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Asymmetric Oxidation of Sulfides by Cyclohexanone Monooxygenase

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Abstract. Cyclohexanone monooxygenase catalyzes the asymmetric oxidazion of numerous alkyl aryl sulfides with the alkyl chain functionalyzed with Cl, CN, vinyl or hydroxy groups. Sulfoxides with enantiomeric excesses up to 99% were obtained. The structure of the sulfide markedly influenced enzyme enantioselectivity.

Previously, we have shown that cyclohexanone monooxygenase from *Acinetobacter* can catalyze the asymmetric sulfoxidation of numerous alkyl aryl sulfides, dialkyl sulfides and dialkyl disulfides.[1] The structure of the sulfide dramatically influenced not only the enantioselectivity but even the enantiopreference of the enzyme which yielded sulfoxides ranging from 99% ee with (R)- configuration to 93% ee with (S)-configuration.[1] In the present work, we have extended the investigation to several alkyl aryl sulfides with the alkyl chain functionalized with Cl, CN, vinyl or hydroxy groups.

The oxidation of functionalized alkyl aryl sulfides by cyclohexanone monooxygenase (**reaction 1**) was coupled to a second enzymatic reaction (**reaction 2**) catalyzed by glucose-6-phosphate dehydrogenase (G6PDH) in order to regenerate NADPH.[1,2]

$$\text{Ar-S-R} + \text{NADPH} + \text{O}_2 + \text{H}^+ \xrightarrow{\text{monooxygenase}} \text{Ar-SO-R} + \text{NADP}^+ + \text{H}_2\text{O} \quad \textbf{(reaction 1)}$$

$$\text{D-Glucose-6P} + \text{NADP}^+ \xrightarrow{\text{G6PDH}} \text{D-Gluconate-6P} + \text{NADPH} + \text{H}^+ \quad \textbf{(reaction 2)}$$

The Table shows the yield and the stereochemistry of the enzymatic reaction with the various substrates. It can be seen that the degrees of conversions did not differ markedly and were in all cases≥60%. The stereoselectivity, however, was highly dependent on substrate structure. A previous investigation showed, as rule of thumb, that the increase of size of the alkyl chain or the introduction of substituents in the phenyl ring had (S)-directing effects and that these effects were cumulative.[1] This rule was less respected in the case of these functionalized sulfides and there were some striking exceptions. For example, in the case of the cyano compounds **5** and **10** the increase of size of the alkyl chain had an (R)-directing effect, and the same effect was observed in the hydroxy compounds **3** and **6** with the introduction of a methyl group in the aromatic ring. Therefore, it is likely that the enantioselectivity depends not only on the bulkiness but also on the lipophilicity and /or electronic characteristics of the substituents.The majority of the sulfoxides had the (S)-configuration and the optical purity was in some cases very high (entries **1,2,7-10**). With the cyano derivatives it was possible to move from the (R) to (S)-sulfoxide, both with ee>90%, by simply introducing a methyl group in the *para* position of the aromatic ring (entries **2** and **10**). The optical purities of the enzymatically prepared functionalized sulfoxides were greater than those of the same sulfoxides obtained by chemical oxidation with *t*-BuOOH in the presence of a chiral titanium complex.[3] Sulfides functionalized with ester groups were not oxidized by the enzyme and those containing keto groups preferentially underwent Baeyer-Villiger oxidation.[4]

Table. Cyclohexanone monooxygenase catalyzed oxidation of functionalyzed alkyl aryl sulfides to sulfoxides.

entry	sulfide	yield %	ee %	sulfoxide configuration[a]
1	C_6H_5-S-CH=CH_2	73	99[b]	R
2	C_6H_5-S-CH_2-CN	90	92[b]	R
3	*p*-CH_3-C_6H_4-S-$(CH_2)_2$-OH	66	13[b]	R
4	C_6H_5-S-$(CH_2)_2$-CN	61	14[c]	S
5	*p*-CH_3-C_6H_4-S-$(CH_2)_2$-CN	71	61[c]	S
6	C_6H_5-S-$(CH_2)_2$-OH	62	77[b]	S
7	C_6H_5-S-$(CH_2)_3$-OH	60	85[b]	S
8	C_6H_5-S-$(CH_2)_2$-Cl	75	93[c]	S
9	*p*-CH_3-C_6H_4-S-$(CH_2)_2$-Cl	65	93[c]	S
10	*p*-CH_3-C_6H_4-S-CH_2-CN	95	98[b]	S

[a] The absolute configurations were determined by comparison with the chemically prepared sulfoxides using chiral HPLC.[b] Determined by HPLC on Chiralcel OD.[c] Determined by HPLC on Chiralcel OB.

EXPERIMENTAL SECTION

Materials. Phenyl vinyl sulfide and 2-(phenylthio)ethanol were bought from Aldrich. The other sulfides were synthesised according to the literature.[5] Sulfoxides corresponding to entries **1,2** and **10** are known in the optically active form.[3,6] Sulfoxides corresponding to entries **3-9** were prepared from the correspondent sulfide by oxidation with *t*-BuOOH in the presence of a chiral titanium complex[3] and their absolute configuration was attributed on the basis of Kagan model.[7] NADP, glucose-6-phosphate and glucose-6-phosphate dehydrogenase were purchased from Sigma.Cyclohexanone monooxigenase from *Acinetobacter* NCIB 9871 was prepared as previously described.[1]All other chemicals were reagent grade.

Enzymatic oxidation. The sufide (0.7 mmol) was magnetically stirred in 20 ml of 0.05 M Tris-HCl buffer, pH 8.6, containing 3 μmol NADP, 2 mmol glucose-6-phosphate, 10 units of cyclohexanone monooxygenase and 40 units of glucose-6-phosphate dehydrogenase. After overnight reaction, the solution was extracted with 3 portions (20 ml each) of ethyl acetate and the organic extract was dried and evaporated.

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