Hydrogenation reactions using $scCO_2$ as a solvent in microchannel reactors

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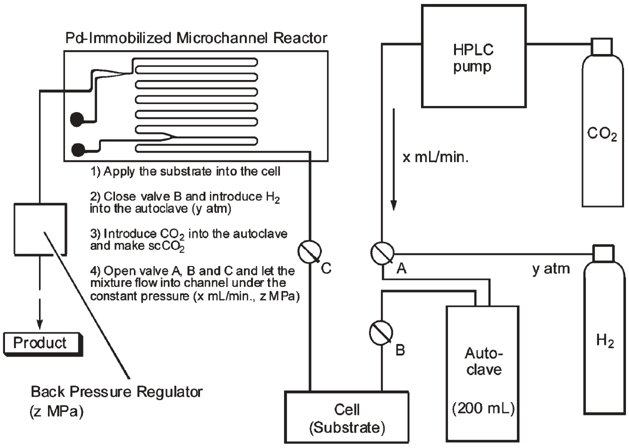
We have developed an effective microfluidic system for hydrogenation reactions in $scCO_2$; the reactions proceeded very rapidly (within 1 second), by making the best use of $scCO_2$ and utilizing the large specific interfacial area of the microchannel reactor, and high reaction productivity was attained in each channel.

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 especially, the solubility of hydrogen in solvents is an important factor for the reaction rate. Furthermore, the interfacial area between the gas (hydrogen), liquid (substrate and solvent), and solid (catalyst) plays a significant role, and an increased interfacial area can lead to a high reaction rate. We have recently reported hydrogenation reactions using a Pd-immobilized microchannel reactor,† which showed high efficiency by realizing a large interfacial area among the three phases.[2]

On the other hand, supercritical carbon dioxide ($scCO_2$) has attracted much interest as an ideal solvent because of its abundance, low cost, and non-toxicity. While $scCO_2$ has a liquid-like aspect, allowing dissolution of many organic compounds, it has also a gas-like aspect, retaining very high miscibility with other gases including hydrogen. Therefore, $scCO_2$ provides a quite effective environment for heterogeneous reactions using gas materials, and a variety of examples of hydrogenation reactions in $scCO_2$ have been reported.[3] We intended to use $scCO_2$ in hydrogenation reactions in microchannel reactors to increase productivity of the reaction in each channel. Herein we describe an effective and productive microfluidic system for hydrogenation reactions in $scCO_2$ using a Pd-immobilized microchannel reactor.

We selected a microchannel reactor having a channel 200 μm in width, 100 μm in depth, and 40 cm in length on a glass plate (3 cm × 7 cm). The Pd-immobilized microchannel reactor was prepared according to the method reported previously.[2] First, amino groups were introduced onto the surface of the glass channel. We used microencapsulated (MC) palladium[4] as the Pd source, and a solution of the MC Pd was passed through the microchannel reactor. It was then heated at 150 °C for 5 hours to bring about cross-linking of the polymer.[5] This sequence was repeated several times and finally the desired Pd-immobilized microchannel was successfully prepared. We determined the loading of palladium catalyst by ICP analysis and found that *ca.* 10 μg of palladium was introduced. We found that the catalyst covered the whole surface of the channel, making a thin layer. The overall system for hydrogenation reactions using $scCO_2$ is shown in Fig. 1. We connected a cell which was durable under high pressure, into which substrates were injected, to a 200 mL autoclave, used to make $scCO_2$ containing dissolved hydrogen. The pressure inside the channel was controlled by a back-pressure regulator which was positioned at the end of the microchannel reactor. A typical experimental method for conducting the reaction was as follows: first, the substrate was supplied into the cell which was kept at 50 °C. Hydrogen and CO_2 were entered successively into the autoclave kept at 50 °C, where $scCO_2$ containing dissolved hydrogen was prepared. Finally, this fluid was transferred *via* the cell into the channel, kept at *ca.* 60 °C, where the dissolved substrate was converted to the desired product. During the reaction, CO_2 was supplied continuously at a constant flow rate, and the product was collected at the exit of the back-pressure regulator.

We were pleased to find that a variety of substrates were converted to the desired products in nearly quantitative yields (Table 1). Terminal and *trans* olefins and triple bonds were reduced smoothly, and selective reduction of a triple bond was also conducted in the presence of a benzyloxy group. Surprisingly, the reaction time (mean residence time of the substrate inside the channel) was estimated to be *less than 1 second* in each case, and a quite efficient hydrogenation system has been achieved. It is assumed that inside the channel the substrate, hydrogen, and the catalyst can interact very effectively due to the large surface area of the catalyst. Moreover, it is noteworthy that the productivity of the system was much increased compared to that of our previous



1) Apply the substrate into the cell
2) Close valve B and introduce H_2 into the autoclave (y atm)
3) Introduce CO_2 into the autoclave and make $scCO_2$
4) Open valve A, B and C and let the mixture flow into channel under the constant pressure (x mL/min., z MPa)

Fig. 1 System for hydrogenation reactions.

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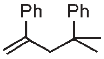
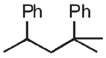
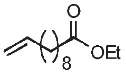
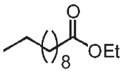
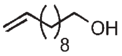
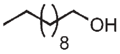
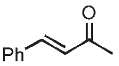
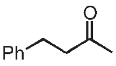
Table 1 Hydrogenation reaction

$$\text{Substrate (0.20 mmol)} \xrightarrow[\text{scCO}_2\text{ (z = 9 MPa), liq. CO}_2\text{; y = 1.0 mL/min. ca. 50 °C, (channel ; ca. 60 °C), 2 hrs}]{\text{Pd-Immobilized Microchannel Reactor, H}_2\text{ (x = 9 atm)}} \text{Product}$$

Run	Substrate	Product	Yield (%)[a]
1			94
2			96
3			Quant.
4			91
5			92[b]
6			91

[a] Isolated yield. [b] NMR yield.

triphase microfluidic system[2] (from 0.01 mmol h^{-1} per channel to 0.1 mmol h^{-1} per channel), presumably because the solubility of hydrogen was greatly increased by using $scCO_2$ as a solvent and mass transfer needed for the reactions occurred smoothly. In addition to the high reactivity, the system has several practical advantages. The microchannel reactor was reused several times without loss of activity. It would be possible to conduct scaled-up reactions by using a number of channels in parallel.[6]

In conclusion, we have developed an effective and productive microfluidic system for hydrogenation reactions using $scCO_2$ as a solvent.[7] To the best our knowledge, this is the first example of the synthetic application of microchannels using $scCO_2$ as a reaction medium.[8] The reactions proceeded within 1 second by making the best use of $scCO_2$ as a solvent and utilizing the large surface area of the catalyst. In addition, high reaction productivity was attained in each channel. Several practical advantages of this reaction should also be noted. Further improvement of this system toward applications to asymmetric catalysis and large-scale synthesis are now in progress.

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Notes and references

† The microchannel reactor is a device which has a very small channel (micrometre-sized in width and depth and centimetre- to metre-sized in length) in a glass plate.[9] A similar device is used mainly in the field of analytical chemistry.[10] One of the most important features of this device is a large specific interfacial area which rises to 10,000 ~ 50,000 $m^2\ m^{-3}$, as opposed to only 100 $m^2\ m^{-3}$ for conventional reactors used in chemical processes.[6]

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