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Three-Component Coupling Based on Flash Chemistry. Carbolithiation of Benzyne with Functionalized Aryllithiums Followed by Reactions with Electrophiles

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ABSTRACT: A flow microreactor method for three-component coupling of benzyne was developed based on flash chemistry. *o*-Bromophenyllithium generated from 1-bromo-2-iodobenzene and a functionalized aryllithium generated from the corresponding aryl halide were mixed at –70 °C. In the subsequent reactor *o*-bromophenyllithium is decomposed to generate benzyne without affecting the functionalized aryllithium at –30 °C, and carbolithiation of benzyne with the aryllithium took place spontaneously. The resulting functionalized biaryllithium was reacted with an electrophile in the subsequent reactor to give the corresponding three-component coupling product. The precise optimization of reaction conditions using the temperature – residence time mapping is responsible for the success of the present transformation. The present method has been successfully applied to the synthesis of boscalid.

Arynes including benzyne are highly reactive intermediates, and extensive studies on their synthetic applications have been reported so far.[1,2] In particular, carbometalation of benzyne serves as a powerful method for constructing organic structures containing an *o*-disubstituted benzene ring.[3] Although it is well known that *o*-halophenyllithiums serve as good precursors of benzyne, it is difficult to use them for carbolithiation because various organolithium species are generated simultaneously, which compete with each other.

Schlosser reported a smart way of controlling the carbolithiation of benzyne by adding an *o*-dihalobenzene to an aryllithium. The reaction proceeds by a chain mechanism.[4,5] Benzyne generated from *o*-halophenyllithium reacts with an aryllithium to give a biaryllithium, which undergoes halogen/lithium exchange with *o*-dihalobenzene to give a biaryl halide as a product regenerating *o*-halophenyllithium. However, the method suffers from the limitation of the substrates because of the requirement of delicate balance of the reactivity of organolithium intermediates (*vide infra*, Scheme 1).

If the biaryllithiums formed by carbolithiation could be used for reactions with various electrophiles at will, the carbolithiation method should serve as powerful and straightforward tansition metal-free three-component synthesis of *ortho*-disubstituted benzenes. Such transformations, however, seem to be very difficult or impossible in batch because of short lifetimes of the intermediates.

Flash chemistry[6] solves the problem. We report here carbolithiation of benzyne generated from an *o*-halophenyllithium with aryllithiums followed by reactions of the resulting biaryllithiums with subsequently added electrophiles using an integrated flow microreactor system[7,8,9] (Figure 1). It should be emphasized that the present flash method enables the use of short-lived aryllithiums bearing electrophilic functional groups such as cyano and nitro groups giving three-component coupling products bearing such functionalities.

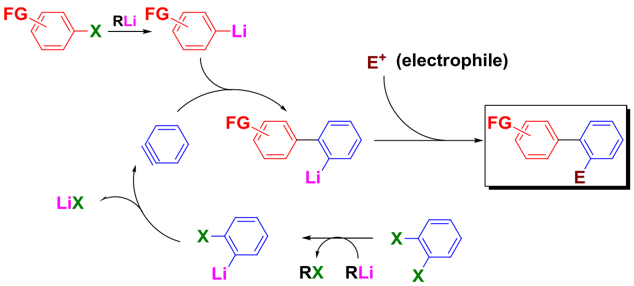


Figure 1. Carbolithiation of benzyne with aryllithiums. Consecutive three-component coupling with subsequently added electrophiles.

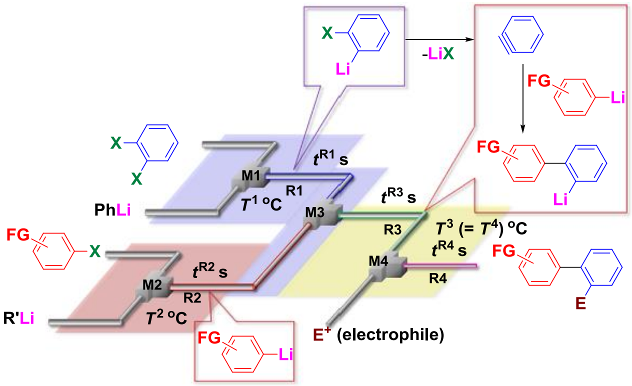


Figure 2. An integrated flow microreactor system for the three-component coupling of benzyne, functionalized aryllithiums, and electrophiles. T-shaped micromixers: **M1**, **M2**, **M3** and **M4**, microtube reactors: **R1**, **R2**, **R3** and **R4**.

We envisaged that space integration of reactions[10] using the integrated flow microreactor system shown in Figure 2 enables the present transformation involving multiple short-lived reactive intermediates.[11] An *o*-halophenyllithium and an aryllithium are generated by halogen/lithium exchange in **M1**/**R1** and **M2**/**R2**, respectively. They are mixed in **M3**. In **R3**, the *o*-halophenyllithium is selectively decomposed to generate benzyne without affecting the aryllithium, which adds to benzyne spontaneously. The resulting biaryllithium is allowed to react with an electrophile in **M4** and **R4** to give the corresponding three-component coupling product. To achieve these transformations in a harmonious way, the residence time and the temperature for each step should be precisely controlled.

First, we optimized the conditions for generating and accumulating *o*-halophenyllithiums from *o*-dihalobenzenes using a flow microreactor system[12] shown in Figure 3. The reactions of 1,2-dibromobenzene, 1-bromo-2-iodobenzene, and 1,2-

diiodobenzene were carried with varying the temperature (T^1) and the residence time in **R1** (t^{R1}), and *o*-halophenyllitiums were trapped with benzaldehyde. The yields of the products are plotted against T^1 and t^{R1} as contour maps with scattered overlays (Figure 4). In the case of 1,2-dibromobenzene using BuLi as a lithiating agent, the yields at short residence times are low, because bromine/lithium exchange is not so fast. The yield increases with an increase in the residence time, and then decreases because of the decomposition to generate benzyne. In the case of 1-bromo-2-iodobenzene using PhLi as a lithiating agent, the yields at short residence times are high because iodine/lithium exchange is faster. At longer residence times the decomposition to benzyne takes place. In the case of 1,2-diiodobenzene using PhLi as a lithiating agent, the yields at short residence times are high, but the yield decrease very quickly with an increase in the residence time, presumably because *o*-iodophenylithium is less stable than *o*-bromophenyllithium. Based on these results, we chose to generate *o*-bromophenyllithium as a precursor of benzyne from 1-bromo-2-iodobenzene. In this case the highest yield (93%) was obtained at –70 °C with the residence time of 0.16 s, and therefore these conditions were used for the subsequent studies. Also, it should be noted that the temperature-residence time maps in Figure 4 give crucial information about the conditions for benzyne generation.

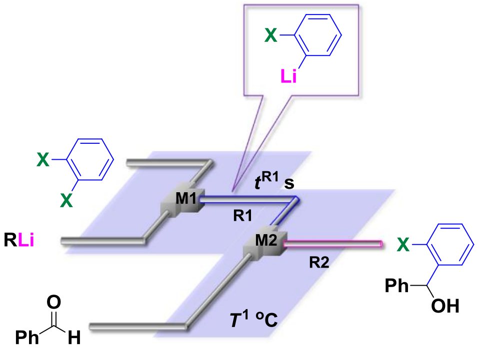


Figure 3. A flow microreactor system for generation and accumulation of o-halophenyllithiums. T-shaped micromixers: **M1** and **M2**, microtube reactors: **R1** and **R2**.

Next, we examined the generations of benzyne from *o*-bromophenyllithium in the presence of *p*-chlorophenyllithium using an integrated flow microreactor system (Figure 2). The carbolithiation of benzyne with *p*-chlorophenyllithium followed by the reaction with added electrophiles should take place. Thus, 1-bromo-2-iodobenzene was reacted with PhLi (T^1 = –70 °C, t^{R1} = 0.22 s) at **M1** and **R1** to give *o*-bromophenyllithium, which is stable at this temperature within 1 s as indicated in Fig 4b. 1-Bromo-4-chlorobenzene was reacted with *n*-BuLi (T^2 = 0 °C, t^{R1} = 0.31 s)[13] at **M2** and **R2** to generate *p*-chlorophenyllithium, and the resulting solution was cooled to –70 °C (T^1). The two organolithium species were mixed at **M3** at –70 °C (T^1), and the mixture was warmed to –30 °C (T^3) in **R3** (t^{R3} = 2.69 s) (See the Supporting Information for details). Because *o*-bromophenyllithium decomposes completely at –50 °C within 2.4 s (Figure 4b), such decomposition should take place very quickly at –30 °C to generate benzyne. In contrast, *p*-chlorophenyllithium, which is generated at 0 °C, should be stable at –30 °C. Thus, flash generated benzyne reacted with *p*-chlorophenyllithium in **R3** to give the corresponding biaryllithium, which was transferred to **M4**, where an electrophile was added. The reaction in **R4** (T^4 (= T^3) = –30 °C, t^{R4} = 1.06 s) gave the final three-component coupling products.

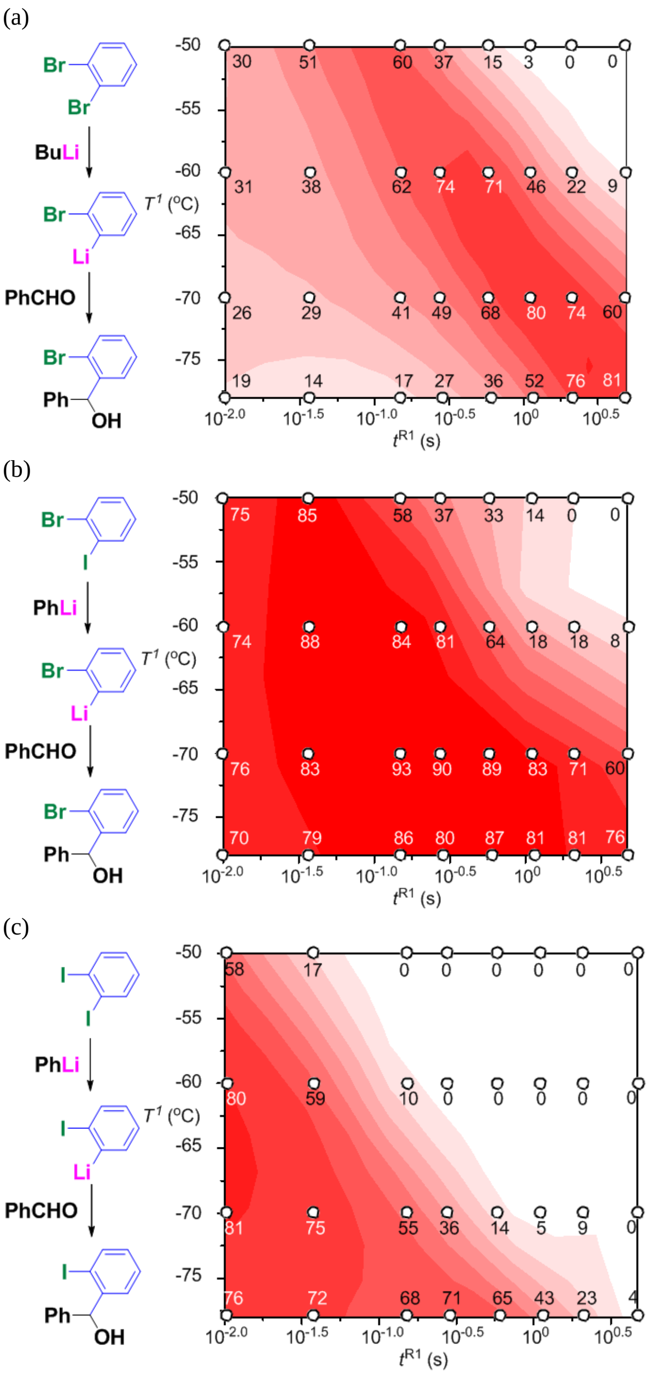
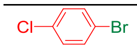
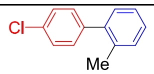
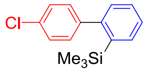
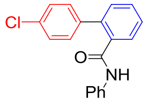
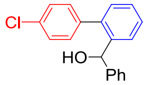
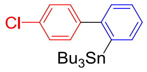
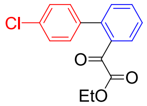
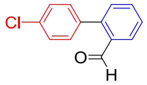
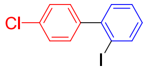
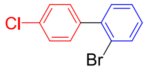
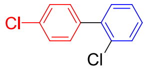
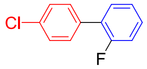
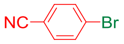
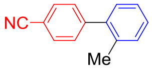
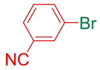
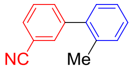
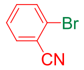
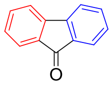
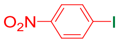
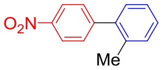
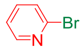
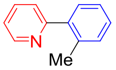
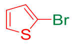
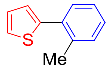


Figure 4. Temperature (T^1) - residence time (t^{R1}) maps for the halogen/Li exchange reaction of (a) 1,2-dibromobenzene with *n*-BuLi, (b) 1-bromo-2-iodobenzene with PhLi and (c) 1,2-diiodobenzene with PhLi followed by reaction with benzaldehyde in the flow microreactor.

Various electrophiles such as methyl trifluoromethanesulfonate, trimethylsilyl trifluoromethanesulfonate, phenyl isocyanate, benzaldehyde, tributyltin chloride, diethyl oxalate, and methyl formate were effective (Table 1). Notably, selective reaction of biaryllithiums with diethyl oxalate using a flow microreactor was achieved to obtain α-keto esters with high selectivity by virtue of fast 1 : 1 micromixing.[14] Moderate yields for these reactions seem to be attributed to inevitable competitive reactions of benzyne with other organolithium species that should be present in the reaction mixture, such as *o*-bromophenyllithium and biaryllithiums.

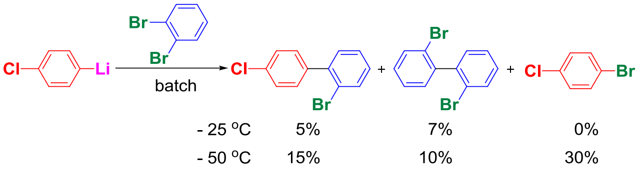
Table 1. Three-component coupling of benzyne, aryllithiums, and electrophiles using the integrated flow microreactor system.[a]

	electrophile	product	yield (%)
	MeOTf[b]		73
	TMSOTf[b]		53
	PhCNO[b]		63
	PhCHO[b]		69
	Bu_3SnCl[b]		58
	$(CO_2Et)_2$[b]		62
	HCO_2Me[b]		54
	I_2[b]		51
	CBr_4[b]		63
	C_2Cl_6[b]		64
	NFSI[b,c]		71
	MeOTf[d]		63
	MeOTf[d]		70
	–[e]		71
	MeOTf[f]		50
	MeI[g]		50
	MeOTf[d]		58

[a] The reactions were usually carried out with 0.6 mmol/min of 1-bromo-2-iodobenzene. [b] R'Li = BuLi, t^{R2} = 0.31 s, T^2 = 0 °C, [c] T^3 = –50 °C, [d] R'Li = BuLi, t^{R2} = 0.31 s, T^2 = –30 °C, [e] R'Li = BuLi, t^{R2} = 0.16 s, T^2 = –20 °C, [f] R'Li = PhLi, t^{R2} = 1.18 s, T^2 = –70 °C, [g] R'Li = BuLi, t^{R2} = 2.36 s, T^2 = –30 °C

Halogenating agents such as tetrabromomethane, iodine, hexachloroethane and *N*-fluorobenzenesulfonimide (NFSI) were also effective as electrophiles, and the corresponding biaryl halides were obtained.[15] It should be noted that similar products were difficult to obtain selectively by the chain reaction via in situ halogen transfer. For example, the reaction of *p*-chlorobenzene and *o*-dibromobenzene in a batch macro reactor led to the formation of a mixture of desired 2-bromo-4'-chlorobiphenyl and undesired 2,2'-dibromobiphenyl at –25 °C (Scheme 1). At lower temperatures such –50 °C, the yield of the desired product slightly increased, but a significant amount of undesired 4-chlorobromobenzene was also obtained. In the present flash method, however, desired 2-bromo-4'-chlorobiphenyl was obtained selectively in a good yield (Table 1).

Scheme 1



In addition to *p*-chlorophenyllithium, various aryllithiums bearing electrophilic functional groups[16] can be used for the present three-component coupling. For example, *o*-, *m*-, and *p*-cyanophenyllithiums generated at –20 − –30 °C using BuLi (t^{R2} = 0.16 − 0.31 s),[17] and *p*-nitrophenyllithium generated at –30 °C using PhLi (t^{R2} = 0.31 s)[18] were successfully used in this transformation. Benzyne were generated without affecting such functionalized aryllithiums. The carbolithiation followed by the subsequent reactions with electrophiles gave the three-component coupling products. Such transformations are very difficult or impossible to achieve using conventional batch reactors. Heteroaryllithiums such as 2-pyridyllithium (T^2 = –30 °C, t^{R2} = 2.36 s) and 2-thiophenyllithium (T^2 = –30 °C, t^{R2} = 0.31 s)[19] can also be used for the three-component coupling, because they are also stable at –30 °C within a second or so.

To demonstrate the utility of the present flash method, we examined the application to the synthesis of boscalid,[20,21] an important fungicide, which belongs to the class of succinate dehydrogenase inhibitors. Benzyne generation from *o*-bromophenyllithium and the carbolithiation with 4-chlorophenyllithium followed by the reaction with tosyl azide gave 4'-chloro-2-azidobiphenyl in 60% yield (Figure 5). Reduction with $NaBH_4$ followed by the reaction with 2-chloronicotinoyl chloride gave boscalid in 88% yield (53% overall yield from 1-bromo-2-iodobenzene).

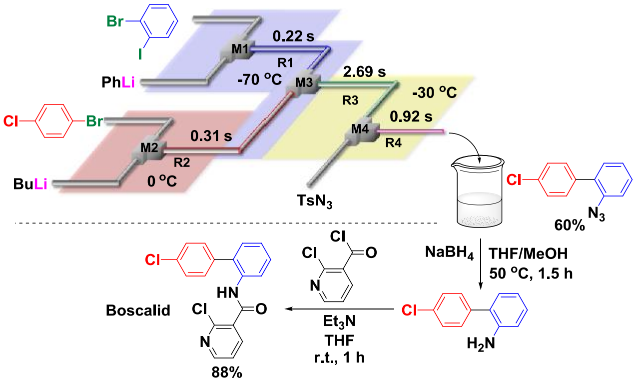


Figure 5. Synthesis of boscalid.

In conclusion, flash chemistry using integrated flow microreactor systems enabled three-component coupling of benzyne generated from *o*-bromophenyllithium, functionalized aryllithiums, and electrophiles. The precise control of the reaction conditions based on the relative stability of the organolithium species that are involved in the benzyne formation and the carbolithiation is responsible for the success of the transformation. Further work is in progress to explore the full scope of this useful three-component coupling and its applications in organic synthesis.

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Supporting Information Available: Experimental procedures, spectroscopic data of compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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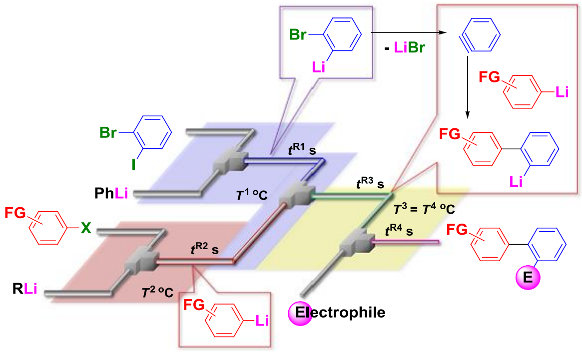

Precise control of the temperatures and the residence times