Enzyme Catalysis in the Synthesis of Ipatasertib, AKT Inhibitor

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Biotransformations have the potential to deliver enantiopure active pharmaceutical ingredients (API) in an economic fashion. The highly efficient asymmetric synthesis of Akt kinase inhibitor ipatasertib generates all three stereogenic centers using bio- or metal catalysis: (i) a kinetic resolution of the starting material using a nitrilase gives access to the (R)-nitrile; (ii) a diastereoselective biocatalytic reduction of a sterically demanding bicyclic ketone creates the (R,R)-alcohol; (iii) the side chain of the synthesis is based on a Ru-catalyzed asymmetric hydrogenation of a vinylogous carbamic acid to produce (S)-α-aryl-β-amino acid. All three catalytic steps proceed with high stereoselectivity.
The presentation focuses on the process development of the two biocatalysis steps highlighting the opportunity to tune the enzymes by protein engineering. The key features of the enzymes – enantioselectivity, stability and activity – have been improved.