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Flow Chemistry at the Extremes: Turning Complex Reactions into Scalable Processes

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1.1 Introduction

The use of flow chemistry within the pharmaceutical industry is often used to facilitate the discovery of an active pharmaceutical ingredient (API) or to make its manufacturing route more efficient. Through the combined efforts of academia and industry, significant advances have been made in the field of flow chemistry, which in turn has led to a prevalence of this technology in high-impact settings. The benefits of running reactions in flow are well documented in a number of comprehensive reviews [1–17]. With these reviews, how flow setups can range drastically in their complexity has become obvious. Flow systems in early-stage pharmaceutical settings tend to be automation-intensive platforms, focused on reaction scouting, automated optimization, or library synthesis. For later-stage programs, however, the focus becomes designing highly efficient routes to synthesizing intermediates or final APIs. Depending on the setting, however, the same practical considerations need to be addressed before setting up a reaction in flow. Do reactions need to be run at very low or very high temperatures? Would improved heat transfer and mixing optimize yields and selectivity? If the synthetic route involves the use of a hazardous species, can flow be used to generate this material *in situ*? Is an alternate energy source such as light or current required? If the answer to any of these questions is yes, flow chemistry should be explored. If reactions are heterogeneous or sluggish, however, conventional batch reactors may still be preferred (Table 1.1). In this chapter, a number of examples from the pharmaceutical industry will be discussed where flow chemistry shows obvious advantages over batch techniques. These examples can likely be used as a basis for running future reactions in flow before running reactions in batch. Over time, a number of trends have emerged, and more and more often, specific types of chemistry are preferentially being run in flow on a large scale (Figure 1.1).

Table 1.1 Examples of when and when not to use flow chemistry in the pharmaceutical industry.

| When TO use flow	When NOT TO use flow
High-/low-temperature applications	Heterogeneous/slurries
In situ use of hazardous intermediates	Slow reaction rates
Reactions mediated by alternative energy sources (photochemistry)	

Flow reactor equipment
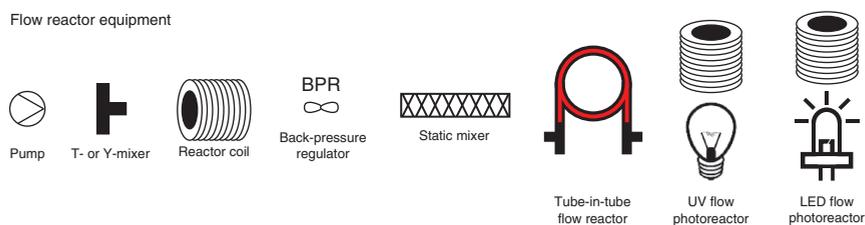
Figure 1.1 Legend for flow reactor equipment.

1.2 Temperature Extremes

Flow chemistry has remained a tried and true method for running low- and high-temperature reactions ever since the field started taking off in the early 2000s. Due to the high surface-area-to-volume ratios, flow reactors have unmatched heat transfer, often times leading to high yields and clean reaction profiles. For cryogenic reactions, flow reactors are readily able to dissipate any exotherms that may be generated. As a result, reactions that run at cryogenic temperatures in batch can frequently be run at higher temperatures in flow. Flow reactors can also reach temperatures that may otherwise be unattainable in batch, thus accelerating reaction rates and resulting in chemistry that is not feasible in batch. High-temperature reactions can also be run much safer in flow as active reactor volumes are lower in comparison to batch systems. In this section, a number of examples of flow chemistry at these two temperature extremes will be discussed in the context of the pharmaceutical industry.

1.2.1 Cryogenic Flow Chemistry

To grasp the differences in cooling a batch reactor versus a flow reactor, it is easiest to first envision cooling a large round-bottom flask. The heat transfer in this instance mainly occurs at the walls of the flask, meaning that as a flask size increases, the effective cooling of the reaction changes and temperature gradients are likely being formed across the reactor. In order to ensure proper reaction control, it is necessary to have excellent mixing and to add reagents in a dropwise manner to keep temperatures from fluctuating. Flow reactors, however, have dimensions on the order
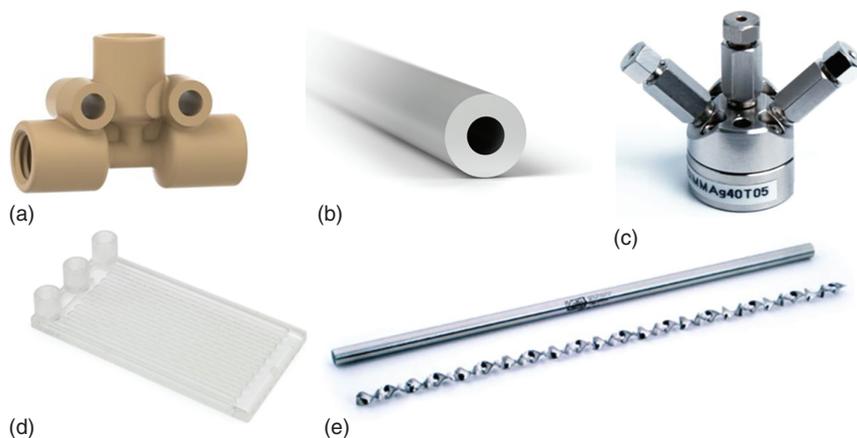
Figure 1.2 Examples of mixers for use in flow chemistry. (a) Standard T-mixer, (b) narrow-bore tubing, (c) IMM static mixer, (d) microchip mixer, or (e) Koflo static mixer.

of millimeters, which result in efficient cooling and limited hotspots. Being able to rapidly dissipate exotherms results in reactions that can be run much more cleanly and at potentially higher temperatures. It is also worth noting that while a 500 ml reaction in batch would likely require at least a 1 l reactor, the same-sized reaction in flow would require a far smaller reactor volume (potentially even a few milliliters). As opposed to a stir bar or impeller, flow reactors can be mixed using a number of options that vary depending on scale (Figure 1.2).

1.2.1.1 Organolithium Chemistry in Flow

Perhaps one of the most prevalent types of flow chemistry involves the use of organolithium species such as *n*-butyllithium or lithium diisopropylamide [18]. While in batch, these reactions are predominately run at −78 °C or lower, for safety and selectivity reasons. For these reason, running these reactions on large scale in batch can be somewhat limiting if these concerns are not mitigated. As a result, more and more examples of organolithium-mediated flow chemistry are being described within the literature. Frequently, these examples can be classified as "flash chemistry," a term coined by the Yoshida group, where reactions take place on the order of milliseconds to seconds [19].

1.2.1.1.1 Boronate Synthesis

Flow examples using organolithiums commonly involve a rapid deprotonation/transmetalation followed by a quench with some sort of electrophile such as a boronate (Scheme 1.1). These flow processes are completed typically by the use of some form of aqueous quench in batch, leading to the isolation of the desired product. A number of examples have been described to generate aryl boronates from both academic and industry laboratories. Ley's group has used the commercially available Polar Bear reactor to prepare gram quantities of (4-chloro-2-fluoro-3-methoxyphenyl)boronic acid [20, 21]. In this instance, the
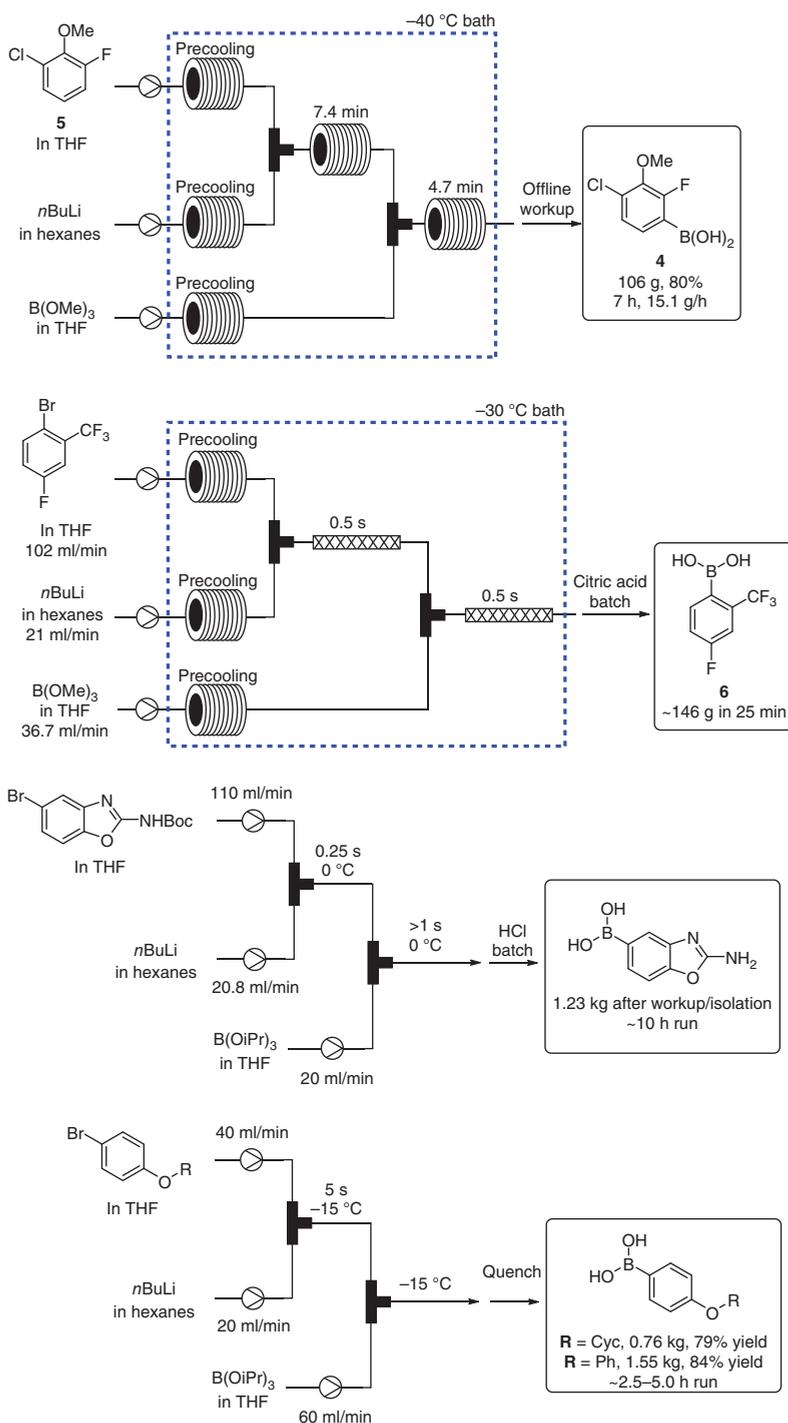
Scheme 1.1 Continuous flow boronate synthesis.

o-lithiation/quench occurred at −50 °C and was capable of preparing >100 g of product within seven hours.

Similarly, Novartis has reported a flow borylation based upon the transmetalation strategy [22]. Both the metalation and boronate quench occur at −30 °C, with a total residence time in the reactor of just one second. When used in scale-up mode, this process proves to be of incredibly high throughput, generating 146 g of product in just 25 minutes. The process operates at incredibly high flow rates, which coupled with the short reaction times allows kilos of this material to be generated in short order if needed. Takeda has exemplified two lithiation–borylation sequences that are used to generate kilogram quantities of various boronates [23, 24]. As with the work by Novartis, these examples could be characterized as "flash" chemistry, as their combined residence times are on the order of seconds. In the first reported example, a Boc-protected aminobenzoxazole is borylated at 0 °C. When run ~10 hours, 1.23 kg of the final boronate is isolated. Similarly, Takeda later reported their efforts to synthesize two aryl ether boronates on a large scale using a very similar procedure. Again, the use of flow chemistry permitted these reactions to occur at −15 °C, much higher than the norm for these types of reactions, allowing 0.75–1.55 kg of final material to be prepared in less than 5 hours. In all the cases described earlier, the use of flow has shown to be beneficial over traditional batch reactions. All processes are rapidly scaled and can operate effectively at temperatures >−78 °C. Not only does this increase in temperature provide some increase in kinetics, but also in many cases the warmer temperature can boost solubility, making the reactors far more stable for long-term operation.

1.2.1.1.2 Formylation

Similar to the boronate synthesis, aldehydes are frequently synthesized via a two-step flow process using organolithium species (Scheme 1.2). Again, a lithium–halogen exchange is carried out at low temperature in flow, followed by a rapid quench with *N,N*-dimethylformamide to afford the final product. Large-scale flow runs using this chemistry have been described by chemists at both Merck and Takeda. At Merck, a route to synthesize kilograms of a formylated intermediate was developed [25]. In this case, a lithium salt was used as a starting material in order to avoid competing deprotonation and transmetalation during and after treatment with the organolithium species. This lithium salt was mixed with *n*BuLi, and the resultant dianion was treated with a solution of dimethylformamide (DMF) in tetrahydrofuran (THF), to afford the formylated product. At Takeda, a similar formylation was carried on a substrate containing both an isopropoxycarboxylate and a cyano group [26]. These two functional groups led to rapid decomposition and by-product formation. Reaction times in this instance were on the order of milliseconds. While the flow process was initially screened at −50 °C, exotherms in the cooling bath were observed, as was an increase in reaction pressure. As both of these observations would hinder scale-up efforts, the temperature was dropped to −60 °C without having a deleterious effect on the reaction outcome. Although not high yielding (237 g of final product represents ~40% isolated yield), the product was otherwise unattainable in batch. Flow chemistry however makes this route
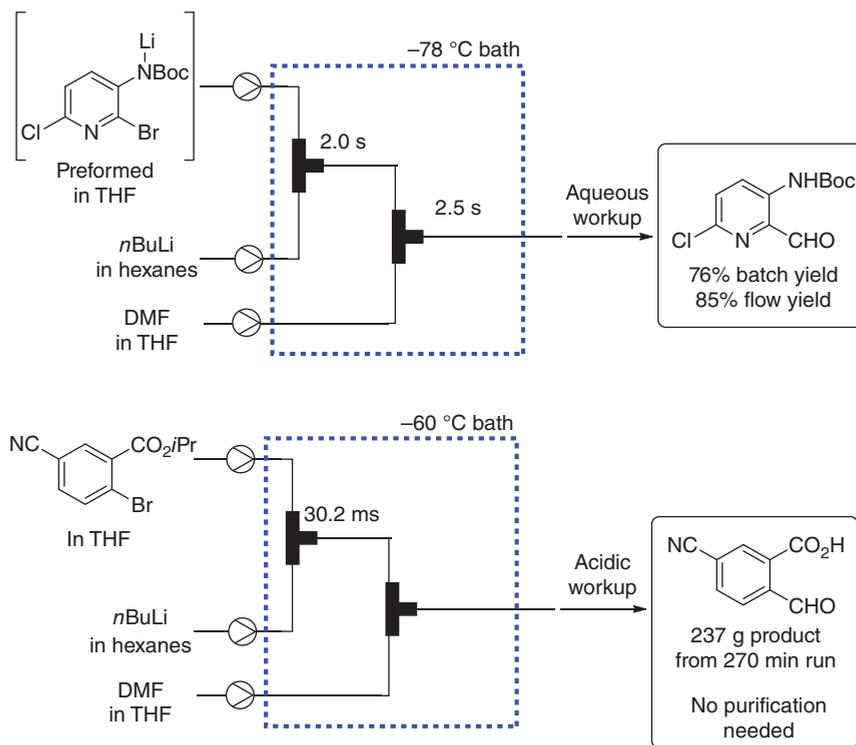
Scheme 1.2 Examples of continuous flow formylations.

tractable, benefitting from the rapid heat transfer and the rapid quench of the lithiated species. Another key to the success of these processes is their simplified batch workups. In both cases, substrates were subjected to an acidic workup followed by extraction. Final products were obtained following concentration, and further purification was deemed unnecessary.

1.2.1.1.3 Carboxylation

A flow carboxylation route was described by SARcode in the synthesis of Lifite-grast (Scheme 1.3) [27, 28]. After noting issues with the batch carboxylation process, an alternative, high-yielding flow method was developed. A feedstock of tetram-ethylethylenediamine (TMEDA) mixed with the dichloride intermediate was treated with a solution of nBuLi at $-78\,°C$ in flow, generating an anion species that was mixed with CO_2 gas. The output of the reactor was again subjected to an aqueous workup in batch to yield the desired product. The flow process described earlier was utilized to prepare $>22\,kg$ of the carboxylic acid material, typically in 4–5 kg, run with isolated yields consistently between 88% and 91%. This carboxylation process is complimentary to the borylation and formylation procedures described earlier as it highlights how a gas can be used to quench the lithiated species to generate high-value compounds.
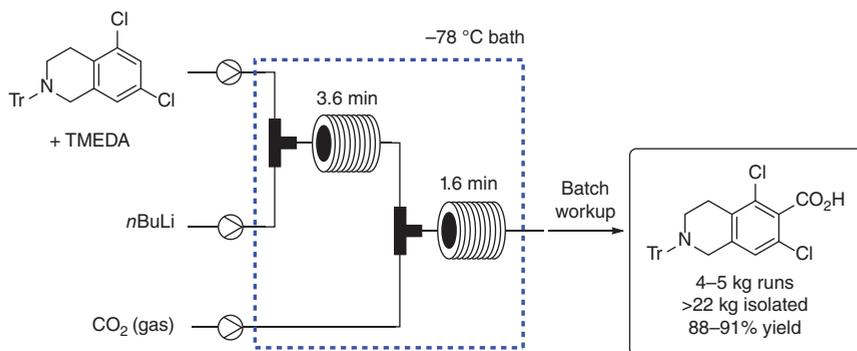
Scheme 1.3 Cryogenic flow carbonylation by SARcode. Source: Based on Refs. [27, 28].

1.2.1.1.4 Nucleophilic Addition

In their synthetic campaign toward eribulin mesylate, flow chemistry was utilized in two separate processes by Eisai (Scheme 1.4) [29]. Following a cryogenic flow reduction of an ester using DIBAL-H, *n*BuLi was used in flow to couple an advance sulfone intermediate to an aldehyde. In their work, a process was developed that takes <5 seconds to complete. While the process was previously run in batch at −70 °C, the flow process was capable of being run at 10 °C in flow due to the enhanced heat transfer exhibited with this type of reactor.
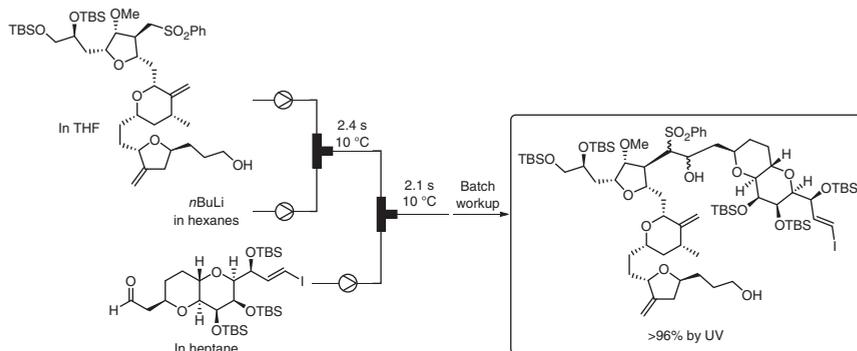
Scheme 1.4 Flow-enabled syntheses of eribulin mesylate intermediates. Source: Fukuyama et al. [29] / American Chemical Society.

1.2.1.1.5 Halomethyllithium Species

Both dichloromethyllithium and bromomethyllithium have proven to be versatile building blocks in organic synthesis; however their utility is somewhat limited due to their unstable nature, even at very low temperatures. To circumvent issues with these reagents, members of pharma and academia have resorted to flow chemistry in order to facilitate their use. At Novartis, it was discovered that dichloromethyllithium could be formed from dichloromethane and *n*BuLi at −30 °C (Scheme 1.5) [30]. In their setup, the deprotonation and quenching steps both took place in
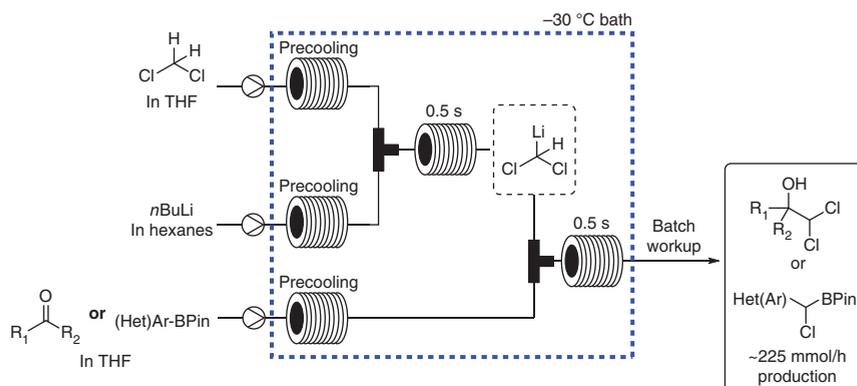
**Scheme 1.5** Dichloromethyllithium generation in flow. Source: Hafner et al. [30] / American Chemical Society.

0.5 seconds. The dichloromethyllithium intermediate has a very short lifetime and is consumed almost immediately after it is generated. A series of carbonyl species are dichloromethylated, which provides an intermediate that is amenable to heterocycle synthesis. Furthermore, a series of boronates could be homologated by switching the reactor input to an aryl boronic ester. While the manuscript describes gram scale productions within five minutes, the process is capable of generating ~225 mmol/h of product.

A similar continuous flow boronate homologation has been reported, resulting in a process used to generate hundreds of kilograms of material in a good manufacturing practice (GMP) setting (Scheme 1.6) [31, 32]. Similar to the example highlighted by Novartis, dichloromethyllithium is prepared in flow by mixing nBuLi and dichloromethane. This reagent stream is subsequently mixed with a solution of the boronate and collected in a batch reactor containing $ZnCl_2$ in THF to facilitate the rearrangement to the desired product. After two additional steps, the final product vaborbactam could be completed.
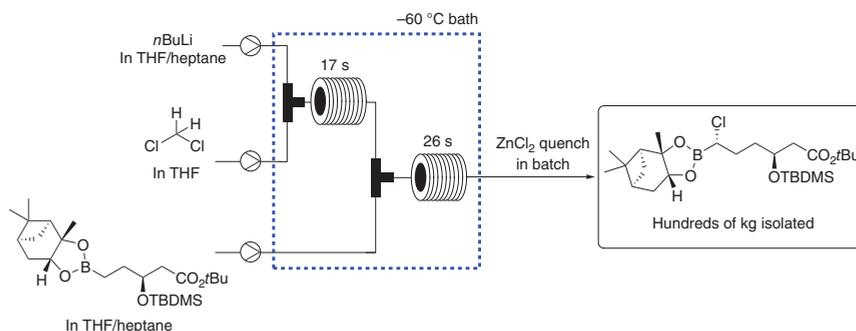
Scheme 1.6 Kilogram-scale flow homologation using dichloromethyllithium. Source: Based on Stueckler et al. [31].

Kappe and coworkers have demonstrated the utility of bromomethyllithium in flow. Similar to dichloromethyllithium, bromomethyllithium has extreme temperature sensitivity and, as a result, frequently needs to be used at around −120 °C. In flow, however, it has been observed to be stable between −80 and −20 °C. Upon treatment of a series of ketones with bromomethyllithium, a bromomethyl alkoxy intermediate forms, which cyclizes to a terminal epoxide upon warming to ambient temperature. A series of epoxides are prepared using this route in high yield, as is a complex chloromethyl epoxide that is an important building block in the synthesis of the drug fluconazole (Scheme 1.7).
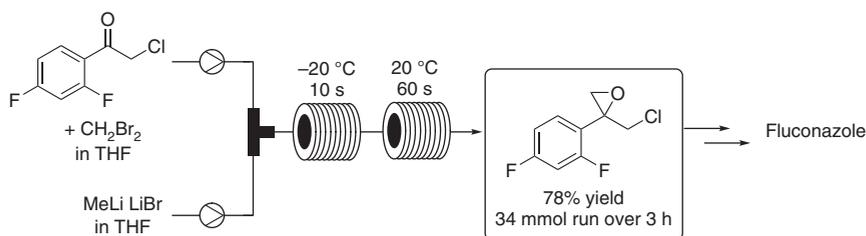

Scheme 1.7 The use of bromomethyllithium in the synthesis of fluconazole.

1.2.1.1.6 Mannich-Type Additions

A series of Mannich-type additions to sulfinyl imines has been reported by Merck and Eli Lilly, both generating >100 kg of material in continuous flow (Scheme 1.8). At Merck, a continuous flow route was explored in the synthesis of the verubecestat intermediate [33, 34]. Similar to the continuous flow formylation previously described by Merck, it was determined that it was optimal to preform the lithiated starting material in batch. This reagent stream was mixed with the aryl sulfinyl imine through a static mixer at high flow rates to afford the desired intermediate. In total, >100 kg of the intermediate was generated using this route, corresponding to an 88% yield. As there were concerns about the temperature stability of the lithiated starting material, the flow route was utilized due to its ability to better control exotherms caused when mixing the two reagent streams.

Similarly, chemists at Eli Lilly used flow chemistry to produce 185 kg of an isoquinoline intermediate of LY3154207, a dopamine D1 receptor-positive allosteric modulator [35]. In this process, a dibromo intermediate undergoes a lithium–halogen exchange at −70 °C and is treated with a chiral sulfinyl imine to generate an intermediate that, upon treatment with HCl, is converted to a chiral primary amine. The final tetrahydroisoquinoline intermediate was isolated after two subsequent batch steps (cyclization then deprotection). Overall, flow chemistry was beneficial in this instance for two reasons. First, the ability to telescope reactions reduced the total number of isolations that were required in the scale-up run. Second, the use of flow once again aided in the control of exotherms caused by the use of an organolithium. As a result, the scaling of this chemistry proved only to be successful in flow, and the batch route was abandoned. Also included in
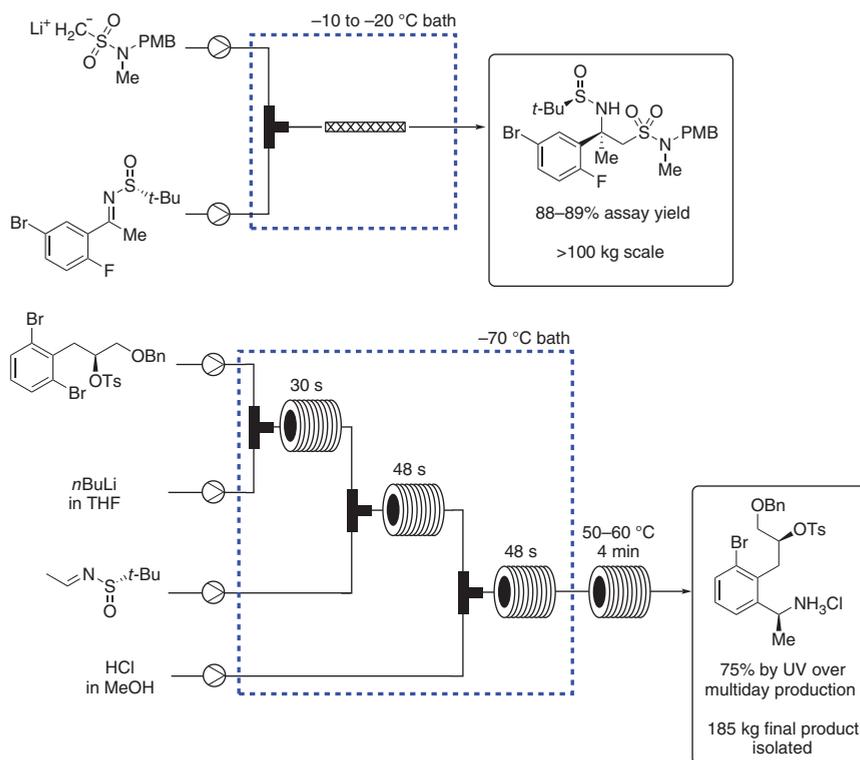
**Scheme 1.8** Continuous flow Mannich-type syntheses from Merck and Eli Lilly.

the manuscript is an honest discussion about the trials and tribulations of running such a process on a scale >100 kg, as well as potential solutions to the problems highlighted.

1.2.1.2 Cyanation

Scientists at Gilead have performed a cryogenic flow cyanation on plant scale in the synthesis of an intermediate of remdesivir (Scheme 1.9) [36]. In order to achieve high levels of selectivity in this transformation, temperatures between −30 and −40 °C are preferred. While a batch process was used for early deliveries, much larger batches of material were processed using a flow setup, proving to have high selectivity as well as better control over reaction conditions. The manuscript highlights the optimization of the flow process from early-stage work, where a commercial Vapourtec reactor was used to prepare 9 g product per hour of material to the late-stage work where a custom-built plant-scale reactor was capable of generating nearly 2 kg of product per hour.

1.2.2 High-Temperature Flow Chemistry

Flow reactors have the ability to be run at elevated temperatures due to their ability to be pressurized. In doing so, traditional reaction solvents such as THF and EtOH can
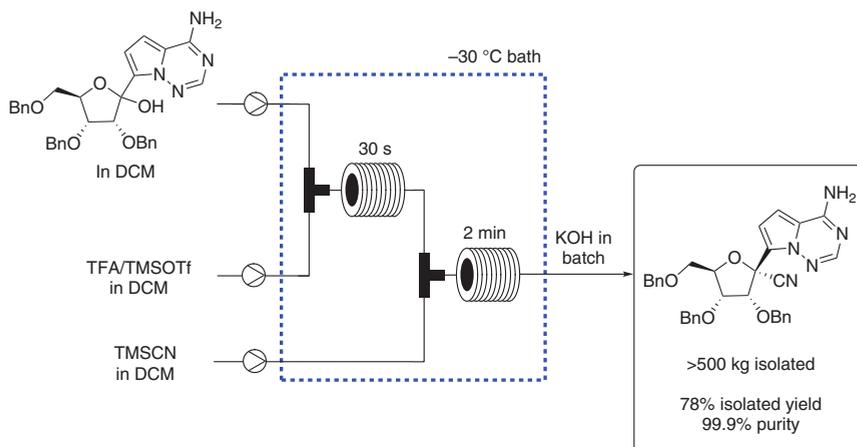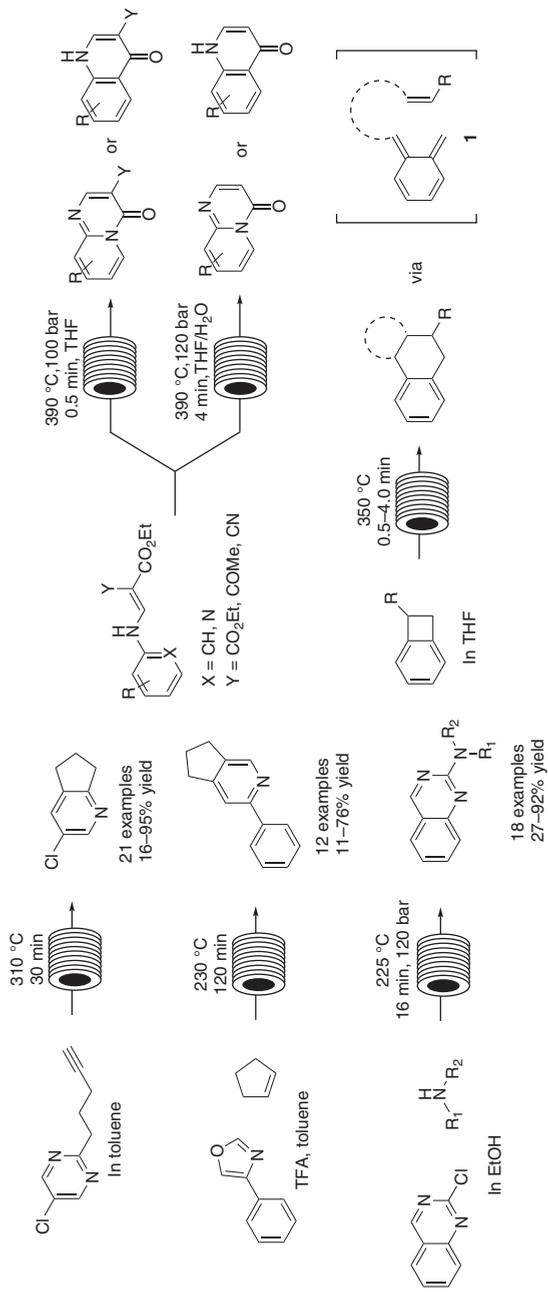
Scheme 1.9 Continuous flow cyanation work from Gilead. Source: Vieira et al. [36] / American Chemical Society.

be used at temperatures well above their boiling point, and the need for high-boiling, less favorable solvents can be mitigated. A number of smaller-scale operations have been reported by Roche, where a series of annulated pyridines were synthesized using a flow reactor coupled with a gas chromatograph oven [37, 38]. A commercial flow reactor capable of reaching 450 °C, the Phoenix from Thales Nano, has been used for parallel library synthesis of aminated heterocycles [39], as well as cyclization reactions such as the Gould–Jacobs [40–42] and Diels–Alder [43]. In all cases, solvents such as toluene, THF, and ethanol were used at temperatures between 230 and 390 °C (Scheme 1.10). Additionally, a series of substrates are synthesized in all cases, and reactions are generally proceeded in modest to high yield.

A high-temperature, additive-free *N*-Boc deprotection using the Phoenix has also been described (Scheme 1.11) [44]. Instead of treating substrate with acid, it was discovered that heating substrates to 300 °C for two minutes afforded quantitative yield to a wide variety of substrates. Furthermore, two multistep syntheses using a Boc deprotection are highlighted in which nearly 200 mg of material can be generated in under 10 minutes. Both processes also avoid any intermediate purification steps.

While the preceding examples were not carried out on particularly large scale, more examples are being reported where high-temperature flow chemistry can be carried out on scale. A flow-based Hemetsberger–Knittel indole formation has been reported by O'Brien et al. where an acrylazide is cyclized at temperatures between160 and 220 °C [45]. This process has inherent safety benefits as low volumes of azide are superheated at any given moment. In AbbVie discovery chemistry, this methodology was applied to the synthesis of various indoles and azaindoles on multigram scale (Scheme 1.12) (Bogdan, A. R., AbbVie Inc, North Chicago IL, Unpublished results).

Much larger-scale, high-temperature applications have been reported by Actelion Pharmaceuticals and Eli Lilly (Scheme 1.13). A flow-mediated Overman rearrangement at 220 °C was used to synthesize an intermediate for an API, capable of being

In toluene

310 °C
30 min

Cl

21 examples
16–95% yield

230 °C
120 min

TFA, toluene

12 examples
11–76% yield

225 °C
16 min, 120 bar

In EtOH

H
R$_1$–N–R$_2$

18 examples
27–92% yield

N–R$_2$
R$_1$

X = CH, N
Y = CO$_2$Et, COMe, CN

H
N
Y
CO$_2$Et
X
R

390 °C, 100 bar
0.5 min, THF

390 °C, 120 bar
4 min, THF/H$_2$O

350 °C
0.5–4.0 min

In THF

R

via

R

1

or

or

N
H
Y
O
R

N
Y
O
R

N
H
O
R

N
O
R

Scheme 1.10 Examples of high-temperature flow chemistry using standard solvents at elevated temperatures.
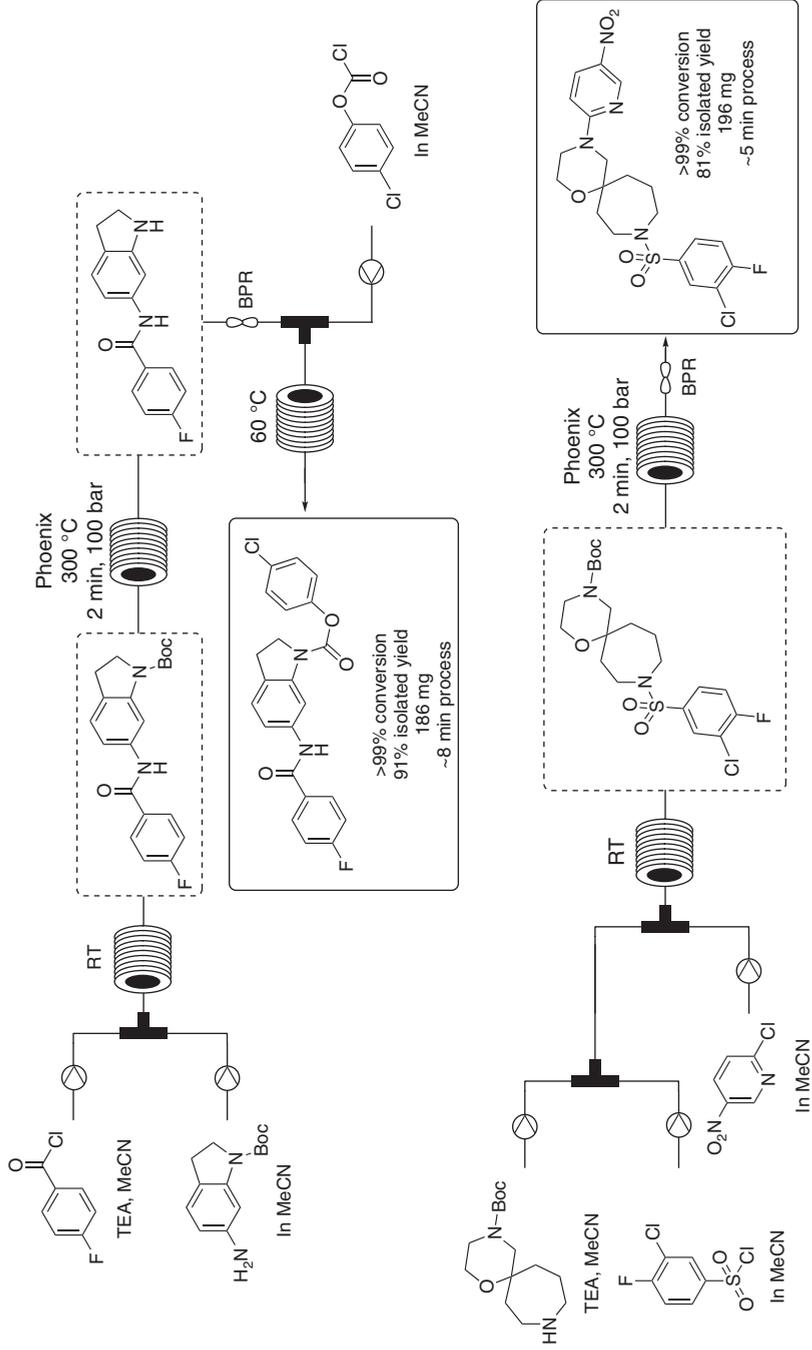
Scheme 1.11 Multistep syntheses carried out using high-temperature Boc deprotection. Source: Bogdan et al. [44] / American Chemical Society.
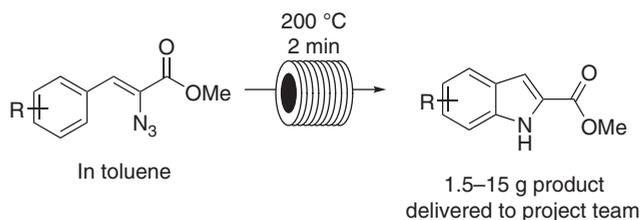
Scheme 1.12 Scale-up of indole using high-temperature-mediated indole formation in flow. Source: Bogdan, A. R., AbbVie Inc, North Chicago IL, Unpublished results.
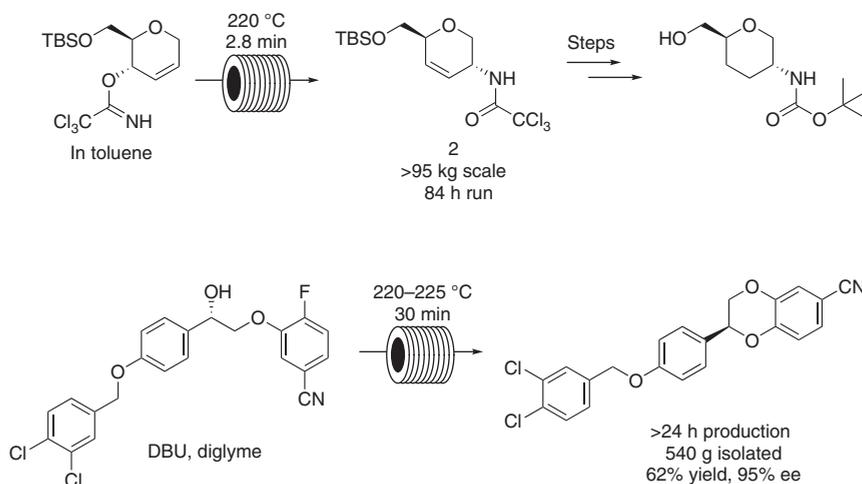
Scheme 1.13 High-temperature flow chemistry on large scale.

carried out on >95 kg scale over the course of 84 hours. The process benefited by high levels of heat transfer, enabling a quantitative yield of the desired compound. Eli Lilly has demonstrated a high-temperature ring cyclization in flow to enable the delivery of >500 g of material in support of early phase development [46]. Specifically, an intramolecular SnAr was developed where the combination of high heat, an organic base, and a less polar solvent led to high yields and enantioselectivity. Using more traditional SnAr conditions in batch resulted in higher impurity formation.

1.3 *In Situ* Use of Hazardous Reagents

A key benefit of flow chemistry is its ability to generate reactive or unstable intermediates and use them immediately in subsequent reaction steps. This has been highlighted previously in a number of cryogenic reactions. In addition, it can be applied at higher temperatures and can be used quite effectively on a large scale. Species such as these can also be prepared at ambient temperatures. By preparation of these species *in situ*, storage issues are mitigated, as are various other safety concerns.
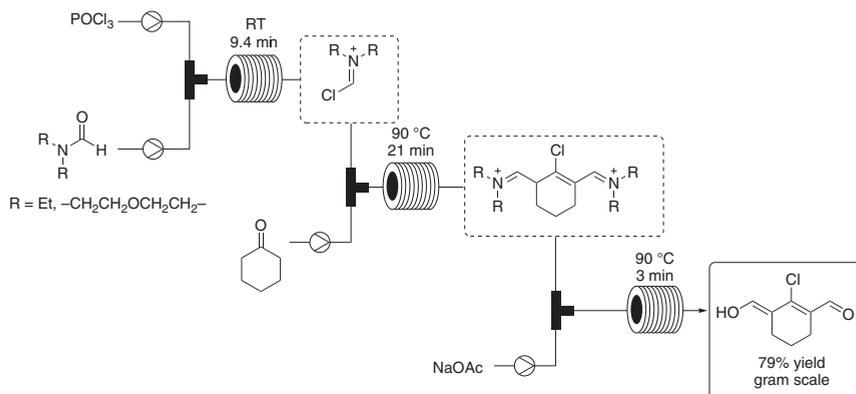
1.3.1 Vilsmeier Reagent

The Vilsmeier reagent is a versatile formylating agent, typically prepared by the treatment of DMF and phosphorus oxychloride ($POCl_3$). However, thermal stability issues with this reagent can cause concern when being used on a large scale (specifically in exothermic processes). For this reason, a number of examples highlight preparing the Vilsmeier reagent in flow and using it directly in subsequent reaction steps (Scheme 1.14). In one such example, a series of pyrroles are formylated using a multistep flow process [47]. First, the DMF and $POCl_3$ are mixed at ambient temperature for 90 seconds, generating small quantities of the Vilsmeier reagent, which is subsequently mixed with the heterocycles being formylated. Output on this system can be in the grams per hour range. The process was later applied on an industrial scale, in flow in the synthesis of Vildagliptin [48]. Similar to the prior example, the Vilsmeier reagent is prepared at ambient temperature but is now reacted with an advanced intermediate to generate a cyanopyrrolidine at a rate of 5.8 kg/h/l.

Alternative Vilsmeier chemistry has been employed using diethylformamide (DEF) or *N*-formylmorpholine (NFM) as opposed to DMF (Scheme 1.15) [49]. Upon treatment of cyclohexanone with the Vilsmeier reagent and the subsequent reaction
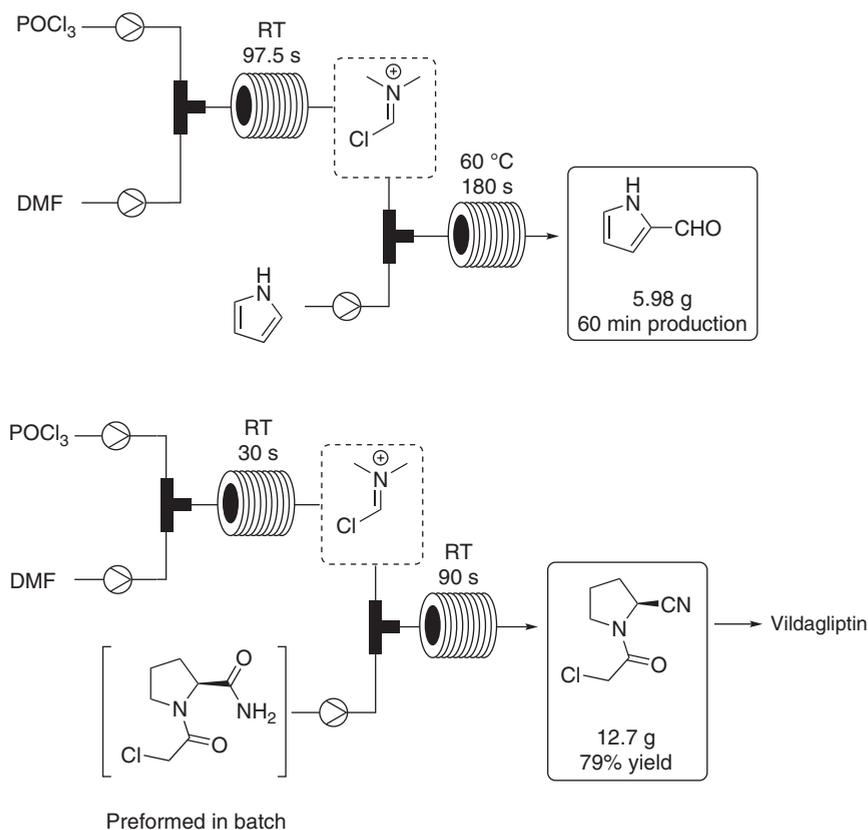
**Scheme 1.14** Applications of *in situ* generated Vilsmeier reagent.

Scheme 1.15 Alternative Vilsmeier reagent use in flow. Source: Carrera et al. [49] / American Chemical Society.

with sodium acetate, 2-chloro-1-formyl-3-(hydroxymethylene)cyclohex-1-ene can be obtained in high yield. The described process not only benefits from not isolating the Vilsmeier reagents in large quantities but also relies on more environmentally friendly formamides than previously reported examples.

1.3.2 Phosgene

Phosgene is another versatile chemical in organic synthesis; however, its hazards are well known, and large-scale use is avoided if possible. Flow chemistry again can be used to generate this hazardous reagent on the fly. In this work, a solution of phosgene in toluene is prepared by mixing triphosgene and tributylamine in flow for five seconds and immediately reacted with a tetrahydroisoquinoline [50]. The developed process has the potential to result in vast amounts of material, given that 64 g of material was isolated in under five minutes (Scheme 1.16).
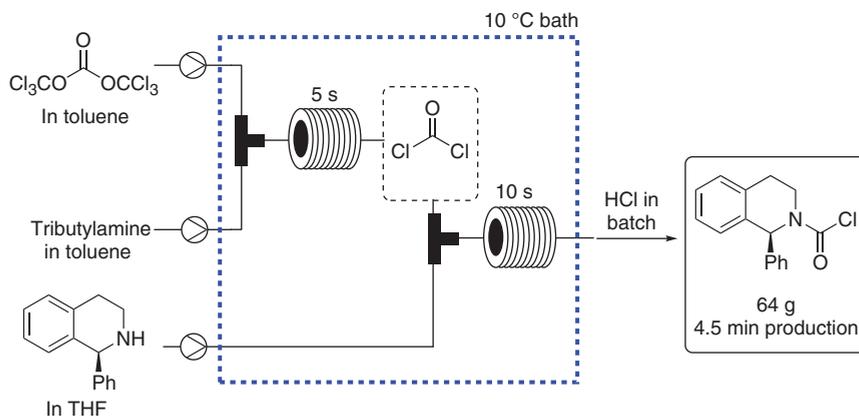
**Scheme 1.16** Synthesis and reaction of phosgene **31** in flow.
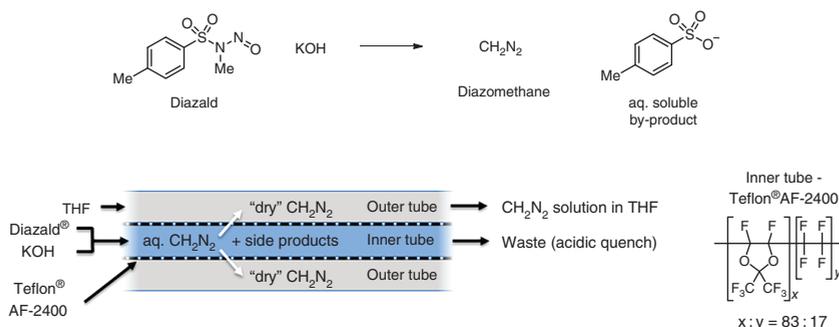
Figure 1.3 Schematic of a tube-in-tube reactor and the structure of Teflon AF-2400.
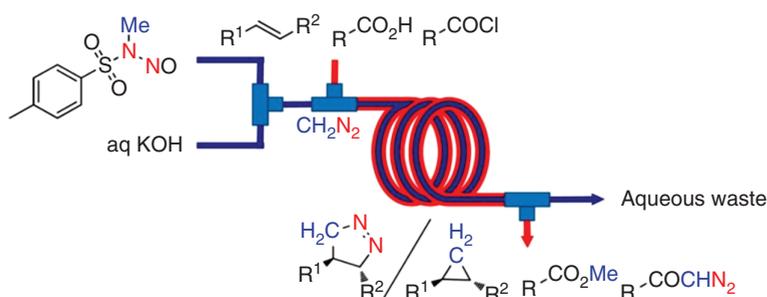
1.3.3 Diazomethane

Diazomethane (CH_2N_2) is a versatile reagent in organic synthesis; however, its use is limited due to the safety concerns associated with its use [51]. This reagent, however, is gaining broader utility due to recent advances in flow chemistry technology, specifically with the development of tube-in-tube reactors or other gas-permeable membranes. With a tube-in-tube reactor, an inner gas-permeable tube (commonly made of Teflon AF-2400) is housed within a larger, standard piece of tubing. Gases permeate through the Teflon AF-2400 into the outer stream, where reactions can take place (Figure 1.3). For the examples to be highlighted, Diazald and potassium hydroxide are mixed within the inner tube of the tube-in-tube reactor and the generated gas permeates out into a reaction or solvent stream.

The Kappe group has pioneered the generation of diazomethane using tube-in-tube reactors [52]. In this case, a series of reactions are carried out to synthesize cyclopropanes, methyl esters, and α-diazocarbonyls (Figure 1.4). A stream of reactant is passed through the outer tube of the tube-in-tube reactor to generate a product. A multistep process was later developed where the α-diazocarbonyls was treated with HCl to generate α-chloromethyl ketones on gram scale, in excellent yield [53]. Similarly, by treating the α-diazocarbonyl species with water, followed by irradiation with ultraviolet (UV) light, a series of homologated amino acids could be prepared in a multistep continuous flow process (Scheme 1.17) [54].

Scientists at AbbVie have developed the diazomethane reactor in flow technology (DRIFT) platform to automate diazomethane production, in both library and scale-up format [55]. A key difference between the DRIFT platform and the examples highlighted earlier is that DRIFT prepares an anhydrous solution of diazomethane in THF in the outer tube of the tube-in-tube reactor, which is used in downstream reactions (Figure 1.5). During development, it was noted that when running reactions in the outer tube of the tube-in-tube reactor, results were inconsistent and long-term use was not feasible. On the DRIFT platform, a small library of cyclopropyl boronates was synthesized in modest yield with an output of up to 190 mg/h (Scheme 1.18). The DRIFT platform continues to be applied to various projects in support of discovery chemistry programs.
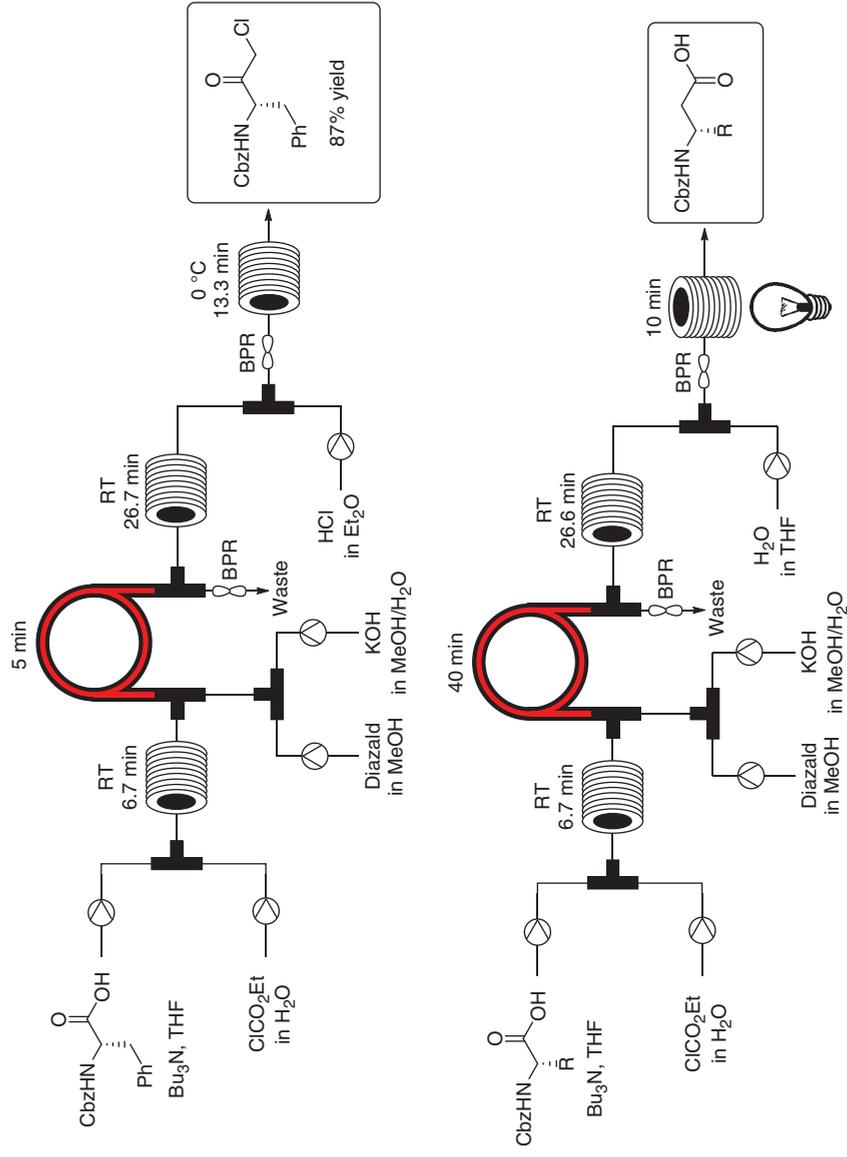
Scheme 1.17 Multistep continuous flow diazomethane chemistry. Source: Based on Pinho et al. [54].

Figure 1.4 Tube-in-tube reactor using diazomethane technology.
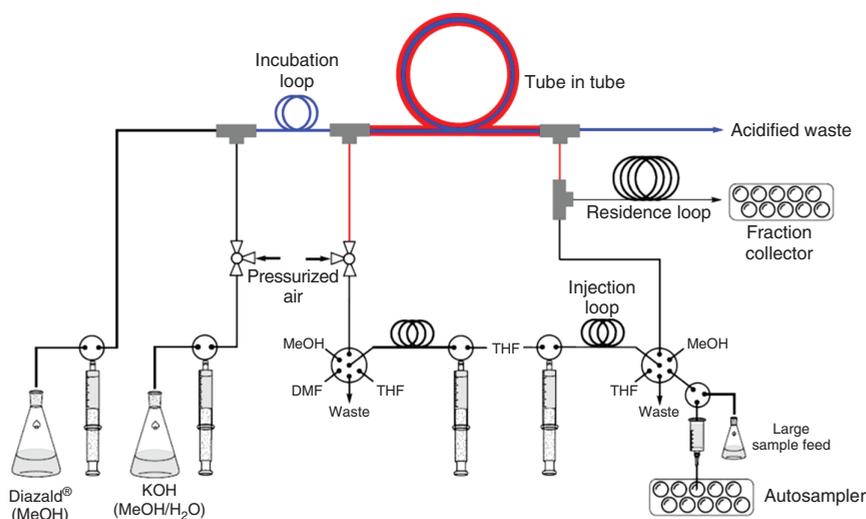
Figure 1.5 Schematic of the DRIFT flow reactor.

While many of the aforementioned diazomethane reactions are high yielding, they are limited by their output. To address this, the Kappe group has developed hybrid batch/flow procedure for facile scaling of diazomethane reactions [56]. A coil of AF-2400 tubing is submerged within a batch reaction vessel, and substrates are added. Diazomethane is generated by mixing Diazald and KOH in flow, and diazomethane permeates out of the AF-2400 tubing, converting starting materials to product (Figure 1.6). Larger scales can be achieved by adding additional coils of the AF-2400 tubing. This process was reported to synthesize >40 g of methyl benzoate during an eight hour run.

More recent examples of diazomethane chemistry have emerged in flow chemistry, where the diazomethane gas is extracted by way of a gas-permeable membrane (Figure 1.7) [57]. In this case, substrates are treated with a gaseous stream of diazomethane in a nitrogen carrier gas, as opposed to an organic solvent. Examples highlighted using this approach include methyl ester formation, as well as the cyclopropanation of styrene. In both instances, multigram per hour outputs were noted,
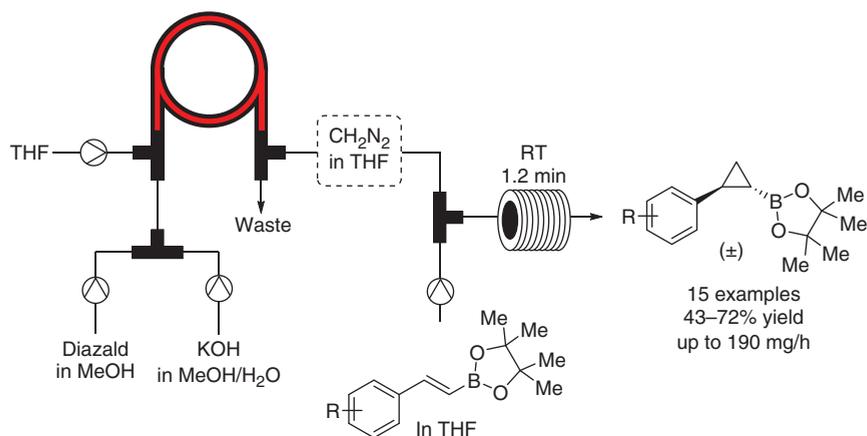
Scheme 1.18 Library production using tube-in-tube diazomethane reactor.
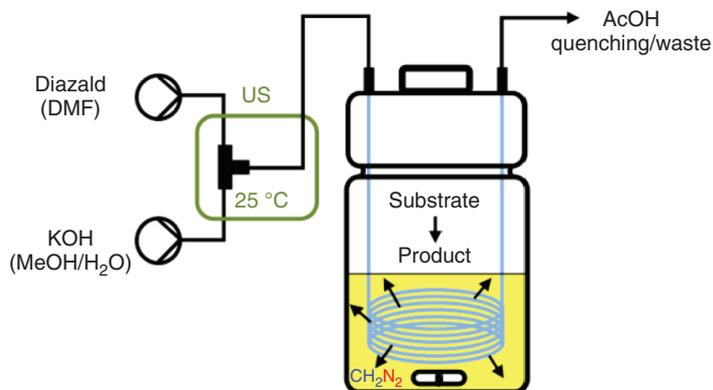
Figure 1.6 New approach for running tube-in-tube reactions with diazomethane in batch using Teflon AF-2400 coil.

where a relatively small amount of diazomethane was present at a given time. As such, this route is proposed as a method to be used in small-scale manufacturing in the event that diazomethane is required for synthesis.

1.4 Photochemistry on Scale

Photochemistry on scale has gained far more attention over the past decade, thanks to a variety of simple flow reactors [58–63]. In many cases, the systems can rapidly be prepared using traditional photoreactor equipment, coupled with a pump and some tubing (Figure 1.8). Many of the benefits of running a flow photochemical reaction are the result of short path lengths (i.e. tubing diameter). For this reason, there have been a number of gram- to kilogram-scale processes developed using flow chemistry, using either UV or visible light sources. (In Chapter 3 the reader could
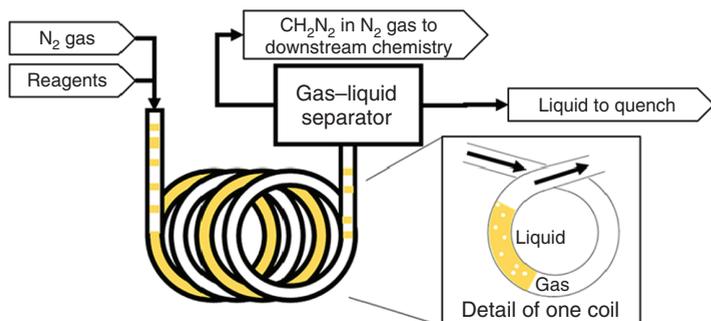
Figure 1.7 Diazomethane generation using gas–liquid separator. Source: Sheeran et al. [57] / American Chemical Society.
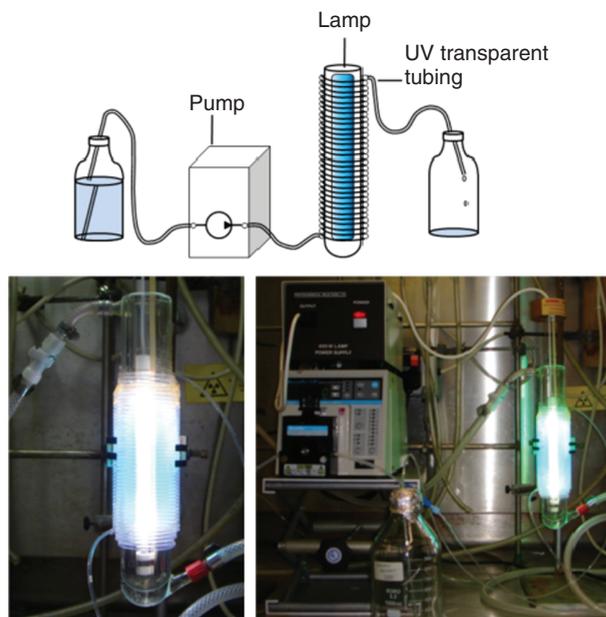
Figure 1.8 Example of flow photochemical reactor.

also find several examples of photochemical transformation in continuous flow at smaller scale, useful for medicinal chemistry).

Flow photochemical reactors can be readily prepared to accommodate various scales of chemistry. While a number of microscale photoreactors are available, larger-scale operations can be achieved by wrapping tubing around an immersion well or a glass/quartz sleeve. A standard setup has been highlighted by the Booker-Milburn group [64], which has subsequently been utilized in various industrial and academic applications.

Scientists at Vertex have utilized flow photochemistry to generate lactams on multigram scale via a light-catalyzed rearrangement of spiro-oxaziridines

(Scheme 1.19) [65]. Examples highlighted within the manuscript are high yielding and often have shorter reaction times than corresponding batch reactions. Similarly, the Booker-Milburn used a photochemical Paternò–Büchi reaction to reach a key intermediate in the synthesis (+)-goniofufurone (Scheme 1.19) [66]. After 83 hours of continuous processing, 42 g of intermediate (2 : 1 mixture of regioisomers) was obtained in a 97% isolated yield.
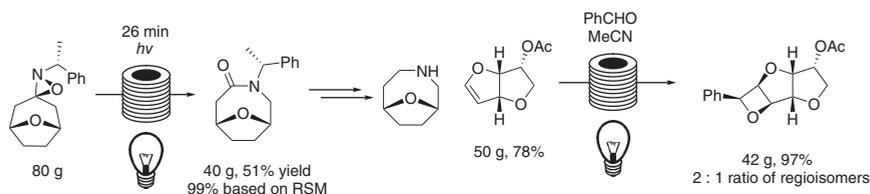
Scheme 1.19 Flow photochemistry-enabled rearrangements. Source: Cochran and Waal [65] / American Chemical Society.

Flow photochemistry is not just limited to traditional UV light sources. Recently, a number of examples have been exemplified using longer wavelength light sources such as LEDs. Enamine, for example, has expanded the scope of scalable flow processes by generating 1 kg of a hi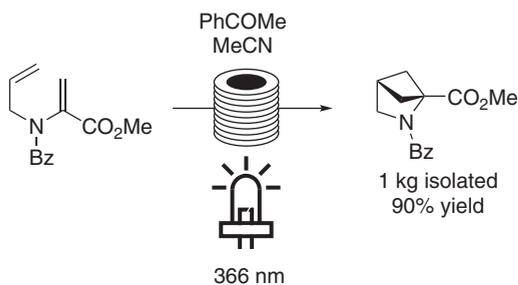gh-value 2,4-methanopyrrolidine intermediate (Scheme 1.20) [67]. The process was carried out using a 366 nm light source and run continuously for one day. The resulting compound was subsequently converted to dozens of methanopyrrolidine substrates.

Scheme 1.20 Flow preparation of 2,4-methanopyrrolidine intermediate. Source: Levterov et al. [67] / American Chemical Society.

A fair amount of research has additionally been undertaken to synthesize the highly strained 1,4-cubanedicarboxylate (Scheme 1.21). Early examples of photochemistry to synthesize this compound were run on pilot scale, isolating nearly 3 kg of material over the course of 173 hours (~1 week) [68]. The apparatus described within uses a 6.4 l quartz flow cell, used in conjunction with a 2 kW medium-pressure mercury lamp. While this represents an impressive example of flow photochemistry on scale, the process uses highly specialized equipment and required further optimization of the light sources. Linclau and coworkers have since reported a simplified, laboratory-scale flow photochemical reactor capable of
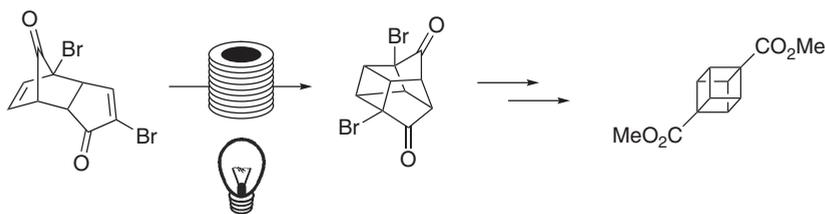
Scheme 1.21 Flow-mediated synthesis of 1,4-cubanedicarboxylate.

generating ~40 g material per day [69]. In this example, cheap 310 nm UV lamps are used and provide clean conversion. In developing a simplified, yet scalable synthesis, the process could be further adapted to synthesize additional sp³-rich building blocks such as this.

A series of simplified trifluoromethylation papers were published by Stephenson's group, where trifluoroacetic anhydride was used as the trifluoromethylating agent [70, 71]. Early examples were reported to be scalable up to 100 g in flow (Scheme 1.22). The process was further explored to trifluoromethylate, an additional pyrrole on roughly 1 kg scale in 24 hours. In the large-scale reactor, PFA tubing was wrapped around three blue LED lamps and submerged in a garbage bin to provide cooling (Figure 1.9).
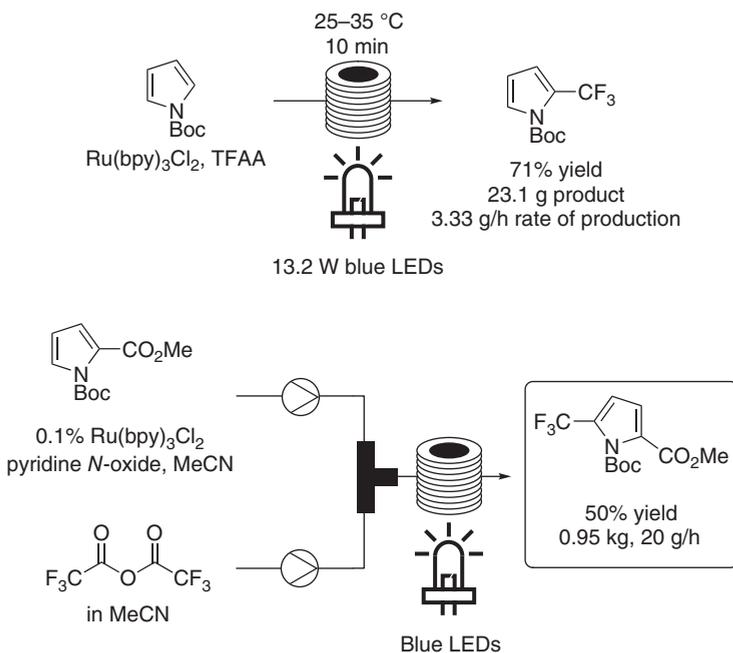
Scheme 1.22 Trifluoromethylation in flow using trifluoroacetic anhydride.

Scientists at Merck have reported the use of a flow photochemical reactor to synthesize bicyclo[1.1.1]pentane (BCP) trifluoroborate salts (Scheme 1.23) [72]. Up to

Figure 1.9 Scale-up of flow trifluoromethylation.
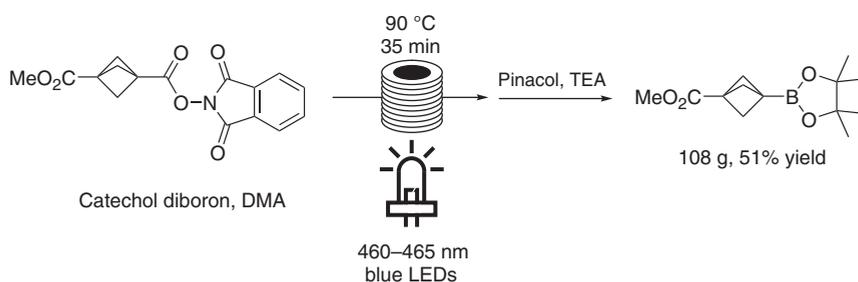
Scheme 1.23 Flow synthesis of bicyclo[1.1.1]pentane (BCP) trifluoroborate salts. Source: VanHeyst et al. [72] / American Chemical Society.

100 g of BCP pinacol esters are synthesized in flow, before being converted to the corresponding trifluoroborate salt in batch. In doing so, a jacketed photoreactor was prepared capable of heating/cooling reactions while being irradiated with 465 nm blue LEDs.

A number of manuscripts highlight efforts to push flow photochemistry to a large scale (Figure 1.10). A photoreactor capable of kilograms per day output has been reported by Merck [73]. The reactor overall has a small footprint (fitting within a standard fume hood) and can be built from a number of readily available pieces. The light source on this reactor consists of a series of high-power LED connected to a heat sink to assist with dissipating temperature. Amgen, in collaboration with Asymchem, has developed a production-scale photoreactor that was demonstrated to prepare >50 kg of a [2+2] cycloaddition product from a single run [74]. In their setup, a series of high watt 365 nm LED panels were used to irradiate a 29 l reactor coil. These examples highlight how there are relatively few limitations on the scale that can be achieved using photochemistry. A lot of this technology is facilitated by the development of new LED light sources of varying power and wavelength. Coupled with the narrow path lengths of flow chemistry, photochemistry is no longer a thing of the past and will continue to gain more utility across the chemical industry.

Figure 1.10 Examples of large-scale photoreactors built by Merck (left) and Amgen (right).

1.5 Conclusion and Outlook

In conclusion, there exists a litany of examples where flow chemistry has obvious advantages over traditional batchwise processes. By this point, most major pharmaceutical companies have developed large-scale flow operations that can deliver hundreds of grams, if not hundreds of kilograms, of material in relatively short order.

Reactions being run at high- and low-temperature extremes are no longer novel, small-scale processes. Cryogenic "flash" reactions have shown great promise. Coupled with proper pumps and mixing, incredibly high-throughput processes can be developed to synthesize valuable building blocks in API development. At the other end of the spectrum, reactions that were found to behave well under high-heat have been readily scaled up in flow. Issues of superheating large reactor volumes are mitigated using a flow process, and temperatures well above solvent boiling points can be used. In both the low- and high-temperature examples, flow has inherent safety advantages as well as superb control over reaction parameters. Looking forward, it is anticipated that the volume of examples highlighting these temperature extremes will continue to increase.

Flow chemistry also offers the ability to generate hazardous reagents *in situ*, eliminating the hazards associated with working with these materials on larger scale. Reagents such as the Vilsmeier reagent and phosgene can be used on large scale, without even having to isolate or store these materials prior to their use. Other reagents such as diazomethane are also gaining more traction in synthetic chemistry due to newer, safer methods of use.

A final area seeing continuous growth is the area of photochemistry. Thanks to new, improved light sources, as well as a rapid expansion of photoredox reactions, more and more examples of flow photochemistry are being highlighted to enhance scalability. Both simplified and complex systems have been developed to address concerns of scalability in photochemistry. Now, an area that was once viewed as limited by scale can be used to prepare tens of kilograms of material. This area, too, will likely continue to grow, specifically as more cross-coupling reactions are developed and run on larger scale.

The lowest hanging fruit in the flow chemistry realm is likely the expansion of scalable flow electrochemistry. This is viewed almost as a complementary tool as photoredox chemistry, where an alternative energy source is used to facilitate a reaction. A few examples exist already, highlighting the scalability of these processes, which shows great promise in the future of the field (some of them are presented in Chapter 3) [75, 76]. Initial reports demonstrate how >100 g of material can be prepared via electrochemistry in flow, and its growth within pharma will likely increase over time.

While the initial uptake of flow chemistry in the pharmaceutical industry was slow, we have reached a point where these processes are safely and effectively being applied on scale. Companies have either implemented their own infrastructure or are working with contract manufacturing organizations (CMOs)/contract research organizations (CROs) to enable this technology. Very large deliveries of compound are now being handled exclusively in flow, whereas a similar process would not have been considered a few years ago. As time goes by, new applications of flow will continue to emerge, and the barriers to apply this technology will continue to fade. And while not all reactions benefit from being run in flow, there are a number of applications where flow chemistry should potentially be explored as a first pass.

Notes

The authors declare no competing financial interest.

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