Flow chemistry for designing sustainable chemical synthesis

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ABSTRACT
An efficiently designed continuous flow chemical process can lead to significant advantages in developing a sustainable chemical synthesis or process. These advantages are the direct result of being able to impart a higher degree of control on several key reactor and reaction parameters. Furthermore, these controls can be utilized to increase the sustainability value of the chemical synthesis or process. This article will examine the contributions from a continuous flow reactor and the advantages which are gained when compared to a batch reactor. Additionally, an expanded detail of these advantages will be presented and used to explain the contribution they have which can increase the sustainability of a chemical synthesis or chemical process.

INTRODUCTION
An efficiently designed flow chemical process can play a significant role in the development of a sustainable chemical synthesis and eventual chemical process. The advantages associated with continuous flow reactor technology also aids in increasing the control of several design and reaction parameters. One example is the ability to maintain a reaction temperature above a solvent’s boiling point (super heating) to obtain a faster reaction. Other benefits include, the ability to achieve efficient heat and mass transfer which lowers operation costs and leads to superior kinetic control of the reaction. Many flow reactors allow for process intensification, which also leads to lowering operation, maintenance and capital expenditures. As well as a minimized physical footprint. Steady-state conditions are also easily maintained due to a reduced reaction volume within the reactor and decreased residence time in the reaction zone. While there are obvious advantages gained from this reactor configuration and design, an influence on the reaction chemistry that can be achieved is also a key benefit.

Flow reactors allow for the ease of performing sequential reactions, often suitable for reactions involving unstable or non-competitive reaction intermediates. With only a small quantity of an intermediate (hazardous or non-hazardous) being generated at any given time, reactions schemes that were previously not under consideration are now open for investigation. The ability for in-flow work-up and analysis of the product can also be incorporated into reaction design and allow for real-time synthesis or facilitated product switch over to be performed. Reactions requiring the use of gases (especially hazardous) can now be safely introduced into the flow path in a stoichiometric manner. Thus, eliminating the need to use wasteful excess quantities of reagents and now expanding the chemistries available to achieve synthesis of the desired product. Process scale-up has also been demonstrated to be facile and rapid, which decreases the quantities of resources, energy and time committed to go from bench to pilot to process level. Reactions can be easily pressurized and this is especially useful for dissolving gaseous reactants into the flow reactants. The high surface area to volume ratio offered by these reactors provides the opportunity for rapid heating and cooling, which also offers cost savings and reduced process utility requirements. By having the ability to vary several reaction parameters online (i.e. during the run), reactions can be quickly optimized. A physical property benefit of flow configuration reactors is the enhanced and efficient mixing that results from the smaller reaction volume. This enhanced kinetic energy allows for attaining selective organic transformations at lower temperatures, with lesser or no solvents and catalysts. Furthermore, the entire flow process can be easily automated and multicomponent reactions can be performed by introducing additional reactants at any point in the flow. This versatility also includes those reactions with multi-phase liquid components. For reactions that require very short residence times at varying temperature conditions these can also be easily performed in a continuous flow reactor. These reactions are not possible in traditional batch reactors.

To further explain this, the resulting accelerated reaction kinetics observed are the direct result of achieving higher pin-point reaction temperatures, while the bulk reactor temperature remains considerably lower. These higher pin-point reaction temperatures are the result of an increased frequency of molecular collisions and reactor wall effects, which contribute thermal heat at the reactive site of the molecule(s). Additionally, the heat gained by this effect is also effectively utilized since efficient heat transfer is achieved within the continuous flow reactor (reaction zone). These effects and efficiencies aid in lowering the energy
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Fig.: Microstructured reactor with 3D-helix mixing

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When performed may take from several hours to several days to complete. When these reactions are attempted in a continuous flow and under process intensified conditions, this results in a decrease in reaction time to as low as minutes. This also aid in scaling-up to the process level and are more cost-effective and sustainable. Continuous flow reactors are also shown to allow reactions to be designed which avoid traditional protection-deprotection steps seen in organic synthesis. This can dramatically improve the overall atom economy of the reaction and reduce the number of reaction steps (1) needed to synthesize the desired product. This feature also contributes directly to improving the reaction’s synthetic efficiency and improves the overall greenness and sustainability of the reaction.

Another benefit gained is in the area of low temperatures used on the industrial scale. The need to achieve these temperatures is a daunting task and adds heavily to process and operation costs and increases the process’ and worker’s safety. These conditions are unavoidable since these unstable intermediates often require temperatures on the order of -78°C to maintain their stability and complete the desired reaction. However, these lower temperatures may be achieved by using liquid nitrogen or dry ice in organic solvent coupled with using a flow reactor integrated with efficient mixers. The combination allows for completing these reactions at safer and less energy demanding conditions. For example, the preparation of organolithium compounds is a common step in organic synthesis. The reaction used for their preparation, as well as with other highly active electrophiles, is very fast and not easy to handle especially at large scale. This poses a challenge and requires the careful addition of reacting substrates, which hinders their production at large scale.

The preparation of organolithium compounds in a flow microreactor allows for carrying out the reaction at higher temperatures relative to batch conditions. Yoshida et al. carried out sequential Br-Li exchange reactions of p-, m-, and o-dibromo benzenes using microtubre reactors equipped with micromixers (Scheme 1) (2, 3). The first step, lithiation
In general, reaction kinetics determines product selectivity. But, for faster reactions (faster when compared to mixing rate), selectivity problems occur primarily due to inefficient mixing. To explain, if substrate A is mixed with substrate B to afford product P and has the potential to form undesired product U, the kinetics favor the desired product, P. This only occurs if the rate of formation of P is greater than rate of formation of U (the formation of U occurs when P reacts with one of the substrates, e.g. A) (Figure 1).

However, if the reaction takes place rapidly and the rate of mixing is relatively slow, the likely formation of undesired products increases.

By having efficient heat transfer, lower reaction and operation costs and energy use results. This effect was demonstrated by Rutjes and coworkers by reporting the selective Swern–Moffatt oxidation of benzyl alcohol to benzaldehyde in an automated flow microreactor (Scheme 2) (4). The enhanced heat transfer achieved lead to reducing the number of side reactions, such as the Pummerer rearrangement, and thus avoided the formation of side-products. This increase in product selectivity reduces the number of separation steps (or stages) needed, leading to capital and energy savings. As for the chemistry, the enhanced heat transfer observed allowed for achieving a reaction time of 32 ms and afforded a 96% yield at 70°C whereas, the same reaction under batch conditions requires -78°C.

Kirschneck and Tekautz have also significantly improved the industrial process by demonstrating this synthesis in a continuous flow reactor (3). Employing a StarLam 3000 microreactor, the productivity observed was an increase of two-fold (3.6 t h⁻¹) with a residence time of 60s. The reaction time for a comparable batch process was 4 hours in a 10000 L reactor. The overall process changes help significantly lower energy consumption.

Tandem operations in a continuous flow reactor allows for performing a sequence of organic transformations in one continuous flow operation (5). This is feasible with effective mixing, excellent temperature and reaction time (residence time) control. When compared to traditional batch operations, additional benefits such as improved operation and worker safety, less process time, decreased labor costs, and more economical margins are achieved. A suitable example is the synthesis of oxamaritidine by the Ley group. This process comprises seven synthetic steps and involves the use of microfluidic pumps, columns of supported reagents, packed catalyst cartridges and scavengers, all combined into one continuous flow operation (Scheme 3) (6). The overall product yield for this reaction is >40% with a product purity of >90%. Using this continuous operation, reaction completion occurs in as few as six hours whereas, the batch operation runs over three days. However, this type of tandem processes imparts several challenges, such as the continuous separation of any excess reagents and the effective removal of metal contaminants from the reaction.

Researchers are also investigating the integration of biphasic systems for solvent extractions (7) and continuous distillation (8) in flow. But, this approach is currently only limited to volatile solvents.

CONTRIBUTION TO SUSTAINABLE APPROACHES FOR CHEMICAL SYNTHESIS

Product selectivity is important when competing side reactions which produce undesired by-products exists.
product, U, is higher even though the rate of its formation is relatively less. This is the result of substrate molecule, A, undergoing reaction with product molecule, P, which is in its vicinity for a relatively longer period of time due to relatively slow mixing and thus taking longer to reach a homogenous mixture. This problem occurs in a batch chemical reactor and is known as “disguised chemical selectivity” (9, 10). Yoshida et al. also described this product selectivity concept and how it can be overcome by using the efficient mixing generated in continuous flow reactors (11). This product selectivity issue is illustrated in the preparation of phenylboronic acid from phenylboronic acid trimethylster and phenyl magnesium bromide (Scheme 4) (12). The competitive formation of diphenyl boronic acid takes place by reacting phenylboronic acid with phenyl magnesium bromide. When the reaction is carried out under batch conditions, the yield of the desired phenylboronic acid is 70.6% whereas the yield of the undesired product is 13.8%. When this reaction is attempted in a continuous flow tubular reactor equipped with multilaminar micromixers, the selectivity of the desired product rises significantly. In this scenario, phenylboronic acid was obtained in 93.9% selectivity and the diphenyl boronic acid species was obtained with only 0.6% selectivity. It was also reported the concentration of reactants and reaction temperature play a role in the selectivity distribution observed.

A significant advantage associated with the use of continuous flow reactors is the ability to perform more aggressive organic transformations with greater safety. At any given time, only a small quantity of reactants are exposed to these reaction conditions, thus reducing the risk involved when reacting hazardous reagents. Also, the risks associated in handling high temperatures in large batch reactors can be easily addressed by using continuous flow synthesis. The safety profile of the gas-liquid flow processes is increased considerably when compared to batch processes. With the advent of commercially available instruments like the ThalesNano H-Cube™ / X-Cube™, it has become simpler to handle hydrogenations, ozonolysis, and other gas-liquid reactions. Examples of handling and using hazardous solids (like CsF) in a continuous flow setup was described by Noel and coworkers (13) in the palladium catalysed synthesis of aryl fluorides from aryl triflates in a CsF packed-bed reactor. This continuous flow configuration requires a simple setup using a single syringe pump taking advantage of the low solubility of CsF in the reaction medium. This allowed for ease of control of the reaction mixture, created efficient mixing and handled the high pressure and temperatures.

**CONCLUSIONS**

An increase in the greenness and sustainability of chemical processes can be realized by employing continuous-flow reactors. This process intensified technique can lead to achieving reactions conditions which lead to reduced reaction time and waste generation, avoiding ultra low temperature conditions, increasing the overall atom-economy, widening the safety window and reducing the overall energy consumption to name a few. Research results presented show that continuous-flow technology can be developed to meet the requirements of industry and help in contributing to more green and sustainable chemical production processes. However, for efficient use of flow technology there are challenges which need to be addressed such as understanding the transformation of batch processes to those of flow, understanding reaction kinetics within these reactors and implementation of scale-up procedures. The advantages of on-demand and on-site synthesis helps in eliminating problems associated with transportation, recycle and reuse. Additionally, the increasing demand for continuous flow technology and their promising results may help in the substantial development of eco-friendly and greener organic transformations.

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**REFERENCES AND NOTES**

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