

Conference Review

The 3rd Frontiers in Organic Synthesis Technology” (FROST3) focusing on the “Progress in Flow Chemistry”, organized jointly by the Flow Chemistry Society and Akadémiai Kiadó Zrt. (a Wolters Kluwer company – publisher of the *Journal of Flow Chemistry*) was held in Budapest on the 11th–13th October 2011. 58 people attended from all over the world, and 11 internationally renowned speakers presented their latest results. Since the last conference held in 2009 we have witnessed a rapid development of flow chemistry technologies, both in the applications and the reactor design.

Ferenc Darvas (Florida International University), chairman of the Flow Chemistry Society addressed a welcome speech to the audience.

In the opening presentation **Timothy Jamison** (MIT, Boston) reported several case studies in continuous flow multi-step synthesis applying various set-ups of their home made tubular reactors. On-demand generation of catalysts based on irradiation applications of photochemistry in continuous flow; superheating of low-boiling point solvents at high pressure resulted in a very short reaction time. He also gave examples of the safe application of hazardous reagents (HN₃, DIBALH) in various reactions in flow.

Paul Watts (University of Hull) discussed the application of microreactor and flow technology in various chemical reactions from mg to multikg scale. He also reported rapid optimization of reactions and scale-up of processes. He clearly differentiated the utility of ‘micro’ reactors (series of interconnecting channels – 10–300 μm in a planar surface) and ‘flow’ (or meso) reactors that have dimensions >300 μm (up to 5 mm).

Aaron Beeler (Boston University) described the synthesis of compound libraries containing unique (complex) molecules typically in 1–3 steps applying pulse flow technology. He also reported reaction screening of various complex molecules upon irradiation in a flow photochemical device in the absence and in the presence of photosensitizers.

Christian Stevens (Ghent University) gave an overview on how microreactor technology broadened the scope of industrial reactions. Better control of dangerous reactions (e.g. using HCN) and the flexibility of synthetic capacity would shorten the “time-to-market” period. Examples were also shown for the transformation of glycerol in flow originating from biodiesel production, which is a renewable building block.

Brian Wittkamp (Mettler-Toledo) presented the evolution of *in-situ* analytical probes leading to the development of *in-line* analytical devices. Faster structural information in real time would help to elucidate the reaction mechanism/



From left to right: *Claude De Bellefon* Associate Editor, *Volker Hessel* Regional Editor, *Ferenc Darvas* and *Paul Watts* Associate Editors, *C. Oliver Kappe* Editor-in-Chief, *Balazs Reffy* Senior Publishing Editor, *Pete Licence* Associate Editor.

pathway; the start and endpoint of the reaction; and allow stoichiometric reaction control in multi-step synthesis lines. The sensitivity is in the sub millimolar range. In-line analytics allows monitoring reactive intermediates and self-optimizing chemical reactions.

Richard Jones (ThalesNano, Budapest) described how to access novel chemical space through high temperature flash synthesis. He discussed the opportunities of flash chemistry and demonstrated it through various case studies (supercritical esterification, novel heterocycle synthesis using Gould Jacobs reaction under high p/T and vacuum flash pyrolysis). This technology could contribute to providing novel chemotypes for drug discovery.

C. Oliver Kappe (Karl-Franzens-University of Graz) demonstrated that high-temperature flow chemistry can also be a process intensification tool. Rapid heat transfer and temperature control of the reaction system; control of residence/reaction times could all contribute to the successful translation of microwave-assisted synthesis to flow chemistry and to opening novel process windows. He introduced and compared the performance of high-temperature/pressure flow reactors through several examples.

Dominique Roberge (Lonza Inc.) gave an overview on the industrial design, scale-up and the use of microreactors. The industrial design relies on the 3 different reaction categories: Type A reactions (Very fast <1 s, controlled by the mixing process), Type B reactions (Rapid reaction 10 s to 30 min, predominantly kinetically controlled); and Type C reactions (Slow reaction >30 min, Batch processes with thermal hazard). The industrial design includes the various ways of intensive mixing, to ensure the rapid mass transfer, and heat exchange.

Volker Hessel (Eindhoven University of Technology) in his presentation focused on how to reach novel process windows with process-design intensification by microreactors. He also set the Roadmap to Future Chemistry. Future factories could readily speed up chemistry through efficient transport, and realize a high level of system integration. Several case studies demonstrated the power of the method in the field of immobilized catalyst design, biocatalysis, hazardous reactions, click chemistry, superheated processes, etc.

Claude de Bellefon (CNRS Lyon) presented their latest results on designing multiphase microstructured flow reactors. First he discussed the major elements of the catalytic reactor design including mass transfer/heat and light management. Various reactors were described including reactors using segmented flow as well as a falling film reactor that uses a free gas/liquid bi-continuous contactor. He also investigated the kinetics of the reactors.

Sean Newton (Univ. Cambridge) described the application of an in-line analytical tool (React IR) in the synthesis of natural products ('flow-assisted natural product synthesis') and active drug molecules. ReactIR was used to automatically control the stream in multistep reactions based on the intensity of the intermediates. He also described the development of a tube-in-tube reactor for gas-liquid flow reactions.

Apart from the lectures, a panel discussion was organized with the participation of the speakers, who answered previously collected questions. Examples include: What is the key for adapting the flow technology by the industry? The speakers mentioned human factors ("will be adapted more by the younger generation", "education and training started among the undergraduates"), technological factors ("more advanced technologies", "*in-line* analytics"), economical and safety factors ("efficiency and safety are key drivers"), market factors ("a new market is required to sell instruments, immobilized catalysts", etc.). What are the major limitations of flow technology? The speakers referred to viscous material or precipitation; batch to flow transition, the lack of in-line purification; in multistep synthesis there is a dilution effect, a lack of immobilized catalysts and enzymes.

A poster session was also held for young investigators.

The majority of the Editorial board of the *Journal of Flow Chemistry* participated on the meeting either as speakers or as attendees. *Editor-in-Chief*, C. Oliver Kappe (Karl-Franzens-University of Graz); *Associate Editors*, Claude De Bellefon (CNRS Lyon), Ferenc Darvas (Florida International University), Pete Licence (University of Nottingham), Paul Watts (University of Hull); *Research Highlights Editor*, Toma N. Glasnov (Karl-Franzens-University of Graz); *Regional Editors*, Aaron Beeler (Boston University), Volker Hessel (Eindhoven University of Technology) attended the meeting.

György Dormán

Honorary Associate Professor
University of Szeged