

Photoenzymatic Stereoablative Enantioconvergence of γ-Chiral Oximes via Hydrogen Atom Transfer

Background/Objective

Traditional industrial manufacturing methods to produce enantioenriched molecules from racemic mixtures, such as resolution, deracemization, and enantioconvergent catalysis, primarily either separate enantiomers without altering their structures or functionalize the enantiomer's stereocenters at or proximal to functional groups. However, there are challenges in enantioselectively forging C–H bonds remote from functional groups with these methods. We introduced a photoenzymatic hydrogen-atom-transfer strategy for the stereoablative enantioconvergence of γ -chiral oximes using repurposed flavin-dependent ene-reductases (EREDs) to overcome this limitation.

Approach

A photoinduced single electron reduction of the γ -chiral oxime by an ERED generated an iminyl radical, which then underwent stereoablative 1,5-HAT at the γ -stereocenter. Subsequent chiral reconstruction through enzymatic HAT and spontaneous imine hydrolysis yielded the γ -chiral ketone. Optimization included identifying the best ERED, leaving group, and buffer conditions. After directed evolution of ERED, the best mutants were used for substrate scope investigations.

Results

We successfully performed enantioconvergence of stereocenters that are remote from functional groups. Hydrogen bonding and steric effects from key amino acid residues had significant effects on both the stereoablation and remote stereocenter reconstruction, which synergistically determined the success of this approach.

Significance/Impacts

This work can potentially be used to produce structurally complicated chiral molecules such as agrochemicals from their racemic analogues and broadens the synthetic utility of photoenzymatic catalysis.

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Process diagram of photoenzymatic enantioconvergence.



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