Keep the flow: in-line technologies for pure products

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Abstract of the entire section

Flow reactor technology represents one of the enabling technologies introduced in the last decade to advance the sustainability of organic synthesis and shows many advantages compared with batch methods, including increased safety, high control of reaction parameters, quick reaction optimization, possibility of automation and in-line work-up and purifications.[1] Indeed, flow synthesis cuts across several traditional boundaries within the sequential scaling routes of synthesis such as research scale, re-synthesis, kilo labs and full scale manufacturing/formulation, combining aspects of both chemical optimization and process intensification. Continuous production is often cited as both eco-friendly and economic, mainly due to the higher energy efficiency and reduced consumption of resources that can be achieved in comparison with traditional batch production[2]. Theoretically, if a sequence of stepwise reactions can be set up using the same solvent or simply applying an exchanging solvent mechanism, the firstly well optimized reactions could be processed in tandem. In this way the reaction mixture for the first step becomes the reagent for the next one creating a telescoped sequence. If on one side this ideal scenario is not so easy to perform due to the need to quench reactions, work-up intermediates, and consequently purify the stream between the different transformations, on the other side it is possible to combine other enabling technologies to obtain in-line filtration, in-line extraction, in-line distillation, and in-line purification to maintain a continuous flowing sequence.

Solid supported reagents and scavengers in flow chemistry

Original title of the considered paper: Multistep synthesis using modular flow reactor: Bestman-Ohira reagent for the formation of alkynes and triazoles.

Bibliography of the considered paper: Ian R. Banxendale, Steven V. Ley, Andrew C. Mansfield, Christopher D. Smith, Angewandte Chemie International Edition, 2009, 48, 4017-4021.

[1] I. R. Baxenadale J. Chem. Technol. Biotechnol., 2013, *88*, 519-552

[2] M. Planchesteiner, M. L. Contente, J. Cassidy, F. Molinari, L. Tamborini, F. Paradisi. Green Chem 2017, *19*, 372-375.

Summary of the considered paper:

In this paper the authors report on the application of the Bestmann-Ohira reagent (dimethyl-1-diazo-2-oxopropylphosphonate) for the preparation of terminal acetylenes under flow conditions, using a commercially available pumping system Vapourtec R2+/R4 and heated convection-flow coils (CFC) in combination with packed Omnifit glass tubes containing appropriate scavenger materials to ensure the high quality of the exiting desired products. Because of the superheating of the solvent, pressure within the system was kept due to an in-line 100 psi back-pressure regulator while mixing of the reagents: appropriate aldehydes (1.3 equiv) and Bestmann-Ohira reagent (1 equiv) in methanol or acetonitrile used as solvent with potassium *tert*-butoxide (1.2 equiv) in methanol, was achieved with a simple T-piece. After a residence time of 35 minutes using CFC as reactor (10 mL, 100 °C) the flow stream was directed through a series of scavenger columns. Quadrapure benzylamine resin (QP-BZA) operating at 70 °C was employed for removing the excess of aldehyde, Amberlyst-15 sulfonic acid (A-15) cartridge was subsequently employed for the removal of the base and the protonation of any phosphoric residues coming from the reagent and finally Amberlyst-21 dimethyl amine (A-21) resin gave the pure acetylene (Fig. 1). The final flow-stream was collected and evaporated to afford the desired product with the yields indicated in Fig.1.

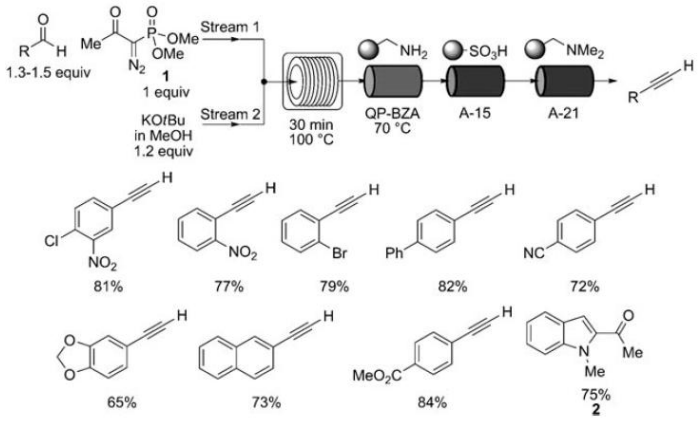

Figure. 1 Flow synthesis of terminal alkynes

Subsequently the flow sequence was incorporated in an extended process for the preparation of triazoles starting from alcohols, Bestmann-Ohira reagent and azides by multi-component couplings through multistep operation in the flow equipment. When the first stream with the appropriate aldehyde and Bestmann-Ohira reagent additionally contained an azide using acetonitrile as solvent, the reaction firstly followed the same trend explained above, but the fresh acetylene products passing through the CFC and

the scavenging columns underwent a further cycloaddition with the azide (Fig.2). This is achieved employing an immobilized copper(I) catalyst using A-21 resin (A-21 CuI) as basic support to give the triazole product, while a further Quadrapure thiourea (QP-TU) flow tube is necessary to ensure any leached copper during the cycloaddition process is removed in one step (Fig. 2).

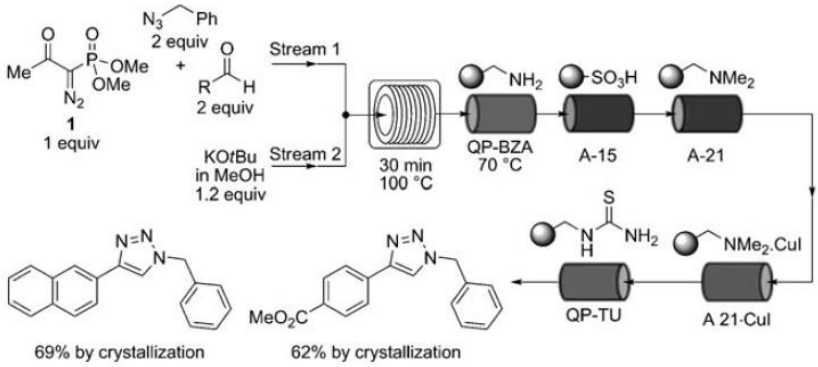

Figure 2. Two-step formation of triazoles from aldehydes

In those cases where the aldehyde was less available as starting material than the corresponding alcohol and the alcohol could be easily oxidized, the latter was used as reactant with the Bestmann-Ohira reagent coupled with an appropriate azide in acetonitrile instead of the aldehyde. The new generated stream was passed through an Omnifit tube packed with pre-activated PS-TsO-TEMPO at 60 °C, able to selectively oxidize the alcohol into the corresponding aldehyde without affecting the other reaction components. The deriving reaction mixture was then mixed with *tert*-butoxide in methanol trough the T-piece and subsequently passed through the CFC at 100 °C followed by the A-21 CuI resin for the formation of the triazole product. After that, four different purification steps, QP-TU, QP-BZA, A-15, A-21, were employed to obtain the desired triazole with 55% of yield and 95% of chemical purity (Fig. 3).

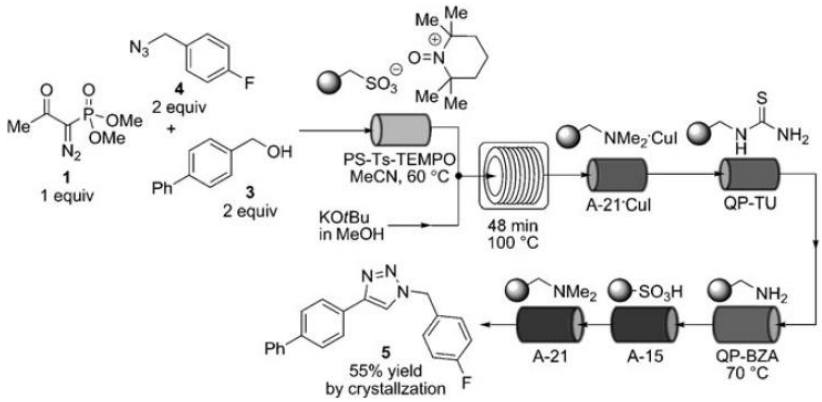

Figure 3. Three-step synthesis of triazole from alcohol

Comment of the considered paper

Solid supported reagents have widely dominated product purification in flow multi-step processes especially after the introduction of the concept of automation in organic synthesis extensively developed by Prof. Ley and his research group based in Cambridge[3]. At first glance, a publication with just two examples for the first extended flow process, and only one for the total synthesis using an alcohol as starting material may not seem one of the most noteworthy paper in this field. A deeper reading showed that, on one side, the reaction represented in Fig.2 links together an important product coupling process (azide and acetylene) with the preparation of potentially hazardous substrates (azide and acetylene) contained within the flow reactor. On the other side, this publication opened the path not just to a multi-step synthesis but also to an in-line multi-step purification. In fact, in the paper described above the part of in-line purification employing solid supports is well displayed especially in the multi-step total synthesis of triazole where we can observe a continuous sequence of four different functionalized supports to capture four different chemical species and finally obtain the desired clean product. Supported reagents are reactive species associated with heterogeneous support material[4]. Ideally, the use of such reagents should trap the impurities from the flow stream giving a pure product without any traditional work-up procedure (*i.e.,* chromatography, crystallization, distillation) fulfilling either electrostatic or covalent interactions

[3] B. Hinzen, S. V. Ley *J. Chem. Soc. Perkin Trans.* **1997**, *1*, 1907 –1908.
B. Hinzen, R. Lenz, S. V. Ley *Synthesis* **1998**, 977 – 979.
[4] S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson,A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer,S. J. Taylor *J. Chem. Soc. Perkin Trans.* **2000,** *1*, 3815 – 4195.

between the solid matrix and the unwanted species. The synthesis, including the in-line purification part described by Ley and co-workers, is a clear example of minimization of laboratory intensive operations, costs, space and enhanced safety for the chemists which do not to manipulate hazardous intermediates. Moreover, thanks to the extensive use of scavengers, a wide range of functionalised supports are now commercially available. However, while these materials are universally used for many applications, they have some limitations, especially when used in certain conditions. Aside from the higher per-mole cost compared with solution-phase equivalents[5], the solid matrix depletion over time negates the time/scale consistency that benefits flow chemistry, especially on large scale. Increasing the amount of the solid-supported reagents for the reaction scale-up or sequential runs, leads to unwanted and scale-depended dispersion/diffusion phenomena. As the solid-supported reagent cannot normally be processed/recycled continuously without parallel complex regeneration schemes and interruption of the flow sequence, such systems cannot operate in a real continuous fashion. Another important aspect to consider as a limiting step in flow synthesis is the low solubility of starting materials/resulting products during the flow operations. Crystallized species can block the reactor especially in its micro-tube part and of course this problem needs careful consideration before starting a multi-step reaction sequence. In-line scavenging processes which increase the purity of the flow stream can worsen the situation by making the precipitation a more likely occurrence. Consequently, this aspects have to be considered especially in the preparation of a library where different starting materials could have different solubility, or in the setting up of an unknown reaction. In both cases is recommended to initially run the reaction in a diluted mode to avoid blockage of the system. If running the reaction over a longer period of time can still generate a significant amount of desired product, a further evaluation on how to increase the concentration of the starting material (and therefore of the product) can be undertaken.

Original title of the considered paper: Continuous synthesis and purification by direct coupling of a flow reactor with simulated moving-bed chromatography

[5] www. sigmaaldrich.com

Bibliography of the considered paper: Alexander G. O'Brien, Zoltán Horváth, François Lévesque, Ju Weon Lee, Andreas Seidel-Morgenstern, Peter Seeberger Angewandte Chemie International Edition, 2012, 51, 7028-7030.

Summary of the considered paper:

In the cited paper, Seeberger and co-workers report on the association between flow synthesis and an in-line purification method using SMB (Simulated moving-bed) chromatography for the continuous production of pure product. To demonstrate their approach, the nucleophilic substitution (S_NAr) reaction of 2,4-difluronitrobenzene (1) with morpholine (Fig.4) affording a mixture of different products was selected as an example of complex reaction mixture to purify. Taking into account the possibility to change solvents, concentrations, and flow rate between the synthesis and the purification step, an initial experiment using a commercial flow reactor, Vapourtec R2+/R4 was set up. Solution 1 and morpholine, using ethanol as solvent, were mixed in a T-tube and heated at 100 °C in a steel loop connected with an in-line back pressure regulator (8 bar) to obtain the following mixture of products: ortho-2, para-2 and a disubstituted product 3, while the formation of salt 4, in this preliminary part was removed by batch aqueous extraction.

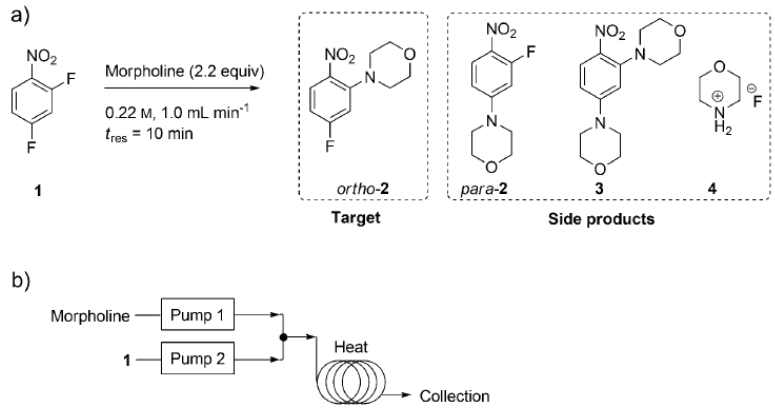

Figure 4. a) SNAr reaction of 2,4-difluoronitrobenzene (1) with morpholine under continuous flow condition; b) Plan of the flow system.

Subsequently, for the purification of the target compound (ortho-2), a classical four-zone SMB chromatography requiring that the desired product elutes as the first or the last compound in the mixture was selected (in this specific case, the ortho-2 component eluted last, when a reversed-phase chromatography was used). SMB-chromatography employed six in-series columns connected end to end,

while a counter-current between mobile and stationary phase (hydrophobic stationary phase and hydrophilic mobile phase) is simulated by shifting the two in-let and out-let following the direction of the mobile phase at stabilized times called shift time (171 s). Eluent and reaction mixture are inserted at opposite ends, while the tightly-retained target compound (extract) and the weakly-retained side products (raffinate) are collected at the two remaining positions. The feed input was provided directly by the flow reactor, but separate pumps drove any different zone (Fig.5).

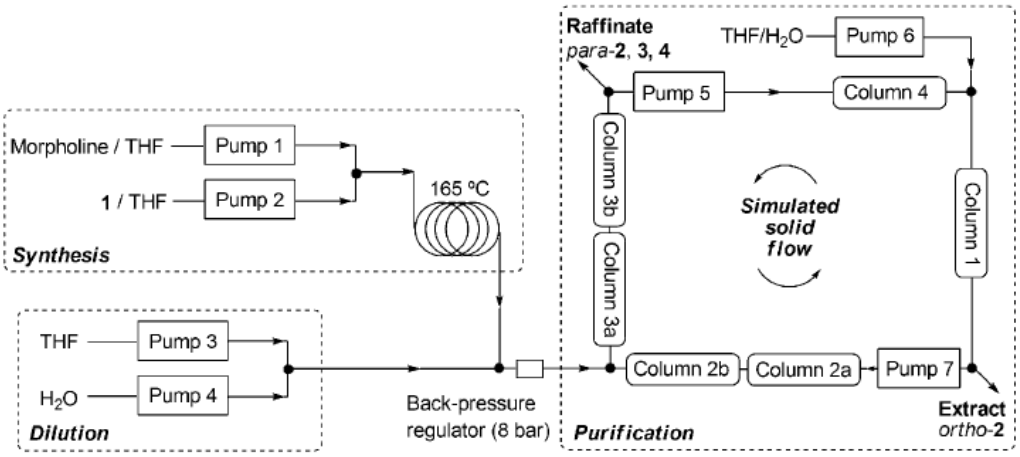

Figure 5. Schematic diagram of the directly coupled system

As predicted before, both solvents and concentration of the crude mixture were changed. Instead of using ethanol, because of the poor performance in the purification step, the authors replaced it with THF as ideal solvent for the described reaction (higher selectivity for the ortho-2 was observed) and a mixture of THF and water (40/60 v/v) for the in-line purification step. The temperature was increased at 165 °C ensuring a complete consumption of the starting material, while a second set of pumps was used to dilute the stream deriving from the flow reactor. After the connection of the two instruments, the flow reactor did not tolerate the high pressure generated in the SMB system so the flow rate was reduced from 10 mL/min to 5 mL/min by decreasing the dilution pumps. Because of the reduced feed flow rate, the feed throughput was kept by increasing the feed concentration. Fractions of the extract and raffinate were collected every cycles and analyzed by HPLC giving over 99% of purity for the ortho-2 while the raffinate contained the remaining products with just a small amount of ortho-2. In the final cycle, 89% of the desired product was obtained with equivalent purity between the fractions collected during the start-up and washing of the system.

Commentary of the considered paper

In-line purification is a bottleneck in continuous synthesis and often can negate the benefits associated with the use of flow reactors, unless the undesired products can be removed by precipitation or liquid-liquid extraction[6]. Solid supported reagents scavenging side products, as already explained in the comment of the previous paper, show limited lifetimes and cannot be operated in a continuous sequence without a regeneration process interrupting the flow procedure. Despite the development of numerous automated tools to increase the automation of this time- and cost-consuming task and reduce the environmental burden, often chemists necessitate to resort to batch chromatography columns for the separation of complex mixture of products, especially when they have same functional groups[7].

The paper described above was selected because it was the first example of successful coupling of flow synthesis and in line purification mediated by SMB chromatography to continuously produce a clean product. SMB chromatography processes, invented in 1960's by Broughton and co-workers[8] for the large scale-separation of n-paraffins is currently used in many industrial applications (e.g., petrochemical, food, and pharmaceutical industries). The basic concept behind the SMB chromatography is the simulation of the movement of the stationary phase in the opposite direction of the fluid to achieve a counter-current flow, rather than flowing fluids through one static bed. SMB chromatography utilizes, as explained in the selected paper, switching valves (different ports switching at finely calculated intervals) and multiple small chromatography columns, usually more than four, to induce what is effectively a counter-current movement of the stationary and mobile phase increasing the productivity with respect to batch method (single large column). The valve shifting time represents the counter-current stationary phase velocity. Rather than applying a feed containing the reaction mixture and a stationary phase and collecting fractions sequentially with one column, all fluid streams are simultaneously applied and withdrawn at appropriate points between the columns. When running at a steady state, the various stages of separation are carried out simultaneously by different columns in a continuous cycle. Despite this, the SMB chromatography presents several drawbacks: higher investment and maintenance costs, higher complexity compared to

[6] R. L. Hartman, J. R. Naber, K. F. Jensen, S. L. Buchwald *Angew. Chem. Int. Ed.* **2010**, *49*, 899-903.
T. Noël, S. Kuhn, A. J. Musacchio, K. F. Jensen, S. L. Buchwald *Angew. Chem. Int. Ed.* **2011**, *50*, 5943-4946.
[7] S. Newton, C. F. Carter, C. M. Pearson, L. de C. Alves, H. Lange, P. Thansandote, S. V. Ley *Angew. Chem. Int. Ed.* **2014**, *53*, 4915-4920.
[8] D.B. Broughton, G.G. Gerhold US Patent 2, 985,589 (1961)

single column operations, the most important is that currently available SMB systems are limited to a selection between the most strongly/weakly retained compound of a reaction mixture. Moreover, it seems not suitable for solvent gradient purification and a deep consideration of the pressure generated by the SMB system has to be considered before the connection with flow reactors.

In conclusion, SMB chromatography clearly has a great potential, in fact the method could be applied to various purification problems in the complex synthesis of organic compounds which generates several side products, it requires however a detailed evaluation of the operating conditions (e.g., linear adsorption isotherms, Henry constant, generated pressure) before the direct connection to a second instrument. The system highlighted in O'Brien paper is one the first true in-line purification system which is connected to a flow reactor and shows the potential to be widely applicable also in the case of multi-step reactions in a continuous flow but more development is necessary before SMB chromatography can became the most widely used in-line purification system.

Immiscible phase extractors connected with flow reactors

Original title of the considered paper: A prototype continuous-flow liquid-liquid extraction system using open-source technology.

Bibliography of the considered paper: Matthew O' Brien, Peter Koos, Duncan L. Browne, Steven L. Ley. Organic & Biomolecular Chemistry, 2012, 10, 7031-7036.

Summary of the considered paper:

The paper of Ley and co-workers reported on a step by step multi-disciplinary approach for the construction of a gravity based liquid–liquid separator able to continuously extract two different immiscible solvents. Using a combination of chemistry, engineering and informatics skills, a lighter phase (e.g., water) was firstly vigorously mixed with a heavier phase (e.g., dichloromethane) and then passed through a chamber presenting a coloured plastic ball for the recognition of the interface zone by the controlling software. At the steady state, the floating ball with a density in between the two liquids represents the demarcation point between the two solvents easily controlled by the programme. In fact, a web cam directly connected to the software, monitored the position of the flowing ball sending images back to it. The control system, elaborating the obtained information, can keep constant the phase level of the two

different fluids adjusting the flow rates of the up-stream pumps. The proof of concept study was carried on using a flow condensation to form hydrazones (Fig.6). The starting material containing benzaldehyde and pyridinium toluenesulfonat used as catalyst (PPTS 2 mol%) in DCM was reacted with a DCM second solution containing an excess of phenylhydrazine in a flow coil. The deriving reaction stream was then mixed using a T-tube, with a phosphoric acid water solution (1 M) to extract the unreacted hydrazine. The flow rate and loop dimension were set up to give a complete conversion in 48 s. An in-line mixer equipped with magnetic stirrer bars was positioned after the described junction to ensure the mixing of the organic and aqueous phase. The resulting biphasic stream was directed into a glass column containing the floating ball whose position was used to control the level of the different phases by the controlling software.

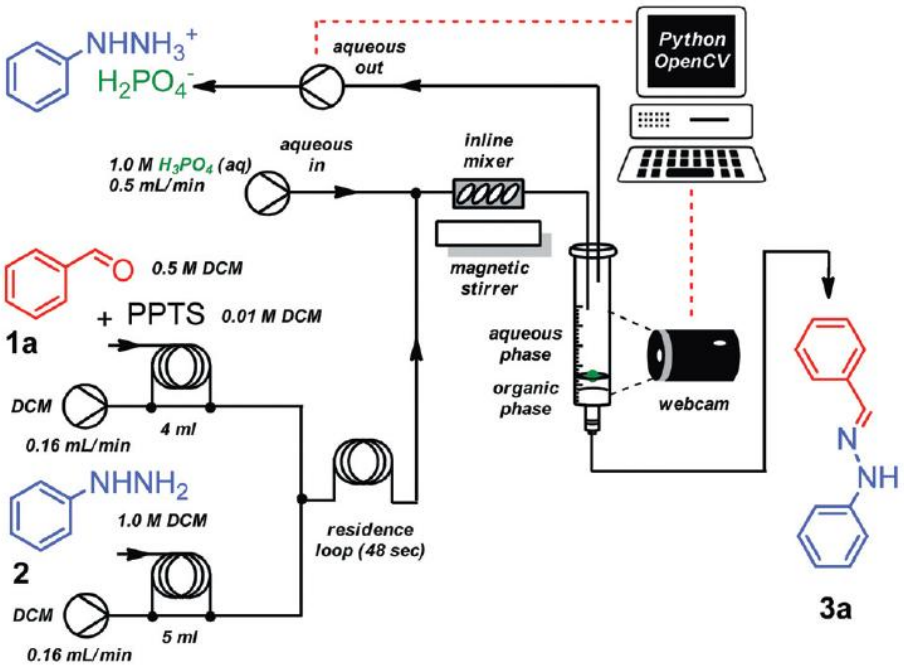

Figure 6. Flow set up used for hydrazone formations

These conditions were used for the synthesis and the in-line purification *via* extraction of a series of hydrazones in quantitative yield. As further examples of the application of this new separator, the epoxidation of a series of allylic alcohols with excess of *m*-CPBA and the BF3 promoted formation of dithianes starting from aldehydes were carried out. In the first case the excess of *m*-CPBA and its side products were extracted with a solution of sodium thiosulfate and bicarbonate. A residence time of 10 min was necessary to obtain complete conversion. In the second case, aldehydes stream and propane-dithiol-BF3 stream were reacted for 60 s before mixing the derived solution with aqueous sodium hydroxide to

quench the reaction and finally extract the dithiol excess. In all the reactions, product isolation was simply achieved by extraction of the reagent excess/impurities and solvent removal under reduced pressure.

Comment of the considered paper:

One of the more common work-up procedure in the laboratory is the liquid-liquid extraction based on the mixing and subsequent separation of different immiscible solvents. Although liquids can easily be continuously processed using pumps (extraction is the first way to purify also at industrial scale)[9], this process is considered one the most manually intensive and time/space lab consuming processes. It is not surprisingly, therefore, that a significant effort has been put into the development of machine-assisted platforms to automatically perform such a standard procedure. Ley and co-workers reported on the development of a liquid-liquid extraction system that could allow for the separation of any immiscible couple of solvents by using cheap and readily available hardware in combination with open-source software. The most important aim of the authors is the development of a purification system in continuous easy to modify and improve according to the needs of the operator and based on an easy way to separate two immiscible liquids with different densities: gravity. The base of this principle is that the target compound is in the denser phase such as dichloromethane while the impurities or side products in the light phase, for example aqueous phase. However, in order to have a truly continuous sequence of reaction synthesis and purification mediated by in-line extraction, several issues need to be considered. Firstly, after solvent mixing, phases have to be separated quickly to ensure a complete partition before the point of division. Secondly, the size of the vessel employed for the separation is a critical part of the process: it has to be sufficient to allow the phases to overcome surface forces which are dominant at very small scales. This can introduce a certain grade of dispersion/mixing. In fact, if on one side a vessel with a minimum width could minimize the volume mixing, and consequently the dispersion issue, on the other side a too narrow vessel can leave the phases without room to settle properly. The authors overcame the dispersion problem using a 10 mm diameter vertical cylinder. In fact it was a reasonable dimension for the continuous separation of a segmented flow of DCM/water as explained in the paper. Regarding the mixing of the two phases before their separation, a fast mixing was achieved using a 4 PTFE coated cylindrical magnets in a

[9] R. K. Sinnott, G. Towler *Chemical Engineering Design*, Butterworth-Heineman/Elsevier, Oxford, **2009**

4.7 mm bore tube through which the biphasic mixture was passed. This allowed the emulsification of the DCM phase with aqueous phase in a fast way (less than a second) and the immediate re-formation of the biphasic flow stream before passing into the separation vessel where heavy and light phases are separated by gravity. Another important issue to be addressed is the control of the interface position. They developed a "computer-vision" composed by a web-cam to constantly monitor the interface and a software based on open-sources and freely distributed libraries. The smart movement to facilitate the recognition of the interface position was to place a coloured plastic ball with a density in between the heavy and light phase. This was the reference point used by the software to calculate the height of the heavy phase and consequently to control the up-stream pumps. The system was able to keep constant (0.25 cm^3) the heavy phase for long period minimizing both dispersion and mixing problems. A significant advantage of such system with respect to solid supports is that reducing and keeping these volumes fixed, any dispersion will be scale independent. The paper presented is a clear example of a multidisciplinary approach (chemistry, engineering, and informatics) to reach the final aim, introduced by Prof. Ley, to have a complete automation in organic chemistry for a more efficient, and sustainable and innovative processes.

Original title of the considered paper: Multistep continuous-flow microchemical synthesis involving multiple reactions and separations.

Bibliography of the considered paper: Hemantkumar R. Sahoo, Jason G. Kralj, Klavs F. Jensen. Angewandte Chemie International Edition 2007, 46, 5704-5708

Summary of the considered paper:

In the selected paper, Jensen and colleagues reported on a surface-tension-based continuous micro-extractor for the separation of immiscible fluids such as gas-liquid and organic-aqueous phase. They described a full multi-step continuous microchemical synthesis of carbamates using the Curtius rearrangement of isocyanate including an "in between" purification step mediated by extraction and separation (Fig.7).

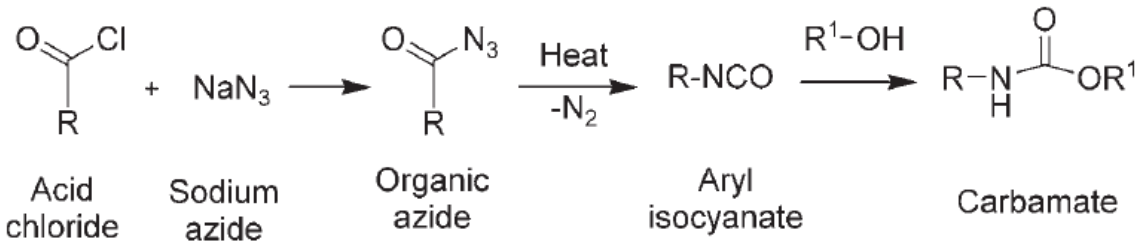

Figure 7. Carbamate synthesis as a case study

In the first step aqueous azide reacts with acid chloride to obtain the organic azide (the transformation of benzoyl chloride to benzoyl azide was achieved with a 98% conversion in 200 min of residence time). The subsequent continuous separation of the crude mixture was realized with the use of a micro-extractor coated with a high density thin porous (size: 0.1-1 µm range) fluoro-polymer membrane selectively wetted with organic solvent. The wetting with the organic solvent was used to prevent that the aqueous phase passes through the membrane while an imposed pressure drives the organic phase through its pores. An integrated pressure-control system keeps the desired trans-membrane pressure conditions. The throughput increases with the increasing pressure difference across the membrane. The maximum pressure limit is the capillary one. The second step was performed by heating the organic azide (90 °C) and packing the micro-device using a solid acid catalyst (H-modernite solid acid catalyst, HS-690 Wako Chemicals) to obtain a complete conversion into the corresponding isocyanate. The removal of the generated nitrogen was performed firstly in a second membrane separator by passing through the pores of the membrane the liquid phase, whereas the gas one did not. In the third step there was the generation of carbamate by mixing the previously formed isocyanate with the alcohol in a successive micro-reactor obtaining a complete conversion. In the second part of the paper a vial replaced the second gas-liquid extractor and was used also as a liquid supply for three subsequent concurrent different carbamate reactions: methyl phenyl carbamate, ethyl phenyl carbamate and benzyl phenyl carbamate (Fig.8).

In this second sequence the driving force for the separation of the gas/liquid phase was the density. Firstly, the vial was pressurized with helium leaving a small hole for the nitrogen to escape. Tube diameters and their lengths were adjusted for the control of the flow rate in the three different micro-reactor systems. Subsequently the vial was kept open and three syringe pumps were connected to the three different micro-

reactors. Despite the fact that this last method required more instruments, it was chosen has the best option. Continuous synthesis was operated for one week without any interruption of the flow and no change in the system performance.

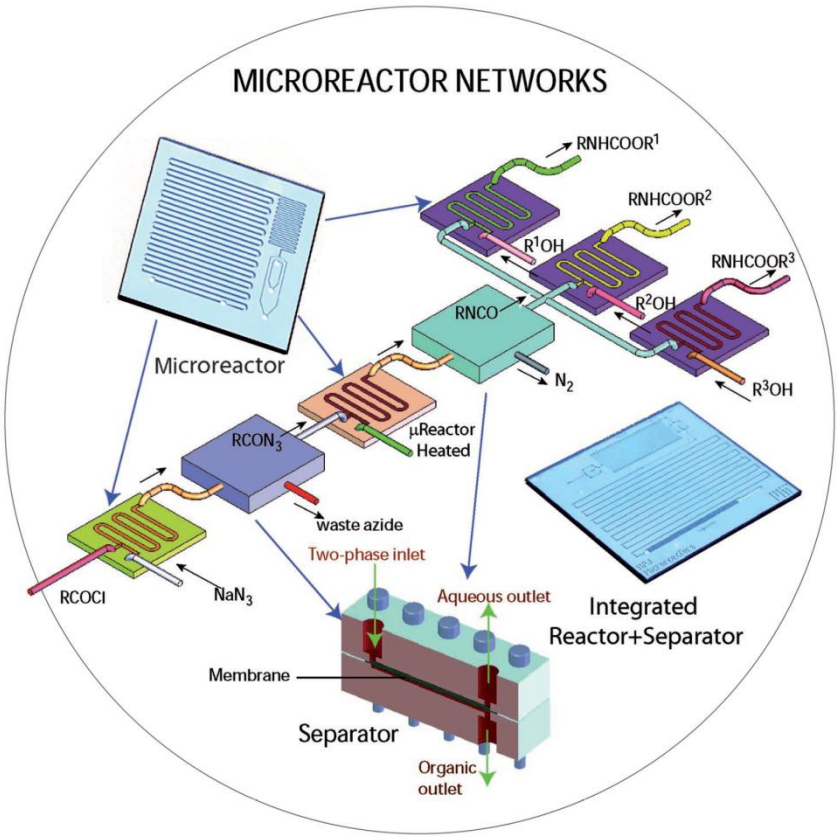

Figure 8. Reaction scheme of parallel synthesis of the three analogous carbamates.

Comment of the considered paper:

A typical chemical synthesis involves a sequence of multiple reactions with work-up between a precedent and successive steps. As it is known, extraction is considered the first step of the purification of a crude mixture. Typical work describing microchemical synthesis has been limited to a single reaction step[10], multiple reaction steps without any intermediate work-up[11], multiple steps with precipitation and

[10] V. Hessel, H. Lowe *Chem. Eng. Technol*. **2005**, *28*, 267-284.
P. Watts, C. Wiles *Chem. Eng. Technol.* **2007**, *30*, 329-333.
A. J. deMello *Nature* **2006**, 442, 394-402.
[11] H. Usutani, Y. Tomida, A. Nagaki, H. Okamoto, T. Nokami, J-i Yoshida *J. Am. Chem. Soc.* **2007**, *129*, 3046-3047.
D. Belder, M. Ludwig, L. W. Wang, M. T. Reetz *Angew. Chem. Int. Ed.* **2006**, *45*, 2463-2466.

consequent solid capture[12], or off-line work-up. The paper cited above is an elegant example of the potential of micro-reactors in multi-step synthesis with in-line purification mediated by an integrated micro-separator. The authors choice of carbamates, themselves active biological compounds and useful building blocks, is a good example as their synthesis leads to the formation of hazardous intermediates (azide and isocyanate), and is difficult to scale up using conventional batch methods. Moreover, in batch mode, the azide is typically gently heated to temperatures not much beyond the decomposition point to avoid uncontrolled release of energy[13]. The authors, performing the above describe reaction, took full advantage of continuous flow conditions: consumption of the intermediates *in situ* increasing the safety of the process, excellent heat transfer and chemical inertness using glass-coated silicon based micro-reactors, possibility of higher temperatures reducing the reaction time to obtain a complete conversion of the desired product and in-line purification extraction mediated without interruption of the flow. Solvent compatible micro-reactors combined with extraction systems allow continuous multistep synthesis from nanoliter to milliliter quantities and offer the possibility to quickly scale up the process to reach industrial scale. Moreover, this methodology avoids the use of precipitation and solid-phase capture agents as well as immobilized agents for scavenging reactive species, and it reduces the cost and the need of replacing/regenerating the solid phase. The basic principle of the liquid-liquid extractor described by Jensen and co-workers is the surface tension forces between the immiscible fluids instead of gravity as presented by Ley an co-workers. By exploiting the laminar flow features of micro-fluids devices, extraction happened by contacting of immiscible liquids in concurrent or counter-current flow.[14] Even though these systems offer the potential for more than one equilibrium extraction stage, often modest separation due to low ratios of interfacial surface to micro-channel volume was observed.[15] Phase separation in these systems is achieved by a small interfacial area to preserve the capillary pressure to balance the imposed driving pressure. Although systems using selective wetting of expanded porous materials and related phenomena

[12] I. R. Baxendale, J. Deeley, C. M. Griffiths-Jones, S. V. Ley, S. Saaby, G. K. Tranmer *Chem. Commun.* **2006**, *24*, 2566-2668.
I. R. Baxendale, C. M. Griffiths-Jones, S. V. Ley, G. K. Tranmer *Synlett.* **2006**, 427-430.
[13] G. L'Abbe *Chem. Rev.* **1969**, *69*, 345-363.
[14] A. Aota, M. Nonaka, A. Hibara, T. Kitamori *Angew. Chem. It. Ed.* **2007**, *46*, 878-880.
[15] T. Maruyama, H. Matsushita, J-i. Uchida, F. Kubota, N. Kamiya, M. Goto *Anal. Chem*. **2002**, *76*, 4495-4500.
M. Tokeshi, T. Minagawa, K. *J. Chromatogr. A* **2000**, *894*, 19-23.

have been used to separate aqueous and organic biphasic mixtures,[16] their operation often requires quite careful control of the pressure differential across the membrane, placing limitation on their use. Additionally such system do not easily allow separation of immiscible organic liquid pairs (MeCN-Hexane, fluorous-non-fluorous) [17], and their life span is strictly related to the degradation of the coating membrane and its gradual dissolution in the flowing solvent or its susceptibility to chemical attacks. On the other hand, the versatility of this micro-devices was highlighted by not only the possibility of a liquid-liquid extraction but also a separation of gas-liquid phase as described in the carbamate synthesis. Instead, the replacement of the second micro-extractor with an open vial lead to have an unpressurized system and, on the other side, it requires the use of three different syringe pumps making the experimental set up bulkier and more expensive than the active pressure-drive system. The novelty of this system is the continuous multi-step synthesis with "in between purification *via* extraction" with the concurrent synthesis of three different compounds. This process could be expanded to a number of different compounds, and the described continuous operation mode could be scaled up by increasing the run time or the number of concurrent systems.

Distillation apparatus in flow chemistry

Original title of the considered paper: Multistep microchemical synthesis enabled by microfluidic distillation

Bibliography of the considered paper: Ryand L. Hartman, John R. Naber, Stephen L. Buchwald, Klavs F. Jensen. Angewandte Chemie International Edition 2010, 49, 899-903.

Summary of the considered paper:

Buchwald and Jensen joint effort yielded the first example of a microfluid process in which distillation was used to achieve a solvent switch in telescoped chip-based reaction system for the preparation of aryl triflate and subsequent Heck reaction. This integrated process was comprised of different steps: aryl triflate synthesis step, obtained by reacting phenol with trifilic anhydride in the presence of N,N-

[16] E. Kolehmainen and I. Turunen *Chem. Eng. Process.* **2007**, *46*, 834–839;
C. H. Hornung, M. R. Mackley,I. R. Baxendale and S. V. Ley *Org. Procecc Res. Dev*. **2007,** *11*, 399–405;
O. K. Castell, C. J. Allender and D. A. Barrow *Lab Chip* **2009**, *9*, 388–396;

[17] E. Perperi, Y. L. Huang, P. Angeli, G. Manos and D. J. Cole-Hamilton *J. Mol. Catal. A: Chem*. **2004**, *221*, 19–27;
E. L. Teo, G. K. Chuah, A. R. J. Huguet, S. Jaenicke, G. Pande, Y. Z. Zhu *Catal. Today* **2004**, *97*, 263–270;
J. F. B. Hall, X. Han, M. Poliakoff, R. A. Bourne and M. W. George *Chem. Commun.* **2012**, *48*, 3073–3075.

diisopropylethylamine (DIPEA); a membrane based liquid-liquid extraction step by mixing the organic phase (dichloromethane, DCM) with aqueous HCL and for the production of segmented flow in the microchannel before the separation of the two different immiscible phases; a gas-liquid segmented flow was formed by combining nitrogen with the flow stream in the distillation device in which DCM containing the desired triflate was switch in favour of either toluene or dimethylformamide (DMF); and finally a reaction between the resulting solution and the n-butyl vinyl ether using a palladium catalyst at 125 °C. Distillation firstly was carried out at 70 °C, above the boiling point of DCM (40 °C) but below that one of toluene (110 °C) or DMF (153 °C). Under these conditions, DCM was selectively vaporized whereas the desired triflate product remained in the liquid phase. A subsequent gas-liquid separation at the end of the distillation apparatus was conducted with a polytetrafluoroethylene (PTFE) membrane letting to the liquid phase to pass trough but not the gas one by exploiting the differences in their surface tension (Fig. 9).

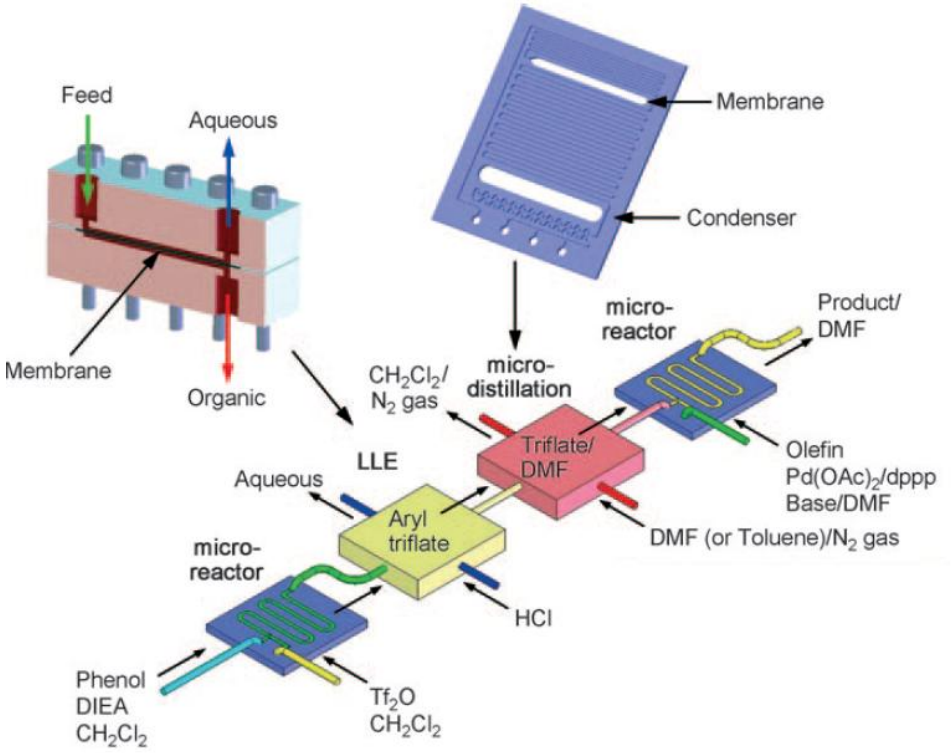

Figure 9. Reaction and separation scheme for continuous flow synthesis involving solvent switch using microfluid distillation

An increase in the distillation temperature was subsequently studied. Analysis of the sample exiting the last microreactor elucidated the extent of the reaction (Tab.1) in which the residence time are shown; DCM

composition, conversion of aryl triflate and yield of the Heck product with increasing of distillation temperature.

Table 1: Residence time (t), CH_2Cl_2 composition, conversion, and yield as a function of distillation temperature.

T [°C]	t [min]	CH_2Cl_2 [vol%]	Conv. ±s.d. [%][a]	Yield ±s.d. [%][a]
110	5.1	9.6	47.1±8.7	42.8±5.9
120	5.5	7.1	67.6±4.5	57.5±4.1
125	8.1	6.0	96.3±0.4	76.8±0.7

[a] s.d. = standard deviation for three samples.

Increasing the temperature increases the amount of volatile solvent separated from the stream containing the product, which decreased the volume fraction of DCM, increased the concentration of the triflate, and decreased the flow rate of the product stream. Increasing the concentration of the aryl triflate entering the final reactor increased the reaction rate but decreased the total flow rate resulting in a longer residence time. Batch experiments were conducted in order to understand the influence of residual DCM on Heck reaction and it was found that the reaction was more efficient in pure DMF, and increasing the fraction of DCM decreased the product yield (reduction of the triflate was observed). The process describe by Jensen *et al*. also was integrated with PID: proportional-integral-derivative for the fine control and regulation of the temperature in every reaction step.

Comment of the considered paper:

When a flow multi-step synthesis process is designed, one of the major consideration that has to be taken into account is the solvent compatibility between the different reaction steps. If in an ideal process both solvent and reagent concentration should not be changed, and any extraction/separation processes are avoided, in reality, such scenario is not feasible due the inevitable necessity to quench, work-up and purify crude reaction mixtures. Moreover, solvent switching is considered a very time consuming process and most of the times it is performed by manual intervention between the different stages. Despite the major of the attention is now paid to the development of automated devices and new strategies for handling

solids in flow, few new example of in-line evaporation and distillation were reported[18]. The distillation process is an important method for the separation of crude reaction mixtures and can allow for both in-line purification and solvent exchange. Distillation procedures operate by exploiting the differences in volatility between components in the same liquid mixture and their most notable limitation is that they can be applied just for liquids and not inflammable reaction mixtures. Another aspect to consider, especially upon increasing of the temperature of the distillation processes in multi-step flow synthesis, is a fundamental change of the operations, as demonstrated in the selected paper by Jensen *et al*. Adjusting just the temperature, without taking into account the flow rate, can potentially change the entire outcome of the downstream process. Traces of the desired product could be found in the vapour phase and loss of a product in a chemical reaction is a common goal to aim for. Maximization of the solvent separation and minimization of the product loss can be achieved using a more selective separation device or performing multistage distillation with lower operating temperatures. Despite the fact that microfluid distillation, based exclusively on boiling point differences, is challenging because of the domination of the surface forces over gravity (especially in micro-scale processes), by using a gas-liquid segmented flow in connection with gas-liquid separators these limitations could be overcome.[19] Moreover, combining microfluid distillation with multiple reaction steps can offer an important tool for synthetic organic chemistry. For example, the procedure presented in the paper cited above about in-line switch of solvents during a flow synthesis by microfluid distillation can be potentially used as in-line product purification. A notable advantage of this process is that the gaseous stream leaving the device can be passed through a condenser to recover the evaporated solvent, ready for recycling. Furthermore, the integration of multiple distillation stages can offer more selective separation and/or purification without interrupting the multi-step synthesis.

Handling of solids in a flow chemistry reactor

Original title of the considered paper: End-to-end continuous manufacturing of pharmaceuticals: integrated synthesis, purification, and final dosage formation.

[18] B. J. Deadman, C. Battilocchio, E. Sliwinski, S. V. Ley *Green Chem* **2013**, *15*, 2050-2055
B. Z. Cvetković, O. Lade, L. Marra, V. Arima, R. Rinaldi, P. S. Dittrich *RCS Adv*. **2012**, *2*, 11117-11122
[19] R. L. Hartman, H. R. Sahoo, B. C. Yen, K.F. Jensen *Lab Chip* **2009**, *9*, 1843-1849

Bibliography of the considered paper: Salvatore Mascia, Patrick L. Heider, Haitao Zhang, Richard Lakerveld, Brahim Benyahia, Paul I. Barton, Richard D. Braatz, Charles L. Cooney, James M. B. Evans, Timothy F. Jamison, Klavs F. Jensen, Allan S. Myerson, and Bernhardt L. Trout Angewandte Chemie International Edition, 2013, 52, 12359–12363.

Summary of the considered paper:

In the selected paper Trout *et al*. reported on the first end-to-end integrated continuous process for the preparation of a pharmaceutical product. The plant described in the paper starts from a chemical precursor and performs all the intermediate reactions, separations, crystallizations, drying, and formulation, which results in a formed final tablet in one finely controlled process. The results presented in the paper are referred to ten days of continuous operations. The target API is aliskiren hemifumarate which is formulated as tablets containing 112 mg of the free base form of aliskiren. The process (Fig. 10) starts with reagent 1 that is melted and pumped into a tubular reactor at 100 °C, where it is mixed with amine 2 (10 equiv) and acid catalyst 3 (1 equiv), and reacts reversibly to compound 4. Workup is performed in-line by adding water and ethyl acetate under pressure to solubilize the reagents before cooling. The biphasic stream is separated using a membrane-based liquid–liquid separator that is scaled up from microfluidic flow applications. The organic phase contains only 1 and 4, whereas the aqueous phase removes 2 and 3. The separated organic phase is fed into a two-stage, mixed suspension, mixed product removal (MSMPR) crystallization process. The solution is cooled to 5 °C and mixed with the anti-solvent heptane. The slurry is then fed into an *ad hoc* built continuous filter. A thin layer of slurry is formed over a rotating porous plate, and is washed with ethyl acetate and ethanol. Vacuum is applied to the back side of the plate, and pulls the mother liquor and wash solvent through; then, the purified wet cake is scraped off and conveyed into another vessel. The concentration of compound 4 was monitored by a density flow cell and kept at 26.2 wt%. The second reaction is an acid-catalyzed removal of the Boc protecting group. This is carried out in a tubular reactor), where concentrated HCl is mixed with the slurry of 4 in ethyl acetate. Control of the concentration of 4 is necessary to maintain the appropriate equivalents of acid (16 equiv) in the reactor. The reaction is rapidly quenched on-line with NaOH (25 wt%), which would result in a large increase in temperature if performed in a batch process. Under continuous flow, the temperature of the reaction mixture exiting the quench

remains at around 40 °C, without any cooling. Work-up of the organic phase containing intermediate 5 requires a few steps. The main goal is to reduce the amount of water. The stream is continuously diluted with acetate causing the precipitation of NaCl salt deriving from the previous quench. Microfiltration membranes remove the solid. The concentration of the exiting solution was measured with an inline UV flow cell that is used to control the dilution stream. Lastly, the stream is passed through a packed column of molecular sieves to remove water. A final crystallization is performed to create and purify the final salt 6. Fumaric acid is added at a slight excess (0.55 equiv of acid relative to 5). The material initially forms the salt in the first MSMPR vessel at 20 °C, and then the yield is further increased by cooling in a second MSMPR vessel at -10 °C. The material was filtered and the wet cake diluted to the desired concentration as reported before. SiO_2 was added as excipient, important for the formulation of the API. Drying was also carried out in a device built *ad hoc*, and the final tablets with a defined geometry are formed using an extruder. The tablets are finally analyzed and met specifications for drug product quality.

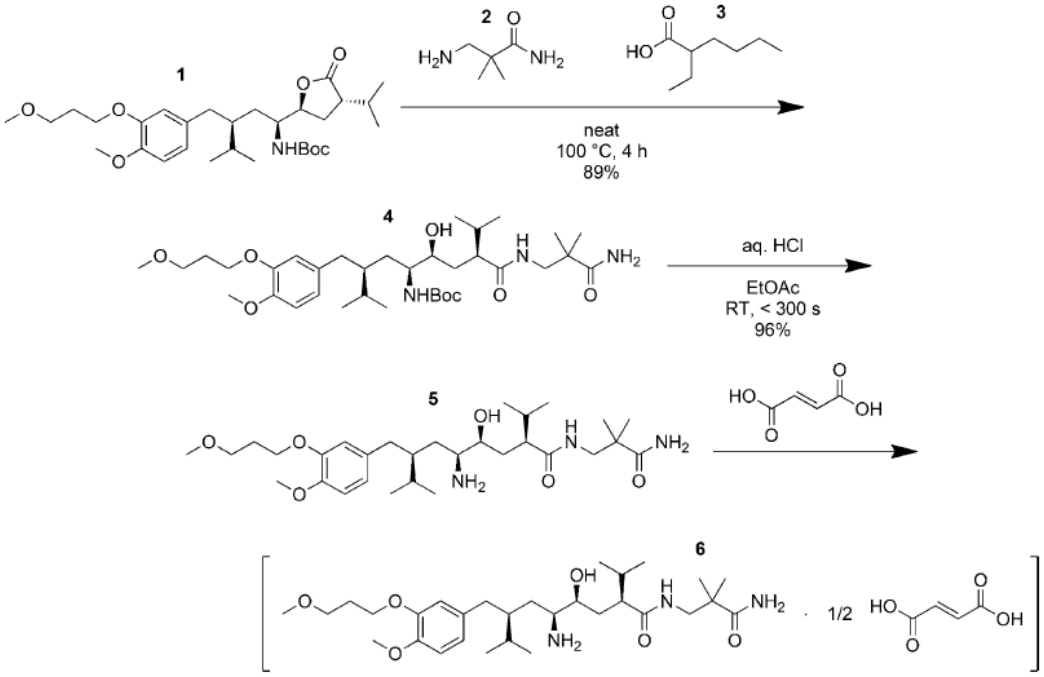

Figure 10. Synthetic steps from intermediate 1 to aliskiren hemifumarate (6)

Comment of the considered paper:

Despite the promising results of flow chemistry technology, there are still many hurdles to be overcome during the implementation of continuous processes. These include the development of flow chemistry connected devices able to process dry solids and solid-laden fluids. In fact, clogging of solids is a critical

problem in a flow reactor. One of the most important element for monitoring clogging events is the measure of pressure that always increases when there is formation of suspensions. Even though an ideal design of a multi-step process has to avoid precipitation, strategies to bring the process at the steady state or to prevent critical obstruction were studied. Switching the valves of the reactants and briefly flushing the reactor with an appropriate auxiliary solubilizing solvent immediately before the problematic point could be an option.[20] Alternatively sonication or pulse agitation while the reactants are flowing through the reactor can prevent the formation of particulate.[21] A number of specifically engineered reactors and plants were also developed for the continuous reaction with slurries,[22] and the paper selected is a very good example. Unfortunately, all these strategies are tailored and applied to specific synthetic problems, while a general solution is not available yet. During reactions involving precipitation, it is usually necessary to separate the solid fraction from the liquid one before any other additional steps. There are two desired outcomes that can be achieved through the design of a crystallization and filtration process: collection of the solid (filter cake residue) or collection of liquid (filtrate). In the cited paper whose importance is the innovation of a continuous process able to perform not only the chemical reactions but also the pharmaceutical formulation (tablets containing 112 mg of the free base form of aliskiren), two different crystallizations and filtration process lowering the temperature and using vacuum supported devices are carried out. In this case, in fact the aim of the system was to collect solids for downstream steps. The crystallizations and filtration/washings are optimized to minimize the amount of impurities carried into subsequent steps. The three temperature zones in the vacuum dryer expose the API to high temperatures for a shorter time, once the majority of the solvent is removed. Liquid-liquid separators were scaled up to microfluid to a larger flow application. Solids were handled with less difficulties in flow, where the solvents are mixed at temperatures above their boiling points, whereas in a batch process, cooling of the crude reaction mixture results in a highly viscous liquid that is difficult to mix. Because of improvements in the downstream steps using continuous flow technology the number of unit operation was reduced from 21 in

[20] C. B. Kelly, X. Lee, N. E. Leadbeater *Tetrahedron Lett.* **2011**, *52*, 263-265.
[21] J. Sedelmeier, S. V. Ley, I. R. Baxendale, M. Baumann *Org. Lett* **2010**, *12*, 3618-3621.
[22] C. Amador, A. Gavriilidis, P. Angeli *Chem. Eng. J.* **2004**, 101, 379-390.
B. Buisson, S. Donegas, D. Wray, A. Parracho, J. Gable, P. Caze, J. Jorda, C. Guermeur *Chim. Oggi* **2009**, 27, 12-14
S. L. Poe, M. A. Cummings, M. P. Haaf, D. T. McQuade *Angew. Chem. Int. Ed.* **2006**, 45, 1544-1548

batch to 14 in flow and the total process residence time 47 h, is nearly an order of magnitude shorter than the batch one (300 h). This provides a platform to test newly developed continuous technologies within the context of a fully integrated production system, and to investigate the system-wide performance of multiple interconnected unit. The process was designed to integrate several new pieces of continuous equipment and to avoid difficulties with the handling of solids, and to eliminate solvent swaps. The selected paper is an excellent example of academia-industry collaboration to obtain a fully designed, automated continuous plant for the development of a process which covers both the interest for a new flow-synthesis and the aspects connected with the formulation of the pharmaceutical that is ready to go on the market.

Conclusions

With the selected papers we tried to cover the essential aspects of in-line purification connected with flow reactors. With increasing automation in organic chemistry involving modern developments in technology, including computing, hardware and robotics the reaction outcomes can be rapidly maximized. This multi-disciplinary approach extended not only to chemistry but also to biology, engineering and materials science provides the key to success for the development of machine-integrated processes at industrial level. Technological advancements are constantly affecting the scientific world and while humans remain more important than machines, it is without doubt a wise move to design automated devices that are inherently more efficient than ourselves and can work in a continuous manner dramatically increasing the productivity.