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Instantaneous Carbon−Carbon Bond Formation Using a Microchannel Reactor with a Catalytic Membrane

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Instantaneous catalytic molecular transformation is an important goal in chemical synthesis. Recently, microreactor systems offering many fundamental as well as practical advantages have been considered as innovative devices for chemical experimentation.[1−3] 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 because of the vast interfacial area and the close distance of the molecular diffusion path in the narrow space of the microreactors.[4,5] More recently, Kobayashi et al. developed a microchannel reactor bearing a palladium catalyst immobilized on the wall to realize highly efficient hydrogenation under triphase (solid (catalyst)−liquid (substrate solution)−gas (molecular hydrogen)) conditions.[6] Considering that the majority of chemical reactions are carried out by mixing two unique solutions of reactants, it is not surprising that the catalyst-immobilized microreactor for liquid−solid−liquid triphase reaction systems would be an eagerly awaited device. 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 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, where a catalytic cross-coupling reaction is depicted as a typical example. We report here the introduction of the polymer membrane of a palladium complex inside a microchannel reactor via a self-assembling complexation of a polymeric phosphine ligand and a palladium species at the interface of two parallel laminar layers flowing through the microchannel. Its use in the palladium-catalyzed carbon−carbon bond forming reactions of aryl halides and arylboronic acids under microflow conditions, where the instantaneous production of biaryl compounds was achieved quantitatively within 4 s of residence time in the defined channel region, is also discussed.

Polymer deposition at the laminar interface was originally reported by Whitesides et al. for the acid−base reaction of a polymeric sulfonate salt and a polymeric ammonium salt,[7] but, 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. The formation of the palladium-complex membrane, poly(acrylamide)−triarylphosphine−palladium (PA−TAP−Pd) (Figure 2a),[8] was carried out with a microchannel reactor[9] having a channel pattern of 100 μm width, 40 μm depth, 140 mm length, and a Y-junction (Figure 2 B). We charged the ethyl acetate solution of PA−TAP (5.0 mM; solution A) and the aqueous solution of $(NH_4)_2PdCl_4$ (1.7 mM; solution B) oppositely into the microchannel at 25 °C for 10 min with a flow rate of 5.0 μL/min. Two-phase parallel laminar flow was formed under the flowing conditions and a polymer membrane was precipitated at the interface between the two parallel flows. Parts C and D of Figure 2 show the microscopic images of the membrane of PA−TAP−Pd from the top and cross sections, respectively.[10]

Table 1. Suzuki−Miyaura Coupling Using the Microchannel Reactor Having a Catalytic Membrane.[a]

$$\mathrm{Ar\text{-}I} + \mathrm{Ar'\text{-}B(OH)_2} \longrightarrow \mathrm{Ar\text{-}Ar'}$$

entry	Ar	Ar′	yield (%) of Ar–Ar′
1[b]	C_6H_5	4-$MeOC_6H_4$	99[c]
2		3-MeC_6H_4	96
3		2-MeC_6H_4	99
4	3-$EtOCOC_6H_4$	4-$MeOC_6H_4$	99
5	3-ClC_6H_4		88
6	4-$CF_3C_6H_4$		99[cd]

[a] Aryl iodide (6.3 mM in $CH_3CO_2C_2H_5$/*i*-C_3H_7OH (2/5); flow rate: 2.5 μL/min), arylboronic acids (9.4 mM in 18.3 mM aq Na_2CO_3; flow rate: 5.0 μL/min), 50 °C, residence time = 4 s. [b] Aryl iodide (12.5 mM in *i*-C_3H_7OH), arylboronic acids (18.8 mM in 37.5 mM aq Na_2CO_3). [c] TOF = 600 h^{-1} [d] A total of 240 μg/h of the coupling product was isolated by use of 1 microreactor.

To explore the utility of the microchannel bearing the PA−TAP−Pd membrane in catalytic organic transformations, we preliminarily elected to study the palladium-catalyzed cross-coupling of aryl halides with arylboronic acids (the so-called Suzuki−Miyaura reaction).[11] Representative results are shown in Table 1. We were very pleased to find that the coupling reaction proceeded smoothly in the channel and was completed within only 4 s to give a quantitative yield of the desired biaryl product. Thus, a solution of aryl iodide in EtOAc/2-PrOH (6.3 mM; solution C)) and an aqueous solution arylboronic acid with Na_2CO_3 (9.4 mM; solution D) were oppositely introduced into the membrane-divided channels at 50 °C with a flow rate of 2.5 μL/min (for solution C) and 5.0 μL/min (for solution D), respectively, and two parallel laminar layers flowed to pass through the channel in 4 s.[12] The resulting organic/aqueous microstream was collected from the outlet of the channel to afford a quantitative yield of the corresponding biaryls (Table 1). The chemical yield and structure of the products were determined by GC[13] and ^{1}H NMR. Electron-deficient as well as electron-rich aryl halides readily coupled with arylboron reagents bearing para, meta, and ortho EWG- and EDG-substituents to give the corresponding biaryls in 88−99% yield. This coupling reaction includes two

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10.1021/ja066697r CCC: $33.50 © 2006 American Chemical Society

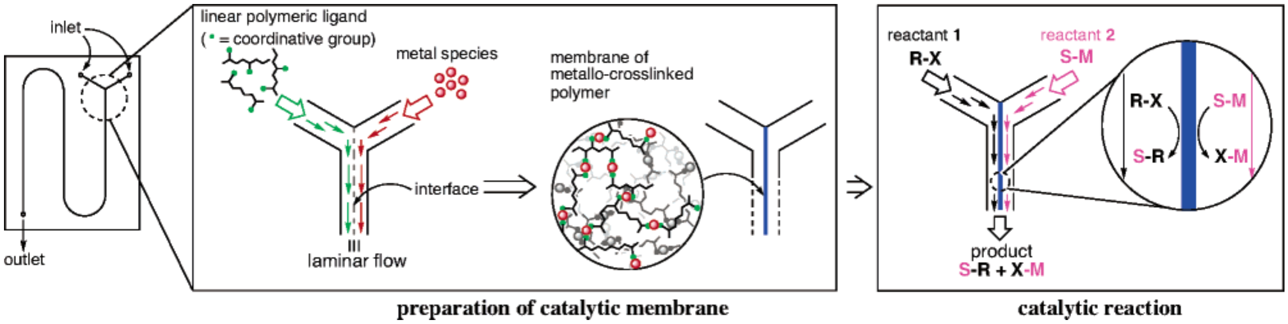

Figure 1. Concept of a microchannel-flow reaction system divided by a catalytic membrane.

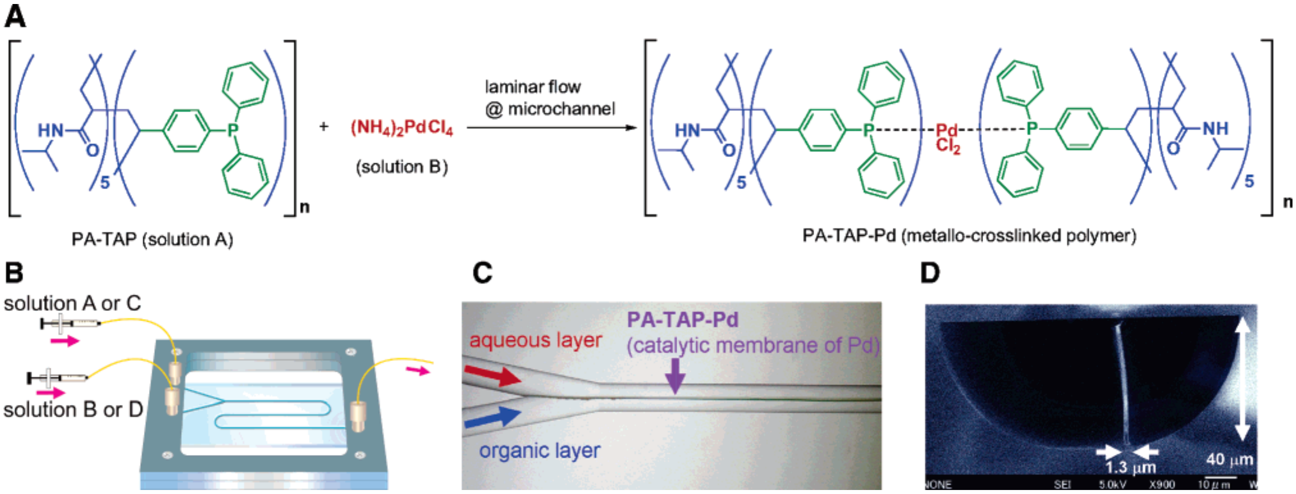

Figure 2. Formation of catalytic membrane inside a microchannel: (A) metallo-cross-linking formation of PA−TAP−Pd polymer; (B) reaction apparatus; (C) microscopic view of the membrane formation (top view); (D) microscopic (SEM) view of the membrane inside the channel (cross section).

intermolecular reaction steps—(i) oxidative addition forming the arylpalladium intermediate on the membrane and (ii) reaction of the arylboronic acid with the resulting arylpalladium intermediate to give the biaryl product—each of which has a unique reaction rate. By using this catalytic membrane-divided microchannel reactor, the fine optimization of the reaction conditions was made possible easily 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 involving multiple intermolecular steps offers a great advantage.

The microchannel reactor equipped with a catalytic membrane of a polymeric palladium complex should promote other palladium-catalyzed reactions. Furthermore, self-assembling formation of polymeric metal complexes is rapidly becoming an important protocol to provide polymeric catalysts.[14,15] The formation and use of a catalytic membrane inside a microchannel reactor should find widespread utility in a variety of catalytic organic transformations.

Acknowledgment. This work was supported by the CREST program, sponsored by the JST. We also thank the JSPS and the MEXT for partial financial support of this work.

Supporting Information Available: Experimental details and characterization data for the catalytic membrane and the cross-coupling reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA066697R