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Diversity-oriented synthesis of cyclohexenes by combining enzymatic intermolecular Diels- Alder reactions and decarboxylative functionalizations

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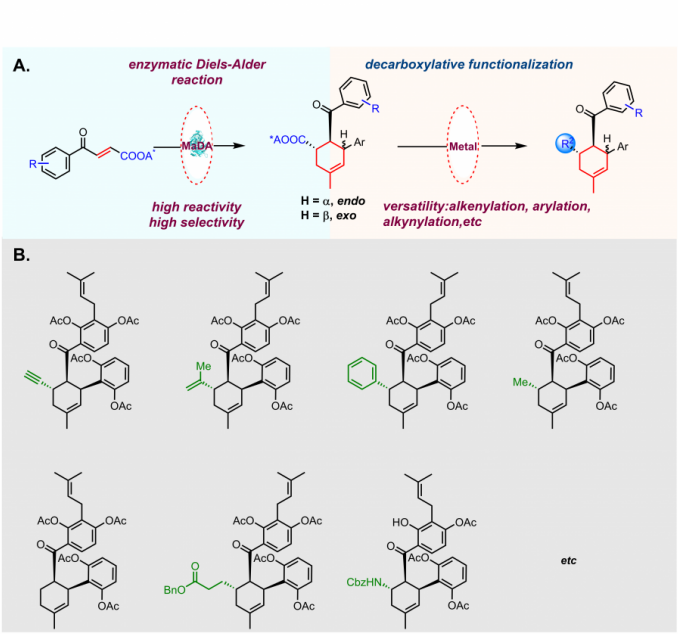
PURPOSE OF THE ABSTRACT

Substituted cyclohexanes are common scaffolds found in both natural products and drug molecules. Diels-Alderases that can efficiently catalyze intermolecular Diels-Alder reactions to generate cyclohexene ring systems have received considerable interest. However, the synthetic power of Diels-Alderases is incomparable with chemo-catalysts due to their limited substrate scopes. Here, we report a new chemo-enzymatic strategy for the diversity-oriented syntheses of functionalized cyclohexenes. A natural Diels-Alderase variant M3 were generated with focused rational iterative site-specific mutagenesis, which shows a 34-fold increase in catalytic efficiency, broad substrate scope, and good to perfect stereoselectivity. Diverse transition-metal-catalyzed decarboxylative coupling reactions were sequentially used to functionalize the enzymatic Diels-Alder products. This work offers an efficient synthetic route to structurally diverse cyclohexenes that are not accessible by solely biocatalysis or chemo-catalysis and illustrates how chemo-catalysis can cooperate with biocatalysis to expand the synthetic application of biocatalysts.

FIGURES



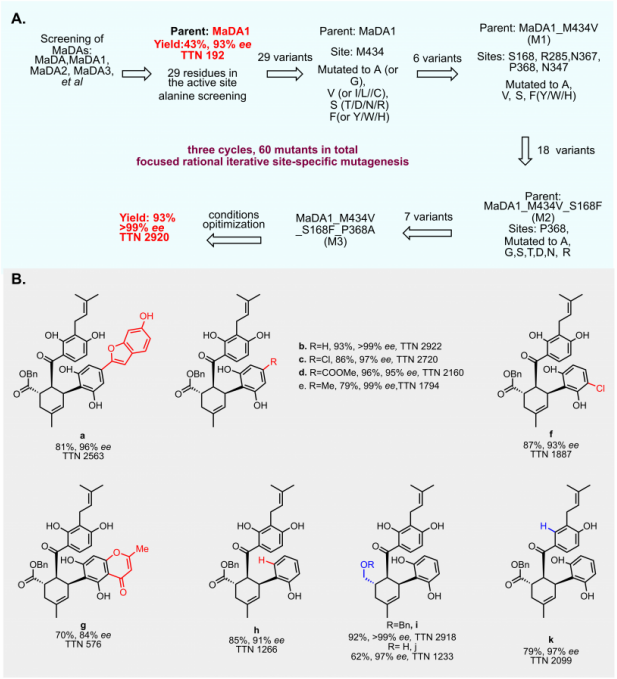


FIGURE 1

Chemoenzymatic strategy toward the diversity-oriented synthesis of enantiopure cyclohexenes

A. General workflow for the chemoenzymatic strategy

B. Synthesized structurally diverse enantiopure cyclohexanes

FIGURE 2

Protein engineerig of MaDA1 and substrate scope of MaDA1_M3

A. General workflow for protein engineering

B. Substrate scope of MaDA1_M3-catalyzed intermolecular Diels-Alder reactions

KEYWORDS

intermolecular Diels-Alderase | decarboxylative functionalization | diversity-oriented synthesis | chemoenzymatic synthesis

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