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Flow Chemistry

Deciding Whether To Go with the Flow: Evaluating the Merits of Flow Reactors for Synthesis

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The fine chemicals and pharmaceutical industries are transforming how their products are manufactured, where economically favorable, from traditional batchwise processes to continuous flow. This evolution is impacting synthetic chemistry on all scales—from the laboratory to full production. This Review discusses the relative merits of batch and micro flow reactors for performing synthetic chemistry in the laboratory.

From the Contents

1. Introduction

Synthetic chemistry has advanced significantly through the application of traditional batchwise techniques. Recent interest, however, in the continuous flow production of fine chemicals has motivated a re-evaluation of how synthetic transformations are performed at the laboratory, intermediary, and manufacturing scales.[1] This evolution from batch to flow reactor design is not without controversy,[2] which can be expected with any disruptive technology. One should not invest time and capital for the sake of popular technique. Instead, an informed decision should be made to select the best reactor design based on the underlying transport processes and chemical kinetics that govern a desired reaction and reactor combination. Furthermore, such a decision should ultimately be made by chemists and engineers working together.

The application of small scale flow reactors (microreactors) in the laboratory environment can sometimes offer considerable advantages over batch reactor designs, but it depends on the nature of the chemistry, reactor design principles, and the overall goal. Faster kinetic information can be obtained by carrying out reactions in automated flow reactor systems, which in turn reduce development times.[3] Alternatively, batch reactors, such as 96-well plates, can be excellent tools in the rapid discovery of reactions. Time is expensive and time saved is a valuable reward in both academic research and process development. In process development, precise control over reaction conditions represents important aspects of microreactors that surpass the traditional flask.[1p,4] Flow reaction concepts become particularly important when reaction time scales are on the order of heat and mass transport time scales. A reduction in hazardous waste, safer synthesis of hazardous compounds, and the isolation of compounds sensitive to air and/or moisture represent additional advantages of flow reactors. These and other benefits of applying microreactors for synthetic transformations have been reviewed extensively.[1]

Chemical synthesis of fine chemicals and pharmaceuticals is often complex involving multiple reaction and separation steps, each with alternate pathways and technical approaches.[1a,5] Methodologies have traditionally been developed with batch technology, and this approach has worked quite well. However, performing reactions in flow can offer economic advantages over batch in terms of time, safety, and space.[1o,q,4,6] Nonetheless, scaling from the laboratory to production is not trivial.[7] Mixing in flow systems is relatively well characterized[8] in comparison to agitated batch vessels, which makes scaling of the former less ambiguous and hence faster. Fundamental differences in mixing and heat transport distinguish batch from flow reactors, and there is a close relationship between the choice of synthesis route and reactor design. For example, synthetic routes designed with flow in mind present the opportunity for flash chemistry[1r,9] and telescoping reaction steps. Alternatively, very slow transformations that cannot be accelerated by elevated heating and cooling are often best handled in batch reactors.

The choice of reactor design is influenced by a variety of factors, but reaction classification should not dictate this choice alone. Recent reviews highlight a broad cross section of the synthetic transformations relevant to fine chemical production.[1o,10] Most reactions important to the petrochemical and commodity chemical industries are heterogeneous catalytic processes, and these industries have for decades exploited the advantages of performing heterogeneous reactions in flow. The synthesis of fine chemicals in flow presents new and exciting challenges and opportunities for both homogeneous and heterogeneous transformations.

Chemical synthesis in flow has grown rapidly and has already been reviewed extensively[1] so yet another review is not our objective. Rather, our aim is to provide chemists and engineers with information useful in deciding whether to carry out reactions in batch or in flow reactors. Towards that goal we review reaction engineering and heat and mass transport concepts governing conventional batch and micro-

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chemical systems in laboratory environments. Although we mainly focus on principles as they relate to homogeneous reactions, the working concepts can be extended to heterogeneous reactions even though the transforming of homogeneous catalytic systems often represents a significant chemistry challenge. We employ selected examples to illustrate the underlying concepts and conclude by discussing the current limitations and outlook for future advances in reaction technology.

2. The Reality of Mixing

Mixing of reagents is typically the first consideration as the degree of mixing often influences the outcome of reactions. Conversion and selectivity are critically dependent on the quality of mixing when the rate of reaction is higher than the speed of mixing. However, even in the case of slow reactions, mixing inhomogeneity and corresponding spatial and temporal variations in reaction conditions can reduce yield. Batch reactors exhibit different mixing mechanisms as compared to microfluidic systems. These differences in mechanisms must be considered when choosing a reactor design to perform a particular chemical transformation.

2.1. Mixing at the Molecular Scale: Micromixing

The small length scales of microfluidic systems constrain fluid flow to the laminar regime. Viscous forces typically dominate over inertial forces (i.e., Reynolds number, $Re < 1$), and the absence of turbulence makes mixing dependent upon diffusion between fluids. This mixing at the molecular scale is referred to as *micromixing* and is often passive in nature (i.e., no mechanical energy is applied beyond pumping).[11] Figure 1 illustrates several examples of passive micromixing.

In homogeneous systems, side-by-side contact of miscible fluid streams, or lamination (see Figure 1 a),[11d] mixing is achieved by diffusion of molecules across the neighboring streams.[12] For a binary system, it can easily be shown that the characteristic time for the molecular diffusion of molecule A through a solution of molecule B and over a distance, x (x = diffusion path length), is inversely proportional to the molecular diffusivity, D_{AB} [Eq. (1)].

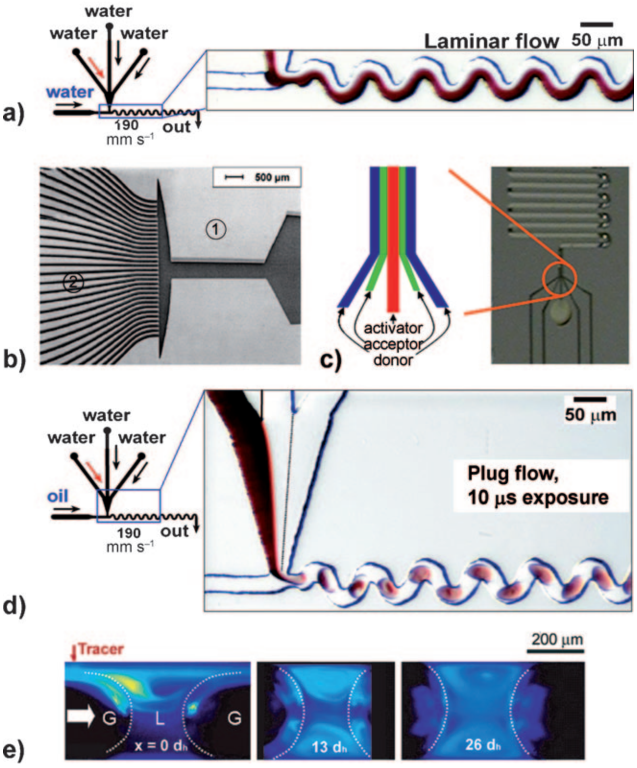

Figure 1. a,b) Examples of passive mixing in microfluidic devices. a) Side-by-side contact of pure water with a water stream containing a dye.[14] b) SEM image of a slit-shaped interdigital micromixer for the formation of multi-lamellae.[13] ① Mixing zone with focusing and reopening sections; ② interdigital flow distribution zone. c) Stacking of different reagents controls order of their contacts.[15] d,e) Examples of mixing with multiphase flows. d) Combining aqueous with organic liquids in a hydrophobic microchannel results in the formation of plugs, which rapidly mix the dye present in the aqueous phase.[14] e) Analogous mixing behavior is observed in gas-liquid segmented flows due to circulation within dispersed droplets. (Reprinted with permission from Ref. [16]. Copyright 1999 American Chemical Society.)

$$t = \frac{x^2}{D_{AB}} \tag{1}$$

In order to ensure a uniform concentration across the channel, the time it takes for a molecule to flow from the entrance to the exit of a microchannel (i.e., the residence time) must be greater than t. The value of x depends on the

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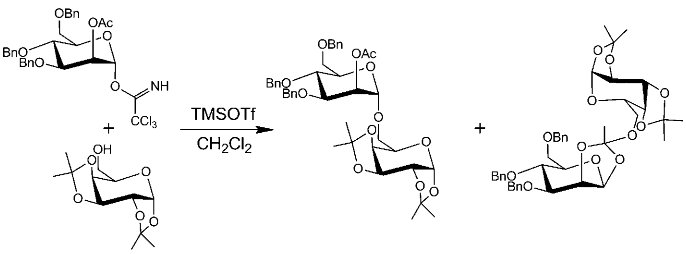
number of neighboring streams (or lamellae).[13] For the injection of two inlets, a uniform concentration is realized when a molecule diffuses one-half the microchannel width. For example, when two streams are contacted in a single 500 μm wide channel, the time required to reach a uniform concentration is approximately 30 s for a typical diffusivity of $10^{-9}\ \mathrm{m^2\,s^{-1}}$. This time scale is relatively long when considering fast reactions that go to completion in a matter of seconds or even minutes. For this reason, considerable efforts have been devoted to engineering micromixers with reduced length scales, such as those realized in the multi-lamellae arrangement of Figure 1 b.[13,17] Reducing the channel width to 40 μm yields a much faster mixing time of 0.2 s. Multiple laminate mixers have also been combined to handle large process flows (e.g., $4.0\ \mathrm{L\,h^{-1}}$).[18]

Another advantage of microreactors is ordering fluids in laminar flow as originally demonstrated for a number of diverse chemical examples.[19] In the case study in Figure 1 c, multiple reagent streams are "stacked" to control the order of contact of the reagents and minimize side reactions in the glycosylation reaction shown in Scheme 1.[15] This arrangement ensures that the donor only reaches the activator in the presence of the acceptor limiting the formation of an undesired orthoester product. Such ordered contact of fluids is difficult to achieve in a batch flask, which can lead to imprecise control over the mixing and hence the reaction conditions.



Scheme 1. The mannosylation of diisopropylidene galactose with mannosyl trichloroacetimidate upon activation with TMSOTf in dichloromethane. This glycosylation forms a desired product and an orthoester side product.[15] TMSOTf = trimethylsilyl trifluoromethanesulfonate.

In multiphase flows (e.g., gas–liquid, liquid–liquid, solid–liquid, and combinations thereof) in microfluidic systems, the transport distances between phases are reduced and the interfacial area significantly enhanced.[20] As an example, Table 1 gives the surface area per reactor volume of a typical microreactor (140 μL) filled with a homogeneous liquid, the interfacial contact between gas and liquid in the same microreactor, a 250 mL round bottom flask, and the interfacial contact between a liquid and a gaseous headspace. It is obvious that the microreactor offers at least two orders of magnitude greater surface area in both homogeneous and heterogeneous scenarios with corresponding two orders of magnitude improvements in performance of mass transfer limited reactions. The mixing performance can be further enhanced by the use of flow reactors packed with solids ("packed-beds") that further increase the interfacial area.[21]

Table 1: A comparison of the surface area per reactor volume for a typical microreactor and a round bottom flask.

Reactor type	Specific area $[\mathrm{m^2\,m^{-3}}]$
Microreactor[a]	10^4
Microreactor (gas–liquid)[b]	5000
250 mL Round bottom flask	80
Round bottom flask with headspace[c]	20

[a] For a reactor volume of 140 μL and a 400×400 μm channel. [b] Assumes equivalent volume of gas and liquid with an average gas plug length of 2× the channel width. [c] Assumes the flask to be half filled with liquid.

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Mass transport between phases is problematic in large scale reactors, whether it is in flow or batch. Increasing the interfacial contact between phases directly influences the overall mass transport coefficient, $k_L a$. Consequently, the interfacial mass transport coefficient observed in a microreactor can range from $0.05–15\ \mathrm{s^{-1}}$ as compared to $0.001–0.02\ \mathrm{s^{-1}}$ in standard laboratory-scale reactors.[21c,22]

The creation of a segmented flow, "slugs" of one fluid in the second fluid moving through the reactor, also enhances mixing relative to the homogeneous case, as is shown in Figure 1 d.[14] In this example, the microchannel surface is hydrophobic and thus the oil phase wets the walls while the aqueous phase forms isolated segments within which mixing occurs rapidly compared to the homogeneous case (Figure 1 a). The fluid in contact at the wall is stationary (i.e., the velocity is zero and thus the fluid does not slip at the wall). The no-slip fluid flow boundary condition at the walls gives rise to circulation within dispersed droplets, which resembles mixed, micro-scale batch reactors (Figure 1 e).[14,16,22–23] Advantages of enhanced micromixing by multiphase flows have been well documented in a number of synthesis related applications[11e,f,24] including most recently, library generation[25] and catalyst screening.[26]

2.2. Active Mixing and Mixing at Larger Scales: Macromixing

Active mixing in microfluidic systems is achieved by applying external forces (Figure 2). Magnetic microimpellers have been engineered to drive mixing in a continuous stirred microreactor (Figure 2a),[27] but the small dimensions mean that *Re* is small and mixing less effective than in larger vessels. The unsteady injection of fluids through side channels can significantly enhance mixing through oscillating pumps (Figure 2b).[28] Peristaltic pumps (Figure 2c) built with poly(dimethyl siloxane) (PDMS)[29] provide rapid mixing when fluids are cycled through herringbone mixers,[30] but the chemical compatibility of elastomers is often a challenge.[31] Ultrasonic mixers have been engineered by direct contact of devices with a piezoceramic (Figure 2d).[32] Fluctuation of electric and magnetic fields and forcing thermal gradients have also been used to induce mixing.[11d,17a,33] Periodically changing the flow rate can disrupt fluid flow and also result in enhanced mixing.[34] Reviews give additional creative ways to achieve both passive and active micromixing along with a more extensive discussion of the governing principles.[11]

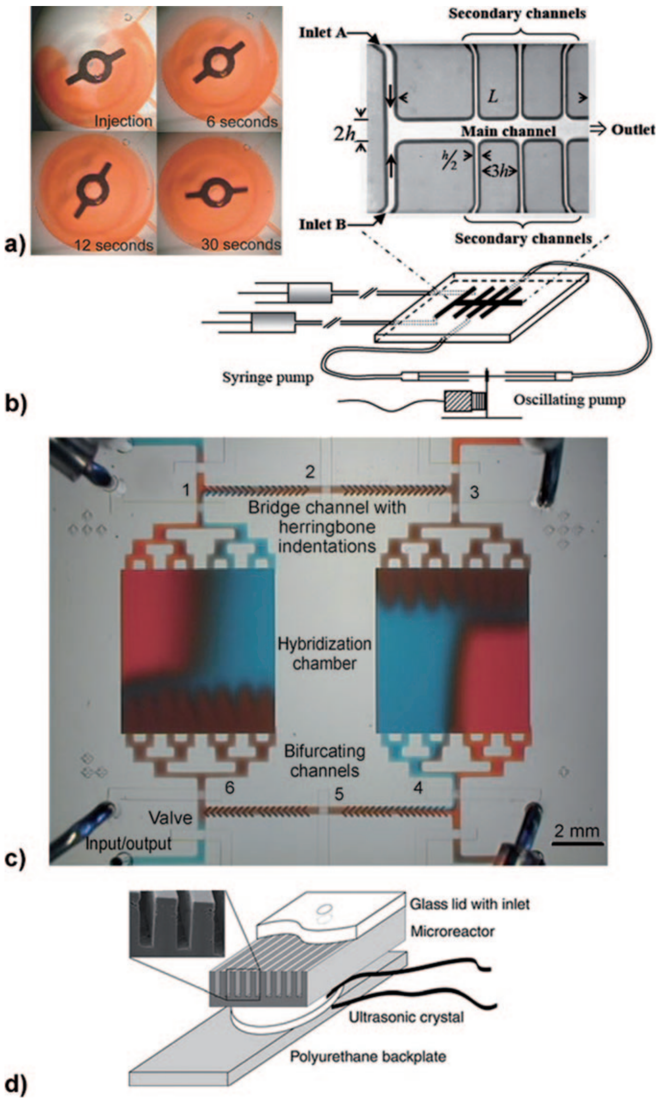


Figure 2. Examples of active mixing in microfluidic devices. a) A microbioreactor with integrated magnetic microstirrer. The images show a sequence of photographs during the mixing of dye.[27] b) An unsteady vortex motion imposed by an oscillating pump through side channels can significantly improve mixing in a microfluidic channel (Reproduced by permission of The Royal Society of Chemistry).[28] c) Chaotic mixing is realized by directing fluid flow through herringbone mixers with elastic, pneumatic peristaltic pumps.[30] d) An ultrasonic mixer by the integration of piezoceramic crystals and microfluidic devices.[32a]

In laboratory scale flask reactors, macromixing is realized by way of mechanical agitation (Figure 3), and it is strongly dependent on the power consumption for a given reactor and the circulation time of a neutrally buoyant particle. Patterns in batch reactors are chaotic and take the form of laminar, turbulent, or transitional flows. For flow in a cylindrical pipe, the flow is considered to be laminar when $Re < 2100$ and fully turbulent when $Re > 4000$. Classification for mixing in a batch vessel, however, depends on the impeller (or stir bar) being used. The Reynolds number of a vessel is expressed in terms of the impeller diameter, d_{imp}, and is given by Equation (S1) (see Supporting Information). The flow is laminar in the vessel for $Re < 100$, and turbulent for $Re > 10^4$, and for a range between 100 and 10^4, the flow is transitional.[35] Most laboratory scale reactors are laminar or transitional while production scale reactors are generally turbulent. In the transitional regime, the flow is turbulent at the impeller (or stir bar) and laminar in remote parts of the batch vessel.[35,36] In batch vessels, mixing is influenced by Reynolds number as well as geometrical factors of a given impeller, such as the pitch and number of blades. In fact, considerable efforts have been made in recent years to better understand and thus improve mixing in batch vessels because scaling from the

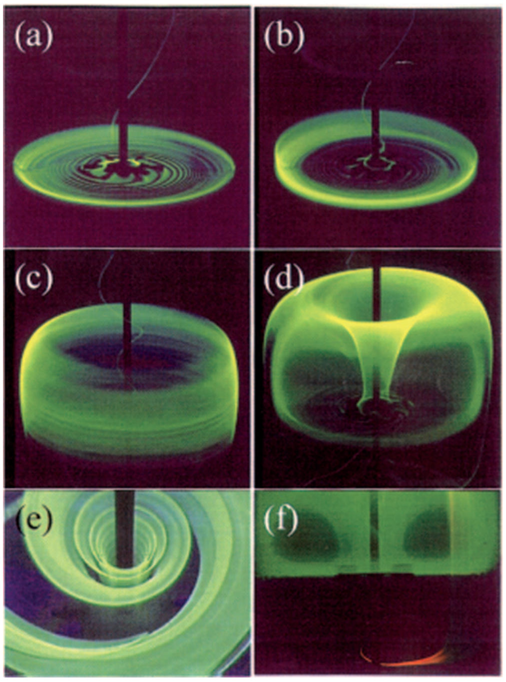


Figure 3. A sequence of snapshots illustrating how fluorescent dye is dispersed in a stirred vessel. The evolution of dye by the stirring action is shown at a) 3, b) 5, c) 10, and d) 30 s. e) A Helical ribbon is observed to form after 3 min. f) The dye is confined, or segregated, to the upper compartment of the vessel.[38c]

laboratory to industrial reactors is ambiguous.[7,37] Laboratory stirrers, such as magnetic stir bars, are less efficient when compared to a 3-blade propeller with 4 static baffles. Thus, complex stirrer designs such as multi-blade agitators and static baffles have been integrated to minimizing segregation with chaotic mixing.[38]

As an example of macromixing, Figure 3 shows the evolution of laminar mixing in a 20 L stirred tank.[38c] For $Re = 20$, a fluorescent dye (rhodamine G) was injected close to the shaft of a single impeller into the the 20 L vessel filled with glycerin. Exposure to UV light illustrates a sequence of snapshots taken at 3, 5, 10, and 30 s (Figure 3 a–d) as the dye was dispersed within the vessel. A pattern of nested spirals is observed after 30 s (Figure 3 d) while Figure 3 e shows the formation of a helical ribbon after 3 min of mixing. Interestingly, the dye remains confined to the upper compartment of the tank (Figure 3 f). The regions with and without dye are segregated from one another in that the exchange of molecules takes place by diffusion.[39] This classical segregation presents challenges in terms of batch mixing processes. If undisturbed, then the dye would eventually diffuse across lamellae to other regions within the vessel. Reducing the vessel dimensions (e.g., 250 mL flask) helps to decrease the diffusion time described by Equation (1), but it may not eliminate segregation altogether in laminar mixing. Moreover, the time scale for such diffusion could be on the order of a reaction time scale.

As a measure of the time scale for macromixing, let us now consider the case of the mixing of water-like fluid (at 20 °C) in a 250 mL cylindrical flask (diameter, $d_{flask} = 55$ mm) with a 2.5 cm magnetic stir bar set to 500 rpm. In this case, mixing is transitional from laminar to turbulent (see Supporting Information). In this regime, the limiting mixing time is dependent upon liquid circulation rather than diffusion. The mixing time based on liquid circulation, $\Theta_{95\%}$ (e.g., the time to be considered 95 % mixed), is estimated for the transitional regime to be (8.3 ± 1.4) s.[35,36b] The time for 99 % mixing ($\Theta_{99\%}$) increases to (19.1 ± 3.3) s.

The batch mixing time can vary by an order of magnitude depending on the stir rate (Figure 4 a), and it can change by as much as four orders of magnitude depending on the type of impeller, rotation speed, and ratio of d_{imp}/d_{flask} (Figure 4 b)—a 3-blade propeller at 300 rpm is less efficient than 6-blade turbine at 600 rpm. Consequently, efforts must be undertaken to estimate the mixing time for a specific agitator design. Correlations such as Equation (S4) can be applied to estimate the mixing time, but the best approach involves the experimental measurement for a given reactor.

Macromixing is also inherent to large scale flow equipment. Continuously stirred tank reactors (CSTRs) are essentially batch equipment with inlets and outlets so the mixing characteristics parallel those described above. The important issues for flow in tubes are achieving rapid cross streamwise mixing and reducing dispersion. These goals are typically achieved by using static mixers that use fixed shapes inside the flow tube to divide, twist, and recombine the fluid to create progressively thinner fluid layers with enhanced transport between layers. Enhanced mixing can also be realized by using obstacles (e.g., solid rods, rings, spheres) packed inside the tubes to generate flow separations and vortices, but high Re flows are required.[40]

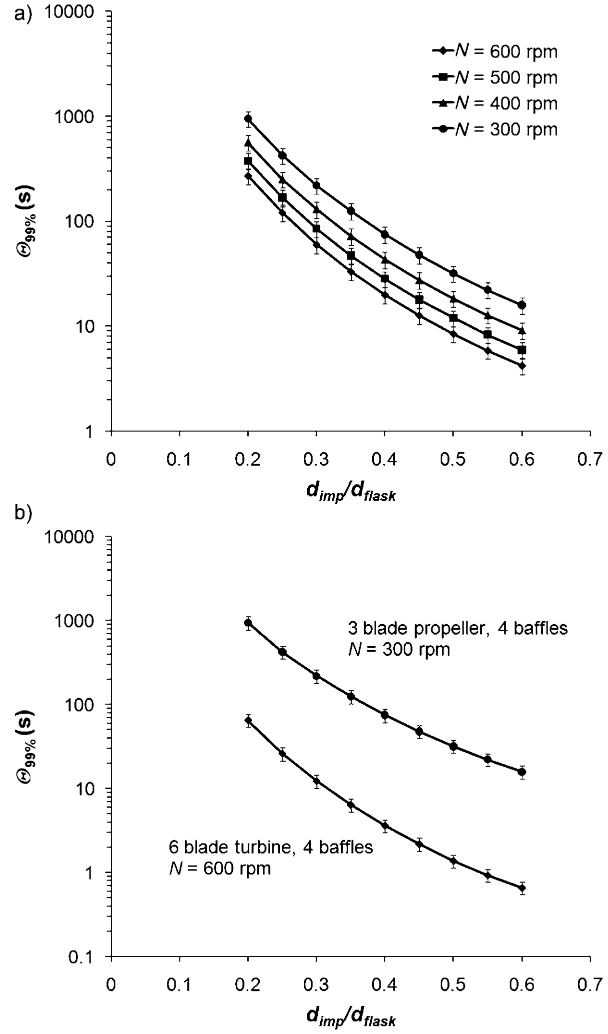


Figure 4. Time to achieve 99 % mixing ($\Theta_{99\%}$) as a function of the ratio of impeller to tank diameter for various stir rates and impeller designs. (Details of the method of calculation[35] are given in the Supporting Information)

2.3. Why do We Care About the Reaction Rate Relative to Mass Transport?

From the above review on mixing phenomena, there exists a time scale for mixing processes, which is dependent on the mixing mechanism. A reaction time scale is defined by the kinetics. This intrinsic time scale is measured in the absence of transport limitations (such as inadequate mixing) and is predicted by the appropriate rate model and parameters. The undetected existence of transport limitations leads to falsification of experimentally measured kinetics. The relative importance of reaction and transport effects is represented by the Damköhler number, Da, as the ratio of the reaction rate relative to the mass transport rate (e.g., [reaction rate]/[mass transport rate]).[41] The mass transport rate in a microreactor is the diffusion rate [Eq. (1)], and hence the Damköhler number can be written for an n^{th} order reaction as

$$Da_F = \frac{k_r C_0^{n-1}}{\left[\frac{2D_{AB}}{x^2}\right]} \tag{2}$$

where k_r is the specific reaction rate and C_0 is the initial reagent concentration. In batch vessels, the mass transport rate can take a form of 1) the diffusion rate when segregation exists and 2) the time for macroscopic mixing due to liquid circulation. For ideal mixing (i.e., no segregation), Equation (2) can alternatively be expressed in terms of the circulation mixing time, $\Theta_{99\%}$, for a batch reactor:

$$Da_B = \frac{k_r C_0^{n-1}}{\left[{}^{1}/_{\Theta_{99\%}}\right]} \tag{3}$$

In general, chemical transformations are reaction rate limited when $Da < 1$ and mixed mass transport-reaction rate limited when $Da \approx 1$. When $Da > 1$, experimentally measured reaction rates are controlled by mass transport.

The importance of the magnitude of the Da number depends on the primary goal of carrying out a reaction. For example, in syntheses with multiple reactions, maximizing yield or selectivity of the desired product is typically best accomplished when transport limitations are eliminated (i.e., $Da < 1$), but can be difficult in production scenarios. Reaction screening applications, on the other hand, can tolerate $Da \approx 1$. This is especially true when the main goal involves the identification of reactivity without optimizing conditions or kinetic parameters. For mechanistic investigations and the extraction of accurate rate models, a synthetic transformation should be reaction rate limited (i.e., $Da < 1$). Otherwise, the experimentally measured kinetic models and parameters cannot be used accurately to predict production operations upon scaling up. Synthetic transformations performed under mass transport limited conditions (i.e., $Da > 1$) mask the potential discovery of reactions, mechanisms, and effective catalyst–ligand combinations.

The Bourne and Villermaux–Dushman methods, which rely on competing reaction and diffusion rates,[42] are experimental approaches to characterize mixing. In the latter method, which has been particularly popular in micromixer studies,[42a,c,43] small diffusion lengths brought about by successful micromixing inhibit a competing reaction (i.e., triiodide formation) detectable by UV/Vis spectroscopy. Triiodide detection is possible when the time scale for mixing is on the order of or greater than the rate of formation of acetic acid (i.e., poor mixing). Thus, the experimental approach can elucidate relative mixing performance in a number of configurations, including batch and flow. As shown in Figure 5, a variety of flow and batch scenarios yields entirely different mixing results.[42a] The dropwise addition of HCl to a glass batch reactor filled with $I^-/IO_3^-/NaAc$ solution illustrates the need for stirred agitation. In the case of flow, a micromixer having channel widths of 40 μm showed enhanced mixing over macroscopic mixing tees and the batch reactors. For a more detailed analysis, Falk and Commenge have recently reported the performance of different micromixer designs.[44]

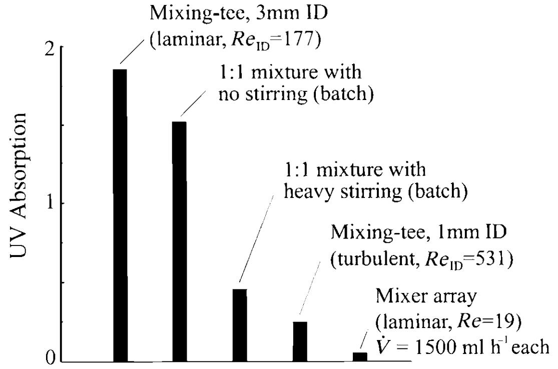
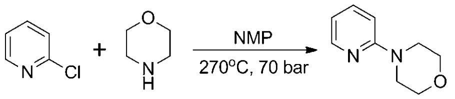
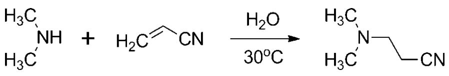
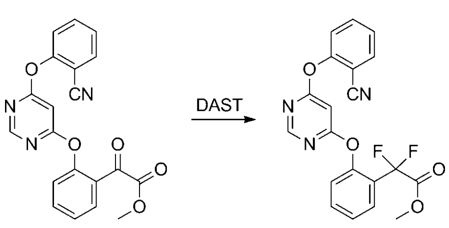
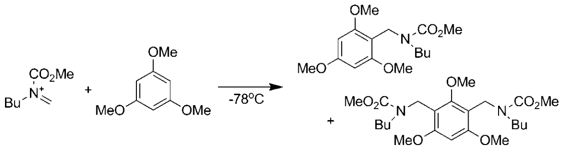
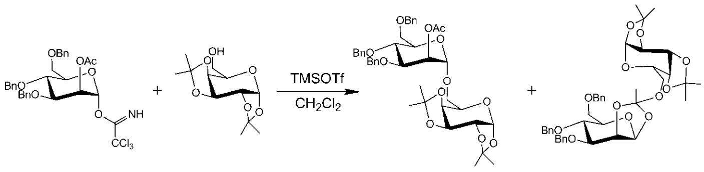
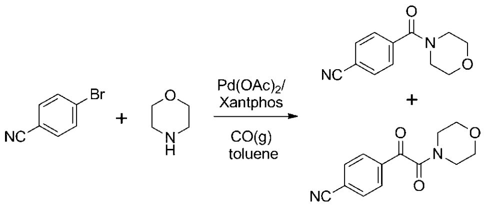
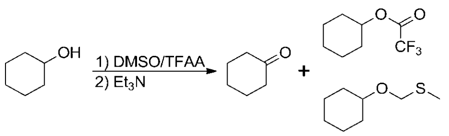


Figure 5. Comparison of mixing of a mixer array having a channel width of 40 μm and a depth of 300 μm to that of batch and continuous-flow macrosystems at a fixed volume flow of 1500 mL h^{-1} for each inlet (Reprinted with permission from.[42a] Copyright 1999 American Chemical Society.).

In batch reactors, it must be demonstrated that increases in agitation (e.g., impeller speed) have no effect on the rate of a reaction. Moreover, kinetic studies must be carried out at speeds well above the minimum observed to influence a reaction rate. This approach ensures that $Da < 1$. Otherwise, $Da \geq 1$ and the measured kinetics actually describe a mixed mass transfer-reaction rate controlled or a mass transfer controlled reaction. These conditions hold for both homogeneous and heterogeneous systems (e.g., slurry, an aqueous-organic biphasic mixture, the bubbling of a gas through liquid, or various combinations).

Mixing limitations may exist for virtually any chemical reaction as higher temperature and pressure conditions are pursued and more efficient catalysts discovered. The decomposition of reagents, products, and catalyst may ultimately limit how fast we can accurately perform reactions while extracting useful kinetic information. Certain classes of chemical transformations are susceptible to mixing limitations even at ambient or cryogenic temperatures.[45] Such reactions generally go to completion within seconds to several minutes. Table 2 shows selected examples of these fast homogeneous reactions and a few others that have been performed in microflow. In one example, the Friedel–Crafts aminoalkylation of aromatic compounds with *N*-acyliminium ion pools is particularly fast and involves the formation of competitive byproducts.[9c] When the time scale for mixing is greater than the reaction time scale (i.e., $Da > 1$), there is a concentration gradient of the compounds throughout the reactor. Under these conditions, a greater local concentration of the monoalkylated product exists, and effectively accelerates the reaction with the excess *N*-acyliminium ion to form the dialkylated product. This aminoalkylation was performed (at −78 °C) by injecting reagents into a T-shaped tube mixer (diameter 500 μm), an IMM (Institut für Mikrotechnik Mainz GmbH) micromixer with a channel width of 25 μm, and by the drop wise addition of *N*-acyliminium ion into a 50 mL flask.[9c] Carrying out the reaction in batch and in the T-shaped mixer resulted in virtually identical yields of monoalkylation (ca.

Table 2: Selected examples in which enhanced mixing in microflow directly influences the outcome.

Reaction type	Example[a]	Benefit from microflow reactor	Highlight	Ref.
C–N Bond formation (e.g., direct amination, Michael additions)		Reaction accelerated by operating at elevated temperature and pressure	82% Yield in 8 min; batch reaction requires days for unactivated substrates	[52]
		Enhanced mixing accelerated reaction—able to screen conditions for several reactions	98.7% Yield in 1.6 min; batch reaction takes 16–24 h	[53]
Electrophilic substitution of aromatics (e.g., haloganation, Friedel–Crafts aminoalkylation, nitration)		Selective fluorination with DAST, which is volatile, reacts violently with water, and undergoes dismutation above 90 °C	94% Yield without the aforementioned hazards/ challenges	[54]
		Fast mixing eliminated the competitive formation of dialkylation product	92% Yield of monoalkylation product; batch reaction yielded 36%	[9c]
Natural product synthesis (e.g., Glycosylation)		Laminar flow allowed control and optimization of selectivity through precise ordering and contact of reagents	Orthoester favored at −70 °C and < 1 min, whereas desired product was favored at −60 to −40 °C and ca. 3.5 min; difficult to control in batch reactors	[15]
Organometallic (e.g., Heck aminocarbonylation)		Optimization of selectivity at elevated temperature and pressure; enhanced mass transport through gas–liquid segmented flow	Amide favored at high temperatures and α-ketoamide favored at lower temperatures	[24e]
Oxidation (e.g., Moffatt–Swern type)		Fast micromixing prevented by-product formation by Pummerer rearrangement	88% Yield of carbonyl compound at 20 °C in 10 ms; batch yield of 19% at −20 °C	[9d]

[a] NMP = *N*-methylpyrrolidone; DAST = diethylaminosulfur trifluoride; DMSO = dimethyl sulfoxide; TFAA = trifluoroacetic acid.

36%) and dialkylation (ca. 31%) products. However, reducing the channel dimensions in flow, and hence the diffusion length scale, increased the yield and selectivity of the monoalkylation product to 92%. This example illustrates the importance of rapidly establishing a uniform concentration within a given reactor before a competing reaction has time to proceed.

Table 2 also includes aminocarbonylation as an example where gas-liquid contact in microflow (e.g., Figure 1 d and e) enables precise control over selectivity. Heterogeneous reactions such as halogenations,[46] hydrogenation,[21a,c,47] hydrolysis,[48] nitration,[49] and palladium-catalyzed C–C bond formation,[50] to name a few, have been carried out in microflow with advantages over traditional batch. In fact, any heterogeneous reaction has the potential for mass transport limitations, which could be addressed using microflow reactors. Consequently, microflow reactors have become useful tools for industrially relevant synthesis routes.[1o,4,6b,51] However, mixing is not the only challenge in designing reactors—heat addition and removal also influence the accuracy of kinetic information.

3. If You Can't Stand the Heat, Get Out of the Flask

Our discussion of mixing illustrates the close ties between synthetic chemistry and reaction engineering. The process of developing the most efficient pathway to the desired compound is often an arduous and laborious task in itself; however the selection of reactor type for these transformations cannot be overlooked. Consideration to the synthesis route alone runs the risk of flawed reaction optimization and kinetic investigations, resulting in longer and more costly development times during reaction scale up and a lower knowledge baseline for the reaction. Effective heat transfer is one reactor property that warrants deliberation when choosing a flask or microflow reactor. First, we will consider how the characteristic length scale alone plays a role in selecting the appropriate reactor configuration, and then we will discuss the importance of the material of construction.

Selecting the appropriate reactor for heat transfer purposes is related to the ratio of two different time scales—a comparison of the time scale of reaction to the time scale for heat removal/addition. For exothermic reactions, the rate of heat transfer in a reaction system is dependent on several factors:

- rate of heat generated from the reaction, $-r\Delta H_{rxn}$;
- rate of heat removed from reaction mixture through conduction or convection to the reactor wall;
- rate of heat removed from the reactor wall through conduction to the surroundings.

These factors are similar for endothermic reactions, but with the heat flow in the opposite direction. In order to achieve near isothermal conditions and avoid exothermal heat leading to runaway reaction or explosive mixtures, it is necessary to ensure that the rate of heat generation is equal to the heat removal rate. Even moderate temperature rises, say 5 °C, play detrimental roles in kinetic and optimization investigations because the observed reaction rate can be approximately 20 % higher than if the reaction was ran isothermally. For syntheses with degradation, by-product reactions, or catalytic reaction systems with multiple elementary steps, this error is compounded since the temperature rise affects each reaction rate.

Vigorous stirring in a flask reactor leads to convective heat transfer in the reaction mixture. The convective heat transfer coefficient (h) is related to the flow rates and is difficult to measure, but can often be estimated by correlations.[55] With knowledge of this parameter, the heat of reaction (ΔH_{rxn}), adiabatic temperature rise (ΔT_{ad}), and vessel dimensions (diameter, d_B) we can make a useful comparison of heat generation and removal represented by the ratio:

$$\beta_B = \frac{\text{heat generated}}{\text{heat removed}} = \frac{-r\Delta H_{rxn}\, d_B}{6\Delta T_{ad}\, h} \tag{4}$$

For flow systems, thermal conduction from the center of the channel to the reactor walls is the driving force for heat transfer. The ratio of heat generation and removal is then estimated as:

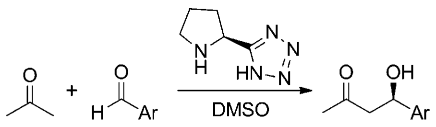
$$\beta_B = \frac{-r\Delta H_{rxn} d_F^2}{4\Delta T_{ad}\kappa} \tag{5}$$

where d_F is the diameter of the flow reactor channel, and κ is the thermal conductivity of the reaction mixture. For either reactor configuration, heat removal need not be a concern when the respective β value is less than 1.

Taking a close look into these β values provides insight into the benefits of microreactors for exothermic reactions. Thermal resistances to heat transfer in the reaction mixture are $1/h$ and d_F/κ for flask and microflow reactors, respectively. As a point of comparison for typical organic reactions, a 10 mm flask reactor with a stir bar spinning at 650 rpm and a microreactor with 400 × 400 μm reactor channels have similar internal thermal resistances. As the size of the microreactor channel increases, the internal resistance to heat transfer increases linearly. For flask reactors, however, the relationship between this internal resistance and the reactor size is difficult to quantify because the convective heat transfer is dependent upon the flask size, stir bar size, agitation, and liquid level. The uncertainty in quantifying these effects illustrates the difficulty that can be involved in scaling up batch reactions.

The rate of heat generation, $-r\Delta H_{rxn}$, is captured in the numerators of the β values and is dependent on the particular reaction and the reaction conditions. For decades, we have controlled this heat generation term by performing reactions at lower temperatures, at lower reagent concentrations, or in a semi-batch method where one reagent is slowly adding to the reaction mixture. However, rather than being satisfied that we can control the heat generation rate by operating a reaction inefficiently, it is useful to focus on new technology that enables reactions to proceed at more aggressive conditions.

However, enhancing heat transfer rates with flow technology is not necessary for all reactions. Using our heat transfer β numbers, let's look at an organocatalytic aldol reaction (Scheme 2) by Seeberger[56] that was highlighted in a recent essay.[2] This reaction has a modest heat of reaction (ΔH_{rxn}) and was performed at 0.1 M. The value of β_B for this reaction using typical benchtop equipment is approximately 1×10^{-2}, compared to a value of β_F of 4×10^{-4} when this reaction is performed in a microreactor. Since both β values



Scheme 2. Aldol reaction performed in microflow reactor and flask reactor.[2]

are much smaller than one, we would not expect heat transfer to play a dominate role in this reaction, as verified experimentally by Valera et al. (Figure 6).

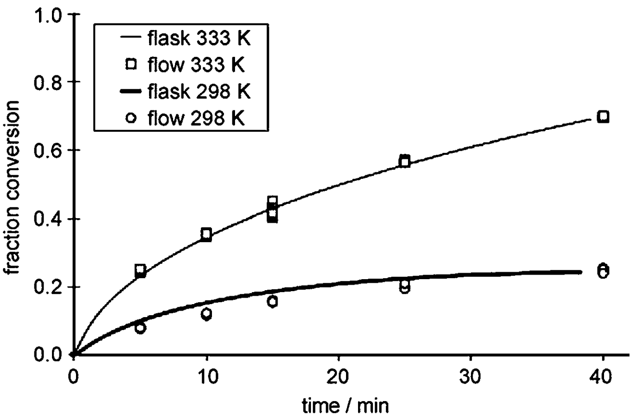
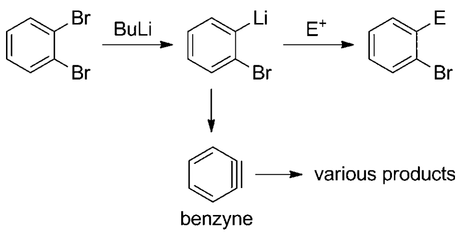


Figure 6. Slow, mildly exothermic reactions such as shown in Scheme 2 have similar reaction results in microflow and batch reactors.[2]

This similarity in heat transfer rates between batch and microreactors vanishes under conditions where the reaction rate increases. Lithiations, for example, are fast, highly exothermic reactions that are commonly involved in pharmaceutical synthesis. Controlling the heat generation and removal rates is particularly important in these reactions because the associated temperature rise increases the degradation and the by-product formation rates. The selective lithiation of 1,2-dibromobenzene with subsequent electrophilic addition (Scheme 3) by Yoshida provides an example for our discussion.[9b] Translating the reaction conditions to a 10 mL batch reactor gives a β_B value of 6.3, indicating that the heat removal from a flask is a concern and that the reaction benefits from being performed in a microreactor ($\beta_F = 0.2$). Although conventionally performed at −100 °C to mitigate the exothermal heat, higher reaction temperatures were explored in the work using a stainless steel micro flow system that consisted of micromixers and tubes (Figure 7 a). After profiling the reaction space (Figure 7 b), the maximum yield of bromobenzene of 75 % was found at residence times of less than a second.



Scheme 3. Selective lithiation performed in stainless steel micro flow reactor system.[9b]

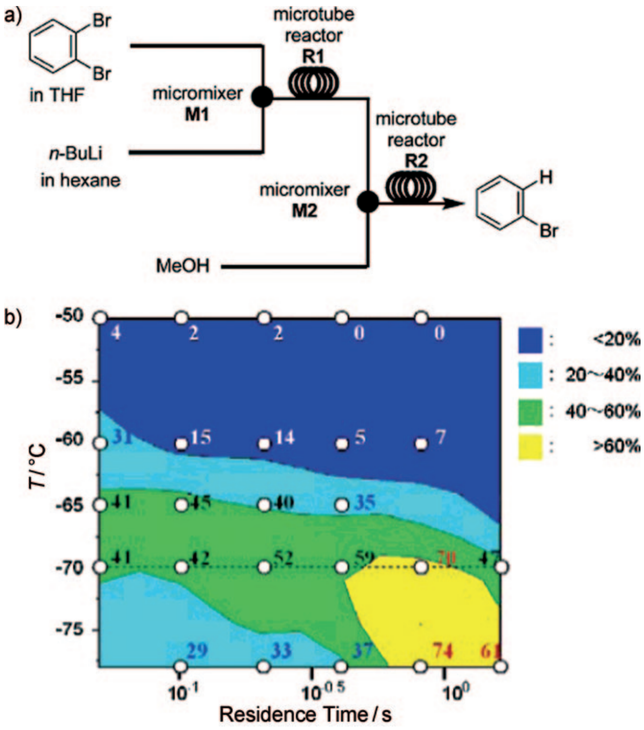


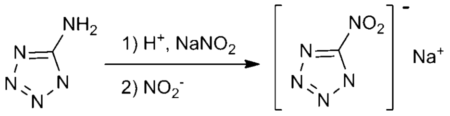
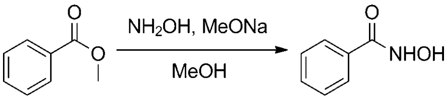
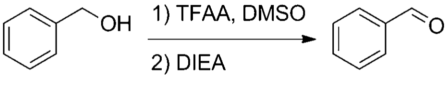
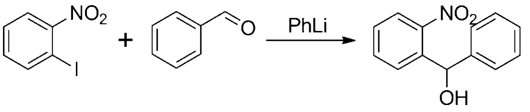
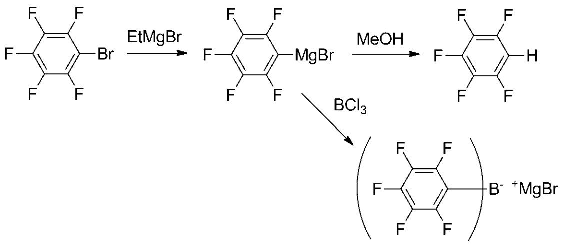
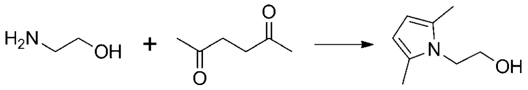
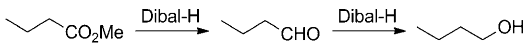
Figure 7. a) Microflow reactor system used for Scheme 3 and b) bromobenzene yields observed for various reaction temperature and residence time (Reprinted with permission from Ref. [9b]. Copyright 2007 American Chemical Society).

The authors performed 25 continuous flow screening experiments to find the residence time and temperature that resulted in the maximum bromobenzene yield. Even if this reaction could be accurately performed at these small reaction times in a flask reactor, the time and energy involved to obtain this data would be extraordinary. First, the flask is charged with solvent and substrate and cooled to cryogenic temperatures. After reaching thermal equilibrium, *n*BuLi is slowly added in a drop-wise manner to prevent a temperature spike associated with the addition. After allowing ample time for lithiation, the electrophile is slowly added in a drop-wise manner before raising the reaction temperature to promote the electrophilic addition. This procedure is repeated for each experiment. Alternatively, performing these reactions in microreactors greatly reduces the experimental preparation time because numerous sequential experiments at various residence times and reaction temperatures can be conducted after the initial loading of reagents onto a pump. Furthermore, the waiting period between each addition is removed since the high heat transfer rates in microflow reactors ensures that the reagents are at temperature before reaction.

The advantages from the increased heat transfer rates of microreactors over flask reactors extends to other fast, exothermic reactions, including Grignard,[57] alkylation,[58] and free-radical reactions.[9e] These benefits are more prominent in multiphase reactors, where the enhanced heat transfer in flow reactors prevents the formation of local "hot-spots". Consequently, a higher degree of control over product selectivity is gained by performing exothermic, multiphase reactions in a microreactor, with examples including nitration[49] and direct fluorination.[46] Additional examples in which the large heat removal rates in microreactors improved the reaction performance are given in Table 3.

As our previous example discussed, heat transfer is not typically a concern for slow, energetic reactions. But heat removal for these conventionally slow reactions becomes a growing concern as the rates are increased by operating them at unconventional conditions. For example, the fast heat transfer in microreactors enables "green" processing, where the reaction is performed without the use of a solvent.[59] Additionally, reactions can be accelerated by operating at higher temperature and pressures, such as the case with catalytic hydrogenation[21a,c,47] and aza Diels–Alder[60] reactions. Fast heat transfer and uniform temperature control also enable reactions to be explored with supercritical solvents in microreactors, which has been beneficial for the synthesis of uniform quantum dots,[61] esterification,[62] and catalyst-free transesterification.[63] Similar to our previous procedures, selecting the appropriate reactor configuration for these accelerated reactions involves an analysis of the β metrics for both the flask and the microreactors at these aggressive conditions.

Table 3: Selected examples where enhanced heat transfer in flow directly influenced the reaction outcome.

Reaction type	Example[a]	Benefit from microflow reactor	Highlight	Ref.
Diazotization of aromatic amines (e.g., Sandmeyer reaction)		Removal of exothermal heat prevented product degradation	Kinetic investigation used to scale up to 2.8 g h^{-1} production	[43]
Electrophilic substitution of aromatics (e.g., halogenation, Friedel–Crafts aminoalkylation, nitration)		Prevention of exothermal heat provides safer handling of hydryoxylamine	Improved hydroxamic acid synthesis with various substrates	[64]
Oxidation		Enhanced heat transfer reduces by-product formation	96 % Yield at 70 °C, typically performed in batch at −78 °C	[65]
Organometallic (e.g., lithiation, Grignard)		Fast heat transfer equilibrated reaction solutions quickly to provide rapid sequential experimentation	Screened kinetically and thermodynamically transformations of *o*-, *m*- , and *p*-nitrophenyllithium reagents	[66]
		Runaway reaction prevented and precise control over reaction progress	97 % yield of pentafluorobenzene in 5 s; difficult to control in batch	[57b]
Paal–Knorr		Faster heat transfer allowed the reaction to run neat	Production rate of 136 g h^{-1}	[67]
Reduction		Fast heat transfer stabilizes organometallic intermediate	Similar reaction results were observed at temperatures 20 °C higher than batch experiments	[68]

[a] DIEA = ethyldiisopropylamine; dibal-H = diisopropylaluminum hydride.

3.1. Sometimes it's what's on the outside that counts

Our discussion on the benefits on reaction performance from the heat transfer rates of flow reactors has thus far been limited to internal resistances. For certain conditions, however, thermal conduction through the reactor wall will limit the overall heat transfer rate. The conductivity is dependent upon reactor material, and values for common flow reactors used in organic synthesis are listed in Table 4. An interfacial balance on the heat flux at the reactor wall surface provides a ratio, known as the Biot number, *Bi*, that relates the internal and the external resistances to heat transfer,

Table 4: Thermal conductivity values for common microflow reactor materials.

Microflow reactor type	Conductivity [$\mathrm{W\,m\,K^{-1}}$]
Teflon	0.1
Stainless steel	10
Silicon	150

$$Bi = \frac{\kappa_{rxn}}{\kappa_{wall}}\left(1-\frac{d_i}{d_o}\right) \quad (6)$$

where k_{rxn} and k_{wall} are the thermal conductivities of the reaction mixture and the reactor wall, respectively, and d_i and d_o are the inner and outer diameters of the reactor channel. This ratio should be of order one or lower for fast exothermic reactions. As the form of this ratio indicates, accomplishing the ideal ratio can be achieved by selecting a reactor material that has a high thermal conductivity ($\kappa_{rxn} \ll \kappa_{wall}$), or by designing a reactor with thin channel walls. However, for Teflon and stainless steel tube reactors where d_o is fixed by commercial vendors, this latter design approach requires one to select reactors with larger d_i values, which can have an undesirable effect on the mixing through the reactor.

In order to demonstrate the role reactor material can play in a reaction, we return to the lithiation example (Scheme 3). An estimate of the temperature profile created by the exothermal heat of this reaction can be plotted as a function of the reactor length for various reactor materials and dimensions. For this particular reaction, the selection of reactor material and wall thickness plays an important role in the effective heat transfer (Figure 8). Teflon, for example, does not appear to be an appropriate reactor material for lithium-halogen exchange. Stainless steel and silicon both experience the exothermal heat caused by this near instantaneous reaction, but then quickly dissipate the heat.

Reactors with a higher thermal conductivity also give experimenters more control over reaction conditions. Performing reactions at higher temperatures in a flask reactor involves heating the solvent to the desired temperature followed by adding the reaction solutions. Adding the reaction mixtures as "shots" to the reactor not only results in concentration gradients, but also affects the temperature. Consequently, the initial rate of the reaction is investigated at unknown, non-uniform conditions.

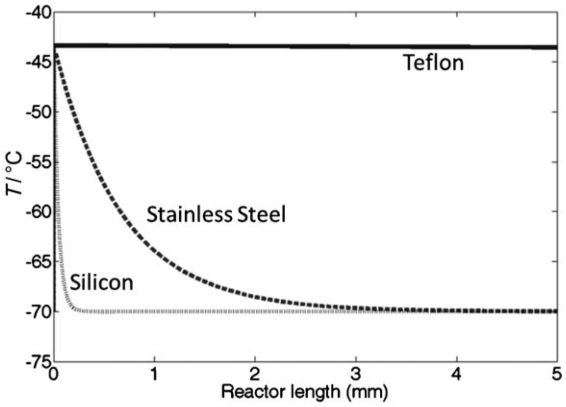


Figure 8. Estimated temperature profile for a reaction condition used in Scheme 3 with Teflon, stainless steel, and silicon flow reactor types for inner diameter of 1 mm and $\Delta H_{rxn} = 155\ \mathrm{kJ\,mol^{-1}}$.[69]

The high conductivity of metal microflow reactors and the ability to operate reactions isothermally removes this uncertainty. Additionally, by incorporating a halo-etch into a silicon microreactor (Figure 9),[70] the reaction mixture can experience two different temperature zones. In the cooled section, the reaction solution streams thoroughly mix to create a uniform solution, and then react at the desired temperature in the heated zone. For most organic syntheses, the small reactor length scale and the high thermal conductivity of silicon ensure that the reaction solution heats to temperature in less than a second. This type of reactor, which has been used for applications in chemical synthesis at elevated temperatures and pressures[70,71] as well as in growth of quantum dots at supercritical conditions,[61,72] enables the reaction to be explored under well-defined conditions, which improves kinetic investigations and scale up procedures.

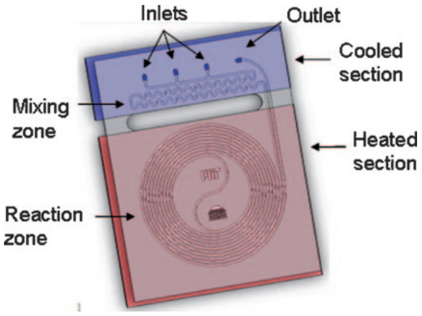


Figure 9. Halo-etch reactor design that was used to uniformly mix aminolysis reaction at cooler temperatures, and then react at desired temperature.[70]

4. Reaction Knowledge is Power

Numerous process chemistry problems, such as reaction optimization, successful scale-up, and improved process control are more easily solved with information on reaction kinetics. However, this reaction knowledge only has value if it captures the intrinsic kinetics—the reaction parameters that describe the reaction rate without mass and heat transfer limitations. As discussed, imperfect mixing or sluggish heat transfer influences the observed reaction rate; thereby providing misleading kinetic information. Although lumping transport phenomenon with reaction effects into "observed kinetic" parameters may be acceptable for describing the reaction performance in the laboratory, this information has no prediction power when conducting the reaction in a different reactor configuration. Obtaining this necessary kinetic information with the appropriate degree of accuracy on the bench scale, however, can be difficult if sufficient reagent material is not available or if information rich reaction conditions cannot be achieved. Therefore, when considering the use of a flask or a microflow reactor for kinetic investigations, two questions should be considered:

- Will the microflow reactor offer more accurate results than that of a flask?
- Will the kinetic information be obtained more efficiently in a microflow or flask reactor?

From our previous discussion on the importance of mixing in reactions, it is apparent that micro flow reactors are ideal instruments for studying fast reactions where conversion is near completion after approximately 1 s. The kinetics and the product distribution for these fast reactions are dictated by the degree of micromixing throughout the reactor.[45] Interdigital micromixers, such as those developed by IMM GmbH,[73] have characteristic mixing time constants of approximately 10 ms; thus creating a uniform mixture at the onset of reaction. These micromixers have been used to profile numerous reactions where fast mixing was imperative, including Michael additions,[74] nitrations,[75] and oligosaccharide syntheses.[53] The rapid mixing in micro flow systems is also beneficial for reactions with energetic intermediates,[76] as is exemplified in a recent kinetic investigation of tetrazole synthesis through a diazonium salt.[43] Additionally, the fast heat transfer in microreactors simplifies the kinetic investigations of highly exothermic reactions because the absence of exothermal heat suppresses side reactions. This feature is particularly important for Grignard reactions and oxidations.[9d,77]

Slower and less energetic reactions, on the other hand, have mixing and heat transfer time scales that are faster than the reaction time scales. This relative comparison of time scales indicates that a kinetic investigation in a microreactor provides just as accurate information as reaction data from a flask. This equality was again highlighted in the example organocatalytic aldol reaction (Scheme 2). This comparison of the measured kinetics in a flask and a microreactor was made for reaction conditions corresponding to 0.5 M and 60 °C, resulting in a conversion of approximately 70 % in 40 min. If the reaction was studied at more aggressive conditions, such as elevated temperatures and higher reagent concentrations, the reaction time scale approaches that of the mixing and heat transfer scales. Therefore, deciding upon a reactor type for kinetic investigations must involve analyzing the reaction conditions rather than simply assigning a reactor type based upon reaction category.

Regardless of the mixing and heat transfer rates in a reactor, kinetic investigations in micro flow reactors with online analysis capabilities have lower experimental variances than that of typical batch reactors. For example, determining the rate constant for reactions that involve a volatile reagent or those that operate under reflux in flask reactors are complicated by the uncertainty of the distribution of compounds in the liquid phase and the headspace.[70] This uncertainty does not typically exist in a flow reactor. For moderately fast reactions, samples taken from the flask for analysis can continue to react if not quenched appropriately, or degrade if not analyzed immediately; thereby introducing flaws to the kinetic analysis. In-situ spectroscopic[78] or calorimetric[79] measurements in flask reactors can be used to avoid these concerns, but concentration and temperatures gradients as well as slow instrument scan rates can convolute kinetic results for fast reactions. These complications are mitigated in microreactors through the use of a on-chip quench stream and incorporating online spectroscopic measurements, such as UV/Vis/NIR,[80] ATR-FTIR,[81] Raman,[82] XAS,[83] and NMR.[84] Precise quantification of the highly functional compounds in pharmaceuticals and fine chemicals by spectroscopic measurements alone is not likely to be preferred over HPLC, GC-MS or LCMS.[85] These chromatographic technologies are easily integrated with microflow systems through the use of actuated 6-way valves[86] or with an appropriate injection method.[87] Additional online analytical techniques for microreactors and the associated benefits have been previously reviewed.[88]

Let us consider the trade-off between accuracy of kinetic parameter estimates and efficiency of information gained from experiments in micro flow and flask reactors. Due to the nature of complex reaction mechanisms, different rate models will appear similar over a range conditions. For example, a first order irreversible, a second order irreversible, and a first order reversible could all have similar experimental outcomes over a range of conditions when experimental variance is considered. To gain the necessary reaction insight, experiments at a variety of conditions must be performed to discriminate between the potential rate models. With batch reactors, results from numerous experiments can be achieved quickly by running reactions in parallel, such as with a 96-well plate. However, gathering information in this manner is likely to be inefficient and runs the risk of yielding no discriminative information, if not properly planned. Sequential experimentation with feedback, where data from an experiment is collected, analyzed, and used to select the next set of experimental conditions, has been shown to be an effective approach for reaction modeling with minimal experimentation.[3b,89] This approach would be tedious for batch experimentation, but it is readily incorporated with flow systems. With the appropriate statistical algorithm, precise estimates of various terms in a reaction model, such as the pre-exponential, the activation energy, and mass transfer coefficient, can also be obtained in relatively few sequential experiments. Due to the nonlinear form of reaction kinetics, therefore, a few intelligently selected experiments performed in a flow system will provide better insight than the abundance of data that can be collected through parallel reactions or inline monitoring of a reaction in a flask.

A potential challenge of using microreactors for accurate kinetic and reaction scale up investigations is the residence time distribution. The laminar flow operation in a microreactor creates a parabolic velocity profile - material moving along the center of the reactor channel flows faster than the material near the walls. This variation in velocity translates to a variation in the amount of time that the reaction material spends in the reactor. This residence time distribution can be measured using tracer injection methods[90] or approximated by using well-established flow models.[41,90] These distributions can be used to assess if dispersion plays an important role in the reaction results of a flow system and to predict the appropriate operating conditions of larger reactors for successful scale up.

If axial dispersion is not measurable, the microflow reactor is said to operate as an ideal "plug flow reactor" or PFR (not to be confused with the slug-flow fluid dynamic behavior used in continuous flow microreactors[11e]). Because reactor length in a flow reactor is the equivalent to time in a flask reactor, kinetic results for flask and microflow reactors are identical if the Damköhler number and β heat transfer metric are less than one for these reactors. The degree of axial dispersion is evaluated by a Bodenstein number, Bo, which relates the axial convective forces from flow to the back-mixing from axial dispersion,

$$Bo = \frac{UL}{D^*} \tag{7}$$

where U is the average velocity of the reaction stream, L is the length of the reactor, and D^* is the dispersion coefficient. Small Bo values indicate that there is a large deviation from plug flow, but a small value does not necessarily indicate that there is a large deviation from the results that would be obtained in a PFR. To make this assessment, we need to incorporate the kinetic time scale and residence time. For first order reaction kinetics with a conversion of X, the deviation from plug flow has a magnitude of $\ln(1-X)^2/Bo$;[91] therefore reactor dimensions and conditions should be selected such that $\ln(1-X)^2/Bo \ll 1$ to ensure that the kinetic data is accurate for reaction optimization and scale up applications. Comparison of PFR and dispersion models for reaction rate expressions other than first order have been provided in previous reports.[92] At times this analysis is performed with a similar metric, the Péclet number, Pe,

$$Pe = \frac{UL}{D_{AB}} \tag{8}$$

where the molecular diffusion coefficient, D_{AB}, is used to characterize the radial diffusion. Because D^* is typically much larger than D_{AB}, careful attention should be given to the various correlations and formulae used to characterize axial dispersion.[41]

Alternatively, reaction kinetics can be determined without the effects of dispersion by introducing an immiscible liquid, to create reaction droplets. This droplet-based approach has been used to measure the millisecond single-turnover kinetics of RNase A.[93] Additionally, the efficiency of this kinetic study was improved by recording fluorescent measurements at various positions along the microreactor to obtain multiple time measurements of a single reaction droplet. Incorporating an inert gas phase to create slug-flow is also a method to narrow residence time distributions,[20a,22] i.e., reduce dispersion.

Although there are certain conditions where micro flow and flask reactors perform similarly, there is always more certainty of how reactor design factors influence mixing and heat transfer rates in flow than in flask reactors. This confidence is due to the well-understood rates of diffusion and conduction in comparison to the ill characterized convective forces (mixing effects) that dominate in batch reactors. These accurate transport phenomenon rates combined with the knowledge of the intrinsic reactions kinetics can be used to find the optimal reaction conditions and scale up conditions. Ensuring that these transport and kinetic rates remain constant for a reaction scale up by a factor of 10 has been demonstrated for a Sonogashira reaction for 100 g production scale.[94] Further investigations promise to impact how scale up to even larger production rates can be achieved using the information gained from microreactor studies.[3]

5. Decision Analysis

Microflow reactors are not a panacea for the poor outcome of all chemical reactions. As we have shown, there are certain situations when performing a reaction in a flow reactor is advantageous over performing the reaction in a flask reactor. In other situations, when the reaction rate is significantly slower than mixing or heat transfer, the flow reactor provides identical results to the flask reactor. This comparison does not imply a recommendation to discard flask reactors and explore all reactions only in micro flow reactors. It would also be imprudent to advise that all reactions of a certain type be performed in flow reactors. Instead, there is a natural thought progression involved in deciding whether a reaction should be performed in a flask or flow reactor. Although features of the chemical reaction, such as precipitations, solubility limitations, and material compatibility, should be partly considered to ensure successful flow operations, this analysis is based on the relevant reaction times scales. This decision roadmap for this process is presented in Figure 10, and the questions asked at the various nodes relate to the concepts discussed above.

Identifying the goal of the experiments is the first step involved in this decision tree. We categorize most experiments performed in a synthesis lab as either discovery or process chemistry. In discovery, combinatorial chemistry approaches are employed to obtain semi-quantitative data and to determine which species result in a reaction. For the majority of these applications, superior mixing and heat transfer is not a primary concern because the results are used to determine if any of the desired products are formed; rather than to quantify the reaction speed. Discovery experiments value high throughput, and automated liquid handlers and 96-

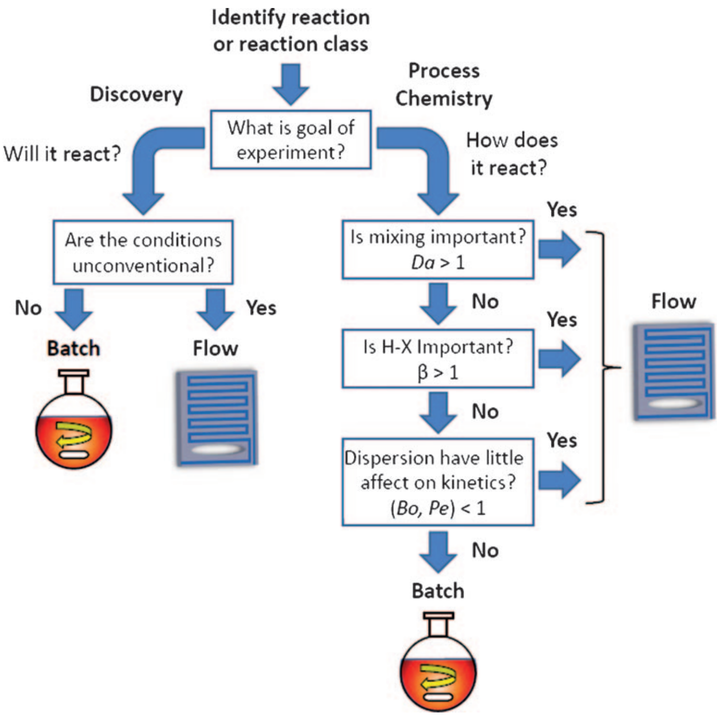


Figure 10. Decision roadmap for flow chemistry. (H-X stands for heat transfer)

well plate reactors are excellent equipment for these applications. If the mixing and heat transfer time constants are on the same order of magnitude as the reaction time constant ($Da_F \approx \beta \approx 1$) for these discovery experiments, then performing these experiments in a microreactor system may be beneficial.[95] Using a micro flow system for discovery experiments may also be advantageous over the 96-well plate reactor if process conditions, such as temperature and residence time, are varied in addition to reaction partners.[96] Further efficiency is seen with the potential to include in-line analysis and feedback mechanisms in the microreactor system to drive the discovery experiments towards the most likely to succeed outcomes.[97]

The objective of process chemistry experiments, on the other hand, is to characterize the reaction over a range of operating conditions for optimization and kinetic investigations. It is therefore imperative in these investigations to decouple the reaction rate from the mixing and heat transfer rates. A series of questions need to be answered to determine if better reaction results would be obtained in a microreactor over a flask reactor. Is the mixing rate expected to be important relative to the reaction rate? In other words, what would be the value of Da_B if this reaction were performed in a specified flask reactor? This assessment can be done by estimating the mixing time scale with Equation (4) (when $100 < Re < 1000$) and approximating the kinetic rate constant from previously recorded reaction data or information from a similar type of reaction. If $Da_B \geqslant 1$, then the use of a microreactor system is warranted. The next question is what is the magnitude of the heat generation rate from the reaction compared to the heat removal rate capabilities of the flask reactor? If $\beta_B \leqslant 1$, there is no incentive to go with a microreactor for the enhanced heat transfer. However, $\beta_B \geqslant 1$ denotes the reaction will likely benefit from being operated in a microreactor. Finally, if these calculations imply that better reaction performance can be achieved in a microreactor, the reactor should be designed to avoid axial dispersion at the investigated conditions. While this approach is more involved than deciding to always go with the flow or to never go with the flow, thoughtful consideration to the interaction between reaction and reactor features is the most promising method to obtain the desirable reaction results.

6. Challenges and Opportunities

Our discussion has been limited to selecting the appropriate reactor for a single reaction, but seldom is a synthesis limited to one reaction. Perhaps the greatest feature of the flask reactor is its flexibility to adapt to multi-stage syntheses. One flask serves as a reactor, extractor, distillation unit, and crystallizer. This versatility makes the flask reactor suitable for multi-step synthesis, but a considerable amount of time is involved in the preparation and completion of these stages. Advances in microreactor technologies have been developed and are continuously being refined to improve the speed of these work-up processes in a continuous-flow manner.[98] Combining microreactors and separators together creates a microchemical system,[99] enabling the entire synthesis to benefit from the smaller length scales. Novel design features and control strategies that provide robust operations and address the potential long lag-times and material loss associated with process dynamics will be paramount in making microchemical systems standard staples in research chemistry labs. Telescoping steps, or a "one-pot synthesis", will further advance production processes but requires a deeper understanding of the rate models, kinetic parameters, and selectivity gained in the laboratory. The ability to operate these microchemical systems at aggressive conditions will lead to the discovery of synthesis pathways that were previously viewed as unrealistic. Furthermore, it will be necessary to expand continuous-flow technologies to ensure that micro flow reactions are compatible with pharmaceutical and fine chemical reactions that evolve insoluble products.[100]

While reaction performance is critical in the selection of a reactor configuration, at times, the most important factor to selecting reactor configuration may be the speed at which results can be obtained. Microflow reactors that are integrated with inline analysis and feedback algorithms can provide reaction information more efficiently than flask reactors, but the speed at which this information is collected may be slower than simply running numerous experiments in parallel with flask reactors. Incorporating in situ detection techniques that analyze the entire microflow reactor channel are promising methods to rapidly gain reaction information. Alternatively, developing inexpensive, reliable, plug-and-play peripherals to microflow reactors, such as pumps and detectors, will make parallel experimentation in microflow reactors practical. The development of these technologies will also greatly impact the applications of microchemical systems.

Our discussion of continuous-flow reactors focused on tubular reactors or microreactors, because the residence time in these devices is analogous to reaction time in a batch reactor. The continuous stirred tank reactor (CSTR) is an agitated vessel with an inlet and an outlet, and is another continuous-flow reactor type that is useful in the development of pharmaceutical reactions.[101] Because back-mixing is at a maximum in these reactor designs, reaction rates with positive order kinetics are inherently slower in CSTRs than in flask reactors or microreactors. Despite this inherent inefficiency, CSTRs are growing in popularity because of their ability to more robustly handle reactions that involve solid precipitates.[102] Due to their size, these reactors may be more common in the scale up stages of a compound. As chemists and engineers become more familiar with the capabilities and limitations of continuous-flow reactors in pharmaceutical and fine chemical research and development, it will be interesting to investigate what reaction metrics are the most crucial for deciding *how* to go with the flow and when to use tubular, stirred tanks, or cascaded reactors.

For process chemistry, it could be argued that the goal of a laboratory experiment is to gain information to sufficiently understand the reaction at the larger scale. Although the scale up from a flask reactor to a large batch reactor is notoriously difficult,[7] it is surmised that scale up from small flow reactors will be straightforward. Yet examples of this scale up are scarce. Identification, validation, and demonstration of the appropriate scale up methods and considerations are required to validate the use of continuous-flow reactors on multiple scales in chemical synthesis, in particular for multiphase systems. Using the accurate wealth of reaction information gained from microreactors, including the intrinsic chemical kinetics, will enable process chemists and engineers to design the optimal large-scale reactor, whether it is a batch reactor or a continuous-flow reactor.

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