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resonance as an energy source

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A practical method for heterogeneously-catalyzed Mizoroki–Heck reaction: flow system with adjustment of microwave resonance as an energy source

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ABSTRACT

The microwave-assisted and continuous-flow Mizoroki–Heck reaction using a heterogeneous palladium catalyst supported on the anion-exchange resin DIAION WA30 (7% Pd/WA30) is described. The microwave resonance is finely adjusted to 2.4 GHz according to the electric permittivity of the reaction medium for efficient heating. Organic solvents, such as acetonitrile, *N*,*N*-dimethylacetamide, and toluene, can be sufficiently heated even with a low intensity of microwave irradiation in a 7% Pd/WA30-packed, glass tube-shaped catalyst cartridge, which was designed based on the electric permittivity of the solvents. The catalyst cartridge can be continuously reused at least 5 runs without exchange.

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1. Introduction

The development of heterogeneous Pd catalysts has long been underway in the field of process chemistry because of their recoverability, reusability, and lower metal contaminated property to the product based on their insolubility, which in turn reduce environmental and economic burden. Heterogeneous Pd catalysts have been used for various crosscoupling reactions,¹⁻⁴ including the Pd-catalyzed Mizoroki– Heck reaction between aryl halides and alkenes for the preparation of multi-substituted alkene moieties, which are often contained in key intermediates of organic syntheses.⁵ The practical progress in the heterogeneously catalyzed Mizoroki-Heck reaction in the last decade concerns the use of $\mathrm{flow}^{\mathrm{6-14}}$ and microwave (MW) heating technologies.^{7,8,10,11,14}

The application of heterogeneous Pd catalysts to the flow reaction has several advantages resulting from the narrow and closed reaction path, including sufficient contact between the reagents and catalysts packed in the cartridge and prevention of ignition by the combustible catalyst that is totally sealed from air (oxygen). The reported flow-type Mizoroki–Heck reaction uses Pd(OAc)₂^{8c,10a,12} as a homogeneous system and of Pd/C¹², Pd(0) on an ion-exchange-functionalized monolithic polymer¹³, and poly(vinylpyridine)-doped Pd^{11a} as a heterogeneous system.

Although MW heating has also been attractive because of its specific characteristics, such as direct and rapid heating leading to a short reaction time, increased product yield, and energy and resource savings, MW-assisted syntheses have generally been inappropriate for the scale-up in the batch system because of the limited penetration depth of the MW.^{12,15a} The combination of flow technology with MW heating would be a solution, but only a few examples of the MW-assisted continuous-flow Mizoroki-Heck reaction have been reported to date.^{8a,10,11c,14} In particular, the use of a heterogeneous Pd catalyst for the flow-MW Mizoroki-Heck reaction is limited to Organ's study, where the reaction was carried out using their own equipment with an attached Pd-coated capillary as a flow path, at the flow rate of 0.010 mL min⁻¹ under 2.45 GHz MW irradiation of 0- $300 \text{ W} (\sim 200 \text{ °C})$.^{14c} Although the method could be used for the Mizoroki-Heck reaction of aryl iodides to afford the desired coupling products in moderate to excellent yields, there is room for improvement from the perspective of use of a readily exchangeable catalyst cartridge and reaction conditions, such as the energy efficiency of MW heating, flow rates, and temperature, for the practical utility of the MW-assisted continuous-flow chemistry.

Recently, well-improved stoichiometric methods were developed for the Fischer indole synthesis and Diels-Alder reaction by Akai^{15a} and for the Wolf-Staudinger reaction by Ley^{15b} using a MW-applied continuous-flow reactor prepared by Saida FDS, Inc. This reactor consists of 1) a pumping system together with a backpressure regulator, 2) a single-mode MW generator and resonant cavity, 3) a control device for the MW generation, and 4) a personal computer (PC) to manage the conditions including the MW irradiation (Fig. 1a). A distinctive feature of this instrument is that it can generate a uniform electromagnetic field in the resonant cavity by a solidstate device for telecommunications; the irradiation frequency could be quickly and finely adjusted by the immediate feedback on the reflected power and electric field in the cavity. The best resonance was maintained based on the changes in the electric permittivity of the reaction mixture. We now describe a novel method for the Mizoroki–Heck reaction using the same flow reactor equipped with a MW heating device and a catalyst cartridge (Fig. 1a–c), which is heterogeneously catalyzed by our recently developed *N*,*N*-dimethylamino-functionalized anion-exchange resin-embedded Pd (7% Pd/WA30).^{16–18}



Fig. 1 (a) System for the continuous-flow MW-assisted synthesis: 1) pumping system and backpressure regulator, 2) MW generator and resonant cavity, 3) control devise, and 4) PC. (b) 7% Pd/WA30 (203 mg) packed in a cartridge (cartridge A), which was developed for using MeCN as the solvent and coated by a polytetrafluoroethylene tubular film for safety reasons. (c) 7% Pd/WA30 (~600 mg) packed in a cartridge (cartridge B) which was developed for the use of toluene as the solvent.

2. Results and discussion

2.1. Solvent heating efficiency in the presence of 7% Pd/WA30

A glass coiled tube was used by Akai et al. in the resonant cavity for the reactions to achieve efficient heating based on the long residence time of the reaction mixture in the MW heating space; however, heterogeneous catalysts were extremely difficult to be packed into and removed from the coiled tube. We examined two kinds of straight glass tubes as catalyst cartridges instead of the coiled tube. A straight glass tube (internal diameter, 3 mm; internal volume, approximately 2 mL) with a glass filter to fix the catalyst (cartridge A) was designed for maintaining the resonant frequency at 2.40-2.50 GHz in the absence of the Pd catalyst based on the electric permittivity of acetonitrile (MeCN), which is used as the solvent. Likewise, the other tube (cartridge B) with a partially bugging section (internal diameter, 8 mm) at the center was tuned for toluene (internal volume, 3.6 mL), and the glass filter was placed at the bottom of the bulging part. These catalyst cartridges A and B were selected according to the electric permittivity of reaction solvents.

On the bottom side of cartridge A were placed glass beads (0.991–1.397 mm diameter) and a cotton plug (entrance side) as a platform, so that the Pd catalyst could be located in the middle of the tube. 7% Pd/WA30 was then densely packed over the cotton plug, and then, another cotton plug (exit side) was placed on the catalyst, which would not be moved under the increased pressure by a flow of solvent or reaction mixture. Glass beads were again placed on the second cotton plug to fill the vacant space and stabilize the MW resonance (Fig. 1b). Glass beads and 7% Pd/WA30 were also placed in cartridge B using a procedure similar to that in the case of cartridge A, and 7% Pd/WA30 was located in the bulging part (Fig. 1c).

Table 1 shows the influence of the flow rate and the output power of the MW on the solvent temperature at the exit of the 7% Pd/WA30-packed cartridge using a thermocouple at a backpressure of 1 MPa. When MeCN was allowed to flow through cartridge A at 0.3 mL min⁻¹, the solvent temperature increased to 70 °C under 5 W MW irradiation (Table 1, Entry 1) and 114 °C under 10 W MW irradiation (entry 2). A decrease in the flow rate to 0.15 mL min⁻¹ hardly affected the temperature (entries 1 vs. 3 and 2 vs. 4). A similar heating effect was observed in N,N-dimethylacetamide (DMA); the temperature was increased by the raised MW output power (entries 5 vs. 6 and 7 vs. 8), while the flow rate from 0.15 to 0.3 mL min⁻¹ was not very important for the temperature change (entries 5 vs. 7, and 6 vs. 8). EtOAc, cyclopentyl methyl ether (CPME), and toluene were also effectively heated under 10 W MW irradiation rather than under 5 W MW irradiation (Entries 9 vs. 10, 11 vs. 12, and 13 vs. 14). The Mizoroki-Heck reaction was conducted at the conditionally controlled temperature below 100 °C by taking into account the thermostability of the DIAION WA30 catalyst support (ca. 100 °C).¹⁶

Table 1. Temperature of solvents heated at the exit of the7% Pd/WA30-packed cartridge under the continuous-flowand MW irradiation conditions

Entry	Solvent	Flow rate (mL min ⁻¹)	Microwave (W)	Temperature (°C) ^a
1 ^{b,c}	MeCN	0.3	5	70
2 ^b	MeCN	0.3	10	114
3 ^b	MeCN	0.15	5	70
4 ^b	MeCN	0.15	10	115
5 ^b	DMA	0.3	5	65

6 ^b	DMA	0.3	10	91
7 ^b	DMA	0.15	5	69
8 ^b	DMA	0.15	10	94
9 ^b	EtOAc	0.15	5	79
10 ^b	EtOAc	0.15	10	111
11 ^b	CPME	0.15	5	90
12 ^b	CPME	0.15	10	119
13 ^c	Toluene	0.3	5	95
14 ^c	Toluene	0.3	10	126

^a Solvent temperature at the steady state was directly measured using a thermocouple installed at the exit of the cartridge.

^b Cartridge A developed for MeCN was used.

^c Cartridge B developed for toluene was used.

2.2. 7% Pd/WA30-catalyzed Mizoroki-Heck reaction

When a solution of 4'-iodoacetophenone 1 (0.1 M), *n*-butyl acrylate (1.2 equiv), and tributylamine (Bu₃N, 1.5 equiv) in MeCN was once passed through the 7% Pd/WA30 in cartridge A at the flow rate of 0.3 mL min⁻¹ under MW irradiation (5 W), mixture of the starting material 1, butyl 3-(4а 4,4'-diacetylbiphenyl **3**, acetylphenyl)acrylate 2. and acetophenone 4 was obtained in 46%, 30%, 16%, and 5% yields, respectively (Table 2, Entry 1).¹⁹ A decrease in the flow rate to 0.15 mL min⁻¹ led to a better conversion yield of 2 (53%) by extension of the contact time of the reagents with the catalyst during the MW irradiation (Entry 2). DMA could also be used as a solvent to afford 2 in 59% yield under 10 W MW irradiation without any detection of 4 (Entry 4). However, further decease in the flow rate to 0.05 mL min⁻¹ resulted in the increase of the yields of byproducts 3 and 4. Although 1 was well consumed in toluene, significant amounts of the byproducts 3 and 4 were generated (Entry 6). To minimize the formation of byproducts. DMA was chosen as the appropriate solvent. When the amounts of *n*-butyl acrylate (2 equiv) and Bu₃N (3 equiv) were increased, an excellent conversion yield of 1 (92%) was achieved (Entries 7 and 8). Furthermore, the reaction successfully proceeded even under a higher concentration (0.25 M) leading to a reduction in the amount of solvent and a facile increase in the production scale (Entry 9). However, the yield of 2 decreased at a higher concentration (0.5 M), and serious deiodization of **1** was observed (Entry 10).²⁰

Table 2. 7% Pd/WA30-catalyzed flow-type Mizoroki-Heck reaction assisted by microwave irradiation

							ЧО ₂ Du						
				+ 🔊	7% Pd/ Bu ₃ N (2	WA30 z equiv)	L +		Ac]		
			Ac	y e	quiv Di flc	MA wave		Ac	~	Ac			
			1 (x M)		Single	e-pass	Ac 2	3		4			
Entry	х	у	Z	Solvent	Microwave (W)	Flow rate (min ⁻¹)	(mL	Temperature (°C) ^a	Yield (%)) <mark>b</mark>			
									1	2	3	4	
1	0.1	1.2	1.5	MeCN	5	0.3		80–98	46	30	16	5	

4	Tetrahedron										
					ACCEPT	ED MANUS	CRIPT				
2	0.1	1.2	1.5	MeCN	5	0.15	65-80	27	53	9	5
3	0.1	1.2	1.5	DMA	5	0.15	80-87	55	36	4	0
4	0.1	1.2	1.5	DMA	10	0.15	83–96	33	59	9	0
<mark>5</mark>	<mark>0.1</mark>	<mark>1.2</mark>	<mark>1.5</mark>	DMA	<mark>10</mark>	<mark>0.05</mark>	<mark>80–132</mark>	<mark>12</mark>	<mark>46</mark>	<mark>31</mark>	<mark>11</mark>
6°	0.1	1.2	1.5	Toluene	10	0.15	63–71	5	44	17	33
<mark>7</mark>	0.1	2	1.5	DMA	10	0.15	78–92	0	87	6	0
<mark>8</mark>	0.1	2	3	DMA	10	0.15	80–95	4	92	4	0
<mark>9</mark>	0.25	2	3	DMA	10	0.15	80-100	trace	93 (91) ^d	0	0
<mark>10</mark>	0.5	2	3	DMA	10	0.15	80–106	0	60	1	25

^a The temperature, which was raised by the passing of only solvent through the catalyst cartridge, is indicated as a lower temperature in each entry. The temperature increased up to the higher one during the reaction by the passing of the reaction mixture through the cartridge.²¹

^b Yields were determined by ¹H NMR using 1,4-dioxane as the internal standard.

^c 7% Pd/WA30 (600 mg) was packed in cartridge B.

^d Isolated yield.

The coupling reaction of 3'-iodoacetophenone with *n*-butyl acrylate under 10 W MW irradiation afforded the desired crosscoupling product in a better yield when using a 0.25 M solution compared with that in the reaction using 0.1 M solution (34% vs. 62%; Table 3, Entries 3 and 4) in the same manner as the case of 4'-iodoacetophenone (Table 2, entries 6 and 8 and Table 3, entries 1 and 2). The yield of the product was significantly increased by circulation of the reaction solution (0.25 M) for 7.5 h (93% isolated yield, Entry 5).

To expand the substrate scope, three sets of reaction condition were used: 1) condition A, where a solution of an aryl iodide (0.1 M), *n*-butyl acrylate (2 equiv), and Bu₃N (1.5 equiv) in DMA was passed through the 7% Pd/WA30-packed cartridge A only once (single-pass manner) under MW irradiation; 2) condition B, where a solution of an aryl iodide (0.25 M), *n*-butyl acrylate (2 equiv), and Bu₃N (3 equiv) in DMA was passed through the 7% Pd/WA30-packed cartridge A only once (single-pass manner) under MW irradiation; 3) condition C, a solution of an aryl iodide (0.25 M), *n*-butyl acrylate (2 equiv), and Bu₃N (5 equiv) in DMA was passed through the 7% Pd/WA30-packed cartridge A by circulation under MW irradiation, when the conditions A and B are ineffective.

The aryl iodides except for 1 showed poor reaction efficiency, regardless of the electron density of their aromatic rings under the single-pass conditions (entries 3, 4, 7, 9, 11, 12, 14, 17, and 19). The electron-deficient nitro-, ester-, and halogen-substituted iodobenzenes were coupled with n-butyl acrylate to give the desired Mizoroki-Heck products in good to excellent yields under condition C (entries 8, 10, 13, and 15). In the case of 2'iodoacetophenone, the reaction proceeded with difficulty even under condition C, probably because of the steric hindrance around the reaction center (entry 6). Unsubstituted and electronenriched iodoarenes were also good substrates for the reaction and produced the corresponding cinnamates in good yields under condition C (entries 16, 18, 20, and 21). In addition to the acrylates (entries 2 and 22), styrene, which is less reactive in the Mizoroki-Heck reaction as compared to the electron-deficient alkenes, was applicable to the present reaction (condition C, entry 24). The reactions generally proceeded in a clean manner without any formation of byproducts except in three cases, wherein homo-coupling biaryls (entries 8 and 10)²² or dialkene (entry 11)^{23,24} were generated by using iodoarenes or 4-iodobromobenzene as the substrates for the reaction with *n*-butyl acrylate, respectively.

Table 3. Scope of substrates								
	7% Pd/WA30 Conditions A: Bu ₃ N (1.5 equiv) DMA (10 mL) <i>Single-pass</i>							
\checkmark		Conditio	DMA (4 r	nL)				
		Conditio	ns C: Bu ₃ N (5 e DMA (4 r <i>Circulatic</i>	ass equiv) nL) on	R ₂			
	+ / R ₂	Mic	rowave irradiati	on (
	0	0.15	5 mL min ⁻¹	L	$\frac{1}{1}R_1$			
1 mmol	2 equiv							
Entry	\mathbf{R}^1	\mathbb{R}^2	Condition	Temperat ure (°C)	Yield (%) ^a			
1	4-Ac	CO ₂ Bu	А	78–92	87			
2	4-Ac	CO_2Bu	В	80–104	93 (91) ^b			
3	3-Ac	CO ₂ Bu	А	70–89	34			
4 ^c	3-Ac	CO ₂ Bu	В	80–101	62			
5	3-Ac	CO ₂ Bu	С	77–97	100 (93) ^b			
6^d	2-Ac	CO ₂ Bu	С	80–98	15 (15) ^b			
7	$4-NO_2$	CO ₂ Bu	А	67–97	16			
8	$4-NO_2$	CO ₂ Bu	С	80–94	76 (76) ^b			
9	4-CO ₂ Et	CO ₂ Bu	А	62–97	33			
10	4-CO ₂ Et	CO ₂ Bu	С	80-100	$-(78)^{b}$			
<mark>11</mark>	<mark>4-Br</mark>	CO ₂ Bu	B	<mark>80-121</mark>	<mark>– (69)</mark>			
<mark>12</mark>	4-C1	CO ₂ Bu	А	73–93	65			
13 ^e	4-C1	CO ₂ Bu	С	70–119	88 (91) ^b			
<mark>14</mark>	4-F	CO ₂ Bu	А	80–96	36			
<mark>15</mark>	4-F	CO ₂ Bu	С	80–90	57 (57) ^b			
16 ^f	Н	CO ₂ Bu	С	80–95	86 (86) ^b			
<mark>17</mark>	4-Me	CO ₂ Bu	А	68–90	13			
18 ^g	4-Me	CO ₂ Bu	С	80–100	70 (65) ^b			
<mark>19</mark>	4-MeO	CO ₂ Bu	А	7095	31			

20 ^{f,g}	4-MeO	CO ₂ Bu	С	80-10000	E69 (73) ^b D
21	3-MeO	CO ₂ Bu	С	80–95	- (51) ^b
<mark>22</mark>	4-Ac	CO ₂ Bn	В	80-100	86 (91) ^b
<mark>23</mark>	4-Ac	Ph	А	70–95	11
<mark>24</mark>	4-Ac	Ph	С	80–97	30 (30) ^b

^a Yields were determined by ¹H NMR using 1,4-dioxane as the internal standard.

^b Isolated yield.

^c 5 equivalents of Bu₃N were used.

^d 12 W Microwave irradiation was used.

e 15 W Microwave irradiation was used.

^f 14 W Microwave irradiation was used.

^g 3 equivalents of Bu₃N were used.

The MW effect for heating the DMA solutions of aryl iodide derivatives under the flow conditions was investigated to clarify whether the MW heating affects the efficiency of the Mizoroki-Heck reaction (Table 4). When the DMA solutions of parasubstituted iodoacetophenone and iodoanisole were passed through the 7% Pd/WA30-packed cartridge A at the rate of 0.15 mL min⁻¹ under the 10 W MW-irradiated conditions, the temperature increased to 105 °C and 99 °C, respectively (entries and 3). On the other hand, the meta-substituted 1 iodoacetophenone and iodoanisole were heated up to 95 °C and 94 °C, respectively (entries 4 and 5). Effective heating was observed in the case of the electron-deficient iodobenzene derivatives, which were more reactive than the electron-rich derivatives, regardless of the para- or meta-substitution (entries 1 and 2 vs. 3; entries 4 vs. 5). A distinctive observation was that para-substitution of iodobenzene with a methoxy group led to a greater increase in the temperature of the DMA solution and the reaction yield as compared to those for meta-substitution (entries 3 vs. 5; Table 3, entries 20 vs. 21), although iodoarenes bearing an electron-enriched substituent at the meta-position are generally more reactive than the corresponding para-isomers in palladium-catalyzed cross-coupling reactions using conventional heating apparatus.^{17,18,25} These results indicate that the heating efficiency by MW irradiation would be dependent on the structure of the iodoarenes and closely related to their reactivity toward the present Mizoroki-Heck reaction. The heating test using other substances, n-butyl acrylate and Bu₃N, was also carried out as a background, but these compounds had a smaller effect on heating than iodoarenes (entry 6).

Table 4. Effect of	MW irradiation	on heating of DMA
solution of aryl iod	lides under flow	conditions

Entry	Solute	Temperature (°C) ^a
1	4-Ac-C ₆ H ₄ -I	105
2	4-Cl- <mark>C₆H4</mark> -I	100
3	4-MeO- <mark>C₀H₄</mark> -I	99
4	3-Ac-C ₆ H ₄ -I	95
<mark>5</mark>	3-MeO- <mark>C₀H₄</mark> -I	94
<mark>б</mark> ь	<i>n</i> -Butyl acrylate + Bu ₃ N	91

^a The highest temperature is indicated.

 $^{\rm b}$ A solution of *n*-butyl acrylate (2 mmol) and Bu₃N (3 mmol) in DMA (4 mL) was used

A comparative experiment of the heating systems was carried out using KeyChem-H[®] (YMC Co., Ltd.), which is a continuous flow-device equipped with a heating oven (hot air-mediated heating system) (Scheme 1). The mixture of 1 (0.25 M), *n*-butyl Acrylate (2 equiv), and Bu_3N (3 equiv) in DMA was passed through the 7% Pd/WA30-packed cartridge at the flow rate of 0.1 mL min⁻¹ at 100 °C to produce the mixture of the unreacted **1** (9%), desired Mizoroki–Heck product (**2**, 87%), and homocoupling product (**3**, 4%). This result indicated that the MW irradiation facilitated the Mizoroki–Heck reaction because of the rapid and efficient heating properties (Scheme 1 vs. Table 2, entry 8).²⁶

1	+ CO Bu =	7% Pd/WA30 Bu ₃ N (3 equiv)	- 2 + 3 + 4
0.25 M	2 equiv	DMA, 100 °C 0.1 mL min ⁻¹	¹ H NMR yield 1/2/3/4
		Single-pass	= 9 / 87 / 4 / 0

Scheme 1 Flow Mizoroki–Heck reaction using a heating oven (without MW irradiation)

Significant Pd leaching may emerge as an important issue in heterogeneously catalyzed cross-coupling reactions, especially under flow conditions.^{9a} After the 7% Pd/WA30-catalyzed cross-coupling reaction between **1** and *n*-butyl acrylate under the present MW-assisted flow conditions, the Pd concentration in the recovered reaction mixture was measured by the atomic absorption analysis. As the result, revealed that the Pd species were hardly leached from the catalyst in the cartridge (~1%, 1.249 ppm). The small amount of contaminating Pd species in the recovered mixture could be removed during the process of **2** using silica-gel column chromatography; no Pd species were observed in the purified **2** (< 1 ppm; detection limit).

Next, the reuse of 7% Pd/WA30-packed cartridge under the Mizoroki–Heck reaction conditions was examined using 1 and *n*-butyl acrylate (Table 5). The catalyst cartridge could be repeatedly used for at least five runs without exchange of 7% Pd/WA30.²⁷

Γ	able	5.	Reuse	test	of	catal	lyst	cartric	lge
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1	+	7% Pd/WA30 Bu ₃ N (3 equiv)	7 –	-
1 mmol	2 equiv	DMA (4 mL) 10 W Microwave 0.15 mL min ⁻¹ Single-pass	<u>-</u> T	J

Runs	Temperature (°C) ^a	Yield (%) ^b		
		1	2	3
1st	111	0	98	2
2nd	107	0	98	2
3rd	108	0	92	6
4th	112	0	98	2
5th	106	0	87	5

^a The top temperature is indicated.

 $^{\rm b}$ Yields were determined by $^{\rm l}{\rm H}$ NMR using 1,4-dioxane as the internal standard.

3. Conclusion

We have developed a heterogeneously-catalyzed Mizoroki– Heck reaction using a MW-assisted continuous-flow reactor. Organic solvents could be effectively heated in the Pd/WA30packed cartridge under mild MW irradiation (5–15 W), which was precisely adjusted for the best resonance. Various aryl iodides and alkenes could be used for the present reactions. Since Pd species were hardly leached into the reaction mixture and the trace amount of Pd species was easily removed by purification, M the reaction system would be suitable for practical application. The 7% Pd/WA30-packed cartridge could be used 5 times without exchange. Further research aimed at extending the MW-assisted continuous flow system to other types of heterogeneous catalysis is in progress in our laboratory.

4. Experimental section

4.1. General

All reagents and solvents were obtained from commercial sources and used without further purification. 7% Pd/WA30 was prepared according to our previous study.^{18a} The microwave-applied continuous-flow reactor was made by Saida FDS Inc. The melting point was determined on a Sansyo melting point apparatus SMP-300. IR spectra (neat) were measured using a Bruker Alpha FT-IR spectrometer. The ¹H and ¹³C NMR spectra were recorded on JEOL AL 400 (400 MHz for ¹H NMR and 100 MHz for ¹³C NMR) or JEOL ECA-500 (500 MHz for ¹H NMR and 125 MHz for ¹³C NMR). Chemical shifts (δ) were expressed in ppm and internally referenced (δ = 0.00 ppm for TMS/CDCl₃ for ¹H NMR and 77.0 ppm for CDCl₃ for ¹³C NMR). High resolution mass spectra were measured by Shimadzu hybrid LCMS-IT-TOF (LCMS-IT-TOF).

4.2. Preparation of catalyst cartridge

7% Pd/WA30-packed cartridge A: Glass beads (0.991–1.397 mm diameter, 25 mg) were put on the glass filter, which was placed in a straight glass tube (cartridge A), then a small amount of cotton (ca. 7 mg) was placed on the glass beads. The 7% Pd/WA30 (203 mg) was tightly filled on the cotton plug by tapping the tube (3.8 cm catalyst layer in height), and another cotton plug (ca. 7 mg) was then placed on the catalyst to prevent movement of the 7% Pd/WA30 from the cartridge. Finally, more glass beads (250 mg) were placed on the cotton plug.

7% Pd/WA30-packed cartridge B: The 7% Pd/WA30 of (600 mg) was placed on a glass filter attached to the bottom of the bulging part (internal diameter, 8 mm) of the straight tube (internal diameter, 3 mm) (cartridge B), and glass beads (ca. 400 mg) were then placed on the catalyst.

4.3. Solvent heating test

Into the 7% Pd/WA30-packed cartridge A was flowed MeCN (50 mL) from an Erlenmeyer flask acting as a reservoir at the flow rate of 0.30 or 0.15 mL min⁻¹ along with irradiation of 5 or 10 W MW under a 1 MPa back-pressure. The temperature was measured using a thermocouple at the exit of the cartridge to avoid MW irradiation of the thermocouple. The MW irradiation was maintained until the temperature reached the steady state. DMA, EtOAc, and CPME (10 mL) was also flowed into the 7% Pd/WA30-packed cartridge A and the temperature was measured by a procedure similar to that for the MeCN.

In the case of toluene (50 mL), the temperature change was investigated in a setup similar to MeCN and DMA except for the use of cartridge B.

4.4. General procedure for Mizoroki-Heck reaction

Single-pass manner (conditions A and B): A solution of iodoarene (1 mmol), alkene (2 mmol), and Bu_3N (condition A, 1.5 mmol; condition B, 3 mmol) in DMA (condition A, 10 mL; condition B, 4 mL) was prepared in a vial and flowed into cartridge A packed with 7% Pd/WA30 at the flow rate of 0.15 mL min⁻¹ along with the MW irradiation (10 W) under the 1 MPa back-pressure in a single-pass manner. After the entire solution in

the vial had passed through the catalyst cartridge, additional DMA (15 mL) was passed through the path to wash out the remaining reagents (total operation time: ca. 140 min). To the collected mixture were added EtOAc (20 mL) and H₂O (10 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (20 mL). The combined organic layers were washed with H_2O (20 mL × 4) and brine (20 mL), dried over Na₂SO₄, and concentrated in vacuo. To the residue was added CDCl₃ (ca. 1.5 mL) and 1,4-dioxane (8.53 µL, 100 µmol) as an internal standard, and the yield was determined by ¹H NMR. The ¹H NMR sample was diluted with EtOAc (15 mL), washed three times with sat. aq. CuSO₄ (5 mL) and H₂O (10 mL), dried over Na₂SO₄, concentrated in vacuo. The residue was purified by silica gel column chromatography using hexane/EtOAc (10 : 1) as the eluent to give the corresponding substituted alkenes as the Mizoroki-Heck reaction product.

Circulation manner (condition C): When the TLC analysis revealed that the aryl iodide still remained unreacted after a single-pass of the reaction solution through the catalyst cartridge, both the starting and ending parts of the flow path were dipped into the reaction solution in a reservoir for circulation. After 7.5 h of circulation at the flow rate of 0.15 mL min⁻¹, the flow path was washed with DMA (15 mL). The recovered mixture was treated according to a procedure similar to that described for the single-pass setup.

4.5. Heating efficiency of aryl iodides

Into the 7% Pd/WA30-packed cartridge A was flowed a solution of iodoarene (1 mmol) in DMA (4 mL) from an Erlenmeyer flask acting as a reservoir at the flow rate of 0.15 mL min⁻¹ along with irradiation of 10 W MW under a 1 MPa back-pressure. The temperature was measured using a thermocouple at the exit of the cartridge to avoid MW irradiation of the thermocouple. The MW irradiation was maintained until the temperature reached the steady state. The heating efficiency of a solution of *n*-butyl acrylate (2 mmol) and Bu_3N (3 mmol) in DMA (4 mL) was also investigated in a procedure similar to that for iodoarenes.

4.6. Flow Mizoroki–Heck reaction using a heating oven (without MW irradiation)

A solution of 4'-iodoacetophenone (246 mg, 1 mmol), n-butyl acrylate (285 µL, 2 mmol), and Bu₃N (716 µL, 3 mmol) in DMA (4 mL) was prepared in a vial and passed through the 7% Pd/WA30-packed (203 mg) cartridge in heated oven at 100 °C at the flow rate of 0.1 mL min⁻¹ in a single-pass manner using KeyChem-H[®] (YMC Co., Ltd). After the whole solution of in the vial was flowed to the catalyst cartridge, additional DMA (15 mL) was passed through the path to wash out the remaining reagents. To the collected mixture were added EtOAc (20 mL) and H₂O (10 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (20 mL). The combined organic layers were washed with $H_2O~(20~\text{mL}\times4)$ and brine (20 mL), dried over Na₂SO₄, concentrated in vacuo. To the residue was added CDCl₃ (ca. 1.5 mL) and 1,4-dioxane (8.53 µL, 100 µmol) as an internal standard. The desired product was produced in 87% yield determined by ¹H NMR analysis.

4.7. Pd-leaching test

A solution of 4'-iodoacetophenone (246 mg, 1 mmol), *n*-butyl acrylate (285 μ L, 2 mmol), and Bu₃N (716 μ L, 3 mmol) in DMA (4 mL) was prepared in a vial and passed through the 7% Pd/WA30-packed [203 mg (14.21 mg as Pd species)] cartridge at the flow rate of 0.15 mL min⁻¹ under MW irradiation (10 W) at 1 MPa back-pressure in a single-pass manner. After the entire

solution in the vial had passed through the catalyst cartridge, the MANpath was rinsed with additional DMA (15 mL) to wash out the remaining reagents. The combined DMA solution was diluted with EtOAc (20 mL) and washed with H₂O (10 mL), and the layers were separated. The aqueous layer was further extracted with EtOAc (20 mL). The combined organic layers were washed with H_2O (20 mL × 4) and brine (20 mL), and was transferred to a 100 mL volumetric flask together with additional EtOAc. Its atomic absorption analysis indicated that 1.249 ppm (124.9 µg) of Pd species were eluted from the 7% Pd/WA30-packed cartridge into the organic layers. The combined aqueous layers were also transferred to a 100 mL volumetric flask together with additional H₂O and its atomic absorption analysis indicated that Pd species were not detected in the aqueous layer (< 1 ppm; detection limit). The total Pd amounts leached from the catalyst was found to be 124.9 μ g (ca. 1% of Pd).

The crude compounds obtained from the reaction using a solution of 4'-iodoacetophenone (246 mg, 1 mmol), *n*-butyl acrylate (285 μ L, 2 mmol), and Bu₃N (716 μ L, 3 mmol) in DMA (4 mL) under condition B was purified by silica gel column chromatography using hexane/EtOAc (10 : 1) as the eluent to give **2** (223 mg). The purified **2** was solved in EtOAc (100 mL) using 100 mL volumetric flask. Its atom absorption analysis indicated that no Pd species were observed (< 1 ppm; detection limit).

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- In comparison with the Pd catalyst embedded on the unsubstituted 18. polystyrene-divinylbenzene polymer (10% Pd/HP20), 7% Pd/WA30 was found to much more effectively catalyze the Suzuki-Miyaura reaction of 4'-chloroacetophenone with phenylboronic acid under the batch conditions due to the ligand effect of tert-amino groups on DIAION WA30, see References and notes 17b. For 10% Pd/HP20, see (a) Monguchi, Y.; Fujita, Y.; Endo, K.; Takao, S.; Yoshimura, M.; Takagi, Y.; Maegawa, T.; Sajiki, H. Chem. Eur. J. 2009, 15, 834-837; (b) Monguchi, Y.; Sakai, K.; Endo, K.; Fujita, Y.; Niimura, M.; Yoshimura, M.; Mizusaki, T.; Sawama, Y.; Sajiki, H. ChemCatChem 2012, 4 546-558. A piece of DIAION WA30 is not finely powdered but spherically shaped, and the future is an advantage for the flow reactions to maintain the continuous, stable, and smooth flow of reaction mixtures in the catalyst cartridge.
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- 20. The use of EtOAc (4 mL) or CPME (4 mL) as a solvent for the present Mizoroki–Heck reaction of 1 (1 mmol) with *n*-butyl acrylate (2 mmol) in the presence of Bu₃N (3 mmol) under 10 W MW irradiation at the 0.15 mL min⁻¹ flow rate led to a poor formation of 2 in only a 19% or 29% yield, respectively.
- 21. The heating effect of the MW irradiation depends on an electric permittivity of the solution or solvent passing through a catalyst cartridge. Since the reaction mixture contains aryl halide, alkene, tributylamine, and products, which have each inherent electric permittivity, the electric permittivity of the mixture differs from

that of DMA. The change of the permittivity of the reaction ED MANUSCRIP' solution as well as exothermic phenomenon of the reaction would cause the change of temperature during the reaction.

- 22. 4,4'-Dinitro-1,1'-biaryl was observed in the ¹H NMR spectrum of the crude product when 4-iodonitrobenzene was used as the substrate. The homo-coupling product from ethyl 4-iodobenzoate was also obtained in 5% yield.
- 23. Di-*n*-butyl (*E*,*E*)-*p*-benzenediacrylate was obtained in 11% yield during the reaction of *n*-butyl acrylate with 4-iodo-bromobenzene.
- 24. The use of 4'-bromoacetophenone or 3-iodopyridne as the substrate for the reaction with *n*-butyl acrylate resulted in the recovery of haloarene under the present reaction conditions. The coupling reaction of 1 with cinnamaldehyde as a disubstituted alkene intricately proceeded. The use of (2-iodophenyl)acrylate for the intramolecular cross-coupling reaction led to a formation of complex mixture.
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- 27. Although the temperature rose over 100 °C, which is the maximum operating temperature of DIAION WA30 (see References and notes 16), in each run during the reuse study, the catalyst could be reused without any loss of the catalyst activity.