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COMMUNICATION

Flow Synthesis of Arylboronic Esters Bearing Electrophlic Functional Groups and Space Integration with Suzuki-Miyaura Coupling Without Intentionally Added Base†

Aiichiro Nagaki,[a] Yuya Moriwaki,[a] and Jun-ichi Yoshida*[a]

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We found that an integrated flow microreactor system enables the preparation of boronic esters bearing electrophilic functional groups using organolithium chemistry and that it allows for their use in Suzuki-Miyaura cross-coupling without intentionally added base. Based on this method, cross-coupling of two aryl halides bearing electrophilic functional groups was accomplished to obtain corresponding biaryl compounds in one flow.

Arylboronic acids and esters have found widespread applications in transition-metal-catalyzed reactions, as represented by Suzuki-Miyaura cross-coupling.[1] The most commonly utilized method to prepare these boron compounds is the reaction of Grignard or organolithium reagents with trialkyl borates.[2] Although this traditional approach has been still used widely, it cannot be applied to substrates bearing electrophilic functional groups such as an alkoxycarbonyl, a cyano and a nitro group.[3] Such arylboronic esters can be prepared from aryl halides or aryl triflates via palladium-catalyzed cross-coupling reactions with tetraalkoxydiboron or dialkoxyhydroborane[4] and these methods tolerate a wide range of such functional groups.[5] The borylation of arylamines has been also recently developed.[6] However, these methods are not suitable for large-scale synthesis, especially in industry, because borylating reagents such as tetraalkoxydiboron and dialkoxyhydroborane are very expensive. Therefore, there is still a great demand for the synthesis of arylboronic esters bearing electrophilic functional groups using Grignard or organolithium reagents and trialkyl borates.

We have recently reported that highly reactive and unstable aryllithiums bearing electrophilic functional groups such as an alkoxycarbonyl, a cyano, a nitro, and a ketone carbonyl group can be rapidly generated and used in a subsequent reaction before decomposition in a flow microreactor system[7,8,9] by virtue of an extremely short residence time (flash chemistry[10]).[11] This finding prompted us to then study the preparation of arylboronic esters having electrophilic functional groups.[12]

Recently, Buckwald *et al.* reported the synthesis of boronic esters via lithiation in flow and their use for Suzuki-Miyaura cross-coupling,[13] but the method cannot be applicable to synthesis of boronic esters bearing electrophilic functional groups because of long residence times.[14] However, flash chemistry would enable the preparation of arylboronic esters having electrophilic functional groups. Moreover, its integration[15] with Suzuki-Miyaura cross-coupling[16] with aryl halides having electrophilic functional groups would lead to the cross-coupling of two aryl halides bearing electrophilic functional groups, hence providing a powerful method for synthesizing polyfunctionalized biaryl compounds (Figure 1). Here we report that our idea works and that a wide range of arylboronic esters bearing electrophilic functional groups can be synthesized based on flash chemistry. We also report that space integration with Suzuki-Miyaura cross-coupling could be achieved without intentionally added base by using the integrated flow microreactor system.

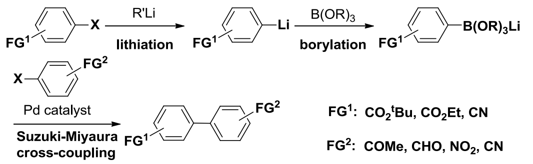

Fig. 1 Functionalized biaryls synthesis by lithiation, borylation, and Suzuki-Miyaura cross-coupling sequence. For the functional groups: FG.

Our initial study aiming at the synthesis of boronic esters having electrophilic functional groups was carried out using the flow microreactor system consisted of two T-shaped micromixers and two microtube reactors shown in Figure 2.

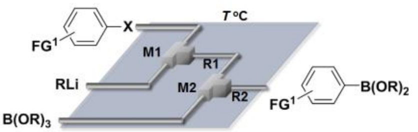

Fig. 2 A flow microreactor system for synthesis of functionalized boronic esters based on X/Li exchange reaction of aryl halides followed by borylation (micromixers: **M1** and **M2**, microtube reactors: **R1** and **R2**).

The reactions of isopropoxyboronic acid pinacol ester with aryllithiums, which was generated by the X/Li exchange, were examined to obtain arylboronic acid pinacol esters (Table 1). Notably, alkoxycarbonyl, cyano, and nitro groups tolerated under the individually optimized conditions, although such functional

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[a] *Department of Synthetic and Biological Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, 615-8510 Kyoto, Japan. Fax: +81-75-383-2725; Tel: +81-75-383-2726; E-mail:yoshida@sbchem.kyoto-u.ac.jp*

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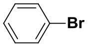
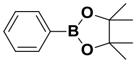
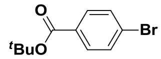
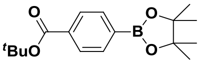
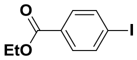
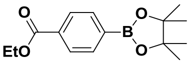
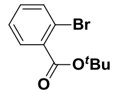
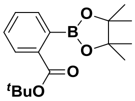
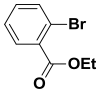
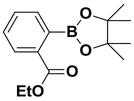
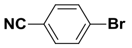
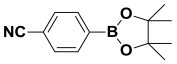
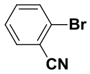
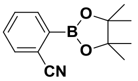
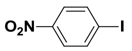
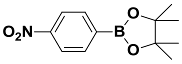
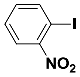
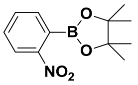
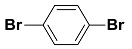
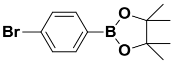
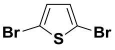
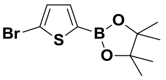
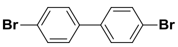
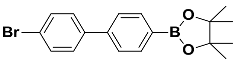
groups easily undergo decomposition in conventional batch reactions. It is also noteworthy that simple phenylboronic acid pinacol ester was obtained at higher temperatures such as 24 °C.[17] Furthermore, arylboronic esters having one bromine atom on the aromatic ring was also easily synthesized from dibromo compounds, although such a transformation is very difficult to achieve using conventional batch reactors because of the formation of a significant amount of dilithiated species.

Table 1 Synthesis of functionalized boronic esters by halogen-lithium exchange reactions of aryl halides followed by borylation.

Ar-Br	RLi	T (°C)	t^{R1} (s)	Ar-B(OR)$_2$	yield (%)[a]
	*n*-BuLi	24	3.14		92
	*s*-BuLi	-28	0.055		75
	PhLi	-58	0.055		69
	*s*-BuLi	-28	0.055		84
	*s*-BuLi	-48	0.055		64
	*n*-BuLi	0	0.055		85
	*n*-BuLi	24	0.055		83
	PhLi	-28	0.055		64
	PhLi	-28	0.055		80
	*n*-BuLi	24	0.014		83
	*n*-BuLi	24	0.014		73
	*n*-BuLi	0	0.055		86

[a] The yield of the product was determined by GC analysis.

Next, we examined space integration of borylation of funtionalized aryl halides (Ar^{1}X) and Suzuki-Miyaura cross-coupling with functionalized aryl halides (Ar^{2}X) using an integrated flow microreactor system comprising five micromixers and five microtube reactors (Figure 3). We chose to study cross-coupling of *tert*-butyl *p*-bromobenzoate (Ar^{1}X) and *p*-bromobenzonitrile (Ar^{2}X) as a model reaction. In this case B(OMe)$_3$ was used as a borylating agent.

tert-Butyl *p*-bromobenzoate was reacted with *s*-BuLi (T^1 = -28 °C, t^{R1} = 0.081 s) at **M1** and **R1** to give *p-tert*-butoxycarbonylphenyllithium, which was treated with B(OMe)$_3$ at **M2** and **R2**. The resulting arylboronic acid dimethyl ester was hydrolyzed at **M3** and **R3** before the cross-coupling with *p*-bromobenzonitrile was carried out at **M5** and **R5** using a highly reactive Pd catalyst prepared in **M4** and **R4.**[18] The effect of hydrolysis conditions is interesting as depicted in Table 2. Hydrolysis using 1.0 or 3.0 equiv of KOH in H$_2$O at 30 °C is not so effective. The coupling product was obtained only in low yields. Hydrolysis without using KOH was better. When the reaction was carried out at higher temperatures such as 50 °C in the absence of KOH, the cross-coupling product was obtained in high yields. Although the detailed mechanism is not clear, the nature of the substituents on boron in the hydrolyzed compound seems to significantly affect its reactivity for cross-coupling.[19]

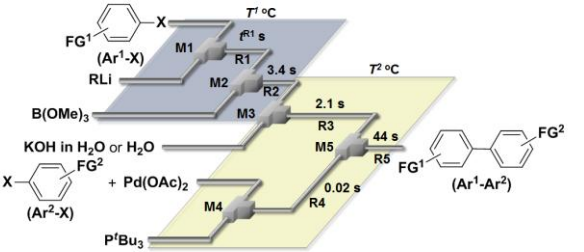


Fig. 3 An integrated flow microreactor system for cross-coupling of Ar^{1}X and Ar^{2}X. T-shaped micromixers: **M1**, **M2**, **M3**, **M4** and **M5**, microtube reactors: **R1**, **R2**, **R3**, **R4** and **R5**.

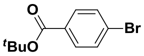
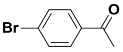
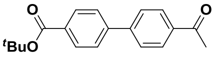
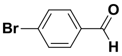
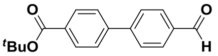
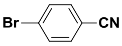
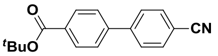
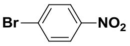
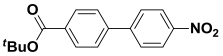
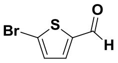
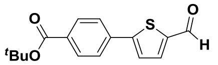
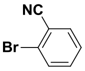
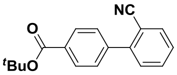
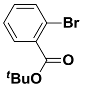
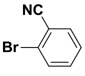
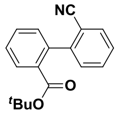
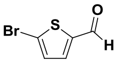
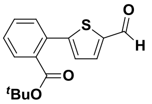
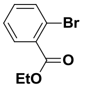
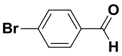
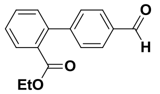
Table 2 Cross-coupling reaction from *tert*-butyl *p*-bromobenzoate (Ar^{1}X) and *p*-bromobenzonitrile (Ar^{2}X).[a]

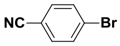
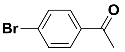
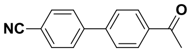
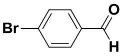
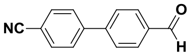
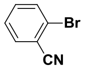
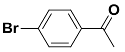
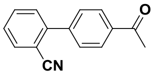
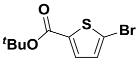
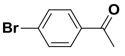
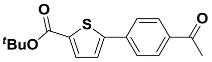
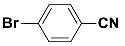
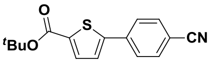
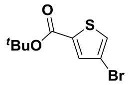
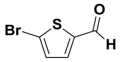
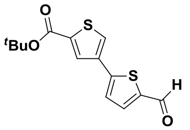
temperature T^2 (°C)	hydrolysis condition	yield (%)
30	KOH (3 eq) in H$_2$O	7
30	KOH (1 eq) in H$_2$O	15
30	H$_2$O	64
50	H$_2$O	97

[a] The yield of the product was determined by GC analysis.

The present integrated method was successfully applied to cross-coupling of various aryl halides bearing electrophilic functional groups as shown in Table 3. Biaryls bearing such funtional groups on both aromatic rings could be easily synthesized in high yields in one flow. The reaction with heteroaryl halides bearing electrophilic functional groups can be also achieved.

Table 3 Cross-coupling of Ar^{1}X and Ar^{2}X using the integrated flow microreactor system.[a]

Ar^{1}X	Ar^{2}X	Ar^1-Ar^2	yield (%)[b]
			62[c]
			70[c]
			97 (91[c])
			81[c]
			80[c]
			72[c]
			87[d]
			69[e]
			52[f]

			77[g,h]
			90[g,h]
			61[e,g]
			81[c]
			73
			91[c]

[a] *s*-BuLi was used as a lithiating reagent unless otherwise stated. [b] The yield of the product was determined by GC analysis. [c] Isolated yield. [d] The resulting mixture was stirred for 10 min. [e] The resulting mixture was stirred for 5 min. [f] The resulting mixture was stirred for 30 min. [g] *n*-BuLi was used as a lithiating reagent. [h] The resulting mixture was stirred for 2 min.

In conclusion, we found that various arylboronic esters bearing electrophilic functional groups could be prepared by halogen-lithium exchange followed by borylation. Space integration with Suzuki-Miyaura cross-coupling was achieved by using integrated flow microreactor systems enabling cross-coupling of two aryl halides bearing electrophilic functional groups. It is interesting that Suzuki-Miyaura cross-coupling proceeds without intentionally added base. The method greatly enhances the synthetic utility of aryllithium compounds and adds a new dimension to the chemistry of cross-coupling. Further work is in progress to explore the full scope of this useful transformation and its synthetic applications.

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