

Tetrapeptide-Catalyzed Dynamic Kinetic Resolution Grants Access to Helically Chiral Loratadine Analogues

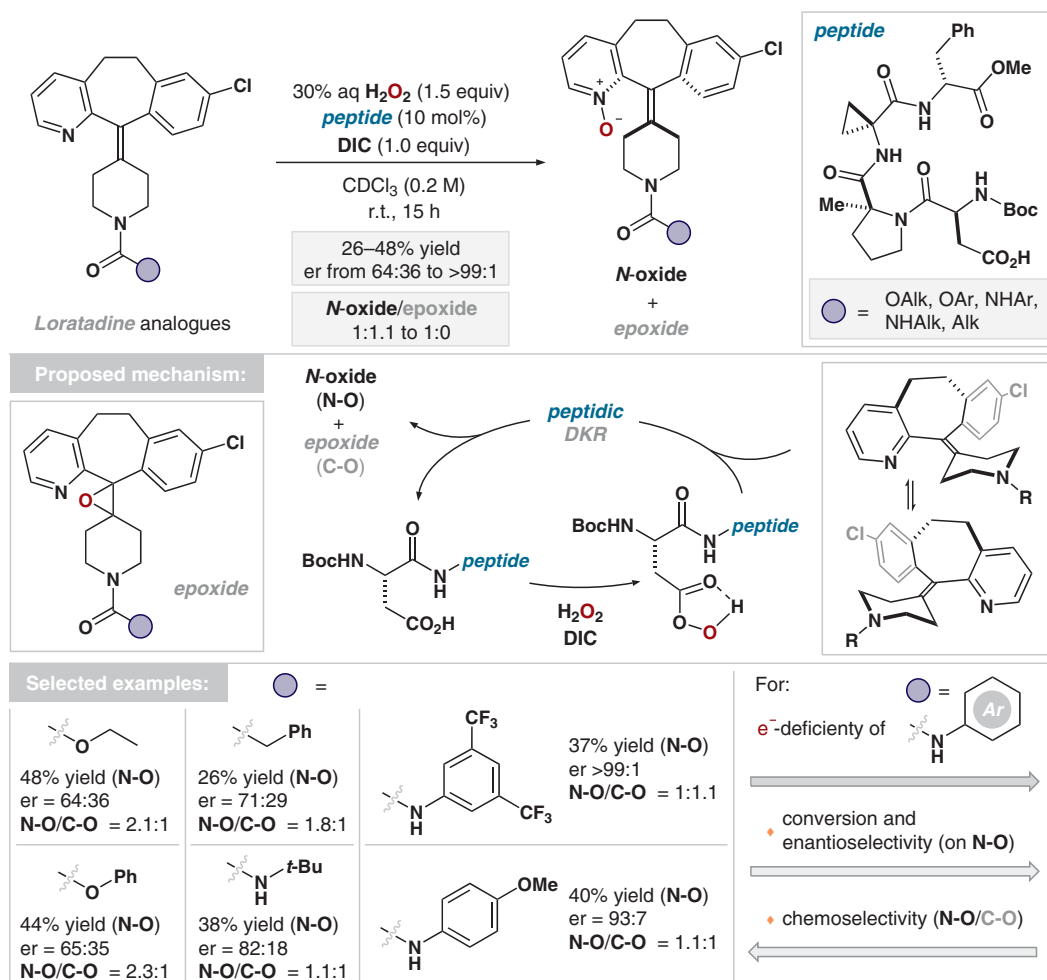
Category

Organo- and Biocatalysis

Key words

peptide catalysis
 asymmetric catalysis
 dynamic kinetic resolution
 loratadine
 helical chirality

Synfact
 of the Month



Significance: Miller and co-workers report a peptide-catalyzed dynamic kinetic resolution of analogues of the antihistamine loratadine to yield the corresponding helically chiral *N*-oxides with moderate yields and poor to excellent enantiomeric ratios. Notably, the challenging differentiation between the substrate's pyridine ring and its adjacent alkene moiety could be achieved to favor *N*- over *C*-oxidation with moderate to high chemoselectivities. The resulting products were found to be configurationally stable at physiological temperatures.

Comment: Building upon their initial investigations (*J. Am. Chem. Soc.* **2019**, *141*, 18624), the authors expanded their work to include challenging loratadine-type substrates. The resulting conformationally rigidified enantioenriched products had significantly different antagonist activities toward the human histamine H_1 receptor, which binds preferentially to the (–)-enantiomer of the compounds. The identified configuration–bioactivity correlation paves the way for the development of more-efficient therapeutics.