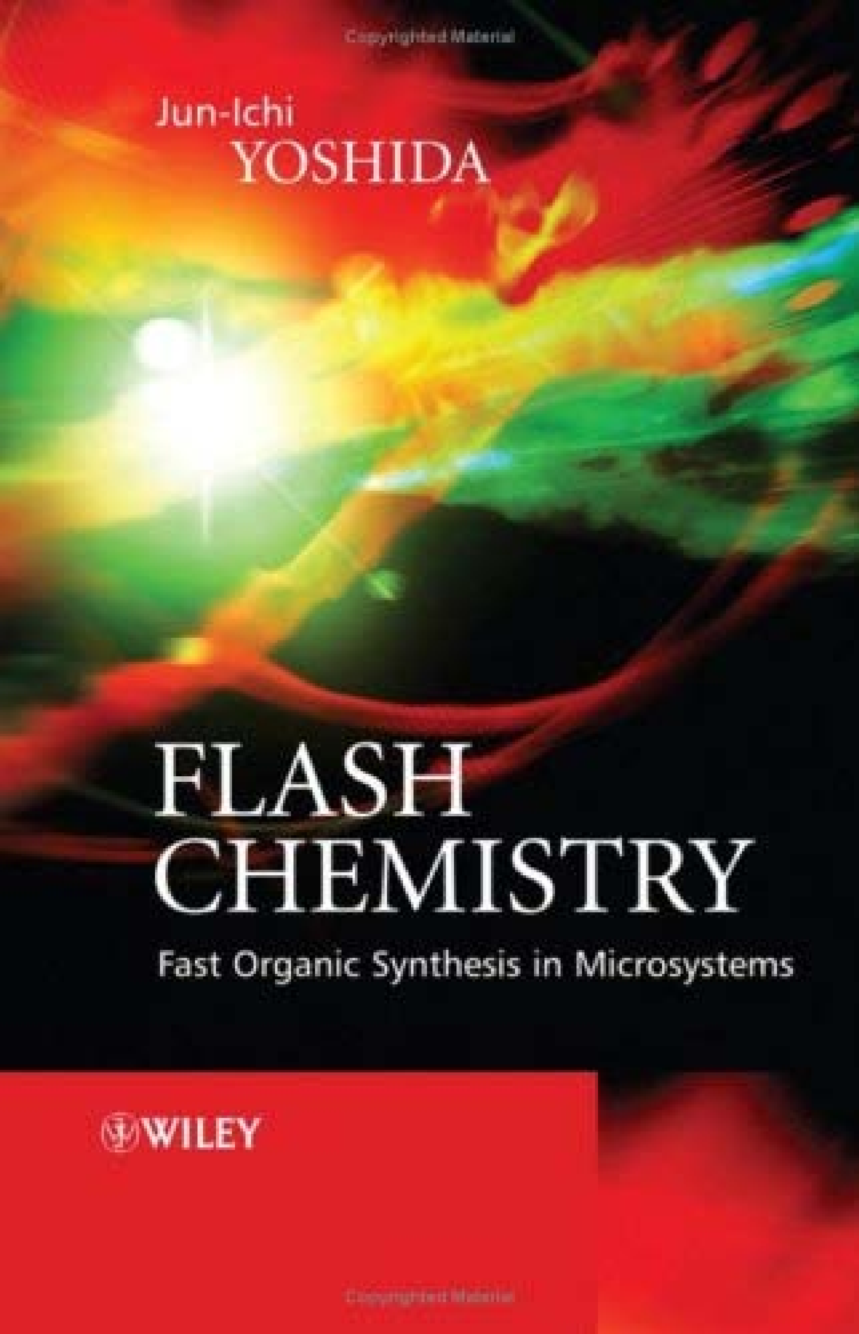

Jun-Ichi
YOSHIDA

FLASH CHEMISTRY

Fast Organic Synthesis in Microsystems

WILEY

1

Introduction

We tend to think that what we usually do is appropriate. This is often true in our daily life. However, it is not necessarily true in the field of science. For example, we usually run reactions in a centimeter size flask in an organic chemistry laboratory. Why? The reason is probably, that the sizes of the flasks are similar to the size of our hands. However, the sizes of the flasks are not necessarily appropriate from a molecular-level viewpoint. Flasks are often too big for the control of molecular reactions. Scientifically, smaller reactors such as microreactors provide a much better molecular environment for reactions. What about reaction times? Reactions in laboratory synthesis usually take minutes to hours to obtain a product in a sufficient amount. Why? It is probably because a time interval of minutes to hours is acceptable and convenient for human beings. In such a range of time, we can recognize how the reaction proceeds. We start a reaction, wait for a while, and stop it in this range of time. If reactions are too fast, it is difficult to determine how the reaction proceeds, because the reaction is complete too soon after it is started. Therefore, we have chosen reactions that complete in a range of minutes to hours. Another reason is that we are able to conduct only such reactions that require minutes to hours for completion in a controlled way. In other words, in laboratory synthesis, we cannot conduct faster reactions that complete within milliseconds to seconds, because they are too fast to control. In such cases, significant amounts of unexpected compounds are obtained as by-products. In addition, extremely fast reactions sometimes lead to explosions. However, we should keep in mind that such limitations of reaction

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time for chemical synthesis are only applicable for flask chemistry that we usually do in a laboratory.

1.1 FLASK CHEMISTRY

Based on conventional flask chemistry, 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, such as materials, pharmacy, and medicine. 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, as stated above. Reaction times in conventional organic synthesis usually range from minutes to hours. The rapid progress in science and technology based on organic compounds means the demand to produce desired compounds in a highly time-efficient way has been increasing. To meet such demands and to achieve rapid synthesis of a variety of organic compounds, acceleration of organic synthesis is highly desirable. For this purpose, flash chemistry, where much faster reactions are conducted in a controlled and selective way to produce desired products, is greatly needed.

We are still running chemical reactions using much of the same apparatus that was used in the eighteenth and nineteenth centuries (Figure 1.1). The sizes of the flasks are determined not by any scientific

Figure 1.1 Ugo Schiff (1834–1915) (provided by the University of Florence)

reasons but probably by the size of our hands. It is not necessary to use reactors of flask size for studies of chemical reactions and synthesis of compounds. Therefore, if we free ourselves from the constraints of flask chemistry, we can expect to have the chance to conduct much faster reactions in a highly controlled and selective way to synthesize desired compounds. There should be many fast reactions that we have not yet explored because of the constraints of the reaction environment. Such constraints should be removed to further develop the efficiency and utility of organic synthesis. In order to do this, we need microflow systems as a new environment for chemical reactions.

1.2 FLASH CHEMISTRY

The word 'flash' is not new in the history of chemistry. Flash chromatography[1] is one of the fundamental techniques for separating organic compounds in laboratory synthesis. In fact, flash chromatography is very popular with organic chemists as a convenient and effective method for separation in daily laboratory work. For synthesis, flash vacuum pyrolysis[2] is also a well-known technique that has been available for many years. Flash laser photolysis[3] is widely used for mechanistic studies because it serves as a powerful method for generating reactive species in a very short period of time. However, flash laser photolysis does not seem to be suitable for chemical synthesis because it is rather difficult to produce a large amount of compounds using this technique. In the 'flash chemistry' proposed here, a substrate undergoes extremely fast reactions to give a desired product very quickly in a highly selective manner. Reaction times rage from milliseconds to seconds (Figure 1.2). Because flash chemistry

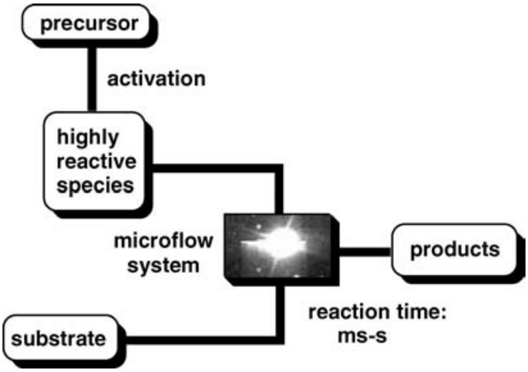

Figure 1.2 Schematic diagram of flash chemistry

uses a continuous flow system, it is fairly easy to make a larger quantity of compounds than one can expect from the size of the reactor. In any case, the word 'flash' is very common in chemistry, but the term 'flash chemistry' is uncommon.

It is important to propose new words for the developments in new fields of science and technology; as Wittgenstein wrote in his book:[4] 'A new word is like a fresh seed thrown on the ground of the discussion'. A Japanese poet, Toson Shimazaki, also wrote in the preface of his collection of poems:[5] 'A new word leads to a new life'. Therefore, it seems useful and productive to introduce the expression 'flash chemistry'.

1.3 FLASK CHEMISTRY OR FLASH CHEMISTRY

At the molecular level, chemical reactions take place in the range of 10^{-13}–10^{-12} s (see Chapter 2), while reaction times range from minutes to hours (10^{2}–10^{5} s) in a flask (Figure 1.3). The size of molecules is in the range of 10^{-10}–10^{-8} 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 1.3. In flash chemistry, we use a reactor, the size of which ranges from 10^{-6} to 10^{-3} m. The

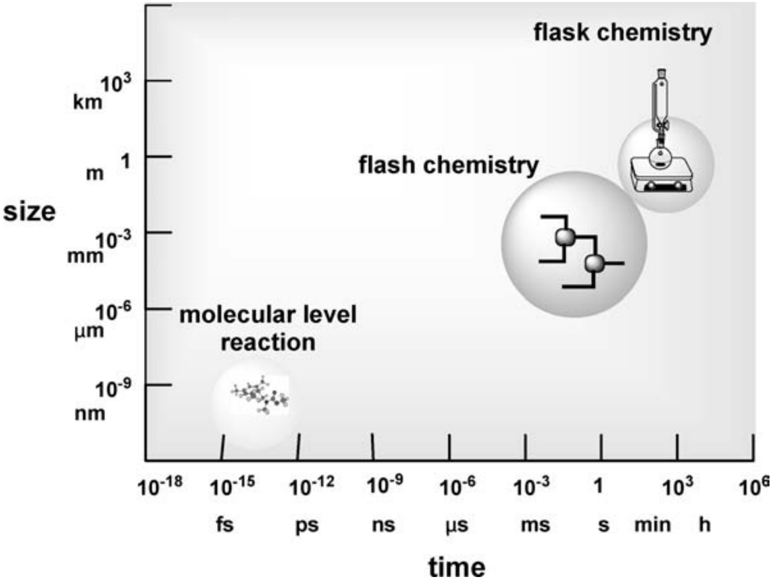

Figure 1.3 Time–space relationship for chemical reactions

reaction time ranges from 10^{-3} to 1 s. 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 flask chemistry.

This book provides an outline of the concept of flash chemistry for conducting extremely fast reactions in a highly controlled manner using microflow systems. In the following chapters, we will discuss the background, the principles, and applications of flash chemistry.

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2

The Background to Flash Chemistry

2.1 HOW DO CHEMICAL REACTIONS TAKE PLACE?

What is a chemical reaction? How does it take place? These questions are the most fundamental questions of chemistry, and they are the last to be solved. In order to deal with flash chemistry, however, let us begin with a consideration of such fundamental questions.

When we consider a chemical reaction, there are two viewpoints; a macroscopic one and a molecular level one. It was only about a hundred years ago when the reality of molecules was established. In 1905, Einstein proposed a theory of Brownian motion, and later (1908–1912) Perrin proved it by experimental work. They showed that Brownian motion is caused by the collision of molecules on small particles (micrometer size). Although some scientists at the time considered that molecules only had a virtual existence that was useful to explain chemical phenomena, since then, no scientist has doubted the existence of molecules. Since that time a molecular point of view has become very popular in chemistry, although it is rather difficult to see molecules directly even with the present technology.

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2.1.1 Macroscopic View of Chemical Reactions

Let us begin with a consideration of chemical reactions from a macroscopic point of view. From a macroscopic viewpoint, a chemical reaction is defined as a transformation of a substance into another substance. There are various types of chemical reactions. For example, chemical reactions are divided into organic reactions and inorganic reactions based on the nature of the major substances that participate in the reaction. These days, organometallic reactions, which involve compounds having both organic and inorganic components, have become very popular in chemical synthesis. Chemical reactions are also classified into gas-phase reactions, solution- or liquid-phase reactions, solid-phase reactions, supercritical-fluid reactions, gas/solid-phase reactions, gas/liquid-phase reactions, liquid/liquid-phase reactions, solid/solid-phase reactions, and so on, based on the phase or phases where the reaction takes place. Based on the source of energy that promotes the reaction, chemical reactions are classified into thermal reactions, photochemical reactions, electrochemical reactions, and so on.

Although there are many types of reactions in chemistry, the basic principles of the ways in which reactions proceed seem to be common to them all. Our predecessors considered these ways and made extensive studies on the principles of chemical reactions.

2.1.2 Thermodynamic Equilibrium and Kinetics

Let us consider the energy change associated with a chemical reaction (Figure 2.1). Transformation from a reactant to a product often gives rise to the release or absorption of energy. If equilibrium exists between the reactant and the product, the amount of the reactant and that of the product in the system are determined by the energy difference between them as well as temperature. If two products are formed in the equilibrium,

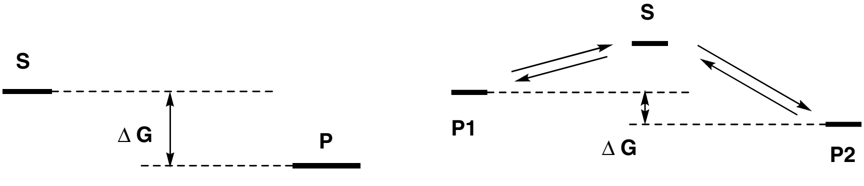

Figure 2.1 Energy change associated with a chemical reaction. S: Substrate, P, P1, P2: Product, ΔG: Gibbs free energy change

the product selectivity is also determined by the energy difference between the two products as well as the temperature. Therefore, if a thermodynamic equilibrium exists between a reactant and a product, we can play only a small role in controlling the reaction, because each substance has its inherent energy. We can only change the temperature to shift the equilibrium.

In general, chemical reactions are not necessarily explained in terms of thermodynamic equilibrium. In fact, many reactions do not proceed, in a practical sense, even when the products are energetically much more stable than the starting materials. Such reactions should be thermodynamically very favorable. Why do such reactions not proceed spontaneously? It is because the reactions are too slow and do not proceed at an appreciable rate. In such cases we say the reactants are kinetically stable. If the reactions leading to the products have a very slow rate, the reactants do not change appreciably for a long time.

Many organic substances, which are the key to the existence of life on earth, are stable under the conditions in which we live, because they are kinetically stable. The present atmosphere on earth contains a significant amount of dioxygen (O_2, oxygen gas). We know that the reactions of hydrocarbons and dioxygen are energetically very favorable because hydrogen combines with oxygen to give the energetically more stable water, and carbon combines with oxygen to give the energetically more stable carbon dioxide. The reactions should be energetically very favorable and highly exothermic. However, many hydrocarbons and substances containing hydrocarbon units, including substances that constitute our bodies, are stable in air. Otherwise, life could not exist in air. It is possible because the reactions of such hydrocarbons with dioxygen are very slow at normal temperatures. At elevated temperatures, however, the reactions become faster and proceed at appreciable rates. For example, hydrocarbons burn in air. Burning or combustion is the reaction with dioxygen (Figure 2.2). When we light a hydrocarbon substance with a match, the local temperature becomes very high, and the reaction with dioxygen takes place to give water and carbon dioxide.[1] As a result of the initial reaction, an enormous amount of heat is generated, which raises the temperature of the atmosphere nearby. Then the next reaction takes place and generates more heat to promote further reactions until most of the hydrocarbon substance is consumed. On the other hand, if we do not light the mixture with a match, nothing happens at an appreciable rate.

Most organic substances are kinetically stable in air; otherwise they could not exist. Major forms of life, including our bodies, consist of organic substances such as DNA, proteins, sugars, lipids, and so on. The

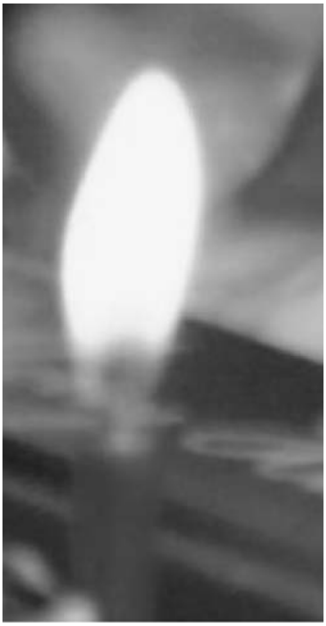

Figure 2.2 A flame of candle produced by combustion of organic compounds

existence of life in the present atmosphere on earth containing a significant amount of dioxygen relies on the kinetic stability of organic substances in air.

2.1.3 Kinetics

Chemical reactions may occur rapidly or slowly. What determines the rate of a chemical reaction? How fast can chemical reactions be? Prior to such a discussion, quantitative statements of the rate of a chemical reaction are necessary. The rate of a chemical reaction is defined as the amount of the substance reacted per unit time. If the reaction takes place in a homogeneous solution, the rate of chemical reaction can be defined as the amount of a substance reacted per unit volume per unit time rather than its total amount. The amount per unit volume is simply the concentration. The rate of a chemical reaction often depends on the concentrations of reactants and other substances that participate in the reaction. In the simplest case, the rate increases linearly with an increase in the concentration of the reactant:

$$\text{rate} = k[\text{reactant}]$$

In such a case, the proportionality constant is called the rate constant of the reaction, and is indicated by the symbol k. Therefore, the value of k determines the rate of a chemical reaction. For bimolecular reactions, the rate increases with the increase in the concentrations of the two reactants:

$$\text{rate} = k[\text{reactant A}]\,[\text{reactant B}]$$

Svante Arrhenius studied how the rates of chemical reactions vary with temperature and in 1889 he presented the following well-known formula:

$$k = A\exp(-E_a/RT)$$

where A is the pre-exponential factor, R is the gas constant, and T is the absolute temperature. The units of the pre-exponential factor are identical to those of the rate constant and vary depending on the order of the reaction. E_a is called the activation energy. This formula tells us that the rate of a reaction increases with increase in temperature, T. What is the nature of the activation energy? Arrhenius postulated an activated complex as a hypothetical state between a reactant and a product, and the activation energy is the height of the energy barrier needed to reach the activated complex (Figure 2.3). Therefore, activation energy is the energy difference between the reactant and the activated complex. The introduction of the concept of the activated complex opens a molecular-level view to chemical reactions. Such a view leads to reaction dynamics, and analysis of reactions from a molecular-level viewpoint. From a molecular-level viewpoint, activation energy is defined as the amount of energy required to convert a reactant molecule to an activated complex. What is the nature of the activated complex? At the time of Arrhenius, it was difficult to answer

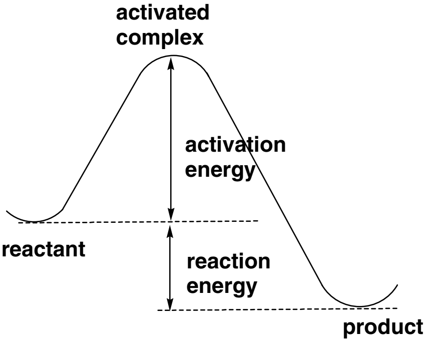

Figure 2.3 Diagram of a reaction and the activated complex

this question. In order to gain an insight into the activated complex, we had to wait until the 1930s.

2.1.4 Transition State Theory

Henry Eyring and Michael Polanyi independently developed transition state theory, which gave a meaning to the activated complex (Figure 2.4). They explained chemical reactions in terms of the movement of a hypothetical particle on the potential surface defined by energy and the geometry of the atoms that participate in the reaction. The transition state is a saddle point on the potential surface between the reactant and the product. It was believed that the transition state should be passed extremely rapidly and that it would be almost impossible to observe it experimentally.

Figure 2.5 illustrates an example of a reaction profile involving a transition state (TS) obtained by DFT calculations.[2] An *N*-acyliminium ion reacts with an olefin through the transition state in which both the C—C and C—O distances become shorter than in the reactant complex. In the vibrational analysis, the TS has only one negative eigenvalue, whereas the reactant and the product have no negative eigenvalues.

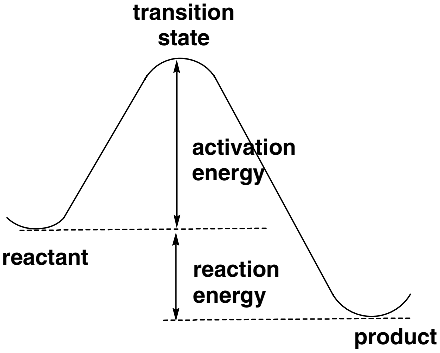

Figure 2.4 Diagram of a reaction and the transition state

2.1.5 Femtosecond Chemistry and Reaction Dynamics

In the 1980s, owing to the significant advancement of femtosecond laser flash photolysis technology, it became possible to observe transition states experimentally. In 1 fs (10^{-15} s), a very short period of time, even light can only travel 0.3 μm. Laser photolysis by femtosecond pulses can activate molecules to give a coherent state where the energy and vibration phases of all the molecules are the same. Therefore, we can observe the collective

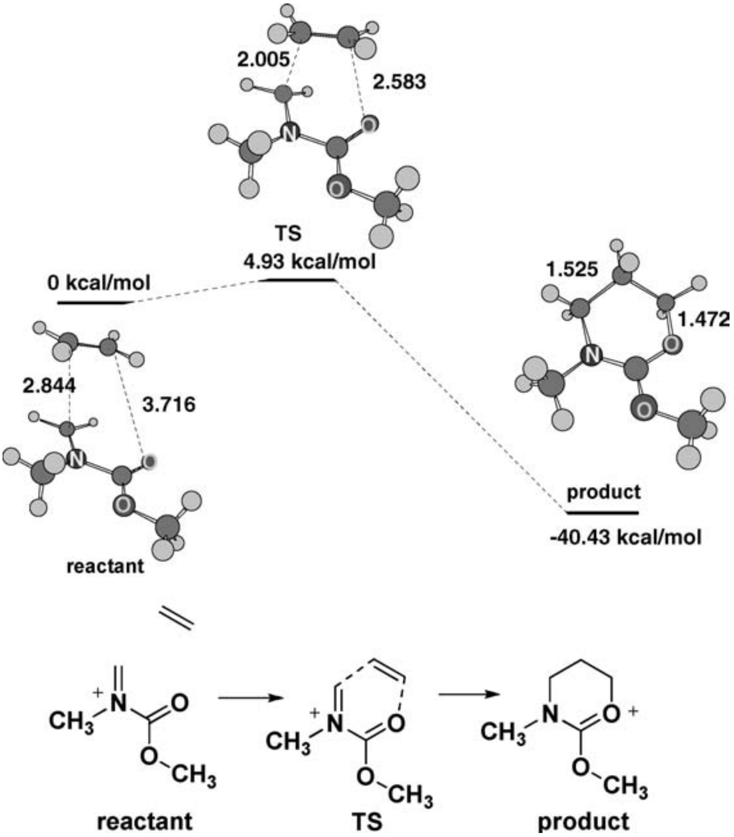

Figure 2.5 An example of reaction profile involving transition state obtained by DFT calculations. The [4 + 2] cycloaddition of *N*-acyliminium ion and ethylene[2a]

behavior of molecules that move and vibrate from the same state coherently. Ahmed Zewail showed by using this technique that the time required for molecules to react from reactants to products through the transition state is several hundred femtoseconds.[3] This is a similar order of time to that required for a molecular vibration. By virtue of Zewail's work, we know today how fast chemical reactions really are (Figure 2.6).

2.1.6 Reactions for Dynamics and Reactions for Synthesis

Are chemical reactions that occur under the conditions of synthesis and those promoted by femtosecond laser photolysis the same or not? If not, what is the difference? Such naive questions may come to mind. In

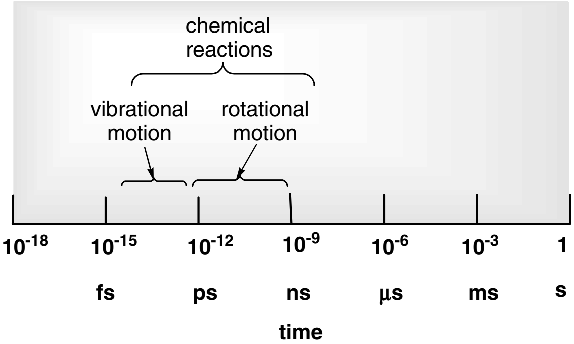

Figure 2.6 Time scales. The relevance to chemical changes

femtosecond chemistry, molecules are activated coherently and only molecules activated in a very short period have enough energy and can participate in a subsequent reaction. Therefore, the time for conversion of activated molecules to product molecules is the same as the time for conversion of a single activated molecule to a single product molecule. Generally, it is very difficult to observe the behavior of a single molecule experimentally. Therefore, it is difficult to measure the reaction time for a single molecule. However, coherent preparation of activated molecules by femtosecond laser pulses enables us to measure the reaction time for a single molecule because the behavior of a large number of molecules can be observed experimentally.

It should be noted that coherent activation can be easily achieved for a so-called unimolecular reaction such as:

$$\mathbf{A} \rightarrow \mathbf{P} \tag{2.1}$$

In this type of reaction, reactant molecule **A** can be activated coherently by photochemical irradiation using a femtosecond laser pulse, and activated **A** undergoes a subsequent reaction without collision with other molecules. It is very difficult, in principle, to adjust collisions of two molecules coherently. Therefore, it is rather difficult to apply femtosecond laser pulse technology to conduct a bimolecular reaction, shown in Equation (2.2), like a unimolecular reaction. It is difficult to achieve the collision of two molecules **A** and **B** coherently.

$$\mathbf{A} + \mathbf{B} \rightarrow \mathbf{P} \tag{2.2}$$

In reactions under preparative conditions in flasks, in biological systems, and so on, reactant molecules are activated individually and participate in the reaction to give product molecules through the transition state at different times. In femtosecond chemistry, however, activation takes place at the same time by a very short laser pulse. After that, no activation takes place. Therefore, the reaction takes place coherently, especially in unimolecular cases. In reactions under normal conditions, however, the activation of reactants takes place continuously. A reactant molecule obtains energy by collision with other molecules. If the energy is sufficient to cross the barrier of the transition state, the reaction proceeds to give a product molecule. The excess energy is transferred to other molecules. Then the next molecule obtains enough energy and participates in the reaction. Therefore, the reaction time, i.e. the time required for the conversion of all reactant molecules to product molecules, is much longer than several hundred femtoseconds. It should be kept in mind that the time required for the conversion of a single reactant molecule to a single product molecule is, in principle, the same in both femtosecond chemistry and normal chemistry. We may say that some reactions are very slow. In this case, it is not true that reactant molecules move very slowly on the potential energy surface. Instead, the reactant molecules move very quickly, but less frequently. The frequency with which molecules cross the transition state toward the products is low.

2.1.7 Bimolecular Reactions in the Gas Phase

Let us consider how chemical reactions proceed in a little more detail by looking at a gas phase bimolecular reaction of molecules **A** and **B** to give molecule **P** [Equation (2.2)]. Molecules are dancing in space. There are three types of motion possible for molecules; translational motion, rotational motion, and vibrational motion. The reaction occurs through collisions of **A** and **B**. Generally, in the bimolecular reaction between **A** and **B**, when **A** and **B** collide and if the kinetic energy is sufficient, the reaction proceeds by changing the kinetic energy to potential energy for the reaction. The effectiveness of the collisions is also affected by the orientation in space of reactant molecules **A** and **B** when they collide with each other. Through the transition state, the product **P** is formed. If the reaction is exoergonic, **P** has excess energy for the reaction, and this energy is partitioned into translational, rotational, and vibrational energies. In the bulk gas phase, the product molecule soon collides with other molecules, which gives rise to energy transfer to other molecules. Then other sets of **A** and **B** obtain enough energy for the reaction and collide to give another molecule of product **P**.

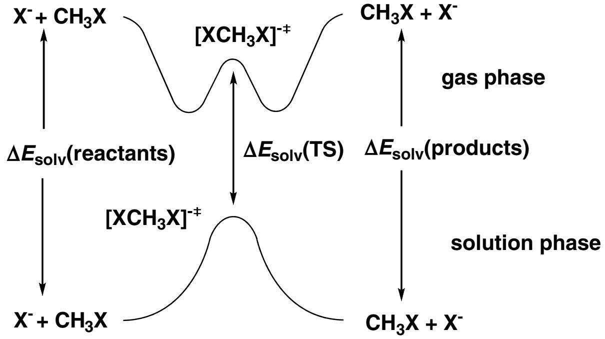

Figure 2.7 Potential energy surfaces of the gas phase and solution phase S_N2 reaction of CH_3X and X^-

In Figure 2.7, the potential energy surface of the gas phase S_N2 reaction of CH_3X and X^- is shown as an example.[4] The reaction has a double-well potential. CH_3X and X^- collide to form a precomplex. If the precomplex has enough energy, it undergoes a displacement reaction through a transition state. The resulting complex dissociates to give the products, CH_3X and X^-.

2.1.8 Bimolecular Reactions in the Solution Phase

What kinds of events happen in the solution phase? When a solute dissolves in a solvent, the solute molecules become surrounded by solvent molecules by virtue of attraction of the solvent molecules to the solute molecules. This event is called solvation. Solvation stabilizes reactant and product molecules, as well as transition states, in solution. Therefore, the potentials of solution-phase reactions are different from those for gas-phase reactions, as shown in Figure 2.7.

Solvation takes place within 100–1000 fs. Reactions in the solution phase take place in a cage of solvent molecules. Bimolecular reactions in the solvent cage take place within several hundred femtoseconds, whereas collisions in the gas phase take place in the order of picoseconds. In the solvent cage, molecules **A** and **B** collide with each other, and a successful collision leads to reaction to give product **P**. Excess energy from **P** is transferred to solvent molecules by the subsequent collision with solvent molecules. Therefore, one of the most important roles of the solvent is removal of heat generated in the reaction. In the solution phase, the rate of a chemical reaction is determined by the activation energy. This is mostly true. However, if the activation energy is very small, the observed rate of reaction is determined not by the crossing of the barrier by the caged reactants **A** and **B** but by the rate of the reactants getting into the cage. In this case, the rate is determined by the rate of diffusion of the reactants in the solvent molecules (see Section 6.1.3).

2.1.9 Fast Chemical Synthesis Inspired by Reaction Dynamics

As described above, the progress of reaction dynamics showed how chemical reactions take place. Is it possible to apply the methods and techniques of reaction dynamics to chemical synthesis? If we can activate all the molecules at once, the chemical reaction takes place and finishes within several hundred femtoseconds. If it is possible, synthesis can be complete within several hundred femtoseconds. Such a method leads to the ultimate acceleration of chemical synthesis.

However, the requirements for chemical synthesis and those for reaction dynamics studies are different. In chemical dynamics studies, we activate starting molecules at once and observe the subsequent reaction. Coherency of the activation is important but the number of activated molecules is not so important as long as we can observe them. In chemical synthesis, however, the number of molecules which participate in the reaction is much more important because it directly relates to productivity. Therefore, all the molecules in the system should be activated, but coherency of the activation is less important. We usually synthesize compounds on the 10^{-4}–10^{0} mol scale in laboratories and on the 10^{3}–10^{8} mol scale in chemical plants. Such amounts of molecules should be activated in a very short period for time-efficient chemical synthesis.

It is also worth noting that many reactions consist of two or more reaction components in chemical synthesis, because they are useful to construct molecules; however, most reaction dynamics studies deal with unimolecular reactions because it is difficult to arrange coherent collisions of two molecules. In time-efficient chemical synthesis, it is also important to know how to achieve collisions of two molecules in a very short period to accelerate bimolecular reactions.

There is another problem in chemical synthesis. If large amounts of molecules are activated and allowed to collide with other molecules to react in a very short period, there may be the problem of heat removal in the case of exothermic reactions. Many synthetically useful reactions are highly exothermic. However, if most of the starting molecules react in a very short period, a significant amount of heat should be generated in that time, which leads to an explosion. The use of a large amount of solvent may be effective for preventing the explosion, but it is not effective from the viewpoint of productivity. Therefore, another effective means of heat removal is needed when conducting extremely fast reactions.

Thus, the requirements of reaction dynamics and of chemical synthesis are different. Therefore, it seems to be practically impossible to conduct synthetic reactions in several hundred femtoseconds (10^{-15} s) or picoseconds (10^{-12} s). However, very recently it became possible to conduct chemical reactions in milliseconds (10^{-3} s) to seconds on a preparative scale by using microflow systems. Although the timescale is still quite different by 9–13 orders of magnitude, it leads to a significant acceleration in chemical synthesis. Based on these arguments, the concept of flash chemistry has been proposed. In flash chemistry, extremely fast reactions are conducted under preparative conditions in a highly controlled manner, and the desired products are formed in the twinkling of an eye. Reaction time ranges from milliseconds to seconds.

The following chapters provide more details of flash chemistry and its applications in laboratory synthesis and industrial production.

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3

What is Flash Chemistry?

It is important to define the concept of flash chemistry before we proceed to the following chapters which discuss its details. Although the definition might change with progress in the technologies related to this field, flash chemistry in this book can be defined as follows: *Flash chemistry is a field of chemical synthesis where extremely fast reactions are conducted in a highly controlled manner to produce desired compounds with high selectivity*. In flash chemistry, a substrate is activated to a reactive species with built-in, high-energy content that reacts with another substrate (Figure 3.1a) or a substrate is allowed to react with a highly reactive reagent (Figure 3.1b) to drive an extremely fast reaction resulting in the desired compound in a very short period. There are, of course, many variations of flash chemistry. For example, in some cases, an activated substrate undergoes a spontaneous subsequent unimolecular reaction to give a product. In other cases, the reaction of a highly reactive species with a substrate generates a second reactive species that reacts with another substrate to give a product. Multi-step synthesis may also be accomplished based on the concept of flash chemistry. It is noteworthy that multi-step synthesis based on reactive intermediates can be realized by flash chemistry (Figure 3.2). A highly reactive intermediate reacts with a substrate to generate a second reactive intermediate, which reacts with a second substrate to give a third reactive intermediate. The third reactive intermediate reacts with a fourth substrate to give a fourth reactive intermediate, and so on. As a result, in flash chemistry, the reaction time usually ranges from milliseconds to seconds, much shorter than that in

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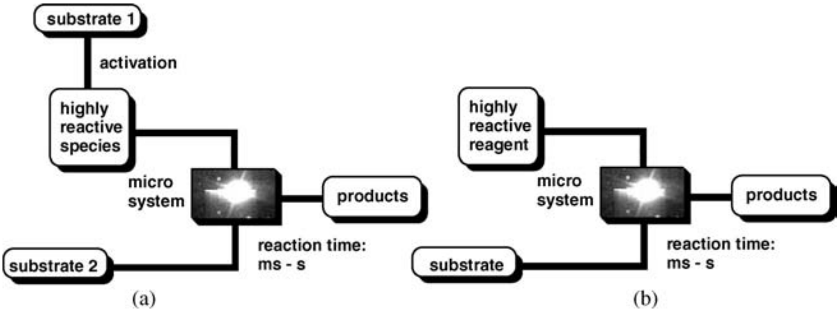

Figure 3.1 Schematic diagrams of flash chemistry

flask chemistry, although the typical reaction times might change with progress in related technologies in the future.

It should be noted that flash chemistry is a new field of chemical synthesis. It is not a field of reaction mechanism and analysis. This is the point. For mechanistic studies much faster reactions can be conducted without any problem using current technologies. However, conducting extremely fast reactions on a preparative scale has been rather difficult. For synthesis, a relatively large amount of compounds should be produced, although the reaction scale depends on the purpose. In any case, the productivity of flash chemistry should be equal to or higher than conventional ways of chemical synthesis, because the final purpose is the same. At the present stage, the productivity of flash chemistry ranges from mg/min to kg/min, although this might change with progress in the technology of microdevices and microreactors. It is also noteworthy that flash chemistry

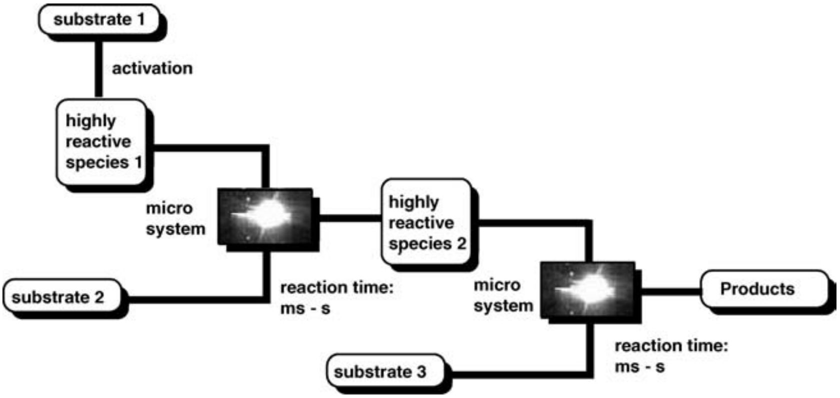

Figure 3.2 Multi-step synthesis based on reactive intermediates

serves as a new method for chemical science, where new and extremely fast reactions that are difficult to perform by conventional methods can be developed. Such reactions may lead to the creation of new materials and new biologically active compounds. Moreover, there should be many scientific challenges that can be accomplished using flash chemistry.

In Chapter 4, we will discuss why flash chemistry is necessary. In Chapter 5, methods for the activation of molecules for flash chemistry will be discussed, because highly reactive species should be generated in order to accomplish flash chemistry. In Chapter 6, the problems associated with conducting extremely fast reactions and solutions to such problems will be discussed. In order to accomplish flash chemistry a device or a system for conducting an extremely fast reaction is crucial. In Chapter 7, we will briefly touch on state-of-the-art technologies of microflow systems, which are essential for flash chemistry. In subsequent chapters, some applications of flash chemistry in organic synthesis and polymer synthesis will be demonstrated.

4

Why is Flash Chemistry Needed?

4.1 CHEMICAL REACTION, AN EXTREMELY FAST PROCESS AT MOLECULAR LEVEL

Why is fast chemical synthesis needed? The most appropriate answer to this question is because we can just do it with our present knowledge and technologies. Extremely fast reactions that are complete within a second used to be difficult to control on a preparative scale because we were using conventional macrobatch reactors. However, we are now able to conduct such reactions in a controlled manner with the aid of microflow systems constructed with micro-structured reactors and microreactor technology.

As we have already discussed in Chapter 2, 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 through a transition state. Bimolecular reactions also take similar reaction times at the molecular level.[1] 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. If we can conduct the reaction in this way on a preparative scale, the synthesis finishes within several hundred femtoseconds. From a technical point of view, we are presently far from that point. Reaction times for chemical synthesis usually range

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from minutes to hours using macrobatch reactors, such as flasks in laboratory organic synthesis and industrial production. However, we now have new tools for conducting much faster reactions in a controlled way, i.e. microflow systems. Although the reaction time is still much longer than femto- and picoseconds, it can be reduced to the range of milliseconds to seconds.

However, another reason why flash chemistry is needed is that our way of synthesizing compounds is currently changing. For example, combinatorial synthesis of chemical libraries 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.

4.2 RAPID CONSTRUCTION OF CHEMICAL LIBRARIES

Recently, it has been widely recognized that rapid creation of a collection of compounds, called a compound library or a chemical library, serves as a powerful method for the discovery of new drugs and functional materials.[2] A large number of structurally distinct molecules can be synthesized at one time based on the combinatorial principle, and they are submitted for assay or test. This new field of chemistry is called ‘combinatorial chemistry’. The key to combinatorial chemistry is that a large number of analogs are synthesized using the same type of reaction with different combinations of building components (see below). Combinatorial chemistry does not increase the possibility of discovering desired compounds per number of synthesized candidates in comparison with the conventional way of synthesis followed by testing. However, combinatorial chemistry increases the possibility of discovery per unit time. In combinatorial chemistry a large number of compounds are synthesized and tested very quickly, because the reaction conditions for each combination of building components are very similar and many reactions can be conducted at one time using an automated synthesizer.

Combinatorial synthesis, in which molecules are constructed by combining several different components, serves as a very efficient way of constructing such chemical libraries. The use of different starting molecular units for each component can quickly lead to a large number of product molecules. Such libraries may contain a compound having a desired biological activity or physical property. For example, construction of molecules with two components of diversity leads to the formation of $N_1 \times N_2$ possible structures, where N_1 and N_2 are the number of different molecular units utilized for each component. An example of parallel combinatorial synthesis is shown in Figure 4.1.

The combinatorial chemical library approach has caused a major cultural change in laboratory chemical research and chemists are now performing many reactions at a time using automated synthesizers. The effectiveness of this approach depends on how rapidly we create chemical libraries. Therefore, each reaction should be as fast as possible in order to achieve library synthesis in a highly time-efficient manner.

In combinatorial chemistry, however, much attention has been paid to the development of new methods for separating and isolating products quickly, because the total efficiency of the synthesis has been limited by the ability to separate and isolate products in a pure form. In solid-phase synthesis,[4] molecules are bound on a solid, such as polymer beads, and are synthesized step-by-step in a reactant solution. Separation is simple and easy. Products on the solid support are separated by simple filtration from other side products derived from a reagent and any unchanged reagent, which are usually soluble in solvents. In solution-phase synthesis, various protocols have been developed for easy and rapid separation. For example, polymer-assisted synthesis, including soluble polymer synthesis,[5] polymer supported reagents[6] and catalysts,[7] microencapsulation,[8] polymeric scavenger,[9] and resin capture approaches[10] have enjoyed fast-growing applications. The phase-tag approach[11] also serves as a powerful tool for strategic separation and recovery. In this approach a range of reactions can be conducted under homogeneous conventional conditions because all chemical entities that participate in the reactions are relatively small molecules; however, the products can still be easily separated by a simple phase separation with the aid of a tag. The tag can be removed after separation to obtain the desired product (removable phase tags). With such powerful methods for separation, we should reconsider the acceleration of chemical reactions for building a large number of molecules very quickly. Reactions themselves should be more time efficient.

In this context, click chemistry has been explored as a method for rapid synthesis of compound libraries. In click chemistry,[12] compounds are rapidly synthesized through heteroatom links by a set of powerful, highly reliable, and selective reactions, such as Huisgen's 1,3-dipolar cycloaddition reactions.[13] Click chemistry uses chemical building blocks with built-in high-energy content to drive a spontaneous and irreversible linkage reaction with appropriate complementary sites in other blocks,

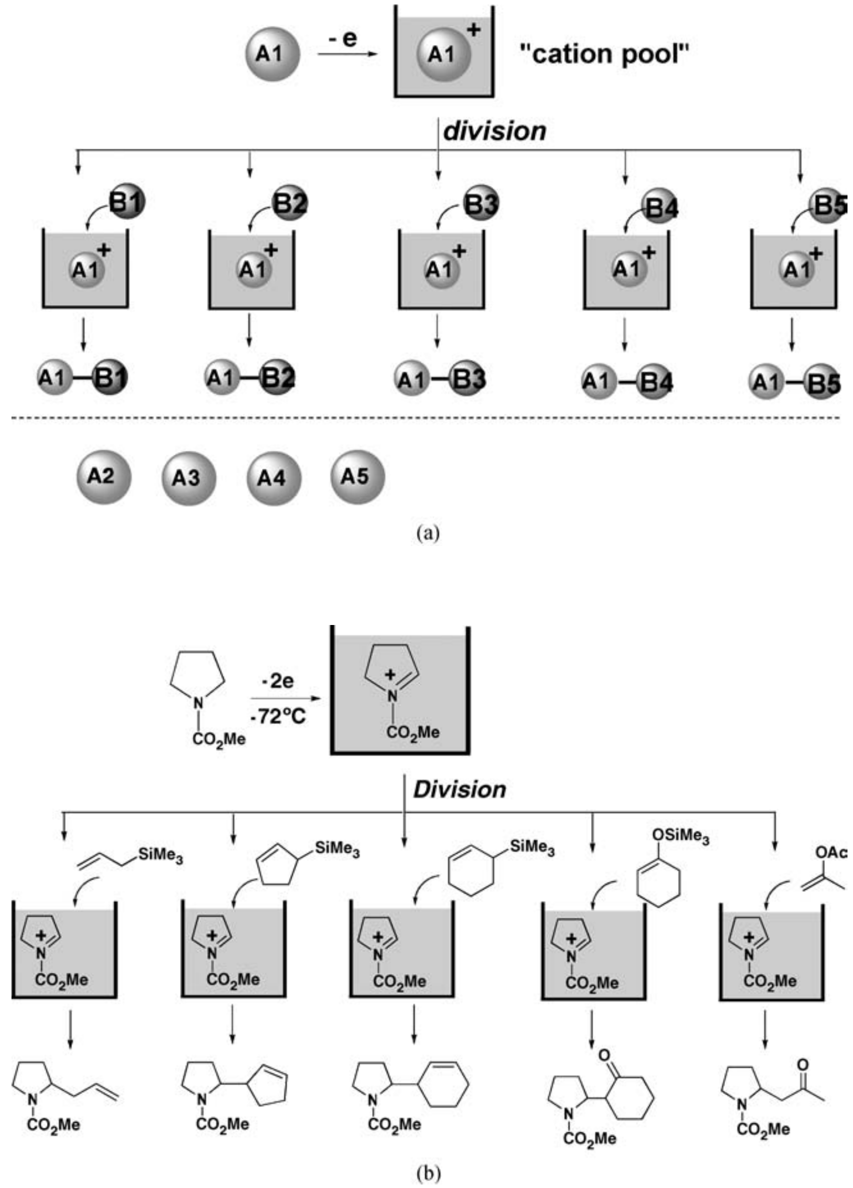


Figure 4.1 Parallel combinatorial synthesis based on the cation-pool method.[3] (a) Schematic diagram; (b) example based on the reaction of *N*-acyliminium ion pools with carbon nucleophiles

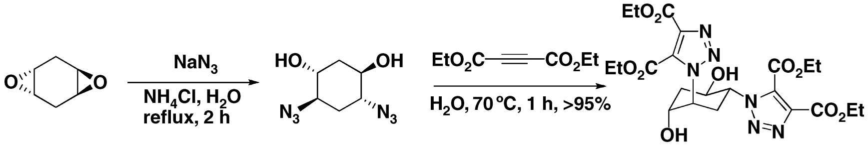


Figure 4.2 Example of click chemistry[12]

such as olefins. For example, R-N_3 serves as such a highly reactive building block (Figure 4.2). Therefore, reactions used in click chemistry are usually very fast and compound libraries can be constructed very quickly. Recently an integrated microflow system for library synthesis based on *in situ* click chemistry has been developed.[14]

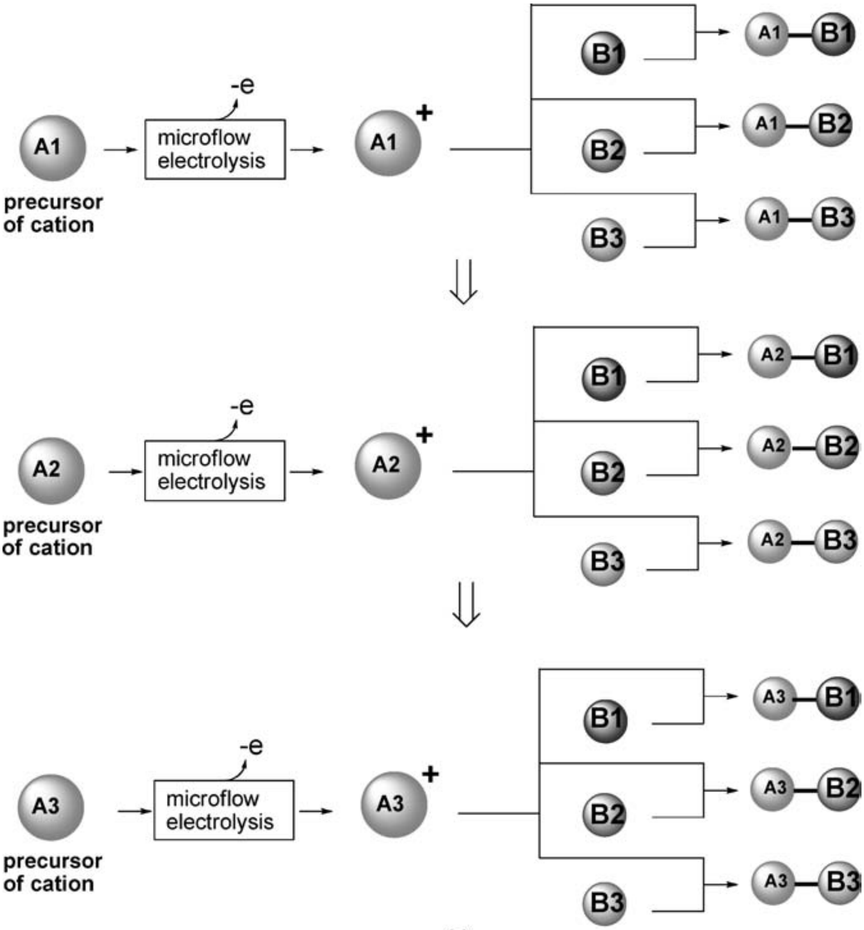
If much faster reactions are available for chemical synthesis, compound libraries can be constructed more rapidly. Although batch processes using a robot or an automated synthesizer can be applied, continuous sequential combinatorial synthesis by flow switching[15] seems more suitable for this purpose (Figure 4.3). In sequential combinatorial synthesis, different compounds are synthesized in one flow by changing a building block as the result of flow switching. Irrespective of the approach, extremely fast reactions are needed for rapid construction of compound libraries to discover new materials and biologically active compounds in a time-efficient manner.

4.3 RAPID SYNTHESIS OF RADIOACTIVE POSITRON EMISSION TOMOGRAPHY PROBES

Recently, a great demand for fast chemical synthesis has emerged in the clinical field. Positron emission tomography (PET) is a medical imaging technique that produces a three-dimensional image or map of functional processes in the body. The common PET probes contain radionuclides such as ^{11}C, ^{15}O, ^{13}N, ^{18}F, and ^{82}Rb, the lifetimes of which are very short, for example, $t_{1/2}$ of ^{18}F is 110 min. Therefore, PET probes have to be synthesized when they are needed. It is also important to note that PET probes should be synthesized at a place very close to a patient because the transport time should be as short as possible. On-demand, on-site synthesis of radioactive PET probes requires flash chemistry.

The most commonly used PET probe is ^{18}F-fluorodeoxyglucose (FDG).[16] The synthesis of ^{18}F-FDG has been carried out as follows. In the first step, ^{18}F-KF is produced by irradiation of ^{18}O-water with

10–18 MeV protons in a cyclotron. The second step of the synthesis is the reaction of ^{18}F-KF with acetyl-protected 2-*O*-trifluoromethanesulfonyl-β-D-mannopyranose (Figure 4.4a). Trifluoromethanesulfonate (triflate) is used because it is an excellent leaving group and therefore the reaction is very fast. With other leaving groups, such as tosylate, mesylate, iodide, bromide, and chloride, the reaction is slower. Commonly, aminopolyether (Kryptofix 2.2.2) is used as a catalyst to enhance the reaction of the triflate. The reaction takes about 5 min in refluxing acetonitrile. The third step is removal of the protecting groups under acidic or basic



(a)

Figure 4.3 Serial combinatorial synthesis based on the cation flow method.[15a] (a) Schematic diagram; (b) example based on the reaction of *N*-acyliminium ion pools with carbon nucleophiles

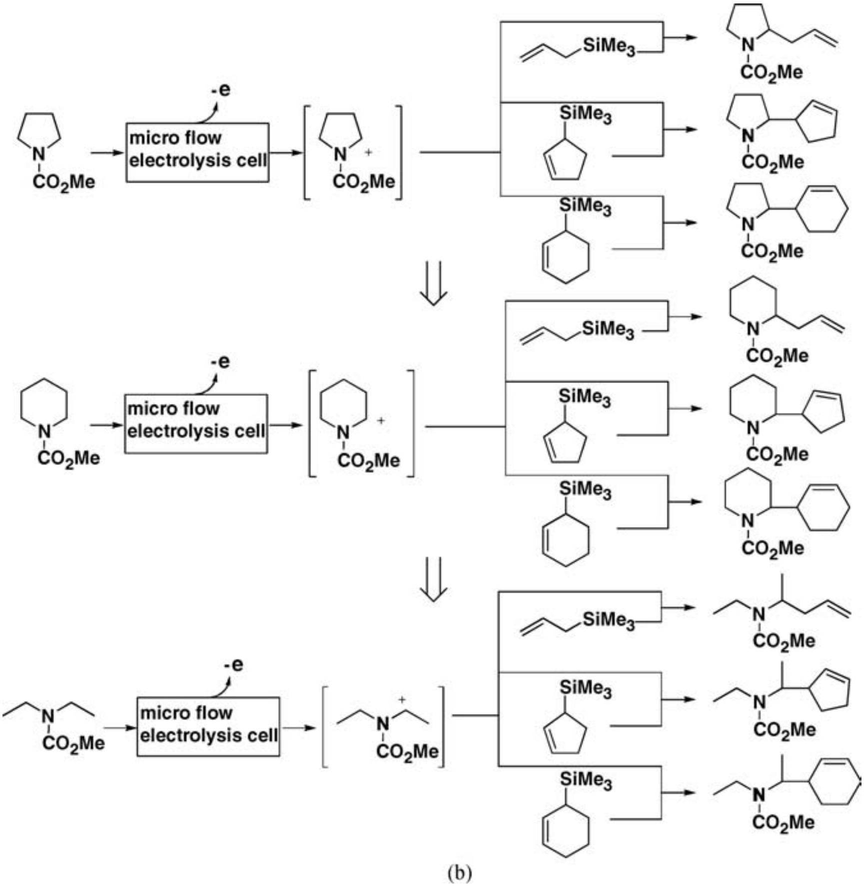


Figure 4.3 (*Continued*)

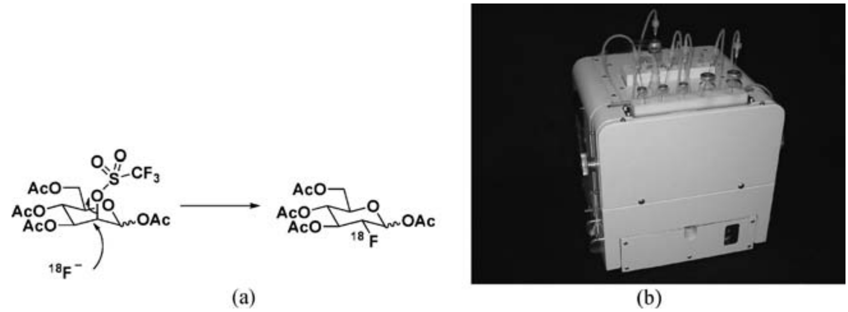


Figure 4.4 (a) Synthesis of ^{18}F-FDG by nucleophilic substitution; (b) automated synthesizer of ^{18}F-FDG (F200, Copyright Sumitomo Heavy Industries, Ltd.)

conditions. The final step is purification through a sequence of anion exchange column, reverse phase column, and alumina column. The overall synthesis should be complete very quickly because of the short lifetime of ^{18}F. Therefore, fast chemical reactions are really needed in this field. Although ^{18}F-FDG has been synthesized practically using a batch-type reactor (Figure 4.4b), the use of a micro-chip reactor has been reported in the literature.[17]

Not only probes containing radionuclides but also other very unstable compounds may be used as drugs in the clinical field using on-demand, on-site synthesis based on flash chemistry in the future. A drug is synthesized near a patient very quickly when it is required and is dosed to the patient as quickly as possible. If such a technique becomes possible, drugs of very short lifetimes can be used in the clinical field. Therefore, flash chemistry may change the approach to medical treatment.

4.4 ON-DEMAND RAPID SYNTHESIS IN INDUSTRY

For industrial production of chemical compounds, it is obvious that faster reactions are better than slower reactions as long as they are controllable. With faster reactions, a greater quantity of compounds can be produced per unit time. The productivity per unit volume of a reactor also increases with increase in the reaction rate. The use of extremely fast reactions in conjunction with flow systems may lead to a smaller size of reactor in chemical plants, which leads to lower cost for investment in plants and equipment. In addition, faster synthesis leads to lower cost of labor because the working hour per unit weight of products is shorter.

A more important point is that faster reactions in conjunction with flow systems make on-demand synthesis easier. Some chemical plants in the future are likely to be closer to customers. Therefore, distribution of a large number of small-scale rapid production units and their on-demand operation may become more popular.[18] Such a situation may be beneficial from an environmental point of view because energy for storing and transporting chemical products can be saved. Chemical production close to the customers seems advantageous for easy recycling of chemical products. In some cases hazardous chemical intermediates can be produced very close to the place for subsequent transformations, avoiding the risk of their storage and transportation. It is also worth noting that rapid on-demand synthesis may be beneficial from an economic point of view because of increased adjustability and flexibility of production to any change in market demands.

4.5 CONCLUSIONS

Based on the arguments described above, it is reasonable to conclude that the demand for fast reactions for chemical synthesis is increasing from the viewpoints of both laboratory research and industrial production. Rapid chemical synthesis may lead to new possibilities not only for chemistry but also for other fields, such as pharmacy and medicine. In the following chapters, we will discuss how flash chemistry can be realized in laboratory and industrial synthesis.

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[18] For example, IMPULSE (Integrated Multiscale Process Units with Locally Structured Elements) Project. See: http://www.impulseproject.net/.

5

Methods of Activating Molecules

In flash chemistry, extremely fast reactions are conducted in a highly controlled manner, and desired products are formed very quickly. Reaction times range from milliseconds to seconds. 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. There are several methods for activation, including thermal, photochemical, electrochemical, and chemical methods. In this chapter, we briefly survey these methods.

5.1 THERMAL ACTIVATION OF ORGANIC MOLECULES

5.1.1 High Temperature Reactions

Conducting reactions at elevated temperatures is a straightforward way of activating molecules to enable reactions. To elevate the reaction temperature, high pressure is often required because organic compounds of low molecular weights are vaporized at high temperatures. Although there are many examples of reactions using conventional high pressure batch systems, the use of microflow systems has received significant research interest. For example, Pd-catalyzed aminocarbonylation of halobenzenes

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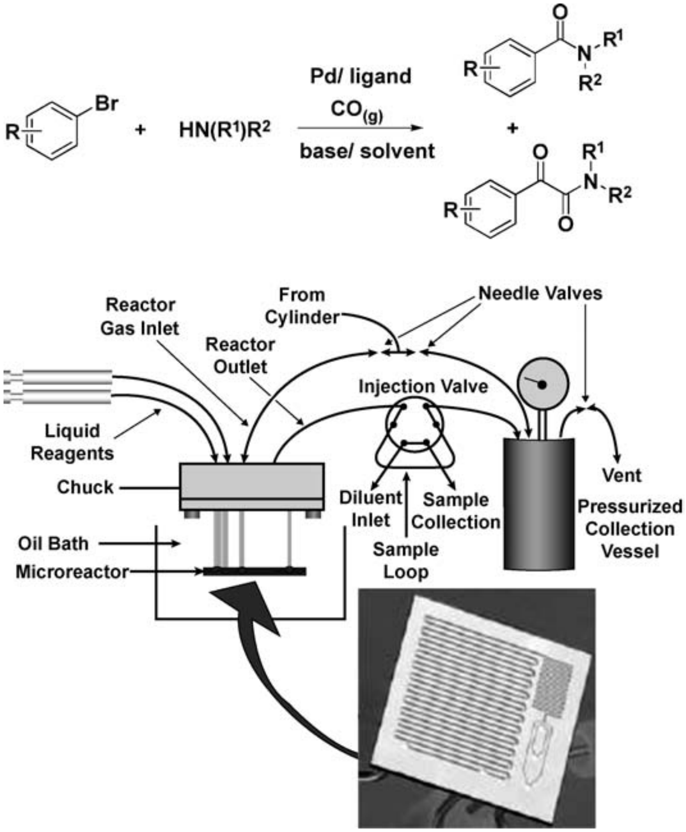
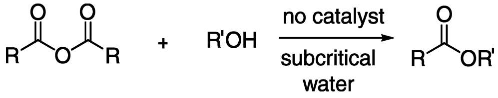


Figure 5.1 Aminocarbonylation of halobenzene by microflow system at elevated temperatures and pressures[1]. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission

has been carried out using the microflow system shown in Figure 5.1 at elevated temperatures and pressures.[1]

Reactions in supercritical and subcritical fluids are also effective for thermal activation.[2] For example, highly selective and rapid acylation of alcohols proceeds in subcritical water using a microflow system (Scheme 5.1).[3] The reaction is free from hydrolysis of the acid anhydride used.



Scheme 5.1 Acylation of alcohols in subcritical water

5.1.2 Flash Vacuum Pyrolysis

Flash vacuum pyrolysis (FVP) is well known as a powerful method for conducting thermal reactions in organic synthesis.[4] In FVP, a suitable precursor is subjected to very high temperatures (e.g. 400–700 °C) with a steady stream of inert carrier gas flowing through a sample chamber under relatively high vacuum conditions. An electric furnace is often used to heat the chamber. Therefore, FVP is really an example of flash chemistry. This method allows a substrate molecule to pass through a very hot part of the reactor within a second or so. The residence time should be set long enough for reaction to complete to give the desired product in good yield but not long enough for decomposition to occur, resulting in undesired products. The concept of flash chemistry is already well known among chemists and has been utilized in organic synthesis for many years. For example, benzocyclobutenone is synthesized by FVP of 2-toluic acid chloride at an oven temperature of 630 °C.[5] The reaction is conducted at a constant rate of 40–60 drops min^{-1}. The elimination of HCl at high temperature produces a highly reactive diene, which cyclizes to give benzocyclobutenone as shown in Figure 5.2.

Let us briefly touch on two more examples of FVP in the literature, although FVP has been used for many other useful transformations in the synthesis of organic compounds.

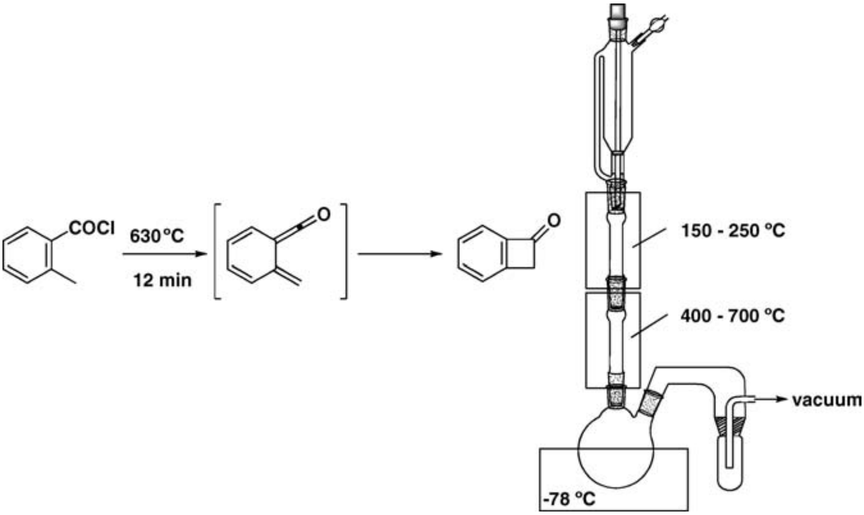
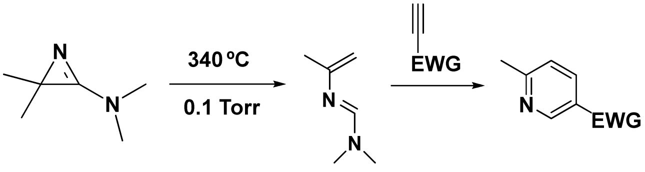


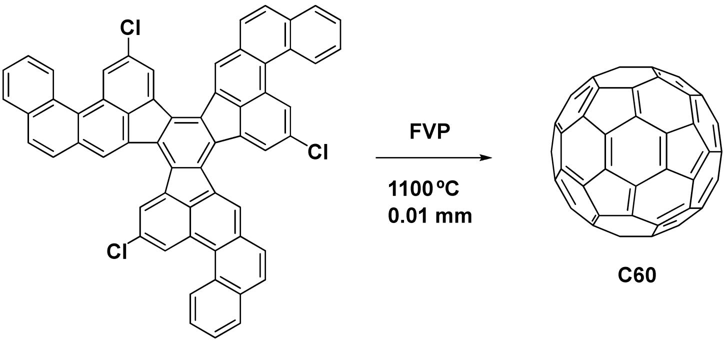
Figure 5.2 Conversion of 2-toluic acid chloride to benzocyclobutenone and the apparatus for FVP[5]



Scheme 5.2 FVP of an aziridine derivative

A highly reactive azadiene, which is a useful intermediate for the synthesis of nitrogen containing compounds, has been synthesized using FVP (Scheme 5.2). Slow evaporation of an aziridine derivative through an 80 cm hot glass tube (340 °C, 0.1 Torr) filled with glass beads gives the corresponding azadiene. The azadiene thus obtained undergoes a Diels-Alder reaction with acetylene derivatives having an electron-withdrawing group (EWG) to give the corresponding pyridine derivatives.[6]

One of the most fascinating recent applications of FVP is the synthesis of C_{60}.[7] Pyrolysis of the chlorinated hydrocarbon shown in Scheme 5.3 has been carried out at an oven temperature of 1100 °C with a steady stream of nitrogen carrier gas flowing through a sample chamber from a thin capillary connected to a 1 atm reservoir (final pressure with nitrogen flowing: 0.01 mmHg). C_{60} is effectively produced in one operation, although the structures of intermediates are not clear.



Scheme 5.3 Final step in the synthesis of C_{60} using FVP

5.1.3 Microwave Reactions

Microwave irradiation has received significant research attention to accelerate thermal reactions.[8] In conventional methods, reactants are heated by an external heat source such as a hot-water bath or an oil bath. Heat is driven through the walls of a reaction flask; however, this

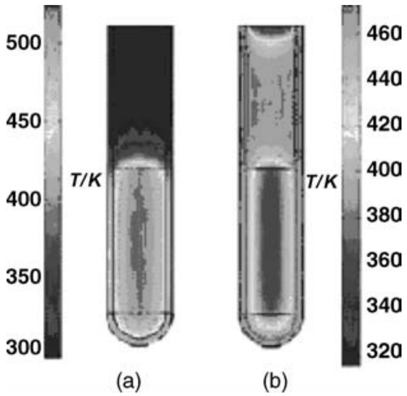
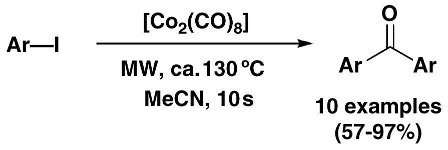


Figure 5.3 Inverted temperature gradients in microwave versus oil-bath heating: difference in the temperature profiles (finite element modeling) after 1 min of microwave irradiation (a) and treatment in an oil bath (b). Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission

energy-transferring process is indirect and therefore inefficient. In the microwave reactions, microwaves couple with the substrate and/or solvent molecules and thermally activate them directly. Therefore, the energy transfer can be highly efficient (Figure 5.3).

In fact, such thermal acceleration by microwaves is known to be significant for many organic and organometallic reactions.[9] The reaction usually takes a matter of minutes or so. However, in the following example, where aryl iodides and $Co_2(CO)_8$ react to give the corresponding symmetrically substituted ketones, the reaction is complete in 10 s (Scheme 5.4).[10]

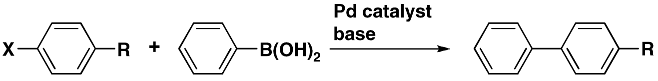
In most cases microwave reactions have been conducted in a batch system, but very recently the use of a microflow system for microwave reactions has been reported. For example, Suzuki–Miyaura coupling of aryl halides with phenylboronic acid to form biaryls is promoted by microwave irradiation of the supported Pd catalyst (Table 5.1).[11] A thin, gold film patch located on the outside surface of the base of a glass microreactor is quite effective for absorbing microwaves.



Ar = Ph, 3-thiophenyl, 1-naphthyl
4-MeOC_6H_4, 2-MeC_6H_4, 4-ClC_6H_4,
$4\text{-CF}_3C_6H_4$, 2-(NC)C_6H_4, 4-RC(O)C_6H_4,

Scheme 5.4 Microwave driven reaction of aryl iodides with $Co_2(CO)_8$

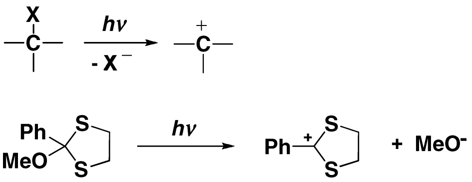
Table 5.1 Suzuki–Miyaura coupling of aryl halides with phenylboronic acid under various conditions



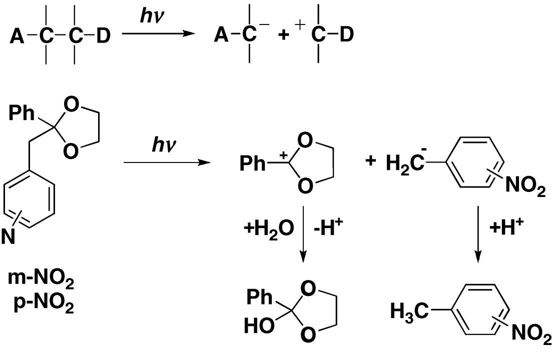
Heating method	MW power/W	Temp./°C	Conv./%
Room temperature	0	25	0
Oil bath	0	130	65
MW heating only	150	94–98	71
MW heating plus gold coating	55	90–102	99

5.2 PHOTOCHEMICAL ACTIVATION

The photochemical method is another way of activating molecules. Although the photochemical method is a powerful way of generating reactive species, the requirement that the molecules should contain some chromophore, a part of the molecule that absorbs light, is a significant limitation from a synthetic point of view. There are many examples of photochemical activation of organic molecules. In this section, however, we will only briefly discuss laser flash photolysis (LFP).[12] In LFP, a short pulse of excimer laser is flashed onto a substrate solution, which often leads to bond dissociation to generate short-lived reactive intermediates, such as free radicals, carbocations, and carbanions. LFP serves as an excellent method for the instantaneous generation of a reactive intermediate in uniform concentration. An example is the generation of carbocations by photo-initiated carbon–heteroatom bond cleavage. A general scheme for generation of a carbocation by direct photoheterolysis of a carbon–heteroatom bond and an example are shown in Scheme 5.5.



Scheme 5.5 Photochemical generation of reactive carbon species by carbon–heteroatom bond cleavage (X, leaving group)



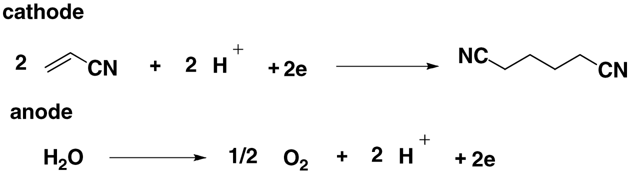
Scheme 5.6 Photochemical generation of reactive carbon species (A, acceptor group; D, donor group)

Cleavage of a carbon–carbon bond having suitable acceptor and donor groups also takes place photochemically giving rise to simultaneous formation of a carbocation and a carbanion, as shown in Scheme 5.6.

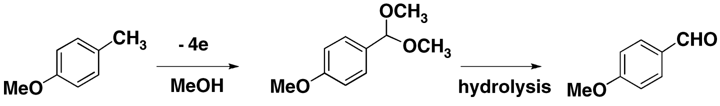
Although, LFP has been utilized successfully for mechanistic studies, few examples have been reported for applications in organic synthesis because it is rather difficult to scale up.

5.3 ELECTROCHEMICAL ACTIVATION

The electrochemical method is also quite effective for activating organic molecules. Electrochemical synthesis has a fairly long history; Henry Kolbe established its basis by showing that electrolysis of carboxylic acids leads to efficient homo-coupling of carbon radicals produced by decarboxylation.[13] Kolbe electrolysis is still a powerful and straightforward method for carbon–carbon bond formation in organic synthesis. Thousands of electrochemical reactions for synthesis have been developed,[14] some of which, including reductive dimerization of acrylonitrile to adiponitrile (Scheme 5.7) and oxidative methoxylation of toluene



Scheme 5.7 Reductive dimerization of acrylonitrile (Baizer-Monsanto process)

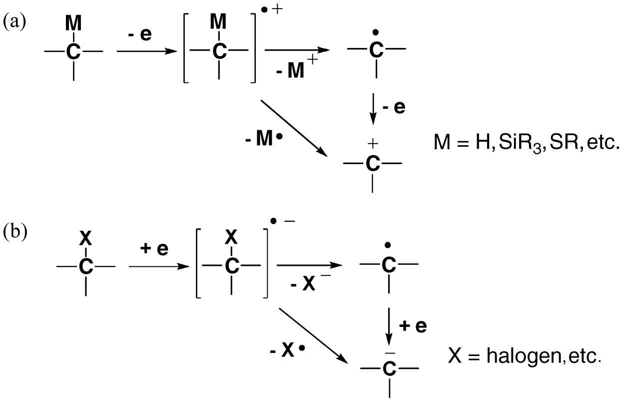


Scheme 5.8 Oxidative methoxylation of *p*-methoxytoluene

derivatives to benzaldehyde dimethyl acetal (Scheme 5.8), are utilized in the chemical industry.

Electrochemistry serves as one of the most straightforward ways to generate highly reactive reagents under mild conditions.[15] Highly reactive radical cations, carbocations, carbon free radicals, carbanions, and radical anions can be generated electrochemically at room temperature or below as shown in Scheme 5.9. For example, one-electron oxidation of organic compounds having M (M = H, SiR_3, SR, etc.) leads to the formation of radical cations, which often lose M^+ (M = H, SiR_3) to generate carbon free radicals (Scheme 5.9a). Further oxidation of free radicals affords the corresponding carbocations (Scheme 5.9a). In some cases (for example, M = SR), M is eliminated as a radical to generate a carbocation directly. However, reduction of organic compounds having a leaving group X (X = halogen, etc.) leads to the formation of a negatively charged carbanion via carbon free radicals (Scheme 5.9b). In some cases a carbanion is generated directly from the radical anion by the loss of the X radical.

A combination of the pulse electrolysis and the stopped-flow method has been used to study the reactivity of radical cations.[16] A highly reactive transient radical cation can be generated very rapidly and its extremely fast reaction analyzed by the stopped-flow method. The



Scheme 5.9 Electrochemical generation of reactive carbon species

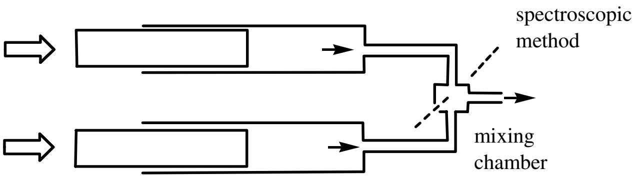
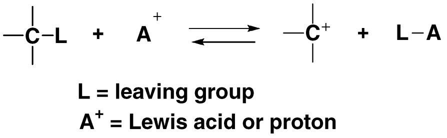


Figure 5.4 The stopped-flow method

stopped-flow method has been utilized for many years by chemists to facilitate the study of the kinetics and mechanisms of very fast reactions (Figure 5.4).[17] In this 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. Usually a spectroscopic method, such as UV spectroscopy, is used to determine the concentration of a reactant or a product. It should be noted, however, that both pulse electrolysis and the stopped-flow method are unsuitable for chemical synthesis of a large quantity of compounds, although they serve as powerful tools for mechanistic studies. We need a continuous-flow system for synthesis and production.

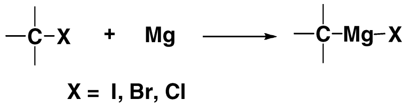
5.4 CHEMICAL ACTIVATION

Carbocations can be generated by photochemical and electrochemical activation as described in the previous sections. However, the most popular method for carbocation generation for organic synthesis is a chemical activation using a proton or a Lewis acid.[18] In this method, a proton or a Lewis acid is used to activate a leaving group, and then the heterolysis of the bond between the carbon and the leaving group occurs to generate the carbocation. These steps are reversible, and the equilibrium usually lies to the precursor side except for the cases of very stable carbocations. Therefore, several species often exist in the solution as an equilibrium mixture. Then, a nucleophile, which is usually present in the solution, attacks the carbocation to give the final product, as shown in Scheme 5.10.



$$-\overset{|}{\underset{|}{C}}-L + A^+ \rightleftharpoons -\overset{|}{\underset{|}{C}}{}^+ + L-A$$

Scheme 5.10 Acid-promoted generation of a carbocation

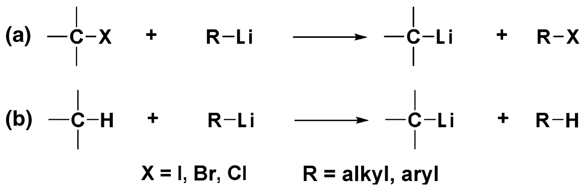


Scheme 5.11 Preparation of Grignard reagents

Organometallic compounds serve as carbanion equivalents, because most of them are highly reactive carbon nucleophiles. For example, one of the most popular classes of organometallic compounds, Grignard reagents or organomagnesium halides, which have a carbon–magnesium bond, react as a carbanion equivalent with various electrophiles. Grignard reagents are usually prepared by the reaction of organic halides with magnesium metal, as in Scheme 5.11. Typical solvents are diethyl ether and tetrahydrofuran (THF). Because organic halides are not nucleophilic and the Grignard reagents thus obtained are highly nucleophilic, the reaction of organic halides with magnesium metal can be seen as a chemical activation of organic compounds. Highly reactive Grignard reagents can serve as powerful reagents in flash chemistry.

Organolithium compounds are also highly reactive carbanion equivalents. Usually, the reactivity of organolithium compounds is higher than that of the corresponding organomagnesium compounds (Grignard reagents). Organolithium compounds are usually prepared by a halogen–lithium exchange reaction or a hydrogen–lithium exchange reaction (Scheme 5.12). This is because direct reaction of organic halides with lithium metal is rather difficult in laboratory synthesis. However, highly reactive *n*-butyllithium, *sec*-butyllithium, and *tert*-butyllithium are commercially available and they serve as useful reagents for halogen–lithium and hydrogen–lithium exchange reactions to make various organolithium compounds.

A variety of organometallic compounds have been developed and they are widely utilized in organic synthesis, although the extent of nucleophilicity depends on the nature of the metal and substituents on the carbon.



Scheme 5.12 Preparation of organolithium compounds: (a) halogen–lithium exchange reaction; (b) hydrogen–lithium exchange reaction

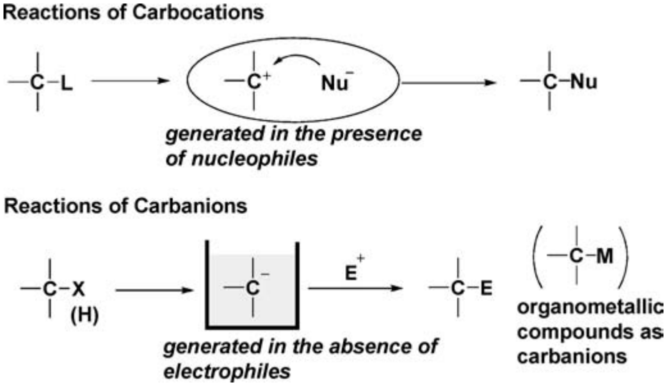
However, we will not go into detail here. Instead, let us keep in mind that making organometallic compounds with metals or other organometallic compounds is a useful method for activating organic molecules to generate highly nucleophilic carbanion equivalents, which are very useful reagents in flash chemistry.

5.5 ACCUMULATION OF REACTIVE SPECIES

In flash chemistry, we have to activate molecules to generate highly reactive species. However, it is important to note that the concentration of the thus-generated reactive species should be high enough to drive the reaction at high speed. Otherwise, the reaction is slow even if the reactivity of the species is very high.

From this point of view, we should remind ourselves that the manner in which we carry out the reactions of carbocations is different from that for carbanions or organometallic compounds (Scheme 5.13). Usually, carbanions are generated and accumulated in a solution in the absence of electrophiles. After the generation process, such as a halogen–metal or hydrogen–metal exchange reaction, is complete, an electrophile is added to the solution of the thus-generated carbanion to achieve a desired transformation. Therefore, the concentration of the carbanion or organometallic compound is relatively high and the reaction should be very fast.

In contrast, carbocations are usually generated in the presence of nucleophiles. This is probably because carbocations are considered to be highly unstable and transient in conventional reaction media and should



Scheme 5.13 Reactions of carbocations and carbanions

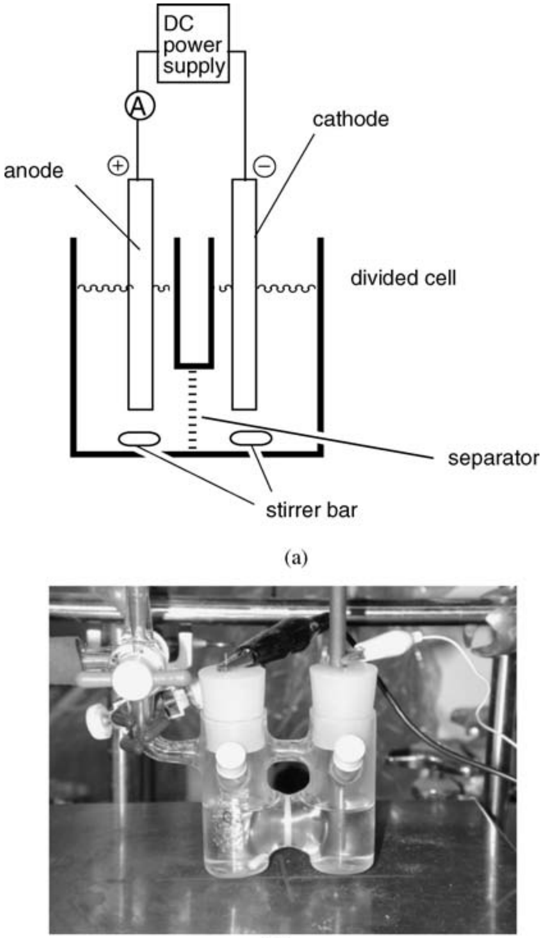
be trapped by nucleophiles immediately after their generation *in situ*. Olah's extensive work in the 1960s, however, showed that carbocations can be long-lived species in superacid medium.[19] Although the superacid medium is quite effective for detection and characterization of carbocationic species, its use as a reaction medium for chemical synthesis is rather limited. Therefore, carbocations are still generated in the presence of nucleophiles in synthesis, and the reactions suffer from the limitation of the variation of nucleophiles. Nucleophiles that do not survive under the conditions of carbocation generation cannot be used. Another important point is that the concentration of a carbocation is usually very low under normal conditions because of the unfavorable equilibrium. In this situation, it is rather difficult to use carbocations in flash chemistry. In order to accomplish carbocationic flash chemistry we need to accumulate highly reactive carbocations in a solution at a relatively high concentration.

Therefore, development of a new method that enables the generation and accumulation of carbocations or organic cations in the absence of nucleophiles is highly desirable to achieve extremely fast chemical cationic reactions. In the next section, we will discuss the realization of this method in detail.

5.5.1 The Cation-pool Method

A new method for the generation and accumulation of highly reactive organic cations in the absence of a nucleophile (the cation-pool method) based on electrochemical activation has been developed.[20] The electrolysis is normally carried out at low temperatures, such as −78 °C, to avoid decomposition of unstable organic cations. Carrying out preparative electrolyses at such low temperatures was considered difficult, probably because of the high viscosity of the solution, which in turn inhibits the movement of ions carrying the charge. By choosing an appropriate solvent and a supporting electrolyte, however, electrolysis at such a low temperature can be accomplished to generate and accumulate organic cations. A divided cell having a sintered glass separator is used to avoid the electrochemical reduction of anodically generated carbocations as shown in Figure 5.5.

A low-temperature electrochemical oxidation system for the generation of cation pools is shown in Figure 5.6. The DC power supply is not very expensive, and the reactions can be easily conducted with normal laboratory techniques that are used for the handling of air-sensitive reagents at low temperatures.



(a)

(b)

Figure 5.5 Schematic diagram (a) and photograph (b) of an H-type divided cell for the cation-pool method

Tetrabutylammonium tetrafluoroborate (Bu_4NBF_4) is usually used as a supporting electrolyte, and dichloromethane (CH_2Cl_2) is suitable as the solvent because of its low viscosity at low temperatures. Trifluoromethanesulfonic acid (CF_3SO_3H or TfOH) is added in the cathodic chamber to facilitate the reduction of protons in the cathodic process. It should be noted that both an anodic process and a cathodic process take place simultaneously in electrochemical reactions, and both processes should proceed smoothly to promote the overall reaction.

After generation of a cation, a suitable nucleophile, such as an organic or organometallic compound, is added to the cation pool to accomplish a

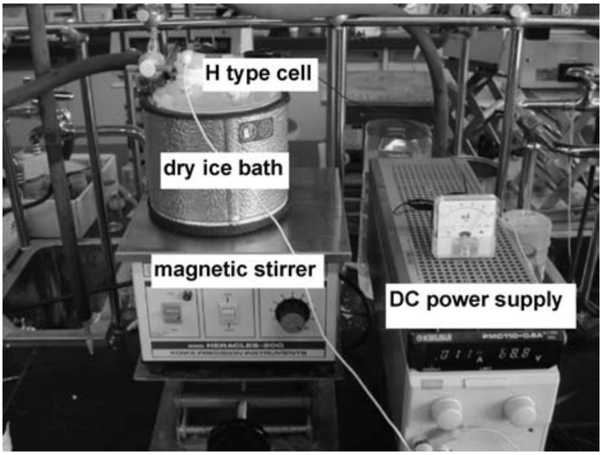


Figure 5.6 Electrochemical system for the generation of cation pools

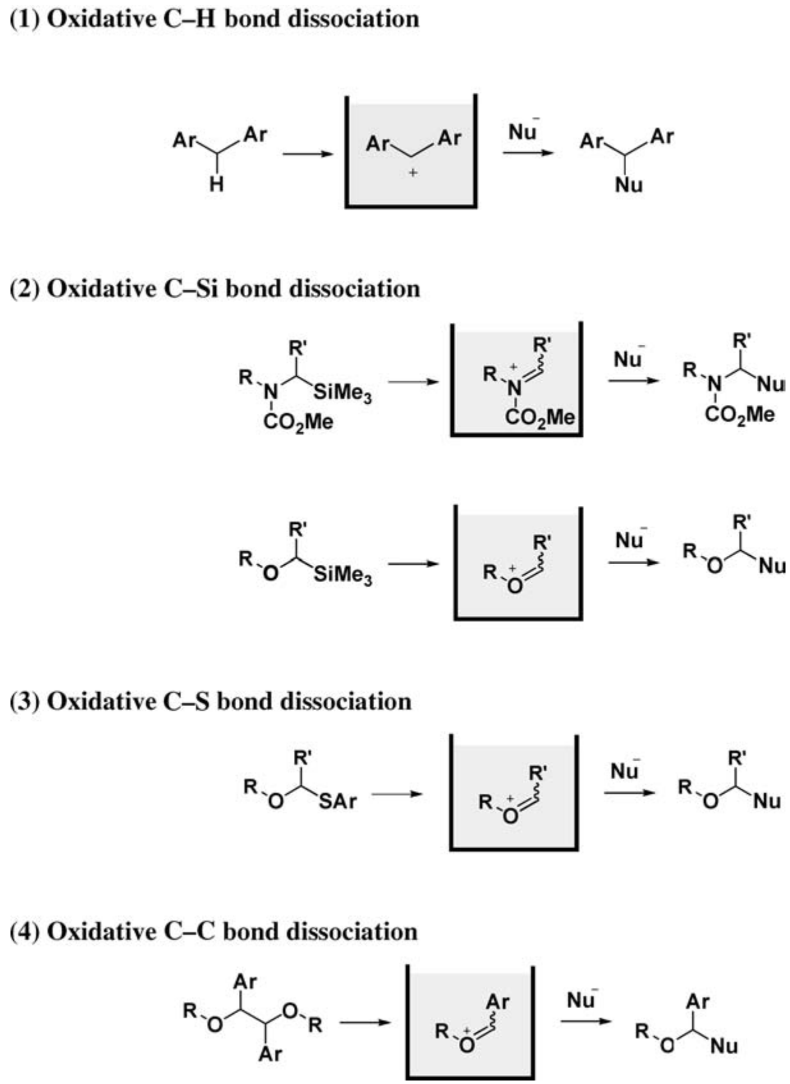
desired reaction. The method has been successfully applied for the generation and reaction of *N*-acyliminium ions, alkoxycarbenium ions, and diarylcarbenium ions.

5.5.1.1 Methods for generating cation pools

Four methods can be used for generating cation pools: oxidative C—H bond dissociation; oxidative C—Si bond dissociation; oxidative C—S bond dissociation; and oxidative C—C bond dissociation (Scheme 5.14). In the following sections, we will briefly discuss the principles and applications of these methods.

5.5.1.2 Generation of N-acyliminium ion pools by C—H bond dissociation

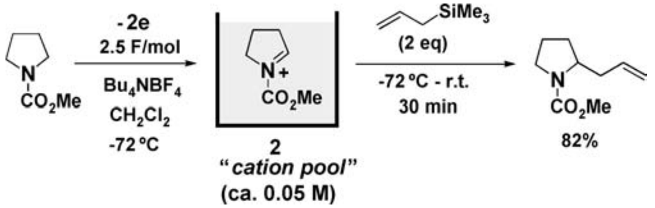
It is well known that oxidation of carbamates leads to the formation of *N*-acyliminium ions[21] via dissociation of the C—H bond α to nitrogen. Electrochemical,[22] metal-catalyzed,[23] and chemical methods[24] to accomplish this transformation have been reported in the literature. The transformation serves as a useful tool for organic synthesis, although only compounds of high oxidation potentials, such as methanol and cyanide ion, can be used as nucleophiles. It should be noted that *N*-acyliminium ions, which do not have a stabilizing group, had been considered to be only



Scheme 5.14 Methods for generating cation pools

transient intermediates until the cation-pool method was developed because they had not been detected spectroscopically except for the cases that involved additional stabilizing groups.

The following example illustrates how a cation pool of an *N*-acyliminium ion is generated and used for a subsequent reaction. Low-temperature electrolysis of pyrrolidine carbamate in Bu_4NBF_4/CH_2Cl_2 gives a solution of the corresponding *N*-acyliminium ion as a single species,[25] as



Scheme 5.15 Generation and reaction of *N*-acyliminium cation pool from pyrrolidine carbamate

demonstrated by NMR analysis (^{1}H NMR: 9.38 ppm from the methine proton; ^{13}C NMR: 193.36 ppm from the methine carbon) (Scheme 5.15).[26] These chemical shifts indicate that there is a high positive charge on the carbon and that the *N*-acyliminium ion is formed as an ionic species. In the next step, the addition of allyltrimethylsilane to the solution affords the corresponding allylated product in 82% yield.

The *N*-acyliminium ion can be characterized by FT-IR spectroscopy as well.[27] The starting pyrrolidine carbamate exhibits an absorption at 1694 cm^{-1}, resulting from the carbonyl stretching, while the *N*-acyliminium ion generated by the cation-pool method exhibits an absorption at 1814 cm^{-1} (Figure 5.7). The higher wave number of the cation is consistent with the formation of a positive charge on the nitrogen adjacent to the

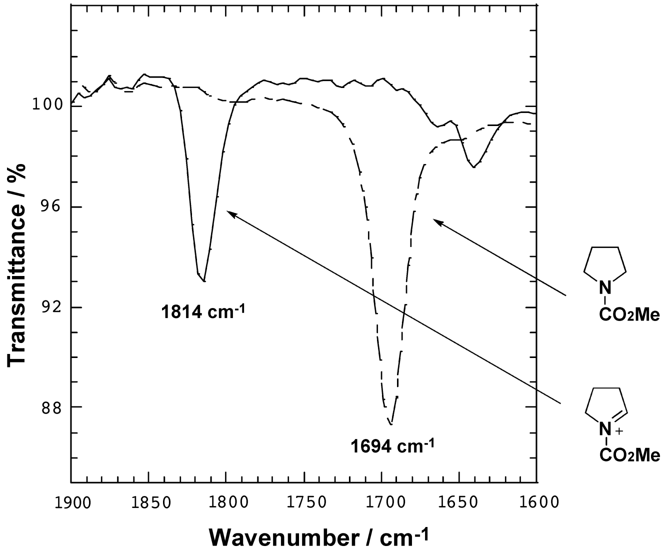
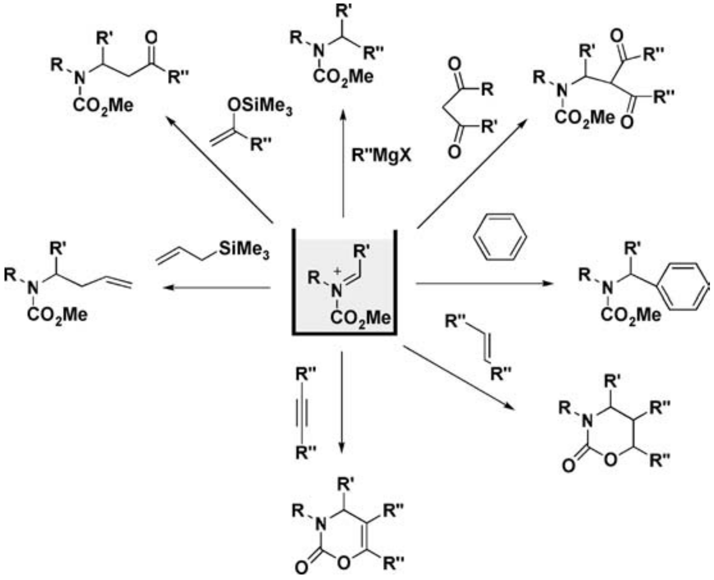


Figure 5.7 FT-IR spectrum of methyl pyrrolidinecarboxylate and *N*-acyliminium ion. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission

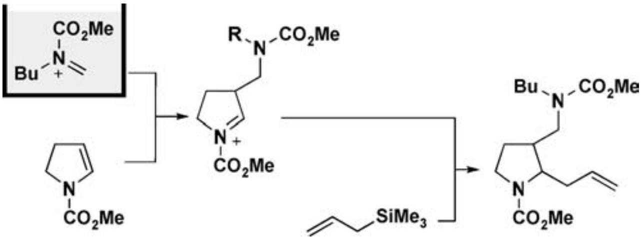


Scheme 5.16 Reactions of *N*-acyliminium ion pools

carbonyl carbon. The shift to higher wave number is also supported by density functional theory calculations,[28] which indicate that the wave numbers for the C=O vibration of model compounds $(CH_3)_2N(CO_2CH_3)$ and $CH_3N^+(=CH_2)CO_2CH_3$ are 1734 and 1856 cm^{-1}, respectively.

N-Acyliminium ion pools react with various carbon nucleophiles as summarized in Scheme 5.16. For example, allylsilanes, silyl enol ethers, Grignard reagents, and 1,3-dicarbonyl compounds serve as good nucleophiles.[29] Aromatic and heteroaromatic compounds also react as nucleophiles with *N*-acyliminium ion pools to give Friedel-Crafts-type alkylation products.[30] *N*-Acyliminium ions are known to serve as electron-deficient 4π components and undergo [4 + 2] cycloaddition with alkenes and alkynes.[31] Usually these reactions take place very quickly, and therefore *N*-acyliminium ion pools serve as effective reagents for flash chemistry.

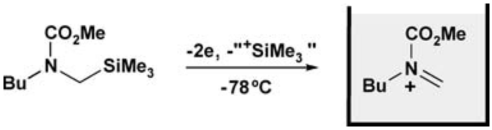
The reaction of an *N*-acyliminium ion pool with an alkene or alkyne followed by trapping of the resulting carbocation by water leads to the formation of the corresponding carbohydroxylation product.[32] Cationic sequential one-pot, three-component coupling reactions of an *N*-acyliminium ion can also be accomplished using an electron-rich olefin and a suitable nucleophile that traps the thus-generated cationic intermediate as shown in Scheme 5.17.[33]



Scheme 5.17 Sequential one-pot, three-component coupling of an *N*-acyliminum ion pool

5.5.1.3 *Generation of N-acyliminium ion pools by C—Si bond dissociation*

The use of a silyl group as an electroauxiliary is quite effective for the cation-pool method.[34] The concept of an electroauxiliary[35] has been developed for accomplishing selective electron-transfer-driven reactions. An electroauxiliary activates substrate molecules toward electron transfer and controls a reaction pathway that would favor the formation of the desired products. For example, pre-introduction of an electroauxiliary, such as a silyl group, to a carbon α to nitrogen gives rise to selective introduction of a nucleophile on the carbon to which the auxiliary has been attached. In fact, the introduction of a silyl group decreases the oxidation potentials of carbamates. Therefore, the electrolysis can be carried out more easily. Control of regiochemistry by the silyl group is also advantageous if we use unsymmetrical carbamates, because the C—Si bond is cleaved selectively without affecting the C—H bonds. The example in Scheme 5.18 demonstrates the control of regiochemistry by the silyl group in the generation of an *N*-acyliminium ion.



Scheme 5.18 Regioselective generation of an *N*-acyliminium ion pool by oxidative C—Si bond dissociation

5.5.1.4 *Generation of alkoxycarbenium ion pools by C—Si bond dissociation*

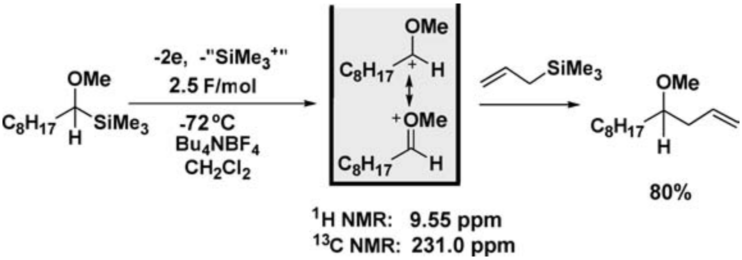
Alkoxycarbenium ions are widely utilized as reactive intermediates in organic synthesis.[36] It should be noted that other nomenclatures, such as oxonium ions, oxocarbenium ions, and carboxonium ions, have also been used for carbocations stabilized by an adjacent oxygen atom. Irrespective of the nomenclature, we often draw structures having a carbon-oxygen double bond for these types of cations.

Generation of alkoxycarbenium ions is often carried out by treatment of the corresponding acetals or their derivatives with a Lewis acid in the presence of a carbon nucleophile. This type of reaction serves as an efficient method for carbon–carbon bond formation under acidic conditions. Mechanistic studies of Lewis-acid promoted reactions of acetals using NMR spectroscopy showed the presence of Lewis acid-acetal complexes in the solution, but alkoxycarbenium ions were never detected.[37] The absence of signals resulting from alkoxycarbenium ions in the NMR spectra, however, does not necessarily rule out their intermediacy in the reactions with nucleophiles. Therefore, it was imperative to accomplish the reactions of spectroscopically characterized, nonstabilized alkoxycarbenium ions with carbon nucleophiles. The cation-pool method made this possible and opened a new chapter in the chemistry of alkoxycarbenium ions.

If we consider the generation and accumulation of alkoxycarbenium ions by C—H bond dissociation, ethers might be our first choice as precursors of alkoxycarbenium ions by analogy with the carbamate cases from the analogy of the *N*-acyliminium ion pool case. However, the oxidation potentials of ethers, especially aliphatic ethers, are very high. Therefore, it is rather difficult to oxidize aliphatic ethers selectively under the usual electrochemical conditions. The regioselectivity is also a problem. Even if the oxidation of ethers takes place, a mixture of two regioisomeric alkoxycarbenium ions should be generated.

These problems can be solved using the concept of an electroauxiliary.[38] The pre-introduction of a silyl group as an electroauxiliary on one of the carbons adjacent to the oxygen decreases the oxidation potential of dialkyl ethers by virtue of the orbital interaction. In fact, alkoxycarbenium ion pools can be generated by low-temperature electrochemical oxidation of α-silyl ethers through the selective C—Si bond dissociation.[39] The resulting solution of alkoxycarbenium ion exhibits a ^{1}H NMR signal at 9.55 ppm from the methine proton, and a ^{13}C NMR signal at 231.0 ppm from the methine carbon (Scheme 5.19). These chemical shifts suggest the presence of a high positive charge on the carbon, and are consistent with those of an alkoxycarbenium ion generated in superacid media, as reported by Olah and Forsyth.[40]

The thus-generated alkoxycarbenium ion is stable only at temperatures below approximately −50 °C. Above this temperature, it decomposes.



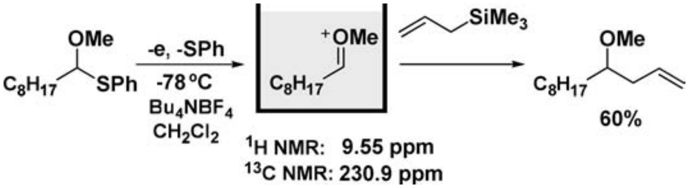
Scheme 5.19 Generation and reaction of alkoxycarbenium ion pool

The stability of alkoxycarbenium ions can be increased by the introduction of an ether functionality in an appropriate position by virtue of effective intramolecular coordination of the ether oxygen to the cationic carbon.[41]

The reactions of alkoxycarbenium ions generated by the cation-pool method with various carbon nucleophiles, such as substituted allylsilanes and enol silyl ethers, take place very quickly to give the corresponding coupling products in good yields. It should be noted that the reactions of alkoxycarbenium ion pools with such nucleophiles are much faster than the Lewis-acid-promoted reactions of acetals with similar nucleophiles because the concentration of the cationic species in the cation-pool method is much higher.

5.5.1.5 Generation of alkoxycarbenium ion pools by oxidative C—S bond cleavage

Alkoxycarbenium ion pools can also be generated by electrochemical oxidative C—S bond dissociation (Scheme 5.20).[42] Arylthio (ArS) groups are known to also serve as effective electroauxiliaries for the electrochemical oxidation of heteroatom compounds.[43] The introduction of an ArS group decreases the oxidation potential and the C—S bond



Scheme 5.20 Generation and reaction of alkoxycarbenium pool by C—S bond cleavage

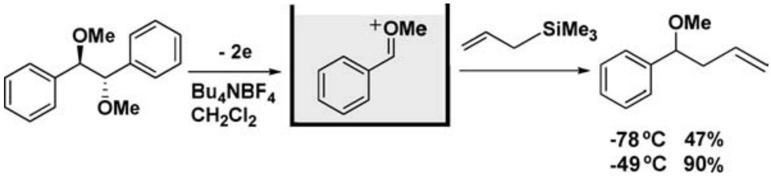
is cleaved selectively without affecting the C—H bonds to generate the corresponding alkoxycarbenium ion.

The obtained solution exhibits a single set of signals in the ^1H and ^{13}C NMR spectra because of the alkoxycarbenium ion. The chemical shifts are quite similar to those obtained by the oxidative C—Si bond dissociation described in the previous section, indicating the formation of the alkoxycarbenium ion.

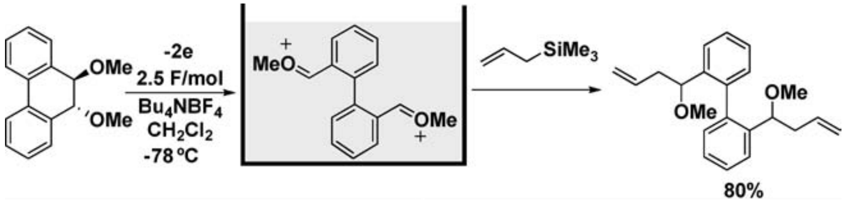
5.5.1.6 Generation of alkoxycarbenium ion pools by oxidative C—C bond dissociation

Oxidative C—C bond dissociation is well known in the literature,[44] and alkoxycarbenium ion pools can also be generated by oxidative C—C bond dissociation. For example, low temperature electrochemical oxidation of 1,2-dimethoxy-1,2-diphenylethane in the absence of a nucleophile leads to the formation of a pool of the corresponding alkoxybenzyl cation, which reacts with allyltrimethylsilane to give the allylated product in the next step (Scheme 5.21).[45] It is important to note that a slightly higher temperature is required for the effective cleavage of the C—C bond. It is also interesting that the two diastereomers of the precursor exhibit similar reactivity.

A major advantage of the C—C bond dissociation approach is the easy generation of dications,[46] if we employ cyclic compounds as starting materials. Such dications may provide powerful intermediates for the construction of various molecular architectures. For example, low temperature electrochemical oxidation of a cyclic compound leads to the formation of the corresponding dication through the C—C bond dissociation (Scheme 5.22). The ^{13}C NMR spectrum indicates that the two cationic centers are equivalent. The highly reactive dication thus accumulated reacts with two equivalents of allyltrimethylsilane to give the corresponding diallylated compound very quickly.



Scheme 5.21 Generation and reaction of cation pool by C—C bond dissociation



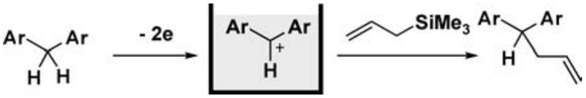
Scheme 5.22 Generation and reaction of dication pool

5.5.1.7 Generation of diarylcarbenium ion pools by C—H bond dissociation

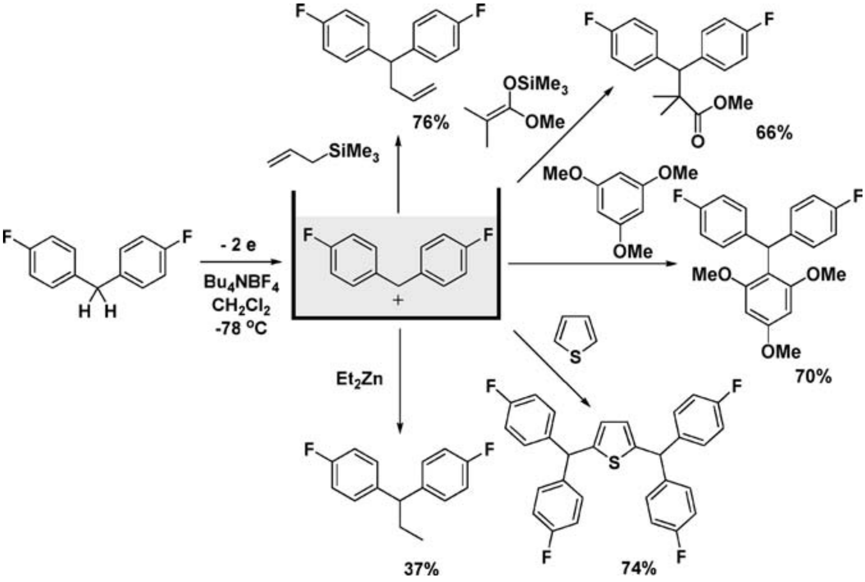
Diarylcarbenium ions have received significant research interest from a mechanistic viewpoint. Some diarylcarbenium ions are stable[47] and their reactivities toward nucleophiles have been extensively studied.[48] It is also worth noting that diarylcarbenium ions may serve as versatile intermediates for the synthesis of aryl-substituted compounds having interesting functions. Diarylcarbenium ions have often been generated from the corresponding alcohols and halides by ionization in superacid.[49] LFP has also been utilized as a method for the generation of diarylcarbenium ions.[50] Although some stable diarylcarbenium ions can be prepared using such methods,[51] the cation-pool method may serve as a general and convenient method for the generation and accumulation of reactive diarylcarbenium ions.

Low-temperature electrochemical oxidation of various diarylmethanes in Bu_4NBF_4/CH_2Cl_2 leads to the formation of diarylcarbenium ion pools, which react with allyltrimethylsilane very quickly to give the corresponding allylated diarylmethanes (Scheme 5.23). Although the use of simple diphenylmethane as a precursor gives only a complex mixture, the use of diarylmethanes having para substituents works very well. In addition to electron-donating substituents, weak electron-withdrawing substituents are effective.

The accumulation of diarylcarbenium ion can be confirmed by NMR spectroscopy. For example, a solution of bis(*p*-flurorophenyl)carbenium ion exhibits a signal at 192.6 ppm because of the carbenium carbon. This



Scheme 5.23 Generation of diarylcarbenium ion pools by C—H bond dissociation



Scheme 5.24 Reactions of diarylcarbenium ion pools

chemical shift is very close to that (193.3 ppm) of the same cation generated in a superacid medium (SO_2ClF).[52] Cold spray ionization mass spectrometry analysis (spray temperature: −20 °C) also supports its formation ($m/z = 203$).

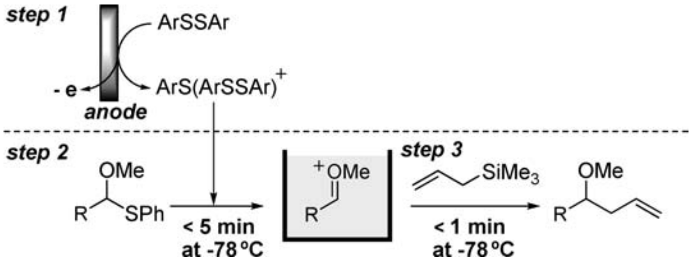
As exemplified in Scheme 5.24, the dicarylcarbenium ion pool reacts with various nucleophiles including allylsilanes and ketene silyl acetals very quickly. Friedel-Crafts-type reactions with aromatic and heteroatomatic compounds also take place smoothly. Therefore, diarylcarbenium ion pools serve as powerful reagents for flash chemistry.

5.5.1.8 Chemical generation of cation pools. The indirect cation-pool method

Chemical generation of cation pools is also effective. As an active reagent used for the cation generation is prepared electrochemically, this method is called the indirect cation-pool method. The method involves three steps. In the first step, an active reagent is generated and accumulated electrochemically. In the second step, the active reagent thus generated is allowed to react with a precursor to generate a cation pool. In the third step, the cation pool thus generated is allowed to react with a nucleophile.[53]

Chemical generation has the following advantage over the electrochemical method. In the electrochemical cation-pool method, organic cations are generated by low-temperature electrochemical oxidation of their precursors. Electrochemical reactions take place only on the surface of the electrode, so the accumulation of organic cations usually takes several hours on a laboratory scale. This means that the lifetime of the organic cation should be longer than the accumulation time. Therefore, the applicability of the electrochemical method strongly depends on the stability of the organic cation that is accumulated. In chemical generation, however, the reaction takes place in a homogeneous solution and therefore very rapidly. The reactions usually require less than 5 min at −78 °C. Using the chemical method, in principle, less stable organic cations can be generated very quickly and used for subsequent reactions before they decompose.

The following example demonstrates the utility of the indirect cation-pool method. The first step is the electrochemical generation of $ArS(ArSSAr)^+$,[54] which was characterized by NMR and CSI-MS. $ArS(ArSSAr)^+$ serves as a quite effective chemical reagent for the generation of alkoxycarbenium ions from α-ArS-substituted ethers, presumably because of its high thiophilicity (Scheme 5.25). The conversion is complete within 5 min at −78 °C. The alkoxycarbenium ion pool thus obtained exhibits similar stability and reactivity to that obtained with the direct electrochemical method. Therefore, alkoxycarbenium ion pools generated by the indirect method also serve as powerful reagents for flash chemistry.

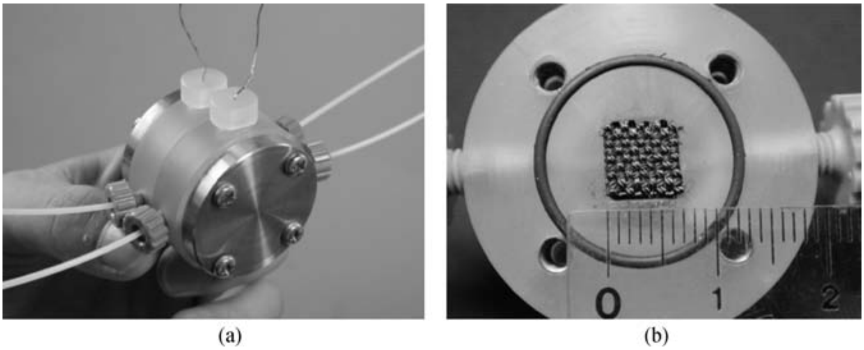


Scheme 5.25 Indirect cation-pool method

5.6 CONTINUOUS GENERATION OF REACTIVE SPECIES IN A FLOW SYSTEM

In flash chemistry, it is necessary to use highly reactive species at high concentrations to accomplish extremely fast reactions. Therefore, highly reactive species are generated and accumulated in solution before being used for flash chemistry. However, continuously generating solutions of reactive species in a flow system would be more convenient for flash chemistry because subsequent reactions of flash chemistry in microflow systems can be easily combined with generation of reactive species. In this context, the cation-flow method has been developed. In the cation-flow method, highly reactive organic cations are generated using an electrochemical microflow reactor, where the electrolysis is carried out continuously at low temperature (Figure 5.8).

The electrochemical microflow reactor is constructed from diflone and stainless steel bodies by a mechanical manufacturing technique. The anodic chamber and the cathodic chamber are separated by a PTFE diaphragm. The anodic chamber is equipped with a carbon felt anode (7 mm × 7 mm × 5 mm) made of carbon fibers (ϕ 10 μm). The cathodic chamber is equipped with a platinum wire cathode. Typically, a 0.05 M solution of a precursor of a cation containing supporting electrolyte (Bu_4NBF_4, 0.3 M) in CH_2Cl_2 is introduced at −72 °C by syringe pumping to the anodic chamber. A solution of Bu_4NBF_4 and trifluoromethanesulfonic acid (TfOH) as a proton source is introduced to the cathodic chamber. The cationic intermediate that is generated by low-temperature electrolysis is immediately allowed to react with a nucleophile to obtain the desired product.



(a) (b)

Figure 5.8 Electrochemical microflow reactor for the cation-flow method: (a) outside; (b) inside (anodic part). Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission

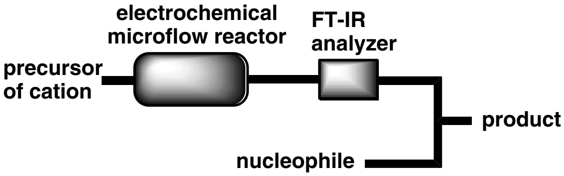


Figure 5.9 Schematic diagram of the cation-flow system

It is important to construct a monitoring device in the flow system to detect any reactive intermediate. FT-IR spectroscopy can be applied for the in-line monitoring of *N*-acyliminium ions generated by low temperature flow electrolysis. As stated in the previous section, a starting carbamate exhibits an absorption at ca. 1695 cm^{-1} resulting from the carbonyl stretching, while an *N*-acyliminium ion exhibits an absorption at 1815 cm^{-1}. Thus, the generation of the cation can be monitored by an FT-IR spectrometer (attenuated total reflection method) equipped with a low-temperature flow cell attached to the outlet of the electrochemical microflow reactor. The formation of an *N*-acyliminium ion is indicated by absorption at 1815 cm^{-1}, which increases with an increase in the electric current. A schematic diagram of the cation-flow system equipped with an in-line FT-IR analyzer is shown in Figure 5.9.

In the cation-flow method, only the anodic oxidation is used for the synthesis. The cathodic counterpart is a sacrificial reaction, such as generation of H_2 from H^+ (TfOH). Paired electrolysis,[55] in which both the anodic oxidation and the cathodic reduction contribute to the formation of the final product(s), is highly advantageous from the viewpoint of efficiency and economy. This idea indeed works. By using a paired microflow electrochemical system, an organic cation is generated by anodic oxidation and a carbanion equivalent is generated by cathodic reduction, both of which are allowed to react with each other to give the corresponding coupling product.

For example, the anodic oxidation of a silyl-substituted carbamate to generate a solution of *N*-acyliminium ion and the cathodic reduction of cinnamyl chloride in the presence of chlorotrimethylsilane to generate the corresponding allylsilane[56] can be carried out simultaneously in a single electrochemical microflow cell under continuous flow conditions (Figure 5.10). The *N*-acyliminium ion, the anodic product, is allowed to react with the allylsilane, the cathodic product, to give the coupling product.

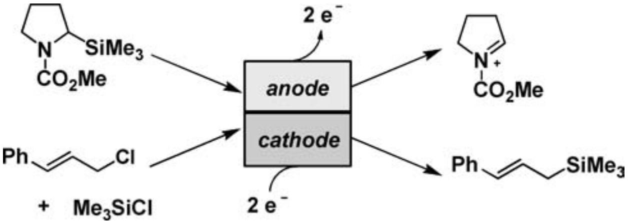


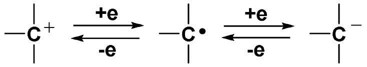
Figure 5.10 Paired electrolysis to generate cation and anion equivalents using a microflow system

5.7 INTERCONVERSION BETWEEN REACTIVE SPECIES

Up to this point we have looked at the generation of carbanions (or organometallic compounds as carbanion equivalents) and carbocations. Carbon radicals are also among the most fundamental reactive species in organic chemistry and are widely utilized in synthesis. Is it possible to generate and accumulate carbon radicals in solution? The answer is no, except for very stable carbon radicals. At least with our current technology of chemical reactions, it is impossible to accumulate reactive carbon radicals in a solution and use them for synthetic reactions, because carbon radicals readily undergo spontaneous homo-coupling reactions. However, considering how to generate reactive carbon radicals in a short period and using them for synthetic reactions in a controlled manner is not meaningless.

Carbon radicals are usually generated by homolytic cleavage of a carbon–heteroatom bond. Usually the homolytic cleavage takes place in a radical chain process, which is initiated by thermolysis of a radical initiator. Radical chain reactions are usually very fast because radical intermediates are highly reactive. If we want to generate a carbon radical at high concentration similar to the case of the cation-pool method, however, it is necessary to use a stoichiometric amount of a radical initiator to generate reactive carbon radicals in a short period. However, such reaction is likely to lead to an explosion and is extremely dangerous.

The redox-mediated method is another way to generate carbon radicals. One-electron oxidation of neutral organic compounds having a carbon-heteroatom bond produces radical cation intermediates that decompose to give carbon radicals (Scheme 5.9a). Carbon radicals can also be generated by one-electron reduction followed by bond cleavage

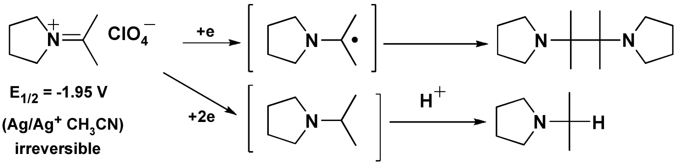


Scheme 5.26 Redox interconversions of carbocation, carbon radical, and carbanion

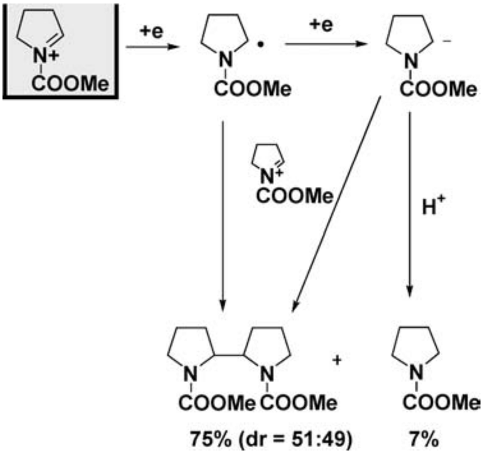
(Scheme 5.9b). For example, the one-electron oxidation of metal enolates leads to the generation of free radical species.[57] In this case, the carbon radical center is generated adjacent to an electron-withdrawing carbonyl group, and therefore oxidation of carbon radicals to cations is not favorable. Oxidative generation of carbon radicals, however, often suffers from the problem of over-oxidation, which is especially serious for the generation of electron-rich radicals. Carbon radicals are often oxidized to the corresponding carbocations very quickly under oxidative conditions because carbon radicals are often more easily oxidized than their precursors. In the case of reductive generation, carbon radicals are often reduced to the corresponding carbanions under these conditions. Therefore, the over-reduction problem is also serious.

The use of cation pools as precursors of carbon radicals solves the problem, because carbocations are more easily oxidized than carbon radicals in many cases. In fact, it is well known that one-electron reduction of a carbocation leads to the formation of the corresponding carbon radical. Therefore, the reduction of cation pools should lead to the formation of carbon radicals (Scheme 5.26).

The pioneering work of Conant showed that the one-electron reduction of pyridinium ion by low-valent vanadium produces the corresponding carbon radical, which dimerizes to give a homocoupling product.[58] Savéant studied the electrochemical reduction of stable iminium salts, and observed two reduction waves in the polarograms (Scheme 5.27).[59] The first wave corresponds to the one-electron reduction process for which dimerization occurs. This process presumably involves formation of the carbon centered radical. The second wave is concerned with the formation of the amine by two-electron reduction. Wayner performed extensive work on oxidation and reduction potentials of carbon radicals.[60] A modulated



Scheme 5.27 Reduction of iminium ion



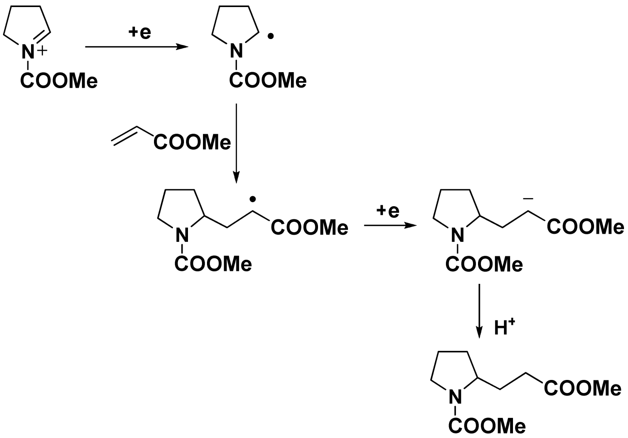
Scheme 5.28 Reduction of *N*-acyliminium ion pool. Radical homocoupling

photolysis technique was used for radical generation, and phase-sensitive voltammetry was used for the measurements. Arnett studied the redox potentials of the xanthyl system, where both the cation and the anion can be generated in the same solvent.[61] The reduction of the cation to the radical takes place at a less negative potential than the reduction of the radical to an anion.

The electrochemical reduction of an *N*-acyliminium ion pool generated from pyrrolidine carbamate at constant-current conditions at −78 °C in a divided cell gives the corresponding homo-coupled product (Scheme 5.28), indicating the formation of the carbon radical by one-electron reduction.[62] When zinc powder is used as a reducing agent, the simply reduced product is formed as the major product together with a small amount of the homo-coupled product. Two-electron reduction of the *N*-acyliminium ion seems to take place predominantly to produce the corresponding carbanion, which is trapped by a proton in the reaction medium to give the simply reduced product.

The radical generated by the reduction of an *N*-acyliminium ion pool can be trapped with an electron-deficient olefin, such as acrylate ester, which is known to be a good radical acceptor (Scheme 5.29).[63] In the presence of a large excess amount of proton, a 1:1 adduct is obtained in good yield. A mechanism involving radical addition to the electron-deficient olefin followed by one-electron reduction to give the carbanion or enolate anion that is trapped by a proton has been suggested.

Carbon radicals can be generated by the reduction of cation pools and this method might serve as an effective method for the generation of



Scheme 5.29 Addition of a carbon radical generated from an *N*-acyliminium ion pool to an electron-deficient olefin

carbon radicals in a short period. This reductive generation of carbon radicals seems to be more easily controlled in comparison with other methods, such as thermolysis of the radical precursor. Therefore, the reduction of cation pools may serve as an effective radical-generating system for flash chemistry. Oxidation of carbanions should also serve as an effective radical-generating system as demonstrated by the reduction of metal enolates. Although the lifetimes of carbon radicals are much shorter than the reaction time of flash chemistry at present, it is hoped that further development of microflow technology will enable the use of carbon radicals as reagents for flash chemistry.

5.8 CONCLUSIONS

Activation of substrate molecules to generate highly reactive species constitutes an important element of flash chemistry. Generation of highly reactive species as reagents is also important. A variety of methods, including thermal, photochemical, electrochemical, and chemical methods, are available to generate and accumulate carbanions (organometallic compounds as equivalents) and carbocations. Such species may undergo extremely fast reactions. Carbon radicals are often 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.

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6

Control of Extremely Fast Reactions

Generation of highly reactive species is one of the key elements of flash chemistry, as was shown in Chapter 5. Another important element of flash chemistry is the control of extremely fast reactions of highly reactive species to obtain the desired products selectively. Selectivity of chemical reactions is often determined by kinetics. For extremely fast reactions, however, kinetics often cannot be used because of the lack of homogeneity of the reaction environment when they are conducted in macrobatch reactors, such as flasks. Therefore, such reactions are not controllable in conventional macrobatch reactors. In this chapter, we discuss in detail what kinds of problems are encountered in macrobatch reactors and how to solve such problems without slowing the reactions.

6.1 MIXING

Chemical reactions in organic synthesis are usually conducted by mixing two reaction components, such as substrate/reagent, substrate/catalyst, or substrate/substrate, in a solution phase. Molecules of the reaction components come together and collide with each other upon mixing to accomplish the chemical reaction and give the desired products. Although synthetic organic chemists have rather neglected the importance of mixing,

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the outcomes of chemical reactions are sometimes very sensitive to the manner of mixing.

Is it possible to obtain a homogeneous solution by the addition of one reaction component to the other component before the chemical reaction starts? This can be achieved in practice if the mixing time is much shorter than the reaction time. In other words, if the reaction is slower than the mixing, the reaction mainly proceeds, in practice, in a homogeneous solution. However, it is sometimes not possible to obtain a homogeneous solution before a significant amount of reaction takes place. In such cases, reactions are much faster than mixing, and the reaction proceeds before homogeneity of the solution has been established. In flash chemistry, extremely fast reactions are conducted using highly reactive substrates or reagents. Such reactions may be faster than mixing. Therefore, the manner of mixing should strongly affect the outcome of the reaction. In this section, we discuss the importance of mixing in performing extremely fast reactions.

6.1.1 How Does Mixing Take Place?

Let us consider the reaction of **A** and **B** to give product **P** in a conventional macrobatch reactor, such as a round-bottomed glass flask (Figure 6.1). What kinds of processes occur when a solution of **A** is added to a solution of **B**, which is stirred magnetically or mechanically? In order to simplify the discussion, we ignore the solvent. Thus, let us consider the addition of **A** to **B**.

Mixing in a solution phase is defined as a phenomenon that creates homogeneity of all species in the solution. One might think that such homogeneity is achieved immediately after **A** is added to the solution of **B** with vigorous stirring, but this is not true. It takes time to achieve

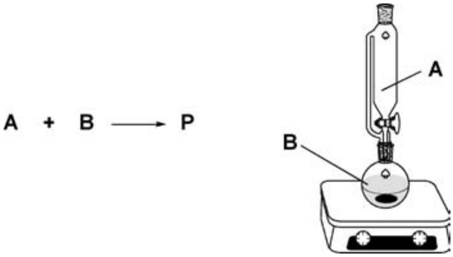


Figure 6.1 Reaction of **A** and **B** to give **P** in a conventional macrobatch reactor

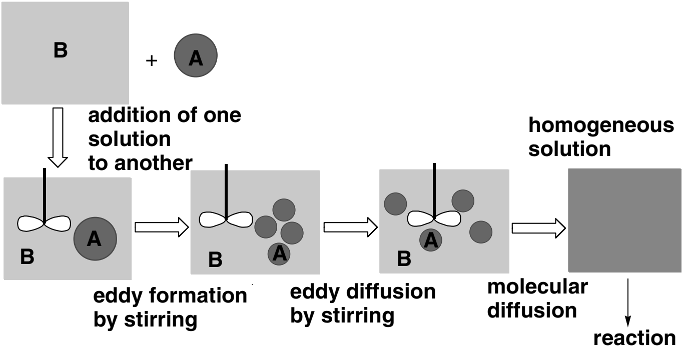


Figure 6.2 Processes occurring in the mixing of **A** and **B**

homogeneity even with maximum turbulence produced by vigorous stirring (Figure 6.2).

According to Rys's paper,[1] the mixing takes places as follows:

> If we add a solution of species **A** to a solution of species **B**, eddies of solution **A** in solution **B** are created. As a first approximation, these eddies can be considered as spherical drops with constant mean radius *R*. The lifetime of such an eddy can be estimated to be 0.01–1 s. The radius *R* depends on the intensity of the turbulence created by mixing and may be controlled, for example, by mechanical stirring. From the theory of turbulence, one can estimate the minimum mean size of such elements of liquid. For the common solvents water, methanol, and ethanol, the mean minimum radius *R* of the eddies in optimal turbulence is approximately 10^{-2} to 10^{-3} cm.

The second step is eddy diffusion by stirring. The eddies that are formed diffuse into the solution. The last part of mixing takes place by molecular diffusion. During this step, the eddies are destroyed to achieve homogeneity of the solution at a molecular level. This is the slowest step in a mixing process. Therefore, molecular diffusion is the key step in a mixing process. The time needed for molecular diffusion is proportional to the square of the length of the diffusion path. This means that the diffusion time depends strongly on the size of the eddies. This is consistent with the fact that mixing takes place faster when the solution is stirred more vigorously. The mean radius *R* of eddies is reduced by increasing the intensity of turbulence. However, it should be kept in mind that, according to Rys, the mean minimum radius *R* of eddies in optimal turbulence is approximately 100–10 μm. This means that it takes at least 0.05–5 s to obtain a homogeneous solution through molecular diffusion by stirring (see below).

Table 6.1 Relationship between diffusion time and size

Diffusion time (s)	Size
0.0005	1 μm
0.05	10 μm
5	100 μm
500	1 mm

Diffusion time is calculated for D (diffusion coefficient) $= 1 \times 10^{-5}$ cm^2/s.

6.1.2 Molecular Diffusion and Brownian Motion

The relationship between diffusion time and size is shown in Table 6.1. The time required for molecular diffusion increases in proportion to the square of the diffusion path.[2] For small molecules in water, in the case of something the size of bacteria, i.e. 1 μm, the diffusion time is 0.0005 s or 0.5 ms. When the size increases to 10 μm, which is the size of a typical animal cell, the diffusion time is 0.05 s. Molecular diffusion still takes place in a very short period in a space of such a size. Therefore, stirring is not necessary for normal reactions in a reactor of cell size, because all reaction components are distributed everywhere in the reactor within 0.05 s by molecular diffusion. When the size increases to 100 μm, the diffusion time increases to 5 s. For a size of 1 mm, the diffusion takes 500 s or ca. 8 min. This is not a very short period from a human perspective. From the viewpoint of a biologist, single-cell organisms do not require a circulatory system because of the short diffusion times, but such a system is essential for larger organisms because diffusion does not work efficiently for larger body sizes.[3]

The theory of molecular diffusion has been derived from the theory of Brownian motion, which is the physical phenomenon that small particles immersed in a fluid move randomly. Let us briefly touch on Brownian motion.[4,5] The theory of Brownian motion was established by Einstein in 1905. In that year, he published three important papers: the theory of Brownian motion; an explanation of the photoelectric effect; and the special theory of relativity. According to his Brownian motion theory, the fluid molecules move at random by thermal movement, and therefore a small particle would receive a random number of impacts of random strength and from random directions in any short period. If the particle is sufficiently small, this random collision by the fluid molecules would cause the particle to move about randomly, as described by Brown. Einstein's theory of Brownian motion was demonstrated experimentally by Perrin. Both theoretical and experimental studies showed that Brownian motion is caused by random collisions of small particles with the fluid molecules, and these studies provide convincing evidence for the physical existence of molecules.

The theory of molecular diffusion has been developed based on the theory of Brownian motion. Molecular diffusion is defined as the net action of molecules to minimize a concentration gradient. In other words, diffusion is the movement of molecules from an area of higher concentration to an area of lower concentration until equilibrium is reached. This molecular movement is caused by random thermal movement of each molecule.

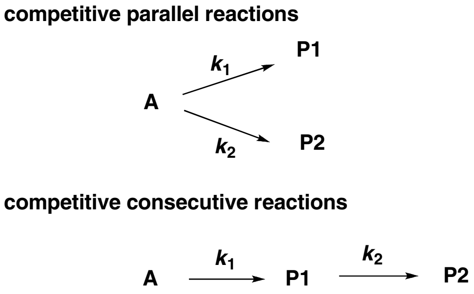
Diffusion time increases in proportion to the square of the diffusion path according to:

$$t = \frac{d^2}{2D} \tag{6.1}$$

where t is the elapsed time since diffusion began, d is the mean distance traveled by the diffusing solute molecule along one axis after elapsed time t, and D is the diffusion coefficient of a solute molecule in solution. The value of D depends on both the physical characteristics of the solute molecule and those of the solvent. For small molecules or ions in aqueous solution, typical values of D range from 1×10^{-5} to 3×10^{-5} cm^2/s. For macromolecules, D is usually much smaller.

6.1.3 Disguised Chemical Selectivity

How does a reaction take place when it proceeds faster than mixing? What kinds of problems are encountered when extremely fast reactions are conducted by mixing two reaction components? It is known that when the reaction is faster than mixing, product selectivity of the reaction is often not determined by the kinetics, but by the manner of mixing. Of course, if only one product can be produced under any conditions, there is no problem of product selectivity. However, if there is a possibility that two or more products are produced by competing reactions, we have to consider the product selectivity. There are, in principle, two cases for competing reactions, i.e. competitive parallel



Scheme 6.1 Competitive parallel reactions and competitive consecutive reactions

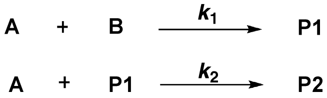
reactions and competitive consecutive reactions, although there are many variations (Scheme 6.1).

In competitive parallel reactions, the reaction of compound **A** to give product **P1** competes with the reaction of **A** to give product **P2**. Both reactions take place simultaneously. If the rate constant k_1 for the first reaction is much larger than k_2 for the second reaction, we expect the predominant formation of **P1** over **P2**.

In competitive consecutive reactions, a first product **P1** that is formed in the first reaction of **A** undergoes a further reaction to give a second product **P2**. If the rate constant k_1 for the first reaction is much larger than k_2 for the subsequent reaction, it is possible, in principle, to stop the reaction to obtain **P1** predominantly. If k_2 is larger than k_1, it seems difficult to stop the reaction at the **P1** stage.

Let us focus on the competitive consecutive reaction shown in Scheme 6.2. In the first step, compound **A** reacts with compound **B** to give a first product, **P1**. In the second step, **P1** reacts with another molecule of **A** to give a second product, **P2**.

This type of reaction scheme is fairly common in organic synthesis. If the second reaction is faster than the first reaction ($k_1 < k_2$), it is difficult to stop the reaction at the first stage. **P2** is formed as a major product. If the first reaction is faster than the second reaction ($k_1 > k_2$), there is a chance to obtain **P1** selectively. When one equivalent of **A** relative to **B** is used, **P1** should be obtained selectively. In other words, when the stoichiometric ratio of two reaction components is approximately unity (**A/B** = 1), the selectivity for the primary product **P1** should be high. Experiments,



Scheme 6.2 Competitive consecutive reactions of **A** and **B**

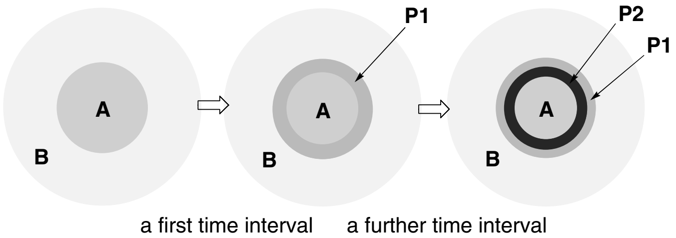


Figure 6.3 Schematic representation of mixing determined reaction course for competitive consecutive reactions

however, often contradict this kinetically based prediction.[6] When the reaction is faster than mixing, simple kinetics arguments based on the homogeneity of the solution do not work. A significant amount of **P2** is formed even if $k_1 > k_2$. When the reaction is faster than mixing, the product selectivity of such competitive consecutive reactions is not determined by kinetics, but by the manner of mixing. Rys called such selectivity 'disguised chemical selectivity'. If the reaction is slower than the mixing, the reaction proceeds in a homogeneous solution. In this case, we can define the concentrations of **A** and **B**, and arguments based on kinetics work with such concentrations. However, if the reaction is faster than mixing, the reaction proceeds before homogeneity of the solution has been established. In such fast reactions, it is meaningless to define concentrations of **A** and **B** based on the total volume of the solution, because the solution is not homogeneous. Therefore, arguments based on kinetics do not work. Instead, the outcome of the reaction is strongly affected by the manner of mixing (Figure 6.3).

Why is such disguised selectivity observed for extremely fast reactions? Rys explained it as follows:

> After a first time interval, **A** and **B** will have reacted at the periphery of an eddy to produce the primary product **P1**. In a further time interval, a molecule **A** can react with a further molecule **B** to form **P1**, but only if it succeeds in diffusing through the peripheral zone of **P1** molecules already formed without being trapped there by the substance **P1** in a reaction affording the secondary product **P2**. This succeeds less often, the longer the relaxation time of the diffusion process is in comparison to the relaxation time of the secondary reaction. In the extreme case, a mixing controlled reaction will convert all the **P1** into **P2** before the molecule **A** finds a further molecule **B**. Thus, at the end of the reaction practically only the secondary product **P2** is present, and no primary product **P1** can be detected. In this case, the selectivity k_1/k_2 loses its influence on the product distribution.

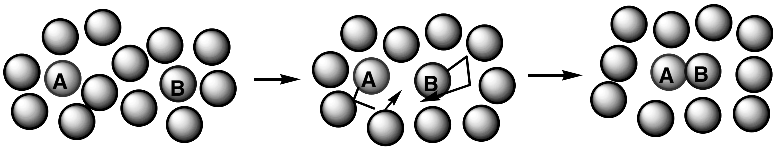


Figure 6.4 Reaction of molecules **A** and **B** in a solvent cage

The importance of mixing and molecular diffusion for extremely fast chemical reactions can be stated in a different way from a molecular-level viewpoint (Figure 6.4). As Levine wrote in his textbook of reaction dynamics:[7]

> If the chemical reaction is fast, the observed rate is determined not by the crossing of the chemical barrier by the caged reactants but by the rate of the reactants diffusing towards one another and getting into the cage.

The problem of disguised chemical selectivity often occurs in macrobatch reactors, such as flasks, because mixing of the solution with a mechanical or magnetic stirrer is not fast enough. In addition, it is worth noting that the mixing problem is even more serious for industrial reactors of larger scale. Therefore, the selectivity problem due to mixing is one of the key issues in flash chemistry, although synthetic organic chemists have not paid much attention to its importance so far. How can the problem of disguised chemical selectivity be solved?

6.1.4 Lowering the Reaction Temperature

The most straightforward way to solve the problem of disguised chemical selectivity is to decrease the rate of the reaction to make it slower than the mixing rate. In order to decrease the reaction rate, several techniques have conventionally been used. Probably the simplest and most straightforward method is to lower the reaction temperature. In fact, decreasing the reaction temperature usually leads to an increase in product selectivity. For example, the enantiomeric excess (ee) of an asymmetric reaction usually increases with a decrease in reaction temperature. In general, the rate of a chemical reaction decreases with a decrease in temperature. Therefore, the mixing rate is expected to become faster than the reaction rate. However, it should also be noted that the rate of mixing, or the rate of molecular diffusion, also decreases with a decrease in the temperature. Molecular diffusion is also based on thermal motions of the molecules, and the viscosity of the solution increases with a decrease in temperature.

6.1.5 The High Dilution Method

In a bimolecular reaction, for example, the reaction between **A** and **B**, the reaction rate depends on the concentrations of **A** and **B**. Therefore, at very low concentrations or in high dilution conditions, the reaction rate decreases significantly and mixing becomes relatively faster than reaction.

Figure 6.5 shows the high-dilution trident for the Rh-catalyzed intramolecular reaction of a diazo ketone.[8] The round-bottomed flask is charged with dry freshly distilled dichloromethane and rhodium diacetate dimer. This heterogeneous mixture is stirred at high speed and heated to a rapid reflux without bumping. The addition funnel is charged with a solution of 1-diazo-4-phenyl-2-butanone diluted with dichloromethane. As soon as the high-dilution trident reservoir fills up and begins to overflow back into the round-bottomed flask, dropwise addition of the diazo ketone solution is initiated (1 : 20, one drop of diazo ketone solution to every 20 drops of solvent entering the trident reservoir from the condenser). The high-dilution trident in this example dilutes the diazo ketone solution to 10^{-3}–10^{-4} M before it reaches the reaction mixture.

In this case, the desired reaction is an intramolecular reaction, and the undesired intermolecular reaction might be avoided under these high-dilution conditions. The high-dilution technique might also be effective for improving the selectivity of competitive consecutive reactions, although the overall reaction time should be greatly reduced in comparison with that required under normal conditions.

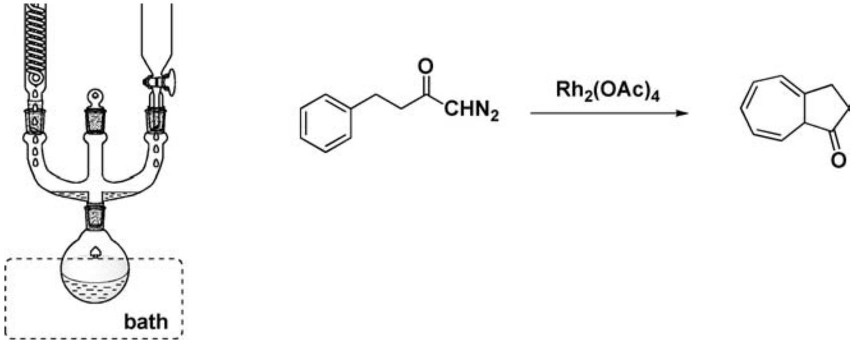


Figure 6.5 High-dilution trident for Rh-catalyzed reaction of a diazo ketone[8]

6.1.6 Micromixing

There is another way to solve the problem of disguised chemical selectivity of extremely fast competitive reactions, which does not need to slow the reactions, i.e. micromixing, based on microstructures that makes the diffusion path very short.

With the advancement of microfabrication technology to make various kinds of microstructures, microdevices for chemical reactions have been developed. Micro-fabricated devices for chemical reactions are generally called microreactors and they are expected to produce a revolutionary change in chemical synthesis.

Although there are many types of micro-fabricated devices or microreactors, micromixers are fairly popular. Extremely fast mixing can be achieved by virtue of a very short diffusion path using small segments of solutions to be mixed. Such small segments are usually made by the stream distribution using microstructures. The size of the segments can be made smaller than 100–10 μm, the minimum size of eddies produced by stirring. Many micromixers have a stream contraction part immediately after the mixing part. In such a case, the segment size can be as small as the order of micrometers. Therefore, extremely fast mixing can be achieved because of the very short diffusion path. Even if the reaction is extremely fast, the use of a micromixer might lead to a chance to give a kinetically based selectivity, which is difficult to achieve using a conventional macrobatch reactor.

The principle and structures of micromixers will be discussed in Chapter 7. In the following sections, we focus on an example of the effectiveness of micromixing for conducting extremely fast reactions with a high level of control of product selectivity, with the emphasis on its principle.

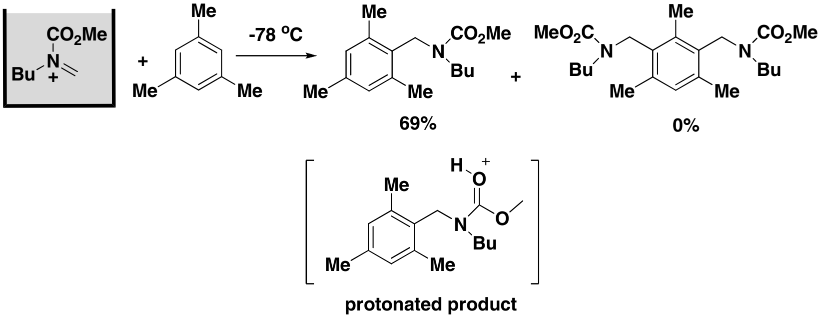
6.1.7 Friedel-Crafts Alkylation Using an *N*-Acyliminium Ion Pool

In a previous section (Section 6.1.3), we discussed the problem of disguised chemical selectivity for extremely fast competitive consecutive reactions. This problem could be solved using micromixers, in which the mixing takes place in a very short period by virtue of a small diffusion path caused by the microstructure. Friedel-Crafts alkylation using *N*-acyliminium ion pools provides a nice example of the effectiveness of micromixing.[9]

6.1.7.1 Reaction of an N-acyliminium ion pool with 1,3,5-trimethylbenzene using a macrobatch reactor

The Friedel-Crafts reaction[10,11] of an *N*-acyliminium ion pool with 1,3,5-trimethylbenzene in a conventional macrobatch reactor with magnetic stirring gives the monoalkylation product in 69% yield as shown in Scheme 6.3. The dialkylation product is not produced in an appreciable amount. It is well known that the monoalkylation product is usually more reactive than the parent compound because an alkyl group is electron donating. Therefore, it is generally difficult to stop the reaction at the monoalkylation stage. The experimental result, however, is contrary to this expectation. The observed selective monoalkylation can be explained in terms of protonation of the monoalkylation product. The monoalkylation reaction generates a proton, which protonates the monoalkylation product, and the protonated carbamate moiety should be strongly electron withdrawing. Therefore, the protonated form of the monoalkylation product is less reactive than the starting material, 1,3,5-trimethylbenzene. Thus, the second alkylation is slower than the first alkylation, which results in the selective formation of the monoalkylation product. This is consistent with the prediction based on the kinetics. Therefore, kinetics arguments work in this reaction.

Protonation of the product is confirmed by ^{13}C NMR studies. The neutral form of the monoalkylation product exhibits signals due to the carbonyl carbon at 155.0 and 155.4 ppm (two rotamers), whereas the addition of $HBF_4{\cdot}OMe_2$ causes a downfield shift of the signals (157.5 and 157.7 ppm). This is consistent with protonation at the carbonyl oxygen, which made the carbonyl carbon more electron deficient. The ^{13}C NMR spectrum of the product solution obtained by the reaction also



Scheme 6.3 Friedel-Crafts reaction of 1,3,5-trimethylbenzene with *N*-acyliminium ion

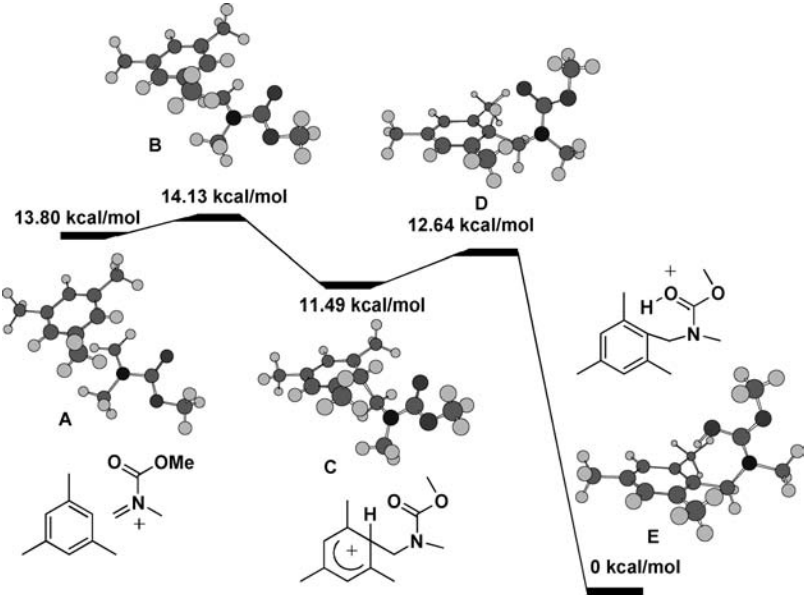


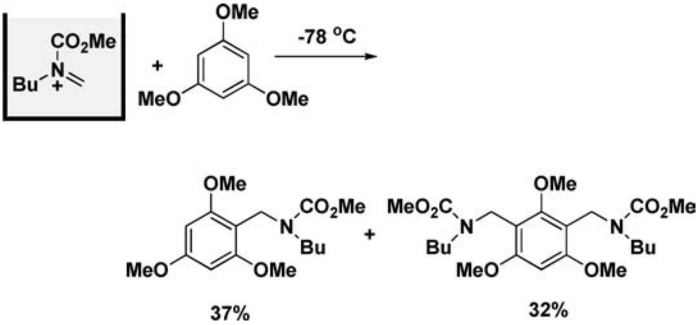
Figure 6.6 Energy diagram for the reaction of *N*-methoxycarbonyl-*N*-methyliminium ion with 1,3,5-trimethylbenzene. Copyright 2005 American Chemical Society

exhibits signals at 157.6 and 157.8 ppm, suggesting the formation of the proto-nated form of the monoalkylation product.

The protonation is also supported by DFT calculations [B3LYP/6-31G(d)]. The energy diagram obtained by the calculations for a model system (*N*-methoxycarbonyl-*N*-methyliminium ion with 1,3,5-trimethylbenzene) in the gas phase is shown in Figure 6.6. The calculations indicate that complex **A**, which is formed prior to the reaction, is converted into the Wheland complex **C** through transition state **B**. In the next step, complex **C** is converted to **E** through transition state **D**, where the proton on the benzene ring is transferred to the carbonyl oxygen atom. Therefore, the protonated form **E** is produced as the final product. It is also noteworthy that the present reaction is exothermic (ca. 14 kcal/mol), and the activation energy is very small (ca. 0.3 kcal/mol) indicating that the reaction is very fast.

6.1.7.2 *Reaction of an N-acyliminium ion pool with 1,3,5-trimethoxybenzene using a macrobatch reactor*

In the case of the reaction with 1,3,5-trimethylbenzene, the product selectivity is consistent with the prediction based on the kinetics. The



Scheme 6.4 Friedel-Crafts reaction of 1,3,5-trimethoxybenzene with *N*-acyliminium ion in a macrobatch reactor

first alkylation is faster than the second alkylation and the monoalkylation product is obtained selectively. Therefore, there is no problem of the disguised chemical selectivity. Let us move on to a faster reaction, the reaction with 1,3,5-trimethoxybenzene.

Because alkoxyl groups are more electron donating than alkyl groups, 1,3,5-trimethoxybenzene is considered to be more reactive than 1,3,5-trimethylbenzene. Therefore, the reaction of 1,3,5-trimethoxybenzene is expected to be much faster than that of 1,3,5-trimethylbenzene, and there might be a chance to observe disguised chemical selectivity. Indeed, the reaction of the *N*-acyliminium ion pool with 1,3,5-trimethoxybenzene in a macrobatch reactor resulted in the formation of a mixture of the monoalkylation product and the dialkylation product (1 : 1), as shown in Scheme 6.4. The reverse addition gave essentially the same result. The simultaneous addition of two solutions to a batch reactor also gave a similar result. These observations contrast sharply with the case of 1,3,5-trimethylbenzene. Because the monoalkylation product seems to be protonated to deactivate the aromatic ring toward electrophilic substitution, the first product should be less reactive than the starting aromatic compound. Therefore, the second alkylation is expected to be slower than the first alkylation. Based on these arguments, the observed product selectivity cannot be explained in terms of the kinetics based on the relative reaction rates. Thus, it seems reasonable to consider that the observed selectivity is disguised chemical selectivity, which is ascribed to reaction being faster than mixing.

6.1.7.3 Reaction of an N-acyliminium ion pool with 1,3,5-trimethoxybenzene using a micromixer

The use of a microflow system consisting of a multilamination-type micromixer (see Chapter 7) and a microtube reactor solves the problem

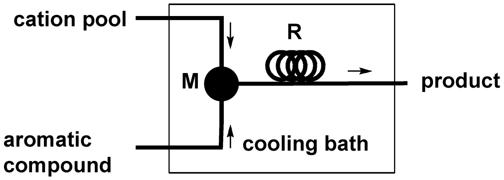


Figure 6.7 Microflow system for Friedel-Crafts alkylation of aromatic compounds with an *N*-acyliminium ion (**M**, micromixer; **R**, microtube reactor)

dramatically. Solutions of *N*-acyliminium ion and 1,3,5-trimethoxybenzene are introduced to a micromixer by a syringe pumping technique at −78 °C, and the product solution is immediately quenched with triethylamine to avoid further reactions as shown in Figure 6.7. The results are given in Table 6.2.

Table 6.2 Friedel-Crafts reaction of 1,3,5-trimethoxybenzene with an *N*-acyliminium ion using a microflow system

Micromixer (reactor)	Monoalkylation product (%)	Dialkylation product (%)	Monoalkylation product : dialkylation product
T-shaped mixer ($\phi = 500\,\mu m$)	36	31	54 : 46
YM-1 micromixer	50	14	78 : 22
IMM micromixer (channel width = $25\,\mu m$)	92	4	96 : 4

When a T-shaped mixer is used, the product selectivity is essentially the same as for the macrobatch reactor (Scheme 6.4). The use of the YM-1 mixer, a splitting-and-recombination-type micromixer (see Chapter 7), increases the selectivity, however, a significant amount of dialkylation product is still produced. The use of the IMM multilamination-type micromixer results in excellent selectivity of the monoalkylation product. The amount of dialkylation product is very small. Therefore, the product selectivity strongly depends on the manner of mixing.

6.1.7.4 Estimation of relative rates of the first alkylation and the second alkylation

In the previous sections, we assumed that the second alkylation is slower than the first alkylation because the alkoxycarbonylamino moiety in the

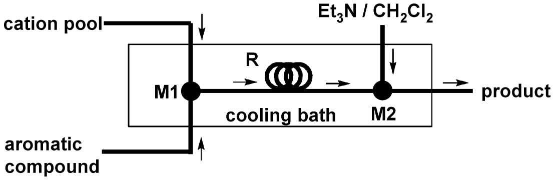


Figure 6.8 Microflow system for estimation of relative rates for the reaction of aromatic compounds with the *N*-acyliminium ion pool (M1, M2, micromixers; R, microtube reactor)

monoalkylation product should be protonated, leading to deactivation of the aromatic ring.

This assumption can be confirmed at least qualitatively by the following experiments using the microflow system shown in Figure 6.8. A solution of an aromatic compound and that of the *N*-acyliminium ion pool were mixed with a micromixer, and the resulting mixture was introduced to a microtube reactor where the reaction took place. After some residence time, which was adjusted by the length of the reactor and the flow rate, triethylamine was introduced through the second micromixer to quench the reaction. The reaction of 1,3,5-trimethoxybenzene was almost complete within the residence time of 0.03 s. Monoalkylation product was obtained in 78% yield. The reaction of the monoalkylation product, which was prepared in a separate experiment, with the *N*-acyliminium ion was found to be much slower. A significant amount of the monoalkylation product remained unchanged with a residence time of 0.03 s. With a longer residence time (0.30 s), however, a significant amount of the monoalkylation product was consumed to give the dialkylation product. These experiments showed that the second alkylation is much slower than the first alkylation but that both reactions are very fast. Therefore, the selectivity observed with the macrobatch reactor is not ascribed to the normal kinetics. It is disguised chemical selectivity due to reaction being faster than mixing. In contrast, the selectivity observed with the microflow system seems very close to the kinetically predicted selectivity.

6.1.7.5 Fluid dynamics simulation

It is important to know how mixing can influence the selectivity of chemical reactions, and computational fluid dynamics (CFD) simulations are quite helpful in providing a deeper insight into this issue.[12] The calculations are based on a laminar flow model where mixing takes place only by molecular diffusion (Figure 6.9). Let us focus on the competitive

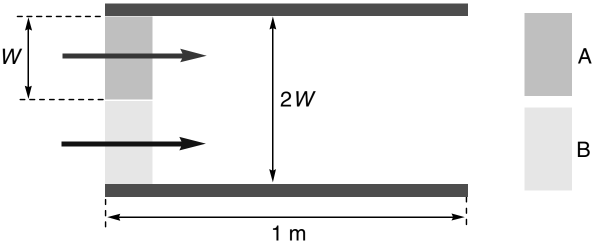


Figure 6.9 Models of micromixer for CFD simulation. *W*, width

consecutive reaction shown in Scheme 6.2 under isothermal conditions, whereby **A** reacts with **B** to give **P1**, and **P1** reacts with **A** to give **P2**. In the laminar flow model, solutions of **A** and **B** are fed to a microstructure at the flow rate of 0.1 m/s, and the length of the reactor is 1 m. To carry out the CFD simulations, we need to make assumptions about several physical properties of the reactant fluids, and the assumptions are as follows: the physical properties of the two reactant fluids are the same, that is, the density is 1.317×10^3 kg/m^3, the molecular diffusion coefficient is 10^{-9} m^2/s, and the viscosity is 0.00119 Pa s; the initial concentrations of the two reactants are 0.01 mol/L. The first reaction has a rate constant this is 100 times higher than that of the second reaction ($k_1/k_2 = 100$). Usually, organic chemists carry out reactions without knowing these physical properties of reactants and solvents, because it is rather difficult to obtain the information on such properties, especially those for reactive intermediates. However, it is hoped that such data will be accumulated and that organic chemists can use them for simulation before the first trial of a reaction in the future.

As shown in Table 6.3, when $k_1 = 10^4$ L/(mol s), for ideal mixing, where **A** and **B** are mixed completely immediately after being introduced to the microstructure, the selectivity **P1**/**P2** = 97/3. This is the selectivity based on the kinetics. The use of a micromixer of 100 μm lamination width leads to **P1**/**P2** = 75/25. A decrease in the lamination width causes an increase in the selectivity, which becomes very close to the selectivity for ideal mixing.

It is interesting to note that an increase in the absolute values of k_1 and k_2 causes dramatic changes in the product selectivity. When $k_1 = 10^6$ L/(mol s), the selectivity is reversed for a lamination width of 100 μm, even if k_1 is 100 times larger than k_2. Presumably, the reaction time and mixing time are similar or the reaction is faster than mixing, and therefore, the selectivity is disguised. The decrease of lamination width gives rise to a remarkable increase in the selectivity favoring the formation of **P1**. When the lamination width is 2.5 μm, high selectivity (**P1**/**P2** = 95/5), which is close to the

Table 6.3 Product yields and distribution obtained by CFD simulation

Reaction rate constants	Mixer	Lamination width (μm)	P1 (% yield)	P2 (% yield)	P1 : P2
$k_1 = 10^4$ L/(mol s)	Ideal mixing	–	94.6	2.7	97 : 3
$k_2 = 10^2$ L/(mol s)	(a)	100	60.6	19.7	75 : 25
	(b)	25	89.6	4.5	95 : 5
	(c)	2.5	94.7	2.6	97 : 3
$k_1 = 10^6$ L/(mol s)	Ideal mixing	–	94.6	2.7	97 : 3
$k_2 = 10^4$ L/(mol s)	(a)	100	14.5	42.7	25 : 75
	(b)	25	36.1	31.9	53 : 47
	(c)	2.5	90.5	4.7	95 : 5

kinetically based selectivity (selectivity for ideal mixing), is obtained. The simulation clearly indicates the dramatic effect of the lamination width. This means that the diffusion width and diffusion time strongly affect the product selectivity of the reaction.

6.1.8 Micromixing as a Powerful Tool for Flash Chemistry

The discussions in the previous sections illustrate that the phenomenon of disguised chemical selectivity can be observed for extremely fast competitive consecutive reactions, such as Friedel-Crafts reactions of highly reactive aromatic compounds with *N*-acyliminium ion pools. The study also speaks well for the potential of micromixing to effect extremely fast chemical transformations that are difficult to perform in a controlled manner using macrobatch reactors. Micromixing can provide a solution to the problem of disguised chemical selectivity that complicates the reactions using conventional macrobatch methods. It is also noteworthy that the problem of competitive consecutive reactions is closely related to molecular weight and molecular weight distribution control in polymer synthesis. Therefore, micromixing also serves as a powerful method for the control of polymerization (see Chapter 9).

6.1.9 Disguised Chemical Selectivity in Competitive Parallel Reactions

It is important to know what kind of reactions may suffer from the problem of disguised chemical selectivity when mixing is slower than

$$\mathrm{A} + \mathrm{B} \xrightarrow{k_1} \mathrm{P1}$$

$$\mathrm{A} + \mathrm{C} \xrightarrow{k_2} \mathrm{P2}$$

Scheme 6.5 Bimolecular competitive parallel reactions

reaction. In general, there are two types of competitive reactions, i.e. competitive parallel reactions and competitive consecutive reactions. In the previous sections, we have discussed competitive consecutive reactions, which may suffer from the problem. So, let us now discuss competitive parallel reactions. Although there are many patterns for competitive parallel reactions, one of the general schemes is shown in Scheme 6.5.

A good example of competitive parallel reactions, available in the literature, is called the Dushman reaction (Scheme 6.6) (see also Chapter 7).[13–14] The reaction consists of two processes involving protons, i.e., an ultrafast reaction (neutralization of the acid) and a fast reaction (I_2 formation by an acid-catalyzed redox reaction between iodide ion and iodate ion). Thus, mixing of a strong acid (HCl) and a solution of I^-, IO_3^-, and CH_3CO_2Na (sodium acetate) leads to a combination of two processes. If the mixing is very fast, the ultrafast process masks the slower second process. Therefore, no absorption of radiation due to iodine is detected. If the mixing is not fast, however, imperfect mixing leads to local high concentrations of acid, which promotes the second reaction to form I_2. The amount of I_2 formed is determined by UV analysis at 352 nm. Observation of the color indicates that mixing is not so efficient. In fact, this reaction has been utilized for the evaluation of the efficiency of mixing.

Disguised chemical selectivity of competitive parallel reactions caused by slower mixing has been discussed by Rys based on the eddy model as follows:[1]

> If the reaction of **A** with **B** is faster than that with **C**, then in the first time interval more of the product **P1** will be formed in the boundary zone of the eddy. At a later point in time an **A** molecule must, in order to react with another **B** molecule, penetrate a zone that has become enriched in the compound **C** which is less reactive than **B**. For this reason the reactivity of **C** appears at this time to be greater than predicted from the selectivity k_1/k_2. In the extreme case of a mixing-controlled reaction the measured product distribution becomes 1 : 1. In this case the selectivity k_1/k_2 loses its influence.

$$\mathrm{H^+} + \mathrm{CH_3CO_2^-} \longrightarrow \mathrm{CH_3COO_2H} \quad \textbf{(ultrafast)}$$

$$6\,\mathrm{H^+} + \mathrm{IO_3^-} + 5\,\mathrm{I^-} \longrightarrow 3\,\mathrm{I_2} + 3\,\mathrm{H_2O} \quad \textbf{(fast)}$$

Scheme 6.6 Dushman reaction used for evaluation of mixing rate

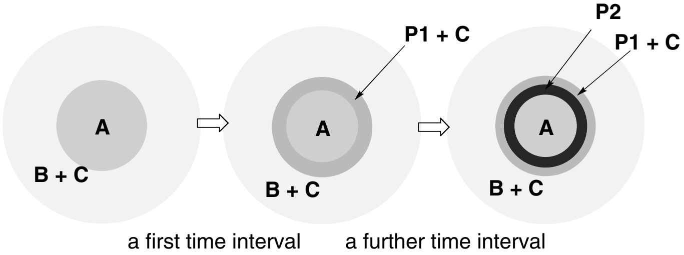


Figure 6.10 Schematic representation of mixing-determined reaction course for competitive parallel reactions (the configurations of the reaction components were changed by the author)

The Dushman reaction is useful for evaluation of mixing rate and efficiency. From the viewpoint of synthesis, as can be easily recognized from Figure 6.10, we do not have to worry about bimolecular competitive parallel reactions, as far as intermolecular competition is concerned. If **C** is not added to the reaction system, **P1** is produced selectively. There is no chance of the reaction of **A** with **C** to produce **P2** in the absence of **C**. However, if two competing reactions take place in different parts of a single substrate molecule under the same conditions (**B** and **C**), this is the issue of regioselectivity or chemoselectivity. There is another type of competitive parallel reactions. In this case, a reagent attacks the substrate from two different faces of the same functional group. This is the issue of stereoselectivity. In these cases, however, it seems difficult to solve the problem by fast mixing. Such selectivity may be disguised by inefficient temperature control. Local variation of temperature may lead to lower selectivity than is expected from the kinetics at the bulk temperature. In such a case, precise temperature control using microflow systems (see below) should be a powerful way to solve the problem.

6.2 TEMPERATURE CONTROL

Up to this point, we have discussed the importance of fast mixing in conducting extremely fast reactions in a highly controlled manner. Another important issue should be considered when extremely fast reactions are conducted on a preparative scale.

6.2.1 Exothermicity of Fast Reactions

Fast reactions are often highly exothermic. The energy diagram shown in Figure 6.11 seems useful for discussion, although it might be over-simplified.

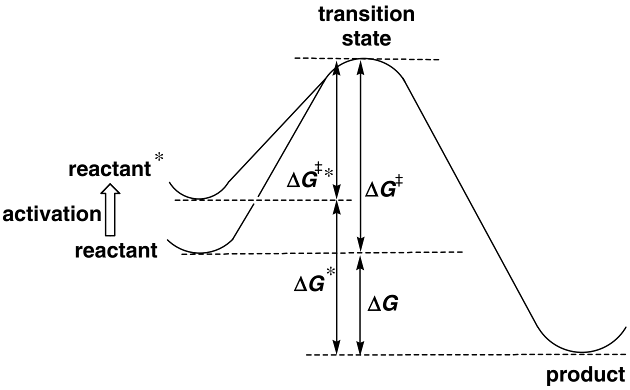


Figure 6.11 Energy profile of a reaction associated with activation of a reactant

Activation of a reactant molecule (to a reactant*) leads to a decrease in the activation energy of the reaction (from $\Delta G^{\ddagger}$ to $\Delta G^{\ddagger *}$), which leads to a higher reaction rate. However, activation of a reactant molecule leads to an increase in the reaction free energy (from ΔG to ΔG^{*}), which often makes the reaction more exothermic. An exothermic reaction may lead to a temperature increase in the reaction environment if heat transfer is not efficient. Such a case might be problematic. The product may undergo further reactions or decomposition, which leads to the formation of undesired by-products. Therefore, the selectivity of a reaction, in general, decreases with an increase in the temperature.

The Bell–Evans–Polanyi principle rationalizes the increase in rates of many reactions with increase in exothermicity (the release of heat by a system as a reaction occurs) by describing the transition states as a blend of reactant and product configurations.[15] As shown in Figure 6.12, the

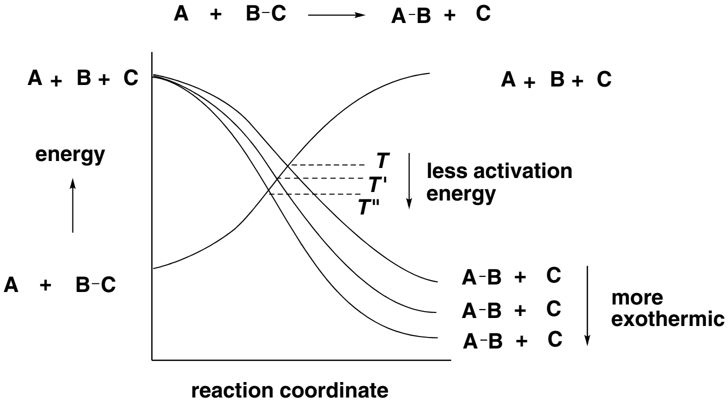


Figure 6.12 Relationship between activation energy and exothermicity

more exothermic the reaction is, the less activation energy the reaction requires. A decrease in activation energy leads to an increase in the reaction rates.

6.2.2 Hammond's Postulate

We usually tend to consider that faster reactions are more exothermic based on the reaction diagram shown in Figure 6.12. However, in many instances, highly exothermic reactions are exceedingly slow. For example, the reactions of many organic compounds with dioxygen (O_2) are usually highly exothermic, but usually the reactions take place only slowly at room temperature because the energy barriers are very high (as discussed in Chapter 2). Therefore, there is no general relationship between the free energies of the reactions and their rates.

As for the general correlation between reaction rates and thermodynamics, Hammond's postulate[16] is very popular among organic chemists. He wrote in his original paper:

> While there is no completely general correlation between the rates and free energies of chemical reactions, there are many instances in which the most stable products are formed at the most rapid rates from a series of similarly constituted reactants. In certain other reactions, the less stable products seem to be formed at the more rapid rates with considerable regularity.

Hammond's postulate is as follows:

> If two states, as for example, a transition state and an unstable intermediate, occur consecutively during a reaction process and have nearly the same energy content, their interconversion will involve only a small organization of the molecular structures.

From Hammond's postulate, it may be reasonable to consider that in endothermic reactions the energy levels of transition states are close to those of the products, which may be highly reactive species. Therefore, an energetically less demanding reaction ($\Delta G_2 < \Delta G_1$) leading to **P2** should have a lower activation energy ($\Delta G_2^{\ddagger} < \Delta G_2^{\ddagger}$) than an energetically more demanding reaction leading to **P1**, and the former reaction should occur at a more rapid rate (Figure 6.13).

However, in exothermic reactions, the energy levels of transition states are close to those of the reactants. Therefore, product stability has nothing

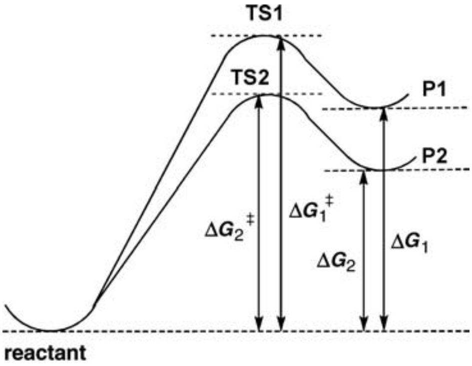


Figure 6.13 Energy profile of endothermic reactions

to do with the energy levels of the transition state and reaction rates. This is especially true for extremely fast reactions. Thus, the energy diagram of the reaction may be either case (a) or case (b) in Figure 6.14. Therefore, there is no completely general correlation between the rates and free energies of chemical reactions.

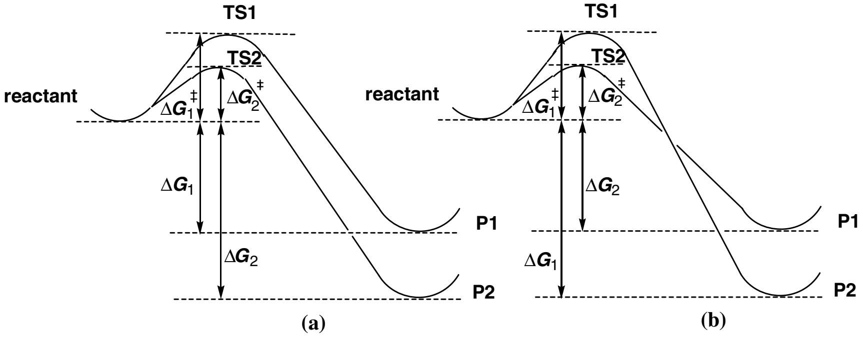


Figure 6.14 Energy profiles of exothermic reactions

6.2.3 The Friedel-Crafts Reaction

Hammond discussed electrophilic aromatic substitution in his paper. A typical energy profile of the reaction is presented in Figure 6.15, where **A** is a reactant, **B** is a π-complex, **D** is a σ-complex, and **C** and **E** are transition states, through which **D** is formed and destroyed, respectively. The transition state of the rate-determining step (**C** or **E**) is closely related to **D**.

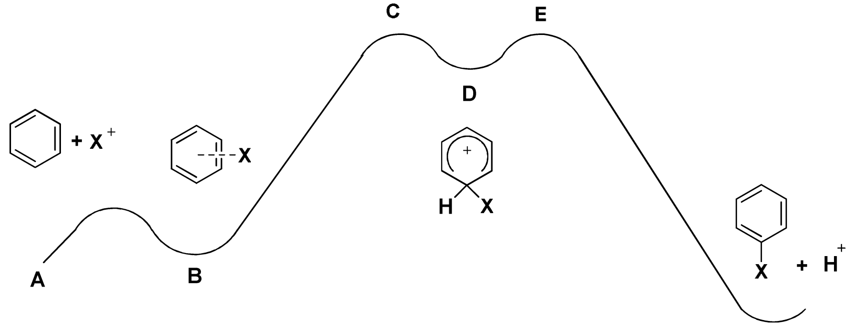


Figure 6.15 Energy profile of an electrophilic aromatic substitution

In Section 6.1.7, we discussed the Friedel-Crafts reaction of aromatic compounds with an *N*-acyliminium ion. We can draw similar energy profiles for the reaction of benzene and 1,3,5-trimethylbenzene based on DFT calculations, although the energy levels of reactants are high because an *N*-acyliminium ion is a highly reactive species. It can be seen from these energy profiles that the energy barrier for the reaction of 1,3,5-trimethylbenzene is much lower than that of benzene. It is consistent with the well-accepted reactivity of aromatic compounds. The methyl group is an electron donating, and therefore, an activating group for electrophilic substitution. Therefore, 1,3,5-trimethylbenzene is more reactive than benzene. According to Hammond's postulate, we do not need to calculate the transition states, because the σ-complex should be closely related to the transition states. In fact, in the case of benzene, the σ-complex is 3.3 kcal/mol less stable than the π-complex. This means the energy barrier should be larger than 3.3 kcal/mol. In the case of 1,3,5-trimethylbenzene, however, the σ-complex is more stable than the π-complex. This means that **TS1** is more closely related to the π-complex and the barrier should be very low. In fact, according to the calculation **TS1** is only 0.33 kcal/mol less stable than the π-complex. Similarly, **TS2** is more closely related to the σ-complex. According to the calculation **TS2** is 2.2 kcal/mol less stable than the σ-complex (Figure 6.16).

Therefore, the reaction of 1,3,5-trimethylbenzene is faster than the reaction of benzene. However, it is important to note that the reaction of benzene is more exothermic than the reaction of 1,3,5-trimethylbenzene. Therefore, there is no general correlation between the activation energies and free energies of chemical reactions. This means that there is no correlation between the rates and exothermicity. However, it is also broadly true that fast reactions are often highly exothermic, although there are many exceptions.

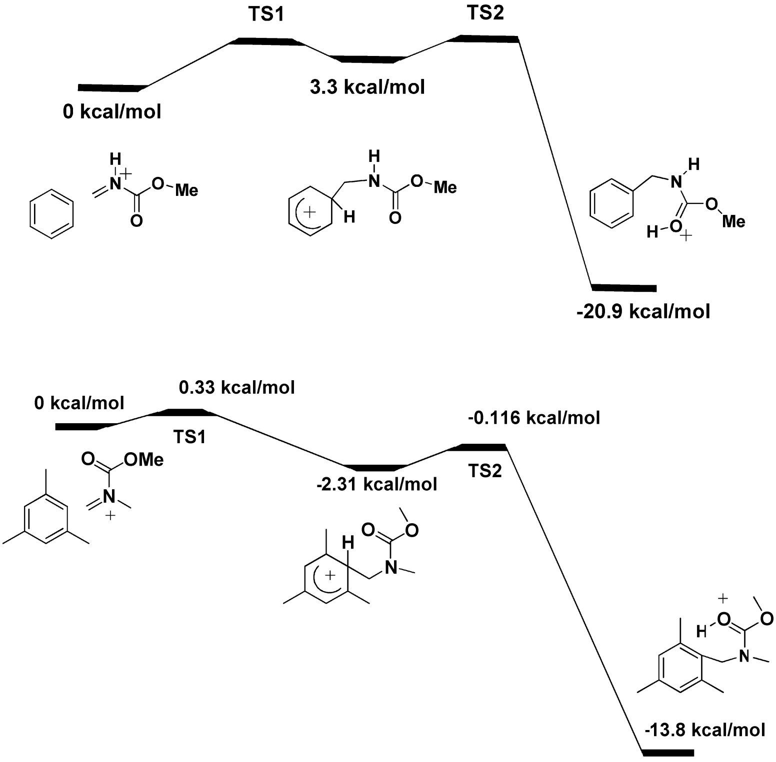


Figure 6.16 Energy level diagram for Friedel-Crafts reactions of aromatic compounds with an *N*-acyliminium ion

6.2.4 Solvent

Although there is no general correlation between the rates and free energies of chemical reactions, reactions used in flash chemistry are often highly exothermic. One of the most popular ways to control reaction heat is to use a large amount of solvent. Solvent molecules take thermal energy from the product molecules. Therefore, solvent molecules can play the role of a sink of thermal energy, and the use of a large amount of solvent is quite effective for temperature control. Another effect of solvent is dilution, i.e. the decrease in the concentration of substrate molecules. As described in the previous section, a decrease in the concentration causes a decrease in the reaction rate of bimolecular reactions. Therefore, heat generated by the reaction per unit time decreases with the decrease in the concentrations of reactants.

Although the use of a relatively large amount of solvent is effective for a small scale laboratory experiment, it should be noted that the final removal of heat is, in principle, ascribed to heat transfer through the wall of the reactor. Therefore, heat transfer is especially important for a large-scale production in industry.

6.2.5 Heat Transfer

The most straightforward method for effective temperature control is heat transfer. Efficient heat transfer to remove heat from the reaction system is the key to conducting highly exothermic reactions, although synthetic chemists have not paid significant attention to this issue.

The rate of heat transfer is important for successfully conducting reactions. If heat transfer is slow, the energy liberated by a reaction is accumulated in the system and the temperature in the reactor increases, causing undesired side reactions. Efficient heat transfer is essential for the conduction of highly exothermic reactions in a controlled way in flash chemistry.

Heat transfer is the passage of thermal energy from a hot body to a cold body. It occurs through conduction, convection, and radiation, or a combination of these.

Conduction is the thermal energy transfer through direct molecular contact. Conduction occurs between molecules, both solute and solvent molecules in solution. Conduction in solution is analogous to molecular diffusion in solution. The amount of heat transferred by conduction is expressed by:

$$\frac{Q}{t} = -kS\frac{T1-T2}{d} \tag{6.2}$$

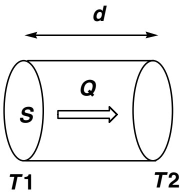


Figure 6.17 Heat transfer by conduction

where Q is the amount of heat transferred, t is the time taken, k is the conductivity of the material (the variation of conductivity with temperature is usually small over a small range of temperatures), S is the surface area through which the heat is transferred, d is the distance between the two ends of the system, $T1$ is the temperature at the higher temperature end and $T2$ is the temperature at the lower temperature end. Equation (6.2) shows that the surface area (S) and the distance between the two ends (d) are very important for efficient heat transfer.

Conduction also takes place in solids through vibration of adjacent atoms or molecules or electron diffusion from atom to atom. It also occurs between solutions and solids.

Convection is heat transfer associated with heat-induced fluid motion, which may be either free (or natural) convection or forced convection.

Radiation is thermal energy transported from surfaces of higher temperature to surfaces of lower temperature by electromagnetic radiation. No medium is necessary, and the heat transfer can take place through a vacuum.

In flash chemistry in the solution phase, conduction and convection play major roles in heat transfer. Heat transfer occurs through the solution by conduction and convection. For conduction, a short distance in microspace is advantageous. A more important issue to consider is the heat transfer through the reactor wall, because heat generated by the reaction should eventually be removed from the reaction system. Heat transfer through the reactor wall plays a major role for this purpose. The high surface-to-volume ratio of microspaces is advantageous from this point of view.

In general, volume is equal to length cubed while surface area is equal to length squared. When the length is decreased, the surface-to-volume ratio increases (Figure 6.18). Thus, a feature of microspaces is that they have

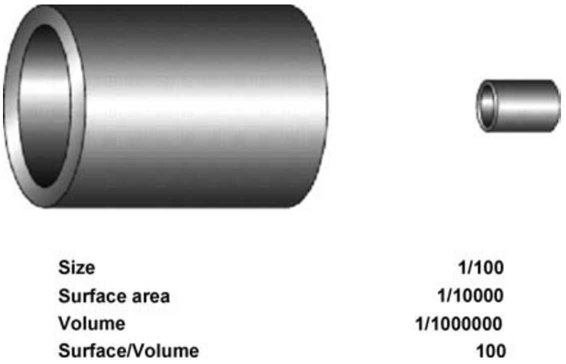


Figure 6.18 Results of downsizing

large surface-to-volume ratios compared with macrospaces. Heat is transferred between the interior and exterior of a reactor via the reactor surface; therefore, in a microreaction system or a microreactor–with its greater surface area per unit volume–heat transfer occurs rapidly by conduction, making precise temperature control possible.

6.2.6 Precise Temperature Control in Microflow Systems

It is reasonable to consider that heat transfer through the reactor wall is very fast in microsystems in comparison with macrosystems because of the high surface-to-volume ratio of microspaces as described above. However, it is rather difficult to evaluate the interior temperature of microsystems. Physical methods for temperature measurement seem to be problematic. The introduction of a thermometer inside a microsystem might change the nature of the flow, because the volume of a thermometer is not negligible in comparison with the volume of the microreaction space. It is also important to note that the heat capacity of the thermometer and heat transfer through the thermometer cannot be ignored because the volume of the solution in the microreaction space is very small.

Chemical methods can also be applied for the measurement of the interior temperature of microsystems. A fluorescent molecular thermometer using temperature-induced phase transitions seems to be quite attractive,[17] but it needs a transparent window on the wall of the microchannel for the optical measurement. However, this may change the heat transfer ability of the wall.

There is another chemical method for evaluating the temperature control ability of a reactor; the method uses thermal decomposition of radical initiators.[18] Let us briefly touch on this method (Figure 6.19).

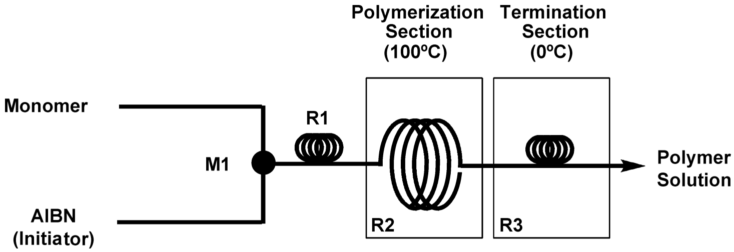


Figure 6.19 System for evaluation of heat transfer in microsystems (M1, T-shaped mixer; R1, R2, R3, microtube reactors). The experiments in the absence of a monomer are conducted without using M1 and R1

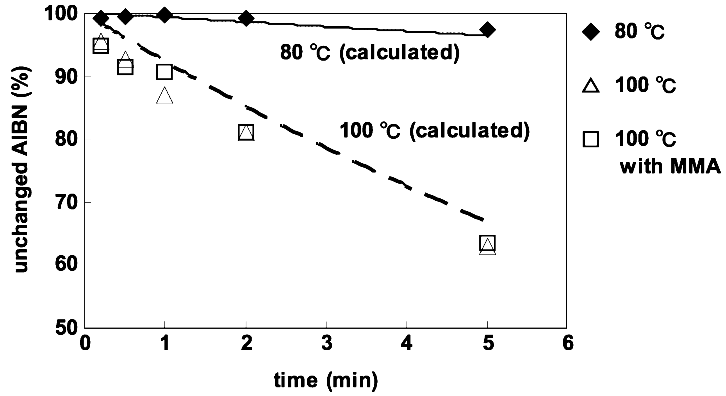


Figure 6.20 Thermal decomposition of AIBN in the microreactor. Copyright 2005 American Chemical Society

A solution of azobisisobutyronitrile (AIBN), which is one of the most popular radical initiators, in toluene is introduced to a microflow system, which is heated in an oil bath (80 or 100 °C). Aliquots of the outlet solution are collected and the amount of unchanged AIBN in the outlet solution is determined by high-performance liquid chromatography (HPLC).

The percentage of unchanged AIBN is plotted against the residence time in Figure 6.20. The plots fit to the calculated values very well based on the bath temperature according to Equation (6.3), which was reported in the literature.[19] This means that the inside temperature of the microtube reactor (stainless tube, inner diameter 500 μm) is very close to the bath temperature.

$$k_d(\mathrm{s}^{-1}) = 1.58 \times 10^{15} \exp(-129/RT) \qquad (6.3)$$

Such measurements can also be performed while a chemical reaction, such as polymerization, is taking place in the microtube reactor. For example, the decomposition of AIBN is carried out in the presence of methyl methacrylate (MMA). In this case, radical polymerization of MMA takes place and a significant amount of heat due to the polymerization is generated in the microtube reactor. However, the plots fit well to the calculated values based on the bath temperature according to Equation (6.3). This means that the heat generated by the polymerization is efficiently removed through the wall of the microtube reactor, demonstrating the superior heat transfer ability of the microreactor. Of course, the efficiency strongly depends on the inner size of the microstructure, the material and the thickness of the reactor wall.

6.3 RESIDENCE TIME CONTROL

Another important point to consider when extremely fast reactions are conducted is the lifetimes of any reactive intermediates. Fast chemical reactions often involve the generation and reactions of reactive intermediates. The lifetime of such a reactive intermediate is usually very short, and it might decompose before a substrate is added to accomplish a desired reaction. For example, organometallic compounds, such as organolithium or organomagnesium compounds, are usually generated in the absence of substrates except for Barbier-type reactions.[20] Such organometallic compounds are sometimes very unstable and difficult to handle at normal temperatures because of their fast decomposition. Therefore, reactions are usually conducted at very low temperatures. Lowering the reaction temperature, however, causes significant deceleration of the reaction. Therefore, an effective method for controlling such reactive species without deceleration of the reaction is highly desirable in flash chemistry.

If such an unstable reactive species can be transferred to another location to be used in the subsequent reaction before it decomposes, the reaction can be conducted without lowering the temperature. If it is possible to do so, chemical conversions that are impossible in a conventional way should be made possible in some cases. In order to accomplish chemical reactions in such a way, we need a flow reactor with a short residence time.

What is residence time? Residence time is the length of time that the solution remains inside the reactor. The residence time can be easily calculated (Figure 6.21).

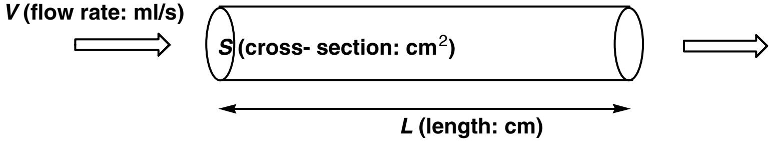


Figure 6.21 Residence time

$$\text{Residence time (s)} = \frac{S \times L}{V} \tag{6.4}$$

where S is the cross-section, L is the length and V is the flow rate.

It should be kept in mind, however, that the residence time calculated in this way is the mean residence time. There is a distribution of residence times in a reactor. The flow speed of the fluid near the channel wall surface

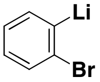


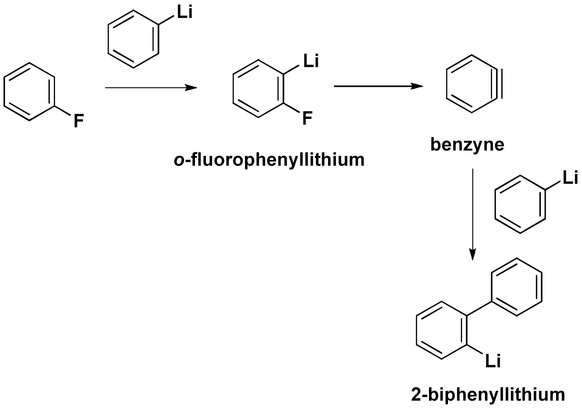
Figure 6.22 Structure of *o*-bromophenyllithium

is different from that in the middle of the channel. However, in a microchannel, the diffusion perpendicular to the flow should occur very quickly because of the short channel width. In any case, the residence time can be greatly reduced by adjusting the size and length of the microchannels and the flow speed. This feature of microreactors is extremely useful in controlling reactive species.

In the following sections, we will focus on *o*-bromophenyllithium (Figure 6.22) as an example of a highly reactive, unstable intermediate, and on the control of its generation and reactions based on residence time control.

6.3.1 The Discovery of Benzyne. The Concept of Reactive Intermediates

o-Bromophenyllithium is a member of the *o*-halophenyllithiums. Before discussing the generation and reactions of *o*-bromophenyllithium, let us briefly touch on the interesting chemistry of *o*-halophenyllithiums and benzyne. It is well known that *o*-halophenyllithium species undergo rapid elimination of halolithium to form benzyne. In the 1940s, Wittig observed that the reaction of phenyllithium with fluorobenzene leads to the formation of 2-biphenyllithium (Scheme 6.7). His interpretation was as follows:



Scheme 6.7 Reaction of fluorobenzene with phenyllithium

In the first step ortho-lithiation of fluorobenzene takes place to give *o*-fluorophenyllithium, which loses LiF to give benzyne. The addition of another molecule of phenyllithium to benzyne gives 2-biphenyllithium. This interpretation is quite reasonable for us today, but Wittig hesitated for years to publish his interpretation, because at that time, there was no concept of a reactive intermediate. Hoffmann wrote in his special article on Wittig's achievement:[21]

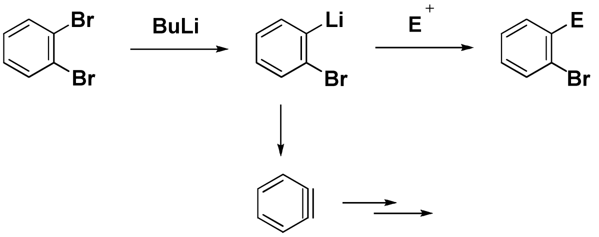
> There was no perception of reactive intermediates in the mind of most German chemists. The only thing that mattered in a reaction was the starting material and the product. In line with this, the carbocation concept of Meerwein had not yet found general acceptance. To postulate such a novel reactive intermediate back in those days could easily have put an academic career at risk.

After extensive works by Wittig,[22] Roberts and colleagues,[23] and Huisgen and colleagues[24] unveiled the features of this interesting intermediate having a carbon–carbon triple bond, Wittig then accepted dehydrobenzene (which he called benzyne) as a reality.

6.3.2 *o*-Bromophenyllithium[25]

Although benzyne has enjoyed many applications in organic synthesis, *o*-halophenyllithium, its precursor, has been rather difficult to use for synthetic reactions, especially when the halogen atom is iodine or bromine, because the elimination is too fast.[26] Such elimination can be avoided by the use of a metal other than lithium. For example, *o*-bromophenylmagnesium compounds are known to be more stable than the corresponding organolithium compound, and they serve as useful reagents in organic synthesis.[27] However, their reactions with electrophiles should be slower than those of *o*-bromophenyllithium. The use of other metals that avoid the elimination should also lead to deceleration of the reaction. From the viewpoint of flash chemistry, however, reactions should be conducted without deceleration.

Let us focus on the generation and reactions of *o*-bromophenyllithium without deceleration. Ortho-lithiation of bromobenzene is not suitable for the generation of *o*-bromophenyllithium, because the bromine–lithium exchange reaction is very fast. Therefore, the bromine–lithium exchange reaction of *o*-dibromobenzene using butyllithium (BuLi) is the method of choice (Scheme 6.8).



Scheme 6.8 Bromine–lithium exchange reaction of *o*-dibromobenzene

The bromine–lithium exchange reaction of *o*-dibromobenzene is usually carried out 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 reducing the residence time using a microflow system, the reaction can be conducted at −78 °C and *o*-bromophenyllithium can be effectively trapped with an electrophile before decomposition. Figure 6.23 shows a schematic diagram of the microflow system, in which reactions using methanol as an electrophile are conducted with varying temperatures and flow rates.

As profiled in Figure 6.24, the yield is very low at temperatures higher than −60 °C, presumably because of the decomposition of the *o*-bromophenyllithium intermediate to benzyne. At lower temperatures, the yield increases with a decrease in the temperature because of slower benzyne formation. A further decrease in temperature, however, results in a decrease in the yield, because the bromine–lithium exchange reaction does not complete at such low temperatures within the residence time.

The effect of the residence time is interesting as shown in Figure 6.25. At −70 °C, the yield increases with the residence time and becomes a

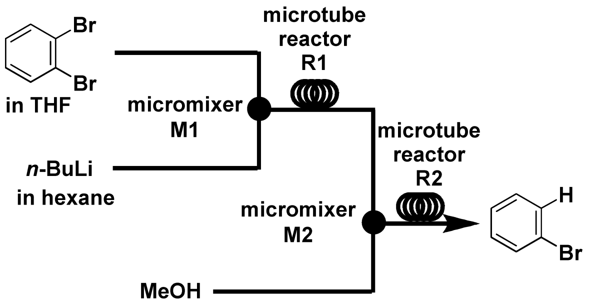


Figure 6.23 Microflow system for the bromine–lithium exchange reaction of *o*-dibromobenzene

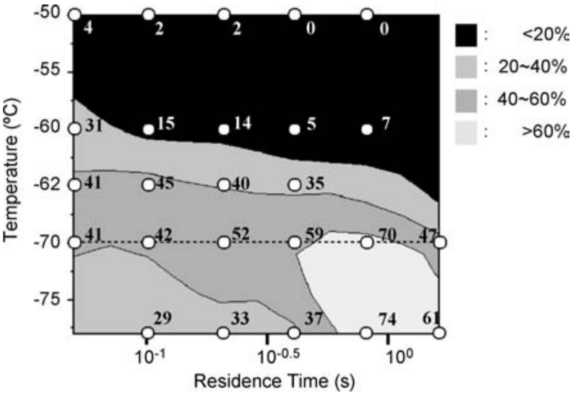


Figure 6.24 Effects of temperature and residence time on the yield of bromobenzene. Contour plot with scatter overlay of the yields (%). Copyright 2007 American Chemical Society

maximum at 0.8 s. This phenomenon can be explained in terms of the progress of the bromine–lithium exchange with the residence time. Further increase of the residence time causes a decrease in the yield, presumably because of benzyne formation.

It is noteworthy that an efficient way of controlling the generation and reactions of highly reactive intermediates can be accomplished by virtue of the precise residence-time control and temperature control inherent in microflow systems. 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, although efficient mixing devices that ensure mixing times shorter than residence times are being used. Therefore, microflow systems consisting of micromixers and microtube reactors serve as a powerful tool for mechanistic studies of reactions involving highly reactive intermediates.

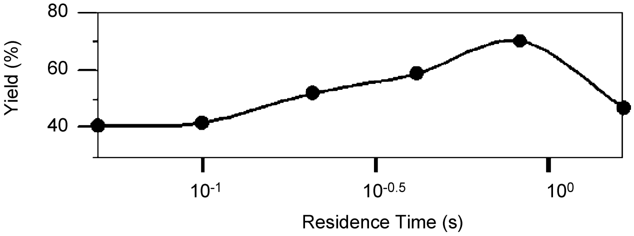


Figure 6.25 Effect of residence time at −70 °C. Copyright 2007 American Chemical Society

6.4 CONCLUSIONS

There are problems inherent in conducting extremely fast reactions in a controlled manner. If a reaction is faster than the mixing process, the reaction takes place before the homogeneity of the solution is achieved. In such cases, arguments based on kinetics do not work, and product selectivity is determined by the manner of mixing (disguised chemical selectivity). In order to obtain predictable selectivity close to kinetically based selectivity, extremely fast mixing is necessary. Mixing occurs because of molecular diffusion. The 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 micromixer results in a mixing speed unobtainable in a macroreactor.

Fast reactions are usually highly exothermic. Therefore, heat removal is also an important factor in controlling 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 microsystems, making precise temperature control possible.

Fast reactions often involve highly unstable intermediates, which decompose very quickly, making reaction control difficult. Residence time control serves as a solution to this problem. If unstable reactive species can be transferred to another location, they can be used in the next reaction before they decompose. The residence time can be greatly reduced by adjusting the length of microchannels and the flow speed. This feature of microflow systems is quite useful in controlling extremely fast reactions involving highly reactive unstable intermediates. Therefore, chemical conversions that are impossible in conventional chemistry should be made possible using microflow systems.

Based on these arguments, it is reasonable to conclude that microflow systems are essential tools for performing flash chemistry. In the following chapter, we will discuss the details of microflow systems consisting of microfluidic devices.

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7

Microfluidic Devices and Microflow Systems

> We carry out synthesis in a 19th-century style – we have better glass, better analytical tools. But there hasn't been a real advance.
>
> A. J. Bard (*Chem. Eng. News* **1998,** *January 12*)

Generation of highly reactive species is one of the key elements of flash chemistry as shown in Chapter 5. Another important element of flash chemistry is the control of extremely fast reactions of highly reactive species as described in Chapter 6. Microflow-reaction technology serves as an excellent technique for the purpose, compared with conventional macrobatch-reaction technology (flask-reaction technology). Without microflow-reaction technology, extremely fast reactions in flash chemistry would often be uncontrollable and the desired products would not be obtained with high selectivity. In this chapter, we discuss microfluidic devices and microflow systems (which are composed of microfluidic devices, for conducting extremely fast chemical reactions) that have been developed since the 1990s.

7.1 BRIEF HISTORY

The idea of chemical synthesis using microflow systems is not particularly new. Bard proposed the concept of an integrated chemical synthesizer in

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Table 7.1 Fields of chemistry that have benefited from microfluidic devices

- Chemical analysis
  - Micrototal analysis system
  - Lab-on-a-chip
  - Synthesis for screening
- Combinatorial synthesis[2]
  - Synthesis for process development
  - Synthesis for industrial production
- Microchemical plants

his book entitled *Integrated Chemical Systems*,[1] which was published in 1994. The idea has been realized step by step over the past two decades with progress in the technology of designing and fabricating microstructured devices for chemical reactions. The microtechnology has witnessed steady advances in making various types of microfluidic devices and has opened up new opportunities for carrying out chemical reactions using microflow systems composed of such devices. Microfabrication processing in the electronics and semiconductor industries, micromachining in mechanical engineering, microelectromechanical systems (MEMS), and microfluidics have developed independently and fused together in interdisciplinary approaches. By virtue of the progress in such technologies, the use of microfluidic devices in chemistry has begun. Various fields in chemistry, including analysis and synthesis, that have benefited from microfluidic devices and microflow systems are listed in Table 7.1.

7.1.1 Microflow Systems for Chemical Analysis

With the technology of fluidic devices having microstructures in hand, a new field of chemistry emerged in the 1990s and has received significant research interest: the micrototal analysis system (μTAS) or lab-on-a-chip technology (Figure 7.1).[3] This field focuses mainly on the integration of chemical systems for measurements and analysis using a microchip. Chemical analysis systems on a glass chip (usually centimeter size) with microchannels (usually micrometer-size cross-section and centimeter-size length) etched in the glass are prepared using microfabrication technology. Various applications of the system include capillary electrophoresis-based separations of amino acids on a microchip, which

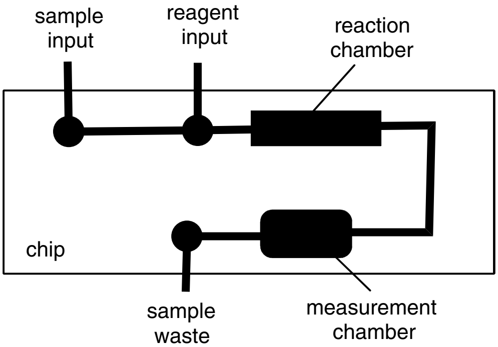


Figure 7.1 The concept of lab-on-a-chip[3]

allows analysis in seconds. Electro-osmotic pumping is often used to drive fluid flow, and manipulation of the applied voltage controls the directions of the flows within the chip.

The rapid progress in this field meant that the 1st International Conference on Micrototal Analysis System was held at Twente University, The Netherlands, in 1994.[4] Since then, tremendous developments have been achieved in this field throughout the world.

7.1.2 Microflow Systems for Chemical Synthesis

The application of microfluidic devices to chemical synthesis started somewhat later. In the mid-1990s, synthetic chemists and chemical engineers realized the importance of microflow systems composed of microfluidic devices for the synthesis and production of chemical substances. Enormous advances have been made over the past two decades in studies on synthetic reactions using microflow systems, microunit operations, and microproduction systems.[5] The 1st International Conference on Microreaction Technology (IMRET) was held in 1997 by the German Society for Chemical Engineering and Biotechnology, DECHEMA.[6] Since then, the IMRET meetings have been frequently held in Germany and the USA. During such meetings, the opinion has become that microfluidic devices and microflow systems will make a revolutionary change in chemical synthesis and production,[6–9] because they exhibit numerous advantages stemming from the small size of the microstructures, making possible chemical conversions that are impossible in macrobatch systems.

There are two approaches to the use of microflow systems for chemical synthesis; i.e. synthesis for screening and synthesis for production. In the former case, the benefit of microflow systems dealing with small quantities of compounds is quite advantageous for making a number of compounds for screening very quickly at relatively low costs. In the latter case, the advantages of microflow systems over conventional macrobatch systems stem from the small sizes and the high surface-to-volume ratio of the space for the reaction. Such features enable precise temperature control and high efficiency of heterogeneous mass transfer providing better ways for producing chemicals in a highly selective fashion. Short residence times in reactors may also be advantageous from the viewpoint of the control of highly unstable reactive intermediates. The advantages of microflow systems for easy modulation and the possibility of combining reactors in parallel promising a quick means for scale-up also warrant comment. In Japan, the 1st International Workshop on MicroChemical Plants was held in 2003, and since then, progress in microchemical plants and related fields has been reported at the Workshop annually.

7.2 CHARACTERISTIC FEATURES OF MICROFLOW SYSTEMS

The characteristic features of microsystems stem from the small size of the space in the microstructures. Therefore, microsystems are not necessarily small systems in total size. They can be large in total size as long as they contain microstructures that can be used for chemical reactions. This sharply contrasts with the concept of a lab-on-a-chip, which should be small in total size. It is also important to note that microsystems are normally set up as flow-type reactors with a constant flow of solutions through a microstructured reaction chamber or channel. Although the reactor's capacity at any one time is small, total production capacity over time is much greater than may be imagined. Therefore, microflow systems are not necessarily used solely to produce small quantities of chemical substances. In fact, a microfluidic device has been developed that fits in the palm of the hand but can produce several tons of a product per year (see Chapter 10).

Stemming from the small sizes and high surface-to-volume ratio of the microstructures, microflow systems composed of microfluidic devices have the following characteristic features (Table 7.2):

Table 7.2 Characteristic features of microflow systems

Small size	Fast mixing because of the small diffusion path Short residence time
High surface-to-volume ratio	Precise temperature control (fast heat transfer) Fast mass transfer at the phase boundary

(1) Fast mixing: Many chemical reactions consist of combining two substances. Mixing occurs as a result of molecular diffusion, as described in Chapter 6. The 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 microstructure results in a mixing speed unobtainable in a macrosystem.

(2) Precise temperature control: In general, volume is proportional to length cubed, while surface area is proportional to length squared. When the length is shortened, therefore, the surface-to-volume ratio increases. Thus, a feature of microspaces is that they have large surface-to-volume ratios compared with macrospaces. Heat is transferred between the interior and exterior of a reactor system via the reactor surface. Therefore, in a microsystem–with its greater surface area per unit volume–heat transfer occurs rapidly, making precise temperature control possible. Thus, local temperature variation can be minimized in microsystems, whereas macrosystems often suffer from a problem of hot spots.

(3) Fast mass transfer at the phase boundary: Another characteristic feature of microsystems 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 more efficient.[7] The rate of mass transfer increases with an increase in the phase boundary surface-to-volume ratio.

(4) Short residence time: The length of time that the solution remains inside the reactor is called the residence time. In a flow system, the residence time can be adjusted by changing the length of the channels and flow speed. In microflow systems, the residence time can be greatly reduced because of the small size of the channel. This feature of microflow systems is extremely useful in controlling reactive species. In short, unstable reactive species can be transferred to another location to be used in the next reaction before they decompose. Therefore, chemical conversions that are impossible in

macrobatch or macroflow systems should become possible using microflow systems.

7.3 MICROSTRUCTURED FLUIDIC DEVICES

A microstructured fluidic device that is used for conducting chemical reactions is called a microreactor. A microreactor is a reactor containing microstructures for chemical reactions. The size of the microstructure inside a microreactor usually ranges from several micrometers to several hundred micrometers. Various types of microstructured fluidic devices, such as microchip reactors and microtube reactors, have been developed for chemical reactions. Micromixers often serve as microreactors because reactions take place immediately after mixing. In some cases, external energies, such as thermal, photo, and electric energies, are provided in the microspace to promote the chemical reactions. For such purposes, special microreactors have been developed.

7.3.1 Microchip Reactors

Microchip reactors are very popular because they are widely utilized for chemical analysis and measurements. Microchip reactors are composed of a network of micrometer-sized channels etched into a solid microchip (plate), which is made of a number of materials, such as glass, silicon, metals, and polymers. Various channel fabrication technologies, including photolithography, hot embossing, powder blasting, injection molding, and laser microforming are available, but the method of choice depends on the material used for a solid microchip and the size and shape of the microchannels. The microchip having a network of channels is usually covered with another chip (plate), which can be made from the same material or a different material. The channel network is connected to pumps or reservoirs by suitable tubes. Sometimes, connectors between the microchip and the tubes are problematic. If aqueous solutions are used for the reaction, the tubes can be fitted to the microchip using a conventional bonding agent. However, in cases where organic solvents are used for reactions, such a method may be inappropriate because the bonding agent often dissolves in organic solvents. In such cases, a metal frame having joints is used to connect the inlet and outlet tubes. The metal frame is connected to both sides of a solid chip using some sealing and fixed with

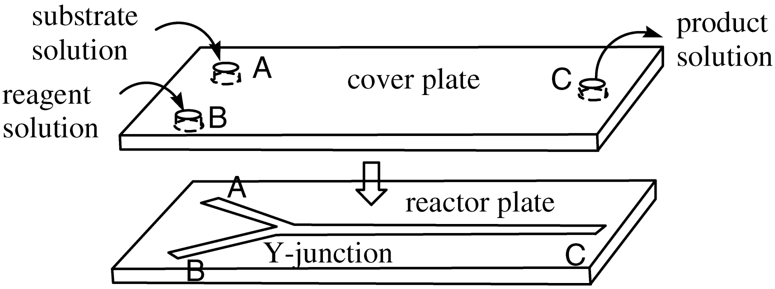


Figure 7.2 Simple microchip reactor with a Y-shaped junction

screws. Solutions are introduced to the channel network by various pumping techniques, such as syringe pumping and electro-osmotic flow (EOF).

Microchip reactors often contain a mixing part, such as a T-shaped or Y-shaped junction. A typical example is shown in Figure 7.2. A substrate solution and a reagent solution are introduced to inlets A and B, respectively, through holes in the cover plate. The inlet tubes are connected to the holes. The two solutions are combined at a Y junction and a reaction takes place in a reactor channel etched on the reactor plate. Then, a product solution comes out from outlet C on the cover plate.

Microchip reactors are normally used to synthesize small quantities of compounds for screening purposes (Figures 7.3 and 7.4). The flow rate is usually very low (μl/min or nl/min). Therefore, microchip reactors are

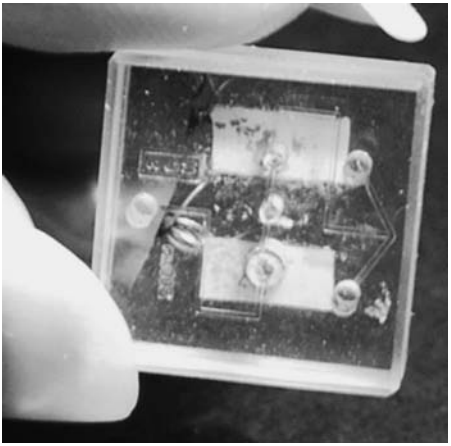


Figure 7.3 Glass microchip reactor (Prof. Haswell, UK)

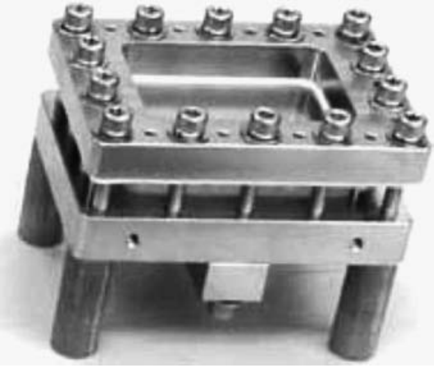


Figure 7.4 Microchip reactor having a metal framework for connecting tubes (Dainippon Screen Mfg. Co., Ltd)

not suitable for the synthesis of the large quantity of compounds required in the industrial production of chemicals. Heat exchange in microchip reactors can be achieved by either dipping the whole reactor in a temperature-controlled bath or passing cooling or heating media above or below the chip using another plate having channels for heat exchange .

7.3.2 Microtube Reactors

There is another type of microfluidic device for conducting chemical synthesis, i.e. a microtube reactor. A solution of reactants is passed through a tube of micrometer size, and the reaction takes place inside the tube. One of the most important advantages of microtube reactors is the ease of fabrication. Stainless steel tubes and Teflon tubes of various inner diameters (>250 μm) are commercially available. Joints for such tubes are also commercially available. Therefore, one can easily make a network of microtube reactors by cutting a commercially available microtube of an appropriate inner diameter into suitable lengths and connecting them with joints. A T-shaped joint or a commercially available micromixer can be used to connect microtube reactors to make a mixing point. The flexibility of network structures and ease of disassembly–reassembly of networks are both advantages of microflow systems consisting of microtube reactors.

Another advantage of microtube reactors is good heat exchange ability. Heat transfer can occur equally in all directions perpendicular to the flow direction through the inner surface and outer surface of the tube wall,

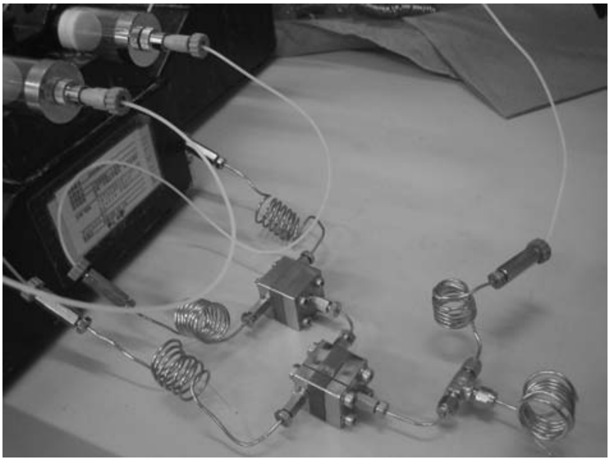


Figure 7.5 Microflow system composed of microtube reactors and micromixers

because the thickness of the wall is equal in all directions perpendicular to the flow direction. This is not the case for microchip reactors. In laboratory-scale experiments, a network of microtube reactors is often dipped in a cooling or heating bath to control the temperature inside the reactor. For industrial purposes, however, shell and tube systems are often used in combination with a circulating system. As for the material of microtube reactors, stainless steel is greatly superior to polymers from the viewpoint of heat transfer. Figure 7.5 shows a microflow system composed of stainless steel microtube reactors and micromixers. Teflon tubes are used to connect the system with syringe pumps.

Plastic microcapillary flow disk (MFD) reactors have been constructed from a flexible, plastic microcapillary film (MCF), comprising parallel capillary channels with diameters in the range of 80–250 μm. MCFs are wound into spirals and heat treated to form solid disks. These reactors are capable of carrying out continuous flow reactions at elevated temperatures and pressures with a controlled residence time.[8]

7.3.3 Micromixer

Micromixers are the key elements of microflow systems for flash chemistry because extremely fast mixing is essential for conducting an extremely fast reaction between two reaction components As described in Chapter 6, the conventional approach to mixing often leads to disguised chemical selectivity. Fast mixing[9] by virtue of a short diffusion path in

Table 7.3 Types of micromixers

Passive or active	Mixing driving force	Type
Active mixing	Diffusion and external energy	High-frequency vibration (ultrasonic wave) Low-frequency vibration
Passive mixing	Diffusion	Contacting of two sub-streams Injection of many sub-streams of two components Manifold splitting and recombination Injection of many small sub-streams of one component in a main stream of another component Decrease of diffusion path perpendicular to the flow
	Diffusion and stream energy	Collision of two high energy sub-streams

microstructures[10] is often effective in solving such problems, and a product selectivity close to kinetically predicted selectivity can be attained.

There are two basic methods in micromixing: active and passive (Table 7.3). In active mixing, external energy is input to induce mixing. Various types of external energies including supersonic and low-frequency vibrations have been examined. Complex instruments are needed to harness the external energy in active micromixing. However, only the inertial forces of the solution flow are used without adding any external energy in passive micromixing. The simplicity of the inner structures of such devices means that passive micromixers are more popular than active micromixers. In passive micromixing, the flow energy is used to restructure the flow in a way that results in short diffusion paths to promote extremely fast mixing. There are several ways to accomplish passive micromixing; for example, multilamination,[11] injection of many small sub-streams of one component in a main stream of another component, decrease of the diffusion path perpendicular to the flow direction, manifold splitting and recombination, periodic injection of small fluid segments, and collision of microsegments in the center of the mixer.[12]

7.3.4 Passive Micromixers

Many types of passive micromixers have been developed based on various principles. Some of them are commercially available. In the following sections, we shall briefly discuss the principles and the structures of some passive micromixers.

7.3.4.1 Y-shaped and T-shaped micromixers

Contacting of two streams is the simplest way of mixing based on molecular diffusion. Y-shaped micromixers are based on this principle, as shown in Figure 7.6. T-shaped micromixers are also categorized into this type, if the flow rate is low. However, if the flow rate is very high, they may be categorized into micromixers based on collision of two high energy streams. Y-shaped and T-shaped micromixers are very popular in microchip reactors and they are frequently used for analytical purposes.

As shown in Figure 7.6, a laminar flow is usually predominant in a Y-shaped mixer, and in such a case, mixing takes place only by molecular diffusion. Therefore, the mixing time and efficiency strongly depends on the lamination width. This means that mixers of smaller channel width have better mixing efficiency than those of larger channel width.

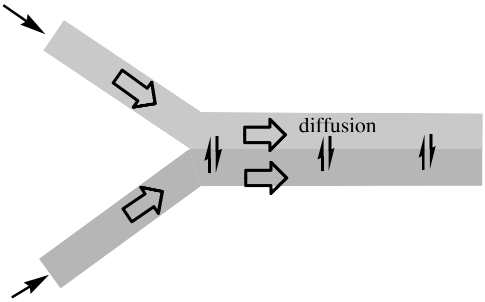
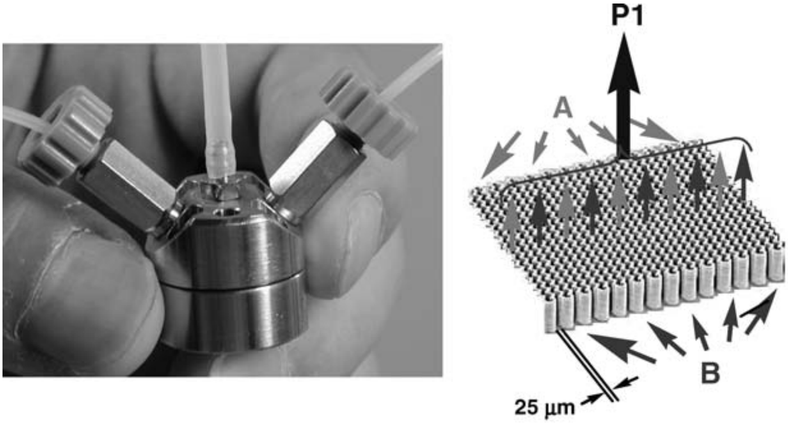


Figure 7.6 Principle of Y-shaped mixer

7.3.4.2 Interdigital multilamination micromixer

In the case of Y- or T-shaped micromixers, a decrease in the channel width to shorten mixing time leads to a decrease of production volume per unit time. To solve this problem interdigital multilamination micromixers have been developed. In this type of micromixer, two fluids are separated into many small narrow streams, which are arranged to contact each other alternately. The mixing takes place at interfaces of such sub-streams by molecular diffusion. The IMM (Institute of Microtechnik Mainz) single



(a) (b)

Figure 7.7 (a) Photograph of an IMM single mixer and (b) its microstructure for liquid distribution

mixer is an example of this type of micromixer and is one of the most popular (Figure 7.7).

In the IMM single mixer, the solutions to be mixed are introduced into the mixing element as two counter-flows, and the solution stream into an interdigital channel configuration (solution distribution part). In the next stage, an alternating flow configuration consisting of the lamellae of the two solutions is generated by means of a slit that is located above the interdigital-channel unit for distribution of the solutions. Then, the laminated flow leaves the channel unit perpendicular to the direction of the feed flows through the slit, and mixing takes place in a very short period by virtue of the short diffusion path between the multilaminated streams in the slit (mixing part).

The general scheme of the principle of this type of micromixer is shown in Figure 7.8. The solutions to be mixed are distributed into several segments of flows of small width in alternating configuration using the microstructure of the device (solution distribution part). Mixing takes place in the resulting stream from the alternating multilamination configuration through the interfaces of the segments of flows by virtue of the short diffusion path, and a homogeneous solution is produced in a short period (mixing part). It is noteworthy that the mixing efficiency or speed often depends on the flow rate (see below). In the low flow rate region, the mixing efficiency is rather low. To achieve sufficiently fast mixing, one should use a micromixer in the appropriate flow rate range that is characteristic of the device. This means that the flow energy might also

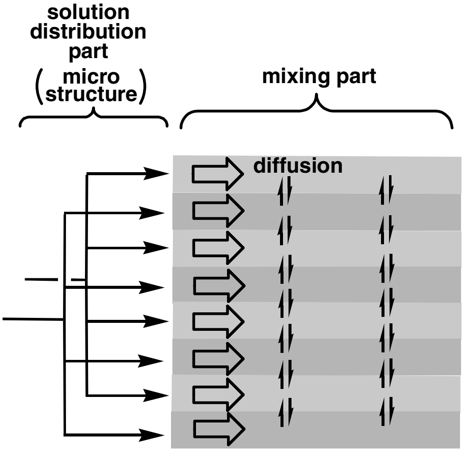


Figure 7.8 Principle of a multilamination-type micromixer

play an important role in the mixing in real interdigital multilamination micromixers.

A mixing element inside the IMM single mixer has been manufactured using LIGA technology. [LIGA is the German acronym for (X-ray) lithography (Lithographie), electroplating (Galvanoformung), and molding (Abformung).] The LIGA process was developed in the early 1980s at the Karlsruhe Nuclear Research Center (currently known as the Forschungszentrum Karlsruhe or Karlsruhe Research Center). The Karlsruhe Research Center is one of the most active research groups in microfabrications and microreactor technology. The LIGA technology consists of sputter, lithography, etching, electroforming, aligned bonding, forming, surface micromachining, bulk micromachining and microassembly. The first LIGA technology was developed using X-rays produced by a synchrotron (X-ray LIGA). Other types of LIGA technologies, which differ in the radiation and preform used, such as UV-LIGA and Silicon-LIGA, are also used.

7.3.4.3 Triangular micromixers and the SuperFocus micromixer[13]

In interdigital multilamination micromixers, the small thickness of the lamellae leads to short diffusion paths, resulting in fast mixing. Further thinning of the liquid lamellae should lead to shorter diffusion paths and faster mixing. The IMM single mixer applied this concept by shrinking the channel width in the slit. A further extension of this concept leads to the

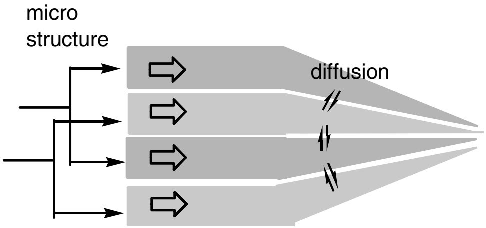


Figure 7.9 Principle of a multilamination micromixer with triangular-shaped mixing chamber

development of triangular mixers (Figure 7.9), which are much more effective than the corresponding rectangular interdigital multilamination mixers (Figure 7.8). The decrease in diffusion path length perpendicular to the flow is responsible for faster mixing.

In the SuperFocus micromixer, the focusing ratio is significantly increased in comparison with the triangular micromixer. For example, a focusing ratio of 100 can be attained, whereas that for the triangular micromixer is <10. The mixing time of the SuperFocus micromixer is much shorter than those of the triangular and rectangular micromixers, as shown in Table 7.4. Extremely fast mixing in the range of milliseconds has been achieved using the SuperFocus micromixer.

Table 7.4 Comparison of mixing performance of three interdigital micromixers (8 L/h)

Type of mixer	Mixing time for mixing residual of 0.05
Rectangular	2.48 s
Triangular	59 ms
SuperFocus	3.5 ms

7.3.4.4 Manifold split-and-recombination micromixer

Manifold split-and-recombination micromixers are also popular and powerful micromixers.[14] In this type of micromixer, two solutions to be mixed are introduced into a channel and combined. Then, the mixture is split into two streams in such a way that each stream contains segments of two different solutions. The two streams are then introduced into the next channel and recombined so that the number of solution segments increases, as shown in Figure 7.10.

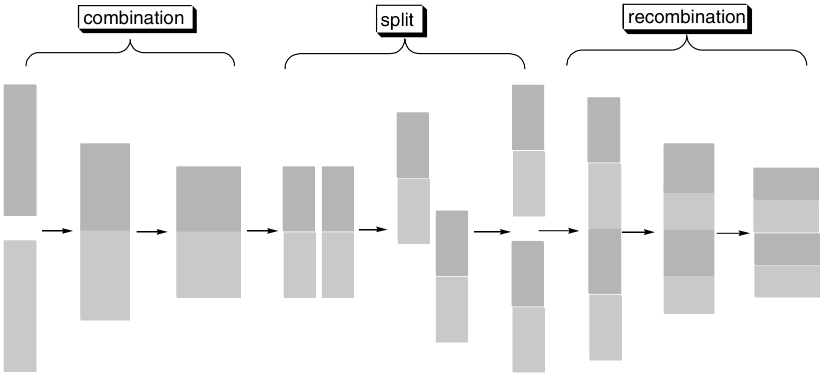


Figure 7.10 Principle of a single manifold split-and-recombination operation

When two solutions enter the micromixer, the number of segments is doubled in one split-and-recombination operation. Therefore, in this method, the number of solution segments is increased exponentially by repeating the operation sequentially along the channel (Figure 7.11). After the *n*th split-and-recombination iteration, the number of segments increases to 2^{n+1}. This operation decreases the diffusion path significantly because the size of each solution segment decreases rapidly as the number of segments increases. Therefore, molecular diffusion takes place in a short period to make a homogeneous solution very quickly.

The Toray Hi-mixer is a special type of manifold split-and-recombination micromixer. The structure of the Hi-mixer is shown Figure 7.12.[15] In the Hi-mixer, when two layers of the solutions enter the mixing element, they are split into eight layers by using twist walls in the element. Therefore, in this method, the number of layers increases exponentially by repeating the operation (4^n after the *n*th iteration).

The Yamatake YM-1 micromixer is another type of split-and-recombination micromixer (Figure 7.13). As shown in Figure 7.13, the two solutions to be mixed are distributed into many streams in the first part of the mixer. Then, several split-and-recombination operations are performed sequentially to increase the number of segments, leading to fast mixing because of the short diffusion path.

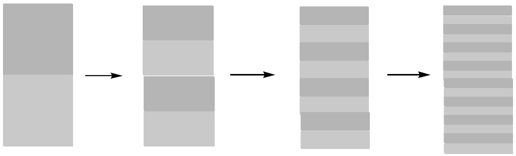
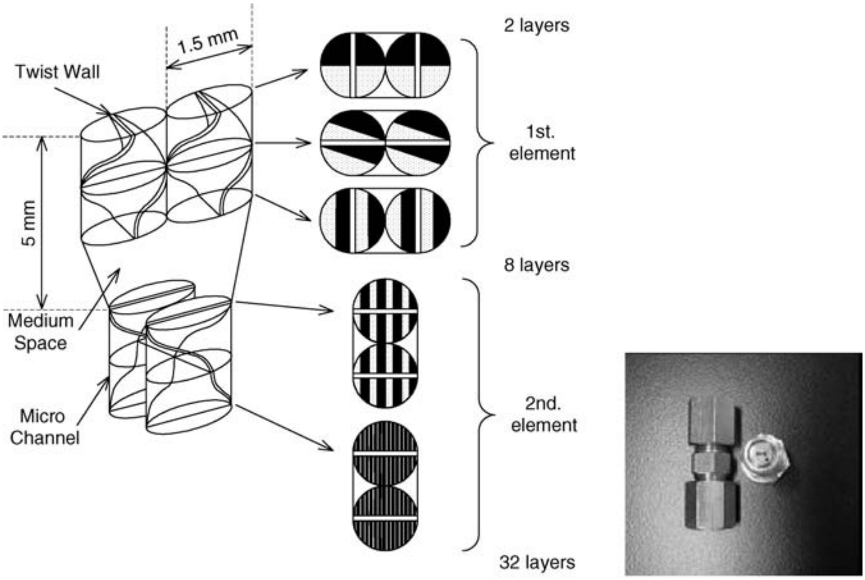
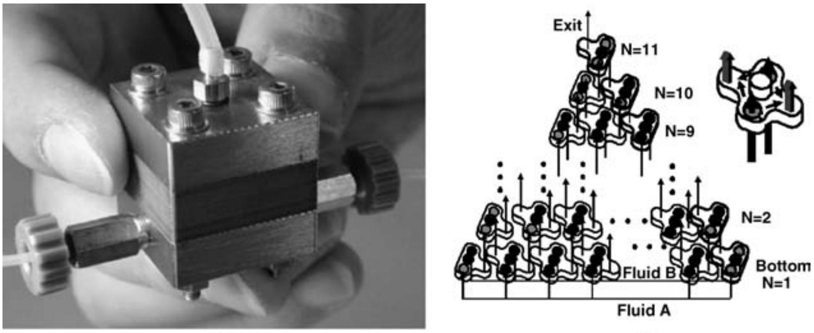


Figure 7.11 Principle of multiple manifold split-and-recombination operations



(a) (b)

Figure 7.12 (a) Structure and (b) photograph of the Toray Hi-mixer. Copyright 2005 American Chemical Society



(a) (b)

Figure 7.13 Yamatake YM-1 micromixer. (a) Photograph and (b) schematic diagram of the mixing element. Copyright 2005 American Chemical Society

7.3.4.5 T-shaped micromixers[16]

Although T-shaped micromixers are very simple in structure and are easy to fabricate by conventional mechanical machining technology, they can be very effective in achieving fast mixing (Figure 7.14). At a low flow

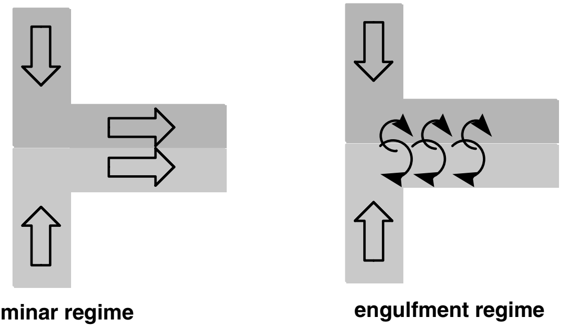


Figure 7.14 T-shaped micromixer showing the laminar and engulfment regimes

speed, mixing efficiency is rather low because of the laminar flow regime. However, when the flow speed exceeds a critical value, the intensity of mixing increases significantly. The engulfment flow regime caused by stream energy seems to be responsible for fast mixing. The threshold velocity depends on the size and shape of the microchannels. T-shaped micromixers with 250–500 µm inner diameter are popular. The reduced possibility of clogging is also an advantage of simple T-shaped micromixers, because the channel size is large compared with multilamination-type micromixers.

7.3.4.6 Micromixers based on collision of microsegments[15]

As an extension of the T-shaped micromixer, a micromixer based on collisions between microsegments has been developed. As shown in Figure 7.15, solutions to be mixed are divided into several segments using microchannels on the mixing plate. The solution segments meet at the center of the mixing plate with high velocity. The annular channels on the inlet plate play a role in uniformly feeding two solutions into the inlets of the microchannels on the mixing plate. The mixed solution leaves the device through the center channel.

7.3.4.7 Chaotic micromixers

A passive method for mixing streams of steady pressure-driven flows in microchannels at low flow rates has been developed. It is known to be difficult to mix solutions in microchannels at low flow rates because of the laminar nature of the flow. In such cases, molecular diffusion across the channels is slow. To solve this problem, a protocol for mixing based on transverse flows has been developed.[17] To generate transverse flow,

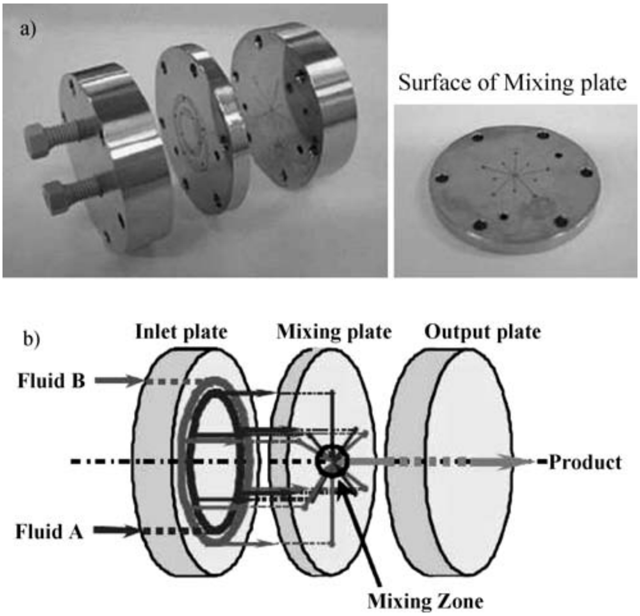


Figure 7.15 (a) Photograph of the inlet plate, mixing plate and outlet plate and (b) schematic diagram of the liquid flow. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission

ridges are placed on the floor of the channel at an oblique angle. This type of micromixer is called a chaotic micromixer (Figure 7.16).

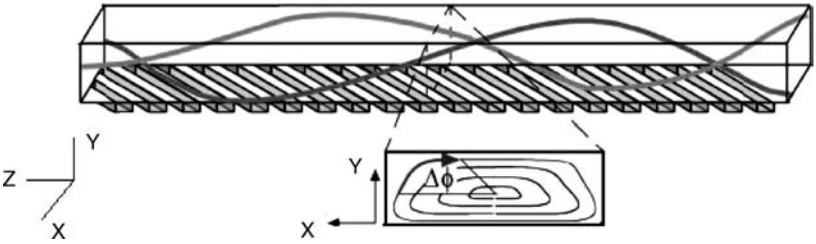


Figure 7.16 Chaotic micromixer[17]

7.3.4.8 *Anti-fouling micromixer*

The use of micromixers having microstructures sometimes suffers from clogging problems because of the small channel size. If the reaction yields a solid product or a solid side product, the channels of micromixers, which are micrometer-sized, might get clogged. Anti-fouling micromixers, such

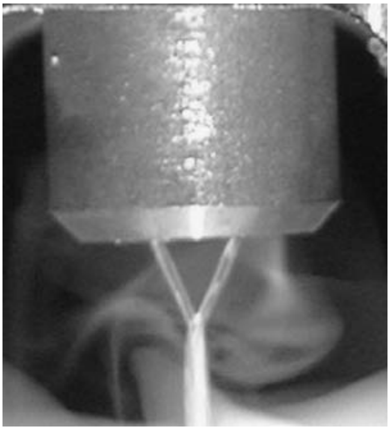


Figure 7.17 Jet micromixer[18]

as jet micromixers, have been developed to avoid the clogging problem. Jet micromixers are based on fast mixing by turbulence caused by merging high-velocity jets (Figure 7.17).[18] The mixing takes place in an open space to avoid clogging. This type of micromixer has been applied to the synthesis of powders and particles. They are also suitable for organic reactions that lead to precipitation such as quaternization of tertiary amines and base-promoted amide formation.[19]

There is another type of anti-fouling micromixer, i.e. a concentric multi-layered cylindrical micromixer (Figure 7.18).[20] Clogging of the

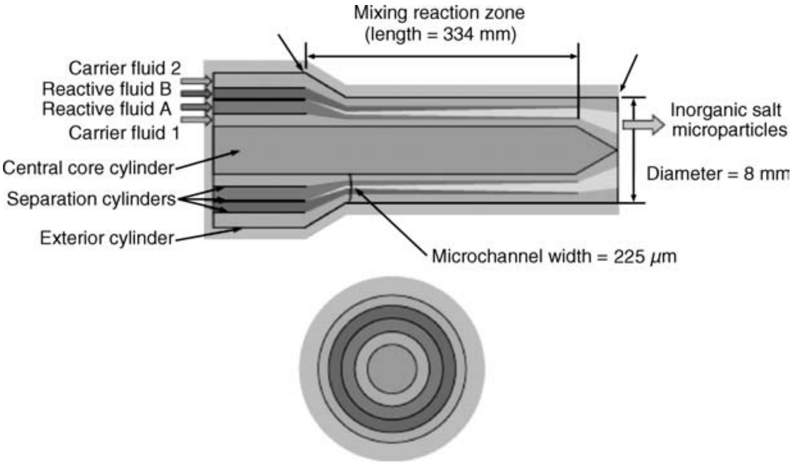


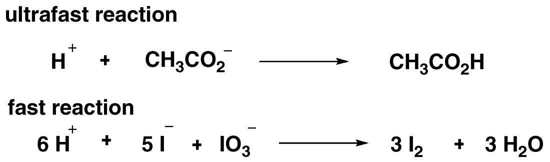
Figure 7.18 Concentric multi-layered cylindrical micromixer. Copyright 2002 The American Association for the Advancement of Science

micromixer is usually caused by the sedimentation and aggregation of microparticles on the walls of the microstructure. However, this problem has been solved by a concentric multi-layered cylindrical micromixer based on interface contact mixing. The mixer has a central core surrounded by concentric cylinders through which solutions flow. Solutions introduced in the spaces between the walls of the concentric cylinders take on the shape of the concentric cylinders on a micrometer scale. Carrier solutions or fluids that do not contribute to the reaction are passed through the reactor along the reactor's walls, thereby preventing the reactive solutions from coming into contact with the reactor walls. In other words, the reactive solutions are released between these carrier solutions so that the interface between the reactive solutions where the microparticles form does not come into contact with the device walls. Therefore, clogging can be avoided. This type of micromixer serves as a powerful tool for continuous manufacturing of microparticles with good control of particle size and particle size distribution without clogging.

7.3.4.9 Mixing efficiency and flow rate

It is important to note that mixing efficiency strongly depends on flow rate and that each micromixer has its characteristic flow rate range for efficient mixing. Therefore, we have to choose an appropriate flow rate to achieve fast mixing. If the flow rate is fixed, we have to choose a suitable micromixer at that flow rate.

The efficiency of mixing is usually determined by a standard chemical method, the so-called Dushman reaction.[21,22] Mixing of a strong acid (HCl) and a solution of I^-, IO_3^-, and CH_3CO_2Na (sodium acetate) leads to a combination of an ultrafast reaction (neutralization of the acid) and a fast reaction (I_2 formation by an acid promoted redox reaction between iodide ions and iodate ions) as shown in Scheme 7.1. These two reactions having H^+ as a common reaction component compete in a parallel way. If the mixing is very fast, the ultrafast process masks the slower second



Scheme 7.1 Ultrafast reaction and fast reaction promoted by H^+

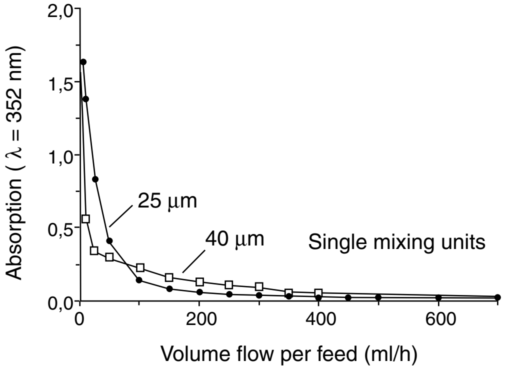


Figure 7.19 Effect of flow rate on the mixing efficiency of IMM single mixers with mixing elements of 25 and 40 µm[22]

process. Therefore, no absorption due to I_2 at 352 nm is detected. If the mixing is not very fast, however, imperfect mixing leads to a local increase in concentration of acid, which catalyzes the slower reaction to form I_2. The amount of I_2 thus formed can be determined by UV analysis.

Figure 7.19 shows the dependence of the mixing efficiency (rate) of the IMM single mixer on the flow rate. The increase of the flow rate causes a decrease in the absorption at 352 nm due to I_2, which means an increase in the mixing rate. Above a flow rate of 100 ml/h, extremely efficient mixing can be achieved. The mixing efficiency also depends on the size of the channels in the distribution unit. When the flow rate exceeds 50 ml/h, the mixer with 25 µm channels exhibits better mixing ability than that with 40 µm channels.

7.3.5 Microheat Exchanger

Many reactions that are used in flash chemistry are highly exothermic, and fast heat removal is essential for the conduction of such reactions with a high level of controllability. However, the use of heat exchangers is very rare in conventional laboratory organic synthesis using flasks. Temperature control is usually carried out by dipping a reaction flask in a cooling or heating bath. The heat exchange ability of this type of system is not sufficient for conducting extremely fast and highly exothermic reactions. Therefore, microheat exchangers are very important devices for flash chemistry. In many cases, reactions take place in a heat exchanger, and therefore, it is difficult to distinguish between microheat exchangers and

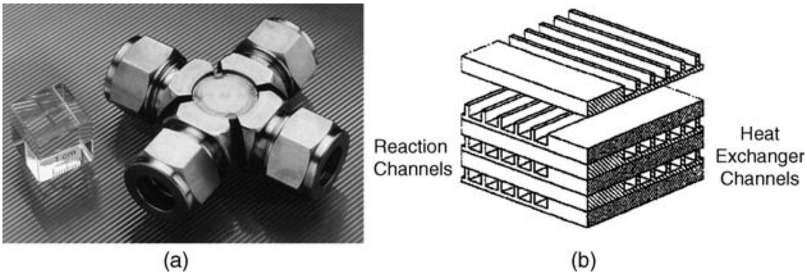


Figure 7.20 (a) Photograph of the cross flow microheat exchanger and (b) schematic diagram of the exchange element. (Karlsruhe Research Center, Germany)

microreactors. Although many types of heat exchangers have been developed, only a few examples are discussed here.

A microheat exchanger developed at the Karlsruhe Research Center (Figure 7.20) is one of the most popular. This microheat exchanger has a high heat exchange coefficient [up to 20 000 W/(m^2 K)] and a high throughput [up to 6500 kg/h (water)]. The channels for reacting solutions are separated from the channels for heating medium or coolant by thin metal walls. A high surface-to-volume ratio and thin walls seem to be responsible for the extremely fast and efficient heat exchange.

This heat exchanger has been made by mechanical fabrication of metallic materials combined with a diffusion-bonding technique. The first step of the fabrication is the processing of the metallic foils. Precision turning and milling are applied. In the second step, the processed metallic foils are cut into regularly sized plates. In the third step, the resulting microstructured metal plates are stacked between two base plates and are diffusion bonded under high pressure and high temperature in a vacuum. In the last step, a microstructured body, which consists of thousands of microchannels, is welded into a housing unit with tubes or fittings by electron beam welding.

A shell and tube microheat exchanger (Figure 7.21) is another type of microheat exchanger.[15] This heat exchanger consists of 55 stainless steel microtubes (inner diameter 490 µm, length 200 mm), which are placed in a shell (inner diameter 16.7 mm, length 200 mm). A coolant is circulated through the shell to control the temperature inside the microtube reactors. The normal flow rate of this heat exchanger is 100 ml/min.

7.3.6 Photochemical Microflow Reactor

Photochemistry is a powerful method for generating reactive species as described in Chapter 5, and therefore, photochemical microflow reactors

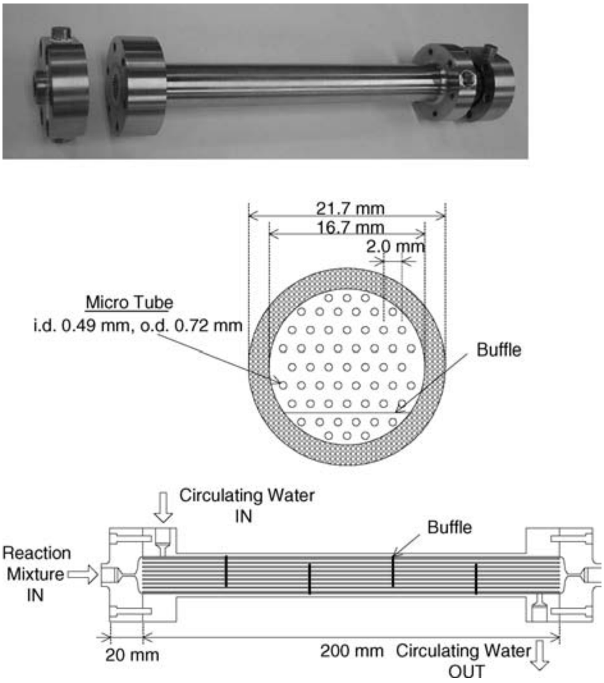


Figure 7.21 Shell and tube microheat exchanger. Copyright 2005 American Chemical Society

are important tools in flash chemistry. It is well known that light intensity attenuates exponentially with increasing optical path length according to the Lambert–Beer law. This feature of photochemistry is often a problem when photochemical synthesis is conducted using a macrobatch reactor, because it is difficult to scale up the reaction to increase the production volume. Increase in the reactor size usually leads to increase in the optical path length, and therefore, the efficiency of a photochemical reaction decreases with scale-up. The use of microflow reactors, which can produce a significant decrease in the optical path length, may solve the problem. Various types of photochemical microflow reactors have been developed and used for photochemical reactions such as [2 + 2] cycloaddition reactions.[23]A typical example of a photochemical microflow reactor is shown in Figure 7.22.[24] This reactor has cooling channels under the reaction channels. Because photoirradiation often causes heat generation and temperature increase, those devices having a heat exchange unit are quite effective. Photochemical microflow reactors containing a catalyst, such as TiO_2, have also been developed.[25]

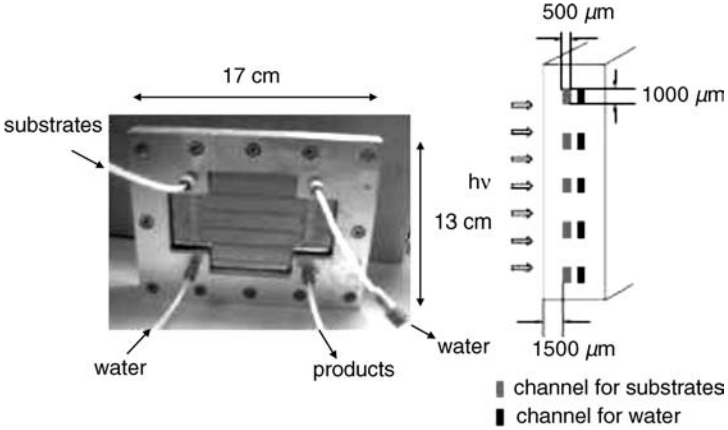


Figure 7.22 Photochemical microflow reactor containing cooling channels under the reaction channels[24]

7.3.7 Electrochemical Microflow Reactor

Electrochemistry also serves as a powerful method for generating highly reactive species under mild conditions. Electrochemical reactions in organic solvents, however, suffer from large ohmic resistance between the two electrodes due to low conductivity of the organic solvents. Another problem is low efficiency of mass transfer between a bulk solution and the electrode surface. These problems can be solved using electrochemical microflow reactors. A short distance between two electrodes diminishes the ohmic resistance and minimizes the loss of energy and heat formation. A high surface-to-volume ratio of the reactor leads to a high electrode-surface-to-solution-volume ratio, which facilitates the mass transfer on the surface of the electrodes.

An electrochemical microflow reactor consisting of a plate-to-plate electrode configuration mounted in a nonconducting housing has been developed.[26] As shown in Figure 7.23, a 75 μm thick polyimide foil between the working electrode and the counter electrode defines a unique distance. This polyimide foil contains microstructured slits (250 μm wide).

An electrochemical microflow reactor, which is composed of diflone and stainless steel bodies produced by a mechanical manufacturing technique, is shown in Figure 7.24.[27] The reactor consists of a two-compartment electrochemical cell, which is divided by a PTFE membrane. Carbon felt (7 mm × 7 mm × 5 mm) made of carbon fibers ($\phi = 10\ \mu m$) is used as the electrode.

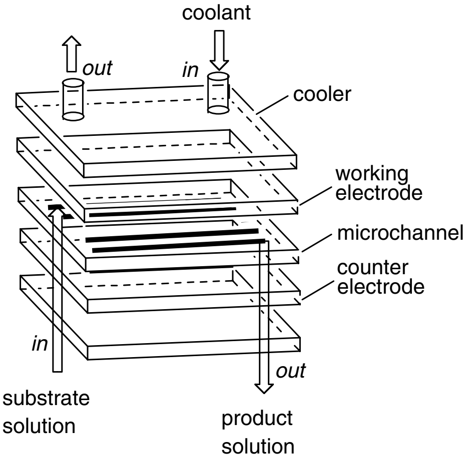


Figure 7.23 Electrochemical microflow reactor with a plate-to-plate electrode configuration

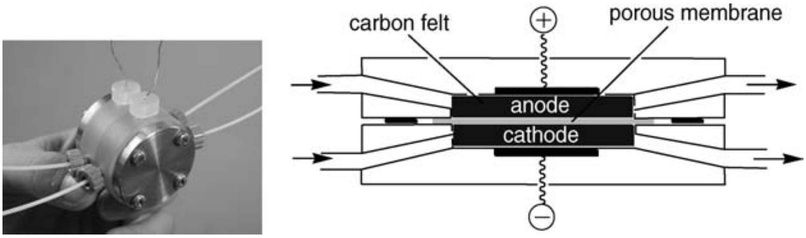


Figure 7.24 Electrochemical microflow reactor using a carbon felt electrode. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission

Various electrochemical organic reactions have been carried out using electrochemical microflow reactors.[28] Sometimes, electrolysis can be conducted without intentionally added supporting electrolyte by virtue of the extremely short distance between the anode and the cathode.[29]

7.3.8 Catalyst-containing Microflow Reactor

The high surface-to-volume ratio inherent in microspace is advantageous for catalyst loading. Therefore, many microflow reactors containing a catalyst bound to the surface of the wall have been developed. Early examples involve the loading of a palladium catalyst on the alumina surface of the channels fabricated on the aluminum platform.[30] Although there are many types of catalyst-containing microflow reactors, only a few types are discussed here.

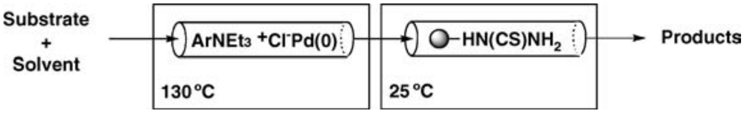


Figure 7.25 Catalytic reaction system based on a monolithic reactor cartridge derivatized with Pd(0) nanoparticles

Microflow reactors having a solid catalyst or a solid-supported catalyst packed in the microchannel are the most popular and are widely utilized for many reactions, including metal-catalyzed reactions and enzymatic reactions.[31] For example, a catalytic reaction system composed of a monolithic reactor cartridge derivatized with Pd(0) nanoparticles in-line with a scavenging cartridge to capture palladium residues has been developed (Figure 7.25).[32] A glass column is used as the reactor. It should be noted that the glass column is not micrometer size, although the size of the channels between the monolithic supported Pd nanoparticles should be important. This system has been successfully utilized for Mizoroki–Heck reactions of aryl iodides and activated alkenes.

Microreactors containing a solid-supported organic catalyst have also been developed. For example, solid-supported 1,5,7-triazabicyclo-[4.4.0] undec-3-ene is introduced to a microtube reactor (Figure 7.26).[33] This packed-bed microreactor has been used for Knoevenagel condensation

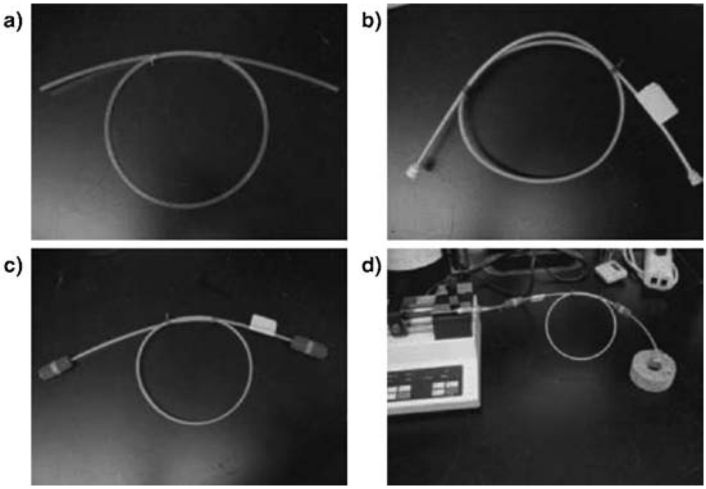


Figure 7.26 Assembly of a microreactor system: empty tubing (a) filled with AO resin (b) with filter caps (c), and attached to syringe pumps (d)[33]. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission

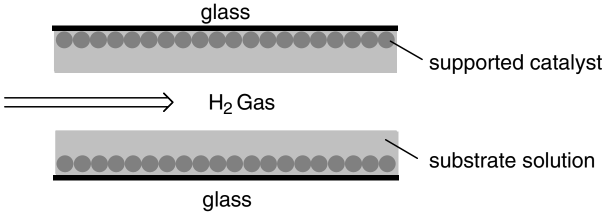


Figure 7.27 Microflow reactor containing supported catalyst

reactions. An HPLC column oven can be used to control the temperature of the reaction system.

A catalyst can be loaded on the surface of the channel wall of a glass microchip reactor. Such a microreactor has been used for gas/liquid/solid three-phase catalytic reactions, as shown in Figure 7.27.[34]

A microreactor in which a catalyst is installed as a membranous compsite at the center of the microchannel, has been developed.[35] The construction of this microreactor is based on the technique of polymer deposition at the laminar interface.[36] The palladium-complex membrane, poly(acrylamide)-triarylphosphine-palladium, is produced in the microchip reactor having a channel pattern of 100 μm width, 40 μm depth, and 140 mm length by charging an ethyl acetate solution of poly(arylamide) and a triarylphosphine and an aqueous solution of $(NH_4)_2PdCl_4$ using a Y junction (Figure 7.28). This catalyst-containing microreactor has been successfully used for Suzuki–Miyaura coupling reactions of aryl halides with arylboronic acids.

7.3.9 Microflow Reactors for High-pressure and High-temperature Conditions

High-pressure and high-temperature conditions are a simple but powerful way of activating organic compounds (see Chapter 5); and reactions in supercritical fluids have received significant research interest. Supercritical fluids, especially supercritical CO_2, have also attracted research interest from the viewpoint of the ease of product separation.

The microflow system for high-pressure and high-temperature conditions shown in Figure 7.29 has been developed.[37] In this system, substrates collide and mix rapidly with an aqueous solution at ambient temperature and high pressure (ca. 25 MPa). The resulting mixture is heated rapidly to the desired high temperature. This microflow system has been successfully used for copper-free Sonogashira coupling[38] in

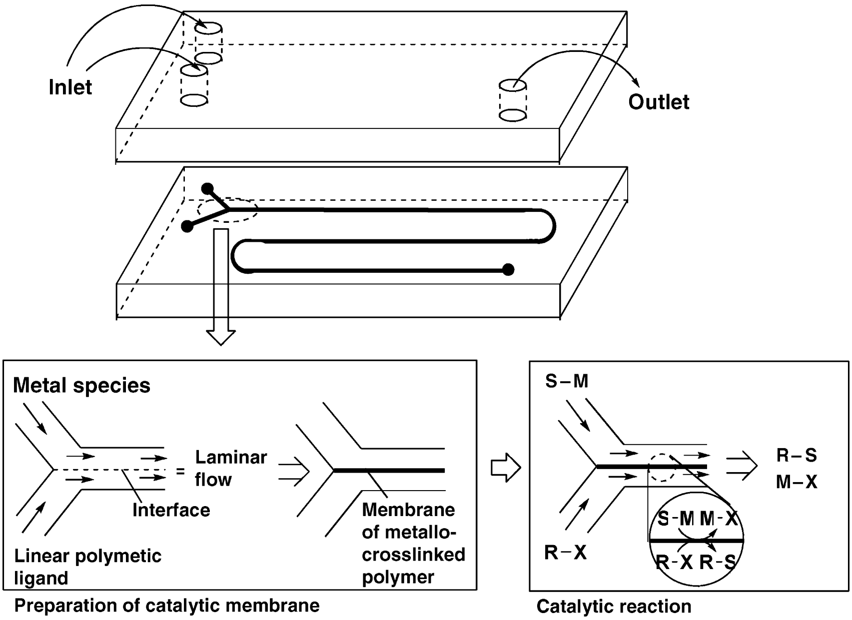


Figure 7.28 Microchip reactor with a catalytic membrane

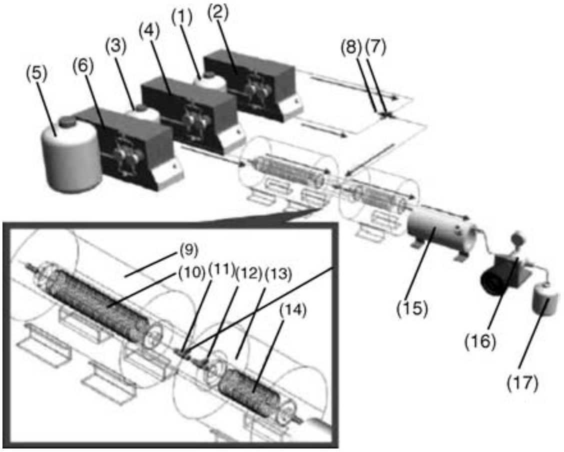
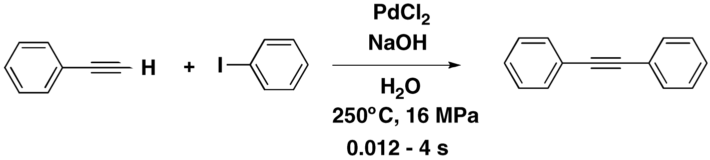


Figure 7.29 Diagram of the microflow system for Sonogashira coupling in high-pressure and high-temperature water. (1) Storage tank (substrates); (2), (4), (6) high-pressure liquid pumps; (3) storage tank (aqueous solution of $PdCl_2$ and NaOH); (5) storage tank (degassed distilled water); (7) micromixer; (8), (12) thermocouples; (9), (13) electric furnaces; (10) tubular coil; (11) micromixer (quick-heating part); (14) tube reactor; (15) cooler; (16) high-pressure regulator; (17) recovery tank.[37] Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission



Scheme 7.2 Copper-free Sonogashira coupling reaction in supercritical water

high-pressure and high-temperature water (Scheme 7.2). For example, the reaction of phenylacetylene with iodobenzene gave diphenylacetylene in nearly quantitative yield with a residence time of 0.1–4.0 s at 250 °C and 16 MPa in the presence of 2 mol% $PdCl_2$ as catalyst and NaOH as base.

Microflow systems for other high-pressure reactions have also been reported in the literature.[39]

7.4 CONCLUSIONS

As demonstrated in this chapter, a number of microfluidic devices of various structures and sizes for extremely fast mixing, heat exchanging and residence time control have been developed based on conventional and modern fabrication technologies. Microflow systems composed of such microfluidic devices are expected to serve as powerful tools for conducting extremely fast, highly exothermic reactions in a highly controlled manner to effect flash chemistry, where desired products are formed within milliseconds to seconds.

Examples of flash chemistry that take advantage of characteristic features of microflow systems will be demonstrated in the following chapters.

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8

Applications of Flash Chemistry in Organic Synthesis

There are many possibilities for flash chemistry in organic synthesis.[1–2] 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 accelerated significantly using microflow systems. Fast reactions may also cause selectivity problems and kinetically based product 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 microflow systems 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. There is another important point in flash chemistry, namely the control of highly reactive, short-lived reactive intermediates. 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 macrobatch reactors should become possible in flash chemistry using microflow systems. In this chapter, we discuss some examples of such applications of flash chemistry, although there are many other examples in the literature.

Flash Chemistry: Fast Organic Synthesis in Microsystems Jun-ichi Yoshida
ISBN: 978-0-470-03586-3

8.1 HIGHLY EXOTHERMIC REACTIONS THAT ARE DIFFICULT TO CONTROL IN MACROBATCH REACTORS

8.1.1 Fluorination

Reactions of elemental fluorine (F_2) with organic compounds are usually extremely fast and highly exothermic (ΔH is ca. -400 kJ/mol). The reaction is often explosive. Therefore, such reactions are difficult to control using conventional macrobatch reactors, although direct fluorination using F_2 is the most straightforward way to synthesize fluorine-containing organic compounds.[3,4] However, the use of a microflow system serves as an effective way to perform such reactions in a controlled manner. Pioneering work using microflow systems by Chambers and Spink was reported in 1999,[5] and since then direct fluorination using microflow systems has been studied extensively.[6] A microflow reactor composed of a block of nickel (or copper) having a microchannel covered with a block of polychlorotrifluoroethene, shown in Figure 8.1, is used. Reactants and solvent are injected via a syringe and syringe pump, while F_2 in N_2 is introduced directly from a small cylinder via a mass-flow controller. A liquid/gas mixture generates a *cylindrical flow* where the liquid forms an outer cylinder coating the reactor surface, while the gas

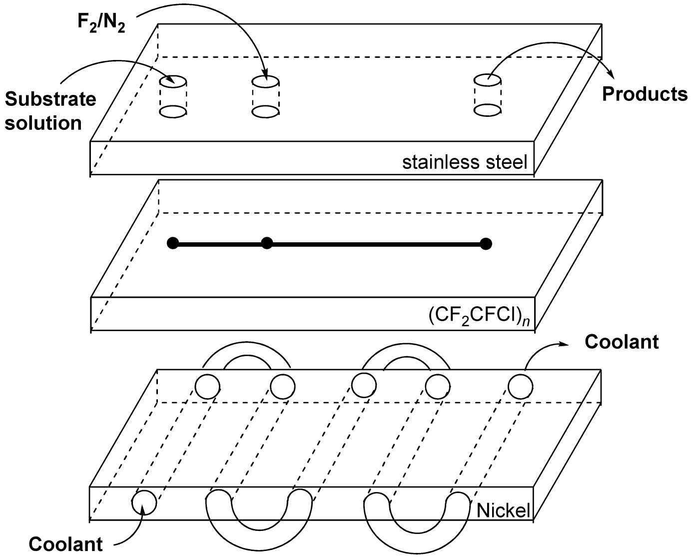
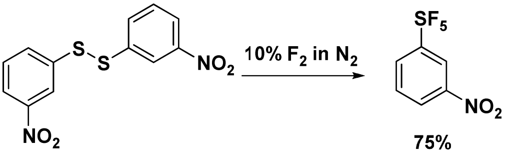


Figure 8.1 Microreactor for direct fluorination with F_2

flows through the center. The heat produced in the reaction is effectively removed through the cooling channels located below the reaction channel.

Using the microflow system, various selective fluorination reactions can be carried out. For example, fluorination of β-dicarbonyl compounds proceeds with high efficiency (Table 8.1). Fluorination of organosulfur compounds can also be carried out using microflow systems, as shown in Scheme 8.1.



Scheme 8.1 Fluorination reaction of di(*m*-nitrophenyl)disulfide

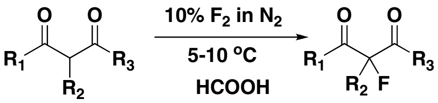
Direct fluorination of toluene, which is a highly exothermic process, can be conducted in a microflow system consisting of a microreactor built by silicon processing and metal deposition techniques in a safe and efficient manner.[7] Gas and liquid reagents are brought into contact concurrently at room temperature in the reactor. Both slug and annular-dry flows are obtained depending on liquid velocities relevant to gas/liquid reactions. During annular-dry flow operation, a combined selectivity of *o*-, *m*-, and *p*-fluorotoluenes of up to 24% has been obtained at toluene conversions of 58%. The highest selectivity toward ring fluorination has been obtained when acetonitrile was used as the solvent.

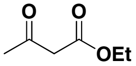
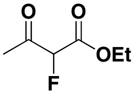
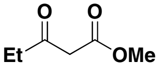
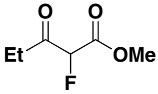
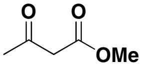
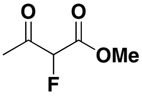
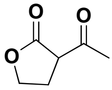
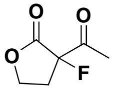
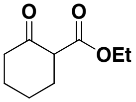
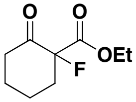
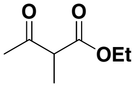
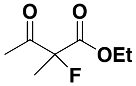
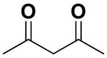
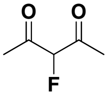
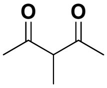
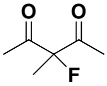
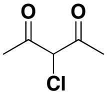
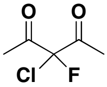
Falling-film gas/liquid microreactors, as shown in Figure 8.2, are also useful for direct fluorination of organic compounds, such as toluene with F_2 (Scheme 8.2).[8] In this reactor a liquid reactant falls down through the channels and the gas also falls down on to the surface of the liquid flow to attain a high gas/liquid surface-to-volume ratio to accelerate the gas/liquid reaction.

8.1.2 Chlorination and Bromination

Chlorination reactions are also highly exothermic and the use of microflow systems is quite effective for conducting the reaction in a controlled manner. Various chlorination reactions including chlorination of toluene derivative to obtain benzyl chlorides, chlorination of acetic acid to obtain chloroacetic acid, and radical chlorination of alkanes using microflow systems have been reported.[9]

Table 8.1 Directed fluorinations of various 1,3-ketoesters and 1,3-diketoesters in formic acid using a nine channel microflow reactor



1,3-Dicarbonyl	Major product	Conversion (%)	Yield (%)
		100	69
		100	68
		100	82
		100	83
		100	74
		92	49
		100	76
		100	91
		100	86

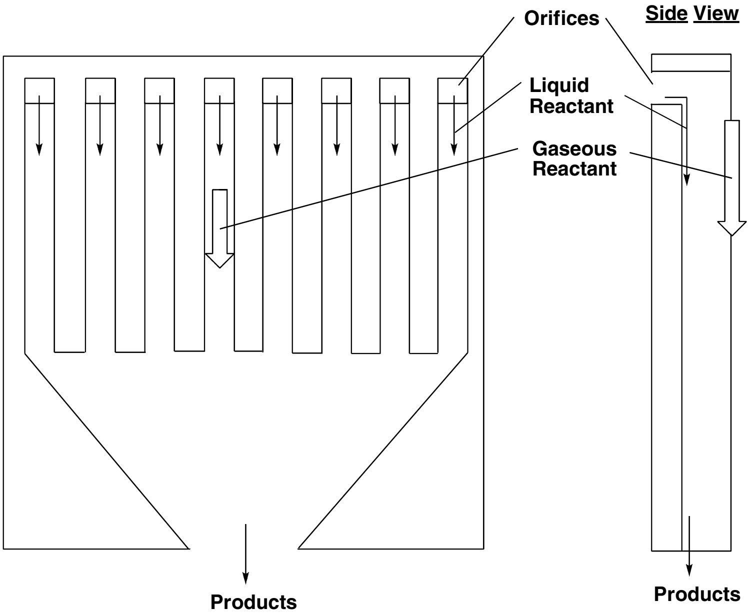
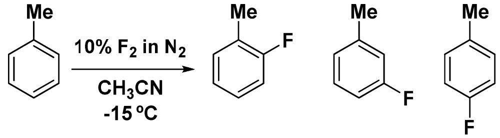


Figure 8.2 Principle of liquid and gaseous reactants in contact in a falling-film microflow reactor

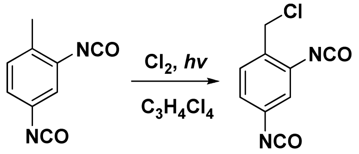
For example, thermally induced radical chlorination of alkanes can be conducted in a microtube reactor having microheat transfer modules.[10]

The photochemical chlorination of toluene-2,4-diisocyanate has also been reported (Scheme 8.3).[11] A falling-film microflow reactor is used with irradiation of gaseous chlorine, through a quartz window, enabling the *in situ* generation of chlorine radicals. The optimal residence time is 9 s at 130 °C, and benzyl chloride-2,4-diisocyanate is produced in 81.0% yield.

Bromination is also exothermic, and microflow systems serve as an excellent way to conduct these reactions. For example, the aromatic electrophilic substitution reaction of toluene and thiophene with Br_2 has been reported in the literature.



Scheme 8.2 Fluorination of toluene in a falling-film microflow reactor



Scheme 8.3 Photochemical chlorination of toluene-2,4-diisocyanate

8.1.3 Nitration

Nitration reactions are quite useful for the synthesis of nitrogen-containing compounds, such as pharmaceuticals, agricultural chemicals, and pigments. Most nitration reactions are very fast and extremely exothermic, and therefore are difficult to control in macrobatch reactors. It is also noteworthy that subsequent reactions lead to the formation of multinitration compounds, which are often explosive and dangerous to handle. Such a feature makes nitration reactions potentially extremely hazardous. A method for conducting nitration in a controlled manner is highly desirable, especially from an industrial point of view. The use of microflow systems for nitration reactions has been studied extensively. An early example involves nitration of benzene under two-phase conditions.[12] Good conversions were obtained for residence times of a few seconds. Better mass transfer in a microchannel seems to be responsible for the high efficiency. The importance of mass transfer is also supported for the plug flow system, in which an internal circulation flow takes place to give good mixing. This leads to effective suppression of subsequent polynitration.[13] It is also reported that the reaction of toluene with fuming HNO_3 in a silicon microflow reactor leads to selective formation of mononitrotoluene.[14] Mononitrotoluene was obtained in high yields with the residence time of a few seconds (Figure 8.3).

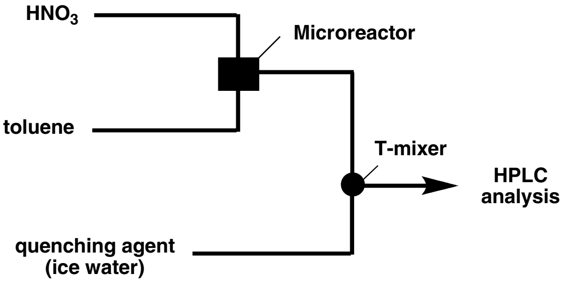


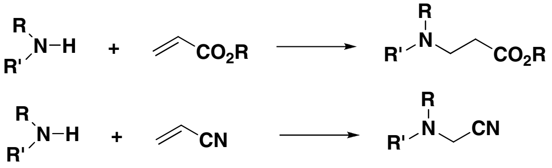
Figure 8.3 Microreaction process coupled with HPLC analysis for the nitration of toluene using fuming HNO_3

Autocatalytic nitration of phenol in a microflow system has been extensively studied.[15] Higher yields of nitrophenols were obtained when the nitration of phenol was performed in a microflow system presumably because of enhanced heat exchange and good mixing properties. Very rapid radical propagation in a confined volume also seems to be responsible. The nitration of heteroaromatic compounds, such as pyrazole and indole derivatives, as well as pyridine-*N*-oxide has also been conducted using a microflow system.[16]

The reactions shown above, and others,[17] indicate that electrophilic nitration of aromatic compounds serves as a good example of flash chemistry, and microflow systems will be widely utilized for conducting these types of violent and hazardous reactions under highly controlled conditions in industry in the future.

8.1.4 1,4-Addition Reactions of Amines

1,4-Addition reactions of amines to α,β-unsaturated carbonyl compounds and nitriles serve as a useful method for making a carbon–nitrogen bond. However, some of these reactions are highly exothermic and conventional macrobatch processes often require slow addition of an unsaturated compound to a dilute amine solution to ensure temperature control. Therefore, the reaction time is usually very long (17–25 h). The use of a microflow system that allows rapid mixing and heat removal leads to a much faster reaction in a controlled manner (Scheme 8.4).[18] The reaction time ranges from 1 min to 30 min. The space–time yields for the microflow system are much higher than those of conventional macrobatch systems, in the best case by a factor of about 650 (Table 8.2).

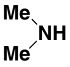
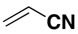
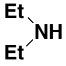
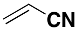
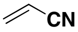
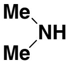
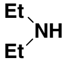


Scheme 8.4 1,4-Addition of amine

8.1.5 Halogen–magnesium Exchange Reactions

Although Grignard reagents are usually prepared by the reaction of organic halides with magnesium metal, halogen–magnesium exchange reactions are sometimes used for the generation of Grignard reagents that

Table 8.2 1,4-Addition of amine with α,β-unsaturated carbonyl compounds using a microflow system

Amine	α,β-Unsaturated carbonyl compounds	Yield (%)
		99
		99
		99
		98
		98
		99

are difficult to prepare by the direct method.[19] However, such reactions are often difficult to control in macrobatch reactors, especially on a large scale, because they are highly exothermic. Usually, slow addition has been used to avoid rapid temperature increase, and efficient heat removal has been a crucial point for industrial applications of halogen–magnesium exchange reactions.

The halogen–magnesium exchange reaction of ethylmagnesium bromide (EtMgBr) with bromopentafluorobenzene (BPFB) is well known and this reaction is used to produce pentafluorophenylmagnesium bromide (PFPMgBr) in industry.[20] The reaction is highly exothermic and slow addition is essential to avoid a rapid temperature increase.

The halogen–magnesium exchange reaction of BPFB and EtMgBr can be conducted in a microflow system composed of a T-shaped micromixer and microtube heat exchanger shown in Figure 8.4.[21] The formation of PFPMgBr can be easily confirmed by protonation with methanol to give pentafluorobenzene (PFB). As shown in Figure 8.5, using a microtube with an inner diameter of 250 μm, the yield did not vary significantly with the residence time, indicating that the mixing in the tube was very fast and that the reaction completed very rapidly. PFB is obtained in excellent yield

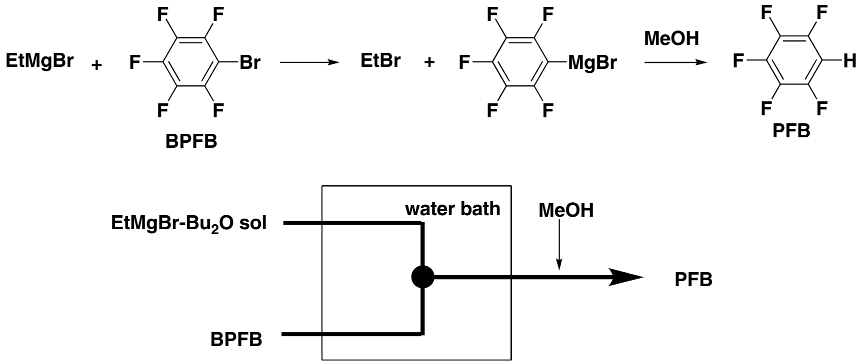


Figure 8.4 Microflow reaction system for the reaction of BPFB with EtMgBr

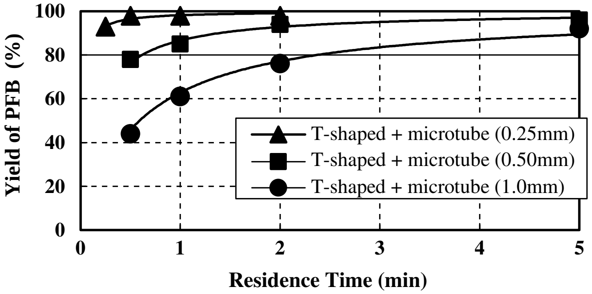


Figure 8.5 Effect of the diameter of the microtube reactor

within a residence time of 1 min. In contrast, using a microtube with an inner diameter of 1.0 mm, the yield increased gradually with an increase in the residence time, indicating lower efficiency of the mixing in a microtube of this size.

The halogen–magnesium exchange reaction between C_2F_5I and MeMgCl has also been carried out using a microflow reactor (Figure 8.6).[22] The reaction is complete at −6 °C within the residence time of 0.9 min with an excess amount of MeMgCl. The thus-formed 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.

8.1.6 Oxidation of an Alkene with H_2O_2/HCO_2H

Oxidation of alkenes with a peracid is an exothermic reaction and, to avoid explosion, the temperature should be maintained at levels that do

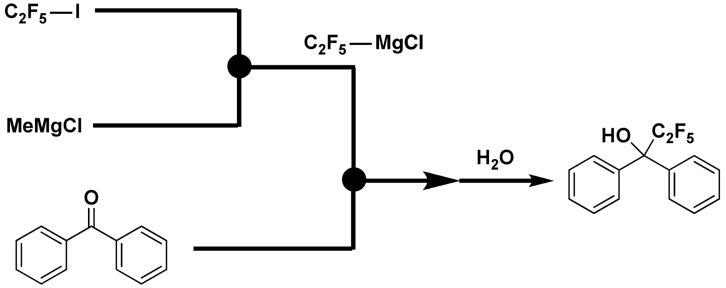
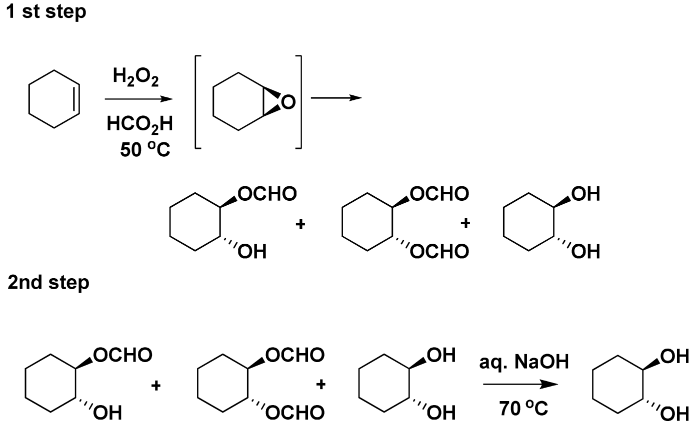


Figure 8.6 Grignard exchange reaction of C_2F_5I with MeMgCl followed by reaction with benzophenone in a microflow system

not cause decomposition of the peracid. For example, in the oxidation of cyclohexane, cyclohexane is added slowly from a dropping funnel to a mixture of H_2O_2 and HCO_2H to maintain the temperature of the reaction mixture between 40 °C and 45 °C in a macrobatch system (Scheme 8.5).[23] If the addition is fast, the temperature rises rapidly. In addition to slow addition, the use of a large amount of solvent is also essential to obtain good controllability. The use of a microflow system composed of a T-shaped micromixer and a microtube reactor is advantageous for this reaction.[24] The reaction can be carried out at a higher concentration of H_2O_2 with a residence time of 60 s. Subsequent hydrolysis can also be conducted in a microflow reactor, giving 1,2-cyclohexanediol as a colorless solid, while the marcrobatch process gives the same product as a brown solid. Milder reaction conditions seem to be responsible for the better purity of the product.



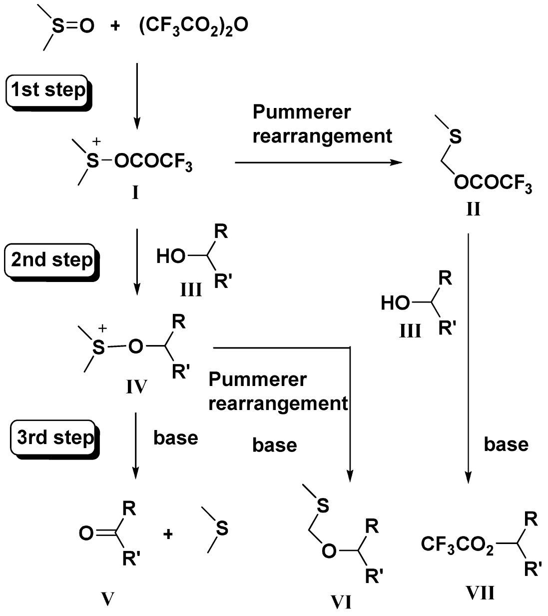
Scheme 8.5 Synthesis of *trans*-1,2-cyclohexanediol from cyclohexene

8.2 REACTIONS IN WHICH A REACTIVE INTERMEDIATE EASILY DECOMPOSES IN MACROBATCH REACTORS

Decomposition of a reactive intermediate is also a common problem in organic synthesis. This issue is important when a reactive intermediate should be generated in the absence of a substrate. In macrobatch 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. In such a case, a subsequent reaction using the intermediate cannot be performed. Therefore, the generation of reactive intermediates is usually carried out at very low temperatures to avoid undesired decomposition of the reactive intermediates. In flash chemistry using a microflow system, a reactive intermediate can be easily and rapidly transferred for use in a subsequent reaction, because the residence time can be reduced significantly. Therefore, such reactions can be carried out at much higher temperatures than those required for macrobatch processes. It is also expected that chemical conversions that are impossible in conventional macroreactors can be made possible using microflow reactors.

8.2.1 Swern–Moffatt Oxidation

Oxidation with dimethyl sulfoxide (DMSO), which is known as Swern–Moffatt oxidation, is one of the most versatile and reliable methods for the oxidation of alcohols to carbonyl compounds and is widely utilized in laboratory organic synthesis.[25] Avoidance of heavy metals such as Mn and Cr is also advantageous from an environmental point of view. Various methods for the activation of DMSO have been developed, and activation with trifluoroacetic anhydride (TFAA) is frequently employed in modern organic synthesis.[26] It is well known that a reactive species generated by the activation of DMSO undergoes an inevitable side reaction, the Pummerer rearrangement. Therefore, the reactions using conventional macrobatch reactors must be carried out at low temperatures (−50 °C or below), at which the side reaction is very slow. However, the requirement for such low temperatures causes severe limitations in the industrial use of this highly useful reaction. Recently, it was found that the reaction can be carried out at much higher temperatures, such as 0 °C and room temperature, by taking advantage of characteristic features of microflow systems.[27]



Scheme 8.6 Proposed mechanism for Swern–Moffatt oxidation using TFAA

A mechanism suggested for Swern–Moffatt oxidation with TFAA is shown in Scheme 8.6. In the first step, DMSO reacts with TFAA to form cationic reactive species **I**, which is known to be stable only below −30 °C.[28] At higher temperatures, rearrangement of **I** takes place to give species **II**. The reaction of **II** with an alcohol **III** upon treatment with a base leads to formation of a major by-product, trifluoroacetic acid (TFA) ester **VII**. Therefore, the first step should be carried out below −50 °C. In the second step, reactive species **I** is allowed to react with an alcohol **III** at or below −50 °C to obtain intermediate **IV**. **IV** may also undergo the Pummerer rearrangement to give a methyl thiomethyl (MTM) ether **VI** upon treatment with a base. In the third step, **IV** is treated with a base (usually triethylamine) to obtain the desired carbonyl compound **V** and dimethyl sulfide.

It is important to note that the first step and the second step are relatively fast. In a macrobatch system, however, it takes time (a minute or so) to complete the addition of a reagent or a substrate. During that time the reactive intermediate might decompose. In a microflow system, however, the reaction time can be greatly reduced to avoid decomposition of the unstable reactive intermediates. The concept of reactive intermediate control based on a short residence time, which we have already discussed in Chapter 6, can be applied in this case.

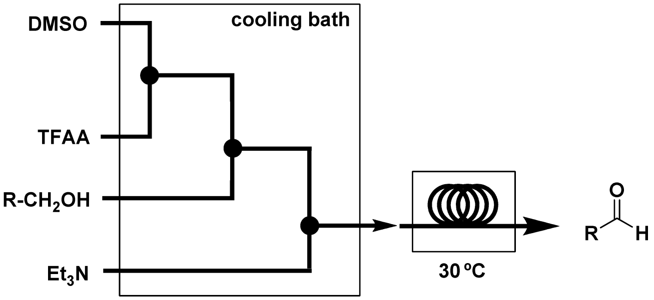


Figure 8.7 Microflow system for Swern–Mofatt oxidation

The reaction using a microflow system consisting of multilamination-type micromixers and stainless microtube reactors (Figure 8.7) has been conducted as follows: a solution of DMSO in CH_2Cl_2 and a solution of TFAA in CH_2Cl_2 are introduced to the first micromixer (M1) using a syringe-pumping technique. The resulting solution is passed through microtube reactor R1 and the solution thus obtained is mixed with a solution of an alcohol in the second micromixer (M2). The solution obtained by the reaction in microtube reactor R2 is mixed with a solution of triethylamine in the third micromixer (M3). The solution is then introduced to microtube reactors R3 and R4, where the proton elimination takes place to produce the corresponding carbonyl compound. The residence time in each reactor is as follows: R1, 0.01–2.4 s; R2, 1.2 s; R3, 1.2 s; R4, 5.9 s.

The oxidation of primary, secondary, cyclic, and benzylic alcohols takes place smoothly to give the corresponding carbonyl compounds in good yield and with good selectivity at −20 °C (residence time at R1: 2.4 s). However, the reactions with a conventional macrobatch reactor (a 30 ml glass flask with magnetic stirring) at the same temperature lead to the formation of significant amounts of trifluoroacetates and the yields of the carbonyl compounds are rather low. The dramatic effect of the microflow system seems to be ascribed to short residence times that enable fast transfer of the reactive species to the next reactor before decomposition. Precise temperature control (small local deviation of temperature in the reactor) and extremely fast and efficient mixing by virtue of a short diffusion path in the micromixer also play important roles. The results obtained with cyclohexanol are shown in Table 8.3.

Attempts to further increase the reaction temperature, however, leads to lower yields of the desired carbonyl compounds (32% for cyclohexanol at 0 °C). Presumably, Pummerer rearrangement of the reactive species **I** takes place to give **II** at this temperature within the residence time of 2.4 s. The

Table 8.3 Swern–Moffatt oxidation of cyclohexanol using a microflow system and a macrobatch system

Method	Residence time R1 (s)	Temperature (°C)	Conversion (%)	Selectivity of cyclohexanone (%)	Selectivity of MTM ether (VI) (%)	Selectivity of TFA ester (VII) (%)
Microflow	2.4	−20	88	88	6	5
	0.01	0	90	89	7	1
	0.01	20	81	88	5	2
Macrobatch		−20	86	19	2	70
		−70	88	83	10	5

problem can be solved by shortening the residence time at R1 to 0.01 s. In this case the desired carbonyl compound **V** was obtained in good yield even at 0 °C. More important is the fact that the reaction can be conducted even at room temperature (20 °C) to obtain **V** in good yield. The success of the Swern–Moffatt oxidation at room temperature seems to be attributable to the extremely short residence time, which ensures rapid transfer of the highly unstable reactive species **I** to the next reactor before it decomposes.

8.2.2 Organolithium Reactions

Organolithium compounds serve as useful carbanion equivalents in organic synthesis. Reactions of organolithium compounds with electrophiles, such as carbonyl compounds, are usually very fast and highly exothermic. Therefore, these reactions are sometimes especially difficult to control. It is important to note that slow addition of an organolithium compound to a solution of an electrophile is often necessary to maintain the controllability when the reaction is conducted on a large scale. Such slow addition leads to deceleration of the reaction. Another important issue is the stability of organolithium compounds. Organolithium compounds are often unstable at room temperature or higher temperatures. Therefore, they should be generated at very low temperatures. Although laboratory-scale reactions can be easily carried out at such low temperatures using a dry ice acetone bath, conducting industrial-scale batch reactions is problematic. The requirement of such low temperatures causes severe limitations in the industrial application of highly useful organolithium reactions.

In Chapter 6, we discussed highly reactive and unstable *o*-bromophenyllithium, which readily decomposes to benzyne.[29] Such decomposition of organolithium compounds can be avoided using a microflow system. Organolithium reactions can be carried out at much higher temperatures at higher rates in microflow systems. Therefore, flash chemistry serves as a powerful method for organolithium chemistry.

Aryllithium compounds that do not have a leaving group, such as bromine, at a β-position are much more stable. For example, *m*-methoxyphenyllithium can be generated in a macrobatch reactor at −78 °C on a laboratory scale, but this temperature is still problematic from an industrial point of view. However, the bromine–lithium exchange reaction of bromobenzene derivatives can be accomplished in a microflow reactor at 0 °C (Figure 8.8).[30] The mixing of 3-methoxybromobenzene with *n*-butyllithium leads to efficient generation of 3-methoxyphenyllithium within a residence time of 0.19 min. The organolithium compound thus formed is then allowed to react with an electrophile, such as dimethylformamide (DMF), in the flow system at 0 °C. The residence time is 0.15 min. The success of this two-step transformation at much higher temperatures than those required for the conventional batch processes should be attributed to fast heat exchange and efficient temperature control in the microflow system.

Bromine–lithium exchange reactions of *p*- and *m*-dibromobenzenes can be conducted in a microflow system at 20 °C,[31] which is much higher than that for *o*-dibromobenzene. The residence time ranges from 10^{-1} to 10^{1} s. The resulting aryllithium intermediates react with various electrophiles (E^1). The second bromine-exchange reaction can be conducted in one flow and the resulting aryllithium intermediates are

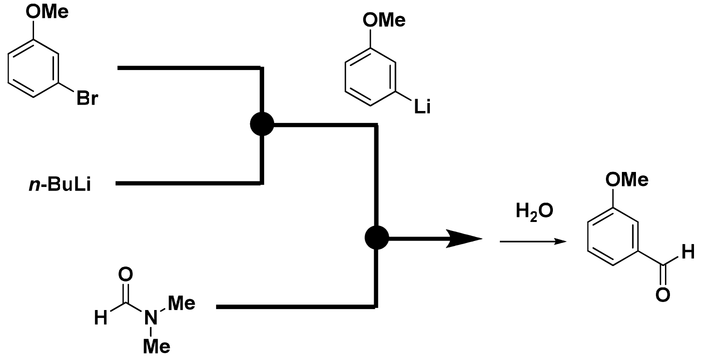


Figure 8.8 Bromine–lithium exchange reaction of 3-methoxybromobenzene followed by reaction with DMF

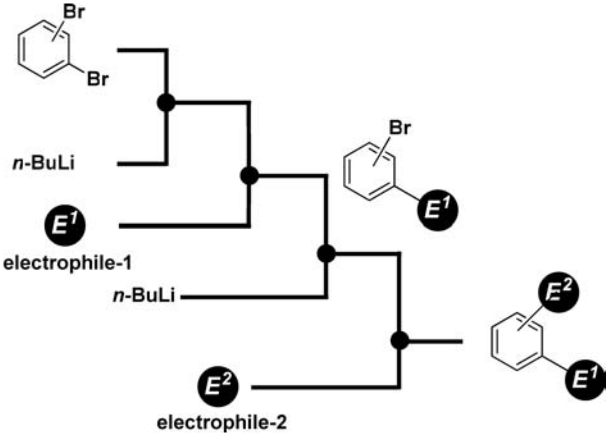


Figure 8.9 Microflow system for sequential introduction of two electrophiles into dibromobenzene

allowed to react with various electrophiles (E^2) to obtain the corresponding disubstituted benzenes using a microflow system consisting of four micromixers (M1, M2, M3, and M4) and four microtube reactors (R1, R2, R3, and R4) (Figures 8.9 and 8.10). This method provides a simple, straightforward, and quick way to introduce two electrophiles on a benzene ring.

The sequential introduction of two electrophiles into *o*-dibromobenzene has also been established using the microflow system. The first bromine–

Figure 8.10 Microflow system composed of four micromixers and four microtube reactors

lithium exchange reaction followed by reaction with an electrophile is carried out at −78 °C and the second bromine–lithium exchange reaction followed by reaction with an electrophile is carried out at 0 °C.

8.3 REACTIONS WITH PRODUCTS WHICH EASILY DECOMPOSE IN MACROBATCH REACTORS

Reactions with products which 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 microflow system provides a solution to this problem. In the nitration reactions discussed in the previous section, the product is still reactive under the reaction conditions. Therefore, overreaction to give polynitration, which may lead to an explosion, is also a problem. In this section, we discuss another example of this category.

8.3.1 Dehydration of an Allylic Alcohol to Give a Diene as an Unstable Product

Acid-catalyzed dehydration of allylic alcohols to give the corresponding conjugate dienes is well known. Figure 8.11 shows an example.[32]

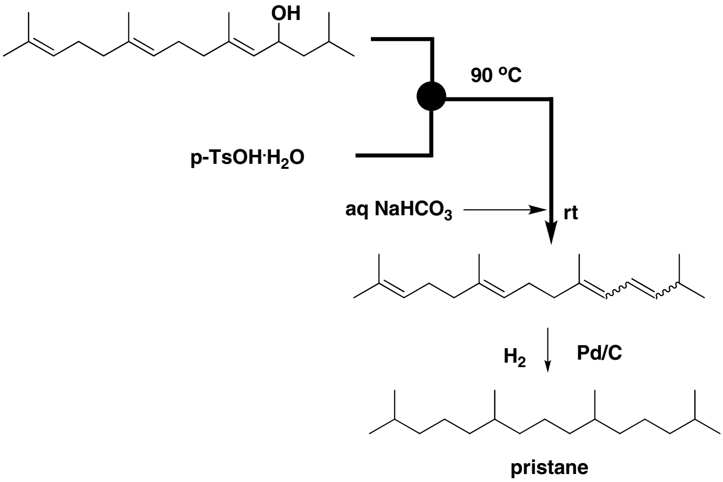


Figure 8.11 Acid-catalyzed dehydration of an allylic alcohol and its application in pristane synthesis

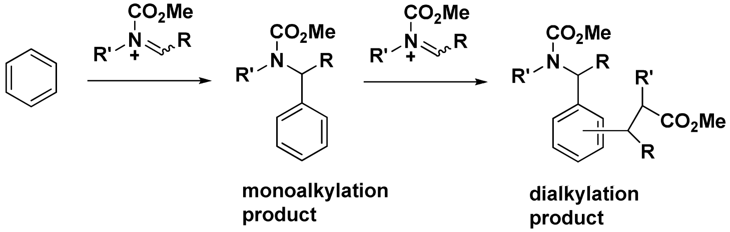
When the reaction was performed on a 100 mg scale, the diene was obtained in 55% yield as a mixture of (*E*)- and (*Z*)-stereoisomers. However, when the scale was increased to 100 g, various by-products, such as cyclized products or alkyl group-migrated compounds, were produced presumably because of acid-catalyzed reactions of the diene. The formation of such by-products can be reduced using a microflow system composed of a micromixer and a microtube reactor. Thus, a solution of the allylic alcohol in tetrahydrofuran (THF) was mixed with a solution of *p*-toluenesulfonic acid (*p*-TsOH) in THF/toluene at 90 °C. After the reaction mixture was allowed to flow for 47 s, the reaction was quenched with a saturated $NaHCO_3$ solution at room temperature. In this case the desired diene was obtained in 80% yield. It is noteworthy that the acid-mediated by-products were not detected. This process was applied to the synthesis of pristane, a biologically important natural product that is widely used as an adjuvant for monoclonal antibody production.

8.4 REACTIONS IN WHICH UNDESIRED BY-PRODUCTS ARE PRODUCED IN THE SUBSEQUENT REACTIONS IN MACROBATCH REACTORS

In cases where reactions give multiple products, product selectivity is an important issue from a synthetic point of view. Usually much effort is made to increase the amount of a desired product and to decrease the amounts of undesired products. We have already discussed competitive consecutive reactions and competitive parallel reactions in Chapter 6.

8.4.1 Friedel-Crafts Reactions[33]

In Chapter 6 we discussed the remarkable mixing effect of Friedel-Crafts reactions. Let us briefly review it and then discuss its application to various aromatic and heteroaromatic compounds (Scheme 8.7). Friedel-Crafts reaction of 1,3,5-trimethoxybenzene with a highly reactive electrochemically generated *N*-acyliminium ion pool using a conventional macrobatch reactor results in the formation of an essentially 1:1 mixture of the monoalkylation product and the dialkylation product. The reaction is very fast and is complete within 1 s even at −78 °C.



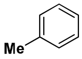
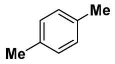
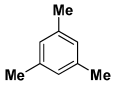
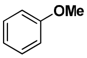
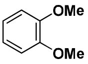
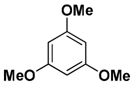
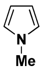
Scheme 8.7 Friedel-Crafts reaction of aromatic compounds with *N*-acyliminium ion pool

Therefore, the observed selectivity is the disguised chemical selectivity caused by an extremely fast reaction. The reaction using a microflow system, however, gives rise to a dramatic increase in the product selectivity. The monoalkylation product was obtained in excellent selectivity and the amount of dialkylation product was very small. In this case, a solution of the *N*-acyliminium ion and that of trimethoxybenzene are introduced to a multilamination-type micromixer at −78° C and the product solution leaving the device was immediately quenched with triethylamine in order to avoid the consecutive reactions. Extremely fast 1:1 mixing using the micromixer and efficient heat transfer in the microflow system seem to be responsible for the dramatic increase in the product selectivity.

Friedel-Crafts reactions with the *N*-acyliminium ion can be applied to other aromatic compounds and the observed product selectivities are summarized in Table 8.4. For less reactive aromatic compounds, such as toluene, *p*-xylene, and 1,3,5-trimethylbenezene, the monoalkylation products are selectively obtained even in a macrobatch reactor with magnetic stirring. However, a dramatic effect of micromixing is generally observed for the alkylation of highly reactive aromatic compounds, such as methoxybenezene, 1,2-dimethoxybenzene, and 1,3,5-trimethoxybenzene. The selectivity observed for a macrobatch reactor seems to be disguised chemical selectivity. Use of a microflow system solved the problem, and the monoalkylation product was obtained in high selectivity.

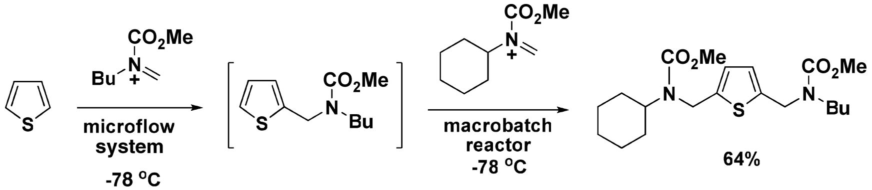
The outcome of the reaction with heteroaromatic compounds is also affected by the manner of mixing. For example, the reaction with thiophene using a microflow system took place smoothly to give the monoalkylation product exclusively, while the reaction in a macrobatch reactor gave a significant amount of the dialkylation product. A similar tendency was also observed for the reaction of furan and *N*-methylpyrrole. These results indicate that the reactions with such heteroaromatic compounds also suffer from the problem of disguised chemical selectivity

Table 8.4 Reaction of *N*-acyliminium ion pool with various aromatic and heteroaromatic compounds

Aromatic compound	Nucleophilicity parameter	Method	Temperature (°C)	% Yield of monoalkylation product	% Yield of dialkylation product
	−4.47	macrobatch	0	62	0
	−4.18	macrobatch	0	67	0
		macrobatch	−78	69	0
	−1.18	macrobatch	−78	24	31
		microflow	−78	26	0
		macrobatch	−78	13	14
		microflow	−78	34	0
	3.40	macrobatch	−78	37	32
		microflow	−78	92	4
	−0.40	macrobatch	−78	14	27
		microflow	−78	84	0
	1.45	macrobatch	−78	11	5
		microflow	−78	39	trace
	6.18	macrobatch	−78	33	28
		microflow	−78	60	6

in macrobatch reactions and that the problem could be solved by micromixing.

It should be noted here that the nucleophilicity parameters reported by Mayr[34] serve as good indicators. Compounds having a nucleophilicity number higher than ca. −1 suffer from the problem of disguised chemical



Scheme 8.8 Sequential alkylation of thiophene with two different *N*-acyliminium ions

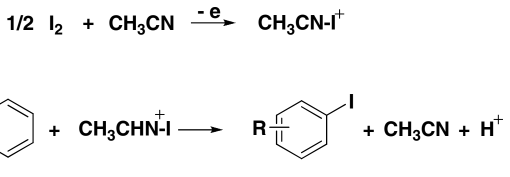
selectivity. In such cases, the reaction seems to be faster than mixing in a macrobatch reactor, and a microflow system consisting of a micromixer solvesthe problem.

The use of a microflow system enables sequential alkylation reactions with two different *N*-acyliminium ions as alkylating agents (Scheme 8.8). The first alkylation of thiophene was carried out using a microflow system to obtain the monoalkylation product, which was directly subjected to the second alkylation with a different *N*-acyliminium ion to obtain the dialkylation product. In the second alkylation, the use of a microflow system is not necessary because the third alkylation seems to be very slow at −78 °C.

8.4.2 Iodination of Aromatic Compounds

Aromatic iodides are important intermediates in the synthesis of functional materials and biologically active compounds.[35] Although various methods for the synthesis of aromatic iodides have been developed,[36] direct iodination of aromatic rings serves as one of the most straightforward routes.[37]

The electrochemically generated 'I$^+$' serves as a powerful iodinating reagent for direct iodination of aromatic compounds. Miller and co-workers reported that the electrochemical oxidation of iodine (I_2) in acetonitrile gives CH_3CNI^+ (equivalent of I^+) (Scheme 8.9) and that this



Scheme 8.9 Iodination of aromatic compounds using 'I$^+$' electrochemically generated in acetonitrile

reagent reacts with aromatic compounds to give the corresponding iodinated aromatic compounds, although CH_3CNI^+ was not well characterized spectroscopically.[38]

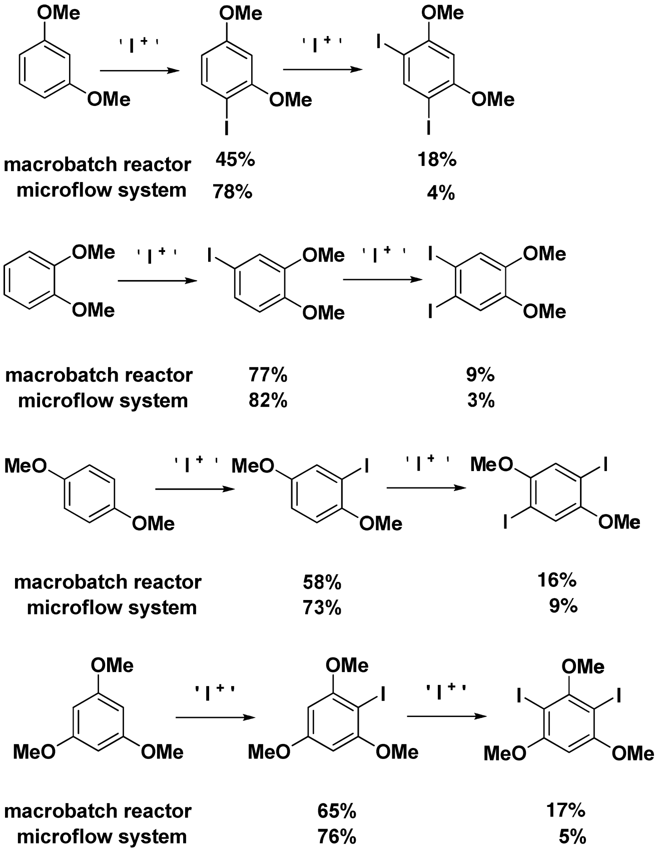
Direct iodination of aromatic compounds using this highly reactive iodinating reagent, however, suffers from a diiodination problem, because the reaction is very fast. Even if 1 equiv of iodinating reagent is used, diiodination takes places in the case of highly reactive aromatic compounds in a macrobatch reactor. For example, the reaction of 1,3-dimethoxybenzene with the electrochemically generated I^+ (theoretically 1.35 equiv based on 1,3-dimethoxybenzene) using a macrobatch reactor at 0 °C gives rise to the formation of the monoiodo compound as a major product (45% yield) with a significant amount of the diiodo compound (18% yield). The monoiodo compound should be less reactive than the parent compound because the iodo group is an electron-withdrawing deactivating group. Therefore, the formation of the diiodo compound can be ascribed to disguised chemical selectivity because reaction is faster than mixing.

The use of a microflow system composed of a micromixer and a microtube reactor solves the diiodination problem, as shown in Scheme 8.10.[39] The yield of monoiodo compound is 78%, whereas the yield of the diiodo compound is 4%. A significant increase in the product selectivity can also be accomplished for other highly reactive aromatic compounds.

The effect of micromixing in the iodination reaction is smaller than that observed for the Friedel-Crafts alkylation using *N*-acyliminium ions. The smaller effect seems to be ascribed to the smaller rate of iodination, because computational fluid dynamics simulation indicated that the effect of the micromixing on the product selectivity of a competitive consecutive reaction increases with an increase in the reaction rate. Therefore, the electrochemically generated 'I^+' seems to be less reactive than the *N*-acyliminium ions.

8.4.3 Reaction of Phenylmagnesium Bromide with Boronic Acid Trimethyl Ester

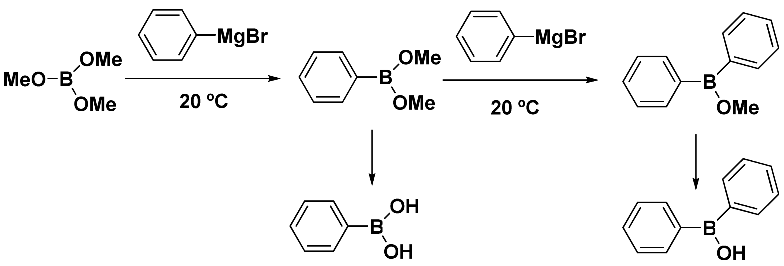
Aryl and alkyl boron compounds have received significant research attention as building blocks in organic synthesis. One of the most straightforward methods for making such compounds is the reaction of a boronic acid ester with a Grignard reagent. However, the reaction



Scheme 8.10 Product selectivity of iodination of aromatic compounds with electrochemically generated 'I^+'

suffers from the problem of multisubstitution. Even if only 1 equiv of a Grignard reagent is used, multisubstituted compounds are often produced in significant amounts in a laboratory-scale marcrobatch reactor. The first reaction should be faster than the subsequent reactions, because the introduction of an organic group on boron deactivates the compound. Therefore, the formation of multisubstitution products seems to be attributed to disguised chemical selectivity because reaction is faster than mixing. In fact, the use of a microflow system composed of a micromixer gives rise to a significant increase in the product selectivity, as shown in Table 8.5.[40] It is also noteworthy that slow addition, which is essential for the macrobatch process to keep control of the reaction, is not necessary in the microflow system. The residence time in the microflow system is 5 s.

Table 8.5 Product selectivity of the reaction of phenylmagnesium bromide with boronic acid trimethyl ester



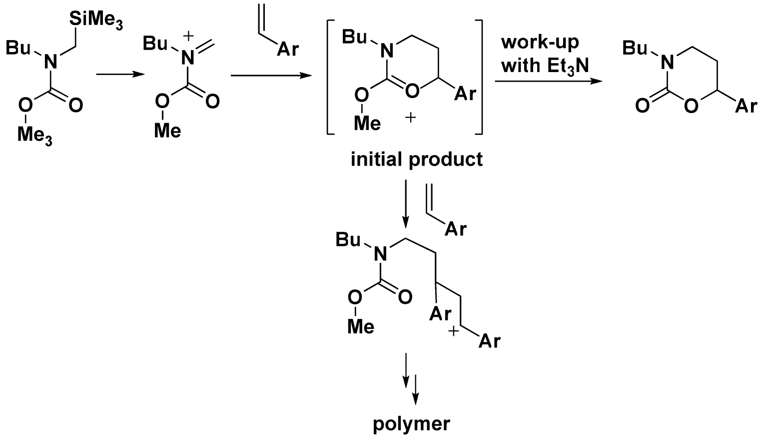
	Reaction time		
laboratory scale macrobatch reactor	22 min	85.1%	13.8%
microflow system	5 s	98.9%	0.6%

8.4.4 [4 + 2] Cycloaddition Reaction of *N*-acyliminium Ion with Olefin[41]

N-Acyliminium ions are versatile intermediates in organic synthesis; they not only react with various nucleophiles such as electron-rich aromatic and heteroaromatic compounds but also undergo cycloaddition reactions with unsaturated compounds.[42] It is especially noteworthy that *N*-acyliminium ions serve as electron-deficient 4π components in [4 + 2] cycloaddition with alkenes and alkynes.[43] This reaction serves as a useful method for the construction of heterocyclic rings containing a nitrogen atom. Acyclic structures containing amino and hydroxyl groups can also be synthesized from the initially formed cyclic compounds.

The reactions with alkyl-substituted alkenes proceed to give the cycloadducts in good yields. Presumably, the cyclic cationic compound is formed as an initial product, which then undergoes the Me-O cleavage reaction upon treatment with triethylamine during the work-up to give the neutral compound as the final product (Scheme 8.11).

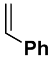
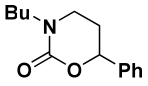
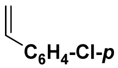
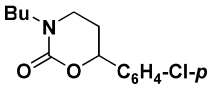
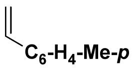
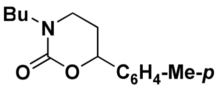
However, the reaction with styrene gives rise to the formation of a significant amount of polymeric by-products. The cationic compound seems to react with another molecule of styrene, and further reactions eventually give rise to the formation of the polymer. This is also assigned to a problem of competitive consecutive fast reactions. In fact, the yield of the cycloadduct strongly depends on the method of mixing, as shown in Table 8.6. Although the addition of styrene to a solution of the



Scheme 8.11 [4 + 2] Cycloaddition using *N*-acyliminium ion with olefins

N-acyliminium ion (method A) gives the cycloadduct in 57% yield, the addition of a solution of the *N*-acyliminium ion to styrene (method B) gives the cycloadduct in only 20% yield and a significant amount of the polymeric product (ca. 80% based on styrene) is formed, presumably because of the higher initial concentration of styrene. The simultaneous addition of two reaction components (method C) gives essentially the same results as method A.

Table 8.6 Mixing effect of the reaction of *N*-acyliminium ion with styrene derivatives

Alkene	Cycloadduct	% yield			
		Method A	Method B	Method C	Microflow system
		57	20	55	79
		43	12	54	70
		45	16	58	66

However, the use of a microflow system composed of a multilamination micromixer and a microtube reactor gives rise to a significant increase in the yield of the cycloadduct (79%) at the expense of the amount of the polymer (ca. 20% based on styrene). The fast and efficient 1:1 mixing by a micromixer seems to be responsible. The extremely fast mixing might cause the cationic product to be formed at a very low concentration of styrene, which leads to the effective formation of the neutral cycloadduct. Similar mixing effects have also been observed for *p*-chloro- and *p*-methylstyrenes.

Many organic reactions suffer from the formation of significant amounts of polymeric by-products. Faster reactions than mixing might be responsible in many cases. To avoid such undesirable side reactions, slow addition and high dilution techniques are often used. The examples shown here, however, indicate that such reactions can be conducted much more easily and selectively using a microflow system without deceleration by slow addition or high dilution conditions.

8.4.5 Biphasic Azo-coupling Reactions

Azo-coupling reactions of aromatic compounds with arene diazonium salts, which are usually very fast, have been successfully carried out in

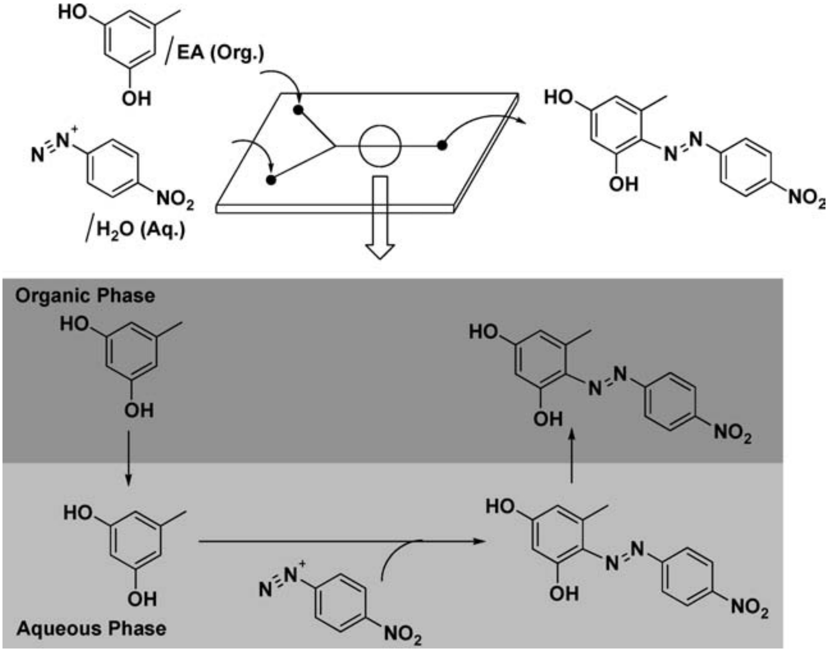


Figure 8.12 Phase transfer diazo-coupling reaction in a microflow system

microflow systems in a controlled manner.[45–49] For example, a two-phase reaction of 5-methylresorcinol with 4-nitrobenzene diazonium tetrafluoroborate took place within a few seconds to give the corresponding azo-coupling product. In this case, undesirable reaction of the product with a second diazonium salt to give the bisazo product did not appreciably occur. It is interesting to note that fast removal of the desired monodiazo product from the aqueous phase to the organic phase by virtue of the large specific interfacial area and short diffusion path in the microchannel seems to be responsible for the observed high selectivity (Figure 8.12).

8.5 REACTIONS THAT CAN BE ACCELERATED USING MICROFLOW SYSTEMS

In this section, we discuss the cases where the use of microflow reactors allows us to conduct reactions under unconventional conditions, such as high temperatures, which significantly accelerate the rates of the reactions. In the macrobatch processes, however, the use of such reaction conditions may cause undesirable side reactions, such as the decomposition or subsequent reactions of products. Precise temperature control and short residence time, which minimize the consecutive side reactions, are responsible for successful reactions in microflow systems.

8.5.1 Acceleration of Reactions at High Temperatures

Amide bond formation, which is an important reaction in organic synthesis and peptide synthesis, has been achieved in a microflow system.[44] As shown in Figure 8.13, the reaction of an acid fluoride and an amine, which are derived from the corresponding amino acids, in the presence of *N*-methylmorpholine has been carried out at several temperatures. The reaction was complete in 3 min at 90 °C, and the yield of the dipeptide was excellent.[45] Reaction at higher temperatures and/or for a prolonged period leads to a decrease in the yield of the dipeptide and an increase in the yield of the tripeptide. Residence-time control in a microflow system is quite effective in reducing the amount of undesired tripeptide by-products. Some other examples, which are combined with fluorous tag technology,[46] are shown in Scheme 8.12. In the first case, the reaction was complete in 3 min at 90 °C, whereas the corresponding conventional

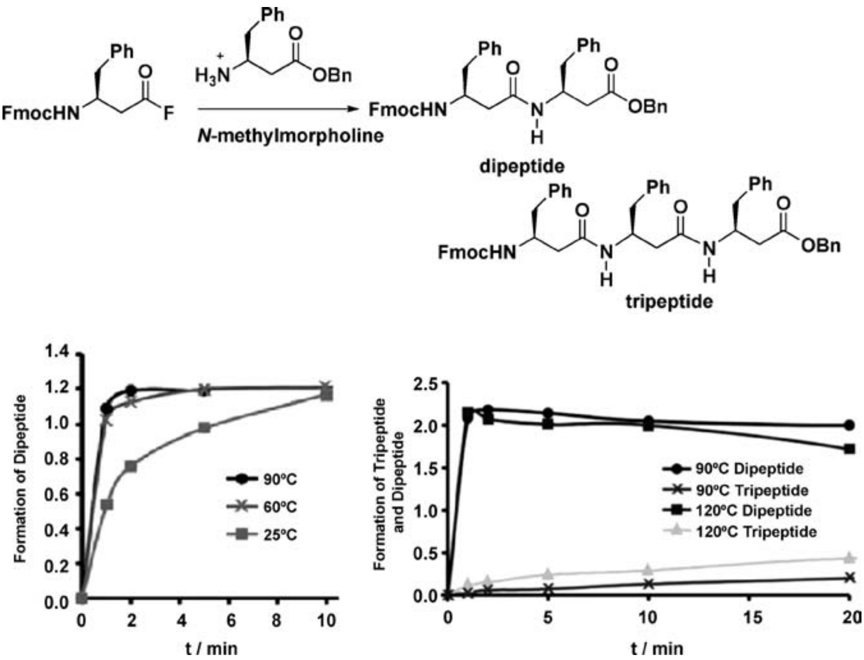
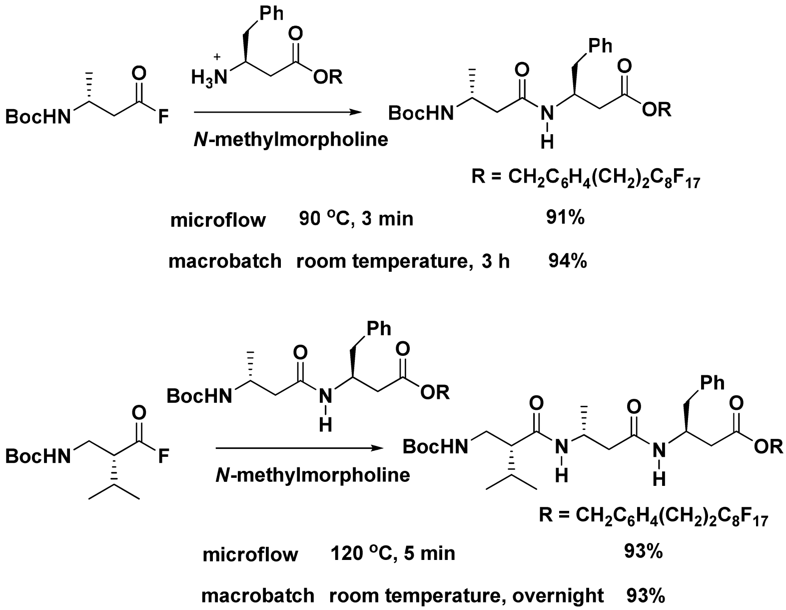


Figure 8.13 Synthesis of dipeptides in a microflow system. Effect of temperature and residence time. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission



Scheme 8.12 Synthesis of peptides using a microflow system at high temperatures

solution phase synthesis using a macrobatch reactor took 3 h at room temperature to obtain a similar yield. In the second example, the reaction was carried out at 120 °C and finished very quickly. These examples demonstrate that microflow systems allow us to conduct reactions at unconventionally high temperatures in a controlled manner as a consequence of the short residence time.

8.5.2 Acceleration of Radical Reactions Using Quickly Decomposing Radical Initiators

Free-radical chain reactions serve as a powerful method for the construction of carbon frameworks. Because the lifetimes of carbon radical intermediates are usually very short, the reactions take place very quickly. Microflow systems are advantageous for acceleration of such reactions. For example, tributyltin hydride-mediated radical reactions of organic halides to form the corresponding cyclized products have been successfully conducted in a microflow system (Figure 8.14).[47] The reaction time could be significantly reduced using quickly decomposing radical initiators such as V-70 instead of AIBN, which is frequently used as a radical initiator in organic synthesis. In this case, reaction is complete within 1 min. The 10 h half-life decomposition temperature of V-70 is 30 °C, whereas that of AIBN is 65 °C. Using this reaction, a key intermediate of furofuran lignin synthesis has been produced on a gram scale.

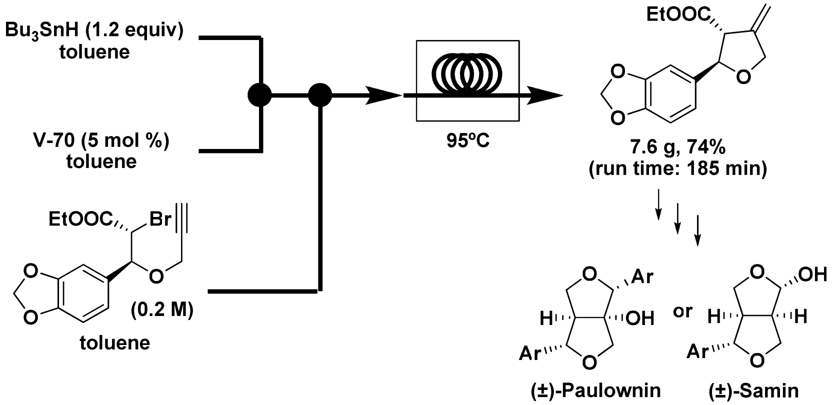


Figure 8.14 Free-radical cyclization reaction in a microflow system

8.5.3 Acceleration by Controlled Mass Transfer

An interesting method for achieving reactions at an unconventionally fast rate has been developed based on controlled mass transfer in a microchannel. Suzuki–Miyaura coupling of aryl iodides and arylboronic acids in a microchannel bearing a membrane containing a Pd catalyst proceeds very quickly (Figure 8.15).[48] A solution of an aryl iodide in EtOAc/2-PrOH and an aqueous solution of an arylboronic acid with Na_2CO_3 are introduced to the microchannels at 50 °C. The reaction is complete with a residence time of 4 s, which is much shorter than that for conventional batch reactors. The controlled mass transfer through the catalyst-containing membrane, which should be very fast by virtue of the short diffusion path and high surface-to-volume ratio of the microflow system, seems to be responsible for the acceleration of the catlalytic reaction. The corresponding biaryls have been obtained in 88–99% yield.

Suzuki–Miyaura coupling can be conducted under electro-osmotic flow (EOF) conditions.[49] In this case, the Pd catalyst is immobilized in the channel (Figure 8.16). The injection of 4-bromobenzonitrile for 5 s with a 25 s injection interval into a continuous stream of phenyl boronic acid gives 4-cyanobiphenyl in 67% yield.

Microwave irradiation assists the reaction. For this purpose, a glass chip microreactor equipped with a 10–15 nm gold film patch located on the outside surface of the bottom plate is used.[50]

Suzuki–Miyaura coupling has also been conducted in a capillary reactor (400 μm inner diameter).[51] A commercial-scale continuous flow system consisting of a 14.5 cm × 25.4 mm column packed with Pd catalyst has also been developed.[52] In this case, supercritical carbon dioxide is used as a reaction medium.

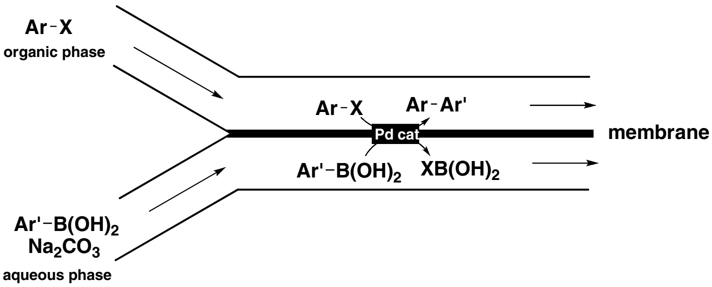


Figure 8.15 Suzuki–Miyaura coupling in a microflow system having a membrane containing a Pd catalyst

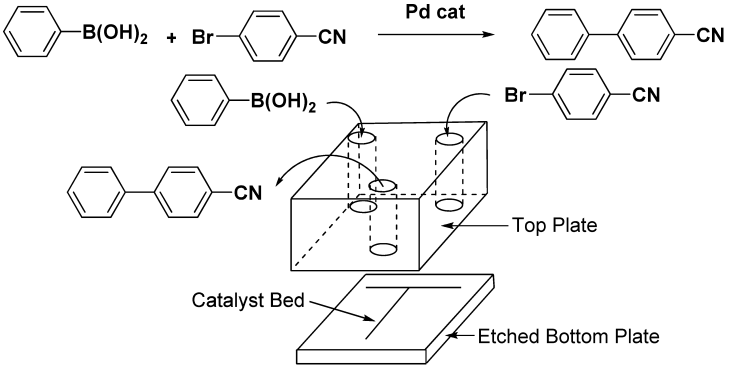


Figure 8.16 Schematic diagram of a microchip reactor for Suzuki–Miyaura coupling

8.5.4 Acceleration by Microwaves

As discussed in Chapter 5, microwave irradiation serves as a method for accelerating organic reactions. For example, Suzuki–Miyaura coupling reactions, ring-closing metathesis reactions, nucleophilic aromatic substitution reactions, and Wittig reactions have been carried out in the microflow system shown in Figure 8.17 with microwave irradiation.[53] Glass capillary tubes of varying internal diameters (200–1150 μm) were used. Good yields were obtained with a residence time of several minutes. This reaction system can be applied for other nucleophiles, such as amines (Scheme 8.13).

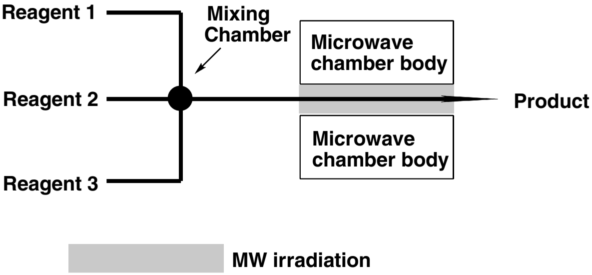
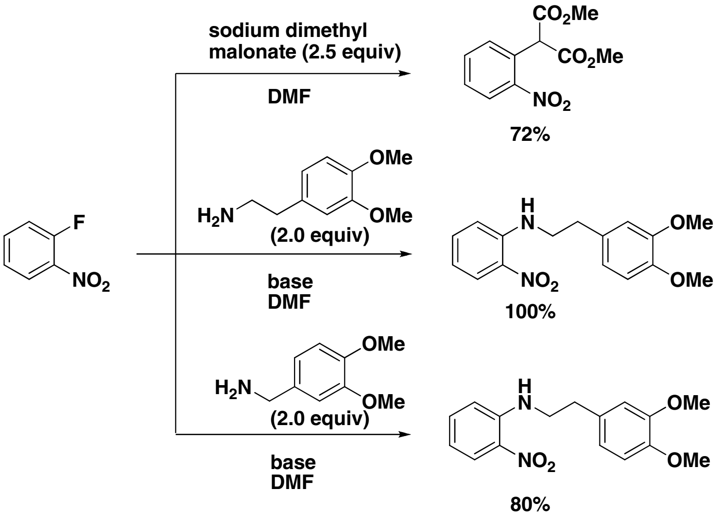


Figure 8.17 Microflow system for a microwave-assisted reaction

8.5.5 Acceleration by High-pressure and High-temperature Conditions

High-pressure and high-temperature conditions are effective for flash chemistry. It has been reported that copper-free Sonogashira coupling



Scheme 8.13 Nucleophilic aromatic substitution reactions using a microflow system with microwave irradiation

reactions can be conducted in a microflow system in high-pressure, high-temperature water.[54] For example, phenylacetylene reacts with iodobenzene to give diphenylacetylene in nearly quantitative yield in the presence of $PdCl_2$ and NaOH (Figure 8.18 and Scheme 8.14). In the first step, organic substrates are mixed with an ambient aqueous solution at a high pressure of around 25 MPa. The resulting mixture containing

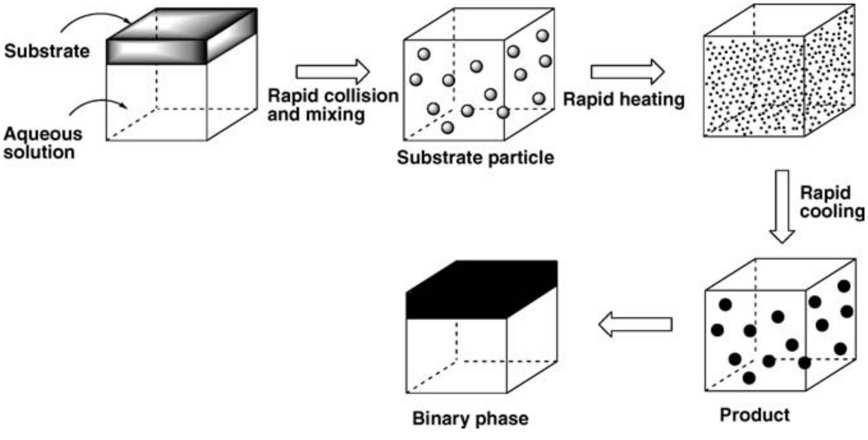
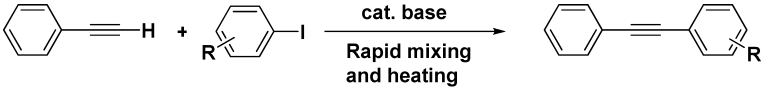


Figure 8.18 Schematic illustration of an organic reaction in high-pressure, high-temperature water



Scheme 8.14 Sonogashira coupling in high-pressure, high-temperature water

substrate particles (nm–µm size) is heated rapidly to 250 °C. Rapid cooling of the reaction mixture gives a biphasic mixture containing the desired product. The reaction time ranges from 0.1 to 4 s. It is also noteworthy that the reaction does not require organic solvents. Sonogashira coupling has also been carried out successfully in a microflow system using an ionic liquid as a reaction medium.[55]

8.6 CONCLUSIONS

There are many examples of flash chemistry in organic synthesis using various methods for acceleration. Because of space limitations, our discussion in this chapter is not an exhaustive compilation of all known examples. Rather, it is a sampling of sufficient variety to illustrate the principles, features, and advantages. These examples speak well for the future possibilities of flash chemistry in organic synthesis, not only from an academic point of view, but also from the viewpoint of industrial production.

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9

Polymer Synthesis Based on Flash Chemistry

9.1 POLYMERIZATION

Polymers cover a large class of natural and synthetic materials with a variety of properties and purposes. Nowadays, synthetic polymers are considered to be indispensable materials. We use synthetic polymers, such as polyethylene, polystyrene, poly(vinyl chloride), polycarbonate, polyamides, polyesters, and silicones, in nearly every area of industry and daily life. Natural polymers, such as rubber and cellulose, have also been widely used for centuries.

Polymers are usually made up of many small molecules all joined together by covalent bonds to form long chains, as proposed by Staudinger in the 1920s. Indeed, *poly-* means 'many' and *-mer* means 'part' or 'segment'. Small molecules that can join together to make a long polymer chain are called monomers (*mono* meaning 'one'). The process by which monomer molecules bond together to form polymers is called polymerization (Scheme 9.1).

Polymers that consist of repeated long chain structures of the same monomer units are called homopolymers, whereas polymers consisting of different monomers are referred to as copolymers. Polymerization to make copolymers is called copolymerization. There are several types of copolymers, such as random copolymers with random sequences of

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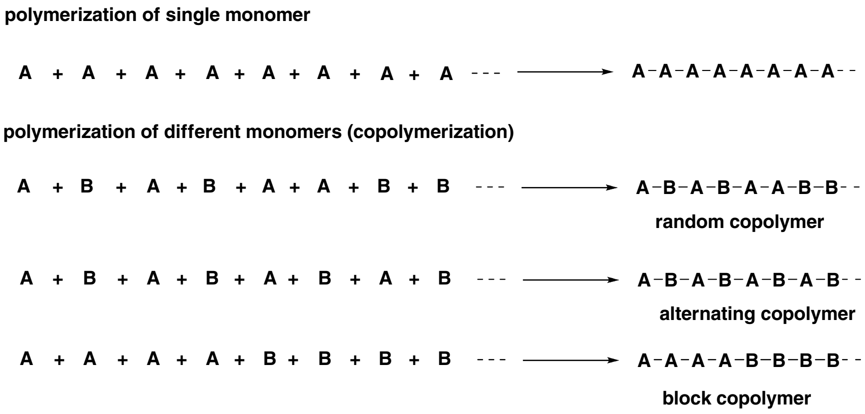
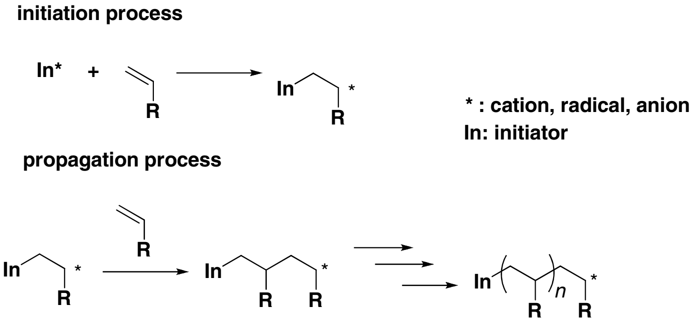


Scheme 9.1 Polymerization and copolymerization

monomers A and B, alternating copolymers with regular alternating A and B, and block copolymers composed of two homopolymer subunits. Copolymers composed of more than two monomers are also synthesized and used. Block copolymers composed of two or more monomers have attracted significant research interest because they can form nanostructures with different physical properties. The living polymerization technique (see below) serves as a powerful method for making such block copolymers.

9.2 CHAIN-GROWTH POLYMERIZATION AND STEP-GROWTH POLYMERIZATION

There are two ways in which monomers combine with one another to form polymer chains, namely, chain-growth polymerization and step-growth polymerization. Chain-growth polymerization involves an initiation process, a propagation process, and a termination process (Scheme 9.2). The initiation process involves the reaction of an active initiator with a monomer to give an active polymer of low molecular weight. The propagation step involves the reaction of an active polymer end with a monomer to give another active polymer of higher molecular weight. The polymer chains grow to high molecular weight rapidly until a termination reaction occurs to kill the active site. The rate of the chain-growth process is usually very high, because the active polymer chain end is usually highly reactive. Propagation processes are usually exothermic because new chemical bonds such as carbon–carbon bonds

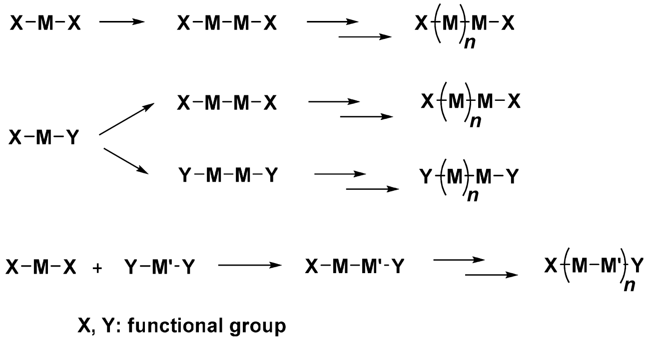


Scheme 9.2 Initiation and propagation processes of chain-growth polymerization (addition polymerization of vinyl monomers)

are formed during the process. This means that the amount of heat generated per unit time is usually very large, because propagation processes are very fast.

Addition polymerization of vinyl monomers is one of the most popular classes of chain-growth polymerization. Depending on the nature of the active species, the polymerizations are categorized as cationic, radical, or anionic. These polymerizations are usually very fast and highly exothermic.

Step-growth polymerization involves a stepwise covalent bond forming reaction between functional groups of two monomers, between a functional group of a monomer and of a polymer end, or between functional groups of two polymer ends (Scheme 9.3). Because the propagating polymers and monomers do not contain an active species, such as cations, radicals, or anions, the polymer chains increase in molecular weight very slowly at lower conversions and only reach moderately high molecular



Scheme 9.3 Step-growth polymerization

weights at very high conversion. Polycondensation, such as polyaminde formation, is classified as a step-growth polymerization.

9.3 MOLECULAR WEIGHT AND MOLECULAR-WEIGHT DISTRIBUTION

In polymer synthesis, the control of polymer chain structures, such as tacticity, chain length, and branching, is a very important issue because physical and chemical properties of polymers strongly depend on such structural features. For example, increasing the chain length tends to decrease chain mobility, while increasing both the toughness and the glass transition temperature (T_g). Therefore, the control of molecular weight is very important. Unlike small molecules, however, the molecular weight of a polymer does not have a single unique value; a given polymer has a distribution of molecular weights, depending on the way it is produced. Therefore, control of the molecular-weight distribution is also an important issue in polymer chemistry. In fact, the precise control of molecular weight and molecular-weight distribution is still at the forefront of the research in the field of polymer synthesis.

The ratio between weight-average molecular weight (M_w) and number-average molecular weight (M_n) is often used as an index (M_w/M_n or polydispersity index, PDI) to express the molecular-weight distribution. If all of the polymer chains have the same length, $M_w/M_n = 1$ and the polymer is monodisperse. Usually, M_w is larger than M_n, therefore $M_w/M_n > 1$. However, it should be noted that even if M_w/M_n (or PDI) is very close to 1, such as 1.04, as shown in Figure 9.1, the polymer has a significantly wide distribution of molecular weights ($2000 < M_n < 5000$), although the number average is 3500.

9.4 CATIONIC POLYMERIZATION

9.4.1 Conventional Cationic Polymerization

Cationic polymerization is one of the most fundamental methods for synthesizing polymers.[2,3] A general scheme for the cationic polymerization of vinyl monomers having a cation stabilizing group (R) is shown in Scheme 9.4. In general, proton acids or carbocations generated from their precursors by acid-promoted ionization reactions [4–6] are used as

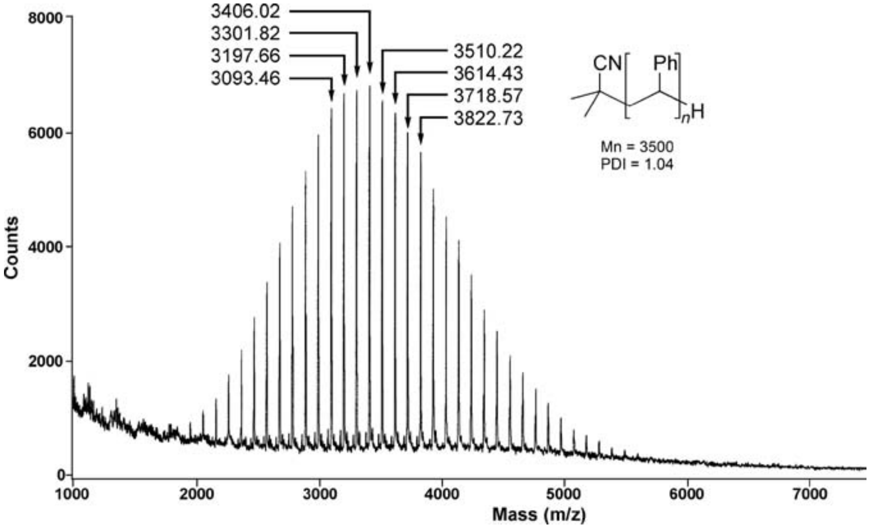
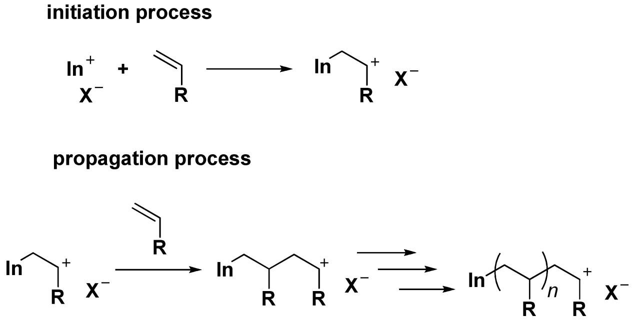


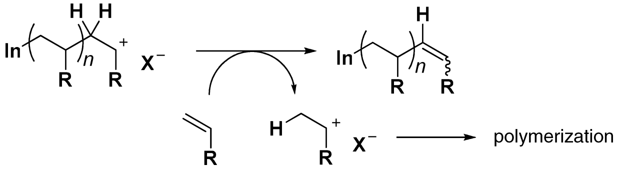
Figure 9.1 MALDI-TOF-MS spectrum of chain-end modified polystyrene obtained by Te-mediated polymerization[1]

initiators. The initiation usually involves the addition of a proton or a cationic species (In^+) to a carbon–carbon double bond of a vinyl monomer to produce a carbocationic intermediate associated with a counter anion (X^-), which is derived from the initiator.

In the propagation step, the carbocationic active polymer end adds to the monomer to give the next carbocationic polymer intermediate, which adds to another monomer. The polymerization can be terminated by the addition of a nucleophile or a base to trap an active carbocationic polymer end to obtain a stable dead polymer chain.



Scheme 9.4 Cationic polymerization of vinyl monomers



Scheme 9.5 Chain-transfer reactions as side reactions in cationic polymerization

A chain transfer reaction may also take place during the polymerization. The chain transfer to monomer is the most problematic from the viewpoint of molecular weight control and molecular-weight distribution control. The β-proton of the carbocationic intermediate is inherently acidic because of the presence of a positive charge on the carbon, whereas monomers used in cationic polymerization are inherently nucleophilic or basic because the cation-stabilizing group is electron-donating. Therefore, β-proton abstraction from the carbocationic polymer end by the monomer is inevitable and is very difficult to suppress (Scheme 9.5). Then, the polymer chain stops the propagation and another chain propagation starts from the protonated monomer.

9.4.2 Living Cationic Polymerization[4]

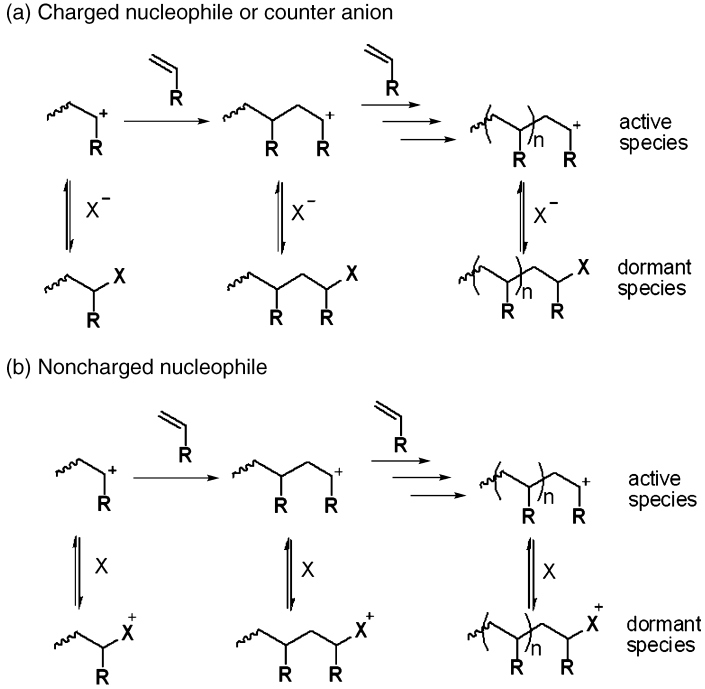
For a long time, cationic polymerization has been considered to be very difficult to control to obtain polymers of narrow molecular-weight distribution. Usually, molecular weights are unpredictable and M_w/M_n is far from one. An active species at the propagating polymer end is a carbocation or an onium ion, which reacts with olefin monomers extremely rapidly. The active polymer end is also highly unstable and readily participates in chain-transfer reactions by loss of β-protons leading to uncontrollable molecular-weight distributions.

The discovery of living cationic polymerization was an epoch-making event in polymer science and technology. There are three key issues in living cationic polymerization:

1. controlled initiation;
2. equilibrium between active species and dormant species; and
3. conditions to suppress chain transfer.

Initiation is a very important issue in controlling molecular weight and its distribution. To control the degree of polymerization based on the monomer/initiator ratio, the initiation reaction should be very fast and quantitative. Therefore, in controlled/living polymerization, the apparent initiation rate is usually comparable with, or larger than, the propagation rate.

The second key issue in living cationic polymerizations is the establishment of a dynamic equilibrium between active (growing) and dormant species to maintain a low concentration of active species. The growing chain end is represented by the Winstein equilibrium, as shown in Scheme 9.6, although the nature of the actual active (growing) species at the polymer end is still not completely understood. When the exchange between the active and dormant species is faster than propagation, good controllability of molecular-weight distribution can be attained. Therefore, much effort has been devoted to developing efficient systems for the equilibrium between active and dormant species. Various counter anions, Lewis acids (catalysts), and noncharged nucleophiles, which react with carbocationic active polymer ends to form more stable dormant species have been developed to control the exchange process.



Scheme 9.6 Equilibrium between active species and dormant species in living cationic polymerization

The equilibrium between active species and dormant species is also helpful in preventing chain-breaking processes, such as termination and transfer reactions.

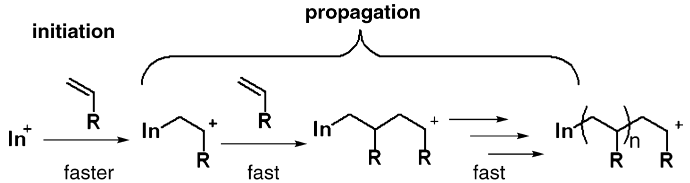
9.4.3 Ideal Living Cationic Polymerization

The living cationic polymerization developed so far is quasi-living polymerization, according to Kennedy.[5] In fact, chain transfer and termination are reversible. The rates of these reversible processes are higher than propagation so that the only significant monomer consuming process is propagation. Therefore, the major drawback of such quasi-living cationic polymerization is a slow propagation because the concentration of active species is very low. Usually, controlled/living polymerization is 10^7–10^8 times slower than polymerization without equilibrium between active and dormant species.

How can the controlled cationic polymerization be achieved without such deceleration due to the equilibrium to obtain polymers of narrow molecular-weight distribution? It may be ideal (or truly) living polymerization, in which all the propagating polymer chains are active all the time, whereas both chain-transfer and termination processes are absent during the time of polymerization (Scheme 9.7). There is no equilibrium between active species and dormant species to slow the propagation. Living anionic polymerization of styrenes and dienes developed in the 1950s[6] is fairly close to the ideal living polymerization, although the active species is anionic. However, it is believed to be very difficult to realize such systems in cationic polymerization. Therefore, development of ideal living polymerization is one of the major challenges of flash chemistry.

In ideal living polymerization, the following points are essential requirements:

1. All polymer chains should start propagating at the same time.
2. Each polymer chain in the system should react with monomer at the same rate.



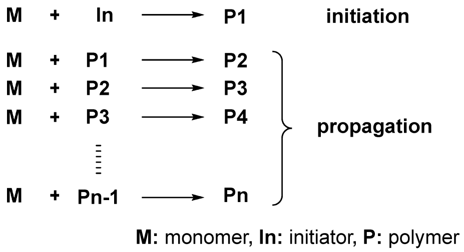
Scheme 9.7 Ideal living cationic polymerization

3. No reaction to break the polymerization by forming dead polymer chains occurs during the polymerization. Therefore, no termination reactions and no chain-transfer reactions take place.
4. The polymerization stops only when there is no monomer available in the system.
5. The polymerization can be restarted when the same or a different monomer is added. The use of a different monomer leads to block copolymerization.
6. When some reagent that forces the polymerization to stop is added, the polymerization is really terminated to make dead polymer chains.

9.4.4 Fast Initiation and Mixing

The essence of ideal living polymerization includes faster initiation than propagation and the absence of both termination and chain transfer during the polymerization. Ideal living cation polymerization may be realized based on the concept of flash chemistry. By making use of high-speed mixing, precise temperature control, and the short residence time that are characteristic of microreactors, ideal living cationic polymerization that does not require a stabilizer of the active propagating species may be realized.

Both the reaction of an initiator (In) with a monomer (M) and the reactions of propagating polymer (Pn) with a monomer (M) are very fast (Scheme 9.8). Therefore, we have to consider the possibility of disguised chemical selectivity, which is observed for Friedel-Crafts reactions of reactive aromatic compounds and a cation pool. If mixing is slow, the consecutive propagation reactions take place before all of the initiators react with monomers, even if the consecutive propagation reactions are slower than the initiation reaction. This is also an example of disguised



Scheme 9.8 Initiation and propagation as competitive consecutive reactions

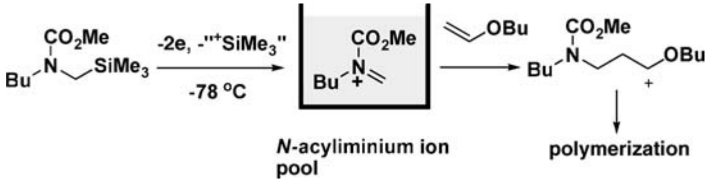
chemical selectivity for extremely fast competitive consecutive reactions. In such a case, it is difficult to control molecular weight based on monomer/initiator ratio. Control of molecular-weight distribution is also difficult, because initiation still occurs while some polymer chain is propagating. Therefore, the use of a highly efficient micromixer for extremely fast mixing of an initiator solution and a monomer solution is essential for ensuring that initiation is faster than propagation.

In the case of quasi-living polymerization based on the equilibrium, propagation is significantly decelerated. Therefore, initiation conducted by normal addition/stirring in a batch reactor is still faster than propagation. However, in ideal living polymerization, such equilibrium is absent and propagation involving the active carbocationic polymer end and a monomer is very fast. Therefore, the mixing should be faster than the initiation and propagation processes.

9.4.5 Cation-pool Initiated Polymerization of Vinyl Ethers Using a Microflow System[7]

The requirement of extremely fast initiation can be met by the use of a highly reactive cation pool as an initiator, which we have already discussed in the previous chapters. In fact, the use of the less sterically demanding, highly reactive *N*-acyliminium ion shown in Scheme 9.9 is quite effective for polymerization of vinyl ethers.

As expected, the use of a conventional macroreactor with magnetic stirring gives rise to very poor molecular-weight distribution control ($M_w/M_n = 2.25–2.56$), although the yield of polymer is quantitative. A microsystem consisting of two micromixers (M1 and M2) and a microtube reactor (R) (Figure 9.2) is, however, quite effective for the control of molecular weight and molecular-weight distribution ($M_w/M_n = 1.14$). It should be noted that excellent control of molecular-weight distribution can be attained without a dynamic equilibrium between active and dormant species, which is essential for conventional living cationic



Scheme 9.9 Cation-pool initiated polymerization of vinyl ethers

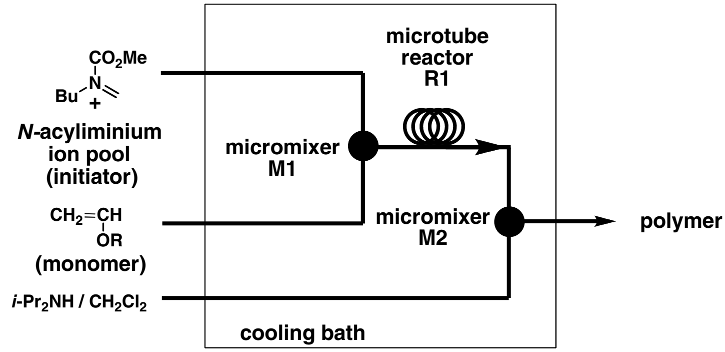


Figure 9.2 Microsystem for polymerization. M1, M2, micromixers; R1, microtube reactor

polymerization. Therefore, there is no deceleration of propagation and the polymerization is complete within a residence time of 1 s at −78 °C. The present method serves as a new method for control of the molecular-weight distribution without the deceleration inherent in the equilibrium.

The fact that the molecular weight increased linearly with the increase of monomer/initiator ratio, as shown in Figure 9.3, suggests that the chain-transfer reaction does 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 the excellent molecular-weight distribution control.

The NMR studies of the polymer obtained by the polymerization followed by the quenching with the addition of allyltrimethylsilane using the microsystem indicates that the *N*-acyliminium ion initiating group was really incorporated into the polymer chain and that the carbocationic

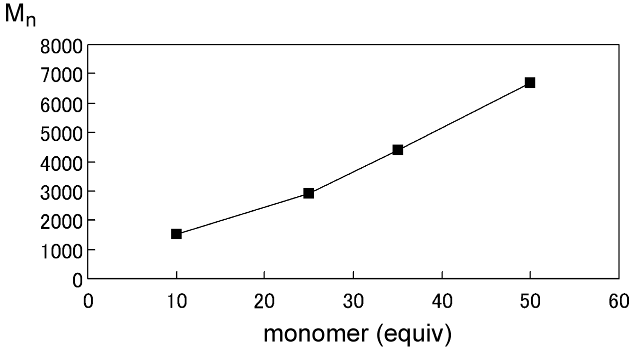


Figure 9.3 Plot of molecular weight against the amount of monomer used for the polymerization

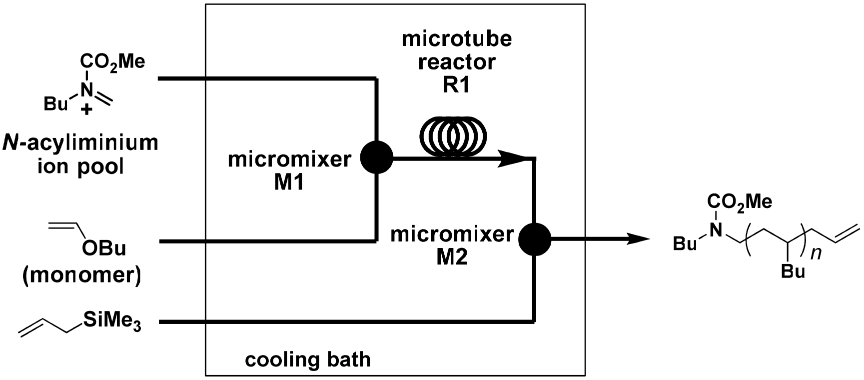


Figure 9.4 *N*-Acyliminium ion pool-initiated polymerization of *n*-butyl vinyl ether terminated by allyltrimethylsilane

polymer end was quantitatively trapped by the added allyltrimethylsilane (Figure 9.4). Therefore, the polymer end can be used as a living reactive species for the subsequent reaction with various nucleophiles. Thus, the present method serves as an efficient method for the synthesis of polymers having various functional groups at the terminal.

9.4.6 Livingness of the Microflow System-controlled Cationic Polymerization

In Section 9.4.1 we discussed ideal living polymerization. Let us examine the livingness of the microflow system-controlled cationic polymerization here.

1. All polymer chains should start propagating at the same time. The initiating reagents, such as cation pools, are highly reactive and the initiation process should be very fast. The fast micromixing of an initiator solution and a monomer solution may ensure the immediate generation of a homogeneous solution before polymerization. Therefore, propagation of each polymer chain seems to start in a very short period of time, although the detailed experimental evidence, such as reaction rates, has not been obtained as yet.
2. Each polymer chain in the system should react with each monomer at the same rate.

3. No reaction to break the polymerization by forming dead polymer chains occurs during the polymerization. Therefore, no termination reactions and no chain-transfer reactions take place. Excellent molecular weight and molecular-weight distribution controls support these two requirements are satisfied in a practical sense.
4. The polymerization stops only when there is no monomer available in the system.
5. The polymerization can be restarted when the same or a different monomer is added. The use of a different monomer leads to block copolymerization. Within the short residence time in a microflow system at low temperature, the polymer chain was really living. In fact, block copolymerization by adding the second monomer in the microflow system has already been achieved by using a strong proton acid, such as trifluoromethanesulfonic acid (TfOH), as an initiator in a microflow system (see Section 9.4.8).
6. When some reagent that forces the polymerization to stop is added, the polymerization is really terminated to make dead polymer chains. When a nucleophilic reagent such as allyltrimethylsilane was added, the polymerization terminated to give a stable dead polymer that could be well characterized by NMR spectroscopy.

Therefore, all requirements for living polymerization seem to be satisfied, at least in a practical sense, in the microflow system controlled cationic polymerization. The livingness strongly depends on the reaction time. In a very short period of time highly reactive intermediates, in this case reactive propagating polymer ends, can survive and they can be utilized for subsequent reactions when different monomers or a terminating reagent are added. This concept is quite similar to that discussed in Section 6.3.

9.4.7 Comparison Between Conventional Living Cationic Polymerization and Microflow System-controlled Cationic Polymerization

The example discussed in the previous sections illustrates the potential of microflow systems, in conjunction with a strong acid initiator, such as a cation pool, to effect cationic polymerization in a highly controlled manner without the deceleration inherent in the dynamic equilibrium

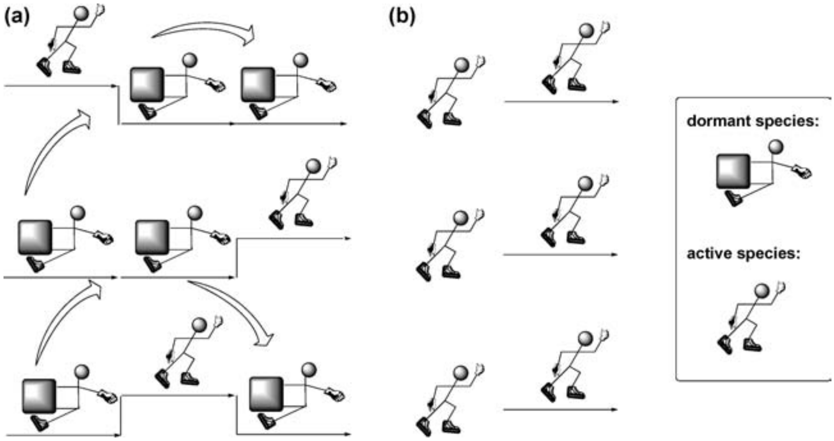


Figure 9.5 Two different types of living polymerization: (a) conventional living polymerization; and (b) microflow system-controlled living polymerization

between active and dormant species. The molecular-weight distribution can be controlled by extremely fast micromixing, and the polymer end can be used as the living reactive species for subsequent reactions within a short residence time. The microflow system-controlled polymerization seems to be very close to ideal living polymerization.

The microflow system-controlled method contrasts sharply with conventional living polymerization. It is like a marathon race as shown in Figure 9.5a. The start line is very clear. However, most of the polymer chains are resting and only a small number of polymer chains are active to take part in propagation because of the equilibrium between active species and dormant species. It is like great winds blowing on high hills. The dormant species are reactivated to active polymer but the resting time is much longer than the running time. Therefore, the overall polymerization is very slow and takes a long time.

The microflow system controlled polymerization is completely different (Figure 9.5b). It is a sprint race. It finishes within a second or so. The initiation is accomplished by fast micromixing of a very reactive initiator and a monomer. After flash initiation, all of the polymer chains undergo propagation without resting and the goal line is clear because of precise residence-time control in the microflow system. Polymer chains are still alive before quenching at the goal line. If a suitable reagent is added at the goal line, the active polymer chains can be utilized for further reactions.

9.4.8 Microflow System-controlled Cationic Polymerization Initiated by CF_3SO_3H[8]

In the previous section we discussed cationic polymerization in a microsystem, which leads to a high degree of molecular-weight distribution control without the deceleration inherent in the dynamic equilibrium between active and dormant species that is essential for conventional living polymerization. However, the need for low-temperature electrochemical generation of a cation-pool initiator might be a major drawback from the viewpoint of practical polymer synthesis. Recently, it has been found that a similar microflow system-controlled method can be applied to proton-initiated polymerization. Because various Brønsted acids are commercially available, this method may serve as a convenient way for practical polymerization. In fact, CF_3SO_3H has been found to serve as a good initiator.

A microflow system consisting of a T-shaped micromixer (inner diameter: 250 mm) and a microtube reactor (inner diameter: 500 mm, length: 50 cm) with pre-cooling units (inner diameter: 1.0 mm, length: 2 m) has been used. The polymerization is complete within the residence time of 0.37–1.5 s (almost quantitative yield). A high level of molecular-weight distribution control ($M_w/M_n = 1.2$) can be attained even at −25 °C. It is important to note that very low temperatures such as −78 °C, which might be an obstacle to industrial-scale applications, are not required for the present system. The slightly lower reactivity of TfOH compared with cation pools, as well as fast mixing and efficient heat transfer in the microflow system, seems to be responsible for the observed high degree of molecular-weight distribution control.

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 shown in Figure 9.6 (R1: 20 cm, R2: 50 cm). The polymerization of IBVE (isobutyl vinyl ether) (10 equiv based on TfOH initiator) followed by MeOH quenching at the second micromixer (M2) gives the homopolymer. The introduction of the second monomer [NBVE (n-butyl vinyl ether) or EVE (ethyl vinyl ether)] at the second micromixer (M2) results in the formation of a polymer of higher molecular weight with narrow molecular-weight distribution (Figure 9.7). Block copolymerization can be carried out with any combination and with either order of monomer

Table 9.1 Block polymerization using the microflow system

Monomer 1	Monomer 2	M_n	M_w/M_n
IBVE	–	1360	1.18
IBVE	NBVE	2260	1.43
IBVE	EVE	1780	1.54
NBVE	–	1010	1.24
NBVE	IBVE	1670	1.45
NBVE	EVE	1940	1.55
EVE	–	860	1.16
EVE	IBVE	2100	1.54
EVE	NBVE	2100	1.41

addition, as shown in Table 9.1. This demonstrates that the present method serves as an effective method for the synthesis of block copolymers. Therefore, microflow system-controlled polymerization serves as a good method for the synthesis of structurally well-defined block copolymers, which have attracted significant research interest in materials science.

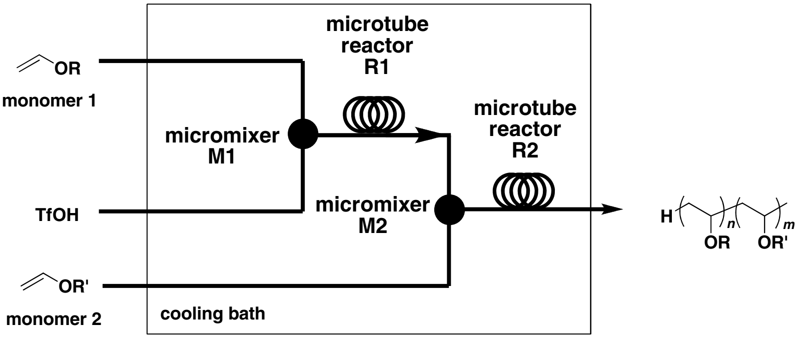


Figure 9.6 Microflow system for cationic block copolymerization

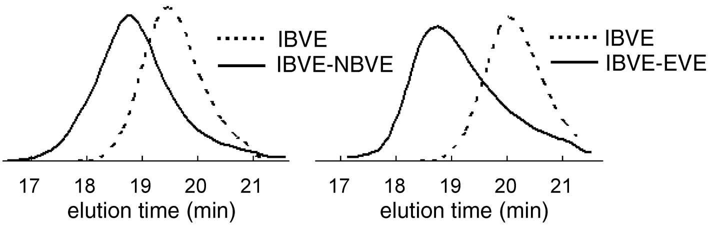


Figure 9.7 GPC traces of copolymerization with different monomers. Reproduced by permission of The Royal Society of Chemistry

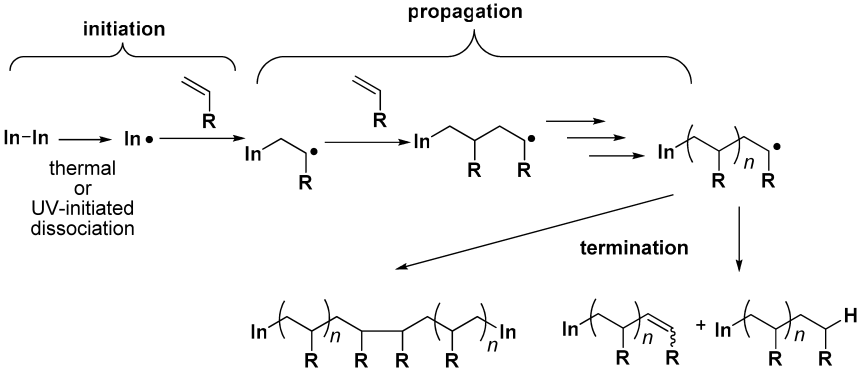
9.5 FREE-RADICAL POLYMERIZATION

Free-radical polymerization is an important process for the synthesis of polymers because free radicals are compatible with a wide variety of functional groups that are not compatible with ionic and metal-catalyzed polymerization. Therefore, free-radical polymerization is the most widely used method to produce polymers in industry.

9.5.1 Conventional Free-radical Polymerization

Free-radical polymerization is usually initiated by thermal or UV-initiated decomposition (usually homolytic dissociation) of a suitable radical initiator (Scheme 9.10). For example, thermal decomposition of AIBN (azobisisobutyronitrile) gives N_2 and carbon radicals, which initiate polymerization of vinyl monomers.

The termination usually occurs in a bimolecular fashion. It is well known that two carbon radicals couple together very rapidly. In fact, the two propagating polymer chains couple to give a dead polymer chain with the chain length equal to the sum of the two propagating chains. There is another possibility for termination. Carbon radicals are also known to undergo disproportionation reactions. In fact, the two propagating polymer chains undergo disproportionation reactions to give dead polymer chains with the chain length equal to those of the propagating chains. The chain transfer reaction, which takes place between a propagating polymer chain and the monomer, the solvent molecules, or a transfer agent, gives one dead polymer chain and a new radical, which can initiate polymerization to make another active polymer chain.



Scheme 9.10 General scheme for radical polymerization

The lengths of polymer chains obtained in radical polymerization are not monodisperse, even under ideal conditions.[9] If termination occurs only by radical coupling, $M_w/M_n = 1.5$ as a consequence of the statistical distribution of products. If termination occurs by disproportionation, $M_w/M_n = 2$.

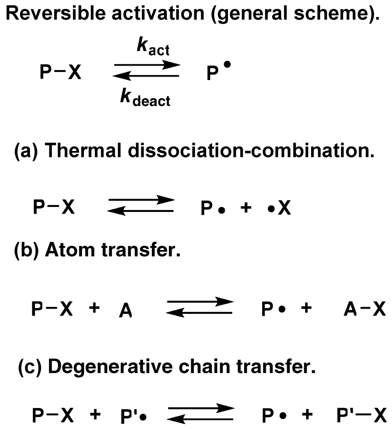
Most polymerizations of vinyl monomers are highly exothermic. Also, radical polymerization usually takes place very rapidly, and a significant amount of heat is generated in a short period of time. Therefore, rapid heat removal to enable precise temperature control is essential for carrying out free-radical polymerization in a highly controlled manner. Polymerization reactions in conventional macrobatch reactors often suffer from inefficient heat removal and the lack of homogeneity of the reactor temperature, which eventually give rise to a low level of molecular-weight distribution control. Thus, a major concern with free-radical polymerization is the controllability of the reaction temperature from both academic and industrial viewpoints.

The increase in viscosity during the course of polymerization is also a problem. Increase in viscosity causes inefficient mixing in the system, which in turn leads to inefficient heat transfer producing hot spots where undesired side reactions may take place.

9.5.2 Living-radical Polymerization

Living polymerization technology has also been developed for free-radical polymerization.[10] The synthesis of functionalized macromolecules with defined structures by controlled/living radical polymerization is becoming increasingly important because radicals are compatible with a wide variety of polar functional groups, which do not tolerate ionic and metal-catalyzed polymerization conditions. Various systems including nitroxide-mediated polymerization (NMP),[11] atom-transfer radical polymerization (ATRP),[12] reversible addition-fragmentation chain transfer (RAFT),[13] and organotellurium-mediated living-radical polymerization (TERP)[14] have been developed so far.

One of the key issues of controlled/living-radical polymerizations is establishing a dynamic equilibrium between active (growing) and dormant species to maintain a low concentration of active species. In other words, the active carbon-centered radical species are reversibly generated from dormant species, although there is much debate over the mechanism (Scheme 9.11). This equilibrium is helpful in preventing chain-breaking processes, such as terminating radical-coupling and



Scheme 9.11 Equilibrium between active species and dormant species in radical polymerization

chain-transfer reactions. Therefore, good controllability of molecular weight and molecular-weight distribution can be attained.

Living-radical polymerization can be performed using microflow systems and several studies have been reported in the literature. Such studies mainly focus on making numbers of polymers for screening using minimum quantities of raw materials.[15]

Despite its synthetic potential, the most important disadvantage of this method is the long time required for completion of the polymerization (>10 h), even at relatively high temperatures (>80 °C). So, living-radical polymerization is not a suitable technique for flash chemistry.

9.5.3 Emulsion and Suspension Polymerization

In bulk- and solution-phase free-radical polymerization, there is a tradeoff between molecular weight and polymerization rate. This is especially true for controlled/living radical polymerization. In emulsion polymerization, however, high molecular weight polymers can be made at fast polymerization rates. Emulsion polymerization is a type of radical polymerization that is frequently used for making polymers of high molecular weight. The most common type of emulsion polymerization is an oil-in-water emulsion, in which droplets of monomer (the oil) are emulsified with surfactants in a continuous phase of water.

Suspension polymerization is a similar method. In this process a monomer, or a mixture of monomers, is dispersed by mechanical agitation

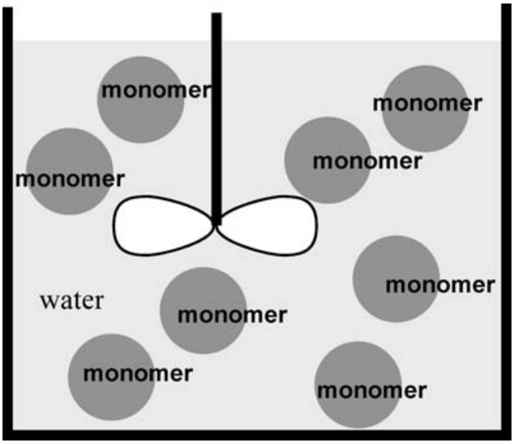


Figure 9.8 Schematic diagram of emulsion and suspension polymerizations. Each droplet is a type of microbatch reactor having a high surface-to-volume ratio

in a continuous liquid phase, usually water, in which the monomer droplets are polymerized while they are dispersed by continuous agitation and an additional stabilizer. Suspension polymerization is also known as pearl polymerization, bead polymerization, or granular polymerization.

In emulsion and suspension polymerizations, the continuous water phase serves as an excellent conductor of heat and allows the heat to be removed from the system (Figure 9.8). Therefore, the polymerization can be conducted at a high rate. This is a kind of flash chemistry without using micro devices. Instead, the reaction is carried out in small size droplets. The high surface-to-volume ratio of droplets is responsible for the fast heat transfer.

9.5.4 Radical Polymerization in Microflow Systems

Radical polymerization can be conducted in microflow systems. A typical system for laboratory-scale radical polymerization that consists of a mixer and microtube reactors is shown in Figure 9.9.[16]

A monomer solution and an initiator solution are mixed at a T-shape micromixer M1 and microtube reactor R1. In this case fast mixing of the two solutions is not important, because radical polymerization does not start until the temperature is elevated sufficiently for thermal decomposition of a radical initiator, such as AIBN. Therefore, the combination of a T-shape micromixer and a short microtube reactor is sufficient for producing a homogeneous solution before polymerization starts.

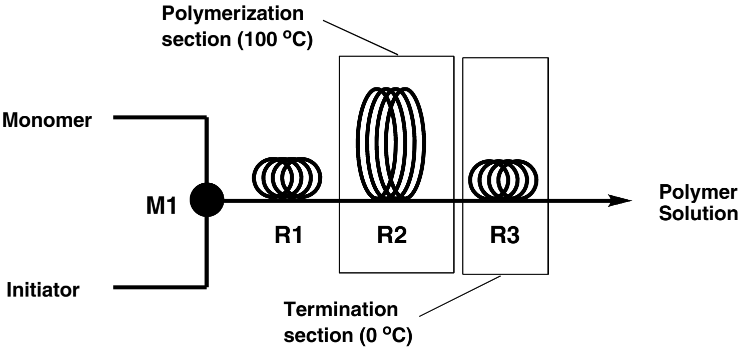


Figure 9.9 Microflow system for polymerization. M1, T-shape micromixer; R1, R2, R3, microtube reactors

Polymerization occurs in microtube reactor R2, because its temperature is set high enough to decompose the initiator. Then, the mixture is introduced to the third microtube reactor R3, where polymerization is stopped by cooling.

Let us briefly touch on polymerization of typical vinyl monomers using the microflow system. It is well known that the polymerization of butyl acrylate (BA) is very fast, highly exothermic, and very difficult to control in a macrobatch reactor. As shown in Figure 9.10, the molecular-weight distribution is not narrow. Polymerization in a microflow system is also very fast and is almost complete within the residence time of 5 min (Figure 9.11). However, the superior molecular-weight distribution

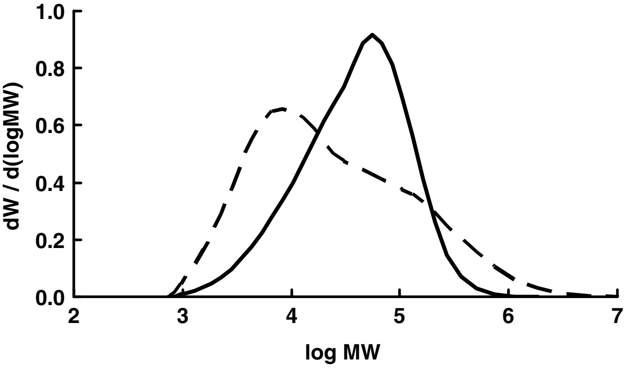


Figure 9.10 Molecular-weight distribution of poly(butyl acrylate) produced by the microflow system (——) and the macrobatch reactor (- - - - - -) (residence time or reaction time was 4 min). Copyright 2005 American Chemical Society

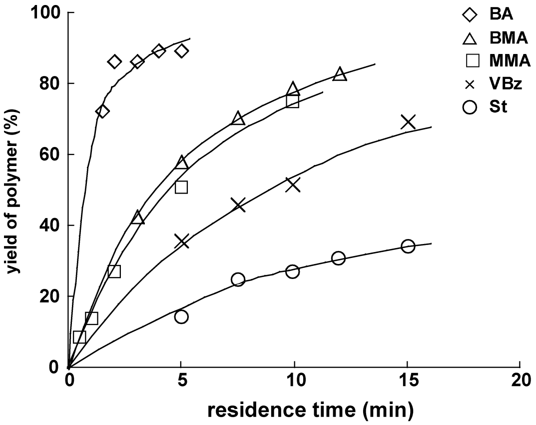


Figure 9.11 Relative rates of polymerization in the microflow system. Copyright 2005 American Chemical Society

control can be attained in the microflow system shown in Figure 9.9. In fact, M_w/M_n for the polymerization in the microflow system is much smaller than that obtained in a macrobatch system (Table 9.2). The significant increase in the temperature seems to be responsible for the large M_w/M_n observed for the polymerization in a macrobatch reactor. In the case of a microflow system, however, the efficient heat transfer through the wall of the reactor presumably reduces the temperature increase caused by the polymerization, and consequently yields a polymer with smaller M_w/M_n. A smaller local deviation of the temperature in the microflow reactor also seems to be responsible for the narrower molecular weight distribution. The local heterogeneity of temperature and also the cooling rate to stop the polymerization may be responsible for the smaller

Table 9.2 Effect of the microflow system on molecular-weight distribution control

Monomer	Propagation rate constant k_p (L/mol/s) at 30 °C[17]	M_w/M_n in macrobatch system	M_w/M_n in microflow system	Effect of microflow system
BA	3496	10.0	3.3	Large
BMA	1410	2.6	2.0	Medium
MMA	248	2.4	1.8	Medium
VBz	185	2.0	2.0	Small
St	106	1.9	1.7	Small

M_w/M_n. The significant improvement in the molecular-weight distribution might be ascribed to the suppression of transfer reactions.

Polymerization of benzyl methacrylate (BMA) is much slower than that of BA. Although the yield of the polymer increased with an increase in the residence time, the polymerization did not complete within 12 min. The value of M_w/M_n was much smaller than that for BA, both in the microflow system and the macrobatch system. The effect of the microflow system on molecular-weight distribution control is, however, smaller than for the BA case. Probably, temperature control for BMA polymerization is better than that for BA polymerization, even in the macrobatch system, because heat generation per unit time for BMA polymerization seems to be much less than that for BA polymerization.

A similar tendency is observed for the polymerization of methyl methacrylate (MMA). Although the yield of the polymer increased with an increase of residence time, the polymerization did not complete within 10 min. Therefore, MMA polymerization is slower than BA polymerization. The molecular-weight distribution is also narrower than that for BA polymerization in both the macrobatch system and the microflow system. Similar to the case of BMA, the effect of the microflow system is smaller than for the BA case.

Vinyl benzoate (VBz) polymerization is slower than MMA polymerization. It is noteworthy that M_w/M_n for the polymer obtained in the microflow system is very similar to that for the macrobatch system, suggesting that the superior heat removal ability of the microflow system is not important for molecular-weight distribution control in VBz polymerization. This is presumably because the heat generation in VBz polymerization is smaller and controllable even in the macrobatch system on the laboratory scale.

Polymerization of styrene (St) is much slower than polymerization of VBz, because a significant amount of the monomer remains unchanged even after a residence time of 15 min. M_w/M_n is similar to that for the macrobatch system, indicating that the heat removal ability of the reactor is not important in this case.

Studies on the relative rates of the polymerization are helpful in obtaining a deeper insight into the effect of the microflow system on molecular-weight distribution control. It can be seen from Figure 9.11, where the polymer yield obtained in the microflow system is plotted against the reaction time (residence time) for each monomer, that the rate of polymerization increases in the order St < VBz < MMA < BMA < BA. This trend is consistent with the propagation rate constants reported in the literature (Table 9.2). It is reasonable to consider that a similar order is applicable for the heat generated per unit time. Faster reactions are usually more exothermic.[18] It is also noteworthy that heat is generated in a shorter period of time when polymerization is faster. The polymerization of BA is the fastest, and therefore heat generated per unit time seems to be largest for BA polymerization. This means that BA polymerization needs the most rapid heat removal. Therefore, the effect of the microflow system is the most significant for BA polymerization. However, the polymerization of St is the slowest, and therefore the St polymerization is easy to control even in the macrobatch system. These considerations are consistent with the relative effect of the microflow system on the molecular-weight distribution control (BA > BMA, MMA > VBz, St).

In summary, microflow systems are quite effective for molecular-weight distribution control of very fast, highly exothermic free-radical polymerizations. The superior heat transfer ability of the microflow system in comparison with conventional macrobatch systems seems to be responsible for the high molecular-weight distribution controllability. It should be noted that the controllability is much lower than is achieved by conventional living free-radical polymerization, because residence time control does not work for controlling radical intermediates. The lifetime of a radical intermediate is usually much shorter than the residence time in a microflow system. It is also noteworthy that the more rapid and exothermic the polymerization is, the more effective the microflow system is. These facts speak well for the potentiality of microflow systems in the control of highly exothermic free-radical polymerization without deceleration by reversible termination.

9.5.5 Simulation of Free-radical Polymerization in Microflow Systems[19]

Numerical simulations of styrene free-radical polymerization in microflow systems have been reported. The simulations were carried out for three model devices, namely, an interdigital multilamination micromixer, a Superfocus interdigital micromixer, and a simple T-junction. The simulation method used allows the simultaneous solving of partial differential equations resulting from the hydrodynamics, and thermal and mass transfer (convection, diffusion and chemical reaction).

It is interesting that the simulations indicate that the thermal transfer in such microdevices is high enough to ensure isothermal conditions in spite of the heat released by the polymerization reaction. Moreover, the

Superfocus interdigital multilamination micromixer can achieve better control than a macrobatch reactor, and the PDI obtained is very close to the theoretical limiting value of 1.5. As the characteristic dimension of the microdevice increases the reactive medium cannot be fully homogenized by diffusion transport before leaving the system, resulting in a high PDI and a loss in control of the polymerization.

9.6 CONCLUSIONS

The concept of flash chemistry can be applied to polymer synthesis.[24] Cationic polymerization can be conducted in a highly controlled manner by virtue of the inherent advantage of extremely fast micromixing and fast heat transfer. An excellent level of molecular weight control and molecular-weight distribution control can be attained without deceleration caused by equilibrium between active species and dormant species. The polymerization is complete within a second or so. The microflow system-controlled cationic polymerization seems to be close to ideal living polymerization within a short residence time.

Free-radical polymerization can also be conducted in microflow systems. 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.

Further applications of flash polymerization in microflow systems will hopefully appear in the field of polymer science and technology in the future.

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Flash Chemistry

Flash Chemistry: Fast Organic Synthesis in Microsystems Jun-ichi Yoshida
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Flash Chemistry

Fast Organic Synthesis in Microsystems

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Contents

Preface

The main objective of this book is to provide, in a concise form, a current overall picture of flash chemistry; background, principles, devices, and applications in organic and polymer synthesis. Because of space limitations our discussion in this book is not an exhaustive compilation of all known examples. Rather, it is a sampling of sufficient variety to illustrate the concept and the scope of flash chemistry. I usually focus on the works that have been done in my group as examples because I know them in more detail than other works reported in the literature. I hope that these examples and the accompanying discussions will serve as a guide to the potential of flash chemistry.

I thank the members of my research group, especially Prof. Seiji Suga and Dr. Aiichiro Nagaki, and the members of the NEDO (New Energy and Industrial Technology Development Organization, Japan) projects, who did extensive work that is demonstrated in this book. I also acknowledge many discussions over the years with the members of GRAMS (Groups for Research on Automated Flow and Microreactor Synthesis) in Kinki Chemical Society, especially Prof. Ilhyong Ryu, and the members of the international research community of microreactor synthesis, especially Prof. Holger Löwe, Prof. Volker Hessel, Dr. Jürgen J. Brandner, Prof. Shinji Hasebe, and Prof. Kazuhiro Mae.

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August 2008

Jun-ichi Yoshida

10

Industrial Applications of Flash Chemistry

Flash chemistry is expected to produce a paradigm shift not only in laboratory chemical synthesis but also in the industrial production of chemicals and drugs. Microflow systems are essential for conducting extremely fast reactions in flash chemistry, and it is often assumed that microflow systems can be used only in laboratory synthesis and in small-scale productions. It is often considered that large-scale productions cannot be carried out using microflow systems. However, this is not true. Microflow systems can be used for production on a relatively large scale. For example, some pilot plants on tons per year scale have already been constructed based on microflow technology.

In general, there are two ways to increase the production volume: (i) increase the reactor size; and (ii) numbering-up of reactors.[1] The former approach is usually used for macrobatch processes. However, in microflow processes, the numbering-up approach is often used. The production volume is increased by increasing the number of reactors used. This feature of microflow processes may provide a bonus in industry. In conventional macrobatch processes, the enlargement of reactor size from a laboratory flask to a production vessel often causes a variety of problems, such as declining yield and selectivity, and low reproducibility. Resolving these issues requires reinvestigation of reaction conditions, which involves a lot of time and manpower. However, for microflow processes, the production volume can be increased by simply numbering-up the reactors without changing the size of the microchannels. In some cases, numbering-up is performed inside the system (inner numbering-up). In this case, it is not

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necessary to increase the number of pumps and bulbs in the total system. In principle, the outcome of the reaction does not change by numbering-up. Therefore, a shift from laboratory synthesis to industrial production can be possible without changing the reaction conditions. Consequently, a major reduction in the lag-time between the research and development stage and the industrial production stage can be expected for microflow processes.

It is true that numbering-up is the only way to increase the production volume for microflow systems because a change in the channel size usually changes the outcome of the reaction. However, the numbering-up approach also has limitations. For example, it is generally very difficult to operate 1000 microflow reactors in parallel. Therefore, an increase in the channel size should also be considered, even for microflow processes. From the viewpoint of industrial production, the size of a microstructure should be as large as possible, provided it maintains the features of the microspace that are necessary for controlling a particular reaction. Sometimes, only one dimension of the reactor structure should be kept in the micrometer size, and the other dimensions should be increased to the macrolevel to produce an increase in the production volume. In addition, millimeter-scale structures, rather than micrometer-scale structures, may be acceptable for performing reactions on an industrial scale. It should be kept in mind that even these cases are examples of flash chemistry.

Both the scaling-up and numbering-up approaches are important for increasing the production volume in microflow processes. The number of reactors should be as low as possible, and the size of the reactor structure should be as large as possible, to the extent that the efficiency and selectivity of a reaction are acceptable. Flexibility is important in the designing of microflow processes and reactors based on flash chemistry in industrial production.[2] The key points for the scaling-up and numbering-up approaches are:

Scaling-up:

- Scale-up of the reactor often leads to a lower efficiency and selectivity.
- Effort and time are needed for scale-up.
- Scale-up to the extent that efficiency and selectivity are acceptable.

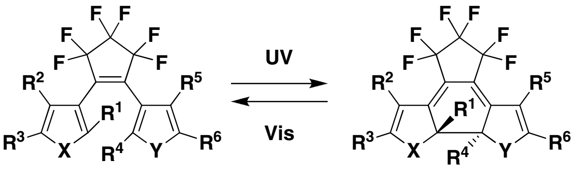
Numbering-up:

- Numbering-up involves the same efficiency and selectivity.
- Less effort and time are needed to increase the production volume.
- It is difficult to operate a large number of systems in parallel.
- Minimum numbering-up as far as the production volume is acceptable.

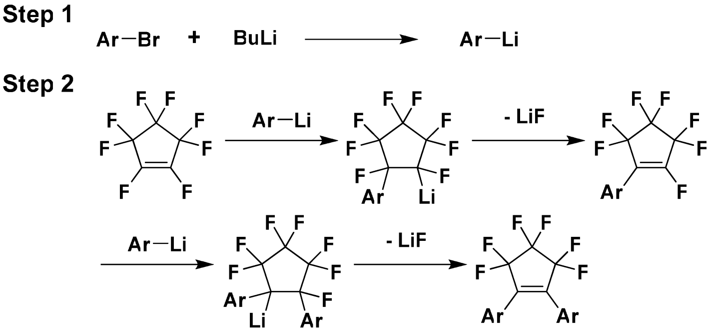
Recently, microchemical plants have emerged as an important new trend in the chemical industry, and they are expected to produce a revolutionary change in achieving a more compact and knowledge-intensive industry that can produce chemicals in a much faster and more controlled manner. This trend has been accelerated by the increase in concern over the global environment that aims at saving natural resources and energy. Some examples are presented in this chapter to illustrate the benefits of flash chemistry from the viewpoint of the industrial production of chemical substances.

10.1 SYNTHESIS OF DIARYLETHENE AS A PHOTOCHROMIC COMPOUND (MICROMETER-SIZE SINGLE-CHANNEL REACTOR)

Diarylethenes have received significant research interest from both academia and industry, because some of these compounds exhibit remarkable changes in color by reversible switching of two distinct isomers (photochromism), which is accomplished by absorption of different wavelengths of light, as exemplified by Scheme 10.1.[3] The most promising photochromic diarylethene candidates include 1,2-diarylhexafluorocyclopentenes, which have been synthesized by the reaction of two equivalents of aryllithium compounds with octafluorocyclopentene (Scheme 10.2). The first step in the synthesis of diarylethenes is the halogen–lithium exchange reaction of an aryl bromide with butyllithium, which has already been discussed in Chapter 8. This reaction should be carried out at low temperatures, e.g. −78 °C, because aryllithium compounds are often unstable and decompose at higher temperatures. In the next step, the aryllithium compounds are allowed to react with octafluorocyclopentene.[4] Usually, 2 mol of the aryllithium compound react with 1 mol of octafluorocyclopentene, presumably via a two-fold addition–elimination sequence, to give the desired diarylethenes. Therefore, the method is suitable for the synthesis of symmetrical diarylethenes.



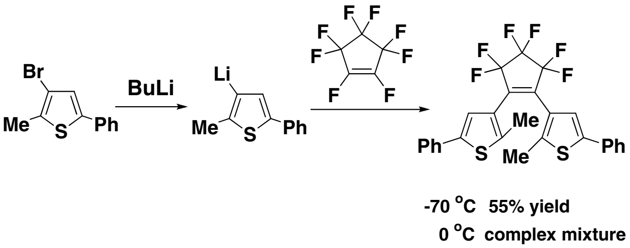
Scheme 10.1 Photochromic diarylethene



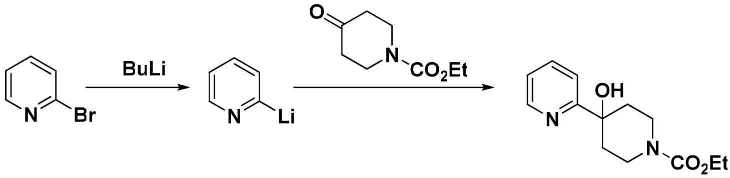
Scheme 10.2 Synthesis of diarylethenes

As described above, the diarylethene synthesis should be carried out at low temperatures, such as −78 °C, in a macrobatch reactor to avoid any undesirable side reactions. However, the requirement of such low temperatures has been an obstacle to industrial-scale applications. For example, the reaction shown in Scheme 10.3 needs to be carried out at −70 °C and the optimized yield on an industrial scale is 55%. Carrying out the reaction at 0 °C leads to the formation of a complex mixture.

The use of a microflow system is effective in solving this problem, and a pilot plant for the halogen–lithium exchange reaction of aryl bromides and heteroaryl bromides with butyllithium (Scheme 10.4) has already



Scheme 10.3 Synthesis of diarylethene in a macrobatch system



Scheme 10.4 Halogen–lithium exchange reaction of bromopyridine and subsequent reaction with a ketone

Figure 10.1 Pilot plant for the halogen–lithium exchange reaction. Copyright FUJIFILM FINECHEMICALS CO., LTD.

been built, as shown in Figure 10.1.[5] The organolithium intermediate obtained is allowed to react with electrophiles, and the reaction can be conducted at 0–20 °C with a high selectivity to obtain the desired compounds in good yields. Efficient heat transfer of the microflow system seems to minimize the local deviation of temperature, avoiding any undesired side reactions. Precise control of the residence time may also be responsible for diminishing the decomposition of organolithium compounds, and the reaction can be conducted continuously without encountering any problems, such as pressure drop.

With successful, pilot-scale halogen–lithium exchange reactions in microflow systems in hand, a microflow system consisting of two T-shaped micromixers (M1 and M2) [Swagelok Union Tee; inner diameter: 2.3 mm (M1), and 1.3 mm (M2)], and stainless steel microtube reactors (R1 and R2): (diameter: 800 μm, length: 1–2 m) has been constructed, as shown in Figure 10.2.[6] It should be noted that microtube reactors with a relatively large inner diameter are used to obtain high production volumes, although they are still of micrometer size. The inner diameter of the T-shaped micromixers is of millimeter size to avoid excessive pressure drop. Stainless steel is the material of choice for the mixers and reactors because of its high heat-exchange property and its mechanical strength from the viewpoint of industrial applications

A solution of an aryl bromide (0.3 M) in THF and a solution of butyllithium (1.5 M) in hexane are introduced to M1 at a flow rate of 7.50 and 1.50 mL/min, respectively. The resulting mixture is allowed to react in R1 (residence time: 3.4–6.7 s). Then, the outlet solution is introduced to M2, where a solution of octafluorocyclopentene

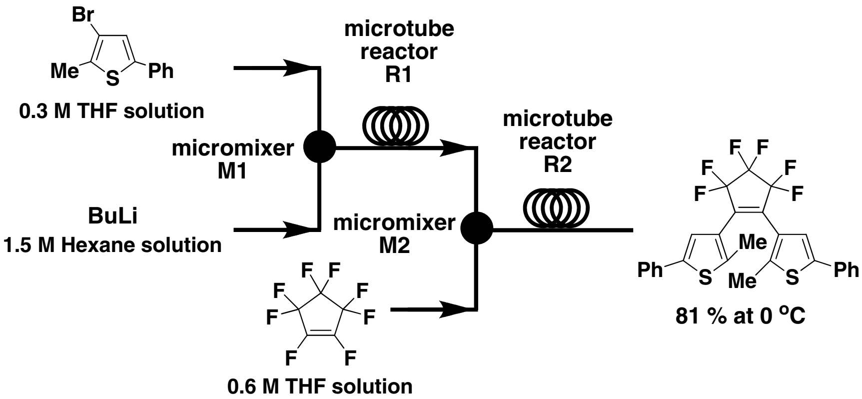


Figure 10.2 Synthesis of diarylethene in a microflow system

(0.750 M) in THF is introduced (flow rate: 1.50 mL/min). The resulting mixture is allowed to react in R2 (residence time: 2.9–5.7 s).

The reaction temperature has been optimized using 3-bromo-2-methyl-5-phenylthiophene as an aryl bromide. As shown in Figure 10.3, the yield of the desired diarylated product increases with temperature, presumably because the rate of reaction increases with temperature. The highest yield was obtained at 0 °C. At temperatures above 0 °C, the yield decreases significantly, probably because of the decomposition of the aryllithium intermediate. It is noteworthy that the reaction in a macrobatch system at 0 °C gives a complex mixture, and that low temperatures such as −70 °C are essential for the success of the reaction in a macrobatch system.

The optimized yield is 81% at 0 °C and the total residence time is ca. 6 s. Therefore, the synthesis of diarylethenes can be accomplished at 0 °C, which is easily attained in industry, by virtue of an effective temperature

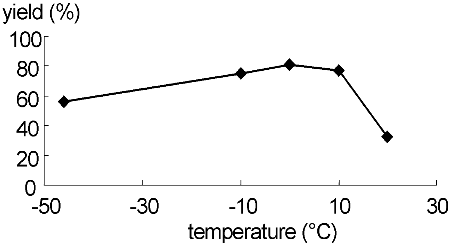


Figure 10.3 Effect of temperature on the synthesis of diarylethene in a microflow system. (Residence time for **R1** = 3.4 s and for **R2** = 2.9 s). Reproduced by permission of The Royal Society of Chemistry

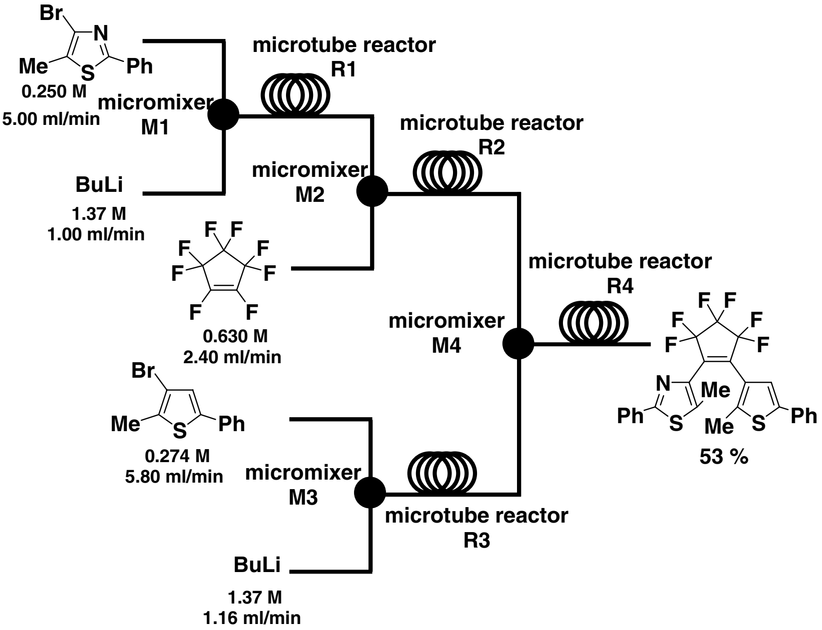


Figure 10.4 Synthesis of unsymmetrical diarylethenes in a microflow system

and residence time control in a microflow system. It is important to note that the productivity is 2 mmol/min, which is not too low for the production of functional materials.

Selective synthesis of unsymmetrical diarylethenes can also be successfully accomplished using two different aryl bromides sequentially. Figure 10.4 illustrates the synthesis of an unsymmetrical diarylethene. The ring-closed isomer obtained by photo-irradiation of the product exhibited a different color from those of the corresponding symmetrical disubstituted compounds. This result shows the possibility of fine-tuning the physical properties by introducing different heteroaromatic substituents on the alkene framework by taking advantage of a microflow system.

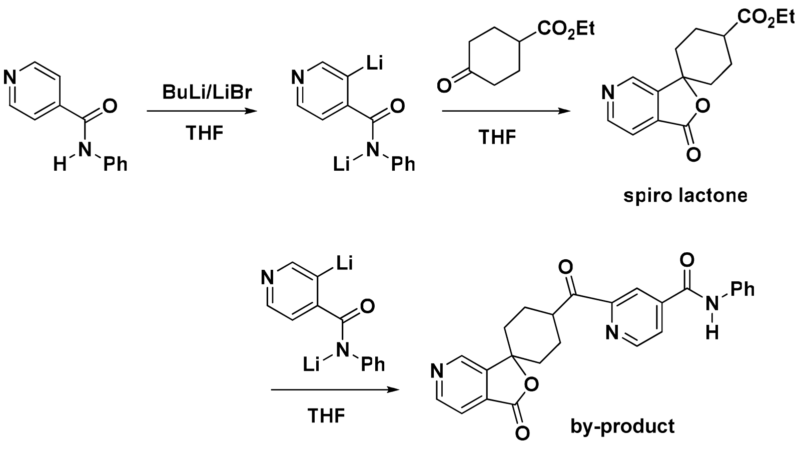
The successful synthesis of unsymmetrical diarylethenes using two different aryl bromides in a single flow speaks well for the potential of microflow systems in making new functional materials, which would be otherwise difficult to synthesize in a conventional manner. Acceptable productivity from the viewpoint of industrial production of functional materials can be attained using microtube reactors with a relatively large inner diameter (800 μm) without numbering-up.

10.2 SYNTHESIS OF A PHARMACEUTICALLY INTERESTING SPIRO LACTONE FRAGMENT OF NEUROPEPTIDE Y (MILLIMETER-SIZE SINGLE-CHANNEL REACTOR)

In addition to halogen–lithium exchange reactions, hydrogen–lithium exchange reactions have also been widely used to prepare organolithium compounds in laboratory syntheses. These reactions are also carried out at low temperatures, such as −78 °C, because they are usually highly exothermic, and the organolithium compounds produced are unstable and decompose at higher temperatures. Although laboratory-scale reactions can be easily carried out at such temperatures, industrial-scale macrobatch reactions are problematic. The requirement for such low temperatures causes severe limitations in the industrial use of these highly useful reactions.

The use of a microflow system for hydrogen–lithium exchange reactions has been examined by the pharmaceutical industry.[7] Efficient heat transfer is expected to prevent decomposition of the organolithium intermediates and to improve the product selectivity. The target compound is a spiro lactone fragment of neuropeptide Y, which is a receptor antagonist for the treatment of obesity. [Obesity is an increasingly common global disease, which the World Health Organization (WHO) has identified as one of the ten leading health risks in the world.]

The starting phenyl isonicotinamide is treated with butyllithium in the presence of LiBr to obtain the dilithiated intermediate (Scheme 10.5). The



Scheme 10.5 Hydrogen–lithium exchange reaction of phenyl isonicotinamide and subsequent reaction with a ketone to synthesize spiro lactone

Table 10.1 Synthesis of a spiro lactone in a pilot-scale batch plant

Tank size (L)	Jacket temperature (°C)	Inner temperature (°C)	Addition time (min)	Yield (%)
800	−90	−66	15	82.9
800	−82	−64	29	75.6
800	−75	−63	56	70.2
800	−70	−62	111	66.9
2000	−90	−66	36	77.3

reaction is highly exothermic ($\Delta H = -366$ kJ/mol) and the reaction temperature needs to be kept below −60 °C to avoid decomposition of the intermediate. In the next step, the dilithiated intermediate is allowed to react with ethyl 4-oxocyclohexanecarboxylate to produce the desired spiro lactone as a cis/trans mixture. This reaction is also highly exothermic ($\Delta H = -196$ kJ/mol) and needs to be carried out below −60 °C. The ester part of the spiro lactone can react with another dilithiated intermediate to give a by-product.

In a pilot-scale batch process using an 800 L tank, the first lithiation is conducted by adding BuLi to a phenyl isonicotinamide solution while keeping the inner temperature below −60 °C. In the second step, the dilithiated intermediate is added to 4-oxocyclohexanecarboxylate. Because no major problems are encountered in the first step, the second reaction is carried out while varying the temperatures and the addition rate (Table 10.1). Under these conditions, the maximum yield of the desired compound is 82.9%. When the scale of the second reaction is increased to 2000 L at the same jacket temperature (addition time: 36 min), the yield decreases to 77.3%, indicating difficulty in scaling-up this type of reaction.

In the microflow process above, reactions conducted in a system composed of static mixers (inner diameter: 3.4 mm, length: 155 mm) and stainless steel tube reactors (inner diameter: 0.25–2 mm, length: 10 cm–20 m) have been examined (Figure 10.5). Yields greater than 90% are obtained for a jacket temperature of −80 °C (Table 10.2). The residence time is estimated to be approximately 20 s. A 10% increase in the product yield can be ascribed to improved heat removal, which avoids any decomposition of the dilithiated intermediate and a subsequent reaction. The yield decreases with increasing jacket temperature. It is also interesting that the cis/trans selectivity changes significantly on varying the temperature.

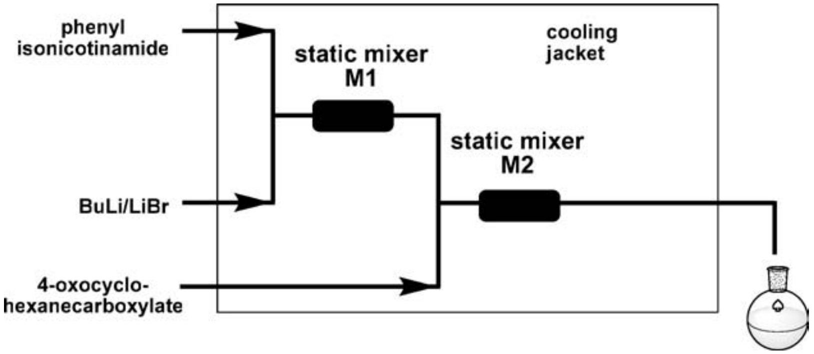


Figure 10.5 Flow system composed of static micromixers and millimeter-sized tube reactors

Table 10.2 Synthesis of the spiro lactone using the flow system

Jacket temperature (°C)	Flow rate (ml/h)	Spiro lactone (%)	cis/trans	By-product (%)	Unchanged phenyl isonicotinamide (%)
−80	200	92.5	1.10	0.5	5.5
−80	200	93.3	1.12	0.8	6.9
−80	228	92.4	1.12	0.8	6.5
−10	320	51.8	1.75	32.5	10.1
−40	320	67.8	1.39	15.1	7.9
−80	430	90.9	1.18	1.9	8.1

This example illustrates the utility of millimeter-sized tube reactors in industrial production, which opens various possibilities for the application of flash chemistry in industry.

10.3 GRIGNARD EXCHANGE PROCESS (INTERNAL NUMBERING-UP)

Grignard reagents are useful reagents in organic synthesis and are widely utilized in laboratory synthesis[8] and in the industrial production of fine chemicals.[9] Although Grignard reagents are usually prepared by the reaction of organic halides with magnesium metal, Grignard exchange reactions (halogen–magnesium exchange reactions) are sometimes used for Grignard reagents that are difficult to prepare using a direct method.[10] Halogen–magnesium exchange reactions are usually very fast and highly exothermic, so they are difficult to control, especially in large-scale syntheses. The halogen–magnesium exchange reaction of ethylmagnesium bromide (EtMgBr) with bromopentafluorobenzene (BPFB) to give pentafluorophenylmagnesium bromide (PFPMgBr) has already been discussed in Chapter 8, so we will focus on the industrial application of this reaction in this section.[11] PFPMgBr is an intermediate compound in the production of tetrakis(pentafluorophenyl)borate, derivatives of which are useful compounds in metallocene catalyzed polymerization and photopolymerization. Usually, slow addition is used to avoid a rapid increase in temperature in the industrial process. Therefore, it takes a long time to complete the addition and therefore, the overall time efficiency is low.

It is crucial to increase the capacity of the reactor for industrial applications, and to increase the capacity of a heat exchanger in a microflow system; a shell and tube microheat exchanger, which contains 55 microtubes ($\phi = 490\,\mu$m) in the shell has been developed (Figure 10.6, see also Chapter 7). This is an example of internal numbering-up. The heat exchanger has only one inlet and one outlet, although it contains 55 microtubes inside.

Another important point that should be considered in industrial applications of microflow systems is an increase in the flow rate to increase productivity, because productivity depends on the flow rate as well as the cross-sectional area of the microchannel. Therefore, it is necessary to construct a system that avoids an increase in the pressure drop with increasing flow rate. The pressure drop in a system strongly depends on the structure and size of the micromixer used. As shown in Figure 10.7 the use of a T-shaped mixer leads to a small pressure drop, whereas the use of a

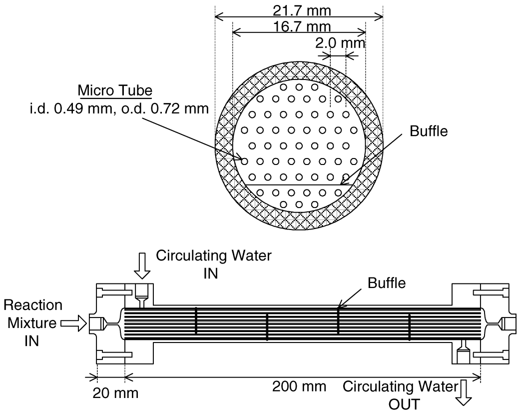


Figure 10.6 Shell and tube microheat exchanger. Copyright 2005 American Chemical Society

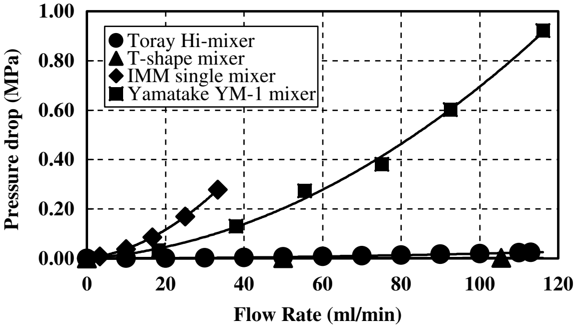


Figure 10.7 Plots of the pressure drop (DP) against flow rate (medium-scale reaction system). Effect of the structure of the micromixers. Copyright 2005 American Chemical Society

multilamination-type micromixer (an IMM single mixer) gives rise to a rapid increase in the pressure drop with increasing flow rate. The use of a Yamatake YM-1 mixer also gives rise to a significant increase in the pressure drop. However, the use of a Toray Hi-mixer is successful, and no appreciable pressure drop is observed until the flow rate reaches 100 mL/min (see Chapter 7 for the structures of these micromixers). However, the use of a T-shaped micromixer results in low yield at lower flow rates (<70 mL/min). This is presumably because of the low mixing efficiency of the T-shaped mixer at low flow rate, such as 25 mL/min. In contrast, the use of the Toray Hi-mixer gives rise to the formation of PFB (pentafluorobenzene), after protonation, in high yields, even at lower flow rate.

A microflow system for relatively large-scale production (i.e., a pilot plant) composed of a Toray Hi-mixer connected to a shell and tube microheat exchanger has been constructed (Figures 10.8 and 10.9). The

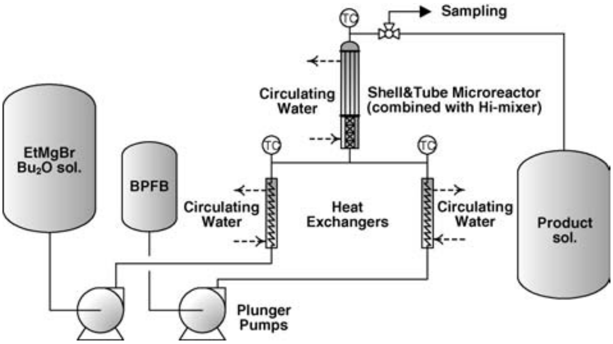


Figure 10.8 Schematic diagram of the pilot plant. Copyright 2005 American Chemical Society

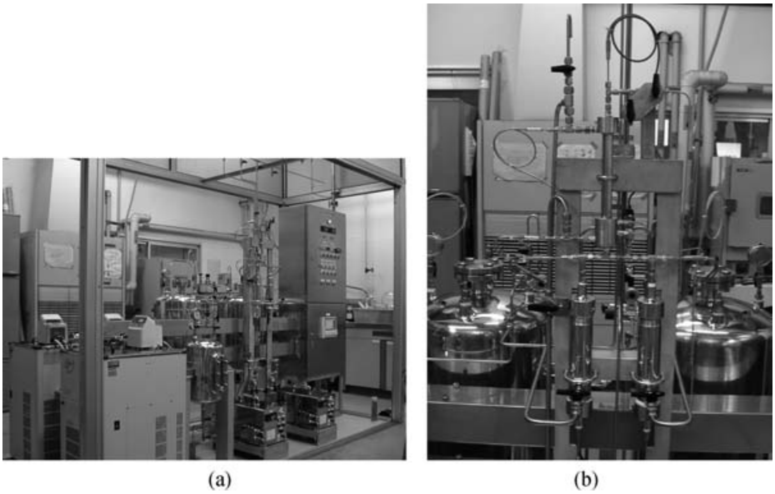

(a) (b)

Figure 10.9 Photographs of the pilot plant: (a) Full view; (b) microreactor. Copyright 2005 American Chemical Society

reaction temperature was automatically controlled at 20 °C by circulating water in the shell of the heat exchanger. An EtMgBr solution in dibutyl ether (1.3 M) and BPFB (8.0 M, neat) were introduced into the micromixer at 20 °C. The residence time in the device was ca. 5 s. The product solution containing PFPMgBr was immediately quenched using methanol.

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). It should also be emphasized that the industrial-scale production, which has been carried out using a batch reactor (10 m^3), was accomplished by numbering-up only four microflow systems of the present scale. The use of microflow systems should lead to a significant decrease in investment compared with current batch process.

The example described above indicates that microflow systems consisting of a specially designed micromixer and a microheat exchanger consisting of 55 microtube reactors are effective for conducting very fast and highly exothermic reactions, such as Grignard exchange reactions. Fast mixing and efficient heat transfer, which are inherent advantages of microsystems, seem to be responsible for the effective control of the reaction. The residence time is ca. 5 s. The data obtained on continuously operating the pilot plant demonstrate that the concept of flash chemistry can be applied to relatively large-scale production by internal numbering-up, and speaks well for its potential in the chemical industry.

10.4 RADICAL POLYMERIZATION PROCESS (NUMBERING-UP)

Polymerization[12] is an important process for the synthesis of polymers in the chemical industry, and the use of microflow systems has attracted significant research interest.[13]

As for radical polymerizations, the AXIVA group reported that the premixing of a monomer with an initiator using a micromixer is effective for the radical polymerization of acrylates.[14] The fraction of high-molecular-weight polymer decreased significantly using a micromixer in the premixing process before being fed into a millimeter-scale tube reactor for polymerization.

In Chapter 9, we mentioned that the use of microreactors leads to a significant improvement in the control of the molecular-weight distribution in free radical polymerization by virtue of superior heat-transfer efficiency.[15] Free-radical polymerization reactions are usually highly exothermic, so precise temperature control is essential to carry out these reactions in a highly controlled manner. Thus, from an industrial viewpoint, a major concern with free-radical polymerization is the controllability of the reaction temperature. Temperature control often arises as a serious problem during the scale-up of a bench process to industrial production. In this section, we will discuss the numbering-up of microreactors to increase production volumes in radical polymerization in industry.

The shell and tube microreactor shown in Figure 10.10 has been developed to increase the throughput. This is an internal numbering-up approach because the reactor is composed of 94 microtubes (stainless steel, inner diameter: 510 μm, length: 600 mm) in a shell (inner diameter: 60 mm, length: 600 mm). The total volume of all the microtubes is 9.6 ml. The shell is divided into two sections. Hot oil is introduced into the first part of the shell (length: 500 mm), and a coolant is introduced into the second part (length: 100 mm).

The radical polymerization of butyl acrylate (BA) and methyl methacrylate (MMA) initiated by AIBN in this numbering-up reactor (94 microtubes) exhibits a similar molecular weight and molecular-weight distribution control as those carried out in a laboratory microflow system containing a single microtube reactor. However, for the same reaction time in the BA polymerization, the polymer yield obtained with the numbering-up reactor is lower than that obtained using the single microtube reactor. This is explained as follows. In the MMA polymerization process, the viscosity of the solution does not vary, because the yield of the

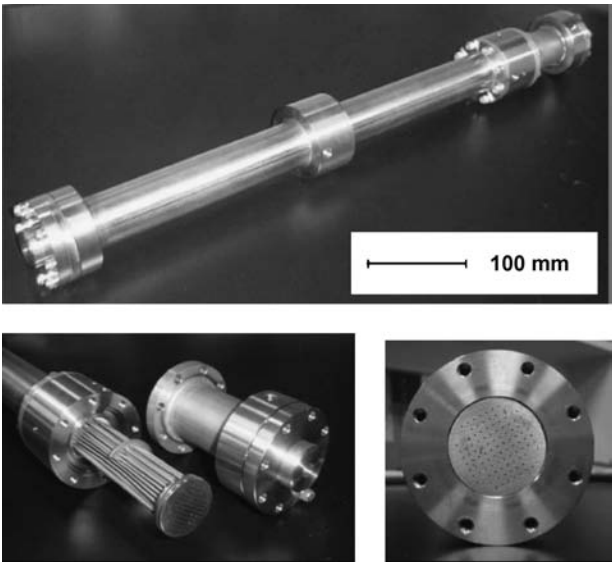
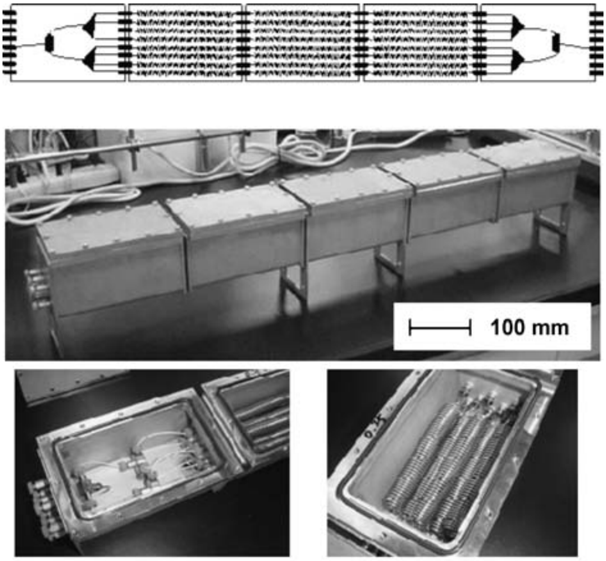


Figure 10.10 Photographs Showing the outside and inside of an internal numbering-up reactor. Copyright 2006 American Chemical Society

polymer is relatively low. However, in the BA polymerization, the viscosity of the solution increases significantly because the BA polymerization process is very fast. Therefore, the decrease in the yield in the BA polymerization process in the numbering-up reactor is attributed to the lack of flow uniformity. Some channels, presumably those located in the outer part of the reactor shell, become clogged because of the increase in viscosity. Thus, the number of effective channels decreases, causing a decrease in the average residence time. This leads to a lower yield of the polymer. The nonuniform flow is a major problem associated with numbering-up microflow reactors.

Uniformity of the flow rate is one of the most important factors for the design of numbering-up reactors. Another numbering-up reactor, composed of eight microtubes, has been designed and fabricated to attain uniformity of the flow rate (Figure 10.11). This reactor consists of five shells, which are coupled by tube connectors. The length of each shell is 178 mm, and the total length of the reactor is 904 mm. In the first shell, a single inlet tube branches into eight tubes under cooling conditions. Figure 10.12 shows the tube-branch structure using simple couplers. Polymerization is carried out in Shells 2–4, in which eight stainless steel coiled microtubes are placed (inner diameter: 250, 500, 1000 μm, length:



#1 Shell
(Tube divided section)

#2~4 Shell
(Reactor section)

Figure 10.11 Schematic diagram and photographs of the numbering-up reactor. Copyright 2006 American Chemical Society

1950 mm). The microtubes are heated by hot oil circulating in the shells. In the final shell, the microtubes are combined into a single tube, and polymerization is terminated by cooling.

This numbering-up reactor has the following excellent features from the viewpoint of industrial applications. First, there are only eight parallel

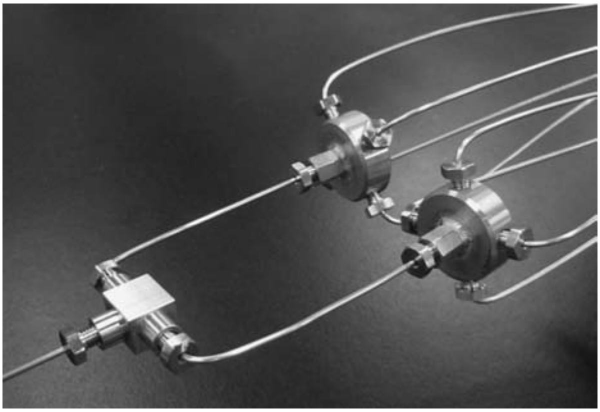


Figure 10.12 Tube-branch structure using simple couplers. Copyright 2006 American Chemical Society

microtubes, and the uniformity of the flow rate can be easily verified by measuring the outlet flows of all the microtube reactors that are not combined into a single tube in the final shell. The second feature is that the inner diameter of the microtubes can be easily varied. Microtube reactors of different inner diameters can be used for the polymerization in each shell. In general, high heat-transfer efficiency is needed at the early stage of the polymerization, because the monomer concentration is high and a large amount of heat of polymerization is liberated at this stage. Microtubes with a small inner diameter, which have excellent heat-transfer properties because of their high surface-to-volume ratio, are advantageous. However, such small inner diameter microtubes suffer from a high pressure drop. Therefore, it is reasonable to use microtube reactors with a small inner diameter only in the early stage of the polymerization. In the later stage of the polymerization, the microtubes with a larger inner diameter should be used to minimize the pressure drop and to increase the reactor volume to attain a high throughput. The larger reactor volume of the microtubes of larger inner diameter is advantageous, because a relatively long residence time is needed for completion of the polymerization.

In fact, the value of M_w/M_n for the polymerization using a single microtube reactor with three different inner diameters (250, 500 and 1000 μm) is smaller than that obtained using a single microtube reactor with a fixed inner diameter (500 or 1000 μm). Presumably, the high heat exchange properties of the first microtube (250 μm) are responsible for controlling the early stage of polymerization, which is highly exothermic. The later part of the polymerization is not so exothermic because the concentration of the monomer is lower. Therefore, microtubes with large inner diameters are sufficient to control the polymerization. This is a good example of the scale-up of a microflow system, where the size of the microstructures is increased as far as the controllability is acceptable. The third feature is the simplicity of the structure of the device. Complex fabrication is not required in the construction of the reactor, leading to minimizing in the cost of fabrication. It is also noteworthy that each microtube can be easily replaced in the case of clogging.

The polymerization of BA has been conducted using a combination of microtubes with different inner diameters (inner diameter: 250 μm, length: 1950 mm × 8 + inner diameter: 500 μm, length: 1950 mm × 8 + inner diameter: 1000 μm, length: 1950 mm × 8, total reactor volume: 16.1 ml). The values of the yield, molecular weight, and M_w/M_n for the polymerization of BA in the numbering-up reactor with different inner

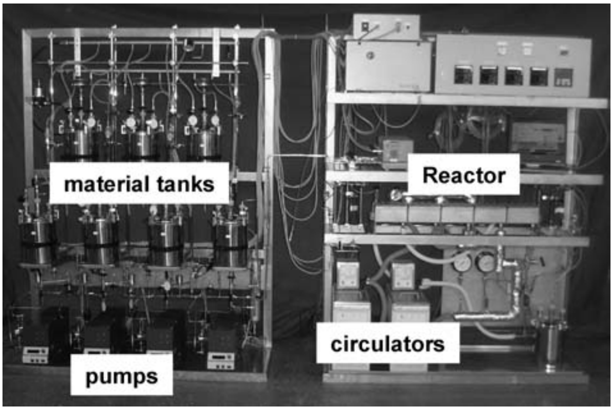


Figure 10.13 Photograph of the pilot plant. Copyright 2006 American Chemical Society

diameters are similar to those obtained using a single microtube reactor with different inner diameters. Thus, this numbering-up reactor does not suffer from the problem of a lack of uniform flow.

A pilot plant composed of a T-shaped micromixer (inner diameter: 250 μm) and a numbering-up reactor containing eight microtubes has been constructed (Figure 10.13). The width of the pilot plant was 3.5 m, and the depth was 0.9 m. A schematic diagram of the pilot plant is shown in Figure 10.14. A monomer (MMA, neat, 9.4 mol/L) is introduced using a plunger pump from a 10 L stainless steel tank with a flow rate of 30 or 55 mL/h and an initiator solution (AIBN in toluene, 0.05 or 0.09 mol/L) is introduced using a plunger pump from a 10 L stainless steel tank at a flow rate of 30 or 55 ml/h. The residence time is 18.4 or 10 min, respectively. The reaction temperature is automatically controlled at 100 °C by circulating hot oil in the shells and the cooling temperature is also automatically controlled at 25 °C by circulating water in the shells. The product solution is introduced into a 10 L stainless steel tank.

A most important technical point for the commercialization of microreactor polymerization is a stable, continuous operation without any problems, such as clogging. Thus, continuous operation using the above pilot plant was carried out over a period of 6 days at a flow rate of 30 ml/h (for MMA) and 30 ml/h (for AIBN). The operation was continuous without observing any increase in the pressure and the temperature of the reactor. The values of the yield, molecular weight, and M_w/M_n of the synthesized polymers did not change during the operation. The total volume of fluid passing through the process was 10 L, and the weight of

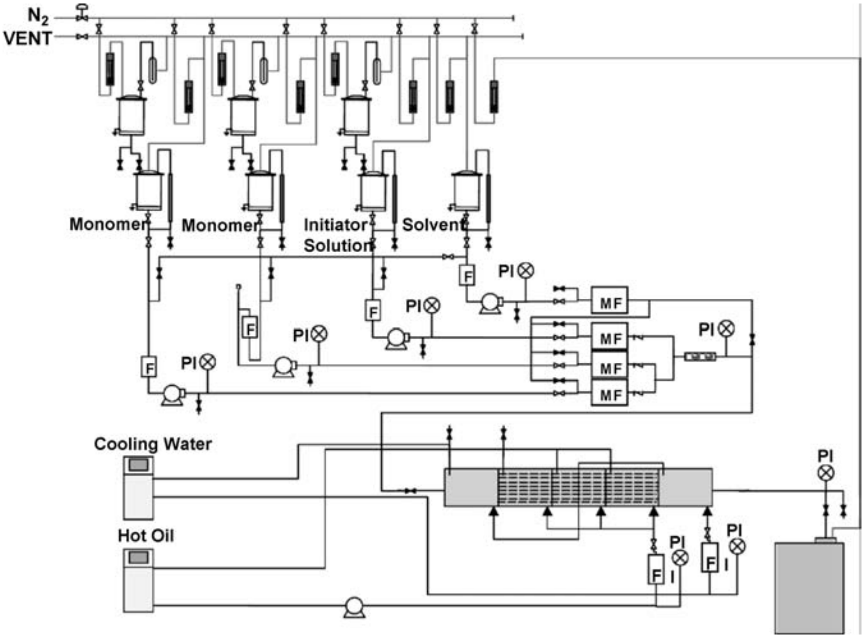


Figure 10.14 Schematic diagram of the pilot plant. Copyright 2006 American Chemical Society

product was estimated to be 2.5 kg after 1 week. The productivity can be increased by increasing the flow rate (55 and 55 ml/h, respectively). In this case, the total fluid volume was 19 L, and the weight of product was 4.0 kg after 1 week (Figure 10.15).

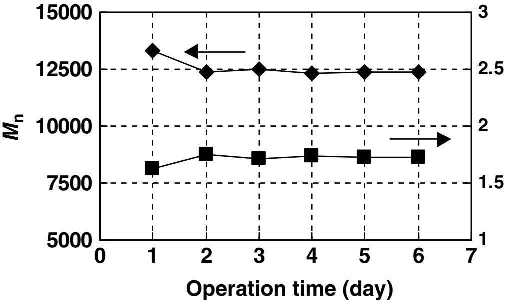


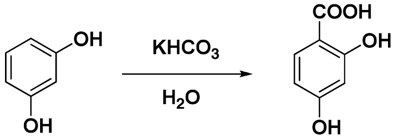
Figure 10.15 Plots of the molecular weight and M_w/M_n for poly(methyl methacrylate) versus operation time for continuous operation of the pilot plant for 6 days. Polymerization temperature = 100 °C, cooling temperature = 25 °C, [MMA] = 9.4 mol/L (neat), [AIBN] = 0.094 mol/L, flow rate = 55 and 55 ml/h, respectively, residence time = 10.0 min. Copyright 2006 American Chemical Society

The example described above indicates that a numbering-up microflow system consisting of several microtube reactors is quite effective for conducting radical polymerization. Precise temperature control by effective heat transfer, which is one of the inherent advantages of microflow systems, seems to be responsible for the effective control of the molecular-weight distribution. The data obtained with the continuous operation of the pilot plant demonstrate that the microflow system can be applied to relatively large-scale production, and speaks well for the potential of microchemical plants in the polymer industry.

10.5 OTHER EXAMPLES OF INDUSTRIAL APPLICATIONS OF FLASH CHEMISTRY

There are many other approaches to industrial applications of flash chemistry, although available information is limited. Let us briefly touch on some examples. The Kolbe-Schmitt synthesis serves as a useful standard method to introduce a carboxyl group into phenols (Scheme 10.6).[16] The Kolbe-Schmitt synthesis has been widely used in industry, and there are many variants of this transformation. Microflow systems can be used for conducting the Kolbe-Schmitt synthesis under aqueous high-pressure conditions.[17] A decrease in reaction times by an order of magnitude (a few tens of seconds instead of minutes) and increase in space–time yields by orders of magnitude can be attained using a microflow system. For example, a microflow system composed of five parallel capillaries (inner volume: 9 ml) has a productivity of 555 g/h, whereas the productivity of a macrobatch reactor (1 L flask) is 28 g/h.

The increase in production volume of the phenylboronic acid process using a microflow system has been studied.[18] At the laboratory stage, a throughput of 10 L/h is achieved using a minimixer, enabling the



Scheme 10.6 Kolbe-Schmitt synthesis

production of 6 kg of phenylboronic acid per day. Using higher capacity pumps, a throughput of 100 L/h is achievable with a caterpillar mixer, equivalent to the production of 20 ton/year of phenylboronic acid.

Integration of a microreactor (StarLam 3000 IMM microreactor) in an existing production plant (two-step batch process) has also been reported; the reaction type is unveiled in the paper by Kirschneck and Tekautz.[19] Installing a microreactor in the first reaction step leads to an increase in the capacity of the macrobatch process. An overall throughput of 3.6 ton/h has been achieved and the system has been running in production for more than a year.

Clariant reported that microreaction technology can be applied to the production of pigments on the pilot plant scale.[20] The azo pigments produced in a microreactor exhibited better color properties compared with azo pigments produced in macrobatch reactors.

10.6 FLASH CHEMISTRY AS A POWERFUL MEANS OF SUSTAINABLE CHEMICAL SYNTHESIS

Flash chemistry in industry has several advantages from the viewpoint of green sustainable synthesis. In 1987, the United Nations Commission on Environment and Development (the Brundtland Commission) called for a form of sustainable development that meets the needs of the present without compromising the ability of future generations to meet their own needs.

There are two key issues:

1. Development is not just about bigger profits and higher standards of living for a minority. It should be about making life better for everyone.
2. This should not involve destroying or recklessly using up our natural resources, nor should it involve polluting the environment.

The most widely accepted definition of green chemistry is ‘The design, development, and implementation of chemical processes and products to reduce or eliminate substances hazardous to human health and the environment’.[21] Anastas and Warner developed 12 principles of green chemistry,[22] which help to explain what the above definition means in practice.

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. In flash chemistry, chemical reactions are conducted as fast as they want to go. The characteristic features of microspaces mean that they serve as much better reaction environments than macrobatch reactors.
2. Energy saving. Conventionally, cooling is often used to attain acceptable controllability of fast reactions. However, the requirement of such low temperatures has been an obstacle to industrial-scale applications because of the energy requirements for cooling. The use of microflow systems 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 microflow systems leads to a high selectivity of the products. Therefore, less waste is produced.
4. On-demand and on-site synthesis. Synthesis based on extremely fast reactions using microflow systems enables on-demand and on-site synthesis. This leads to less energy for transportation. Production at a place close to the final users of chemical substances also enables easy recycling of substances. Such production is also beneficial from the viewpoint of concern about chemicals by residents who live close to production sites, leading to better understanding of the benefits and risks of chemicals.

10.7 CONCLUSIONS

In conclusion, several attempts at industrial applications of flash chemistry have already been made to meet the demands of the pharmaceutical and chemical industries, although more progress is urgently needed in the scaling-up and numbering-up of microflow reactors and continuous operation of microchemical plants under commercial conditions. It is also important to note that flash chemistry is expected to serve as a powerful means of green sustainable synthesis.

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Outlook for Flash Chemistry

The principles and examples of flash chemistry using microflow systems have been discussed in the previous chapters. Microflow systems serve as an effective method for the control of fast reactions. Extremely fast reactions can be conducted without deceleration in a highly controlled manner by virtue of characteristic features of microsystems, such as fast mixing, fast heat transfer, and short residence time. Synthetic reactions can be much faster when they are released from the restriction of a flask.

There is no doubt that flash chemistry using microflow systems will become a powerful research and development tool for synthetic chemistry. Reactions that would be impossible without microflow systems should become possible, as well as the development of many entirely new reactions. For example, microflow systems enable the generation of highly unstable reactive species that are then swiftly transferred to another location to undergo a further reaction in a controlled manner. Flash chemistry is also expected to play a major role in material production on an industrial scale. Reactions that are difficult to control using the methods of conventional macrobatch reactors can be controlled and carried out based on the concept of flash chemistry using microflow systems Furthermore, there are great expectations that the shift from synthesis in the laboratory to industrial production can be rapidly carried out using microflow systems.

It is also noteworthy that flash chemistry serves not only as a powerful tool for chemical synthesis in academia and industry but also as a fantastic tool to gain a deeper understanding of the individual and collective

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behavior of molecules. We can observe reactions as they are without decelerating using low temperatures or additives.

Therefore, the concept of flash chemistry may lead to a paradigm shift in laboratory chemical studies and industrial chemical production. It is hoped that various types of flash chemistry based on different methods of activating molecules and generating reactive reagents or intermediates, which may undergo a variety of reactions, will be developed and widely utilized in chemical research and in chemical plants to meet the demands of rapid and selective synthesis of various organic small molecules and polymers in the future.

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