Sustainable Catalysis: enzyme-mediated synthesis of high value chemicals and pharmaceuticals in Flow Reactors

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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]

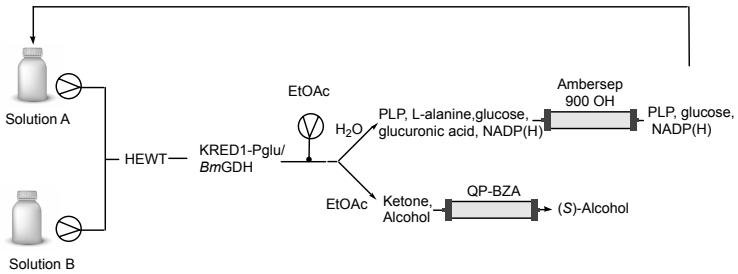

Figure 1: Ultra-efficient multi-enzyme interconversion of amines into alcohols

With this technology, we have been able to successfully achieve the synthesis of metabolic intermediates of biogenic amines, such as hydroxytyrosol, tryptophol, histaminol (Figure 2), for which chemical synthesis is hampered by very low yields.[4]

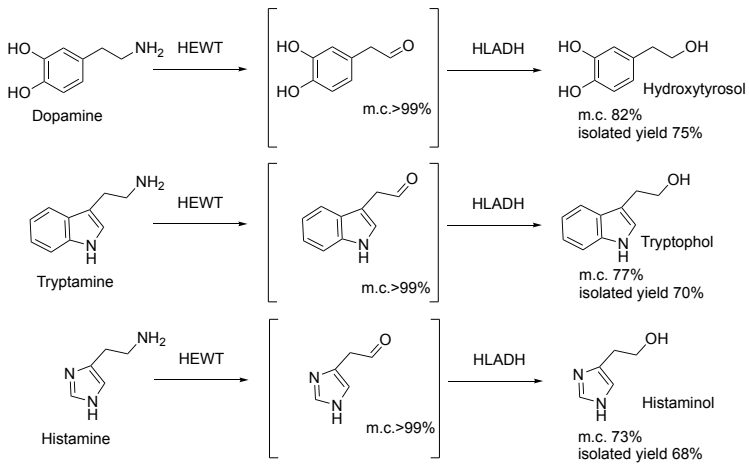

Figure 2: Telescoped reactions for the synthesis of hydroxytyrosol, tryptophol, histaminol

The application of flow biocatalysis then can span to the synthesis of a much broader set of molecules as it is now apparent that the technology can offer solutions to current synthetic problems maintaining a very low environmental impact.

Finally, in this talk, the challenge of substrate/product insolubility in flow set-ups will be discussed. The use of inlets of solvents (such as toluene or EtOAc) upstream of the column can be explored when the enzyme tolerates well non-aqueous systems, in cases were the product is insoluble and is not released by the column. However, when the starting material is insoluble, the conversion rates can be dramatically affected. In this case, the use of small amount of surfactants can be successfully implemented as we have demonstrated for the hydrolysis of naproxen (Figure 3).[5]

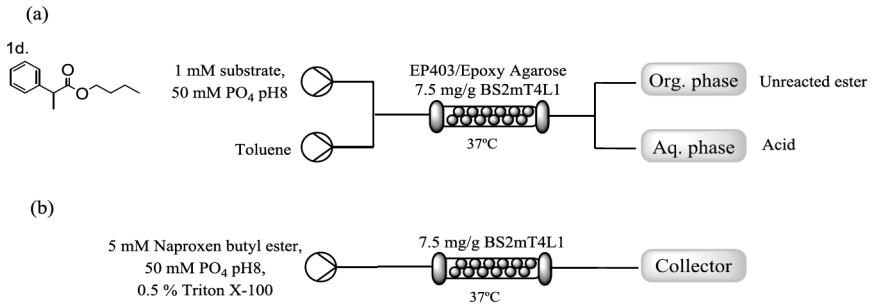

Figure 3: Setup of the flow reactor (a) with toluene and (b) with Triton X for the hydrolysis of naproxen.

Keywords: cascade reactions, ex-vivo biosynthesis, transaminases, dehydrogeanses, hydrolases

References

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