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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 an intentionally added base was achieved. A continuous operation has been done successfully for over 21 hours.

Chemical synthesis in flow microreactor systems[1–3] has received significant research interest from both academia and industry. Recent investigations revealed significant features of flow microreactor systems involving fast mixing stemming from short diffusion paths and fast heat transfer by virtue of high surface-to-volume ratios, which are advantageous to increase the selectivity of chemical reactions. A short residence time in a microchannel is beneficial for controlling highly reactive intermediates. By taking advantage of such features of flow microreactor systems, various chemical reactions for organic synthesis have been developed so far.[4] Crosscoupling reactions[5] 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 reactions with the use of recyclable catalytic materials became an innovative synthetic methodology that perfectly fits the current need for more environmentally friendly procedures. In fact, recently, successful examples using heterogeneous palladium catalysts 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 costs in terms of time and waste.[6]

Several examples of supported palladium catalysts have been reported for use in flow microreactors, using monoliths,[7] polyurea-encapsulated $Pd(OAc)_2$ (PdEnCat),[8] silica[9] and magnetic nanoparticle supports.[10] 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.[11]

Suzuki–Miyaura coupling[12] of arylboronic acids and their derivatives has 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 a desired transformation,[13] and their purification often causes great difficulties. Therefore, integration of borylation and Suzuki–Miyaura coupling is strongly needed to improve the efficiency of their overall transformation.[14] Recently, Buchwald *et al.* reported boronic esters that were synthesized *via* lithiation in flow, which were subsequently used for Suzuki–Miyaura coupling.[15] We have also reported[16] that a wide range of arylboronic esters bearing electrophilic functional groups can be synthesized based on flash chemistry[17] using a 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. The use of heterogeneous Pd catalysts should serve as a more environmentally benign process because there is no need for easy separation and reuse

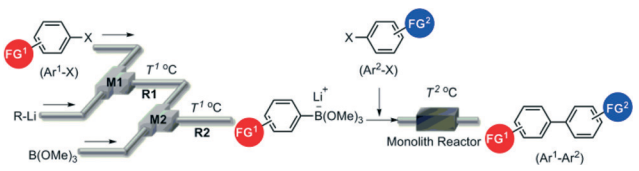

Fig. 1 Flow microreactor system for lithiation, borylation, Suzuki–Miyaura coupling (micromixers: **M1** and **M2**, microtube reactors: **R1** and **R2**).

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of catalysts. Herein, we report the space integration[18] 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 the borylation of aryl halides (Ar^1X) and Suzuki–Miyaura coupling of aryl halides (Ar^2X) using a monolith reactor (Fig. 1). The halogen–lithium exchange of bromobenzene (Ar^1X) in THF with *n*-BuLi in hexane followed by the reaction with $B(OMe)_3$ in THF was selected as a model 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.

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

The polymer monolith containing an immobilized Pd catalyst was prepared by the following method (Fig. 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 × 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^{-1}. 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^{-1} to reduce Pd(II) adsorbed on the surface of the monoliths. SEM images of the monolith before and after Pd-immobilization are shown in Fig. 3a and b, respectively. As shown in Fig. 3c, Pd nanoparticles are immobilized on the surface of the polymer.

A typical procedure for the integration of lithiation, borylation, and Suzuki–Miyaura coupling is as follows: bromobenzene (0.10 M in THF) (flow rate: 6.0 mL min^{-1}) and a solution of *n*-BuLi (0.60 M in hexane) (flow rate: 1.0 mL min^{-1}) were introduced into **M1** (ϕ = 500 μm) and **R1** (ϕ = 1000 μm, L = 25 cm (t^{R1} = 1.7 s)) at T^1 = 0 °C by using syringe pumps to give phenyllithium. The reaction with trimethoxyborane (0.12 M in THF) (flow rate: 5.0 mL min^{-1}) was carried out in **M2** (ϕ = 500 μm) and **R2** (ϕ = 1000 μm, L = 50 cm (t^{R2} = 2.0 s)) at the same temperature (T^1 = 0 °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 (°C)

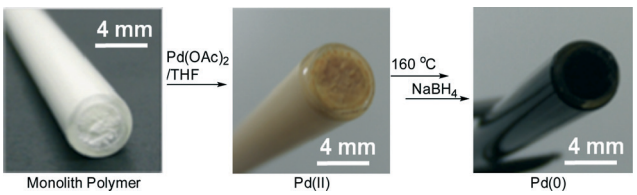


Fig. 2 Immobilization of Pd on the polymer monolith in a flow reactor.

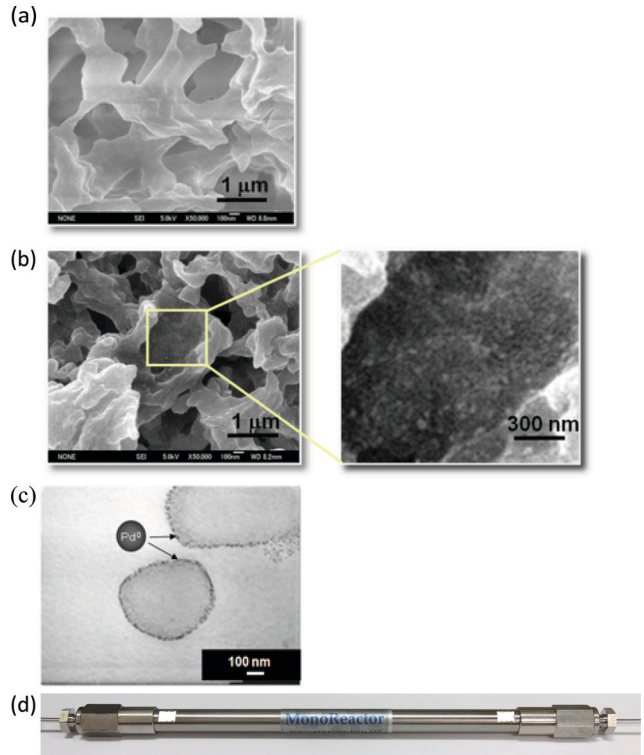


Fig. 3 (a) SEM image of the polymer monolith before treatment with $Pd(OAc)_2$, (b) SEM image of the polymer monolith after treatment with $Pd(OAc)_2$ and reduction with $NaBH_4$, (c) TEM image of the cross section of the skeletons with Pd nanoparticles in the polymer monolith, and (d) a picture of a flow reactor (size: 4.6 mmID × 150 mm length).

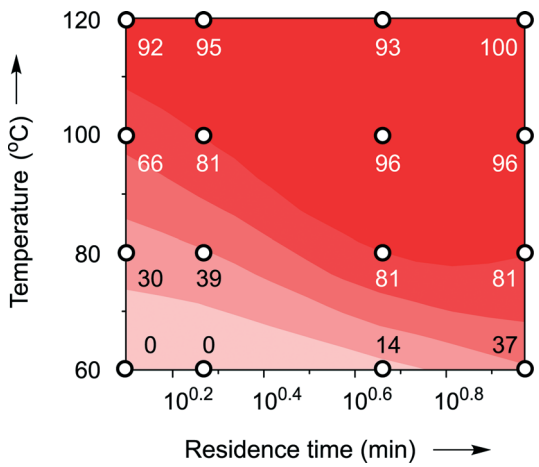
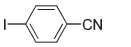
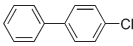
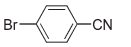
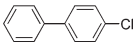
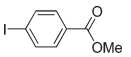
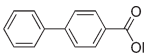
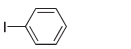
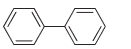
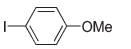
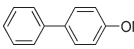
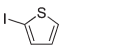
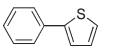
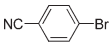
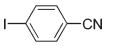
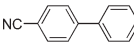
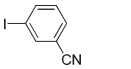
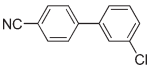
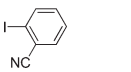
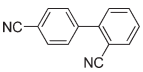
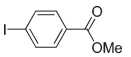
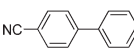
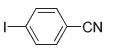
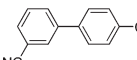
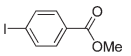
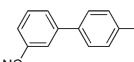
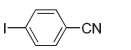
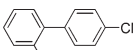
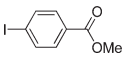
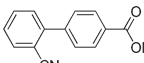
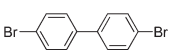
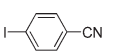
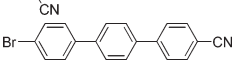
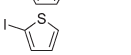
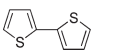
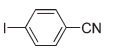
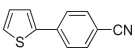


Fig. 4 Temperature (T^2)–the residence time (t^R) map for the crosscoupling of bromobenzene and *p*-bromobenzonitrile using the monolith reactor. Contour plots with scattered overlay of the yields of biphenyl-4-carbonitrile (%), which are indicated by small circles.

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

Ar^1X	Conditions of lithiation and borylation		Ar^2X	Product	Yield[a] (%)	
	t^{R1} (s)	T^1 (°C)			A	B
	1.7	0			96	100
					0	3
					76	87
					6	41
					1	29
					86	92
	0.059	0			68	91
					17	83
					12	91
					34	84
	0.059	0			63	97
					15	87
	0.059	24			63	98
					2	52
	0.059	0			—	54[b]
	1.7	0			83	94
					78	87
					71	86

[a] Determined by GC. [b] Isolated yield.

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).

As profiled in Fig. 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 a 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 completed within a few minutes. It is interesting that the Suzuki–Miyaura coupling proceeds without any additional base. Hereafter, we carried out the coupling reactions under conditions A (100 °C, t^R = 4.7 min) and B (120 °C, t^R = 9.4 min).

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,[19] although such

Fig. 5 Synthesis of adapalene.

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,[20] 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).

Lastly, we applied the presented method to the synthesis of adapalene,[21] 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 (Fig. 5). A scaled-up synthesis was also achieved by simply extending the 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.

Conclusions

In conclusion, an efficient synthesis method of asymmetrical 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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