Organic Process Research & Development **2005**, *9*, 787−791

Grignard Exchange Reaction Using a Microflow System: From Bench to Pilot Plant

Hideo Wakami[†] and Jun-ichi Yoshida*[,‡]

The Research Association of Micro Chemical Process Technology (MCPT) and Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan

Abstract:

The Grignard exchange reaction of ethylmagnesium bromide (EtMgBr) and bromopentafluorobenzene (BPFB) to give pentafluorophenylmagnesium bromide (PFPMgBr) was carried out using small- and medium-scale microflow systems consisting of a micromixer and a microheat exchanger. The results indicate that the microflow systems are quite effective. On the basis of the data obtained, a pilot that involves the Toray Hi-mixer connected to a shell and tube microheat exchanger was constructed. Continuous operation for 24 h was accomplished without any problem to obtain pentafluorobenzene (PFB) after protonation (92% yield).

1. Introduction

Grignard reagents are useful reagents in organic syntheses and are widely utilized in laboratory syntheses[1] and industrial production of fine chemicals.[2] Although Grignard reagents are usually prepared by the reaction of organic halides with magnesium metal, Grignard exchange reactions (halogen−magnesium exchange reactions) are sometimes used for Grignard reagents that are difficult to prepare by the direct method.[3] Because Grignard exchange reactions are usually very fast and highly exothermic, they are difficult to control, especially in large-scale syntheses. Usually, slow addition has been used to avoid rapid temperature increase. Therefore, efficient heat removal has been a crucial point for industrial applications of this useful reaction.

Recently, microflow systems have been utilized for chemical reactions because they are expected to make a revolutionary change in chemical synthesis from the viewpoint of not only laboratory synthesis but also industrial production.[4−6] Characteristic features of microflow systems involve extremely fast mixing by virtue of short diffusion path and efficient heat transfer owing to high surface-to-volume ratio. These features are quite advantageous for conducting extremely fast and highly exothermic reactions. In some cases, product selectively can be enhanced signficantly by the use of microflow systems.[7] Easy numbering-up of microsystems for increasing the amount of production are also beneficial from the viewpoint of industrial production.[8]

Thus, we envisioned that the use of a microflow system solves the problem associated with the application of Grignard exchange reactions to industrial production. Herein, we report the results of our study on the Grignard exchange reaction using microflow systems.

We focused on the reaction of ethylmagnesium bromide with bromopentafluorobenzene (BPFB) to give pentafluorophenylmagnesium bromide (PFPMgBr) (Scheme 1).[9] PFPMgBr has been produced by this method in industry, because it is difficult to prepare by the direct method using

* Author for correspondence. E-mail: yoshida@sbchem.kyoto-u.ac.jp.
† MCPT. Present Address: Nippon Shokubai.
‡ Department of Synthetic Chemistry and Biological Chemistry.

(1) For example: Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*; Prentice Hall: New York, 1954.

(2) For example: Banno, T.; Hayakawa, Y.; Umeno, M. *J. Organomet. Chem.* **2002**, *653*, 288.

(3) For example: Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.

(4) (a) Ehrfeld, W., Ed. *Microreaction Technology*; Springer: Berlin, 1998. (b) Ehrfeld, W.; Hessel, V.; Löwe, H. *Microreactors*; Wiley-VCH: Weinheim, 2000. (c) Manz, A., Becker, H., Eds. *Microsystem Technology in Chemistry and Life Sciences*; Springer, Berlin, 1999. (d) Jensen, K. F. *Chem. Eng. Sci*. **2001**, *56*, 293. (e) Hessel, V.; Hardt, S.; Löwe, H. *Chemical Micro Process* Engineering; Wiley-VCH: Weinheim, 2004.

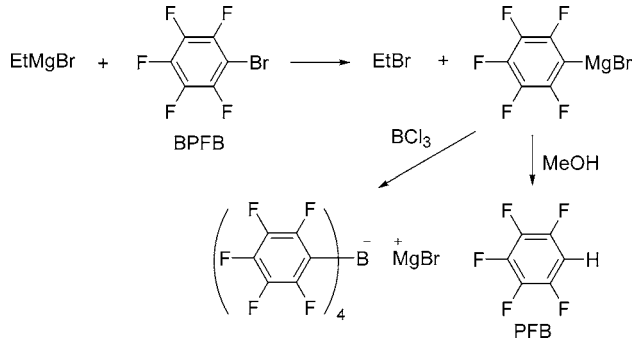
(5) Organic synthesis: e.g., (a) Salimi-Moosavi, H.; Tang, T.; Harrison, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 8716. (b) Chambers, R. D.; Spink, R. C. H. *Chem. Commun.* **1999**, 883. (c) de Bellefon, C.; Tanchoux, N.; Caravieilhes, S.; Grenouillet, P.; Hessel, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 3442. (d) Suga, S.; Okajima, M.; Fujiwara, K.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 7941. (e) Yoshida, J.; Suga, S. *Chem. Eur. J.* **2002**, *8*, 2650. (f) Watts, P.; Wiles, C.; Haswell, S. J.; Pombo-Villar, E.; Styring, P. *Chem. Commun.* **2001**, 990. (g) Hisamoto, H.; Saito, T.; Tokeshi, M.; Hibara, A.; Kitamori, T. *Chem. Commun.* **2001**, 2662. (h) Sands, M.; Haswell, S. J.; Kelly, S. M.; Skelton, V.; Morgan, D. O.; Styring, P.; Warrington, B. *Lab Chip* **2001**, *1*, 64. (i) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Lab Chip* **2001**, *1*, 100. (j) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Chem. Commun*. **2002**, 1034. (k) Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett*. **2002**, *4*, 1691. (l) Ueno, M.; Hisamoto, H.; Kitamori, T.; Kobayashi, S. *Chem. Commun.* **2003**, 936. (m) Garcia-Egido, E.; Spikmans, V.; Wong, S. Y. F.; Warrington, B. H. *Lab Chip* **2003**, *3*, 73. (n) Lai, S. M.; Martin-Aranda, R.; Yeung, K. L. *Chem. Commun.* **2003**, 218. (o) Mikami, K.; Yamanaka, M.; Islam, M. N.; Kudo, K.; Seino, N.; Shinoda, M. *Tetrahedron Lett.* **2003**, *44*, 7545. (p) Kobayashi, J.; Mori, Y.; Okamoto, K.; Akiyama, R.; Ueno, M.; Kitamori, T.; Kobayashi, S. *Science* **2004**, *304*, 1305. (q) Wu, T.; Mei, Y.; Cabral, J. T.; Xu, C.; Beers, K. L. *J. Am. Chem. Soc*. **2004**, *126*, 9880. (r) Nagaki, A.; Kawamura, K.; Suga, S.; Ando, T.; Sawamoto, M.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 14702. (s) Horcajada, R.; Okajima, M.; Suga, S.; Yoshida, J. *Chem. Commun.* **2005**, 1303. (t) Yoswathananont, N.; Nitta, K.; Nishiuchi, Y.; Sato, M. *Chem. Commun*. **2005**, 40.

(6) Reviews: e.g., (a) DeWitt, S. H. *Curr. Opin. Chem. Biol.* **1999**, *3*, 350. (b) Okamoto, H. *J. Synth. Org. Chem., Jpn.* **1999**, *57*, 805. (c) Sugawara, T. *Pharmacia* **2000**, *36*, 34. (d) Wörz, O.; Jäckel, K. P.; Richter, Th.; Wolf, A. *Chem. Eng. Sci.* **2001**, *56*, 1029. (e) Haswell, S. J.; Middleton, R. J.; O'Sullivan, B.; Skelton, V.; Watts, P.; Styring, P. *Chem. Commun*. **2001**, 391. (f) de Mello, A.; Wootton, R. *Lab Chip* **2002**, *2*, 7N. (g) Fletcher, P. D. I.; Haswell, S. J.; Pombo-Villar, E.; Warrington, B. H.; Watts, P.; Wong, S. Y. F.; Zhang, X. *Tetrahedron* **2002**, *58*, 4735. (h) Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 406. (i) Hessel, V.; Löwe, H. *Chem. Eng. Technol*. **2005**, *28*, 267. (j) Watts, P.; Haswell, S. J. *Chem. Eng. Technol.* **2005**, *28*, 290.

(7) It is reported that the product distribution of competitive reactions can be influenced by the effectiveness of micromixing: (a) Ehrfeld, W.; Golbig, K.; Hessel, V.; Löwe, H.; Richter, T. *Ind. Eng. Chem. Res*. **1999**, *38*, 1075. (b) Suga, S.; Nagaki, A.; Yoshida, J. *Chem. Commun.* **2003**, 354. (c) Suga, S.; Nagaki, A.; Tsutsui, Y.; Yoshida, J. *Org. Lett.* **2003**, *5*, 945. (d) Yoshida, J.; Nagaki, A.; Iwasaki, T.; Suga, S. *Chem. Eng. Technol*. **2005**, *28*, 259. (e) Nagaki, A.; Togai, M.; Suga, S.; Aoki, N.; Mae, K.; Yoshida, J. *J. Am. Chem. Soc*. **2005**, *127*, 11666.

10.1021/op0501500 CCC: $30.25
Published on Web 10/01/2005

Scheme 1



magnesium metal. The formation of PFPMgBr was confirmed by the protonation with methanol to give pentafluorobenzene (PFB). Industrially, PFPMgBr has been used for the reaction with BCl_3 to give tetrakis(pentaflurophenyl)-borate, derivatives of which are utilized in metallocene-catalyzed polymerization and photopolymerization.

2. Experimental Section

Grignard Reagent. A solution of ethylmagnesium bromide (EtMgBr) in dibutyl ether was prepared by the reaction of bromoethane (38.73 g, 0.355 mol) and magnesium turnings (9.38 g, 0.389 mol) in dibutyl ether (180 g) at 20 °C. The concentration of EtMgBr was determined as 1.3 M by the acid/base titration.

GC Analysis. The yield of the product was determined by GC analysis with Shimadu GC-17A equipped with a DB-WAX clolumn (L 30 m × i.d. 0.53 mm × T 1.00 μm) using ethyleneglycol diethyl ether as an internal standard.

Small-Scale Reaction System. The small-scale reactions were carried out using a microflow system consisting of two syringe pumps, a micromixer, and a microtube heat exchanger. A schematic diagram of the system is shown in Figure 1. A solution of EtMgBr (1.3 M, flow rate: 0.038−1.233 mL/min) and BPFB (neat, 8.0 M, flow rate: 0.006−0.202 mL/min) were introduced to a micromixer by syringe pumping, and the resulting solution was introduced to a

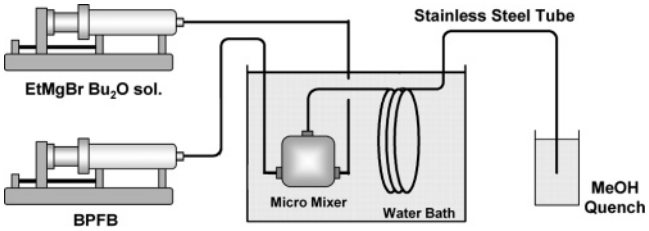


Figure 1. **Schematic diagram of the small-scale reaction system.**

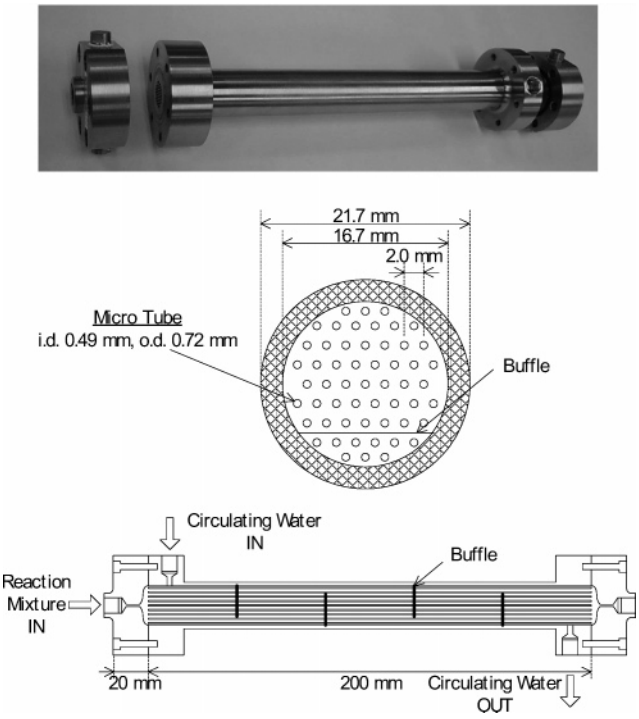


Figure 2. **Shell and tube microheat exchanger.**

microtube heat exchanger. The micromixer and the microtube heat exchanger were dipped in a water bath, the temperature of which was maintained at 20 °C. As a micromixer, a T-shaped mixer (i.d. 800 μm) and an IMM single mixer (ver. 2, channel width 40 μm) were examined. As a heat exchanger, three microtubes of different diameter (i.d. 250 μm × 1.8 m, i.d. 500 μm × 3.6 m, i.d. 1000 μm × 0.9 m) were examined. The reaction was quenched by the addition of an excess amount of methanol to the reaction mixture at the outlet of the microtube heat exchanger.

Shell and Tube Microheat Exchanger. A shell and tube microheat exchanger shown in Figure 2 was developed to conduct the reaction at higher flow rate (ca. 100 mL/min). The heat exchanger consists of 55 microtubes (i.d. 490 μm × 200 mm), which are placed in the shell (i.d. 16.7 mm × 200 mm) as shown in Figure 2. A coolant (water) is circulated through the shell. The flow distribution of microtubes was not determined.

Medium-Scale Reaction System. With the shell and tube microheat exchanger in hand, medium-scale reactions were conducted using several different types of micromixers.[10] A T-shaped mixer (i.d. 800 μm), an IMM single mixer (ver. 2, channel width 40 μm),[7a] a Yamatake YM-1 mixer,[11] and a Toray Hi-mixer (Toray Engineering) shown in Figure 3 were examined.

(8) The use of microreactors toward industrial production: e.g., (a) Pennemann, H.; Watts, P.; Haswell, S. J.; Hessel, V.; Löwe, H. *Org. Process. Res. Dev.* **2004**, *8*, 422. (b) Schwalbe, T.; Autze, V.; Hohmann, M.; Stirner, W. *Org. Process Res. Dev.* **2004**, *8*, 440. (c) Zhang, X.; Stefanick, S.; Villani, F. J. *Org. Process Res. Dev.* **2004**, *8*, 455. (d) Liu, S.; Fukuyama, T.; Sato, M.; Ryu, I. *Org. Process Res. Dev.* **2004**, *8*, 477. (e) Hessel, V.; Hofmann, C.; Löwe, H.; Meudt, A.; Scherer, S.; Schönfeld, F.; Werner, B. *Org. Process Res. Dev.* 2004, *8*, 511. (f) Iwasaki, T.; Yoshida, J. *Macromolecules* **2005**, *38*, 1159. (g) Kawaguchi, T.; Miyata, H.; Ataka, K.; Mae, K.; Yoshida, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 2413. (h) Chambers, R. D.; Fox, M. A.; Holling, D.; Nakano, T.; Okazoe, T.; Sandford, G. *Chem. Eng. Technol.* **2005**, *28*, 344.

(9) Respess, W. L.; Tamborski, C. *J. Organomet. Chem.* **1968**, *11*, 619.

(10) Micromixing: e.g., (a) Kakuta, M.; Bessoth, F. G.; Manz, A. *Chem. Rec.* **2001**, *1*, 395. (b) Stroock, A. D.; Dertinger, S. K. W.; Ajdari, A.; Meziæ, I.; Stone, H. A.; Whitesides, G. M. *Science* **2002**, *295*, 647. (c) Johnson, T. J.; Ross, D.; Locascio, L. E. *Anal. Chem.* **2002**, *74*, 45. (d) Seong, G. H.; Crooks, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 13360. (e) Song, H.; Tice, J. D.; Ismagilov, R. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 767. (f) Zheng, B.; Roach, L. S.; Ismagilov, R. F. *J. Am. Chem. Soc.* **2003**, *125*, 11170. (g) Song, H.; Ismagilov, R. F. *J. Am. Chem. Soc.* **2003**, *125*, 14613. (h) Bayer, T.; Himmler, K. *Chem. Eng. Technol.* **2005**, *28*, 285. (i) Nagasawa, H.; Aoki, N.; Mae, K. *Chem. Eng. Technol.* **2005**, *28*, 324.

(11) Aoki, N.; Hasebe, S.; Mae, K. *Chem. Eng. J.* **2004**, *101*, 323

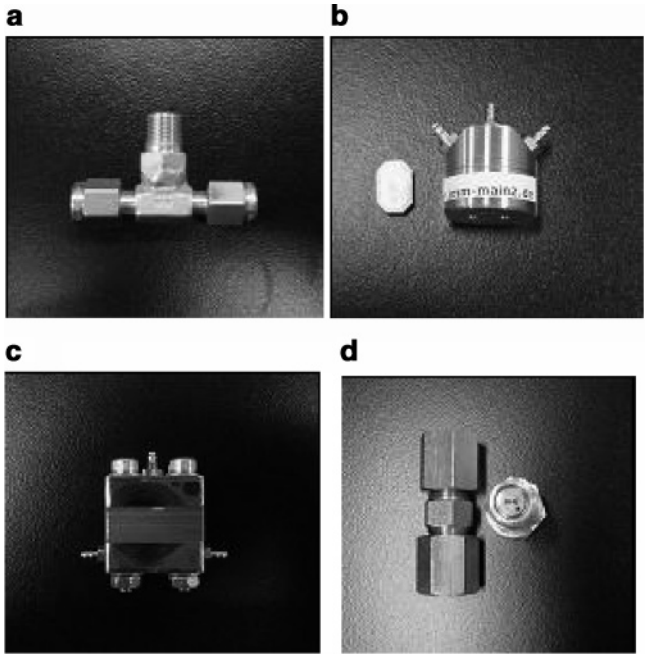
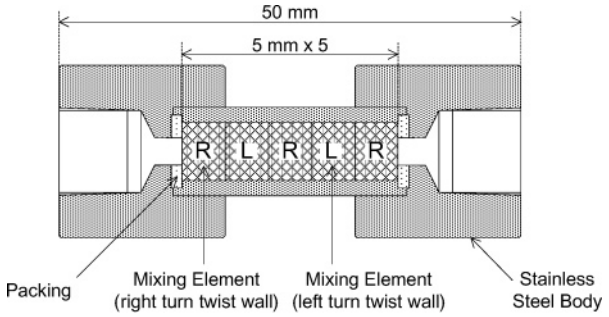


Figure 3. **Micromixers used for the medium-scale reaction system. (a) T-shaped mixer (ϕ = 2 mm). (b) IMM single mixer (40 μm). (c) Yamatake YM-1 mixer (400 μm). (d) Toray Hi-mixer (1.5 mm).**

Let us briefly touch on how mixing takes place in these micromixers. In the T-shaped mixer, two streams are allowed contact with each other. If the diameters are sufficiently small, the laminar mixing is predominant. If the diameters are large and flow velocities are high, turbulent mixing seems to be predominant. The type of mixing also depends on the fluid viscosity and the flow velocity. In the IMM single mixer, two fluids are introduced into the mixing element as two counterflows and the fluids stream into an interdigital channel configuration. In the next stage, a periodical flow configuration consisting of the lamellae of the two fluids is generated, which leaves the mixing element perpendicular to the direction of the feed flows. Because of the short diffusion path in multilaminar configuration, the mixing takes place very fast. The YM-1 micromixer is a manifold splitting and recombination type micromixer, in which the mixing channel path, i.e., the geometry, is split and recombined. The Hi-mixer is another type of manifold splitting and recombination mixer. The structure of the mixer is shown in Figure 4.

Measurement of Pressure Drop. The pressure drop of the system consisting of a micromixer and the shell and tube heat exchanger was measured by flowing water at 20 °C using Fuji-techno plunger pumps. The pressure at the inlet of the mixer and that at the outlet of the heat exchanger were measured using diaphragm-type pressure meters.

Pilot Plant. A pilot plant consisting of the Hi-mixer and the shell and tube heat exchanger was constructed. A schematic diagram of the pilot plant is shown in Figure 5. Plunger pumps (Fuji-techno) were used for introducing a EtMgBr solution (1.3 M) from a 60-L stainless steel tank at the flow rate of 32 mL/min and for introducing BPFB (neat, 8.0 M) from a 10-L stainless steel tank at the flow rate of 5.3 mL/min. The residence time was ca. 5 s. The reaction temperature was automatically controlled at 20 °C by circulating water in the shell and tube reactor. The product solution containing PFPMgBr was introduced to a 60-L stainless steel tank. For the determination of the yield, aliquots of the product solution were taken and were immediately quenched by methanol to obtain pentafluorobenzene (PFB).



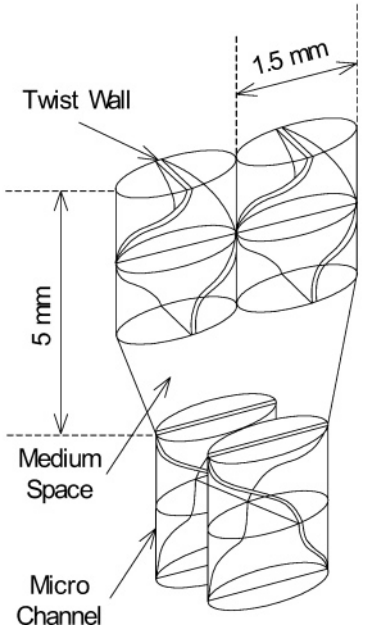


Figure 4. **Structure of Toray Hi-mixer.**

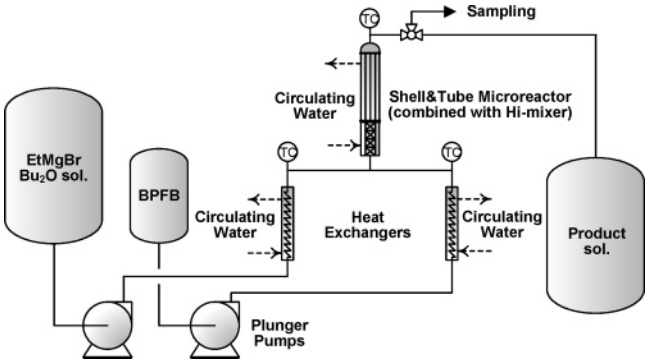


Figure 5. **Schematic diagram of the pilot plant.**

3. Results and Discussion

Small-Scale Reaction System. The Grignard exchange reaction of EtMgBr and BPFB was carried out using a small-scale reaction system with a T-shaped mixer and a microtube

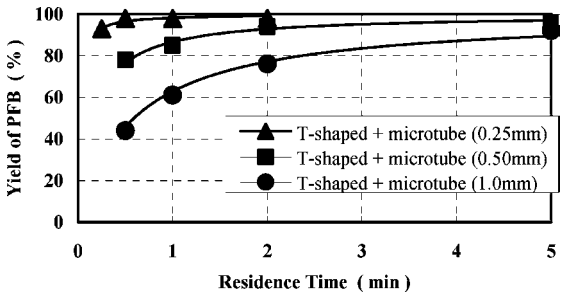


Figure 6. **Plots of the yield of PFB against residence time obtained with the T-shape mixer connected to the microtube heat exchanger. Effect of the diameter of the microtube.**

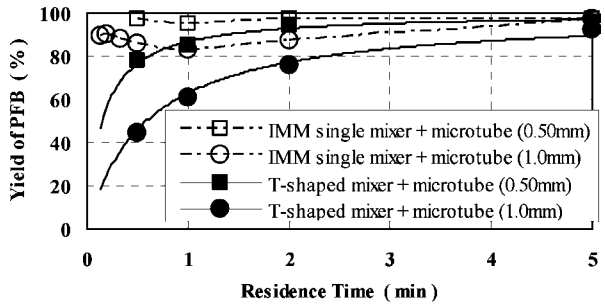


Figure 7. **Plots of the yield of PFB against residence time obtained with the T-shaped mixer and the IMM single mixer.**

heat exchanger. The residence time was varied by changing the flow rate. As depicted in Figure 6, the yield of PFB increased with the increase of the residence time, indicating that the mixing also takes place in the microtube heat exchanger. The effect of the diameter of the microtube heat exchanger is interesting. With the microtube of 0.25 mm diameter, the yield did not vary significantly with the residence time, indicating that the mixing in the tube was very fast and that the reaction completed very rapidly. In contrast, with the microtube of 1.0 mm diameter, the yield increased gradually with the residence time, indicating lower efficiency of the mixing in the microtube. These results indicate that the chemical reaction was fast under the conditions and that the progress of the reaction was determined by the mixing.

Next, the effect of the nature of the micromixer was examined. As shown in Figure 7. the IMM single mixer gave the better yields of the product. The present observation indicates that the mixing in the IMM single mixer was faster than the mixing in the T-shaped micromixer. The small-size multilamination configuration in the IMM single mixer seems to be responsible for greater mixing rate.

It should be noted that PFB was obtained in 97% yield when the IMM single mixer was used together with the microtube heat exchanger of 0.5 mm diameter. This yield is comparable to those obtained by laboratory-scale batch reaction (reactor size: 300 mL) and commercial-scale batch reaction (reactor size: 10 m^3).

Medium-Scale Reaction System. To increase the capacity of the microtube heat exchanger, we have developed a new shell and tube microheat exchanger, which contains 55 microtubes ($\phi = 0.49$ mm) in the shell (Figure 2). Thus, we constructed medium-scale reaction systems, which consist

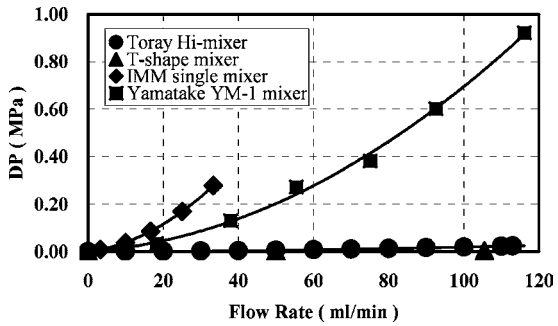


Figure 8. **Plots of pressure drop (DP) against flow rate (medium-scale reaction system). Effect of the nature of micromixer.**

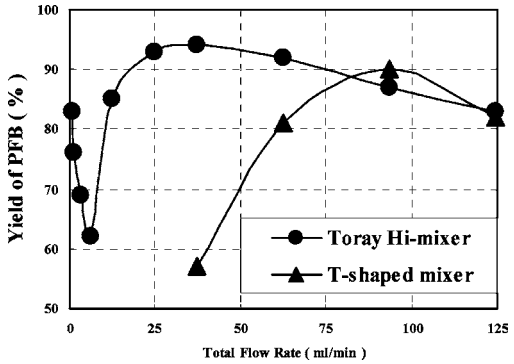


Figure 9. **Plots of the yield of PFB against flow rate (medium-scale reaction system).**

of several types of micromixers and the shell and tube microheat exchanger.

At first, the pressure drop of the system was measured using water flow before carrying out the reaction. The results are summarized in Figure 8. Although the use of the T-shaped mixer caused little pressure drop, the use of the IMM single mixer resulted in rapid increase of the pressure drop with the increase of the flow rate. The use of the Yamatake YM-1 mixer also gave rise to a significant increase of the pressure drop. The use of Toray Hi-mixer was, however, quite successful. No appreciable pressure drop was observed until the flow rate reached 100 mL/min.

Next, the Grignard exchange reaction was conducted using the medium-scale systems with the T-shaped mixer and the Hi-mixer. It can easily be seen from Figure 9 that the use of the T-shaped mixer resulted in low yield at lower flow rate. This is presumably because of low mixing efficiency of the T-shaped mixer at low flow rate. On the contrary, the use of the Toray Hi-mixer gave rise to the formation of PFB in high yields even at lower flow rate, although yield decreased significantly with the decrease of the flow rate below 25 mL/min. The increase of the yield at very low flow rate seems to be attributed to the increase of the residence time. A similar tendency was reported for the extraction processes using micromixers.[12]

Pilot Plant. On the basis of the results obtained with medium-scale reaction systems, a pilot plant, which involves the Toray Hi-mixer connected to the shell and tube microheat exchanger was constructed (Figures 5 and 10).

(12) Benz, K.; Jäckel, K.-P.; Regenauer, K.-J.; Schiewe, J.; Drese, K.; Ehrfeld, W.; Hessel, V.; Löwe, H. *Chem. Eng. Technol.* **2001**, *24*, 11.

Figure 10. **Picture of the pilot plant.**

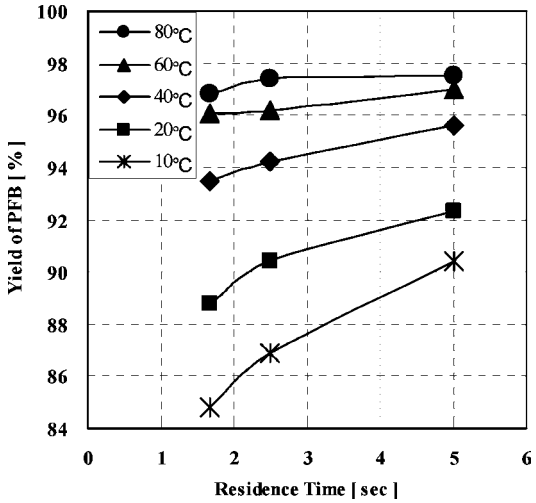


Figure 11. **Plots of the yield of PFB against residence time at various temperatures (pilot plant).**

The effect of residence time on the yield was examined at various temperatures, and the results are summarized in Figure 11. At lower temperatures, the yield increased with the increase of the residence time. This observation indicates that the mixing is not fast at lower temperatures because of smaller rates of diffusion and/or smaller rates of reaction. On the other hand, the yield did not vary with the flow rate at higher temperatures. Presumably, the mixing was very fast and completed within 2 s at such temperatures because of fast diffusion.

On the basis of the results obtained above, the continuous operation was carried out at 20 °C with the residence time of 5 s for 24 h in order to examine the durability of the production using the pilot plant. As shown in Figure 12, the yield of PFB did not change appreciably throughout the operation time. The reaction temperature and the pressure also did not change appreciably as shown in Figure 13.

Thus, we confirmed that for 24 h the pilot plant can be operated smoothly without any problem to obtain the product

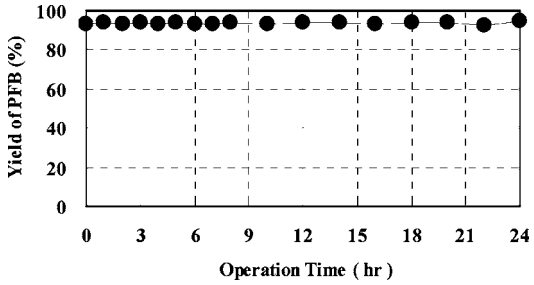


Figure 12. **Plots of the yield of PFB for 24 h continuous operation of the pilot plant.**

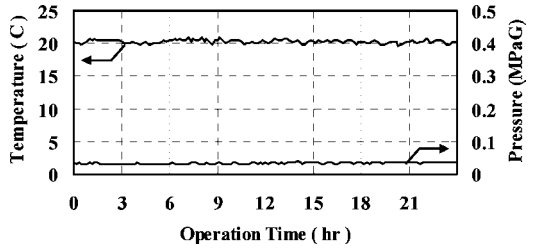


Figure 13. **Plots of the temperature and pressure for 24 h continuous operation of the pilot plant.**

(92% GC yield, corresponds to 14.7 kg of the product). It should also be emphasized that the industrial-scale production, which had been carried out using a batch reactor (10 m^3), could be accomplished by adding only four microflow systems of the present scale. The use of the microflow systems should lead to a significant decrease in investment compared with that for the current batch process.

4. Conclusion

The results described above indicate that microflow systems consisting of a micromixer and a microheat exchanger are quite effective for conducting very fast and highly exothermic reactions such as Grignard exchange reactions. Fast mixing and efficient heat transfer, which are inherent advantages of microsystems, seem to be responsible for the effective control of the reaction. The data obtained with the continuous operation using the pilot plant demonstrate that the microflow system can be applied to relatively large-scale production and speak well the potentiality of microchemical plants in industry.

Acknowledgment

This work was carried out in the Advanced Research Institute of Microchemical Systems, Katsura Int'tech Center, Graduate School of Engineering, Kyoto University, and was financially supported by the Project of Micro Chemical Technology for Production, Analysis, and Measurement Systems of NEDO, Japan.

Received for review August 12, 2005.

OP0501500