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A New Enabling Technology for Convenient Laboratory Scale Continuous Flow Processing at Low Temperatures

Duncan L. Browne,[†] Marcus Baumann,[†] Bashir H. Harji,[‡] Ian R. Baxendale,[†] and Steven V. Ley[*,†]

Innovative Technology Centre, Department of Chemistry, University of Cambridge,
Lensfield Road, Cambridge, CB2 1EW, U.K., and Cambridge Reactor Design,
Unit D2 Brookfield Business Centre, Cottenham, CB24 8PS, U.K.

theitc@cam.ac.uk

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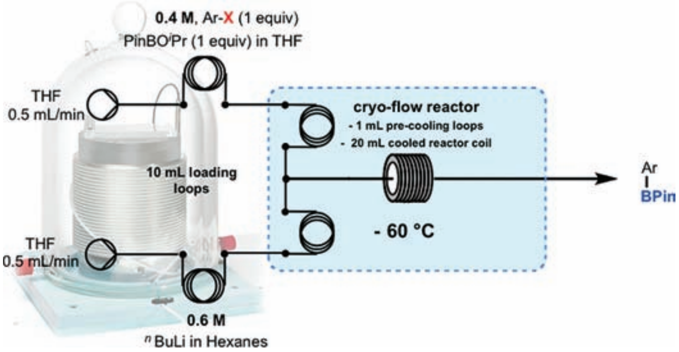
ABSTRACT



A new machine for conducting continuous flow processes at low temperatures on a laboratory scale is reported. The use of this cryogenic flow reactor has been demonstrated by the preparation of a variety of (hetero)aromatic boronic acids and esters via lithium halogen exchange chemistry. Furthermore, scale-up of the reaction conditions not only demonstrates the application of this device for the preparation of useful building blocks but also combines the ability to process *n*-butyllithium directly through pump heads attached to the unit.

The use of flow processing methods for organic synthesis continues to grow in popularity.[1] Both micro- and mesoscale flow systems offer their own validated individual benefits while also demonstrating some common shared advantages.[2] For example microscale flow systems have led naturally toward the rapid analysis of reactions. Such data inevitably lead to a greater understanding of reaction dynamics.[3] Alternatively, mesoscale flow processes continue to impress with their ability to permit the telescoping of reactions that lead to the production of complex entities from simple chemical inputs.[4] This process is greatly facilitated by the use of polymer supported scavengers and reagents, including both bead and monolith based supports which in many cases negate labor intensive work-up and purification steps familiar to batch mode methods.[5] Other advantages are achieved by conducting continuous processing to more easily scale out synthesis processes. Moreover, any exothermic phenomena are readily

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[†] University of Cambridge.

[‡] Cambridge Reactor Design.

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monitored and controlled due to greatly improved heat transfer in flow systems. The concept of segmented flow affords the chemist with associated safety improvements in the form of generating and immediately using hazardous intermediates.[6] Despite these obvious advantages we and others have been actively identifying problematic areas associated with flow synthesis and developing appropriate solutions.

Figure 1. Cryostatic mesoscale flow reactor: 'polar bear'.

By way of illustration we have extensively used ReactIR as an inline device to detect both product formation and the dispersion of material.[7] The pumping of additional reaction streams can then be triggered in real time to accurately match the stoichiometries of the new input stream to that of the dispersed plug. Furthermore, a tube-in-tube gas permeable membrane reactor has been devised for the safe handling of reactive gases in a research environment.[8] Likewise, both an agitating cell reactor and the use of ultrasound have been developed for the continuous processing of solids and suspensions.[9] Here we report the first use of a new, cryogenic mesoscale flow device which is capable of reaching and maintaining low temperatures precisely down to −89 °C *for prolonged periods of time*.

Since low temperatures are an essential component of many modern reaction processes, a range of cryostatic systems or cooling baths have been employed both for batch and flow mode operation.[10] Under flow conditions additional features need to be addressed such as solvent freezing, water ingress, and accurate temperature control. While some solutions to this problem are available, none are without some difficulty or inconvenience of use especially over long time periods. For example, peripheral cooling/heating units require consumable liquids/oils which operate within specific temperatures and must be changed accordingly, which is often a time-consuming process. Alternatively, cryogenic consumables such as cardice have been employed; however, after relatively short periods of time the processes must be stopped to replenish the depleted cryogenic materials. The new reactor reported here, termed 'polar bear', uses compact refrigerator technology to maintain low temperatures (Figure 1).[11]

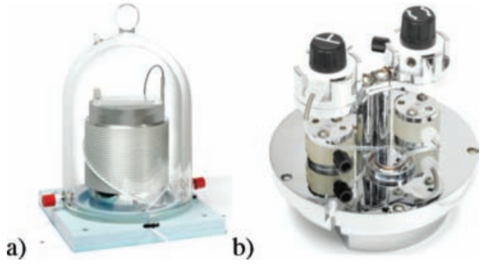

Figure 2. (a) Cooled flow coil with chip cooling unit. (b) Precooling loop unit.

The refrigerating unit supplies cooling to a pipe which is in contact with a metal casing. A coiled tube reactor with volumes up to 20 mL wound round a metal cylinder slides over the cooled metal casing. There are two methods available for the introduction of reactants to the cooled coil, a flow chip unit and a precooling loop unit (Figure 2a and b). Both units are fastened to the top of the metal casing allowing them to be efficiently cooled. In this work the precooled loop unit (Figure 2b, depicted as the 1 mL

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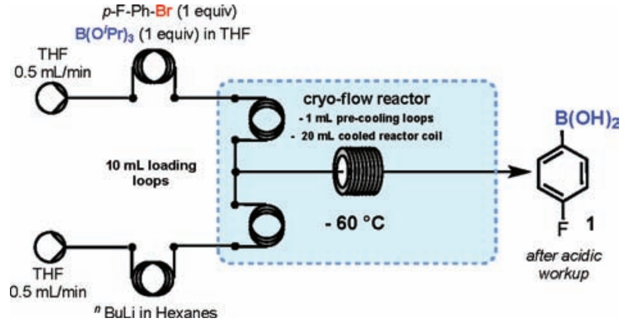
(11) This setup can be purchased from: http://www.cambridgereactordesign.com/.

loops within the blue cooled zone shown in the schematic diagrams) was used exclusively. The whole system is contained inside a removable, double-walled glass dome which serves to prevent condensation and frosting of the cooled parts. The temperature of the coil and mounted unit can be conveniently set via a digital interface (PT100, to one decimal place) and monitored by a thermocouple where the probe is positioned between the metal casing and the coil. The precooling loop unit allows the two individual streams to be cooled prior to their union at the T-valve before subsequently passing into the cooled reactor coil. Additionally, the cryogenic reactor permits the user to directly load into the precooled loops making it also useful for small scale iterative synthesis employing unstable materials. In order to test this new reactor we opted to study the generation and *in situ* quenching of lithium halogen exchange reactions with boron containing electrophiles. The application of boron containing compounds (acids, esters, trifluoroboronates, and *N*-methyliminodiacetic acid derivatives) in synthesis requires little justification. Their versatility and application for forging C–C, C–N, and C–O bonds are well established and are therefore attractive precursors for flow based chemical synthesis.[12]

Table 1. Preliminary Concentration Studies for the Preparation of Boronic Acids



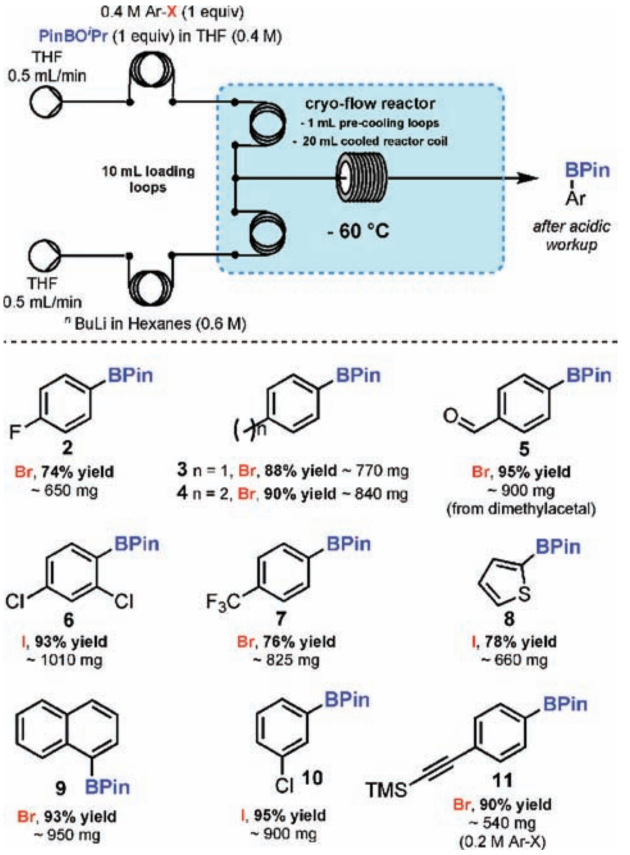
entry	[^{n}BuLi] M	[*p*-F-Ph-Br] M	yield[a]
1	0.15	0.10	68%
2	0.30	0.20	70%
3	0.45	0.30	75%
4	*0.60*	*0.40*	*77% (430 mg)*

[a] Purity of boronic acids could be further enhanced by trituration with Et$_2$O.

Our initial reaction setup employed 10 mL loops prior to the reactor (these loops were external from the housing dome and thus held at room temperature, as depicted in the schematic diagrams). A mixture of *para*-fluorobromobenzene and triisopropylborate dissolved in dry THF was injected in one loop, while the other loop was loaded with *n*-butyllithium in dry hexanes.

Using THF as the system solvent and setting the reactor to −60 °C, pumping was initiated at 0.5 mL/min. Mindful of the potential for boronate salt complexes to precipitate from solution and block the reactor tubing, we began by assessing workable concentrations; our results are outlined in Table 1. Pleasingly, merging a 0.10 M solution of the aryl halide and boron electrophile with a 0.15 M solution of *n*-butyllithium resulted in the clean formation of the desired boronic acid **1**, after acidic aqueous workup (Table 1, entry 1). Moreover, precipitation was not observed at these concentrations; indeed, this reaction performed well up to 0.40 M loadings of the aryl-halide (Table 1, entry 4; at concentrations above this, thick precipitates were observed in the reactor loop and pumping was therefore ceased). Nevertheless, with these conditions in hand, they were applied to the preparation of the pinacol (pin) boronate ester analogue **2** by switching the electrophile from B(O^{i}Pr)$_3$ to PinBO^{i}Pr and achieved very similar yields of product (Scheme 1). In terms of scope of the lithiation reactions in the new reactor, we were able to process a number of substrates at these concentrations without incident. Synthesis of aldehyde **5** was achieved from a dimethylacetal precursor which was simultaneously deprotected to the aldehyde upon acidic workup of the boronate complex. A number of other boronic esters were secured in a similar fashion such as the 2-thiophene pinacol boronate **8** and the

Scheme 1. Segmented Flow Synthesis of Boronic Esters Using the New Cryo-Flow Reactor (purities greater than 95%)



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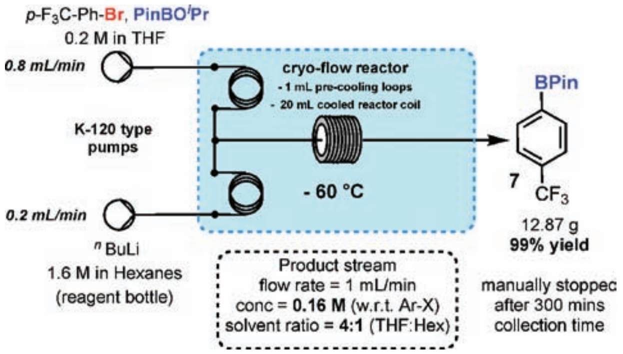
(12) *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005.

silyl protected acetylene derivative **11**. Having established a suitable procedure to demonstrate the ability of the new cryo-flow reactor to process lithiation reactions in a segmented fashion, attention was turned to *continuous* processing at low temperatures without the requirement for external cryostatic materials. From the outset we anticipated some potential issues with translating the segmented method directly into a continuous process, namely being able to keep the product flowing continuously and pumping butyllithium through the K-120 piston pump heads without seizing. Indeed, in an attempt to directly apply the segmented flow conditions to a continuous process it was found that pumping could only be maintained for approximately 45 min. After this period the cooled reactor coil became blocked by a thick slurry, presumably the boronate complex. Unlike the segmented procedure, the incoming solvent stream that would keep the segment moving was now a reagent stream also producing a thick product suspension.

In order to deal with this blockage an obvious solution was to lower the concentration and increase the content of the more polar solvent in the product stream (currently 0.2 M and 1:1 THF to hexane respectively). Another factor we wished to consider in order to keep the process simple was the current requirement to preformulate butyllithium solutions, which is not an attractive process on scale.

We therefore designed a continuous process which could employ butyllithium obtained directly from the reagent bottle. Our final optimized conditions for this process are shown in Scheme 2. Pleasingly, when the arylhalide was delivered to the reactor coil at 0.8 mL/min at a 0.2 M concentration and the butyllithium at 0.2 mL/min at 1.6 M we could process the reaction for extended periods (> 5 h). Notably, under these conditions, both the concentration and solvent ratios in the product stream prevented blockages (0.16 M and 4:1 THF to hexanes respectively). Furthermore, the prolonged processing of butyllithium through commonly employed piston based pump heads is notable. For this process, the first 30 min of eluent (30 mL) from the reactor were discarded (this material contains mismatched stoichiometries of reactants whenever pumps are started simultaneously but set at different flow rates), and the following flow was collected for the next 300 min (300 mL). This material was then treated to an acidic workup procedure and provided the desired product in 99% yield and in excellent purity (~ 95% by ^{1}H NMR spectroscopy) without chromatography.

Scheme 2. Continuous Process



In summary, the new cryogenic flow device has been used to process a number of lithium halogen exchange reactions leading to a variety of boronic acids and esters. A brief adjustment of concentration furthermore permitted the continuous processing at −60 °C for 5 h without recourse to cryostatic consumables. Also of importance was the ability to use *n*-butyllithium as delivered directly from the reagent bottle through the piston pump heads. Notably, during these studies the cryo-flow reactor was kept at −60 °C for 12 days (288 h) without any noticeable frosting of the flow cell device.

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Supporting Information Available. Experimental procedures and full characterization (^{1}H and ^{13}C NMR data and spectra, IR, and HRMS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.