FSA-Catalyzed Carboligation: New Synthetic Opportunities from an Ancient Enzyme Scaffold

Sebastian A. Junker,[a] Madhura V. Rale,[a] Anna Szekrényi,[b] Xavier Garrabou[b] , Pere Clapés,[b] Wolf-Dieter Fessner[a]*

[a]Institut für Organische Chemie und Biochemie, Technische Universität Darmstadt, Petersenstraße 22, 64287 Darmstadt, Germany; [b]Catalonia Institute for Advanced Chemistry, CSIC, Jordi Girona 18-26, 08034 Barcelona, Spain

E-mail: junker@mail.oc.chemie.tu-darmstadt.de

Aldol reactions constitute a powerful methodology for carbon-carbon bond formation in synthetic organic chemistry. Biocatalytic carboligation offers a green, uniquely regio- and stereoselective tool to perform this transformation. New enzymes from the transaldolase scaffold, such as fructose-6-phosphate aldolase (FSA) from *E. coli*, were recently shown to be unusually flexible in their substrate scope,[1] which renders them particularly valuable for the synthesis of complex polyfunctional targets.[2] So far, wild-type FSA has been demonstrated to utilize dihydroxypropanone, hydroxypropanone, 1-hydroxybutanone, and hydroxyethanal as aldol donor components for highly stereoselective carboligation reactions.

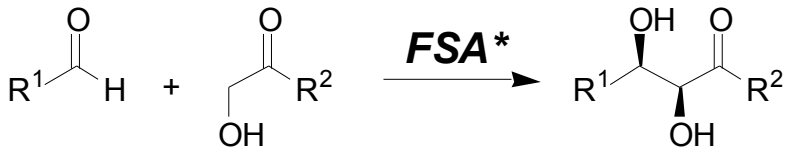

Figure 1. Aldol formation catalyzed by variant fructose-6-phosphate aldolases (FSA*).

In this work we demonstrate the utility of rational protein engineering to design variant FSA mutant proteins (FSA*) that offer an extended tolerance for donor substrate modifications towards the creation of novel products that are of commercial interest.[3]

[1] Rale, M.; Schneider, S.; Sprenger, G. A.; Samland, A. K.; Fessner, W.-D. *Chem. Eur. J.* **2011**, 17, 2623-2632

[2] Samland, A. K.; Rale, M.; Sprenger, G. A.; Fessner, W.-D. *ChemBioChem* **2011**, *14*, in press (DOI: 10.1002/chem.201002942)

[3] (a) Castillo, J. A.; Calveras, J.; Casas, J.; Mitjans, M.; Vinardell, M. P.; Parella, T.; Inoue, T.; Sprenger, G. A.; Joglar, J.; Clapés, P. *Org. Lett.* **2006,** *8*, 6067-6070; (b) Garrabou, X.; Castillo, J. A.; Guerard-Helaine, C.; Parella, T.; Joglar, J.; Lemaire, M.; Clapes, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 5521-5525; (c) Castillo, J. A.; Guerard-Helaine, C.; Gutierrez, M.; Garrabou, X.; Sancelme, M.; Schuermann, M.; Inoue, T.; Helaine, V.; Charmantray, F.; Gefflaut, T.; Hecquet, L.; Joglar, J.; Clapes, P.; Sprenger, G. A.; Lemaire, M. *Adv. Synth. Catal.* **2010**, *352*, 1039-1046.