Catalytic cascade reactions for syntheses of sartans in continuous flow

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The Project

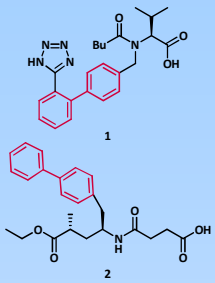

Figure 1: Target molecules valsartan **1** and sacubitril **2**.

The scope of the ONE-FLOW project* [1] is to translate 'vertical hierarchy' of chemical multistep synthesis into self-organising 'horizontal hierarchy' of a compartmentalized flow reactor system. Our part in this project is the development of catalytic cascade reactions for the syntheses of valsartan **1** and sacubitril **2** (Fig. 1). The compounds are well known as active pharmaceutical ingredients (APIs) in a combination drug for the treatment of hypertension and chronic heart failure (Entresto®, Novartis) [2]. The key step of the synthetic route, the formation of the biaryl unit, is a Suzuki-Miyaura cross coupling reaction which will be catalyzed by a novel heterogeneous palladium catalyst [3,4]. An immobilized enzyme will accomplish the final product formation via hydrolysis. To create large interfacial area for the catalytic reactions and to keep the reagents separated until required, the catalysts will be embedded in Pickering emulsions [5], which will be developed together with Prof. B. Binks, University of Hull.

The Reactor

In a first attempt it is planned to use the so-called plug & play reactor (Fig. 2) [6] for the catalytic cascade reactions. The plug & play reactor is a modular fixed bed reactor featuring exchangeable reaction segments as well as modules for heating/cooling and mixing (Fig. 2) [6]. The reaction media flow through 1 mm tubes embedded in channels filled with heating/cooling media, in this way ensuring both turbulent mixing and rapid heat transfer. Commercially available HPLC columns filled with catalyst particles serve as fixed-bed reactors and contribute to the high flexibility of the device. With this approach, gas-solid, liquid-solid as well as gas-liquid-solid reactions can be realized within the upper performance limits of 200 °C and 40 bar.

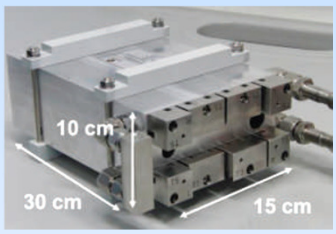

Figure 2: Scheme of the plug & play reactor [6].

The Cascade

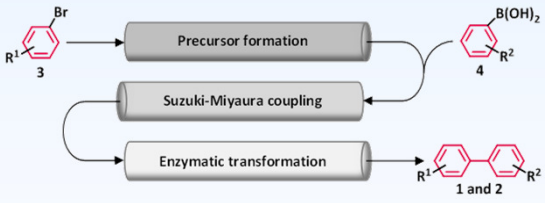

Figure 3: Targeted integrated multistep syntheses of APIs **1** and **2** in continuous flow.

The synthesis of active pharmaceutical ingredients **1** and **2** is aimed to proceed via the multi-step catalytic pathway shown in Fig. 3. After formation of a bromo-substituted drug precursor from **3**, the Suzuki-Miyaura coupling with the boronic acid derivative **4** will be catalyzed by the heterogeneous palladium catalyst [3,4]. The subsequent enzymatic transformation leads to the final APIs **1** and **2**. While we currently work on the optimization of the reaction conditions of the single steps, the next step is to employ the compartmentalized catalysts in a continuous flow set-up.

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References:
[1] https://one-flow.org
[2] Lau, S. H.; Bourne, S. L.; Martin, B.; Schenkel, B.; Penn, G.; Ley, S. V. *Org. Lett.* **2015**, *17*, 5436-5439.
[3] Lichtenegger, G. J.; Maier, M.; Hackl, M.; Khinast, J. G.; Gössler, W.; Griesser, T.; Kumar, V. S. P.; Gruber-Woelfler, H.; Deshpande, P. A. *J. Mol. Catal. A: Chem*. **2016**, *426*, 39-51.
[4] Gruber-Woelfler, H.; Radaschitz, P. F.; Feenstra, P. W.; Haas, W.; Khinast, J. G. *J. Catal.* **2012,** *286*, 30-40.
[5] Chen, Z.; Zhao, C.; Ju, E.; Ji, H.; Ren, J.; Binks, B. P.; Qu, X. *Adv. Mater.* **2016,** *28*, 1682-1688.
[6] Lichtenegger, G. J.; Tursic, V.; Kitzler, H.; Obermaier, K.; Khinast, J. G.; Gruber-Woelfler, H. *Chem. Ing. Tech*. **2016**, *88*, 1518-1523.