Editorial

Flow chemistry is becoming increasingly popular in both academia and industry. What started off as an engineering curiosity has been embraced in the last decade by the chemistry community. Performing chemical reactions in flow reactors offers an increased control over the reaction conditions due to enhanced mass- and heat-transfer phenomena and can increase process safety and substantial reduction of the reaction times. Consequently, flow chemistry has been applied to a wide range of reaction types, some of which are difficult or impossible to carry out in conventional batch reactors.

The aim of this special issue is to gather together some of the most exciting work in flow chemistry by research groups in North America. In total 13 different research groups have agreed to contribute to this North America themed issue.

The issue kicks off with an interesting review from Dr. Xiao Wang (Harvard Medical School) on the use of continuous-flow reactors for hydroformylation reactions. The focus of this review is on catalyst design and how it can be retained or recuperated to increase the turnover number. A contribution from Jamison *et al.* (MIT) describes the continuous-flow preparation and purification of atropine, which displays anticholinergic and antiparasympathetic properties. Using three consecutive in-line liquid–liquid extractions resulted in a purity of >98% for the desired atropine. Another advantage of flow chemistry is the ability to prepare sensitive compounds in situ. This principle was demonstrated by McQuade *et al.* (Florida State University). They prepared three Zn–hydroxyquinoline complexes by directing the hydroxyquinoline ligands over a cartridge with crystalline sodium diethylzinc hydride. This strategy allowed to use this pyrophoric material outside of the glove box. Collins *et al.* (Université de Montréal) report an efficient flow methodology to prepare 11- to 26-membered macrocycles (14 examples) via a Cu-catalyzed azide–alkyne cycloaddition. A phase separation strategy was used to enable the use of relatively high concentrations. Another demonstration of the usefulness of flow chemistry for the preparation of API's was provided by Gupton *et al.* (Virginia Commonwealth University). They developed an efficient continuous-flow protocol for the synthesis of telmisartan (81% isolated yield) via a key Suzuki-Miyaura coupling to connect two functionalized benzimidazoles. Leadbeater *et al.* (University of Connecticut) demonstrated the preparation ethyl levulinate under superheated reaction conditions (270 °C) which could be performed in the absence of an acid catalyst. Continuous-flow technology can be also advantageous for applications in chemical biology. Jones *et al.* (Northeastern University) used a microreactor strategy to functionalize antibodies with an appropriate linker in a time-efficient fashion. The small length scales of microreactors is particularly advantageous for photochemical applications. The research team of Aaron Beeler (Boston University), one of the guest editors of this themed issue, demonstrated that a photochemical flow system can be used for rapid deprotection of amines in a multistep continuous flow synthesis. The photolabile 9-hydroxymethylxanthene protecting group proves to be stable under a wide variety of reaction conditions but could be easily removed under UV irradiation in flow. The scalability of ozonolysis reactions represents a challenging undertaking. Microreactors provide high mass transfer characteristics for gas–liquid reactions, however, the throughput remains low. Jensen *et al.* (MIT) demonstrated that mass transfer characteristics of a Corning advanced flow reactor are of the same order of magnitude as those obtained in a microreactor, however, the throughput can be significantly increased. The advanced flow reactor is an interesting reactor containing heart-shaped split-and-recombine mixers and enables an ozonolysis reaction to be scaled efficiently. Microreactor clogging is probably one of the greatest challenges for flow chemistry. Hartman *et al.* (University of Alabama) describe the phenomena associated with microreactor clogging in commercially available capillary tubing utilized for Pd-catalyzed aminations. Their paper gives some recommendations for overcoming clogging of microreactors. Gonzalez *et al.* (National Risk Management Research Laboratory) report an efficient and sustainable multicomponent reaction to prepare chromenes. Zuckerman *et al.* (Lawrence Livermore National Laboratory) have developed a safe protocol to prepare the highly explosive compound 2,6-diamino-3,5-

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dinitropyrazine-1-oxide (LLM-105) via a continuous-flow nitration reaction. The Moffatt-Swern oxidation is another classical reaction which is difficult to carry out in batch due to low temperatures (−70 °C) that are required to temper the exotherm. Marquardt *et al.* (MarqMetrix Inc., Seattle) have developed a continuous-flow for the Moffatt-Swern oxidation, which allowed them to work at −20 °C.

As you can see, this issue offers a lot of interesting research on flow chemistry from research labs in North America. Many of the aspects, that have brought flow chemistry to the forefront of R&D, are discussed in this issue. It is our firm belief that this special issue should be at the top of your reading list. We would like to express our gratitude to the colleagues and friends who contributed to this special issue their excellent papers.

Enjoy this special issue of *Journal of Flow Chemistry.*

Timothy Noël and Aaron Beeler
Guest Editors