Organolithium Chemistry in Flow: Continuous Synthesis of Boronic Acids within 1 second

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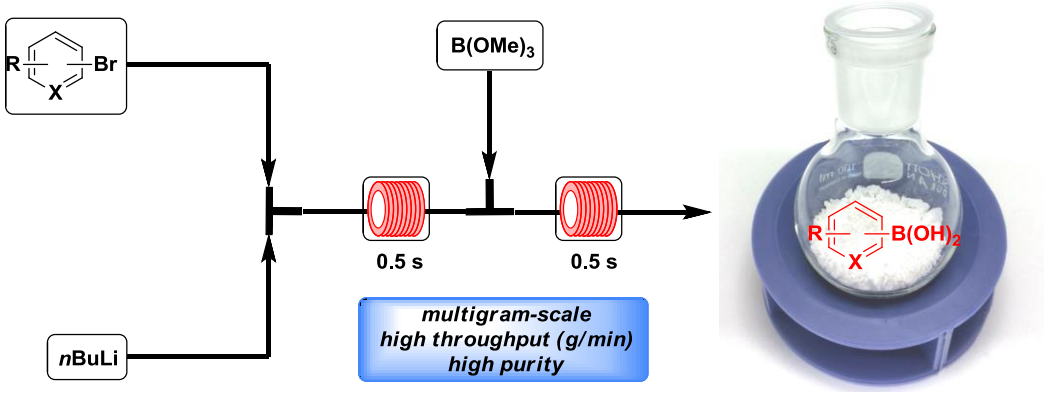
Continuous manufacturing (CM) or Continuous Flow Chemistry as a technical innovation aims to complement traditional batch operations by opening access to chemistries not easily accomplished in standard batch equipment, such as the handling of highly reactive or unstable intermediates.[1] As such, organolithium compounds are important intermediates in the pharmaceutical industry due to their high reactivity and broad applicability in organic synthesis.



Herein, we present the benefits and limitations of a simple continuous flow setup for handling and performing of organolithium chemistry on the multigram scale. The developed metalation platform embodies a valuable complement to existing methodologies, as it combines the benefits of *Flash Chemistry* (chemical synthesis on a time scale of <1 s) with remarkable throughput (g/min) while mitigating the risk of blockages.[2] The broad scope and high functional group tolerance was demonstrated by the synthesis of various boronic acids on multigram-scale (throughput ~ 300 mmol/h) in very high purity (>95% at 210 nm, after an extractive workup).

In addition a scale-up concept was developed, allowing for the rapid scale-up to even higher throughputs (~ 1800 mmol/h).[3]

[1] B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem., Int. Ed.* **2015**, *54*, 6688-6729.
[2] A. Hafner, M. Meisenbach, J. Sedelmeier, *Org. Lett.* **2016**, *18*, 3630-3633.
[3] A. Hafner, P. Filipponi, L. Piccioni, M. Meisenbach, B. Schenkel, F. Venturoni, J. Sedelmeier, *Org. Process Res. Dev.* **2016**, submitted.