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

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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 dialkoxyhydroborane4 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, and a nitro group can be rapidly generated and used in a subsequent reaction before decomposition in a flow microreactor system7,8,9 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 integration15 with Suzuki-Miyaura cross-coupling16 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.

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

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
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 dilliated species.

Hydrolysis using 1.0 or 3.0 equiv of KOH in H₂O 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

Next, we examined space integration of borylation of functionalized aryl halides (Ar'X) and Suzuki-Miyaura cross-coupling with functionalized aryl halides (Ar²X) 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'X) and p-bromobenzenonitrile (Ar²X) 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 (Tᵢ = -28 °C, tᵢ = 0.081 s) at M1 and R1 to give p-tert-butoxy carbonylphenyllithium, 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-bromobenzenonitrile 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.
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.

Notes and references


