# Organic Electrochemistry, Microreactors, and Their Synergy

*by Jun-ichi Yoshida*

Driven by remarkable improvements in our understanding of factors governing organic reactions, the role of organic synthesis has been expanded to various fields of science and technology, such as new materials and new medicinal agents. Because of rapid progress in such fields, demands for producing desired organic compounds in a highly efficient and environmentally benign manner have been increasing. In order to meet such demands, synergy between organic electrochemistry and microreactors is expected to play a central role. This article will provide a brief outline of this new fascinating approach.

## Microreactors

Microtechnology is no longer merely the province of computers and the rest of the electronics field, but is now moving into many different areas of science and technology such as mechanics, optics, and fluids. These days downsizing has been also occurring in the chemistry. The advantage of downsizing is that it provides better efficiencies while also answering society's demands for conservation of resources and energy. The micro device used for conducting chemical reactions is called a microreactor.[1,2] A microreactor is a reactor with microchannels on the micrometer scale. Microreactors are not necessarily used solely to produce small amounts of chemical substances. Although the reactor's capacity at any one time is small, total production capacity over time is much greater than may be imagined because microreactors are normally set up as flow-type reactors with a continuous flow of solution through the reaction chamber. In fact, there are microreactors, though they fit in the palm of the hand, that can produce several tons of a product per year.

The characteristics of microreactors can influence the very essence of chemical reactions in the following ways.

*Mixing.*—Most chemical reactions are conducted by combining two substances. The major part of mixing occurs due to molecular diffusion. Time needed for molecular diffusion is proportional to the square of the length of the diffusion path. Therefore, the marked shortening of the diffusion path in a microreactor results in a mixing speed unobtainable in a macro reactor.

*Energy transfer.*—In general, when length is shortened, surface-to-volume ratio increases, because volume is equal to length cubed while surface area is equal to length squared. Thus, a feature of micro spaces is that they have large surface-to-volume ratios compared to macro spaces. Therefore, energy transfer occurs rapidly through an interface in micro spaces.

*Mass transfer.*—Another characteristic of microreactors derived from their much greater surface-to-volume ratios is that they make phase boundary reactions such as gas/liquid, liquid/liquid or solid/liquid reactions including electrode processes more efficient, because mass transfer through or on an interface is very fast.

*Residence time.*—The length of time that the solution remains inside the reactor (the residence time) can be greatly reduced by adjusting the length of microchannels and flow speed. This feature of microreactors is extremely useful in controlling short-lived reactive species, which can be transferred to another location to be used in the next reaction before they decompose. Therefore, chemical conversions that are impossible in macroreactors should be made possible by using microreactors.

*Integration.*—Integrated microflow reactor systems can be easily constructed enabling multi-step synthesis using highly unstable reactive intermediates (Fig. 1).

*Scaling up.*—Scaling-up of chemical reactions from the laboratory flask scale to the industrial production scale suffers from a variety of problems such as decreasing yield and selectivity. Solving these issues requires examination of the reaction conditions, wasting much time and manpower. When using microreactors, however, the production volume can be increased by increasing the operation time and the number of reactors, if necessary, without changing the size of the reactors. Thus, a shift to industrial production is possible without changing the reaction conditions that were most suitable at the laboratory scale. Consequently, the usual lag time between research and development on the one hand, and industrial production on the other, can be expected to be greatly reduced with microreactors.

Microreactors have been expected to make a revolutionary change in chemical synthesis. For example, highly exothermic, extremely fast reactions are usually carried out by slowly adding one of the reaction components to the other. The rate of the reaction is determined by the rate of the addition. These types of reactions can be conducted at a natural rate using microreactors. Fast reactions may also cause selectivity problems; kinetically based selectivity is not obtained because the reaction proceeds before homogeneity of the solution has been achieved by mixing. In such cases, the reactions need to be slowed down by decreasing the temperature, decreasing concentrations, or adding additives. However, the use of microreactors enables conducting such reactions



**Fig. 1.** *An integrated microflow reactor system consisting of four micromixers and four microtube reactors.*

without slowing down and production with kinetically based selectivity. Another important point is the control of highly reactive, short-lived reactive intermediates. Chemical conversions that are difficult to achieve using conventional marobatch reactors should become possible using microreactors.

## Organic Electrochemistry

Organic electrochemistry provides a straightforward, efficient, and tunable method for generating a wide variety of reactive intermediates that are useful in organic synthesis. In fact, radical cations and radical anions can be generated by electrochemical reactions of neutral organic compounds. Carbocations, carbon free radicals, and carbanions can also be generated by subsequent bond-dissociation or bond-forming processes. One of the major advantages of the electrochemical method is the absence of byproducts derived from chemical reagents that are needed for the chemical method. Therefore, the electrochemical method provides a better environment for subsequent reactions of thus-generated reactive species. These reactive carbon species have been utilized in various synthetic transformations, especially carbon-carbon bond formations. Oxidation and reduction of functional groups are also important transformations in organic synthesis. A number of such synthetic transformations have been discovered and developed using organic electrochemistry as "greener" procedures so far. In addition to conventional protocols, various new strategies in organic electrochemistry have been developed as follows.[3]

*Intramolecular control.*—Methods using functional groups that control the reactivity of substrate molecules and reaction pathways are often used in organic synthesis. A method for such intramolecular control has also been developed in organic electrochemistry; the introduction of a functional group that promotes the electron transfer and controls the reaction pathway. Such a functional group is called an electroauxiliary. Use of electroauxiliaries enables selective electrochemical transformations that are difficult to achieve by conventional ways.

*Reaction media.*—Reaction media such as solvents and supporting electrolytes play important roles in organic electrochemistry. Recent developments enable the use of ionic liquids and supercritical fluids as solvents for electrolysis. Solid-supported electrolytes and mediators have also been developed. An interesting method, in which the electrolysis can be conducted under homogeneous traditional conditions yet the products can still be easily separated from the reaction media by simple operations, is also noteworthy.

*Reaction conditions.*—Electrochemical reactions for organic synthesis have been usually carried out at or near room temperature. However, recent progress in electrochemical reactors enables us to perform electrochemical reactions under high-temperature and/or high-pressure conditions. Such technology led to the use of supercritical fluids as reaction media. It is also noteworthy that electrolysis can be conducted at very low temperatures, enabling us to generate and accumulate unstable reactive species such as organic cations (cation pool method) (Fig. 2). The use of ultrasound in electrochemical synthesis has also attracted significant research interest.

## Synergy Between Organic Electrochemistry and Microreactors

Though organic electrochemistry serves as a powerful method for organic synthesis, there are some problems inherent in conducting electrode processes in organic solvents. For example, conductivity of common organic solvents is low. Therefore, cell voltage is usually higher than that for aqueous systems. Reactions on the surface of the electrodes suffer from low mass transfer problem causing smaller productivity compared with homogeneous chemical reactions. Therefore, the design of appropriate devices for electrolysis is very important. Use of organic salts such as tetraalkylammonium salts that are soluble in organic solvents as supporting electrolytes also causes a problem of separation and recycling after the electrolysis. Such issues might be a barrier to applications of the organic electrochemistry in synthesis and production. However, the application of microreactors serves as a solution to the problems of conventional macrobatch electrochemical synthesis; small distance between the electrodes avoids high ohmic drop. High electrode surface-to-reactor volume ratio in electrochemical microreactors is also advantageous for mass transfer on the surface of the electrodes.

A microflow electrochemical reactor having a plate-to-plate electrode configuration mounted in a nonconducting housing has been developed (Fig. 3).[4] The working electrode and the counterelectrode are separated using a spacer between them. The distance between the electrodes ranges in the micro meter order. The reactor was successfully used for the anodic oxidation of *p*-methoxytoluene to give *p*-methoxybenzaldehyde dimethyl acetal.

Oxidative generation of an unstable *N*-acyliminium ion was also conducted in a microflow electrochemical system (Fig. 4).[5] This method is called the cation-
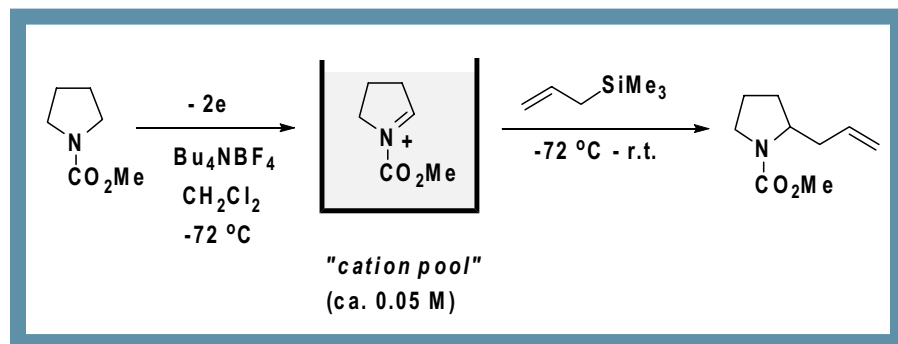


**FIG. 2.** *Generation of* N-*acyliminum cation pool.*
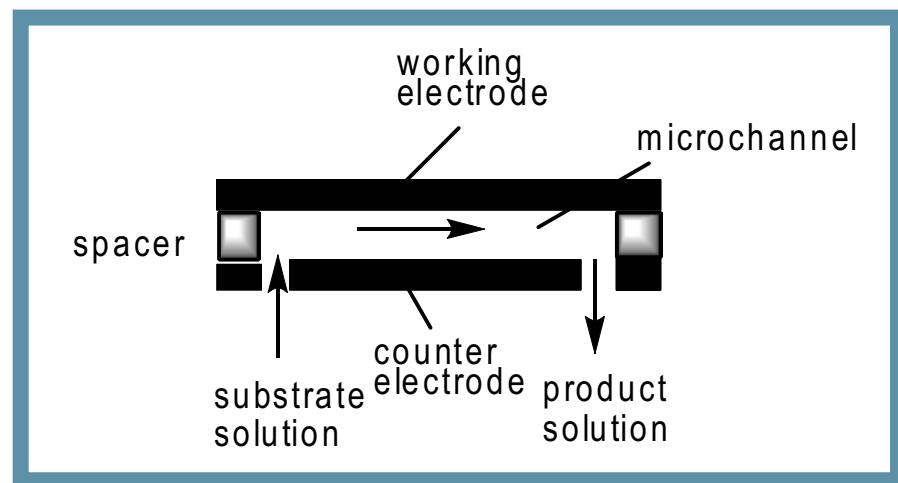


**FIG. 3.** *A microreactor for electrochemical synthesis having a plate-to-plate electrode configuration.*
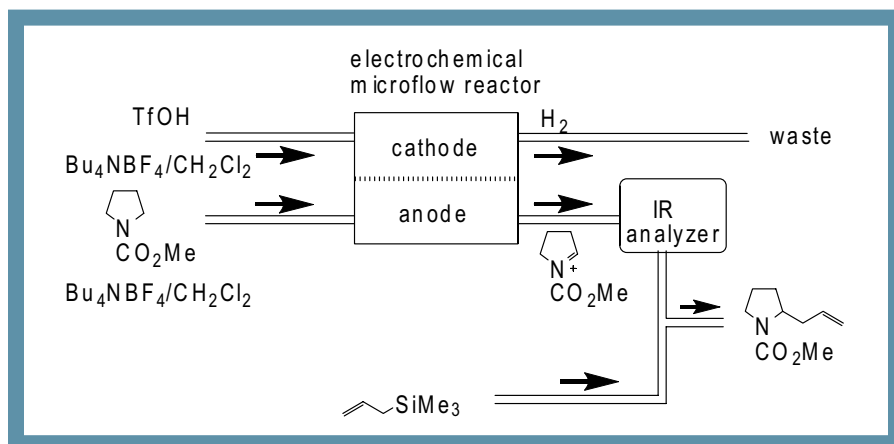
**Fig. 4.** *Schematic diagram of the "cation flow" system.*



**Fig. 5.** *Flow cell for the cation flow system.*

flow method. The *N*-acyliminium ion was characterized by in-line ATIR analysis. A paired microflow electrochemical system has also been developed where an organic cation is generated by anodic oxidation and a carbanion equivalent is generated by cathodic reduction; both intermediates are allowed to react to give the corresponding coupling product.[6]

One of the advantages of microreactor is that a laminar flow is predominant whereas a turbulent flow is predominant in macroreactor. By taking advantage of a parallel laminar flow in a microflow electrochemical reactor, the generation of an *N*-acyliminium ion followed by trapping with an easily oxidizable carbon nucleophile such as allyltrimethylsilane was achieved (Fig. 6).[7] The laminar flow prevents the oxidation of allyltrimethylsilane at the anode. Only the precursor is oxidized to generate the *N*-acyliminium ion, which diffuses to the center of the microchannel and reacts with allyltrimethylsilane there.

Electrochemical microreactors enable us to conduct electrolysis without an intentionally added supporting electrolyte. Using a simple electrochemical microflow system having a parallel electrode configuration, a paired electrolysis consisting of one electron oxidation of ferrocene and the two electron-two proton reduction of tetraethyl ethylenetetracarboxylate in ethanol was achieved without electrolyte.[8] The small distance between the electrodes seems to be responsible for conductivity. In this system, liquid flow and current flow are perpendicular. The anodic oxidation of furans in methanol can also be carried out without intentionally added electrolyte using a microflow system of parallel electrode configuration (Fig. 7).[9]

There is another type of microflow system that can be used for electrolyte-free electrolysis. In this system, two carbon fiber electrodes are separated by a spacer (porous membrane) at a distance of the micrometer order (Fig. 8).[10] An
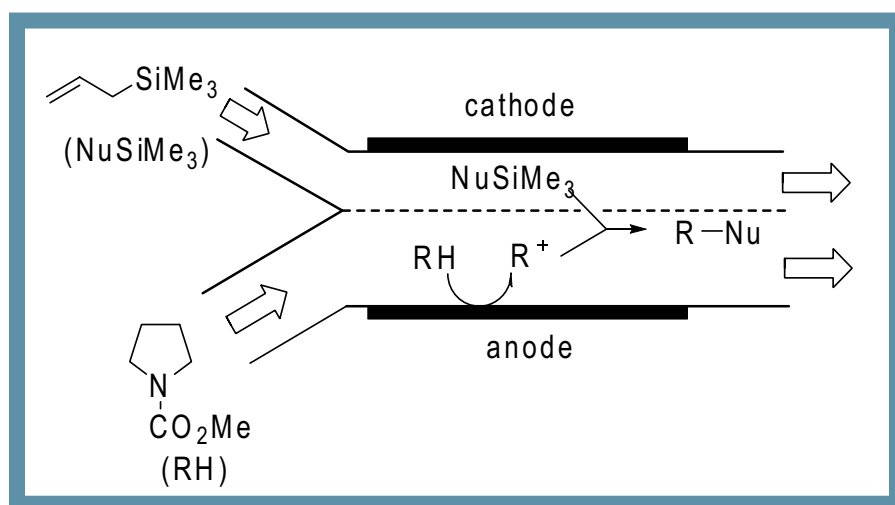


**Fig. 6.** *Parallel laminar microflow system for the generation and reaction of* N-*acyliminium ion.*
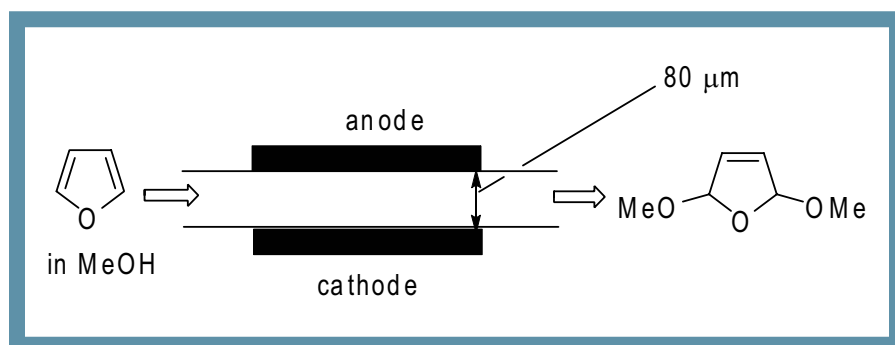


**Fig. 7.** *Electrochemical oxidation of furan in a microflow reactor without intentionally added electrolyte.*

anodic solution flows through the spacer membrane into the cathodic chamber. The product solution leaves the system from the cathodic chamber. In this system, the electric current flow and the liquid flow are parallel. Using this electrochemical microreactor, the anodic methoxylation of *p*-methoxytoluene was accomplished effectively without intentionally added electrolyte.

Electrochemical microreactor systems serve as an effective tool for combinatorial chemical chemistry. A microchip-based molecular library construction system using a 1 cm² chip having an array of 1,024 individually addressable Pt electrodes was developed (Fig. 9).[11] The 2,4-DNP derivative was introduced at the selected electrodes by the electrochemical process. The chip

was treated with a rabbit anti-2,4-dinitrophenol antibody that is conjugated to a fluorescent probe. Imaging using an epifluorescence microscope showed that only the selected electrodes exhibited fluorescence. This experiment proved that the selected electrodes could be selectively modified chemically at will, showing the possibility of building addressable libraries on an array of microelectrodes. This approach has been expanded to other addressable libraries using a mass spectrometry cleavable linker for monitoring reactions.[12] Selective coumarin synthesis and real-time signaling of antibody-coumarin binding based on microchip technology have also been reported.[13]

Although parallel syntheses enjoy versatile applications in combinatorial chemistry, a continuous sequential method based on serial microflow electrolysis by simple flow switching is also useful (Fig. 10).[5] The potential of this method is demonstrated by the synthesis of nine compounds from three precursors (S) of N-acyliminium ions (S+) and three allylsilanes (Nu).

Another way of collaboration is conducting extremely fast reactions using electrochemically generated reactive species in a microreactor. Our way of synthesizing compounds is currently changing. For example, combinatorial synthesis of chemical libraries has become very popular in academia and industry. On-site on-demand synthesis and production are expected to be popular in the future. These new trends in chemical synthesis increase the demand for fast chemical synthesis, flash chemistry.[1f] To accomplish extremely fast reactions, we often need to activate molecules to make substrates with built-in high energy content or prepare highly reactive reagents that react very quickly with substrates. For such purposes, organic electrochemistry serves as one of the most straightforward ways.[14] Highly reactive species such as radical cations, cations, free radicals, anions, and radical anions can be generated electrochemically at room temperature or below.

There are several problems in conducting extremely fast reactions in a preparative scale. For example, fast reactions are usually highly exothermic. Therefore, heat removal is often a limiting factor in controlling extremely fast reactions. Microreactors serve as a good technology for conducting such highly exothermic reactions by virtue of fast heat transfer due to high surface-to-volume ratio. It is also well known that product selectivity of extremely fast reactions often depends on how reactants are mixed (disguised chemical selectivity),[15] and micromixing serves as an effective method for improving the product selectivity of extremely fast reactions.

Friedel–Crafts reactions of aromatic compounds with electrochemically generated highly reactive N-acyliminium ion pools provide nice examples of the collaboration (Fig. 11).[16] The reaction of trimethoxybenzene with an N-acyliminium ion using a conventional macrobatch reactor resulted in the formation of an essentially 1:1 mixture of a monoalkylation product and a dialkylation product. The monoalkylation product undergoes the subsequent reaction with the N-acyliminium ion, presumably because the reaction occurs faster than mixing. In fact, the reaction completed within a second. The reaction using a microreactor system consisting of a micromixer, however, resulted in a dramatic increase in the product selectivity. The monoalkylation product was obtained with excellent selectivity and the amount of dialkylation product was very small. Extremely fast 1:1 mixing using the micromixer seems to be responsible for the dramatic increase in the selectivity. Similar micro effect was also observed for iodination of aromatic compounds with electrochemically generated I+.[17]

The collaboration between organic electrochemistry and microreactors can be applied to polymer synthesis. For example, cationic polymerization can be conducted in a highly controlled manner by virtue of the inherent advantage of extremely fast micromixing and fast heat transfer. In fact, an excellent level of molecular-
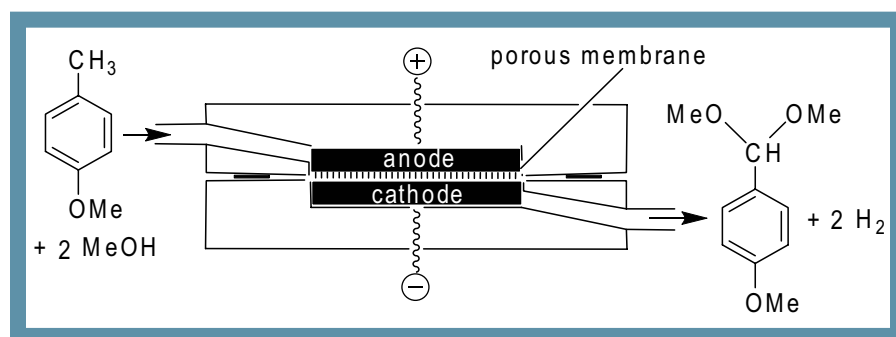


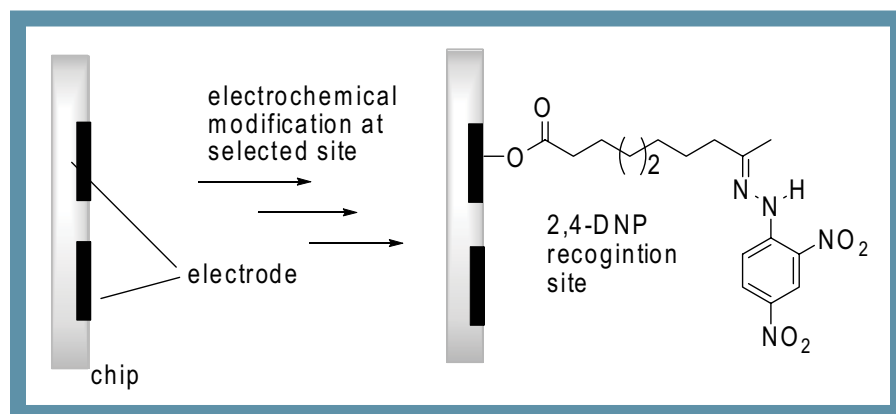**FIG. 8.** *Methoxylation of N-methoxycarbonyl pyrrolidine.*



**FIG. 9.** *Microchip reactor having addressable platinum electrodes and addressable library building.*
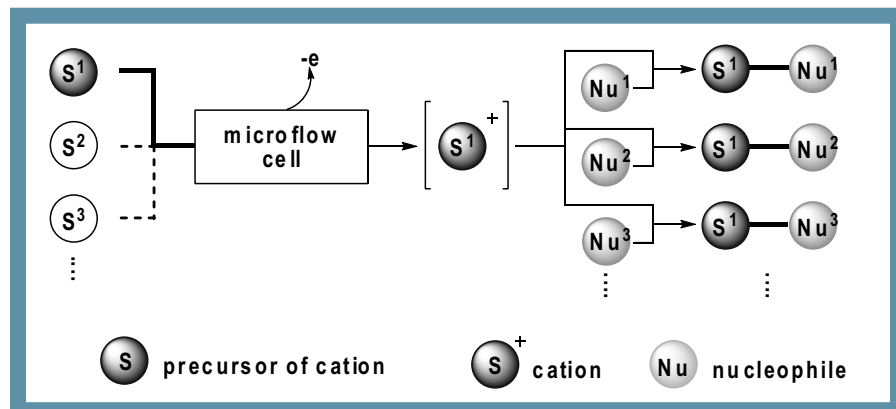


**FIG. 10.** *Sequential combinatorial synthesis based on the cation flow method.*

weight control and molecular-weight distribution control can be attained in the electrogenerated *N*-acyliminium ion initiated polymerization of vinyl ethers using a microreator (Fig. 12).[18] The polymerization is complete within a second or so. The molecular weight increases with an increase in the monomer/initiator ratio, indicating that chain-transfer reactions do not play an important role. The microflow system-controlled cationic polymerization seems to be close to ideal living polymerization within a short residence time. The end-functionalization was successfully achieved by adding a suitable reagent instead of the terminator.

## Future Outlook

Organic electrochemistry has a long history and has witnessed a steady march in the progress of our understanding of factors governing electrode processes involving reactive intermediates. Various applications have been developed both in academia and industry. It is noteworthy, however, that there are still some problems inherent in conducting electrochemical reactions of organic compounds in a preparative scale. Such problems can be solved by the collaboration with microreactor chemistry, which has emerged very recently as a promising science and technology. Some examples have been demonstrated in this article. There must be many other possibilities for the collaboration. It is hoped that various applications of the collaboration will be developed and widely utilized in laboratory synthesis and industrial production to meet future demands for efficient synthesis and production of various organic molecules and polymers. ∎

## About the Author

**Jun-ichi Yoshida** is presently a professor in the Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University. His research interests include a broad range of organic chemistry and organic electrochemistry, such as reactive intermediates and organic electron transfer reactions. He is also studying organic synthesis using microflow reactors, which can influence the very essence of chemical reactions. Recently Prof. Yoshida has proposed a concept of flash chemistry for carrying out extremely fast reactions in organic synthesis by using integrated microflow systems. Reaction times range from milliseconds to seconds. He may be reached at yoshida@sbchem.kyoto-u.ac.jp.

**Fig. 11.** *A microreactor system for selective Friedel-Crafts monoalkylation.* **M**: *micromixer.* **R**: *microtube reactor.*

|  | monoalkylation product | dialkylation product |
| --- | --- | --- |
| microreactor | 92% | 4% |
| flask | 37% | 32% |



**Fig. 12.** *A microreactor system for controlled/living cationic polymerization.* **M1, M2**: *micromixers.* **R1, R2**: *microtube reactors. The polymerization was normally carried out at -78˚C.*

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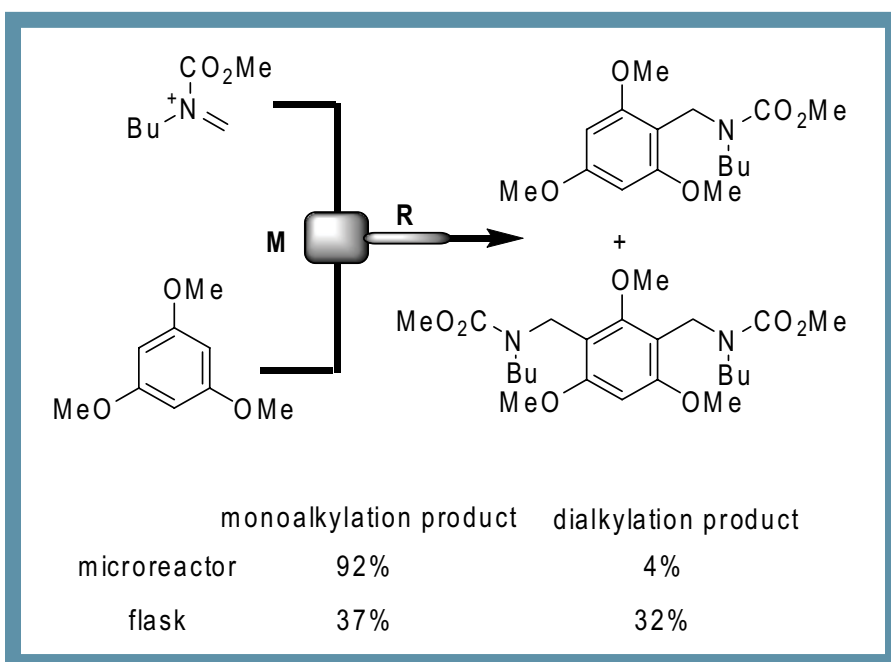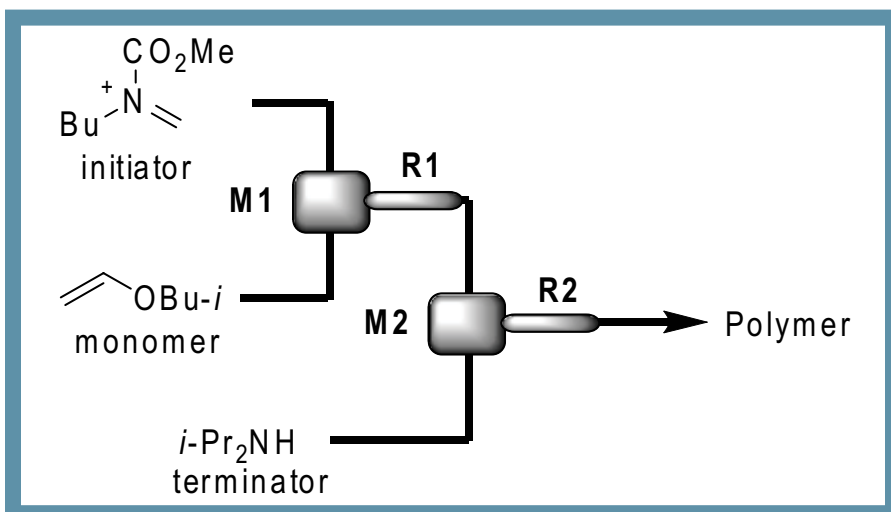
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