

Chapter 2

Controlling Residence Time

Abstract For a batch reaction, the conditions within a reactor (the concentrations of materials and products) change with time. In contrast, for a flow reaction, the conditions within a reactor remain constant with time, but the conditions differ at different locations within the reactor. The reaction time for a flow reaction can be controlled by controlling the residence time in the flow reactor. Quench-flow method, in which a quenching reagent is added at the exit of the reactor to quantify the products with the residence time being varied, is effective for analyzing flow reactions. In a reaction involving an intermediate that easily decompose, a product can be obtained in a high yield only when a quencher is added in a time range during which a sufficient amount of the intermediate is produced and most of the intermediate is yet to decompose. Although a batch reactor can be used if the reaction is slow, a flow reactor is needed for a fast reaction (high-resolution reaction time control). Because the reaction rate depends on temperature, the temperature–residence time map, which can be obtained by the quench-flow method at different temperatures, is effective in optimizing the flow reaction conditions to obtain the product in a high yield.

2.1 Introduction

Chapter 1 describes the need to depart from flask reactions that researchers have long been accustomed to and move our focus on flow reactions to understand flow microreactor synthesis. This chapter describes one of the specific characteristics of flow reactions, i.e, residence time, and explores how such a characteristic can be used in controlling chemical synthesis.

A flow reaction is usually carried out at a steady state after some period of time passes from the initiation of the operation. At a specific location in the reactor, the concentrations of chemical species including starting materials, products, and reaction intermediates are temporally constant. However, the concentrations of the chemical species differ at different locations in the reactor. In contrast, the

concentrations of chemical species in a batch reactor, such as a flask, are constant at any location in the reactor after the reaction is started, as long as the solution is stirred sufficiently and is kept under well-controlled temperatures. However, the concentrations of the chemical species in the batch reactor change with time. These characteristics of flow reactions and batch reactions are described in Chap. 1.

2.2 Monitoring the Progress of a Reaction in a Flow Reactor: Inline Analysis

A question now is how we can monitor the progress of a reaction occurring in a flow reactor. The reactor using a microchip may be entirely imaged to determine the concentrations of specific chemical species at various locations. However, imaging the microtube reactor is not so easy. Also, types of chemical species that can be imaged are rather limited, and the accuracy of the method depends on the nature of the chemical species that we want to quantify. The concentrations of chemical species at different locations in a flow reactor may also be measured by sensors or measuring devices installed at the different locations in the reactor (inline analysis). A simpler method is to measure the concentrations by inline analysis at the exit of the reactor.

An example of such inline analysis is shown in Fig. 2.1, in which a flow attenuated total reflection (ATR) infrared spectrometer is installed at the exit of the

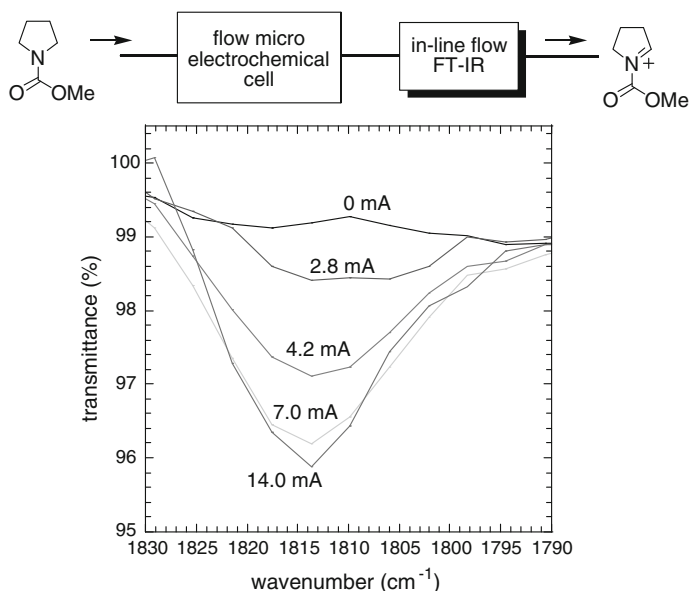


Fig. 2.1 An example of inline flow ATR analysis of an *N*-acyliminium ion generated by flow electrolysis [1]

reactor to analyze an *N*-acyliminium ion generated by anodic oxidation in the electrochemical flow reactor. The *N*-acyliminium ion shows a characteristic absorption at 1814 cm^{-1} due to carbonyl stretching vibration. The absorption intensity increases with the electric current, indicating that the concentration of the *N*-acyliminium ion increases with an increase in the current. Further increase in the current does not cause the increase in the concentration of the *N*-acyliminium ion. In this case, the concentration of the *N*-acyliminium ion can be determined by the inline flow ATR analysis.

2.3 Monitoring the Progress of a Reaction in a Flow Reactor: Quench-Flow Method [2, 3]

Inline analysis cannot be applied to quantitative analysis of all chemical species. Another method of monitoring the progress of a reaction is to add a quenching reagent (terminator) at the exit of the reactor and analyze the products with the residence time being varied by changing the length of the reactor or by changing the flow rate (quench-flow method). The products can be analyzed by conventional method for quantitative analysis such as gas chromatography or high-performance liquid chromatography, with which multiple chemical compounds can be analyzed at a time. Even in the case of a reactive species that is unstable and decomposes in a short time, a quenching reagent can instantaneously react with the species and convert it into a stable compound, which can then be analyzed by conventional methods to estimate the concentration of the active species.

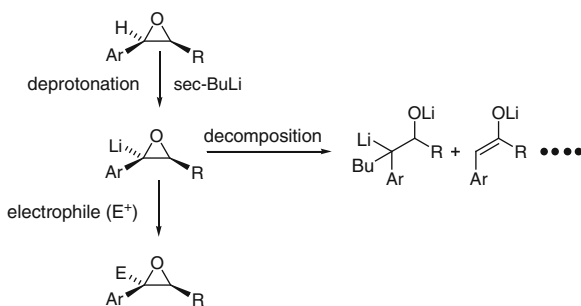
2.4 Generation and Reactions of Oxiranyllithiums: An Example of Quench-Flow Method [4, 5]

As described above, reactions in flow reactors can be analyzed by the quench-flow method. In the example described below, you will see how effective the quench-flow method is for tracing the reaction and optimizing the reaction conditions.

Oxiranyllithium species are useful intermediates in organic synthesis and react with various electrophiles to give substituted epoxides [6–12]. The treatment of epoxides having an electron-withdrawing group such as an aryl group and a silyl group with *s*-BuLi leads to removal of a proton attached to the carbon bearing the group. This generates an oxiranyllithium species as shown in Fig. 2.2. The oxiranyllithium species is known to undergo decomposition accompanied by opening of the three-membered ring. Preventing such decomposition is crucial in the synthesis of substituted epoxides using oxiranyllithiums.

For example, deprotonation of styrene oxide **1** to generate oxiranyllithium **2** in the presence of TMEDA (tetramethylethylenediamine) followed by the reaction

Fig. 2.2 Generation and reaction of oxiranyllithium



with methyl iodide at low temperatures such as $-95\text{ }^{\circ}\text{C}$ in a batch reactor gives the desired compound **3** in a reasonable yield. However, the reaction at higher temperatures such as $-78\text{ }^{\circ}\text{C}$ in the absence of TMEDA gives rise to a significant decrease in the yield (Fig. 2.3).

A typical procedure for this reaction in a batch reactor is as follows. A THF solution of styrene oxide **1** was placed in a 20-mL round-bottom flask. While the solution was being stirred with a magnetic stirrer in a dry ice cooling bath set at $-78\text{ }^{\circ}\text{C}$, a $s\text{-BuLi}$ solution was added with stirring. After being kept at the same temperature for a minute, a THF solution of methyl iodide was added. The desired product **3** was obtained in only 34 % yield, suggesting that a large portion of the oxiranyllithium species **2** decomposed during the time required by the dropping of

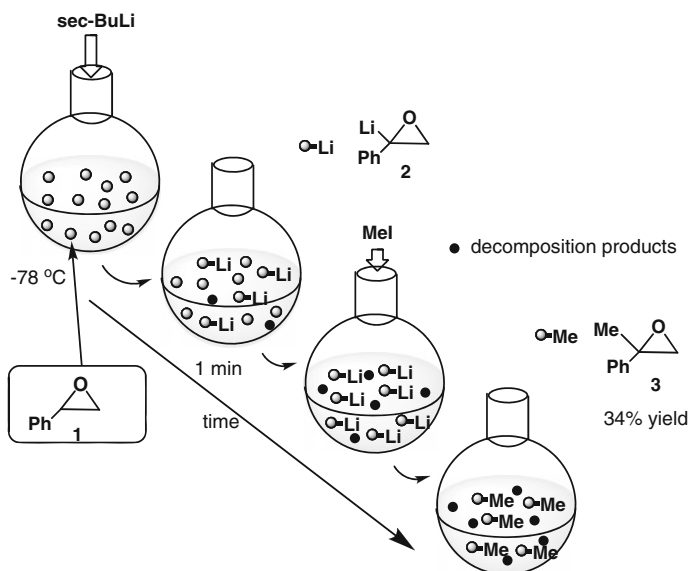


Fig. 2.3 Deprotonation of styrene oxide (**1**) to generate oxiranyllithium **2** followed by its reaction with methyl iodide (MeI) in a flask at $-78\text{ }^{\circ}\text{C}$

s-BuLi and the subsequent stirring to complete the conversion. To avoid such decomposition, the reaction should be carried out at lower temperatures in the presence of TMEDA.

The generation of oxiranyllithium **2** followed by its reaction with methyl iodide using a flow reactor can be carried out as follows (Fig. 2.4): A THF solution of styrene oxide **1** and a solution of *s*-BuLi are first mixed in a micromixer **M1**. Oxiranyllithium **2** is generated in microreactor **R1**. Subsequently, a THF solution of methyl iodide is added by using a micromixer **M2**. Oxiranyllithium **2** reacts with methyl iodide in a microreactor **R2** to produce the corresponding methylated product **3**, the concentration of which is determined by gas chromatography using an internal standard. The concentration of **2** is considered to be equal to that of **3** because we assume the reaction of **2** with methyl iodide is very fast. It is important to set an appropriate residence time in **R1**. The residence time should be sufficient for full conversion of **1** to **2**. However, the residence time should not be too long to allow decomposition of **2**.

The temperature is very important in controlling reactions because the rate of chemical reactions generally depends on the temperature. First, the reaction was conducted at $-78\text{ }^{\circ}\text{C}$ with the residence time being varied by changing the length of the reactor while keeping the flow rate constant. The amount of unchanged starting material **1** and that of product **3**, which were determined by gas chromatography, are plotted in Fig. 2.5 as a function of the residence time. Although these plots were obtained from separate experiments varying in the length (*L*) of the reactor **R1**, similar results must be obtained, in principle, for a single experiment using a long

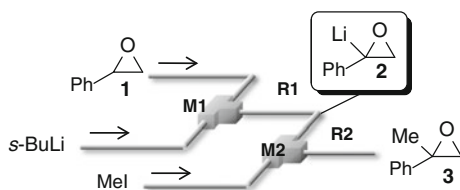


Fig. 2.4 Generation of oxiranyllithium **2** followed by its reaction with methyl iodide in a flow reactor

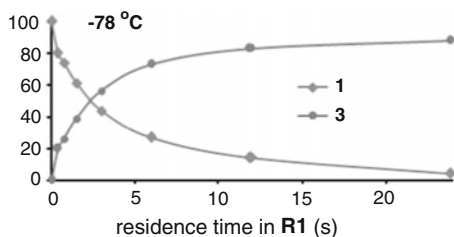


Fig. 2.5 Plots of recovery of **1** and yield of **3** against the residence time at $-78\text{ }^{\circ}\text{C}$

flow reactor on which several analysis devices are attached at separate positions of the reactor. The recovery of **1** decreases and the yield of **3** increases with an increase in the residence time. In other words, the reaction proceeds with increasing residence time. Most of **1** is consumed in the residence time of about 25 s. This indicates that the reaction between styrene oxide (**1**) and *s*-BuLi is complete within the period of about 25 s.

The product **3** results from the reaction of oxiranyllithium **2** with methyl iodide, and thus, the content of the reactor is oxiranyllithium **2** before methyl iodide is added. More specifically, the molecules of the starting material **1** are deprotonated by *s*-BuLi while flowing in the reactor, and most of the starting material **1** is converted into oxiranyllithium **2** in 25 s. Figure 2.6 is a schematic view of this phenomenon. At -78° , almost no oxiranyllithium species **2** decomposed in the residence time of 25 s, which is said to be the time necessary for deprotonation. This phenomenon is explained by the results indicating that the amount of the starting material **1** decreases with increasing residence time and the amount of product **3** increases monotonously accordingly.

In this manner, a flow reaction can have a short residence time, allowing the oxiranyllithium species **2**, which is an unstable reactive species with a short lifetime, to react with methyl iodide before the species decomposes. In contrast, a batch reaction cannot be completed in a short reaction time due to the time for its conduction needed for the reaction. A batch reaction on an extremely small scale may be completed within a reaction time of 1 min or less, but a batch reaction on a large scale cannot be completed in a short time because the dropping of *s*-BuLi to a solution of **1** requires an additional time. Fast dropping in a batch reactor may cause rapid increase in the temperature which accelerates the decomposition of **2**. Thus, flow microreactor synthesis can offer crucial advantages.

Although the reaction was conducted at -78°C above, the reaction is now conducted at a higher temperature. Typically, a reaction proceeds at a higher rate at a higher temperature. Thus, the reaction at a higher temperature is expected to complete in a shorter residence time. However, we must note that the reaction to produce oxiranyllithium **2** by deprotonation occurs at a higher rate as intended, but

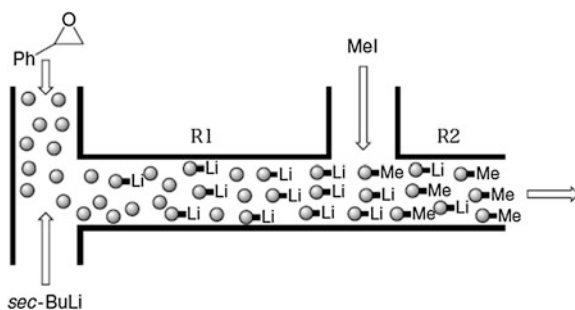
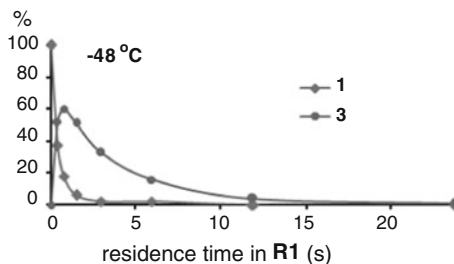


Fig. 2.6 Schematic view of deprotonation of styrene oxide (**1**) to generate oxiranyllithium **2** followed by its reaction with methyl iodide in a flow reactor

Fig. 2.7 Plots of recovery of **1** and yield of **3** against time at $-48\text{ }^{\circ}\text{C}$



the oxiranyllithium also decomposes at a higher rate. Focusing on this, the results for a reaction at $-48\text{ }^{\circ}\text{C}$ (Fig. 2.7) will now be discussed.

At short residence times, the amount of the starting material or styrene oxide **1** decreases rapidly and the amount of the product **3** increases rapidly with the increasing residence time. After reaching its maximum yield of about 60 %, the amount of the product **3** decreases with the increasing residence time. The decreasing amount of the product **3** indicates that the intermediate oxiranyllithium **2** has decomposed in the reactor. The oxiranyllithium **2** starts to decompose before the starting material, styrene oxide **1**, is entirely deprotonated and converted into the oxiranyllithium **2**. In other words, the generation and the decomposition of oxiranyllithium **2** are not completely separable.

In contrast, at $-78\text{ }^{\circ}\text{C}$, the generation and the decomposition of oxiranyllithium **2** are completely separable. The starting material **1** almost entirely converts into oxiranyllithium **2** before the oxiranyllithium **2** starts to decompose. Adding an electrophile thus allows the effective use of the oxiranyllithium **2** to obtain the desired product **3** in a high yield. However, this cannot occur at $-48\text{ }^{\circ}\text{C}$, indicating that simply controlling the residence time would not necessarily control the reaction, because the reaction rate usually depends on temperature. It is thus important to control temperature as well as residence time to allow the reaction to proceed selectively to obtain the desired product in a high yield.

2.5 General Consideration on Controlling Reactions Involving Unstable Intermediates [13]

General consideration on controlling reactions will now be described. Let us focus on a reaction in which a starting material (**S**) undergoes reaction to generate an unstable intermediate (**I**) with time while **I** decomposes with time to give a by-product (**B**) (Fig. 2.8). When a sufficient amount of intermediate **I** accumulates, an appropriate quencher (**Q**) is to be added to obtain a desired product (**P**). We will now qualitatively explore the conditions under which a batch reaction can produce a desired product in a high yield, and the cases for which a flow reaction is needed by simple calculations based on the kinetics.

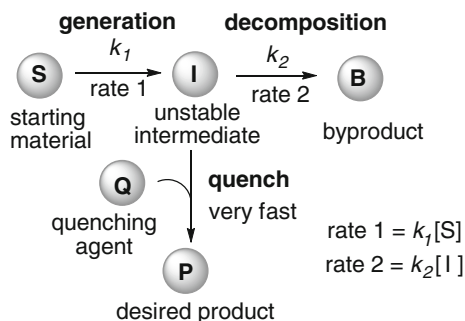


Fig. 2.8 General scheme of the reaction involving an unstable intermediate (I) which is trapped by a quenching agent (Q) to give a desired product (P)

To simplify calculations, the generation and the decomposition of intermediate I are assumed to be first-order reactions, and the reaction of I with Q are assumed to occur at a sufficiently higher rate. Figure 2.9 shows temporal changes in the concentrations of starting material S, intermediate I, and by-product B, where the rate constant of generation reaction of I k_1 is 10 h^{-1} , which is 100 times the rate constant of decomposition of I k_2 , and the initial concentration of S is 100.

The concentration of starting material S decreases with the increasing reaction time, and the concentration of intermediate I increases accordingly. In about 0.5 h, most of S is consumed and the concentration of I reaches its maximum. The concentration of I decreases with the further increase in the reaction time, because I decomposes into the by-product B. To obtain product P in a yield of 90 % or higher, quencher Q is to be added within the time range of about 0.25–0.6 h. This means that the reaction can be conducted in a flask without problems with its operations.

The situations change when the reaction is faster. A reaction at $k_1 = 10 \text{ s}^{-1}$ will now be discussed. The unit has been changed from hour to second, and thus, the reaction occurs at a rate that is 3600 times higher than the rate of the reaction described above. Although the concentration profiles shown in Fig. 2.10 are the

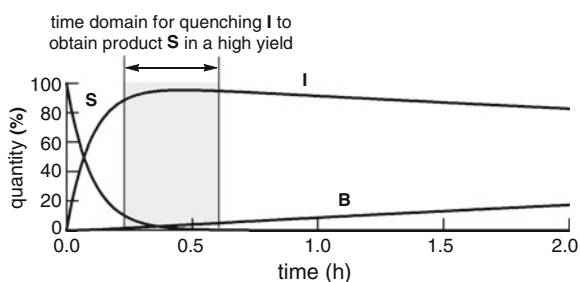


Fig. 2.9 Variation of the concentrations of starting material S, intermediate I, and by-product B with the reaction time for a slow reaction ($k_1 = 10 \text{ h}^{-1}$)

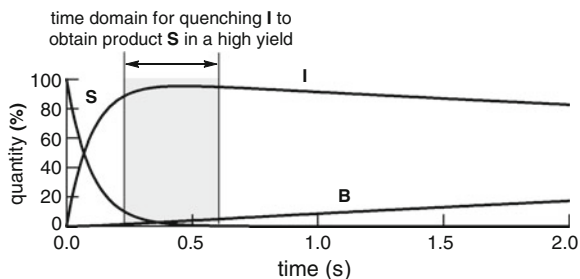


Fig. 2.10 Variation of the concentrations of starting material **S**, intermediate **I**, and by-product **B** with the reaction time for a fast reaction ($k_1 = 10 \text{ s}^{-1}$)

same, the reaction occurs in a different time unit, or specifically in seconds. In this case, product **P** can be obtained in a yield of 90 % or higher in the time range of about 0.25–0.6 s. This means that the reaction cannot be accomplished in a flask and that use of a flow microreactor is indispensable for such reactions. A flow reactor can set a reaction time precisely in an appropriate time range of the order of seconds or less and therefore allows product **P** to be obtained in a high yield. We call this high-resolution reaction time control. Notably, high-resolution reaction time control actually needs not only a flow reactor but also a microspace. We will discuss this in details in Chap. 3 and subsequent chapters.

However, the flow reactions also have limitations. If the generation and the decomposition of an intermediate occur at reaction rates substantially competing with each other, the maximum yield will be substantially low. This specifically occurs when k_1 and k_2 are substantially the same. In this case, controlling the residence time will not allow a product to be obtained in a high yield. One such example is the reaction of styrene oxide at -48°C as described above. In this case, lowering the temperature may separate the generation and the decomposition of intermediate **I**, and product **P** can be obtained in a high yield. When decomposition of **I** is faster than the generation of **I**, the desired product **P** mostly cannot be obtained under any condition. In this way, the flow reactions are also limited by the reaction kinetics.

We should keep in mind that heat transfer is also a key to the success of controlling unstable short-lived intermediates. The oxiranyllithium species can be used efficiently in the flow reactor not only because the reaction time can be set short in the flow reactor but also because heat generated in the deprotonation can be removed quickly by taking advantage of fast heat transfer, which is unique to microreactors, rather than to flow reactors. An important factor is the small diameter of the reactor and the large surface area per unit volume. To allow smooth generation and reaction of the oxiranyllithium species, the reactor thus must be a flow microreactor, instead of simply being a flow reactor.

2.6 Temperature–Residence Time Mapping

The reaction rate typically depends on temperature. The reaction rate usually increases with an increase in the temperature. The time required in a flow reaction also depends on temperature. Therefore, it is reasonable and also useful to plot the degree by which the reaction proceeds (the conversion of the starting material and/or the yield of the product) against both temperature and residence time based on the quench-flow method. Figures 2.11 and 2.12 are contour maps showing the plots of the conversion rate and the yield versus temperature and residence time for reactions in which oxiranyllithium is generated from styrene oxide and reacted with methyl iodide [4, 5]. The conversion of the starting material and the yield of the product are low at a lower temperature and a shorter residence time. The conversion and the yield increase with an increase in temperature and residence time. However, further increase in temperature and residence time causes a decrease in the yield because of decomposition of the oxiranyllithium intermediate. With this contour

Fig. 2.11 Plots of the conversion of styrene oxide **1** against temperature and residence

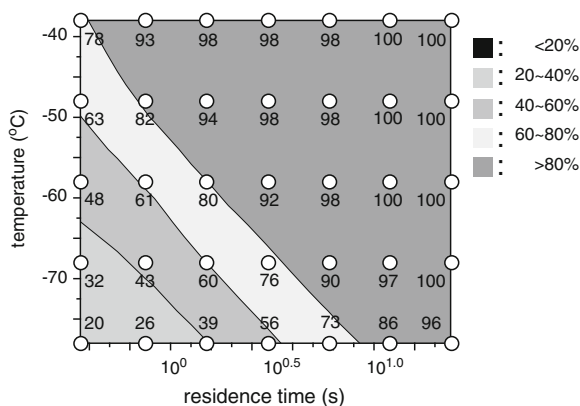
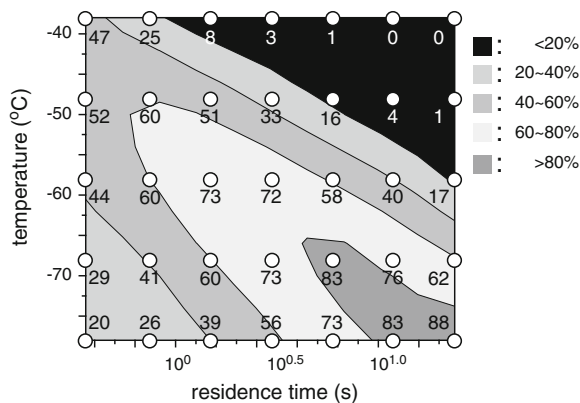


Fig. 2.12 Plots of the yield of methylated product **3** against temperature and residence



map, it is easy to determine the optimal temperature and residence time. Therefore, the temperature–residence time map serves as a powerful tool in analyzing flow reactions and optimizing the reaction conditions. Chapter 4 describes how to use the temperature–residence time map in detail.

2.7 Looking Forward

High-resolution reaction time control based on controlling the residence time discussed in this chapter is one of the most important features of flow microreactor synthesis. This feature enables chemical synthesis that cannot be done in batch. Some examples will be discussed in the following chapters.

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