Reflections on Five Decades of Biocatalysis in Non-Conventional Media

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A personal reflection on the development of biocatalysis in non-conventional media over 5 decades is presented. In the 1970s and 1980s there was a clear distinction between processes for bulk chemicals manufacture on the one hand and fine chemicals and pharma on the other hand, and never the twain shall meet. Bulk chemicals production involved the use of heterogeneous catalysts and hydrocarbons as substrates, mainly in the gas phase. In contrast, fine chemicals and pharmaceuticals were produced using stoichiometric quantities of reagents dissolved in organic solvents, i.e. in the liquid phase.

In the 1980s it gradually became apparent, to astute observers at least, that environmental concern was encouraging the development of processes that minimize chemical waste, i.e. catalytic processes rather than processes involving archaic stoichiometric reagents.[1] At the same time biocatalytic methods for the synthesis of semi-synthetic penicillins and cephalosporins were being developed, particularly by the companies Gist-Brocades and DSM in the Netherlands. The driving force was the possibility to replace the environmentally unfriendly reagents and solvents used in the classical syntheses, e.g. carbon tetrachloride and dichloromethane.

In the1990s the trend towards the use of catalytic processes in fine chemicals manufacture continued unabated and was reinforced, in 1992, by new legislation introduced by the FDA, that encouraged the marketing of chiral drugs as single enantiomers. This led to widespread interest in catalytic asymmetric synthesis. Initially focused mainly on catalytic asymmetric hydrogenation but it was soon realized that enzymatic methods, aided by developments in protein engineering, had many advantages, in particular the near perfect enantioselectivities and environmentally friendly reaction conditions. This trend, aided by the many developments in molecular biology, continued in the following decades in this century.

No matter which technology is used it generally requires the use of solvent. However, as was already observed in the 1990s: the whole question of solvents in organic synthesis needed to be re-examined. Not only should the solvent be environmentally benign, the overall process should involve its facile removal and recycling in a circular economy. Hence, in the last three decades a wide variety of non-conventional solvents has been studied, both with chemo- and biocatalysts. Major examples are bio-based solvents, ionic liquids, deep eutectic solvents, supercritical carbon dioxide, aqueous micelles and mixtures thereof. Advantages and limitations of the various possibilities are briefly delineated.

1. M. A. Murphy, *Substantia*. An International Journal of the History of Chemistry, 2023, 7(2), 41-55, Firenze University Press. www.fupress.com/substantia DOI: 10.36253/Substantia-2140