Editorial

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In issue #4, I would like to commemorate our colleague and friend Prof. Jun-ichi Yoshida, who passed away on Saturday, September 14, 2019. He was one of our regional editors at *Journal of Flow Chemistry*. He also served as the president of the National Institute of Technology Suzuka College and was emeritus professor of Kyoto University. Most of all we will remember Prof. Yoshida for his excellent work in Flow Chemistry. He coined the term “Flash Chemistry” for ultrafast reactions which can be done selectively in microreactors by taking advantage of the fast mixing and the excellent heat control. He also pioneered the so-called “cation pool” method, which allowed to accumulate anodically radical cations at low temperature. These could be subsequently converted in the presence of nucleophiles in a very controlled and reliable fashion.

Generally, one cannot overstate the achievements of Prof. Yoshida in Flow Chemistry. He can rightfully be called one of the pioneers and legends of the field. Many of us, including myself, have found inspiration in his early work and have tried to follow his lead at the outset of our career.

On a personnel level, I always enjoyed talking to Jun-ichi. He was very supportive to young flow chemists. He was very social and loved drinking a good glass of wine or sake.

Prof. Yoshida’s death is a great loss for the scientific community and we will miss him dearly.

Prof. Dr. Jun-ichi Yoshida (1952–2019)

Timothy Noël.
November 19th, 2019.
Eindhoven, The Netherlands.

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Meet The Flow Chemist

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Education	1997–2002 Studies in chemistry Georg-August University Goettingen 2006 PhD in physical chemistry Georg-August University Goettingen on the kinetics of radical polymerization 2006–2008 Research Associate at the Centre for Advanced Macromolecular Design at the University of New South Wales 2008–2010 Senior Research Scientist Karlsruhe Institute of Technology
Position	2010–2017 Assistant/Associate professor Hasselt University 2018- Guest professor Hasselt University
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- 1) When did you start with flow chemistry? Describe the first paper or the first experiments.

At the beginning of my independent academic career we were facing batch-to-batch variation issues in our polymer synthesis projects and were looking for practical solutions. Since I was exposed to flow chemistry already during my PhD, we quickly came to the decision that we should try microreactors and bought our first reactor. Initially, we only wanted to use the reactor as a tool to produce precursor polymers on demand, but very quickly we realized the exiting opportunities that flow chemistry offered to polymer chemistry in general and made this a research topic in its own right. Our reactions did not just become more reliable as we had first expected, but also the precision of the materials that we made improved tremendously. Within a really short time span, flow chemistry had become the largest branch in our research and we started to build our own reactors.

- 2) What are the main benefits of flow that convinced you to use and implement this technology in your research?

My all time favorite is still reproducibility. Being able to redo a synthesis with almost the same result over time makes my physical chemistry heart that beats in this synthetic chemist's body jump with joy. This allows us to do so many things, from precise kinetic studies to running synthetic projects without issues from batch to batch variations. But right after reproducibility it is the easiness by which we can use flow chemistry in a modular fashion, ranging from classical reactor

telescoping to introduction of online monitoring. It is just such a big playground to work on, and we never run out of possibilities.

- 3) What do you think the future holds for flow chemistry?

We have seen over a short period of time how microreactors and flow chemistry has grown from an oddity to mainstream chemical synthesis. Just a decade ago, there weren't many people working in the field, and now almost every larger chemistry institute will have at least one dedicated research group working on flow processes. Photochemistry or electrochemistry have almost become unthinkable without the involvement of flow processes. Yet, in my opinion the true revolution is yet to come. The increasing integration of online monitoring gives access to a whole new way of doing chemistry. Since flow rates can be dynamically adjusted in flow reactions, screening and reaction optimization becomes much easier, and eventually can be taken over by machine-learning algorithms. Paraphrasing a famous quote, one should be careful with predictions, especially when they concern the future. But I think within a decade or two we will see a massive digitalization in chemical synthesis, and flow reactors will play a central role in this change. The job of a bench chemist is about to fundamentally change.

- 4) Do you have any relevant tips for newcomers in the field?

Don't be shy! I hear so often that researchers hesitate to step into flow chemistry, thinking they would need more knowledge in chemical engineering and/or would need to

buy expensive equipment. Both isn't necessarily true. Flow equipment can be surprisingly cheap when it is custom designed. And while flow chemistry requires a researcher to think in flow rates rather than reaction times, no deeper engineering knowledge is really required. Others have figured all these things out already for you. Most flow chemists will be happy to provide the help you need to step into it. Homogenous reactions are an ideal starting point to find your way, and you can grow from there. Using flow is much easier than you may think.

Provide your three most relevant papers related to flow chemistry, and describe in one or two sentences why they are noteworthy.

1. Precise polymer synthesis via autonomous self-optimizing flow reactors. M. Rubens, J.H. Vrijsen, J. Laun, T. Junkers, *Angew. Chem. Int. Ed.* **2019**, 58, 3183–3187. (As mentioned above, machine-assisted flow synthesis has the capacity to be a game changer in chemical synthesis. In this paper, we explored the combination of a flow reactor with online size-exclusion chromatography and machine-learning algorithms. The precision that these machines can reach are marvelous, and compound libraries are built without much human intervention.)
2. Kinetic Control of Aggregation Shape in Block Copolymer Self-Assembly. A.-L. Buckinx, K. Verstraete, E. Baeten, R. Tabor, A. Sokolova, N. Zaquen, T. Junkers, *Angew. Chem. Int. Ed.* **2019**, 58, 13,799–13,802. (Flow chemistry has not only advantages in pure synthesis, but can also deliver distinctive advantages for example in self-assembly or nanostructures. In this paper we showed how block copolymer self-assembly in a micromixer provides a much better alternative to classical batch-based approaches.)
3. Precision Synthesis of Acrylate Multiblock Copolymers from Consecutive Microreactor RAFT Polymerizations. J. Vandenberg, T. M. Ogawa, T. Junkers, *J. Polym. Sci. Polym. Chem.* **2013**, 51, 2366–2374. (This was one of our first publications on microreactor polymerizations, and I still highlight it in my talks today. It's simple, and yet demonstrates the high potential of flow chemistry for polymer synthesis ever so nicely.)

Meet The Flow Chemist

Name	Joerg Sedelmeier
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- 1) When did you start with flow chemistry? Describe the first paper or the first experiments.

I was first exposed to continuous flow technologies in 2008 as a postdoctoral researcher in the laboratories of Professor Ley at Cambridge University. Over two years in the legendary ITC flow laboratory I was lucky enough to work with fantastic people. We explored all sorts of chemistries and translated these into flow mode. We tackled chemical challenges and found innovative solutions to technical issues/obstacles. It was a truly great experience and ever since I have a passion for continuous flow technologies. Consequently, I join the Continuous Manufacturing Unit at Novartis in Switzerland for a second postdoc to learn what it means to develop and scale up flow processes in the pharmaceutical industry. Throughout my years as a permanent employee at Novartis and more recently at Hoffmann La Roche, I am supervising postdoctoral candidates in the discipline of flow chemistry to pass on my knowledge, passion and experiences.

- 2) What are the main benefits of flow that convinced you to use and implement this technology in your research?

In my role as a process chemist, I have been involved in late stage process development, clinical supplies and launch activities. Every project is different and has its individual issues and challenges. What remains constant across all processes I developed over the years is the uncertainty whether on scale-up from laboratory to (pilot) plant scale any unforeseen surprises arise. That is true in particular for organometallic chemistry where mixing behavior and thermal aspects are of high importance.

The benefits of high surface area to volume ratio and enhanced mass transfer and better heat management allow us to develop elegant processes for highly exothermic and rapid transformations. Exactly these chemical transformations are among the most challenging ones to be scaled in a reliable and robust fashion. Here, continuous flow technology strikes.

- 3) What do you think the future holds for flow chemistry?

Academic research groups across the globe demonstrate beautiful chemical flow process and technologies. Also, numerous pharmaceutical and biotech companies invest in continuous flow operations on drug substance and drug product. Overall, I feel that continuous flow technology today receives the required appreciation as a complementary technology to traditional batch manufacture. I believe that we will see more continuous operations on large scale in the near future.

- 4) *Do you have any relevant tips for newcomers in the field?*

Running an initial chemical reaction in flow mode is not rocket science. However, the learning curve can be rather steep and a coworker skilled in the art supporting the first trails is advisable. My advice would be to go to the lab and experience what it means to cut and connect tubings, to maintenance pumps, to unclog reactors and to learn about basic engineering aspects such as mixing time, residence time and Reynolds number etc.

Provide your three most relevant papers related to flow chemistry, and describe in one or two sentences why they are noteworthy.

- 1) Andreas Hafner, Mark Meisenbach, and Joerg Sedelmeier*, *“Flow Chemistry on Multigram Scale: Continuous Synthesis of Boronic Acids within 1 s”* *Org. Lett.* **2016**, 18, 3630.
- 2) Andreas Hafner, Paolo Filippini, Lorenzo Piccioni, Mark Meisenbach, Berthold Schenkel, Francesco Venturoni, and Joerg Sedelmeier*, *“A Simple Scale-up Strategy for Organolithium Chemistry in Flow Mode: From Feasibility to Kilogram Quantities”* *Org. Process Res. Dev.* **2016**, 20, 1833.

The timelines in the pharmaceutical industry for process development and supply are often very aggressive. These two conceptual manuscripts describe a toolbox approach to accelerate the development of boronic acid derivative in continuous flow mode using highly reactive organolithium reagents. A simple and robust laboratory setup provides already throughputs of about 5 mmol/min and the corresponding scale up setup of 30 mmol/min (370 g/h). This toolbox approach allows for fast feasibility assessment and scale-up to kilogram quantities in a short period of time without any need for re-development.

- 3) Andreas Hafner,* Valentina Mancino, Mark Meisenbach, Berthold Schenkel, and Joerg Sedelmeier*,

“Dichloromethylithium: Synthesis and Application in Continuous Flow Mode” Org. Lett. 2017, 19, 786.

The applicability of dichloromethylithium (DCMLi) as a reagent in organic synthesis, especially on a larger scale, is limited due to the labile nature of the metallic species. The generation of DCMLi from dichloromethane and nBuLi in traditional batch mode requires very low cryogenic temperatures (IT = −78 to −100 °C) to suppress consecutive degradation pathways. In continuous flow mode, DCMLi was “made & consumed” in 1 s and was successfully used for the synthesis of α,α dichloro carbinols and *Matteson* homologation of boronic esters.