



Enzyme-Controlled Stereoselective Radical Cyclisation to Arenes Enabled by Metalloredox Biocatalysis

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BACKGROUND

Biocatalysis is a critical topic that drives innovation in many industries including pharmaceuticals, energy, and agriculture. Until recently, only a small set of biochemistries from nature's catalytic repertoire has been explored to synthesize a relatively narrow range of value-added compounds. The majority of privileged synthetic transformations, particularly those allowing for stereoselective C–C bond formation, are not present in the state-of-the-art biocatalytic toolbox. Advances from mechanistic enzymology and structural biology have furnished invaluable insights into the molecular mechanism and structural basis of enzymatic machineries, inspiring a campaign of repurposing and evolving natural enzymes to catalyze nonnatural reactions. However, achieving high levels of stereocontrol for free radical-mediated transformations has been a challenge in asymmetric biocatalysis.

DESCRIPTION

Researchers at the University of California, Santa Barbara have developed a novel metalloredox biocatalysis strategy that introduces high levels of stereocontrol over free radical-mediated transformations, allowing access to useful chiral compounds that were not previously available via other catalytic means. The researchers utilized directed evolution of natural cytochromes P450 to generate enzymes able to catalyze asymmetric radical cyclisation to arenes through a nonnatural electron transfer mechanism. The engineered P450s can give rise to either antipode of the product with excellent total turnover numbers (up to 12,000). Another engineered radical cyclase, P450_{arc3}, permitted efficient kinetic resolution of racemic chloride substrates (S factor = 18). Furthermore, a proton-coupled electron transfer (PCET) mechanism for the radical-polar crossover step suggests the potential of haem carboxylate as a base catalyst. Collectively, these emerging new-to-nature activation modes provide an exciting opportunity to evolve enzymes capable of imposing excellent stereocontrol over fleeting free radical intermediates, an objective that has long eluded small-molecule catalysis due to the inherent difficulties to induce asymmetry with free radical chemistry.

ADVANTAGES

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OTHER INFORMATION

KEYWORDS

Biocatalysis, biochemistry,
synthetic chemistry, enzymes,
Pharmaceuticals, energy,
agriculture

CATEGORIZED AS

- **Biotechnology**
- Food
- Health
- Industrial/ Energy

RELATED CASES

2023-854-0

- ▶ Enables access to useful chiral compounds that were previously unavailable or difficult to synthesize
- ▶ Excellent stereocontrol over fleeting free radical intermediates
- ▶ Provides green chemistry alternative to conventional manufacturing
- ▶ More efficient than traditional methods

APPLICATIONS

- ▶ Biochemistry
- ▶ Pharmaceuticals
- ▶ Energy
- ▶ Agriculture

PATENT STATUS

Country	Type	Number	Dated	Case
Patent Cooperation Treaty	Reference for National Filings	WO 2024/138228	06/27/2024	2023-854

Patent Pending

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- ▶ Compositions, Systems, and Methods for Stereoselective Synthesis of Non-Canonical Amino Acids
- ▶ Compositions, Systems, and Methods for Stereoselective Decarboxylative Radical Cyclization
- ▶ Engineered Metalloenzymes for Stereocontrolled Atom Transfer Radical Addition
- ▶ Systems, Compositions And Methods Of Metalloprotein-Catalyzed Fluorination, Azidation, Thiocyanation and Hydroxylation