Biocatalytic dealkylation toolbox for organic synthesis

Maximilian Wutscher,[a] Verena Scheibelreiter [a] Stefan Giparakis [a] Christian Stanetty [a]
Florian Rudroff [a]
[a] TU Wien, Getreidemarkt 9, 1060 Vienna, Austria
maximilian.wutscher@tuwien.ac.at

Complex organic syntheses often necessitate the employment of orthogonal protecting groups. Among these, methyl ethers and their alkyl derivatives stand out due to their properties, as they are easily integrated, cost-effective and chemically resilient. However, their removal demands harsh and often environmentally detrimental conditions, substantially narrowing their applicability in complex molecule synthesis.

Enzymes can catalyse dealkylation under gentle conditions by harnessing molecular oxygen as an oxidizing agent. Our objective is to develop an utmost general biocatalytic solution by applying redox-active enzymes for O-dealkylation. The ultimate aim is to develop a versatile toolkit for organic chemists, facilitating the precise removal of O-alkyl side chains with regio- and chemo selectivity.

We have chosen members of the CYP450 oxidoreductase family as starting point for our development. Generally, these biocatalysts need redox partners to complete their enzymatic cycle. For this reason, we selected self-sufficient mutants of CYP450 BM3, which contain these redox partners fused to the enzyme, providing higher activity and ease of handling.

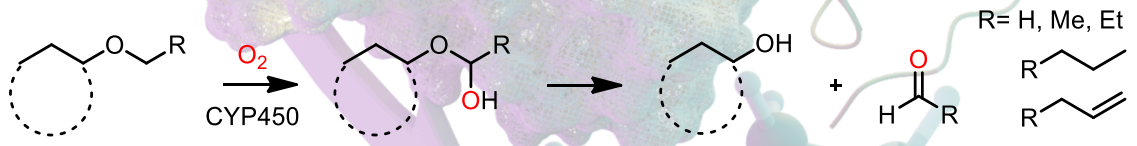

Figure 1: Demethylation of protected alcohol substrates

In this sense we have already tested a substrate library which contains different aliphatic, aromatic, and carbohydrate alkyl ethers with encouraging results, thus providing a promising starting point towards an effective dealkylation methodology under environmentally friendly conditions.

Haines, D.C., Tomchick, D.R., Machius, M., Peterson, J.A.
(2001) Biochemistry 40: 13456-13465