Flow Chemistry Processes for Reactions Utilizing Unstable Intermediates: Applications Toward Pharmaceutical Production

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Contents

Chapter 1

General Introduction

1. Flow chemistry technologies for pharmaceutical production processes: as a tool of process chemistry

The evolution and prosperity of humankind so far has been notably supported by advances in medical technology, namely the creation of increasingly superior medicines. However, the history of the creation of excellent medicines has not always been positive, as it includes some sobering stories of drug-induced diseases.[1] Specific examples include the thalidomide problem that occurred before the establishment of chiral drug synthesis technology,[2] subacute myelo-optic neuropathy (SMON) caused by inadequate regulations for Active Pharmaceutical Ingredient (API) standards (Quinoform),[3] drug-induced hepatitis,[4] and drug-induced AIDS.[5] It is no exaggeration to say that advances in pharmaceutical manufacturing technology have often resulted from the battles to overcome these social issues.

As technologies for pharmaceutical production advance, quality controls for the APIs are strictly required, not only for improving API assays in drugs, but for reducing the quantity of impurities and conducting suitable evaluations of their effects on metabolic pathways.[6] Therefore, the establishment of strategies to manage impurities in APIs and related intermediates must be addressed at the very core of process development. According to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), impurities can be classified into the following categories: [7]

- Organic impurities (process and drug related)
- Inorganic impurities

- Residual solvents

Organic impurities can arise during the manufacturing process and/or storage of the new drug substance. They can be identified or unidentified, volatile or non-volatile, and include:

- Starting materials
- By-products
- Intermediates
- Degradation products
- Reagents, ligands and catalysts

Inorganic impurities can result from the manufacturing process. They are normally known and identified and include:

- Reagents, ligands and catalysts
- Heavy metals or other residual metals
- Inorganic salts
- Other materials (*e.g.* filter aids, charcoal)

Solvents are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance. Since these are generally of known toxicity, the selection of appropriate controls is easily accomplished.

In terms of evolutional changes in pharmaceutical production, process chemistry has been playing a key role in reducing these impurities.[8] It has been noted that most of the impurities are generated in reaction steps as side products, therefore, process chemists have often focused on controlling these side reactions.[9]

Considering the reaction processes, conventional pharmaceutical productions mainly consist of batch processes, which are selected for the initial investigations at an early stage of pharmaceutical development and the best ones are applied for the final scale-up manufacturing. Although the batch processes are generally reliable methods, not only for pharmaceuticals but also many industrial chemicals, plastics and agrochemicals, there are severe limitations for some specific reactions, *i.e.* utilizing water-reactive substances and oxygen-reactive substances,[10] reactions requiring cryogenic conditions,[11] handling of high potency or hazardous

compounds,[12] and reactions employing highly unstable intermediates.[13] To address these limitations, some flow chemistry technologies have been studied and developed for process chemistry and scale-up productions.[14] Herein, we have focused our attention on two topics related to the methodology of organic chemistry in pharmaceutical production processes; "Flow flash chemistry" and "Process chemistry for scale-up productions".

Flow flash chemistry

In the hitherto development and refinement of reactions by organic chemists, the main research subjects have been the study of reactants (*e.g.* reagents, catalysts, ligands), and reaction conditions (*e.g.* solvents, temperature, pressure). However, attempts to create micrometer-sized flow paths using microfabrication techniques and to use them as chemical reactors for chemical reactions have spread rapidly[15] in the last 25 years. These reactors are generally called microreactors, flow-microreactors, or flow reactors.

The terms for describing these reactors have been variously defined. For example, Ehrfeld *et al.* proposed "The microreactor is a device that performs a reaction in a channel (microchannel) of an equivalent diameter, usually less than 500 μm. However, it is not necessary that all the lateral dimensions along the flow axis are in the μm region, and only a part required depending on the application may be in the μm region."[16] Also, flow-microreactors are defined as performing chemical reactions in a "flow" and "micro region". Watts *et al.* stated a "microreactor is defined as a device that contains micro structured features, with a submillimetre dimension, in which chemical reactions are performed in a continuous manner."[17]

The main features of these flow-microreactors can be summarized as follows:

(1) High speed mixing (precise mixing)

(2) Precise temperature control (heat removal effect)

(3) Precise residence time control (residence time distribution control)

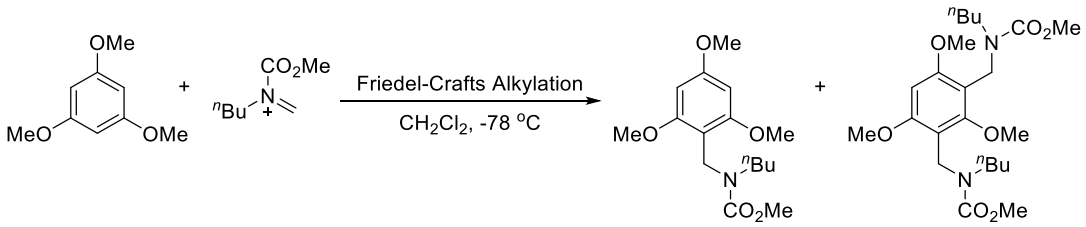
Superior flow synthesis has focused on taking advantage of these features for reaction development.

Initially, chemical reactions using flow-microreactors were mostly used as a means for carrying out analytical chemistry, but a few decades ago they also began to be used in organic synthesis reactions, and several examples

of reaction efficiency arising from the specific features of flow reactors have been reported.[18,19] Some of the notable examples have been termed "Flash Chemistry".[20]

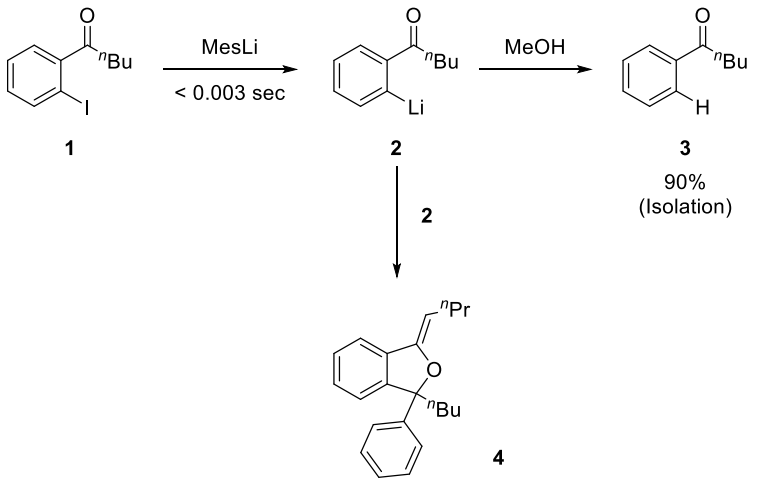
Controlling an unstable cation in a flow system is one of the typical examples of flow flash chemistry. For example, a Friedel-Crafts alkylation reaction utilizing a "cation pool" as an alkylation reagent can be cited as an example that takes advantage of the features of high-speed mixing and precise temperature control.[21] When this reaction is carried out in a conventional batch reactor, it is difficult or impossible to stop the reaction at monoalkylation, and side reaction (overreaction) leading to polyalkylation is a major problem. However, Yoshida *et al.* succeeded in carrying out selective monoalkylation reactions by taking advantage of flow-microreactors (Scheme 1).

Scheme 1. Selective monoalkylation by Friedel-Crafts reaction utilizing a flow-microreactor



Furthermore, an example of a protecting-group-free synthesis using organolithium compounds has been reported by Yoshida *et al.*[22] In general, organolithium species react with ketones very rapidly, and therefore ketone carbonyl groups should be protected before an organolithium reaction, if they are not involved in the desired transformation. However, it was shown that a flow microreactor enables such protecting-group-free organolithium reactions by greatly reducing the residence time (0.003 s or less). Aryllithium species bearing ketone carbonyl groups are generated by iodine–lithium exchange reactions of the corresponding aryl iodides with mesityllithium and are reacted with various electrophiles using a flow-microreactor system (Figure 1). This is another example of flow flash chemistry for handling an unstable anion.

Figure 1. Protecting-group-free synthesis using organolithium compounds by flow flash chemistry



Then, we defined the purpose of our studies as, to control reactions *via* unstable intermediates by using flow-microreactors and the application of flow-microreactors to process chemistry and scale-up synthesis. Hitherto, there have been very few examples of the "reaction control of unstable intermediates" using flow-microreactors, and successful applications will open up a new field of research and development. Specifically, in addition to the features of high-speed mixing and precise temperature control of microreactors, the ability to precisely control residence time and residence time distribution is considered to be a great advantage for reactions involving unstable intermediates.

When a reaction is performed in a batch reactor, the intermediate formed immediately after initiation of the reaction must remain in the reactor until all the raw materials are consumed. Thereafter, another reactant is added and the process proceeds to the next stage. Under these batch reaction conditions, intermediate decomposition and side reactions are likely to occur. On the other hand, in a flow-microreactor, the compound (and/or intermediates) produced by the reaction can be immediately moved to the next location and used for the subsequent reaction. Therefore, by utilizing flow reactors, it is thought that problems such as intermediate decomposition and side reactions can be avoided, and thus, even reactions *via* unstable intermediates can be easily controlled and utilized.[2,3] An example of exploring a novel flow chemistry method and the subsequent post processing is discussed in Chapters 2 and 3.[24,25]

Process chemistry for scale-up productions

Scale-up synthesis is the result of a culmination of process research. In pharmaceutical development, numerous experiments are carried out from the initial synthesis in medicinal chemistry to the establishment of a production method for product synthesis. Many of the manufacturing methods are greatly changed from those employed for the initial synthesis in medicinal chemistry, through process research; *e.g.* changes to starting material, synthetic route, intermediate, purification procedure, separation process. These changes are generally recognized as establishing a more robust synthesis method to maintain constant product quality and reduce costs. Through the investigations for process research and development, the starting materials, waste, energy, equipment, production time, cost, as well as environmental impact of the process are reduced as much as possible. In addition, the productivity and safety of the process can be improved.

In process research, experiments in the laboratory are generally carried out on a small scale of several milligrams to several grams. However, a process chemistry route in which the synthetic route is established on a scale of several grams or less, often causes new problems when scaled up to kilogram scale. Typical difficulties and concerns related to scale-up synthesis are;

- Difficulties in precise control of reactant molar ratio
- Difficulties in precise control of reaction temperature
- Inefficiency in mixing
- Increase of related substances (impurities)
- Increased risk of human exposure to hazardous materials
- Psychological and physical hurdles for safely handling unstable intermediates
- Necessity for safety-oriented manufacturing methods

Some of these items can be understood and addressed with calculated “scale-up factors”, but not all the items can be precisely quantified, and the possibility of increased side reactions during scale-up must always be considered. The most important thing is to make it possible to perform the target reaction with reproducibility and understand any side reactions and their reaction mechanisms.

However, many batch-type reactions (for almost all current processes) have established manufacturing

methods that cannot thoroughly eliminate the risk of scale-up. Typical examples of reactions without adequate investigation are organometallic reactions, especially organolithium reactions in batch chemistry. Thus, many process chemists have been focusing their attention on understanding such reactions and how to use them for production.

In the course of process development, numerous unknown side reactions and side products are observed. For sustaining the quality of APIs, process chemists must address unprecedented challenges, by not only making the most of current knowledge but also through exploring new discoveries. In Chapter 4, an example of the process understanding required for scale-up production using a new application of flow chemistry is described.[26]

2. Organolithium reactions in flow chemistry

Since its full-scale research and development was started worldwide in the 1990s, Flow Chemistry (FC) has received much attention and is becoming one of the most useful and indispensable technologies for a variety of chemical syntheses, ranging from pharmaceuticals and agrochemicals to plastics and the chemicals used in organic electronic devices. Although chemical synthesis using FC technology has received significant research interest, both from academia and industry, the potential of this technology has not yet been fully utilized for scale-up productions, due to a lack of general and robust flow reactors for transferring laboratory process development to scale up production.

When addressing stoichiometric organometallic reactions in process development, precise control of reaction temperatures is generally required in order to suppress side reactions, especially for organolithiums, Grignard reagents, organozinc-mediated reactions, *etc*., and, therefore, prolongation of reaction time is regarded as unavoidable.[27] Although stoichiometric organometallic reactions have limitations, these reactions, specifically organolithium reactions, are still an essential tool to make new C-C bonds for constructing the frameworks of organic compounds.

Herein, organolithium chemistry is looked at from a process chemistry perspective, focusing on three topics; efficiency of organolithium reactions in flow chemistry, control of side reactions with solvent, and control of alkylation side reactions.

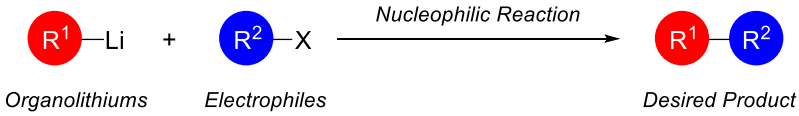
Efficiency of organolithium reactions in flow chemistry

Reactions using organometallic reagents are at the core of synthetic organic chemistry, and organolithium reagents are one of the most important among them.[28] The organolithium reaction is a chemical conversion in which a highly reactive organometallic lithium species is used, as a reactant or intermediate, to react with an electrophile. When an organolithium intermediate is handled in a batch reactor, a cryogenic condition is generally required for the manufacturing process in order to control side reactions, and the risk of ignition issues, due to their spontaneously combustible and water-reactive nature, must be constantly kept in mind. Further,

when conducting manufacturing outsourcing, it is necessary to find and investigate subcontractors that have suitable reaction facilities dedicated to cryogenic conditions, and the number of such experienced and available subcontractor candidates is often extremely limited.

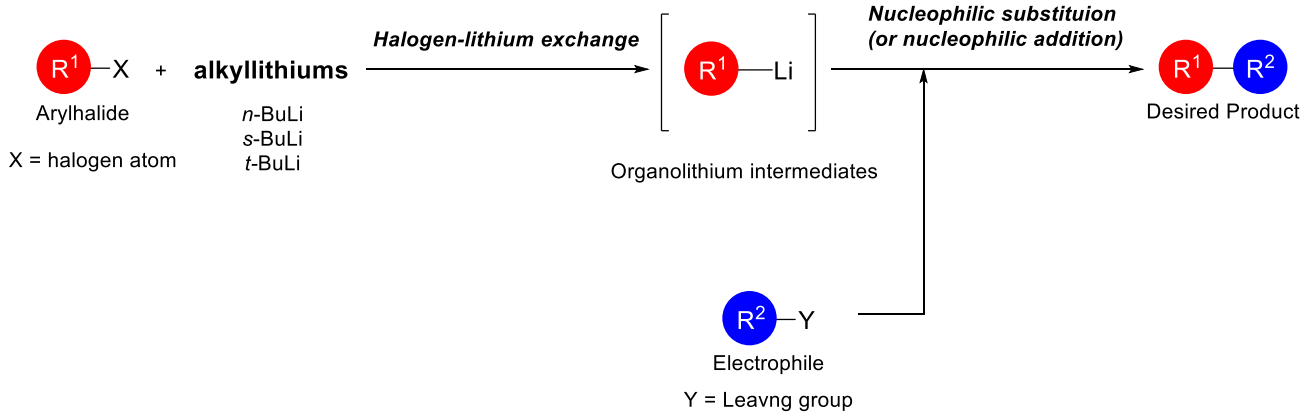
Although process development to avoid the organolithium reaction has often been carried out, the usefulness of the reaction is undoubted and the benefits are numerous. For example, functionalization of substrates can be performed easily by carrying out a nucleophilic reaction between an organolithium reagent and electrophiles (Scheme 2).

Scheme 2. Nucleophilic substitution reactions between organolithiums and electrophiles



One of the well-known typical procedures for generating such organolithium intermediates is the halogen-lithium exchange reaction between aryl halides and alkyllithiums. Various organolithium intermediates can be generated by halogen-lithium exchange reaction using the commercially available reagents, *n*-BuLi, *s*-BuLi and *t*-BuLi (Scheme 3).[2 9]

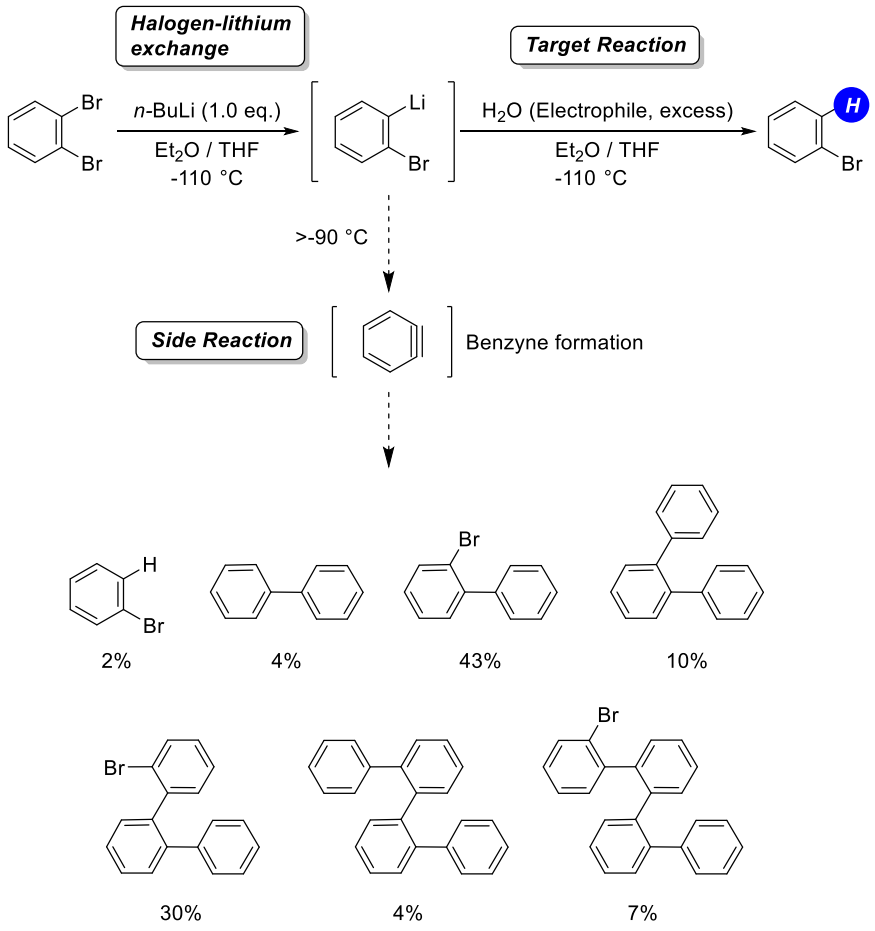
Scheme 3. Generation of organolithiums by halogen-lithium exchange and their reaction with electrophiles



Although halogen-lithium exchange is a highly useful method for generating organolithium species, there are

a few problems. For example, in halogen-lithium exchange reactions using a batch reactor, it is necessary to carry out the reaction under a low temperature condition of about -78 °C because of problems such as the instability of the generated organolithium species. In particular, the generation of highly unstable organolithium species that decompose almost immediately, must be performed and used under extremely low temperatures in batch (*e.g.* -100 °C)[30], which thus precludes their use in many cases (Scheme 4).

Scheme 4. Example of a halogen-lithium exchange reaction that requires cryogenic conditions



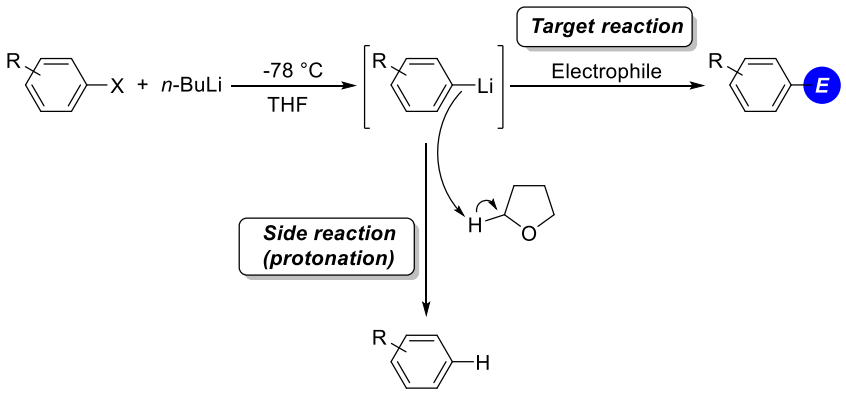
This is considered to be one of the major reasons for the poor performance of organolithium reactions in batch. Thus the emergence of novel synthetic chemical methods capable of stably generating such unstable organolithium intermediate species has been greatly desired, and flow-microreactors, as a tool for handling such unstable intermediates, have been increasingly studied.

Control of side reactions arising from solvent -proton transfers between solvent and organolithiums-

Organolithiums are widely used in the pharmaceutical industry and a major advantage is their high reactivity, but this may also lead to unexpected side reactions. Unstable intermediates that are difficult to control in batch reactors can be handled relatively easily in flow.[31] In particular, the effectiveness of flow reactors for chemical reactions using organolithium species is tremendous, and it is expected that it can be applied to various pharmaceutical synthesis processes. The superior handling of unstable intermediates is particularly useful in terms of controlling side reactions.

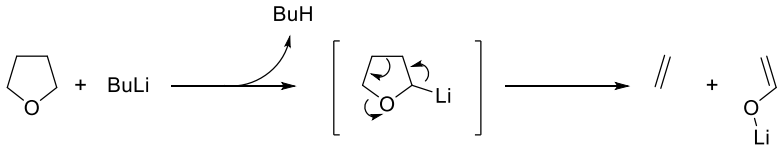
One of the typical side-products derived from highly unstable organolithium intermediates is the protonated product (Scheme 5).

Scheme 5. Protonation as a side reaction for organolithium intermediates



It has been reported that organolithiums are protonated in solvents such as THF. The organolithiums cleave THF smoothly to give butane, ethylene and the lithium enolate of acetaldehyde (Scheme 6).[32] In some cases, the protonation from solvent occurs in a very short time, and the target reactions become impossible in batch reactors.

Scheme 6. Protonation as a side reaction for organolithiums in THF solvent

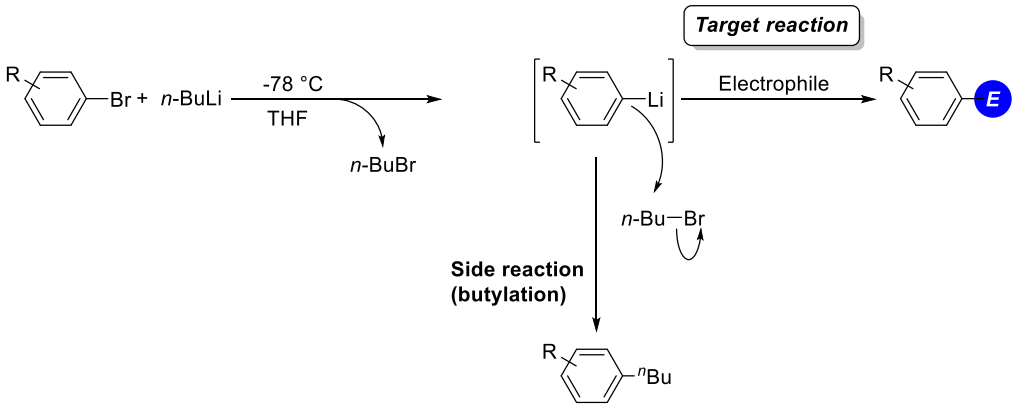


Chapter 2 describes an example of controlling a highly unstable organolithium intermediate from undergoing protonation as a side reaction, and allowing the subsequent borylation reaction to be efficiently carried out in THF solvent. The generated lithium intermediate is a dianion and the strict controls required are described in detail.

Control of alkylation side reactions - butylation of organolithiums by butylbromide generated by halogen-lithium exchange

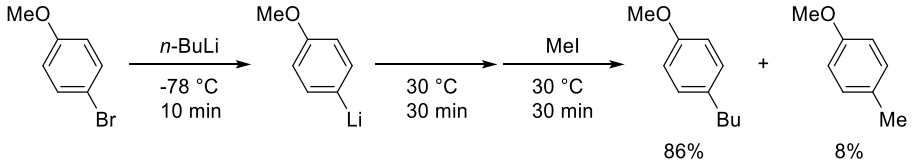
As mentioned above, the halogen-lithium exchange reaction is an extremely effective synthetic procedure, which has been widely used for generating organolithiums. However, the generated organolithium intermediate is often unstable and highly reactive, which means the reaction is generally carried out under cryogenic conditions in batch reactors. In addition, there is a potential side reaction involving the alkyl halide that is generated after the initial halogen-lithium exchange, which may lead to an alkylated side-product being formed (Scheme 7).

Scheme 7. Alkylations of organolithiums as a side reaction



Typical examples of butylation as a side reaction were reported by Yoshida, *et al.* in 2012.[33] The lithiated species generated after halogen-lithium exchange, ArLi, reacted with BuX because the desired subsequent reaction step was slower, which may often be the case. In their experiments in batch, the undesired butylated product was obtained as the major product (Scheme 8).

Scheme 8. Example of butylation as side reaction mainly giving the undesired product

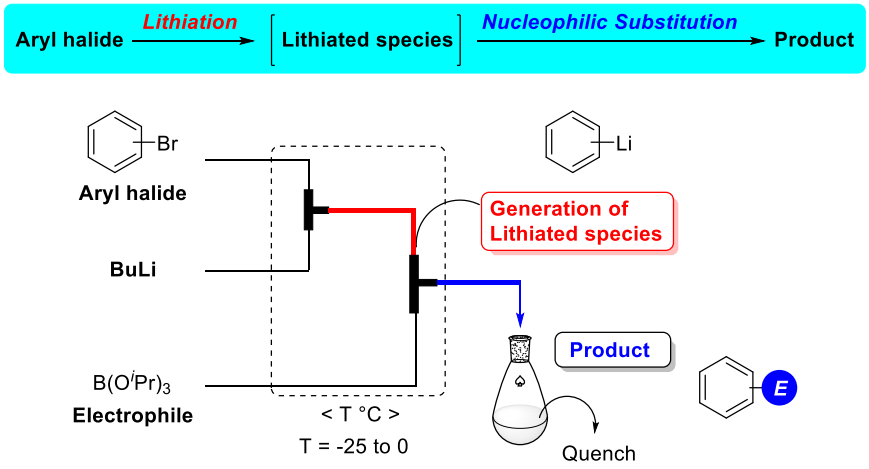


Chapter 3 shows that flow chemistry is very useful for suppressing these side reactions. In addition, the flow chemistry process was also applied to other boronic acid syntheses, and examples of the process development are described.

3. Application of flow chemistry for scale-up production: development of a lithiation-borylation process for kilogram-scale production

In Chapters 2 and 3, useful examples of applying flow chemistry to decrease side reactions are described. The target compounds of both chapters are boronic acids and the flow chemistry processes for lithiation-borylation are described (Figure 2).

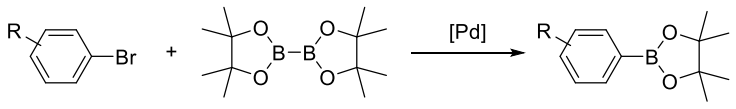
Figure 2. Flow chemistry process for boronic acid synthesis utilizing a lithiation-borylation process (Chapters 2 and 3)



Comparing process development by flow chemistry with batch chemistry, it is widely agreed that organolithiums can be more easily handled and cryogenic conditions are more avoidable using flow, however, there are still very few examples of scale-up productions using flow chemistry processes. After the flow process for a lithiation-borylation procedure was established, as described in chapters 2 and 3, an investigation on the scale-up procedure for boronic acid production was conducted.

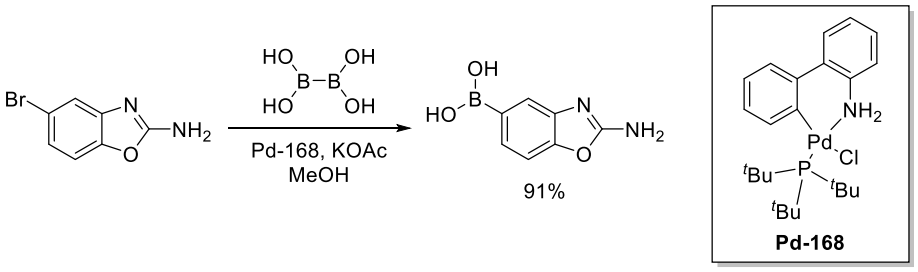
Boronic acid compounds occupy an important position in pharmaceutical synthesis processes, as the Miyaura borylation reaction has become widely used as an efficient production method (Scheme 9).[3 4]

Scheme 9. Miyaura borylation process



A modified Miyaura borylation process using tetrahydroxydiboron has also been reported, which avoids the use of bis(pinacolato) diboron and the subsequent need to hydrolyze the resulting boronic ester to obtain the corresponding acid (Scheme 10).[3 5]

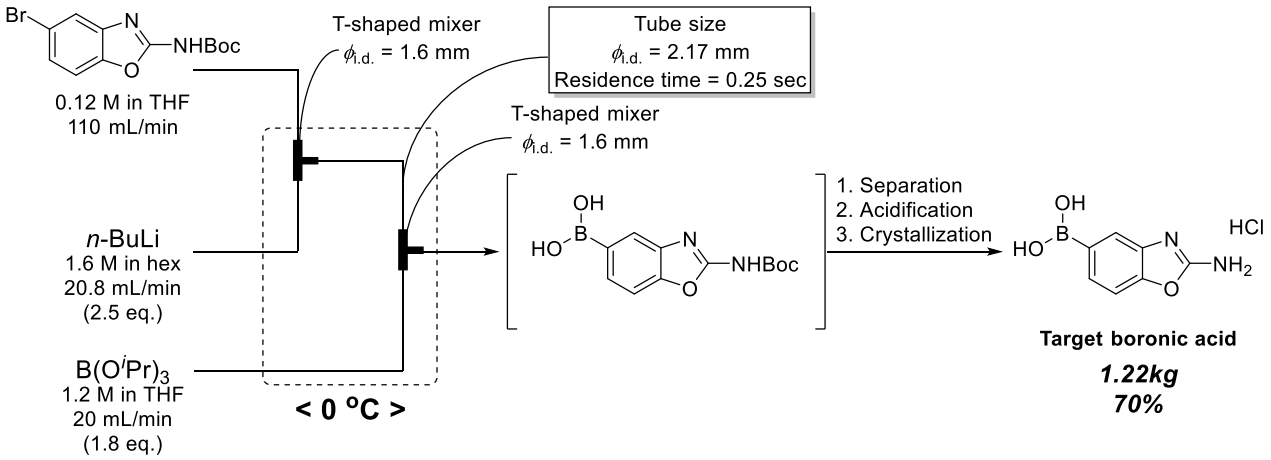
Scheme 10. Development and Scale-up of an Efficient Miyaura Borylation Process Using Tetrahydroxydiboron



However, palladium catalysts and phosphine ligands are essential in the Miyaura borylation processes and any residue of these in the resulting boronic acid product may become a serious problem in downstream processing. On the other hand, boronic acid syntheses utilizing lithiation-borylation processes offer useful alternative routes that avoid the Pd catalysts and ligands, as well as the subsequent problems associated with their removal.

In order to realize process development and a manufacturing process for boronic acid synthesis using a lithiation-borylation flow reactor, a scale-up study was carried out for a synthesis with an extremely unstable dianion species as an intermediate, and a kilogram scale production was successfully achieved (Figure 3).

Figure 3. Scale up synthesis for boronic acid



In Chapter 4, a detailed example of scale-up for production of a boronic acid synthesis utilizing a lithiation-borylation flow process is described.

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Chapter 2

Development and Scale-up of a Flow Chemistry Lithiation−Borylation Route to a Key Boronic Acid Starting Material

Abstract

A flow chemistry process for the synthesis of a key boronic acid starting material was developed utilizing flow flash chemistry that allowed formation and subsequent productive reaction of an unstable organolithium intermediate. Rapid scale-up from Discovery Chemistry and process optimization to kilogram-scale production was achieved using a short residence time (0.25 s) and noncryogenic temperature (0 °C), without the need to increase the number of reactors. A comparison of the flow process with a Miyaura borylation process suggested some potential benefit in the overall process operating efficiency from avoiding the use of Pd and genotoxic boron reagents.

Introduction

Boronic acids are widely used in the synthesis of active pharmaceutical ingredients (APIs), most notably due to their key role in Suzuki−Miyaura cross-coupling reactions, and improved strategies for their synthesis are of constant interest. Although the most atom-efficient and cost-effective route to boronic acids involves the metal-halogen exchange of a halide starting material, commonly using an organolithium reagent followed by quenching with a trialkyl borate, this method is often restricted by its poor functional group tolerance.[1] Thus, the more versatile strategy involving a palladium-catalyzed Miyaura borylation is often used, which not only suffers from lower atom efficiency and cost effectiveness, but also some of the most commonly used boron sources (e.g., bis(pinacolato)diboron, B_2Pin_2, and bis-boronic acid, BBA) have recently been identified as positive for mutagenicity in the Ames assay and are therefore potential sources of genotoxic impurities.[2]

Flow chemistry (FC) technology has received much interest in recent years, both from academia and industry, for expanding the scope while reducing the cost of synthesis, with applications for pharmaceuticals, agrochemicals, plastics, and fine chemicals.[3,4] However, due to the vast buildup of batch chemistry capability, both in availability and operator experience, coupled with the lack of proven robust flow reactor technology and know-how for transferring laboratory flow process development to scale up production, FC applications have not yet been widely employed in API manufacturing.

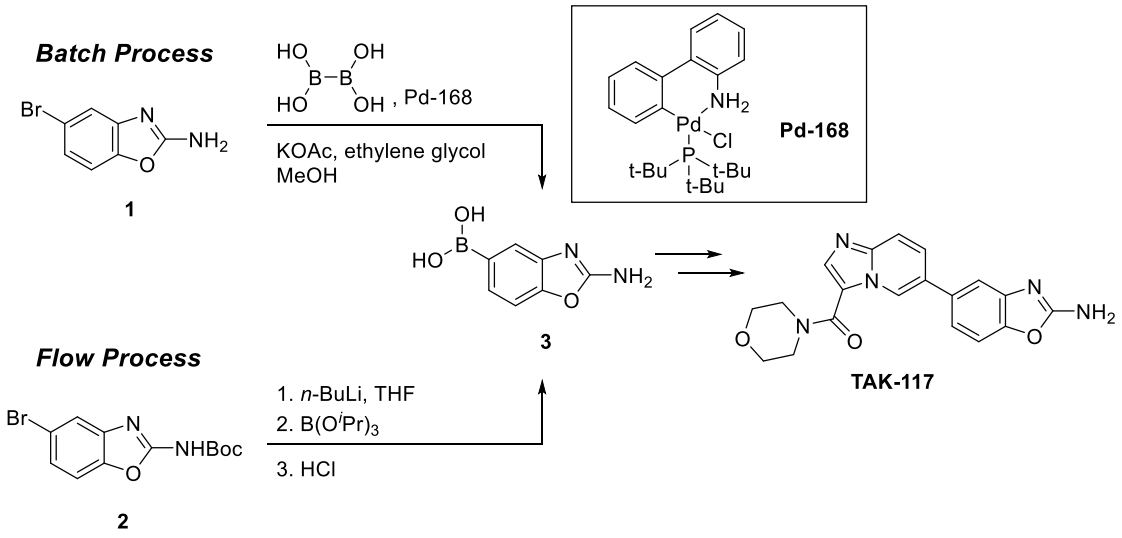
One of the opportunities for utilizing FC in the production of APIs that has emerged involves the capability to rapidly and safely handle unstable organolithium compounds to achieve reactions that are otherwise extremely difficult, or impossible under batch conditions.[5,6] Thus, FC lithiation-borylation[7] was explored as a potential alternative route to obtain aryl boronic acid **3** (Figure 1), which is a key starting material in the manufacturing process of TAK-117, a selective PI3Kα inhibitor currently in Phase 1b clinical trials. In the original batch process, a high loading of a palladium catalyst, $Pd(PPh_3)_2Cl_2$, and costly borylating reagent, B_2Pin_2, were utilized, and the cost of these two reagents accounted for more than half of the raw material costs for TAK-117.[8]

The lithiation−borylation strategy, if successful, offered the potential to avoid both the use of a costly

catalyst, reducing the cost of raw materials, and BBA, which has been shown to be prone to oxygen-mediated degradation and a source of potentially genotoxic impurities (especially important given the close proximity to the final API in the TAK-117 synthesis). An alternative batch synthesis of **3** utilizing organometallic chemistry, with either *n*-BuLi or sec-BuLi, was unsuccessful, with severe "gumming" issues being observed and no desired compound being obtained.

Therefore, the flow process for lithiation−borylation of the aryl bromide **1** and its N-boc protected analogue **2** was investigated, to be used in conjunction with a batch workup and isolation. The use of BBA was also being investigated concurrently with the work described in this manuscript that led to the development of a more efficient batch Miyaura borylation process (Figure 1).[8]

Figure 1. Batch Miyaura borylation and flow chemistry lithiation-borylation routes for the synthesis of the key aryl boronic acid, **3**.



Experimental Section

1. 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-5 μm, 12 nm) 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 the 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 **3**, **4**, **1**, **5**, and **2** (Figures 1 and 2) eluted at relative retention times (RRT) of 1.6, 2.3, 3.2, 4.4, and 8.3 min, respectively.

2. General Laboratory Scale Experimental Procedure

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 **2** dissolved in THF as a 0.12 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 1.2 M solution of tri(propan-2-yloxy)borane, ($B(O^iPr)_3$) freshly prepared in anhydrous THF. 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 typically 0.25 s, which resulted in a 12.5 cm tube being used when a flow rate of 20.0 mL/min and 3.3 mL/min was used for Feedstocks A and B. Shimadzu-GLC tee pieces (part no.: 6010-72357) were used as mixers. The investigation of the residence time for the borylation

showed that 1 s 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, precooling 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 300 mL flask containing 36 mL (6 vol.) of water for quenching. When the experimental run was concluded (typically after 8 min of operation, 6.0 g/19.2 mmol of compound **2**), the reaction mixture was extracted with toluene (30 mL, 5 vol.). The organic layer was further extracted with water (36 mL, 6 vol.), 0.2 M NaOH (36 mL, 6 vol.), and finally a second portion of water (36 mL, 6 vol.). The combined aqueous layers were acidified to a pH of 1 using conc. HCl (6 mL, 3.75 equiv) and extracted three times with EtOAc (3 × 36 mL, 3 × 6 vol.). The combined organic layers were distilled to 3 vol. under vacuum and the solvent exchanged to toluene by adding 3 portions of toluene (3 × 36 mL, 3 × 6 vol.) and distilling under vacuum at 40 °C to 2 vol. Finally, toluene (36 mL, 6 vol.) and 4M HCl (15 mL, 3.13 equiv) were added, and the reaction mixture was heated to 55 ± 5 °C for 2 h until deprotection of the tertbutyloxycarbonyl (Boc) group was complete as indicated by HPLC analysis (specification NMT 1.0% of compound **4**, Figure 2). The resulting slurry was cooled to 5 ± 5 °C over 1 h and aged at that temperature for a total of 2 h before being filtered. The wet-cake was washed with EtOAc (18 mL, 3 vol.) and dried under vacuum at 45 °C to afford compound **3** as white to offwhite crystals in 79% yield (3.26 g) and 98.9% purity.

3. Scale-up Experimental Procedure

Three gear pumps equipped with mass flow meters (Bronkhorst, mini-CORI-Flow) were used to pump the solutions of the three reagents. Feedstock A consisted of compound **2** dissolved in anhydrous THF as a 0.12 M solution and was pumped at 110.0 mL/min. Feedstock B was commercially available 1.6 M *n*-BuLi in hexane used directly from the supplied bottle and pumped at 20.8 mL/min, while feedstock C was a 1.2 M solution of $B(O^iPr)_3$ freshly prepared in anhydrous THF, pumped at 20.0 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 0.25 s, which resulted in a 15 cm long tube (ID 2.17 mm) being used with the above flow rates. Swagelok tee pieces (ID 1.3 mm, part number: SS-100-3) were used as mixers. The precooling 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 the thermal mass flow meters, the product stream was collected, and the process was run for a total of 10 h 14 min to afford compound **4** in 94.4% HPLC purity.

The collected product stream was quenched with H_2O (6 vol.) and toluene (5 vol.) to allow for efficient liquid−liquid extraction, as compound **4** was found to readily transfer to the basic aqueous phase. The organic layer was then further extracted with water (6 vol.) and aqueous sodium hydroxide (0.2 M, 6 vol.) followed by a second portion of water (6 vol.). The combined extracts were acidified with conc. HCl (to pH = 1), and the product was extracted back into ethyl acetate (3 × 6 vol.). For the subsequent deprotection, the organic phase was washed with water (6 vol.), concentrated to 3 vol., and the ethyl acetate was exchanged with toluene (3 × 6 vol.). The removal of the Boc group was carried out by adding 3.1 equiv of 4 M HCl(aq) to the toluene phase followed by heating (55 ± 5 °C) for 2 h. The resulting slurry was filtered, washed with water (3 vol.) and EtOAc (3 vol.), and dried to afford compound **3** as a white crystalline powder in 70% yield (1.23 kg) and 97.7% purity.

Results and discussion

1. Preliminary Feasibility Studies

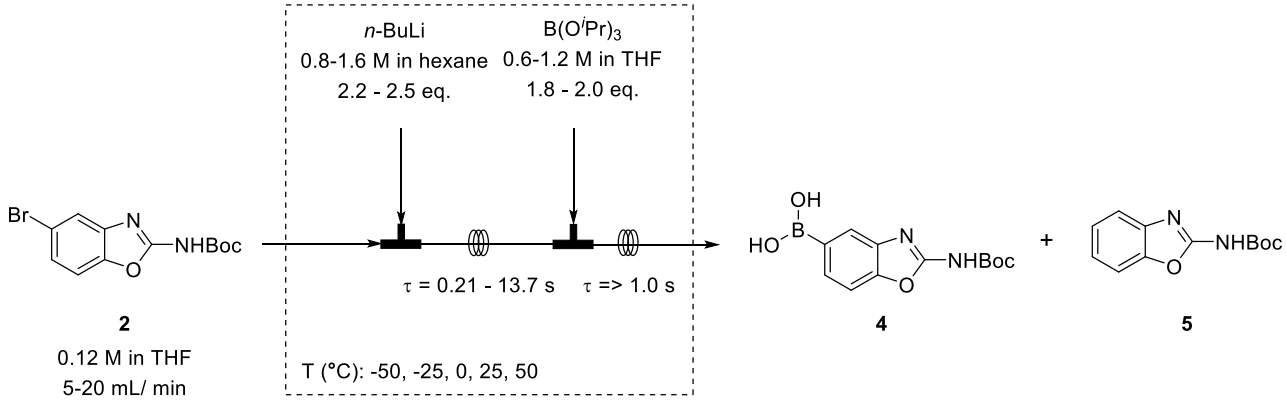
Initial studies focused on the lithiation of compound **1**. Accordingly a 0.3 M solution of the aryl bromide **1** in THF was pumped through a T-shaped mixer (ID = 0.5 mm) at 5 mL/min and allowed to react with 1.1 equiv of a 1.6 M *n*-BuLi solution in n-hexane, pumped at 1 mL/min. The reactor was cooled to 0 °C as it was anticipated that the high surface area to volume ratio and efficient heat transfer achievable under plug flow conditions would negate the need for the cryogenic temperatures that are generally required for batch lithiation. A residence time of 0.5 s was initially evaluated, and the product of the first reaction was quenched with MeOH pumped at 3 mL/min and introduced via a second T-shape mixer. Unfortunately, the tube rapidly clogged, presumably due to the precipitation of the insoluble lithiated product. Other solvents such as 1,2-dimethoxyethane and toluene were also investigated, but without success.

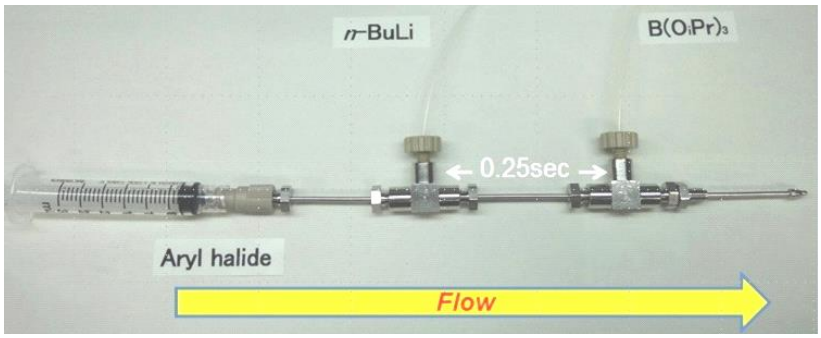
In an attempt to avoid clogging, the lithiation was next investigated using the Coflore agitated cell reactor, which is designed to handle slurries and immiscible liquids through the use of wider channels and dynamic mixing that can achieve suspension of solids.[9] Reactions were conducted at the lower temperature of -20 °C to compensate for the larger reaction volume (5−6 mL) and less efficient heat transfer compared to the narrow tube reactor, but even with residence times as high as 2−3 s, no desired product was observed. Although the reactor blockage was avoided, mostly starting material was recovered, suggesting that the solid formation and blockage was the result of deprotonation of the free amine.

It was considered that the protection of the free amine would improve the solubility of the resulting lithiated species and improve conversion. Thus, a number of protecting groups were evaluated (acetyl, trifluoroacetyl, tert-butyloxycarbonyl [Boc], and carboxybenzyl), and treatment of the Boc-protected aryl bromide **2** with 2.5 equiv of *n*-BuLi at 0 °C with a residence time of 13.71 s was found to afford 82% lithium−halogen exchange, as determined through quenching with $B(O^iPr)_3$. All other protecting groups resulted in no lithiation. In addition treatment of a mixture of compound 2 and $B(O^iPr)_3$ with *n*-BuLi resulted in low conversions (<20%). It is noteworthy that, when batch lithiation−borylation was attempted for aryl bromide **2** at -78 °C or higher

temperatures, the reaction only gave a complex mixture, in stark contrast to the result using FC, and emphasizing the necessity of using flow conditions for successfully performing this reaction.

Figure 2. Experimental setup and ranges of process parameters explored during the optimization of the flow synthesis of aryl boronic acid **4**





2. Flow Chemistry Optimization Studies

The experimental setup and process parameters investigated for the optimization of the lithiation−borylation of **2** are shown in Figure 2, while the results for the optimization of the residence time for the lithiation step are shown in Table 1. The borylation was accomplished using $B(O^iPr)_3$ for all the experiments as it was found to give high yields without blockage and was considered to be of reasonable cost. The residence time for the borylation was set at a minimum of 1.0 s for all experiments performed and was not found to be critical. Trimethoxyborate was also investigated but was found to afford compound **4** in lower

yields (ca. 50%).

It was found that reducing the residence time through shortening the length of the flow reactor, without changing the flow rate and therefore mixing efficiency of the T-shaped mixer, resulted in higher conversions. Surprisingly just 0.21 s were sufficient to generate the dianion and afford compound **4** in 86.7% with 6.2% debromination (Table 1, entries 1−3).

Table 1. Effect of Residence Time and T-Mixer ID (i.e., Mixing) on the Lithiation Step[a]

Entry	Flow rate of Feedstock A (mL/ min)	τ (s) (Lithiation)	T-mixer ID (mm)	HPLC area%		
				2	**5**	**4**
1	5	13.71	0.5	0.4	6.1	82.3
2	5	0.86	0.5	N.D.	8.4	83.7
3	5	0.21	0.5	N.D.	6.2	86.7
4	5	0.86	1.0	N.D.	10.6	78.1
5	20	0.21	1.0	N.D.	4.6	88.8

[a] Feedstock A (compound **2**) was pumped at 5 or 20 mL/min through a T-mixer and allowed to react with 2.5 equiv of *n*-BuLi (0.8 M) in hexane at 0 °C. The resulting solution was quenched in the second T-mixer with 2.0 equiv of $B(O^iPr)_3$ in THF (0.6 M).

The effect of wider diameter T-mixers (1.0 vs 0.5 mm ID) was then investigated, in an attempt to reduce the risk of blockage and improve productivity. It was found that the larger T-shaped mixers afforded lower conversions and higher levels of debromination at 5 mL/min (83.7 and 78.1% of **4** for the 0.5 and 1.0 mm mixers, respectively, Table 1, entries 2 and 4).

However, as the flow rate and hence mixing efficiency was increased, the larger T-shaped mixers gave improved results, affording 88.8% of compound **4** at 20 mL/min compared to 86.7% at 5 mL/min (Table 1, entries 3 and 5).

Subsequently, the use of more concentrated *n*-BuLi (1.6 M) was investigated and found to afford similar

results to using 0.8M *n*-BuLi (Table 1, entry 5 and Table 2, entry 1) generating compound **4** in 86.3% purity. Interestingly it was found that 1.8 equiv of *n*-BuLi resulted in just 73.8% conversion of **2** (Table 2, entry 4), while 2.2 equiv were required to achieve its full conversion (Table 2, entry 2).

Table 2. Optimization of the Stoichiometry of n-BuLi and $B(O^iPr)_3$[a]

Entry	*n*-BuLi (eq.)	$B(O^iPr)_3$ (eq.)	τ (s) (Lithiation)	HPLC area%		
				2	**5**	**4**
1	2.5	2.0	0.25	N.D.	6.9	86.3
2	2.2	2.0	0.25	N.D.	7.2	86.6
3	2.0	2.0	0.26	2.6	9.0	81.6
4	1.8	2.0	0.26	26.2	12.7	51.5
5	2.2	1.4	0.25	N.D.	7.3	86.5
6	2.2	1.6	0.25	N.D.	7.7	88.0
7	2.2	1.8	0.25	N.D.	7.7	88.2

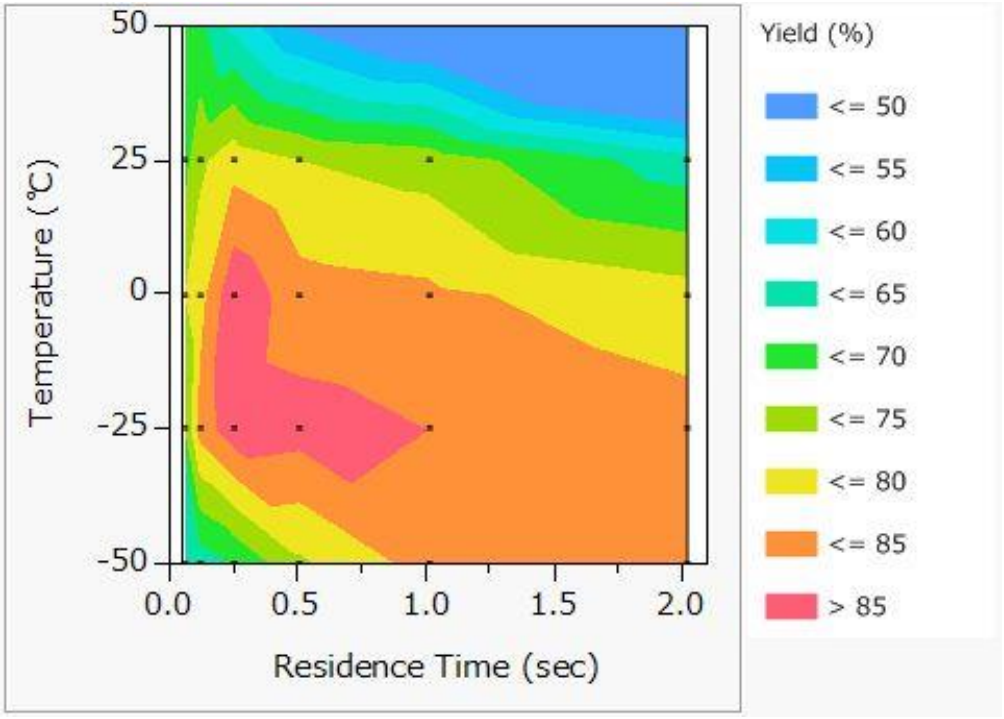
[a] Feedstock A (compound **2**) was pumped at 20 mL/min through a 1.0 mm ID T-mixer with a 1.6 M solution of n-BuLi in hexane at 0 °C. The resulting product was quenched in the second T-mixer with a 0.6 M solution of $B(O^iPr)_3$ in THF.

Finally the stoichiometry of the borylating reagent with respect to aryl bromide 2 was optimized. A small increase in the HPLC purity of **4** was obtained as the amount of $B(O^iPr)_3$ was increased from 1.4 to 1.8 equiv (86.5−88.2%; Table 2, entries 5−7), that then decreased slightly to 86.6% when 2.0 equiv were used (Table 2, entry 2). Therefore, 1.8 equiv of $B(O^iPr)_3$ and 2.2 equiv of *n*-BuLi were selected for further optimization, as these conditions afforded complete conversion and product with the highest purity (88.2%), minimizing the amount of debromimation.

The contour plot shown in Figure 3 was constructed using JMP software (SAS) to optimize the lithiation residence time as well as the reaction temperature and define a robust operating range for scale-up. A total of

30 experiments were conducted investigating six residence times (0.06−2.0 s) and five temperatures (-50 °C, -25 °C, 0 °C, 25 °C, 50 °C).

Figure 3. Contour plot of calculated HPLC yields for aryl boronic acid **4**, obtained at different temperatures and lithiation residence times.



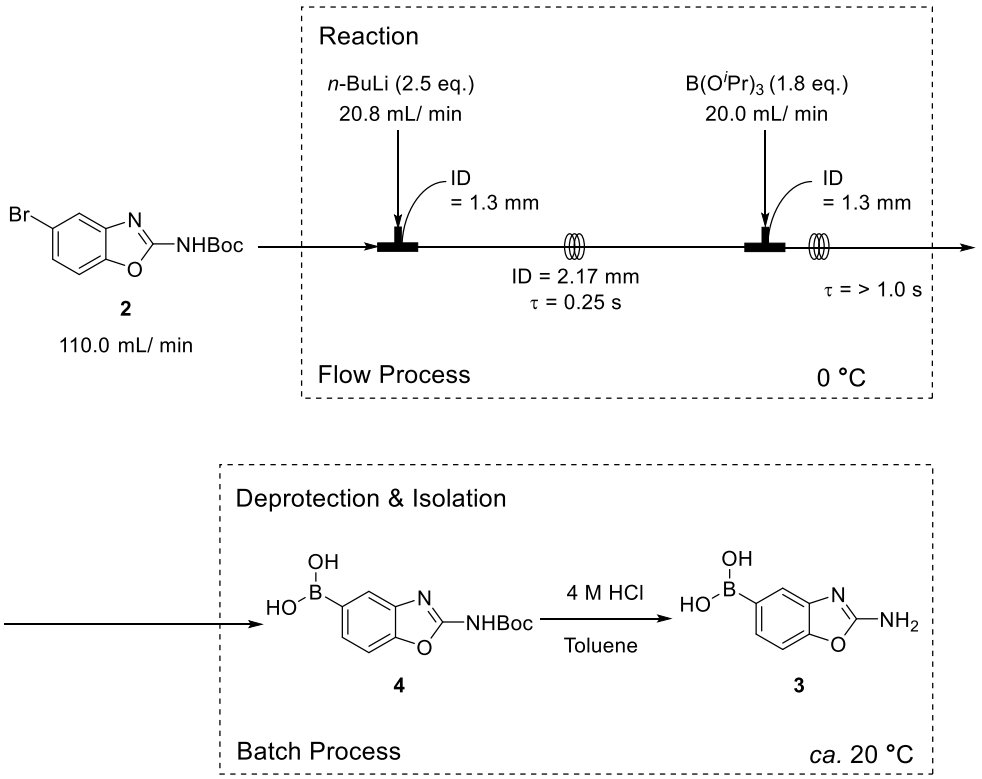
Both temperature and residence time were found to be key process parameters with a narrow operating range affording yields >85%. The reaction at 0 °C did not appear to be particularly robust as the yield dropped when residence times of >0.25 s were used, presumably due to the decomposition of the generated lithiated species. Furthermore, at residence times <0.25 s, incomplete lithiation was observed. A wider operating window was obtained at -25 °C, and excellent yields were obtained with residence times of 0.25-1.0 s. Lowering the temperature to -50 °C slowed down the transmetalation process, while increasing it above 0 °C resulted in the decomposition of the lithiated species affording yields <60%. Therefore, the optimal conditions for scale-up were determined to be a residence time of 0.25 s at -25 °C.

3. Scale-up Studies.

The optimized conditions for yield and purity (2.5 equiv of *n*-BuLi, 1.8 equiv of $B(O^iPr)_3$ at -25 °C) were scaled-up to produce approximately 1 kg of aryl boronic acid **3** over an extended run. Initially compound **2**, *n*-BuLi and $B(O^iPr)_3$ were pumped at 110.0 mL/min, 20.8 mL/min, and 20.0 mL/min, respectively, through a 1.00mmID SS tube, which was 550 mm long in order to achieve the desired residence time. Clogging was observed within 5 min presumably due to the precipitation of the aryllithium intermediate, which may have formed faster due to the greater mixing efficiency observed at these higher flow rates. The purity of the generated product was also higher at 91.6% with only 6.8% debromination observed, also supporting improved mixing efficiency during scale-up. Increasing the ID of the tube to 2.17 mm did not mitigate the clogging that was observed within 5 min of operation.

However, increasing the temperature to 0 °C and using the wider diameter tube (2.17 mm) alleviated the clogging issues, and the process was successfully run for 10 h 14 min to afford compound 4 in 92.0% purity with 4.4% debromination and 98.2% conversion (Figure 4). For the scale-up production, two identical reactors were set up so that, if the pressure exceeded 0.30 MPa, the flow from the pumps could be immediately switched to the second, back-up, reactor to allow for continuous operation. HPLC analysis of the product stream prior to workup and isolation indicated an 80−85% yield, which was consistent with the laboratory experiments. After workup, deprotection, and isolation, a total of 1.23 kg of the target aryl boronic acid was manufactured with 97.7% purity, which was successfully usetested in the subsequent Suzuki coupling reaction to afford TAK-117.

Figure 4. Experimental setup for the scale-up of the flow chemistry lithiation−borylation process.



A comparison of the raw material costs for the flow route utilizing lithiation−borylation with those for the batch Miyaura borylation procedure using BBA showed the former to be higher. Although the flow route avoided the costly Pd catalyst and BBA used in the Miyaura borylation, the cost saving was offset by the need for Boc-protection of the amine group.

Conclusion

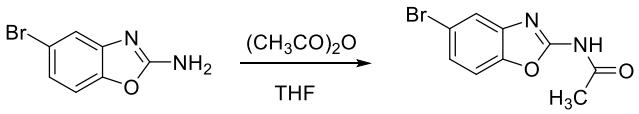
An alternative route for a key boronic acid starting material was investigated utilizing flow flash chemistry[10,11] techniques, and a lithiation−borylation process that was difficult if not impossible to control in batch was successfully developed into a kilo-scale process. Although the cost of raw materials for the route was found to be greater than for the Miyaura borylation batch process using BBA, the flow process had potential benefits arising from avoiding the use of Pd and potentially mutagenic boron reagents, such as BBA or B_2Pin_2.

Supporting information

NMR

^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker Avance 500 (500 MHz) spectrometer. Chemical shifts were shown by ppm. The abbreviations used are as follows: s = singlet, d = doublet, m = multiplet, dd = doublet of doublets, brs = broad singlet. HRMS spectra were taken on a Thermo Fisher Scientific LTQ Orbitrap Discovery.

1. Synthesis of CH_3CO-1

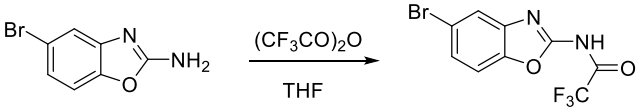


1 **CH_3CO-1**

A suspension of **1** (5.0 g, 23.5 mmol) in THF (2 v/w, 10 mL) was stirred at 45±5 ℃ and cooled to 25℃ after all the **1** crystals were dissolved. To the solution of **1** was added dropwise acetic anhydride (5.0 g, 49.3 mmol, 2.1 eq.) at 25±5 ºC followed by stirring at 25℃ for 3h. The reaction mixture was heated to 40±5 ºC and stirred for 5h. HPLC analysis (condition 1) at 5h reaction time showed no starting material (t_R=12.5) remaining. The reaction mixture was cooled down to 25±5 ºC. The product was isolated by filtration, rinsed with THF (15 mL, 3 v/w) and dried *in vacuo* at 50 ºC giving a light brown crystalline solid (3.75 g, 62.5%, HPLC 98.8%) of acetylated **1**.

^{1}H NMR (500 MHz, DMSO-d_6) δppm 2.22 (s, 3 H), 7.42 (dd, *J*=8.67, 2.05 Hz, 1 H), 7.60 (d, *J*=8.51 Hz, 1 H), 7.79 (d, *J*=1.89 Hz, 1 H), 11.77 (s, 1 H)

2. Synthesis of CF_3CO-1



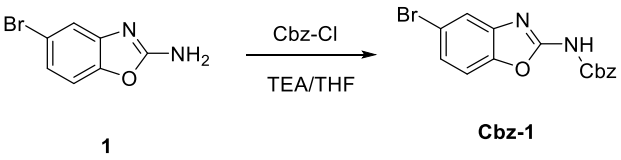
1 **CF_3CO-1**

A suspension of **1** (5.0 g, 23.5 mmol) in THF (3 v/w, 15 mL) was stirred at 45±5 ℃ and cooled to 25℃ after all the **1** crystals were dissolved. To the solution of **1** was added dropwise trifluoroacetic anhydride (10.4 g, 49.3 mmol, 2.1 eq.) at 25±5 ºC followed by stirring at 25℃ for 3h. The reaction mixture was heated to 35±5 ºC and stirred for 2h. The reaction mixture was cooled down to 25±5 ºC. The product was isolated by filtration, rinsed with THF (10 mL, 2 v/w) and dried *in vacuo* at 50 ºC giving a light brown crystalline solid (4.18 g, 57.5%) of trifluoroacetylated-**1**.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.57 (dd, *J*=8.83, 1.89 Hz, 1 H) 7.65 (d, *J*=1.89 Hz, 1 H) 7.68 (d, *J*=8.83 Hz, 1 H)

^{19}F NMR (471 MHz, DMSO-d_6)δppm -75.34 (br. s., 1 F)

3. Synthesis of Cbz-1



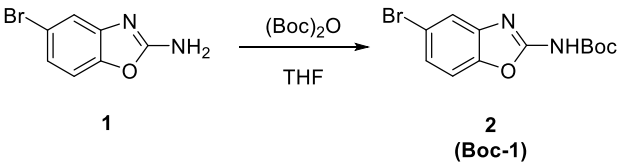
1 **Cbz-1**

1. A suspension of **1** (5.0 g, 23.5 mmol) and Et_3N(5.0g, 49.3 mmol) in THF (3 v/w, 15 mL) was stirred at 45±5 ℃ and cooled to 25℃ after all the **1** crystals were dissolved. To the solution of **1** was added dropwise Cbz chloride (8.4 g, 49.3 mmol, 2.1 eq.) at 25±5 ºC followed by stirring at 25℃ for 3h. The reaction mixture was heated to 50±5 ºC and stirred overnight. The reaction mixture was cooled down to 25±5 ºC. The product was isolated by filtration, rinsed with THF (10 mL, 2 v/w) and dried *in vacuo* at 50 ºC giving a pale red crystalline solid, 7.73 g (94.7%) of crude Cbz-**1**.

2. A solution of crude Cbz-**1** (7.73 g) in THF (4.1 v/w, 32 mL) was stirred at 60±5 ℃ and cooled to 25℃. The slurry was stirred at 25℃ for 1h. The product was isolated by filtration, rinsed with THF (10 mL, 1.3 v/w). The resulting crystals were reslurried in THF (3.0 v/w, 23 mL) and water (1.0 v/w, 7.7 mL) and the slurry was stirred at 60±5 ℃ for 1h. The product was isolated by filtration, rinsed with THF (10 mL, 1.3 v/w) and dried *in vacuo* at 50 ºC giving a pale red crystalline solid (2.18g, 26.7%, HPLC 96.6%) of Cbz-**1**.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 5.24 (s, 2 H) 7.29-7.78 (m, 8 H) 11.88 (s, 1 H)

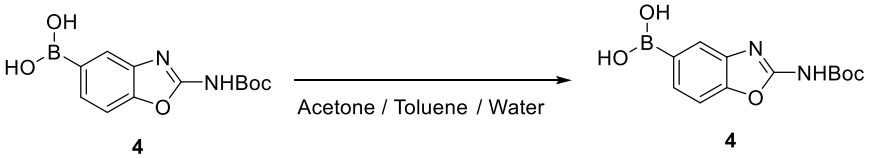
4. Synthesis of 2 (Boc-1)



1 **2 (Boc-1)**

A suspension of **1** (5.0 g, 23.5 mmol) in THF (10 v/w, 50 mL) was stirred at 5±5 ℃ and Boc anhydride (6.1 g, 28.1 mmol, 1.2 eq.) was added after all the **1** crystals were dissolved. To the solution of **1** and Boc anhydride was added DMAP (5.73 g, 46.9 mmol, 2.0 *eq*.) at 5±5 ºC followed by stirring at RT overnight (21 h). TLC analysis (EtOAc) showed the presence of 1 to 2% of starting material and 5% of the di-Boc product, with no starting material remaining. Then, the reaction mixture was quenched with aqueous 1M sodium hydrogensulfate (10 vol) at RT. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 vol). All organic layers were combined and washed with brine solution (10 vol). The layers were separated and the organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated and co-evaporated with heptanes (2 x 10 vol) to obtain crude solid. Crude solid was triturated with heptanes (20 vol) at 50 ℃ to 60 ℃ for 1 hour. The hot slurry was filtered and the solid cake was washed with heptanes (2 x 2 vol) and dried. The structure of the compound was confirmed by 1H NMR. Compound **2** (4.5 g) was obtained as beige crystalline powder.

5. Purification of 4

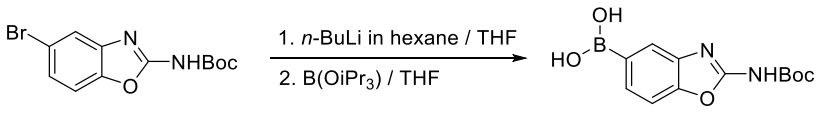


4 **4**

To the reaction mixture of Boc-ML826 was added EtOAc (10 v/w, 60 mL), and the combined mixture was

extracted with water (12 v/w, 72 mL). Water (12 v/w, 72 mL) was added to the organic layer again and extracted. This operation was repeated 2 more times. To the water layer was added dropwise conc. HCl (8 mL, 1.3 w/w) and extracted with EtOAc (12 v/w, 72 mL). The water layer was extracted with EtOAc (12 v/w, 72 mL) again. This operation was repeated 2 more times. The organic layer was concentrated under reduced pressure and acetone (3 v/w, 18 mL) was added to the residue. The organic layer was concentrated again under reduced pressure and acetone (2 v/w, 12 mL) was added to the residue. The residue was heated to 40±5 ℃ and cooled down to 25±5 ℃ after all the crystals were dissolved. To the solution was added dropwise toluene (0.5 v/w, 3 mL) and water (1 v/w, 6 mL) at 25±5 ºC followed by stirring at 25 ℃ for 1h. Then, the mixture was cooled to 5±5 ºC followed by stirring at 5±5 ºC for 2h. The product was isolated by filtration, rinsed with acetone/water (2:1, 1 v/w, 6mL) and dried *in vacuo* at 50 ºC giving a white crystalline solid (2.4 g, 45.5%, HPLC 99.0%) of pure Boc-ML826.

6. Synthesis of 4 (Batch result)



2 **4**

A suspension of **2** (3.0 g, 9.6 mmol) and super dehydrated THF (26.7 v/w, 80 mLl) was stirred at 50±5 ℃ under N_2 atmosphere and cooled to -78℃ after all the **2** crystals was dissolved. To the solution of **2** was added dropwise *n*-BuLi (1.6M in hexane, 13.2 mL, 21.1 mmol, 2.2 eq.) at -78 ºC followed stirring at -78℃ for 1h. To the reaction mixture was added dropwise $B(O^iPr)_3$ (3.3 g, 17.3 mmol, 1.8 eq.) in THF (9.6 v/w, 28.8 mL) at -78 ºC followed by stirring at -78 ℃ for 2h. The reaction mixture was warmed to 25±5 ºC and stirred for 4h. To the reaction mixture was added toluene (5 v/w, 15 mL) and the combined mixture was extracted with water (6 v/w, 18 mL). Water (6 v/w, 18 mL) was added to the organic layer and extracted again. This operation was repeated 3 more times. To the water layer was added dropwise conc. HCl (4 mL, 1.3 w/w) and extracted with toluene (6 v/w, 18mL). The water layer was extracted with toluene (6 v/w, 18mL) again. This operation

was repeated 3 more times. The organic layer was concentrated under reduced pressure. To the residue was added toluene (10 v/w, 30 mL) and the combined mixture was stirred at 80±5 ºC. To the mixture was added dropwise 4M HCl aq. (12 mL, 48 mmol, 5.0 eq.), followed by rinsing with water (3 v/w, 9 mL) and stirring at 80±5 ℃ for 4h. HPLC analysis at 4h reaction time showed no starting material (t_R=11.0) remaining. The mixture was cooled down to 25±5 ºC and stirred for 2h. The mixture was cooled down to 0±5 ℃ and stirred for 2h. The product was isolated by filtration, rinsed with toluene (3v/w, 9 mL) and cooled water (4 v/w, 12 mL). The product was dried *in vacuo* at 50 ℃ giving a white crystalline solid (0.69g, 33.4%, HPLC area 94.8%) of **4**.

7. Contour plot (Figure 3)

Experimental data for the contour plot shown in Figure 3 was obtained using the flow system shown below and the data shown in Table 3 (data at -78 ℃ was not used for Figure 3).

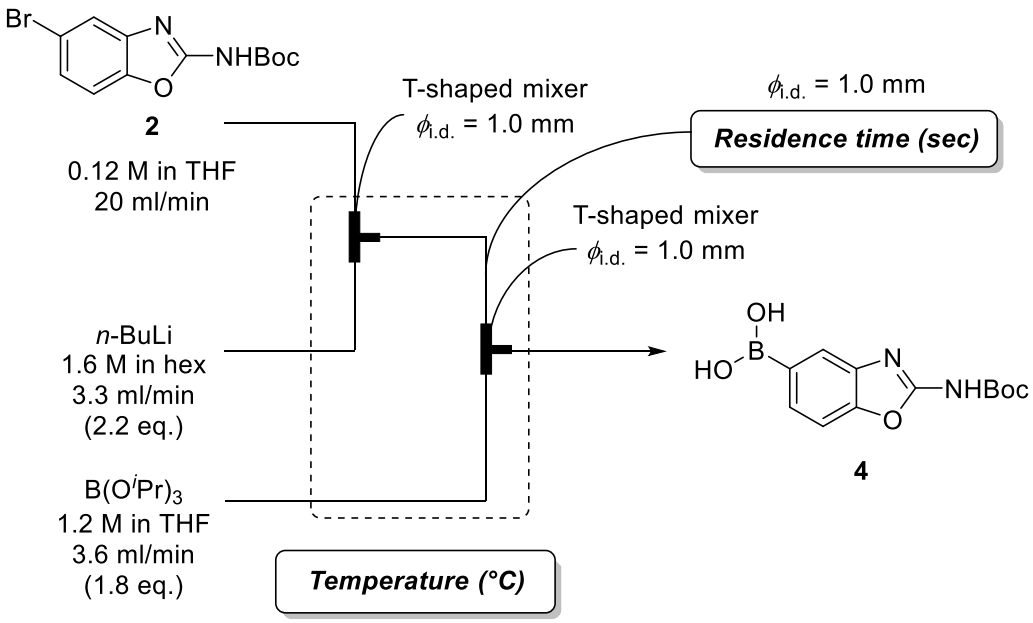


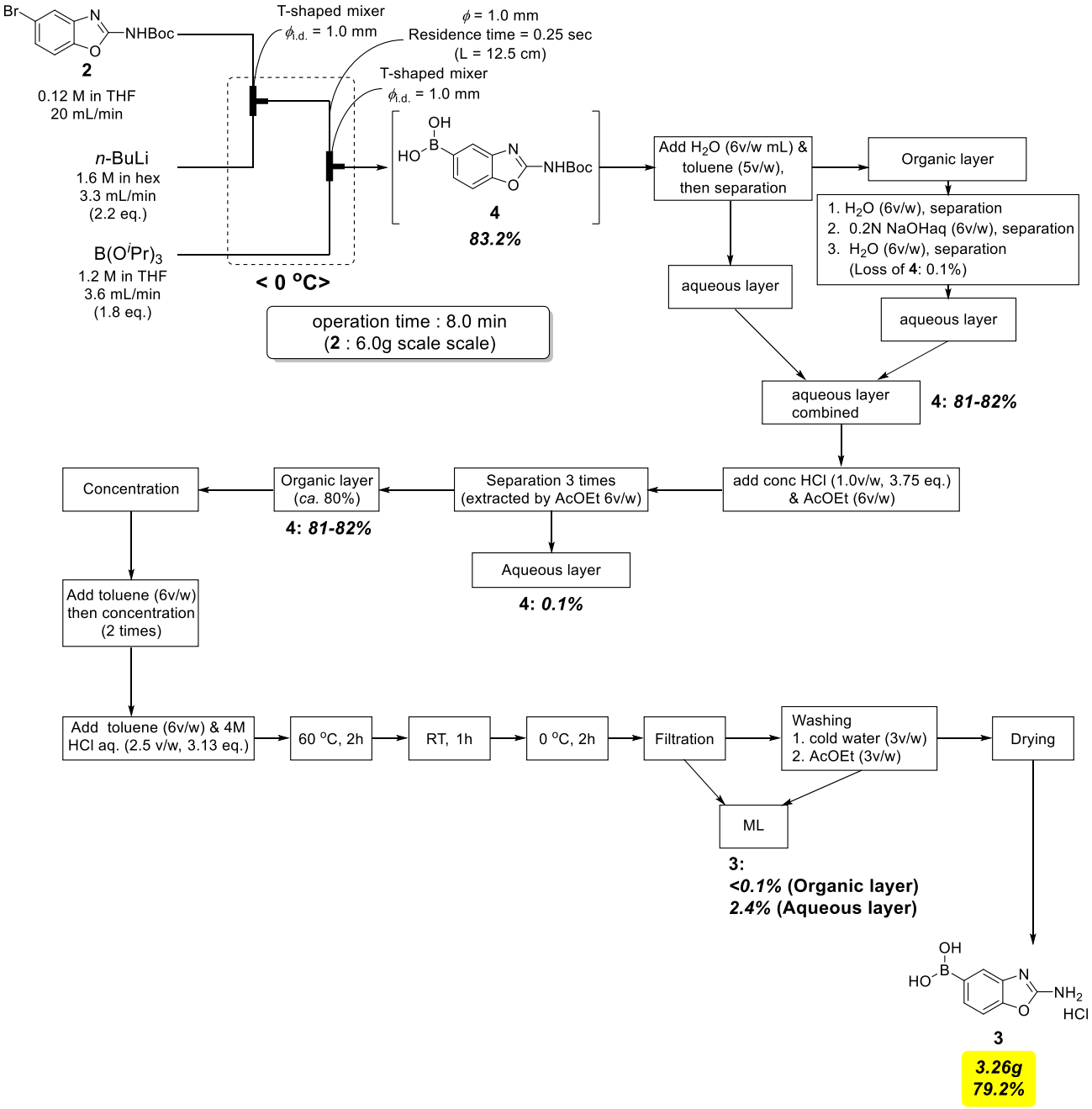
Table 3. Effect of residence time and temperature

Run	Residence time (sec)	Temperature (°C)	Yield of **4**[a] (%)	Run	Residence time (sec)	Temperature (°C)	Yield of **4**[a] (%)
1	0.06	50	62	19	0.51	50	49
2		25	68	20		25	75
3		0	75	21		0	82
4		-25	70	22		-25	87
5		-50	32	23		-50	74
6		-78	40	24		-78	71
7	0.12	50	66	25	1.01	50	41
8		25	74	26		25	73
9		0	78	27		0	81
10		-25	82	28		-25	88
11		-50	62	29		-50	82
12		-78	40	30		-78	85
13	0.25	50	59	31	2.02	50	17
14		25	78	32		25	62
15		0	86	33		0	77
16		-25	88	34		-25	82
17		-50	65	35		-50	80
18		-78	45	36		-78	77

[a] Determined by HPLC.

8. Flow system and procedure for compound 3 flow synthesis

The complete flow synthetic route, including work-up and isolation process, for **3** is shown below.



<Full procedure for obtaining compound **3** >

1. Connect a T-shaped mixer (SUS, $\phi_{i.d}$ = 1.0 mm) and tube reactor (SUS, $\phi_{i.d.}$= 1.0 mm) with a residence time of about 0.25 seconds (12.5 cm) for the halogen-lithium exchange reaction.
2. Prepare compound **2** in fresh dried THF solution (0.12M) as a starting material and keep under nitrogen atmosphere.
3. Prepare *n*-butyllithium in *n*-hexane solution (1.6M) as a starting material and keep under nitrogen atmosphere.
4. Prepare triisopropoxyborate in fresh dried THF solution (1.2M) as a starting material and keep under nitrogen atmosphere.
5. Dip the flow system of tubes and connectors in a cooling bath (temperature: 0 ^{o}C) and pump the three starting material solutions through the flow system at the indicated flow rates.
6. After reaching steady state (15 seconds after starting flow), collect the reaction solution from the outlet for 8 minutes (quench with 36 mL of H_2O).
7. Add toluene (30 mL) and agitate for 10 min.
8. Stop agitating and allow the solution to stand for more than 5 min.
9. Separate the collected solution into an aqueous layer and an organic layer (1st).
10. Add distilled water (36 mL) to the organic layer and agitate for 10 min.
11. Stop agitating and allow the solution to stand for more than 5 min.
12. Separate the mixture again into an aqueous layer and organic layer (2nd).
13. Add 0.2M NaOH *aq*. (36 mL) to the organic layer and agitate for 10 min.
14. Stop agitating and allow the solution to stand for more than 5 min.
15. Separate the mixture again into an aqueous layer and organic layer (3rd).
16. Add distilled water (36 mL) to the organic layer and agitate for 10 min.
17. Stop agitating and allow the solution to stand for more than 5 min.
18. Separate the mixture again into an aqueous layer and organic layer (4th).
19. Combine the aqueous layers and acidify with 12M HCl *aq*. (6 mL) (to pH 1.0)

20. Add ethyl acetate (36 mL) to the aqueous layer and agitate for 10 min.
21. Stop agitating and allow the solution to stand for more than 5 min.
22. Separate the mixture into an aqueous layer and organic layer (1st).
23. Add ethyl acetate (36 mL) to the aqueous layer and agitate for 10 min.
24. Stop agitating and allow the solution to stand for more than 5 min.
25. Separate the mixture again into an aqueous layer and organic layer (2nd).
26. Add ethyl acetate (36 mL) to the aqueous layer and agitate for 10 min.
27. Stop agitating and allow the solution to stand for more than 5 min.
28. Separate the mixture again into an aqueous layer and organic layer (3rd).
29. Combine the organic layers and concentrate (1st).
30. Add toluene (36 mL) and concentrate (2nd).
31. Add toluene (36 mL) again and concentrate (3rd).
32. Add toluene (36 mL) and 4M HCl *aq*. (15 mL).
33. Heat the resulting solution (internal temperature, 50-60 °C) while agitating for 2h.
34. Confirm de-Boc reaction completion by HPLC.
35. Cool the resulting slurry (internal temperature, 20-30 °C), and then keep for 1 hour under agitation.
36. Cool the resulting slurry (internal temperature, 0-10 °C), and then keep for 2 hours under agitation.
37. Filter the resulting slurry and wash the crystals with water (0-10 °C, 18 mL).
38. Wash the crystals with ethyl acetate (18 mL).
39. Dry the crystals obtained in a vacuum oven (45±5°C) to give white crystals.

Yield: 3.26 g (79%)

Compound 3 ((2-aminobenzo[*d*]oxazol-5-yl)boronic acid hydrochloride): The title compound was prepared according to the procedure shown above, and isolated as white crystals (3.26 g, 79% yield). ^{1}H NMR

(500 MHz, DMSO-d_6) δ 7.55–7.65 (m, 1H), 7.71-7.80 (m, 1H), 7.81-7.87 (m, 1H), 9.83-10.33 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 109.71, 110.65, 116.98, 128.74, 130.31, 146.61, 159.71.

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Chapter 3

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

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 kilogram-scale production. Some of the key benefits of flow flash chemistry were utilized, both to avoid side reactions and to enable dianion chemistry that is difficult to perform successfully in batch reactions. The examples showed further perspectives on the utility of flow technologies for process development.

Introduction

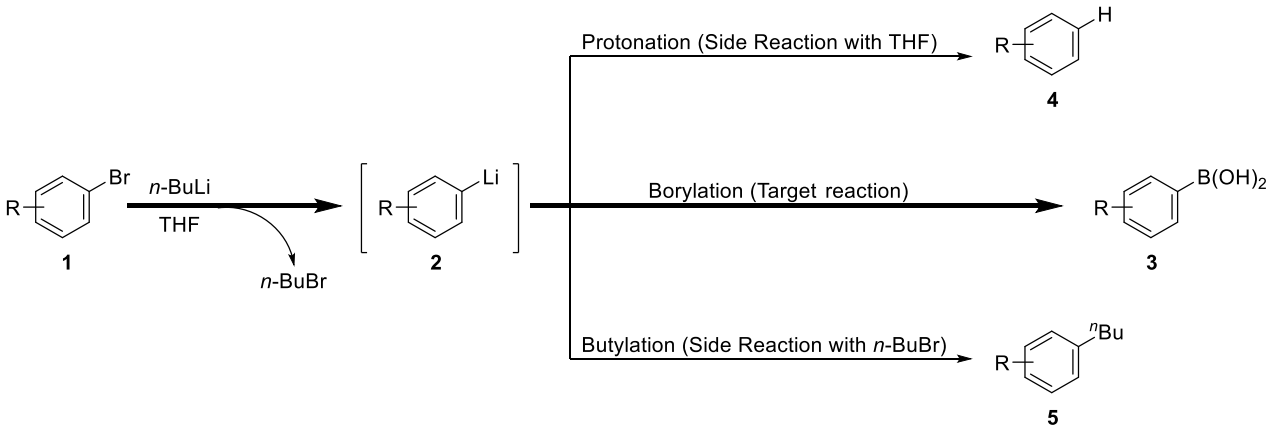
Since its full-scale research and development was started worldwide in the 1990s, flow chemistry (FC) has received much attention and is becoming one of the most useful and indispensable technologies for a variety of chemical syntheses, ranging from pharmaceuticals and agrochemicals to plastics and chemicals.[1,2] 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 compared with conventional batch processes. While FC technologies have received significant research interest from both academia and industry,[3,4] because of 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 successful handling of 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 precise control of the residence time and temperature, 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 to generate organolithiums, and *n*-BuLi is especially used as a reagent. However, 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]

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

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

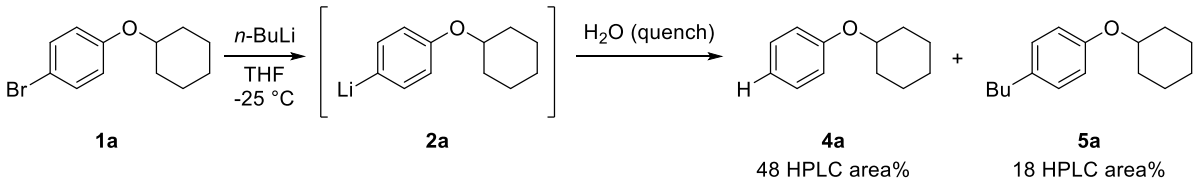


Results and Discussion

1. Feasibility Study and 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. On the basis of 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)



1a **2a** **4a** 48 HPLC area% **5a** 18 HPLC area%

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

Figure 1. Setup for a flow feasibility study of halogen−lithium exchange.

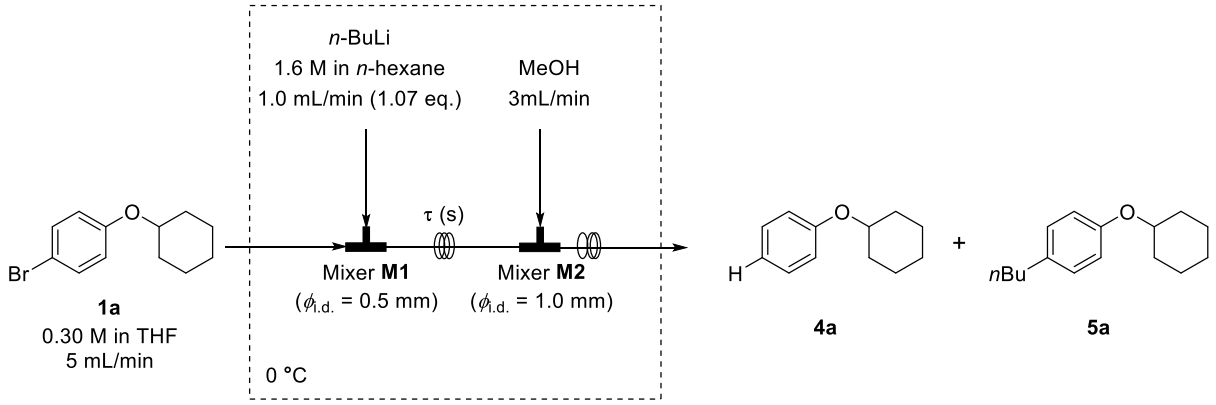


Table 1. Feasibility Study of the Lithiation

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

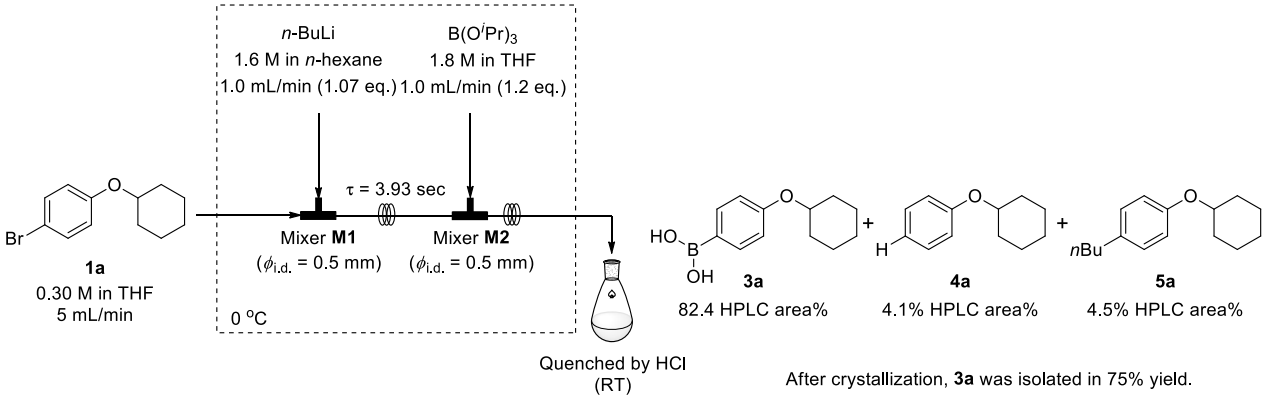
The initial experiments for the feasibility study were conducted with 1.07 equiv of *n*-BuLi, a reaction temperature of 0 °C, and residence times of 0.24−31.42 s. When less than 1 s was allowed for lithiation, not all of the raw materials were converted, showing the minimum time required to consume all of 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 a residence time of more than 3.93 s was used for lithiation. Surprisingly, the protonated compound (**4a**), representing the desired product pathway, was obtained in the highest yield in Table

1, 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 results showed that about 1.07 equiv of *n*-BuLi was sufficient for the bromine−lithium exchange reaction and ca. 4 s 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.

Therefore, the conditions in Table 1, entry 3 were used as the optimized conditions for the halogen−lithium exchange reaction at 0 °C, and then further investigation of the borylation was carried out (Figure 2).

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



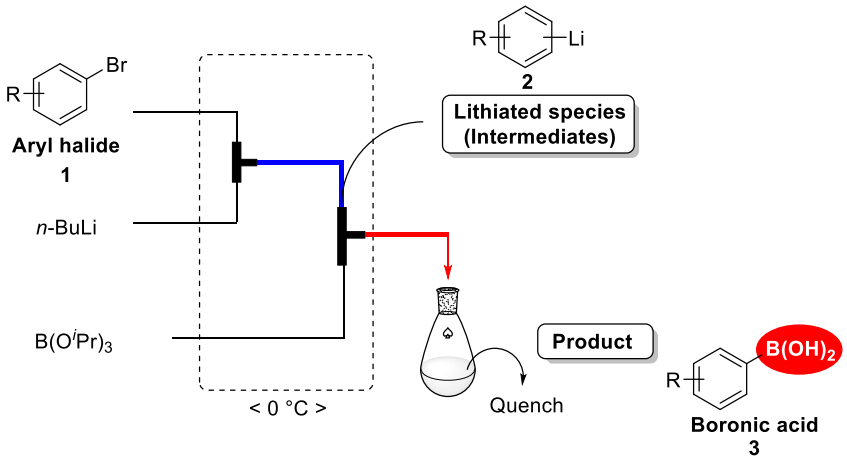
As shown in Figure 2, the flow synthesis of boronic acid **3a** was achieved in good yield through minimization of the major side reactions. Crystallization in batch was conducted after the flow reaction, and the boronic acid was isolated as white crystals in 75% yield.

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 obtain boronic acids starting from aryl bromides 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 ethers, the desired boronic acids were obtained in good yield using residence times of a few seconds for the lithiation (Table 2, entries 1−3).

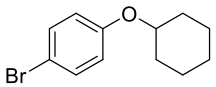
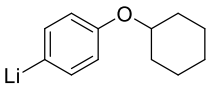
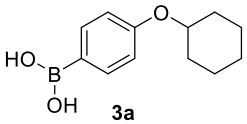
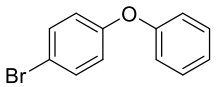
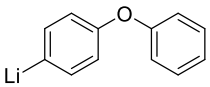
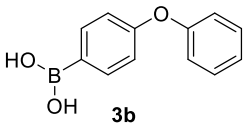
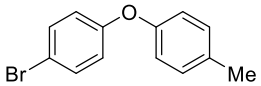
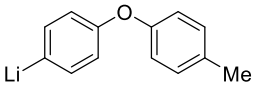
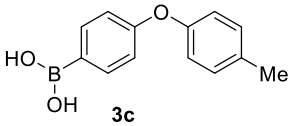
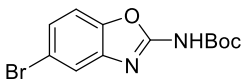
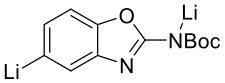
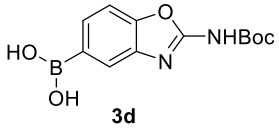
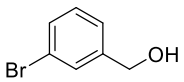
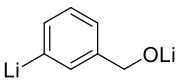
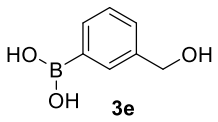
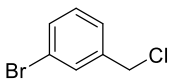
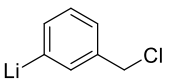
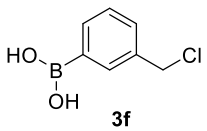
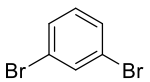
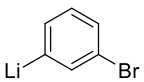
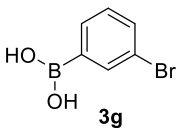
Surprisingly, when the bromine−lithium exchange reaction was conducted on aryl bromides that included heteroaromatic rings, the optimized residence time was 0.25 s, even though more than 2 equiv of n-BuLi was required to detach the bromine atom (Table 2, entry 4). It is thought that more than 2 equiv of n-BuLi was essential for this reaction because 1 equiv 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 2 equiv of n-BuLi (entry 5). Interestingly, although it was really important to control the residence time to less than 1 s in entry 4, ca. 13 s was required for conversion of raw material **1e** to generate the lithiated species **2e**.

Moreover, selective halogen−lithium exchange reactions were attempted for aryl bromides including one more halide (Table 2, entries 6 and 7). When both aryl bromide and benzyl chloride were present, the bromine atom was converted selectively, and the corresponding desired product was obtained (**3f**). Also, a monoselective bromine−lithium exchange reaction was achieved for 1,3-dibromobenzene (**1g**) in an excellent yield after

borylation.

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

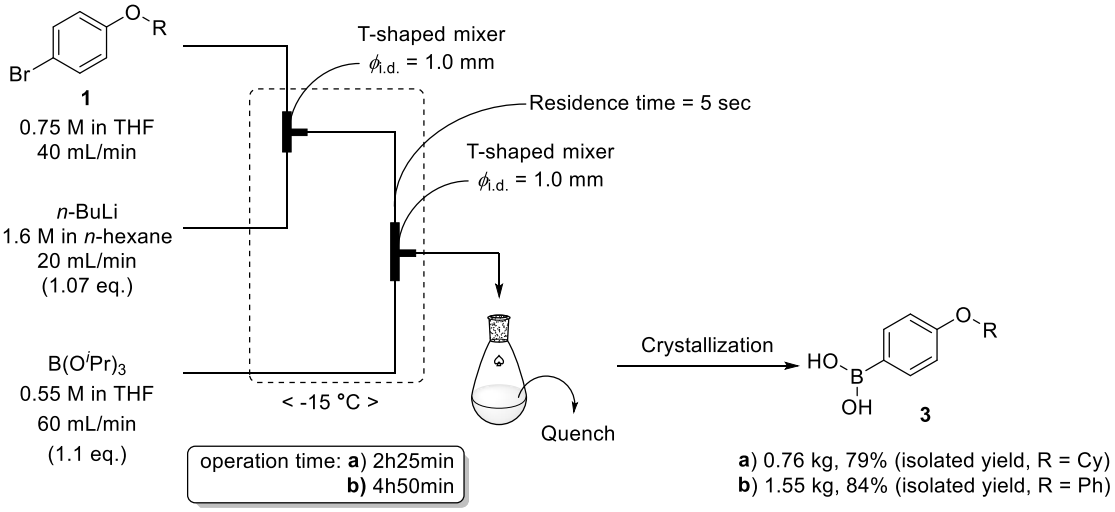
entry	Aryl halide	Intermediates	Products	τ (sec)	*n*-BuLi (eq.)	Yield[a]
1	 **1a**	 **2a**	 **3a**	3.9	1.07	82
2	 **1b**	 **2b**	 **3b**	9.4	1.07	83
3	 **1c**	 **2c**	 **3c**	3.9	1.07	89
4[b]	 **1d**	 **2d**	 **3d**	0.25	2.2	88
5	 **1e**	 **2e**	 **3e**	13	2.4	90
6	 **1f**	 **2f**	 **3f**	1.9	1.2	80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

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

3. Scaled-Up Production

Scaled-up production of boronic acids 3a and 3b was conducted. In order to improve the productivity, the concentrations of raw materials and the flow rates were increased from the lab conditions, and because of 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 h 25 min for the flow mode (Figure 4). The obtained product showed good quality and did not include side products 4a and 5a. Also, 1.55 kg of 3b was manufactured in excellent yield, and its quality was sufficient to carry out the subsequent reaction.

Figure 4. Scaled-up production of **3**



EXPERIMENTAL SECTION

1. HPLC Method

The HPLC method used for IPC analysis as well as for analysis of the purity of boronic acid **3** employed a YMC-Pack ODS-A 150 mm × 4.6 mm (S-5um, 12 nm) column maintained at 25 °C. Acetonitrile 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% mobile phase A, moving to 80% A over 15 min, eluting at 80% A for 15 min, and then moving back to 50% A over 15 min. The final composition was maintained at 50% for 15 min to re-equilibrate the column.

Compounds **1a**−**g**, **3a**−**g**, **4a**, **4b**, **4d**, and **5a** eluted at relative retention times of 32.5 min (**1a**), 29.2 min (**1b**), 31.2 min (**1c**), 8.3 min (**1d**), 3.6 min (**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**).

2. General Lab-Scale Experimental Procedure (Flow Synthesis of 3a−c and 3e−g; Table 2)

All of the chemicals were purchased from Wako Pure Chemical Industries and used without further purification. All of the solvents used were reagent grade, unless otherwise specified. Three microsyringe pumps (Fusion 100, ISIS Ltd., Osaka, Japan) 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. 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), 0.55 M (entry 3), 1.5 M (entry 5), 1.0 M (entry 6), 1.74 M (entry 7)). All of the 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 (i.d.) 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. A Shimadzu-GLC tee piece (0.50 mm i.d., part no. 6010-72357) was used as a mixer for feedstocks A and B, and a Shimadzu-GLC tee piece (1.0 mm i.d., custommade 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 s was sufficient for the reaction to go to completion, and longer times were not found to be detrimental.

To ensure that the reactants were sufficiently cooled before mixing, precooling loops (L = 50 cm, i.d. = 1.0 mm) were used, and the reactors for both the lithiation and borylation steps were submerged in a cooling bath set at 0 °C before the three pumps were initiated. 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.

3. Scale-Up Production

3.1. 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. Feedstock C was a 0.55 M solution of $B(O^iPr)_3$ freshly prepared in anhydrous THF and pumped at 60.0 mL/min. All of the feedstocks were maintained under an atmosphere of nitrogen. The reactors were fabricated from SS tubing with an i.d. of 2.17 mm and 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 first resulted in a 318 cm long tube (1.00 mm i.d.) and second a 67.5 cm long tube (1.00 mm i.d.) being used with the above flow rates. Shimadzu-GLC tee pieces (1.0 mm i.d., custom-made item) were used as mixers. The precooling loops (L = 1 m, i.d. = 2.17 mm) and reactors for both the lithiation and borylation steps were submerged in a cooling bath set at 0 °C before the three pumps were initiated. 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 h 25 min to afford compound **3a** with 89.9% HPLC purity and (b) 4 h 50 min to afford compound **3b** with 93.8% HPLC purity.

3.2. Workup Procedure for Isolating 3a

The collected product stream from the FC process was quenched with 1 M aqueous HCl (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 with n-heptane (4.78 kg), and agitated in an ice bath. The resulting slurry was filtered and washed with ice-cooled n-heptane (1.19 kg) to afford compound 3a as a white crystalline powder in 79% yield (0.76 kg) with 97.4% purity.

3.3. Workup Procedure for Isolating 3b

The collected product stream from the FC process was quenched with 2 M aqueous HCl (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 with 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) with 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, such as (1) protonation by the THF solvent and (2) butylation by *n*-BuBr generated from bromine−lithium exchange between aryl bromide and n-BuLi, was 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 of production to kilogram 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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Chapter 4

Development of a scale-up process for lithiation-borylation utilizing flow chemistry

Abstract

A scale up process for boronic acid synthesis using flow chemistry was developed. Introducing a boryl group onto halogen atom position *via* a halogen-lithium exchange reaction is a very useful technique in synthetic organic chemistry, however, extremely low temperature conditions are often required. In this chapter, application of flow chemistry technology to a reaction *via* a very unstable lithium intermediate that cannot be controlled with a batch reactor is described.

As a result, the desired boronic acid was obtained in a good yield, while avoiding cryogenic conditions, and an efficient production method was established. Details of a scale-up investigation, method development of countermeasures against clogging risks, and successful production results on the kg scale are described.

Introduction

Flow Chemistry technology in chemical synthesis is a technology that has received much attention, not only from academia but also from industry.[1,2] In recent years, there have been many efforts to apply this technology to drug substance manufacturing processes, for both drugs and drug candidate compounds.[3,4,5]

Unlike chemical batch reactors, flow chemistry reactors conduct chemical reactions in a "micro channel", allowing precise control of residence time and a significant increase in the specific surface area (reactor surface area/volume) compared to batch reactors, which allows for precise temperature control.[6,7] With this technology, the generation and control of unstable active species that could not be realized in conventional batch manufacturing processes can be performed, and side reactions can be suppressed. In addition, it is possible to safely handle reagents that are considered dangerous in batch production, as well as contain highly bioactive compounds so as to reduce the amount of exposure to the human body. Examples of the profits that have been derived from utilizing flow chemistry have become almost too numerous to count.[8,9] However, examples of applying flow chemistry technology to actual drug substance manufacturing processes are still limited.

In this chapter, an example of our efforts in the process chemistry department where we have studied flow chemistry applications from the laboratory level to the production scale is shown.

Results and discussion

1. Application of flow chemistry technologies to pharmaceutical production processes

Numerous merits from the introduction of flow chemistry technology in synthetic chemistry have already been reported, and the following advantages and features can be mentioned regarding the introduction of flow chemistry technology in pharmaceutical manufacturing.[10]

- Compared with large plant reactors used for batch operations, the reaction temperature can be accurately controlled within a narrow temperature range, and a highly reliable manufacturing method can be established.

- Often applicable to reaction conditions that are difficult to obtain in batch, such as short-time reactions at high or very low temperatures, and minimizing safety concerns for such chemical reactions.
- Since continuous operation without an isolation operation is possible, unstable intermediates can be led to a subsequent reaction or post-processing location, and decomposition of the unstable intermediate can be minimized.
- It can contribute to the reduction of waste amount and the improvement of reaction selectivity
- By making the catalyst in a fixed bed, the catalyst concentration can be partially increased, and the reaction can be terminated quickly.
- Easy to contain highly bioactive compounds, reduce exposure to workers, and improve safety
- Since the scale-up factor is smaller than for batch, the time required for scale-up study can be shortened.
- Compared to batch, the devices can be designed more compactly and they are excellent for on-demand manufacturing.

There are various potential merits of flow compared to batch, as summarized above. However, as mentioned in the introduction, in reality, there are only a few examples in which flow chemistry has been successfully applied to actual manufacturing processes of pharmaceuticals. By introducing this technology into our process chemistry research, we have begun efforts toward flow technology development to provide drug substances and intermediates in a timely and high quality manner and to realize cost-competitive manufacturing processes.

2. Generation and utilization of unstable intermediates in flow chemistry

In order to take advantage of flow chemistry technology, we first focused on reaction development and controlling the reactivity of unstable reaction intermediates.[11,12]

Generation of unstable reaction intermediates and effective utilization of them for target reactions are one of the critical issues for developing chemical processes, and conventional batch reactors generally require

cryogenic conditions for such reactions. In addition, once an unstable intermediate is generated it must be converted efficiently before decomposition (before side reactions occur), which results in decreased yields and increased impurities from side reactions. This is one of the major hurdles for process development using batch reactors.[13]

In particular, organolithium species are generally considered unstable, and even if an addition reaction following the generation of an organolithium species is performed under cryogenic conditions, it is often difficult or impossible to control the intermediate.[14] However, it has been reported that the desired reactions can be carried out with high yield under simpler reaction conditions in flow than in batch.[15] This is because highly efficient mixing in flow allows clean generation of the organolithium species, which are short-lived unstable active species, under precise temperature control arising from efficient heat exchange. It has also been reported that a variety of product libraries can be synthesized by reacting organolithium species with various electrophiles.[16,17]

However, there have been many challenges on the road to achieving actual manufacturing. The inner diameter of a device that performs a flow reaction is generally several tens of micrometers to a few millimeters, and if a slurry is generated in such a narrow flow path, it may immediately block and the operation of the device will become severely impeded or impossible. In addition, when considering scale-up, it is important to reproduce the experimental results obtained on a small scale at a large scale. One of the solutions for scale-up in flow is the numbering-up method, in which numerous identical reactors are operated in parallel. However, in actual cases, it is difficult or impossible to achieve and verify the consistent flow rate of all the fluids required (reactant and reagent solutions) in parallel when numbering-up reactors. Thus, it is generally thought that responding to all the needs for flow scale-up by the numbering up method is not realistic. To address these technical problems, we selected the generation and reaction of unstable intermediates, especially chemical reactions using organolithium species, and started investigating process development using flow chemistry technology.

3. Application of flow chemistry towards boronic acid synthesis utilizing organolithium intermediates

Generally, reactions that deal with organolithiums have large reaction heat and the intermediates are highly

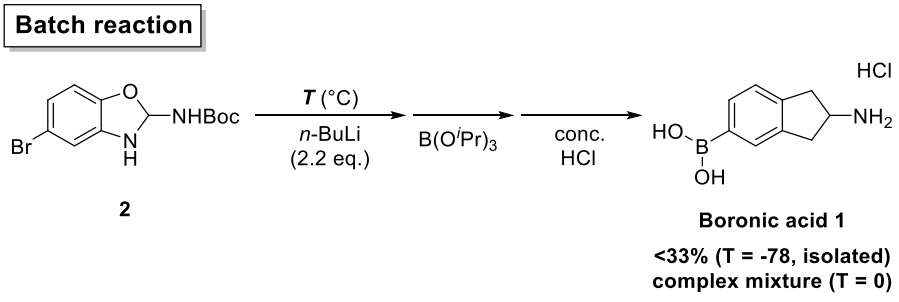
unstable, so when using a batch reactor, most cases require cryogenic conditions, as described above. However, when the flow chemistry technique is used, since rapid heat exchange is possible, the reaction temperature itself can be raised above that possible in the batch reactor, and cryogenic reaction conditions can often be avoided. In addition, an increase in yield and a reduction in impurities are expected by efficient use of unstable active species in flow.

Boronic acids and boronic acid esters were selected as target compounds for the organolithium reaction using flow chemistry technology. The reason for this is that boronic acids and boronic acid esters are easy to handle, and in current pharmaceutical manufacturing processes they are frequently used as important raw materials for Suzuki-Miyaura coupling. However, the cost is often high, and it is desired to establish more efficient novel manufacturing methods that can be operated at lower cost.

Boronic acid **1**, an important intermediate for drug candidate compounds, was an expensive and difficult-to-obtain raw material, and was synthesized in-house by the Miyaura-borylation batch reaction.[18] However, since some palladium used in the Miyaura-borylation reaction remains mixed in the product, a scavenger treatment for removing palladium is required, and the post-treatment process becomes complicated.

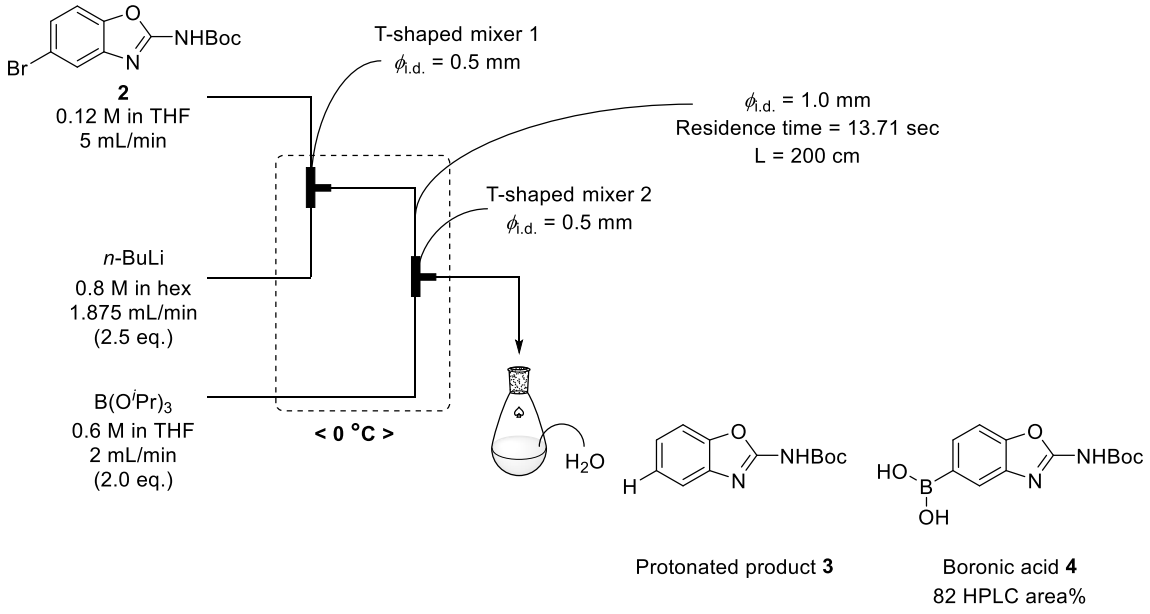
The synthesis of boronic acid **1** was subjected to a lithiation reaction using a batch reactor, and the desired boronic acid was obtained in only 33% yield even when the reaction was carried out at −78 °C with 2.2 eq. of *n*-BuLi, and a large amount of impurity residue was produced, which contaminated the product. Further, when this reaction was carried out at 0 °C, boronic acid **1** was not obtained, and the reaction solution became a complex mixture that was difficult to analyze (Scheme 1).

Scheme 1. Reactions in batch results



After obtaining these results, we began to investigate the reaction using a flow reactor. First, a trial experiment was performed under the conditions shown in Figure 1.

Figure 1. Feasibility experiment for boronic acid synthesis by flow reactor



A flow system was constructed to capture the organolithium intermediate by triisopropoxyborane in tetrahydrofuran (THF) as the electrophile. The raw material aryl halide solution (**2**) was prepared as a THF solution at a concentration of 0.12 M, and 2.5 equivalents of a *n*-BuLi in *n*-hexane solution diluted to 0.8 M was used. After mixing the two liquids in the T-shaped mixer 1 (inner diameter 0.5 mm) and generating the organolithium intermediate after a residence time of 13.71 seconds, the 0.6 M triisopropoxyborane (B(O^{i}Pr)$_3$, 2.0 eq.) solution was added at T-shaped mixer 2.

The reaction solution thus obtained was quenched with tap water and the amount of boronic acid produced was analyzed. The result confirmed that boronic acid **3** was produced at a HPLC area% of 82% even at a reaction temperature of 0 °Cand showed that an organolithium reaction, which was difficult to control in a batch reactor, could be well controlled in a flow reactor. Therefore, the reaction conditions were examined in more detail.

4. Process development of boronic acid synthesis by flow chemistry

Under the above conditions, the raw material **2** was completely consumed, so we next considered reducing the residence time.

Control of the residence time by varying the flow rate also has the effect of changing the mixing efficiency at the T-shaped mixer, therefore, the effect on the residence time of changing the length of tube for lithiation (not changing for flow rate) was investigated. The result, surprisingly, showed that the raw material **2** completely disappeared even with a very short reaction time of about 0.2 seconds, and as the residence time was shortened, the HPLC area ratio of boronic acid **4** was improved (Figure 2, Table 1).

Figure 2. Investigation of residence time and the consumption of raw material in thelithiation step

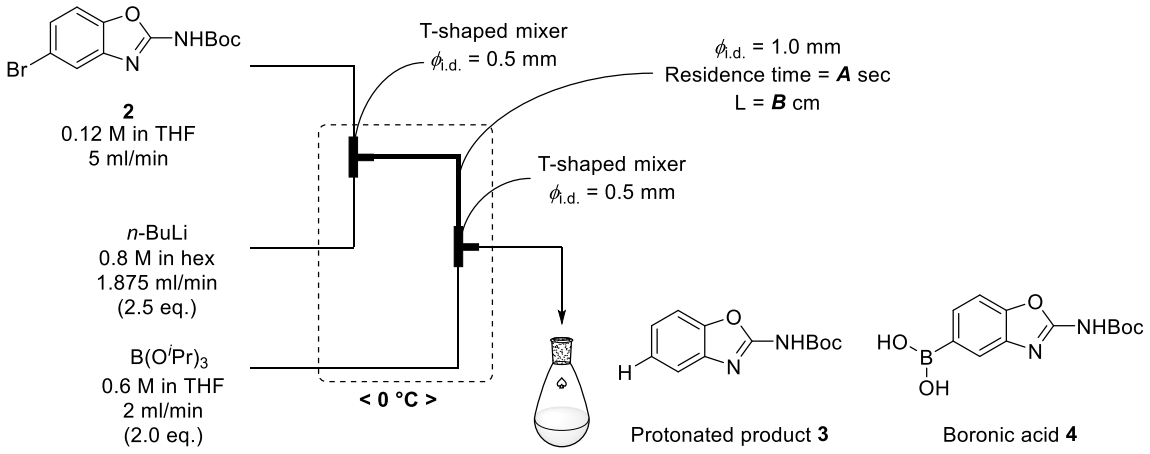


Table 1. Experimental results for residence time

Run	***A*** sec (***B*** cm)	HPLC area%		
		2	**3**	**4**
1	13.71 sec (200 cm)	0	6	82
2	0.86 sec (12.5 cm)	N.D.	8	84
3	0.21 sec (3.0 cm)	N.D.	6	87

Subsequently, a scale-up study aimed at improving the productivity was conducted. In scale-up using flow chemistry technology, solution concentration as well as flow rate is a major factor affecting productivity. However, in this scale-up study, the solubility of the raw material solution **2** in THF was low, so we investigated the method of increasing the flow rate only, and fixing the concentration of **2** to 0.12 M in THF solution, which is close to the upper limit of saturation solubility. In the previous experiment, the raw material (**2**) solution was examined at a delivery rate of 5 ml / min. However, even when the residence time was 0.21 seconds, **2** was completely consumed (Table 1, Run 3). Based on these results, the residence time of the lithiation reaction was set to 0.21 seconds or more to complete the halogen-lithium exchange reaction, and the effect of changing the flow rate and mixer internal diameter was investigated (Figure 3, Table 2).

Figure 3. Experiment to improve productivity (flow rate)

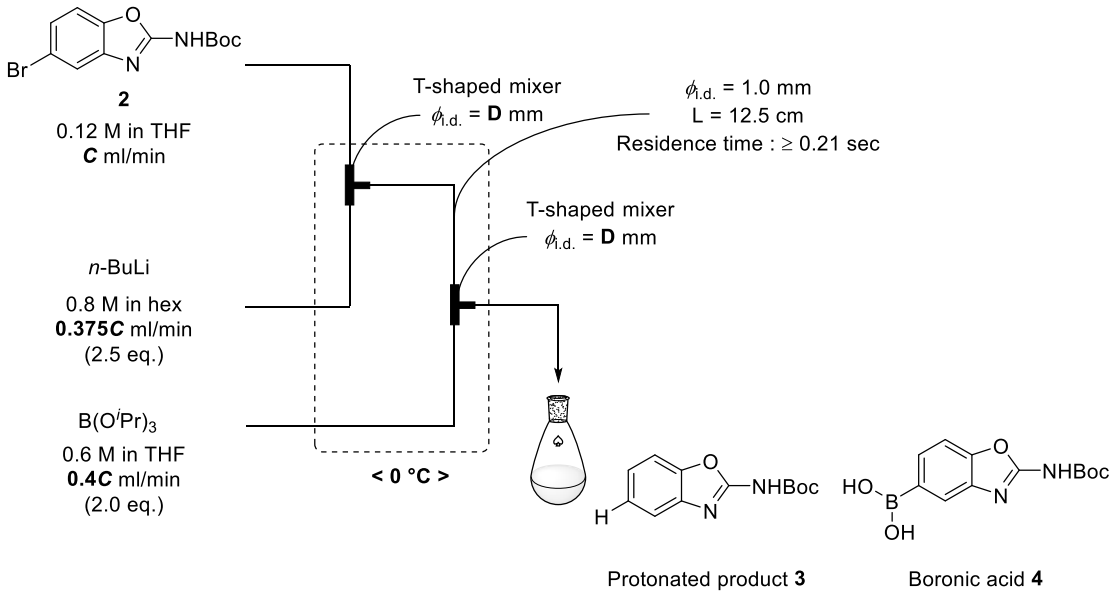


Table 2. Results of examination of productivity (flow velocity) and mixer inner diameter

Run	***C*** (ml/min)	***D*** (mm)	***Residence time*** (sec)	HPLC area%		
				2	**3**	**4**
1	5	0.5	0.86	N.D.	8	84
2	5	1.0	0.86	N.D.	11	78
3	10	1.0	0.43	N.D.	9	83
4	20	1.0	0.21	N.D.	5	89

In general, when the flow rate is increased, the pressure loss inside the flow path increases, and the burden on the pump increases. In order to reduce this influence, the flow path preferably has a larger inner diameter. For this reason, the internal diameter of the mixer was increased from 0.5 mm to 1.0 mm, but the HPLC ratio of the desired boronic acid **4** decreased due to the decrease in mixing efficiency (Run 1 vs Run 2). However, when the flow rate was increased to 2 or 4 times higher, the HPLC ratio of boronic acid **4** was improved (Run 3 & Run 4). This result suggests that, even if the flow path diameter is increased, the influence of the decrease in the mixing efficiency can be suppressed by increasing the flow rate, and the productivity can be improved.

Further optimization of the lithiation was then carried out to see if the excess of *n*-BuLi could be reduced, as any reduction to the 2.5 equivalents used would give significant cost saving at large scale (Figure 4, Table 3). The results showed that the equivalent of *n*-BuLi could be reduced, but more than 2 equivalents of BuLi was required, and a 1.6 M solution of *n*-BuLi was successfully applied for this reaction.

Thus, it was concluded that 2.2 equivalent of *n*-BuLi was optimum for fully converting **2**, and this condition was utilized thereafter.

Figure 4. Optimization for the equivalent of *n*-BuLi

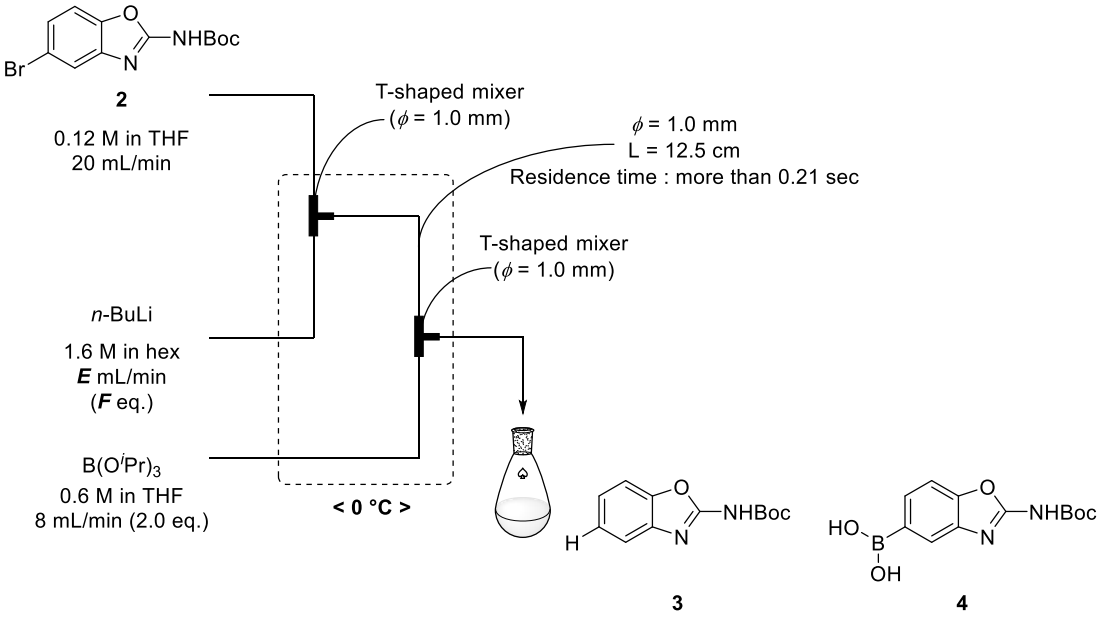


Table 3. Optimization for the equivalent of *n*-BuLi

Run	***E*** (ml/min)	***F*** (eq.)	HPLC area%		
			2	**3**	**4**
1	3.75	2.5	N.D.	7	86
2	3.6	2.4	N.D.	7	86
3	3.3	2.2	N.D.	7	87
4	3.0	2.0	3	9	82
5	2.7	1.8	26	13	52
6	2.25	1.5	80	12	N.D.

Similarly, the optimum equivalent of borylating reagent was investigated, and the 1.8 equivalents of triisopropoxyborane condition was found to give the highest area% (Figure 5, Table 4, Run 2). Therefore, that condition was chosen for further scale-up.

Figure 5. Optimization for the equivalent of borylating reagent

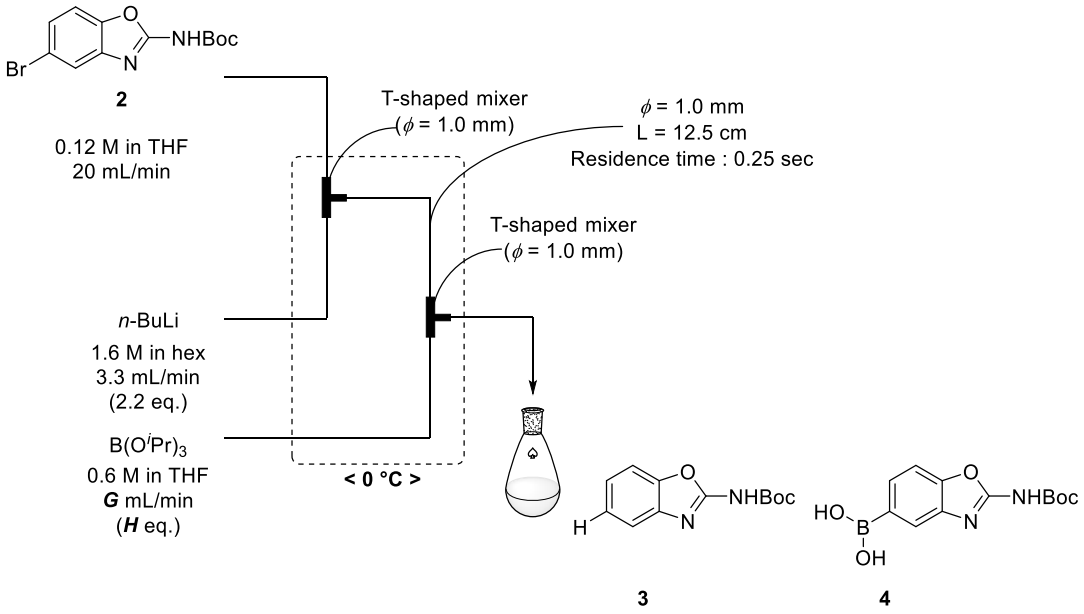
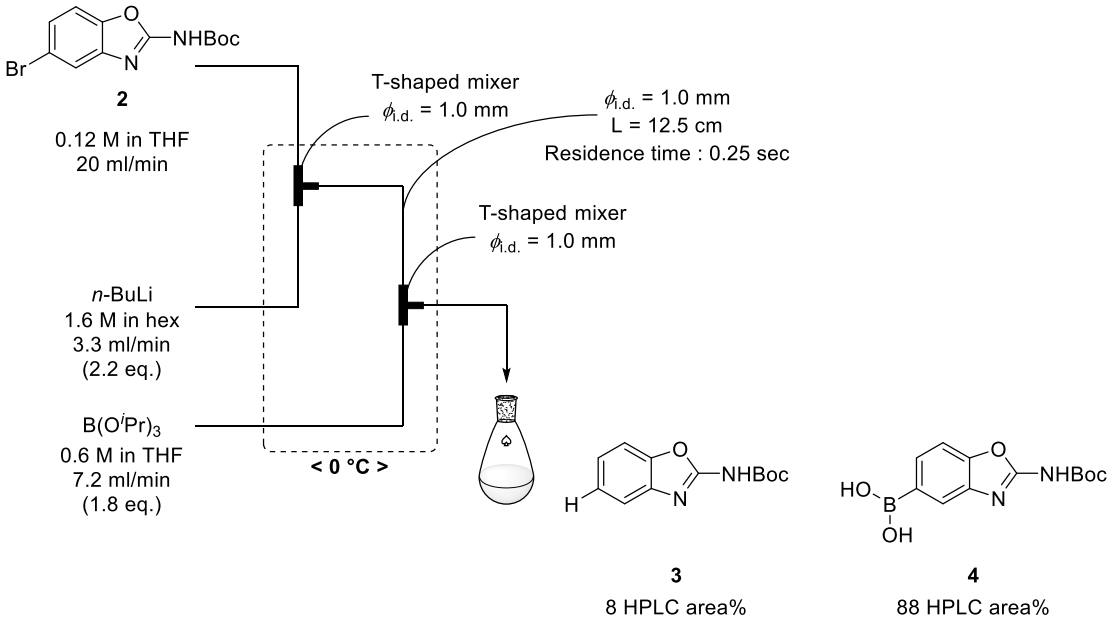


Table 4. Optimization for the equivalent of borylating reagent

Run	***G*** (ml/min)	***H*** (eq.)	HPLC area%		
			2	**3**	**4**
1	8.0	2.0	N.D.	7	87
2	7.2	1.8	N.D.	8	88
3	6.4	1.6	N.D.	8	88
4	5.6	1.4	N.D.	7	87
5	4.8	1.2	N.D.	7	85
6	4.0	1.0	N.D.	7	71

As described above, optimization of the equivalents of *n*-BuLi and $B(O^iPr)_3$ was performed, and boronic acid **4** was obtained at a high production rate under the conditions of 2.2 equivalents of *n*-BuLi and 1.8 equivalents of $B(O^iPr)_3$. (Figure 6).

Figure 6. Results of lithiation reaction with 2.2 equivalents of *n*-BuLi and 1.8 equivalents of $B(O^iPr)_3$



Based on these results, it was considered that the reaction could be scaled up for synthesizing boronic acid **4** by using a flow reactor and the conditions of Figure 6. In actual production, however, considering the operability, it is necessary to know the range of reaction conditions within which the unstable intermediate can be controlled efficiently. Therefore, the effect of residence time and reaction temperature was further investigated (Figure 7, Table 5).

Figure 7. Experiment on the influence of residence time and reaction temperature

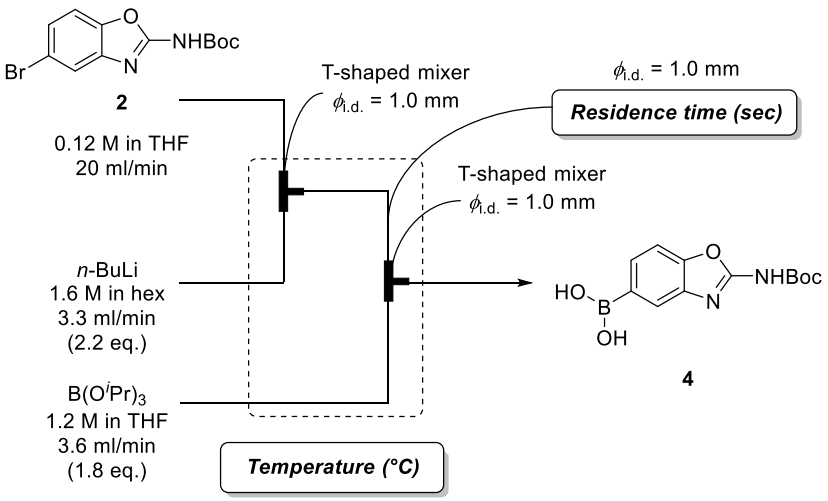


Table 5. Effect of residence time and temperature

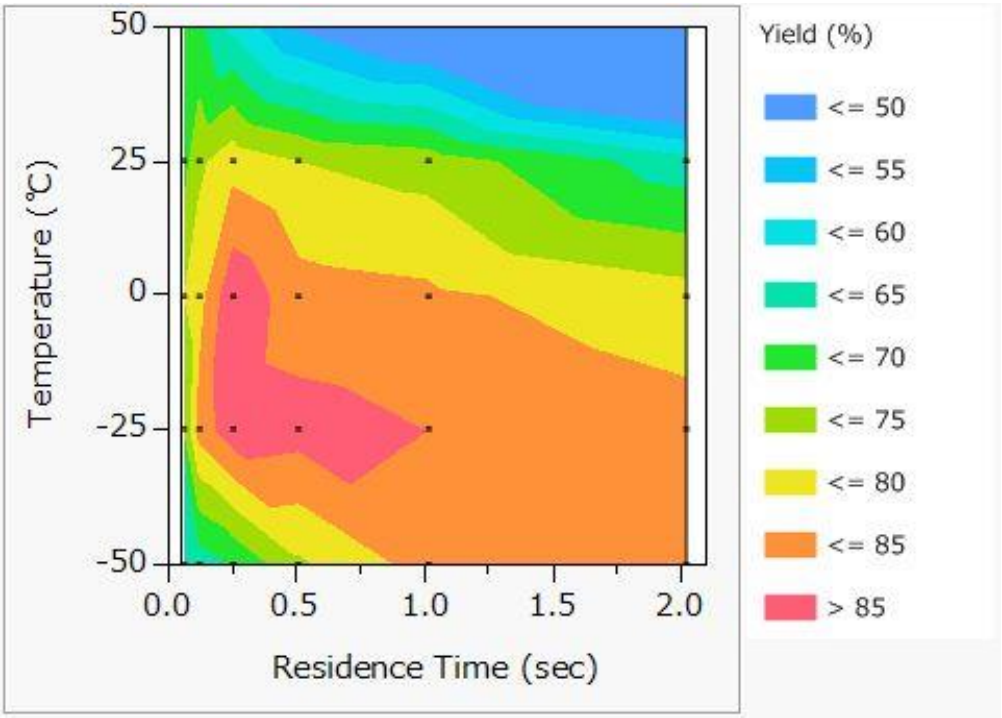
Run	Residence time (sec)	Temperature (°C)	Yield of **4**[a] (%)	Run	Residence time (sec)	Temperature (°C)	Yield of **4**[a] (%)
1	0.06	50	62	19	0.51	50	49
2		25	68	20		25	75
3		0	75	21		0	82
4		-25	70	22		-25	87
5		-50	32	23		-50	74
6		-78	40	24		-78	71
7	0.12	50	66	25	1.01	50	41
8		25	74	26		25	73
9		0	78	27		0	81
10		-25	82	28		-25	88
11		-50	62	29		-50	82
12		-78	40	30		-78	85
13	0.25	50	59	31	2.02	50	17
14		25	78	32		25	62
15		0	86	33		0	77
16		-25	88	34		-25	82
17		-50	65	35		-50	80
18		-78	45	36		-78	77

[a] Determined by HPLC.

Figure 8 shows the result of examining how the residence time and the reaction temperature affect the yield, with the liquid feeding conditions shown in Figure 7. Each plot in Figure 8 is the actual residence time and reaction temperature, and each yield is shown as a contour map. Specifically, when the reaction temperature was −25 °C, the yield was 85% or more when the residence time was about 0.2 to 1.0 seconds, and the maximum yield was 88% when 0.25-1.0 seconds. On the other hand, at a reaction temperature of 0 °C, only when the

residence time was about 0.25 seconds, did the yield exceed 85% (87% in this case), and the experimental results showed that the yield decreased as the residence time was extended.

Figure 8. Two-dimensional mapping (contour plot) of the effect of residence time and reaction temperature on yield[19]



Based on these results, we decided to conduct a scale-up study assuming actual production.

5. Scale-up study using flow chemistry

From the experimental results in the previous section, it was found that the production yield in the reaction solution was about 88% when the intermediate was controlled accurately at −25 °C and the residence time was about 0.25 seconds. Therefore, using these conditions, we conducted a final confirmation experiment at a flow rate that assumed production on an actual machine (Figure 9, Table 6).

Based on the flow rate of **2** that was sent at a flow rate of 20 ml / min in the previous studies, the scale-up conditions were changed as follows. First, the flow rate of **2** was increased to 88 ml / min, the inner diameter of the T-shaped mixer was 1.6 mm, and the tube for the halogen-lithium exchange reaction was 1.0 mm in inner

diameter. In this case, however, the initial effluent from the start of the experiment showed a good reaction result, but the lithiation section became clogged, and eventually the solution could not be pumped (Run 1). The reason for the clogging is not clear, but it was confirmed that the concentration of **2** in the mixed solution of THF and *n*-hexane in the lithiation section was below the saturation solubility at -25 °C. Therefore, it appears that in the scaled-up experiment, due to the greatly improved mixing efficiency from the increased the flow rate, the halogen-lithium exchange was completed earlier in the corresponding section (the intermediate lithium species was generated earlier than in the laboratory experiment), and it is thought that the earlier completion of halogen-lithium exchange may have led to the precipitation and clogging at the lithiation step.

Figure 9. Pre-manufacturing trace experiment using actual production scale set-up

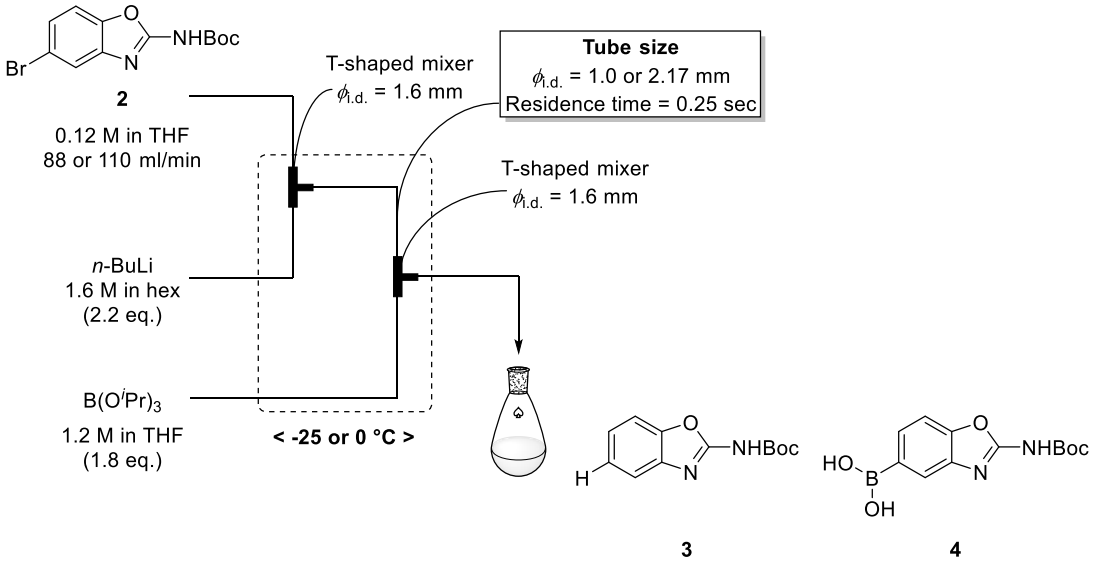


Table 6. Results of pre-manufacturing experiments

Run	Tube size (mm($\phi_{i.d.}$) × mm)	HPLC area%			Inside Pressure (MPa)	Remarks
		2	**3**	**4**		
1 (-25 °C)	1.0 × 550	0	7	92	0.20	Flow rate (SM): 88 ml/min Blockage occurred
2 (-25 °C)	2.17 × 150	0	3	95	---	Flow rate (SM): 110 ml/min Blockage occurred
3 (0 °C)	2.17 × 150	2	4	92	0.11	Flow rate (SM): 110 ml/min Reaction temperature: 0 °C (no blockage)

Since clogging occurred in the lithiation section, the tubing of the section was changed to an inner diameter of 2.17 mm and the flow rate was increased to 110 ml / min, then an experiment aimed at avoiding clogging was performed while maintaining the residence time at 0.25 seconds. However, in this case as well, although the initial reaction solution showed good experimental results, the tubing became blocked during the operation and the reactant flow was stopped (Run 2). Thus, as described above, if the cause of the blockage is due to the precipitation of an intermediate, it was concluded that it will be practically impossible to operate reliably for a long time under the condition of −25 °C. Therfore, we refocused on the previous Figure 8 and examined resetting the conditions. Under the conditions of -25 °C and residence time of 0.25 seconds, the production yield in the reaction solution was the highest at 88%, but from the viewpoint of maintaining a yield of 85% or more, the following three conditions were also possible.

(1) Temperature of 0 °C and residence time of 0.25 seconds

(2) Temperature of -25 °C and residence time is 0.5 seconds

(3) Temperature of -25 °C and residence time of 1.0 seconds

However, since precipitation occured at -25 °C and a residence time of 0.25 seconds, the risk of clogging was considered to be high under conditions (2) and (3) where the residence time is further extended. Therefore, an

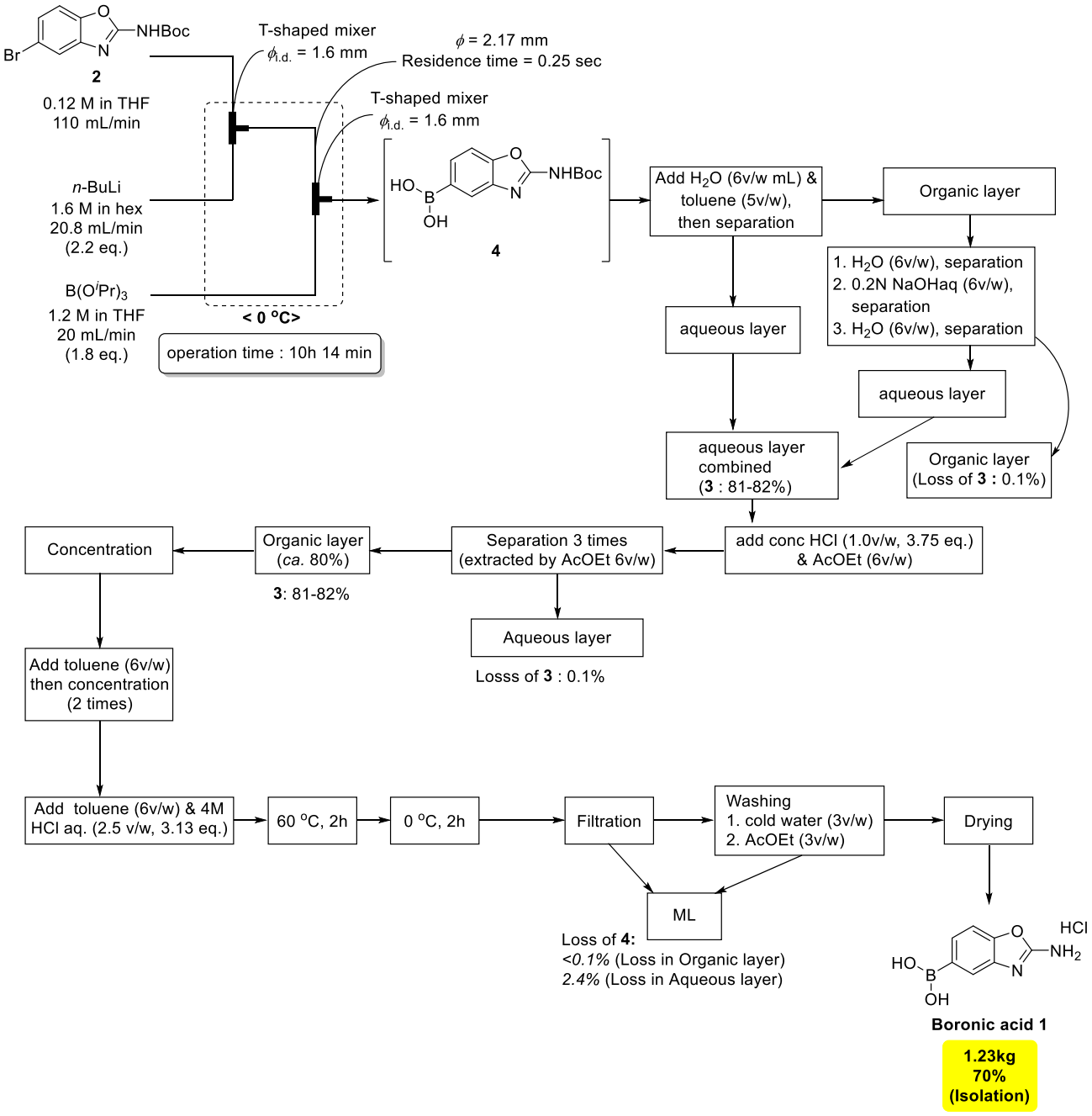
experiment was conducted under the condition (1), and it was found to be possible to operate without clogging. The obtained reaction solution showed the formation of boronic acid **4** at 92% HPLC area % value (Run 3). Thus, it was decided to produce boronic acid **4** by operating for a long time using the condition (1).

6. Production of boronic acid 4

Manufacturing at kg scale was conducted using the conditions found in the previous section at 0 °C. Continuous operation without clogging was possible for about 10 hours, and the resulting reaction solution was subjected to a post-processing step, so that boronic acid **4** was finally obtained at 1.23 kg (isolation yield 70%) (Figure 10).

As described above, acquiring data appropriately before manufacturing is considered a crucial task for conducting process chemistry research, and it was shown to be so for achieving scale-up using flow chemistry technology. In particular, it gives indispensable information when handling chemical reactions *via* unstable intermediates, as in this case.

Figure 10. Boronic acid **4** production results



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Conclusion

A flow chemistry process for boronic acid synthesis utilizing lithiation-borylation was developed, and investigation for scale-up and application to a manufacturing process was described.

The results show that flow chemistry technology is useful for organolithium reactions, which are difficult or impossible to control with batch reactors, and even extremely unstable lithium intermediates can be handled. In addition, after optimization on a gram scale, we were able to show an efficient and smooth scale-up to kilogram levels by a method that does not rely on numbering up.

In order to apply flow chemistry technology to actual pharmaceutical manufacturing, there are a number of issues, such as GMP compliance, but it is considered that the technology offers various merits and it can be used reliably. Both chemical reactions in batch reactors and flow reactors have strengths and weaknesses, and we expect the emergence of chemical processes that use both synergistically to maximize their respective advantages. It is hoped that the results shown in this chapter will serve as a guide and encouragement for further development of flow manufacturing processes.

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   To be submitted.

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   Mitsuhisa Yamano, Masatoshi Yamada, Hirotsugu Usutani.
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1. Selective Monolithiation of Arenes Using Microreactor (Oral presentation)
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   Hirotsugu Usutani
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   Hirotsugu Usutani, Takashi, Nihei, Charles D. Papageorgiou, David G. Cork
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   6th Conference on Frontiers in Organic Synthesis Technology
   （Hungary, Budapest, October 18-20, 2017）

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    Hirotsugu Usutani
    Kansai Branch of The Society of Chemical Engineering, Japan.
    Micro process forefront series -A place for sharing and interaction to foster industry transformation and challenge-
    (Osaka Science & Technology Center (Osaka), October 31st, 2017)

11. Application of flow chemistry to drug substance synthesis (Oral presentation, Request Lecture)
    Hirotsugu Usutani
    Technical Information Institute Co., Ltd.
    Seminar
    （Technical Information Institute (Tokyo), November 16th, 2017）

12. Development and scale-up of a flow flash chemistry process for a key boronic acid intermediate (Oral presentation, Invited Lecture)
    Hirotsugu Usutani
    Kinka Chemical Society Japan, Group for Research on Automated Flow and Microreactor Synthesis
    The First International Conference on Automated Flow and Microreactor Synthesis（ICAMS-1）

(Osaka, January 18-20, 2018)

13. Examples of Utilizing Flow Chemistry in API Manufacturing (Oral presentation, Request Lecture)
Hirotsugu Usutani
Okayama Microreactor Net
The 29th Symposium
(Okayama University, Tsushima Campus (Okayama), July 20th, 2018)

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