ENGINEERED ALDOLASES FOR ASYMMETRIC CARBON-CARBON BOND FORMATION

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Stereoselective carbon–carbon bond formation is a pivotal process in the asymmetric construction of the skeletal frameworks of complex chiral molecules from simple starting materials. Catalytic C–C coupling through aldol addition is particularly valuable in asymmetric synthesis because of its potential for stereodivergent product generation, by which multiple stereoisomeric products can be derived from common synthetic building blocks.[1]

Using enzyme catalysis (i.e. carboligases), molecular complexity can be rapidly built up under mild conditions, without the need for protecting sensitive or reactive functional groups, with high chemical efficiency and often with uncompromised stereochemical fidelity.[2] In this sense, suitably engineered already known and newly discovered carboligases are promising candidates to fuel future developments in the field. Aldolases catalyze a highly ordered, stereoselective addition of a carbon nucleophile (i.e., the aldol donor), which typically is a ketone enolate (class II) or transiently formed enamine equivalent (Class I), to a carbonyl electrophile (i.e., the aldol acceptor), which typically is an aldehyde.

In this seminar a thermostable Class I D-fructose-6-phospate aldolase (FSA), a Class II 2-keto-3-deoxy-L-rhamnonate aldolase (YfaU), and a 3-methyl-2-oxobutanoate hydroxymethyltransferase (KPHMT) with promiscuous aldolase activity, all of them from *E. coli*, will be presented for a diverse synthetic applications (Figure 1).[3] Wild-type and variants of these aldolases will be discussed in terms of substrate tolerance, stereoselectivity and product formation.

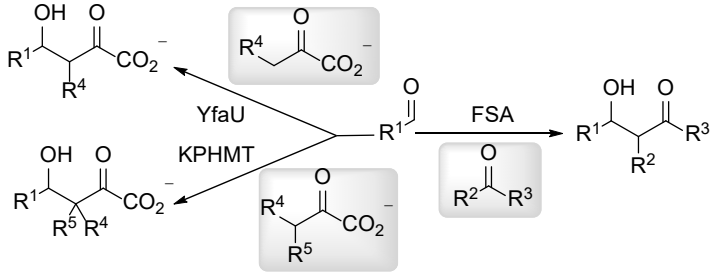

Figure 1. Aldol addition catalyzed by FSA, YfaU and KPHMT.

[1] R. Mahrwald, *Modern Aldol Reactions, Vol. 2: Metal Catalysis*, Wiley-VCH, Weinheim, **2004**.

[2] P. Clapés, in *Biocatalysis in Organic Synthesis Vol. 2* (Eds.: K. Faber, W.-D. Fessner, N. J. Turner), Georg Thieme Verlag KG, Stuttgart (Germany), **2015**, pp. 31-92.

[3] a) R. Marín-Valls, K. Hernández, M. Bolte, T. Parella, J. Joglar, J. Bujons, P. Clapés, *J. Am. Chem. Soc.* **2020**, *142*, 19754-19762; b) R. Marín-Valls, K. Hernández, M. Bolte, J. Joglar, J. Bujons, P. Clapés, *ACS Catal.* **2019**, *9*, 7568-7577; c) R. Roldán, K. Hernandez, J. Joglar, J. Bujons, T. Parella, I. Sánchez-Moreno, V. Hélaine, M. Lemaire, C. Guérard-Hélaine, W.-D. Fessner, P. Clapés, *ACS Catal.* **2018**, *8*, 8804-8809; d) S. Junker, R. Roldan, H.-J. Joosten, P. Clapés, W.-D. Fessner, *Angew. Chem. Int. Ed.* **2018**, *57*, 10153-10157; e) K. Hernández, J. Joglar, J. Bujons, T. Parella, P. Clapés, *Angew. Chem. Int. Ed.* **2018**, *57*, 3583-3587; f) D. Güclü, A. Szekrenyi, X. Garrabou, M. Kickstein, S. Junker, P. Clapés, W.-D. Fessner, *ACS Catal.* **2016**, *6*, 1848-1852; g) A. Szekrenyi, X. Garrabou, T. Parella, J. Joglar, J. Bujons, P. Clapés, *Nat. Chem.* **2015**, *7*, 724-729.

Prof. Dr. Pere Clapés is currently a full professor and head of the Biotransformation and Bioactive molecules group at the Institute for Advanced Chemistry of Catalonia (IQAC) of the CSIC. He studied Chemistry at the University of Barcelona and obtained his PhD from the same University in 1988. After his PhD, he moved to the Center for Chemical and Chemical Engineering, University of Lund (Sweden) as postdoc until 1990. In 1993 he started his independent scientific career as Research associate (Cientifico Titular) in the IQAC-CSIC and became full professor in 2010.

His scientific career is focused on investigations of enzymes as catalysts in organic synthesis, in particular on the exploitation of carboligases in asymmetric carbon-carbon bond formation. These include aldolases utilizing dihydroxyacetone phosphate, unphosphorylated DHA derivatives, benzaldehyde derivatives, amino acids, and 2-oxoacids as donors. Other enzymes include transaminases, keto-, imino- and amino reductases. His mid/long term scientific goal is to provide a groundbreaking biocatalyst platform to perform new-to-nature C–X bond formation reactions for a wide variety of molecules within a living cell, expanding the portfolio of available biocatalytic reactions and opening new biosynthetic routes inaccessible by conventional biocatalysis. He has published more than 190 research works including scientific papers, patents and book chapters in the field of biocatalysis.