

**Integration of Borylation of Aryllithiums and Suzuki–Miyaura Coupling Using Monolithic Pd Catalyst**

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## Catalysis, Science and Technology

## COMMUNICATION

## Integration of Borylation of Aryllithiums and Suzuki–Miyaura Coupling Using Monolithic Pd Catalyst

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**Integration of the preparation of arylboronic esters via aryllithiums and Suzuki–Miyaura coupling using monolithic Pd catalyst without intentionally added base was achieved. Continuous operation has been done successfully for over 21 hours.**

Chemical synthesis in flow microreactor systems<sup>1,2,3</sup> has received significant research interests from both academia and industry. Recent investigations revealed significant features of flow microreactor systems involving fast mixing stemming from short diffusion path and fast heat transfer by virtue of high surface-to volume ratio, which are advantageous to increase the selectivity of chemical reactions. Short residence time in a microchannel is beneficial for controlling highly reactive intermediates. By taking advantages of such features of flow microreactor systems, various chemical reactions for organic synthesis have been developed so far.<sup>4</sup> Crosscoupling reactions<sup>5</sup> that serve as a powerful method for carbon–carbon bond formation are also a fascinating field in the applications of flow microreactor systems. Especially, flow reaction with the use of recyclable catalytic materials becomes an innovative synthetic methodology that perfectly fits the current need for more environmentally friendly procedures. In fact, recently successful examples using heterogeneous palladium catalyst have been reported and they serve as useful and practical procedures for the recovery and reuse of the catalysts while obtaining the desired product with minimal cost in terms of time and waste.<sup>6</sup>

Several examples of supported palladium catalysts have been reported for use in flow microreactors, using monoliths,<sup>7</sup>

polyurea-encapsulated Pd(OAc)<sub>2</sub> (PdEnCat),<sup>8</sup> silica<sup>9</sup> and magnetic nanoparticle supports.<sup>10</sup> Among them, monolith based devices have good flow characteristics when coupled with the highly controlled surface properties associated with the formation of nano-, micro- and mesoporous structures, and they therefore represent ideal supports for reagents and catalysts where contact time and temperature can be spatially and temporally mediated.<sup>11</sup>

Suzuki–Miyaura coupling<sup>12</sup> of arylboronic acids and their derivatives have been extensively used because of their air and moisture stability. Although some arylboronic acids are commercially available, it is often necessary to prepare appropriate arylboronic acids for desired transformation,<sup>13</sup> and their purification often causes great difficulties. Therefore, integration of borylation and Suzuki–Miyaura coupling is strongly needed to improve the efficiency of overall transformation.<sup>14</sup> Recently, Buchwald *et al.* reported boronic esters were synthesized via lithiation in flow and they are subsequently used for Suzuki–Miyaura coupling.<sup>15</sup> We have also reported<sup>16</sup> that a wide range of arylboronic esters bearing electrophilic functional groups can be synthesized based on flash chemistry<sup>17</sup> using flow microreactor and that the reaction can be integrated with Suzuki–Miyaura coupling of aryl halides having electrophilic functional groups leading to the crosscoupling of two aryl halides bearing electrophilic functional groups. However, these flow methods are based on homogeneous Pd catalysts. Use of heterogeneous Pd catalysts should serve as more environmentally benign processes because of no need for easy separation and reuse of catalysts. Herein, we report space integration<sup>18</sup> of the preparation of arylboronic esters via aryllithiums and Suzuki–Miyaura coupling using a flow reactor packed with a polymer monolith containing an immobilized Pd catalyst.

First, the solubility of lithium arylborates was tested before integrating borylation of aryl halides (Ar<sup>1</sup>X) and Suzuki–Miyaura coupling of aryl halides (Ar<sup>2</sup>X) using a monolith reactor (Figure 1). Halogen–lithium exchange of bromobenzene (Ar<sup>1</sup>X) in THF with *n*-BuLi in hexane followed by the reaction with B(OMe)<sub>3</sub> in THF was selected as a model

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reaction. After the borylation reactions, the solubility of the resulting arylboronic ester in a coupling solvent was checked. Various solvents including THF, methanol, and ethanol were added, and it turned out that a clear solution was obtained when methanol was added.

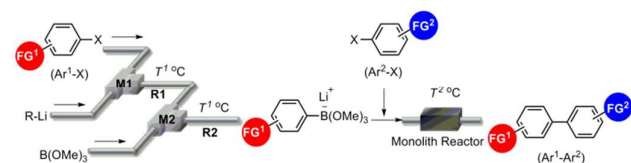


Figure 1. Flow microreactor system for lithiation, borylation, Suzuki–Miyaura coupling (micromixers: **M1** and **M2**, microtube reactors: **R1** and **R2**).

Next, we examined reaction integration of the borylation of aryl halides ( $\text{Ar}^1\text{X}$ ) and Suzuki–Miyaura coupling with aryl halides ( $\text{Ar}^2\text{X}$ ). A flow reactor packed with a polymer monolith containing immobilized Pd was used.

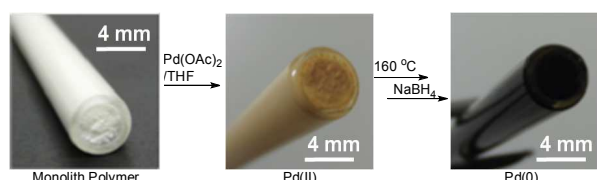


Figure 2. Immobilization of Pd on the polymer monolith in a flow reactor.

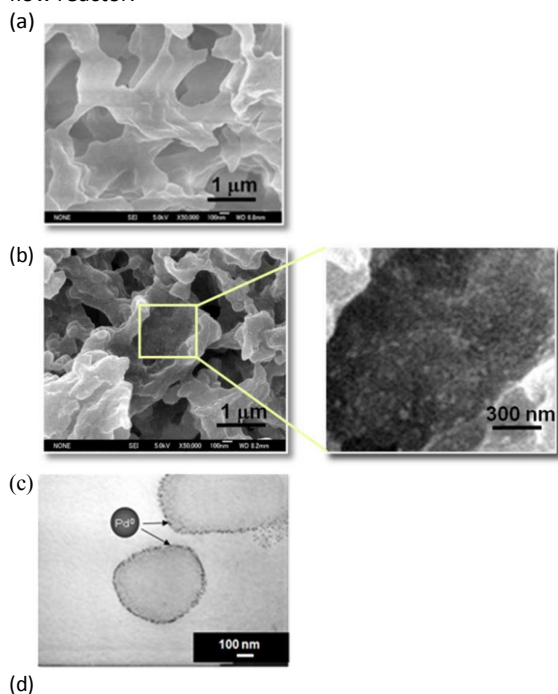


Figure 3. (a) SEM image of polymer monolith before treatment with  $\text{Pd}(\text{OAc})_2$ , (b) SEM image of polymer monolith after treatment with  $\text{Pd}(\text{OAc})_2$  and reduction with  $\text{NaBH}_4$ , (c) TEM image of cross section of skeletons with Pd nano particles in polymer monolith, and (d) a picture of a flow reactor (size: 4.6 mmID x 150 mm length).

The polymer monolith containing an immobilized Pd catalyst was prepared by the following method (Figure 2). 1,3-Bis(*N,N*-diglycidylaminomethyl)cyclohexane was added to a solution of poly(ethylene glycol)(PEG, molecular mass = 200), 4,4'-diaminodicyclohexylmethane, and 6-(phenylamino)-1,3,5-triazine-2,4-dithiol and the mixture was stirred at room temperature for 30 min. The resultant homogeneous solution was poured into a cylindrical stainless steel column (an empty HPLC column, 4.6 mmID x 150 mm length) and the column was annealed at 100 °C. A THF solution containing palladium acetate (0.5 wt%) was injected into the column at 0.05 ml/min. The column adsorbed with palladium acetate was annealed in PEG (molecular mass = 300). Then, aqueous solution of sodium borohydride (0.5 wt%) was injected into the column at 0.05 ml/min to reduce Pd(II) adsorbed on the surface of the monoliths. SEM images of the monolith before and after Pd-immobilization are shown in Figures 3a and 3b, respectively. As shown in Figure 3c, Pd nano particles are immobilized on the surface of the polymer.

A typical for integration of lithiation, borylation, and Suzuki–Miyaura coupling is as follows: Bromobenzene (0.10 M in THF) (flow rate: 6.0 mL/min) and a solution of *n*-BuLi (0.60 M in hexane) (flow rate: 1.0 mL/min) were introduced to **M1** ( $\phi = 500 \mu\text{m}$ ) and **R1** ( $\phi = 1000 \mu\text{m}$ ,  $L = 25 \text{ cm}$  ( $t^{R1} = 1.7 \text{ s}$ )) at  $T^1 = 0 \text{ }^\circ\text{C}$  by using syringe pumps to give phenyllithium. The reaction with trimethoxyborane (0.12 M in THF) (flow rate: 5.0 mL/min) was carried out in **M2** ( $\phi = 500 \mu\text{m}$ ) and **R2** ( $\phi = 1000 \mu\text{m}$ ,  $L = 50 \text{ cm}$  ( $t^{R2} = 2.0 \text{ s}$ )) at the same temperature ( $T^1 = 0 \text{ }^\circ\text{C}$ ). The resulting solution was collected in a vessel. Then, a solution of *p*-iodobenzonitrile (0.033 M in MeOH) was added and the mixture was passed through the monolith reactor at  $T^2 \text{ }^\circ\text{C}$  using a plunger pump. The reaction was carried out with various residence times ( $t^R$ ) in the monolith reactor, and at various temperatures ( $T^2$ ).

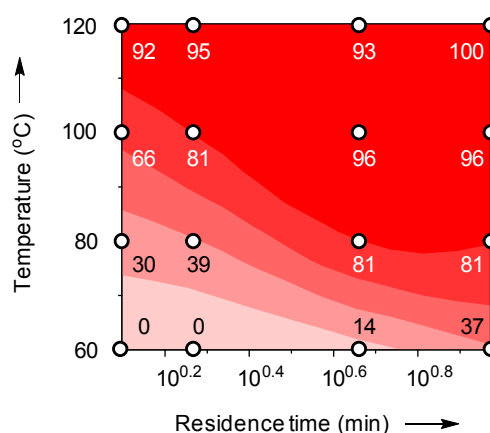


Figure 4. Temperature ( $T^2$ ) - the residence time ( $t^R$ ) map for the crosscoupling of bromobenzene and *p*-bromobenzonitrile using the monolith reactor. Contour plots with scattered overlay of the yields of biphenyl-4-carbonitrile (%), which are indicated by small circles.

As profiled in Figure 4, the yield of biphenyl-4-carbonitrile significantly depends upon both  $T^2$  and  $t^R$ . At 100 °C, the yield increased with an increase in  $t^R$  because of the progress of the crosscoupling reaction. The coupling product was obtained in a good yield (>93%) with  $t^R$  longer than 4.7 min. The reaction at 120 °C resulted in a slightly better yield ( $t^R = 9.4$  min, quantitative yield). Notably, the crosscoupling reactions were complete within a few minutes. It is interesting that Suzuki–Miyaura coupling proceeds without any additional base. Hereafter, we carried out the coupling reactions under condition A (100 °C,  $t^R = 4.7$  min) and condition B (120 °C,  $t^R = 9.4$  min).

Table 1. Crosscoupling of  $Ar^1X$  and  $Ar^2X$  using the flow microreactor

$Ar^1-X$	conditions of lithiation and borylation		$Ar^2-X$	product	yield (%) <sup>a</sup>	
	$t^R$ (s)	$T^1$ (°C)			A	B
	1.7	0			96	100
					0	3
					76	87
					6	41
					1	29
	1.7	0			86	92
					68	91
					17	83
					12	91
	0.059	0			34	84
					63	97
					15	87
					63	98
	0.059	24			2	52
					63	98
	0.059	0			54 <sup>b</sup>	
	1.7	0			83	94
					78	87
					71	86

<sup>a</sup> Determined by GC. <sup>b</sup> Isolated yield.

The present flow microreactor method was successfully applied to the crosscoupling of various functional aryl and heteroaryl iodides as coupling partners. In contrast, the use of aryl bromides resulted in much lower yields, because the coupling reaction was much slower. Notably, a cyano group tolerated the optimized conditions<sup>19</sup>, although such functional

groups easily undergo decomposition in conventional batch reactions. Therefore, biaryls bearing electrophilic functional groups on both aromatic rings were synthesized in flow. Furthermore, a triaryl compound having one bromine atom on one of the aromatic rings was also synthesized via the lithiation of 4,4'-dibromobiphenyl,<sup>20</sup> although such a transformation is very difficult to achieve using conventional batch reactors because of the formation of a significant amount of dilithiated species.

Lastly, we applied the presented method to the synthesis of adapalene<sup>21</sup>, which is used in the treatment of acne, psoriasis, and photoaging. The coupling of lithium [3-(1-adamantyl)-4-methoxyphenyl]trimethoxyborate and methyl 6-iodo-2-naphthoate was carried out in the monolith reactor and the desired product was produced in 86% yield (Figure 5). Scaled-up synthesis was also achieved by simply extending operation time to 21 h. The desired product was obtained in gram scale (1.55 g) without any appreciable decrease in the catalytic activity. Finally, the hydrolysis with NaOH in 1,2-propanediol gave the corresponding adapalene in 89% yield.

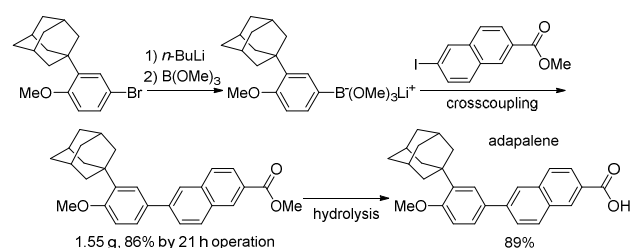


Figure 5. Synthesis of adapalene

## Conclusions

In conclusion, an efficient synthetic method of unsymmetrical biaryls was developed by integrating lithiation, borylation, and Suzuki–Miyaura coupling using a flow reactor packed with a polymer monolith containing an immobilized Pd catalyst. The present method was successfully used for various coupling reactions including the synthesis of adapalene. Further work is in progress to explore the full scope of this useful transformation and its synthetic applications.

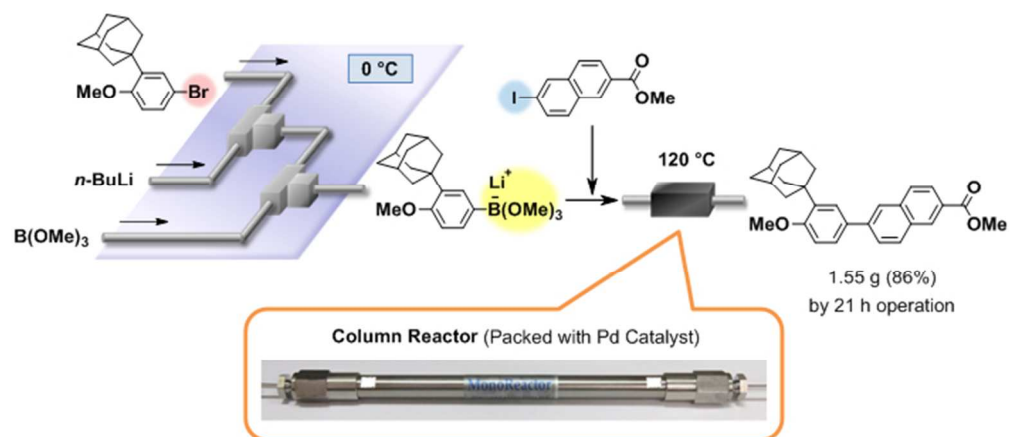
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Integration of the preparation of arylboronic esters and Suzuki–Miyaura coupling using monolithic Pd catalyst was successfully achieved.



186x81mm (96 x 96 DPI)