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Palladium on Carbon-Catalyzed Suzuki-Miyaura Coupling Reaction Using an Efficient and Continuous Flow System

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Abstract: The continuous flow Suzuki-Miyaura reaction between various haloarenes and arylboronic acids was successfully achieved within only *ca*. 20 s during the single-pass through a cartridge filled with palladium on carbon (Pd/C). No palladium leaching was observed in the collected reaction solution by atomic absorption spectrometry (detection limit: 1 ppm).

Keywords: flow reaction; ligand-free; palladium on carbon; single-pass; Suzuki-Miyaura coupling

1. Introduction

The palladium-catalyzed Suzuki-Miyaura coupling reaction between aryl halides and arylboronic acids is one of the most useful methodologies for the construction of a biaryl unit constituting a partial structure of some natural products, pharmaceuticals, and functional polymers, such as organic electroluminescence (EL) materials [1–3]. However, palladium metal as the active catalyst species should be removed from the product as an undesired waste after the reaction when the homogeneous catalyst was used. In addition to the effort and cost for the required removal process of the palladium waste, the unrecoverability of the expensive palladium catalysts is also a drawback. Therefore,

the development of practical protocols for the Suzuki-Miyaura cross-coupling reaction is demanded from the perspective of green chemistry.

In the past few years, the use of heterogeneous flow systems in synthetic organic chemistry has become increasingly popular [4–7]. The systems use an apparatus for delivering a substrate solution into a cartridge filled with a heterogeneous catalyst. Since the flow channel in the catalyst cartridge passing the substrate solution is sufficiently narrow, the reaction efficiency should be enhanced due to the intimate contact of the catalyst with the substrate and reagents in comparison to a batch-type reaction using flasks or reaction vessels. The immobilized transition-metal catalyst, which often indicates a risk of ignition under atmospheric conditions, is enclosed in a completely-sealed cartridge during the flow-type reaction; hence, the reactions could be carried out in a safe manner. Furthermore, the removal of the metal residue from each reaction solution should not be necessary, and the catalyst can be reused unless metal leaching is observed. Taking great advantage of these features, we recently developed effective flow-type hydrogenation methods using several different types of catalysts possessing broad substrate applicabilities [8]. Several flow Suzuki-Miyaura cross-coupling reactions have also been reported using a heterogeneous catalyst [6,9-11] as well as a homogeneous catalyst [6,12-15]. The supports for the heterogeneous palladium catalysts included a polyionic polymer [9], phosphine ligand-functionalized silica [10], activated carbon [11], and alumina [11]. Although the heterogeneous flow Suzuki-Miyaura coupling reactions in these reports efficiently proceeded, there is still room for improvement; thus, the reaction solution was continuously passed through the catalyst cartridge many times in the closed circulation reaction system to complete the reaction in the case of polyionic polymer-supported palladium [9]. The palladium catalyst on phosphine ligand-functionalized silica is commercially available but rather expensive [10]; high temperature (150 °C) and excess amount of base (3 equiv) were applied in the preceding paper by Mateos et al. using readily available 10% Pd/C or 10% Pd/Al₂O₃ as a catalyst [11]. An efficient batch-type ligand-free Suzuki-Miyaura coupling reaction catalyzed by Pd/C at room temperature in aqueous media has been developed in our laboratory [16]. In this paper, we have demonstrated a practical protocol for the ligand-free Pd/C-catalyzed flow Suzuki-Miyaura reaction under mild conditions (25–100 °C), which is completed within only 20 s during the single-pass of the substrate solution through the catalyst cartridge.

2. Results and Discussion

We first investigated the flow rate of the 10% Pd/C-catalyzed Suzuki-Miyaura cross-coupling between 4-iodoacetophenone (1 mmol) and phenylboronic acid (1.1 mmol) in the presence of sodium carbonate (Na₂CO₃, 1.5 mmol) in EtOH/H₂O (10 mL/10 mL) (Table 1). The 4-iodoacetophenone solution in EtOH/Et₂O (v/v = 1:1, 0.05 M) was passed through the catalyst cartridge (*ca.* 0.3 mL inside volume) only once at 1 mL/min, 2 mL/min, or 3 mL/min and 25 °C, and the temperature was increased in incremental steps (50 °C, 75 °C, then 100 °C) when the reaction was incomplete at the lower step. The reaction progress was impeded by the flow rate faster than 1 mL/min (Entries 1 *vs.* 2 and 4), and some of the 4-iodoacetophenone (1) remained unreacted (6%) even at 100 °C in the case of the 3 mL/min flow rate (Entry 5). Furthermore, the amount of Na₂CO₃ could be hardly decreased from 1.5 equiv at room temperature (Entries 1 *vs.* 6 and 7). Since it takes only approximately 20 s for the substrate solution

to move through the catalyst cartridge even at the 1 mL/min flow rate, the following investigations were carried out using 3 equiv of Na₂CO₃ at the 1 mL/min flow rate.

A	IC → 1 + ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓	$B(OH)_{2} \xrightarrow[Flow, EtOH-H_{2}O(1:1)]{10\% Pd/C} Ac \xrightarrow{10\% Pd/C} Ac \xrightarrow{2} 2$		2
Entry	Flow rate (mL/min)	Temperature (°C)	Na ₂ CO ₃ (equiv)	¹ H NMR ratio 1:2
1	1	25	1.5	0:100 (100) ^a
2	2	25	1.5	21:79
3	2	100	1.5	0:100
4	3	25	1.5	32:68
5	3	100	1.5	6:94
6	1	25	1.2	56:44
7	1	25	1.0	100:0
		^a Isolate yield.		

Table 1. Flow rate and base use study.

The general applicability of iodo- and bromobenzenes to the present flow cross-coupling reaction was evaluated (Table 2, Figure S1). Electron-deficient iodobenzenes bearing an acetyl or ethoxycarbonyl group on the benzene nucleus were smoothly cross-coupled with phenylboronic acid at 25 or 75 °C to afford the corresponding biaryls in good yields (Entries 1-3). The phenylation of the electron-sufficient methyl- or methoxy-substituted iodobenzene with phenylboronic acid was completed at 75 °C (Entries 4 and 5). Besides phenylboronic acid, both the 3- and 4-acetylphenylboronic acids could be used for the present cross-coupling with any iodides in nearly quantitative yields (Entries 6-8). Although the reactivity of the 4-methoxyphenylboronic acid was slightly lower compared to an unsubstituted phenylboronic acid and the 3- and 4-acetylphenylboronic acids, the application of heat resulted in completion of the reaction (Entries 1, 2, 4, 6 and 7 vs. 9-11). Iodotoluenes were found to be good substrates regardless of the substitution pattern on the aromatic nucleus (Entries 11-13). The cross-coupling of 2,4-dimethoxyphenylboronic acid with 4-iodoanisole also well proceeded in spite of the bulkiness of a methoxy group on the aromatic ring of phenylboronic acid adjacent to the coupling site and the electron sufficient property (Entry 14). The bromoarenes bearing an electron-withdrawing substituent on the aromatic nucleus could also be applied to the present 10% Pd/C-catalyzed flow Suzuki-Miyaura reaction under the one-pass operating conditions (Entries 15–18).

The Pd leaching from 10% Pd/C into the reaction solution during the present flow cross-coupling reaction between 4-iodoacetophenone (10 mmol) and phenylboronic acid (1.1 equiv) at room temperature was measured by atomic absorption spectrometry (Table 3, Figure S2). No leached palladium species was detected in both the organic and aqueous layers after the phase separation due to the addition of EtOAc and H₂O to the collected reaction solution (<1 ppm detection limit) (Entries 1 and 2) [17]. It would be mechanistically impossible to prevent the leaching of palladium into the collected reaction solution from the immobilized catalysts under the flow cross-coupling reaction conditions, since Pd(II) species, which are generated by the oxidative addition of haloarenes to Pd(0) metals on the support,

should be separated from the support and flown out with solvent, as well-discussed in the reference [17]. In the present case, the reaction was carried out at 25 °C, very slow flow rate of the reaction mixture (1 mL/min), and low substrate concentration (0.05 M). These conditions may be reasons why the palladium leaching was not observed, although a possible low sensitivity for the detection could not be completely excluded.

R1_/=	=\	R ²	10% Pd/ Na ₂ CO ₃	C (1.5 equiv) R ¹ //	$= \sqrt{R^2}$
0.05 M		+ $B(OH)_2$ Flow (1 mL/min) EtOH-H ₂ O (1 : 1) <u>Single-Pass</u>			
Entry	X	R^1	R^2	Temperature (°C)	Yield (%) ^a
1 [9]	Ι	4-Ac	Н	25	100
2 [16]	Ι	4-CO ₂ Et	Н	25	92
3 [18]	Ι	2-CO ₂ Et	Н	75	88
4 [9]	Ι	4-Me	Н	75	91
5 [16]	Ι	4-OMe	Н	75	81
6 [19]	Ι	4-Ac	3-Ac	25	99
7 [18]	Ι	4-CO ₂ Et	4-Ac	25	91
8 [9]	Ι	4-OMe	4-Ac	75	97
9 [9]	Ι	4-Ac	4-OMe	50	89
10 [18]	Ι	4-CO ₂ Et	4-OMe	75	97
11 [20]	Ι	4-Me	4-OMe	75	100
12 [21]	Ι	3-Me	4-OMe	75	98
13 [21]	Ι	2-Me	4-OMe	75	98
14 [22]	Ι	4-OMe	2,4-di-OMe	100	78
15 [9]	Br	4-Ac	Н	50	90
16 [16]	Br	4-CO ₂ Et	Н	100	78
17 [9]	Br	4-Ac	4-OMe	50	97
18 [18]	Br	4-CO ₂ Et	4-OMe	75	100

Table 2. Scope of Substrate.

^a Isolate yield.

Table 3. Leaching test of the Pd.

1 2	1Organic2Aquous0:100		<1 ppm <1 ppm	
Entry	Layer	¹ H NMR ratio 1:2	Pd leaching	
1 0.05 M	B(OH)2	Flow, EtOH-H ₂ O (1 : 1) 25 °C <u>Single-Pass</u>	2	
		10% Pd/C Na ₂ CO ₃		

^a Isolate yield.

3. Experimental Section

3.1. General Procedure

All reagents and solvents were obtained from commercial sources and used without further purification. 10% Pd/C (dry type) was obtained from the N.E. Chemcat Co. (Tokyo, Japan). The ¹H NMR spectra were measured by a JEOL (Tokyo, Japan) JMN AL-400 spectrometer (400 MHz for ¹H NMR and 100 MHz for ¹³C NMR) in CDCl₃ as the solvent. Chemical shifts (δ) were expressed in ppm and internally referenced (0.00 ppm for tetramethylsilane/CDCl₃ for ¹H NMR and 77.0 ppm for CDCl₃ for ¹³C NMR). Mass spectra (EI) were taken by a JEOL (Tokyo, Japan) JMS Q1000GC Mk II Quad GC/MS. All products are known compounds.

3.2. Typical Procedure for the Palladium on Carbon-Catalyzed Cross-Coupling Reaction under Flow Conditions

A solution of Na₂CO₃ (159 mg, 1.50 mmol) in water (10 mL) was mixed with a solution of aryl halide (1.00 mmol) and arylboronic acid (1.10 mmol) in EtOH (10 mL). The resulting solution was passed though the catalyst-packed cartridge (10% Pd/C (99.4 mg); 30 mm long-cartridge, *ca.* 0.3 mL internal volume) once at 1 mL/min at 25, 50, 75, or 100 °C using H-Cube[®] (ThalesNano Nanotechnology, Inc., Budapest, Hungary) as the flow reactor. The collected reaction solution was diluted with H₂O (10 mL) and EtOAc (10 mL), and separated into two layers. The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (Hexane/EtOAc, 10:1) to give the analytically-pure coupling product. The ¹H NMR spectra of the products were identical to those in the literature; see supplementary information.

3.3. Leaching Test of Palladium (Table 3)

A solution of Na₂CO₃ (1.59 g, 15.0 mmol) in water (100 mL) was mixed with a solution of 4'-iodoacetophenone (2.46 g, 10.0 mmol) and phenylboronic acid (1.34 g, 11.0 mmol) in EtOH (100 mL). The resulting solution was passed though the catalyst-packed cartridge (10% Pd/C (99.4 mg); 30 mm long-cartridge, *ca.* 0.3 mL internal volume) once at 1 mL/min at 25 °C using H-Cube[®] (ThalesNano Nanotechnology, Inc., Budapest, Hungary) as a flow reactor. The collected reaction solution was diluted with H₂O (20 mL) and EtOAc (20 mL), and separated into two layers. The aqueous layer was further extracted with EtOAc (2×20 mL), and the combined organic layers were washed with brine (10 mL), and dried over MgSO₄. The resulting dried solution was concentrated *in vacuo* and transferred to a 100-mL volumetric flask. Then, MeOH was added to 100 mL. The aqueous layer was also concentrated and transferred to another 100-mL volumetric flasks were measured using an atomic absorption spectrophotometer (Shimadzu, Kyoto, Japan, AA-7000), and no palladium species were detected. The solution was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 10:1) to give 4-acetyl-1,1'-biphenyl (1.94 g, 9.89 mmol, 99%).

4. Conclusions

We have developed a continuous flow Pd/C-catalyzed Suzuki-Miyaura coupling reaction under mild conditions. Aryl iodides smoothly underwent the coupling with various arylboronic acids. The reaction times required to complete the cross-coupling were only 20 s during the single-pass of the reaction solution through the catalyst cartridge. The present reaction provides a standard reaction conditions for the practical application of the flow Suzuki-Miyaura cross-coupling reaction between various aryl iodides and arylboronic acids.

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Author Contributions

Hironao Sajiki, Yasunari Monguchi, and Tomohiro Hattori contribute to the experimental design. Tomohiro Hattori and Aya Tsubone contribute to all the experimental data collection. Tomohiro Hattori wrote the first draft of the manuscript that was then extensively improved by Yoshinari Sawama, Yasunari Monguchi, and Hironao Sajiki.

Conflicts of Interest

The authors declare no conflict of interest.

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