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Photoenzymatic asymmetric [2+2] cycloaddition reaction

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PURPOSE OF THE ABSTRACT

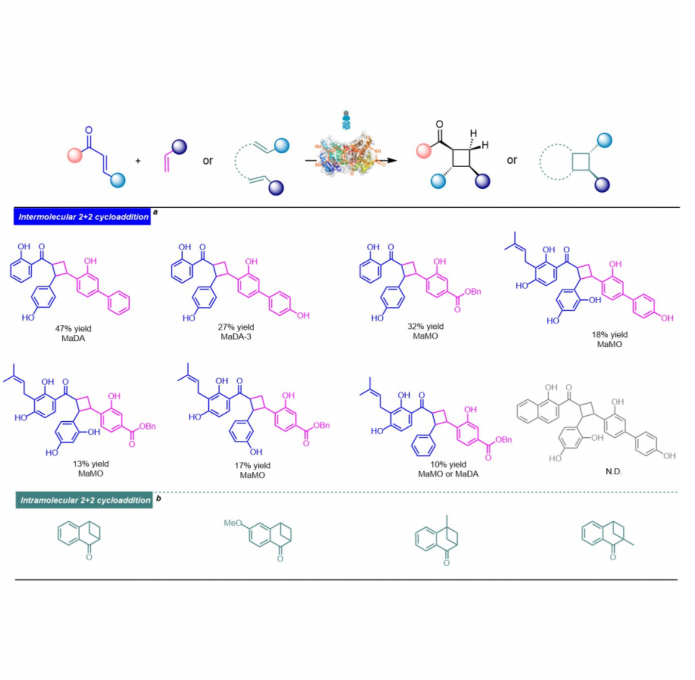
Cyclobutanes are important structural motifs in organic chemical synthesis, drug discovery and natural products. At present, the asymmetric [2+2] cycloaddition reaction is one of the most effective ways to obtain the chiral cyclobutane skeletons. Traditional methods mainly include the three strategies of polarized [2+2] cycloaddition, [2+2] cycloaddition catalyzed by transition metals and [2+2] cycloaddition catalyzed by photocatalysis with assist of chiral ligands. However, these reactions have some defects, such as limited substrate type, high temperature for thermodynamically driven reactions, expensive chiral catalyst or chiral ligand are needed for stereoselectivity control, and yield and stereoselectivity need to be further improved.

On the other hand, enzymatic catalysis has been widely concerned because of its reaction efficiency and high selectivity, chemenzymatic synthesis has been widely concerned. More and more enzymatic reactions have been developed in industry and research. However, there are far fewer reaction types that can be realized by enzyme catalysis than traditional chemical reactions, and there are still many reaction types that cannot be realized by enzyme catalysis. Therefore, it is urgent to develop the hybrid catalytic function of enzymes to enable them to perform the non-natural catalytic function.

In recent years, some unnatural photochemical reactions involving flavin-dependent enzymes have been reported. In this regard, we proposed the use of flavin-dependent enzymes combined with photochemistry to carry out intermolecular asymmetric [2+2] cycloaddition reactions. In order to realize the construction of multi-chiral substituted cyclobutanes with high stereoselectivity without expensive transition metals and chiral ligands under mild conditions. Further combine structural biology, photochemistry, and computational chemistry to study the reaction mechanism, with a view to discovering new reaction mechanisms and inspiring synthetic ideas.

At present, through the screening of reaction conditions, with the help of a series of FAD dependent intermolecular Diels–Alderases and oxidases and FMN dependent ene reductases, we have achieved the photoenzymatic intermolecular/intramolecular [2+2] cycloaddition reaction . Through a series of spectral experiments and DFT calculations, we have basically confirmed that the mechanism of the reaction may be initiated by the triplet-triplet energy transfer between FAD/FMN and the substrate. This is the first case of natural photoenzymatic reaction based on energy transfer and the first case of photoenzymatic [2+2] cycloaddition

FIGURES



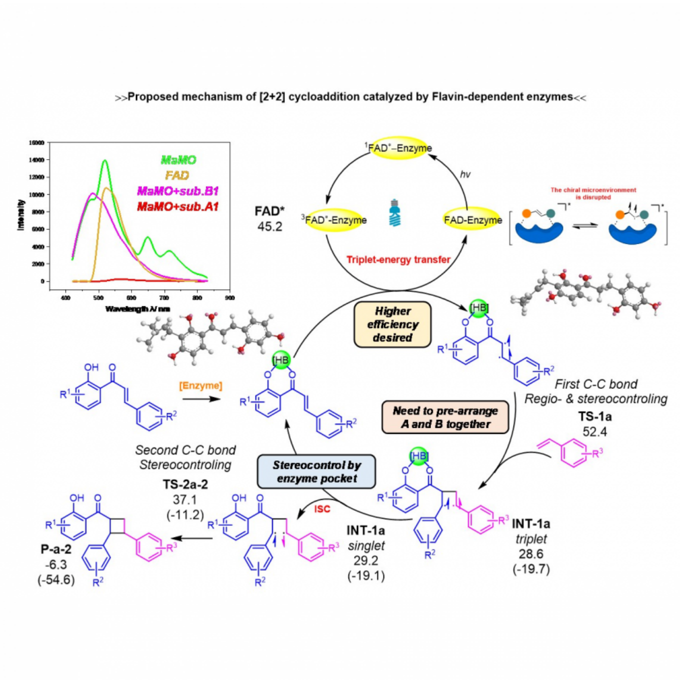


FIGURE 1

Photoenzymatic asymmetric [2+2] cycloaddition reaction

a: The intermolecular 2+2 cycloaddition was catalyzed by Diels Alderases and oxidase reported previously

b: The intramolecular 2+2 cycloaddition was catalyzed by Ene reductase

FIGURE 2

Proposed mechanism of [2+2] cycloaddition catalyzed by Flavin-dependent enzymes

Mechanistically, our [2+2] cycloaddition proceeds via energy transfer from the triplet flavins to the chalcone 1, which undergoes intermolecular cyclization to generate diradical intermediate 2. Then the cycloadduct 4 is constructed through ISC.

KEYWORDS

Photoenzymatic | Asymmetric [2 + 2] cycloaddition | Energy tansfer | Directed evolution

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