

# Spaciant solvent factory towards a bio-chemocascade in ONE-FLOW project : a combined experimental and computational strategy

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## Spaciant Solvent Factory towards a Bio-chemocascade in ONE-FLOW Project:

### A combined experimental and computational strategy

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### 1. Introduction

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 are operated as 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 provide (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 are 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-Flow’ reactions of the chemo- and biocascade, while separating bio- and organic catalysts as well as the pure product in different phases (Fig. 1).

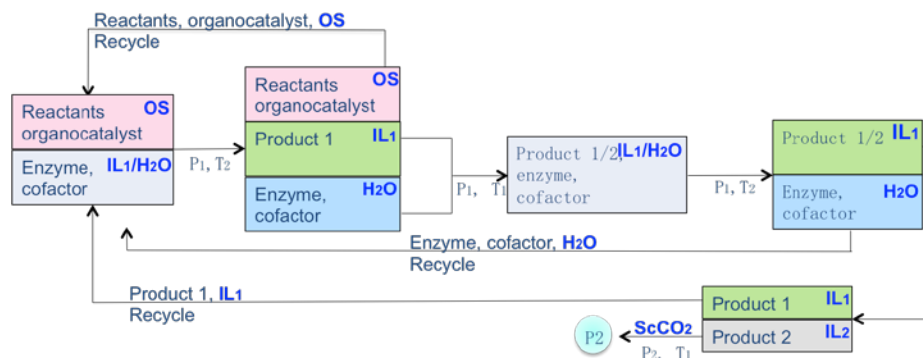


Figure 1. Reaction scheme of cascade.

### 2. Methods

The whole ‘One-Flow’ solvent screening methodology is given in Fig 2. Firstly, a large database of conventional organic solvents (about 8,000) and/or ionic liquids (ILs; about 40,000) is generated from the COSMOthermX software. Then, solvents are excluded which might take part in the reaction to narrow the screening space. For instance, since acetone is involved in the reaction, compounds with ketone/carbonyl moieties and groups that can react with acetone are eliminated. Furthermore, relevant physical properties and the environmental profile of solvents is rated to screen out solvents that are easy-to-operate, safe, and environmental-friendly. Afterwards, thermodynamic properties of the different solvents are calculated according to different separation strategies proposed for the reaction system. The top solvent candidates after this step are carefully evaluated by experiments to finally identify the practically suitable solvent or solvent systems.

### 3. Results and discussion

We follow Kragl et al. in choosing a mixture of ethoxylated ionic liquid Ammoeng 110<sup>TM</sup> and 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 110<sup>TM</sup> in batch. We found up to 5 metastable phases which coalesce with time to fewer phases (Fig.3). 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.

We identified 2,2'-oxybis-butane as best conventional solvent and 1-butyl-3-methyl-imidazolium trifluoroacetate as best ionic liquid candidate using the solvent screening methodology. The top 5 conventional solvents and 2 ILs candidates pre-identified from the simulation rating are further evaluated by means of experiments. This will then guide to the solvent which finally will be implemented in our "Multi-Step Spaciant Solvent Factory" to achieve green chemo-biocatalytic cascades.

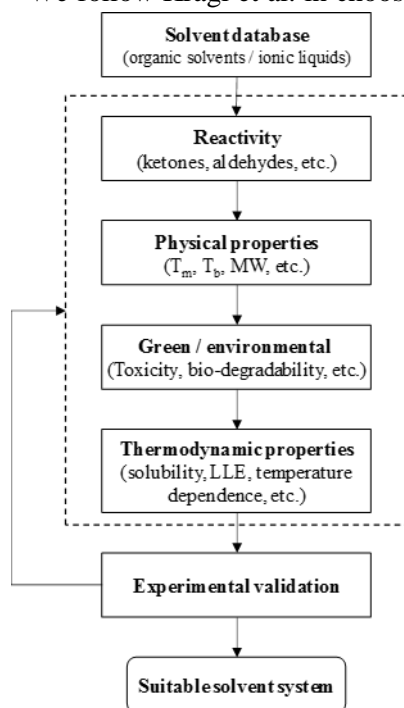


Figure 2. Solvent screening scheme.

### 4. Conclusions

The unique ability of functional solvents, like ionic liquids, ScCO<sub>2</sub>, as temperature switchable liquid/liquid phase systems, opens up a new sustainable platform for the chemical synthesis and separation of liquid products. Key solvents in the Spaciant Solvent Factory were identified by simulation of the 3-step flow cascade chemistry from 3-chlorobenzaldehyde to (1R,3S)-1-(3-chlorophenyl)butane-1,3-diol. Based on this a complete functional multiphase flow scheme (Fig. 1) has been proposed which is now experimentally verified.

### 5. Acknowledgements

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### Keywords

Solvent factory; cascades; integrated reactor-separator; multiphase system.

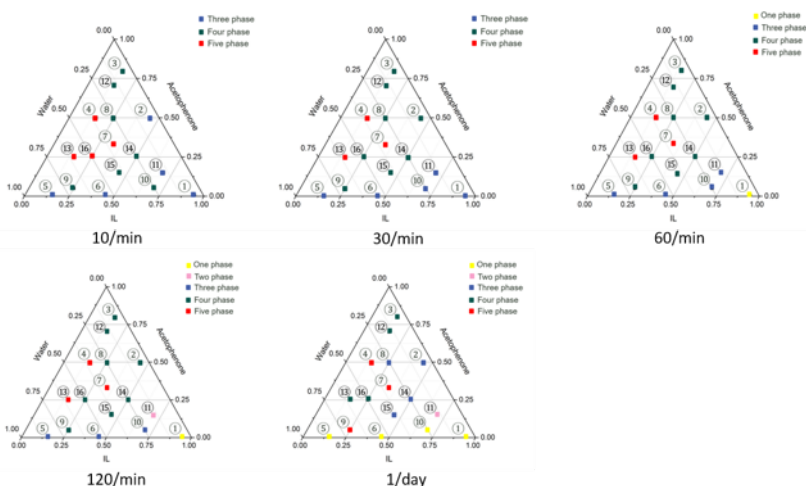


Figure 3. Liquid-liquid phase equilibria – time evaluation.