

Compositions, Systems, and Methods for Stereoselective Decarboxylative Radical Cyclization

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BACKGROUND

Due to their intriguing photophysical and photochemical activities, naturally occurring photoenzymes, which require a steady influx of light for catalysis, have long captivated biochemists and biocatalysis researchers. Although natural evolution has largely selected against photoenzymatic catalysis, the high-energy intermediates confined in photoenzymes provide fertile ground for creating novel photoenzymatic reactions through excited-state biocatalysis. The recent groundbreaking discovery and mechanistic elucidation of algae-derived fatty acid photodecarboxylases (FAPs) underscored their exceptional synthetic potential, as these flavin adenine dinucleotide (FAD)-dependent photoenzymes allow the efficient photodecarboxylation of abundant and/or easily accessible carboxylic acid substrates via a radical mechanism. Important previous work on FAPs has focused on expanding the substrate scope of their native photodecarboxylation activity, but, to- date, no new-to-nature activities of flavin-dependent FAPs have been developed.

DESCRIPTION

Researchers at the University of California, Santa Barbara have used the fundamental principles of mechanistic organic chemistry, to repurpose fatty acid photodecarboxylases (FAPs), the most recently discovered member of natural photoenzymes, to catalyze photoredox radical C–C bond formation not previously encountered in nature. Through enzyme mining and engineering, the team has developed a collection of radical photocyclases (RAPs) to facilitate decarboxylative radical cyclization with excellent levels of chemo-, enantio-, and diastereoselectivities. A high-throughput experimental workflow allowed the directed evolution of FAPs to furnish an orthogonal set of radical photocyclases capable of accessing all four stereoisomers of stereochemical dyads in a diastereo- and enantiodivergent fashion. Such fully stereodivergent processes are unprecedented in asymmetric radical biocatalysis. Together, the development of stereoselective RAPs significantly expanded the catalytic repertoire of natural photoenzymes, affording powerful tools to tame the stereochemistry of free radical-mediated reactions.

ADVANTAGES

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OTHER INFORMATION

KEYWORDS

biochemistry, biocatalysis,
photoenzymes, enzymes,
pharmaceuticals,
agrochemicals, synthetic
chemistry

CATEGORIZED AS

- ▶ **Biotechnology**
- ▶ Health
- ▶ Other

RELATED CASES

2024-843-0

- ▶ Allows the directed evolution of natural photoenzyme to enable asymmetric radical cyclization
- ▶ Offers powerful tools to tame the stereochemistry of free radical-mediated reactions

APPLICATIONS

- ▶ Pharmaceuticals
- ▶ Agrochemicals

PATENT STATUS

Patent Pending

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- ▶ Compositions, Systems, and Methods for Stereoselective Synthesis of Non-Canonical Amino Acids
- ▶ Engineered Metalloenzymes for Stereocontrolled Atom Transfer Radical Addition
- ▶ Systems, Compositions And Methods Of Metalloprotein-Catalyzed Fluorination, Azidation, Thiocyanation and Hydroxylation
- ▶ Enzyme-Controlled Stereoselective Radical Cyclisation to Arenes Enabled by Metalloreredox Biocatalysis

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