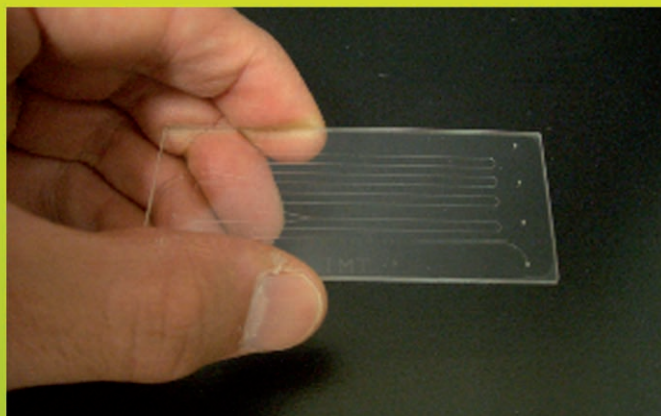


Multiphase Organic Synthesis in Microchannel Reactors

Juta Kobayashi, Yuichiro Mori, and Shū Kobayashi*^[a]

Microchannel reactors



Traditional style (flasks)

Abstract: “Miniaturization” is one of the most important aspects in today’s technology. Organic chemistry is no exception. The search for highly effective, controllable, environmentally friendly methods for preparing products is of prime importance. The development of multiphase organic reactions in microchannel reactors has gained significant importance in recent years to allow novel reactivity, and has led to many fruitful results that are not attainable

in conventional reactors. This Focus Review aims to shed light on how effectively multiphase organic reactions can be conducted with microchannel reactors by providing examples of recent remarkable studies, which have been grouped on the basis of the phases involved.

Keywords: heterogeneous catalysis • microchannel reactors • multiphase reactions • surfaces • synthetic methods

1. Introduction

Multiphase catalytic reactions have played an important role not only in research laboratories but also in chemical and pharmaceutical industries.^[1] Multiphase reactions are defined as reactions that are composed of different phases, that is, gas phase, liquid phase, and solid phase, and are classified according to the phases involved, such as gas–liquid, gas–liquid–liquid, or gas–liquid–solid reactions. Although numerous multiphase catalytic reactions are known and many are used in industry, these reactions are still more difficult to conduct than homogeneous reactions, because the efficiency of the interactions and mass transfer between different phases must be taken into consideration. Whereas several types of devices for multiphase reactions have been developed so far to overcome these problems (e.g. mechanically agitated reactors, cocurrent or countercurrent packed-bed reactors, bubble-column or spray-column reactors), most are designed to increase the interfacial area between the phases by vigorous stirring or by means of additional equipment.^[1,2] Although these reactors are specially designed for multiphase reactions, the development of more-effective and simple devices that can produce such a high interfacial area has been a much-sought-after goal.

A microchannel reactor, which has been used mainly in the field of analytical chemistry, was recently also applied in the field of organic chemistry.^[3–5] A microchannel reactor is a device that has a very small channel (generally nanometer

to micrometer range in width and depth and centimeter to meter range in length) etched in a solid material. This reactor can provide many fundamental and practical advantages for organic synthesis stemming from its small size as well as flow-reactor chemical processes. There are many general advantages to using microchannel reactors in organic synthesis:

- One of the most important features of microchannel reactors is a high surface-area/volume ratio. The specific surface areas of microchannel reactors lie between 10000 and 50000 m²m⁻³, whereas those of traditional reactors are generally about 100 m²m⁻³ and in rare cases reach 1000 m²m⁻³. This feature allows suitable environments for multiphase reactions to be established on the interfacial area between different phases such as liquid–liquid, gas–liquid, and gas–liquid–solid reactions.
- Peculiar flow regimes of microchannel reactors that are not attainable in ordinary column reactors can be realized, such as laminar flow (liquid–liquid), pipe flow (gas–liquid), and so on. An effective mass transfer between different phases can be expected based on such flow systems. Also, the chemical properties of the inner surface of the channel (for example, owing to the silanol groups of the glass) sometimes affect the reactions greatly.
- The short molecular-diffusion distance as a result of the very narrow channel space allows the rapid mixing of the reaction mixture. This can lead to high reaction rates.
- Highly efficient heat transfer allows rapid heating and cooling and makes it easy to control the temperature of a reaction mixture. The development of hot spots is suppressed, and undesirable side reactions are hindered.
- The reaction system can be scaled up readily by using a number of microchannel reactors in parallel (“numbering up”). In this case, the optimization of the reaction

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conditions, which is required every time for scaling up conventional batch systems, is not necessary.

- As the products are flowing constantly out of a channel, the concentration of starting materials should be always constant, thus leading to high efficiency for reactions.
- The products are obtained in the required amounts on demand. If a catalyst is immobilized in the channel, the products are isolated from the catalyst without any treatment.
- The actual reaction space is very small, and thus the reactions can be conducted more safely when explosive compounds are used.

These advantages have enabled us to conduct organic reactions more effectively, smoothly, and easily, and, above all, many types of multiphase organic reactions have been explored and developed accordingly. Herein we show examples of multiphase organic reactions in microchannel reactors and demonstrate how microchannel reactors are truly effective for multiphase catalysis. Reactions are categorized on the basis of the phases involved.

2. Two-Phase Reactions

2.1. Gas-Liquid Reactions

2.1.1. Fluorination

Direct fluorination with molecular fluorine is accompanied by the generation of much heat, and its control is difficult. In 1999, direct fluorination with molecular fluorine in a microchannel reactor (width and depth: $\approx 500 \mu\text{m}$) was examined.^[6] The microchannel reactor was made of nickel, and fluorine gas (diluted in nitrogen gas) was introduced into the channel through a mass-flow controller. The view of the inside of the channel was cylindrical flow (the liquid forms an outer cylinder, coating the reactor surface, with the gas flowing through the center), which leads to a large interfacial area. The system was found to be effective for the synthesis of fluorinated sulfide derivatives and for the fluorination of ketoesters. In the case of less-reactive substrates, products were obtained in higher yields in a microchannel reactor than in a batch system. Perfluorination was also demonstrated.

Abstract in Japanese:

「小型化」は現代社会の様々な分野において最も重要なキーワードの一つとなっているが、有機化学においても例外ではない。有用な化合物を合成する上で、高効率かつ制御容易であり、環境に対する負荷を最小限に抑える反応系を追究することは、近年ますますクローズアップされている省資源、省エネルギーという社会的要請からも最重要課題であると言える。そのような中、新たな反応デバイスとしてマイクロチャネルリアクターが注目されている。なかでも、マイクロチャネルリアクターを用いる多相系有機反応の開発は、近年目覚ましい発展を遂げており、従来の反応容器ではみられなかった反応性を基に、様々な実りある研究成果が報告されている。本稿においては、マイクロチャネルリアクターを用いる多相系有機反応に焦点を置き、それぞれの多相系反応ごとに注目すべき知見を紹介する。

The direct fluorination of toluene with molecular fluorine was investigated in gas/liquid microreactors: a falling-film microreactor (FFMR) and a micro bubble column (MBC) made of stainless steel (Figure 1).^[7] The FFMR, developed for this study, generates a thin falling film (several $10 \mu\text{m}$ thick), which flows as a result of gravitational forces. This is performed on a platelet comprising a large number of microchannels (cross-section: $100 \mu\text{m} \times 300 \mu\text{m}$). The MBC consists of a mixing unit equipped with $20\text{-}\mu\text{m}$ deep gas- and liquid-feeding channels with widths of 7 and $20 \mu\text{m}$, respectively, and a reaction unit comprising an array of parallel microchannels. Two types of reaction unit were utilized



Juta Kobayashi received his PhD in 2006 from the Graduate School of Pharmaceutical Sciences, The Univ. of Tokyo (Japan). His research interests in his PhD course focused on the development of multiphase organic reactions in microchannel reactors. Other than chemistry, he is also interested in piano playing, reading, sports (cycling, basketball), photography, and fishing.



Yuichiro Mori was born in 1972 in Kanazawa, Japan. He earned his PhD on the development of catalyst systems in water under the supervision of Prof. Shū Kobayashi in 2001 and he became Assistant Prof. at the Graduate School of Pharmaceutical Sciences at the Univ. of Tokyo. Since 2003, he is a group leader in the Kobayashi Highly Functionalized Reaction Environments Project in the Japan Science and Technology Agency (JST). His research is focused on organic reactions in microreactors.

Editorial Board Member



Shū Kobayashi was born in Tokyo (1959) and received his PhD in 1988 (under Prof. T. Mukaiyama, The Univ. of Tokyo). After 11 years at the Science Univ. of Tokyo, he moved to The Univ. of Tokyo (1998). His research involves the development of new synthetic methods and catalysts, organic reactions in water, solid-phase synthesis, total synthesis, and organometallic chemistry. He received the Springer Award in Organometallic Chemistry (1997), the IBM Science Award (2001), the Organic Reactions Lecturer Award (2002), the Mitsui Chemical Catalysis Science Award, the JSPS Prize (2005), and an Arthur C. Cope Scholar Award (2006).

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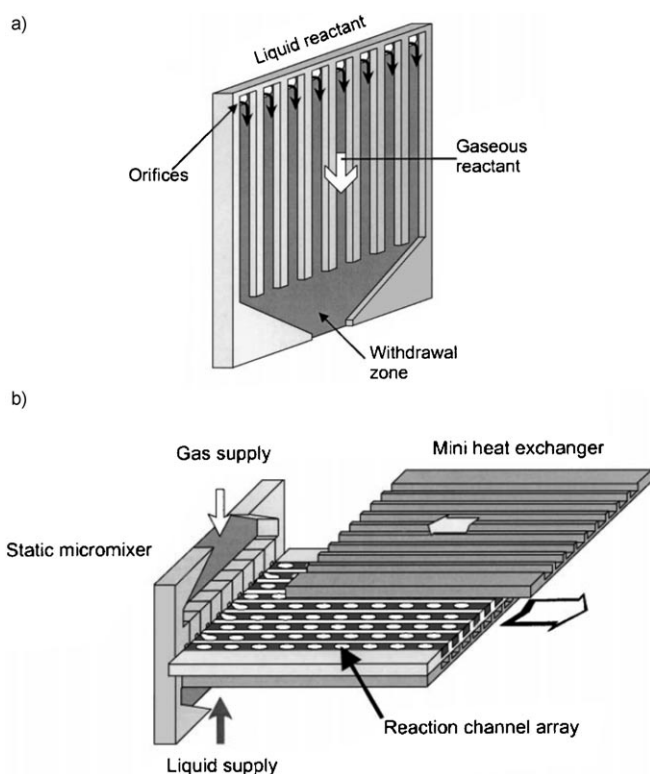


Figure 1. a) Falling-film microreactor. b) Micro bubble column. Reprinted, with permission, from reference [7].

($50\ \mu\text{m} \times 300\ \mu\text{m}$ and $300\ \mu\text{m} \times 100\ \mu\text{m}$ channel cross-section). The experiments included measurements at high substrate concentrations and high fluorine content diluted in a nitrogen carrier gas. The results were compared with the performance of a laboratory bubble column, which served as a technological benchmark. Owing to the formation of liquid layers, the microreactors provide very large interfacial areas, up to $40\,000\ \text{m}^2\ \text{m}^{-3}$, which by far exceed those of a laboratory bubble column as well as all other devices applied. It was found that the reactor performance, expressed as space-time yield and represented in a selectivity-conversion diagram, was by far superior to that of the laboratory benchmark owing to enhanced mass and heat transfer.

A novel microchannel reactor was designed, and the direct fluorination of toluene was demonstrated.^[8] The reactor was constructed from silicon and pyrex instead of metals, and thin silicon oxide and nickel films were used as anticorrosion coatings (Figure 2). Gas-liquid contacting patterns in the microchannels were systematically characterized by flow visualization, and a "flow-regime map" was represented by changing the flow rates of the gas and the liquid and observing the distribution of the gas and liquid phases (annular, wavy annular, slug, bubbly, and annular dry). The monofluorinated product was obtained with the highest selectivity when acetonitrile was used as a solvent. When the conversion of toluene was 58%, the selectivity of the monofluorinated product was 24%.

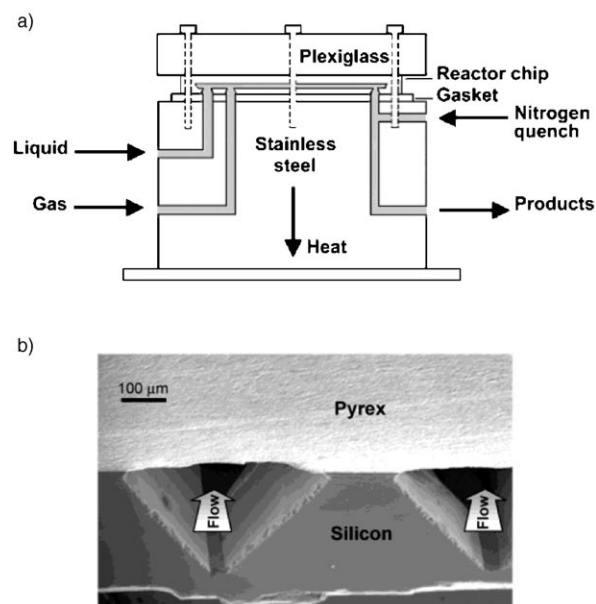


Figure 2. a) Packaging scheme of the reactor chip used for carrying out fluorination. b) Cross-sectional scanning electron micrograph of the microchannels in the central region.^[8]

2.1.2. Carbonylative Coupling Reaction

The synthesis of secondary amides by carbonylative cross-coupling of aryl halides with benzylamine with carbon monoxide (gas) was conducted in a glass microstructured reactor and represents the first reported gas-liquid carbonylation reaction.^[9] The reaction channel is 5 m long and has an average width and depth of $200\ \mu\text{m}$ and $75\ \mu\text{m}$, respectively (Figure 3). Three different aryl halide substrates (iodobenzene, 4-iodoanisole, and 2-bromopyridine) were used to test the microreaction carbonylation procedure. The liquid and gaseous reagents are mixed on the chip by using a mixing-tee configuration. An annular flow regime is imposed on the system whereby a thin film of the liquid is forced to the sur-

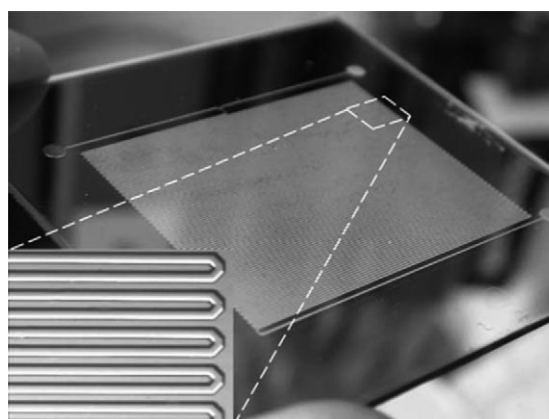


Figure 3. A photograph of the microfluidic chip used in the carbonylation reactions (prior to chromium removal and bonding during the course of chemical wet etching). The area taken up by the microchannel footprint on the glass substrate is approximately $50 \times 50\ \text{mm}^2$.^[9]

face wall of the microchannel while the gas flows through the center, thus generating a very high interfacial area. The mean residence time of the microreactions was estimated to be less than 2 min for all the flow rates examined. Batch reactions were carried out over a 10-min time period to assess the performance of the microreactor. As a result, the microreactions, even with their much shorter residence times, allowed higher yields than batch reactions. The increase in yields of the microreactions can be attributed to two factors: the increased interfacial gas–liquid contact area generated within the microstructured reactor and the increase in carbon monoxide pressure resulting from the back pressure produced in the system.

2.2. Gas–Solid Reactions

2.2.1. Hydrogenation

The gas-phase partial hydrogenation of *cis,trans,trans*-1,5,9-cyclododecatriene was also realized in microreactors.^[10] Microstructured wafers made of aluminum were anodically oxidized to form a surface alumina layer with appropriate regular pore systems, followed by impregnation with a palladium-containing precursor, as well as drying, calcining and reducing in hydrogen. Thus, catalytic activated wafers were stacked and caged in a stainless-steel housing equipped with diffusors and connectors for reactant inlet and product outlet, finally resulting in a microchannel reactor.

Hydrogenation of cyclododecatriene was carried out in the microchannel reactor, and partially hydrogenated cyclododecene (CDE) was obtained in 90% yield at a conversion of 98%. The excellent product yield was attributed to lack of temperature and velocity gradients over the whole passage through the microchannels, which stemmed from the μm dimension of the uniform flow channels.

2.3. Liquid–Liquid Reactions

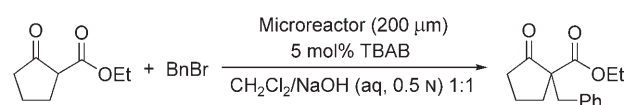
2.3.1. Aldol Reaction

To date, fluoros biphasic catalysis has attracted a great deal of attention particularly with respect to environmentally friendly chemical processes.^[11] The first example of fluoros biphasic catalysis in a microchannel was reported, and a dramatic increase in reactivity of Mukaiyama aldol reactions in fluoros media through a “fluorous nanoflow” system was shown.^[12] Even at low concentrations ($< 0.0001\text{ M}$) of a Lewis acid catalyst ($\text{Sc}[\text{N}(\text{SO}_2\text{C}_8\text{F}_{17})_2]_3$) in nonpolar fluoros solvents, the reaction was complete within seconds of a biphasic contact time. A borosilicate microreactor was used (60 μm in width, 30 μm in depth, 1, 2, and 3 cm in length), and the substrates in a hydrocarbon solvent and the catalyst in a fluorocarbon solvent were introduced through two inlets. In this case, laminar flow sometimes resulted and allowed a very short diffusion of molecules with a large interfacial area between the two phases. The aldol reaction of benzaldehyde with the trimethylsilyl

enol ether derived from methyl 2-methylpropanoate was completed within seconds, even in the presence of only 0.0625 mol% of the catalyst. They also conducted a control experiment with a normal batch system, which gave only a poor yield after vigorous stirring at 55°C for 2 h under the same catalyst and substrate concentrations. Further experiments revealed that a narrower width and longer length of the channel and longer contact time gave better results. Quite recently, the authors also succeeded in the application of their nanoflow system to a Baeyer–Villiger oxidation.^[13]

2.3.2. Alkylation

Phase-transfer alkylation reactions proceeded smoothly in the presence of an ammonium salt in a glass microchannel reactor (200 μm in width, 100 μm in depth, 45 cm in length) (Scheme 1).^[14] An organic phase containing a substrate (β -



Scheme 1. Phase-transfer benzylation reaction of ethyl 2-oxocyclopentanecarboxylate with benzyl bromide. (TBAB = tetra-*n*-butylammonium bromide)

ketoester) and an alkylating agent (e.g. benzyl bromide) and an aqueous phase containing a phase-transfer catalyst (tetra-butylammonium bromide) and sodium hydroxide were introduced into the microchannel reactor through each inlet (Figure 4). Optical microscopic studies showed that the organic phase formed small droplets (segments) inside the aqueous tube and that the interfacial area was extended. The extended interfacial area seemed to accelerate the reactions, and the reaction rate was higher in the microchannel reactor than in a round-bottomed flask with vigorous stirring. In the microchannel reactor, the reactions of various substrates and alkylation agents proceeded in high yields within ten minutes. The width of the microchannel reactor was also important as the reaction rate was higher in a thinner microchannel reactor.

2.3.3. Isomerization of Allylic Alcohols

High-throughput screening (HTS) of catalysts is of great importance for rapid processes in pharmaceutical and chemical industries. A new concept allows the HTS of catalysts in a liquid–liquid and a gas–liquid reaction in a microreactor.^[15] Two test reactions were chosen for the demonstration (isomerization of allylic alcohols (liquid–liquid) and asymmetric hydrogenation (gas–liquid)). A micromixer and a tubular reactor were assembled for a liquid–liquid HTS test system, and pulse injections of the catalyst (aqueous phase) and the substrate (*n*-heptane phase) were operated (Figure 5). The pulses allowed perfect mixing in the micromixer, and an *n*-heptane/water emulsion was formed that was stable for more than 10 min without noticeable separation. The system was used to screen a catalyst library for isomerization (including rhodium, ruthenium, palladium, and nickel catalysts

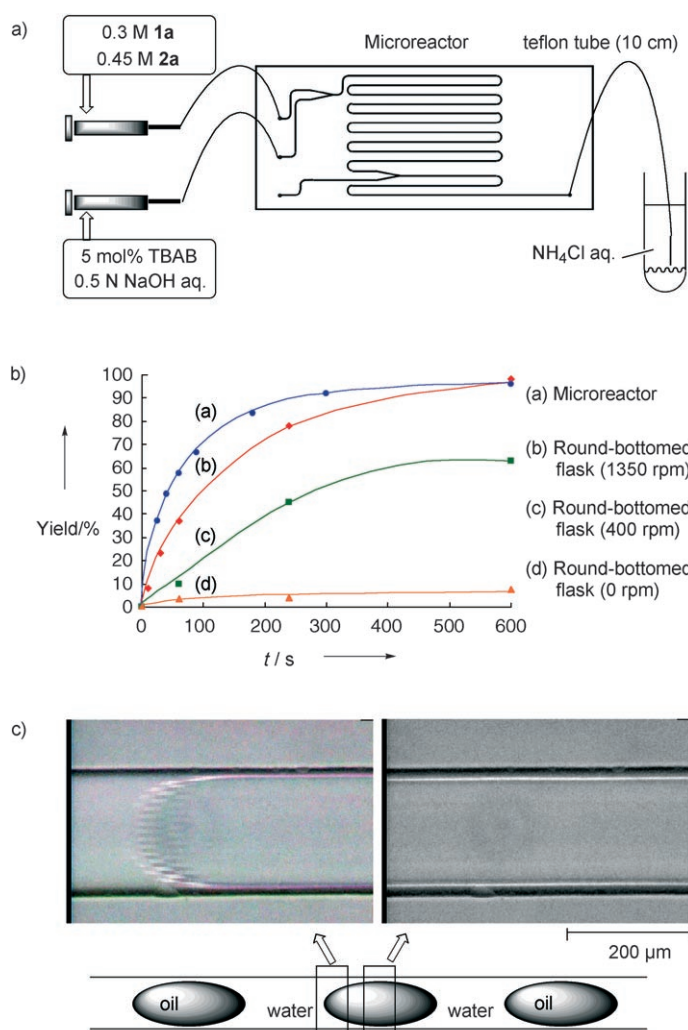


Figure 4. a) An experimental system for phase-transfer alkylation. b) The profile of the alkylation in a microreactor and standard batch systems. c) The shape of the segment (optical microscope).^[14]

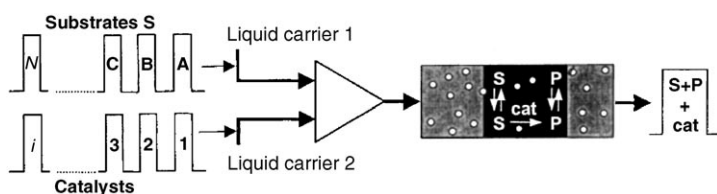


Figure 5. Schematic representation of the principle used for high-throughput sequential screening of i catalysts and N substrates. The substrate S is thus converted into product P .^[15]

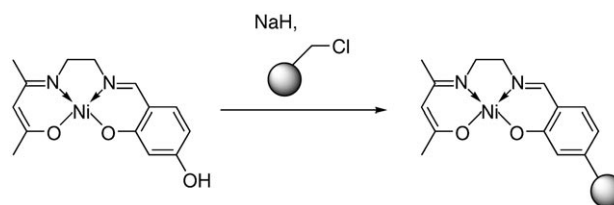
combined with several sulfonated phosphane or diphosphane ligands). As a consequence, the results obtained in the microreactor were in good agreement with those in a traditional well-mixed batch reactor, proving the validity of the concept. The concept was also extended to gas–liquid asymmetric hydrogenation reactions. The success was ascribed to good mass and heat transport in the microreactor, to which many enantio- and regioselective reactions are sensitive. Some advantages over traditional parallel batch opera-

tions include smaller sample amounts, a larger range of operating conditions, and fewer, simpler electromechanical moving parts.

2.4. Liquid–Solid Reactions

2.4.1. Kumada–Corriu Reaction

A pressure-driven microchannel reactor (internal diameter 100–200 μm) was used for the Kumada–Corriu reaction.^[16] The nickel catalyst was immobilized on Merrifield resin polymer beads and was held in place within the channel by plugs of glass wool (typical catalyst bed lengths ranged from 2 to 10 mm) (Scheme 2). The reaction was performed by feeding a mixture of equimolar solutions of the aryl halide and a Grignard reagent through the reactor at known flow rates. The reaction rates in flow reactors and in batch reactions were compared, and the reaction rate of the flow system was found to be over three orders of magnitude higher than that of a batch reaction.



Scheme 2. Immobilization of nickel catalyst onto Merrifield resin for Kumada–Corriu reaction.

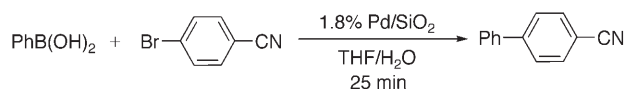
2.4.2. Suzuki–Miyaura Coupling Reaction

Suzuki–Miyaura coupling reactions were conducted in a microchannel (300 μm width and 115 μm depth) etched into glass and sealed with a top plate.^[17] A microporous silica structure was immobilized within the channels, which acted as both a micropump when electroosmotic flow (EOF) was used for the mobilization and as an immobilization technique for the catalyst bed (1.8% palladium on silica). This was the first report of the combined use of EOF with the microporous silicate structure in a flow injection microreactor to perform palladium-catalyzed organic synthesis.

A T-shaped microchannel reactor with reservoirs at the end of each channel was used. These were reservoirs for the substrate solutions (phenylboronic acid and 4-bromobenzonitrile, both in aqueous THF (75 %)). The coupling reaction was conducted by using EOF for mobilization, and the effect of various kinds of flow injection methods on the yields of 4-cyanobiphenyl were investigated (Scheme 3). Interestingly, it was found that the addition of a base was not required, presumably because the water associated with the aqueous THF undergoes partial ionization to form hydroxide species. A control experiment showed that the system gave the desired product in higher yield than did the corresponding batch system. Furthermore, the palladium contaminant in the crude product was in the range of 1.2–1.6 ppb,

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indicating a very low rate of leaching from the catalytic bed. More recently, a microwave based technique was also reported that is capable of delivering heat locally to a heterogeneous Pd-supported catalyst located within a microreactor device.^[18]



Scheme 3. Reaction scheme for the coupling of 4-bromobenzonitrile and phenylboronic acid in a microreactor.

2.4.3. Dehydration of Alcohols

The dehydration of alcohols was catalyzed by sulfated zirconia in a glass microchannel reactor.^[19] The channels were 200 μm wide, 80 μm deep, and 30 mm long (in a Z-shaped configuration). The top plate was prepared from a polydimethylsiloxane (PDMS) resin, the mating face of which was coated with a thin layer of PDMS and activated catalyst dusted over the surface. Finally, a reactor was prepared in which one wall of the channel was catalytically active. The in situ heater was fabricated from nichrome wire immobilized in a PDMS top plate.

Hexan-1-ol was pumped through the reactor chip at a flow rate of 3 $\mu\text{L min}^{-1}$ at 155 $^\circ\text{C}$ (reaction temperature). The conversion of hexan-1-ol into hexene averaged between 85 and 95 %, whereas 30 % conversion is common in large-scale reactors. Furthermore, the reactor was used constantly over 3 days with no decrease in performance. Ethanol was also used as a substrate and allowed the successful production of ethene, ethane, and methane.

2.4.4. Photoreduction

Methylene blue was reduced in a microcapillary that had TiO_2 as a photocatalyst on the inner wall.^[20] A colloid solution of TiO_2 -coated SiO_2 with a core-shell structure was first prepared by using a surfactant to generate a surface charge on the particles (Figure 6). Silica capillaries with a glass inner wall (length: 5 cm, internal diameter: 530 and 200 μm) were used as the microreactors. The capillary was filled with the solution and dried overnight at 88 $^\circ\text{C}$. The TiO_2 was introduced and coated on the inner wall of the microcapillary by the self-organization of SiO_2 . Control experiments were also conducted in a capillary simply coated with TiO_2 without SiO_2 and in one without any coating. The capillary with the $\text{TiO}_2/\text{SiO}_2$ coating gave the best conversion rate among those tried; the corresponding batch system gave a lower conversion rate. The higher conversion rate attained with the $\text{TiO}_2/\text{SiO}_2$ -coated capillary was attributed not only to a larger surface/volume ratio but also to the absorption properties of SiO_2 .

Furthermore, a simple method for the preparation of a nanostructure on a microchannel surface for immobilization of an enzyme was also developed, and the enzyme-immobilized microreactor showed high efficiency for hydrolysis.^[21]

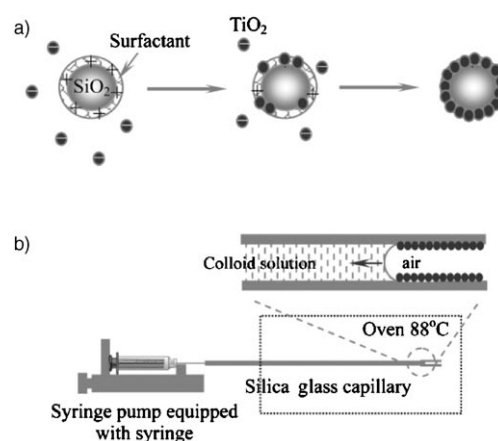


Figure 6. a) Schematic representation of the preparation of $\text{SiO}_2/\text{TiO}_2$ core-shell particles. The anionic TiO_2 (black spots) was readily attached to the surface of the cationic polyethylenimine-covered SiO_2 and gradually neutralized it. b) Coating the inner wall of the microcapillary with TiO_2 . One end of the capillary was connected to a syringe, and the other was placed in the colloid solution. The capillary was filled with solution by drawing a vacuum with the syringe. With one end closed, the capillary was dried at 88 $^\circ\text{C}$.^[20]

2.4.5. Esterification

A systematic study of the influence of the channel surface in glass microchips was carried out and is illustrated for the acid-catalyzed esterification of 9-pyrenebutyric acid.^[22] The on-chip reactions were carried out in a 197-mm long, 200- μm wide, and 100- μm deep borosilicate microchannel under pressure-driven flow conditions. The reagent flows were controlled by two 100- μL syringes. The products were transferred directly from the outlet silica fiber to a MALDI-TOF mass spectrometer sample plate in a continuous-flow fashion, and HPLC was used for the quantitative determination of the conversions. The target reaction was performed both in glass microchips and in conventional laboratory-scale glassware under the same conditions with solutions of 9-pyrenebutyric acid in ethanol (10^{-4} M) and sulfuric acid in ethanol (10^{-4} M), both at room temperature and at 50 $^\circ\text{C}$. No ester was formed in the laboratory-scale experiment, even at 50 $^\circ\text{C}$, whereas the ester was obtained in high yield in the on-chip experiment. The experiments were also repeated in a glass fiber whose inner surface had been coated by the reaction of the silanol groups with lipophilic octadecyltrichlorosilane. In this case no product formation could be detected, substantiating the effect of the microchannel surface on the reaction, such as activation of ethanol by a large number of acidic hydroxy groups within the glass microreactor and the uncoated silica fiber. The results demonstrated the important contribution of surface phenomena to the “chip effect” which lead to higher yields in much shorter reaction times than observed on a conventional laboratory scale.

2.4.6. Oxidation

A simple capillary microreactor with a porous gold catalyst was developed for the oxidation of glucose.^[23] A glass capillary tube for a microreactor (i.d.: 400 μm , length: 5 cm) and

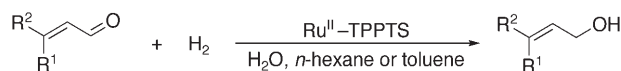
a porous seastar skeleton as a template for fabricating a porous gold catalyst (pore diameter: 10–20 μm) were employed. The capillary tube and reservoirs connected at both ends of the capillary were filled with a phosphate buffer solution of D-glucose mixed with the porous gold catalyst. Electrokinetic pumping was used to introduce the glucose through the channels in which the porous gold catalyst was present. Under the optimal conditions, the yield of gluconic acid reached 99%, whereas conventional methods afford gluconic acid in only 48% yield. The higher reactivity was ascribed to the formation of active sites on the surface of the gold catalyst under an applied voltage as well as to the higher surface area of the porous sponge catalyst. Furthermore, no significant loss of activity of the catalyst was observed after repeated use (five times).

3. Three-Phase Reactions

3.1. Gas-Liquid-Liquid Reactions

3.1.1. Hydrogenation

Ru-catalyzed chemoselective hydrogenation of an α,β -unsaturated aldehyde in capillary microreactors was reported (Scheme 4).^[24] Polytetrafluoroethylene (PTFE) capillaries



Scheme 4. Multiphase catalytic chemoselective hydrogenation of α,β -unsaturated aldehyde with Ru^{II} -TPPTS. TPPTS=sodium triphenylphosphane trisulfonate.

(i.d.: 500, 750, 1000 μm ; length: 3, 6, 12 m, respectively) that could withstand high pressures of up to 3.0 MPa were used. An aqueous solution of RuCl_3 and TPPTS was pretreated under a hydrogen atmosphere to make an active Ru^{II} -TPPTS complex, and 3-methylcrotonaldehyde and citral were dissolved in organic solvents. The aqueous phase and the organic phase were introduced into a T-shaped mixer. After the flow, the mixture was exposed to hydrogen gas through another T-shaped mixer. Repeating units of gas-liquid-liquid then reached a capillary reactor, where the reaction proceeded. They examined the effects of several parameters such as flow rate of the aqueous phase and hydrogen, temperature, and inner diameter of the capillary. Under the optimal conditions alternate slugs composed of two liquid phases were formed; hydrogen bubbles were contained in the organic phase (Figure 7). The inner diameter of the capillary reactor plays a key role in mass-transfer-limited reactions such as hydrogenation. Narrower channels increase specific interfacial area and strengthen inner circulation within the organic slugs.

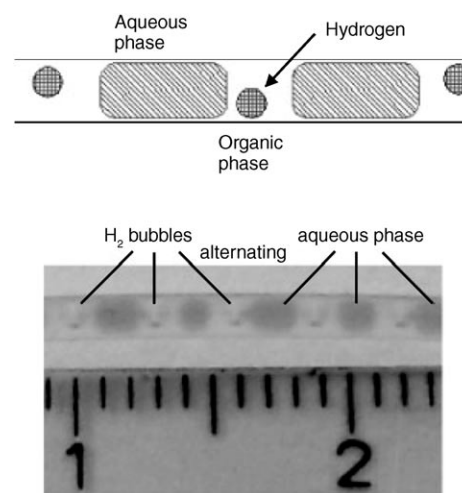


Figure 7. Gas-liquid-liquid flow in the capillary reactor.^[24]

3.2. Gas-Liquid-Solid Reactions

3.2.1. Hydrogenation

It should be noted again that one of the most important features of microchannel reactors is high specific interfacial area. The power of this technique is demonstrated in gas-liquid-solid triphase reactions as follows, in which the interfacial area between each phase plays a crucial role for accelerating the reactions. An effective and simple device for hydrogenation reactions in microchannel reactors was developed.^[25] A glass microchannel reactor with a 200- μm wide, 100- μm deep, and 45-cm long channel was used, and the palladium catalyst was immobilized on the surface of the channel. The solution of the substrate and hydrogen gas were allowed to flow into the channel from the two inlets (Figure 8). An ideal flow system is that in which the gas flows through the center of the channel and the liquid along the inner surface of the channel where the catalyst is present (pipe flow). This system allows an efficient gas-liquid-solid interaction owing to the large interfacial areas and the short path required for molecular diffusion in the very narrow channel space, which is not attainable in normal batch systems.

Although there had been several reports concerning the immobilization of metals on a glass wall, lowered reactivity and leaching of the metals during reactions were sometimes serious problems. In this work, a new method for the immobilization of the Pd catalyst was developed to overcome such problems.^[26,27]

Microencapsulated (MC) Pd, prepared from $[\text{Pd}(\text{PPh}_3)_4]$ and a functionalized copolymer, was used as the Pd source by following the method originally developed for immobilization. Amine groups were introduced in advance onto the surface of the glass channel, a solution of the MC Pd was then passed through the microchannel to allow the reaction with the amine group, and after calcination at 150 $^\circ\text{C}$ to ensure cross-linking of the polymer, the desired Pd-immobilized microchannel reactor was successfully prepared. Mi-

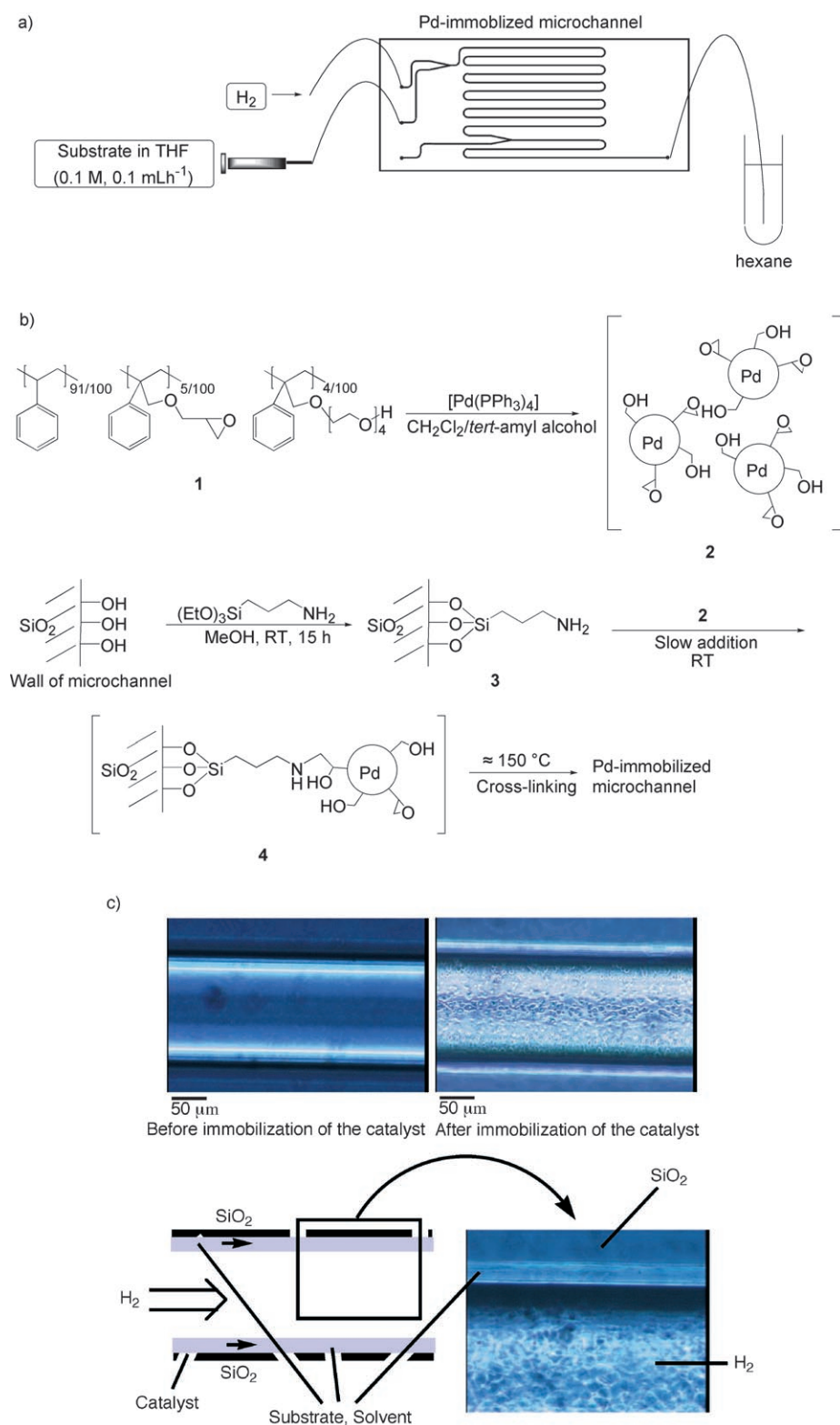


Figure 8. a) Experimental hydrogenation system in a microchannel reactor. b) Immobilization of the Pd catalyst. c) View of the microchannel reactor without and with the Pd catalyst and the appearance of the reaction system. See Table 1 for substrate scope.^[25]

croscopically showed that the inner surface of the channel was covered by the polymer containing the palladium catalyst.

Hydrogenation of benzalacetone was carried out in the Pd-immobilized microchannel reactor thus prepared. When the flow rate of hydrogen was relatively slow, alternate slugs of the liquid and gas were observed, and the yield was insufficient. The reaction was then carried out with an increased flow rate of hydrogen and a decreased flow rate of the substrate, and the ideal flow system (pipe flow) was found to afford the product quantitatively. In that case, the mean residence time (which equals the reaction time) of the starting materials was only 2 min.

Reduction of other olefins and alkynes was examined, and also the removal of a benzyl ether and of a carbamate group was conducted (Table 1). It was found that the reactions proceeded smoothly in all cases to afford the corresponding products in quantitative yields. Furthermore, chemoselective reduction was also successfully conducted, and a triple-bond moiety was reduced without removal of a benzyl ether moiety. Comparison with the reaction kinetics of the ordinary batch system showed that the reaction proceeded much faster in the case of the microchannel reactor. Furthermore, in most cases Pd was not detected in the product solutions by inductively coupled plasma (ICP) analysis, and the microchannel reactors were reused several times without loss of activity.

One might say that *micro*-channel reactors are a drawback for the reaction scale due to the inherent *micro*-property. Although it is theoretically possible to scale up reactions by using a number of chips in parallel (numbering up), practical and spatial problems are still encountered; examples of numbering up have been reported.^[28,29] Quite recently, the suitability of microchannel reactors even for large-scale synthesis in hydrogenation was

Table 1. Substrate scope of the hydrogenation reaction in a Pd-immobilized microchannel reactor.

Substrate		Pd-immobilized microchannel reactor, H ₂ (1 mL min ⁻¹)		Product	
		THF, RT, <2 min.			
Substrate	Product	Yield [%] ^[a]	Substrate	Product	Yield [%]
		97 ^[b]			quant.
		quant.			quant.
		quant.			quant. ^[d]
		quant.			quant. ^[d]
		quant.			quant. ^[e]
		quant.			quant. ^[e]
		quant. ^[c]			97 ^[f]

[a] Yields were determined by ¹H NMR spectroscopy. [b] 4-Phenyl-2-butanol (3%) was also obtained. [c] Yield of isolated product: 97%. [d] EtOH was used as solvent. Flow rate of the substrate: 0.05 mL h⁻¹. The reaction was carried out at approximately 50 °C. Actual residence time was less than 1 min. [e] The reaction was conducted at about 50 °C. [f] Conditions: H₂ (2 mL min⁻¹, 1,2-dichloroethane, ±50 °C.

demonstrated by utilizing capillary column reactors, which are inexpensive, easy to handle, and occupy less space.^[30]

A fused silica capillary (i.d.: 200 μm, length: 40 cm) instead of the microchannel system was selected, and immobilization of the Pd catalyst was conducted by using the same method mentioned above. Nine Pd-immobilized capillaries were then assembled and connected to each other in parallel by using an ordinary 1/16" SUS connector and fixed with a standard epoxy resin-glye (Figure 9). Hydrogenation was conducted with 1-phenyl-1-cyclohexene as a model substrate in the assembled capillaries. Under optimal conditions, the reaction proceeded well to give the desired product in quantitative yield. In that case, the productivity was about 280 times that of the previous microchannel system. Since capillaries themselves occupy only approximately 0.4 mL

(0.11 mL if calculated based on the volume of the space inside the capillaries), quite high space-time yields have been achieved (18.3 mg min⁻¹ mL⁻¹), demonstrating the feasibility of the system for practical chemical synthesis.

The overall mass-transfer coefficients for gas-liquid absorption in a microfabricated packed-bed reactor were compared with traditional multiphase packed-bed reactors.^[31] A microchemical system, which was made of silicon and pyrex glass, consisted of a microfluidic distribution manifold, a microchannel array, and a 25-μm microfilter for immobilizing solid particle materials within a reactor chip (Figure 10). The hydrogenation reaction of cyclohexene catalyzed by Pt/Al₂O₃ was selected as a model multiphase reaction. The catalyst was loaded into the main reaction part, and the reaction was conducted by introducing the substrate and hydrogen into the channel. Analysis showed the overall mass-transfer coefficients to be two orders of magnitude larger than values for standard laboratory-scale reactors.

Hydrogenation of nitrobenzene was catalyzed by palladium by using a falling-film reactor, which was made of stainless steel and had 64 straight, parallel channels (300 μm wide, 100 μm deep, 78 mm long separated by 100-μm walls) (Figure 11).^[32] This device employed thin liquid films less than 100 μm thick that were created by a liquid feed falling under gravity, leading to rapid heat and mass transfer. Several methods to immobilize a palladium catalyst on the wall of the

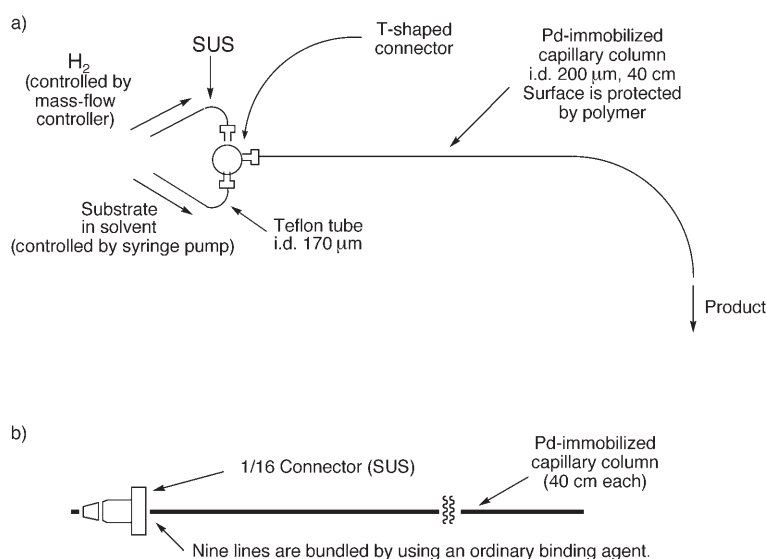


Figure 9. a) System for hydrogenation reaction in Pd-immobilized capillary. b) Assembled Pd-immobilized capillaries for larger-scale synthesis.^[30]

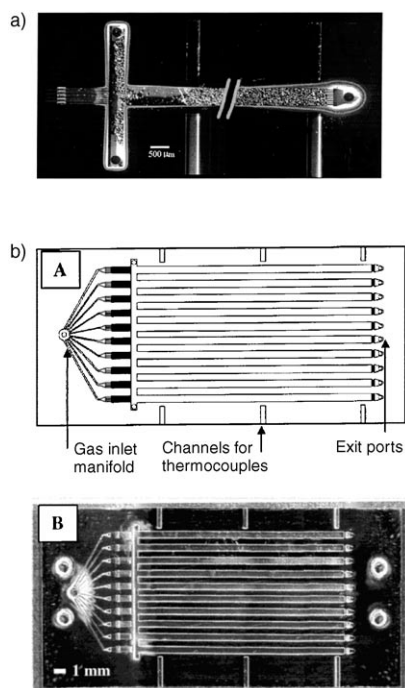


Figure 10. a) The single-channel reactor loaded with activated carbon. b) Multichannel reactor design for hydrogenation. A: Top silicon layer illustrating fluid manifold to 10 parallel fixed-bed reaction channels. B: Photomicrograph of multichannel reactor chip.^[31]

channel, such as sputtering, UV decomposition of palladium acetate, incipient wetness, or impregnation, were examined. Among them incipient wetness gave the highest loading of the catalyst and retained stable activity for a much longer time than any of the other catalysts. This system was found to produce larger amounts of aniline per unit volume under milder conditions than those by a batch system.

Efficient hydrogenation reactions with the use of a gas–liquid–solid microflow system under elevated pressure were developed.^[33] A stainless-steel tube (o.d.: 6.3 mm, i.d.: 1.0 mm, length: 25 cm) with two filters at both ends so as to keep the Pd/C inside the column was used as a reactor (Figure 12). Both the substrate solution and the hydrogen gas are introduced continuously into one end of the fine column packed with Pd/C. From the other end, the hydrogenated product solution emerges continuously. The substrate solution was mixed with the hydrogen gas in a T-shaped mixer, and a forming

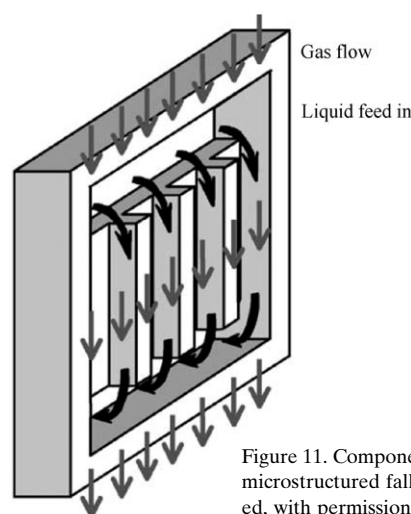
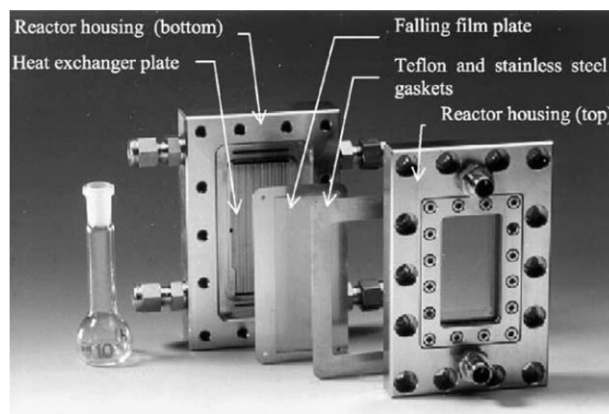


Figure 11. Components and schematic of the microstructured falling-film reactor. Reprinted, with permission, from reference [32].

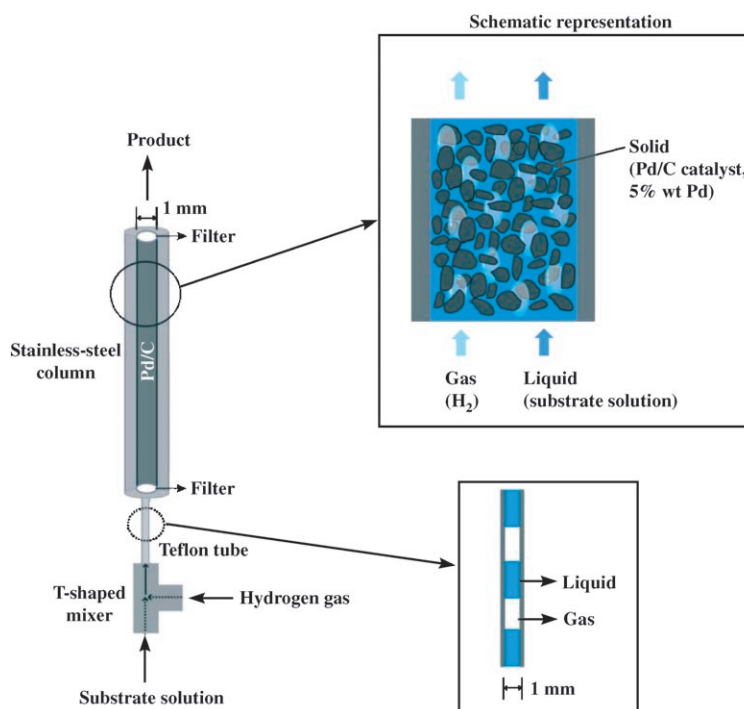


Figure 12. Schematic drawing of the gas–liquid–solid flow reactor.^[33]

plug flow (alternate gas and liquid layers) was then introduced into the tube column packed with Pd/C. The hydrogen pressure was regulated at around 2.5 MPa. The residence time in the column was only 2 min. The substrate solution and hydrogen gas travel through very narrow channels, which are formed between and within the Pd/C porous particles (diameter: $20 \pm 10 \mu\text{m}$), giving rise to enhanced mass transfer between different phases relative to conventional batch reaction systems. The hydrogenation reaction of 4-cyanobenzaldehyde was chosen as a model to evaluate the efficiency of the system, and control experiments were also conducted in a batch system for comparison. It was found that the flow system resulted in a more-efficient hydrogenation reaction than the batch system, promising high potential and wide applicability for many organic reactions with heterogeneous catalysts.

4. Others

4.1. Supercritical Fluids

Supercritical carbon dioxide (scCO_2) has recently attracted much interest as an ideal solvent because of its abundance, low cost, and nontoxicity.^[34] Although scCO_2 has a liquidlike aspect and allows the dissolution of many organic compounds, it also has a gaslike aspect and is highly miscible with gases, including hydrogen. Therefore, scCO_2 provides an effective environment for hydrogenation reactions. Hydrogenation reactions in scCO_2 as a reaction medium in microchannel reactors has been developed.^[35] A 200- μm wide, 100- μm deep, and 40-cm long microchannel reactor in which the palladium catalyst was immobilized (or encapsulated) within a copolymer matrix on the channel surface was used (the same channel as that used in normal hydrogenation reactions mentioned above). The overall system for hydroge-

nation reactions in scCO_2 is shown in Figure 13. A cell into which substrates were injected was connected to a 200-mL autoclave, which was used to make scCO_2 containing dissolved hydrogen. The pressure inside the channel was controlled by a backpressure regulator, which was positioned at the end of the microchannel reactor. To perform hydrogenation reactions, the substrate was supplied into the cell at 50°C . scCO_2 containing dissolved hydrogen was prepared by supplying hydrogen and CO_2 into the autoclave. The resulting fluid was then transferred through the high-pressure cell into the microchannel reactor at 60°C , where the dissolved substrate was converted into the desired product. During the reaction, CO_2 was supplied continuously at a constant flow rate, and the product was collected at the exit for analysis. This system allowed the hydrogenation of a variety of substrates in almost quantitative yields. Significantly, average residence (reaction) times were estimated to be less than 1 s for all reactions. These initial results demonstrated that the substrate, hydrogen, and the catalyst interact efficiently owing to the large surface area of the catalyst and the greatly increased solubility of hydrogen by using scCO_2 as the reaction medium.

4.2. Multistep Synthesis

Although many types of reactions have been found to proceed highly efficiently in microreactors because of the enhanced heat performance, faster diffusion times and reaction kinetics, and improved reaction product selectivity, challenges still remain in applying microreactors to sequential syntheses of fine chemicals and pharmaceuticals. An integrated microfluidic device was developed for the multistep synthesis of a radiolabeled imaging probe.^[36] The synthesis of the ^{18}F -labeled molecular-imaging probe 2-deoxy-2- ^{18}F fluoro-D-glucose (^{18}F FDG), a widely used radiolabeled molecular

probe, was chosen as a model reaction. It should be noted that because of the brief half-life of ^{18}F , rapid synthesis of doses is essential. Five sequential processes— ^{18}F concentration, water evaporation, radiofluorination, solvent exchange, and hydrolytic deprotection—were involved and proceeded in an integrated microfluidic device with high radiochemical yield and purity and with a shorter synthesis time than conventional automated synthesis (Figure 14). Although some of the components required for conducting sequential chemical processes within microfluidics are similar to those previously demonstrated for biological analysis, two additional techni-

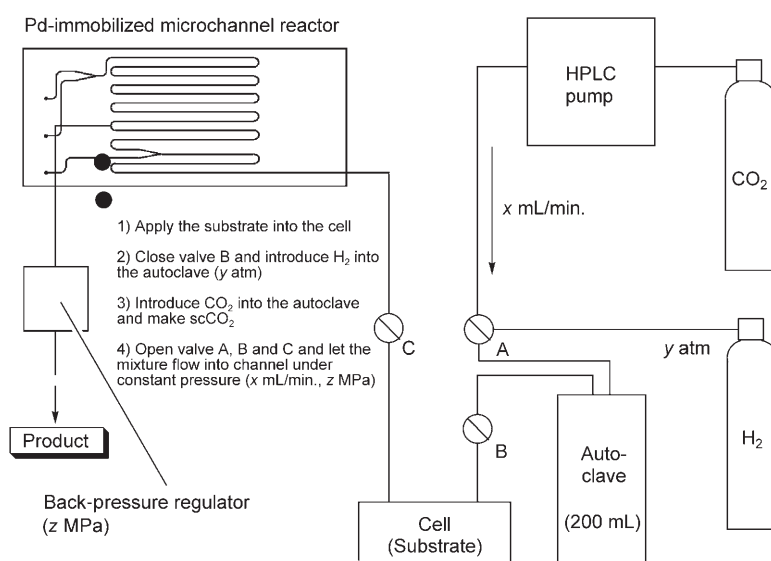


Figure 13. System for hydrogenation in scCO_2 in a Pd-immobilized microchannel reactor.^[35]

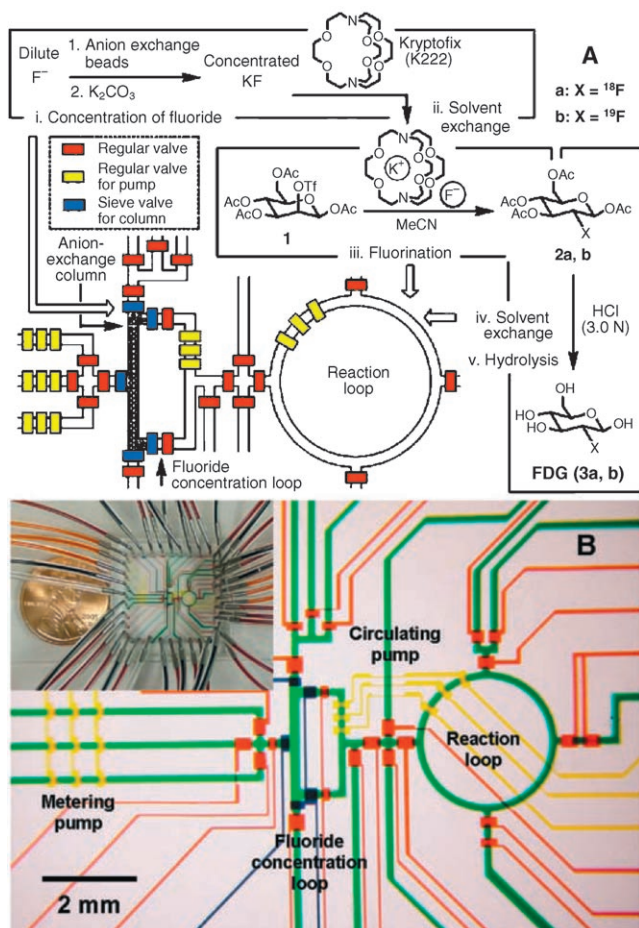


Figure 14. A) Schematic representation of a chemical reaction circuit used in the production of 2-deoxy-2-fluoro-D-glucose (FDG). Five sequential processes (concentration of dilute fluoride ion with the use of a miniaturized anion-exchange column located in a rectangular fluoride concentration loop, solvent exchange from water to dry MeCN, fluorination of the D-mannose triflate precursor **1**, solvent exchange back to water, acidic hydrolysis of the fluorinated intermediate **2a** (or **2b**) in a circular reaction loop) are shown. The final product FDG (**3a,b**) was obtained in nanogram amounts. The operation of the circuit is controlled by pressure-driven valves (red for regular valves (for isolation), yellow for pump valves (for fluidic metering circulation), and blue for sieve valves (for trapping anion exchange beads in the column module)). B) Optical micrograph of the central area of the circuit. The various channels have been loaded with food dyes to help visualize the different components of the microfluidic chip; colors are as in A) (green for fluidic channels). Inset: Actual view of the device; a penny (diameter 18.9 mm) is shown for comparison. Reprinted, with permission, from reference [36].

cal advances should be noted: an in situ ion-exchange column combined with a rotary pump to concentrate radioisotopes and the use of the gas-permeable poly(dimethylsiloxane) (PDMS) matrix as a basic material of the microreactor, which allows solvent exchange to occur within the microfluidic channel through direct evaporation. The sequential production of [^{18}F]FDG was completed in an automated fashion within 14 min. Another chemical reaction circuit was designed with the capacity to allow the synthesis of larger amounts of [^{18}F]FDG, and a sufficient amount of [^{18}F]FDG was produced for several mouse experiments for

micro-PET- and micro-CT-based (PET = positron emission tomography, CT = computed tomography) molecular imaging.

5. Summary and Outlook

This Focus Review has summarized the recent progress in the field of multiphase organic synthesis in microchannel reactors. Many types of multiphase organic reactions have been much improved by making the best use of the properties of microchannel reactors in a variety of aspects. Although the examples shown here all concern multiphase reactions, it is remarkable that homogeneous reactions have also been explored recently, further demonstrating a bright future for microchannel reactors.^[3–5] Organic chemistry has dramatically influenced society, especially in recent decades, with advances in and inventions of medicinal products and functionalized materials. However, experimental tools, systems used, their characteristics, concepts, and properties have remained unchanged for over 100 years. Microchannel reactors have opened the door to innovation in the future of organic synthesis.

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