

## Article

# Development of Facile and Simple Processes for the Heterogeneous Pd-Catalyzed Ligand-Free Continuous-Flow Suzuki–Miyaura Coupling

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**Abstract:** The Suzuki–Miyaura coupling reaction is one of the most widely utilized C–C bond forming methods to create (hetero)biaryl scaffolds. The continuous-flow reaction using heterogeneous catalyst-packed cartridges is a practical and efficient synthetic method to replace batch-type reactions. A continuous-flow ligand-free Suzuki–Miyaura coupling reaction of (hetero)aryl iodides, bromides, and chlorides with (hetero)aryl boronic acids was developed using cartridges packed with spherical resin (tertiary amine-based chelate resin: WA30)-supported palladium catalysts (7% Pd/WA30). The void space in the cartridge caused by the spherical catalyst structures enables the smooth flow of a homogeneously dissolved reaction solution that consists of a mixture of organic and aqueous solvents and is delivered by the use of a single syringe pump. Clogging or serious backpressure was not observed.

**Keywords:** Suzuki–Miyaura coupling; palladium; continuous-flow reaction; ligand-free; chelate resin; aromatic chloride

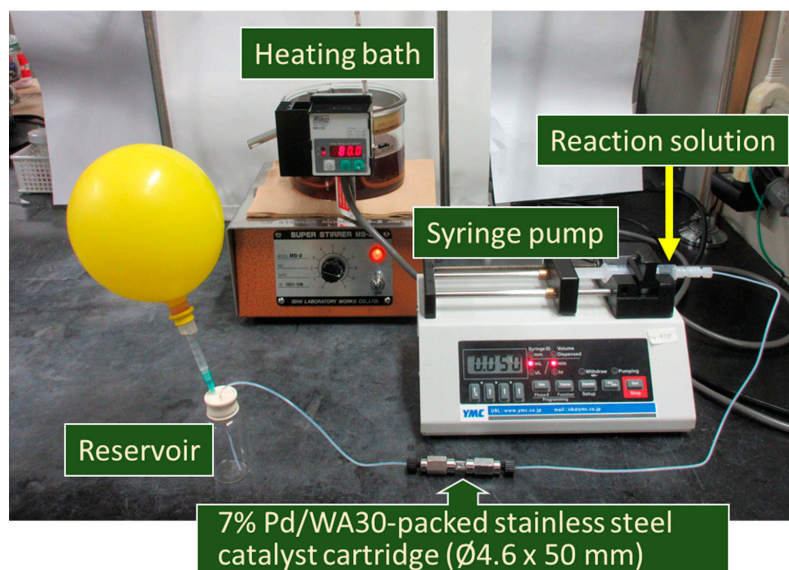
## 1. Introduction

The Suzuki–Miyaura reaction [1–7] is robust and is one of the most reliable C–C bond-forming methods. It is utilized for the production of (hetero)biaryl structures, which are fundamental components of active pharmaceutical ingredients (APIs) [4,8–14], functional materials [15], and natural products [16,17] in a variety of synthetic chemistry fields. The development of a highly active and durable heterogeneous Pd catalyst is important for minimizing toxic metal contamination in the products and reducing environmental pollution caused by metal leaching during the catalytic cycle in transition-metal-catalyzed coupling reactions and treatment after the reactions [18–22].

Continuous-flow reactions using a packed-bed cartridge filled with heterogeneous catalysts attracted considerable research interest as robust and reproducible reaction methods [23–28]. Because small amounts of substrate and reactants in the reaction solution were continuously introduced into the catalyst cartridge via a narrow tube and immediately contacted a large amount of catalyst, a higher reaction efficiency was achieved compared with the corresponding batch reactions using flasks and reaction vessels. Supported Pd catalysts packed in a cartridge can be safely utilized without deactivation or ignition because the catalyst is not exposed to air (especially atmospheric oxygen). Furthermore, the resulting reaction mixture is continuously collected at the outlet of the cartridge without the need of catalyst separation.

The use of commercially abundant and inexpensive aryl boronic acids with inorganic bases is ideal to develop practical Suzuki–Miyaura coupling reactions under both batch and continuous-flow conditions [23–42]. Various heterogeneous Pd-catalyzed continuous-flow Suzuki–Miyaura reactions of aryl halides with aryl boronic acids in the presence of inorganic bases were established [29–42]. The organic and aqueous solvents were mixed in many cases with a pump to dissolve the substrate and reagent without clogging the flow reactors [29–33]. Because a complex optimization process to select reaction conditions such as solvent combination, flow rate, and substrate concentration is required, the use of a single reaction solution in which all reagents are homogeneously dissolved is advantageous. Some research groups developed continuous-flow Suzuki–Miyaura reactions using homogeneously dissolved solvents of H<sub>2</sub>O with highly polar organic solvents, such as alcohols [37,39–41], *N,N*-dimethylformamide (DMF) [34–36], MeCN [38], and tetrahydrofuran (THF) [40], to improve the solubility of aryl halides, aryl boronic acids, and inorganic bases. A continuous-flow ligand-free Suzuki–Miyaura reaction of aryl iodides and bromides with aryl boronic acid in an EtOH/H<sub>2</sub>O mixed single solution using a 10% Pd/C-packed catalyst cartridge was also developed [42]. However, high reaction temperatures and/or backpressures are often achieved using specific and expensive flow devices that are generally difficult to apply scale-up in productive use [34,35,39–42]. There is also a risk of clogging the cartridge and/or outlet of the flow tube by precipitation of reactants and/or products that are generated under harsh reaction conditions [37]. The use of highly dispersed heterogeneous powdered Pd catalysts diluted by silica or celite is an efficient technique to create void spaces and prevent pressure rise and clogging in the catalyst cartridge [29]. Based on these issues, the development of an efficient continuous-flow Suzuki–Miyaura reaction by introducing a homogeneously dissolved reaction solution into a spherical bead-supported Pd catalyst-packed cartridge with an appropriate void space is a suitable methodology to achieve an unrestricted and smooth flow.

Various spherical or monolithic polystyrene/divinylbenzene copolymer-supported (HP20 (Mitsubishi Chemical Corporation) [43], CM (Organo Corporation) [44], and AM (Organo Corporation) [44]) Pd catalysts (Pd/HP20 [20], Pd/CM [21], and Pd/AM [21]) were previously developed and successfully applied to ligand-free Suzuki–Miyaura, Mizoroki–Heck, and Sonogashira-type coupling reactions. Furthermore, a tertiary amine-functionalized polystyrene-divinylbenzene-based basic anion exchange (chelate) resin WA30 (Mitsubishi Chemical Corporation) [45–47]-supported Pd catalyst (7% Pd/WA30) was also developed for the efficient and ligand-free Suzuki–Miyaura reactions of (hetero)aryl iodides, bromides, and chlorides under batch conditions [48,49] and microwave-assisted Mizoroki–Heck reaction under continuous-flow conditions [50]. Herein, new practical, ligand-, and backpressure-free continuous-flow Suzuki–Miyaura reactions of (hetero)aryl iodides, bromides, and chlorides with (hetero)aryl boronic acids using a 7% Pd/WA30-packed catalyst cartridge were established. The spherical structure of 7% Pd/WA30 created an appropriate void space in the cartridge that enabled the smooth flow of the reaction solution. The present continuous-flow Suzuki–Miyaura coupling using 7% Pd/WA30 proceeded efficiently by transferring a solution of aryl halides, aryl boronic acids, and bases by a syringe pump into the catalyst cartridge without any complex reaction system, equipment, and operations (Figure 1).



**Figure 1.** Continuous-flow apparatus for the Suzuki–Miyaura coupling reaction using a 7% Pd/WA30-packed catalyst cartridge.

## 2. Results and Discussions

### 2.1. Continuous-Flow Suzuki–Miyaura Coupling of Aryl Iodides and Bromides with Aryl Boronic Acids

The solubility of a mixture of 4'-iodoacetophenone (**1a**, 0.5 mmol) and phenylboronic acid (**3a**, 1.2 eq., 0.6 mmol) with  $K_3PO_4$ , NaOH, or KOH (2.0 eq., 1.0 mmol) in a mixed solvent of  $H_2O$  and various organic solvents was initially investigated (see Supplementary Materials). As a result, it was observed that the combined use of NaOH or KOH with  $H_2O$  (0.5 mL) and 1,4-dioxane (1.5 mL) formed a homogeneously dissolved solution. In contrast, other combinations of bases with solvents resulted in an inhomogeneous mixture.

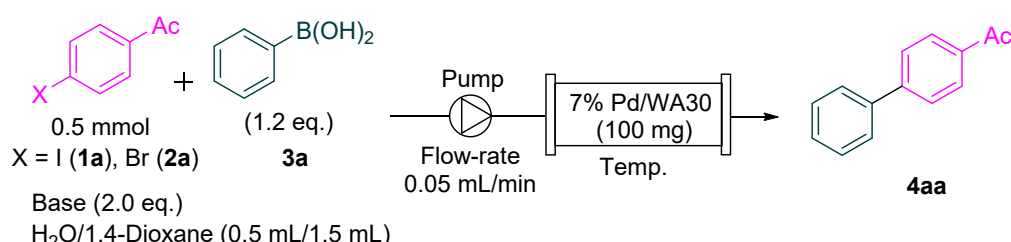
Next, continuous-flow Suzuki–Miyaura reaction efficiencies were investigated by transferring a solution of **1a** (0.5 mmol), **3a** (1.2 eq., 0.6 mmol), and NaOH or KOH (2.0 eq.) in  $H_2O$ /1,4-dioxane (0.5 mL/1.5 mL) into the 7% Pd/WA30 (100 mg)-packed catalyst cartridge using a syringe pump at a flow rate of 0.05 mL/min (Table 1). The coupling reaction proceeded smoothly at 25 °C to obtain the corresponding 4-acetylbiphenyl (**4aa**), and the use of KOH indicated a slightly higher reaction efficiency (95% yield) compared with NaOH (77% yield). However, both reactions were incomplete and a small amount of **1a** (entry 1 vs. 2) remained unchanged. Compound **1a** was completely coupled with **3a** in the presence of KOH and increasing the amount of 7% Pd/WA30 from 100 mg to 200 mg generated **4aa** in quantitative yield, accompanied by turnover number (TON) and turnover frequency (TOF) of 3.8 and  $0.1 \text{ min}^{-1}$ , respectively (entry 3). Furthermore, leached Pd species were never detected in the reaction mixture collected at the outlet of the cartridge using atomic absorption spectrophotometry (AAS, Pd detection limit: 1 ppm, see Supplementary Materials).

Using 4'-bromoacetophenone (**2a**) as a substrate, a higher reaction efficiency was achieved with NaOH compared with KOH to obtain **4aa** in 68% yield (entry 4 vs. 5). The increase in the catalyst cartridge temperature effectively activates the C–Br bond **2a** to produce **4aa** in 74% yield at 60 °C (entry 6). Adding more 7% Pd/WA30 catalyst led to an increase in coupling selectivity and efficiency, resulting in a 95% yield with a TON and TOF of 3.6 and  $0.1 \text{ min}^{-1}$ , respectively (entry 7).

Substrate applicability toward aryl iodides and bromides possessing a variety of functional groups at the 2-, 3-, or 4-positions of the benzene ring with aryl boronic acids was investigated under optimized reaction conditions (aryl iodides for Table 1, entry 3 and bromides for Table 1, entry 7). As the reactivity of 3'-iodoacetophenone (**1b**) and 2'-iodoacetophenone (**1c**) was significantly decreased, probably because of the steric hindrance of the acetyl group, the coupling of 3'-iodo- (**1b**) or 2'-iodoacetophenone (**2b**) with

phenylboronic acid (**3a**) required 1.5 equivalents of **3a** and heating to 80 °C to obtain the corresponding **4aa** in 99% and 83% isolated yield, respectively (Table 2, entries 1 and 3). The detailed reaction optimizations for coupling **1b** and **1c** are shown in the Supplementary Materials. The subsequent Suzuki–Miyaura coupling reactions of iodo- (**1**) and bromoarenes (**2**) and 1.5 equivalents of aryl boronic acids were conducted using a catalyst cartridge packed with 200 mg of 7% Pd/WA30 based on the experimental results provided in the Supplementary Materials. Phenylation of iodoarenes bearing EtO<sub>2</sub>C (**1d**), Me (**1e**), or MeO (**1f**) at the para position of the benzene ring of **3a** smoothly occurred to afford the corresponding biaryls (**4da**, **4ea**, and **4fa**) in high yields (89, 84, and 88%, respectively), regardless of the electronic density of the benzene ring (entries 3–5). Iodobenzene (**1g**) efficiently reacted with 4-MeO- (**3b**) and 4-acetyl-phenylboronic acids (**1f**) to generate the corresponding **4fa** and **4aa** in 72% and 96% yields, respectively (entries 6 and 7). Various bromobenzene derivatives bearing 3-Ac (**2b**), 2-Ac (**2c**), 4-EtO<sub>2</sub>C (**2d**), 4-Me (**2e**), and 4-MeO (**2f**) on the aromatic ring were also coupled with **3a** to produce the desired biaryls (**4ba**, **4ca**, **4da**, **4ea**, and **4fa**) in 43–81% isolated yields (entries 8–12). The arylation of unsubstituted bromobenzene **2g** with **3b**, bearing an electron-donating methoxy group at the para position of the aromatic ring, was smoothly carried out to obtain the corresponding **4fa** in 75% yield (entry 13).

**Table 1.** Optimization of the 7% Pd/WA30-catalyzed continuous-flow Suzuki–Miyaura coupling reaction of 4'-iodo and 4'-bromo acetophenone (**1a** and **2a**) with phenylboronic acid (**3a**).

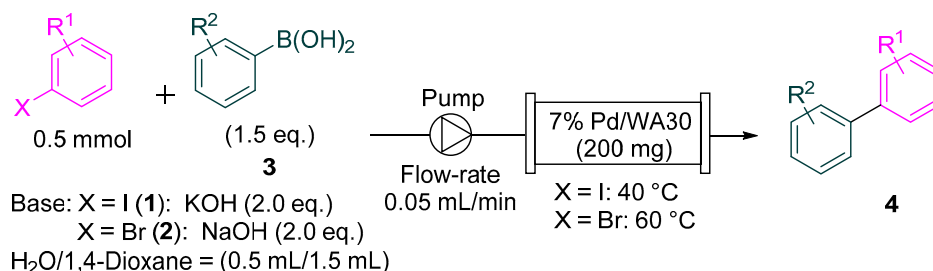


Entry	X	Base	Temp.	<sup>1</sup> H NMR Ratio (1a/2a:4aa)	Yield <sup>1</sup>
1	I	NaOH	25 °C	23:77	77%
2	I	KOH	25 °C	5:95	95%
3 <sup>2</sup>	I	KOH	25 °C	0:100	Quant. <sup>3,4</sup>
4	Br	NaOH	25 °C	35:65	68%
5	Br	KOH	25 °C	57:43	43%
6	Br	NaOH	60 °C	26:76	74%
7 <sup>2</sup>	Br	NaOH	60 °C	0:100	95% <sup>3,5</sup>

<sup>1</sup> Yield was determined by <sup>1</sup>H NMR using 1,1,2,2-tetrachloroethane as an internal standard. <sup>2</sup> An amount of 200 mg 7% Pd/WA30 was used. <sup>3</sup> Isolated yield. <sup>4</sup> turnover number (TON) and turnover frequency (TOF) for the coupling of **1a** with **3a** were 3.8 and 0.1 (min<sup>−1</sup>), respectively. <sup>5</sup> TON and TOF for the coupling of **2a** with **3a** were 3.6 and 0.1 min<sup>−1</sup>, respectively.

Next, the continuous-flow Suzuki–Miyaura reaction using the 7% Pd/WA30-packed catalyst cartridge was applied to heteroaryl iodides and bromides with (hetero)aryl boronic acids (Figure 2). The coupling of 4-iodo pyridine (**1h**) with **3a** efficiently generated the corresponding 4-phenylpyridine (**4ha**) in quantitative yield. However, the coupling of 3- and 2-iodopyridine (**1i** and **1j**) and 4-, 3-, and 2-bromopyridine (**2h**, **2i**, and **2j**) was not successful. Corresponding phenylpyridines (**4ha**, **4ia**, and **4ja**) were obtained in relatively low yields (39%–55%) because of the poorer reactivity, probably based on the electronically biased character of the pyridine nuclei. The use of 2-iodothiophene (**2k**) as substrate led to the corresponding **4ka** in 83% yield. Meanwhile, 5-formyl-2-phenyl-thiophene (**4la**) and 5-formyl-2-phenyl-furan (**4ma**) were obtained from **1l** and **1m**, respectively, under the same flow reaction conditions in moderate yields (both 53%). The heteroaryl–heteroaryl coupling of **1i** with 2-benzofuranboronic acid (**3d**) and 4-dibenzofuranboronic acid (**3e**) effectively provided heterobiaryls (**4id** and **4ie**) in 85% and quantitative yield, respectively.

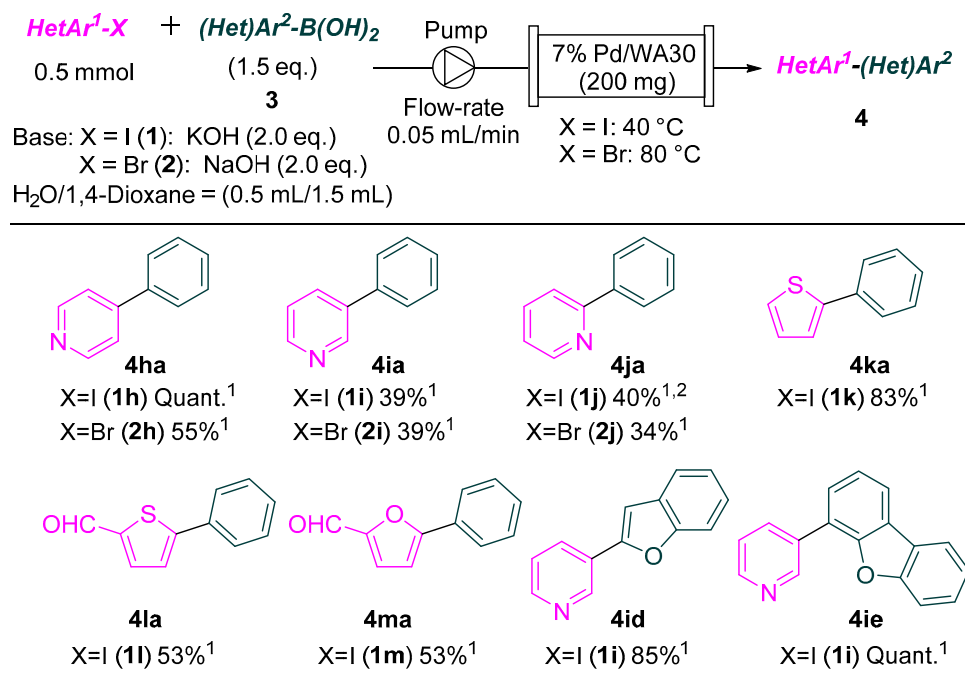
**Table 2.** Scope of substrate for the 7% Pd/WA30-catalyzed continuous-flow Suzuki–Miyaura coupling reaction of 4'-iodo and 4'-bromobenzene derivatives (**1** or **2**) with aryl boronic acid (**3**).<sup>a</sup>



Entry	X	R <sup>1</sup>	R <sup>2</sup>	Product	Yield <sup>1</sup>
1 <sup>2</sup>	I	3-Ac ( <b>1b</b> )	H ( <b>3a</b> )	<b>4ba</b>	Quant. (99)
2 <sup>2</sup>		2-Ac ( <b>1c</b> )	H ( <b>3a</b> )	<b>4ca</b>	83% (83)
3		4-EtO <sub>2</sub> C ( <b>1d</b> )	H ( <b>3a</b> )	<b>4da</b>	89% (89)
4		4-Me ( <b>1e</b> )	H ( <b>3a</b> )	<b>4ea</b>	85% (84)
5		4-MeO ( <b>1f</b> )	H ( <b>3a</b> )	<b>4fa</b>	88% (88)
6		H ( <b>1g</b> )	4-MeO ( <b>3b</b> )	<b>4fa</b>	72% (72)
7 <sup>3</sup>		H ( <b>1g</b> )	4-Ac ( <b>3c</b> )	<b>4aa</b>	Quant. (96)
8	Br	3-Ac ( <b>2b</b> )	H ( <b>3a</b> )	<b>4ba</b>	84% (81)
9		2-Ac ( <b>2c</b> )	H ( <b>3a</b> )	<b>4ca</b>	57% (57)
10		4-EtO <sub>2</sub> C ( <b>2d</b> )	H ( <b>3a</b> )	<b>4da</b>	50% (50)
11		4-Me ( <b>2e</b> )	H ( <b>3a</b> )	<b>4ea</b>	70% (80)
12		4-MeO ( <b>2f</b> )	H ( <b>3a</b> )	<b>4fa</b>	48% (43)
13 <sup>4</sup>		H ( <b>2g</b> )	4-MeO ( <b>3b</b> )	<b>4fa</b>	88% (75)

<sup>1</sup> Yield was determined by <sup>1</sup>H NMR using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yield is shown in parentheses. <sup>2</sup> 1.5 equivalents of **3a** were used at 80 °C. <sup>3</sup> H<sub>2</sub>O/1,4-dioxane (1.0 mL/3.0 mL) was used.

<sup>4</sup> H<sub>2</sub>O/1,4-dioxane (0.8 mL/1.5 mL) was applied.



<sup>1</sup> Isolated yield. <sup>2</sup> 60 °C.

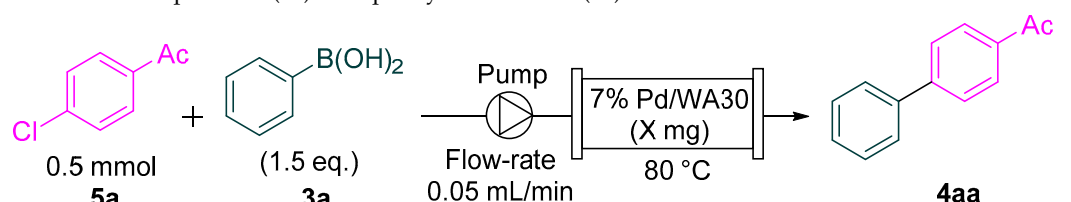
**Figure 2.** Scope of substrates of the 7% Pd/WA30-catalyzed continuous-flow Suzuki–Miyaura coupling reaction of (hetero)aryl iodides and bromides with (hetero)aryl boronic acids.



## 2.2. Continuous-Flow Suzuki–Miyaura Coupling of Aryl Chlorides with Aryl Boronic Acids

Next, the ligand- and backpressure-free continuous-flow Suzuki–Miyaura coupling reaction was conducted to link aryl chlorides with aryl boronic acids. A solution of 4'-chloroacetophenone (**5a**, 0.5 mmol); **3a** (1.5 eq., 0.75 mmol); and NaOH, KOH, or NaOtBu (2.0 eq., 1.0 mmol) in H<sub>2</sub>O/1,4-dioxane (0.5 mL/1.5 mL) was transferred using a syringe pump at 0.05 mL/min flow rate into the 7% Pd/WA30 (100 mg)-packed catalyst cartridge, which was pre-heated at 80 °C in an oil bath (Table 3, entries 1–3). The use of NaOH resulted in a higher yield (23%) of **4aa** compared with that using KOH (19% yield) and NaOtBu (17% yield). An increase of 7% Pd/WA30 from 100 mg to 500 mg increased the conversion of **1a**. However, the yield of the targeted **4aa** was moderate at 45% (entry 4). Furthermore, a decrease in the flow rate from 0.05 mL/min to 0.02 mL/min was ineffective and generated the corresponding **4aa** in 30% yield (entry 5).

**Table 3.** Optimization of 7% Pd/WA30-catalyzed continuous-flow Suzuki–Miyaura coupling reaction of 4'-chloroacetophenone (**5a**) with phenylboronic acid (**2a**).



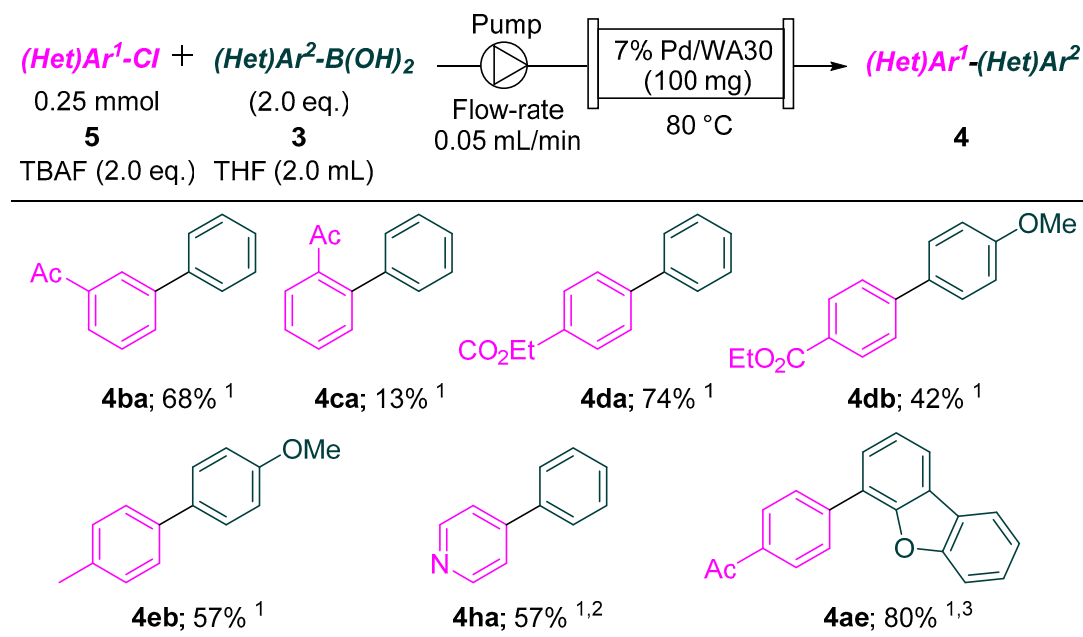
Entry.	Base	Y (mg)	Solvent	<sup>1</sup> H NMR Ratio (5a:4aa)	Yield <sup>1</sup>
1	NaOH	100	H <sub>2</sub> O/1,4-dioxane (0.5/1.5 mL)	74:26	23%
2	KOH	100	H <sub>2</sub> O/1,4-dioxane (0.5/1.5 mL)	81:19	19%
3	NaOtBu	100	H <sub>2</sub> O/1,4-dioxane (0.5/1.5 mL)	82:18	17%
4	NaOH	500	H <sub>2</sub> O/1,4-dioxane (0.5/1.5 mL)	13:87	45%
5 <sup>2</sup>	NaOH	500	H <sub>2</sub> O/1,4-dioxane (0.5/1.5 mL)	57:43	30%
6 <sup>3</sup>	TBAF	100	THF (2.0 mL)	0:100	68%
7 <sup>3</sup>	TBAF	300	THF (2.0 mL)	0:100	68%

<sup>1</sup> Isolated yield. <sup>2</sup> Flow rate of 0.02 mL/min. <sup>3</sup> 0.25 mmol of **5a** and 2.0 equivalents of **2a** were used.

The combination of base and solvent was crucial for developing the continuous-flow Suzuki–Miyaura coupling reaction using 7% Pd/WA30-packed catalyst cartridges, not only to form a homogeneously dissolved reaction solution, but also to achieve a high reaction efficiency. Tetrabutylammonium fluoride (TBAF), which can act as a phase transfer catalyst and/or base, is used for the Pd-catalyzed Suzuki–Miyaura coupling reaction of aryl halides with aryl boronic acids and its esters to activate the Pd catalyst under batch conditions [51–54]. Based on these references, a variety of advantages of TBAF as a base, solubilizing agent, and activator of the 7% Pd/WA30 catalyst were utilized under continuous-flow conditions. After optimizing the reaction solvent (see the Supplementary Materials), it was observed that the addition of 2 equivalents of TBAF efficiently promoted the dissolution of **5a** (0.25 mmol) and **3a** (2.0 eq., 0.50 mmol) in THF (2 mL). Furthermore, the reaction efficiency was considerably increased to achieve a 68% isolated yield by merely transferring a THF solution of **5a**, **3a**, and TBAF over the 7% Pd/WA30 (100 mg)-packed catalyst cartridge (entry 6). Because the increase of 7% Pd/WA30 from 100 mg to 300 mg did not improve the reaction efficiency (entry 6 vs. 7), the combined use of TBAF with THF and 100 mg of 7% Pd/WA30 was adopted as

optimized conditions and used in the substrate applicability study. In the crude mixture of the reaction indicated in entry 6, leached Pd species were never detected with atomic absorption spectrophotometry (AAS, Pd detection limit: 1 ppm, see the Supplementary Materials).

While 3'-chloroacetophenone (**5b**) was coupled with **3a** to obtain **4ba** in 68% yield, the phenylation of 2'-chloroacetophenone (**5c**) with **3a** afforded **4ca** in only 13% yield because of the steric hindrance of the acetyl group (Figure 3). The coupling of ethyl 4-chlorobenzoate (**5d**) with **3a** resulted in a 74% isolated yield of **4da**. Chlorobenzenes bearing 4-EtO<sub>2</sub>C (**5e**) and 4-Me (**5f**) groups reacted with 4-methoxy phenylboronic acid (**3b**), regardless of the electronic properties of the benzene ring, to generate the corresponding biaryls (**4db** and **4eb**) in 42% and 57% yields, respectively. The continuous-flow Suzuki–Miyaura reaction was also applied to the coupling of heteroaryl chlorides. 4-Chloropyridine hydrochloride (**5g**) was phenylated, increasing the amount of TBAF (3.0 eq.) to obtain **4ha** in 57% yield. An isolated yield of 80% of **4ae** was obtained when using a reactive heteroaryl boronic acid (**3e**) as a coupling partner of **5a** with a TON and TOF of 3.0 and 0.8 min<sup>−1</sup>, respectively. Based on these results, the present continuous-flow Suzuki–Miyaura reaction using the 7% Pd/WA30-packed catalyst cartridge was applied to the coupling of various (hetero)aryl chlorides with (hetero)aryl boronic acids in the presence of TBAF instead of NaOH as an additive. However, the reaction efficiency was affected by the electronic properties of the aromatics and the steric hindrance.



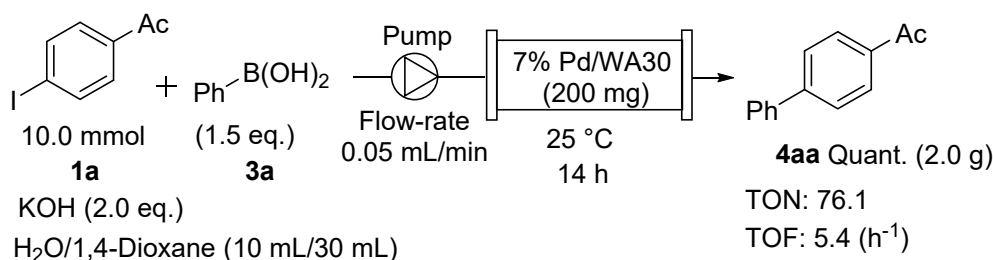
<sup>1</sup> Isolated yield. <sup>2</sup> 3.0 equivalents of tetrabutylammonium fluoride (TBAF) and 1.75 mL of tetrahydrofuran (THF) were used. <sup>3</sup> TON and TOF for the coupling of **5a** with **3e** were 3.0 and 0.8 min<sup>−1</sup>, respectively.

**Figure 3.** Scope of substrates of the 7% Pd/WA30-catalyzed continuous-flow Suzuki–Miyaura coupling reaction of (hetero)aryl chlorides with (hetero)aryl boronic acids.

### 2.3. Application of the Continuous-Flow Suzuki–Miyaura Coupling to Gram-Scale Synthesis

A prolonged backpressure- and ligand-free continuous-flow Suzuki–Miyaura reaction was developed using a 7% Pd/WA30-packed catalyst cartridge. 4'-Iodoacetophenone (**1a**, 10.0 mmol), phenylboronic acid (**2a**, 15.0 mmol), and KOH (20.0 mmol) were dissolved in a mixed solvent of H<sub>2</sub>O (10 mL) and 1,4-dioxane (30 mL). The homogeneously dissolved reaction solution was pumped through the cartridge packed with 200 mg of 7% Pd/WA30 at a flow rate of 0.05 mL/min (Scheme 1). The coupling efficiently and continuously proceeded for 14 h to obtain the corresponding **4aa** in quantitative yield (2.0 g) with a TON and TOF of 76.1 and 5.4 h<sup>−1</sup> and without catalyst deactivation.

during the entire reaction period. Therefore, the continuous-flow Suzuki–Miyaura coupling reaction can be easily applied for prolonged gram-scale biaryl syntheses.



**Scheme 1.** Procedure for the Continuous-Flow Suzuki–Miyaura Coupling Reaction over an Extended Time.

### 3. Materials and Methods

#### 3.1. General Information

All reagents and solvents were obtained from commercial sources (Tokyo Chemical Industry Co., Ltd, Chuo, Tokyo, Japan; FUJIFILM Wako Pure Chemical Industries, Ltd., Osaka, Japan; Sigma-Aldrich Japan Co., Meguro, Tokyo, Japan) and used without further purification. The dimethylamine-immobilized polymer WA30 was obtained from Mitsubishi Chemical Corporation (Chiyoda, Tokyo, Japan). Pd(OAc)<sub>2</sub> was obtained from N.E. Chemcat Corporation (Minato, Tokyo, Japan). Flash column chromatography was performed using Silica Gel 60 N (Kanto Chemical Co. Inc., Chuo, Tokyo, Japan, 63–210 µm spherical, neutral). The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a JEOL ECA-500 (500 MHz for <sup>1</sup>H NMR and 125 MHz for <sup>13</sup>C NMR) and ECZ-400 (400 MHz for <sup>1</sup>H NMR and 100 MHz for <sup>13</sup>C NMR) spectrometers. CDCl<sub>3</sub> was used as solvent for the NMR measurements (LEOL Ltd., Akishima, Tokyo, Japan). The chemical shifts (δ) are expressed in parts per million and internally referenced (0.00 ppm for tetramethylsilane). All <sup>1</sup>H NMR spectra of known products were identical to those reported in the literature.

#### 3.2. Preparation of 7% Pd/WA30

A suspension of dry WA30 (3.00 g, colorless particles) in an ethyl acetate solution (30 mL) of Pd(OAc)<sub>2</sub> (2.12 mmol (226 mg; palladium)) was stirred under argon atmosphere at 25 °C for 4 d. The resulting yellow solid was collected by filtration (1 mm filter paper), washed with H<sub>2</sub>O (10 mL × 3), ethyl acetate (10 mL × 3), and MeOH (10 mL × 3), and dried in vacuo for 24 h. The filtrate was transferred to a 100 mL volumetric flask and diluted to 100 mL with MeOH. Leached Pd species were not detected (detection limit: <1 ppm) in the diluted filtrate using atomic absorption spectrometry (SHIMADZU AA-7000). The collected solid was then stirred with hydrazine monohydrate (NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O) (310.0 µL, 6.37 µmol) in H<sub>2</sub>O (30 mL) for 24 h at 25 °C under argon atmosphere. A pale gray solid was collected by filtration (1 mm filter paper), washed with H<sub>2</sub>O (10 mL × 3) and MeOH (10 mL × 3), and dried in vacuo for 24 h to generate Pd/WA30 (3.23 g). The filtrate was transferred to a 100 mL volumetric flask and diluted to 100 mL with MeOH. Palladium species were not observed in the diluted filtrate (detection limit: <1 ppm). Palladium species absorbed on WA30 were not detected. Thus, the palladium content of Pd/WA30 (ethyl acetate) was estimated to be approximately 7% [(2260)/3230 × 100].

#### 3.3. Experimental Procedures

##### 3.3.1. Procedure for the Continuous-Flow Suzuki–Miyaura Coupling of Aryl Iodides and Bromides with Aryl Boronic Acids

A solution of aryl iodide or bromide (1 or 2, 0.50 mmol), aryl boronic acid (3, 0.75 mmol), and NaOH or KOH (1.0 mmol) in a mixed solvent of H<sub>2</sub>O (0.5 mL) and 1,4-dioxane (1.5 mL) was moved through the 7% Pd/WA30-packed cartridge (Ø 4.6 × 50 mm, SUS-316) by a syringe pump (YMC, YSP-101) at a



flow rate of 0.05 mL/min. After transferring the entire reaction solution, the catalyst cartridge was washed with an additional mixed solvent of H<sub>2</sub>O (5 mL) and 1,4-dioxane (15 mL). The combined reaction mixture and washing solution were extracted with ethyl acetate (40 mL × 2). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to produce the corresponding coupling product **4** (Tables 1 and 2 and Figure 2).

### 3.3.2. Procedure for the Continuous-Flow Suzuki–Miyaura Coupling of Aryl Chlorides with Aryl Boronic Acids

A solution of aryl chloride (**5**, 0.25 mmol), aryl boronic acid (**3**, 0.50 mmol), and tetrabutylammonium fluoride (0.50 mmol; 1 mol/L in THF solution) was moved through the 7% Pd/WA30-packed cartridge (Ø 4.6 × 50 mm, SUS-316) by a syringe pump (YMC, YSP-101) at a flow rate of 0.05 mL/min. After transferring the entire reaction solution, the catalyst cartridge was washed with additional THF (5 mL) and then ethyl acetate (15 mL). The combined reaction mixture and washing solution were concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the corresponding coupling product **4** (Table 3, entry 6 and Figure 3).

### 3.3.3. Procedure for the Continuous-Flow Suzuki–Miyaura Coupling Reaction over an Extended Time

A solution of 4'-iodoacetophenone (**1a**, 2.5 g, 10.0 mmol), phenylboronic acid (**3a**, 1.5 g, 12.0 mmol), and KOH (1.1 g, 20 mmol) in a mixed solvent of H<sub>2</sub>O (10 mL) and 1,4-dioxane (30 mL) was moved through a cartridge packed with 200 mg of 7% Pd/WA30 (Ø 4.6 × 150 mm, SUS-316) by a syringe pump (YMC, YSP-101) at a flow rate of 0.05 mL/min at 25 °C. The reaction solution was collected every 1 h, changing the receiving vessel (1st; 0–1 h, 2nd; 1–2 h, 3rd; 2–3 h, 4th; 3–4 h, 5th; 4–5 h, 6th; 5–6 h, 7th; 6–7 h, 8th; 7–8 h, 9th; 8–9 h, 10th; 9–10 h, 11th; 10–11 h, 12th; 11–12 h, 13th; 12–13 h, 14th; 13–14 h). Each reaction solution was extracted separately with ethyl acetate (10 mL × 2), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. Subsequently, each residue was analyzed by <sup>1</sup>H NMR. The combined residues were purified by silica-gel column chromatography (hexane/ethyl acetate = 15/1) to obtain 4-acethylbiphenyl (**4aa**, 2.0 g, 10 mmol) in quantitative yield (Scheme 1).

## 4. Conclusions

The continuous-flow Suzuki–Miyaura coupling reaction of (hetero)aromatic iodides, bromides, and chlorides with (hetero)aryl boronic acids was developed using 7% Pd/WA30-packed catalyst cartridges, where Pd was immobilized on the spherical chelate resin WA30. The present continuous-flow Suzuki–Miyaura reaction proceeded under ligand- and backpressure-free conditions. Coupling of aromatic iodides and bromides with aryl boronic acids was efficiently conducted by transferring a single reaction solution of aryl halides, aryl boronic acids, and inorganic bases dissolved in H<sub>2</sub>O/1,4-dioxane into a 7% Pd/WA30-packed catalyst cartridge using a syringe pump. Using aryl chlorides as substrates, the addition of TBAF in THF instead of the inorganic base significantly improved the reaction efficiency. The ligand- and backpressure-free continuous-flow Suzuki–Miyaura reaction was also applied to the coupling of heteroaryl halides with heteroaryl boronic acids. The combination of base and solvent is quite crucial for preparing a homogeneously dissolved reaction solution consisting of an aromatic halide, aryl boronic acid, and organic or inorganic base. Furthermore, the provided void space in the cartridge derived from the spherical structures of the 7% Pd/WA30 catalyst enables a smooth flow of the reaction solution using a single syringe pump. Clogging or serious backpressure was not observed. Therefore, the present ligand- and backpressure-free continuous-flow Suzuki–Miyaura coupling reaction is a facile and straightforward continuous-flow method for practical use in a variety of chemistry fields.

**Supplementary Materials:** The following is available online at <http://www.mdpi.com/2073-4344/10/10/1209/s1>, Content 1: General; Content 2: Preparation of 7% Pd/WA30; Content 3: Preparation of catalyst cartridge; Content 4: Experimental procedures; Content 5: Preliminary experiments for the solubility of the reaction solutions; Content 6: Optimization of the continuous-flow Suzuki–Miyaura coupling of 3'-iodoacetophenone and 2'-iodoacetophenone; Content 7: Optimization of a reaction solvent for the continuous-flow Suzuki–Miyaura coupling of 3'-chloroacetophenone under batch conditions; Content 8: Spectroscopic data of products; Content 9: Procedure for the continuous-flow Suzuki–Miyaura coupling reaction over an extended period of time; Content 10: Leaching test for the continuous-flow Suzuki–Miyaura coupling of 4'-iodoacetophenone and 4'-chloroacetophenone; Content 11: References; Content 12:  $^1\text{H}$  and  $^{13}\text{C}$  spectra of products.

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