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# Synthesis of Biaryls Having a Piperidylmethyl Group Based on Space Integration of Lithiation, Borylation and Suzuki-Miyaura Coupling

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Dedicated to the late Professor Jun-ichi Yoshida

**Abstract:** In a flow microreactor, aryllithiums bearing a piperidylmethyl group were generated using *n*-BuLi by precise residence time control and effective temperature control, and then selectively borylated with boronic esters such as 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (BpinO$^i$Pr) and trimethyl borate $B(OMe)_3$ by fast mixing. Moreover, the direct integration with Suzuki-Miyaura cross coupling were successfully achieved to obtain nitrogen-containing biaryl compounds. The present method could be applied for the straight forward synthesis of the key intermediate of a bioactive component bearing a piperidylmethyl-biphenyl framework.

## Introduction

Biaryl compounds bearing aminomethyl groups, such as piperidyl methyl, have attracted much attention because they are potential bioactive reagents (Figure 1).[1]

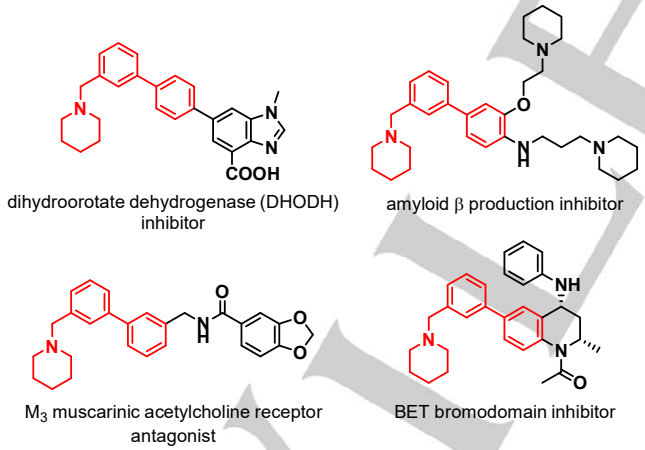


**Figure 1** The nitrogen-containing biaryl compounds.

Biaryls[2] can be synthesized via the two routes shown in figure 2. One route involves two steps: the crosscoupling of aryl halides and arylboronic esters bearing a formyl group, followed by reductive amination (Figure 2a).[3] The amination allows introduction of various amino groups, but a toxic agent such as $NaBH_3CN$ is required, raising concern for the safety. The other route, Suzuki-Miyaura coupling of an arylboronic esters having an aminomethyl group, allows biaryl synthesis in one step without the use of toxic reducing agents (Figure 2b). In general, however, arylboronic esters should be necessary to be prepared by the reaction of a Grignard or organolithium reagent with a trialkyl borate under cryogenic conditions such as -78 °C.

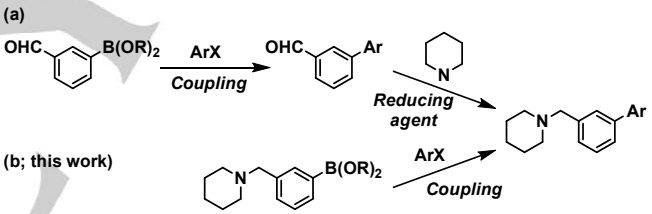


**Figure 2** Reaction pathways for the synthesis of nitrogen-containing biaryl compounds. Ar: aryl group.

We have already reported that aryllithiums bearing functional groups such as cyano, nitro, alkoxycarbonyl and ketone carbonyl group can be rapidly generated and subsequently reacted with boron compounds[4] in flow microreactor systems[5-7] by virtue of an extremely short residence time (flash chemistry[8]).[9] Furthermore, we have integrated arylboronic ester synthesis and Suzuki-Miyaura coupling.[10] Therefore, arylboronic esters having piperidylmethyl groups could be synthesized effectively at higher temperature such as 0 °C in a flow microreactor. Moreover, its integration with Suzuki-Miyaura coupling successfully produced nitrogen-containing biaryls involving a key compound of histone deacetylase (HDAC) inhibitory activity. Herein, we report these results in detail.

## Results and Discussion

First, the lithiation of 1-(3-bromobenzyl)piperidine (**1**) by *n*-butyllithium, followed by reaction with methanol was studied in a conventional batch reactor (Figure 3). The yield of desired product (**3**) was moderate even at -60 °C and decreased with increasing reaction temperature.

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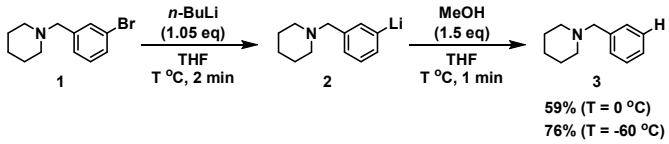


**Figure 3** Br-Li exchange reaction of 1-(3-bromobenzyl)piperidine (**1**) with *n*-BuLi followed by reaction with methanol using a conventional batch reactor.

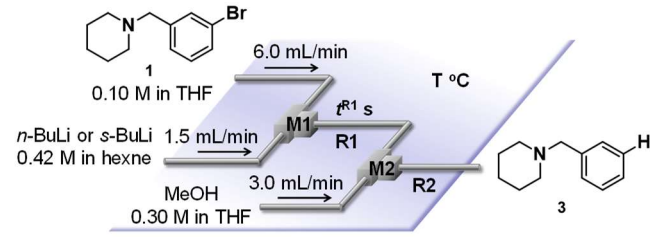


**Figure 4** The flow microreactor system used for the lithiation of 1-(3-bromobenzyl)piperidine (**1**) by *n*-BuLi or *s*-BuLi followed by reaction with methanol.

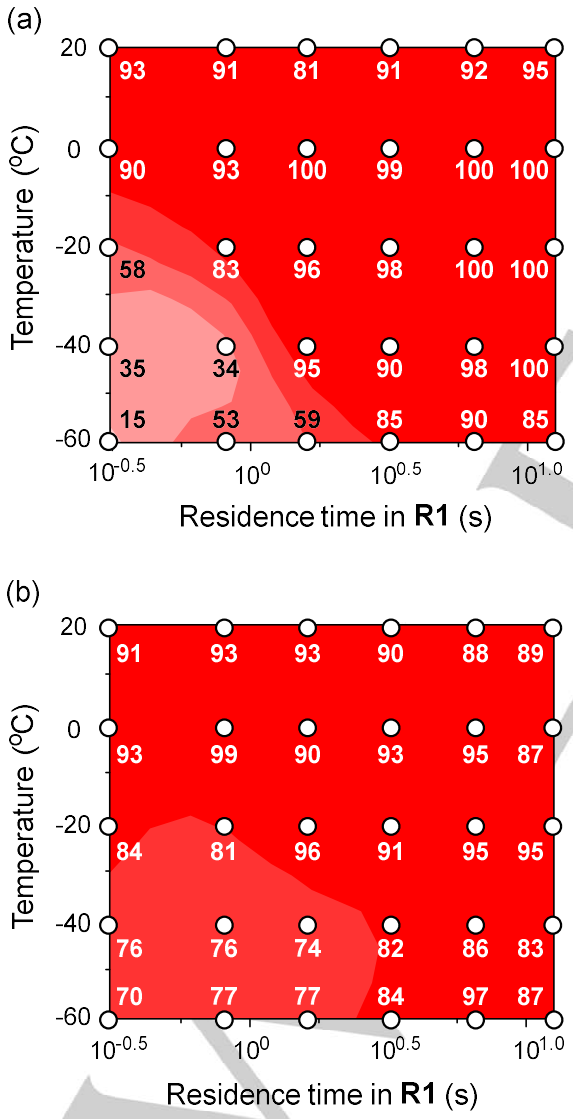


**Figure 5** Effects of temperature and residence time in **R1** on the yield of the protonated product (**3**) from the lithiation of 1-(3-bromobenzyl)piperidine (**1**) with (a) *n*-BuLi and (b) *s*-BuLi followed by trapping with methanol. The numbers at the circles are the yields.

Next, we examined the reactions in a flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**) (Figure 4). Figure 5 shows the stability and reactivity of lithiated 1-(3-bromobenzyl)piperidine (**2**) generated using *n*-BuLi (Figure 5(a)) and *s*-BuLi (Figure 5(b)) at various reaction temperatures and residence times in **R1**. The values beneath the dots are the 1-benzylpiperidine (**3**) yields obtained by trapping **2** with methanol. As shown in Figure 5 (a), lithiation of **1** proceeded very efficiently within the range of T > 0 °C and $t^{R1}$ > 3.1 s. Whereas, at low temperature and short residence time, the yield of **3** was low because the conversion of **1** did not progress sufficiently (See the Supporting Information for details). A similar reaction profile was obtained for *s*-BuLi, although the yield decreased slightly with increasing temperature and residence time.[10] However, *n*-BuLi is the preferable lithiating reagent as it is easier to handle. Borylation, instead of the protonation, also proceeded efficiently under optimized conditions (T = 0 °C, $t^{R1}$ = 6.3 s), resulting in formation of the corresponding arylboronic pinacol ester bearing piperidylamino group in a good yield, which can be used in a Suzuki-Miyaura cross-coupling reaction (See the Supporting Information for details) (Figure 6).

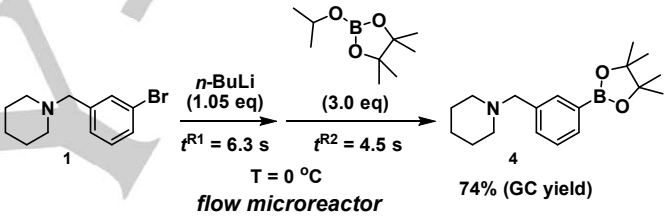


**Figure 6** Generation of lithiated 1-(3-bromobenzyl) piperidine (**2**) followed by reaction with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (BpinO$^i$Pr) in a flow microreactor.

Next, we tried to develop a more practical method using easily available boronic ester $B(OMe)_3$ instead of BpinO$^i$Pr and investigated its direct use in a one-flow Suzuki-Miyaura cross-coupling reaction.[11-12] We have previously reported that the borylation using trialkyl borate and Suzuki-Miyaura cross-coupling can be spatially integrated in a flow microreactor system. However, in general, when the aryl boronic ester is synthesized from aryl metal species and trialkyl borate, it is well known that the reaction efficiency is lower because borinic acid and triaryl boron are formed through competitive consecutive reactions.[13] On the other hand, fast micromixing in a flow microreactor very effectively improves the selectivity of the competitive consecutive reactions.[14]

To investigate the effect of the fast micromixing on the yield of arylboronic ester, the reaction of lithium intermediates with $B(OMe)_3$ was carried out using micromixer **M2** with an inner diameter of 1000, 500 or 250 μm (Figure 7). The resulting boronic ester was hydrolysed in a batch reactor, converted to a more stable arylboronic acid pinacol ester, which was determined by GC. As shown in figure 8, the narrowest micromixer gave the greatest yield of **4**. The results indicate that fast mixing in a flow microreactor very effectively supresses multi-addition and gives high yields of arylboronic esters.

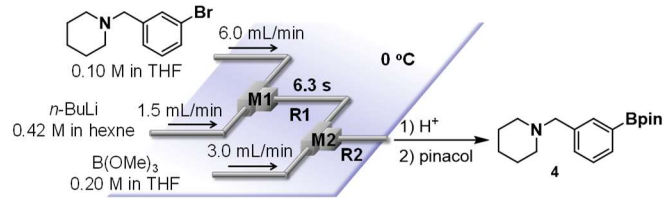


**Figure 7** The flow microreactor system used for the synthesis of arylboronic ester bearing piperidylmethyl group (**4**). "Bpin" means pinacolboranyl group.

**Figure 8** The effect of the inner diameter of the micromixer **M2** on borylation.

Finally, we demonstrated the space integration of the borylation and Suzuki-Miyaura cross-coupling to synthesize a nitrogen-containing biaryl compound using an integrated flow microreactor system consisting of five micromixers and five microtube reactors (Figure 9). Nitrogen-containing biaryl compound (**5**), previously reported to be a synthetic intermediate of a compound with histone deacetylase (HDAC) inhibitory activity, was synthesized by Suzuki-Miyaura cross-coupling of phenylboronic acid having formyl groups and aryl iodide (**6**) (74% yield) followed by reductive amination with piperidine (85% yield, 2 steps: 63% yield).[15] The optimum conditions for the coupling reaction were as previously described.[11] The generated aryllithium intermediate was treated with $B(OMe)_3$ at **M2** and **R2**. To suppress pressure loss, the inner diameter of **M2** was set at 500 μm. The resulting arylboronic acid trimethyl ester was hydrolyzed at **M3** and **R3** and then cross-coupled with aryl iodide (**6**) at **M5** and **R5** using highly reactive Pd catalyst prepared in **M4** and **R4.**[16] The biaryl compound bearing a piperidylmethyl group (**5**) was quantitatively obtained.

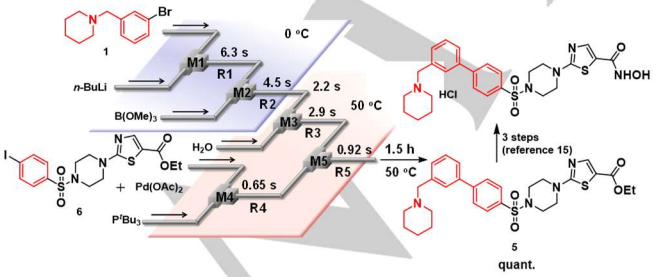


**Figure 9** The integrated flow microreactor system used for the synthesis of an HDAC inhibitor precursor (**5**) by Suzuki-Miyaura cross-coupling. **M1**, **M2**, **M3**, **M4**, and **M5** are T-shaped micromixers, **R1**, **R2**, **R3**, **R4**, and **R5** are microtube reactors.

## Conclusions

We have developed a method, using a flow microreactor, of generating aryllithium species bearing piperidylmethyl groups by precisely controlling temperature and residence time, followed by the synthesis of arylboronic esters by reaction with boronic esters. Furthermore, space integration of borylation with Suzuki-Miyaura cross-coupling reactions was achieved using an integrated flow microreactor system, resulting in the key intermediate of a bioactive component bearing a piperidylmethyl-biphenyl framework.

## Experimental Section

**General procedure for lithiation of 1-(3-bromobenzyl)piperidine (1) followed by the reaction with methanol using a flow microreactor system:** A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**), two microtube reactors (**R1** and **R2**), and three tube pre-cooling units (**P1, P2** and **P3** (inner diameter ϕ = 1000 μm, length L = 100 cm)) was used. A solution of 1-(3-bromobenzyl)piperidine (**1**, 0.10 M in THF) (flow rate: 6.0 mL/min) and a solution of *n*-BuLi or *s*-BuLi (0.42 M in hexane) (flow rate: 1.5 mL/min) were introduced to **M1** by syringe pumps, and the mixture was passed through **R1** (ϕ = 1000 μm, L1 cm). The resulting solution was mixed with methanol (0.30 M in THF) (flow rate: 3.0 mL/min) in **M2**. The mixture was passed through **R2** (ϕ = 1000 μm, L = 100 cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with *sat. aq.* $NH_4Cl$ and was analyzed by GC. The conversion of starting material **1** and yield of product were determined by GC analysis.

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**Keywords:** Borylation • Flow microreactor • Lithiation • Piperidylmethyl group • Suzuki-Miyaura coupling

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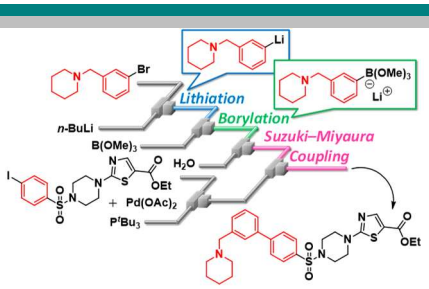
## Entry for the Table of Contents

# COMMUNICATION

A flow microreactor allow for the generation of aryllithiums bearing a piperidylmethyl group and then selectively borylation with boronic esters. Moreover, lithiation, borylation and Suzuki-Miyaura cross coupling could be integrated to obtain nitrogen-containing biaryl compounds such as a synthetic intermediate of a compound with histone deacetylase (HDAC) inhibitory activity.




**Flow Microreactor**

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**Synthesis of Biaryls Having a Piperidylmethyl Group Based on Space Integration of Lithiation, Borylation and Suzuki-Miyaura Coupling**

*one or two words that highlight the emphasis of the paper or the field of the study