Flow Chemistry Society

Founded in 2010

FROST7
2019
SUMMARY

F L O W C H E M I S T R Y S O C I E T Y

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October 29, 2019

The **FROST7**, the seventh event of the **"Frontiers in Organic Synthesis Technology"** conference series was held on the historical Margaret Island in **Budapest, Hungary** on **October 16-18, 2019, organized by the Flow Chemistry Society, Switzerland in collaboration with Diamond Congress, Hungary.**

FROST7 was **chaired** by **György Dormán** (University of Szeged) and **Holger Löwe** (University of Mainz).

The Chairs were supported by **7 Session Chairs**: Siegfried Waldvogel, Aaron Beeler, Simon Kuhn, Timothy Noël, Claude de Bellefon, Adam McCluskey, and C. Oliver Kappe, and **3 Poster referees**: Greig Chisholm, Kerry Gilmore and Mike Organ.

The conference program was designed to discuss the most innovative areas of flow chemistry with great future potential, focusing on flow photochemistry, electrochemistry, emerging technologies and recent trends in flow synthesis.

During the course of three days an outstanding line-up of **3 Keynotes** and **16 Invited Speakers** from 12 countries, 3 continents presented their cutting-edge achievements, innovative concepts, methodologies and technologies.

The presentations of FROST7 were very true to its title and nature:
Frontiers in Organic Synthesis Technology

Presentation highlights:

Progress in key areas: Flow photochemistry:

Aaron Beeler (Boston University) presented how the utility of many transformations for applications in synthesis, such as photochemical reactions to access complex cyclobutanes, reactions of diazo compounds to access structurally and stereochemically diverse cycloheptatrienes, and platforms to facilitate chemical synthesis in space. He emphasized the advantage of using ‘slug-flow’ in photoacycloaddition.
Telmesani, R., White, J. A., & Beeler, A. B. (2018). Liquid-Liquid Slug-Flow-Accelerated [2+2] Photocycloaddition of Cinnamates. ChemPhotoChem, 2(10), 865-869.
He also described the main objectives of the SpaceFlow project: e.g. carrying out useful chemical reactions in a microgravity environment; development of safe practices in the space and a core facility that can be used in the space stations. Chemistry in the space would include biphasic polymerization; and develepinhg new materials under microgravity and vacuum.
https://www.bu.edu/articles/2019/international-space-station-chemical-experiments/
Timothy Noel (TU/e, Eindhoven) gave an overview of his group’s photosynthetic methodology development. He first described an automatic Flow Chemistry Platform for mechganistic studies:
Kuijpers, K. P., Bottecchia, C., Cambié, D., Drummen, K., König, N. J., & Noël, T. (2018). A Fully Automated Continuous-Flow Platform for Fluorescence Quenching Studies and Stern–Volmer Analysis. Angewandte Chemie International Edition, 57(35), 11278-11282.

He exploited the Taylor flow in gas (oxygen) – liquid flow system for the oxidation of both activated and unactivated C-H bonds including selectively oxidize natural scaffolds, as a late stage functionalization.

Laudadio, G., Govaerts, S., Wang, Y., Ravelli, D., Koolman, H. F., Fagnoni, M., ... & Noël, T. (2018). Selective C (sp3)− H aerobic oxidation enabled by decatungstate photocatalysis in flow. Angewandte Chemie, 130(15), 4142-4146.

He also described Fe-catalyzed cross-coupling reactions in flow.

Wei, X. J., Abdiaj, I., Sambiagio, C., Li, C., Zysman-Colman, E., Alcazar, J., & Noel, T. (2019). Visible light-promoted Fe-catalyzed Csp2-Csp3 Kumada cross-coupling in flow. Angewandte Chemie.

Solar Energy was utilized in solvent-resistant and cheap luminescent solar concentrator based photomicroreactors.

Cambié, D., Dobbelaar, J., Riente, P., Vanderspikken, J., Shen, C., Seeberger, P. H., ... & Noel, T. (2019). Energy-Efficient Solar Photochemistry with Luminescent Solar Concentrator Based Photomicroreactors. Angewandte Chemie.

Finally he described the scale-up opportunities using laser beam in photochemical reactions.

Harper, K. C., Moschetta, E. G., Bordawekar, S. V., & Wittenberger, S. J. (2019). A laser driven flow chemistry platform for scaling photochemical reactions with visible light. ACS Central Science, 5(1), 109-115.

C. Oliver Kappe (Univ. Graz) covered the recent advances in flow photochemistry, presented his group's experiences in developing a range of modern and classical photochemical transformations in continuous flow including:

Benzylic bromination:

Chen, Y., de Frutos, O., Mateos, C., Rincon, J. A., Cantillo, D., & Kappe, C. O. (2018). Continuous Flow Photochemical Benzylic Bromination of a Key Intermediate in the Synthesis of a 2-Oxazolidinone. ChemPhotoChem, 2(10), 906-912.

Photoredox selective dehalogenation reactions: (tuning light intensity/wavelength screening)

Steiner, A., Williams, J. D., Rincón, J. A., De Frutos, O., Mateos, C., & Kappe, C. O. (2019). Implementing Hydrogen Atom Transfer (HAT) Catalysis for Rapid and Selective Reductive Photoredox Transformations in Continuous Flow. European Journal of Organic Chemistry, 2019(33), 5807-5811.

Iodoperfluoroalkylation:

Rosso, C., Williams, J. D., Filippini, G., Prato, M., & Kappe, C. O. (2019). Visible-Light-Mediated Iodoperfluoroalkylation of Alkenes in Flow and Its Application to the Synthesis of a Key Fulvestrant Intermediate. Organic Letters. 21, 5341-5345.

[2+2]cycloaddition including smart numbering-up for scale-up:

Williams, J. D., Otake, Y., Coussanes, G., Saridakis, I., Maulide, N., & Kappe, C. O. (2019). Towards a Scalable Synthesis of 2-Oxabicyclo [2.2. 0] hex-5-en-3-one Using Flow Photochemistry. ChemPhotoChem, 3(5), 229-232.

Photochemical bromine generation:

Otake, Y., Williams, J. D., Rincón, J. A., de Frutos, O., Mateos, C., & Kappe, C. O. (2019). Photochemical benzylic bromination in continuous flow using BrCCl 3 and its application to telescoped p-methoxybenzyl protection. Organic & biomolecular chemistry, 17(6), 1384-1388.

Also described scale-up chemistries in HANU large scale photoreactor, which is capable of handling photocatalytic slurry reactions.

Gellért Sipos (ThalesNano, Inc.) introduced their multifunctional photoreactor that is capable of performing batch and flow chemistry applying multiple wavelengths at a time, and shown the first applications of that instrument to a variety of photochemical transformations (including: photoredox transformation, Minisci reaction and side-chain bromination).

Progress in key areas: electrochemistry:

Csaba Janáky (Univ. Szeged) presented his laboratories recent results in electrochemical reduction of CO_2, a method for converting a greenhouse gas into value-added products, utilizing renewable energy. Electrochemical reduction of CO2 is a value-added approach to both decrease the atmospheric emission of carbon dioxide and form valuable chemicals. He presented a zero gap electrolyzer cell, which continuously converts gas phase CO2 to products without using any liquid catholyte.

Endrődi, B., Kecsenovity, E., Samu, A., Darvas, F., Jones, R. V., Török, V., ... & Janáky, C. (2019). Multilayer Electrolyzer Stack Converts Carbon Dioxide to Gas Products at High Pressure with High Efficiency. ACS energy letters, 4(7), 1770-1777.

He also discussed the importance of the catalyst morphology, using N-doped carbon (N-C) catalysts as a model system.

Siegfried Waldvogel (Univ. Mainz) introduced two modern approaches, including the electrosynthetic screening approach for exploiting the electricity driven conversions for synthetic purposes and to install unique selectivity. During electrosynthesis less or no waste generated and unique selectivity could be achieved.

Möhle, S., Zirbes, M., Rodrigo, E., Gieshoff, T., Wiebe, A., & Waldvogel, S. R. (2018). Modern Electrochemical Aspects for the Synthesis of Value-Added Organic Products. Angewandte Chemie International Edition, 57(21), 6018-6041.

He also described a highly modular electrochemical flow cell and its application in electroorganic synthesi such as anodic oxidative cross-coupling reactions.

Gütz, C., Stenglein, A., & Waldvogel, S. R. (2017). Highly modular flow cell for electroorganic synthesis. Organic Process Research & Development, 21(5), 771-778.

He introduced ElectraSyn 2.0 reactor from IKA. ChemElectroChem is a top-ranking electrochemistry journal.

Simon Kuhn (Univ. Leuwen) discussed the design of a electrochemical reactor with ultrasound actuators. As a proof-of-principle paired synthesis of bibenzyl (from benzyl bromide) and acetophenone (from 1-phenyl-ethanol) was described.

New synthesis platforms:

Kerry Gilmore (Max Planck Institute) has introduced their remotely accessible automated flow platforms for the standardized production of chemical data and the development of a radial synthesizer, the first instrument which does not require manual reconfiguration of the instruments between experiments. A chemical assembly system was developed, in which flow-reactor modules are linked together in an interchangeable fashion, thus, lacking the equipment redundancies. Several programmable multi-step syntheses were carried out using the system. The major element of the system is the central switching station.

Ref.:

Ghislieri, D., Gilmore, K., & Seeberger, P. H. (2015). Chemical assembly systems: layered control for divergent, continuous, multistep syntheses of active pharmaceutical ingredients. Angewandte Chemie International Edition, 54(2), 678-682.

He also emphasized that for applying flow reactions it is very important to understand the reaction mechanism, and analyse the degree of influence of the major paramereters.

Ref.:

Chatterjee, S., Moon, S., Hentschel, F., Gilmore, K., & Seeberger, P. H. (2018). An Empirical Understanding of the Glycosylation Reaction. Journal of the American Chemical Society, 140(38), 11942-11953.

Greig Chisholm's (Univ. Glasgow) described a modular robotic platform using a chemical programming language (Chemputer) which formalizes and controls the assembly of the molecules. Synthetic procedures are codified using a scripting language named Chemical Assembly (ChASM) which provides instructions for all currently implemented machine operations and supports the definition of functions and variables. It uses a graph approach–based XDL chemical descriptive language or XDL. The system is batch based and the round-bottom flask could be considered as the "transistor of synthetic chemistry".

The presentation a newly developed approach for direct, standardized translation of literature synthesis procedures into an executable, programmable algorithm. (it provides a direct connection between the conceptual steps and automation of the process).

Steiner, S., Wolf, J., Glatzel, S., Andreou, A., Granda, J. M., Keenan, G., & Cronin, L. (2019). Organic synthesis in a modular robotic system driven by a chemical programming language. Science, 363(6423), eaav2211.

Kitson, P. J., Marie, G., Francoia, J. P., Zalesskiy, S. S., Sigerson, R. C., Mathieson, J. S., & Cronin, L. (2018). Digitization of multistep organic synthesis in reactionware for on-demand pharmaceuticals. Science, 359(6373), 314-319.

Integration of flow synthesis and analytics:

Michael Organ (Ottawa University) described the various in-line purification technologies including continuous in-line extraction (removal of neutral impurities from charged products); simulated-moving-bed chromatography; in-line scavenging, electrophoretic separations; magnetic-separations. He also described the intelligent, multiconfigurative valve, which can also handle solids.

Tilley, M., Li, G., Savel, P., Mallik, D., & Organ, M. G. (2016). Intelligent Continuous Collection Device for High-Pressure Flow Synthesis: Design and Implementation. Organic Process Research & Development, 20(2), 517-524.

He also described IMPACT, the Implementation of Multidimensional in line chromatography technology for flow optimization.

Mimi Hii (Imperial College, London) demonstrated the value of adopting a data-driven approach to the development of synthetic chemistry. She described Synthesis 4.0 in the age of internet.

Bourne, R. A., Hii, K. K. M., & Reizman, B. J. (2019). Introduction to Synthesis 4.0: towards an internet of chemistry. Reaction Chemistry & Engineering, 4(9), 1504-1505.

This new concept is the basis of a new training program and linked to ROAR (Rapid On-Line Analysis of Reaction). Analogy of the Google Map and the Synthetic Map. The elements of the dial-a-molecule system: starting molecules /reagents /parameters/ equipments/ purifications/ electronic notebooks/ data capture/ standardization/ reaction scope and limitations. Flow chemistry provides huge data points and not only the good but also the bad data points should be collected.
Mennen, S. M., Alhambra, C., Allen, C. L., Barberis, M., Berritt, S., Brandt, T. A., ... & Damon, D. B. (2019). The Evolution of High-Throughput Experimentation in Pharmaceutical Development and Perspectives on the Future. Organic Process Research & Development, 23(6), 1213-1242.

New chemistries, reactors, applications:

Claude de Bellefon (CPE Lyon) discussed the recent challenges in continuous flow catalysis, and presented examples concerning reaction-extraction, solid catalysts transport as slurry for hydrogenation reactions, combination of slug or segmented flow (gas/ liquid/ solid) with Open Cell Foams (OCF) as catalyst supports for the exothermic hydrogenation of terpenes or screening of reactions.
Hwang, Y. J., Coley, C. W., Abolhasani, M., Marzinzik, A. L., Koch, G., Spanka, C., ... & Jensen, K. F. (2017). A segmented flow platform for on-demand medicinal chemistry and compound synthesis in oscillating droplets. Chemical Communications, 53(49), 6649-6652.
Heidrun Gruber-Woelfler (Graz University of Technology) discussed novel reactor technologies including 3D printing, focusing on the design and manufacturing of customized milli- and micro reactors for flow chemistry at real and optimized process conditions. The reactor was used for aerobic oxidation of Grignard reagents. The work was done in the framework of CCFlow grant.
Maier, M. C., Lebl, R., Sulzer, P., Lechner, J., Mayr, T., Zadravec, M., ... & Kappe, C. O. (2019). Development of customized 3D printed stainless steel reactors with inline oxygen sensors for aerobic oxidation of Grignard reagents in continuous flow. Reaction Chemistry & Engineering, 4(2), 393-401.
She compared the performance of continuous stirred tank reactors (CSTR) and true flow reactors.
Dusan Boskovic (Fraunhofer Institute) discussed process intensification and optimization, and the utility of continuous flow calorimetry in reaction heat determination as well as process spectroscopy for efficient reaction screening.
Westermann, T., & Mleczko, L. (2015). Heat Management in Microreactors for Fast Exothermic Organic Syntheses. First Design Principles. Organic Process Research & Development, 20(2), 487-494.
Adam McCluskey (University of Newcastle/Australia) showcased how various flow chemistry technologies (flow synthesis, hydrogenation, photochemistry, etc.) have enabled the synthesis of highly cytotoxic compounds targeting protein phosphatases, dynamin GTPase and most recently the arylhydrocarbon receptor. The driving force of the contemporary medchem is to find the most suitable technology for each target synthesis.
Chemoselective flow hydrogenation:

Hizartzidis, L., Tarleton, M., Gordon, C. P., & McCluskey, A. (2014). Chemoselective flow hydrogenation approaches to isoindole-7-carboxylic acids and 7-oxa-bicyclio [2.2. 1] heptanes. RSC Advances, 4(19), 9709-9722.

Photochemical bromination in flow:

Baker, J. R., Gilbert, J., Paula, S., Zhu, X., Sakoff, J. A., & McCluskey, A. (2018). Dichlorophenylacrylonitriles as AhR Ligands That Display Selective Breast Cancer Cytotoxicity in vitro. ChemMedChem, 13(14), 1447-1458.

Jean-Christophe M. Monbaliu lecture illustrated their most recent efforts in designing integrated, modular and scalable continuous flow processes for the preparation of active pharmaceutical ingredients (APIs) and analogs, in particular, the development of a general electrophilic hydroxylamination procedure using N-electrophyles (such as α-chloro-nitroso compounds) towards ketamines. These compounds are toxic and unstable species. For extractive purification Zaiput extractor was used.

Kassin, V. E. H., Gérardy, R., Toupy, T., Collin, D., Salvadeo, E., Toussaint, F., ... & Monbaliu, J. C. M. (2019). Expedient preparation of active pharmaceutical ingredient ketamine under sustainable continuous flow conditions. Green Chemistry. 21, 2952-2966.

Christof Aellig (Lonza AG) discussed solid handling ability and flow patterns of a baffle-less oscillatory flow coil reactor, exampling two reactions, a precipitation reaction and a phase transfer catalysis reaction with potential gas formation.

Eastern-Middle European:

Eastern Europe was represented by **Igor Plazl** (Univ. Ljubljana) who discussed the rapidly developing areas supported by artificial intelligence and machine learning approaches, while **Anna Śrębowata** (Polish Academy of Sciences) presented their applications of continuous-flow catalytic hydrogenation in formation of value-added products.

Flash Poster Presentations:

For the first time at FROST, four young scientists **Katharina Hiebler** (Graz University of Technology, **Christian Haas** (Philipps-Universität Marburg), **Ádám Tajti** (BME Budapest University of Technology and Economics) and **Martinez Morodo Romain** (University of Liège) had a chance to present their unpublished work in a form of a 5 minute flash poster presentation.

The conference was paired with an Open Lab-style program the **Flow Chemistry Academy**, where **the 3 exhibitors Syrris, ThalesNano, and ThalesNano-Energy** presented their instruments in operation, offering the delegates an access to a comprehensive learning experience.

The Flow Chemistry Society, in line with its tradition, encouraged young scientists to submit an original, unpublished work and again awarded excellent performance by granting **The Best Poster** and **2nd Best Poster Awards**. The winners, out of the **23 poster presentations**, were **Clarissa Benzin** (Hochschule Mannheim University) and **Lubomír Vána** (Institute of Chemical Process Fundamentals of the CAS, Prague). The winners were announced and presented with their prize at the **Gala Dinner.**

All together **75 participants** attended the conference, representing **16 countries**: Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Hungary, Italy, Japan, Netherlands, Poland, Slovenia, Switzerland, United Kingdom and United States.

While the number of exhibitors was low (3), the Exhibitors were very satisfied with the generated interest and leads.

The scientific level of FROST7 has been appraised highly by all Participants, and based on the immediate and later feedback, the conference set-up, the arrangement of the auditorium and exhibition area, and all social events, including the Gala dinner boat trip were very satisfactory and greatly appreciated.