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Review

Biocatalysis as an alternative for the production of chiral epoxides: A comparative review

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ABSTRACT

Enantiopure epoxides are remarkably versatile intermediates for the synthesis of numerous biologically active targets, to which considerable efforts have been devoted either chemically or biologically during the past few decades. This review will emphasize the application of biocatalysis as an efficient alternative that complements conventional chemical reactions, with a special focus on the epoxidation reactions catalyzed with monooxygenases and chloroperoxidases and the hydrolytic kinetic resolution catalyzed with epoxide hydrolases. Their scopes and limitations will be elaborately discussed as compared with their chemical counterparts. These biocatalytic approaches have not only provided environmentally friendly alternatives, but also displayed advantages for certain types of enantiopure epoxides, and could serve as potential tools for synthetic chemists.

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Abbreviations: AMO, alkene monooxygenase; CPO, chloroperoxidase; DIPT, Diisopropyl tartrate; EH, epoxide hydrolase; FAD, flavin adenine dinucleotide; HKR, hydrolytic kinetic resolution; NAD, Nicotinamide adenine dinucleotide; NADP, Nicotinamide adenine dinucleotide phosphate; P450, cytochrome P450; SMO, styrene monooxygenase; TBHP, *tert*-butyl hydroperoxide; XMO, xylene monooxygenase.

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1. Introduction

Enantiopure epoxides are well recognized as extremely important building blocks in fine chemical industry, particularly for the synthesis of biologically active compounds and pharmaceuticals due to the increasing demand for single isomers under legislative pressure for safety issues [1–4]. The versatility of the epoxide is attributed to the oxirane function that can be opened by various nucleophiles or undergo elimination, reduction or rearrangements to a multitude of more elaborate intermediates with the retention or inversion of chirality [5–7].

Therefore, the development of efficient synthesis methods for enantiopure epoxides has been a fundamental research area in both organic synthesis and biocatalysis. There are two major approaches to chiral epoxide formation: the direct stereospecific epoxidation of alkenes and the resolution of racemates, such as the hydrolytic kinetic resolution (HKR) of racemic epoxides [8], both of which have been successfully devised by synthetic chemists. The most prominent catalytic reaction is the Sharpless epoxidation which allows the asymmetric epoxidation of prochiral allylic alcohols [9,10]. Other state of the art protocols, such as the Katsuki–Jacobsen epoxidation of unfunctionalized *cis*-substituted alkenes [11–13], and the Shi's epoxidation of *trans*-substituted alkenes[14], provide valuable complements to the Sharpless epoxidation. The Jacobsen HKR is one of the most powerful approaches for kinetic resolution of epoxides [8,15]. Even though the maximum theoretical yield of HKR is restricted to 50%, excellent enantiomeric excesses (ee) have been obtained with a diverse of terminal oxides.

Not as most of the above-mentioned chemical procedures which were catalyzed with transition-metal-based reagents, the biocatalytic procedures have shown remarkable advantages such as biodegradability, highly specific catalysts, and mild reaction conditions [16–18]. It is evident that almost all nature products that contain the oxirane function are non-racemic, which is caused by the chirality of the relative enzymes [19]. There are indeed a huge number of enzymes from microorganisms, plants and animals capable of catalyzing the asymmetric epoxidation or HKR reaction in a regio-, diastereo-, and enantio-selective fashion, such as various monooxygenases, chloroperoxidases (CPO), and epoxide hydrolases (EH). The biocatalytic processes typically yield epoxide products with excellent enantiomeric excesses. They are particularly valuable for those substrates that are poorly accepted by chemical procedures [20,21]. Collectively, the diverse enzymes that could generate enantiopure epoxides exhibit extremely broad substrate spectra. However, individually those enzymes commonly lack flexibility in the accommodation of diverse substrates, which becomes the limiting factor in the selection of the appropriate biocatalysts.

This review would serve as a brief guide of biocatalytic procedures that might be harnessed in organic synthesis to achieve chiral epoxides with high enantio-purity. Several reviews on the preparation of chiral epoxides have been published [3,7,8,22–26]. This review does not seek to provide a comprehensive list of all kinds of synthetic/enzymatic methods, but rather to emphasize the potential of biocatalysis in the preparation of chiral epoxides. Lipase catalyzed kinetic resolution [23] that does not react with the epoxide moiety is not discussed here. The main part of this review describes several predominant enzymatic approaches, including the epoxidation of alkenes by monooxygenase and CPO, and the HKR of racemic epoxides by EH, all of which can afford excellent enantioselectivity. The scope and limitation of those biocatalytic approaches will be discussed as compared with the corresponding classic chemical methods.

2. Monooxygenase as an alternative for the asymmetric epoxidation of alkenes

2.1. Introduction of monooxygenases

Monooxygenases introduce one oxygen atom from molecular oxygen into the substrate, with the other atom reduced to water [27]. The enzymes are involved in a wide variety of biological processes that include drug detoxification, biodegradation of aromatic compounds, biosynthesis of antibiotics and sidrophores, and many others [28–31]. In these reactions, the role of oxygen is not restricted to serving as electron acceptor but involves incorporation into the substrate. NAD(P)H is required as the ultimately reducing agent from which the electrons are delivered to the enzyme–substrate complex via a redox system. The most common cofactor of the monooxygenase complex appears to be either the heme-iron or FAD, while other cofactors, such as non-heme iron, tetrhydropteridine and copper ion, are also found in a wide variety of species [27,32,33].

It has been reported that monooxygenases can carry out an enormous amount of chemical reactions [34–37], among which enzymes that can transform alkenes into the corresponding oxides with excellent enantioselectivities, such as styrene monooxygenase (SMO), xylene monooxygenase (XMO) and alkene/alkane monooxygenase, will be described here in much detail. Other monooxygenases like cytochrome P450 enzymes (P450s) [38–40] and methane monooxygenases [41,42] are not covered because of their low to medium enantioselectivity in asymmetric epoxidation, which makes them impractical for synthetic chemists. For example, it has been reported that P450cam from *Pseudomonas putida* is capable of performing the transfer of *cis*-β-methylstyrene to the (*S*, *R*)-oxide with 78% ee [38]. The same limitation exists for methane monooxygenase, the basic function of which is to catalyze the transformation of methane into methanol, with 14–28% ee for the epoxidation of short-chain alkenes (C2–C4) [41].

2.1.1. Styrene monooxygenase

Styrene monooxygenase (SMO, EC 1.14.13.X) is an enzyme that transforms styrene into (*S*)-styrene oxide in the upper catabolic pathway of styrene degradation [43,44]. It belongs to flavoprotein monooxygenase family and contains a two-component flavoenzyme composed of a FAD-specific styrene epoxidase (StyA) and NADH-specific flavin reductase (StyB), encoded by *StyA* and *StyB* genes [45,46]. SMO is an attractive enzyme for the synthesis of epoxides, owning to its exquisite regio- and enantioselecties, mild reaction conditions, and the adoption of oxygen as an inexpensive nontoxic oxidant [47–50].