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Extended Abstract

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Synthesis of different sulfoxide from its corresponding sulfide by plant enzyme

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Chiral organic sulfoxides are important synthons and chiral auxiliaries in synthetic organic chemistry. Therefore synthesis of chiral sulfoxide is an active area of continuing research interest. The most common method for the preparation of sulfoxide is by the oxidation of their corresponding sulfides. Both the chemical and biological catalysts have been developed for this purpose. Though the reaction conditions for the preparation of chiral organic sulfoxides. With hope that some of them will produce the desired sulfoxidation in a good enantiomeric excess. Being involving biological catalysts are milder and ecofriendly in comparison to those involving chemical catalysts, they are of limited practical use. This communication reports a crude preparation of chloroperoxidase from plant which can be conveniently prepared and used for the transformation of different sulfide to its sulfoxide. This is the report of sulfoxide formation using a plant enzyme. The method for the preparation of enzyme from plant has been developed. The enzymatic characteristics like Km for the substrates sulfide and H2O2, pH and temperature optima of the enzyme have been determined. The enzymatic transformation of different sulfide to its sulfoxide has been demonstrated. Sulfoxides are a wide class of organic compounds containing sulfur and oxygen with general formula RSOR′, where the R and R′ are carbon groups (or hydrogen) and the oxygen is directly bound to the sulfur atom. The unique peculiarity of sulfoxides is represented by the fact that the sulfur atom is a stereogenic centre when $R \neq R^1$ and it assumes a tetrahedral sp^3 hybridization with a lone pair occupying one of the sp^3 orbitals while the oxygen atom forms a d-π bonding with sulfur. Generally, chiral sulfoxides are conformationally stable at ambient temperature and racemise only under harsh conditions. Thanks to their properties, enantiopure sulfoxides have attracted much attention in chemistry as they are found in many natural products and pharmaceutical agents such as the natural antibacterial garlic components allicin, ajoene and garlicnins B-2 and L-1 as well as in the commercial drugs esomeprazole, (+)-sulmazole and armodafinil. Enantiopure sulfoxides are also used in chemistry as chiral ligands for asymmetric organic syntheses, such as the Schiff base ligand 1 or the Skarzewsky's ligand 2. The synthesis of organic compounds containing an enantiopure sulfoxide moiety is an attractive and challenging field in organic chemistry. When considering the synthesis of sulfoxides, research is naturally prone to approach the challenge by looking for an oxidative pathway as sulfoxides are the first oxide of their sulfide counterpart and, therefore, oxidative routes have been the first synthetic choice for many years. The asymmetric synthesis of optically active sulfoxides has relied mainly on the use of chiral auxiliaries or metal catalysts. In the last decades, due to the progresses made in the field of gene cloning, DNA sequencing and engineering and protein expression, a number of biocatalytic methods to construct enantiopure sulfoxides has been reported in literature as well. The vast majority of these enzymatic approaches exploit oxidative enzymes like monooxygenases, peroxidases or cytochromes P450, which convert achiral sulfides into enantioenriched sulfoxides. More recently, the use of reductive enzymes, able to catalyse the stereoselective reduction of racemic sulfoxides, has emerged as a valid alternative to standard oxidative biocatalytic pathways. This minireview aims at highlighting the recent advances made in the last decade in the synthesis of optically active sulfoxides by unconventional biocatalytic methods. While a number of reviews on the synthesis of sulfoxides using oxidising enzymes has been recently reported, this review will focus mainly on the new reductive enzymatic pathways. In addition, the use of unconventional solvents, such as ionic liquids and deep eutectic solvents, in the biocatalytic synthesis of sulfoxides will be discussed, to highlight the advances made in the development of greener and more sustainable synthetic processes. Enantiopure sulfoxides can be obtained by reductive biocatalytic mechanisms where reductive enzymes catalyse the kinetic resolution of sulfoxide racemates by selectively reducing one of the two enantiomers into the corresponding sulfide. Unlike the large pool of oxidative enzymes from which the researcher can chose from, the range of reductive enzymes is still rather small and, indeed, currently limited to only two classes: the methionine sulfoxide reductases (Msr) and the dimethyl sulfoxide (DMSO) reductases (DmsABC). biochemical role of Msr enzymes is the ability of restoring the functionality of damaged proteins containing methionine sulfoxides. In cells, the oxidation of the amino acid methionine (Met) by reactive oxygen species (ROS) occurs frequently during cellular metabolism resulting in the formation of a diastereomeric mixture of Met-(*S*)-sulfoxide [Met-*S*-(O)] and Met-(*R*)-sulfoxide [Met-*R*-(O)]. The original functionality of proteins containing Met-*S*-(O) and Met-*R*-(O) is restored by two subfamilies of Msr enzymes, the methionine sulfoxide reductases A (Msr-A) and the methionine sulfoxide reductases B (Msr-B). These enzymes are capable of reducing the Met-*S*-(O) and Met-*R*-(O) respectively back to the original amino acid Met. Following this natural biochemical reactivity, Msrs have been investigated as biocatalysts to perform the kinetic resolution of exogenous racemic sulfoxide substrates. Despite their activity being known for decades, only in 1992 Broth et al. first sequenced and expressed a recombinant Msr enzyme after cloning the gene from *Escherichia coli*.

The same group reported the cloning, sequencing and expression of the mammalian homologue of *E. coli* MsrA and showed that this enzyme was active on both natural and synthetic substrates and able to reduce a variety of sulfoxide containing compounds, including (*S*)-(−)-methyl *p*-tolyl sulfoxide. However, concrete advances in the kinetic resolution of racemic sulfoxides using Msr enzymes truly happened only in the last five years as the progress and development of more advanced chemical biology techniques allowed research groups to re-evaluate this class of enzymes as biocatalysts. Chen and co-workers observed that a strain of *Pseudomonas monteilii* CCTCC M2013683 was capable of synthesising chiral sulfoxides with 99 % *ee*. Later, the same authors reported the cloning and expression of the MsrA gene from *P. monteilii* CCTCC M2013683 (pmMsrA). In order to assess the ability of pmMsrA to furnish optically pure sulfoxides, the recombinant protein was expressed in *E. coli*, harvested in the resting phase and subsequently subjected to an activity assay using *rac*-**3**. After 24 hours, this whole cell system led to the formation of **4** with 51 % conversion, leaving (*R*)-**3** unreacted >99 % *ee*. Further investigation of pmMsrA revealed that the system could tolerate substrate concentrations up to 5 mM with an optimal cell density of 40 $g_{cdw}\,L^{-1}$ yielding 46 % (*R*)-**3** after 16 h reaction and maintaining an excellent 96 % *ee*. The biocatalyst proved to tolerate halogen substitutions on the aromatic ring of **3** retaining good-to-excellent *ee* values and conversions. MsrAs are selective biocatalysts able to afford the (*R*)-sulfoxide enantiomer. On the other hand, MsrB enzymes show opposite stereoselectivity and prove to be valid biocatalysts for the reduction Met-*R*-(O). However, MsrB enzymes have shown to be far less active and to have a much higher substrate specificity than MsrAs, thus limiting their use in the synthesis of (*S*)-sulfoxides. In 2020, Chen and co-workers reported the first example of kinetic resolution of alkyl aryl sulfoxides using whole cell akMsrB from *Acidovorax* sp. KKS102. The biocatalyst akMsrB was found among a pool of six enzymes that shared 55–92 % sequence identity out of which pmMsrB was able to convert the *R* enantiomers of sulfoxides *rac*-**9 a**–**c** into the corresponding sulfides **10 a**–**c** yielding (*S*)-**9 a**–**c** with >90 % *ee*. Unfortunately, when the same biocatalytic transformation was attempted with the purified enzyme, all activity was lost.

Bottom Note: *This work is partly presented at* 6th World Congress on NATURAL PRODUCT & SYNTHETIC CHEMISTRY June 24-25, 2019 | New York, USA.