Heterogenous biocatalysis in continuous flow systems as a new approach to synthetic chemistry

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Flow chemistry has allowed many industrial processes to be carried out in continuous mode, with higher efficiency and automation. Biocatalysis has caught up with this technique and several examples have been reported in the literature in the last decade. However, the complexity of multi-enzymatic processes in the absence of cellular regulation, has limited their applications to some chemo-enzymatic synthesis, and just a few fully enzymatic processes have been implemented. Among others, the cofactor requirements of redox enzymes, the stability of the biocatalyst, and efficiency of the biotransformations, must be thoroughly optimised. Furthermore, the mobile phase is rarely recovered, minimizing the real environmental impact of enzymatic reactions. Here the steady evolution of flow biocatalysis in our laboratory will be presented,[1,2] moving towards systems of increasing complexity with combinations of several enzymes, which resulted in a breakthrough in the design and implementation of an ultra-efficient zero-waste and closed-loop process with unprecedented atom efficiency and automation (Figure 1).[3]

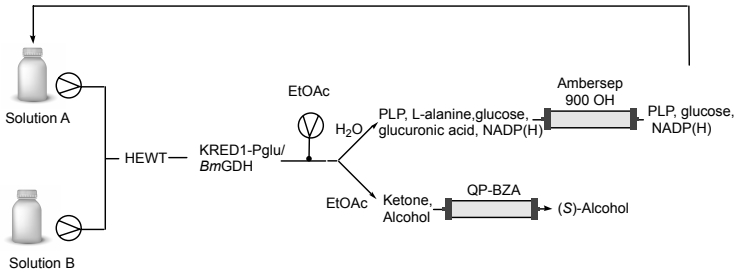

Figure 1: Ultra-efficient multi-enzyme interconversion of amines into alcohols

With this technology, we successfully achieved the synthesis of metabolic intermediates of biogenic amines, such as hydroxytyrosol, tryptophol, histaminol, for which chemical synthesis is hampered by very low yields.[4] Additional examples will show how we have overcome substrate solubility issues as well as "near-industrial scale" synthesis in the lab.[5,6]

Finally, the application of enzyme engineering to probe stability of the cofactor in transaminases,[7] and to enable a novel and facile synthesis of hindered amides and thioesters, will be presented.

References

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