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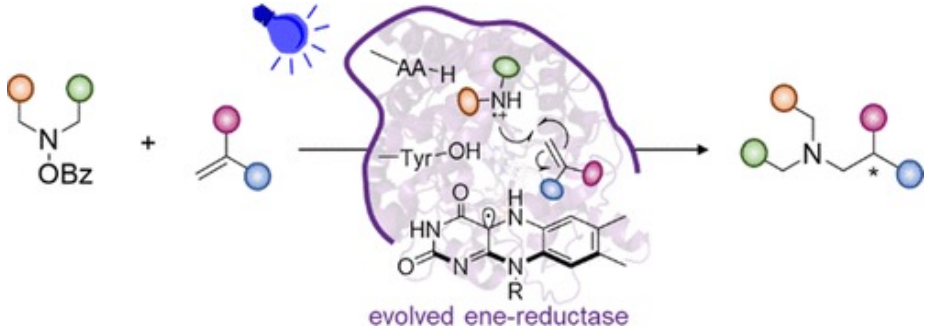
Photoenzymatic Asymmetric Hydroamination for Chiral Alkyl Amine Synthesis

Background/Objective

Chiral alkyl amines are common motifs in natural products, synthetic intermediates, and bioactive molecules. An attractive method to prepare these molecules is through enantioselective radical hydroamination, however, this approach has not been explored with dialkyl amines since designing a catalytic system to generate the nitrogen-centered radical, to suppress deleterious side reactions, and to facilitate enantioselective radical termination is a formidable task. Herein, we describe the application of photoenzymatic catalysis to generate and nitrogen-centered radicals for asymmetric intermolecular hydroamination.

Approach

We explored the nonnatural reactivity of cofactor dependent ene-reductases to generate highly reactive nitrogen-centered radicals and to control them for the enantioselective radical hydroamination. This system uses visible light irradiation of the cofactor within the enzyme to generate the nitrogen-centered radical. This radical reacts with the alkene, and the subsequent radical is terminated by the enzyme through stereoselective hydrogen atom transfer.



Reaction schematic of the photoenzymatic asymmetric hydroamination system.

Results

In this study, we discovered that one amino acid in the active site of the enzyme, N194, decreased the reaction efficiency of the photoenzyme. When we mutated the residue to another residue, tyrosine, the enzyme activity toward the reaction was profoundly increased.

Significance/Impacts

Photoenzymatic catalysis for asymmetric synthesis addresses a long-standing challenge in chemical synthesis and enables the use of biological systems as a chassis to upgrade biomass-derived secondary amines and alkenes for chemical production.

Harrison et al. 2024. "Photoenzymatic Asymmetric Hydroamination for Chiral Alkyl Amine Synthesis." *Journal of the American Chemical Society*. DOI: 10.1021/jacs.4c00620.