BIOCATALYTIC REDUCTION

Chiral heterocycles

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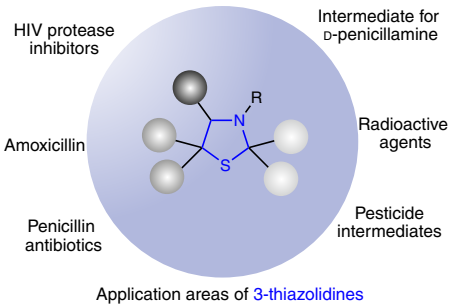

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The 3-thiazolidine ring represents an important structural motif in medicinal chemistry, being present in several drug molecules. The reduction of the C=N double bond in 3-thiazolines as suitable precursors might be an attractive approach for their synthesis. However, this particular reduction of 3-thiazolines is difficult to achieve using conventional reduction methods due to the lability of the thioether functionality and poor enantioselectivities.

Now, a team led by Harald Gröger at the Bielefeld University demonstrates that imine reductase (IRED) enzymes allow the asymmetric reduction of such sulfur-containing heterocyclic imines avoiding undesired ring-opening or other side reactions.

The authors started their experiment by screening 31 recombinantly expressed IREDs for the reduction of two substituted non-prochiral 3-thiazolines into 3-thiazolidines. Subsequently, the substrate scope and enantioselectivity of the most active IREDs was investigated, demonstrating successful reduction of several prochiral 3-thiazolines comprising monocyclic and spiro-type compounds. All tested compounds were transformed in good to excellent conversions.

Next, the authors expanded their work and demonstrated that IREDs can further reduce other sulfur-containing heterocyclic imines, in particular *2H*-1,4-benzothiazines, even when the substrates contained sterically demanding substituents. In fact, the tested IREDs showed better activity for *2H*-1,4-benzothiazines compared to 3-thiazoline. Based on simplified density functional theory studies of model systems in gas-phase, the authors showed that these results are consistent with the specific free energy barriers for reduction of these compounds.

Finally, the authors performed process development of the 3-thiazoline compound 2,2,3-trimethyl-1-thia-4-azaspiro[4.4] non-3-ene. Using an *Escherichia coli* whole-cell catalyst overexpressing an IRED enzyme and a glucose dehydrogenase for in situ cofactor recycling, preparative scale experiments gave high conversion (99%) and enantioselectivity (99% e.e. for the *S*-enantiomer) within 30 h reaction time. The product could be isolated in 78% yield.

Definitely, this methodology is a valuable addition to the biocatalytic toolbox. Such efficient biotransformations on preparative scale with high selectivities are suitable for use by organic chemists. Important applications will likely follow, for example in drug discovery and drug synthesis.

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