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Efficient asymmetric hydrolysis of styrene oxide catalyzed by Mung bean epoxide hydrolases in ionic liquid-based biphasic systems

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ABSTRACT

The asymmetric hydrolysis of styrene oxide to (*R*)-1-phenyl-1,2-ethanediol using Mung bean epoxide hydrolases was, for the first time, successfully conducted in an ionic liquid (IL)-containing biphasic system. Compared to aqueous monophasic system, IL-based biphasic systems could not only dissolve the substrate, but also effectively inhibit the non-enzymatic hydrolysis, and therefore markedly improve the reaction efficiency. Of all the tested ILs, the best results were observed in the biphasic system containing $C_4MIM{\cdot}PF_6$, which exhibited good biocompatibility with the enzyme and was an excellent solvent for the substrate. In the $C_4MIM{\cdot}PF_6$/buffer biphasic system, it was found that the optimal volume ratio of IL to buffer, reaction temperature, buffer pH and substrate concentration were 1/6, 35 °C, 6.5 and 100 mM, respectively, under which the initial reaction rate, the yield and the product *e.e.* were 18.4 mM/h, 49.4% and 97.0%. The biocatalytic process was shown to be feasible on a 500-mL preparative scale.

1. Introduction

Enantiopure chiral epoxides and *ortho*-diols play a crucial role in the synthesis of medicines, pesticides and fine chemicals (Gong and Xu, 2005), and have been employed for production of β-3-adrenergic receptor agonists, anti-obesity drugs, anticancer agents, *N*-methyl-D-aspartate receptor antagonists with neuroprotective properties and nematocides (Archelas and Furstoss, 2001). Among them, (*S*)- or (*R*)-1-phenyl-1,2-ethanediol (PED) is a valuable and versatile chiral building block for the synthesis of pharmaceuticals, agrochemicals, pheromones, and liquid crystals, and so on. (*S*)-PED can also be used as the precursor for the production of chiral biphosphines and chiral initiator for stereoselective polymerization (Nie et al., 2004). Enantiopure epoxides and *ortho*-diols can be prepared by chemical or biological approaches. Recently, much attention has been paid to epoxide hydrolases (EHs) capable of readily catalyzing asymmetric hydrolysis of epoxides to *ortho*-diols (Kumar et al., 2011; Sheng et al., 2011). Pedragosamoreau et al. (1993) first reported the asymmetric hydrolysis of styrene oxide (SO) to (*R*)-PED using EHs-producing *Aspergillus niger* LCP 521 cells, but the product *e.e.* was only 51%. Subsequently, EHs from various microorganisms, plants and animal tissues have been widely adopted for the biocatalytic resolution of chiral epoxides (Chiappe et al., 2007; Sheng et al., 2011). In many cases, the non-enzymatic hydrolysis of some epoxides and the relatively poor solubility of the substrates in aqueous phase resulted in a significant drop in the product *e.e.* and yield, thus limiting the application of the biocatalytic process in aqueous phase.

Recently, two novel EHs, capable of effectively catalyzing enantioconvergent hydrolysis of racemic *p*-nitrostyrene oxide to (*R*)-*p*-nitrophenyl glycol, were discovered from Mung bean and these two EHs could also catalyze (*S*)-SO to (*R*)-PED (Xu et al., 2006). Owing to its cheapness and availability, Mung bean is regarded as a very attractive source of EHs for synthetic purposes. However, due to the poor solubility of SO and its obvious non-enzymatic hydrolysis in aqueous monophasic system, both the product yield and the product *e.e.* of Mung bean EHs-mediated asymmetric hydrolysis of SO were quite low. In order to overcome these limitations, a biphasic system has been examined (Chen et al., 2011), where an aqueous phase contains Mung bean EHs and a water-immiscible organic phase acts as a reservoir for substrate. Despite the fact that an organic solvent-based biphasic system can partially inhibit the non-enzymatic hydrolysis of SO and thus enhance the product *e.e.*, the use of conventional organic solvents in such processes may be problematic because they are generally toxic to biocatalysts (Gong and Xu, 2005; Baldascini and Janssen, 2005). Also, they may be explosive and are usually environmentally harmful. Hydrophobic ionic liquids (ILs) are a promising new class of alternative 'green' solvents that are obvious candidates for a great variety of biocatalytic transformations (Lou et al., 2009; van Rantwijk and Sheldon, 2007). However, to date

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