# Flash chemistry using electrochemical method and microsystems

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This feature article provides a brief outline of the concept of flash chemistry for conducting extremely fast reactions in organic synthesis using electrochemically generated highly reactive species and microsystems.

## Introduction

Organic synthesis has witnessed a steady march in the progress of our understanding of factors governing chemical reactions. With a rational design of synthesis, desired compounds are produced in a highly selective manner. The role of organic synthesis has been extended to various fields of science and technology. Because of rapid progress in such fields, demands for producing desired compounds in a highly time efficient way have been increasing. In order to meet such demands and achieve rapid synthesis of a variety of organic compounds, acceleration of organic synthesis is highly called for. Conventional organic synthesis, however, has been a rather time consuming task. Chemists have been using slow reactions because fast reactions are difficult to control and often give significant amounts of undesired by-products. Reaction time in conventional organic synthesis usually ranges from minutes to hours. In order to achieve more rapid synthesis, the use of much faster reactions in a controlled way is strongly needed. This article provides a brief outline of the concept of flash chemistry for conducting extremely fast reactions in a highly controlled manner with special emphasis on the use of electrochemically generated highly reactive species and microsystems.

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### Why rapid synthesis is needed?

Recently it has been widely recognized that rapid creation of chemical libraries serves as a powerful method for discovery of new drugs and materials.[1] Combinatorial library approach has caused a great cultural change in laboratory synthesis and scientists are now performing many reactions at a time. The effectiveness of this approach depends on how rapidly we create chemical libraries. Therefore, each reactions should be fast in order to achieve library synthesis in highly time efficient manner. In this context, click chemistry has been explored.[2] In click chemistry, useful new compounds and combinatorial libraries are rapidly synthesized through heteroatom links by a set of powerful, highly reliable, and selective reactions, which are usually fast. If much faster reactions are available for synthesis, chemical libraries can be constructed more rapidly. Although rapid batch processing using robotics can be used, continuous sequential combinatorial synthesis by flow switching[3] seems to be more suitable for this purpose. Anyway, extremely fast reactions are needed for rapid synthesis of chemical libraries to create new materials and biologically active compounds.

For industrial production of chemical compounds, it is obvious that faster reactions are better than slower reactions as far as they are controllable. With faster reactions, greater quantity of compounds can be produced per unit time. The use of extremely fast reactions in conjunction with flow systems may leads to smaller size of reactors in chemical plants. It is also noteworthy that faster reactions make on-demand synthesis easier. Chemical plants in future are likely to be closer to customers, and therefore, distribution of a large number of small-scale rapid production units and their

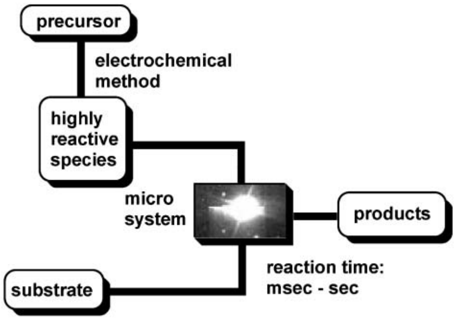


**Fig. 1** General concept of flash chemistry using an electrochemically generated highly reactive species and a microsystem.

on-demand operation should become more popular.[4] Such a situation may be beneficial not only from an environmental point of view but also economically because of increased adjustability and flexibility of production to the change of market demands.

Therefore, development of rapid reactions for chemical synthesis is strongly needed from the view points of both laboratory synthesis and industrial production.

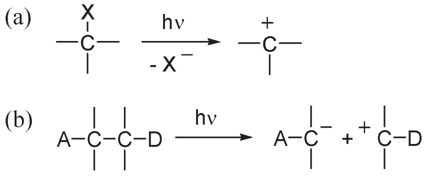
## Acceleration of reactions

In flash chemistry, extremely fast reactions are conducted in a highly controlled manner, and desired products are formed in the twinkling of an eye. Reaction time ranges from milliseconds to seconds.

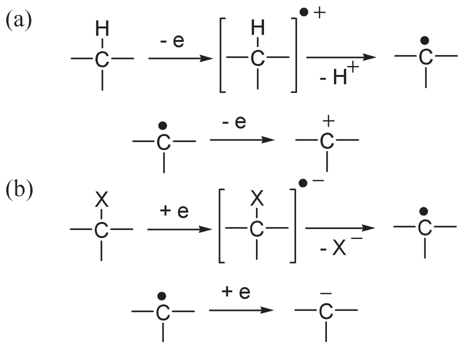
The concept of flash chemistry already exists in organic chemistry.[5] For example, flash vacuum pyrolysis (FVP) is well known as a powerful method for conducting thermal reactions in organic synthesis.[6] In FVP, a suitable precursor is subjected to very high temperatures with a steady stream of inert carrier gas flowing through a sample chamber under relatively high vacuum. This allows molecules to pass through the very hot part of the system within seconds. The residence time is set long enough for reaction to give the desired product but not long enough for decomposition to occur. One of the most fascinating applications of FVP is the synthesis of $C_{60}$.[7]

In order to accelerate thermal reactions, microwave reactions have received significant research interest.[8] In conventional methods, reactants are heated by an external heat source such as an oil bath. Heat is driven through the walls of the flask and this energy transferring process is obviously indirect and therefore inefficient. In the microwave reactions, microwaves couple with the substrate and/or solvent molecules and activate them directly. Therefore, heating is highly efficient. Although such thermal acceleration by microwave is significant, reaction time usually ranges from seconds to minutes. It is also noteworthy that in most cases microwave reactions are conducted in a batch system, although the use of a microflow system for microwave reactions has been reported very recently.[9]

Another popular example of flash chemistry is laser flash photolysis (FLP).[10] A short pulse of excimer laser is flashed to a substrate, which often leads to bond dissociation generating short-lived reactive intermediates such as free radicals, carbocations, and carbanions. FLP serves as an excellent method for an instantaneous generation of a reactive intermediate in uniform concentration. Examples of generating carbocations by photo-initiated carbon–heteroatom bond cleavage are shown in Scheme 1a. The cleavage of carbon–carbon bond having suitable acceptor and donor groups also takes place photochemically giving rise to simultaneous formation of carbocations and carbanions (Scheme 1b).



**Scheme 1** Photochemical generation of reactive carbon species (X: leaving group, A: acceptor group, D: donor group).



**Scheme 2** Electrochemical generation of reactive carbon species (X: leaving group).

Electrochemical method is also quite effective for flash chemistry. Electrochemistry serves as one of the most straightforward ways to make highly reactive reagents under mild conditions.[11] Highly reactive radical cations, cations, free radicals, anions, and radical anions can be generated electrochemically at room temperature or below as shown in Scheme 2. For example, one-electron oxidation of organic compounds leads to the formation of radical cations, which often loose a proton to generate carbon free radicals. Further oxidation of free radicals affords the corresponding carbocations (Scheme 2a). On the other hand, reduction of organic compounds having a leaving group X leads to the formation of negatively charged carbanions *via* carbon free radicals (Scheme 2b).

The combination of the pulse electrolysis and the stopped flow method has been used for the reactivity study of radical cations.[12] A highly reactive transient radical cation was generated very rapidly and its extremely fast reaction was analyzed. The stopped flow method has been utilized by chemists to facilitate the study of the kinetics and mechanisms for fast reactions.[13] In the method two reactants are driven at a high rate into a mixing chamber. The flow is abruptly stopped and the extent of reaction is monitored by measuring a given property of the solution.

Although, laser flash photolysis and pulse electrolysis have been utilized successfully for mechanistic studies, few examples has been reported for applications in organic synthesis. We should keep in mind, however, that photochemistry and electrochemistry serve as powerful methods for rapid generation of highly reactive species that can be used for flash chemistry in synthesis of organic compounds.

## Control of extremely fast reactions using microsystems

Another important element of flash chemistry is the technology for controlling extremely fast reactions of highly reactive species. Without such technology, reactions may not be controllable and desired products are not obtained selectively.

Microsystems seem to be a nice technology for conducting extremely fast reactions. Since the use of microsystems[13] was proposed to serve as an effective method for the synthesis of chemical substances, enormous advances in this field have

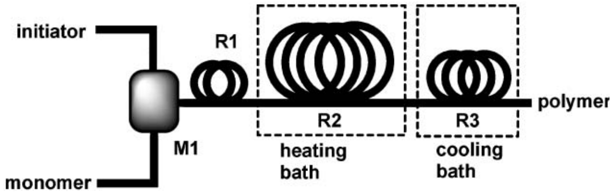


**Fig. 2** A microsystem for radical polymerization. **M1**: micromixer. **R1**, **R2**, **R3**: microtube reactor.

been accomplished. Microsystems have been expected to make a revolutionary change in chemical synthesis,[14–16] because they exhibit numerous advantages stemming from small size and high surface-to-volume ratio of microstructures.

Highly exothermic reactions can be conducted by virtue of efficient mass and heat transfer in microsystems. For example, in radical polymerization, better control of molecular weight distribution has been achieved with a microsystem in comparison with a macro-scale batch system.[17] Highly efficient heat transfer of the microsystem seems to be responsible. It is also important to note that the effect of the microsystem was large for highly exothermic polymerization such as butyl acrylate polymerization, but only a small effect was observed for less exothermic polymerization such as styrene polymerization.

Extremely fast mixing by virtue of a short diffusion path is another important advantageous feature of microsystems.[18] There are several principles of micromixers such as multilamination,[19] injection of many small substreams of one component in a main stream of another component, decrease of diffusion path perpendicular to the flow direction, manifold splitting and recombination, periodic injection of small fluid segments, and collision of micro segments in the centre of the mixer.[20]

It is well known that product selectivity of extremely fast reactions often depends on the way of mixing, and recently it has been recognized that micromixing serves as an effective method for improving the product selectivity of such reactions.[21] It is important to note, however, that the chemistry in microsystems is not different from the chemistry in conventional macro-scale batch reactors. In macro-scale batch reactors, kinetics does not work for extremely fast reactions because of local deviations of concentration due to inefficient mixing. In such cases, microsystems serve as better reaction environments where kinetics works better.

Another important feature of microsystems is residence time control. In microsystems residence time can be adjusted to be shorter than seconds. This feature is important for the reaction involving highly unstable intermediates that decompose very rapidly. Recently, Swern oxidation of alcohols has been accomplished at room temperature using a microsystem.[22] Swern oxidation involves the formation of highly reactive intermediates, which undergo inevitable Pummerer rearrangement at temperatures higher than −30 °C. Such decomposition leads to the formation of undesirable side-products. Therefore, Swern oxidation has been usually carried out at low temperatures such as −50 °C. The control of residence time within 0.01 s by using a microsystem, however, leads to the formation of desired carbonyl compounds in high yields even at 20 °C. This observation demonstrates a striking example of the effectiveness of microsystems for the control of highly reactive intermediates.

**Fig. 3** A multilamination type micromixer (IMM (Institut für Mikrotechnik Mainz GmbH) single mixer).

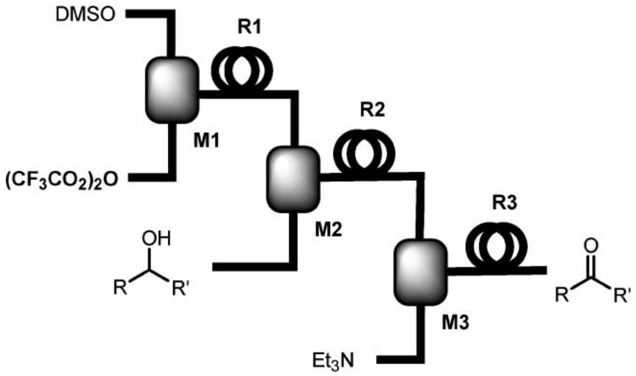


**Fig. 4** A microsystem for room temperature Swern oxidation. **M1**, **M2**, **M3**: micromixer. **R1**, **R2**, **R3**: microtube reactor.

It is also noteworthy that easy modulation and numbering-up of microsystems for increasing the amount of production are also beneficial from a view point of industrial applications. We should keep in mind that microsystems can be used for production of relatively large quantity of compounds. As a matter of fact, pilot plants based on microsystems for tons per year scale production have already been built.

Thus, microsystems are expected to serve as a powerful tool for conducting extremely fast and exothermic reactions in a highly controlled manner to effect "flash chemistry", where desired products are formed within milliseconds to seconds. In the following part of this article, our approach to flash chemistry based on microsystems and electrochemically generated reactive cation pools is demonstrated.

## Electrochemical generation of highly reactive carbocations

In our approach toward flash chemistry, we focused on the electrochemical generation of highly reactive carbocation species. It is well known that carbocations can be effectively generated by the anodic oxidation of suitable precursors. It is also noteworthy that carbocations are usually generated in the presence of a nucleophile in conventional methods because they are not stable and should be trapped immediately after

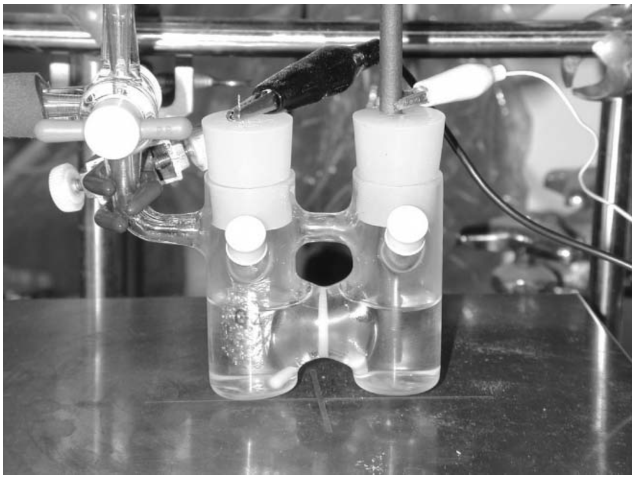


**Fig. 5** An H-type electrochemical cell for the ‘‘cation pool’’ method.

generation. We have developed, however, a new method for generation and accumulation of highly reactive cations in the absence of a nucleophile using low temperature electrolysis (the ‘‘cation pool’’ method).[23] An H-type cell, where the anodic oxidation and the cathodic reduction are carried out in separated chambers, for the ‘‘cation pool’’ method is shown in Fig. 5.

A picture of the low temperature electrochemical oxidation system for the generation of ‘‘cation pools’’ is shown in Fig. 6. The DC power supply is not so expensive and the reaction can be easily carried out with normal laboratory techniques for the handling of air-sensitive reagents at low temperatures.

After generation of the cation, a suitable nucleophile, such as organic and organometallic compounds is added to the ‘‘cation pool’’ to accomplish a desired reaction.

The method has been successfully applied for the generation and reactions of *N*-acyliminium ions and alkoxycarbenium ions (Scheme 3). The use of a silyl group as an electroauxiliary,[24] which activates substrate molecules toward electron transfer and controls the regiochemistry, is sometimes very effective for this method.

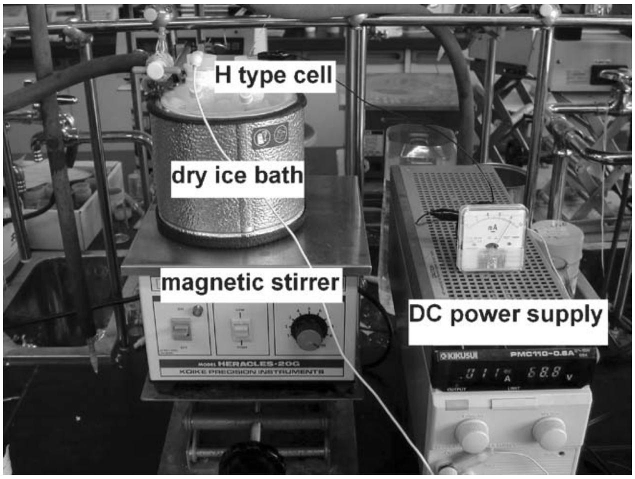
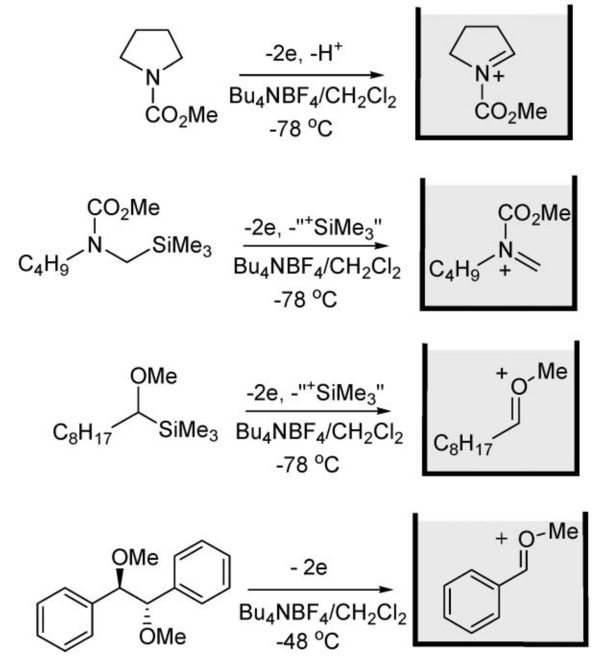


**Fig. 6** An electrochemical system for the generation of ‘‘cation pools’’.



**Scheme 3** The generation of *N*-acyliminium ion pools and alkoxycarbenium ion pools by low temperature electrolysis.

We have also developed a flow method for the generation of *N*-acyliminium ions by using an electrochemical microflow system (the ‘‘cation flow’’ method).[3,23*e*] In the ‘‘cation flow’’ method, a carbocation is generated continuously in a flow system by low temperature electrolysis (Fig. 7 and 8). The generation of the cation can be monitored by a FTIR

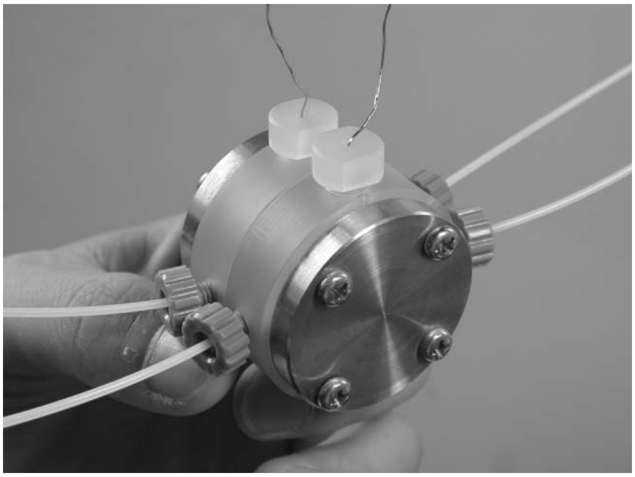


**Fig. 7** An electrochemical microflow reactor for the ‘‘cation flow’’ method.

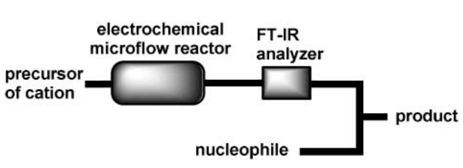


**Fig. 8** Schematic diagram of the ‘‘cation flow’’ system.

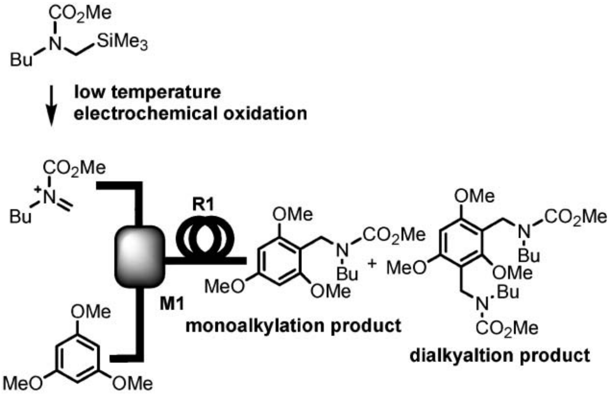
spectrometer (ATR method) equipped with a low temperature flow cell attached to the outlet of the electrochemical microflow reactor.

With the "cation pool" method and the "cation flow" method in hand, we initiated our project directed toward flash chemistry using microsystems.

### Flash chemistry using electrochemically generated highly reactive cations and microsystems

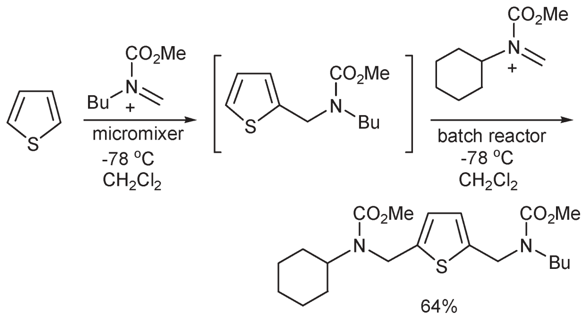
**Selective Friedel–Crafts monoalkylation[25].** We first studied Friedel–Crafts reaction of aromatic compounds with electrochemically generated *N*-acyliminium ion pools. The reaction of trimethoxybenzene with an *N*-acyliminium ion using a conventional macro-scale batch reactor resulted in the formation of an essentially 1 : 1 mixture of a monoalkylation product and a dialkylation product. This is presumably because the reaction is too fast, faster than mixing. The reaction using a microsystem consisting of a multilamination type micromixer, however, gave rise to a dramatic increase in the product selectivity. In this case, a solution of the *N*-acyliminium ion and that of trimethoxybenzene were introduced to the micromixer at −78 °C and the product solution that left from the device was immediately quenched with triethylamine in order to avoid further reactions. The reaction completed within a second. The monoalkylation product was obtained in excellent selectivity and the amount of dialkylation product was very small (Fig. 9). Extremely fast 1 : 1 mixing using the micromixer and efficient heat transfer in the microsystem seem to be responsible for the dramatic increase in the product selectivity.

The sequential alkylation reactions with two different alkylating agents were also achieved (Scheme 4). The first alkylation of thiophene was carried out with the *N*-acyliminium ion using the micromixer to obtain the monoalkylation product, which was directly subjected to the second alkylation with a different *N*-acyliminium ion in a batch reactor to obtain dialkylation product



| | | |
|---|---|---|
| **micro flow system** | **92%** | **4%** |
| **macro batch system** | **37%** | **32%** |

**Fig. 9** A microsystem for selective Friedel–Crafts monoalkylation. **M1**: micromixer. **R1**: microtube reactor.



**Scheme 4** Sequential dialkylation of thiophene using two different *N*-acyliminium ion pools.

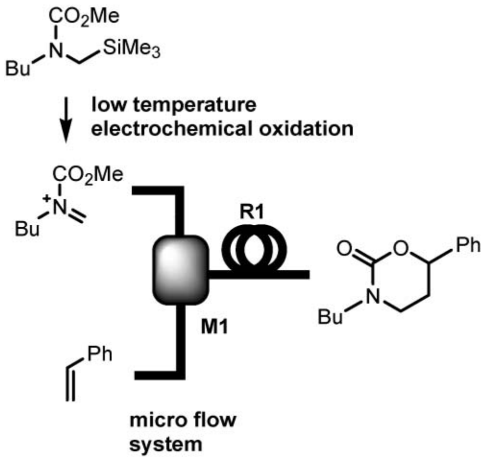


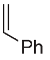
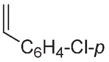
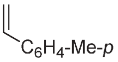
**Fig. 10** A microsystem for selective [4+2] cycloadditon. **M**1: micromixer. **R1**: microtube reactor.

**[4+2] Cycloaddition reactions[26].** The *N*-acyliminium ion pools react rapidly with a variety of dienophiles such as alkenes and alkynes to give the corresponding [4+2] cycloaddition products in high yields. This reaction can be conducted with a microsystem consisting of a multilamination type micromixer and a microtube reactor (Fig 10). For example, the reaction of an *N*-acyliminium ion with styrene gave the corresponding cycloadduct in 79% yield together with a polymeric by-product (*ca.* 20%). It is worth noting that the product selectivity increased by the use of the microsystem. The addition of the cation pool to a solution of styrene in a flask gave the cycloadduct in only 20% yield and a significant amount of styrene polymer (*ca.* 80% yield based on styrene) was formed. The reverse addition gave the cycloaddition product in 57% yield. The simultaneous addition of two reaction components gave essentially the same results as the reverse addition. Similar trends were also observed for other styrene derivatives (Table 1). Extremely fast mixing using the micromixer seems to be responsible for higher product selectivity obtained with the microsystem.

### Controlled/living cationic polymerization[27]

Cationic polymerization reactions seem to be suitable reactions for flash chemistry because they are usually extremely fast even at low temperatures. Because "cation pools" were found to serve as effective initiators of

**Table 1** Effect of the way of mixing on the yield of the cycloadduct[a,b]

| | Yield of the cycloadduct (%)[c] | | | |
|---|---|---|---|---|
| Alkene | Method A | Method B | Method C | Micro-mixing[d] |
|  | 57 | 20 | 55 | 79 |
|  | 43 | 12 | 54 | 70 |
|  | 45 | 16 | 58 | 66 |

[a] Method A: Addition of a solution of an alkene to a solution of the *N*-acyliminium ion at −78 °C. Method B: Addition of a solution of the *N*-acyliminium ion to a solution of an alkene at −78 °C. Method C: Addition of a solution of an alkene and a solution of the *N*-acyliminium ion into a reaction flask simultaneously at −78 °C. [b] Reactions were immediately quenched by triethylamine. [c] Isolated yield. Yields were determined on the basis of dienophiles. [d] A multilamination type micromixer was used.

carbocationic polymerization of vinyl ethers, we initiated the study of cationic polymerization using our "cation pools" and microsystems.

The polymerization of n-butyl vinyl ether using an *N*-acylminium ion pool in a macro-scale batch reactor with stirring gave a polymer in quantitative yield, but the molecular weight distribution was not narrow ($M_w/M_n > 2$). A microsystem consisting of two micromixers (**M1** and **M2**) and a microtube reactor (**R1**), however, was found to be quite effective for the control of molecular weight and molecular weight distribution ($M_w/M_n = 1.14$) (Fig. 11).

It should be noted that in conventional living cationic polymerization a dynamic equilibrium between active and dormant species is essential for the control of molecular weight distribution (Fig. 12).[28] Such equilibrium, however, decelerates the propagation significantly. The present method does not involve such an equilibrium and serves as a new method for molecular weight distribution control without the deceleration inherent in the equilibrium.

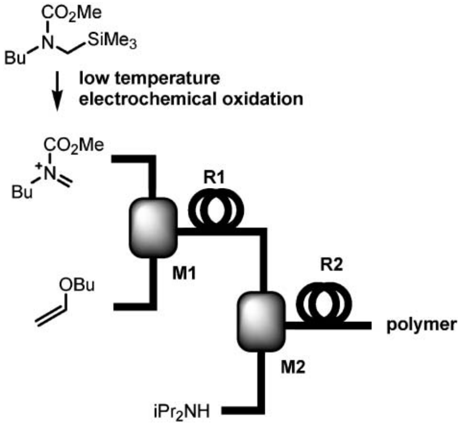


**Fig. 11** A microsystem for controlled/living cationic polymerization. **M1**, **M2**: micromixer. **R1**, **R2**: microtube reactor. The polymerization was normally carried out at −78 °C.

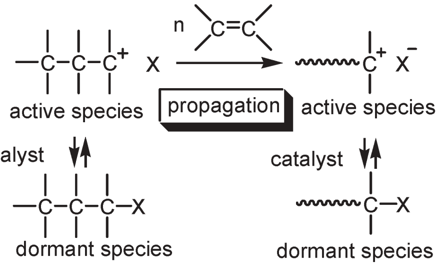


**Fig. 12** Equilibrium between active species and dormant species in conventional living cationic polymerization.

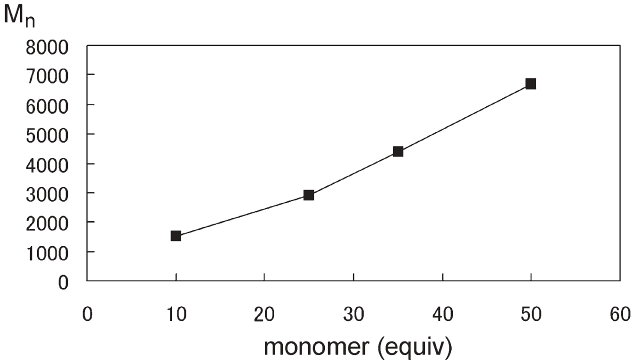


**Fig. 13** Plots of molecular weight against the amount of the monomer used for the polymerization.

The fact that the molecular weight increased linearly with the increase of the amount of monomer as shown in Fig. 13 suggests that the chain transfer reaction did not play a significant role in this system. Extremely fast mixing, effective temperature control, and residence time control by virtue of the microsystem seem to be responsible for excellent molecular weight distribution control.

The NMR studies of the polymer, which was obtained by the polymerization followed by the quenching with the addition of allyltrimethylsilane using the microsystem, indicated that the *N*-acyliminium ion initiating group was really incorporated into the polymer chain and that the carbocationic polymer end was quantitatively trapped by the added allyltrimethylsilane (Fig. 14). Therefore, the polymer end can be used as a living reactive species for the follow-up reaction with various nucleophiles. Thus, the present method serves as an efficient method for the synthesis of polymers having various functional groups at both ends.

## Conclusion

Several examples of flash chemistry using electrochemically generated "cation pools" and microsystems are demonstrated in this feature article. The "cation pool" method serves as an effective method for generating highly reactive species under mild conditions. The use of highly reactive cation leads to extremely fast reactions. Microsystems serves as an effective method for the control of such fast reactions. Extremely fast mixing, efficient heat transfer, and residence time control by virtue of microsystems are responsible. The examples shown in this article hopefully help to illustrate the potential of

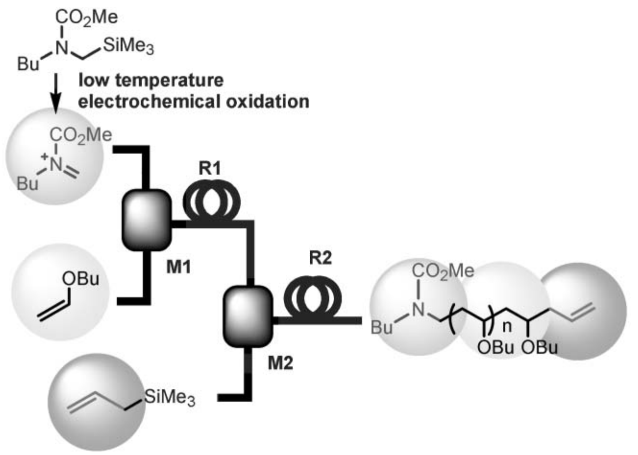


**Fig. 14** *N*-Acyliminium ion pool initiated polymerization of n-buyl vinyl ether terminated by allyltrimethylsilane.

microsystems, in conjunction with "cation pools", to effect flash chemistry in a highly controlled manner. It is hoped that various types of flash chemistry based on different methods for generating reactive species will be developed and widely utilized in laboratory synthesis and in chemical plants to meet demands of rapid synthesis of various organic small molecules and polymers in future.

## Acknowledgements

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