

Palladium Membrane-Installed Microchannel Devices for Instantaneous Suzuki–Miyaura Cross-Coupling

Yoichi M. A. Yamada,^[a] Toshihiro Watanabe,^[a, b] Tomohiko Beppu,^[b]
Naoshi Fukuyama,^[b] Kaoru Torii,^[b] and Yasuhiro Uozumi^{*[a, b]}

Abstract: Instantaneous catalytic carbon–carbon bond-forming reactions were achieved in catalytic membrane-installed microchannel devices that have a polymeric palladium-complex membrane. The catalytic membrane-installed microchannel devices were provided inside the microchannels by means of coordinative and ionic molecular convolution at the interface between the organic and aqueous phases flowing laminarily, in which both non-

crosslinked linear polymer ligands and palladium species dissolved. The palladium-catalyzed Suzuki–Miyaura reaction of aryl, heteroaryl, and alkenyl halides with arylboronic acids and sodium tetraarylborates was performed with the catalytic membrane-installed

microchannel devices to give quantitative yields of biaryls, heterobiaryls, and aryl alkenes within 5 s of residence time in the defined channel region. These microchannel devices were applied to the instantaneous allylic arylation reaction of allylic esters with arylboron reagents under microflow conditions to afford the corresponding coupling products within 1 s of residence time.

Keywords: allylic arylation • membranes • microreactors • palladium • Suzuki–Miyaura reaction

Introduction

Development of multiple-phase reaction systems is becoming an important research subject in synthetic organic chemistry in which, for example, substrates, products, reagents, and catalysts are readily separated by simple phase separation to realize high-throughput and/or green sustainable chemical synthesis.^[1] Since the majority of organic transformations are carried out by mixing solutions of substrates and/or reactants in the presence of a catalyst, the development of liquid–liquid–solid triphase reaction systems (for example, substrates (organic phase)/reagents (aqueous phase)/catalysts (solid phase)) for carbon–carbon bond-forming reactions, the core of organic synthesis, would find a wide range of utility in synthetic chemistry. Recently, microreac-

tor systems that offer many fundamental as well as practical advantages have been developed as innovative devices for rapid organic transformations.^[2] Molecular transformations with catalyst-immobilized microflow reactors are representative examples of these systems, in which the efficiency of various reactions has been found to increase due to the vast interfacial area and the close distance of the molecular diffusion path in the narrow space of the microreactors.^[3] If a catalyst were installed as a membranous composite at the center of the microchannel, two reactants could be oppositely charged into and flow through the divided channel, all the while remaining in contact with the vast interfacial surface of the catalytic membrane from both front and back sides, thereby realizing an instantaneous chemical reaction. This concept is shown schematically in Figure 1, in which a catalytic cross-coupling reaction is depicted as a typical example.

We have previously developed a novel concept for catalyst immobilization, also known as molecular convolution, in which a soluble linear polymer with multiple ligand groups was convoluted with transition metals by means of coordinative or ionic complexation (Scheme 1) to achieve the one-step preparation of the insoluble polymeric metal composite, thus combining heterogeneity and catalytic activity in one system.^[4] We are well aware that the development of catalyst-installed microflow reaction systems still remains as a

[a] Dr. Y. M. A. Yamada, T. Watanabe, Prof. Dr. Y. Uozumi
RIKEN Advanced Science Institute
2-1, Hirosawa, Wako, Saitama 351-0198 (Japan)
Fax: (+81) 48-467-9599
E-mail: uoyamada@riken.jp

[b] T. Watanabe, T. Beppu, N. Fukuyama, K. Torii, Prof. Dr. Y. Uozumi
Institute for Molecular Science (IMS) and the
Graduate School for Advanced Studies
Myodaiji, Okazaki, Aichi 444-8787 (Japan)

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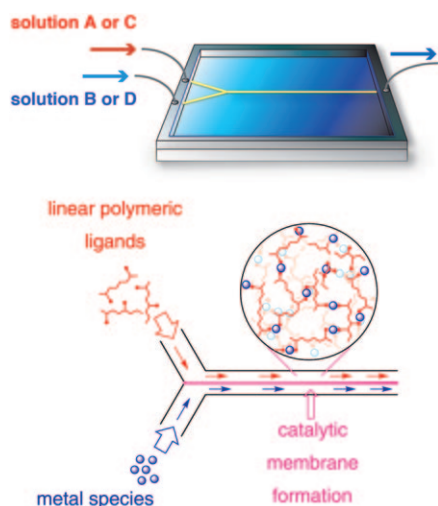
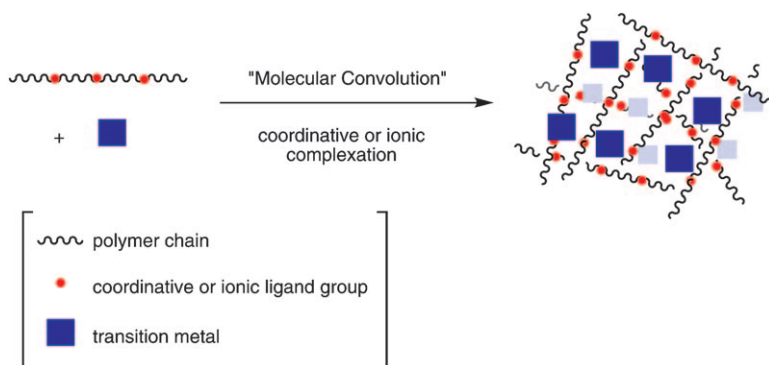


Figure 1. Illustration of a Y-junction microchannel reactor with two inlets and one outlet (top). Concept for the preparation of catalytic membranes at the interface of a laminar flow inside a microchannel reactor (bottom).



Scheme 1. Concept of molecular convolution.

major challenge. Accordingly, the preliminary success of the molecular convolution method led us to examine the installation of the polymeric metal catalysts inside a microchannel reactor by means of the “ship-in-a-bottle” molecular convolution.

Herein we report the formation of a variety of membranous polymeric palladium catalysts inside a microchannel reactor at the laminar flow interface of the channel to develop catalyst-installed microflow chemical-reaction devices. They were applied to the palladium-catalyzed carbon-carbon bond-forming reaction of aryl, heteroaryl, and alkenyl halides with arylboronic acids, the so-called Suzuki-Miyaura reaction, under microflow conditions, in which the instantaneous production of biaryl compounds was achieved quantitatively within 5 s of residence time in the defined channel region. Palladium-catalyzed cross-coupling of allylic esters with arylboron reagents was also accomplished within only 1 s of residence time in the microchannel device.

Results and Discussion

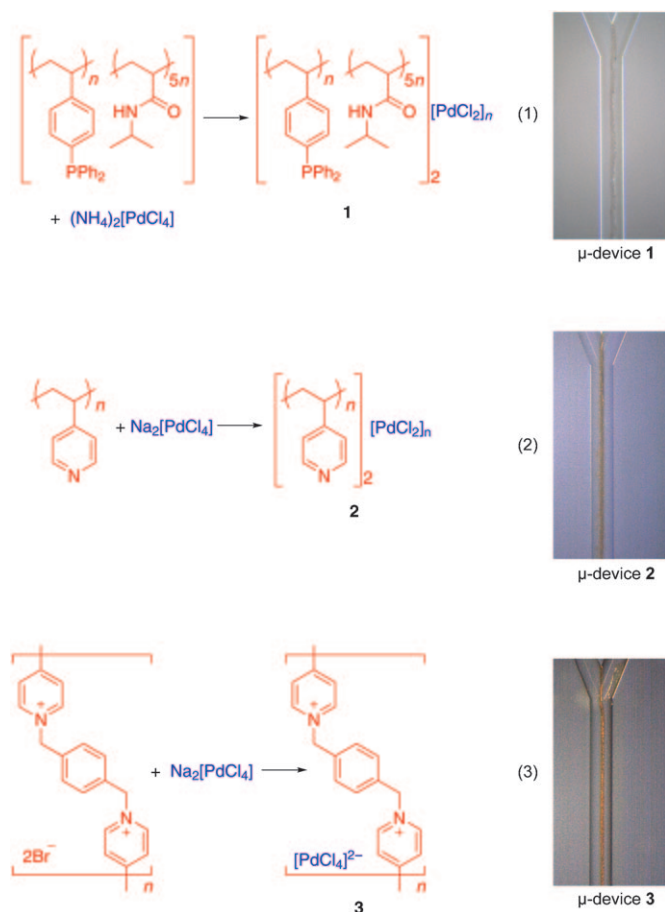
Preparation of catalytic membrane-installed microchannel devices: Polymer deposition at the laminar interface was originally reported by Whitesides et al., for the reaction of a polymeric sulfonate salt and a polymeric ammonium salt.^[5] However, to the best of our knowledge, nothing has appeared in the literature so far on the interfacial deposition of transition-metal complexes with a view toward using them as catalytic membranes except for our preliminary communications.^[6]

The formation of the catalytic membranes was carried out with a glass microchannel reactor^[7] with a Y-junction (Figure 1) and a channel pattern 100 μm wide, 40 μm deep, and 40 or 140 mm long. The coordinative convolution of a poly(acrylamide-triarylphosphine) and palladium species was performed by the installation of an EtOAc solution of poly[(*N*-isopropylacrylamide)₅-*co*-(4-diphenylstyrylphosphine)] (5.0 mM phosphorus unit; solution A) and an aqueous solution of [PdCl₄(NH₄)₂] (1.7 mM; solution B) opposite-

ly into the microchannel at 25 °C with a flow rate of 25 $\mu\text{L min}^{-1}$. The two-phase parallel laminar flow was readily formed under the flowing conditions, and a polymer membrane (PA-TAP-Pd, **1**)^[8] was precipitated at the interface of the laminar flow to give microchannel device **1** (μ -device **1**) [see Equation (1) in Scheme 2]. The palladium-complex membrane of poly(4-vinylpyridine) was also installed into the Y-junction microchannel under similar conditions by means of coordinative convolution, there-

by affording μ -device **2** [Equation (2) in Scheme 2].^[6] The ionic convolution of cationic polyviologen, poly{(4,4'-bipyridyl)-*co*-[1,4-bis(bromomethyl)benzene]} (solution A; Figure 1) and anionic PdCl₄²⁻ (solution B) was carried out under similar microflow conditions to give μ -device **3** [Equation (3) in Scheme 2].

Figures 2 and 3 show the microscopic images of the membrane of PA-TAP-Pd (μ -device **1**) from the top and cross-sections, respectively. Optical microscopic observation showed that a sheet of polymeric Pd membrane was continuously formed at the interface of the laminar flow from the confluent position (Figure 2, position A) to the outlet (position F). The polymeric Pd membrane was readily prepared at the curve positions of the microflow (positions C and E). SEM observations indicated that the polymeric Pd membrane was 1.3 μm thick and 40 μm high (Figure 3a), and that the membrane was stuck to the glassware of the microchannel (Figure 3b). High-resolution SEM images also showed the membrane with a rough “naplike” surface in the size range of several tens of nanometers (Figure 3c and d). The



Scheme 2. Optical microscopic observation of μ -devices 1–3 (width of the tube = 100 μm).

surface area of the amphiphilic membrane should be wide enough to interact with substrates and reactants efficiently. An energy-dispersive spectroscopy (EDS)/SEM observation revealed the existence of palladium, chlorine, and phosphorus atoms in the membrane that was prepared in accordance with a method for $[\text{PdCl}_2(\text{PAr}_3)_2]$ (Figure 3e).^[9] The physical properties of the membrane are shown in Table 1.

The Suzuki–Miyaura reaction with the catalytic membrane-installed microchannel devices: To explore the utility of the microchannel devices in catalytic organic transformations, the synthetic ability of the three types of microchannel devices prepared above (μ -devices 1–3) was examined for the palladium-catalyzed cross-coupling of aryl halides with arylboronic acids (the so-called Suzuki–Miyaura reaction).^[10] Representative results are shown in Scheme 3. Thus, a solution of iodobenzene (**4a**) in EtOAc/*i*PrOH (12.5 mM; solution C, Figure 1) and an aqueous solution of 4-methoxyphenylboronic acid (**5a**) (18.8 mM in 37.5 mM aqueous Na_2CO_3 ; solution D) were oppositely introduced into the membrane-divided channels, μ -devices 1–3, at 50 °C with a flow rate of 2.5 $\mu\text{L min}^{-1}$ (for solution C) and 5.0 $\mu\text{L min}^{-1}$ (for solution D), respectively, and two parallel laminar layers flowed through the channel in 4 s.^[11,12] The resulting organic/aque-

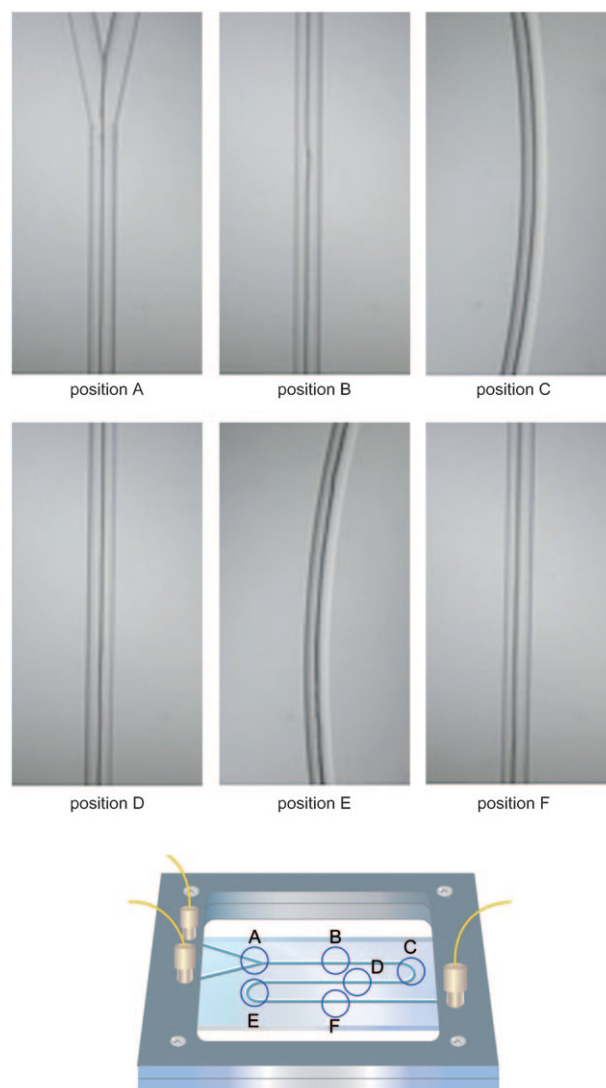


Figure 2. Optical microscopic images of μ -device 1 (the polymer membrane-installed (PA-TAP-Pd)) at positions A–F (width of the tube = 100 μm).

ous microstream was collected from the outlet of the channel. The chemical yield and structure of the products were determined by GC^[13] and $^1\text{H NMR}$ spectroscopy. We were very pleased to find that μ -device 1 with the palladium-complex membrane poly(acrylamide–triarylphosphine)–palladium (PA-TAP-Pd), had been successfully applied to the catalytic reaction to give a quantitative yield of the desired biaryl product. Thus, μ -device 1 promoted the Suzuki–Miyaura reaction of **4a** with **5a** at 50 °C for 4 s of residence time to afford 4-methoxybiphenyl (**6a**) in 99% yield through the continuous 120 min of the flow reaction, whereas μ -devices 2 and 3 gave **6a** in 0 and 15% yield, respectively, under similar conditions. A Pd residue was not detected by inductively coupled plasma atomic-emission spectroscopy (ICP-AES) analysis (detection limit of Pd = 0.044 ppm) in any collected flow samples. Observed superiority of μ -device 1 in the catalytic performance over μ -devices 2 and 3

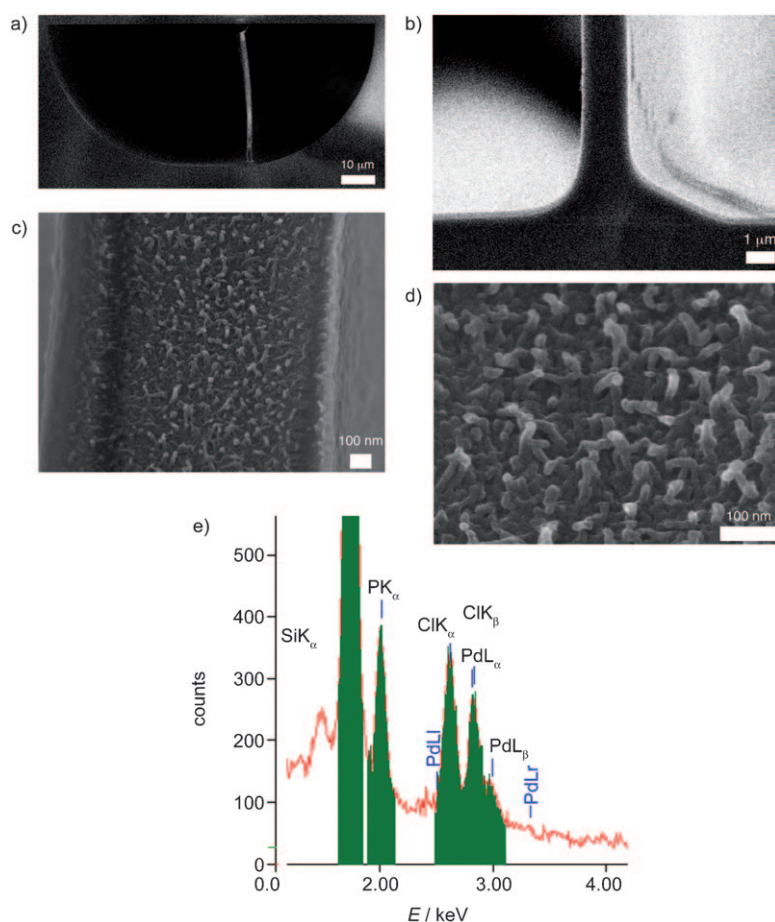
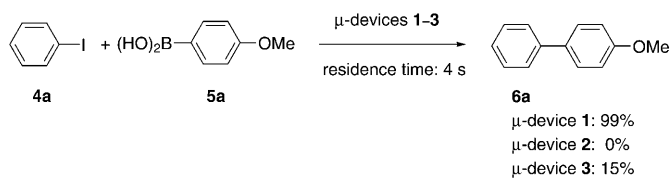


Figure 3. a)–d) SEM images and e) an EDS/SEM spectrum of the cross-section of μ -device **1**. b) Close-up image of (a); c) and d) Close-up images of (b). Scale bar: a) 10 μm , b) 1 μm , c), d) 100 nm.

Table 1. Physical properties of the polymeric palladium membrane in μ -device **1**.

Thickness	1 μm
Height	40 μm
Length	140 mm
Density	1.3
Palladium loading (ICP-AES analysis)	0.50 mmol g^{-1} (3.6 nmol channel^{-1})



Scheme 3. The Suzuki–Miyaura reaction using the catalytic membrane-installed microchannel devices **1–3**. Conditions: **4a** (12.5 mm in *i*PrOH; flow rate: 2.5 $\mu\text{L min}^{-1}$), **5a** (18.8 mm in 37.5 mm aqueous Na_2CO_3 ; flow rate: 5.0 $\mu\text{L min}^{-1}$), 50 $^\circ\text{C}$, residence time = 4 s; turnover frequency (TOF) = 520 h^{-1} .

may be attributed to the nature of the ligand. Thus, μ -device **1** was equipped with a polymeric phosphine–palladium complex, PA–TAP–Pd (**1**), which is known to exhibit

very high catalytic activity in the Suzuki–Miyaura coupling reaction.^[8]

With the instantaneous Suzuki–Miyaura coupling system in hand, we examined the coupling of diverse aryl halides and arylboronic acids using μ -device **1** in which all reactions were completed within 4 s (Table 2). The coupling of iodo-benzene **4a** with the *o*-, *m*-, and *p*-substituted tolylboronic acids **5b–d** was performed at 50 $^\circ\text{C}$ under similar conditions to afford 2-, 3-, and 4-methylbiphenyl in 99, 96, and 75% yield, respectively (Table 2, entries 2–4). Electron-deficient 3-ethoxycarbonyl-1-iodobenzene (**4b**), 1-iodo-4-trifluoromethylbenzene (**4c**), and 1-iodo-3-trifluoromethylbenzene (**4d**) readily coupled with **5a** to give the corresponding biaryl compounds **6e**, **6f**, and **6g** in 99, 99, and 95% yield, respectively (entries 5–7). Electron-rich 3-chloro-1-iodobenzene (**4e**) and 1-iodo-3-methoxybenzene (**4f**) reacted with **5a** to afford the corresponding biaryls **6h** and **6i** in 88 and 82% yield, respectively (entries 8 and 9). The catalytic ability of μ -device **1** was intact during the continuous reaction, as the GC charts of the reaction snapshots at 10–60 min of the reaction time show, thereby affording 99% yield of **6f** (entry 6 in Table 2, and Figure S3 in the Supporting Information).

The reaction system of μ -device **1** was also applied to the cross-coupling reaction of a variety of heteroaryl halides and heteroarylboronic acids, which is among the most important organic transformations for the preparation of optical devices, organic electronics, bioactive compounds, and so on.^[14] Instantaneous preparation of arylthiophenes, arylpyridines, and arylfurans with a flow-reaction device should also be helpful in the high-throughput screening of a variety of candidates for functional materials. The reaction of 2-iodothiophene (**7a**) and 3-iodothiophene (**7b**) with phenylboronic acid (**5e**) was performed with μ -device **1** at 50 $^\circ\text{C}$ to afford 2-phenylthiophene (**8a**) and 3-phenylthiophene (**8b**) in 99 and 99% yield, respectively (Table 3, entries 1 and 3). Sodium tetraphenylborate (**9a**) also proved to be a suitable arylboron reagent for coupling with the thiophene **7a** under similar conditions to give **8a** in 97% yield (entry 2). The coupling of 3-iodopyridine (**7c**) was carried out with **5e** and *o*-methylphenylboronic acid (**5b**) to give both phenylpyri-

Table 2. Suzuki–Miyaura reaction using the catalytic membrane-installed microchannel device **1**.^[a]

Entry	Ar-I (4)	ArB(OH) ₂ (5)	Product	Yield [%]
1 ^[b]	4a	5a	6a	99 ^[c,d]
2	4a	5b	6b	99
3	4a	5c	6c	96
4	4a	5d	6d	75
5	4b	5a	6e	99
6	4c	5a	6f	99 ^[e]
7	4d	5a	6g	95
8	4e	5a	6h	88
9	4f	5a	6i	82

[a] Aryl iodide **4** (6.3 mM in EtOAc/*i*PrOH (2:5); flow rate: 2.5 μL min⁻¹), arylboronic acid **5** (9.4 mM in 18.3 mM aqueous Na₂CO₃; flow rate: 5.0 μL min⁻¹), 50 °C, residence time = 4 s. [b] Aryl iodide (12.5 mM in *i*PrOH), arylboronic acids (18.8 mM in 37.5 mM aqueous Na₂CO₃). [c] TOF = 520 h⁻¹. [d] No palladium or phosphorus residue was detected by ICP-AES analysis in the collected flow sample. [e] 240 μg h⁻¹ of the coupling product was isolated by use of a single microreactor.

dines **8c** and **8d** in 99% yield (entries 4 and 5). Since aryl furfuraldehydes often exhibit biological activity, the development of an efficient protocol for their preparation is important.^[15] μ-Device **1** efficiently promoted the cross-coupling of 5-iodo-2-furaldehyde (**7d**) with **5e** and **5b** to give both the 5-aryl-2-furaldehydes **8e** and **8f** in 99% yield (entries 6 and 7). A heterobiaryl compound 5-thiophen-3-yl-2-furaldehyde (**8g**) was also obtained in 99% yield under similar conditions from **7d** and 3-thiopheneboronic acid (**5f**). The heteroarylboronic acids **5g** and **5h** were coupled with **4a** to afford 2-phenylthiophene (**8a**) and 2-phenylfuran (**8h**) in 87 and 81% yield, respectively.

The microchannel-device-promoted cross-coupling of alkenyl halides was also investigated (Table 4). Thus, the reaction of ethyl *cis*-3-iodoacrylate (**10a**) with **5e** was carried

Table 3. Suzuki–Miyaura reaction of heteroaryl halides using the catalytic membrane-installed microchannel device **1**.^[a]

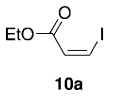
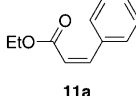
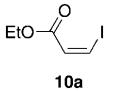
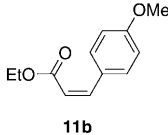
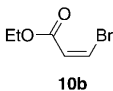
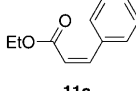
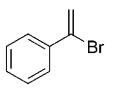
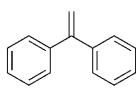
Entry	Aryl halide	Aryl boron reagent	Product	Yield [%]
1	7a	5e	8a	99 ^[b]
2	7a	NaBPh ₄ 9a	8a	97
3	7b	5e	8b	99
4	7c	5e	8c	99
5	7c	5b	8d	99
6	7d	5e	8e	99
7	7d	5b	8f	99
8	7d	5f	8g	99
9	4a	5g	8a	87
10	4a	5h	8h	81

[a] Aryl iodide (6.3 mM in EtOAc/*i*PrOH (2:5); flow rate: 2.5 μL min⁻¹), arylboronic acids (63 mM in 126 mM aqueous Na₂CO₃; flow rate: 2.5 μL min⁻¹), 50 °C, residence time = 5 s. [b] No palladium or phosphorus residue was detected by ICP-AES analysis in the collected flow sample.

out under similar conditions to afford ethyl *cis*-3-cinnamate (**11a**) in 99% yield in which the thermodynamically more stable *trans* isomer was not detected (Table 4, entry 1). The substrate **10a** underwent the coupling reaction with 4-methoxyphenylboronic acid **5a**, thus leading to ethyl *cis*-3-(4-methoxyphenyl)acrylate (**11b**) in 94% yield (entry 2). The reaction of the alkenyl bromides **10b** and **10c** proceeded smoothly to afford **11a** and α-phenylstyrene (**11c**) in 92 and 96% yield, respectively (entries 3 and 4).

This coupling reaction includes two intermolecular reaction steps: 1) the oxidative addition of the aryl halides to the Pd⁰ complex forming an arylpalladium(II) intermediate (Ar-Pd-X) in the matrix of the membranous polymeric palladium complex on the membrane, and 2) the reaction of the arylboronic acid (Ar'B(OH)₂) with the polymeric Ar-Pd-

Table 4. Suzuki–Miyaura reaction of alkenyl halides using the catalytic membrane-installed microchannel device **1**.^[a]

Entry	Aryl halide	Aryl boron reagent	Product	Yield [%]
1	 10a	5e	 11a	99
2	 10a	5a	 11b	94
3	 10b	5e	 11a	92
4	 10c	5e	 11c	96

[a] Alkenyl halides (6.3 mm in EtOAc/*i*PrOH (2:5); flow rate: 2.5 $\mu\text{L min}^{-1}$), arylboronic acids (63 mm in 126 mm aqueous Na_2CO_3 ; flow rate: 2.5 $\mu\text{L min}^{-1}$), 50 °C, residence time = 5 s.

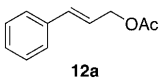
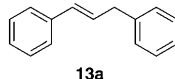
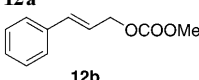
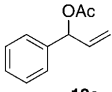
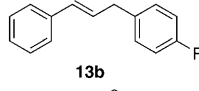
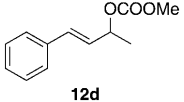
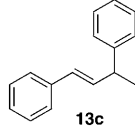
X to give aryl(aryl)palladium(II) (Ar-Pd-Ar') and produce a biaryl product (Ar-Ar'), each of which has a unique reaction rate. With this catalytic membrane-divided microchannel reactor, the fine optimization of the reaction conditions for the intermolecular steps was facilitated by changing the concentration of each reactant solution as well as the individual parallel laminar flow rates. Compared to the conventional flask reaction system, this method of performing a catalytic reaction that involves multiple intermolecular steps offers a great advantage.

Allylic arylation with the catalytic membrane-installed microchannel devices: The synthetic ability of the three types of microchannel devices prepared above (the μ -devices **1–3**) was also examined for allylic arylation of allyl esters with arylboron reagents. Whereas numerous reports on aryl–aryl couplings with arylboron reagents (the Suzuki–Miyaura coupling) have appeared so far, the allyl–aryl coupling, which often requires relatively high reaction temperatures,^[16] has received only scant attention. Successful re-

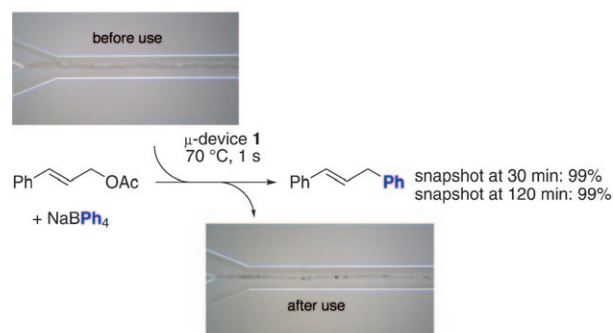
sults for aryl–aryl coupling using the microchannel reactor with a catalytic membrane (vide supra) led us to the idea that the microchannel devices might also promote allyl–aryl coupling with high efficiency.

The allyl–aryl coupling reaction was examined with cinnamyl acetate (**12a**) and sodium tetraphenylborate (**9a**) using μ -devices **1–3**. Thus a solution of **12a** in *i*PrOH (5.8 mm; solution C, Figure 1) and an aqueous solution of **9a** (58 mm; solution D) were oppositely introduced into the membrane-divided channels, μ -devices **1–3** (40 mm long), at 70 °C with a flow rate of 3.0 $\mu\text{L min}^{-1}$. Two parallel laminar layers flowed through the channel in 1 s, and the resulting organic/aqueous microstream was collected from the outlet to afford (*E*)-1,3-diphenylpropene (**13a**) (Table 5, entries 1–3). Determination of the chemical yield and characterization of the product were performed by GC analysis and ¹H NMR spectroscopy. We were pleased to see that the palladium-complex membrane, poly(acrylamide–triarylphosphine)–palladium (PA–TAP–Pd), had been successfully applied to the catalytic reaction. Thus μ -devices **1–3** promoted the allyl–aryl coupling reaction to give **13a** in 99, 77, and 56% yield, respectively. The turnover frequency of μ -device **1** in the catalytic reaction reached 1000 h^{-1} . The catalytic membrane of μ -device **1** was intact during the reaction, and its morphology, as well as its catalytic activity, were similar to that before the catalytic reaction and after the 120 min flow of **12a** and **9a** to afford **13a** in 99% yield continuously (Scheme 4). In this reaction, no palladium or phosphorus species were detected in the collected sample (checked with ICP–AES; Pd < 0.044 ppm and P < 0.076 ppm).

Table 5. Allylic arylation using catalytic membrane-installed microchannel reactors.^[a]

Entry	Allylic ester	Aryl boron reagent	μ -Device	Product	Yield [%] ^[c]
1	 12a	NaBPh_4 (9a)	1	 13a	99 ^[d]
2	12a	9a	2	13a	77
3	12a	9a	3	13a	56
4	12a	$\text{PhB(OH)}_2\text{-Na}_2\text{CO}_3$	1	13a	43
5	 12b	9a	1	13a	99 ^[d]
6	 12c	9a	1	13a	99
7	12a	$\text{NaB(4-F-C}_6\text{H}_4)_4$ 9b	1	 13b	94
8 ^[b]	 12d	9a	1	 13c	57

[a] Conditions: allylic ester or carbonate (5.8 mm in *i*PrOH), arylborate (58 mm in water); flow rate: 3.0 $\mu\text{L min}^{-1}$, 70 °C, residence time 1 s. [b] Flow rate: 2.5 $\mu\text{L min}^{-1}$. [c] In all the reactions, the selectivity of **13** was >99%. [d] No palladium or phosphorus species were detected in the collected sample.

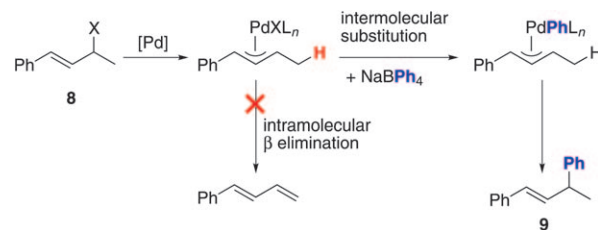


Scheme 4. Allyl-aryl coupling using μ -device **1**. Microscopic observation of μ -device **1** inside a microchannel reactor after the reaction (120 min) of **12a** and **9a**.

Representative results of the allyl-aryl coupling of a variety of allyl esters and arylborate reagents are shown in Table 5. Coupling with $\text{PhB(OH)}_2/\text{Na}_2\text{CO}_3$ (aqueous flow) showed moderate reactivity under otherwise similar conditions to give **13a** in 43% yield (Table 5, entry 4). Both cinnamyl methyl carbonate (**12b**) and the regioisomeric 1-acetoxy-1-phenyl-2-propene (**12c**) also reacted with **9a** under the same conditions to give quantitative yields of **13a** in 1 s (entries 5 and 6), in which no leaching of palladium or phosphorus species was again confirmed by ICP-AES analysis. The microflow reaction of **12a** with sodium tetrakis(4-fluorophenyl)borate (**9b**) under similar conditions gave (*E*)-3-(4-fluorophenyl)-1-phenyl-1-propene (**13b**) in 94% yield (entry 7).

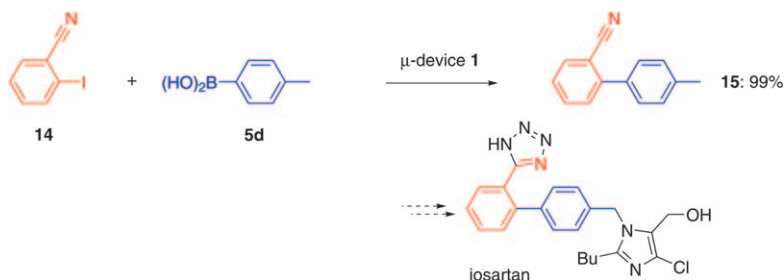
It is noteworthy that the methyl vinyl carbinol carbonate **12d** underwent the palladium-catalyzed allyl-aryl coupling to give the corresponding coupling product **13c** with excellent selectivity, although, under identical conditions, the chemical yield was only moderate (57% yield). The reaction of methyl vinyl carbinol carbonate must proceed through the corresponding π -allylpalladium intermediate that bears the β -sp³-hydride, which often suffers from β elimination under palladium-catalyzed conditions to give the undesired 1,3-dienes (Scheme 5).^[17,18] However, no trace of the 1,3-diene, phenylbutadiene, was observed in the reactions using μ -device **1**, presumably due to the extremely fast intermolecular coupling pathway (versus intramolecular β elimination).

Preparation of pharmaceutical and functional materials using microchannel device **1**: To dem-

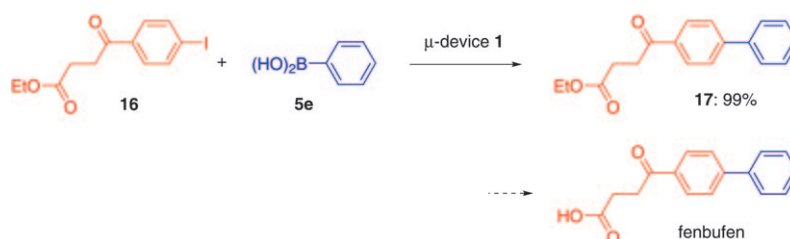


Scheme 5. Intermolecular substitution versus intramolecular β elimination.

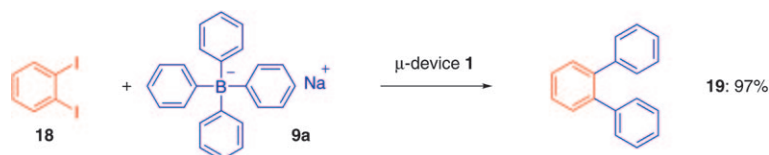
onstrate the utility of the Pd-membrane-installed μ -device **1** in medicinal as well as material science, bioactive compounds and functional materials were prepared with μ -device **1**. Thus, the Suzuki-Miyaura reaction of 2-cyano-1-iodobenzene (**14**) with *p*-tolylboronic acid (**5d**) was carried out with μ -device **1** at 50 °C with 4 s of residence time to afford in 99% yield the synthetic intermediate **15** of losartan, an angiotensin II receptor antagonist used for the treatment of hypertension.^[19] The ethyl ester **17** of fenbufen, a cyclooxygenase inhibitor and a nonsteroidal antiinflammatory drug used to treat inflammation in osteoarthritis, ankylosis spondylitis, and tendinitis, was obtained quantitatively by means of the Suzuki-Miyaura reaction of **16** with **5e** inside μ -device **1** with 5 s of residence time.^[20,21] *ortho*-Terphenyl (**19**), an important skeleton for the preparation of functional cyclic supramolecules and photochromic materials,^[22] was prepared in 97% yield from 1,2-diiodobenzene (**18**) with **9a** under similar conditions. When the reaction of 4-cyano-1-iodobenzene (**20**) with 4-pentylphenylboronic acid (**21**) was performed under similar conditions inside μ -device **1**, a 4'-pentyl-4-cyanobiphenyl (5CB) liquid-crystal compound (**22**)



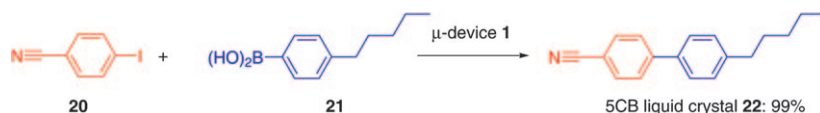
Scheme 6. Preparation of a synthetic intermediate for the preparation of an angiotensin II receptor antagonist, losartan.



Scheme 7. Preparation of fenbufen, a cyclooxygenase inhibitor.



Scheme 8. Preparation of *o*-terphenyl.



Scheme 9. Preparation of a 5CB liquid crystal.

was readily obtained quantitatively from the outlet of μ -device **1**. (Schemes 6–9)

Conclusion

A variety of palladium membranes were installed inside microchannel reactors through the “ship-in-a-bottle” protocol of our molecular convolution method to provide microreaction devices. These microchannel devices were applied to the instantaneous Suzuki–Miyaura reaction and allyl–aryl coupling reaction to afford the corresponding coupling products in quantitative yields within 5 and 1 s of residence time, respectively. μ -Device **1** was applied to the preparation of bioactive compounds as well as functional materials to give the target molecules in high yield. The extension of catalytic membrane-installed microchannel reactors with a variety of convoluted polymeric metal complexes to other organic transformations is currently in progress.

Experimental Section

Preparation of a PdCl₂/PA-TAP membrane inside a microchannel (μ -device **1):** An solution of PA-TAP in EtOAc (5.0 mm phosphorus unit; solution A) and an aqueous solution of [PdCl₂(NH₄)₂] (1.7 mm; solution B) were charged oppositely into the microchannel (100 μ m width, 40 μ m depth, 40–140 mm length) at 25 °C for 10 min with a flow rate of 25 μ L min⁻¹. Two-phase parallel laminar flow was formed under the flowing conditions and yellowish polymer membrane **1** was precipitated out at the interface between the two parallel flows (thickness of membrane **1** = 1 μ m). Elemental analysis calcd (%) for (C₁₀₀H₁₄₄O₁₀N₁₀P₂PdCl₂·5H₂O)_n: C 60.79, H 7.86, N 7.09, P 3.14, Pd 5.39; found: C 60.36, H 7.67, N 6.97, P 2.99, Pd 5.79 (Pd and P were measured with ICP-AES).

Preparation of a PdCl₂/polyPy membrane inside a microchannel (μ -device **2):** An solution of poly(4-vinylpyridine) in EtOAc (5.0 mm pyridine unit; solution A) and an aqueous solution of PdCl₂ (1.7 mm) and NaCl (17 mm) (solution B) were charged oppositely into the microchannel at 25 °C for 5 min with a flow rate of 25 μ L min⁻¹. Two-phase parallel laminar flow was formed under the flowing conditions and yellowish polymer membrane **2** was precipitated out at the interface between the two parallel flows (thickness of membrane **2** = 10 μ m). IR (ATR) $\tilde{\nu}$ = 3476, 1612, 1427, 1221, 1068, 829 cm⁻¹; elemental analysis calcd (%) for

[(PdCl₂)₃(C₇H₇N)₆·CH₃CO₂Et]_n: C 44.17, H 4.03, N 6.72; found: C 44.11, H 4.15, N 7.18.

Preparation of a PdCl₂/polyviologen membrane inside a microchannel (μ -device **3):** A solution of poly{[(4,4'-bipyridyl)-*co*-[1,4-bis(bromomethyl)benzene]]} in *i*PrOH/EtOAc/H₂O (2:1:1) (3.4 mm pyridinium unit; solution A) and an aqueous solution of PdCl₂ (1.7 mm) and NaCl (17 mm) (solution B) were charged oppositely into the microchannel at 25 °C for 5 min with a flow rate of 25 μ L min⁻¹. Two-phase parallel laminar flow was formed under the flowing conditions, and brownish polymer membrane **3** was precipitated out at the interface

between the two parallel flows (thickness of membrane **3** = 10 μ m).

Representative procedure for cross-coupling using the microchannel with a divided PA-TAP-Pd membrane (Table 2, entry 6; μ -device **1):** A solution of 4-trifluoromethylidobenzene (**4c**) in EtOAc/*i*PrOH (2:5; 6.3 mm; solution C) and a solution of 4-methoxyphenylboronic acid (**5a**) and Na₂CO₃ in water (ArB(OH)₂ = 9.4 mm, Na₂CO₃ = 18.3 mm; solution D) were oppositely introduced into the membrane-divided channel μ -device **1** at 50 °C with a flow rate of 2.5 μ L min⁻¹ (for solution C) and 5.0 μ L min⁻¹ (for solution D), respectively, and two parallel laminar layers flowed through the channel in 4 s. The resulting organic/aqueous microstream was collected from the outlet of the channel to afford a quantitative yield (240 μ g h⁻¹) of 4-methoxy-4'-(trifluoromethyl)biphenyl (**6f**). The chemical yield and structure of the product **6f** were determined by GC (based on similarity of GC-MS data with the National Institute of Standards and Technology (NIST) mass database library) and ¹H NMR spectroscopy.

Representative procedure for the allylic arylation reaction using the microchannel with a divided PA-TAP-Pd membrane (Table 5, entry 1; μ -device **1):** A solution of cinnamyl acetate (**12a**) in *i*PrOH (5.8 mm; solution C) and an aqueous solution of sodium tetrakisphenylborate (**9a**) (58 mm; solution D) were oppositely introduced into the membrane-divided channel μ -device **1** at 70 °C with a flow rate of 3.0 μ L min⁻¹, and two parallel laminar layers flowed through the channel in 1 s. The resulting organic/aqueous microstream was collected from the outlet of the channel to afford a quantitative yield of 1,3-diphenyl-1-propene (**13a**).

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- [12] The coupling reaction did not proceed without the catalytic membrane under similar conditions (see section IV in the Supporting Information).
- [13] Several fractions were collected as random snapshots for each reaction shown in Tables 2–5 to demonstrate the stable and high catalytic performance of the microchannel reactor with a divided catalytic membrane (Figures S3 and S4 in the Supporting Information).
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