Biocatalytic oxidation reactions to create sustainable chemistry for the future

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Frank Hollmann is a professor of biocatalysis at the Delft University of Technology (The Netherlands). As a member of the Biocatalysis Group (together with his colleagues Djanashvilli, Hagedoorn, Hanefeld and Paul) he aims at developing biocatalytic synthetic routes for organic chemistry. His particular focus lies on selective oxyfunctionalisation reactions using peroxygenases.

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John M. Woodley is a professor of bioprocess engineering at the Technical University of Denmark (DTU). Working closely with industrial partners, his research team are interested in the scale-up of bioprocesses, with a particular interest in cellular and enzymatic biocatalytic processes.

Oxidation reactions are at the heart of organic chemistry. In industry, the epoxidation of ethylene and propylene or the hydroxylation of benzene for example is conducted at a scale of several million tonnes per year. At the same time, many of the established oxidation processes require relatively harsh reaction conditions and suffer from selectivity issues. As a consequence, the environmental impact of industrial oxidations remains high.

Biocatalysis has a lot to offer here. Enzymes not only operate efficiently under very mild reaction conditions but also excel in terms of selectivity making them attractive alternatives to currently widespread transition metal catalysts for oxidation chemistry.

In this special issue, we have assembled contributions from some of the leaders in the academic research community working on biocatalytic oxidation chemistry. We highlight the current state-of-the-art in the field demonstrating its enormous potential for industrial scale application but also highlighting its current limitations.

Alcohol dehydrogenases have been among the first enzymes investigated for biocatalytic oxidation reactions. The manifold applications of alcohol dehydrogenases for the stereo- and regio-selective oxidation of primary and secondary alcohols are summarised in the contribution by Milagre and coworkers.

While alcohol dehydrogenases transfer the reducing equivalents liberated from the starting materials to nicotinamide cofactors ($NAD(P)^+$), oxidases utilise molecular oxygen as a sacrificial electron acceptor. Hence, oxidases appear promising, more cost-efficient alternatives to $NAD(P)^+$-dependent dehydrogenases. The recent rapid developments in oxidase catalysis are critically summarised and discussed in the contribution by Heath and Turner.

Dehydrogenases and oxidases catalyse dehydrogenation (hydride abstraction) reactions and therefore require pre-existing functional groups such as alcohols or amines for activity. In contrast, (non-) heme iron oxygenases catalyse the insertion of O-atoms (and more) even into non-activated C–H bonds. Hence, these oxygenases often accomplish chemistries, which are not achievable by existing chemical technologies.

The so-called P450 monooxygenases have been forerunners for biocatalytic oxyfunctionalisation chemistry resulting in an enormous portfolio of highly regio- and stereoselective oxyfunctionalisation reactions. This wealth of possibilities is nicely summarised in the contribution by Opperman and co-workers.

More recently, P450 monooxygenases have been challenged as catalysts of choice by the so-called unspecific peroxygenases (UPOs) essentially catalysing the same reactions as P450 monooxygenases but mechanistically far simpler. The rapid development of peroxygenases as catalysts for oxyfunctionalisation chemistry is summarised by Alcalde and co-workers. Xu et al. critically compare both enzyme classes and importantly highlight some limitations *en route* to large-scale application.

Halogenases represent a truly exciting emerging class of oxygenases as for the highly selective introduction of halogens into non-activated C—H bonds where no chemical equivalents are known. The contribution by Buller and coworkers provides a concise introduction to the various halogenases known today, mechanistic insights and provides an overview over synthetic possibilities.

Generally, oxidation reactions yield more reactive products such as occurs with alcohol oxidation or alkene epoxidation. Hence, the products of biocatalytic oxidation reactions themselves serve as starting materials for further transformations. The cascade catalysis concept envisions performing the oxidation step and the subsequent derivatisation step integrated together, eliminating time- and resource-consuming isolation and purification of the intermediates. This fascinating research is introduced in the contribution by Zhi and coworkers.

Despite the wealth of engineered biocatalysts available, oxidative biocatalysis still is underrepresented, especially in the synthesis of commodity and bulk chemicals. Several issues still require intensive R&D efforts before oxidative enzymes become competitive also for these lower value-added compounds. In two contributions by Sieber and co-workers and Bommarius the role of molecular oxygen in enzyme- and process instability is highlighted. Molecular and physico-chemical mechanisms of enzyme inactivation are discussed together with recent strategies to overcome such limitations.

Water is often considered as an ideal solvent from a sustainability point-of-view. However, for a broad range of reactants of interest, water is a sub-optimal solvent limiting traditional biocatalysis to low product titres. Sheldon and co-workers discuss this issue and present some promising green alternatives to water as a process solvent.

Along these lines, the contribution of Kara and coworkers emphasises the potential of process intensification to render biocatalytic oxidation reactions both environmentally and economically more attractive.

We are proud to have assembled contributions from leading researchers in the field of biocatalytic oxidation chemistry. The different aspects highlighted in this special issue give an impressive, though certainly not comprehensive, overview of this dynamic and exciting research field. We hope to enthral students and researchers alike to join us in the quest for greener industrial oxidation processes using enzymes.