Biocatalytic Cascades for the Synthesis of Chiral Amines and Amino Alcohols with Two Stereogenic Centers

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The enzymatic synthesis of chiral amines offers numerous advantages compared to chemocatalytic methods in terms of efficiency, selectivity, environmental sustainability, and applicability with diverse substrates.[1] In this context, my group has focused on the synthesis of α-chiral amines from prochiral ketones using amine dehydrogenases (AmDHs), imine reductases (IReds) and ω-transaminases (ωTAs). For example, we have created a new family of AmDHs from the enzyme scaffold of an ε-deaminating L-lysine dehydrogenase (LysEDH), which was applied for the synthesis of pharmaceutically relevant amines in enantiopure form.[2] AmDHs were also incorporated into biocatalytic cascades with alcohol dehydrogenases (ADHs) to perform the hydride-borrowing conversion of alcohols into α-chiral amines using isolated enzymes, or co-immobilized enzymes, or *E. coli* cells *in vivo*.[3] Notably, some of the mentioned LysEDH variants exhibited a dual ADH-AmDH activity that was harnessed for the first example of a one-pot, one-enzyme alcohol amination.[4]

However, many biologically active compounds contain α-chiral amines or amino alcohols having more than one stereogenic center. These amines can be effectively synthesized via biocatalytic cascades. For example, we have presented a multi-enzymatic route for the formal regio- and stereoselective aminohydroxylation of β-methylstyrene, comprising a selective epoxidation, a hydrolysis, and a hydride-borrowing alcohol amination. This cascade yielded (1*R*,2*R*) and (1*S*,2*R*)-phenylpropanolamines in 59–63% isolated yields and excellent chemo- and stereoselectivities.[3a] A variation of these cascades consisted in the combination of ADH, ωTA, and an alanine dehydrogenase in a redox-neutral network to give access to all four stereoisomers of phenylpropanolamine with excellent selectivities.[5] We have also explored the biocatalytic conversion of α,β-unsaturated ketones to chiral secondary and tertiary amines with two stereogenic centers by combining ene-reductases with imine reductases/reductive aminases. This strategy allowed us to synthesize all four stereoisomers with high d.e. and e.e. (up to >99.8:<0.2), without side-product formation and using ammonium or alkylammonium formate buffer as the sole additional reagent.[6]

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[1] A. R. Alcantara, P. Dominguez de Maria, J. A. Littlechild, M. Schurmann, R. A. Sheldon, R. Wohlgemuth, *ChemSusChem* **2022**, *15*, e202102709.

[2] V. Tseliou, T. Knaus, M. F. Masman, M. L. Corrado, F. G. Mutti, *Nat. Commun.* **2019**, *10*, 3717.

[3] a) M. L. Corrado, T. Knaus, F. G. Mutti, *Green Chem.* **2019**, *21*, 6246-6251; b) W. Böhmer, T. Knaus, F. G. Mutti, *ChemCatChem* **2018**, *10*, 731-735; c) J. A. Houwman, T. Knaus, M. Costa, F. G. Mutti, *Green Chem.* **2019**, *21*, 3846-3857.

[4] V. Tseliou, D. Schilder, M. F. Masman, T. Knaus, F. G. Mutti, *Chem. Eur. J.* **2021**, *27*, 3315-3325.

[5] M. L. Corrado, T. Knaus, F. G. Mutti, *ChemBioChem* **2021**, *22*, 2345-2350.

[6] T. Knaus, M. L. Corrado, F. G. Mutti, *ACS Catal.* **2022**, *12*, 14459-14475.