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A Metalloenzyme Platform for Catalytic Asymmetric Radical Dearomatization
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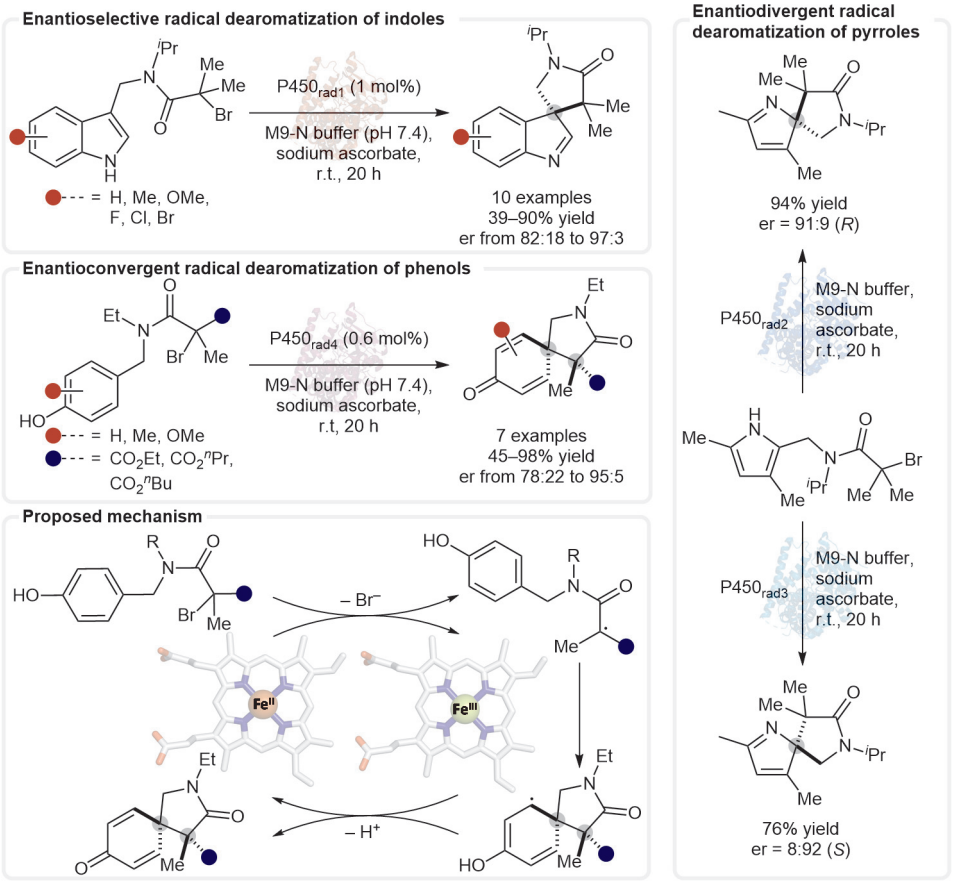
Enzymatic Asymmetric Radical Dearomatization of Electron-Rich Arenes Towards Chiral Spirocycles



Significance: Yang, Liu and co-workers developed a new-to-nature enzymatic strategy for the asymmetric intramolecular dearomatization of electron-rich arenes. By employing directed evolution, they engineered several P450 radical dearomatases ($P450_{rad}$) based on cytochrome P450 enzymes, thereby achieving stereocontrol for the intramolecular radical dearomatization of indoles, pyrroles, phenols, and naphthols. Mechanistically, the redox-active haem cofactor initiated the enzyme-controlled radical formation of the α-bromocarbonyl substrates. The highly reactive radical then undergoes dearomative cyclization and the dearomatized spirocyclic products are obtained after an oxidative-radical crossover and proton transfer.

Comment: By developing a metalloenzyme platform for a new-to-nature asymmetric radical dearomatization, the authors expanded the repertoire of (bio)catalytic reactions and gained control over a challenging stereoselective radical mechanism. In addition to the enantioselective dearomatization of indoles, the enantioconvergent conversion of phenols and the enantiodivergent consumption of pyrroles were also achieved. The obtained chiral (hetero)spirocyclic dearomatized products represent valuable motives that are found in several bioactive compounds and feature adjacent quarternary–quarternary carbon atoms.

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Category
Organo- and Biocatalysis

Key words
radical dearomatization
electron-rich arenes
cytochrome P450
directed evolution
enantioconvergent
enantiodivergent

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