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Asymmetric Thio-Michael Additions Catalyzed by the Enzyme 4-Oxalcrotonate Tautomerase

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PURPOSE OF THE ABSTRACT

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The enzyme 4-oxalcrotonate tautomerase (4-OT) catalyzes multiple promiscuous C-C bond-forming reactions, which find applications in the sustainable synthesis of pharmaceutical precursors and enantioenriched synthons, and proceed via enzyme-bound enamine intermediates. [1–4] Recent protein engineering campaigns unlocked new asymmetric reactions catalyzed by 4-OT proceeding through an enzyme-bound iminium ion intermediate. The C-C bond-forming reaction of Michael-type addition of nitromethane to cinnamaldehydes [5,6] and the C-O bond-forming epoxidation of cinnamaldehyde derivatives using peroxides are examples.[8] In this work, we characterize and optimize a new reactivity of 4-OT, namely the C-S bond-forming Michael-type addition reaction of aliphatic thiols to cinnamaldehyde. Two engineered 4-OT variants were found able to catalyze this addition reaction in a stereospecific manner using a set of aliphatic thiols as nucleophiles and yielding (R)-β-thioenals with conversions up to 97 % and products e.r. up 95:5. Reaction conditions were optimized to avoid the enzyme-catalyzed racemization of the products.

FIGURES

FIGURE 1

FIGURE 2

KEYWORDS

biocatalysis | enzyme promiscuity

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