BIOCATALYSIS

Biosynthesized fluorinated organoborons

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Trifluoromethylated organoborons are valuable synthetic building blocks as they provide access to a wide range of CF_3 -containing molecules via boron-mediated transformations. However, their asymmetric synthesis remains a challenge.

Frances H. Arnold's group has pioneered the application of haem-containing enzymes for the catalysis of abiological carbene transfer reactions. Just one of the many impressive examples is the biocatalytic insertion of carbene reagents into B–H bonds to give chiral organoborane compounds — achieved by reprogramming the enzyme *Rhodothermus marinus* cytochrome *c*.

Now, Kendall N. Houk, Frances H. Arnold and co-workers report the expansion of the synthetic scope of this enzyme to accept trifluorodiazalkanes in asymmetric carbene B–H bond insertion reactions for the synthesis of organofluorine compounds. For this purpose, directed evolution of the wild-type enzyme — that showed no considerable activity for the fluorinated substrates — was performed. Targeted residues for mutation were chosen in order to generate an enzyme active site that is surrounded by a more flexible loop, promoting substrate interactions with the carbene intermediate for increased enzyme activity, and also restricting the

position and orientation of the carbene intermediate, whereby the CF_3 -group points towards the haem pocket and the alkyl substituent towards the solvent, for highly enantioselective C–B bond formation and a broad substrate scope.

Indeed, several steps of directed evolution afforded a mutant enzyme — designated as BOR- CF_3 — which allowed the conversion of a variety of structurally diverse, fluorinated diazoalkane substrates with good turnovers and high enantioselectivities. Notably, several of the synthesized chiral α - CF_3 organoborons appear to not be accessible by current alternative methods. Molecular dynamics simulations elucidated in detail the contributions of the mutations on the activity and stereospecificity of BOR- CF_3 .

Overall, this work is a valuable extension of an enzyme-catalysed abiological reaction, providing new opportunities for the synthetic chemist. The careful design of the study — taking structural and dynamical considerations into account — was the key to generating a broadly applicable and enantioselective biocatalyst.

Jan-Stefan Völler

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