



Combining the ‘two worlds’ of chemocatalysis and biocatalysis towards multi-step one-pot processes in aqueous media

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The combination of biocatalytic and chemocatalytic reactions leading to one-pot processes in aqueous medium represents an economically and ecologically attractive concept in organic synthesis due to the potential to avoid time and capacity consuming and waste producing work-up steps of intermediates. The use of water as a solvent has many advantages. A key feature is the opportunity it provides as *the* solvent in nature to make use of the full range of enzymes. In recent years development of chemoenzymatic one-pot processes in water has emerged tremendously, and proof of concepts for the combination of biotransformations with metal catalysts and organocatalysts were demonstrated. This review will focus on major contributions in this field, which also underline the compatibility of these two ‘worlds’ of catalysis with each other as well as the industrial potential of this one-pot approach.

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Dedicated to Professor Dr. Herman van Bakkum, a pioneer in the field of chemoenzymatic one-pot processes, on the occasion of his 80th birthday.

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Introduction: Concept of chemoenzymatic one-pot processes, their industrial potential and reasons to use water as a solvent

Whereas a strong focus is still on the development of new processes, up to now surprisingly less attention in organic synthesis has been paid towards the combining of synthetic methodologies. In terms of process efficiency as well as sustainability, however, the combining of individual reaction steps has a tremendous potential for decreasing solvent consumption and waste production due to a decrease of the number of overall required work-up steps [1]. By saving such time and capacity consuming and waste producing unit operations, solvent

usage can be dramatically reduced and space-time yields can be significantly improved. Thus, it is not surprising that from an industrial standpoint there is an increased general interest in this topic of one-pot processes. Whereas the combining of reactions belonging to the same type of technology, such as chemocatalysis (in, *e.g.*, domino reactions) on the one and biotransformations (in, *e.g.*, fermentations) on the other hand, is already widely known, combinations of these ‘two worlds’ chemocatalysis and biocatalysis is still in its infancy [2,3]. In particular this is true for the combination of chemocatalysis and biocatalysis for consecutive reactions in aqueous media (Scheme 1). To use water as a solvent is of particular interest for two reasons: First, water is an attractive solvent due to its environmental friendliness (although this is not necessarily the case for the waste water resulting from the reaction), lack of toxicity and low cost. Second, choosing water as a solvent enables the use of the full range of enzymes as water represents the natural reaction media for all enzymes (whereas only a minority of enzyme classes such as lipases are known to act in organic media). In spite of the benefits one can get from such types of one-pot processes, a range of challenges exists including the need for compatibility between the chemocatalytic and biocatalytic reaction steps in addition to ‘general process requirements’ such as high conversions, yields and selectivity.

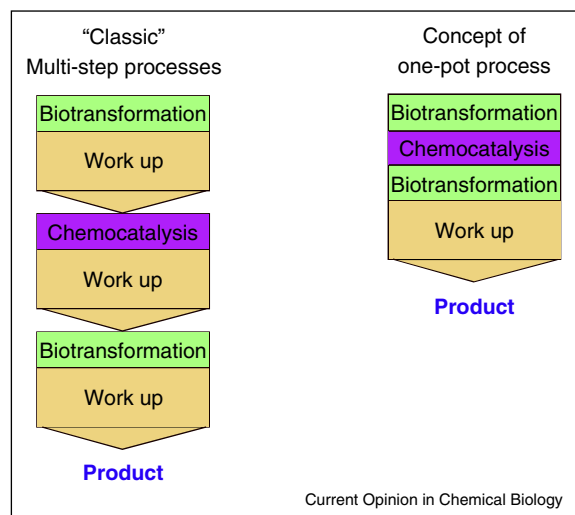
This review will summarize the major contributions in this young research field, most of which have been made in just the past five to 10 years, with a particular focus on work done in the last two to three years.

A brief journey through the early historical developments and pioneering works in chemoenzymatic one-pot synthesis (in water)

The groundbreaking pioneering work in this field was reported in the early 1980s, when the van Bakkum group laid the ground for this development by elegantly combining a heterogenized metal-catalyzed hydrogenation with an enzymatic isomerization (Scheme 2) [4**]. This process has been developed for the synthesis of the sugar substitute D-mannitol starting from D-glucose, which is *in situ* transformed into D-fructose using a D-glucose isomerase. Subsequent heterogeneous Pt-catalyzed hydrogenation then delivered the desired D-mannitol (4) as major product. Later work addressing process development and catalyst improvement was done by both the van Bakkum and Stewart groups [5,6].

In spite of this pioneering work of combining metal and biocatalysis, it is surprising that for more than a decade

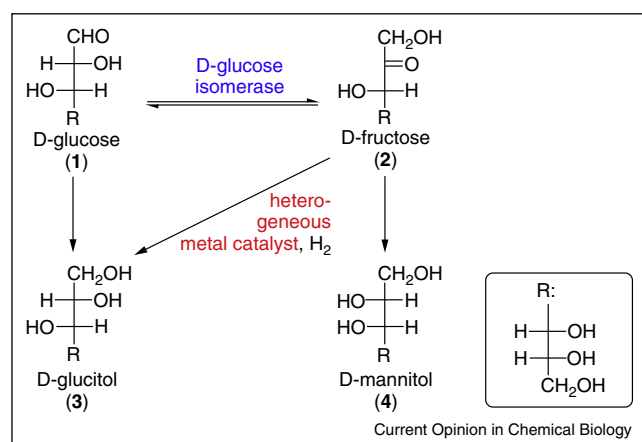
Scheme 1



Comparison of the concepts of ‘classic’ multi-step processes and one-pot processes.

there has been a lack of (at least to a significant extent) further work before next major contributions made for dynamic kinetic resolutions by combining a chemocatalytic racemization and a hydrolase-catalyzed resolution in water. Pioneering work in this field was done by the Williams group jointly with Harris [7,8] on the one hand and the Wang as well as Beller groups [9,10] on the other hand utilizing metal catalysts and organocatalysts, respectively, for racemization. It should be noted (although processes in pure organic media are not be subject to this review) that in parallel a range of dynamic kinetic resolutions of alcohol and amines based on metal-catalyzed racemization and lipase-catalyzed resolution through acylation running in pure organic media was

Scheme 2



The pioneering work in combining a metal-catalyzed transformation with a biotransformation in a one-pot process.

developed towards a matured technology by the groups of Bäckvall, Kim, and Berkessel [3,11–13]. Since such dynamic kinetic resolutions in both aqueous and organic media have been already reviewed comprehensively [3], this concept will not be part of this review. Instead, this review will focus on ‘consecutive chemoenzymatic cascades’ in aqueous media according to Scheme 1, which consist of substrate synthesis (by other routes than racemization) and a following derivatization reaction.

Combination of metal catalysis and biocatalysis towards one-pot processes in aqueous medium

In general a motivation to combine metal catalysis and biocatalysis also results from the facts that both catalyze unique transformations, which often cannot be conducted by means of the other catalytic discipline. Accordingly, from a biocatalysis perspective it is exciting to focus on those metal-catalyzed transformations for combinations, for which enzymatic processes do not exist such as, for example, cross-coupling reactions (Pd catalysis for Heck reaction, Suzuki-reaction), metathesis (Ru-catalysis or Mo-catalysis) and Wacker-oxidation (Pd catalysis). A further metal-catalyzed transformation of wide interest is hydrogenation, and its combination with a subsequent hydrolase-based process represents the first example of a successful combination of a (homogenous) metal-catalyzed asymmetric reaction with a subsequent biotransformation (resolution) reported by Hanefeld, Maschmeyer, Sheldon and co-workers in 2006 [14[•]]. Here *N*-acetyl amino acrylate was enantioselectively hydrogenated with a rhodium-diphosphane-catalyst leading to the *N*-acetyl amino acid (100% conversion, 95% ee), which then undergoes a hydrolysis in the presence of an L-amino acylase to produce L-alanine with 98% conversion and >98% ee.

In addition, organic reaction mixtures from heterogeneously catalyzed hydrogenations turned out to be compatible with subsequent biotransformations. This was demonstrated by the Mihovilovic group for the hydrogenation of cyclic enones conducted in a flow reactor (and optionally a subsequent epimerization with an ion-exchange polymer), followed by a monooxygenase-catalyzed Baeyer-Villiger oxidation to form a lactone with >99% ee, >99% de and a space-time-yield of 3.4 g/(L*d) [15]. This opens up a perspective for also combining heterogeneously catalyzed hydrogenations and biotransformations, where both proceed together in a one-pot process in aqueous reaction medium.

Among industrially relevant palladium-catalyzed reactions, a Suzuki cross-coupling was efficiently combined with an enantioselective biocatalytic reduction jointly by the Gröger and Hummel groups (Scheme 3) [16[•]]. After unsuccessful early attempts, boronic acid **6** as a required reagent for the Pd-catalysis was found to be a critical component due to its strong inhibition of the alcohol

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