Microreactors

DOI: 10.1002/ange.201002490

# A Microchemical System with Continuous Recovery and Recirculation of Catalyst-Immobilized Magnetic Particles**

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Microfluidic systems have provided new concepts and challenging subjects for new chemical processes.[1] The advantages offered are increased surface area to volume ratio, rapid mass- and heat-transfer, enhanced process safety, simple feasibility study for scaling up, and reduced waste. The reaction variables in the confined microscale space can also be controlled in easy and precise ways. Furthermore, it is a challenge in the microfluidic community to develop sophisticated continuous flow systems such as micro-TAS (total analytical system) by integrating several consecutive processes of multistep reaction, separation/purification, and detection into a single-chip device.[2] For heterogeneous catalytic reactions, efforts have been made to take advantage of accelerated kinetics resulting from the shortened diffusion path of the reagents, little or no product contamination, and full resource utilization. Immobilizing catalysts on channel surfaces[3] and packing solid catalysts including mesoporous structures[4] have been attempted. However, the catalyst immobilization on the channel surface is hampered by many difficulties such as tricky immobilizing processes, the need for precise quantitative control of immobilized catalysts, and an inability to replace deactivated or poisoned catalysts. With packed catalyst systems, additional difficulties arise such as pressure drop control, low compatibility with a solid co-catalyst or product (or reactant), and clogging of the flow, which also applies to monolithic and porous silica capillary tube type microreactors as recently reported.[5]

Magnetic particles have recently been shown to be very useful for rapid and facile separation. In particular, magnetic particle embedded materials with various functions have been used for wide application in bioseparation, drug delivery, magnetic resonance imaging, and others.[6] Magnetic particles labeled with cells or proteins can be recovered or sorted in a microfluidic system by applying a magnetic field in the direction perpendicular to the solution flow.[7] Magnetic particle supported catalysts have also been used extensively for catalytic reactions. These supported catalysts particles are typically reclaimed and reused in batch reactions. In microreactors, these particles would be held on the microchannel walls with the magnetic field applied externally. Furthermore, an ideal microchemical system would be one in which the catalyst-immobilized magnetic particles in flowing fluid are continuously separated from the reacting stream in situ and then put into the fresh feed stream so that the catalyst particles can be recirculated and recycled continuously.

Herein, we present a microchemical system for continuous flow catalytic reactions with catalyst-immobilized magnetic particles. The system consists of a microfluidic chip type of microseparator and a capillary microtube reactor. In the separator, the product stream carrying the catalyst-immobilized magnetic particles flows coaxially along with the fresh reactant feed stream that is introduced to the separator. As shown in Figure 1b, the feed stream flows in the bottom half

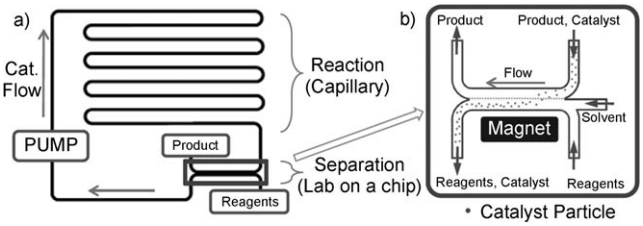


***Figure 1.*** a) Microchemical system consisting of a microseparator chip and a capillary microtube reactor, where magnetic catalyst particles are separated and recirculated. b) Magnetic particles in the product stream in the laminar flow regime move toward the magnet and join the feed stream.

of the microchannel and the magnetic particle carrying product stream flows in the top half. Almost no mixing and thus almost complete separation occurs as a result of laminar flow when the two streams are each led to the reactor for reaction and to the separator outlet to retrieve the product stream. The magnetic field applied to the bottom wall of the channel draws magnetic particles from the product stream to the reactant feed stream, thereby completing the separation of the catalyst particles from the product stream and the placement of the particles in the feed stream for catalyst recirculation and reuse. Although the concept is the same, a two-stage separation scheme had to be devised for efficient and complete separation of the particles (see movie in the Supporting Information). In addition, the capillary microtube facilitates a setup for microchemical reactions that require

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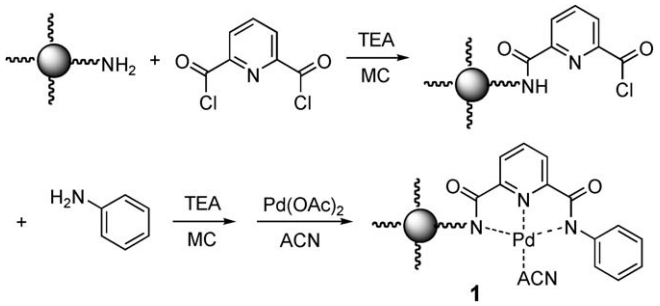
[**] This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (20100000722).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201002490.

high thermal and chemical resistance over an extended period.

The continuous, self-regulated microchemical system allows investigation of catalytic reactions in a way that has never been possible in microsystems. The automatic separation of catalyst particles and recirculation by the microchemical system makes it possible to fully realize the advantages a catalytic microreactor can offer. In addition, a significant reduction in the amount of catalyst used for a reaction can be realized. Furthermore, the microchemical system can be used repeatedly for many different reactions.

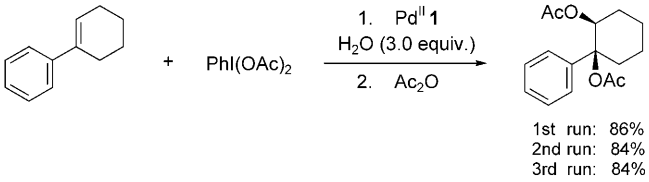
In the preparation of magnetic particles **1** supporting tridentate palladium complexes (Scheme 1),[8] commercially available magnetic particles having silica surfaces functionalized with primary amine group (average size: 1.99 μm, AccuBead, bioneer, Korea) were used. The silica coating of magnetic nanoparticle prevents direct contact of the magnetic core with reagents, which can lead to unwanted interactions. The molecular ligand was immobilized at the silica surface to use the active metal as a catalyst. Typically, the magnetic particles with amine groups were treated with pyridine-2,6-dicarbonyl dichloride in methylene chloride under $N_2$ atmosphere in the presence of excess triethylamine as a base at 40 °C. Subsequently, the terminal acyl group was blocked with aniline. The three nitrogen donors from two amides and one pyridine ring strongly bind the palladium center,[9] generating a tridentate Pd complex immobilized on the silica surface of the magnetic particle. The tridentate structure is intrinsically more stable than mono- or bidentate structures, which leads to a longer catalyst lifetime. There was no observable difference in the shape of the catalyst immobilized particles and the as-received particles, as seen in the SEM image (Figure 1 Sa in the Supporting Information). The amount of palladium measured by inductively coupled plasma atomic emission spectroscopy (ICP-AES) was 0.88 mg in a 100 mg particle (0.083 mmol $g^{-1}$). It should be noted that the same approach leads to immobilization of various molecular metal catalysts, including Cu, Ni, and Co.[10]




***Scheme 1.*** Immobilization of catalyst on silica surface of particles.

Dioxygenation of alkenes is an important reaction in organic chemistry,[11] for which osmium catalysts have been widely used.[12] The recent push for environmentally friendly processes and highly efficient methods has led to efforts to reduce the cost and to avoid toxicity of the catalysts.[13] Pd-catalyzed dioxygenation has led to interesting developments in the vicinal oxygenation of alkenes,[14] in connection with Pd-catalyzed vicinal oxidation including diamination and aminooxygenation based on the $Pd^{II}/Pd^{IV}$ catalyst cycle.[15] In this light, tridentate Pd catalyst **1** is expected to be a good candidate for the oxidation with its inherent long-term stability.

Testing for stable catalytic activity in the face of repeated use of the catalyst was performed in a conventional batch system with dioxygenation of alkene (Scheme 2). The Pd magnetic particle **1** maintained 84–86% yield without degradation of catalytic activity during three repeated dioxygenation reactions. The dispersed magnetic particles in solution were recovered by a NdFeB 35 permanent magnet (20 mm × 8 mm × 10 mm, magnetic field strength: 0.510 G at 1 mm distance) after each reaction.[6] After the third reaction, the amount of palladium on the magnetic particle measured with ICP-AES was 1.97 mg in 230 mg of particles (0.081 mmol $g^{-1}$), which is quite close to the original concentration (0.083 mmol $g^{-1}$). No apparent shape deformation was observed. This result demonstrates that the Pd magnetic particle **1** is robust and reliable as a catalyst for repeated use.




***Scheme 2.*** Stable catalytic activity of the Pd magnetic particles **1** in batch dioxygenation reaction. Standard reaction conditions: 1.65 mol% Pd magnetic particles **1**, DMF/AcOH (1:2), 50 °C, 5 h. Yields were measured by NMR spectroscopy against an internal standard.

Our initial microchemical system with Pd magnetic particle **1** was a PDMS (poly(dimethylsiloxane)) microreactor with a built-in separator for recovering the spent magnetic particles with no recirculation of the recovered particles (Figure 2). The reactor channel was 32 cm long, 300 μm wide, and 50 μm high. The magnetic particles in the red DMF

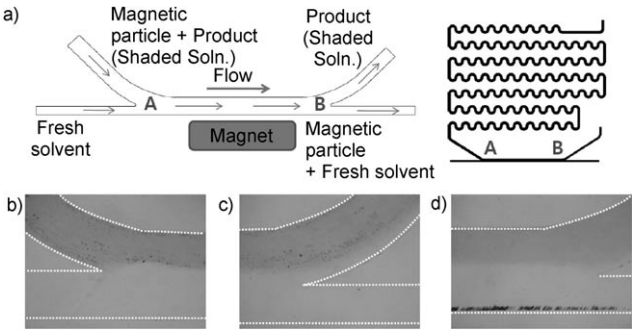



***Figure 2.*** a) Initial microfluidic separator design for continuous recovery of magnetic particle from product solution. b) Captured image at part A: shaded solution is the product solution and black dots are magnetic particles. Captured image at part B in the: c) absence and d) presence of a magnetic field.

solution moved with the laminar flow of the solution in the absence of a permanent magnet (Figure 2c). When a magnetic field was applied, the particles drifted toward the bottom wall (Figure 2d). The field strength was controlled by varying the distance between the channel and the magnet. Typically, 0.4 mol% of magnetic particles in the shaded solution was completely recovered under an external magnetic field of 0.13 G at 10 mm distance at a combined injection rate of the two inlet solutions of 4.5 μL min$^{-1}$ (fluid velocity of 30 cm min$^{-1}$ at the separation point). The yield of dioxygenation of styrene (0.2 mmol) in DMF/AcOH (1:2) at room temperature (3 equiv $H_2O$, 1.2 equiv $PhI(OAc)_2$) was only 21% owing to insufficient retention time (64 s). Furthermore, a lower injection rate or a larger amount of magnetic particles caused diffused mixing of two liquid flows or incomplete separation of the particles from the product solution.

A few lessons were learned with initial design. First, it is better to use a capillary microtube from PTFE (poly(tetrafluoroethylene)), rather than a microchannel engraved into PDMS, because the length of the reactor can be easily controlled with the PTFE tube and the material is much better than PDMS in terms of resistance to swelling and high temperature. Incomplete separation and recovery with the first design taught us that a two-stage separation scheme is needed and that building a recirculation system for the catalyst particles would be better served by fabricating a microfluidic chip type of separator on PDMS as shown in Figure 3. The microchemical system thus designed and

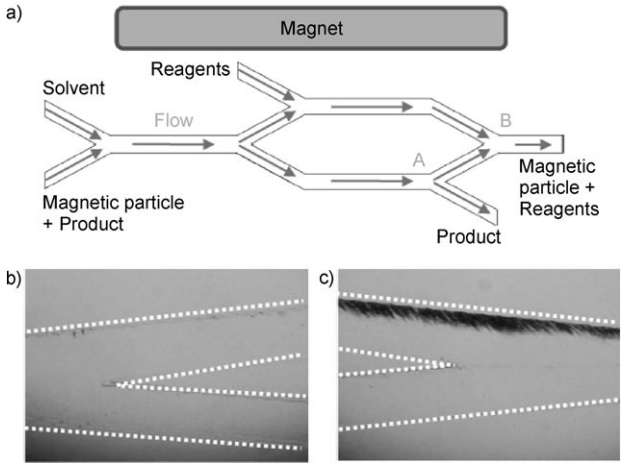
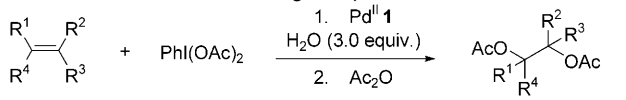


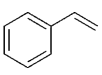
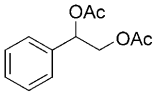
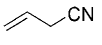
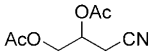
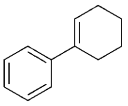
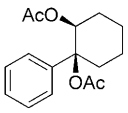
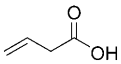
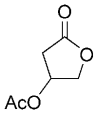

***Figure 3.*** a) Design for continuous recirculation of magnetic particles in the separator part of the microchemical system. Captured image at b) position A, and c) position B.

fabricated consists of a capillary microreactor and a microseparator (see Figure 2S in the Supporting Information). The microreactor was a 260 cm long PTFE tube with an inside diameter of 500 μm. In the separator part (300 μm × 50 μm × 20 mm), the product stream entraining the catalytic magnetic particles merges with the solvent stream, and the particles in the product stream move into the solvent stream as a result of the external magnetic field. Note that little if any mixing occurs between the two streams owing to the laminar nature of the flows. The solvent stream meets up with the reagent stream to feed the reactor with the particles entrained in the feed. Any particles not picked up by the solvent stream that are contained in the product stream are separated at point **A** in Figure 3a and collected into the feed stream at point **B** (see Figure 3b,c). A peristaltic pump continuously circulates the recovered catalyst particles (see movie in the Supporting Information). Note that the way in which the solvent stream is introduced to the separator ensures no mixing between the product stream and the feed stream. Typical operating conditions were a flow rate of 37 μL min$^{-1}$, and a magnetic field of 0.250 G created by placing a NdFeB 35 magnet (20 mm × 8 mm × 10 mm) 5 mm away from the wall with a total system volume of 525.0 μL (PTFE: 510.5 μL; pumping system: 6.3 μL; chip: 8.3 μL). The retention time can be controlled either by the length of the capillary tube or by the amount of catalyst particles.

Three intermolecular and one intramolecular dioxygenation reactions were carried out in the microchemical system (Table 1). The catalyst loading was 0.0037 mmol (3.5 mol%, 45 mg of Pd magnetic particles **1**), the total olefin in the microreactor was 0.105 mmol (0.2 M solution in 525 μL), and 1.2 equiv $PhI(OAc)_2$ was used. The performance of the microchemical system as revealed in Table 1 is excellent. Styrene (Table 1, entry 1) and but-3-enenitrile (Table 1, entry 2) converted into the corresponding dioxygenated products with yields (measured by NMR spectroscopy) of 83% and 89%, respectively, with 14 min retention time. Cyclohex-1-enyl-benzene (Table 1, entry 3) showed an 85% yield with *syn*-addition selectivity for an identical retention time (14 min) at 50°C, which is comparable to that of bulk reaction that could be realized in 5 h of reaction or retention time. In addition, we also tried internal cyclization of but-3-

***Table 1:*** Dioxygenation of alkenes in a microchemical system with continuous recirculation of Pd magnetic particles **1**.[a]




| Entry | Substrate | Product | *T* | Yield |
|---|---|---|---|---|
| 1 |  |  | RT | 83% |
| 2 |  |  | 40°C | 89% |
| 3 |  |  | 50°C | 85%[b] |
| 4 |  |  | 50°C | 84% |

[a] Standard reaction conditions: 3.5 mol% Pd magnetic particles **1**, DMF/AcOH (1:2), 1.2 equiv $PhI(OAc)_2$. Yields were measured by NMR spectroscopy against an internal standard. [b] 3.81 mmol product was formed after 10 h and was analyzed by NMR spectroscopy.

enoic acid to construct the lactone ring, which is an important building block for several natural products. The reaction gave an 84% yield at 50°C (Table 1, entry 4). The microchemical system with catalyst recirculation provides many advantages. It allows one to carry out different reactions in the same system by simply replacing the reagents after washing with fresh solvent for 30 min. No contamination problems were encountered. More importantly, it is also possible to replace the catalyst with fresh catalyst in this case, which is impossible with heterogeneous catalytic system.[3]

To test the robustness and stability of the catalyst activity and the separation efficiency of the magnetic particles over an extended period of time, two reactions (Table 1, entries 1 and 2) were carried out continuously for up to 10 h. It is satisfying that little deviation of the product yield was observed (Figure 4), indicating the excellent durability of catalyst. In addition, the product solution did not contain any black dots

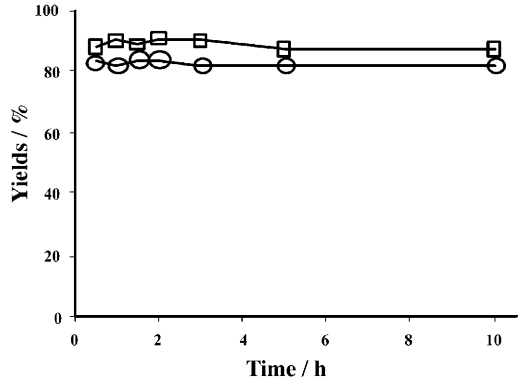



***Figure 4.*** Variation of product yields with reaction time; □: but-3-enenitrile; ○: styrene.

during the 10 h reaction, and no palladium was detected in the solution by ICP-AES. Although 3.5 mol% catalyst was used in the microchemical system as opposed to the 1.65 mol% used in the batch reactor, continuous recycling over 10 h corresponds to 42.9 {10 h × 60 (min h$^{-1}$)/14 min (retention time)} times the batch reaction and therefore the catalyst used per cycle is only 3.5/42.9 (= 0.08) mol%. The productivity comparison between the batch system and the microchemical system can also be made on the basis of the ratio mol-(product) mol(Pd)$^{-1}$ unit time$^{-1}$. In the dioxygenation of cyclohex-1-enyl-benzene (Table 1, entry 3), the three repeated batch systems for 15 h (time for a catalyst recovery was not included) gave 10.27 mmol(product) mmol(Pd)$^{-1}$ h$^{-1}$ {0.5 mmol × (0.86 + 0.84 + 0.84)/(0.5 mmol × 1.65 × 10$^{-2}$)/15 h}. However, the microchemical system for 10 h continuous running generated 102.97 mmol(product) mmol(Pd)$^{-1}$ h$^{-1}$ {3.81 mmol(product)/0.0037 mmol(Pd)/10 h}, which is 10 times the efficiency of the batch system.

In conclusion, we have developed a microchemical system for continuous flow catalytic reactions with catalyst-immobilized magnetic particles. The system consists of a microfluidic chip type of microseparator and a capillary microtube reactor. The separator cleanly separates the product stream from the fresh feed stream and completely recovers spent catalyst particles for them to be recirculated. The continuous, self-regulated microchemical system allows one to investigate catalytic reactions in a way that has never been possible in microsystems. The automatic separation of catalyst particles and recirculation by the microchemical system makes it possible to realize fully the advantages a catalytic microreactor can offer. In addition, a significant reduction in the amount of catalyst used for a reaction can be realized. As illustrated with dioxygenation reactions, only 10% of the catalyst needed for batch reaction is required for the microchemical system. Furthermore, the microchemical system can be used repeatedly for many different reactions with subsequent solvent cleaning. The microchemical system could be applied to various well-known organic chemical processes, and new chemistry could also be tried with the aid of already reported or new magnetic catalyst.

## *Experimental Section*

General description of the dioxygenation in the batch system: To the solution of olefin (0.5 mmol) and Pd magnetic particles **1** (100 mg; 1.65 mol%) in 2.5 mL AcOH/DMF (2:1 by weight), $H_2O$ (1.5 mmol) and $PhI(OAc)_2$ (1.2 equiv; 177 mg) were added. The resulting mixture was stirred for 5 h, and the Pd magnetic particles **1** was separated by a NdFeB 35 permanent magnet. $Ac_2O$ (2 equiv) was added to the solution, and the resultant mixture was stirred overnight at room temperature. After the solvent was removed under reduced pressure, the yield was measured by $^1$H NMR spectroscopy against an internal standard.

General description of the dioxygenation in microfluidic system using the circulation of Pd magnetic particles **1**: The slurry of Pd magnetic particles **1** was introduced into the microreactor by the refill operation of a syringe pump. The total amount of loaded magnetic particle was 45 mg. A peristaltic pump with marprene tube (inside diamter: 250 μm, Watson-Marlow) was used to circulate the solution in the microreactor at a flow rate of 37 μL min$^{-1}$. The fresh solvent and reagents (0.3 M) were introduced at an injection rate of 23.5 μL min$^{-1}$. The total retention time in the microreactor was 14 min. The product separated from the system and was collected. $Ac_2O$ (2 equiv) was added to the collected solution, and the resultant mixture was stirred overnight at room temperature. After the solvent was removed under reduced pressure, the yield was measured by NMR spectroscopy against an internal standard.

Received: April 26, 2010
Revised: May 27, 2010
Published online: August 16, 2010

**Keywords:** heterogeneous catalysis · magnetic particles · microreactors · oxygenation

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