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Enantioselective Biocascade Catalysis with a Single Multifunctional Enzyme

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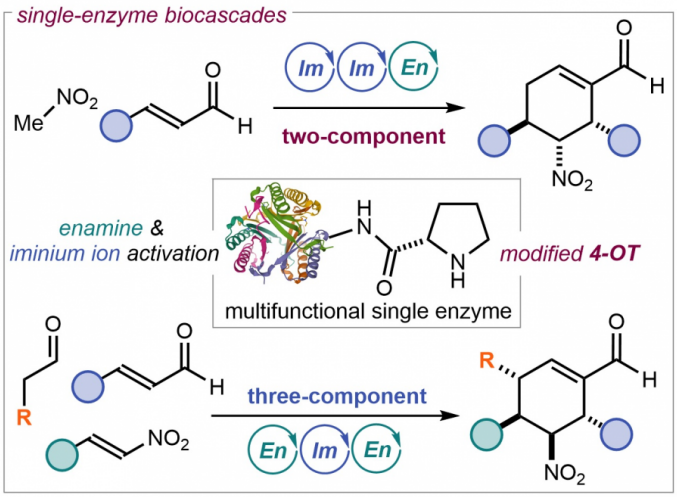
PURPOSE OF THE ABSTRACT

Asymmetric catalytic cascade processes are powerful synthetic tools for rapidly generating structural and stereochemical complexity from simple substrates and in a single step [1]. In biocatalysis, cascades are generally designed by combining multiple enzymes, each catalyzing individual steps of a sequence [2]. Herein, we report a different strategy for biocascades based on a single multifunctional enzyme that can promote multiple stereoselective steps of a domino process by mastering distinct catalytic mechanisms of substrate activation in a sequential way. Specifically, we report the use and further optimization, via fusion and internal His-Tag insertion, of an engineered 4-oxalocrotonate tautomerase (4-OT) with the ability to form both enamines and iminium ions [3] and combine their mechanisms of catalysis in a complex sequence. This approach allowed us to activate aldehydes and enals toward the synthesis of enantiopure cyclohexene carbaldehydes. The multifunctional 4-OT enzymes could promote both a two-component reaction and a triple cascade characterized by different mechanisms and activation sequences demonstrating that biocatalysis can match and even surpass in efficiency the potential of organocascade catalysis [4].

FIGURES



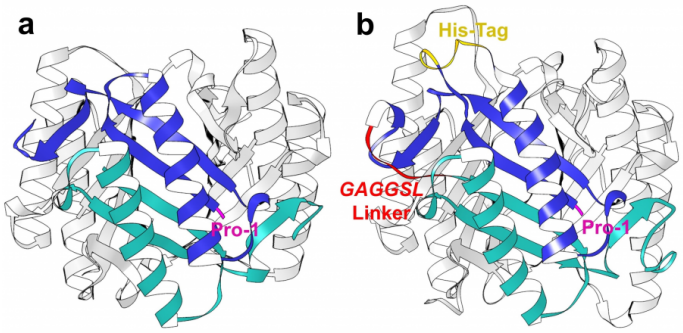


FIGURE 1

A single multifunctional enzyme can promote biocatalytic cascades based on multiple stereoselective steps

a 4-oxalocrotonate tautomerase (4-OT) enzyme can form enamine and iminium ion intermediates from aldehydes and enals to promote both a two-component reaction and a triple cascade characterized by different mechanisms and activation sequences.

FIGURE 2

A genetically fused 4OT with internal His-Tag

a) The homohexameric wild type Pp-4OT in which two monomers (blue and light green) form a dimer. b) Homology model of Pp-4OT-F3 in which the His-Tag (yellow) and the linker (red) have been genetically inserted.

KEYWORDS

biocatalysis | enantioselectivity | cascade reactions | organocatalysis

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