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Triphase Hydrogenation Reactions Utilizing Palladium-Immobilized Capillary Column Reactors and a Demonstration of Suitability for Large Scale Synthesis

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Abstract: We have developed a practical and highly productive system for hydrogenation reactions utilizing capillary column reactors, which occupy less space than ordinary batch systems, are low cost and easy to handle, and show feasibility toward large-scale chemical synthesis. Palladium-containing micelles were immobilized onto the inner surface of the capillaries. Nine palladium-immobilized capillaries were assembled and connected to a T-shaped connector, and hydrogen and a substrate solution were fed to capillaries *via* the connector. Hydrogenation of 1-phenyl-1-cyclohexene (**1**) proceeded smoothly to give phenylcyclohexane in quantitative yield. The capillaries themselves occupy only *ca.* 0.4 mL and a high space-time yield has been achieved (124.3 mg/17 min/0.4 mL). In addition, leaching of palladium was not detected by ICP analysis after reactions.

Keywords: capillary column reactors; heterogeneous catalysis; hydrogenation; immobilization; palladium; synthetic methods

Hydrogenation reactions are among the most fundamental and important transformations, and have been often used in synthetic organic chemistry.[1] In general, hydrogenation reactions can be divided into two types based on the phases involved; homogeneous systems and heterogeneous systems. In the latter cases, the solubility of hydrogen in the solvents employed is an especially important factor affecting the rate of the reaction. Furthermore, the interfacial area between gas (hydrogen), liquid (substrate and solvent), and solid (catalyst) plays a key role, an increased interfacial area can lead to higher reaction rates. We have recently reported hydrogenation reactions using a Pd-immobilized microchannel reactor,[2,3] which showed high efficiency by realizing a large interfacial area between the three phases. Inside the microchannel reactor, the gas phase (hydrogen) passes through the center of the narrow channel, while the liquid phase (the solution of substrates) flows along the surface of the channel where the Pd catalyst exists (pipe flow). The reactions were complete within 2 minutes affording the corresponding products quantitatively. Although the space-time yield[4] of the system was found to be much increased compared to those of the conventional reactors, actual "numbering up" [5] of the glass chips for a large-scale synthesis may still cause practical and spatial problems. Herein we report a more practical and highly productive system utilizing capillary column reactors,[6] which occupy less space, are low cost, and are easy to handle, and show feasibility towards practical large-scale chemical synthesis.

We selected a fused silica capillary (200 μm i.d., 40 cm length) instead of the previous microchannel system.[7] Immobilization of the Pd catalyst onto the inner surface of the capillary was conducted using the microencapsulation method and a related new method called the polymer-micelle-incarceration method (PMI method) which was recently developed in our laboratory.[3,8] First, amine groups were introduced onto the inner surface of the capillary. Microencapsulated Pd (MC Pd) was used as the Pd source, and the modified capillary was filled with the Pd colloidal solution and allowed to stand for 2 days. Finally the capillary was heated at 150 °C. This procedure was carried out several times. We found that 26.7 μg of the Pd catalyst were immobilized after this immobilization process (4 times). We then conducted the hydrogenation using the Pd-immobilized capillary thus obtained. First, one Pd-immobilized capillary was used for optimization of the reaction conditions. The system was assembled as shown in Figure 1. The Pd-immobilized capillary was connected using a T-shaped connector, to a syringe by a Teflon tube, and also connected to a hydrogen cylinder *via* a mass-flow controller by an SUS tube. The substrate solution was supplied by the syringe under the control of a syringe pump, and the

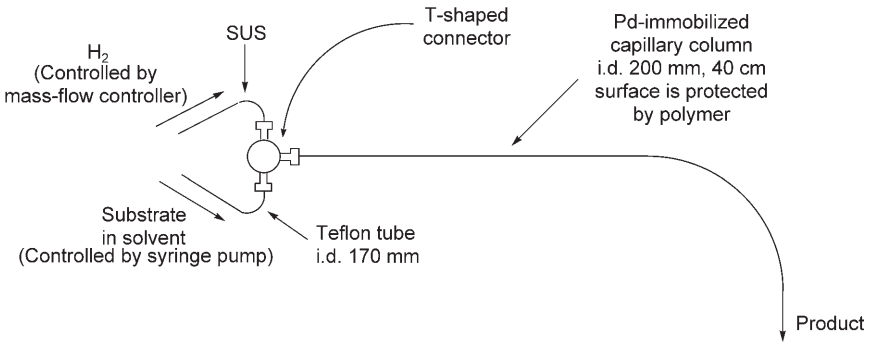


Figure 1. The system for the hydrogenation reaction using one Pd-immobilized capillary.

flow of hydrogen was controlled by a mass-flow controller. Hydrogenation reactions were carried out first under the standard condition (the substrate solution; 0.1 mol/L, 0.1 mL/h, hydrogen; 1 mL/min) using 1-phenylcyclohexene (**1**) as a substrate. Pipe flow (sometimes liquid ring flow)[9] was observed in this system giving the product in quantitative yield. Encouraged by this result, we further examined increased concentrations and flow rates of the substrate solution to realize better productivity. We were pleased to find that the reaction also proceeded quantitatively even when the concentration was increased up to *ca.* 0.8 mol/L and the flow rate of the liquid up to 0.4 mL/h. Under these conditions, *ca.* 32 times higher productivity has been realized (0.32 mmol/h). In addition, the TOF was calculated and found to be *ca.* 1300/h.

Next we examined the feasibility of a larger scale synthesis by using this system. For an initial trial, nine Pd-immobilized capillaries were assembled and connected to each other using ordinary 1/16 SUS connectors and a binding agent (Figure 2). The same system mentioned above was also used for this bundled capillary reactor, and the hydrogenation reaction of **1** was examined under the optimized conditions (the substrate solution; 0.1 mol/L, $0.1 \times 9 = 0.9$ mL/h, hydrogen; $1 \times 9 = 9$ mL/min) (Figure 3). Unfortunately, the liquid and the gas were not distributed uniformly to each line, and the yield was decreased to 89%. We then tried further immobilization of the Pd catalyst twice (totally six times) for each capillary and retried the reaction under the same conditions. In this case, although the distribution was still somewhat problematic, the reaction proceeded well to give the desired product in quantitative yield. We concluded that immobilization of catalyst could compensate for the loss of the uniformity of the flow mode. By using this system, productivity was increased *ca.* 280 times over that of the previous system (2.8 mmol/h, 124.3 mg of the product was obtained in 17 min) (Scheme 1). It should be noted that capillaries themselves occupy less space compared with the previous microchannel reactor (the actual volume of nine capillaries is around only 0.4 mL, and 0.11 mL if calculated based on the volume of the space inside capillaries), and that

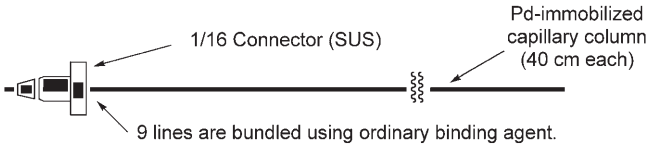


Figure 2. Assembled Pd-immobilized capillaries for larger scale synthesis.

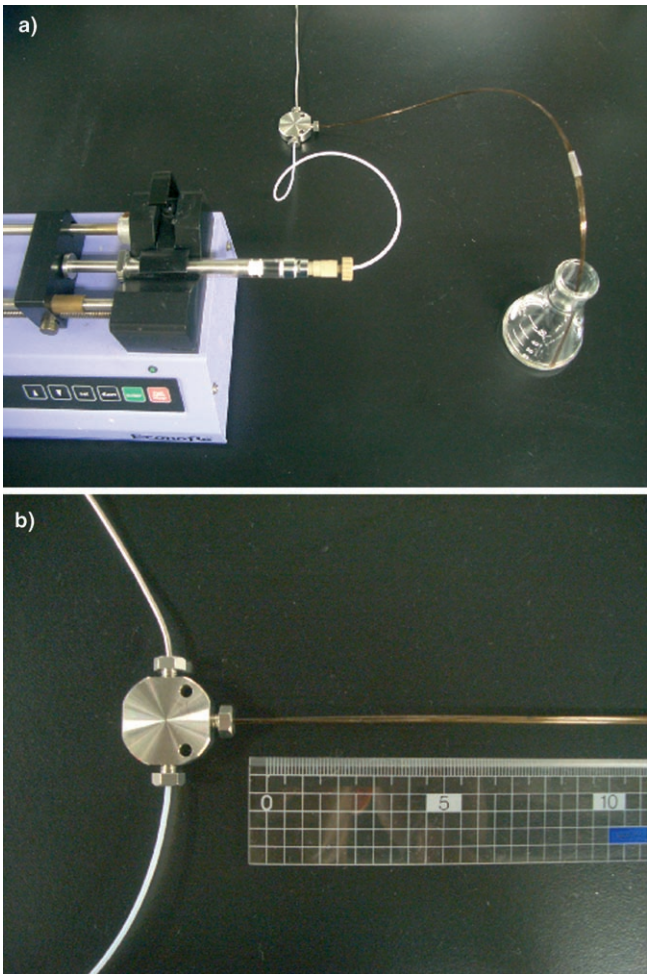
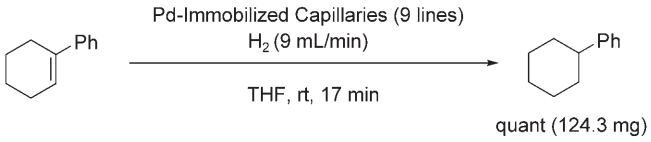


Figure 3. The appearance of the system using assembled Pd-immobilized capillaries for larger scale synthesis.



Scheme 1. Hydrogenation reaction using assembled Pd-immobilized capillaries.

quite high space-time yields have been achieved, which seems to be rather difficult to be realized in normal batch systems (17 mg/mL/min). In addition, significant Pd leaching was not detected by ICP analysis (<0.20 μg) and the reactor was reused several times without loss of activity.

In summary, we have developed a practical and highly productive system using a less space-consuming capillary reactor, and shown a promising result towards a large-scale chemical synthesis. Further improvement of this system towards a kilogram-scale synthesis as well as asymmetric catalysis is now in progress.

Experimental Section

General Methods

^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA300, JNM-LA400 or JNM-LA500 spectrometer in $CDCl_3$. Tetramethylsilane (TMS) served as an internal standard ($\delta=0$) for ^{1}H NMR, and $CDCl_3$ was used as an internal standard ($\delta=77.0$) for ^{13}C NMR. All solvents and chemicals were purified based on standard procedures.

Immobilization of the Pd Catalyst onto the Inner Surface of the Capillary

A fused capillary, T-shaped connector and other tools for connection were purchased from GL Sciences and JASCO. A capillary (200 μm i.d., 40 cm in length) was first treated with 1 N aqueous NaOH/ethanol (1/1, v/v), water, ethanol, and methanol successively to wash and activate the inner surface. A solution of 3-aminopropyltriethoxysilane in methanol (10%, 1.0 mL) was then added slowly to the capillary over 15 hours and the capillary was washed with methanol. Copolymer (styrene:2-[(2-phenylallyloxy)methyl]oxirane:tetraethylene glycol mono-2-phenyl-2-propenyl ether = 92:5:3) (10 mg) and tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$, 10 mg] were dissolved in dichloromethane (0.2 mL) and *t*-amyl alcohol (1.0 mL) at room temperature, and the mixture was stirred overnight at this temperature. The modified capillary was filled with the Pd solution and allowed to stand for 2 days at room temperature, and then flushed with air to remove the excess solution inside the capillary. The capillary was then heated at *ca.* 150 °C for 5 hours. This procedure (the addition of the polymer solution and heating) was carried out several times to give the desired Pd-immobilized capillary. After immobilization (4 times), the catalyst loading was determined by ICP analysis (Pd: 26.7 μg).

Preparation of the Assembled Pd-Immobilized Capillary

Nine Pd-immobilized capillaries were bundled using a compression screw (1/16 in, JASCO) and single ferrule (1/16 in, JASCO) and connected by a standard binding agent.

Hydrogenation using the Assembled Pd-Immobilized Capillary

The assembled Pd-immobilized capillaries, a syringe for feeding the substrate solution and a hydrogen cylinder were joined to each other using a three-way connector. The syringe and the connector were connected by a teflon tube, and an SUS tube was used for the connection between the hydrogen cylinder and the connector *via* a mass-flow controller. 1-Phenylcyclohexene in THF (0.8 mmol of substrate in 1 mL THF) was added using a syringe pump at a constant speed (3.6 mL/h), and hydrogen gas was fed *via* a mass-flow controller at a constant flow rate (9 mL/min). The reaction was conducted at room temperature and the reaction mixture was collected at the end of the capillaries. The reaction was stopped after 17 min and the solvent was removed under vacuum. The conversion was determined by ^{1}H NMR analysis and cyclohexylbenzene was obtained quantitatively (yield: 124.3 mg).

Acknowledgements

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