Catalytic membrane-installed microchannel reactors for one-second allylic arylation[†]

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A variety of catalytic membranes of palladium-complexes with linear polymer ligands were prepared inside a microchannel reactor *via* coordinative and ionic molecular convolution to provide catalytic membrane-installed microdevices, which were applied to the instantaneous allylic arylation reaction of allylic esters and aryl boron reagents under microflow conditions to afford the corresponding coupling products within 1 second of residence time.

Development of multiple-phase reaction systems is becoming an important research subject in synthetic organic chemistry where, 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 organic transformations are often 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 [e.g. substrates (organic phase)/reagents (aqueous phase)/catalysts (solid phase)] would find a wide range of utility in synthetic chemistry. We have previously developed a novel concept for catalyst-immobilization, also known as molecular convolution,² where a soluble linear polymer with multiple ligand groups was convoluted with transition metals via coordinative or ionic complexation (Scheme 1) to achieve the one-step preparation of the insoluble polymeric metal composite, combining heterogeneity and catalytic activity in one system.

Moreover, microchannel reactors recently have been considered innovative devices for rapid organic transformations.^{3,4} While acknowledging the pioneering work in this area, we are aware that the development of catalyst-installed microflow reaction systems still remains a major challenge. The preliminary success of the *molecular convolution* method led us to examine the installation of the polymeric metal catalysts inside



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a micro-channel reactor *via* "ship-in-a-bottle" molecular convolution.

Here, we report the formation of a variety of polymeric palladium membranes inside a micro-channel reactor at the laminar flow interface of the channel to develop the catalyst-installed microflow chemical reaction devices. Palladium-catalyzed cross-coupling of allylic esters with aryl boron reagents was accomplished within only *1 sec* of residence time in the microflow device.

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 so far on the interfacial deposition of transition metal complexes with the view of using them as catalytic membranes except our preliminary communication.⁶

The formation of the catalytic membranes was carried out with a microchannel reactor⁷ having a channel pattern of 100 µm width, 40 µm depth, 40 mm length, and a Y-junction (Fig. 1, left). The coordinative convolution of palladium species and a polymeric phosphine ligand was performed by the installation of an EtOAc solution of poly(acrylamide)triarylphosphine (PA-TAP-Pd, 1)⁸ (5.0 mM; solution A) and an aqueous solution of (NH₄)₂PdCl₄ (1.7 mM) (solution B) oppositely into the microchannel at 50 °C with a flow rate of 20 μ l min⁻¹, according to the method previously reported.⁶ The two-phase parallel laminar flow was readily formed under the flowing conditions, and a polymer membrane 1 was precipitated at the interface of the laminar flow (Scheme 2, eqn (1)). The palladium complex membrane of poly(4-vinylpyridine) was also installed into the Y-junction microchannel under similar conditions (Scheme 2, eqn (2)). The ionic convolution of cationic polyviologen, poly[4,4'-bipyridyl-co-1,4-bis(bromomethyl)benzene], (5.0 mM; solution A) and anionic PdCl₄²⁻ (1.7 mM; solution B) was carried out under



Fig. 1 Illustration of a Y-junction microchannel reactor with two inlets and one outlet (left); concept for the preparation of catalytic membranes at the interface of a laminar flow inside a microchannel reactor (right).

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Scheme 2 Optical microscopic observation of μ-devices 1–3.

similar microflow conditions to give a polymer membrane **3** (Scheme 2, eqn (3)).

The synthetic abilities of the three types of microchannel devices prepared above (μ -devices 1–3) were examined for allylic arylation of allyl esters with aryl boron reagents. While numerous reports on aryl–aryl couplings with arylboron

reagents (the Suzuki–Miyaura coupling) have appeared, the allyl–aryl coupling, which often requires relatively high reaction temperatures,⁹ has received only scant attention. Previously, we reported the preliminary results of the Suzuki–Miyaura coupling of aryl halides and arylboronic acids using a microchannel reactor with the PA-TAP-Pd catalytic membrane where the corresponding biaryl compounds were obtained quantitatively within 4 sec of residence time.⁶ The successful results of the aryl–aryl coupling using the microchannel reactor with a catalytic membrane led us to the idea that the μ -devices could also promote the allyl–aryl coupling with high efficiency.

The allyl-aryl coupling reaction was examined with cinnamyl acetate and sodium tetraphenylborate using the μ -devices 1–3. Thus, a solution of cinnamyl acetate (4a) in *i*-PrOH (5.8 mM; solution A) and an aqueous solution of sodium tetraphenylborate (5a) (58 mM; solution B) were oppositely introduced into the membrane-divided channels, μ -devices 1–3, at 50 °C, with a flow rate of 3.0 µl min⁻¹. Two parallel laminar layers flowed through the channel in 1 second, and the resulting organicaqueous micro stream was collected from the outlet to afford 1,3-diphenyl-1-propene (6a) (Table 1, 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 find that the palladium complex membrane, poly(acrylamide)-triarylphosphine-palladium (PA-TAP-Pd), had been successfully applied to the catalytic reaction. Thus, the **u-devices 1–3** promoted the allyl-aryl coupling reaction to give 1,3-diphenylpropene (6a) in 99%, 77%, and 56% yield, respectively. The turnover frequency of μ -device 1 in the catalytic reaction reached 3000 h^{-1} . The catalytic membrane of μ -device 1 was intact during the reaction, the morphology of which was similar to that before the catalytic reaction after the 120 min flow of 4a and 5a (Scheme 3).

 Table 1
 Allylic arylation using catalytic membrane-installed microchannel reactors^a

| Entry | Allylic ester | Arylboron reagent | µ-device | Conversion (%) | Selectivity (%) | Product | Yield (%) |
|-----------------------|---------------|--------------------------|----------|----------------|-----------------|------------|-----------|
| 1 | GAC 4a | $NaBPh_4$ (5a) | 1 | 99 | >99 | 6a C | 99 |
| 2 | 4a | 5a | 2 | 77 | >99 | 6a | 77 |
| 3 | 4a | 5a | 3 | 56 | >99 | 6a | 56 |
| 4 | 4 a | PhB(OH)2-Na2CO3 | 1 | 43 | >99 | 6a | 43 |
| 5 | OCOOMe 4b | 5a | 1 | 99 | >99 | 6a | 99 |
| 6 | OAc 7 | 5a | 1 | 99 | >99 | 6a | 99 |
| 7 | 4a | $NaB(4-F-C_6H_4)_4$ (5b) | 1 | 94 | >99 | 6b F | 94 |
| 8 ^b | OAc 8a | 5a | 1 | 33 | >99 | <u>у</u> , | 33 |
| 9 ^{<i>b</i>} | OCCOOMe 8b | 5a | 1 | 57 | >99 | 9 | 57 |

^{*a*} Conditions: 4, 7 or 8 (5.8 mM in *i*- C_3H_7OH), 5 (58 mM in water); flow rate: 3.0 μ L min⁻¹, 50 °C, residence time 1 sec. ^{*b*} Flow rate: 2.5 μ L min⁻¹.



Scheme 3 Microscopic observation of μ -device 1 after the reaction (120 min) of 4a and 5a.



Scheme 4 Intermolecular substitution vs. intramolecular elimination.

Representative results of the allyl–aryl coupling of a variety of allyl esters and arylborate reagents are shown in Table 1. Coupling with PhB(OH)₂–Na₂CO₃ (aqueous flow) showed moderate reactivity under otherwise similar conditions to give **6a** in 43% yield (entry 4). Both the regioisomeric 1-acetoxy-1phenyl-2-propene (7) and cinnamyl methyl carbonate (**4b**) also reacted with **5a** under the same conditions to give quantitative yields of **6a** in 1 second (entries 5 and 6). The microflow reaction of **4a** with sodium tetrakis(4-fluorophenyl)borate (**5b**) under similar conditions gave 1-(4-fluorophenyl)-3-phenyl-2propene (**6b**) in 94% yield (entry 7).

It is noteworthy that the methyl vinyl carbinol esters **8a** and **8b** underwent the palladium-catalyzed allyl–aryl coupling to give the corresponding coupling product **9** with excellent selectivity, though, under identical conditions, the chemical yield was moderate (33 and 57% yield, respectively). The reaction of methyl vinyl carbinol esters must proceed *via* the corresponding π -allylpalladium intermediate bearing a β -sp³-hydride which often suffers from β -elimination under the palladium-catalyzed conditions to give the undesired 1,3-dienes (Scheme 4).^{10,11}. 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 (*vs.* intramolecular β -elimination).

In conclusion, a variety of palladium membranes were installed inside microchannel reactors *via* the "ship-in-a-bottle" protocol of our molecular convolution method to provide micro-reaction devices. The μ -devices were applied to the instantaneous allyl–aryl coupling reaction of allylic esters with tetraarylborates to afford the corresponding coupling products in quantitative yields within 1 second of residence time. Extension of catalytic membrane-installed microchannel reactors to other organic transformations is currently in progress.

Notes and references

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