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Effective Utilization of Flow Chemistry: Use of Unstable Intermediates, Inhibition of Side Reactions and Scale-up for Boronic Acid Synthesis

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[2] *Formerly of Takeda Pharmaceutical Company Ltd., Pharmaceutical Sciences, Process Chemistry, Juso-honmachi 2-17-85, Yodogawa-ku, Osaka, 532-8686, Japan*

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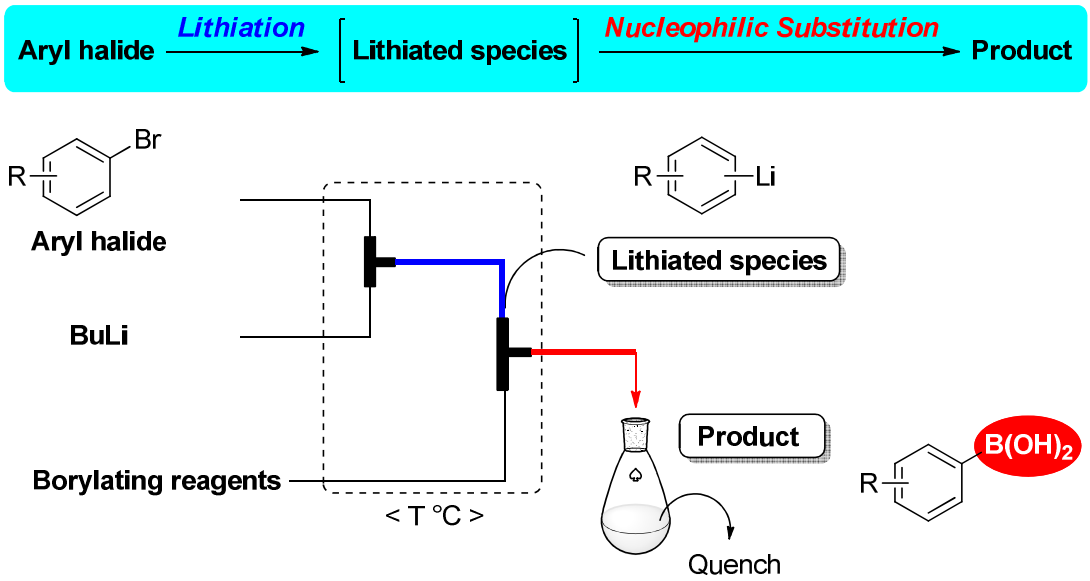


Abstract

Flow chemistry processes for boronic acid syntheses utilizing lithiation-borylation have been developed. The side reactions in the lithiation step that occur in batch were suppressed and unstable lithium intermediates were handled safely. Flow technology was applied to several kinds of boronic acid syntheses and scale-up was successfully conducted to allow kg scale production. Some of the key benefits of flow flash chemistry were utilized, for both avoiding side reactions and enabling dianion chemistry that is difficult to successfully perform in batch reactions. The examples showed further perspectives on the utility of flow technologies for process development.

Keywords: flow chemistry, flash chemistry, side reactions, scale-up, organolithium chemistry, unstable intermediates, dianions, aryl boronic acids

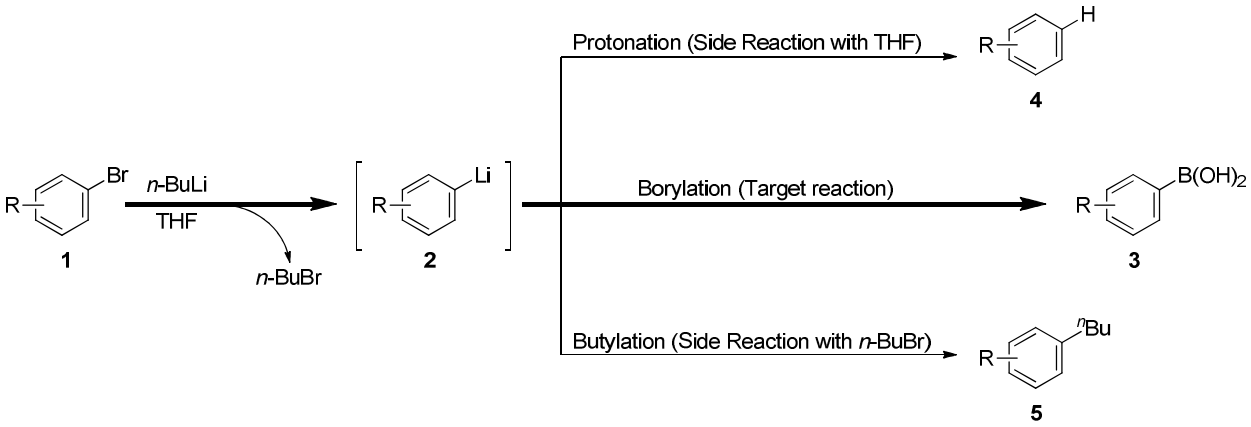
INTRODUCTION

Since its full-scale research and development was started worldwide in the 1990s, Flow Chemistry (FC) has received much attention and it is becoming one of the most useful and indispensable technologies for a variety of chemical syntheses, ranging from pharmaceuticals and agrochemicals to plastics and chemicals.[1,2] FC has several unique features, which most importantly give advantages that can be used to get improved performance and reduced costs, as well as offering the potential for added safety and speed when compared to conventional batch processes. While FC technologies have received significant research interest, both from academia and industry,[3,4] due to a lack of general and robust flow reactors for conducting laboratory process development to scale up production, the potential of this technology has not yet been fully utilized for manufacturing.

Our desire to explore and expand on the FC methodology for process chemistry stems from the fact that it shows good utility for successfully handling unstable intermediates, and we have recently reported an application of FC to a boronic acid synthesis focusing on precise control of residence time and temperature,[5] especially through the use of "flash chemistry".[6,7] In that report, by controlling residence time and temperature precisely, FC was shown to allow an unstable lithium intermediate to be utilized while avoiding the side reaction pathway of protonation, even though organolithiums are well known to be protonated in THF solvent (Scheme 1, side reaction for **4**).[8,9]

Bromine lithium exchange reactions are widely utilized for generating organolithiums, and *n*-BuLi is especially used as a reagent. But, the lithium intermediates thus generated (**2**) often undergo competing side reactions, such as butylation due to reaction between the organolithium intermediate and butyl bromide (Scheme 1, side reaction for **5**).[10]

Scheme 1. Sequence of a Bromine-Lithium Exchange Followed by the Desired Reaction and Side Reactions



In this paper, we demonstrate the use of FC to suppress the typical side reactions (protonation & butylation), and show an application of FC to control highly unstable lithium intermediates, including dianionic forms, for boronic acid syntheses. Furthermore, scale-up production to kg-scale will be disclosed.

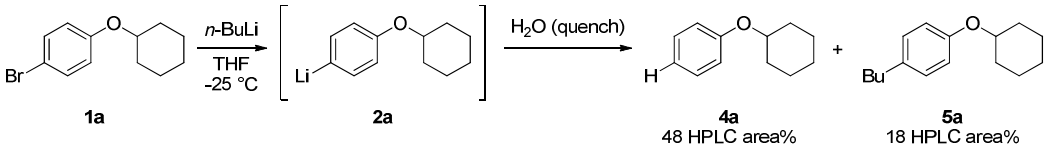
RESULTS AND DISCUSSION

(1) Feasibility Study & Proof-of-Concept

As is well known, FC has already been applied to boronic acid synthesis,[11,12] but the scope of its application is still limited. The key parameters for robust scale-up are the mixing efficiency, temperature, and residence time control, even though there are numerous other parameters to be considered for process development by flow. Based on our previously reported insights,[5] it was planned to utilize FC for the manufacture of (4-(cyclohexyloxy)phenyl)boronic acid (**3a**). When **3a** was synthesized in batch, a side reaction was found to be unavoidable if a halogen-lithium

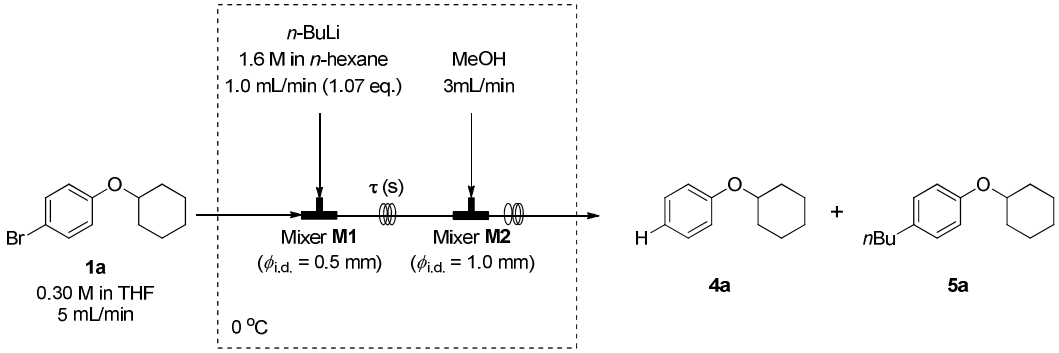
exchange reaction was utilized, with butylation[13] being a major issue even when the reaction was carried out at -25 °C (Scheme 2).

Scheme 2. Unavoidable Side Reaction (Batch Results)



In order to partially suppress the side reaction in batch, a cryogenic condition was required, thus a flow reaction was investigated to develop a milder condition and further decrease the side products. Firstly, as a feasibility study, the halogen-lithium exchange reaction and its quench by MeOH was investigated in a flow set-up (Figure 1, Table 1).

Figure 1. Set-up for a flow feasibility study of halogen-lithum exchange



The initial experiments for the feasibility study were conducted with the conditions of; *n*-BuLi 1.07 eq., reaction temperature 0 °C, and residence times of 0.24-31.42 sec. When less than 1 sec was allowed for lithiation, not all the raw materials were converted, showing the minimum time required to consume all the raw materials. However, as the residence time was increased, more raw material was consumed until **1a** was totally converted to the lithiated species when using

more than 3.93 sec residence time for lithiation. Surprisingly, the protonated compound (**4a**), representing the desired product pathway, was obtained in highest yield in entry 3, and the yield decreased as the residence time for lithiation was prolonged. Furthermore, the side reaction (butylation, **5a**) increased as the residence time increased.

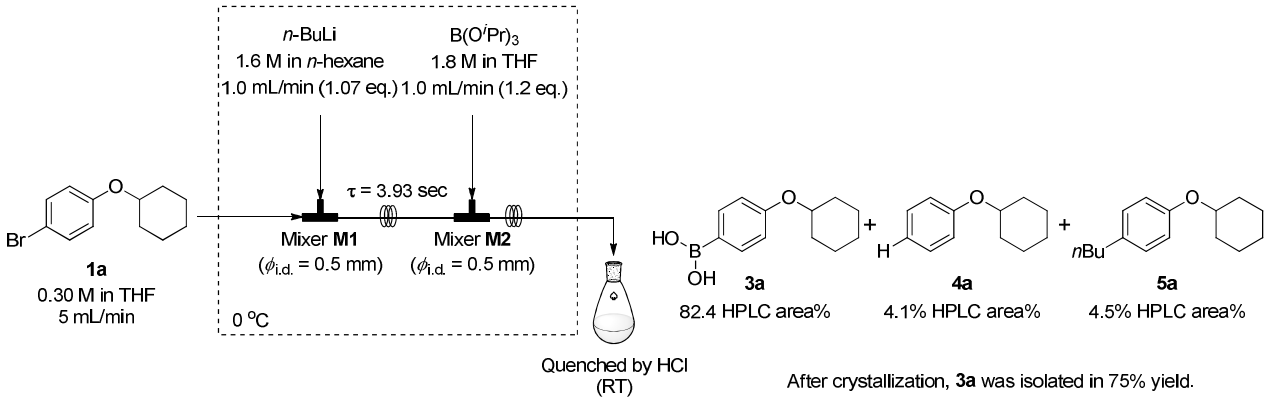
The result showed that about 1.07 eq. of *n*-BuLi was sufficient for the bromine-lithium exchange reaction and *ca.*4 sec was suitable to avoid the side reaction affording **5a**. Too long a residence time increased the side reaction, allowing the reaction of the aryllithium intermediate with *n*-BuBr.

Table 1. Feasibility study of the lithiation

entry	lithiation residence time **τ** (s)	HPLC area%		
		1a	**4a**	**5a**
1	0.24	45.9	51.9	0.0
2	0.98	1.2	95.7	0.3
3	3.93	0.0	96.0	1.1
4	15.71	0.0	92.7	3.5
5	31.42	0.0	90.2	6.0

Therefore, the condition for entry 3 was used as the optimized condition for the halogen-lithium exchange reaction at 0 °C, and then further investigation for the borylation was carried out (Figure 2).

Figure 2. Set-up of the lithiation-borylation flow system for (4-(cyclohexyloxy)phenyl)boronic acid (**3a**) synthesis

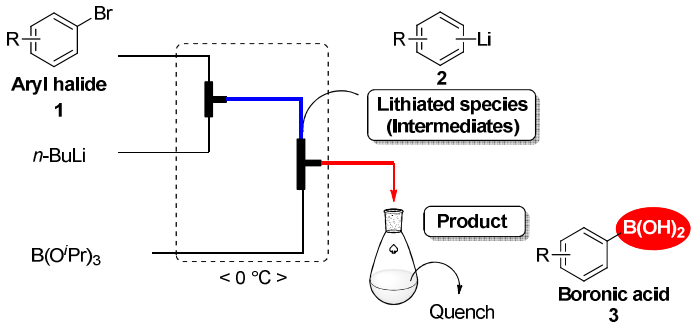


As shown in Figure 2, flow synthesis for boronic acid **3a** was achieved in good yield through minimizing the major side reactions. Crystallization in batch was conducted after flow reaction, and the boronic acid was isolated as white crystals in 75% yield.

(2) Application of Flow for Diversity Oriented Syntheses of Boronic Acids

The flow chemistry process for **3a** was successfully developed at lab scale, and the procedure was applied to other boronic acid syntheses. The concept for a flow process to boronic acids starting from arylbromides as raw materials is shown in Figure 3[14], and a summary of the results obtained after an optimization study on the residence time is shown in Table 2.

Figure 3. Flow chemistry process for boronic acid synthesis



For phenyl ether type compounds, the desired boronic acids were obtained in good yield using a few seconds of residence time for the lithiation (entries 1-3).

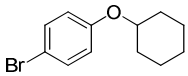
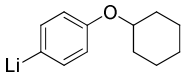
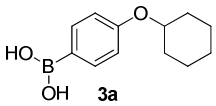
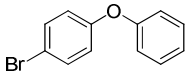
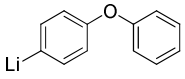
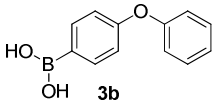
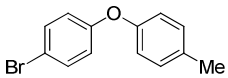
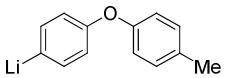
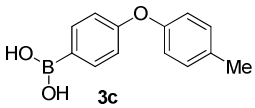
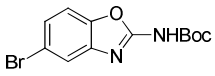
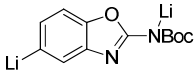
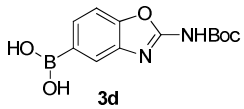
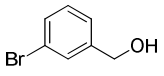
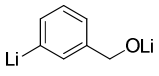
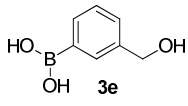
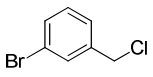
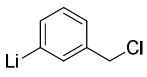
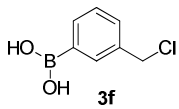
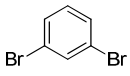
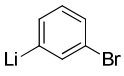
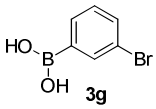
When the bromine-lithium exchange reaction was conducted for aryl bromides that included heteroaromatic rings, surprisingly, the optimized residence time was 0.25 sec, even though more than two equiv. of *n*-BuLi was required for detaching the bromine atom (entry 4). It is thought that more than two equiv. of *n*-BuLi were essential for this reaction because one equivalent of *n*-BuLi was consumed to remove the proton on the Boc-protected nitrogen. Therefore, the dianion intermediate for the boronic acid synthesis was being effectively utilized. Furthermore, from the viewpoint of our attempts to generate and control dianions, bromobenzyl alcohol was also successfully lithiated by utilizing more than two equivalents of *n*-BuLi (entry 5). Although it was really important to control the residence time to less than 1 sec in entry 4, interestingly, *ca.* 13 sec was required for converting raw material (**1e**) to generate the lithiated species (**2e**).

Moreover, selective halogen-lithium exchange reactions were attempted for aryl bromides including one more halide (entries 6 & 7). When both aryl bromide and benzyl chloride were co-existing, the bromine atom was converted selectively and the corresponding desired product

was obtained (**3f**). Also, a mono selective bromine-lithium exchange reaction was achieved for 1,3-dibromobenzene in an excellent yield after borylation (**1g**).

These applications show that FC can contribute to diversity oriented synthesis for boronic acids via various unique/unstable/uncontrollable intermediates, furthermore, it is thought that this technique will be extremely useful in library synthesis.

Table 2. Application of a flow chemistry process to diversity oriented synthesis of boronic acids

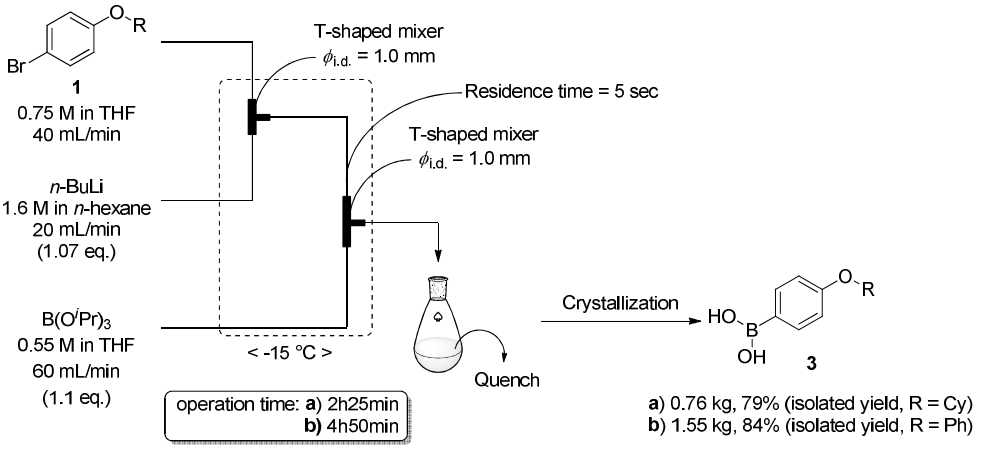
entry	Aryl halide	Intermediates	Products	τ (sec)	*n*-BuLi (eq.)	Yield[a]
1	 **1a**	 **2a**	 **3a**	3.9	1.07	82
2	 **1b**	 **2b**	 **3b**	9.4	1.07	83
3	 **1c**	 **2c**	 **3c**	3.9	1.07	89
4[b]	 **1d**	 **2d**	 **3d**	0.25	2.2	88
5	 **1e**	 **2e**	 **3e**	13	2.4	90
6	 **1f**	 **2f**	 **3f**	1.9	1.2	80
7	 **1g**	 **2g**	 **3g**	7.8	1.1	91

[a] HPLC area%. [b] Previously reported in a reference 5.

(3) Scale-up Productions

Scale-up production for boronic acids **3a** and **3b** was conducted. In order to improve productivity, the concentration of raw materials and the flow rates were increased from the lab conditions, and due to concern about the reduced capacity for thermal exchange, the reaction temperature was lowered to -15 °C. As a result, 0.76 kg of **3a** was manufactured in good yield with an operation time of 2 hours and 25 min for the flow mode (Figure 4). The obtained product showed good quality and didn't include side products **4a** and **5a**. Also, 1.55 kg of **3b** was manufactured in an excellent yield and its quality was sufficient to carry out the subsequent reaction.

Figure 4. Scale up production for **3**



EXPERIMENTAL SECTION

HPLC Method. The HPLC method used for IPC analysis as well as for analyzing the purity of

boronic acid **3** employed a YMC-Pack ODS-A 150×4.6 mm (S-5um, 12nm) column maintained at 25 °C. Acetonitrile (MeCN) was used as Mobile Phase A and a 0.01 M aqueous solution of KH_2PO_4 as Mobile Phase B. The total flow rate was set to 1.0 mL/ min, the injection volume was 5.0 μL and detection was carried out at 220 nm. The total method analysis time was 60 min. A gradient was used starting at 50 % of Mobile Phase A, moving to 80 % over 15 min, eluting at 80 % A for 15 min and then moving back to 50 % over 15 min. The final composition was maintained for 15 min at 50 % to re-equilibrate the column.

Compounds **1a**, **1b**, **1c**, **1d**, **1e**, **1f**, **1g**, **3a**, **3b**, **3c**, **3d**, **3e**, **3f**, **3g**, **4a**, **4b**, **4d**, and **5a** eluted at a relative retention time (RRT) of 32.5 min (**1a**), 29.2 min (**1b**), 31.2 min (**1c**), 8.3 min (**1d**), 3.6min (**1e**), 15.0 min (**1f**), 22.9 min (**1g**), 6.2 min (**3a**), 4.7 min (**3b**), 6.4 min (**3c**), 2.3 min (**3d**), 1.7 min (**3e**), 2.9 min (**3f**), 3.3 min (**3g**), 26.4 min (**4a**), 20.7 min (**4b**), 4.4 min (**4d**), and 42.6 min (**5a**).

General Lab Scale Experimental Procedure (Flow synthesis of 3a, 3b, 3c, 3e, 3f and 3g, Table 2). All chemicals were purchased from Wako Pure Chemical Industries and used without further purification. All solvents used were reagent grade unless otherwise specified. Three microsyringe pumps (ISIS Ltd., Osaka Japan, Fusion 100) were used to pump the solutions of the three reagents. Feedstock A consisted of compound **1** (aryl halide) dissolved in THF as a 0.3 M solution. Feedstock B was commercially available 1.6 M *n*-BuLi in hexane used directly from the supplied bottle, while feedstock C was a solution of triisopropyl borate ($B(O^iPr)_3$) freshly prepared in anhydrous THF (1.8 M (entry 1), 1.0 M (entry 2), 0.55M (entry 3), 1.5 M (entry 5), 1.0 M (entry 6), 1.74 M (entry 7)). All feedstocks were maintained under an atmosphere of nitrogen and made up using anhydrous THF. The reactors were fabricated from stainless steel

(SS) tubing with an internal diameter (ID) of 1 mm and an appropriate length defined by the desired residence time (τ) and flow rates. The residence time for the lithiation step was adjusted by utilizing a suitable tube length determined by the total flow rate of Feedstocks A and B. Shimadzu-GLC tee pieces (ID 0.50 mm, part number: 6010-72357) were used as a mixer for Feedstocks A and B, and a Shimadzu-GLC tee piece (ID 1.0 mm, custom-made item) was used as a mixer for Feedstock C and the resulting solution after lithiation. Investigation of the residence time for the borylation showed that 1 sec was sufficient for the reaction to go to completion and longer times were not found to be detrimental.

To make sure reactants were sufficiently cooled before mixing, pre-cooling loops (L = 50 cm, ID = 1.0 mm) were used, and the reactors for both the lithiation and borylation steps were submerged into a cooling bath set at 0 °C before initiating the three pumps. Once a steady flow was attained without blockage (typically after 15 s of continuous operation), the product stream was diverted to a sampling bottle and analyzed by HPLC.

Scale-up Production

(1)Flow Chemistry Process for Manufacturing

Three diaphragm pumps (TACMINA, TPL1M) were used to pump the solutions of the three reagents. Feedstock A consisted of compound **1** dissolved in anhydrous THF as a 0.75 M solution and was pumped at 40.0 mL/ min. Feedstock B was commercially available 1.6 M *n*-BuLi in hexane used directly from the supplied bottle and pumped at 20.0 mL/ min, while feedstock C was a 0.55 M solution of $B(O^iPr)_3$ freshly prepared in anhydrous THF, pumped at 60.0 mL/ min. All feedstocks were maintained under an atmosphere of nitrogen. The reactors were fabricated from SS tubing with an ID of 2.17 mm of an appropriate length defined by the desired residence time (τ) and flow rates. The residence time for the lithiation step was set to 5 s, which firstly

resulted in a 318 cm long tube (ID 1.00 mm) and secondly a 67.5cm long tube (ID 1.00 mm) being used with the above flow rates. Shimadzu-GLC tee pieces (ID 1.0 mm, custom-made item) were used as mixers. The pre-cooling loops (L = 1 m, ID = 2.17 mm) and reactors for both the lithiation and borylation steps were submerged into a cooling bath set at 0 °C before initiating the three pumps. The temperature in the plug flow reactors was monitored and maintained at approximately 0 °C. After a steady flow was attained, as indicated by thermal mass flow meters, the product stream was collected and the process was run for a total of (a) 2 hrs 25 min to afford compound **3a** in 89.9 % HPLC purity, and (b) 4 hrs 50 min to afford compound **3b** in 93.8 % HPLC purity.

(2) Work up Procedure for Isolating 3a

The collected product stream from the FC process was quenched with 1 M HCl aq. (9.04 kg) and toluene (13.0 kg) to allow for efficient liquid-liquid extraction, as compound **3a** was found to stay in the organic phase. The organic layer was then further washed with water (10 kg), and then concentrated. The resulting residue was dissolved in toluene (1.51 kg), precipitated by *n*-heptane (4.78 kg), and agitated in an ice bath. The resulting slurry was filtered and washed with ice-cooled *n*-heptane (1.19kg) to afford compound **3a** as a white crystalline powder in 79 % yield (0.76 kg) and 97.4 % purity.

(3) Work up Procedure for Isolating 3b

The collected product stream from the FC process was quenched with 2 M HCl aq. (10.65 kg) and ethyl acetate (9.23 kg) to allow for efficient liquid-liquid extraction, as compound **3b** was found to stay in the organic phase. The organic layer was then further washed with water (10 kg), and then concentrated. The resulting residue was dissolved in ethyl acetate (1.80 kg), precipitated

by *n*-heptane (20.40 kg), and agitated in an ice bath. The resulting slurry was filtered and washed with ice-cooled *n*-heptane (5.0 kg) to afford compound **3b** as a white crystalline powder in 84 % yield (1.55 kg) and 97.0 % purity.

CONCLUSION

An FC process for boronic acid synthesis utilizing lithiation-borylation was developed and the usefulness of FC for avoiding side reactions of organolithium intermediates, for example, (1) protonation by THF solvent, (2) butylation by *n*-BuBr generated from bromine-lithium exchange between aryl bromide and *n*-BuLi, were disclosed. Also, FC was shown to be an effective method for diversity oriented boronic acid synthesis, with examples of the application of flow flash chemistry. Unstable intermediates, including dianions, were highly controlled for useful application, and scale-up production to kg-scale was conducted.

We believe that our results show examples that represent good milestones in the use of FC processes for the manufacture of pharmaceuticals, agrochemicals, plastics, and chemicals.

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