Biocatalytic Cleavage of *Para*-Acyloxy Benzyl Ether Protecting Groups

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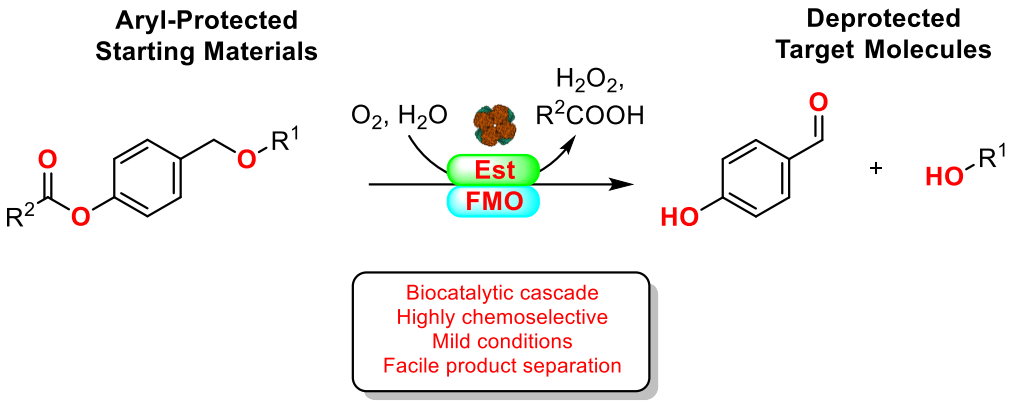

Protecting groups (PGs) are of fundamental importance to synthetic organic chemistry.[1] The use of PGs is strongly disfavoured by the chemical industry due to the inherent reductions in process yield and efficiency. Aryl ethers are still reluctantly relied upon by industry,[2] due to their ease of addition and robustness. Their main drawback is the stern reductive conditions required for their removal. Several methods are available but none are very green or chemoselective, limiting applicability in many cases.

We aim to develop a biocatalytic method for the deprotection of relevant aryl ether protecting groups.[3] *Para*-hydroxy benzyl (PHB) ethers are first derived *in situ* from stable *para*-acyloxy benzyl ethers by the action of a thermostable esterase. PHB ethers are reactive substrates of a class of flavin-containing oxidases (FMOs), yielding *para*-OH benzaldehyde and deprotected target molecule, with consumption of H_2O and O_2, and release of H_2O_2 in a one-pot cascade deprotection reaction. We obtain suitable biocatalyst partners for our cascade *via* library screening and subsequent directed evolution.

Our chemoselective deprotective cascade will improve reaction characteristics and sustainability of aryl ether/amine deprotection relative to current default chemicals methods. Simultaneously, synthetic applicability of aryl ethers in general will be expanded by rendering feasible the deprotection of molecules which are sensitive to hydrogenation.

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[1] Clayden *et al*., Organic Chemistry (Oxford University Press, 2004).
[2] Brown, D.G. & Bostrom, J., *J. Med. Chem.* **59** (2015).
[3] Jobron, L. *et al*., *JACS*, **121** (1998).