Organic LETTERS

Letter

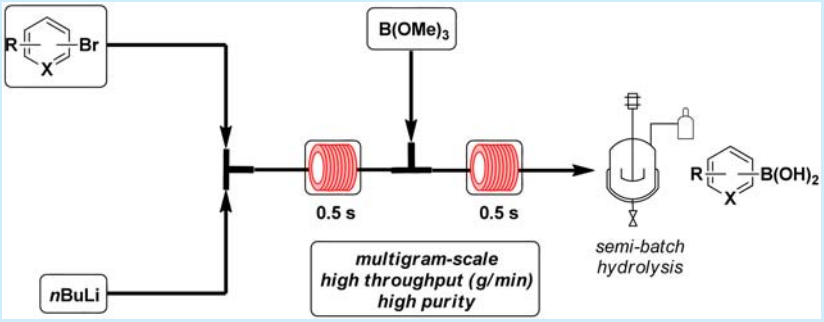
pubs.acs.org/OrgLett

Flow Chemistry on Multigram Scale: Continuous Synthesis of Boronic Acids within 1 s

Andreas Hafner, Mark Meisenbach, and Joerg Sedelmeier*

Novartis Campus, Novartis Pharma AG, 4002 Basel, Switzerland

Supporting Information



ABSTRACT: The benefits and limitations of a simple continuous flow setup for handling and performing of organolithium chemistry on the multigram scale is described. 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.

Continuous manufacturing (CM) as a technical innovation aims to complement traditional batch operations by opening access to chemistries not easily accomplished in standard batch vessels, such as the handling of highly reactive organolithium reagents and the generation and consumption of unstable intermediates.[1] Flow technology permits very good temperature control of low temperature transformations and rapid mixing of organolithium reagents and substrates, all examples of potential benefits over traditional batch mode. When performing organometallic chemistry in continuous flow mode, two alternative strategies apply to control the stability of an aryl lithium intermediate as a function of inner temperature (IT) and residence time (τ) (Figure 1).

As for the first strategy, the inner temperature is accurately controlled to low (cryogenic) temperatures (−50 to −100 °C), thereby increasing the half-life of an aryl lithium intermediate allowing for extended residence times (up to minutes) prior to an electrophilic quench (Figure 1a).[2] In this case, mixing efficiency plays a subordinate role and residence time (reaction time) is optimized to maximize the conversion of an aryl halide to the corresponding aryl lithium intermediate. A typical temperature profile (Figure 1a) for this approach starts at low temperature, e.g. −78 °C, followed by a first exotherm for the Hal/Li exchange, relaxation to −78 °C prior to a second exotherm for the electrophilic quench reaction, and relaxation to the initial starting temperature. This flow regime has several advantages such as an excellent temperature control and a reduced risk for clogging due to the wider reactor dimensions (compared to microstructured devices) and can be successfully applied in case the newly generated aryl lithium species is sufficiently stable at a given temperature and residence time prior to a desired quench.

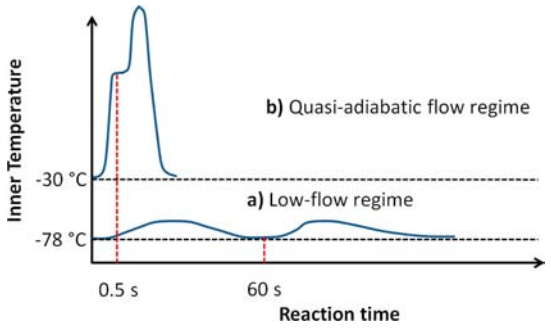


Figure 1. Temperature profile of a low-flow (a) and an quasi-adiabatic flow regime (b).

The second strategy, referred to as *Flash Chemistry* (chemical synthesis on a time scale of <1 s),[3] on the contrary focuses on instantaneous, highly efficient mixing at noncryostatic temperature in combination with very short residence times (<1 s) (Figure 1b). In this case the reaction time is defined by the mixing time and transformations occur under quasi-adiabatic conditions. This type of operation is typically performed in narrow dimensioned micromixers (ID = ∼ 0.25 mm) with excellent mixing properties which avoids decomposition through rapid trapping of the unstable aryl lithium species.

Received: June 10, 2016
Published: July 12, 2016

DOI: 10.1021/acs.orglett.6b01681
Org. Lett. 2016, 18, 3630−3633

There are various examples reported in literature demonstrating the synthetic power of chemical synthesis on a time scale of <1 s such as the generation and quenching of fragile aryl lithium intermediates in the presence of pendant electrophilic functionalities giving access to novel, impressive chemical transformations.[4]

Despite significant developments and advances in the area of organolithium chemistry applying CM technology,[5] an unmet need becomes apparent, when multigram quantities are required in a short period of time. Microscale flow devices used to prepare the initial small quantities of material for medicinal chemistry applications are no longer appropriate for larger scale, since their throughput is in general low (g/h) and maintaining these setups effective over an extended period of time is not easy due to its tiny channels which tend to clog.[2d] Thus, microscale flow processes require time-consuming redevelopment when more material is needed or high throughputs (g/min) are important; e.g during process development in pharmaceutical industry (Figure 2).[5]

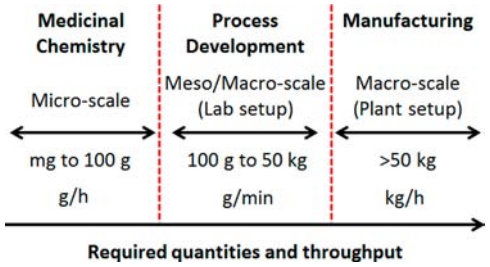


Figure 2. Development phases of a continuous manufacturing process.

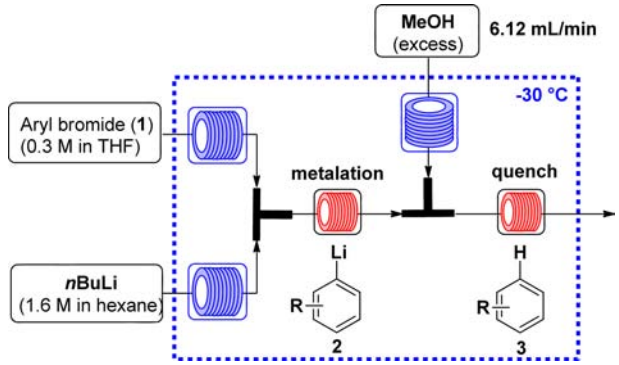
Inspired by the various advantages of *Flash Chemistry*, we envisioned to address this issue by combining the benefits of very fast chemical transformations with high throughputs and a straightforward setup broadly available to the scientific community. A setup fulfilling this criteria not only wouldallow mimicing the concept of flash synthesis in a macroscale device but also would accelerate a potential scale-up process, as it already produces enough material for early development studies (kg/d).

With respect to hardware selection, we were aiming for a simple, easy-to-use, broadly available setup ideally consisting of only ordinary, commercially available T-pieces (ID = 0.5 mm) and PFA tubing (OD = 1.6 mm or OD = 3.2 mm) allowing for flexibility and modularity. However, due to the fact that this setup does not deliver very short (<1 s) mixing times by default, we had to find a way to increase the mixing performance within the T-piece mixer. Röder et al. already demonstrated that the mixing efficiency of a T-piece strongly depends on the applied total flow rate.[6] Therefore, we started investigating the minimum total flow rate required (based on a given macro-lab-scale T-piece mixer with ID = 0.5 mm) to achieve efficient mixing in the range of <1 s under quasi-adiabatic reaction conditions.

For our investigations we used a flow platform for laboratory process development consisting of precooling loops for all reagent streams, PFA tubular reactors, continuous syringe pumps (Syrdos2), and pressure sensors for each reagent stream. The platform is software-controlled (HiTecZang) enabling for online monitoring of temperatures, flow rates, and system pressures as well as safety shut-down actions based upon operator predefined parameters thereby mitigating the risk of safety relevant incidents.

Prior to initiating the practical work, we compromised and defined essential prerequisites to accelerate the development process: (a) usage of commercially available *n*BuLi (1.6 M in hexanes), as no predilution is required and the reagent can be pumped directly from the cylinder; (b) aryl bromide concentration = 0.3 M, as our experience showed that this concentration can be applied to most substrates without problems of clogging; (c) use of PFA tubing as reactors (ID = 0.8 mm); (d) use of PTFE T-pieces[7] (ID = 0.5 mm) as mixing elements; (e) jacket temperature (JT) set to −30 °C, as this is the lowest temperature which is readily available using standard cooling devices (Scheme 1).

Scheme 1. General Setup for the Investigation of Mixing Performance for the Metalation Step: Flow Rate of Aryl Bromide (1) and *n*BuLi Was Changed over Time



Based on the assumption that Hal/Li exchange reactions are mixing-controlled, we started to investigate the mixing time (= reaction time) using the model transformation of 1-bromo-4-fluoro-2-(trifluoromethyl)benzene (**1a**) to 1-fluoro-3-(trifluoromethyl)benzene (**3a**) as depicted in Scheme 1. We assumed that the yield of the proton quenched product **3a** directly corresponds to the mixing performance of our setup and that the mixing performance of a simple T-piece is determined by the total flow rate applied. Therefore, in contrast to the general approach of optimizing the residence time of a reaction to achieve high conversion of starting material (strategy 1), we started optimizing the yield of **3a** *as a function of the total flow rate* (Figure 3).

For this set of experiments, parameters including concentrations, flow rate ratio, temperature, tubing, and T-piece

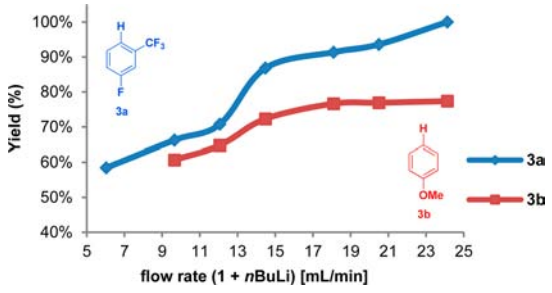


Figure 3. Yield (%) of electron-poor arene **3a** (blue) and electron-rich arene **3b** (red) vs total flow rate (mL/min) using a 100 ms reactor for Hal/Li exchange. Yield was determined via HPLC using biphenyl as internal standard.

DOI: 10.1021/acs.orglett.6b01681
Org. Lett. 2016, 18, 3630−3633

remained unchanged (Scheme 1). The only parameter being adjusted over the course of the experiments was the overall flow rate for the Hal/Li exchange maintaining a flow rate ratio of 4.85:1. The conversion of starting material **1a** to the corresponding MeOH-quenched product **3a** at different flow rates is depicted in Figure 3 (blue).

It can be clearly noticed that at the lower end of flow rates only moderate conversion can be achieved. However, the conversion increases significantly when flow rates >14 mL/min are applied, directly corresponding to the increased mixing efficiency within the T-piece mixer. Full conversion of **1a** → **3a** (yield >99%) was achieved using the described setup at a total flow rate (**1a** + *n*BuLi) of 24.1 mL/min at JT = −30 °C, which is in agreement with mixing times previously investigated by Röder et al.[6]

We were curious if changing the electronic nature of the aryl bromide from electron poor (**1a**) to an electron rich substrate (**1b**) would impact our initial finding, as these substrates tend to react slower in the Hal/Li exchange reaction.

Indeed, under analogous reaction conditions compared to conversion of **1a** → **3a**, 4-bromoanisole (**1b**) was not fully converted with *n*BuLi into the desired proton quenched product and **3b** could be only obtained in 77% yield (Figure 3, red). However, a similar significant increase in yield was observed when a total flow rate (**1b** + *n*BuLi) > 14 mL/min was applied. We decided to extend the residence time of our setup to make our setup more general and suitable for electron-rich as well as electron-poor aryl bromides. Eventually, when the residence time was adjusted to 500 ms, 4-bromoanisole (**1b**) was reacted to anisole (**3b**) in 90% yield at 14.5 mL/min and in 95% yield at a flow rate of >18 mL/min (Figure 4).

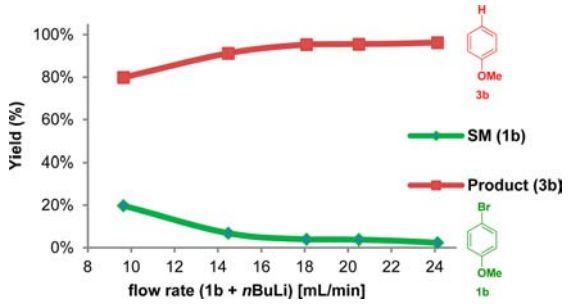


Figure 4. Yield of **3b** (%) vs total flow rate (mL/min) using a 500 ms reactor for Hal/Li exchange. Yield was determined via HPLC using biphenyl as internal standard.

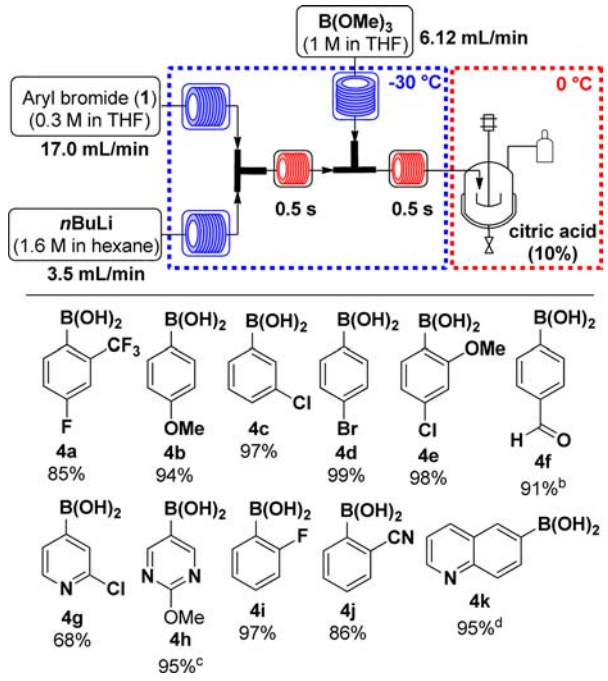
Based on our gained insight and experience we defined the optimal reaction and setup conditions suitable for the transformation of electron-rich and electron-poor aryl bromides. For future projects a total flow rate of 20.5 mL/min was used, as this is seen as a good compromise between throughput, consumption of starting material, and total flow rates achievable for most common laboratory pump modules, which should make our approach attractive also for academic laboratories.[8]

Boronic acids not only are important intermediates for Suzuki cross-coupling reactions, a reaction class of outstanding importance in pharmaceutical industry,[9] but also are coupling partners in many more modern chemical transformations.[10]

To demonstrate the usefulness of the described flow setup we applied our process to the synthesis of a variety of boronic acids. As we assume that the borylation of the lithiated intermediate **1** using trimethyl borate is also mixing-controlled, we imagined that the borylation step can also be performed within 500 ms due to the fact that the second step will benefit from an even higher total flow rate and mixing efficiency within the T-piece mixer. The reaction stream containing the boronate is finally quenched by aqueous citric acid in batch mode.

As summarized in Scheme 2, various boronic acids were rapidly synthesized using the described setup without any

Scheme 2. Multigram Synthesis of Different Boronic Acids within 1 s[a]



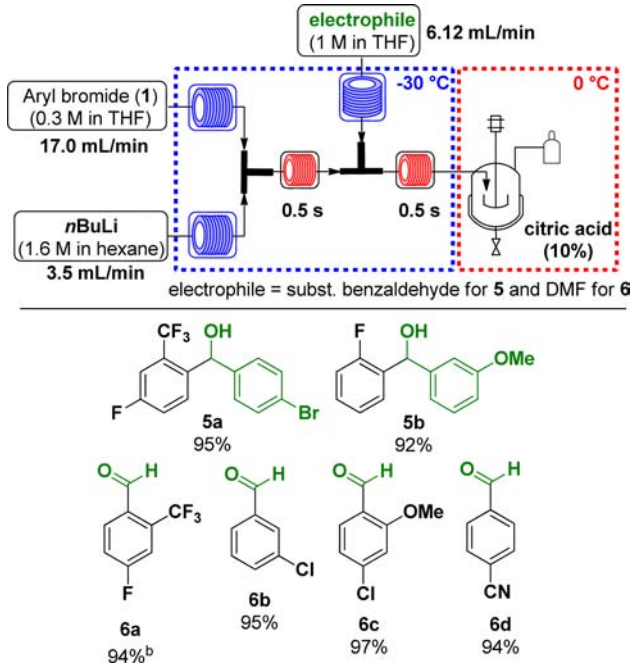
[a]Reactions were performed on 61.2 mmol scale (12 min run). Isolated yield is given. [b]Starting from the corresponding diethyl acetate. [c]System blocked after 8 min, HPLC yield is given (λ = 210 nm). [d]HPLC yield is given (λ = 210 nm) as boronic acid decomposed during workup.

further optimization or adjustments required. Electron-rich (**4b**, **4e**) as well as electron-poor substrates (e.g., **4a**, **4g**, **4i**) were readily converted into the corresponding boronic acids in good to excellent yields with a throughput of 5.1 mmol/min (~1 g/min). Most interestingly, aryl bromides bearing fluorine as well as cyano substituents, which are prone to undergo undesired side reactions or to decompose in the presence of *n*BuLi under conventional batch conditions, could be lithiated and borylated in high yield. Boronic acids bearing an aldehyde functionality (**4f**) are accessible from the corresponding 1-bromo-4-(diethoxymethyl)benzene. It should be noted that all boronic acids were synthesized in high purity (>95% by HPLC at 210 nm) following a simple extractive workup, allowing the straightforward synthesis of highly pure boronic acids in gram scale without the need for a time-consuming purification procedure.

In an effort to further expand the product diversity as well as to demonstrate the broad applicability of our flow platform, the third input stream was changed from trimethyl borate to other electrophiles to prepare compounds such as aldehydes and alcohols in one single operation (Scheme 3).

DOI: 10.1021/acs.orglett.6b01681
Org. Lett. 2016, 18, 3630−3633

Scheme 3. Multigram Synthesis of Alcohols and Aldehydes within 1 s[a]



[a]Reactions were done on 25.5 mmol scale (5 min run). Isolated yield is given. [b]HPLC yield is given (λ = 210 nm) as product is volatile.

In all cases the desired product was obtained in remarkable purity and high yield using the same reaction conditions as previously outlined. This shows the general applicability of this setup for different metalation reactions and allows the rapid and simple synthesis of different compounds in a straightforward manner.

In conclusion, we developed a simple flow setup consisting of broadly available, easy-to-handle macroscale equipment for the synthesis of various compounds following a reaction sequence of Hal/Li exchange and electrophilic quench. By optimizing the yield as a function of the total flow rate rather than residence time, it was possible to synthesize building blocks within a 1 s total reaction time and with a remarkable throughput of ~60 g/h.

This one setup allows for the preparation of small quantities for medicinal chemistry applications as well as for the delivery of larger quantities for early development phases with no need for a redevelopment of the chemical transformation. The straightforward concept greatly enhances the synthetic utility of organolithium moieties and appeals attractively to the scientific community. A concept for the seamless scale-up to larger quantities for late phase development will be reported in due time.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01681.

Detailed experimental procedures and spectral data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: joerg.sedelmeier@novartis.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are very thankful for the support of the Novartis Continuous Manufacturing Unit. In particular, we would like to thank Francesco Venturoni, Julien Haber, Jutta Polenk, Berthold Schenkel, and Christian Fleury. In addition, we would like to thank Christine Waldraff and Stephane Schmitt for analytical support.

■ REFERENCES

(1) (a) Gutmann, B.; Cantillo, D.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2015**, *54*, 6688. (b) Teoh, S. K.; Rathi, C.; Sharratt, P. *Org. Process Res. Dev.* **2016**, *20*, 414. (c) Desai, A. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 9223. (d) Hartman, R. L.; McMullen, J. P.; Jensen, K. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 7502.

(2) (a) Browne, D. L.; Baumann, M.; Harji, B. H.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2011**, *13*, 3312. (b) Newby, J. A.; Blaylock, D. W.; Witt, P. M.; Pastre, J. C.; Zacharova, M. K.; Ley, S. V.; Browne, D. L. *Org. Process Res. Dev.* **2014**, *18*, 1211. (c) Newby, J. A.; Blaylock, D. W.; Witt, P. M.; Turner, R. M.; Heider, P. L.; Harji, B. H.; Browne, D. L.; Ley, S. V. *Org. Process Res. Dev.* **2014**, *18*, 1221. (d) Laue, S.; Haverkamp, V.; Mleczko, L. *Org. Process Res. Dev.* **2016**, *20*, 480. (e) Sleveland, D.; Bjørsvik, H.-R. *Org. Process Res. Dev.* **2012**, *16*, 1121. (f) Kupracz, L.; Kirschning, A. *Adv. Synth. Catal.* **2013**, *355*, 3375.

(3) (a) Yoshida, J. *Flash Chemistry: Fast Organic Synthesis in Microsystems*; Wiley-Blackwell: Hoboken, NJ, 2008. (b) Yoshida, J. *Chem. Commun.* **2005**, 4509. (c) Yoshida, J.; Nagaki, A.; Yamada, T. *Chem. - Eur. J.* **2008**, *14*, 7450.

(4) (a) Nagaki, A.; Kim, H.; Yoshida, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7833. (b) Nagaki, A.; Ichinari, D.; Yoshida, J. *J. Am. Chem. Soc.* **2014**, *136*, 12245. (c) Kim, H.; Min, K.; Inoue, K.; Im, D. J.; Kim, D.; Yoshida, J. *Science* **2016**, *352*, 691. (d) Yoshida, J.; Takahashi, Y.; Nagaki, A. *Chem. Commun.* **2013**, *49*, 9896.

(5) Wheeler, R. C.; Benali, O.; Deal, M.; Farrant, E.; MacDonald, S. J. F.; Warrington, B. H. *Org. Process Res. Dev.* **2007**, *11*, 704.

(6) Schwolow, S.; Hollmann, J.; Schenkel, B.; Röder, T. *Org. Process Res. Dev.* **2012**, *16*, 1513.

(7) Bohlender GmbH. http://www.BOLA.de (accessed Jun 27, 2016).

(8) For example: (a) Syrris Ltd. http://www.syrris.com (accessed Jun 27, 2016). (b) Uniqsis Ltd. http://www.uniqsis.com (accessed Jun 27, 2016). (c) Vapourtec Ltd. http://www.vapourtec.com (accessed Jun 27, 2016).

(9) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Brown, D. G.; Boström, J. *J. Med. Chem.* **2016**, *59*, 4443. (c) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451. (d) Schneider, N.; Lowe, D. M.; Sayle, R. A.; Tarselli, M. A.; Landrum, G. A. *J. Med. Chem.* **2016**, *59*, 4385.

(10) For example: (a) Barluenga, J.; Tomas-Gamasa, M.; Aznar, F.; Valdes, C. *Nat. Chem.* **2009**, *1*, 494. (b) Battilocchio, C.; Feist, F.; Hafner, A.; Simon, M.; Tran, D. N.; Allwood, D. M.; Blakemore, D. C.; Ley, S. V. *Nat. Chem.* **2016**, *8*, 360. (c) Alam, R.; Vollgraff, T.; Eriksson, L.; Szabo, K. J. *J. Am. Chem. Soc.* **2015**, *137*, 11262. (d) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194.

DOI: 10.1021/acs.orglett.6b01681
Org. Lett. 2016, 18, 3630−3633