Biocatalysis: Solving Problems from Chemists with Answers from Nature

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The development of biocatalysis over the past two decades as a powerful methodology in (asymmetric) synthesis has led to the establishment of enzymatic tools able to tackle multiple challenges faced by organic synthetic chemists.[1] In addition to their exquisite selectivity, enzymes are gaining increased attention in the context of sustainable synthesis, as they operate under environmentally friendly reaction conditions and can contribute to the 'greening' of the chemical manufacturing.

In this talk, I will share two examples from our current research that illustrate how biocatalysis can offer attractive approaches to address challenging reactions.

i) we have identified enzymes able to catalyze the asymmetric isomerization of nonactivated C=C bond, leading to the stereocomplementary formation of enantioenriched γ-methyl α,β-butenolide.[2] The reaction mechanism was elucidated and indicates that acid-base catalysis is controlled by a key asymmetric protonation step. By combining this isomerization step with a bioreduction step in a cascade set-up, the formal enzymatic asymmetric reduction of nonactivated C=C bond was possible. Recent efforts are directed to the generation of a dual biocatalyst as a fusion protein to simplify the overall cascade design.

ii) γ- and δ-lactams are – in contrast to smaller β-lactams – molecules with remarkable stability, a feature which appears connected to the increased resonance stabilization of the amide bond and the higher partial C-N double bond character.[3] Their chemical hydrolysis requires harsh reaction conditions (reflux and strong acid) and up to now, no enzyme active on monocyclic γ- and δ-lactams has been reported. The enzymatic cleavage of cyclic amide bonds appears limited to bicyclic Vince lactams,[3] ε-caprolactam[4] and 'lactam-like' compounds. In our work, we aim at establishing a broad-spectrum biocatalytic platform for the ring opening of γ- and δ-lactams. Our approach relies on microbial strains exposed to metabolic pressure through growth on lactams as sole source of C/N and on heterologously expressed enzymes. In this context, we identified strong hydrolytic activity with ATP-dependent oxoprolinases,[5] which can hydrolyze a range of δ-valerolactams under mild reaction conditions.

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