MICROCHEMICAL SYSTEM WITH CONTINUOUS RECOVERY AND RECIRCULATION OF CATALYST-IMMOBILIZED MAGNETIC PARTICLES

Chan Pil Park and Dong-Pyo Kim[*]

National Creative Research Center of Applied Microfluidic Chemistry, Chungnam National University, KOREA

ABSTRACT

A microchemical system for continuous flow catalytic reactions with magnetic catalyst is presented. 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. It would be applicable to various catalytic reactions with aid of already reported magnetic catalyst or new magnetic catalyst.

KEYWORDS: Microreactor, Magnetic particle, Microchemical reaction, Heterogeneous catalyst, Catalyst recycle

INTRODUCTION

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 much reduced waste. The reaction variables in the confined micro-scale 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 multi-step 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 due to shortened diffusion length of reagent, and little or no product contamination, and full resource utilization. Immobilizing catalysts on channel surface[3] and packing solid catalysts including mesoporous structures[4] have been attempted. However, the catalyst-immobilizing on 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 and additional difficulties arise such as pressure drop control, low compatibility with a solid co-catalyst or/and product (or reactant) due to clogging of flow, which also applies to monolithic and porous silica capillary tube type of microreactor as recently reported

EXPERIMENTAL

The slurry of Pd-magnetic particles **1** was introduced into microreactor by the refill operation of a syringe pump, the total amount of loaded magnetic particle was 45 mg. For the circulation of solution with 37 μL/min flow rate in the microreactor, a peristaltic pump with marprene tube (id: 250 μm, Watson-Marlow) was adjusted. The fresh solvent and reagents (0.3 M) were introduced at 23.5 μL/min injection rate. The total retention time in the microreactor was 14 min. The product separated from the system was collected. 2 equiv. Ac_2O was added to the collected solution, and the resultant mixture was stirred overnight at room temperature. After removing solvent under reduced pressure, the NMR yield was recorded using an internal standard.

RESULTS AND DISCUSSION

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, MRI, and others.[6] The magnetic particles labelled with cells or proteins can be recovered or sorted in microfluidic system by applying 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.

In this report, 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 Fig. 1b, the feed stream flows in the bottom half of the microchannel and the magnetic particle carrying product stream flows in the top half. Almost no mixing and thus almost complete separation occurs due to 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. In addition, the capillary microtube facilitates a set-up for microchemical reactions required with high thermal and chemical resistance during 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. Furthermore, a significant reduction in the amount of catalyst used for a reaction can be realized, the microchemical system can be used repeatedly for many different reactions.

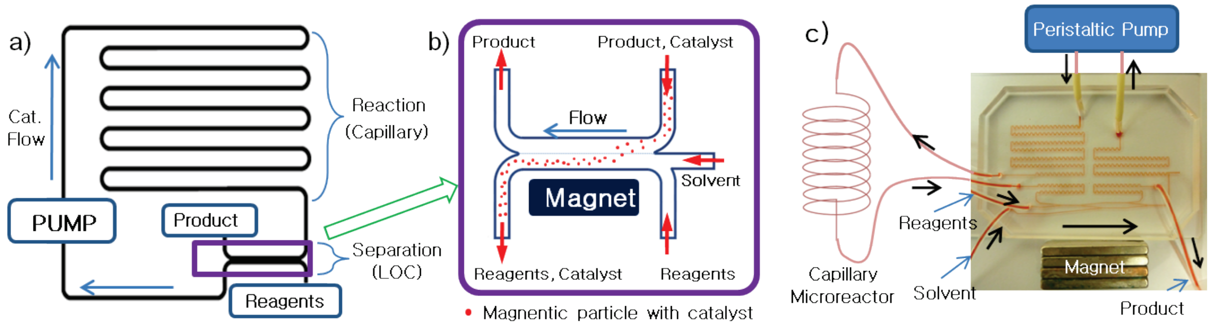

Figure 1. a) Scheme of a microchemical system. b) Magnetic particles in the product stream move toward the magnet and join the feed stream. (c) Overall system.

Our initial microchemical system with magnetic particle was a PDMS (poly(dimethylsiloxane)) microreactor with a built-in separator for recovering the spent magnetic particles with no recirculation of the recovered particles. The reactor channel was 32 cm long, 300 μm wide, and 50 μm high. However the system gave insufficient retention time (64 sec), a lower injection rate or a larger amount of magnetic particles caused a diffused mixing of two liquid flows or an 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 of PTFE (poly(tetrafluoroethylene)), rather than a microchannel engraved into PDMS simply because the length of the reactor can easily be 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 Fig. 2a. The microchemical system thus designed and fabricated consists of a capillary microreactor and a microseparator. The microreactor was simply 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 due to the external magnetic field. Note that there is little if any mixing occurs between the two streams due to the laminar nature of the flows. The solvent stream meets up with the reagent stream, thereby constituting the feed to 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 the figure and collected into the feed stream at point **B** (see Fig. 2b and 2c). A peristaltic pump continuously circulates the recovered catalyst particles. Note that the way the solvent stream is introduced to the separator ensures no mixing between the product stream and the feed stream. Typical operating conditions were 37 μL/min of flow rate, and 0.250 G of magnetic field by placing 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.

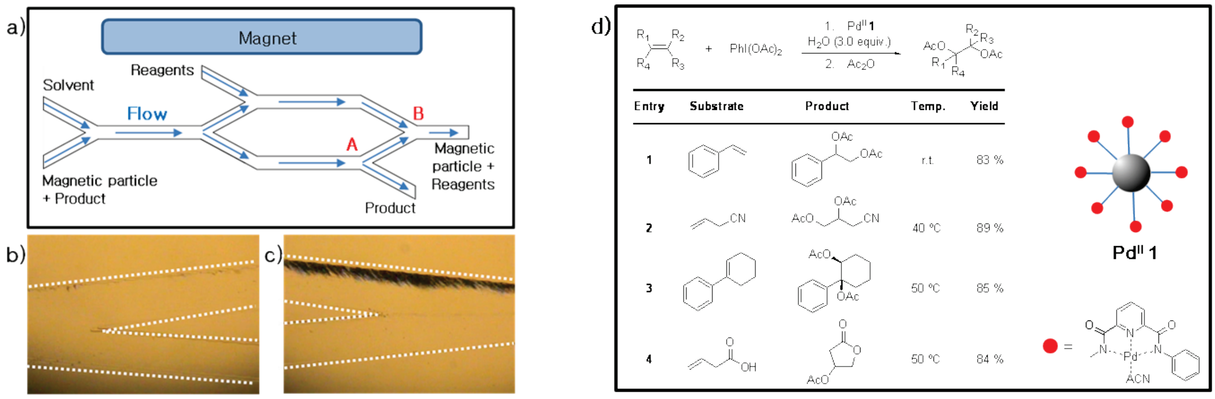

*Figure 2. a) Recirculation of magnetic particles in the separator part. Captured image at b) position **A**, and c) position **B**. d) Dioxygenation of alkenes in microchemical system with continuous recirculation of Pd-magnetic particles **1**.*

Dioxygenation of alkenes is an important reaction in organic chemistry,[8] for which osmium catalysts have widely been used.[9] 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.[10] Pd-catalyzed dioxygenation has led to interesting developments in the vicinal oxygenation of alkenes.[11] In this light, tridentate Pd catalyst **1** is expected to be a good candidate for the oxidation with its inherent long-term stability. Three intermolecular dioxygenations were carried out in the microchemical system, as summarized in Figure 2d. 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 Figure 2d is excellent. Styrene (Entry 1) and but-3-enenitrile (Entry 2) converted to the corresponding dioxygenated products with NMR yields of 83% and 89%, respectively, with 14 min retention time. Cyclohex-1-enyl-benzene (Entry 3) showed an 85% yield with *syn*-addition selectivity for the identical retention time (14 min) at 50 ^{o}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-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 ^{o}C. The microchemical system with catalyst recirculation provides many advantages. It allows one to carry out different reactions in the same system simply by 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 (Entry 1, 2) were carried out continuously for up to 10 h. It is satisfying that only little deviation of the product yield was observed, indicating the excellent durability of catalyst. In addition, the product solution did not contain any black dots during the 10 h reaction, and no palladium in the solution was detected as evidenced by ICP-AES. Although 3.5 mol % catalyst was used in the microchemical system as opposed to 1.65 mol % used in the batch reactor, continuous recycling of 10 h corresponds to 42.9 {10 h × 60 (min/h)/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 mol(product)/mol(Pd)/ per unit time basis. In the dioxygenation of cyclohex-1-enyl-benzene (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)/h {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)/h {3.81 mmol(product)/0.0037 mmol(Pd)/10 h}, which is 10 times efficiency of the batch system.

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.

ACKNOWLEDGEMENTS

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

REFERENCES

[1] a) T. Fukuyama, M. T. Rahman, M. Sato, I. Ryu, *Synlett* **2008**, 151-163; b) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300-2318.
[2] G. M. Whitesides, *Nature*, **2006**, *442*, 368-373.
[3] G. Shore, S. Morin, D. Mallik, M. G. Organ, *Chem. Eur. J.* **2008,** *14,* 1351-1356.
[4] G. H. Seong, R. M. Crooks, *J. Am. Chem. Soc.* **2003**, *124*, 13360-13361.
[5] A. El Kadib, R. Chimenton, A. Sachse, F. Fajula, A. Galarneau, B. Coq, *Angew. Chem. Int. Ed.* **2009**, *48*, 4969-4972.
[6] J. R. Weissleder, K. Kelly, E. Y. Sun, T. Schtatland, l. Josephson, *Nat. Biotechnol.* **2005**, *23*, 1418-1423.
[7] M. A. M. Gijs, F. Lacharme, U. Lehmann, *Chem. Rev.* **2010**, *110,* 1518-1563.
[8] J. L. Bolliger, O. Blacque, C. M. Frech, *Angew. Chem. Int. Ed.* **2007**, *46*, 6514-6517.
[9] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483-2547.
[10] J. Piera, J-E. Bäckvall, *Angew. Chem. Int. ed.* **2008**, *47*, 3506-3523.
[11] a) Y. Li, D. Song, V. M. Dong, *J. Am. Chem. Soc.* **2008**, *130*, 2962-2964; b) C. P. Park, J. H. Lee, K. S. Yoo, K. W. Jung, *Org. Lett.* **2010**, *12*, 2450-2452.