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New Opportunities for Organic Synthesis with Superheated Flow Chemistry

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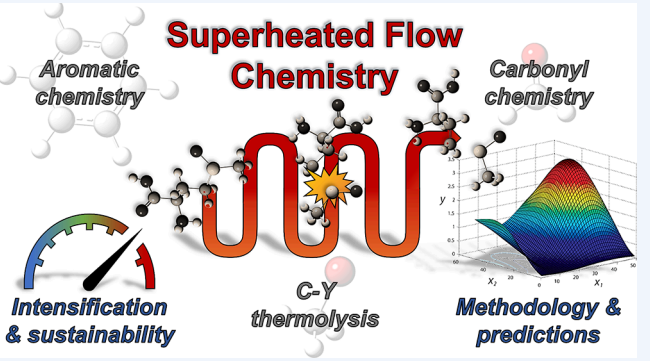
CONSPECTUS: Flow chemistry has brought a fresh breeze with great promises for chemical manufacturing, yet critical deterrents persist. To remain economically viable at production scales, flow processes demand quick reactions, which are actually not that common. Superheated flow technology stands out as a promising alternative poised to confront modern chemistry challenges. While continuous micro- and mesofluidic reactors offer uniform heating and rapid cooling across different scales, operating above solvent boiling points (i.e., operating under superheated conditions) significantly enhances reaction rates. Despite the energy costs associated with high temperatures, superheated flow chemistry aligns with sustainability goals by improving productivity (process intensification), offering solvent flexibility, and enhancing safety.



However, navigating the unconventional chemical space of superheated flow chemistry can be cumbersome, particularly for neophytes. Expanding the temperature/pressure process window beyond the conventional boiling point under the atmospheric pressure limit vastly increases the optimization space. When associated with conventional trial-and-error approaches, this can become exceedingly wasteful, resource-intensive, and discouraging. Over the years, flow chemists have developed various tools to mitigate these challenges, with an increased reliance on statistical models, artificial intelligence, and experimental (kinetics, preliminary test reactions under microwave irradiation) or theoretical (quantum mechanics) *a priori* knowledge. Yet, the rationale for using superheated conditions has been slow to emerge, despite the growing emphasis on predictive methodologies.

To fill this gap, this Account provides a concise yet comprehensive overview of superheated flow chemistry. Key concepts are illustrated with examples from our laboratory's research, as well as other relevant examples from the literature. These examples have been thoroughly studied to answer the main questions *Why? At what cost? How? For what?* The answers we provide will encourage educated and widespread adoption. The discussion begins with a demonstration of the various advantages arising from superheated flow chemistry. Different reactor alternatives suitable for high temperatures and pressures are then presented. Next, a clear workflow toward strategic adoption of superheated conditions is resorted either using Design of Experiments (DoE), microwave test chemistry, kinetics data, or Quantum Mechanics (QM). We provide rationalization for chemistries that are well suited for superheated conditions (e.g., additions to carbonyl functions, aromatic substitutions, as well as C−Y [Y = N, O, S, C, Br, Cl] heterolytic cleavages). Lastly, we bring the reader to a rational decision analysis toward superheated flow conditions. We believe this Account will become a reference guide for exploring extended chemical spaces, accelerating organic synthesis, and advancing molecular sciences.

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INTRODUCTION

From drugs that alleviate pain and cure diseases to additives that preserve food and enhance organoleptic experiences, the comfort of our modern existence largely depends on the availability of an extraordinary diversity of chemicals. For decades, the production of these chemicals has leaned on centralized mass production in large-scale settings with substantial footprints and extended time frames across chains of value. Multiple recent crises have unsettled what we all considered as granted and revealed the feet of clay of these Giants. Emerging technologies breezed fresh hope for reshaping our production modes. What if these emerging technologies ensured both high productivity and effectiveness while maintaining stringent safety standards and minimizing environmental impact? Flow chemistry stands out as a cutting-edge approach able to meet these needs.[5,6] However, only flow processes with short reaction times are typically considered for further scalability trials. Fortunately, superheated flow technology expands the range of reactions that can fit within such a short time frame. (Figure 1).[7]

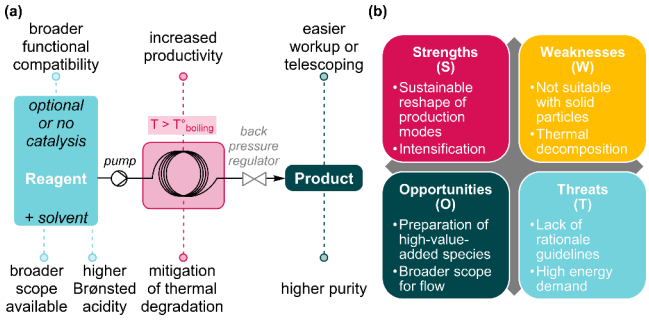

Figure 1. (a) Overview of **SH** flow processes and their advantages. (b) SWOT analysis of **SH** flow chemistry.

Superheated (**SH**) flow chemistry operates at temperatures above the normal boiling point of the solvent, accelerating reaction rates to the extent that, in some cases, the use of a catalyst is not required anymore. The concepts of **SH** and new process windows were introduced by Hessel a decade ago.[7] For example, a second-order reaction (1 M) in water characterized by an activation enthalpy and an activation entropy of 9.8 kcal mol^{-1} and −0.0456 kcal mol^{-1}, respectively, requires 5 days to reach completion (conversion >99%) at room temperature. Carrying out the same reaction at reflux (100 °C) will result in a 35-fold acceleration while under **SH** conditions at 200 °C, a 713-fold acceleration potentially leads to completion within 10 min. The set point temperature to apply depends on the inherent reaction kinetics, which is expressed through Eyring's equation.[8] In addition, exploring the **SH** space also requires the application of a suitable downstream counterpressure. The latter can be determined through Clausius−Clapeyron's equation. This is a necessary condition to keep the solvent from boiling and to prevent the loss of other volatile compounds under **SH** conditions. Downstream counterpressures are generated with back-pressure regulators (BPRs), which are strategically inserted after the **SH** reactor. Various BPR technologies are available, but they usually share the same basic concept: transferring a resistance (cracking or set pressure) to the reactive stream passing through an internal narrow channel. The stream needs to overcome this pressure to flow through. The most common types are spring-loaded and dome-type BPRs. Dome-type BPRs are arguably the most versatile. In dome-type BPRs, a pressurized gas transfers the set pressure through a membrane to the reactive stream. In that case, the set pressure can also be dynamically controlled. The BPR configuration becomes critical when dealing with solid particles, as their presence increases the risk of clogging in the internal narrow channels.

However, navigating the uncharted chemical space of **SH** conditions poses significant challenges given the myriad combinations of temperature and pressure that abound. The increasing accessibility to computational resources[9] and a growing interest in data prediction make it increasingly hard to justify a guesstimate approach to optimizing **SH** flow reactions. To that matter, a range of tools have been developed at the crossroads of various branches of Science and Mathematics; however, there is a lack of rational guidelines to support the widespread adoption of **SH** flow chemistry.

Since its inception in 2013, the Center for Integrated Technology and Organic Synthesis has been pioneering methodologies tailored to flow technology.[10] Our focus crosses over the spectrum from highly[11] to poorly reactive[12] species, with a significant emphasis on operating under **SH** flow conditions. We rely on an interdisciplinary approach which merges quantum mechanics (QM), physical organic chemistry, and process engineering. While computational approaches typically come *a posteriori* to rationalize experimental selectivities[11] or guide corrective actions for suppressing byproducts,[13] we have recently begun to increasingly rely on *a priori* computational intelligence.[1,3,14] Our work has converged toward predictive power tailored specifically to flow reactions[1] that combines machine learning (ML) with quantum mechanics (QM). It provided nongeneric, specifically tailored conditions for each couple of reagents, thus drastically facilitating the exploration of the **SH** space. While we are in the process of generalizing this approach, we aim to leverage this Account as a platform to guide chemists aspiring to explore **SH** flow chemistry.

WHY? ADVANTAGES OF SUPERHEATED FLOW CHEMISTRY

With the ability to significantly accelerate inherent reaction rates, the first advantage that comes to mind is an increased productivity, which can offset heating expenses.[7] A common

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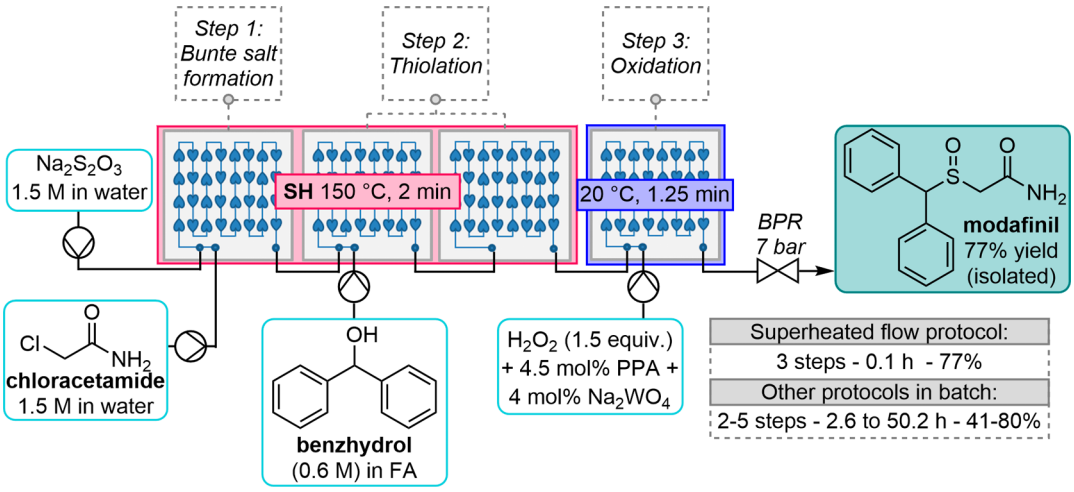

Figure 2. Concatenated flow procedure for the preparation of modafinil relying on two steps performed under **SH** conditions. PPA = Phenylphosphonic acid.

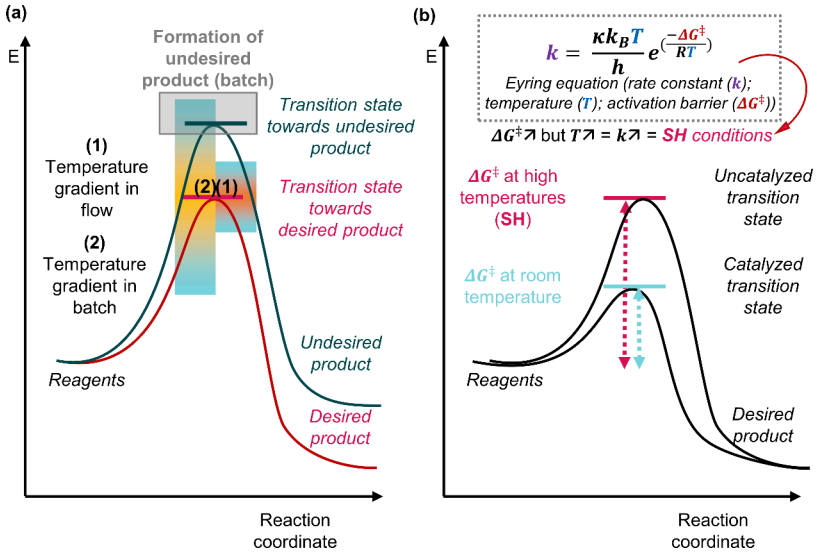

Figure 3. (a) Thermal distribution in flow vs in batch. (b) Comparison between activation under **SH** and catalyzed conditions.

metric used for assessing productivity is the space-time yield (STY). STY is defined as the amount of product formed for a given amount of time in a specified volume. With the significant reduction of reaction time frames under **SH** conditions, thus implicitly of the volume of the reactor as well, the impact of **SH** conditions on the STY becomes obvious.

In 2017, we studied the preparation of methylphenidate hydrochloride, one of the most prescribed medications for ADHD treatment.[15] Photochemical and **SH** conditions were compared in flow for a critical sequence involving diazo species to form a β-lactam intermediate. Intense irradiation (395 nm, 20 °C in toluene) yielded the desired β-lactam intermediate in 97% conversion after 60 min, whereas only 5 min at 180 °C (**SH** toluene, 13 bar; vs 4 h at reflux) achieved full conversion. Lab-scale telescoping with a final step at 110 °C (**SH** methanol, 5 bar, 20 min) led to a daily productivity of 1400 doses. The thermolysis was then transposed to pilot scale, achieving full conversion within 2 min at 180 °C (STY = 4.9 kg h^{-1} L^{-1}).

Another example from our group dealt with the synthesis of the antinarcoleptic drug modafinil (Figure 2).[4] A fully concatenated three-step process was developed, yielding modafinil in 77% within 3.25 min. Remarkably, samples with purity specs matching US Pharmacopeia standards were collected without intermediate purifications.

Steps 1 and 2 were carried out at 115 °C (**SH** water, 7 bar) to meet the requirements of fast reactions under pilot-scale conditions. Step 3, involving hydrogen peroxide and a catalyst, was fast enough to be operated at 20 °C. Comparable protocols using standard conditions in batch required ca. 4 h (excluding intermediate purifications) on a ~ 20 g scale, while here **SH** conditions significantly increased the productivity (STY = 2.1 kg L^{-1} h^{-1}).

Another distinctive advantage comes with the ability to accurately control the reaction time in flow. Exposure to **SH** conditions can be short enough to avoid both chemical degradation and overreaction to undesirable products (Figure 3a). To illustrate this point, let us consider amine monoalkylation: while fastidious wasteful cosmetic steps are required in batch to avoid overalkylation, quick exposure to **SH**

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conditions in flow gave selectively the monomethylated product without any additional steps.[16] Optimum conditions were found at 250 °C (**SH** acetonitrile, 7 bar) within 12 min of residence time. The protocol was amenable to a small library of derivatives (19−96%), including a precursor for the anxiolytic drug diazepam.

Catalysis is often associated with lower activation barriers and hence with accelerated processes. Thermal activation can, to some extent, advantageously replace catalysis while alleviating functional group incompatibility (poisoning) and facilitating downstream purification (Figure 3b). As an example, the usual acid-catalyzed *N*-Boc-deprotection of amines can be performed just by imposing a short thermal shock in flow, as demonstrated by Maguire, Collins,[17] and others.[18,19] Selective deprotection was achieved through precise temperature control. Conditions followed a trend corresponding to the pK_a values of the conjugate acids: *N*-Boc heteroaryl > *N*-Boc aryl > *N*-Boc alkyl amine, with secondary amines exhibiting higher reactivity than primary ones. A telescoped sequence featured the selective deprotection of an aryl *N*-Boc group (**SH** MeCN/acetone, 230 °C, 10 min, 24 bar). It was followed by benzoylation, and final deprotection of the remaining alkyl *N*-Boc group (**SH** MeOH, 230 °C, 45 min, 24 bar), resulting in an overall yield of 52%.

Since the water dissociation constant increases with temperature, **SH** water eliminates the need for acid catalysts.[20] A striking example was reported in 2016 by Kawanami et al. to access 2-arylbenzazoles under flow conditions (Figure 4).[21] In

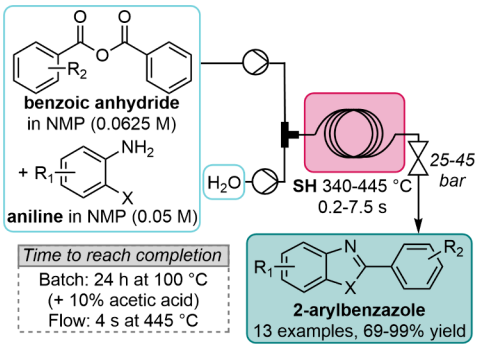

Figure 4. Catalyst-free preparation of 2-arylbenzazoles under **SH** flow conditions. NMP = *N*-Methyl-2-pyrrolidone.

batch, the reaction required substoichiometric acetic acid (10 mol %) to achieve high conversions after 24 h at reflux. However, quick exposure in flow at 445 °C (**SH** water, 45 bar) proceeded in a matter of seconds without acetic acid. Various derivatives were obtained accordingly in moderate to excellent yields.

As an additional valuable asset, **SH** flow chemistry significantly expands the process temperature window for low-boiling point solvents. With solvent choice no longer restricted to boiling point considerations, other criteria such as reaction compatibility, solubility, selectivity, cost, and toxicity can be reevaluated under the new lights of **SH** conditions. In addition, easier downstream processing is accessible, such as simple solvent evaporation. For instance, in a reinvestigation of the Wolff−Kishner reduction under flow conditions, Kappe et al. identified methanol as the most suitable reaction medium (Figure 5).[22] After 22 min at 200 °C (**SH** methanol, 50 bar), the reduced alkane product was isolated in 81% by a simple

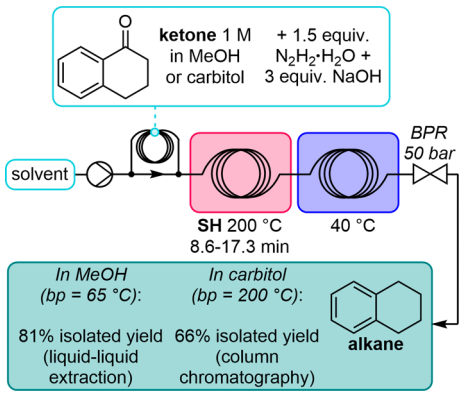

Figure 5. Wolff−Kishner reduction under **SH** flow conditions.

extraction in cyclohexane. By contrast, only 66% were recovered after column chromatography for the reaction using carbitol (2-(2-ethoxyethoxy)ethanol, bp ∼200 °C) for 11 min at 200 °C (**SH**, 15 bar). This process was then extended to various aldehydes and ketones (70−87% isolated yields).

AT WHICH COST? REACTORS SUITABLE FOR SUPERHEATED FLOW CHEMISTRY

Commercial solutions are available for accessing **SH** conditions in flow, from lab to production scales. Despite the rather small diversity of materials, which include polymers (such as pefluoroalkoxyalkane (PFA) and polytetrafluoroethylene (PEEK)), glass, metal alloys (such as Stainless Steel (SS) and Hastelloy) and ceramics (such as Silicon Carbide (SiC)), a wide range of solvents can be processed under **SH** conditions (Figure 6). The material of the reactor typically determines the upper temperature and pressure limits, although seals and connectors sometimes become weak points. Chemical compatibility gains paramount importance due to the extreme mechanical stress of **SH** conditions. While several commercial solutions offer perspectives on seamless scalability, their cost remains a significant barrier. DIY lab-scale flow setups, on the other hand, offer low-tech, low-cost solutions that are broadly adoptable.[23] Affordable and widely available polymer or metal tubings (usually with a 1/16" outer diameter) and parts can be diverted to construct lab-scale prototypes able to explore the vast landscape of **SH** conditions.

SS coil reactors are the most widely utilized due to their high tolerance to mechanical stress (up to 400 °C and 400 bar). In 2022, we reported an intensified Michaelis-Arbuzov protocol for the preparation of valuable alkyl phosphonates as pharmaceutical intermediates using a commercial SS coil reactor.[24] The short exposure (1−2.5 min) to high temperatures ranging from 300 to 340 °C (**SH** trialkylphosphites, 35 bar) was required both to overcome the high activation barrier and to mitigate side-product formation, as supported by a complementary QM study. A small library of alkylphosphonates (34 to >99%) was obtained accordingly starting from alkyl bromides. Outputs of up to 5 kg per day were reported (STY = 41.42 kg L^{-1} h^{-1}), while in batch under standard conditions (100 °C) such reactions would usually require 78 h to complete (STY = 0.00003 kg L^{-1} h^{-1}).

A similar lab-scale SS setup was used for preparing a key enone intermediate for estetrol production, a new-generation pharmaceutical for birth control (Figure 7).[3] As we were commissioned to develop a metal-free synthesis, the *syn-*

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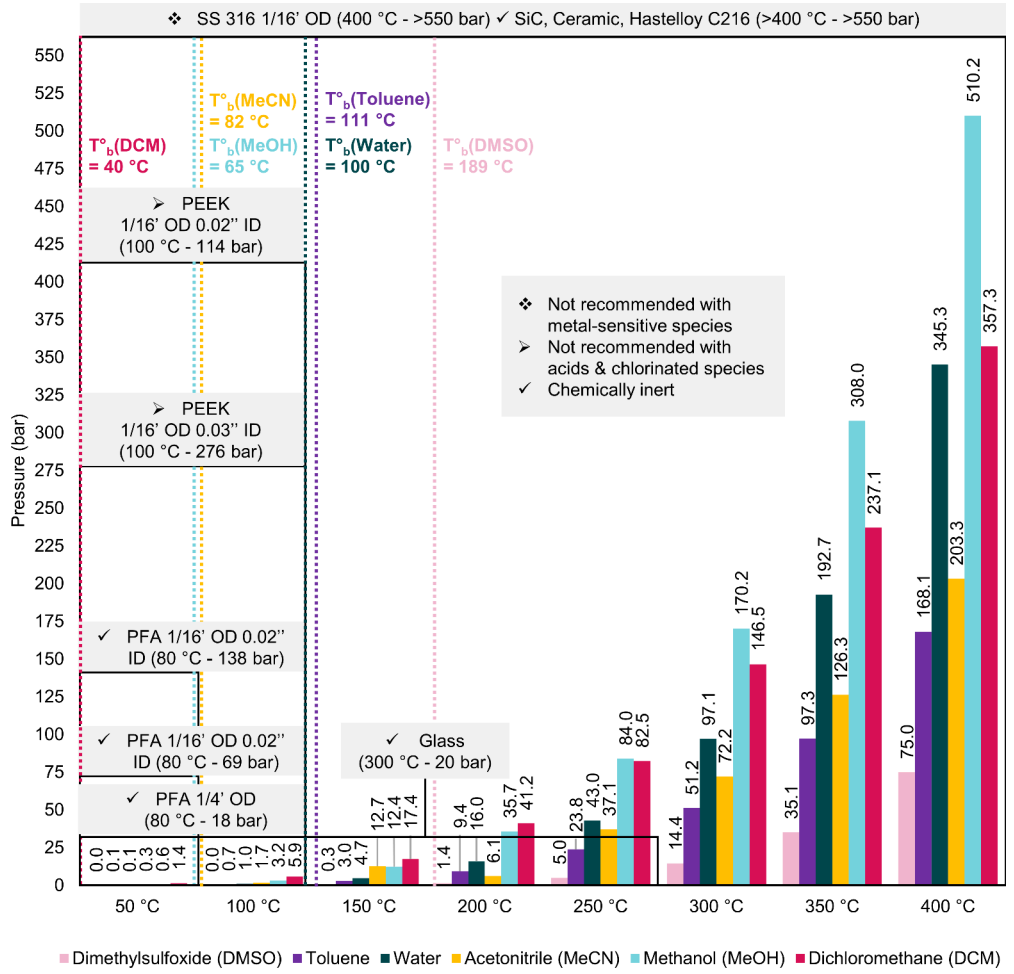

Figure 6. Compatibility of flow reactor materials with the vapor pressure of various solvents at different temperatures. It is important to note that the maximum working pressures are taken at 25 °C and decrease with temperature.

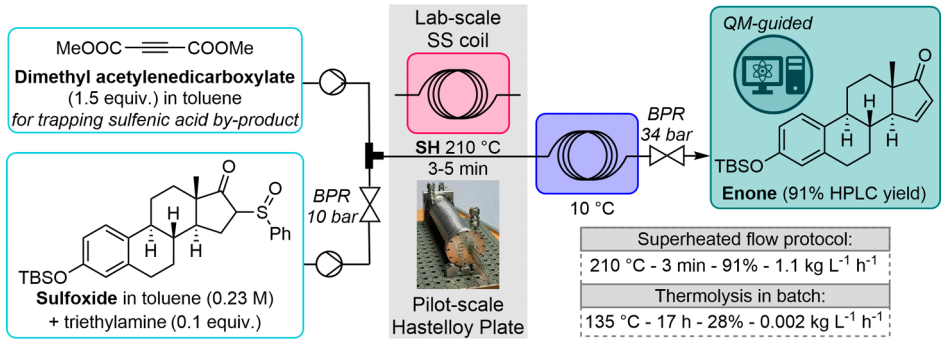

Figure 7. Preparation of a key enone intermediate of estetrol under **SH** flow conditions (at both lab- and pilot-scales) guided by Quantum Mechanics (QM).

sulfoxide elimination appeared as an opportunity.[25] Confronted with highly active hormonal compounds, we opted for a QM approach to select the most suitable sulfoxide derivative. A phenyl sulfoxide derivative met both the lowest activation barrier and affordability criteria. At the lab-scale, the thermolysis reached 90% yield (67% isolated yield) at 210 °C (**SH** toluene, 34 bar) within 6 min. In comparison with batch results in refluxing toluene (28%, 22 h, STY = 0.002 kg L^{-1} h^{-1}), the flow process showed significantly improved metrics (STY = 0.56 kg L^{-1} h^{-1}). The sulfoxide elimination was next successfully transposed (91% yield, STY = 1.13 kg L^{-1} h^{-1}) to a commercial pilot-scale Hastelloy flow reactor with minor readjustments (3 min at 210 °C), leading to an extrapolated forecast of several million doses of estetrol per year.

While the reactor wall is usually not chemically involved in the reaction, some authors took advantage of their reactor not only as a reaction vessel but also as a source of catalytic species. For instance, reactor coils made of copper tubing were advantageously adopted for carrying out azide−alkyne cycloadditions and C−H carbonylation on alkylamines.[26,27] This setup advantageously reduces Cu leaching, even at high

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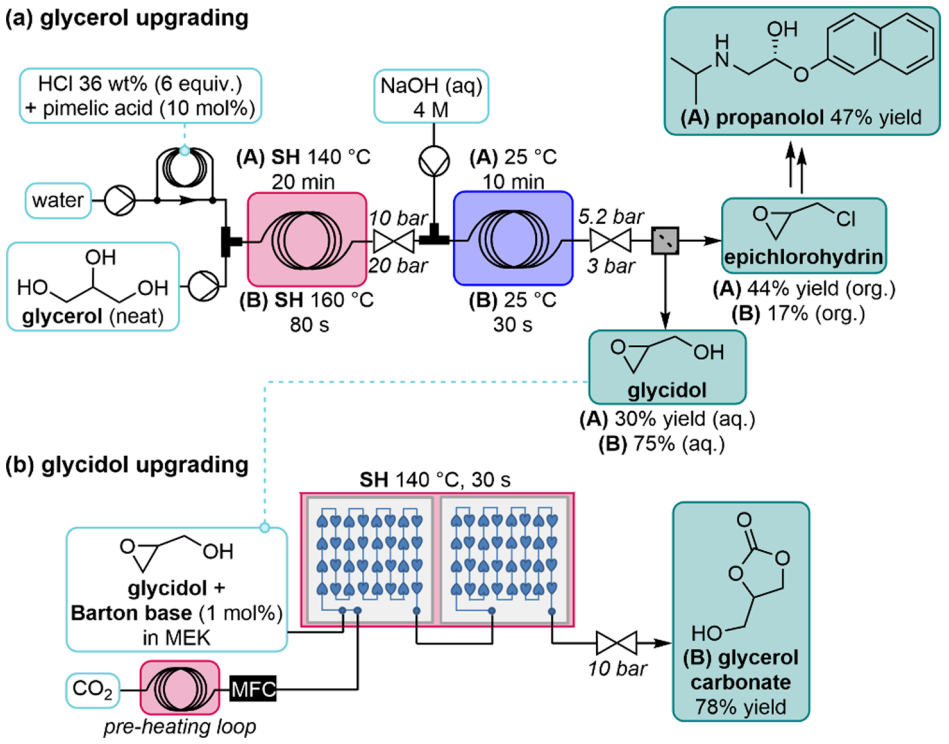

Figure 8. (a) Upgrading of glycerol into epichlorohydrin (optimization with path A) and glycidol (optimization with path B) under **SH** flow conditions using PFA coils. (b) Upgrading of glycidol into glycerol carbonate under **SH** flow conditions using a commercial glass reactor. MEK = Methyl ethyl ketone.

temperatures (150 °C for 8 h), hence simplifying the workup procedure and minimizing the overall environmental footprint.

Polymer materials such as PFA, despite having a much more modest T,P operating window, can sometimes be preferred over SS for chemical compatibility issues. We devoted significant efforts focused on the upgrading of biobased glycerol toward high-value-added chemicals (Figure 8a), such as epichlorohydrin and glycidol. In 2019, a first attempt at developing an intensified flow process toward epichlorohydrin[28] relied on a concatenated chlorination/dehydrochlorination sequence. The chlorination of neat glycerol was carried out in a simple PFA coil reactor with 36 wt % aqueous HCl. With pimelic acid (10 mol %) as the catalyst, the chlorination reached complete conversion in 20 min at 140 °C (**SH** water, 10 bar). It led to a cumulated yield of 81% (35 and 46% for mono- and dichlorohydrins, respectively). The reaction effluent was directly treated with concentrated aqueous NaOH at room temperature, giving a 42% yield of epichlorohydrin. Next, selective extraction enabled the preparation of β-amino alcohol pharmaceuticals. The chlorination step was also revisited to maximize the final output toward glycidol.[2] At 160 °C (**SH** water, 20 bar), with 36 wt % HCl and acetic acid (30 mol %), 89% conversion was achieved within 80 s. Monochlorohydrins were formed as the major products (79%). After dehydrochlorination, glycidol was obtained in 75% yield.

In addition, PFA coils show comparable boundary specifications to commercial glass and SiC pilot-scale reactors, which may be helpful for seamless scalability. For instance, PFA was used in a series of articles studying the preparation of glycerol carbonate. The transesterification of dimethyl carbonate with glycerol using nitrogen-containing organocatalysts was investigated first.[29] Initial studies achieved 98% conversion and 80% selectivity at 135 °C (**SH** dimethyl carbonate, 7 bar), and the process was easily scaled up using a glass mesofluidic reactor (STY = 8.3 kg L^{-1} h^{-1}). Optimization with a cheaper ammonium catalyst required higher temperatures, achieving 95% conversion and 79% selectivity at 180 °C (**SH** dimethyl carbonate, 11 bar) in a SiC mesofluidic reactor (STY = 9.4 kg L^{-1} h^{-1}).[30] However, the high costs of dimethyl carbonate limited its economic viability. Based on the previously mentioned process toward glycidol (Figure 8a), we disclosed another process relying on the organocatalyzed coupling of glycidol and CO_2 (Figure 8b).[2] QM was used to map the catalytic activity and to guide preliminary trials in PFA coils. High mass transfer and careful selection of the reaction medium were crucial for this gas−liquid reaction. Successful scale-up was achieved in a glass mesofluidic reactor with high-efficiency static mixers, with 78% yield at 140 °C (**SH** methyl ethyl ketone, 10 bar) in less than 30 s. The process used 1 mol % of 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (Barton base) as the organocatalytic species, and simply outperformed previous methods (STY = 2.7 kg L^{-1} h^{-1}).

HOW? METHODOLOGIES TO ACCESS SUPERHEATED FLOW CHEMISTRY

Blindly exploring the broad chemical space of **SH** conditions is wasteful and consumes excessive resources and time. Instead, various tools and methodologies are now available for effectively scouting the **SH** space. Since Kappe's seminal contributions, it is customary to run preliminary trials with a microwave batch reactor for an initial assessment of **SH** conditions.[31] Despite usually being restricted to small scales, microwave batch reactors are easily amenable to high temperatures and pressures within sealed vessels. The assets of this methodology were demonstrated, for instance, with the

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challenging preparation of tetrazoles. The latter combined the use of high temperatures and explosive metal azides. Based on a preliminary screening under batch microwave conditions, Kappe et al. reported a safe and scalable flow process for targeting tetrazoles.[32] A model compound was obtained in 91% within 11 min at 140 °C (**SH** acetonitrile, 12 bar, 1.37 kg L^{-1} h^{-1}). The process was scaled up after minor adjustments for safety reasons (112.5 °C, 12 min, 12 bar, 1.18 kg L^{-1} h^{-1}), and upgraded with an in-line quench and Process Analytical Technology (Figure 9). A similar procedure was used as a

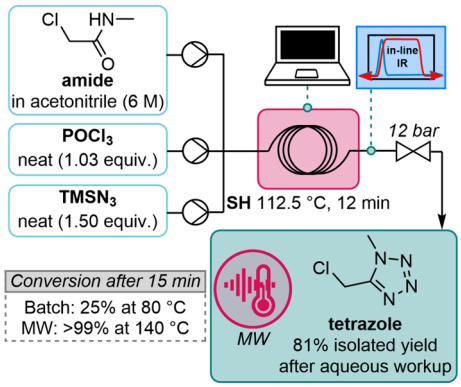

Figure 9. Transposition of a microwave (MW) protocol for preparing tetrazoles under **SH** flow conditions.

critical step along a seven-step sequence toward cannabinoid receptor type 2 (CB2) agonist RG7774 (**SH** 190 °C, MeCN, 20 bar), with a 2-fold increase in overall yield (53%).[33]

If a microwave batch reactor is not available and the construction of a prototype lab-scale flow setup is not prohibitive, then the optimization of **SH** conditions can be accelerated using a Design-of-Experiment (DoE) approach. DoE can be multiobjective and can help in the assessment of intercorrelations between various parameters.[34] For example, Carofiglio et al. optimized a flow procedure for the selective monobromination of a porphyrin.[35] In batch, *N*-bromosuccinimide (3 equiv) was added dropwise over 4 h on the substrate in refluxing chloroform. With a 17-experiment DoE in flow, the authors accessed optimized conditions. High selectivity (86%) and yield (80%) were obtained within 30 min at 120 °C (**SH** chloroform) with half the excess of bromination agent. Despite a modest productivity (STY of 0.002 kg L^{-1} h^{-1}), the DoE guidance appeared advantageous. Nevertheless, it is worth mentioning that setting the DoE boundaries for **SH** conditions is quite challenging given the vast (T, P) space it concerns.

A hybrid method combining DoE with preliminary microwave tests is an effective alternative to setting these boundaries. This approach was developed for the preparation of care product additive allantoin (Figure 10).[36] A preliminary investigation under microwave batch conditions enabled the identification of both homogeneous conditions and safeguard temperature and pressure boundaries to prevent decomposition. These boundaries were next translated under flow conditions, and an 8-experiment DoE was carried out for further optimization. Complete conversion to high-purity allantoin (99%) was obtained within 6 min at 120 °C (**SH** water, 6 bar, STY = 0.775 kg L^{-1} h^{-1}).

A priori knowledge of the inherent kinetics of a given reaction can be a major asset in foreseeing the potential acceleration impact of **SH** conditions (Figure 11). Exper-

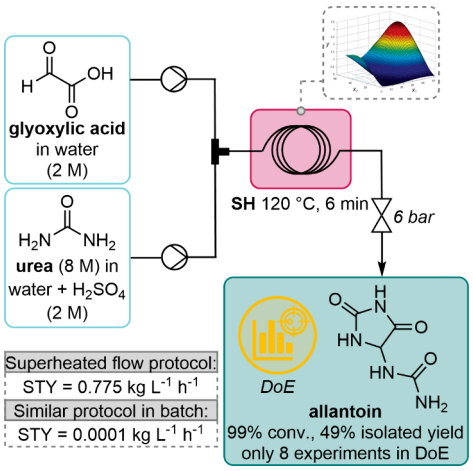

Figure 10. Preparation of allantoin under **SH** flow conditions based on a DoE approach.

imental kinetics studies require a substantial amount of work and starting materials, though new methods have been developed in flow to address this issue.[37,38] Quantum mechanics (QM) approaches, on the other hand, offer a waste-free, resource-conservative method to study reaction kinetics through *in silico* computations. It is particularly suitable when resources are scarce or when high-toxicity compounds are involved. However, QM requires insights into the mechanism and to access transition states for rate-determining steps, which can be tedious and computationally expensive. Artificial intelligence provides additional tools to alleviate these constraints.[39]

To illustrate the experimental determination of inherent kinetics as a guide, let us consider Scholl's report on a Krapcho dealkoxycarbonylation in 2019. The authors carried out kinetics experiments in flow and in batch at 145 and 160 °C in dimethyl sulfoxide.[40] As similar results were obtained, the authors concluded that neither significant mixing nor diffusion effects were involved in flow. A model was constructed based on the batch kinetics data, the extrapolation of which accurately predicted the reaction's output under **SH** conditions. Process intensification in flow was then successfully implemented with a quick exposure (160 s) at 200 °C (**SH** dimethyl sulfoxide, 7 bar). The conversion reached 99.9% (STY of 0.251 g h^{-1} mL^{-1}) under these conditions. However, it should be noted that batch kinetics models cannot always be extrapolated to predict kinetics in flow due to specific mixing and/or dispersion effect attributes. In this case, a specific model constructed on kinetics data generated in flow must be followed.[41]

As mentioned earlier, we developed an upstream DFT study for preparing a key intermediate of estetrol.[3] *A priori* kinetics information was extracted to predict an ideal set of reagents, temperature, and concentration suitable for scalable flow conditions. This QM method provided accurate kinetics data, and accelerated the optimization process with minimal waste generation. However, it required taxing computational resources. The latter was addressed in a follow-up study on electrophilic aminations (Figure 12).[1] More specifically, we studied the reaction of nitrosoarenes and silyl enol ethers, which is barely represented in the literature. Our method, which relied on a QM-based ML model, bypassed the reliance on any prior experimental data. It accurately predicted ideal

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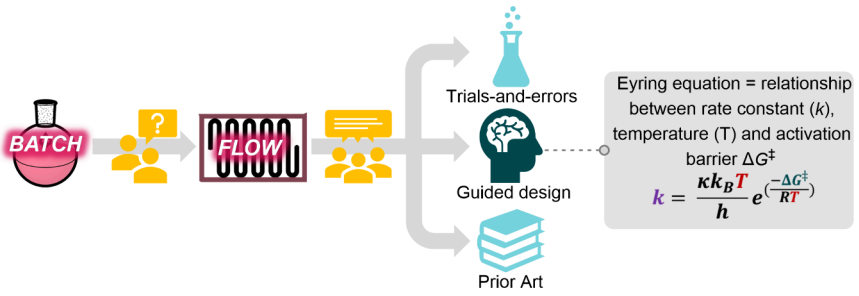

Figure 11. Guided design of **SH** flow protocols based on the *a priori* knowledge of inherent kinetics for a given reaction.

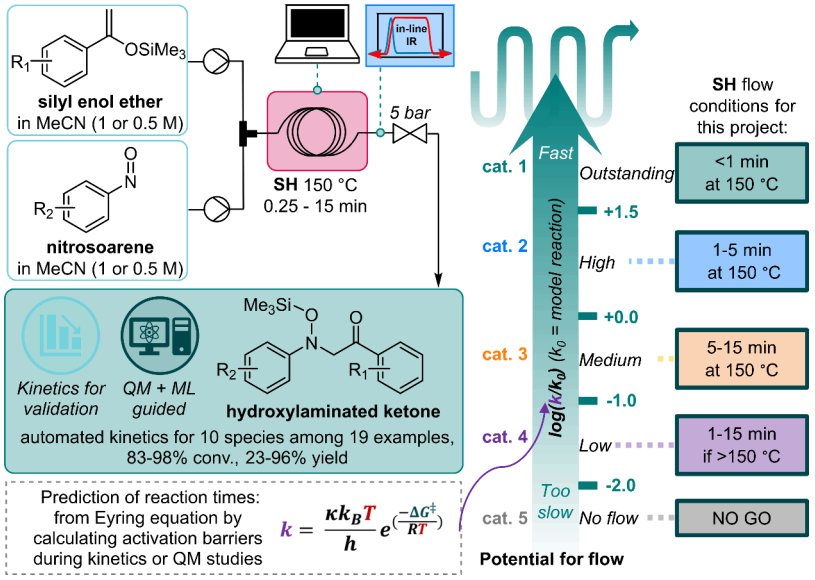

Figure 12. Preparation of aminated compounds under **SH** flow conditions based on a combined QM and ML approach.

flow conditions within minutes based on reagent properties, thus eliminating the need for time-consuming transition state computations. This model assessed the potential for transposition to flow conditions by creating discriminating categories. Nineteen novel compounds were obtained accordingly in moderate to excellent yields (**SH** acetonitrile, 150 °C, 5 bar) after executing a single set of nongeneric conditions specifically tailored to each combination of reagents.

SCOPE OF REACTIONS

The scope of reactions that can be accelerated with **SH** conditions is broad. It typically concerns reactions associated with high activation barriers, typically above 25 kcal mol^{-1}, which usually reflects the involvement of inherently stable bounds and sluggish partners.

Sigma bonds are usually seen as stable, and their heterolytic cleavage can benefit from **SH** flow conditions (Figure 13a), especially for C−Y bonds (where Y = N, O, S, C, Br, Cl). Breaking heteroatom bonds typically requires more energy than breaking bonds between the same atoms (except for C−C thermolysis). For example, we revisited the preparation of ketamine through a concatenated three-step synthesis (Figure 13b).[42] While the two first steps were endowed with fast inherent kinetics, the final step involved an α-iminol thermal C−C rearrangement that appeared more challenging. A preliminary QM study indicated that high temperatures were needed to trigger this thermolysis. While experiments in batch required the addition of HCl to both accelerate the reaction (30 min refluxing dichlorobenzene) and precipitate ketamine hydrochloride, this solution was not transposable in flow for evident clogging issues. We opted for neutral **SH** conditions in flow. At 220 °C (**SH** ethanol, 35 bar), 71% conversion was observed (with 78% selectivity toward ketamine). In the presence of Montmorillonite K10, the reaction temperature could be lowered to 180 °C (**SH** ethanol, 35 bar), and 75% conversion (95% selectivity) was obtained after 5 min of residence time.

As another illustration, we studied C−O thermolysis processes through deoxydehydration (DODH) reactions. The DODH reaction is a valuable synthetic transformation that connects vicinal diols to olefins (Figure 13c).[43] In the presence of acidic assistance, a rate-determining C−O bond-breaking step led to a transient dioxocarbene species, which readily decomposed to form the desired olefin. Optimal conditions (250 °C, **SH** ethanol, 17 bar, 6 min) with glycerol premixed with triethyl orthoformate (1 equiv) and 10 mol % formic acid yielded 86% toward allyl alcohol. The reaction was then adapted to a more complex vicinal polyol (erythritol).[44] The presence of 2 neighboring vicinal diols drastically increased the complexity of the potential output, giving access to a range of valuable products. However, fine-tuning under **SH** flow conditions allowed for selective control over single apical, internal, and double DODH. QM insights revealed how specific structural features of diol substrates impact the final dioxocarbene decomposition.

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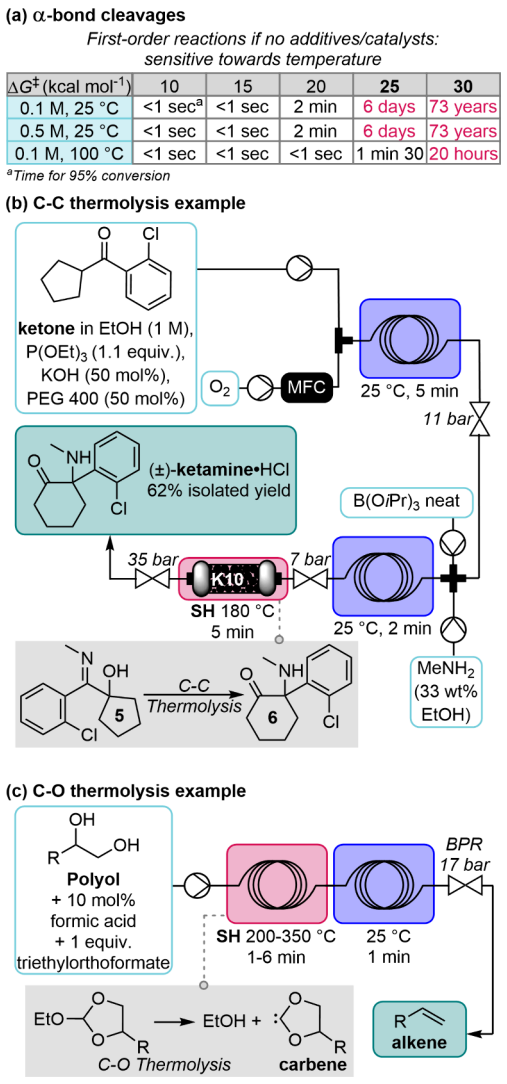

Figure 13. (a) Rationale for σ-bond cleavages under **SH** flow conditions. (b) Preparation of ketamine. (c) Deoxydehydration (DODH) of polyols.

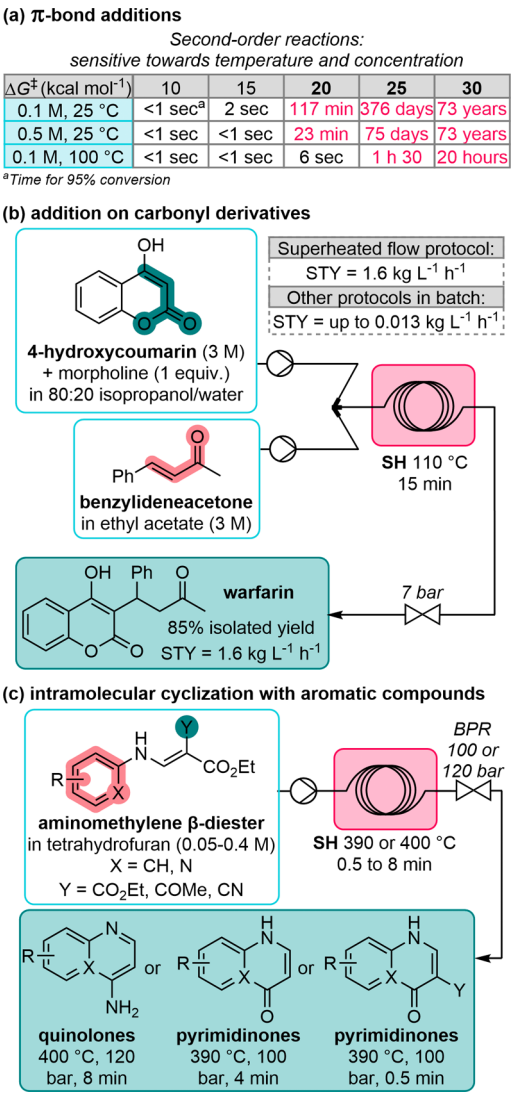

Figure 14. (a) Rationale for π-bond additions under **SH** flow conditions. (b) Preparation of warfarin. (c) Intramolecular cyclization of heterocycles.

The next section concerns weak π electrophiles, starting with carbonyl compounds. Among them, bulky ketones, esters, carboxylic acids, carbonates, and amides are usually considered the least reactive. Their lack of reactivity originates from the combination of diverse steric, electronic, and stereoelectronic effects. In conjunction with weak nucleophiles, the forecast for reaction completion within a reasonable time frame is rather dull. However, **SH** conditions could compensate for the lack of reactivity and help bring completion back within a few minutes (Figure 14a), as demonstrated by Fukuyama et al. in the sulfonic acid-catalyzed protection aldehydes,[45] by Zhang, Zou and co-workers in the Pinnick oxidation of aldehydes,[46] or by Wang et al. in the acylation and methanolysis of amides under flow conditions.[47,48]

In a study published in 2023, we reported **SH** conditions to overcome the sluggish nature of benzylideneacetone toward sterically hindered 4-hydroxycoumarin for preparing essential pharmaceutical warfarin (Figure 14b).[49] The gold standard reaction to produce racemic warfarin is notoriously slow. Our plan was to use **SH** conditions to bring the reaction time frame within the comfort zone for flow processes. However, extensive degradation was observed at 140 °C. Instead, the reaction conditions were modified to accommodate for morpholine-assisted (10 equiv) Michael addition in a solvent mixture comprising isopropanol, water, and ethyl acetate to prevent clogging. At 110 °C (**SH** solvent mixture), remarkably high conversion (90%) and selectivity (95%) were achieved within 15 min. The STY of 1.5 kg $h^{-1}L^{-1}$ was several orders of magnitude higher than the prior art (12 h under standard batch conditions, 40% yield).

Lastly, the most stable π systems involve aromatic derivatives. Nucleophilic or electrophilic aromatic substitutions involve an unfavorable rate-determining step during which the aromaticity is temporarily lost with the concomitant formation of a rather high-energy intermediate. In 2016, Bodgan et al. revisited the nucleophilic aromatic substitution of heterocycles by amines.[50] A DoE approach was implemented to determine the most efficient temperature/pressure/residence time combination. The optimum at 225 °C and 16 min (**SH** ethanol, 120 bar) was determined and then used for preparing a large scope of 2-aminoquinazolines in moderate to high yields (27−90% isolated yields). One year later, the same group modified and automated their reactor for synthesizing

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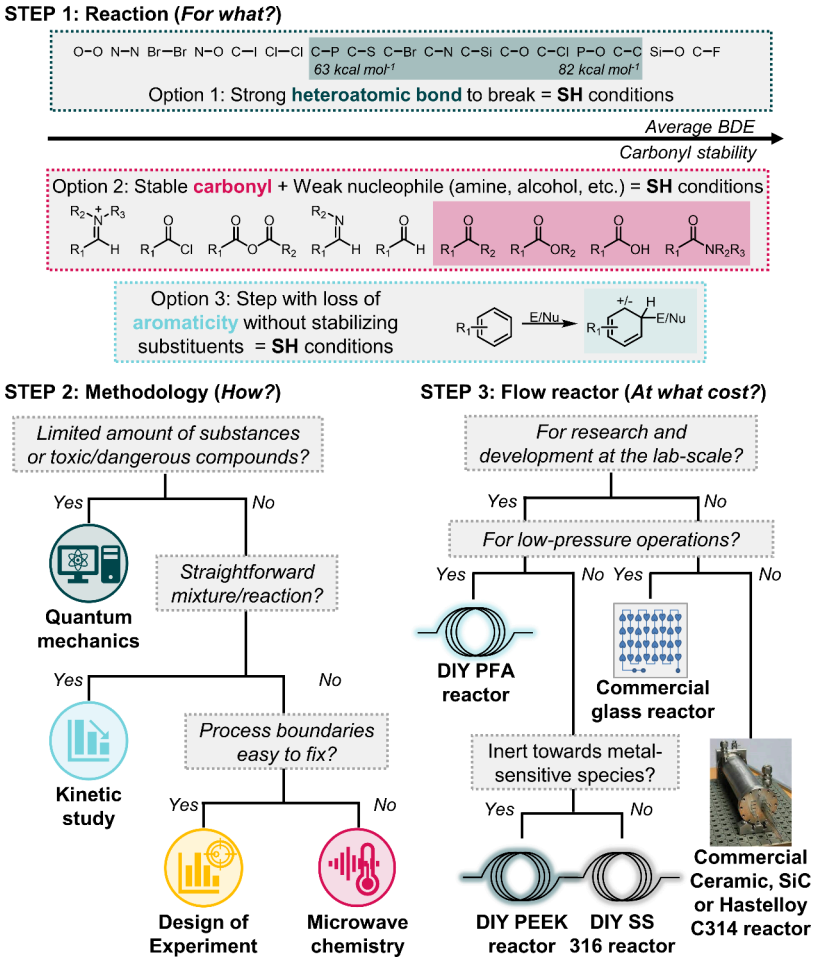

Figure 15. Guide for developing flow processes under **SH** flow conditions.

pyrimidinones and quinolones (Figure 14c).[51] Optimal conditions of the Gould-Jacobs thermal cyclization were again determined through a DoE approach. These compounds were easily prepared and isolated in high yields (32−96%) at 390 °C and 0.5 min residence time (**SH** tetrahydrofuran, 100 bar). Increasing the residence time to 4 min, and the pressure to 120 bar led to a clean tandem cyclization/decarboxylation process (46−84% yield). Another tandem cyclization/hydrolysis/decarboxylation process at 400 °C (**SH** tetrahydrofuran, 8 min, 120 bar) produced 4-aminopyrazolopyridines (41−78% yield).

■ CONCLUSION – GUIDE

SH flow chemistry holds significant potential to intensify the preparation of many value-added compounds, as illustrated in this Account with examples ranging from pharmaceuticals to biobased chemicals. Instead of a formal conclusion, we wish to provide supporting guidelines to help chemists seize the opportunity to adopt **SH** flow chemistry in their daily routines (Figure 15). The first step is to determine whether the planned chemistry could benefit from **SH** conditions (Step 1). These conditions provide the necessary energy to activate energetic pathways, enabling reactions to occur in just a few minutes. This approach is particularly suitable when weak nucleophiles are added to poorly reactive carbonyls (option 1), when strong C−Y bonds need to be cleaved (option 2), or when aromaticity needs to be temporarily lost (option 3).

However, before rushing into reaction optimization under **SH** conditions, it is critical to integrate appropriate tools and gather guidance (Step 2). When some chemicals have limited availability or are hazardous (toxic or highly reactive compounds), computations are highly recommended (option 1). In all other cases, experimental kinetics can be collected either in batch or in flow, depending on the likelihood of thermal degradation (option 2). Complex reactions associated with many variables and objectives require statistical modeling with DoE (option 3). It is also recommended to run a few preliminary trials under microwave batch conditions, alone or in combination with DoE (option 4), to set boundaries for safe **SH** process conditions preventing decomposition. The development of innovative methods in Quantum Mechanics, and smart tools in Artificial Intelligence will most certainly contribute to further strengthening these assessments.

The final endeavor (Step 3) should aim at selecting the most suitable flow setup. Whether it is a DIY solution or a commercial setup does not matter significantly, at least for lab-scale optimization of **SH** conditions. Critical parameters to consider include the chemical and mechanical compatibilities under the high constraints of the **SH** chemical space. When scalability is considered, commercial solutions emphasizing seamless scalability become obvious options. The rapid development of new materials and additive manufacturing strategies will certainly contribute to opening new opportunities.

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These guidelines draw upon our longstanding experience in the area and are designed to shift from traditional guesstimate optimization toward a more rational, less wasteful and resource-intensive process. **SH** conditions can be routinely integrated into the chemistry toolbox, resulting in higher productivity, easier workup procedures, increased purity profiles, and a much broader scope of reactions amenable to flow conditions. This expanded scope will not only rely on revisiting existing batch reactions but also on inventing new reactions that have never been explored before. With **SH** conditions, chemists can push the boundaries of chemical synthesis, uncovering novel pathways and mechanisms that were previously unattainable with conventional methods.[52]

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Author Contributions

CRediT: **Pauline Bianchi** conceptualization, writing-original draft; **Jean-Christophe M Monbaliu** funding acquisition, project administration, supervision, writing-review & editing.

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Notes

The authors declare no competing financial interest.

Biographies

Pauline Bianchi obtained her Master's in Chemical Sciences at the University of Liège (Belgium) in 2020. She is currently doing her Ph.D. as a Fellow of the National Science Foundation (F.R.S.-FNRS) under the supervision of Prof. J.-C. M. Monbaliu. As a recipient of a postdoctoral fellowship from the Belgian American Educational Foundation (BAEF), she will join Prof. K. Houk at UCLA at the end of 2024.

Jean-Christophe M. Monbaliu is currently Professor of Organic Chemistry at the University of Liège and Principal Investigator at the WEL Research Institute. He is an organic chemist who was trained at the Université catholique de Louvain, Belgium (PhD, 2008). After several postdoctoral experiences at world-leading institutions (Ghent University; University of Florida; Massachusetts Institute of Technology), he came back to Belgium with a rich background in organic synthesis, chemical engineering, and flow process technologies. He created the Center for Integrated Technology and Organic Synthesis (CiTOS) in 2013 at the University of Liège. Monbaliu also leads the first European Corning® Advanced-Flow Reactor Qualified Lab. In 2022, Monbaliu founded FloW4all, a Flow Technology Platform in Wallonia that focuses on training, technology transfer, and services for Industry.

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