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Peroxygenase-catalyzed enantioselective sulfoxidations

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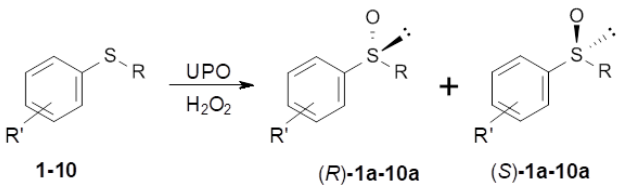
Abstract: The performances of the unspecific peroxigenase from *Agrocybe aegerita* (*Aae*UPO) in the asymmetric sulfoxidation of substituted aryl alkyl sulfides were here investigated. A small library of differently substituted aryl alkyl sulfoxides was successfully synthesized from the corresponding sulfides in the presence of *Aae*UPO and H_2O_2. All the sulfoxides were obtained as (*R*)-enantiomers, regardless the substitution pattern both on the aromatic ring and the alkyl chain, in up to >99% conversion and >99% ee. An overview about the biocatalytic entries to chiral sulfoxides is also presented here *via* a comparison between the results obtained with *Aae*UPO and performances of the chloroperoxidase from *Caldariomyces fumago*, and three different Baeyer-Villiger monooxygenases. To the best our knowledge, this is the first example of a systematic investigation of the *Aae*UPO synthetic potential in the asymmetric oxidation of hetero atoms, *i.e.* the pro-stereogenic sulfur of sulfides.

Chiral sulfoxides are valuable compounds that find several applications as synthons in the preparation of biologically active molecules as well as chiral auxiliaries in asymmetric synthesis.[1] Among the different methods aimed at the efficient preparation of optically pure sulfoxides, enzyme-catalyzed enantioselective oxidation of prochiral sulfides has been widely investigated in the last decades.[1a,c,2] In particular, the best results, in terms of both enantioselectivity and conversions, have been obtained with the chloroperoxidase (CPO) from *Caldariomyces fumago*,[2a-b,3] and different monooxygenases,[4] in particular Baeyer-Villiger monooxygenases (BVMOs),[2b,4a-e] in the presence of either H_2O_2 or O_2 as oxidant, respectively.

Unspecific peroxygenases (UPOs, EC 1.11.2.1) represent an emerging class of biocatalysts with a wide range of potential applications in different oxyfunctionalization reactions.[3c,5] They are extracellular heme-thiolate enzymes produced by several fungi with no significant sequence homology to cytochrome P450s and only distantly related to CPO (~ 30% sequence similarity). Based on a catalytic mechanism resembling the "peroxide shunt" pathway of P450s, they show a peroxide-dependent monooxygenase activity resulting e.g., in the hydroxylation of different alkane and aromatic compounds, in alkene epoxidation and *O*- and *N*-dealkylation reactions.

The best characterized UPO (*Aae*UPO) has been identified in 2004 from the edible mushroom *Agrocybe aegerita*[6] and its structural and functional features have been largely investigated in the last years.[5,7] Moreover, the practical application of *Aae*UPO in useful synthetic biotransformations has been recently implemented by developing improved systems for enzyme production/optimization[8] and for the efficient set-up of preparative-scale reactions.[9]

In recent reviews of the current state-of-the-art on applications of peroxygenases,[3c,5] sulfoxidations are commonly listed among the wide number of possible reactions catalyzed by UPOs. However, to the best of our knowledge, only preliminary information is available so far about the exploitation of UPOs, including *Aae*UPO, in the (enantioselective) oxyfunctionalisation of sulfides to sulfoxides.[10] Specifically, the enantioselective oxidation of thioanisole (**1**, Scheme 1 and Table 1) to the corresponding (*R*)-**1a** sulfoxide has been previously reported.[10a] However, neither the conversion nor the enantiomeric excess (ee) of the obtained product were shown in this conference communication. The only other example has been reported a couple of years later about the *S*-oxidation of the heterocyclic compound dibenzothiophene by using both whole cells basidiomycetes and purified UPOs.[10b] Although investigated to a deeper extent, this reaction was not suitable to get information about the enantioselectivity of *Aae*UPO given the symmetrical nature of the substrate.



1-10 (*R*)-**1a-10a** (*S*)-**1a-10a**

Scheme 1. UPO-catalyzed sulfoxidation of aryl alkyl sulfides **1**-**10** (see Table 1 for structure details).

The aim of this work was to assess the performances of *Aae*UPO in the asymmetric synthesis of different chiral sulfoxides, thus filling this gap in the knowledge of the biocatalytic potential of the unspecific peroxygenases.

The ability of *Aae*UPO of catalyzing the sulfoxidation of the model substrate **1** was further investigated by testing a peroxygenase preparation easily obtained from the wild-type *Agrocybe aegerita* TM-A1 (DSM 22459) strain[6] as described in the literature (see Supporting information for details). In a first set of reactions, the starting concentration of both the substrate **1** and the oxidant H_2O_2 were kept at 1 mM to avoid the well-

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described peroxide-dependent inactivation of the enzyme.[5b,9c,11] Reactions with *Aae*UPO were carried out at 20°C in citrate phosphate buffer (10 mM, pH 7.0), in the presence of 20% (*v*/*v*) CH_3CN as cosolvent, and stopped at scheduled times by extraction with ethyl acetate to analyze the obtained crude mixtures by means of HPLC on a chiral column (see Supporting Information for further details). Control reactions were performed in the absence of the enzyme or the oxidant. Under these reaction conditions, the (*R*)-sulfoxide **1a** could be obtained after 20 min in quantitative yields and 80% ee (Table 1, Fig. S1 in Supporting Information). *Aae*UPO showed a good operative stability, retaining >90% of the starting activity for at least 2 h (as assayed by spectrophotometric measurement of the activity with 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) as substrate). No formation of by-products, and in particular of the corresponding over-oxidation sulfone product, was observed, even when performing a control reaction with the racemic mixture of **1a** sulfoxides as substrates. The same result was previously reported also for CPO-catalyzed sulfoxidations,[3] while, differently from CPO, *Aae*UPO showed negligible activity (<1% conversion) in the oxidation of **1** when using *tert*-butyl hydroperoxide (*t*-BuOOH) as oxidant. However, this finding is not surprising since the use of *t*-BuOOH as an alternative to H_2O_2 showed to be challenging also in other oxyfunctionalization reactions catalyzed by *Aae*UPO.[9a] Additionally, the apparent K_M (21 mM) and k_{cat} ($4.2 \cdot 10^5$ s^{-1}) kinetic parameters, estimated by interpolating with the Michealis-Menten equation the initial reaction rate data obtained at fixed (1 mM) H_2O_2 concentration and increasing concentration of **1** (1-50 mM, see Supporting Information for details), look compatible with further practical application of this biocatalyst by process development.

To confirm this, the concentration of **1** was increased to 10 mM (35 µmol in 3.5 mL final volume). As mentioned before, the *in situ* H_2O_2 concentration is the critical point in the operative stability of peroxygenases. Among the several options described in the literature to face this issue,[3c,9c] we opted for a simple step-wise addition of a concentrated H_2O_2 solution (35 µmol added in 10 aliquots at 30 min intervals in the first 4.5 h, then the reaction was maintained for additional 2.5 h without further oxidant addition). The residual *Aae*UPO activity in the reaction solution, conversion of substrate **1** and ee value of the formed product were monitored at scheduled times.

As shown in Figure 1, the controlled supplementation of H_2O_2 allowed to obtain a >95% conversion of **1** into **1a** without observing dramatic drops of enzyme activity during oxidant addition (~60% residual activity after the first 5 h). In agreement with previous studies,[11] the application of an optimized starting substrate/H_2O_2/enzyme ratio allowed a minimization of the catalase side-activity, which has been suggested as the main responsible of UPOs inactivation. In fact, only one equivalent of oxidant was required to obtain an almost complete conversion of the target substrate, thus suggesting the lack of significant H_2O_2 consumption by dismutation to O_2 and H_2O. A possible protective effect of the substrate toward peroxide-induced inactivation, previously investigated by Karich and coauthors for UPO-catalyzed hydroxylation reactions,[11] was suggested also in this case by the superior operative stability shown by *Aae*UPO at low (<50%) conversion degrees. The ee value of the formed (*R*)-sulfoxide **1a** was unaltered (80%) during the whole reaction time. The scalability of *Aae*UPO-catalyzed sulfoxidations was further demonstrated in the semi-preparative scale synthesis of **1a** performed on 0.2 mmol of substrate **1** (see Supporting Information for further details).

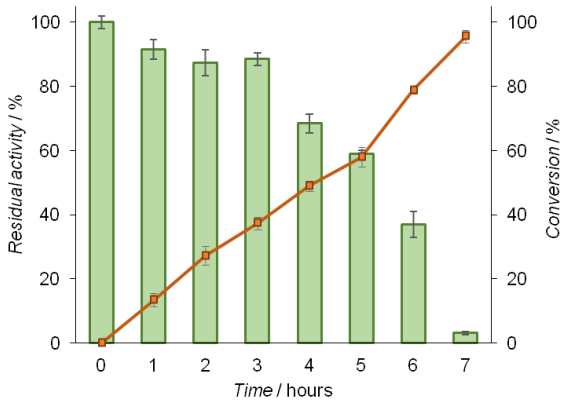

Figure 1. Sulfoxidation of **1** (10 mM) catalyzed by *Agrocybe aegerita* UPO in the presence of H_2O_2 as oxidant. Green bars, residual UPO activity; red line, conversion of **1** into **1a**.

In addition to thioanisole **1**, the versatility of *Aae*UPO in promoting enantioselective sulfoxidations was further studied by testing a panel of differently substituted aryl alkyl sulfides (**2-10**, Table 1). The obtained conversions and ee values of sulfoxide products were compared with those available in the literature for CPO and three different BVMOs (CHMO, PAMO and HAPMO) for the biooxidation of the same compounds.

In general, *Aae*UPO converted the tested aryl alkyl sulfides into the corresponding sulfoxides with good conversions, with the exception of the *o*-substituted substrate **2** (35%) and the *p*-cyanophenyl methyl sulfide **6** (<5%). The formation of the (*R*) enantiomer of the sulfoxide products was always observed (the (*S*) product was obtained only in the case of **10a** due to a change in the CIP priority rules) with good to excellent enantioselectivity (70->99% ee).

Electron donating groups in the *para* position of the aromatic ring seemed to be well tolerated (entry **4**, **5** and **7**), as well as substitution on the *meta* carbon atom (entry **3**), while the presence of an electron withdrawing substituent in *para* dramatically affected the biocatalytic oxidation (entry **6**). The best results in terms of enantiomeric excess were obtained when a substituent was introduced on the R-group: the vinyl thioanisole **8**, as well as the cyclopropyl derivative **9**, were converted into the corresponding (*R*)-sulfoxides with >99% ee. However, a decrease of both conversion and ee value was observed with compound **10**. This fact could be possibly ascribed to the presence of a flexible CH_2-OMe R substituent allowing a higher conformational freedom and more than one energetically equivalent conformations during the binding with

the active site, or, alternatively, to the presence of a coordinating oxygen atom on the R substituent.

Interestingly, during the biocatalytic sulfoxidation of **8** only the (*R*) enantiomer of sulfoxide **8a** was recovered, suggesting a faster kinetic for the sulfoxidation in comparison with olefin epoxidation, another example of UPO-catalyzed reactions largely reported in the literature.[3c,5]

Coming to the comparison with other biocatalyzed sulfoxidations, it is not surprising to observe pretty similar results in terms of conversions and enantioselectivity with CPO, as it is, as mentioned before, an enzyme structurally related to UPOs. With the exception of **5**, *Aae*UPO usually achieved better conversions, but slight lower ee values than CPO, the stereoselectivity being in both cases toward the formation of the (*R*) enantiomer.

As far as BMVOs concern, only few data are available about our panel of substrates for the enzymes from *Acinetobacter calcoaceticus* (CHMO)[4a] and *Thermobifida fusca* (PAMO),[4c] in most cases showing less impressive performances than UPO (and CPO), both in terms of conversion and enantiomeric excesses. Instead, a full set of data was reported on the asymmetric sulfoxidation of **1-10** catalyzed by the HAPMO enzyme from *Pseudomonas fluorescens*.[4d] Interestingly, satisfactory results were obtained with HAPMO in most cases, the formation of the (*S*)-enantiomers of sulfoxides **1a-10a** being achieved with good conversion (except for substrates **3** and **4**) and very good enantiomeric excesses, with the only exception of compound **4**. The strict (*S*)-selectivity previously shown by HAPMO is herein well complemented by the preference toward the formation of the (*R*)-sulfoxides demonstrated by *Aae*UPO, thus enabling a fully biocatalytic access to both the enantiomers of sulfoxides **1a-10a**. However, while different BVMOs have been successfully used to produce chiral sulfoxides by kinetic resolutions of racemic sulfoxides,[4] this was not true for *Aae*UPO as we have shown that this peroxygenase catalyzes the asymmetric *S*-oxidation of sulfides, but do not accept sulfoxides as substrates.

In conclusion, a small library of differently substituted aryl alkyl sulfoxides was successfully synthesized from the corresponding sulfides in the presence of *Aae*UPO and H_2O_2 with up to >99% ee and conversion. All the obtained sulfoxides were (*R*)-enantiomers, regardless the substitution pattern both on the aromatic ring and the alkyl chain. As previously shown for other oxyfunctionalization reactions, the preparative exploitation of *Aae*UPO (and likely also of other UPOs) in asymmetric sulfoxidations requires a very careful control of the *in situ* concentration of the oxidant H_2O_2 to avoid enzyme inactivation. However, both the lack of over-oxidation side-activities and the stereocomplementarity with other biocatalysts suggest that UPOs may have a good potential as useful tools in the obtainment of chiral sulfoxides.

Table 1. Comparison of UPO-catalyzed sulfoxidations with literature data for CPO and the Baeyer-Villiger monooxygenases CHMO, PAMO, and HAPMO.

Substrate	R	R'	UPO[a]		CPO[b]		CHMO[c]		PAMO[d]		HAPMO[e]	
			c [%][f]	*ee* [%][f]	*c* [%]	*ee* [%]	*c* [%]	*ee* [%]	*c* [%]	*ee* [%]	*c* [%]	*ee* [%]
1	CH_3	H	>99	80 (*R*)	>99	98 (*R*)	88	99 (*R*)	94	44 (*R*)	96	99 (*S*)
2	CH_3	*o*-Cl	35	74 (*R*)	33	85 (*R*)	35	32 (*R*)	n.a.[g]	n.a.	76	96 (*S*)
3	CH_3	*m*-Cl	>99	90 (*R*)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	42	93 (*S*)
4	CH_3	*p*-Cl	>99	93 (*R*)	77	90 (*R*)	78	51 (*S*)	n.a.	n.a.	37	44 (*S*)
5	CH_3	*p*-CH_3	83	90 (*R*)	98	91 (*R*)	94	37 (*S*)	68	10 (*R*)	77	99 (*S*)
6	CH_3	*p*-CN	<5	n.d.[h]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	64	96 (*S*)
7	CH_3	*p*-OCH_3	87	70 (*R*)	72	90 (*R*)	81	51 (*S*)	47	25 (*R*)	78	99 (*S*)
8	$CH{=}CH_2$	H	85	>99 (*R*)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	78	98 (*S*)
9	C_3H_5	H	95	>99 (*R*)	n.a.	n.a.	n.a.	n.a.	67	48 (*R*)	74	97 (*S*)
10	CH_2OCH_3	H	50	81 (*S*)[i]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	63	98 (*R*)[i]

[a] substrate, 1 mM; H_2O_2, 1 mM, UPO, 0.15 U mL^{-1}, 0.166 μM ; 10 mM citrate phosphate buffer, pH 7.0, 2% (*v*/*v*) CH_3CN; 20°C; 20 min. [b] substrate, 9 mM; H_2O_2, 2 eq. (added portionwise in 13 aliquots), CPO, 0.144 μM; 50 mM citrate buffer, pH 5.0; 25°C; 1 h. [3b] [c] substrate, 40 mM; $NADP^+$, 0.15 mM; glucose-6-phosphate (G6P), 0.1 M; CHMO, 0.3 U mL^{-1}; glucose-6-phosphate dehydrogenase (G6PDH), 2.5 U mL^{-1}; 50 mM Tris/HCl buffer, pH 8.6; 25°C; 24 h. [4a] [d] substrate, 20 mM; $NADP^+$, 0.02 mM; G6P, 2 eq.; PAMO, 1 U mL^{-1}; G6PDH, 10 U mL^{-1}; 50 mM Tris/HCl buffer, pH 9.0; 25°C; 24 h. [4c] [e] substrate, 20 mM; $NADP^+$, 0.02 mM; G6P, 1.5 eq.; HAPMO, 1 U mL^{-1}; G6PDH, 10 U mL^{-1}; 50 mM Tris/HCl buffer, pH 9.0; 25°C; 24 h. [4d] [f] Conversions and enantiomeric excesses calculated on the basis of chiral HPLC analysis (see Supporting Information for details). [g] n.a.: not available from literature data. [h] n.d.: not determined. [i] Absolute configuration is reversed due to a change in the substituent priority according to the sequence rules.

Experimental Section

Agrocybe aegerita strain TM-A1 (DSM 22459) was grown in 2 L-shaken flasks containing 0.5 L of 30 g L^{-1} soybean peptone. The culture was maintained at 25°C and monitored daily for accumulation of UPO activity, as well as of possible contaminant laccase activities, in the culture medium. After 14-15 days, the mycelium was filtrated and the UPO was recovered from the culture medium by ammonium sulfate precipitation. Detailed methods are reported in the Supporting Information. The analytical scale biooxidation of aryl alkyl sulfides was performed by adding each substrate (1 mmol) to a 20% solution of CH_3CN in citrate phosphate buffer (10 mM, pH 7.0, 1 mL final volume) containing H_2O_2 (1 eq, 1 mM) and UPO (0.15 U mL^{-1}, 0.166 μM). Extraction with AcOEt allowed the recovery of the desired oxidized product to be analysed by HPLC on chiral column. The absolute configurations of the obtained products were determined by comparing the t_R reported in literature for the (*R*) and (*S*) enantiomers of compounds **1a**-**10a** in the same analytic conditions. Suitable racemic mixtures of sulfoxides to be used as NMR and HPLC standards were prepared by chemical sulfoxidations by adding dropwise *m*CPBA (1.2 eq, 0.5 M in $CHCl_3$) to a $CHCl_3$ solution of the desired aryl alkyl sulfide at 0°C (substrates **1-10**, 1 eq, 50 mM, 2 mL final volume). After stirring the mixture for 30-60 min, racemic sulfoxides **1a-10a** were obtained by extraction with AcOEt, drying over sodium sulfate and *in vacuum* concentration. Product were obtained in good isolated yields (70-90%) and characterized by ^{1}H NMR and HPLC analysis on chiral column.

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Keywords: unspecific peroxigenase •enantioselectivity • chiral sulfoxides • biocatalysis • asymmetric oxidation

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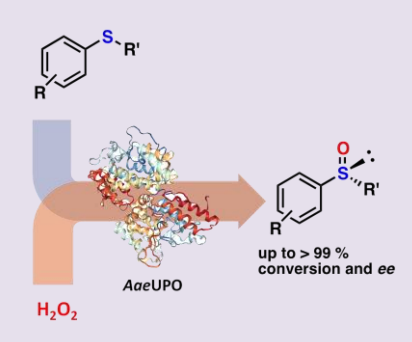
Entry for the Table of Contents

COMMUNICATION

The biocatalytic enantioselective oxidation of prochiral sulfides in the presence of a fungal unspecific peroxygenase from *Agrocybe aegerita* and hydrogen peroxide as oxidant was investigated. The synthesis of differently substituted (*R*)-aryl alkyl sulfoxides was achieved with up to >99% conversion and >99% ee.



*Ivan Bassanini, Erica E. Ferrandi, Marta Vanoni, Gianluca Ottolina, Sergio Riva, Michele Crotti Elisabetta Brenna, Daniela Monti**

Page No. – Page No.

Peroxygenase-catalyzed enantioselective sulfoxidations