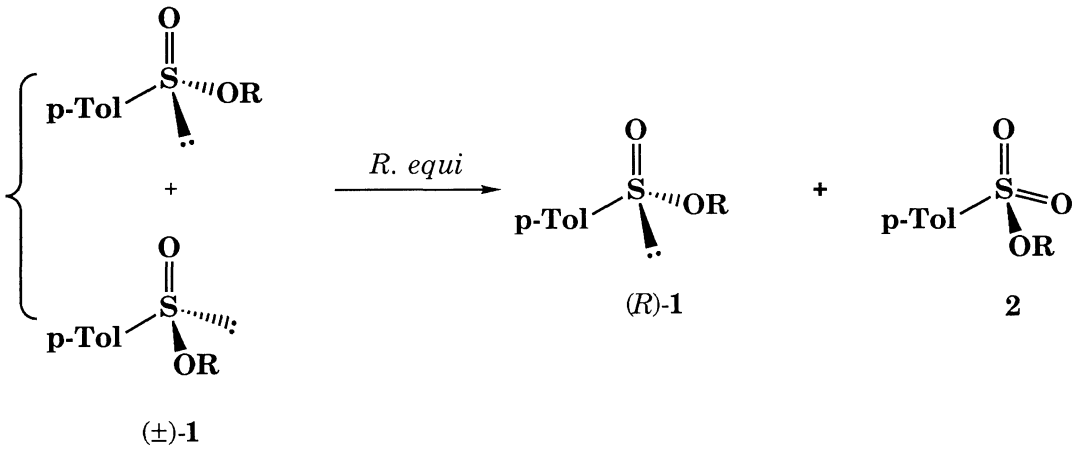

Table 1. Enantioselective Oxidation of *p*-Toluenesulfinates[a]

R	Cult. /day	Recovery/%	e.e./%[b]	Yield of **2**/%
C_2H_5	4	36	72	13
C_2H_5	7	25	91	10
n-C_6H_{13}	3	32	84	36
n-C_8H_{17}	3	39	76	33

a) Substrate concentration was made up to 0.1% to the medium.

b) Determined by HPLC analysis with CHIRALCEL OB (Daicel Chemical Industries Ltd.): eluent, hexane/iso-PrOH = 9/1; flow rate, 0.5 ml/min.

probably accounted for by assuming that enzymatic hydrolysis of sulfinate competes with oxidation. As shown in Table 1, sulfinic esters bearing an alcohol residue with a long alkyl chain such as hexanol and octanol were liable to be oxidized smoothly.

Electronic effects of para-substituents on the reactivity of hexyl sulfinates are summarized in Table 2. It is clear that electron density on sulfur atom is critical to smooth oxidation. As a nitro group strongly inhibited the reaction, the reaction is supposed to

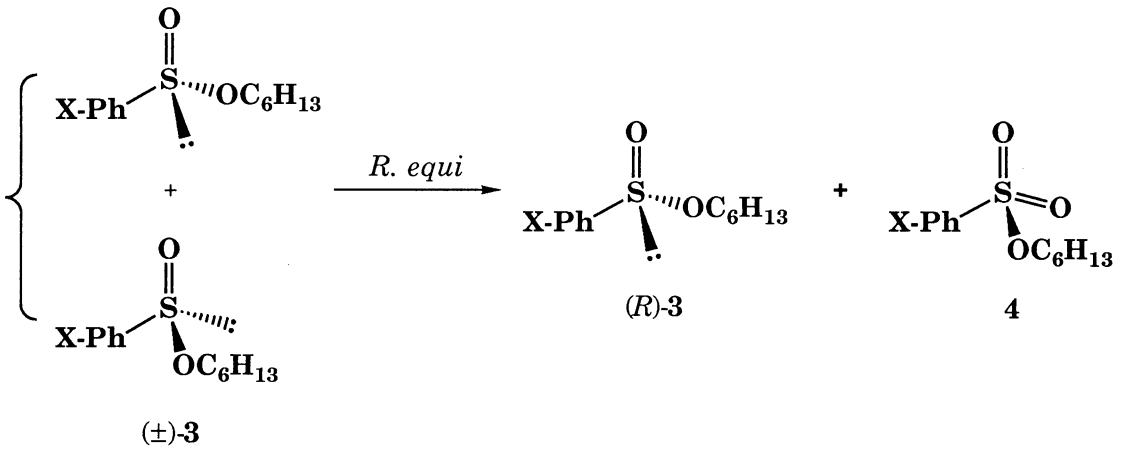

Table 2. Effect of *para*-Substituents on Reactivity of Arenesulfinates[a)]

X	Recovery/%	e.e./%[b)]	Yield of **4**/%	E value[c)]
H	47	62	31	6
CH_3	32	84	36	5
MeO	32	>99	48	12
NO_2	73	0	9	–

a) Cultivation was done for 3 days at 30 °C. Concentration of substrates was made up to 0.1%.

b) Determined by HPLC analysis.

c) Calculated according to the following equation.[11)]

E=ln[(1-c)(1-e.e.)]/ln[(1-c)(1+e.e.)], where c=conversion yield.

proceed via electrophilic attack of an active oxygen species.[10)] On the other hand, when the substrate has a methoxy group, the enantioselectivity was high and the reaction afforded optically pure sulfinate in an agreeable yield.

The carbon source for the growth of the bacterium is essential for the present oxidation to proceed. When the microorganism was grown on glucose instead of hexadecane, added hexyl (±)-*p*-toluenesulfinate was recovered quantitatively after 3-day incubation. These facts strongly indicate that the oxidase catalyzing the enatioselective oxidation of sulfinates is induced in the cell by the action of hexadecane which needs oxygenase to be metabolized. The same phenomenon was observed in the case of oxidation of sulfides.[2)]

In conclusion, (*R*)-sulfinic acid esters of high optical purity were obtained via enantioselective microbial oxidation of the corresponding racemates. Electron-donating

substituents on the aromatic ring and the presence of relatively long alkyl chain as alcoholic part of the ester were favorable for highly selective oxidation.

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6) The medium consists of $(NH_4)_2HPO_4$ (10 g), K_2HPO_4 (2 g), $MgSO_4 \cdot 7H_2O$ (0.3 g), $FeSO_4 \cdot 7H_2O$ (10 mg), $ZnSO_4 \cdot 7H_2O$ (8 mg), $MnSO_4 \cdot 4H_2O$ (8 mg), yeast extract (0.1 g), and H_2O to make 1000 ml (pH 7.2).
7) All products were identified by comparing the spectroscopic data with those of authentic specimen.
8) $[\alpha]_D^{24}$ −72° (c 0.3, acetone); lit $[\alpha]_D^{19}$ +124° (c 3.35, acetone).
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