Biocatalytic Heteroaromatic Amide Formation in Water Enabled by a Catalytic Tetrad and Two Access Tunnels

Biocatalytic Aminolysis of Esters in Water – Scalable and Sustainable Synthesis of Heteroaromatic Amides

**Significance:** Zukic et al. report a biocatalytic method that provides access to the variety of sterically demanding, heteroaromatic amides. Lipase HXN-200 from *Sphingomonas sp.* is used as a catalyst that enables the formation of amide bonds by ester aminolysis. The reaction proceeds in an aqueous medium, which is consistent with the principles of green chemistry and yet competition of water as a nucleophile has been virtually eliminated. High chemoselectivity of the process is possible due to the catalytic tetrad in the enzyme active site.

**Comment:** Water – the optimal solvent for biocatalysts can act as a competing substrate in reactions catalyzed by lipases. The authors succeeded in overcoming the hydrolysis of ester starting material or product despite a considerable excess of water by utilizing the selectivity of lipase from *Sphingomonas sp.* In addition, the enzyme can efficiently work with sterically bulky starting materials, allowing access to pharmaceutically relevant molecules. The scalability of the method shows how biocatalysis can be used in an industrially applicable synthesis protocol.