Enhanced Reaction Efficiency in Continuous Flow

Review

Israel Journal of Chemistry

DOI: 10.1002/ijch.200((full DOI will be filled in by the editorial staff))

Enhanced Reaction Efficiency in Continuous Flow

Peter D. Morse,[a],† Rachel L. Beingessner[a],† and Timothy F. Jamison*[a]

We are delighted to contribute to this issue honoring two of our scientific heroes. T. F. J. also thanks Stuart L. Schreiber for his mentorship and intellectual fearlessness that continue to inspire.

Abstract: Continuous flow reactors are an enabling tool that can significantly benefit chemical reactions, especially those that are path length dependent (e.g. photochemical), mixing or transport dependent (e.g. gas-liquid), exothermic or utilize hazardous or unstable intermediates. In this review, we demonstrate how the nearly instantaneous mixing, exceptionally fast mass transfer, safe access to high temperatures and pressures and high surface area-to-volume ratio can be leveraged to improve product yield, reaction rates and/or selectivity. By showcasing five synthetic methodologies examined by our group, it is hoped that the reader will gain an appreciation of the accessible and transformative nature of flow chemistry for improving existing transformations, enabling rapid optimization as well as for developing new methodologies that depend on precise parameter controls.

Keywords: flow chemistry • process intensification • microreactors • photochemistry • synthetic methods

1. Introduction

Continuous flow chemistry is an enabling tool that has tremendous potential to transform the way we construct molecules in the lab, by improving synthetic efficiency and providing new strategies for organic synthesis.[1] In a continuous flow platform, reservoirs of reactive reagents and substrates are pumped together and mixed in narrow diameter tubing under precisely controlled conditions, such that only a small quantity of the starting materials undergo the desired reaction at once. Along with decreasing safety risks, this synthetic approach can enable rapid reaction optimization and streamline multistep processes.[2] Additionally, the unique physical parameters of flow reactors such as the enhanced mixing and high surface area-to-volume ratio, can provide opportunities for uncovering new chemical reactivities with facile scale-up potential that would otherwise be difficult or improbable to achieve using standard batch techniques. [1]

Figure 1 illustrates some of the common equipment that may be implemented in a flow platform[3] along with the corresponding schematic representations used herein. Briefly, liquid handling pumps are used to introduce homogenous solutions in the system, whereas mass flow controllers (MFCs) introduce gasses from pressurized tanks. Reactors can be of a tubular type (inner diameter micron to low millimeter range) constructed from various polymers such as perfluoroalkoxy alkanes (PFAs), or a fixed bed type, wherein the reaction mixture is passed through a solid-supported catalyst or reagent. To combine two or more reagent streams together at precise rates, various mixers are utilized. Back pressure regulators (BPRs) pressurize the system and enable solvents to be superheated. Finally, check valves are used to prevent backward flow and membrane separators permit in-line separation of organic and aqueous phases.

In this review, we provide five methodology-based case studies from our group in which the reaction efficiency, either in terms of the chemical reactivity (e.g. reaction rates, yield) and/or product selectivity, was enhanced by using a continuous flow synthesis strategy. Each of these case studies aims to highlight one or more of the benefits of flow relative to batch processes, including the (1) superior mixing capabilities, (2) enhanced mass transfer, (3) safe access to extreme temperatures and pressures and the (4) high surface area-to-volume ratio.

2. Case Studies Demonstrating Enhanced Reaction Efficiency in Flow

Case Study 1: Enhanced Mixing in Flow - Selective Reduction of Esters to Aldehydes

The reduction of esters using diisobutylaluminum hydride (DIBAL) at low temperatures offers a potentially direct method to access the aldehyde functional group.[4] In practice however, the ester is often over-reduced to the alcohol, resulting in product mixtures and lowering the overall yield of the desired aldehyde.[5] To circumvent this challenge, chemists

[a] Peter D. Morse, Rachel L. Beingessner, Timothy F. Jamison
Department of Chemistry, Massachusetts Institute of Technology
77 Massachusetts Avenue, Cambridge, MA, 02139
phone: 617-253-2135
fax: 617-258-7500
e-mail: tfj@mit.edu

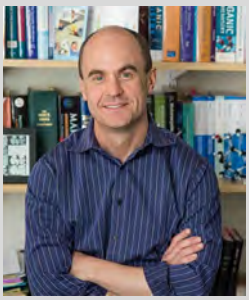
† These authors contributed equally to this work.

often resort to a multistep, more tedious route involving reduction of the ester to the primary alcohol, followed by oxidation.

In 2012, our group showed that this multistep batch approach can be avoided by performing the DIBAL reduction of esters to their corresponding aldehydes in a simple continuous flow set-up illustrated in Table 1.[6] It consists of two reactors (R1 and R2) constructed from standard PFA tubing and three precooling loops (P1-P3) submerged in a cooling bath. T-shaped mixers combine the streams of reagents introduced by syringe pumps including the in-line methanol quench.

Peter Morse was born in Concord, MA. He attended the University of Connecticut, where he obtained a B.S. majoring in Structural Biology and Chemistry. In 2010, he joined the lab of David Nicewicz as a graduate student at the University of North Carolina at Chapel Hill. His work there focused on the development of new synthetic methods in the burgeoning field of photoredox catalysis. After obtaining his PhD in 2015, Peter moved back to Massachusetts where he is now a postdoctoral researcher in the lab of Tim Jamison. His current research focuses on developing new methods to synthesize bioactive molecules in flow.

Rachel Beingessner studied Biochemistry (BSc) and Organic Chemistry (MSc) at the University of Waterloo in Canada. After obtaining her PhD in Chemistry at the University of Ottawa in 2007, she joined the National Institute for Nanotechnology – National Research Council Canada for postdoctoral training in the area of Supramolecular Nanomaterials and then transitioned to a staff research position after one year. In 2015, she moved to the United States and joined the Chemistry Department at MIT where she currently works as a Research Scientist.



Tim Jamison was born in San Jose, CA, and grew up in neighbouring Los Gatos, CA. He received his undergraduate education at UC Berkeley, where he conducted research in the laboratory of Prof. Henry Rapoport for nearly three years. He was then a Fulbright Scholar with Prof. Steven A. Benner at the ETH Zurich, and thereafter he undertook his PhD studies at Harvard University with Prof. Stuart L. Schreiber. He then moved to the laboratory of Prof. Eric N. Jacobsen at Harvard University, where he was a Damon Runyon-Walter Winchell postdoctoral fellow. In 1999, he began his independent career at MIT where he currently holds the positions of Professor and Head of the Chemistry Department.

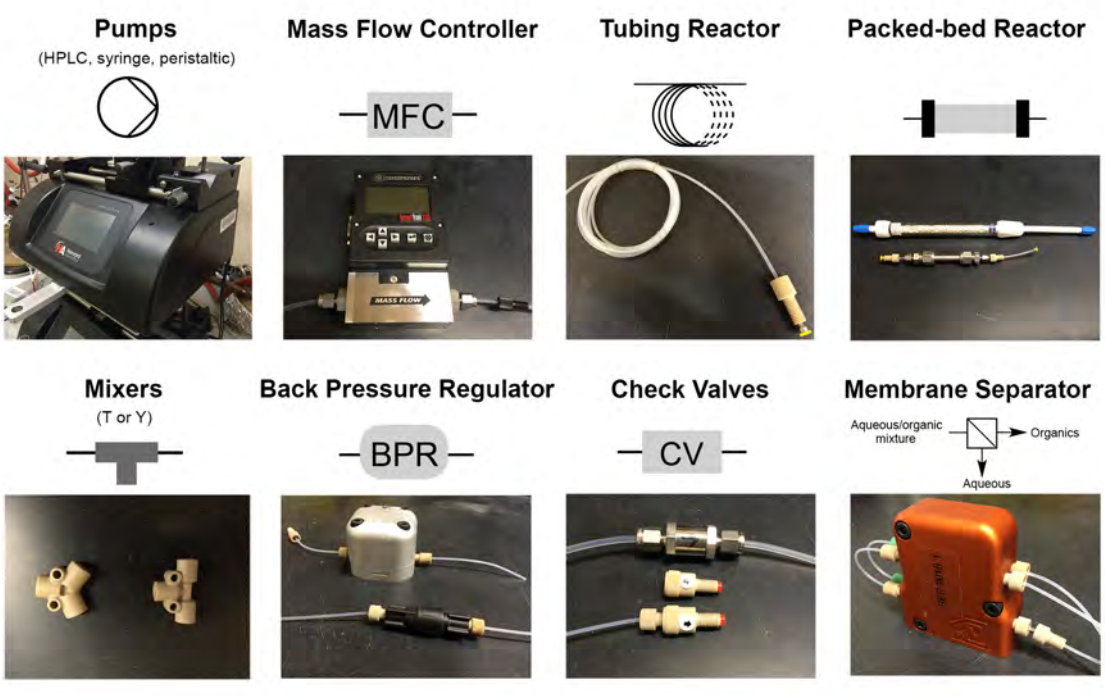
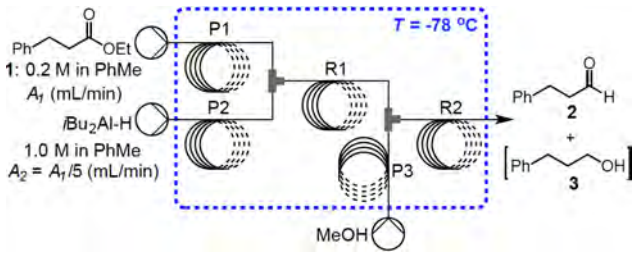


Figure 1. Representative images of some common flow equipment, each with their schematic picture.

Using the reduction of ethyl hydrocinnamate **1** as an example (Table 1), we showed that at the fastest flow rate (A_1 = 30 mL/min) and thus shortest residence time (t_R) examined, essentially full conversion to the corresponding aldehyde **2** is achieved at a constant R1 volume and temperature of -78 °C. This is due to the additional energy that is provided at the high flow rates to mix the streams of DIBAL and the ester.[6] Importantly, at all flow rates (A_1 = 5, 10 and 30 mL/min), aldehyde release and over-reduction are prevented as a result of the rapid in-line mixing and quenching of the organoaluminum intermediate by the methanol. Without inclusion of this in-line quench, over-reduction is observed even at -78 °C.

As may be expected, the selectivity for the aldehyde decreases with increasing temperature, although the degree of over-reduction is greatly reduced compared to the corresponding batch reaction at the same temperature.[6] At -20 °C and higher, the outcome is largely independent of the t_R, suggesting that higher flow rates are necessary for selectivity, since the reaction is very fast at these higher temperatures. Thus, not only does this flow platform alleviate the selectivity issues commonly encountered in batch for the DIBAL reduction of esters, but the results suggest that the implementation of mixing devices that approach ideal mixing[7] may improve other transformations that present selectivity challenges. By extrapolating the throughput using the fastest flow rate examined (30 mL/min), 10.4 mols (>1.8 kg) of **1** per day can be selectively reduced to aldehyde **2** using a 23 µL reactor.

Table 1. Effect of t_R on the continuous DIBAL reduction of ethyl hydrocinnamate **1**.



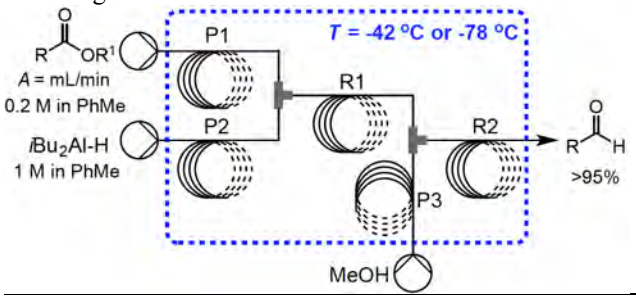
Entry	*R1* (µL)	A_1 (mL/min)	t_R (s)	Selectivity[a] **2**	**1**	**3**
1	23	5	0.23	36	64	0
2	23	10	0.11	50	50	0
3	**23**	**30**	**0.04**	**96**	**4**	**0**
4	228	5	2.28	43	57	0
5	228	10	1.14	61	39	0
6	**228**	**30**	**0.38**	**97**	**3**	**0**
7	684	5	6.84	57	43	0
8	684	10	3.42	85	15	0
9	**684**	**30**	**1.14**	**96**	**3**	**1**

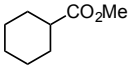
[a] The selectivity was determined by GC analysis. P1-P3: precooling loops; R1, R2; reactors; *A* = flow rate.

As the rate of reduction depends on the structure of the substrate, obtaining high selectivity with different esters required tuning the reaction parameters for each. This process was readily accomplished using the simple flow system, and as shown in Table 2, the stoichiometry, flow rate, t_R and temperature were readily optimized to afford >95% gas chromatography (GC) yields of the desired aldehydes in all cases, thereby highlighting the generality and practicality of this approach.[6] In a subsequent study, we further showed that the DIBAL reduction can be used as part of a one-flow multistep sequence wherein the generated aldehyde undergoes a two-carbon homologation to provide α,β-unsaturated esters.[8] A variety of α,β-unsaturated esters were prepared in excellent yields and higher olefin selectivity compared to batch methods using similar reagents.

As illustrated herein, and also demonstrated with various examples of flash chemistry[9] described in the literature, a flow platform can be a very powerful tool for improving the selectivity[10] of a chemical transformation, by virtue of the highly controlled reaction parameters. The specific flow conditions (flow rate, temperature, t_R, stoichiometry) developed and optimized in this particular study could be useful to those considering scaling-up the reduction of the common starting esters shown in Table 2, or perhaps incorporating this highly selective transformation into a more complex reaction sequence.

Table 2. Scope of the selective reduction of esters in flow under individually optimized conditions. In all cases the corresponding aldehyde yield was >95% as determined by GC using an internal standard.



Entry	Starting Ester	DIBAL (equiv)	*A* (mL/min)	t_R (s)	*T* (°C)
1[a]	Ph$\sim$$CO_2Et$	1.0	30	0.04	-78
2[a]	Ph$\sim$$CO_2Me$	1.2	5	6.6	-42
3		1.1	10	8	-78
4[a]	$C_7H_{15}CO_2Me$	1.2	5	15.2	-78
5	TBSO$\sim$$CO_2Et$	1.6	5	15	-42
6	TBSO$\sim$$CO_2Me$	1.5	5	15	-78

[a] The yield of the corresponding alcohol was 0% except for Entries 1 (1%), 2 (2%) and 4 (2%).

Case Study 2: Enhanced Rate of Mass Transfer and High Surface Area-to-Volume Ratio in Flow - Improved Reactivity in Functionalized Phenol Synthesis

Functionalized phenols are widely present in an array of natural products, agrochemicals and pharmaceuticals[11] and are typically prepared by nucleophilic aromatic substitution reactions,[12] oxidative methods using aryl boronic acids/esters[13] and by hydroxylation of aromatic derivatives using transition-metal catalysis.[14] Despite the wide-utility of these substrates however, these typical synthetic strategies have limited functional-group tolerance, high costs and toxicity, and generally require harsh reaction conditions.[12-14] An alternative approach to these methods is the aerobic oxidation of aryl Grignard reagents using pure O_2.[15] Unfortunately, this direct strategy suffers from dismal yields in batch due to the low reactivity of the aryl radical species (Figure 2) towards O_2, which leads to undesired radical coupling reactions or hydrogen abstraction with substrates or solvent molecules. As a simple demonstration of the impracticality of this reaction, bubbling O_2 for 5 h at a rate of 0.3 mL/min into a flask containing phenylmagnesium bromide (25 mL, 0.2 M in THF) under ambient conditions, affords the desired phenol in only 15% yield.[16] By performing the same reaction in flow however, we can take advantage of the high surface area-to-volume ratio and increased rate of mass transfer to overcome this crippling reactivity challenge. In our preliminary investigations for example, we showed that the same phenylmagnesium bromide solution (0.2 mL/min) can be oxidized using pure O_2 (0.3 mL/min) (1.5:1 ratio, O_2:Grignard reagent, *v/v*) under ambient conditions, to provide phenol in 53% yield and in only 2.7 min.[16]

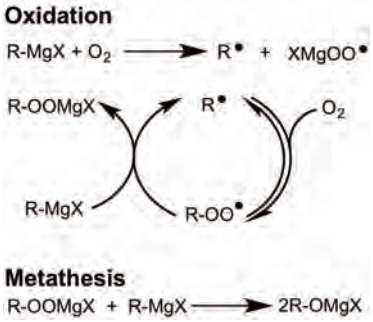


Figure 2. Proposed mechanism for the oxidation of Grignard reagents with O_2.

Given the drastic improvement in yield in this preliminary result, we chose to further tackle the economic and practicality (safety) issues associated with using pure O_2, by substituting it with pressurized air. A flow-set up was devised such that compressed air and a pre-cooled Grignard solution were directed toward a PFA tubing reactor upon meeting at a PEEK Y-mixer. Although air is presumably less reactive than pure O_2 (due to the lower concentration of O_2), nearly quantitative generation of phenol was achieved with a t_R of only 3.4 min, using a gas/liquid ratio of 3:1 *v/v* for the segmented flow at a pressure 250 psi and a temperature -25 °C.[16] As may be expected, lower temperatures decreased the conversion of the starting organometallic reagent, and higher temperatures promoted unwanted side reactions.

Athough phenol itself is a high-value chemical, the merits of this flow system were fully recognized by the scope of the substituted phenols prepared. As shown in Figure 3, a variety of substrates with electron-rich groups were oxidized in good yields to provide compounds **4** – **16** under the optimized conditions (t_R = 3.4 min, 250 psi, -25 °C). Electron-deficient phenylmagnesium reagents as well as magnesiated pyridine rings were also transformed to the oxidized products, **17** – **22** and **23** – **25** respectively, in good yields by simply raising the reaction temperatures (-10 °C to 25 °C).[16]

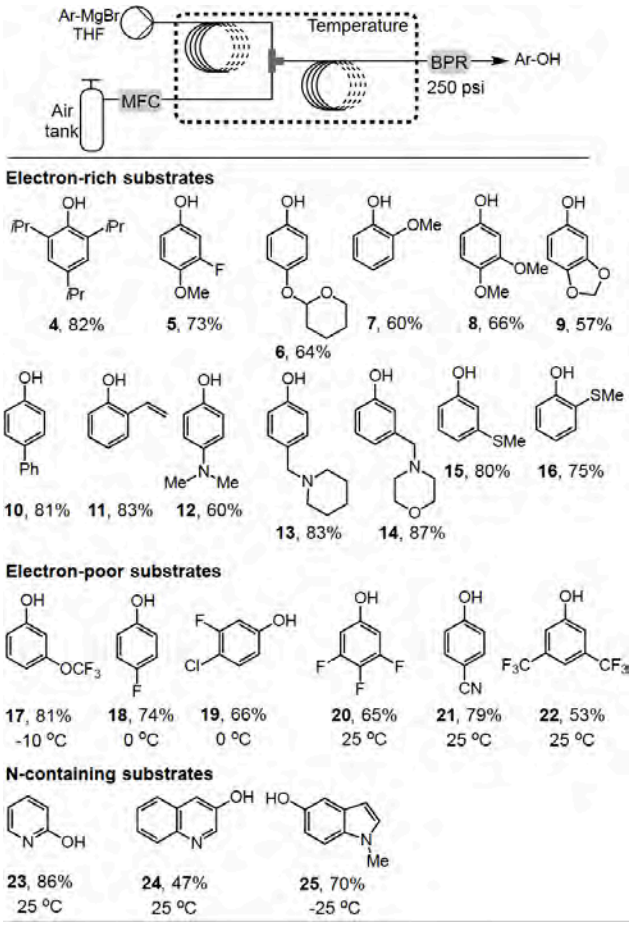


Figure 3. Preparation of functionalized phenols by aerobic oxidation of Grignard reagents using continuous flow. Unless otherwise indicated, reactions were performed in a cooling bath at -25 °C. Yields are isolated after silica gel chromatography.

To further illustrate the potential of the system and take advantage of the ability to telescope multistep sequences in flow, we demonstrated that *ortho*-substituted organomagnesium substrates can be generated in-line via the formation of benzyne from a 1,2-dihalobenzene starting material.[16] Using the modified set-up presented in Figure 4, the nucleophile was directed to meet with excess isopropyl magnesium chloride lithium chloride at a PEEK T-mixer and then undergo deprotonation in reactor

1 (R1) at 25 °C. The mixture was then merged at the PEEK T-mixer with a stream of 1,2-dihalobeneze in THF. *In situ* benzyne formation and nucleophilic addition proceeded in reactor 2 (R2) under thermal conditions. After passing through a check valve, the reaction solution then entered the same flow system described in Figure 3 for the aerobic oxidation step. As shown in Figure 4, this convenient flow process enabled numerous *ortho*-functionalized phenols (**26** – **33**) to be generated within a total linear t_R of only 14 min.

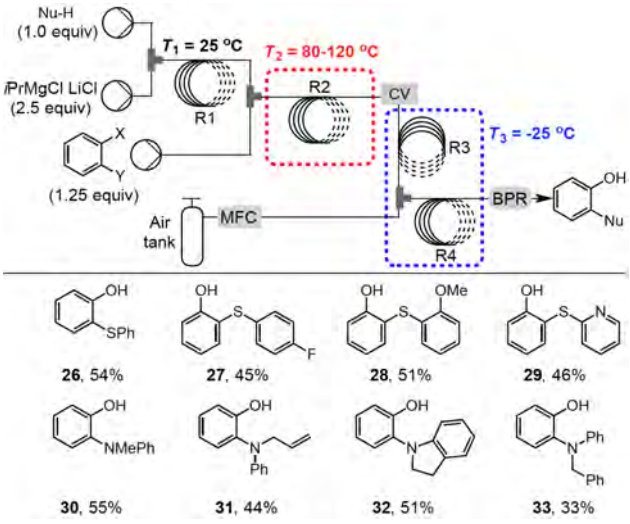


Figure 4. Continuous flow synthesis of *ortho*-functionalized phenols. Yields are isolated after silica gel chromatography. R1 – R4; reactors.

As presented in this case study, the utilization of a flow platform to perform aryl Grignard oxidation reactions successfully overcame the inherent reactivity challenges observed under batch conditions. It provides a potentially green and more economical alternative to preparing these important materials than what is typically implemented.[12-14] More generally, this study highlights the merits of continuous flow for biphasic gas-liquid reactions[2, 17] and adds to the repertoire of examples in the literature involving molecular oxygen in flow.[18]

Case Study 3: High Temperature Reactions in Flow – Enhanced Reaction Rate in Epoxide Aminolysis Reactions Relative to Batch and Enhanced Selectivity Relative to Microwave Reactions Due to Lack of Reactor Headspace

β-amino alcohols are functional groups commonly found in active pharmaceutical ingredients (APIs) such as indaceterol (**39**), a compound developed by Novartis and approved by the US Food and Drug Administration for the treatment of chronic obstructive pulmonary disease (Figure 5).[19] Perhaps the most direct method for accessing β-amino alcohols is the opening of an epoxide with an amine nucleophile (e.g. an aminolysis reaction). For example, the indaceterol precursor **36** has been prepared in this manner in batch by reacting epoxide **34** with amine **35** under thermal conditions (Figure 5A).[19] After 15 h, the product **36** was obtained in 69% yield, along with the bis-alkylated adduct **37** and regioisomeric product **38** in 12% and 8% yield, respectively. A preliminary investigation in our lab into the use of homogeneous and solid supported acid catalysts for this transformation (under batch conditions) proved far less successful, with little or no product being formed.[20]

In general, microwave reactors[21] as well as continuous flow reactors each have the ability to reach high temperatures and pressures not readily attainable under batch conditions. Flow reactors accomplish this effect through the use of BPRs, which pressurize the system, thereby preventing superheated solutions from entering the gas phase. Both of these reactor types have been used to significantly improve the reaction rates of numerous organic transformations.[22] In 2007, Lindsay and coworkers demonstrated an efficient epoxide aminolysis reaction using microwave heating.[23] Several years later, our group in collaboration with the Jensen group at MIT, presented the use of microreactor technology for aminolysis reactions and directly compared the results to analogous reactions carried out using microwave heating.[20] We showed for example, that under both optimized microwave (Figure 5B) and heated flow (Figure 5C) conditions, the indacaterol precursor (**36**) could be obtained in 1/60th the time of the reported batch conditions (15 min vs 15 h) and with similar product yields. In terms of the scale-up potential using these two techniques, microwave irradiation is limited by the short penetration depths into reaction media,[24] whereas the throughput in flow can be readily increased by scaling-up the reactor volume or numbering-up the devices (scale-out).

While both microwave and flow reactors can improve reaction rates relative to batch, as previously demonstrated, a flow platform can potentially lead to a better reaction outcome (e.g. product selectivity) when using reagents that are more volatile than the solvent. This is because microwave vessels, while pressurized, possess a head space where low-boiling reagents can accumulate during the irradiation period. Since flow reactors do not have this head space, this effect is not observed. For example, the opening of 2-(phenoxymethyl)oxirane (1 M in ethanol) with *tert*-butylamine under microwave conditions (150 °C, 30 min) was found to occur at the terminal position with high selectivity, but the exact product distributions depended on the reaction volume (Table 2, Entry 1 and 2).[20] Specifically, as the total volume of the reaction solution in the 5 mL vial decreased from 2 mL (Entry 2) to 1 mL (Entry 1), the yield of the undesired bis-alkylated product increased. Since *tert*-butylamine has a boiling point lower than the ethanol solvent (46 °C vs 78.4 °C), a greater portion of the amine nucleophile resided in the headspace of the microwave reactor, reducing the effective concentration in solution, which therefore promoted the formation of the bis-alkylated product.[20] Switching to a continuous flow microreactor successfully avoided this issue with varied total reaction volumes providing nearly identical product distributions (Table 3, Entry 3). The same outcome was likewise observed with the opening of 2-phenyloxirane with *tert*-butylamine, (Table 2, Entry 4 - 6), although in this case the β-opened isomer was also generated. Notably,

in both examples the yield of the desired α-opened products in flow mirrored the yields obtained under microwave conditions, but only when using the 2 mL reaction volume in the 5 mL vial. [20] Overall, this highlights the ability of flow reactors to overcome such volatility issues and thus has the potential to be valuable in the development of any number of reactions involving low-boiling reagents.

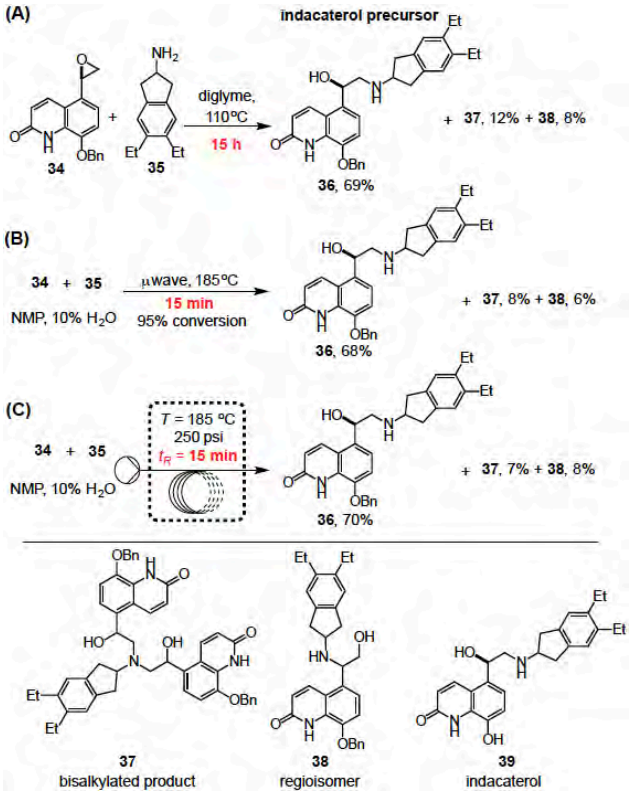
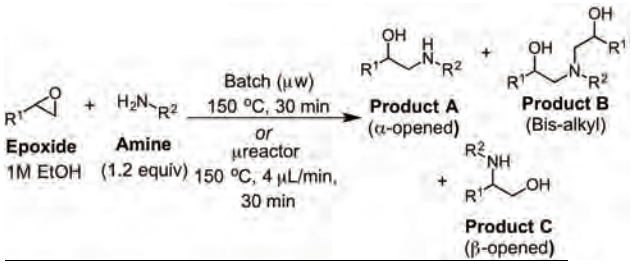


Figure 5. Synthesis of the indacaterol precursor (**36**) via a (A) batch approach and using (B) microwave irradiation and (C) continuous flow.

Table 3. Comparison of aminolysis reactions under microwave and continuous flow conditions. All yields are calculated by HPLC analysis with an internal standard.



			Products		
Entry	**Epoxide**	**Cond. (psi)**	**A %**	**B %**	**C %**
1		Batch[a] (μw)	75	24	-
2		Batch[b] (μw)	82	17	-
3		μreactor (250)	82	16	-
4		Batch[a] (μw)	57	21	7
5		Batch[b] (μw)	62	19	10
6		μreactor (250)	62	16	7

[a] 1 mL volume in a 5 mL vial; [b] 2 mL volume in a 5 mL vial.

Case Study 4: High Surface Area-to-Volume Ratio in Flow – Improved Throughput in Visible Light Photoredox Catalyzed Reactions

Photochemical reactions[25] such as those promoted by visible or UV-radiation[26] are a powerful class of transformations that often allow bond formations to be accomplished which are orthogonal or complementary to more traditional polar mechanisms. Translating these reactions to larger scales is particularly challenging however, since light penetration through a reaction vessel rapidly declines with increasing path length, as described by the Beer-Lambert law.[27] Moreover, efficient photocatalysts such as those used for visible light photoredox catalyzed reactions,[28] also necessarily possess high molar extinction coefficients, which further exacerbates the situation. For instance, for a 1 mM solution of the commonly employed complex $Ru(bpy)_3Cl_2$ (ε = 13,000 $M^{-1}cm^{-1}$), 99% of the photons are absorbed by the reaction medium within the first 1.5 mm from the surface of the vessel, leaving little radiation for the remaining internal volume.[29] The high surface area-to-volume ratio and correspondingly

short path lengths in a flow reactor[30] such as the one shown in Figure 6[31] however, can be leveraged to significantly improve the irradiation efficiency of a reaction mixture. The use of a PFA tubing reactor with an inner diameter of 0.762 mm for example, enables 90% of the incident radiation to be absorbed by a $Ru(bpy)_3Cl_2$ catalyst (typical concentration of 1 mM) at the thickest portion of the tubing.[31]

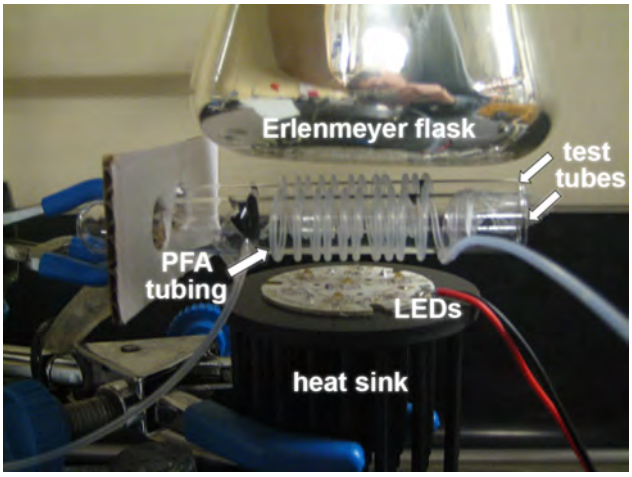


Figure 6. Photoreactor consisting of 0.762 mm inner diameter PFA tubing used for visible light photoredox catalyzed reactions in flow. The irradiation source is commercially available blue LED lights. A silver mirrored Erlenmeyer flask reflects additional light back towards the reactor. Reproduced with permission from Ref 31. Copyright (2012) John Wiley & Sons, Inc.

Research studies involving the use of flow reactors to improve the efficiency of visible light photoredox reactions have been carried out independantly by various groups including Seeberger,[32] Gagné,[33] as well as by ours in collaboration with Stephenson group currently at the University of Michigan.[31] As shown in Figure 7 for example, we have examined the oxidative generation of iminium ions **41** in flow from tetrahydroisoquinoline **40**, followed by trapping with a variety of nucleophiles. Carrying out these reactions using the reactor shown in Figure 6 provided the corresponding products **42a-d** with a t_R of only 0.5 min. This translates to a throughput of 5.75 mmol/h, which compares very favourably to the previously reported batch conditions, whereby a throughput of only 0.081 mmol/h was realized in the case of **42a**.[34]

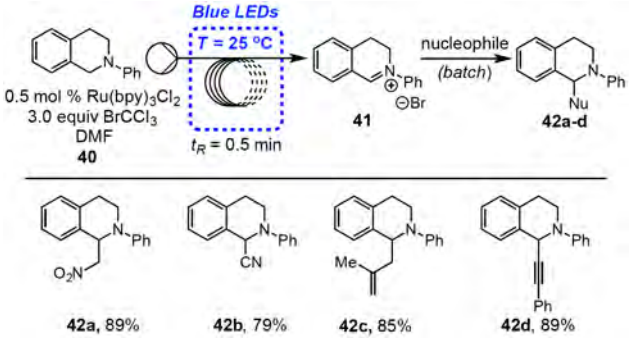


Figure 7. Synthesis of α-functionalized amines in flow.

A number of transformations involving catalytic cycles in which $Ru(bpy)_3Cl_2$ serves as a one electron reductant of the chosen substrate were also very efficient in flow (Figure 8).[31] Bromomalonate **43** for example, was successfully reduced by this method, which after bond scission, formed alkyl radicals that underwent intramolecular radical cyclization to generate **44** in good yield and with a very short t_R of 1 min. In the case of **45**, the more strongly reducing $Ir(ppy)_2(dtbbpy)PF_6$ catalyst was used to induce the cascade cyclization from the less activated amide substrate **46** in 71% yield. [31]

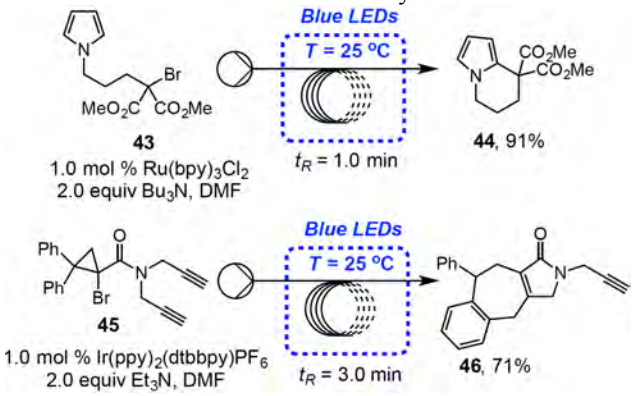


Figure 8. Intramolecular radical reactions in flow.

A number of intermolecular reactions were also demonstrated in flow.[31] Several indole derivative functionalizations (**49a-b**) for example, were accomplished in high yields with a t_R as short as 1.0 min (Figure 9A). The functionalization of substrate **50,** similar to that used in the key step of the total synthesis of Gliocladin C, was also accomplished, giving the desired product **52** with a throughput approximately three times greater than had been accomplished in batch (Figure 9B).[35] This highlights the advantages of flow for the synthesis and scaling-up of complex synthetic intermediates for further studies.

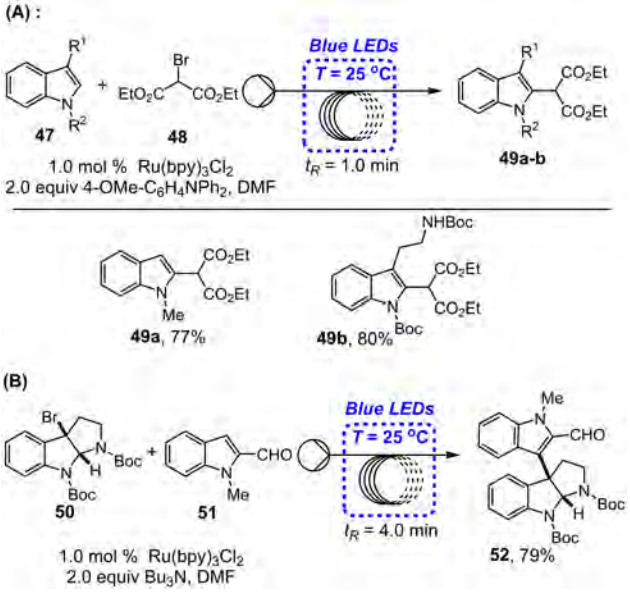


Figure 9. Intermolecular indole (A) functionalization and (B) coupling in flow.

Case Study 5: High Surface Area-to-Volume Ratio in Flow – Improved Throughput of Ultraviolet Photochemical Synthesis of and Catalysis by Ruthenium Cyclopentadiene Complexes

The cationic ruthenium complex $CpRu(MeCN)_3PF_6$ (**55**) shown in Figure 10, is a versatile catalyst that has been successfully used in a variety of organic transformations[36] owing to its interesting properties such as high π-affinity, ability to participate in reversible redox cycles, and the lability of the acetonitrile ligands.[37] It is typically prepared from the precursor sandwich complex **53** via the photoactive excited a^3E_1 state **54** under ultraviolet light.[37c] Although high-yielding on small scales, the synthesis requires approximately 12 h to complete beginning from 1.70 g of starting material in a 250 mL quartz photolysis reactor.[38] A decreased yield is also likely to be observed upon scaling up due to the aforementioned challenges with irradiating larger vessels.

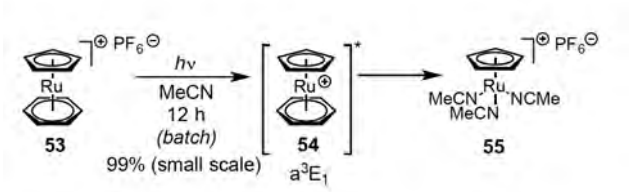


Figure 10. Synthesis of the cationic ruthenium complex $CpRu(MeCN)_3PF_6$ under batch conditions.

However, by leveraging the high surface-to-volume ratio in a flow platform, complex **55** can be synthesized in a very efficient manner.[39] We have shown for example, that at a concentration of 0.06 M in MeCN, complex **55** can be obtained in >99% yield and with >99% purity in a t_R of only 5 min. The flow platform used for the synthesis consisted of high purity PFA tubing coiled around the quartz cooling well of a standard mercury lamp, all of which was contained inside a photobox that fit within a laboratory fume hood. Overall, this flow procedure enabled a throughput of 1.56 g/h of **55**, which is ten times greater than the batch protocol (Figure 11).

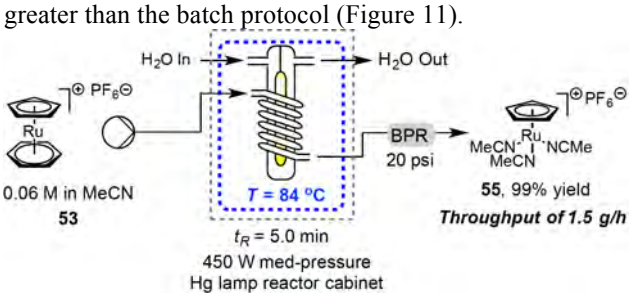


Figure 11. Synthesis of the cationic ruthenium complex $CpRu(MeCN)_3PF_6$ under continuous flow conditions.

While continuous flow proved invaluable for the high throughput synthesis of the cationic ruthenium complex **55**, we speculated that photochemical transformations utilizing this catalyst could be further streamlined in flow. More specifically, we reasoned that the catalytically active species of **55** formed from the substitution of the labile acetonitrile ligands by solvent molecules or by a substrate (e.g. **57**, Figure 12) could be generated directly by intercepting the excited intermediate **54** (Figure 10).[40] This would avoid the need for isolating **55** and enable the use of the inexpensive and stable sandwich complex **53** as a direct catalyst for chemical reactions.

Indeed, using an ene-yne cycloisomerization reaction as a model system, substrate **56** underwent full conversion to the isomerized product **58** (*E*/*Z*, 22:1) in flow with a t_R of only 2.5 min using 5 mol % of complex **53** and under UV irradiation (Figure 12A).[39] The photochemical flow set-up for this reaction utilized quartz tubing since it is more chemically inert than PFA and has superior transparency for improved reaction efficiency. A Pyrex filter was also implemented to attenuate alkene isomerization. Notably, in comparison to this flow reaction, irradiating the same solution containing 5 mol % of complex **53** under batch conditions with a mercury lamp in a quartz round bottom flask for 30 min, resulted in no observable conversion (Figure 12B). Evidently, the higher surface area-to-volume ratio in a flow system is a critical factor for generating sufficient quantities of the catalytically active intermediate **57** directly from **53**. This demonstrates the utility of flow reactors for uncovering new photochemical reactivity pathways that might otherwise not be detected under batch conditions.

A series of intermolecular reactions in flow were also succesfully carried using 10 mol % of **53**, though longer residence times were necessary to reach full conversion; 10 min without the presence of a pyrex filter and 20 min when one was in place (Table 4).[39] A variety of coupling partners were succesfully employed, and gave the desired diene products in yields ranging from 60% – 93%. In many cases, the yields obtained in flow were comparable or higher than that obtained in batch using the cationic ruthenium complex $CpRu(MeCN)_3PF_6$ (**55**), which requires an additional step to synthesize (*vide supra*). A notable feature of this flow reaction is that the sandwich precatalyst **53** can be quantitatively recovered from the reaction and re-used without any noticeable loss in reactivity. Overall, in addition to the improved throughputs, this study demonstrates that photochemical reactors can be a beneficial tool for developing new UV radiation-promoted photochemical reactions due to the increased efficiency of irradiation.

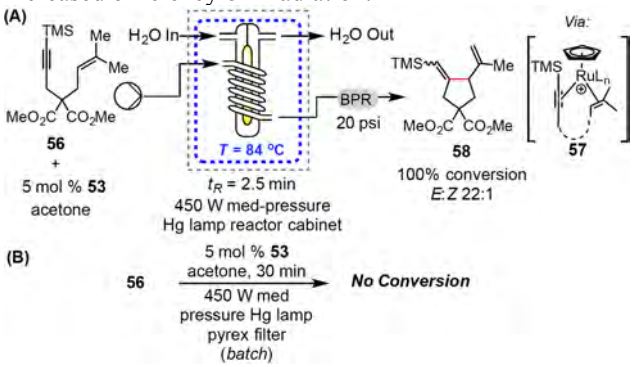
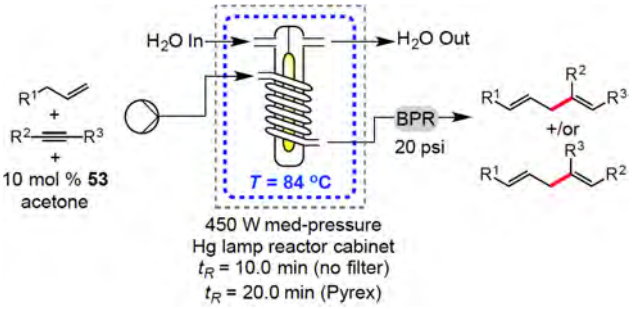
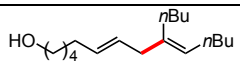
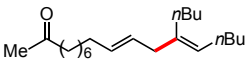
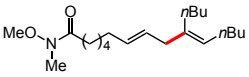
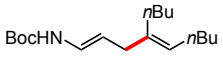
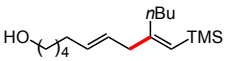
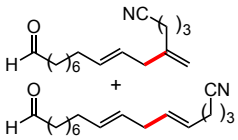


Figure 12. Comparison of the photochemical intramolecular ene-yne cycloisomerization reaction of **56** in (A) flow and (B) batch under otherwise identical conditions.

Table 4. Comparison of yields between intermolecular ene-yne cycloisomerization reactions in flow using photochemical activation of catalyst **53** and batch conditions using catalyst **55**.



Entry	Product	Filter	Flow yield (%)	Batch yield (%)[a]
1		-	93	90
2		-	60	66
3		Pyrex	62	93
4		Pyrex	70	50
5		Pyrex	85	89
6		Pyrex	58[b]	86[b]

[a] Batch reactions were all performed using 10 mol % of **55** in acetone [b] rr = 1:1

3. Summary

The synthetic methodologies described herein illustrate how flow technology enabled and made practical, various reactions that were either low yielding, had poor product selectivity or were simply not observed under batch conditions. For several of these examples, the reaction rates were also dramatically enhanced in flow, thereby improving the overall throughput. These successes were achieved by taking advantage of diverse aspects of the physical properties of flow reactors, such as their enhanced mixing capabilities, efficient heat and mass transport, access to high temperatures and high surface-area-to-volume ratios.

Whether used for the synthesis of fine chemicals, active pharmaceutical ingredients or functional materials,[1] continuous flow chemistry has tremendous potential to expand and streamline our synthetic capabilities, both in the lab and on industrial scales. The development of new technologies, such as in-line analytical tools, remains a growing field that will further serve to drive innovations in this field.

Acknowledgements

We thank the Novartis-MIT Center for Continuous Manufacturing, the Bill and Melinda Gates Foundation, and the Defense Advanced Research Project Agency (DARPA) for their generous financial support over the past several years.

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