RECENT ADVANCES IN ORGANIC SYNTHESIS IN FLOW

Reported by Emily Mumford March 12, 2019

BENEFITS OF ORGANIC SYNTHESIS IN FLOW

Flow chemistry has emerged as a useful engineering solution to some of the commonly encountered problems in the production of fine chemicals. Benefits of flow chemistry can include shorter reaction times, higher selectivities, easy scalability, greener synthesis, safer and/or reduced handling of dangerous reagents, better mixing, and access to higher temperatures and pressures. The basic components of a flow reactor- pumps, tubing, junctions, and reactor beds- can be connected in various orders or in tandem, allowing access to multistep and multicomponent reactions.

SYNTHETIC METHODS IN FLOW

Flow equipment enables a precise level of control over residence time, temperature, and mixing in the generation and trapping of highly reactive intermediates, preventing their over-reaction or decomposition, and resulting in high product selectivities. Recent work by the Yoshida group demonstrated high levels of selectivity in the trapping of aryllithium reagents in the presence of multiple electrophiles, which was enabled by better mixing and high flow rates.[1] Other work by this group demonstrated carbolithiation of benzyne and trapping of the biaryllithium by a variety of electrophiles.[2]

MULTI-STEP SYNTHESIS OF ACTIVE PHARMACEUTICAL INGREDIENTS IN FLOW

The development of multistep reactions in semi- and fully continuous flow has been successfully extended to include formulation of active pharmaceutical ingredients (APIs). The synthesis and formulation of aliskiren hemifumarate (Tekturna), a high blood pressure medication, from an advanced intermediate to a standard-dose tablet in fully continuous flow was a landmark achievement in this area.[3] The efficient chemical throughput in flow reactors has also been demonstrated in the "on-demand" production of APIs. In a modular, highly compact setup combining flow reactors with in-line extraction, crystallization, and formulation steps, commercially available chemicals can be transformed to drugs meeting USP standards at a rate of hundreds to thousands of doses per day.[4]

The enantioselective synthesis of Rolipram in flow was accomplished by Kobayashi and coworkers.[5] Packed-bed reactors were used at every step, with a polystyrene-supported calcium Pybox catalyst used for the key enantioselective addition of a 1,3-dicarbonyl compound to a β-nitrostyrene. The physical removal of products from catalysts was enabled by running this reaction in flow, which led to higher turnover numbers than batch, as well as simplified purification.[6]

Flow chemistry also facilitates the synthesis of drug candidates by reducing the need for handling of toxic high-containment intermediates and APIs. The Eli Lilly flow synthesis of prexasertib monolactate monohydrate, a checkpoint kinase 1 inhibitor, was operated under current good manufacturing practices conditions and provided material for human clinical trials.[7] This synthesis involves the production and automated purification of an intermediate with an occupational exposure limit of 1 μg/m^3.

HIGH-THROUGHPUT SCREENING AND AUTOMATED OPTIMIZATION IN FLOW

The use of in-line analysis by HPLC or LC-MS has made high-throughput screening and automated optimization of both discrete and continuous variables possible in flow. The high-throughput screening of discrete variables in the Suzuki-Miyaura reaction on a nanomolar scale in flow was undertaken by researchers at Pfizer.[8] Screening in flow enabled high efficiency (>1500 reactions/ day), use of stock solutions of reaction components in solvents different from the carrier solvent, and screening on a small scale which could not be carried out with volatile solvents at elevated temperatures in batch.

The application of flow chemistry to the automated optimization of continuous variables was demonstrated by Jamison and coworkers in a modular, reconfigurable flow reactor equipped with bays for heating, cooling, photochemistry, packed-bed reactors, and liquid-liquid extraction.[9] A patent has been filed for this system, which could improve access to flow chemistry and organic synthesis to non-experts, give faster optimization times, allow library synthesis and substrate scope evaluation under highly reproducible conditions, and enable the automated synthesis of useful amounts of fine chemicals.

THE FUTURE OF FLOW

Key challenges that remain in the application of flow to organic synthesis are the handling of solids, reliable translation of established chemistry from batch to flow, and the perception of flow as too specialized or inaccessible. However, flow will undoubtably continue to be a viable method for running organic reactions from a micro- to process scale, and efforts to meet these challenges will surely bring access to new and more efficient chemistry.

References:

1. Yoshida, J. et al. *Angew. Chem. Int. Ed.* **2015**, 54, 1914.
2. Yoshida, J. et al. *J. Am. Chem. Soc.* **2014**, 136, 12245.
3. Trout, B. et al. *Angew. Chem. Int. Ed.* **2013**, 52, 12359.
4. Jamison, T.; Jensen, K.; Myerson, A. et al. *Science* **2016**, 352, 61.
5. Kobayashi, S. et al. *Nature* **2015**, 520, 329.
6. Kobayashi, S. et al. *Chem. Eur. J.* **2012**, 18, 13624.
7. Cole, K. et al. *Science* **2017**, 356, 1144.
8. Perera, D.; Richardson, P.; Sach, N. et al. *Science* **2018**, 359, 429.
9. Jensen, K.; Jamison, T. et al. *Science* **2018**, 361, 1220.