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Precise Regulation of the substrate selectivity of BVMO to Minimize Overoxidation of sulfoxide

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PURPOSE OF THE ABSTRACT
Oxidases-catalyzed molecular functionalization is undoubtedly one of the most attractive research areas. Highly selective oxidation reaction is critical for chiral molecules construction. A large number of studies have focused on modification of the stereoselectivity and regioselectivity of oxidases, but the problem of overoxidation caused by the poor substrate selectivity is still unsolvable. Baeyer–Villiger monooxygenases can catalyze the asymmetric oxidation of sulfides to chiral sulfoxides. However, BVMOs can also catalyze the undesired overoxidation of sulfoxides to sulfones, which limits their synthetic application. To minimize this overoxidation, the present study aimed to establish a precise method for regulating the substrate selectivity of BVMOs in sulfide oxidation. The sulfone content of variant F277L was less than 1% (mol/mol), compared with 65% for the wild-type AcPSMO, in the pyrmetazole oxidation reaction after 24 h. The methodology for precise control of substrate selectivity developed in this work will also help to enhance the substrate specificity of other oxygenases and solve the long-standing overoxidation problem in other biooxidation reactions.

Before this work, understanding of the structural basis of the substrate selectivity in sulfide oxidation is elusive. In this work, crystal structure determination, molecular dynamics simulations, and QM/MM computations were conducted to elucidate the mechanism of sulfide/sulfoxide substrate selectivity in BVMOs. Furthermore, the redesigned mutants of AcPSMO according to the mechanism we elucidated were also successfully applied for the controllable synthesis of other three chiral prazole sulfoxides. These insights will hopefully lead to a general approach to further mitigate the overoxidation of sulfoxide to sulfone by other BVMOs in a predictable manner. The sulfur atom oxidation mechanism elucidated in this work also sheds light on the electrophilic oxygenation paradigm of BVMOs.

FIGURES

FIGURE 1

FIGURE 2

KEYWORDS

Baeyer-Villiger monooxygenase | chiral sulfoxide | protein engineering | substrate selelctivity

BIBLIOGRAPHY