Microreactors

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A Gold-Immobilized Microchannel Flow Reactor for Oxidation of Alcohols with Molecular Oxygen[**]

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Many advantages of continuous flow reactors have been previously discussed in the literature.[1] In particular, when the size of the pipe diameter is reduced, specific effects arise as a result of high specific interfacial surface area per unit volume. Recently, microchannel reactors with widths and depths in the micrometer dimension have also been applied in the field of synthetic chemistry.[2] Such reactors offer reaction environments with large interfacial areas between different phases, and thus efficiently promote liquid–liquid, gas–liquid, and gas–liquid–solid reactions.[3] Furthermore, they allow precise control of reaction variables, and ensure increased safety in conducting chemical reactions. We have recently developed a palladium-immobilized[4] microfluidic device to perform triphase hydrogenation reactions and found that the substrates were converted into the desired products quantitatively within two minutes.[5] Moreover, we have also reported hydrogenation reactions using supercritical carbon dioxide as a solvent[6] and utilized capillary column reactors[7] to increase productivity. We envisioned that the concept could be extended to the aerobic oxidation of alcohols with an appropriate immobilized metal catalyst.

The oxidation of alcohols to carbonyl compounds is among the most fundamental and important transformations in synthetic organic chemistry.[8] Typical oxidation methods, however, rely on the use of stoichiometric amounts of inorganic oxidants,[9] and thus lead to the generation of a large amount of chemical wastes. Heterogeneous catalytic systems that utilize molecular oxygen as an oxidant can overcome such drawbacks;[10] however, the gas–liquid–solid reactions involved often suffer from insufficient reactivity. The development of a novel method for accelerating such multiphase reactions is, therefore, a much sought-after goal.

Although several catalytic reactions using microchannel reactors have been reported, only a few examples that utilize metal-catalyzed aerobic oxidation of alcohols are known.[11] Herein, we describe a novel gold-immobilized microchannel reactor for the efficient catalytic oxidation of alcohols with molecular oxygen. We selected a polysiloxane-coated capillary column (50 cm length, 250 μm inner diameter), which contained 50% phenyl and 50% *n*-cyanopropyl functionalities on silicon atoms with a film thickness of 0.25 μm on the walls of the microchannel (Figure 1).

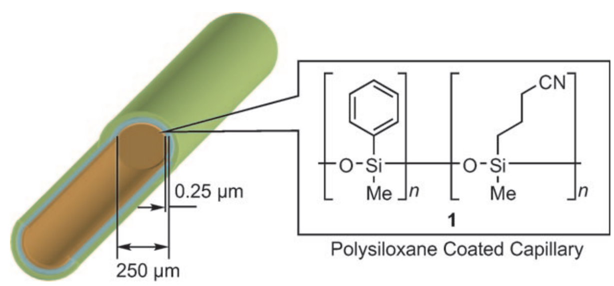
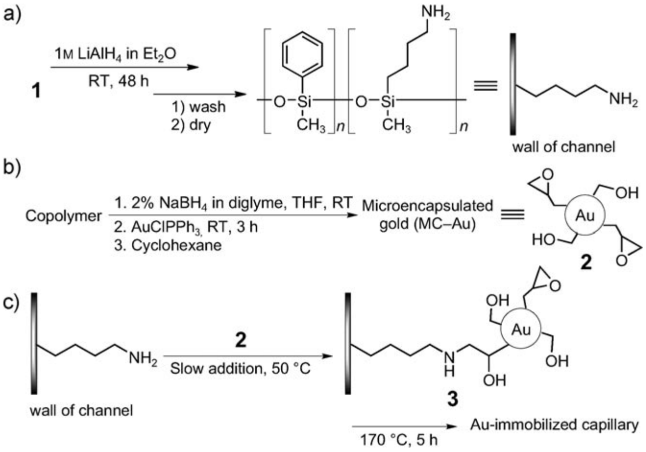


Figure 1. Polysiloxane-coated capillary column.

The preparation method of a gold-immobilized capillary column reactor is summarized in Scheme 1. At first the cyanopropyl groups were reduced to the corresponding primary amine group using lithium aluminum hydride ($LiAlH_4$; Scheme 1a). Microencapsulated gold (MC-Au) (**2**), prepared from chlorotriphenylphosphine gold ($AuClPPh_3$) and copolymer in THF solution, was used as a gold source for the immobilization (Scheme 1b).[12] A colloi-



Scheme 1. Immobilization of the gold catalyst. a) Reduction of the cyano group to an amine. b) Preparation of microencapsulated gold. c) Immobilization of the gold catalyst.

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dal solution of the MC-Au was then slowly pumped into the modified capillary column to form **3** and, finally, the capillary column was heated at 170 °C for 5 h. Cross-linking of the copolymer occurs during heating and results in the desired gold-immobilized capillary column.

The oxidation reaction system was assembled as shown in Figure 2. The gold-immobilized capillary column was attached to a T-shaped connector, which was connected to another T-shaped connector by a teflon tube. A gas cylinder containing oxygen was connected to the T-shaped connector to which the capillary column was attached. The flow of oxygen gas was controlled by a mass-flow controller, which was made of stainless-steel tubing (SUS tube). Solutions of the substrates in an organic solvent (1,2-dichloroethane) and aqueous potassium carbonate (K_2CO_3) were introduced using syringes under the control of two syringe pumps. The solutions containing the substrate and aqueous K_2CO_3 merged at the T-shaped connector before meeting the oxygen gas at the second T-shaped connector prior to their flow through the gold-immobilized capillary column.

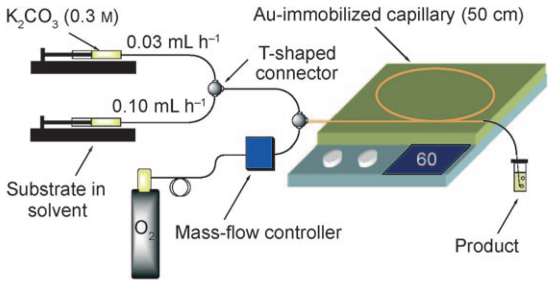

Figure 2. Experimental setup of the gold-catalyzed oxidation reactions.

The multiphase oxidation reactions were first carried out using 1-phenylethanol as substrate. After optimization of the reaction conditions, complete conversion of 1-phenylethanol was attained (Table 1). Changing the solvent from 1,2-dichloroethane to THF or α,α,α-trifluorotoluene did not improve the reactivity, and higher concentrations of substrate resulted in lower conversions. Increasing the flow rate of the aqueous K_2CO_3 solution or oxygen gas did not affect the conversion, whereas decreasing the flow rate of the substrate solution improved the conversion of 1-phenylethanol. It should be noted that a pipe-flow three-phase system could be created under these conditions,[5] and that the oxidation was more efficient than previous methods using microchannel reactors.[11]

Table 1: The standard conditions for multiphase oxidation reactions.

Inlet	Conditions
substrate in solvent	0.1 M in 1,2-dichloroethane, 0.1 mL h^{-1}
K_2CO_3 (aq)	0.3 M in water, 0.03 mL h^{-1}
O_2 (gas)	1.5 mL min^{-1}

The feasibility of the continuous flow capillary column reactor was also confirmed using the standard conditions, as shown in Table 1. It was found that 1-phenylethanol was converted into the corresponding ketone in excellent conversion without loss of activity: 99 % conversion was retained after 4 days and no leaching of gold was observed (Table 2).[13]

Table 2: Evaluation of the catalytic activity.[a]

t [h]	0–12	12–24	24–48	48–72	72–84	84–96
Conv. [%][b]	96	98	99	99	99	99

[a] 1-Phenylethanol as substrate. [b] Determined by GC analysis.

We also found that the system was stabilized after several hours because slightly lower conversion of the substrate was observed at the beginning of the reaction.

The scope of the aerobic oxidation of alcohols using the gold-immobilized capillary column reactor was studied using benzylic, aliphatic, allylic, and other alcohols (Table 3). In most cases, the alcohols were successfully oxidized to the corresponding ketones in excellent yields. The oxidation of benzyl alcohol led to a low yield of the expected aldehyde, although full conversion was observed (Table 3, entry 9). However, when we used a Au/Pd-immobilized capillary column reactor,[14,15] the desired aldehyde was obtained selectively in high yield (Table 3, entry 10). It is noteworthy that the capillary column reactor can accommodate the bimetallic Au/Pd system.

Table 3: Oxidation of alcohols using the gold-immobilized capillary column reactor.[a]

$$\underset{(0.1\ \text{mL h}^{-1})}{\underset{0.1\ \text{M}}{\text{Substrate}}} \xrightarrow[\substack{0.3\ \text{M}\ K_2CO_3\ \text{aq (0.9 equiv)}\\ \text{1,2-dichloroethane},\ T\ [^\circ\text{C}]}]{\substack{O_2\ (1.5\ \text{mL min}^{-1})\\ \text{Au-immobilized capillary column}}} \underset{\text{(ketone or aldehyde)}}{\text{Product}}$$

Entry	Substrate	T [°C]	Conv. [%][b]	Yield [%][b]
1	PhCH(OH)Me	60	> 99	99
2	p-MeOC$_6$H$_4$CH(OH)Me	60	> 99	99
3	p-FC$_6$H$_4$CH(OH)Me	60	> 99	99
4	p-ClC$_6$H$_4$CH(OH)Me	70	> 99	99
5	*trans*-PhCH=CHCH(OH)Me	70	> 99	99
6	2-thienyl-CH(OH)Me	60	> 99	99
7[c]	Ph(CH$_2$)$_2$CH(OH)Me	65	> 99	89
8	1-Indanol	60	> 99	99
9	PhCH$_2$OH	60	> 99	53
10[d]	PhCH$_2$OH	50	> 99	92
11[d]	p-MeC$_6$H$_4$CH$_2$OH	60	> 99	95

[a] Unless otherwise stated, the reactions were carried out as follows: substrates in dichloroethane (0.1 M, 0.1 mL h^{-1}), aqueous K_2CO_3 (0.3 M, 0.03 mL h^{-1}), and O_2 (1.5 mL min^{-1}). [b] Determined by GC analysis. [c] The reactions were carried out as follows: substrates (0.05 M) and aqueous K_2CO_3 (0.6 M). [d] Au/Pd-immobilized capillary column reactor was used instead of Au-immobilized capillary column reactor. 100% water was used instead of aqueous K_2CO_3.

In summary, we have developed a gold-immobilized capillary column reactor for the oxidation of alcohols with molecular oxygen. The oxidation of various alcohols proceeded easily to give the corresponding aldehydes and ketones in good to excellent yields. No leaching of gold was observed, and the gold-immobilized capillary column could be continuously used for at least four days without loss of activity. To the best our knowledge, this is the first example of a microreactor that allowed full conversion of alcohols by aerobic oxidation of alcohols in microchannels. Further investigations to apply this system to other transformations are in progress.

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[11] The catalytic systems previously reported were only applied to limited substrates due to gas-phase reactions under extremely high temperature (400 °C)[11a] or insufficient reactivity with deactivation of the catalyst:[11b] a) E. Cao, A. Gavriilidis, W. B. Motherwell, *Chem. Eng. Sci.* **2004**, *59*, 4803; b) E. Cao, W. B. Motherwell, A. Gavriilidis, *Chem. Eng. Technol.* **2006**, *29*, 1372.

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[13] The efficiency of this microflow system was confirmed by several comparative experiments. For example, we confirmed that the mean residence time of our system is 90 s. When we conducted the oxidation of 1-phenylethanol using the same catalyst in a batch system for 90 s, the yield was 1 %. On the other hand, when the same oxidation was conducted using Au/C in a batch system for 90 s, only a trace amount of the product ($<0.1\,\%$) was obtained. Furthermore, 'micro' dimension in this system is crucial. When a larger column (20 mm × 300 mm) was used, about 60 % yield was obtained in 60 min (mean residence time) in the aerobic oxidation of 1-phenylethanol. Although we do not have data for 90 s (mean residence time), the yield decreased to $<30\,\%$ in 30 min (mean residence time) in the larger flow system.

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[15] The results shown here also demonstrate that the present reactor can be prepared using other metal catalysts.