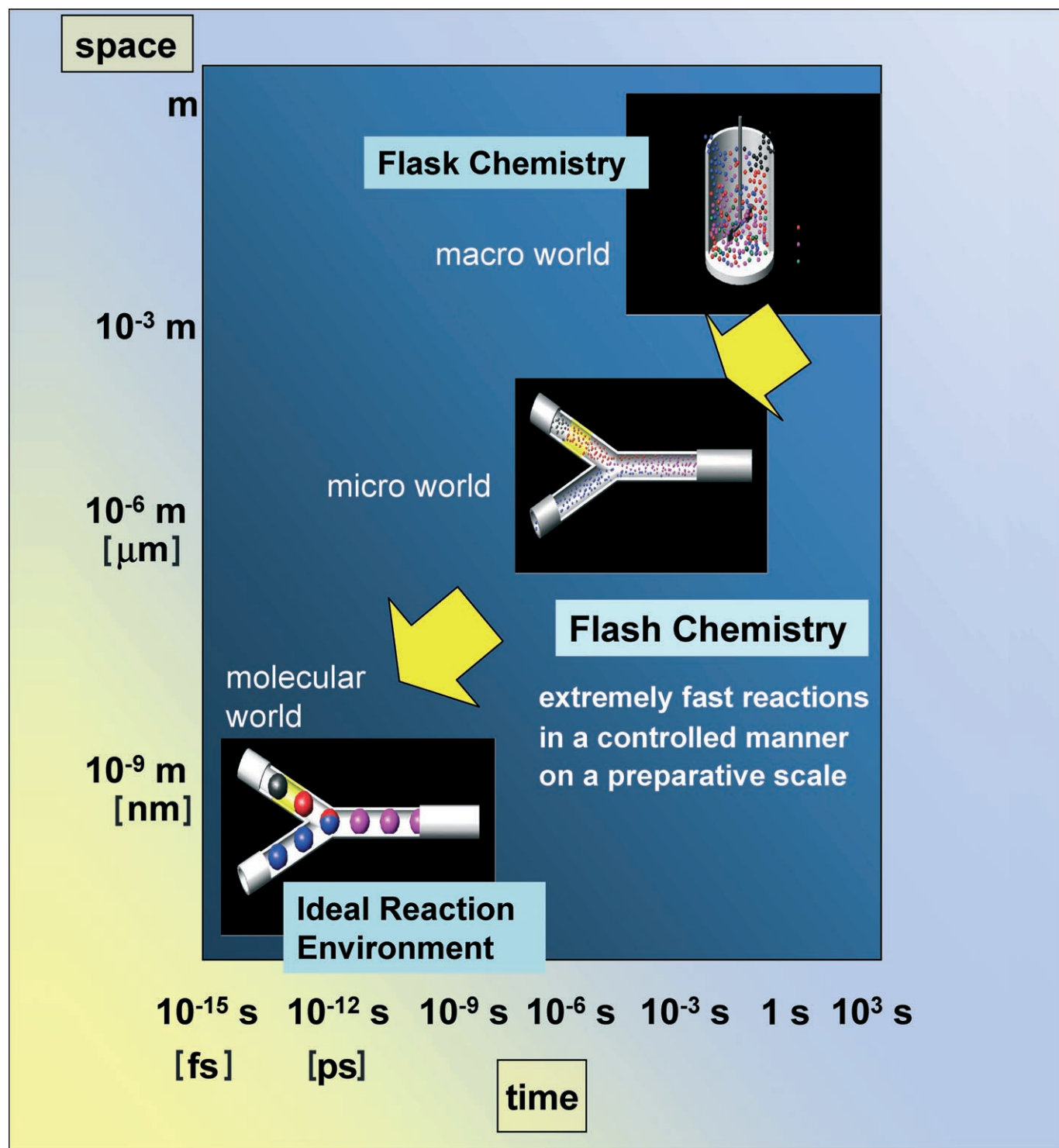# Flash Chemistry: Fast Chemical Synthesis by Using Microreactors

Jun-ichi Yoshida, Aiichiro Nagaki, and Takeshi Yamada[a]

Abstract: This concept article provides a brief outline of the concept of flash chemistry for carrying out extremely fast reactions in organic synthesis by using microreactors. Generation of highly reactive species is one of the key elements of flash chemistry. Another important element of flash chemistry is the control of extremely fast reactions to obtain the desired products selectively. Fast reactions are usually highly exothermic, and heat removal is an important factor in controlling such reactions. Heat transfer occurs very rapidly in microreactors by virtue of a large surface area per unit volume, making precise temperature control possible. Fast reactions often involve highly unstable intermediates, which decompose very quickly, making reaction control difficult. The residence time can be greatly reduced in microreactors, and this feature is quite effective in controlling such reactions. For extremely fast reactions, kinetics often cannot be used because of the lack of homogeneity of the reaction environment when they are conducted in conventional reactors such as flasks. Fast mixing using micromixers solves such problems. The concept of flash chemistry has been successfully applied to various organic reactions including a) highly exothermic reactions that are difficult to control in conventional reactors, b) reactions in which a reactive intermediate easily decomposes in conventional reactors, c) reactions in which undesired byproducts are produced in the subsequent reactions in conventional reactors, and d) reactions whose products easily decompose in conventional reactors. The concept of flash chemistry can be also applied to polymer synthesis. Cationic polymerization can be conducted with an excellent level of molecular-weight control and molecular-weight distribution control.

Keywords: green chemistry · microreactors · polymerization · synthetic methods

Introduction

Organic synthesis has witnessed a steady march in the progress of our understanding of factors governing chemical reactions. 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 fast synthesis of a variety of organic com-

pounds, acceleration of organic reactions is highly sought after. However, chemists have used 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 faster synthesis, the use of much faster reactions in a controlled way is highly desirable. This concept article provides an outline of the concept of flash chemistry[1] for conducting extremely fast reactions in a highly controlled manner using microstructured-flow reactors or microreactors.[2]

Concept of Flash Chemistry

Flash chemistry is defined as a field of chemical synthesis where extremely fast reactions are conducted in a highly controlled manner to produce desired compounds with high selectivity. Reaction times range from milliseconds to seconds. (Figure 1).[1]
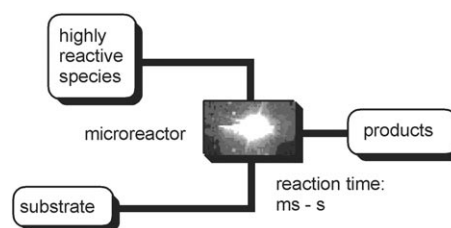

Figure 1. General concept of flash chemistry using a microreactor.

Why Is Flash Chemistry Needed?

Why is fast chemical synthesis needed? The reason why flash chemistry is needed is we can just do it. Chemical reactions are essentially extremely fast processes at the molecular level. It takes several hundred femtoseconds for the conversion of a single starting molecule to a single product molecule. Therefore, if all reactant molecules in a reactor react at once or coherently, the reaction time should be several hundred femtoseconds. This is the scientific limit of reaction times. From a technical point of view, we are presently far from that point. Reaction times for chemical synthesis usually range from minutes to hours using macrobatch reactors such as flasks in laboratory organic synthesis and industrial production. However, today we have new tools for conducting much faster reactions in a controlled way, that is, microreactors.

The time required for a single molecule to react from a reactant to a product through the transition state is in the range of 10^{-14}–10^{-13} s, while the time required for all molecules in a flask react usually ranges from minutes to hours

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$(10^2$–10^4 s). The size of molecules is in the range of 10^{-10}–10^{-9} m, whereas the size of a flask ranges from 10^{-2} to 10^0 m. So, there is a rough correlation between the reaction time and the size of the reaction environment as shown in Figure 2. In flash chemistry, we use a reactor, the size of which ranges from 10^{-6} to 10^{-3} m. Therefore, it is easy to understand that the size of the reaction environment of flash chemistry is closer to the size of the molecular level reaction environment than is that of conventional flask chemistry. Although the reaction time in flash chemistry is still much longer than femto- and picoseconds, it can be reduced to the range of 10^{-3} to 1 s.
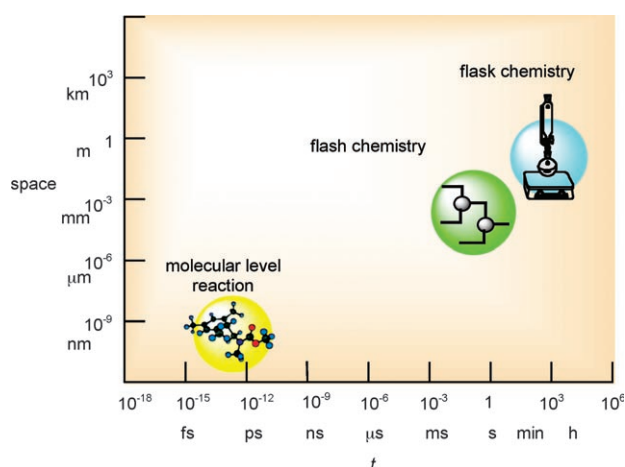

Figure 2. Time/space relationship for chemical reactions.

Another reason why flash chemistry is needed today is that our way of synthesizing compounds is currently changing. For example, combinatorial synthesis of chemical libraries[3] has become very popular in academia and industry, and on-site on-demand synthesis is expected to be popular in the future. These new trends in chemical synthesis increase the demand for flash chemistry.

Methods of Activating Molecules

To accomplish such 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. Thermal, photochemical, and electrochemical reactions serve as effective methods for such purpose. For example, flash vacuum pyrolysis (FVP) is well known as a powerful method for conducting thermal reactions in organic synthesis. Other popular examples of flash chemistry are laser flash photolysis (FLP) and pulse electrolysis. Although, such reactions have been successfully utilized for mechanistic studies, few examples have been reported for applications in organic synthesis.

Activation of substrate molecules to generate highly reactive species constitutes an important element of flash chemistry. Generation and accumulation of highly reactive species as reagents is also important. A variety of methods are available to generate and accumulate carbanions (organometallic compounds as equivalents) and carbocations,[4] which may undergo extremely fast reactions.

Carbon radicals are difficult to accumulate in solution because their lifetime is very short. However, carbon radicals can be generated in a short period using redox conversions of carbanions or carbocations. With these methods for generating highly reactive species in hand, we can accomplish extremely fast reactions in flash chemistry.

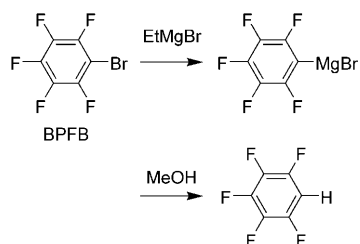## Control of Extremely Fast Reactions by Using Microreactors

Another important element of flash chemistry is the technology for controlling extremely fast reactions involving highly reactive species. Without such technology, reactions may not be controllable and desired products are not obtained selectively. Microreactors seem to be a good technology for conducting extremely fast reactions. Since the use of microreactors was proposed to serve as an effective method for the synthesis of chemical substances, enormous advances in this field have been accomplished. Microreactors have been expected to make a revolutionary change in chemical synthesis, because they exhibit numerous advantages stemming from small size and high surface-to-volume ratio of microstructures.

Fast reactions are usually highly exothermic. Therefore, heat removal is also an important factor in controlling the extremely fast reactions. Heat transfer takes place through the surface of the reactor. By taking advantage of the fact that microspaces have a large surface area per unit volume compared with macrospaces, heat transfer occurs very rapidly in microreactors, making precise temperature control possible.

Another important feature of microreactors is residence time control. In microreactors residence time can be adjusted to less than seconds. This feature is important for the reaction involving highly unstable intermediates that rapidly decompose.

Extremely fast mixing by virtue of a short diffusion path is also an important advantageous feature of microreactors. It is well known that product selectivity of extremely fast reactions often depends on how reactants are mixed,[5] and recently it has been recognized that micromixing serves as an effective method for improving the product selectivity of extremely fast reactions. In conventional reactors kinetics sometimes does not work for extremely fast reactions because of local deviations of concentration due to inefficient mixing (Figure 3b). In such cases, microreactors serve as much better reaction environments where kinetics is more efficient (Figure 3c). In other words, microreactors provide a reaction environment close to an ideal reactor in molecular size (Figure 3a), even if preparative scale reactions are conducted. It is important to note, however, that the chemistry

in microreactors is not different from the chemistry in conventional reactors, such as flasks.

It is also important to note that using a continuous flow system composed by microreactors, it is fairly easy to make

Figure 3. Reactors for chemical reactions: a) ideal reactor in molecular size, b) conventional macrobatch reactor, c) microreactor.

a larger quantity of compounds than one can expect from the size of the reactor. Easy modulation and numbering-up of microreactors for increasing the amount of production are also beneficial from the viewpoint of industrial applications. Indeed, pilot plants based on microreactors for tons per year scale production have already been built.

Thus, microreactors 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 sections, some examples of flash chemistry based on microreactors will be demonstrated.

Applications of Flash Chemistry in Organic Synthesis

There are many applications of flash chemistry in organic synthesis.[6] Because of space limitations, our discussion in this article is not an exhaustive compilation of all known examples. Rather, it is a sampling of sufficient variety to illustrate the principles, features, and advantages.

Highly exothermic reactions that are difficult to control in conventional reactors: Highly exothermic, extremely fast reactions are usually carried out by slowly adding one of the reaction components to the other. Therefore, the total reaction performance depends on the adding rate. Microreactors make the reactions be controllable even under the relatively high concentration conditions to increase the total performance of the reaction.

Direct halogenation reactions of organic compounds by using F_2 serve as good examples of such cases. Reactions of F_2 with organic compounds are usually extremely fast and highly exothermic. The reaction is often explosive. Therefore, such reactions are difficult to control using conventional reactors, although the direct fluorination using F_2 is the most straightforward way to synthesize fluorine-containing organic compounds. However, the use of a microreactor serves as an effective way to perform such reactions in a controlled manner. A pioneering work by Chambers and Spink was reported in 1999,[7] and since then direct fluorination using microreactors has been studied extensively.[8] For example, fluorination of 1,3-dicarbonyl compounds can be easily accomplished as shown in Scheme 1.

$R^1 = CH_3$, $R^2 = H$, $R^3 = OEt$	69%
$R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3$	76%
$R^1 = CH_3$, $R^2 = CH_3$, $R^3 = CH_3$	91%

Scheme 1. Direct fluorination of 1,3-dicarbonyl compounds using a microreactor.

Fluorination of other organic compounds such as aromatic compounds by using microreactors,[9] and the halogenation with Cl_2, and Br_2 using microreactors[10] have also been reported.

Other highly exothermic organic reactions including nitration,[11] H_2O_2 oxidation,[12] and 1,4-addition of amines to activated olefins[13] can be also carried out in controlled manners using microreactors.

Organometallic reactions are often very fast and highly exothermic. For example, the halogen–metal exchange reactions are usually highly exothermic and slow addition is essential to avoid a rapid temperature increase when the reaction is carried out in a conventional reactor.

The halogen–magnesium exchange reaction of bromopentafluorobenzene (BPFB) and EtMgBr has been used in industrial production (Scheme 2). Usually, slow addition is used to avoid a rapid increase in temperature. Therefore, it takes a long time to complete the addition and therefore, the overall time efficiency is low. This reaction can be conducted in highly controlled manner using a microreactor.[14]

A pilot plant composed of a micromixer connected to a shell and tube microheat exchanger has been constructed (Figure 4). The residence time in the device was about 5 s. The reaction temperature was automatically controlled at

Scheme 2. Halogen–magnesium exchange reaction of BPFB and EtMgBr.

20 °C by circulating water in the shell of the heat exchanger. The pilot plant was operated smoothly without any problems for a period of 24 h to obtain 14.7 kg of the product (92 % yield).

Figure 4. Picture of the pilot plant for the halogen-magnesium exchange reaction of BPFB and EtMgBr.

The halogen–magnesium exchange reaction between C_2F_5I and MeMgCl has also been carried out using a microreactor (Figure 5).[15] The reaction is complete at −6 °C within the residence time of 0.9 min. The resulting C_2F_5MgCl is allowed to react with benzophenone at −4 °C to give the addition product in 86 % yield after hydrolysis. The residence time for the second step is 8 min.
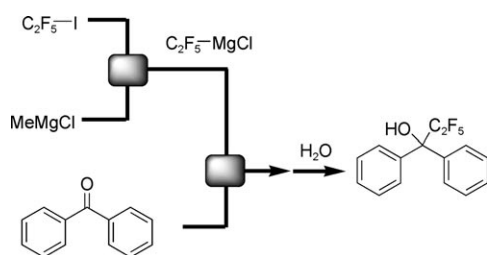
Figure 5. Grignard exchange reaction of C_2F_5I with MeMgCl followed by reaction with benzophenone in a microreactor system.

Microreactors have also been applied to halogen–lithium exchange reactions[16] and hydrogen–lithium exchange reactions.[17]

Reactions in which a reactive intermediate easily decomposes in conventional reactors: There is another important point in flash chemistry, the control of highly reactive, short-lived reactive intermediates. In conventional processes, generation of such an intermediate takes minutes or hours. If the lifetime of the intermediate is shorter than the generation or accumulation time, it is difficult to obtain a solution of that intermediate. The intermediate undergoes decomposition during the accumulation. However, using microreactor systems, unstable reactive intermediates can be transferred to another location to be used in the next reaction before they decompose. Therefore, chemical conversions that are impossible in conventional reactors, such as flasks, should become possible in flash chemistry.

Swern–Moffatt oxidation involves the formation of highly unstable intermediates, which undergo an inevitable Pummerer rearrangement at temperatures higher than −30 °C. Therefore, the reaction should be carried out at low temperatures to avoid such decomposition leading to the formation of undesirable by-products. The requirement of such low temperatures causes severe limitations in the industrial use of this highly useful reaction. The control of residence time within 0.01 s by using a microreactor system, however, leads to the formation of desired carbonyl compounds in high yields even at 20 °C (Figure 6 and Table 1).[18] This observation demonstrates a striking example of the effectiveness of microreactors for the control of highly reactive intermediates.

The bromine–lithium exchange reaction of *o*-dibromobenzene to produce *o*-bromophenyllithium is usually carried out
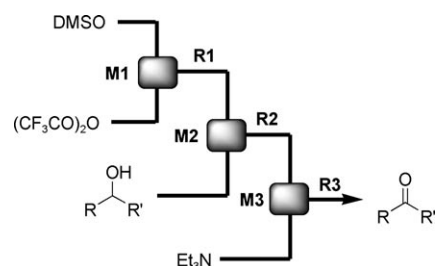

Figure 6. A microreactor system for room temperature Swern-Moffatt oxidation. **M1**, **M2**, **M3**: micromixers. **R1**, **R2**, **R3**: microtube reactors.

Table 1. Swern-Moffatt oxidation of cyclohexanol using a microreactor and a flask.

Method	Residence time t_{R1} [s]	T [°C]	Selectivity of cyclohexanone [%]
micro-reactor	2.4	−20	88
	0.01	0	89
	0.01	20	88
flask		−20	19
		−70	83

at −110 °C or below in flask chemistry because the elimination of LiBr to form benzyne is very fast even at −78 °C. However, by shorting of the residence time using a microreactor system, the reaction can be conducted at −78 °C and o-bromophenyllithium can be effectively trapped with an electrophile.[19] Figure 7 illustrates a schematic diagram of the microreactor system, in which reactions using methanol as an electrophile are conducted with varying temperatures and flow rates.
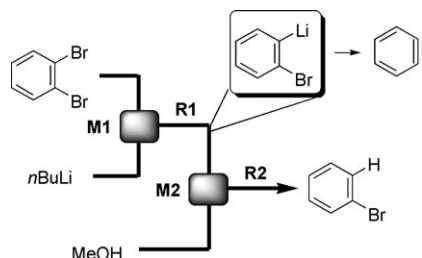

Figure 7. Microreactor system for the Br-Li exchange reaction of o-dibromobenzene. **M1**, **M2**: micromixers. **R1**, **R2**: microtube reactors.

Using the temperature/residence time profile shown in Figure 8, the reaction conditions were easily optimized. Thus, unstable o-bromophenyllithium can be transferred to the next location to be used in the reaction with an electrophile before it decomposes. It is also important to note that the present temperature-residence time profile is quite effective in revealing the stability and reactivity of highly reactive intermediates.
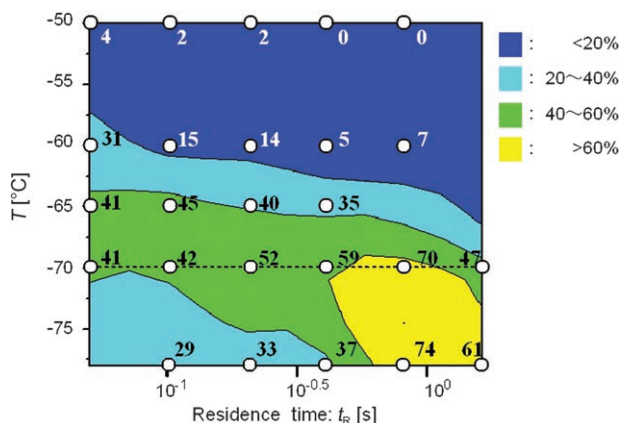
Figure 8. Effects of temperature and residence time on the yield of bromobenzene. Contour plot with scatter overlay of the yields (%).

Based on the optimized conditions, the sequential introduction of two electrophiles into o-dibromobenzene has also been established using the microreactor system consisting of four micromixers and four microtube reactors (Figure 9). The first bromine–lithium exchange reaction followed by reaction with an electrophile is carried out at −78 °C and the second bromine–lithium exchange reaction followed by the reaction with an electrophile is carried out at 0 °C (Table 2).

Table 2. Sequential reactions of o-dibromobenzene with two electrophiles using the microreactor system.

Electrophile (E¹)	Electrophile (E²)	Product	Yield [%]
MeOTf	Me₃SiCl		67
	Bu₃SnCl		62
	(benzaldehyde)		61
	(acetophenone)		53
(benzaldehyde)	Me₃SiCl		74
	Bu₃SnCl		58
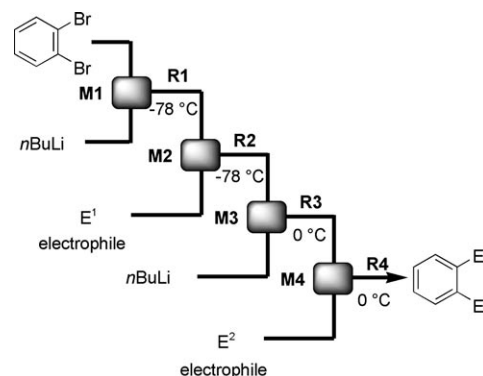
Figure 9. A microreactor system for the sequential introduction of two electrophiles into o-dibromobenzene. **M1**, **M2**, **M3**, **M4**: micromixers. **R1**, **R2**, **R3**, **R4**: microtube reactors.

Reactions in which undesired byproducts are produced in the subsequent reactions in conventional reactors: Fast reactions may also cause selectivity problems and kinetically based product selectivity is not obtained (disguised chemical selectivity) 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 the control of such reactions without slowing down. The reaction can be conducted at a natural rate and products are obtained in a short period with kinetically based selectivity.

Friedel–Crafts reaction of aromatic compounds with electrochemically generated highly reactive N-acyliminium ion pools provides a nice example of the effectiveness of microreactors in solving such selectivity problems.[20] 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 (Figure 10). The monoalkylation product undergoes the subsequent reaction with the *N*-acyliminium ion, presumably because the reaction occurs faster than mixing. The reaction using a microreactor system consisting of a micromixer, however, resulted in a dramatic increase in the product selectivity. The reaction completed within a second. 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 product selectivity.

	monoalkylation product	dialkylation product
microreactor	92%	4%
flask	37%	32%
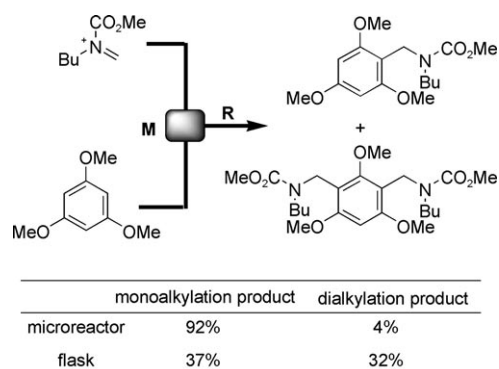
Figure 10. A microreactor system for selective Friedel-Crafts monoalkylation. **M**: micromixer. **R**: microtube reactor.

There are other examples of this type of reactions, such as iodination of aromatic compounds with electrochemically generated I$^+$ (Scheme 3),[21] a reaction of a Grignard reagent with phenylboronic acid trimethyl ester (Table 3),[22] and [4+2] cycloaddition of *N*-acyliminium ion with styrene.[23]

	flask	microreactor
	45%	78%
	18%	4%
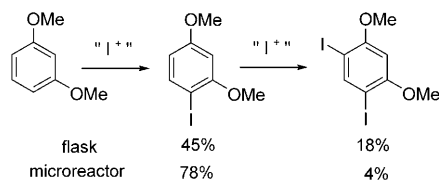
Scheme 3. Product selectivity of iodination of aromatic compounds with electrochemically generated "I$^+$".

Reactions in which the products easily decompose in conventional reactors: Reactions in which the products easily decompose under the reaction conditions are problematic. In such cases, the reactions should be quenched immediately after the formation of the products. Flash chemistry in a microreactor provides a solution to this problem.

Acid-catalyzed dehydration of allylic alcohols to give the corresponding conjugate dienes serves as a good example of this type of reactions.[24] In a macrobatch reactor, various byproducts, such as cyclized products or alkyl group-migrated

Table 3. Product selectivity of the reaction of phenylmagnesium bromide with boronic acid trimethyl ester.

Reaction time		Monophenyl product [%]	Diphenyl product [%]
laboratory scale conventional reactor	22 min	85.1	13.8
microreactor	5 s	98.9	0.6

compounds were produced presumably because of acid-catalyzed reactions of the diene. Fukase and co-workers reported that the formation of such byproducts can be significantly reduced using a microreactor system composed of a micromixer and a microtube reactor (Figure 11). After the reaction mixture was allowed to flow for 47 s, the reaction was quenched with a saturated $NaHCO_3$ solution. In this case the desired diene was obtained in 80% yield.
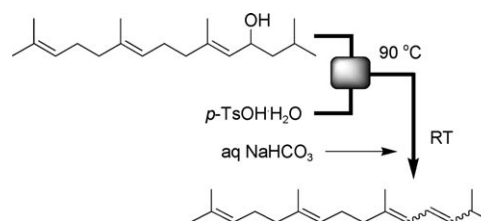

Figure 11. Acid-catalyzed dehydration of allylic alcohol using a microreactor system.

Applications of Flash Chemistry in Polymer Synthesis

The concept of flash chemistry can be applied to polymer synthesis.[25] Polymerization of olefin monomers has been considered to be very difficult to control to obtain polymers of narrow molecular-weight distribution. In general, it is difficult to start propagation at the same time for all polymer chains. An active species at the propagating polymer end reacts with olefin monomers extremely rapidly and exothermically. The active polymer end is also highly unstable and readily participates in chain-transfer reactions leading to uncontrollable molecular weight distributions. Conventional polymerization processes using macrobatch reactors suffer from such problems. However, microreactors solve such problems and serve as a powerful method for molecular weight and molecular-weight distribution control.

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-weight control and molecular-weight distribution control can be attained in the *N*-

acyliminium ion initiated polymerization of vinyl ethers using a microreator (Figure 12).[26] The polymerization is complete within a second or so. The molecular weight in-
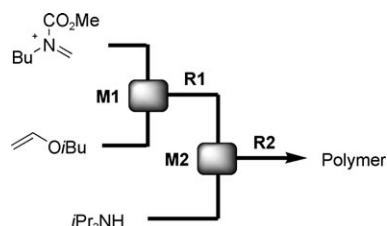

Figure 12. A microreactor system for controlled/living cationic polymerization. **M1**, **M2**: micromixers. **R1**, **R2**: microtube reactors. The polymerization was normally carried out at −78 °C.

creases with an increase in the monomer/initiator ratio, indicating that chain-transfer reactions do not play an important role (Figure 13). The microflow system-controlled cationic polymerization seems to be close to ideal living polymerization within a short residence time.
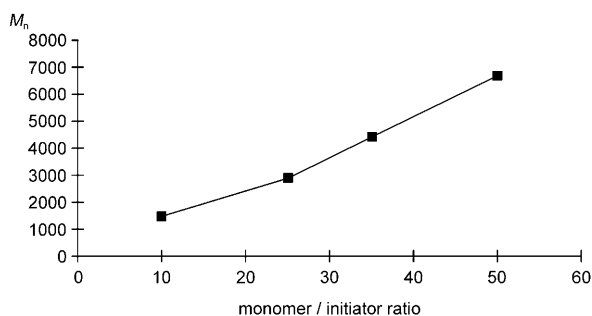
Figure 13. Plots of molecular weight against the monomer/initiator ratio used for the polymerization.

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.[27] Such equilibrium, however, decelerates the propagation significantly. The microreactor 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.

CF_3SO_3H has been found to serve as a good initiator for microflow system controlled cationic polymerization.[28] Because CF_3SO_3H is commercially available, this method may serve as a convenient way for practical polymerization. One of the advantages of living polymerization is that the method allows flexible synthesis of structurally defined block copolymers composed of different monomers, which would offer greater opportunities for the synthesis of organic materials with interesting properties. Indeed block copolymerization has been achieved using the microflow system-controlled cationic polymerization.

Free-radical polymerization can also be conducted in microreactors.[29] A fairly good level of molecular-weight control and molecular-weight distribution control can be attained, although the level is not as high as those of conventional living-radical polymerizations.[30] A pilot plant for radical polymerization based on numbering-up of the microreactors has been developed.[31] Many other studies on radical polymerization using microreactors have been reported in the literature.[32] Numerical simulations of free-radical polymerization in microreactors[33] and living-radical polymerization based on a dynamic equilibrium between active and dormant species using microreactors[34] have also been reported.

Conclusion

As demonstrated in the previous sections, fast reactions that are difficult to control or impossible to perform in conventional chemistry should be made possible using flash chemistry in microreactors. The examples shown in this article and many other examples in the literature illustrate the potential of flash chemistry using microreactors. It is also important to note that flash chemistry can contribute to green, sustainable chemical synthesis in the following ways.

1) **Little or no use of auxiliary substances**: Flash chemistry avoids the use of auxiliary substances that slow down reactions to obtain better controllability.
2) **Energy saving**: Conventionally, cooling is often used to attain acceptable controllability of fast reactions. The use of microreactor enables reactions to be conducted at higher temperatures, minimizing the energy required for controlling these reactions.
3) **High selectivity**: Better controllability by virtue of the inherent properties of microreactors leads to a high selectivity of the products. Therefore, less waste is produced.
4) **One-demand and on-site synthesis**: Synthesis based on extremely fast reactions using microreactors enables on-demand and on-site synthesis. This leads to less energy for transportation.

It is hoped that various types of applications of flash chemistry will be developed and widely utilized in laboratory synthesis and industrial production to meet future demands for fast synthesis of various organic molecules and polymers.

Acknowledgement

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