

# Synthesis of Phenylboronic Acids in Continuous Flow by Means of a Multijet Oscillating Disc Reactor System Operating at Cryogenic Temperatures

Dagfinn Sleveland<sup>†</sup> and Hans-René Bjørsvik<sup>\*,†,‡</sup><sup>†</sup>Department of Chemistry, University of Bergen, Allégaten 41, N-5007 Bergen, Norway<sup>‡</sup>Fluens Synthesis, Thormøhlensgate 55, N-5008 Bergen, Norway

## S Supporting Information

**ABSTRACT:** A multijet oscillating disk (MJOD) millireactor system suitable for operating at cryogenic temperatures has been developed, assembled, and investigated. This new reactor system (cryoMJOD) was realized with the purpose to prepare various phenylboronic acids in a continuous two (three)-step telescoped synthetic process at temperatures in the interval  $-50$  to  $-75$  °C. In this process, *n*-butyllithium was reacted with a phenylbromide to provide the corresponding phenyllithium derivative, whereupon a borate was added under the formation of target product phenylboronic acid in good selectivity and medium-to-good yield (50–75%). These results were competitive with results previously revealed in the literature. The residence times of the telescoped two-step process were considerably shorter compared to those of batch mode operations for the identical syntheses. The flow process was optimized by means of statistical experimental design and multivariate regression, upon which the process was utilized for the production of a series of phenylboronic acid derivatives, all in medium-to-good yield. One of the substrates, 4-methoxyphenylboronic acid, was submitted for throughput improvements, resulting in a process with capability to produce the product phenylboronic acid in a quantity of  $2.0 \text{ kg} \times \text{day}^{-1}$ .

## ■ INTRODUCTION

Continuous flow chemistry in terms of microreactor technology has during the past two decades been implemented both in the academic laboratory as well as within industrial R&D and production of fine- and pharmaceutical chemicals.<sup>1</sup> A number of flow reactor suppliers have been established that offer a variety of different flow reactor systems and equipment.<sup>2</sup> The major part of the suppliers provides microreactor technology dedicated to flow chemistry in solution phase only. However, other technologies have also been developed and adopted for processing slurries using a flow chemistry platform. Recently, Ley and collaborators<sup>3</sup> investigated the potential for processing slurries in a reaction that produced a nonsoluble salt during the course of the reaction. Such operations are generally impossible to conduct in a microreactor due to clogging of the micro-sized flow channel. For this purpose, a “Coflore” agitating cell reactor (ACR)<sup>4</sup> that roughly operates according to the principles of a continuously stirred tank reactor (CSTR)<sup>5</sup> was utilized. In our laboratory we have also demonstrated the use of the multijet oscillating disk (MJOD) reactor system (Fluens Synthesis)<sup>6</sup> for heterogeneous reactions, namely by successfully conducting the Hoffmann rearrangement reaction<sup>7</sup> that involved a heterogeneous reaction system.<sup>8</sup> Hulshof and collaborators<sup>9</sup> have demonstrated the use of the continuous flow microwave reactor system “FlowSynth” by Milestone srl<sup>2c</sup> to conduct two processes in heterogeneous phase, namely a biocatalyzed esterification of (*R,S*)-1-phenylethanol with vinyl acetate and esterification of (*S*)-pyroglutamic acid with *n*-decanol.

The MJOD reactor technology previously reported from our laboratory,<sup>8</sup> was designed, manufactured, and developed as a general reactor platform for conducting flow reactions under

standard solution-phase reaction conditions in a temperature range of  $-10$  to  $+150$  °C, and multiphase (gas–solid–liquid) conditions. A recently disclosed paper from our laboratory demonstrates the MJOD flow reactor as a platform for conducting gas–liquid phase, namely molecular oxygen as the terminal oxidant in an organocatalyzed epoxidation of olefins,<sup>10</sup> for catalytic processes including processes that require inert gas (Ar, N<sub>2</sub>) conditions, and for reactions that involve slurries or precipitates of solids during the course of the reaction.

Another important application area for flow chemistry lately visited by three different research groups involves reactions and processes that require cryogenic temperatures in batch. Werner and collaborators<sup>11</sup> have investigated the preparation of phenylboronic acids in flow using micromixers combined with tubular reactors. Ley and collaborators<sup>12</sup> reported a study involving an in-house developed microreactor system dedicated for low-temperature reactions. By means of this system, a series of pinacol boronate esters and 4-fluorophenylboronic acid were prepared at cryogenic temperatures. Buchwald and collaborators<sup>13</sup> also disclosed results that involved flow synthesis of phenylboronic acids at room temperature or above. A flow process setup was used, which was integrated with one more step that permitted production of various substituted biphenyls via the Suzuki reaction. Herein we will reveal results from a project that encompassed design and development of a cryoMJOD flow reactor and results from the development of a highly effective two-step telescoped process for the synthesis

**Special Issue:** Continuous Processes 2012

**Received:** February 25, 2012

**Published:** April 16, 2012

of a reagent of paramount importance in organic synthesis, namely phenylboronic acids.

The importance of this reagent was confirmed by the award of the Nobel Prize<sup>14</sup> in chemistry in 2010 to Akira Suzuki. Suzuki and collaborators published two papers<sup>15</sup> in 1979 on the discovery of a new versatile and practical palladium-catalyzed reaction, today known as the *Suzuki reaction*.<sup>16</sup> This reaction involves an organoboron compound as a coupling partner with a vinyl or an aryl halide in a palladium-catalyzed cross coupling. The reaction was shown to take place by base activation of the organoboron reagents to produce the corresponding boronate intermediates, which facilitate a transmetalation reaction that implies an organic group transfer from boron to the palladium catalyst whereby two organic moieties are coupled under release from palladium. The reaction was also extended to include coupling reactions with alkyl groups and arylboronic acids, which can also take part in the palladium-catalyzed cross-coupling reaction. More than 30 years of research, innovation, and development have resulted in a copious body of total syntheses that lead to unsymmetrical substituted biphenyls, some of which have great benefit to society and life. Examples of such products are the fungicide, Boscalid,<sup>17</sup> and the pharmaceutical chemical valsartan<sup>18</sup> that is an AT<sub>1</sub> angiogenesis receptor that dilates blood vessels and reduces the blood pressure. Furthermore, compounds bearing the boronic acid moiety have also been investigated as an antineoplastic<sup>19</sup> protease inhibitor,<sup>20</sup> and a number of other medicinal remedies.<sup>21–23</sup>

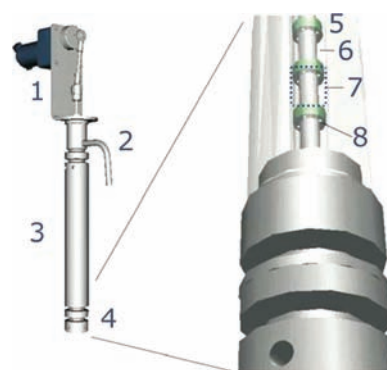
The goal of the project disclosed herein was two-fold, namely (1) to design and realize a flow reactor suitable for performing continuous flow processes at cryogenic temperatures based on the multijet oscillating disk (MJOD) reactor system that previously was designed and developed in our laboratories<sup>8</sup> and (2) to utilize this new flow chemistry equipment as a reactor platform for development and synthesis of a series of phenylboronic acid derivatives.

## METHODS AND RESULTS

**The MJOD Flow Reactor System.** Figure 1 displays a general three-dimensional (3D) drawing of a MJOD reactor that includes (1) the oscillator section, (2) the output section, (3) the reactor body, and (4) the input section. In addition, a number of auxiliary supporting units, such as feeding pumps, a cryostat with a circulating pump, a precooling unit (heat exchanger) placed prior to the input section, and reservoirs for raw materials, solvents, and final product were utilized.

The right-hand side of Figure 1 shows a transparent, bottom-up view of the input section, including a small fraction of the reactor zone (reactor body). The MJOD assembly is located in the center of the reactor tube. The outer shell of the reactor body forms a ring-shaped room (cavity) that encapsulates the whole length of the reactor tube through which the cooling fluid (pure ethanol) was circulated. The whole length of the cryoMJOD flow reactor body was encapsulated using a polyethylene foam insulation sleeve with a wall thickness of  $l_{\text{wt}} = 13$  mm.

Due to the advantageous contact surface ratio vs the net reactor volume, an outstanding heat transfer capacity was attained. A variable-frequency and variable-amplitude oscillator was used for the vertical “piston movement” of the MJOD unit. An electric motor connected to a cam mechanism was used to power the up–down movement of the MJOD assembly. In addition, the cam assembly provides control of the amplitude



**Figure 1.** Three-dimensional drawing of the MJOD millireactor (left) shows the four various sections, (1) the oscillator section, (2) the output section, (3) the reactor body, and (4) the input section. A fraction of the reactor body (3) and the input section (4) are shown in enlarged view to the right in the figure. The reactor body consists of the heat exchanger chamber that surrounds the reactor tube where the multijet oscillating disk (MJOD) assembly is inserted. The MJOD unit comprises the perforated discs (5) that are fixed on the oscillator piston shaft with “the spacers” (6). This MJOD unit is connected to the (1) oscillator unit that transfers an oscillating vertical (up–down) movement of this “numerous-headed” piston.

by linear translation of the cam assembly to a predefined position (i.e., the distance to the motor shaft). Frequencies in the range of  $f = 1–10$  Hz and amplitudes in the range of  $A = 0.5–15$  mm can be achieved by adjusting the motor speed and the cam assembly. Various types of feeding pumps can be used to feed the substrate, reagents, catalysts, and solvents into the MJOD reactor through the feeding channels of the input section, which is located at the bottom of the vertically placed reactor body. The substrate and various reagents are continuously pumped into the reactor tube via the input section, which implies that the reaction mixture is pushed upwards in the reactor tube practically without backmixing.<sup>24</sup> From the input section, the reaction mixture passes through the jets of the MJOD discs from one reaction cavity upwards to the next one. Together with the up–down movements of the MJOD discs, the tightening of the cross section (that is the tiny jets in one of the MJOD discs) creates vortices and thus an extremely good mixing of the reacting components. The postreaction mixture (that it is the mixture that comes out from the output section) is collected in suitable batches for workup. The temperature control for the MJOD reactor body was performed by means of a thermostat and a circulator pump. Previous studies in our laboratory have shown that the MJOD reactor system possesses an outstanding mass and heat transfer ability for the system, which in general results in a significantly increased reaction rate.

**Modification of the MJOD Flow Reactor for Utilization at Cryogenic Temperatures.** The parts of the reactor section were manufactured identical to those of the general MJOD flow reactor model. The MJOD unit was constructed by four-jet ( $d_{\text{jet}} = 1.25$  mm) discs; in total 133 pieces (pcs) were used, which correspond to 132 interdisc cavities, each of a volume of  $V_{\text{cavity}} \approx 0.65$  mL. The four-jet disks that cover the entire cross section of the tubular reactor ( $D = 10$  mm) were manufactured with Teflon for the general MJOD model and were replaced by discs manufactured with Polyzene for the cryogenic model. Three reagent supply (inlet) lines of the input section were used. These were connected to precision piston- or syringe-feeding pumps. One input line at the output section of the MJOD

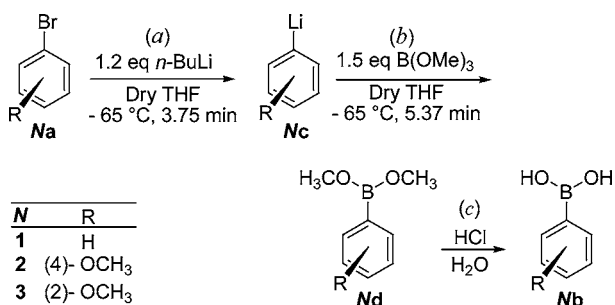
reactor was connected to a pressurized gas tank containing argon. The argon flow was adjusted to a pressure slightly above atmospheric pressure.

The cooling fluid, pure ethanol, was cooled and regulated by a thermostat (temperatures were selected in the range of  $-50$  to  $-75$  °C, as measured in the cooling fluid) and circulated through the heat exchanger. The cam mechanism and electrical motor that constitute the oscillator was tuned to provide oscillations with an amplitude of  $A = 5$  mm with a frequency  $f \approx 2$  Hz.

**Screening, Development and Suboptimization of the Telescoped Lithiation and Boronation Process.** The syntheses of phenylboronic acid **1b** and derivatives comprise two distinct synthetic steps that are both conducted at cryogenic temperature. Werner et al.<sup>11</sup> have studied the production of phenylboronic acid in flow using micromixer/tubular reactors at room temperature and even higher. Recently, Ley and collaborators<sup>12</sup> and Buchwald and collaborators<sup>13</sup> demonstrated the synthesis of phenylboronic acids in microreactor systems, although only under restricted production capacity. Concurrently with the recently disclosed studies,<sup>12,13</sup> we were in progress with the design and development aiming at approaching an MJOD flow reactor system suitable for cryogenic temperatures. This flow reactor system was designed in such a way that it was possible to introduce a reagent at various positions in the flow reactor and thus at various time intervals during the course of a reaction. Such an MJOD reactor body enables performing two or more different reactions in a telescoped manner, which is a requirement for the process leading to phenylboronic acid derivatives.

**The Batch Record.** The three-step synthesis leading to phenylboronic acid **1a** is performed at cryogenic temperatures under inert (argon) atmosphere. The first step (a) of Scheme 1

Scheme 1



consists of a reaction between a bromobenzene **a** and *n*-butyllithium, which provides the corresponding phenyllithium derivative **c**. Then in the second, but telescoped step (b), a boron reagent is introduced, which reacts with the phenyllithium intermediate **c** that was produced during the course of reaction step *a* to provide the target product phenylboronic acid **1b** after an acidic quench, step *c*, of Scheme 1.

**Implementation of the Synthesis on the MJOD Flow Reactor.** A cryoMJOD flow reactor setup based on the conventional addition sequence was assembled as shown in the process flowchart of Figure 2a. In this process setup, the substrate (in reservoir R1) was pumped with pump P1, and the *n*-BuLi reagent (diluted in pentane and placed in reservoir R2) was pumped with pump P2. The two separate tubes from P1 and P2, respectively, were connected to a precooler (C/HE2)

at the entrance (the input section) to the flow reactor. From this point and throughout the reactor part  $L_1$  of the reactor body, the substrate and the reagent were thoroughly mixed by the MJOD unit. Then, at the beginning (at the lower point) of the reactor part  $L_2$  of the reactor body, a third input line was connected. By means of the pump P3, this tube supplied the borate reagent from reservoir R3. The target product was received and collected at the output section at the end of (at the top) the reactor part  $L_2$ . The two reservoirs R4 and R5 contained anhydrous hexane and anhydrous THF, respectively. When the reagent reservoirs and substrate reservoirs were emptied, the feeding from the each solvent reservoir was connected to the respective feeding pumps.

Each of the two reactor parts,  $L_1$  and  $L_2$ , corresponds to a certain reaction residence time, which was a function of the flow rate within the reactor body, and thus the pump rates.

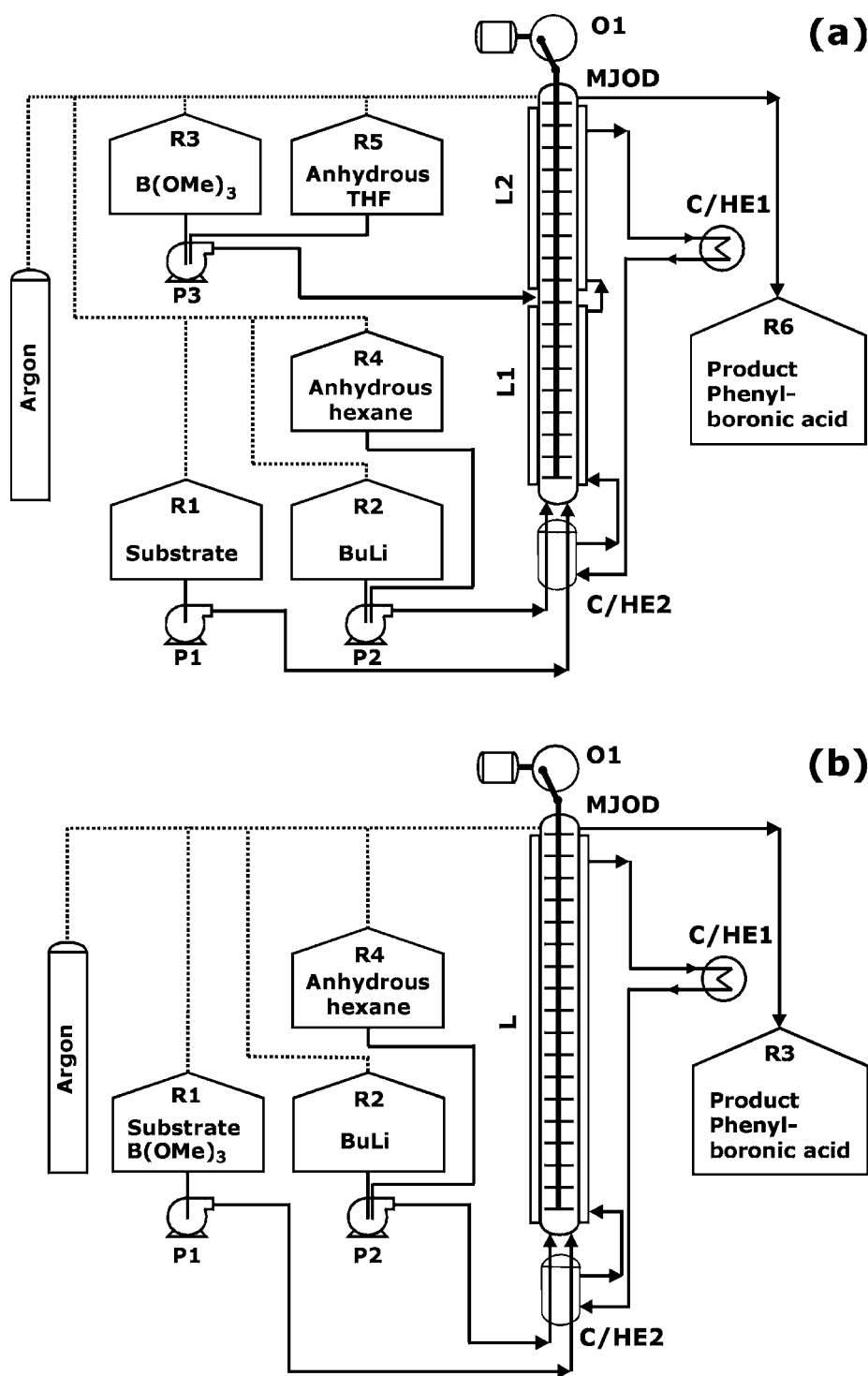
**Exploratory Flow Experiments.** The initial experiments using the process setup of Figure 2a were rather discouraging, because only low yields and selectivity were achieved. Since we were, at the outset, unfamiliar with operating the MJOD flow reactor system under cryogenic temperatures and with the different experimental parameter settings, the existing batch records were copied too strictly. In practice, initially relatively long residence times were applied when various reaction temperatures were explored. Table 1 provides a small selection of the results in this initial phase of the experimental work carried out with a cryoMJOD flow reactor as shown in the flow diagram in Figure 2a.

Based on earlier experience with the MJOD flow reactor<sup>8</sup> and the results of the new exploratory experiments (Table 1), the reaction time was considerably reduced and reaction temperatures were used in accordance with previously published batch records.

Some few different substrates were also used in the screening study. However, this approach did not appear to have any significant influence on the outcome. For further exploration and development of the flow process 1-bromo-4-methoxybenzene **2a** was selected as substrate. We decided to postpone a more thorough investigation of the influence of various functional groups in the substrate and to focus on establishing and optimizing a flow chemistry record.

**Optimization of the cryoMJOD Flow Process.** A simple statistical experimental design<sup>25</sup> aimed at investigating the influence of two experimental variables,  $x_1$  as the reactor residence time [min] and  $x_2$  as the reaction temperature [°C]. The exploratory experiments, using substrate **2a**, revealed that both of these variables ( $x_1, x_2$ ) possess a major influence on the outcome of the reaction. Thus, a full factorial design including two center-point experiments,  $2^k + 2 = 2^2 + 2 = 6$  experiments was generated and conducted with the cryoMJOD flow reactor. The experimental design (1–6) with corresponding responses is summarized in Table 2.

The model matrix  $[1 \ x_1 \ x_2 \ x_1 \times x_2]$  was multivariate correlated to the response vector by using multiple linear regression (MLR).<sup>26</sup> The estimated model with numerical values of the regression coefficients is provided in eq 1. Figure 3 shows the isocontour projection of the response surface (contour map) using eq 1. The product statistics estimated for the model provided in eq 1 were:  $R^2 = 0.714$  and RMSEP = 7.71.



**Figure 2.** Flow diagrams for two setups (a) and (b) for the multijet oscillating disk (MJOD) flow reactor systems. P: pump; R: reservoir, (R4's contain anhydrous hexane, R5's contain anhydrous THF); O: oscillator [ $A = 0.5\text{--}5\text{ mm}$ ;  $f = 0.5\text{--}3\text{ Hz}$ ], C/HE1: cryostat/heat exchanger,  $T = -65\text{ }^{\circ}\text{C}$ . C/HE2: precooler ( $T = -65\text{ }^{\circ}\text{C}$ ) for substrate and reagents, each line (tube length) of  $500\text{ mm}$  with internal diameter of  $d = 1.5\text{ mm}$ . MJOD: multijet oscillating disk reactor [ $K = 133\text{ discs}$  of  $d = 9.8\text{ mm}$ ; each disc has four jets of  $d = 1.25\text{ mm}$ , with reactor tube lengths,  $L_1 = 1530\text{ mm}$ ,  $L_2 = 960\text{ mm}$ , and  $L = L_1 + L_2 = 2490\text{ mm}$  with internal diameter of  $d_i = 10\text{ mm}$ ].

$$\begin{aligned}
 y &= f(x_1, x_2) \\
 &= 59.66 - 3.75 \times x_1 - 6.75 \times x_2 - 12.75 \times x_1 \times x_2
 \end{aligned}
 \quad (1)$$

The blue-colored lines and numbers displayed in the contour map of Figure 3 exhibit the yield predicted by the model of eq

1. The numbers printed in black are the actual results achieved at the current experimental settings (entries 1–5 of Table 2). By means of this contour map, the first step optimization was attempted. With the goal to further optimize the yield, a moderate extrapolation was performed. By using the settings  $x_1 = +1.5$  and  $x_2 = -2.0$  (in coded units), the contour map (model eq 1) predicts a yield of  $\sim 100\%$ . However, when the actual

Table 1. Introductory experiments<sup>a</sup>

entry	reactor platform	substrate	$n_{\text{substrate}}$ [mmol]	temp. [°C]	residence time [min]		product	
					step 1	step 2	yield [%]	
1	MJOD	3a	15.0	-50	30	45	3b	10 <sup>b</sup>
2	MJOD	3a	15.0	-60	15	22	3b	40 <sup>b</sup>
3	MJOD	3a	15.0	-70	15	22	3b	61 <sup>c</sup>
4	Batch	3a	13.3	-78	120	240	3b	74 <sup>c</sup>
5	MJOD	3a	14.0	-70	10	15	3b	57 <sup>c</sup>
6	MJOD	3a	14.0	-70	5.0	7.4	3b	72 <sup>c</sup>
7	Batch	2a	25.0	-78	110	180	2b	69 <sup>d</sup>
8	MJOD	2a	42.0	-70	3.0	4.3	2b	71 <sup>d</sup>
9	MJOD	2a	42.0	-65	9.62	–	2b	50 <sup>d,e</sup>

<sup>a</sup>2a = 1-bromo-4-methoxybenzene, 2b = 4-methoxyboronic acid. 3a = 1-bromo-2-methoxybenzene, 3b = 2-methoxyphenylboronic acid. <sup>b</sup>Isolated by column chromatography. <sup>c</sup>Isolated by crystallization and filtration from mother liquor. <sup>d</sup>Isolated by acidic extraction. <sup>e</sup>The reaction was performed in one step of length  $L_1 + L_2$

Table 2. Full factorial design with center-point experiments  $2^2 + 2$  for investigation of the relation between the reaction temperature and the residence time of substrate 2a

entry	experimental design <sup>a</sup>		response
	$x_1$	$x_2$	yield [%] <sup>b</sup>
1	-1	-1	52
2	+1	-1	70
3	-1	+1	64
4	+1	+1	31
5 <sup>c</sup>	0	0	72
6 <sup>c</sup>	0	0	69
7	+1.5	-2	69

<sup>a</sup>A quantity of 40 mmol of the substrate 2a was used in each of the experiments.  $x_1$  the reactor residence time [min] [-1, 0, +1] = (3.00 + 4.30, 3.75 + 5.37, 4.50 + 6.45) [min].  $x_2$  the reaction temperature [°C] [-1, 0, +1] = (-70, -65, -60) [°C]. <sup>b</sup>Percent isolated yield. <sup>c</sup>The experiment was performed two times, providing a mean yield of 71%.

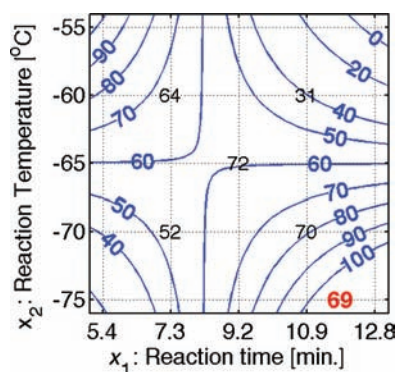


Figure 3. Response surface plot (isocontour map) describing the performance (yield) of the reaction as a function of the two variables,  $x_1$ , reaction time (reactor residence time), and  $x_2$ , reaction temperature, were varied.

experiment was conducted in the laboratory, the predicted yield was not achieved; instead, yield was only 69% (printed in red in the contour map).

On the basis of this result, one might preliminarily conclude that the response surface ascends and reaches a maximum in a yield at approximately 70% and then levels off. However, this limited screening design included only two of the experimental variables; thus, some of the other variables that were not systematically investigated can be of significance and at a fixed

level outside the region investigated herein. Further attempt to optimize the process was not performed.

**Improvement of the Throughput.** A high reactor throughput is of paramount importance in chemical production. In the current case, a maximized throughput can be obtained by (1) reducing the reactor residence time, (2) increasing the concentration of the reactants, or (3) by a combination of (1) and (2). For the process leading to phenylboronic acid derivatives, the MJOD flow reactor residence time was optimized as described in the previous section and could not be shortened more, at least not for the substrate 1-bromo-4-methoxybenzene 2a that was utilized during the optimization study above.

Thus, we turned our efforts towards investigating the performance of our flow process using various concentrations of the substrate 2a. For this investigation again the cryoMJOD flow reactor setup of Figure 2a was utilized.

A series of experiments involving substrate concentrations in the range of 0.18–1.34 mmol  $\times$  mL<sup>-1</sup> was carried through. Detailed reaction conditions with corresponding results for this series of experiments are summarized in Table 3.

At the highest concentration (entry 6, Table 3), the cryoMJOD flow process did not operate properly due to a high backpressure, which was caused by the high viscosity of the reaction mixture. The experiments of entries 1–5 of Table 3 provided all good isolated yields (60–75%) of target product 4-methoxyphenylboronic acid 2b. Variations in the outcome appeared to be due to workup difficulties.

Our effort to improve the throughput of the flow process was successfully completed, starting out from a capacity of 0.35 kg  $\times$  day<sup>-1</sup> and approaching a throughput of >2.0 kg  $\times$  day<sup>-1</sup>. This throughput capacity improvement corresponds to an improvement of approximately 6 times the capacity of the initial process.



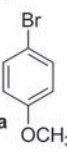
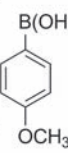
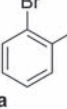
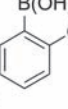
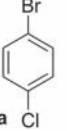
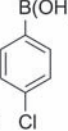
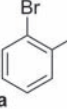
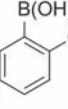
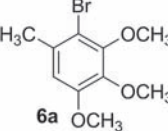
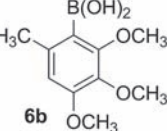
**Investigation of the Versatility of the Flow Process to Phenylboronic Acid Derivatives.** Next, the versatility of our two-step telescoped flow synthesis process described in the previous sections was investigated. Thus, a small selection of substituted bromobenzenes (Table 4) that were submitted to our flow process, was made. This selection was based on our interest for the target products, but these substrates also represent a span in substitution pattern from nonsubstituted at entry 1 to the crowded ring of substrate in entry 6. For comparison purposes, the corresponding batch mode process<sup>27</sup> was also carried out for the same series of substrates. Both series of experiments revealed comparable results, see Table 4.

Table 3. Conditions and results of reactions testing increased concentrations of substrate 2a

entry	$n_{\text{substrate}}$ [mmol]	$C_{\text{substrate}}$ [mmol $\times$ mL <sup>-1</sup> ]		residence time [min]		ratio THF:pentane		isolated yield [%]	production capacity <sup>a</sup>	
		step 1	step 2	step 1	step 2	step 1	step 2		[g $\times$ h <sup>-1</sup> ]	[kg $\times$ day <sup>-1</sup> ]
1	40	0.18	0.17	3.75	5.37	10.1	10.8	72	14.7	0.35
2	80	0.40	0.33	3.75	4.89	3.8	4.5	60 <sup>b</sup>	27.0	0.65
3	120	0.60	0.50	3.75	4.88	9.1	10.0	64 <sup>c</sup>	43.8	1.05
4	160	0.86	0.67	3.75	4.55	5.7	6.9	75	72.9	1.75
5	200	1.15	0.83	3.75	4.22	3.5	4.7	64	84.0	2.02
6 <sup>d</sup>	240	1.34	1.00	3.75	4.38	2.7	3.3	–	–	–

<sup>a</sup>Production based on the isolated yield. The production capacity in the [kg  $\times$  day<sup>-1</sup>] unit is calculated on the basis of the observed production capacity [g  $\times$  h<sup>-1</sup>]. <sup>b</sup>Difficult workup <sup>c</sup>The workup procedure was not scaled up properly <sup>d</sup>The experiment failed due to a high viscosity of the reaction mixture, causing a backpressure that exceeded the pressure of the feeding pump.

Table 4. Series of bromobenzenes (1a–6a) for the preparation of the corresponding phenylboronic acids (1b–6b) using the cryoMJOD flow reactor

#	Substrate	Product	Isolated yield %	
			MJOD	Batch
1			60	65
2			72	69
3			77	86
4			66	59
5			48	52
6			54	36

The small variations in isolated yield between the flow and batch protocols can be justified by product losses during the experimental workup procedure that involved precipitation of solid product followed by filtration.

The isolated yields were according to literature,<sup>28</sup> exemplifying that our flow synthesis process operates reasonably well with both electron-donating and -withdrawing substituents in the substrates.

The literature reports a large variation in the isolated yields of phenylboronic acid derivatives. For example, the isolated yields for 4-methoxyphenylboronic acid **2b**<sup>29</sup> and 4-chlorophenylboronic acid **4b**,<sup>29a,c</sup> were reported in the range of 59–91% and 34–74%, respectively.

The only experiment with a substantial difference between the cryoMJOD flow reactor and the batch mode is reported in entry 6 of Table 4. This substrate contains three methoxy substituents and one methyl group, which give a very electron-rich and activated aromatic ring.

The isolated yield obtained for product **6b** with the cryoMJOD reactor (entry 6 in Table 4) is significantly higher compared to that with the batch mode protocol, corresponding with 50% relative improvement. This improvement can be due to the much shorter residence time in the flow reactor. The flow process we have developed requires only one-sixth of the residence time as demanded by a typical batch mode protocol in order to achieve a complete conversion of charged substrate.

**An Alternative cryoMJOD Flow Process Record.** Li and collaborators<sup>30</sup> have previously demonstrated that if the borate reagent and the substrate were mixed before the *n*-BuLi reagent was added, an increased yield could be achieved in some cases, while the contrary was observed for some other substrates. For example, when 1-bromo-4-methoxybenzene **2a** was used as substrate, a substantially reduced yield (26%)<sup>31</sup> was achieved compared to the standard addition method for batch reactions (96%).<sup>31</sup>

In order to explore this approach, and thus potentially simplify the flow reactor setup by changing from setup a to setup b of Figure 2, our test experiment using the cryoMJOD reactor resulted in a slightly lower yield (50% isolated yield) compared to the outcome (72% isolated yield) when the standard addition method was used (with the setup of Figure 2a). Compared to the batch protocol of Li and collaborators,<sup>30</sup> we achieved approximately a 2-fold yield with our modified flow process, although lower than that of the setup using the telescoped fashion (Figure 2a). The process performance with the setup of Figure 2b was in line with the batch record disclosed by Li and collaborators, but with higher yield. The conversion of the bromoderivative was in the range 70–75%.

## EXPERIMENTAL SECTION

**General Methods.** NMR spectra were recorded on a Bruker Spectrospin DMX 400 with field strength of 400 MHz for <sup>1</sup>H nuclei and 100 MHz for the <sup>13</sup>C nuclei. Chemical shifts were calibrated using the solvent peaks. High-resolution mass spectra were recorded on a JEOL AccuTOF T100LC spectrometer operated in DART mode.

Starting materials and reagents were purchased commercially and used without further purification unless indicated

otherwise. Anhydrous THF and hexane were prepared by distillation over sodium and benzophenone under nitrogen.

**General Procedure for Flow Experiments (setup Figure 2a).** Prior to utilization, the reactor system was flushed with argon. The pumps were connected before the reactor was cooled to  $-65\text{ }^{\circ}\text{C}$ . All reservoirs and the reactor were kept under argon at all times via a manifold. PTFE-tubing (i.d. 1.6 mm) was utilized.

A dried Schlenk flask designated as reservoir 1 (R1) was charged with 1-bromo-4-methoxybenzene **2a** (5.06 mL, 40.0 mmol) and anhydrous THF (190 mL). A second dried Schlenk flask designated as reservoir 2 (R2) was charged with 2.0 M *n*-BuLi in pentane (24.0 mL, 48.0 mmol, 1.2 equiv). A syringe designated as reservoir 3 (R3) was charged with trimethyl borate (6.76 mL, 60.0 mmol, 1.5 equiv) and dry THF (13.5 mL).

The tubing leading to the reactor from the three reservoirs, R1, R2, and R3, were filled with the solutions before the reaction was started so that they would enter the reactor immediately as soon as the pumps were started.

The oscillator was started, and the substrate (R1) was pumped into the reactor at  $11.0\text{ mL} \times \text{min}^{-1}$  using pump (P3) drive FMI QBG-MB-Q485<sup>32</sup> and pump head Q1-SSY. *n*-BuLi in pentane (R2) was pumped into the reactor at  $1.34\text{ mL} \times \text{min}^{-1}$  using pump drive FMI QG20-2-MB-Q485<sup>32</sup> and pump head Q1-CKC-W. The pump head of P2, Q1-CKC-W, was protected from the outside atmosphere by pumping anhydrous hexane (mixture of isomers) through the gland port with a syringe pump ( $1\text{ mL} \times \text{min}^{-1}$ ) and drained to the waste container.

Trimethyl borate (R3) was pumped into the reactor at a rate of  $1.13\text{ mL} \times \text{min}^{-1}$  by means of a syringe pump. However, the pump P3 was started after 3.75 min, which corresponds to the residence time of reaction step 1. At that point of time, the pumps P1 and P2 had filled the reactor body up to the P3 inlet point. The postreaction mixture started to leave the output section after a total residence time of 9.12 min.

The first 60 mL of reaction mixture was thrown away before 120 mL of reaction mixture was collected into a round-bottom flask containing saturated ammonium chloride solution (120 mL) under stirring. The reaction mixture leaving the reactor was clear and colorless. The last 60 mL of reaction mixture was also thrown away. After 17.7 min, the reservoirs R1 and R2 were empty, and the pumps were switched to pumping dry THF. After 21.5 min, the reservoir R3 was empty.

The pumps and reactor were washed with anhydrous THF followed by acetone before the reactor was emptied through one of the bottom inlets, and the reactor was dried overnight with a stream of  $\text{N}_2$ . The pump head of P2 was disassembled, washed with water, and dried in an oven at a temperature of  $100\text{ }^{\circ}\text{C}$ .

The volume of the collected fraction was measured before the organic solvents were removed under reduced pressure. The remaining aqueous phase was acidified with 3 M HCl. The aqueous phase was then extracted with dichloromethane ( $3 \times 50\text{ mL}$ ), and the combined organic phase was washed with saturated NaCl solution ( $1 \times 50\text{ mL}$ ) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solution was filtered and the solvent removed using a rotary evaporator under reduced pressure, giving a white semisolid contaminated with a yellow-colored oil.

The crude product was stirred with hexane (mixture of isomers) ( $15\text{ mL} \times 3$ ). The solvent was removed on a Büchner filter. The filter cake was dried to provide a white-colored

powder. The yield (in the range 54–77%) was adjusted according to the volume collected from the output section of the MJOD reactor. All reactions proceeded with full conversion of the bromobenzene.

**Procedure for Flow Experiment (setup Figure 2b).** Prior to utilization, the reactor system was flushed with argon. The pumps were connected before the reactor was cooled down to  $-65\text{ }^{\circ}\text{C}$ . All reservoirs and the reactor were kept under argon at all times via a manifold. PTFE-tubing (i.d. 1.6 mm) was utilized.

A dried Schlenk flask designated as reservoir 1 (R1) was charged with 1-bromo-4-methoxybenzene **2a** (5.31 mL, 42.0 mmol), trimethyl borate (7.09 mL, 63.0 mmol, 1.5 equiv) and anhydrous THF (200 mL). A second dried Schlenk flask designated as reservoir 2 (R2) was charged with 2.0 M *n*-BuLi in pentane (25.2 mL, 50.4 mmol, 1.2 equiv). The tubing leading to the reactor from the two reservoirs were filled with the solutions before the reaction was started so that they would enter the reactor immediately as the pumps were started. The oscillator was started and the substrate and borate (R1) was pumped into the reactor at  $11.2\text{ mL} \times \text{min}^{-1}$  using pump drive FMI QBG-MB-Q485 and pump head Q1-SSY. *n*-BuLi (R2) was pumped into the reactor at  $1.32\text{ mL} \times \text{min}^{-1}$  using pump drive FMI QG20-2-MB-Q485 and pump head Q1-CKC-W. The pump head of P2, Q1-CKC-W, was protected from the outside atmosphere by pumping anhydrous hexane (mixture of isomers) through the gland port with a syringe pump at  $1\text{ mL} \times \text{min}^{-1}$ . This solution passed through the pump head and into a waste container.

The first 60 mL of reaction mixture were thrown away before 120 mL of reaction mixture was collected into a round-bottom flask containing saturated ammonium chloride (120 mL) under stirring. The solution coming out of the reactor was clear and colorless. The last 60 mL of reaction mixture was also thrown away. After 19.2 min R1 and R2 were empty, and the pumps were switched to pumping dry THF, giving a residence time of 3.75 min in reaction step one and 5.87 min in step two. The pumps and reactor were washed with anhydrous THF followed by acetone before the reactor was emptied of solvent through one of the bottom inlets, and the reactor was dried overnight with a stream of  $\text{N}_2$ . The pump head of P2 was disassembled, washed with water, and dried in an oven at a temperature of  $100\text{ }^{\circ}\text{C}$ .

The volume of the collected fraction (114 mL) was measured before the organic solvents were removed under reduced pressure. The remaining aqueous phase was acidified with 3 M HCl. The aqueous phase was then extracted with dichloromethane ( $3 \times 50\text{ mL}$ ), and the combined organic phase was washed with a saturated NaCl solution ( $1 \times 50\text{ mL}$ ) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solution was filtered and the solvent removed under reduced pressure, giving a white semisolid contaminated with yellow oil. The solid was stirred in hexane (mixture of isomers) ( $3 \times 15\text{ mL}$ ). The solvent was then removed on a Büchner filter. The isolated solid product was air-dried to provide a white powder (1.51 g), which corresponds to an isolated yield of 50% after adjusting according to the volume collected from the reactor.

**General Procedure for Batch Experiments.** A dried Schlenk flask was charged with 1-bromo-4-methoxybenzene **2a** (1.28 mL, 10.0 mmol) and anhydrous THF (48 mL) under argon. It was cooled in a dry ice bath ( $-78\text{ }^{\circ}\text{C}$ ) for 5 min before adding 2.0 M *n*-BuLi in pentane (6.0 mL, 12.0 mmol, 1.2 equiv) dropwise over 20 min using a syringe pump. After

addition, it was left under stirring for 1 h before adding trimethyl borate (1.69 mL, 15.0 mmol, 1.5 equiv) as a neat liquid and stirred for 30 min. The mixture was allowed to warm to room temperature and stirred for another 1.5 h. The mixture was quenched in a saturated ammonium chloride solution (30 mL), and the organic solvents were removed under reduced pressure. The remaining aqueous phase was acidified with 3 M HCl. The aqueous phase was extracted with dichloromethane (3 × 25 mL), and the combined organic phase was washed with saturated NaCl solution (1 × 25 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solution was filtered and the solvent removed under reduced pressure, giving a white semisolid contaminated with a yellow oil. The crude product was stirred with hexane (mixture of isomers) (15 mL × 3). The solvent was removed on a Büchner filter. The filter cake was dried to provide a white-colored powder.

**Phenylboronic Acid (1b).** [98-80-6], C<sub>6</sub>H<sub>7</sub>BO<sub>2</sub>, MW 121.93. Bromobenzene **1a** (4.26 mL, 40.0 mmol) was used in the flow experiment. The experiment was conducted as described above in the general procedure for flow experiments. A sample (108 mL) of the reaction mixture was collected from the output section of the MJOD flow reactor. This sample was worked up to provide a white powder (1.32 g), which corresponds to an isolated yield of 60%. The corresponding batch experiment, utilizing **1a** (1.06 mL, 10.0 mmol), provided an isolated yield of 65% (0.75 g). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.24 (dd, 2H, J<sub>1</sub> = 8.0 Hz, J<sub>2</sub> = 1.4 Hz), 7.59 (tt, 1H, J<sub>1</sub> = 7.4 Hz, J<sub>2</sub> = 1.4 Hz), 7.50 (m, 2H).

**4-Methoxyphenylboronic Acid (2b).** [5720-07-0], C<sub>7</sub>H<sub>9</sub>BO<sub>3</sub>, MW 151.96. 1-Bromo-4-methoxybenzene **2a** (5.06 mL, 40.0 mmol) was used in the flow experiment. The experiment was conducted as described above in the general procedure for flow experiments. A sample (114 mL) of the reaction mixture was collected from the output section of the MJOD flow reactor. This sample was worked up to provide a white powder (2.07 g), which corresponds to an isolated yield of 72%. The corresponding batch experiment, utilizing **2a** (1.26 mL, 10.0 mmol), provided an isolated yield of 69% (1.05 g). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.15 (d, 2H, J = 8.1 Hz), 6.99 (d, 2H, J = 8.1 Hz), 3.87 (s, 3H).

**2-Methoxyphenylboronic Acid (3b).** [5720-06-9], C<sub>7</sub>H<sub>9</sub>BO<sub>3</sub>, MW 151.96. 1-Bromo-2-methoxybenzene **3a** (5.14 mL, 40.0 mmol) was used in the flow experiment. The experiment was conducted as described above in the general procedure for flow experiments. A sample (111 mL) of the reaction mixture was collected from the output section of the MJOD flow reactor. This sample was worked up to provide a white powder (2.17 g), which corresponds to an isolated yield of 77%. The corresponding batch experiment utilizing **3b** (1.28 mL, 10.0 mmol) provided an isolated yield of 86% (1.30 g). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.84 (d, 1H, J = 7.3 Hz), 7.44 (t, 1H, J = 7.8 Hz), 7.02 (t, 1H, J = 7.3 Hz), 6.90 (d, 1H, J = 8.3 Hz), 6.26 (s, 2H), 3.90 (s, 3H).

**4-Chlorophenylboronic Acid (4b).** [1679-18-1], C<sub>6</sub>H<sub>6</sub>BClO<sub>2</sub>, MW 156.37. 1-Bromo-4-chlorobenzene **4a** (7.735 g, 40.0 mmol) was used in the flow experiment. The experiment was conducted as described above in the general procedure for flow experiments. A sample (120 mL) of the reaction mixture was collected from the output section of the MJOD flow reactor. This sample was worked up to provide white, fluffy needles (2.07 g), which corresponds to an isolated yield of 66%. The corresponding batch experiment, utilizing **4a** (1.934 g, 10.0 mmol), provided an isolated yield of 59% (0.93

g). <sup>1</sup>H NMR (400 MHz, deut-DMSO): δ 7.82 (d, 2H, J = 8.0 Hz), 7.39 (d, 2H, J = 8.0 Hz).

**2-Methylphenylboronic Acid (5b).** [16419-60-6], C<sub>7</sub>H<sub>9</sub>BO<sub>2</sub>, MW 135.96. 2-Bromo-1-methylbenzene **5a** (4.63 mL, 40.0 mmol) was used in the flow experiment. The experiment was conducted as described above in the general procedure for flow experiments. A sample (117 mL) of the reaction mixture was collected from the output section of the MJOD flow reactor. This sample was worked up to provide a white powder (1.28 g), which corresponds to an isolated yield of 48%. The corresponding batch experiment, utilizing **5a** (1.16 mL, 10.0 mmol), provided an isolated yield of 52% (0.71 g). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.20 (d, 1H, J = 7.4 Hz), 7.44 (t, 1H, J = 7.4 Hz), 7.27 (m, 2H), 2.80 (s, 3H).

**2,3,4-Trimethoxy-6-methylphenylboronic Acid (6b).** [212573-50-7], C<sub>10</sub>H<sub>15</sub>BO<sub>5</sub>, MW 226.03. 2-Bromo-3,4,5-trimethoxy-1-methylbenzene **6a** (10.550 g, 40.0 mmol) was used in the flow experiment. The experiment was conducted as described above in the general procedure for flow experiments. A sample (114 mL) of the reaction mixture was collected from the output section of the MJOD flow reactor. This sample was worked up to provide a white powder (2.30 g), which corresponds to an isolated yield of 54%. The corresponding batch experiment, utilizing **6a** (2.638 g, 10.0 mmol), provided an isolated yield of 36% (0.81 g). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.54 (s, 1H), 5.85 (s, 1.74H), 3.92 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 2.50 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 160.0, 155.5, 142.8, 139.7, 111.6, 77.9, 62.5, 61.5, 56.5, 24.2. HRMS (DART): *m/z* (MH<sup>+</sup>) calcd for C<sub>10</sub>H<sub>16</sub>BO<sub>5</sub> 227.10908, found 227.10925.

**Long Time Run Flow Experiment.** Prior to the experiment, the three main pumps (P1, P2, and P3) were connected to the input sections of the MJOD reactor, and the reactor was flushed with argon before it was cooled to a temperature of -65 °C. All the reagent and substrate reservoirs, the product collector tank, and the reactor tube were kept under argon throughout the experiment through an argon distribution manifold. The reservoir R1 (a dried borosilicate flask [5 L]), was charged with 1-bromo-4-methoxybenzene **2a** (68.5 mL, 542 mmol) and anhydrous THF (2600 mL). Reservoir R2 (a dried Schlenk flask [500 mL]) was charged with 2.0 M *n*-BuLi in pentane (325 mL, 650 mmol, 1.2 equiv). Reservoir R3 (a dried Schlenk flask [500 mL]) was charged with trimethyl borate (91.6 mL, 813 mmol, 1.5 equiv) and anhydrous THF (183 mL). Reservoir R4 (a dried Schlenk flask [500 mL]) was charged with anhydrous hexane (400 mL, mixture of isomers). Reservoir R5 (a dried Schlenk flask [500 mL]) was charged with dried THF (400 mL). The interconnecting tubing from the various reservoirs to the pumps and further to the input sections of the MJOD reactor were filled with the various reagent and substrate solutions in order to prepare for initiating the reaction, allowing entrance to the reactor at the identical time. The substrate (R1) was pumped into the reactor at a rate of 11.1 mL × min<sup>-1</sup> using a piston pump (P1).<sup>33</sup> *n*-BuLi in pentane (R2) was pumped into the reactor at a rate of 1.36 mL × min<sup>-1</sup> using a piston pump (P2). Trimethyl borate (R3) was pumped into the reactor at a rate of 1.14 mL × min<sup>-1</sup> with a piston pump (P3). Barrier liquid (R4) was pumped through the pump head of P2 by pump P4 at a rate of 1.6 mL × min<sup>-1</sup>. Barrier liquid (R5) was pumped by P5 at a rate of 1.3 mL × min<sup>-1</sup>. The various reservoirs and pumps were interconnected to the MJOD reactor body input sections by means of PTFE tubing (1.6 mm



i.d.) connected to the various reservoirs by means of rubber taps/seals.

The pumps, P1, P2, P4, and the oscillator were started simultaneously. The pumps P3 and P5 were started 3.75 min later, which corresponds to the residence time of reaction step 1. At that point of time, the pumps P1 and P2 had filled the reactor body up to the P3 inlet point. The postreaction mixture started to leave the output section after a total residence time of 9.12 min.

The reactor was run for 4 h before the reservoirs were empty. The postreaction mixture (~3200 mL) was collected in four equal amounts (800 mL each) in four flasks, each containing saturated NH<sub>4</sub>Cl solution (320 mL) under stirring. The reactor was washed with anhydrous THF (200 mL) for 15 min, and this wash was collected in the last of the four collection flasks. The pumps, P1, P2, P3, and the reactor were washed with acetone before the reactor was emptied of solvent through one of the bottom inlets, and the reactor was dried overnight with a stream of N<sub>2</sub>. The pump heads of P2 and P3 were dismantled, washed with water, and dried at 100 °C.

**Workup.** The organic solvents were removed under reduced pressure. The combined aqueous solutions (~1300 mL) were acidified with 3 M HCl (120 mL). Because of the large volume a continuous liquid–liquid extractor was utilized instead of a separatory funnel. Dichloromethane (500 mL × 3) was refluxed in the extractor for 2.5 h each time to extract the organic compounds. The combined organic fractions (~1600 mL) were split into two parts and each washed with a saturated sodium chloride solution (250 mL). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and filtered, and the solvent was removed under reduced pressure using a rotary evaporator to obtain a white solid contaminated with a yellow oil.

The resulting crude was stirred with hexane (mixture of isomers) (50 mL × 3). The solvent was removed on a filter nutch to provide a white-colored powder. The filtrate was evaporated, giving another two crops with the same method to achieve a total isolated yield of 55%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.15 (d, 2H, J = 8.1 Hz), 6.99 (d, 2H, J = 8.1 Hz), 3.87 (s, 3H).

#### Experimental Conditions for the Investigation of the Throughput Capacity of the cryoMJOD Flow Reactor.

**Experiment at 40 mmol scale:** R1: 1-bromo-4-methoxybenzene **2a** (5.06 mL, 40.0 mmol) and anhydrous THF (192 mL). R2: *n*-BuLi in pentane 2.0 M (24.0 mL, 48.0 mmol, 1.2 equiv). R3: trimethyl borate (6.76 mL, 60.0 mmol, 1.5 equiv) and anhydrous THF (13.5 mL). P1: 11.13 mL × min<sup>-1</sup>, P2: 1.36 mL × min<sup>-1</sup>, and P3: 1.14 mL × min<sup>-1</sup>. Residence time in L1: 3.75 min and L2: 5.37 min. V<sub>sample</sub> = 114 mL, reaction mixture was collected at the output section of the MJOD reactor giving the product **2b** as a white powder in 2.07 g, 72% isolated yield.

**Experiment at 80 mmol scale:** R1: 1-bromo-4-methoxybenzene **2a** (10.1 mL, 80.0 mmol) and anhydrous THF (144 mL). R2: *n*-BuLi in pentane 2.0 M (48.0 mL, 96.0 mmol, 1.2 equiv). R3: trimethyl borate (13.5 mL, 120 mmol, 1.5 equiv) and anhydrous THF (27.0 mL). P1: 9.52 mL min<sup>-1</sup>, P2: 2.96 mL × min<sup>-1</sup>, and P3: 2.50 mL × min<sup>-1</sup>. Retention time L1: 3.75 min, L2: 4.89 min; 110 mL reaction mixture was collected giving the product **2b** as a white powder in 3.37 g, 60% isolated yield.

**Experiment at 120 mmol scale:** R1: 1-bromo-4-methoxybenzene **2a** (15.2 mL, 120 mmol) and anhydrous THF (156 mL). R2: *n*-BuLi in pentane 10.0 M (14.4 mL, 144 mmol, 1.2 equiv) and hexanes, mixture of isomers, (14.4 mL). R3:

trimethyl borate (20.3 mL, 180 mmol, 1.5 equiv) and anhydrous THF (20.3 mL). P1: 10.68 mL × min<sup>-1</sup>, P2: 1.80 mL × min<sup>-1</sup>, P3: 2.53 mL min<sup>-1</sup>. Retention time L1: 3.75 min, L2: 4.88 min; 111 mL reaction mixture was collected giving the product **2b** as a white powder in 5.42 g, 64% isolated yield.

**Experiment at 160 mmol scale:** R1: 1-bromo-4-methoxybenzene **2a** (20.3 mL, 160 mmol) and anhydrous THF (128 mL). R2: *n*-BuLi in pentane 10.0 M (19.2 mL, 192 mmol, 1.2 equiv) and hexane, mixture of isomers, (19.2 mL). R3: trimethyl borate (27.0 mL, 240 mmol, 1.5 equiv) and anhydrous THF (27.0 mL). P1: 9.91 mL × min<sup>-1</sup>, P2: 2.57 mL × min<sup>-1</sup>, P3: 3.62 mL × min<sup>-1</sup>. Retention time L1: 3.75 min, L2: 4.55 min; 105 mL reaction mixture was collected giving the product **2b** as a white powder in 8.02 g, 72% isolated yield.

**Experiment at 200 mmol scale:** R1: 1-bromo-4-methoxybenzene **2a** (25.3 mL, 200 mmol) and anhydrous THF (100 mL). R2: *n*-BuLi in pentane 10.0 M (24.0 mL, 240 mmol, 1.2 equiv) and hexane, mixture of isomers, (24.0 mL). R3: trimethyl borate (33.8 mL, 300 mmol, 1.5 equiv) and anhydrous THF (33.8 mL). P1: 9.02 mL × min<sup>-1</sup>, P2: 3.46 mL × min<sup>-1</sup>, P3: 4.87 mL × min<sup>-1</sup>. Retention time L1: 3.75 min, L2: 4.22 min; 105 mL reaction mixture was collected giving the product **2b** as a white powder in 8.52 g, 64% isolated yield.

**Experiment at 240 mmol scale:** R1: 1-bromo-4-methoxybenzene **2a** (30.4 mL, 240 mmol) and anhydrous THF (91 mL). R2: *n*-BuLi in pentane 10.0 M (28.8 mL, 288 mmol, 1.2 equiv) and hexane, mixture of isomers, (28.8 mL). R3: trimethyl borate (40.5 mL, 360 mmol, 1.5 equiv) and anhydrous THF (20.3 mL). P1: 8.47 mL × min<sup>-1</sup>, P2: 4.01 mL × min<sup>-1</sup>, P3: 4.24 mL × min<sup>-1</sup>. Retention time L1: 3.75 min, L2: 4.38 min. The experiment failed due to high backpressure caused by the high viscosity of the reaction mixture.

## CONCLUSION

We have designed and realized modifications of the multijet oscillating disk (MJOD) millireactor system that allows the reactor system also to be utilized as a flow reactor platform for conducting reactions under cryogenic conditions using a cryostat circulator as cooling source. Subsequently, a two-step synthetic process was investigated at cryogenic temperatures using the prototypes and resulting in a flow reactor model that operated according to our predefined requirements.

This cryoMJOD flow reactor operates with net volumes at multimilliliter scale rather than at the microliter scale, which is the normal volume of commercially available flow reactor systems. Moreover, the flow reactor setup involves a reactor construction that allows accomplishment of two-step telescoped reactions. This reactor setup was utilized for developing a telescoped flow-process comprising two steps: (1) lithiation of a phenylbromide and (2) reaction between the phenyllithium derivate and trimethyl borate or other borates.

## ASSOCIATED CONTENT

### Supporting Information

<sup>1</sup>H NMR spectra of all compounds. The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra and HRMS data for 2,3,4-trimethoxy-6-methylphenylboronic acid **6b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## ■ AUTHOR INFORMATION

## Corresponding Author

\* E-mail: hans.bjorsvik@kj.uib.no. Telephone: +47 55 58 34 52, and fax: +47 55 58 94 90.

## Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

Mr. Gianfranco Liguori and Mr. Steinar Vatne are acknowledged for excellent technical assistance in connection with the realization and manufacturing of the various parts that constitute the dedicated MJOD flow reactor system for low-temperature reactions. D.S. is grateful to the Department of Chemistry at the University of Bergen for funding of the research fellowship.

## ■ REFERENCES

- (1) (a) Watts, P.; Haswell, S. J. *Chem. Soc. Rev.* **2005**, *34*, 235–246. (b) Brivio, M.; Verboom, W.; Reinhoudt, D. N. *LabChip* **2006**, *6*, 329–344. (c) Ahmed-Omer, B.; Brandt, J. C.; Wirth, T. *Org. Biomol. Chem.* **2007**, *5*, 733–740. (d) Watts, P.; Wiles, C. *Chem. Commun.* **2007**, 443–467. (e) Wirth, T., Ed. *Microreactors in Organic Synthesis*; Wiley-VCH: New York, 2008; pp 1–297. (f) Yoshida, J.; Nagaki, A.; Yamada, T. *Chem.—Eur. J.* **2008**, *14*, 7450–7459. (g) Special Issue on Flow Chemistry. *ChemSusChem* **2012**, *5*(2), 215–350.
- (2) (a) Syrris Ltd. <http://www.syrris.com/>. (b) Chemtrix BV <http://www.chemtrix.com/>. (c) Uniqsis Ltd. <http://www.uniqsis.com/>. (d) Milestone srl <http://www.milestonesrl.com/>.
- (3) Browne, D. L.; Deadman, B. J.; Ashe, R.; Baxendale, I. R.; Ley, S. V. *Org. Process Res. Dev.* **2011**, *15*, 693–697.
- (4) AM Technology: <http://www.amtechuk.com/>.
- (5) Peacock, D. G., Richardson, J. F., Eds. *Chemical and Biochemical Reactors and Process Control*. In *Chemical Engineering*, 3rd. ed.; Butterworth-Heinemann: Oxford, 1994; Vol. 3.
- (6) Fluens Synthesis <http://www.FluensSynthesis.com/>.
- (7) (a) Hofmann, A. W. *Ber.* **1881**, *14*, 2725–2736. (b) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893–2903.
- (8) Liguori, L.; Bjorsvik, H.-R. *Org. Process Res. Dev.* **2011**, *15*, 997–1009.
- (9) Dressen, M. H. C. L.; van de Kruijs, B. H. P.; Meuldijk, J.; Vekemans, J. A. J. M.; Hulshof, L. A. *Org. Process Res. Dev.* **2010**, *14*, 351–361.
- (10) Spaccini, R.; Liguori, L.; Punta, C.; Bjorsvik, H.-R. *ChemSusChem* **2012**, *5*, 261–265.
- (11) Hessel, V.; Hofmann, C.; Löwe, H.; Meudt, A.; Scherer, S.; Schönfeld, F.; Werner, B. *Org. Process Res. Dev.* **2004**, *8*, 511–523.
- (12) Brown, D. L.; Baumann, M.; Harji, B. H.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2011**, *13*, 3312–3315.
- (13) Shu, W.; Pellegatti, L.; Oberli, M. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 10665–10669.
- (14) (a) Heck, R. F.; Negishi, E.-i.; Suzuki, A. *Scientific Background of the Nobel Prize in Chemistry 2010. Palladium-Catalyzed Cross Couplings in Organic Synthesis*; The Royal Swedish Academy of Sciences: Stockholm, Sweden; October 6, 2010; [http://www.nobelprize.org/nobel\\_prizes/chemistry/laureates/2010/advanced-chemistryprize2010.pdf](http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/advanced-chemistryprize2010.pdf). (b) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6722–6737.
- (15) (a) Miyaura, N.; Yamada, Y.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437–3440. (b) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866–867.
- (16) (a) Tidwell, J. H.; Peat, A. J.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 7164–7168. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (c) Kawasaki, I.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1998**, *48*, 1887–1901. (d) Kawaski, I.; Yamashita, M.; Ohta, S. *Chem. Pharm. Bull.* **1996**, *44*, 1831–1839. (e) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; pp 49–
97. (f) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263–303. (g) Suzuki, A.; Brown, H. C. Suzuki Coupling. In *Organic Syntheses via Boranes*; Aldrich Chemical Company: Milwaukee, 2003; Vol. 3, pp 1–314. (h) Zapf, A. Coupling of Aryl and Alkyl Halides with Organoboron Reagents (Suzuki Reaction). In *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2004; *1*, pp 211–229. (i) Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc.* **2004**, *126*, 10313–10318. (j) Coleman, R. S.; Lu, X.; Modolo, I. *J. Am. Chem. Soc.* **2007**, *129*, 3826–3827.
- (17) Glasnov, T. N.; Kappe, C. O. *Adv. Synth. Catal.* **2010**, *352*, 3089–3097.
- (18) Goossen, L. J.; Melzer, B. *J. Org. Chem.* **2007**, *72*, 7473–7476.
- (19) Adams, J.; Elliot, P. *J. Oncogene* **2000**, *19*, 6687–6692.
- (20) Groviak, M. P. *Am. J. Ther.* **2001**, *8*, 321–328.
- (21) Westmark, P. R.; Smith, B. D. *J. Am. Chem. Soc.* **1994**, *116*, 9343–9344.
- (22) Weston, G. S.; Blázquez, F.; Baquero, F.; Schoichet, B. K. *J. Med. Chem.* **1998**, *41*, 4577–4586.
- (23) James, T. D.; Sandanayake, K.; Iguchi, R.; Shinkai, S. K. *J. Med. Chem. Soc.* **1995**, *117*, 8982–8987.
- (24) In the MJOD flow reactor, backmixing is dependent on the fluid flow rate and the oscillating frequency. With a very low fluid flow rate from the feeding pumps (via the input section) and a high frequency of the oscillator, backmixing will in some degree take place. In the case of the MJOD reactor we say that backmixing occurs when there is backflow from a reactor cavity (the volume between two discs) to a cavity at a step closer (lower step) to the input section.
- (25) Box, G. E. P.; Hunter, W. G.; Hunter, J. S. *Statistics for Experimenters*. In *An Introduction to Design, Data Analysis, and Model Building*; Wiley: New York, 1978.
- (26) (a) Draper, N. R.; Smith, H. *Applied Regression Analysis*, 3rd ed.; Wiley: New York, 1998. (b) Montgomery, D. C.; Peck, E. A. *Introduction to Linear Regression Analysis*; Wiley: New York, 1982.
- (27) The process conditions were identical, except for the reactor residence time (3.75 min + 5.37 min) that was according to the literature; see, e.g., ref 29a and the Experimental Section for more details.
- (28) Wenjie, L.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394–5397.
- (29) (a) Fukuda, T.; Sudo, E.; Shimokawa, K.; Iwao, M. *Tetrahedron* **2008**, *64*, 328–338. (b) Wang, C.; Rakshit, S.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 14006–14008. (c) Lloud, D. G.; Hughes, R. B.; Zisterer, D. M.; Williams, D. C.; Fattorusso, C.; Catalanotti, B.; Campiani, G.; Meegan, M. J. *J. Med. Chem.* **2004**, *47*, 5612–5615.
- (30) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394–5397.
- (31) The reported result was measured by HPLC as described by Li and collaborators, reference 30.
- (32) Information about FMI pumps can be found at <http://www.fmipump.com/>.
- (33) Pump P1: FMI QBG-MB-Q485 and pump head Q1-SSY. Pumps P2 and P3: FMI QG20-2-MB-Q485 and pump head Q1-CKC-W. Pump P4: FMI QG20-2-MB-Q485 and pump head Q1-SSY. Pump P5: FMI QD-2-MB and pump head Q0-SSY. <http://www.fmipump.com/>.