Category

Innovative Drug Discovery and Development

Key words

biocatalysis

piperidines

amine oxidase

ene-imine reductase

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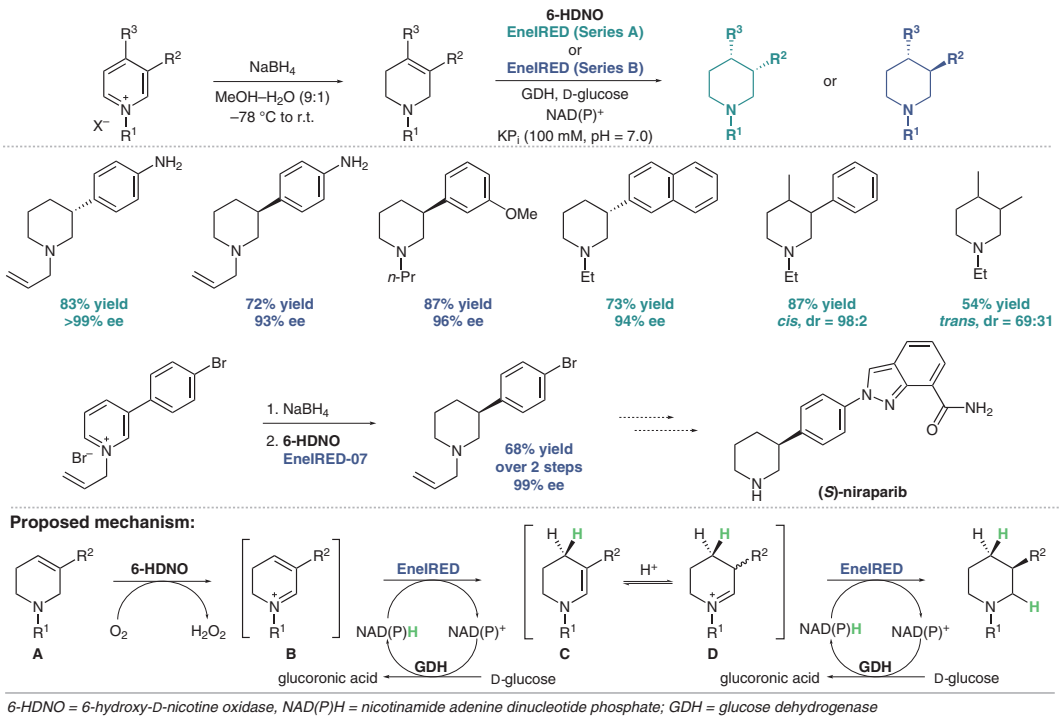
Synthesis of Stereoenriched Piperidines via Chemo-Enzymatic Dearomatization of Activated Pyridines

J. Am. Chem. Soc. **2022**, *144*, 21088–21095, DOI: 10.1021/jacs.2c07143.

Harnessing Biocatalytic Cascades to Access Pharmaceutically Relevant Piperidines



6-HDNO = 6-hydroxy-D-nicotine oxidase, NAD(P)H = nicotinamide adenine dinucleotide phosphate; GDH = glucose dehydrogenase

Significance: Saturated heterocycles such as piperidines are prevalent structural motifs in pharmaceuticals. However, the synthesis of chiral piperidines with various substitution patterns remains challenging, especially the access to 3- and 3,4-disubstituted derivatives. Turner et al. developed a chemo-enzymatic approach to synthesize 3-substituted piperidines via the dearomatization of pyridinium salts. The new methodology enables the synthesis of pharmaceutically relevant building blocks in high enantioselectivity, such as a 3-arylpiperidine en route to PARP-inhibitor niraparib.

Comment: The key step of the piperidine synthesis by Turner et al. is an amine oxidase/ene-imine reductase (EneIRED) biocatalytic cascade. The first step of the cascade involves the oxidation of the chemically generated tetrahydropyridine **A** using amine oxidase 6-HDNO to generate pyridinium ion **B**. The latter undergoes reduction to enamine intermediate **C** via an EneIRED-mediated conjugate addition of a hydride. Enamine **C** is in equilibrium with iminium intermediate **D** from which an EneIRED-mediated reduction to the desired piperidine enantiomer via dynamic kinetic resolution takes place. Screening of various EneIRED panels resulted in the identification of complementary EneIRED series **A** and **B** which allow the synthesis of either enantiomer of a desired substrate. This article has also been highlighted with a different focus in the section "Organo- and Biocatalysis" of this issue: *Synfacts* **2023**, *19*, 293.

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Synfacts 2023, 19(03), 0310 Published online: 13.02.2023
DOI: 10.1055/s-0042-1752400; **Reg-No.:** A01223SF