BIOTRANS
LA ROCHELLE 2023

N°1113 / PC
TOPIC(s) : Enzyme discovery and engineering / (Chemo)enzymatic strategies

Biocatalytic C–H Functionalization to Construct C–N Bonds via Nitrene Transfer

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PURPOSE OF THE ABSTRACT

Over the past decade, the Arnold laboratory has ventured beyond the native oxidation activities of cytochrome P450 monooxygenases to develop an array of non-natural functions based on transfer of nitrene-like intermediates, which paves the way for the efficient and selective biocatalytic construction of C–N bonds. To expand the repertoire of biocatalytic C–H amination via nitrene transfer, the group has pursued two main avenues: (1) introducing new nitrene precursors (nitrene donors) and (2) targeting various C–H bonds (nitrene acceptors). Within these two categories, we present the development of engineered cytochrome P411 enzymes (P450 monooxygenases with serine as the heme-ligating residue) for a diverse set of C–N bond-forming reactions. We will describe an efficient, selective, and scalable enzymatic platform for the enantioselective propargylic primary amination of alkynes using hydroxylamine derivatives as the nitrene precursor. Furthermore, we identified cytochrome P411 enzymes capable of catalyzing enantioenriched tertiary C–H primary amination, addressing a notorious challenge in chemical synthesis. Additionally, we developed a biocatalytic platform for enantioselective intramolecular C(sp3)–H amination to form chiral N-heterocycles using alkyl and aryl azides as nitrene precursors. These enzymatic aminations can be coupled with a P411-based carbene transferase or a tryptophan synthase to generate an α-amino lactone or a non-canonical amino acid, respectively, underscoring the power of new-to-nature biocatalysis in complexity-building chemical synthesis.

FIGURES

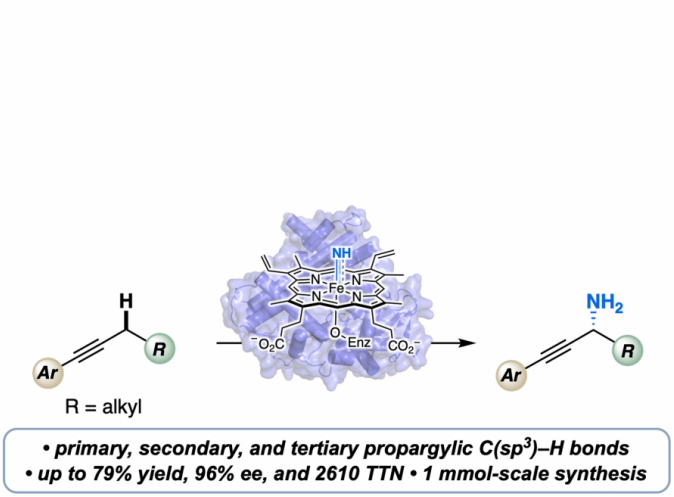

FIGURE 1

Enantioselective propargylic C-H amination

An efficient, selective, and scalable enzymatic platform for the enantioselective propargylic primary amination of alkynes using hydroxylamine derivatives as the nitrene precursor.

FIGURE 2

KEYWORDS

biocatalytic C-H functionalization | protein engineering | propargyl and alpha-tertiary amines | N-heterocycles

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