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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).

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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)	

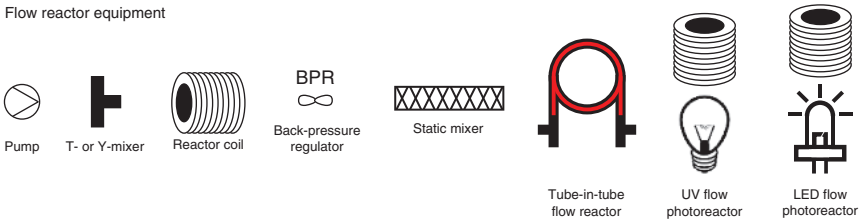


Figure 1.1 Legend for flow reactor equipment.

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

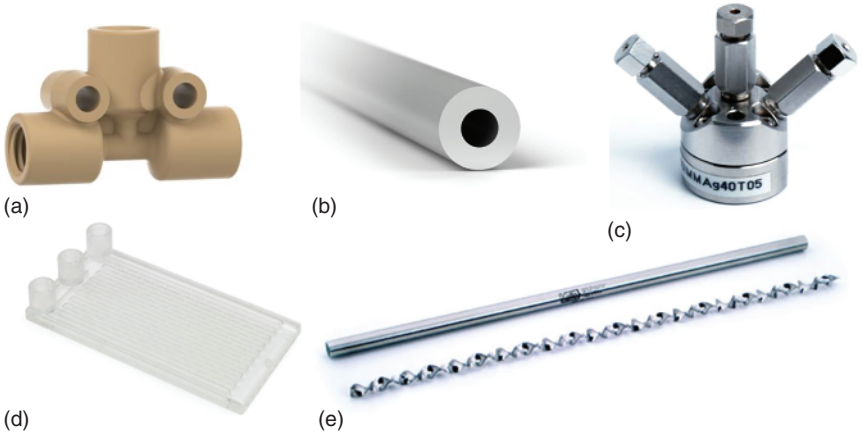


Figure 1.2 Examples of mixers for use in flow chemistry. (a) Standard T-mixer, (b) narrow-bore tubing, (c) IMM static mixer, (d) microchip mixer, or (e) Koflo static mixer.

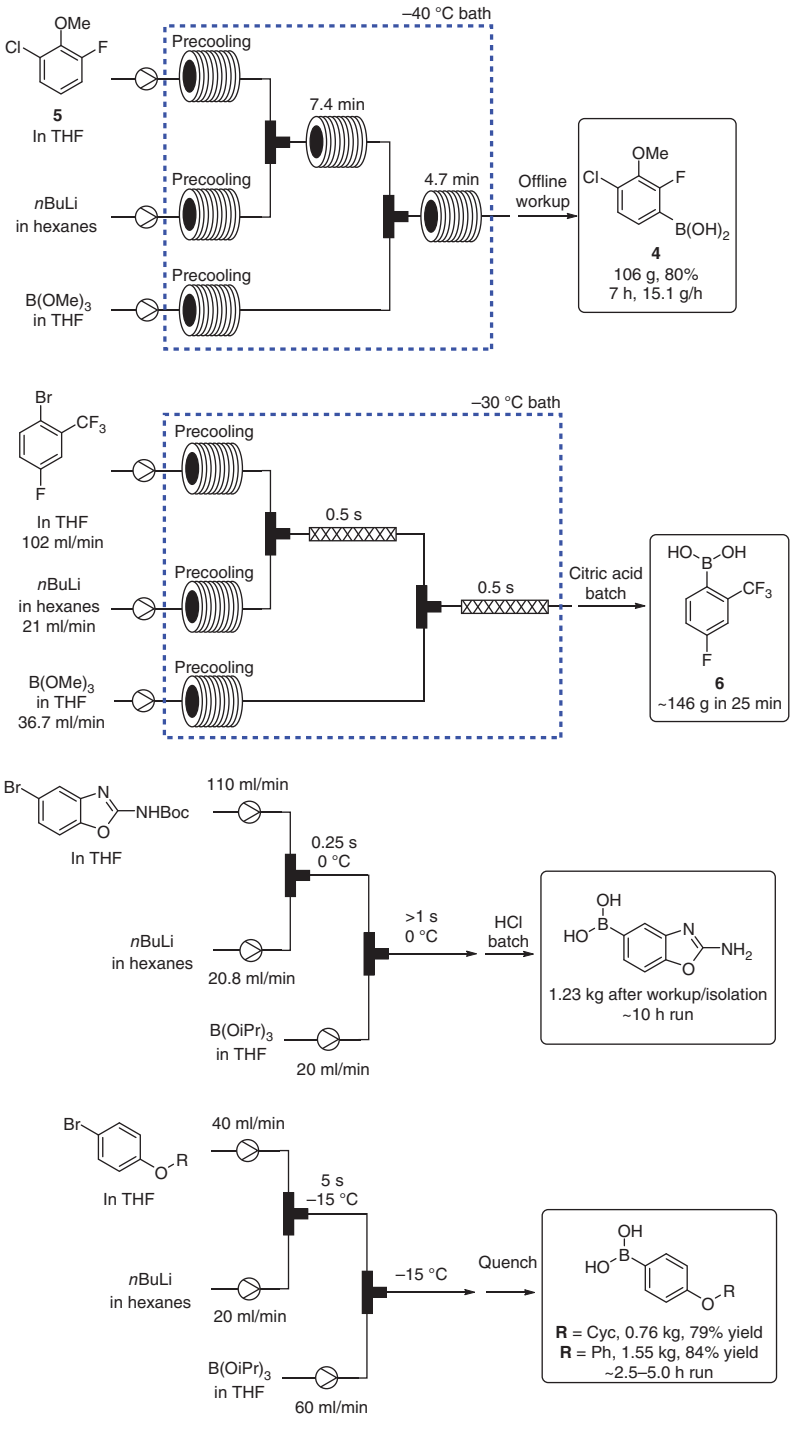
of millimeters, which result in efficient cooling and limited hotspots. Being able to rapidly dissipate exotherms results in reactions that can be run much more cleanly and at potentially higher temperatures. It is also worth noting that while a 500 ml reaction in batch would likely require at least 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



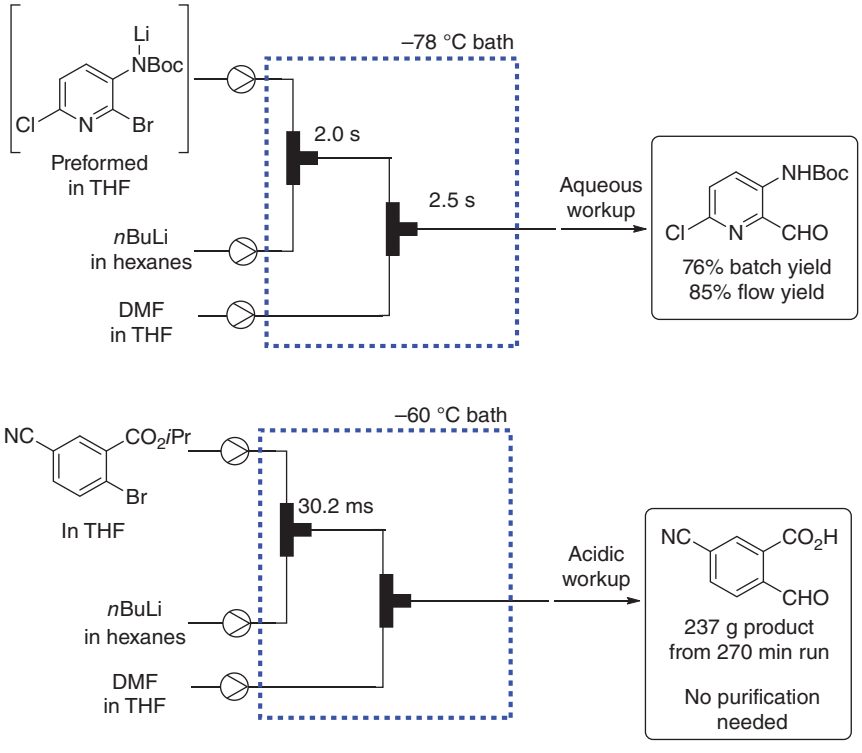
Scheme 1.1 Continuous flow boronate synthesis.

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

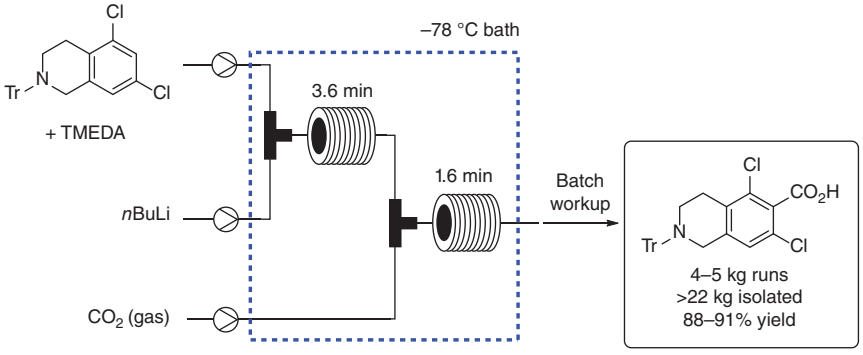


Scheme 1.2 Examples of continuous flow formylations.

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

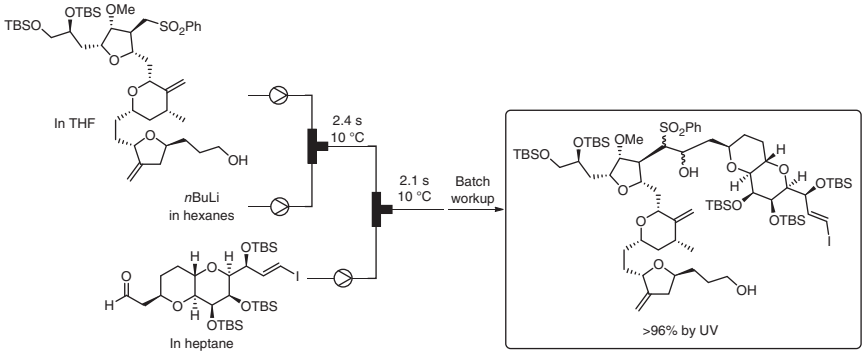
A flow carboxylation route was described by SARcode in the synthesis of Lifitegrast (Scheme 1.3) [27, 28]. After noting issues with the batch carboxylation process, an alternative, high-yielding flow method was developed. A feedstock of tetramethylethylenediamine (TMEDA) mixed with the dichloride intermediate was treated with a solution of *n*BuLi 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

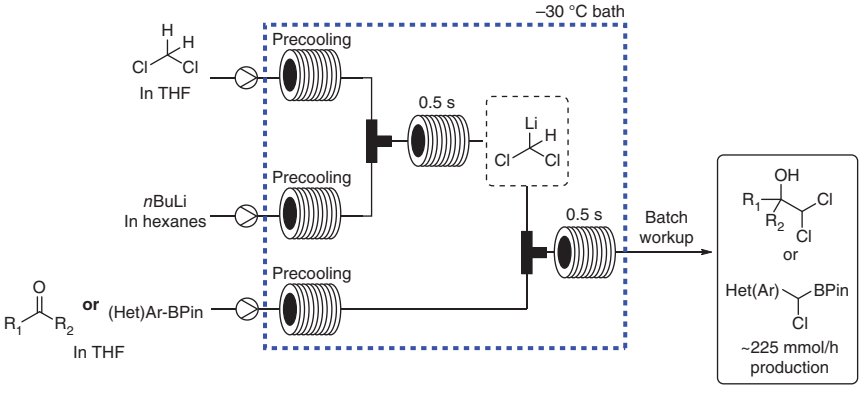
In their synthetic campaign toward eribulin mesylate, flow chemistry was utilized in two separate processes by Eisai (Scheme 1.4) [29]. Following a cryogenic flow reduction of an ester using DIBAL-H, *n*BuLi was used in flow to couple an advance sulfone intermediate to an aldehyde. In their work, a process 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

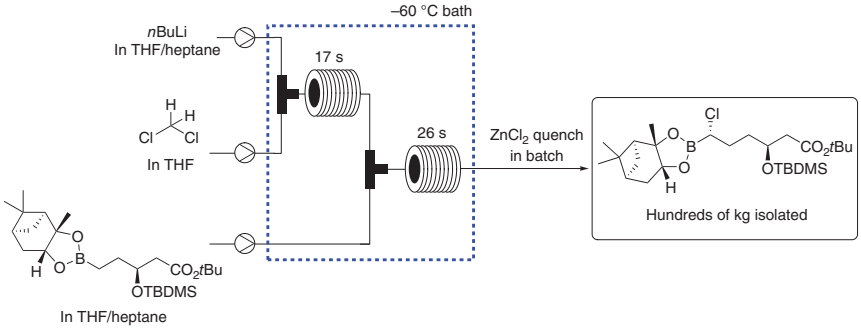
Both dichloromethyllithium and bromomethyllithium have proven to be versatile building blocks in organic synthesis; however their utility is somewhat limited due to their unstable nature, even at very low temperatures. To circumvent issues with these reagents, members of pharma and academia have resorted 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.

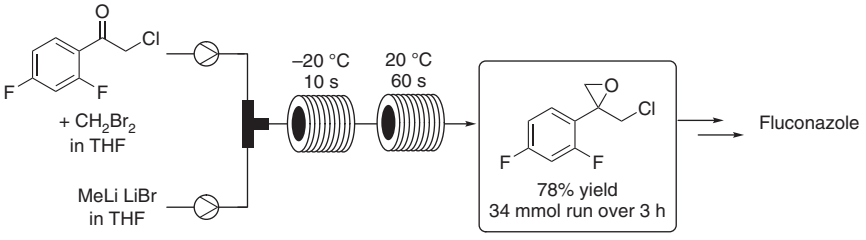
0.5 seconds. The dichloromethyllithium intermediate has a very short lifetime and is consumed almost immediately after it is generated. A series of carbonyl species are dichloromethylated, which provides an intermediate that is amenable to heterocycle synthesis. Furthermore, a series of boronates could 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 *n*BuLi 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).

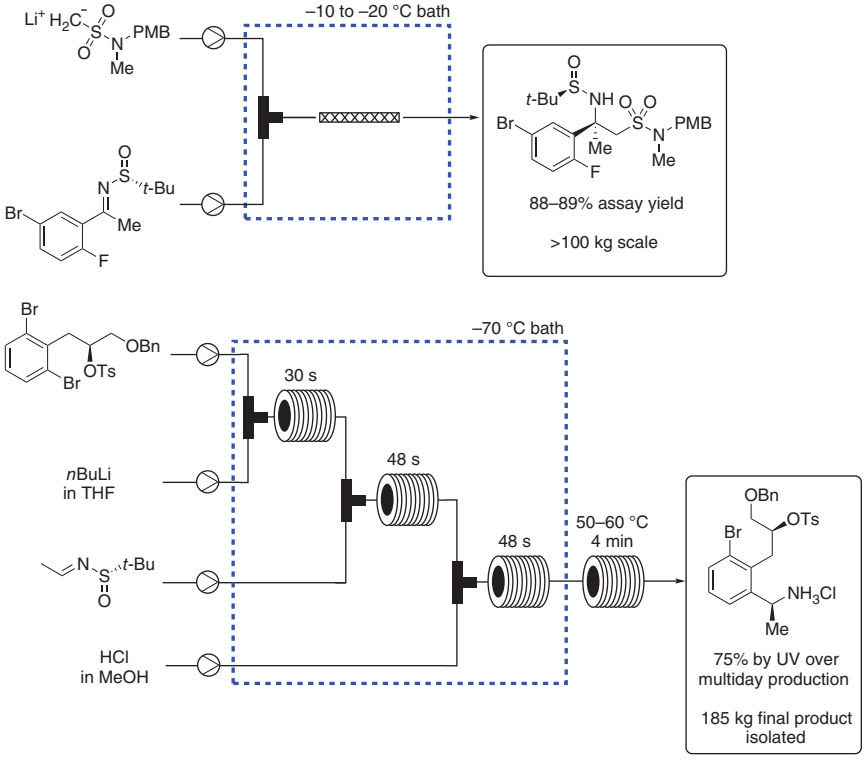


Scheme 1.7 The use of bromomethyllithium in the synthesis of fluconazole.

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.

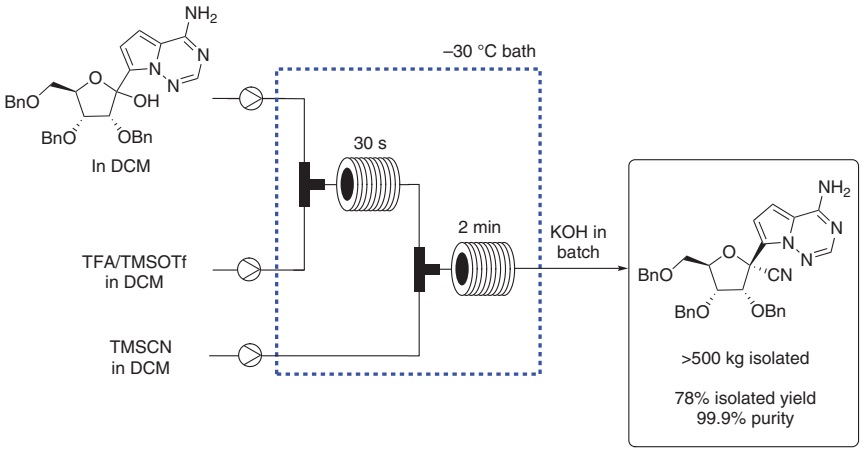
the manuscript is an honest discussion about the trials and tribulations of running such a process on a scale >100 kg, as well as potential solutions to the problems highlighted.

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



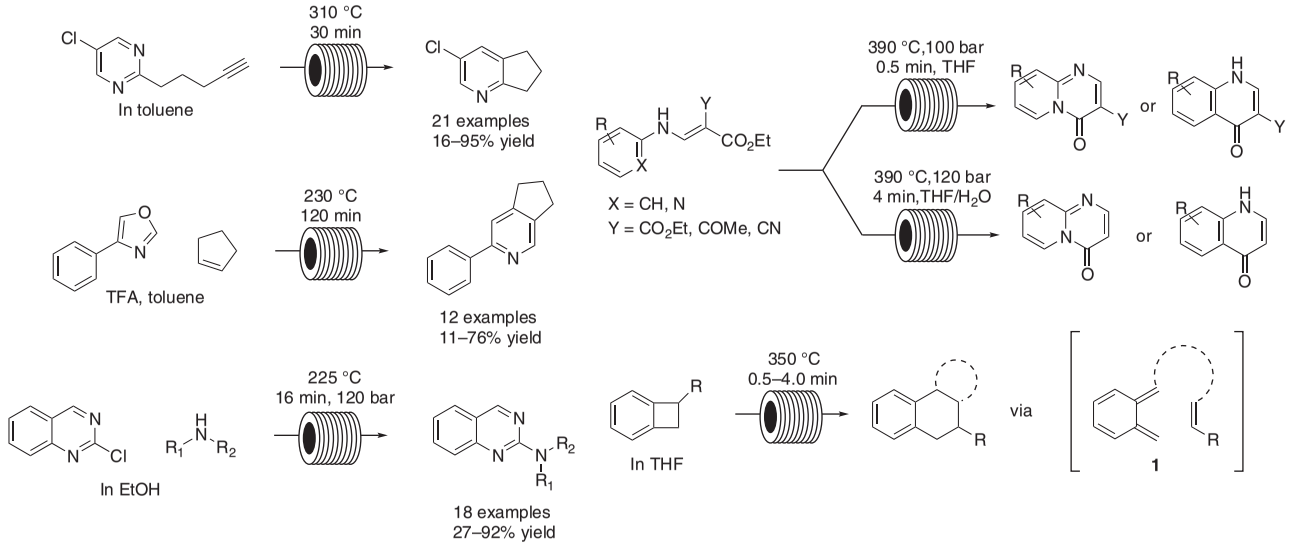
Scheme 1.9 Continuous flow cyanation work from Gilead. Source: Vieira et al. [36] / American Chemical Society.

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.

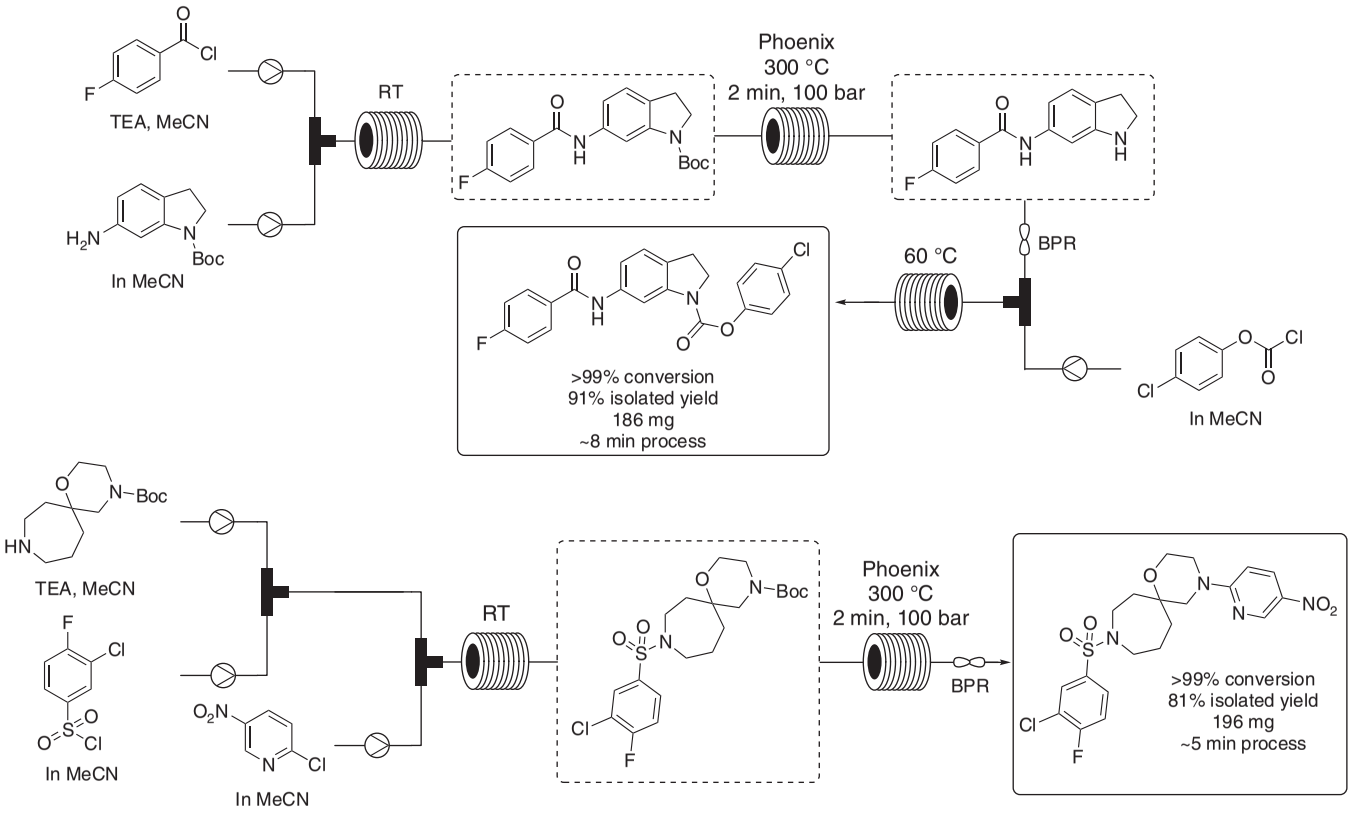
A high-temperature, additive-free *N*-Boc deprotection using the Phoenix has also been described (Scheme 1.11) [44]. Instead of treating substrate with acid, it was discovered that heating substrates to 300 °C for two minutes afforded quantitative yield to a wide variety of substrates. Furthermore, two 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).

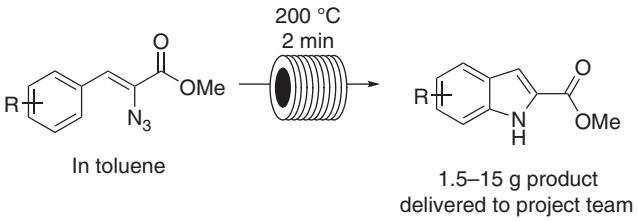
Much larger-scale, high-temperature applications have been reported by Actelion Pharmaceuticals and Eli Lilly (Scheme 1.13). A flow-mediated Overman rearrangement at 220 °C was used to synthesize an intermediate for an API, capable of being



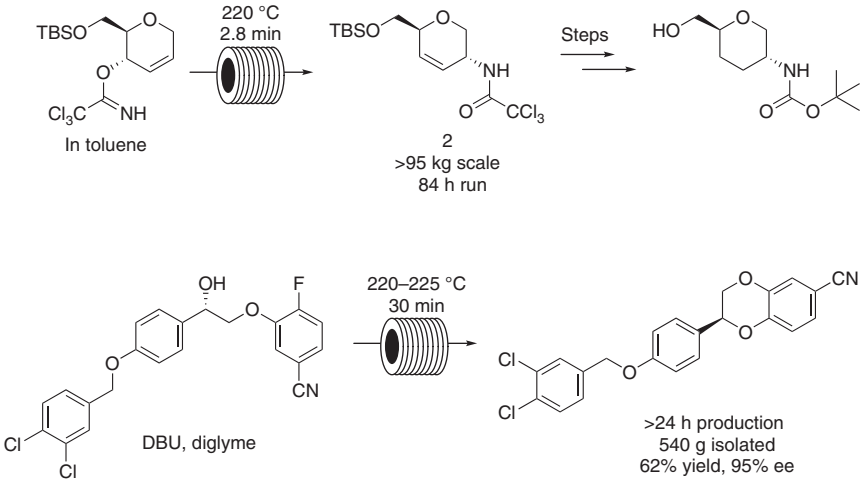
Scheme 1.10 Examples of high-temperature flow chemistry using standard solvents at elevated temperatures.



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.

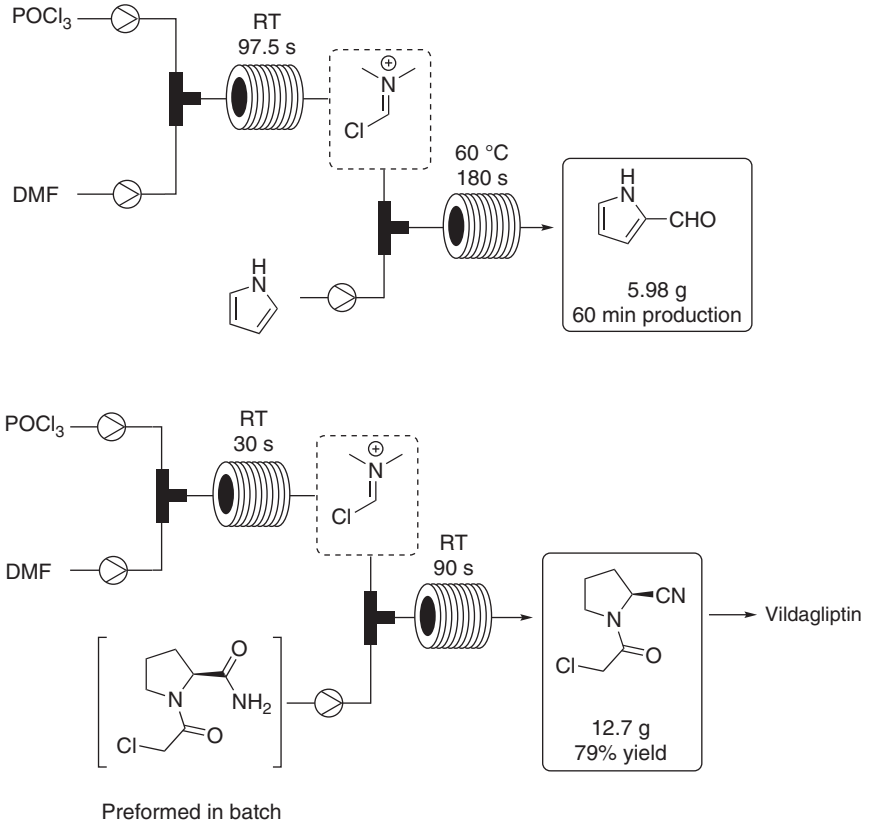
1.3 *In Situ* Use of Hazardous Reagents

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.

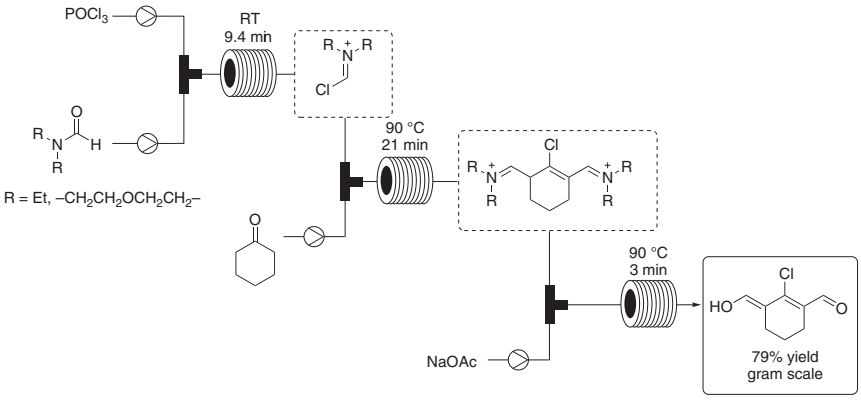
1.3.1 Vilsmeier Reagent

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.

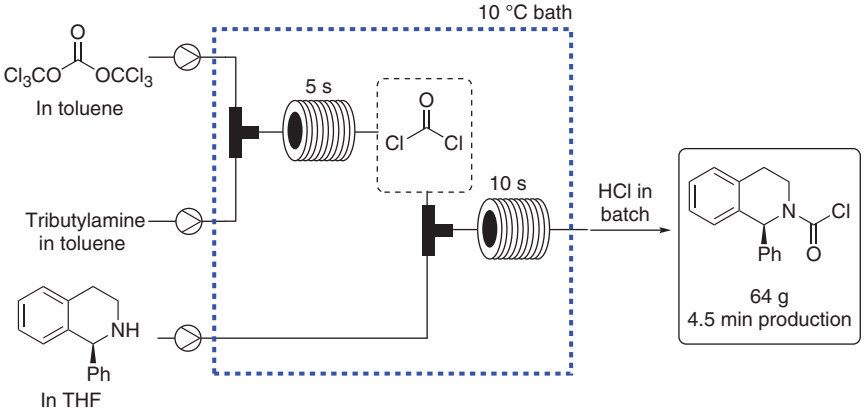


Scheme 1.15 Alternative Vilsmeier reagent use in flow. Source: Carrera et al. [49] / American Chemical Society.

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.