Spaciant Solvent Factory towards Bio-chemocatalysis in ONE-FLOW: Combined computational and Experimental Strategy

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An entirely new reactor concept for multi-step organic reactions and particularly for homogeneous-bio catalysis cascades is presented based on the combination of micro-flow continuous processing and functional solvent multi-phase systems. The latter provide compartmentalized flow reactor/separator systems with 'horizontal hierarchy' – as opposed to the 'vertical hierarchy' of common multi-step flow syntheses (or batches) with their consecutive reactors-separators. Such flow cascade processing ideally needs just one reactor passage ('ONE-FLOW'; www.one-flow.org). This 'Green-Solvent Spaciant Factory' will fluidically open and close interim reaction compartments (create spaces = 'spaciant'). The tasks are to enable (a) orthogonality during reaction, (b) recycling of catalysts and reactants, (c) purification of products, (d) enable high-c processing, (e) ensure activity and stability of the catalyst.

In green catalysis, integrated processes of selective transformation and separation were found capable of directly providing pure products, including the reuse of all the elements of the reaction system, e.g. catalysts, solvents, etc. [1]. In recent years, the unsurpassed selectivity of enzymes for chemical reactions, combined with the excellent solvent properties of ionic liquids (ILs), has provided an excellent setting for carrying out sustainable chemical transformations. In our case, a functional solvents system shall serve as integrated reactor-separator for the 3-step flow cascade chemistry from 3-chlorobenzaldehyde to (1R,3S)-1-(3-chlorophenyl)butane-1,3-diol [2]. Aim is to facilitate one-pot reactions of the chemo- and biocascade, while separating bio- and organic catalysts as well as the pure product in different phases (Fig. 1).

We follow Kragl et al. in choosing a mixture of ethoxylated ionic liquid Among 110TM and the aqueous buffer solution as phase separator for the biocatalyst, which can also increase the activity and stability of the employed alcohol dehydrogenase [3]. To achieve multiphases, the presence of

butyrophenone as co-solvent is needed. Accordingly, we investigated the phase behaviour of the system water/butyrophenone/Ammoeng 110TM in batch. We found up to 5 metastable phases which turn with time to fewer phases in batch. This phase diversity is now implemented in continuous operation, with the expectation to form complex composed, switchable segmented flow which acts as integrated reactor/separator.

The large diversity of ILs (>10 exp 6) and conventional solvents (> 7000) opens up possibility for solvent modelling via the COSMO-RS method to search for the best solvent for the organic catalyst and product in regard to solubility. Then, based on the obtained relative solubility, the further screening steps are followed under consideration of constraints regarding the reactivity, thermodynamic and physical properties, costs and NFPA. We identified 2,2'-oxybis-butane as best conventional solvent and 1-butyl-3-methyl-imidazolium trifluoroacetate as best ionic liquid candidate. The top 5 conventional solvents and 2 ILs candidates pre-identified from simulation work are further evaluated by means of experiments. These will then guide to the solvent which finally will be implemented in our "Multi-Step Solvent Factory" to achieve the green chemo-biocascade to yield (1R,3S)-1-(3-chlorophenyl)butane-1,3-diol.

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References

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Keywords

Solvent factory; cascades; bio- and organic catalysts; integrated reactor-separator; multiphase system.