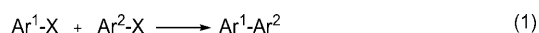


Cross-Coupling in a Flow Microreactor: Space Integration of Lithiation and Murahashi Coupling**

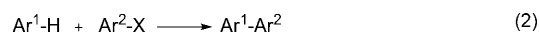
Aiichiro Nagaki, Akira Kenmoku, Yuya Moriwaki, Atsushi Hayashi, and Jun-ichi Yoshida*

Cross-coupling reactions of aryl metals with organic halides serve as a powerful method for carbon–carbon bond formation in the synthesis of a variety of functional materials and biologically active compounds.^[1] Aryl–boron, aryl–silane, aryl–tin, aryl–zinc, and aryl–magnesium compounds are often used for these cross-coupling reactions because these organometallic compounds are relatively stable. In contrast, the use of less stable but more reactive aryllithium compounds in cross-coupling has been rather limited,^[2,3] although many aryl metals including arylboron compounds are often prepared from aryllithium compounds. In 1979 Murahashi et al. reported pioneering work on the palladium-catalyzed cross-coupling of organolithium compounds with organic halides.^[4] Since then, to the best of our knowledge, additional studies have not been reported, one of the major reasons being that X–Li exchange of ArX with BuLi, which is one of the most powerful methods for generating ArLi, leads to the formation of BuX. However, ArLi reacts with BuX if the subsequent coupling is slow. This is indeed the case. Usually, cross-coupling reactions take hours to reach completion at room temperature or higher temperatures, whereas reactions of ArLi with alkyl halides such as BuX are complete within minutes at 0°C. If this problem is solved, the combination of X–Li exchange and Murahashi coupling will then enable the cross-coupling of two aryl halides, hence providing a powerful method in organic synthesis [Eq. (1)].^[5,6] Though *t*BuLi does not suffer from this problem, the use of two equivalents of highly reactive *t*BuLi is not suitable for large-scale laboratory synthesis and industrial production.

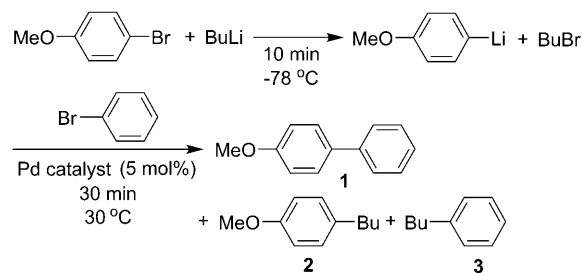


Recently we reported that Br–Li exchange reactions of ArBr and the subsequent reactions with electrophiles could be conducted in flow microreactor systems.^[7–10] This finding

prompted us to then study the integration^[11] of the Br–Li exchange and Murahashi coupling in a flow microreactor system.^[12] Herein we report that the Murahashi coupling can be much faster than the competing reaction with alkyl halides if an appropriate catalyst is used, and that the space integration^[13] of Br–Li exchange and Murahashi coupling using an integrated flow microreactor system enables the cross-coupling of two different aryl bromides (Ar¹Br and Ar²Br). In addition, H–Li exchange is also effective for the generation of ArLi in some cases, especially for heteroaryl substrates, and therefore, we also report that the space integration of H–Li exchange with Murahashi coupling enables the cross-coupling of Ar¹H and Ar²Br [Eq. (2)].



First, we focused on the coupling of *p*-methoxyphenyllithium, which was generated by the Br–Li exchange reaction of *p*-bromoanisole, in a macrobatch system. *p*-Methoxyphenyllithium reacted with BuBr, which was inevitably generated in the Br–Li exchange of Ar¹Br with BuLi, within 30 minutes at 30°C to give *p*-butylmethoxybenzene (**2**, 86% yield). Having this information in hand, we examined the reaction with bromobenzene as a coupling partner to give *p*-methoxybiphenyl (**1**; Scheme 1). The use of [Pd(PPh₃)₄] as a catalyst resulted in the formation of the coupling product **1** in very low yield (Table 1, entry 1), and a significant amount of **2** was produced as a by-product. Butylbenzene (**3**) was also produced, presumably from Br–Li exchange between *p*-methoxyphenyllithium and bromobenzene^[14] followed by the reaction of the resulting phenyllithium with BuBr to give **3**. For this process to work we had to improve the rate of the palladium-catalyzed cross-coupling to minimize this side reaction. Thus, we searched for a catalyst that makes the coupling reaction of Ar¹Li and Ar²Br much faster. The use of [Pd(P^{*t*}Bu)₃]₂, [Pd₂(dba)₃] and **L1**, [Pd₂(dba)₃] and **L2**, [Pd₂(dba)₃] and **L3**, [Pd₂(dba)₃] and **L4**, [Pd(acac)₂], Pd(OAc)₂,



Scheme 1. Integration of Br–Li exchange and Murahashi coupling in a conventional macrobatch reactor.

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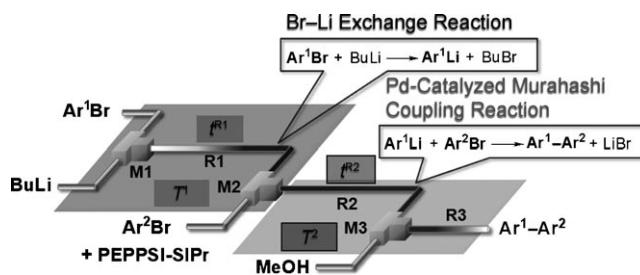
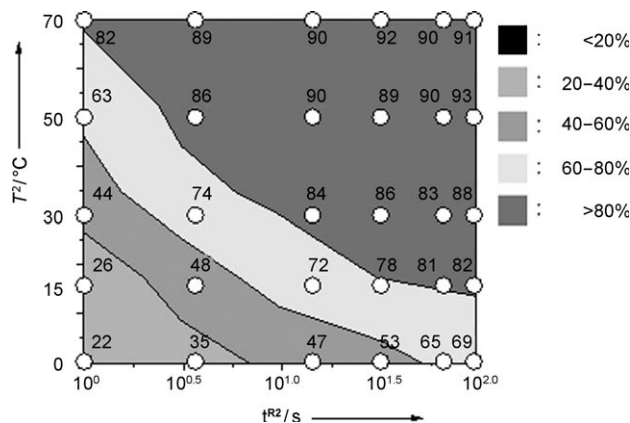
Table 1: Cross-coupling of *p*-methoxyphenyllithium with bromobenzene in a conventional macrobatch reactor.^[a]

Entry	Pd catalyst	Yield [%] ^[b]		
		1	2	3
1	[Pd(PPh ₃) ₄]	4	38	37
2	[Pd(PtBu ₃) ₂]	2	44	45
3	[Pd ₂ (dba) ₃] and L1	3	38	39
4	[Pd ₂ (dba) ₃] and L2	14	34	34
5	[Pd ₂ (dba) ₃] and L3	8	34	35
6	[Pd ₂ (dba) ₃] and L4	18	31	30
7	[Pd(acac) ₂]	4	28	40
8	Pd(OAc) ₂	18	20	22
9	PdCl ₂ /PPh ₃ /CH ₃ Li	5	35	33
10	PdCl ₂ (CH ₃ CN) ₂	2	30	35
11	PEPPSI-IPr	53	11	3
12	PEPPSI-SIPr	73	10	1

[a] A solution of BuLi (2.36 mmol) in *n*-hexane was added dropwise (1 min) to a solution of *p*-bromoanisole (2.20 mmol) in THF contained in a 25 mL round-bottomed flask at -78°C . After the mixture had been stirred for 10 min, a solution of the Pd catalyst (0.0760 mmol) and bromobenzene (1.52 mmol) in THF was added. The mixture was stirred for 30 min at 30°C . [b] Reported yields, based on bromobenzene, were determined by GC analysis using an internal standard (pentadecane). The yield of **2** was based on *p*-bromoanisole. **L1**: 2-(dicyclohexylphosphino)biphenyl. **L2**: 2-(di-*tert*-butylphosphino)biphenyl (JohnPhos). **L3**: 2,6-(dimethoxy)-2'-dicyclohexylphosphinobiphenyl (SPhos). **L4**: 2-(dimethylamino)-2'-dicyclohexylphosphinobiphenyl (DavePhos). acac = acetylacetonate, dba = dibenzylideneacetone, PEPPSI-IPr = [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride, PEPPSI-SIPr = [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride.

PdCl₂/PPh₃/CH₃Li, and [PdCl₂(CH₃CN)₂] did not improve the yield of the coupling product **1** (Table 1, entries 2–10).^[15] However, we found that the use of a palladium catalyst bearing a carbene ligand developed by Organ and co-workers^[16] led to a faster cross-coupling relative to the occurrence of the side reactions, and the yield of **1** increased significantly at the expense of the undesired by-products **2** and **3**. Because PEPPSI-SIPr was superior to PEPPSI-IPr, hereafter we used PEPPSI-SIPr as the catalyst (Table 1, entries 11 and 12).

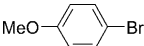
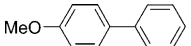
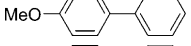
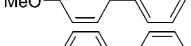
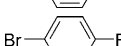
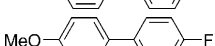
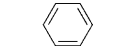
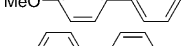
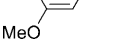
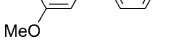
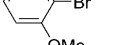
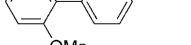
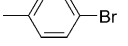
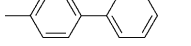
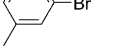
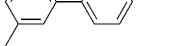
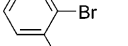
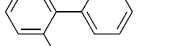
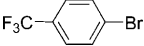
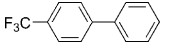
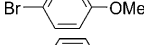
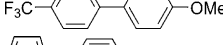
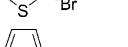
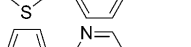
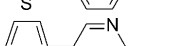
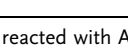
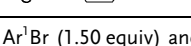
Next, we examined the reaction using a flow microreactor system comprising three micromixers (M1, M2, and M3) and three microtube reactors (R1, R2, and R3; Figure 1). We have already reported that ArLi can be generated by Br–Li exchange of ArBr at 0°C and 20°C in a flow microreactor system,^[10] though much lower temperatures (for example -78°C) are required for a conventional macrobatch reaction. Therefore, *p*-methoxyphenyllithium was generated using M1 ($\phi = 500\ \mu\text{m}$)^[17] and R1 ($T^1 = 0^{\circ}\text{C}$, $t^{R1} = 2.6\ \text{s}$), and was allowed to react with bromobenzene in the presence of PEPPSI-SIPr using M2 ($\phi = 250\ \mu\text{m}$)^[17] and R2. The reaction was quenched by adding methanol, which protonated the unchanged *p*-methoxyphenyllithium very quickly (M3 and R3). As profiled in Figure 2,^[18] the yield significantly depends upon both the temperature (T^2) and the residence time (t^{R2}) in R2 (see the Supporting Information for details). At 30°C , the yield of **1** increased with t^{R2} because of the progress of the cross-coupling reaction. The coupling product **1** was obtained in good yield ($t^{R2} > 16\ \text{s}$, $> 80\%$), and the amounts of the undesired by-products were very small (**2**: 7%, **3**: 2%). The

**Figure 1.** Integrated flow microreactor system for the cross-coupling (micromixers: M1, M2, and M3, microtube reactors: R1, R2, and R3).**Figure 2.** Effects of the temperature (T^2) and the residence time (t^{R2}) in R2 upon the yield of **1** in the PEPPSI-SIPr-catalyzed cross-coupling of *p*-bromoanisole with bromobenzene using the integrated flow microreactor system. Counter plot with scatter overlay of the yields of **1** (%), which are indicated by small circles.

reaction at 50°C gave a slightly better yield of **1** ($t^{R2} > 16\ \text{s}$, ca. 90 %),^[19] and hereafter we carried out the coupling reactions at 50°C . Notably, the cross-coupling reactions were complete within the overall residence time of one minute, and the productivity of the present system is reasonable for laboratory scale synthesis ($15.6\ \text{g h}^{-1}$ of **1**).

The present flow microreactor method could be applied to the cross-coupling of various aryl bromides (Table 2). In the first step, Ar¹Br was reacted with BuLi at 0°C . In the second step, the resulting Ar¹Li was reacted with Ar²Br in the presence of PEPPSI-SIPr to give the cross-coupling product Ar¹–Ar². The overall transformation was complete within a minute or so. The reactions could be successfully carried out with *para*-, *meta*-, and *ortho*-bromoanisoles, and *para*-, *meta*-, and *ortho*-bromotoluenes (Ar¹Br; Table 2, entries 1–11). Though the reaction with aryl bromides (Ar²Br) as coupling partners gave the products in good yields, the use of aryl chloride resulted in much lower yields (Table 2, entry 2), because the coupling reaction was much slower. The use of aryl iodide also gave rise to lower yields (Table 2, entry 3), because an I–Li exchange reaction between Ar¹Li and Ar¹I took place. The introduction of a methyl group and a fluorine atom in Ar² did not affect the reaction, although the yields were somewhat lower (Table 2, entries 4 and 5). The reaction of Ar¹Br having an electron-withdrawing group such as CF₃

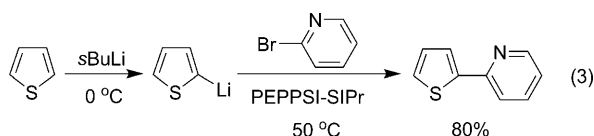
Table 2: Cross-coupling of Ar¹Br and Ar²X using the integrated flow microreactor system.^[a]

Entry	Ar ¹ Br	Ar ² X	Ar ¹ -Ar ²	Yield [%] ^[b]
1				93 (90) ^[c]
2				20 ^[d]
3				32 ^[e]
4				71
5				54
6				76 ^[c,f]
7				71
8				82
9				75
10				71
11				59
12				64 ^[c,f]
13				58 ^[c,f]
14				78 ^[g]
15				87 ^[g]
16				80 ^[f,g]

[a] Ar²X was reacted with Ar¹Li, which was generated from Ar¹Br (1.50 equiv) and BuLi (1.50 equiv) at 0 °C ($t^{\text{R1}} = 2.6$ s), in the presence of PEPPSI-SIPr (0.05 equiv) in THF at 50 °C ($t^{\text{R2}} = 94$ s) using the flow microreactor system. [b] Determined by GC analysis using an internal standard (pentadecane). [c] Yield of the isolated product. [d] Chlorobenzene was recovered in 60% yield [e] Significant amounts of by-product such as **2** and **3** (**2**: 57%, **3**: 23%) were produced. [f] Ar¹Br (1.80 equiv) and BuLi (1.80 equiv) were used. [g] CPME was used as solvent in the presence of TMEDA (3.00 equiv) for the coupling. CPME = cyclopentyl methyl ether, TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

also took place to give the coupling products in good yields (Table 2, entries 12 and 13). The method could also be applied to heteroaryl bromides (Table 2, entries 14–16). For example, the coupling of 2-bromothiophene with 2- and 3-bromopyridines gave the coupling products in good yields.

Notably, the H–Li exchange could be used to generate Ar¹Li in the case of heteroaromatic compounds such as thiophene. Reaction with Ar²Br led to the cross-coupling of Ar¹H and Ar²Br. Thus, thiophene was deprotonated with *s*BuLi at 0 °C using a flow microreactor ($t^{\text{R1}} = 11$ s) [Eq. (3)].



solution of aryl bromide (Ar¹Br; 0.314 M in THF; flow rate: 7.5 mL min^{−1}) and a solution of *n*-butyllithium (1.57 M in *n*-hexane; flow rate: 1.5 mL min^{−1}) were introduced to M1 ($\phi = 500$ μ m) by plunger pumps. The resulting solution was passed through R1 ($\phi = 500$ μ m, $L = 200$ cm) and was mixed with a solution of aryl bromide (Ar²Br; 0.523 M in THF) and PEPPSI-SIPr (26.2 mM in THF; flow rate: 3.0 mL min^{−1}) in M2 ($\phi = 250$ μ m). The resulting solution was passed through R2 was mixed with methanol (flow rate: 5.0 mL min^{−1}) in M3 ($\phi = 500$ μ m). The resulting solution was passed through R3 ($\phi = 1000$ μ m, $L = 100$ cm). The inner pressure of the system was adjusted to give a continuous steady flow using a back pressure regulator, which was located at the outlet of the system. After a steady state was reached, the product solution was collected for 1.0 min. Then, the reaction mixture was poured into water. The organic phase was separated and the aqueous phase was extracted with diethyl ether. The combined organic phase was concentrated, and the resulting crude product was purified by flash chromatography

Experimental Section

General procedure: A flow microreactor consisting of three T-shaped micro-mixers (M1, M2, and M3), three micro-tube reactors (R1, R2, and R3) and four tube precooling units [P1 (inner diameter $\phi = 1000$ μ m, length $L = 100$ cm), P2 ($\phi = 1000$ μ m, $L = 100$ cm), P3 ($\phi = 1000$ μ m, $L = 100$ cm), and P4 ($\phi = 1000$ μ m, $L = 100$ cm)] was used. A

on silica gel with subsequent preparative gel permeation chromatography on. GC yields were obtained by analyzing the combined organic phases using an internal standard.

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